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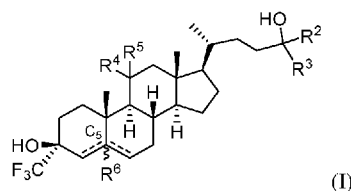
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(54) Title: OXYSTEROLS AND METHODS OF USE THEREOF



(57) Abstract: Compounds are provided according to Formula (I): and pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof; wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are as defined herein. Compounds of the present invention are contemplated useful for the prevention and treatment of a variety of conditions.



## OXYSTEROLS AND METHODS OF USE THEREOF

### Related Applications

[0001] This application claims priority to and the benefit of U.S. Provisional Application Number 62/409,761 filed October 18, 2016, U.S. Provisional Application Number 62/409,767 filed October 18, 2016, U.S. Provisional Application Number 62/409,772 filed October 18, 2016, U.S. Provisional Application Number 62/409,774 filed October 18, 2016, and U.S. Provisional Application Number 62/409,764 filed October 18, 2016, each of which are incorporated herein by reference in their entirety.

### Background of the Invention

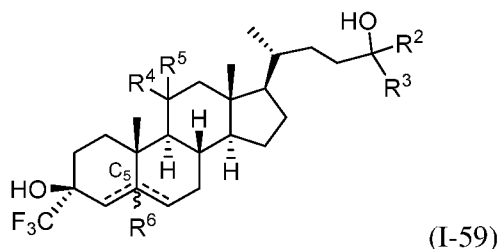
[0002] NMDA receptors are heteromeric complexes comprised of NR1, NR2, and/or NR3 subunits and possess distinct recognition sites for exogenous and endogenous ligands. These recognition sites include binding sites for glycine, and glutamate agonists and modulators. NMDA receptors are expressed in the peripheral tissues and the CNS, where they are involved in excitatory synaptic transmission. Activating these receptors contributes to synaptic plasticity in some circumstances and excitotoxicity in others. These receptors are ligand-gated ion channels that admit  $\text{Ca}^{2+}$  after binding of the glutamate and glycine, and are fundamental to excitatory neurotransmission and normal CNS function. Positive modulators may be useful as therapeutic agents with potential clinical uses as cognitive enhancers and in the treatment of psychiatric disorders in which glutamatergic transmission is reduced or defective (see, *e.g.*, Horak et al., J. of Neuroscience, 2004, 24(46), 10318-10325). In contrast, negative modulators may be useful as therapeutic agents with potential clinical uses in the treatment of psychiatric disorders in which glutamatergic transmission is pathologically increased (*e.g.*, treatment resistant depression).

[0003] Oxysterols are cholesterol analogs that are modulators of NMDA receptor function. There is a need for new oxysterols that modulate the NMDA receptor for the prevention and treatment of conditions associated with NMDA expression and function. Compounds, compositions, and methods described herein are directed toward this end.

### Summary of the Invention

[0004] Provided herein are substituted oxysterols useful for preventing and/or treating a broad range of disorders, including, but not limited to, NMDA-mediated disorders. Further provided are pharmaceutical compositions comprising the compounds of the present invention, and methods of their use and treatment.

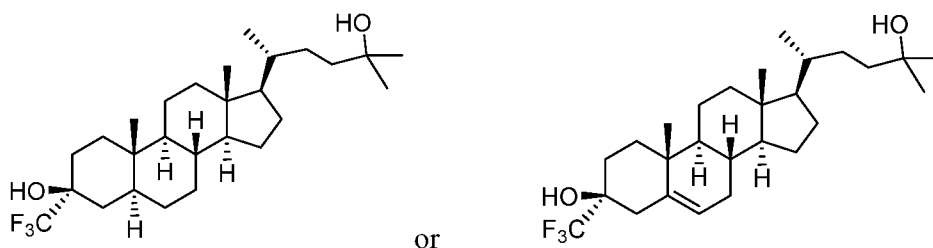
[0005] In one aspect, provided herein are compounds according to Formula (I-59):



or a pharmaceutically acceptable salt thereof, wherein: each of  $R^2$  and  $R^3$  is independently hydrogen, alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), carbocyclyl, or heterocyclyl, or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring; each of  $R^4$  and  $R^5$  is

5 independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), or  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;  $R^6$  is absent or hydrogen; and  $\text{=====}$  represents a single or double bond, wherein when one of  $\text{=====}$  is a double bond, the other  $\text{=====}$  is a single bond; when both of  $\text{=====}$  are single bonds, then  $R^6$  is hydrogen; and when one of  $\text{=====}$  is a double bond,  $R^6$  is absent; provided that the

10 following compounds are excluded:



**[0006]** In some embodiments,  $R^2$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl). In some embodiments,  $R^2$  is haloalkyl (*e.g.*,  $C_1$ - $C_6$  haloalkyl).

**[0007]** In some embodiments, each of  $R^2$  and  $R^3$  is independently alkyl (*e.g.*, substituted

15  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently unsubstituted alkyl (*e.g.*, unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently  $C_1$ - $C_6$  haloalkyl (*e.g.*, trifluoromethyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen, carbocyclyl, or heterocyclyl. In some embodiments, each of  $R^2$  and  $R^3$  is independently  $C_2$ - $C_6$  alkyl (*e.g.*, isopropyl or tert-butyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_3$ - $C_6$  alkyl (*e.g.*, isopropyl or tert-butyl).

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**[0008]** In some embodiments, at least one of  $R^2$  and  $R^3$  is  $C_3$ - $C_6$  alkyl (*e.g.*, isopropyl or tert-butyl), carbocyclyl, or heterocyclyl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring. In some embodiments,  $R^2$  is isopropyl or tert-butyl

25 and  $R^3$  is methyl or hydrogen. In some embodiments,  $R^2$  is substituted isopropyl or substituted tert-butyl and  $R^3$  is unsubstituted methyl or hydrogen. In some embodiments,  $R^2$  is unsubstituted isopropyl or unsubstituted tert-butyl and  $R^3$  is unsubstituted methyl or hydrogen. In some

embodiments,  $R^2$  is tert-butyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted tert-butyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted tert-butyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is methyl. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is substituted methyl. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is unsubstituted methyl. In some embodiments,  $R^2$  is methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted methyl and  $R^3$  is hydrogen.

[0009] In some embodiments, the 3-8 membered ring is heterogeneous or homogeneous.

In some further embodiments, the heterogeneous or homogeneous 3-8 membered ring is substituted with alkyl, haloalkyl, a 3-6 membered ring, substituted or unsubstituted alkoxy, or OH.

[0010] In some embodiments,  $R^4$  is -OH or halo (*e.g.*, -F). In some embodiments,  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group. In some embodiments,  $R^4$  is hydrogen and  $R^5$  is halo (*e.g.*, -F). In some embodiments,  $R^4$  and  $R^5$  are halo (*e.g.*, -F). In some embodiments,  $R^4$  and  $R^5$  are hydrogen.

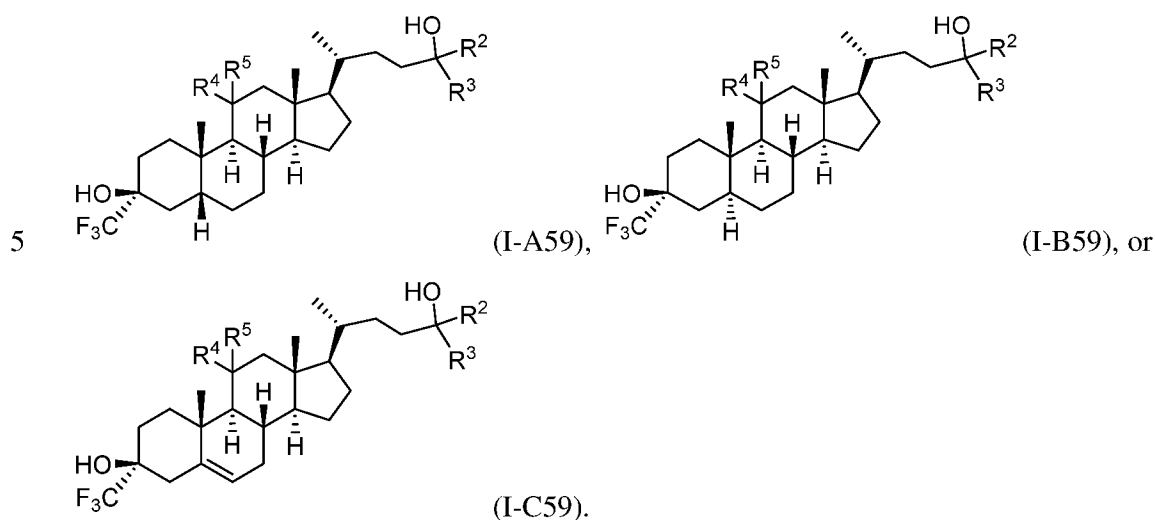
[0011] In some embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 5-membered ring. In some embodiments,  $R^2$  is  $C_2$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted isopropyl or substituted or unsubstituted tert-butyl) and  $R^3$  is  $C_1$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_1$ - $C_6$  alkyl). In some embodiments,  $R^2$  is unsubstituted  $C_2$ - $C_6$  alkyl (*e.g.*, unsubstituted isopropyl or unsubstituted tert-butyl) and  $R^3$  is unsubstituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 6-membered ring.

[0012] In some embodiments,  $R^2$  is carbocyclyl or heterocyclyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  and  $R^3$  are hydrogen. In some embodiments,  $R^2$  is isopropyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted isopropyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted isopropyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered carbocyclic (*e.g.*, cyclohexyl) or heterocyclic (*e.g.*, tetrahydrofuranyl or tetrahydropyranyl) ring. In some embodiments, the carbocyclic or heterocyclic ring is substituted (*e.g.*, ring substituted with 1 or 2 halo or alkyl groups). In some embodiments,  $R^2$  is cyclobutyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is tetrahydropyranyl and  $R^3$  is hydrogen.

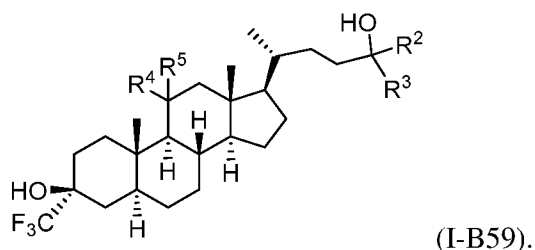
[0013] In some embodiments,  $R^2$  is substituted cyclobutyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted tetrahydropyranyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$

is unsubstituted cyclobutyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted tetrahydropyranyl and  $R^3$  is hydrogen.

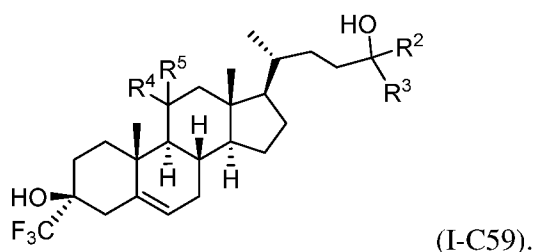
**[0014]** In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-A59), (I-B59), or (I-C59):



**[0015]** In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-B59):

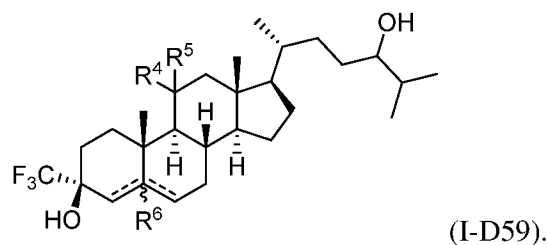


10 **[0016]** In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-C59):

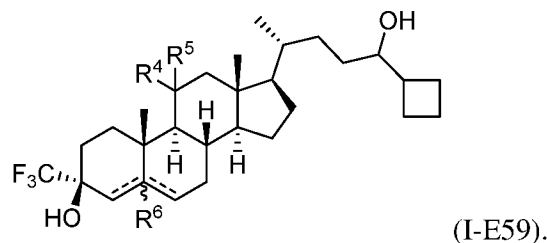


**[0017]** In some embodiments, at least one of  $R^2$  and  $R^3$  is hydrogen,  $C_1$ - $C_6$  alkyl, carbocyclyl, or heterocyclyl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring. In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-D59):

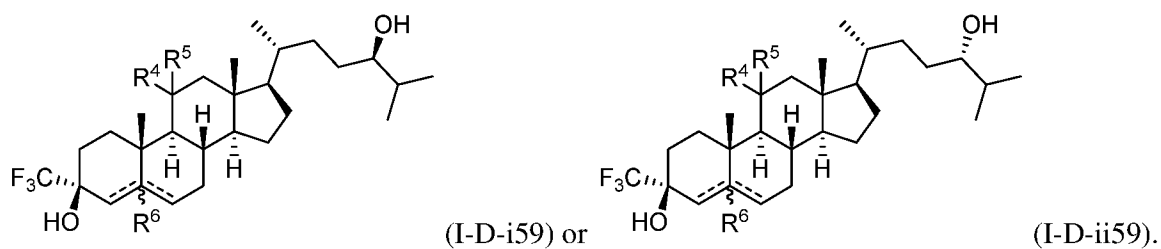
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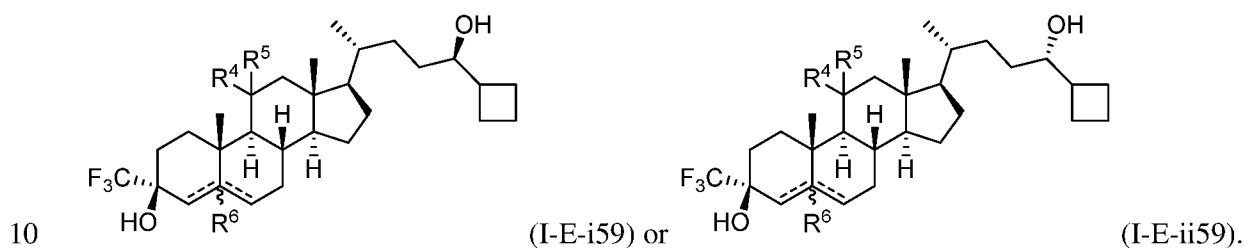
[0018] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-E59):



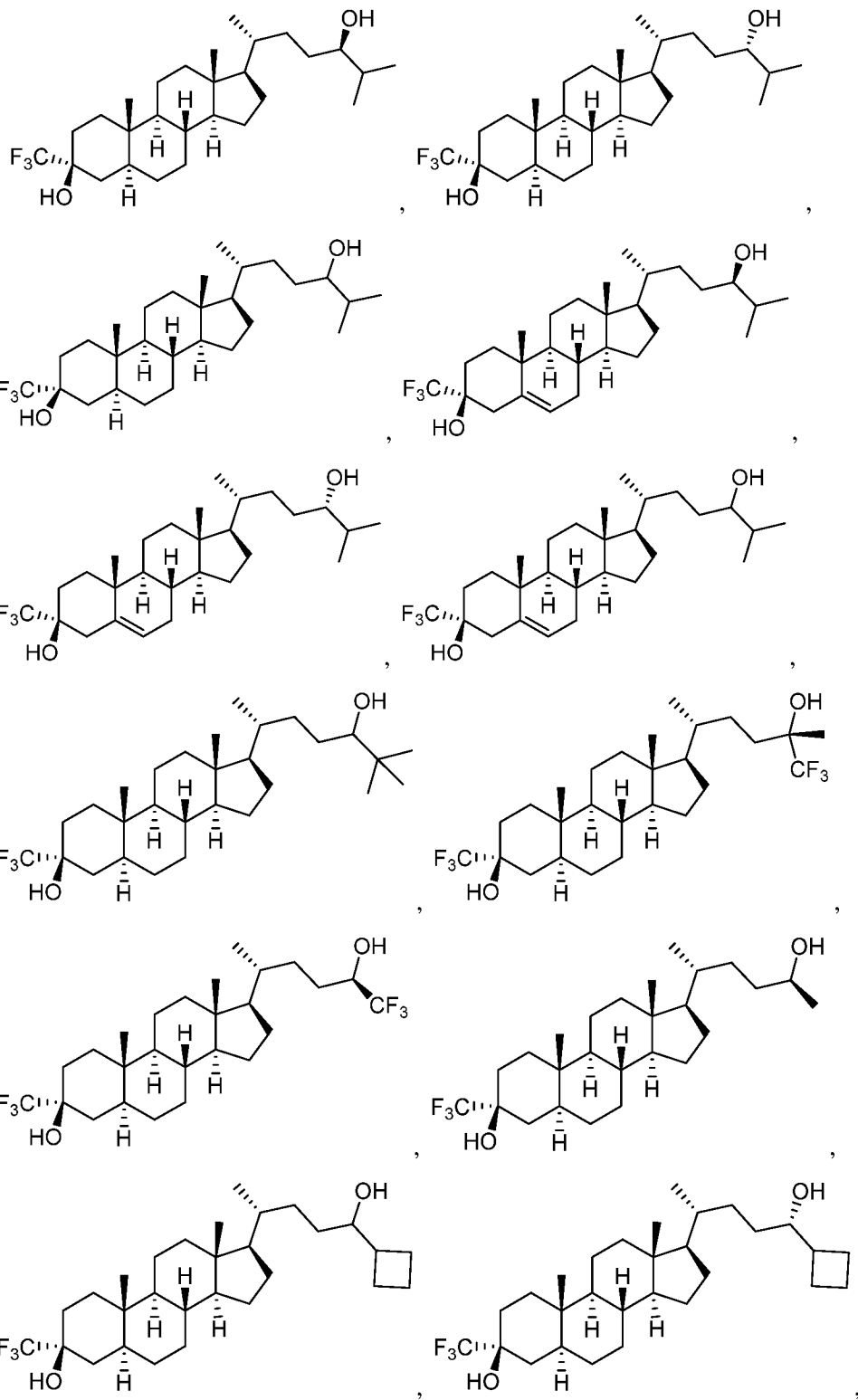
5 [0019] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-D-i59) or (I-D-ii59):

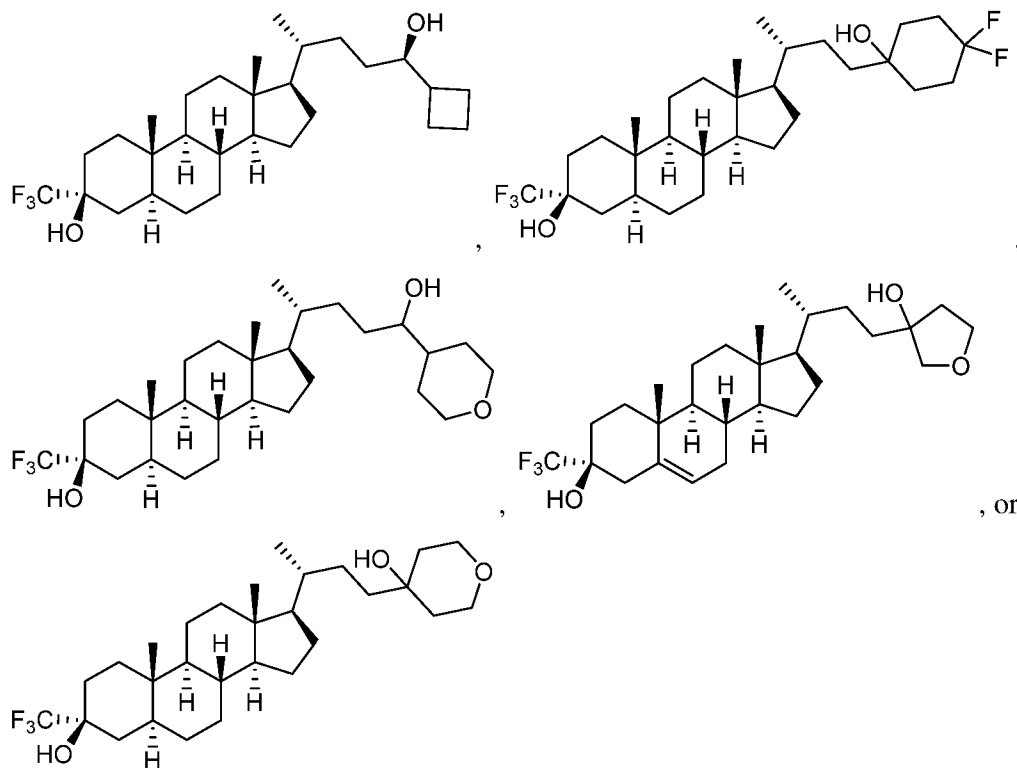


[0020] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-E-i59) or (I-E-ii59):



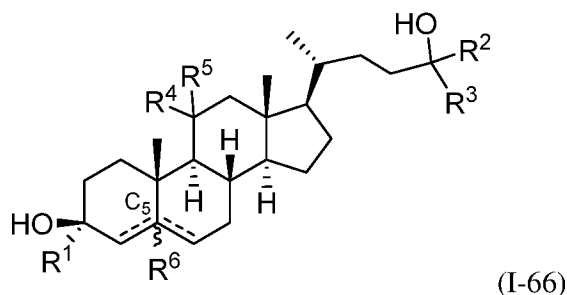
[0021] In some embodiments, the compound is:





[0022] In one aspect, provided herein are compounds according to Formula (I-66):

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or a pharmaceutically acceptable salt thereof, wherein: R<sup>1</sup> is alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl); R<sup>2</sup> is aralkyl, heteroaralkyl, aryl, or heteroaryl; R<sup>3</sup> is hydrogen, alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl), carbocyclyl, heterocyclyl, aryl, or heteroaryl; each of R<sup>4</sup> and R<sup>5</sup> is independently hydrogen, halo, or -OR<sup>C</sup>, wherein R<sup>C</sup> is hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl (*e.g.*, unsubstituted or substituted C<sub>1</sub>-C<sub>3</sub> alkyl), or R<sup>4</sup> and R<sup>5</sup>, together with the carbon atom to which they are attached form an oxo group; R<sup>6</sup> is absent or hydrogen; and  $\text{-----}$  represents a single or double bond, wherein when one of  $\text{-----}$  is a double bond, the other  $\text{-----}$  is a single bond; when both of  $\text{-----}$  are single bonds, then R<sup>6</sup> is hydrogen; and when one of  $\text{-----}$  is a double bond, R<sup>6</sup> is absent.

[0023] In some embodiments, R<sup>1</sup> is alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl). In some embodiments, R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl (*e.g.*, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, or -CF<sub>3</sub>). In some embodiments, R<sup>1</sup> is -CH<sub>3</sub>,

$-\text{CF}_3$ , or  $-\text{CH}_2\text{CH}_3$ . In some embodiments,  $\text{R}^1$  is  $-\text{CH}_2\text{OR}^A$ , wherein  $\text{R}^A$  is  $\text{C}_1$ - $\text{C}_6$  alkyl (*e.g.*,  $\text{C}_1$ - $\text{C}_3$  alkyl).

[0024] It should be appreciated that  $\text{C}_1$ - $\text{C}_6$  alkyl, aralkyl, heteroaralkyl, aryl, carbocyclyl, heterocyclyl, aryl, heteroaryl or heteroaryl can be substituted or unsubstituted, for example with cyano, halogen, OH, or alkoxy.

[0025] In some embodiments,  $\text{R}^2$  is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), or aralkyl (*e.g.*, substituted or unsubstituted benzyl). In some embodiments,  $\text{R}^2$  is phenyl (*e.g.*, substituted or unsubstituted phenyl), pyridyl (*e.g.*, substituted or unsubstituted pyridyl), or benzyl (*e.g.*, substituted or unsubstituted benzyl).

[0026] In some embodiments,  $\text{R}^3$  is hydrogen or alkyl (*e.g.*,  $\text{C}_1$ - $\text{C}_6$  alkyl). In some embodiments,  $\text{R}^3$  is hydrogen, unsubstituted alkyl (*e.g.*, unsubstituted  $\text{C}_1$ - $\text{C}_6$  alkyl), or haloalkyl (*e.g.*,  $-\text{CF}_3$ ).

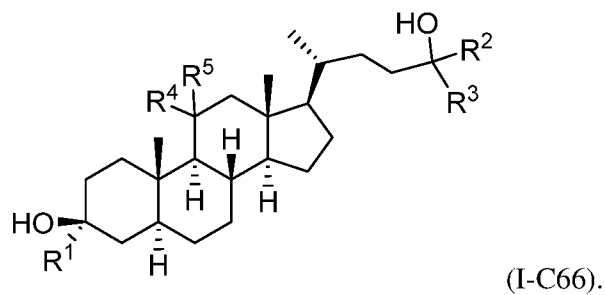
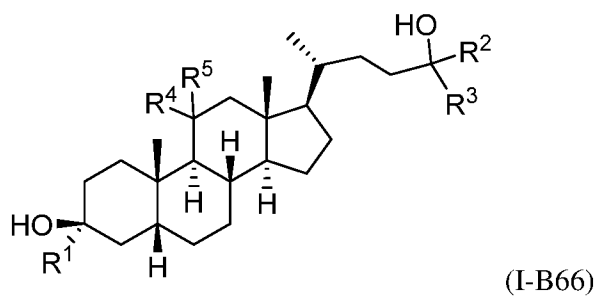
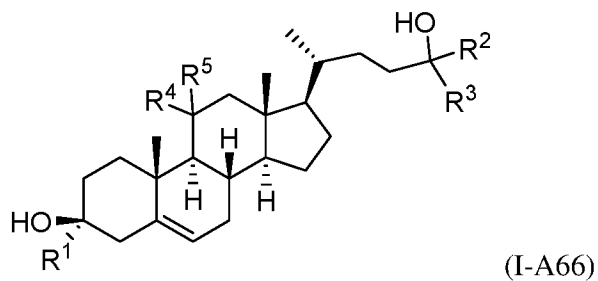
[0027] In some embodiments,  $\text{R}^4$  is  $-\text{OH}$  or halo (*e.g.*,  $-\text{F}$ ).

[0028] In some embodiments,  $\text{R}^4$  and  $\text{R}^5$ , together with the carbon atom to which they are attached form an oxo group. In some embodiments,  $\text{R}^4$  is hydrogen and  $\text{R}^5$  is halo (*e.g.*,  $-\text{F}$ ). In some embodiments,  $\text{R}^4$  and  $\text{R}^5$  are halo (*e.g.*,  $-\text{F}$ ). In some embodiments,  $\text{R}^4$  and  $\text{R}^5$  are hydrogen.

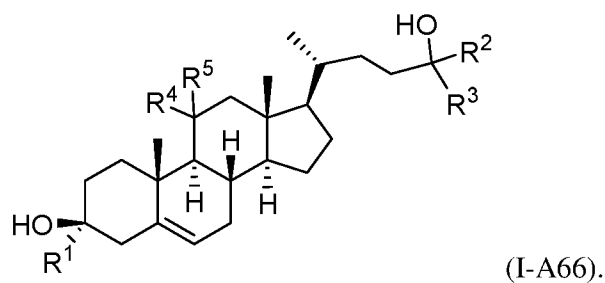
[0029] In some embodiments,  $\text{R}^2$  is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), aralkyl (*e.g.*, substituted or unsubstituted aralkyl, *e.g.*, substituted or unsubstituted benzyl), or heteroaralkyl and  $\text{R}^3$  is hydrogen or alkyl (*e.g.*, unsubstituted  $\text{C}_1$ - $\text{C}_6$  alkyl, *e.g.*,  $\text{C}_1$ - $\text{C}_6$  haloalkyl). In some embodiments,  $\text{R}^2$  is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), aralkyl (*e.g.*, substituted or unsubstituted aralkyl, *e.g.*, substituted or unsubstituted benzyl), or heteroaralkyl and  $\text{R}^3$  is hydrogen,  $-\text{CH}_3$ , or  $-\text{CF}_3$ .

[0030] In some embodiments,  $\text{R}^1$  is alkyl (*e.g.*,  $\text{C}_1$ - $\text{C}_6$  alkyl),  $\text{R}^2$  is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), aralkyl (*e.g.*, substituted or unsubstituted aralkyl, *e.g.*, substituted or unsubstituted benzyl), or heteroaralkyl, and  $\text{R}^3$  is hydrogen,  $-\text{CH}_3$ , or  $-\text{CF}_3$ . In some embodiments,  $\text{R}^1$  is  $-\text{CH}_3$  or  $-\text{CH}_2\text{CH}_3$ ,  $\text{R}^2$  is unsubstituted phenyl, unsubstituted pyridyl, or unsubstituted benzyl, and  $\text{R}^3$  is hydrogen,  $-\text{CH}_3$ , or  $-\text{CF}_3$ .

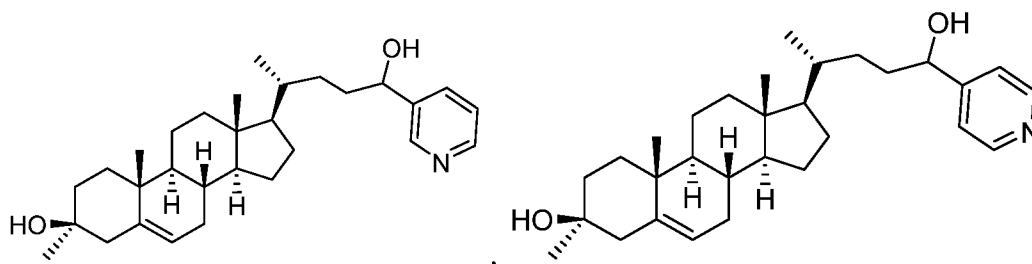
[0031] In some embodiments, the compound of Formula (I-66) is selected from a compound of Formula (I-A66), (I-B66), or (I-C66):

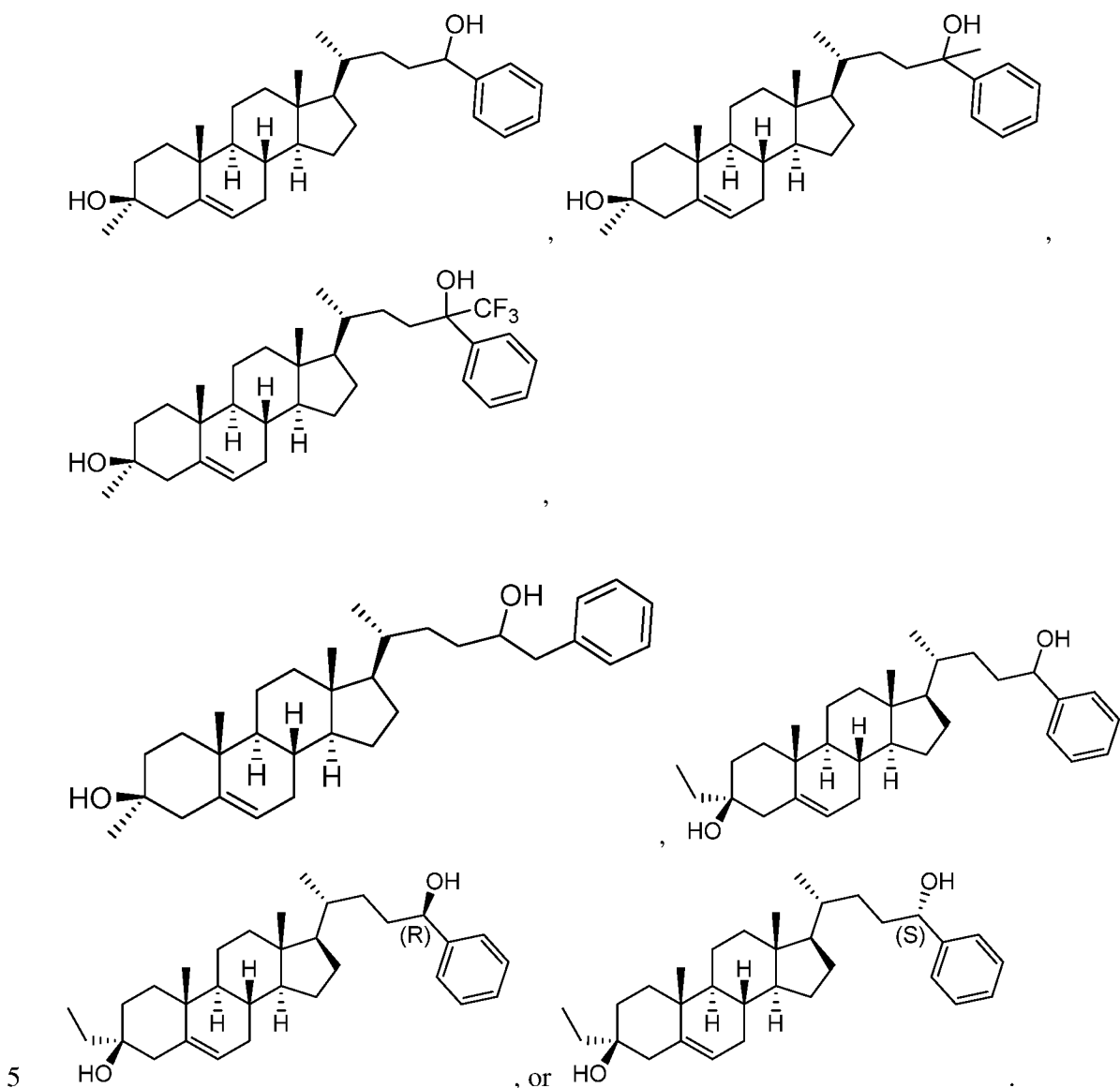


- 5 [0032] In some embodiments, the compound of Formula (I-66) is selected from a compound of Formula (I-A66):

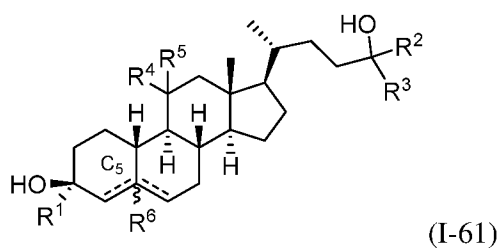


- [0033] In some embodiments, the compound is:



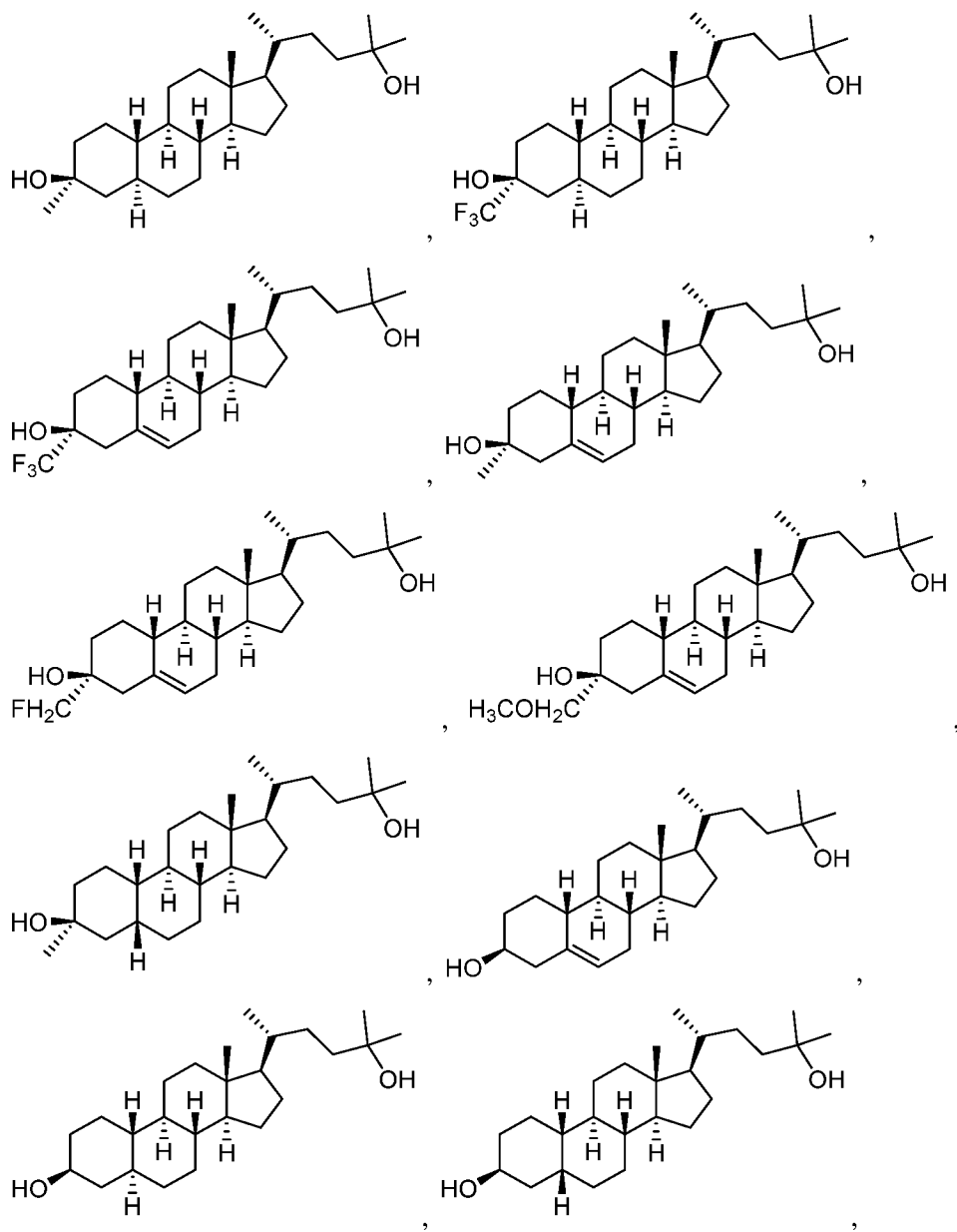


[0034] In one aspect, provided herein are compounds according to Formula (I-61):

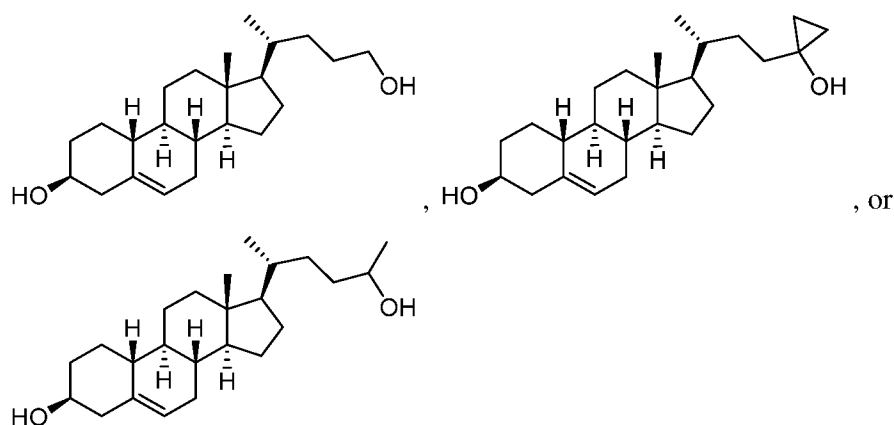


10 or a pharmaceutically acceptable salt thereof, wherein:  $R^1$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl); each of  $R^2$  and  $R^3$  is independently hydrogen, alkyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached for a 3-8 membered ring; each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is

hydrogen or alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl), or R<sup>4</sup> and R<sup>5</sup>, together with the carbon atom to which they are attached form an oxo group; R<sup>6</sup> is absent or hydrogen; and        represents a single or double bond, wherein when one of        is a double bond, the other        is a single bond; when both of        are single bonds, then R<sup>6</sup> is hydrogen; and when one of        is a double bond, R<sup>6</sup> is absent; provided that the following compounds are excluded:



10



[0035] In some embodiments,  $R^1$  is alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl) or hydrogen. In some  
 5 embodiments,  $R^1$  is  $C_2$ - $C_6$  alkyl (*e.g.*,  $C_3$ - $C_6$  alkyl) or hydrogen. In some embodiments,  $R^1$  is  
 substituted or unsubstituted  $C_2$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_3$ - $C_6$  alkyl) or  
 hydrogen. In some embodiments,  $R^1$  is methyl or ethyl (*e.g.*, substituted or unsubstituted methyl  
 or substituted or unsubstituted ethyl). In some embodiments,  $R^1$  is substituted or unsubstituted  
 methyl or substituted or unsubstituted ethyl. In some embodiments,  $R^1$  is trifluoromethyl. In  
 10 some embodiments,  $R^1$  is  $-CH_2OR^A$ , wherein  $R^A$  is  $C_1$ - $C_6$  alkyl (*e.g.*,  $C_1$ - $C_3$  alkyl).

[0036] In some embodiments,  $R^2$  is hydrogen or  $C_1$ - $C_6$  alkyl, (*e.g.*,  $C_2$ - $C_6$  alkyl). In some  
 embodiments,  $R^2$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl (*e.g.*, substituted or  
 unsubstituted  $C_2$ - $C_6$  alkyl). In some embodiments,  $R^2$  is hydrogen. In some embodiments,  $R^2$  is  
 isopropyl (*e.g.*, substituted or unsubstituted isopropyl). In some embodiments,  $R^2$  is substituted  
 15 or unsubstituted isopropyl. In some embodiments,  $R^2$  is haloalkyl (*e.g.*,  $C_1$ - $C_6$  haloalkyl).

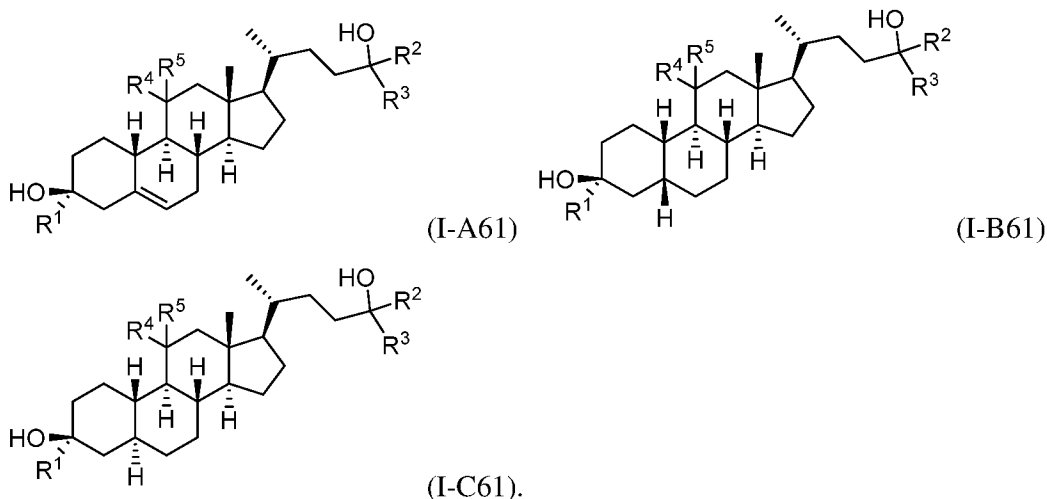
[0037] In some embodiments, each of  $R^2$  and  $R^3$  is independently alkyl (*e.g.*,  $C_1$ - $C_6$   
 alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently substituted or  
 unsubstituted alkyl (*e.g.*, substituted or unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some  
 embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached for a 3-8  
 20 membered ring. In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_1$ - $C_6$   
 alkyl (*e.g.*  $C_2$ - $C_6$  alkyl). In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  
 substituted or unsubstituted  $C_1$ - $C_6$  alkyl, (*e.g.* substituted or unsubstituted  $C_2$ - $C_6$  alkyl). In some  
 embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_3$ - $C_6$  alkyl (*e.g.*, isopropyl). In  
 some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or substituted or unsubstituted  
 25  $C_3$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted isopropyl).

[0038] In some embodiments,  $R^4$  is  $-OH$  or halo (*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  
 $R^5$ , together with the carbon atom to which they are attached form an oxo group. In some

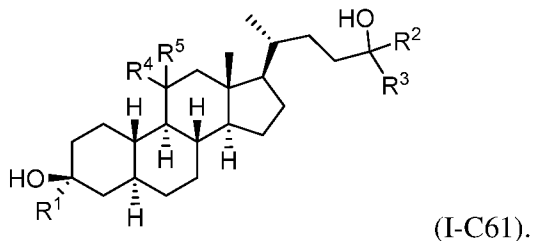
embodiments,  $R^4$  is hydrogen and  $R^5$  is halo (*e.g.*, -F). In some embodiments,  $R^4$  and  $R^5$  are halo (*e.g.*, -F). In some embodiments,  $R^4$  and  $R^5$  are hydrogen.

[0039] In some embodiments,  $R^2$  and  $R^3$  are hydrogen. In some embodiments,  $R^2$  is  $C_1$ - $C_6$  alkyl and  $R^3$  is  $C_2$ - $C_6$  alkyl (*e.g.*,  $C_3$ - $C_6$  alkyl). In some embodiments,  $R^2$  is substituted or unsubstituted  $C_1$ - $C_6$  alkyl and  $R^3$  is substituted or unsubstituted  $C_2$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_3$ - $C_6$  alkyl). In some embodiments,  $R^1$  is ethyl (*e.g.*, substituted or unsubstituted ethyl) and  $R^2$  and  $R^3$  are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments,  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl. In some embodiments,  $R^1$  is ethyl,  $R^2$  is isopropyl, and  $R^3$  is hydrogen. In some embodiments,  $R^1$  is substituted or unsubstituted ethyl,  $R^2$  is substituted or unsubstituted isopropyl, and  $R^3$  is hydrogen. In some embodiments,  $R^1$  is ethyl,  $R^2$  is isopropyl, and  $R^3$  is methyl. In some embodiments,  $R^1$  is substituted or unsubstituted ethyl,  $R^2$  is substituted or unsubstituted isopropyl, and  $R^3$  is substituted or unsubstituted methyl.

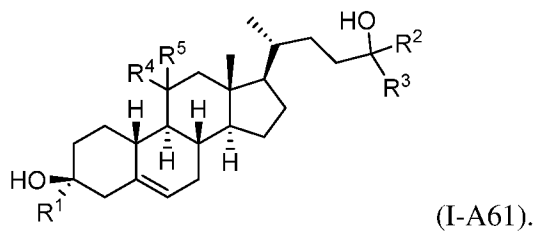
[0040] In some embodiments, the compound of Formula (I-61) is a compound of Formula (I-A61), (I-B61), or (I-C61):



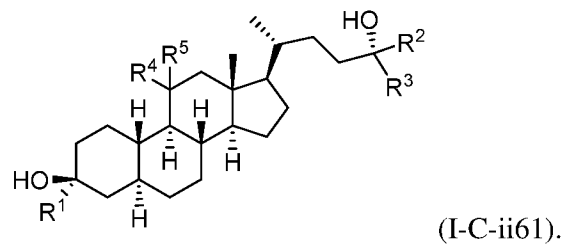
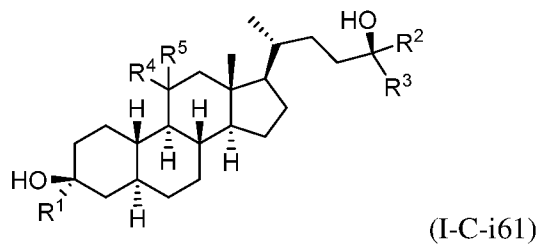
[0041] In some embodiments, the compound of Formula (I-61) is selected from a compound of Formula (I-C61):



[0042] In some embodiments, the compound of Formula (I-61) is selected from a compound of Formula (I-A61):

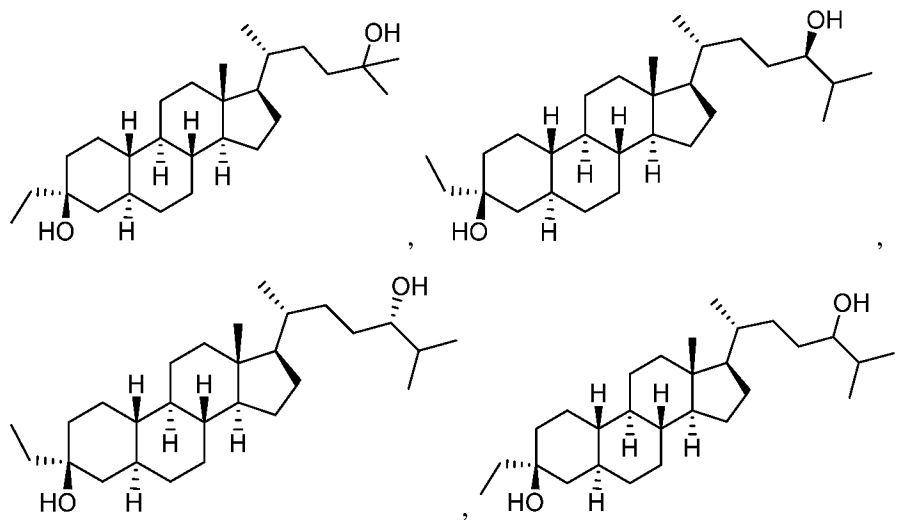


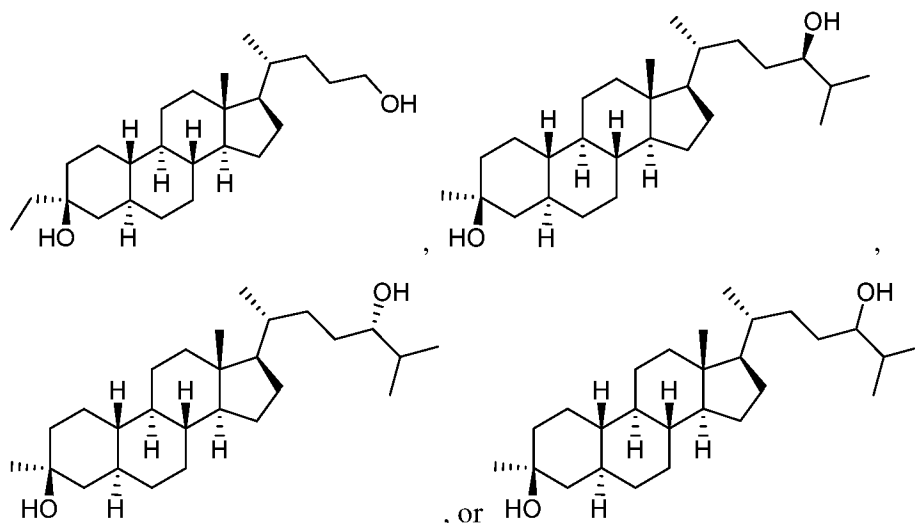
[0043] In some embodiments, the compound of Formula (I-61) is selected from a compound of Formula (I-C-i61) or (I-C-ii61):



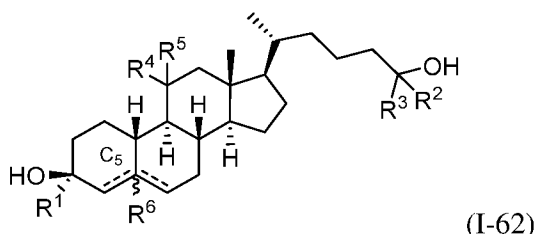
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[0044] In some embodiments, the compound is:





[0045] In one aspect, the present invention features a compound of Formula (I-62):



or a pharmaceutically acceptable salt thereof, wherein:  $R^1$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl); each of  $R^2$  and  $R^3$  is independently hydrogen, alkyl, carbocyclyl, or heterocyclyl or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 membered ring; each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), or  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;  $R^6$  is absent or hydrogen; and  $\text{-----}$  represents a single or double bond, wherein when one of  $\text{-----}$  is a double bond, the other  $\text{-----}$  is a single bond; when both of  $\text{-----}$  are single bonds, then  $R^6$  is hydrogen; and when one of  $\text{-----}$  is a double bond,  $R^6$  is absent.

[0046] In some embodiments,  $R^1$  is alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl). In some embodiments,  $R^1$  is substituted or unsubstituted  $C_2$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_3$ - $C_6$  alkyl). In some embodiments,  $R^1$  is methyl or ethyl (*e.g.*, substituted or unsubstituted methyl or substituted or unsubstituted ethyl). In some embodiments,  $R^1$  is substituted or unsubstituted methyl or substituted or unsubstituted ethyl. In some embodiments,  $R^1$  is trifluoromethyl. In some embodiments,  $R^1$  is  $-\text{CH}_2\text{OR}^A$ , wherein  $R^A$  is  $C_1$ - $C_6$  alkyl (*e.g.*,  $C_1$ - $C_3$  alkyl).

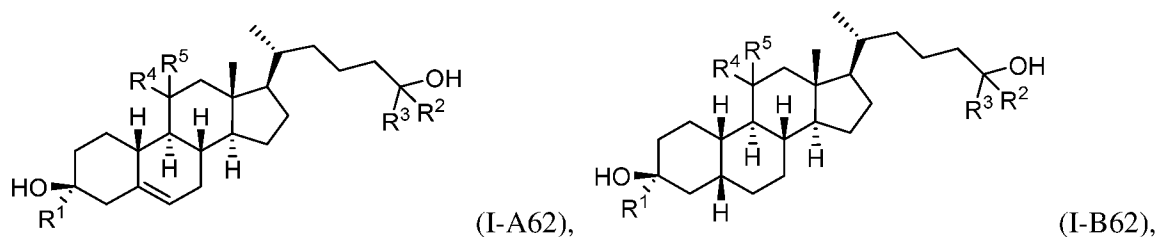
[0047] In some embodiments,  $R^2$  is hydrogen or  $C_1$ - $C_6$  alkyl, (*e.g.*,  $C_2$ - $C_6$  alkyl). In some embodiments,  $R^2$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_2$ - $C_6$  alkyl). In some embodiments,  $R^2$  is haloalkyl, (*e.g.*,  $C_1$ - $C_6$  haloalkyl).

[0048] In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_1$ - $C_6$  alkyl (*e.g.*  $C_2$ - $C_6$  alkyl). In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl (*e.g.* substituted or unsubstituted  $C_2$ - $C_6$  alkyl). In some  
5  
embodiments, each of  $R^2$  and  $R^3$  is independently alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl) or hydrogen. In some  
embodiments, each of  $R^2$  and  $R^3$  is independently substituted or unsubstituted alkyl (*e.g.*,  
substituted or unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments,  $R^2$  and  $R^3$ , together  
with the carbon atom to which they are attached, form a 3-8 membered ring.

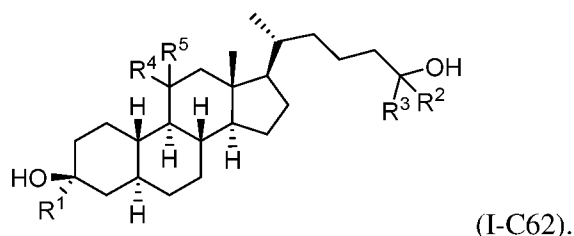
[0049] In some embodiments,  $R^4$  is  $-OH$  or halo (*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  
 $R^5$ , together with the carbon atom to which they are attached form an oxo group. In some  
10  
embodiments,  $R^4$  is hydrogen and  $R^5$  is halo (*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  $R^5$  are halo  
(*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  $R^5$  are hydrogen.

[0050] In some embodiments,  $R^1$  is ethyl (*e.g.*, substituted or unsubstituted ethyl) and  $R^2$   
and  $R^3$  are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments,  $R^1$  is  
substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

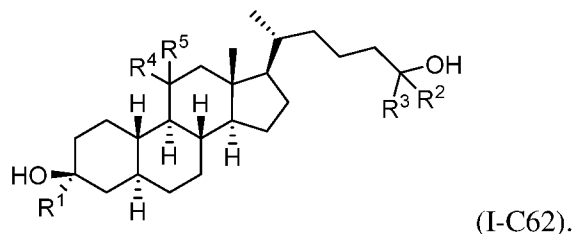
15 [0051] In some embodiments, the compound of Formula (I-62) is a compound of  
Formula (I-A62), (I-B62), or (I-C62):



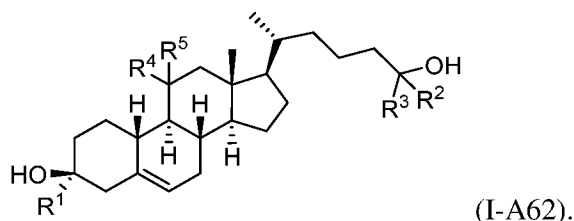
or



20 [0052] In some embodiments, the compound of Formula (I-62) is selected from a  
compound of Formula (I-C62):

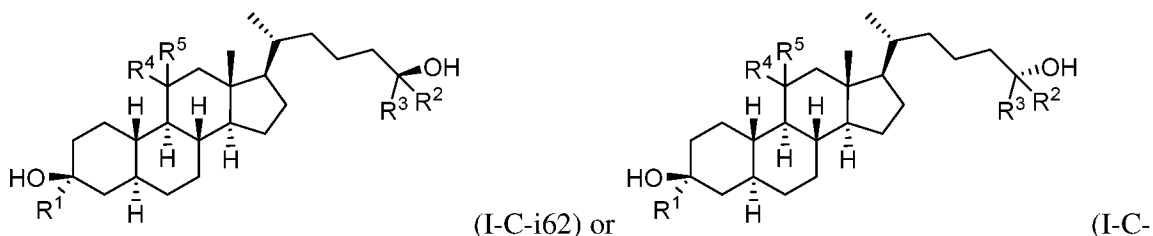


[0053] In some embodiments, the compound of Formula (I-62) is selected from a compound of Formula (I-A62):

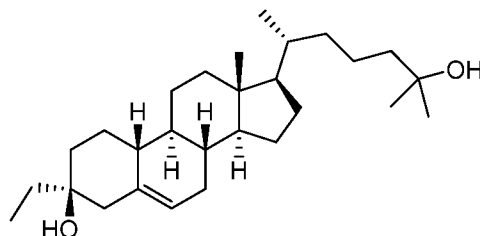


[0054] In some embodiments, R<sup>1</sup> is ethyl (*e.g.*, substituted or unsubstituted ethyl) and R<sup>2</sup> and R<sup>3</sup> are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments, R<sup>1</sup> is substituted or unsubstituted ethyl and R<sup>2</sup> and R<sup>3</sup> are substituted or unsubstituted methyl.

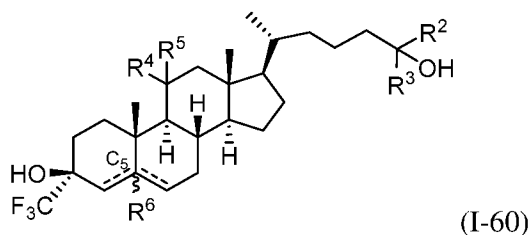
[0055] In some embodiments, the compound of Formula (I-62) is selected from a compound of Formula (I-C-i62) or (I-C-ii62):



[0056] In some embodiments, the compound is



[0057] In one aspect, provided herein are compounds according to Formula (I-60):



or a pharmaceutically acceptable salt thereof, wherein: each of R<sup>2</sup> and R<sup>3</sup> is independently hydrogen, alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl), carbocyclyl, heterocyclyl, aryl, or heteroaryl, or R<sup>2</sup> and R<sup>3</sup>, together with the carbon atom to which they are attached form a 3-8 membered ring; each of R<sup>4</sup> and R<sup>5</sup> is independently hydrogen, halo, or -OR<sup>C</sup>, wherein R<sup>C</sup> is hydrogen or alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub>

alkyl), or R<sup>4</sup> and R<sup>5</sup>, together with the carbon atom to which they are attached form an oxo group; R<sup>6</sup> is absent or hydrogen; and  $\text{-----}$  represents a single or double bond, wherein when one of  $\text{-----}$  is a double bond, the other  $\text{-----}$  is a single bond; when both of  $\text{-----}$  are single bonds, then R<sup>6</sup> is hydrogen; and when one of the  $\text{-----}$  is a double bond, R<sup>6</sup> is absent.

5 In some embodiments, R<sup>2</sup> is alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl) or hydrogen. In some embodiments, R<sup>2</sup> is haloalkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> haloalkyl). In some embodiments, R<sup>2</sup> is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl) or hydrogen. In some embodiments, R<sup>2</sup> is aryl or heteroaryl.

10 In some embodiments, each of R<sup>2</sup> and R<sup>3</sup> is independently alkyl (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl) or hydrogen. In some embodiments, each of R<sup>2</sup> and R<sup>3</sup> is independently substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl) or hydrogen. In some embodiments, each of R<sup>2</sup> and R<sup>3</sup> is independently unsubstituted alkyl (*e.g.*, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl) or hydrogen. In some embodiments, each of R<sup>2</sup> and R<sup>3</sup> is independently C<sub>1</sub>-C<sub>6</sub> haloalkyl (*e.g.*, trifluoromethyl) or hydrogen. In some embodiments, 15 each of R<sup>2</sup> and R<sup>3</sup> is independently aryl or heteroaryl. In some embodiments, R<sup>2</sup> and R<sup>3</sup>, together with the carbon atom to which they are attached form a 3-membered ring.

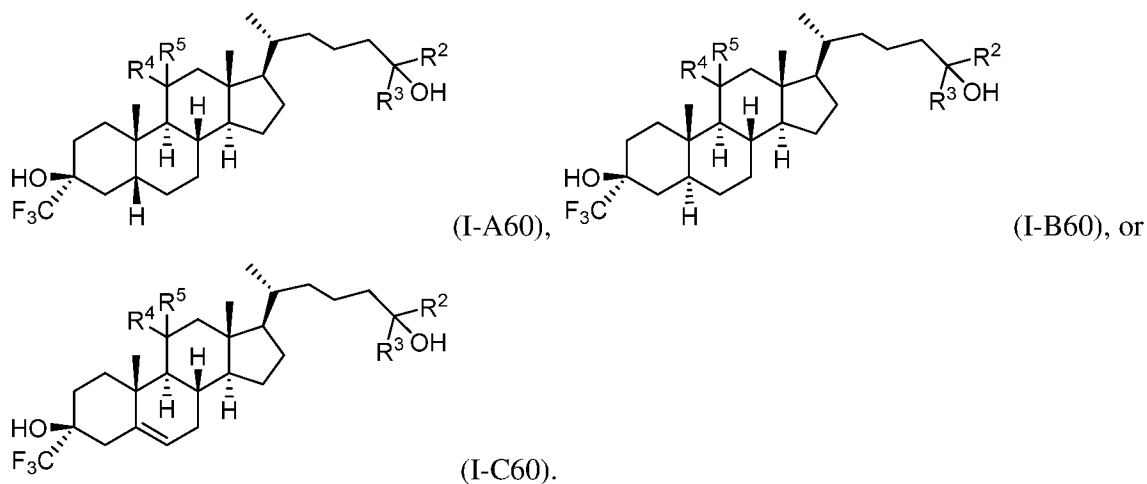
In some embodiments, R<sup>2</sup> and R<sup>3</sup>, together with the carbon atom to which they are attached form a cyclopropane. In some embodiments, R<sup>2</sup> and R<sup>3</sup>, together with the carbon atom to which they are attached form a 3-8 membered carbocyclic or heterocyclic 20 ring.

In some embodiments, R<sup>2</sup> is carbocyclyl or heterocyclyl and R<sup>3</sup> is hydrogen. In some embodiments, R<sup>2</sup> is trifluoromethyl and R<sup>3</sup> is hydrogen. In some embodiments, R<sup>2</sup> is aryl or heteroaryl and R<sup>3</sup> is hydrogen. In some embodiments, R<sup>2</sup> and R<sup>3</sup> are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments, R<sup>2</sup> and R<sup>3</sup> is substituted 25 methyl. In some embodiments, R<sup>2</sup> and R<sup>3</sup> is unsubstituted methyl.

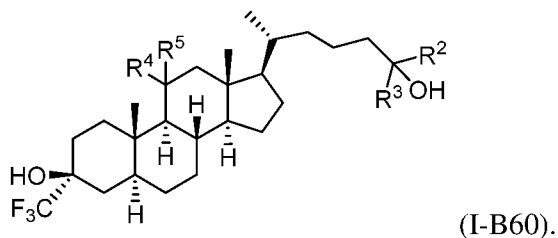
In some embodiments, R<sup>4</sup> is -OH or halo (*e.g.*, -F). In some embodiments, R<sup>4</sup> and R<sup>5</sup>, together with the carbon atom to which they are attached form an oxo group.

In some embodiments, R<sup>4</sup> is hydrogen and R<sup>5</sup> is halo (*e.g.*, -F). In some embodiments, R<sup>4</sup> and R<sup>5</sup> are halo (*e.g.*, -F). In some embodiments, R<sup>4</sup> and R<sup>5</sup> are 30 hydrogen.

In some embodiments, the compound of Formula (I-60) is selected from a compound of Formula (I-A60), (I-B60), or (I-C60):



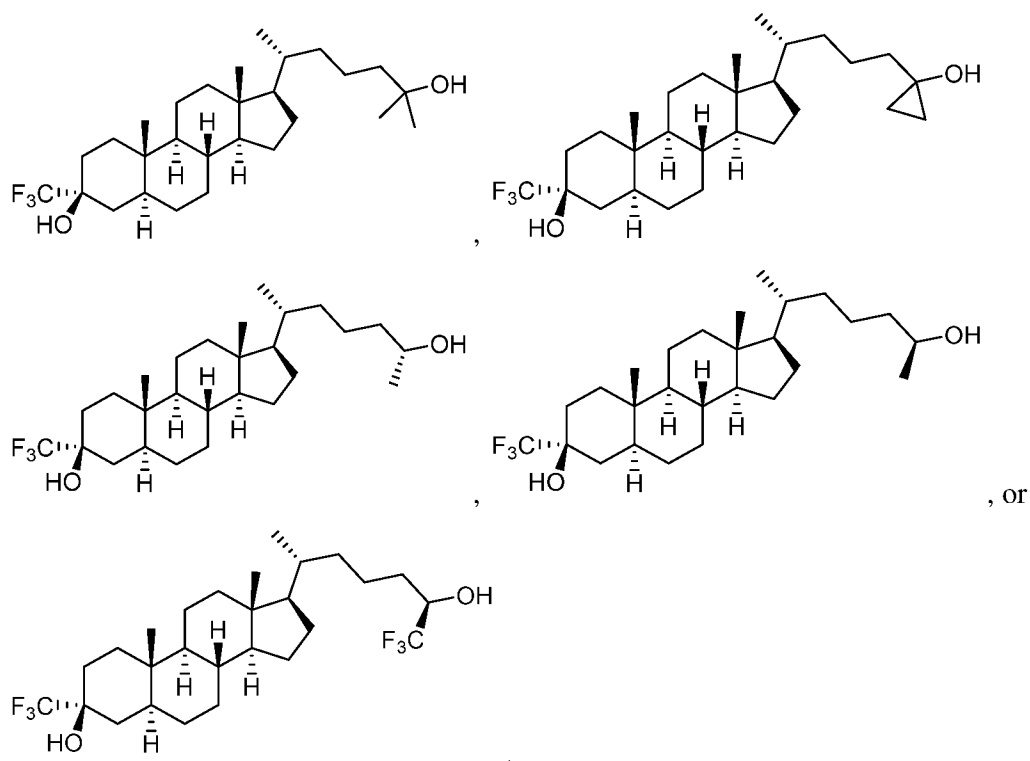
In some embodiments, the compound of Formula (I-60) is selected from a compound of Formula (I-B60):



In some embodiments, at least one of  $R^2$  and  $R^3$  is  $C_1$ - $C_6$  alkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 membered ring.

In some embodiments,  $R^2$  is methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  and  $R^3$  are hydrogen.

In some embodiments, the compound is:



5 [0058] In an aspect, provided herein is a pharmaceutical composition comprising a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0059] In an aspect, provided herein is a method of inducing sedation or anesthesia comprising administering to a subject an effective amount of a compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

10 [0060] In an aspect, provided herein is a method for treating or preventing a disorder described herein, comprising administering to a subject in need thereof an effective amount of a compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

15 [0061] In some embodiments, the disorder is a metabolic disorder.

[0062] In some embodiments, the disorder is an autoimmune disorder.

[0063] In some embodiments, the disorder is rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

20 [0064] In some embodiments, the disorder is a gastrointestinal (GI) disorder *e.g.*, constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) (*e.g.*, ulcerative colitis, Crohn's disease), structural disorders affecting the GI, anal disorders (*e.g.*, hemorrhoids,

internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula), colon polyps, cancer, or colitis.

[0065] In some embodiments, the disorder is inflammatory bowel disease.

[0066] In some embodiments, the disorder is cancer, diabetes, or a sterol synthesis disorder.

[0067] In some embodiments, the disorder is Neuropsychiatric lupus, Depression, OCD, Huntington's disease, ALS, Alzheimer's, Dementia, Parkinson's, MS, Acute liver failure, Glycine encephalopathy, Tinnitus, Neuropathic pain, Migraine, Genetic epilepsy, Seizure, Ataxia, Levodopa-induced dyskinesia, Fragile X, Rett syndrome, Autism Spectrum disorders, Tourette's, Schizophrenia, and Traumatic brain injury.

[0068] In an aspect, provided herein is a method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof. In some embodiments, the CNS-related condition is an adjustment disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia (*e.g.*, frontotemporal dementia), dissociative disorder, eating disorder, mood disorder (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia), substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.*, Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis disorders, pain (including acute and chronic pain; headaches, *e.g.*, migraine headaches), encephalopathy secondary to a medical condition (including hepatic encephalopathy and anti-NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, or tinnitus.

[0069] In some embodiments, the disorder is Huntington's disease. In some embodiments, the disorder is Parkinson's disease. In some embodiments, the disorder is an inflammatory disease (*e.g.*, lupus).

[0070] In some embodiments, the disorder is a sterol synthesis disorder.

[0071] In some embodiments, the disorder is Smith-Lemli-Opitz Syndrome (SLOS). In some embodiments, the disorder is desmosterolosis. In some embodiments, the disorder is

sitosterolemia. In some embodiments, the disorder is cerebrotendinous xanthomatosis (CTX). In some embodiments, the disorder is Mevalonate Kinase Deficiency (MKD). In some embodiments, the disorder is SC4MOL gene mutation (SMO Deficiency). In some embodiments, the disorder is Niemann-Pick disease. In some embodiments, the disorder is autism spectrum disorder (ASD). In some embodiments, the disorder is associated with phenylketomuria.

[0072] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description, Examples, and Claims.**

## Definitions

### *Chemical Definitions*

[0073] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75<sup>th</sup> Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5<sup>th</sup> Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3<sup>rd</sup> Edition, Cambridge University Press, Cambridge, 1987.

[0074] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0075] The “enantiomeric excess” (“e.e.”) or “% enantiomeric excess” (“%e.e.”) of a composition as used herein refers to an excess of one enantiomer relative to the other enantiomer present in the composition. For example, a composition can contain 90% of one enantiomer, *e.g.*, the S enantiomer, and 10% of the other enantiomer, *i.e.*, the R enantiomer.

5 [0076] 
$$\text{e.e.} = (90-10)/100 = 80\%.$$

[0077] Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.

[0078] The “diastereomeric excess” (“d.e.”) or “% diastereomeric excess” (“%d.e.”) of a composition as used herein refers to an excess of one diastereomer relative to one or more  
10 different diastereomers present in the composition. For example, a composition can contain 90% of one diastereomer, and 10% of one or more different diastereomers.

[0079] 
$$\text{d.e.} = (90-10)/100 = 80\%.$$

[0080] Thus, a composition containing 90% of one diastereomers and 10% of one or more different diastereomers is said to have a diastereomeric excess of 80%.

15 [0081] In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be  $^2\text{H}$  (D or deuterium) or  $^3\text{H}$  (T or tritium); carbon may be, for example,  $^{13}\text{C}$  or  $^{14}\text{C}$ ; oxygen may be, for example,  $^{18}\text{O}$ ; nitrogen may be, for example,  $^{15}\text{N}$ , and the like. In other embodiments, a particular isotope (*e.g.*,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{18}\text{O}$ , or  $^{15}\text{N}$ ) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%,  
20 at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

[0082] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example “C<sub>1-6</sub> alkyl” is intended to encompass, C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>1-6</sub>, C<sub>1-5</sub>, C<sub>1-4</sub>, C<sub>1-3</sub>, C<sub>1-2</sub>, C<sub>2-6</sub>, C<sub>2-5</sub>, C<sub>2-4</sub>, C<sub>2-3</sub>, C<sub>3-6</sub>, C<sub>3-5</sub>, C<sub>3-4</sub>, C<sub>4-6</sub>, C<sub>4-5</sub>, and C<sub>5-6</sub> alkyl.

[0083] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention. When describing the invention, which may include compounds, pharmaceutical compositions  
30 containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated,  
35 the term “substituted” is to be defined as set out below. It should be further understood that the

terms “groups” and “radicals” can be considered interchangeable when used herein. The articles “a” and “an” may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example “an analogue” means one analogue or more than one analogue.

5 [0084] “Aliphatic” refers to an alkyl, alkenyl, alkynyl, or carbocyclyl group, as defined herein.

[0085] “Cycloalkylalkyl” refers to an alkyl radical in which the alkyl group is substituted with a cycloalkyl group. Typical cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 10 cyclooctylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, and cyclooctylethyl, and the like.

[0086] “Heterocyclalkyl” refers to an alkyl radical in which the alkyl group is substituted with a heterocyclyl group. Typical heterocyclalkyl groups include, but are not limited to, pyrrolidinylmethyl, piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, 15 pyrrolidinyloethyl, piperidinylethyl, piperazinylethyl, morpholinylethyl, and the like.

[0087] “Aralkyl” is a subset of alkyl and aryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group.

[0088] “Alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“C<sub>1-20</sub> alkyl”). In some embodiments, an alkyl group 20 has 1 to 12 carbon atoms (“C<sub>1-12</sub> alkyl”). In some embodiments, an alkyl group has 1 to 10 carbon atoms (“C<sub>1-10</sub> alkyl”). In some embodiments, an alkyl group has 1 to 9 carbon atoms (“C<sub>1-9</sub> alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C<sub>1-8</sub> alkyl”). In some embodiments, an alkyl group has 1 to 7 carbon atoms (“C<sub>1-7</sub> alkyl”). In some 25 embodiments, an alkyl group has 1 to 6 carbon atoms (“C<sub>1-6</sub> alkyl”, also referred to herein as “lower alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C<sub>1-5</sub> alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C<sub>1-4</sub> alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C<sub>1-3</sub> alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C<sub>1-2</sub> alkyl”). In some embodiments, an alkyl group has 1 30 carbon atom (“C<sub>1</sub> alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C<sub>2-6</sub> alkyl”). Examples of C<sub>1-6</sub> alkyl groups include methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), n-propyl (C<sub>3</sub>), isopropyl (C<sub>3</sub>), n-butyl (C<sub>4</sub>), tert-butyl (C<sub>4</sub>), sec-butyl (C<sub>4</sub>), iso-butyl (C<sub>4</sub>), n-pentyl (C<sub>5</sub>), 3-pentanyl (C<sub>5</sub>), amyl (C<sub>5</sub>), neopentyl (C<sub>5</sub>), 3-methyl-2-butanyl (C<sub>5</sub>), tertiary amyl (C<sub>5</sub>), and n-hexyl (C<sub>6</sub>). Additional examples of alkyl groups include n-heptyl (C<sub>7</sub>), n-octyl (C<sub>8</sub>) and the like. Unless 35 otherwise specified, each instance of an alkyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more

substituents; *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C<sub>1-10</sub> alkyl (*e.g.*, -CH<sub>3</sub>). In certain embodiments, the alkyl group is substituted C<sub>1-10</sub> alkyl. Common alkyl abbreviations include Me (-CH<sub>3</sub>), Et (-CH<sub>2</sub>CH<sub>3</sub>), iPr (-CH(CH<sub>3</sub>)<sub>2</sub>), nPr (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), n-Bu (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), or i-Bu (-CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>).

**[0089]** “Alkylene” refers to an alkyl group wherein two hydrogens are removed to provide a divalent radical, and which may be substituted or unsubstituted. Unsubstituted alkylene groups include, but are not limited to, methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), propylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), butylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), pentylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), hexylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), and the like. Exemplary substituted alkylene groups, *e.g.*, substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted methylene (-CH(CH<sub>3</sub>)-, -(C(CH<sub>3</sub>)<sub>2</sub>)-), substituted ethylene (-CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-), substituted propylene (-CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-), and the like. When a range or number of carbons is provided for a particular alkylene group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. Alkylene groups may be substituted or unsubstituted with one or more substituents as described herein.

**[0090]** “Alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon double bonds), and optionally one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon triple bonds) (“C<sub>2-20</sub> alkenyl”). In certain embodiments, alkenyl does not contain any triple bonds. In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C<sub>2-10</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C<sub>2-9</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C<sub>2-8</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C<sub>2-7</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C<sub>2-6</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C<sub>2-5</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C<sub>2-4</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C<sub>2-3</sub> alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C<sub>2</sub> alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C<sub>2-4</sub> alkenyl groups include ethenyl (C<sub>2</sub>), 1-propenyl (C<sub>3</sub>), 2-propenyl (C<sub>3</sub>), 1-butenyl (C<sub>4</sub>), 2-butenyl (C<sub>4</sub>), butadienyl (C<sub>4</sub>), and the like. Examples of C<sub>2-6</sub> alkenyl groups include the aforementioned C<sub>2-4</sub> alkenyl groups as well as pentenyl (C<sub>5</sub>), pentadienyl (C<sub>5</sub>), hexenyl (C<sub>6</sub>), and the like. Additional examples of alkenyl

include heptenyl (C<sub>7</sub>), octenyl (C<sub>8</sub>), octatrienyl (C<sub>8</sub>), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain  
5       embodiments, the alkenyl group is unsubstituted C<sub>2-10</sub> alkenyl. In certain embodiments, the alkenyl group is substituted C<sub>2-10</sub> alkenyl.

**[0091]**       “Alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon triple bonds), and optionally one or more carbon-carbon double bonds (*e.g.*, 1, 2,  
10       3, or 4 carbon-carbon double bonds) (“C<sub>2-20</sub> alkynyl”). In certain embodiments, alkynyl does not contain any double bonds. In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C<sub>2-10</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C<sub>2-9</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C<sub>2-8</sub> alkynyl”). In some  
15       embodiments, an alkynyl group has 2 to 7 carbon atoms (“C<sub>2-7</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C<sub>2-6</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C<sub>2-5</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C<sub>2-4</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C<sub>2-3</sub> alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C<sub>2</sub> alkynyl”). The one or more carbon-carbon triple bonds can be internal (such  
20       as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C<sub>2-4</sub> alkynyl groups include, without limitation, ethynyl (C<sub>2</sub>), 1-propynyl (C<sub>3</sub>), 2-propynyl (C<sub>3</sub>), 1-butenyl (C<sub>4</sub>), 2-butenyl (C<sub>4</sub>), and the like. Examples of C<sub>2-6</sub> alkenyl groups include the aforementioned C<sub>2-4</sub> alkynyl groups as well as pentynyl (C<sub>5</sub>), hexynyl (C<sub>6</sub>), and the like. Additional examples of alkynyl  
25       include heptynyl (C<sub>7</sub>), octynyl (C<sub>8</sub>), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents; *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C<sub>2-10</sub> alkynyl. In certain embodiments, the alkynyl group is substituted C<sub>2-10</sub> alkynyl.

**[0092]**       The term “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, which further comprises 1 or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron, silicon, phosphorus) within the parent chain, wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, *i.e.*, between the point  
35       of attachment. In certain embodiments, a heteroalkyl group refers to a saturated group having

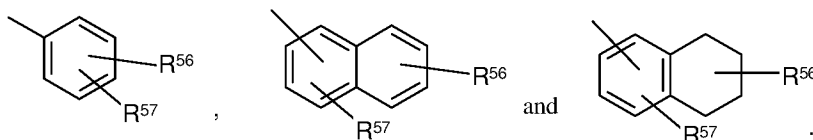
from 1 to 10 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC<sub>1-10</sub> alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC<sub>1-9</sub> alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC<sub>1-8</sub> alkyl”). In some  
 5 embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC<sub>1-7</sub> alkyl”). In some embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms (“heteroC<sub>1-6</sub> alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms (“heteroC<sub>1-5</sub> alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to  
 10 4 carbon atoms and 1 or 2 heteroatoms (“heteroC<sub>1-4</sub> alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom (“heteroC<sub>1-3</sub> alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom (“heteroC<sub>1-2</sub> alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“heteroC<sub>1</sub> alkyl”). In some embodiments, a heteroalkyl  
 15 group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms (“heteroC<sub>2-6</sub> alkyl”). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC<sub>1-10</sub> alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC<sub>1-10</sub>  
 20 alkyl.

**[0093]** “Aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14  $\pi$  electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C<sub>6-14</sub> aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C<sub>6</sub> aryl”; *e.g.*,  
 25 phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C<sub>10</sub> aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C<sub>14</sub> aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the  
 30 number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene,  
 35 pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene,

rubicene, triphenylene, and trinaphthalene. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is unsubstituted C<sub>6-14</sub> aryl. In certain embodiments, the aryl group is substituted C<sub>6-14</sub> aryl.

**[0094]** In certain embodiments, an aryl group substituted with one or more of groups selected from halo, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, cyano, hydroxy, C<sub>1</sub>-C<sub>8</sub> alkoxy, and amino.

**[0095]** Examples of representative substituted aryls include the following



wherein one of R<sup>56</sup> and R<sup>57</sup> may be hydrogen and at least one of R<sup>56</sup> and R<sup>57</sup> is each independently selected from C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, 4-10 membered heterocyclyl, alkanoyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, NR<sup>58</sup>COR<sup>59</sup>, NR<sup>58</sup>SOR<sup>59</sup>, NR<sup>58</sup>SO<sub>2</sub>R<sup>59</sup>, COOalkyl, COOaryl, CONR<sup>58</sup>R<sup>59</sup>, CONR<sup>58</sup>OR<sup>59</sup>, NR<sup>58</sup>R<sup>59</sup>, SO<sub>2</sub>NR<sup>58</sup>R<sup>59</sup>, S-alkyl, SOalkyl, SO<sub>2</sub>alkyl, Saryl, SOaryl, SO<sub>2</sub>aryl; or R<sup>56</sup> and R<sup>57</sup> may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O, or S. R<sup>60</sup> and R<sup>61</sup> are independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocyclyl, C<sub>6</sub>-C<sub>10</sub> aryl, substituted C<sub>6</sub>-C<sub>10</sub> aryl, 5-10 membered heteroaryl, or substituted 5-10 membered heteroaryl.

**[0096]** “Fused aryl” refers to an aryl having two of its ring carbon in common with a second aryl or heteroaryl ring or with a carbocyclyl or heterocyclyl ring.

**[0097]** “Heteroaryl” refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.*, having 6 or 10  $\pi$  electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on

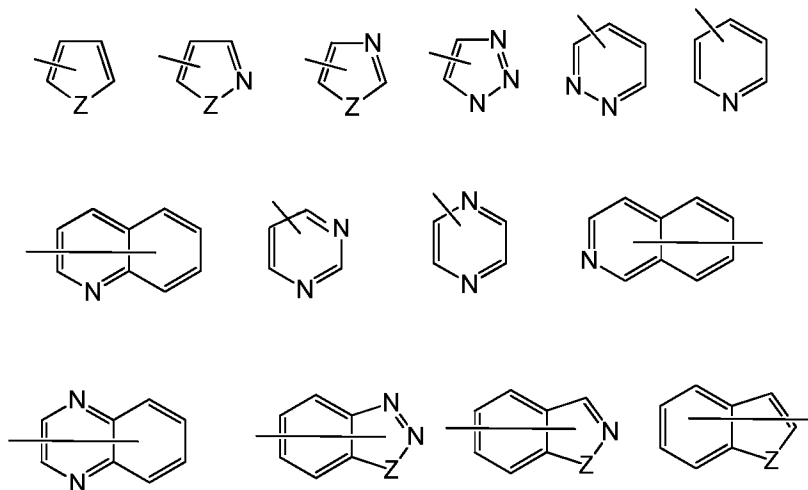
the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinoliny, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

**[0098]** In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heteroaryl”). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

**[0099]** Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–

bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indoliziny, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

**[00100]** Examples of representative heteroaryls include the following:



wherein each Z is selected from carbonyl, N, NR<sup>65</sup>, O, and S; and R<sup>65</sup> is independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocyclyl, C<sub>6</sub>-C<sub>10</sub> aryl, and 5-10 membered heteroaryl.

**[00101]** “Carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C<sub>3-10</sub> carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C<sub>3-8</sub> carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C<sub>3-6</sub> carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C<sub>3-6</sub> carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C<sub>5-10</sub> carbocyclyl”). Exemplary C<sub>3-6</sub> carbocyclyl groups include, without limitation, cyclopropyl (C<sub>3</sub>), cyclopropenyl (C<sub>3</sub>), cyclobutyl (C<sub>4</sub>), cyclobutenyl (C<sub>4</sub>), cyclopentyl (C<sub>5</sub>), cyclopentenyl (C<sub>5</sub>), cyclohexyl (C<sub>6</sub>), cyclohexenyl (C<sub>6</sub>), cyclohexadienyl (C<sub>6</sub>), and the like. Exemplary C<sub>3-8</sub> carbocyclyl groups include, without limitation, the aforementioned C<sub>3-6</sub> carbocyclyl groups as well as cycloheptyl (C<sub>7</sub>), cycloheptenyl (C<sub>7</sub>), cycloheptadienyl (C<sub>7</sub>), cycloheptatrienyl (C<sub>7</sub>), cyclooctyl (C<sub>8</sub>), cyclooctenyl (C<sub>8</sub>), bicyclo[2.2.1]heptanyl (C<sub>7</sub>), bicyclo[2.2.2]octanyl (C<sub>8</sub>), and the like. Exemplary C<sub>3-10</sub> carbocyclyl groups include, without limitation, the aforementioned C<sub>3-8</sub> carbocyclyl groups as well as cyclononyl (C<sub>9</sub>), cyclononenyl (C<sub>9</sub>), cyclodecyl (C<sub>10</sub>), cyclodecenyl (C<sub>10</sub>), octahydro-1*H*-indenyl (C<sub>9</sub>), decahydronaphthalenyl

(C<sub>10</sub>), spiro[4.5]decanyl (C<sub>10</sub>), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or contain a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) and can be saturated or can be partially unsaturated. “Carbocyclyl” also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C<sub>3–10</sub> carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C<sub>3–10</sub> carbocyclyl.

**[00102]** In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C<sub>3–10</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C<sub>3–8</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C<sub>3–6</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C<sub>5–6</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C<sub>5–10</sub> cycloalkyl”). Examples of C<sub>5–6</sub> cycloalkyl groups include cyclopentyl (C<sub>5</sub>) and cyclohexyl (C<sub>6</sub>). Examples of C<sub>3–6</sub> cycloalkyl groups include the aforementioned C<sub>5–6</sub> cycloalkyl groups as well as cyclopropyl (C<sub>3</sub>) and cyclobutyl (C<sub>4</sub>). Examples of C<sub>3–8</sub> cycloalkyl groups include the aforementioned C<sub>3–6</sub> cycloalkyl groups as well as cycloheptyl (C<sub>7</sub>) and cyclooctyl (C<sub>8</sub>). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C<sub>3–10</sub> cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C<sub>3–10</sub> cycloalkyl.

**[00103]** “Heterocyclyl” or “heterocyclic” refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3–10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the

heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system.

Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

**[00104]** In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“5–10 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heterocyclyl”). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

**[00105]** Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenlyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridiny, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation,

piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C<sub>6</sub> aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

**[00106]** “Nitrogen-containing heterocyclyl” group means a 4- to 7- membered non-aromatic cyclic group containing at least one nitrogen atom, for example, but without limitation, morpholine, piperidine (*e.g.* 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (*e.g.* 2-pyrrolidinyl and 3-pyrrolidinyl), azetidine, pyrrolidone, imidazoline, imidazolidinone, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Particular examples include azetidine, piperidone and piperazone.

**[00107]** “Hetero” when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbonyl groups described above such as alkyl, *e.g.*, heteroalkyl, cycloalkyl, *e.g.*, heterocyclyl, aryl, *e.g.*, heteroaryl, cycloalkenyl, *e.g.*, cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

**[00108]** “Acyl” refers to a radical -C(O)R<sup>20</sup>, where R<sup>20</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, as defined herein. “Alkanoyl” is an acyl group wherein R<sup>20</sup> is a group other than hydrogen. Representative acyl groups include, but are not limited to, formyl (-CHO), acetyl (-C(=O)CH<sub>3</sub>), cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl (-C(=O)Ph), benzylcarbonyl (-C(=O)CH<sub>2</sub>Ph), —C(O)-C<sub>1</sub>-C<sub>8</sub> alkyl, -C(O)-(CH<sub>2</sub>)<sub>t</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), -C(O)-(CH<sub>2</sub>)<sub>t</sub>(5-10 membered heteroaryl), -C(O)-(CH<sub>2</sub>)<sub>t</sub>(C<sub>3</sub>-C<sub>10</sub> cycloalkyl), and -C(O)-(CH<sub>2</sub>)<sub>t</sub>(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4. In certain embodiments, R<sup>21</sup> is C<sub>1</sub>-C<sub>8</sub> alkyl, substituted with halo or hydroxy; or C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocyclyl, C<sub>6</sub>-C<sub>10</sub> aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, halo, unsubstituted

C<sub>1</sub>-C<sub>4</sub> alkoxy, unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, unsubstituted C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkoxy or hydroxy.

**[00109]** “Alkoxy” refers to the group -OR<sup>29</sup> where R<sup>29</sup> is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

**[00110]** In certain embodiments, R<sup>29</sup> is a group that has 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of amino, substituted amino, C<sub>6</sub>-C<sub>10</sub> aryl, aryloxy, carboxyl, cyano, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, 4-10 membered heterocyclyl, halogen, 5-10 membered heteroaryl, hydroxyl, nitro, thioalkoxy, thioaryloxy, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)<sub>2</sub>- and aryl-S(O)<sub>2</sub>-. Exemplary ‘substituted alkoxy’ groups include, but are not limited to, -O-(CH<sub>2</sub>)<sub>t</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), -O-(CH<sub>2</sub>)<sub>t</sub>(5-10 membered heteroaryl), -O-(CH<sub>2</sub>)<sub>t</sub>(C<sub>3</sub>-C<sub>10</sub> cycloalkyl), and -O-(CH<sub>2</sub>)<sub>t</sub>(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocyclyl groups present, may themselves be substituted by unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, halo, unsubstituted C<sub>1</sub>-C<sub>4</sub> alkoxy, unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, unsubstituted C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkoxy or hydroxy. Particular exemplary ‘substituted alkoxy’ groups are -OCF<sub>3</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCH<sub>2</sub>Ph, -OCH<sub>2</sub>-cyclopropyl, -OCH<sub>2</sub>CH<sub>2</sub>OH, and -OCH<sub>2</sub>CH<sub>2</sub>NMe<sub>2</sub>.

**[00111]** “Amino” refers to the radical -NH<sub>2</sub>.

**[00112]** “Oxo group” refers to -C(=O)-.

**[00113]** “Substituted amino” refers to an amino group of the formula -N(R<sup>38</sup>)<sub>2</sub> wherein R<sup>38</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino protecting group, wherein at least one of R<sup>38</sup> is not a hydrogen. In certain embodiments, each R<sup>38</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> alkenyl, C<sub>3</sub>-C<sub>8</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, 5-10 membered heteroaryl, 4-10 membered heterocyclyl, or C<sub>3</sub>-C<sub>10</sub> cycloalkyl; or C<sub>1</sub>-C<sub>8</sub> alkyl, substituted with halo or hydroxy; C<sub>3</sub>-C<sub>8</sub> alkenyl, substituted with halo or hydroxy; C<sub>3</sub>-C<sub>8</sub> alkynyl, substituted with halo or hydroxy, or -(CH<sub>2</sub>)<sub>t</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), -(CH<sub>2</sub>)<sub>t</sub>(5-10 membered heteroaryl), -(CH<sub>2</sub>)<sub>t</sub>(C<sub>3</sub>-C<sub>10</sub> cycloalkyl), or -(CH<sub>2</sub>)<sub>t</sub>(4-10 membered heterocyclyl), wherein t is an integer between 0 and 8, each of which is substituted by unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, halo,

unsubstituted C<sub>1</sub>-C<sub>4</sub> alkoxy, unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, unsubstituted C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkoxy or hydroxy; or both R<sup>38</sup> groups are joined to form an alkylene group.

[00114] Exemplary “substituted amino” groups include, but are not limited to, -NR<sup>39</sup>-C<sub>1</sub>-C<sub>8</sub> alkyl, -NR<sup>39</sup>-(CH<sub>2</sub>)<sub>t</sub>-(C<sub>6</sub>-C<sub>10</sub> aryl), -NR<sup>39</sup>-(CH<sub>2</sub>)<sub>t</sub>-(5-10 membered heteroaryl), -NR<sup>39</sup>-(CH<sub>2</sub>)<sub>t</sub>-(C<sub>3</sub>-C<sub>10</sub> cycloalkyl), and -NR<sup>39</sup>-(CH<sub>2</sub>)<sub>t</sub>-(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4, for instance 1 or 2, each R<sup>39</sup> independently represents H or C<sub>1</sub>-C<sub>8</sub> alkyl; and any alkyl groups present, may themselves be substituted by halo, substituted or unsubstituted amino, or hydroxy; and any aryl, heteroaryl, cycloalkyl, or heterocyclyl groups present, may themselves be substituted by unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, halo, unsubstituted C<sub>1</sub>-C<sub>4</sub> alkoxy, unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, unsubstituted C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or unsubstituted C<sub>1</sub>-C<sub>4</sub> haloalkoxy or hydroxy. For the avoidance of doubt the term ‘substituted amino’ includes the groups alkylamino, substituted alkylamino, alkylarylamino, substituted alkylarylamino, arylamino, substituted arylamino, dialkylamino, and substituted dialkylamino as defined below. Substituted amino encompasses both monosubstituted amino and disubstituted amino groups.

[00115] “Carboxy” refers to the radical -C(O)OH.

[00116] “Cyano” refers to the radical -CN.

[00117] “Halo” or “halogen” refers to fluoro (F), chloro (Cl), bromo (Br), and iodo (I). In certain embodiments, the halo group is either fluoro or chloro.

[00118] “Haloalkyl” refers to an alkyl radical in which the alkyl group is substituted with one or more halogens. Typical haloalkyl groups include, but are not limited to, trifluoromethyl (-CF<sub>3</sub>), difluoromethyl (-CHF<sub>2</sub>), fluoromethyl (-CH<sub>2</sub>F), chloromethyl (-CH<sub>2</sub>Cl), dichloromethyl (-CHCl<sub>2</sub>), tribromomethyl (-CH<sub>2</sub>Br), and the like.

[00119] “Hydroxy” refers to the radical -OH.

[00120] “Nitro” refers to the radical -NO<sub>2</sub>.

[00121] “Thioketo” refers to the group =S.

[00122] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” carbocyclyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement,

cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

**[00123]** Exemplary carbon atom substituents include, but are not limited to, halogen, –CN, –NO<sub>2</sub>, –N<sub>3</sub>, –SO<sub>2</sub>H, –SO<sub>3</sub>H, –OH, –OR<sup>aa</sup>, –ON(R<sup>bb</sup>)<sub>2</sub>, –N(R<sup>bb</sup>)<sub>2</sub>, –N(R<sup>bb</sup>)<sub>3</sub><sup>+</sup>X<sup>–</sup>, –N(OR<sup>cc</sup>)R<sup>bb</sup>, –SH, –SR<sup>aa</sup>, –SSR<sup>cc</sup>, –C(=O)R<sup>aa</sup>, –CO<sub>2</sub>H, –CHO, –C(OR<sup>cc</sup>)<sub>2</sub>, –CO<sub>2</sub>R<sup>aa</sup>, –OC(=O)R<sup>aa</sup>, –OCO<sub>2</sub>R<sup>aa</sup>, –C(=O)N(R<sup>bb</sup>)<sub>2</sub>, –OC(=O)N(R<sup>bb</sup>)<sub>2</sub>, –NR<sup>bb</sup>C(=O)R<sup>aa</sup>, –NR<sup>bb</sup>CO<sub>2</sub>R<sup>aa</sup>, –NR<sup>bb</sup>C(=O)N(R<sup>bb</sup>)<sub>2</sub>, –C(=NR<sup>bb</sup>)R<sup>aa</sup>, –C(=NR<sup>bb</sup>)OR<sup>aa</sup>, –OC(=NR<sup>bb</sup>)R<sup>aa</sup>, –OC(=NR<sup>bb</sup>)OR<sup>aa</sup>, –C(=NR<sup>bb</sup>)N(R<sup>bb</sup>)<sub>2</sub>, –OC(=NR<sup>bb</sup>)N(R<sup>bb</sup>)<sub>2</sub>, –NR<sup>bb</sup>C(=NR<sup>bb</sup>)N(R<sup>bb</sup>)<sub>2</sub>, –C(=O)NR<sup>bb</sup>SO<sub>2</sub>R<sup>aa</sup>, –NR<sup>bb</sup>SO<sub>2</sub>R<sup>aa</sup>, –SO<sub>2</sub>N(R<sup>bb</sup>)<sub>2</sub>, –SO<sub>2</sub>R<sup>aa</sup>, –SO<sub>2</sub>OR<sup>aa</sup>, –OSO<sub>2</sub>R<sup>aa</sup>, –S(=O)R<sup>aa</sup>, –OS(=O)R<sup>aa</sup>, –Si(R<sup>aa</sup>)<sub>3</sub>, –OSi(R<sup>aa</sup>)<sub>3</sub> –C(=S)N(R<sup>bb</sup>)<sub>2</sub>, –C(=O)SR<sup>aa</sup>, –C(=S)SR<sup>aa</sup>, –SC(=S)SR<sup>aa</sup>, –SC(=O)SR<sup>aa</sup>, –OC(=O)SR<sup>aa</sup>, –SC(=O)OR<sup>aa</sup>, –SC(=O)R<sup>aa</sup>, –P(=O)<sub>2</sub>R<sup>aa</sup>, –OP(=O)<sub>2</sub>R<sup>aa</sup>, –P(=O)(R<sup>aa</sup>)<sub>2</sub>, –OP(=O)(R<sup>aa</sup>)<sub>2</sub>, –OP(=O)(OR<sup>cc</sup>)<sub>2</sub>, –P(=O)<sub>2</sub>N(R<sup>bb</sup>)<sub>2</sub>, –OP(=O)<sub>2</sub>N(R<sup>bb</sup>)<sub>2</sub>, –P(=O)(NR<sup>bb</sup>)<sub>2</sub>, –OP(=O)(NR<sup>bb</sup>)<sub>2</sub>, –NR<sup>bb</sup>P(=O)(OR<sup>cc</sup>)<sub>2</sub>, –NR<sup>bb</sup>P(=O)(NR<sup>bb</sup>)<sub>2</sub>, –P(R<sup>cc</sup>)<sub>2</sub>, –P(R<sup>cc</sup>)<sub>3</sub>, –OP(R<sup>cc</sup>)<sub>2</sub>, –OP(R<sup>cc</sup>)<sub>3</sub>, –B(R<sup>aa</sup>)<sub>2</sub>, –B(OR<sup>cc</sup>)<sub>2</sub>, –BR<sup>aa</sup>(OR<sup>cc</sup>), C<sub>1–10</sub> alkyl, C<sub>1–10</sub> haloalkyl, C<sub>2–10</sub> alkenyl, C<sub>2–10</sub> alkynyl, C<sub>3–10</sub> carbocyclyl, 3–14 membered heterocyclyl, C<sub>6–14</sub> aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, =NN(R<sup>bb</sup>)<sub>2</sub>, =NNR<sup>bb</sup>C(=O)R<sup>aa</sup>, =NNR<sup>bb</sup>C(=O)OR<sup>aa</sup>, =NNR<sup>bb</sup>S(=O)<sub>2</sub>R<sup>aa</sup>, =NR<sup>bb</sup>, or =NOR<sup>cc</sup>;

**[00124]** each instance of R<sup>aa</sup> is, independently, selected from C<sub>1–10</sub> alkyl, C<sub>1–10</sub> haloalkyl, C<sub>2–10</sub> alkenyl, C<sub>2–10</sub> alkynyl, C<sub>3–10</sub> carbocyclyl, 3–14 membered heterocyclyl, C<sub>6–14</sub> aryl, and 5–14 membered heteroaryl, or two R<sup>aa</sup> groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups;

**[00125]** each instance of R<sup>bb</sup> is, independently, selected from hydrogen, –OH, –OR<sup>aa</sup>, –N(R<sup>cc</sup>)<sub>2</sub>, –CN, –C(=O)R<sup>aa</sup>, –C(=O)N(R<sup>cc</sup>)<sub>2</sub>, –CO<sub>2</sub>R<sup>aa</sup>, –SO<sub>2</sub>R<sup>aa</sup>, –C(=NR<sup>cc</sup>)OR<sup>aa</sup>, –C(=NR<sup>cc</sup>)N(R<sup>cc</sup>)<sub>2</sub>, –SO<sub>2</sub>N(R<sup>cc</sup>)<sub>2</sub>, –SO<sub>2</sub>R<sup>cc</sup>, –SO<sub>2</sub>OR<sup>cc</sup>, –SOR<sup>aa</sup>, –C(=S)N(R<sup>cc</sup>)<sub>2</sub>, –C(=O)SR<sup>cc</sup>, –C(=S)SR<sup>cc</sup>, –P(=O)<sub>2</sub>R<sup>aa</sup>, –P(=O)(R<sup>aa</sup>)<sub>2</sub>, –P(=O)<sub>2</sub>N(R<sup>cc</sup>)<sub>2</sub>, –P(=O)(NR<sup>cc</sup>)<sub>2</sub>, C<sub>1–10</sub> alkyl, C<sub>1–10</sub>

haloalkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl, or two R<sup>bb</sup> groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups;

**[00126]** each instance of R<sup>cc</sup> is, independently, selected from hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> haloalkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl, or two R<sup>cc</sup> groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups;

**[00127]** each instance of R<sup>dd</sup> is, independently, selected from halogen, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, -SO<sub>2</sub>H, -SO<sub>3</sub>H, -OH, -OR<sup>ee</sup>, -ON(R<sup>ff</sup>)<sub>2</sub>, -N(R<sup>ff</sup>)<sub>2</sub>, -N(R<sup>ff</sup>)<sub>3</sub><sup>+</sup>X<sup>-</sup>, -N(OR<sup>ee</sup>)R<sup>ff</sup>, -SH, -SR<sup>ee</sup>, -SSR<sup>ee</sup>, -C(=O)R<sup>ee</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>ee</sup>, -OC(=O)R<sup>ee</sup>, -OCO<sub>2</sub>R<sup>ee</sup>, -C(=O)N(R<sup>ff</sup>)<sub>2</sub>, -OC(=O)N(R<sup>ff</sup>)<sub>2</sub>, -NR<sup>ff</sup>C(=O)R<sup>ee</sup>, -NR<sup>ff</sup>CO<sub>2</sub>R<sup>ee</sup>, -NR<sup>ff</sup>C(=O)N(R<sup>ff</sup>)<sub>2</sub>, -C(=NR<sup>ff</sup>)OR<sup>ee</sup>, -OC(=NR<sup>ff</sup>)R<sup>ee</sup>, -OC(=NR<sup>ff</sup>)OR<sup>ee</sup>, -C(=NR<sup>ff</sup>)N(R<sup>ff</sup>)<sub>2</sub>, -OC(=NR<sup>ff</sup>)N(R<sup>ff</sup>)<sub>2</sub>, -NR<sup>ff</sup>C(=NR<sup>ff</sup>)N(R<sup>ff</sup>)<sub>2</sub>, -NR<sup>ff</sup>SO<sub>2</sub>R<sup>ee</sup>, -SO<sub>2</sub>N(R<sup>ff</sup>)<sub>2</sub>, -SO<sub>2</sub>R<sup>ee</sup>, -SO<sub>2</sub>OR<sup>ee</sup>, -OSO<sub>2</sub>R<sup>ee</sup>, -S(=O)R<sup>ee</sup>, -Si(R<sup>ee</sup>)<sub>3</sub>, -OSi(R<sup>ee</sup>)<sub>3</sub>, -C(=S)N(R<sup>ff</sup>)<sub>2</sub>, -C(=O)SR<sup>ee</sup>, -C(=S)SR<sup>ee</sup>, -SC(=S)SR<sup>ee</sup>, -P(=O)<sub>2</sub>R<sup>ee</sup>, -P(=O)(R<sup>ee</sup>)<sub>2</sub>, -OP(=O)(R<sup>ee</sup>)<sub>2</sub>, -OP(=O)(OR<sup>ee</sup>)<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-10 membered heterocyclyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>gg</sup> groups, or two geminal R<sup>dd</sup> substituents can be joined to form =O or =S;

**[00128]** each instance of R<sup>ee</sup> is, independently, selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, C<sub>6-10</sub> aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>gg</sup> groups;

**[00129]** each instance of R<sup>ff</sup> is, independently, selected from hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-10 membered heterocyclyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl, or two R<sup>ff</sup> groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>gg</sup> groups; and

**[00130]** each instance of R<sup>gg</sup> is, independently, halogen, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, -SO<sub>2</sub>H, -SO<sub>3</sub>H, -OH, -OC<sub>1-6</sub> alkyl, -ON(C<sub>1-6</sub> alkyl)<sub>2</sub>, -N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -N(C<sub>1-6</sub> alkyl)<sub>3</sub><sup>+</sup>X<sup>-</sup>, -NH(C<sub>1-6</sub> alkyl)<sub>2</sub><sup>+</sup>X<sup>-</sup>, -NH<sub>2</sub>(C<sub>1-6</sub> alkyl)<sup>+</sup>X<sup>-</sup>, -NH<sub>3</sub><sup>+</sup>X<sup>-</sup>, -N(OC<sub>1-6</sub> alkyl)(C<sub>1-6</sub> alkyl), -N(OH)(C<sub>1-6</sub> alkyl), -

NH(OH), -SH, -SC<sub>1-6</sub> alkyl, -SS(C<sub>1-6</sub> alkyl), -C(=O)(C<sub>1-6</sub> alkyl), -CO<sub>2</sub>H, -CO<sub>2</sub>(C<sub>1-6</sub> alkyl), -OC(=O)(C<sub>1-6</sub> alkyl), -OCO<sub>2</sub>(C<sub>1-6</sub> alkyl), -C(=O)NH<sub>2</sub>, -C(=O)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OC(=O)NH(C<sub>1-6</sub> alkyl), -NHC(=O)(C<sub>1-6</sub> alkyl), -N(C<sub>1-6</sub> alkyl)C(=O)(C<sub>1-6</sub> alkyl), -NHCO<sub>2</sub>(C<sub>1-6</sub> alkyl), -NHC(=O)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -NHC(=O)NH(C<sub>1-6</sub> alkyl), -NHC(=O)NH<sub>2</sub>, -C(=NH)O(C<sub>1-6</sub> alkyl), -OC(=NH)(C<sub>1-6</sub> alkyl), -OC(=NH)OC<sub>1-6</sub> alkyl, -C(=NH)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -C(=NH)NH(C<sub>1-6</sub> alkyl), -C(=NH)NH<sub>2</sub>, -OC(=NH)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OC(NH)NH(C<sub>1-6</sub> alkyl), -OC(NH)NH<sub>2</sub>, -NHC(NH)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -NHC(=NH)NH<sub>2</sub>, -NHSO<sub>2</sub>(C<sub>1-6</sub> alkyl), -SO<sub>2</sub>N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>NH(C<sub>1-6</sub> alkyl), -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>C<sub>1-6</sub> alkyl, -SO<sub>2</sub>OC<sub>1-6</sub> alkyl, -OSO<sub>2</sub>C<sub>1-6</sub> alkyl, -SOC<sub>1-6</sub> alkyl, -Si(C<sub>1-6</sub> alkyl)<sub>3</sub>, -OSi(C<sub>1-6</sub> alkyl)<sub>3</sub>, -C(=S)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, C(=S)NH(C<sub>1-6</sub> alkyl), C(=S)NH<sub>2</sub>, -C(=O)S(C<sub>1-6</sub> alkyl), -C(=S)SC<sub>1-6</sub> alkyl, -SC(=S)SC<sub>1-6</sub> alkyl, -P(=O)<sub>2</sub>(C<sub>1-6</sub> alkyl), -P(=O)(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OP(=O)(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OP(=O)(OC<sub>1-6</sub> alkyl)<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, C<sub>6-10</sub> aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R<sup>gg</sup> substituents can be joined to form =O or =S; wherein X<sup>-</sup> is a counterion.

**[00131]** A “counterion” or “anionic counterion” is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.*, F<sup>-</sup>, Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>), NO<sub>3</sub><sup>-</sup>, ClO<sub>4</sub><sup>-</sup>, OH<sup>-</sup>, H<sub>2</sub>PO<sub>4</sub><sup>-</sup>, HSO<sub>4</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup> sulfonate ions (*e.g.*, methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), and carboxylate ions (*e.g.*, acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

**[00132]** Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR<sup>aa</sup>, -N(R<sup>cc</sup>)<sub>2</sub>, -CN, -C(=O)R<sup>aa</sup>, -C(=O)N(R<sup>cc</sup>)<sub>2</sub>, -CO<sub>2</sub>R<sup>aa</sup>, -SO<sub>2</sub>R<sup>aa</sup>, -C(=NR<sup>bb</sup>)R<sup>aa</sup>, -C(=NR<sup>cc</sup>)OR<sup>aa</sup>, -C(=NR<sup>cc</sup>)N(R<sup>cc</sup>)<sub>2</sub>, -SO<sub>2</sub>N(R<sup>cc</sup>)<sub>2</sub>, -SO<sub>2</sub>R<sup>cc</sup>, -SO<sub>2</sub>OR<sup>cc</sup>, -SOR<sup>aa</sup>, -C(=S)N(R<sup>cc</sup>)<sub>2</sub>, -C(=O)SR<sup>cc</sup>, -C(=S)SR<sup>cc</sup>, -P(=O)<sub>2</sub>R<sup>aa</sup>, -P(=O)(R<sup>aa</sup>)<sub>2</sub>, -P(=O)<sub>2</sub>N(R<sup>cc</sup>)<sub>2</sub>, -P(=O)(NR<sup>cc</sup>)<sub>2</sub>, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> haloalkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl, or two R<sup>cc</sup> groups attached to a nitrogen atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups, and wherein R<sup>aa</sup>, R<sup>bb</sup>, R<sup>cc</sup> and R<sup>dd</sup> are as defined above.

**[00133]** These and other exemplary substituents are described in more detail in the **Detailed Description, Examples, and Claims**. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

*Other definitions*

[00134] The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and  $N^+(C_{1-4}alkyl)_4$  salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[00135] A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.* infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or a non-human animal, *e.g.*, a mammal such as primates (*e.g.*, cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. The terms “human,” “patient,” and “subject” are used interchangeably herein.

[00136] Disease, disorder, and condition are used interchangeably herein.

[00137] As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or  
5 retards or slows the progression of the disease, disorder or condition (“therapeutic treatment”), and also contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition (“prophylactic treatment”).

[00138] In general, the “effective amount” of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this  
10 art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, health, and condition of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[00139] As used herein, and unless otherwise specified, a “therapeutically effective  
15 amount” of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term  
20 “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

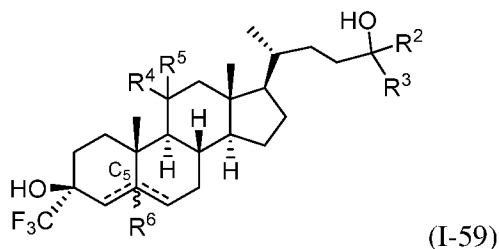
[00140] As used herein, and unless otherwise specified, a “prophylactically effective  
25 amount” of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease, disorder or condition. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the  
30 prophylactic efficacy of another prophylactic agent.

### **Detailed Description of Certain Embodiments of the Invention**

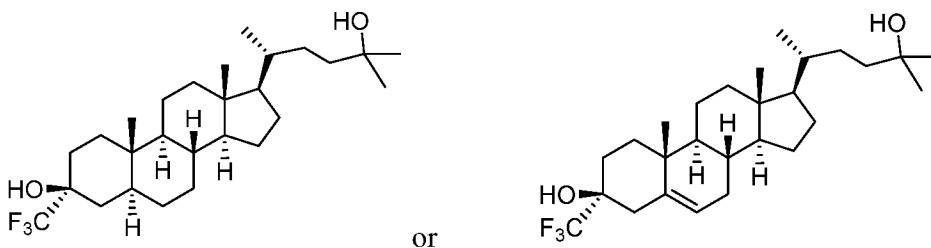
[00141] As generally described herein, the present invention provides substituted  
oxysterols useful for preventing and/or treating a broad range of disorders, including, but not  
35 limited to, NMDA-mediated disorders.

## Compounds

[00142] In one aspect, provided herein are compounds according to Formula (I-59):



- 5 or a pharmaceutically acceptable salt thereof, wherein: each of  $R^2$  and  $R^3$  is independently hydrogen, alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), carbocyclyl, or heterocyclyl, or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring; each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), or  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;  $R^6$  is
- 10 absent or hydrogen; and  $\text{=====}$  represents a single or double bond, wherein when one of  $\text{=====}$  is a double bond, the other  $\text{=====}$  is a single bond; when both of  $\text{=====}$  are single bonds, then  $R^6$  is hydrogen; and when one of  $\text{=====}$  is a double bond,  $R^6$  is absent; provided that the following compounds are excluded:



- 15 [00143] In some embodiments,  $R^2$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl). In some embodiments,  $R^2$  is haloalkyl (*e.g.*,  $C_1$ - $C_6$  haloalkyl).
- [00144] In some embodiments, each of  $R^2$  and  $R^3$  is independently alkyl (*e.g.*, substituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently unsubstituted alkyl (*e.g.*, unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments, each of
- 20  $R^2$  and  $R^3$  is independently  $C_1$ - $C_6$  haloalkyl (*e.g.*, trifluoromethyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen, carbocyclyl, or heterocyclyl. In some embodiments, each of  $R^2$  and  $R^3$  is independently  $C_2$ - $C_6$  alkyl (*e.g.*, isopropyl or tert-butyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_3$ - $C_6$  alkyl (*e.g.*, isopropyl or tert-butyl).
- 25 [00145] In some embodiments, at least one of  $R^2$  and  $R^3$  is  $C_3$ - $C_6$  alkyl (*e.g.*, isopropyl or tert-butyl), carbocyclyl, or heterocyclyl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring. In some embodiments,  $R^2$  is isopropyl or tert-butyl

and  $R^3$  is methyl or hydrogen. In some embodiments,  $R^2$  is substituted isopropyl or substituted tert-butyl and  $R^3$  is unsubstituted methyl or hydrogen. In some embodiments,  $R^2$  is unsubstituted isopropyl or unsubstituted tert-butyl and  $R^3$  is unsubstituted methyl or hydrogen. In some embodiments,  $R^2$  is tert-butyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted tert-butyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted tert-butyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is methyl. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is substituted methyl. In some embodiments,  $R^2$  is trifluoromethyl and  $R^3$  is unsubstituted methyl. In some embodiments,  $R^2$  is methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted methyl and  $R^3$  is hydrogen.

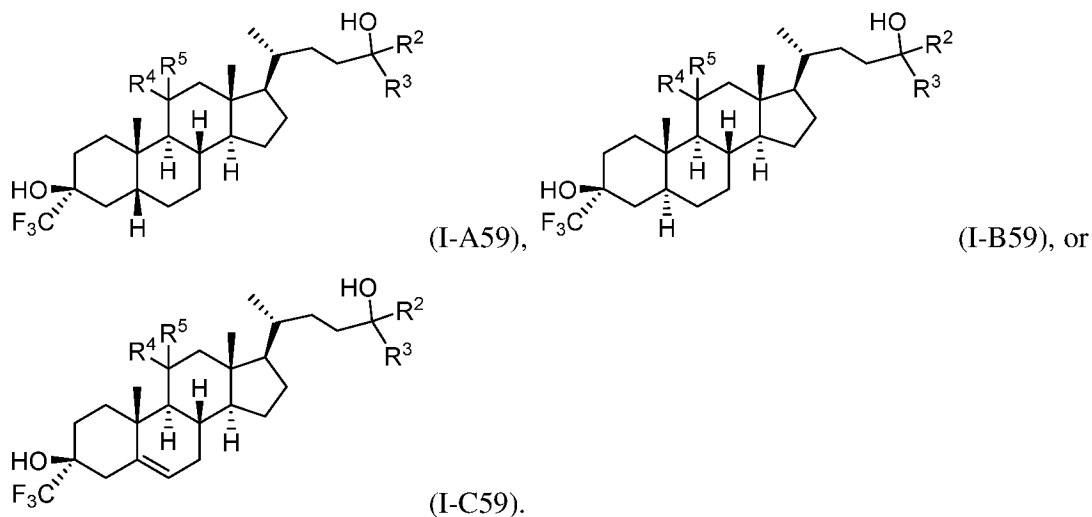
**[00146]** In some embodiments,  $R^4$  is  $-OH$  or halo (*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group. In some embodiments,  $R^4$  is hydrogen and  $R^5$  is halo (*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  $R^5$  are halo (*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  $R^5$  are hydrogen.

**[00147]** In some embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 5-membered ring. In some embodiments,  $R^2$  is  $C_2-C_6$  alkyl (*e.g.*, substituted or unsubstituted isopropyl or substituted or unsubstituted tert-butyl) and  $R^3$  is  $C_1-C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_1-C_6$  alkyl). In some embodiments,  $R^2$  is unsubstituted  $C_2-C_6$  alkyl (*e.g.*, unsubstituted isopropyl or unsubstituted tert-butyl) and  $R^3$  is unsubstituted  $C_1-C_6$  alkyl. In some embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 6-membered ring.

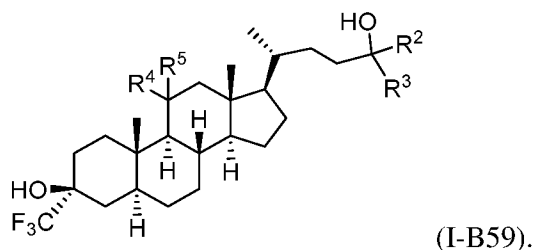
**[00148]** In some embodiments,  $R^2$  is carbocyclyl or heterocyclyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  and  $R^3$  are hydrogen. In some embodiments,  $R^2$  is isopropyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted isopropyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted isopropyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered carbocyclic (*e.g.*, cyclohexyl) or heterocyclic (*e.g.*, tetrahydrofuranyl or tetrahydropyranyl) ring. In some embodiments, the carbocyclic or heterocyclic ring is substituted (*e.g.*, ring substituted with 1 or 2 halo or alkyl groups). In some embodiments,  $R^2$  is cyclobutyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is tetrahydropyranyl and  $R^3$  is hydrogen.

**[00149]** In some embodiments,  $R^2$  is substituted cyclobutyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is substituted tetrahydropyranyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted cyclobutyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted tetrahydropyranyl and  $R^3$  is hydrogen.

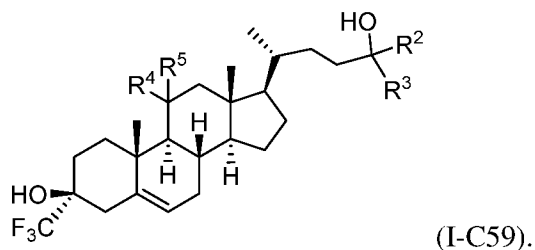
[00150] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-A59), (I-B59), or (I-C59):



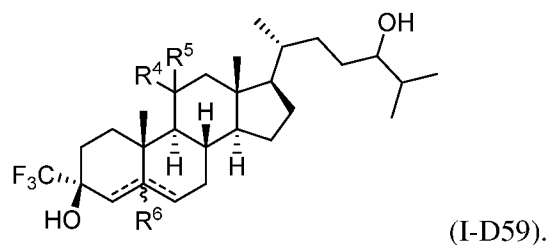
5 [00151] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-B59):



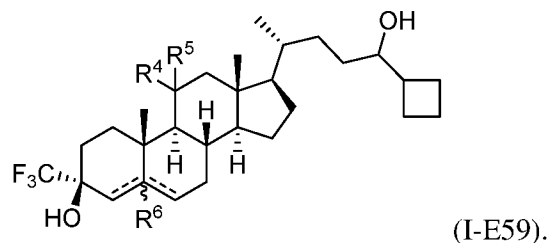
[00152] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-C59):



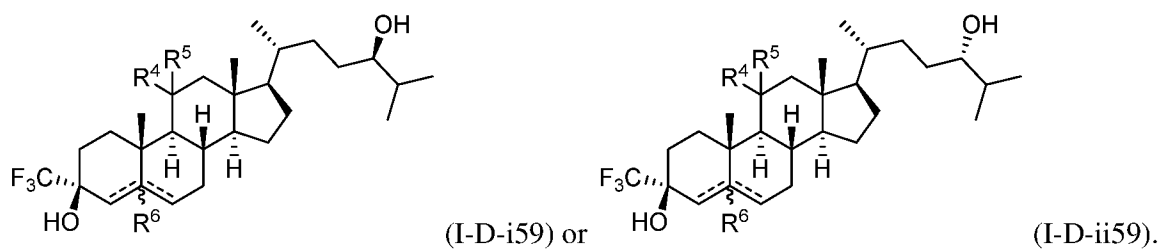
10 [00153] In some embodiments, at least one of  $R^2$  and  $R^3$  is hydrogen,  $C_1$ - $C_6$  alkyl, carbocyclyl, or heterocyclyl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring. In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-D59):



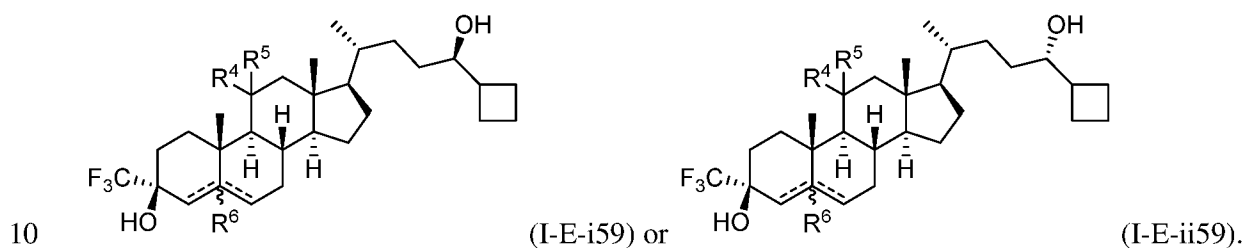
[00154] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-E59):



5 [00155] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-D-i59) or (I-D-ii59):

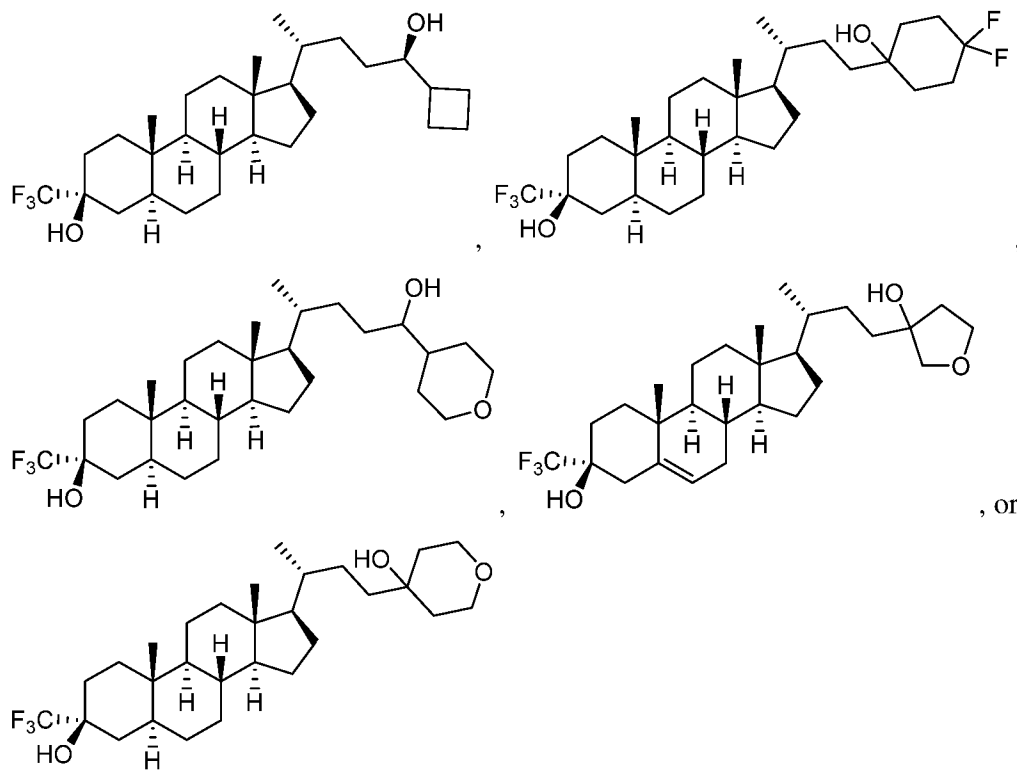


[00156] In some embodiments, the compound of Formula (I-59) is selected from a compound of Formula (I-E-i59) or (I-E-ii59):

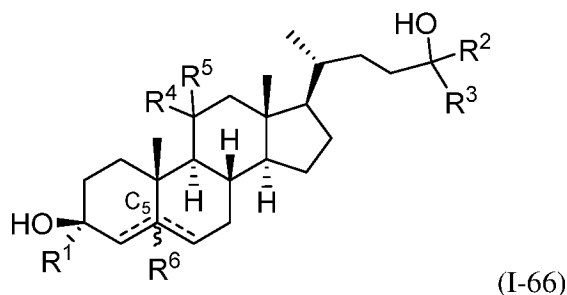


[00157] In some embodiments, the compound is:





5 [00158] In one aspect, provided herein are compounds according to Formula (I-66):



or a pharmaceutically acceptable salt thereof, wherein:  $R^1$  is alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl);  $R^2$  is aralkyl, heteroaralkyl, aryl, or heteroaryl;  $R^3$  is hydrogen, alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), carbocyclyl, heterocyclyl, aryl, or heteroaryl; each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or  $C_1$ - $C_3$  alkyl (*e.g.*, unsubstituted or substituted  $C_1$ - $C_3$  alkyl), or  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;  $R^6$  is absent or hydrogen; and  $\text{-----}$  represents a single or double bond, wherein when one of  $\text{-----}$  is a double bond, the other  $\text{-----}$  is a single bond; when both of  $\text{-----}$  are single bonds, then  $R^6$  is hydrogen; and when one of  $\text{-----}$  is a double bond,  $R^6$  is absent.

[00159] In some embodiments,  $R^1$  is alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl). In some embodiments,  $R^1$  is  $C_1$ - $C_6$  alkyl (*e.g.*,  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{OCH}_3$ , or  $-\text{CF}_3$ ). In some embodiments,  $R^1$  is  $-\text{CH}_3$ ,

–CF<sub>3</sub>, or –CH<sub>2</sub>CH<sub>3</sub>. In some embodiments, R<sup>1</sup> is –CH<sub>2</sub>OR<sup>A</sup>, wherein R<sup>A</sup> is C<sub>1</sub>–C<sub>6</sub> alkyl (*e.g.*, C<sub>1</sub>–C<sub>3</sub> alkyl).

[00160] In some embodiments, R<sup>2</sup> is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), or aralkyl (*e.g.*, substituted or unsubstituted benzyl). In some embodiments, R<sup>2</sup> is phenyl (*e.g.*, substituted or unsubstituted phenyl), pyridyl (*e.g.*, substituted or unsubstituted pyridyl), or benzyl (*e.g.*, substituted or unsubstituted benzyl).

[00161] In some embodiments, R<sup>3</sup> is hydrogen or alkyl (*e.g.*, C<sub>1</sub>–C<sub>6</sub> alkyl). In some embodiments, R<sup>3</sup> is hydrogen, unsubstituted alkyl (*e.g.*, unsubstituted C<sub>1</sub>–C<sub>6</sub> alkyl), or haloalkyl (*e.g.*, –CF<sub>3</sub>).

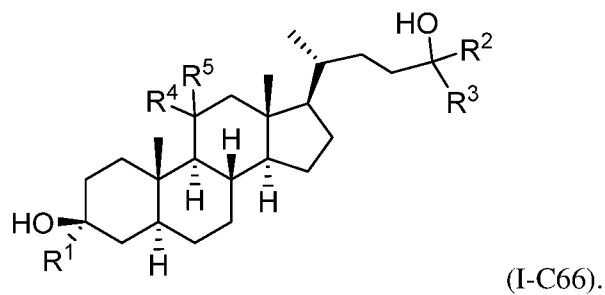
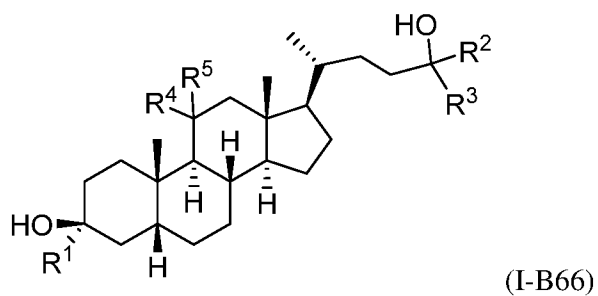
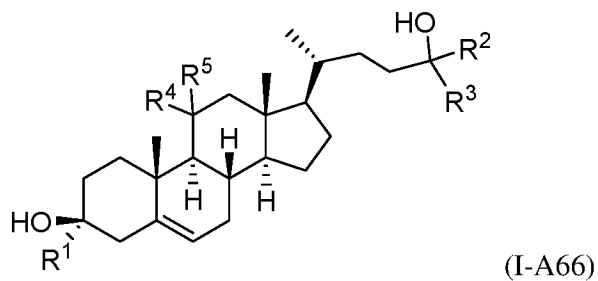
[00162] In some embodiments, R<sup>4</sup> is –OH or halo (*e.g.*, –F).

[00163] In some embodiments, R<sup>4</sup> and R<sup>5</sup>, together with the carbon atom to which they are attached form an oxo group. In some embodiments, R<sup>4</sup> is hydrogen and R<sup>5</sup> is halo (*e.g.*, –F). In some embodiments, R<sup>4</sup> and R<sup>5</sup> are hydrogen.

[00164] In some embodiments, R<sup>2</sup> is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), aralkyl (*e.g.*, substituted or unsubstituted aralkyl, *e.g.*, substituted or unsubstituted benzyl), or heteroaralkyl and R<sup>3</sup> is hydrogen or alkyl (*e.g.*, unsubstituted C<sub>1</sub>–C<sub>6</sub> alkyl, *e.g.*, C<sub>1</sub>–C<sub>6</sub> haloalkyl). In some embodiments, R<sup>2</sup> is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), aralkyl (*e.g.*, substituted or unsubstituted aralkyl, *e.g.*, substituted or unsubstituted benzyl), or heteroaralkyl and R<sup>3</sup> is hydrogen, –CH<sub>3</sub>, or –CF<sub>3</sub>.

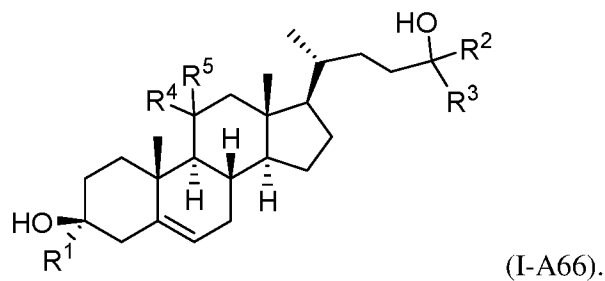
[00165] In some embodiments, R<sup>1</sup> is alkyl (*e.g.*, C<sub>1</sub>–C<sub>6</sub> alkyl), R<sup>2</sup> is aryl (*e.g.*, substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl), heteroaryl (*e.g.*, substituted or unsubstituted heteroaryl, *e.g.*, substituted or unsubstituted pyridyl), aralkyl (*e.g.*, substituted or unsubstituted aralkyl, *e.g.*, substituted or unsubstituted benzyl), or heteroaralkyl, and R<sup>3</sup> is hydrogen, –CH<sub>3</sub>, or –CF<sub>3</sub>. In some embodiments, R<sup>1</sup> is –CH<sub>3</sub> or –CH<sub>2</sub>CH<sub>3</sub>, R<sup>2</sup> is unsubstituted phenyl, unsubstituted pyridyl, or unsubstituted benzyl, and R<sup>3</sup> is hydrogen, –CH<sub>3</sub>, or –CF<sub>3</sub>.

[00166] In some embodiments, the compound of Formula (I-66) is selected from a compound of Formula (I-A66), (I-B66), or (I-C66):

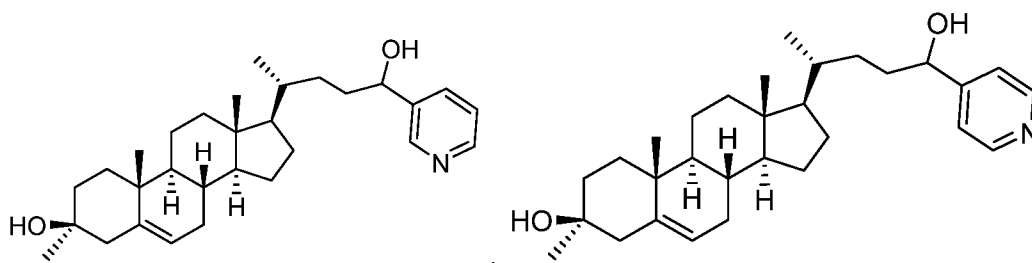


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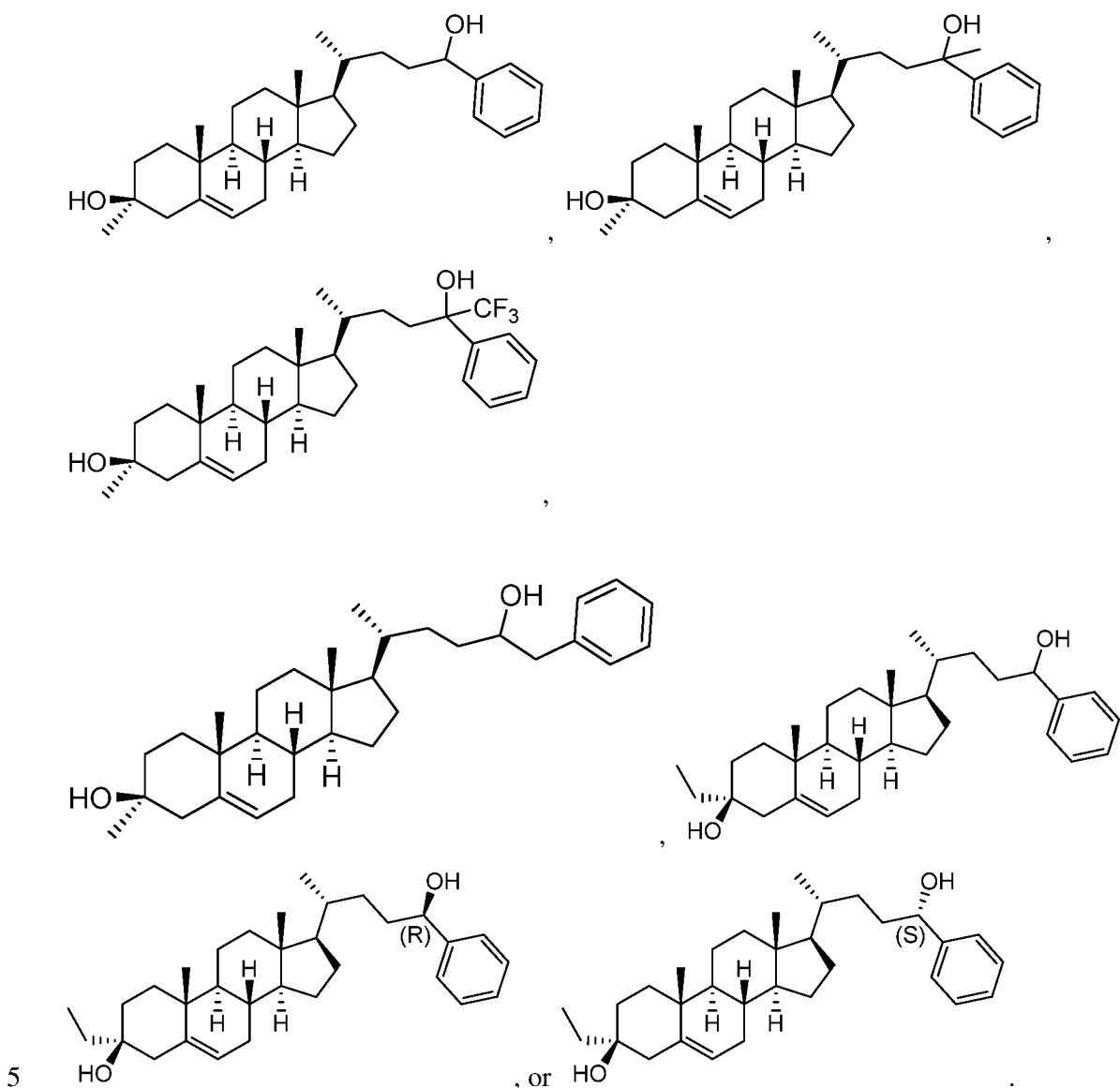
**[00167]** In some embodiments, the compound of Formula (I-66) is selected from a compound of Formula (I-A66):



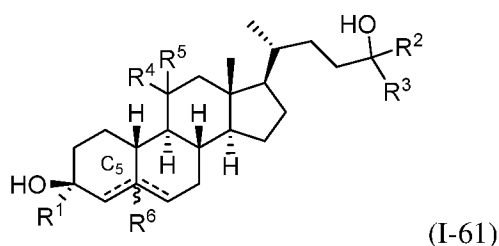
**[00168]** In some embodiments, the compound is:



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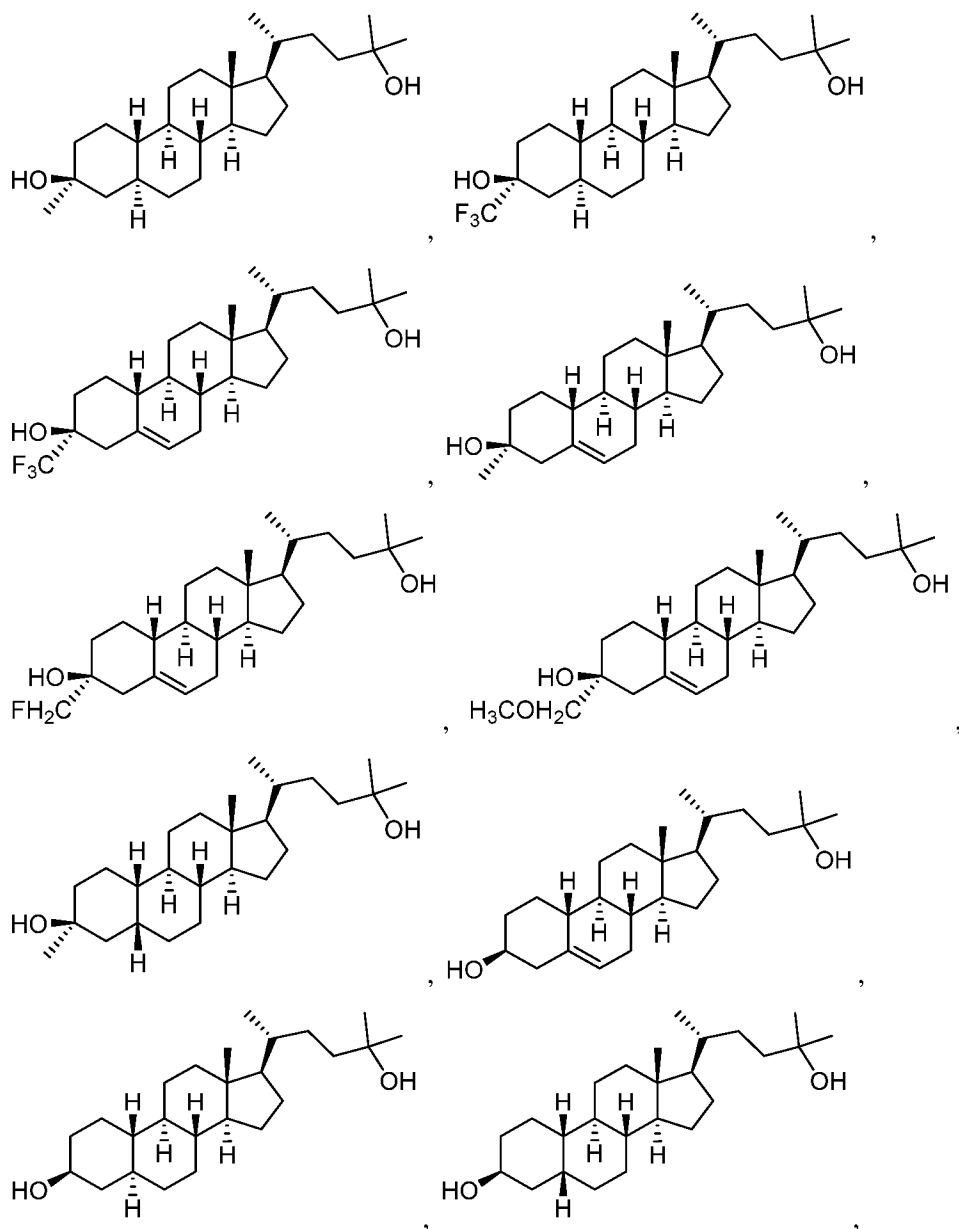
[00169] In one aspect, provided herein are compounds according to Formula (I-61):

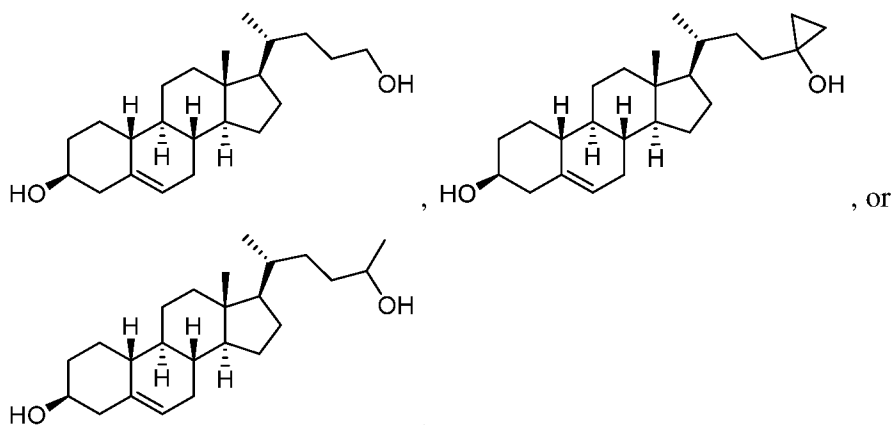


10 or a pharmaceutically acceptable salt thereof, wherein:  $R^1$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl); each of  $R^2$  and  $R^3$  is independently hydrogen, alkyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached for a 3-8 membered ring; each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), or  $R^4$  and  $R^5$ , together with the carbon atom to which they

are attached form an oxo group;  $R^6$  is absent or hydrogen; and  $\text{=====}$  represents a single or double bond, wherein when one of  $\text{=====}$  is a double bond, the other  $\text{=====}$  is a single bond; when both of  $\text{=====}$  are single bonds, then  $R^6$  is hydrogen; and when one of  $\text{=====}$  is a double bond,  $R^6$  is absent; provided that the following compounds are excluded:

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[00170] In some embodiments,  $R^1$  is alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl) or hydrogen. In some  
 5 embodiments,  $R^1$  is  $C_2$ - $C_6$  alkyl (*e.g.*,  $C_3$ - $C_6$  alkyl) or hydrogen. In some embodiments,  $R^1$  is  
 substituted or unsubstituted  $C_2$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_3$ - $C_6$  alkyl) or  
 hydrogen. In some embodiments,  $R^1$  is methyl or ethyl (*e.g.*, substituted or unsubstituted methyl  
 or substituted or unsubstituted ethyl). In some embodiments,  $R^1$  is substituted or unsubstituted  
 methyl or substituted or unsubstituted ethyl. In some embodiments,  $R^1$  is trifluoromethyl. In  
 10 some embodiments,  $R^1$  is  $-CH_2OR^A$ , wherein  $R^A$  is  $C_1$ - $C_6$  alkyl (*e.g.*,  $C_1$ - $C_3$  alkyl).

[00171] In some embodiments,  $R^2$  is hydrogen or  $C_1$ - $C_6$  alkyl, (*e.g.*,  $C_2$ - $C_6$  alkyl). In some  
 embodiments,  $R^2$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl (*e.g.*, substituted or  
 unsubstituted  $C_2$ - $C_6$  alkyl). In some embodiments,  $R^2$  is hydrogen. In some embodiments,  $R^2$  is  
 isopropyl (*e.g.*, substituted or unsubstituted isopropyl). In some embodiments,  $R^2$  is substituted  
 15 or unsubstituted isopropyl. In some embodiments,  $R^2$  is haloalkyl (*e.g.*,  $C_1$ - $C_6$  haloalkyl).

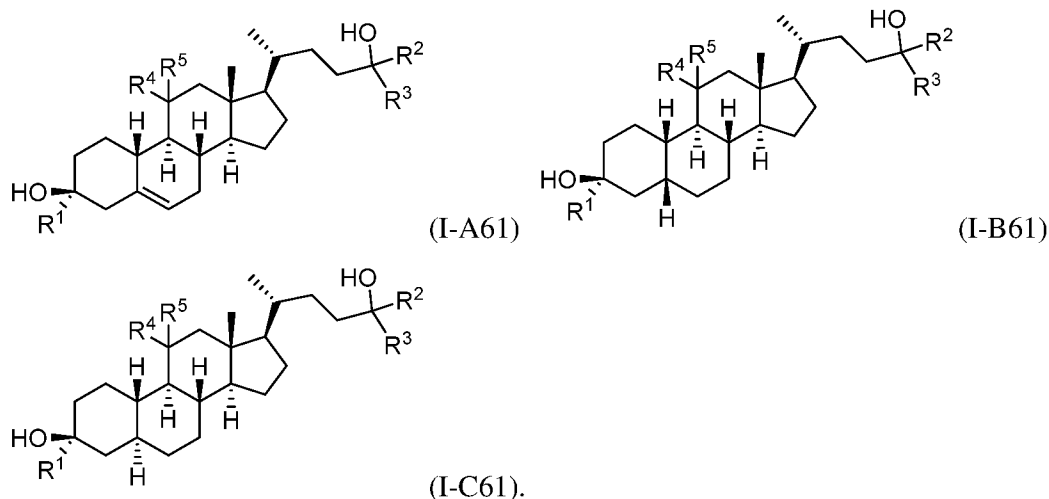
[00172] In some embodiments, each of  $R^2$  and  $R^3$  is independently alkyl (*e.g.*,  $C_1$ - $C_6$   
 alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently substituted or  
 unsubstituted alkyl (*e.g.*, substituted or unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some  
 embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached for a 3-8  
 20 membered ring. In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_1$ - $C_6$   
 alkyl (*e.g.*  $C_2$ - $C_6$  alkyl). In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  
 substituted or unsubstituted  $C_1$ - $C_6$  alkyl, (*e.g.* substituted or unsubstituted  $C_2$ - $C_6$  alkyl). In some  
 embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_3$ - $C_6$  alkyl (*e.g.*, isopropyl). In  
 some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or substituted or unsubstituted  
 25  $C_3$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted isopropyl).

[00173] In some embodiments,  $R^4$  is  $-OH$  or halo (*e.g.*,  $-F$ ). In some embodiments,  $R^4$  and  
 $R^5$ , together with the carbon atom to which they are attached form an oxo group. In some

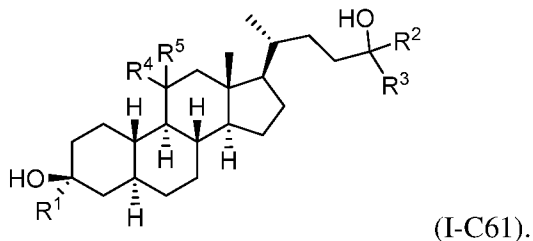
embodiments,  $R^4$  is hydrogen and  $R^5$  is halo (*e.g.*, -F). In some embodiments,  $R^4$  and  $R^5$  are halo (*e.g.*, -F). In some embodiments,  $R^4$  and  $R^5$  are hydrogen.

[00174] In some embodiments,  $R^2$  and  $R^3$  are hydrogen. In some embodiments,  $R^2$  is  $C_1$ - $C_6$  alkyl and  $R^3$  is  $C_2$ - $C_6$  alkyl (*e.g.*,  $C_3$ - $C_6$  alkyl). In some embodiments,  $R^2$  is substituted or unsubstituted  $C_1$ - $C_6$  alkyl and  $R^3$  is substituted or unsubstituted  $C_2$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_3$ - $C_6$  alkyl). In some embodiments,  $R^1$  is ethyl (*e.g.*, substituted or unsubstituted ethyl) and  $R^2$  and  $R^3$  are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments,  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl. In some embodiments,  $R^1$  is ethyl,  $R^2$  is isopropyl, and  $R^3$  is hydrogen. In some embodiments,  $R^1$  is substituted or unsubstituted ethyl,  $R^2$  is substituted or unsubstituted isopropyl, and  $R^3$  is hydrogen. In some embodiments,  $R^1$  is ethyl,  $R^2$  is isopropyl, and  $R^3$  is methyl. In some embodiments,  $R^1$  is substituted or unsubstituted ethyl,  $R^2$  is substituted or unsubstituted isopropyl, and  $R^3$  is substituted or unsubstituted methyl.

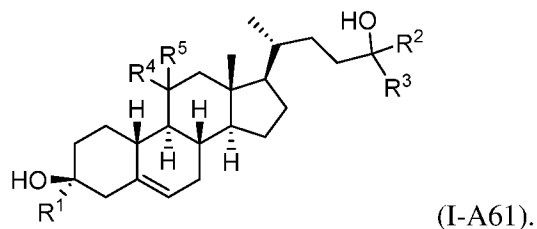
[00175] In some embodiments, the compound of Formula (I-61) is a compound of Formula (I-A61), (I-B61), or (I-C61):



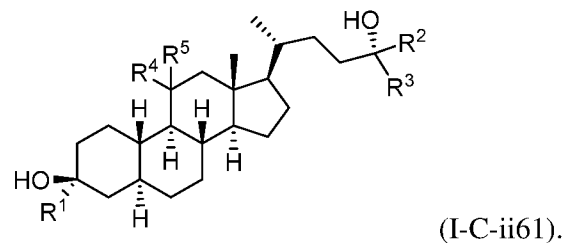
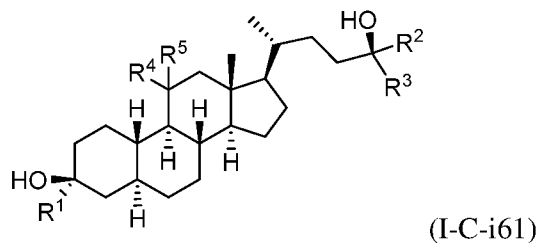
[00176] In some embodiments, the compound of Formula (I-61) is selected from a compound of Formula (I-C61):



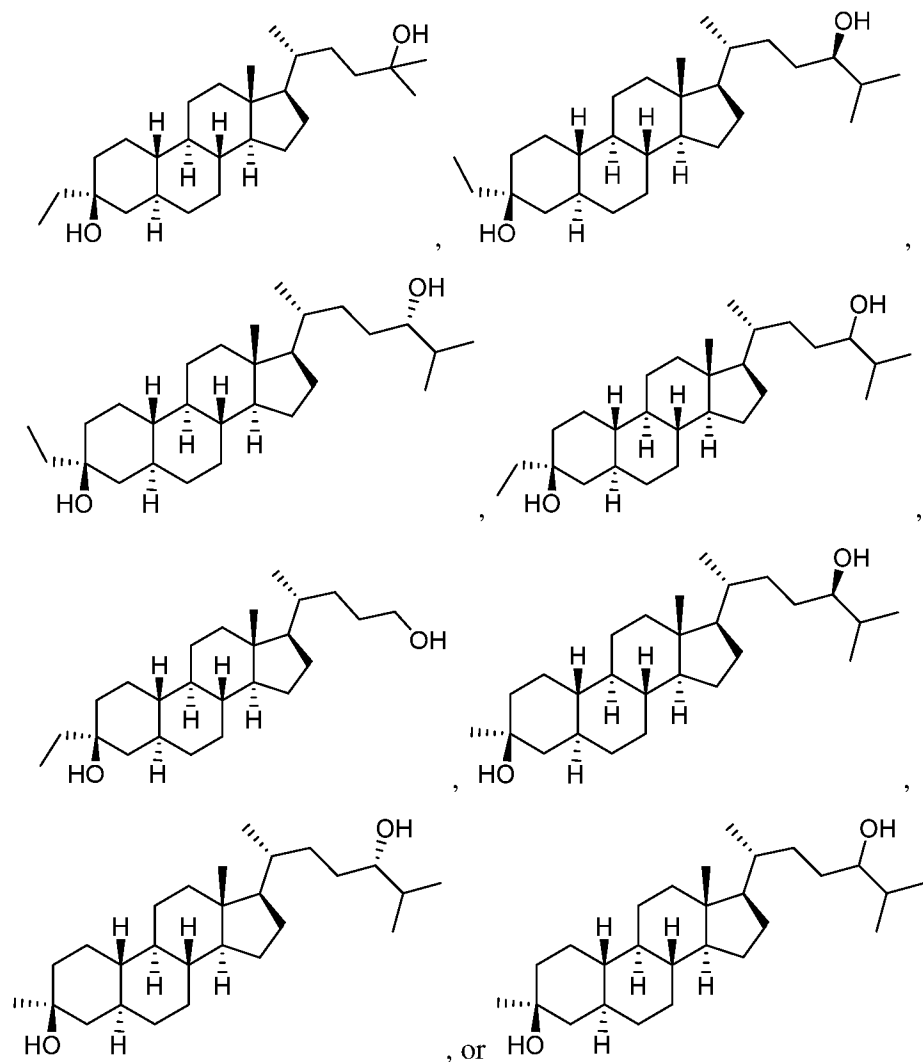
[00177] In some embodiments, the compound of Formula (I-61) is selected from a compound of Formula (I-A61):



[00178] In some embodiments, the compound of Formula (I-61) is selected from a compound of Formula (I-C-i61) or (I-C-ii61):

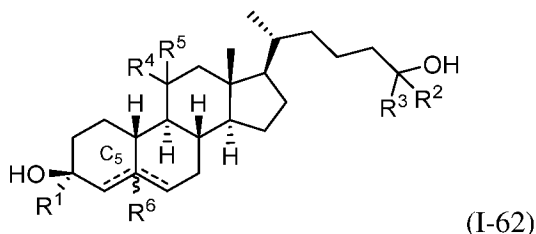


5 In some embodiments, the compound is:



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[00179] In one aspect, the present invention features a compound of Formula (I-62):



or a pharmaceutically acceptable salt thereof, wherein:  $R^1$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl); each of  $R^2$  and  $R^3$  is independently hydrogen, alkyl, carbocyclyl, or heterocyclyl or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 membered ring; each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl), or  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;  $R^6$  is absent or hydrogen; and  $\text{-----}$  represents a single or double bond, wherein when one of  $\text{-----}$  is a double bond, the other  $\text{-----}$  is a single bond; when both of  $\text{-----}$  are single bonds, then  $R^6$  is hydrogen; and when one of  $\text{-----}$  is a double bond,  $R^6$  is absent.

[00180] In some embodiments,  $R^1$  is alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl). In some embodiments,  $R^1$  is substituted or unsubstituted  $C_2$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_3$ - $C_6$  alkyl). In some embodiments,  $R^1$  is methyl or ethyl (*e.g.*, substituted or unsubstituted methyl or substituted or unsubstituted ethyl). In some embodiments,  $R^1$  is substituted or unsubstituted methyl or substituted or unsubstituted ethyl. In some embodiments,  $R^1$  is trifluoromethyl. In some embodiments,  $R^1$  is  $-\text{CH}_2\text{OR}^A$ , wherein  $R^A$  is  $C_1$ - $C_6$  alkyl (*e.g.*,  $C_1$ - $C_3$  alkyl).

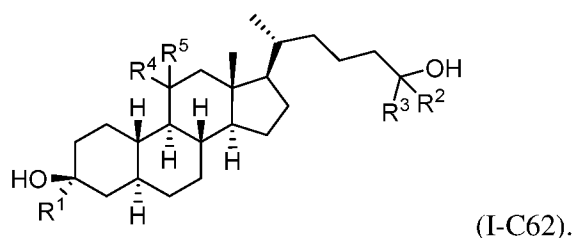
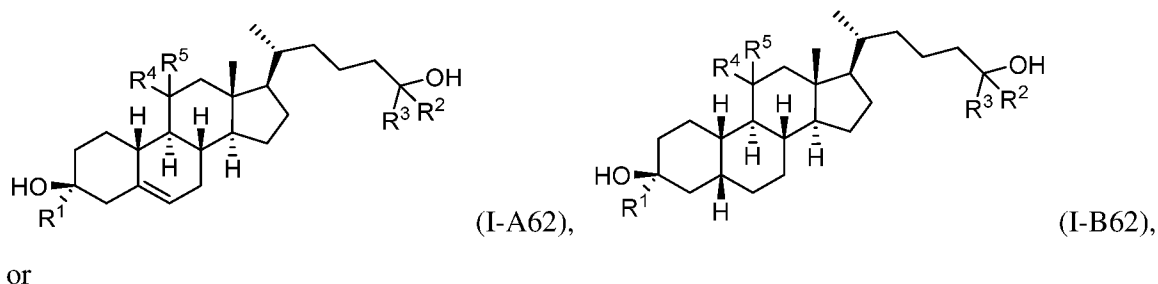
[00181] In some embodiments,  $R^2$  is hydrogen or  $C_1$ - $C_6$  alkyl, (*e.g.*,  $C_2$ - $C_6$  alkyl). In some embodiments,  $R^2$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_2$ - $C_6$  alkyl). In some embodiments,  $R^2$  is haloalkyl, (*e.g.*,  $C_1$ - $C_6$  haloalkyl).

[00182] In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_1$ - $C_6$  alkyl (*e.g.*,  $C_2$ - $C_6$  alkyl). In some embodiments, each of  $R^2$  and  $R^3$  is independently hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl (*e.g.*, substituted or unsubstituted  $C_2$ - $C_6$  alkyl). In some embodiments, each of  $R^2$  and  $R^3$  is independently alkyl (*e.g.*,  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments,  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 membered ring.

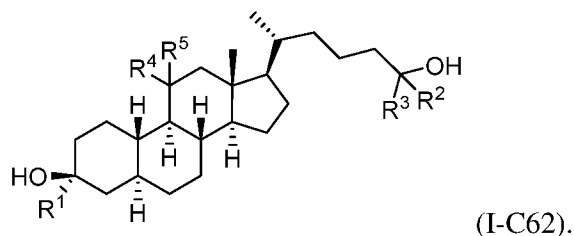
[00183] In some embodiments,  $R^4$  is  $-\text{OH}$  or halo (*e.g.*,  $-\text{F}$ ). In some embodiments,  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group. In some embodiments,  $R^4$  is hydrogen and  $R^5$  is halo (*e.g.*,  $-\text{F}$ ). In some embodiments,  $R^4$  and  $R^5$  are halo (*e.g.*,  $-\text{F}$ ). In some embodiments,  $R^4$  and  $R^5$  are hydrogen.

[00184] In some embodiments,  $R^1$  is ethyl (*e.g.*, substituted or unsubstituted ethyl) and  $R^2$  and  $R^3$  are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments,  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

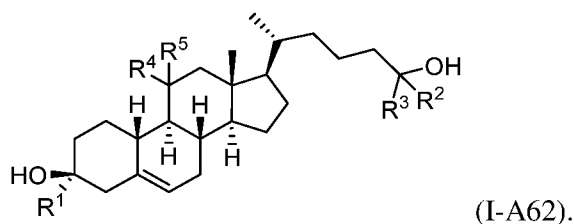
[00185] In some embodiments, the compound of Formula (I-62) is a compound of  
 5 Formula (I-A62), (I-B62), or (I-C62):



[00186] In some embodiments, the compound of Formula (I-62) is selected from a  
 10 compound of Formula (I-C62):

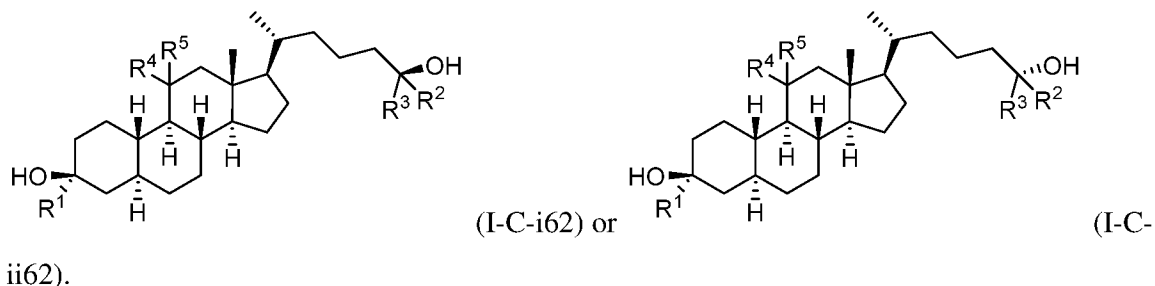


[00187] In some embodiments, the compound of Formula (I-62) is selected from a  
 compound of Formula (I-A62):

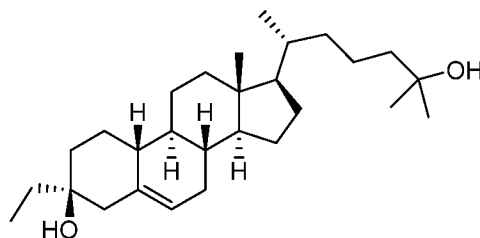


15 [00188] In some embodiments,  $R^1$  is ethyl (*e.g.*, substituted or unsubstituted ethyl) and  $R^2$  and  $R^3$  are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments,  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

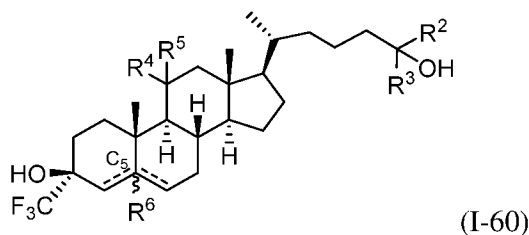
[00189] In some embodiments, the compound of Formula (I-62) is selected from a  
 compound of Formula (I-C-i62) or (I-C-ii62):



[00190] In some embodiments, the compound is



[00191] In one aspect, provided herein are compounds according to Formula (I-60):



or a pharmaceutically acceptable salt thereof, wherein: each of  $R^2$  and  $R^3$  is independently hydrogen, alkyl (e.g.,  $C_1$ - $C_6$  alkyl), carbocyclyl, heterocyclyl, aryl, or heteroaryl, or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring; each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or alkyl (e.g.,  $C_1$ - $C_6$  alkyl), or  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;  $R^6$  is absent or hydrogen; and  $\text{-----}$  represents a single or double bond, wherein when one of  $\text{-----}$  is a double bond, the other  $\text{-----}$  is a single bond; when both of  $\text{-----}$  are single bonds, then  $R^6$  is hydrogen; and when one of the  $\text{-----}$  is a double bond,  $R^6$  is absent.

In some embodiments,  $R^2$  is alkyl (e.g.,  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments,  $R^2$  is haloalkyl (e.g.,  $C_1$ - $C_6$  haloalkyl). In some embodiments,  $R^2$  is substituted or unsubstituted alkyl (e.g., substituted or unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments,  $R^2$  is aryl or heteroaryl.

In some embodiments, each of  $R^2$  and  $R^3$  is independently alkyl (e.g.,  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently substituted or unsubstituted alkyl (e.g., substituted or unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen. In some embodiments, each of  $R^2$  and  $R^3$  is independently unsubstituted alkyl (e.g.,

unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl) or hydrogen. In some embodiments, each of R<sup>2</sup> and R<sup>3</sup> is independently C<sub>1</sub>-C<sub>6</sub> haloalkyl (*e.g.*, trifluoromethyl) or hydrogen. In some embodiments, each of R<sup>2</sup> and R<sup>3</sup> is independently aryl or heteroaryl. In some embodiments, R<sup>2</sup> and R<sup>3</sup>, together with the carbon atom to which they are attached form a 3-membered ring.

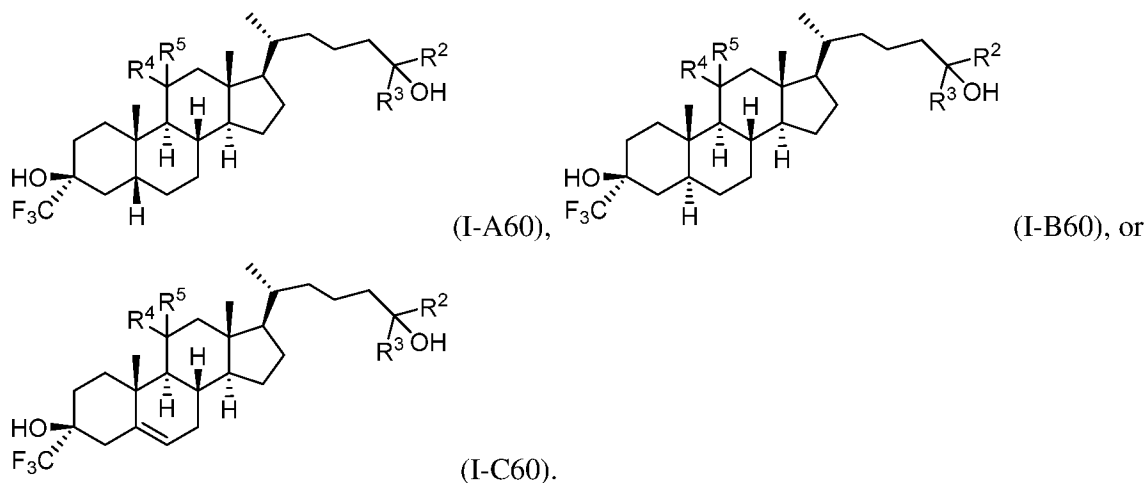
5 In some embodiments, R<sup>2</sup> and R<sup>3</sup>, together with the carbon atom to which they are attached form a cyclopropane. In some embodiments, R<sup>2</sup> and R<sup>3</sup>, together with the carbon atom to which they are attached form a 3-8 membered carbocyclic or heterocyclic ring.

In some embodiments, R<sup>2</sup> is carbocyclyl or heterocyclyl and R<sup>3</sup> is hydrogen. In some embodiments, R<sup>2</sup> is trifluoromethyl and R<sup>3</sup> is hydrogen. In some embodiments, R<sup>2</sup> is aryl or heteroaryl and R<sup>3</sup> is hydrogen. In some embodiments, R<sup>2</sup> and R<sup>3</sup> are methyl (*e.g.*, substituted or unsubstituted methyl). In some embodiments, R<sup>2</sup> and R<sup>3</sup> is substituted methyl. In some embodiments, R<sup>2</sup> and R<sup>3</sup> is unsubstituted methyl.

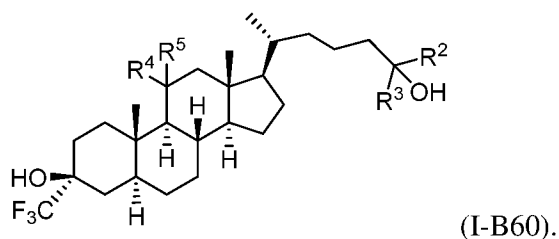
In some embodiments, R<sup>4</sup> is –OH or halo (*e.g.*, –F). In some embodiments, R<sup>4</sup> and R<sup>5</sup>, together with the carbon atom to which they are attached form an oxo group.

15 In some embodiments, R<sup>4</sup> is hydrogen and R<sup>5</sup> is halo (*e.g.*, -F). In some embodiments, R<sup>4</sup> and R<sup>5</sup> are halo (*e.g.*, -F). In some embodiments, R<sup>4</sup> and R<sup>5</sup> are hydrogen.

In some embodiments, the compound of Formula (I-60) is selected from a compound of Formula (I-A60), (I-B60), or (I-C60):



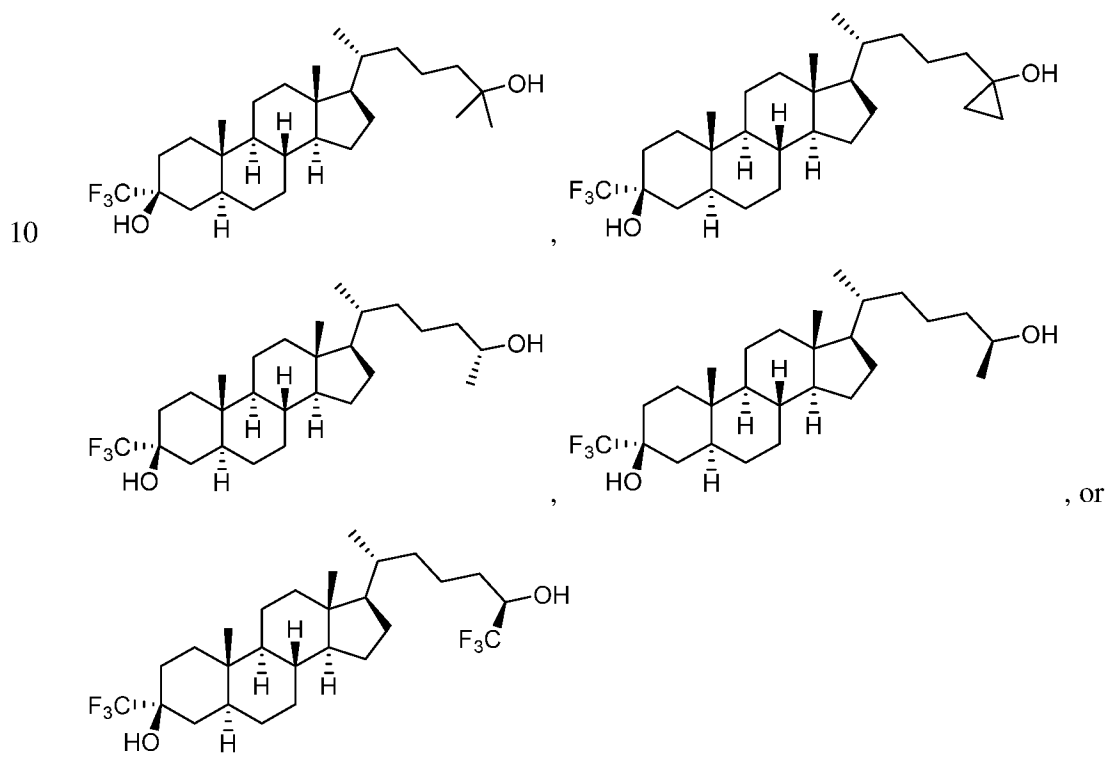
In some embodiments, the compound of Formula (I-60) is selected from a compound of Formula (I-B60):



In some embodiments, at least one of  $R^2$  and  $R^3$  is  $C_1$ - $C_6$  alkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 membered ring.

In some embodiments,  $R^2$  is methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  is unsubstituted methyl and  $R^3$  is hydrogen. In some embodiments,  $R^2$  and  $R^3$  are hydrogen.

In some embodiments, the compound is:



**[00192]** In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be  $^2\text{H}$  (D or deuterium) or  $^3\text{H}$  (T or tritium); carbon may be, for example,  $^{13}\text{C}$  or  $^{14}\text{C}$ ; oxygen may be, for example,  $^{18}\text{O}$ ; nitrogen may be, for example,  $^{15}\text{N}$ , and the like. In other embodiments, a particular isotope (e.g.,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{18}\text{O}$ , or  $^{15}\text{N}$ ) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at

least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

5 *Pharmaceutical Compositions*

[00193] In another aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of Formula I-59, I-66, I-61, I-62, or I-60.

10 [00194] When employed as pharmaceuticals, the compounds provided herein are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

[00195] In one embodiment, with respect to the pharmaceutical composition, the carrier is a parenteral carrier, oral or topical carrier.

15 [00196] The present invention also relates to a compound of Formula I-59, I-66, I-61, I-62, or I-60 or pharmaceutical composition thereof for use as a pharmaceutical or a medicament.

[00197] Generally, the compounds provided herein are administered in a therapeutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

20 [00198] The pharmaceutical compositions provided herein can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds provided herein are preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

25 [00199] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (from about 0.1 to about 50% by weight or preferably

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from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00200] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00201] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[00202] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[00203] The compounds provided herein can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[00204] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of *Remington's Pharmaceutical Sciences*, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[00205] The above-described components for orally administrable, injectable, or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of *Remington's The Science and Practice of*

Pharmacy, 21st edition, 2005, Publisher: Lippincott Williams & Wilkins, which is incorporated herein by reference.

[00206] The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in *Remington's Pharmaceutical Sciences*.

[00207] The present invention also relates to the pharmaceutically acceptable formulations of a compound of Formula I-59, I-66, I-61, I-62, or I-60. In one embodiment, the formulation comprises water. In another embodiment, the formulation comprises a cyclodextrin derivative. The most common cyclodextrins are  $\alpha$ -,  $\beta$ - and  $\gamma$ - cyclodextrins consisting of 6, 7 and 8  $\alpha$ -1,4-linked glucose units, respectively, optionally comprising one or more substituents on the linked sugar moieties, which include, but are not limited to, methylated, hydroxyalkylated, acylated, and sulfoalkylether substitution. In certain embodiments, the cyclodextrin is a sulfoalkyl ether  $\beta$ -cyclodextrin, *e.g.*, for example, sulfobutyl ether  $\beta$ -cyclodextrin, also known as Captisol®. See, *e.g.*, U.S. 5,376,645. In certain embodiments, the formulation comprises hexapropyl- $\beta$ -cyclodextrin. In a more particular embodiment, the formulation comprises hexapropyl- $\beta$ -cyclodextrin (10-50% in water).

[00208] The present invention also relates to the pharmaceutically acceptable acid addition salt of a compound of Formula I-59, I-66, I-61, I-62, or I-60. The acid which may be used to prepare the pharmaceutically acceptable salt is that which forms a non-toxic acid addition salt, *i.e.*, a salt containing pharmacologically acceptable anions such as the hydrochloride, hydroiodide, hydrobromide, nitrate, sulfate, bisulfate, phosphate, acetate, lactate, citrate, tartrate, succinate, maleate, fumarate, benzoate, para-toluenesulfonate, and the like.

[00209] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

[00210] **Exemplary Formulation 1 – Tablets:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active compound per tablet) in a tablet press.

[00211] **Exemplary Formulation 2 – Capsules:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active compound per capsule).

[00212]        **Exemplary Formulation 3 – Liquid:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, (125 mg) may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water may then be added to produce a total volume of 5 mL.

[00213]        **Exemplary Formulation 4 – Tablets:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active compound) in a tablet press.

[00214]        **Exemplary Formulation 5 – Injection:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

[00215]        **Exemplary Formulation 6 – Tablets:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 90-150 mg tablets (30-50 mg of active compound per tablet) in a tablet press.

[00216]        **Exemplary Formulation 7 – Tablets:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 30-90 mg tablets (10-30 mg of active compound per tablet) in a tablet press.

[00217]        **Exemplary Formulation 8 – Tablets:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 0.3-30 mg tablets (0.1-10 mg of active compound per tablet) in a tablet press.

[00218]        **Exemplary Formulation 9 – Tablets:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 150-240 mg tablets (50-80 mg of active compound per tablet) in a tablet press.

[00219] **Exemplary Formulation 10 – Tablets:** A compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 270-450 mg tablets (90-150 mg of active compound per tablet) in a tablet press.

[00220] Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[00221] For the prevention and/or treatment of long-term conditions the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of the compound provided herein, with preferred doses each providing from about 0.1 to about 10 mg/kg, and especially about 1 to about 5 mg/kg.

[00222] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[00223] When used to prevent the onset of a CNS-disorder, the compounds provided herein will be administered to a subject at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Subjects at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

#### *Methods of Treatment and Use*

[00224] Compounds of the present invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, and pharmaceutically acceptable salts thereof, as described herein, may be used in methods of effecting positive allosteric modulation of an PMDA receptor in a subject in need thereof, comprising administering to the subject a compound of effecting negative allosteric modulation of an NMDA receptor in a subject in need thereof, comprising administering to the subject a compound of Formula.

[00225] Compounds of the present invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, and pharmaceutically acceptable salts thereof, as described herein, are generally designed to modulate NMDA function, and therefore to act as oxysterols for the treatment and

prevention of, *e.g.*, CNS-related conditions in a subject. In some embodiments, the compounds described herein, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, and pharmaceutically acceptable salts thereof, as described herein, are generally designed to penetrate the blood brain barrier (*e.g.*, designed to be transported across the blood brain barrier).

5 Modulation, as used herein, refers to, for example, the inhibition or potentiation of NMDA receptor function. In certain embodiments, the compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, acts as a negative allosteric modulator (NAM) of NMDA, and inhibit NMDA receptor function. In certain embodiments, the present invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, acts as a positive allosteric modulator (PAM) of NMDA, and potentiate NMDA receptor function. In certain embodiments, the compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, blocks or reduces the potentiation or inhibition of NMDA receptor function by a naturally-occurring substrate. Such compounds do not act as negative allosteric modulators (NAMs) or positive allosteric modulators (PAMs) of NMDA. In some embodiments, the disorder is cancer. In some embodiments, the disorder is diabetes. In some embodiments, the disorder is a sterol synthesis disorder. In some embodiments, the disorder is a gastrointestinal (GI) disorder, *e.g.*, constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) (*e.g.*, ulcerative colitis, Crohn's disease), structural disorders affecting the GI, anal disorders (*e.g.*, hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula), colon polyps, cancer, or colitis. In some embodiments, the disorder is inflammatory bowel disease.

[00226] Exemplary conditions related to NMDA-modulation include, but are not limited to, gastrointestinal (GI) disorder, *e.g.*, constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) (*e.g.*, ulcerative colitis, Crohn's disease), structural disorders affecting the GI, anal disorders (*e.g.*, hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula), colon polyps, cancer, colitis, and CNS conditions, *e.g.*, as described herein.

[00227] Exemplary conditions (*e.g.*, CNS conditions) related to NMDA-modulation include, but are not limited to, adjustment disorders, anxiety disorders (including obsessive-compulsive disorder, posttraumatic stress disorder, social phobia, generalized anxiety disorder), cognitive disorders (including Alzheimer's disease and other forms of dementia including cortico-basal dementia- progressive supranuclear palsy, frontal-temporal dementia, primary progressive aphasia, Parkinson's disease dementia, and Lewy body dementia), dissociative disorders, eating disorders, mood disorders (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorders

(including schizoaffective disorder), sleep disorders (including insomnia), substance abuse-related disorders, personality disorders (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.*, Shank3)), neurodevelopmental disorders (including Rett syndrome), multiple sclerosis, sterol synthesis disorders, Smith-Lemli-Opitz syndrome, pain (including acute pain, chronic pain, and neuropathic pain), seizure disorders (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease, Tuberous Sclerosis Complex (TSC), and infantile spasms), stroke, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral ischemia, traumatic brain injury, movement disorders (including Huntington's disease and Parkinson's disease) attention deficit disorder, attention deficit hyperactivity disorder, metabolic encephalopathies (including phenylketonuria), post-partum psychosis, syndromes associated with high titers of anti-NMDA receptor antibodies (including anti-NMDA receptor encephalitis), neurodegenerative disorders, neuroinflammation, neuropsychiatric lupus, Niemann-Pick C disorder, and tinnitus.

**[00228]** In certain embodiments, compounds of the present invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, can be used to induce sedation or anesthesia.

**[00229]** In certain embodiments, the compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, is useful in the treatment or prevention of adjustment disorders, anxiety disorders (including obsessive-compulsive disorder, posttraumatic stress disorder, social phobia, generalized anxiety disorder), cognitive disorders (including Alzheimer's disease and other forms of dementia including cortico-basal dementia-progressive supranuclear palsy, frontal-temporal dementia, primary progressive aphasia, Parkinson's disease dementia, and Lewy body dementia), dissociative disorders, eating disorders, mood disorders (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorders (including schizoaffective disorder), sleep disorders (including insomnia), substance abuse-related disorders, personality disorders (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.*, Shank3)), neurodevelopmental disorders (including Rett syndrome), multiple sclerosis, sterol synthesis disorders, Smith-Lemli-Opitz syndrome, pain (including acute pain, chronic pain, and neuropathic pain), seizure disorders (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease, Tuberous Sclerosis Complex (TSC), and infantile spasms), stroke, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral ischemia, traumatic brain injury, movement disorders (including Huntington's disease and Parkinson's disease) attention deficit disorder, attention deficit hyperactivity disorder, metabolic encephalopathies (including

phenylketoneuria), post-partum psychosis, syndromes associated with high titers of anti-NMDA receptor antibodies (including anti-NMDA receptor encephalitis), neurodegenerative disorders, neuroinflammation, neuropsychiatric lupus, Niemann-Pick C disorder, and tinnitus.

**[00230]** In certain embodiments, the compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, is useful in the treatment or prevention of adjustment disorders, anxiety disorders (including obsessive-compulsive disorder, posttraumatic stress disorder, social phobia, generalized anxiety disorder), cognitive disorders (including Alzheimer's disease and other forms of dementia including cortico-basal dementia- progressive supranuclear palsy, frontal-temporal dementia, primary progressive aphasia, Parkinson's disease dementia, and Lewy body dementia), substance abuse-related disorders, dissociative disorders, eating disorders mood disorders (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorders (including schizoaffective disorder), personality disorders (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.*, Shank3)), or post-partum psychosis.

**[00231]** In certain embodiments, the compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, is useful in the treatment or prevention of neurodevelopmental disorders (including Rett syndrome), multiple sclerosis, sterol synthesis disorders, Smith-Lemli-Opitz syndrome, pain (including acute pain, chronic pain, and neuropathic pain), seizure disorders (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease, Tuberous Sclerosis Complex (TSC), and infantile spasms), stroke, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral ischemia, traumatic brain injury, movement disorders (including Huntington's disease and Parkinson's disease) attention deficit disorder, attention deficit hyperactivity disorder, metabolic encephalopathies (including phenylketoneuria), syndromes associated with high titers of anti-NMDA receptor antibodies (including anti-NMDA receptor encephalitis), neurodegenerative disorders, neuroinflammation, neuropsychiatric lupus, Niemann-Pick C disorder, or tinnitus.

**[00232]** In some embodiments, a compound of the invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60 that acts as a PAM of NMDA receptor function can be useful in the treatment or prevention of conditions (*e.g.*, CNS-related conditions) including schizophrenia or other psychotic disorders (including schizoaffective disorder), sleep disorders (including insomnia), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.*, Shank3)), multiple sclerosis, movement disorders (including Huntington's disease and Parkinson's disease), attention deficit disorder, attention deficit hyperactivity disorder, metabolic encephalopathies (including phenylketoneuria), post-partum psychosis, and

syndromes associated with high titers or anti-NMDA receptor antibodies (including anti-NMDA receptor encephalitis).

[00233] In some embodiments, a compound of the invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, that acts as a NAM of NMDA receptor function can be useful in the treatment or prevention of conditions (*e.g.*, CNS-related conditions) including anxiety disorders (including obsessive-compulsive disorder, posttraumatic stress disorder, social phobia, generalized anxiety disorder), mood disorders (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), personality disorders (including obsessive-compulsive personality disorder), neurodevelopmental disorders (including Rett syndrome), pain (including acute and chronic pain), seizure disorders (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease, and Tuberous Sclerosis Complex (TSC)), stroke, traumatic brain injury, adjustment disorders, neuropsychiatric lupus, and tinnitus.

[00234] In some embodiments, a compound of the invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, that acts as a PAM or a NAM of NMDA receptor function can be useful in the treatment or prevention of conditions (*e.g.*, CNS-related conditions) including cognitive disorders (including Alzheimer's disease and other forms of dementia including cortico-basal dementia- progressive supranuclear palsy, frontal-temporal dementia, primary progressive aphasia, Parkinson's disease dementia, and Lewy body dementia), sterol synthesis disorders, and eating disorders.

[00235] In another aspect, provided is a method of treating or preventing brain excitability in a subject susceptible to or afflicted with a condition associated with brain excitability, comprising administering to the subject an effective amount of a compound of the present invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, or a pharmaceutically acceptable salt thereof.

[00236] In yet another aspect, the present invention provides a combination of a compound of the present invention, *e.g.*, a compound of Formula I-59, I-66, I-61, I-62, or I-60, or pharmaceutically acceptable salt thereof, and another pharmacologically active agent. The compounds provided herein can be administered as the sole active agent or they can be administered in combination with other agents. Administration in combination can proceed by any technique apparent to those of skill in the art including, for example, separate, sequential, concurrent and alternating administration.

#### *Movement Disorders*

[00237] Also described herein are methods for treating a movement disorder. As used herein, "movement disorders" refers to a variety of diseases and disorders that are associated

with hyperkinetic movement disorders and related abnormalities in muscle control. Exemplary movement disorders include, but are not limited to, Parkinson's disease and Parkinsonism (defined particularly by bradykinesia), dystonia, chorea and Huntington's disease, ataxia, tremor (e.g., essential tremor), myoclonus and startle, tics and Tourette syndrome, Restless legs syndrome, stiff person syndrome, and gait disorders.

[00238] **Tremor** is an involuntary, at times rhythmic, muscle contraction and relaxation that can involve oscillations or twitching of one or more body parts (*e.g.*, hands, arms, eyes, face, head, vocal folds, trunk, legs). Tremor includes hereditary, degenerative, and idiopathic disorders such as Wilson's disease, Parkinson's disease, and essential tremor, respectively; metabolic diseases (*e.g.*, thyroid-parathyroid-, liver disease and hypoglycemia); peripheral neuropathies (associated with Charcot-Marie-Tooth, Roussy-Levy, diabetes mellitus, complex regional pain syndrome); toxins (nicotine, mercury, lead, CO, Manganese, arsenic, toluene); drug-induced (narcoleptics, tricyclics, lithium, cocaine, alcohol, adrenaline, bronchodilators, theophylline, caffeine, steroids, valproate, amiodarone, thyroid hormones, vincristine); and psychogenic disorders. Clinical tremor can be classified into physiologic tremor, enhanced physiologic tremor, essential tremor syndromes (including classical essential tremor, primary orthostatic tremor, and task- and position-specific tremor), dystonic tremor, parkinsonian tremor, cerebellar tremor, Holmes' tremor (*i.e.*, rubral tremor), palatal tremor, neuropathic tremor, toxic or drug-induced tremor, and psychogenic tremor. Other forms of tremor include cerebellar tremor or intention tremor, dystonic tremor, essential tremor, orthostatic tremor, parkinsonian tremor, physiological tremor, psychogenic tremor, or rubral tremor.

[00239] **Cerebellar tremor or intention tremor** is a slow, broad tremor of the extremities that occurs after a purposeful movement. Cerebellar tremor is caused by lesions in or damage to the cerebellum resulting from, *e.g.*, tumor, stroke, disease (*e.g.*, multiple sclerosis, an inherited degenerative disorder).

[00240] **Dystonic tremor** occurs in individuals affected by dystonia, a movement disorder in which sustained involuntary muscle contractions cause twisting and repetitive motions and/or painful and abnormal postures or positions. Dystonic tremor may affect any muscle in the body. Dystonic tremors occurs irregularly and often can be relieved by complete rest.

[00241] **Essential tremor** or benign essential tremor is the most common type of tremor. Essential tremor may be mild and nonprogressive in some, and may be slowly progressive, starting on one side of the body but affect both sides within 3 years. The hands are most often affected, but the head, voice, tongue, legs, and trunk may also be involved. Tremor frequency may decrease as the person ages, but severity may increase. Heightened emotion, stress, fever,

physical exhaustion, or low blood sugar may trigger tremors and/or increase their severity.

Symptoms generally evolve over time and can be both visible and persistent following onset.

[00242]        **Orthostatic tremor** is characterized by fast (*e.g.*, greater than 12 Hz) rhythmic muscle contractions that occurs in the legs and trunk immediately after standing. Cramps are felt in the thighs and legs and the patient may shake uncontrollably when asked to stand in one spot. Orthostatic tremor may occur in patients with essential tremor.

[00243]        **Parkinsonian tremor** is caused by damage to structures within the brain that control movement. Parkinsonian tremor is often a precursor to Parkinson's disease and is typically seen as a "pill-rolling" action of the hands that may also affect the chin, lips, legs, and trunk. Onset of parkinsonian tremor typically begins after age 60. Movement starts in one limb or on one side of the body and can progress to include the other side.

[00244]        **Physiological tremor** can occur in normal individuals and have no clinical significance. It can be seen in all voluntary muscle groups. Physiological tremor can be caused by certain drugs, alcohol withdrawal, or medical conditions including an overactive thyroid and hypoglycemia. The tremor classically has a frequency of about 10 Hz.

[00245]        **Psychogenic tremor** or hysterical tremor can occur at rest or during postural or kinetic movement. Patient with psychogenic tremor may have a conversion disorder or another psychiatric disease.

[00246]        **Rubral tremor** is characterized by coarse slow tremor which can be present at rest, at posture, and with intention. The tremor is associated with conditions that affect the red nucleus in the midbrain, classical unusual strokes.

[00247]        **Parkinson's disease** affects nerve cells in the brain that produce dopamine. Symptoms include muscle rigidity, tremors, and changes in speech and gait. **Parkinsonism** is characterized by tremor, bradykinesia, rigidity, and postural instability. Parkinsonism shares symptoms found in Parkinson's disease, but is a symptom complex rather than a progressive neurodegenerative disease.

[00248]        **Dystonia** is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements or postures. Dystonic movements can be patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

[00249]        **Chorea** is a neurological disorder characterized by jerky involuntary movements typically affecting the shoulders, hips, and face.

[00250]        **Huntington's Disease** is an inherited disease that causes nerve cells in the brain to waste away. Symptoms include uncontrolled movements, clumsiness, and balance problems. Huntington's disease can hinder walk, talk, and swallowing.

[00251] **Ataxia** refers to the loss of full control of bodily movements, and may affect the fingers, hands, arms, legs, body, speech, and eye movements.

[00252] **Myoclonus and Startle** is a response to a sudden and unexpected stimulus, which can be acoustic, tactile, visual, or vestibular.

5 [00253] **Tics** are an involuntary movement usually onset suddenly, brief, repetitive, but non-rhythmical, typically imitating normal behavior and often occurring out of a background of normal activity. Tics can be classified as motor or vocal, motor tics associated with movements while vocal tics associated with sound. Tics can be characterized as simple or complex. For example simple motor tics involve only a few muscles restricted to a specific body part.

10 [00254] **Tourette Syndrome** is an inherited neuropsychiatric disorder with onset in childhood, characterized by multiple motor tics and at least one vocal tic.

[00255] **Restless Legs Syndrome** is a neurologic sensorimotor disorder characterized by an overwhelming urge to move the legs when at rest.

[00256] **Stiff Person Syndrome** is a progressive movement disorder characterized by  
15 involuntary painful spasms and rigidity of muscles, usually involving the lower back and legs. Stiff-legged gait with exaggerated lumbar hyperlordosis typically results. Characteristic abnormality on EMG recordings with continuous motor unit activity of the paraspinal axial muscles is typically observed. Variants include “stiff-limb syndrome” producing focal stiffness typically affecting distal legs and feet.

20 [00257] **Gait disorders** refer to an abnormality in the manner or style of walking, which results from neuromuscular, arthritic, or other body changes. Gait is classified according to the system responsible for abnormal locomotion, and include hemiplegic gait, diplegic gait, neuropathic gait, myopathic gait, parkinsonian gait, choreiform gait, ataxic gait, and sensory gait.

25

#### *Mood disorders*

[00258] Also provided herein are methods for treating a mood disorder, for example clinical depression, postnatal depression or postpartum depression, perinatal depression, atypical depression, melancholic depression, psychotic major depression, catonic depression, seasonal  
30 affective disorder, dysthymia, double depression, depressive personality disorder, recurrent brief depression, minor depressive disorder, bipolar disorder or manic depressive disorder, depression caused by chronic medical conditions, treatment-resistant depression, refractory depression, suicidality, suicidal ideation, or suicidal behavior.

[00259] **Clinical depression** is also known as major depression, major depressive disorder  
35 (MDD), severe depression, unipolar depression, unipolar disorder, and recurrent depression, and

refers to a mental disorder characterized by pervasive and persistent low mood that is accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. Some people with clinical depression have trouble sleeping, lose weight, and generally feel agitated and irritable. Clinical depression affects how an individual feels, thinks, and behaves and may lead to a variety of emotional and physical problems. Individuals with clinical depression may have trouble doing day-to-day activities and make an individual feel as if life is not worth living.

**[00260] Postnatal depression (PND)** is also referred to as **postpartum depression (PPD)**, and refers to a type of clinical depression that affects women after childbirth. Symptoms can include sadness, fatigue, changes in sleeping and eating habits, reduced sexual desire, crying episodes, anxiety, and irritability. In some embodiments, the PND is a treatment-resistant depression (e.g., a treatment-resistant depression as described herein). In some embodiments, the PND is refractory depression (e.g., a refractory depression as described herein).

**[00261]** In some embodiments, a subject having PND also experienced depression, or a symptom of depression during pregnancy. This depression is referred to herein as) **perinatal depression**. In an embodiment, a subject experiencing perinatal depression is at increased risk of experiencing PND.

**[00262] Atypical depression (AD)** is characterized by mood reactivity (*e.g.*, paradoxical anhedonia) and positivity, significant weight gain or increased appetite. Patients suffering from AD also may have excessive sleep or somnolence (hypersomnia), a sensation of limb heaviness, and significant social impairment as a consequence of hypersensitivity to perceived interpersonal rejection.

**[00263] Melancholic depression** is characterized by loss of pleasure (anhedonia) in most or all activities, failures to react to pleasurable stimuli, depressed mood more pronounced than that of grief or loss, excessive weight loss, or excessive guilt.

**[00264] Psychotic major depression (PMD)** or psychotic depression refers to a major depressive episode, in particular of melancholic nature, where the individual experiences psychotic symptoms such as delusions and hallucinations.

**[00265] Catatonic depression** refers to major depression involving disturbances of motor behavior and other symptoms. An individual may become mute and stuporose, and either is immobile or exhibits purposeless or bizarre movements.

**[00266] Seasonal affective disorder (SAD)** refers to a type of seasonal depression wherein an individual has seasonal patterns of depressive episodes coming on in the fall or winter.

[00267] **Dysthymia** refers to a condition related to unipolar depression, where the same physical and cognitive problems are evident. They are not as severe and tend to last longer (*e.g.*, at least 2 years).

[00268] **Double depression** refers to fairly depressed mood (dysthymia) that lasts for at least 2 years and is punctuated by periods of major depression.

[00269] **Depressive Personality Disorder (DPD)** refers to a personality disorder with depressive features.

[00270] **Recurrent Brief Depression (RBD)** refers to a condition in which individuals have depressive episodes about once per month, each episode lasting 2 weeks or less and typically less than 2-3 days.

[00271] **Minor depressive disorder** or minor depression refers to a depression in which at least 2 symptoms are present for 2 weeks.

[00272] **Bipolar disorder or manic depressive disorder** causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). During periods of mania the individual may feel or act abnormally happy, energetic, or irritable. They often make poorly thought out decisions with little regard to the consequences. The need for sleep is usually reduced. During periods of depression there may be crying, poor eye contact with others, and a negative outlook on life. The risk of suicide among those with the disorder is high at greater than 6% over 20 years, while self-harm occurs in 30-40%. Other mental health issues such as anxiety disorder and substance use disorder are commonly associated with bipolar disorder.

[00273] **Depression caused by chronic medical conditions** refers to depression caused by chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress.

[00274] **Treatment-resistant depression** refers to a condition where the individuals have been treated for depression, but the symptoms do not improve. For example, antidepressants or psychological counseling (psychotherapy) do not ease depression symptoms for individuals with treatment-resistant depression. In some cases, individuals with treatment-resistant depression improve symptoms, but come back. **Refractory depression** occurs in patients suffering from depression who are resistant to standard pharmacological treatments, including tricyclic antidepressants, MAOIs, SSRIs, and double and triple uptake inhibitors and/or anxiolytic drugs, as well as non-pharmacological treatments (*e.g.*, psychotherapy, electroconvulsive therapy, vagus nerve stimulation and/or transcranial magnetic stimulation).

[00275] **Suicidality, suicidal ideation, suicidal behavior** refers to the tendency of an individual to commit suicide. Suicidal ideation concerns thoughts about or an unusual preoccupation with suicide. The range of suicidal ideation varies greatly, from *e.g.*, fleeting thoughts to extensive thoughts, detailed planning, role playing, incomplete attempts. Symptoms

include talking about suicide, getting the means to commit suicide, withdrawing from social contact, being preoccupied with death, feeling trapped or hopeless about a situation, increasing use of alcohol or drugs, doing risky or self-destructive things, saying goodbye to people as if they won't be seen again.

- 5 [00276]        **Symptoms** of depression include persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism, worthlessness, low energy, restlessness, difficulty sleeping, sleeplessness, irritability, fatigue, motor challenges, loss of interest in pleasurable activities or hobbies, loss of concentration, loss of energy, poor self-esteem, absence of positive thoughts or plans, excessive sleeping, overeating, appetite loss, insomnia, self-harm, thoughts of  
10 suicide, and suicide attempts. The presence, severity, frequency, and duration of symptoms may vary on a case to case basis. Symptoms of depression, and relief of the same, may be ascertained by a physician or psychologist (e.g., by a mental state examination).

#### *Anxiety Disorders*

- 15 [00277]        Provided herein are methods for treating anxiety disorders. **Anxiety disorder** is a blanket term covering several different forms of abnormal and pathological fear and anxiety. Current psychiatric diagnostic criteria recognize a wide variety of anxiety disorders.

- [00278]        **Generalized anxiety disorder** is a common chronic disorder characterized by long-lasting anxiety that is not focused on any one object or situation. Those suffering from  
20 generalized anxiety experience non-specific persistent fear and worry and become overly concerned with everyday matters. Generalized anxiety disorder is the most common anxiety disorder to affect older adults.

- [00279]        In **panic disorder**, a person suffers from brief attacks of intense terror and apprehension, often marked by trembling, shaking, confusion, dizziness, nausea, difficulty  
25 breathing. These panic attacks, defined by the APA as fear or discomfort that abruptly arises and peaks in less than ten minutes, can last for several hours and can be triggered by stress, fear, or even exercise; although the specific cause is not always apparent. In addition to recurrent unexpected panic attacks, a diagnosis of panic disorder also requires that said attacks have chronic consequences: either worry over the attacks' potential implications, persistent fear of  
30 future attacks, or significant changes in behavior related to the attacks. Accordingly, those suffering from panic disorder experience symptoms even outside of specific panic episodes. Often, normal changes in heartbeat are noticed by a panic sufferer, leading them to think something is wrong with their heart or they are about to have another panic attack. In some cases, a heightened awareness (hypervigilance) of body functioning occurs during panic attacks,

wherein any perceived physiological change is interpreted as a possible life threatening illness (i.e. extreme hypochondriasis).

[00280]        **Obsessive compulsive disorder** is a type of anxiety disorder primarily characterized by repetitive obsessions (distressing, persistent, and intrusive thoughts or images) and compulsions (urges to perform specific acts or rituals). The OCD thought pattern may be likened to superstitions insofar as it involves a belief in a causative relationship where, in reality, one does not exist. Often the process is entirely illogical; for example, the compulsion of walking in a certain pattern may be employed to alleviate the obsession of impending harm. And in many cases, the compulsion is entirely inexplicable, simply an urge to complete a ritual triggered by nervousness. In a minority of cases, sufferers of OCD may only experience obsessions, with no overt compulsions; a much smaller number of sufferers experience only compulsions.

[00281]        The single largest category of anxiety disorders is that of **phobia**, which includes all cases in which fear and anxiety is triggered by a specific stimulus or situation. Sufferers typically anticipate terrifying consequences from encountering the object of their fear, which can be anything from an animal to a location to a bodily fluid.

[00282]        **Post-traumatic stress disorder** or **PTSD** is an anxiety disorder which results from a traumatic experience. Post-traumatic stress can result from an extreme situation, such as combat, rape, hostage situations, or even serious accident. It can also result from long term (chronic) exposure to a severe stressor, for example soldiers who endure individual battles but cannot cope with continuous combat. Common symptoms include flashbacks, avoidant behaviors, and depression.

### *Epilepsy*

[00283]        Epilepsy is a brain disorder characterized by repeated seizures over time. Types of epilepsy can include, but are not limited to generalized epilepsy, *e.g.*, childhood absence epilepsy, juvenile myoclonic epilepsy, epilepsy with grand-mal seizures on awakening, West syndrome, Lennox-Gastaut syndrome, partial epilepsy, *e.g.*, temporal lobe epilepsy, frontal lobe epilepsy, benign focal epilepsy of childhood.

### *Epileptogenesis*

[00284]        Epileptogenesis is a gradual process by which a normal brain develops epilepsy (a chronic condition in which seizures occur). Epileptogenesis results from neuronal damage precipitated by the initial insult (*e.g.*, status epilepticus).

*Status epilepticus (SE)*

[00285] Status epilepticus (SE) can include, *e.g.*, convulsive status epilepticus, *e.g.*, early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, *e.g.*, generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; and periodic lateralized epileptiform discharges. Convulsive status epilepticus is characterized by the presence of convulsive status epileptic seizures, and can include early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus. Early status epilepticus is treated with a first line therapy. Established status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line therapy, and a second line therapy is administered. Refractory status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line and a second line therapy, and a general anesthetic is generally administered. Super refractory status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line therapy, a second line therapy, and a general anesthetic for 24 hours or more.

[00286] Non-convulsive status epilepticus can include, *e.g.*, focal non-convulsive status epilepticus, *e.g.*, complex partial non-convulsive status epilepticus, simple partial non-convulsive status epilepticus, subtle non-convulsive status epilepticus; generalized non-convulsive status epilepticus, *e.g.*, late onset absence non-convulsive status epilepticus, atypical absence non-convulsive status epilepticus, or typical absence non-convulsive status epilepticus.

*Seizure*

[00287] A seizure is the physical findings or changes in behavior that occur after an episode of abnormal electrical activity in the brain. The term “seizure” is often used interchangeably with “convulsion.” Convulsions are when a person’s body shakes rapidly and uncontrollably. During convulsions, the person’s muscles contract and relax repeatedly.

[00288] Based on the type of behavior and brain activity, seizures are divided into two broad categories: generalized and partial (also called local or focal). Classifying the type of seizure helps doctors diagnose whether or not a patient has epilepsy.

[00289] Generalized seizures are produced by electrical impulses from throughout the entire brain, whereas partial seizures are produced (at least initially) by electrical impulses in a relatively small part of the brain. The part of the brain generating the seizures is sometimes called the focus.

[00290] There are six types of generalized seizures. The most common and dramatic, and therefore the most well-known, is the generalized convulsion, also called the grand-mal seizure.

In this type of seizure, the patient loses consciousness and usually collapses. The loss of consciousness is followed by generalized body stiffening (called the "tonic" phase of the seizure) for 30 to 60 seconds, then by violent jerking (the "clonic" phase) for 30 to 60 seconds, after which the patient goes into a deep sleep (the "postictal" or after-seizure phase). During grand-

mal seizures, injuries and accidents may occur, such as tongue biting and urinary incontinence.

**[00291]** Absence seizures cause a short loss of consciousness (just a few seconds) with few or no symptoms. The patient, most often a child, typically interrupts an activity and stares blankly. These seizures begin and end abruptly and may occur several times a day. Patients are usually not aware that they are having a seizure, except that they may be aware of "losing time."

**[00292]** Myoclonic seizures consist of sporadic jerks, usually on both sides of the body. Patients sometimes describe the jerks as brief electrical shocks. When violent, these seizures may result in dropping or involuntarily throwing objects.

**[00293]** Clonic seizures are repetitive, rhythmic jerks that involve both sides of the body at the same time.

**[00294]** Tonic seizures are characterized by stiffening of the muscles.

**[00295]** Atonic seizures consist of a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall.

Seizures described herein can include epileptic seizures; acute repetitive seizures; cluster seizures; continuous seizures; unremitting seizures; prolonged seizures; recurrent seizures; status epilepticus seizures, e.g., refractory convulsive status epilepticus, non-convulsive status epilepticus seizures; refractory seizures; myoclonic seizures; tonic seizures; tonic-clonic seizures; simple partial seizures; complex partial seizures; secondarily generalized seizures; atypical absence seizures; absence seizures; atonic seizures; benign Rolandic seizures; febrile seizures; emotional seizures; focal seizures; gelastic seizures; generalized onset seizures; infantile spasms; Jacksonian seizures; massive bilateral myoclonus seizures; multifocal seizures; neonatal onset seizures; nocturnal seizures; occipital lobe seizures; post traumatic seizures; subtle seizures; Sylvian seizures; visual reflex seizures; or withdrawal seizures. In some embodiments, the seizure is a generalized seizure associated with Dravet Syndrome, Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex, Rett Syndrome or PCDH19 Female Pediatric Epilepsy.

#### *Abbreviations*

PCC: pyridinium chlorochromate; t-BuOK: potassium tert-butoxide; 9-BBN: 9-borabicyclo[3.3.1]nonane; Pd(*t*-Bu<sub>3</sub>P)<sub>2</sub>: bis(tri-tert-butylphosphine)palladium(0); AcCl: acetyl chloride; *i*-PrMgCl: Isopropylmagnesium chloride; TBSCl: tert-Butyl(chloro)dimethylsilane; (*i*-

PrO)<sub>4</sub>Ti: titanium tetraisopropoxide; BHT: 2,6-di-*t*-butyl-4-methylphenoxide; Me: methyl; *i*-Pr: iso-propyl; *t*-Bu: tert-butyl; Ph: phenyl; Et: ethyl; Bz: benzoyl; BzCl: benzoyl chloride; CsF: cesium fluoride; DCC: dicyclohexylcarbodiimide; DCM: dichloromethane; DMAP: 4-dimethylaminopyridine; DMP: Dess-Martin periodinane; EtMgBr: ethylmagnesium bromide; EtOAc: ethyl acetate; TEA: triethylamine; AlaOH: alanine; Boc: *t*-butoxycarbonyl. Py: pyridine; TBAF: tetra-*n*-butylammonium fluoride; THF: tetrahydrofuran; TBS: *t*-butyldimethylsilyl; TMS: trimethylsilyl; TMSCF<sub>3</sub>: (Trifluoromethyl)trimethylsilane; Ts: *p*-toluenesulfonyl; Bu: butyl; Ti(OiPr)<sub>4</sub>: tetraisopropoxytitanium; LAH: Lithium Aluminium Hydride; LDA: lithium diisopropylamide; LiOH.H<sub>2</sub>O: lithium hydroxide hydrates; MAD: methyl aluminum bis(2,6-di-*t*-butyl-4-methylphenoxide); MeCN: acetonitrile; NBS: N-bromosuccinimide; Na<sub>2</sub>SO<sub>4</sub>: sodium sulfate; Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>: sodium thiosulfate; PE: petroleum ether; MeCN: acetonitrile; MeOH: methanol; Boc: *t*-butoxycarbonyl; MTBE: methyl tert-butyl ether; DMSO: dimethylsulfoxide; DMF: N,N-dimethylformamide; 9-BBN: 9-borabicyclo[3.3.1]nonane; MePPh<sub>3</sub>Br: bromo(methyl)triphenylphosphorane; MeMgBr: Methylmagnesium bromide; MeLi: methyl lithium; NaHCO<sub>3</sub>: sodium bicarbonate.

### Examples

[00296] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

[00297] Unless otherwise indicated, the stereochemistry assigned herein (*e.g.*, the assignment of “R” or “S” to the C24 position of the steroid) may be tentatively (*e.g.*, randomly) assigned. For example, a C24 position may be drawn in the “R” configuration when the absolute configuration is “S.” A C24 position may also be drawn in the “S” configuration when the absolute configuration is “R.”

[00298] The absolute configuration of an asymmetric center can be determined using methods known to one skilled in the art. In some embodiments, the absolute configuration of an asymmetric center in a compound can be elucidated from the X-ray single-crystal structure of the compound. In some embodiments, the absolute configuration of an asymmetric center elucidated by the X-ray crystal structure of a compound can be used to infer the absolute configuration of a corresponding asymmetric center in another compound obtained from the same or similar synthetic methodologies. In some embodiments, the absolute configuration of an asymmetric center elucidated by the X-ray crystal structure of a compound can be used to

infer the absolute configuration of a corresponding asymmetric center in another compound coupled with a spectroscopic technique, *e.g.*, NMR spectroscopy, *e.g.*,  $^1\text{H}$  NMR spectroscopy or  $^{19}\text{F}$  NMR spectroscopy.

## Materials and Methods

5 [00299] The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent  
10 used, but such conditions can be determined by one skilled in the art by routine optimization.

[00300] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For  
15 example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

[00301] The compounds provided herein may be isolated and purified by known standard procedures. Such procedures include (but are not limited to) recrystallization, column  
20 chromatography, HPLC, or supercritical fluid chromatography (SFC). The following schemes are presented with details as to the preparation of representative oxysterols that have been listed herein. The compounds provided herein may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

Exemplary chiral columns available for use in the separation/purification of the  
25 enantiomers/diastereomers provided herein include, but are not limited to, CHIRALPAK® AD-10, CHIRALCEL® OB, CHIRALCEL® OB-H, CHIRALCEL® OD, CHIRALCEL® OD-H, CHIRALCEL® OF, CHIRALCEL® OG, CHIRALCEL® OJ and CHIRALCEL® OK.

[00302]  $^1\text{H}$ -NMR reported herein (*e.g.*, for the region between  $\delta$  (ppm) of about 0.5 to about 4 ppm) will be understood to be an exemplary interpretation of the NMR spectrum (*e.g.*,  
30 exemplary peak integrations) of a compound. Exemplary general method for preparative HPLC: Column: Waters RBridge prep 10  $\mu\text{m}$  C18, 19\*250 mm. Mobile phase: acetonitrile, water ( $\text{NH}_4\text{HCO}_3$ ) (30 L water, 24 g  $\text{NH}_4\text{HCO}_3$ , 30 mL  $\text{NH}_3\cdot\text{H}_2\text{O}$ ). Flow rate: 25 mL/min.

[00303] Exemplary general method for analytical HPLC: Mobile phase: A: water (10 mM  $\text{NH}_4\text{HCO}_3$ ), B: acetonitrile Gradient: 5%-95% B in 1.6 or 2 min Flow rate: 1.8 or 2 mL/min; Column: XBridge C18, 4.6\*50mm, 3.5  $\mu\text{m}$  at 45 C.

[00304] Exemplary general method for SFC: Column: CHIRALPAK® AD CSP (250 mm \* 30 mm, 10  $\mu\text{m}$ ), Gradient: 45% B, A=  $\text{NH}_3\text{H}_2\text{O}$ , B= MeOH, flow rate: 60 mL/min. For example, AD\_3\_EtOH\_DEA\_5\_40\_25ML would indicate: "Column: Chiralpak AD-3 150x4.6mm I.D., 3um Mobile phase: A:  $\text{CO}_2$  B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp: 35°C".

### EXAMPLE 1: NMDA potentiation

#### *NMDA potentiation*

#### Whole-cell Patch Clamp of Mammalian Cells (Ionworks Barracuda (IWB))

[00305] The whole-cell patch-clamp technique was used to investigate the effects of compounds on GluN1/GluN2A glutamate receptors expressed in mammalian cells.

[00306] HEK293 cells were transformed with adenovirus 5 DNA and transfected with cDNA encoding the human GRIN1/GRIN2A genes. Stable transfectants were selected using G418 and Zeocin-resistance genes incorporated into the expression plasmid and selection pressure maintained with G418 and Zeocin in the medium. Cells were cultured in Dulbecco's Modified Eagle Medium/Nutrient Mixture (D-MEM/F-12) supplemented with 10% fetal bovine serum, 100 $\mu\text{g}/\text{ml}$  penicillin G sodium, 100  $\mu\text{g}/\text{ml}$  streptomycin sulphate, 100 $\mu\text{g}/\text{ml}$  Zeocin, 5 $\mu\text{g}/\text{ml}$  blasticidin and 500 $\mu\text{g}/\text{ml}$  G418.

[00307] Test article effects were evaluated in 8-point concentration-response format (4 replicate wells/concentration). All test and control solutions contained 0.3% DMSO and 0.01% Kolliphor® EL (C5135, Sigma). The test article formulations were loaded in a 384-well compound plate using an automated liquid handling system (SciClone ALH3000, Caliper LifeSciences). The measurements were performed using Ion Works Barracuda platform following this procedure:

#### Electrophysiological Procedures:

[00308] Intracellular solution (mM): 50 mM CsCl, 90 mM CsF, 2 mM  $\text{MgCl}_2$ , 5 mM EGTA, 10 mM HEPES. Adjust to pH 7.2 with CsOH.

[00309] Extracellular solution, HB-PS (composition in mM): NaCl, 137; KCl, 1.0;  $\text{CaCl}_2$ , 5; HEPES, 10; Glucose, 10; pH adjusted to 7.4 with NaOH (refrigerated until use).

[00310] Holding potential: -70 mV, potential during agonist/PAM application: -40 mV.

#### Recording procedure:

[00311] Extracellular buffer is loaded into the PPC plate wells (11  $\mu$ L per well). Cell suspension will be pipetted into the wells (9  $\mu$ L per well) of the PPC planar electrode.

[00312] Whole-cell recording configuration is established via patch perforation with membrane currents recorded by on-board patch clamp amplifiers.

5 [00313] Two recordings (scans) are performed. First, during pre-application of test article alone (duration of pre-application - 5 min) and second, during test articles and agonist (EC<sub>20</sub> L-glutamate and 30  $\mu$ M glycine) co-application to detect positive modulatory effects of the test article.

[00314] Test Article Administration: The first pre-application consists of the addition of  
10 20  $\mu$ L of 2X concentrated test article solution and, second, of 20  $\mu$ L of 1X concentrated test article and agonist at 10  $\mu$ L/s (2 second total application time).

## EXAMPLE 2: NAM and PAM

### Whole-cell Patch Clamp of Mammalian Cells (Ionworks Barracuda (IWB))

15 The whole-cell patch-clamp technique was used to investigate the effects of positive allosteric modulating activity of test compounds on GluN1/GluN2A and GluN2B glutamate receptors expressed in mammalian cells.

HEK293 cells were transformed with adenovirus 5 DNA and transfected with cDNA encoding the human GRIN1/GRIN2A genes. Stable transfectants were selected using G418 and Zeocin-  
20 resistance genes incorporated into the expression plasmid and selection pressure maintained with G418 and Zeocin in the medium. Cells were cultured in Dulbecco's Modified Eagle Medium/Nutrient Mixture (D-MEM/F-12) supplemented with 10% fetal bovine serum, 100 $\mu$ g/ml penicillin G sodium, 100  $\mu$ g/ml streptomycin sulphate, 100 $\mu$ g/ml Zeocin, 5 $\mu$ g/ml blasticidin and 500 $\mu$ g/ml G418.

25 Test article effects were evaluated in 8-point concentration-response format (4 replicate wells/concentration). All test and control solutions contained 0.3% DMSO and 0.01% Kolliphor® EL (C5135, Sigma). The test article formulations were loaded in a 384-well compound plate using an automated liquid handling system (SciClone ALH3000, Caliper LifeSciences). The measurements were performed using Ion Works Barracuda platform following  
30 this procedure:

#### Electrophysiological Procedures:

- a) Intracellular solution (mM): 50 mM CsCl, 90 mM CsF, 2 mM MgCl<sub>2</sub>, 5 mM EGTA, 10 mM HEPES. Adjust to pH 7.2 with CsOH.

- b) Extracellular solution, HB-PS (composition in mM): NaCl, 137; KCl, 1.0; CaCl<sub>2</sub>, 5; HEPES, 10; Glucose, 10; pH adjusted to 7.4 with NaOH (refrigerated until use).
- c) Holding potential: -70 mV, potential during agonist/PAM application: -40 mV.

#### Recording procedure:

- 5 a) Extracellular buffer will be loaded into the PPC plate wells (11 µL per well). Cell suspension will be pipetted into the wells (9 µL per well) of the PPC planar electrode.
- b) Whole-cell recording configuration will be established via patch perforation with membrane currents recorded by on-board patch clamp amplifiers.
- 10 c) Two recordings (scans) will be performed. First, during pre-application of test article alone (duration of pre-application - 5 min) and second, during test articles and agonist (EC<sub>20</sub> L-glutamate and 30 µM glycine) co-application to detect positive modulatory effects of the test article.

Test Article Administration: The first pre-application will consist of the addition of 20 µL of 2X concentrated test article solution and, second, of 20 µL of 1X concentrated test article and agonist at 10 µL/s (2 second total application time).

#### Potentiating effect of positive allosteric modulators (PAM) on the channel

Potentiating effect of positive allosteric modulators (PAM) on the channel will be calculated as

$$20 \quad \% \text{ activation} = (I_{\text{PAM}} / I_{\text{EC}_{10-30}}) \times 100\% - 100\%$$

where  $I_{\text{PAM}}$  will be the L-glutamate EC<sub>10-30</sub> - elicited current in presence of various concentrations of test articles and  $I_{\text{EC}_{20}}$  will be the mean current elicited with L-glutamate EC<sub>20</sub>.

PAM concentration-response data will be fitted to an equation of the form:

$$25 \quad \% \text{ Activation} = \% \text{ L-glutamate EC}_{20} + \{(\% \text{ MAX} - \% \text{ L-glutamate EC}_{20}) / [1 + ([\text{Test}] / \text{EC}_{50})^N]\},$$

where [Test] will be the concentration of PAM (test article), EC<sub>50</sub> will be the concentration of PAM producing half-maximal activation, N will be the Hill coefficient, % L-glutamate EC<sub>20</sub> will be the percentage of the current Elicited with L-glutamate EC<sub>20</sub>, % MAX is the percentage of the current activated with the highest dose of PAM co-admitted with L-glutamate EC<sub>20</sub> and %  
30 Activation will be the percentage of the current elicited with L-glutamate EC<sub>10-30</sub> at each PAM concentration.

The maximal amplitude of the evoked currents are measured and defined as Peak Current Amplitude (PCA).

#### Automated patch-clamp system (QPatch HTX):

In this study, HEK 293 cells stably transfected with glutamate-activated channels of the GRIN1/2A subtype will be used together with submaximal NMDA concentrations (300  $\mu$ M NMDA, co-application with 8  $\mu$ M Glycine) to investigate the negative allosteric modulation of the test compounds.

#### *Cell Culture*

In general, cells will be passaged at a confluence of about 80% to-90%. For electrophysiological measurements cells will be harvested at a confluence of about 80% to 90% from sterile culture flasks containing culture complete medium. Cells will be transferred as suspension in PBS to the QPatch 16X or QPatch HTX system to the centrifuge / washer directly.

*Standard Laboratory Conditions:* Cells will be incubated at 37°C in a humidified atmosphere with 5% CO<sub>2</sub> (rel. humidity about 95%).

*Culture media:* The cells will be continuously maintained in and passaged in sterile culture flasks containing a 1:1 mixture of Dulbecco's modified eagle medium and nutrient mixture F-12 (D-MEM/F-12 1x, liquid, with L-Glutamine) supplemented with 10% fetal bovine serum, 1% Penicillin/Streptomycin solution, and 50  $\mu$ M AP-5 blocker.

*Antibiotics:* The complete medium as indicated above is supplemented with 100  $\mu$ g/mL hygromycin, 15  $\mu$ g/mL blasticidin and 1  $\mu$ g/mL puromycin.

*Induction of Expression:* 2.5  $\mu$ g/mL tetracycline is added 24 h before start of experiments.

#### *Dose Formulation*

Dose levels are in terms of test compounds, as supplied. Vehicle will be added to achieve a stock concentration of 10 mM (storage at -10°C to -30°C). A further stock solutions of 1.0 mM will be prepared in DMSO. Details of stock solution usage (thawing, dose formulations) will be documented in the raw data. The time period of stock solution usage will be detailed in the report.

#### *Test Compound Concentrations*

Dose levels are in terms of test compounds, as supplied. Vehicle will be added to achieve a stock concentration of 10 mM (storage at -10°C to -30°C). A further stock solutions of 1.0 mM will be prepared in DMSO. Details of stock solution usage (thawing, dose formulations) will be

documented in the raw data. The time period of stock solution usage will be detailed in the report.

One test concentration of 1.0  $\mu$ M will be tested.

- 5 All test solutions will be prepared by diluting the stock solutions with either Mg-free bath solution only or Mg-free bath solution containing NMDA (300  $\mu$ M) and glycine (8.0  $\mu$ M) shortly prior to the electrophysiological experiments and kept at room temperature (19°C to 30°C) when in use. 0.1% DMSO will be used as vehicle.

*Frequency of preparation:* For each test concentration, fresh solutions of test compounds will be prepared every day.

- 10 *Stability of dose formulation:* All preparation times will be documented in the raw data. Any observations regarding instability of test compounds will be mentioned in the raw data.

*Storage of dose formulation:* On the day of experimentation dose formulations will be maintained at room temperature (19°C to 30°C) when in use.

#### *Bath Solutions*

- 15 For preparing the experiments and for formation of the giga-ohm-seal, the following **standard bath solution** will be used:

Sodium Chloride: 137 mM; Potassium Chloride: 4 mM; Calcium Chloride: 1.8 mM;  
Magnesium Chloride: 1 mM; HEPES: 10 mM; D-Glucose: 10 mM; Cremophor: 0.02%; pH  
(NaOH): 7.4

- 20 The 1x bath solution will be prepared by diluting 10x bath solution without Glucose and 100x Glucose solution with water at least every 7 days. Both stock solutions have been prepared prior to the experimental start of the present study and stored at 1°C to 9°C (10x bath solution) or -10°C to -30° (100x Glucose solution). The batch number(s) of the bath solution(s) used in the experiments will be documented in the raw data. When in use, the 1x bath solution will be kept  
25 at room temperature (19°C to 30°C). When not in use, the 1x bath solution will be stored at 1°C to 9°C.

After the giga-seal was formed the following **Mg-free bath solution** will be used:

Sodium Chloride: 137 mM; Potassium Chloride: 4 mM; Calcium Chloride; 2.8 mM; HEPES: 10 mM; D-Glucose: 10 mM; **Cremophor**: 0.02%; pH (NaOH): 7.4

- 30 This Mg-free bath solution will be prepared as a 1x solution and stored at 1°C to 9°C. It will be prepared freshly at least every 10 days.

### *Intracellular Solution*

The 1x intracellular solution will be thawed every day out of a frozen 1x intracellular solution, which has been prepared prior to the experimental start of the present study, aliquoted and stored at -10°C to -30°C. When in use, the 1x intracellular solution will be kept at room temperature (19°C to 30°C). Remaining 1x intracellular solution will be stored in the fridge (1°C to 9°C). The 1x intracellular solution will include the components outlined below:

Potassium Chloride: 130 mM; Magnesium Chloride: 1 mM; Mg-ATP: 5 mM; HEPES: 10 mM; EGTA: 5 mM; pH (KOH): 7.2

### *Cell Treatment*

For this study, cells will continuously be perfused with NMDA/Glycine, Test Compound or Test Compound/NMDA/Glycin.

In every case, at least 30-second prewash steps with a test compound will be performed in between applications. For details see Table A below.

Each experiment type will be analyzed in at least n=3 isolated cells. The NMDA and Glycine stock solutions will be prepared prior to the experimental start of the present study, stored frozen (-10°C to -30°C) until the day of experimentation. Shortly prior to the electrophysiological experiments, frozen stock solutions will be thawed and diluted.

Control: The effect of vehicle (0.1% DMSO) and D-(-)-2-Amino-5-phosphonopentanoic acid (AP-5) (100 µM) will be measured at three cells every second week, in order to assure successful expression of NMDA receptors.

The 50 mM stock solution of AP-5 has been prepared prior to the experimental start of the present study, aliquoted and stored frozen (-10°C to -30°C) until the day of experimentation. Shortly prior to the electrophysiological experiments the frozen stock solution will be thawed and then diluted in Mg-free bath solution containing NMDA (300 µM) and glycine (8.0 µM), to give a final perfusion concentration of 100 µM.

### *Experimental Procedure*

Cells are transferred as suspension in serum-free medium to the QPatch HTX system and kept in the cell storage tank / stirrer during experiments. All solutions applied to cells including the intracellular solution will be maintained at room temperature (19°C to 30°C).

During the sealing process **standard bath solution** described above will be used. All solutions applied to cells including the pipette solution will be maintained at room temperature (19°C to

30°C). After formation of a Gigaohm seal between the patch electrodes and transfected individual HEK293 cells only **Mg-free bath solution** will be perfused and the cell membrane will be ruptured to assure electrical access to the cell interior (whole-cell patch-configuration).. Inward currents will be measured upon application of 300  $\mu$ M NMDA (and 8.0  $\mu$ M Glycine) to patch-clamped cells for 5 sec. During the entire experiment the cells will be voltage-clamped at a holding potential of -80 mV.

For the analysis of test compounds, NMDA receptors will be stimulated by 300  $\mu$ M NMDA and 8.0  $\mu$ M Glycine and test compound combinations described below. Thirty-second prewash steps with a test compound will be performed in between applications.

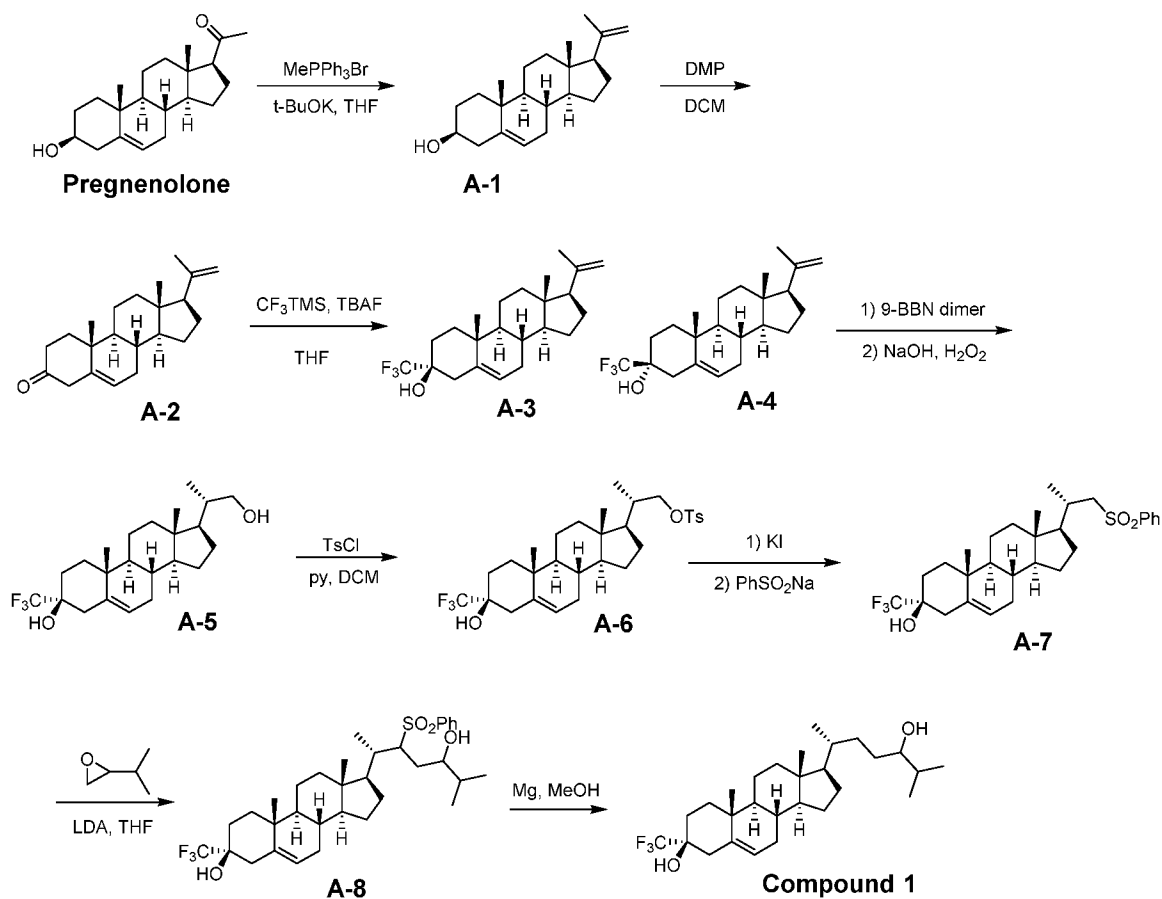
10 Table A: Application Protocol; use dependence of test compounds

Appl. #	Duration (s)	Application
1	4	NMDA / Glycine
2	30	Bath
3	4	NMDA / Glycine
2 repetitions		
4	30	1 $\mu$ M Test Compound
5	4	1 $\mu$ M Test Compound + NMDA / Glycine
6 repetitions		
6	30	Bath
7	4	NMDA / Glycine
2 repetitions		

Table B: Application Protocol; control experiments

Appl. #	Duration (s)	Application
1	4	NMDA / Glycine
2	30	Bath
3	4	NMDA / Glycine
2 repetitions		

4	30	Bath
5	4	NMDA / Glycine
6 repetitions		
6	30	Bath
7	4	NMDA / Glycine + 100 $\mu$ M AP-5
2 repetitions		

**EXAMPLE 3. Synthesis of Compound 1.**

- 5 [00315] **Step 1.** To a mixture of  $\text{MePPh}_3\text{Br}$  (1.28 kg, 3.6 mol) in THF (4.5 L) was added  $t\text{-BuOK}$  (404 g, 3.6 mol) at  $15^\circ\text{C}$  under  $\text{N}_2$ . The resulting mixture was stirred at  $50^\circ\text{C}$  for 30 mins. Pregnenolone (950 g, 2.9 mol) was added in portions below  $65^\circ\text{C}$ . The reaction mixture was stirred at  $50^\circ\text{C}$  for 1 hour. The combined mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous (1 L) at  $15^\circ\text{C}$ . THF layer was separated. The aqueous was extracted with  $\text{EtOAc}$  (2 x 2 L). The

combined organic phase was concentrated under vacuum to give a solid. The solid was further purified by trituration with MeOH/H<sub>2</sub>O (1:1, 15 L) at reflux to give **A-1** (940 g, 99%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.32 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 3.58-3.46 (m, 1H), 2.36-2.16 (m, 2H), 2.08-1.94 (m, 2H), 1.92-1.62 (m, 9H), 1.61-1.39 (m, 6H), 1.29-1.03 (m, 4H), 1.01 (s, 3H), 0.99-0.91 (m, 1H), 0.59 (s, 3H).

**[00316]** **Step 2.** To a solution of **A-1** (800 g, 2.54 mol) in DCM (8 L) was added DMP (2.14 kg, 5.08 mol) in portions at 35°C. The reaction mixture was stirred at 35°C for 20 mins. The reaction mixture was filtered. The filtered cake was washed with DCM (3 x 1 L). The combined organic phase was washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>/saturated NaHCO<sub>3</sub> aqueous (3:1, 2 x 1.5 L), brine (1.5 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **A-2** (794 g, crude) as a solid, which was used for next step directly.

**[00317]** **Step 3.** To a solution of TBAF (3.04 mL, 1 M in THF, 3.04 mmol, Aldrich) in THF (100 mL) was added TMSCF<sub>3</sub> (25.8 g, 182 mmol) followed by a solution of **A-2** (19 g, 60.8 mmol) in THF (100 mL) dropwise at 0°C. The mixture was stirred at 0°C for 30 mins. To the mixture was added TBAF (200 mL, 1 M in THF, 200 mmol) at 0°C. The mixture was stirred at 0°C for another 30 mins. To the mixture was added saturated aqueous NH<sub>4</sub>Cl (100 mL) and the mixture was concentrated in vacuum. To the residue was added PE/EtOAc (400 mL, 1:1), the organic layer was separated, which was combined with other two batches (2 x 10 g of **A-2**). The combined organic layer was washed with water (300 mL), brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give an oil. The residue was dissolved in DCM (150 mL) and diluted with PE (750 mL). The solution was poured into a silica gel column (500 g, 100~200 mesh) and eluted with PE:DCM:EtOAc = 5:1:0.05 to 5:1:0.1 to give **A-4** (12 g, 17% yield) as an oil and impure **A-3**. The impure **A-3** was re-crystallized from MeCN (250 mL) to give purified **A-3** (6.5 g) as a solid. **A-3** recovered from the MeCN filtrate was subjected to silica gel chromatography (PE:DCM:EtOAc = 50:1:1 to 20:1:1) to give a crude product which was re-crystallized from MeCN (20 mL) to give purified **A-3** (1 g, 16% total yield) as a solid.

**Note:** **A-3** and **A-4** were identified from <sup>3</sup>J<sub>H,CF<sub>3</sub></sub> (FDCS). (*J. Org. Chem.* **2015**, 80, 1754.).

**A-3:** **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.43-5.33 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H); 2.49 (s, 2H); 2.11-1.97 (m, 4H), 1.95-1.32 (m, 14H), 1.30-0.98 (m, 7H), 0.59 (s, 3H).

**A-4:** **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.54-5.41 (m, 1H), 4.86 (s, 1H), 4.72 (s, 1H); 2.78-2.65 (m, 1H); 2.18-1.97 (m, 3H), 1.95-1.35 (m, 16H), 1.32-0.98 (m, 7H), 0.59 (s, 3H).

**[00318]** **Step 4.** To a solution of **A-3** (8 g, 20.9 mmol) in THF (80 mL) was added 9-BBN dimer (5.85 g, 24 mmol). The mixture was stirred at 40°C for 1 h. The mixture was cooled to 0°C. To the mixture was added EtOH (12 mL), NaOH (41.8 mL, 5 M, aq.) and H<sub>2</sub>O<sub>2</sub> (20.9 mL, 10 M, aq.) dropwise. The mixture was stirred at 50°C for 1 h and then cooled. To the

mixture was added Na<sub>2</sub>SO<sub>3</sub> (100 mL, 25%, aq.). The mixture was extracted with EtOAc (300 mL). The organic layer was separated, purified by silica gel column (PE:EtOAc = 10:1 to 5:1) to give **A-5** (7.1 g, 85%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.32 (m, 1H), 3.64 (dd, *J* = 3.2, 10.4 Hz, 1H), 3.37 (dd, *J* = 6.8, 10.4 Hz, 1H), 2.49 (s, 2H), 2.32-1.92 (m, 4H), 1.92-1.70 (m, 4H), 1.70-1.29 (m, 8H), 1.29-0.91 (m, 11H), 0.71 (s, 3H).

**[00319]**        *Step 5.* To a solution of **A-5** (7.1 g, 17.7 mmol) in DCM (30 mL) and pyridine (21 mL) was added TsCl (6.74 g, 35.4 mmol). The mixture was stirred at 15°C for 2 hrs. To the mixture was added water (5 mL) and the mixture was stirred at 15°C for 2 hrs. The mixture was concentrated in vacuum. To the residue was added water (100 mL) and EtOAc (200 mL). The organic layer was separated, washed with HCl (100 mL, 0.1 M), water (100 mL) and brine (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **A-6** (9.8 g, 100%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.48-5.29 (m, 1H), 3.97 (dd, *J* = 2.4, 9.2 Hz, 1H), 3.77 (dd, *J* = 6.4, 9.2 Hz, 1H), 2.48 (s, 2H), 2.45 (s, 3H), 2.10-1.88 (m, 5H), 1.82-1.35 (m, 9H), 1.30-0.82 (m, 12H), 0.64 (s, 3H).

**[00320]**        *Step 6.* To a solution of **A-6** (1.05 g, 1.89 mmol) in DMF (5 mL) was added KI (1.25 g, 7.56 mmol). The mixture was stirred at 50°C for 1 h. To the mixture was added PhSO<sub>2</sub>Na (0.93 g, 5.67 mmol). The mixture was stirred at 50°C for 2 hrs. To the mixture was added water (10 mL) and DCM (30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum and triturated form PE/DCM (10 mL, 5:1) to give **A-7** (600 mg, 61%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.98-7.87 (m, 2H), 7.70-7.52 (m, 3H), 5.39-5.31 (m, 1H), 3.14 (d, *J* = 14.0 Hz, 1H), 2.85 (dd, *J* = 9.6, 14.0 Hz, 1H), 2.48 (s, 2H), 2.20-1.88 (m, 5H), 1.88-1.68 (m, 4H), 1.60-1.33 (m, 5H), 1.30-0.82 (m, 12H), 0.66 (s, 3H).

**[00321]**        *Step 7.* To a solution of i-Pr<sub>2</sub>NH (576 mg, 5.70 mmol) in THF (10 mL) was added n-BuLi (1.9 mL, 2.5 M in hexane, 4.75 mmol) at -70°C. The mixture was warmed to 0°C. A solution of **A-7** (1 g, 1.9 mmol) in THF (8 mL) was added at -70°C. The mixture was stirred at -70°C for 1 h. To the mixture was added a solution of 2-isopropylloxirane (245 mg, 2.85 mmol) in THF (2 mL) at -70°C. The mixture was stirred at -70°C for 1 h, warmed to 10°C and stirred at 10°C for 16 hrs. To the mixture was added NH<sub>4</sub>Cl (5 mL, sat. aq.). The mixture was extracted with EtOAc (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **A-8** (1.2 g crude) as an oil.

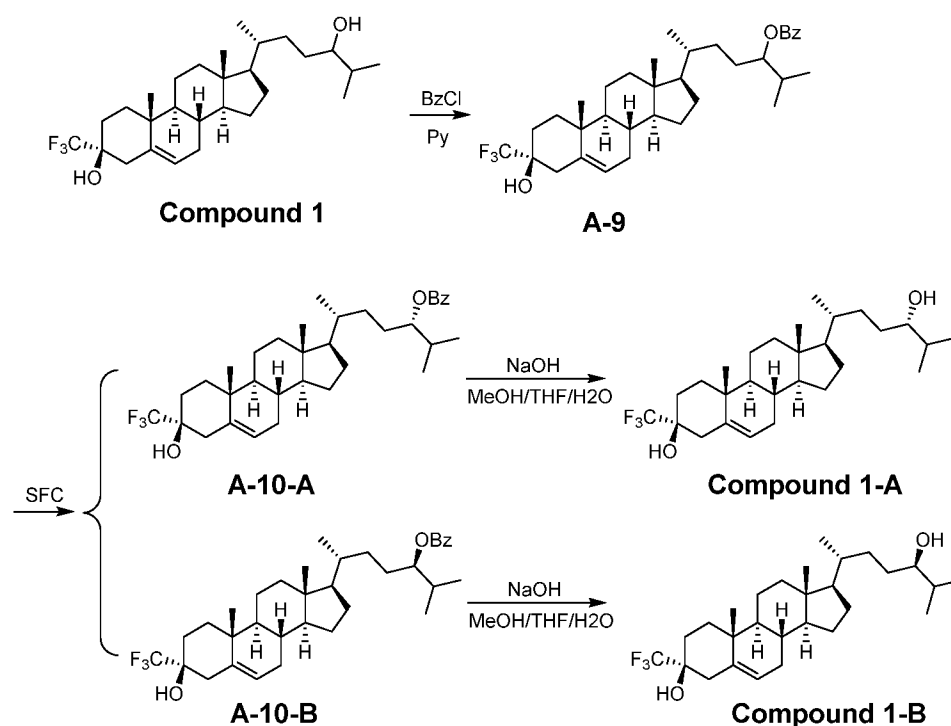
**[00322]**        *Step 8.* To a solution of **A-8** (1.2 g, 1.96 mmol) in MeOH (60 mL) was added NiBr<sub>2</sub> (5 mg, 0.023 mmol) and Mg powder (3.79 g, 156 mmol) was added in portions within 30

mins at 60°C. The mixture was stirred at 60°C for 10 mins. The mixture was poured into HCl (160 mL, 2 M) and extracted with PE/EtOAc (2 x 200 mL, 1:1). The combined organic layer was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum and purified by silica gel column (100~200 mesh, PE:EtOAc = 50:1 to 10:1) twice to give a crude product, which was purified by silica gel column (200~300 mesh, PE:DCM:acetone = 1:1:0.01) twice, re-crystallized from MeCN/water (3:1, 5 mL) to give **Compound 1** (50 mg, 5%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.41-5.32 (m, 1H), 3.39-3.28 (m, 1H), 2.49 (s, 2H), 2.10-1.92 (m, 4H), 1.90-1.60 (m, 5H), 1.55-1.33 (m, 8H), 1.31-1.10 (m, 6H), 1.09-0.90 (m, 15H), 0.68 (s, 3H).

LCMS Rt = 1.278 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>28</sub>H<sub>44</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 453, found 453.

#### EXAMPLE 4. Syntheses of Compounds 1-A and 1-B.



**[00323] Step 1.** To a solution of **Compound 1** (100 mg, 0.212 mmol) in pyridine (3 mL) was added benzoyl chloride (59.7 mg, 0.425 mmol) at 25°C. The reaction was stirred at 25°C for 16 hrs. The reaction was quenched by water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give crude product. The crude product was purified by a silica gel column (PE/EtOAc= 10/1) to give desired product **A-9** (150 mg, crude) as a solid.

LCMS Rt = 1.544 min in 2 min chromatography, 30-90 AB, MS ESI calcd. For C<sub>35</sub>H<sub>49</sub>F<sub>3</sub>O<sub>3</sub> [M+Na]<sup>+</sup> 597, found 597.

[00324] **Step 2.** **A-9** (580 mg, 1.00 mmol) was purified by SFC separation (column: AD (250 mm \* 30 mm, 5  $\mu$ m), gradient: 45% B (A=  $\text{NH}_3\text{H}_2\text{O}$ , B= MeOH), flow rate: 60 mL/min) to give **A-10-A** (200 mg, 34%, 95.5% d.e. by SFC (Column: Chiralpak AD-3 100 $\times$ 4.6mm I.D., 3 $\mu$ m, Mobile phase: A:  $\text{CO}_2$  B:iso-propanol (0.05% DEA).

5 Gradient: from 5% to 40% of B in 4.5min and hold 40%, for 2.5 min, then 5% of B for 1min. Flow rate: 2.8mL/min Column temperature:40°C)) as a solid and **A-10-B** (215 mg, 37%, 99.5% d.e. by SFC (Column: Chiralpak AD-3 100 $\times$ 4.6mm I.D., 3 $\mu$ m, Mobile phase: A:  $\text{CO}_2$  B:iso-propanol (0.05% DEA).

[00325] Gradient: from 5% to 40% of B in 4.5min and hold 40%, for 2.5 min, then 5% of  
10 B for 1min. Flow rate: 2.8mL/min Column temperature:40°C)) as a solid.

**A-10-A:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.07-8.02 (m, 2H), 7.58-7.52 (m, 1H), 7.48-7.41 (m, 2H), 5.37-5.35 (m, 1H), 4.99-4.94 (m, 1H), 2.48-2.46 (m, 2H), 2.04-1.89 (m, 4H), 1.82-1.65 (m, 5H), 1.51-1.35 (m, 7H), 1.27-1.08 (m, 4H), 1.05 (s, 4H), 1.02-0.92 (m, 13H), 0.64 (s, 3H).

**A-10-B:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.07-8.02 (m, 2H), 7.59-7.52 (m, 1H), 7.49-7.40 (m,  
15 2H), 5.37-5.35 (m, 1H), 5.01-4.92 (m, 1H), 2.48-2.46 (m, 2H), 2.03-1.90 (m, 5H), 1.83-1.66 (m, 3H), 1.83-1.66 (m, 1H), 1.51-1.37 (m, 8H), 1.23-1.11 (m, 3H), 1.05-1.00 (m, 5H), 0.99 - 0.90 (m, 12H), 0.66 (s, 3H).

[00326] **Step 2a.** To a solution of **A-10-A** (215 mg, 0.374 mmol) in THF (2 mL) and MeOH (2 mL) was added NaOH (400 mg, 10 mmol) and  $\text{H}_2\text{O}$  (2 mL) at 25°C. The solution was  
20 stirred at 50°C for 48 hrs. The reaction solution was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give crude product which was triturated with MeCN (2 x 5 mL) to give desired product **Compound 1-A** (148 mg, 84%) as a solid.

**Compound 1-A:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  5.38-5.36 (m, 1H), 3.33-3.31 (m, 1H), 2.49-2.48  
25 (m, 2H), 2.08-1.92 (m, 4H), 1.89-1.61 (m, 5H), 1.52-1.37 (m, 5H), 1.32-1.09 (m, 7H), 1.06-0.96 (m, 7H), 0.96-0.87 (m, 10H), 0.68 (s, 3H). LCMS Rt = 1.497 min in 2 min chromatography, 30-90 AB, MS ESI calcd. For  $\text{C}_{28}\text{H}_{44}\text{F}_3\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  453, found 453.

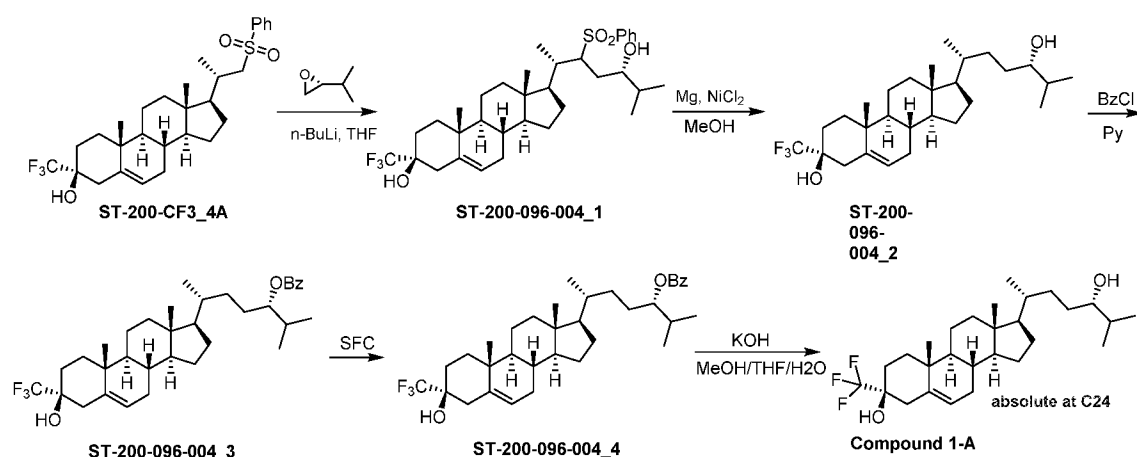
[00327] **Step 2b.** To a solution of **A-10-B** (200 mg, 0.348 mmol) in THF (2 mL) and MeOH (2 mL) was added NaOH (400 mg, 10 mmol) and  $\text{H}_2\text{O}$  (2 mL) at 25°C. The solution was  
30 stirred at 50°C for 48 hrs. The reaction solution was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give crude product, which was triturated with MeCN (2 x 5 mL) to give desired product **Compound 1-B** (139 mg, 85%) as a solid.

**Compound 1-B:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  5.38-5.36 (m, 1H), 3.33-3.31 (m, 1H), 2.49-2.48 (m, 2H), 2.12-1.92 (m, 5H), 1.89-1.40 (m, 12H), 1.29-1.11 (m, 5H), 1.09-0.98 (m, 6H), 0.95-0.89 (m, 10H), 0.69 (s, 3H)

**LCMS** Rt = 1.500 min in 2 min chromatography, 30-90 AB, MS ESI calcd. For  $\text{C}_{28}\text{H}_{44}\text{F}_3\text{O}$

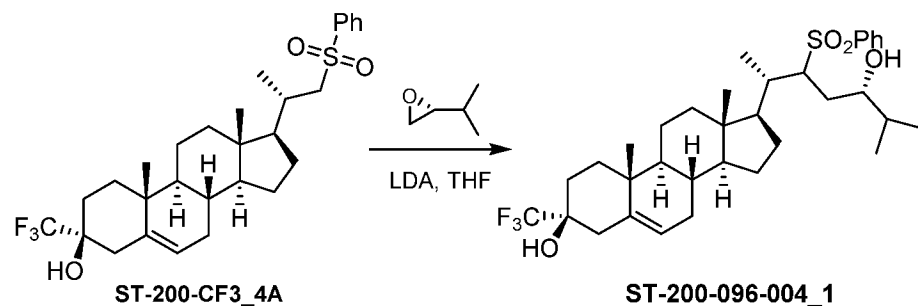
5  $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  453, found 453.

**[00328] Synthesis of Compound 1-A – absolute stereochemistry**



**[00329]** The experimental procedures of intermediate ST-200-CF3\_4A or A-7 can be found in Example 3.

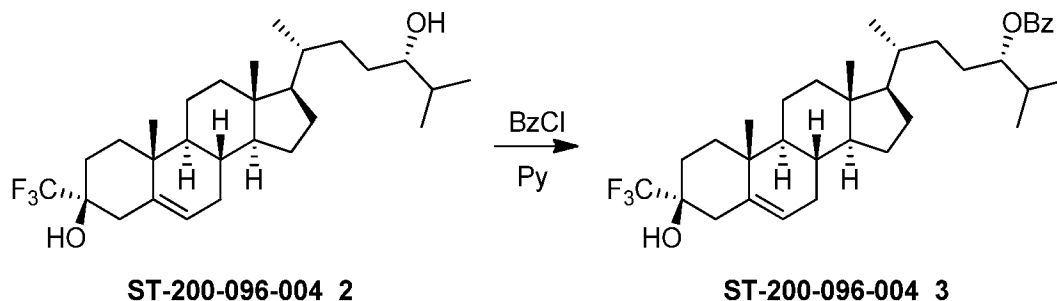
10 **[00330] Synthesis of ST-200-096-004\_1**



To a solution of ST-200-096-004\_1 (450 mg, 0.736 mmol) in methanol (30 mL) was added Mg powder (883 mg, 36.8 mmol) under  $\text{N}_2$  at  $65^\circ\text{C}$ . The reaction mixture was quenched with HCl (50 mL) dropwise until the solution became clear. The reaction solution was extracted with EtOAc (3 x 30mL). The combined organic layer was washed with sat.  $\text{NaHCO}_3$  (50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by flash column (0~12% of EtOAc in PE) to give ST-200-096-004\_2 (150 mg, 43%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.40-5.34 (m, 1H), 3.37-3.25 (m, 1H), 2.55-2.40 (m, 2H), 2.09-1.91 (m, 4H), 1.90-1.70 (m, 3H), 1.69-1.56 (m, 4H), 1.54-1.35 (m, 6H), 1.34-0.97 (m, 12H), 0.96-0.86 (m, 9H), 0.68 (s, 3H).

**[00331] Synthesis of ST-200-096-004\_3**



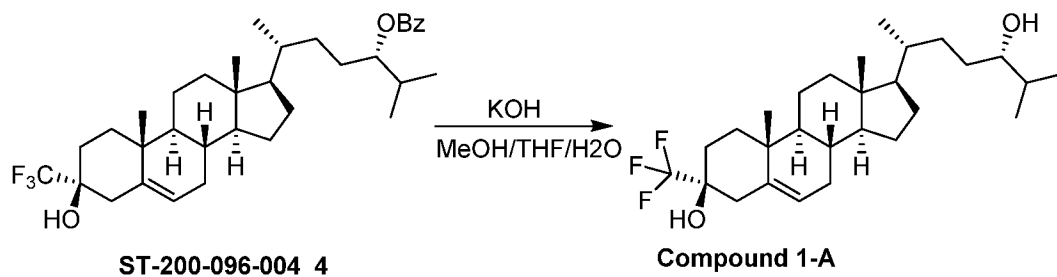
To a solution of **ST-200-096-004\_2** (150 mg, 0.318 mmol) in pyridine (3 mL) was added BzCl (134 mg, 0.954 mmol) at 0°C and the reaction was stirred at 25°C for 2 h. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 x 40 mL). The organic layer was washed with brine (5 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude was purified by silica gel column (PE/EtOAc = 10/1 to 4/1) to give **ST-200-096-004\_3** (120 mg, 66%) as a solid.

The **ST-200-096-004\_3** (120 mg, 0.208 mmol) was separated by SFC (column: AD (250mm\*30mm, 5um)), gradient: 25-25% B (0.1%NH<sub>3</sub>H<sub>2</sub>O IPA)) to give **ST-200-096-004\_4** (100 mg, 84%) as a solid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 8.05 (d, *J* = 8Hz, 2H), 7.55 (t, *J* = 8Hz, 1H), 7.44 (t, *J* = 8Hz, 2H), 5.38-5.34 (m, 1H), 4.98-4.91 (m, 1H), 2.48 (s, 2H), 2.09-1.89 (m, 4H), 1.86-1.67 (m, 4H), 1.53-1.34 (m, 10H), 1.17-1.00 (m, 7H), 0.99-0.91 (m, 12H), 0.64 (s, 3H).

SFC Rt = 3.473 min in 10 min chromatography, AD\_ IPA (DEA) \_5\_40\_2, 8ML\_8MIN, 100%de.

#### [00332] Synthesis of Compound 1-A



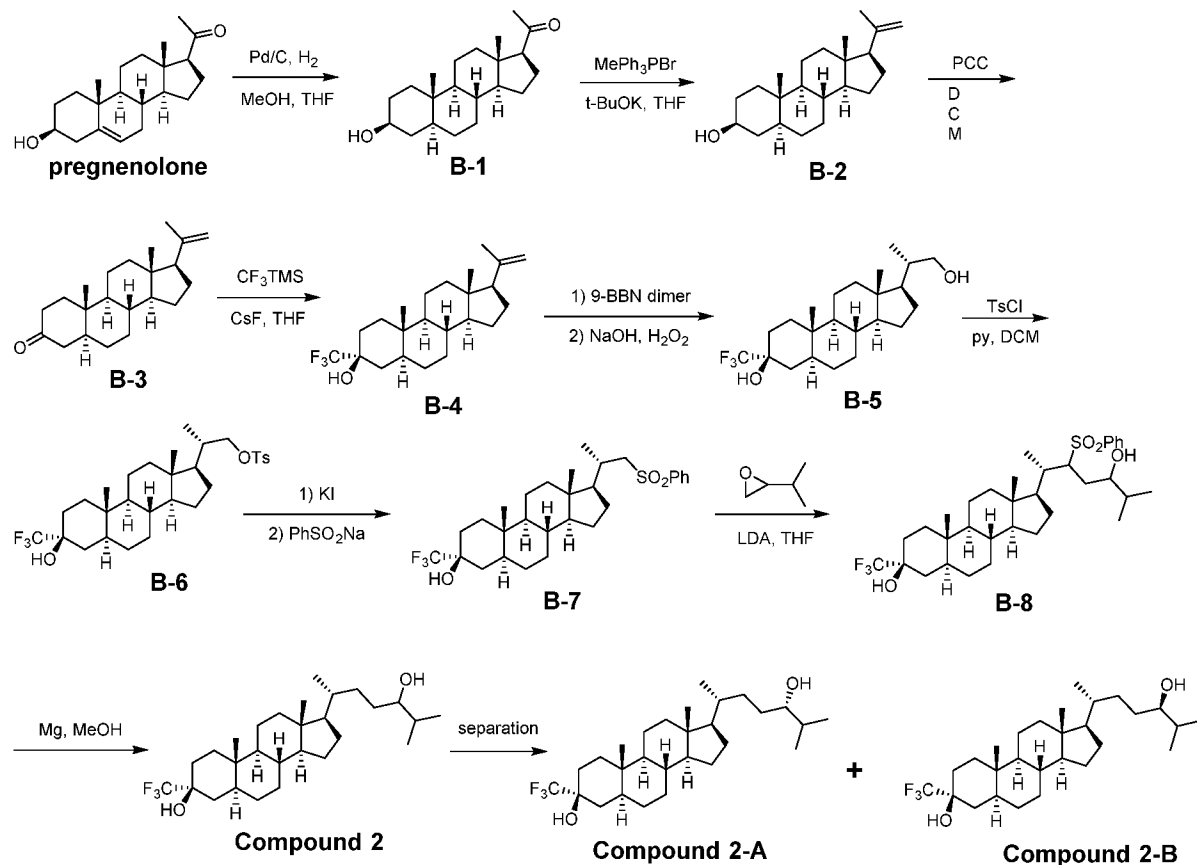
To a solution of **ST-200-096-004\_4** (100 mg, 0.173 mmol) in THF(2 mL) and MeOH (1 mL) and water(1 mL) was added KOH(48.5 mg, 0.865 mmol). The mixture was stirred at 60°C for 16 hrs. The mixture was poured into water (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layer was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (PE/EtOAc=5/1 to 3/1) to give **Compound 1-A** (48 mg, 59%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 3.35-3.28 (m, 1H), 2.49 (m, 2H), 2.09-1.93 (m, 4H), 1.89-1.59 (m, 6H), 1.54-1.22 (m, 10H), 1.20-0.97 (m, 9H), 0.95-0.89 (m, 9H), 0.68 (s, 3H).

LCMS Rt = 1.265 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For

5 C<sub>28</sub>H<sub>44</sub>F<sub>3</sub>O [M-H<sub>2</sub>O+H] = 453, found 453.

### EXAMPLE 5. Syntheses of Compounds 2, 2-A, and 2-B.



10 [00333] **Step 1.** To a solution of pregnenolone (50 g, 157 mmol) in THF (750 mL) and MeOH (500 mL) was added Pd/C (20 g, 10%, dry). The mixture was stirred under H<sub>2</sub> (25 psi) at 25°C for 72 hrs. The mixture was filtered. The filtrate was concentrated in vacuum to give **B-1** (47 g, 94%) as a solid.

15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.69-3.51 (m, 1H), 2.51 (t, *J* = 8.8 Hz, 1H), 2.21-2.12 (m, 1H), 2.11 (s, 3H), 2.05-1.98 (m, 1H), 1.88-1.77 (m, 1H), 1.77-1.53 (m, 6H), 1.48-1.08 (m, 11H), 1.05-0.85 (m, 2H), 0.80 (s, 3H), 0.73-0.63 (m, 1H), 0.60 (s, 3H).

[00334] **Step 2.** To a suspension of MePPh<sub>3</sub>Br (78.5 g, 220 mmol) in THF (250 mL) was added t-BuOK (24.6 g, 220 mmol). The mixture was stirred at 50°C for 1 h. To the mixture was added **B-1** (47 g, 147 mmol). The mixture was stirred at 50°C for 1 h. To the mixture was added

water (100 mL) and EA (500 mL). The organic layer was separated, concentrated in vacuum to give a crude product, which was triturated from MeOH/water (1000 mL, 1:1) at 50°C. The mixture was filtered after cooled and the solid was washed with MeOH/water (2 x 500 mL, 1:1), dried in vacuum to give **B-2** (45 g, 97%) as a solid.

5 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.84 (s, 1H), 4.70 (s, 1H), 3.69-3.51 (m, 1H), 2.08-1.98 (m, 1H), 1.88-1.62 (m, 10H), 1.61-1.50 (m, 2H), 1.48-0.85 (m, 13H), 0.81 (s, 3H), 0.70-0.60 (m, 1H), 0.56 (s, 3H).

[00335] **Step 3.** To a solution of **B-2** (45 g, 142 mmol) in DCM (500 mL) was added silica gel (90 g) and PCC (45.7 g, 213 mmol). The mixture was stirred at 20°C for 3 hrs. To the mixture was added PE (500 mL). The mixture was filtered through a pad of silica gel and the solid was washed with PE/DCM (1:1, 2 L). The combined filtrate was concentrated to give **B-3** (44 g, 98%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.85 (s, 1H), 4.71 (s, 1H), 2.48-2.20 (m, 3H), 2.12-1.98 (m, 3H), 1.90-1.49 (m, 10H), 1.47-1.08 (m, 8H), 1.01 (s, 3H), 0.99-0.71 (m, 2H), 0.58 (s, 3H).

15 **Step 4.** To a solution of **B-3** (20 g, 63.5 mmol) in THF (300 mL) was added CsF (19.2 g, 127 mmol). To the mixture was added TMSCF<sub>3</sub> (18.0 g, 127 mmol) dropwise at 10°C. The mixture was stirred at 10°C for 2 hrs. To the mixture was added TBAF (127 mL, 1 M in THF, 127 mmol) at 10°C. The mixture was stirred at 20°C for 3 hrs. To the mixture was added water (200 mL). The mixture was concentrated in vacuum to remove THF. To the residue was added EtOAc (300 mL). The organic layer was separated, washed with water (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum, triturated from PE:DCM (500 mL, 20:1), re-crystallized from MeCN (200 mL) to give **B-4** (7.1 g) as a solid. The filtrate of trituration and re-crystallization was combined, concentrated in vacuum, purified by silica gel column (PE:EtOAc = 30:1 to 10:1) twice to give impure **B-4** which was re-crystallized from MeCN (200 mL) to give **B-4** (7.6 g, total yield 60%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.84 (s, 1H), 4.70 (s, 1H), 2.11-1.98 (m, 3H), 1.88-1.47 (m, 13H), 1.45-1.05 (m, 9H), 1.00-0.89 (m, 1H), 0.85 (s, 3H), 0.78-0.68 (m, 1H), 0.56 (s, 3H).

[00336] **Step 5.** To a solution of **B-4** (14.7 g, 38.2 mmol) in THF (150 mL) was added 9-BBN dimer (10.7 g, 43.9 mmol). The mixture was stirred at 40°C for 1 h. The mixture was cooled to 0°C. To the mixture was added EtOH (21.8 mL), NaOH (76.3 mL, 5 M, aq.) and H<sub>2</sub>O<sub>2</sub> (38.1 mL, 10 M, aq.) dropwise. The mixture was stirred at 50°C for 1 h. To the mixture was added Na<sub>2</sub>SO<sub>3</sub> (200 mL, 25%, aq.) after cooled. The mixture was extracted with EtOAc (500 mL). The organic layer was separated, concentrated in vacuum and triturated from water (400 mL) to give **B-5** (15 g, 98%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.68-3.58 (m, 1H), 3.40-3.30 (m, 1H), 2.11-1.91 (m, 2H), 1.89-1.72 (m, 2H), 1.70-1.45 (m, 8H), 1.42-1.06 (m, 11H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.00-0.88 (m, 2H), 0.85 (s, 3H), 0.75-0.68 (m, 1H), 0.67 (s, 3H).

[00337] **Step 6.** To a solution of **B-5** (15 g, 17.7 mmol) in DCM (60 mL) and pyridine (42 mL) was added TsCl (14.1 g, 74.4 mmol). The mixture was stirred at 15°C for 2 hrs. To the mixture was added water (2 mL) and the mixture was stirred at 15°C for 16 hrs. To the mixture was added water (100 mL). The mixture was extracted with PE/EtOAc (2:1, 300 mL). The organic layer was separated, washed with HCl (200 mL, 1 M), water (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **B-6** (23 g, crude) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.96 (dd, *J* = 3.2, 9.2 Hz, 1H), 3.76 (dd, *J* = 6.8, 9.2 Hz, 1H), 2.45 (s, 3H), 2.10-1.98 (m, 1H), 1.92-1.78 (m, 2H), 1.71-1.30 (m, 11H), 1.30-0.88 (m, 13H), 0.83 (s, 3H), 0.72-0.62 (m, 1H), 0.61 (s, 3H).

[00338] **Step 7.** To a solution of **B-6** (23 g, 41.3 mmol) in DMF (100 mL) was added KI (27.3 g, 165 mmol). The mixture was stirred at 50°C for 1 h. To the mixture was added PhSO<sub>2</sub>Na (20.1 g, 123 mmol). The mixture was stirred at 50°C for 16 hrs. To the mixture was added DCM (200 mL), water (400 mL) and PE (2:1, 400 mL) with stirring. The organic layer was separated, washed with water (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to 150 mL in vacuum and a solid was formed. The mixture was filtered, washed with PE (100 mL), dried in vacuum to give **B-7** (12 g, 55%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95-7.88 (m, 2H), 7.70-7.61 (m, 1H), 7.60-7.51 (m, 2H), 3.13 (d, *J* = 13.2 Hz, 1H), 2.84 (dd, *J* = 9.2, 14.0 Hz, 1H), 2.20-1.89 (m, 4H), 1.88-1.44 (m, 8H), 1.43-0.88 (m, 15H), 0.83 (s, 3H), 0.72-0.65 (m, 1H), 0.63 (s, 3H).

[00339] **Step 8.** To a solution of i-Pr<sub>2</sub>NH (573 mg, 5.67 mmol) in THF (10 mL) was added BuLi (1.88 mL, 2.5 M in hexane, 4.72 mmol) at -70°C. The mixture was warmed to 0°C.

A solution of **B-7** (1 g, 1.89 mmol) in THF (8 mL) was added at -70°C. The mixture was stirred at -70°C for 1 h. To the mixture was added a solution of 2-isopropylloxirane (243 mg, 2.83 mmol) in THF (2 mL) at -70°C. The mixture was stirred at -70°C for 1 h, 10°C for 16 hrs and 50°C for 2 hrs. To the mixture was added NH<sub>4</sub>Cl (5 mL, sat. aq.). The mixture was extracted with EtOAc (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum and purified by silica gel column (PE:EtOAc=12:1 to 8:1) to give **B-8** (0.5 g, 43%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95-7.85 (m, 2H), 7.70-7.52 (m, 3H), 3.63-3.46 (m, 1H), 3.44-3.31 (m, 1H), 2.18-1.61 (m, 8H), 1.55-1.11 (m, 13H), 1.11-0.78 (m, 18H), 0.72-0.60 (m, 2H), 0.50-0.40 (m, 3H).

[00340] **Step 9.** To a solution of **B-8** (0.5 g, 0.815 mmol) in MeOH (50 mL) was added NiBr<sub>2</sub> (2 mg, 0.009 mmol). Then magnesium powder (2.22 g, 91.4 mmol) was added in portions

within 30 mins at 60°C. The mixture was stirred at 60°C for 1 h. The mixture was poured into citric acid (200 mL, 10% aq.) and extracted with PE/EtOAc (2 x 200 mL, 1:1). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum, purified by silica gel column (PE:EtOAc = 20:1 to 10:1) to give

5 **Compound 2** (290 mg, 67%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.37-3.28 (m, 1H), 2.12-2.01 (m, 1H), 2.00-1.91 (m, 2H), 1.87-1.77 (m, 2H), 1.71-1.58 (m, 5H), 1.50-1.00 (m, 19H), 0.96-0.88 (m, 10H), 0.85 (s, 3H), 0.72-0.67 (m, 1H), 0.67-0.64 (m, 3H). **LCMS** Rt = 1.340 min in 2.0 min chromatography, 30-90 AB, No MS signal. **HRMS** ESI calcd. for C<sub>28</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 455.3495, found 455.3489.

10 **[00341]** **Step 10.** **Compound 2** (264 mg) was separated by silica gel column twice (300~400 mesh, 30\*250mm, PE:EtOAc=30:1 to 15:1) to give **Compound 2-A** (56 mg, 21%) and **Compound 2-B** (101 mg, 38%) both as solids.

**[00342]** The diastereomeric ratio of **2-A** and **2-B** was assessed by conversion of the alcohol to a benzoate ester: To a solution of **Compound 2-B** (8 mg, 0.017 mmol) in DCM (0.5 mL) was added pyridine (132 mg, 1.68 mmol) and BzCl (23.7 mg, 0.169 mmol). The mixture was stirred at 25°C for 20 mins. To the mixture was added PE (5 mL). The mixture was washed with NaHCO<sub>3</sub> (2 mL, sat. aq.), HCl (2 mL, 1M, aq.), NaHCO<sub>3</sub> (2 mL, sat. aq.), purified by prep-TLC (PE:DCM=1:1) to give **2-B-Bz** for SFC analysis (98.7% de ("Column: Chiralpak AD-3 150x4.6mm I.D., 3um Mobile phase: A: CO<sub>2</sub> B:iso-propanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35oC")).

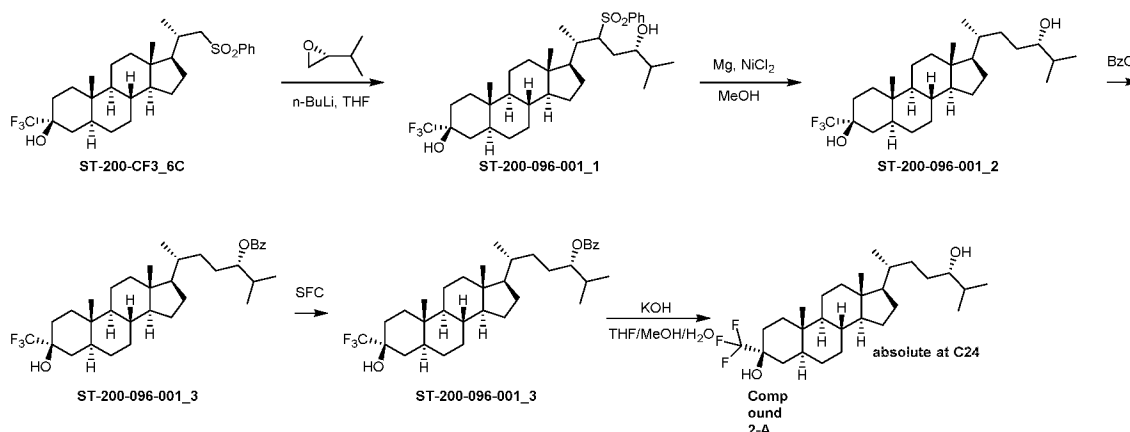
**[00343]** To a solution of **Compound 2-A** (3 mg, 0.006 mmol) in DCM (0.5 mL) was added pyridine (50 mg, 0.633 mmol) and BzCl (8.9 mg, 0.063 mmol). The mixture was stirred at 25°C for 20 mins. To the mixture was added PE (5 mL). The mixture was washed with NaHCO<sub>3</sub> (2 mL, sat. aq.), HCl (2 mL, 1M, aq.), NaHCO<sub>3</sub> (2 mL, sat. aq.), purified by prep-TLC (PE:DCM=1:1) to give **2-A-Bz** for SFC analysis (95.0% d.e. (Column: Chiralpak AD-3 150x4.6mm I.D., 3um Mobile phase: A: CO<sub>2</sub> B:iso-propanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35 °C)).

30 **Compound 2-A:** **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.37-3.28 (m, 1H), 2.12-2.01 (m, 1H), 2.00-1.91 (m, 2H), 1.87-1.77 (m, 2H), 1.71-1.58 (m, 5H), 1.50-1.00 (m, 19H), 0.96-0.88 (m, 10H), 0.85 (s, 3H), 0.72-0.67 (m, 1H), 0.65 (s, 3H). **LCMS** Rt = 1.329 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>28</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 455, found 455.

**Compound 2-B:** **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.37-3.28 (m, 1H), 2.12-2.01 (m, 1H), 2.00-1.91 (m, 2H), 1.87-1.77 (m, 2H), 1.71-1.58 (m, 4H), 1.50-1.30 (m, 10H), 1.30-1.00 (m, 10H),

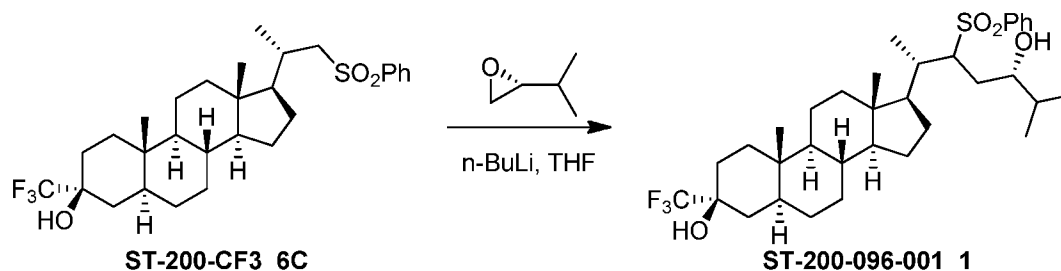
0.96-0.88 (m, 10H), 0.85 (s, 3H), 0.72-0.67 (m, 1H), 0.66 (s, 3H). LCMS Rt = 1.333 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for  $C_{28}H_{46}F_3O$   $[M+H-H_2O]^+$  455, found 455.

**[00344] Synthesis of Compound 2-A – absolute stereochemistry**



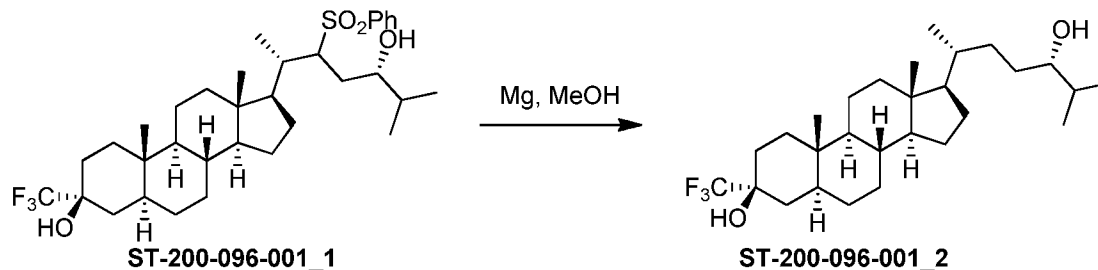
- 5 **[00345]** The experimental procedures of intermediate **ST-200-CF3\_6C** can be found Example 5.

**[00346] Synthesis of ST-200-096-001\_1**



- 10 To THF (1 mL) was added n-BuLi (0.948 mL, 2.5 M in hexane, 2.37 mmol), followed by adding a solution of **ST-200-CF3\_6C** (500 mg, 0.949 mmol) in THF (4 mL) at  $-70^{\circ}\text{C}$ . After stirring at  $-70^{\circ}\text{C}$  for 30 mins, (2R)-2-(propan-2-yl)oxirane (122 mg, 1.42 mmol) was added at  $-70^{\circ}\text{C}$ . The mixture was warmed to  $25^{\circ}\text{C}$  gradually and stirred at  $25^{\circ}\text{C}$  for 16 hrs. The mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  (15 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give **ST-200-096-001\_1** (560 mg, crude) as an oil, which was used directly for next step.

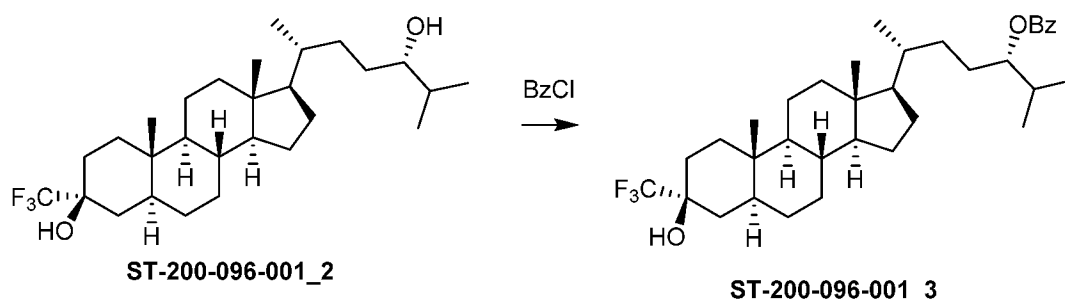
**[00347] Synthesis of ST-200-096-001\_2**



To a solution of **ST-200-096-001\_1** (560 mg, 0.913 mmol) in methanol (30 mL) was added Mg powder (1.09 g, 45.6 mmol) under N<sub>2</sub> at 65°C. The reaction mixture was quenched with HCl (60 mL) dropwise until the solution became clear. The reaction solution was extracted with EtOAc (3 x 30mL). The combined organic layer was washed with sat. NaHCO<sub>3</sub> (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~12% of EtOAc in PE) to give **ST-200-096-001\_2** (150 mg, 46%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.35-3.26 (m, 1H), 2.10-1.91 (m, 3H), 1.88-1.76 (m, 2H), 1.71-1.62 (m, 4H), 1.52-1.35 (m, 6H), 1.32-1.20 (m, 7H), 1.17-0.98 (m, 6H), 0.95-0.87 (m, 10H), 0.86-0.80 (m, 4H), 0.72-0.61 (m, 4H).

#### 10 [00348] Synthesis of ST-200-096-001\_3



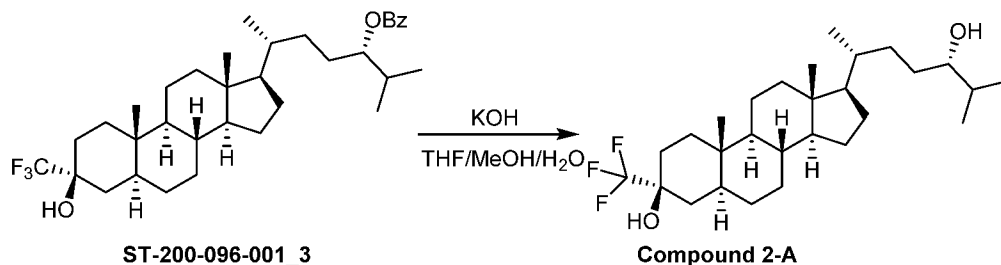
To a solution of **ST-200-096-001\_2** (200 mg, 0.423 mmol) in pyridine (3 mL) was added BzCl (177 mg, 1.26 mmol) at 0°C and the reaction was stirred at 25°C for 2 h. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 x 40 mL). The organic layer was washed with brine (5 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude was purified by silica gel column (PE/EtOAc = 10/1 to 4/1) to give **ST-200-096-001\_3** (150 mg, 62%) as an oil.

The **ST-200-096-001\_3** (150 mg, 0.26 mmol) was separated by SFC (column: AD (250mm\*30mm, 5um)), gradient: 30-30% B (A = 0.1%NH<sub>3</sub>H<sub>2</sub>O IPA)) to give **ST-200-096-001\_3** (120 mg, 81%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.05 (d, *J* = 8Hz, 2H), 7.55 (t, *J* = 8Hz, 1H), 7.44 (t, *J* = 8Hz, 2H), 4.98-4.91 (m, 1H), 2.09-1.89 (m, 4H), 1.86-1.61 (m, 6H), 1.53-1.34 (m, 8H), 1.27-1.03 (m, 8H), 0.99-0.95 (m, 8H), 0.92-0.83 (m, 7H), 0.71-0.61 (m, 4H).

SFC Rt = 4.117 min in 10 min chromatography, AD\_3\_IPA\_EtOH\_5\_40\_25ML, 99%de.

#### 25 [00349] Synthesis of Compound 2-A

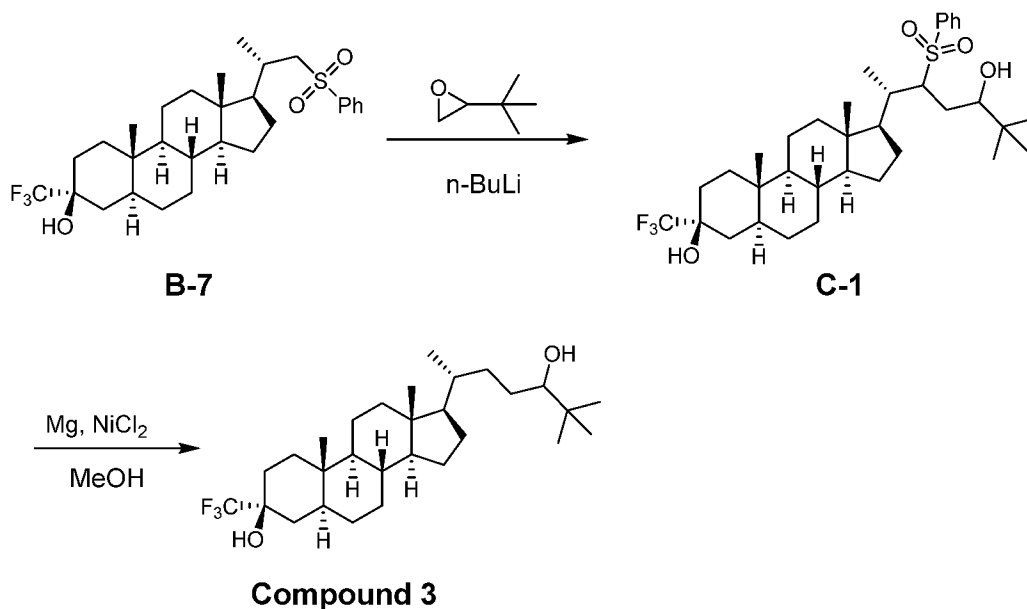


To a solution of **ST-200-096-001\_3** (120 mg, 0.208 mmol) in THF (2 mL) and MeOH (1 mL) and water (1 mL) was added KOH (57.7 mg, 1.03 mmol). The mixture was stirred at 60°C for 16 hrs, poured into water (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layer was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (PE/EtOAc=5/1 to 3/1) to give **Compound 2-A** (82 mg, 83%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.34-3.28 (m, 1H), 2.10-1.92 (m, 3H), 1.88-1.75 (m, 2H), 1.71-1.60 (m, 5H), 1.54-1.34 (m, 7H), 1.32-0.98 (m, 12H), 0.93-0.87 (m, 10H), 0.85 (s, 3H), 0.74-0.68 (m, 1H), 0.65 (s, 3H).

MS MS ESI calcd. For C<sub>28</sub>H<sub>47</sub>F<sub>3</sub>O<sub>2</sub>Na [M+Na<sup>+</sup>] = 495, found 495.

#### EXAMPLE 6. Synthesis of Compound 3.

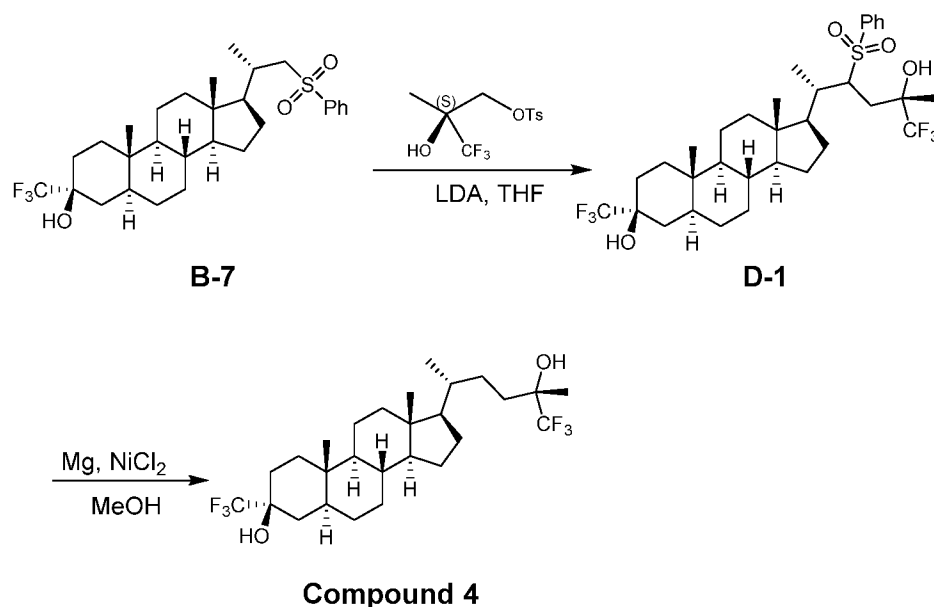


**[00350]** *Step 1.* To a solution of n-BuLi (568 μL, 2.5 M in hexane, 1.42 mmol) in THF (0.5 mL) at -65°C under N<sub>2</sub> was added a suspension of **B-7** (300 mg, 0.5695 mmol) in THF (2.5 mL) drop-wise. The mixture was stirred for 30 minutes at -65°C. 2-(tert-butyl)oxirane (68.4 mg, 0.6834 mmol) was added drop-wise at -65°C. The mixture was stirred for another 30 minutes and then warmed to 25°C gradually and stirred at 25°C for 16 hours. The reaction mixture was

quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL), extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **C-1** (380 mg, crude) as a solid, which was used directly for the next step.

- 5 **[00351]** **Step 2.** To a solution of **C-1** (380 mg, 0.6062 mmol) and  $\text{NiCl}_2$  (7.81 mg, 0.06062 mmol) in dry methanol (20 mL) was added Mg powder (580 mg, 24.2 mmol) in 4 portions under  $\text{N}_2$  with stirring at  $50^\circ\text{C}$ . The reaction mixture was stirred at  $60^\circ\text{C}$  for 1 hour. The reaction mixture was cooled and poured into ethyl acetate (150 mL). The mixture was washed with 1 M  $\text{HCl}$  (3 x 200 mL), saturated  $\text{NaHCO}_3$  aqueous (200 mL), brine (200 mL), dried over  $\text{Na}_2\text{SO}_4$ ,  
 10 filtered and concentrated under vacuum to give a solid, which was purified by silica gel chromatography (PE:EtOAc=8:1) to afford impure **Compound 3** (310 mg) as a solid, which was purified by triturating in PE/DCM (15 mL/1 mL) to give **Compound 3** (46 mg, 15%) as a solid.  
 $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.16-3.05 (m, 1H), 2.09-2.01 (m, 1H), 2.01-1.92 (m, 2H), 1.89-1.76 (m, 2H), 1.73-1.60 (m, 3H), 1.52-1.33 (m, 8H), 1.32-0.93 (m, 12H), 0.93-0.87 (m, 12H),  
 15 0.85 (s, 4H), 0.73-0.61 (m, 4H).  
 $^{19}\text{F NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  78.66.  
**LCMS**  $R_t$  = 1.354 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for  $\text{C}_{29}\text{H}_{48}\text{F}_3\text{O}$  [ $\text{M}-\text{H}_2\text{O}+\text{H}$ ] $^+$  469, found 469.

## 20 **EXAMPLE 7. Synthesis of Compound 4.**



- [00352]** **Step 1.** To a solution of diisopropylamine (0.2 mL) in THF (0.2 mL) was added butyllithium (0.57 mL, 2.5 M in n-hexane) at  $-70^\circ\text{C}$ . The mixture was warmed to  $25^\circ\text{C}$  and

stirred at 25°C for 30 minutes. The mixture was cooled to -70°C and a solution of **B-7** (250 mg, 16.5 mmol) in THF (3 mL) was added. After stirring at -70°C for 1 h, (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate, see Example 30. (169 mg, 0.57 mmol) was added at -70°C. The mixture was warmed to 25°C and stirred at this temperature for 16 hours.

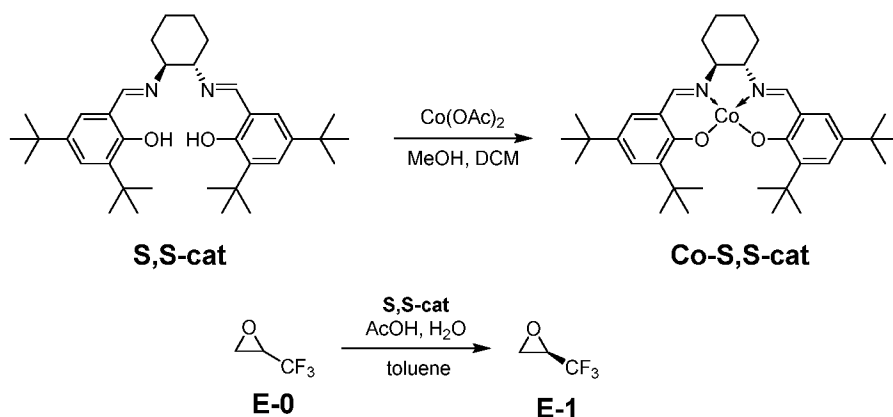
- 5 The mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (5 mL). The mixture was extracted with EtOAc (2 x 8 mL), washed with brine (2 x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum to give a crude product **D-1** (300 mg, crude) as an oil, which was used in the next step directly.

- [00353] **Step 2.** To a solution of **D-1** (300 mg, crude) in MeOH (15 mL) was added Mg powder (549 mg, 22.9 mmol) and NiCl<sub>2</sub> (5 mg) at 60°C. The mixture was stirred at 60°C for 1h. EtOAc (20 mL) and aq. HCl (30 mL) was added. The mixture was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water (3 x 50 mL), sat. NaHCO<sub>3</sub> (2 x 50 mL), brine (2 x 50 mL) to give a crude product, which was purified by flash column (0-30% of EtOAc in PE) to give **Compound 4** (100 mg, impure), which was triturated with CH<sub>3</sub>CN (5 mL) at 25°C to give **Compound 4** (50 mg, 50%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.10-1.90 (m, 3H), 1.85-1.75 (m, 3H), 1.70-1.60 (m, 5H), 1.50-1.30 (m, 6H), 1.25-1.00 (m, 14H), 0.90-0.80 (m, 7H), 0.70-0.55 (m, 4H).

LCMS Rt = 1.264 min in 2 min chromatography, 30-90 AB, MS ESI calcd. For C<sub>27</sub>H<sub>41</sub>F<sub>6</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 495, found 495.

## 20 EXAMPLE 8. Synthesis of Compound E-1.



[00354] **Step 1.** To a solution of **S,S-cat** (2 g, 3.65 mmol) in anhydrous DCM (30 mL) was added a solution of cobalt(II) acetate (775 mg, 4.38 mmol) in MeOH (30 mL) under nitrogen at 20°C. The mixture was stirred for 30 mins at 20°C and at 0°C for 1 h. The

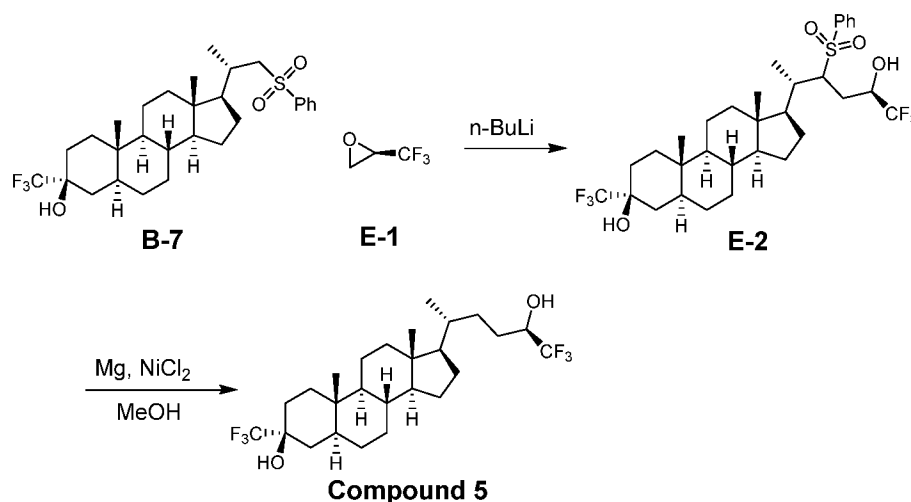
precipitated solid was filtered, washed with cold MeOH (2 x 30 mL) and dried in vacuum to give **Co-S,S-cat** (1.6 g, 73%) as a solid.

**[00355]** *Step 2.* To a solution of **Co-S,S-cat** (1.07 g, 1.78 mmol) in toluene (30 mL) was added AcOH (1.12 g, 18.7 mmol). The mixture was stirred at 20°C for 30 mins. The solution was concentrated in vacuum to give a solid. The resulting catalyst residue was dissolved in neat **E-0** (100 g, 892 mmol) at 20°C, the reaction mixture was cooled to 0°C, and water (8.82 g, 490 mmol) was added dropwise. The mixture was warmed to 20°C and stirred for 48 hrs. **E-1** (44 g) was isolated by distillation from the reaction mixture.

**[00356]**  $^1\text{H NMR}$  (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.96 (s, 1H), 3.11-2.98 (m, 2H).

The e.e. of **E-1** was determined by opening the epoxide with benzylamine. **E-1** (200 mg, 1.78 mmol) was added to dry benzylamine (190 mg, 1.78 mmol), and the mixture was stirred at 20°C for 2 hrs. A solid precipitated, which was triturated from petroleum ether to afford the product (260 mg, 67%) as a solid. The e.e. of this product was determined to be 100% by chiral HPLC (Column: CD-PH 250\*4.6mm I.D., 5 $\mu$ m; Mobile phase: from 10% to 80% of B in A (A:Water with 0.069% TFA B:Acetonitrile); Flow rate: 0.8mL/min; Column Temperature : 30 °C).

#### EXAMPLE 9. Synthesis of Compound 5.



**[00357]** *Step 1.* To a solution of *n*-BuLi (0.704 mL, 2.5 M in hexane, 1.76 mmol) in THF (0.5 mL) at -65°C under N<sub>2</sub> was added a suspension of **B-7** (310 mg, 0.588 mmol) in THF (2.5 mL) dropwise and the reaction was stirred for 30 minutes at -65°C. A solution of **E-1** (78.9 mg, 0.705 mmol) was added dropwise at -65°C. The mixture was stirred for another 30 minutes and then warmed to 25°C gradually and stirred at 25°C for 16 hours. The reaction mixture was quenched by saturated NH<sub>4</sub>Cl aqueous (30 mL), extracted with ethyl acetate (3 x 20 mL). The

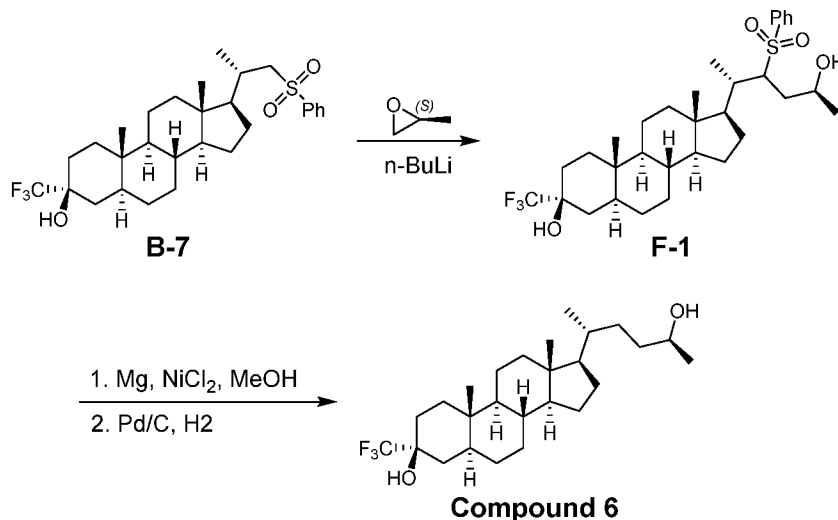
combined organic phase was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **E-2** (300 mg, crude) as a solid, which was used directly for the next step.

**[00358]** *Step 2.* To a solution of **E-2** (300 mg, 0.469 mmol) and nickel (II) chloride (15.1 mg, 0.117 mmol) in dry methanol (20 mL) was added magnesium powder (454 mg, 18.7 mmol) under N<sub>2</sub> with stirring at 50°C to initiate continuous hydrogen generation. The reaction mixture was stirred at 60°C for 1 hour. The reaction mixture was quenched by 2M HCl (100 mL) dropwise at 10 °C until the solid was dissolved. After extracting with EtOAc (2 x 150 mL), the combined organic layer was washed with sat. NaHCO<sub>3</sub> aq. (300 mL), brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a solid, which was purified by silica gel chromatography (PE:THF=12:1) to give the product. The residue was re-crystallized from MeCN (10 mL) to afford **Compound 5** (41 mg, 18%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.75-3.65 (m, 1H), 2.10-1.95 (m, 3H), 1.90-1.75 (m, 2H), 1.73-1.66 (m, 5H), 1.56-1.30 (m, 14H), 1.29-1.01 (m, 5H), 1.00-0.85 (m, 3H), 0.84 (s, 3H), 0.67-0.60 (m, 4H).

LCMS Rt = 1.226 min in 2.0 min chromatography, 30-90 AB.

#### EXAMPLE 10. Synthesis of Compound 6.



**[00359]** *Step 1.* To a solution of *n*-BuLi (0.568 mL, 2.5 M in hexane, 1.42 mmol) in THF (0.5 mL) at -65°C under N<sub>2</sub> was added a suspension of **B-7** (250 mg, 0.474 mmol) in THF (2.5 mL) dropwise. After stirring at -65°C for 30 minutes, a solution of (2*S*)-2-methyloxirane (32.9 mg, 0.568 mmol) was added dropwise at -65°C. The mixture was stirred for another 30 minutes and then warmed to 25°C gradually and stirred at 25°C for 16 hours. The reaction mixture was

quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL), and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **F-1** (250 mg, crude) as a solid, which was used directly for the next step.

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**[00360]**      *Step 2.* To a solution of **F-1** (250 mg, 0.427 mmol) and nickel (II) chloride (13.7 mg, 0.106 mmol) in dry methanol (20 mL) was added magnesium powder (413 mg, 17.0 mmol) under  $\text{N}_2$  with stirring at  $50^\circ\text{C}$  to initiate continuous hydrogen generation. The reaction mixture was stirred at  $60^\circ\text{C}$  for 1 hour. The reaction mixture was quenched by 2M HCl (100 mL) which was added dropwise at  $10^\circ\text{C}$  until the solid was dissolved. After extracting with EtOAc (2 x 150 mL), the combined organic layer was washed with sat.  $\text{NaHCO}_3$  aq. (300 mL), brine (300 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give a solid, which was purified by silica gel chromatography (PE/THF=12/1) to give impure **Compound 6** (100 mg, containing 12% of 22,23-olefin by NMR) as a solid. To a solution of the impure **Compound 6** (100 mg, 0.224 mmol) in EtOAc (10 mL) was added Pd/C (26.5 mg, 0.224 mmol) under  $\text{N}_2$  to remove the undesired olefin. The mixture was degassed under vacuum and purged with  $\text{H}_2$  several times. The mixture was stirred for 2 hrs at  $25^\circ\text{C}$  under  $\text{H}_2$ . The mixture was filtered and the filtrate was concentrated in vacuum to give residue. The residue was purified by re-crystallization from MeCN (10 mL) to give **Compound 6** (35 mg, 19%) as a solid.

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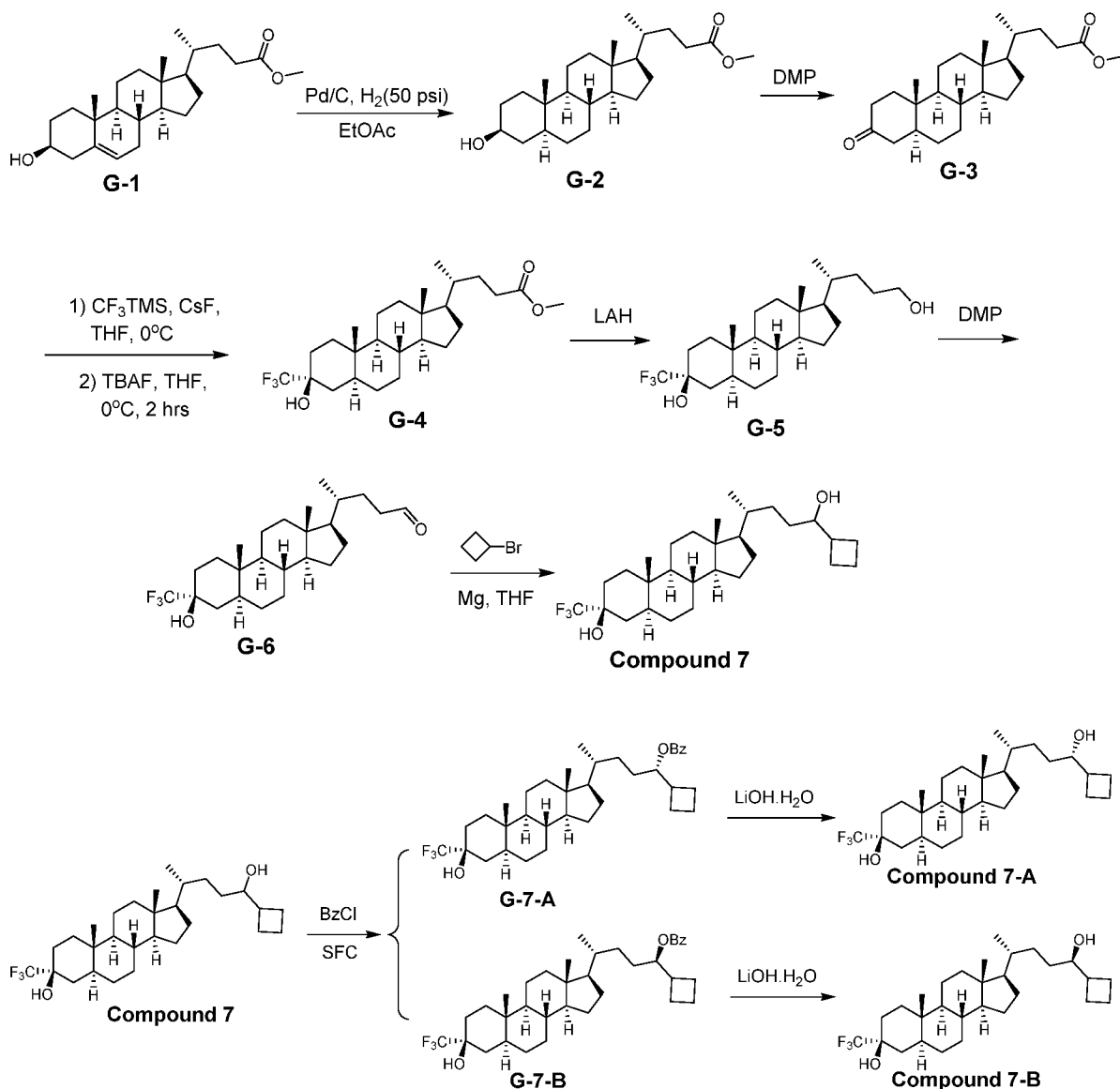
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$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.75-3.65 (m, 1H), 2.10-1.95 (m, 3H), 1.90-1.75 (m, 2H), 1.73-1.66 (m, 4H), 1.56-1.30 (m, 8H), 1.29-1.01 (m, 14H), 1.00-0.85 (m, 4H), 0.84 (s, 3H), 0.67-0.60 (m, 4H).

LCMS Rt = 1.222 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for  $\text{C}_{28}\text{H}_{42}\text{F}_3\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  427, found 427.

25

#### EXAMPLE 11. Syntheses of Compounds 7, 7-A, and 7-B.



5 **[00361]** X-ray data of Compound 7 confirmed stereochemistry of Compound 7-A and Compound 7-B.

10 **[00362]** **Step 1.** To a solution of compound **G-1** (5.0 g, 12.8 mmol) in EtOAc (150 mL) was added Pd/C (1.0 g), then the mixture was stirred under hydrogen (50 psi) at 50 °C overnight. The mixture was filtered through a pad of celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: petroleum ether : ethyl acetate = 15:1) to afford the pure product **G-2** (3.7 g, 74 %).

**[00363]**  $^1\text{H NMR}$ : (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.66 (s, 3H), 3.53-3.62 (m, 1H), 2.40-2.30 (m, 1H), 2.26-2.18 (m, 1H), 1.97-1.62 (m, 6H), 1.60-1.20 (m, 13H), 1.18-0.93 (m, 6H), 0.92 (d,  $J=6.8\text{Hz}$ , 3H), 0.90-0.82 (m, 1H), 0.79 (s, 3H), 0.64-0.59 (m, 4H).

[00364] **Step 2.** To a solution of **G-2** (10 g, 25.6 mmol) in DCM (200 mL) was added DMP (19.5 g, 46 mmol) at 25°C. The mixture was stirred at 25°C for 30 min. Water (80 mL) was added followed by NaHCO<sub>3</sub> (20 g) and the mixture was filtered. The filtrate was extracted with DCM (100 mL), washed with Na<sub>2</sub>SO<sub>3</sub> (2 x 300 mL) and brine (2 x 300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>,  
5 filtered, concentrated in vacuum to give a crude product **G-3** (9 g) as a solid, which was used in the next step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.66 (s, 3H), 2.41-2.29 (m, 1H), 2.27-2.16 (m, 1H), 2.10-1.91 (m, 3H), 1.88-1.62 (m, 6H), 1.52-0.98 (m, 16H), 0.97-0.87 (m, 4H), 0.84 (s, 3H), 0.73-0.63 (m, 4H).

[00365] **Step 3.** To a mixture of **G-3** (7 g, 18.0 mmol) and CsF (5.46 g, 36.0 mmol) in  
10 THF (70 mL) was added drop wise TMSCF<sub>3</sub> (5.11 g, 36.0 mmol) at 0°C. The mixture was stirred and kept below 10°C for 10 min. TBAF (45.0 mL, 1 M in THF, 45.0 mmol) was added at 10°C and the mixture was stirred and kept below 10°C for 10 min. After that, the mixture was treated with water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The  
15 residue was purified by silica gel chromatograph (PE/EtOAc= 5/1) to afford **G-4** (5.55 g, 67%), 4H), 0.84 (s, 3H), 0.73-0.63 (m, 4H).

[00366] **Step 4.** To a suspension of LiAlH<sub>4</sub> (1.03 g, 27.4 mmol) in THF (80 mL) was added a solution of **G-4** (6.3 g, 13.7 mmol) in THF (20 mL) under N<sub>2</sub> dropwise at 0°C. The reaction was stirred at 25°C for 2 h. The reaction was quenched with water/THF (1/10, 40 mL)  
20 followed by adding 2 M HCl (100 mL) at 0°C. The mixture was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford **G-5** (5 g, crude) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.61 (s, 2H), 2.11-1.92 (m, 4H), 1.90-1.77 (m, 2H), 1.73-1.60 (m, 5H), 1.52-0.98 (m, 17H), 0.96-0.87 (m, 4H), 0.85 (s, 3H), 0.73-0.64 (m, 4H).

[00367] **Step 5.** To a solution of **G-5** (3 g, 6.96 mmol) in DCM (30 mL) was added DMP (5.89 g, 13.9 mmol) at 20°C. The reaction mixture was stirred at 20°C for 20 min and quenched with saturated NaHCO<sub>3</sub> aqueous (30 mL) at 20°C. The mixture was filtered. The DCM layer was separated and the aqueous phase was extracted with DCM (30 mL). The combined organic phase was washed with saturated Na<sub>2</sub>SO<sub>3</sub> aqueous (3 x 50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>,  
30 filtered and concentrated in vacuum, the residue was triturated from CH<sub>3</sub>CN (5 mL) at 20°C to give **G-6** (1.3 g, 44%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.78-9.75 (t, *J* = 2.00 Hz, 1H), 2.51-2.20 (m, 2H), 2.11-1.74 (m, 6H), 1.74-0.97 (m, 19H), 0.96-0.87 (m, 4H), 0.85 (s, 3H), 0.73-0.67 (m, 1H), 0.65 (s, 3H).

[00368] **Step 6.** To a suspension of Mg (2 g, 82.2 mmol) and I<sub>2</sub> (10 mg) in THF (2 mL)  
35 was added a solution of bromocyclobutane (5 g, 37.0 mmol) in THF (8 mL) at 60°C dropwise.

The mixture was stirred at 60°C for 1 h. The mixture was diluted with THF (10 mL) and used directly. The Grignard reagent was added to a solution of **G-6** (0.6 g, 1.40 mmol) in THF (5 mL) at 0°C. The mixture was stirred at 0°C for 1 h and quenched with NH<sub>4</sub>Cl (10 mL, sat. aq.). The mixture was extracted with EtOAc (3 x 20 mL). The organic layer was separated, concentrated in vacuum, purified by silica gel (PE/EtOAc=20/1 to 5/1) to give a crude product, which was re-crystallized from MeCN/H<sub>2</sub>O (5/2, 15 mL) to give **Compound 7** (250 mg, 37%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.49-3.38 (m, 1H), 2.40-2.25 (m, 1H), 2.10-1.90 (m, 5H), 1.90-1.60 (m, 9H), 1.57-1.18 (m, 14H), 1.17-0.96 (m, 6H), 0.96-0.86 (m, 4H), 0.84 (s, 3H), 0.73-0.62 (m, 4H).

HPLC Rt = 6.10 min in 8.0 min chromatography, 50-100 AB.

MS ESI calcd. for C<sub>29</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 467, found 467.

[00369] **Step 7.** To a solution of **Compound 7** (200 mg, 0.412 mmol) in DCM (5 mL) was added pyridine (650 mg, 8.23 mmol) and BzCl (347 mg, 2.47 mmol). The mixture was stirred at 25°C for 1 h. The mixture was treated with H<sub>2</sub>O (5 mL) and washed with HCl (10 mL, 1 M, aq.), NaHCO<sub>3</sub> (10 mL, sat. aq.), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum to give a crude product, which was purified by silica gel column (PE/EtOAc=10/1) to give 300 mg of impure product. The impure product was separated by SFC (column: Chiralpak AD-3 50\*4.6mm I.D., 3μm); Condition: Base-IPA; Gradient: 5-40% B; flow rate: 4 mL/min) to give **G-6-A** (75 mg, 31%, t<sub>R</sub> = 5.282 min, 100% d.e. ("Column: Chiralpak AD-3 150x4.6mm I.D., 3μm Mobile phase: A: CO<sub>2</sub> B:iso-propanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C")) and **G-6-B** (88 mg, 36%, t<sub>R</sub> = 4.827 min, 100% d.e. ("Column: Chiralpak AD-3 150x4.6mm I.D., 3μm Mobile phase: A: CO<sub>2</sub> B:iso-propanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C"))).

[00370] **Step 8a.** To a solution of **G-7-A** (75 mg, 0.127 mmol) in THF (5 mL) and MeOH (1 mL) was added a suspension of LiOH.H<sub>2</sub>O (399 mg, 9.52 mmol) in water (1 mL). The mixture was stirred at 60°C for 24 h. After removing the organic solvent in vacuum, the mixture was treated with H<sub>2</sub>O (5 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (2 x 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum. The residue was triturated from CH<sub>3</sub>CN (2 mL) at 25°C to give **Compound 7-A** (43 mg, 70%) as a solid.

[00371] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.49-3.41 (m, 1H), 2.37-2.26 (m, 1H), 2.10-1.75 (m, 10H), 1.75-1.60 (m, 4H), 1.52-1.15 (m, 16H), 1.15-0.93 (m, 4H), 0.92-0.82 (m, 7H), 0.73-0.62 (m, 4H).

HPLC Rt = 6.78 min in 8.0 min chromatography, 30-90 AB.

MS ESI calcd. for C<sub>29</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 467, found 467.

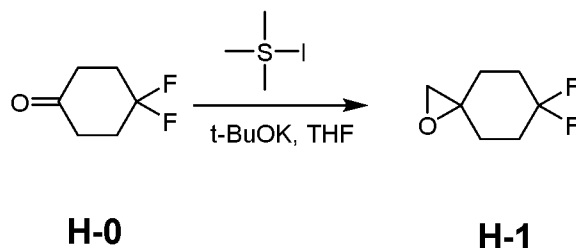
**[00372]**      *Step 8b.* To a solution of **G-7-B** (88 mg, 0.149 mmol) in THF (5 mL) and MeOH (1 mL) was added a suspension of LiOH.H<sub>2</sub>O (406 mg, 9.68 mmol) in water (1 mL). The mixture was stirred at 60°C for 24 h. After removing the organic solvent in vacuum, the mixture was treated with H<sub>2</sub>O (5 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (2 x 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum. The residue was triturated from CH<sub>3</sub>CN (2 mL) at 25°C to give **Compound 7-B** (52 mg, 72%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.48-3.37 (m, 1H), 2.39-2.26 (m, 1H), 2.10-1.74 (m, 10H), 1.72-1.61 (m, 4H), 1.53-1.19 (m, 13H), 1.19-0.94 (m, 7H), 0.94-0.80 (m, 7H), 0.73-0.62 (m, 4H).

HPLC Rt = 6.78 min in 8.0 min chromatography, 30-90 AB

MS ESI calcd. for C<sub>29</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 467.3495, found 467.3.

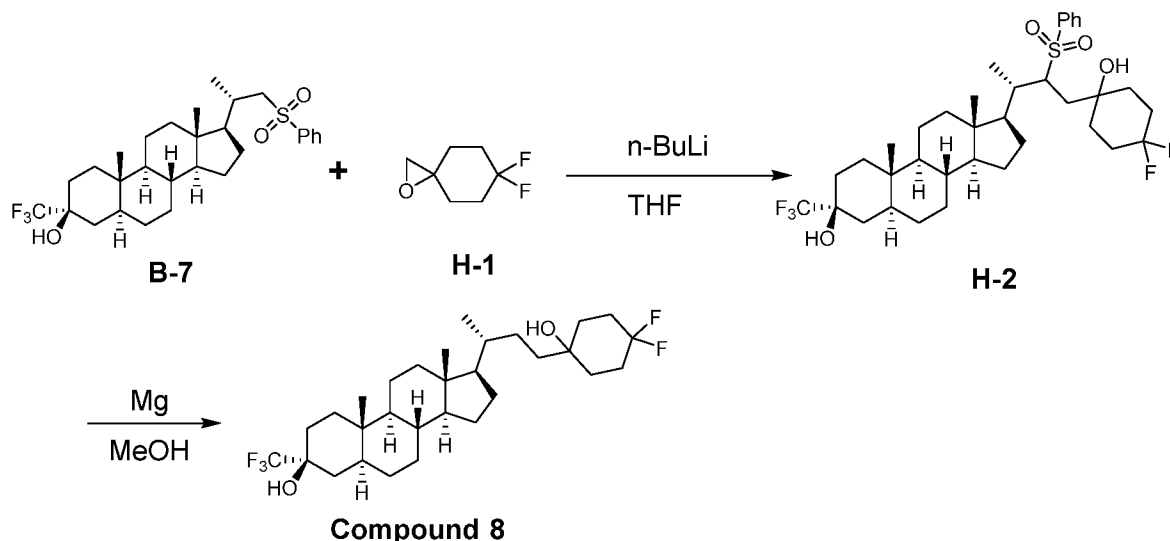
#### EXAMPLE 12. Synthesis of Compound H-1



**[00373]**      To a suspension of Me<sub>3</sub>SI (3.93 g, 19.3 mmol) in THF (20 mL) was added a solution of t-BuOK (3.33 g, 29.8 mmol) in THF (10 mL) under N<sub>2</sub> at 15°C. The suspension was stirred at 15°C for 30 mins. A solution of **H-0** (2 g, 14.9 mmol) in THF (5 mL) was added dropwise at 15°C. The mixture was stirred at 15°C for 16 hrs. The mixture was quenched with Sat.NH<sub>4</sub>Cl (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **H-1** (1.8 g, 82%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.72 (s, 2H), 2.20-1.85 (m, 8H).

#### EXAMPLE 13. Synthesis of Compound 8.



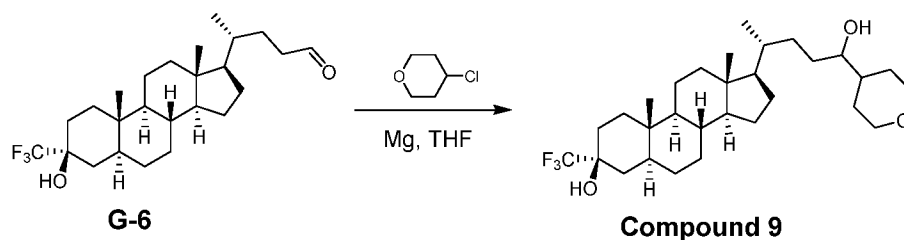
[00374] **Step 1.** To a solution of THF (5 mL) and BuLi (3.78 mL, 2.5 M in hexane, 9.47 mmol) was added a solution of **B-7** (2 g, 3.79 mmol) in THF (15 mL) at -70°C. After stirring at -70°C for 1 h, a solution of **H-1** (1.68 g, 5.68 mmol) in THF (5 mL) was added at -70°C. The mixture was stirred at -70°C for another 1 h. The mixture was warmed to 25°C and stirred for 16 hrs and quenched by adding NH<sub>4</sub>Cl (50 mL, sat. aq.). The mixture was extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, and purified by combi-flash (0-10% of EtOAc in PE) to give **H-2** (250 mg, 10%) as a solid and 1.8 g of starting material which was recycled.

[00375] **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.00-7.92 (m, 2H), 7.73-7.65 (m, 1H), 7.63-7.52 (m, 2H), 3.62-3.55 (m, 1H), 2.37-2.28 (m, 1H), 2.15-1.94 (m, 4H), 1.94-1.85 (m, 6H), 1.85-1.55 (m, 5H), 1.55-1.43 (m, 6H), 1.43-1.10 (m, 10H), 1.10-0.90 (m, 3H), 0.90-0.70 (m, 6H), 0.70-0.57 (m, 1H), 0.55 (s, 3H).

[00376] **Step 2.** To a solution of **H-2** (250 mg, 0.37 mmol) in MeOH (15 mL) was added Mg powder (355 mg, 14.8 mmol) at 55°C. The mixture was stirred at 60°C for 16 hrs. The mixture was quenched with HCl (50 mL, 1N) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **Compound 8** (55 mg, 28%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.20-1.73 (m, 9H), 1.73-1.58 (m, 7H), 1.58-0.85 (m, 11H), 0.85-1.00 (m, 8H), 1.00-0.86 (m, 5H), 0.85 (s, 3H), 0.72-0.62 (m, 4H).

**LCMS** Rt = 1.286 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>30</sub>H<sub>46</sub>F<sub>5</sub>O [M-H<sub>2</sub>O+H]<sup>+</sup> 517, found 517.

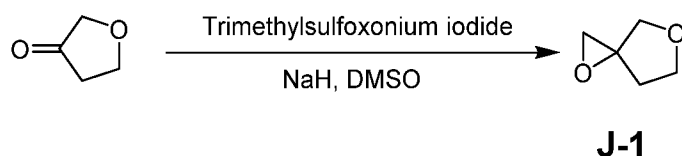
**EXAMPLE 14. Synthesis of Compound 9.**

[00377] To a suspension of Mg (1.37 g, 56.5 mmol) and I<sub>2</sub> (10 mg) in THF (2 mL) was added a solution of 4-chlorotetrahydro-2H-pyran (2.72 g, 22.6 mmol) in THF (8 mL) at 60°C dropwise. The mixture was stirred at 60°C for 2 h. The mixture was diluted with THF (10 mL) and used directly. The Grignard reagent was added to a solution of **G-6** (0.55 g, 1.28 mmol) in THF (5 mL) at 0°C. The mixture was stirred at 0°C for 1 h and treated with NH<sub>4</sub>Cl (10 mL, sat. aq.). The mixture was extracted with EtOAc (3 x 20 mL). The organic layer was separated, concentrated in vacuum, purified by silica gel column (PE/EtOAc=20/1 to 5/1) to give a crude product, which was re-crystallized from CH<sub>3</sub>CN (10 mL) to give **Compound 9** (180 mg, 27%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.05-3.97 (m, 2H), 3.41-3.25 (m, 3H), 2.10-1.91 (m, 3H), 1.88-1.57 (m, 7H), 1.55-1.33 (m, 11H), 1.33-0.96 (m, 12H), 0.96-0.86 (m, 4H), 0.85 (s, 3H), 0.72-0.63 (m, 4H).

HPLC Rt = 4.73 min in 8.0 min chromatography, 50-100 AB.

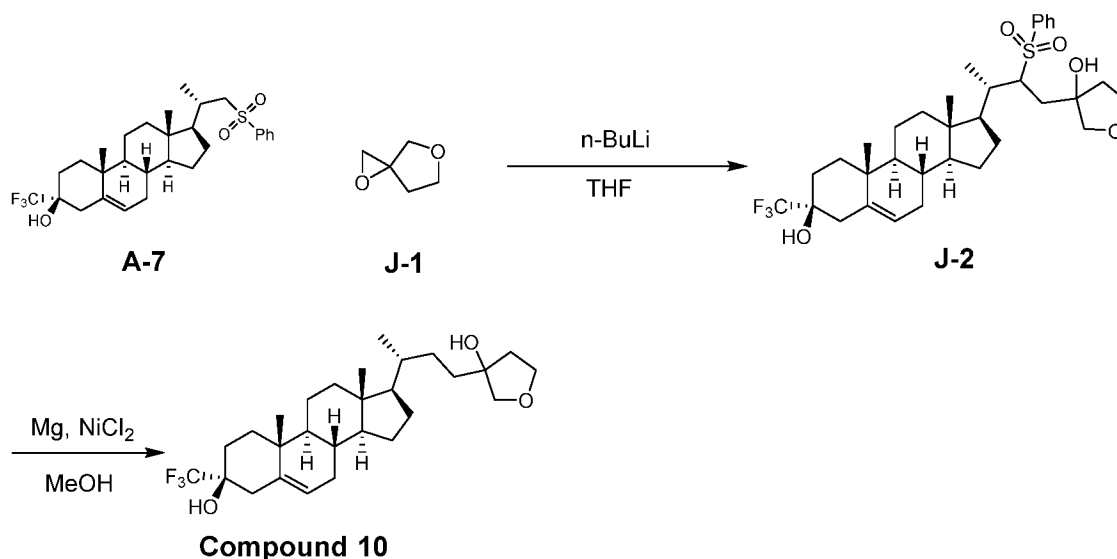
MS ESI calcd. for C<sub>30</sub>H<sub>48</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 497, found 497.

**EXAMPLE 15. Synthesis of Compound J-1.**

[00378] To a mixture of trimethylsulfoxonium iodide (30.6 g, 150 mmol) in THF (100 mL) was added NaH (5.98 g, 60% in mineral oil, 150 mmol) in portions at 0°C under N<sub>2</sub>. The mixture was stirred at 0°C for 30 mins. Dihydrofuran-3(2H)-one (10 g, 116 mmol) in DMSO (100 mL) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 2 hours. The mixture was poured into ice-water (500 mL) in portions, extracted with DCM (2 x 500 mL). The combined organic phase was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 30°C. The residue was purified by Combi-flash (EtOAc in PE, 0%~40%) to afford **J-1** (1.5 g, 13 %) as an oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.11-3.90 (m, 3H), 3.66 (d,  $J$  = 10.0 Hz, 1H), 3.03 (d,  $J$  = 4.4 Hz, 1H), 2.94 (d,  $J$  = 4.0 Hz, 1H), 2.34-2.23 (m, 1H), 2.00-1.88 (m, 1H).

#### EXAMPLE 16. Synthesis of Compound 10.



5

**[00379]**        **Step 1.** To a solution of *n*-BuLi (0.95 mL, 2.38 mmol, 2.5 M) in THF (2 mL) under  $\text{N}_2$  at  $-70^\circ\text{C}$  was added a suspension of **A-7** (see Example 3) (500 mg, 0.95 mmol) in THF (5 mL) drop-wise to give a suspension. After stirring at  $-70^\circ\text{C}$  for 30 min, a solution of **J-1** (238 mg, 2.38 mmol) in THF (3 mL) was added. Then the reaction was stirred at  $-70^\circ\text{C}$  for 10 min and  $20^\circ\text{C}$  for 16 hours. The reaction was quenched with *sat.*  $\text{NH}_4\text{Cl}$  (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product **J-2** (500 mg) as a solid, which was used directly in next step.

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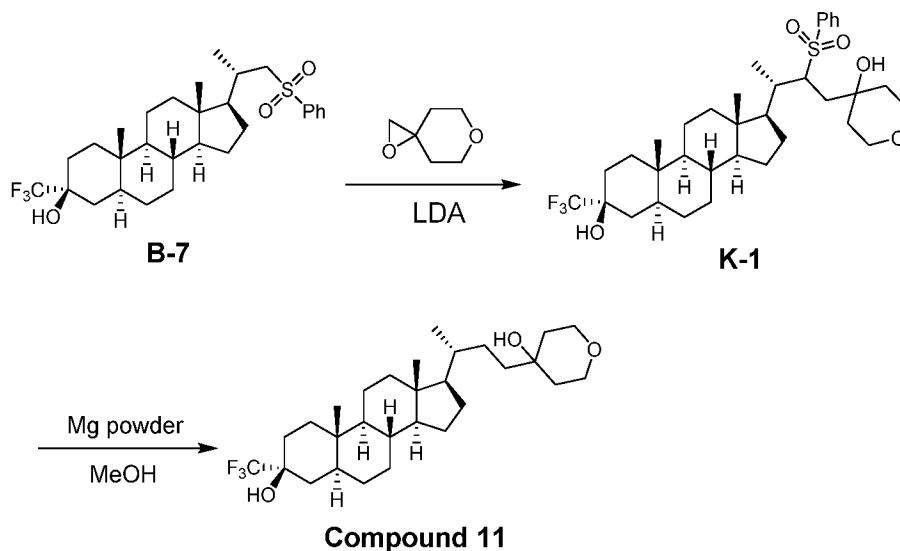
15    **LCMS** Rt = 0.925 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for  $\text{C}_{34}\text{H}_{47}\text{F}_3\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  647, found 647.

**[00380]**        **Step 2.** To a solution of **J-2** (300 mg, 0.48 mmol) in 20 mL of dry methanol under  $\text{N}_2$  was added magnesium turnings (466 mg, 19.2 mmol) (activated with 0.5% aqueous HCl, water, dry ethanol, and MTBE) and  $\text{NiCl}_2$  (12.4 mg, 0.96 mmol) with stirring at  $55^\circ\text{C}$  to initiate continuous hydrogen generation. After the addition of a further two batches of 466 mg of magnesium turnings, most of the starting material was consumed. The reaction mixture was quenched by 2M HCl (100 mL) which was added dropwise at  $10^\circ\text{C}$  until solid was dissolved. After extraction with DCM (3 x 80 mL), the combined organic phase was washed with brine (100 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by Combi-  
25    flash (0%~50% of EtOAc in PE) to afford **Compound 10** (46 mg, 20%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.43-5.32 (m, 1H), 4.08-3.98 (m, 1H), 3.95-3.85 (m, 1H), 3.75-3.66 (m, 1H), 3.59-3.51 (m, 1H), 2.53-2.45 (m, 2H), 2.11-1.87 (m, 6H), 1.82-1.65 (m, 4H), 1.54-1.38 (m, 7H), 1.33-1.12 (m, 6H), 1.08-0.92 (m, 9H), 0.79-0.61 (m, 4H).

**LCMS**  $R_t$  = 1.121 min in 2 min chromatography, 30-90 AB, **MS ESI** calcd. for  $\text{C}_{30}\text{H}_{46}\text{F}_3\text{O}_3\text{NNa}$   $[\text{M}+\text{MeCN}+\text{Na}]^+$  548, found 548.

#### EXAMPLE 17. Synthesis of Compound 11.



**[00381]** **Step 1.** To a solution of  $n\text{-BuLi}$  (452  $\mu\text{L}$ , 2.5 M in hexane, 1.13 mmol) in THF (0.5 mL) at  $-65^\circ\text{C}$  under  $\text{N}_2$  was added a suspension of **B-7** (200 mg, 0.3797 mmol) in THF (2.5 mL) was added drop-wise and stirred for 30 minutes at  $-65^\circ\text{C}$ . After that, diisopropylamine (114 mg, 1.13 mmol) was added at  $-65^\circ\text{C}$ , followed by adding 1,6-dioxaspiro[2.5]octane (65.0 mg, 0.5695 mmol) was added drop-wise at  $-65^\circ\text{C}$ . The mixture was stirred for another 30 minutes and then warmed to  $25^\circ\text{C}$  gradually and stirred at  $25^\circ\text{C}$  for 16 hour. The reaction mixture was quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL), extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **K-1** (380 mg, crude) as a solid, which was used directly for the next step.

20

**[00382]** **Step 2.** To a solution of **K-1** (0.348 g, 0.543 mmol) in MeOH (20 mL) was added Mg (0.520 g, 21.7 mmol) and  $\text{NiCl}_2$  (3.51 mg, 0.0271 mmol) at  $60^\circ\text{C}$ . The mixture was stirred at  $60^\circ\text{C}$  for 1 hour. The reaction mixture was cooled to  $25^\circ\text{C}$ . The mixture was added in HCl (20 mL, 1 M in water). The mixture was extracted with EtOAc (2 x 20 mL), washed with  $\text{NaHCO}_3$  (2 x 40 mL) and brine (2 x 40 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated in vacuum. The

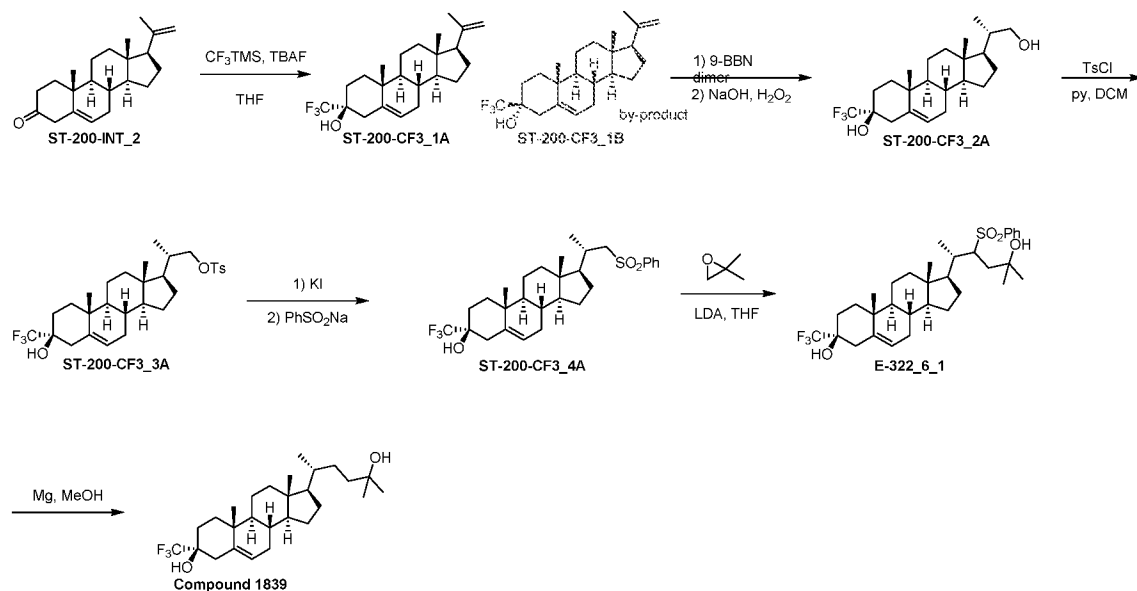
25

crude residue was purified by silica gel column (PE/EtOAc=10/1 to 2/1) to give 66 mg of impure **Compound 11** as a solid, which was triturated from CH<sub>3</sub>CN (5 mL) at 25°C to give **Compound 11** (30 mg, 11%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.84-3.64 (m, 4H), 2.11-1.90 (m, 3H), 1.87-1.61 (m, 6H), 1.51-1.20 (m, 16H), 1.18-0.96 (m, 7H), 0.94-0.80 (m, 7H), 0.74-0.61 (m, 4H).

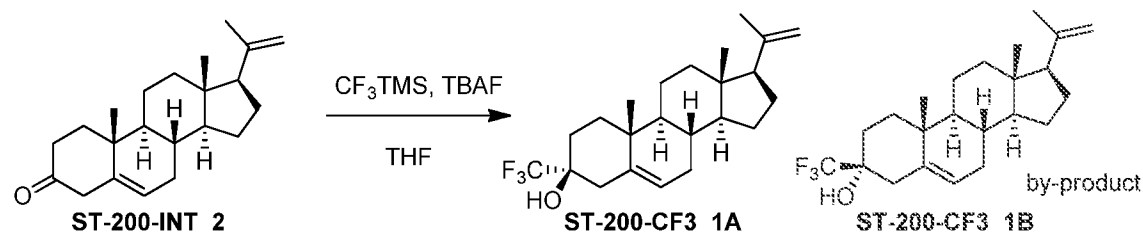
LCMS Rt = 1.170 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>29</sub>H<sub>46</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 483, found 483.

### EXAMPLE 18: Synthesis of Compound 1839



[00383] The experimental of intermediate ST-200-INT\_2, or A2, can be found in Example 3.

### [00384] Synthesis of ST-200-CF3\_1A



A solution of ST-200-INT\_2 (9.5 g, 30.4 mmol) and TMSCF<sub>3</sub> (12.9 g, 91.2 mmol) in THF (50 mL) was added dropwise within 30 mins at 0°C to a suspension of CsF (462 mg, 3.04 mmol) in THF (100 mL). The mixture was stirred at 10°C for 16 hrs. TLC showed the starting material remained. The mixture was cooled to 0°C. TBAF (3 mL, 1 M in THF, 3 mmol, Aldrich) was added to the mixture at 0°C. The mixture was stirred at 10°C for 1 h. TBAF (91.2 mL, 1 M in THF, 91.2 mmol) was added to the mixture. The mixture was stirred at 10°C for another 1 h. The

mixture was concentrated in vacuum. The residue was dissolved in EtOAc (100 mL), washed with water (3 x 100 mL) and concentrated in vacuum to yield a crude product, which was combined with another batch of 9.5 g **ST-200-INT\_2**, purified by silica gel column (PE:EtOAc = 30:1 to 20:1) in four parts to give **ST-200-CF3\_1B** (2.3 g, purity 83%, yield 8%) and **ST-200-CF3\_1A** (6.2 g, purity 32%, yield 8%). 3.0 g of impure **ST-200-CF3\_1A** was used in the step directly and another 3.2 g was purified by silica gel column (PE:EtOAc = 30:1 to 20:1) and re-crystallized from MeCN (10 mL) to give **ST-200-CF3\_1A** (0.5 g, purity 94%).

**Note:** **ST-200-CF3\_1A** and **ST-200-CF3\_1B** were identified from  $^3J_{H,CF_3}$  (FDCS). (*J. Org. Chem.* 2015, 80, 1754)

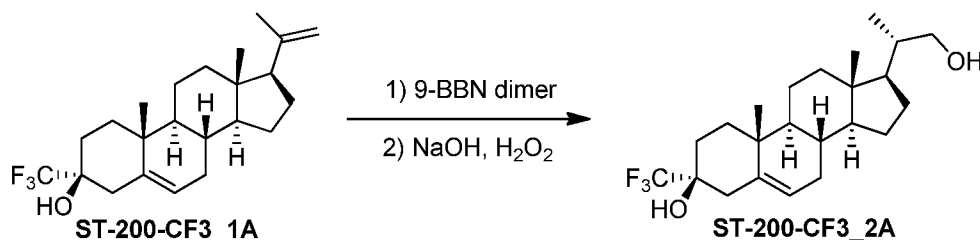
#### 10 **ST-200-CF3\_1A:**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.43-5.33 (m, 1H), 4.85 (s, 1H); 4.71 (s, 1H); 2.49 (s, 2H); 2.11-1.97 (m, 4H), 1.95-1.32 (m, 14H), 1.30-0.98 (m, 7H), 0.59 (s, 3H).

#### **ST-200-CF3\_1B:**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.54-5.41 (m, 1H), 4.86 (s, 1H); 4.72 (s, 1H); 2.78-2.65 (m, 1H); 2.18-1.97 (m, 3H), 1.95-1.35 (m, 16H), 1.32-0.98 (m, 7H), 0.59 (s, 3H).

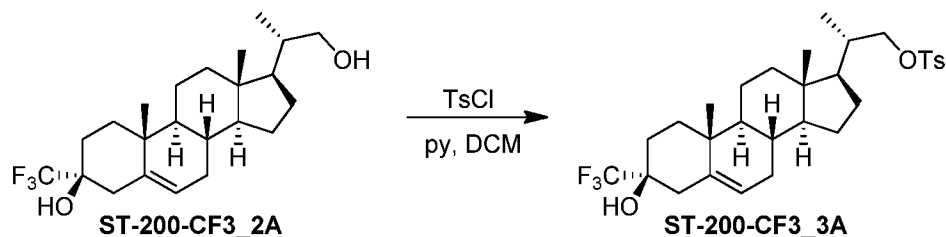
#### [00385] **Synthesis of ST-200-CF3\_2A**



9-BBN dimer (2.19 g, 9.01 mmol) was added to a solution of **ST-200-CF3\_1A** (3 g, impure) in THF (35 mL). The mixture was stirred at 40°C for 1 h. Next, EtOH (4.5 mL), NaOH (15.6 mL, 5 M, aq.) and  $\text{H}_2\text{O}_2$  (7.83 mL, 10 M, aq.) were added dropwise and the mixture was cooled to 0°C. The mixture was stirred at 50°C for 1 h.  $\text{Na}_2\text{SO}_3$  (100 mL, 10%, aq.) was added to the mixture after cooling. The mixture was extracted with EtOAc (100 mL). The organic layer was separated, purified by silica gel column (PE:EtOAc = 10:1 to 7:1) to give **ST-200-CF3\_2A** (1.2 g, purity 79%, yield 30%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.42-5.32 (m, 1H), 3.64 (dd,  $J = 2.8, 10.4$  Hz, 1H), 3.36 (dd,  $J = 6.8, 10.4$  Hz, 1H), 2.50 (s, 2H), 2.32-1.92 (m, 4H), 1.92-1.70 (m, 4H), 1.70-1.29 (m, 8H), 1.29-0.91 (m, 11H), 0.71 (s, 3H).

#### [00386] **Synthesis of ST-200-CF3\_3A**

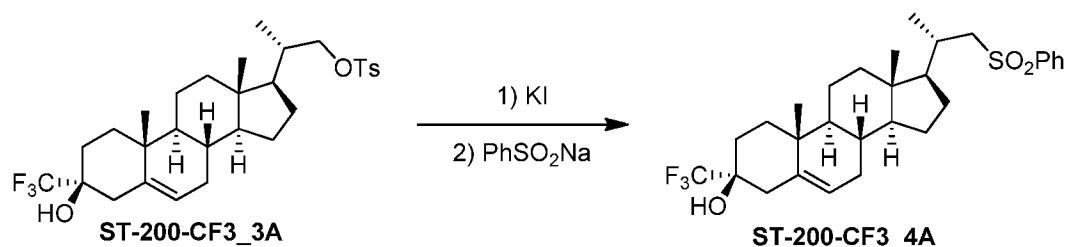


TsCl (1.14 g, 5.98 mmol) was added to a solution of **ST-200-CF3\_2A** (1.2 g, 2.99 mmol) in DCM (5 mL) and py (3.5 mL). The mixture was stirred at 15°C for 2 hrs. PE (10 mL) was added to the mixture. The mixture was washed with water (10 mL) and brine (10 mL), dried over

5  $\text{Na}_2\text{SO}_4$ , filtered, concentrated in vacuum and purified by silica gel column (PE:DCM:EtOAc = 5:1:0.3 to 5:1:0.4) to give **ST-200-CF3\_3A** (1.05 g, 64%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J = 8.4$  Hz, 2H), 7.34 (d,  $J = 8.4$  Hz, 2H), 5.40-5.33 (m, 1H), 3.97 (dd,  $J = 2.8, 9.2$  Hz, 1H), 3.77 (dd,  $J = 6.4, 9.2$  Hz, 1H), 2.48 (s, 2H), 2.45 (s, 3H), 2.10-1.88 (m, 5H), 1.82-1.35 (m, 9H), 1.30-0.82 (m, 12H), 0.64 (s, 3H).

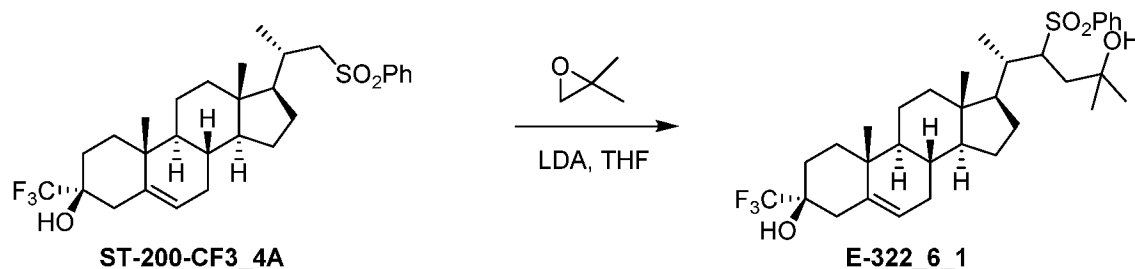
#### 10 [00387] Synthesis of **ST-200-CF3\_4A**



KI (1.25 g, 7.56 mmol) was added to a solution of **ST-200-CF3\_3A** (1.05 g, 1.89 mmol) in DMF (5 mL). The mixture was stirred at 50°C for 1 h. To the mixture was added  $\text{PhSO}_2\text{Na}$  (0.93 g, 5.67 mmol). The mixture was stirred at 50°C for 2 hrs. Water (10 mL) and DCM (30 mL) were added to the mixture. The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated in vacuum and triturated from PE/DCM (10 mL, 5:1) to give **ST-200-CF3\_4A** (600 mg, 61%) as a solid.

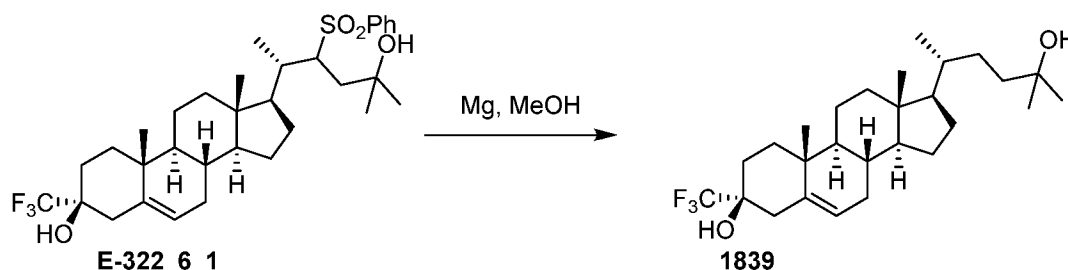
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98-7.87 (m, 2H), 7.70-7.52 (m, 3H), 5.39-5.31 (m, 1H), 3.14 (d,  $J = 14.4$  Hz, 1H), 2.85 (dd,  $J = 9.6, 14.0$  Hz, 1H), 2.48 (s, 2H), 2.20-1.88 (m, 5H), 1.88-1.68 (m, 4H), 1.60-1.33 (m, 5H), 1.30-0.82 (m, 12H), 0.64 (s, 3H).

#### [00388] Synthesis of **E-322\_6\_1**



Diisopropylamine (3.76 mmol, 380 mg) was added to THF (2 mL) under N<sub>2</sub> at -70°C, followed by an addition of n-BuLi (3.42 mmol, 1.36 mL, 2.5M in hexane 3.0 eq). The reaction was allowed to warm to 15°C and was then re-cooled to -70°C. A suspension of **ST-200-CF3\_4A** (1.14 mmol, 600 mg) in THF (5 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, a solution of 2,2-dimethyloxirane (2.28 mmol, 218 mg, 2.0 eq.) in THF (1 mL) was added over 5 min (slightly exothermic, keeping internal T < -70°C). Then reaction was stirred at 15°C for 12 hrs. The reaction was quenched with sat. NH<sub>4</sub>Cl (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **ST-200-CF3\_5A** (600 mg, crude) as a foam.

#### 10 [00389] Synthesis of 1839

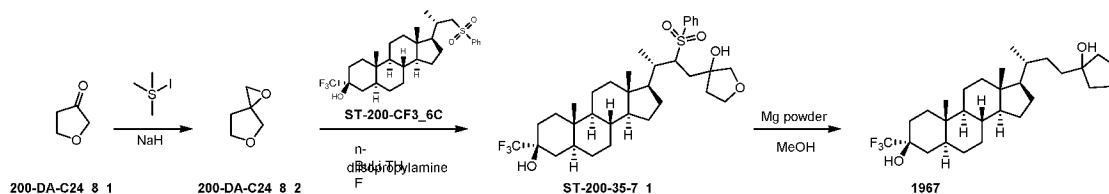


Mg powder (960 mg, 40 mmol) was added to a solution of **E-322\_6\_1** (600 mg, 1 mmol) in MeOH (10 mL) at 55°C. The reaction mixture was stirred at 60°C under N<sub>2</sub> for 2 hrs. The mixture was quenched with HCl (100 mL, 2 M) until the reaction became clear and extracted with DCM (3 x 20 mL). The combined organic phase was washed with sat. NaHCO<sub>3</sub> (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by combi-flash (0-10% of EtOAc in PE) to give 170 mg impure product, which was purified again by *prep*-HPLC (column: DuraShell 150\*25mm\*5um), gradient: 75-100% B (A= 0.05% HCl/H<sub>2</sub>O, B= MeCN), flow rate: 30 mL/min to give **1839** (66 mg, 14%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.37-5.36 (m, 1H), 2.48 (s, 2H), 2.10-1.92 (m, 4H), 1.90-1.70 (m, 3H), 1.62-1.58 (m, 2H), 1.56-1.35 (m, 7H), 1.34-1.22 (m, 3H), 1.21-1.07 (m, 10H), 1.06 (s, 3H), 1.05-0.98 (m, 2H), 0.93 (d, J = 6.8 Hz, 3H), 0.68 (s, 3H).

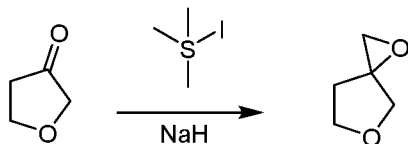
LCMS Rt = 1.277 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>42</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 439, found 439.

#### EXAMPLE 19: Synthesis of 1967



[00390] The synthesis of **ST-200-CF3\_6C** or **B7** can be found in Example 5.

[00391] **Synthesis of 200-DA-C24\_8\_2**



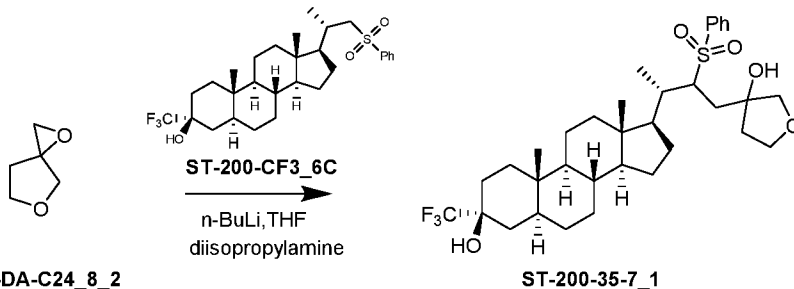
**200-DA-C24\_8\_1**

**200-DA-C24\_8\_2**

Sodium hydride (18.0 g, 60% in mineral oil, 452 mmol) was added in portions to a mixture of trimethylsulfonium iodide (92.2 g, 452 mmol) in THF (300 mL) at 0°C under N<sub>2</sub>. The mixture was stirred at 0°C for 30 min. Dihydrofuran-3(2H)-one (30 g, 348 mmol) in DMSO (300 mL) was added drop-wise at 0°C. The reaction mixture was stirred at 25°C for 16 hours. The mixture was poured into ice-water (500 mL) in portions, extracted with DCM (2 x 500 mL). The combined organic phase was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 30°C to give **200-DA-C24\_8\_2** (32 g, crude) as an oil. 3 g from the residue was purified by column (Al<sub>2</sub>O<sub>3</sub>, PE) to afford **200-DA-C24\_8\_2** (0.6 g) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.09-3.90 (m, 4H), 3.03 (d, *J* = 4.4 Hz, 1H), 2.93 (d, *J* = 4.4 Hz, 1H), 2.28 (td, *J* = 8.0, 13.6 Hz, 1H), 1.93 (m, 1H).

[00392] **Synthesis of ST-200-35-7\_1**

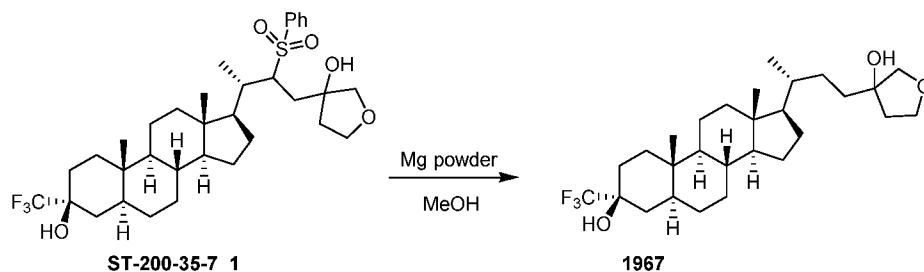


**200-DA-C24\_8\_2**

**ST-200-35-7\_1**

A suspension of **ST-200-CF3\_6C** (500 mg, 0.9493 mmol) in THF (2.5 mL) was added dropwise to a solution of n-BuLi (1.13 mL, 2.5 M in hexane, 2.84 mmol) in THF (0.5 mL) at -65°C under N<sub>2</sub>. The mixture was stirred for 30 minutes at -65°C. Diisopropylamine (286 mg, 2.84 mmol) was added at -65°C. Next, **200-DA-C24\_8\_2** (95.0 mg, 0.9493 mmol) was added drop-wise at -65°C. The mixture was stirred for another 30 minutes and then warmed to 25°C gradually. The reaction mixture was stirred at 25°C for 16 hours, quenched by saturated NH<sub>4</sub>Cl aqueous (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **ST-200-35-7\_1** (900 mg, crude) as a solid, which was used directly for the next step.

[00393] **Synthesis of 1967**



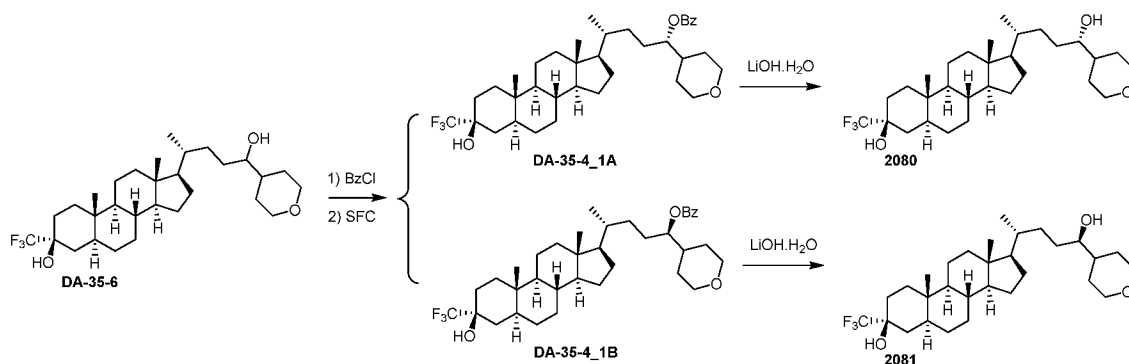
Mg (686 mg, 28.6 mmol) was added to a solution of crude **ST-200-35-7\_1** (900 mg) in MeOH (10 mL). Next, the reaction mixture was stirred at 60°C for 2 h under N<sub>2</sub>. Aqueous HCl (10 mL, 4 M) was added to the reaction mixture, then was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude product. The crude product was purified by silica gel chromatography (PE/EtOAc = 30/1 to 10/1) to give impure **1967** (460 mg) as a solid.

The impure **1967** (460 mg) was purified by re-crystallization from MeCN (2 mL) to give **1967** (175 mg) as a solid. The mother liquid was concentrated in vacuum to give impure **ST-200-35-7** (220 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.10-4.00 (m, 1H), 3.95-3.85 (m, 1H), 3.75-3.65 (m, 1H), 3.55-3.50 (m, 1H), 2.10-2.00 (m, 2H), 2.00-1.85 (m, 3H), 1.85-1.75 (m, 2H), 1.75-1.56 (m, 5H), 1.55-1.40 (m, 6H), 1.40-1.20 (m, 7H), 1.20-1.00 (m, 5H), 1.00-0.88 (m, 4H), 0.85 (s, 3H), 0.75-0.68 (m, 1H), 0.66 (s, 3H).

LCMS Rt = 1.148 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>30</sub>H<sub>48</sub>F<sub>3</sub>NO<sub>3</sub>Na[M+MeCN+Na]<sup>+</sup> 550, found 550.

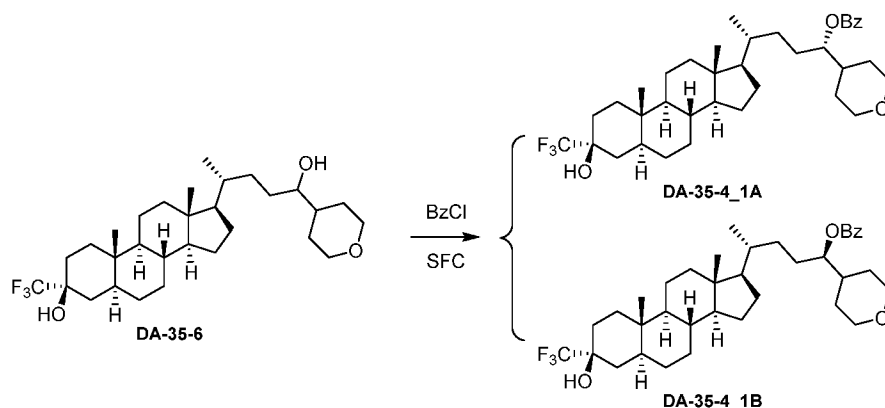
#### EXAMPLE 20: Synthesis of 2080 and 2081



[00394] Stereochemistry confirmed by Xray data.

[00395] The experimental of Intermediate **DA-35-6** can be found in Example 14.

[00396] Synthesis of **DA-35-4\_1A** & **DA-35-4\_1B**



Py (498 mg, 6.30 mmol) and BzCl (531 mg, 3.78 mmol) were added to a solution of **DA-35-6** (130 mg, 0.252 mmol) in DCM (5 mL). The mixture was stirred at 25°C for 6 h and quenched by adding H<sub>2</sub>O (5 mL). The mixture was washed with HCl (10 mL, 1 M, aq.), NaHCO<sub>3</sub> (10 mL, sat. aq.), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuum to give a crude product. The crude product was purified by silica gel column (PE: EtOAc =20:1 to 10:1) to give **DA-35-4\_1** (170 mg, impure). The impure **DA-35-4\_1** (170 mg) was separated by SFC (column: Chiralpak AD-3 50\*4.6mm I.D., 3um); Condition: Base-IPA; Gradient: 5-40% B; flow rate: 4 mL/min) to give **DA-35-4\_1A** (56 mg, 36%, Rt = 4.889 min, 100%de) and **DA-35-4\_1B** (80 mg, 51%, Rt = 5.283 min, 100%de).

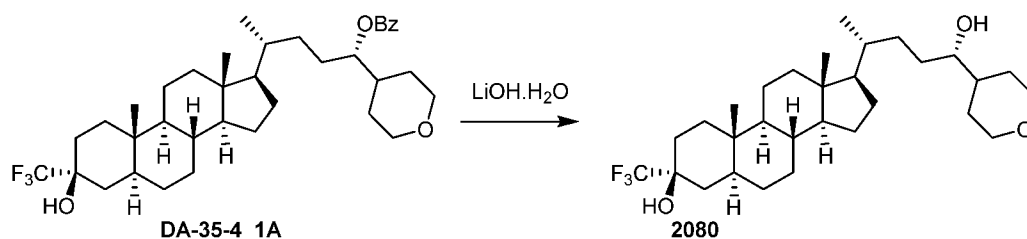
#### DA-35-4\_1A:

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 5.04-4.94 (m, 1H), 4.06-3.94 (m, 2H), 3.44-3.32 (m, 2H), 2.10-1.84 (m, 4H), 1.84-1.58 (m, 8H), 1.53-1.23 (m, 12H), 1.22-0.94 (m, 8H), 0.94-0.80 (m, 7H), 0.72-0.57 (m, 4H).

#### DA-35-4\_1B:

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 5.05-4.96 (m, 1H), 4.03-3.93 (m, 2H), 3.44-3.30 (m, 2H), 2.10-1.59 (m, 12H), 1.53-1.23 (m, 12H), 1.22-0.94 (m, 8H), 0.93-0.81 (m, 7H), 0.72-0.60 (m, 4H).

#### [00397] Synthesis of 2080



A solution of LiOH.H<sub>2</sub>O (284 mg, 6.78 mmol) in water (1 mL) was added to a solution of **DA-35-4\_1A** (56 mg, 0.090 mmol) in THF (5 mL) and MeOH (1 mL). The mixture was stirred at 50°C for 20 h. The mixture was concentrated in vacuum and treated with H<sub>2</sub>O (5 mL). The

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.05-3.95 (m, 2H), 3.40-3.25 (m, 3H), 2.05-1.95 (m, 2H), 1.85-1.80 (m, 2H), 1.75-1.25 (m, 17H), 1.24-0.90 (m, 16H), 0.89-0.75 (m, 3H), 0.65-0.60 (m, 4H). **LCMS** Rt = 1.205 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>30</sub>H<sub>48</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 497, found 497.

Chemical reaction scheme showing the conversion of DA-35-4\_1B to 2081. DA-35-4\_1B is a complex steroid molecule with a trifluoromethyl group, a hydroxyl group, and a side chain ending in a benzyl-protected alcohol. The reaction is catalyzed by  $\text{LiOH} \cdot \text{H}_2\text{O}$ , resulting in the removal of the benzyl group and the formation of a free hydroxyl group in the product, 2081.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.05-3.95 (m, 2H), 3.40-3.25 (m, 3H), 2.05-1.90 (m, 4H), 1.89-1.60 (m, 8H), 1.59-1.35 (m, 10H), 1.34-0.95 (m, 11H), 0.94-0.75 (m, 7H), 0.65-0.60 (m, 4H).  
**LCMS** Rt = 1.205 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>30</sub>H<sub>48</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 497, found 497.

200-TBU-E<sub>1</sub>  $\xrightarrow[5\text{ M HCl, } 0^\circ\text{C}]{\text{NaNO}_2}$  200-TBU-E<sub>2</sub>  $\xrightarrow[\text{THF, } 0^\circ\text{C}]{\text{LAH}}$  200-TBU-E<sub>3</sub>  $\xrightarrow{\text{KOH}}$  200-TBU-E<sub>4</sub>

200-TBU-E<sub>4</sub>  $\xrightarrow[\text{THF}]{\text{n-BuLi}}$  ST-200-CF<sub>3</sub>-6C (500 mg)  $\rightarrow$  DA-31-2<sub>1</sub>

DA-31-2<sub>1</sub>  $\xrightarrow[2.\text{ Pd(OH)}_2, \text{ H}_2]{1.\text{ Mg powder, MeOH}}$  DA-31-2 (2184)

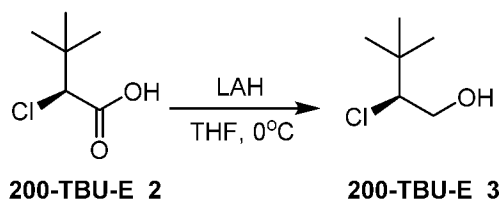
[00400]            **Synthesis of 200-TBU-E 2**



**200-TBU-E\_1** (131 g, 998 mmol) was dissolved in 1690 mL of 5 N hydrochloric acid. The mixture was cooled to 0°C and a precooled solution of sodium nitrite (109 g, 1.59 mol) in 400 mL of water was added drop-wise, then the reaction mixture was kept below 5°C. After 5 hr, the mixture was stirred at 25°C for 12 hrs. Solid sodium carbonate (100 g) was added carefully in small portions. The reaction mixture was extracted with isopropyl ether (500 mL\*2). The combined organic phases was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was isolated by distillation to afford **200-TBU-E\_2** (48 g, 32%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.12 (s, 1H), 1.13 (s, 9H).

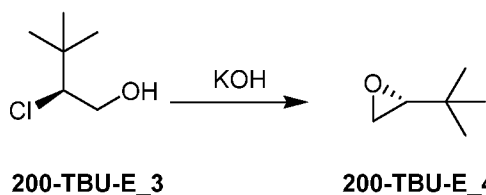
**[00401]          Synthesis of 200-TBU-E\_2**



LiAlH<sub>4</sub> (14.4 g, 381 mmol) was added to a solution of **200-TBU-E\_2** (48 g, 318 mmol) in THF (500 mL) at 0°C. The mixture was warmed to 25°C and stirred at 25°C for 30 mins. Water/THF (100 mL, 1/1) was added and the pH was adjusted to 2~3 with HCl (1 mol/L). The mixture was extracted with EA (2 x 500 mL), washed with brine (2 x 200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuum to give **200-TBU-E\_3** (36 g, crude) as a solid. This product was used in the next step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.92-3.86 (m, 2H), 3.68-3.63 (m, 1H), 1.04 (s, 9H).

**[00402]          Synthesis of 200-TBU-E\_4**

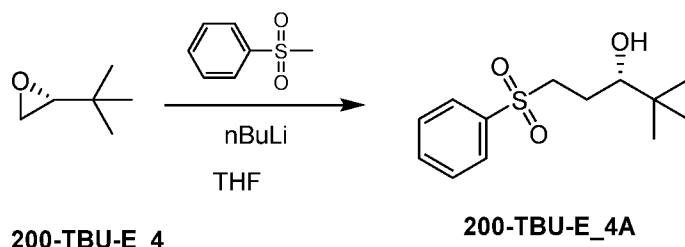


**200-TBU-E\_3** (16 g, 117 mmol) was added to a solution of potassium hydroxide (13.1 g, 234 mmol) in water (13 ml) at 0°C. The ice bath was replaced by a water bath at 20°C. As the cyclization reaction proceeded, a precipitate of potassium chloride formed. After 10 min, the

bath temperature was raised slowly to 50°C. The product was isolated by distillation to afford **200-TBU-E\_4** (6 g, 51.2%) as an oil. 100%ee after protected with UV group.

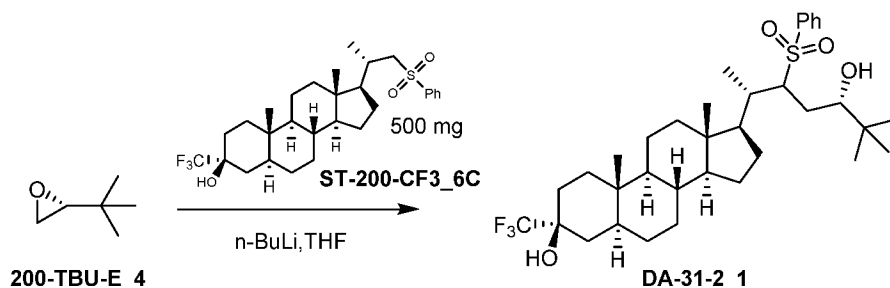
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.73-2.71 (m, 1H), 2.64-2.63 (m, 1H), 2.62-2.59 (m, 1H), 0.91 (s, 9H).

5 [00403] **Method for ee checking of chiral epoxide**



n-BuLi (2.5 M, 1.99 mmol, 0.8 mL) was added dropwise to a solution of (methanesulfonyl)benzene (342 mg, 2.19 mmol) in THF (5 mL) was under N<sub>2</sub> at -70°C. After stirring at -70°C for 30 min, a solution of 200-TBU-E\_4 (100 mg, 0.998 mmol) was added. Then reaction was stirred at stirred at 25oC for 12 hours. The mixture was poured into ice-water (100 mL) and extracted with EA (2 X 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE/EA = 5/1) to afford 200-TBU-E\_4A (80 mg, 31.3%) as an oil. The ee % of product was determined to be 100% by chiral HPLC.

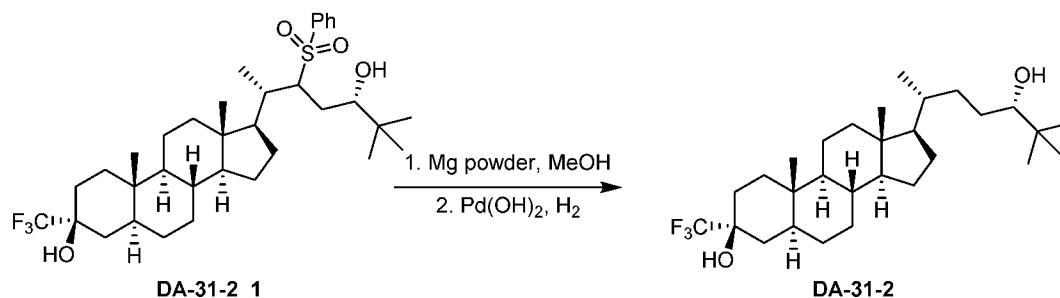
15 [00404] **Synthesis of DA-31-2\_1**



n-BuLi (0.416 mL, 2.5 M, 1.03 mmol) was added to a solution of diisopropylamine (110 mg, 1.09 mmol) in THF (1 mL) under N<sub>2</sub> at -70°C. The resulting mixture was stirred at 0°C for 30 min. The mixture was re-cooled to -70°C. To the mixture was added **ST-200-CF3\_6C** (250 mg, 0.474 mmol) in THF (2 mL) at -70°C. The reaction mixture was stirred at -70°C for 1 hour. (R)-2-(tert-butyl)oxirane (56.8 mg, 0.568 mmol) in THF (1 mL) was added at -70°C. The reaction mixture was warmed to 15°C slowly and stirred at 15°C for 16 h. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (20 mL) at 0°C. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give crude **DA-31-2\_1** (300 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95-7.85 (m, 2H), 7.68-7.63 (m, 1H), 7.60-7.50 (m, 2H), 3.45-3.35 (m, 2H), 3.25-3.15 (m, 1H), 2.60-2.55 (m, 1H), 2.10-1.60 (m, 6H), 1.55-1.20 (m, 11H), 1.20-1.00 (m, 7H), 0.93 (s, 9H), 0.90-0.80 (m, 5H), 0.70-0.50 (m, 3H), 0.45 (s, 3H).

[00405] **Synthesis of DA-31-2**

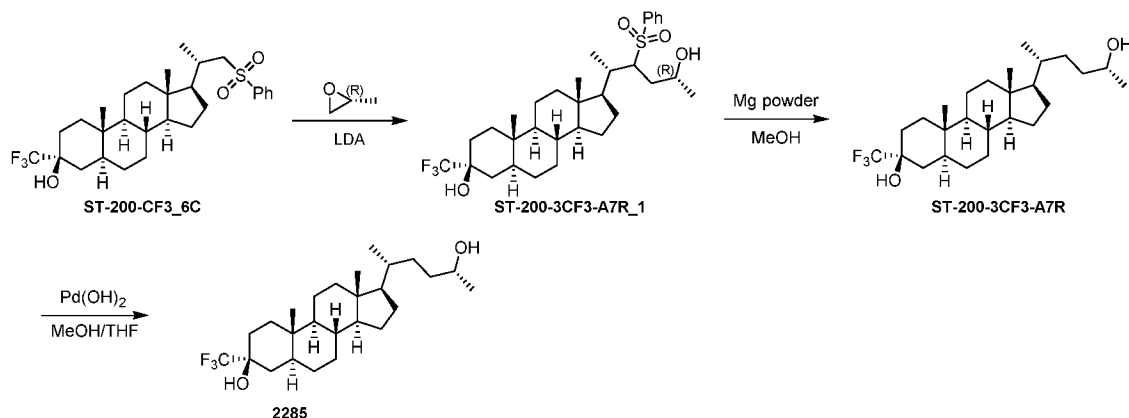


Mg (229 mg, 9.55 mmol) was added to a solution of **DA-31-2\_1** (300 mg, 0.478 mmol) in MeOH (5 mL). Next, the reaction was stirred at 60°C for 2 h under N<sub>2</sub>. Aqueous HCl (10 mL, 4 M) was added to the reaction mixture, then extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude product. The crude product was purified by silica gel chromatography (PE/EtOAc = 30/1 to 10/1) to give impure **DA-31-2** (100 mg, impure) as a solid. Dry Pd(OH)<sub>2</sub>/C (50 mg) was added to a solution of **DA-31-2** (100 mg, impure, 0.205 mmol) in MeOH/THF = 1/1 (4 mL). Next, the reaction mixture was stirred at 50 °C for 16 h under H<sub>2</sub> and 50 Psi. The reaction mixture was filtered through a pad of Celite and washed with THF (3 x 5 mL). The combined organic layer was concentrated in vacuum to give a crude **DA-31-2** (85 mg) as a solid, which was purified by re-crystallization from MeCN (2 mL) to give **DA-31-2** (60 mg, 71%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.20-3.05 (m, 1H), 2.10-1.90 (m, 3H), 1.90-1.60 (m, 7H), 1.55-1.40 (m, 5H), 1.40-1.10 (m, 14H), 1.10-1.00 (m, 3H), 0.93 (s, 9H), 0.89 (s, 3H), 0.75-0.66 (m, 1H), 0.65 (s, 3H).

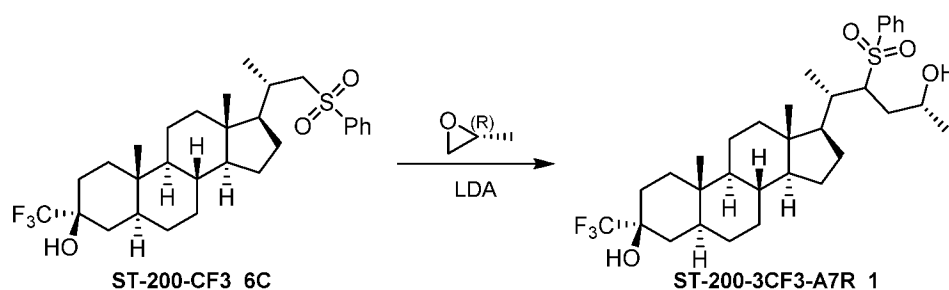
LCMS Rt = 1.356 min in 2.0 min chromatography, 30-90 AB, purity 99%, MS ESI calcd. for C<sub>29</sub>H<sub>48</sub>F<sub>3</sub>O[M-H<sub>2</sub>O+H]<sup>+</sup> 469, found 469.

**EXAMPLE 22: Synthesis of 2285**



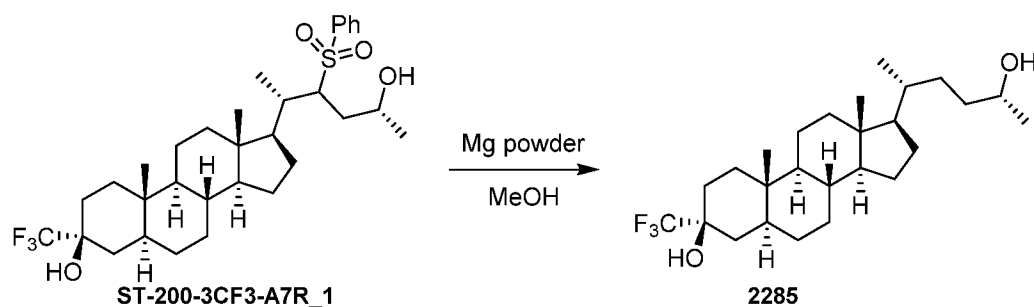
[00406] The synthesis of **ST-200-CF3\_6C** or **B7** can be found in Example 5.

[00407] **Synthesis of ST-200-3CF3-A7R\_1**



- 5 A suspension of **ST-200-CF3\_6C** (250 mg, 0.475 mmol) in THF (2.5 mL) was added dropwise to a solution of n-BuLi (568  $\mu\text{L}$ , 2.5 M in hexane, 1.42 mmol) in THF (0.5 mL) at  $-78^\circ\text{C}$  under  $\text{N}_2$ . The mixture was stirred for 30 minutes at  $-78^\circ\text{C}$ . A solution of 2-(methyl)oxirane (41.3 mg, 0.712 mmol) was added dropwise at  $-78^\circ\text{C}$ . The mixture was stirred for another 30 min and then warmed to  $25^\circ\text{C}$  gradually. The reaction mixture was stirred at  $25^\circ\text{C}$  for 16 hour. The reaction
- 10 mixture was quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL), extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **ST-200-3CF3-A7R\_1** (340 mg, crude) as a solid, which was used directly for the next step.

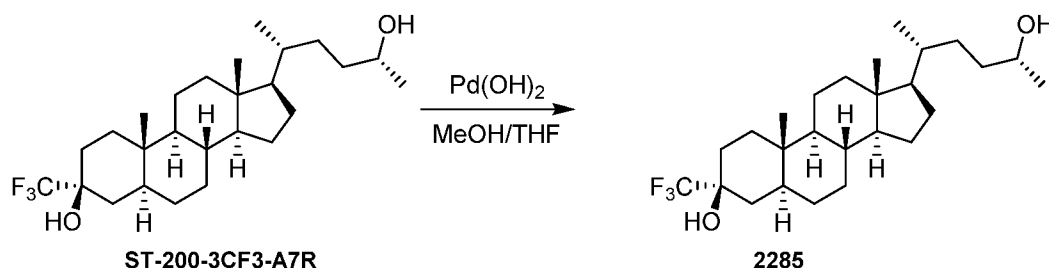
[00408] **Synthesis of 2285**



Mg powder (556 mg, 23.2 mmol) was added to a solution of **ST-200-3CF3-A7R\_1** (340 mg, 0.581 mmol) in dry methanol (30 mL) under  $\text{N}_2$  at  $60^\circ\text{C}$ . The reaction mixture was quenched by

2 M HCl (50 mL) added dropwise at 10°C until the solid was dissolved. After extraction with EtOAc (2 x 50 mL), the organic layer was washed with sat. NaHCO<sub>3</sub> (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column, eluted with PE/EtOAc=20/1 to 5/1, to give **2285** (80 mg, impure containing some 22-23 olefin) as a solid, which was used for next step without further purification.

#### [00409] Synthesis of ST-200-3CF3-A7R



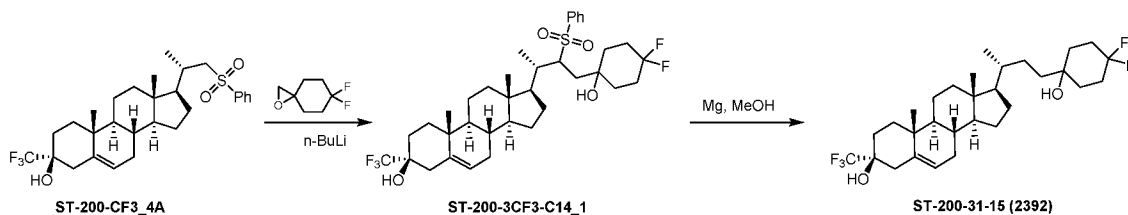
Pd(OH)<sub>2</sub> (20%, 126 mg, 0.180 mmol) was added to a solution of **2285** (80 mg, 0.180 mmol) in MeOH/THF (10 mL/10 mL) under Ar. After degassing three times with N<sub>2</sub> and H<sub>2</sub>, the reaction mixture was stirred for 16 h at 50°C under H<sub>2</sub> atmosphere (50 psi). The desired product was produced, the catalyst was removed by suction, and the filtrate was concentrated to give **2285** (50 mg, impure) as a solid, which was triturated with MeCN (3 mL) at 25°C to give **2285** (36 mg, 45%) as a solid.

#### **2285**

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 3.74-3.72 (m, 1H), 2.08-2.06 (m, 1H), 2.00-1.91 (m, 2H), 1.88-1.75 (m, 2H), 1.74-1.59 (m, 3H), 1.52-1.22 (m, 13H), 1.21-0.96 (m, 10H), 0.95-0.86 (m, 4H), 0.85 (s, 3H), 0.73-0.62 (m, 4H)

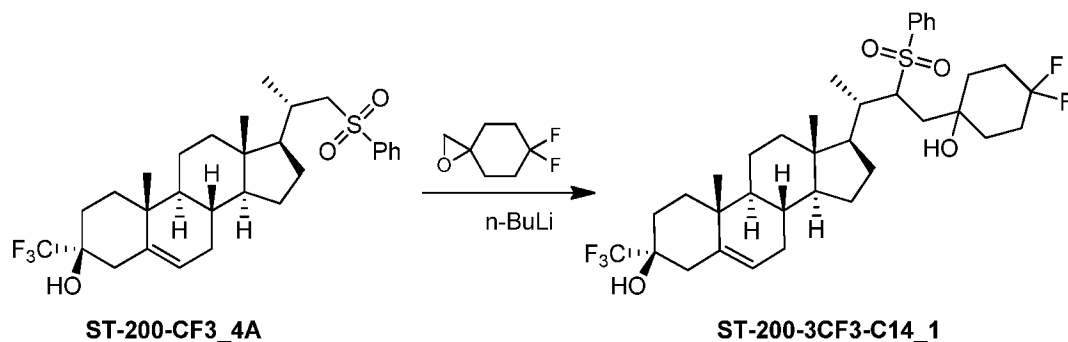
LCMS Rt = 1.199 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>26</sub>H<sub>42</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 427, found 427.

#### EXAMPLE 23: Synthesis of 2392



The experimental of intermediate **ST-200-CF3\_4A** or **A7** can be found in Example 3.

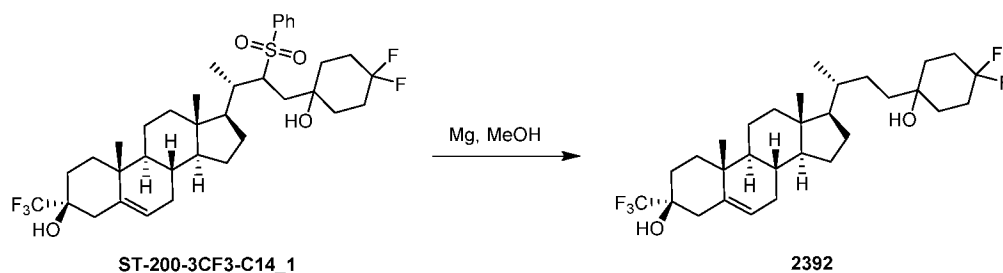
#### [00411] Synthesis of ST-200-3CF3-C14\_1



BuLi (0.476 mL, 2.5 M in hexane, 1.19 mmol) was added to THF (0.5 mL). A solution of **ST-200-CF3\_4A** (250 mg, 0.476 mmol) in THF (3 mL) was added at  $-70^{\circ}\text{C}$ . The mixture was stirred at  $-70^{\circ}\text{C}$  for 1 h. 6,6-difluoro-1-oxaspiro[2.5]octane (210 mg, 1.42 mmol) was added at  $-70^{\circ}\text{C}$ .

- 5 The mixture was stirred at  $-70^{\circ}\text{C}$  for another 1 h. The mixture was warmed to  $25^{\circ}\text{C}$  and stirred for 16 hrs.  $\text{NH}_4\text{Cl}$  (50 mL, sat. aq.) was added to the mixture, then the mixture was extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give **ST-200-3CF3-C14\_1** (300 mg, crude) as a solid, which was used directly for the next step.

#### 10 [00412] Synthesis of 2392

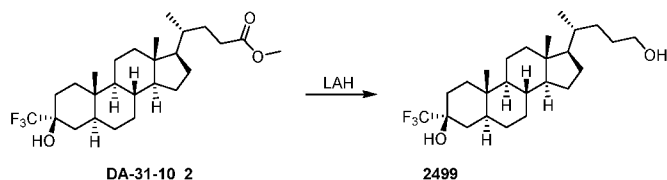


A solution of **ST-200-31-15\_1** (300 mg, 0.445 mmol) in MeOH (20 mL) was heated at  $55^{\circ}\text{C}$ . Mg powder (427 mg, 17.8 mmol) was added in one portion at  $55^{\circ}\text{C}$ . The mixture was refluxed at  $65^{\circ}\text{C}$  for 1 h. The mixture was quenched with HCl (50 mL, 1N) until the reaction became clear, then was extracted with DCM (2 x 30 mL). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give impure product (110 mg), which was purified again by SFC (column: AD(250mm\*30mm,5um), gradient: 35-35% B (A= 0.1% $\text{NH}_3/\text{H}_2\text{O}$ , B= MeOH ), flow rate: 60 mL/min) to give **2392** (72 mg, 30%) as a solid.

- 20  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.38-5.35 (m, 1H), 2.49 (s, 2H), 2.20-1.81 (m, 9H), 1.80-1.71 (m, 3H), 1.70-1.58 (m, 5H), 1.56-1.36 (m, 7H), 1.35-1.22 (m, 2H), 1.20-1.08 (m, 4H), 1.06 (s, 3H), 1.04-0.92 (m, 6H), 0.68 (s, 3H).

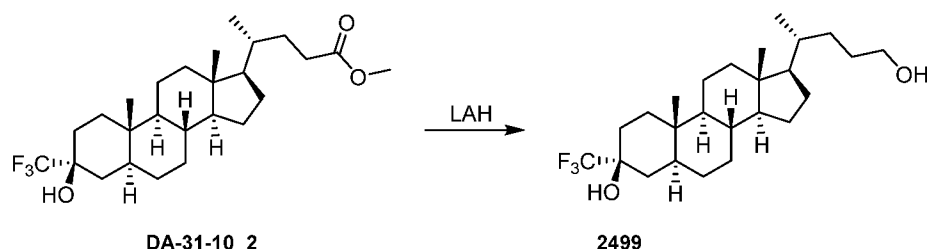
**LCMS** Rt = 1.248 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for  $\text{C}_{30}\text{H}_{44}\text{F}_5\text{O} [\text{M}+\text{H}-\text{H}_2\text{O}]^+$  515, found 515.

### EXAMPLE 24: Synthesis of 2499



**[00413]** The synthesis of **DA-31-10 2** can be found in Example 11.

5 [00414] Synthesis of 2499

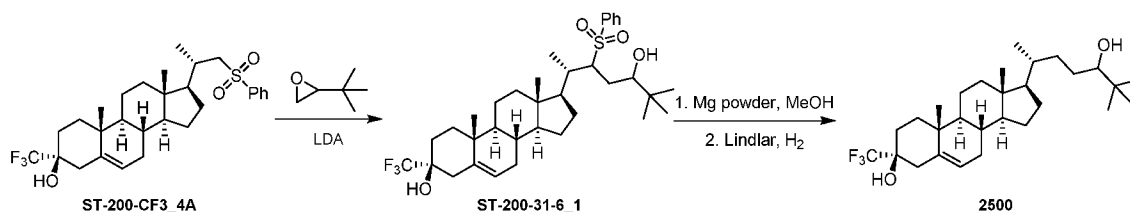


To a suspension of  $\text{LiAlH}_4$  (1.03 g, 27.4 mmol) in THF (80 mL) was added a solution of **DA-31-10\_2** (6.3 g, 13.7 mmol) in THF (20 mL) under  $\text{N}_2$  dropwise at  $0^\circ\text{C}$ . The reaction was stirred at  $25^\circ\text{C}$  for 2 h. The reaction was quenched with water/THF (1/10, 40 mL). To the mixture was added 2 M HCl (100 mL) at  $0^\circ\text{C}$  and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with brine (300 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to afford **2499** (5 g, crude) as a solid. 100 mg of the impure **DA-31-10\_3** was triturated with  $\text{CH}_3\text{CN}$  (5 mL) at  $25^\circ\text{C}$  for 3 hours to give **2499** (52 mg, 52%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.70-3.50 (m, 2H), 2.10-1.90 (m, 3H), 1.85-1.75 (m, 2H), 1.70-1.60 (m, 4H), 1.50-1.20 (m, 14H), 1.15-0.80 (m, 12H), 0.70-0.60 (m, 4H).

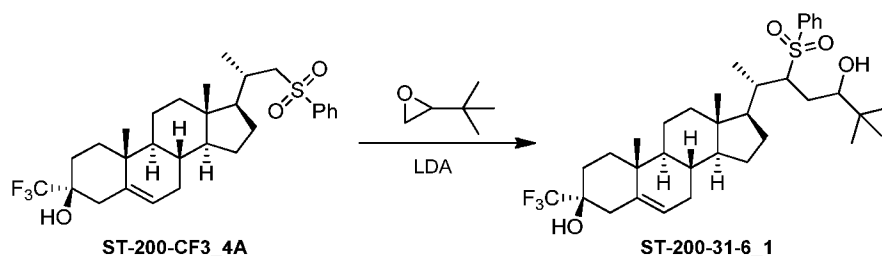
LCMS Rt = 1.179 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. For  $C_{25}H_{40}F_3O$   $[M+H-H_2O]^+$  413, found 413.

### EXAMPLE 25: Synthesis of 2500



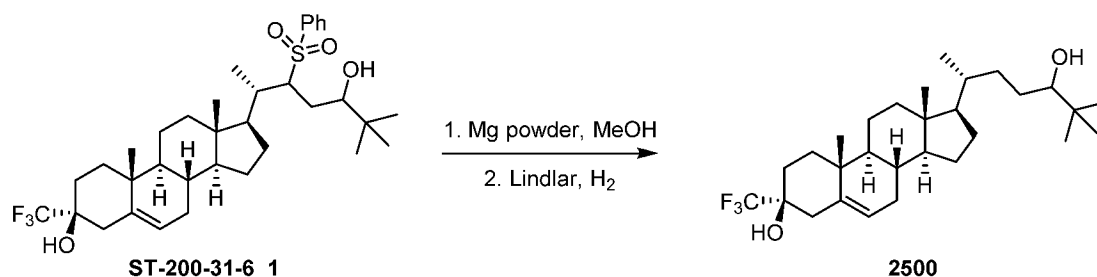
**[00415]** The experimental of intermediate **ST-200-CF3\_4A** can be found in Example 3.

**[00416]      Synthesis of ST-200-31-6 1**



n-BuLi (568  $\mu$ L, 2.5 M in hexane, 1.42 mmol) was added to a solution of diisopropylamine (143 mg, 1.42 mmol) in THF (0.5 mL) at  $-78^{\circ}\text{C}$  under  $\text{N}_2$ . A suspension of **ST-200-CF3\_4A** (250 mg, 0.476 mmol) in THF (2.5 mL) was added dropwise. The mixture was stirred for 30 minutes at  $-78^{\circ}\text{C}$ . A solution of 2-(tert-butyl)oxirane (71.5 mg, 0.715 mmol) was added dropwise at  $-78^{\circ}\text{C}$ . The mixture was stirred for another 30 min and then warmed to  $25^{\circ}\text{C}$  gradually. The reaction mixture was stirred at  $25^{\circ}\text{C}$  for 16 hour. The reaction mixture was quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL), extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **ST-200-31-6\_1** (350 mg, crude) as a solid, which was used directly for the next step.

#### [00417] Synthesis of 2500

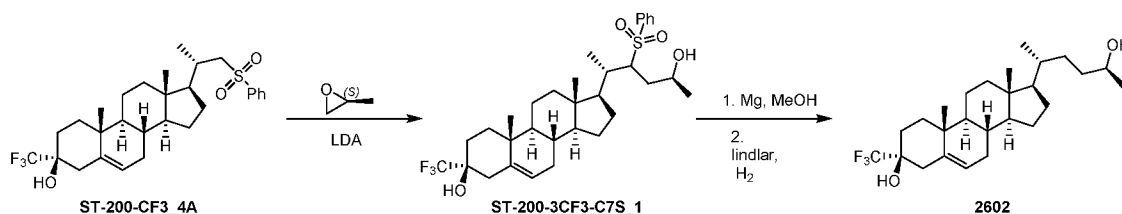


A solution of **ST-200-31-6\_1** (350 mg, 0.6081 mmol) in MeOH (25 mL) was heated at  $60^{\circ}\text{C}$ . Mg powder (584 mg, 24.3 mmol) was added in four portions at  $60^{\circ}\text{C}$ . The mixture was stirred at  $60^{\circ}\text{C}$  for 1h. The mixture was quenched with HCl (50 mL, 2 M) until the reaction became clear and extracted with DCM (2 x 50 mL). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give 112 mg of impure product as a solid, which was triturated with MeCN (3 mL) at  $25^{\circ}\text{C}$  to give 70 mg as a solid. The 70 mg product was dissolved in THF (8 mL) and treated with Lindlar (100 mg) under  $\text{N}_2$ . The mixture was degassed under vacuum and purged with  $\text{H}_2$  (15 psi) several times. The mixture was stirred for 2 hrs at  $25^{\circ}\text{C}$  under  $\text{H}_2$  (15 psi). The mixture was filtered and the filter was concentrated in vacuum. The residue was purified by flash column (0-20% EtOAc in PE) to afford pure 2500 (20 mg) as a solid.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  5.40-5.30 (m, 1H), 3.20-3.00 (m, 1H), 2.50-2.45 (s, 2H), 2.05-2.00 (m, 4H), 1.96-1.33 (m, 13H), 1.33-1.20 (m, 7H), 1.20-0.80 (m, 16H), 0.68 (s, 3H).

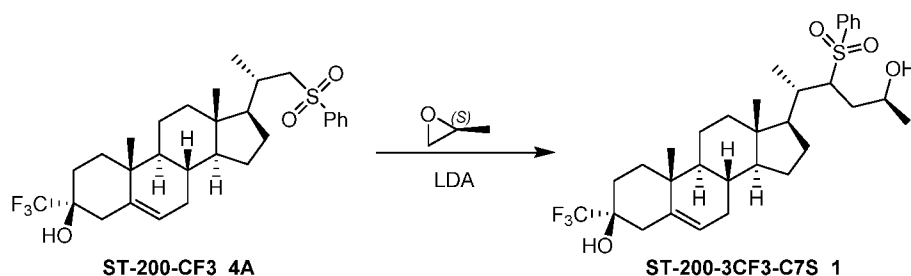
LCMS Rt = 1.404 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For  $C_{28}H_{46}F_3O$   $[M-H_2O+H]^+$  467, found 467.

### EXAMPLE 26: Synthesis of 2602



[00419] The experimental of intermediate **ST-200-CF3\_4A** or **A7** can be found in Example 3.

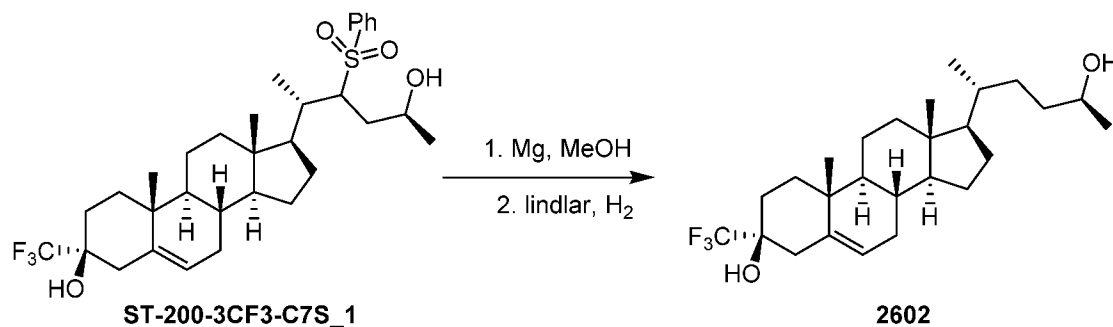
### [00420] Synthesis of ST-200-3CF3\_C7S\_1



10 A suspension of **ST-200-CF3\_4A** (250 mg, 0.476 mmol) in THF (2.5 mL) was added dropwise to a solution of n-BuLi (0.568 mL, 2.5 M in hexane, 1.42 mmol) in THF (0.5 mL) at  $-65^{\circ}\text{C}$  under  $N_2$ . The mixture was added diisopropylamine (143 mg, 1.42 mmol) and stirred for 30 minutes at  $-65^{\circ}\text{C}$ . A solution of (S)-2-methyloxirane (33.1 mg, 0.571 mmol) was added dropwise at  $-65^{\circ}\text{C}$ . The mixture was stirred for another 30 minutes and then warmed to  $25^{\circ}\text{C}$  gradually. The reaction

15 mixture was stirred at  $25^{\circ}\text{C}$  for 16 hours. The reaction mixture was quenched by saturated  $NH_4Cl$  aqueous (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $Na_2SO_4$ , filtered and concentrated under vacuum to give **ST-200-3CF3-C7S\_1** (250 mg, crude) as a solid, which is used directly for the next step.

### 20 [00421] Synthesis of 2602

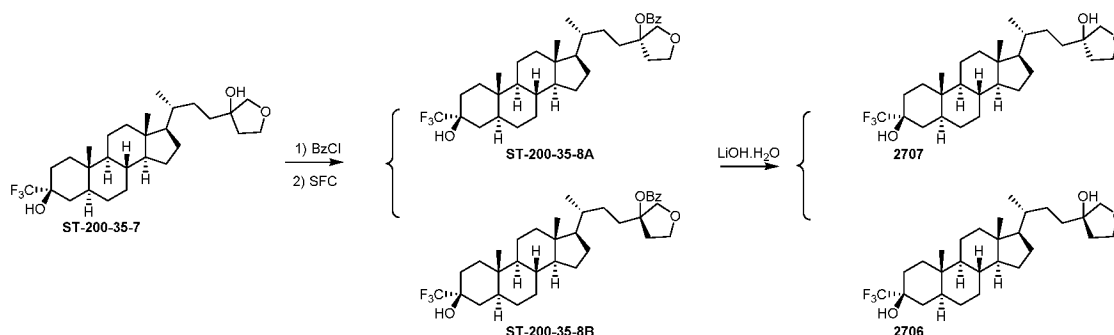


Mg powder (415 mg, 17.1 mmol) was added to a solution of **ST-200-3CF3-C7S\_1** (250 mg, 0.428 mmol) and nickel (II) chloride (13.8 mg, 0.107 mmol) in dry methanol (20 mL) under N<sub>2</sub> and the mixture was stirred at 50°C to initiate continuous hydrogen generation. The reaction mixture was stirred at 60°C for 1 hour. Next, the reaction mixture was quenched by 2M HCl (100 mL) which was added dropwise at 10 °C until solid was dissolved. After extracting with EtOAc (2 x 150 mL), the combined organic layer was washed with sat. NaHCO<sub>3</sub> aq.(300 mL), brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a solid, which was purified by silica gel chromatography (PE:EtOAc=4:1) to give 100 mg of solid (the residue was containing 13% 22, 23 alkene). The impure residue was dissolved in THF (20 mL) was added Lindlar (15.9 mg, 0.225 mmol) under N<sub>2</sub>.The mixture was degassed under vacuum and purged with H<sub>2</sub> several times. The mixture was stirred for 2 hrs at 25°C under H<sub>2</sub>. The mixture was filtered and the filter was concentrated in vacuum. The residue was purified by SFC (column: C2 250mm\*30mm, 10um), gradient: 35-35% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O, B= EtOH), flow rate: 50 mL/min) to give **2602** (16 mg, 54 %) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-35 (m, 1H), 3.75-3.65 (m, 1H), 2.50-2.45 (m, 2H), 2.10-1.70 (m, 7H), 1.69-1.50 (m, 6H), 1.49-1.20 (m, 10H), 1.19-0.90 (m, 11H), 0.68 (s, 3H).

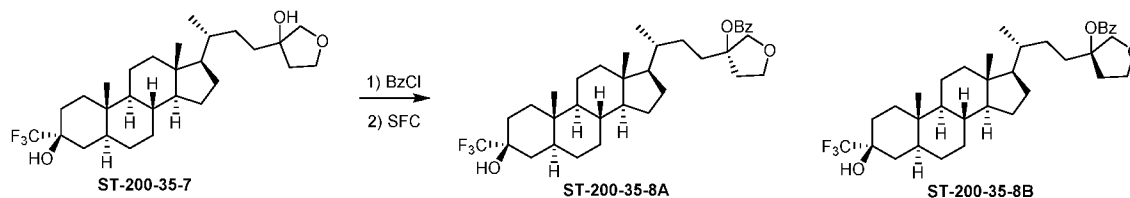
LCMS Rt = 1.202 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>26</sub>H<sub>40</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 425, found 425.

## EXAMPLE 27: Synthesis of 2706 and 2707



[00422] The experimental of intermediate **ST-200-CF3\_4A** can be found in Example 3. ST-200-35-7 can be found in Example 19. The stereochemistry of 2707 was confirmed by X-ray.

## [00423] Synthesis of ST-200-35-8A/8B



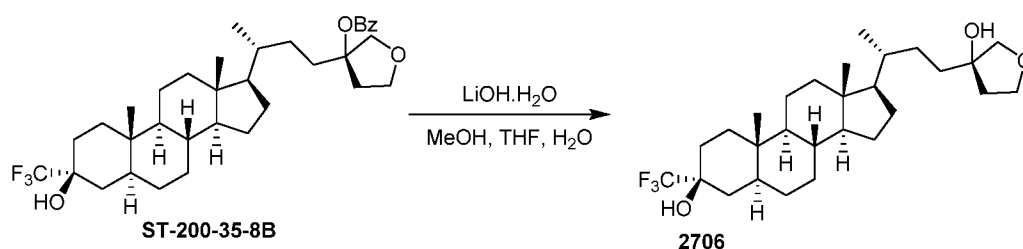
BzCl (258 mg, 1.84 mmol) was added to a solution of **ST-200-35-7** (300 mg, 0.616 mmol) in pyridine (5 mL) at 0°C. The mixture was stirred for 1 h at 0°C. To the mixture was added water (10 mL) at 0°C and extracted with DCM (3 x 10 mL). The organic layer was washed with 1M HCl (10 mL), saturated Na<sub>2</sub>CO<sub>3</sub> (10 mL) and brine. The mixture was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by prep-TLC (PE/EA= 5/1) to give a mixture. The mixture was separated by SFC twice (Instrument: MG-II; Method: Column: AD(250mm\*30mm,5um); Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O EtOH; Begin B: 40%; End B: 40%; FlowRate(ml/min): 60; Injections: 90) to give peak 1 (Rt = 5.134 min) as **ST-200-35-8B** (44 mg, 12%) and peak 2 (Rt = 5.766 min) **ST-200-35-8A** (38 mg, 10%) both as a solid.

#### 10 **ST-200-35-8B:**

SFC Rt = 5.134 min in 10.0 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 100%de.

#### **ST-200-35-8A:**

#### [00424] **Synthesis of 2706**



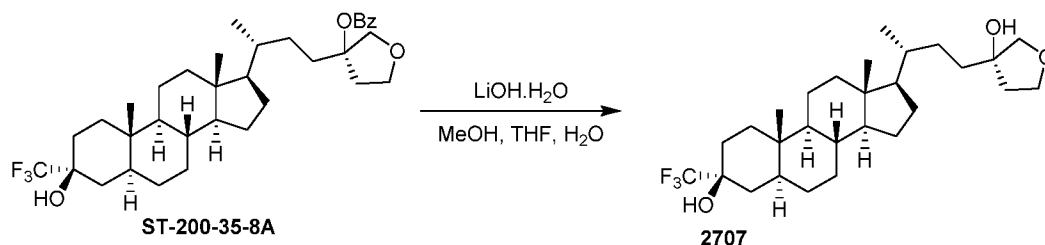
15 MeOH (0.2 mL), water (0.2 mL) and LiOH.H<sub>2</sub>O (31.2 mg, 0.744 mmol) were added to a solution of **ST-200-35-8B** (44 mg, 0.0744 mmol) in THF (0.4 mL). The mixture was stirred at 50°C for 16 h. EtOAc (5 mL) and water (2 mL) were added to the mixture. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum and triturated from MeCN (1 mL) to give **2706** (24 mg, 66%) as a solid.

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.02 (q, *J* = 8.0 Hz, 1H), 3.93-3.83 (m, 1H), 3.69 (d, *J* = 9.2 Hz, 1H), 3.55 (d, *J* = 9.2 Hz, 1H), 2.10-1.79 (m, 7H), 1.75-1.59 (m, 5H), 1.55-0.99 (m, 18H), 0.98-0.88 (m, 4H), 0.85 (s, 3H), 0.75-0.60 (m, 4H).

HPLC Rt = 3.97 min in 8.0 min chromatography, 50-100\_AB\_E, purity 100%.

MS MS ESI calcd. for C<sub>28</sub>H<sub>44</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 469.3288, found 469.3244.

#### 25 [00425] **Synthesis of 2707**



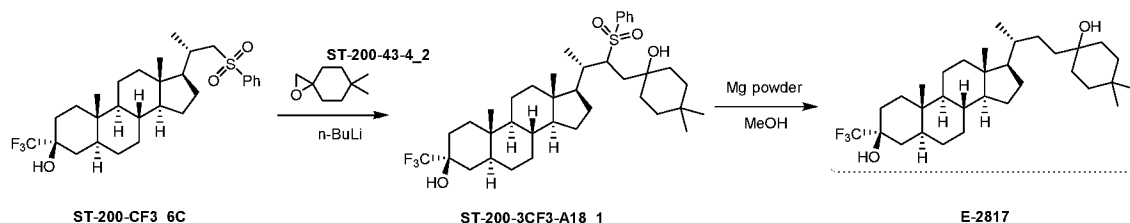
MeOH (0.2 mL), water (0.2 mL) and LiOH.H<sub>2</sub>O (26.9 mg, 0.642 mmol) were added to a solution of **ST-200-35-8A** (38 mg, 0.0643 mmol) in THF (0.4 mL). The mixture was stirred at 50°C for 16 h. EtOAc (5 mL) and water (2 mL) were added to the mixture. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum and triturated from MeCN (1 mL) to give **2707** (21 mg, 67%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.02 (q, *J* = 8.0 Hz, 1H), 3.94-3.85 (m, 1H), 3.69 (d, *J* = 9.2 Hz, 1H), 3.54 (d, *J* = 9.2 Hz, 1H), 2.10-1.59 (m, 13H), 1.55-0.99 (m, 17H), 0.98-0.88 (m, 4H), 0.85 (s, 3H), 0.75-0.62 (m, 4H).

HPLC Rt = 3.93 min in 8.0 min chromatography, 50-100\_AB\_E, purity 100%.

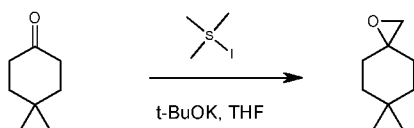
MS MS ESI calcd. for C<sub>28</sub>H<sub>44</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 469.3288, found 469.3244.

### EXAMPLE 28: Synthesis of E-2817



[00426] The synthesis of **ST-200-CF3\_6C** can be found in Example 5.

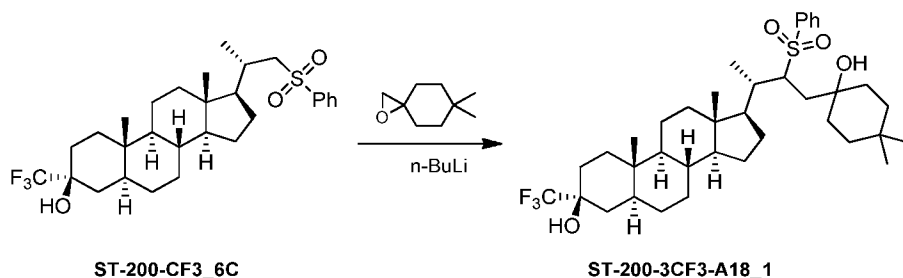
15 [00427] The synthesis of **ST-200-43-4\_2**.



To a suspension of t-BuOK (3.53 g, 31.6 mmol) in THF (30 mL) was added Me<sub>3</sub>SiI (4.18 g, 20.5 mmol) under N<sub>2</sub> at 15°C. The suspension was stirred at 15°C for 30 min. To the mixture was added a solution of **200-DA-E31\_1A** (2 g, 15.8 mmol) in 10 ml of THF dropwise at 15°C. The mixture was stirred at 15°C for 16 hrs. The mixture was quenched with sat.NH<sub>4</sub>Cl (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuum to give **200-DA-E31\_1** (1.8 g, 81%) as a liquid.

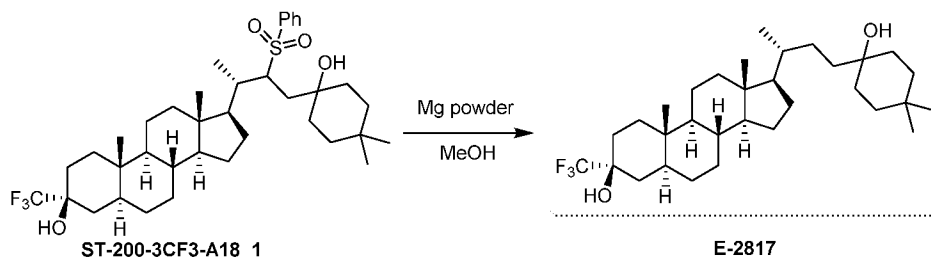
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.58 (s, 2H), 1.90-1.80 (m, 1H), 1.70-1.55 (m, 2H), 1.54-1.45 (m, 3H), 1.40-1.30 (m, 2H), 1.00-0.90 (m, 6H).

25 [00428] Synthesis of **ST-200-3CF3-A18\_1**



First, n-BuLi (0.5 mL, 2.5 M in hexane, 1.25 mmol) was added To THF (0.5 mL) . A solution of **ST-200-CF3\_6C** (250 mg, 0.4746 mmol) in THF (3 mL) was added at -70°C. The mixture was stirred at -70°C for 1 h. **ST-200-43-4\_2** (133 mg, 0.9492 mmol) was added at -70°C. The mixture was stirred at -70°C for another 1 h. The mixture was warmed to 25°C and stirred for 16 hrs. The reaction mixture was quenched by adding NH<sub>4</sub>Cl (50 mL, sat. aq.) and extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub> , filtered, and concentrated to give **ST-200-3CF3-A18\_1**(390 mg, crude) a soild, which was used directly for the next step.

#### 10 [00429] Synthesis of E-2817

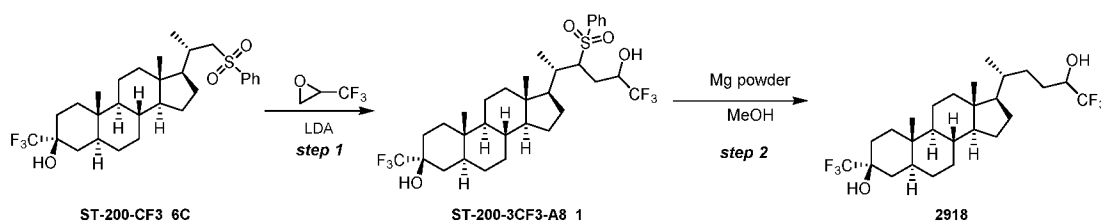


A solution of **ST-200-3CF3-A18\_1** (390 mg, 0.5847 mmol) in MeOH (25 mL) was heated at 60°C. Mg powder (500 mg, 20.8 mmol) was added in four portions at 60°C. The mixture was stirred at 60°C for 1h. The mixture was quenched with HCl (50 mL, 2 M) until the reaction became clear and extracted with DCM (2 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> , filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give 135 mg of a solid. The impure product was purified by flash column (0-20% of EtOAc in PE) to give **E-2817** (101 mg, 75%) as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ 2.08-2.03 (m, 1H), 1.98-1.88 (m, 2H), 1.78-1.73 (m, 2H), 1.73-1.60 (m, 3H), 1.60-1.45 (m, 12H), 1.45-1.27 (m, 7H), 1.27-1.19 (m, 9H), 1.19-1.00 (m, 6H), 0.93-0.84 (m, 9H), 0.75-0.64 (s, 4H).

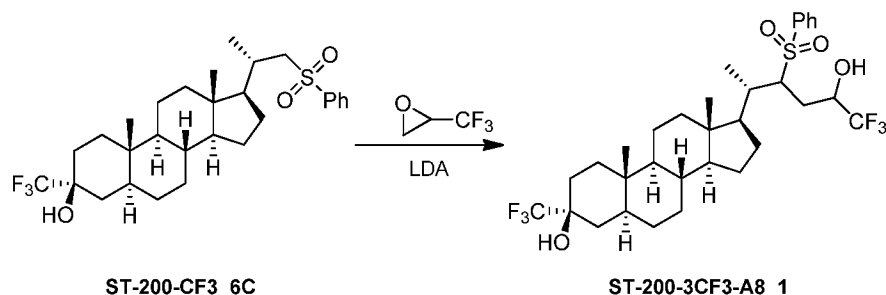
LCMS Rt = 1.463 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>32</sub>H<sub>52</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 509, found 509.

#### 25 EXAMPLE 29: Synthesis of 2918



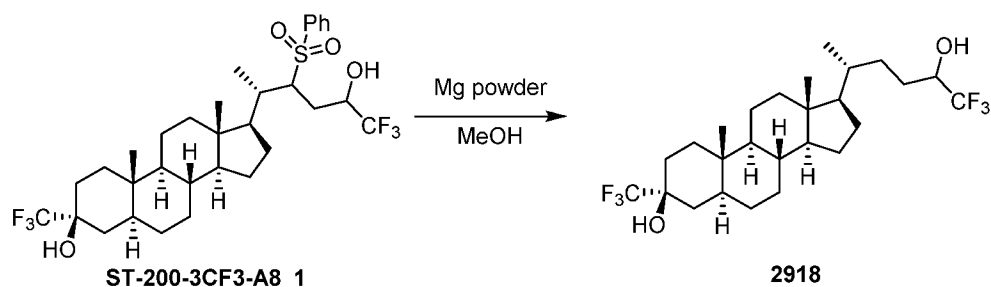
[00430] The synthesis of **ST-200-CF3\_6C** can be found in Example 5.

[00431] **Synthesis of ST-200-3CF3-A8\_1**



- 5 A suspension of **ST-200-CF3\_6C** (250 mg, 0.475 mmol) in THF (2.5 mL) was added dropwise to a solution of n-BuLi (568  $\mu$ L, 2.5 M in hexane, 1.42 mmol) in THF (0.5 mL) at  $-78^{\circ}\text{C}$  under  $\text{N}_2$ . The mixture was stirred for 30 min at  $-78^{\circ}\text{C}$ . A solution of 2-(trifluoromethyl)oxirane (79.7 mg, 0.712 mmol) was added dropwise at  $-78^{\circ}\text{C}$ . The mixture was stirred for another 30 min and then warmed to  $25^{\circ}\text{C}$  gradually. The reaction mixture was stirred at  $25^{\circ}\text{C}$  for 16 hours. The
- 10 reaction mixture was quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **ST-200-3CF3-A8\_1** (340 mg, crude) as a solid, which was used directly for the next step.

[00432] **Synthesis of 2918**

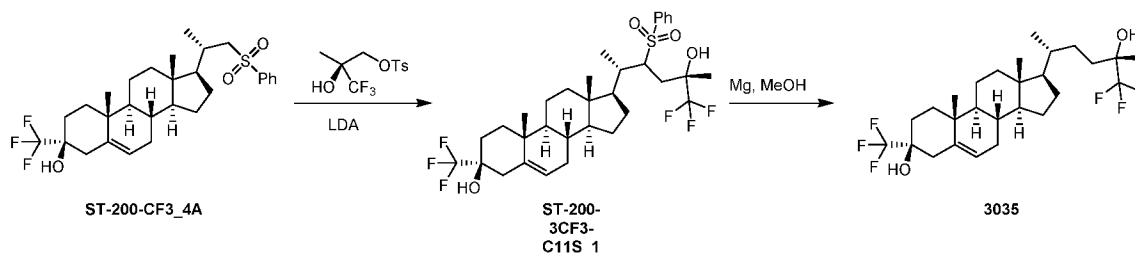


- 15 A solution of **ST-200-3CF3-A8\_1** (340 mg, 0.5322 mmol) in MeOH (25 mL) was heated at  $60^{\circ}\text{C}$ . Mg powder (508 mg, 21.2 mmol) was added in four portions at  $60^{\circ}\text{C}$ . The mixture was stirred at  $60^{\circ}\text{C}$  for 1 h. The mixture was quenched with HCl (50 mL, 1N) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over
- 20  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give 63 mg of a solid, which was triturated from DCM and hexane to give **2918** (5 mg, 2% ).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.90-3.80 (m, 1H), 2.20-1.70 (m, 6H), 1.70-1.50 (m, 7H), 1.50-1.25 (m, 5H), 1.25-1.10 (m, 5H), 1.10-0.80 (m, 12H), 0.70-0.65 (m, 4H).

LCMS Rt = 1.219 min in 2 min chromatography, 30-90 AB, purity 100%.

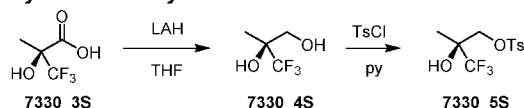
## 5 EXAMPLE 30: Synthesis of 3035



[00433] The experimental of intermediate **ST-200-CF3\_4A** can be found in Example 3.

[00434] The synthesis of the tosylate:

**Synthesis of tosylate:**



- 10 To a suspension of  $\text{LiAlH}_4$  (45.3 g, 1.26 mol) in THF (1 L) was added dropwise a solution of **7330\_3S** (100 g, 632 mmol) in THF (500 mL) at  $0^\circ\text{C}$  and the inner temperature raised to about  $50^\circ\text{C}$ . After addition, the mixture was stirred at  $70^\circ\text{C}$  for 16 hours. The mixture was quenched with HCl (1 L, 3 M aq.) to pH = 2 and extracted with MTBE (3 x 500 mL). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure ( $<40^\circ\text{C}$ )
- 15 to give **7330\_4S** (92 g, crude) as an oil.

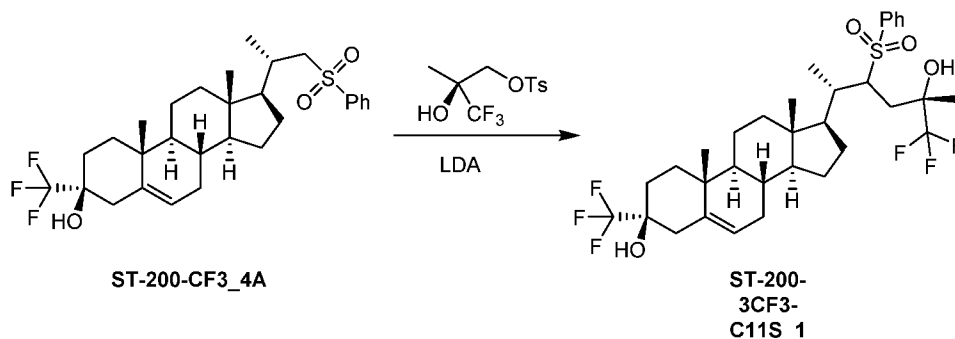
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.96-3.92 (m, 1H), 3.58-3.53 (m, 1H), 3.08 (s, 1H), 1.98-1.89 (m, 1H), 1.38 (s, 3H).

- To a solution of **7330\_4S** (50 g, 346 mmol) in pyridine (300 mL) was added 4-methylbenzene-1-sulfonyl chloride (98.9 g, 519 mmol) in portions during 5 minutes at  $0^\circ\text{C}$ . The reaction solution
- 20 was stirred at  $20^\circ\text{C}$  for 16 hrs. The reaction mixture was quenched with 2N HCl (400 mL) to pH = 1-2 at  $0^\circ\text{C}$ . The inner temperature was maintained below  $30^\circ\text{C}$  and the mixture was extracted with MTBE (3 x 200 mL). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by column (0-10% of EtOAc in PE) to give **7330\_5S** (93 g, 90%, 99.42% ee) as an oil.

- 25  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d,  $J = 7.6$  Hz, 2H), 7.37 (d,  $J = 8.0$  Hz, 2H), 4.13-4.03 (m, 2H), 2.99 (s, 1H), 2.46 (s, 3H), 1.37 (s, 3H),

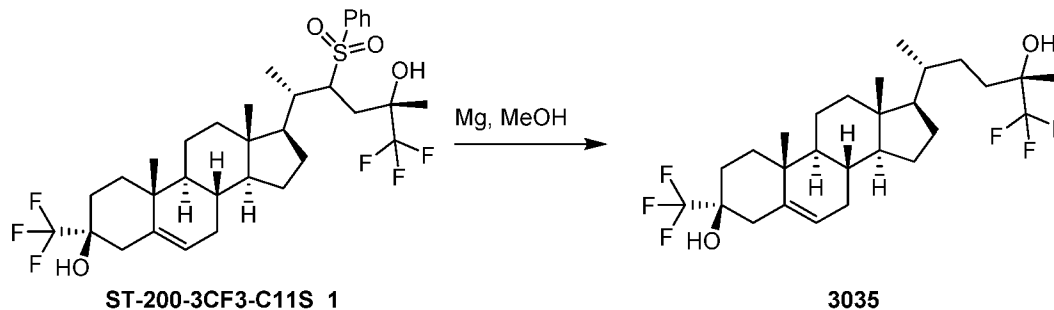
LCMS Rt = 1.103 min in 2.0 min chromatography, 10-80 AB, purity 100%, no MS detected.

[00435] **Synthesis of ST-200-3CF3-C11S\_1**



A suspension of **ST-200-CF3\_4A** (250 mg, 0.48 mmol) in THF (4 mL) was added dropwise to a solution of n-BuLi (0.48 mL, 2.5 M in hexane, 1.19 mmol) in THF (1 mL) at -70°C under N<sub>2</sub>. After stirring for 30 minutes at -70°C, diisopropylamine (120 mg, 1.19 mmol) was added dropwise at -70°C, followed by adding (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (212 mg, 0.71 mmol) dropwise at -70°C. The mixture was stirred for another 30 min and then warmed to 25°C gradually. The reaction mixture was stirred at 25°C for 24 hour. The reaction mixture was quenched by saturated NH<sub>4</sub>Cl aqueous (5 mL), extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **ST-200-3CF3-C11S\_1** (480 mg, crude), which was used directly.

**[00436] Synthesis of 3035**



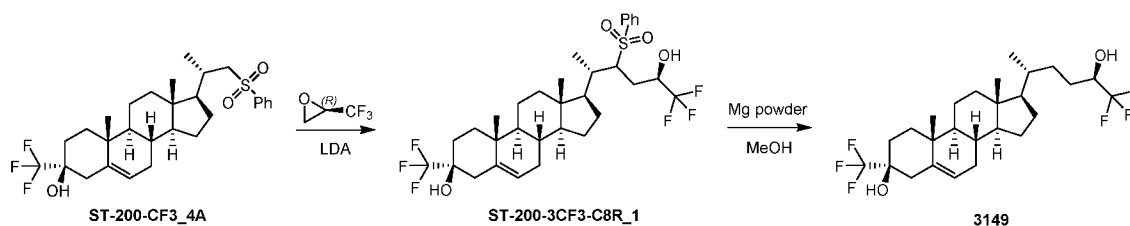
Mg powder (705 mg, 29.4 mmol) and NiCl<sub>2</sub> (1 mg, 0.007 mmol) were added with stirring to a solution of **ST-200-3CF3-C11S\_1** (480 mg, 0.74 mmol) in 50 mL of anhydrous MeOH under N<sub>2</sub> at 60°C. The reaction mixture was quenched by 2 M HCl (10 mL) until the solid was dissolved. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat. NaHCO<sub>3</sub> (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give a crude product, which was further purified by re-crystallized from MeCN (10 mL) at 85°C to give **3035** (53 mg, 21%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.41-5.34 (m, 1H), 2.53-2.46 (s, 2H), 2.08-1.92 (m, 4H), 1.91-1.58 (m, 7H), 1.54-1.35 (m, 7H), 1.33-1.30 (s, 3H), 1.29-1.08 (m, 5H), 1.07-1.05 (s, 3H), 1.05-0.91 (m, 5), 0.73-0.63 (s, 3).

LCMS  $R_t$  = 1.213 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 99%.

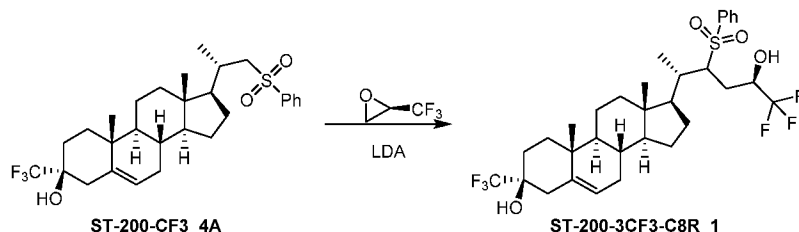
5

### EXAMPLE 31: Synthesis of 3149



[00437] The experimental of intermediate **ST-200-CF3\_4A** can be found in Example 3.

### [00438] Synthesis of ST-200-3CF3\_C8R\_1



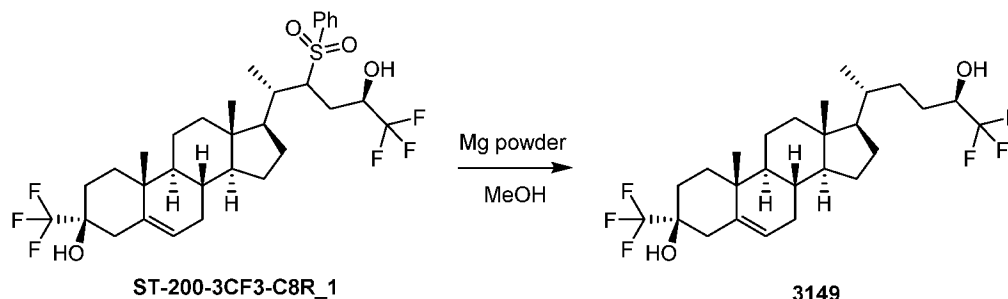
10

A suspension of **ST-200-CF3\_4A** (250 mg, 0.476 mmol) in THF (2.5 mL) was added dropwise to a solution of n-BuLi (0.568 mL, 2.5 M in hexane, 1.42 mmol) in THF (0.5 mL) at  $-65^\circ\text{C}$  under  $\text{N}_2$ . After adding diisopropylamine (143 mg, 1.42 mmol) and stirring for 30 minutes at  $-65^\circ\text{C}$ , a solution of (R)-2-(trifluoromethyl) oxirane (63.9 mg, 0.571 mmol) was added dropwise at  $-65^\circ\text{C}$ .

15 The mixture was stirred for another 30 minutes and then warmed to  $25^\circ\text{C}$  gradually. The reaction mixture was stirred at  $25^\circ\text{C}$  for 16 hours. The reaction mixture was quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **ST-200-3CF3-C8R\_1** (250 mg, crude) as a solid, which was used directly for

20 the next step.

### [00439] Synthesis of 3149



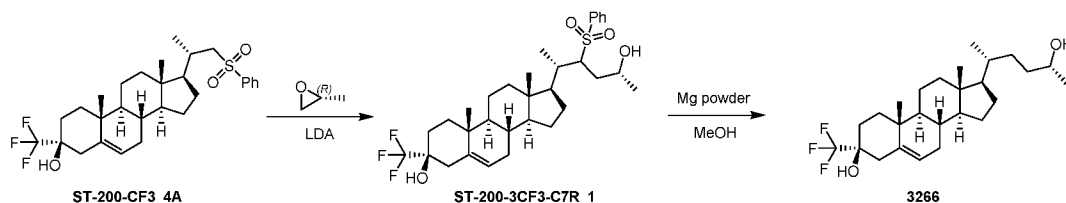
Mg powder (379 mg, 15.6 mmol) was added to a solution of **ST-200-3CF3-C8R\_1** (250 mg, 0.392 mmol) and nickel (II) chloride (12.7 mg, 0.098 mmol) in dry methanol (50 mL) under N<sub>2</sub> at 50°C. While adding Mg, the mixture was stirred to initiate continuous hydrogen generation. Next, the reaction mixture was stirred at 60°C for 1 hour. The reaction mixture was quenched by 2M HCl (100 mL) which was added dropwise at 10 °C until solid was dissolved. After extracting with EtOAc (2 x 150 mL), the combined organic layer was washed with sat. NaHCO<sub>3</sub> aq. (300 mL), brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a solid, which was purified by silica gel chromatography (PE/THF=4/1) to give a crude product, which was re-crystallized from MeCN (10 mL) to give a impure product (30 mg, 15%). The impure product (30 mg, 0.068 mmol) was purified by SFC (column: AD 250mm\*30mm, 10um), gradient: 20-20% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O, B= EtOH), flow rate: 60 mL/min) to give **3149** (12 mg, 40%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 3.75-3.65 (m, 1H), 2.50-2.45 (m, 2H), 2.10-1.70 (m, 11H), 1.69-1.50 (m, 10H), 1.49-0.90 (m, 10H), 0.69 (s, 3H).

HPLC Rt = 6.25 min in 1.2 min chromatography, 30-90 AB, purity 98%.

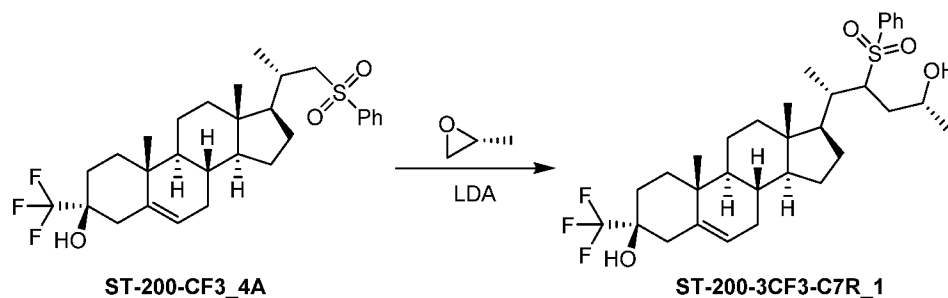
HRMS ESI calcd. for C<sub>26</sub>H<sub>39</sub>F<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 497.2849, found 497.2842.

### EXAMPLE 32: Synthesis of 3266



[00440] The experimental of intermediate **ST-200-CF3\_4A** can be found in Example 3.

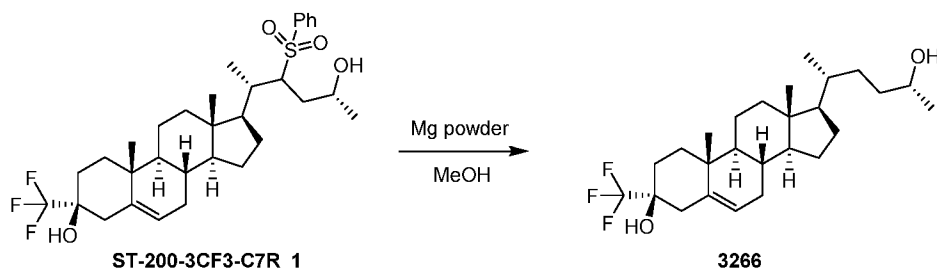
### [00441] Synthesis of ST-200-3CF3-C7R\_1



A suspension of **ST-200-CF3\_4A** (250 mg, 0.476 mmol) in THF (4 mL) was added dropwise to a solution of n-BuLi (568 mL, 2.5 M in hexane, 1.42 mmol) in THF (1 mL) at -65°C under N<sub>2</sub>. After stirring at -65°C 30 minutes, diisopropylamine (143 mg, 1.42 mmol) was added at -65°C. After that, (R)-2-methyloxirane (82.4 mg, 1.42 mmol) was added dropwise at -65°C. The

mixture was stirred for another 30 minutes and then warmed to 25°C gradually. The reaction mixture was stirred at 25°C for 16 hours. The reaction was quenched with sat. NH<sub>4</sub>Cl aq. (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product as a solid, which was used directly for the next step.

**[00442] Synthesis of 3266**

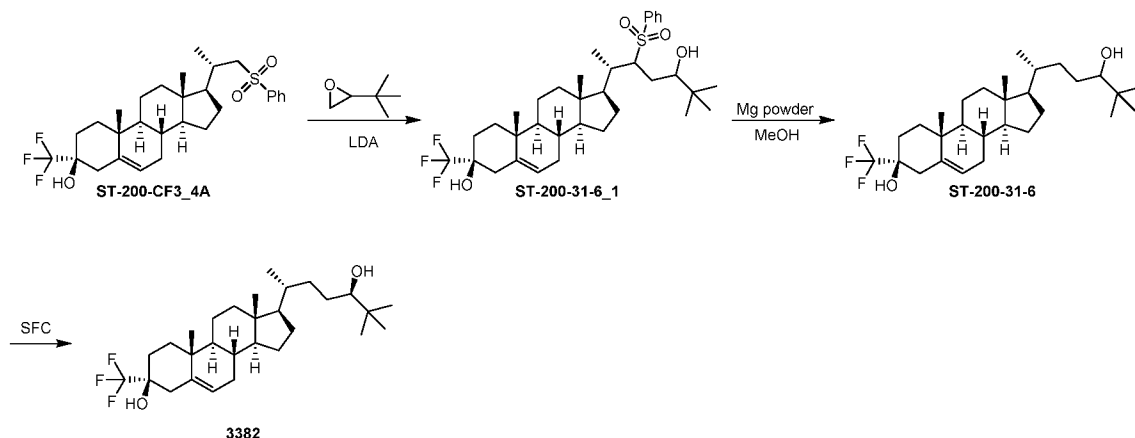


Mg powder (410 mg, 17.1 mmol) was added in four portions by stirring into a solution of **ST-200-3CF3\_C7R\_1** (250 mg, 0.428 mmol) and NiCl<sub>2</sub> (5.52 mg, 0.043 mmol) in dry methanol (20 mL) under N<sub>2</sub> at 50°C. After stirring at 60 °C for 1 hour, the mixture was quenched with HCl (50 mL, 1N) until the reaction became clear and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. The residue was purified by flash column (0-15 % of EtOAc in PE) to give an impure product (100 mg, 0.225 mmol, impure, containing 13 % 22,23 alkene). Lindlar catalyst (200 mg, 0.225 mmol) was added to a solution of impure product in THF (20 mL) under N<sub>2</sub>. The mixture was degassed under vacuum and purged with H<sub>2</sub> several times. The mixture was stirred for 2 hours at 25 °C. The reaction mixture was filtered through a pad of Celite and washed with THF (3 x 10 mL). The filtrate was concentrated to give a impure product, which was triturated from n-hexane(10 mL) at 68°C for 2 hours to give a impure product as a solid. The impure product was purified by silica gel chromatography (PE/EtOAc = 0 to 5/1) to give **3266** (48 mg, impure) as a solid, which was purified by SFC(Column: AD (150×4.6mm, 3um), Gradient: 5%-40% B ( A: CO<sub>2</sub> B: ethanol ) Flow rate: 2.5mL/min) to afford **3266** (10 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.33. (m, 1H), 3.78-3.65 (m, 1H), 2.52-2.45 (m, 2H), 2.08-1.65 (m, 7H), 1.58-1.32 (m, 7H), 1.32-1.23 (m, 4H), 1.23-0.75 (m, 16H), 0.68 (s, 3H).

LCMS Rt = 1.149 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>26</sub>H<sub>40</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 425, found 425.

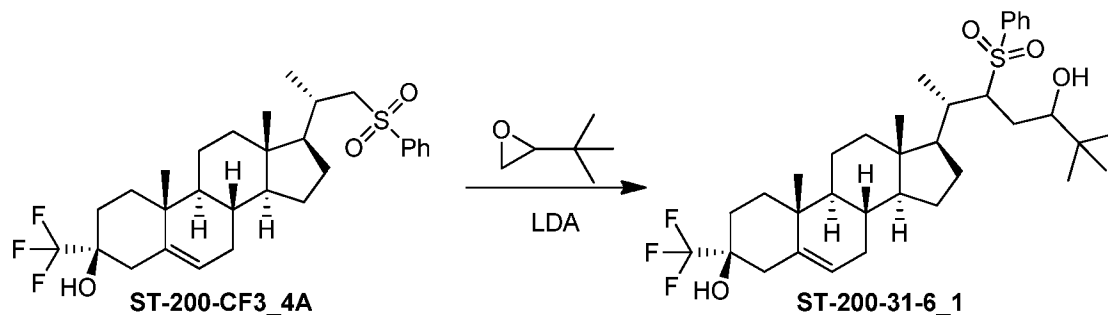
**EXAMPLE 33: Synthesis of 3382**



[00443] Stereochemistry was assigned based on synthesis with chiral epoxide, see Example 35 for synthesis.

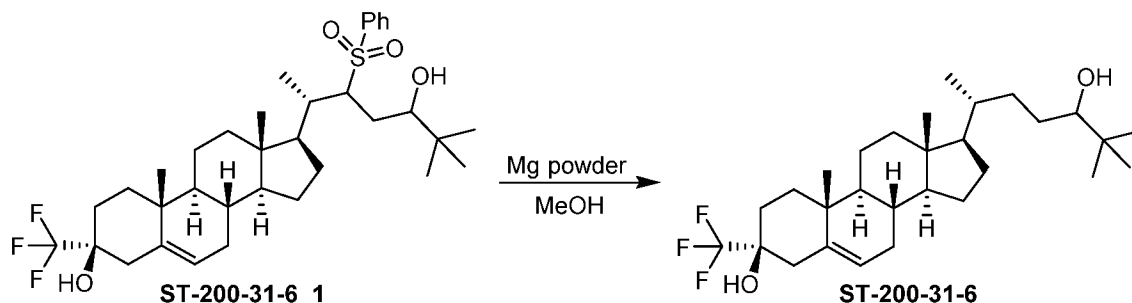
[00444] The experimental of intermediate **ST-200-CF3\_4A** can be found in Example 3.

5 [00445] **Synthesis of ST-200-31-6\_1**



A suspension of **ST-200-CF3-4A** (500 mg, 0.95 mmol) in THF (4 mL) was added dropwise to a solution of n-BuLi (0.95 mL, 2.5 M in hexane, 2.38 mmol) in THF (1 mL) at -70°C under N<sub>2</sub>. After stirring for 30 minutes at -70 °C, a solution of diisopropylamine (240 mg, 2.38 mmol) was added dropwise at -70 °C, followed by adding a solution of 2-(tert-butyl)oxirane (142 mg, 1.42 mmol) dropwise at -70 °C . The mixture was stirred at -70 °C for another 30 min and then warmed to 25 °C gradually. After stirring for at 25 °C for 24 hour, the reaction mixture was quenched by saturated NH<sub>4</sub>Cl aqueous (5 mL), extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **ST-200-31-6\_1** (650 mg,crude), which was used directly.

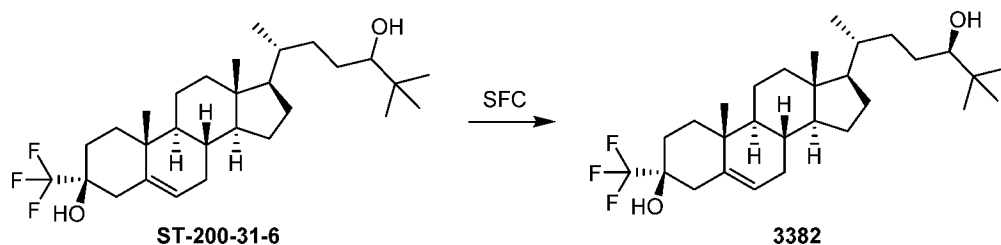
[00446] **Synthesis of ST-200-31-6**



Mg powder (998 mg, 41.6 mmol) and NiCl<sub>2</sub> (5 mg, 0.05 mmol) were added with stirring to a solution of **ST-200-31-6** (650 mg, 1.04 mmol) in 100 mL of anhydrous MeOH under N<sub>2</sub> at 60°C. The reaction mixture was quenched by 2 M HCl (50 mL) until solid was dissolved. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with sat. NaHCO<sub>3</sub> (150 mL), brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~15 % of EtOAc in PE) to give impure **ST-200-31-6** as a solid. Lindlar catalyst (200 mg) was added to a solution of the **ST-200-31-6** in EtOAc (10 mL) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> for three times. Then the solution was hydrogenated under 15 psi of hydrogen at 25°C for 4 h. The mixture was filtered through a pad of celite and washed with EtOAc (3 x 10 mL). The filtrate was concentrated and concentrated to give **ST-200-31-6** (210 mg, 43%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.39-5.34 (m, 1H), 3.18-3.06 (m, 1H), 2.49 (s, 2H), 2.17 (s, 1H), 2.02-1.58 (m, 7H), 1.53-1.29 (m, 9H), 1.22-0.97 (m, 10H), 0.95-0.84 (m, 13H), 0.72-0.65 (m, 3H).

#### [00447] Synthesis of 3382



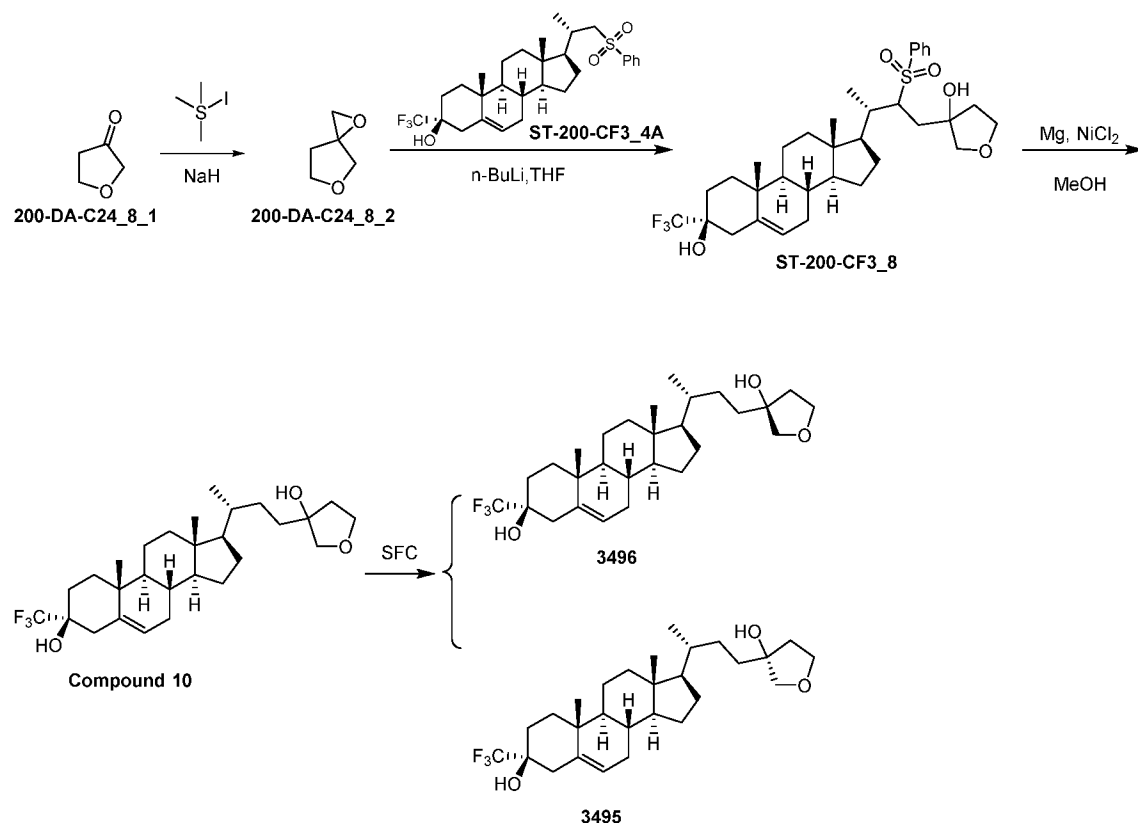
**ST-200-31-6** (210 mg, 0.43 mmol) was purified by SFC (column: AD (250mm\*30mm,10um)), gradient: 20-20% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O, B= EtOH ), flow rate: 50 mL/min) to give **3382** (90 mg, 43%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.34 (m, 1H), 3.19-3.12 (m, 1H), 2.48 (s, 2H), 2.09-1.67 (m, 8H), 1.53-1.23 (m, 12H), 1.22-0.98 (m, 8H), 0.95-0.84 (m, 12H), 0.69 (s, 3H).

LCMS Rt = 1.440 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>29</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 467, found 467.

SFC\_E1 Rt = 4.337 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, purity: 100%.

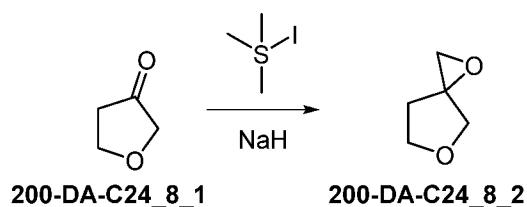
### EXAMPLE 34: Synthesis of 3495 and 3496



5

[00448] The stereochemistry for 3496 was determined by X-ray data. The experimental of intermediate ST-200-CF3\_4A can be found in Example 3.

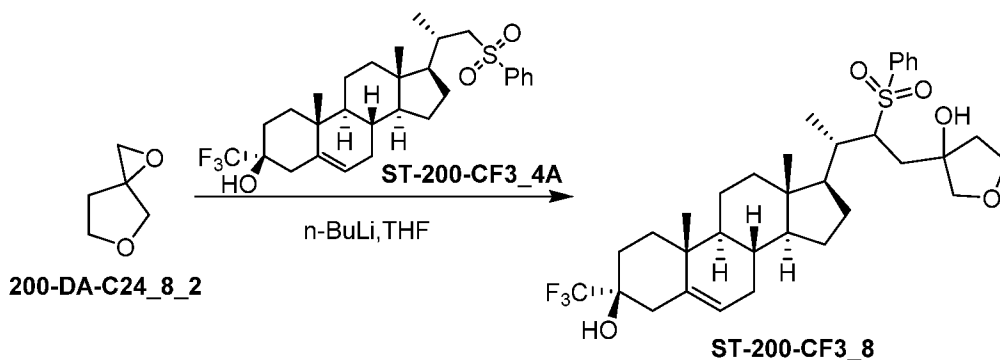
### [00449] Synthesis of 200-DA-C24\_8\_2



- 10 Sodium hydride (5.98 g, 60% in mineral oil, 150 mmol) was added in portions to a mixture of trimethylsulfonium iodide (30.6 g, 150 mmol) in THF (100 mL) at 0°C under N<sub>2</sub>. The mixture was stirred at 0°C for 30 min. Dihydrofuran-3(2H)-one (10 g, 116 mmol) in DMSO (100 mL) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 2 hours. The mixture was poured in portions into ice-water (500 mL) and extracted with DCM (2 x 500 mL). The
- 15 combined organic phase was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and

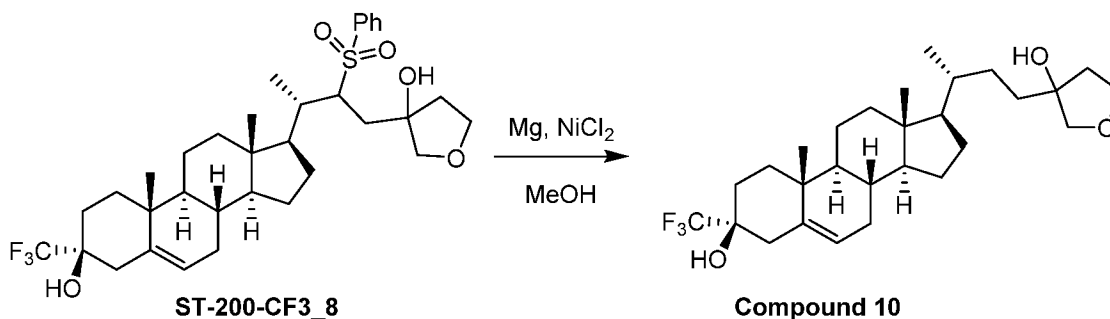
concentrated to afford **200-DA-C24\_8\_2** (4 g, crude, 34%) as an oil at 18°C, which was used directly for the next step.

**[00450] Synthesis of ST-200-CF3\_8**



- 5 Butyllithium (2.71 mL, 2.5 M in n-hexane, 6.79 mmol) was added to a solution of diisopropylamine (714 mg, 7.33 mmol) in THF (3 mL) at -70°C. The mixture was warmed to 0°C and stirred at 0°C for 30 minutes. The mixture was cooled to -70°C and **200-DA-C24\_8\_2** (300 mg, 2.99 mmol) in THF (2 mL) was added. The mixture was stirred at -70°C for 1 h. **ST-200-CF3\_4A** (1.42 g, 2.71 mmol) in THF (2 mL) was added at -70°C. The mixture was warmed to 25°C and stirred at this temperature for 16 hours. The mixture was quenched with Sat  $\text{NH}_4\text{Cl}$  (10 mL). The mixture was extracted with EtOAc (2 x 10 mL). The organic phase was washed with brine (2 x 10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated in vacuum. The crude product purified by flash column (0~50% of EtOAc in PE) to give **ST-200-CF3\_8** (280 mg, 17%) as a solid, which was used directly for the next step.

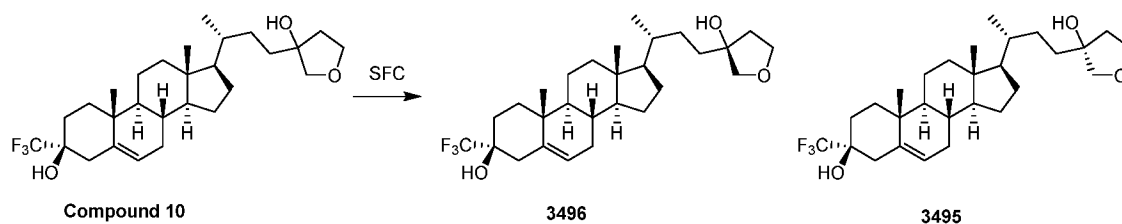
**[00451] Synthesis of Compound 10**



- Nickel (II) chloride (580  $\mu\text{g}$ , 4.48  $\mu\text{mol}$ ) and Mg powder (435 mg, 17.9 mmol) were added in four portions to a solution of **ST-200-CF3\_8** (280 mg, 0.448 mmol) in 50 mL of dry methanol under  $\text{N}_2$  at 60°C. The reaction mixture was quenched by 1M HCl (150 mL) which was added dropwise until solid was dissolved. After extracting with EtOAc (3 x 50 mL), the organic layer was washed with sat.  $\text{NaHCO}_3$  (50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give **Compound 10** (210 mg, 97%) as a solid.

$^1\text{H}$  NMR  $\text{CDCl}_3$  400MHz  $\delta$  5.39-5.35 (m, 1H), 3.93-3.82 (m, 1H), 3.72-3.68 (m, 1H), 3.59-3.51 (m, 1H), 2.49 (s, 2H), 2.10-1.80 (m, 8H), 1.80-1.62 (m, 4H), 1.60-1.39 (m, 7H), 1.39-1.12 (m, 6H), 1.12-0.91 (m, 9H), 0.69 (s, 3H).

**[00452] Synthesis of 3495 and 3496**



**10** (280 mg, 0.577 mmol) was purified by SFC (column: AS (250mm\*30mm,5um), gradient: 20-20% B (A= 0.1% $\text{NH}_3/\text{H}_2\text{O}$ , B= EtOH ), flow rate: 60 mL/min) to give **3495** (20 mg, 7%) as a solid and **3496** (32 mg, 11%) as a solid.

**3495**

$^1\text{H}$  NMR  $\text{CDCl}_3$  400MHz  $\delta$  5.39-5.35 (m, 1H), 4.05-3.98 (m, 1H), 3.93-3.85 (m, 1H), 3.72-3.68 (m, 2H), 3.59-3.51 (m, 1H), 2.49 (s, 2H), 2.05-1.72 (m, 9H), 1.55-1.40 (m, 7H), 1.72-1.40 (m, 7H), 1.40-0.90 (m, 9H), 0.69 (s, 3H).

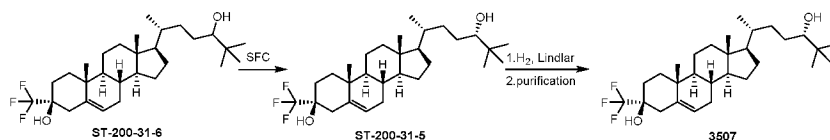
LCMS Rt = 1.081 min in 2.0 min chromatography, 30-90AB\_2MIN\_E.M, purity 100%, MS ESI calcd. for  $\text{C}_{28}\text{H}_{42}\text{F}_3\text{O}_2$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  467, found 467.

**3496**

$^1\text{H}$  NMR  $\text{CDCl}_3$  400MHz  $\delta$  5.39-5.35 (m, 1H), 4.05-3.98 (m, 1H), 3.90-3.85 (m, 1H), 3.72-3.68 (m, 1H), 3.59-3.51 (m, 1H), 2.49 (s, 2H), 2.05-1.72 (m, 10H), 1.68-1.1.60 (m, 2H), 1.52-1.25 (m, 8H), 1.25-0.92 (m, 13H), 0.69 (s, 3H).

LCMS Rt = 1.095 min in 2.0 min chromatography, 30-90AB\_2MIN\_E.M, purity 100%, MS ESI calcd. for  $\text{C}_{28}\text{H}_{42}\text{F}_3\text{O}_2$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  467, found 467.

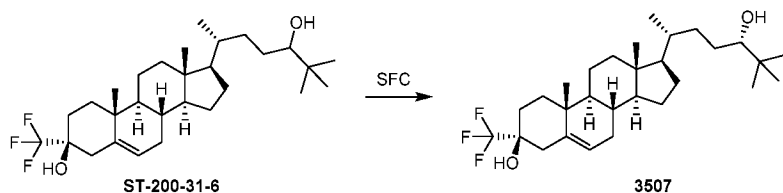
**EXAMPLE 35: Synthesis of 3507**



**[00453]** Stereochemistry assigned based on synthesis with chiral epoxide.

**[00454]** The experimental of intermediate **ST-200-31-6** can be found in Example 33.

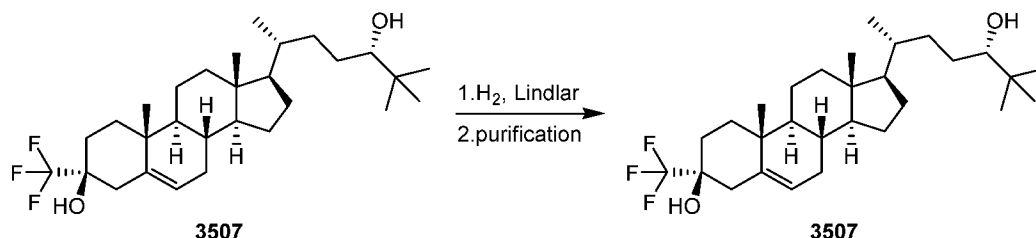
**[00455] Synthesis of ST-200-31-5**



**ST-200-31-6** (210 mg, 0.43 mmol) was purified by SFC (column: AD (250mm\*30mm,10um)), gradient: 20-20% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O, B= EtOH ), flow rate: 50 mL/min to give impure **3507** (100 mg, 45%) as a solid.

- 5 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.33 (m, 1H), 3.15-3.06 (m, 1H), 2.48 (s, 2H), 2.08-1.92 (m, 4H), 1.89-1.57 (m, 6H), 1.53-1.23 (m, 8H), 1.21-0.97 (m, 10H), 0.96-0.83 (m, 12H), 0.68 (s, 3H).

**[00456] Synthesis of 3507**



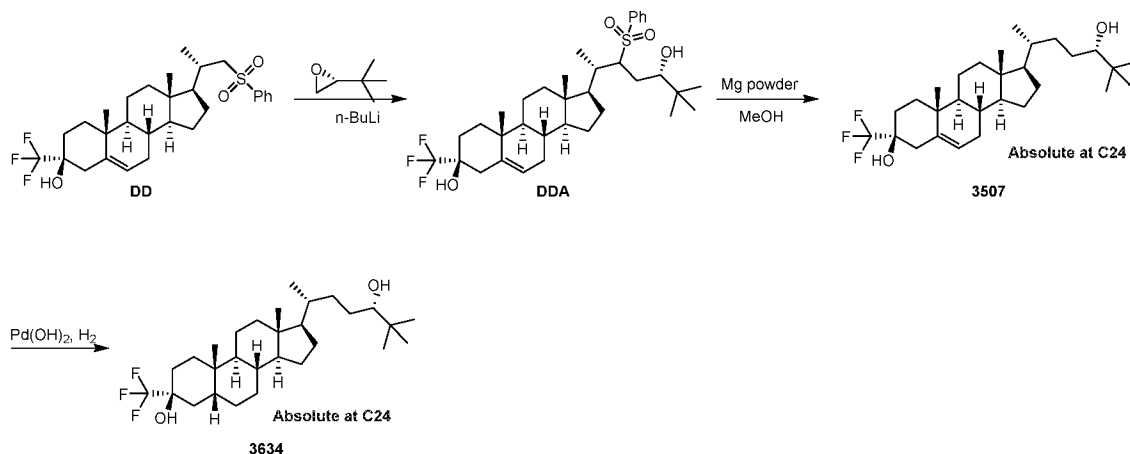
- 10 Lindlar catalyst (100 mg) was added to a solution of impure sample (100 mg, 0.21 mmol, 22,23-olefin included) in EtOAc (5 mL) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> for three times. Then the solution was hydrogenated under 15 psi of hydrogen at 25°C for 4 h. The mixture was filtered through a pad of celite and washed with EtOAc (3 x 10 mL). The filtrate was concentrated to give a solid. <sup>1</sup>H NMR showed there was still contained
- 15 12.5% 22,23-olefin. The impure **3507** was dissolved in THF/MeOH (3/3 mL) and treated with Lindlar (100 mg) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> for three times. Then the solution was hydrogenated under 15 psi of hydrogen at 25°C for 4 h. The mixture was filtered through a pad of celite and washed with THF (3 x 10 mL). The filtrate was concentrated and triturated from PE (5 mL) to give **3507** as a solid, which was triturated in n-
- 20 hexane (5 mL) at 25°C to give **3507** (40 mg, 40%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.34 (m, 1H), 3.13-3.06 (m, 1H), 2.48 (s, 2H), 2.09-1.94 (m, 4H), 1.89-1.57 (m, 6H), 1.54-1.34 (m, 6H), 1.32-1.08 (m, 5H), 1.07-0.97 (m, 7H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.68 (s, 3H).

**LCMS** Rt = 1.298 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>29</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 467, found 467.

**SFC** \_E1 Rt = 3.887 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 100%de.

Synthesis confirming stereochemistry for 3507 and 3634



To a solution of THF (0.5 mL) was added n-BuLi (0.8 mL, 2.5 M in hexane, 2 mmol), was added a solution of **DD** (420 mg, 0.8 mmol) in THF (2 mL) at -70°C. After stirring at -70°C for 1 h, (R)-2-(tert-butyl)oxirane (120 mg, 1.2 mmol) in THF (0.5 mL) was added at -70°C. The mixture was stirred at -70°C for another 1 h and warmed to 25°C and stirred for 16 hours. The reaction mixture was quenched with sat. NH<sub>4</sub>Cl (10 mL) and extracted with EtOAc (2 x 5 mL). The organic layer was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue (400 mg) was used directly for next step.

To a mixture of **DDA** (400 mg, crude) in MeOH (30 mL) was added NiCl<sub>2</sub> (8.29 mg, 0.64 mmol) at 25°C. Then the mixture was warmed to 60°C, Mg powder (671 mg, 25.5 mmol) was added in three batches. The reaction was quenched with HCl (1M, 10 mL), the mixture was extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash-combi (0~30% of EtOAc in PE) to give **3507** (110 mg, impure) as a solid, which was further purified by SFC ((column: AD(250mm\*30mm,10um)), gradient: 30-30% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O IPA, B= EtOH ), flow rate: 50 mL/min) to give **3507** (100 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.34 (m, 1H), 3.14-3.02 (m, 1H), 2.48 (s, 2H), 2.10-1.91 (m, 3H), 1.90-1.69 (m, 4H), 1.69-1.51 (m, 6H), 1.51-1.27 (m, 7H), 1.22-0.98 (m, 8H), 0.98-0.92 (m, 3H), 0.89 (s, 9H), 0.68 (s, 3H).

LCMS Rt = 1.322 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>29</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 467, found 467.

SFC Rt = 3.804 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 100%de.

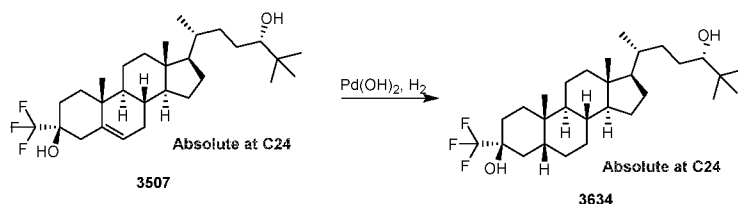
To a solution of **3507** (70 mg) in THF (10 mL) was added Pd(OH)<sub>2</sub>/C (20%, dry, 100 mg). The mixture was stirred under H<sub>2</sub> (50 psi) at 50°C for 18 h. The mixture was filtered and concentrated in vacuum. The residue was purified by flash-combi (0~15% of EtOAc in PE) to give **3634** (13 mg, 19%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.17-2.98 (m, 1H), 2.14-1.78 (m, 4H), 1.78-1.60 (m, 6H), 1.57-1.34 (m, 7H), 1.34-1.00 (m, 13H), 0.98 (s, 3H), 0.92 (m, 3H), 0.89 (s, 9H), 0.65 (s, 3H).

LCMS Rt = 1.349 min in 2.0 min chromatography, 30-90\_AB\_E, purity 100%, no MS signal.

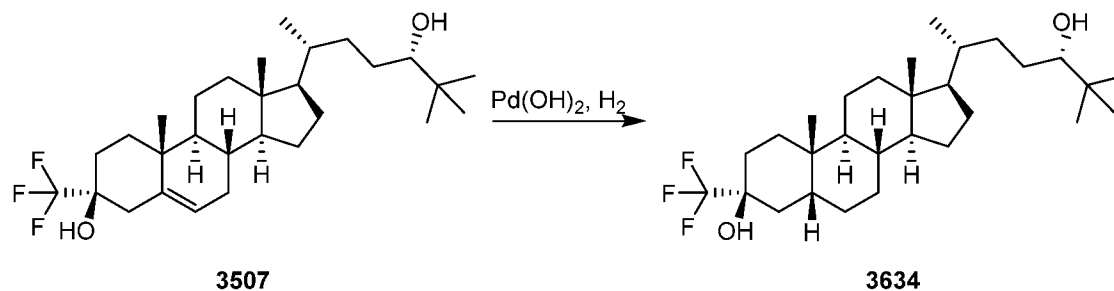
MS MS ESI calcd. for  $\text{C}_{29}\text{H}_{48}\text{F}_3\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  469, found 469.

## 5 EXAMPLE 36: Synthesis of 3634



[00457] The experimental procedures of intermediate **3507** can be found in Example 3.

## [00458] Synthesis 3634



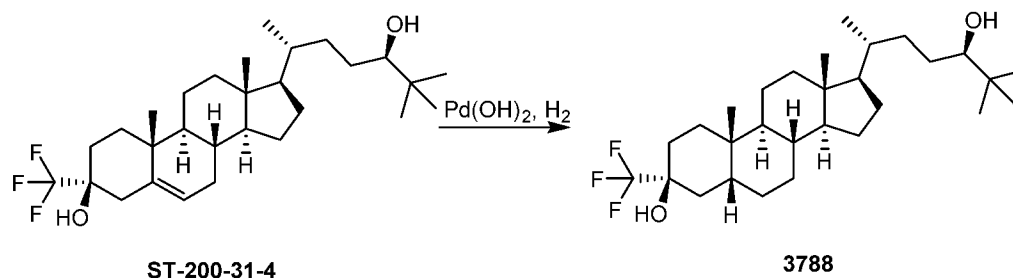
To a solution of **3507** (70 mg) in THF (10 mL) was added  $\text{Pd}(\text{OH})_2/\text{C}$  (20%, dry, 100 mg). The mixture was stirred under  $\text{H}_2$  (50 psi) at  $50^\circ\text{C}$  for 18 h. The mixture was filtered and concentrated in vacuum. The residue was purified by flash-combi (0~15% of EtOAc in PE) to give **3634** (13 mg, 19%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.17-2.98 (m, 1H), 2.14-1.78 (m, 4H), 1.78-1.60 (m, 6H), 1.57-1.34 (m, 7H), 1.34-1.00 (m, 13H), 0.98 (s, 3H), 0.92 (m, 3H), 0.89 (s, 9H), 0.65 (s, 3H).

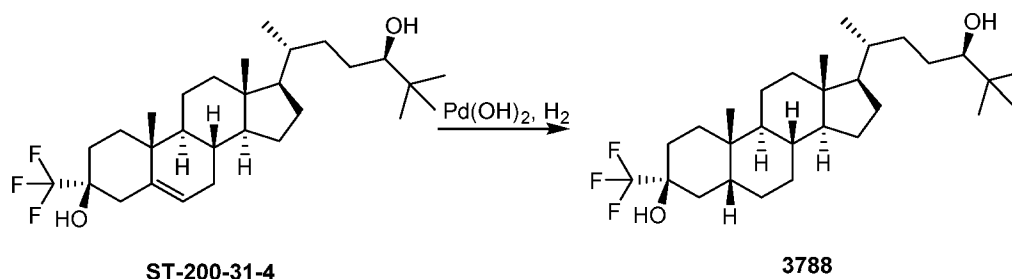
LCMS Rt = 1.349 min in 2.0 min chromatography, 30-90\_AB\_E, purity 100%, no MS signal.

MS MS ESI calcd. for  $\text{C}_{29}\text{H}_{48}\text{F}_3\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  469, found 469.

## 20 EXAMPLE 37: Synthesis of 3788



[00459] The experimental of intermediate **ST-200-31-4** can be found in Example 33.

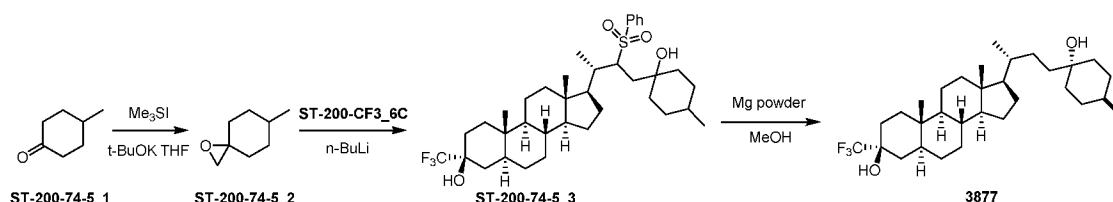
**[00460] Synthesis of 3788**

Pd(OH)<sub>2</sub>/C (100 mg) was added to a solution of **ST-200-31-4** (60 mg, 0.12 mmol) in THF/MeOH (5 mL/5 mL) and the mixture was degassed and back-filled with H<sub>2</sub> three times.

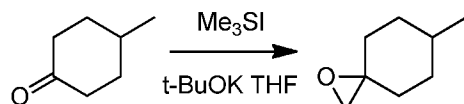
- 5 Next, the reaction was stirred at 50°C under 50 psi of H<sub>2</sub> for 16 h. The reaction mixture was filtered through a pad of celite washed with EtOAc (100 mL). The filtrate was concentrated to give impure **ST-200-31-3B** as a solid. To a solution of the impure **ST-200-31-4** in THF/MeOH (3 mL/3 mL) was added Pd(OH)<sub>2</sub>/C (50 mg) and the mixture was degassed and back-filled with H<sub>2</sub> for 3 times. After that, the reaction was stirred at 50°C under 50 psi of H<sub>2</sub> for 72 h. The reaction mixture was filtered through a pad of celite washed with EtOAc (100 mL). The filtrate was concentrated to give 40 mg of crude product, which was triturated in n-hexane (2 x 3 mL) to give **3788** (7 mg, 17%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.19-3.08 (m, 1H), 2.13-1.81 (m, 4H), 1.77-1.58 (m, 4H), 1.54-1.35 (m, 9H), 1.34-1.01 (m, 13H), 1.01-0.96 (m, 3H), 0.94-0.86 (m, 12H), 0.66 (s, 3H).

- 15 **LCMS** Rt = 1.313 min in 2.0 min chromatography, 30-90AB\_2MIN\_E, purity 98%, MS ESI calcd. for C<sub>29</sub>H<sub>48</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 469, found 469.

**EXAMPLE 38: Synthesis of 3877 and 3886**

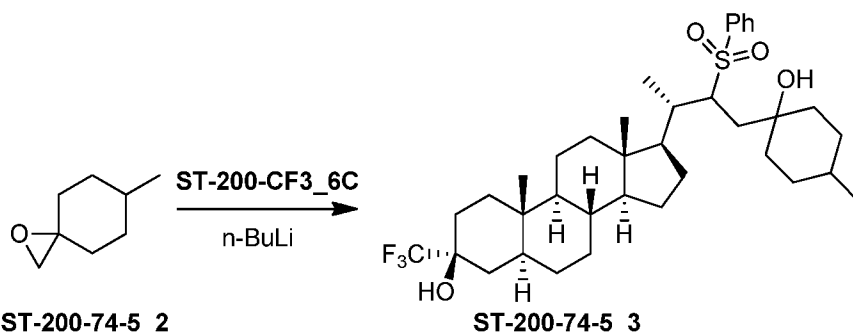
- 20 **[00461]** Stereochemistry for 3877 is shown below; assigned by NMR.

**[00462] Synthesis of ST-200-74-5\_1****ST-200-74-5\_1****ST-200-74-5\_2**

Me<sub>3</sub>Si (4.71 g, 23.1 mmol) was added to a suspension of t-BuOK (3.98 g, 35.6 mmol) in THF (40 mL) under N<sub>2</sub> at 35°C. After stirring at 35°C for 30 mins, a solution of **ST-200-74-5\_1** (2 g,

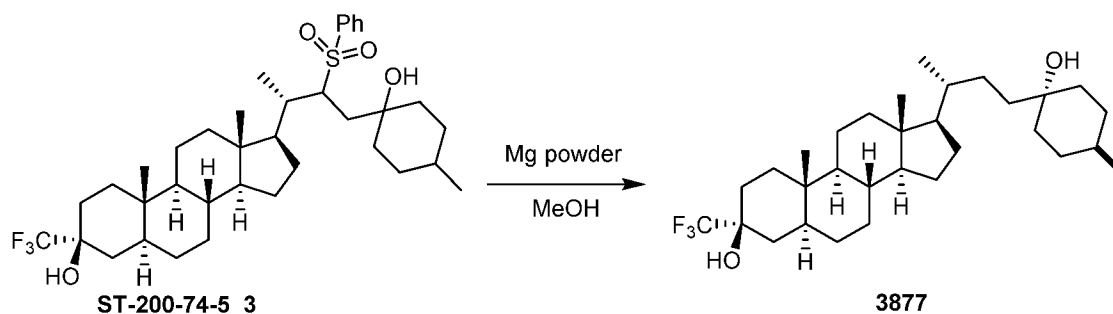
17.8 mmol) was added dropwise at 35°C. The mixture was stirred at 35°C for 16 hrs, quenched with sat.NH<sub>4</sub>Cl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **ST-200-74-5\_2** (1.8 g, crude) as liquid which was used directly for next step.

5 [00463] **Synthesis of ST-200-74-5\_3**



n-BuLi (0.948 mL, 2.5 M in hexane, 2.37 mmol) was added to THF (5 mL). A solution of **ST-200-CF3\_6C** (500 mg, 0.949 mmol) in THF (15 mL) was added at -70°C. After stirring at -70°C for 1 h, 6-methyl-1-oxaspiro[2.5]octane (358 mg, 2.84 mmol) was added at -70°C. The mixture was stirred at -70°C for another 1 hour, then warmed to 15°C and stirred for 16 hrs. After quenching with NH<sub>4</sub>Cl (50 mL), the mixture was extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, and purified by combi-flash (0-20% of EtOAc in PE) to give **ST-200-74-5\_3** (350 mg, crude) as a solid, which was used directly for the next step.

15 [00464] **Synthesis of 3877**



A solution of **ST-200-74-5\_3** (350 mg, 0.536 mmol) in MeOH (30 mL) was heated at 65°C. Mg powder (513 mg, 21.4 mmol) was added in one portion at 65°C. The mixture was refluxed at 65°C for 1h. The mixture was quenched with HCl (40 mL, 2N) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by silica gel chromatography (0-12% of EtOAc in PE) to give **3877** (12 mg, 4%) as a solid.

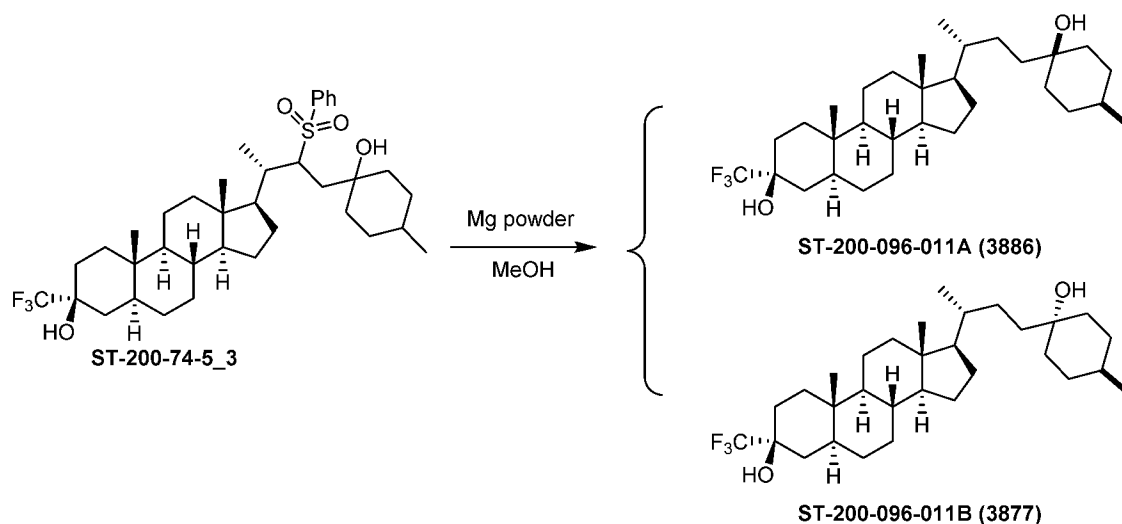
**3877:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.11-1.90 (m, 3H), 1.89-1.74 (m, 2H), 1.73-1.58 (m, 5H), 1.53-1.43 (m, 6H), 1.42-1.19 (m, 14H), 1.18-0.96 (m, 7H), 0.96-0.80 (m, 10H), 0.74-0.60 (m, 4H).

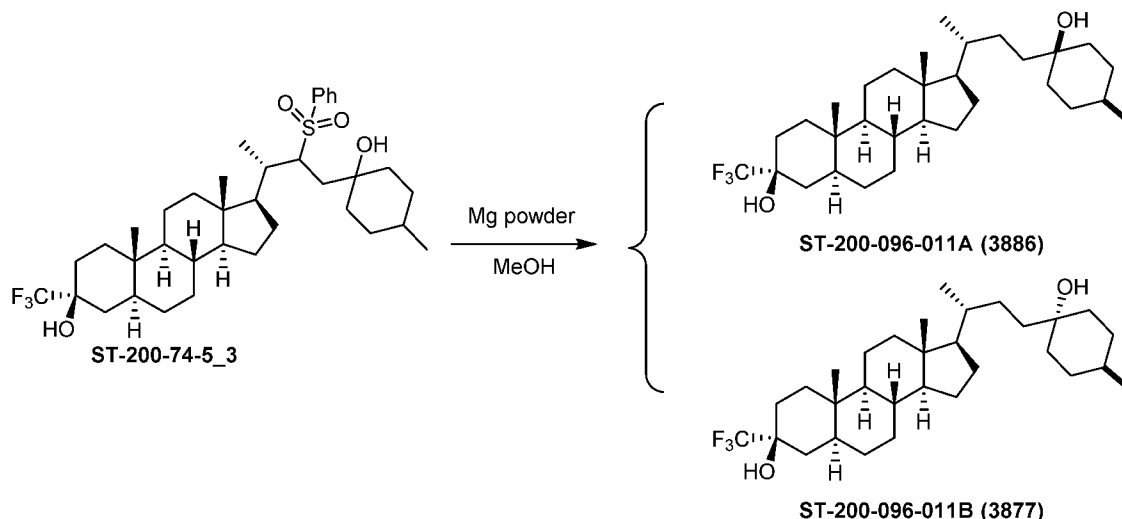
LCMS Rt = 1.728 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%.

MS ESI Scan (2.939-3.092 min, 10 scans) Frag=50.0 V, 80-100\_1\_4min.m, MS ESI calcd. For

5 C<sub>31</sub>H<sub>51</sub>F<sub>3</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 535, found 535.



[00465] Synthesis of ST-200-096-011A/B



To a solution of **ST-200-74-5\_3** (700 mg, 1.07 mmol) in MeOH (40 mL) was added NiCl<sub>2</sub> (27.6 mg, 0.214 mmol) and Mg powder (1.02 g, 41.8 mmol) at 65°C in one portion. The mixture was stirred at 65°C for 10 minutes. Another Mg powder (513 mg, 22.3 mmol) was added in one portion. After stirring at 65°C for 10 minutes, the mixture was quenched with HCl (200 mL, 1N) and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by combi-flash (0-15% of EtOAc in PE) to give **ST-200-096-011A** (63 mg, 11%, Peak 1) and **ST-200-096-011B** (114 mg, 20%, Peak 2) as a solid.

3877

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.09-1.93 (m, 3H), 1.90-1.76 (m, 2H), 1.73-1.57 (m, 8H), 1.51-1.34 (m, 8H), 1.33-1.18 (m, 6H), 1.17-0.98 (m, 8H), 0.97-0.87 (m, 7H), 0.84 (s, 3H), 0.73-0.63 (m, 4H).

**LCMS** Rt = 1.391 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%.

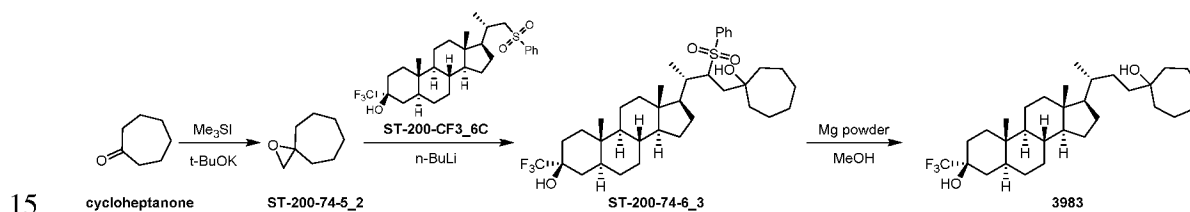
5 **MS** ESI Scan (1.955-2.16 min, 8 scans) Frag=50.0 V, 80-100\_1\_4min.m, MS ESI calcd. For C<sub>31</sub>H<sub>51</sub>F<sub>3</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 535, found 535.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.09-2.00 (m, 2H), 1.99-1.89 (m, 1H), 1.87-1.76 (m, 2H), 1.71-1.61 (m, 3H), 1.55-0.42 (m, 10H), 1.41-1.19 (m, 13H), 1.14-0.96 (m, 6H), 0.95-0.86 (m, 7H), 0.84 (s, 3H), 0.72-0.62 (m, 4H).

10 **LCMS** Rt = 1.450 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%.

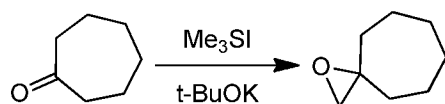
**MS** ESI Scan (1.938-2.617 min, 9 scans) Frag=50.0 V, 80-100\_1\_4min.m, MS ESI calcd. For C<sub>31</sub>H<sub>51</sub>F<sub>3</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 535, found 535.

### EXAMPLE 39: Synthesis of 3983



[00466] See Example 5 for synthesis of ST-200-CF3\_6C.

### [00467] Synthesis of ST-310-15-2\_2



cycloheptanone

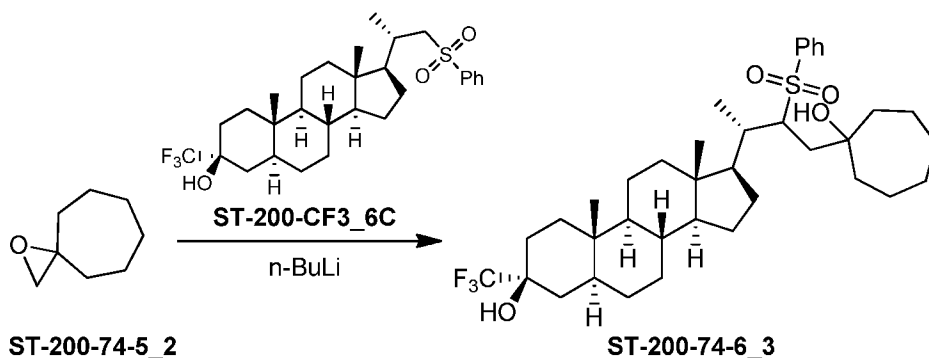
ST-200-74-5\_2

A solution of Me<sub>3</sub>Si (13.6 g, 66.7 mmol) and t-BuOK (17.8 mL, 5M in THF, 89.0 mmol) in

20 DMSO (100 mL) was stirred and heated at 25°C for 30 min under N<sub>2</sub>. Cycloheptanone (5 g, 44.5 mmol) was added to the reaction mixture and stirred at 25°C for 3 hrs. The reaction was treated with water (300 mL), extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with water (2 x 300 mL), brine (2 x 300 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **ST-200-74-5\_2** (4 g, 71%) as a liquid.

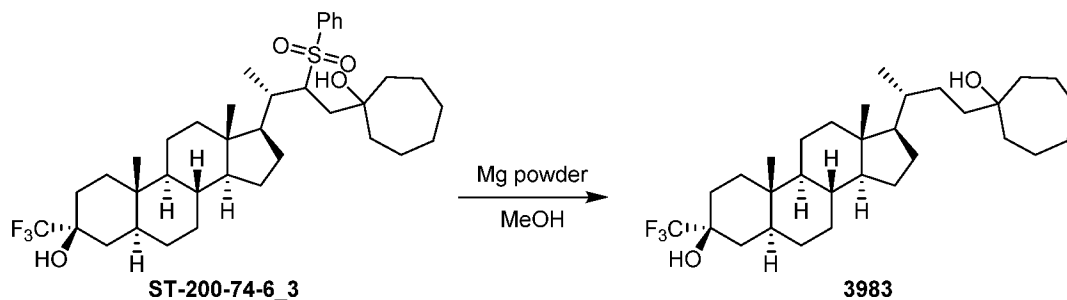
25 **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.59 (s, 2H), 1.72-1.50 (m, 12H).

### [00468] Synthesis of ST-310-15-2\_3



Added n-BuLi (0.568 mL, 1.42 mmol, 2.5 M in hexane) was added to a solution of **ST-200-CF3\_6C** (300 mg, 0.569 mmol) in THF (3 mL) at -70°C under N<sub>2</sub>. After cooling to -70°C, 1-oxaspiro [2.6] nonane (107 mg, 0.853 mmol) was added. The reaction was allowed to warm to 25°C and was stirred for 12 hours at 25°C. The reaction was quenched with NH<sub>4</sub>Cl (10 mL, sat. aq.), water (50 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was concentrated to give a residue, which was purified by silica gel chromatography (PE/EtOAc=10/1~5/1) to give compound **ST-200-74-6\_3** (200 mg, impure) as an oil. The crude mixture was used directly for the next step.

#### 10 [00469] Synthesis of 3983

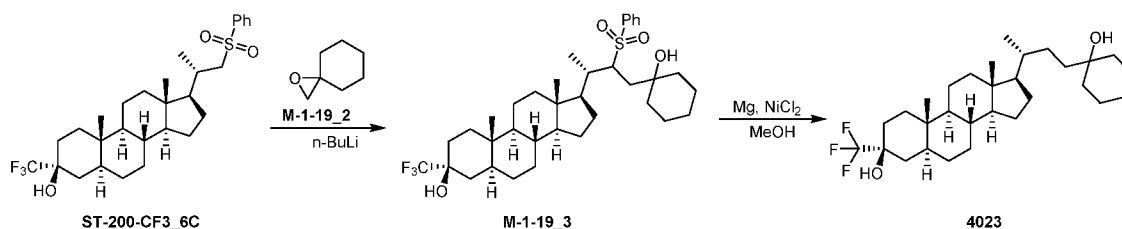


A solution of **ST-200-74-6\_3** (200 mg, 306 umol) in MeOH (50 mL) was heated to 60°C. Mg powder (371 mg, 15.3 mmol) was added in four portions at 60°C. After stirring at 60°C for 1 h, the mixture was quenched with HCl (50 mL, 2 M) until the reaction became clear and extracted with EtOAc (2 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated and purified by flash column (0-40% of EtOAc in PE) to give **3983** (15 mg, 12%) as a solid.

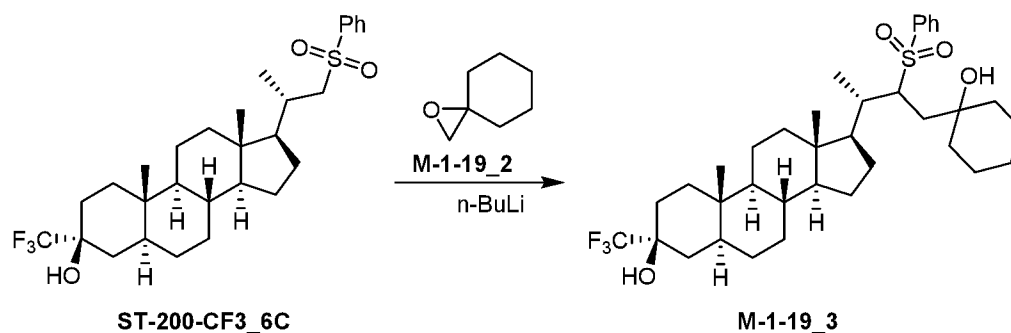
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.12-2.00 (s, 1H), 1.99-1.92 (m, 2H), 1.89-1.77 (m, 2H), 1.74-1.57 (m, 10H), 1.57-1.52 (m, 6H), 1.41-1.17 (m, 13H), 1.16-0.95 (m, 7H), 0.94-0.82 (m, 6H), 0.72-0.63 (m, 4H).

LCMS Rt = 0.690 min in 2 min chromatography, 30-90 AB, purity 100%.

HRMS MS ESI calcd. for C<sub>31</sub>H<sub>50</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 495, found 495.

**EXAMPLE 40: Synthesis of 4023**

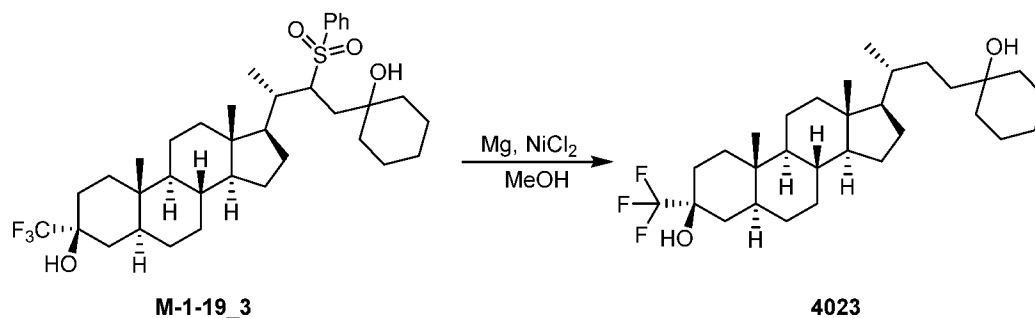
[00470] The synthesis of **ST-200-CF3\_6C** can be found in Example 5.

**[00471] Synthesis of M-1-19\_3**

5

n-BuLi (2.5 M, 1.42 mmol, 0.568 mL) was added to THF (2 mL) under N<sub>2</sub> at -70°C. Next, a suspension of **ST-200-CF3\_6C** (300 mg, 0.569 mmol) in THF (2 mL) was added drop-wise to give a suspension. After stirring at -70°C for 30 min, a solution of 1-oxaspiro [2.5] octane (126 mg, 1.13 mmol) was added. The reaction was stirred at 25°C for 16 hours. The mixture was poured into ice-water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **M-1-19\_3** (280 mg, crude) as a solid, which was used directly for the next step.

10

**[00472] Synthesis of 4023**

15

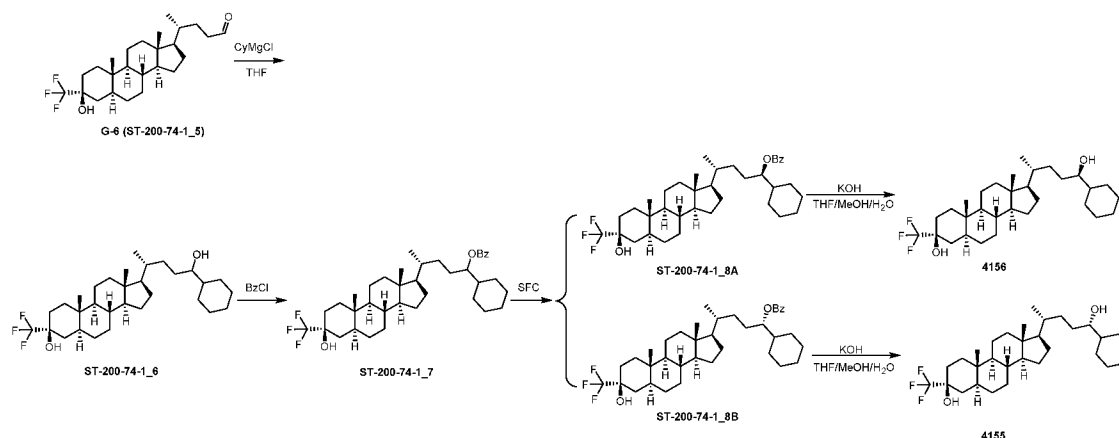
Mg (212 mg, 8.75 mmol) and NiCl<sub>2</sub> (11.3 mg, 0.088 mmol) were added to a solution of **M-1-19\_3** (280 mg, 0.438 mmol) in 20 mL of dry methanol at 25°C. The mixture was stirred at 50°C for 1 h. The mixture was quenched by 2M HCl (50 mL) at 10°C until solid was dissolved. The mixture was extracted with EtOAc (50 mL). The organic layers were washed with sat. NaHCO<sub>3</sub>

(50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel column eluted with PE/EtOAc = 10/1 to afford **4023** (38 mg, 14%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.08-2.02 (m, 1H), 2.01-1.94 (m, 2H), 1.89-1.78 (m, 2H), 1.71-1.59 (m, 5H), 1.53-1.32 (m, 13H), 1.30-1.05 (m, 13H), 1.03-0.83 (m, 9H), 0.72-0.85 (m, 4H).

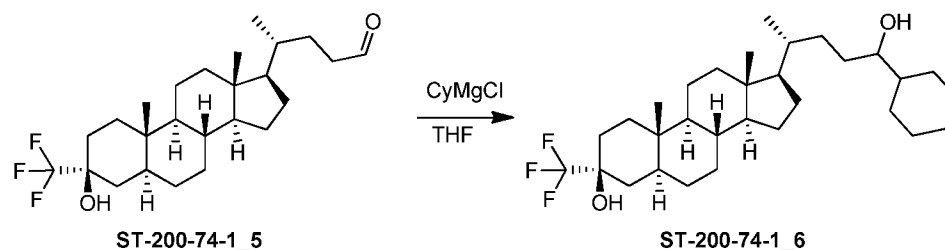
5 MS MS ESI calcd. for C<sub>30</sub>H<sub>48</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 481, found 481.

#### EXAMPLE 41: Synthesis of 4155 and 4156



[00473] See Example 11 for synthesis of ST-200-74-1\_5.

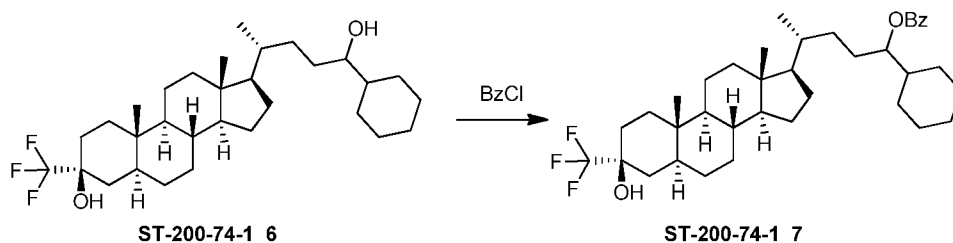
10 [00474] Synthesis of ST-200-74-1\_6



cyclohexylmagnesium chloride (2.55 mL, 5.1 mmol, 2M in THF) was added dropwise to a solution of **ST-200-74-1\_5** (440 mg, 1.02 mmol) in THF (10 mL) at 0°C. The mixture was stirred at 25°C for 1 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with (PE/EtOAc = 5/1) to afford **ST-200-74-1\_6** (400 mg, 77%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.32-3.28 (m, 1H), 2.28-2.23 (m, 1H), 2.08-2.02 (m, 1H), 1.98-1.79 (m, 6H), 1.58-1.34 (m, 15H), 1.30-1.00 (m, 15H), 0.95-0.83 (m, 8H), 0.72-0.65 (m, 4H).

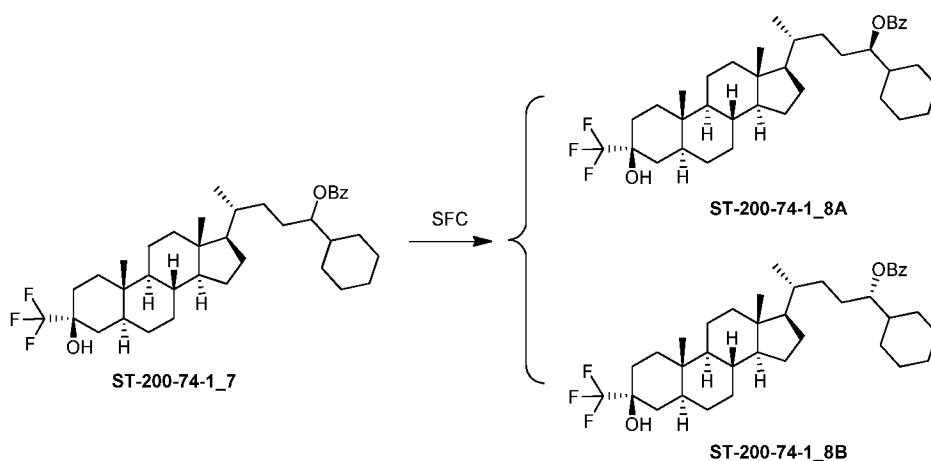
20 [00475] Synthesis of ST-200-74-1\_7



Benzoyl chloride (164 mg, 1.17 mmol) was added to a solution of **ST-200-74-1\_6** (400 mg, 0.78 mmol) in Pyridine (4 mL) at 25°C. The mixture was stirred at 25°C for 12 hrs. The mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel column eluted with (PE/EtOAc = 10/1) to afford **ST-200-74-1\_7** (315 mg, 65%) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.06-8.04 (m, 2H), 7.62-7.50 (m, 1H), 7.46-7.43 (m, 2H), 4.98-4.90 (m, 1H), 2.07-2.04 (m, 1H), 1.95-1.92 (m, 1H), 1.82-1.55 (m, 10H), 1.54-1.30 (m, 10H), 1.28-1.05 (m, 13H), 0.99-0.93 (m, 10H), 0.67-0.61 (m, 4H).

#### [00476] Synthesis of ST-200-74-1\_8A, 8B



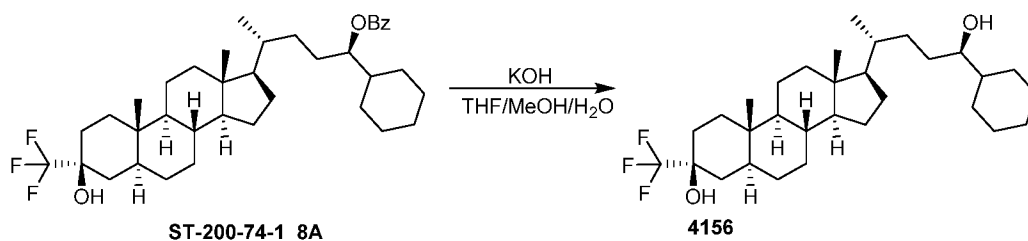
**ST-200-74-1\_7** (315 mg) was purified by SFC (Column: AD (250mm\*30mm, 5μm), Condition: 0.1% NH<sub>3</sub>.H<sub>2</sub>O, IPA, Gradient: from 40% to 40%, FlowRate (ml/min): 60 mL/min, 25°C) to afford **ST-200-74-1\_8A** (115 mg, 37%) and **ST-200-74-1\_8B** (108 mg, 35%) as a solid.

#### **ST-200-74-1\_8A**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.06-8.03 (m, 2H), 7.58-7.53 (m, 1H), 7.46-7.43 (m, 2H), 4.98-4.90 (m, 1H), 2.07-2.02 (m, 1H), 1.96-1.91 (m, 2H), 1.84-1.62 (m, 12H), 1.53-1.24 (m, 11H), 1.22-0.96 (m, 12H), 0.94-0.83 (m, 7H), 0.70-0.64 (m, 1H), 0.61 (s, 3H).

#### **ST-200-74-1\_8B**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.06-8.03 (m, 2H), 7.58-7.53 (m, 1H), 7.46-7.43 (m, 2H), 4.98-4.90 (m, 1H), 2.07-1.91 (m, 3H), 1.84-1.69 (m, 7H), 1.67-1.48 (m, 9H), 1.43-1.32 (m, 4H), 1.30-1.02 (m, 13H), 1.01-0.84 (m, 9H), 0.7-0.62 (m, 4H).

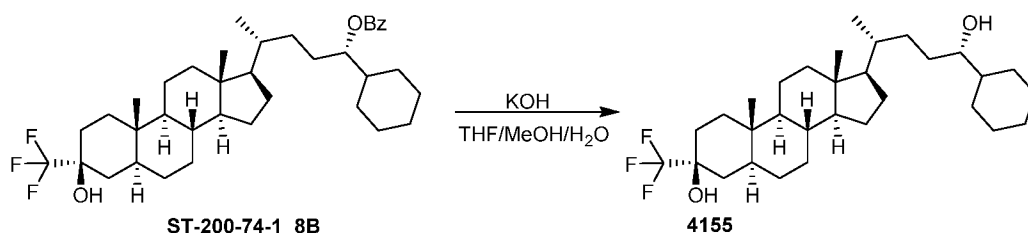
**[00477] Synthesis of 4156**

KOH (52.1 mg, 0.93 mmol) was added to a solution of **ST-200-74-1\_8A** (115 mg, 0.186 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL). The mixture was stirred at 60°C for 16 hrs.

- 5 The mixture was poured into water (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layer was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (PE/EtOAc=5/1 to 3/1) to give **4156** (56 mg, 59%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.31-3.27 (m, 1H), 2.08-2.02 (m, 1H), 1.98-1.93 (m, 2H), 1.84-1.72 (m, 5H), 1.70-1.60 (m, 7H), 1.51-1.46 (m, 2H), 1.42-1.36 (m, 3H), 1.34-1.11 (m, 13H), 1.06-0.85 (m, 13H), 0.72-0.65 (m, 4H).

MS/MS ESI calcd. for C<sub>31</sub>H<sub>50</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 495, found 495.

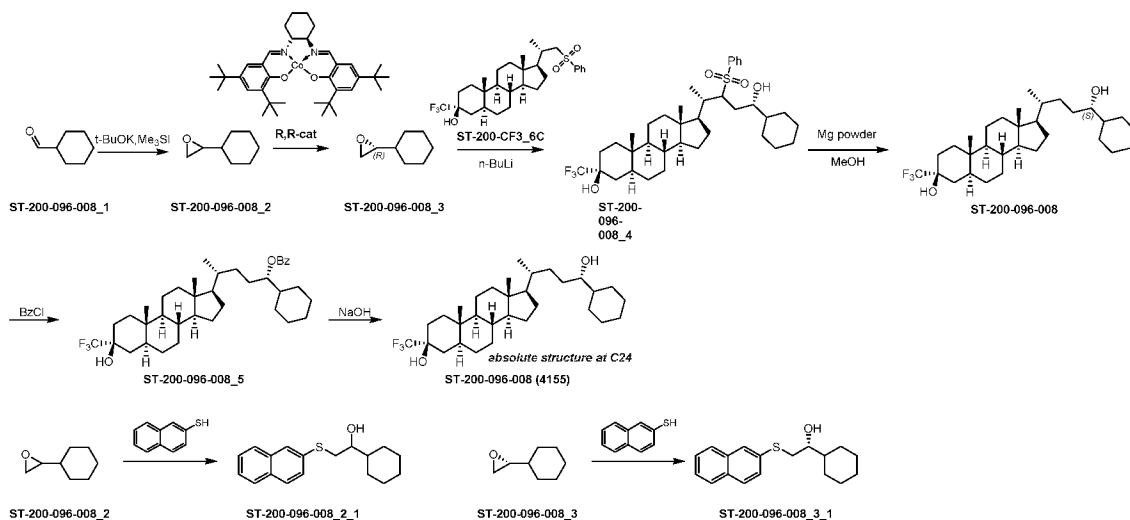
**[00478] Synthesis of 4155**

- 15 KOH (49 mg, 0.875 mmol) was added to a solution of **ST-200-74-1\_8B** (108 mg, 0.175 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL). The mixture was stirred at 60°C for 16 hrs. The mixture was poured into water (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layer was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (PE/EtOAc=5/1 to 3/1) to give **4155** (56 mg, 62%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.31-3.27 (m, 1H), 2.08-2.02 (m, 1H), 1.98-1.93 (m, 2H), 1.84-1.72 (m, 5H), 1.70-1.60 (m, 6H), 1.51-1.34 (m, 9H), 1.31-0.97 (m, 17H), 0.95-0.85 (m, 6H), 0.72-0.65 (m, 4H).

MS MS ESI calcd. for C<sub>31</sub>H<sub>51</sub>F<sub>3</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 535, found 535.

- 25 Synthesis confirming stereochemistry of 4155



To a suspension of  $\text{C}_3\text{H}_9\text{IS}$  (117 g, 578 mmol) in THF (300 mL) was added a solution of  $t\text{-BuOK}$  (99.6 g, 890 mmol) in THF (400 mL) slowly under  $\text{N}_2$  at  $30^\circ\text{C}$ . The suspension was stirred at  $30^\circ\text{C}$  for 30 min. Then **ST-200-096-008\_1** (50 g, 445 mmol) in 100 mL of THF was added dropwise to the mixture at  $0^\circ\text{C}$ . After stirring at  $30^\circ\text{C}$  for 16 hrs, the mixture was poured into sat. $\text{NH}_4\text{Cl}$  (600 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phase was washed with brine (400 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at  $40^\circ\text{C}$  under reduced pressure to give **ST-200-096-008\_2** (55 g, crude) as a liquid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.75-2.65 (m, 2H), 2.55-2.50 (m, 1H), 1.90-1.80 (m, 1H), 1.78-1.58 (m, 4H), 1.30-1.00 (m, 6H)

To a suspension of  $\text{C}_3\text{H}_9\text{IS}$  (117 g, 578 mmol) in THF (300 mL) was added a solution of  $t\text{-BuOK}$  (99.6 g, 890 mmol) in THF (400 mL) slowly under  $\text{N}_2$  at  $30^\circ\text{C}$ . The suspension was stirred at  $30^\circ\text{C}$  for 30 min. Then **ST-200-096-008\_1** (50 g, 445 mmol) in 100 mL of THF was added dropwise to the mixture at  $0^\circ\text{C}$ . After stirring at  $30^\circ\text{C}$  for 16 hrs, the mixture was poured into sat. $\text{NH}_4\text{Cl}$  (600 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phase was washed with brine (400 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at  $40^\circ\text{C}$  under reduced pressure to give **ST-200-096-008\_2** (55 g, crude) as a liquid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.75-2.65 (m, 2H), 2.55-2.50 (m, 1H), 1.90-1.80 (m, 1H), 1.78-1.58 (m, 4H), 1.30-1.00 (m, 6H)

To a solution of  $\text{R,R-cat}$  (190 mg, 0.316 mmol) in toluene (3 mL) was added AcOH (189 mg, 3.16 mmol). The mixture was stirred at  $25^\circ\text{C}$  under air for 30 min and concentrated in vacuum to leave a crude brown solid. The resulting catalyst residue was dissolved in 2-cyclohexyloxirane (10 g, 79.2 mmol) at  $25^\circ\text{C}$ . The reaction flask was cooled to  $0^\circ\text{C}$ , and  $\text{H}_2\text{O}$  (783 g, 43.5 mmol) was added dropwise over 5 min. After stirring at  $25^\circ\text{C}$  for 24 hrs, ((2R)-2-cyclohexyloxirane (2 g, 15.8 mmol, 20.0%) was isolated by distillation from the reaction mixture. To a solution of **ST-200-096-008\_3** (50 mg, 0.396 mmol) and TEA (39.9 mg, 0.396 mmol) in MeOH (3 mL) was

added naphthalene-2-thiol (63.4 mg, 0.396 mmol) at 25°C. After stirring at 25°C for 2 hrs, the ee% of (2R)-2-cyclohexyloxirane was determined to be 82.7% by chiral HPLC.

**SFC Peak 1:** Rt = 2.033 min in 10 min chromatography, Chiralpak AD-3 100×4.6mm I.D., 3µm, 82.7%ee.

- 5 To THF (1 mL) was added BuLi (1.12 mL, 2.5 M in hexane, 2.82 mmol). A solution of **ST-200-CF3\_6C** (600 mg, 1.13 mmol) in THF (6 mL) was added at -70°C. The mixture was stirred at -70°C for 1 h. (2R)-2-cyclohexyloxirane (213 mg, 1.69 mmol) was added at -70°C. After stirring at 30°C and stirred for 16 hrs, the reaction mixture was quenched with sat.NH<sub>4</sub>Cl (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer were washed with NH<sub>4</sub>Cl (50  
10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to give crude product (700 mg) as a foam solid, which was used for next step directly.

- To a solution of **ST-200-096-008\_4** (700 mg, 1.07 mmol) in MeOH (60 mL) was added NiCl<sub>2</sub> (27.6 mg, 0.214 mmol) and Mg powder (1.02 g, 42.8 mmol) at 65°C in one portion. The mixture was stirred at 65°C for 10 minutes. Another Mg powder (513 g, 21.4 mmol) was added in one  
15 portion. After stirring at 65°C for 10 minutes, the mixture was quenched with HCl (120 mL, 1N) and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by combi-flash (0-15% of EtOAc in PE) to give **ST-200-096-008** (300 mg, 55%) as a solid.

- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.35-3.25 (m, 1H), 2.10-2.01 (m, 1H), 2.00-1.91 (m, 1H), 1.78-  
20 1.72 (m, 5H), 1.71-1.58 (m, 9H), 1.56-1.10 (m, 19H), 1.09-0.98 (m, 4H), 0.97-0.86 (m, 4H), 0.84 (s, 3H), 0.72-0.60 (m, 4H)

- To a solution of **ST-200-096-008** (300 mg, 0.585 mmol) in pyridine (5 mL) was added benzoyl chloride (164 mg, 1.17 mmol) at 25°C. After stirring at 25°C for 12 hours, the mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic  
25 layers was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel column eluted with (PE/EtOAc = 10/1) to afford **ST-200-096-008\_5** (300 mg) as a solid, which was separated by SFC (column: AD(250mm\*30mm,5µm), gradient: 35-35% B (A= 0.05%NH<sub>3</sub>/H<sub>2</sub>O, B= MeOH ), flow rate: n/a mL/min) to give 100% de product (190 mg, 52% yield for 2 steps) as a solid.

- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.08-8.01 (m, 2H), 7.58-7.52 (m, 1H), 7.58-7.40 (m, 2H), 4.98-  
30 4.90 (m, 1H), 2.19-2.10 (m, 2H), 1.97-1.89 (m, 1H), 1.83-1.58 (m, 12H), 1.56-1.35 (m, 8H), 1.34-0.95 (m, 15H), 0.94-0.89 (m, 3H), 0.88-0.79 (m, 4H), 0.70-0.59 (m, 4H).

**SFC Peak 1:** Rt = 5.105 min and Peak 2 Rt = 5.644 min in 10 min chromatography,

AD\_3\_EtOH\_DEA\_5\_40\_25ML ("Column: Chiralpak AD-3 150×4.6mm I.D., 3µm Mobile

phase: A: CO<sub>2</sub> B: iso-propanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5 mL/min Column temp.: 35°C ).

**SFC Peak 1:** Rt = 5.313 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 100.0% de.

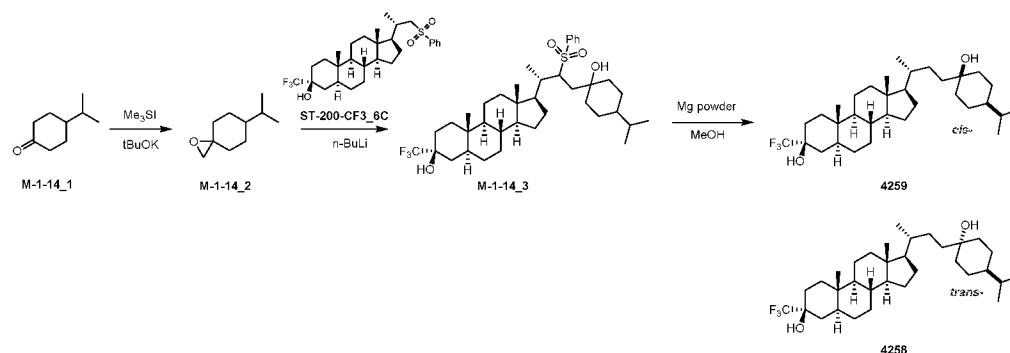
- 5 To a solution of **ST-200-096-008\_5** (190 mg, 0.308 mmol) in THF (2 mL) and MeOH (4 mL) and water (1 mL) was added NaOH (246 mg, 6.16 mmol). After stirring at 50°C for 16 hrs, the mixture was poured into water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (PE/EtOAc=5/1 to 3/1) to give **ST-200-096-008** (126 mg, 80%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.35-3.25 (m, 1H), 2.10-2.01 (m, 2H), 2.00-1.91 (m, 1H), 1.78-1.72 (m, 5H), 1.71-1.58 (m, 5H), 1.56-1.50 (m, 5H), 1.49-1.18 (m, 13H), 1.17-0.95 (m, 8H), 0.94-0.86 (m, 4H), 0.84 (s, 3H), 0.70-0.61 (m, 4H).

**LCMS** Rt = 1.389 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%.

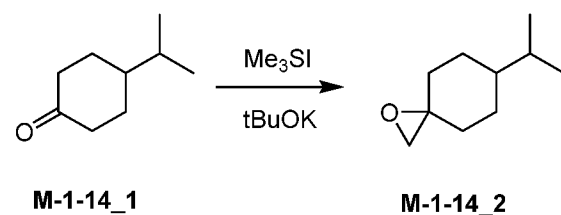
- 15 **MS** ESI Scan (1.981-2.144 min, 11 scans) Frag=50.0 V, 80-100\_1\_4min.m, MS ESI calcd. For C<sub>31</sub>H<sub>51</sub>F<sub>3</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 535, found 535.

#### EXAMPLE 42: Synthesis of 4258 and 4259



- 20 **[00479]** The stereochemistry for 4259 was confirmed by Xray data. The synthesis of **ST-200-CF3\_6C** can be found in Example 5.

#### **[00480]** Synthesis of M-1-14\_2

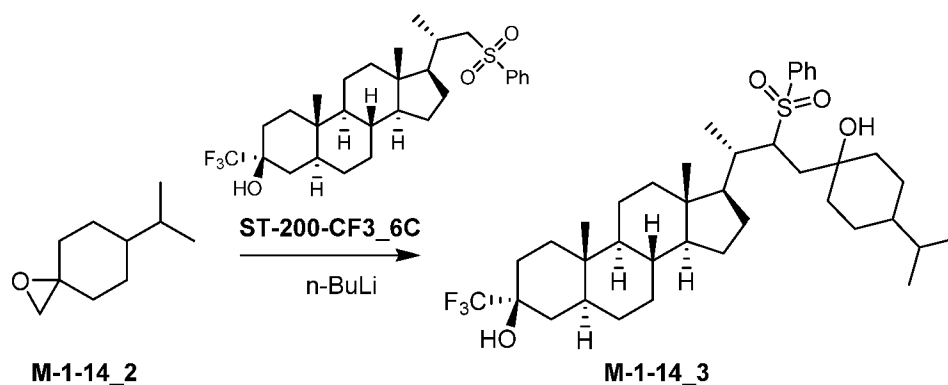


- 25 To a suspension of Me<sub>3</sub>Si (1.88 g, 9.26 mmol) in THF (10 mL) was slowly added a solution of t-BuOK (1.59 g, 14.2 mmol) in THF (5 mL) under N<sub>2</sub> at 15°C. The suspension was stirred at

15°C for 30 min. Then a solution of **M-1-14\_1** (1 g, 7.13 mmol) in 5 ml of THF was added dropwise to the mixture at 0°C. After addition, the mixture was stirred at 15°C for 16 hrs. The reaction was quenched with sat. NH<sub>4</sub>Cl (60 mL) and extracted with MTBE (3 x 30 mL). The combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under reduced pressure to give **M-1-14\_2** (1 g, crude) as a liquid.

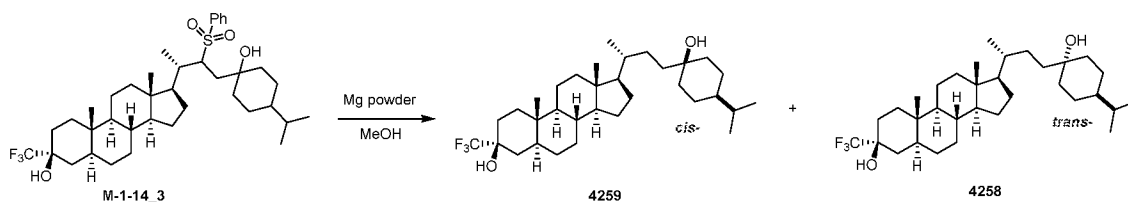
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.65-2.55 (m, 2H), 1.90-1.80 (m, 3H), 1.74-1.66 (m, 1H), 1.60-1.46 (m, 1H), 1.42-1.22 (m, 2H), 1.21-1.10 (m, 3H), 0.92-0.80 (m, 6H).

[00481] **Synthesis of M-1-14\_3**



To THF (0.5 mL) was added n-BuLi (0.568 mL, 2.5 M in hexane, 1.42 mmol) at -70°C. A solution of **ST-200-CF3\_6C** (300 mg, 0.569 mmol) in THF (2.5 mL) was added dropwise at -70°C. After stirring at -70°C for 1 h, 6-isopropyl-1-oxaspiro[2.5]octane (131 mg, 0.853 mmol) was added. The mixture was stirred at -70°C for another 1 h. Then the reaction mixture was warmed to 15°C and stirred for 16 hrs. The mixture was quenched with NH<sub>4</sub>Cl (50 mL, sat. aq.) and extracted with EtOAc (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **M-1-14\_3** (350 mg, crude) as a solid, which was used for next step directly.

[00482] **Synthesis of 4259 and 4258**



To a solution of **M-1-14\_3** (350 mg, 0.513 mmol) in MeOH (30 mL) was added NiCl<sub>2</sub> (13.2 mg, 0.102 mmol) and Mg powder (492 mg, 20.5 mmol) at 65°C in one portion. After stirring at 65°C for 10 minutes, another Mg powder (244 mg, 10.2 mmol) was added in one portion. The mixture was stirred at 65°C for another 10 minutes. The mixture was quenched with HCl (50 mL, 2N) until the reaction became clear and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat. NH<sub>4</sub>Cl (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and

purified by silica gel chromatography (0-15% of EtOAc in PE) to give **4258** (24 mg, 8.6%, 4258) and **4259** (50 mg, 18%, 4259) as a solid.

**4258**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.10-2.01 (m, 1H), 2.00-1.92 (m, 2H), 1.89-1.56 (m, 12H), 1.51-1.33 (m, 8H), 1.32-1.18 (m, 6H), 1.17-0.98 (m, 9H), 0.98-0.89 (m, 4H), 0.88-0.83 (m, 9H), 0.74-0.63 (m, 4H).

**HPLC** Rt = 7.214 min in 10.0 min chromatography, 50-100AB\_E, purity 98.8%.

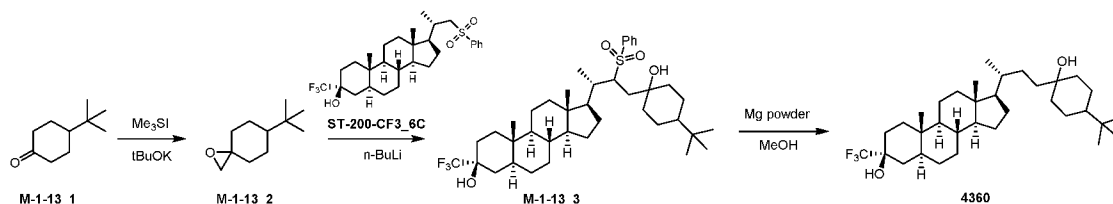
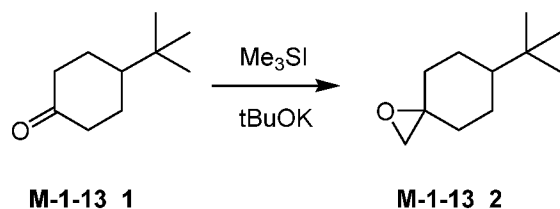
**MS** 80-100\_1\_4min.m, MS ESI calcd. for C<sub>33</sub>H<sub>54</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 523, found 523.

**4259**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.10-2.01 (m, 1H), 1.98-1.91 (m, 2H), 1.89-1.75 (m, 2H), 1.73-1.569 (m, 6H), 1.55-1.33 (m, 11H), 1.32-1.14 (m, 10H), 1.13-0.92 (m, 7H), 0.91-0.83 (m, 12H), 0.73-0.62 (m, 4H).

**LCMS** Rt = 1.816 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

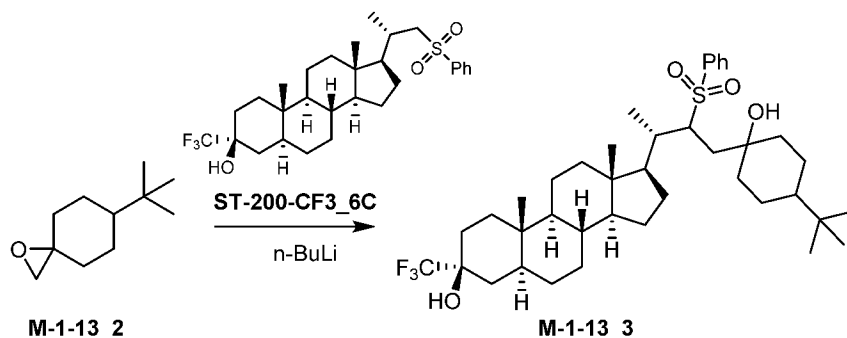
**MS** 80-100DB\_1\_4min.m, MS ESI calcd. for C<sub>33</sub>H<sub>54</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 523, found 523.

**EXAMPLE 43: Synthesis of 4360****[00483] Synthesis of M-1-13\_2**

To a suspension of C<sub>3</sub>H<sub>9</sub>IS (17.1 g, 84.2 mmol) in THF (100 mL) was added a solution of t-BuOK (14.4 g, 129 mmol) in THF (50 mL) slowly under N<sub>2</sub> at 15°C. The suspension was stirred at 15°C for 30 min. Then **M-1-13\_1** (10 g, 64.8 mmol) in 50 ml of THF was added dropwise to the mixture at 0°C. After addition, the mixture was stirred at 15°C for 16 hrs. The mixture was poured into sat.NH<sub>4</sub>Cl (300 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under reduced pressure to give **M-1-13\_2** (9 g, crude) as a liquid.

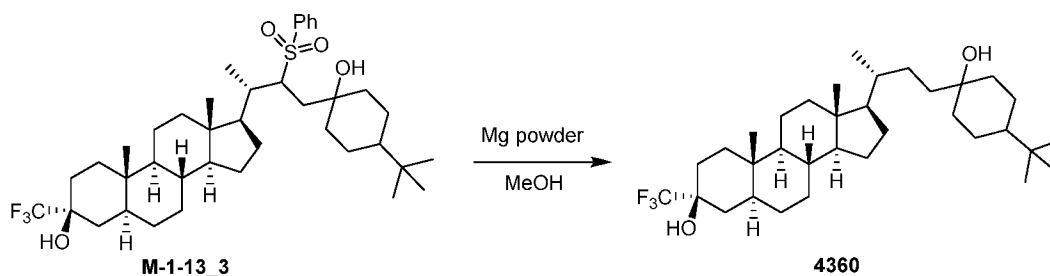
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.65-2.55 (m, 2H), 1.92-1.72 (m, 4H), 1.42-1.22 (m, 3H), 1.21-1.01 (m, 2H), 0.88 (s, 9H).

## [00484] Synthesis of M-1-14\_3



To THF (0.5 mL) was added n-BuLi (0.568 mL, 2.5 M in hexane, 1.42 mmol). A solution of **ST-200-CF3\_6C** (300 mg, 0.569 mmol) in THF (2.5 mL) was added at -70°C. After stirring at -70°C for 1 h, 6-(tert-butyl)-1-oxaspiro[2.5]octane (143 mg, 0.853 mmol) was added at -70°C. The mixture was stirred at -70°C for another 1 h, then warmed to 15°C and stirred for 16 hrs. The reaction was quenched with sat. NH<sub>4</sub>Cl (50 mL) and extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **M-1-13\_3** (350 mg, crude) as a solid, which was used for next step directly.

## 10 [00485] Synthesis of 4360

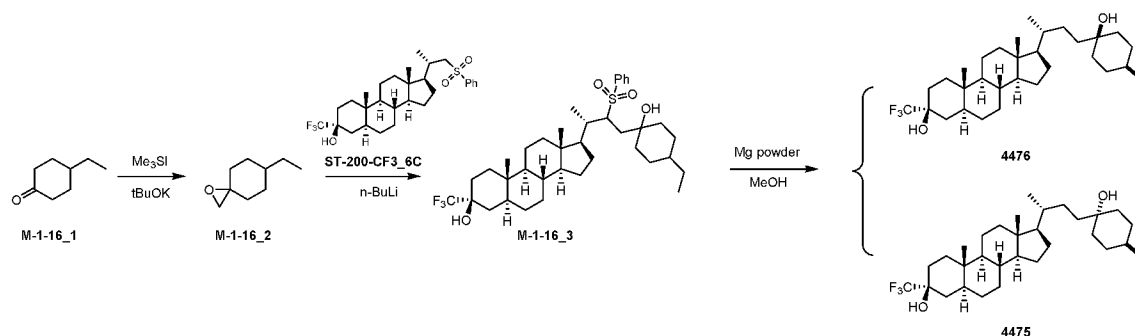


To a solution of **M-1-13\_3** (350 mg, 0.503 mmol) in MeOH (30 mL) was added NiCl<sub>2</sub> (12.8 mg, 0.100 mmol) and Mg powder (482 mg, 20.1 mmol) at 65°C in one portion. The mixture was stirred at 65°C for 10 minutes. Then another batch of Mg powder (240 mg, 10.0 mmol) was added at 65°C in one portion. The mixture was stirred at 65°C for another 10 minutes. The reaction was quenched with HCl (50 mL, 2N) until the reaction became clear and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat. NH<sub>4</sub>Cl (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give **4360** (30 mg, 11%) as a solid.

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.10-2.02 (m, 1H), 1.99-1.91 (m, 2H), 1.87-1.77 (m, 2H), 1.72-1.56 (m, 7H), 1.53-1.43 (m, 4H), 1.42-1.19 (m, 13H), 1.19-0.97 (m, 7H), 0.96-0.88 (m, 5H), 0.88-0.82 (m, 12H), 0.72-0.64 (m, 4H).

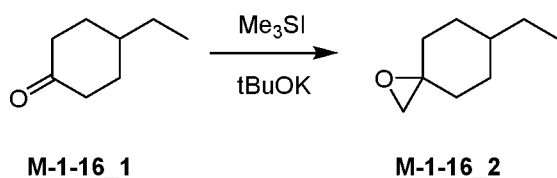
**HPLC** Rt = 7.685 min in 10.0 min chromatography, 50-100AB\_E, purity 98.3%.

**MS** 80-100\_1\_4min.m, MS ESI calcd. for C<sub>34</sub>H<sub>56</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 537, found 537.

**EXAMPLE 44: Synthesis of 4475 and 4476**

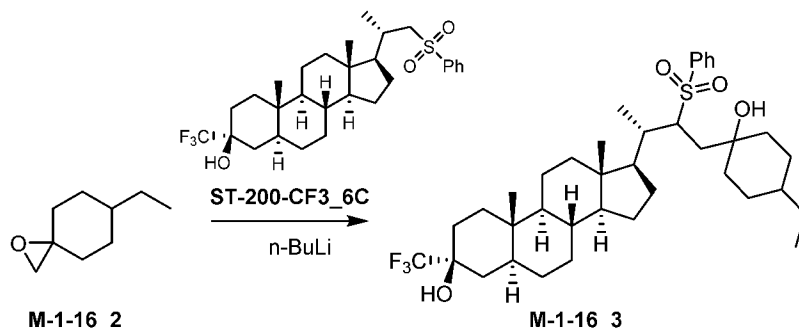
[00486] The stereochemistry for 4476 was confirmed by X-ray data.

5 [00487] The synthesis of **ST-200-CF<sub>3</sub>\_6C** can be found in Example 5.

**[00488] Synthesis of M-1-16\_2**

To a suspension of Me<sub>3</sub>Si (2.08 g, 10.2 mmol) in THF (10 mL) was added a solution of t-BuOK (1.76 g, 15.8 mmol) in THF (5 mL) slowly under N<sub>2</sub> at 15°C. The suspension was stirred at 15°C for 30 mins. Then **M-1-16\_1** (1 g, 7.13 mmol) in THF (5 mL) was added dropwise to the mixture at 0°C. After the addition, the mixture was stirred at 15°C for 16 hrs. The mixture was poured into sat.NH<sub>4</sub>Cl (60 mL), extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under reduced pressure to give **M-1-16\_2** (800 mg, crude) as a liquid.

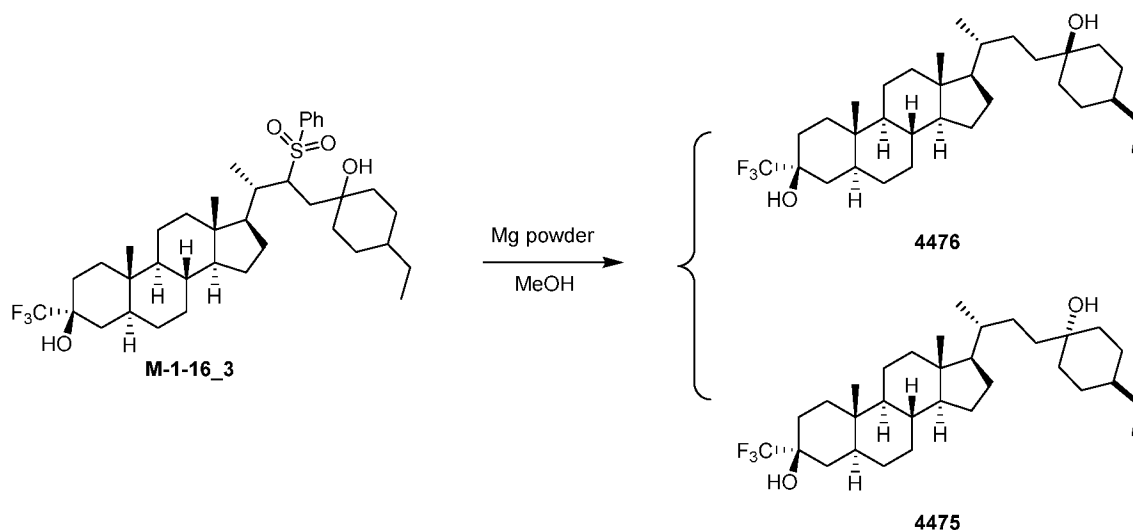
15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.67-2.53 (m, 2H), 1.94-1.70 (m, 4H), 1.64-1.00 (m, 8H), 0.97-0.83 (m, 3H).

**[00489] Synthesis of M-1-16\_3**

n-BuLi (0.756 mL, 2.5 M in hexane, 1.89 mmol) was diluted with THF (0.5 mL). A solution of **ST-200-CF<sub>3</sub>\_6C** (400 mg, 0.759 mmol) in THF (2.5 mL) was added dropwise at -70°C. The mixture was stirred at -70°C for 1 h. 6-methoxy-1-oxaspiro[2.5]octane (158 mg, 1.13 mmol) was

added at  $-70^{\circ}\text{C}$ . The mixture was stirred at  $-70^{\circ}\text{C}$  for another 1 h. The mixture was warmed to  $15^{\circ}\text{C}$  and stirred for 16 hrs. To the mixture was added  $\text{NH}_4\text{Cl}$  (15 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give **M-1-12\_3** (350 mg, crude) as an oil, which was used for the next step directly.

**[00490] Synthesis of 4476 and 4475**



To a solution of **M-1-16\_3** (350 mg, 0.524 mmol) in MeOH (30 mL) was added  $\text{NiCl}_2$  (20 mg, 0.157 mmol) and Mg powder (626 mg, 26.1 mmol) at  $65^{\circ}\text{C}$  in one portion. The mixture was stirred at  $65^{\circ}\text{C}$  for 1 hr. The mixture was quenched with HCl (30 mL, 2N) until the reaction became clear and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat.  $\text{NH}_4\text{Cl}$  (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give 34 mg, 12.3%, **4476** as a solid and 57 mg, 21%, **4475** as a solid.

**4476**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.11-2.02 (m, 1H), 2.01-1.92 (m, 2H), 1.90-1.76 (m, 3H), 1.75-1.60 (m, 7H), 1.59-1.55 (m, 2H), 1.52-1.43 (m, 3H), 1.42-1.19 (m, 13H), 1.17-0.96 (m, 9H), 0.94-0.90 (m, 3H), 0.89-0.83 (m, 6H), 0.74-0.62 (m, 4H).

**LCMS**  $\text{Rt} = 1.591$  min in 2 min chromatography, 30-90 AB, purity 100%, no MS signal.

**MS:** MS ESI calcd. For  $\text{C}_{32}\text{H}_{52}\text{F}_3\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  509, found 509.

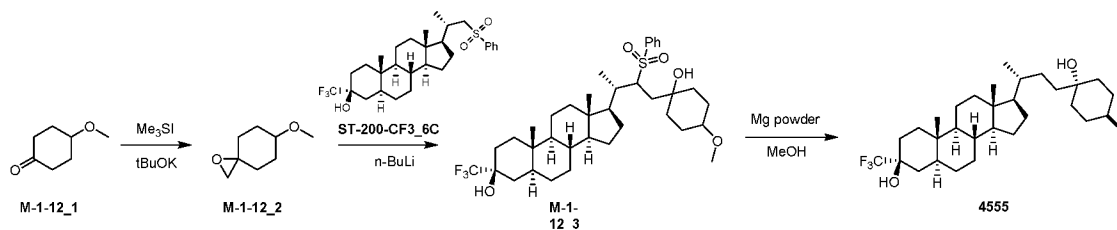
**4475**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.11-2.02 (m, 1H), 2.00-1.91 (m, 2H), 1.89-1.75 (m, 2H), 1.73-1.52 (m, 10H), 1.51-1.33 (m, 7H), 1.32-1.18 (m, 10H), 1.17-0.96 (m, 7H), 0.95-0.81 (m, 10H), 0.73-0.62 (m, 4H).

**LCMS**  $\text{Rt} = 1.679$  min in 2 min chromatography, 30-90 AB, purity 100%, no MS signal.

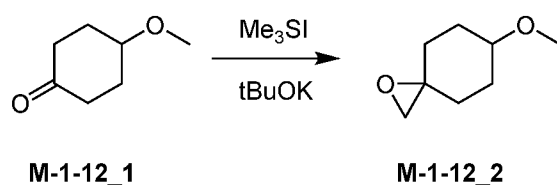
MS: MS ESI calcd. For  $C_{32}H_{52}F_3O$   $[M+H-H_2O]^+$  509, found 509.

#### EXAMPLE 45: Synthesis of 4555 and 4585



5 [00491] The synthesis of ST-200-CF<sub>3</sub>\_6C can be found in Example 5.

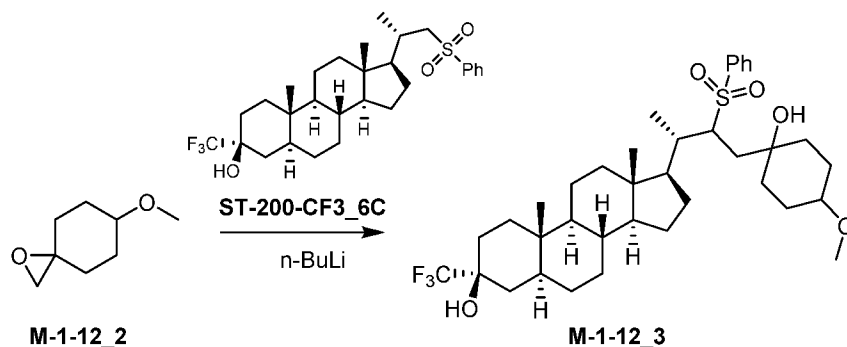
#### [00492] Synthesis of M-1-12\_2



A solution of t-BuOK (1.74 g, 15.6 mmol) in THF (5 mL) was slowly added to a suspension of  $C_3H_9IS$  (2.06 g, 10.1 mmol) in THF (10 mL) under  $N_2$  at 15°C. The suspension was stirred at 15°C for 30 min. Then M-1-12\_1 (1 g, 7.80 mmol) in 5 mL of THF was added dropwise to the mixture at 0°C. After stirring at 15°C for 16 hours, the mixture was poured into sat.  $NH_4Cl$  (60 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine (100 mL), dried over  $Na_2SO_4$ , filtered, and concentrated at 40°C under reduced pressure to give M-1-12\_2 (1 g, crude) as liquid.

15 <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.48-3.25 (m, 4H), 2.68-2.26 (m, 2H), 1.98-1.85 (m, 2H), 1.84-1.66 (m, 3H), 1.65-1.55 (m, 2H), 1.48-1.41 (m, 1H).

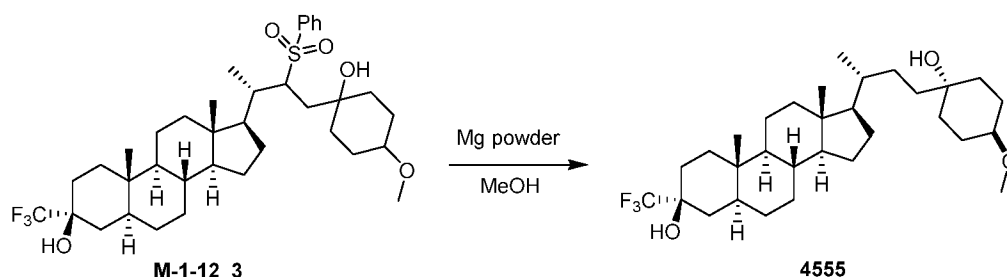
#### [00493] Synthesis of A-1-12\_3



[00494] n-BuLi (0.568 mL, 2.5 M in hexane, 1.42 mmol) was added to THF (0.5 mL). A solution of ST-200-CF<sub>3</sub>\_6C (300 mg, 0.569 mmol) in THF (2.5 mL) was added at -70°C. After stirring at -70°C for 1 h, 6-methoxy-1-oxaspiro[2.5]octane (121 mg, 0.853 mmol) was added at -

70°C. The mixture was stirred at -70°C for another 1 h. The mixture was warmed to 15°C and stirred for 16 hrs. The reaction mixture was quenched with NH<sub>4</sub>Cl (50 mL, sat. aq.) and extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **M-1-12\_3** (350 mg, crude) as a solid, which was used for next step directly.

**[00495] Synthesis of 4555**

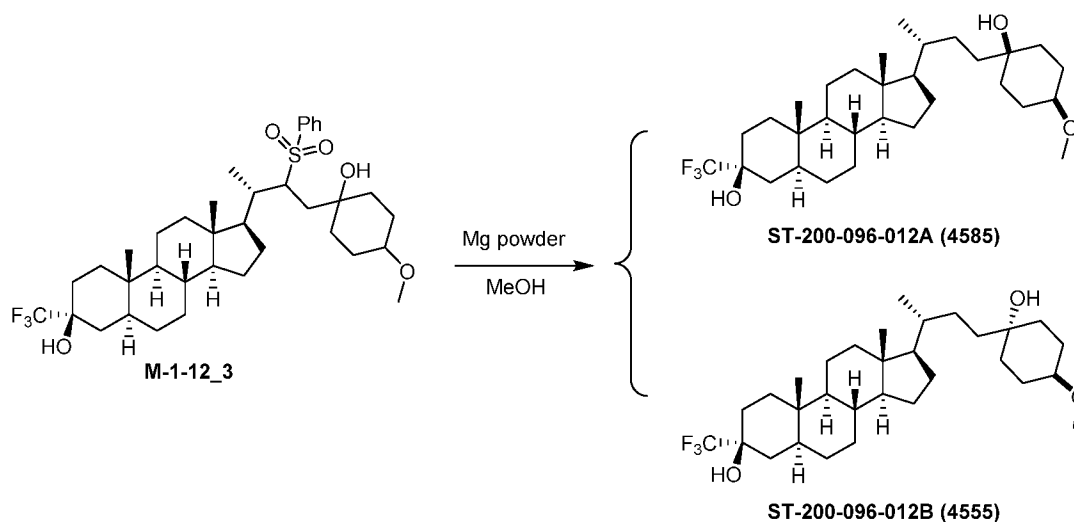


NiCl<sub>2</sub> (13.4 mg, 0.104 mmol) and Mg powder (501 mg, 20.9 mmol) were added in one portion to a solution of **M-1-12\_3** (350 mg, 0.523 mmol) in MeOH (40 mL) at 65°C. The mixture was stirred at 65°C for 10 minutes. Another portion of Mg powder (250 mg, 10.4 mmol) was added. After stirring at 65°C for 10 minutes, the mixture was quenched with HCl (60 mL, 1N) and extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by combi-flash (0-15% of EtOAc in impure **M-12** (100 mg) as a solid, which was hydrogenated (dry Pd(OH)<sub>2</sub> (40 mg), MeOH (10 mL), 50°C, 50psi for 48hrs). The suspension was filtered and the filtrate was concentrated and purified by combi-flash (0-30% of EtOAc in PE) to give pure **4555** (6 mg, 15%, 4555) as a solid.

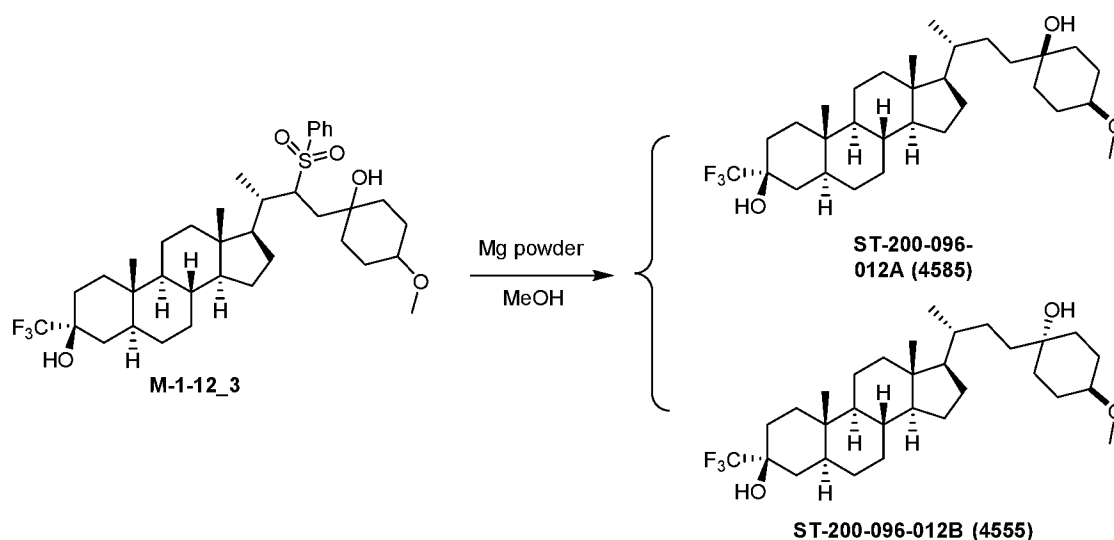
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.34 (s, 3H), 3.17-3.07 (m, 1H), 2.10-2.01 (m, 1H), 2.00-1.91 (m, 2H), 1.88-1.75 (m, 4H), 1.71-1.57 (m, 6H), 1.52-1.43 (m, 4H), 1.42-1.32 (m, 5H), 1.31-1.18 (m, 7H), 1.17-1.06 (m, 5H), 1.05-0.96 (m, 2H), 0.95-0.87 (m, 4H), 0.84 (s, 3H), 0.73-0.63 (m, 4H).

LCMS Rt = 1.321 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

MS 50-100\_1\_4min.m, MS ESI calcd. for C<sub>31</sub>H<sub>51</sub>F<sub>3</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup> 551, found 551.



**[00496]      Synthesis of ST-200-096-012A/B**



To a solution of **M-1-12\_3** (500 mg, 0.747 mmol) in MeOH (40 mL) was added NiCl<sub>2</sub> (19.2 mg, 0.149 mmol) and Mg powder (715 mg, 29.8 mmol) at 65°C in one portion. The mixture was stirred at 65°C for 10 minutes. Another Mg powder (355 mg, 14.9 mmol) was added in one portion. The mixture was stirred at 65°C for 10 minutes again, quenched with HCl (200 mL, 1N) and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by combi-flash (0-15% of EtOAc in PE) to give **ST-200-096-012A** (57 mg, 14%, Peak 1) and **ST-200-096-012B** (26 mg, 6.6%, Peak 2) as a solid.

**4555**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.34 (s, 3H), 3.17-3.07 (m, 1H), 2.09-1.91 (m, 3H), 1.88-1.76 (m, 4H), 1.70-1.61 (m, 5H), 1.56-1.44 (m, 6H), 1.43-1.19 (m, 11H), 1.17-0.95 (m, 7H), 0.95-0.85 (m, 4H), 0.84 (s, 3H), 0.72-0.61 (m, 4H).

LCMS Rt = 1.269 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

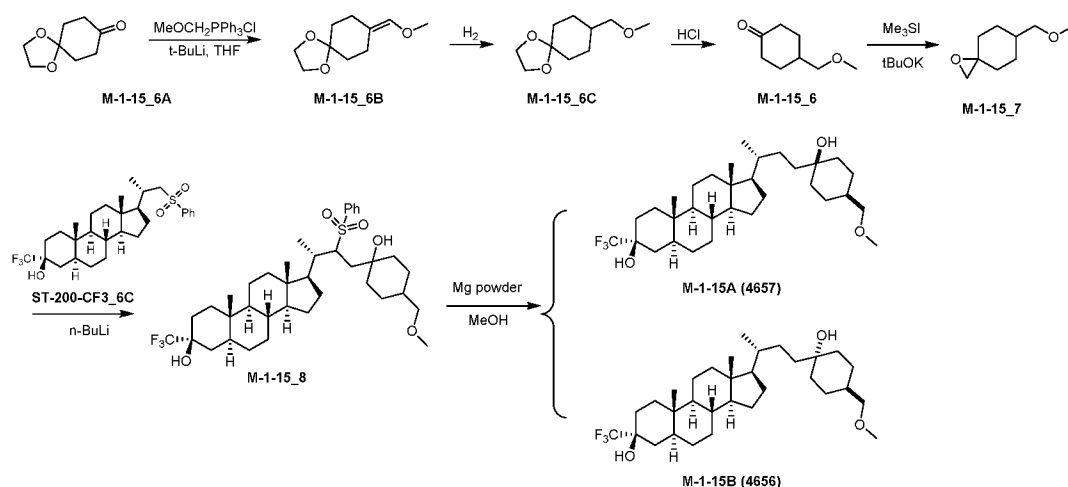
MS 50-100\_1\_4min.m, MS ESI calcd. for C<sub>31</sub>H<sub>51</sub>F<sub>3</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup> 551, found 551.

## 4585

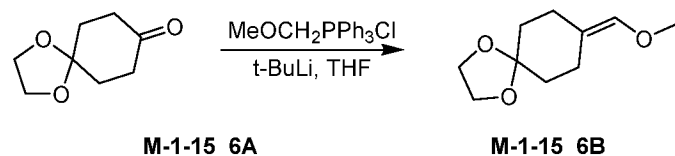
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.39-3.34 (m, 1H), 3.31 (s, 3H), 2.11-2.02 (m, 2H), 1.98-1.91 (m, 1H), 1.87-1.75 (m, 4H), 1.73-1.60 (m, 6H), 1.56-1.33 (m, 10H), 1.32-1.05 (m, 10H), 1.04-0.93 (m, 3H), 0.93-0.86 (m, 4H), 0.84 (s, 3H), 0.72-0.63 (m, 4H).

5 **LCMS**  $R_t$  = 1.257 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

**MS** 50-100\_1\_4min.m, MS ESI calcd. for  $\text{C}_{31}\text{H}_{51}\text{F}_3\text{O}_3\text{Na}$   $[\text{M}+\text{Na}]^+$  551, found 551.

**EXAMPLE 46: Synthesis of 4656 and 4657**

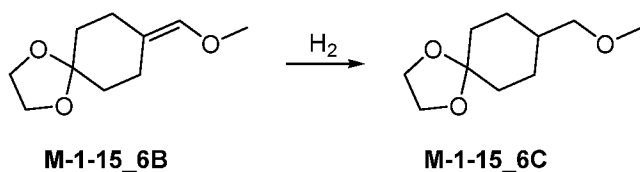
10 **[00497]** The synthesis of **ST-200-CF3\_6C** can be found in Example 5.

**[00498] Synthesis of M-1-15\_6B**

Tert-butyllithium (44.3 mL, 12.9 mmol, 1.3 M in n-hexane) was added to a solution of chloro(methoxymethyl)triphenylphosphorane (21.9 g, 64 mmol) in THF (100 mL) at 0°C. After stirring for 1 hour at 0°C, **M-1-15\_6A** (5 g, 32.0 mmol) in THF (30 mL) was added at 0°C and the reaction mixture was stirred at 15°C for 12 hours. The reaction mixture was quenched with water (60 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give the crude. The crude was purified by column chromatography with PE/EA = 20/1-3/1 to give **M-1-15\_6B** (5.55 g, 94%) as an oil.

20  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.78 (s, 1H), 3.97-3.91 (m, 4H), 3.53 (s, 3H), 2.31 (t,  $J$ =6.4 Hz, 2H), 2.1-2.06 (m, 2H), 1.68-1.59 (m, 4H).

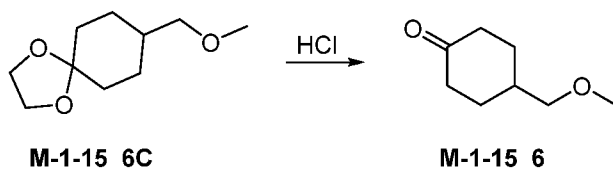
**[00499] Synthesis of M-1-15\_6C**



Pd/C (1 g) under N<sub>2</sub> at 10°C was added to solution of **M-1-15\_6B** (5.55 g, 30.1 mmol) in methanol (60 mL). The suspension was degassed under vacuum and purged with H<sub>2</sub> three times. The mixture was stirred under H<sub>2</sub> (50 psi) at 25°C for 16 hours to give a suspension. The reaction mixture was filtered through a pad of Celite (2 cm) and the filter cake was washed with methanol (3 x 20 mL). The filtrate was concentrated to give **M-1-15\_6C** (4.95 g, 88%) as an oil.

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>) δ = 3.97-3.88 (m, 4H), 3.32 (s, 3H), 3.20 (d, *J*=6.5 Hz, 2H), 1.75 (br d, *J*=9.3 Hz, 4H), 1.68-1.47 (m, 3H), 1.31-1.17 (m, 2H).

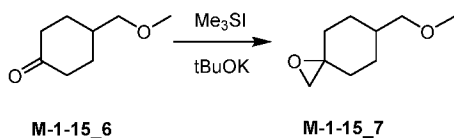
**[00500] Synthesis of M-1-15\_6**



HCl (13.0 mL, 5 M) was added to a solution of **M-1-15\_6C** (2 g, 10.7 mmol) in THF (20 mL). The reaction mixture was stirred at 10°C for 48 hours, then 25°C for 2 hours. The reaction mixture was concentrated to give a residue, which was basified to pH~10 with NaOH (2 M) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **M-1-15\_6** (1.25 g, 82%) as a liquid.

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>) δ 3.35 (s, 3H), 3.30-3.25 (m, 2H), 2.44-2.28 (m, 4H), 2.15-2.06 (m, 2H), 2.05-1.95 (m, 1H), 1.50-1.37 (m, 2H).

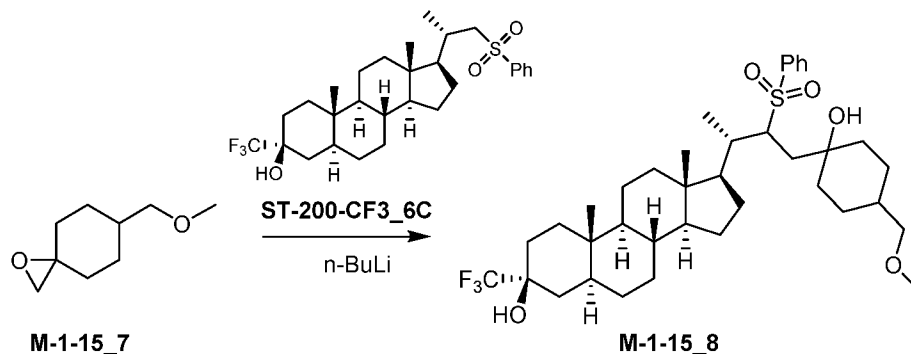
**[00501] Synthesis of M-1-15\_7**



A solution of t-BuOK (787 mg, 7.02 mmol) in THF (2.5 mL) was slowly added to a suspension of Me<sub>3</sub>IS (930 mg, 4.56 mmol) in THF (5 mL) was added under N<sub>2</sub> at 15°C. After stirring at 15°C for 30 min, then **M-1-15\_6** (0.5 g, 3.51 mmol) in 2.5 ml of THF was added drop wise to the mixture at 0°C. After the addition, the mixture was stirred at 15°C for 16 hours, quenched with sat. NH<sub>4</sub>Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **M-1-15\_7** (410 mg, crude) as a liquid.

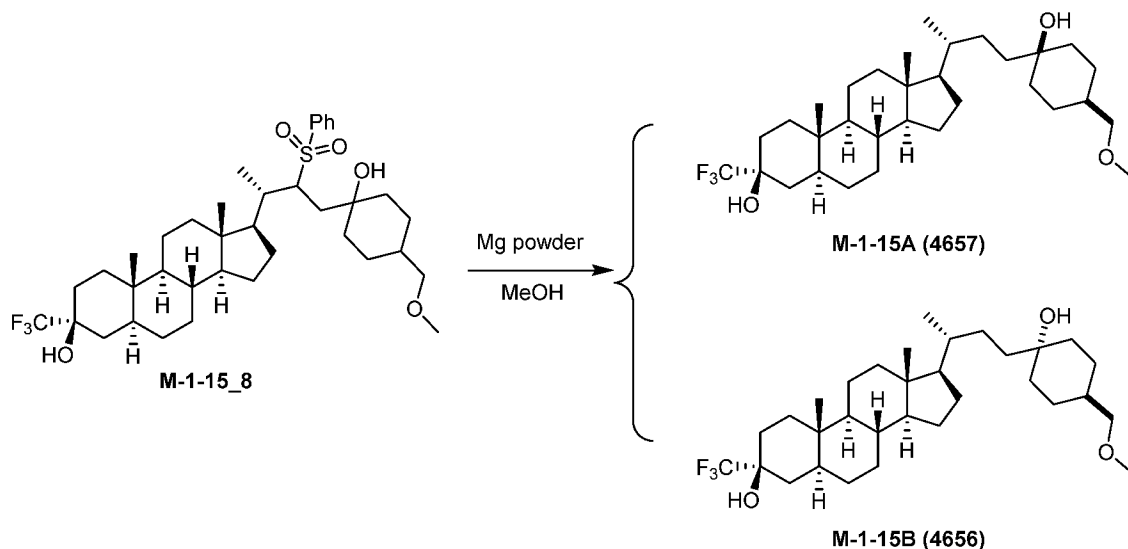
<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>) δ 3.34 (s, 3H), 3.30-3.25 (m, 2H), 2.65-2.55 (m, 2H), 1.95-1.80 (m, 4H), 1.75-1.60 (m, 1H), 1.40-1.15 (m, 4H).

**[00502] Synthesis of M-1-15\_8**



- 5 A solution of n-BuLi (0.472 mL, 2.5 M in hexane, 1.18 mmol) was added to THF (0.5 mL). A solution of **ST-200-CF3\_6C** (250 mg, 0.474 mmol) in THF (2.5 mL) was added to the mixture at -70°C. The mixture was stirred at -70°C for 1 hour. **M-1-15\_7** (111 mg, 0.711 mmol) was added at -70°C. After stirring at -70°C for another 1 hour, the mixture was warmed to 15°C and stirred for 16 hrs. The reaction mixture was quenched with NH<sub>4</sub>Cl (50 mL, sat. aq) and extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **M-1-15\_8** (250 mg, crude) as a solid, which was used for next step directly.
- 10

**[00503] Synthesis of M-1-15A & M-1-15B**



- 15 NiCl<sub>2</sub> (9.48 mg, 0.0732 mmol) and Mg powder (350 mg, 14.6 mmol) were added in one portion to a solution of **M-1-15\_8** (350 mg, 0.513 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 10 minutes. Then another portion of Mg powder (175 mg, 7.32 mmol) was added at 65°C. After stirring at 65°C for another 10 minutes, the mixture was quenched with HCl (50 mL, 2N) until the reaction became clear and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat. NH<sub>4</sub>Cl (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered,

concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give **M-1-15A** (22 mg, 11%, **4656**,) and **M-1-15B** (54 mg, 27%, **4657**) as a solid.

#### NMA-1-15A (**4656**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.27 (s, 3H), 3.24-3.19 (m, 2H), 2.10-2.02 (m, 1H), 1.99-1.92 (m, 2H), 1.88-1.77 (m, 2H), 1.76-1.55 (m, 10H), 1.52-1.34 (m, 8H), 1.32-1.21 (m, 5H), 1.19-0.98 (m, 9H), 0.96-0.87 (m, 4H), 0.84 (s, 3H), 0.72-0.62 (m, 4H).

LCMS Rt = 1.327 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

MS 50-100\_1\_4min.m, MS ESI calcd. for C<sub>32</sub>H<sub>52</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 525, found 525.

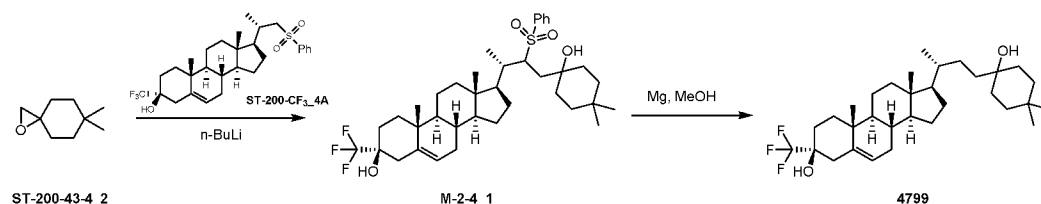
#### NMA-1-15B (**4657**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.33 (s, 3H), 3.23-3.19 (m, 2H), 2.10-2.01 (m, 1H), 1.99-1.92 (m, 2H), 1.88-1.77 (m, 2H), 1.73-1.55 (m, 8H), 1.53-1.43 (m, 5H), 1.41-1.20 (m, 12H), 1.19-1.07 (m, 4H), 1.06-0.96 (m, 3H), 0.96-0.86 (m, 4H), 0.84 (s, 3H), 0.72-0.62 (m, 4H).

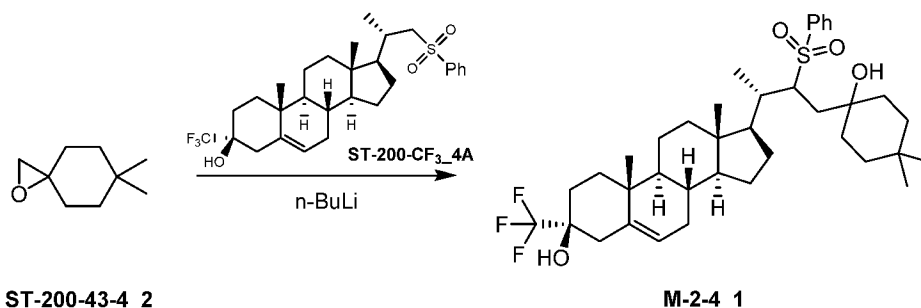
LCMS Rt = 1.377 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

MS 50-100\_1\_4min.m, MS ESI calcd. for C<sub>32</sub>H<sub>52</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 525, found 525.

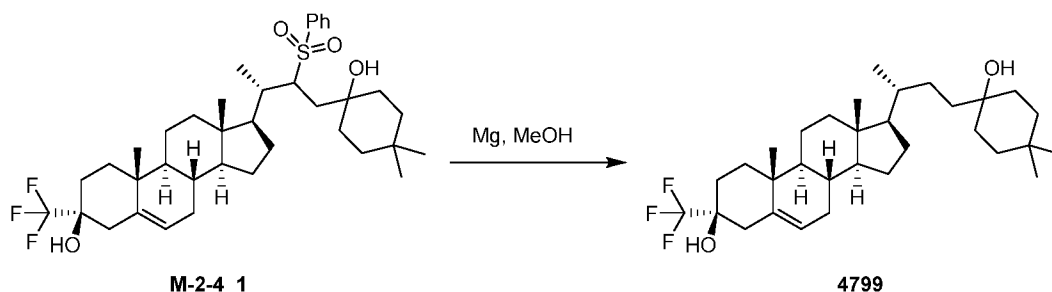
### EXAMPLE 47: Synthesis of 4799



#### [00504] Synthesis of M-2-4\_1



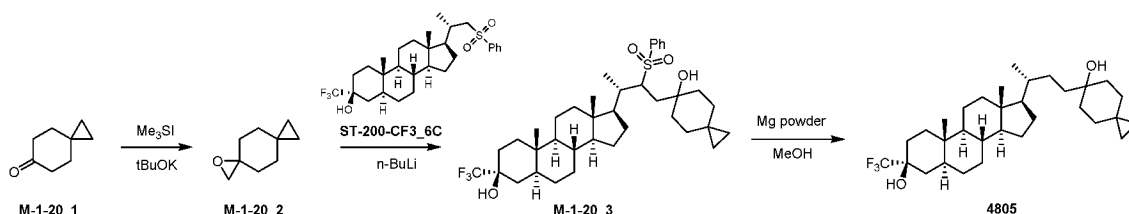
A solution of n-BuLi (0.476 mL, 2.5 M in hexane, 1.19 mmol) was added to THF (0.5 mL). A solution of **ST-200-CF<sub>3</sub>\_4A** (250 mg, 0.476 mmol) in THF (2.5 mL) was added at -70°C. After stirring at -70°C for 1 hour, **ST-200-43-4\_2** (100 mg, 0.714 mmol) was added to the mixture at -70°C. The mixture was stirred at -70°C for another 1 hour. The mixture was warmed to 15°C, stirred for 16 hrs, quenched with NH<sub>4</sub>Cl (50 mL, sat. aq) and extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **M-2-4\_1** (250 mg, crude) as a solid, which was used for next step directly.

**[00505] Synthesis of 4799**

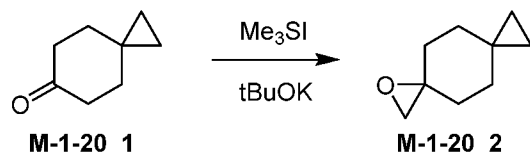
NiCl<sub>2</sub> (9.71 mg, 0.075 mmol) and Mg powder (360 mg, 15.0 mmol) were added in one portion to a solution of **M-2-4\_1** (250 mg, 0.375 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 10 minutes. Then another portion of Mg powder (180 mg, 7.5 mmol) was added at 65°C. After stirring at 65°C for another 10 minutes, the mixture was quenched with HCl (50 mL, 2N) until the reaction became clear and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat. NH<sub>4</sub>Cl (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give **4799** (56 mg, 28%) as a solid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.33 (m, 1H), 2.48 (s, 2H), 2.08-1.92 (m, 4H), 1.91-1.69 (m, 3H), 1.62-1.56 (m, 2H), 1.53-1.45 (m, 9H), 1.44-1.35 (m, 4H), 1.34-1.23 (m, 2H), 1.22-1.04 (m, 10H), 1.04-0.97 (m, 2H), 0.96-0.90 (m, 6H), 0.87 (s, 3H), 0.68 (s, 3H).

LCMS Rt = 1.439 min in 2.0 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>50</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 507, found 507.

**EXAMPLE 48: Synthesis of 4805**

**[00506]** The synthesis of **ST-200-CF3\_6C** can be found in Example 5.

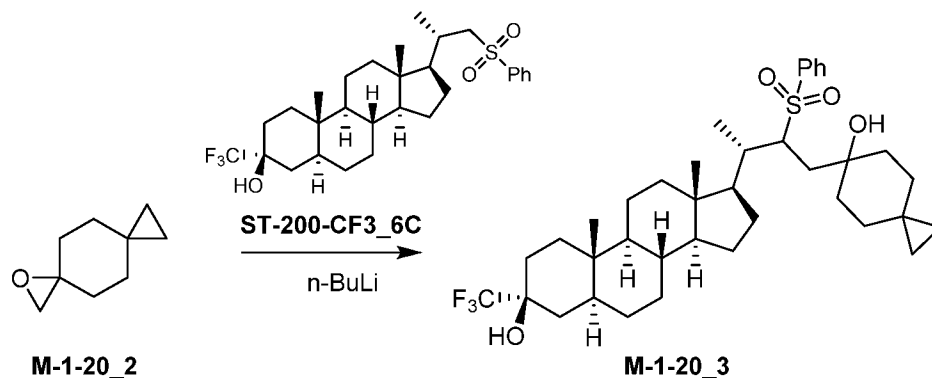
**[00507] Synthesis of M-1-20\_2**

A solution of t-BuOK (902 mg, 8.04 mmol) in THF (4 mL) was slowly added to a suspension of C<sub>3</sub>H<sub>9</sub>IS (1.06 g, 5.22 mmol) in THF (5 mL) under N<sub>2</sub> at 15°C. After stirring at 20°C for 30 min, **M-1-20\_1** (500 mg, 4.02 mmol) in 1 mL of THF was added dropwise to the mixture at 0°C. After

addition, the mixture was stirred at 20°C for 16 hours, quenched with sat. NH<sub>4</sub>Cl (40 mL) and extracted with MTBE (3 x 20 mL). The combined organic phase was washed with brine (2 x 60 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under reduced pressure to give **M-1-20\_2** (390 mg, crude) as a liquid.

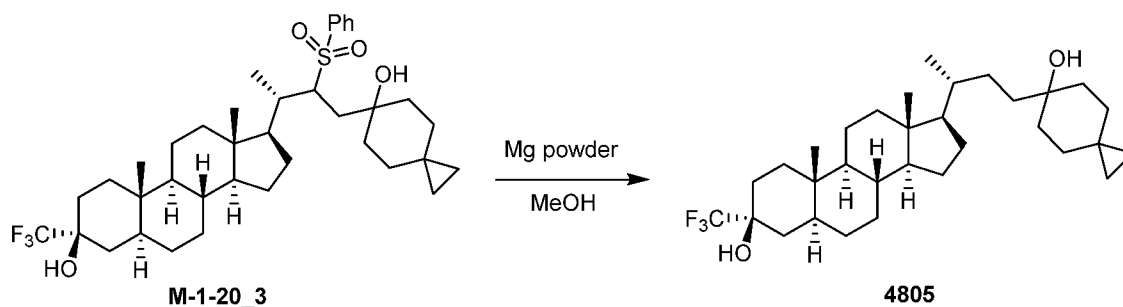
- 5 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.63 (s, 2H), 1.74-1.53 (m, 6H), 1.41-1.27 (m, 2H), 0.37-0.26 (m, 4H).

[00508] **Synthesis of M-1-20\_3**



- A solution of n-BuLi (0.472 mL, 2.5 M in hexane, 1.18 mmol) was added to THF (0.5 mL). A solution of **ST-200-CF3\_6C** (250 mg, 0.474 mmol) in THF (2.5 mL) was added at -70°C. After stirring at -70°C for 1 h, **M-1-20\_2** (98.2 mg, 0.711 mmol) was added at -70°C. The mixture was stirred at -70°C for another 1 h, warmed to 15°C for 16 hours, quenched with NH<sub>4</sub>Cl (50 mL, sat. aq) and extracted with EtOAc (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **M-1-20\_3** (250 mg, crude) as a solid, which was used for next step directly.

[00509] **Synthesis of 4805**



- NiCl<sub>2</sub> (9.71 mg, 0.075 mmol) and Mg powder (360 mg, 15.0 mmol) were added in one portion to a solution of **M-1-20\_3** (250 mg, 0.375 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 10 minutes. Then another portion of Mg powder (180 mg, 7.5 mmol) was added at 65°C. After stirring at 65°C for another 10 minutes, the mixture was quenched with HCl (50 mL, 2N) until the reaction became clear and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat. NH<sub>4</sub>Cl (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered,

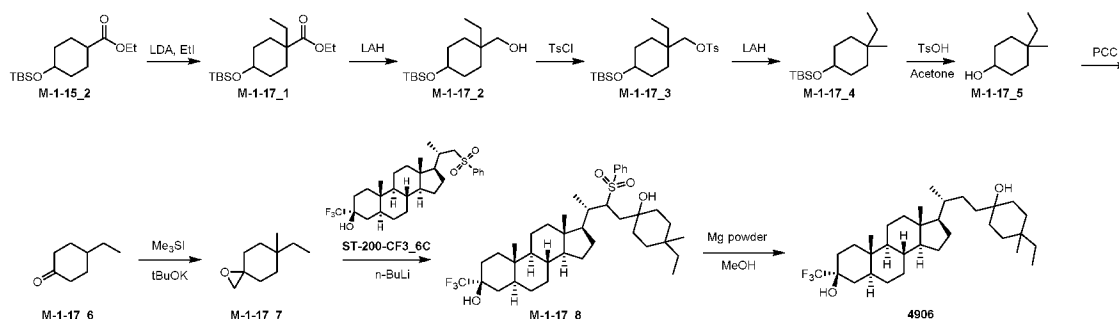
concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give **4805** (150 mg, 76%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.11-1.94 (m, 3H), 1.89-1.60 (m, 9H), 1.54-1.35 (m, 9H), 1.34-1.19 (m, 6H), 1.18-1.06 (m, 5H), 1.05-0.88 (m, 8H), 0.85 (s, 3H), 0.74-0.62 (m, 4H), 0.33-0.15 (m, 4H).

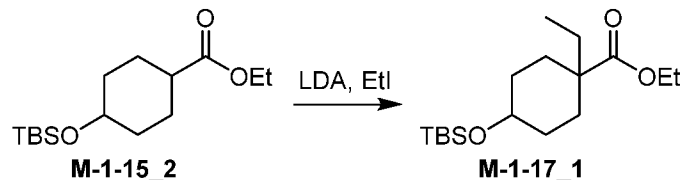
LCMS Rt = 1.414 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

MS 80-100\_1\_4min.m, MS ESI calcd. for C<sub>32</sub>H<sub>51</sub>F<sub>3</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 547, found 547.

#### EXAMPLE 49: Synthesis of 4906

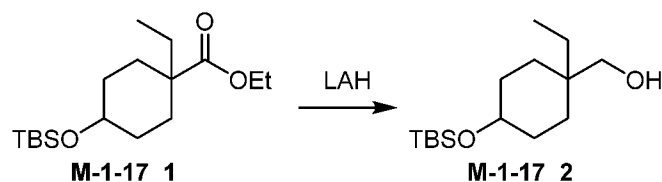


#### [00510] Synthesis of M-1-17\_1



A solution of n-butyllithium (64 mL, 160 mmol, 2.5 M in hexane) was added to a solution of diisopropylamine (17.6 g, 174 mmol) in THF (30 mL) at -70°C. The mixture was warmed to 0°C and stirred at 0°C for 30 minutes. The mixture was cooled to -70°C and **M-1-15\_2** (20 g, 69.8 mmol) in THF (20 mL) was added. The mixture was stirred at -70°C for 1 h. Ethyl iodide (43.5 g, 279 mmol) was added. The mixture was warmed to 15°C and stirred at 15°C for 5 hours. The mixture was quenched with Sat NH<sub>4</sub>Cl (30 mL). The mixture was extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude **M-1-17\_1** (21, crude) as an oil.

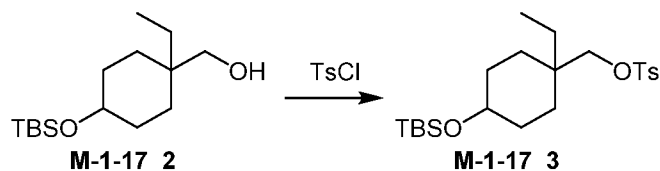
#### [00511] Synthesis of M-1-17\_2



LiAlH<sub>4</sub> (5.05 g, 133 mmol) was added in five portions to a solution of **M-1-17\_1** (21 g, 66.7 mmol) in THF (100 mL) at 0°C under N<sub>2</sub>. The mixture was stirred at 20°C for 4 hours. To the mixture water (20 mL) was added at 0°C. HCl (100 mL, 1 mol/L) was added. The aqueous phase was extracted with EtOAc (50 mL x 2). The combined organic phase was washed with saturated brine (2 x 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give **M-1-17\_2** (16.5 g, 91%) as an oil.

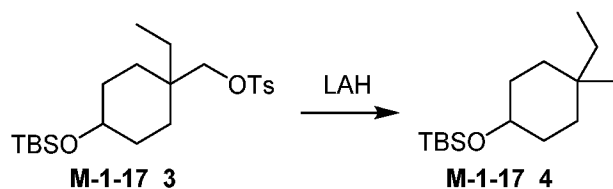
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.70-3.55 (m, 1H), 3.55-3.45 (m, 2H), 1.70-1.55 (m, 5H), 1.55-1.10 (m, 9H), 0.95-0.88 (m, 9H), 0.041 (s, 6H).

**[00512] Synthesis of M-1-17\_3**



1-methyl-1H-imidazole (7.44 g, 90.7 mmol) and TEA (12.2 g, 121 mmol) were added to a solution of **M-1-17\_2** (16.5 g, 60.5 mmol) in DCM (100 mL) at 15°C. TsCl (23.0 g, 121 mmol) was added to the solution. The reaction mixture was stirred at 15°C for 2 hours. The mixture was washed with water (2 x 100 mL), brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **M-1-17\_3** (24 g, crude) as an oil.

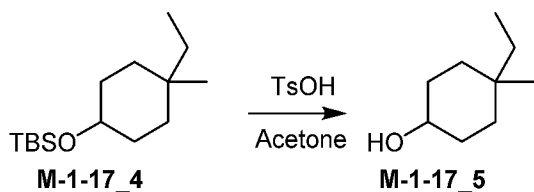
**[00513] Synthesis of M-1-17\_4**



LiAlH<sub>4</sub> (5.32 g, 140 mmol) was added in five portions to a solution of **M-1-17\_3** (24 g, 56.2 mmol) in THF (100 mL) at 0°C under N<sub>2</sub>. The mixture was stirred at 20°C for 4 hours. Water (20 mL) was added to the mixture at 0°C. HCl (100 mL, 1 mol/L) was added. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with saturated brine (2 x 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **M-1-17\_4** (13 g, crude) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.60-3.50 (m, 1H), 1.95-1.70 (m, 3H), 1.70-1.01 (m, 12H), 1.01-0.68 (m, 10H), 0.043 (s, 6H).

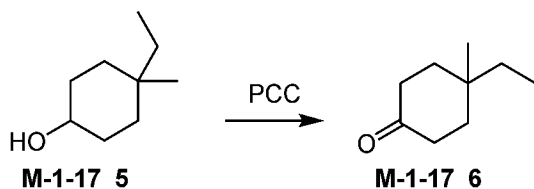
**[00514] Synthesis of M-1-17\_5**



*p*-TsOH (7.23 g, 38.9 mmol) was added to a solution **M-1-17\_4** (10 g, 38.9 mmol) in acetone (50 mL). The reaction mixture was stirred at 15°C for 2 h. Water was added and was extracted with EtOAc (2 x 30 mL). The combined organics were washed with NaHCO<sub>3</sub> (20 mL, 10%) and brine (30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure. The residue was purified by flash column (0~20% of EtOAc in PE) to give **M-1-17\_5** (6 g, crude) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.70-3.50 (m, 1H), 1.80-1.60 (m, 4H), 1.60-1.40 (m, 5H), 1.40-1.01 (m, 4H), 0.91-0.75 (m, 4H).

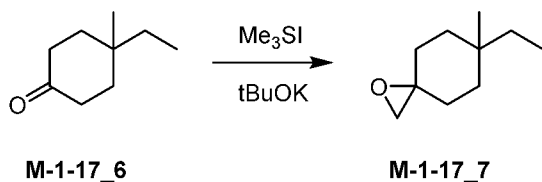
10 **[00515]          Synthesis of M-1-17\_6**



DMP (17.8 g, 42 mmol) was added to a solution of **M-1-17\_5** (3 g, 21 mmol) in DCM (20 mL). Next, H<sub>2</sub>O (7.55 mg, 0.42 mmol) was added to the solution. The reaction was stirred at 15°C for 30min. Aqueous saturated NaHCO<sub>3</sub> (10 mL) solution, aqueous saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) solution were added to the reaction mixture. The mixture was extracted with DCM (2 x 20 mL). The combined organic layer was washed with aqueous saturated NaHCO<sub>3</sub> (2 x 20 mL) solution and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum and purified by flash column (0~10% of EtOAc in PE) to give **M-1-17\_6** (2.5 g, 85%) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.40-2.28 (m, 4H), 1.72-1.60 (m, 4H), 1.49-1.40 (m, 2H), 1.02 (s, 3H), 0.92-0.85 (m, 3H).

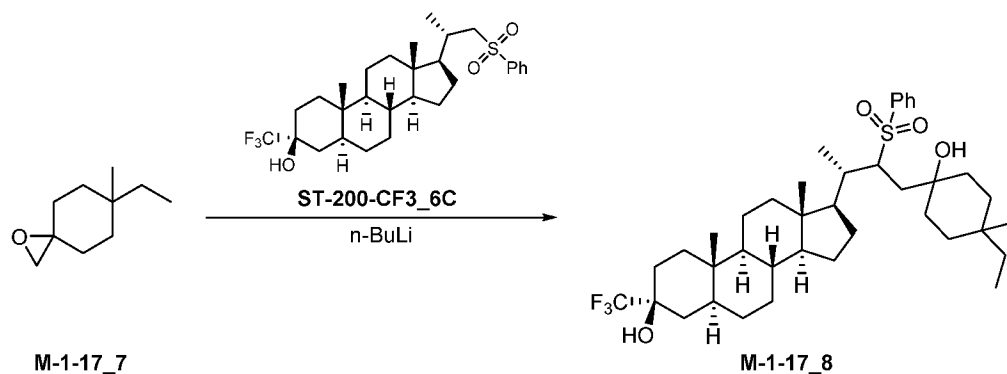
20 **[00516]          Synthesis of M-1-17\_7**



**M-1-17\_6** (1 g, 7.13 mmol) was added to a stirred solution of trimethylsulfoxonium iodide (3.12 g, 14.2 mmol) and *t*-BuOK (1.75 g, 15.6 mmol) in THF (10 mL) at 0°C. The reaction mixture was stirred at 10°C for 16 hours. The reaction mixture was poured into saturated aqueous NH<sub>4</sub>Cl (15 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic

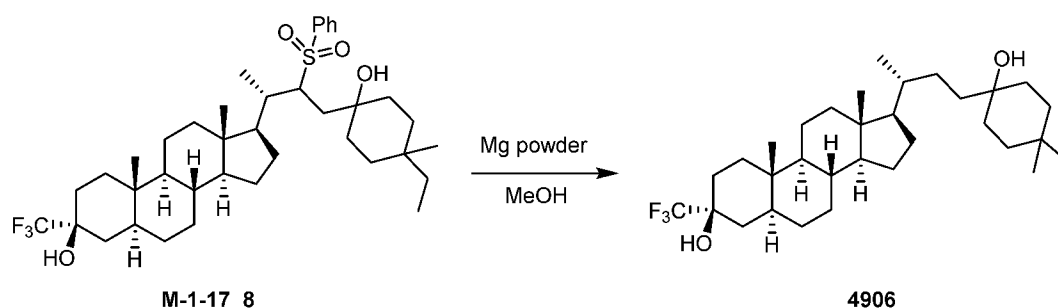
layers were washed with brine (20 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give **M-1-17\_7** (360 mg, crude) as an oil.

**[00517] Synthesis of M-1-17\_8**



- 5 A solution of n-BuLi (0.568 mL, 2.5 M in hexane, 1.42 mmol) was added to THF (0.5 mL). A solution of **ST-200-CF3\_6C** (300 mg, 0.474 mmol) in THF (2.5 mL) was added at  $-70^\circ\text{C}$ . After stirring at  $-70^\circ\text{C}$  for 1 h, **M-1-17\_7** (131 mg, 0.853 mmol) was added at  $-70^\circ\text{C}$ . The mixture was stirred at  $-70^\circ\text{C}$  for another 1 h, warmed to  $15^\circ\text{C}$  and stirred for 16 hours. The reaction mixture was quenched with  $\text{NH}_4\text{Cl}$  (10 mL, sat. aq) and extracted with EtOAc (2 x 20 mL). The organic
- 10 layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give **M-1-15\_8** (387 mg, crude) as an oil, which was used for the next step directly.

**[00518] Synthesis of 4906**

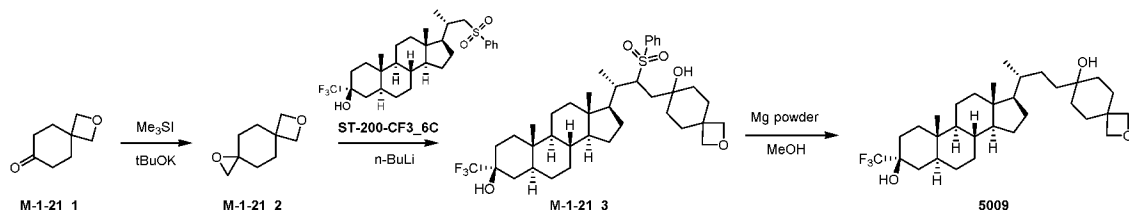


- 15  $\text{NiCl}_2$  (14.6 mg, 0.113 mmol) and Mg powder (550 mg, 22.9 mmol) were added in one portion to a solution of **M-1-17\_8** (387 mg, 568  $\mu\text{mol}$ ) in MeOH (40 mL) at  $65^\circ\text{C}$ . After stirring at  $65^\circ\text{C}$  for 10 minutes, another batch of Mg powder (266 mg, 11.1 mmol) was added in one portion at  $65^\circ\text{C}$ . The mixture was stirred at  $65^\circ\text{C}$  for another 10 minutes. The reaction mixture was cooled to  $20^\circ\text{C}$  and quenched by HCl (30 mL, 2 M). The resulting mixture was extracted with EtOAc (3 x 70 mL). The combined organic layers were washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (70 mL),
- 20 brine (70 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give the crude. The crude was purified by column chromatography with PE/EtOAc = 0/1-5/1. The solvent was removed to give **4906** (56 mg, 18%) as a solid.

$^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$  2.12-2.00 (m, 1H), 2.00-1.93 (m, 1H), 1.90-1.80 (m, 1H), 1.78-1.60 (m, 2H), 1.59-1.50 (m, 7H), 1.49-1.33 (m, 12H), 1.32-1.15 (m, 9H), 1.14-1.0 (m, 7H), 0.99-0.90 (m, 3H), 0.89-0.80 (m, 8H), 0.75-0.70 (m, 1H), 0.70-0.60 (s, 3H).

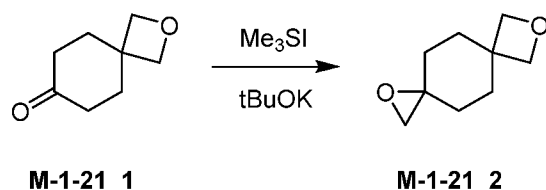
LCMS Rt = 1.550 min in 2.0 min chromatography, 30-90AB\_E, purity 100%; special MS ESI calcd. for  $\text{C}_{33}\text{H}_{56}\text{F}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  541, found 541.

### EXAMPLE 50: Synthesis of 5009



[00519] The synthesis of ST-200-CF3\_6C can be found in Example 5.

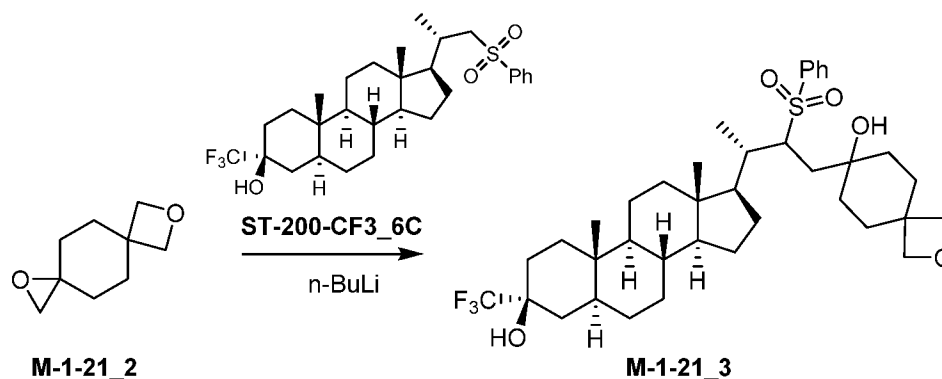
### 10 [00520] Synthesis of M-1-21\_2



A solution of  $\text{t-BuOK}$  (797 mg, 7.12 mmol) in THF (3 mL) was added slowly by stirring into a suspension of  $\text{C}_3\text{H}_9\text{IS}$  (942 mg, 4.62 mmol) in THF (5 mL) under  $\text{N}_2$  at  $15^\circ\text{C}$ . After stirring at  $20^\circ\text{C}$  for 30 min, M-1-21\_1 (500 mg, 3.56 mmol) in 2 ml of THF was added dropwise to the mixture at  $0^\circ\text{C}$ . After addition, the mixture was stirred at  $20^\circ\text{C}$  for 16 hrs, quenched with sat.  $\text{NH}_4\text{Cl}$  (40 mL) without monitor and extracted with MTBE (3 x 20 mL). The combined organic phase was washed with brine (2 x 60 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at  $40^\circ\text{C}$  under reduced pressure to give M-1-21\_2 (360 mg, crude) as a liquid.

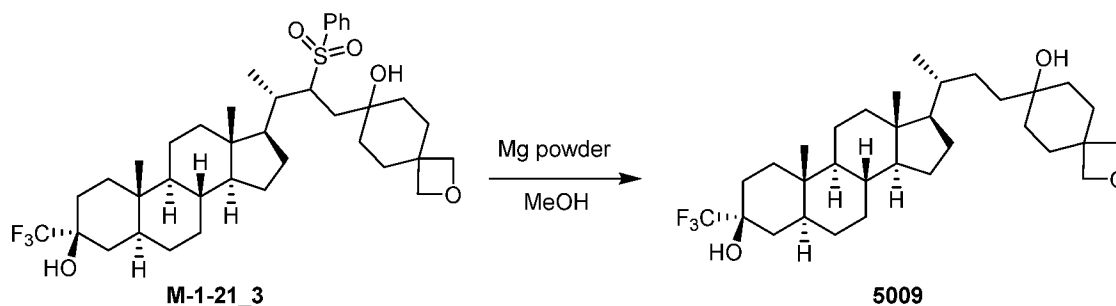
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.47-4.42 (m, 4H), 2.61 (s, 2H), 2.06-1.90 (m, 4H), 1.68-1.58 (m, 2H), 1.51-1.41 (m, 2H).

### [00521] Synthesis of M-1-21\_3



A solution of n-BuLi (0.472 mL, 2.5 M in hexane, 1.18 mmol) was added to THF (0.5 mL). A solution of **ST-200-CF3\_6C** (250 mg, 0.474 mmol) in THF (2.5 mL) was added at -70°C. After stirring at -70°C for 1 h, **M-1-21\_2** (109 mg, 0.711 mmol) was added at -70°C. The mixture was stirred at -70°C for another 1 h and then warmed to 15°C for 16 hrs. The reaction mixture was quenched with NH<sub>4</sub>Cl (50 mL, sat. aq) and extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **M-1-21\_3** (250 mg, crude) as a solid, which was used for next step directly.

**[00522]      Synthesis of 5009**



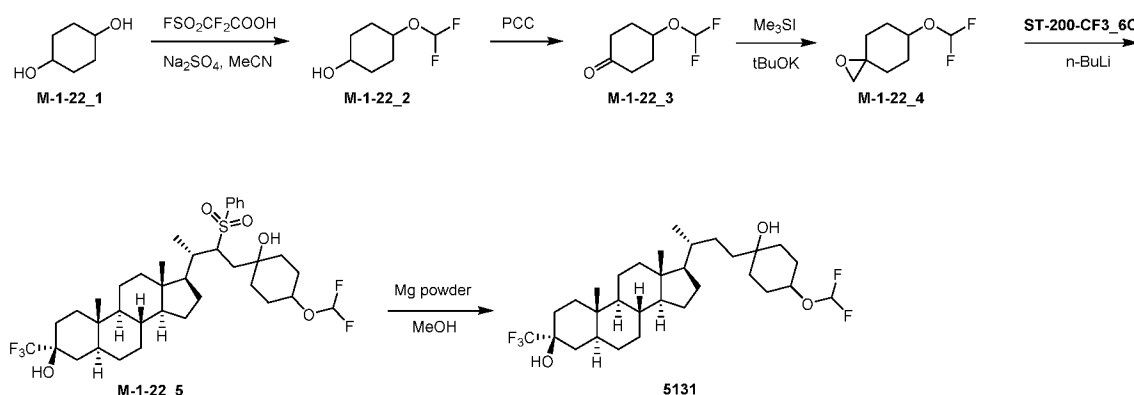
NiCl<sub>2</sub> (9.49 mg, 0.0733 mmol) and Mg powder (350 mg, 14.6 mmol) were added in one portion to a solution of **M-1-21\_3** (250 mg, 0.367 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 10 minutes. Then another Mg powder (178 mg, 7.34 mmol) was added at 65°C in one portion. After stirring at 65°C for another 10 minutes, the mixture was quenched with HCl (50 mL, 2N) until the reaction became clear and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with sat. NH<sub>4</sub>Cl (50 mL), NaHCO<sub>3</sub> (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give impure **5009** (200 mg), which was further purified by combi-flash (0-10% of Acetone in DCM) then recrystallized to give 120 mg still impure product. DMAP (13.4 mg, 0.11 mmol) and BzCl (77.3 mg, 0.550 mmol) were added to a solution of impure **5009** (60 mg, 0.110 mmol) in Py (5 mL). The reaction mixture was stirred at 20°C for 2 hrs. The reaction was quenched with sat. NH<sub>4</sub>Cl (30 mL) and extracted with MTBE (2 x 15 mL). The combined organic phase was washed with brine (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, and purified by prep-TLC (PE: EtOAc = 5:1) to give desired product (40 mg, 56%) as a solid. To a solution of above (40 mg, 0.062 mmol) in MeOH (3 mL), THF (1 mL) and H<sub>2</sub>O (1 mL) was added NaOH (49.5 mg, 1.24 mmol). After stirring at 50°C for 1h, the reaction mixture was quenched with water (5 mL) and extracted with EtOAc (2 x 3 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by combi-flash (0-30% of EtOAc in PE) to give **5009** (17 mg, 50%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.73 (s, 2H), 3.31 (s, 2H), 2.10-1.90 (m, 3H), 1.88-1.72 (m, 4H), 1.71-1.58 (m, 5H), 1.56-1.41 (m, 7H), 1.40-1.31 (m, 5H), 1.30-1.15 (m, 7H), 1.14-0.93 (m, 5H), 0.92-0.86 (m, 4H), 0.85 (s, 3H), 0.70-0.60 (m, 4H).

LCMS Rt = 1.282 min in 2.0 min chromatography, 30-90AB\_E, purity 100%.

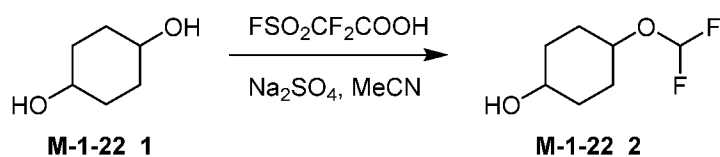
5 MS 50-100\_1\_4min.m, MS ESI calcd. for  $\text{C}_{32}\text{H}_{50}\text{F}_3\text{O}_2$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  523, found 523.

#### EXAMPLE 51: Synthesis of 5131



[00523] The synthesis of **ST-200-CF3\_6C** can be found in Example 5.

10 [00524] **Synthesis of M-1-22\_2**

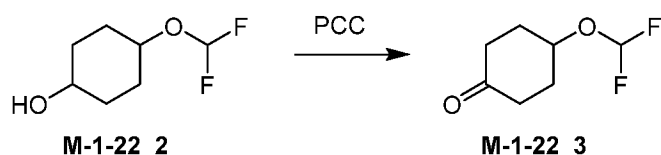


A solution of  $\text{FSO}_2\text{CF}_2\text{COOH}$  (18.3 g, 103 mmol) in  $\text{CH}_3\text{CN}$  (30 mL) was added dropwise over a period of 1 hour to a mixture of **M-1-22\_1** (10 g, 86 mmol) and  $\text{Na}_2\text{SO}_4$  (6.1 g, 43 mmol) in  $\text{CH}_3\text{CN}$  (120 mL) at 40 to 45°C. After addition, the solution was poured into water (200 mL).

15 The aqueous phase was extracted with DCM (3 x 100 mL). The combined organic phase was washed with saturated brine (2 x 200 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash column (0~100% of EtOAc in PE) to give **M-1-22\_2** (6 g, crude) as an oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.42-6.02 (m, 1H), 4.30-4.10 (m, 1H), 3.80-3.60 (m, 1H), 2.20-1.30 (m, 8H).

20 [00525] **Synthesis of M-1-22\_3**

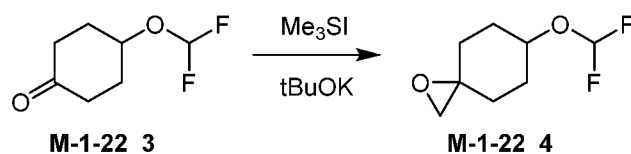


Silica gel (5 g) and  $\text{PCC}$  (15.5 g, 72.2 mmol) were added to a suspension of **M-1-22\_2** (6 g, 36.1 mmol) in DCM (100 mL) at 20°C. After stirring at 20°C for 2 hours, the mixture was filtered and

the filter cake was washed with DCM (100mL). The combined filtrate was concentrated in vacuum and purified by flash column (0~100% of EtOAc in PE) to give crude product **M-1-22\_3** (3.5 g, 59%) as a oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.52-6.10 (m, 1H), 4.65-4.55 (m, 1H), 2.70-2.55 (m, 2H), 2.40-2.25 (m, 2H), 2.23-2.11 (m, 2H), 2.10-1.98 (m, 2H).

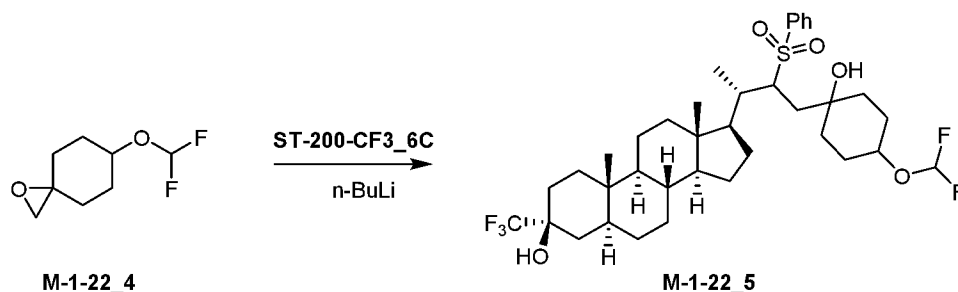
[00526] **Synthesis of M-1-22\_4**



**M-1-22\_3** (3.1 g, 18.8 mmol) was added to a stirred solution of trimethylsulfoxonium iodide (4.97 g, 24.4 mmol) and t-BuOK (4.21 g, 37.6 mmol) in THF (60 mL) at 0°C. After stirring at 20°C for 16 hours, the reaction mixture was poured into saturated aqueous NH<sub>4</sub>Cl (90 mL) and extracted with EtOAc (3 x 120 mL). The combined organic layers were washed with brine (120 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **M-1-22\_4** (1.9 g, crude) as an oil, which was purified by combi-flash (0-10% of EtOAc in PE) to give pure **M-1-22\_4** (300 mg, 23%) as an oil.

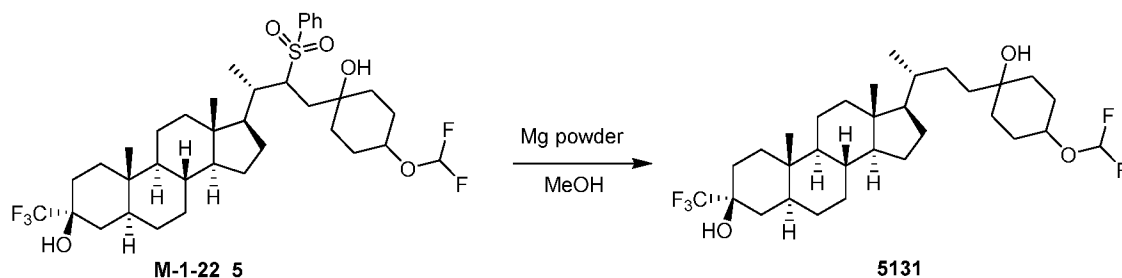
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.50-6.02 (m, 1H), 4.46-4.35 (m, 0.6H), 4.33-4.23 (m, 0.4H), 2.65 (s, 2H), 2.07-1.86 (m, 5H), 1.74-1.58 (m, 2H), 1.47-1.36 (m, 1H).

[00527] **Synthesis of M-1-22\_5**



A solution of n-BuLi (378 μL, 2.5 M in hexane, 0.947 mmol) was added to THF (0.5 mL). A solution of **ST-200-CF3\_6C** (200 mg, 0.379 mmol) in THF (2 mL) was added at -70°C. The mixture was stirred at -70°C for 1 h. **M-1-22\_4** (101 mg, 0.568 μmol) was added. After stirring at -70°C for 1 h and 15°C for 16 hours, the reaction mixture was quenched with sat.NH<sub>4</sub>Cl (10 mL) and extracted with EtOAc (2 x 5 mL). The organic layer was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **M-1-22\_5** (200 mg, crude) as a solid, which was used for the next step directly.

[00528] **Synthesis of 5131**



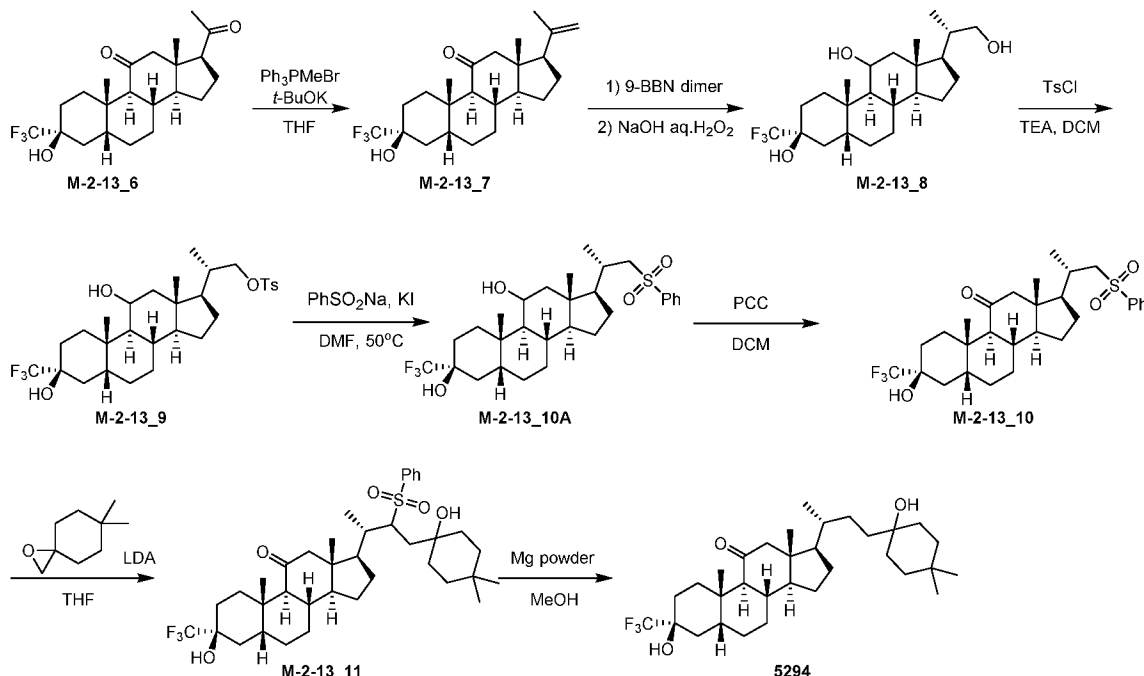
NiCl<sub>2</sub> (7.13 mg, 0.0566 mmol) and Mg powder (270 mg, 11.3 mmol) were added in one portion to a solution of **M-1-22\_5** (200 mg, 0.283 mmol) in MeOH (30 mL) at 65°C. After stirring at 65°C for 10 minutes, another batch of Mg powder (135 mg, 5.66 mmol) was added at 65°C in one portion. The mixture was stirred at 65°C for another 10 minutes, cooled to 20°C, quenched by HCl (20 mL, 2 M) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with saturated aqueous NH<sub>4</sub>Cl (50 mL), brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude, which was purified by combi-flash (0-15% of EtOAc in PE) to give **5131** (2 mg, 1.25%, 5131) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.45-6.02 (m, 1H), 4.12-4.00 (m, 1H), 2.11-2.02 (m, 1H), 1.97-1.92 (m, 2H), 1.85-1.77 (m, 6H), 1.71-1.62 (m, 5H), 1.51-1.43 (m, 4H), 1.41-1.34 (m, 5H), 1.33-1.25 (m, 4H), 1.24-1.19 (m, 2H), 1.16-0.99 (m, 7H), 0.93-0.87 (m, 4H), 0.84 (s, 3H), 0.68-0.63 (m, 4H).

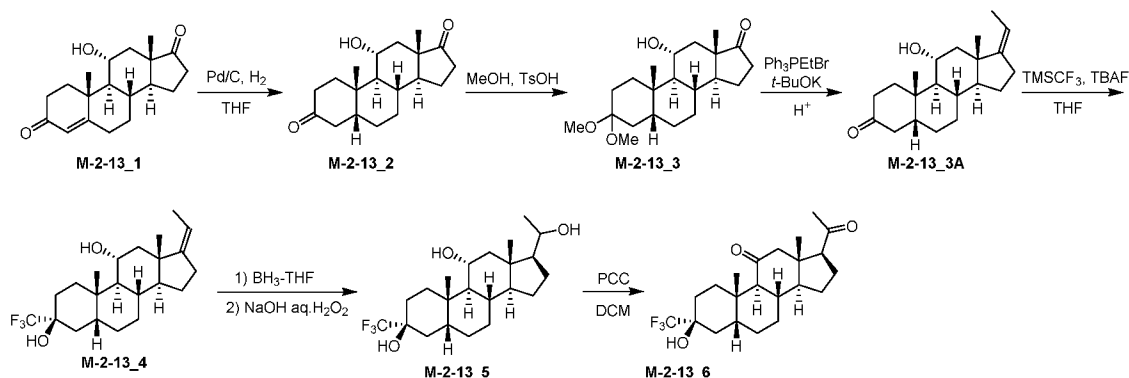
**LCMS** Rt = 5.826 min in 10.0 min chromatography, 50-100AB\_E, purity 96.3%.

**MS** 50-100\_1\_4min.m, MS ESI calcd. for C<sub>31</sub>H<sub>48</sub>F<sub>5</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 547, found 547.

## EXAMPLE 52: Synthesis of 5294



[00529] The synthesis of M-2-13\_6:



To a solution of **M-2-13\_1** (50 g, 165 mmol) in THF (500 mL) was added Pd/C (5 g, 10%) and pyridine (2.5 mL). Then the solution was hydrogenated under H<sub>2</sub> balloon at 25°C for 16 hrs. The mixture was filtered through a pad of celite and the filtrate was concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (500 mL), washed with aq HCl (100 mL, 1M), brine (300 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **M-2-13\_2** (63 g, crude) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.08-3.95 (m, 1H), 2.82-2.72 (m, 1H), 2.71-2.58 (m, 2H), 2.52-2.31 (m, 1H), 2.31-2.21 (m, 1H), 2.21-2.03 (m, 4H), 2.02-1.87 (m, 2H), 1.70-1.60 (m, 3H), 1.58-1.45 (m, 3H), 1.43-1.22 (m, 4H), 1.14 (s, 3H), 0.88 (s, 3H).

To a suspension of **M-2-13\_2** (43 g, 141 mmol) in MeOH (200 mL) was added 4-methylbenzenesulfonic acid (2.42 g, 14.1 mmol) at 25°C under N<sub>2</sub>. The mixture was stirred at 60°C for 16 hrs. The reaction mixture was quenched with TEA (2 mL) and concentrated in vacuum to give **M-2-13\_3** (50 g, crude) as an oil, which was used directly for next step without further purification.

To a suspension of EtPPh<sub>3</sub>Br (158 g, 426 mmol) in THF (300 mL) was added t-BuOK (47.8 g, 426 mmol) at 25°C under N<sub>2</sub>. The mixture was stirred at 60°C for 30 mins. To the mixture was added **M-2-13\_3** (50 g, 142 mmol) in THF (300 mL) at 60°C. The mixture was stirred at 60°C for 16 hrs. The mixture was added sat. NH<sub>4</sub>Cl solution (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give crude product (200 g), which was used directly in next step without further purification. To a solution of the 200 g crude product in THF (500 mL) was added HCl (137.0 mL, 2 M in THF) at 25°C. The reaction was stirred at 25°C for 1 h. The reaction was quenched with sat. NaHCO<sub>3</sub> solution (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give crude product (220 g). The crude product was purified by a silica gel column (PE/EtOAc=

10/1-6/1) to give **M-2-13\_3A** (43 g, impure), which was triturated with (PE/EtOAc= 1/1) to give **M-2-13\_3A** (18 g, pure, 42%) as a solid.

[00532] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.19-5.08 (m, 1H), 4.06-3.96 (m, 1H), 2.80-2.57 (m, 4H), 2.44-2.33 (m, 1H), 2.28-2.14 (m, 2H), 2.03-1.96 (m, 1H), 1.94-1.76 (m, 3H), 1.68-1.64 (m, 4H), 1.61-1.50 (m, 3H), 1.44-1.19 (m, 5H), 1.14 (s, 3H), 1.03-1.00 (m, 1H), 0.90 (s, 3H).

To a solution of **M-2-13\_3A** (8.7 g, 27.4 mmol) in THF (100 mL) was added TBAF (2.05 mL, 2.05 mmol, 1M in THF) and TMSCF<sub>3</sub> (7.79 g, 54.8 mmol) under N<sub>2</sub> at 10°C. The mixture was stirred at 10°C for 1 h. To the mixture was added TBAF solution (82.1 mL, 82.1 mmol, 1M in THF). The mixture was stirred at 25°C for another 1 h. The mixture was concentrated in vacuum.

The residue was dissolved in EtOAc (100 mL), washed with water (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum to afford crude product (10 g), which was combined with the batch of 6.9 g of crude product (prepared from 5.8 g of **M-2-13\_3A**) and purified by a silica gel column (PE/EtOAc= 8/1-3/1) to give **M-2-13\_4** (1.1 g, 6%) as colorless oil and **M-2-13\_4A** (9.3 g, 53%) as a solid

**M-2-13\_4:**

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 5.17-5.08 (m, 1H), 4.01-3.89 (m, 1H), 2.62-2.56 (m, 1H), 2.44-2.32 (m, 2H), 2.28-2.15 (m, 1H), 2.00-1.88 (m, 3H), 1.87-1.73 (m, 3H), 1.69-1.59 (m, 6H), 1.55-1.25 (m, 6H), 1.23-1.13 (m, 2H), 1.09 (s, 3H), 0.95-0.89 (m, 1H), 0.87 (s, 3H).

**M-2-13\_4A:**

[00533] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.18-5.07 (m, 1H), 4.02-3.88 (m, 1H), 2.59 (dd, *J* = 11.8 Hz, *J* = 5.0 Hz, 1H), 2.46-2.30 (m, 2H), 2.29-2.13 (m, 1H), 2.02 (s, 1H), 1.99-1.73 (m, 5H), 1.70-1.61 (m, 4H), 1.55-1.26 (m, 8H), 1.23-1.13 (m, 2H), 1.09 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 1H), 0.87 (s, 3H).

To a solution of **M-2-13\_4** (1.1 g, 2.84 mmol) in THF (30 mL) was added Borane-

tetrahydrofuran complex (11.3 mL, 11.3 mmol, 1 M in THF) at 25°C under N<sub>2</sub>. The solution was stirred at 25°C for 1 h. After cooling to 0°C, a solution of EtOH (30 mL) and NaOH (5.67 mL, 5M in H<sub>2</sub>O, 28.4 mmol) was added very slowly. After addition, H<sub>2</sub>O<sub>2</sub> (2.84 mL, 28.4 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 25°C under N<sub>2</sub> for 1 h. Water (100 mL) was added to the solution and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **M-2-13\_5** (1 g, crude) as colorless oil, which was directly used for next step.

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 3.95-3.78 (m, 1H), 3.72-3.65 (m, 1H), 2.71-2.62 (m, 1H), 2.47-2.40 (m, 1H), 2.19-2.11 (m, 1H), 2.10-2.05 (m, 1H), 2.04-2.01 (m, 1H), 2.00-1.84 (m, 3H), 1.77-

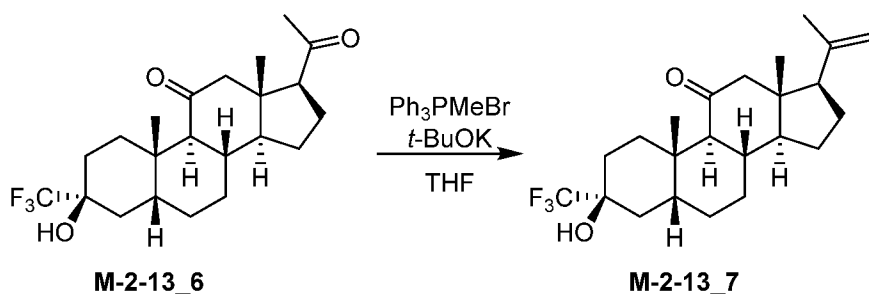
1.62 (m, 5H), 1.50-1.27 (m, 10H), 1.21-1.14 (m, 3H), 1.11 (s, 3H), 0.98-0.93 (m, 1H), 0.67 (s, 3H).

To a solution of **M-2-13\_5** (1 g, 2.47 mmol) in DCM (30 mL) was added silica gel (3 g) and PCC (2.65 g, 12.3 mmol) at 25°C. The reaction was stirred at 25°C for 16 hrs. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 5/1) to give **M-2-13\_6** (720 mg, 73%) as a solid. The solid was triturated with MeCN (10 mL) to afford **M-2-13\_6** (12 mg) as a solid and organic layer was concentrated in vacuum to afford **M-2-13\_6** (700 mg, 99%) as a solid which was used directly for next step.

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 2.75 (t, *J* = 9.0 Hz, 1H), 2.63-2.43 (m, 3H), 2.33-2.17 (m, 2H), 2.10 (s, 3H), 2.02-1.75 (m, 6H), 1.74-1.70 (m, 1H), 1.68 (s, 1H), 1.66-1.58 (m, 1H), 1.53-1.22 (m, 7H), 1.21 (s, 3H), 0.58 (s, 3H).

LCMS Rt = 0.911 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>22</sub>H<sub>32</sub>F<sub>3</sub>O<sub>3</sub> [M +H]<sup>+</sup> 401, found 401.

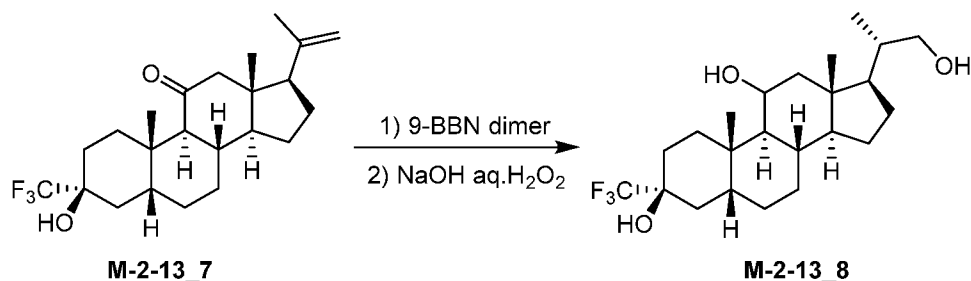
#### [00534] Synthesis of M-2-13\_7



t-BuOK (835 mg, 7.45 mmol) was added to a suspension of MePPh<sub>3</sub>Br (2.66 g, 7.45 mmol) in THF (30 mL) at 25°C under N<sub>2</sub>. After stirring at 50°C for 30 mins, the mixture was added to a solution of **M-2-13\_6** (600 mg, 1.49 mmol) in THF (30 mL) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was quenched with sat.NH<sub>4</sub>Cl solution (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **M-2-13\_7** (4 g, crude) as an oil, which was purified by combi-flash (EtOAc in PE, 10%) to afford **M-2-13\_7** (540 mg, 12%) as a solid.

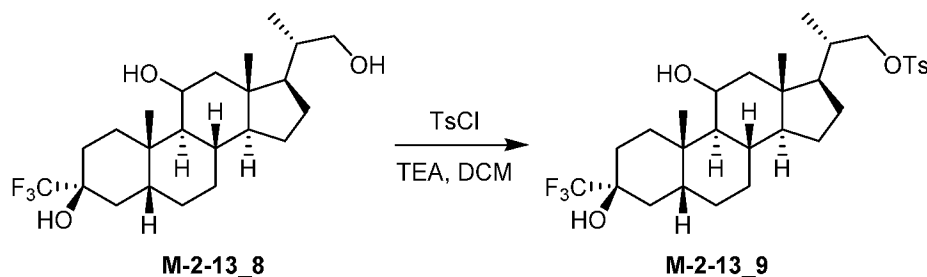
<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 4.89 (s, 1H), 4.71 (s, 1H), 2.53-2.20 (m, 6H), 2.02-1.73 (m, 7H), 1.72-1.60 (m, 5H), 1.56-1.23 (m, 7H), 1.21 (s, 3H), 0.53 (s, 3H).

#### [00535] Synthesis of M-2-13\_8



9-BBN dimer (988 mg, 4.05 mmol) was added to a solution of **M-2-13\_7** (540 mg, 1.35 mmol) in THF (20 mL) at 0°C under N<sub>2</sub>. The solution was stirred at 25°C for 16 hrs. After cooling to 0°C, a solution of EtOH (10 mL) and NaOH (2.70 mL, 5M in H<sub>2</sub>O, 13.5 mmol) were added very slowly. After addition, H<sub>2</sub>O<sub>2</sub> (1.35 mL, 13.5 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 50°C under N<sub>2</sub> for 1 h. The mixture was cooled to 30°C, diluted with water (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **M-2-13\_8** (2 g, crude) as an oil, which was directly used in next step without further purification.

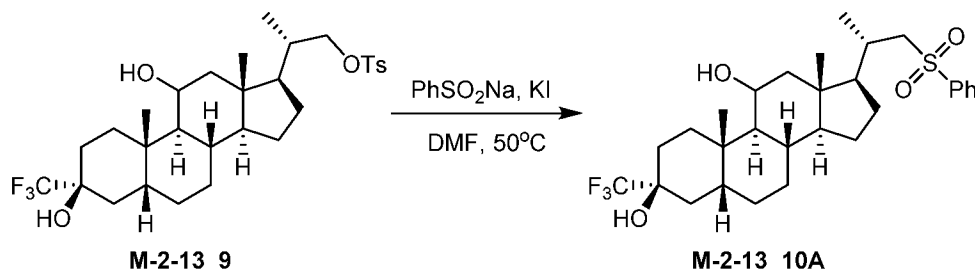
**[00536] Synthesis of M-2-13\_9**



TsCl (4.55 g, 23.9 mmol) was added to a solution of **M-2-13\_8** (2 g, crude) in DCM/TEA (16 mL/2.3 mL) at 25°C. The mixture was stirred at 40°C for 2 hrs. The reaction was quenched with water (20 mL) and extracted with DCM (2 x 30 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford crude product, which was purified by combi-flash column (EtOAc in PE, 12%~15%) to afford **M-2-13\_9** (580 mg, 21%) as an oil.

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.15-4.13 (m, 1H), 3.98-3.94 (m, 1H), 3.81-3.76 (m, 1H), 2.45 (s, 3H), 2.12-2.06 (m, 1H), 2.02-1.89 (m, 3H), 1.85-1.63 (m, 8H), 1.53-1.29 (m, 6H), 1.22 (s, 3H), 1.19-1.02 (m, 6H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 3H).

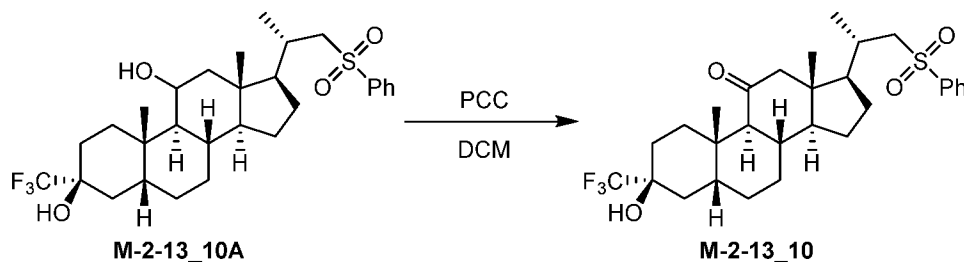
**[00537] Synthesis of M-2-13\_10A**



KI (838 mg, 5.05 mmol) was added to a solution of **M-2-13\_9** (580 mg, 1.01 mmol) in DMF (6 mL) at 25°C under N<sub>2</sub>. After stirring at 50°C for 2 hours under N<sub>2</sub>, the reaction mixture was treated with PhSO<sub>2</sub>Na (820 mg, 5.00 mmol) and stirred at 50°C for 16 hrs. The reaction mixture was cooled to 25°C and treated with water (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with saturated brine (2 x 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by a silica gel column (PE/EtOAc = 8/1~5/1) to afford **M-2-13\_10A** (460 mg, 85%) as a solid.

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.93-7.88 (m, 2H), 7.68-7.62 (m, 1H), 7.60-7.53 (m, 2H), 4.15-4.12 (m, 1H), 3.15-3.09 (m, 1H), 2.87-2.80 (m, 1H), 2.13-2.07 (m, 2H), 2.03-1.89 (m, 3H), 1.83-1.64 (m, 6H), 1.47-1.27 (m, 5H), 1.23-1.18 (m, 7H), 1.18-0.95 (m, 7H), 0.87 (s, 3H).

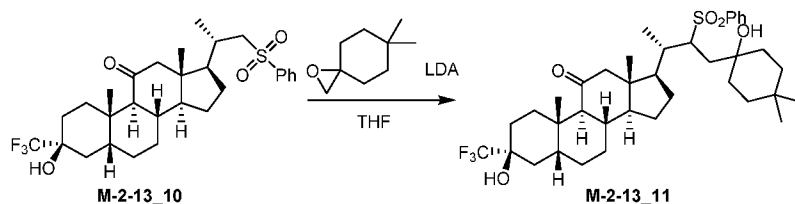
**[00538] Synthesis of M-2-13\_10**



Silica gel (600 mg) and PCC (571 mg, 2.65 mmol) were added to a solution of **M-2-13\_10A** (480 mg, 0.884 mmol) in DCM (15 mL) at 25°C. After stirring at 25°C for 16 hrs, the reaction mixture was filtered and the filtrate was concentrated in vacuum to afford crude product, which was purified by combi-flash column (EtOAc in PE, 15%) to afford **M-2-13\_10** (280 mg, 59%) as a solid.

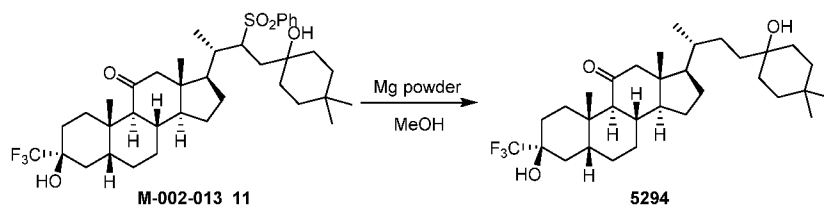
<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.93-7.88 (m, 2H), 7.69-7.62 (m, 1H), 7.60-7.54 (m, 2H), 3.13-3.08 (m, 1H), 2.92-2.82 (m, 1H), 2.61-2.54 (m, 1H), 2.32-2.28 (m, 1H), 2.23-2.16 (m, 1H), 2.14-2.01 (m, 1H), 1.98-1.84 (m, 4H), 1.78-1.65 (m, 5H), 1.53-1.32 (m, 6H), 1.27-1.24 (m, 4H), 1.19 (s, 3H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.62 (s, 3H).

**[00539] Synthesis of M-2-13\_11**



DIPA (233 mg, 2.31 mmol) and n-BuLi (0.852 mL, 2.5 M in hexane, 2.13 mmol) were added to THF (0.5 mL) at  $-78^{\circ}\text{C}$  under  $\text{N}_2$ . The mixture was warmed to  $0^{\circ}\text{C}$ . After re-cooling to  $-78^{\circ}\text{C}$ , a solution of **M-2-13\_10** (330 mg, 0.610 mmol) in THF (2.5 mL) was added. The mixture was stirred at  $-78^{\circ}\text{C}$  for 1 h and treated with 6,6-dimethyl-1-oxaspiro[2.5]octane (128 mg, 0.915 mmol). The mixture was stirred at  $-78^{\circ}\text{C}$  for another 1 h, warmed to  $25^{\circ}\text{C}$  and stirred at  $25^{\circ}\text{C}$  for 16 hrs. The reaction mixture was quenched with  $\text{NH}_4\text{Cl}$  (50 mL, sat. aq) and extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give crude product (380 mg) as an oil, which was used directly for next step without further purification.

#### [00540] Synthesis of 5294



Mg powder (1.07 g, 44.6 mmol) was added to a solution of **M-002-013\_11** (380 mg, 0.558 mmol) in 40 mL of dry methanol under  $\text{N}_2$  at  $60^{\circ}\text{C}$ . The reaction mixture was quenched with HCl (50 mL, 1 M in  $\text{H}_2\text{O}$ ) dropwise at  $10^{\circ}\text{C}$  until solid was dissolved. After extracting with DCM (2 x 100 mL), the organic layer was washed with sat.  $\text{NaHCO}_3$  (50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by flash column eluted with PE/EtOAc= 10/1-8/1 to give **5294** (35 mg, impure) as an oil. **5294** (35 mg, impure) was purified by a silica gel column (PE/EtOAc= 10/1-8/1) to give **5294** (20 mg, impure) as an oil. **5294** (20 mg, 0.037 mmol) was purified by a silica gel column (DCM/acetone= 40/1) for the third time to give **5294** (18 mg, impure) as an oil. The impure **5294** (18 mg, impure) was purified by *prep.* HPLC (column: Xtimate C18 150 \* 25 mm \* 5  $\mu\text{m}$ , gradient: 90-100% B (A= 0.1%TFA-ACN, B= acetonitrile), flow rate: 30 mL/min) to give **5294** (1.9 mg, 11%) as a solid.


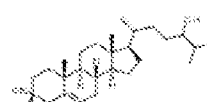
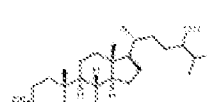
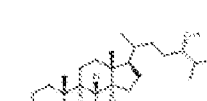
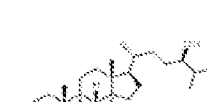
**$^1\text{H}$  NMR** (400MHz,  $\text{CDCl}_3$ )  $\delta$  2.59-2.43 (m, 2H), 2.37-2.16 (m, 2H), 2.05-1.84 (m, 3H), 1.76-1.65 (m, 3H), 1.51-1.38 (m, 14H), 1.26-1.20 (m, 14H), 0.93 (s, 3H), 0.91-0.86 (m, 7H), 0.63 (s, 3H).


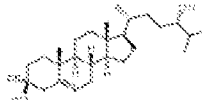
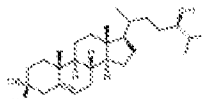
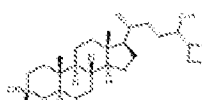
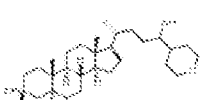
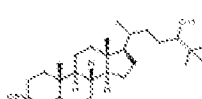
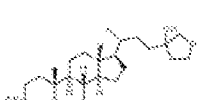
**LCMS**  $R_t$  = 1.284 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For  $\text{C}_{32}\text{H}_{50}\text{F}_3\text{O}_2$   $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$  523, found 523.

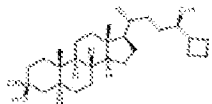
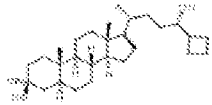
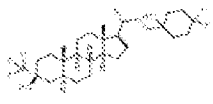
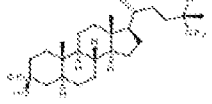
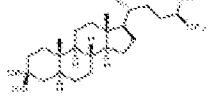
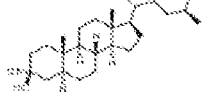
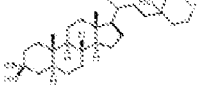
**EXAMPLE 53. Biological data.**

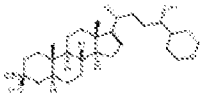

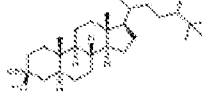
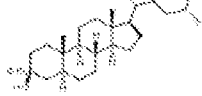
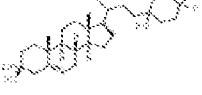
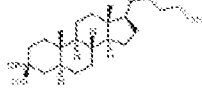
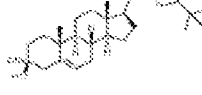
**[00541]** Experiments were conducted as described in Example 2. The results are shown in Table 2-59.

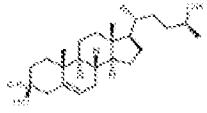
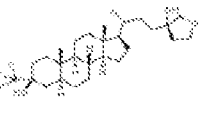
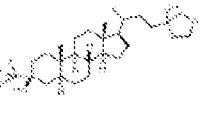
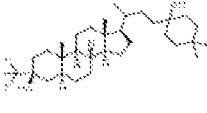
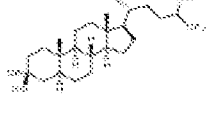
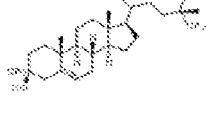
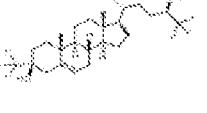
5 Table 2-59.



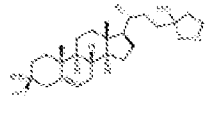
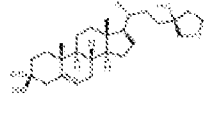
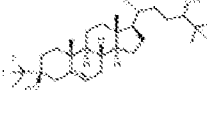
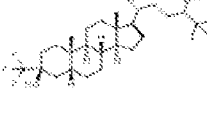
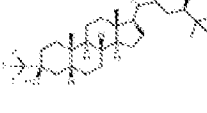
	Compound	Avg EC50 2A (nM)	Avg Emax 2A (%)	Avg EC50 2B (nM)	Avg Emax 2B (%)
	1839	295.4	493.3	148.2	568.5
	1	144.9	887.0	70.9	441.9
	2	162.7	708.9	147.1	605.2
	2A	157.9	652.6	339.1	1239.9
	2B	130.7	624.6	142.8	965.3

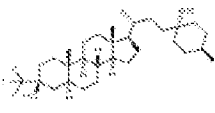
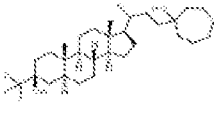
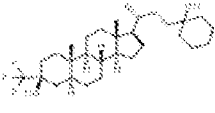
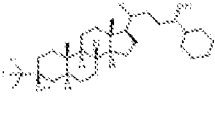
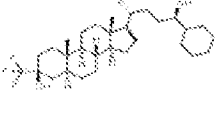
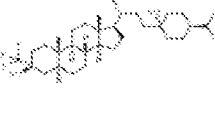
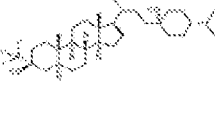
	10	125.4	631.7	101.6	362.3
	1-A	109.4	274.6	81.2	250.1
	1-B	31.6	262.5	33.6	284.6
	7	299.5	516.3	286.9	483.6
	9	316.6	180.6	234.0	271.4
	3	185.2	555.6	338.0	531.8
	1967	170.8	347.4	113.3	373.9

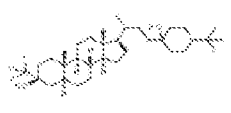
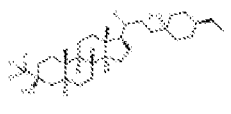
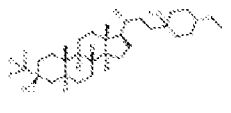
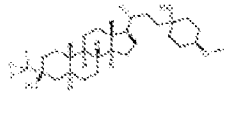
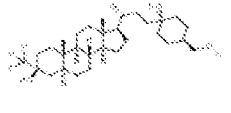
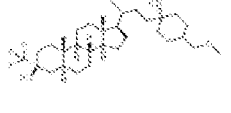
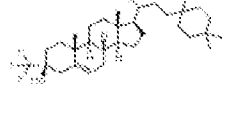
	7-B	346.8	355.7	305.8	352.1
	7-A	247.5	544.2	187.3	431.0
	8	446.1	401.7	372.4	321.7
	4	201.2	663.0	212.5	462.9
	5	181.8	619.0	260.4	454.8
	6	247.7	136.6	733.2	162.7
	11	116.9	151.2	104.3	157.4

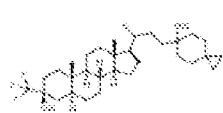
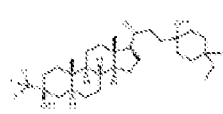
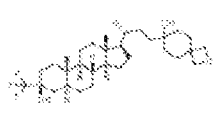
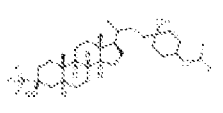
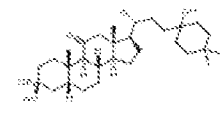
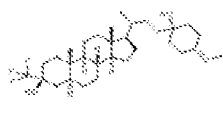
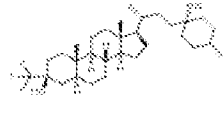
	2080	165.1	77.2	186.9	146.9
	2081	128.8	125.8	174.7	214.9
	2184	65.8	233.7	80.0	257.5
	2285	763.6	204.7	494.3	219.6
	2392	104.4	230.1	47.5	166.2
	2499	768.1	179.8	750.7	237.6
	2500	63.3	302.6	91.1	300.1

	2602	288.6	162.6	279.0	366.6
	2706	>10000	96.8	124.0	139.3
	2707	119.0	112.8	102.7	259.0
	E-2817	5065.7	29.9	5373.5	20.4
	2918	298.0	532.0	338.9	506.1
	3035	61.0	323.4	75.7	611.3
	3149	69.7	292.1	60.7	471.7

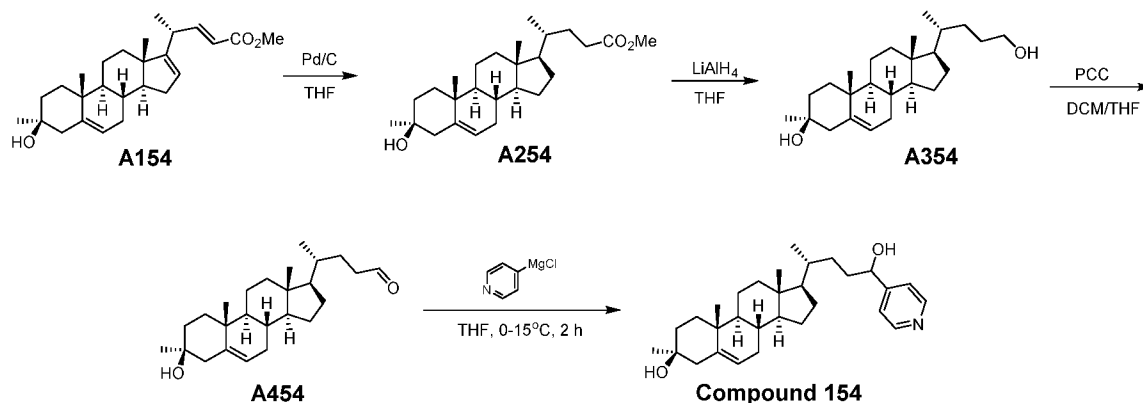
 3266	147.5	82.6	377.4	134.7
 3382	67.6	309.2	125.8	460.6
 3495	96.7	107.2	168.4	145.9
 3496	35.11	319.0	47.6	369.3
 3507	165.0	165.5	190.7	241.1
 3634	422.6	220.6	404.5	378.7
 3788	1317.9	229.4	1121.4	410.2

	3877	>10000	42.4	512.1	71.1
	3983	88.1	175.9	248.0	300.4
	4023	515.9	322.1	405.7	418.3
	4155	441.7	163.5	611.9	198.1
	4156	>10000	10.6	>10000	20.1
	<sup>120s</sup> 4258	1025.3	183.9	640.5	241.7
	<sup>00s</sup> 4259	>10000	-13.3	>10000	24.3

	4360	>10000	38.1	>10000	14.6
	4475	461.3	363.5	265.7	354.6
	4476	>10000	-3.3	>10000	10.4
	4555	>10000	22.8	>10000	31.9
	4656	1601.0	134.4	2164.5	122.0
	4657	422.2	74.0	129.5	62.9
	4799	>10000	36.1	760.2	32.8

 4805	356.1	175.3	362.3	129.4
 4906	>10000	8.8	>10000	14.8
 5009	>10000	27.5	>10000	14.5
 5131	33.6	52.9	>10000	39.0
 5294	>10000	32.4	>10000	13.9
 4585	214.6	72.2	166.3	123.0
 3886	53.4	106.0	50.1	164.1

**EXAMPLE 54: Synthesis of Compound 154**



*Step 1:* To a solution of **A154** (2 g, 5.01mmol) (see WO2014/160480 for synthesis) and Pd/C (200 mg, 10%) in THF (30 mL) was hydrogenated under 15 psi of hydrogen at 25°C for 3 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuum to afford crude **A254** (1.8 g) as a solid.

*Step 2:* To a solution of **A254** (1.8 g, 4.47 mmol) in THF (25 mL) was added a solution LiAlH<sub>4</sub> (339 mg, 8.94 mmol) in THF (5 mL) drop wise below 15°C. The solution was stirred at 15°C for 2 h. The reaction was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (20 mL) at 0°C. The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (2 x 30 mL) and concentrated in vacuum to afford crude **A354** (1.6 g) as a solid.

*Step 3:* A mixture of **A354** (1.6 g, 4.27 mmol) in DCM (10 mL) and THF (10 mL) was added PCC (2.27 g, 10.6 mmol) at 25°C. The reaction was stirred at 25°C for 3 hrs. The solution was filtered and the filter cake was washed with DCM (25 mL). The combined filtrate was concentrated in vacuum. The residue was purified by silica gel column, eluting with PE/EtOAc = 8/1 to give **A454** (0.9 g, 54%) as a solid.

#### *Step 4*

##### *Step 4a: Generation of 4-pyridylmagnesium chloride solution*

To a suspension of 4-bromopyridine hydrochloride (1 g, 5.14 mmol) in THF (4 mL) was added isopropylmagnesium chloride (5.1 mL, 2 M in THF, 10.2 mmol) at 0°C. The mixture was stirred at 15°C for 1 h. The 4-pyridylmagnesium chloride solution (ca. 0.5 M in THF) was used directly.

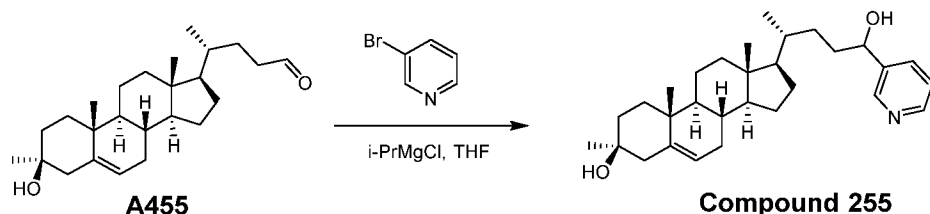
*Step 4b:* To a solution of **A454** (100 mg, 0.268 mmol) in THF (1 mL) was added freshly prepared 4-pyridylmagnesium chloride (5.36 mL, ca. 0.5 M in THF, 2.68 mmol) at 0°C. The mixture was stirred at 15°C for 1 h. To the mixture was added NH<sub>4</sub>Cl (2 mL, 10% aq.). The mixture was extracted with EtOAc (10 mL). The organic layer was separated, purified by prep-TLC (DCM:MeOH = 15:1), re-crystallized from MeCN (2 mL) and dried in vacuum to give **Compound 154** (31 mg, 26%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.57 (d, *J* = 4.4 Hz, 2H), 7.28-7.26 (m, 2H), 5.34-5.26 (m, 1H), 4.71-4.58 (m, 1H), 2.47-2.37 (m, 1H), 2.03-1.90 (m, 4H), 1.85-1.61 (m, 5H), 1.56-1.46 (m, 8H), 1.39-1.04 (m, 9H), 1.04-0.85 (m, 9H), 0.70-0.62 (m, 3H).

LCMS Rt = 0.806 min in 2.0 min chromatography, 30-90AB, MS ESI calcd. for C<sub>30</sub>H<sub>46</sub>NO<sub>2</sub>

5 [M+H]<sup>+</sup> 452, found 452.

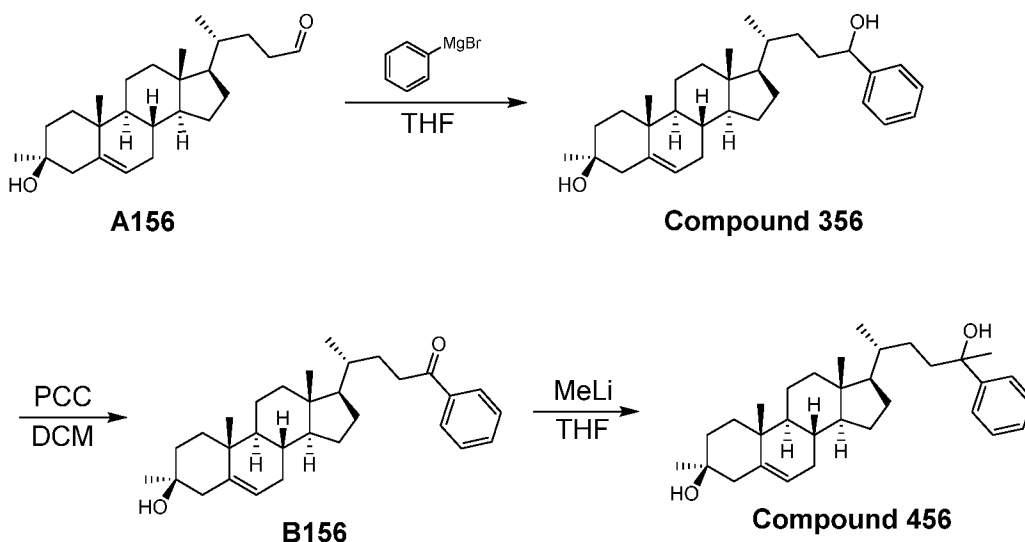
#### EXAMPLE 55. Synthesis of Compound 255.



10 To a solution of 3-bromopyridine (423 mg, 2.68 mmol) in THF (10 mL) under N<sub>2</sub> was added i-PrMgCl (1.34 mL, 2.68 mmol, 2M) dropwise at 15°C. The reaction was stirred at 15°C for 30 min. A solution of **A455** (100 mg, 0.268 mmol) was added. The reaction was stirred at 15°C for 2 h. The reaction was quenched with saturated NH<sub>4</sub>Cl (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography (MeOH in DCM gradient, 0%-10%) to afford crude product (50 mg), which was then recrystallized from MeCN (15 mL) to afford **Compound 255** (8 mg, 7% yield) as a solid.

15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.60-8.55 (m, 1H), 8.55-8.51 (m, 1H), 7.73-7.68 (m, 1H), 7.32-7.28 (m, 1H), 5.32-5.27 (m, 1H), 4.73-4.63 (m, 1H), 2.45-2.37 (m, 1H), 2.01-1.65 (m, 9H), 1.56-20 1.33 (m, 9H), 1.28-1.04 (m, 8H), 1.03-0.86 (m, 9H), 0.66 (s, 3H).

#### EXAMPLE 56. Syntheses of Compounds 356 and 456.



*Step 1:* To a solution of **A456** (300 mg, 0.8 mmol) in THF (5 mL) was added phenylmagnesium bromide (2.01 mL, 1 M in ether, 2.01 mmol) dropwise at -60°C. The mixture was stirred at 25°C for 1 h. The mixture was poured into water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford **Compound 356** (315 mg, crude) as a solid. 115 mg of **Compound 356** was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150\*30mm\*4um, gradient: 95% B (water (0.05% HCl)-ACN), flow rate: 25 mL/min) to give **Compound 356** (31 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.34-7.28 (m, 4H), 7.27-7.24 (m, 1H), 5.31-5.30 (m, 1H), 4.57-4.51 (m, 1H), 2.45-2.42 (m, 1H), 2.02-1.96 (m, 3H), 1.95-1.78 (m, 5H), 1.60-1.52 (m, 9H), 1.20-0.72 (m, 18H), 0.72-0.71 (m, 3H).

LCMS Rt = 1.248 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>31</sub>H<sub>43</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 415, found 415.

*Step 2:* A mixture of **Compound 356** (200 mg, 0.44 mmol) in DCM (3 mL) was added PCC (190 mg, 0.89 mmol) at 25°C for 1 h. The solution was filtered and the filtered cake was washed with DCM (2 x 10 mL). The combined filtrate was concentrated in vacuum. The residue was purified by silica gel column eluted with (PE/EtOAc = 10/1) to give **B156** (150 mg, 72%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.01-7.95 (m, 2H), 7.58-7.54 (m, 1H), 7.50-7.45 (m, 2H), 5.32-5.30 (m, 1H), 3.03-2.90 (m, 2H), 2.41-2.40 (m, 1H), 2.05-1.96 (m, 7H), 1.52-1.48 (m, 9H), 1.17-0.94 (m, 16H), 0.70 (s, 3H).

*Step 3:* To a solution of **B156** (80 mg, 0.18 mmol) in THF (5 mL) was added dropwise MeLi (0.28 mL, 1.6 M in ether, 0.4 mmol) at -60°C. The mixture was stirred at 25°C for 1 h. The mixture was poured into water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined

organic layer was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated.

The residue was purified by prep-HPLC separation (column: Phenomenex Synergi C18

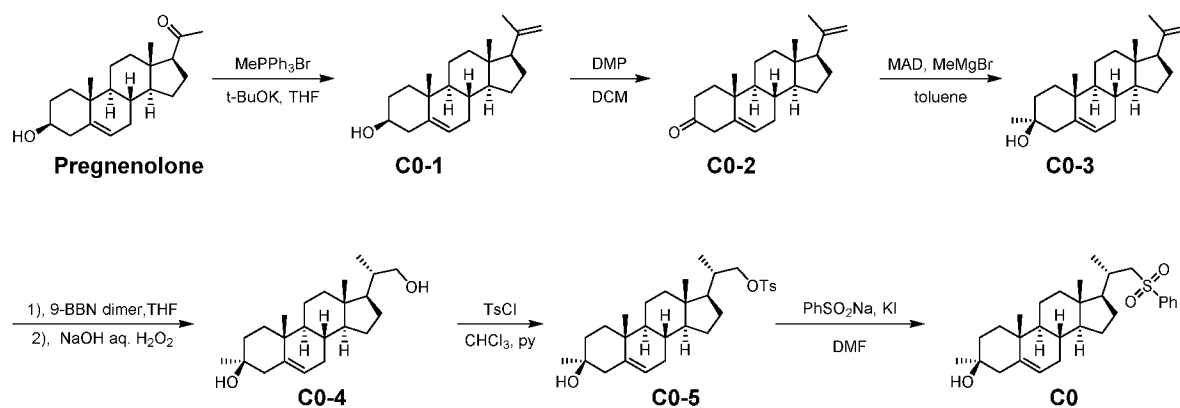
150\*30mm\*4um, gradient: 65-95% B (water (0.05% HCl)-ACN), flow rate: 25 mL/min) to give

**Compound 456** (24 mg, 29%) as a solid.

- 5 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.42-7.40 (m, 2H), 7.32-7.28 (m, 2H), 7.20-7.17 (m, 1H), 5.29-5.28 (m, 1H), 2.43-2.40 (m, 1H), 1.98-1.93 (m, 4H), 1.75-1.50 (m, 16H), 1.48-0.88 (m, 18H), 0.67-0.65 (m, 3H).

LCMS Rt = 1.289 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

## 10 EXAMPLE 57. Synthesis of Compound C0



*Step 1:* To a mixture of MePPh<sub>3</sub>Br (1.28 kg, 3.6 mol) in THF (4.5 L) was added  $t\text{-BuOK}$  (404 g, 3.6 mol) at 15°C under N<sub>2</sub>. The resulting mixture was stirred at 50°C for 30 min. Pregnenolone (950 g, 2.9 mol) was added in portions below 65°C. The reaction mixture was stirred at 50°C for 1 hour. The combined mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (1 L) at 15°C and the THF layer was separated. The aqueous layer was extracted with EtOAc (2 x 2 L). The combined organic phase was concentrated under vacuum to give a solid. The solid was further purified by trituration with MeOH/H<sub>2</sub>O (1:1, 15 L) at reflux to give **C0-1** (940 g, 99%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.32 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 3.58-3.46 (m, 1H), 2.36-2.16 (m, 2H), 2.08-1.94 (m, 2H), 1.92-1.62 (m, 9H), 1.61-1.39 (m, 6H), 1.29-1.03 (m, 4H), 1.01 (s, 3H), 0.99-0.91 (m, 1H), 0.59 (s, 3H).

*Step 2:* To a solution of **C0-1** (800 g, 2.54 mol) in DCM (8 L) was added DMP (2.14 kg, 5.08 mol) in portions at 35°C. The reaction mixture was stirred at 35°C for 20 mins. The reaction mixture was filtered. The filtered cake was washed with DCM (3 x 1 L). The combined organic

phase was washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>/saturated NaHCO<sub>3</sub> aqueous (3:1, 2 x 1.5 L), brine (1.5 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **C0-2** (794 g, crude) as a solid, which was used for next step directly.

*Step 3:* To a solution of BHT (1.97 kg, 8.94 mol) in toluene (1 L) was added AlMe<sub>3</sub> (2.14 L, 2.0 M in toluene, 4.28 mol) drop-wise below 25°C under N<sub>2</sub> atmosphere. The resulting mixture was stirred at 25°C for 1 hour. **C0-2** (794 g, 2.16 mol) in DCM (3 L) was added at -70°C. The mixture was stirred at -70°C for 1 hour. MeMgBr (862 mL, 3.0 M in diethyl ether, 2.59 mol) was added at -70°C. The reaction mixture was stirred at -70°C for 10 min. The mixture was quenched by saturated citric acid (3 L), extracted with EtOAc (2 x 2 L). The combined organic phase was washed with brine (2 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a residue, which was triturated from MeCN (3 L) at 25°C to give **C0-3** (340 g, 43%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.34-5.26 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 2.50-2.35 (m, 1H), 2.07-1.94 (m, 3H), 1.91-1.84 (m, 1H), 1.83-1.63 (m, 8H), 1.58-1.33 (m, 6H), 1.27-1.13 (m, 3H), 1.12 (s, 3H), 1.10-1.05 (m, 1H), 1.02 (s, 3H), 1.00-0.92 (m, 1H), 0.58 (s, 3H).

*Step 4:* To a mixture of **C0-3** (149 g, 453 mmol) and 9-BBN dimer (127 g, 520 mmol) was added THF (1 L) at 15°C under N<sub>2</sub>. The reaction mixture was stirred at 60°C for 1 hour. The mixture was cooled to 15°C. EtOH (208 g, 4.53 mol) was added at 15°C. NaOH aqueous (906 mL, 5 M, 4.53 mol) was added drop-wise at 15°C. H<sub>2</sub>O<sub>2</sub> (514 g, 30%, 4.53 mol) was added dropwise at 15°C. The obtained mixture was stirred at 60°C for 1 hour. A solid was produced. The solid was washed with ethanol (200 mL) to give a solid, which was triturated with EtOH (2.3 L) at reflux and water (2.5 L) at 80°C successively to give **C0-4** (131 g, 84%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.35-5.24 (m, 1H), 3.67-3.61 (m, 1H), 3.42-3.33 (m, 1H), 2.50-2.35 (m, 1H), 2.07-1.92 (m, 3H), 1.88-1.65 (m, 3H), 1.60-1.38 (m, 9H), 1.37-1.26 (m, 1H), 1.26-1.12 (m, 4H), 1.11 (s, 3H), 1.08 (s, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H), 1.00-0.91 (m, 1H), 0.70 (s, 3H).

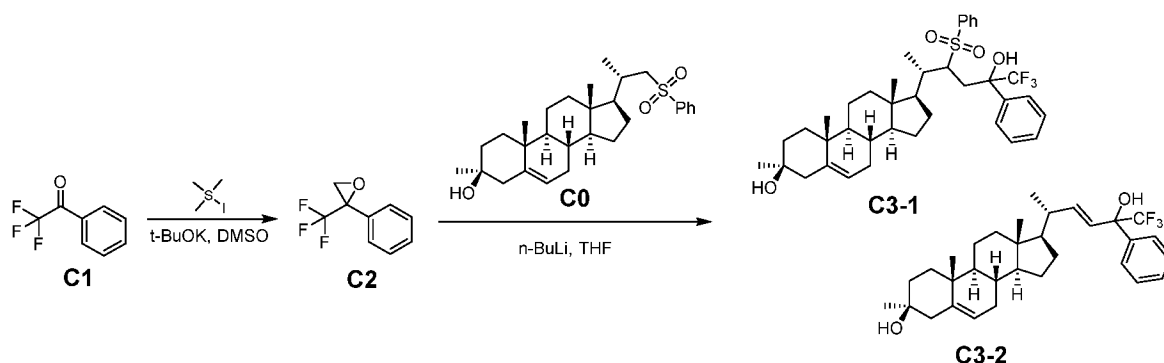
*Step 5:* To a solution of **C0-4** (131 g, 378 mmol) in CHCl<sub>3</sub> (600 mL) and pyridine (420 mL) was added TsCl (187 g, 982 mmol) at 15°C. The mixture was stirred at 15°C for 2 hrs. The reaction mixture was concentrated under vacuum to remove most of CHCl<sub>3</sub>. Water (3 L) was added. A solid was produced and filtered. The solid was washed with water (6 x 4 L) and dissolved in DCM (3.5 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **C0-5** (177 g, 94%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.34-5.25 (m, 1H), 3.96 (dd, *J* = 3.2, 9.6 Hz, 1H), 3.79 (dd, *J* = 6.4, 9.2 Hz, 1H), 2.45 (s, 3H), 2.50-2.35 (m, 1H), 2.02-1.88 (m, 3H), 1.81-1.61 (m, 4H), 1.58-1.33 (m, 8H), 1.24-1.12 (m, 4H), 1.11 (s, 3H), 1.09-1.01 (m, 2H), 1.00 (s, 3H), 0.98-0.86 (m, 3H), 0.64 (s, 3H).

*Step 6:* To a solution of **C0-5** (177 g, 353 mmol) in DMF (1.8 L) was added KI (281 g, 1694 mmol) at 15°C. The mixture was stirred at 60°C for 1 h. To the DMF mixture was added PhSO<sub>2</sub>Na (211 g, 1.06 mol). The mixture was stirred at 60°C for 2 hrs. The reaction mixture was cooled to 25°C. The mixture was poured into water (20 L) and some solid was produced. The mixture was filtered. The filtered cake was washed with water (3 x 2 L) and dissolved in DCM (5 L). The solution was washed with water (2 x 1 L), brine (2 x 1 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum to give a crude product as a solid, which was re-crystallized from toluene (2.5 L) to give **C0** (121 g, 73%) as a solid. The re-crystallization filtrate was concentrated under vacuum to give a crude **C0** (20 g) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.69-7.61 (m, 1H), 7.61-7.53 (m, 2H), 5.31-5.24 (m, 1H), 3.14 (d, *J* = 14.0 Hz, 1H), 2.85 (dd, *J* = 9.2, 14.0 Hz, 1H), 2.50-2.35 (m, 1H), 2.16-2.03 (m, 1H), 2.01-1.88 (m, 3H), 1.80-1.64 (m, 3H), 1.56-1.34 (m, 7H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.17-1.11 (m, 3H), 1.10 (s, 3H), 1.08-1.01 (m, 2H), 1.00 (s, 3H), 0.98-0.87 (m, 2H), 0.65 (s, 3H).

#### EXAMPLE 58. Syntheses of Compound C3-1 and C3-2.



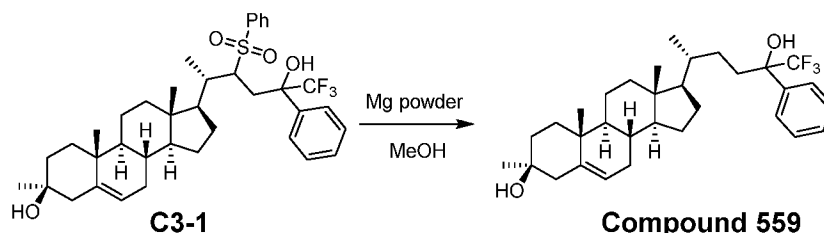
*Step 1:* To a solution of t-BuOK (3.22 g, 28.7 mmol) in DMSO (30 mL) was added trimethylsulfonium iodide (6.42 g, 31.5 mmol) at 20°C and stirred for 30 min under N<sub>2</sub>. A solution of **C1** (5 g, 28.7 mmol) in DMSO (8 mL) was added and stirred for 16 h at 20°C. The reaction mixture was diluted with EtOAc (50 mL) and water (50 mL). The aqueous layer was back-extracted with EtOAc (50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 3/1) to give **C2** (1.9 g, 35%) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.55-7.52 (m, 2H), 7.43-7.35 (m, 3H), 3.43-3.40 (m, 1H), 2.95-2.92 (m, 1H).

*Step 2:* To THF (2 mL) under N<sub>2</sub> at -70°C was added n-BuLi (1.7 mL, 4.24 mmol). After that, a suspension of **C0** (500 mg, 1.06 mmol) in THF (5 mL) was added drop-wise to give a

suspension. After stirring at -70°C for 30 min, a solution of **C2** (398 mg, 2.12 mmol) in THF (2 mL) was added. Then reaction was stirred at -70°C for 10 min and then stirred at 20°C for 16 hours. The reaction mixture was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give crude product which was purified by a silica gel column (PE/EtOAc = 10/1) to give **C3-1** (320 mg, 46%) as a solid and **C3-2** (50 mg, impure). **C3-1** was used directly for the next step. **C3-2** was purified by HPLC separation (column: Phenomenex Synergi C18 150\*30mm\*4um, gradient: 82-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) to give **Compound C3-1** (25 mg, 5%) as a solid.

#### EXAMPLE 59. Synthesis of Compound 559.

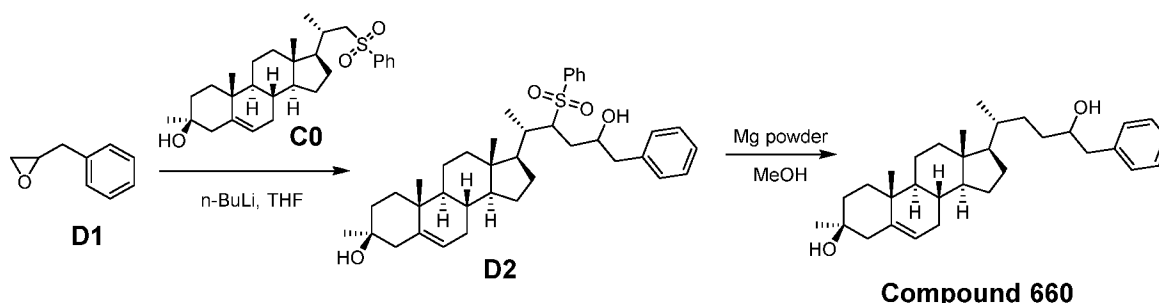


To a solution of **C3-1** (320 mg, 0.486 mmol) in MeOH (10 mL) was added Mg powder (349 mg, 14.5 mmol) was added at 60°C. The mixture was stirred at 60°C for 2 h. Then another portion of Mg powder (349 mg, 14.5 mmol) was added. The final reaction was stirred at 60°C for 16 hours. The mixture was quenched with HCl (100 mL, 1 M) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by a silica gel column (PE/EtOAc = 10/1 to 8/1) to give **Compound 559** (20 mg, 6%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52-7.50 (m, 2H), 7.43-7.31 (m, 3H), 5.29-5.28 (m, 1H), 2.43-2.40 (m, 1H), 2.29-2.28 (m, 1H), 2.10-1.60 (m, 7H), 1.52-1.21 (m, 8H), 1.19-0.94 (m, 14H), 0.93-0.91 (m, 5H), 0.63 (d, *J* = 10.8 Hz, 3H).

LCMS Rt = 1.465 min in 2 min chromatography, 10-80 AB, MS ESI calcd. for C<sub>32</sub>H<sub>44</sub>F<sub>3</sub>O [M-H<sub>2</sub>O+H]<sup>+</sup> 501, found 501.

#### EXAMPLE 60. Synthesis of Compound 660, 6051, and 6052.



*Step 1:* To THF (2 mL) under N<sub>2</sub> at -70°C was added n-BuLi (1.7 mL, 4.24 mmol). After that, a suspension of **C0** (500 mg, 1.06 mmol) in THF (5 mL) was added drop-wise to give a suspension. After stirring at -70°C for 30 min, a solution of **D1** (284 mg, 2.12 mmol) in THF (2 mL) was added. Then reaction was stirred at -70°C for 10 min and then stirred at 20°C for 16 hours. The reaction mixture was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give crude product which was purified by a silica gel column (PE/EtOAc = 10/1) to give **D2** (60 mg, 9%) as a solid.

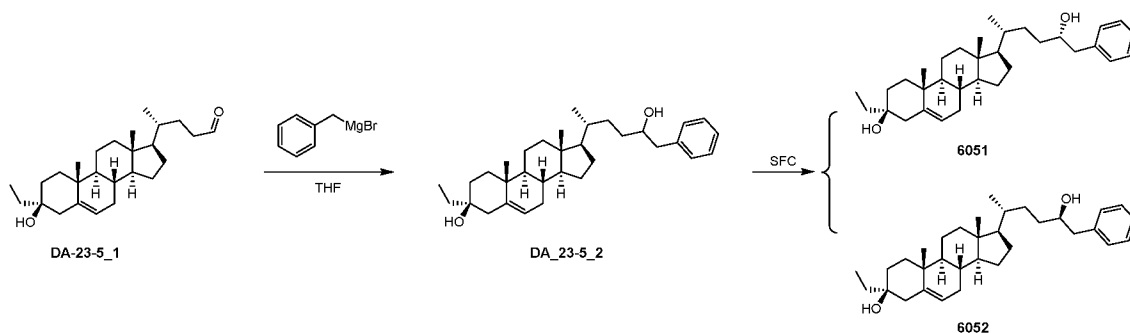
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.91-7.81 (m, 2H), 7.69-7.49 (m, 3H), 7.33-7.31 (m, 2H), 7.24-7.20 (m, 2H), 7.12-6.98 (m, 1H), 5.32 - 5.28 (m, 1H), 3.26-3.23 (m, 1H), 2.88-2.65 (m, 2H), 2.57-2.47 (m, 1H), 2.42-2.38 (m, 1H), 2.27-2.07 (m, 1H), 2.04-1.61 (m, 9H), 1.53-1.30 (m, 9H), 1.19-0.93 (m, 11H), 0.93-0.60 (m, 4H), 0.43 (s, 2H).

*Step 2:* To a solution of **D2** (118 mg, 0.195 mmol) in MeOH (3 mL) was added Mg powder (280 mg, 11.7 mmol) at 60°C. The final reaction was stirred at 60°C for 16 hours. The mixture was quenched with HCl (100 mL, 1M) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by a silica gel column (PE/EtOAc = 10/1 to 8/1) to give **Compound 660** (32 mg, 35%) as a solid.

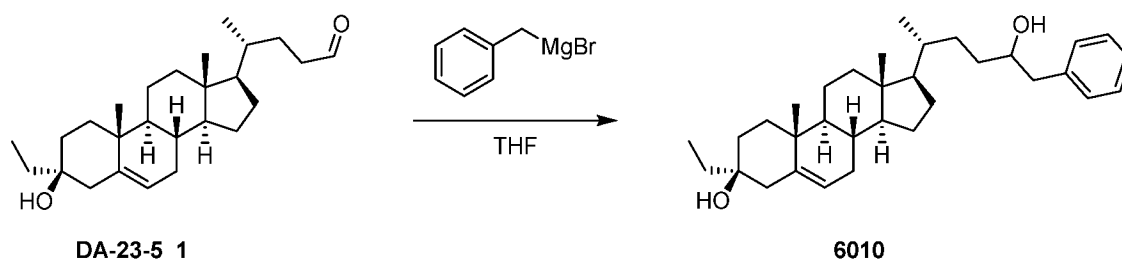
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.32-7.30 (m, 2H), 7.25-7.21 (m, 3H), 5.31-5.29 (m, 1H), 3.77-3.75 (m, 1H), 2.89-2.81 (m, 1H), 2.63-2.57 (m, 1H), 2.44-2.40 (m, 1H), 2.06-1.92 (m, 3H), 1.91-1.60 (m, 5H), 1.58-1.21 (m, 12H), 1.20-0.88 (m, 15H), 0.68 (s, 3H).

LCMS Rt = 1.466 min in 2 min chromatography, 10-80 AB, MS ESI calcd. for C<sub>32</sub>H<sub>47</sub>O [M-H<sub>2</sub>O+H]<sup>+</sup> 447, found 447.

[00542] Synthesis of 6010, 6051, and 6052



[00543] **Synthesis of 6010**

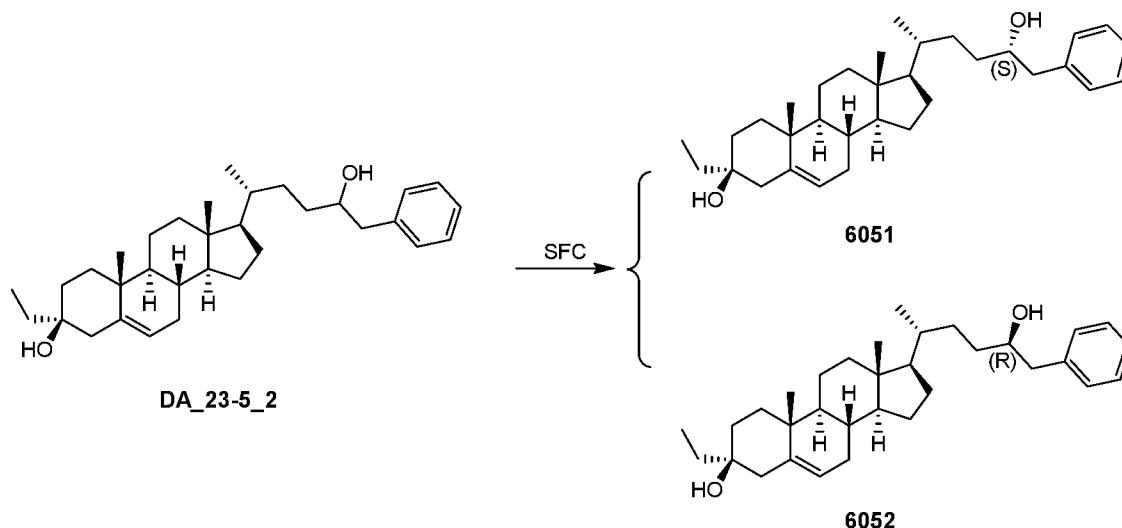


To a solution of **DA-23-5\_1** (400 mg, 1.03 mmol) in THF (6 mL) was added benzylmagnesium bromide (10.3 mL, 10.3 mmol, 1M in THF) at  $-70^{\circ}\text{C}$  under  $\text{N}_2$ . Then the mixture was stirred at  $25^{\circ}\text{C}$  for 1 h. The reaction was treated with Sat.  $\text{NH}_4\text{Cl}$  (10 mL), EtOAc (10 mL) and  $\text{H}_2\text{O}$  (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated. The residue was purified by flash column (PE/EA = 100/1 to 12/1) to give **DA-23-5\_2 (6010)** (222 mg, 45%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.28 (m, 2H), 7.25-7.15 (m, 3H), 5.30-5.20 (m, 1H), 3.80-3.70 (m, 1H), 2.90-2.30 (m, 3H), 2.05-1.60 (m, 9H), 1.50-1.30 (m, 9H), 1.30-0.90 (m, 16H), 0.90-0.80 (m, 3H), 0.68 (s, 3H).

LCMS Rt = 1.356 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. For  $\text{C}_{33}\text{H}_{49}\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  461, found 461.

[00544] **Synthesis of 6051 and 6052**



DA-23-5\_2 (180 mg) was purified by SFC (Column: AD(250mm\*30mm,10um); Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH, 40% B; FlowRate(ml/min): 60) to give impure **6051** (75 mg, 42%) and impure **6052** (80 mg, 45%). The impure **6051**(75 mg, 0.156 mmol) was

5 triturated from MeCN (5 mL) at 25°C to give **6051** (40 mg, 54%) as a solid. The impure **6052** (80 mg) was triturated from MeCN (5 mL) at 25°C to give **6052** (48 mg, 60%) as a solid.

#### **6051**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.28 (m, 2H), 7.25-7.15 (m, 3H), 5.30-5.20 (m, 1H), 3.80-3.70 (m, 1H), 2.90-2.30 (m, 3H), 2.05-1.60 (m, 9H), 1.50-1.30 (m, 9H), 1.30-0.90 (m, 16H), 0.90-0.80 (m, 3H), 0.68 (s, 3H).

LCMS Rt = 1.444 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd.

For C<sub>33</sub>H<sub>49</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 461, found 461.

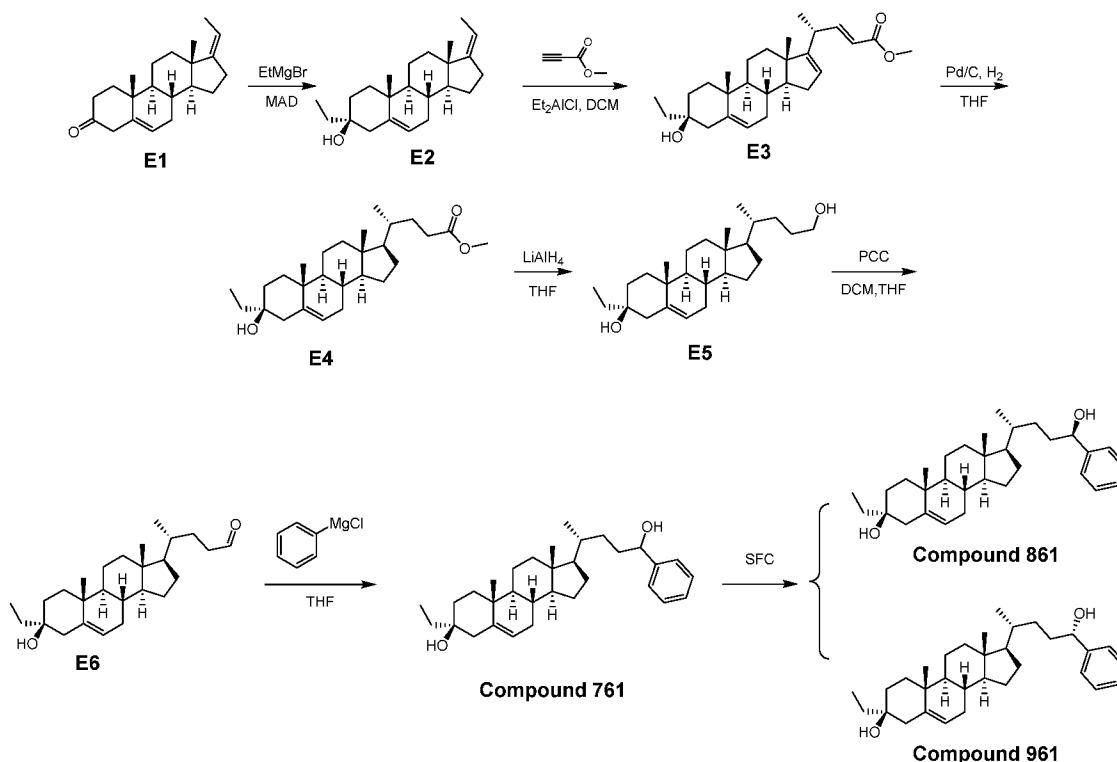
#### **6052**

15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.28 (m, 2H), 7.25-7.15 (m, 3H), 5.30-5.20 (m, 1H), 3.80-3.70 (m, 1H), 2.90-2.30 (m, 3H), 2.05-1.60 (m, 9H), 1.50-1.30 (m, 9H), 1.30-0.90 (m, 16H), 0.90-0.80 (m, 3H), 0.68 (s, 3H).

LCMS Rt = 1.446 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd.

For C<sub>33</sub>H<sub>49</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 461, found 461.

### 20 **EXAMPLE 61. Syntheses of Compounds 761, 861, and 961.**



*Step 1:* To a solution of 2,6-di-tert-butyl-4-methylphenol (220 g, 1.0 mol) in toluene (250 mL) was added  $\text{AlMe}_3$  (250 mL, 501 mmol, 2 M in toluene) dropwise below  $25^\circ\text{C}$ . The solution was stirred at  $25^\circ\text{C}$  for 1 h. Then a solution of **E1**, synthesis can be found in WO2017007840 (50 g, 167 mmol) in  $\text{DCM}$  (400 mL) was added dropwise at  $-78^\circ\text{C}$ . After stirring at  $-78^\circ\text{C}$  for 1 h,  $\text{EtMgBr}$  (167 mL, 501 mmol, 3M in ethyl ether) was added dropwise at  $-78^\circ\text{C}$ . The resulting solution was stirred at  $-78^\circ\text{C}$  to  $-50^\circ\text{C}$  for 3 h. The reaction was quenched with saturated citric acid (100 mL) at  $-78^\circ\text{C}$ . After stirring at  $25^\circ\text{C}$  for 30 min, the resulting mixture was filtered and the filtrate was extracted with  $\text{DCM}$  (3 x 100 mL). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude product was combined and purified by a silica gel column ( $\text{PE}/\text{EtOAc} = 5/1$ ) to give 38 g of the crude product as a solid, which was recrystallized from  $\text{PE}$  to give **E2** as a solid (13.5 g, 13%).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ) 400MHz  $\delta$  5.33-5.26 (m, 1H), 5.23-5.10 (m, 1H), 2.45-1.90 (m, 6 H), 1.78-0.70 (m, 28H).

*Step 2:* To a solution of **E2** (13 g, 39.5 mmol) and methyl propiolate (8.29 g, 98.7 mmol) in anhydrous  $\text{DCM}$  (100 mL) under  $\text{N}_2$  at  $0^\circ\text{C}$  was added diethylaluminum chloride (1 M in hexane, 158 mL, 158 mmol) dropwise. The mixture was stirred at  $20^\circ\text{C}$  for 16 hours. The reaction mixture was poured into ice-water, extracted with  $\text{DCM}$  (3 x 300 mL). The extracts were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel ( $\text{PE}/\text{EtOAc} = 5/1$ ) to give **E3** (14 g, 86%) as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 400MHz δ 6.93 (dd, *J* = 15.6Hz, 8.0Hz, 1H), 5.81 (d, *J* = 8.0Hz, 1H), 5.42-5.38 (m, 1H), 5.33-5.24 (m, 1H), 3.73 (s, 3H), 3.05-2.95 (m, 1H), 2.40-2.30 (m, 1H), 2.10-1.95 (m, 3H), 1.90-1.65 (m, 4H), 1.60-1.25 (m, 9H), 1.88 (d, *J* = 7.2 Hz, 3H), 1.15-0.95 (m, 6H), 0.84 (t, *J* = 7.6Hz, 3H), 0.78 (s, 3H).

5 *Step 3:* To a solution of **E3** (9 g, 21.8 mmol) in THF (100 mL) was added Pd/C (2 g, wet 10%) at 15°C. After degassing and back-fill with H<sub>2</sub> for three times, the reaction mixture was stirred for 16 h at 15°C with H<sub>2</sub> balloon. The mixture was filtered through a pad of celite. The filtrate was concentrated *in vacuo* to give crude **E4** (8.7 g, crude) as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 400MHz δ 5.35-5.25 (m, 1H), 3.69 (s, 3H), 2.40-2.15 (m, 4H), 2.10-1.40 (m, 10 17H), 2.15-0.80 (m, 16H), 0.70 (s, 3H).

*Step 4:* To a solution of **E4** (5 g, 12.0 mmol) in THF (100 mL) was added lithium aluminium hydride (1.13 g, 30.0 mmol) at 0°C. Then the reaction was stirred at 25°C for 5 min. Then the reaction was quenched by aqueous NH<sub>4</sub>Cl solution (50 mL) and aqueous citric acid (30 mL) to pH= 4-5. Then the reaction solution was extracted with EtOAc (3 x 100 mL). The combined 15 organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give crude product **E5** (4 g, 80%) as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 400MHz δ 5.35-5.25 (m, 1H), 3.18-3.05 (m, 2H), 2.40-2.32 (m, 1H), 2.08-1.80 (m, 18H), 1.80-0.80 (m, 19H), 0.68 (s, 3H).

*Step 5:* To a solution of **E5** (1 g, 2.57 mmol) in DCM (15 mL) and THF (15 mL) was added PCC 20 (1.10 g, 5.14 mmol). The resulting reaction mixture was stirred at 25°C for 2 hours. The combined organic phase was dried, concentrated and purified by flash chromatography (0-15% of EtOAc in PE) to give **E6** (700 mg, 70%) as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 400MHz δ 9.77 (s, 1H), 5.30-5.26 (m, 1H), 2.46-2.35 (m, 2H), 2.04-1.57 (m, 12H), 1.50-0.83 (m, 23H), 0.68 (m, 3H).

25 *Step 6:* To a solution of **E6** (400 mg, 1.03 mmol) in THF (10 mL) was added phenylmagnesium chloride (3.5 mL, 1.5 mmol, 3M in ether) at -70°C under N<sub>2</sub>. Then the mixture was stirred at 20°C for 20 min. The reaction was treated with saturated NH<sub>4</sub>Cl (4 mL), EtOAc (5 mL), and H<sub>2</sub>O (3 mL). The mixture was extracted with EtOAc (3 x 6 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum, 30 purified by column chromatography on silica gel (PE/EA = 30/1 to 10/1) to give **Compound 761** (300 mg, 62%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.30 (m, 4H), 7.30-7.20 (m, 1H), 5.32-5.26 (m, 1H), 4.64-4.52 (m, 1H), 2.38-2.34 (m, 1H), 2.06-1.88 (m, 3H), 1.86-1.15 (m, 24H), 1.12-1.00 (m, 3H), 1.00-0.78 (m, 7H), 0.66 (s, 3H).

LCMS Rt = 1.303 min in 2 min chromatography, 30-90 AB, MS ESI calcd. For C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

Step 7: **Compound 761** (300 mg) was purified by SFC (Column: OD (250mm\*30mm,10um); Condition: 0.1%NH<sub>3</sub>-H<sub>2</sub>O ETOH, 40% B; Flow Rate (ml/min): 60) to give **Compound 861** (40 mg, 22%) as a solid and **Compound 10** (59 mg, 33%) as a solid.

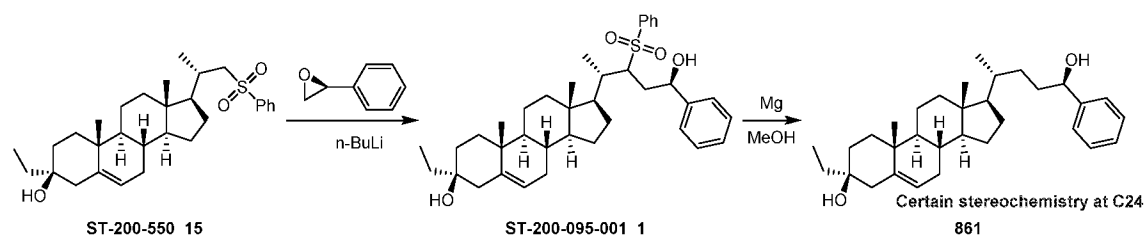
**Compound 861:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39-7.30 (m, 4H), 7.30-7.20 (m, 1H), 5.32-5.26 (m, 1H), 4.64-4.52 (m, 1H), 2.39-2.34 (m, 1H), 2.06-1.90 (m, 3H), 1.86-1.15 (m, 24H), 1.12-1.00 (m, 3H), 1.00-0.80 (m, 7H), 0.66 (s, 3H).

LCMS Rt = 1.413 min in 2 min chromatography, 30-90AB\_2MIN\_E, MS ESI calcd. For C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

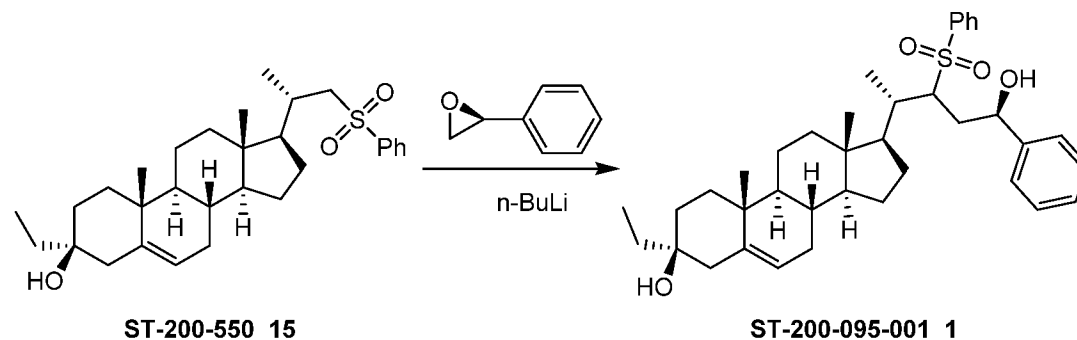
**Compound 961:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39-7.30 (m, 4H), 7.30-7.20 (m, 1H), 5.31-5.26 (m, 1H), 4.64-4.52 (m, 1H), 2.39-2.34 (m, 1H), 2.06-1.90 (m, 3H), 1.86-1.35 (m, 17H), 1.28-1.20 (m, 2H), 1.20-0.80 (m, 13H), 0.66 (s, 3H).

LCMS Rt = 1.425 min in 2 min chromatography, 30-90AB, MS ESI calcd. For C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

[00545] Synthesis of 861 to determine stereochemistry



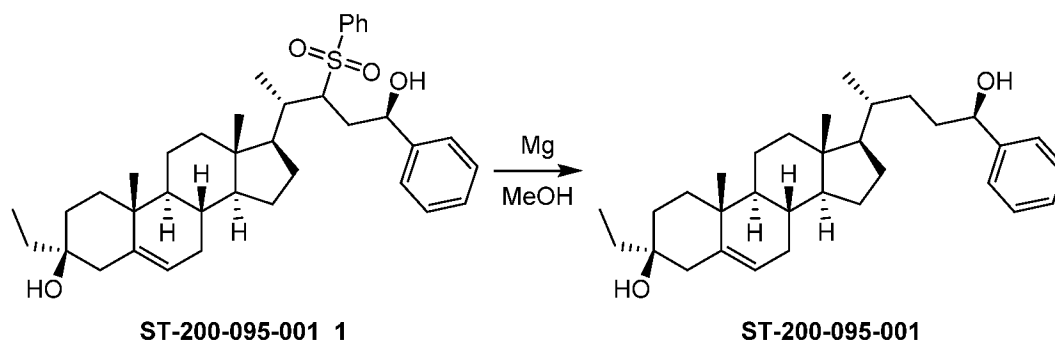
[00546] Synthesis of ST-200-095-001\_1



To a freshly distilled anhydrous THF (1 mL) was added n-BuLi (2.47 mL 6.18 mmol, 2.5 M in n-hexane) drop-wise at -70°C. Then a solution of **ST-200-550\_15** (1 g, 2.06 mmol) in anhydrous THF (10 mL) was drop-wise. After stirring at -70°C for 1 h, (2S)-2-phenyloxirane (371 mg, 3.09 mmol) was added at -70°C and the reaction was stirred for another 1 h. The reaction mixture was stirred at 25°C (room temperature) for 12 h. The reaction was quenched by saturated NH<sub>4</sub>Cl.aq (100 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combine organic

phase was washed with saturated brine (2 x 50 mL), drive over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **ST-200-095-001\_1** (1.1 g, crude) as an oil, which was used directly for the next step.

**[00547] Synthesis of ST-200-095-001**



To a solution of **ST-200-095-001\_1** (1.1 g, crude) in MeOH (100 mL) was added Mg powder (2.17 g, 90.5 mmol) and NiCl<sub>2</sub> (40 mg) at 25°C under N<sub>2</sub>. After stirring at 60°C for 1h under N<sub>2</sub>, the reaction mixture was quenched with HCl (300 mL, 1 M) until the reaction became clear. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with saturated brine (2 x 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 8/1 to 5/1) to afford **ST-200-095-001** (0.65 g, 77%, impure) as a solid.

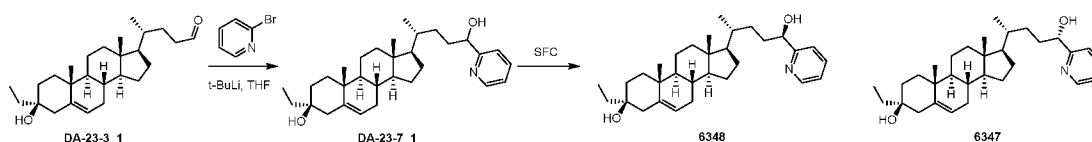
The **ST-200-095-001** (650 mg, 1.39 mmol) was re-crystallized from MeCN (40 mL) to give **ST-200-095-001** (580 mg, 69%, impure) as a solid.

The **ST-200-095-001** (300 mg, 0.6455 mmol) was purified by SFC (Instrument: SFC-16, Column:OD(250mm\*30mm,5um), Condition:0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH, Begin B:45%, End B:45%, FlowRate(ml/min):60, Injections:70) to give **ST-200-095-001** (256 mg, 59%) as a solid.

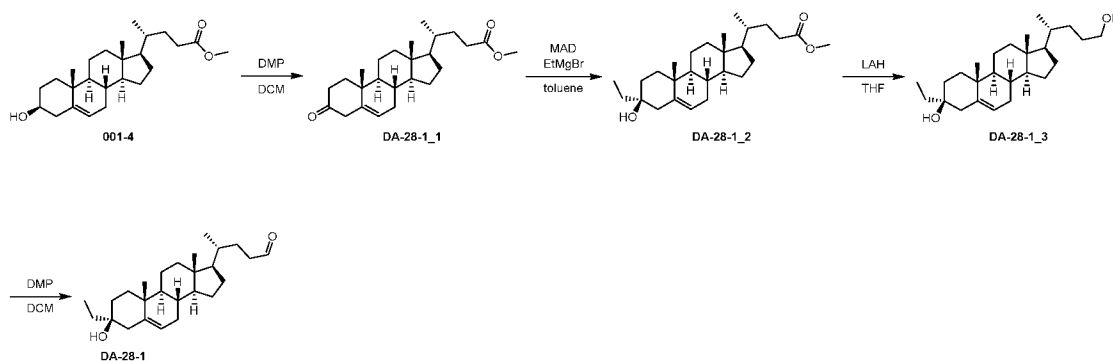
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.88-7.81 (m, 4H), 7.80-7.23 (m, 3H), 5.32-5.25 (m, 1H), 4.65-4.61 (m, 1H), 2.40-2.30 (m, 1H), 2.06-1.90 (m, 3H), 1.88-1.64 (m, 5H), 1.51-1.05 (m, 15H), 1.04-0.79 (m, 12H), 0.66 (s, 3H).

LCMS Rt = 1.287 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

**EXAMPLE 63: Synthesis of 6347 and 6348**



**[00548] Synthesis of DA-23-3\_1 (aka DA-28-1).**



To a solution of **001-4** (50 g, 128 mmol) in DCM (800 mL) was added DMP (108 g, 256 mmol) at 30°C. The reaction mixture was stirred at 30°C for 10 minutes. And H<sub>2</sub>O (2.3 g, 128 mmol) was added dropwise. The reaction mixture was quenched with Saturated NaHCO<sub>3</sub> aqueous (500 mL) until pH of the aqueous layer became about 9. The mixture was filtered. The DCM layer was separated and the aqueous phase was extracted with DCM (100 mL). The combined organic phase was washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous (600 mL), brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **DA-28-1\_1** (108 g, crude) as an oil. The reaction was conducted in parallel for 2 times.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.30-5.26 (m, 1H), 3.67 (s, 3H), 3.30-3.22 (m, 1H), 2.85-2.79 (m, 1H), 2.50-2.15 (m, 4H), 2.08-1.96 (m, 3H), 1.90-1.71 (m, 2H), 1.56-1.45 (m, 6H), 1.44-1.19 (m, 3H), 1.17 (s, 3H), 1.15-0.97 (m, 5H), 0.96-0.88 (m, 3H), 0.70 (s, 3H).

To a solution of **BHT** (367 g, 1.67 mmol) in toluene (1000 mL) under nitrogen at 0°C was added trimethylaluminum (2 M in toluene, 418 mL, 837 mmol) dropwise. The mixture was stirred at 0°C for 30 min and used directly as a solution of MAD (0.59 M in toluene) without further purification. To the solution of **MAD** (0.59 M in toluene, 1410 mL, 837 mmol) under nitrogen at -78°C was added a solution of **DA-28-1\_1** (108 g, 279 mmol) in toluene (500 mL) dropwise. The mixture was stirred at -78°C for 30 min. EtMgBr (3 M in diethyl ether, 278 mL, 837 mmol, 3M in ether) was added dropwise. The resulting mixture was stirred at -78 °C for 1 hr. The reaction mixture was poured to ice-cooled aqueous citric acid (1000 mL), extracted with EtOAc (2 x 500 mL). The combined organic layer was washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (0-20% of EtOAc in PE) to give **DA-28-1\_2** (95 g, impure) as an oil. The reaction was conducted in parallel for 2 times.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.30-5.26 (m, 1H), 3.65 (s, 3H), 2.48-2.18 (m, 4H), 2.08-1.91 (m, 2H), 1.90-1.76 (m, 4H), 1.75-1.61 (m, 4H), 1.60-1.48 (m, 5H), 1.47-1.22 (m, 5H), 1.17 (s, 1H), 1.16-1.02 (m, 3H), 1.01-0.96 (m, 2H), 0.95-0.90 (m, 1H), 0.89-0.82 (m, 4H), 0.81-0.76 (m, 2H), 0.67 (s, 3H).

To a solution of **DA-28-1\_2** (60 g, 144 mmol) in THF (1200 mL) under N<sub>2</sub> at 0°C was added LiAlH<sub>4</sub> (8.19 g, 216 mmol) in portions. The reaction was stirred at 20°C for 30 min. The reaction was quenched with 2 M HCl (600 mL) at 0°C till pH of the aqueous phase was about 2. The mixture was filtered. The solid was collected and the aqueous layer was extracted with EtOAc (2 x 400 mL). The combined organic phase was washed with sat. NaHCO<sub>3</sub> (600 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product, which was purified with the solid by trituration with MeCN (800 mL) to give **DA-28-1\_3** (45 g, 81%) as a solid.

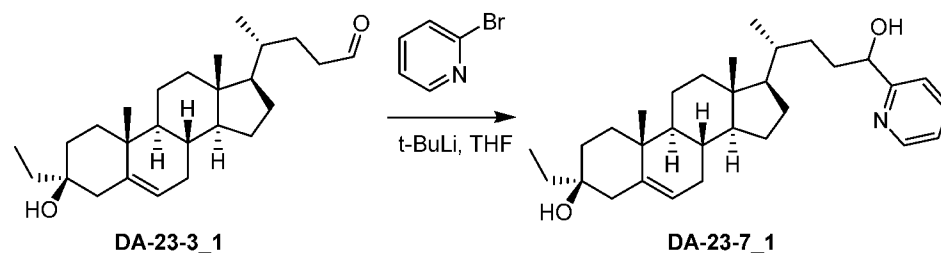
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.30-5.26 (m, 1H), 3.65-3.56 (m, 2H), 2.40-2.32 (m, 1H), 2.10-2.00 (m, 1H), 1.99-1.90 (m, 2H), 1.89-1.58 (m, 5H), 1.56-1.31 (m, 10H), 1.30-1.19 (m, 3H), 1.18-1.03 (m, 8H), 1.02-0.88 (m, 5H), 0.87-0.78 (m, 3H), 0.68 (s, 3H).

To a solution of **DA-28-1\_3** (45 g, 115 mmol) in DCM (800 mL) was added DMP (97.5 g, 230 mmol) at 20°C. The reaction mixture was stirred at 20°C for 10 min. The reaction mixture was quenched with Saturated NaHCO<sub>3</sub> aqueous (500 mL) at 20°C. The mixture was filtered. The DCM layer was separated and the aqueous phase was extracted with DCM (200 mL). The combined organic phase was washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous (3 x 500 mL), sat. NaHCO<sub>3</sub> (500 mL), water (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. Combined with another batch from 25 g of **DA-28-1\_3**, the crude product was triturated with MeCN (500 mL) to give **DA-028-1** (48 g) as a solid. 500 mg of impure **DA-28-1** was purified by flash column (0-15% of EtOAc in PE) to give **DA-28-1** (194 mg, 39%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.77 (s, 1H), 5.30-5.27 (m, 1H), 2.50-2.32 (m, 3H), 2.05-1.94 (m, 3H), 1.93-1.67 (m, 3H), 1.66-1.58 (m, 3H), 1.56-1.22 (m, 10H), 1.20-1.04 (m, 4H), 1.02 (s, 3H), 1.00-0.90 (m, 5H), 0.89-0.80 (m, 3H), 0.68 (s, 3H).

LCMS Rt = 1.229 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>26</sub>H<sub>41</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 369, found 369.

#### [00549] Synthesis of **DA-23-7\_1**

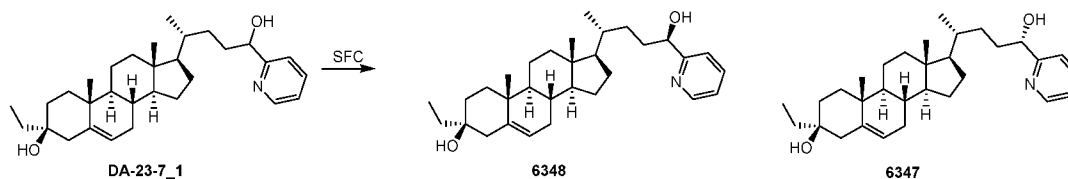


Pyridin-2-yllithium (437 mg, 5.15 mmol) was added to a solution of **DA-23-3\_1** (400 mg, 1.03 mmol) in THF (3 mL) at -70°C. The mixture was stirred at 25°C for 1 hr. The mixture was quenched with Sat. NH<sub>4</sub>Cl (20 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (30 mL x 3), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum

to give a crude product, which was purified by silica gel chromatography (PE/EtOAc = 30/1 to 6/1) to afford **DA-23-7\_1** (200 mg, 42%) as a solid.

<sup>1</sup>H NMR CDCl<sub>3</sub> Bruker\_P\_400MHz δ 8.59-8.55 (m, 1H), 7.72-7.64 (m, 1H), 7.25-7.16 (m, 2H), 5.32-5.24 (m, 1H), 4.75-4.62 (m, 1H), 4.10-4.00 (m, 1H), 2.40-2.30 (m, 1H), 2.07-1.30 (m, 16H), 1.30-0.80 (m, 20H), 0.65 (s, 3H).

#### [00550] Synthesis of 6347 and 6348



(Stereochemistry randomly assigned).

The compound **DA-23-7\_1** (510 mg, 1.08 mmol) was purified by SFC (Column: Chiralpak AS-3 150×4.6mm I.D., 3μm Mobile phase: A: CO<sub>2</sub> B: ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5min Flow rate: 2.5mL/min Column temp.: 35°C) to afford **6348** (60 mg, 30%) as solid and **6347** (60 mg, 30%) as a solid.

#### 6348

<sup>1</sup>H NMR CDCl<sub>3</sub> Bruker\_P\_400MHz δ 8.59-8.51 (m, 1H), 7.72-7.64 (m, 1H), 7.25-7.17 (m, 2H), 5.32-5.24 (m, 1H), 4.73-4.62 (m, 1H), 4.05-4.01 (m, 1H), 2.40-2.31 (m, 1H), 2.07-1.67 (m, 6H), 1.66-1.57 (m, 3H), 1.50-1.29 (m, 9H), 1.28-1.19 (m, 2H), 1.18-1.03 (m, 5H), 1.03-1.00 (m, 3H), 1.00-0.94 (m, 1H), 0.94-0.88 (m, 4H), 0.88-0.82 (m, 3H), 0.68 (s, 3H).

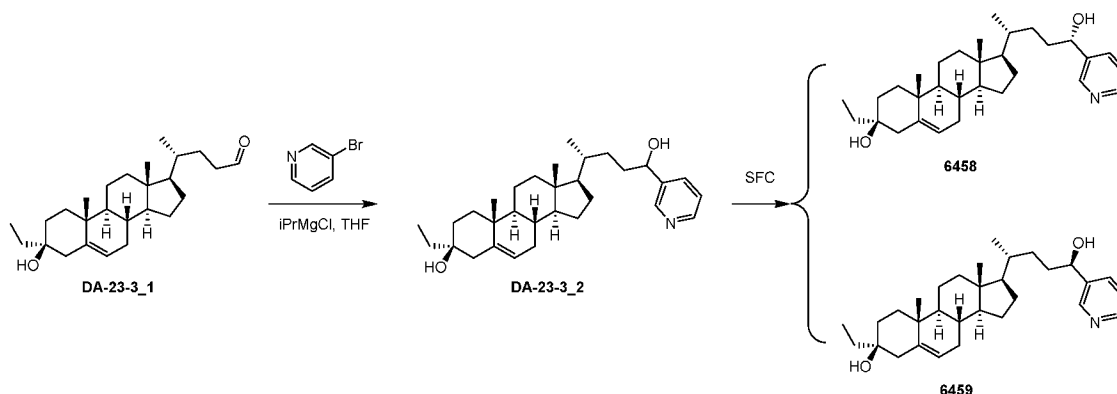
LCMS Rt = 0.839 min in 2 min chromatography, 30-90AB, purity 99%, MS ESI calcd. For C<sub>21</sub>H<sub>48</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 466, found 466.

#### 6347

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.57-8.51 (m, 1H), 7.71-7.65 (m, 1H), 7.25-7.17 (m, 2H), 5.35-5.23 (m, 1H), 4.75-4.67 (m, 1H), 4.12-4.06 (m, 1H), 2.41-2.31 (m, 1H), 2.08-1.91 (m, 3H), 1.88-1.67 (m, 4H), 1.67-1.58 (m, 1H), 1.50-1.32 (m, 6H), 1.31-1.14 (m, 4H), 1.13-1.03 (m, 4H), 1.03-1.01 (m, 2H), 1.01-0.93 (m, 2H), 0.93-0.89 (m, 4H), 0.89-0.81 (m, 4H) 0.68 (s, 3H).

LCMS Rt = 0.825 min in 2 min chromatography, 30-90AB, purity 99%, MS ESI calcd. For C<sub>21</sub>H<sub>48</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 466, found 466.

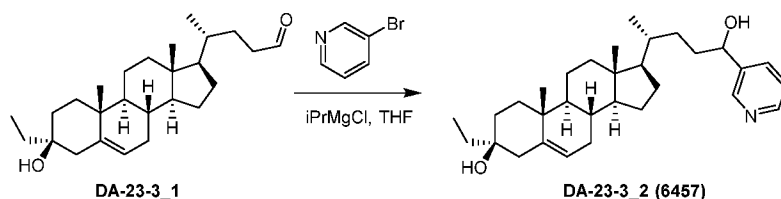
#### EXAMPLE 64: Synthesis of 6457, 6458, and 6459



[00551] Stereochemistry assigned based on NMR data.

[00552] The experimental of intermediate **DA-23-3\_1** could be found in Example 63.

5 [00553] **Synthesis of DA-23-3\_2 (6457)**

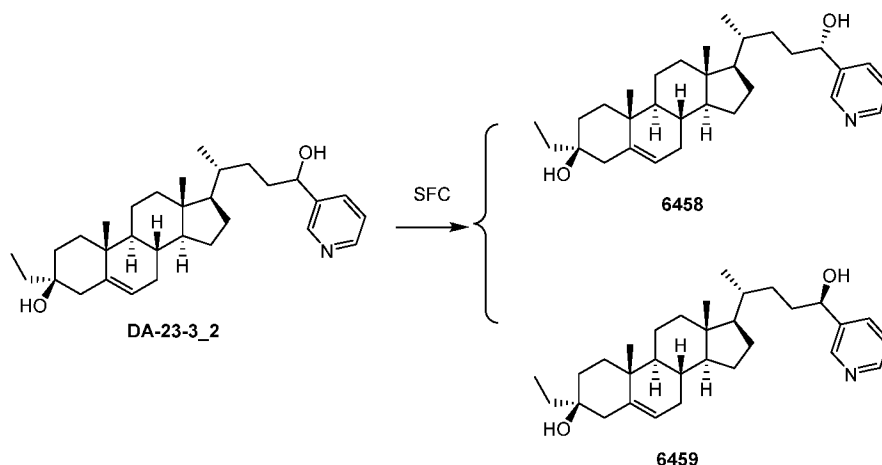


Isopropylmagnesium chloride (20.6 mL, 41.2 mmol, 2 M in THF) was added to a suspension of 3-bromopyridine (6.50 g, 41.2 mmol) in THF (10 mL) at 0°C. The mixture was stirred at 25°C for 1 h. After cooling to 0°C, a solution of **DA-23-3\_1** (800 mg, 2.06 mmol) in THF (10 mL) was added. The mixture was stirred at 25°C for 2 h. To the mixture was added NH<sub>4</sub>Cl (50 mL, 10% aq.). Combined with another batch from 100 mg of **DA-23-3\_1**, the mixture was extracted with EtOAc (2x50 mL). The organic layer was separated. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. The residue was purified by flash column (0~100% of EtOAc in PE) to afford impure **DA-23-3\_2** (560 mg, 58%) as a solid. The impure **DA-23-3\_2** (560 mg, 1.20 mmol) was triturated from MeCN (20 mL) at 25°C to give **DA-23-3\_2** (406 mg, 73%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.60-8.50 (m, 2H), 7.72-7.68 (m, 1H), 7.28-7.17 (m, 1H), 5.32-5.25 (m, 1H), 4.22-4.10 (m, 1H), 2.40-2.30 (m, 1H), 2.10-1.92 (m, 4H), 1.92-1.68 (m, 4H), 1.68-1.53 (m, 6H), 1.53-1.35 (m, 4H), 1.35-1.01 (m, 10H), 1.01-0.80 (m, 9H), 0.66 (s, 3H).

LCMS Rt = 0.921 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. For C<sub>31</sub>H<sub>48</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 466, found 466.

[00554] **Synthesis of 6458 and 6459**



**DA-23-3\_2** (378 mg, 0.811 mmol) was purified by SFC (column:

AD(250mm\*30mm,10um), gradient: 40-40% B (A= 0.1%NH<sub>3</sub>H<sub>2</sub>O IPA), flow rate: 60 mL/min) to give **DA-23-9** (110 mg, 29%) as a solid and **DA-23-10** (120 mg, 31.8%) as a

solid.

#### 6458

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.55-8.45 (m, 2H), 7.70-7.60 (m, 1H), 7.25-7.18 (m, 1H), 5.25-5.18 (m, 1H), 4.15-4.05 (m, 1H), 2.30-2.20 (m, 1H), 2.10-1.85 (m, 4H), 1.90-1.62 (m, 5H), 1.52-1.28 (m, 10H), 1.28-0.95 (m, 9H), 0.95-0.80 (m, 6H), 0.80-0.75 (m, 3H), 0.59 (s, 3H).

**LCMS** Rt = 0.926 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. For C<sub>31</sub>H<sub>48</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 466, found 466.

**SFC** \_E1 Rt = 1.603 min in 10 min chromatography, AD\_3\_IPA\_DEA\_40\_25ML, 100%de.

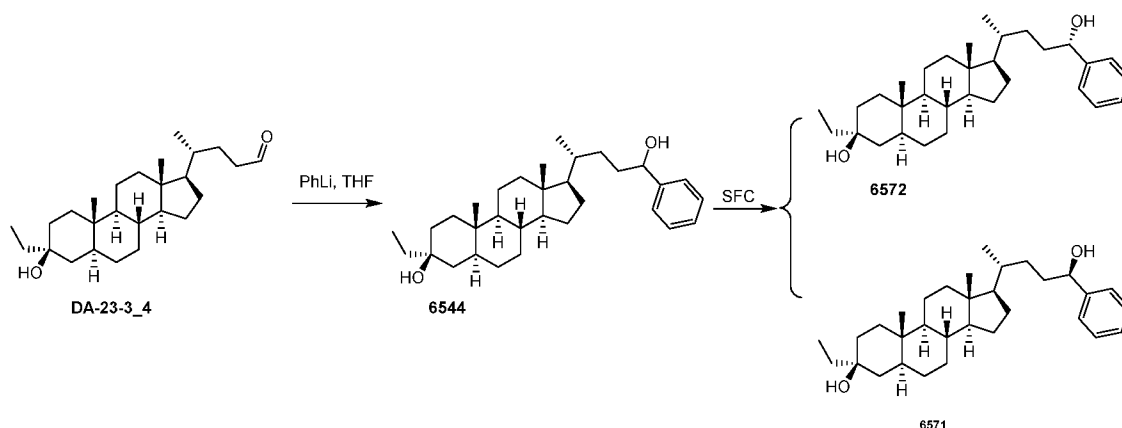
#### 6459

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.55-8.45 (m, 2H), 7.70-7.60 (m, 1H), 7.25-7.18 (m, 1H), 5.25-5.18 (m, 1H), 4.15-4.05 (m, 1H), 2.30-2.20 (m, 1H), 2.01-1.65 (m, 7H), 1.61-1.53 (m, 3H), 1.53-1.29 (m, 8H), 1.25-1.12 (m, 4H), 1.12-0.88 (m, 12H), 0.88-0.75 (m, 3H), 0.59 (s, 3H).

**LCMS** Rt = 0.928 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. For C<sub>31</sub>H<sub>48</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 466, found 466.

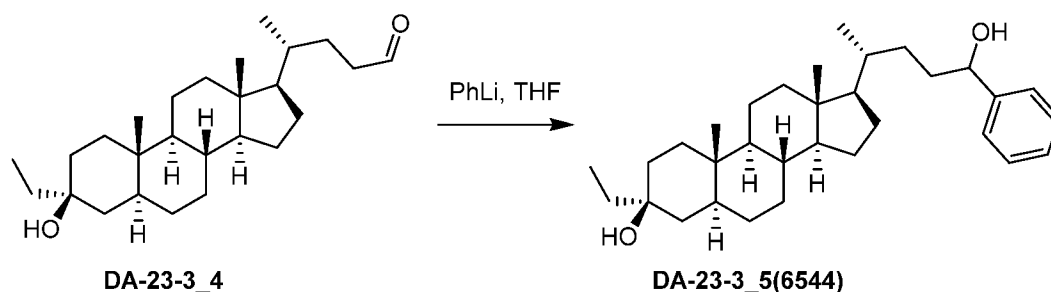
**SFC** \_E1 Rt = 2.037 min in 10 min chromatography, AD\_3\_IPA\_DEA\_40\_25ML, 98%de.

#### EXAMPLE 65: Synthesis of 6544, 6571, and 6572



[00555] The experimental of intermediate **DA-23-3\_4** can be found in Example 67.

[00556] **Synthesis of DA-23-3\_5**

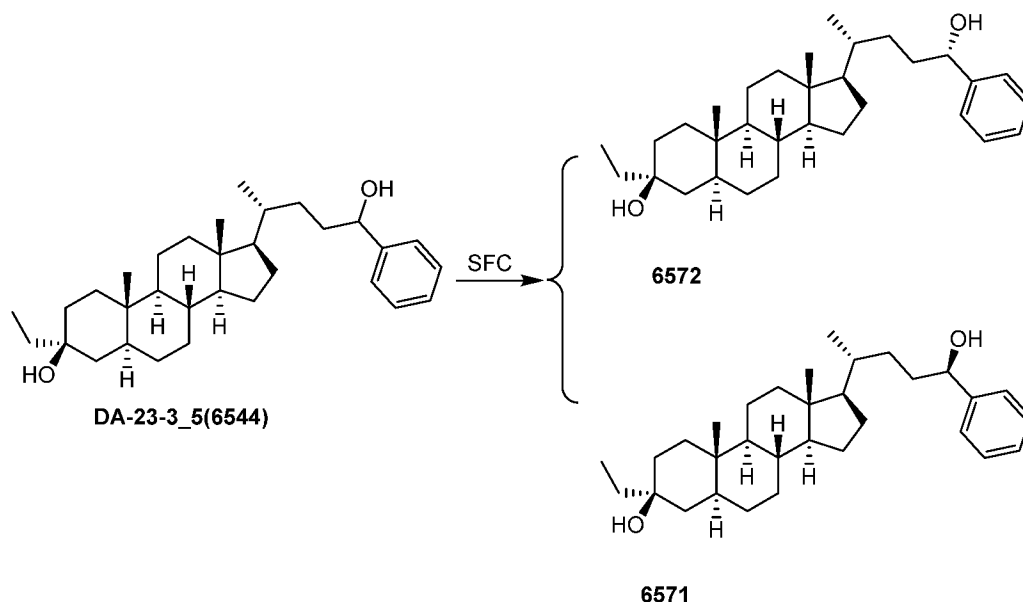


- 5 PhLi (1.71 mL, 1.5 M in ether, 2.57 mmol) was added to a solution of **DA-23-3\_4** (200 mg, 0.514 mmol) in THF (5 mL). The mixture was stirred at 25 °C for 4 h. After cooling, the mixture was treated with NH<sub>4</sub>Cl (10 mL, sat.). The mixture was extracted with EtOAc (20 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give an oil. The mixture was purified by silica gel chromatography (PE/EtOAc = 0 to 4/1) to afford **DA-23-3\_5** (110 mg, 46.0 %) as a solid. **DA-23-3\_5** (20 mg) was used to delivery.
- 10

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 5H), 4.61 (brs, 1H), 1.95-1.88 (m, 1H), 1.80-1.50 (m, 8H), 1.50-1.15 (m, 13H), 1.15-0.83 (m, 15H), 0.82 (s, 3H), 0.68-0.55(m, 4H).

LCMS Rt = 1.286 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for C<sub>32</sub>H<sub>47</sub>[M+H-2H<sub>2</sub>O]<sup>+</sup> 431, found 431.

- 15 [00557] **Synthesis of 6571 and 6572**



**DA-23-3\_5** (90 mg, 192  $\mu$ mol) was purified by SFC (Column: AD (150 $\times$ 4.6 mm, 3  $\mu$ m), Gradient: 5 %-40 % B ( A: CO<sub>2</sub> B: ethanol ) Flow rate: 2.5 mL/min ) to afford **DA-23-13** (6 mg, 7 %) as a solid and **DA-23-14** (8 mg, 9 %) as a solid.

#### 5 **6571**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.25 (m, 5H), 4.62 (brs, 1H), 2.00-1.75 (m, 8H), 1.50-1.30 (m, 8H), 1.30-1.05 (m, 10H), 1.05-0.83(m, 10H), 0.82 (s, 3H), 0.68-0.55(m, 4H).

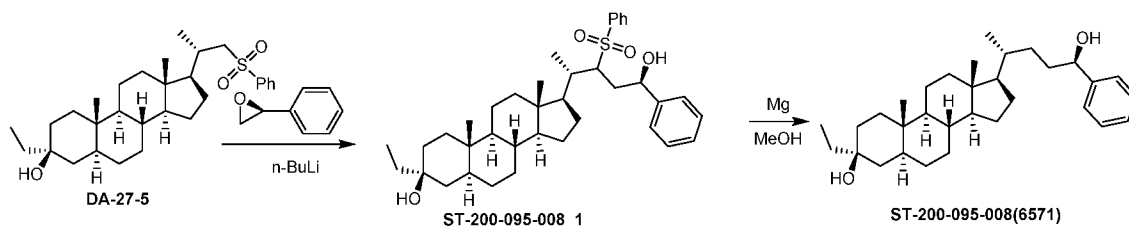
LCMS Rt = 1.262 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for C<sub>32</sub>H<sub>47</sub>[M+H-2H<sub>2</sub>O]<sup>+</sup> 431, found 431.

#### 10 **6572**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.25 (m, 5H), 4.62 (brs, 1H), 1.95-1.88 (m, 1H), 1.80-1.50 (m, 9H), 1.50-1.15 (m, 13H), 1.15-0.83(m, 14H), 0.81 (s, 3H), 0.68-0.55(m, 4H).

LCMS Rt = 1.258 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>47</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 431, found 431.

#### 15 **[00558]** Synthesis of 6571 to confirm stereochemistry at C24.



To a solution of **DA-27-5** (400 mg, 0.8217 mmol) in anhydrous THF (3 mL) was added n-BuLi (0.984 mL, 2.46 mmol, 2.5M in n-hexane) drop-wise at -70°C under N<sub>2</sub>. After stirring at -70°C for 30 min. a solution of (2S)-2-phenyloxirane (147 mg, 1.23 mmol) in anhydrous THF (0.5 mL) was added drop-wise at -70°C. The reaction mixture was stirred at -70°C for another 1 h and

then stirred at 25°C (room temperature) for 12 h. The reaction was quenched by saturated NH<sub>4</sub>Cl.aq (50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combine organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **ST-200-095-008\_1** (0.5 g, crude) as an oil. The crude residue was directly used the next step.

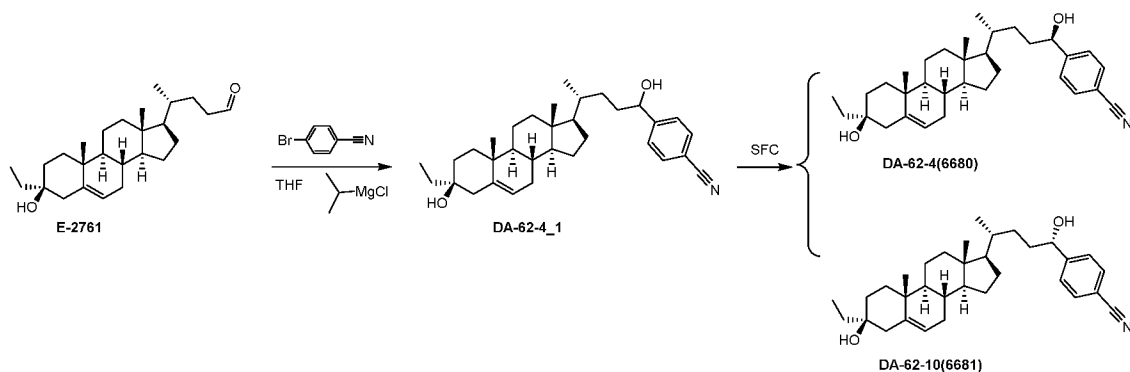
To a solution of **ST-200-095-008\_1** (0.5 g, crude) in MeOH (50 mL) was added Mg powder (0.986 g, 41.1 mmol) and NiCl<sub>2</sub> (20 mg) at 25°C under N<sub>2</sub>. After stirring at 60°C for 1 h, the reaction mixture was quenched with HCl (100 mL, 1 M) until the reaction became clear. The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated NaHCO<sub>3</sub>.aq (2 x 50 mL) and washed whit brine (2 x 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 8/1 to 5/1) to afford **ST-200-095-008** (250 mg, impure) as a solid, which was re-crystallized from MeCN (20 mL) at 82°C reflux for 30 mins. The mixture stirred was cool to 25°C (room temperature). The suspension was filtration in vacuum to get **ST-200-095-008** (200 mg, impure) as a solid. The **ST-200-095-008** (200 mg, 0.428 mmol) was by SFC (Instrument: SFC-16, Column:OD(250mm\*30mm,5um), Condition:0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH, Begin B:45%, End B:45%, FlowRate(ml/min):60, Injections:70) to give **ST-200-095-008** (148 mg, 38%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38-7.31 (m, 4H), 7.30-7.24 (m, 2H), 4.58-4.54 (m, 1H), 1.96-1.73 (m, 4H), 1.67-1.59 (m, 4H), 1.54-1.14 (m, 15H), 1.13-0.86 (m, 13H), 0.84-0.80 (m, 3H), 0.68-0.59 (m, 4H).

LCMS Rt = 1.306 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>47</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 431, found 431.

SFC Rt = 5.523 min in 10 min chromatography, OD\_3\_EtOH\_DEA\_5\_40\_25ML ("Column: Chiralcel OD-3 150×4.6mm I.D., 3um Mobile phase: A: CO<sub>2</sub> B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C"), 100%de.

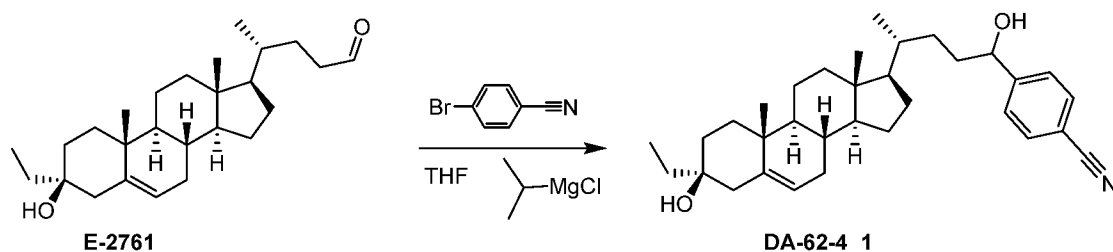
#### EXAMPLE 66: Synthesis of 6680 and 6681



[00559] The stereochemistry at C24 is randomly assigned.

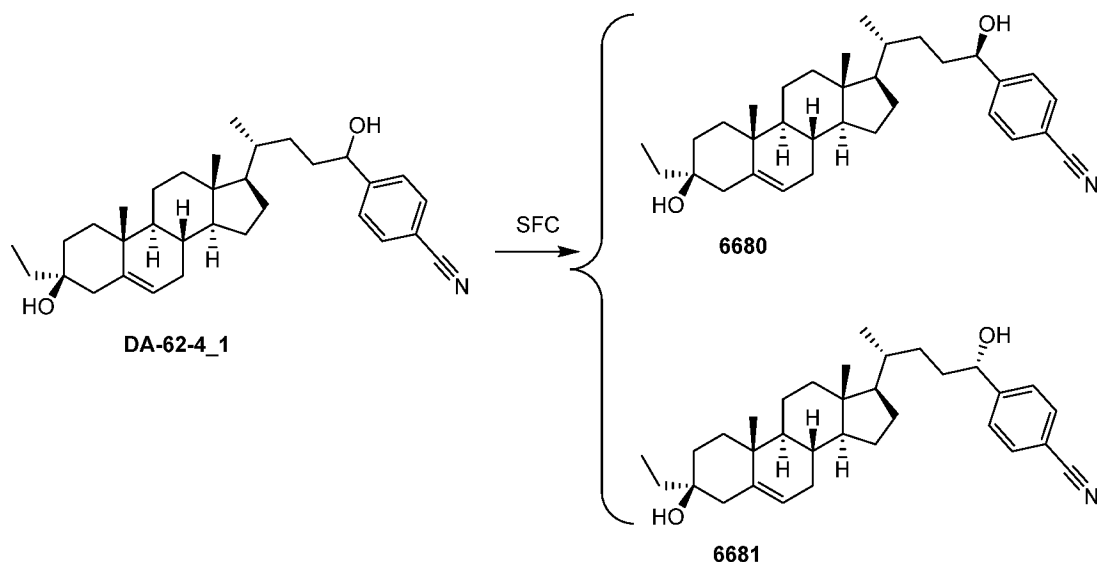
[00560] The experimental of intermediate **E-2761** can be found in Example 63 or Example 60.

5 [00561] **Synthesis of DA-62-4\_1**



Isopropylmagnesium chloride (2 M, 2.59 mL) was added dropwise to a solution of 1-bromo-4-cyanobenzene (940 mg, 5.19 mmol) in THF (10 mL) at 0 °C under N<sub>2</sub>. After stirring at 0 °C for 2 h, a solution of **E-2761** (200 mg, 0.517 mmol) in THF (10 mL) was added at 0 °C under N<sub>2</sub>. The mixture was stirred at 0 °C for 2 h and treated with saturated aqueous NH<sub>4</sub>Cl (30 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 200 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil, which was purified by flash column (0~20 % of EtOAc in PE) to give **DA-62-4\_1** (140 mg, 55 %) as a solid.

15 [00562] **Synthesis of 6680 and 6681**



**DA-62-4\_1** (140 mg, 0.285 mmol) was purified by SFC (Column: AD (150×4.6 mm, 3  $\mu$ m), Gradient: 5 %-40 % B ( A: CO<sub>2</sub> B: ethanol ) Flow rate: 2.5 mL/min ) to afford **DA-62-4**(32.0 mg, 23%) as a solid and **DA-62-10** (33.0 mg, 24%) as a solid. The chiral center at C24 was assigned randomly.

**6680:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.68-7.60 (m, 2H), 7.50-7.40 (m, 2H), 5.30-5.25 (m, 1H), 4.72-4.62 (m, 1H), 2.40-2.30 (m, 1H), 2.08-1.85 (m, 4H), 1.80-1.55 (m, 6H), 1.50-1.32 (m, 8H), 1.25-1.00 (m, 10H), 1.00-0.75 (m, 9H), 0.66 (s, 3H).

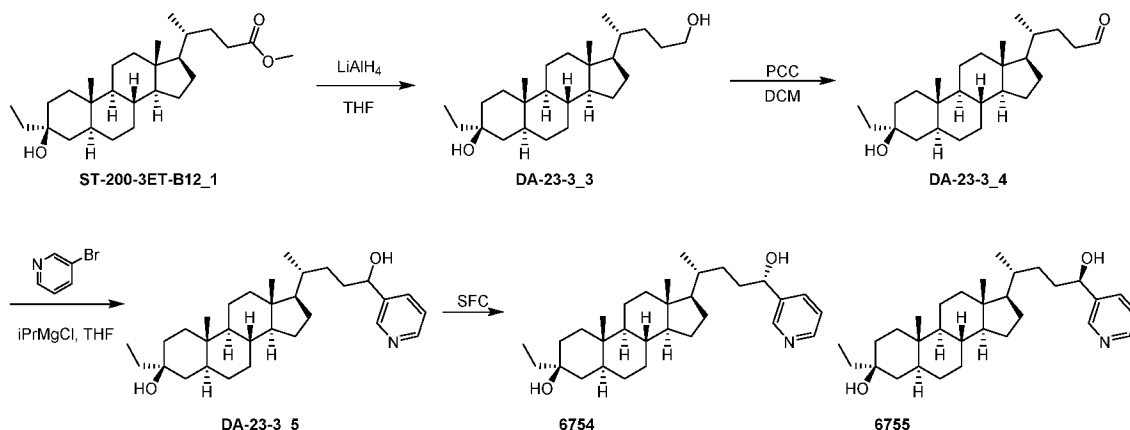
**LCMS** Rt = 1.170 min in 2.0 min chromatography, 30-90 AB, purity 98 %, MS ESI calcd. for C<sub>33</sub>H<sub>46</sub>NO [M+H-H<sub>2</sub>O]<sup>+</sup> 472, found 472.

**6681**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.68-7.60 (m, 2H), 7.50-7.40 (m, 2H), 5.30-5.25 (m, 1H), 4.72-4.62 (m, 1H), 2.40-2.30 (m, 1H), 2.08-1.85 (m, 4H), 1.80-1.55 (m, 6H), 1.50-1.32 (m, 8H), 1.25-1.00 (m, 10H), 1.00-0.75 (m, 9H), 0.66 (s, 3H).

**LCMS** Rt = 1.174 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for C<sub>33</sub>H<sub>46</sub>NO [M+H-H<sub>2</sub>O]<sup>+</sup> 472, found 472.

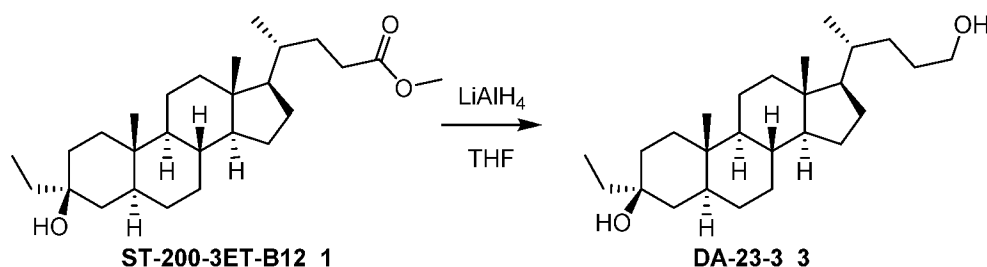
**EXAMPLE 67: Synthesis of 6754 and 6755**



[00563] The stereochemistry for 6754 and 6755 has been assigned based on NMR data.

[00564] The synthesis of ST-200-3ET-B12\_1 can be found in Example 125.

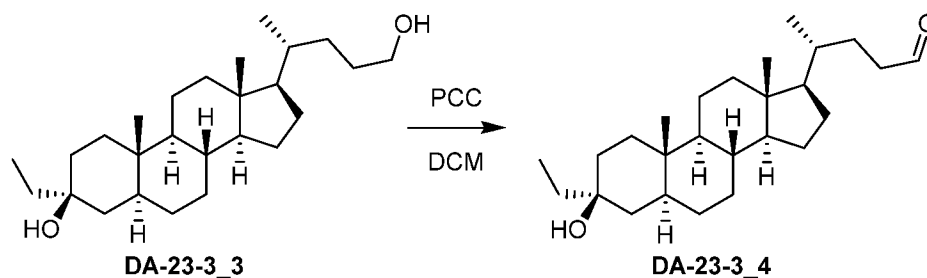
[00565] **Synthesis of DA-23-3\_3**



LiAlH<sub>4</sub> (198 mg, 2.54 mmol) was added in three portions to a solution of ST-200-3ET-B12\_1 (1.1 g, 2.62 mmol) in THF (10 mL) at 0°C under N<sub>2</sub>. After stirring at 20°C for 1 hour, the mixture was quenched with water (10 mL) at 0°C, followed by adding HCl (10 mL, 1 mol/L). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated brine (2 x 10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~50% of EtOAc in PE) to give DA-23-3\_3 (1 g, 98%) as a solid.

<sup>1</sup>H NMR CDCl<sub>3</sub> 400MHz δ 3.65-3.55 (m, 2H), 1.98-1.92 (m, 1H), 1.88-1.75 (m, 1H), 1.70-1.40 (m, 13H), 1.40-1.19 (m, 7H), 1.19-0.98 (m, 7H), 0.98-0.80 (m, 11H), 0.66-0.61 (m, 4H).

[00566] **Synthesis of DA-23-3\_4**

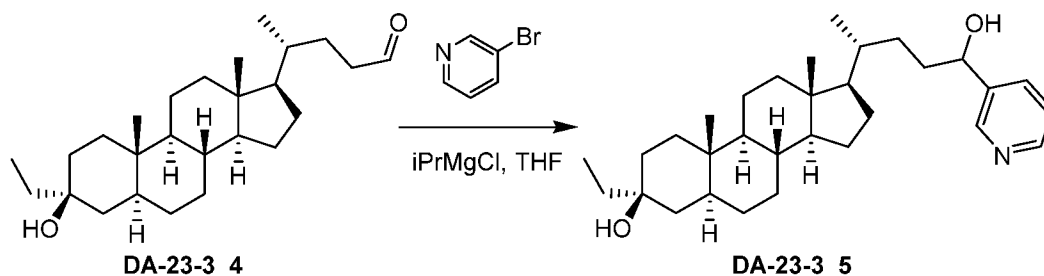


To a solution of DA-23-3\_3 (1 g, 2.55 mmol) in anhydrous DCM (30 mL) was added silica gel (1 g) and PCC (1.09 g, 5.10 mmol). After stirring at 20°C for 1 hours, the reaction mixture was

filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (PE/EA = 50/1 to 10/1 ) to give **DA-23-3\_4** (600 mg, 60%) as a solid.

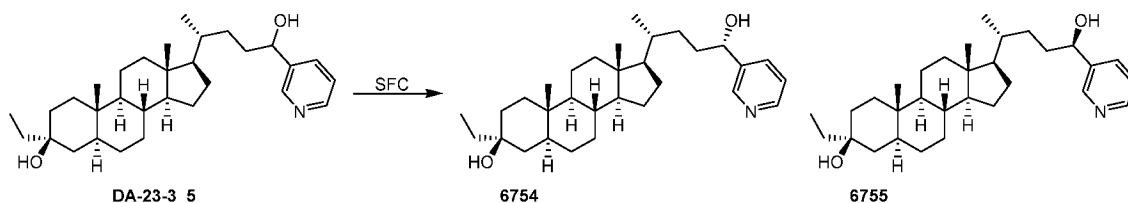
<sup>1</sup>H NMR CDCl<sub>3</sub> 400MHz δ 9.98-9.97 (m, 1H), 2.50-2.20 (m, 2H), 2.05-1.50 (m, 3H), 1.50-1.19 (m, 15H), 1.19-0.99 (m, 7H), 0.99-0.82 (m, 12H), 0.70-0.55 (m, 4H).

5 **[00567] Synthesis of DA-23-3\_5**



Isopropylmagnesium chloride (7.70 mL, 15.4 mmol, 2 M in THF) was added to a suspension of 3-bromopyridine (2.43 g, 15.4 mmol) in THF (10 mL) at 0°C. The mixture was stirred at 25°C for 1 hour. To the fresh prepared pyridin-3-ylmagnesium chloride (2.12 g, 15.4 mmol) was added **DA-23-3\_4** (300 mg, 0.771 mmol) in THF (10 mL) at 0°C. The mixture was stirred at 25°C for 2 hours and quenched with NH<sub>4</sub>Cl (20 mL, 10% aq.). The mixture was extracted with EtOAc (2 x 20 mL). The organic layer was separated. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to afford **DA-23-3\_5** (280 mg, crude) as a solid.

**[00568] Synthesis of 6754 and 6755**



190 mg of **DA-23-3\_5** was separated with SFC (Column: AD(250mm\*30mm,10um); Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O IPA, 40% B; FlowRate(ml/min): 60;) to give **6754** (34 mg, impure) and **6755** (35 mg, impure) as a solid.

34 mg of impure **6754** was re-cystallized from MeCN (5 mL) at 70°C to give **6754** (14 mg) as a solid.

35 mg of impure **6755** was re-cystallized from MeCN (5 mL) at 70°C to give **6755** (19 mg) as a solid.

**6457:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.65-8.50 (m, 2H), 7.75-7.60 (m, 1H), 7.35-7.27 (m, 1H), 4.75-4.60 (m, 1H), 2.00-1.60 (m, 8H), 1.55-1.15 (m, 14H), 1.10-0.75 (m, 18H), 0.70-0.50 (m, 4H).

LCMS Rt = 0.846 min in 2 min chromatography, 30-90AB\_E, purity 99.8%, MS ESI calcd. For C<sub>31</sub>H<sub>50</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 468, found 468.

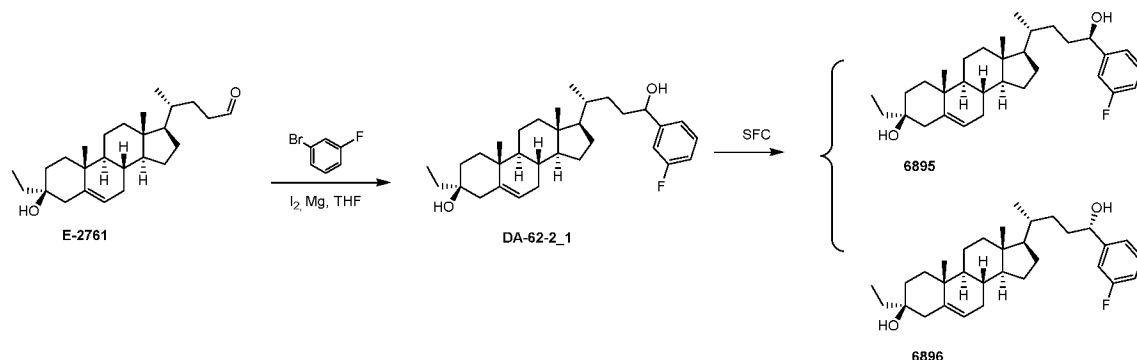
6755

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.65-8.50 (m, 2H), 7.75-7.60 (m, 1H), 7.35-7.27 (m, 1H), 4.75-4.60 (m, 1H), 2.00-1.60 (m, 8H), 1.55-1.15 (m, 15H), 1.10-0.75 (m, 17H), 0.70-0.50 (m, 4H).

LCMS Rt = 0.836 min in 2 min chromatography, 30-90AB\_E, purity 98.3%, MS ESI calcd. For

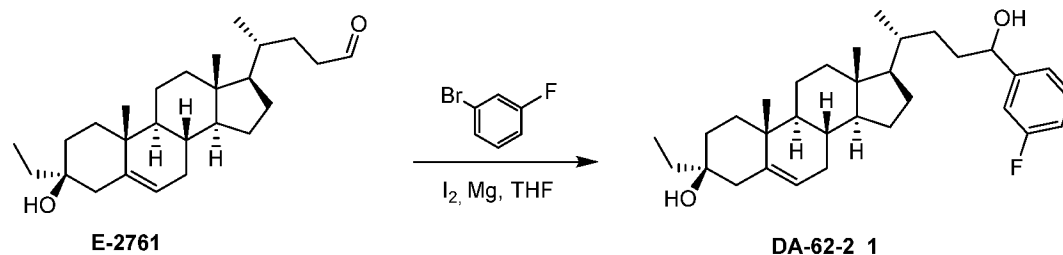
5 C<sub>31</sub>H<sub>50</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 468, found 468.

### EXAMPLE 68: Synthesis of 6895 and 6896



[00569] The experimental of intermediate **E-2761** can be found in Example 63.

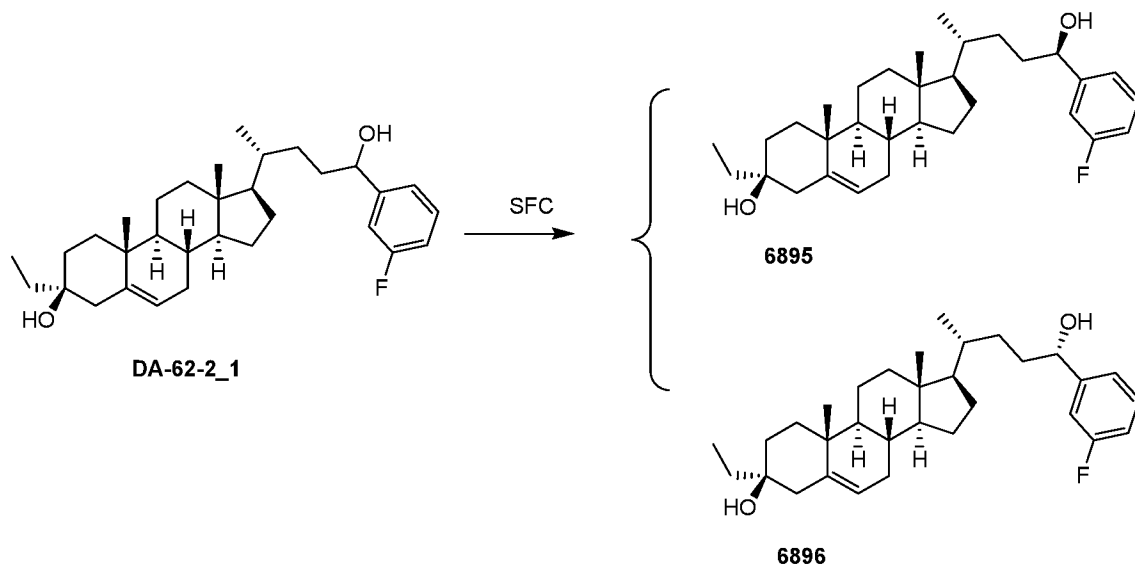
### 10 [00570] Synthesis of DA-62-2\_1



1-bromo-3-fluorobenzene (900 mg, 5.14 mmol) was added to a suspension of magnesium (124 mg, 5.14 mmol) and a small amount of iodine (130 mg, 0.514 mmol) in tetrahydrofuran (3 mL). After stirring for 2 h at 50°C, a solution **E-2761** (200 mg, 0.517 mmol) in THF(10 mL) was added at 15 °C under N<sub>2</sub>. The mixture was stirred at 15 °C for 2 h and quenched with saturated aqueous NH<sub>4</sub>Cl (30 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil. The mixture was purified by flash column (0~20% of EtOAc in PE) to give **DA-62-2\_1** (120 mg, 48%) as a solid.

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 1H), 7.10-7.02 (m, 2H), 7.00-6.90 (m, 1H), 5.30-5.25 (m, 1H), 4.68-4.55 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.90 (m, 3H), 1.90-1.50 (m, 7H), 1.50-1.30 (m, 8H), 1.30-1.15(m, 3H), 1.15-0.86(m, 13H), 0.86-0.80 (m, 3H), 0.66(s, 3H).

### [00571] Synthesis of 6895 and 6896



**DA-62-2\_1** (120 mg, 0.248 mmol) was purified by SFC (Column: AD (150×4.6 mm, 3  $\mu$ m), Gradient: 5 %-40 % B ( A: CO<sub>2</sub> B: ethanol ) Flow rate: 2.5 mL/min ) to afford **6895** (32.0 mg, 27 %) as a solid and **6896** (40.0 mg, 34 %) as a solid.

5 **6895:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.25 (m, 1H), 7.10-7.02 (m, 2H), 7.00-6.90 (m, 1H), 5.30-5.25 (m, 1H), 4.68-4.55 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.90 (m, 3H), 1.90-1.50 (m, 7H), 1.50-1.30 (m, 8H), 1.30-1.13 (m, 4H), 1.13-0.86 (m, 12H), 0.86-0.78 (m, 3H), 0.66 (s, 3H).

LCMS Rt = 1.263 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for

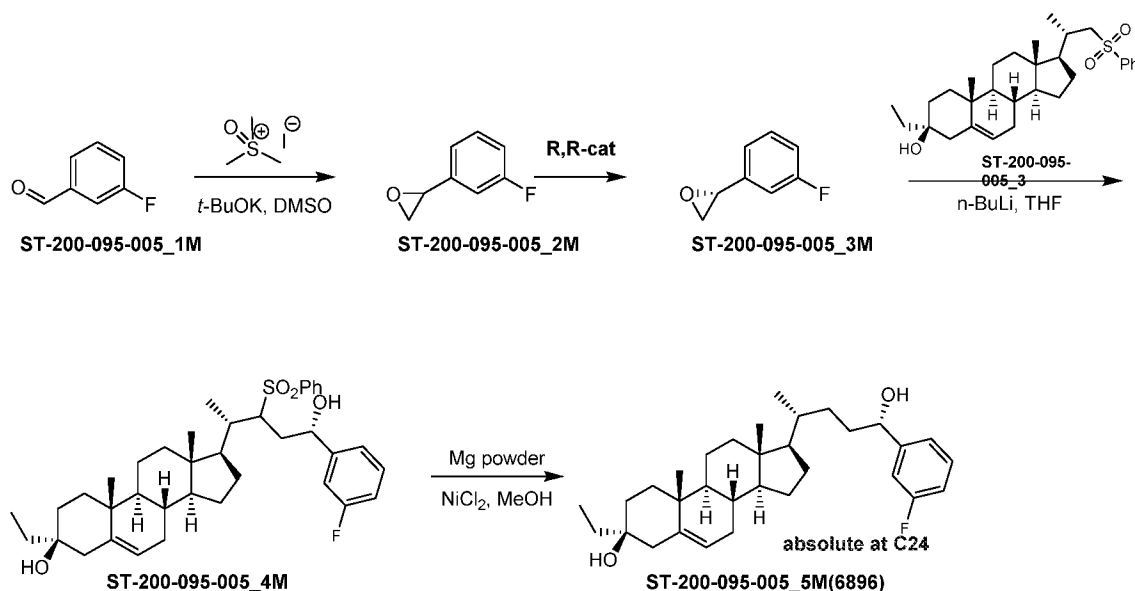
10 C<sub>32</sub>H<sub>44</sub>F [M+H-2H<sub>2</sub>O]<sup>+</sup> 447, found 447.

**6896 :**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.25 (m, 1H), 7.10-7.02 (m, 2H), 7.00-6.90 (m, 1H), 5.30-5.25 (m, 1H), 4.65-4.53 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.90 (m, 3H), 1.90-1.50 (m, 7H), 1.50-1.30 (m, 8H), 1.30-0.86 (m, 16H), 0.86-0.80 (m, 3H), 0.66 (s, 3H).

15 LCMS Rt = 1.261 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for C<sub>32</sub>H<sub>44</sub>F [M+H-2H<sub>2</sub>O]<sup>+</sup> 447, found 447.

[00572] Synthesis of 6896 to confirm stereochemistry.



To a mixture of trimethylsulfoxonium iodide (106 g, 482 mmol) in DMSO (200 mL) and THF (150 mL) was added *t*-BuOK (53.9 g, 482 mmol). The mixture was stirred at 40°C for 1 hour. The solution was then cooled to 0°C and **ST-200-095-005\_1M** (30 g, 241 mmol) in THF (50 mL) was added at 0°C. The reaction mixture was stirred 30 minutes and poured into H<sub>2</sub>O (300 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with H<sub>2</sub>O (2 x 100 mL), brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~1% of EtOAc in PE) to give product **ST-200-095-005\_2M** (32 g, 96%) as an oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 1H), 7.10-7.01 (m, 1H), 7.01-6.80 (m, 2H), 3.80-3.78 (m, 1H), 3.20-3.10 (m, 1H), 2.75-2.70 (m, 1H).

To a solution of **R,R-cat** (86.9 mg, 0.144 mmol) in toluene (5 mL) was added AcOH (88.8 mg, 1.48 mmol). The mixture was stirred at 25°C open to air for 30 min and concentrated in vacuum to leave a crude solid. The resulting catalyst residue was dissolved in **ST-200-095-005\_2M** (5 g, 36.1 mmol) at 25°C. The reaction flask was cooled to 0°C, and H<sub>2</sub>O (356 mg, 19.8 mmol) was added dropwise over 5 min. The reaction was allowed to warm to 25°C and stirred 16 hrs. The reaction mixture was purified directly by silica gel chromatography (PE%=100%) to afford **ST-200-095-005\_3M** (2 g, 40%) as an oil. The ee% was 100%.

**[00573]** **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 1H), 7.10-7.01 (m, 1H), 7.01-6.80 (m, 2H), 3.80-3.78 (m, 1H), 3.20-3.10 (m, 1H), 2.75-2.70 (m, 1H).

**[00574]** To a THF (1 mL) under N<sub>2</sub> at -70°C was added *n*-BuLi (2.5 M, 3.09 mmol, 1.23 mL). After that, a solution of **ST-200-095-005\_3** (300 mg, 0.618 mmol) in THF (2 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, a solution of **ST-200-095-005\_3M** (341 mg, 2.47 mmol) in THF (2 mL) was added. Then reaction was stirred at

stirred at 25°C for 16 hours. The mixture was poured into ice-water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **ST-200-095-005\_4M** (500 mg, crude) as a solid, which was used directly for the next step.

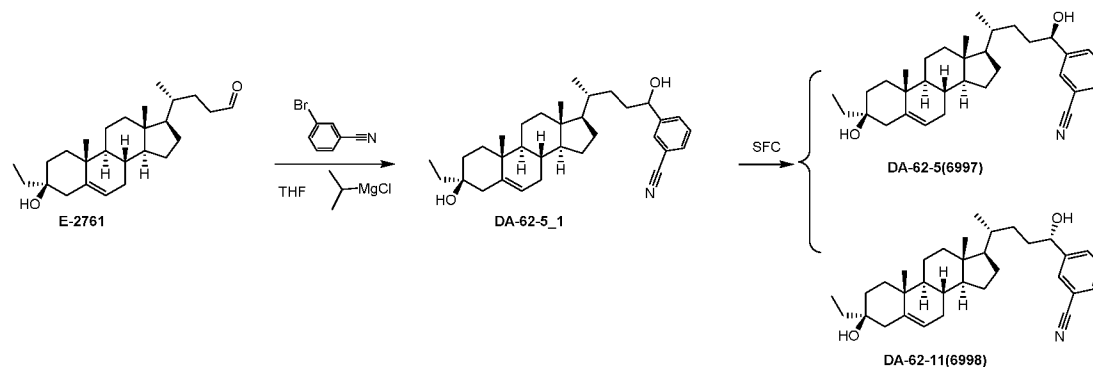
- 5 To a solution of **ST-200-095-005\_4M** (500 mg, 0.802 mmol) in MeOH (100 mL) was added NiCl<sub>2</sub> (5 mg) and Mg powder (768 mg, 32.0 mmol) at 65°C in four portions. The reaction mixture was cooled to 25°C and quenched by saturated aqueous NH<sub>4</sub>Cl (100 mL). The mixture was stirred for 1 hour. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) and re-crystallized from DCM/*n*-hexane (0.5mL/10 mL) at 25°C to give **ST-200-095-005\_5M** (20 mg, 29%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.27 (m, 1H), 7.15-7.01 (m, 1H), 7.01-6.80 (m, 2H), 5.27-5.25 (m, 1H), 4.65-4.60 (m, 1H), 2.40-2.30 (m, 1H), 2.02-1.85 (m, 3H), 1.75-1.65 (m, 7H), 1.65-1.25 (m, 7H), 1.25-1.01 (m, 10H), 0.66 (s, 3H).

LCMS Rt = 1.287 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>44</sub>FO [M+H-2H<sub>2</sub>O]<sup>+</sup> 447, found 447.

[00575]

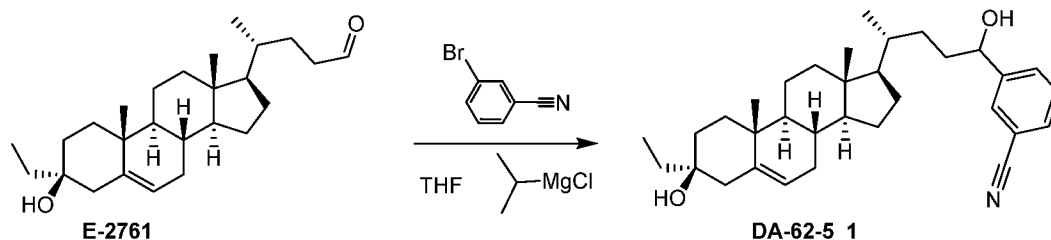
## 20 EXAMPLE 69: Synthesis of 6997 and 6998



[00576] Stereochemistry at C24 was assigned based on NMR data.

[00577] The experimental of intermediate **E-2761** can be found in Example 63.

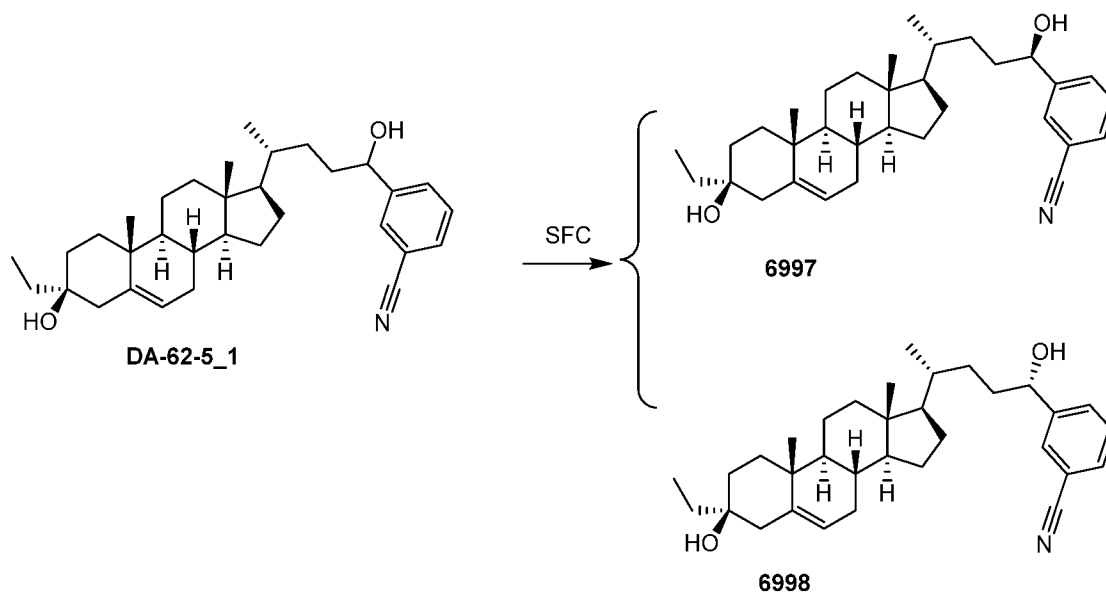
[00578] **Synthesis of DA-62-5\_1**



Isopropylmagnesium chloride (2 M, 2.58 mL) was added dropwise to a solution of 1-bromo-3-cyanobenzene (936 mg, 5.17 mmol) in THF (10 mL) at 0°C under N<sub>2</sub>. After stirring at 0°C for 2 h, a solution of **E-2761** (200 mg, 0.517 mmol) in THF (10 mL) was added at 0°C under N<sub>2</sub>. The mixture was stirred at 0°C for 2 h and quenched with saturated aqueous NH<sub>4</sub>Cl (30 mL) was added. The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil. The mixture was purified by flash column (0~20% of EtOAc in PE) to give **DA-62-5\_1** (140 mg, 55%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.70-7.65 (m, 1H), 7.60-7.50 (m, 2H), 7.50-7.40 (m, 1H), 5.30-5.28 (m, 1H), 4.72-4.52 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.50 (m, 5H), 1.50-1.30 (m, 9H), 1.30-1.15 (m, 4H), 1.15-0.88 (m, 15H), 0.88-0.78 (m, 4H), 0.66 (s, 3H).

**[00579] Synthesis of 6997 and 6998**



**DA-62-5\_1** (140 mg, 0.285 mmol) was purified by SFC (Column: AD (150×4.6 mm, 3 μm), Gradient: 5 %-40 % B ( A: CO<sub>2</sub> B: ethanol ) Flow rate: 2.5 mL/min ) to afford **DA-62-5** (30.0 mg, 22%) as a solid and **DA-62-11** (38.0 mg, 27%) as a solid.

**6997 :**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 1H), 7.10-7.02 (m, 2H), 7.00-6.90 (m, 1H), 5.30-5.25 (m, 1H), 4.68-4.55 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.90 (m, 3H), 1.90-1.50 (m, 7H), 1.50-1.30 (m, 8H), 1.30-0.86 (m, 16H), 0.86-0.76 (m, 3H), 0.66(s, 3H).

**LCMS** Rt = 1.202 min in 2.0 min chromatography, 30-90 AB, purity 99 %, MS ESI calcd. for

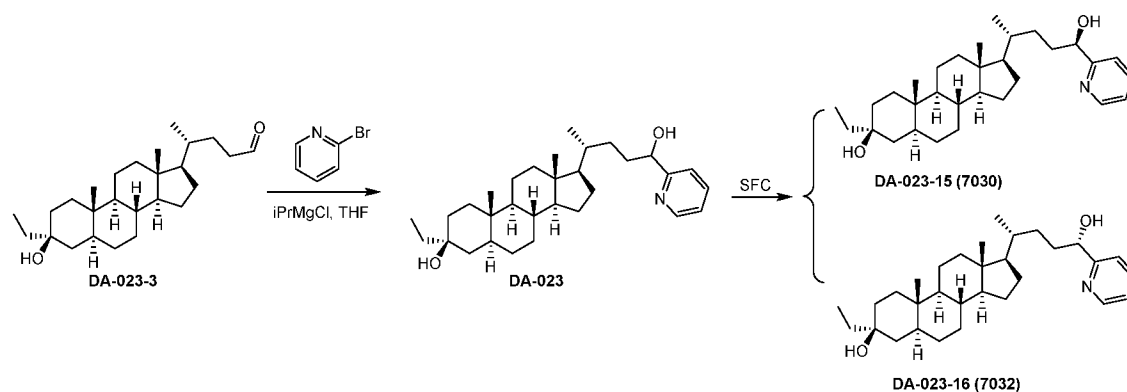
5 C<sub>33</sub>H<sub>46</sub>NO [M+H-H<sub>2</sub>O]<sup>+</sup> 472, found 472.

**6998 :**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 1H), 7.10-7.02 (m, 2H), 7.00-6.90 (m, 1H), 5.30-5.25 (m, 1H), 4.65-4.53 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.90 (m, 4H), 1.90-1.50 (m, 7H), 1.50-1.30 (m, 7H), 1.30-0.86 (m, 16H), 0.86-0.80 (m, 3H), 0.66 (s, 3H).

10 **LCMS** Rt = 1.194 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for C<sub>33</sub>H<sub>46</sub>NO [M+H-H<sub>2</sub>O]<sup>+</sup> 472, found 472.

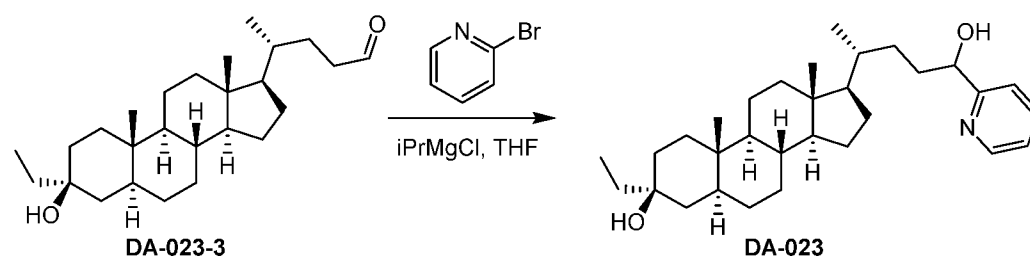
### EXAMPLE 70: Synthesis of 7030 and 7032



15 **[00580]** Stereochemistry assigned based on NMR data.

**[00581]** The experimental of intermediate **DA-023-3** can be found in Example 126.

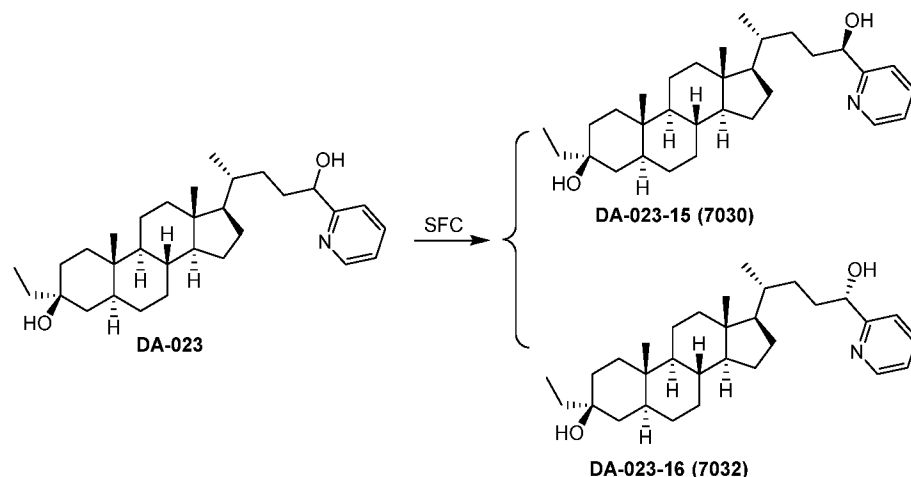
**[00582]** **Synthesis of DA-023**



Isopropylmagnesium chloride (1.29 mL, 2 M in THF, 2.58 mmol) was added to a suspension of  
 20 2-bromopyridine (407 mg, 2.58 mmol) in THF (4 mL) at 0°C. The mixture was stirred at 25°C  
 for 2 h. 5.35 mL of the freshly prepared pyridin-2-ylmagnesium bromide (5.35 mL, ca. 0.48 M  
 in THF, 2.57 mmol) was added to a solution of **DA-023-3** (200 mg, 514 μmol) in THF (5 mL) at  
 0°C. The mixture was stirred at 25°C for 16 hrs. The mixture was poured into water (20 mL) and  
 extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine (30 mL),

dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (PE/EtOAc = 5/1 to 3/1) to give **DA-023** (150 mg, 63%) as a solid.

**[00583] Synthesis of DA-023-15,16**



- 5 **DA-023** (150 mg) was purified by SFC (Column: AS (250mm\*30mm, 5um), Condition: 0.1% NH<sub>3</sub>H<sub>2</sub>O IPA, Gradient: from 25% to 25%, Flow Rate (ml/min): 50mL/min, 25°C) to afford **DA-023-15** (31 mg, 21%) and **DA-023-16** (55 mg, 37%) as a solid.

**7030:**

- 10 <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.53 (d, *J* = 4 Hz, 1H), 7.70-7.65 (m, 1H), 7.25-7.24 (m, 1H), 7.20-7.17 (m, 1H), 4.71-4.68 (m, 1H), 1.95-1.90 (m, 1H), 1.84-1.51 (m, 12H), 1.47-1.13 (m, 11H), 1.12-0.81 (m, 16H), 0.63-0.58 (m, 4H).

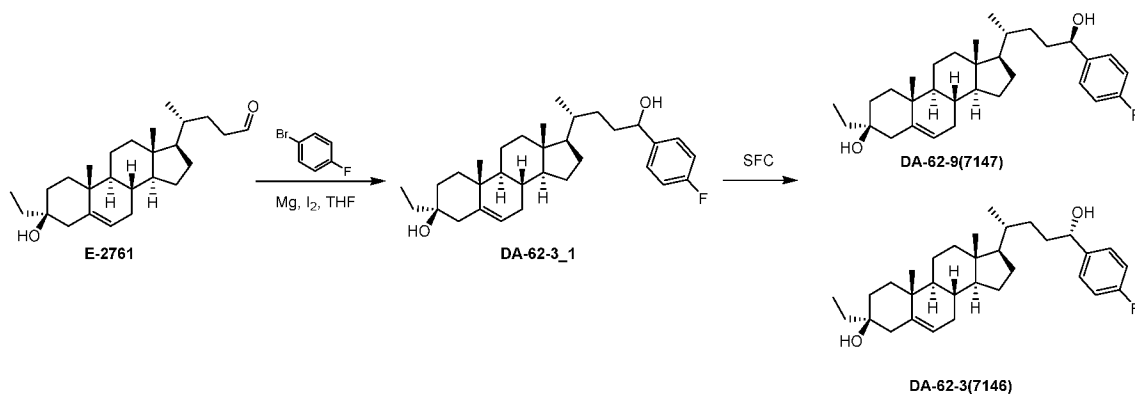
LCMS Rt = 0.923 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>31</sub>H<sub>50</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 468, found 468.

**7032:**

- 15 <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.53 (d, *J* = 4 Hz, 1H), 7.70-7.65 (m, 1H), 7.25-7.24 (m, 1H), 7.20-7.17 (m, 1H), 4.71-4.68 (m, 1H), 1.95-1.83 (m, 2H), 1.81-1.31 (m, 16H), 1.28-1.03 (m, 9H), 1.00-0.81 (m, 13H), 0.63-0.58 (m, 4H).

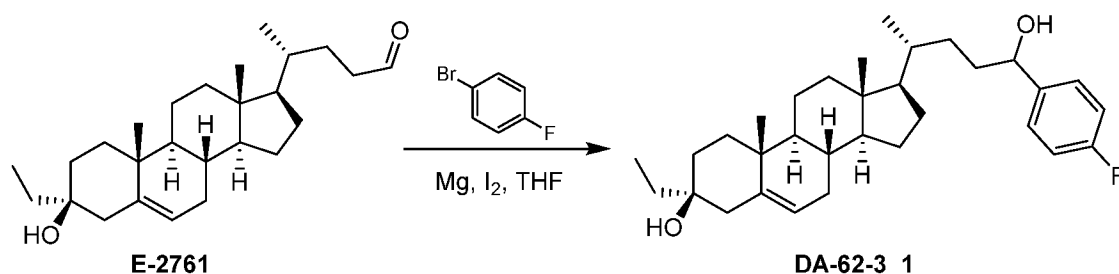
LCMS Rt = 0.914 min in 2.0 min chromatography, 30-90 AB, purity 99.5%, MS ESI calcd. For C<sub>31</sub>H<sub>50</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 468, found 468.

**EXAMPLE 71: Synthesis of 7147 and 7146**



[00584] The experimental of intermediate **E-02761** can be found in Example 63.

[00585] **Synthesis of DA-62-3\_1**

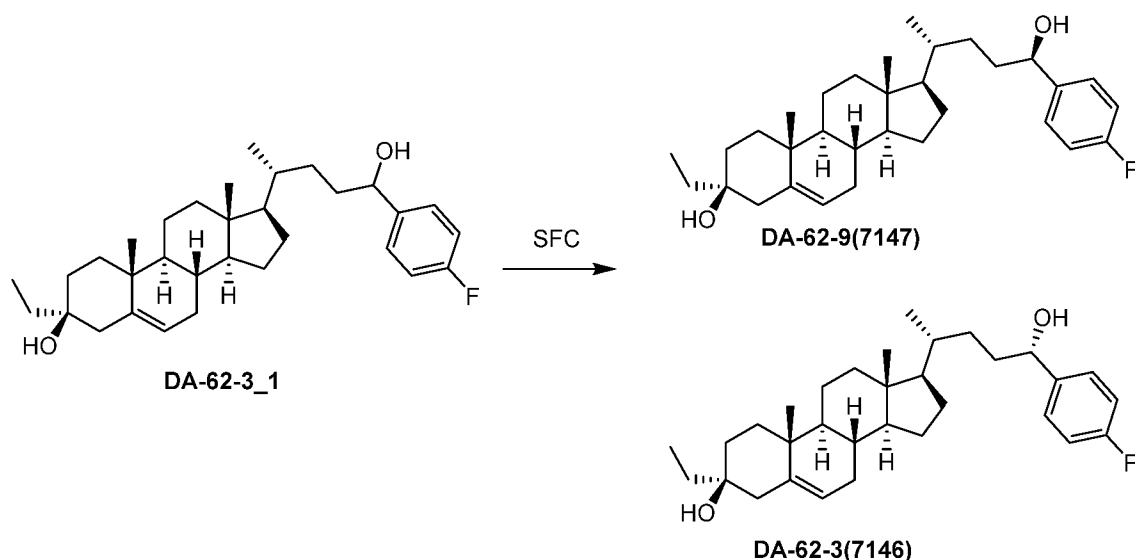


- 5 1-bromo-4-fluorobenzene (900 mg, 5.14 mmol) was added to a suspension of magnesium (124 mg, 5.14 mmol) and a small amount of iodine (130 mg, 0.514 mmol) in tetrahydrofuran (10 mL). The mixture was stirred for 2 h at 50 °C. A solution of **E-2761** (200 mg, 0.517 mmol) in THF (10 mL) was added to the Grignard mixture at 15 °C under N<sub>2</sub>. The mixture was stirred at 15 °C for 2 h and quenched with saturated aqueous NH<sub>4</sub>Cl(30 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil, which was purified by flash column (0~20% of EtOAc in PE) to give **DA-62-3\_1** (120 mg, 48%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 2H), 7.08-6.95(m, 2H), 5.28 (brs, 1H), 4.63-4.53 (m, 1H), 2.38-2.30 (m, 1H), 2.00-1.50 (m, 10H), 1.50-1.28 (m, 8H), 1.28-1.00 (m, 10H), 1.00-0.80(m, 9H), 0.66(s, 3H).

LCMS Rt = 1.453 min in 2.0 min chromatography, 30-90 AB, purity 84 %, MS ESI calcd. for C<sub>32</sub>H<sub>44</sub>F [M+H-2H<sub>2</sub>O]<sup>+</sup> 447, found 447.

[00586] **Synthesis of 7146 and 7147**



**DA-62-3\_1** (120 mg, 248  $\mu\text{mol}$ ) was purified by SFC (Column: AD (150 $\times$ 4.6mm, 3 $\mu\text{m}$ ), Gradient: 5%-40% B ( A:  $\text{CO}_2$  B: ethanol ) Flow rate: 2.5mL/min ) to afford **7146** (30 mg, 25%) as a solid and **7147** (27 mg, 23%) as a solid.

#### 5 **7146**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.25 (m, 2H), 7.08-6.95 (m, 2H), 5.28 (brs, 1H), 4.63-4.53 (m, 1H), 2.38-2.30 (m, 1H), 2.05-1.85 (m, 3H), 1.75-1.50 (m, 7H), 1.50-1.28 (m, 7H), 1.28-0.86 (m, 15H), 0.85-0.80 (m, 3H), 0.66 (s, 3H).

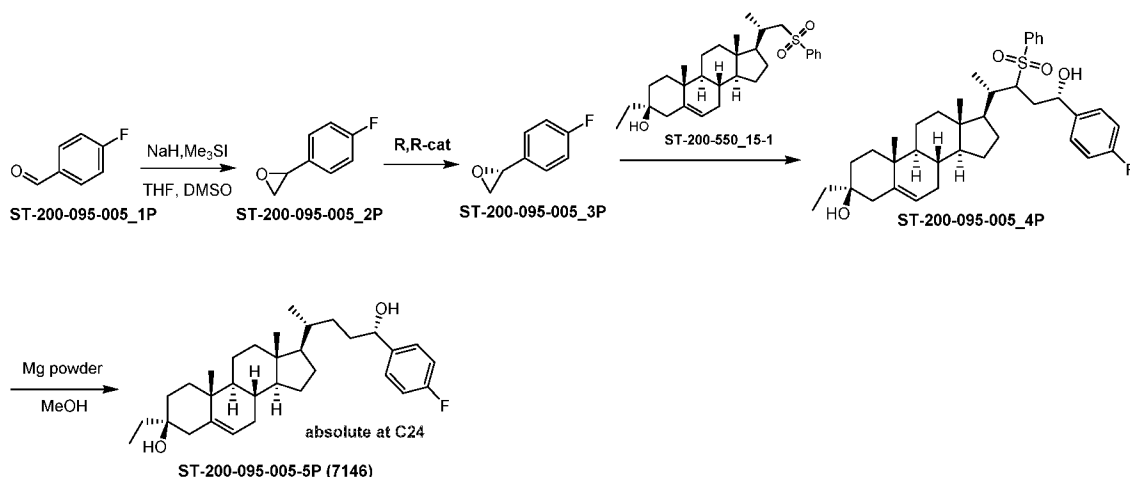
LCMS Rt = 1.434 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for  $\text{C}_{32}\text{H}_{44}\text{F}$   $[\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  447, found 447.

#### **7147**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.25 (m, 1H), 7.10-7.02 (m, 2H), 7.00-6.90 (m, 1H), 5.30-5.25 (m, 1H), 4.65-4.53 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.90 (m, 3H), 1.90-1.50 (m, 7H), 1.50-1.28 (m, 8H), 1.28-0.86 (m, 16H), 0.86-0.80 (m, 3H), 0.66(s, 3H).

15 LCMS Rt = 1.437 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for  $\text{C}_{32}\text{H}_{44}\text{F}$   $[\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  447, found 447.

[00587] **Synthesis of 7146 to determine stereochemistry**



To a solution of Me<sub>3</sub>SiI (32.8 g, 161 mmol) in DMSO (100 mL) and THF (50 mL) was added NaH (6.43 g, 60%, 161 mmol) at 25°C. The reaction mixture was stirred for 20 mins at 25°C, then was cooled to 0°C and added 4-fluorobenzaldehyde (10 g, 80.5 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h, treated with water (200 mL) and extracted with EtOAc (2 x 200 mL). The organic phase was washed with water (2 x 200 mL), brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product, which was purified by combi flash (EtOAc/PE=0-5%) to give **ST-200-095-005-2P** (5.5 g, impure) as colorless oil, which was purified by combi flash (EtOAc/PE=0-1%) to give **ST-200-095-005-2P** (4.0 g, 73%) as an oil.

**LCMS** Rt = 1.192 min in 7 min chromatography, 30-90CD\_7MIN\_E, purity 99%, MS ESI calcd.

**SFC** Peak 1: Rt = 2.209 min and Peak 2 Rt = 2.407 min in 10 min chromatography, O1\_EtOH\_DEA\_5\_40\_25ML ("Column:(S,S)Whelk-O1 250\*4.6mm,5um, Mobile phase: A: CO<sub>2</sub> B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C").

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.20-7.16 (m, 2H), 6.99-6.94 (m, 2H), 3.79-3.76 (m, 1H), 3.08-3.05 (m, 1H), 2.71-2.68 (m, 1H).

To a solution of R,R-cat (69.4 mg, 0.115 mmol) in toluene (5 mL) was added AcOH (70.8 mg, 1.18 mmol). The mixture was stirred at 25°C open to air for 30 min and concentrated in vacuo to leave a crude solid. The resulting catalyst residue was dissolved in **ST-200-095-005-2P** (4 g, 28.9 mmol) at 25°C. The reaction flask was cooled to 0°C, followed by adding H<sub>2</sub>O (284 mg, 15.8 mmol) dropwise over 5 min. The reaction was allowed to warm to 25°C and stirred for 16 hrs. The reaction mixture was purified directly by silica gel chromatography (PE%=100%) to afford **ST-200-095-005-3P** (460 mg, 11%) as an oil. The ee% was 97%.

**LCMS** Rt = 1.605 min in 2 min chromatography, 10-80CD\_3MIN\_E, purity 94%, DAD1 A, Sig=220.

**SFC** Peak 1: Rt = 2.202 min and Peak 2 Rt = 2.398 min in 10 min chromatography, O1\_EtOH\_DEA\_5\_40\_25ML ("Column:(S,S)Whelk-O1 250\*4.6mm,5um, Mobile phase: A: CO<sub>2</sub> B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C").

- 5 **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.20-7.16 (m, 2H), 6.99-6.94 (m, 2H), 3.79-3.76 (m, 1H), 3.08-3.05 (m, 1H), 2.71-2.68 (m, 1H).

To a THF (5 mL) under N<sub>2</sub> at -70°C was added n-BuLi (2.5 M, 4.12 mmol, 1.64 mL). After that, a suspension of **ST-200-550\_15-1** (800 mg, 1.65 mmol) in THF (5 mL) was added drop-wise to give a suspension. After stirring at -70°C for 30 min, a solution of **ST-200-095-005\_3P** (455 mg, 3.30 mmol) was added. Then reaction was stirred at stirred at 25°C for 16 hours. The mixture was poured into ice-water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **ST-200-095-005\_4P** (1 g, crude) as an oil, which was used directly for the next step.

- 15 To a solution of **ST-200-095-005\_4P** (1 g, crude) in MeOH (50 mL) was added NiCl<sub>2</sub> (5 mg) and Mg powder (1.533 g, 64.0 mmol) at 65°C in four portions. The reaction mixture was cooled to 20°C and quenched by HCl (1M, 100 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the crude, which was purified by flash column (0~5% of EtOAc in PE) to give **ST-200-095-005\_5P** (41 mg, 5%) as a solid.

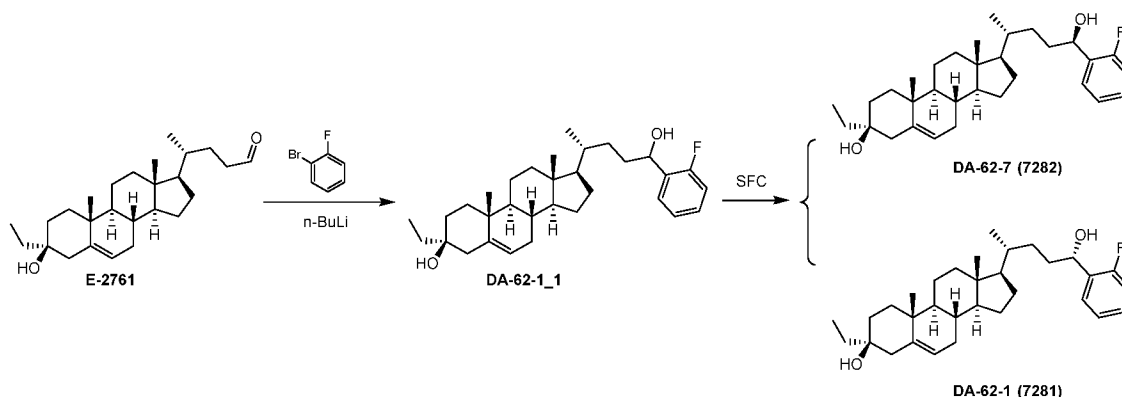
20 **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.27 (m, 2H), 7.05-6.98 (m, 2H), 5.35-5.31 (m, 1H), 4.62-4.58 (m, 1H), 2.41-2.31 (m, 1H), 2.10-1.90 (m, 4H), 1.75-1.58 (m, 8H), 1.52-1.05 (m, 14H), 1.02 (s, 3H), 1.00-0.76 (m, 8H), 0.66 (s, 3H).

25 **LCMS** Rt = 1.272 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>44</sub>F [M+H-2H<sub>2</sub>O]<sup>+</sup> 447, found 447.

**SFC** Peak 1: Rt = 2.124 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_40\_25ML ("Column:(S,S)Whelk-O1 250\*4.6mm,5um, Mobile phase: A: CO<sub>2</sub> B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C").

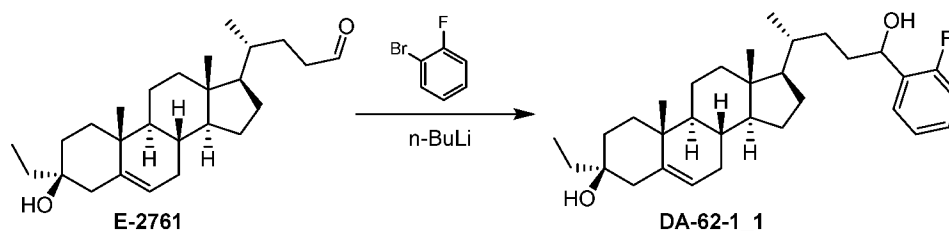
30

#### **EXAMPLE 72: Synthesis of 7281 and 7282**



[00588] The experimental of intermediate **E-2761** can be found in Example 63.

[00589] **Synthesis of DA-62-1\_1**

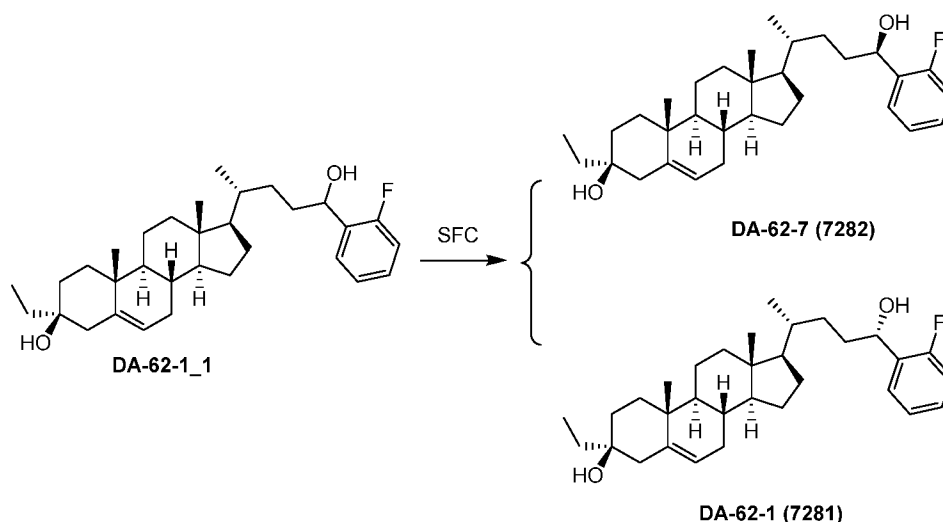


5 n-BuLi(2.5 M, 2.05 mL) was added dropwise to a solution of 1-bromo-2-fluorobenz(900 mg, 5.14 mmol) in THF(10 mL) at -78 °C under N<sub>2</sub>. After stirring at -78 °C for 30 min, a solution of **E-2761** (200 mg, 0.517 mmol) in THF(10 mL) was added at -78 °C under N<sub>2</sub>. The mixture was stirred at -78 °C for 30 min and quenched with saturated aqueous NH<sub>4</sub>Cl(30 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil, which was purified by flash column (0~20% of EtOAc in PE) to give **DA-62-1\_1** (110 mg, 44%) as a solid.

15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.50-7.42 (m, 1H), 7.25-7.10 (m, 2H), 7.10-6.96 (m, 1H), 5.32-5.25 (m, 1H), 5.02-4.92 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.50 (m, 9H), 1.50-1.32 (m, 8H), 1.32-1.18 (m, 3H), 1.18-0.75 (m, 17H), 0.66 (s, 3H).

LCMS Rt = 1.380 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for C<sub>32</sub>H<sub>44</sub>F [M+H-2H<sub>2</sub>O]<sup>+</sup> 447, found 447.

[00590] **Synthesis of 7281 and 7282**



**DA-62-1\_1** (110 mg, 227  $\mu\text{mol}$ ) was purified by SFC (Column: AD (150 $\times$ 4.6mm, 3 $\mu\text{m}$ ), Gradient: 5%-40% B ( A:  $\text{CO}_2$  B: ethanol ) Flow rate: 2.5mL/min ) to afford **DA-62-1** (12 mg, 11%) as a solid and **DA-62-7** (30 mg, impure) as a solid. The impure **DA-62-7** (30 mg, impure) was purified by SFC (Column: AD (150 $\times$ 4.6mm, 3 $\mu\text{m}$ ), Gradient: 5%-40% B ( A:  $\text{CO}_2$  B: ethanol ) Flow rate: 2.5mL/min ) to afford **DA-62-7** (6 mg, 6%) as a solid.

#### 7281

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48-7.42 (m, 1H), 7.26-7.10 (m, 2H), 7.06-6.96 (m, 1H), 5.32-5.25 (m, 1H), 5.02-4.92 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.50 (m, 11H), 1.50-1.30 (m, 7H), 1.30-1.18 (m, 2H), 1.18-0.75 (m, 17H), 0.66 (s, 3H).

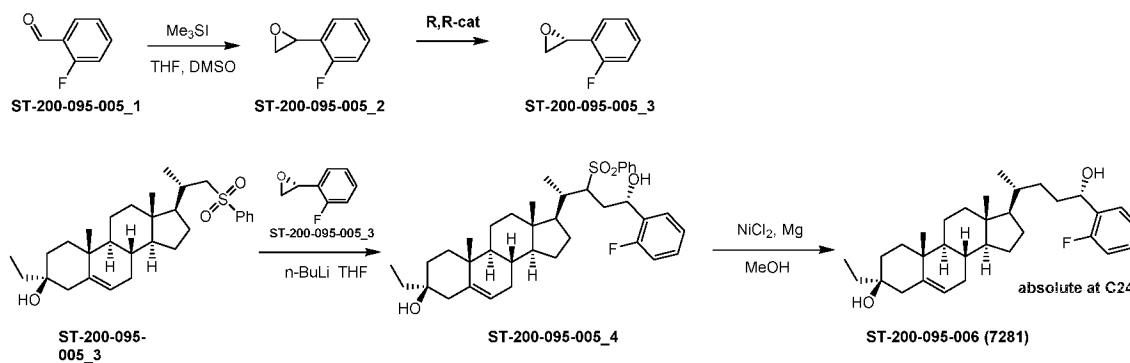
LCMS Rt = 1.362 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for  $\text{C}_{32}\text{H}_{44}\text{F}$   $[\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  447, found 447.

#### 7282

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48-7.42 (m, 1H), 7.26-7.10 (m, 2H), 7.06-6.96 (m, 1H), 5.32-5.25 (m, 1H), 5.02-4.92 (m, 1H), 2.40-2.30 (m, 1H), 2.05-1.50 (m, 10H), 1.50-1.32 (m, 8H), 1.32-0.86 (m, 16H), 0.86-0.78 (m, 3H), 0.66 (s, 3H).

HPLC Rt = 5.32 min in 7 min chromatography, 50-100 AB, purity 98 %, MS MS ESI calcd. for  $\text{C}_{32}\text{H}_{44}\text{F}$   $[\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  447, found 447.

[00591] **Synthesis to determine stereochemistry.**



To a solution of Me<sub>3</sub>SOI (123 g, 562 mmol) in DMSO (150 mL) and THF (75 mL) was added t-BuOK (63 g, 562 mmol) in portions at 25°C. The mixture was stirred at 40°C for 30 min. Then **ST-200-095-005\_1** (35 g, 281 mmol) in 75 mL of THF was added dropwise to the mixture at 0°C. After stirring at 25°C for 1 h, the mixture was poured into ice-water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum. The residue was purified by silica gel column eluted with (PE/EtOAc = 20/1) to afford **ST-200-095-005\_2** (24 g, 62%) as an oil.

**[00592]** <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 7.22-7.16 (m, 1H), 7.13-7.02 (m, 2H), 6.99-6.95 (m, 1H), 4.07 (t, *J* = 4Hz, 1H), 3.11-3.08 (m, 1H), 2.71-2.70 (m, 1H).

To a solution of **R, R-cat** (86.9 mg, 0.144 mmol) in toluene (5 mL) was added AcOH (86.4 mg, 1.44 mmol). The mixture was stirred at 25°C for 30 mins. The solution was concentrated in vacuum to give a crude solid. The resulting catalyst residue was dissolved in **ST-200-095-005\_2** (5 g, 36.1 mmol) at 25°C, the reaction mixture was cooled to 0°C, and water (356 mg, 19.8 mmol) was added dropwise. The mixture was warmed to 25°C and stirred for 16 hrs. The product was purified by silica gel column (PE/EtOAc=12/1 to 8/1) to give **ST-200-095-005\_3** (1 g, 20%) as an oil.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 7.22-7.16 (m, 1H), 7.13-7.08 (m, 1H), 7.06-7.02 (m, 1H), 6.99-6.95 (m, 1H), 4.07 (t, *J* = 4Hz, 1H), 3.11-3.08 (m, 1H), 2.71-2.70 (m, 1H).

**SFC** Peak 1: Rt = 2.015 min in 10 min chromatography, SS Whelk

O1\_EtOH\_DEA\_5\_40\_25ML ("Column:(S,S)Whelk-O1 250\*4.6mm,5um, Mobile phase: A: CO<sub>2</sub> B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C"), 97.1%ee.

To a THF (2 mL) under N<sub>2</sub> at -70°C was added n-BuLi (2.5 M, 1.54 mmol, 0.616 mL). After that, a suspension of **ST-200-095-005\_3** (300 mg, 0.618 mmol) in THF (2 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, a solution of (2R)-2-(2-fluorophenyl)oxirane (127 mg, 0.926 mmol) was added. The reaction was stirred at 25°C for 16 hours. The mixture was poured into ice-water (20 mL) and extracted with EtOAc (2

x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **ST-200-095-005\_4** (350 mg, crude) as a solid, which was used directly for the next step.

To a solution of **ST-200-095-005\_4** (350 mg, 0.561 mmol) and nickel (II) chloride (7 mg, 0.056 mmol) in MeOH (30 mL) was added Mg (294 mg, 11.2 mmol) was added at 25°C. The mixture was stirred at 50°C for 1 h. After cooling, the mixture was quenched with HCl (100 mL, 2M) until the reaction became clear and extracted with EtOAc (2 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered concentrated and purified by a silica gel column (PE/EtOAc = 10/1 to 3/1) to give **ST-200-095-006** (150 mg, 56%) as a solid.

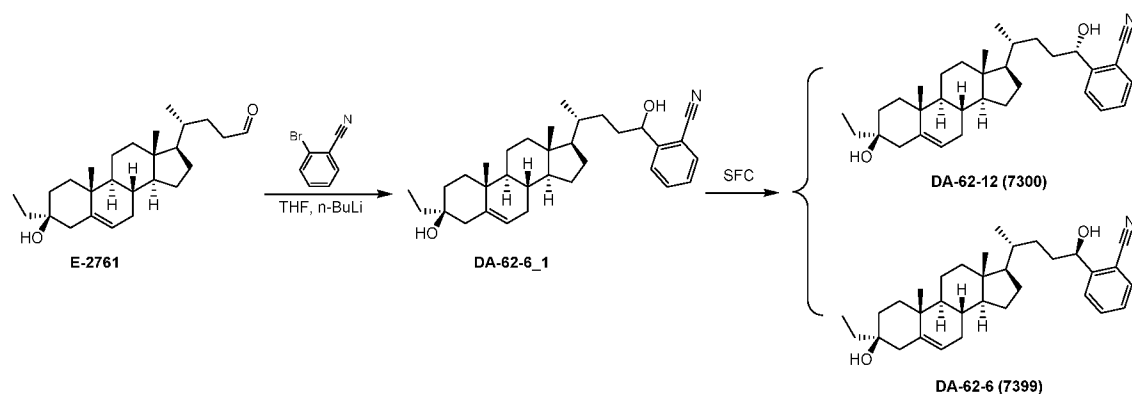
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.44 (t, *J* = 8 Hz, 1H), 7.25-7.21 (m, 1H), 7.15 (t, *J* = 8 Hz, 1H), 7.02 (t, *J* = 8 Hz, 1H), 5.28-5.26 (m, 1H), 5.00-4.90 (m, 1H), 2.39-2.32 (m, 1H), 2.04-1.86 (m, 4H), 1.84-1.60 (m, 7H), 1.55-1.32 (m, 9H), 1.29-0.99 (m, 10H), 0.96-0.90 (m, 4H), 0.84 (t, *J* = 8 Hz, 3H), 0.66 (s, 3H).

LCMS Rt = 1.290 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>32</sub>H<sub>44</sub>F [M-2H<sub>2</sub>O+H<sup>+</sup>] = 447, found 447.

SFC Rt = 5.494 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML ("Column: Chiralpak AD-3 150×4.6mm I.D., 3μm Mobile phase: A: CO<sub>2</sub> B: ethanol (0.05% DEA)

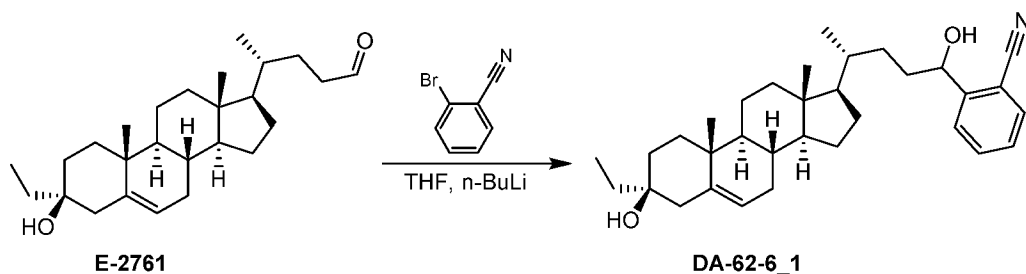
Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5 mL/min Column temp.: 35°C"), 98.86%de.

### EXAMPLE 73: Synthesis of 7300 and 7399



[00593] The stereochemistry has been randomly assigned. The experimental of intermediate **E-2761** can be found in Example 63.

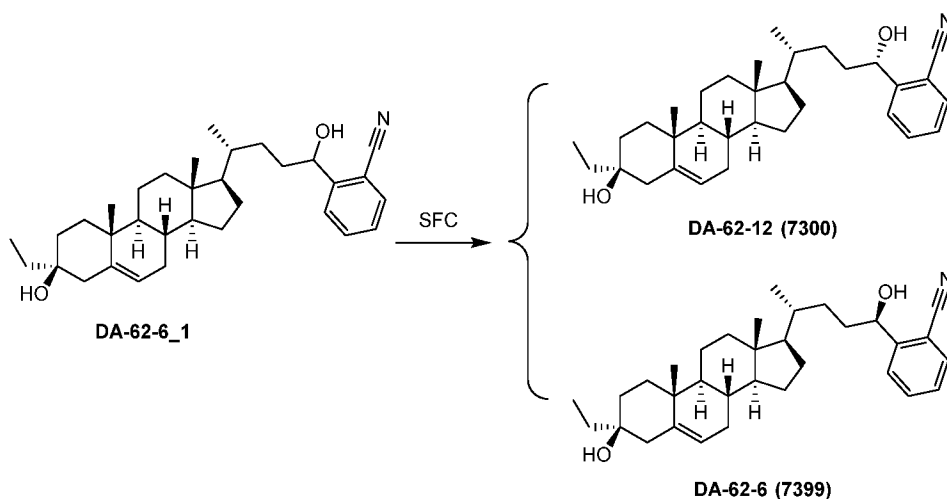
### [00594] Synthesis of DA-62-6\_1



n-BuLi (2.5 M, 3.09 mL) was added dropwise to a solution of 2-bromobenzonitrile (1.41 g, 7.75 mmol) in THF(10 mL) at -78°C under N<sub>2</sub>. The mixture was stirred at -78°C for 30 min. **E-2761** (600 mg, 1.55 mmol) in THF(10 mL) was added at -78°C under N<sub>2</sub>. The mixture was stirred at -78°C for 30 min and quenched with aqueous NH<sub>4</sub>Cl (30 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil, which was purified by flash column (0~20% of EtOAc in PE) to give **DA-62-6\_1** (300 mg, impure) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.90-7.80 (m, 1H), 7.60-7.40(m, 2H), 7.40-7.26 (m, 1H), 5.50-5.40(m, 1H), 5.30 (brs, 1H), 2.42-2.30 (m, 1H), 2.10-1.50 (m, 9H), 1.60-1.30 (m, 4H), 1.30-0.90(m, 20H), 0.90-0.75(m, 4H), 0.66(s, 3H).

**[00595] Synthesis of 7399 and 7300**



**DA-62-6\_1** (300 mg, 0.612 mmol) was purified by SFC (Column: AD (150×4.6mm, 3μm), Gradient: 5%-40% B ( A: CO<sub>2</sub> B: ethanol ) Flow rate: 2.5mL/min ) to afford **DA-62-6** (30.0 mg, impure) as a solid and **DA-62-12** (80 mg, impure) as solid. Impure **DA-62-6** (30 mg, 0.0612 mmol) was purified by SFC (Column: AS(250mm×30mm,5μm), Gradient: 25%-25% B ( A: CO<sub>2</sub> B: 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH) Flow rate: 60mL/min ) to afford **DA-62-6** (4 mg, 13%) as solid. Impure **DA-62-12** (80 mg, 0.163) was purified by SFC (Column: AS(250mm×30mm,5μm), Gradient: 25%-25% B ( A: CO<sub>2</sub> B: 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH) Flow rate: 60mL/min ) to afford an

impure solid, which was triturated from H<sub>2</sub>O (10 mL) at 90°C to give **DA-62-12** (3 mg, 4%) as a solid.

**7399:**

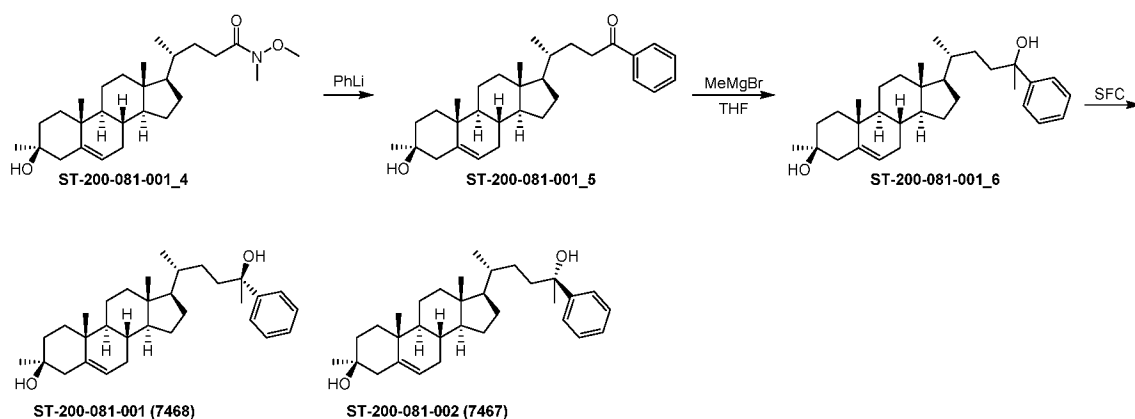
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.88-7.80 (m, 1H), 7.58-7.42 (m, 2H), 7.35-7.30 (m, 1H), 5.45-5.36 (m, 1H), 5.30-5.27 (m, 1H), 2.40-2.30 (m, 1H), 2.10-1.90 (m, 4H), 1.85-1.50 (m, 8H), 1.50-1.30 (m, 5H), 1.30-1.88 (m, 17H), 0.86-0.76 (m, 3H), 0.66 (s, 3H).

LCMS Rt = 0.908 min in 2.0 min chromatography, 30-90 AB, purity 95 %, MS ESI calcd. for C<sub>33</sub>H<sub>48</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 490, found 490.

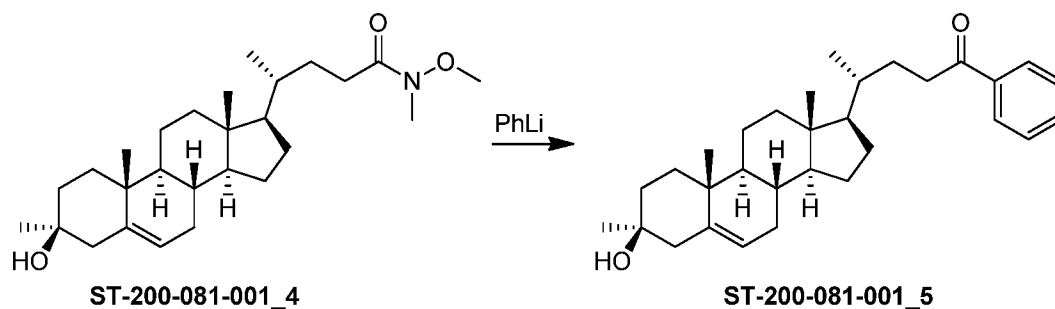
**7300:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.88-7.75 (m, 1H), 7.58-7.40 (m, 2H), 7.30-7.26 (m, 1H), 5.50-5.40 (m, 1H), 5.30-5.25 (m, 1H), 2.40-2.37 (m, 1H), 2.10-1.50 (m, 13H), 1.50-1.10 (m, 14H), 1.10-0.76 (m, 10H), 0.66 (s, 3H).

LCMS Rt = 0.923 min in 2.0 min chromatography, 30-90 AB, purity 94 %, MS ESI calcd. for C<sub>33</sub>H<sub>48</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 490, found 490.

**EXAMPLE 74: Synthesis of 7467 and 7468**

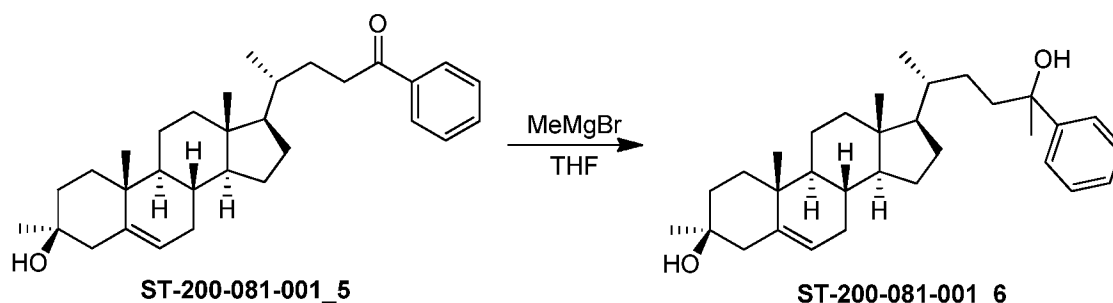
[00596] The stereochemistry was randomly assigned. The experimental of intermediate ST-200-081-001\_4 could be found in Example 127.

**[00597] Synthesis of ST-200-081-001\_5**

To a solution of **ST-200-081-001\_4** (1.3 g, 3.01 mmol) in THF (10 mL) was added PhLi (7.5 mL, 2 M in ether, 15 mmol) at 0°C under N<sub>2</sub> and the mixture was stirred at 25°C for 30 minutes. After quenching with saturated NH<sub>4</sub>Cl (40 mL), the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum to give **ST-200-081-001\_5** (1.6 g, crude) as a solid, which was used directly without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.01-7.93 (m, 2H), 7.63-7.29 (m, 7H), 5.34-5.27 (m, 1H), 3.08-2.83 (m, 2H), 2.47-2.38 (m, 1H), 2.01-1.67 (m, 7H), 1.52-1.14 (m, 11H), 1.11 (s, 3H), 1.03-0.97 (m, 7H), 0.69 (s, 3H).

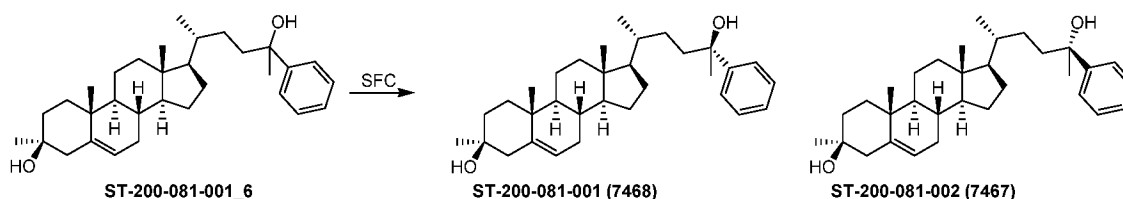
#### 10 [00598] Synthesis of ST-200-081-001\_6



To a solution of **ST-200-081-001\_5** (1.6 g, 3.56 mmol) in THF (10 mL) was added MeLi (11.1 mL, 2 M in ether, 17.8 mmol) at 0°C under N<sub>2</sub> and the mixture was stirred at 25°C for 30 minutes. The reaction mixture was quenched by saturated NH<sub>4</sub>Cl (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with brine (60 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered, concentrated in vacuum and purified by flash column (0~30% of EtOAc in PE) to give **ST-200-081-001\_6** (1 g, 57%) as a solid.

LCMS Rt = 1.374 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

#### 20 [00599] Synthesis of 7467 and 7468



**ST-200-081-001\_6** (1 g, 2.15 mmol) was purified by SFC (column: AD(250mm\*30mm,5um)), gradient: 40-40% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O, B= EtOH ), flow rate: 60 mL/min) to give impure **ST-200-081-001** (Peak 1, 390 mg, 39%) and impure **ST-200-081-002** (Peak 2, 220 mg, 22%) as a solid. To a solution of impure **ST-200-081-001** (390 mg) in THF (15 mL) was added Pd(OH)<sub>2</sub>/C (wet, 300 mg) and the mixture was degassed and back-filled with H<sub>2</sub> for 3 times. After that, the

reaction was stirred at 15°C under 15 psi of H<sub>2</sub> for 4 h. The reaction mixture was filtered through a pad of celite washed with THF (100 mL). The filtrate was concentrated and purified by SFC (column: AD (250mm\*30mm,5um)), gradient: 40-40% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O, B= EtOH ), flow rate: 60 mL/min) to give **ST-200-081-001** (270 mg, 71%) as a solid. Impure **ST-200-081-002** was triturated in boiling MeCN (200 mL) concentrated in vacuum to give **ST-200-081-002** (208 mg, 94%) as a solid.

**ST-200-081-001 (7468):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.46-7.39 (m, 2H), 7.37-7.29 (m, 2H), 7.26-7.21 (m, 1H), 5.33-5.26 (m, 1H), 2.46-2.37 (m, 1H), 2.01-1.64 (m, 9H), 1.56-1.53 (m, 5H), 1.52-1.12 (m, 10H), 1.10 (s, 3H), 1.09-1.01 (m, 3H), 0.99 (s, 3H), 0.97-0.86 (m, 5H), 0.62 (s, 3H).

LCMS Rt = 1.359 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

SFC Rt = 5.916 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 100%de.

**ST-200-081-002 (6467):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45-7.39 (m, 2H), 7.36-7.31 (m, 2H), 7.25-7.19 (m, 1H), 5.33-5.26 (m, 1H), 2.47-2.37 (m, 1H), 2.01-1.57 (m, 10H), 1.55-1.31 (m, 12H), 1.21-1.12 (m, 2H), 1.10 (s, 3H), 1.08-1.02 (m, 2H), 0.99 (s, 3H), 0.98-0.85 (m, 6H), 0.63 (s, 3H).

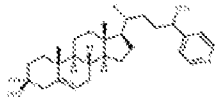
LCMS Rt = 1.367 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 429, found 429.

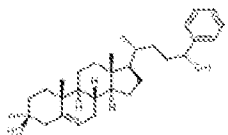
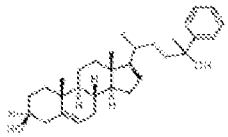
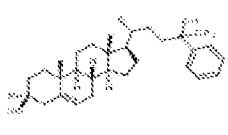
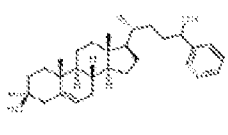
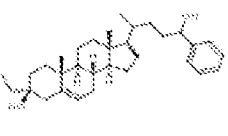
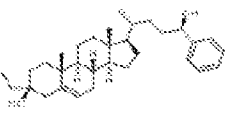
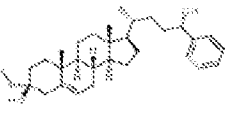
SFC Rt = 6.397 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 97.26%de.

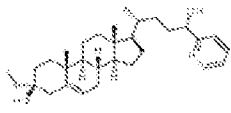
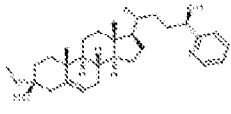
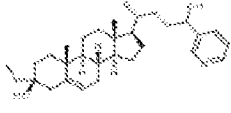
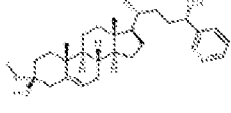
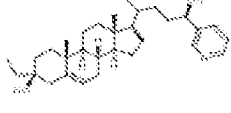
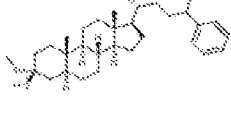
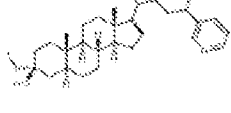
**EXAMPLE 74B. Biological data**

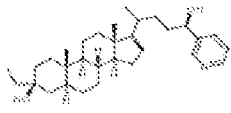
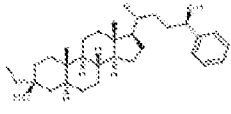
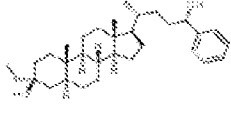
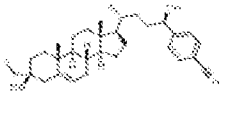
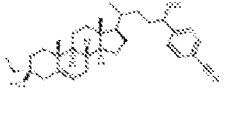
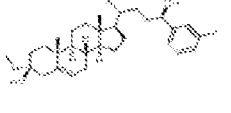

[00600] The Experiments were conducted as described in Example 2 and the results are reported in Table 2-66..

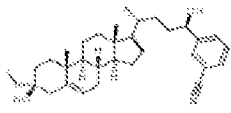
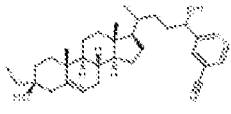
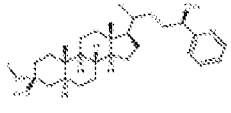
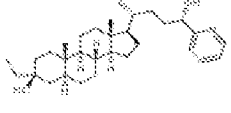
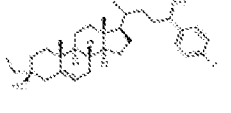
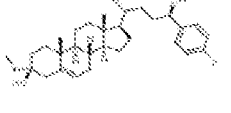
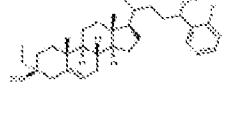
**Table 2-66**



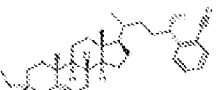
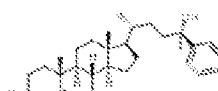
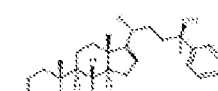

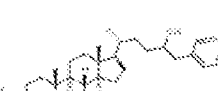
	Compound	Avg EC50 2A (nM)	Avg Emax 2A (%)	Avg EC50 2B (nM)	Avg Emax 2B (%)
	154	>10000	18.2	>10000	56.8

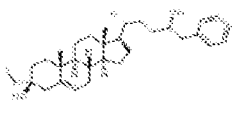
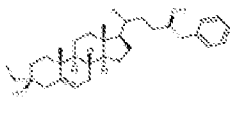
	356	414.6	59.6	923.4	156.3
	456	6710.0	53.4	6746.8	74.8
	559	1571.3	204.3	1564.3	373.2
	255	646.4	159.4	153.0	131.8
	761	475.9	301.6	249.1	197.3
	861	199.6	183.1	246.9	389.8
	961	616.7	138.5	179.8	97.4

	6347	268.3	64.7	310.7	131.9
	6348	259.61	79.65	663.21	132.91
	6457	731.9	198.3	523.6	168.1
	6458	>10000	30.9	928.9	79.4
	6459	1327.1	156.2	909.0	184.2
	6544	558.8	253.2	497.7	414.6
	6754	>10000	22.3	>10000	38.8

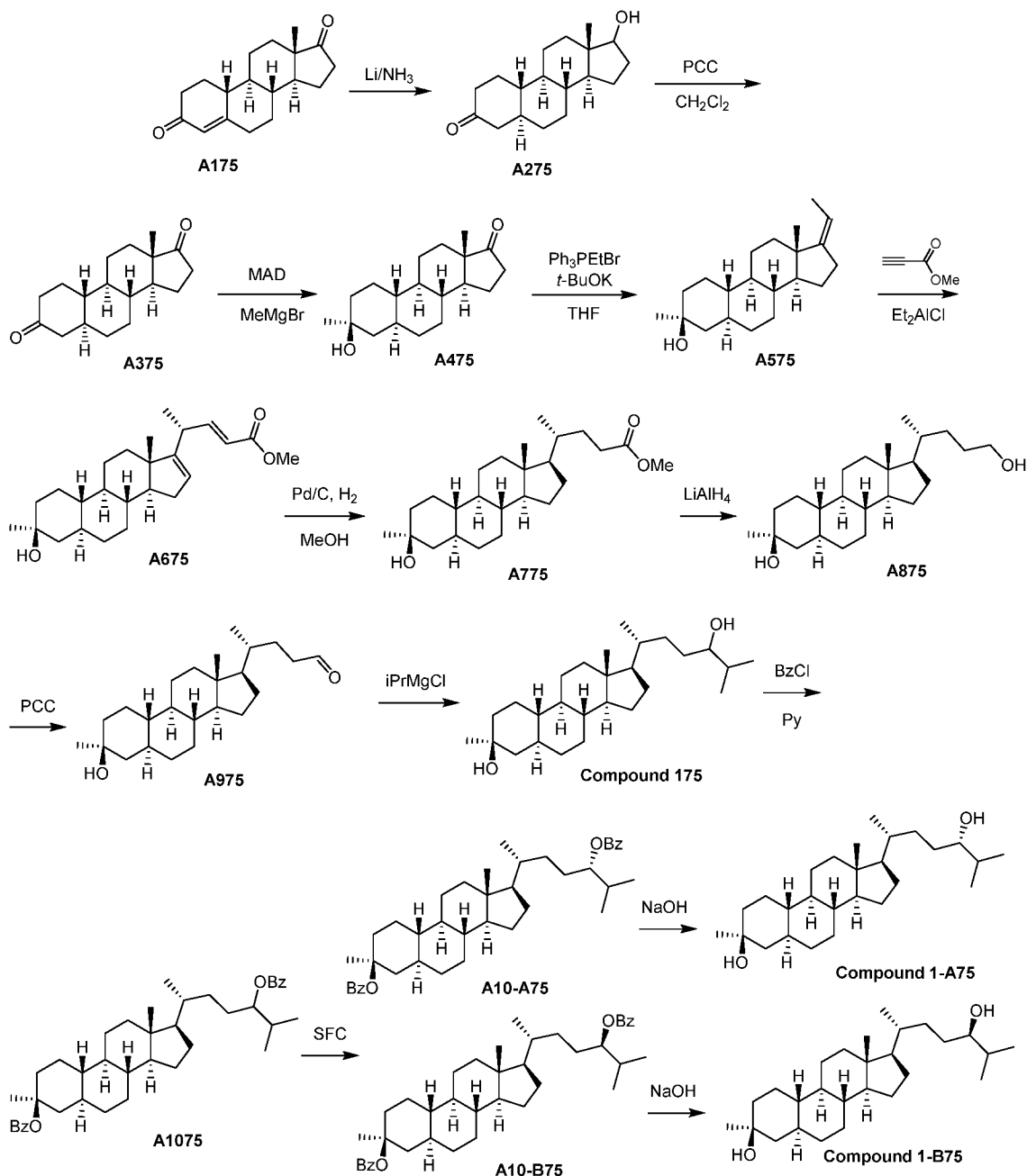
	6755	>10000	22.8	>10000	44.2
	6571	189.8	157.5	266.6	241.0
	6572	378.5	128.9	1341.5	250.6
	6680	1370.7	175.4	464.4	123.4
	6681	365.3	171.6	359.9	165.3
	6895	174.1	240.9	328.8	354.3
	6896	518.9	215.9	1676.0	402.2

	6997	373.4	327.2	414.3	314.7
	6998	357.6	337.9	304.3	303.4
	7030	>10000	28.3	>10000	74.7
	7032	>10000	28.3	874.3	63.8
	7146	119.8	103.7	215.9	167.4
	7147	147.0	200.5	91.7	241.5
	7281	248.37	98.1	302.7	125.7

	7282	95.9	208.3	173.7	289.7
	7399	696.1	150.1	1581.2	179.5
	7300	>10000	37.5	>10000	46.9
	7467	>10000	20.5	>10000	8.8
	7468	61.4	273.4	54.2	317.4
	660	700.6	195.2	516.8	281.1
	6010	1104.9	238.7	1573.5	184.0

	6051	500.2	292.7	1262.1	292.4
	6052	425.9	101.8	232.3	92.2

**EXAMPLE 75: Syntheses of Compounds 175, 1A75, and 1B75.**



**Step 1.** To freshly prepared liquid ammonia (1.0 L) was added lithium (12.7 g, 1.82 mol) in portions at  $-70^\circ\text{C}$ . The mixture became deep blue. After stirring at  $-70^\circ\text{C}$  for 1 h, a solution of **A175** (50 g, 183 mmol) and t-butanol (26.9 g, 364 mmol) in dry THF (600 mL) was added to this mixture with strong stirring, and the temperature was maintained below  $-60^\circ\text{C}$ . The resultant mixture was stirred at  $-70^\circ\text{C}$  for 2 hrs. Ammonium chloride (150 g) was added to reaction mixture. The mixture was warmed to  $25^\circ\text{C}$  and stirred for 16 hrs. The reaction mixture was neutralized with aq.  $\text{HCl}$  (2.5 M, 1000 mL) and filtered. The filtrate was extracted with  $\text{EtOAc}$

(1 Lx2), washed with brine (1 L), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford **A2** (45 g, crude) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.65-3.57 (m, 1H), 2.06-1.66 (m, 5H), 1.43-0.75 (m, 16H), 0.74 (s, 3H), 0.73-0.59 (m, 3H).

5 **Step 2.** To a solution of **A275** (43 g, 155 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (600mL) was added silica gel (75 g, w/w=1/1.5) and pyridinium chlorochromate (52.3 g, 243 mmol) at 25°C. The mixture was stirred at 25°C for 2 hrs. The mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography on silica gel (PE/EtOAc=20/1 to 5/1) to afford **A375** (22.0 g, 50%) as a solid.

10 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.52-2.38 (m, 2H), 2.38-2.28 (m, 3H), 2.15-2.05 (m, 2H), 2.05-1.65 (m, 5H), 1.55-1.40 (m, 2H), 1.40-1.15 (m, 6H), 1.15-0.92 (m, 1H), 0.90 (s, 3H), 0.89-0.80 (m, 1H), 0.80-0.65 (m, 1H).

**Step 3.** To a solution of BHT (48 g, 218 mmol) in toluene (120 mL) was added AlMe<sub>3</sub> (2 M in toluene, 120 mL, 218 mmol) at 0°C and stirred at 10°C for 1 h. To the MAD solution (109 mmol in 120 mL toluene) was added a solution of **A375** (10 g, 36.4 mmol) in DCM (30 mL) at -78°C. After stirring at -78°C for 1 h, MeMgBr (36.3 mL, 109 mmol) was added at -78°C. The mixture was stirred at -78°C for 20 mins. The reaction mixture was treated with saturated citric acid (50 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (80 mL). The organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a crude product, which was purified by flash column (0~30% of EtOAc in PE) to give **A476** (6 g, 57%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.50-2.45 (m, 1H), 2.13-1.96 (m, 1H), 1.95-1.70 (m, 6H), 1.70-1.60 (m, 2H), 1.58-1.45 (m, 1H), 1.45-0.95 (m, 13H), 0.95-0.83 (m, 4H), 0.80-0.65 (m, 2H).

**Step 4.** To a suspension of PPh<sub>3</sub>EtBr (22.9 g, 61.8 mmol) in THF (30 mL) was added t-BuOK (6.93 g, 61.8 mmol) at 20°C. After stirring at 40°C for 30 min, a solution of **A475** (6 g, 20.6 mmol) in THF (20 mL) was added at 40°C and the reaction mixture was stirred at 40°C for 1 h. The reaction mixture was poured into 50 g of crushed ice and stirred for 15 minutes. The organic layer was separated and the water phase was extracted with EtOAc (30 mL). The combined organic phase was concentrated *in vacuo* to give a thick oil. The residue was dissolved in 90 mL of MeOH at 60°C, following by treating with 90 mL of water. A precipitate formed. After stirring at 60°C for 1h, the precipitate was collected by filtration and washed with a solution of MeOH/water (15mL/15mL) and dried under vacuum to give the product **A575** as a solid.

30 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.18-5.06 (m, 1H), 2.42-2.29 (m, 1H), 2.29-2.10 (m, 2H), 1.95-1.84 (m, 1H), 1.84-1.46 (m, 10H), 1.46-1.25 (m, 2H), 1.25-1.05 (m, 10H), 1.05-0.80 (m, 5H), 0.75-0.60 (m, 2H).

**Step 5.** To a solution of **A575** (4.8 g, 3.30 mmol) and methyl propiolate (4.21 mL, 47.4 mmol) in anhydrous dichloromethane (100 mL) under N<sub>2</sub> at 0°C was added dropwise diethylaluminum chloride (1.0 M in toluene, 63.2 mL, 63.2 mmol). The mixture was stirred at 20°C for 16 hours. The reaction mixture was quenched with aqueous citric acid (100 mL) at 0°C carefully, and the inner temperature was maintained below 10°C. The resultant mixture was filtered through a pad of celite and extracted with DCM (2 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give crude **A675** as a solid. Combined with another batch, the crude product was purified by flash column (0~30% of EtOAc in PE) to give 6 g of impure product as a solid. The solid was recrystallized from DCM/PE (20 mL/80 mL) to give 3.1 g of pure product as a solid. The mother liquid was concentrated to give 2.8 g of the product as a solid. A total of 5.9 g of the product was obtained (79% yield).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.96 (dd, *J* = 8.0, 15.6 Hz, 1H), 5.83 (dd, *J* = 0.8, 15.6 Hz, 1H), 5.45-5.38 (m, 1H), 3.75 (s, 3H), 3.10-2.96 (m, 1H), 2.10-2.03 (m, 1H), 1.95-1.55 (m, 9H), 1.45-0.85 (m, 18H), 0.80-0.60 (m, 3H).

**Step 6.** To a solution of **A675** (3 g, 7.76 mmol) in EtOAc (100 mL) was added Pd/C (100 mg, 10%, wet) and the mixture was degassed and back-filled with H<sub>2</sub> for 3 times. The reaction was stirred at 15°C under 15 psi of H<sub>2</sub> for 16 hrs. The reaction mixture was filtered through a pad of celite washed with EtOAc (20 mL). The filtrate was concentrated to give 3 g of **A775** as an oil, which was used directly for the next step.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.66 (s, 3H), 2.43-2.30 (m, 1H), 2.30-2.15 (m, 1H), 1.95-1.50 (m, 10H), 1.50-0.96 (m, 17H), 0.96-0.80 (m, 5H), 0.75-.050 (m, 5H).

**Step 7.** To a solution of **A775** (3 g, 7.68 mmol) in THF (100 mL) was added LiAlH<sub>4</sub> (580 mg, 15.3 mmol) at 0°C under N<sub>2</sub>. After stirring at this temperature for 1 h, the reaction mixture was treated with water (2 mL) and then the pH was adjusted to 1-2 with saturated citric acid. The water phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 2.5 g of crude **A875**, which was used directly for the next step.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.70-3.50 (m, 2H), 2.00-1.78 (m, 3H), 1.78-1.52 (m, 8H), 1.52-1.30 (m, 4H), 1.30-0.98 (m, 15H), 0.98-0.80 (m, 5H), 0.75-0.55 (m, 5H).

**Step 8.** To a solution of **A875** (2.5 g, 6.89 mmol) in DCM (200 mL) was added PCC (2.94 g, 13.7 mmol) and silica gel (5 g). After stirring at 20°C for 2 h, the reaction was filtered through a pad of celite washed with DCM (2 x 20 mL). The filtrate was concentrated to give 3 g of crude mixture, which was purified by flash column (0~30% of EtOAc in PE) to give 1.5 g of the product as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.76 (t, *J* = 1.2 Hz, 1H), 2.53-2.28 (m, 2H), 2.00-1.50 (m, 12H), 1.50-0.98 (m, 13H), 0.98-0.80 (m, 6H), 0.75-0.55 (m, 6H).

**Step 9.** To a solution of **A975** (1.5 g, 4.16 mmol) in THF (100 mL) was added iPrMgCl (6.20 mL, 12.4 mmol) at 0°C. The reaction was stirred at this temperature for 1 h and quenched by adding water (50 mL) and saturated citric acid solution (100 mL). The mixture was then extracted with EtOAc (2 x 100 mL). The organic layers were combined and washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrate. The crude residue was purified by flash column (0~20% of EtOAc in DCM) to 1.4 g of the product as a solid. **Compound 175** (1.3 g) was triturated with MeCN (50 mL) at 80°C to give **175** (350 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.38-3.25 (m, 1H), 1.98-1.92 (m, 1H), 1.92-1.76 (m, 2H), 1.76-1.50 (m, 9H), 1.50-1.40 (m, 4H), 1.40-0.97 (m, 14H), 0.97-0.80 (m, 12H), 0.73-0.53 (m, 5H). LCMS Rt = 1.309 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 369, found 369.

**Step 10.** To a solution of **175** (700 mg, 1.72 mmol) in pyridine (5 mL) was added BzCl (723 mg, 5.15 mmol) at 0°C and the reaction was stirred at 20°C for 18 h to give a solution. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (2 x 20 mL). The organic layer was washed with brine (5 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash column (0~10% of EtOAc in PE) to give 920 mg of an oil. The crude product was separated by SFC (AD(250mm\*30mm,5um)), 0.1% NH<sub>3</sub>H<sub>2</sub>O-EtOH to give 280 mg of peak 1 as **A10-A75** as a solid and 285 mg of peak 2 as **A10-B75** as a solid.

**A10-A75:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 8.4Hz, 2H), 8.01 (d, *J* = 8.4Hz, 2H), 7.58-7.48 (m, 2H), 7.48-7.36 (m, 4H), 5.00-4.90 (m, 1H), 2.40-2.30 (m, 1H), 2.30-2.20 (m, 1H), 2.00-1.85 (m, 3H), 1.80-1.30 (m, 13H), 1.30-0.88 (m, 22H), 0.88-0.70 (m, 1H), 0.70-0.50 (m, 4H).

**A10-B75:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 8.4Hz, 2H), 8.01 (d, *J* = 8.4Hz, 2H), 7.58-7.48 (m, 2H), 7.48-7.36 (m, 4H), 5.00-4.92 (m, 1H), 2.47-2.28 (m, 1H), 2.28-2.20 (m, 1H), 2.00-1.85 (m, 3H), 1.80-1.45 (m, 13H), 1.30-0.85 (m, 22H), 0.85-0.70 (m, 1H), 0.70-0.50 (m, 4H).

**Step 11.** To a solution of **A10-A** (280 mg, 0.46 mmol) in THF (5 mL) and MeOH (5 mL) was added NaOH (200 mg, 5.00 mmol) and H<sub>2</sub>O (2 mL) at 25°C. Then the solution was stirred at 50°C for 16 h. The reaction solution was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 3:1) to give a solid, which was then triturated in hot MeCN (5 mL) to give the desired product **Compound 1-A75** (102 mg, 55%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.38-3.25 (m, 1H), 1.98-1.92 (m, 1H), 1.92-1.76 (m, 2H), 1.76-1.50 (m, 9H), 1.50-1.40 (m, 2H), 1.40-0.97 (m, 17H), 0.97-0.80 (m, 11H), 0.73-0.55 (m, 5H).

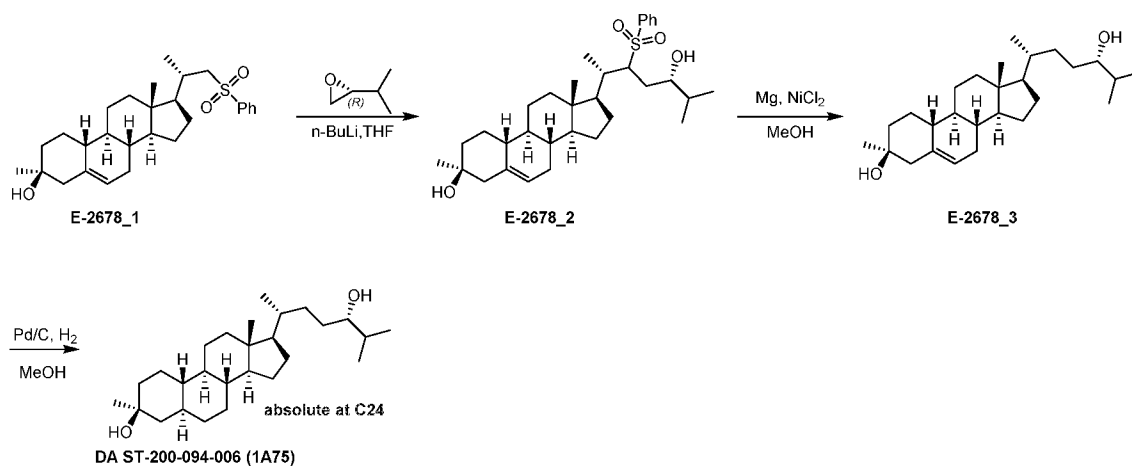
**LCMS** Rt = 1.323 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 369, found 369.

**Step 12.** To a solution of **A10-B75** (285 mg, 0.47 mmol) in THF (5 mL) and MeOH (5 mL) was added NaOH (200 mg, 5.00 mmol) and H<sub>2</sub>O (2 mL) at 25°C. Then the solution was stirred at 50°C for 16 h. The reaction solution was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 3:1) to give a solid, which was then triturated in hot MeCN (2 x 1 mL) to give desired product **Compound 1-B75** (18 mg, 10%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.38-3.25 (m, 1H), 1.98-1.92 (m, 1H), 1.92-1.77 (m, 2H), 1.77-1.50 (m, 4H), 1.50-1.30 (m, 6H), 1.30-0.97 (m, 17H), 0.97-0.80 (m, 12H), 0.73-0.55 (m, 5H).

**LCMS** Rt = 1.320 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 369, found 369.

[00601] Synthesis of 1A75 to confirm stereochemistry.



To THF (0.5 mL) under N<sub>2</sub> at -70°C was added  $n\text{-BuLi}$  (2.5 M, 2.18 mmol, 0.872 mL). After that, a suspension of **E-2678\_1** (400 mg, 0.875 mmol) in THF (3 mL) was added drop-wise to give a suspension. After stirring at -70°C for 30 min, a solution of (2R)-2-(propan-2-yl)oxirane (112 mg, 1.31 mmol) in THF (0.5 mL) was added. Then reaction was stirred at 25°C for 16 hours. The mixture was poured into ice-water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **E-2678\_2** (380 mg, crude) as a solid, which was used directly in the next step.

To a solution of **E-2678\_2** (380 mg, 0.7 mmol) and nickel (II) chloride (4.53 mg, 0.035 mmol) in MeOH (30 mL) was added Mg powder (336 mg, 14 mmol) was added at 25°C. The mixture was stirred at 50°C for 1 h. After cooling, the mixture was quenched with HCl (100 mL, 2M) until the reaction became clear and extracted with EtOAc (2 x 50 mL). The combined organic

phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered concentrated and purified by a silica gel column (PE/EtOAc = 10/1 to 3/1) to give **E-2678\_3** (140 mg, 50%) as a solid.

The **E-2678\_3** (140 mg, 0.347 mmol) was separated by SFC (column: AD (250mm\*30mm, 5 $\mu$ m)), gradient: 40-40% B (A= 0.1% $\text{NH}_3\text{H}_2\text{O}$  ETOH), flow rate: 50 mL/min) to give **E-2678\_3** (95 mg, 34%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  5.42-5.38 (m, 1H), 3.35-3.26 (m, 1H), 2.20-2.14 (m, 1H), 2.10-1.89 (m, 4H), 1.87-1.59 (m, 6H), 1.54-1.16 (m, 12H), 1.13-0.97 (m, 7H), 0.95-0.75 (m, 11H), 0.68 (s, 3H).

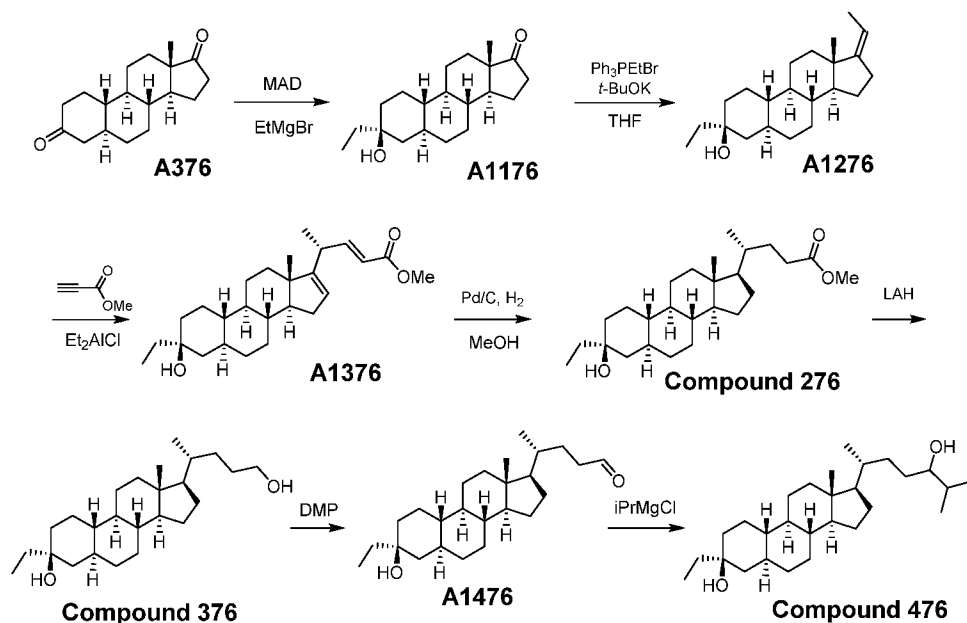
SFC Rt = 5.305 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 98.5%de.

To a solution of **E-2678\_3** (95 mg, 0.235 mmol) in MeOH (10 mL) was added Pd/C (0.1 g, <1% water). Then the solution was hydrogenated under 50 psi of hydrogen at 50°C for 16 hrs. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuum. The residue was purified by combi-flash (0-15% of EtOAc in PE) to afford **DA ST-200-094-006** (23 mg, 24%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.35-3.28 (m, 1H), 1.99-1.62 (m, 7H), 1.55-1.33 (m, 7H), 1.31-1.20 (m, 7H), 1.17-0.97 (m, 10H), 0.93-0.75 (m, 11H), 0.73-0.65 (m, 5H).

LCMS Rt = 1.269 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For  $\text{C}_{27}\text{H}_{45}$  [M-2 $\text{H}_2\text{O}$ +H] = 369, found 369.

## EXAMPLE 76. Syntheses of Compounds 276, 376, and 476.



**Step 1.** To a solution of BHT (41.9 g, 190.58 mmol) in toluene (100 mL) under  $\text{N}_2$  at 0°C was added  $\text{AlMe}_3$  (47.6 mL, 2 M in toluene, 95.2 mmol) drop-wise. The mixture was stirred at 25°C

for 1 h. To the mixture was added a solution of **A376** (9.21 g, 33.6 mmol) in DCM (30 mL) at -78°C. After stirring at -78°C for 1 h, EtMgBr (33.3 mL, 100 mmol) was added at -78°C. The mixture was stirred at -78°C for 1.5 h. The reaction mixture was treated with saturated citric acid (50 mL). The organic phase was separated, extracted with EtOAc (80 mL). The organic phase  
5 was washed with brine (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give **A1176** (5.2 g, 51%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.47-2.40 (m, 1H), 2.11-2.00 (m, 1H), 1.96-1.77 (m, 6H), 1.69-1.63 (m, 2H), 1.58-1.50 (m, 3H), 1.38-1.20 (m, 6H), 1.56-0.97 (m, 5H), 0.90-0.87 (m, 6H), 0.80-0.64 (m, 2H).

**Step 2.** To a suspension of PPh<sub>3</sub>EtBr (18.2 g, 49.1 mmol) in THF (20 mL) was added *t*-BuOK (5.50 g, 49.1 mmol) at 20°C. After stirring at 40°C for 30 mins, a solution of **A1176** (5 g, 16.4 mmol) in THF (20 mL) was added at 40°C and the reaction mixture was stirred at 40°C for 1 h. The reaction mixture was poured into 50 g of crushed ice and stirred for 15 minutes. The organic layer was separated and the water phase was extracted with EtOAc (30 mL). The combined  
15 organic phase was concentrated in vacuum to give thick oil. The residue was dissolved in 90 mL of MeOH at 60°C, following by treating with 90 mL of water and a large amount of a precipitate appeared. After stirring at 60°C for 1 h, the precipitate was collected by filtration and washed with a solution of MeOH/water (15 mL/15 mL), dried in vacuum to give **A1276** (5.0 g, 96%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.14-5.09 (m, 1H), 2.39-2.33 (m, 1H), 2.25-2.14 (m, 2H), 1.87-1.75 (m, 3H), 1.66-1.63 (m, 5H), 1.58-1.54 (m, 5H), 1.34-1.25 (m, 2H), 1.19-1.03 (m, 7H), 0.90-0.84 (m, 8H), 0.73-0.64 (m, 2H).

**Step 3.** To a solution of **A1276** (4.5 g, 14.2 mmol) and methyl propiolate (3.78 mL, 42.6 mmol) in anhydrous dichloromethane (100 mL) under N<sub>2</sub> at 0°C was added dropwise Et<sub>2</sub>AlCl (1.0 M in toluene, 56.8 mL, 56.8 mmol). The mixture was stirred at 20°C for 16 hrs. The reaction mixture was quenched with aqueous saturated citric acid (100 mL) at 0°C carefully, and the inner temperature was maintained below 10°C. The resultant mixture was filtered through a pad of celite and washed with DCM (2 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give impure **A1376** as a solid. The crude  
25 product was combined with another batch of impure product from 0.5 g of **A1276**, purified by flash column (0~30% of EtOAc in PE) to give **A1376** (6 g, 95%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.93 (dd, *J* = 8.0, 15.6 Hz, 1H), 5.80 (dd, *J* = 1.2, 15.2 Hz, 1H), 5.39-5.39 (m, 1H), 3.73 (s, 3H), 3.02-2.97 (m, 1H), 2.07-2.01 (m, 1H), 1.85-1.52 (m, 8H), 1.35-0.96 (m, 10H), 0.90-0.84 (m, 8H), 0.76-0.66 (m, 6H).

**Step 4.** To a solution of **A1376** (6 g, 14.9 mmol) in EtOAc (100 mL) was added Pd/C (1 g, 10%, wet) and the mixture was degassed with H<sub>2</sub> for 3 times. After that, the reaction was stirred at 15°C under 15 psi of H<sub>2</sub> for 16 hrs. The reaction mixture was filtered through a pad of celite and washed with EtOAc (30 mL). The filtrate was concentrated to give **Compound 276** (5.8 g, 96%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.66 (s, 3H), 2.39-2.31 (m, 1H), 2.25-2.17 (m, 1H), 1.95-1.92 (m, 1H), 1.85-1.78 (m, 4H), 1.68-1.61 (m, 3H), 1.57-1.52 (m, 5H), 1.42-1.40 (m, 2H), 1.35-1.26 (m, 3H), 1.15-1.02 (m, 8H), 0.92-0.82 (m, 8H), 0.81-0.79 (m, 1H), 0.72-0.59 (m, 4H). LCMS R<sub>t</sub> = 1.334 min in 2 min chromatography, 30-90AB, MS ESI calcd. For C<sub>26</sub>H<sub>43</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 387, found 387.

**Step 5.** To a solution of **Compound 276** (also **175 in Example 75**) (200 mg, 0.494 mmol) in THF (40 mL) was added LAH (56.1 mg, 1.48 mmol) at 0°C under N<sub>2</sub>. After stirring at this temperature for 1 h, the reaction mixture was treated with water (2 mL), adjusted to pH = 1-2 with saturated citric acid. The water phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **Compound 376** (120 mg, 65%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.63-3.60 (m, 2H), 1.96-1.93 (m, 1H), 1.85-1.78 (m, 3H), 1.68-1.52 (m, 10H), 1.48-1.38 (m, 3H), 1.34-1.25 (m, 4H), 1.13-1.07 (m, 9H), 0.93-0.83 (m, 8H), 0.73-0.59 (m, 4H).

LCMS R<sub>t</sub> = 3.826 min in 2 min chromatography, 30-90AB, MS ESI calcd. For C<sub>25</sub>H<sub>43</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 359, found 359.

**Step 6.** To a suspension of DMP (2.24 g, 5.30 mmol) in DCM (18 mL) was added a solution of **Compound 376** (1 g, 2.65 mmol) in DCM (10 mL) at 20°C. The reaction was stirred for 1 h at 20°C. The mixture was quenched with saturated NaHCO<sub>3</sub> aqueous (20 mL) at 20°C. The mixture was filtered and the organic layers were separated and the aqueous was extracted with DCM (2 x 20 mL). The combined phase was washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous (50 mL), brine (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give the crude product, which was purified by flash column (0~30% of EtOAc in PE) to give **A1476** (920 mg, 93%) as a solid.

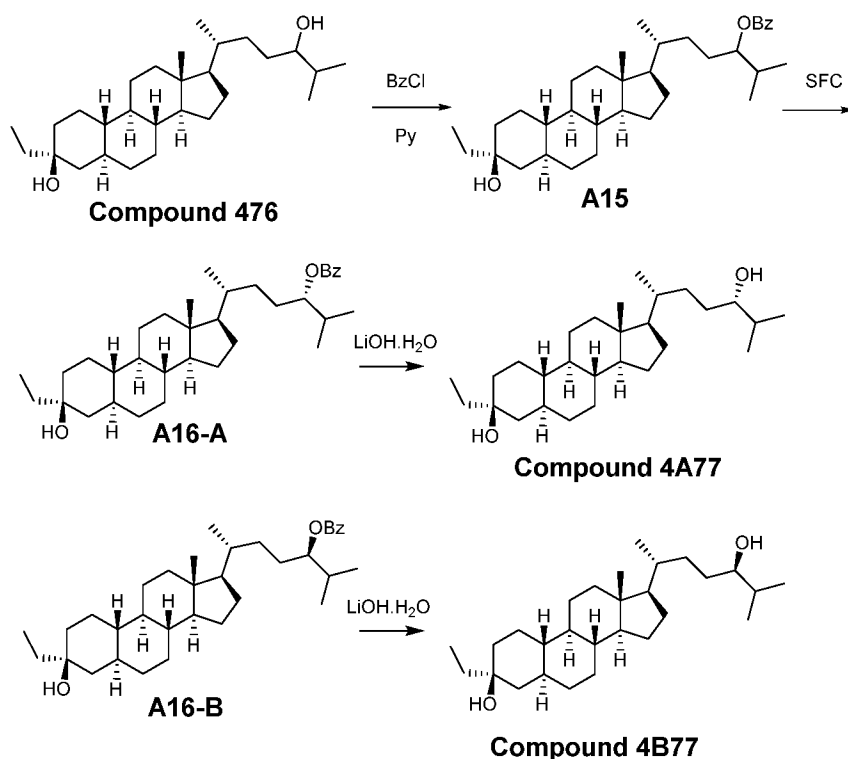
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.76 (s, 1H), 2.47-2.41 (m, 1H), 2.40-2.32 (m, 1H), 1.97-1.92 (m, 1H), 1.86-1.78 (m, 3H), 1.68-1.52 (m, 6H), 1.44-1.41 (m, 1H), 1.35-1.22 (m, 6H), 1.12-1.03 (m, 8H), 0.92-0.79 (m, 10H), 0.78-0.57 (m, 4H).

**Step 7.** To a solution of **A1476** (910 mg, 2.42 mmol) in THF (60 mL) was added *i*PrMgCl (12.1 mL, 24.2 mmol) at 0°C. The reaction was stirred at this temperature for 1 h. The reaction was quenched by adding water (30 mL) and saturated citric acid solution (30 mL). The mixture was

extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrate to give an oil, which was purified by silica gel column (PE : EtOAc = 50:1 to 4:1) to give **Compound 476** (900 mg, 89%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.32-3.30 (m, 1H), 1.96-1.93 (m, 1H), 1.85-1.78 (m, 3H), 1.68-1.52 (m, 12H), 1.43-1.02 (m, 16H), 0.93-0.83 (m, 13H), 0.70-0.61 (m, 4H). **LCMS** R<sub>t</sub> = 1.371 min in 2 min chromatography, 30-90AB, MS ESI calcd. For C<sub>28</sub>H<sub>47</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 383, found 383.

#### Example 77. Syntheses of Compounds 4A77 and 4B77.



**Step 1.** To a solution of **Compound 476** (800 mg, 1.91 mmol) in pyridine (20 mL) was added BzCl (402 mg, 2.86 mmol) at 0°C and the reaction was stirred at 20°C for 18 h. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 x 40 mL). The organic layer was washed with brine (5 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude was purified by silica gel column (PE/EtOAc = 50/1 to 4/1) to give **A15** (600 mg, 60%) as an oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 5.00-4.92 (m, 1H), 2.05-1.20 (m, 13H), 1.20-0.75 (m, 30H), 0.75-0.50 (m, 5H).

**A15** was purified by SFC (column: AD (250mm\*30mm, 5μm)), gradient: 40-40% B (A= NH<sub>3</sub>/H<sub>2</sub>O, B= MeOH), flow rate: 60mL/min) to give **A16-A** (116 mg, 19.4%) and impure **A16-B** (230 mg).

**A16-A:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (d,  $J = 8.0$  Hz, 2H), 7.55 (t,  $J = 7.2$  Hz, 1H), 7.45 (d,  $J = 8.0$  Hz, 2H), 5.00-4.92 (m, 1H), 2.05-1.83 (m, 2H), 1.83-1.20 (m, 11H) 1.20-0.75 (m, 30H), 0.75-0.50 (m, 5H).

**A16-B:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.04 (d,  $J = 8$  Hz, 2H), 7.55 (t,  $J = 7.2$  Hz, 1H), 7.45 (d,  $J = 8.0$  Hz, 2H), 5.00-4.92 (m, 1H), 2.05-1.42 (m, 15H), 1.40-1.15 (m, 4H) 1.14-0.75 (m, 24H), 0.73-0.50 (m, 5H).

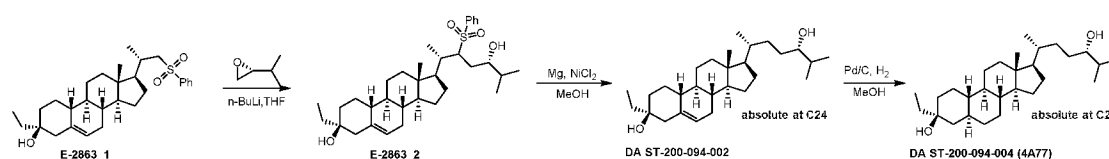
**Step 2.** To a solution of **A16-A** (116 mg, 221  $\mu\text{mol}$ ) in THF (2 mL) and MeOH (2 mL) was added LiOH (52.6 mg, 2.20 mmol) and  $\text{H}_2\text{O}$  (1 mL) at  $25^\circ\text{C}$ . Then the solution was stirred at  $50^\circ\text{C}$  for 24 h. The reaction solution was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give crude product (91 mg), which was purified by flash column (0~5% of acetone in DCM,  $25^\circ\text{C}$ ) to give **Compound 4A77** (45 mg, 50%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.33-3.31 (m, 1H), 1.96-1.85 (m, 1H), 1.84-1.77 (m, 3H), 1.68-1.62 (m, 5H), 1.56-1.52 (m, 5H), 1.44-1.33 (m, 4H), 1.31-1.17 (m, 5H), 1.14-0.99 (m, 8H), 0.92-0.79 (m, 13H), 0.73-0.56 (m, 5H). **LCMS**  $R_t = 1.347$  min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for  $\text{C}_{28}\text{H}_{47} [\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  383, found 383.

**Step 3.** To a solution of **A16-B** (130 mg, 248  $\mu\text{mol}$ ) in THF (2 mL) and MeOH (2 mL) and  $\text{H}_2\text{O}$  (1 mL) was added lithium hydroxide hydrate (104 mg, 2.48 mmol) at  $25^\circ\text{C}$ . Then the solution was stirred at  $50^\circ\text{C}$  for 16 h. The reaction was dilute with water (10 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers was washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatograph (PE/EtOAc = 10/1) to afford **Compound 4B77** (59 mg, 57%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.33-3.31 (m, 1H), 1.97-1.88 (m, 1H), 1.84-1.77 (m, 3H), 1.68-1.59 (m, 6H), 1.55-1.52 (m, 5H), 1.46-1.37 (m, 1H), 1.33-1.15 (m, 6H), 1.14-0.99 (m, 9H), 0.94-0.79 (m, 12H), 0.85-0.78 (m, 1H), 0.73-0.56 (m, 5H). **LCMS**  $R_t = 1.357$  min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for  $\text{C}_{28}\text{H}_{46} [\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  383, found 383.

Synthesis to confirm stereochemistry



To THF (0.5 mL) was added  $n\text{-BuLi}$  (2.5 M, 2.12 mmol, 0.848 mL) under  $\text{N}_2$  at  $-70^\circ\text{C}$ . After that, a suspension of **E-2863\_1** (400 mg, 0.849 mmol) in THF (3 mL) was added dropwise to give a suspension. After stirring at  $-70^\circ\text{C}$  for 30 min, a solution of (2R)-2-(propan-2-yl)oxirane (86.9 mg, 1.01 mmol) in THF (0.5 mL) was added. The reaction was stirred at  $25^\circ\text{C}$  for

16 hours. The mixture was poured into ice-water (20 mL) and extracted with EA (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **E-2863\_2** (430 mg, crude) as a solid, which was used directly for the next step.

- 5 To a solution of **E-2863\_2** (430 mg, 0.772 mmol) and nickel (II) chloride (5 mg, 0.0386 mmol) in MeOH (30 mL) was added Mg powder (369 mg, 15.4 mmol) at 25°C. The mixture was stirred at 50°C for 1 h. After cooling, the mixture was quenched with HCl (100 mL, 2M) until the reaction became clear and extracted with EtOAc (2 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by a silica gel column (PE/EtOAc = 10/1 to 3/1) to give **DA ST-200-094-002** (160 mg, 50%) as a solid, which was separated by SFC (column: AD (250mm\*30mm, 5um)), gradient: 40-40% B (A= 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH), flow rate: 50 mL/min) to give **DA ST-200-094-002** (85 mg, 53%, 50 mg for delivery) as a solid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.38 (m, 1H), 3.35-3.26 (m, 1H), 2.25-2.21 (m, 1H), 2.07-1.77 (m, 7H), 1.70-1.59 (m, 3H), 1.54-1.36 (m, 7H), 1.32-0.99 (m, 11H), 0.96-0.75 (m, 14H), 0.68 (s, 3H).

LCMS Rt = 1.291 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>28</sub>H<sub>47</sub>O [M-H<sub>2</sub>O+H] = 399, found 399.

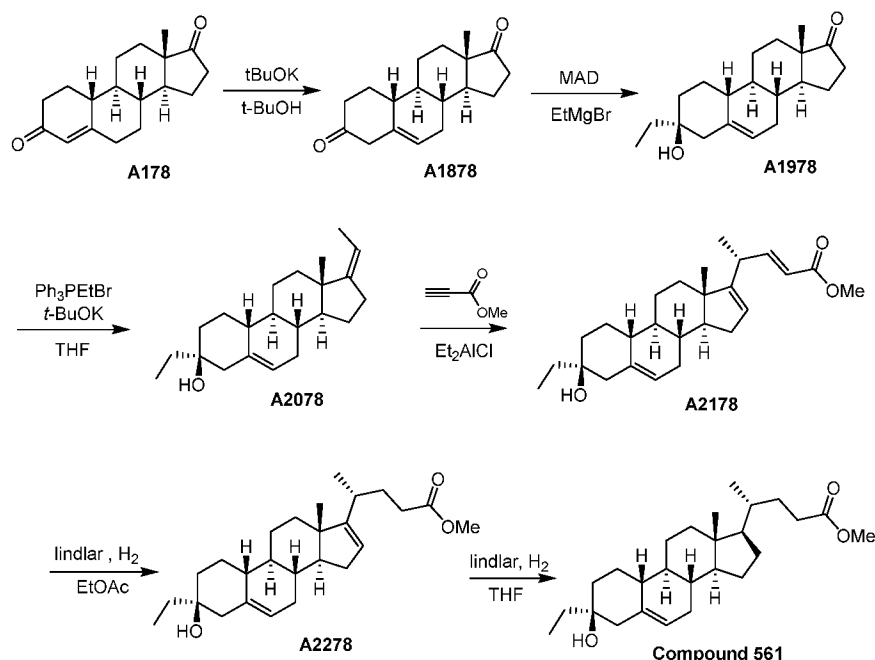
SFC Rt = 5.654 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 96.8%de

- To a solution of **DA ST-200-094-002** (35 mg, 0.0839 mmol) in MeOH (6 mL) was added Pd/C (0.1 g, <1% water). Then the suspension was hydrogenated under 50 psi of hydrogen at 50°C for 16 hrs. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuum. The residue was purified by flash column (PE/EtOAc=10/1 to 5/1) to give **DA ST-200-094-004** (7 mg, 20%) as a solid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 3.35-3.28 (m, 1H), 2.00-1.91 (m, 1H), 1.87-1.74 (m, 3H), 1.71-1.56 (m, 6H), 1.54-1.35 (m, 8H), 1.32-1.17(m, 5H), 1.14-0.94 (m, 9H), 0.93-0.76 (m, 13H), 0.73-0.62 (m, 4H).

LCMS Rt = 1.350 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>28</sub>H<sub>47</sub> [M-2H<sub>2</sub>O+H] = 383, found 383.

### 30 Example 78. Synthesis of Compound 561.



**Step 1.** *t*-BuOH (300 mL) was charged into a three-neck round bottom flask under nitrogen at 35°C and stirred under nitrogen gas bubbling for 10 mins. *t*-BuOK (45.2 g, 403 mmol) was added to the mixture and stirred under nitrogen gas bubbling for 15 mins. **A178** (10 g, 36.7 mmol) was added to the above mixture and stirred under nitrogen gas bubbling at 35°C for 1.5 hrs. The reaction mixture was poured to 10% aqueous acetic acid (500 mL) and stirred for 15 mins. Water (200 mL) was added to the aqueous and stirred for 30 mins. The pH of the mixture was adjusted to 7~8 with sodium bicarbonate (60 g). The mixture was stirred for 30 mins. The mixture was extracted with PE (3 x 400 mL). The organic layer was separated, washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated below 40°C to give **A1878** (11 g, crude) as an oil.

<sup>1</sup>H NMR CDCl<sub>3</sub> (400 MHz, CDCl<sub>3</sub>) δ 5.55-5.47 (m, 1H), 3.16-2.94 (m, 2H), 2.52-2.33 (m, 4H), 2.19-1.93 (m, 6H), 1.75-1.61 (m, 2H), 1.56-1.48 (m, 1H), 1.40-1.33 (m, 3H), 1.29-1.22 (m, 1H), 1.01-0.92 (m, 4H).

**Step 2.** To solution of BHT (52.3 g, 238 mmol) in anhydrous toluene (150 mL) under N<sub>2</sub> at 0°C was added trimethylaluminum (2 M in toluene, 55.0 mL, 110 mmol) drop-wise. The mixture was stirred at 15°C for 1 hour and cooled to -70°C. Then **A1878** (10 g, 36.7 mmol) in toluene (50 mL) was added below -60°C. The resulting mixture was stirred at -70°C for 1 hour. Ethylmagnesium bromide (36.6 mL, 3.0 M in diethyl ether, 110 mmol) was added drop-wise below -60 °C. The reaction mixture was stirred at -70°C for another 1 hour. The reaction mixture was quenched with saturated citric acid (400 mL) at -70°C. The mixture was warmed to 15°C slowly and extracted with ethyl acetate (3 x 400 mL). The combined organic layer was washed

with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by Combi-flash (0%~30% of EtOAc in PE) to afford **A1978** (7.6 g, 69%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.39-5.32 (m, 1H), 2.43-2.33 (m, 1H), 2.22-2.15 (m, 1H), 2.05-1.86 (m, 6H), 1.80-1.70 (m, 2H), 1.65-1.52 (m, 2H), 1.47-1.29 (m, 5H), 1.26-1.13 (m, 4H), 0.85-0.76 (m, 8H).

**Step 3.** To a suspension of PPh<sub>3</sub>EtBr (38.9 g, 105 mmol) in THF (200 mL) under N<sub>2</sub> was added t-BuOK (11.7 g, 105 mmol) at 40°C. After stirring at 20°C for 10 min, **A19** (8 g, 26.4 mmol) was added. The reaction mixture was stirred at 40°C for 1 h. The reaction was quenched with aqueous NH<sub>4</sub>Cl (250 mL) at 0°C and extracted with EtOAc (3 x 200 mL). The combined organic phase was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by Combi-flash (0%~30% of EtOAc in PE) to afford **A2078** (7.2 g, 87%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.36-5.29 (m, 1H), 5.12-5.01 (m, 1H), 2.36-2.25 (m, 1H), 2.23-2.05 (m, 3H), 2.00-1.73 (m, 5H), 1.62-1.48 (m, 7H), 1.43-1.32 (m, 3H), 1.28-1.06 (m, 5H), 0.86-0.73 (m, 8H).

**Step 4.** To a solution of **A2078** (7 g, 22.2 mmol) and methyl propiolate (4.66 g, 55.5 mmol) in DCM (200 mL) were added diethylaluminum chloride (88.8 mL, 88.8 mmol, 1 M in hexane) at 0°C under N<sub>2</sub> drop-wise. The reaction mixture was stirred at 25°C for 16 h. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (100 mL) solution, acidified with saturated aqueous citric acid solution to pH=5, extracted with DCM (2 x 200 mL). The combined organic layer was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude product. The crude product was purified by silica gel column (PE/EtOAc = 4/1) to give **A2178** (6.20 g, 70%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.00-6.90 (m, 1H), 5.85-5.75 (m, 1H), 5.40-5.30 (m, 2H), 3.73 (s, 3H), 3.05-2.95 (m, 1H), 2.30-2.20 (m, 1H), 2.10-1.75 (m, 9H), 1.75-1.50 (m, 3H), 1.50-1.20 (m, 9H), 0.95-0.80 (m, 5H), 0.78 (s, 3H).

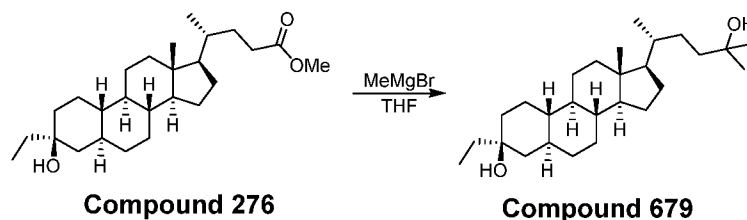
**Step 5.** To a solution of **A2178** (800 mg, 2.00 mmol) in EtOAc (50 mL) was added lindlar catalyst (500 mg) and the reaction mixture was stirred at 20°C for 4 h under H<sub>2</sub>. The reaction mixture was filtered with filter paper and concentrated in vacuum to give a crude product. The crude product was purified by silica gel column (PE/EtOAc = 10/1) to give **A2278** (650 mg, crude).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.35 (m, 2H), 3.66 (s, 3H), 2.50-2.40 (m, 1H), 2.35-2.25 (m, 2H), 2.15-2.05 (m, 1H), 2.05-1.95 (m, 3H), 1.95-1.75 (m, 3H), 1.75-1.55 (m, 3H), 1.55-1.40 (m, 7H), 1.40-1.25 (m, 3H), 1.10-1.00 (m, 4H), 1.00-0.85 (m, 4H), 0.85-0.80 (m, 1H), 0.75 (s, 3H).

**Step 6.** To a solution of **A22** (300 mg, 0.748 mmol) in THF (10 mL) was added lindlar catalyst (500 mg) and the reaction mixture was stirred at 20°C for 4 h under H<sub>2</sub>. The reaction mixture was filtered with filter paper and concentrated in vacuum to give a crude product. The crude product was purified by silica gel column (PE/EtOAc = 10/1) to give an impure product. The impure product was purified by prep-HPLC (0.1% TFA as additive). Most of MeCN was removed by concentration and the remaining solvent was removed by lyophilization to give **561** (27 mg, 9%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 3.66 (s, 3H), 2.40-2.30 (m, 1H), 2.30-2.20 (m, 2H), 2.10-1.80 (m, 8H), 1.55-1.40 (m, 6H), 1.40-1.20 (m, 5H), 1.20-1.00 (m, 5H), 1.00-0.90 (m, 3H), 0.90-0.75 (m, 4H), 0.75-0.70 (m, 1H), 0.68 (s, 3H). LCMS Rt = 1.299 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>26</sub>H<sub>41</sub>O<sub>2</sub>[M+H-H<sub>2</sub>O]<sup>+</sup> 385, found 385.

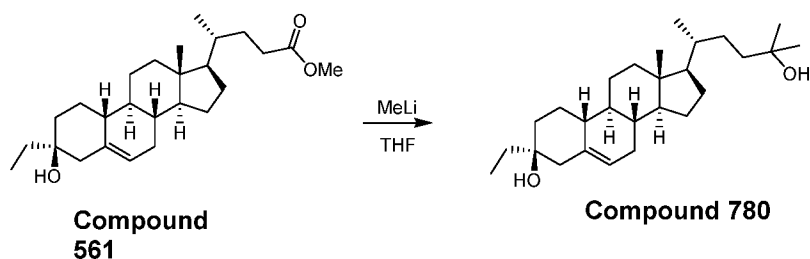
#### Example 79. Synthesis of Compound 679.



To a solution of **276** (150 mg, 0.37 mmol) in THF (5 mL) was added MeMgBr (616 μL, 3 M in ether) drop-wise at 0°C under N<sub>2</sub>. After that, the reaction mixture was stirred at 20°C for 1 h. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (15 mL) solution, extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude product. The crude product was recrystallized from MeCN (10 mL) to give **679** (32 mg, 21%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.05-1.95 (m, 1H), 1.90-1.80 (m, 3H), 1.65-1.60 (m, 3H), 1.60-1.55 (m, 2H), 1.45-1.25 (m, 8H), 1.25-1.15 (m, 8H), 1.15-1.00 (m, 10H), 0.95-0.80 (m, 8H), 0.75-0.55 (m, 5H). LCMS Rt = 1.282 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 369, found 369.

#### EXAMPLE 80. Synthesis of Compound 780

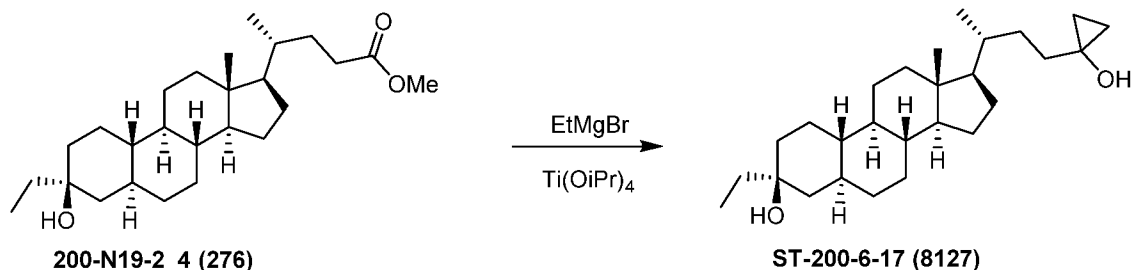


To a solution of **561** (300 mg, impure, 0.745 mmol) in THF (10 mL) was added MeLi (2.32 mL, 3.72 mmol, 1.6M in THF). The mixture was stirred at 25°C for 30 minutes. The mixture was quenched with sat.NH<sub>4</sub>Cl (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-15% of EtOAc in PE) to give **780** (37 mg, 12%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 2.26-2.20 (m, 1H), 2.10-1.75 (m, 7H), 1.68-1.58 (m, 2H), 1.56-1.37 (m, 7H), 1.36-1.24 (m, 4H), 1.23-1.17 (m, 8H), 1.16-0.99 (m, 5H), 0.96-0.90 (m, 3H), 0.89-0.76 (m, 5H), 0.68 (s, 3H).

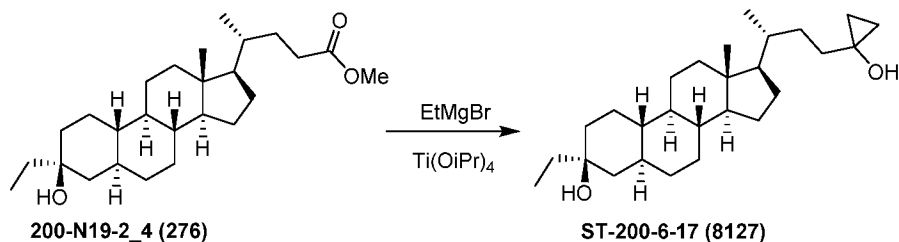
LCMS Rt = 1.222 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>27</sub>H<sub>43</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 367, found 367.

#### EXAMPLE 81: Synthesis of 8127



[00602] The experimental of intermediate **200-N19-2\_4** or **276** can be found in Example 76.

#### [00603] Synthesis of 8127



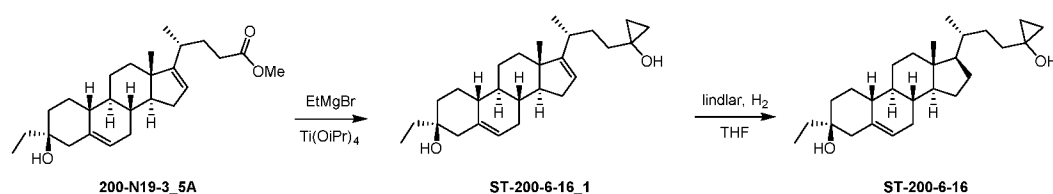
Ti(i-PrO)<sub>4</sub> (140 mg, 0.5 mmol) and EtMgBr (0.6 mL, 3 M in Et<sub>2</sub>O, 1.72 mmol) were added to a solution of **200-N19-2\_4** (200 mg, 0.5 mmol) in THF (2 mL) at 25°C. After that, the reaction mixture was stirred at 25°C for 15 min under N<sub>2</sub>. The reaction mixture was quenched with

saturated aqueous  $\text{NH}_4\text{Cl}$  (10 mL) solution and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give a crude product. The crude product was purified by silica gel column (EtOAc/PE = 5/1) to afford an impure product, which was triturated from n-hexane (5 mL) at 25°C to give **8127** (58 mg, 46%).

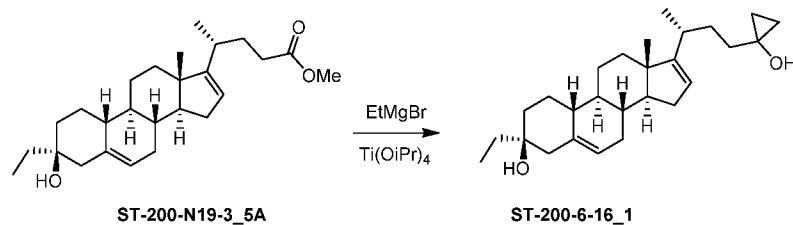
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.99-1.91 (m, 1H), 1.88-1.59 (m, 10H), 1.48-1.21 (m, 6H), 1.18-0.97 (m, 10H), 0.94-0.81 (m, 9H), 0.79-0.56 (m, 8H), 0.47-0.38 (m, 2H).

LCMS  $R_t$  = 1.356 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. For  $\text{C}_{27}\text{H}_{43}$   $[\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  367, found 367.

#### EXAMPLE 82: Synthesis of 8245



#### [00604] Synthesis of ST-200-6-16\_1

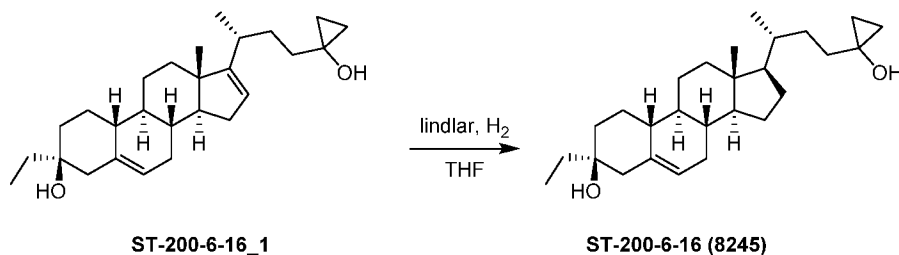


The synthesis for ST-200-N19-3\_5A can be found in Example 78.  $\text{Ti}(\text{i-PrO})_4$  (212 mg, 0.75 mmol) was added to a solution of **200-N19-3\_5A** (300 mg, 0.75 mmol) in THF (2.5 mL), followed by adding EtMgBr (0.9 mL, 3 M in  $\text{Et}_2\text{O}$ , 2.6 mmol) at 25°C. Next, the reaction mixture was stirred at 25°C for 15 min under  $\text{N}_2$ . The reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 mL) solution and extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give a crude product. The crude product was purified by silica gel column (EtOAc/PE = 5/1) to afford a crude product as a solid, which was purified by re-crystallized from MeCN (5 mL) at 85°C to give impure product as a solid. The impure sample was further purification by SFC (column: OD(250mm\*30mm,10um)), gradient: 25-25% B (0.1%  $\text{NH}_3\text{H}_2\text{O}$  ETOH), flow rate: 60 mL/min) to give **ST-200-6-16\_1** (110 mg, 44%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.44-5.38 (m, 1H), 5.33-5.28 (m, 1H), 2.29-2.21 (m, 1H), 2.15-1.94 (m, 5H), 1.93-1.79 (m, 3H), 1.78-1.57 (m, 6H), 1.52-1.21 (m, 10H), 1.06-0.98 (m, 3H), 0.92-0.82 (m, 5H), 0.77 (s, 3H), 0.75-0.69 (m, 2H), 0.47-0.39 (m, 2H).

LCMS Rt = 1.219 min in 2.0 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for  $\text{C}_{27}\text{H}_{41}\text{O}[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  381, found 381.

**[00605] Synthesis of 8245**

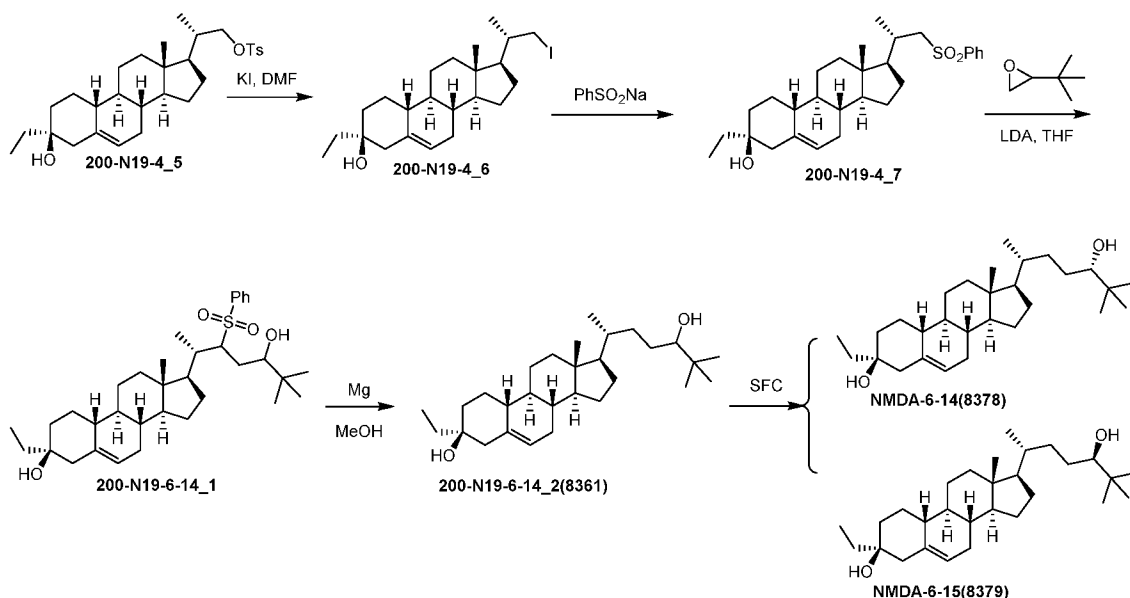


Lindlar catalyst (100 mg) was added to a solution of **ST-200-6-16\_1** (78 mg, 0.2 mmol) in THF (5 mL) and the mixture was degassed and backed-filled with  $\text{H}_2$  3 times. After that, the reaction mixture was stirred at  $25^\circ\text{C}$  for 4 h under  $\text{H}_2$ . The reaction mixture was filtered through a pad of celite washed with THF (100 mL) and concentrated in vacuum to give a crude product, which was re-crystallized from MeCN (5 mL) at  $85^\circ\text{C}$  to give **ST-200-6-16** (32 mg, 41 %).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.43-5.34 (m, 1H), 2.27-2.19 (m, 1H), 2.07-1.72 (m, 8H), 1.67-1.59 (m, 3H), 1.55-1.37 (m, 7H), 1.34-0.96 (m, 10H), 0.94-0.91 (m, 3H), 0.89-0.82 (m, 4H), 0.76-0.70 (m, 2H), 0.68 (s, 3H), 0.48-0.37 (m, 2H).

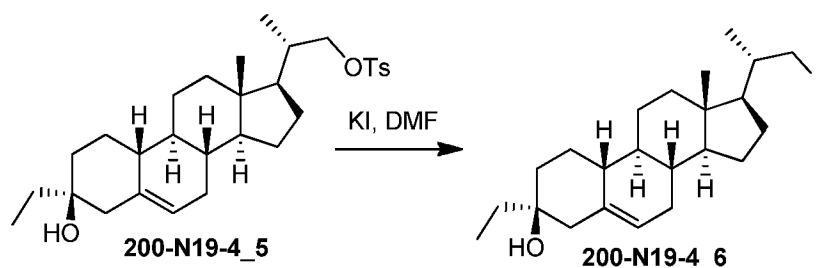
LCMS Rt = 1.186 min in 2.0 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for  $\text{C}_{27}\text{H}_{43}\text{O}[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  383, found 383.

**EXAMPLE 83: Synthesis of 8361, 8378, and 8379**



[00606] The synthesis of **200-N19-4\_5** can be found in Example 94.

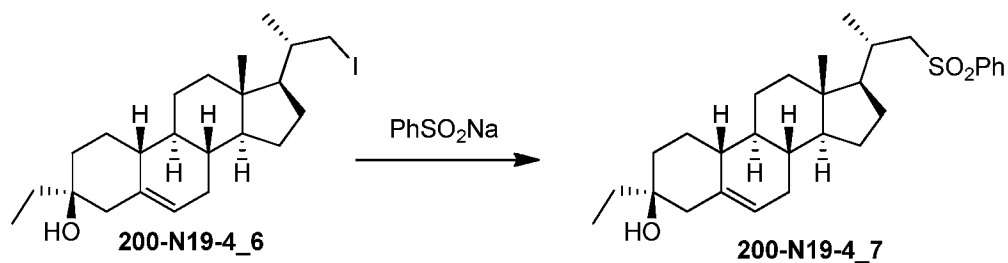
[00607] **Synthesis of 200-N19-4\_6**



- 5 KI (28.0 g, 169 mmol) was added to a solution of **200-N19-4\_5** (17 g, 33.9 mmol) in DMF (200 mL) at 25°C. The mixture was stirred at 50°C for 2 hours. Half of the reaction mixture was poured into water (500 mL). The suspension was extracted with PE (700 mL). The combined organic phase was washed with saturated brine (2 x 500 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **200-N19-4\_6** (8.5 g, crude) as an oil. The other half of the reaction mixture was used directly for the next step.
- 10

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 3.35-3.30 (m, 1H), 3.20-3.10 (m, 1H), 2.25-2.15 (m, 1H), 2.05-1.76 (m, 8H), 1.69-1.34 (m, 9H), 1.30-1.13 (m, 7H). 0.92-0.75 (m, 6H). 0.71 (s, 3H).

[00608] **Synthesis of 200-N19-4\_7**

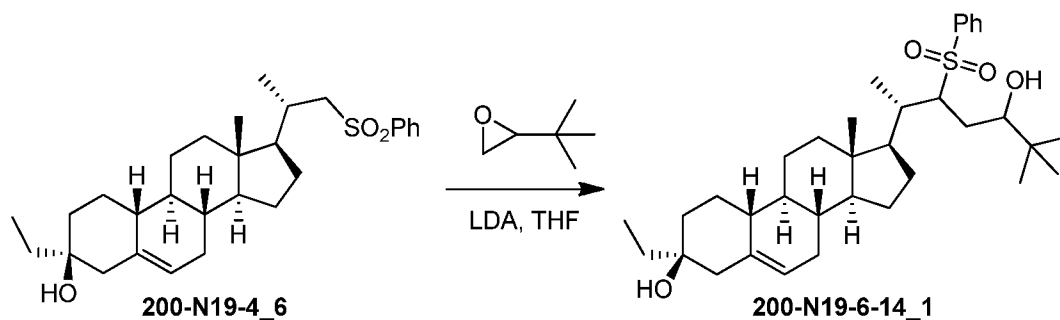


15

PhSO<sub>2</sub>Na (9.15 g, 55.8 mmol) was added to the reaction mixture from the previous step at 25°C. The mixture was stirred at 50°C for 3 hours. The reaction mixture was poured into water (500 ml) and some solid was produced. The mixture was filtered. The filter cake was washed with water (2 x 500 ml). The resulting filter cake was dissolved in DCM (500 mL), washed with water (2 x 500 mL). The combined organic phase was washed with saturated brine (2 x 500 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **200-N19-4\_7** (8.5 g, crude) as a solid, which was re-crystallized from MeCN (50 mL) at reflux (82°C). After cooling to 25 °C, the mixture was filtered and concentrated in vacuum to get **200-N19-4\_7** (5 g, 59%) as a solid. Mother liquor filtered and concentrated to give another 2 g of solid.

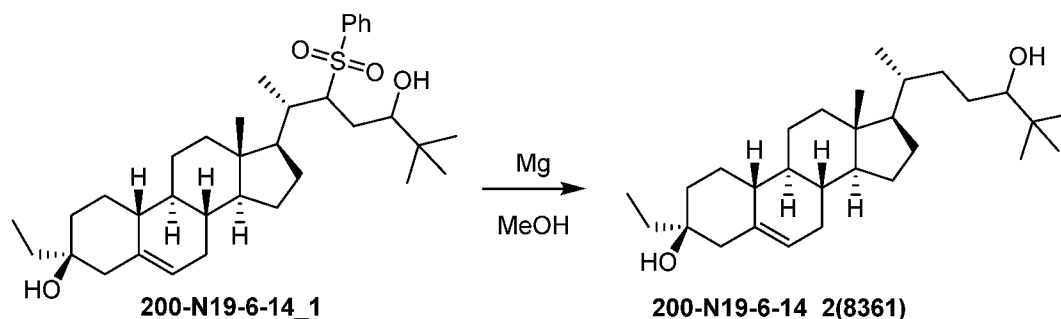
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.92-7.88 (m, 2H), 7.65-7.53 (m, 3H), 5.38-5.33 (m, 1H), 3.18-3.10 (m, 1H), 2.90-2.80 (m, 1H), 2.25-2.16 (m, 1H), 1.88-1.60 (m, 9H), 1.59-1.35 (m, 5H), 1.29-1.05 (m, 11H), 0.88-0.77 (m, 5H), 0.65 (s, 3H).

[00609] **Synthesis of 200-N19-6-14\_1**



n-BuLi (2 mL, 2.5 M, 5.08 mmol) was added to a solution of diisopropylamine (0.73 mL, 5.08 mmol) in THF (1 mL) under N<sub>2</sub> at -70°C. The resulting mixture was warmed to 25°C and stirred at 25°C for 30 min. After re-cooling to -70°C, a solution of **200-N19-4\_6** (0.6 g, 1.27 mmol) in THF (3 mL) was added at -70°C. The reaction mixture was stirred at -70°C for 1 hour. 2-(tert-butyl)oxirane (152 mg, 1.52 mmol) was added at -70°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 18 hours. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (10 mL) at 0°C, extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a crude product, which was purified by flash column (0~30% of PE in EtOAc, 50 mins) to give **200-N19-6-14\_1** (550 mg) as a solid, which was used directly for the next step.

[00610] **Synthesis of 200-N19-6-14\_2 (8361)**



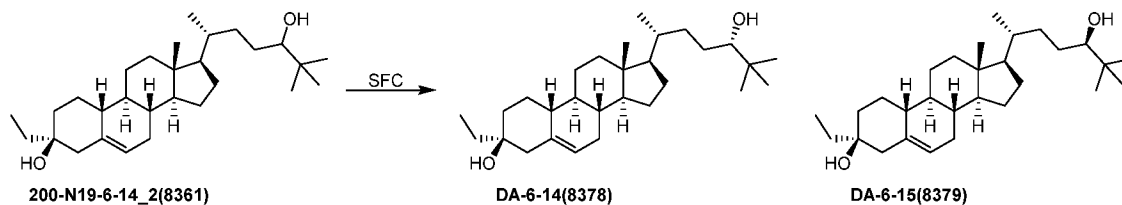
Mg (1.16 g, powder) was added to a solution of **200-N19-6-14\_1** (550 mg, crude) in MeOH (40 mL) at 65°C. The mixture was stirred at 65°C for 3 hours and quenched by adding HCl (50 mL, 2 M in water). The mixture was extracted with EtOAc (2 x 50 mL). The organic layers were washed with water (2 x 100 mL), sat. NaHCO<sub>3</sub> (2 x 100 mL), brine (2 x 80 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product, which was purified by flash column (0~20% of PE in EtOAc, 60 mins) to give **200-N19-6-14\_2** (190 mg) as a solid.

**200-N19-6-14\_2** (45 mg) was re-crystallized from MeCN at 70°C to give **200-N19-6-14\_2** (35 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.30 (m, 1H), 3.40-3.00 (m, 1H), 2.30-2.15 (m, 1H), 2.10-1.60 (m, 9H), 1.55-1.40 (m, 6H), 1.25-1.00 (m, 11H), 0.95-0.75 (m, 18H), 0.68 (s, 3H).

LCMS Rt = 1.338 min in 2 min chromatography, 30-90AB\_E, purity 98%, MS ESI calcd. For C<sub>29</sub>H<sub>49</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 413.

#### [00611] Synthesis of 8378 and 8379



**200-N19-6-14\_2** (145 mg) was separated by SFC (Column: AD (250mm\*30mm,10um); Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH, 40%B; FlowRate(ml/min): 60) to give impure **DA-6-14** (70 mg) and impure **DA-6-15** (60 mg) both as a solid. The impure **DA-6-15** (60 mg) was triturated with MeCN (5 mL) at 25°C to give **DA-6-15** (27 mg, pure) as a solid. The impure **DA-6-14** (70 mg) was triturated with MeCN (5 mL) at 25°C to give **DA-6-14** (27 mg, pure) as a solid.

#### 8378:

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.30 (m, 1H), 3.40-3.00 (m, 1H), 2.30-2.15 (m, 1H), 2.10-1.60 (m, 10H), 1.55-1.40 (m, 5H), 1.25-1.00 (m, 11H), 0.95-0.75 (m, 18H), 0.68 (s, 3H).

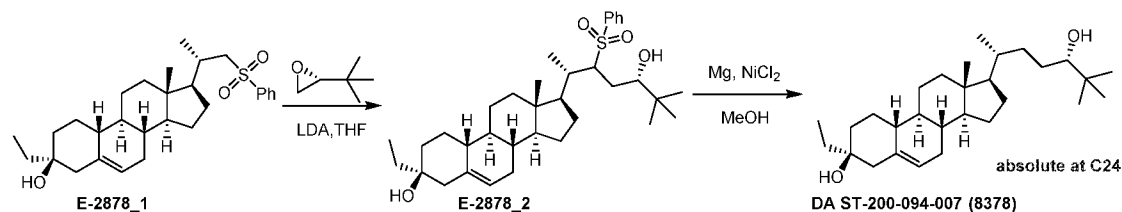
LCMS Rt = 1.334 min in 2 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. For C<sub>29</sub>H<sub>47</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 395.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.30 (m, 1H), 3.40-3.25 (m, 1H), 2.25-2.15 (m, 1H), 2.05-1.75 (m, 7H), 1.70-1.60 (m, 2H), 1.50-1.30 (m, 8H), 1.20-1.05 (m, 11H), 1.00-0.75 (m, 16H), 0.68 (s, 3H).

LCMS Rt = 1.327 min in 2 min chromatography, 30-90AB\_E, purity 99%, MS ESI calcd. For

5 C<sub>28</sub>H<sub>47</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 395.

### Synthesis of 8378 to determine stereochemistry



To a solution of diisopropylamine (0.262 mL, 1.82 mmol) in THF (0.5 mL) under N<sub>2</sub> at -78°C was added n-BuLi (0.676 mL, 2.5 M, 1.69 mmol). The resulting mixture was warmed to 0°C and stirred at 0°C for 10 mins. After re-cooling to -78°C, a solution of **E-2878\_1** (200 mg, 0.425 mmol) in THF (1.5 mL) was added at -78°C. The reaction mixture was stirred at -78°C for 1 hr. (R)-2-(tert-butyl)oxirane (51.0 mg, 0.510 mmol) was added at -78°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 16 hrs. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (10 mL) at 0°C, extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **E-2878\_2** (250 mg, crude) as a solid, which was used directly for the next step.

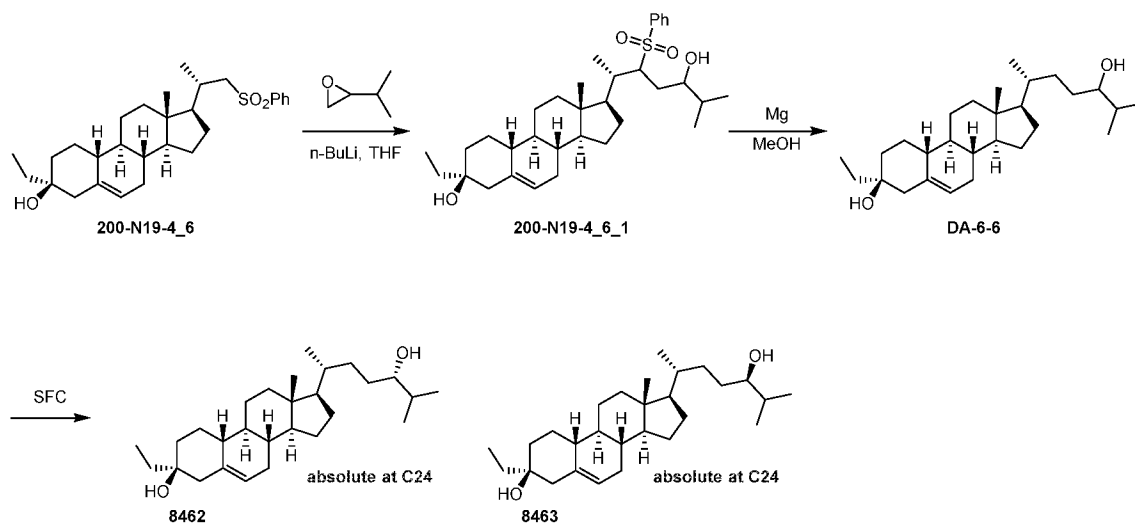
To a solution of **E-2878\_2** (250 mg, crude) in MeOH (30 mL) was added Mg powder (840 mg, 35.0 mmol) and NiCl<sub>2</sub> (20 mg) at 60°C. The mixture was stirred at 60°C for 5 hrs. The reaction was quenched by HCl (50 mL, 2 M in water). The mixture was extracted with EtOAc (2 x 50 mL). The organic layers were washed with water (2 x 100 mL), sat. NaHCO<sub>3</sub> (2 x 100 mL), brine (2 x 80 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product which was purified by flash column (0~20% of EtOAc in PE) to give **ST-200-094-007** (100 mg, 53%, impure, 96% de) as a solid. The impure product was re-purified by SFC separation (column: AD (250 mm \* 30 mm, 5 um), condition: 0.1% NH<sub>3</sub>H<sub>2</sub>O EtOH, Begin B: 40%, End B: 40%) to give **ST-200-094-007** (70 mg, 100% de, impure) as a solid. The **ST-200-094-007** (70 mg) was purified by recrystallization (n-BuOH/H<sub>2</sub>O=4/1) to give **ST-200-094-007** (9 mg, pure,) as a solid and **ST-200-094-007** (60 mg, impure) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.30 (m, 1H), 3.40-3.00 (m, 1H), 2.30-2.15 (m, 1H), 2.10-1.60 (m, 10H), 1.55-1.40 (m, 5H), 1.25-1.00 (m, 11H), 0.95-0.92 (m, 4H), 0.90 (s, 9H), 0.88-0.82 (m, 5H), 0.68 (s, 3H).

LCMS Rt = 1.334 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>29</sub>H<sub>47</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 395, found 395.

SFC Rt = 5.182 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 100% de.

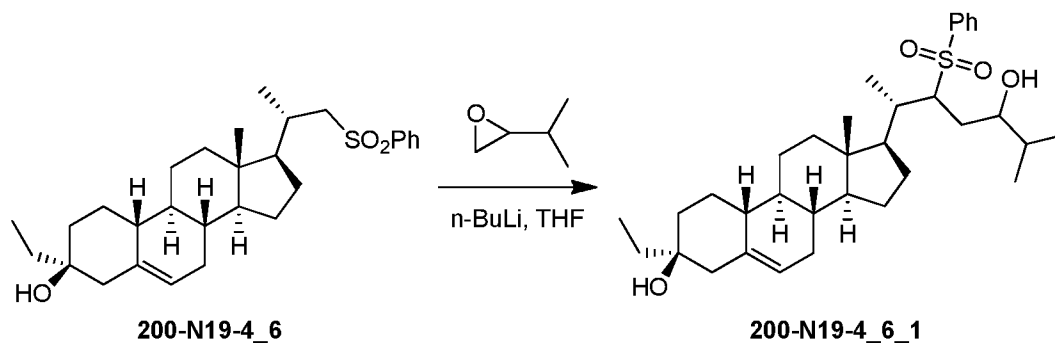
#### EXAMPLE 84: Synthesis of 8462 and 8463



[00612] The synthesis of 200-N19-4\_6 can be found in Example 83.

[00613] During the synthesis of 8462 from chiral epoxide, 8462 was proved to be S-configuration at C24 and 8463 was proved to be R-configuration at C24. See below.

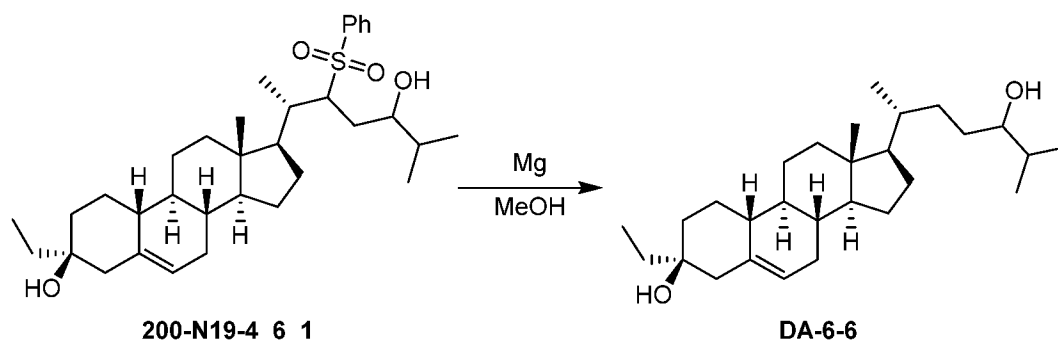
[00614] Synthesis of 200-N19-4\_6\_1



[00615] To THF (5 mL) under N<sub>2</sub> at -70°C was added n-BuLi (4.23 mL, 2.5 M in n-hexane, 10.6 mmol). To the mixture was added dropwise a solution of ST-200-N19-4\_6 (2 g, 4.24 mmol) in THF (15 mL) at -70°C. The reaction mixture was stirred at -70°C for 1 hour. 2-isopropoxyloxirane (437 mg, 5.08 mmol) was added at -70°C. The reaction mixture was warmed to

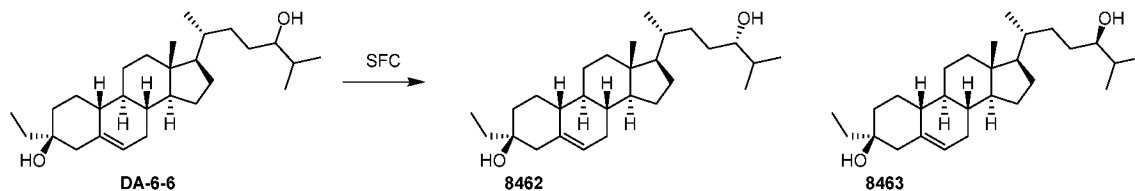
25°C slowly and stirred at 25°C for 16 hours. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (50 mL). The mixture was extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with brine (2 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give st-**200-N19-4\_6\_1** (2 g, crude) as an oil, which was used for the next step directly.

**[00616] Synthesis of DA-6-6**



**[00617]** To a solution of **200-N19-4\_6\_1** (2 g, 3.59 mmol) in MeOH (100 mL) was added Mg (4.35 g, 179 mmol) at 65°C. The mixture was stirred at 65°C for 1h. Aq. HCl (70 mL, 2 M in water) was added. The mixture was extracted with EtOAc (3 x 50 mL), washed with sat. NaHCO<sub>3</sub> (2 x 150 mL), brine (2 x 100 mL) to give a crude product, which was purified by flash column (0-10% of EtOAc in PE, 60 mins) to give **DA-6-6** (600 mg, 40%) as a solid.

**[00618] Synthesis of 8462 and 8463**



**DA-6-6** (600 mg) was separated by SFC (Column: AD(250mm\*30mm,10um); Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH, 40%B; FlowRate(ml/min): 60) to give **8462** (152 mg, 25%) and **8463** (137 mg, 23%) as a solid.

**8462**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.35 (m, 1H), 3.37-3.25 (m, 1H), 2.27-2.19 (m, 1H), 2.08-1.87 (m, 4H), 1.86-1.75 (m, 3H), 1.71-1.58 (m, 3H), 1.52-1.35 (m, 6H), 1.34-1.17 (m, 7H), 1.16-0.97 (m, 5H), 0.97-0.90 (m, 8H), 0.89-0.82 (m, 5H), 0.81-0.75 (m, 1H), 0.68 (s, 3H).

**LCMS** Rt = 1.285 min in 2.0 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. for C<sub>28</sub>H<sub>47</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 399, found 399.

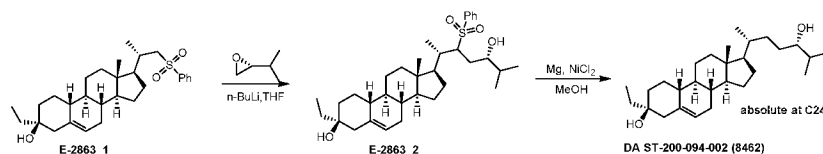
**8463**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.41-5.35 (m, 1H), 3.37-3.25 (m, 1H), 2.27-2.19 (m, 1H), 2.07-1.93 (m, 3H), 1.90-1.78 (m, 3H), 1.63-1.50 (m, 5H), 1.48-1.34 (m, 7H), 1.33-1.15 (m, 7H), 1.14-0.98 (m, 3H), 0.98-0.89 (m, 9H), 0.88-0.82 (m, 4H), 0.81-0.75 (m, 1H), 0.68 (s, 3H).

LCMS Rt = 1.278 min in 2.0 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. for

5 C<sub>28</sub>H<sub>47</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 399, found 399.

### Synthesis to confirm stereochemistry



To THF (0.5 mL) was added n-BuLi (2.5 M, 2.12 mmol, 0.848 mL) under N<sub>2</sub> at -70°C. After  
 10 that, a suspension of **E-2863\_1** (400 mg, 0.849 mmol) in THF (3 mL) was added dropwise to  
 give a suspension. After stirring at -70°C for 30 min, a solution of (2R)-2-(propan-2-yl)oxirane  
 (86.9 mg, 1.01 mmol) in THF (0.5 mL) was added. The reaction was stirred at 25°C for  
 16 hours. The mixture was poured into ice-water (20 mL) and extracted with EA (2 x 30 mL).  
 The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and  
 15 concentrated in vacuum to afford **E-2863\_2** (430 mg, crude) as a solid, which was used directly  
 for the next step.

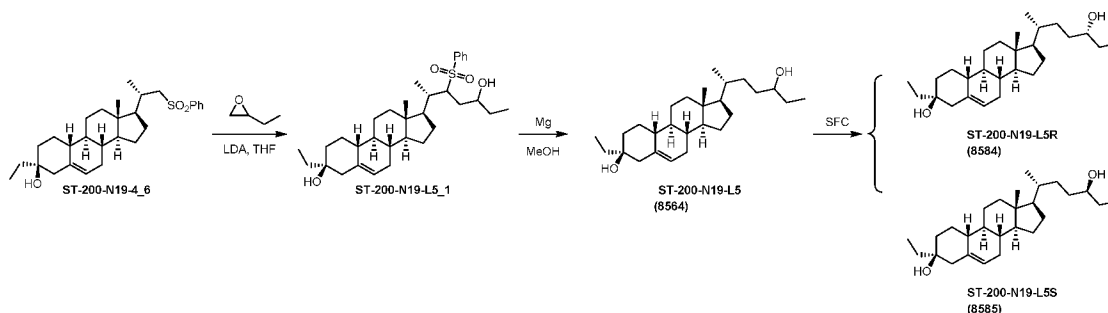
To a solution of **E-2863\_2** (430 mg, 0.772 mmol) and nickel (II) chloride (5 mg, 0.0386 mmol)  
 in MeOH (30 mL) was added Mg powder (369 mg, 15.4 mmol) at 25°C. The mixture was stirred  
 at 50°C for 1 h. After cooling, the mixture was quenched with HCl (100 mL, 2M) until the  
 20 reaction became clear and extracted with EtOAc (2 x 50 mL). The combined organic phase was  
 dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by a silica gel column (PE/EtOAc = 10/1  
 to 3/1) to give **DA ST-200-094-002** (160 mg, 50%) as a solid, which was separated by SFC  
 (column: AD (250mm\*30mm, 5um)), gradient: 40-40% B (A= 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH), flow rate:  
 50 mL/min) to give **DA ST-200-094-002** (85 mg, 53%, 50 mg for delivery) as a solid.

25 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.38 (m, 1H), 3.35-3.26 (m, 1H), 2.25-2.21 (m, 1H), 2.07-  
 1.77 (m, 7H), 1.70-1.59 (m, 3H), 1.54-1.36 (m, 7H), 1.32-0.99 (m, 11H), 0.96-0.75 (m, 14H),  
 0.68 (s, 3H).

LCMS Rt = 1.291 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For  
 C<sub>28</sub>H<sub>47</sub>O [M-H<sub>2</sub>O+H] = 399, found 399.

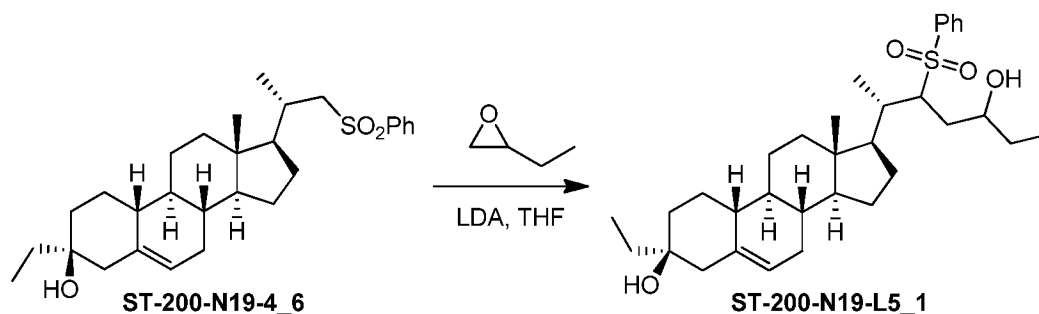
30

### EXAMPLE 85: Synthesis of 8564, 8584, and 8585



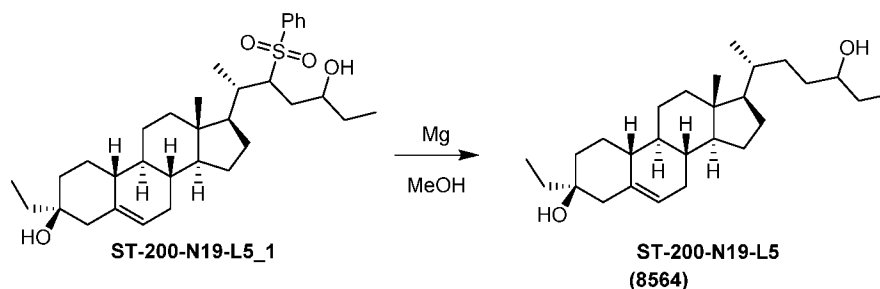
[00619] The experimental of intermediate **ST-200-N19-4\_6** can be found in Example 83.

[00620] **Synthesis of ST-200-N19-L5\_1**



- 5 A suspension of **ST-200-N19-4\_6** (500 mg, 1.06 mmol) in THF (4 mL) was added dropwise to a solution of n-BuLi (1.05 mL, 2.5 M in hexane, 2.65 mmol) in THF (1 mL) at -70°C under N<sub>2</sub>. After stirring for 30 minutes at -70°C, a solution of diisopropylamine (267 mg, 2.65 mmol) was added dropwise at -70°C, followed by adding a solution of 2-ethyloxirane (114 mg, 1.59 mmol) dropwise at -70°C. The mixture was stirred at -70°C for another 30 min and then warmed to 25°C
- 10 gradually. The reaction mixture was stirred at 25°C for 24 hours, quenched by saturated NH<sub>4</sub>Cl aqueous (5 mL), extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **ST-200-N19-L5\_1** (610 mg, crude) as a solid, which was used directly.

[00621] **Synthesis of ST-200-N19-L5**

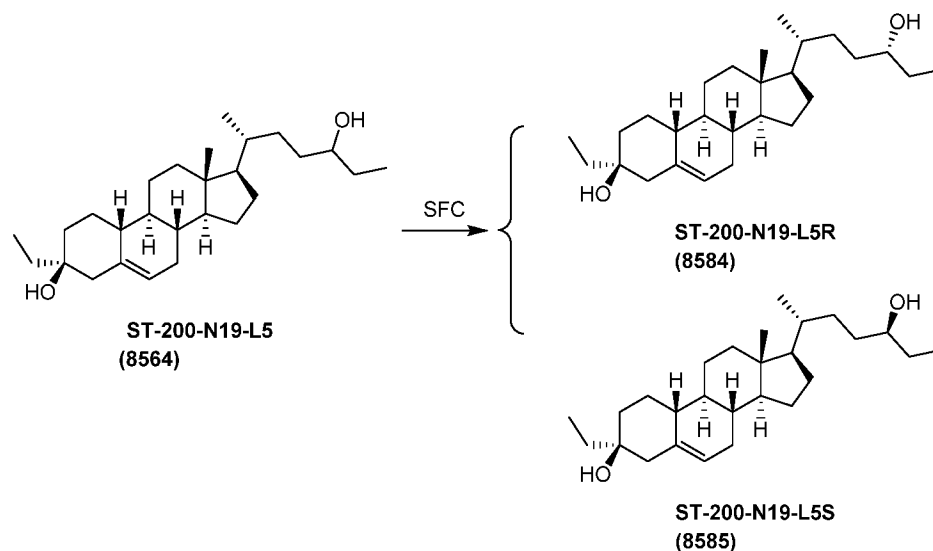


- 15 Mg powder (1.07 g, 44.8 mmol) and NiCl<sub>2</sub> (5 mg, 0.05 mmol) were added to a solution of **ST-200-N19-L5\_1** (610 mg, 1.1 mmol) in 100 mL anhydrous MeOH and stirred under N<sub>2</sub> at 60°C. The reaction mixture was quenched by 2 M HCl (50 mL) until solid was dissolved. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with sat.

NaHCO<sub>3</sub> (150 mL), brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~15 % of EtOAc in PE) to give **ST-200-N19-L5** (240 mg, 53%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.34 (m, 1H), 3.54-3.42 (m, 1H), 2.28-2.18 (m, 1H), 2.08-1.61 (m, 8H), 1.55-1.36 (m, 10H), 1.34-0.98 (m, 11H), 0.97-0.73 (m, 11H), 0.71-0.63 (m, 3H).  
**LCMS** Rt = 1.349 min in 2.0 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 385, found 385.

**[00622] Synthesis of ST-200-N19-L5R & ST-200-N19-L5S**



**ST-200-N19-L5** (208 mg, 0.52 mmol) was purified by SFC (column: AD (250mm\*30mm,10um)), gradient: 40-40% B (A= 0.1%NH<sub>3</sub>/H<sub>2</sub>O, B= EtOH ), flow rate: 60 mL/min) to give **ST-200-N19-L5R** (80 mg, 38%) and **ST-200-N19-L5S** (70 mg, 33%) as a solid.

**8584**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.36 (m, 1H), 3.52-3.41 (m, 1H), 2.27-2.19 (m, 1H), 2.07-1.77 (m, 7H), 1.67-1.56 (m, 2H), 1.54-1.38 (m, 8H), 1.33-0.98 (m, 12H), 0.97-0.90 (m, 6H), 0.88-0.79 (m, 5H), 0.68 (s, 3H).

**LCMS** Rt = 1.353 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 385, found 385.

**SFC** Rt = 5.762 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, purity: 100%.

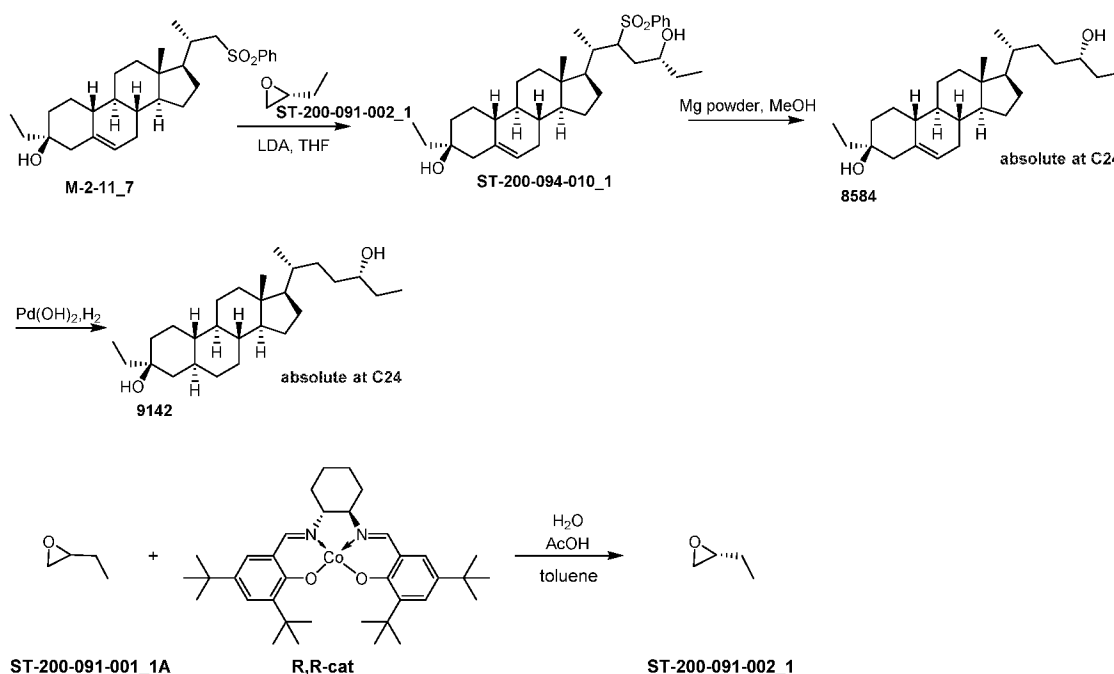
**8585**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.36 (m, 1H), 3.53-3.43 (m, 1H), 2.27-2.19 (m, 1H), 2.08-1.77 (m, 7H), 1.68-1.56 (m, 2H), 1.54-1.32 (m, 10H), 1.29-0.97 (m, 10H), 0.97-0.89 (m, 6H), 0.88-0.74 (m, 5H), 0.68 (s, 3H).

**LCMS** Rt = 1.353 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for  $C_{27}H_{45}O$   $[M+H-H_2O]^+$  385, found 385.

**SFC** Rt = 6.041 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, purity: 95%.

**Synthesis to determine stereochemistry (8584 and 9142).**



To a solution of **M-2-11\_7** (400 mg, 0.849 mmol) in anhydrous THF (3 mL) was added n-BuLi (1.01 mL, 2.54 mmol, 2.5 M in n-hexane) drop-wise at  $-70^{\circ}\text{C}$  under  $N_2$ . After stirring at  $-70^{\circ}\text{C}$  for 30 mins, a solution of (R)-2-ethyloxirane (91.5 mg, 1.27 mmol) in anhydrous THF (0.5 mL) was added drop-wise at  $-70^{\circ}\text{C}$ . The reaction mixture was stirred at  $-70^{\circ}\text{C}$  for another 1 h and then stirred at  $25^{\circ}\text{C}$  (room temperature) for 12 h. After heating at  $60^{\circ}\text{C}$  for 2 h, the reaction was quenched by saturated aqueous  $NH_4Cl$  (50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combine organic phase was washed with saturated brine (2 x 50 mL). dried over anhydrous  $Na_2SO_4$ . filtered and concentrated in vacuum to give **ST-200-94-10\_1** (0.4 g, crude) as an oil, which was used directly of the next step.

To a solution of **ST-200-094-010\_1** (0.4 g, crude) in MeOH (50 mL) was added Mg powder (883 mg, 36.8 mmol) and  $NiCl_2$  (20 mg) at  $25^{\circ}\text{C}$  under  $N_2$ . After stirring at  $60^{\circ}\text{C}$  for 1 h, the reaction mixture was quenched with HCl (100 mL, 1 M) until the reaction became clear. The aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic phase was washed with saturated  $NaHCO_3$ .aq (2 x 50 mL), washed saturated brine (2 x 50 mL), dried over anhydrous  $Na_2SO_4$ , filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 8/1) to afford **8584** (180 mg, 61%) as a solid.

The **ST-200-094-010** (180 mg, 0.447 mmol) was purified by SFC (Column:AD(250mm\*30mm,5um), Condition:0.1%NH<sub>3</sub>H<sub>2</sub>O IPA, Begin B:40%, End B:40%) to afford **8584** (120 mg, 67%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  5.40-5.37 (m, 1H), 3.48-3.46 (m, 1H), 2.25-2.21 (m, 1H), 2.05-1.74 (m, 7H), 1.65-1.40 (m, 13H), 1.38-1.07 (m, 11H), 1.06-0.96 (m, 6H), 0.85 (s, 3H), 0.68 (s, 3H).

**LCMS** = 1.277 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 385, found 385.

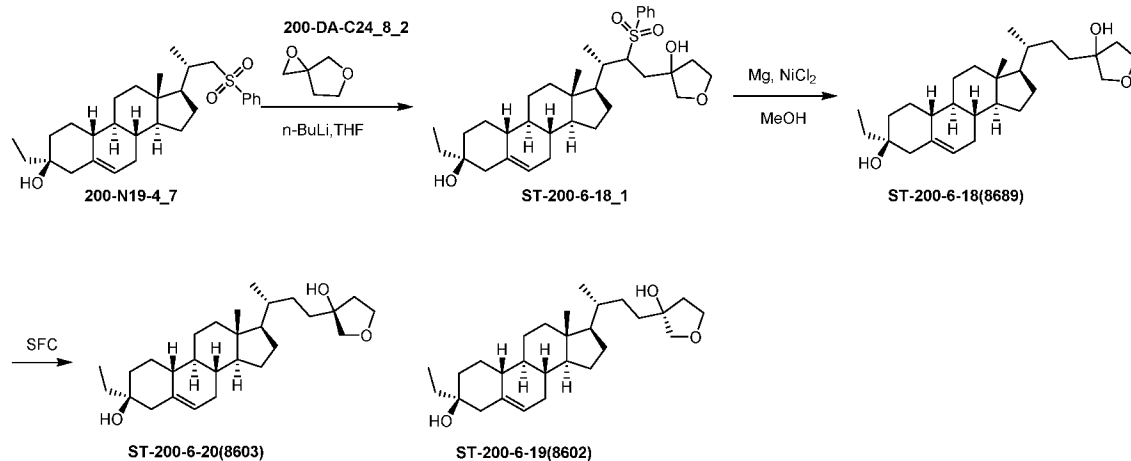
**SFC** Rt = 5.736 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 99.5%de.

A solution of **8584** (88 mg, 0.2185 mmol) and Pd(OH)<sub>2</sub> (80 mg) in MeOH (10 mL) was hydrogenated under 50 psi of hydrogen at 50°C for 12 hours. The reaction mixture was filtered through a pad of celite and the filter cake was washed with THF (3 x 100 mL). The filter liquor was concentrated in vacuum. The residue was purified by flash column (10~25% of EtOAc in PE) to give **9142** (27 mg, 31%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  3.50-3.41 (m, 1H), 1.99-1.91 (m, 1H), 1.87-1.74 (m, 3H), 1.70-1.60 (m, 3H), 1.53-1.19 (m, 12H), 1.18-0.97 (m, 11H), 0.96-0.78 (m, 12H), 0.75-0.54 (m, 5H).

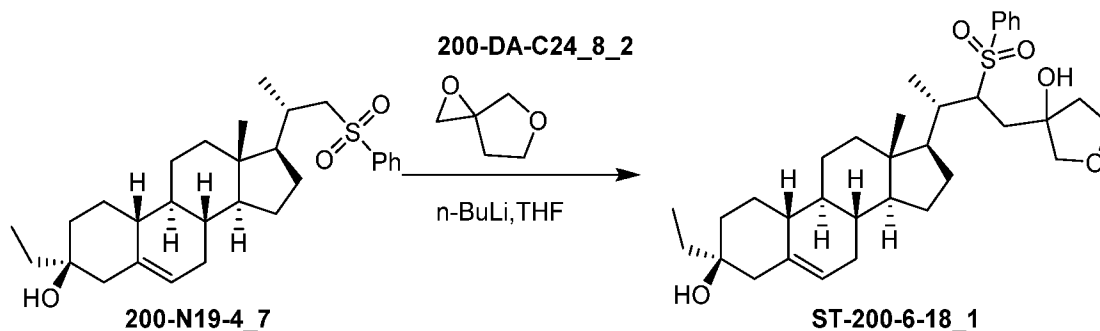
**LCMS** Rt = 1.292 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 369, found 369.

## EXAMPLE 86: Synthesis of 8689, 8602, and 8603



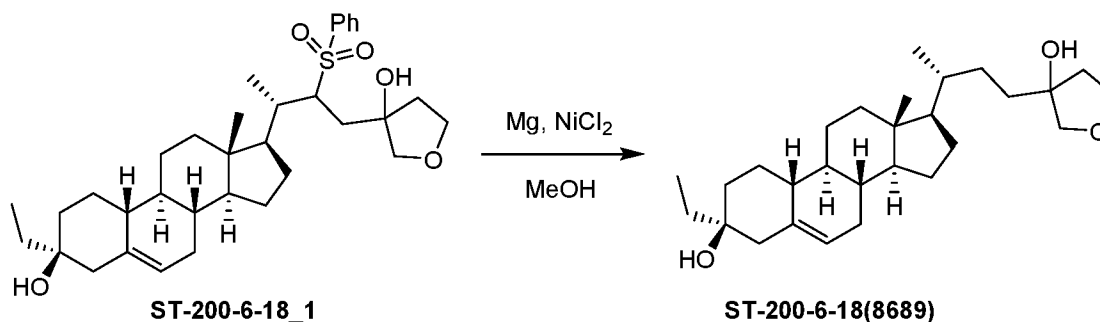
[00623] The experimental of intermediate **200-DA-C24\_8\_2** can be found in Example 15 and the synthesis of **200-N19-4\_7** can be found in Example 83.

[00624] **Synthesis of ST-200-6-18\_1**



A suspension of **200-N19-4\_7** (600 mg, 1.29 mmol) in THF (8 mL) was added dropwise to a solution of n-BuLi (1.54 mL, 2.5 M in hexane, 3.87 mmol) in THF (2 mL) at -65°C under N<sub>2</sub>. The mixture was stirred for 30 minutes at -65°C. Next, diisopropylamine (390 mg, 3.87 mmol) was added at -65°C, followed by adding **200-DA-C24\_8\_2** (387 mg, 3.87 mmol) dropwise at -65°C. The mixture was stirred for another 30 minutes and then warmed to 25°C gradually and stirred at 25°C for 16 hours. The reaction was quenched with saturated NH<sub>4</sub>Cl aq. (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and to give **ST-200-6-18\_1** (610 mg, crude) as an oil, which was used directly for the next step.

**[00625] Synthesis of ST-200-6-18**



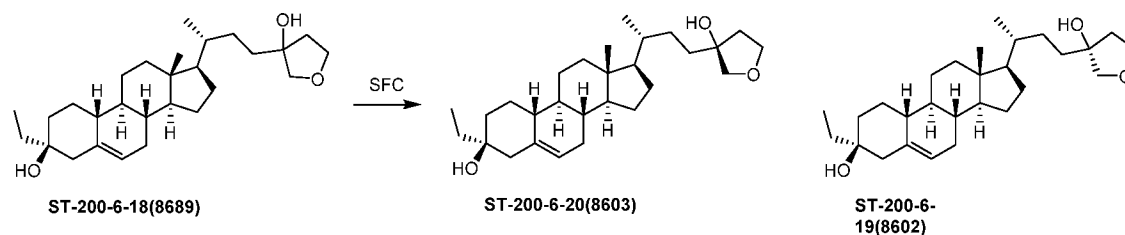
Mg powder (1.01 g, 42.9 mmol) was added in 4 portions by stirring with a solution of **ST-200-6-18\_1** (610 mg, 1.06 mmol) and NiCl<sub>2</sub> (13.6 mg, 0.106 mmol) in dry methanol (100 mL) under N<sub>2</sub> at 50°C. The reaction mixture was stirred at 60°C for 1 hour. The mixture was quenched with HCl (100 mL, 1 N) until the reaction became clear and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. The residue was purified by flash column (0-30 % of EtOAc in PE) to give 140 mg of product as a solid and 100 mg of impure product as a solid. The 140 mg product (0.325 mmol) was re-crystallized triturated from MeCN (10 mL) at 82°C to give **ST-200-6-18** (80 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 4.05-3.95 (m, 1H), 3.95-3.83 (m, 1H), 3.72-3.62 (m, 1H), 3.55-3.45 (m, 1H), 2.50-2.40 (m, 1H), 2.05-1.55 (m, 13H), 1.50-1.32 (m, 7H), 1.32-1.03 (m, 9H), 1.03-0.75 (m, 8H), 0.68 (s, 3H).

LCMS Rt = 1.086 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for

5 C<sub>28</sub>H<sub>45</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 413, found 413.

[00626] **Synthesis of ST-200-6-19 & ST-200-6-20**



Stereochemistry was confirmed by Xray data for 8603.

100 mg of **ST-200-6-18** (0.232 mmol) was purified by SFC (Column: AD (150×4.6mm, 3μm),

10 Gradient: 5%-40% B ( A: CO<sub>2</sub> B: ethanol ) Flow rate: 2.5mL/min ) to afford **ST-200-6-19** (16.0 mg, 16 %) as a solid and **ST-200-6-20** (17.0 mg, 17 %) as a solid.

**8602**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 4.05-3.95 (m, 1H), 3.95-3.83 (m, 1H), 3.72-3.62 (m, 1H), 3.55-3.48 (m, 1H), 2.30-2.15 (m, 1H), 2.05-1.55 (m, 12H), 1.50-1.32 (m, 7H),  
15 1.32-1.03 (m, 10H), 1.03-0.70 (m, 8H), 0.68 (s, 3H).

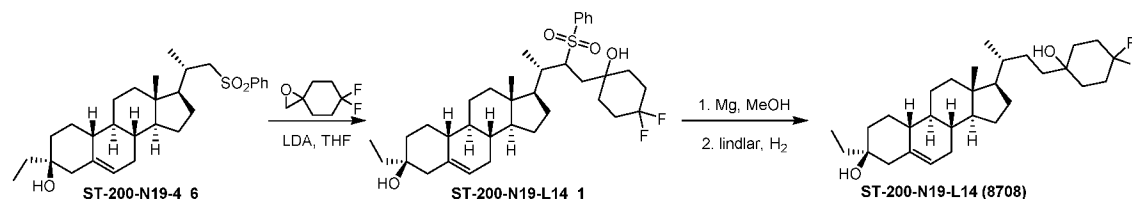
LCMS Rt = 1.088 min in 2.0 min chromatography, 30-90 AB, purity 100 %, MS ESI calcd. for C<sub>28</sub>H<sub>45</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 413, found 413.

**8603**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 4.05-3.95 (m, 1H), 3.95-3.83 (m, 1H), 3.72-3.62 (m, 1H), 3.55-3.48 (m, 1H), 2.50-2.40 (m, 1H), 2.05-1.55 (m, 13H), 1.50-1.32 (m, 6H),  
20 1.32-1.03 (m, 10H), 1.00-0.75 (m, 8H), 0.68 (s, 3H).

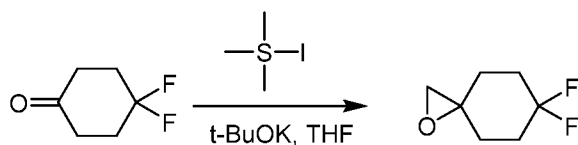
LCMS Rt = 1.084 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>28</sub>H<sub>45</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 413, found 413.

25 **EXAMPLE 87: Synthesis of 8708**



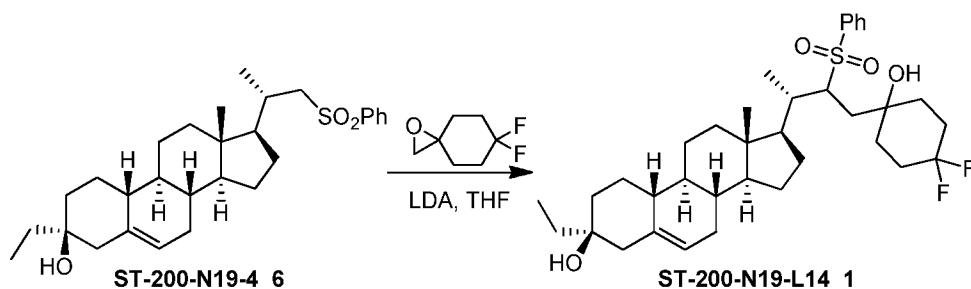
[00627] The experimental of intermediate **ST-200-N19-4\_6** can be found in Example 83.

[00628] The synthesis of the epoxide :

**200-DA-E31\_1****200-DA-E31\_2**

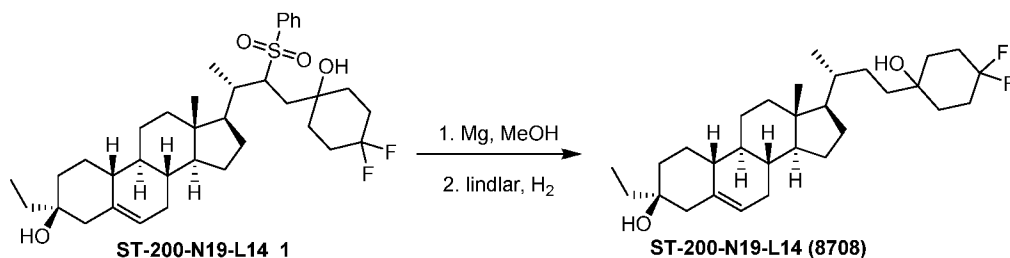
To a suspension of  $\text{Me}_3\text{SI}$  (3.93 g, 19.3 mmol) in THF (20 mL) was added a solution of  $\text{t-BuOK}$  (3.33 g, 29.8 mmol) in THF (10 mL) under  $\text{N}_2$  at  $15^\circ\text{C}$ . The suspension was stirred at  $15^\circ\text{C}$  for 30 mins. A solution of **200-DA-E31\_1** (2 g, 14.9 mmol) in THF (5 mL) was added dropwise at  $15^\circ\text{C}$ . The mixture was stirred at  $15^\circ\text{C}$  for 16 hrs. The mixture was quenched with Sat.  $\text{NH}_4\text{Cl}$  (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give **200-DA-E31\_2** (1.8 g, 82%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.72 (s, 2H), 2.20-1.85 (m, 8H).

**[00629] Synthesis of ST-200-N19-L14\_1**

A suspension of **ST-200-N19-4\_6** (200 mg, 0.42 mmol) in THF (4 mL) was added dropwise to a solution of  $n\text{-BuLi}$  (0.4 mL, 2.5 M in hexane, 1.06 mmol) in THF (1 mL) at  $-70^\circ\text{C}$  under  $\text{N}_2$ . The mixture was stirred for 30 min at  $-70^\circ\text{C}$ . A solution of diisopropylamine (107 mg, 1.06 mmol) was added dropwise at  $-70^\circ\text{C}$ , then a solution of 6,6-difluoro-1-oxaspiro[2.5]octane (94.4 mg, 0.64 mmol) was added dropwise at  $-70^\circ\text{C}$ . The mixture was stirred for another 30 min and then warmed to  $25^\circ\text{C}$  gradually. The reaction mixture was stirred at  $25^\circ\text{C}$  for 24 hours. The reaction mixture was quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (5 mL), extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **ST-200-N19-L14\_1** (290 mg, crude) as a solid, which was used directly for the next step.

**[00630] Synthesis of ST-200-N19-L14**

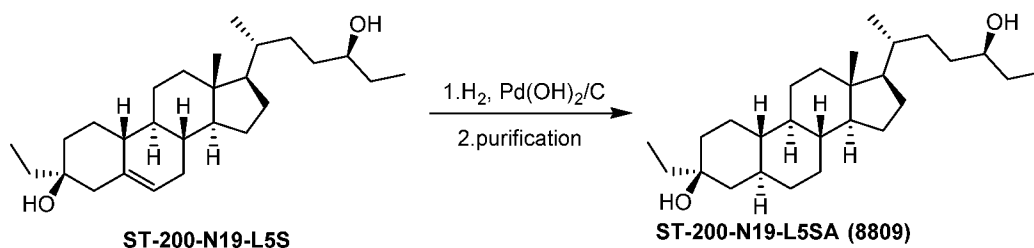


Mg powder (448 mg, 18.7 mmol) and NiCl<sub>2</sub> (5 mg, 0.05 mmol) were added to a solution of **ST-200-N19-L14\_1** (290 mg, 0.47 mmol) in 50 mL of anhydrous MeOH by stirring under N<sub>2</sub> at 60°C. The reaction mixture was quenched by 2 M HCl (50 mL) until solid was dissolved. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with Sat. NaHCO<sub>3</sub> (150 mL), brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~15 % of EtOAc in PE) to give a solid (<sup>1</sup>H NMR showed the product contained 10% 22,23-olefin). To a solution of **ST-200-N19-L14** in EtOAc (5 mL) was added Lindlar catalyst (100 mg) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> for three times. Then the solution was hydrogenated under 15 psi of hydrogen at 25°C for 4 h. The mixture was filtered through a pad of celite and washed with EtOAc (3 x 10 mL). The filtrate was concentrated and concentrated to give impure **ST-200-N19-L14** as a solid (<sup>1</sup>H NMR showed the product contained 8% 22,23-olefin). Lindlar catalyst (100 mg) was added to a solution of **ST-200-N19-L14** in THF/MeOH (3/3 mL) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> for three times. Then the solution was hydrogenated under 15 psi of hydrogen at 25°C for 4 h. The mixture was filtered through a pad of celite and washed with THF (3 x 10 mL). The filtrate was concentrated and triturated from PE (5 mL) and n-hexane (5 mL) at 25°C to give **ST-200-N19-L14** (19 mg, 31%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.35 (m, 1H), 2.27-2.19 (m, 1H), 2.17-1.76 (m, 11H), 1.69-1.57 (m, 6H), 1.52-1.21 (m, 11H), 1.19-0.98 (m, 6H), 0.97-0.91 (m, 4H), 0.88-0.74 (m, 5H), 0.68 (s, 3H).

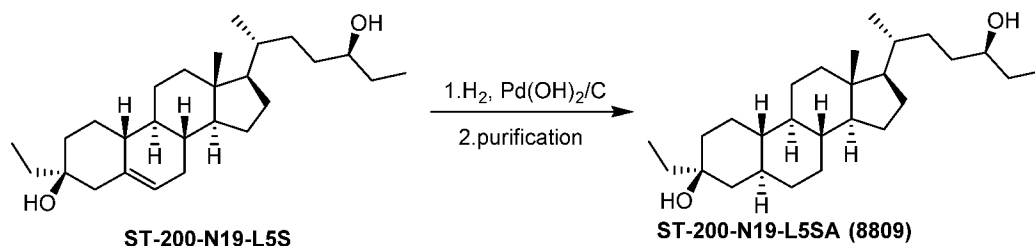
LCMS Rt = 1.252 min in 2.0 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>30</sub>H<sub>47</sub>F<sub>2</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 461, found 461.

#### EXAMPLE 88: Synthesis of 8809



[00631] The experimental of intermediate **ST-200-N19-L5S** can be found in Example 85.

[00632] **Synthesis of ST-200-N19-L5SA**

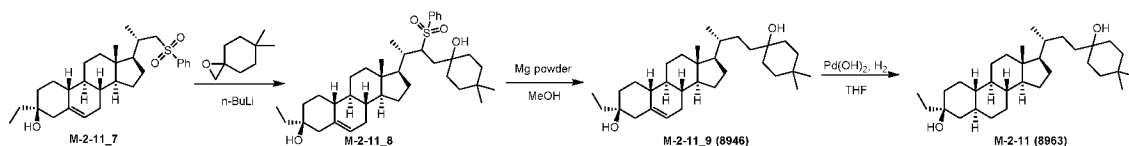


Pd(OH)<sub>2</sub>/C (100 mg) was added to ST-200-N19-L5S (45 mg, 0.11 mmol) in THF/MeOH (5 mL/5 mL). The mixture was degassed and back-filled with H<sub>2</sub> 3 times. Next, the reaction was stirred at 50°C under 50 psi of H<sub>2</sub> for 72 h. The reaction mixture was filtered through a pad of celite washed with THF (100 mL). The filtrate was concentrated to give **ST-200-N19-L5SA** as a solid, which was further triturated in n-hexane (3 mL) to give **ST-200-N19-L5SA** (5 mg, 11%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.53-3.43 (m, 1H), 2.07-1.61 (m, 13H), 1.59-1.21 (m, 13H), 1.20-0.99 (m, 8H), 0.98-0.75 (m, 9H), 0.74-0.53 (m, 4H).

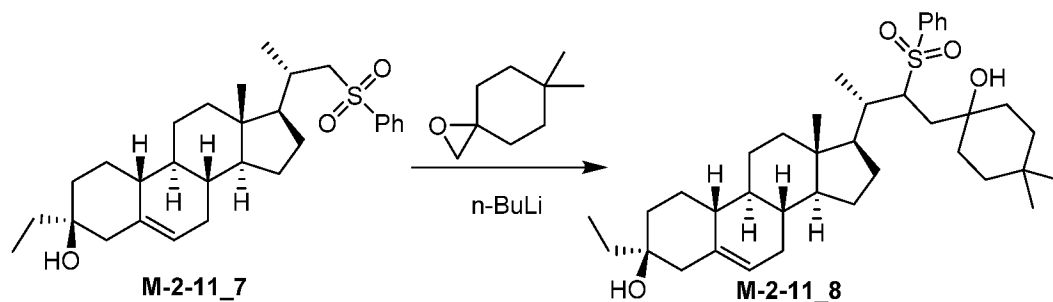
LCMS Rt = 1.267 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 369, found 369.

15 **EXAMPLE 89: Synthesis of 8946 and 8963**



[00633] The synthesis of **M-2-11\_7** can be found in Example 83. The synthesis of the epoxide can be found in Example 28.

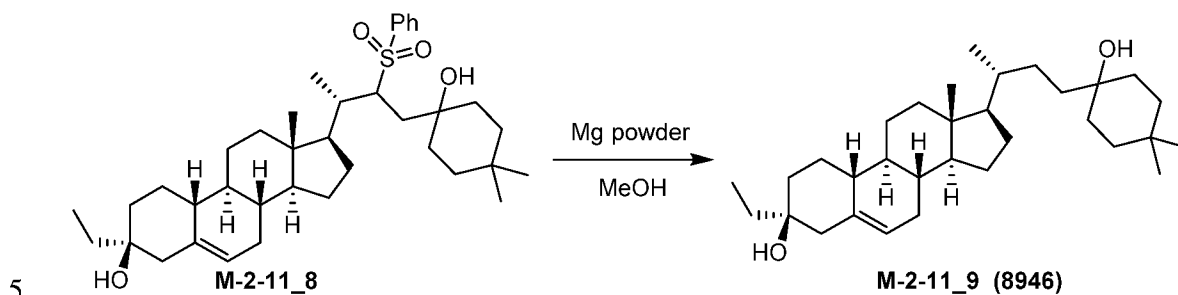
[00634] **Synthesis of M-2-11\_8**



n-BuLi (1.01 mL, 2.54 mmol, 2.5 M in hexane) was added to a solution of **M-2-11\_7** (400 mg, 0.849 mmol) in THF (5 mL) at -70°C under N<sub>2</sub>. After stirring at -70°C for 1 hrs, 6, 6-dimethyl-1-oxaspiro [2.5]octane (236 mg, 1.69 mmol) was added at -70°C. The reaction was allowed to

25°C and stirred at 25°C for 12 hours, quenched with NH<sub>4</sub>Cl (10 mL, sat. aq) and water (30 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were concentrated in vacuum to give **M-2-11\_8** (400 mg, crude) as an oil, which was used directly for the next step.

**[00635] Synthesis of M-2-11\_9**

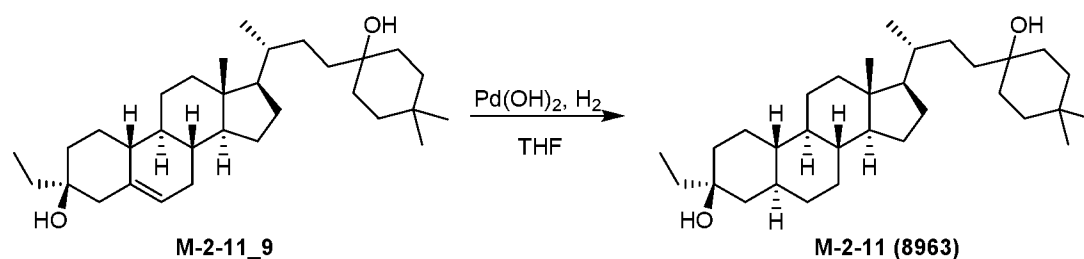


Mg powder (792 mg, 32.6 mmol) was added to a solution of **M-2-11\_8** (400 mg, crude) in MeOH (80 mL) at 50°C. The mixture was stirred at 50°C for 1h. After cooling to 0°C, the mixture was quenched with HCl (50 mL, 2 M) until the reaction became clear and extracted with EtOAc (2 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by flash column (0-40% of EtOAc in PE) to give 150 mg of impure a solid, which was triturated from MeCN (3 mL) at 25°C to give **M-2-11\_9** (120 mg, 40%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.39-5.38 (s, 1H), 2.26-2.21 (m, 1H), 2.05-1.77 (m, 7H), 1.68-1.38 (m, 16H), 1.33-1.00 (m, 14H), 0.96-0.90 (m, 6H), 0.89-0.81 (m, 7H), 0.68 (s, 3H).

15 **LCMS** Rt = 1.651 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>32</sub>H<sub>51</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 435, found 435.

**[00636] Synthesis of M-2-11**

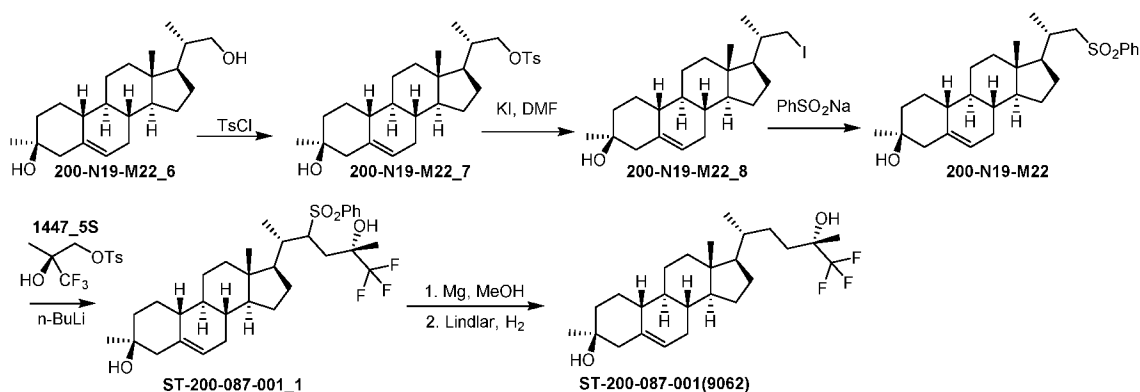


Dry Pd (OH)<sub>2</sub> (118 mg, 0.845 mmol) was added to a solution of **M-2-11\_9** (80 mg, 0.169 mmol) in THF (5 mL) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> 3 times. The mixture was stirred under H<sub>2</sub> (50 psi) at 50°C for 12 hours to give a black suspension. The reaction mixture was filtered through a pad of celite and washed with THF (3 x 30 mL). The filtrate was concentrated in vacuum to get **M-2-11** (20 mg, 25%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.97-1.91 (s, 1H), 1.88-1.76 (m, 4H), 1.69-1.60 (m, 3H), 1.59-1.46 (m, 15H), 1.31-1.06 (m, 14H), 0.94-0.86 (m, 15H), 0.69-0.63 (m, 4H).

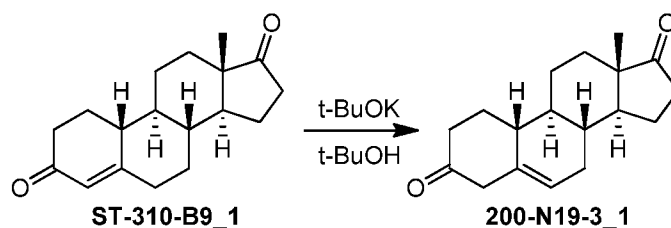
LCMS Rt = 1.718 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for  $C_{32}H_{52}$   $[M+H-2H_2O]^+$  437, found 437.

### EXAMPLE 90: Synthesis of 9062



[00637] Synthesis for the experimental of intermediate **200-N19-M22\_6** (or **M-4-14-2**):

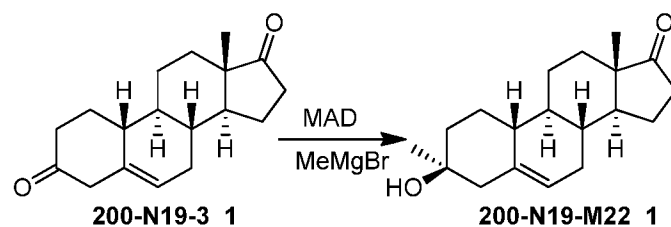
### Synthesis of 200-N19-3\_1



t-BuOH (1.7 L) was charged into a three-neck round bottom flask under  $N_2$  at  $35^\circ C$  and stirred for 10 mins. t-BuOK (292 g, 2.61 mol) was added to the mixture and stirred until the reaction became clear. After that, **ST-310-B9\_1** (65 g, 238 mmol) was added to the above mixture and stirred for 1.5 h at  $35^\circ C$  under  $N_2$ . The reaction mixture was poured into 10% aqueous acetic acid (2 L) and stirred for 30 mins, during which the temperature was maintained below  $10^\circ C$ . Then the mixture was treated with water (1.5 L) and the pH was adjusted to 7~8 with  $NaHCO_3$  and stirred for 30 mins. The aqueous phase was extracted with MTBE (3 L). The organic layer was separated, washed with brine (3 x 1 L), dried over anhydrous  $Na_2SO_4$ , filtered and concentrated below  $35^\circ C$  to give **ST-200-N19-3\_1** (65 g, crude) as an oil. The crude residue was used directly for the next step.

15

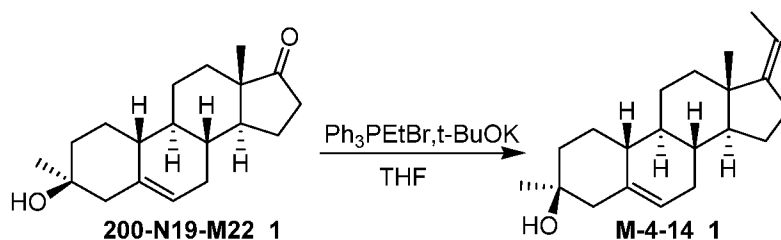
### Synthesis of 200-N19-M22\_1



To a solution of 2,6-di-tert-butyl-4-methylphenol (340 g, 1.54 mol) in toluene (700 mL) was added drop-wise  $\text{AlMe}_3$  (385 mL, 770 mmol, 2 M in toluene) at  $0^\circ\text{C}$ . The mixture was stirred at  $25^\circ\text{C}$  for 1 h and used directly as MAD solution. A solution of **200-N19-3\_1** (60 g, 220 mmol) in anhydrous toluene (200 mL) and anhydrous DCM (200 mL) was added to MAD solution at  $-70^\circ\text{C}$  over a period of 30 mins under  $\text{N}_2$ . The reaction mixture stirring at  $-70^\circ\text{C}$  for 1 h. Then  $\text{MeMgBr}$  (220 mL, 660 mmol, 3M in ethyl ether) was added drop wise at  $-70^\circ\text{C}$  and stirred for 1 h. The reaction was poured into saturated aqueous citric acid (2 L) at  $0^\circ\text{C}$  and stirring for 30 min, extracted with EtOAc (2 x 1 L). The combined organic phase was washed with saturated brine (2 x 1 L), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 5/1) to afford **200-N19-M22\_1** (33 g, 52%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.46-5.42 (m, 1H), 2.25-2.40 (m, 1H), 2.21-1.60 (m, 13H), 1.35-1.21 (m, 4H), 1.13 (s, 3H), 0.98-0.83 (m, 6H).

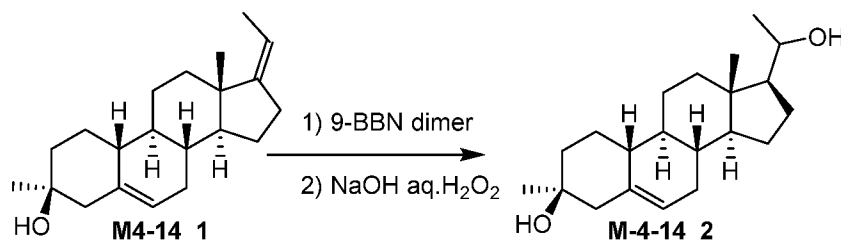
#### Synthesis of M-4-14\_1



To a suspension of  $\text{Ph}_3\text{PEtBr}$  (102 g, 277 mmol) in Anhydrous THF (500 mL) was added t-BuOK (31.0 g, 277 mmol) in one portion at  $25^\circ\text{C}$  under  $\text{N}_2$ . The reaction mixture turned to dark red. After stirring at  $25^\circ\text{C}$  for 30 min, **200-N19-M22\_1** (20 g, 69.3 mmol) was added and stirred for 2 h at  $25^\circ\text{C}$ . The reaction was quenched with aq.  $\text{NH}_4\text{Cl}$  (800 mL) at  $0^\circ\text{C}$ , extracted with EtOAc (2 x 500 mL). The combined organic phase was washed with brine (2 x 500 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 5/1) to afford **M-4-14\_1** (15 g, 72%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.43-5.40 (m, 1H), 5.16-5.10 (m, 1H), 2.41-2.33 (m, 1H), 2.28-1.86 (m, 8H), 1.78-1.71 (m, 1H), 1.69-1.50 (m, 11H), 1.41-1.10 (m, 6H), 0.94-0.81 (s, 3H).

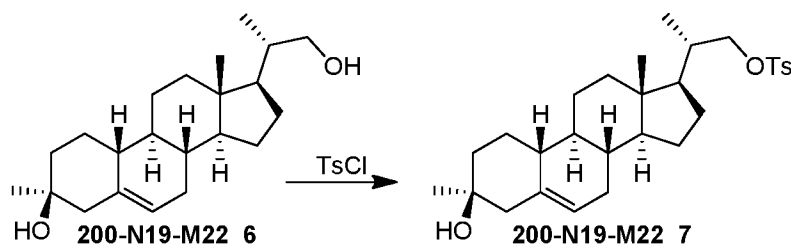
#### Synthesis of M-4-14\_2



[00638] To a solution of **M-4-14\_1** (30 g, 99.8 mmol) in anhydrous THF (500 mL) was added 9-BNN dimer (66.9 g, 299 mmol) and stirred for 30 mins at 0°C under N<sub>2</sub>. The reaction mixture was warmed to 50°C and stirred for 1 h. after cooled to 0°C and EtOH (100 mL) was added. NaOH.aq (99.8 mL, 5M, 499 mmol) was added very slowly. H<sub>2</sub>O<sub>2</sub> (53.0 g, 499 mmol, 30% in water) was added slowly and the inner temperature was maintained below 30°C. The mixture was warmed to 50°C and stirred for 1 h. The reaction mixture was cooled and ice-water (1 L) was added and stirred 30 min. filtered and concentrated in vacuum to give **M-4-11\_2** (30 g, crude) as a solid. The crude material was used directly for the next step.

10 [00639] The synthesis of the tosylate can be found in Example 30.

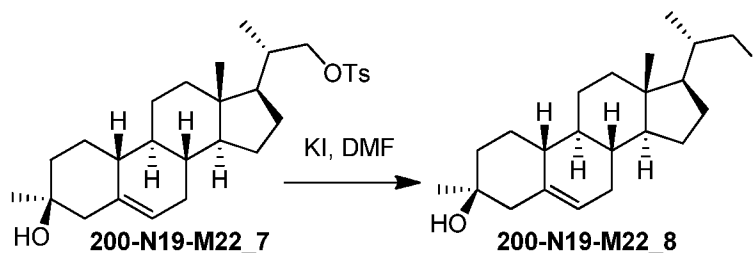
[00640] **Synthesis of 200-N19-M22\_7**



TEA (21 mL) and TsCl (16.0 g, 84.0 mmol) were added to a solution of **200-N19-M22\_6** (7 g, 21.0 mmol) in DCM (150 mL) at 25°C. The mixture was stirred at 40°C for 12 h. To the reaction was added water (200 mL). The aqueous phase was extracted with DCM (2 x 200 mL). The combined organic phase was washed with saturated brine (2 x 200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated was purified by silica gel chromatography (PE/EtOAc = 10/1 to 8/1) to afford **200-N19-M22\_7** (10 g, 98%) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.79-7.76 (m, 2H), 7.34-7.26 (m, 2H), 5.38-5.29 (m, 1H), 3.95-3.93 (m, 1H), 3.74-3.73 (m, 1H), 2.44 (s, 3H), 2.19-2.14 (m, 1H), 2.09-1.97 (m, 3H), 1.92-1.44 (m, 14H), 1.29-1.08 (m, 6H), 1.05-0.88 (m, 5H), 0.63 (s, 3H).

[00641] **Synthesis of 200-N19-M22\_8**

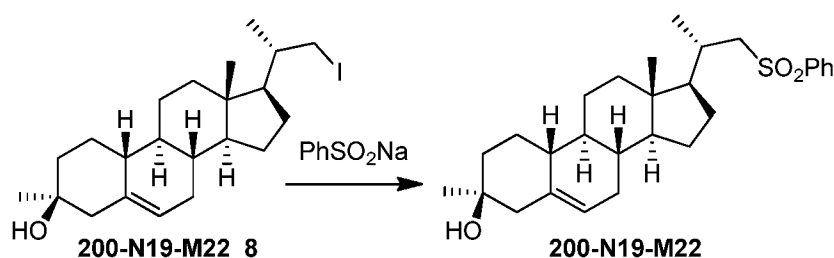


KI (16.9 g, 102 mmol) was added to a solution of **200-N19-M22\_7** (10 g, 20.5 mmol) in DMF (100 mL) at 25°C under N<sub>2</sub>. The mixture was stirred at 50°C for 12 h under N<sub>2</sub>. The residue was poured into ice-water (300 mL) and stirred for 20 min. The aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic phase was washed with saturated brine (2 x 200

mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give **200-N19-M22\_8** (8 g, 88%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.41-5.39 (m, 1H), 3.40-3.28 (m, 1H), 3.23-3.13 (m, 1H), 2.19-2.13 (m, 1H), 2.10-1.71 (m, 9H), 1.63-1.34 (m, 7H), 1.16-0.98 (m, 10H), 0.96-0.77 (m, 2H), 0.72 (s, 3H).

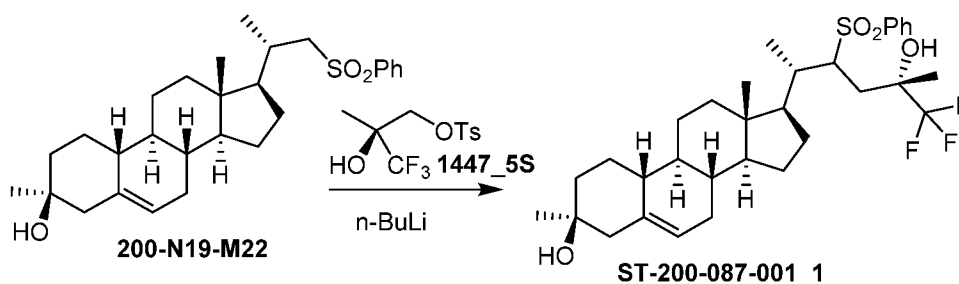
**[00642] Synthesis of 200-N19-M22**



$\text{PhSO}_2\text{Na}$  (9.27 g, 56.5 mmol) was added to a solution of **200-N19-M22\_8** (5 g, 11.3 mmol) in DMF (50 mL) and stirred at  $50^\circ\text{C}$  for 6 h. The reaction mixture was cooled to  $25^\circ\text{C}$  and added water (200 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (2 x 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by a silica gel column (PE/EtOAc = 8/1~5/1) to give **200-N19-M22** (4.0 g) as a solid. The **200-N19-M22** (4.0 g, 8.75 mmol) was re-crystallized from MeCN (50 mL) at  $82^\circ\text{C}$  reflux for 1 hrs. The mixture stirred was cooled to  $25^\circ\text{C}$  (room temperature). The suspension was filtration in vacuum to get **200-N19-M22** (3.5 g, 68%) as a solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94-7.88 (m, 2H), 7.66-7.54 (m, 3H), 5.39-5.37 (m, 1H), 3.17-3.13 (m, 1H), 2.88-2.81 (m, 1H), 2.18-2.12 (m, 1H), 2.11-1.47 (m, 15H), 1.28-1.08 (m, 8H), 1.07-0.74 (m, 5H), 0.65 (s, 3H).

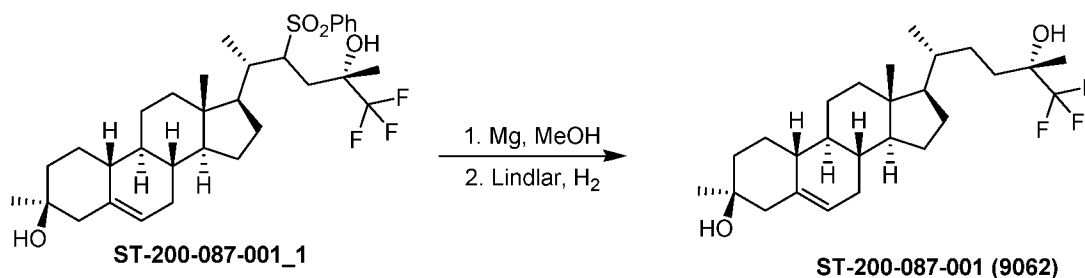
**[00643] Synthesis of ST-200-087-001\_1**



$n\text{-BuLi}$  (1.22 mL, 3.06 mmol, 2.5M in  $n\text{-hexane}$ ) was added dropwise to a solution of **200-N19-M22** (400 mg, 0.876 mmol) in anhydrous THF (3.5 mL) at  $-70^\circ\text{C}$  under  $\text{N}_2$ . After stirring at  $-70^\circ\text{C}$  for 30 mins, a solution of (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (390 mg, 1.31 mmol) in anhydrous THF (0.5 mL) was added drop-wise at  $-70^\circ\text{C}$  and stirred for another 1 h. The reaction mixture was stirred at  $25^\circ\text{C}$  (room temperature)

for 12 h. The reaction was quenched by saturated  $\text{NH}_4\text{Cl}$ .aq (20 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give **ST-200-087-001\_1** (0.4 g, crude) as a solid, which was used directly.

#### 5 [00644] Synthesis of ST-200-087-001



Mg powder (986 mg, 41.1 mmol) and  $\text{NiCl}_2$  (20 mg) were added to a solution of **ST-200-087-001\_1** (0.4 g, crude) in MeOH (50 mL) at  $25^\circ\text{C}$  under  $\text{N}_2$ . After stirring at  $50^\circ\text{C}$  for 1 h under  $\text{N}_2$ , the reaction mixture was quenched with HCl (100 mL, 1 M) until the reaction became clear.

10 The aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 8/1 to 5/1) to afford **ST-200-087-001** (63 mg, 20.7%) as a solid and **ST-200-087-001** (80 mg, impure) as a solid.

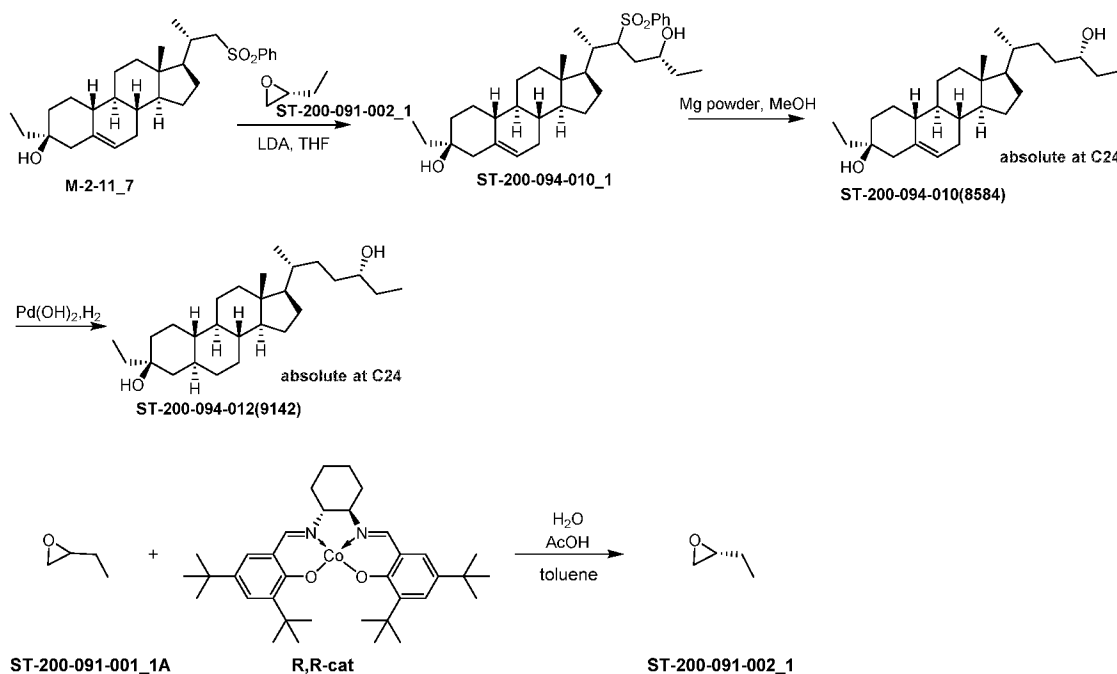
15 Lindlar catalyst (300 mg) was added to a solution of **ST-200-087-001** (143 mg, 0.323 mmol) in anhydrous THF (2 mL) under  $\text{N}_2$ . The suspension was degassed under vacuum and purged with  $\text{H}_2$  for three times. The mixture was stirred under  $\text{H}_2$  (15 psi) at  $25^\circ\text{C}$  for 4 hours to give a black suspension. The reaction mixture was filtered through a pad of Celite and washed with EtOAc (2 x 30 mL). The filtrate was concentrated in vacuum to give **ST-200-087-001** (80 mg, 56%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.41-5.39 (m, 1H), 2.19-2.14 (m, 1H), 2.10-1.61 (m, 11H), 1.54-1.16 (m, 13H), 1.14-0.73 (m, 12H), 0.69 (s, 3H).

LCMS Rt = 1.217 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for  $\text{C}_{26}\text{H}_{40}\text{F}_3\text{O}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  425, found 425.

25

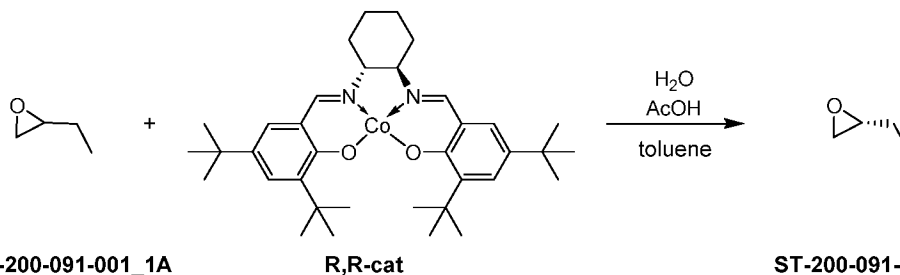
#### EXAMPLE 91: Synthesis of 9142



[00645] The experimental of intermediate M-2-11\_7 can be found in Example 83.

[00646] See Example 85 for stereochemistry synthesis.

[00647] **Synthesis of ST-200-091-002\_1**

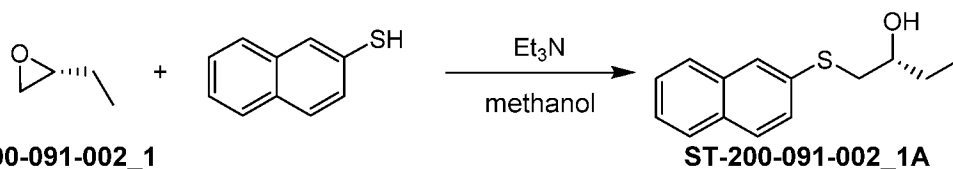


5 **ST-200-091-001\_1A** **R,R-cat** **ST-200-091-002\_1**

To a solution of R, R-cat (166 mg, 0.276 mmol) in toluene (5 mL) was added AcOH (173 mg, 2.89 mmol). The mixture was stirred at 25°C open to air for 30 min and concentrated in vacuo to leave a crude solid. The resulting catalyst residue was dissolved in 2-ethyloxirane (10 g, 138 mmol) at 25°C. The reaction flask was cooled to 0 °C and treated with H<sub>2</sub>O (1.36 g, 75.9 mmol) dropwise over 5 min. The reaction was allowed to warm to 25°C and stir 24 hrs and the reaction mixture was distilled to give (R)-2-ethyloxirane (4.4 g, 61.0 mmol).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.91-2.88 (m, 1H), 2.76-2.71 (m, 1H), 2.49-2.47 (m, 1H), 1.62-1.54 (m, 2H), 1.03-0.97 (m, 3H).

[00648] The ee value of the epoxide was determined as following

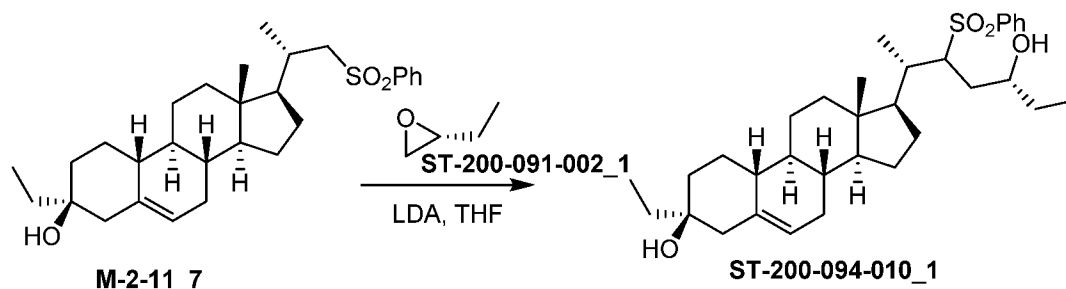


15

To a solution of (2R)-2-ethyloxirane (100 mg, 1.38 mmol) and naphthalene-2-thiol (221 mg, 1.38 mmol) in methanol (10 mL) was added triethylamine (139 mg, 1.38 mmol). The mixture was stirred at 30°C for 16 hrs. The reaction mixture was used directly to determine ee% without any treatment. The ee% was determined to be 93.6%.

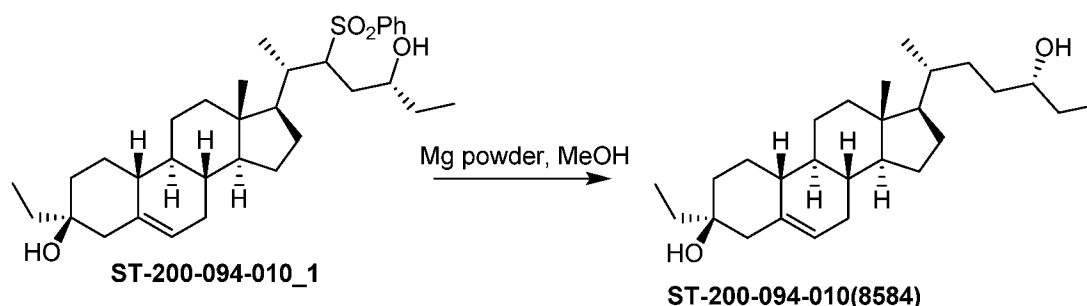
5 **SFC** Rt = 5.287 min in 10 min chromatography, AD-3\_IPA(DEA)\_5\_40\_2.5ML, 93.6%ee.

**[00649] Synthesis of ST-200-094-010\_1**



To a solution of **M-2-11\_7** (400 mg, 0.849 mmol) in anhydrous THF (3 mL) was added n-BuLi (1.01 mL, 2.54 mmol, 2.5 M in n-hexane) drop-wise at -70°C under N<sub>2</sub>. After stirring at -70°C for 30 mins, a solution of (R)-2-ethyloxirane (91.5 mg, 1.27 mmol) in anhydrous THF (0.5 mL) was added drop-wise at -70°C. The reaction mixture was stirred at -70°C for another 1 h and then stirred at 25°C (room temperature) for 12 h. After heating at 60°C for 2 h, the reaction was quenched by saturated aqueous NH<sub>4</sub>Cl (50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combine organic phase was washed with saturated brine (2 x 50 mL). dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. filtered and concentrated in vacuum to give **ST-200-94-10\_1** (0.4 g, crude) as an oil, which was used directly of the next step.

**[00650] Synthesis of ST-200-094-010**



To a solution of **ST-200-094-010\_1** (0.4 g, crude) in MeOH (50 mL) was added Mg powder (883 mg, 36.8 mmol) and NiCl<sub>2</sub> (20 mg) at 25°C under N<sub>2</sub>. After stirring at 60°C for 1 h, the reaction mixture was quenched with HCl (100 mL, 1 M) until the reaction became clear. The aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic phase was washed with saturated NaHCO<sub>3</sub>.aq (2 x 50 mL), washed saturated brine (2 x 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 8/1) to afford **ST-200-094-010** (180 mg, 61%) as a solid.

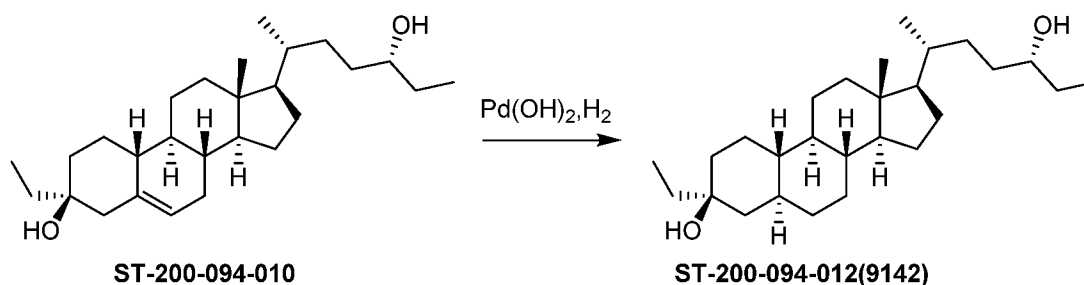
The **ST-200-094-010** (180 mg, 0.447 mmol) was purified by SFC (Column:AD(250mm\*30mm,5um), Condition:0.1%NH<sub>3</sub>H<sub>2</sub>O IPA, Begin B:40%, End B:40%) to afford **ST-200-094-010** (120 mg, 67%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 5.40-5.37 (m, 1H), 3.48-3.46 (m, 1H), 2.25-2.21 (m, 1H), 2.05-1.74 (m, 7H), 1.65-1.40 (m, 13H), 1.38-1.07 (m, 11H), 1.06-0.96 (m, 6H), 0.85 (s, 3H), 0.68 (s, 3H).

LCMS = 1.277 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 385, found 385.

SFC Rt = 5.736 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 99.5%de.

#### 10 [00651] Synthesis of ST-200-094-012



A solution of **ST-200-094-010** (88 mg, 0.2185 mmol) and Pd(OH)<sub>2</sub> (80 mg) in MeOH (10 mL) was hydrogenated under 50 psi of hydrogen at 50°C for 12 hours. The reaction mixture was filtered through a pad of celite and the filter cake was washed with THF (3 x 100 mL). The filter liquor was concentrated in vacuum. The residue was purified by flash column (10~25% of EtOAc in PE) to give **ST-200-094-012** (27 mg, 31%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 3.50-3.41 (m, 1H), 1.99-1.91 (m, 1H), 1.87-1.74 (m, 3H), 1.70-1.60 (m, 3H), 1.53-1.19 (m, 12H), 1.18-0.97 (m, 11H), 0.96-0.78 (m, 12H), 0.75-0.54 (m, 5H).

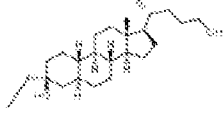
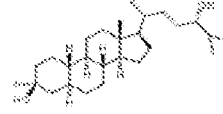
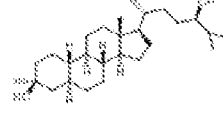
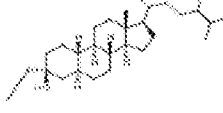
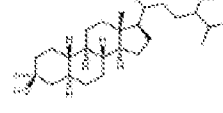
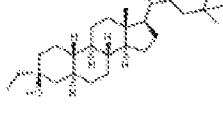
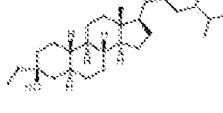
LCMS Rt = 1.292 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 369, found 369.

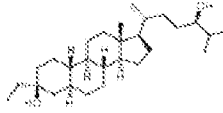
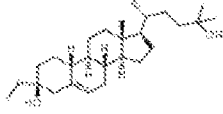
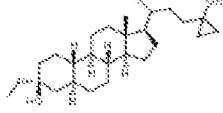
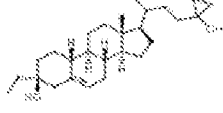
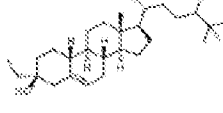
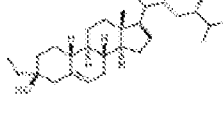
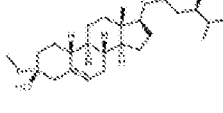
### EXAMPLE 93. Biological Data

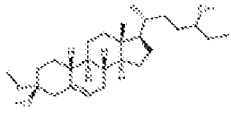
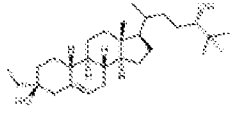
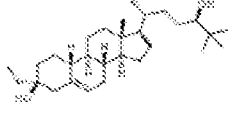
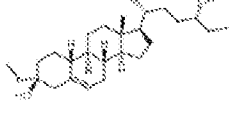
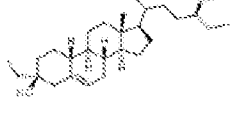
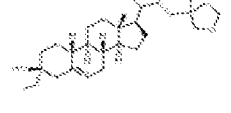

[00652] The experiments were conducted as described in Example 2 and the results are provided in Table 2-61.


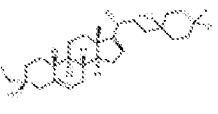
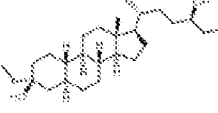
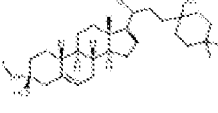
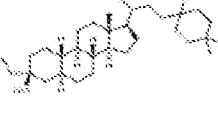
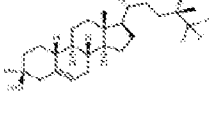
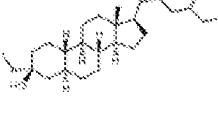
**Table 2-61.**

	Compound	Avg EC50 2A (nM)	Avg Emax 2A (%)	Avg EC50 2B (nM)	Avg Emax 2B (%)

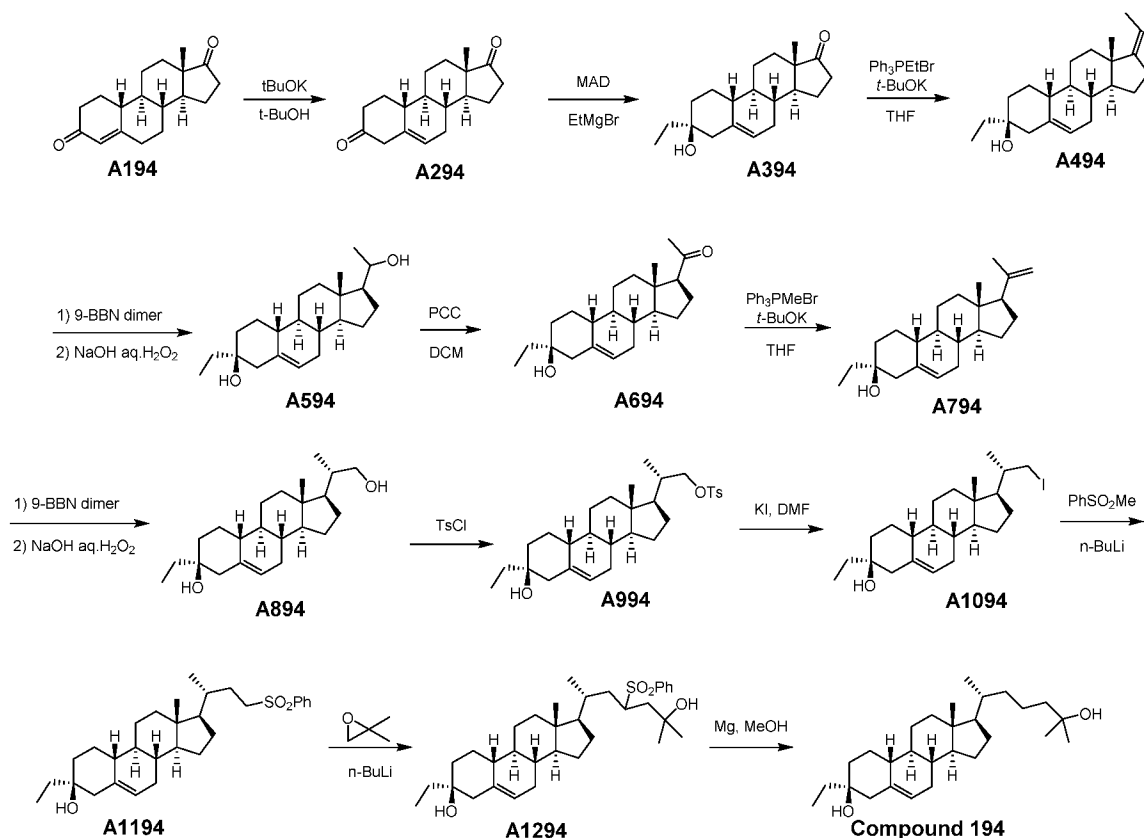
	376	>10000	49.9	>10000	59.8
	1A75	671.1	457.2	439.6	308.0
	1B75	164.9	278.8	183.4	233.1
	476	406.0	811.2	189.5	399.2
	175	574.1	366.7	287.5	279.0
	679	5113.4	104.9	280.0	171.5
	4A77	427.2	382.5	285.2	253.7

	4B77	466.8	466.6	298.2	320.5
	780	340.9	132.1	263.2	169.7
	8127	543.0	135.7	571.2	210.7
	8245	524.5	73.0	267.6	119.5
	8361	87.0	252.0	136.3	308.8
	8462	170.0	273.2	96.2	281.0
	8463	102.5	291.3	85.1	324.2

	8564	468.8	252.5	489.5	310.5
	8378	123.9	195.0	208.3	258.6
	8379	73.4	251.8	78.1	358.6
	8584	332.2	284.3	244.5	363.1
	8585	286.2	194.4	236.7	232.9
	8689	168.6	319.6	174.8	438.6
	8602	1047.1	271.7	433.7	262.3

	8603	134.9	293.5	75.1	270.6
	8708	697.2	117.4	552.7	243.2
	8809	532.9	73.6	160.4	78.2
	8946	1596.2	262.8	1352.5	231.4
	8963	>10000	8.4	>10000	55.9
	9062	34.5	66.5	179.0	52.2
	9142	>10000	41.6	70.4	44.8

**Example 94. Synthesis of Compound 194.**



*Step 1:*  $t\text{-BuOH}$  (350 mL) was charged into a three-neck round bottom flask under nitrogen at  $35^\circ\text{C}$  and stirred under nitrogen gas bubbling for 10 mins.  $t\text{-BuOK}$  (90.5 g, 807 mmol) was added to the mixture and stirred under nitrogen gas bubbling for 15 mins. **A194** (20 g, 73.4 mmol) was added to the above mixture and stirred under nitrogen gas bubbling at  $35^\circ\text{C}$  for 1.5 hrs. The reaction mixture was poured into 10% aqueous acetic acid (500 mL) and stirred for 15 mins below  $35^\circ\text{C}$ . Water (500 mL) was added to the reaction and stirred for 30 mins. The pH of the mixture was adjusted to 7-8 with sodium bicarbonate (500 mL). The mixture was stirred for 30 mins. The mixture was extracted with PE (2 x 500 mL). The organic layer was separated, washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated below  $35^\circ\text{C}$  to give **A294** (17 g, crude) as an oil. The crude residue was used directly for the next step.

*Step 2:* To a solution of 2, 6-di-tert-butyl-4-methylphenol (100 g, 453 mmol) in toluene (300 mL) was added drop-wise  $\text{AlMe}_3$  (113 mL, 226 mmol, 2 M in toluene) at  $0^\circ\text{C}$ . The mixture was stirred at  $25^\circ\text{C}$  for 1 h. A solution of **A294** (10 g, 36.7 mmol) in toluene (50 mL) was added dropwise at  $-70^\circ\text{C}$  and after stirring at  $-70^\circ\text{C}$  for 1 h,  $\text{EtMgBr}$  (36.6 mL, 110 mmol, 3M in ethyl ether) was added drop wise at  $-70^\circ\text{C}$ . The resulting solution was stirred at  $-70^\circ\text{C}$  for 1 hr. The reaction mixture was quenched by saturated citric acid (400 mL) at  $-70^\circ\text{C}$ . After stirring at  $25^\circ\text{C}$  for 10 min, the resulting mixture was filtered and washed with  $\text{EtOAc}$  (2 x 200 mL). The

combined organic layer was separated, washed with brine (2 x 200 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 5/1) to get **A394** (7.6 g, impure) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.40 (m, 1H), 2.51-2.38 (m, 1H), 2.49-2.21 (m, 1H), 2.14-1.88 (m, 5H), 1.86-1.77 (m, 2H), 1.73-1.38 (m, 8H), 1.34-1.22 (m, 4H), 0.95-0.81 (m, 8H).

*Step 3:* To a suspension of PPh<sub>3</sub>EtBr (37.1 g, 100 mmol) in THF (200 mL) under N<sub>2</sub> was added t-BuOK (11.2 g, 100 mmol) at 40°C. After stirring at 20°C for 10 min, **A394** (7.6 g, 25.1 mmol) was added. The reaction mixture was stirred at 40°C for 1 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (200 mL) at 0°C and extracted with EtOAc (3 x 200 mL). The

combined organic phase was washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography (0%-30% of EtOAc in PE) to afford **A494** (5 g, 63%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.35 (m, 1H), 5.20-5.00 (m, 1H), 2.41-2.30 (m, 1H), 2.29-2.12 (m, 3H), 2.09-1.76 (m, 6H), 1.69-1.38 (m, 15H), 1.35-0.94 (m, 7H).

*Step 4:* To a solution of **A494** (2 g, 6.35 mmol) in THF (20 mL) was added 9-BBN dimer (3.09 g, 12.7 mmol) at 0°C under N<sub>2</sub>. The solution was stirred at 60°C for 1h. After cooling to 0°C, a solution of EtOH (20 ml) and NaOH (12.7 ml, 5M, 63.5 mmol) was added very slowly. After addition, H<sub>2</sub>O<sub>2</sub> (2.15 mg, 6.35 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 60°C under N<sub>2</sub> for 1 hour. The mixture was re-cooled to 30°C., water (100 mL) was added to the solution and extracted with EtOAc (100 mL). The organic layer was washed with brine (2 x 100 mL) and then the combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and purified by silica gel chromatography (PE/EtOAc = 2/1 ) to afford impure **A594** (1.6 g) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.35 (m, 1H), 3.75-3.62 (m, 1H), 2.28-2.19 (m, 1H), 2.10-1.75 (m, 7H), 1.71-0.97 (m, 19H), 0.92-0.75 (m, 4H), 0.68 (s, 3H).

*Step 5:* To a solution of **A594** (1.6 g, 4.81 mmol) in DCM (20 mL) was added silica gel (2 g) and PCC (2.07 g, 9.62 mmol). The mixture was stirred at 25°C for 3 hrs. To the mixture was added PE (50 mL) and the mixture was filtered through a pad of silica gel and the solid was washed with PE/DCM (30 mL/30 mL). The mixture was filtered and filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 5/1) to afford impure **A094** (1.2 g) as a solid, which was re-crystallized from MeCN (10 mL) at reflux (82°C) to give **A694** (1.0 g, 84%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 2.61-2.45 (m, 1H), 2.30-2.10 (m, 5H), 2.00-1.75 (m, 6H), 1.70-1.10 (m, 14H), 0.90-0.75 (m, 4H); 0.633 (s, 3H).

**LCMS** Rt = 1.058 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>22</sub>H<sub>33</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 313, found 313.

*Step 6:* To a suspension of Ph<sub>3</sub>PMeBr (11.1 g, 31.4 mmol) in THF (50 mL) under N<sub>2</sub> was added t-BuOK (3.51 g, 31.4 mmol) at 40°C. After stirring at 25°C for 10 min, **A6** (2.6 g, 7.86 mmol)

was added. The reaction mixture was stirred at 40°C for 1 h. The reaction was quenched with aq.NH<sub>4</sub>Cl (100 mL) at 0°C, extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with brine (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography (0%~30%, EtOAc in PE) to afford **A794** (2.4 g, 93%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.35 (m, 1H), 4.86-4.83 (m, 1H), 8.70-4.65 (m, 1H), 2.27-2.20 (m, 1H), 2.10-1.90 (m, 4H), 1.89-1.50 (m, 11H), 1.49-1.30 (m, 3H), 1.28-1.00 (m, 6H), 0.80-0.60 (m, 5H), 0.59 (s, 3H).

*Step 7:* To a solution of **A794** (2.4 g, 7.30 mmol) in THF (40 mL) was added 9-BBN dimer (4.44 g, 18.2 mmol) at 0°C under N<sub>2</sub>. The solution was stirred at 60°C for 1 h. After cooling to 0°C, a

solution of EtOH (30 mL) and NaOH (14.5 mL, 5M, 73.0 mmol) was added very slowly. After addition, H<sub>2</sub>O<sub>2</sub> (7.29 mL, 73.0 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 60°C under N<sub>2</sub> for 1 hour. The mixture was re-cooled to 30°C and water (100 mL) was added to the solution with EtOH (50 mL). A precipitate appeared, which was collected by filtration and concentrated in vacuum to give **A894**

(1.8 g, 71%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.35 (m, 1H), 3.69-3.60 (m, 1H), 3.40-3.30 (m, 1H), 2.25-2.00 (m, 1H), 2.08-1.75 (m, 7H), 1.68-1.60 (m, 2H), 1.55-1.38 (m, 5H), 1.36-1.09 (m, 8H), 1.08-0.93 (m, 4H), 0.89-0.76 (m, 5H), 0.70 (s, 3H).

*Step 8:* To a solution of **A894** (1 g, 2.88 mmol) in chloroform (5.5 mL) and pyridine (3.5 mL)

was added TsCl (1.42 g, 7.48 mmol) at 25°C. The mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under vacuum to remove most of the chloroform. To the obtained pyridine mixture was added water (50 mL). A solid was produced, which was collected by filtration and washed with water (5 x 50 mL). The solid was dissolved in DCM (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **A994** (1.2 g, crude) as an oil, which was used directly for the next step.

*Step 9:* To a solution of **A994** (800 mg, 1.55 mmol) in DMF (6 mL) was added KI (1.23 g, 7.44 mmol) at 25°C. The mixture was stirred at 50°C for 1 hour. The reaction mixture was poured into water (50 mL) with PE (30 mL). The organic phase was washed with brine (2 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **A1094** (700 mg, 96%) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.45-5.35 (m, 1H), 3.36-3.30 (m, 1H), 3.20-3.10 (m, 1H), 2.30-2.20 (m, 1H), 2.07-1.70 (m, 7H), 1.68-1.60 (m, 2H), 1.32-1.14 (m, 8H), 1.13-0.94 (m, 6H), 0.93-0.74 (m, 7H), 0.72 (s, 3H).

*Step 10:* To a solution of PhSO<sub>2</sub>Me (449 mg, 2.88 mmol) in THF (10 mL) was added n-BuLi (1.04 mL, 2.62 mmol, 2.5 M in hexane) at -70°C under N<sub>2</sub>. The mixture was warmed to 0°C. A suspension of **A1094** (600 mg, 1.31 mmol) in THF (10 mL) was added drop-wise at 0°C. After addition, the reaction was allowed to 25°C. The reaction mixture was stirred at 25°C for 1 hour. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (30 mL). To the suspension was added water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was concentrated to give a residue which was purified by silica gel chromatography (PE/EtOAc = 6/1) to give compound **A1194** (1.5 g, impure, containing PhSO<sub>2</sub>Me) as an oil. The oil was further purified by silica gel chromatography (DCM/Acetone=50/1) to give **A1194** (400 mg, 63%) as an oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.90 (d, *J* = 7.6 Hz, 2H), 7.69-7.62 (m, 1H), 7.60-7.51 (m, 2H), 5.40-5.35 (m, 1H), 3.17-3.07 (m, 1H), 3.04-2.93 (m, 1H), 2.22 (dd, *J* = 2.4, 12.8 Hz, 1H), 2.10-1.64 (m, 9H), 1.57-1.35 (m, 7H), 1.31-1.11 (m, 5H), 1.10-0.92 (m, 3H), 0.90-0.82 (m, 7H), 0.81-0.71 (m, 1H), 0.64 (s, 3H).

*Step 11:* To a solution of n-BuLi (0.468 mL, 2.5 M in hexane, 1.17 mmol) in THF (0.5 mL) at -65°C under N<sub>2</sub> was added a suspension of **A1194** (200 mg, 0.39 mmol) in THF (2.5 mL) dropwise. The mixture was stirred for 30 minutes at -65°C. Then 2,2-dimethyloxirane (42.1 mg, 0.585 mmol) was added dropwise at -65°C. The mixture was stirred for another 30 minutes and then gradually warmed to 25°C. The reaction mixture was stirred at 25°C for 16 hours. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **A1294** (210 mg) as an oil, which was used directly for the next step.

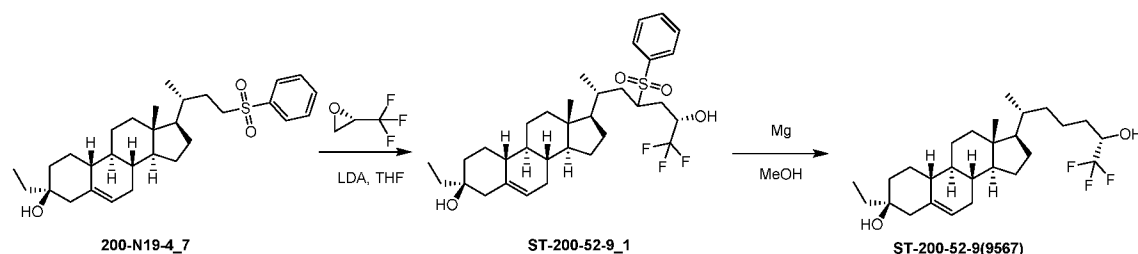
*Step 12:* To a solution of **A1294** (210 mg, 0.3771 mmol) and nickel(II) chloride (5.02 mg, 0.03875 mmol) in dry methanol (100 mL) was added magnesium powder (372 mg, 15.5 mol) in 3 portions under N<sub>2</sub> with stirring at 50°C to initiate continuous hydrogen generation. The reaction mixture was stirred at 60°C for 1 hour. The reaction mixture was quenched with 2 M HCl (30 mL) which was added dropwise at 10°C until the solid was dissolved. After extracting with EtOAc (2 x 50 mL), the combined organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (30 mL), brine (30 mL) then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a solid, which was purified by silica gel chromatography (PE/EtOAc = 10/1) to

give 100 mg of impure product, which was triturated from MeCN (5 mL) to give **Compound 194** (16.5 mg, 11%) as a solid along with 80 mg of impure product.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.36 (m, 1H), 2.23 (dd, *J* = 2.8, 13.2 Hz, 1H), 2.08-1.89 (m, 4H), 1.85-1.76 (m, 3H), 1.67-1.58 (m, 2H), 1.53-1.32 (m, 9H), 1.32-1.23 (m, 4H), 1.21 (s, 6H), 1.20-1.15 (m, 3H), 1.15-0.97 (m, 4H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 4H), 0.83-0.74 (m, 1H), 0.68 (s, 3H).

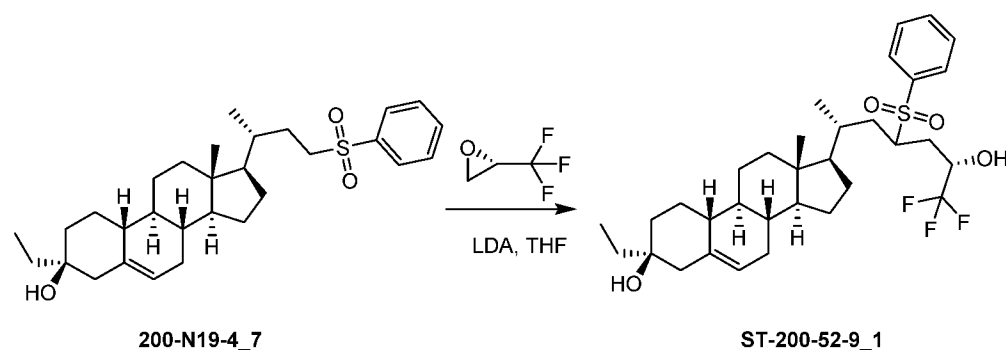
[00653] LCMS Rt = 1.355 min in 2.0 min chromatography, 30-90AB, purity 94.6% (ELSD), MS ESI calcd. for C<sub>28</sub>H<sub>47</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 399, found 399.

## 10 EXAMPLE 95: Synthesis of 9567



[00654] The synthesis of **200-N19-4\_7** can be found in Example 94.

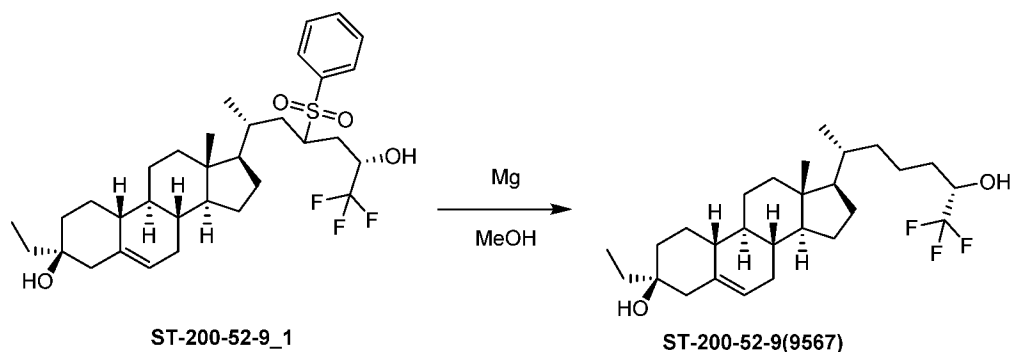
[00655] **Synthesis of ST-200-52-9\_1**



15 n-BuLi (0.99 mL, 2.5 M, 2.47 mmol) was added to a solution of diisopropylamine (0.38 mL, 2.66 mmol) in THF (1 mL) under N<sub>2</sub> at -70 °C. The resulting mixture was warmed to 25°C and stirred at 25 °C for 30 min. After re-cooling to -70°C, a solution of **200-N19-4\_7** (0.3 g, 0.62 mmol) in THF (3 mL) was added at -70 °C. After stirring at -70°C for 1 hour, (S)-2-(trifluoromethyl)oxirane (69.3 mg, 0.62 mmol) was added at -70°C. The reaction mixture was

20 warmed to 25°C and stirred at 25°C for 18 hours. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (6 mL) at 0°C. The mixture was extracted with EtOAc (2 x 8 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a crude product, which was used directly for the next step.

[00656] **Synthesis of ST-200-52-9**

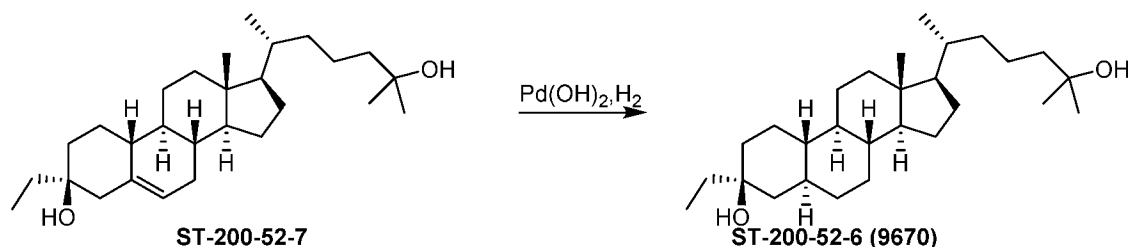


Mg powder (513 mg, 21.4 mmol) was added in 4 portions under N<sub>2</sub> with stirring at 50 °C to a solution of **ST-200-52-9\_1** (320 mg, 0.536 mmol) and NiCl<sub>2</sub> (6.91 mg, 0.054 mmol) in dry methanol (50 mL). After stirring at 60 °C for 1 hour, the mixture was quenched with HCl (50 mL, 1N) until the reaction became clear and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. The residue was purified by flash column (0-15 % of EtOAc in PE) to give **ST-200-52-9** (11 mg, 5 %) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.35 (m, 1H), 3.95-3.83 (m, 1H), 2.25-2.17 (m, 1H), 2.05-1.83 (m, 5H), 1.83-1.75 (m, 3H), 1.75-1.50 (m, 3H), 1.50-1.30 (m, 6H), 1.30-0.98 (m, 11H), 0.94(s, 3H), 0.90-0.72(m, 6H), 0.68(s, 3H).

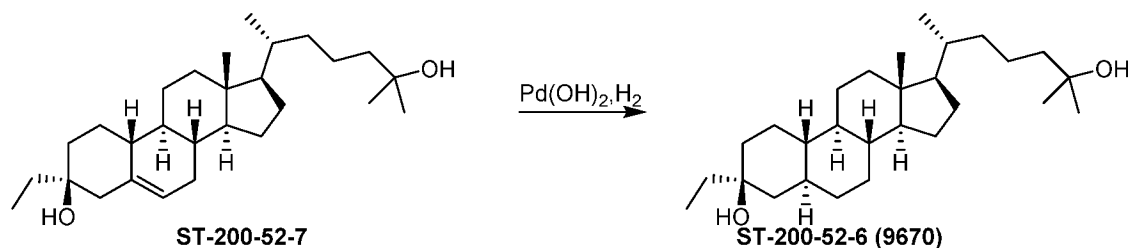
LCMS Rt = 1.253 min in 2.0 min chromatography, 30-90AB\_2MIN\_E, 100 % purity, MS ESI calcd. for C<sub>27</sub>H<sub>42</sub>F<sub>3</sub>O<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 439, found 439.

#### EXAMPLE 96: Synthesis of 9670



[00657] The synthesis of **ST-200-52-7** can be found in Example 94.

[00658] **Synthesis of ST-200-52-6**



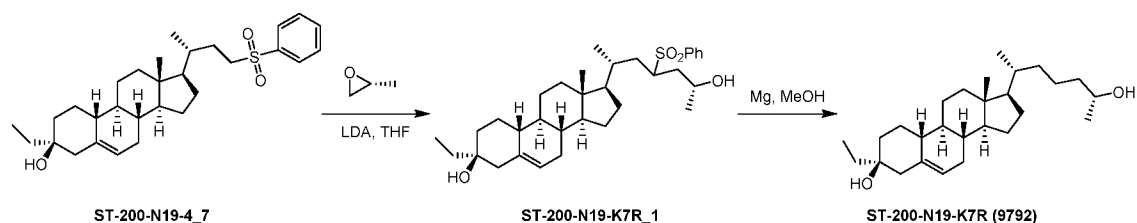
Pd(OH)<sub>2</sub>/C (dry, 200 mg) was added to a solution of **ST-200-52-7** (200 mg, 0.479 mmol) in MeOH (30 mL). The mixture was hydrogenated under 50 psi at 50°C for 48 hrs. The mixture

was filtered, concentrated and purified by combi-flash (0-10% of EtOAc in PE) to give **ST-200-52-6** (33 mg, 16%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.99-1.90 (m, 1H), 1.88-1.75 (m, 3H), 1.69-1.56 (m, 4H), 1.55-1.52 (m, 4H), 1.48-1.32 (m, 5H), 1.31-1.23 (m, 2H), 1.22-1.15 (m, 9H), 1.13-0.99 (m, 9H), 0.95-0.78 (m, 8H), 0.74-0.53 (m, 5H).

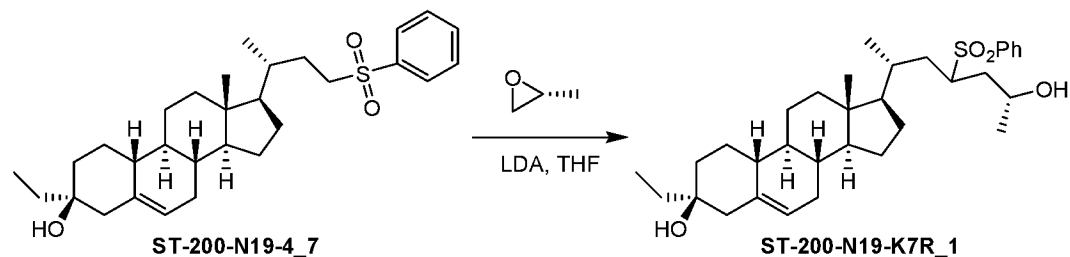
LCMS Rt = 1.299 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>28</sub>H<sub>47</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 383, found 383.

#### EXAMPLE 97: Synthesis of 9792



[00659] The synthesis of **ST-200-N19-4\_7** can be found in Example 94.

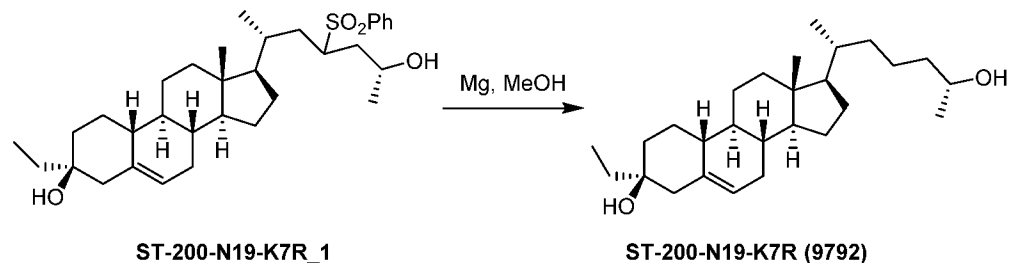
#### [00660] Synthesis of ST-200-N19-K7R\_1



n-BuLi (0.408 mL, 2.5 M, 1.02 mmol, 2.5 eq) was added to THF (0.5 mL) under N<sub>2</sub> at -70°C.

Next, a suspension of **ST-200-N19-4\_7** (200 mg, 0.412 mmol, 1.0 eq.) in THF (1.5 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, (R)-2-methyloxirane (35.8 mg, 0.618 mmol, 1.5 eq.) was added dropwise. Then reaction was stirred at 25°C for 12 hrs. The reaction was quenched with sat.NH<sub>4</sub>Cl (30 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product (250 mg) as a solid, which was used directly for the next step.

#### [00661] Synthesis of ST-200-N19-K7R

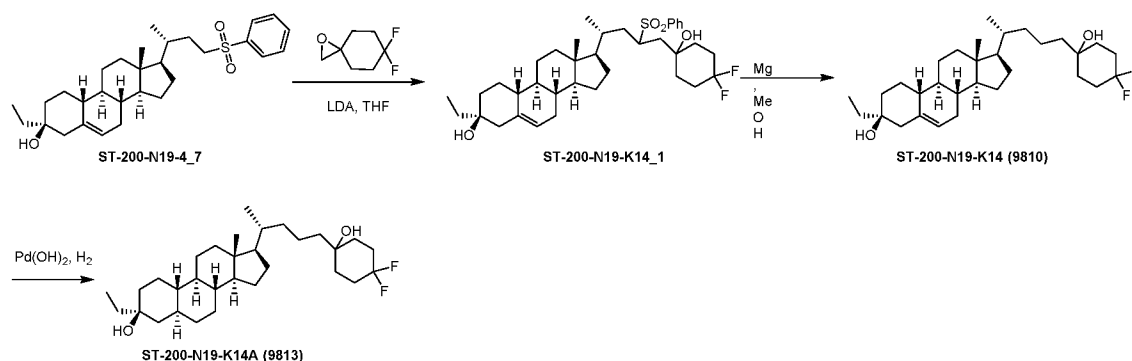


Mg powder (441 mg, 18.4 mmol) was added in one portion to a solution of **ST-200-N19-K7R\_1** (250 mg, 0.46 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 1h. The mixture was quenched with HCl (50 mL, 2 M) until the reaction became clear and extracted with DCM (3 x 15 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **ST-200-N19-K7R** (27 mg, 14%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.36 (m, 1H), 3.87-3.71 (m, 1H), 2.27-2.18 (m, 1H), 2.08-1.88 (m, 4H), 1.87-1.73 (m, 3H), 1.67-1.58 (m, 1H), 1.53-1.34 (m, 9H), 1.31-1.22 (m, 5H), 1.21-1.11 (m, 7H), 1.10-0.98 (m, 3H), 0.95-0.89 (m, 3H), 0.88-0.83 (m, 4H), 0.82-0.74 (m, 1H), 0.67 (s, 3H).

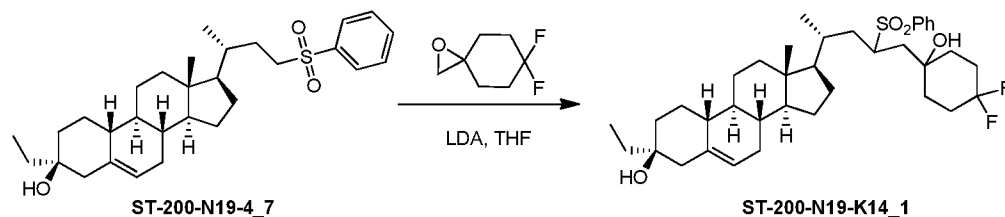
LCMS Rt = 1.246 min in 2.0 min chromatography, 30-90 AB\_E, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 385, found 385.

#### EXAMPLE 98: Synthesis of 9810 and 9813



[00662] The synthesis of **ST-200-N19-4\_7** can be found in Example 94. The synthesis of 6,6-difluoro-1-oxaspiro[2.5]octane can be found in Example 87.

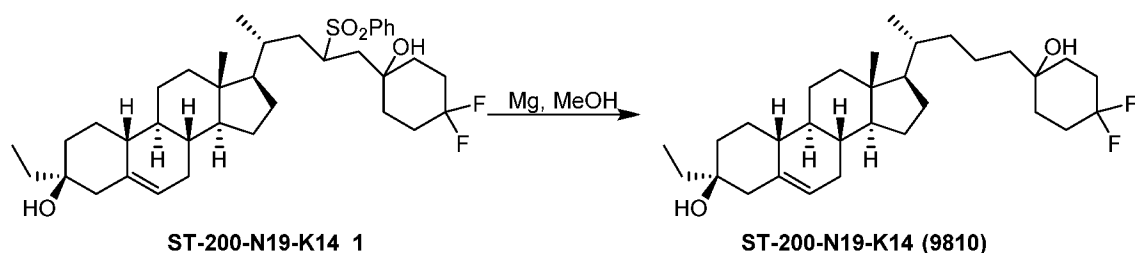
#### [00663] Synthesis of ST-200-N19-K14\_1



n-BuLi (0.656 mL, 2.5 M in hexane, 1.64 mmol) was added to a solution of diisopropylamine (179 mg, 0.442 mmol) in THF (1 mL) under N<sub>2</sub> at -70°C. The mixture was warmed to 25°C. After re-cooling to -70°C, a suspension of **ST-200-N19-4\_7** (200 mg, 0.412 mmol) in THF (5 mL) was added dropwise under N<sub>2</sub>. After stirring at -70°C for 30 min, 6,6-difluoro-1-oxaspiro[2.5]octane (91.5 mg, 0.618 mmol) was added at -70°C. The reaction mixture was warmed to 25°C slowly and stirred at 25°C for 16 hours. The reaction mixture was quenched

with saturated  $\text{NH}_4\text{Cl}$  aqueous (15 mL). The mixture was extracted with EtOAc (2 x 15 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **ST-200-N19-K14\_1** (200 mg, crude) as an oil, which was used directly for the next step.

#### 5 [00664] Synthesis of ST-200-N19-K14

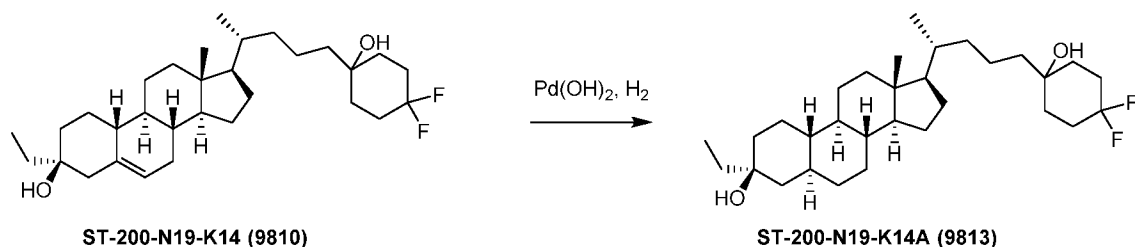


A solution of **ST-200-N19-K14\_1** (200 mg, 0.316  $\mu\text{mol}$ ) in MeOH (30 mL) was heated at  $65^\circ\text{C}$ . Mg powder (302 mg, 12.6 mmol) and  $\text{NiCl}_2$  (12.1 mg, 0.0948  $\mu\text{mol}$ ) were added in one portion at  $65^\circ\text{C}$ . The mixture was reflux at  $65^\circ\text{C}$  for 1 h and quenched with HCl (50 mL, 2N) until the reaction became clear. The mixture was extracted with DCM (3 x 20 mL). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give **ST-200-N19-K14** (100 mg, 64%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.41-5.36 (m, 1H), 2.27-2.20 (m, 1H), 2.19-2.03 (m, 3H), 2.02-1.88 (m, 5H), 1.86-1.73 (m, 3H), 1.71-1.59 (m, 5H), 1.54-1.33 (m, 10H), 1.32-1.15 (m, 6H), 1.14-1.00 (m, 4H), 0.99-0.97 (m, 1H), 0.96-0.89 (m, 3H), 0.88-0.74 (m, 5H), 0.68 (s, 3H).

LCMS Rt = 1.322 min in 2.0 min chromatography, 30-90 AB\_E, purity 100%, MS ESI calcd. for  $\text{C}_{31}\text{H}_{47}\text{F}_2$   $[\text{M}+\text{H}-2\text{H}_2\text{O}]^+$  457, found 457.

#### [00665] Synthesis of ST-200-N19-K14A

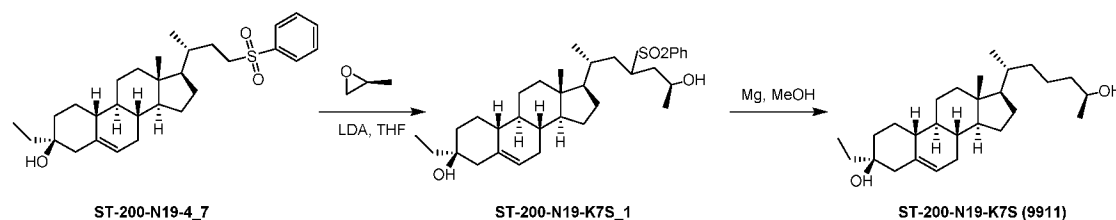


$\text{Pd}(\text{OH})_2$  (70 mg, dry) was added to a solution of **ST-200-N19-K14** (70 mg, 0.142 mmol) in MeOH (20 mL). The mixture was hydrogenated at  $50^\circ\text{C}$  (50 Psi) for 48 hrs. The mixture was filtered, concentrated and purified by combi-flash (0-10% of EtOAc in PE) to give **ST-200-N19-K14A** (20 mg, 28%) as a solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.24-1.99 (m, 2H), 1.97-1.73 (m, 6H), 1.71-1.57 (m, 8H), 1.55-1.32 (m, 8H), 1.30-1.16 (m, 4H), 1.13-0.97 (m, 11H), 0.94-0.78 (m, 8H), 0.74-0.55 (m, 5H).

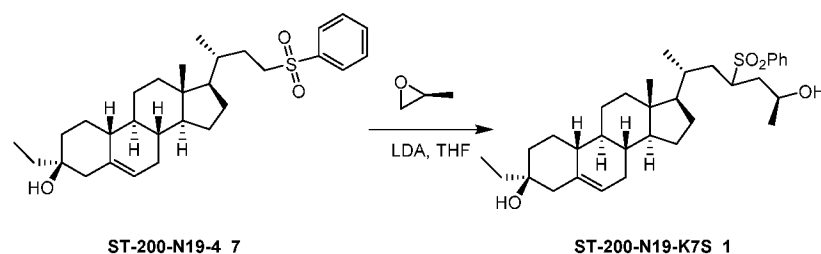
LCMS Rt = 1.344 min in 2.0 min chromatography, 30-90 AB\_E, purity 100%, MS ESI calcd. for  $C_{31}H_{49}F_2$   $[M+H-2H_2O]^+$  459, found 459.

### EXAMPLE 99: Synthesis of 9911



[00666] The experimental of intermediate **ST-200-N19-4\_7** can be found in Example 94.

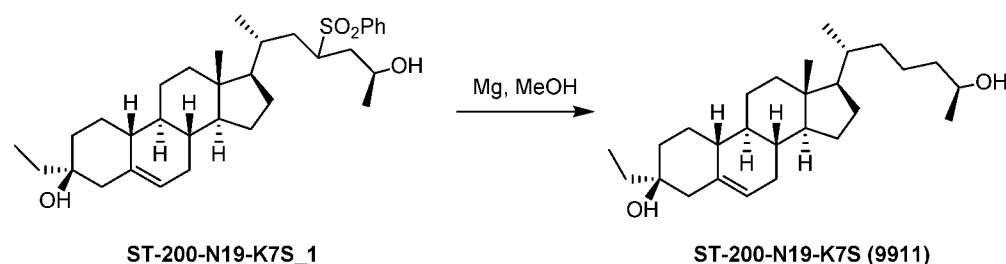
### [00667] Synthesis of ST-200-N19-K7S\_1



n-BuLi (0.408 mL, 2.5 M, 1.02 mmol) was added to THF (0.5 mL) under  $N_2$  at  $-70^\circ C$ . After that, a suspension of **ST-200-N19-4\_7** (200 mg, 0.412 mmol, 1.0 eq.) in THF (1.5 mL) was added dropwise to give a suspension. After stirring at  $-70^\circ C$  for 30 min, (S)-2-methyloxirane (35.8 mg, 0.618 mmol) was added dropwise. Then reaction was stirred at  $25^\circ C$  for 12 hrs. The reaction was quenched with sat.  $NH_4Cl$  (30 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over  $Na_2SO_4$ , filtered and concentrated to give crude product (250 mg) as a solid, which was used directly for the next step.

10                      15

### [00668] Synthesis of ST-200-N19-K7S



Mg powder (357 mg, 14.7 mmol) was added to a solution of **ST-200-N19-K7S\_1** (200 mg, 0.368 mmol) and nickel (II) chloride (9.53 mg, 0.074 mmol) in dry methanol (50 mL) under  $N_2$  and the resulting mixture was stirred at  $50^\circ C$  to initiate continuous hydrogen generation. The reaction mixture was stirred at  $60^\circ C$  for 1 hour. The reaction mixture was quenched by 2M HCl (100 mL) which was added dropwise at  $10^\circ C$  until solid was dissolved. After extracting with EtOAc (2 x 150 mL), the combined organic layer was washed with sat.  $NaHCO_3$  aq. (300 mL),

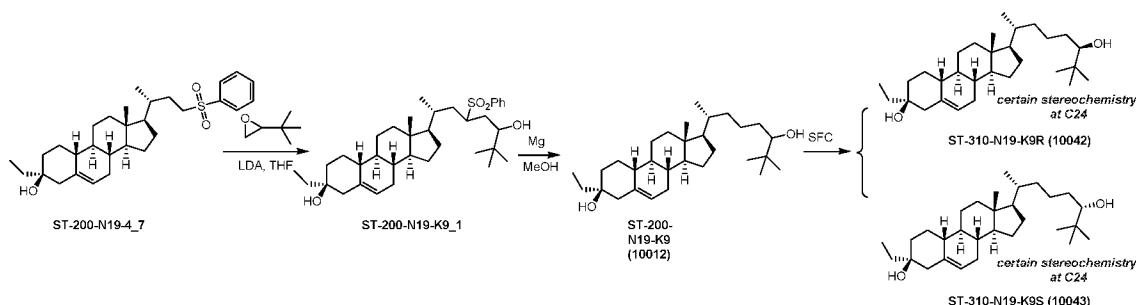
20

brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a solid, which was purified by silica gel chromatography (PE/THF = 4/1) to give a crude residue, which was purified by re-crystallization from MeCN (10 mL) to afford **ST-200-N19-K7S** (52 mg, 35%) as a solid.

- 5 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 3.80-3.70 (m, 1H), 2.25-2.20 (m, 1H), 2.05-1.75 (m, 7H), 1.69-1.15 (m, 20H), 1.14-0.70 (m, 13H), 0.67 (s, 3H).

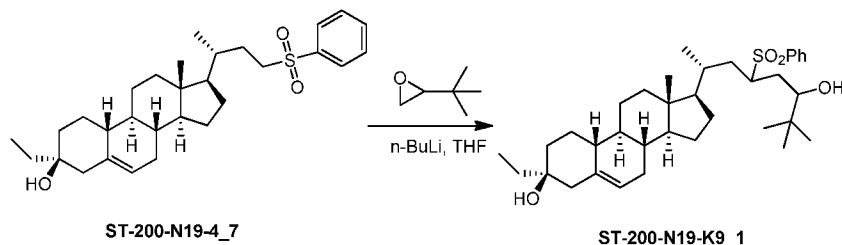
LCMS Rt = 1.241 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for C<sub>27</sub>H<sub>45</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 385, found 385.

# 10 **EXAMPLE 100: Synthesis for 10012, 10042, and 10043**



[00669] The experimental of intermediate **ST-200-N19-4\_7** can be found in Example 94.

## [00670] **Synthesis of ST-200-N19-K9\_1**



- 15 n-BuLi (0.824 mL, 2.5 M, 2.06 mmol) was added to THF (0.5 mL) under N<sub>2</sub> at -70°C. Next, a suspension of **ST-200-N19-4\_7** (400 mg, 0.825 mmol) in THF (3.5 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, 2-(tert-butyl) oxirane (123 mg, 1.23 mmol) was added dropwise. Then reaction was stirred at 25°C for 12 hrs and quenched with sat.NH<sub>4</sub>Cl (30 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over
- 20 Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product (500 mg) as a solid, which was used directly for the next step.

## [00671] **Synthesis of ST-200-N19-K9 (10012)**



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**[00672]**



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The stereochemistry at C25 of 10042 and 10043 was confirmed by asymmetric synthesis of 10042 and 10043 from chiral epoxides.

**ST-200-N19-K9R (10042):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 3.25-3.15 (m, 1H), 2.25-2.20 (m, 1H), 2.10-1.55 (m, 9H), 1.50-1.30 (m, 8H), 1.29-1.00 (m, 11H), 0.95-0.75 (m, 18H), 0.67 (s, 3H).

LCMS Rt = 1.402 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for

5 C<sub>30</sub>H<sub>51</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 427, found 427.

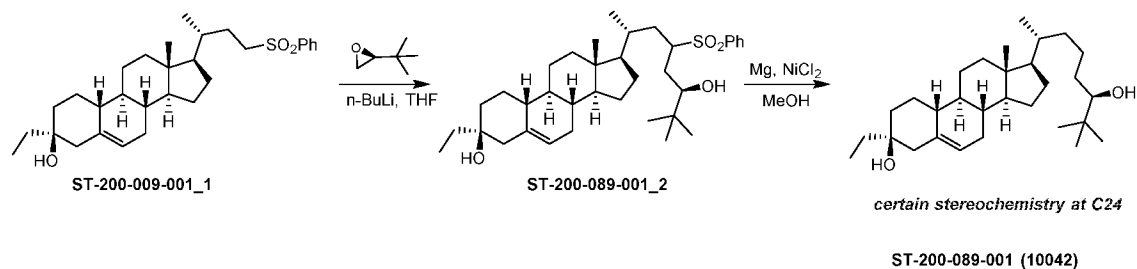
SFC Rt = 6.347 min in 10 min chromatography, AD\_3\_IPA\_DEA\_5\_40\_25ML, 100%de.

**ST-200-N19-K9S (10043):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.35 (m, 1H), 3.25-3.15 (m, 1H), 2.25-2.20 (m, 1H), 2.10-1.75 (m, 7H), 1.74-1.35 (m, 7H), 1.34-1.00 (m, 13H), 0.99-0.75 (m, 19H), 0.67 (s, 3H).

10 LCMS Rt = 1.402 min in 2.0 min chromatography, 30-90 AB, purity 99.2%, MS ESI calcd. for C<sub>30</sub>H<sub>51</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 427, found 427.

SFC Rt = 6.940 min in 10 min chromatography, AD\_3\_IPA\_DEA\_5\_40\_25ML, 99.5%de.

**Synthesis for confirming stereochemistry**

15 **ST-200-009-001\_1** (300 mg, 0.618 mmol) in THF (2 mL, dry) was added to a solution of n-BuLi (0.616 mL, 2.5 M in hexane) in THF (0.5 mL, dry) at -70°C. After stirring at -70°C for 0.5 h, a solution of (S)-2-(tert-butyl)oxirane (92.7 mg, 0.926 mmol) in THF (0.5 mL, dry) was added dropwise. After stirring at 25°C for another 16hrs, the mixture was quenched with sat. NH<sub>4</sub>Cl (5

20 mL). The mixture was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **ST-200-089-001\_2** (360 mg, crude) as a solid, which was used directly for next step.

NiCl<sub>2</sub> (8.85 mg, 0.683 mmol) was added to a mixture of **ST-200-089-001\_2** (360 mg, crude) in MeOH (20 mL) at 25°C. Then the mixture was stirred at 60°C and Mg powder (828 mg, 34.1

25 mmol) was added in three batches for 2 hrs. The reaction was quenched with HCl (1M, 10mL), the mixture was extracted with EtOAc (2 x 15 mL). The combined organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash-combi (0~30% of EtOAc in PE) to give **ST-200-089-001** (115 mg, impure) as a solid, which was further purified by SFC (AD(250mm\*30mm,10um), gradient: 40-40% B (A=

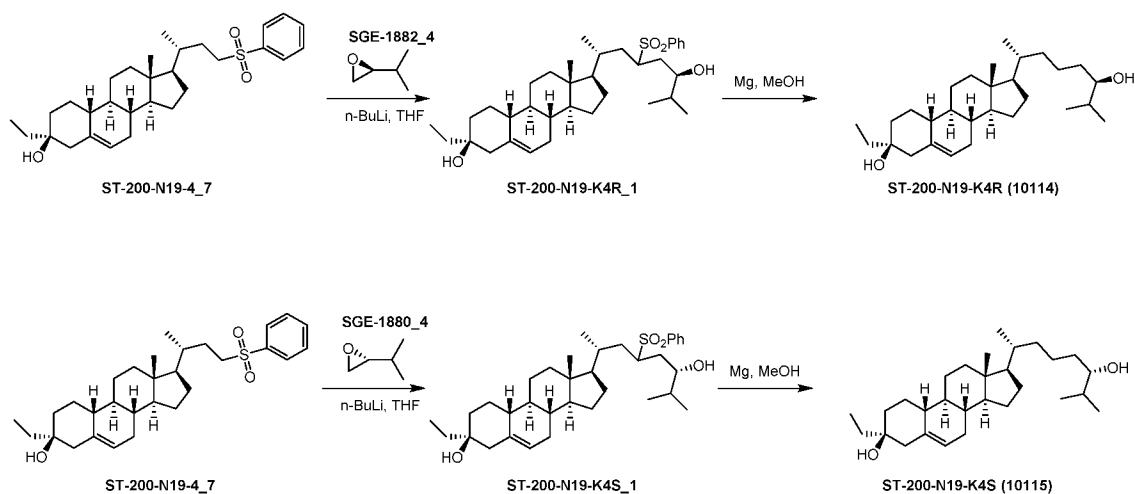
0.1%NH<sub>3</sub>/H<sub>2</sub>O IPA, B= MeOH ), flow rate: 50 mL/min) to give **ST-200-089-001** (77 mg, 28% yield for 2 steps) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ5.41-5.35 (m, 1H), 3.25-3.15 (m, 1H), 2.25-2.20 (m, 1H), 2.10-1.90 (m, 4H), 1.90-1.75 (m, 3H), 1.69-1.50 (m, 3H), 1.50-1.33 (m, 8H), 1.33-1.13 (m, 7H), 1.13-0.98 (m, 4H), 0.98-0.90 (m, 3H), 0.90-0.78 (m, 14H), 0.67 (s, 3H).

LCMS Rt = 1.467 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. for C<sub>30</sub>H<sub>51</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 427, found 427.

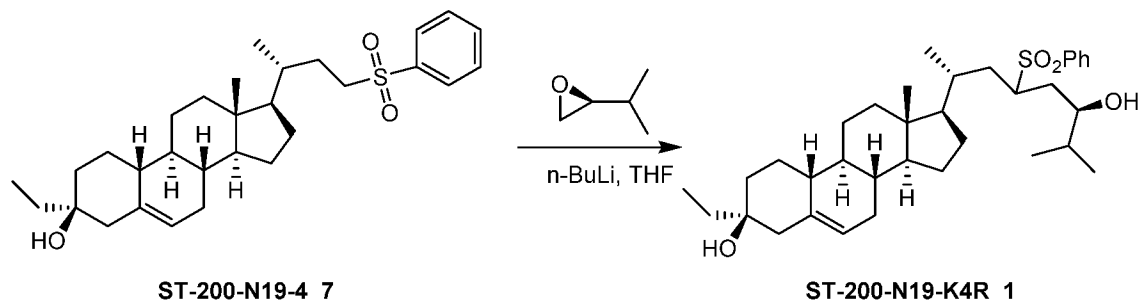
SFC Rt = 6.135 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 100%de.

## 10 EXAMPLE 101: Synthesis for 10114 and 10115

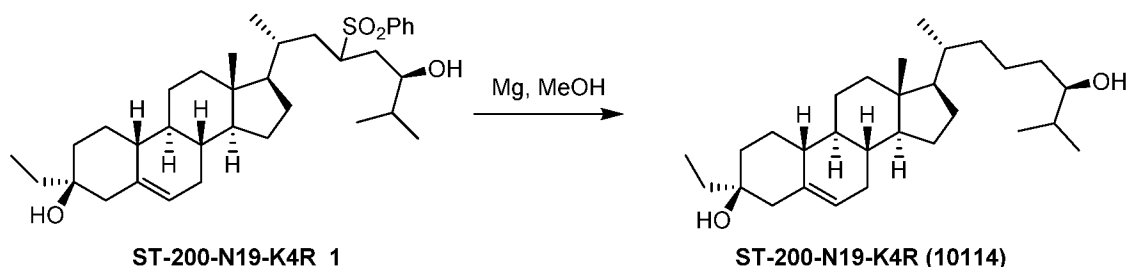


[00673] The synthesis of **ST-200-N19-4\_7** can be found in Example 94.

[00674] **Synthesis of ST-200-N19-K4R\_1**



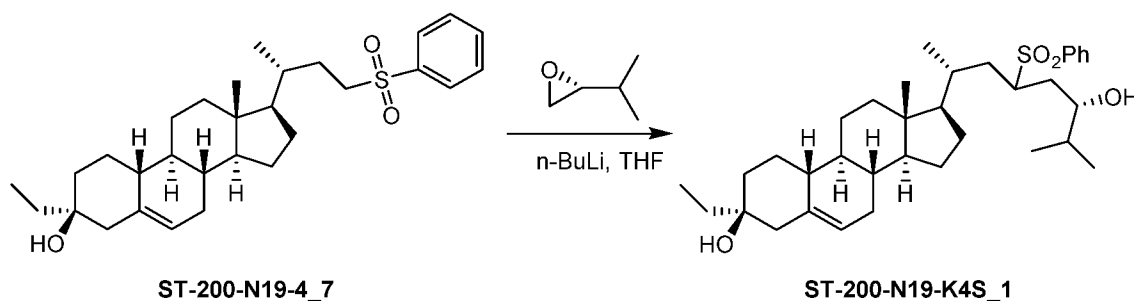
- 15 n-BuLi (0.408 mL, 2.5 M, 1.02 mmol, 2.5 eq) was added to THF (0.5 mL) under N<sub>2</sub> at -70°C. Next, a suspension of **ST-200-N19-4\_7** (200 mg, 0.412 mmol, 1.0 eq.) in THF (1.5 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, (S)-2-isopropylloxirane (53.2 mg, 0.618 mmol, 1.5 eq.) was added dropwise. Then reaction was stirred at 25°C for 12 hrs. The reaction was quenched with sat.NH<sub>4</sub>Cl (30 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product
- 20 (250 mg) as a solid, which was used directly for the next step.

**[00675] Synthesis of ST-200-N19-K4R**

NiCl<sub>2</sub> (11.3 mg, 0.0874 mmol) and Mg powder (417 mg, 17.4 mmol) were added in one portion to a solution of **ST-200-N19-K4R\_1** (250 mg, 0.437 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 1 h. The mixture was quenched with HCl (50 mL, 2 N) until the reaction became clear and extracted with DCM (3 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **ST-200-N19-K4R** (38 mg, 20%) as a solid.

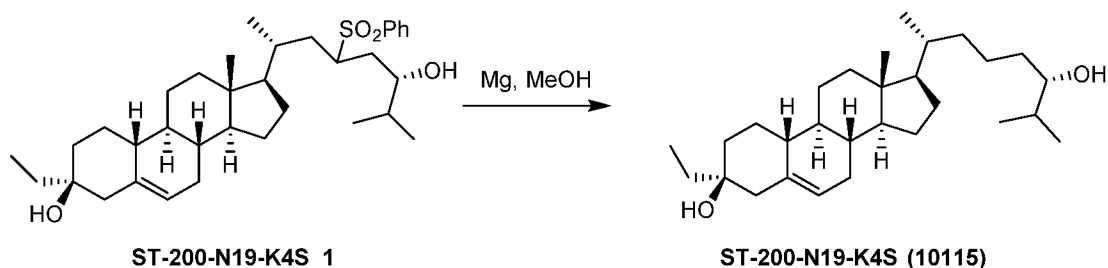
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.41-5.36 (m, 1H), 3.41-3.31 (m, 1H), 2.27-2.20 (m, 1H), 2.07-1.89 (m, 4H), 1.88-1.75 (m, 3H), 1.70-1.59 (m, 3H), 1.54-1.33 (m, 10H), 1.30-1.16 (m, 6H), 1.15-0.97 (m, 4H), 0.95-0.88 (m, 9H), 0.88-0.82 (m, 4H), 0.82-0.74 (m, 1H), 0.68 (s, 3H).

LCMS Rt = 1.362 min in 2.0 min chromatography, 30-90 AB\_E, purity 100%, MS ESI calcd. for C<sub>29</sub>H<sub>49</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 413, found 413.

**[00676] Synthesis of ST-200-N19-K4S\_1**

n-BuLi (0.408 mL, 2.5 M, 1.02 mmol, 2.5 eq) was added to THF (0.5 mL) under N<sub>2</sub> at -70°C. Next, a suspension of **ST-200-N19-4\_7** (200 mg, 0.412 mmol, 1.0 eq.) in THF (1.5 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, (R)-2-isopropylloxirane (53.2 mg, 0.618 mmol, 1.5 eq.) was added dropwise. Then reaction was stirred at 25°C for 12 hrs. The reaction was quenched with sat. NH<sub>4</sub>Cl (30 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product (250 mg) as a solid, which was used directly for the next step.

**[00677] Synthesis of ST-200-N19-K4S**

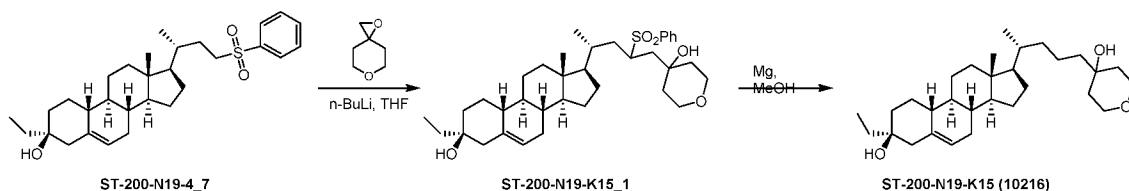


NiCl<sub>2</sub> (11.3 mg, 0.0874 mmol) and Mg powder (417 mg, 17.4 mmol) were added in one portion to a solution of **ST-200-N19-K4S\_1** (250 mg, 0.437 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 1h. The mixture was quenched with HCl (50 mL, 2 N) until the reaction became clear and extracted with DCM (3 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **ST-200-N19-K4S** (36 mg, 19%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.41-5.36 (m, 1H), 3.41-3.31 (m, 1H), 2.27-2.20 (m, 1H), 2.07-1.89 (m, 4H), 1.88-1.75 (m, 3H), 1.71-1.57 (m, 3H), 1.55-1.35 (m, 9H), 1.34-1.23 (m, 4H), 1.22-0.99 (m, 7H), 0.95-0.89 (m, 9H), 0.88-0.82 (m, 4H), 0.82-0.74 (m, 1H), 0.68 (s, 3H).

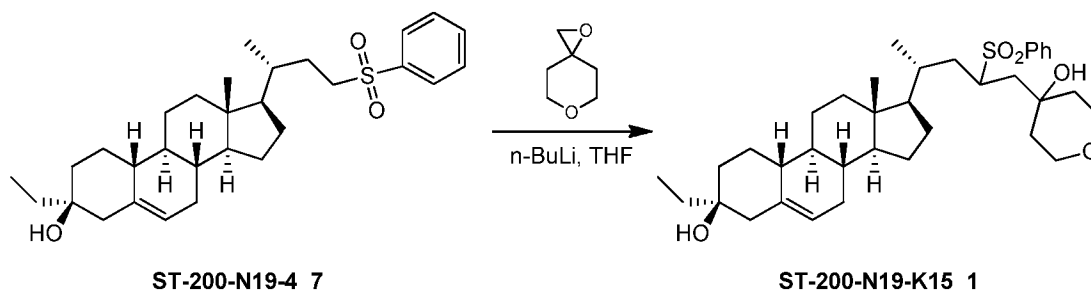
LCMS Rt = 1.356 min in 2.0 min chromatography, 30-90 AB\_E, purity 100%, MS ESI calcd. for C<sub>29</sub>H<sub>49</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 413, found 413.

#### EXAMPLE 102: Synthesis for 10216



[00678] The synthesis of **ST-200-N19-4\_7** can be found in Example 94.

[00679] **Synthesis of ST-200-N19-K15\_1**



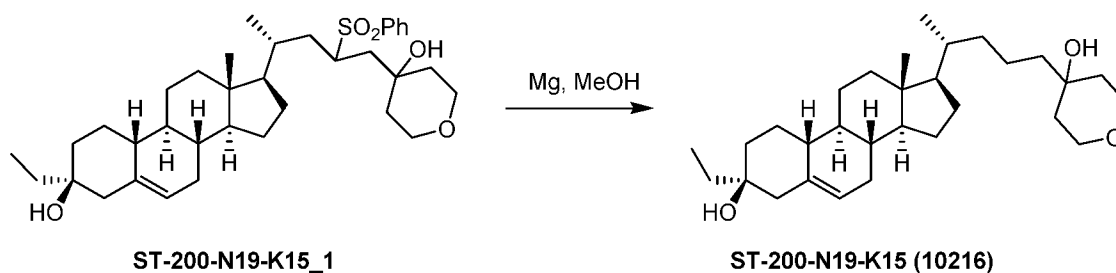
n-BuLi (0.408 mL, 2.5 M, 1.02 mmol, 2.5 eq) was added to THF (0.5 mL) under N<sub>2</sub> at -70°C.

Next, a suspension of **ST-200-N19-4\_7** (200 mg, 0.412 mmol, 1.0 eq.) in THF (1.5 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, 1,6-

dioxaspiro[2.5]octane (70.5 mg, 0.618 mmol, 1.5 eq.) was added dropwise. Then reaction was

stirred at 25°C for 12 hrs. The reaction was quenched with sat.NH<sub>4</sub>Cl (30 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product (250 mg) as a solid, which was used directly for the next step.

**[00680] Synthesis of ST-200-N19-K15**

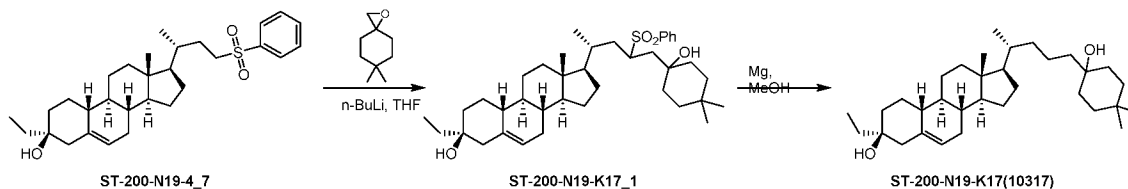


NiCl<sub>2</sub> (10.8 mg, 0.0834 mmol) and Mg powder (398 mg, 16.6 mmol) were added in one portion to a solution of **ST-200-N19-K15\_1** (250 mg, 0.417 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 1h. The mixture was quenched with HCl (50 mL, 2 N) until the reaction became clear and extracted with DCM (3 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **ST-200-N19-K15** (43 mg, 22%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.44-5.33 (m, 1H), 3.81-3.69 (m, 4H), 2.27-2.19 (m, 1H), 2.07-1.88 (m, 4H), 1.87-1.76 (m, 3H), 1.71-1.58 (m, 3H), 1.53-1.32 (m, 11H), 1.31-1.13 (m, 7H), 1.12-1.07 (m, 2H), 1.06-0.95 (m, 3H), 0.94-0.89 (m, 3H), 0.88-0.82 (m, 4H), 0.82-0.75 (m, 1H), 0.68 (s, 3H).

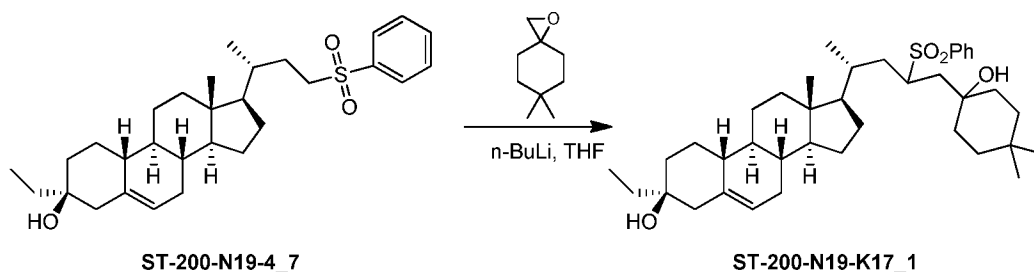
LCMS Rt = 1.200 min in 2.0 min chromatography, 30-90 AB\_E, purity 100%, MS ESI calcd. for C<sub>30</sub>H<sub>47</sub>O [M+H-2H<sub>2</sub>O]<sup>+</sup> 423, found 423.

**EXAMPLE 103: Synthesis for 10317**



**[00681]** The synthesis of **ST-200-N19-4\_7** can be found in Example 94. The synthesis of the epoxide can be found in Example 28.

**[00682] Synthesis of ST-200-N19-K17\_1**

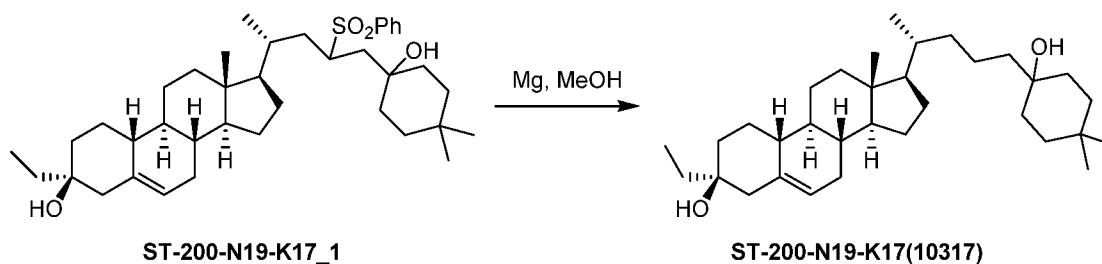


n-BuLi (0.408 mL, 2.5 M, 1.02 mmol, 2.5 eq) was added to THF (0.5 mL) under N<sub>2</sub> at -70°C.

Next, a suspension of **ST-200-N19-4\_7** (200 mg, 0.412 mmol, 1.0 eq.) in THF (1.5 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, 6,6-dimethyl-1-

5 oxaspiro[2.5]octane (86.6 mg, 0.618 mmol, 1.5 eq.) was added dropwise. Then reaction was stirred at 25°C for 12 hrs. The reaction was quenched with sat.NH<sub>4</sub>Cl (30 mL), extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude product (250 mg) as a solid, which was used directly for the next step.

#### [00683] Synthesis of ST-200-N19-K17

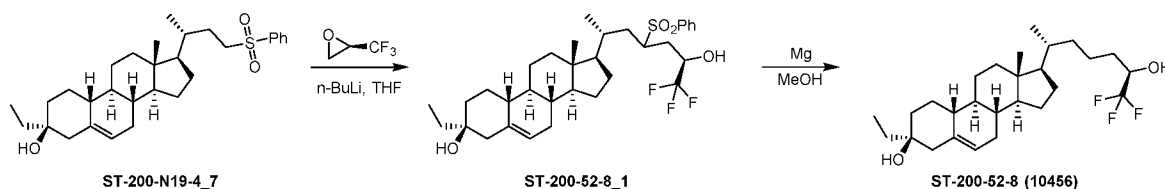


NiCl<sub>2</sub> (10.3 mg, 0.08 mmol) and Mg powder (384 mg, 16.0 mmol) were added in one portion to a solution of **ST-200-N19-K17\_1** (250 mg, 0.4 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 1h. The mixture was quenched with HCl (50 mL, 2 N) until the reaction became clear and extracted with DCM (3 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give impure **ST-200-N19-K17** (58 mg, 30%) as a solid, which was triturated with hexane (3 mL). The mixture was filtered to give pure **ST-200-N19-K17** (33 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.44-5.33 (m, 1H), 2.27-2.2 (m, 1H), 2.07-1.88 (m, 4H), 1.87-1.75 (m, 3H), 1.68-1.57 (m, 2H), 1.52-1.45 (m, 7H), 1.44-1.32 (m, 7H), 1.28-1.15 (m, 8H), 1.14-0.95 (m, 6H), 0.94-0.89 (m, 6H), 0.89-0.82 (m, 7H), 0.82-0.74 (m, 1H), 0.68 (s, 3H).

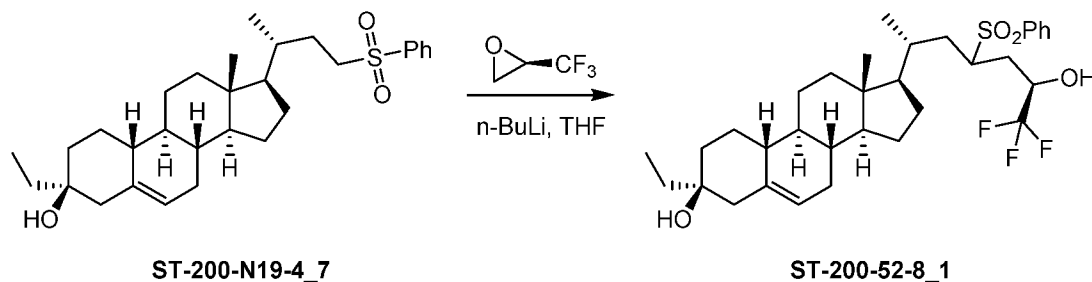
LCMS Rt = 1.516 min in 2.0 min chromatography, 30-90 AB\_E, purity 100%, MS ESI calcd. for C<sub>33</sub>H<sub>53</sub> [M+H-2H<sub>2</sub>O]<sup>+</sup> 449, found 449.

#### EXAMPLE 104: Synthesis for 10456



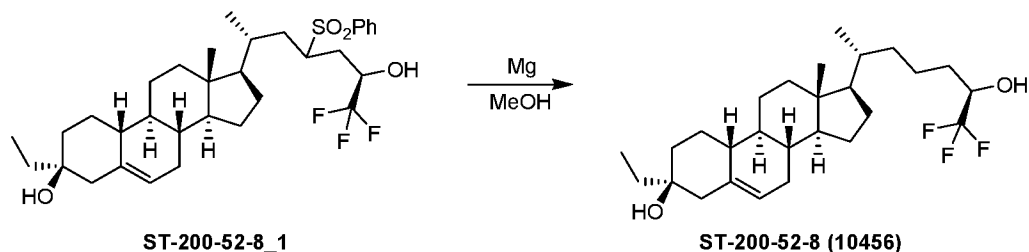
[00684] The synthesis of **ST-200-N19-4\_7** can be found in Example 94.

[00685] **Synthesis of ST-200-52-8\_1**



n-BuLi (0.246 mL, 2.5 M, 0.617 mmol) was added to THF (0.3 mL) under N<sub>2</sub> at -70°C. A solution of **ST-200-N19-4\_7** (0.12 g, 0.247 mmol) in THF (1 mL) was added at -70°C. After stirring at -70°C for 1 hour, (R)-2-(trifluoromethyl)oxirane (41.4 mg, 0.37 mmol) was added at -70°C. The reaction mixture was warmed to 15°C and stirred at 15°C for 18 hrs. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (6 mL) at 0°C. The mixture was extracted with EtOAc (2 x 8 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a crude product **ST-200-52-8\_1** (150 mg, crude) as a solid, which was used directly for the next step.

[00686] **Synthesis of ST-200-52-8**



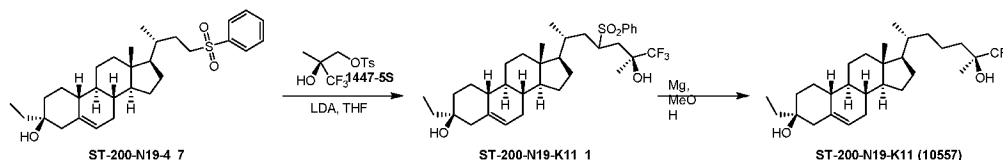
NiCl<sub>2</sub> (6.5 mg, 0.0502 mmol) and Mg powder (240 mg, 10.0 mmol) were added in one to a solution of **ST-200-52-8\_1** (150 mg, 0.251 mmol) in MeOH (30 mL) at 65°C. The mixture was stirred at 65°C for 1h. The mixture was quenched with HCl (50 mL, 2 N) until the reaction became clear and extracted with DCM (3 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **ST-200-52-8** (20 mg, 17%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.43-5.34 (m, 1H), 3.98-3.85 (m, 1H), 2.27-2.19 (m, 1H), 2.06-1.88 (m, 5H), 1.87-1.76 (m, 3H), 1.68-1.57 (m, 4H), 1.53-1.34 (m, 8H), 1.29-1.15 (m, 5H), 1.13-0.98 (m, 4H), 0.95-0.89 (m, 3H), 0.89-0.82 (m, 4H), 0.81-0.74 (m, 1H), 0.68 (s, 3H).

LCMS Rt = 1.255 min in 2.0 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. for

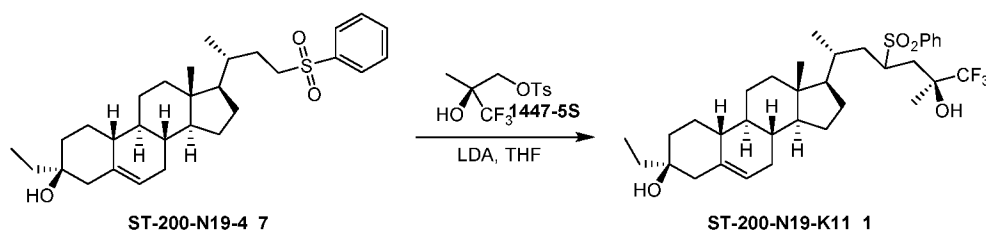
5 C<sub>27</sub>H<sub>42</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 439, found 439.

### EXAMPLE 105: Synthesis for 10557



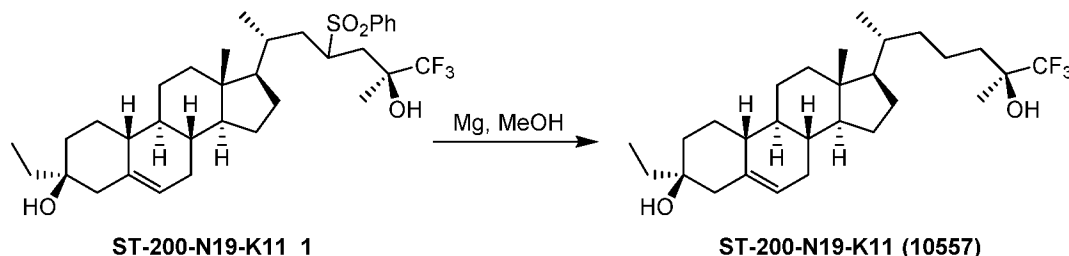
[00687] The synthesis of ST-200-N19-4\_7 can be found in Example 94. The synthesis of  
10 the tosylate can be found in Example 30.

### [00688] Synthesis of ST-200-N19-K11\_1



n-BuLi (0.656 mL, 2.5 M in hexane, 1.64 mmol) was added to a solution of diisopropylamine (179 mg, 1.77 mmol) in THF (1 mL) under N<sub>2</sub> at -70°C. The mixture was warmed to 25°C. After  
15 re-cooling to -70°C, a suspension of ST-200-N19-4\_7 (200 mg, 0.412 mmol) in THF (5 mL) was added dropwise under N<sub>2</sub> at -70°C. After stirring at -70°C for 30 min, (S)-3,3,3-trifluoro-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (184 mg, 0.618 mmol) was added. The reaction mixture was warmed to 25°C slowly and stirred at 25°C for 16hrs. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl aqueous (15 mL). The mixture was extracted with EtOAc (2  
20 x 15 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give ST-200-N19-K11\_11 (200 mg, crude) as an oil, which was used for the next step directly.

### [00689] Synthesis of ST-200-N19-K11

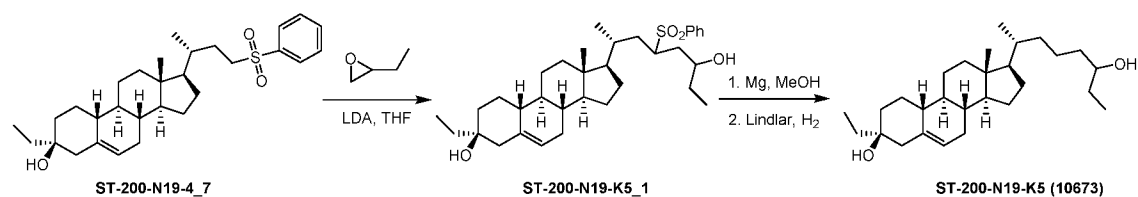


A solution of **ST-200-N19-K11\_1** (200 mg, 0.327 mmol) in MeOH (30 mL) was heated at 65°C. Mg powder (312 mg, 13.0 mmol) and NiCl<sub>2</sub> (12.5 mg, 0.0981 mmol) were added in one portion at 65°C. The mixture was refluxed at 65°C for 1h. The mixture was quenched with HCl (50 mL, 2N) until the reaction became clear and extracted with DCM (3 x 20 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by silica gel chromatography (0-15% of EtOAc in PE) to give impure **ST-200-N19-K11** (26 mg, 17%) as a solid, which was triturated with hexane (3 mL) to give **ST-200-N19-K11** (13 mg, 50%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.41-5.36 (m, 1H), 2.27-2.19 (m, 1H), 2.08-1.95 (m, 3H), 1.93-1.75 (m, 5H), 1.69-1.57 (m, 4H), 1.55-1.37 (m, 7H), 1.34 (s, 3H), 1.30-1.15 (m, 6H), 1.14-0.97 (m, 4H), 0.96-0.89 (m, 3H), 0.88-0.74 (m, 5H), 0.68 (s, 3H).

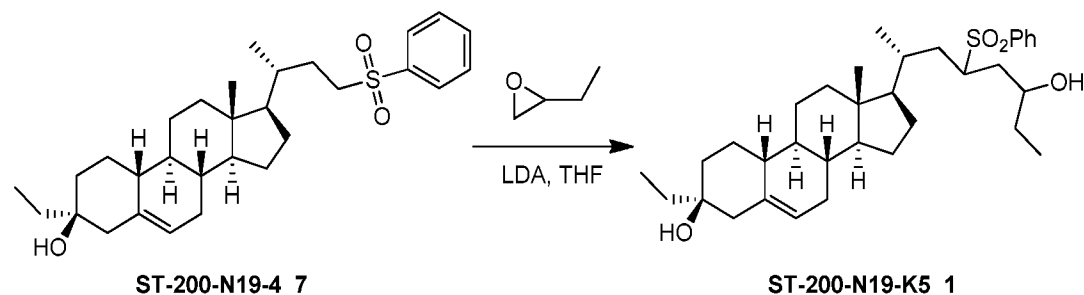
LCMS Rt = 1.261 min in 2.0 min chromatography, 30-90AB\_E, purity 100%, MS ESI calcd. for C<sub>28</sub>H<sub>44</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 453, found 453.

#### EXAMPLE 106: Synthesis for 10673



[00690]      The synthesis of **200-N19-4\_7** can be found in Example 94.

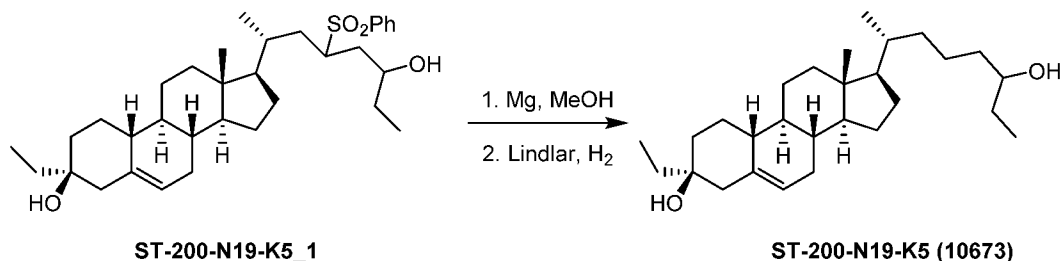
[00691]      **Synthesis of ST-200-N19-K5\_1**



A suspension of **ST-200-N19-4\_7** (400 mg, 0.8251 mmol) in THF (4 mL) was added dropwise at -70°C under N<sub>2</sub> to a solution of n-BuLi (5.0 mL, 2.5 M in hexane, 6.5 mmol) in THF (2 mL) inside sealed tube (10 mL). The mixture was stirred for 30 minutes at -70°C. A solution of diisopropylamine (274 mg, 2.7 mmol) was added dropwise at -70°C, then a solution of 2-ethyloxirane (178 mg, 2.47 mmol) was added dropwise at -70°C. The mixture was stirred for another 30 min and then warmed to 25°C gradually. The reaction mixture was stirred at 25°C for 15 hour. The reaction mixture was quenched by saturated NH<sub>4</sub>Cl aqueous (30 mL), extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (50 mL), dried

over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **ST-200-N19-K5\_1** (450 mg, crude), which was used directly for the next step.

**[00692] Synthesis of ST-200-N19-K5**

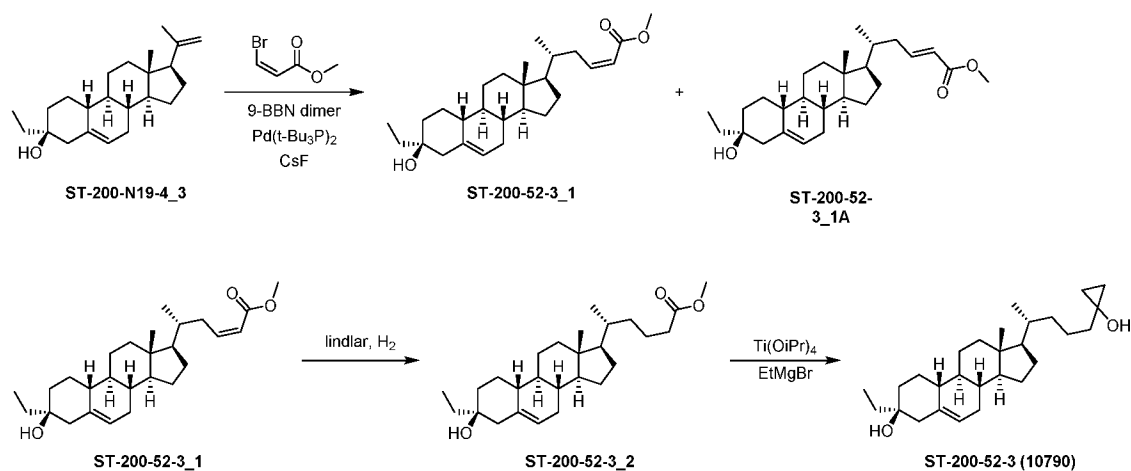


- 5 A solution of **ST-310-N19-K5\_1** (0.45 g, 0.808 mmol) in MeOH (30 mL) was heated at 60°C. Mg powder (775 mg, 32.3 mmol) was added in four portions at 60°C. The mixture was stirred at 60°C for 1h. The mixture was quenched with HCl (30 mL, 2 M) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-30% of EtOAc in PE) to give 330 mg of
- 10 impure product, which was purified by flash column (0-20% of EtOAc in PE) to give pure 150 mg of a solid. The solid (150 mg, 0.873 mmol) in THF (5 mL) was added lindlar catalyst (100 mg). The mixture was stirred at 25°C under H<sub>2</sub> (15 Psi) for 16 hrs. The mixture was filtered and concentrated to give **ST-200-N19-K5** (100 mg, crude) as a solid. The residue was triturated from n-hexane (2 mL) at 20°C to give **ST-200-N19-K5** (50 mg) as solid
- 15 **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.39-5.37 (m, 1H), 3.51 (s, 1H), 2.25-2.21 (m, 1H), 2.05-1.70 (m, 7H), 1.65-1.50 (m, 4H), 1.50-1.25 (m, 10H), 1.25-1.15 (m, 6H), 1.14-1.10 (m, 4H), 0.94-0.91 (m, 6H), 0.88-0.83 (m, 5H), 0.67 (s, 3H).

**LCMS** Rt = 1.269 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 99%, MS ESI calcd. For C<sub>28</sub>H<sub>47</sub>O<sup>+</sup> [M+H-H<sub>2</sub>O]<sup>+</sup> 399, found 399.

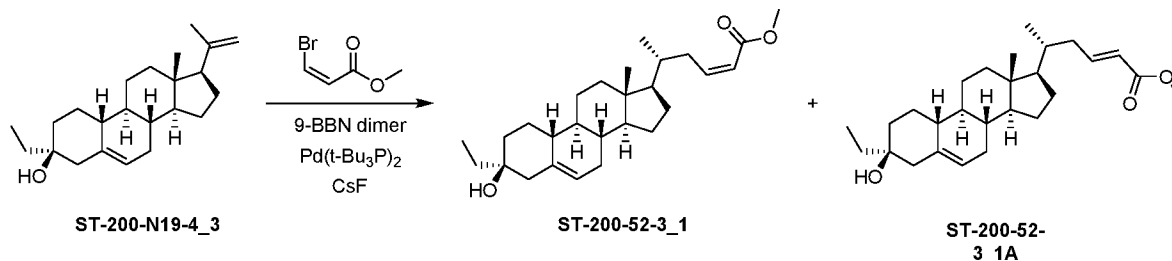
20

**EXAMPLE 107: Synthesis for 10790**



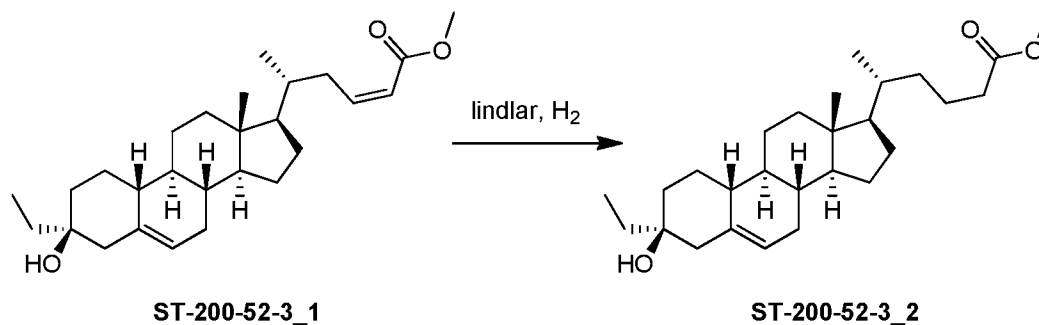
[00693] The experimental of intermediate **ST-200-N19-4\_3** can be found in Example 94.

[00694] **Synthesis of ST-200-52-3\_1, ST-200-52-3\_1A**



- 5 9-BBN dimer (2.22 g, 9.12 mmol) was added to a solution of **200-N19-4\_3** (2 g, 6.08 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere at 30°C. The mixture was stirred at 65°C for 3 hours. The reaction mixture was cooled to 30°C, and (Z)-methyl 3-bromoacrylate (1.20 g, 7.29 mmol), CsF (1.83 g, 12.1 mmol) and Pd(t-Bu<sub>3</sub>P)<sub>2</sub> (310 mg, 0.608 mmol) were added to the mixture. The resulting mixture was stirred at 65°C for 16 hours. The reaction was cooled,
- 10 quenched with water (300 mL), extracted with EtOAc (3 x 300 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give a residue, which was purified by combi-flash (5%-15% of EtOAc in PE) to give **ST-200-52-3\_1** (400 mg, 16%) as a solid, **ST-200-52-3\_1A** (340 mg, 13%) as solid, and the mixture of **ST-200-52-3\_1** and **ST-200-52-3\_1A** (340 mg) as a solid.
- 15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.29-6.23 (m, 1H), 5.82 (d, *J* = 12.0 Hz, 1H), 5.39-5.34 (m, 1H), 3.70 (s, 3H), 2.65-2.55 (m, 2H), 2.23 (dd, *J* = 3.2, 13.2 Hz, 1H), 2.08-1.78 (m, 8H), 1.72-1.58 (m, 5H), 1.53-1.38 (m, 6H), 1.37-0.99 (m, 5H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.70 (s, 3H).

[00695] **Synthesis of ST-200-52-3\_2**



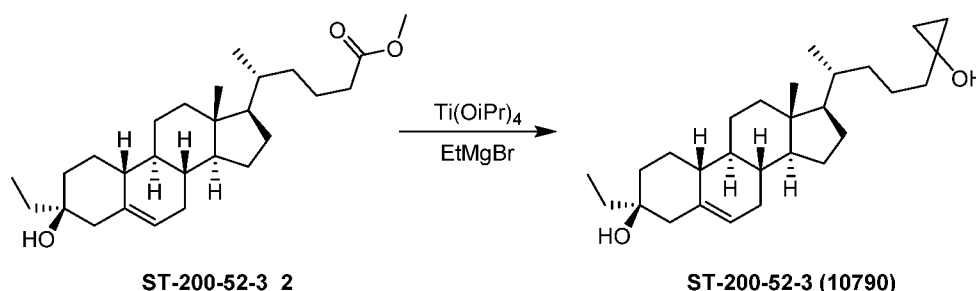
- 20 **ST-200-52-3\_1** (340 mg, 0.8200 mmol) in THF/MeOH (8 mL/8 mL) and Lindlar (600 mg) was stirred at 20°C under H<sub>2</sub> (15psi) for 16 hours. The reaction mixture was filtered and the filtrate cake was washed with DCM (2 x 10 mL), MeOH (2 x 10 mL), THF (2 x 10 mL). The filtrate was concentrated under vacuum to give **ST-200-52-3\_2** (300 mg, crude) as an oil, which was
- 25 triturated in MeOH/H<sub>2</sub>O (5 mL/5 mL) to give **ST-200-52-3\_2** as an oil. The crude oil was further

purified by flash column (0~10% of EtOAc in PE) to give **ST-200-52-3\_2** (240 mg, 80%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.44-5.35 (m, 1H), 3.66 (s, 3H), 2.38-2.17 (m, 3H), 2.02-1.76 (m, 7H), 1.61-1.37 (m, 10H), 1.28-0.99 (m, 9H), 0.96-0.76 (m, 8H), 0.74-0.65 (m, 3H).

5

**[00696] Synthesis of 10790**



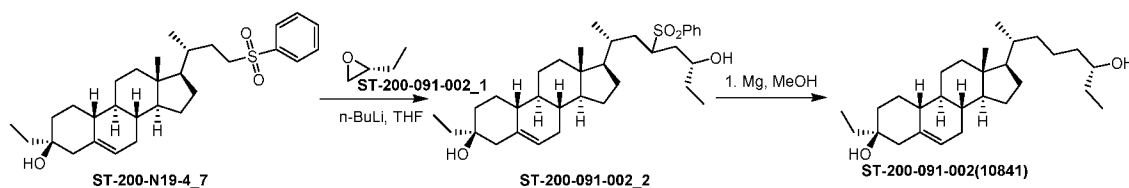
Ti(i-PrO)<sub>4</sub> (163 mg, 0.58 mmol) and EtMgBr (0.7 mL, 3 M in Et<sub>2</sub>O, 2 mmol) were added to a solution of **ST-200-52-3\_2** (240 mg, 0.58 mmol) in THF (2 mL) at 25°C. The reaction mixture was stirred at 25°C for 15 min under N<sub>2</sub>. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) solution and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude product, which was purified by flash column (0~15% of EtOAc in PE) to afford a crude solid. The solid was further triturated from MeCN (5 mL) and purified by silica gel chromatography (PE/EtOAc = 10/1) to afford **ST-200-52-3** (15 mg, 6%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.44-5.35 (m, 1H), 2.27-2.19 (m, 1H), 2.07-1.61 (m, 10H), 1.51-1.34 (m, 8H), 1.31-0.98 (m, 11H), 0.97-0.92 (m, 3H), 0.89-0.82 (m, 5H), 0.76-0.71 (m, 2H), 0.68 (s, 3H), 0.48-0.39 (m, 2H).

LCMS Rt = 1.226 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI

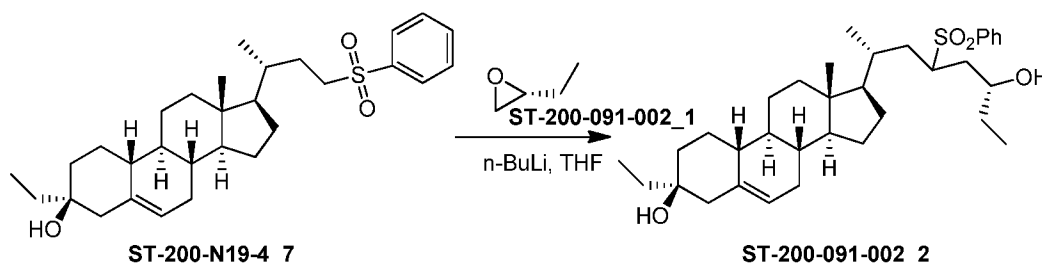
calcd. for C<sub>28</sub>H<sub>45</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 397, found 397.

**EXAMPLE 108: Synthesis of 10841**



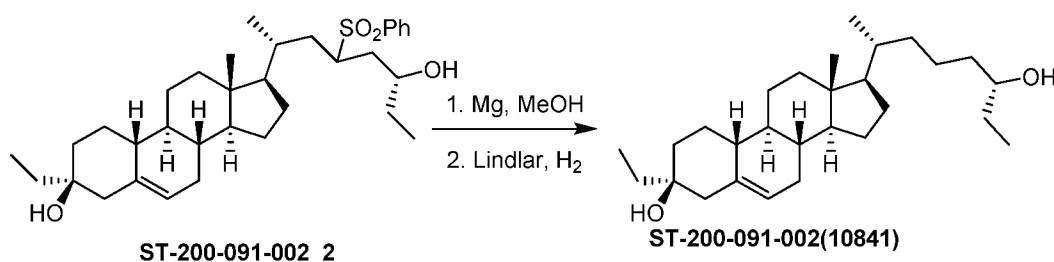
**[00697]** The experimental of intermediate **ST-200-N19-4\_7** can be found in Example 94.

**[00698] Synthesis of ST-200-091-002\_2**



To a solution of **ST-200-N19-4\_7** (500 mg, 1.03 mmol) in anhydrous THF (3 mL) was added n-BuLi (1.23 mL, 3.09 mmol, 2.5M in n-hexane) drop-wise at -70°C under N<sub>2</sub>. The reaction mixture was stirred at -70°C for 30 mins. To the mixture was added a solution of (R)-2-ethyloxirane (111 mg, 1.54 mmol) in anhydrous THF (0.5 mL) drop-wise at -70°C and stirred for another 1 h. The reaction mixture was then stirred at 25°C for 12 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combine organic phase was washed whit saturated brine (2 x 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **ST-200-091-002\_2** (0.5 g, crude) as an oil.

#### [00699] Synthesis of ST-200-091-002

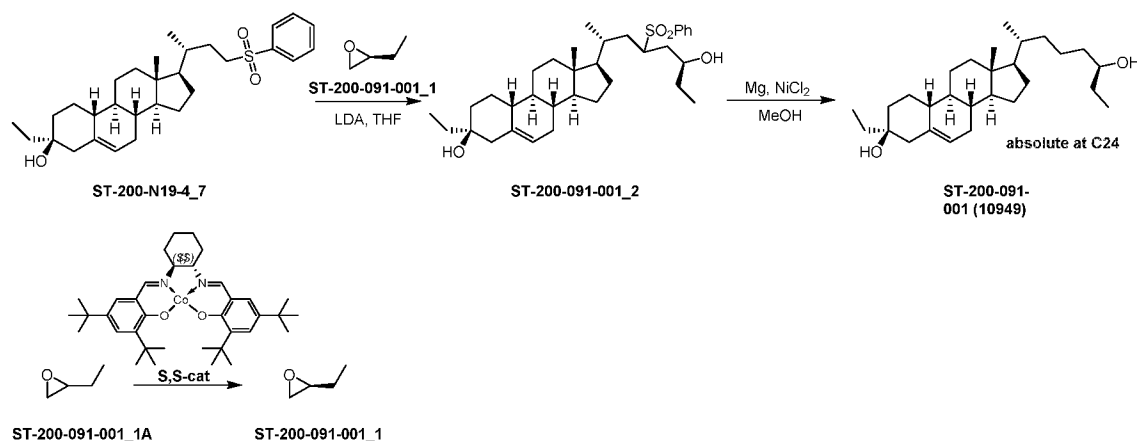


To a solution of **ST-200-091-002\_2** (0.5 g, crude) in MeOH (50 mL) was added Mg powder (1.07 g, 44.8 mmol) and NiCl<sub>2</sub> (20 mg) at 25°C under N<sub>2</sub>. After stirring at 50°C for 1 h, the reaction mixture was quenched with HCl (100 mL, 1 M) until the reaction became clear. The aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 8/1) to afford **ST-200-091-002** (120 mg, 32%) as a solid, which was purified by SFC (Column:AD (250mm\*30mm,5um), Condition:0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH, Begin B:40%, End B:40%) to afford **ST-200-091-002** (50 mg, 42.0%) as a solid.

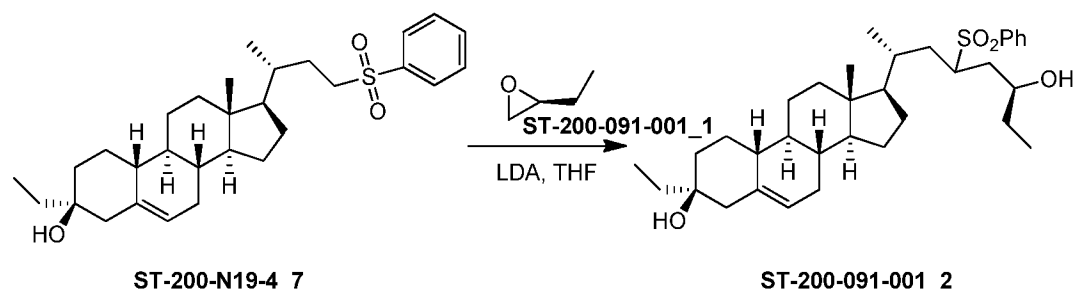
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.38-5.36 (m, 1H), 3.55-3.49 (m, 1H), 2.29-2.20 (m, 1H), 2.05-1.75 (m, 7H), 1.65-1.31 (m, 13H), 1.30-1.15 (m, 7H), 1.14-0.76 (m, 15H), 0.68 (s, 3H).

LCMS Rt = 1.326 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI

calcd. for C<sub>28</sub>H<sub>47</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 399, found 399.

**EXAMPLE 109: Synthesis of 10949**

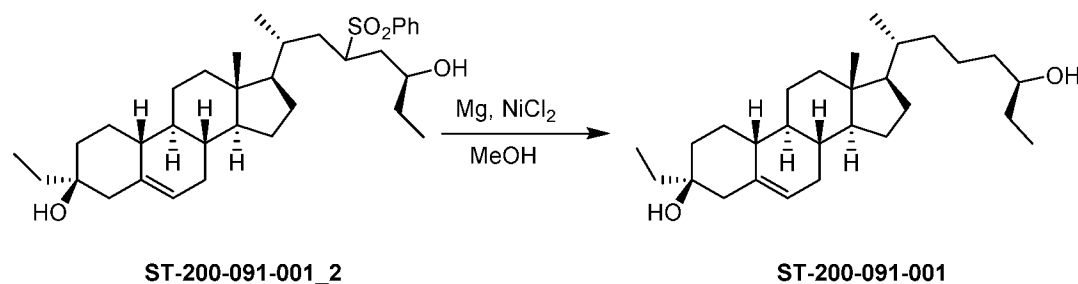
[00700] The experimental of intermediate **ST-200-N19-4\_7** can be found in Example 94.

**[00701] Synthesis of ST-200-091-001\_2**

5

To a THF (0.5 mL) under N<sub>2</sub> at -70°C was added n-BuLi (2.5 M, 2.57 mmol, 1.02 mL). After that, a suspension of **ST-200-N19-4\_7** (500 mg, 1.03 mmol) in THF (3 mL) was added dropwise to give a suspension. After stirring at -70°C for 30 min, a solution of (S)-2-ethyloxirane (88.6 mg, 1.23 mmol) in THF (0.5 mL) was added. Then reaction was stirred at 25°C for 16 hours. The mixture was poured into ice-water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford **ST-200-091-001\_2** (580 mg, crude) as a solid, which was used directly for the next step.

10

**[00702] Synthesis of ST-200-091-001**

15

To a solution of **ST-200-091-001\_2** (580 mg, 4.41 mmol) and nickel (II) chloride (6.73 mg, 0.052 mmol) in MeOH (30 mL) was added Mg powder (499 mg, 20.8 mmol) at 25°C. The

mixture was stirred at 50°C for 1 h. After cooling, the mixture was quenched with HCl (100 mL, 2M) until the reaction became clear and extracted with EtOAc (2 x 50 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by a silica gel column (PE/EtOAc = 10/1 to 3/1) to give **ST-200-091-001** (120 mg, 28%) as a solid.

- 5 The **ST-200-091-001** (120 mg, 0.287 mmol) was separated by SFC (column: AD (250mm\*30mm, 5um)), gradient: 50-50% B (A= 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH), flow rate: 60 mL/min) to give **ST-200-091-001** (58 mg, 14%) as a solid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 5.42-5.38 (m, 1H), 3.57-3.47 (m, 1H), 2.25-2.21 (m, 1H), 2.07-1.88 (m, 4H), 1.86-1.78 (m, 3H), 1.68-1.59 (m, 2H), 1.52-1.31 (m, 12H), 1.29-0.98 (m, 10H),  
10 0.96-0.75 (m, 11H), 0.68 (s, 3H).

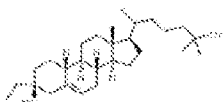
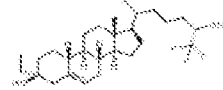
LCMS Rt = 1.318 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For C<sub>28</sub>H<sub>47</sub>O [M-H<sub>2</sub>O+H] + 399, found 399.

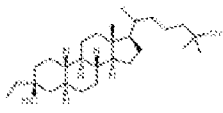
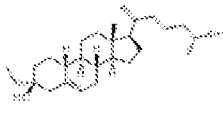
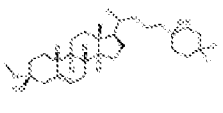
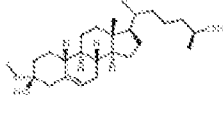
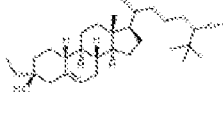
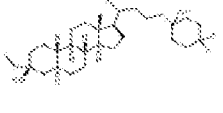

SFC Rt = 6.962 min in 10 min chromatography, AD\_3\_EtOH\_DEA\_5\_40\_25ML, 99.4%de


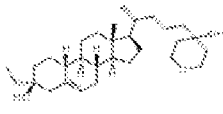

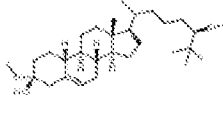
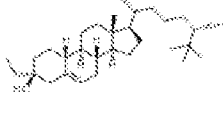
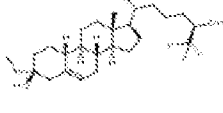
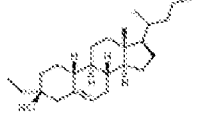
## 15 EXAMPLE 110. Biological data


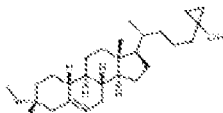
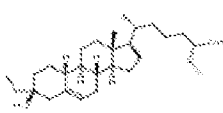
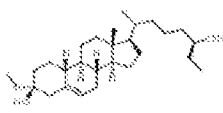
[00703] Experiments conducted as described in Example 2 and results are reported in Table 2-62.

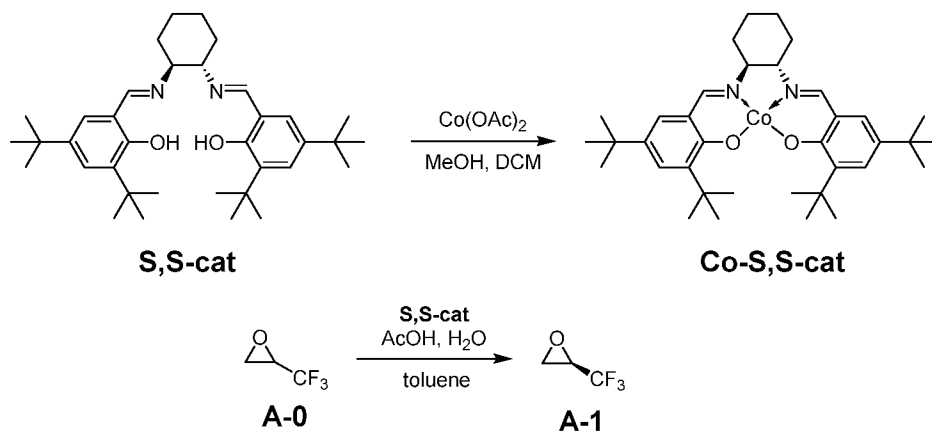
**Table 2-62**

	Compound	Avg EC50 2A (nM)	Avg Emax 2A (%)	Avg EC50 2B (nM)	Avg Emax 2B (%)
	194	200.3	161.8	143.5	192.5
	9567	327.5	104.0	378.1	124.3

	9670	366.1	153.8	219.9	213.2
	9792	334.2	64.5	284.9	58.2
	9810	124.0	87.1	151.2	91.6
	9911	252.6	233.7	287.6	326
	10012	790.0	154.1	909.6	167.6
	9813	469.2	68.7	267.7	99.9
	10114	320.8	146.3	505.6	179.1

	10115	555.9	191.6	458.2	225.6
	10216	1196.8	79.3	445.6	120.7
	10317	>10000	56.7	>10000	59.9
	10042	>10000	65.9	1877.4	112.8
	10043	897.3	145.7	1067.0	210.6
	10456	239.6	230.6	208.6	265.7
	10557	286.8	189.7	191.7	202.5

	10673	253.6	215.5	180.1	213.5
	10790	203.8	159.8	270.5	245.8
	10841	>10000	15.6	>10000	30.1
	10949	66.4	97.4	138.1	147.4

**EXAMPLE 111. Synthesis of Compound A-1**

5

[00704] **Step 1.** To a solution of **S,S-cat** (2 g, 3.65 mmol) in anhydrous DCM (30 mL) was added a solution of cobalt(II) acetate (775 mg, 4.38 mmol) in MeOH (30 mL) under

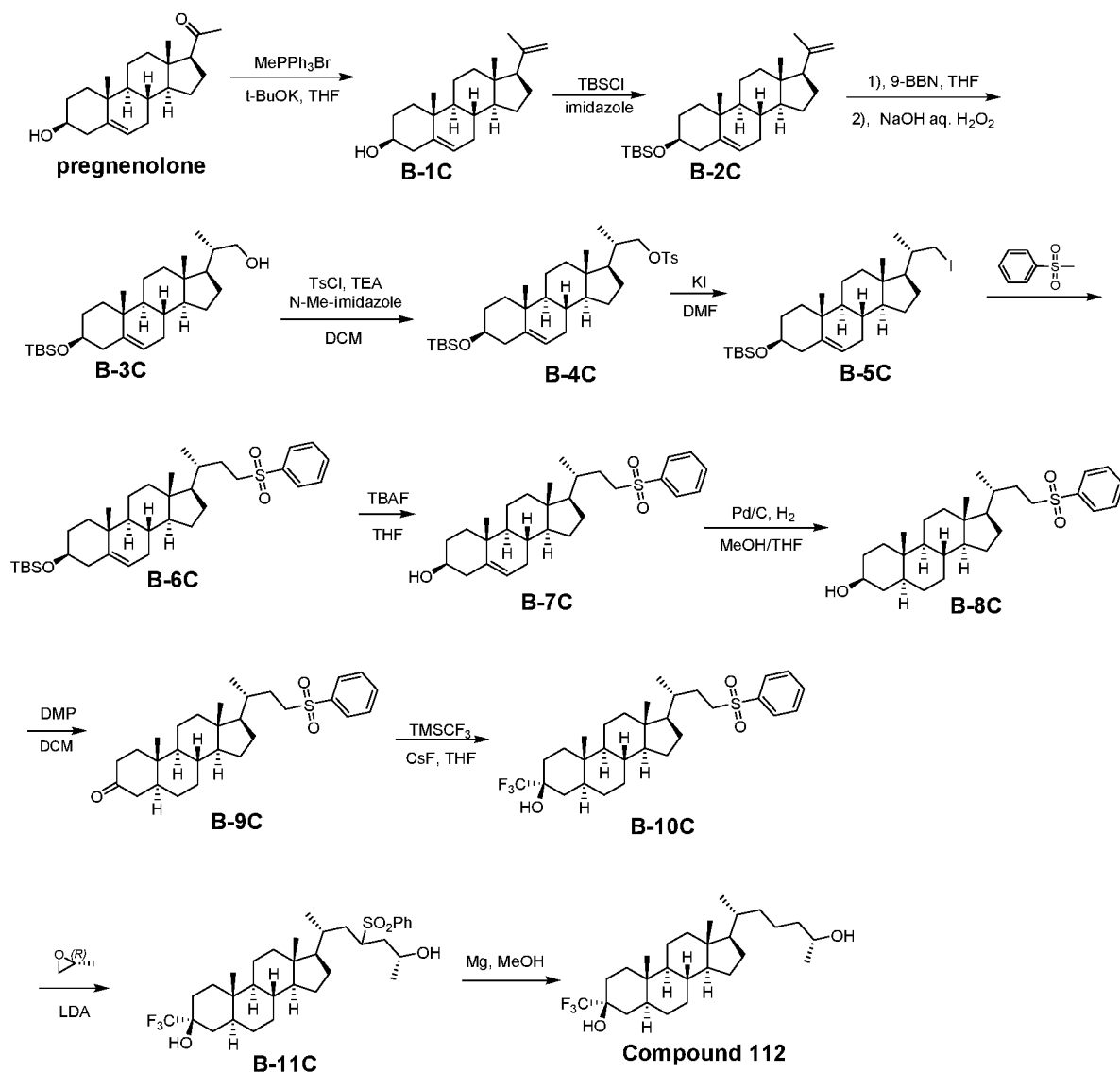
nitrogen at 20°C. The mixture was stirred for 30 mins at 20°C and at 0°C for 1 h. The precipitated solid was filtered, washed with cold MeOH (2 x 30 mL) and dried in vacuum to give **Co-S,S-cat** (1.6 g, 73%) as a solid.

[00705] **Step 2.** To a solution of **Co-S,S-cat** (1.07 g, 1.78 mmol) in toluene (30 mL) was added AcOH (1.12 g, 18.7 mmol). The mixture was stirred at 20°C for 30 mins. The solution was concentrated in vacuum to give a crude solid. The resulting catalyst residue was dissolved in neat **A-0** (100 g, 892 mmol) at 20°C, the reaction mixture was cooled to 0°C, and water (8.82 g, 490 mmol) was added dropwise. The mixture was warmed to 20°C and stirred for 48 hrs. **A-1** (44 g) was isolated by distillation from the reaction mixture.

10 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.96 (s, 1H), 3.11-2.98 (m, 2H).

[00706] The e.e. of **A-1** was determined by opening the epoxide with benzylamine. **A-1** (200 mg, 1.78 mmol) was added to dry benzylamine (190 mg, 1.78 mmol), and the mixture was stirred at 20°C for 2 hrs. A solid precipitated, which was triturated from petroleum ether to afford the product (260 mg, 67%) as a solid. The e.e. of this product was determined to be 100% by chiral HPLC. (Column: CD-PH 250\*4.6mm I.D., 5μm; Mobile phase: from 10% to 80% of B in A (A:Water with 0.069% TFA B:Acetonitrile); Flow rate: 0.8mL/min; Column Temperature : 30°C).

#### EXAMPLE 112. Synthesis of Compound 112.



[00707] **Step 1.** To a mixture of  $\text{MePPh}_3\text{Br}$  (1.28 kg, 3.6 mol) in THF (4.5 L) was added  $t\text{-BuOK}$  (404 g, 3.6 mol) at 15°C under  $\text{N}_2$ . The resulting mixture was stirred at 50°C for 30 min.

- 5 **Pregnenolone** (950 g, 2.9 mol) was added in portions below 65°C. The reaction mixture was stirred at 50°C for 1 hour. The combined mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous (1 L) at 15°C. THF layer was separated. The aqueous was extracted with EtOAc (2 x 2 L). The combined organic phase was concentrated under vacuum to give a solid. The solid was further purified by trituration with MeOH/ $\text{H}_2\text{O}$  (1:1, 15 L) at reflux to give **B-1C** (940 g, 99%) as a solid.
- 10

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.40-5.32 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 3.58-3.46 (m, 1H), 2.36-2.16 (m, 2H), 2.08-1.94 (m, 2H), 1.92-1.62 (m, 9H), 1.61-1.39 (m, 6H), 1.29-1.03 (m, 4H), 1.01 (s, 3H), 0.99-0.91 (m, 1H), 0.59 (s, 3H).

[00708] **Step 2.** To a solution of **B-1C** (4 kg, 12.7 mol) in DCM (30 L) was added imidazole (1.72 kg, 25.4 mol) and TBSCl (2.86 kg, 19.0 mol) at 25°C. The reaction mixture was stirred at 25°C for 16 hrs. The reaction mixture was treated with water (10 L). The organic phase was concentrated to give crude product which was triturated in MeOH (15 L) at reflux to give **B-2C** (5.02 kg, 92%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.38-5.28 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 3.57-3.41 (m, 1H), 2.33-2.11 (m, 2H), 2.10-1.94 (m, 2H), 1.90-1.61 (m, 8H), 1.60-1.38 (m, 6H), 1.28-1.03 (m, 4H), 1.00 (s, 3H), 0.98-0.91 (m, 1H), 0.89 (s, 9H), 0.58 (s, 3H), 0.06 (s, 6H).

[00709] **Step 3.** To a solution of **B-2C** (1.69 kg, 3.94 mol) in THF (8 L) was added 9-BBN dimer (671 g, 2.75 mol) and the reaction was stirred at 25°C under N<sub>2</sub> for 1 h and a solid was formed. To the reaction mixture was added ethanol (2.26 L, 39.4 mol) and NaOH (3.94 L, 5 M, 19.7 mol) and the mixture became clear. Then H<sub>2</sub>O<sub>2</sub> (3.94 L, 10 M, 39.4 mol) was added dropwise at 25°C and the inner temperature was raised to reflux. The mixture was cooled and stirred for 16 hrs and a solid was formed. This was followed by adding Na<sub>2</sub>SO<sub>3</sub> (2.5 L, 20% aq.) and water (5 L) at 25°C. The mixture was stirred for 1 h. After the stirrer was turned off, a clear lower layer and another upper suspension layer were formed. The clear lower layer was discarded. The upper suspension layer was treated with water (20 L). The mixture was stirred for 15 mins. The mixture was filtered. The solid was washed with water until pH < 9 to give the wet product. The wet product **B-3C** was dissolved in DCM (100 L). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to 20 L. The residue was used in the next step directly.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.40-5.23 (m, 1H), 3.70-3.60 (m, 1H), 3.55-3.42 (m, 1H), 3.41-3.31 (m, 1H), 2.31-2.20 (m, 1H), 2.20-2.11 (m, 1H), 2.06-1.91 (m, 2H), 1.89-1.67 (m, 3H), 1.65-1.39 (m, 7H), 1.38-1.08 (m, 6H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.00 (s, 3H), 0.99-0.91 (m, 2H), 0.88 (s, 9H), 0.70 (s, 3H), 0.05 (s, 6H).

[00710] **Step 4.** To a solution of **B-3C** (theoretical mass: 5.2 kg, 11.6 mol) in DCM (15 L) was added N-methyl-imidazole (1.37 L, 17.4 mol) and TEA (3.2 L, 23.2 mol) at 25°C. Then TsCl (2.53 kg, 13.3 mol) was added into the solution in portions to keep the inner temperature between 25 to 30°C. The reaction mixture was stirred at 25°C for 1 h. To the mixture was added water (10 L), citric acid (20%, 1 L). HCl (1 M) was added till pH = 3. The organic layer was separated, washed with water (2 x 10 L), NaHCO<sub>3</sub> (sat. aq. 5 L) and brine (5 L), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **B-4C** (6.63 kg, 95% for 2 steps) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.37-5.25 (m, 1H), 3.96 (dd, *J* = 2.8, 9.2 Hz, 1H), 3.79 (dd, *J* = 6.4, 9.2 Hz, 1H), 3.53-3.41 (m, 1H), 2.45 (s, 3H), 2.32-2.20 (m, 1H), 2.20-2.11 (m, 1H), 2.01-1.88 (m, 2H), 1.84-1.61 (m, 4H), 1.56-1.31 (m,

6H), 1.23-1.02 (m, 5H), 1.02-0.95 (m, 7H), 0.93-0.90 (m, 1H), 0.88 (s, 9H), 0.63 (s, 3H), 0.05 (s, 6H).

[00711] **Step 5.** To a solution of **B-4C** (10 g, 16.6 mmol) in DMF (300 mL) was added KI (6.88 g, 41.5 mmol). The suspension was stirred at 50°C for 2 hrs. The mixture was quenched with water (500 mL) and extracted with PE (3 x 150 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was triturated with EtOAc (50 mL) and filtered to give **B-5C** (7 g, 76%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.32-5.28 (m, 1H), 3.52-3.40 (m, 1H), 3.38-3.30 (m, 1H), 3.20-3.11 (m, 1H), 2.32-2.10 (m, 2H), 2.00-1.90 (m, 1H), 1.90-1.35 (m, 13H), 1.30-1.15 (m, 4H), 1.15-0.96 (m, 6H), 0.96-0.80 (m, 10H), 0.71 (s, 3H), 0.06 (s, 6H).

[00712] **Step 6.** To a solution of (methylsulfonyl) benzene (24.5 g, 157 mmol) in THF (200 mL) was added n-BuLi (57.2 mL, 143 mmol) at -70°C under N<sub>2</sub>. The mixture was stirred at -70°C for 30 minutes. A solution of **B-5C** (40 g, 71.8 mmol) in THF (200 mL) was added dropwise at 25°C. After addition, the reaction was allowed to stir at 25°C for 3h. The reaction was quenched with sat.NH<sub>4</sub>Cl (50 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to give **B-6C** (40 g, 95%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.90-7.86 (m, 2H), 7.68-7.61 (m, 1H), 7.60-7.52 (m, 2H), 5.33-5.29 (m, 1H), 3.50-3.42 (m, 1H), 3.17-3.06 (m, 1H), 3.04-2.96 (m, 1H), 2.31-2.11 (m, 3H), 1.99-1.90 (m, 2H), 1.87-1.67 (m, 5H), 1.51-1.40 (m, 7H); 1.24-0.82 (m, 27H); 0.68-0.58 (m, 3H).

[00713] **Step 7.** To a suspension of **B-6C** (31.0 g, 54.7mmol) in THF (100mL) was added TBAF (21.4kg, 82.0 mmol). The mixture was stirred at 65°C for 1 h. The mixture turned clear. To the mixture was added water (300mL) and stirred at 80°C for 2 h. The mixture was filtered after cooling. The solid was washed with water (300ml), dried in air to give **B-7C** (17g, crude) as a solid, which was used directly for the next step.

[00714] **Step 8.** To a solution of **B-7C** (10.5 g, 22.3 mmol) in MeOH (100 mL) and THF (100 mL) was added Pd/C (2 g, <1% water). Then the solution was hydrogenated under 30 psi of hydrogen at 25°C for 48 h. The reaction was conducted in parallel twice. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuum. The product was triturated by MeCN (100 mL) to afford **B-8C** (15 g, 71%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.91-7.89 (m, 2H), 7.67-7.64 (m, 1H), 7.59-7.55 (m, 2H), 3.60-3.55 (m, 1H), 3.15-3.06 (m, 1H), 3.02-2.94 (m, 1H), 1.89-1.70 (m, 3H), 1.69-1.64 (m, 3H), 1.53-1.20 (m, 12H), 1.15-0.89 (m, 7H), 0.86 (m, 4H), 0.78 (s, 3H), 0.63-0.56 (m, 4H)

[00715] **Step 9.** To a solution of **B-8C** (5.0 g, 10.5 mmol) in DCM (50 mL) was added DMP (8.90 g, 21.0 mmol) at 25°C. The mixture was stirred at 25°C for 30 mins. The reaction

was quenched with saturated aqueous  $\text{NaHCO}_3$  (50 mL) and the pH was adjusted to 7~8. Then saturated  $\text{Na}_2\text{S}_2\text{O}_3$  (100 mL) was added to the solution and extracted with DCM (100 mL). The combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give **B-9C** (4.6 g, crude) as a solid, which was used in the next step without further purification.

5  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96-7.86 (m, 2H), 7.61-7.53 (m, 3H), 3.17-3.04 (m, 1H), 3.03-2.94 (m, 1H), 2.42-2.15 (m, 3H), 2.10-1.80 (m, 4H), 1.73-1.63 (m, 2H), 1.60 (s, 3H), 1.55-1.45 (m, 4H), 1.40-1.24 (m, 5H), 1.24-1.15 (m, 1H); 1.14-1.03 (m, 2H); 0.99 (s, 3H); 0.90-0.84 (m, 4H); 0.74-0.65 (m, 1H); 0.63 (s, 3H).

[00716] **Step 10.** To a solution of **B-9C** (4.6 g, 9.77 mmol) and CsF (2.96 g, 19.5 mmol) in THF (50 mL) was added dropwise  $\text{TMSCF}_3$  (2.77 g, 19.5 mmol) at  $0^\circ\text{C}$ . The mixture was stirred and kept below  $10^\circ\text{C}$  for 30 mins. To the mixture was added TBAF (24.4 mL, 1 M in THF, 24.4 mmol) at  $10^\circ\text{C}$ . The mixture was stirred and kept below  $10^\circ\text{C}$  for 30 mins. To the mixture was added water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The residue was purified by silica gel chromatography (PE/EtOAc = 10/1) to afford **B-10C** (2.4 g, impure) as a solid. The impure **B-10C** (2.4 g) was purified by preparative HPLC (column: Phenomena Luna C18 250\*50mm\*10  $\mu\text{m}$ , gradient: 20-100% B (A= water (0.05% HCl)-ACN, B= acetonitrile), flow rate: 100 mL/min,  $25^\circ\text{C}$ ) to obtain **B-10C** (1.6 g, 30%) as a foam.

20  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91-7.89 (m, 2H), 7.67-7.64 (m, 1H), 7.59-7.55 (m, 2H), 3.16-3.08 (m, 1H), 3.02-2.94 (m, 1H), 2.08-2.02 (m, 2H), 1.91-1.78 (m, 3H), 1.70-1.60 (m, 4H), 1.53-1.01 (m, 13H), 1.07-0.92 (m, 4H), 0.87-0.85 (m, 3H), 0.83 (s, 3H), 0.68-0.63 (m, 1H), 0.61 (m, 3H).

[00717] **Step 11.** To a solution of n-BuLi (440  $\mu\text{L}$ , 2.5 M in hexane, 1.10 mmol) in THF (0.5 mL) at  $-65^\circ\text{C}$  under  $\text{N}_2$  was added a suspension of **B-10C** (200 mg, 0.3698 mmol) in THF (2.5 mL) dropwise. The mixture was stirred for 30 minutes at  $-65^\circ\text{C}$ . Diisopropylamine (111 mg, 1.10 mmol) was added at  $-65^\circ\text{C}$ . After that, (R)-2-methyloxirane (32.2 mg, 0.5547 mmol) was added drop wise at  $-65^\circ\text{C}$ . The mixture was stirred for another 30 minutes and then warmed to  $25^\circ\text{C}$  gradually and stirred at  $25^\circ\text{C}$  for 16 hours. The reaction mixture was quenched by saturated  $\text{NH}_4\text{Cl}$  aqueous (30 mL), extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give **B-11C** (250 mg, crude) as a solid, which was used directly for the next step.

[00718] **Step 12.** To a solution of **B-11C** (250 mg, 0.417 mmol) in MeOH (10 mL) was added Mg powder (398 mg, 16.6 mmol) and added  $\text{NiCl}_2$  (100 mg, 0.771 mmol) was added at  $60^\circ\text{C}$ . The mixture was stirred at  $60^\circ\text{C}$  for 3 hrs. After cooling, the mixture was quenched with HCl (50 mL, 1M) and ice-water (50 mL) until the reaction became clear and extracted with

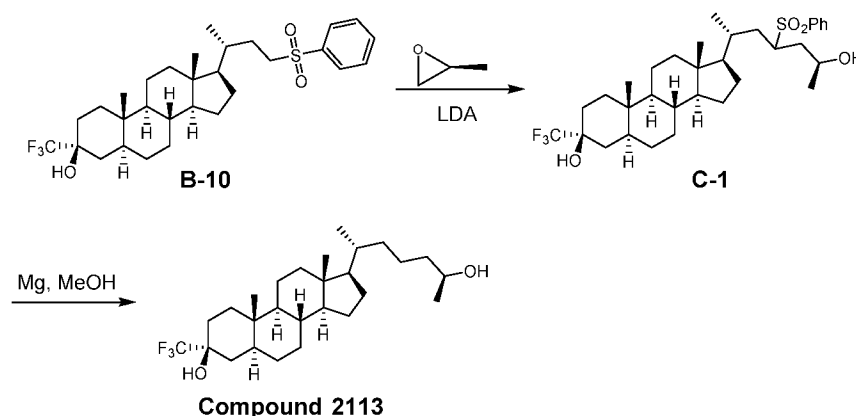
EtOAc (2 x 50 mL). The organic layers were washed with brine (2 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. The residue was purified by a silica gel column (PE/EtOAc = 10/1) to give **Compound 112** (33 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.80-3.76 (m, 1H), 2.08-1.93 (m, 3H), 1.86-1.77 (m, 2H), 1.70-1.62 (m, 3H), 1.54-1.44 (m, 4H), 1.42-1.32 (m, 6H), 1.31-1.22 (m, 5H), 1.20-1.18 (m, 4H), 1.14-0.96 (m, 6H), 0.94-0.86 (m, 4H), 0.85 (s, 3H), 0.70-0.66 (m, 1H), 0.65 (s, 3H).

LCMS Rt = 1.265 min in 2.0 min chromatography, 30-90 AB

MS MS ESI calcd. for C<sub>27</sub>H<sub>44</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 441, found 441

### 10 EXAMPLE 113. Synthesis of Compound 2113.



[00719] **Step 1.** To a solution of n-BuLi (440 μL, 2.5 M in hexane, 1.10 mmol) in THF (0.5 mL) at -65°C under nitrogen was added a suspension of **B-10** (200 mg, 0.3698 mmol) in THF (2.5 mL) was added drop-wise. The mixture was stirred for 30 minutes at -65°C, followed by the addition of diisopropylamine (111 mg, 1.10 mmol). After that, (S)-2-methyloxirane (32.2 mg, 0.5547 mmol) was added drop-wise at -65°C. The mixture was stirred for another 30 minutes and then warmed to 25°C gradually and stirred at 25°C for 16 hours. The reaction mixture was quenched by saturated NH<sub>4</sub>Cl aqueous (30 mL), extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **C-1** (250 mg, crude) as a solid, which was used directly for the next step.

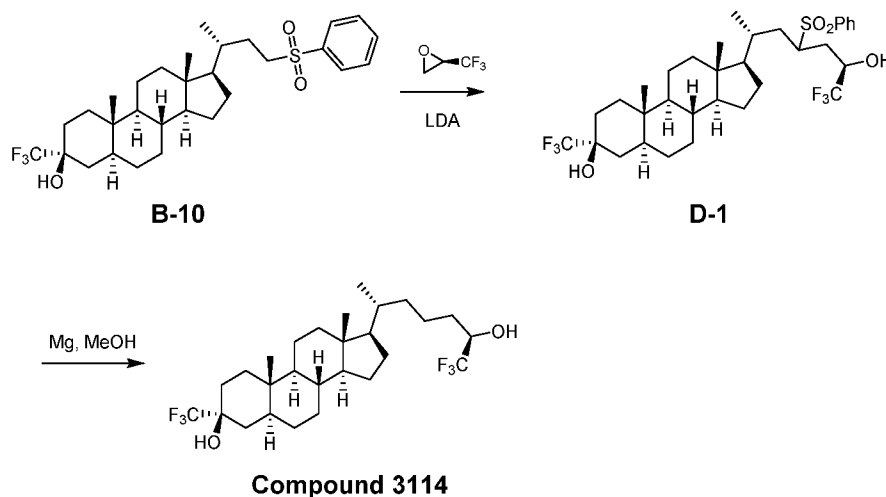
[00720] **Step 2.** To a solution of **C-1** (250 mg, crude) in MeOH (5 mL) was added Mg (202 mg, 8.34 mmol) under nitrogen. After that, the reaction mixture was stirred at 60°C for 1 h under N<sub>2</sub>. Aq. HCl (1M, 10 mL) was added. The mixture was extracted with EtOAc (2 x 10 mL). The organic layer washed with saturated aqueous NaHCO<sub>3</sub> (10 mL) solution and brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude product. The

crude product was purified by silica gel column (EtOAc/PE = 1/10 to 1/5) to give impure **Compound 2113** (100 mg) as a solid, which was re-crystallized from DCM/acetonitrile (5 mL, 2/3) at 25°C to give **Compound 2113** (52 mg, 52%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.79 (s, 1H), 2.08-1.94 (m, 3H), 1.82-1.79 (m, 2H), 1.66-1.01 (m, 28H), 0.91-0.90 (m, 4H), 0.85 (s, 3H), 0.71-0.65 (m, 4H).

LCMS Rt = 1.267 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C<sub>27</sub>H<sub>44</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 441, found 441.

#### EXAMPLE 114. Synthesis of Compound 3114.



**[00721]** **Step 1.** To a solution of diisopropylamine (156 mg, 1.55 mmol) in THF (0.5 mL) was added n-BuLi (0.552 mL, 1.38 mmol, 2.5M in hexane) under N<sub>2</sub> at -70°C. Then a solution of **B-10** (300 mg, 0.554 mmol) in THF (3 mL) was added slowly. The mixture was stirred at -70°C for 30 minutes and then (R)-2-(trifluoromethyl)oxirane (**A-1**) (93.2 mg, 0.831 mmol) was added and the reaction was stirred at 25°C for 16 hrs. The mixture was quenched with saturated NH<sub>4</sub>Cl (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude **D-1** (350 mg) as a solid, which was used directly in the next step.

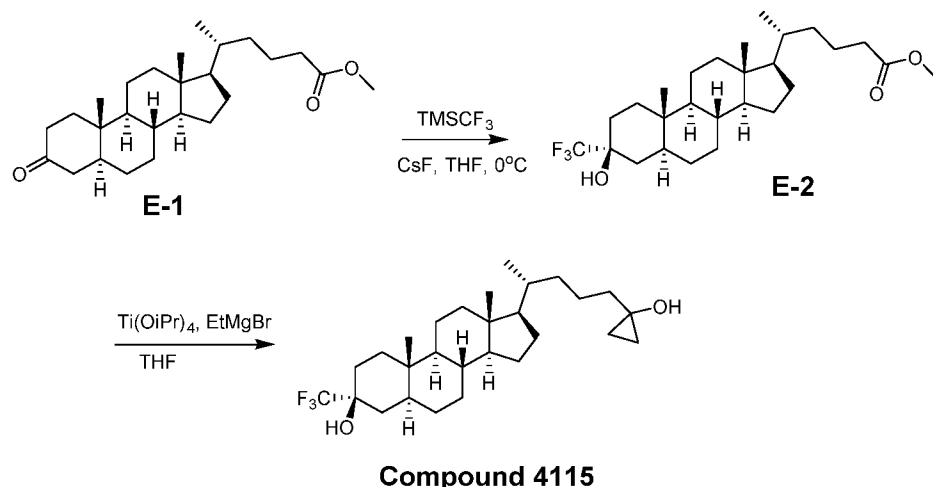
**[00722]** **Step 2.** To a solution of **D-1** (350 mg, 0.536 mmol) in MeOH (30 mL) was added Mg powder (520 mg, 21.4 mmol) at 55°C. The mixture was stirred at 60°C for 30 minutes under N<sub>2</sub>. The mixture was quenched with HCl (50 mL, 1N) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **Compound 3114** (65 mg, 24%) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.93-3.88 (m, 1H), 2.08-2.01 (m, 1H), 2.00-1.92 (m, 3H), 1.85-1.75 (m, 2H), 1.70-1.58 (m, 5H), 1.50-1.32 (m, 8H), 1.31-1.13 (m, 6H), 1.12-0.96 (m, 5H), 0.95-0.92 (m, 4H), 0.90 (s, 3H), 0.70-0.60 (m, 4H).

LCMS Rt = 1.280 min in 2.0 min chromatography, 30-90 AB

5 MS ESI calcd. for C<sub>27</sub>H<sub>41</sub>F<sub>6</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 495, found 495.

#### EXAMPLE 115. Synthesis of Compound 4115.



[00723] **Step 1.** To a solution of **E-1** (200 mg, mmol, preparation described in

10 WO9827106 and US5856535) and CsF (141 mg, 0.99 mmol) in THF (5 mL) was added drop wise TMSCF<sub>3</sub> (150 mg, 0.99 mmol) at 0°C. The mixture was stirred and kept below 10°C for 10 mins. Then TBAF (2.5 mL, 1 M in THF, 2.5 mmol) was added at 10°C and the mixture was stirred and kept below 10°C for 10 mins. The reaction mixture was quenched by adding water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers was washed with  
15 brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatograph (PE/EtOAc= 5/1) to afford **E-2** (146 mg, 59%) as a solid.

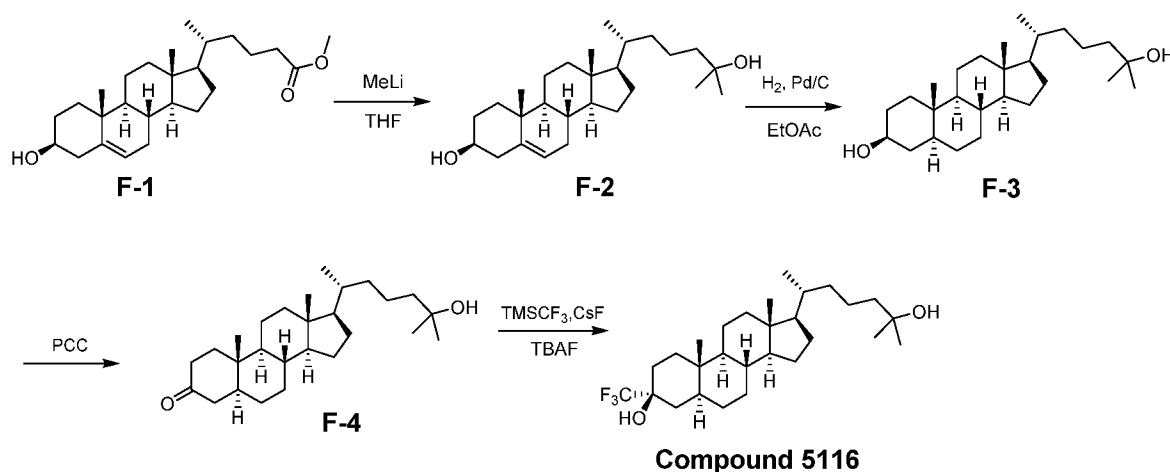
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.66 (s, 3H), 2.31-2.21 (m, 2H), 2.08-1.92 (m, 2H), 1.82-1.77 (m, 2H), 1.71-1.65 (m, 4H), 1.50-1.20 (m, 14H), 1.10-0.99 (m, 5H), 0.92-0.84 (m, 7H), 0.71-0.67 (m, 1H), 0.64 (s, 3H).

20 [00724] **Step 2.** To a solution of **E-2** (146 mg, 0.31 mmol) in THF (1.5 mL) was added Ti(i-PrO)<sub>4</sub> (87.5 mg, 0.31 mmol) and followed by adding EtMgBr (0.36 mL, 3 M in Et<sub>2</sub>O, 1.07 mmol) dropwise at 25°C. After that, the reaction mixture was stirred at 25°C for 15 min under N<sub>2</sub>. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL) solution and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL),  
25 dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a crude product, which was

purified by silica gel column (EtOAc/PE = 5/1) to afford **Compound 4115** (45 mg, 31%) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.10-2.03 (m, 1H), 2.01-1.92 (m, 2H), 1.87-1.77 (m, 2H), 1.75 (s, 1H), 1.72-1.60 (m, 3H), 1.54-1.35 (m, 10H), 1.31-0.98 (m, 12H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.85 (s, 3H), 0.74-0.72 (m, 2H), 0.70-0.67 (m, 1H), 0.65 (s, 3H), 0.45-0.43 (m, 2H). **MS** ESI calcd. For C<sub>28</sub>H<sub>46</sub>F<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 471, found 471.

#### EXAMPLE 116. Synthesis of Compound 5116.



**[00725]** **Step 1.** To a solution of **F-1** (see WO 2017007836 for its synthesis) (7 g, 17.3 mmol) in THF (70 mL) was added MeLi (54.0 mL, 86.4 mmol, 1.6 M in diethyl ether) at 0°C under N<sub>2</sub>. The reaction was warmed to 25°C and stirred at 25°C for 1 h. The reaction was quenched with ice water (200 mL), filtered and extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give **F-2** (8 g, crude) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.4-5.3 (m, 1H), 3.6-3.45 (m, 1H), 2.35-2.25 (m, 2H), 2.05-1.9 (m, 2H), 1.88-1.75 (m, 3H), 1.54-1.26 (m, 15H) 1.24-1.15 (m, 6H), 1.15-1.1 (m, 6H), 1.01-0.95 (m, 3H), 0.93-0.91 (m, 4H), 0.7-0.6 (m, 3H).

**[00726]** **Step 2.** To a solution of **F-2** (2 g, 4.96 mmol) in MeOH/THF (40 mL/10 mL) was added Pd/C (dry, 10%, 0.8 g). After degassing and back-filling with H<sub>2</sub> for three times, the reaction mixture was stirred for 48 h at 50°C in H<sub>2</sub> atmosphere (50 psi). The mixture was filtered and concentrated in vacuum to give **F-3** (2 g, crude) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.65-3.50 (m, 1H), 2.01-1.85 (m, 1H), 1.84-1.75 (m, 2H), 1.73-1.57 (m, 5H), 1.55-1.50 (m, 8H), 1.49-1.3 (m, 6H) 1.29-1.15 (m, 6H), 1.15-0.95 (m, 9H), 0.94-0.8 (m, 3H), 0.79-0.75 (m, 3H), 0.7-0.5 (m, 4H).

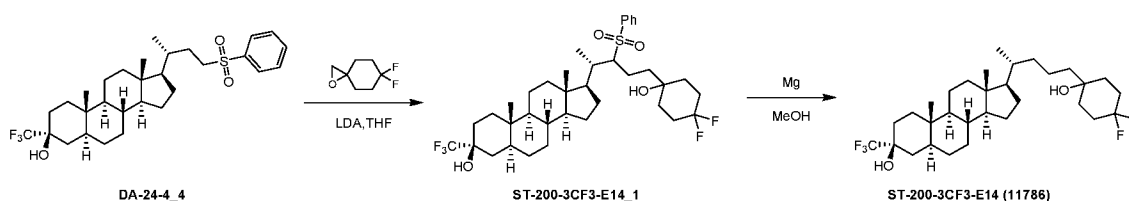
[00727] **Step 3.** To the solution of **F-3** (2.06 g, 5.10 mmol) in DCM (20 mL) was added PCC (2.21 g, 10.2 mmol) at 25°C. The reaction was stirred at 25°C for 2 h. The mixture was concentrated in vacuum to give crude **F-4** (1.6 g), which was purified by column chromatography on silica gel (0-20% of EtOAc in PE) to give **F-4** (1.2 g) as a solid.

5 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.45-2.25 (m, 3H), 2.20-1.9 (m, 3H), 1.82-1.75 (m, 1H), 1.73-1.6 (m, 1H), 1.57-1.25 (m, 14H), 1.24-1.1 (m, 14H) 1.09-0.95 (m, 3H), 0.94-0.79 (m, 3H), 0.77-0.6 (m, 4H).

[00728] **Step 4.** To a solution of **F-4** (100 mg, 248 μmol) in THF (5 mL) was added TMSCF<sub>3</sub> (176 mg, 1.24 mmol) and TBAF (0.5 mL, 1 M in THF, 0.5 mmol). The mixture was stirred at 10°C for 1 h. To the mixture was added TBAF (2.48 mL, 1 M in THF, 2.48 mmol). The mixture was stirred at 30°C for another 2 h. The mixture was concentrated in vacuum. The residue was dissolved in EtOAc (50 mL), washed with water (2 x 50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuum to give crude **Compound 5116** (80 mg) as a solid. 50 mg of crude **Compound 5116** was triturated with acetonitrile (10 mL) at 50°C. Then the precipitate was collected by filtration and concentrated in vacuum to give **Compound 5116** (20 mg).

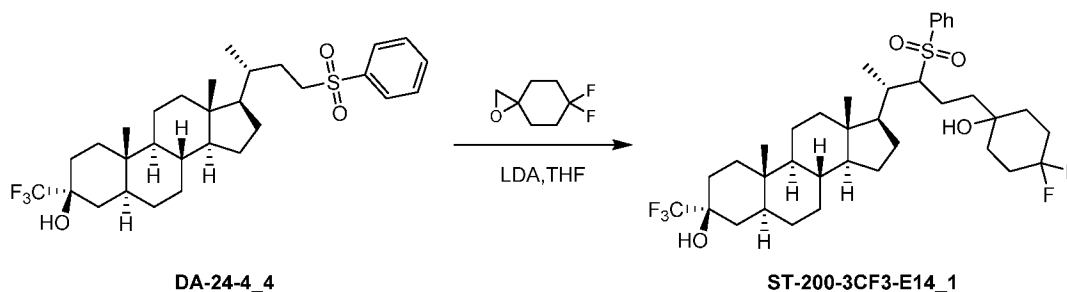
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.13-1.97 (m, 2H), 1.96-1.8 (m, 1H), 1.79-1.7 (m, 2H), 1.69-1.61 (m, 4H), 1.60-1.25 (m, 15H), 1.24-1.15 (m, 6H), 1.14-0.92 (m, 7H), 0.9-0.8 (m, 3H), 0.79-0.76 (m, 3H), 0.75-0.55 (m, 4H). LCMS Rt = 1.305 min in 2 min chromatography, 30-90 AB, MS ESI calcd. For C<sub>28</sub>H<sub>46</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 455, found 455.

#### EXAMPLE 117: Synthesis for 11786



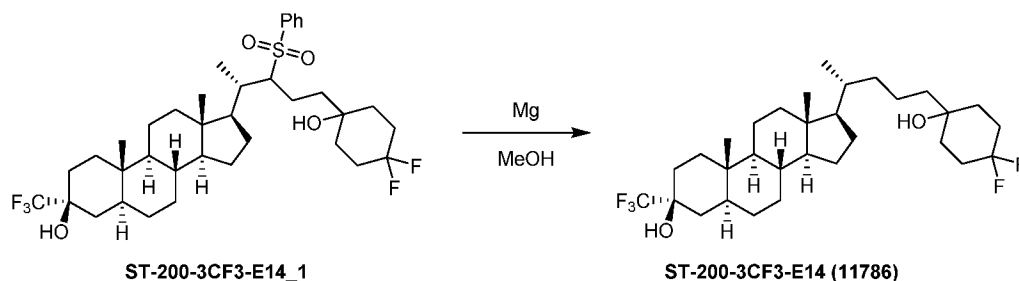
[00729] The synthesis of **DA-24-4\_4** can be found in Example 112. The synthesis of epoxide can be found in Example 87.

#### [00730] Synthesis of ST-200-3CF3-E14\_1



To THF (0.5 mL) was added BuLi (0.368 mL, 2.5 M in hexane, 0.922 mmol). A solution of **DA-24-4-4** (200 mg, 0.369 mmol) in THF (3 mL) was added at -70°C. The mixture was stirred at -70°C for 1 h and *i*Pr<sub>2</sub>NH (104 mg, 1.03 mmol) was added. After 10 minutes, a solution of 6,6-difluoro-1-oxaspiro[2.5]octane (163 mg, 0.553 mmol, 50% purity) was added at -70°C. The mixture was stirred at -70°C for another 1 h. The mixture was warmed to 25°C and stirred for 16 hrs. To the mixture was added NH<sub>4</sub>Cl (50 mL, sat. aq.). The mixture was extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **ST-200-3CF3-E14\_1** (250 mg, crude) as a solid, which was used directly for the next.

**[00731] Synthesis of ST-200-3CF3-E14**

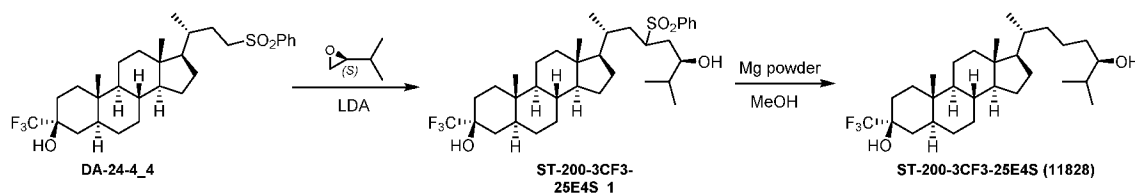


To a solution of **ST-200-3CF3-E14\_1** (250 mg, 0.362 mmol) in MeOH (20 mL) was added Mg powder (349 mg, 14.4 mmol) at 55°C. The mixture was stirred at 60°C for 16 hrs. The mixture was quenched with HCl (50 mL, 1 N) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by flash column (0-10% of EtOAc in PE) to give **ST-200-3CF3-E14** (22 mg, 11%) as a solid.

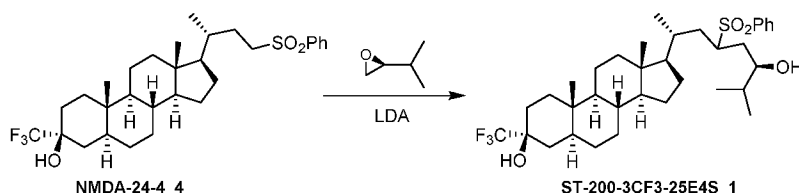
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.10-2.01 (m, 3H), 1.99-1.88 (m, 4H), 1.86-1.72 (m, 2H), 1.70-1.58 (m, 7H), 1.56-1.32 (m, 10H), 1.31-1.13 (m, 7H), 1.11-0.97 (m, 6H), 0.95-0.86 (m, 4H), 0.84 (s, 3H), 0.65 (s, 3H).

LCMS Rt = 1.329 min in 2.0 min chromatography, 30-90 AB, purity 98.9%, the MS did not show molecular ion by different methods.

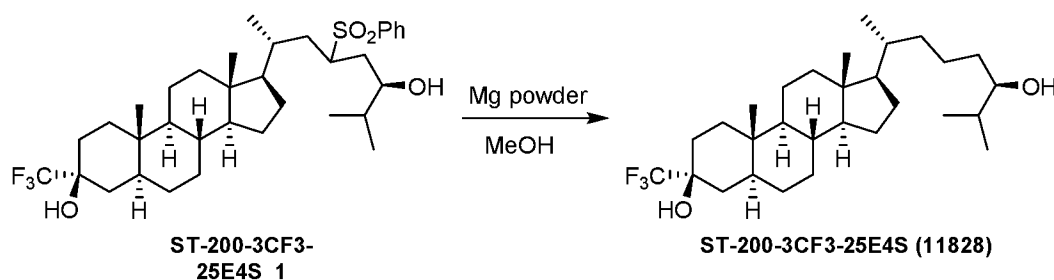
**EXAMPLE 118: Synthesis for 11828**



**[00732]** The synthesis of **DA-24-4\_4** can be found in Example 112.

**[00733] Synthesis of ST-200-3CF3-25E4S\_1**

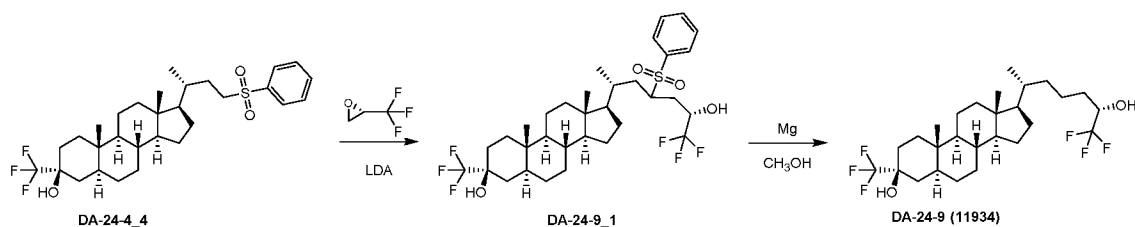
To a solution of n-BuLi (0.46 mL, 2.5 M in hexane, 1.15 mmol) in THF (1 mL) at -70°C under N<sub>2</sub> a suspension of **DA-24-4\_4** (250 mg, 0.46 mmol) in THF (4 mL) was added dropwise. The mixture was stirred for 30 minutes at -70°C. A solution of diisopropylamine (116 mg, 1.15 mmol) was added dropwise at -70°C, then a solution of (S)-2-isopropyloxirane (59.6 mg, 0.69 mmol) was added dropwise at -70°C. The mixture was stirred for another 30 min and then warmed to 25°C gradually. The reaction mixture was stirred at 25 °C for 24 hour. The reaction mixture was quenched by saturated NH<sub>4</sub>Cl aqueous (5 mL), extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give **ST-200-3CF3-25E4S\_1** (500 mg, crude) as a solid, which was used directly for the next step.

**[00734] Synthesis of ST-200-3CF3-25E4S**

To a solution of **ST-200-3CF3-25E4S\_1** (500 mg, 0.8 mmol) in 50 mL of anhydrous MeOH was added Mg powder (763 mg, 31.8 mmol) and NiCl<sub>2</sub> (1 mg, 0.008 mmol) with stirring under N<sub>2</sub> at 60°C. The reaction mixture was quenched by 2 M HCl (50 mL) until solid was dissolved. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with Sat. NaHCO<sub>3</sub> (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~10 % of EtOAc in PE) to give a solid, which was triturated from n-hexane (5 mL) at 25°C to give **ST-200-3CF3-25E4S** (102 mg, 68%) as solid.

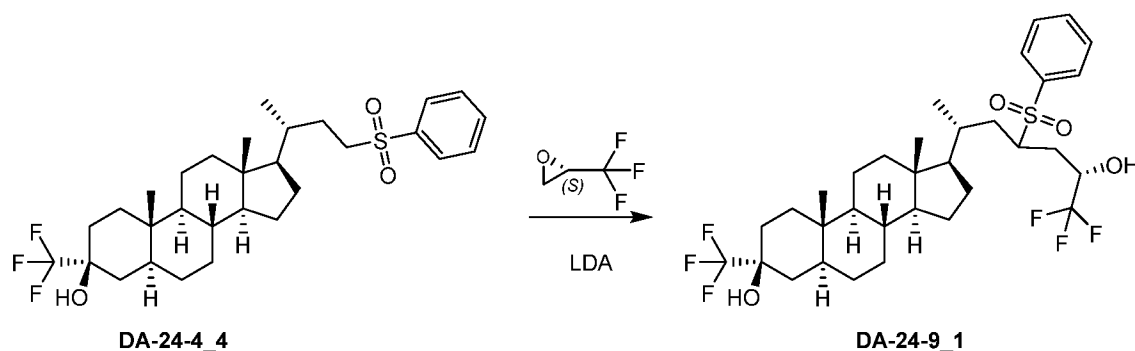
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.44-3.29 (m, 1H), 2.11-1.91 (m, 3H), 1.87-1.60 (m, 6H), 1.52-1.32 (m, 10H), 1.31-0.97 (m, 12H), 0.95-0.88 (m, 10H), 0.86-0.81 (m, 3H), 0.73-0.61 (m, 4H).

LCMS R<sub>t</sub> = 1.503 min in 2 min chromatography, 30-90AB\_2MIN\_E, purity 100%, MS ESI calcd. For C<sub>29</sub>H<sub>48</sub>F<sub>3</sub>O [M+H-H<sub>2</sub>O]<sup>+</sup> 469, found 469.

**EXAMPLE 119: Synthesis for 11934**

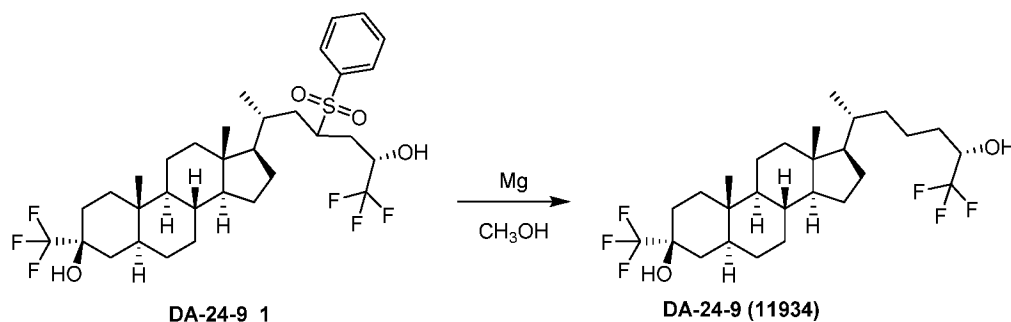
[00735] The synthesis of **DA-24-4\_4** can be found in Example 112.

[00736] **Synthesis of DA-24-9\_1**



To a solution of n-BuLi (552  $\mu$ L, 2.5 M in hexane, 1.38 mmol) in THF (1 mL) at  $-65^{\circ}\text{C}$  under  $\text{N}_2$  was added a suspension of **DA-24-4\_4** (250 mg, 0.462 mmol) in THF (4 mL) was added dropwise. The mixture was stirred for 30 minutes at  $-65^{\circ}\text{C}$ . Diisopropylamine (139 mg, 1.38 mmol) was added at  $-65^{\circ}\text{C}$ . (S)-2-(trifluoromethyl)oxirane (154 mg, 1.38 mmol) was added dropwise at  $-65^{\circ}\text{C}$ . The mixture was stirred for another 30 minutes and then warmed to  $25^{\circ}\text{C}$  gradually. The reaction mixture was stirred at  $25^{\circ}\text{C}$  for 16 hours and quenched with sat.  $\text{NH}_4\text{Cl}$  aq. (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give **DA-24-9\_1** (250 mg, crude) as a solid, which was used directly for the next step.

[00737] **Synthesis of DA-24-9**



To a solution of **DA-24-9\_1** (250 mg, 0.382 mmol) and  $\text{NiCl}_2$  (4.92 mg, 0.038 mmol) in dry methanol (50 mL) was added Mg powder (364 mg, 15.2 mmol) in 4 portions under  $\text{N}_2$  with stirring at  $50^{\circ}\text{C}$ . The reaction mixture was stirred at  $60^{\circ}\text{C}$  for 1 hour. The mixture was quenched with HCl (50 mL, 1N) until the reaction became clear and extracted with EtOAc (3 x 30 mL).

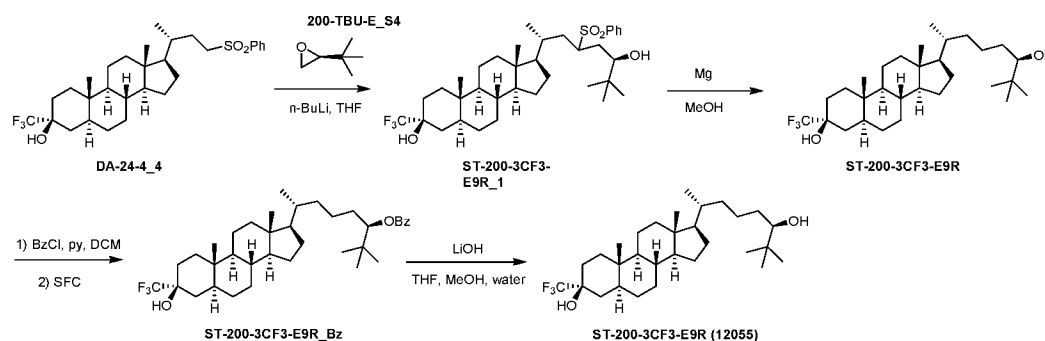
The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. The residue was purified by flash column (0-15% of EtOAc in PE) to give impure **DA-24-9** (65 mg) as a solid, which was triturated from n-hexane (10 mL) at 68°C for 2 h to give **DA-24-9** (23 mg, 12 %) as a solid.

- 5 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.95-3.85 (m, 1H), 2.08-1.90 (m, 4H), 1.70-1.58 (m, 7H), 1.50-1.13 (m, 14H), 1.13-0.98 (m, 5H), 0.98-0.85 (m, 4H), 0.85 (s, 3H), 0.70-0.60 (m, 4H).

**HPLC** Rt = 3.15 min in 8.0 min chromatography, 50-100\_AB\_1.2 ml\_E, purity 100 %.

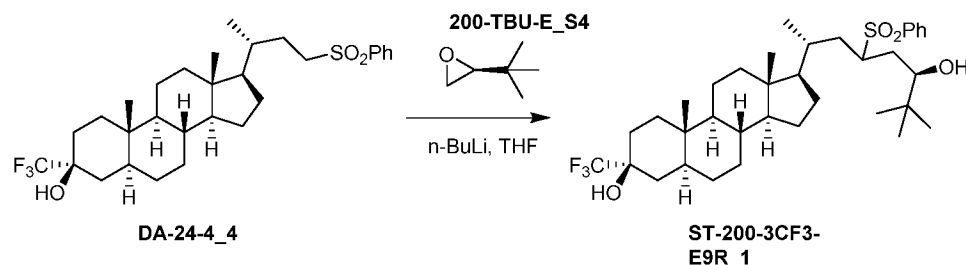
**HRMS** MS ESI calcd. for C<sub>27</sub>H<sub>41</sub>F<sub>6</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 495.3056, found 495.3050.

## 10 EXAMPLE 120: Synthesis of 12055



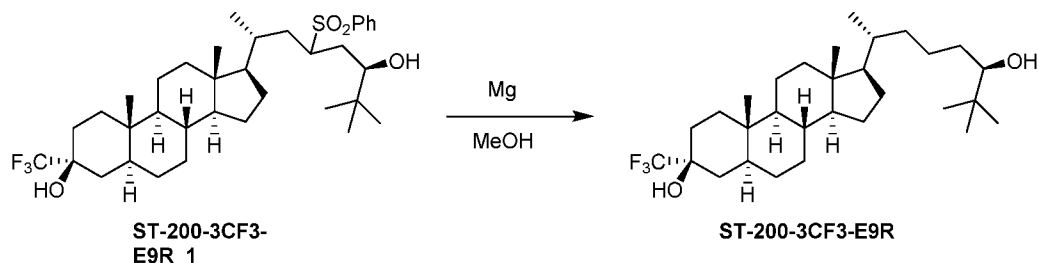
[00738] The synthesis of **DA-24-4\_4** can be found in Example 112.

[00739] **Synthesis of ST-200-3CF3-E9R\_1**



- 15 To THF (0.5 mL) was added BuLi (0.46 mL, 2.5 M in hexane, 1.15 mmol). A solution of **DA-24-4\_4** (250 mg, 0.462 mmol) in THF (3 mL) was added at -70°C. After stirring at -70°C for 1 h, diisopropylamine (130 mg, 1.29 mmol) was added. After 10 minutes, (S)-2-(tert-butyl)oxirane (69.4 mg, 0.693 mmol) was added at -70°C. The mixture was stirred at -70°C for another 1 h. The mixture was warmed to 25°C and stirred for 16 hrs. To the mixture was added NH<sub>4</sub>Cl (50
- 20 mL, sat. aq.). The mixture was extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **ST-200-3CF3-E9R\_1** (250 mg, crude) as a solid, which was used directly for the next step.

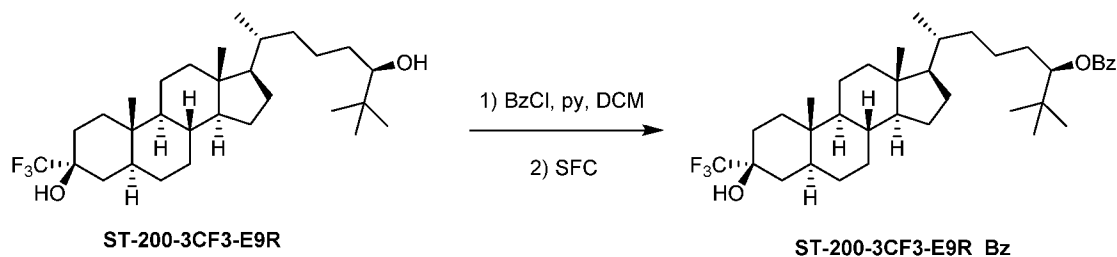
[00740] **Synthesis of ST-200-3CF3-E9R**



To a solution of **ST-200-3CF3-E9R\_1** (250 mg, 0.390 mmol) in MeOH (20 mL) was added Mg powder (374 mg, 15.6 mmol) at 55°C. The mixture was stirred at 60°C for 16 hrs. The mixture was quenched with HCl (50 mL, 1 M) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated. The residue was purified by flash column (0-10% of EtOAc in PE) to give **ST-200-3CF3-E9R** (150 mg, 77%) as a solid. This material was converted to the benzoate ester to facilitate purification of the compound as shown in the next step.

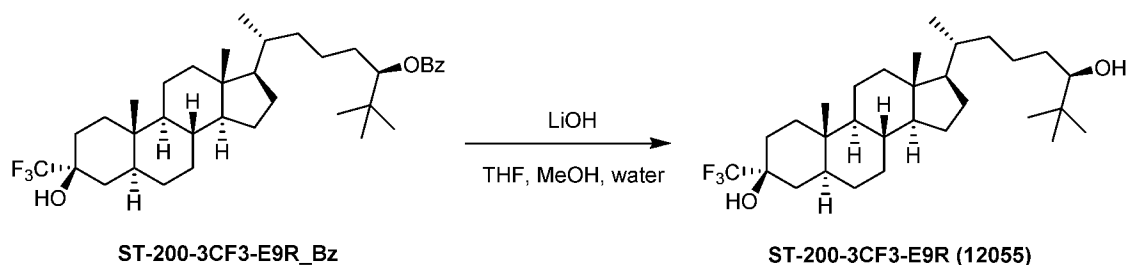
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.22-3.15 (m, 1H), 2.10-1.93 (m, 3H), 1.88-1.75 (m, 2H), 1.72-1.58 (m, 3H), 1.58-0.97 (m, 23H), 0.97-0.80 (m, 15H), 0.75-0.68 (m, 1H), 0.65 (s, 3H).

#### [00741] Synthesis of ST-200-3CF3-E9R\_Bz



To a solution of **ST-200-3CF3-E9R** (180 mg, 0.359 mmol) in DCM (2 mL) was added py (567 mg, 7.18 mmol) and BzCl (251 mg, 1.79 mmol). The mixture was stirred at 25°C for 2 h. The mixture was washed with NaHCO<sub>3</sub> (5 mL, 10% aq), HCl (5 mL, 2 M), purified by prep-TLC (PE:EtOAc=50:1) to give **ST-200-3CF3-E9R\_Bz** (150 mg) as a solid. The crude **ST-200-3CF3-E9R\_Bz** (150 mg) was purified by SFC (Instrument: SFC-14; Column: AD(250mm\*30mm,10um); Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O EtOH; Begin B: 30%; End B: 30%; FlowRate(ml/min): 60ML/MIN; Injections: 180) to give pure **ST-200-3CF3-E9R\_Bz** (100 mg) as an oil.

#### [00742] Synthesis of ST-200-3CF3-E9R

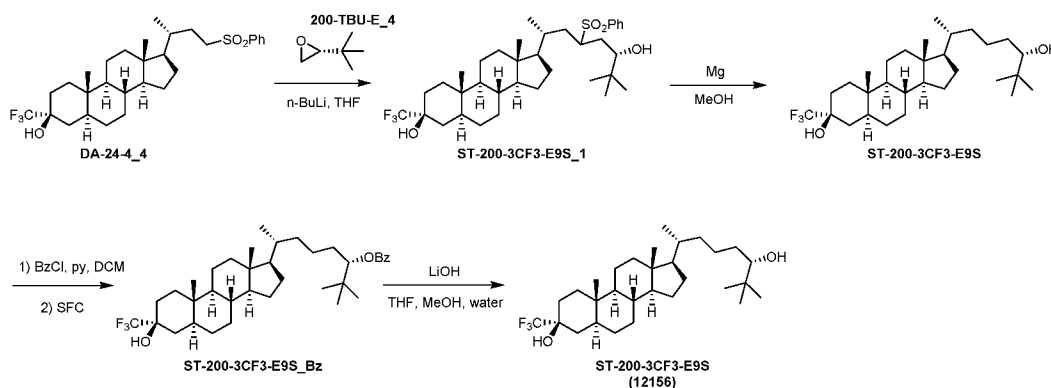


To a solution of **ST-200-3CF3-E9R\_Bz** (100 mg, 0.165 mmol) in THF (1 mL) was added MeOH (0.5 mL), water (0.5 mL) and LiOH.H<sub>2</sub>O (69.2 mg, 1.65 mmol). The mixture was stirred at 50°C for 72 h. To the mixture was added water (2 mL). The mixture was extracted with EtOAc (5 mL). The organic layer was separated, concentrated in vacuum, purified by silica gel column (PE/DCM/EtOAc = 40/1/1 to 20/1/1) to give **ST-200-3CF3-E9R** (60 mg, 73%) as a solid. The impure was re-crystallized from MeCN (0.5 mL) to give **ST-200-3CF3-E9R** (22 mg) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.18 (dd, *J* = 5.2, 10.0 Hz, 1H), 2.10-1.93 (m, 3H), 1.88-1.75 (m, 2H), 1.72-1.58 (m, 4H), 1.55-1.28 (m, 12H), 1.28-0.95 (m, 10H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.85 (s, 3H), 0.75-0.68 (m, 1H), 0.65 (s, 3H).

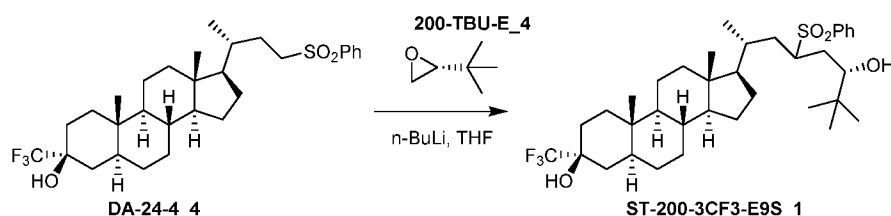
HPLC Rt = 6.63 min in 8.0 min chromatography, 50-100\_AB\_E, purity 97.3%.

#### EXAMPLE 121: Synthesis for 12156

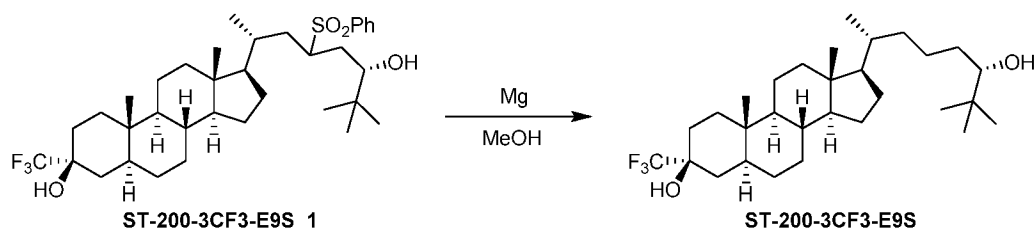


[00743] The synthesis of **DA-24-4\_4** can be found in Example 112.

#### [00744] Synthesis of ST-200-3CF3-E9S\_1

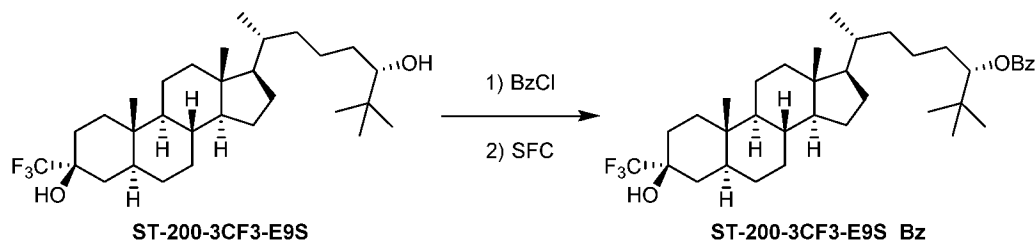


To THF (0.5 mL) was added BuLi (0.46 mL, 2.5 M in hexane, 1.15 mmol). A solution of **DA-24-4\_4** (250 mg, 0.462 mmol) in THF (3 mL) was added at -70°C. After stirring at -70°C for 1 h, diisopropylamine (130 mg, 1.29 mmol) was added. After 10 minutes, (R)-2-(tert-butyl)oxirane (69.4 mg, 0.693 mmol) was added at -70°C. The mixture was stirred at -70°C for another 1 h. The mixture was warmed to 25°C and stirred for 16 hrs. To the mixture was added NH<sub>4</sub>Cl (50 mL, sat. aq.). The mixture was extracted with EtOAc (2 x 30 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give **ST-200-3CF3-E9S\_1** (250 mg, crude) as a solid, which was used directly for the next step.

**[00745] Synthesis of ST-200-3CF3-E9S**

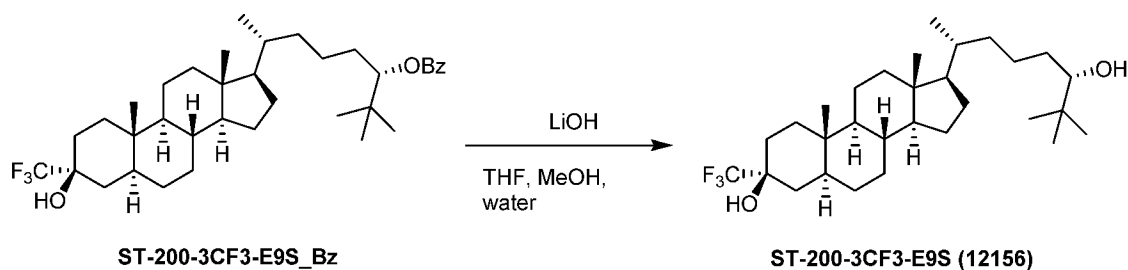
To a solution of **ST-200-3CF3-E9S\_1** (250 mg, 0.390 mmol) and  $\text{NiCl}_2$  (5.03 mg, 0.039 mmol) in dry methanol (20 mL) was added Mg powder (374 mg, 15.6 mmol) in 4 portions under  $\text{N}_2$  with stirring at  $50^\circ\text{C}$ . The reaction mixture was stirred at  $60^\circ\text{C}$  for 1 hour. The mixture was quenched with HCl (50 mL, 1 M) until the reaction became clear and extracted with DCM (2 x 30 mL). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated and purified by flash column (0-10 % of EtOAc in PE) to give **ST-200-3CF3-E9S** (120 mg, 61%) as a solid

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.22-3.12 (m, 1H), 2.10-1.90 (m, 3H), 1.90-1.76 (m, 2H), 1.76-1.58 (m, 4H), 1.58-1.32 (m, 7H), 1.32-0.94 (m, 18H), 0.94-0.88 (m, 9H), 0.85 (s, 3H), 0.65 (m, 4H).

**[00746] Synthesis of ST-200-3CF3-E9S\_Bz**

To a solution of **ST-200-3CF3-E9S** (120 mg, 0.239 mmol) in DCM (2 mL) was added py (377 mg, 4.77 mmol) and BzCl (167 mg, 1.19 mmol). The mixture was stirred at  $25^\circ\text{C}$  for 2 h. The mixture was washed with  $\text{NaHCO}_3$  (5 mL, 10% aq), HCl (5 mL, 2 M), purified by prep-TLC (PE:EtOAc=50:1) to give **ST-200-3CF3-E9R\_Bz** (140 mg) as a solid. The crude **ST-200-3CF3-E9S\_Bz** (140 mg) was purified by SFC (Instrument: SFC-14; Column: AD(250mm\*30mm,10um); Condition: 0.1% $\text{NH}_3\text{H}_2\text{O}$  EtOH; Begin B: 30%; End B: 30%; FlowRate(ml/min): 60ML/MIN; Injections: 60) to give pure **ST-200-3CF3-E9S\_Bz** (100 mg) as an oil.

**[00747] Synthesis of ST-200-3CF3-E9S**



To a solution of **ST-200-3CF3-E9S\_Bz** (100 mg, 0.165 mmol) in THF (1 mL) was added MeOH (0.5 mL), water (0.5 mL) and LiOH.H<sub>2</sub>O (69.2 mg, 1.65 mmol). The mixture was stirred at 50°C for 72 h. To the mixture was added water (2 mL). The mixture was extracted with EtOAc (5 mL). The organic layer was separated, concentrated in vacuum, purified by silica gel column (PE/DCM/EtOAc = 40/1/1 to 20/1/1) to give **ST-200-3CF3-E9S** (60 mg, 73%) as a solid. The impure was re-crystallized from MeCN (1 mL) to give **ST-200-3CF3-E9S** (35 mg) as a solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.22-3.12 (m, 1H), 2.10-1.92 (m, 3H), 1.89-1.78 (m, 2H), 1.72-1.57 (m, 5H), 1.55-1.28 (m, 10H), 1.28-0.93 (m, 11H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.85 (s, 3H), 0.74-0.67 (m, 1H), 0.65 (s, 3H).

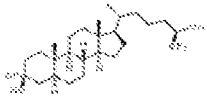

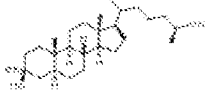
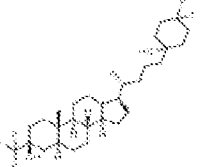


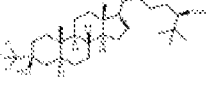
**HPLC** Rt = 6.61 min in 8.0 min chromatography, 50-100\_AB\_E, purity 100%.

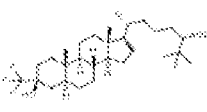
#### EXAMPLE 123: Biological data

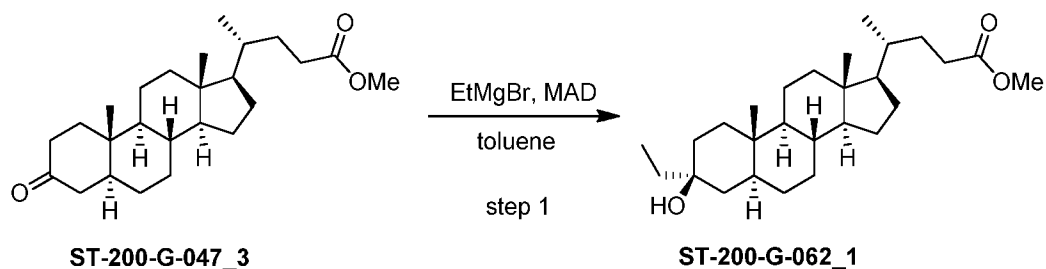
**[00748]** The experiments were conducted as described in Example 2 and the results are shown in Table 2-60.

**Table 2-60**

	Compound	Avg EC50 2A (nM)	Avg Emax 2A (%)	Avg EC50 2B (nM)	Avg Emax 2B (%)
	4115	91.9	186.5	113.6	195.2
	5116	101.7	185.1	130.4	213.8

	3114	382.1	318.0	243.5	293.6
	112	480.1	92.6	478.0	150.8
	2113	380.4	402.7	412.8	285.0
	11786	583.9	152.0	1008.7	151.0
	11828	146.6	142.3	76.9	114.5
	11934	729.2	113.4	469.7	70.0
	12055	506.2	113.8	1134.5	184.7

	12156	153.9	43.2	2456.4	111.2
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**EXAMPLE 125: Synthesis**

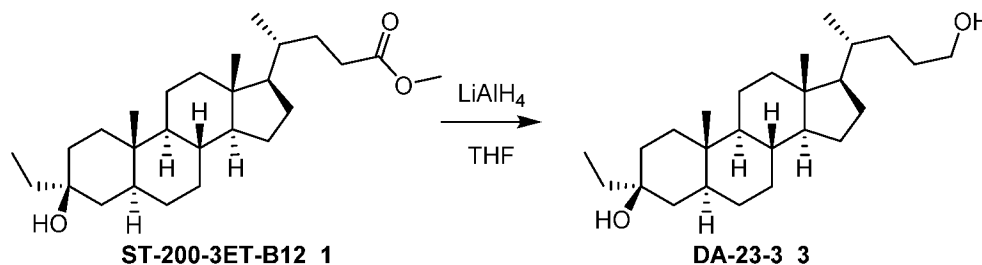
To a solution of 2,6-di-tert-butyl-4-methylphenol (17 g, 77.1 mmol) in toluene (50 mL) was added trimethylaluminum (19.2 mL, 2M in toluene) at 10°C. The mixture was stirred at 20 °C for 1 h. This MAD solution was used in the next step directly without analysis.

To a solution of MAD (77.1 mmol) in toluene (50 mL) was added a solution of (R)-methyl 4-((5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl) pentanoate (5 g, 12.8 mmol) in toluene (20 mL) dropwise at -70°C dropwise under N<sub>2</sub>. The mixture was stirred at -70 °C for 1 hour. A solution of EtMgBr (12.7 mL, 3M) was added dropwise at -70 °C. The mixture was stirred at -70 °C for another 3 hours. When TLC showed most of starting material was consumed and a new spot was produced, the reaction mixture was quenched with citric acid (150 mL, sat. aq.). The reaction was warmed to 25°C. The organic was separated and concentrated in vacuum. The crude was purified by column chromatography on silica gel (EA :PE = 200 : 1 to 10 : 1) to give (R)-methyl 4-((3S,5S,8R,9S,10S,13R,14S,17R)-3-ethyl-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (3.8 g) as a solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.66 (s, 3H), 2.41-2.30 (m, 1H), 2.26-2.15 (m, 1H), 1.94 (td, *J* = 3.3, 12.5 Hz, 1H), 1.90-1.73 (m, 2H), 1.69-1.58 (m, 3H), 1.56-0.84 (m, 28H), 0.82 (s, 3H), 0.64 (s, 4H).

**EXAMPLE 126:**

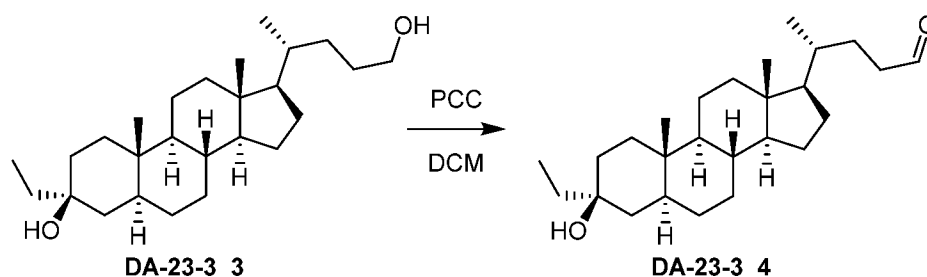
**[00749]      Synthesis of DA-23-3\_3**



LiAlH<sub>4</sub> (198 mg, 2.54 mmol) was added in three portions to a solution of **ST-200-3ET-B12\_1** (1.1 g, 2.62 mmol) in THF (10 mL) at 0°C under N<sub>2</sub>. After stirring at 20°C for 1 hour, the mixture was quenched with water (10 mL) at 0°C, followed by adding HCl (10 mL, 1 mol/L). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated brine (2 x 10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column (0~50% of EtOAc in PE) to give **DA-23-3\_3** (1 g, 98%) as a solid.

<sup>1</sup>H NMR CDCl<sub>3</sub> 400MHz δ 3.65-3.55 (m, 2H), 1.98-1.92 (m, 1H), 1.88-1.75 (m, 1H), 1.70-1.40 (m, 13H), 1.40-1.19 (m, 7H), 1.19-0.98 (m, 7H), 0.98-0.80 (m, 11H), 0.66-0.61 (m, 4H).

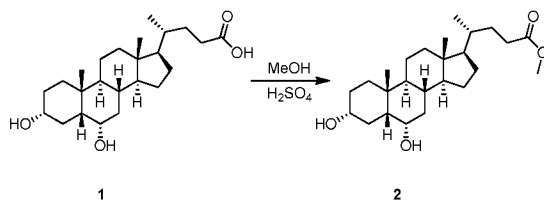
#### Synthesis of DA-23-3\_4



To a solution of **DA-23-3\_3** (1 g, 2.55 mmol) in anhydrous DCM (30 mL) was added silica gel (1 g) and PCC (1.09 g, 5.10 mmol). After stirring at 20°C for 1 hours, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (PE/EA = 50/1 to 10/1 ) to give **DA-23-3\_4** (600 mg, 60%) as a solid.

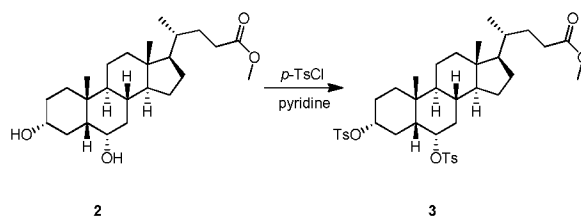
**[00750]** <sup>1</sup>H NMR CDCl<sub>3</sub> 400MHz δ 9.98-9.97 (m, 1H), 2.50-2.20 (m, 2H), 2.05-1.50 (m, 3H), 1.50-1.19 (m, 15H), 1.19-0.99 (m, 7H), 0.99-0.82 (m, 12H), 0.70-0.55 (m, 4H).

#### EXAMPLE 127:

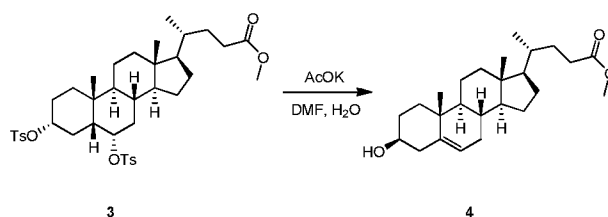


To a solution of compound **1** (100 g, 255 mmol, 1.0 eq) in dry MeOH (500 mL) was added concentrated H<sub>2</sub>SO<sub>4</sub> (14 mL). The mixture was heated to reflux overnight and then cooled to room temperature. The mixture was quenched with aq. saturated NaHCO<sub>3</sub> solution (0.5 L) and then evaporated to remove MeOH. The residue mixture was extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give the product (100 g crude, 96%) as a powder.

**<sup>1</sup>H NMR:** (400 MHz, CDCl<sub>3</sub>) δ 4.09-4.02 (m, 1H), 3.66 (s, 3H), 3.63-3.58 (m, 1H), 2.39-2.31 (m, 1H), 2.25-2.15 (m, 1H), 1.97-1.91 (m, 1 H), 1.91-1.55 (m, 10H), 1.52-1.02 (m, 14H), 0.95-0.88 (m, 6 H), 0.62 (s, 3 H).

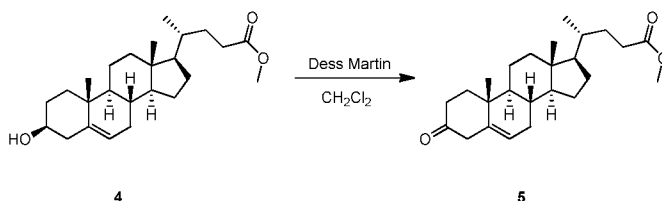


To a solution of compound **2** (250 g, 615 mmol, 1.0 eq) in dry pyridine (0.8 L) was added a solution of TsCl (352 g, 1844 mmol, 3.0 eq) in dry pyridine (200 mL). The mixture was stirred at room temperature for 18 h. Ice chips were added gradually to the mixture, and the precipitated solid was filtered, washed with aq. 10% HCl solution (400 mL x 3) and water (400 mL x 2), and then evaporated to dryness to give crude product (500 g, crude) as a powder, which was used to next step directly

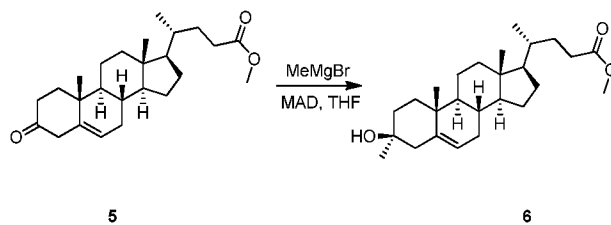


A mixture of compound **3** (250 g crude), CH<sub>3</sub>COOK (24 g, 245 mmol, 0.77 eq), water (150 mL) and DMF (900 mL) was heated at reflux for 24 h. The solution was cooled to room temperature, with ice chips added gradually. The precipitated solid was filtered off and washed with water (100 mL x 2). The crude solid was purified on silica gel column (PE/EtOAc = 8/1) to give compound **4** (40 g, yield 34.3% of two steps) as solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.32-5.38 (m, 1H), 3.66 (s, 3H), 3.47-3.57 (m, 1H), 2.16-2.41 (m, 4H), 1.93-2.04 (m, 2H), 1.74-1.92 (m, 4H), 1.30-1.59 (m, 9H), 0.90-1.19 (m, 12H), 0.68 (s, 3H)

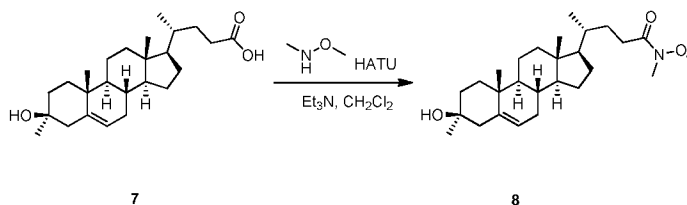


To a solution of compound **4** (33 g, 85 mmol, 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (700 mL) was added Dess-Martin reagent (72 g, 170 mmol, 2.0 eq) in portions at 0 °C. Then the reaction mixture was stirred at room temperature for 1 h. TLC (PE: EA = 3:1) showed the starting material was consumed completely. The reaction mixture was quenched with a saturated aqueous solution of NaHCO<sub>3</sub>/Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> = 1:3 (250 mL). The organic phase was washed with brine (200 mL x 2) and dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated to afford desired product (35 g, crude), which was used in the next step without further purification.



To a solution of MAD (0.42 mol, 3.0 eq) in toluene, freshly prepared by addition of a solution of Me<sub>3</sub>Al (210 mL, 0.42 mmol, 2 M in hexane) to a stirred solution of 2,6-di-*tert*-butyl-4-methylphenol (185 g, 0.84 mol) in toluene (200 mL) followed by stirring for 1 h at room temperature, was added dropwise a solution of compound **5** (54 g, 0.14 mol, 1.0 eq) in toluene (200 mL) at -78 °C under nitrogen. Then the reaction mixture was stirred for 30 min, a solution of MeMgBr (140 mL, 0.42 mol, 3.0 eq, 3 M in ether) was added dropwise at -78 °C. The reaction mixture was warmed to -40 °C and stirred at this temperature for 3 h. TLC (PE: EA = 3:1) showed that the starting material was consumed completely. The mixture was poured into aqueous saturated NH<sub>4</sub>Cl solution (100 mL) and extracted with EtOAc (300 mL x 2). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated to afford crude product. The crude product was purified on silica gel chromatography eluted with PE: EA = 10:1 to give the pure target (30 g, 53%) as powder.

**<sup>1</sup>H NMR:** (400 MHz, CDCl<sub>3</sub>) δ 5.31-5.29 (m, 1H), 3.66 (s, 3H), 2.39-2.33 (m, 2H), 2.24-2.22 (m, 1H), 1.99-1.95 (m, 3H), 1.85-1.68 (m, 4H), 1.59-1.40 (m, 8H), 1.31-1.26 (m, 2H), 1.17-1.01 (m, 11H), 0.93-0.91 (m, 4H), 0.67 (s, 3H).



A mixture of compound **7** (32.0 g, 82.35 mmol), N,O-dimethylhydroxylamine (16.07 g, 164.70 mmol), HATU (37.57 g, 98.82 mmol) and Et<sub>3</sub>N (46.0 mL, 329.40 mmol) in 500 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub> was stirred for 18 h at room temperature. TLC showed the reaction was completed. Then CH<sub>2</sub>Cl<sub>2</sub> was added to the mixture and the resulting solution was washed with water, 1 N HCl aqueous, saturated aqueous NaHCO<sub>3</sub> and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated, purified by silica gel (PE:EtOAc=10:1 to 3:1) to afford the target compound **8** (17.0 g, yield:47.8%) as a solid.

<sup>1</sup>H NMR: (400 MHz, CDCl<sub>3</sub>) δ 5.31-5.29 (m, 1H), 3.69 (s, 3H), 3.17 (s, 3H), 3.03 (s, 2H), 2.47-2.29 (m, 3H), 2.04-1.68 (m, 7H), 1.60-1.43 (m, 7H), 1.38-1.30 (m, 2H), 1.20-1.08 (m, 6H), 1.03-0.91 (m, 8H), 0.68 (s, 3H).

### Other Embodiments

[00751] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00752] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments

have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

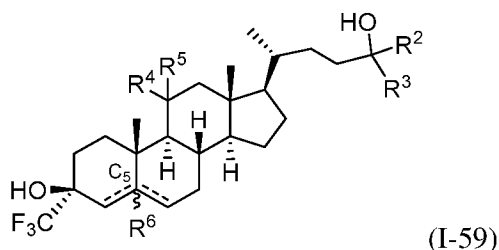
[00753] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00754] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

# Claims

What is claimed is:

1. A compound of Formula (I-59):



or a pharmaceutically acceptable salt thereof, wherein:

each of  $R^2$  and  $R^3$  is independently hydrogen, substituted or unsubstituted  $C_1$ - $C_6$  alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, or

$R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a substituted or unsubstituted 3-8 membered ring;

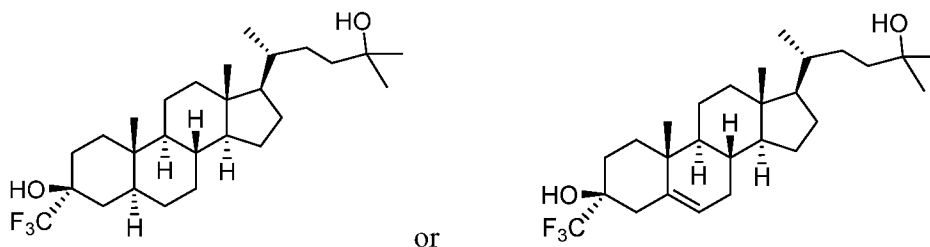
each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl, or

$R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;

$R^6$  is absent or hydrogen; and

===== represents a single or double bond, wherein when one of ===== is a double bond, the other ===== is a single bond; when both of ===== are single bonds, then  $R^6$  is hydrogen; and when one of ===== is a double bond,  $R^6$  is absent;

provided that the following compounds are excluded:



2. The compound of claim 1, wherein  $R^2$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl.

3. The compound of claim 1, wherein  $R^2$  is  $C_1$ - $C_6$  haloalkyl.

4. The compound of claim 1, wherein each of  $R^2$  and  $R^3$  is independently substituted  $C_1$ - $C_6$  alkyl or hydrogen.

5. The compound of claim 1, wherein each of  $R^2$  and  $R^3$  is independently unsubstituted  $C_1$ - $C_6$  alkyl or hydrogen.

6. The compound of claim 1, wherein each of  $R^2$  and  $R^3$  is independently  $C_1$ - $C_6$  haloalkyl or hydrogen.

10 7. The compound of claim 1, wherein each of  $R^2$  and  $R^3$  is independently hydrogen, carbocyclyl, or heterocyclyl.

8. The compound of claim 1, wherein each of  $R^2$  and  $R^3$  is independently  $C_2$ - $C_6$  alkyl or hydrogen.

15

9. The compound of claim 1, wherein each of  $R^2$  and  $R^3$  is independently isopropyl or tert-butyl or hydrogen.

10. The compound of claim 1, wherein at least one of  $R^2$  and  $R^3$  is  $C_3$ - $C_6$  alkyl, carbocyclyl, or heterocyclyl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring.

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11. The compound of claim 1, wherein  $R^2$  is isopropyl or tert-butyl and  $R^3$  is methyl or hydrogen.

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12. The compound of claim 1, wherein  $R^2$  is substituted isopropyl or substituted tert-butyl and  $R^3$  is unsubstituted methyl or hydrogen.

13. The compound of claim 1, wherein  $R^2$  is unsubstituted isopropyl or unsubstituted tert-butyl and  $R^3$  is unsubstituted methyl or hydrogen.

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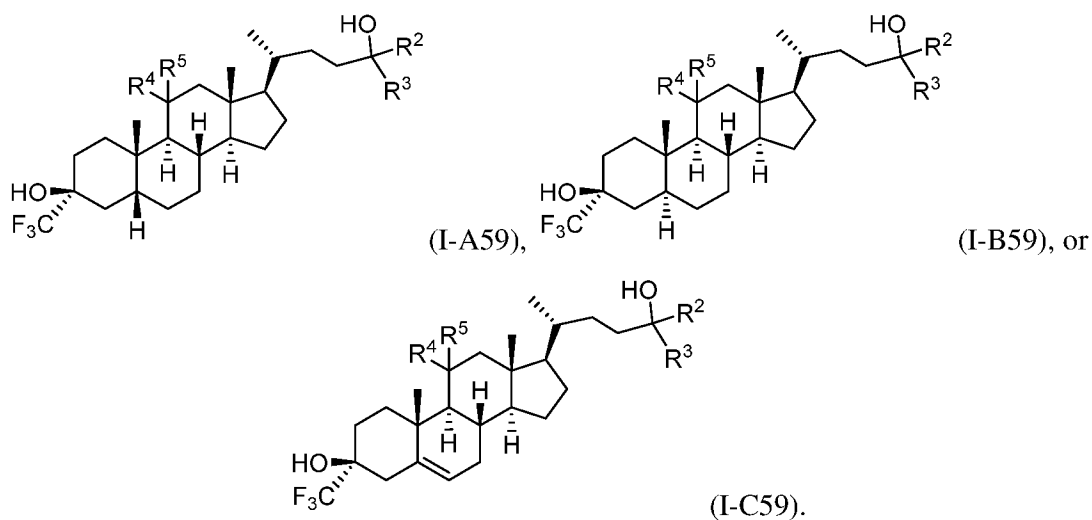
14. The compound of claim 1, wherein  $R^2$  is tert-butyl and  $R^3$  is hydrogen.

15. The compound of claim 1, wherein  $R^2$  is substituted tert-butyl and  $R^3$  is hydrogen.

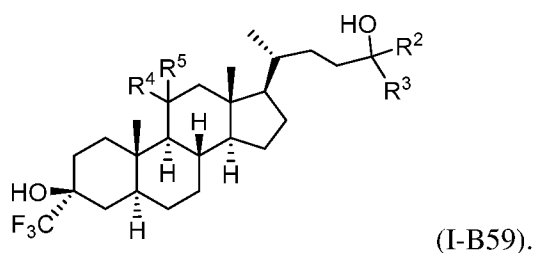
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16. The compound of claim 1, wherein  $R^2$  is unsubstituted tert-butyl and  $R^3$  is hydrogen.
17. The compound of claim 1, wherein  $R^2$  is trifluoromethyl and  $R^3$  is hydrogen.
- 5 18. The compound of claim 1, wherein  $R^2$  is trifluoromethyl and  $R^3$  is methyl.
19. The compound of claim 1, wherein  $R^2$  is trifluoromethyl and  $R^3$  is substituted methyl.
20. The compound of claim 1, wherein  $R^2$  is trifluoromethyl and  $R^3$  is unsubstituted methyl.
- 10 21. The compound of claim 1, wherein  $R^2$  is methyl and  $R^3$  is hydrogen.
22. The compound of claim 1, wherein  $R^2$  is substituted methyl and  $R^3$  is hydrogen.
- 15 23. The compound of claim 1, wherein  $R^2$  is unsubstituted methyl and  $R^3$  is hydrogen.
24. The compound of claim 1, wherein  $R^4$  is  $-OH$  or halo.
25. The compound of claim 1, wherein  $R^4$  and  $R^5$ , together with the carbon atom to which
- 20 they are attached form an oxo group.
26. The compound of claim 1, wherein  $R^4$  is hydrogen and  $R^5$  is halo.
27. The compound of claim 1, wherein  $R^4$  and  $R^5$  are halo.
- 25 28. The compound of claim 1, wherein  $R^4$  and  $R^5$  are hydrogen.
29. The compound of claim 1, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which
- they are attached form a 5-membered ring.
- 30 30. The compound of claim 1, wherein  $R^2$  is  $C_2-C_6$  alkyl and  $R^3$  is  $C_1-C_6$  alkyl.
31. The compound of claim 1, wherein  $R^2$  is unsubstituted  $C_2-C_6$  alkyl and  $R^3$  is
- unsubstituted  $C_1-C_6$  alkyl.

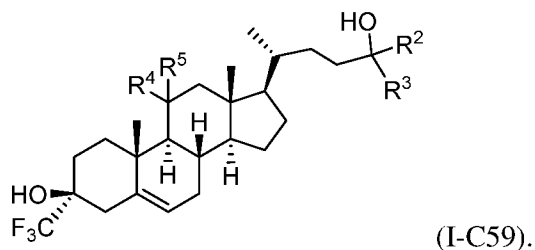
32. The compound of claim 1, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 6-membered ring.
33. The compound of claim 1, wherein  $R^2$  is carbocyclyl or heterocyclyl and  $R^3$  is hydrogen.
34. The compound of claim 1, wherein  $R^2$  and  $R^3$  are hydrogen.
35. The compound of claim 1, wherein  $R^2$  is isopropyl and  $R^3$  is hydrogen.
36. The compound of claim 1, wherein  $R^2$  is substituted isopropyl and  $R^3$  is hydrogen.
37. The compound of claim 1, wherein  $R^2$  is substituted isopropyl and  $R^3$  is hydrogen.
38. The compound of claim 1, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered carbocyclic or heterocyclic ring.
39. The compound of claim 33, wherein the carbocyclic or heterocyclic ring is substituted with 1 or 2 halo or alkyl groups.
40. The compound of claim 1, wherein  $R^2$  is cyclobutyl and  $R^3$  is hydrogen.
41. The compound of claim 1, wherein  $R^2$  is tetrahydropyranyl and  $R^3$  is hydrogen.
42. The compound of claim 1, wherein  $R^2$  is substituted cyclobutyl and  $R^3$  is hydrogen.
43. The compound of claim 1, wherein  $R^2$  is substituted tetrahydropyranyl and  $R^3$  is hydrogen.
44. The compound of claim 1, wherein  $R^2$  is unsubstituted cyclobutyl and  $R^3$  is hydrogen.
45. The compound of claim 1, wherein  $R^2$  is unsubstituted tetrahydropyranyl and  $R^3$  is hydrogen.
46. The compound of claim 1, wherein the compound of Formula (I-59) is selected from a compound of Formula (I-A59), (I-B59), or (I-C59):



47. The compound of claim 1, wherein the compound of Formula (I-59) is selected from a  
5 compound of Formula (I-B59):

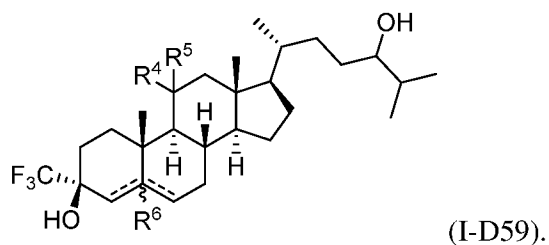


48. The compound of claim 1, wherein the compound of Formula (I-59) is selected from a  
compound of Formula (I-C59):

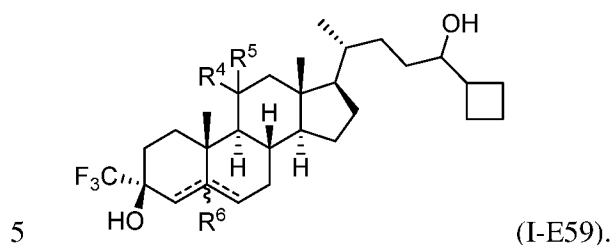


49. The compound of claim 1, wherein at least one of  $R^2$  and  $R^3$  is hydrogen,  $C_1$ - $C_6$  alkyl, carbocyclyl, or heterocyclyl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered ring.

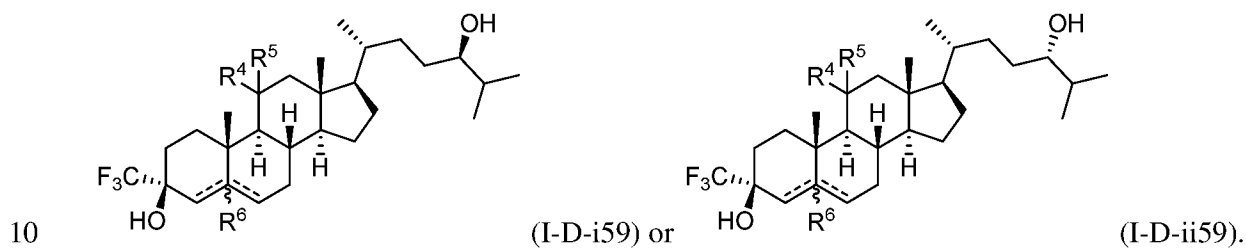
50. The compound of claim 1, wherein the compound of Formula (I) is selected from a  
compound of Formula (I-D59):



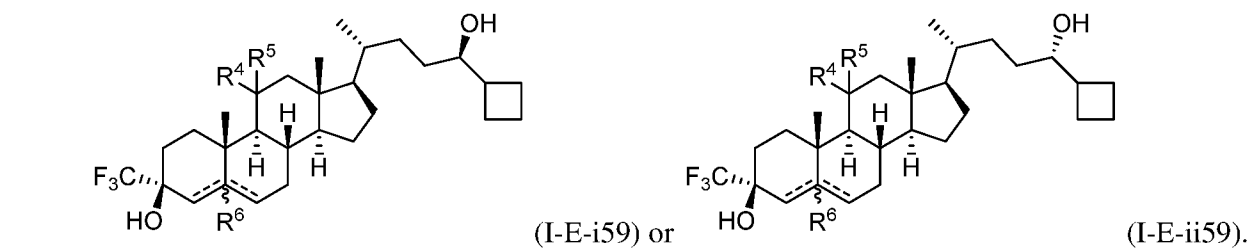
51. The compound of claim 1, wherein the compound of Formula (I-59) is selected from a compound of Formula (I-E59):



52. The compound of claim 1, wherein the compound of Formula (I-59) is selected from a compound of Formula (I-D-i59) or (I-D-ii59):

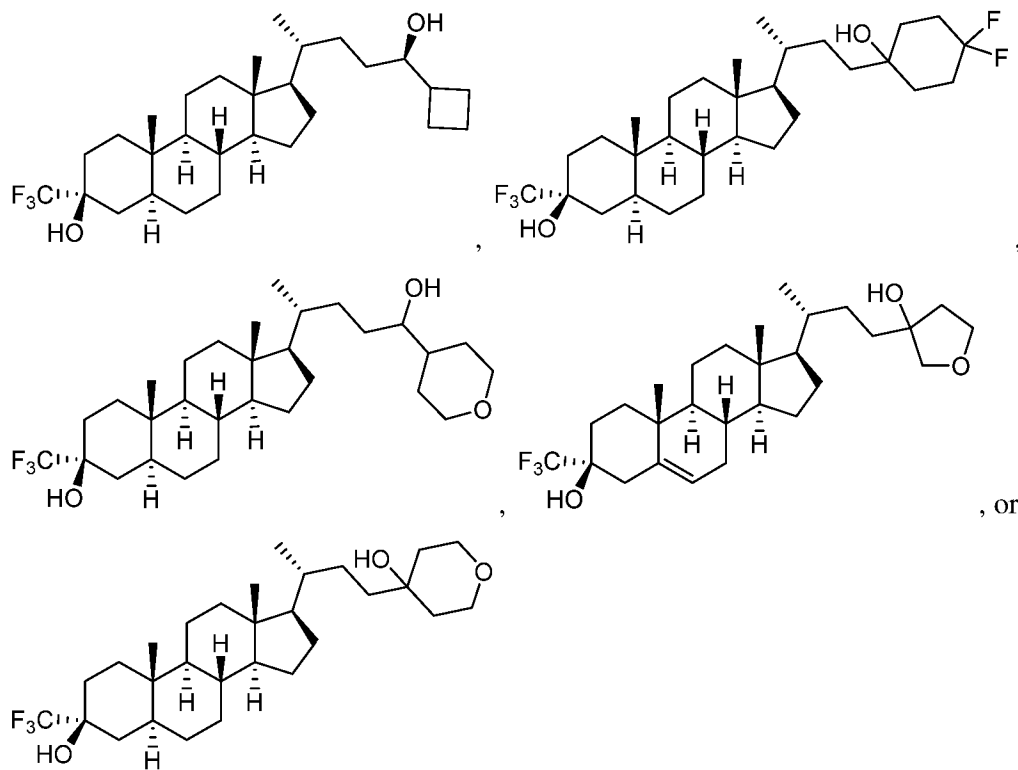


53. The compound of claim 1, wherein the compound of Formula (I-59) is selected from a compound of Formula (I-E-i59) or (I-E-ii59):



54. The compound of claim 1, wherein the compound is:





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55. A pharmaceutical composition comprising a compound of claim 1, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

56. A method for treating or preventing a disorder described herein, comprising  
 10 administering to a subject in need thereof an effective amount of a compound of claim 1, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

57. The method according to claim 56, wherein the disorder is a gastrointestinal (GI)  
 disorder, constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD),  
 15 ulcerative colitis, Crohn's disease, structural disorders affecting the GI, anal disorders, hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula, colon polyps, cancer, or colitis.

58. The method according to claim 56, wherein the disorder is inflammatory bowel disease.

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59. The method according to claim 56, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

60. The method according to claim 56, wherein the disorder is a metabolic disorder.

61. The method according to claim 56, wherein the disorder is an autoimmune disorder.

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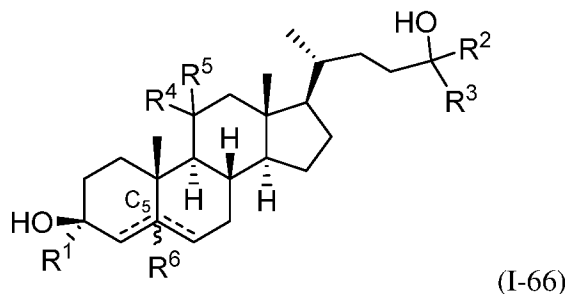
62. The method according to claim 56, wherein the disorder is rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

10 63. A method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound of claim 1, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

64. The method according to claim 63, wherein the CNS-related condition is an adjustment  
15 disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia),  
20 substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins, (Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis disorders, pain (including acute and chronic pain), encephalopathy secondary to a medical condition (including hepatic encephalopathy and anti-  
25 NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, or tinnitus.

30 65. The method according to claim 63, wherein the disorder is a sterol synthesis disorder.

66. A compound of Formula (I-66):



or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  is substituted or unsubstituted  $C_1$ - $C_6$  alkyl;

$R^2$  is substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl,  
5 substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

$R^3$  is hydrogen, substituted or unsubstituted  $C_1$ - $C_6$  alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, aryl, or substituted or unsubstituted heteroaryl;

each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or  
10 unsubstituted or substituted  $C_1$ - $C_3$  alkyl, or

$R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;

$R^6$  is absent or hydrogen; and

===== represents a single or double bond, wherein when one of ===== is a double  
bond, the other ===== is a single bond; when both of ===== are single bonds, then  $R^6$  is  
15 hydrogen; and when one of ===== is a double bond,  $R^6$  is absent.

67. The compound of claim 66, wherein  $R^1$  is substituted  $C_1$ - $C_6$  alkyl.

68. The compound of claim 66, wherein  $R^1$  is unsubstituted  $C_1$ - $C_6$  alkyl.

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69. The compound of claim 66, wherein  $R^1$  is  $-CH_3$ ,  $-CF_3$ , or  $-CH_2CH_3$ .

70. The compound of claim 66, wherein  $R^1$  is  $-CH_2OR^A$ , wherein  $R^A$  is substituted or unsubstituted  $C_1$ - $C_6$  alkyl.

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71. The compound of claim 66, wherein  $R^2$  is substituted or unsubstituted aryl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted pyridyl, or substituted or unsubstituted aralkyl.

72. The compound of claim 66, wherein  $R^2$  is substituted or unsubstituted phenyl, substituted or unsubstituted pyridyl, or substituted or unsubstituted benzyl.

73. The compound of claim 66, wherein  $R^3$  is hydrogen or  $C_1$ - $C_6$  alkyl.

74. The compound of claim 66, wherein  $R^3$  is hydrogen, unsubstituted  $C_1$ - $C_6$  alkyl, or haloalkyl.

75. The compound of claim 66, wherein  $R^4$  is  $-OH$  or halo.

76. The compound of claim 66, wherein  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group.

77. The compound of claim 66, wherein  $R^4$  is hydrogen and  $R^5$  is halo.

78. The compound of claim 66, wherein  $R^4$  and  $R^5$  are halo.

79. The compound of claim 66, wherein  $R^4$  and  $R^5$  are hydrogen.

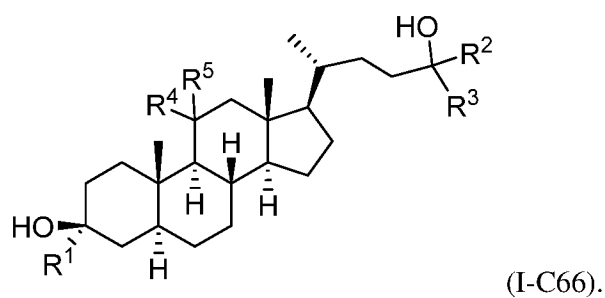
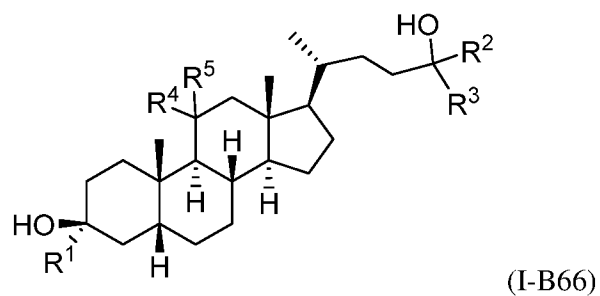
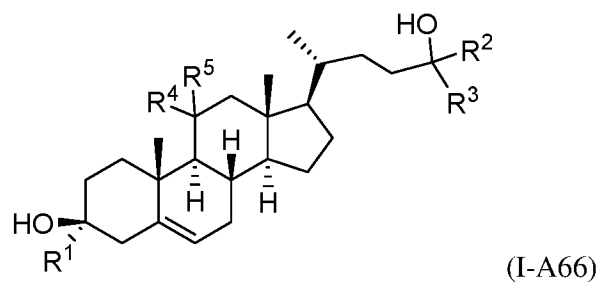
80. The compound of claim 66, wherein  $R^2$  is substituted or unsubstituted aryl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted pyridyl, substituted or unsubstituted aralkyl, substituted or unsubstituted benzyl, or heteroaralkyl and  $R^3$  is hydrogen or unsubstituted  $C_1$ - $C_6$  alkyl, or  $C_1$ - $C_6$  haloalkyl.

81. The compound of claim 66, wherein  $R^2$  is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted pyridyl, substituted or unsubstituted aralkyl, substituted or unsubstituted benzyl, or heteroaralkyl and  $R^3$  is hydrogen,  $-CH_3$ , or  $-CF_3$ .

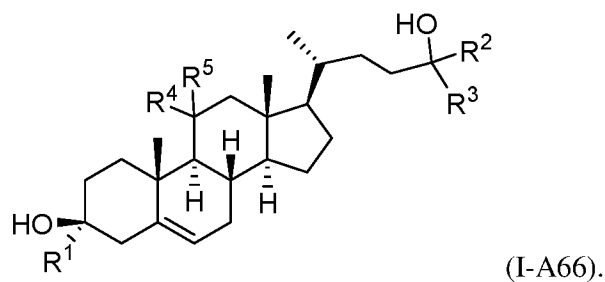
82. The compound of claim 66, wherein  $R^1$  is  $C_1$ - $C_6$  alkyl,  $R^2$  is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted pyridyl, substituted or unsubstituted aralkyl, substituted or unsubstituted benzyl, or heteroaralkyl, and  $R^3$  is hydrogen,  $-CH_3$ , or  $-CF_3$ .

83. The compound of claim 66, wherein  $R^1$  is  $-CH_3$  or  $-CH_2CH_3$ ,  $R^2$  is unsubstituted phenyl, unsubstituted pyridyl, or unsubstituted benzyl, and  $R^3$  is hydrogen,  $-CH_3$ , or  $-CF_3$ .

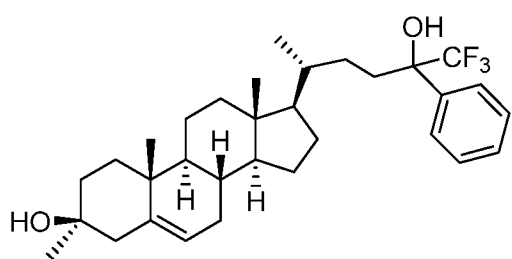
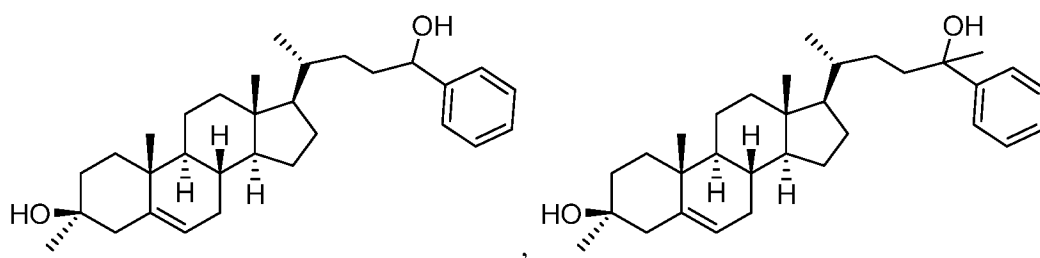
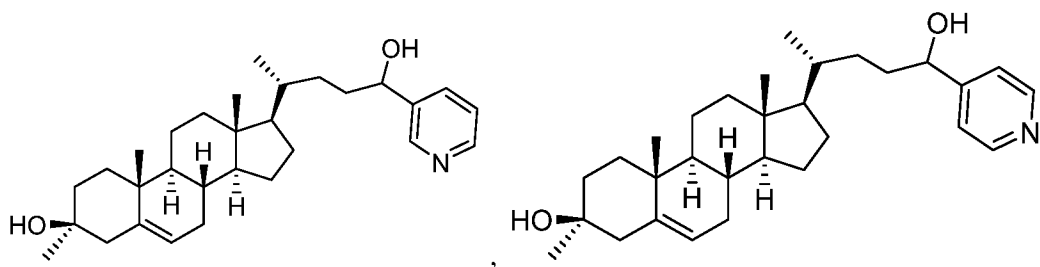
84. The compound of claim 66, wherein the compound of Formula (I-66) is selected from a compound of Formula (I-A66), (I-B66), or (I-C66):



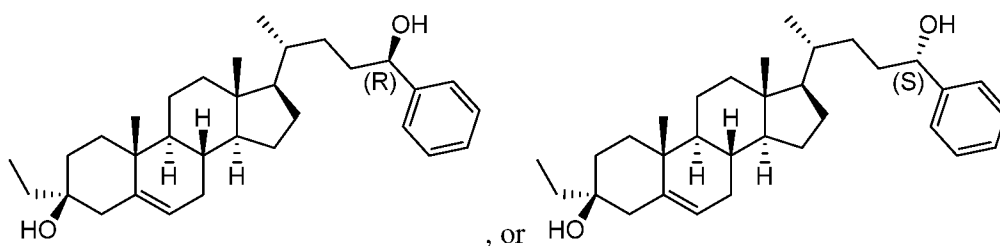
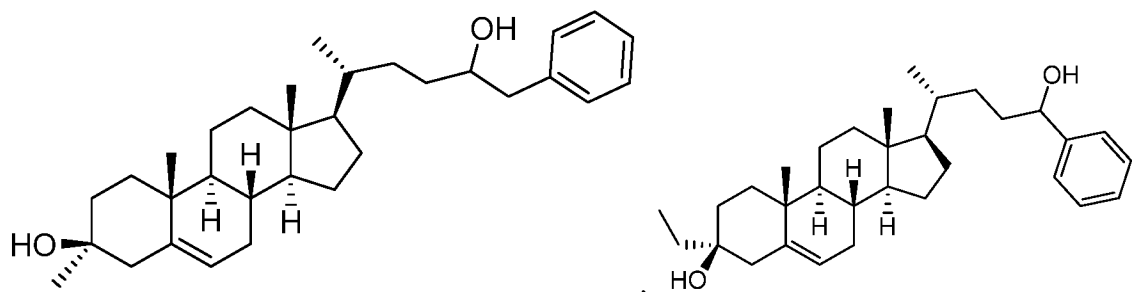
10 85. The compound of claim 66, wherein the compound of Formula (I-66) is selected from a compound of Formula (I-A66):



86. The compound of claim 66, wherein the compound is:



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- 10 87. A pharmaceutical composition comprising a compound of claim 66, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

88. A method for treating or preventing a disorder described herein, comprising administering to a subject in need thereof an effective amount of a compound of claim 66, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

89. The method according to claim 88, wherein the disorder is a gastrointestinal (GI) disorder constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) ulcerative colitis, Crohn's disease, structural disorders affecting the GI, anal disorders, hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula, colon polyps, cancer, or colitis.

90. The method according to claim 88, wherein the disorder is inflammatory bowel disease.

91. The method according to claim 88, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

92. The method according to claim 88, wherein the disorder is a metabolic disorder.

93. The method according to claim 88, wherein the disorder is an autoimmune disorder.

93. The method according to claim 88, wherein the disorder is rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

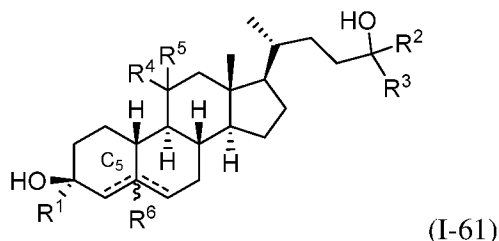
94. A method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound of claim 66, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

95. The method according to claim 94, wherein the CNS-related condition is an adjustment disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia), substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of

proteins (*e.g.*, Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis disorders, pain (including acute and chronic pain), encephalopathy secondary to a medical condition (including hepatic encephalopathy and anti-NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, or tinnitus.

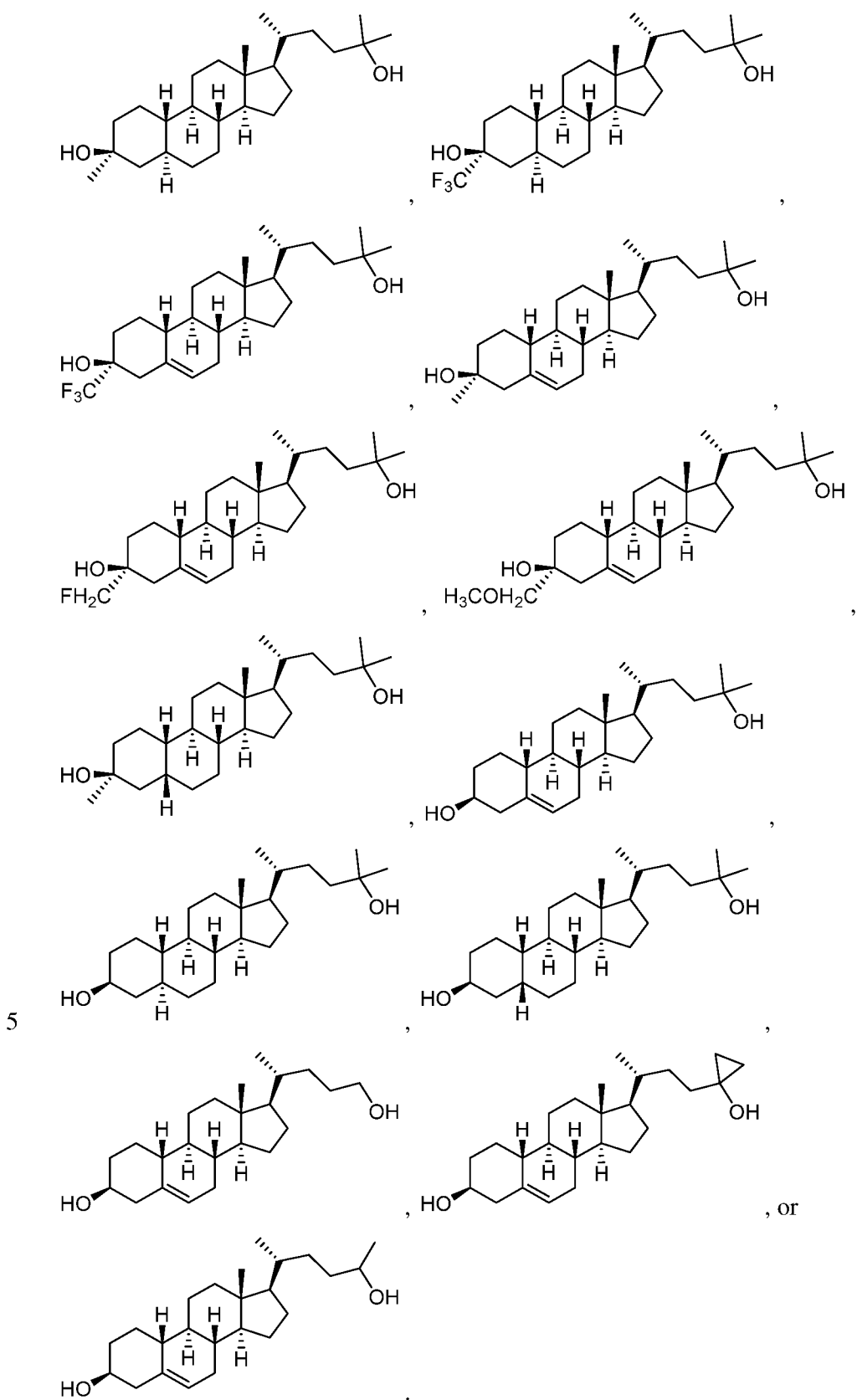
96. The method according to claim 88, wherein the disorder is a sterol synthesis disorder.

97. A compound of Formula (I-61):



or a pharmaceutically acceptable salt thereof, wherein:

- 15  $R^1$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl;  
 each of  $R^2$  and  $R^3$  is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl or  
 $R^2$  and  $R^3$ , together with the carbon atom to which they are attached for a 3-8  
 20 substituted or unsubstituted membered ring;  
 each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl, or  
 $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;  
 25  $R^6$  is absent or hydrogen; and  
 ===== represents a single or double bond, wherein when one of ===== is a double bond, the other ===== is a single bond; when both of ===== are single bonds, then  $R^6$  is hydrogen; and when one of ===== is a double bond,  $R^6$  is absent;  
 provided that the following compounds are excluded:



98. The compound of claim 97, wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl or hydrogen.

99. The compound of claim 97, wherein  $R^1$  is  $C_2$ - $C_6$  alkyl or hydrogen.

100. The compound of claim 97, wherein  $R^1$  is substituted or unsubstituted substituted or  
5 unsubstituted  $C_3$ - $C_6$  alkyl or hydrogen.

101. The compound of claim 97, wherein  $R^1$  is substituted or unsubstituted methyl or substituted or unsubstituted ethyl.

102. The compound of claim 97, wherein  $R^1$  is substituted or unsubstituted methyl or  
10 substituted or unsubstituted ethyl.

103. The compound of claim 97, wherein  $R^1$  is trifluoromethyl.

104. The compound of claim 97, wherein  $R^1$  is  $-CH_2OR^A$ , wherein  $R^A$  is  $C_1$ - $C_6$  alkyl.  
15

105. The compound of claim 97, wherein  $R^2$  is hydrogen or  $C_2$ - $C_6$  alkyl.

106. The compound of claim 97, wherein  $R^2$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$   
20 alkyl.

107. The compound of claim 97, wherein  $R^2$  is hydrogen.

108. The compound of claim 97, wherein  $R^2$  is substituted or unsubstituted isopropyl.  
25

109. The compound of claim 97, wherein  $R^2$  is substituted or unsubstituted isopropyl.

110. The compound of claim 97, wherein  $R^2$  is  $C_1$ - $C_6$  haloalkyl.

111. The compound of claim 97, wherein each of  $R^2$  and  $R^3$  is independently  $C_1$ - $C_6$  alkyl or  
30 hydrogen.

112. The compound of claim 97, wherein each of  $R^2$  and  $R^3$  is independently substituted or  
unsubstituted  $C_1$ - $C_6$  alkyl or hydrogen.  
35

113. The compound of claim 97, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached for a 3-8 membered ring.

114. The compound of claim 97, wherein each of  $R^2$  and  $R^3$  is independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl.

115. The compound of claim 97, wherein each of  $R^2$  and  $R^3$  is independently hydrogen or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl.

116. The compound of claim 97, wherein each of  $R^2$  and  $R^3$  is independently hydrogen, C<sub>3</sub>-C<sub>6</sub> alkyl, or isopropyl.

117. The compound of claim 97, wherein each of  $R^2$  and  $R^3$  is independently hydrogen, substituted or unsubstituted C<sub>3</sub>-C<sub>6</sub> alkyl, or substituted or unsubstituted isopropyl.

118. The compound of claim 97, wherein  $R^4$  is -OH or halo.

119. The compound of claim 97, wherein  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group.

120. The compound of claim 97, wherein  $R^4$  is hydrogen and  $R^5$  is halo.

121. The compound of claim 97, wherein  $R^4$  and  $R^5$  are halo.

122. The compound of claim 97, wherein  $R^4$  and  $R^5$  are fluorine.

123. The compound of claim 97, wherein  $R^4$  and  $R^5$  are hydrogen.

124. The compound of claim 97, wherein  $R^2$  and  $R^3$  are hydrogen.

125. The compound of claim 97, wherein  $R^2$  is C<sub>1</sub>-C<sub>6</sub> alkyl and  $R^3$  is C<sub>2</sub>-C<sub>6</sub> alkyl.

126. The compound of claim 97, wherein  $R^2$  is substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl and  $R^3$  is substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub> alkyl.

127. The compound of claim 97, wherein  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

128. The compound of claim 97, wherein  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

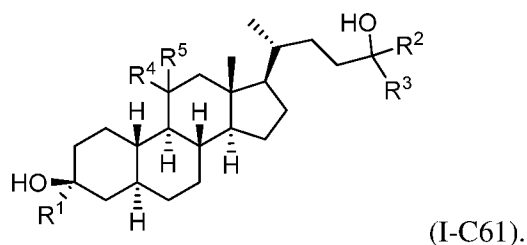
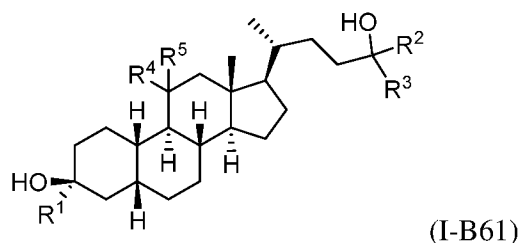
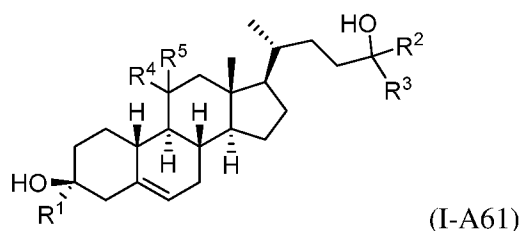
129. The compound of claim 97, wherein  $R^1$  is ethyl,  $R^2$  is isopropyl, and  $R^3$  is hydrogen.

130. The compound of claim 97, wherein  $R^1$  is substituted or unsubstituted ethyl,  $R^2$  is substituted or unsubstituted isopropyl, and  $R^3$  is hydrogen.

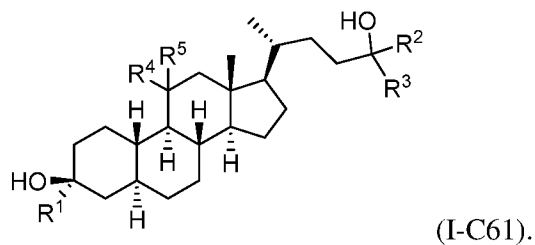
131. The compound of claim 97, wherein  $R^1$  is ethyl,  $R^2$  is isopropyl, and  $R^3$  is methyl.

132. The compound of claim 97, wherein  $R^1$  is substituted or unsubstituted ethyl,  $R^2$  is substituted or unsubstituted isopropyl, and  $R^3$  is substituted or unsubstituted methyl.

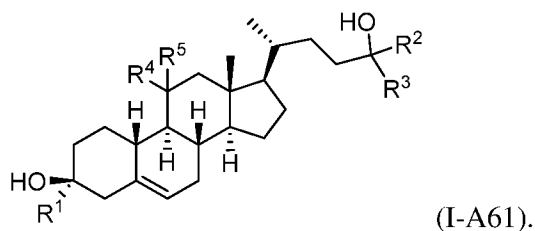
133. The compound of claim 97, wherein the compound of Formula (I-61) is a compound of Formula (I-A61), (I-B61), or (I-C61):



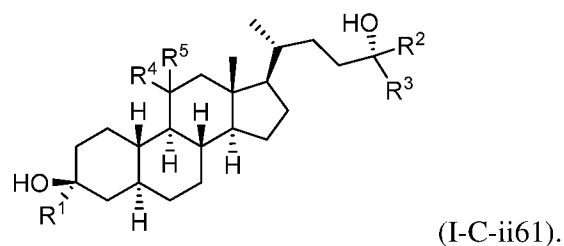
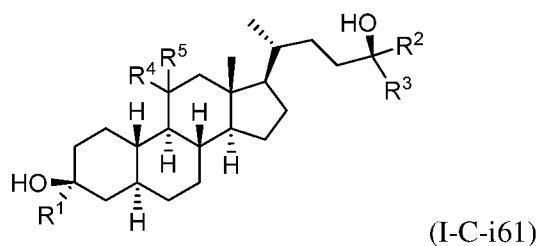
134. The compound of claim 97, wherein the compound of Formula (I-61) is selected from a compound of Formula (I-C61):



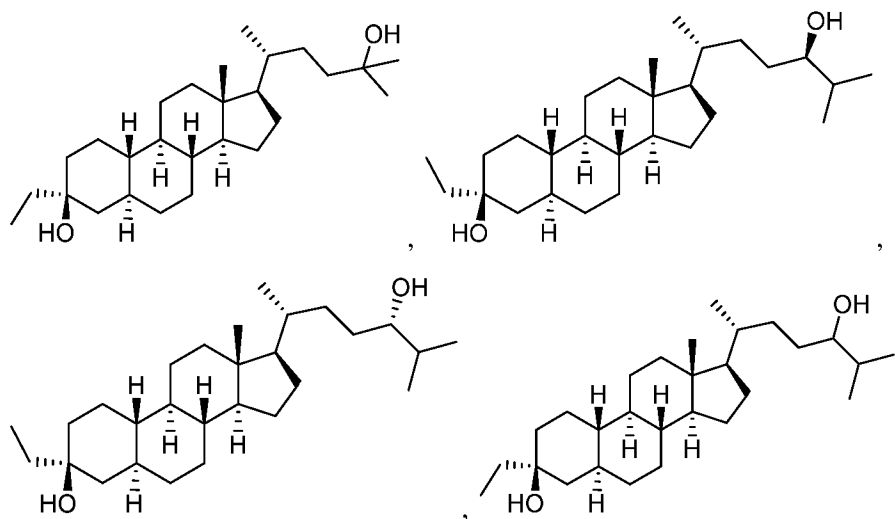
135. The compound of claim 97, wherein the compound of Formula (I-61) is selected from a compound of Formula (I-A61):

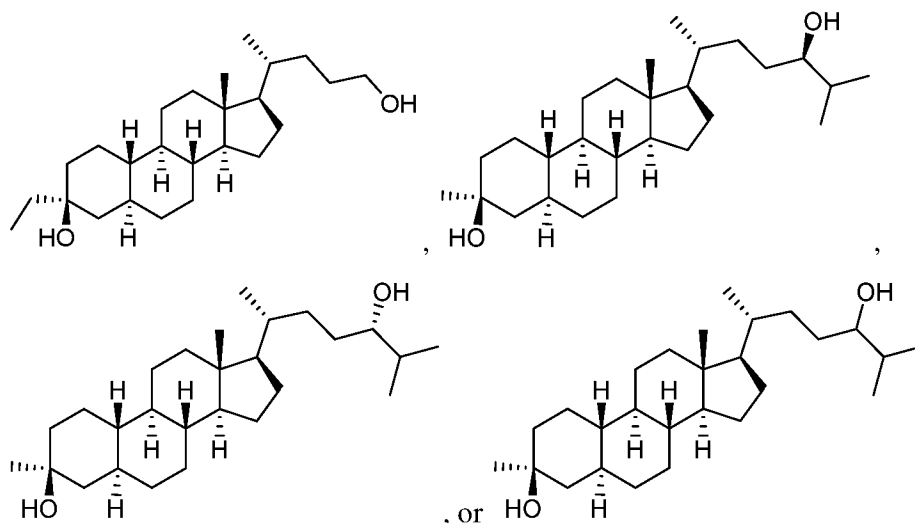


136. The compound of claim 97, wherein the compound of Formula (I-61) is selected from a compound of Formula (I-C-i61) or (I-C-ii61):



137. The compound of claim 97, wherein the compound is:





5 138. A pharmaceutical composition comprising a compound of claim 97, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

139. A method for treating or preventing a disorder described herein, comprising administering to a subject in need thereof an effective amount of a compound of claim 97, or  
10 pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

140. The method according to claim 139, wherein the disorder is a gastrointestinal (GI) disorder, constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, structural disorders affecting the GI, anal disorders,  
15 hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula, colon polyps, cancer, or colitis.

141. The method according to claim 139, wherein the disorder is inflammatory bowel disease.

20 142. The method according to claim 139, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

143. The method according to claim 139, wherein the disorder is a metabolic disorder.

25 144. The method according to claim 139, wherein the disorder is an autoimmune disorder.

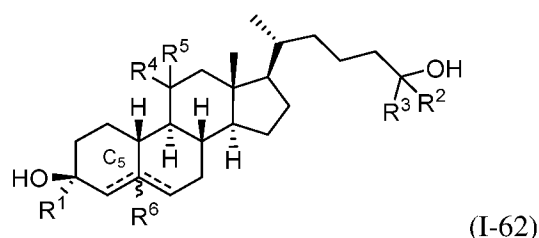
145. The method according to claim 139, wherein the disorder is rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

5 146. A method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound of claim 97, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

147. The method according to claim 139, wherein the CNS-related condition is an adjustment  
10 disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia),  
15 substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (including Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis disorders, pain (including acute and chronic pain), encephalopathy secondary to a medical condition (including hepatic  
20 encephalopathy and anti-NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, or tinnitus.

25 148. The method according to claim 139, wherein the disorder is a sterol synthesis disorder.

149. A compound of Formula (I-62):



30 or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is hydrogen or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;

each of  $R^2$  and  $R^3$  is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl or

$R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 substituted or unsubstituted membered ring;

5 each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl, or

$R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;

$R^6$  is absent or hydrogen; and

10 ===== represents a single or double bond, wherein when one of ===== is a double bond, the other ===== is a single bond; when both of ===== are single bonds, then  $R^6$  is hydrogen; and when one of ===== is a double bond,  $R^6$  is absent.

150. The compound of claim 149, wherein  $R^1$  is  $C_1$ - $C_6$  alkyl.

15

151. The compound of claim 149, wherein  $R^1$  is substituted or unsubstituted  $C_2$ - $C_6$  alkyl.

152. The compound of claim 149, wherein  $R^1$  is substituted or unsubstituted methyl or substituted or unsubstituted ethyl.

20

153. The compound of claim 149, wherein  $R^1$  is substituted or unsubstituted methyl or substituted or unsubstituted ethyl.

154. The compound of claim 149, wherein  $R^1$  is trifluoromethyl.

25

155. The compound of claim 149, wherein  $R^1$  is  $-CH_2OR^A$ , wherein  $R^A$  is  $C_1$ - $C_6$  alkyl.

156. The compound of claim 149, wherein  $R^2$  is hydrogen or  $C_1$ - $C_6$  alkyl.

30 157. The compound of claim 149, wherein  $R^2$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl.

158. The compound of claim 149, wherein  $R^2$  is  $C_1$ - $C_6$  haloalkyl.

159. The compound of claim 149, wherein each of  $R^2$  and  $R^3$  is independently hydrogen or  $C_1$ - $C_6$  alkyl.

160. The compound of claim 149, wherein each of  $R^2$  and  $R^3$  is independently hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl.

161. The compound of claim 149, wherein each of  $R^2$  and  $R^3$  is independently  $C_1$ - $C_6$  alkyl or hydrogen.

162. The compound of claim 149, wherein each of  $R^2$  and  $R^3$  is independently substituted or unsubstituted  $C_1$ - $C_6$  alkyl or hydrogen.

163. The compound of claim 149, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 membered ring.

164. The compound of claim 149, wherein  $R^4$  is  $-OH$  or halo.

165. The compound of claim 149, wherein  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group.

166. The compound of claim 149, wherein  $R^4$  is hydrogen and  $R^5$  is halo.

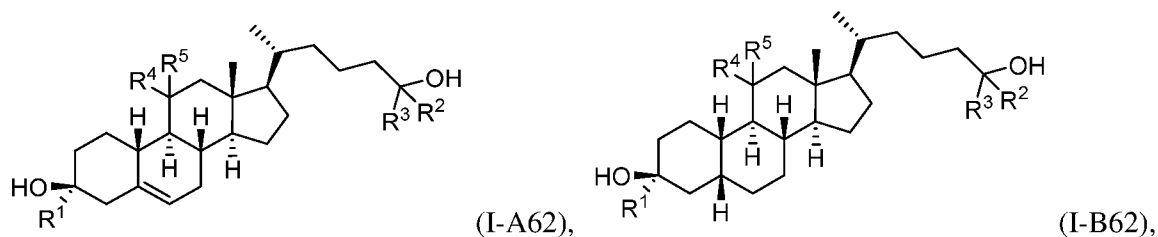
167. The compound of claim 149, wherein  $R^4$  and  $R^5$  are halo.

168. The compound of claim 149, wherein  $R^4$  and  $R^5$  are hydrogen.

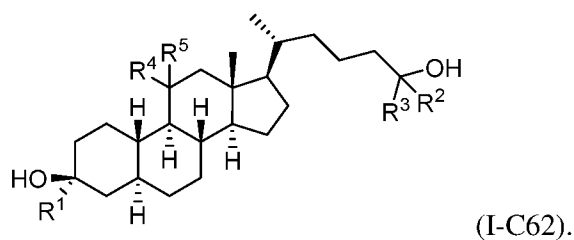
169. The compound of claim 149, wherein  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

170. The compound of claim 149, wherein  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

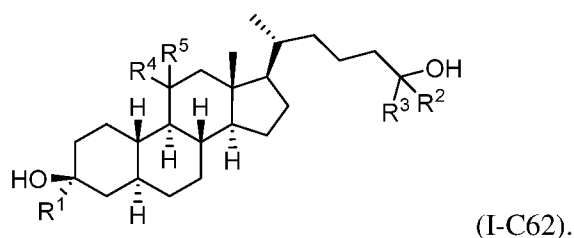
171. The compound of claim 149, wherein the compound of Formula (I-62) is a compound of Formula (I-A62), (I-B62), or (I-C62):



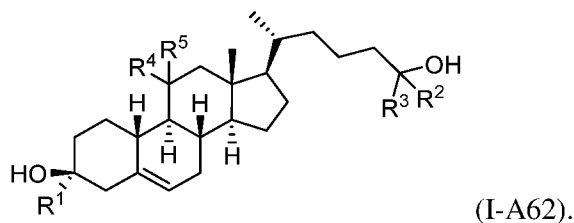
or



- 5 172. The compound of claim 149, wherein the compound of Formula (I-62) is selected from a compound of Formula (I-C62):



- 10 173. The compound of claim 149, wherein the compound of Formula (I-62) is selected from a compound of Formula (I-A62):



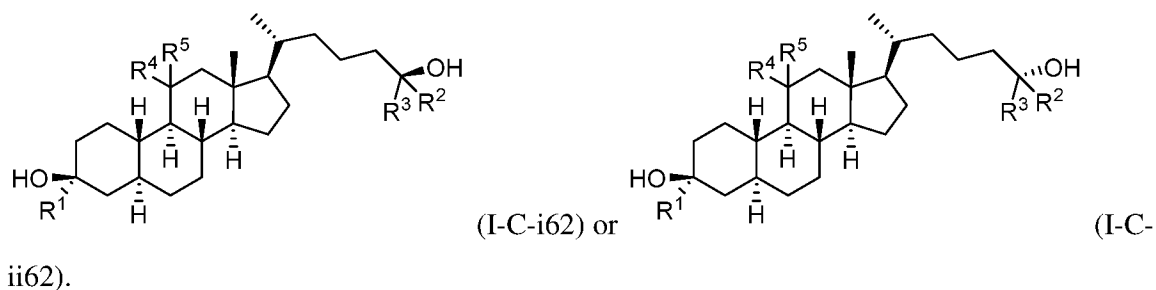
174. The compound of claim 149, wherein  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

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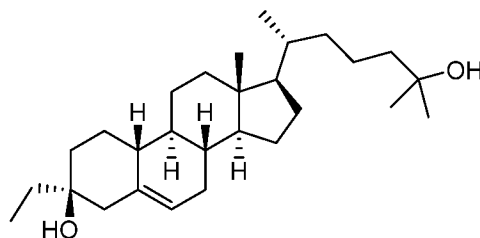
175. The compound of claim 149, wherein  $R^1$  is substituted or unsubstituted ethyl and  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

176. The compound of claim 149, wherein the compound of Formula (I-62) is selected from a compound of Formula (I-C-i62) or (I-C-ii62):

20



177. The compound of claim 149, wherein the compound is



178. A pharmaceutical composition comprising a compound of claim 149, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

179. A method for treating or preventing a disorder described herein, comprising administering to a subject in need thereof an effective amount of a compound of claim 149, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

180. The method according to claim 179, wherein the disorder is a gastrointestinal (GI) disorder, constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, structural disorders affecting the GI, anal disorders, hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula, colon polyps, cancer, or colitis.

181. The method according to claim 179, wherein the disorder is inflammatory bowel disease.

182. The method according to claim 179, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

183. The method according to claim 179, wherein the disorder is a metabolic disorder.

184. The method according to claim 179, wherein the disorder is an autoimmune disorder.

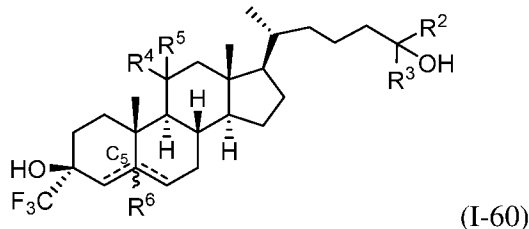
185. The method according to claim 179, wherein the disorder is rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

186. A method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound of claim 149, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

187. The method according to claim 186, wherein the CNS-related condition is an adjustment disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression and postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia), substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (including Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis disorders, pain (including acute and chronic pain), encephalopathy secondary to a medical condition (including hepatic encephalopathy and anti-NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, or tinnitus.

188. The method according to claim 179, wherein the disorder is a sterol synthesis disorder.

189. A compound of Formula (I-60):



or a pharmaceutically acceptable salt thereof, wherein:

each of  $R^2$  and  $R^3$  is independently hydrogen, substituted or unsubstituted  $C_1$ - $C_6$  alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or

5  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a substituted or unsubstituted 3-8 membered ring;

each of  $R^4$  and  $R^5$  is independently hydrogen, halo, or  $-OR^C$ , wherein  $R^C$  is hydrogen or substituted or unsubstituted  $C_1$ - $C_6$  alkyl, or

$R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group;

$R^6$  is absent or hydrogen; and

10  $\text{-----}$  represents a single or double bond, wherein when one of  $\text{-----}$  is a double bond, the other  $\text{-----}$  is a single bond; when both of  $\text{-----}$  are single bonds, then  $R^6$  is hydrogen; and when one of the  $\text{-----}$  is a double bond,  $R^6$  is absent.

190. The compound of claim 189, wherein  $R^2$  is  $C_1$ - $C_6$  alkyl or hydrogen.

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191. The compound of claim 189, wherein  $R^2$  is  $C_1$ - $C_6$  haloalkyl.

192. The compound of claim 189, wherein  $R^2$  is substituted or unsubstituted  $C_1$ - $C_6$  alkyl or hydrogen.

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193. The compound of claim 189, wherein  $R^2$  is aryl or heteroaryl.

194. The compound of claim 189, wherein each of  $R^2$  and  $R^3$  is independently  $C_1$ - $C_6$  alkyl or hydrogen.

25

195. The compound of claim 189, wherein each of  $R^2$  and  $R^3$  is independently substituted or unsubstituted  $C_1$ - $C_6$  alkyl or hydrogen.

196. The compound of claim 189, wherein each of  $R^2$  and  $R^3$  is independently unsubstituted  $C_1$ - $C_6$  alkyl) or hydrogen.

30

197. The compound of claim 189, wherein each of  $R^2$  and  $R^3$  is independently  $C_1$ - $C_6$  haloalkyl or hydrogen.

198. The compound of claim 189, wherein each of  $R^2$  and  $R^3$  is independently aryl or heteroaryl.

199. The compound of claim 189, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-membered ring.

200. The compound of claim 199, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a cyclopropane.

201. The compound of claim 189, wherein  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached form a 3-8 membered carbocyclic or heterocyclic ring.

202. The compound of claim 189, wherein  $R^2$  is carbocyclyl or heterocyclyl and  $R^3$  is hydrogen.

203. The compound of claim 189, wherein  $R^2$  is trifluoromethyl and  $R^3$  is hydrogen.

204. The compound of claim 189, wherein  $R^2$  is aryl or heteroaryl and  $R^3$  is hydrogen.

205. The compound of claim 189, wherein  $R^2$  and  $R^3$  are substituted or unsubstituted methyl.

206. The compound of claim 189, wherein  $R^2$  and  $R^3$  is substituted methyl.

207. The compound of claim 189, wherein  $R^2$  and  $R^3$  is unsubstituted methyl.

208. The compound of claim 189, wherein  $R^4$  is  $-OH$  or halo

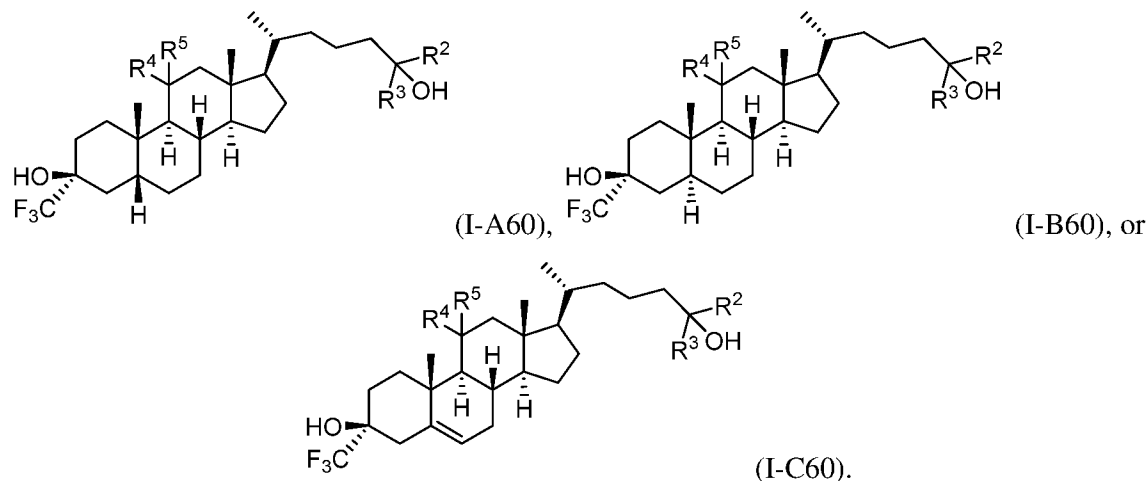
209. The compound of claim 189, wherein  $R^4$  and  $R^5$ , together with the carbon atom to which they are attached form an oxo group.

210. The compound of claim 189, wherein  $R^4$  is hydrogen and  $R^5$  is halo.

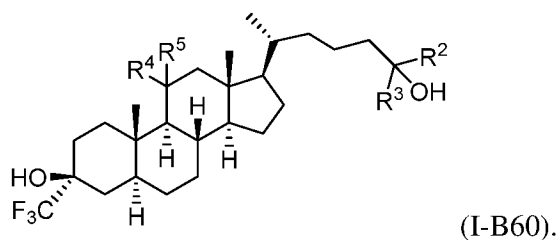
211. The compound of claim 189, wherein  $R^4$  and  $R^5$  are halo.

212. The compound of claim 189, wherein  $R^4$  and  $R^5$  are hydrogen.

213. The compound of claim 189, wherein the compound of Formula (I-60) is selected from a compound of Formula (I-A60), (I-B60), or (I-C60):



214. The compound of claim 189, wherein the compound of Formula (I-60) is selected from a compound of Formula (I-B60):



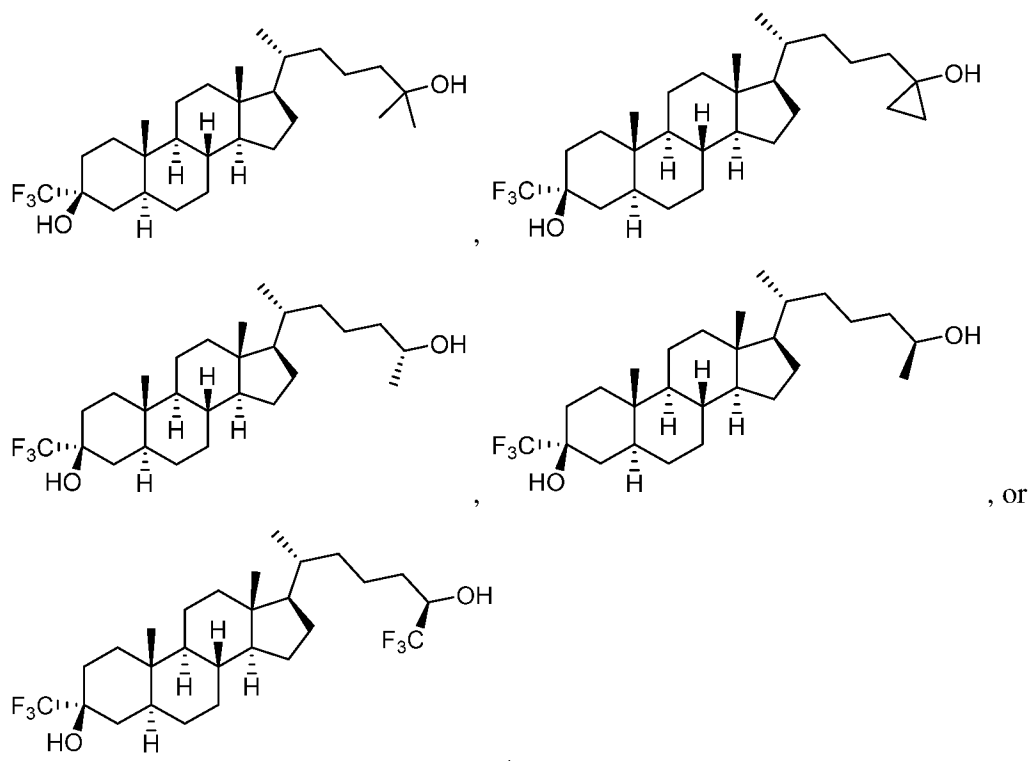
215. The compound of claim 189, wherein at least one of  $R^2$  and  $R^3$  is  $C_1$ - $C_6$  alkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or  $R^2$  and  $R^3$ , together with the carbon atom to which they are attached, form a 3-8 membered ring.

216. The compound of claim 189, wherein  $R^2$  is methyl and  $R^3$  is hydrogen.

217. The compound of claim 189, wherein  $R^2$  is unsubstituted methyl and  $R^3$  is hydrogen.

218. The compound of claim 189, wherein  $R^2$  and  $R^3$  are hydrogen.

219. The compound of claim 189, wherein the compound is:



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220. A pharmaceutical composition comprising a compound of claim 189, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10 221. A method for treating or preventing a disorder described herein, comprising administering to a subject in need thereof an effective amount of a compound of claim 189, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

15 222. The method according to claim 221, wherein the disorder is a gastrointestinal (GI) disorder *e.g.*, constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) ulcerative colitis, Crohn's disease, structural disorders affecting the GI, anal disorders, hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula, colon polyps, cancer, or colitis.

20 223. The method according to claim 221, wherein the disorder is inflammatory bowel disease.

224. The method according to claim 221, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

225. The method according to claim 221, wherein the disorder is a metabolic disorder.

226. The method according to claim 221, wherein the disorder is an autoimmune disorder.

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227. The method according to claim 221, wherein the disorder is rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

10 228. A method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound of claim 189, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

229. The method according to claim 228, wherein the CNS-related condition is an adjustment  
15 disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression and postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia),  
20 substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (including Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis disorders, pain (including acute and chronic pain), encephalopathy secondary to a medical condition (including hepatic  
25 encephalopathy and anti-NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, or tinnitus.

30 230. The method according to claim 221, wherein the disorder is a sterol synthesis disorder.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/057277

A. CLASSIFICATION OF SUBJECT MATTER  
 INV. C07J9/00 A61K31/575 A61P25/28  
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 2015/158903 A1 (UPASANI RAVINDRA B [US] ET AL) 11 June 2015 (2015-06-11) page 99; example 30; compound D4 page 102; example 32; compounds D13,D14 page 105; compound 9 page 106; compound 15 page 109; example 37 claim 1	1-65 66-96
X A	US 2016/022701 A1 (REDDY KIRAN [US] ET AL) 28 January 2016 (2016-01-28) paragraphs [0006], [0007], [0024] - [0043] paragraph [0485] examples 10,11 examples 27,30; compounds D1,D4 page 121; compound 15 example 37	1-65 66-96
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Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 December 2017

Date of mailing of the international search report

20/02/2018

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/057277

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/031930 A1 (MARTINEZ BOTELLA GABRIEL [US] ET AL) 4 February 2016 (2016-02-04) paragraph [0007] claim 1 -----	1-96

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2017/057277

### Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-96

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-96

Oxysterol compounds of formula (I-59) and also compounds of formula (I-66) having an the group R1 being substituted or unsubstituted C1-C6 alkyl; their pharmaceutical compositions and use in medical treatment.

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2. claims: 97-148

Oxysterol compounds of formula (I-61) having a group R1 being hydrogen or substituted or unsubstituted alkyl; their pharmaceutical compositions and their use in medical treatment.

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3. claims: 149-230

Oxysterol compounds of formula (I-62); their pharmaceutical compositions and their use in medical treatment.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/057277

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