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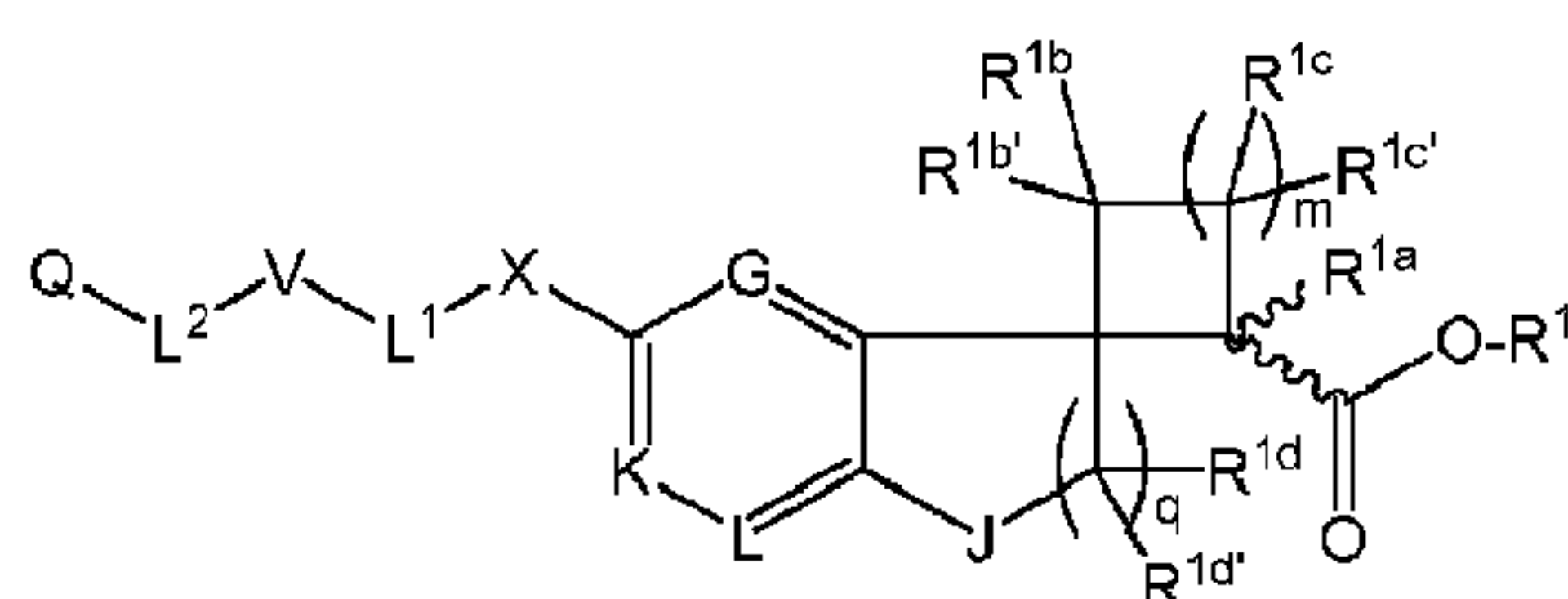
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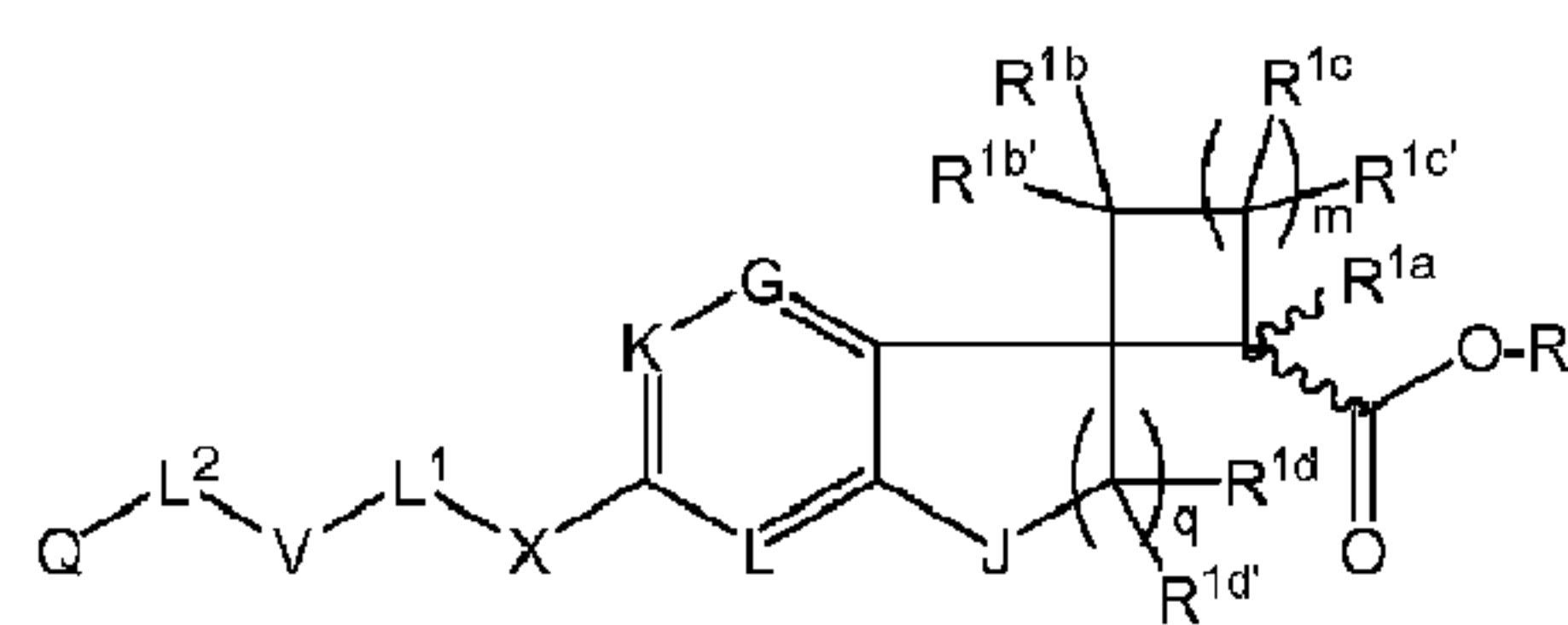
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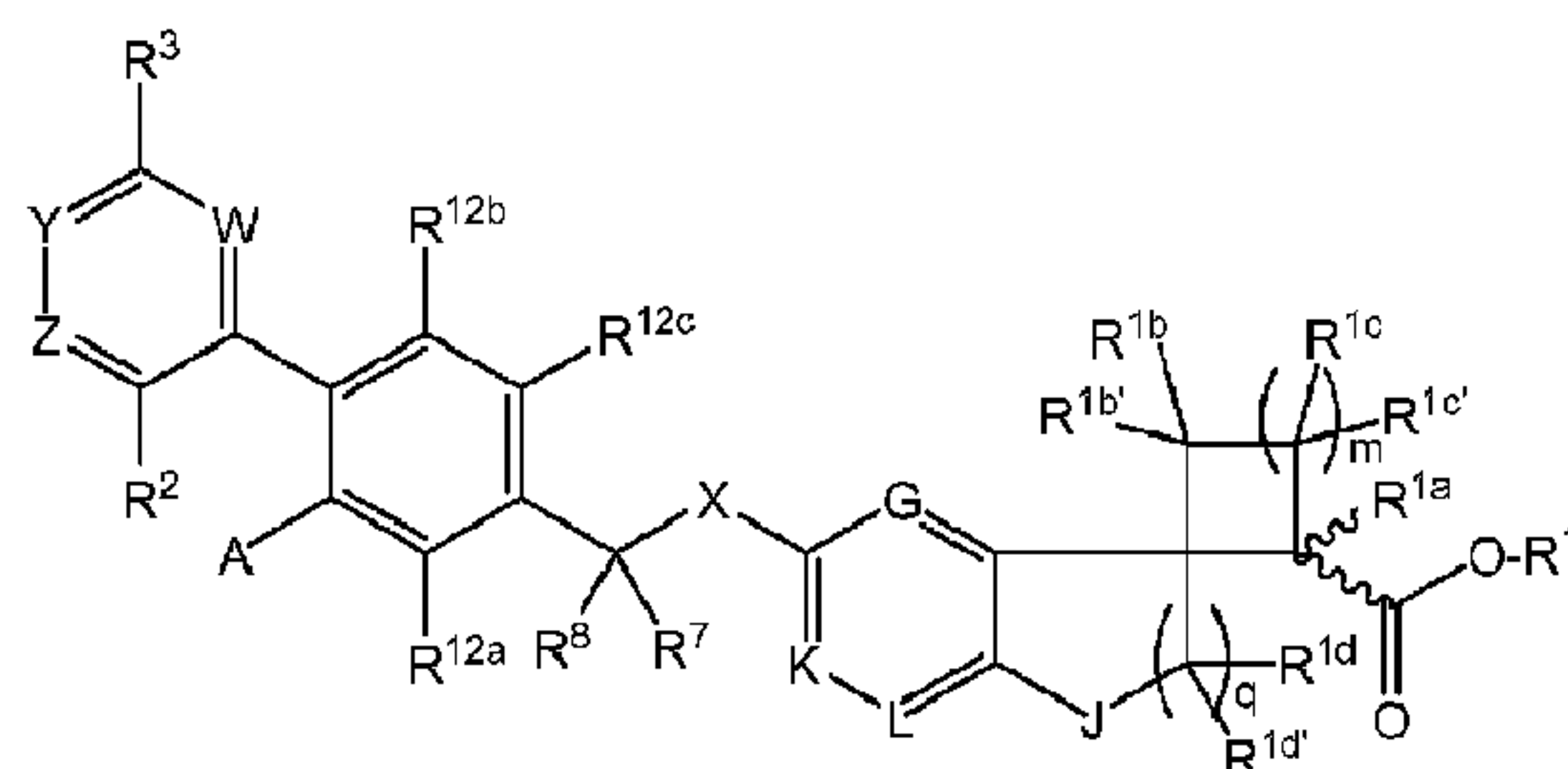
(54) Title: **SPIROCYCLIC GPR40 MODULATORS**



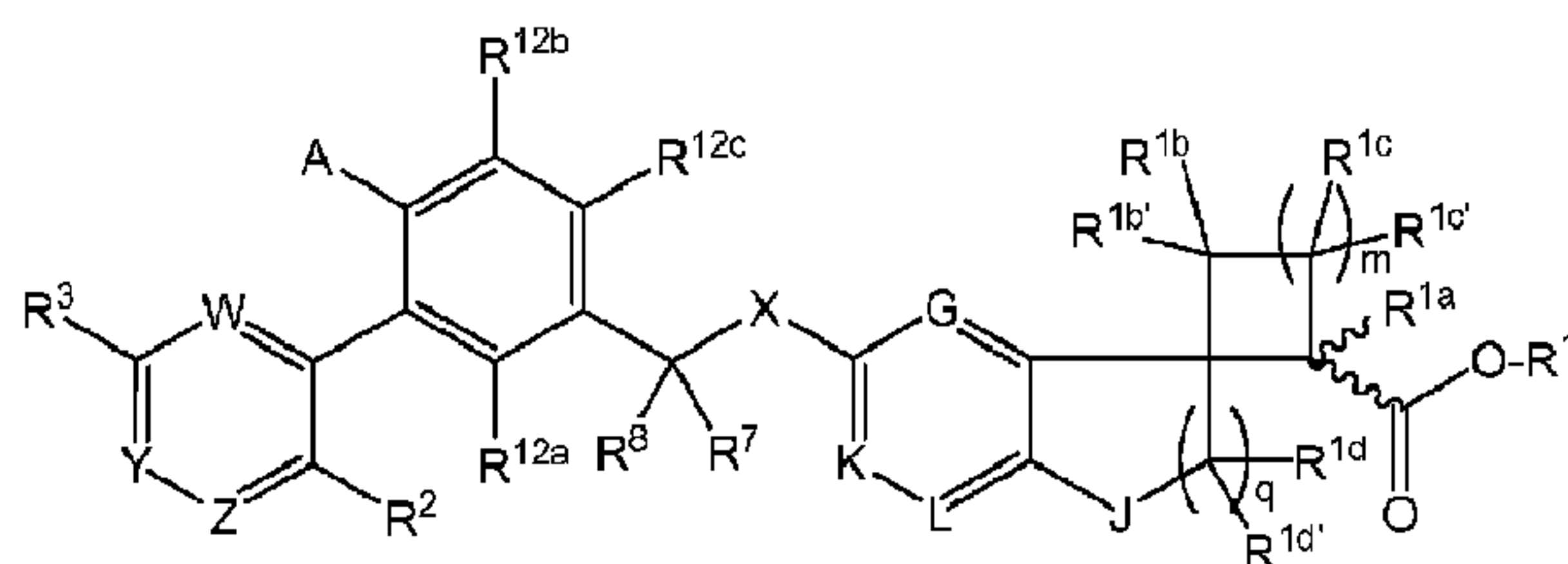
IA



IB



I'A



I'B

(57) **Abrégé/Abstract:**

The present invention provides compounds useful, for example, for treating metabolic disorders in a subject. Such compounds have the general formula IA, IB, I'A or I'B, where the definitions of the variables are provided herein. The present invention also



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(57) **Abrégé(suite)/Abstract(continued)**:

provides compositions that include, and methods for using, the compounds in preparing medicaments and for treating metabolic disorders such as, for example, type II diabetes.

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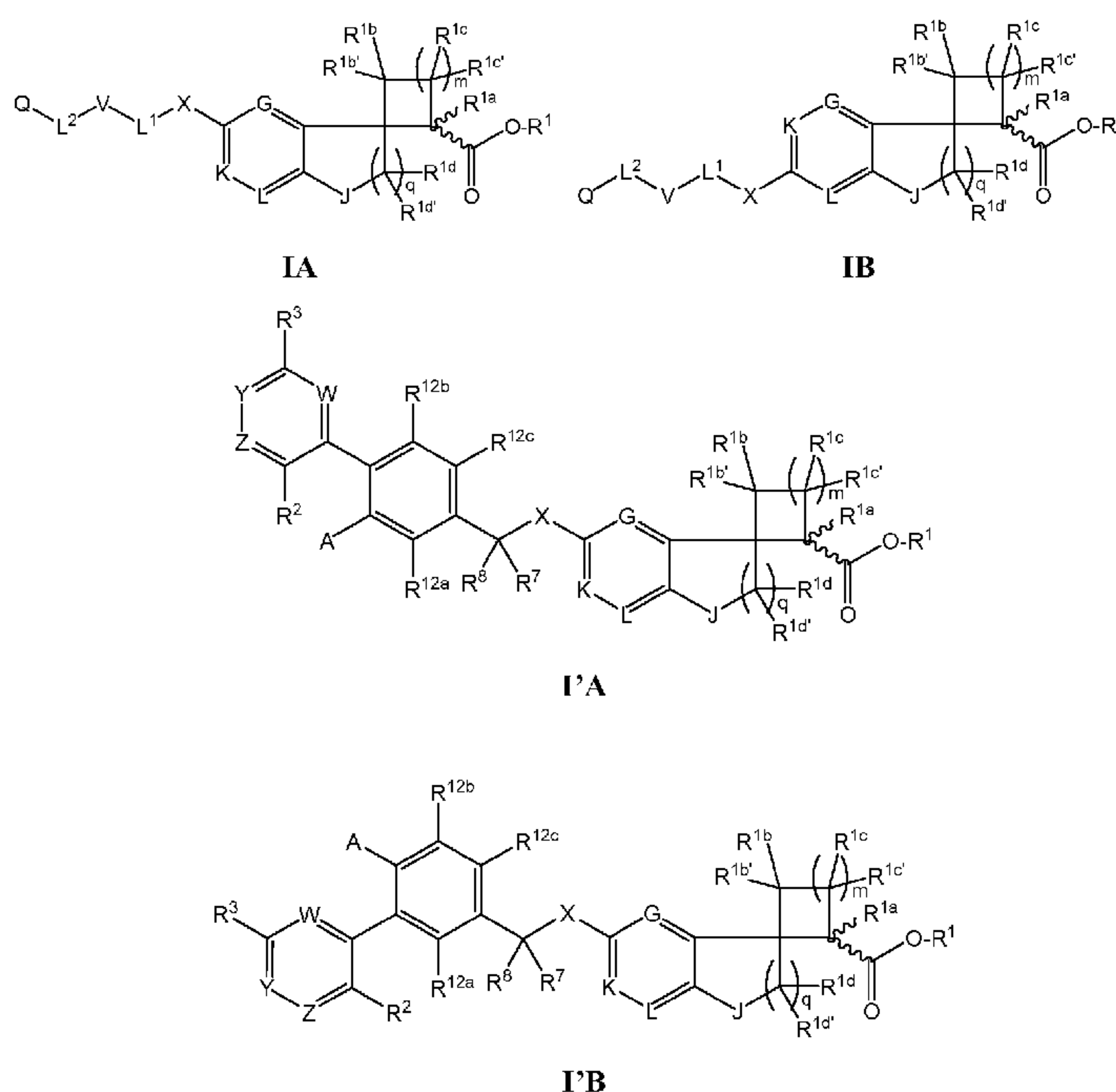
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[Continued on next page]

(54) Title: SPIROCYCLIC GPR40 MODULATORS



(57) Abstract: The present invention provides compounds useful, for example, for treating metabolic disorders in a subject. Such compounds have the general formula IA, IB, I'A or I'B, where the definitions of the variables are provided herein. The present invention also provides compositions that include, and methods for using, the compounds in preparing medicaments and for treating metabolic disorders such as, for example, type II diabetes.

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SPIROCYCLIC GPR40 MODULATORS

2. FIELD OF THE INVENTION

[002] The present invention relates to compounds capable of modulating the G-protein-coupled receptor GPR40, compositions comprising the compounds, and methods for their use for controlling insulin levels *in vivo* and for the treatment of conditions such as type II diabetes, hypertension, ketoacidosis, obesity, glucose intolerance, and hypercholesterolemia and related disorders associated with abnormally high or low plasma lipoprotein, triglyceride or glucose levels.

3. BACKGROUND OF THE INVENTION

[003] The production of insulin is central to the regulation of carbohydrate and lipid metabolism. Insulin imbalances lead to conditions such as type II diabetes mellitus, a serious metabolic disease that afflicts around 5% of the population in Western Societies and over 150 million people worldwide. Insulin is secreted from pancreatic β cells in response to elevated plasma glucose which is augmented by the presence of fatty acids. The recent recognition of the function of the G-protein coupled receptor GPR40 in modulating insulin secretion has provided insight into regulation of carbohydrate and lipid metabolism in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes, cardiovascular disease and dyslipidemia.

[004] GPR40 is a member of the gene superfamily of G-protein coupled receptors ("GPCRs"). GPCRs are membrane proteins characterized as having seven putative transmembrane domains that respond to a variety of molecules by activating intra-cellular signaling pathways critical to a diversity of physiological functions. GPR40 was first identified as an orphan receptor (i.e., a receptor without a known ligand) from a human genomic DNA fragment. Sawzdargo et al. (1997) *Biochem. Biophys. Res. Commun.* 239: 543-547. GPR40 is highly expressed in pancreatic β cells and insulin-secreting cell lines. GPR40 activation is linked to modulation of the G_q family of intra-cellular signaling proteins and concomitant induction of elevated calcium levels. It has

been recognized that fatty acids serve as ligands for GPR40, and that fatty acids regulate insulin secretion through GPR40. Itoh et al. (2003) Nature 422:173-176; Briscoe et al. (2003) J. Biol. Chem. 278: 11303-11311; Kotarsky et al. (2003) Biochem. Biophys. Res. Commun. 301: 406-410.

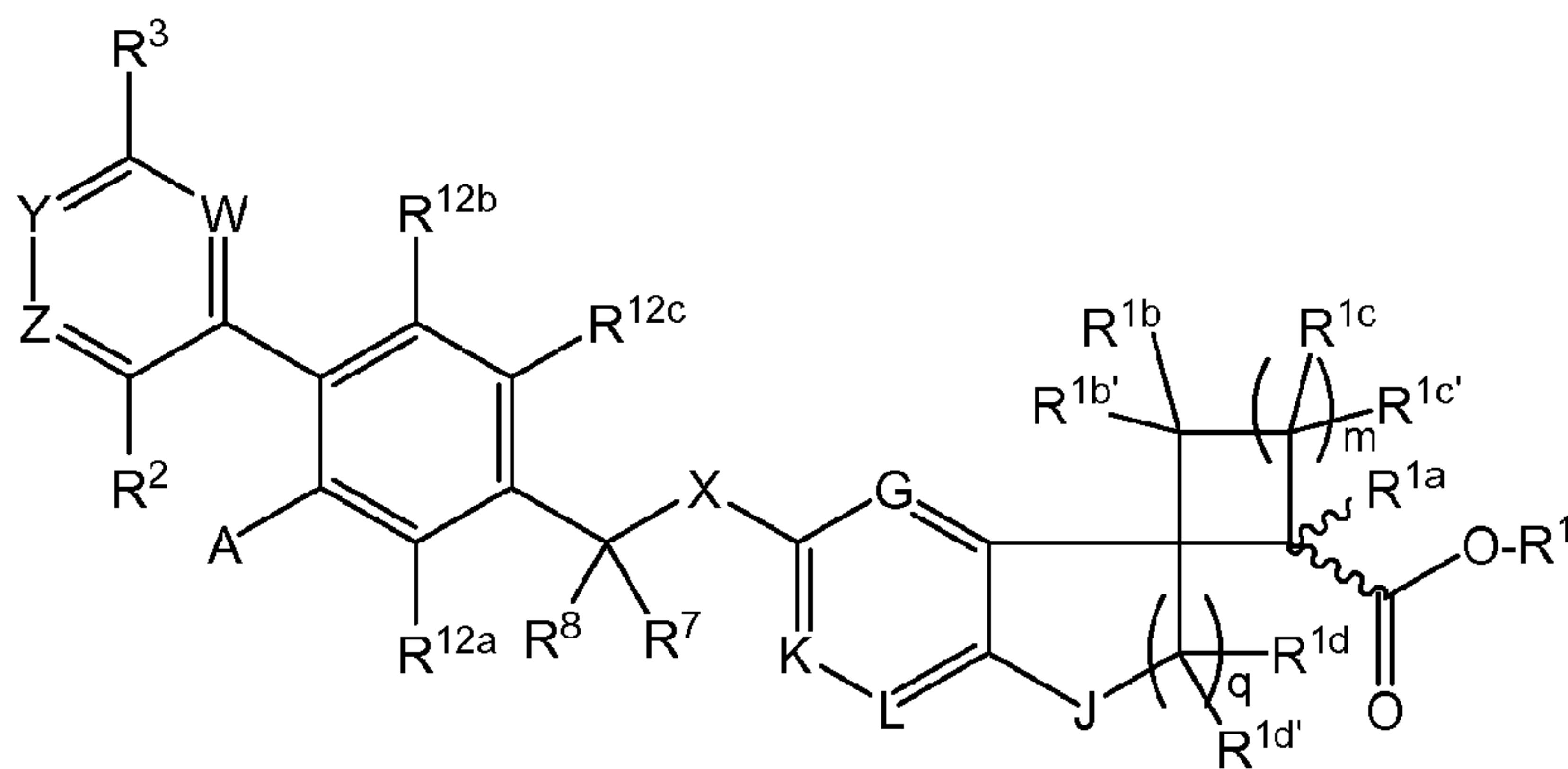
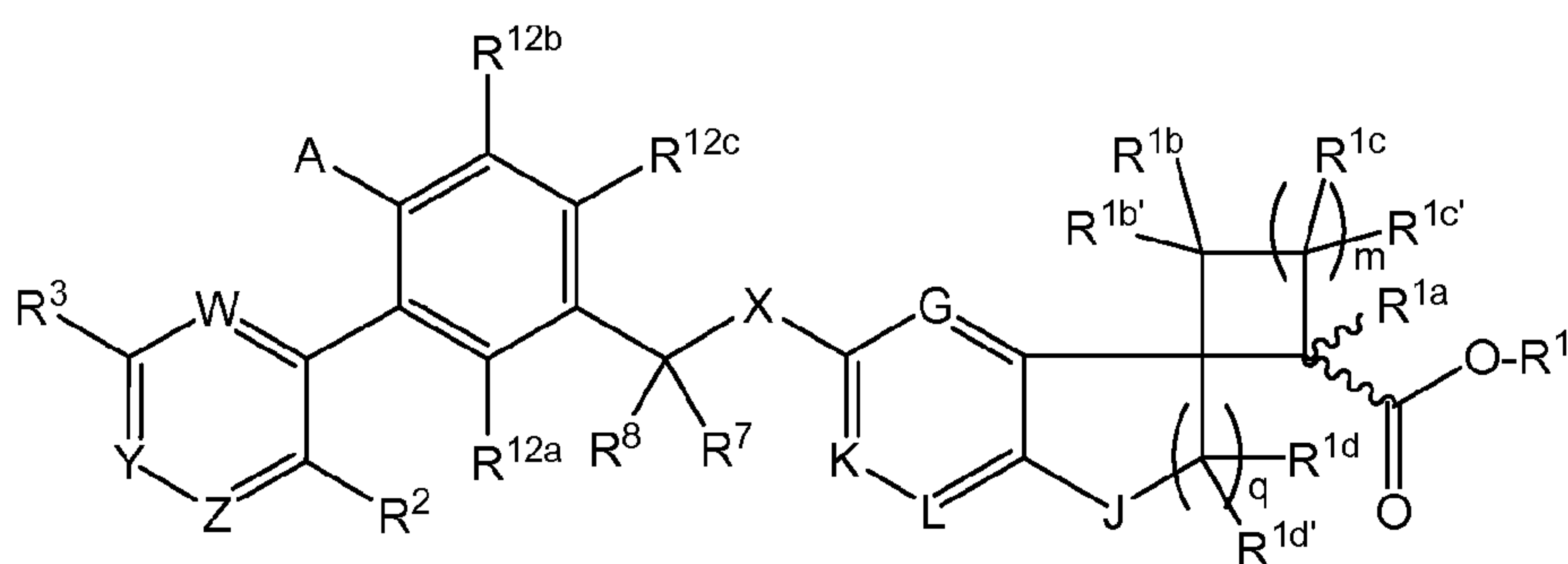
[005] Various documents have disclosed compounds reportedly having activity with respect to GPR40. For example, WO 2004/041266 and EP 1559422 disclose compounds that purportedly act as GPR40 receptor function regulators. WO 2004/106276 and EP 1630152 are directed to condensed ring compounds that purportedly possess GPR40 receptor function modulating action. More recently, WO 2005/086661 U.S. Patent Publication No. 2006/0004012, US Patent Publication No. 2006/0270724, and US Patent Publication No. 2007/0066647 disclose compounds useful for modulating insulin levels in subjects and useful for treating type II diabetes.

[006] Although a number of compounds have been disclosed that reportedly modulate GPR40 activity, the prevalence of type II diabetes, obesity, hypertension, cardiovascular disease and dyslipidemia underscores the need for new therapies to effectively treat these conditions.

4. SUMMARY OF THE INVENTION

[007] Provided herein are compounds, pharmaceutical compositions, and methods useful for treating a condition or disorder such as type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer or edema.

[008] In one aspect, the present invention provides a compound having the formula **I'A** or **I'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. Compounds of formula **I'A** or **I'B** have the following structures:

**I'A****I'B**

where

G is selected from N or CR^{11a};

K is selected from N or CR^{11b};

L is selected from N or CR^{11c};

wherein 0 or 1 of G, L, and K is N;

X is O, S, or NR^a wherein R^a is selected from -H or -(C₁-C₆) alkyl groups;

J is selected from O, S, NR^b, CR^cR^d, C(=O), or -C(=O)-NR^b-; wherein R^b is selected from H and (C₁-C₄)alkyl, and further wherein R^c and R^d are independently selected from H, F, and (C₁-C₄)alkyl;

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N; and further wherein Z is not N if R² is -F; and A and W, when W is C, may join together to form a ring having 5 to 7 ring members of which 0 or 1 is a heteroatom selected from

N, O, or S, and further wherein the ring having 5 to 7 ring members is optionally substituted with $-(C_1-C_8)alkyl$, $-(C_1-C_8)alkenyl$, $-OH$, $-O-(C_1-C_8)alkyl$, $-O-(C_1-C_8)alkenyl$, or halo;

A is selected from $-H$, $-(C_1-C_{12})alkyl$; $-(C_2-C_{12})alkenyl$; $-(C_1-C_{12})alkyl-O-(C_1-C_4)alkyl$; $-(C_1-C_{12})alkyl-OH$; $-(C_1-C_{12})alkyl-O-(C_2-C_4)alkenyl$; $-(C_2-C_{12})alkenyl-O-(C_1-C_4)alkyl$; $-(C_2-C_{12})alkenyl-OH$; $-(C_2-C_{12})alkenyl-O-(C_2-C_4)alkenyl$; $-O-(C_1-C_{12})alkyl$; $-O-(C_2-C_{12})alkenyl$; $-O-(C_1-C_4)alkyl-aryl$; $-S-(C_1-C_{12})alkyl$; $-S-(C_2-C_{12})alkenyl$; $-S(O)-(C_1-C_{12})alkyl$; $-S(O)-(C_2-C_{12})alkenyl$; $-S(O)_2-(C_1-C_{12})alkyl$; $-S(O)_2-(C_2-C_{12})alkenyl$; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)alkyl$ groups; a $-(C_1-C_4)alkyl-heterocyclyl$ wherein the heterocyclyl of the $-(C_1-C_4)alkyl-heterocyclyl$ comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)alkyl$ groups; or a $-O-heterocyclyl$ wherein the heterocyclyl of the $-O-heterocyclyl$ comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)alkyl$ groups; further wherein the alkyl and alkenyl groups of $-(C_1-C_{12})alkyl$, $-(C_2-C_{12})alkenyl$, $-(C_1-C_{12})alkyl-O-(C_1-C_4)alkyl$, $-(C_1-C_{12})alkyl-O-H$, $-(C_1-C_{12})alkyl-O-(C_2-C_4)alkenyl$, $-(C_2-C_{12})alkenyl-O-(C_1-C_4)alkyl$, $-(C_2-C_{12})alkenyl-OH$, $-(C_2-C_{12})alkenyl-O-(C_2-C_4)alkenyl$, $-O-(C_1-C_{12})alkyl$, $-O-(C_2-C_{12})alkenyl$, and $-O-(C_1-C_4)alkyl-aryl$ are unsubstituted or are substituted with from 1 to 4 substituents selected from $-F$, $-Cl$, $-OH$, $(=O)$, $-NH_2$, $NH(C_1-C_4)alkyl$, $-N((C_1-C_4)alkyl)_2$, aryl, unsubstituted $-(C_1-C_2)alkyl$, or unsubstituted $-O-(C_1-C_2)alkyl$;

R^1 is H or $-(C_1-C_6)alkyl$;

R^{1a} is selected from $-H$ and $-(C_1-C_4)alkyl$;

R^{1b} is selected from $-H$ and $-(C_1-C_4)alkyl$;

$R^{1b'}$ is selected from $-H$ and $-(C_1-C_4)alkyl$;

R^{1c} is selected from $-H$ and $-(C_1-C_4)alkyl$;

$R^{1c'}$ is selected from $-H$ and $-(C_1-C_4)alkyl$;

R^{1d} is in each instance independently selected from $-H$, $-F$, and $-(C_1-C_4)alkyl$;

$R^{1d'}$ is in each instance independently selected from $-H$, $-F$, and $-(C_1-C_4)alkyl$;

R^2 is selected from $-H$, $-F$, $-CF_3$, $-Cl$, or $-O-(C_1-C_6)alkyl$;

R^3 is -H, -F, -Cl, -OH, -(C₁-C₄)alkyl, -O-(C₁-C₃)alkyl, or -S-(C₁-C₂)alkyl;

R^7 and R^8 are independently selected from -H and -(C₁-C₄)alkyl;

R^{11a} , R^{11b} , and R^{11c} are independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl;

R^{12a} , R^{12b} , and R^{12c} are independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl;

R^{13} is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl;

m is 0 or 1; and

q is selected from 0, 1, 2, or 3,

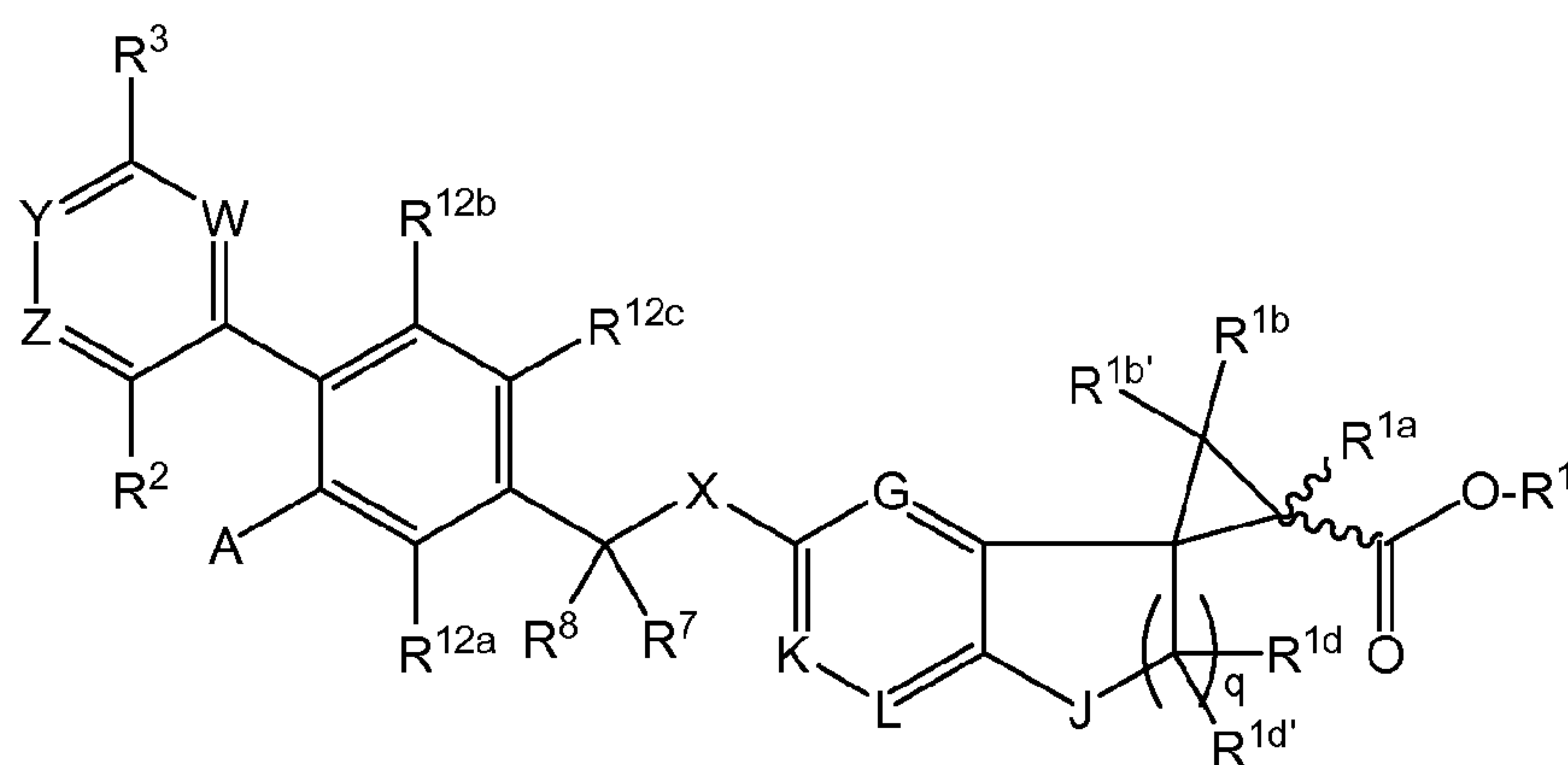
wherein the  bond indicates that the R^{1a} and -C(=O)-O- R^1 may be attached to either side of the ring to which the  is attached and either R or S stereochemistry is allowed.

[009] In some embodiments of the compound of formula **I'A** or **I'B**, R^2 is selected from -H, -F, -CF₃, or -O-(C₁-C₆)alkyl. In some embodiments R^2 is -F. In other embodiments, R^2 is -Cl.

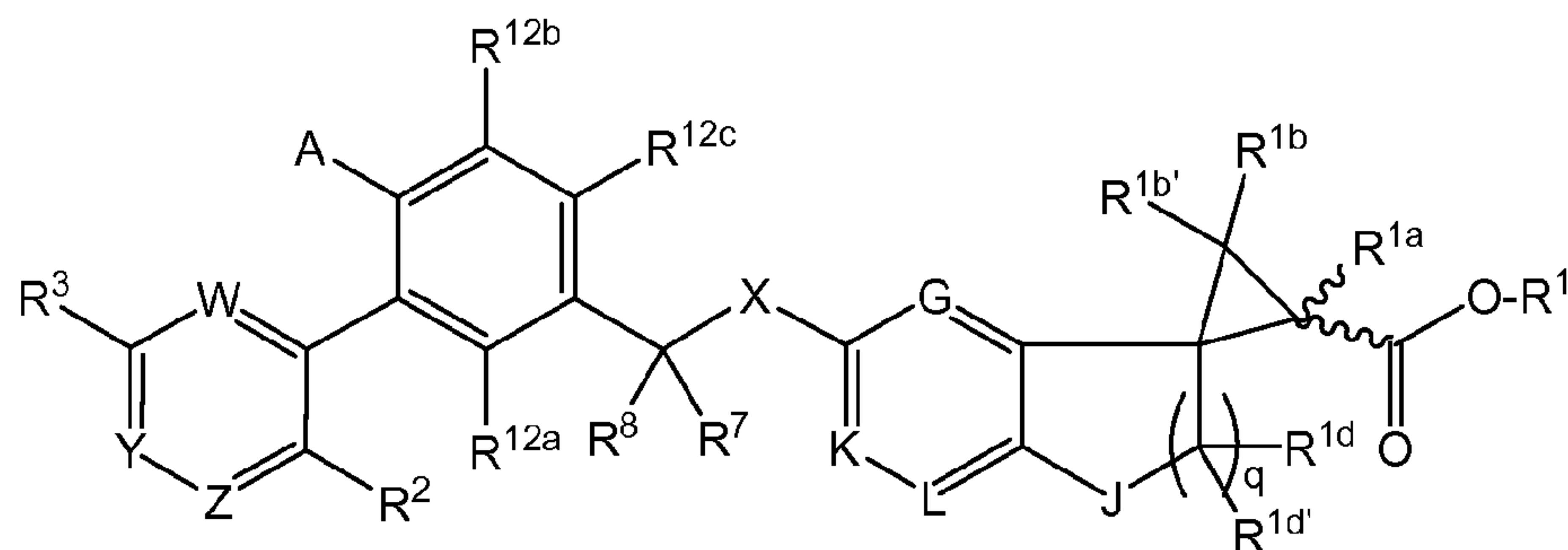
[010] In some embodiments of the compound of formula **I'A** or **I'B**, A is A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-

(C₂-C₄)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, and -O-(C₁-C₄)alkyl-aryl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -(C₁-C₂)alkyl, or unsubstituted -O-(C₁-C₂)alkyl.

[011] In some embodiments, m is 0 such that the compound of formula I'A or I'B is a compound of formula II'A or II'B or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula II'A or II'B have the following structures:



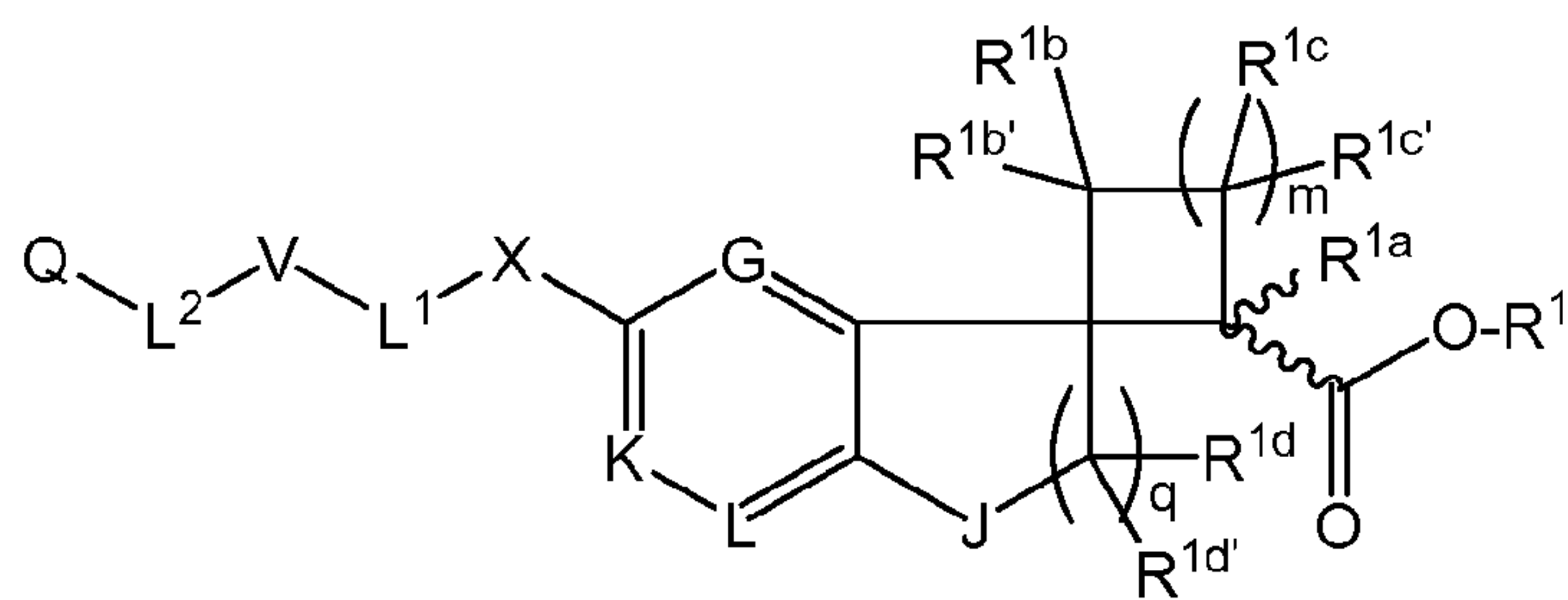
II'A



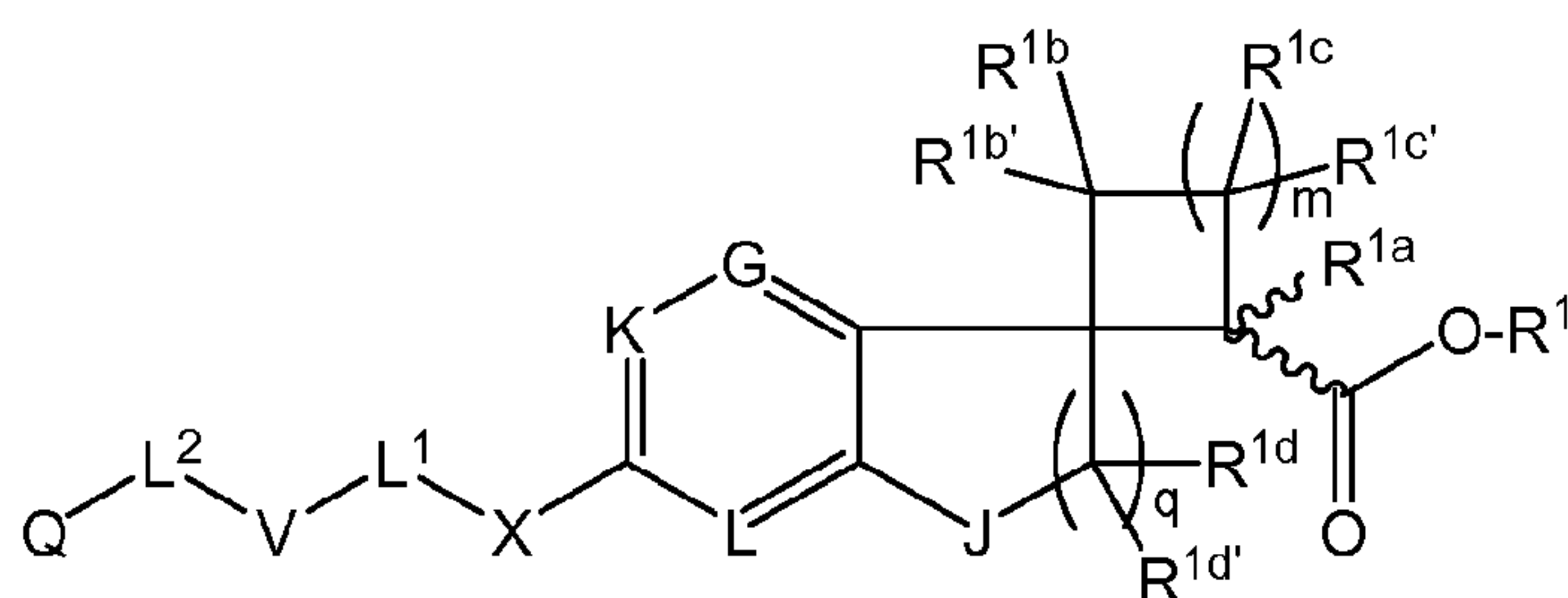
II'B.

[012] In some embodiments, R¹ is H such that the compound is a carboxylic acid. In other embodiments, R¹ is an unsubstituted -(C₁-C₆) alkyl group such as a methyl, ethyl, propyl, butyl, pentyl, hexyl, or isopropyl group. Therefore, in some embodiments, R¹ is a -CH₃ or a -CH₂CH₃ group.

[013] In another aspect, the invention provides a compound having the formula IA or IB or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. Compounds of formula IA and IB have the following structures:



IA



IB

or a pharmaceutically acceptable salt, stereoisomer, or a mixture thereof,
wherein

G is selected from N or CR^{11a};

K is selected from N or CR^{11b};

L is selected from N or CR^{11c};

wherein 0 or 1 of G, L, and K is N;

X is O, S, or NR^a wherein R^a is selected from -H or -(C₁-C₆) alkyl groups;

J is selected from O, S, NR^b, CR^cR^d, C(=O), or -C(=O)-NR^b-; wherein R^b is selected from H and (C₁-C₄)alkyl, and further wherein R^c and R^d are independently selected from H, F, and (C₁-C₄)alkyl;

L¹ is absent or is a (C₁-C₄) alkyl;

V is selected from a (C₄-C₈)cycloalkyl; a (C₆-C₁₀)aryl; a heteroaryl comprising from 5 to 10 ring members of which from 1 to 3 are heteroatoms selected from N, O, and S; a benzo-fused (C₅-C₈)cycloalkyl wherein the cycloalkyl group of the benzo-fused cycloalkyl is bonded to L¹, if present, or is bonded to X if L¹ is absent; a benzo-fused (C₅-C₈)cycloalkyl wherein the aromatic group of the benzo-fused cycloalkyl is bonded to L¹, if present, or is bonded to X if L¹ is absent; a heteroaryl-fused (C₅-C₈)cycloalkyl wherein the cycloalkyl group of the heteroaryl-fused cycloalkyl is bonded to L¹, if present, or is bonded to X if L¹ is absent; or a heteroaryl-fused (C₅-C₈)cycloalkyl wherein the

heteroaryl group of the heteroaryl-fused cycloalkyl is bonded to L^1 , if present, or is bonded to X if L^1 is absent; wherein the (C_6-C_{10}) aryl, heteroaryl, benzo-fused (C_5-C_8) cycloalkyl, and heteroaryl-fused (C_5-C_8) cycloalkyl group are optionally substituted with from 1 to 4 substituents independently selected from F, Cl, Br, OH, $-O(C_1-C_6)$ alkyl groups, $-S(C_1-C_6)$ alkyl groups (C_1-C_6) alkyl groups, $-CF_3$, or a group of formula A wherein A is selected from $-(C_1-C_{12})$ alkyl; $-(C_2-C_{12})$ alkenyl; $-(C_1-C_{12})$ alkyl-O- (C_1-C_4) alkyl; $-(C_1-C_{12})$ alkyl-OH; $-(C_1-C_{12})$ alkyl-O- (C_2-C_4) alkenyl; $-(C_2-C_{12})$ alkenyl-O- (C_1-C_4) alkyl; $-(C_2-C_{12})$ alkenyl-OH; $-(C_2-C_{12})$ alkenyl-O- (C_2-C_4) alkenyl; $-O-(C_1-C_{12})$ alkyl; $-O-(C_2-C_{12})$ alkenyl; $-O-(C_1-C_4)$ alkyl-aryl; $-S-(C_1-C_{12})$ alkyl; $-S-(C_2-C_{12})$ alkenyl; $-S(O)-(C_1-C_{12})$ alkyl; $-S(O)-(C_2-C_{12})$ alkenyl; $-S(O)_2-(C_1-C_{12})$ alkyl; $-S(O)_2-(C_2-C_{12})$ alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups; a $-(C_1-C_4)$ alkyl-heterocyclyl wherein the heterocyclyl of the $-(C_1-C_4)$ alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups; or a $-O$ -heterocyclyl wherein the heterocyclyl of the $-O$ -heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups; further wherein the alkyl and alkenyl groups of $-(C_1-C_{12})$ alkyl, $-(C_2-C_{12})$ alkenyl, $-(C_1-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_1-C_{12})$ alkyl-O-H, $-(C_1-C_{12})$ alkyl-O- (C_2-C_4) alkenyl, $-(C_2-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_2-C_{12})$ alkenyl-OH, $-(C_2-C_{12})$ alkenyl-O- (C_2-C_4) alkenyl, $-O-(C_1-C_{12})$ alkyl, $-O-(C_2-C_{12})$ alkenyl, and $-O-(C_1-C_4)$ alkyl-aryl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), $-NH_2$, $NH(C_1-C_4)$ alkyl, $-N((C_1-C_4)alkyl)_2$, aryl, unsubstituted $-(C_1-C_2)$ alkyl, or unsubstituted $-O-(C_1-C_2)$ alkyl;

L^2 is absent or is selected from O, S, SO, SO_2 , $C(=O)$, (C_1-C_2) alkyl, or NR^x wherein R^x is selected from -H or $-(C_1-C_6)$ alkyl groups;

Q is selected from H, a (C_4-C_8) cycloalkyl; a (C_6-C_{10}) aryl; or a heteroaryl comprising from 5 to 10 ring members of which from 1 to 3 are heteroatoms selected from N, O, and S; wherein the (C_4-C_8) cycloalkyl, (C_6-C_{10}) aryl, and heteroaryl groups are optionally substituted with from 1 to 5 substituents independently selected from F, Cl, Br, OH, $-O(C_1-C_6)$ alkyl groups, $-S(C_1-C_6)$ alkyl groups (C_1-C_6) alkyl groups, or $-CF_3$.

R^1 is H or $-(C_1-C_6)\text{alkyl}$;

R^{1a} is selected from -H and $-(C_1-C_4)\text{alkyl}$;

R^{1b} is selected from -H and $-(C_1-C_4)\text{alkyl}$;

$R^{1b'}$ is selected from -H and $-(C_1-C_4)\text{alkyl}$;

R^{1c} is selected from -H and $-(C_1-C_4)\text{alkyl}$;

$R^{1c'}$ is selected from -H and $-(C_1-C_4)\text{alkyl}$;

R^{1d} is in each instance independently selected from -H, -F, and $-(C_1-C_4)\text{alkyl}$;

$R^{1d'}$ is in each instance independently selected from -H, -F and $-(C_1-C_4)\text{alkyl}$;

R^{11a} , R^{11b} , and R^{11c} are independently selected from -H, -F, -Cl, $-(C_1-C_4)\text{alkyl}$, or $-O(C_1-C_4)\text{alkyl}$;

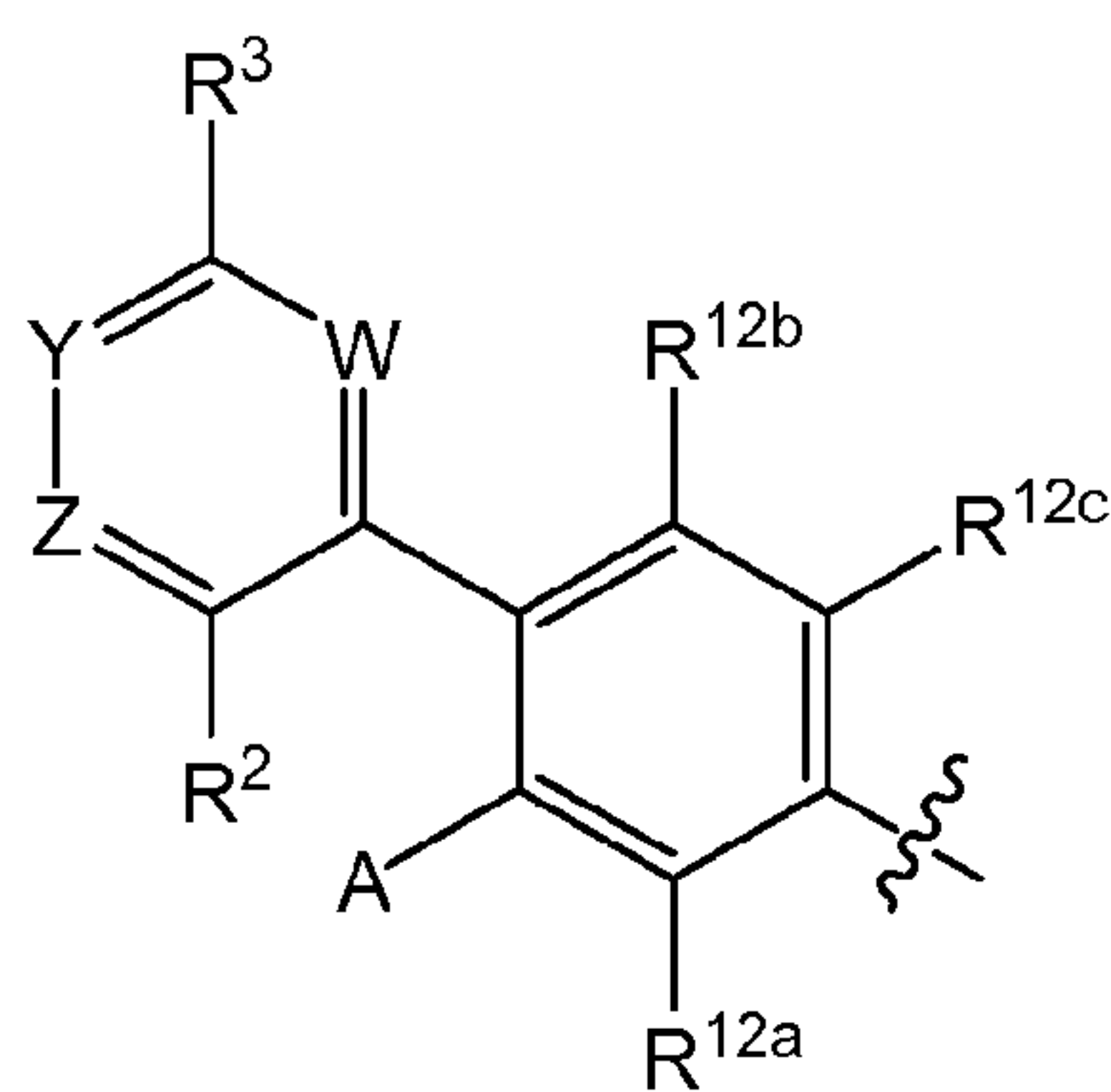
m is 0 or 1; and

q is selected from 0, 1, 2, or 3,

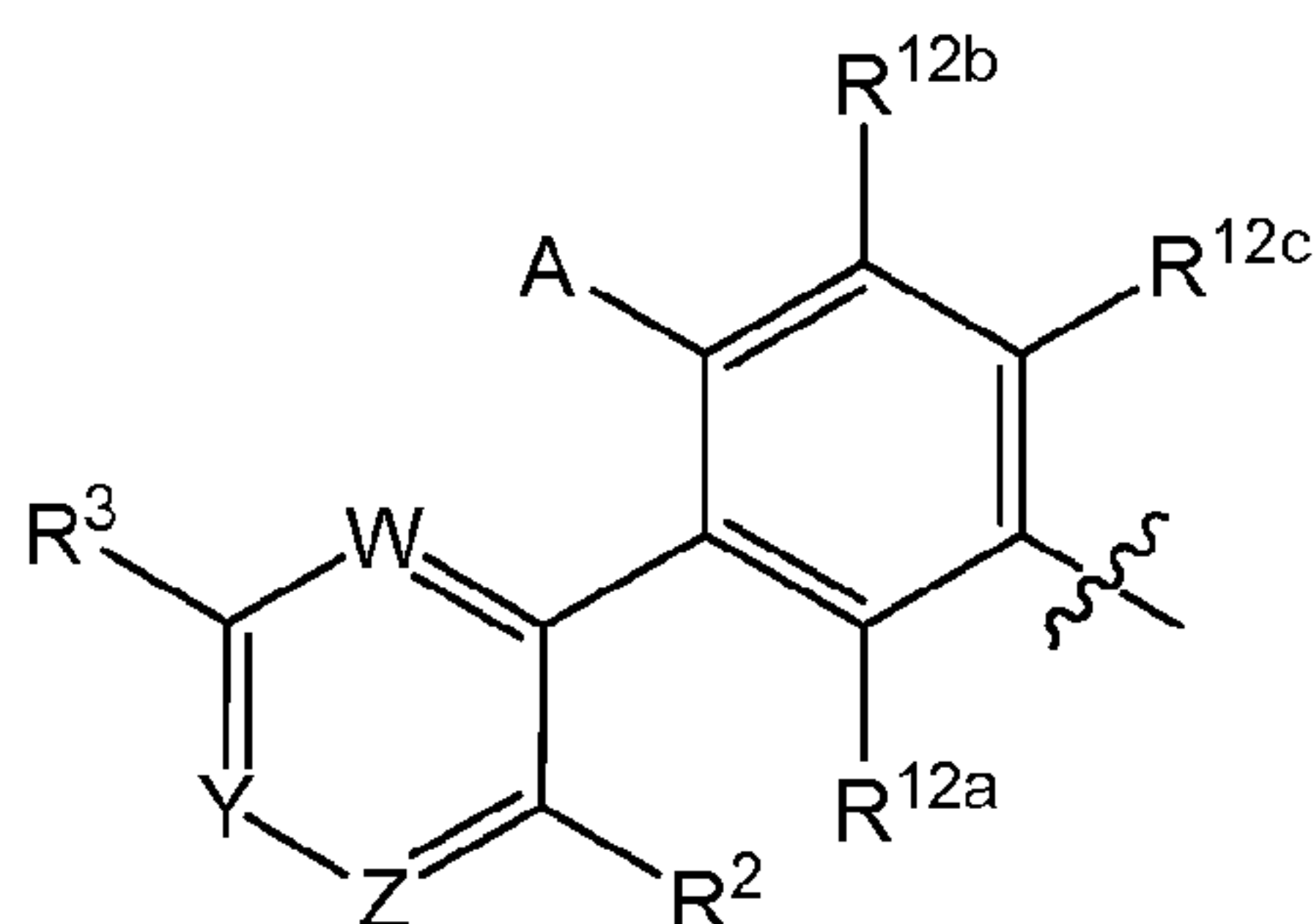
wherein the  indicates that the R^{1a} and $-C(=O)-O-R^1$ may be attached to either side of the ring to which the  is attached and either R or S stereochemistry is allowed.

[014] In some embodiments of the compound of formula **IA** or **IB**,

$Q-L^2-V-\text{[wavy line]}$ has the formula



or



wherein

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N; and further wherein Z is not N if R² is -F;

A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, and -O-(C₁-C₄)alkyl-aryl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -(C₁-C₂)alkyl, or unsubstituted -O-(C₁-C₂)alkyl;

R² is selected from -H, -F, -CF₃, -Cl, or -O-(C₁-C₆)alkyl;

R^3 is -H, -F, -Cl, -OH, -(C₁-C₄)alkyl, -O-(C₁-C₃)alkyl, or -S-(C₁-C₂)alkyl;

R^{12a} , R^{12b} , and R^{12c} are independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl; and

R^{13} is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl, and

the  through the bond indicates the point of attachment to L¹ if present or X if L¹ is absent.

In some such embodiments, R^2 is selected from -H, -F, -CF₃, or -O-(C₁-C₆)alkyl. Therefore, in some embodiments, R^2 is -F. In other embodiments, R^2 is -Cl.

[015] In some embodiments, the compound of any of the embodiments is a salt.

[016] In some embodiments, where two or more chiral centers are present, the compound is a mixture of diastereomers. In some such embodiments, the percentage of one diastereomer is greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99% based on the total diastereomers present in the mixture. In other embodiments, the compound is one specific diastereomer. In some embodiments, the compound is a mixture of enantiomers. In some such embodiments, the mixture comprises both enantiomers where the percent of one enantiomer with respect to both enantiomers is greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. In other embodiments, the compound is a pure single enantiomer. In some embodiments with a single chiral center, the compound comprises a stereomerically pure S-enantiomer. In other embodiments with a single chiral center, the compound comprises a stereomerically pure R-enantiomer. In yet other embodiments with a single chiral center, the compound comprises a mixture of S- and R-enantiomers.

[017] In another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent, or excipient, and a compound of any of the embodiments of the invention.

[018] In another aspect, the invention provides methods for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema. Such methods include administering to a subject in need thereof, a therapeutically

effective amount of a compound of any of the embodiments. In some such embodiments, the disease or condition is type II diabetes. In some embodiments, a compound of any of the embodiments is administered in combination with a second therapeutic agent. In some such embodiments, the second therapeutic agent is metformin, is a thiazolidinedione, is a DPP-IV inhibitor or is a GLP-1 analog. The second therapeutic agent may be administered before, during, or after administration of the compound of any of the embodiments.

[019] In another aspect, the invention provides methods for treating a disease or condition responsive to the modulation of GPR40. Such methods include administering to a subject in need thereof, a therapeutically effective amount of a compound of any of the embodiments.

[020] In another aspect, the invention provides methods for treating a disease or condition mediated, regulated, or influenced by pancreatic β cells. Such methods include administering to a subject in need thereof, a therapeutically effective amount of a compound of any of the embodiments.

[021] In another aspect, the invention provides methods for modulating GPR40 function in a cell. Such methods include contacting a cell with a compound of any of the embodiments.

[022] In another aspect, the invention provides methods for modulating GPR40 function. Such methods include contacting GPR40 with a compound of any of the embodiments.

[023] In another aspect, the invention provides methods for modulating circulating insulin concentration in a subject. Such methods include administering a compound of any of the embodiments to the subject. In some such embodiments, the circulating insulin concentration is increased in the subject after administration whereas in other such embodiments, the circulating insulin concentration is decreased in the subject after administration.

[024] In another aspect, the invention provides the use of a compound of any of the embodiments for treating a disease or condition or for preparing a medicament for treating a disease or condition where the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X,

cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema. In some such embodiments, the disease or condition is type II diabetes. The compounds of the invention may also be used to prepare medicaments that include a second therapeutic agent such as metformin, a thiazolidinedione, or a DPP-IV inhibitor.

[025] In another aspect, the invention provides the use of a compound of any of the embodiments for modulating GPR40 or for use in the preparation of a medicament for modulating GPR40.

[026] In another aspect, the invention provides a therapeutic composition that includes a compound of any of the embodiments and a second therapeutic agent such as those described herein, for example, metformin a thiazolidinedione, or a DPP-IV inhibitor, as a combined preparation for simultaneous, separate, or sequential use in the treatment of a disease or condition mediated by GPR40. In some such embodiments, the disease or condition is type II diabetes. In some embodiments, the compound of any of the embodiments and the second therapeutic agent are provided as a single composition, whereas in other embodiments they are provided separately as parts of a kit.

[027] In some embodiments, the invention provides a compound of any of the embodiments described herein for use as a medicament.

[028] In other embodiments, the invention provides a compound of any of the embodiments described herein for use in modulating GPR40.

[029] In still other embodiments, the invention provides a compound of any of the embodiments described herein for use in a method for treating a disease or condition selected from type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, or edema.

[030] The compounds of the invention may stimulate GLP-secretion. Cells contacted with compounds of the invention may increase GLP-1 secretion. Therefore, in some embodiments, the invention provides a method of stimulating GLP-1 secretion by cells. Such methods typically include contacting a cell capable of producing GLP-1 with

a compound of any of the embodiments set forth herein. Administration of the compounds of the invention to subjects may provide increased levels of GLP-1 in the blood plasma of such subjects. Therefore, in some embodiments, a compound of any of the embodiments described herein may be used to stimulate GLP-1 secretion and increase the blood plasma level of GLP-1 in a subject. In some such embodiments, the compounds of the invention both stimulate GLP-1 secretion and activate GPR40. Therefore, in some embodiments, the compounds of the invention both stimulate GLP-1 secretion and display incretin effect by activating GPR40.

[031] In some embodiments, the invention further provides a method for increasing GLP-1 levels in the blood plasma of a subject. Such methods typically include administering a compound of any of the embodiments to a subject. In some such embodiments, the subject is a diabetic patient. In other such embodiments, the subject is an obese patient. In some embodiments, the invention provides a method for stimulating weight loss in a subject. In such embodiments, a compound of any of the embodiments is administered to a subject in an effective amount to stimulate weight loss in the subject. The compounds of the invention may be administered in the fasted or non-fasted state. Therefore, in some embodiments, a compound of any of the embodiments is administered to a subject prior to a meal. In some such embodiments, the compound is administered 2 hours, 1 hour, 30 minutes, or 15 minutes before a meal. In other embodiments, a compound of any of the embodiments set forth herein is administered to a subject during a meal. In other embodiments, a compound of any of the embodiments described herein is administered to a subject within 2 hours, within 1 hour, within 30 minutes, or within 15 minutes of a meal.

[032] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Abbreviations and Definitions

[033] The terms “treat”, “treating” and “treatment”, as used herein, are meant to include alleviating or abrogating a condition or disease and/or its attendant symptoms. In some instances treating may also involve prevention of symptoms. The terms “prevent”, “preventing” and “prevention”, as used herein, refer to a method of delaying or precluding the onset of a condition or disease and/or its attendant symptoms, barring a

subject from acquiring a condition or disease, or reducing a subject's risk of acquiring a condition or disease.

[034] The term “therapeutically effective amount” refers to that amount of the compound that will elicit the biological or medical response of a tissue, system, or subject that is being sought. The term “therapeutically effective amount” includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated in a subject. The therapeutically effective amount in a subject will vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[035] The term “subject” is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[036] The terms “modulate”, “modulation” and the like refer to the ability of a compound to increase or decrease the function or activity of GPR40 either directly or indirectly. Inhibitors are compounds that, for example, bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction, such as, for instance, antagonists. Activators are compounds that, for example, bind to, stimulate, increase, activate, facilitate, enhance activation, sensitize or up regulate signal transduction, such as agonists for instance. Modulation may occur in vitro or in vivo.

[037] As used herein, the phrases “GPR40-mediated condition or disorder”, “disease or condition mediated by GPR40”, and the like refer to a condition or disorder characterized by inappropriate, for example, less than or greater than normal, GPR40 activity. A GPR40-mediated condition or disorder may be completely or partially mediated by inappropriate GPR40 activity. However, a GPR40-mediated condition or disorder is one in which modulation of GPR40 results in some effect on the underlying condition or disease (e.g., a GPR40 modulator results in some improvement in patient well-being in at least some patients). Exemplary GPR40-mediated conditions and disorders include cancer and metabolic disorders, e.g., diabetes, type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, ketoacidosis, hypoglycemia, thrombotic disorders,

metabolic syndrome, syndrome X and related disorders, e.g., cardiovascular disease, atherosclerosis, kidney disease, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, and edema.

[038] The term “alkyl”, by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which is fully saturated, having the number of carbon atoms designated (e.g., C₁-C₁₀ means one to ten carbons). Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, pentyl, cyclohexyl, (cyclohexyl)methyl, methylcyclohexyl, dimethylcyclohexyl, cyclopropyl, cyclopropylmethyl, methylcyclopropyl, cyclobutyl, cyclobutylmethyl, methylcyclobutyl, cyclopentyl, methylcyclopentyl, cyclopentylmethyl, dimethylcyclopentyl, and homologs and isomers thereof, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. Alkyl groups may be substituted or unsubstituted.

[039] The term “alkenyl”, by itself or as part of another substituent, means a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂-C₈ means two to eight carbons) and one or more double bonds. Examples of alkenyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), cyclopentenyl, cyclohexenyl, 5,5-dimethylcyclopentenyl, 6,6-dimethylcyclohexenyl, cycloheptenyl, cycloheptadienyl, and higher homologs and isomers thereof.

[040] The term “alkynyl”, by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂-C₈ means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, 1- and 3-propynyl, 3-butynyl, and higher homologs and isomers thereof.

[041] The term “alkoxy” refers to a group of formula –O-alkyl where alkyl has the definition provided above. An alkoxy group can have a specified number of carbon atoms. For example, a methoxy group (–OCH₃) is a C₁ alkoxy group. Alkoxy groups typically have from 1 to 10 carbon atoms. Examples of alkoxy group include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, and the like.

[042] The term “cycloalkyl” by itself, or in combination with other terms, represents, unless otherwise stated, a cyclic type of “alkyl” in which 3 or more carbon

atoms form a ring. Thus, the term “cycloalkyl” is meant to be included in the term “alkyl”. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. Cycloalkyl groups typically include from 3 to 14 or 3 to 10 ring members. Cycloalkyl groups may be monocyclic, bicyclic, or multicyclic. Therefore, in addition to the groups described above, cycloalkyl groups include norbornyl and adamantyl groups.

[043] The term “cycloalkenyl” by itself, or in combination with other terms, represents, unless otherwise stated, a cyclic type of “alkenyl” in which 3 or more carbon atoms form a ring that includes at least one carbon-carbon double bond. Thus, the term “cycloalkenyl” is meant to be included in the term “alkenyl”. Examples of cycloalkenyl include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Cycloalkenyl groups typically include from 3 to 14 or 3 to 10 ring members. Cycloalkenyl groups may be monocyclic, bicyclic, or multicyclic.

[044] The term “heterocyclyl” by itself or in combination with other terms, represents, unless otherwise stated, a ring system in which one or more ring members is a heteroatom selected from N, O, or S. The heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. A heterocyclyl group can also be attached to the remainder of the molecule through a carbon atom of the ring. Heterocyclyl groups typically include from 3 to 10 ring members of which 1, 2, or 3 are heteroatoms. Heterocyclyl groups can be saturated or may include some unsaturation. Heterocyclyl groups may also be substituted or unsubstituted. Examples of heterocyclyl groups include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, 4,5-dihydroisoxazol-3-yl, and the like.

[045] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any position of the heteroalkyl group. Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, and -CH₂-CH=N-OCH₃. Up to two heteroatoms may be consecutive, such as, for example, -

CH₂-NH-OCH₃. When a prefix such as (C₂-C₈) is used to refer to a heteroalkyl group, the number of carbons (2 to 8, in this example) is meant to include the heteroatoms as well. For example, a C₂-heteroalkyl group is meant to include, for example, -CH₂OH (one carbon atom and one heteroatom replacing a carbon atom) and -CH₂SH.

[046] To further illustrate the definition of a heteroalkyl group, where the heteroatom is oxygen, a heteroalkyl group is a oxyalkyl group. For instance, (C₂-C₅)oxyalkyl is meant to include, for example -CH₂-O-CH₃ (a C₃-oxyalkyl group with two carbon atoms and one oxygen replacing a carbon atom), -CH₂CH₂CH₂CH₂OH, and the like.

[047] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl”, are meant to include alkyl substituted with halogen atoms which can be the same or different, in a number ranging from one to (2m' + 1), where m' is the total number of carbon atoms in the alkyl group. For example, the term “halo(C₁-C₄)alkyl” is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Thus, the term “haloalkyl” includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with halogen atoms in a number ranging from two to (2m' + 1) halogen atoms). The term “perhaloalkyl” means, unless otherwise stated, alkyl substituted with (2m' + 1) halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term “perhalo(C₁-C₄)alkyl”, is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

[048] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatom ring members selected from the group consisting of N, O and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Heteroaryl groups can be unsubstituted or substituted. In some embodiments, a heteroaryl group includes 1 or 2 heteroatoms. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom or through a carbon atom of the ring. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 5-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl,

4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, dibenzofuryl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 5-benzothiazolyl, 2-benzoxazolyl, 5-benzoxazolyl, benzo[c][1,2,5]oxadiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1H-indazolyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl. Typically an aryl group refers to an aromatic group that includes from 6-10 ring members such that it is a (C₆-C₁₀)aryl group. Typically, heteroaryl groups include 5 to 10 ring members of which 1 or 2 is selected from O, N, or S.

[049] Preferably, the term “aryl” refers to a phenyl or naphthyl group which is unsubstituted or substituted. Preferably, the term “heteroaryl” refers to a pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, furyl, thienyl (thiophenyl), pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, indolyl, isoquinolyl, triazolyl, tetrazolyl, quinoxalyl, or quinolyl group which is unsubstituted or substituted.

[050] For brevity, the term “aryl” when used in combination with other terms (e.g., aryloxy, arylalkoxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term “arylalkyl” is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like). As another example, the term “aryl(C₁-C₄)alkoxy” is meant to include radicals in which an aryl group is attached to an alkyl group having 1 to 4 carbon atoms that is bonded to an O which is attached to the rest of the molecule. Examples include substituted and unsubstituted phenylmethoxy, phenylethoxy, phenylpropoxy, pyridylmethoxy, and the like.

[051] Each of the above terms (e.g., “alkyl,” “alkenyl,” “aryl,” “heterocyclyl” and “heteroaryl”) is meant to include both substituted and unsubstituted forms of the indicated radical, unless otherwise indicated. Preferred substituents for each type of radical are provided below.

[052] Substituents for the alkyl radicals (as well as those groups referred to as alkenyl, alkynyl, cycloalkyl, and heterocyclyl) can be a variety of groups selected from:

-OR', =O, =NR', =N-OR', -NR'R'', R', -SR', halogen, -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR'-SO₂NR''R''', -NR''CO₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -SiR'R''R''', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R, -CN, -(C₂-C₅) alkynyl, -(C₂-C₅) alkenyl, and -NO₂, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R', R'' and R''' each independently refer to hydrogen; unsubstituted (C₁-C₈)alkyl, (C₂-C₈)alkenyl, and heteroalkyl; unsubstituted aryl; unsubstituted heterocyclyl; heterocyclyl substituted with up to three unsubstituted (C₁-C₂)alkyl groups; aryl substituted with one to three halogens, unsubstituted (C₁-C₂)alkyl, -O-(C₁-C₄)alkyl, and -S-(C₁-C₄)alkyl groups; unsubstituted halo(C₁-C₄)alkyl; unsubstituted -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl; unsubstituted -(C₁-C₄)alkyl-aryl; or unsubstituted aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl.

[053] Typically, an alkyl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the present invention. More preferably, an alkyl radical will be unsubstituted or monosubstituted. Most preferably, an alkyl radical will be unsubstituted. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as trihaloalkyl (e.g., -CF₃ and -CH₂CF₃).

[054] Preferred substituents for the alkyl radicals are selected from: -OR', =O, -NR'R'', -SR', halogen, -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'-SO₂NR''R''', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R, -CN, -(C₂-C₅) alkynyl, -(C₂-C₅) alkenyl, R', and -NO₂, where R' and R'' are as defined above. Further preferred substituents are selected from: -OR', =O, -NR'R'', halogen, -OC(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'-SO₂NR''R''', -SO₂R', -SO₂NR'R'', -NR''SO₂R, -CN, -(C₂-C₅) alkynyl, -(C₂-C₅) alkenyl, and -NO₂.

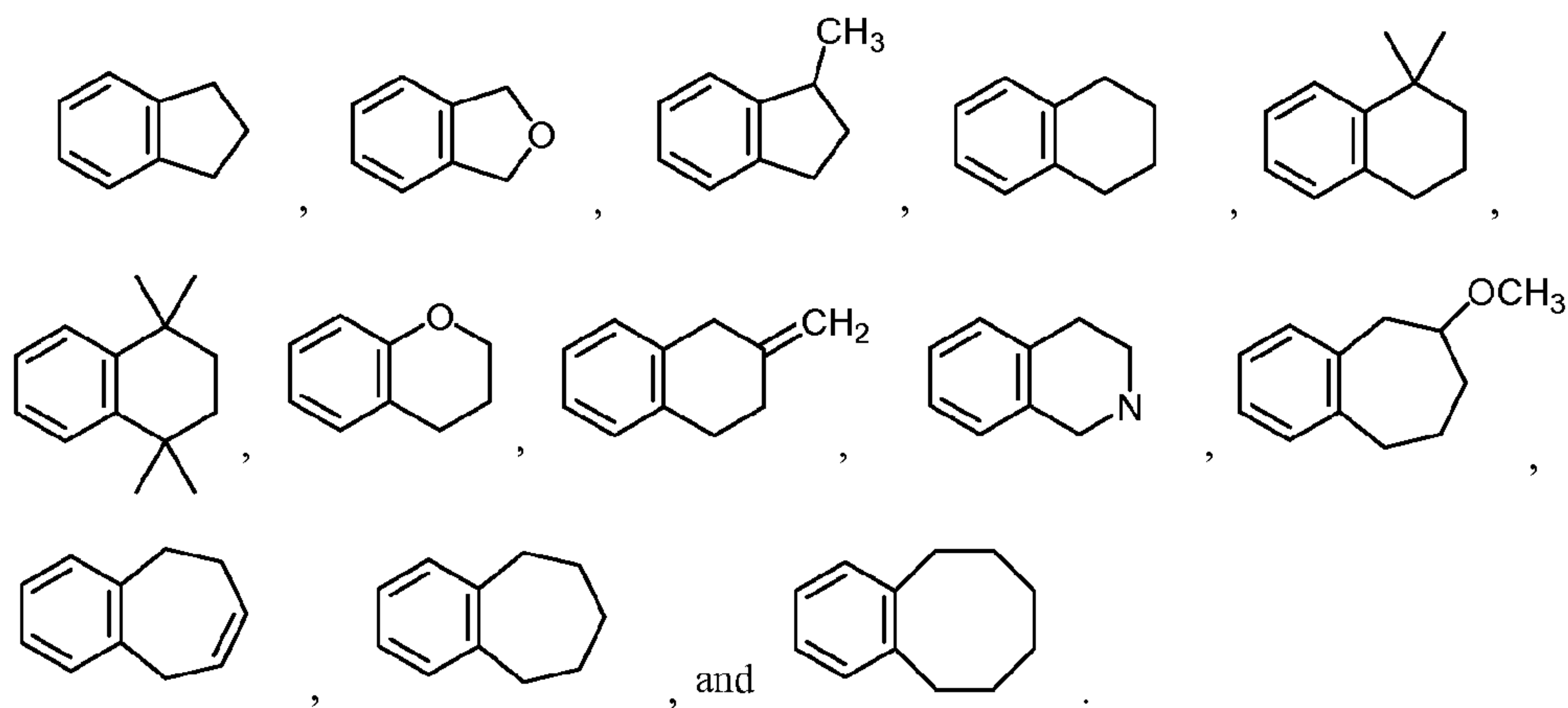
[055] Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR''R''', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a

number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, unsubstituted (C₁-C₈)alkyl and heteroalkyl; unsubstituted aryl and heteroaryl; unsubstituted aryl-(C₁-C₄)alkyl; unsubstituted aryl-O-(C₁-C₄)alkyl; unsubstituted -(C₂-C₅)alkynyl; and unsubstituted -(C₂-C₅) alkenyl.

[056] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂-, or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'-, or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted (C₁-C₆)alkyl. Otherwise, R' is as defined above.

[057] As used herein, the term “heteroatom” is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[058] As used herein, the term “benzo-fused cycloalkyl” is meant to include bicyclic structures in which benzene is fused with a cycloalkane (or cycloheteroalkane). To illustrate, in some embodiments, a “benzo-fused cycloalkyl ring” includes the following structures:



As used herein, the term “heteroaryl-fused (C₅-C₈)cycloalkane ring” has the same meaning as “benzo-fused (C₅-C₈)cycloalkane ring” except the benzene of the benzo-fused (C₅-C₈)cycloalkane ring is replaced with a six-membered heteroaryl ring comprising 1 or 2 nitrogen (N) atoms. As indicated in the structures shown above, the (C₅-C₈)cycloalkane of benzo-fused (C₅-C₈)cycloalkane rings and heteroaryl-fused (C₅-C₈)cycloalkane ring may include only carbon atoms, but may also include one or more heteroatoms. Such heteroatoms typically are selected from O, N, or S. In benzo-fused cycloalkyl and heteroaryl-fused cycloalkyl groups, the cycloalkyl group may be bonded to either the L¹, if present, or X variable or may be bonded to the L², if present, or Q variable. The same is true with respect to the aromatic or heteroaromatic part of the benzo-fused cycloalkyl and heteroaryl-fused cycloalkyl groups.

[059] The term “pharmaceutically acceptable salt” is meant to include a salt of the active compound which is prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compound described herein. When a compound of the invention contains relatively acidic functionalities, a base addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When a compound of the invention contains relatively basic functionalities, an acid addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginine and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge et al. (1977) J. Pharm. Sci. 66:1-19). Certain specific compounds of the invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[060] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the invention.

[061] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the invention which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[062] As used herein, "solvate" refers to a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate. In some embodiments, the compounds, salts of the compounds, tautomers of the compound, and salts of the tautomers may include a solvent or water such that the compound or salt is a solvate or hydrate.

[063] Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the invention and are intended to be within the scope of the invention.

[064] As known by those skilled in the art, certain compounds of the invention may exist in one or more tautomeric forms. Because one chemical structure may only be used to represent one tautomeric form, it will be understood that convenience, referral to a

compound of a given structural formula includes tautomers of the structure represented by the structural formula.

[065] Certain compounds of the invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the invention. Furthermore, atropisomers and mixtures thereof such as those resulting from restricted rotation about two aromatic or heteroaromatic rings bonded to one another are intended to be encompassed within the scope of the invention.

[066] As used herein and unless otherwise indicated, the term “stereoisomer” or “stereomerically pure” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. A bond drawn with a wavy line indicates that both stereoisomers are encompassed.

[067] Various compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers, mixtures of diastereomers or enantiomerically or optically pure compounds. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques,

J., et al., Enantiomers, Racemates and Resolutions (Wiley-Interscience, New York, 1981); Wilen, S. H., et al. (1997) Tetrahedron 33:2725; Eliel, E. L., Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S. H., Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[068] The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Radiolabeled compounds are useful as therapeutic or prophylactic agents, research reagents, e.g., GPR40 assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention. For example, if a variable is said to be H, this means that variable may also be deuterium (D) or tritium (T).

5.2 Embodiments of the Invention

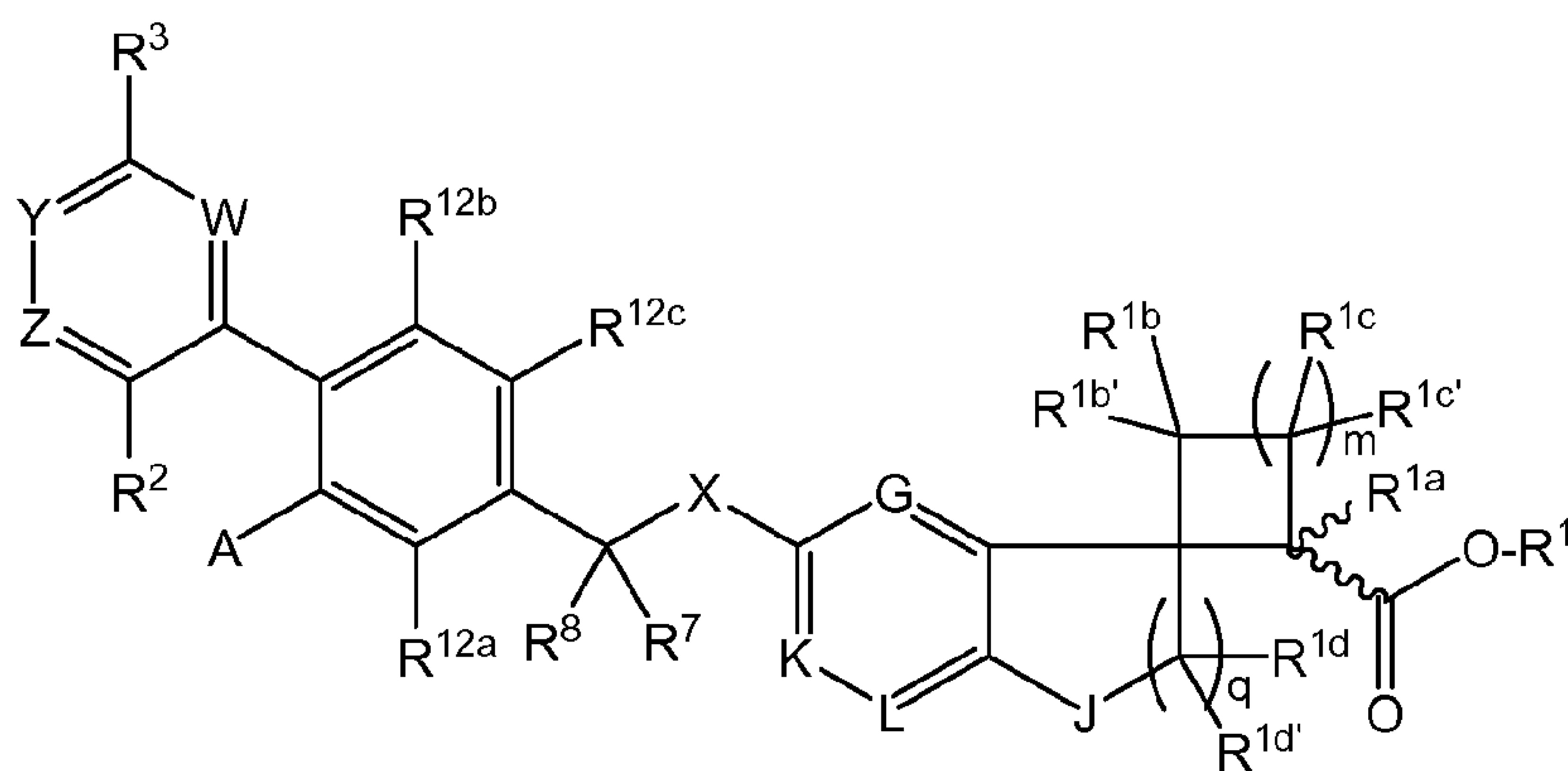
[069] In one aspect, a class of compounds that modulates GPR40 is described herein. Depending on the biological environment (e.g., cell type, pathological condition of the subject, etc.), these compounds can modulate, e.g., activate or inhibit, the actions of GPR40. By modulating GPR40, the compounds find use as therapeutic agents capable of regulating insulin levels in a subject. The compounds find use as therapeutic agents for modulating diseases and conditions responsive to modulation of GPR40 and/or mediated by GPR40 and/or mediated by pancreatic β cells. As noted above, examples of such diseases and conditions include diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, cancer, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, ketoacidosis, hypoglycemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, nephropathy, thrombotic disorders, diabetic neuropathy, diabetic retinopathy, dermatopathy, dyspepsia and edema. Additionally, the compounds are useful for the treatment and/or prevention of complications of these diseases and disorders (e.g., type II diabetes, sexual dysfunction, dyspepsia and so forth).

[070] While the compounds of the invention are believed to exert their effects by interacting with GPR40, the mechanism of action by which the compounds act is not a limiting embodiment of the invention.

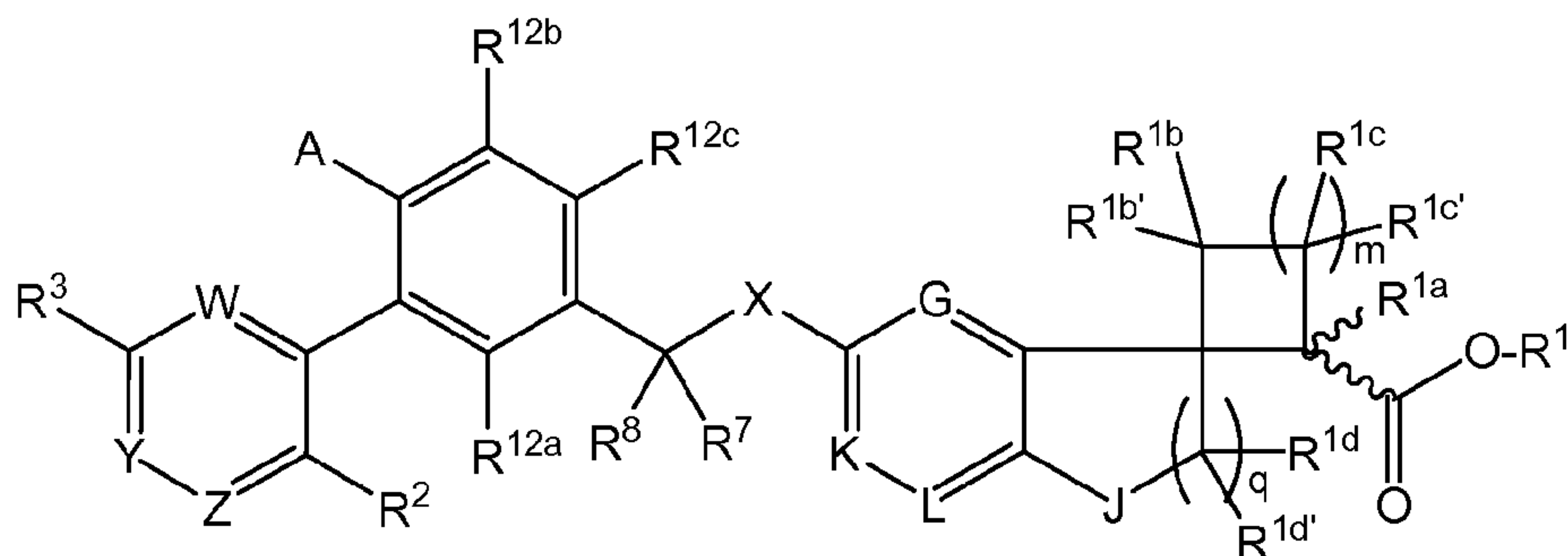
[071] Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein.

5.2.1 Compounds

[072] In one aspect, the present invention provides a compound having the formula **I'A** or **I'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. Compounds of formula **I'A** or **I'B** have the following structures:



I'A



I'B

where

G is selected from N or CR^{11a};

K is selected from N or CR^{11b};

L is selected from N or CR^{11c};

wherein 0 or 1 of G, L, and K is N;

X is O, S, or NR^a wherein R^a is selected from -H or -(C₁-C₆) alkyl groups;

J is selected from O, S, NR^b, CR^cR^d, C(=O), or -C(=O)-NR^b-; wherein R^b is selected from H and (C₁-C₄)alkyl, and further wherein R^c and R^d are independently selected from H, F, and (C₁-C₄)alkyl;

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N; and further wherein Z is not N if R² is -F; and A and W, when W is C, may join together to form a ring having 5 to 7 ring members of which 0 or 1 is a heteroatom selected from N, O, or S, and further wherein the ring having 5 to 7 ring members is optionally substituted with -(C₁-C₈)alkyl, -(C₁-C₈)alkenyl, -OH, -O-(C₁-C₈)alkyl, -O-(C₁-C₈)alkenyl, or halo;

A is selected from -H, -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, and -O-(C₁-C₄)alkyl-aryl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -(C₁-C₂)alkyl, or unsubstituted -O-(C₁-C₂)alkyl;

R¹ is H or -(C₁-C₆)alkyl;

R^{1a} is selected from -H and -(C₁-C₄)alkyl;

R^{1b} is selected from -H and -(C₁-C₄)alkyl;

R^{1b'} is selected from -H and -(C₁-C₄)alkyl;

R^{1c} is selected from -H and -(C₁-C₄)alkyl;

R^{1c'} is selected from -H and -(C₁-C₄)alkyl;

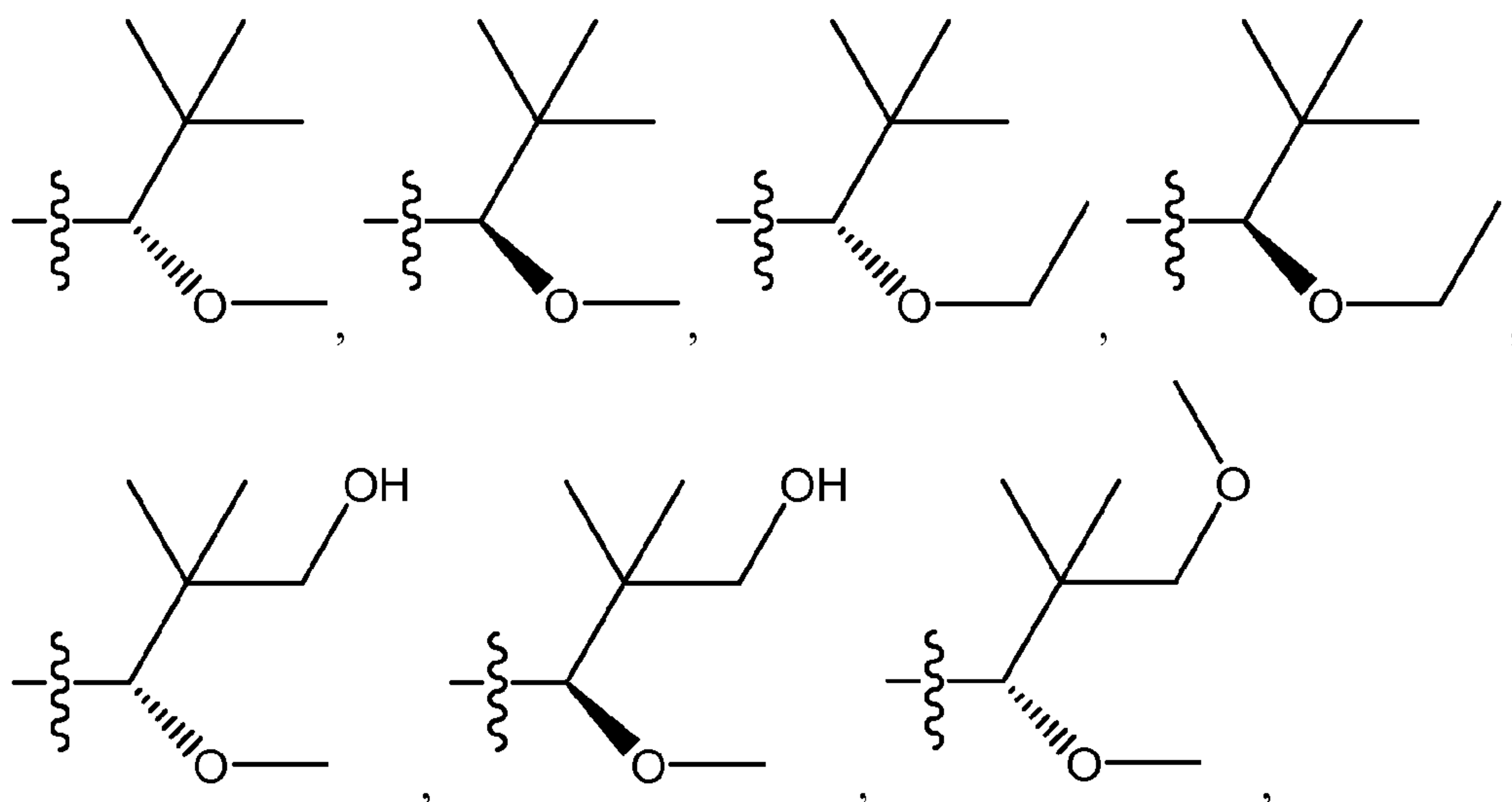
R^{1d} is in each instance independently selected from -H, -F, and -(C₁-C₄)alkyl;
 $R^{1d'}$ is in each instance independently selected from -H, -F, and -(C₁-C₄)alkyl;
 R^2 is selected from -H, -F, -CF₃, -Cl, or -O-(C₁-C₆)alkyl;
 R^3 is -H, -F, -Cl, -OH, -(C₁-C₄)alkyl, -O-(C₁-C₃)alkyl, or -S-(C₁-C₂)alkyl;
 R^7 and R^8 are independently selected from -H and -(C₁-C₄)alkyl;
 R^{11a} , R^{11b} , and R^{11c} are independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O(C₁-C₄)alkyl;
 R^{12a} , R^{12b} , and R^{12c} are independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O(C₁-C₄)alkyl;
 R^{13} is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl;
m is 0 or 1; and
q is selected from 0, 1, 2, or 3,

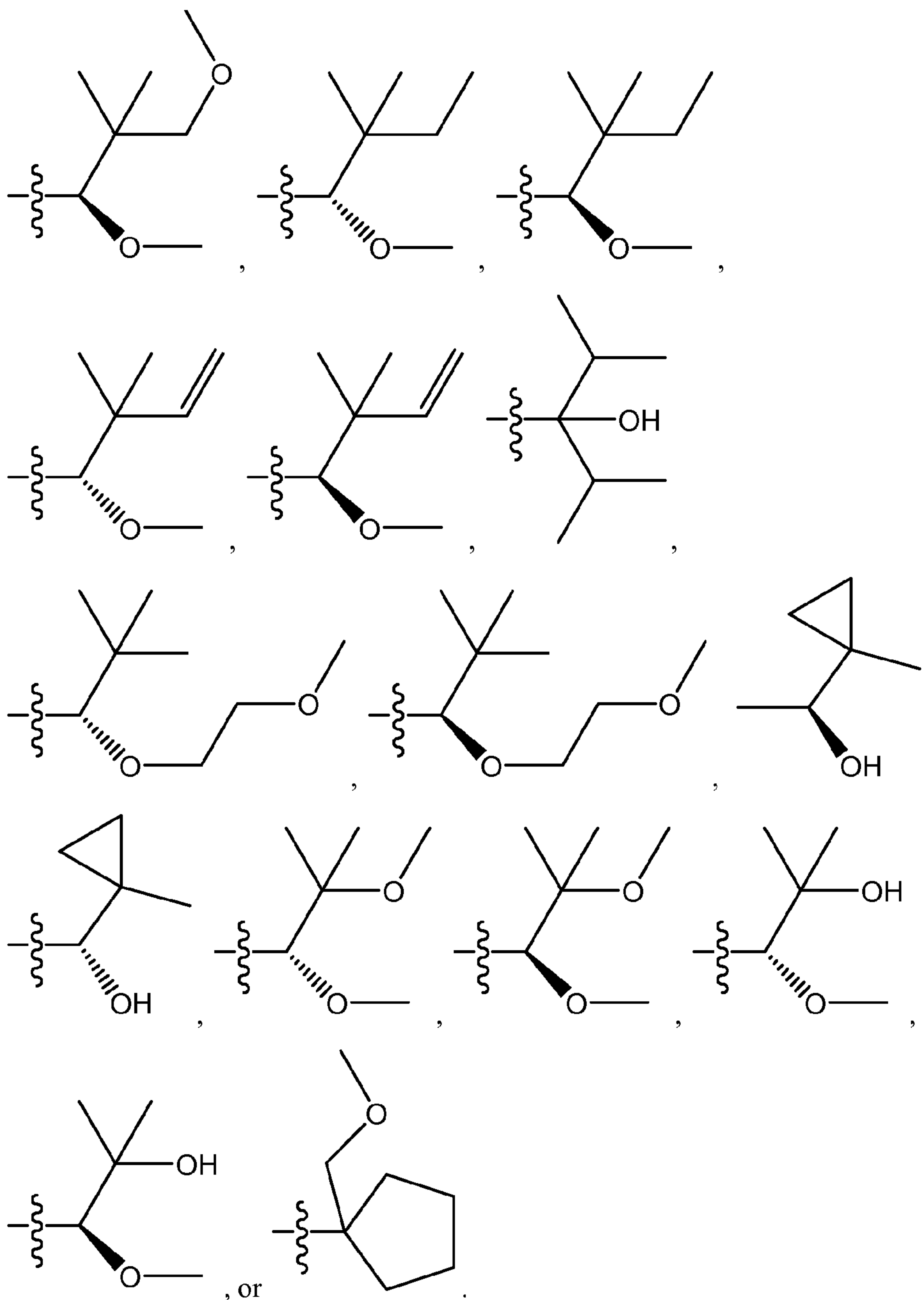
wherein the  indicates that the R^{1a} and -C(=O)-O- R^1 may be attached to either side of the ring to which the  is attached and either R or S stereochemistry is allowed.

[073] In some embodiments of the compound of formula **I'A** or **I'B**, A is A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-

[074] In some embodiments, A is selected from $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, -O- (C_4-C_{12}) alkyl, -O- (C_4-C_{12}) alkenyl, a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups, a $-(C_1-C_4)$ alkyl-heterocyclyl wherein the heterocyclyl of the $-(C_1-C_4)$ alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups, or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups, further wherein the alkyl and alkenyl groups of $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-O-H, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, -O- (C_4-C_{12}) alkyl, or -O- (C_4-C_{12}) alkenyl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C_1-C_4)alkyl, -N((C_1-C_4)alkyl)₂, aryl, unsubstituted -O- (C_1-C_2) alkyl, or unsubstituted $-(C_1-C_2)$ alkyl. In some such embodiments, A is selected from $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, -O- (C_4-C_{12}) alkyl, or -O- (C_4-C_{12}) alkenyl, wherein the alkyl and alkenyl groups of $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-O-H, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, -O- (C_4-C_{12}) alkyl, or -O- (C_4-C_{12}) alkenyl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C_1-C_4)alkyl, -or N((C_1-C_4)alkyl)₂, unsubstituted -O- (C_1-C_2) alkyl, or unsubstituted $-(C_1-C_2)$ alkyl. In some such embodiments, A is selected from $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, wherein the alkyl and alkenyl groups of $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-$

C₁₂)alkenyl-OH, are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -OH, unsubstituted -O-(C₁-C₂)alkyl, or unsubstituted -(C₁-C₂)alkyl. In some such embodiments, A is selected from -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkenyl-OH, wherein the alkyl and alkenyl groups of -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, or -(C₃-C₁₂)alkenyl-OH, are unsubstituted or are substituted with 1 to 4 substituent selected from -F, -OH, unsubstituted -O-(C₁-C₂)alkyl, or unsubstituted -(C₁-C₂)alkyl. In some such embodiments, A is a 5 to 7 membered cycloalkyl or cycloalkenyl group comprising from 1 to 4 methyl groups. In other embodiments, A is a -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, or -(C₃-C₁₂)alkenyl-OH. In some embodiments, each of the alkyl and alkenyl groups of the -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, or -(C₃-C₁₂)alkenyl-OH are unsubstituted whereas in other embodiments, each is substituted with 1 to 4 substituents selected from -OH, unsubstituted -O-(C₁-C₂)alkyl, or unsubstituted -(C₁-C₂)alkyl. In some embodiments, A is a -(C₄-C₈)alkyl-O-(C₁-C₂)alkyl, -(C₄-C₈)alkyl-OH, -(C₄-C₈)alkenyl-O-(C₁-C₂)alkyl, or -(C₄-C₈)alkenyl-OH and each of the alkyl and alkenyl groups of -(C₄-C₈)alkyl-O-(C₁-C₂)alkyl, -(C₄-C₈)alkyl-OH, -(C₄-C₈)alkenyl-O-(C₁-C₂)alkyl, or -(C₄-C₈)alkenyl-OH are unsubstituted or are substituted with 1 substituent selected from -OH, unsubstituted -O-(C₁-C₂)alkyl, or unsubstituted -(C₁-C₂)alkyl. In some such embodiments, at least one of the alkyl or alkenyl groups is branched or comprises a C₃-C₇ cycloalkyl ring. Therefore, in some embodiments, A is selected from

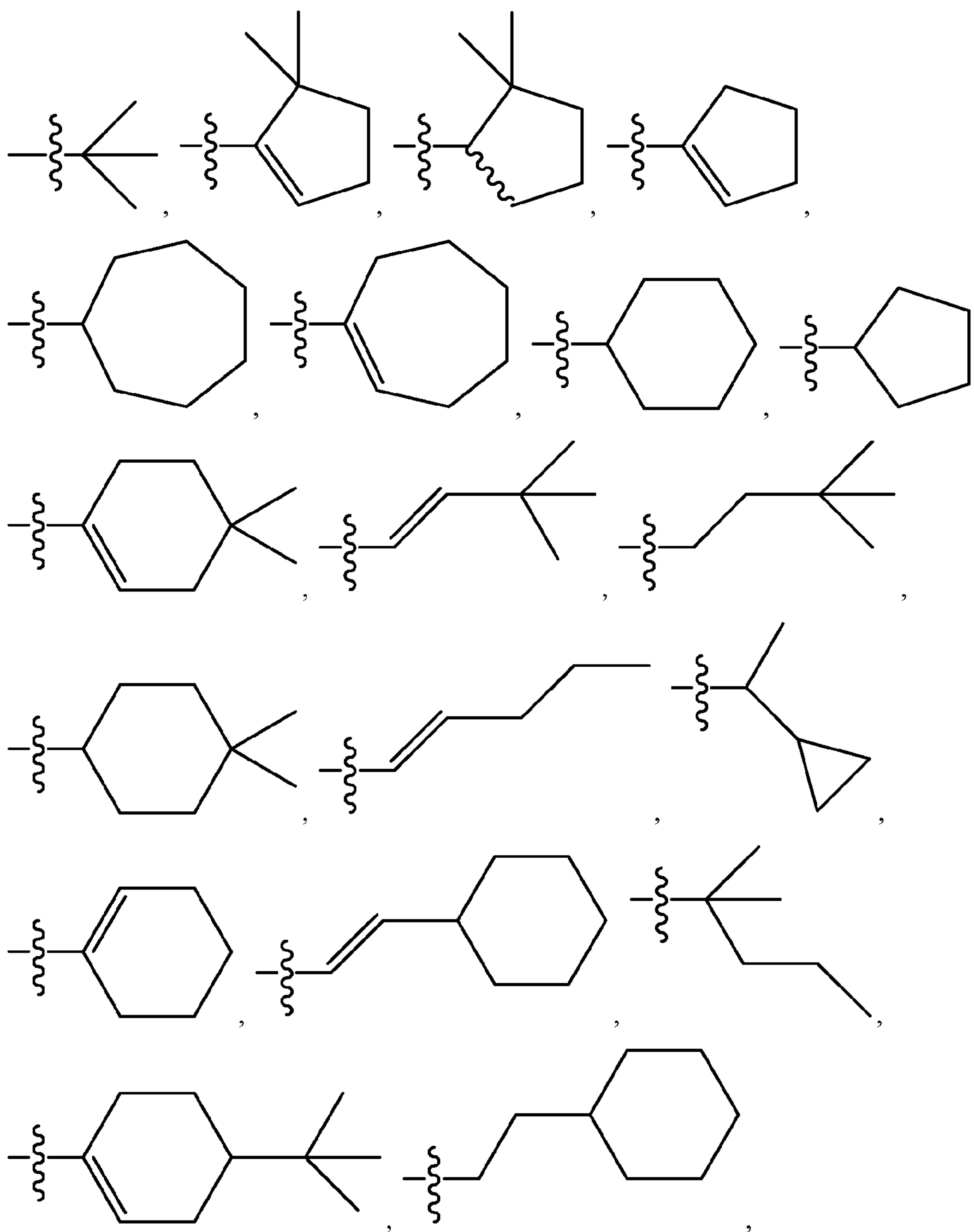


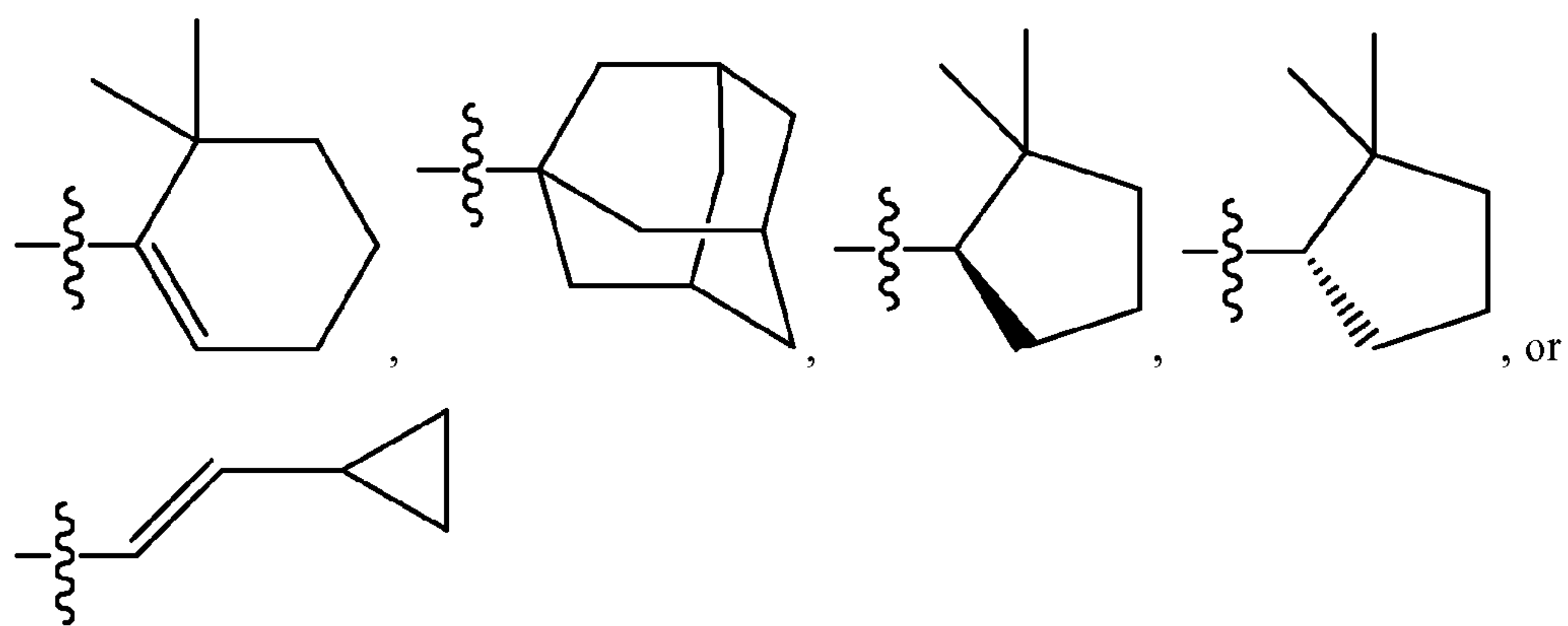


[075] In some embodiments, A is selected from (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, or -O-(C₁-C₄)alkyl-aryl.

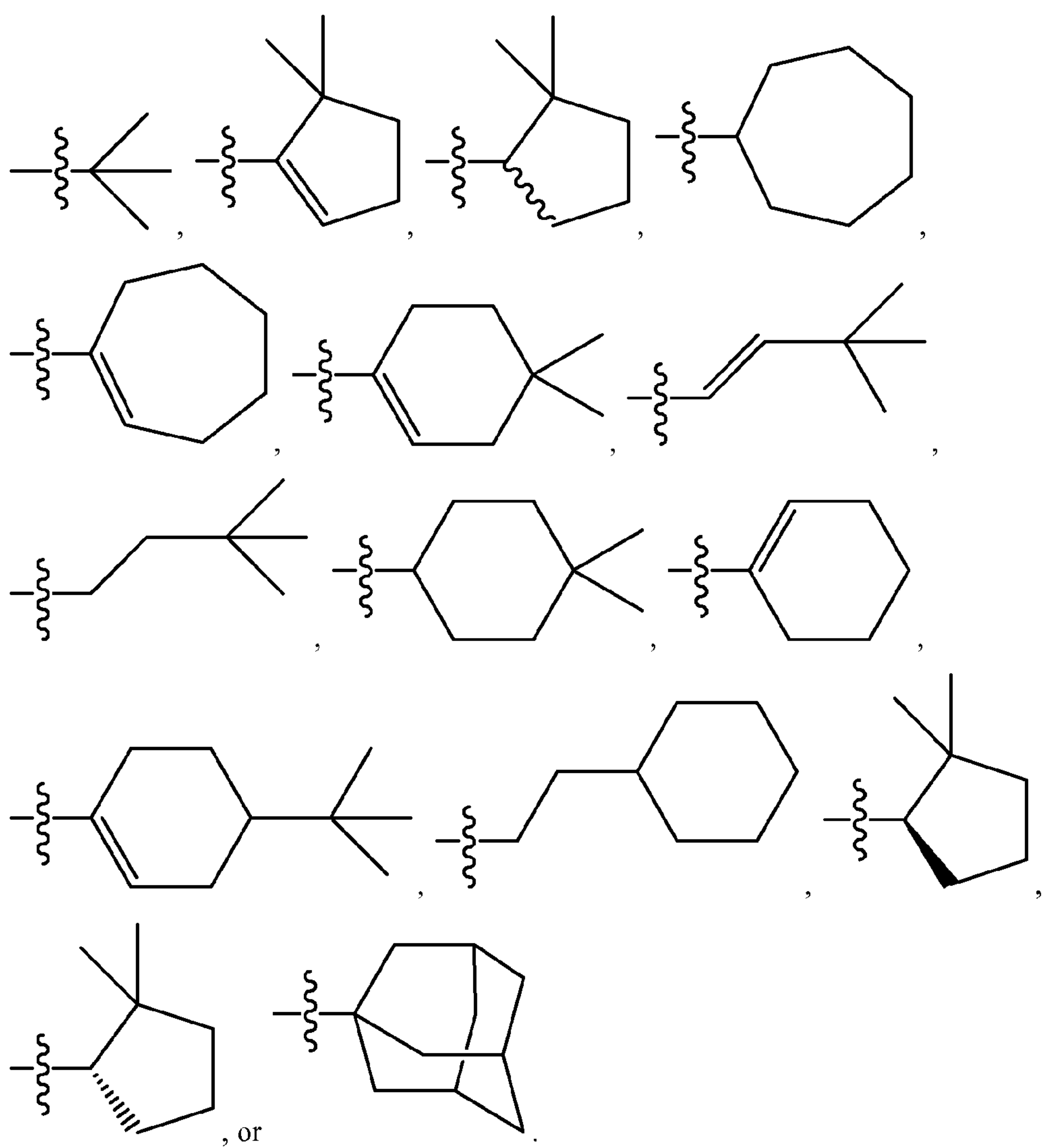
[076] In some embodiments, A is selected from a branched (C₄-C₁₀)alkyl group, a (C₄-C₁₀)alkenyl group, a bicyclic (C₇-C₁₂)alkyl group, an unsubstituted or a substituted (C₅-C₇)cycloalkyl group, or an unsubstituted or a substituted (C₅-

C₇)cycloalkenyl group. In some embodiments, A is an unsubstituted (C₅-C₇)cycloalkyl group, a (C₅-C₇)cycloalkyl group substituted with 1, 2, 3, or 4 methyl groups, an unsubstituted (C₅-C₇)cycloalkenyl group, or a (C₅-C₇)cycloalkenyl group substituted with 1, 2, 3, or 4 methyl groups. In some such embodiments, R³ is methoxy. In some such embodiments, R² is H whereas in other such embodiments, R² is F. In some such embodiments, A is selected from



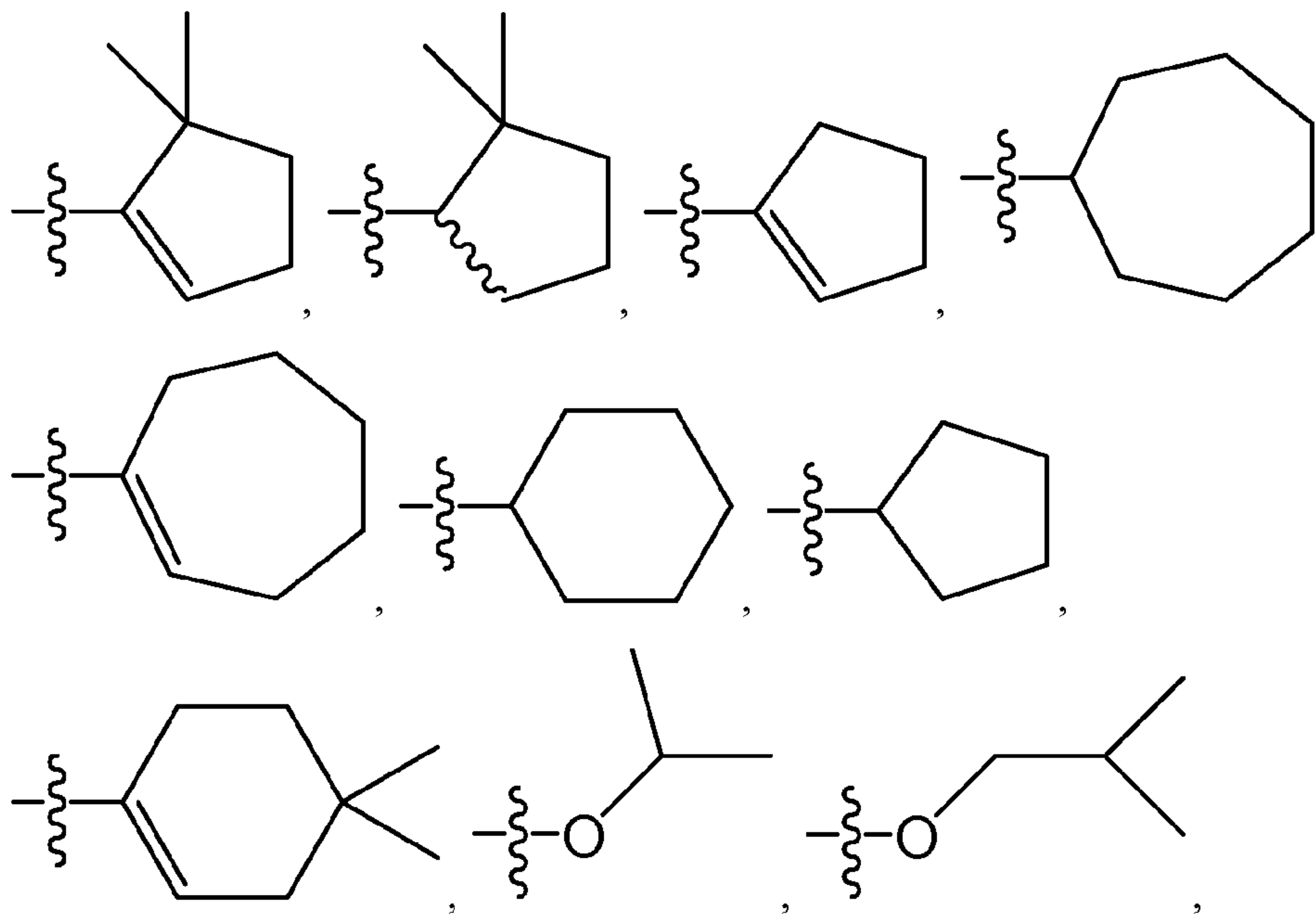


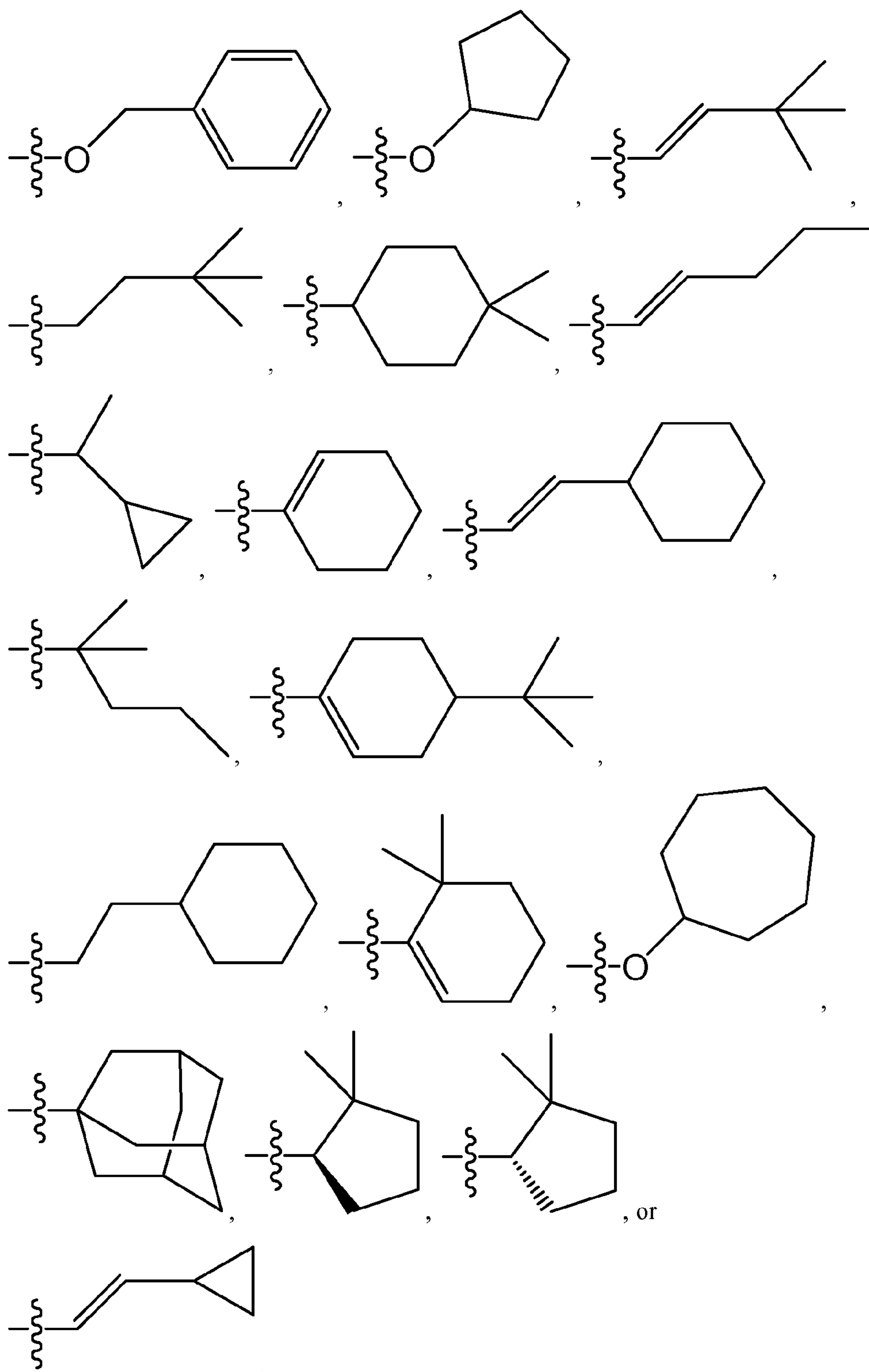
In some such embodiments, A is selected from



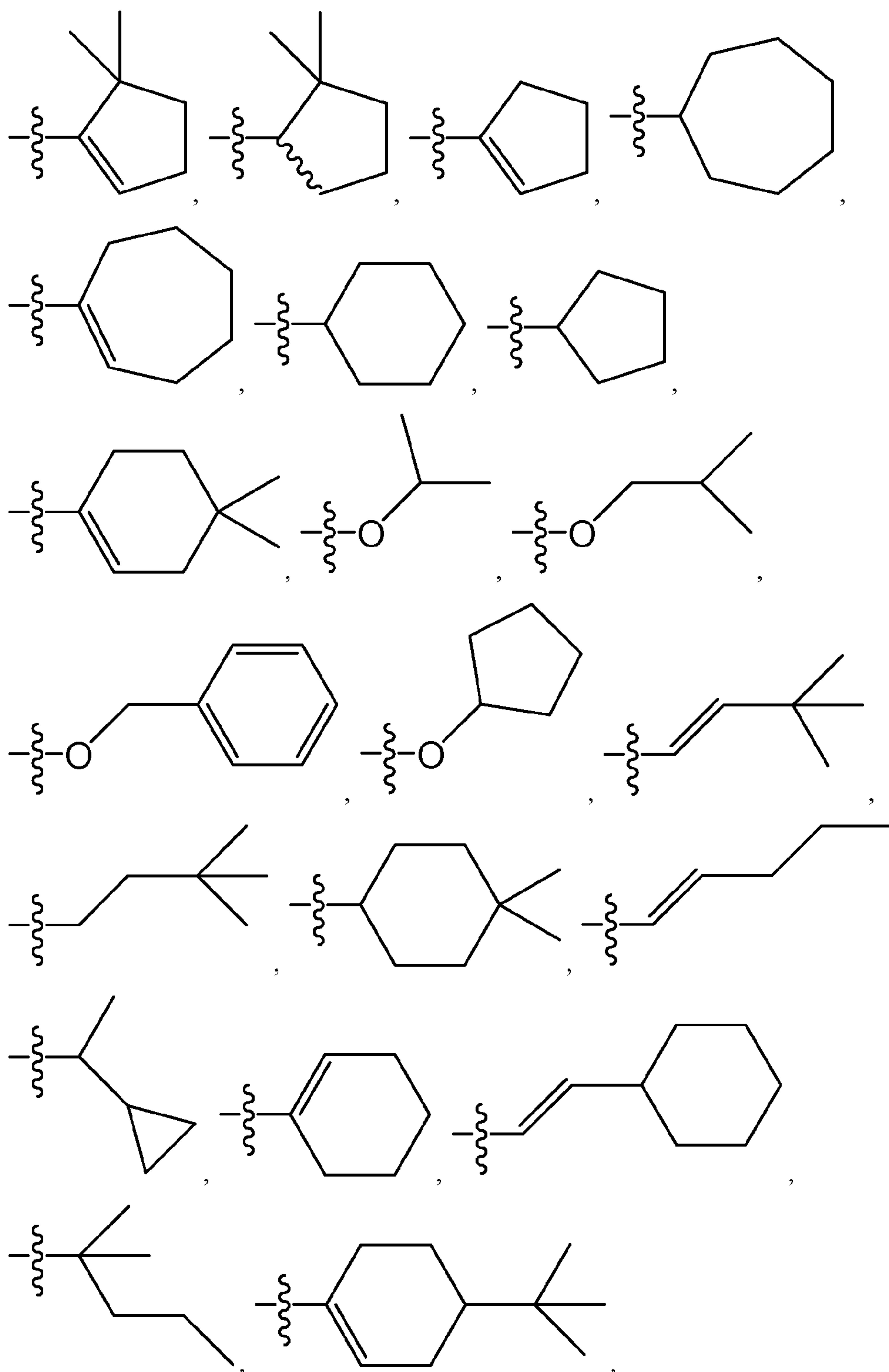
[077] In some embodiments, A is selected from (C₃-C₁₀)alkyl or (C₄-C₁₀)alkenyl. In some such embodiments, A is t-butyl. In other such embodiments, A is an unsubstituted or optionally substituted cyclopentyl, cyclohexyl, or cycloheptyl group. In some such embodiments, A is an unsubstituted cyclopentyl, cyclohexyl, or cycloheptyl group. In some such embodiments, A is a cyclopentyl, cyclohexyl, or cycloheptyl group optionally substituted with 1, 2, 3, or 4 (C₁-C₄)alkyl groups. In some such embodiments, A is a cyclopentyl, cyclohexyl, or cycloheptyl group substituted with a t-butyl group. In other such embodiments A is a cyclopentyl, cyclohexyl, or cycloheptyl group substituted with 1 or 2 methyl groups. In some such embodiments, A is an unsubstituted or optionally substituted cyclopentenyl, cyclohexenyl, or cycloheptenyl group. In some such embodiments, A is an unsubstituted cyclopentenyl, cyclohexenyl, or cycloheptenyl group. In some such embodiments, A is a cyclopentenyl, cyclohexenyl, or cycloheptenyl group optionally substituted with 1, 2, 3, or 4 (C₁-C₄)alkyl groups. In some such embodiments, A is a cyclopentenyl, cyclohexenyl, or cycloheptenyl group substituted with a t-butyl group. In other such embodiments A is a cyclopentenyl, cyclohexenyl, or cycloheptenyl group substituted with 1 or 2 methyl groups.

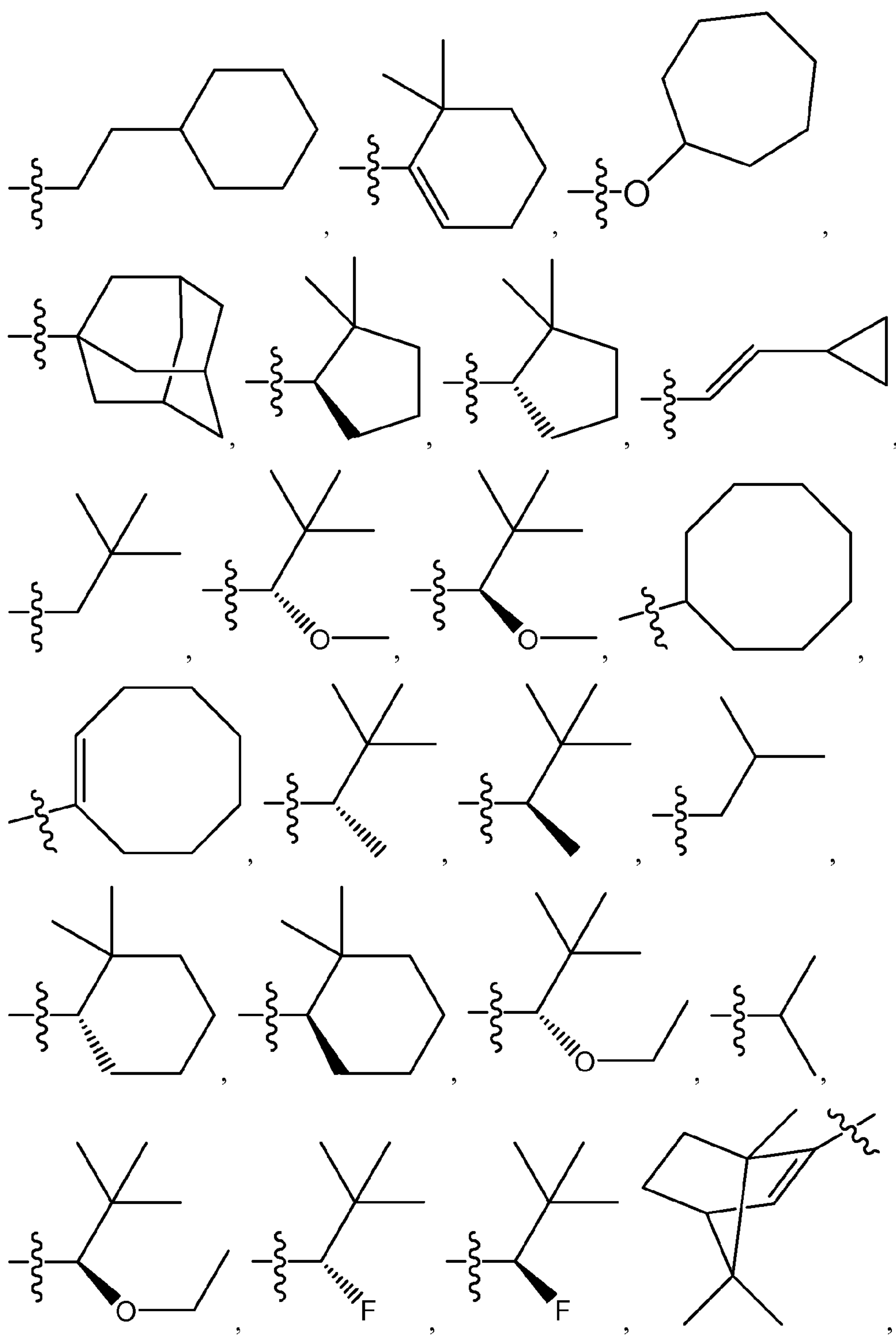
[078] In some embodiments, A is selected from

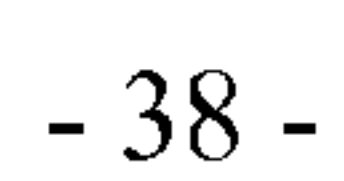


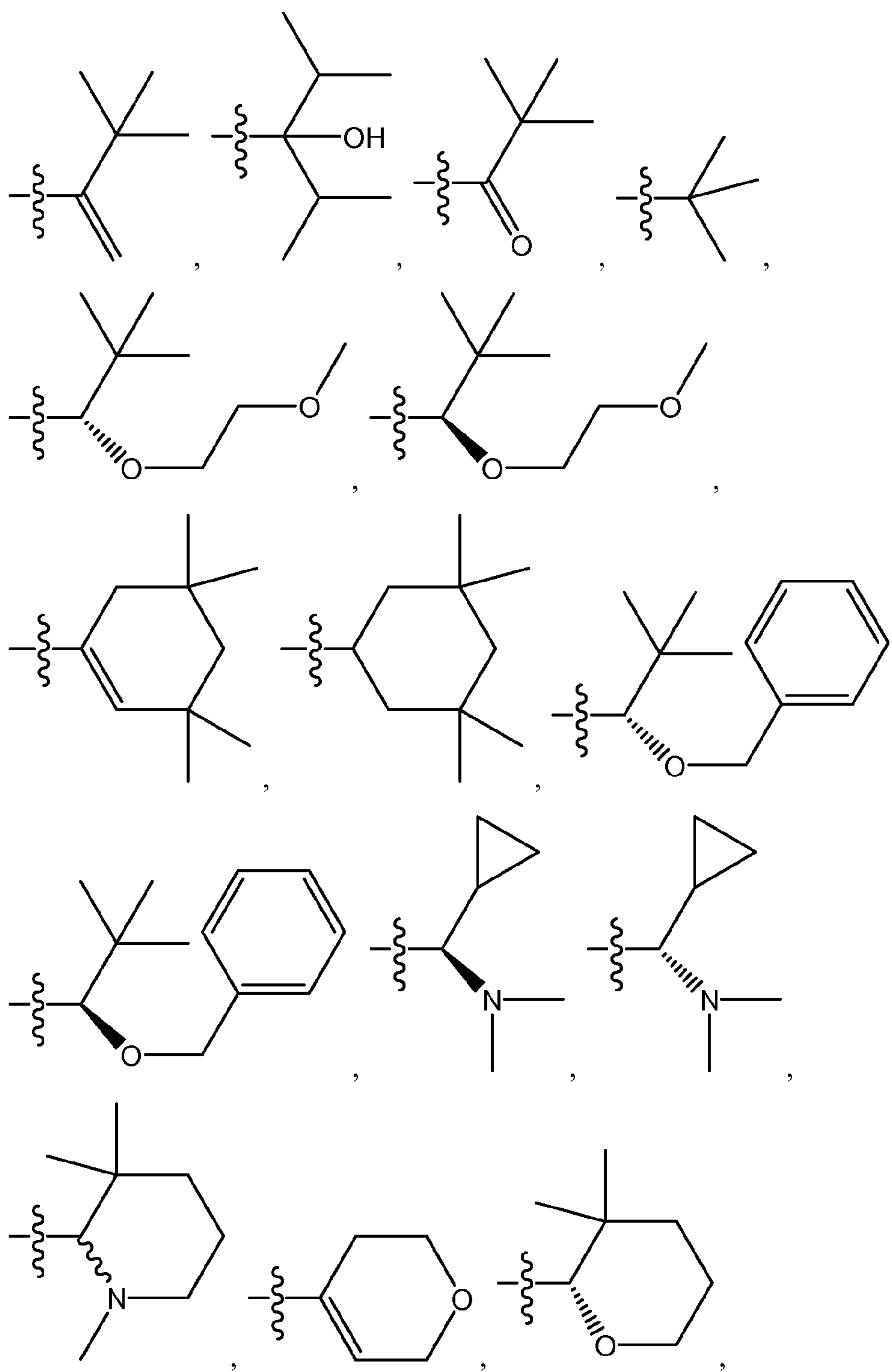


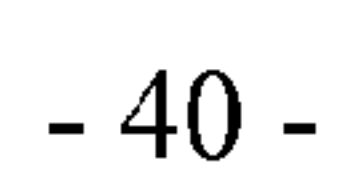
[079] In some embodiments, A is selected from any one or more of

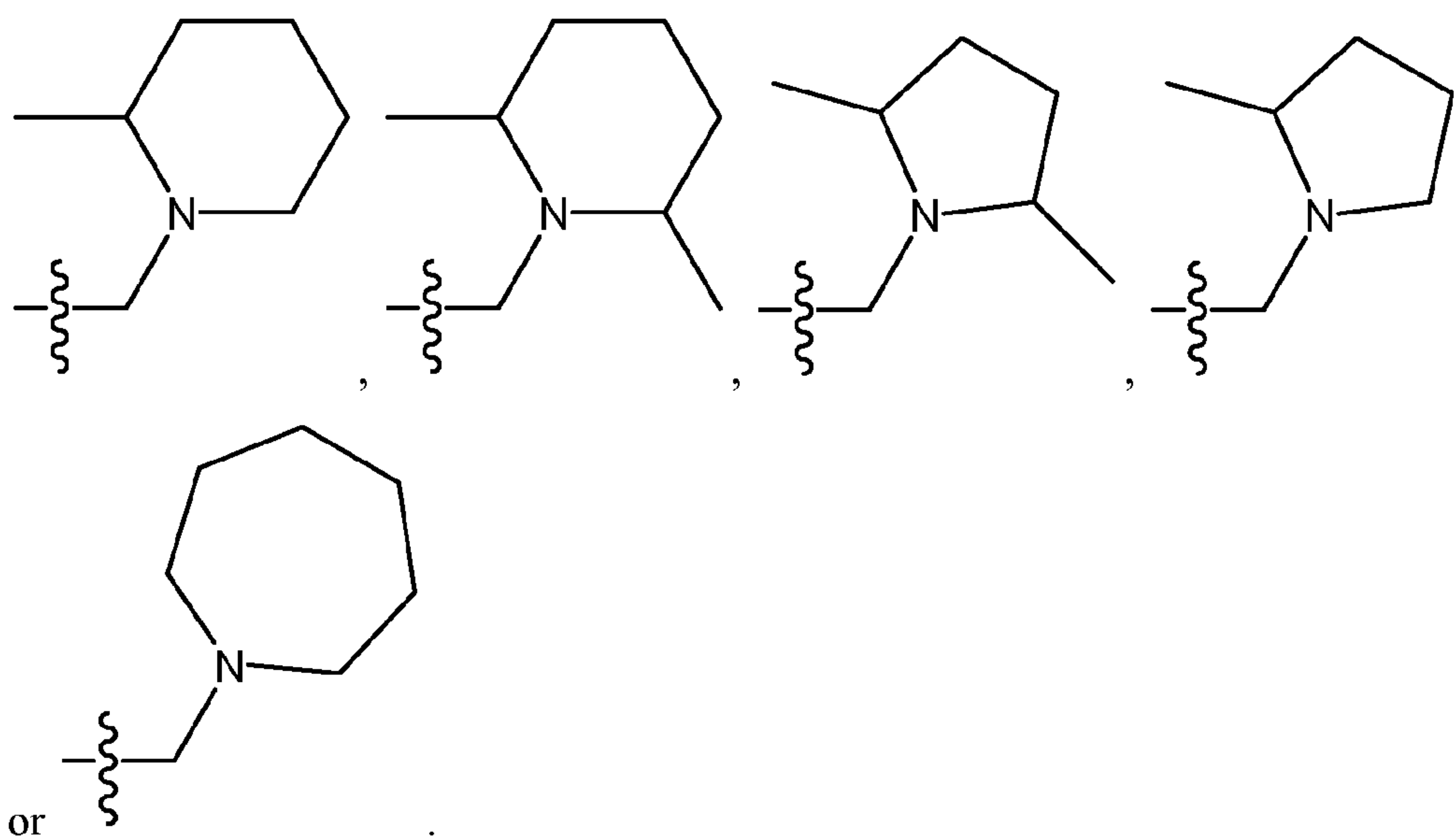






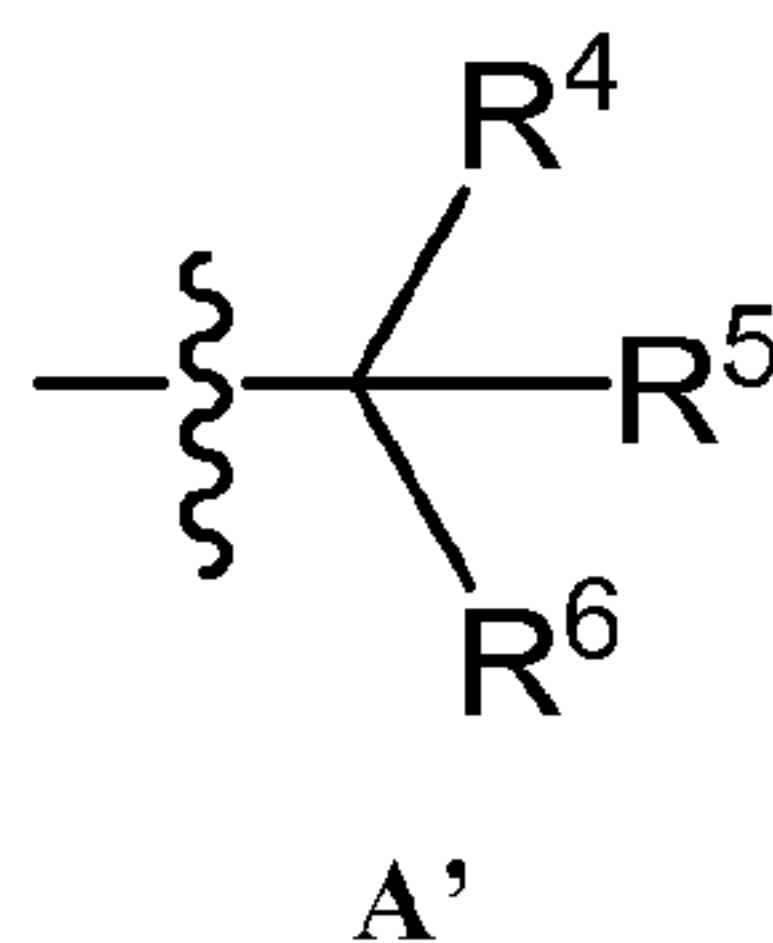






[080]

In some embodiments, A is a group of formula A'.



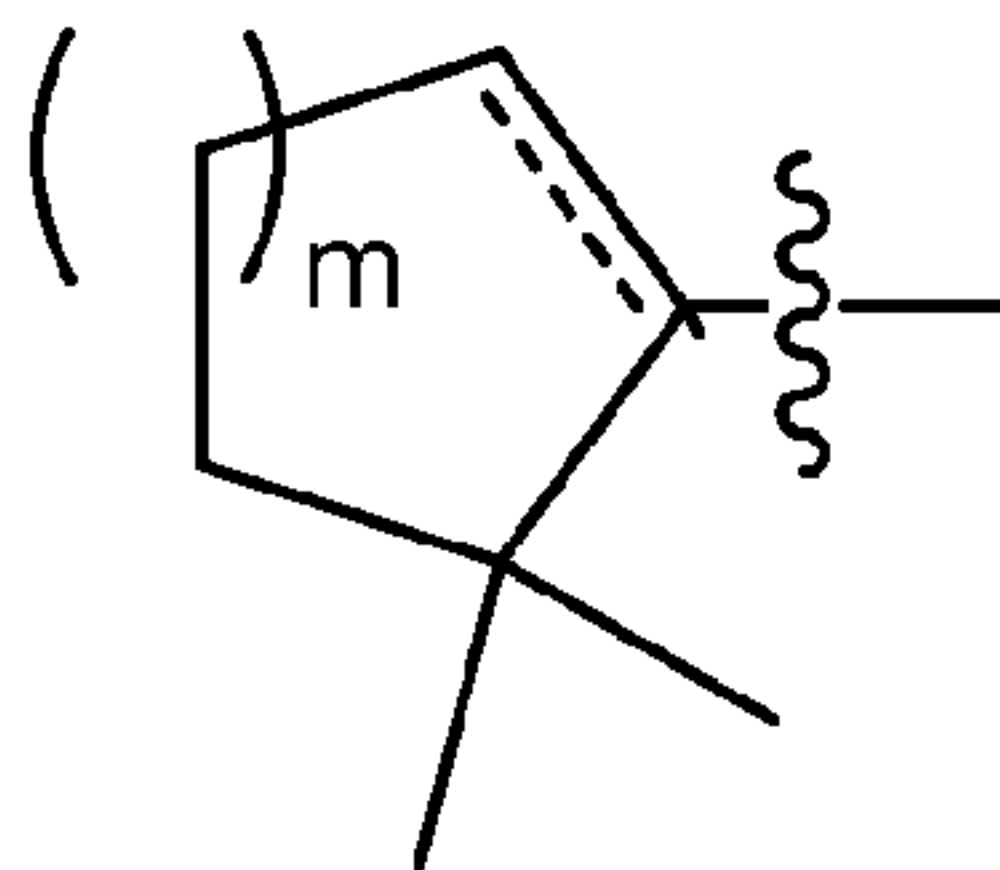
where the wavy line indicates the point of attachment and

R⁴, R⁵, and R⁶ are independently selected from H, F, (C₁-C₄)alkyl, and two of R⁴, R⁵, and R⁶ are other than H; or two or three of R⁴, R⁵, and R⁶ join together to form an optionally substituted saturated or partially unsaturated 3-8 membered monocyclic or bicyclic ring. In some such embodiments, R⁴, R⁵, and R⁶ are independently selected from H and (C₁-C₄)alkyl groups and at least two of R⁴, R⁵, and R⁶ are (C₁-C₄)alkyl groups. In some such embodiments, all three of R⁴, R⁵, and R⁶ are independently selected from (C₁-C₄)alkyl groups. In some such embodiments, two of R⁴, R⁵, and R⁶ are methyl groups. In some such embodiments, each of R⁴, R⁵, and R⁶ is a methyl group. In other embodiments, R⁴, R⁵, and R⁶ are independently selected from H, (C₁-C₄)alkyl groups, or a substituted (C₁-C₄) alkyl group selected from (C₁-C₄)haloalkyl groups, (C₁-C₄)perhaloalkyl groups, or (C₁-C₄)alkoxy(C₁-C₄)alkyl groups. In some such embodiments, at least one of R⁴, R⁵, and R⁶ is a CF₃ group. In other embodiments at least one of R⁴, R⁵, and R⁶ is a methoxymethyl group.

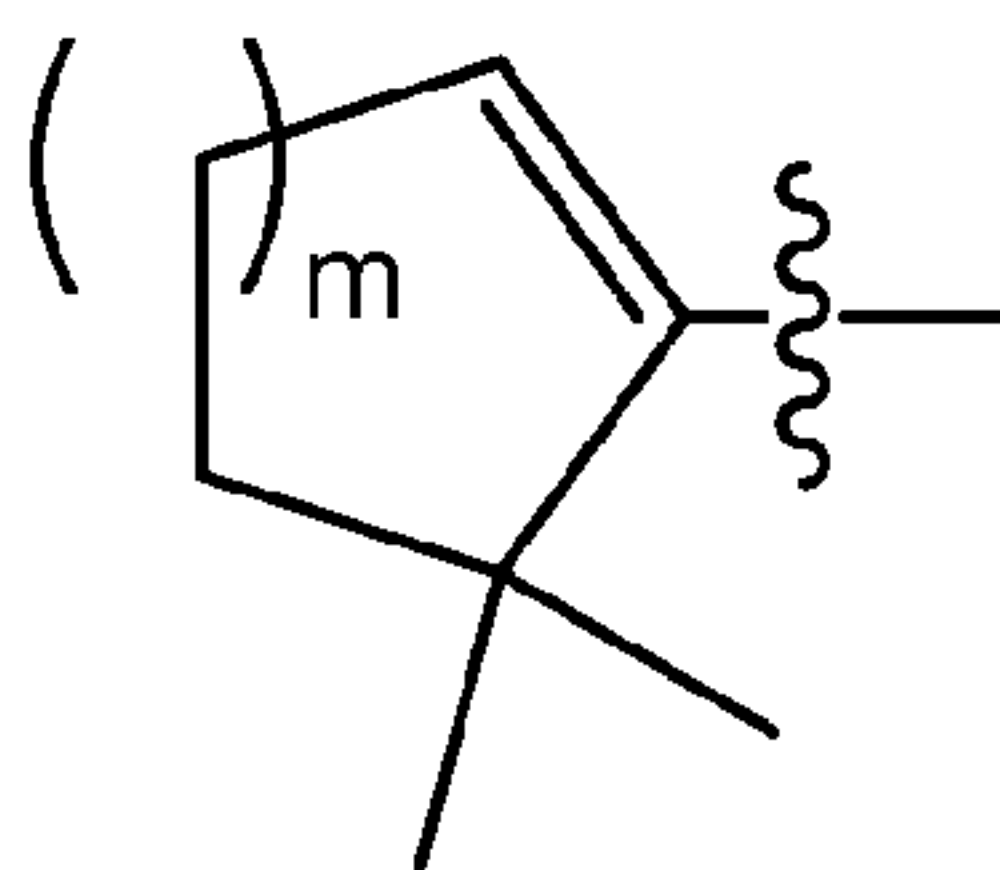
[081] In some embodiments, A is a group of formula **A'** where the wavy line indicates the point of attachment and R^4 , R^5 , and R^6 are independently selected from H, F, OH, -O-(C₁-C₃)alkyl, (C₁-C₆)alkyl and (C₂-C₆)alkenyl, and two of R^4 , R^5 , and R^6 are other than H; or two or three of R^4 , R^5 , and R^6 join together to form an optionally substituted saturated or partially unsaturated 3-8 membered monocyclic or bicyclic ring. In some such embodiments, R^4 , R^5 , and R^6 are independently selected from H, OH, OMe, OEt, (C₁-C₆)alkyl, and (C₂-C₆)alkenyl groups and at least two of R^4 , R^5 , and R^6 are (C₁-C₄)alkyl groups. In some such embodiments, all three of R^4 , R^5 , and R^6 are independently selected from (C₁-C₄)alkyl groups. In some such embodiments, two of R^4 , R^5 , and R^6 are methyl groups. In some such embodiments, each of R^4 , R^5 , and R^6 is a methyl group. In other embodiments, R^4 , R^5 , and R^6 are independently selected from H, (C₁-C₄)alkyl groups, or a substituted (C₁-C₄) alkyl group selected from (C₁-C₄)haloalkyl groups, (C₁-C₄)perhaloalkyl groups, or (C₁-C₄)alkoxy(C₁-C₄)alkyl groups. In some such embodiments, at least one of R^4 , R^5 , and R^6 is a CF₃ group. In other embodiments at least one of R^4 , R^5 , and R^6 is a methoxymethyl group. In other embodiments, at least one of R^4 , R^5 , and R^6 is selected from OH, methoxy, or is ethoxy. In some such embodiments one of R^4 , R^5 , and R^6 is a methoxy. In other such embodiments one of R^4 , R^5 , and R^6 is OH. In other such embodiments one of R^4 , R^5 , and R^6 is ethoxy.

[082] In some embodiments where A is a group of formula **A'**, two of R^4 , R^5 , and R^6 , together with the C atom to which they are attached, join to form a 3-8 or 3-7 membered ring, and the other of R^4 , R^5 , and R^6 is selected from H, an unsubstituted (C₁-C₄)alkyl, or a substituted (C₁-C₄)alkyl. In some embodiments the ring is a carbocyclic ring which may be a fully saturated cycloalkyl ring. In some such embodiments, the 3-8 membered ring is a 5-7 membered ring, a 3-6 membered ring, or a 3-5 membered ring. Examples of such rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl rings. In some such embodiments, two of R^4 , R^5 , and R^6 join to form a cyclopropyl ring. In some such embodiments, the other of R^4 , R^5 , and R^6 is H. In some embodiments two of R^4 , R^5 , and R^6 , together with the C atom to which they are attached, join to form an optionally substituted saturated or partially unsaturated 3-8 or 3-7 membered ring which may be monocyclic or bicyclic, and the other of R^4 , R^5 , and R^6 is selected from H, an unsubstituted (C₁-C₄)alkyl, or a substituted (C₁-C₄)alkyl. In some embodiments the ring only includes carbon ring members. In some such embodiments, the ring includes 0 or 1 double bonds between ring members. In some such

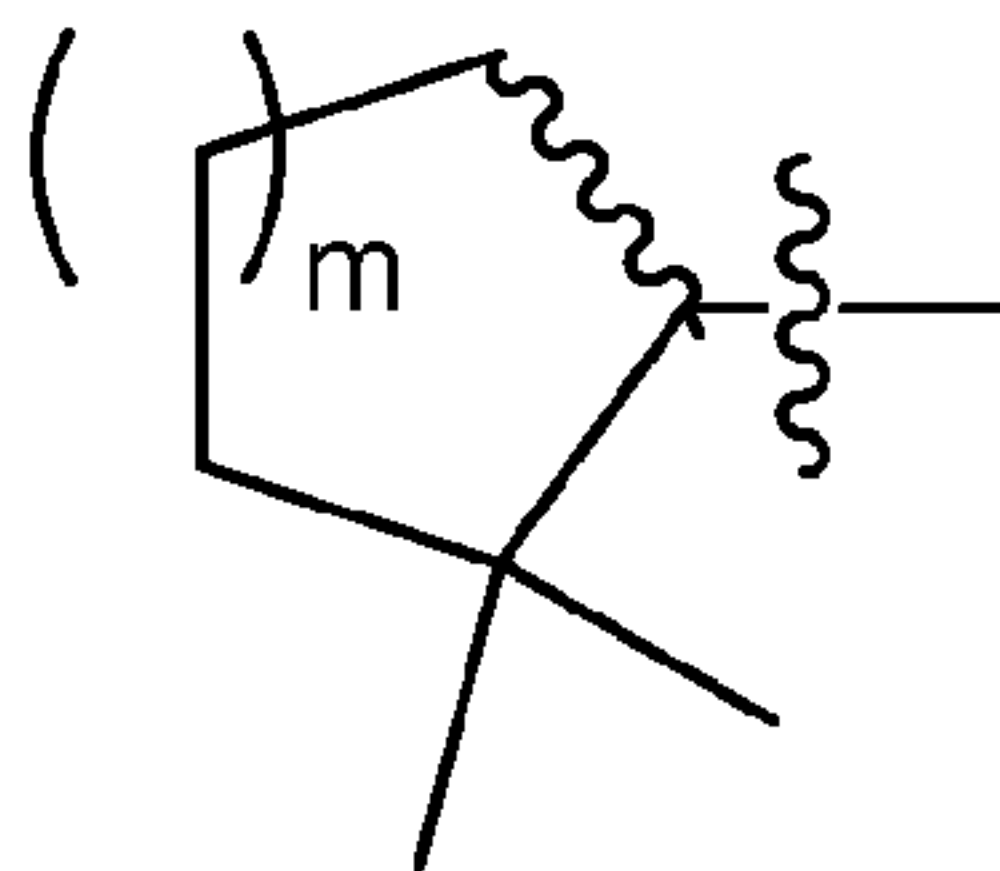
embodiments, the 3-7 membered ring is a 3-6, or a 3-5 membered ring. Examples of such rings include cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cycloheptenyl rings. In some such embodiments, two of R^4 , R^5 , and R^6 join to form an optionally substituted cyclopropyl ring. In some such embodiments, the other of R^4 , R^5 , and R^6 is H. In some such embodiments, two of R^4 , R^5 , and R^6 join to form an optionally substituted cyclopentenyl, cyclohexenyl, or cycloheptenyl ring. In some such embodiments, the other of R^4 , R^5 , and R^6 is H. In some embodiments all three of R^4 , R^5 , and R^6 , together with the C atom to which they are attached, join to form an optionally substituted saturated or partially unsaturated 3-8 membered ring bicyclic ring system. For example, in some embodiments, A may comprise an adamantyl or another bicyclic ring system such as, but not limited to bicyclo[3.2.1]octane, bicyclo[2.2.1]heptane, and the like. In some such embodiments the ring only includes carbon ring members. In some such embodiments, the ring includes 0 or 1 double bonds between ring members. In some embodiments, A is a branched chain (C₄-C₈)alkyl group such as a t-butyl group. In other such embodiments, A is an optionally substituted (C₅-C₇)cycloalkyl group or an optionally substituted (C₅-C₇)cycloalkenyl group. In some such embodiments, the (C₅-C₇)cycloalkyl group or the (C₅-C₇)cycloalkenyl group are substituted with 1, 2, 3, or 4 methyl groups. In some other such embodiments, A has the formula



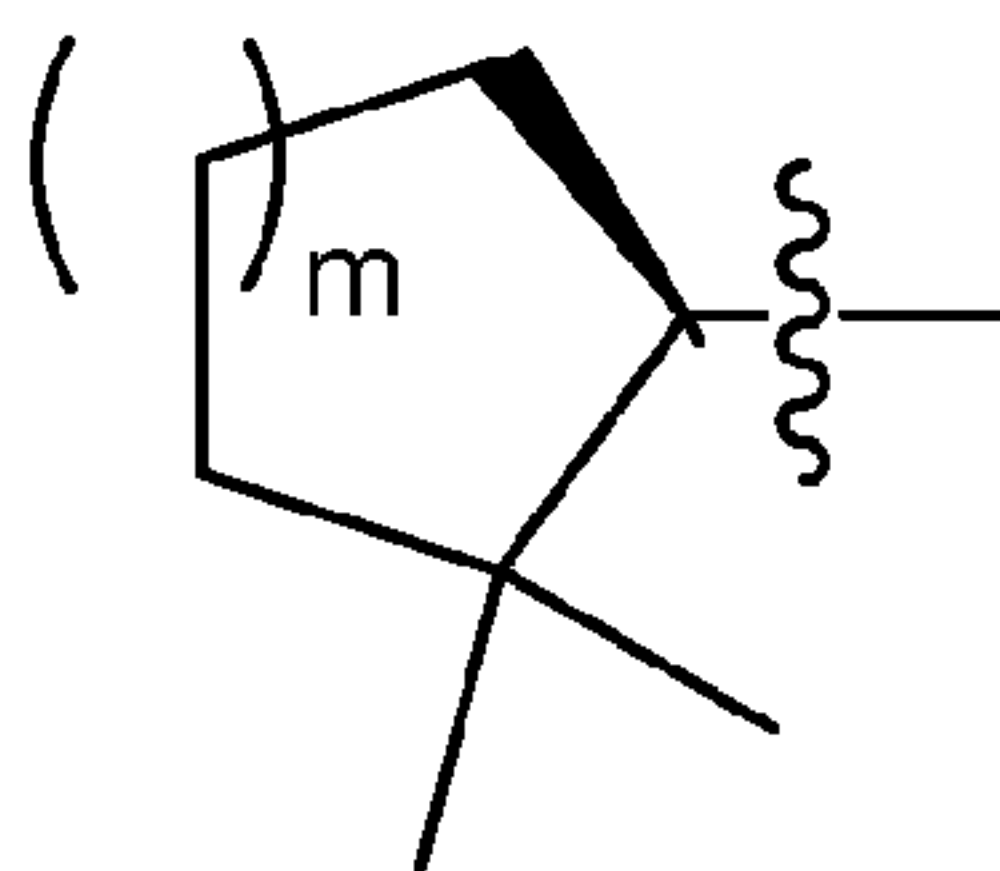
wherein m is 1, 2, or 3, and the dashed line indicates a single or double bond. In some such embodiments, A has the formula



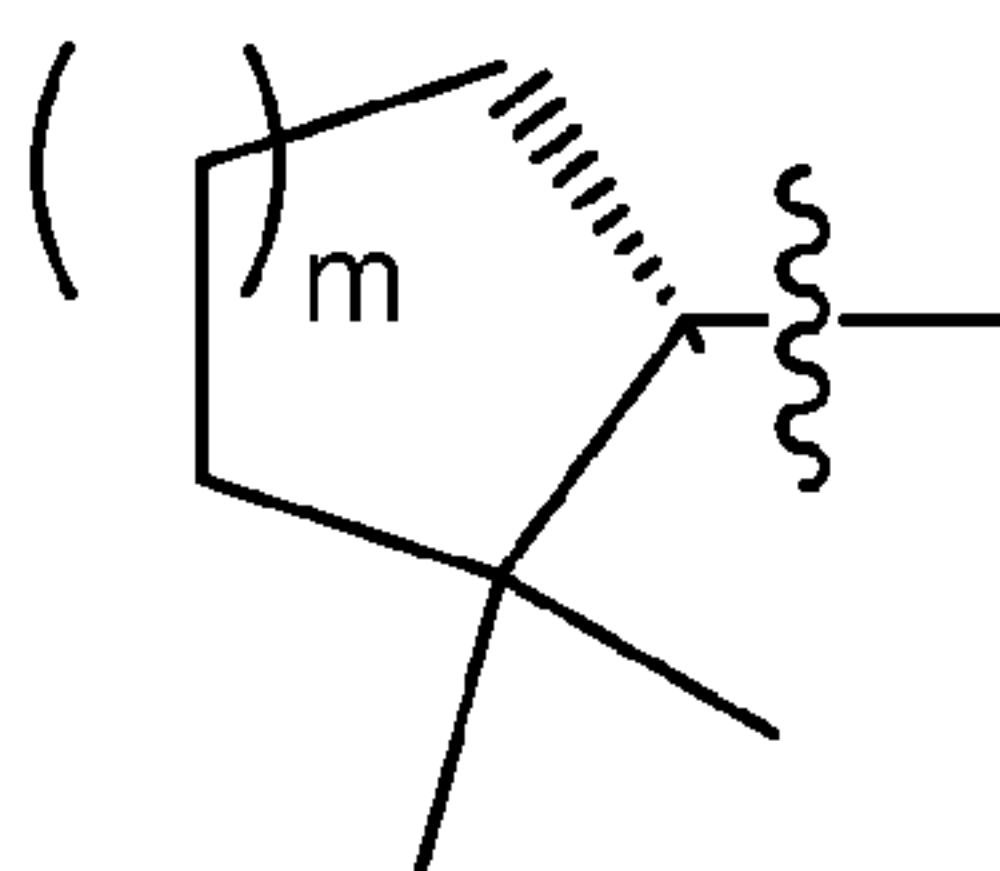
wherein m is 1, 2, or 3. In other such embodiments, A has the formula



wherein m is 1, 2, or 3 and the wavy line indicates that the compound has the R stereochemistry, the S stereochemistry, or a mixture of the R and S stereochemistry with respect to the carbon attached to the rest of the molecule. In some such embodiments, A has the formula

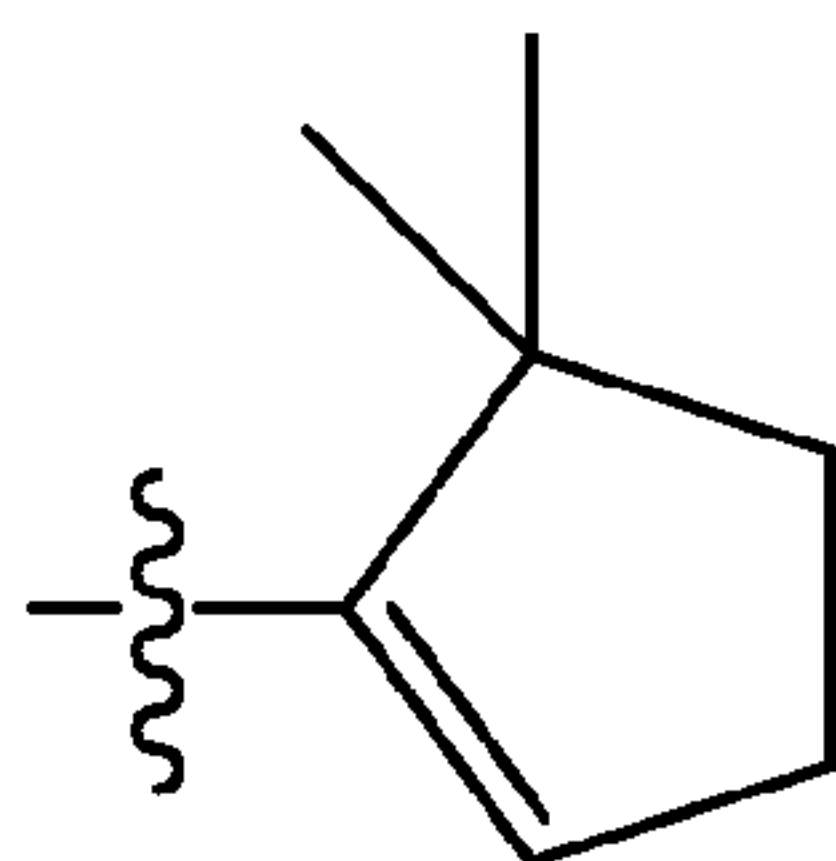


wherein m is 1, 2, or 3. In other embodiments, A has the formula

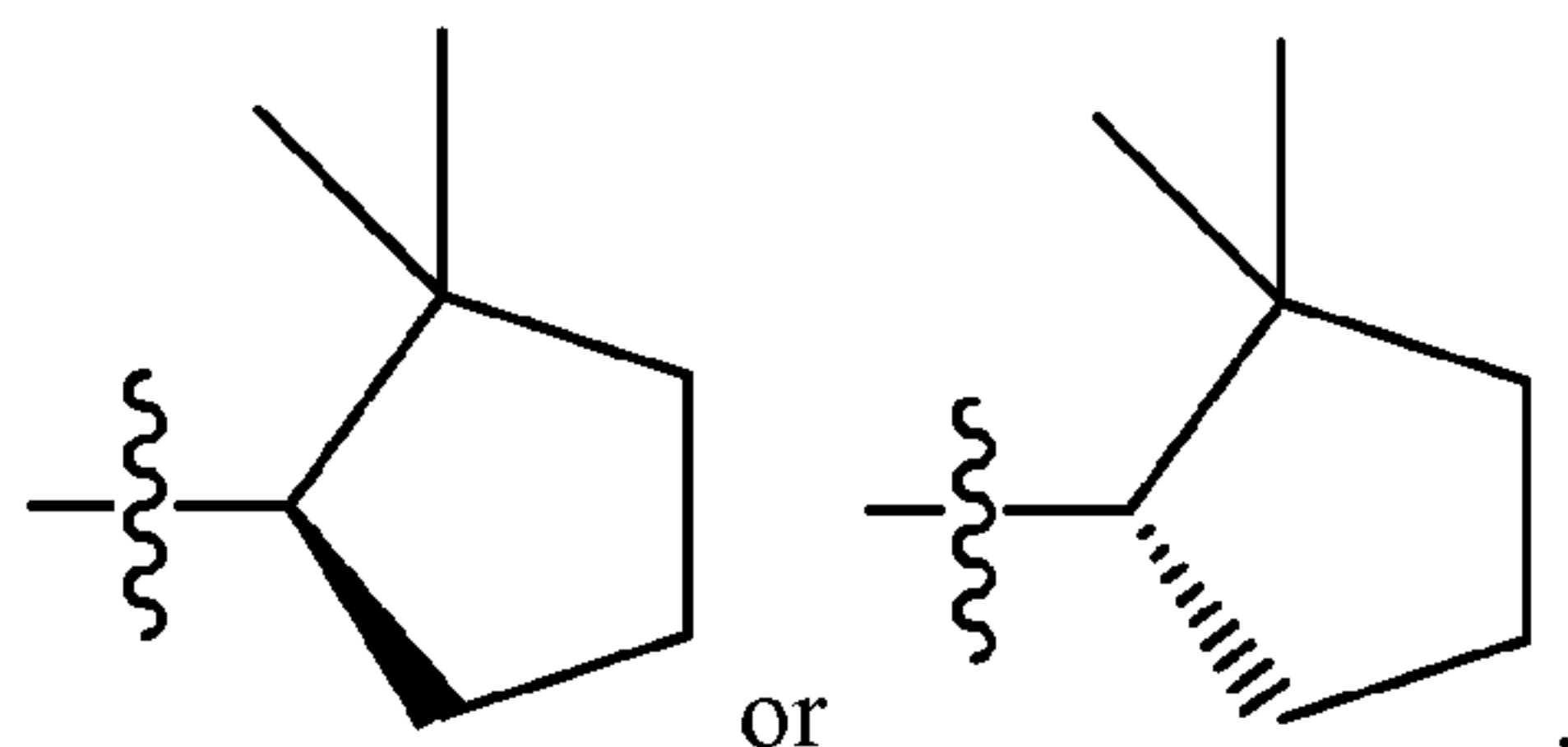


wherein m is 1, 2, or 3. In some embodiments, A is an $-OR^{4a}$ group. In some such embodiments, R^{4a} is selected from a methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, t-butyl, or an isomer thereof. In some embodiments, R^{4a} is selected from such an alkyl group that is substituted. For example, in some embodiments, R^{4a} may be a trihaloalkyl group such as a CF_3 group or another perhaloalkyl group.

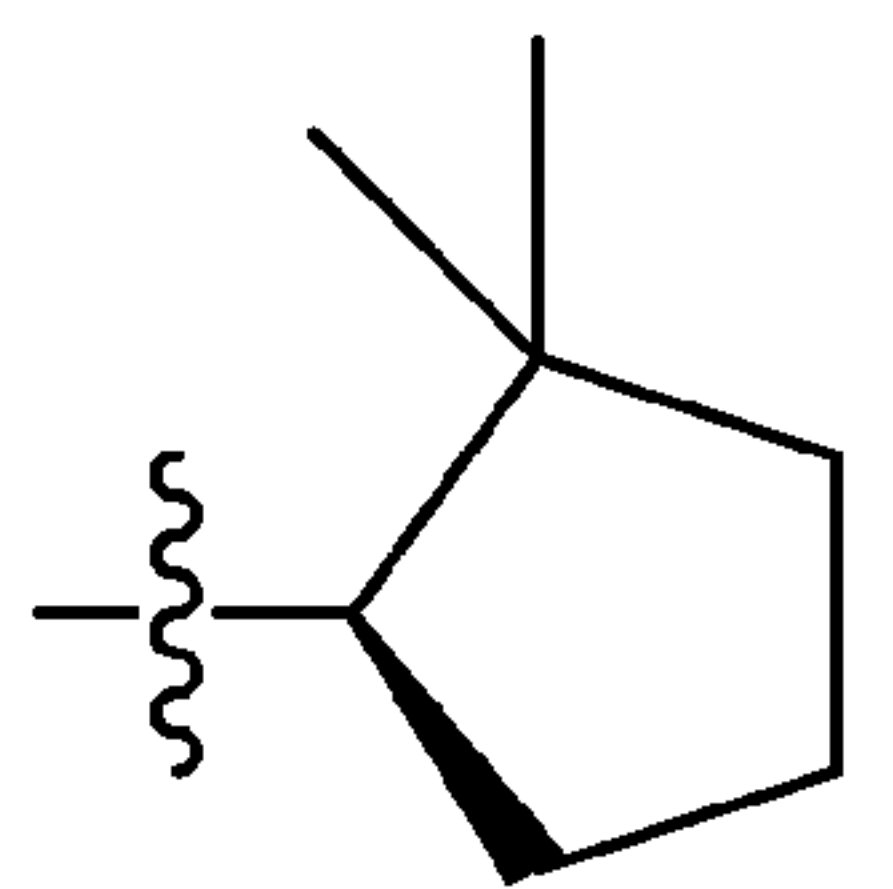
[083] In some embodiments, A is



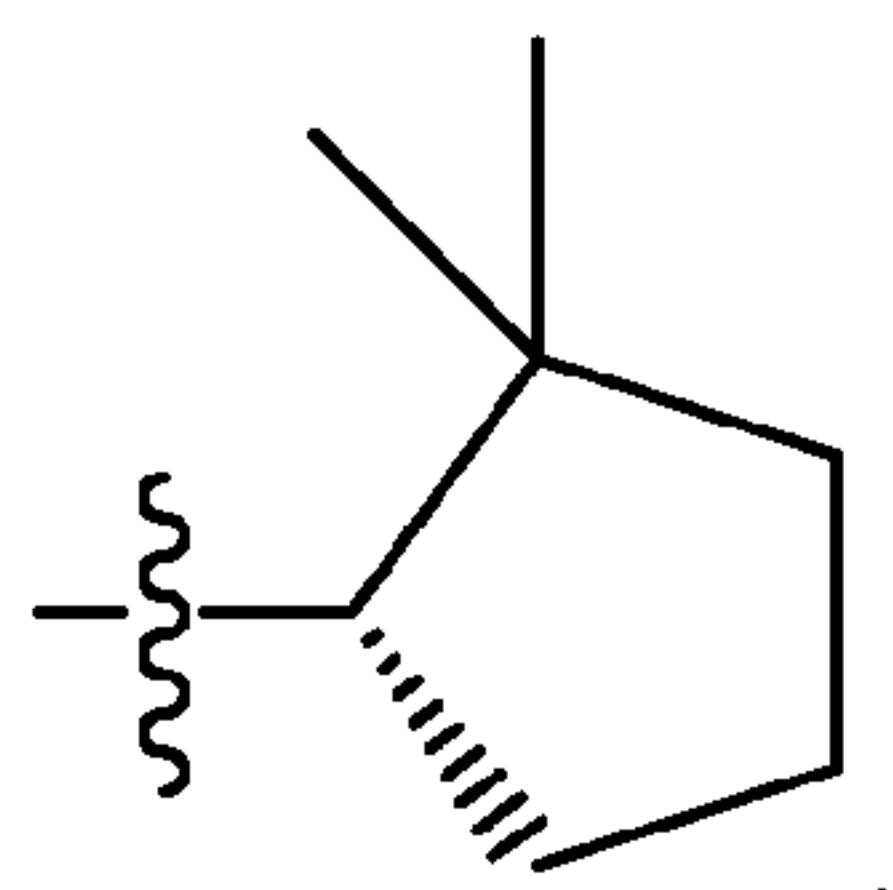
[084] In some embodiments, A is selected from



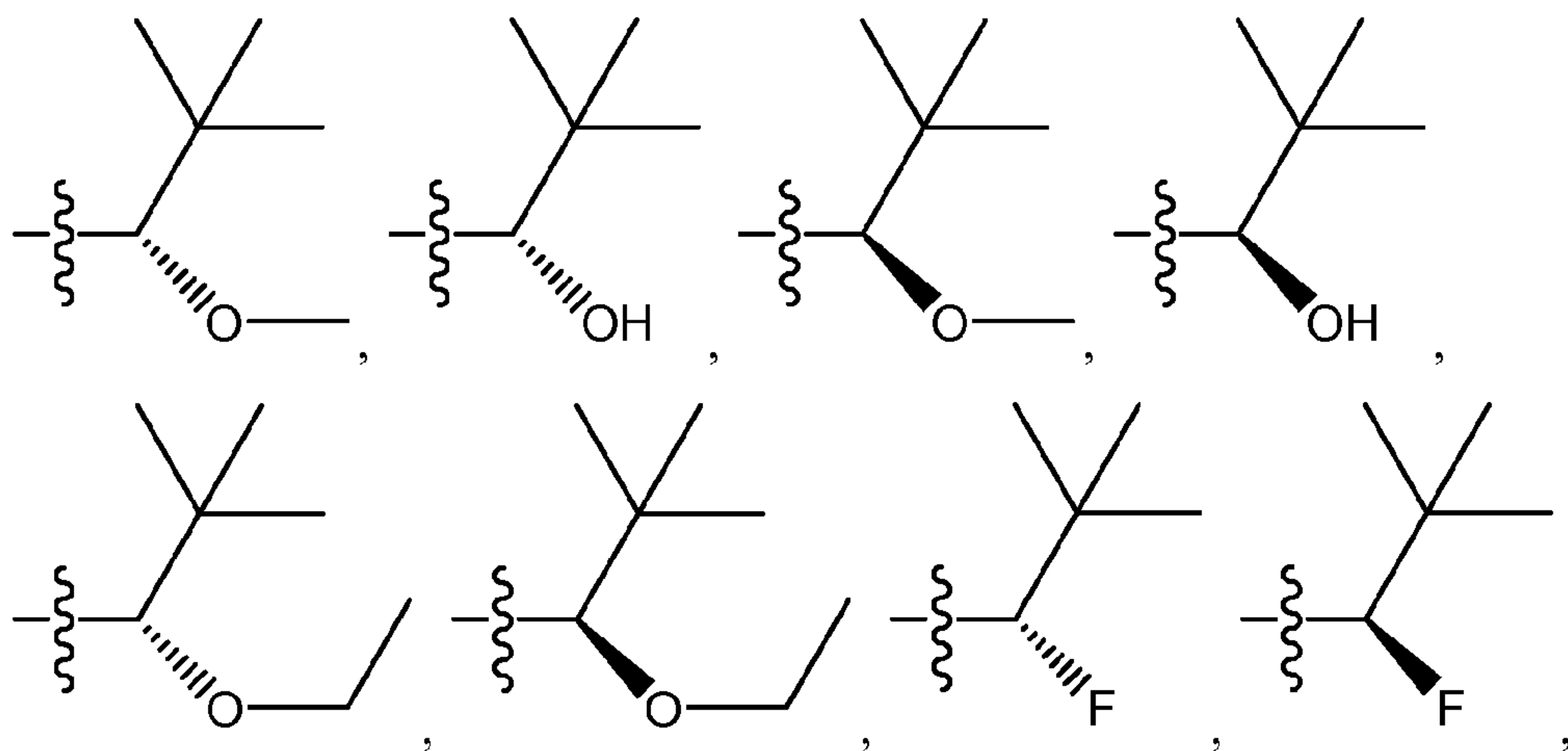
[085] In some embodiments, A is

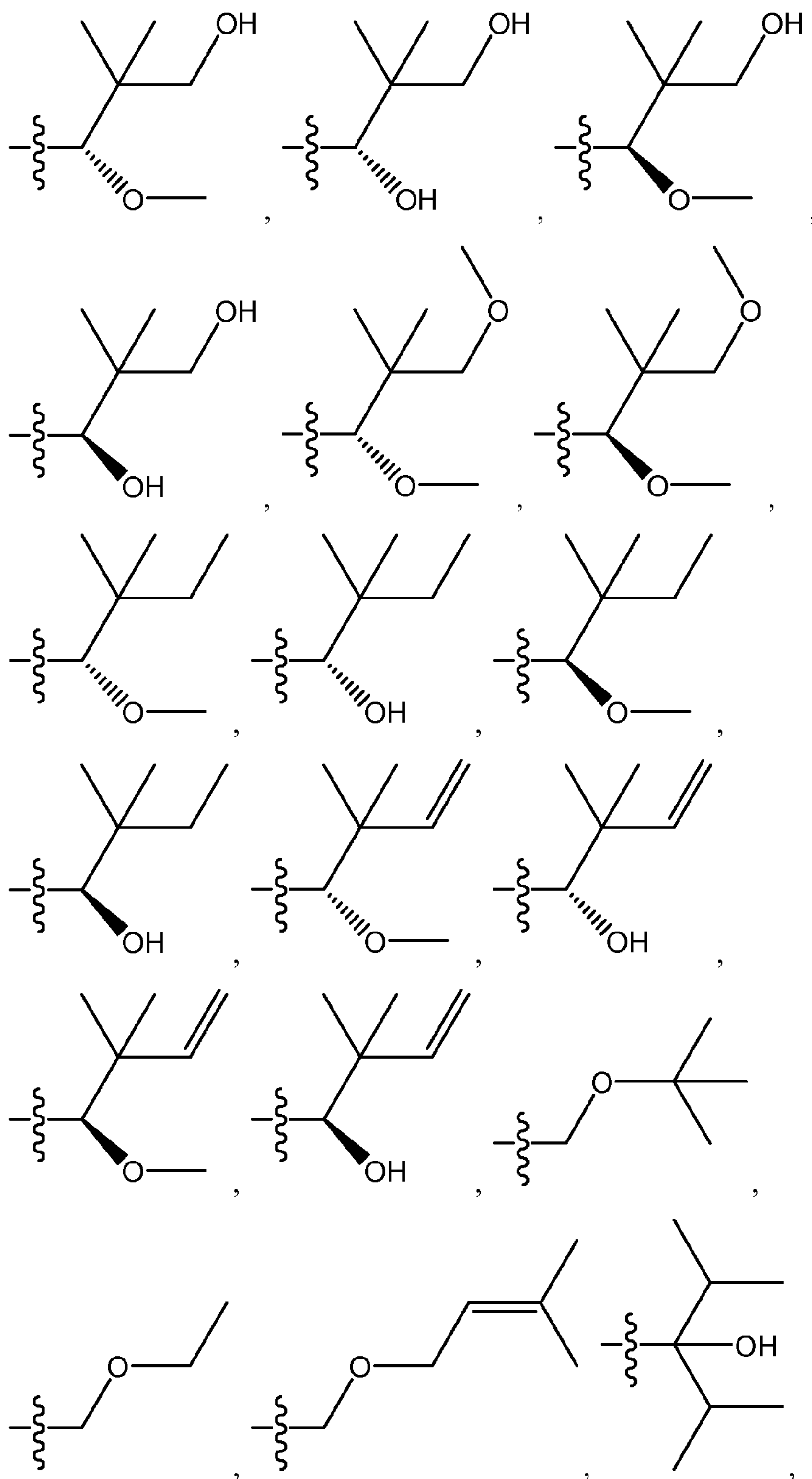


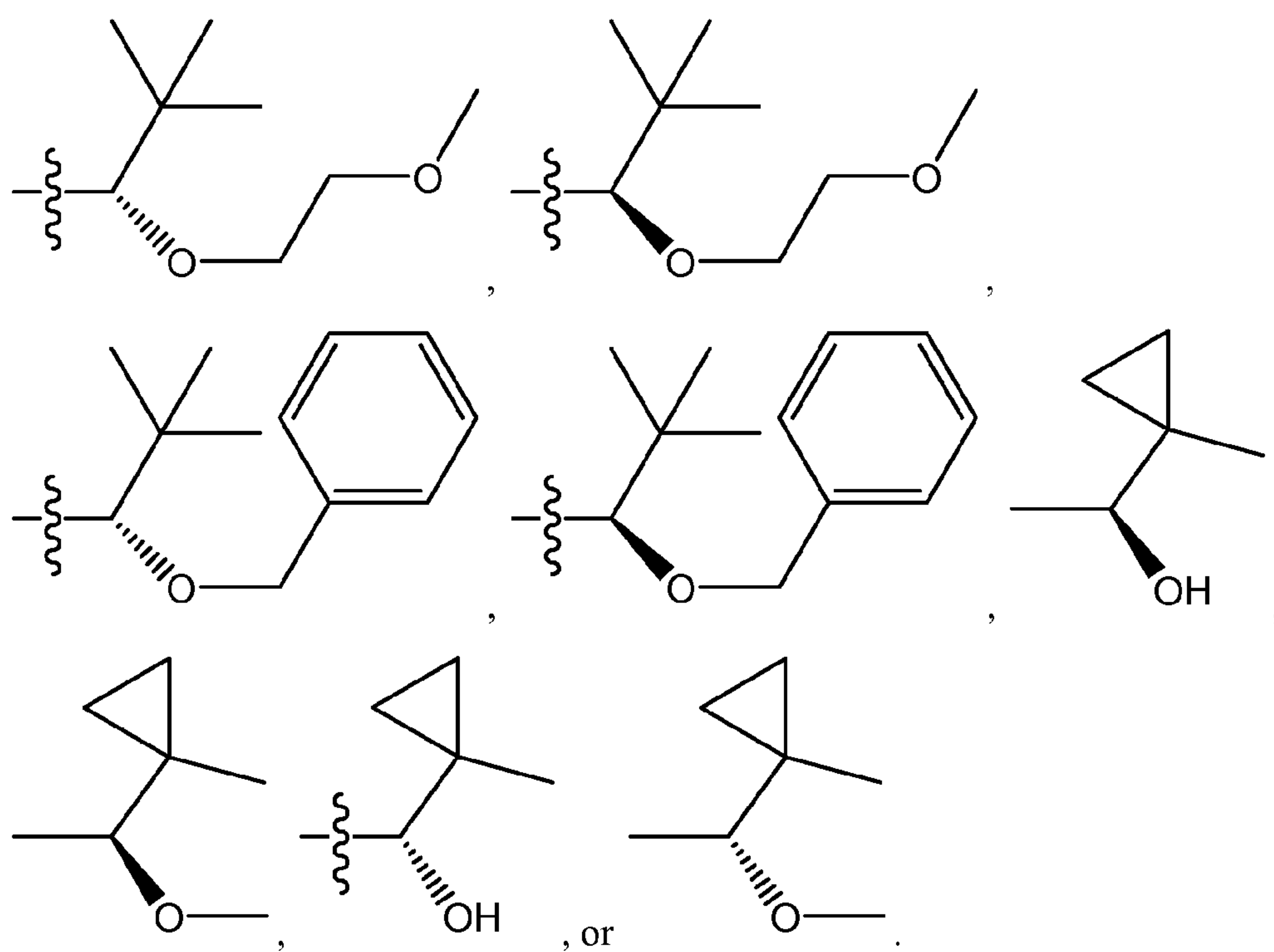
[086] In some embodiments, A is



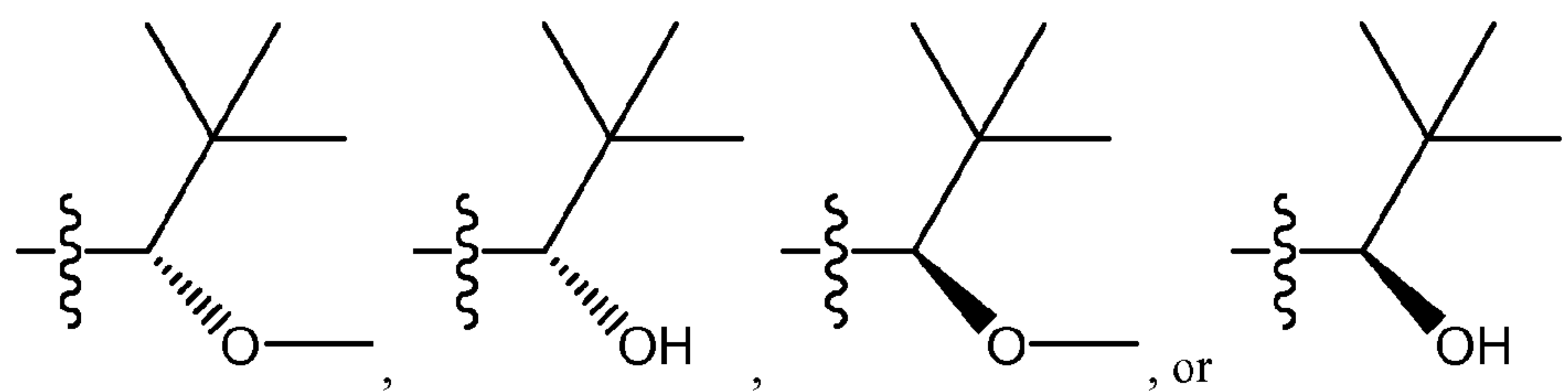
[087] In some embodiments, A is a (C₁-C₁₂)alkyl or is a (C₂-C₁₂)alkenyl group and the (C₁-C₁₂)alkyl or the (C₂-C₁₂)alkenyl group is substituted with at least one A'' group where A'' is selected from -F, -OH, -O-(C₁-C₄)alkyl, -O(C₁-C₄)alkyl-aryl, -O(C₂-C₈)alkenyl, or -O-(C₁-C₄)alkyl-O-(C₁-C₄)alkyl. Therefore, in some embodiments A is selected from any one or all of:



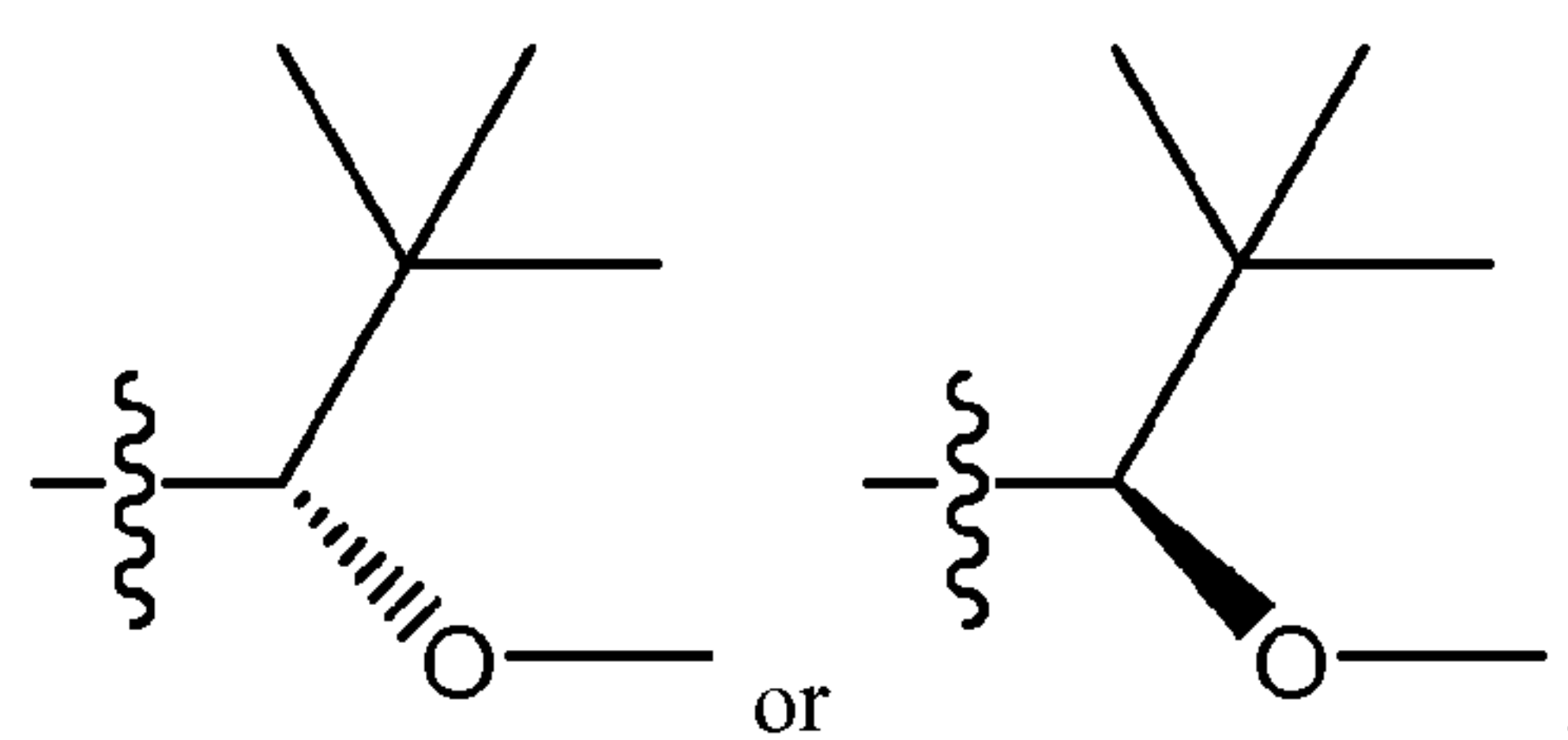




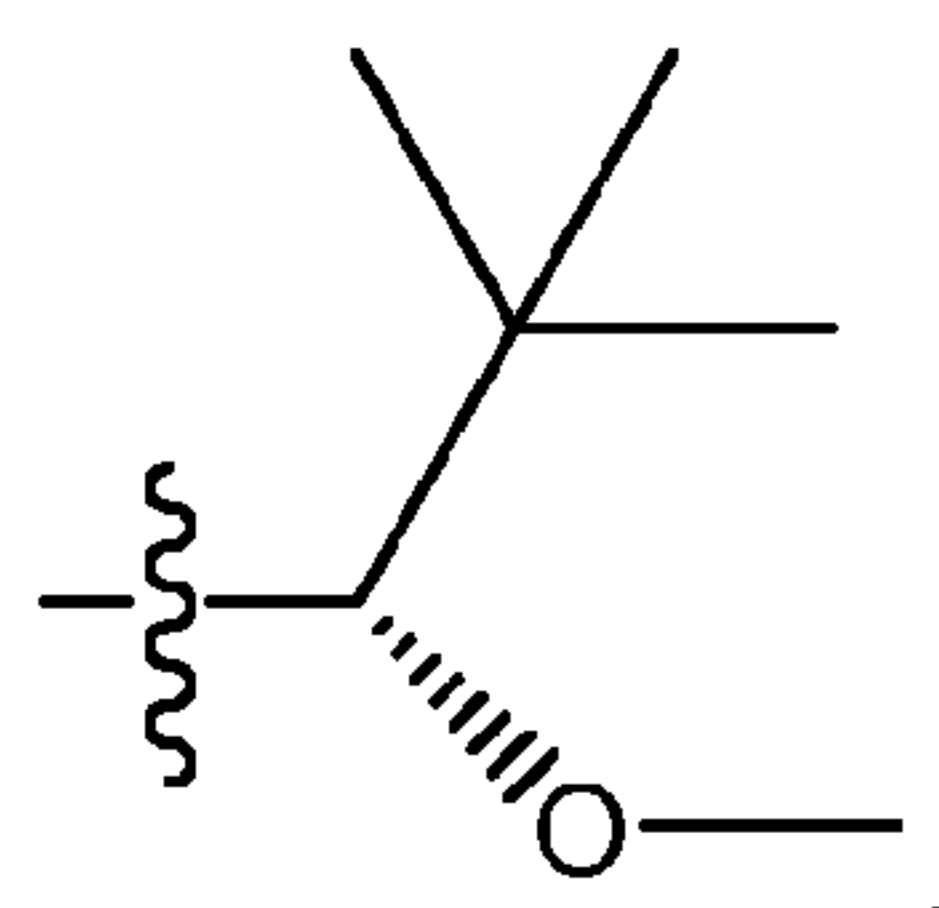
[088] In some embodiments, A is selected from



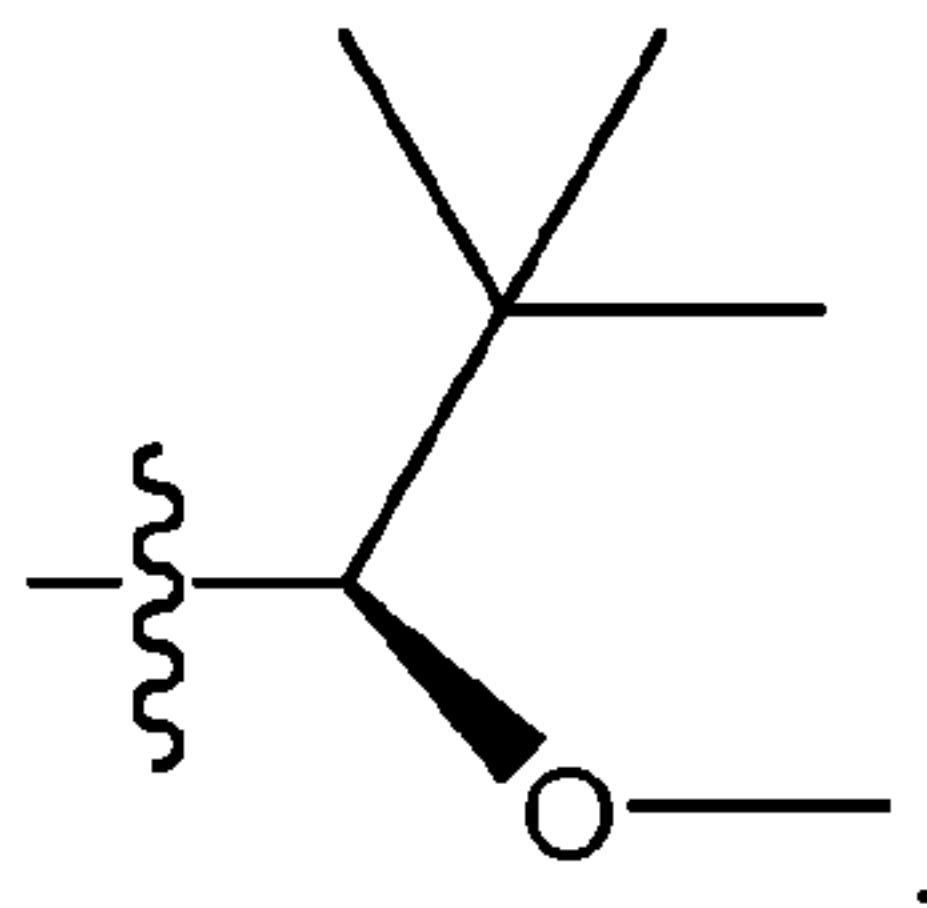
[089] In some embodiments, A is selected from



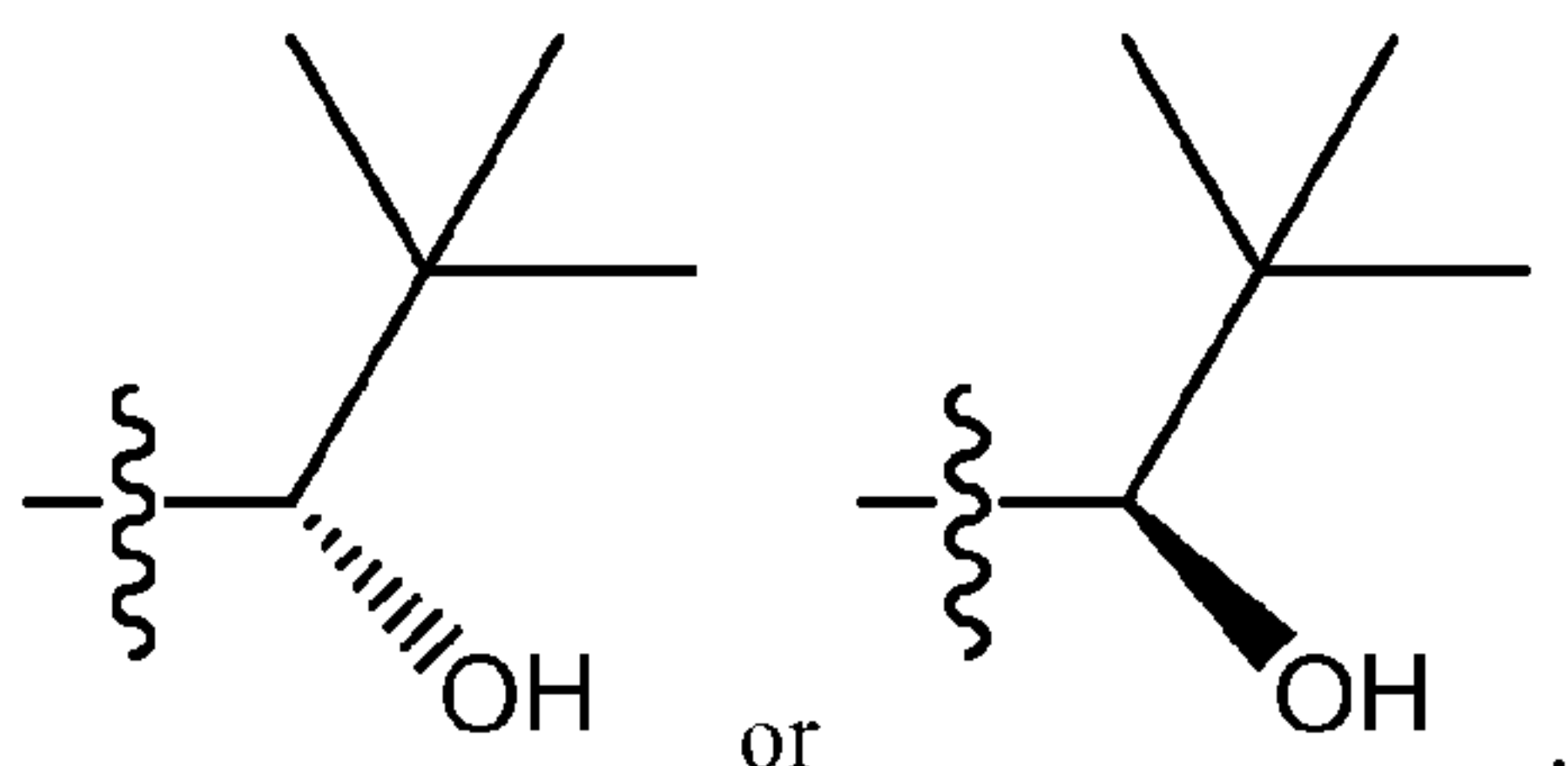
[090] In some embodiments, A is



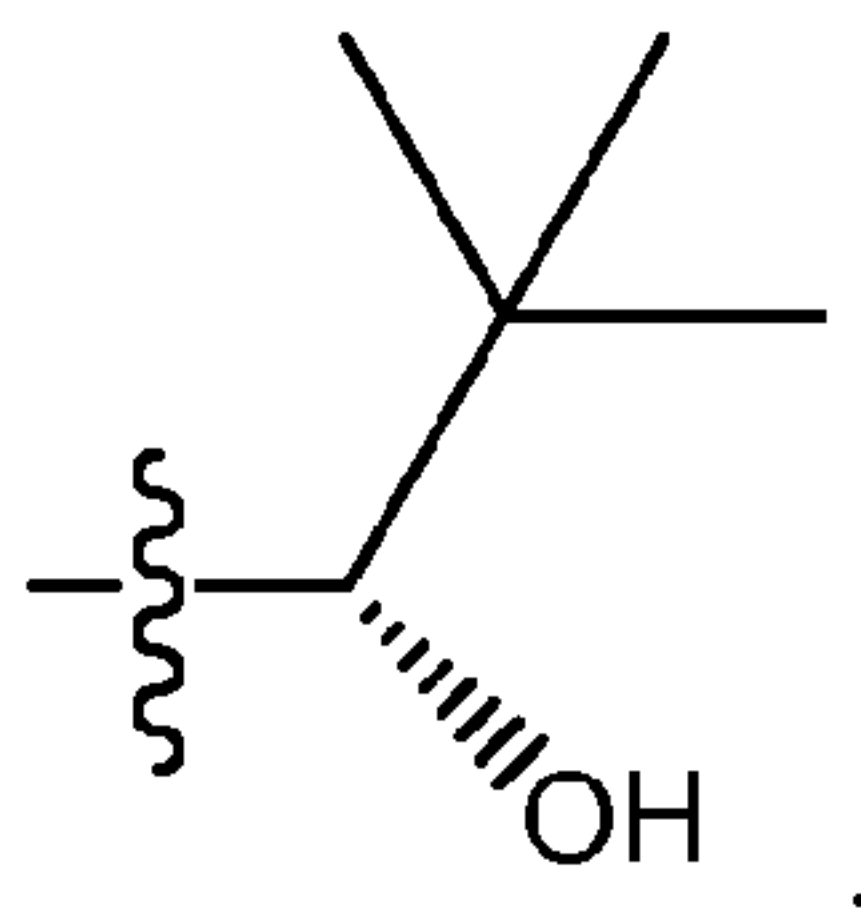
[091] In some embodiments, A is



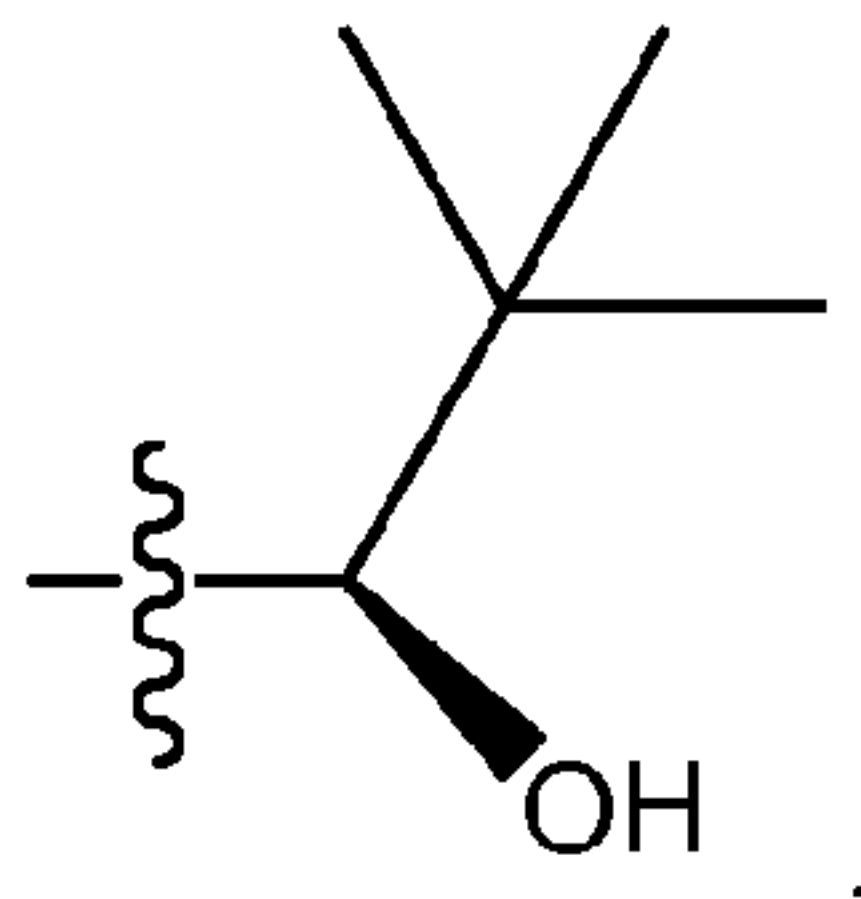
[092] In some embodiments, A is selected from



[093] In some embodiments, A is



[094] In some embodiments, A is



[095] In some embodiments, X is O. In other embodiments, X is S. In still further embodiments X is NR^a. In some embodiments X is NR^a and R^a is selected from H or methyl. In still other embodiments, X is NR^a and R^a is H.

[096] In some embodiments, R³ is -H, -F, -Cl, -OH, -S(C₁-C₂)alkyl, unsubstituted -(C₁-C₄)alkyl, unsubstituted -O(C₁-C₃)alkyl, -(C₁-C₄) alkyl substituted with from 1 to 5 substituents selected from -F, -OH, (=O), or -O(C₁-C₂)alkyl, or substituted -O(C₁-C₃)alkyl, wherein the alkyl group of the substituted -O(C₁-C₃)alkyl is substituted with from 1 to 5 substituents selected from -F, -OH, or -O(C₁-C₂)alkyl. In some embodiments, R³ is selected from -OH, -O(C₁-C₂)alkyl, or -S(C₁-C₂)alkyl. In some embodiments, R³ is selected from -O-Me or -S-Me. In some such embodiments, R³ is

-S-Me. In other such embodiments, R^3 is ethoxy (-O-CH₂CH₃). In still other such embodiments, R^3 is a -O-(C₁-C₂)haloalkyl. Examples of some such groups include -OCF₃ and -OCH₂CF₃. In some embodiments, R^3 is selected from methoxy or ethoxy. In other embodiments, R^3 is a substituted (C₁-C₂)alkyl group such as a -CHF₂ or -CF₃ group. In other embodiments, R^3 is a (C₁-C₃)alkyl group that is substituted with a group such as -OH or with an oxo group. Examples of such groups include, but are not limited to, -C(CH₃)₂OH and -C(=O)-CH₃. In some embodiments, R^3 is selected from -F, -Cl, -OH, -OCH₃, -SCH₃, -OCH₂CH₃, -OCHF₂, -OCF₃, -OCH₂CF₃, -O-cyclopropyl, -CHF₂, -CF₃, -C(=O)-CH₃, -CH(CH₃)₂OH, or -CH₂CH₃. In some such embodiments, R^3 is selected from -OCH₃, -OCH₂CH₃, -OCHF₂, -OCF₃, -OCH₂CF₃, -O-cyclopropyl, -CHF₂, or -CF₃. In some embodiments, R^3 is selected from -F, -Cl, -OCHF₂, -OCH₂CF₃, -OCF₃, -O-cyclopropyl, -CF₃, or -CHF₂. In some embodiments, R^3 is selected from -OCHF₂, -OCH₂CF₃, -OCF₃, -O-cyclopropyl, -CF₃, or -CHF₂.

[0097] In some embodiments, W, Y, and Z are all C-H. In other embodiments W and Z are C-H and Y is N.

[0098] In some embodiments, R^7 and R^8 are independently selected from H and unsubstituted -(C₁-C₄)alkyl. In some such embodiments, R^7 and R^8 are independently selected from H and -CH₃. In some such embodiments, R^7 and R^8 are both H. In some such embodiments, X is O.

[0099] In some embodiments, R^{1a} is H or -CH₃. In some such embodiments, R^{1a} is H.

[0100] In some embodiments, R^{1b} is H or -CH₃. In some such embodiments, R^{1b} is H.

[0101] In some embodiments, $R^{1b'}$ is H or -CH₃. In some such embodiments, $R^{1b'}$ is H.

[0102] In some embodiments, R^{1c} , if present, is H or -CH₃. In some such embodiments, R^{1c} , if present is H. In some embodiments, m is 0 and R^{1c} is absent.

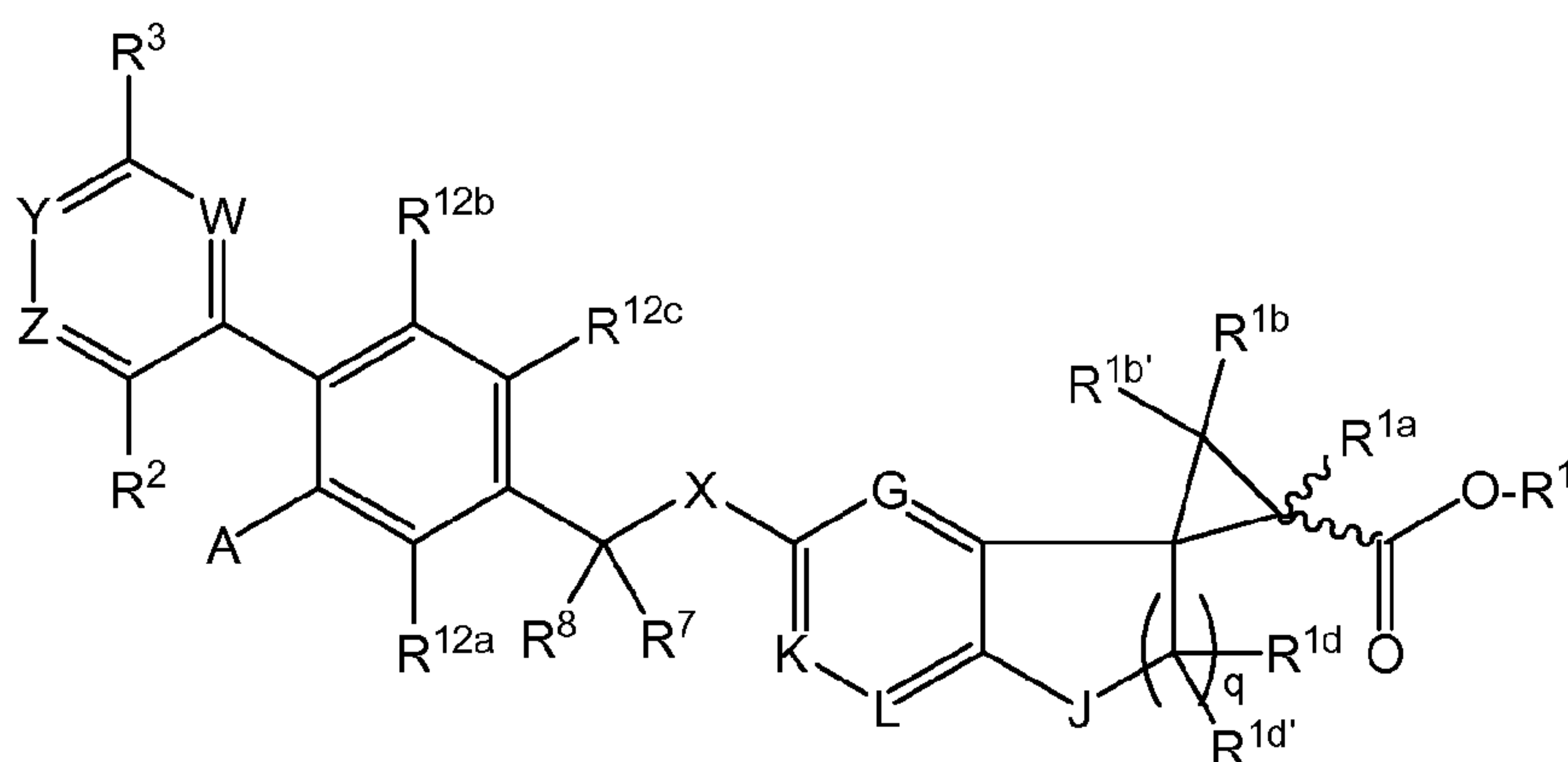
[0103] In some embodiments, $R^{1c'}$, if present, is H or -CH₃. In some such embodiments, $R^{1c'}$, if present, is H. In some embodiments, m is 0 and $R^{1c'}$ is absent.

[0104] In some embodiments, R^{1d} , if present, is H or -CH₃. In some such embodiments, R^{1d} , if present is H. In some embodiments, q is 0 and R^{1d} is absent.

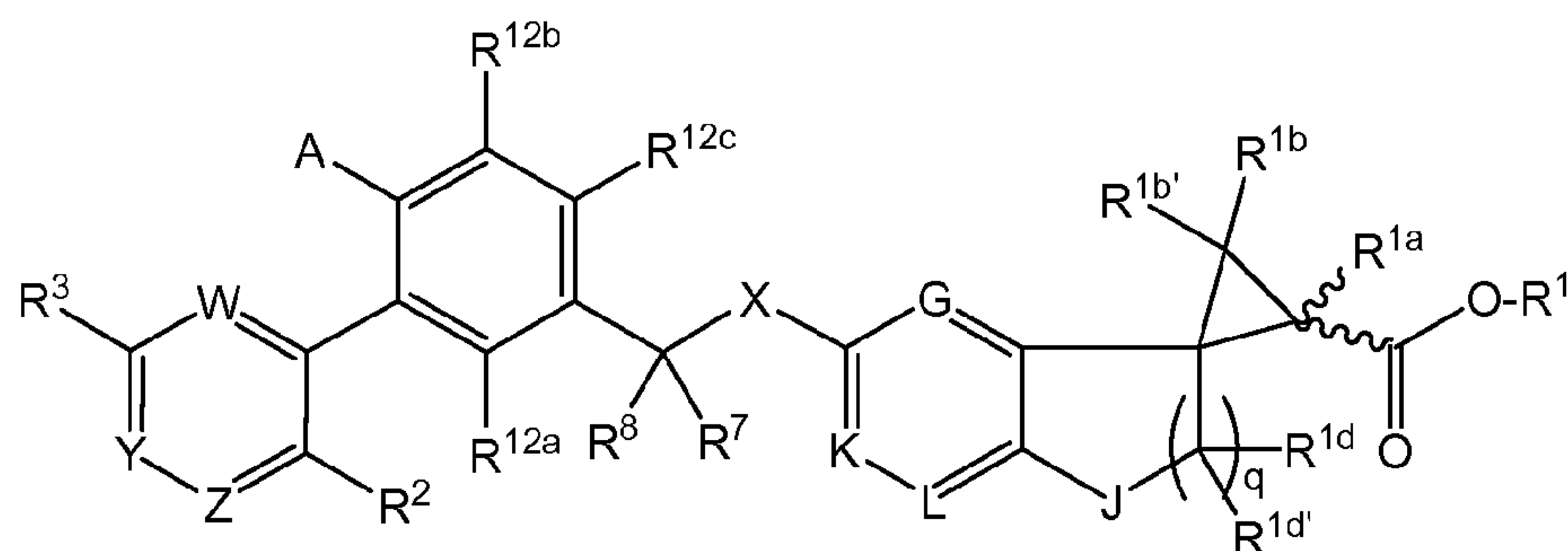
[0105] In some embodiments, $R^{1d'}$, if present, is H or -CH₃. In some such embodiments, $R^{1d'}$, if present, is H. In some embodiments, q is 0 and $R^{1d'}$ is absent.

[0106] In some embodiments q is 0, 1, or 2. In some such embodiments, q is 0. In other such embodiments, q is 1. In still other such embodiments, q is 2.

[0107] In some embodiments of the compounds of formula I'A or I'B, m is 0 such that the compound of formula I'A or I'B is a compound of formula II'A or II'B or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula II'A or II'B have the following structures where each of the variables have any of the definitions provided for any of the embodiments:



II'A



II'B.

[0108] In some embodiments, J is selected from O, S, NR^b, or CR^cR^d; where R^b is selected from H and (C₁-C₄)alkyl, and R^c and R^d are independently selected from H, F, and (C₁-C₄)alkyl.

[0109] In some embodiments, J is O, NR^b, or S. In some such embodiments, J is O. In other such embodiments, J is S. In still other such embodiments, J is NR^b. In some such embodiments J is NR^b and R^b is selected from H and -CH₃. In some such embodiments J is NR^b and R^b is H.

[0110] In other embodiments, J is CR^cR^d . In some such embodiments, R^c and R^d are independently selected from H or $-\text{CH}_3$. In some such embodiments, R^c and R^d are both H. In some such embodiments, q is 0, 1, or 2. In some such embodiments, q is 0. In other such embodiments, q is 1. In still other such embodiments, q is 2. In still other embodiments, J is CR^cR^d ; R^c and R^d are both H; and q is 3. In some embodiments, J is CR^cR^d and R^c and R^d are independently selected from H, F, or $-\text{CH}_3$.

[0111] In still other embodiments, J is selected from $\text{C}(=\text{O})$ or $-\text{C}(=\text{O})-\text{NR}^b$ where R^b is selected from H and $(\text{C}_1-\text{C}_4)\text{alkyl}$.

[0112] In some embodiments, R^2 is selected from -H, -F, $-\text{CF}_3$, or $-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$. In some embodiments, R^2 is selected from F, CF_3 , or $(\text{C}_1-\text{C}_6)\text{alkoxy}$. In some such embodiments, R^2 is selected from F, CF_3 , or $(\text{C}_4-\text{C}_6)\text{alkoxy}$. In some embodiments, R^2 is H or F. In other embodiments, R^2 is F. In still other embodiments, R^2 is H. In other embodiments, R^2 is propoxy, butoxy, or pentoxy. In some such embodiments, R^2 is butoxy. In still further embodiments, R^2 is selected from F or $(\text{C}_3-\text{C}_4)\text{alkoxy}$. In some such embodiments, R^2 is a $-\text{OCF}_3$. In other embodiments, R^2 is a $-\text{CF}_3$ group. In still other embodiments, R^2 is $-\text{Cl}$.

[0113] In some embodiments, the compound has the formula **I'A**.

[0114] In some embodiments, the compound has the formula **I'B**.

[0115] In some embodiments, R^{12c} is H or F. In some such embodiments, R^{12c} is H whereas in other such embodiments, R^{12c} is F. In some such embodiments, R^{12a} and R^{12b} are both H.

[0116] In some embodiments, each of R^{12a} , R^{12b} , and R^{12c} is independently selected from -H, -F, $-\text{Cl}$, unsubstituted $-(\text{C}_1-\text{C}_4)\text{alkyl}$, CF_3 , or $-\text{O}(\text{C}_1-\text{C}_4)\text{alkyl}$.

[0117] In some embodiments, G is CR^{11a} , K is CR^{11b} , and L is CR^{11b} . In other embodiments, G is N, K is CR^{11b} , and L is CR^{11b} . In still other embodiments, G is CR^{11a} , K is N, and L is CR^{11b} . In still further embodiments, G is CR^{11a} , K is CR^{11b} , and L is N.

[0118] In some embodiments, G is CR^{11a} and R^{11a} is H. In other embodiments, G is CR^{11a} and R^{11a} is F.

[0119] In some embodiments, K is CR^{11b} , L is CR^{11c} , and both R^{11b} and R^{11c} are H.

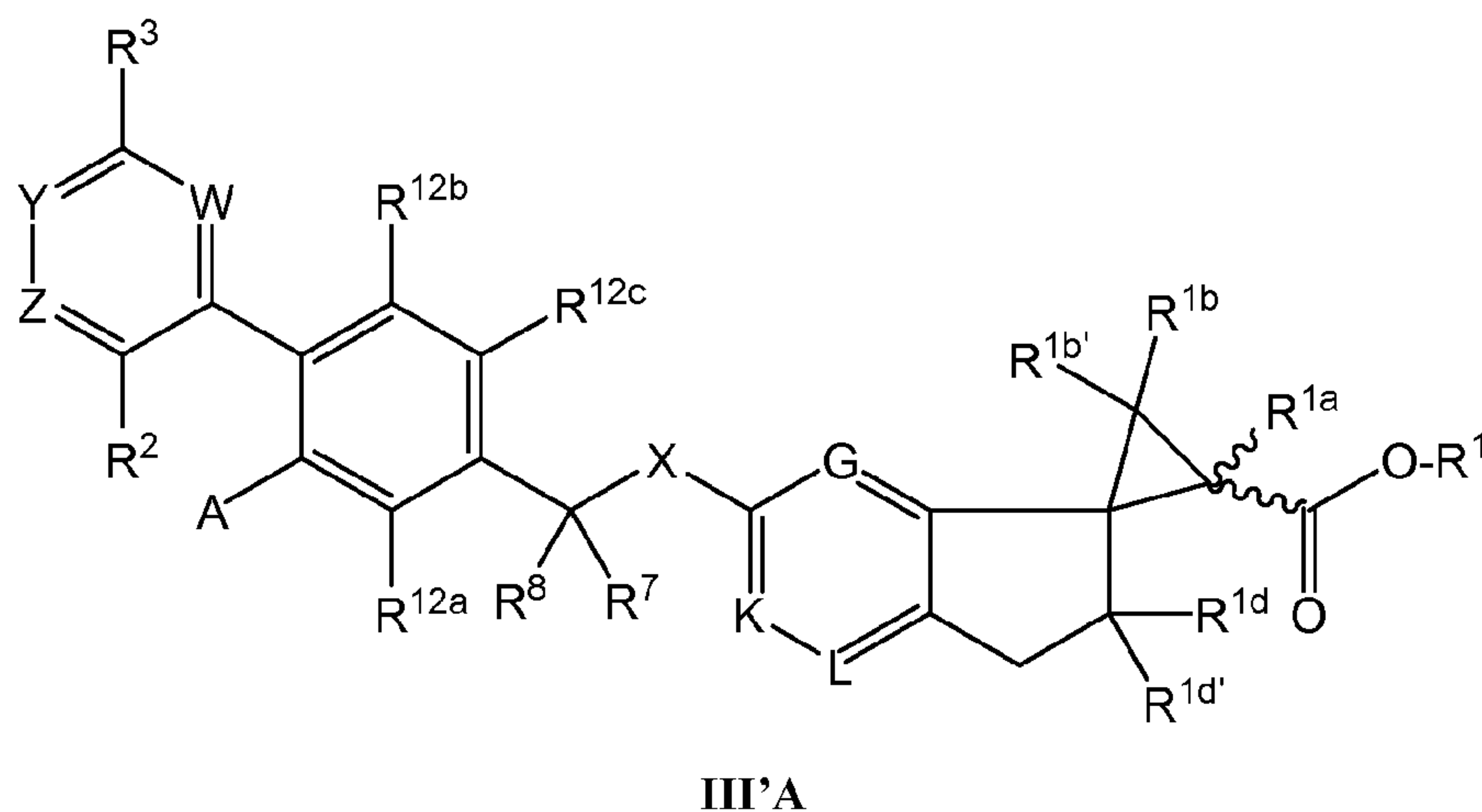
[0120] In some embodiments, G is CR^{11a} ; K is CR^{11b} ; L is CR^{11c} ; R^{11b} , R^{11c} , R^{12a} , and R^{12b} are all H; J is CR^cR^d ; R^c is H; R^d is H; R^{1a} is H; R^{1b} is H; $\text{R}^{1b'}$ is H; R^{1d} , if present, is H; $\text{R}^{1d'}$, if present, is H; W is C-H; Y is C-H or N; Z is C-H; R^2 is F; R^3 is methoxy; R^7

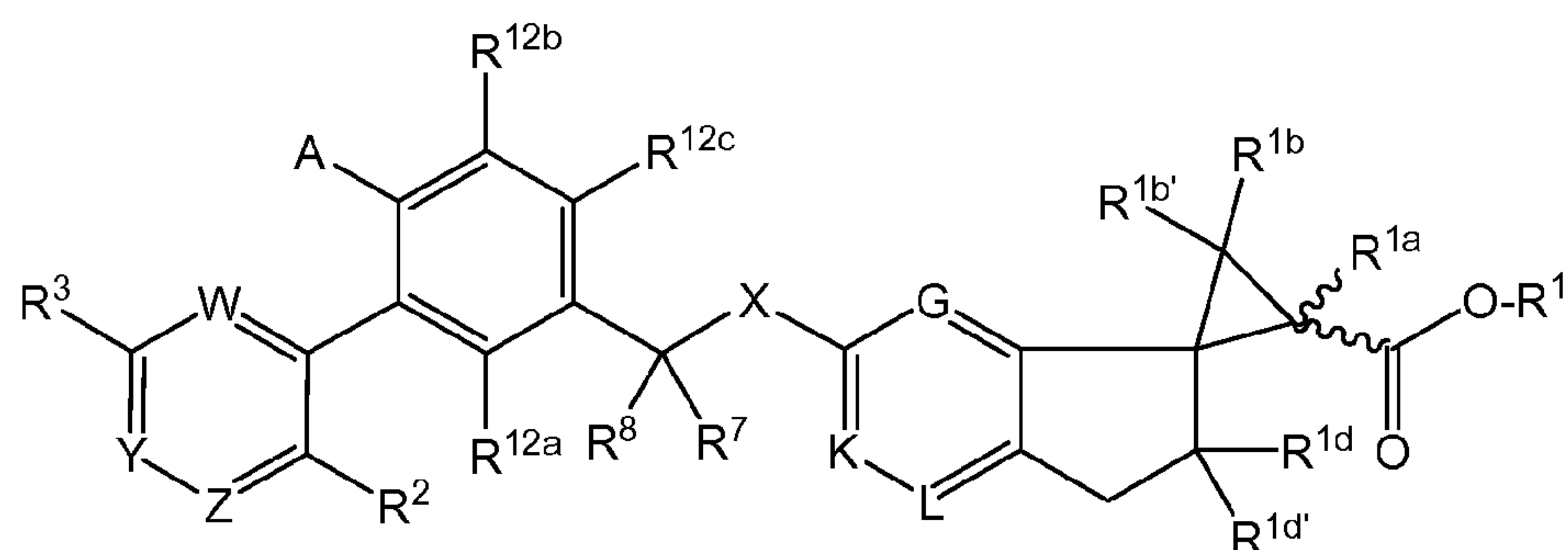
is H; R^8 is H; X is O; m is 0; and q is 0, 1, or 2. In some such embodiments, Y is C-H. In other such embodiments, Y is N. In some such embodiments, q is 0. In other such embodiments, q is 1. In still other such embodiments, q is 2. In some embodiments where q is 1 or 2, R^{1d} and R^{1e} are both H in every instance. In some such embodiments, R^{12c} is H whereas in other such embodiments, R^{12c} is F. In still other such embodiments, R^{11a} is H whereas in other such embodiments, R^{11a} is F.

[0121] In some embodiments, R^{13} is selected from -H, -F, $-(C_1-C_4)alkyl$, and $-O-(C_1-C_4)alkyl$. In some such embodiments R^{13} is H.

[0122] In some embodiments where W is C (a carbon atom), W and A join together to form a ring having 5 to 7 ring members of which 0 or 1 is a heteroatom selected from N, O, or S, and further wherein the ring having 5 to 7 ring members is optionally substituted with $-(C_1-C_8)alkyl$, $-(C_1-C_8)alkenyl$, -OH, $-O-(C_1-C_8)alkyl$, $-O-(C_1-C_8)alkenyl$, or halo. In some such embodiments, W and A join together to form a 5 or 6 membered ring with 0 heteroatoms. In some such embodiments, the ring is unsubstituted. In other such embodiments, the ring is substituted.

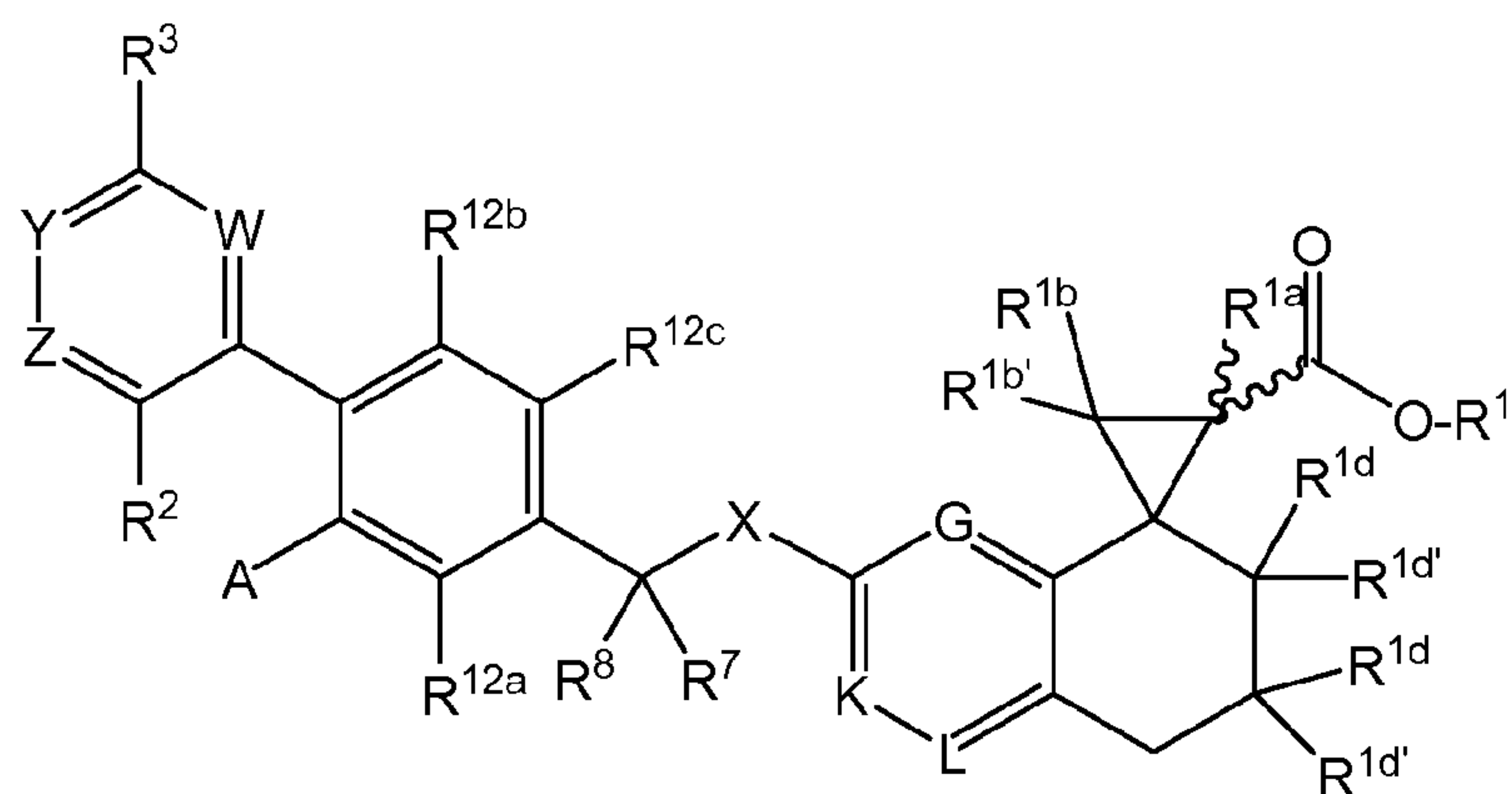
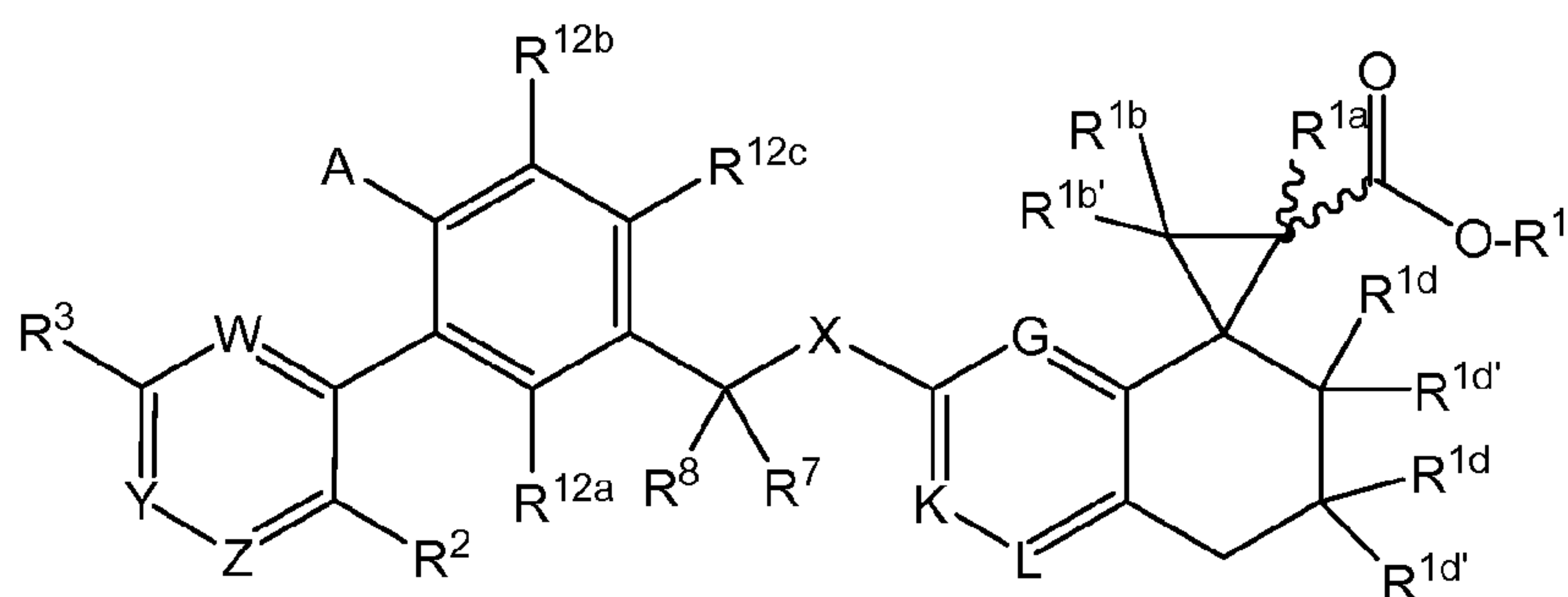
[0123] In some embodiments, the compound of formula **I'A** or **I'B** is a compound of formula **III'A** or **III'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula **III'A** and **III'B** have the following structures where each of the variables has any of the values of any of the embodiments described herein:



**III'B.**

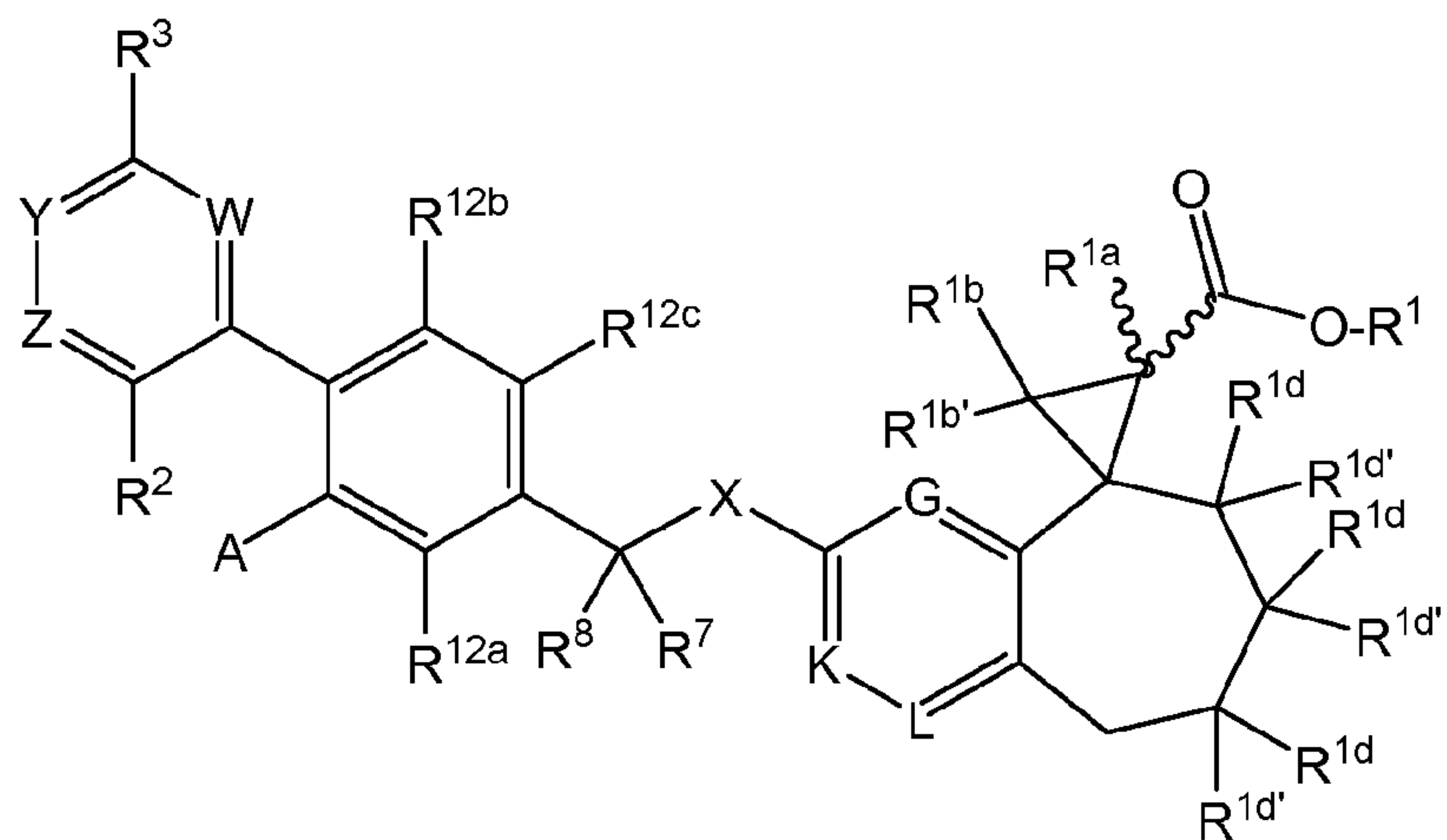
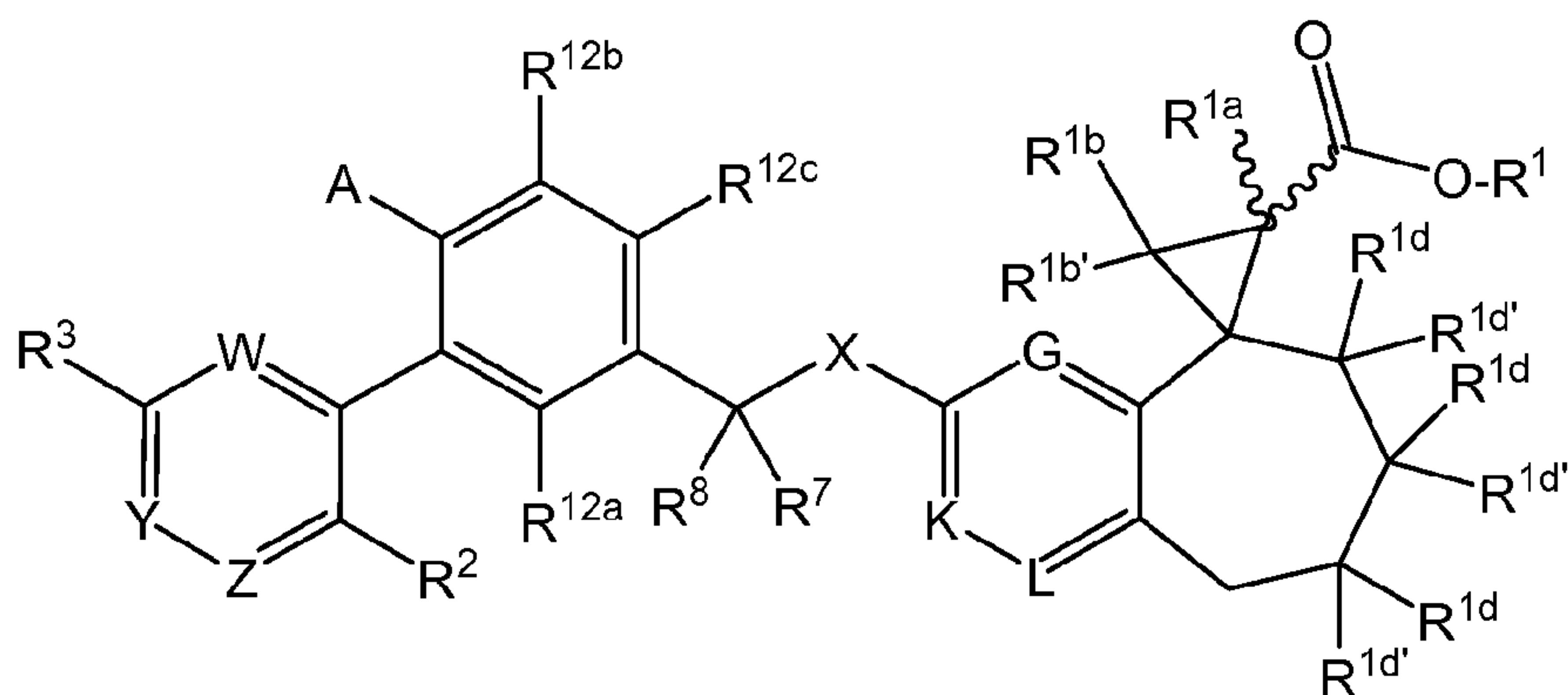
In some such embodiments, R^{1a} , R^{1b} , $R^{1b'}$, R^{1d} , and $R^{1d'}$ are H.

[0124] In some embodiments, the compound of formula **I'A** or **I'B** is a compound of formula **IV'A** or **IV'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula **IV'A** and **IV'B** have the following structures where each of the variables has any of the values of any of the embodiments described herein:

**IV'A****IV'B.**

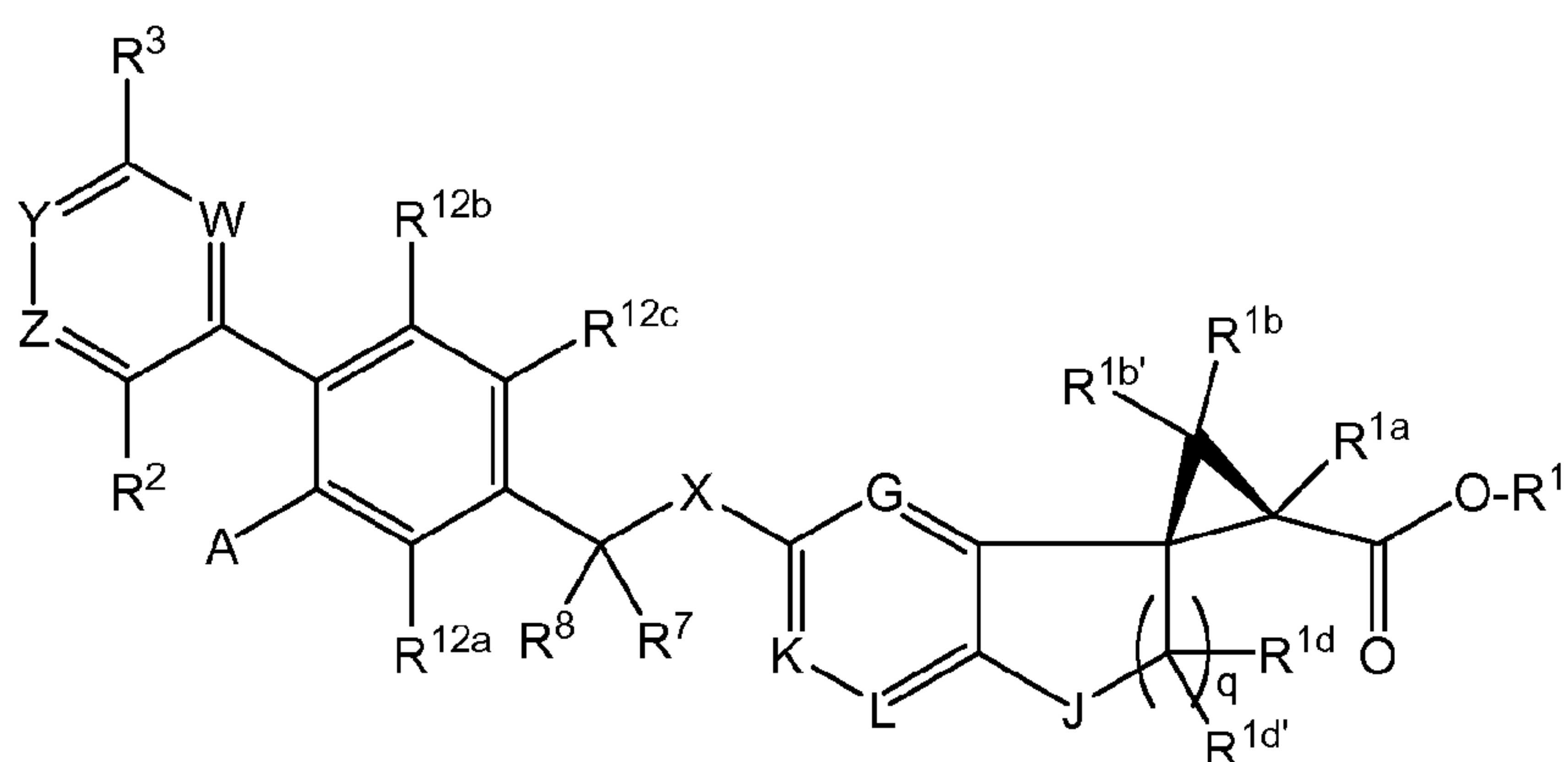
In some such embodiments, R^{1a} , R^{1b} , $R^{1b'}$, and each instance of R^{1d} and $R^{1d'}$ are H.

[0125] In some embodiments, the compound of formula **I'A** or **I'B** is a compound of formula **V'A** or **V'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula **V'A** and **V'B** have the following structures where each of the variables has any of the values of any of the embodiments described herein:

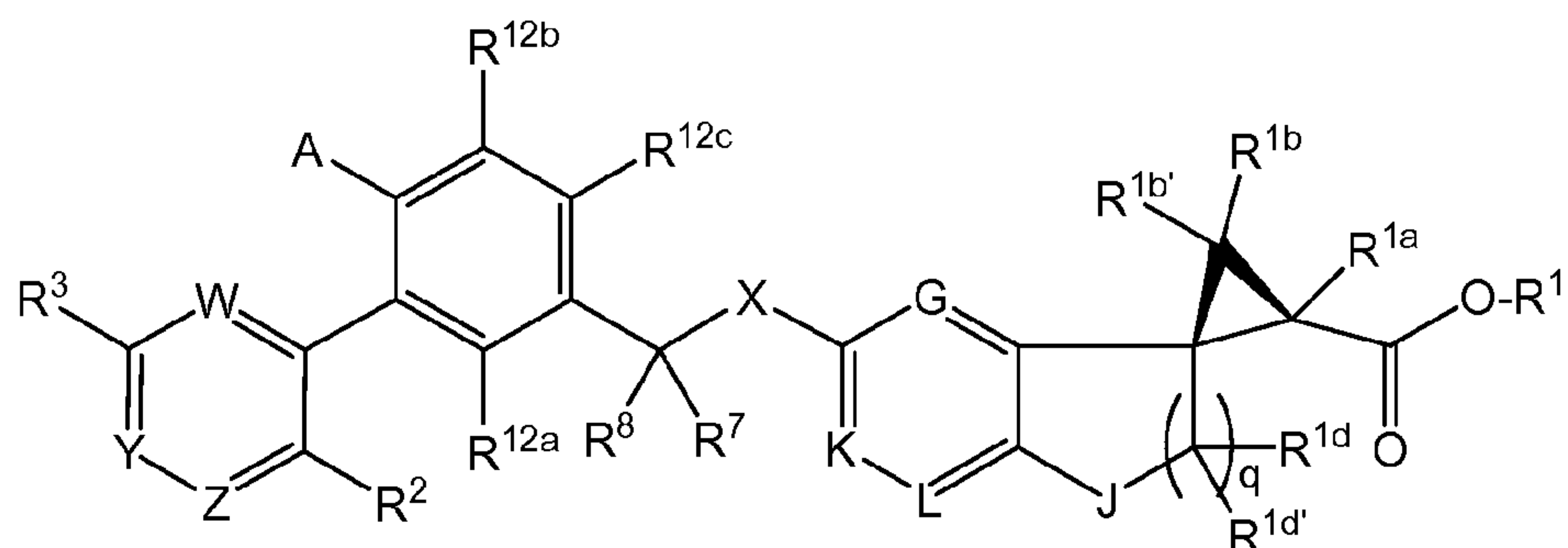
**V'A****V'B.**

In some such embodiments, R^{1a} , R^{1b} , $R^{1b'}$, and each instance of R^{1d} and $R^{1d'}$ are H.

[0126] In some embodiments, the compound of formula **I'A** or **I'B** is a compound of formula **VI'A** or **VI'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula **VI'A** and **VI'B** have the following structures where each of the variables has any of the values of any of the embodiments described herein:



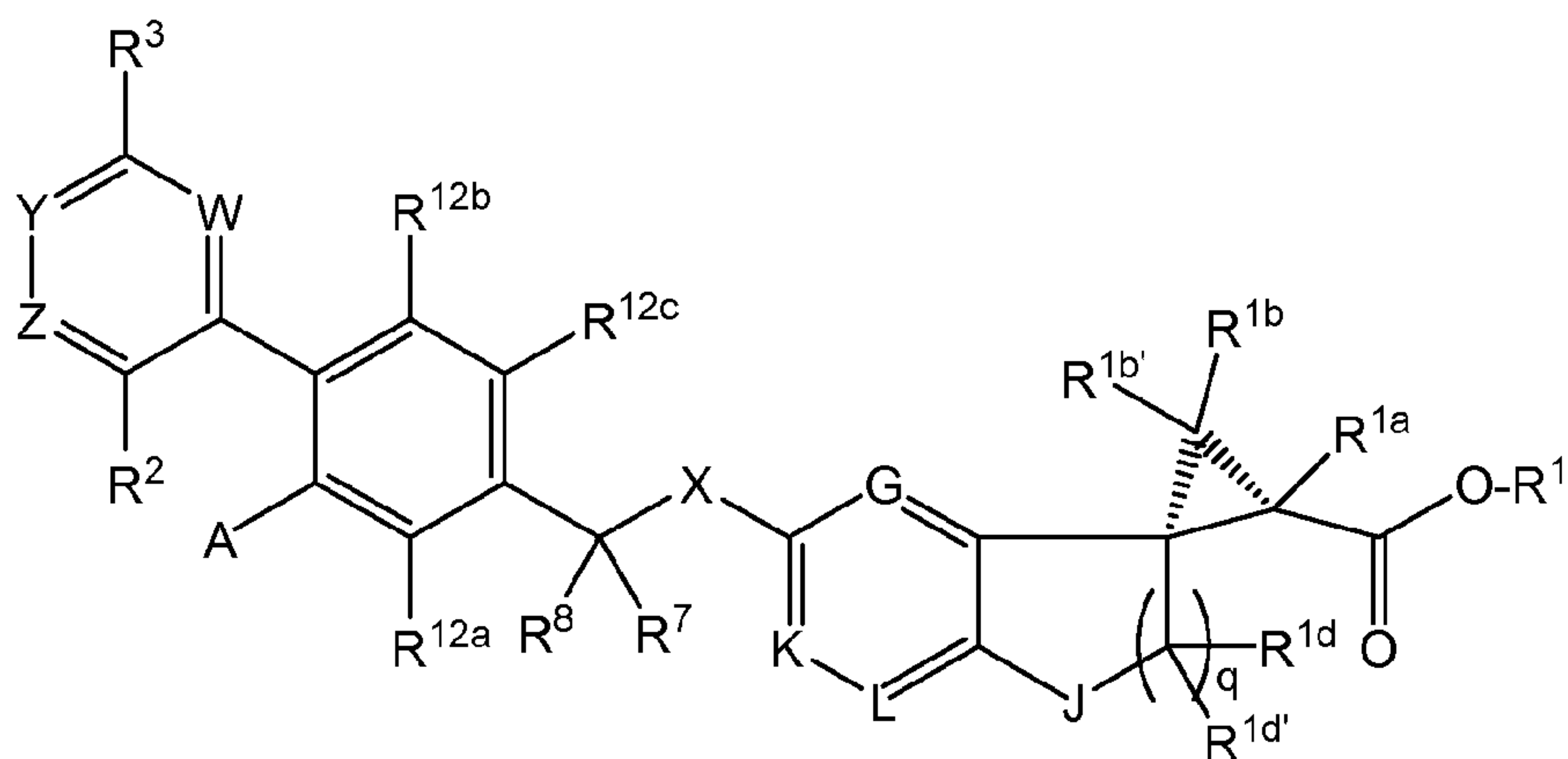
VI'A



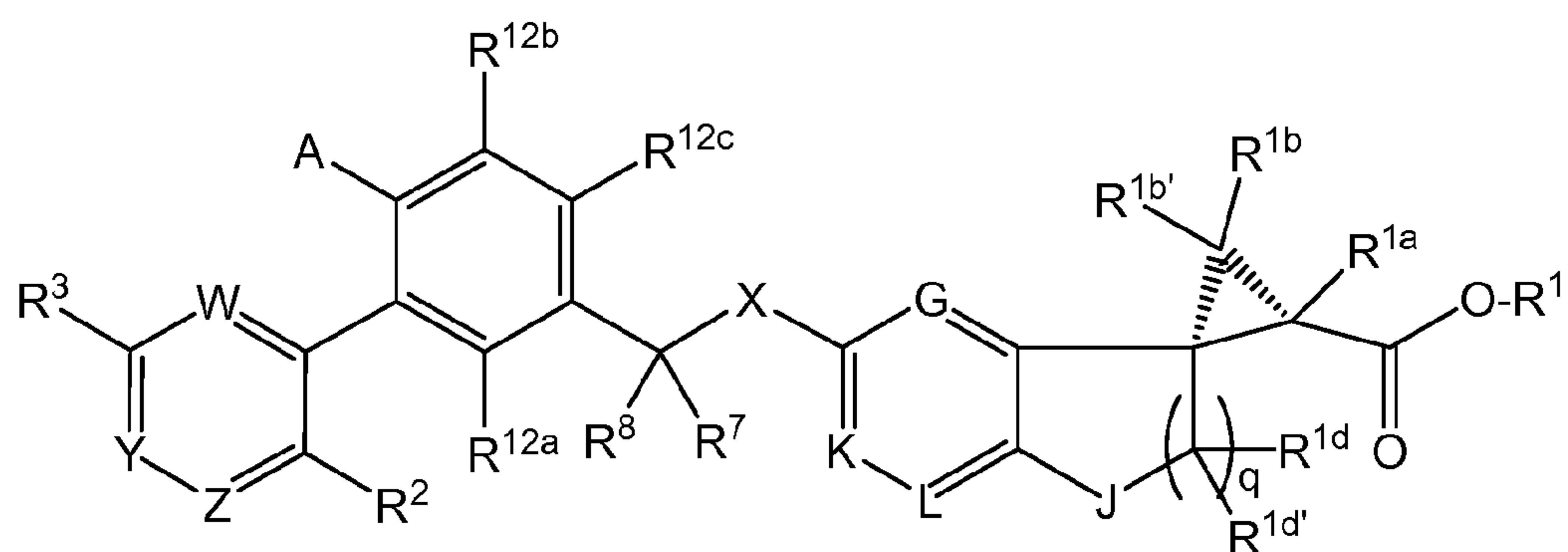
VI'B.

In some such embodiments, R^{1a} , R^{1b} , $R^{1b'}$, and each instance of R^{1d} and $R^{1d'}$ are H.

[0127] In some embodiments, the compound of formula **I'A** or **I'B** is a compound of formula **VII'A** or **VII'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula **VII'A** and **VII'B** have the following structures where each of the variables has any of the values of any of the embodiments described herein:

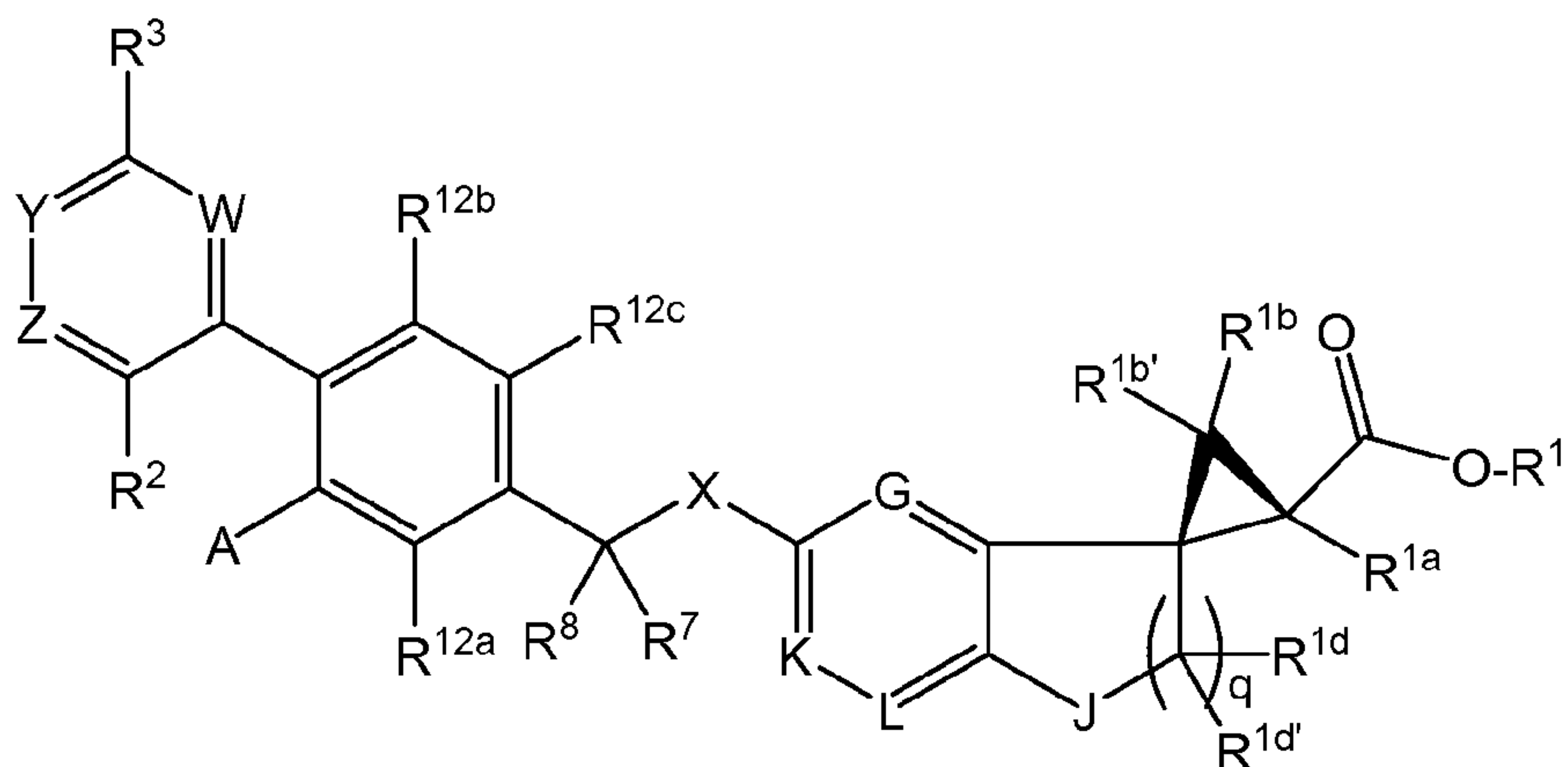
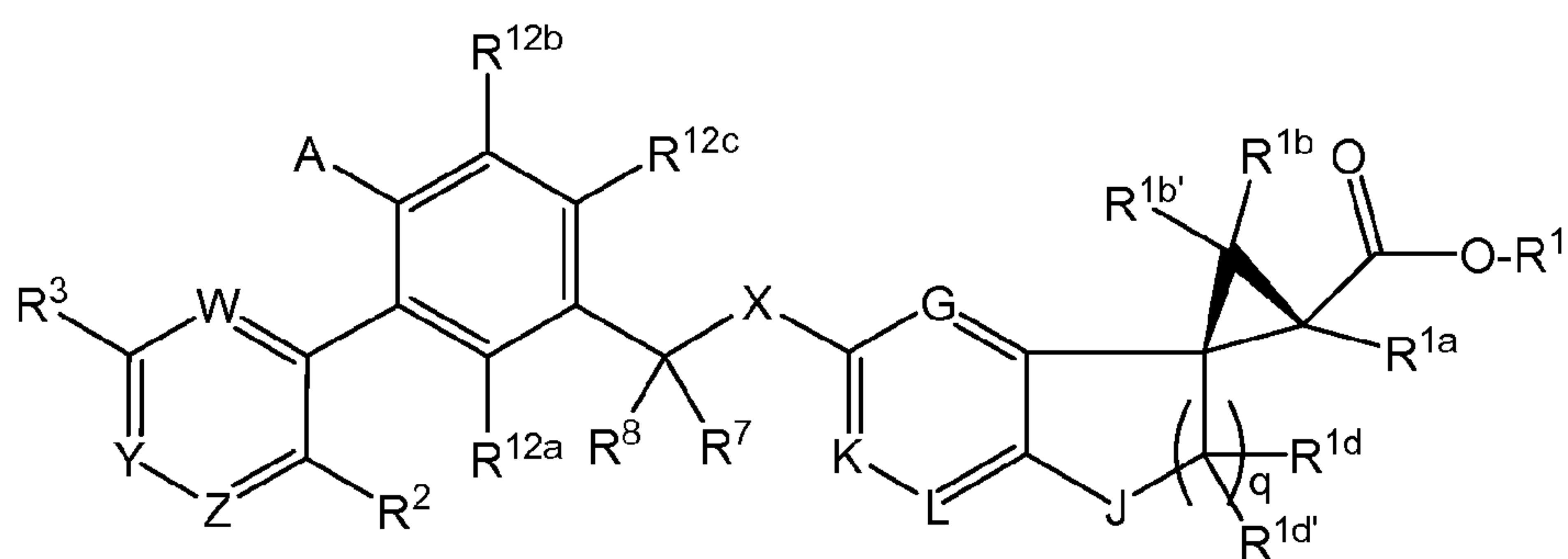


VII'A

**VII'B.**

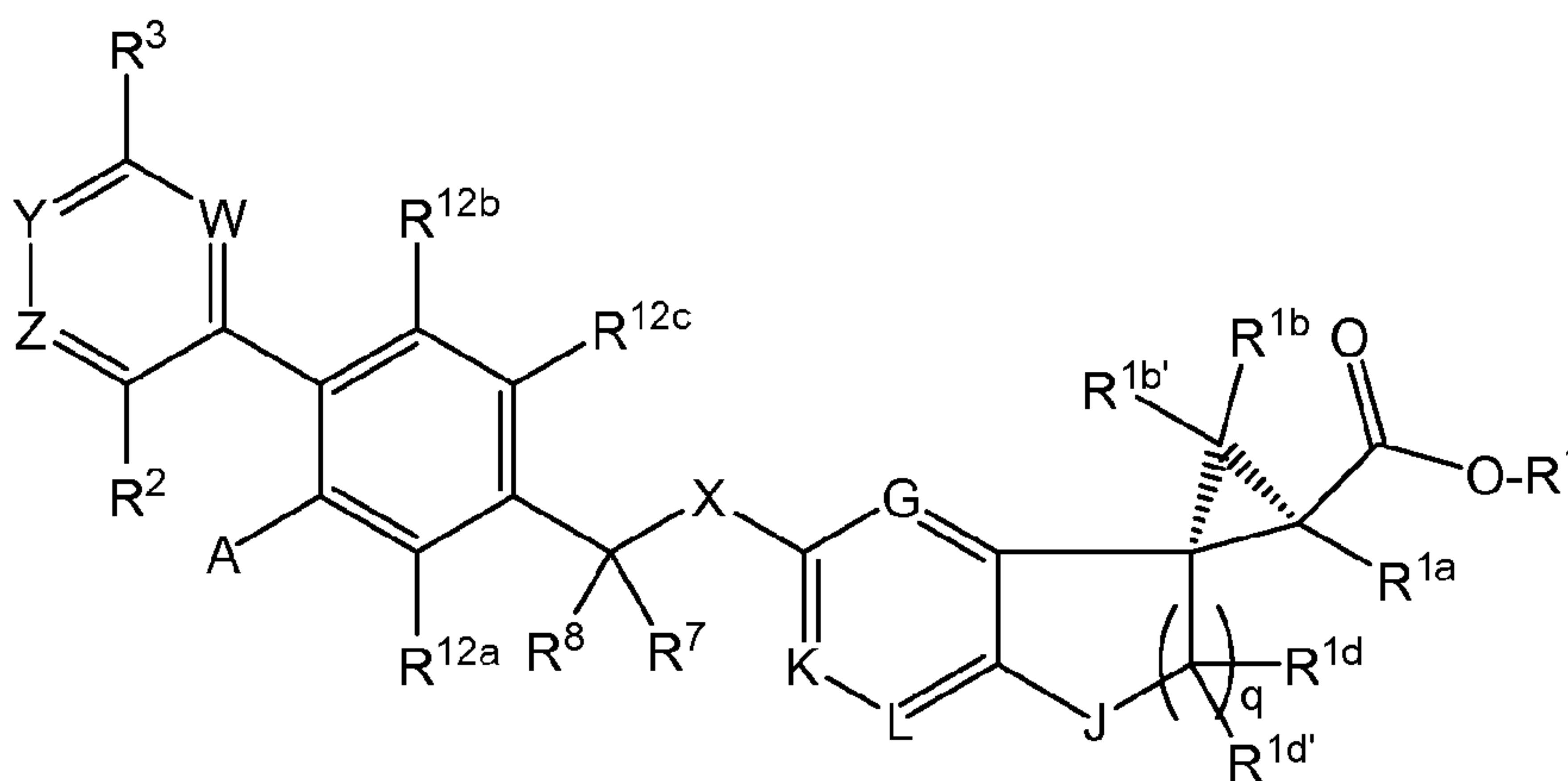
In some such embodiments, R^{1a} , R^{1b} , $R^{1b'}$, and each instance of R^{1d} and $R^{1d'}$ are H.

[0128] In some embodiments, the compound of formula **I'A** or **I'B** is a compound of formula **VIII'A** or **VIII'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula **VIII'A** and **VIII'B** have the following structures where each of the variables has any of the values of any of the embodiments described herein:

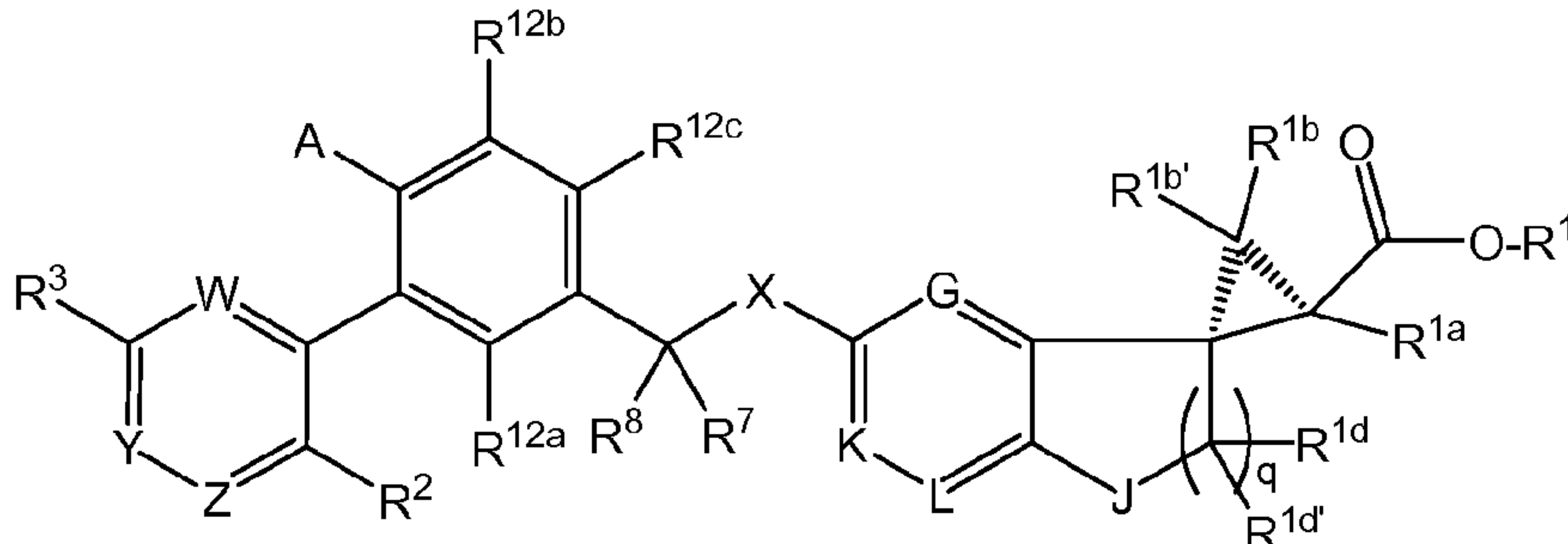
**VIII'A****VIII'B.**

In some such embodiments, R^{1a} , R^{1b} , $R^{1b'}$, and each instance of R^{1d} and $R^{1d'}$ are H.

[0129] In some embodiments, the compound of formula **I'A** or **I'B** is a compound of formula **IX'A** or **IX'B** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. The compounds of formula **IX'A** and **IX'B** have the following structures where each of the variables has any of the values of any of the embodiments described herein:



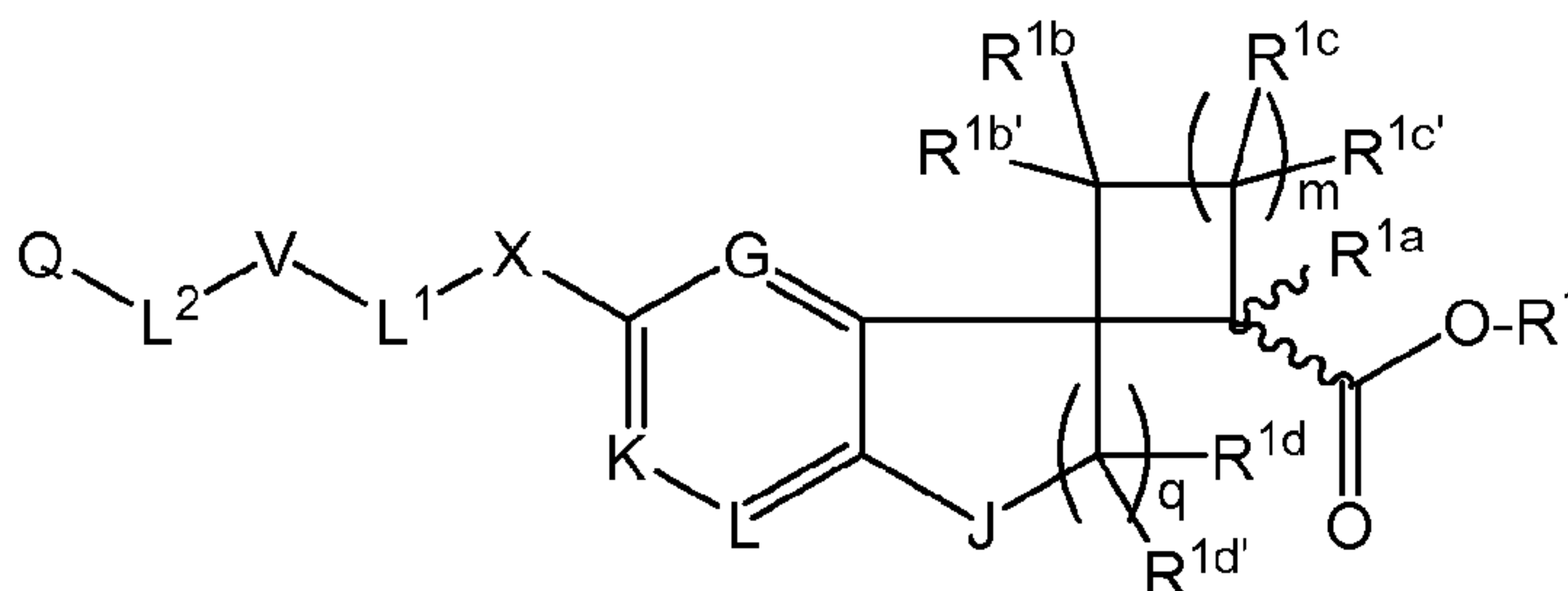
IX'A



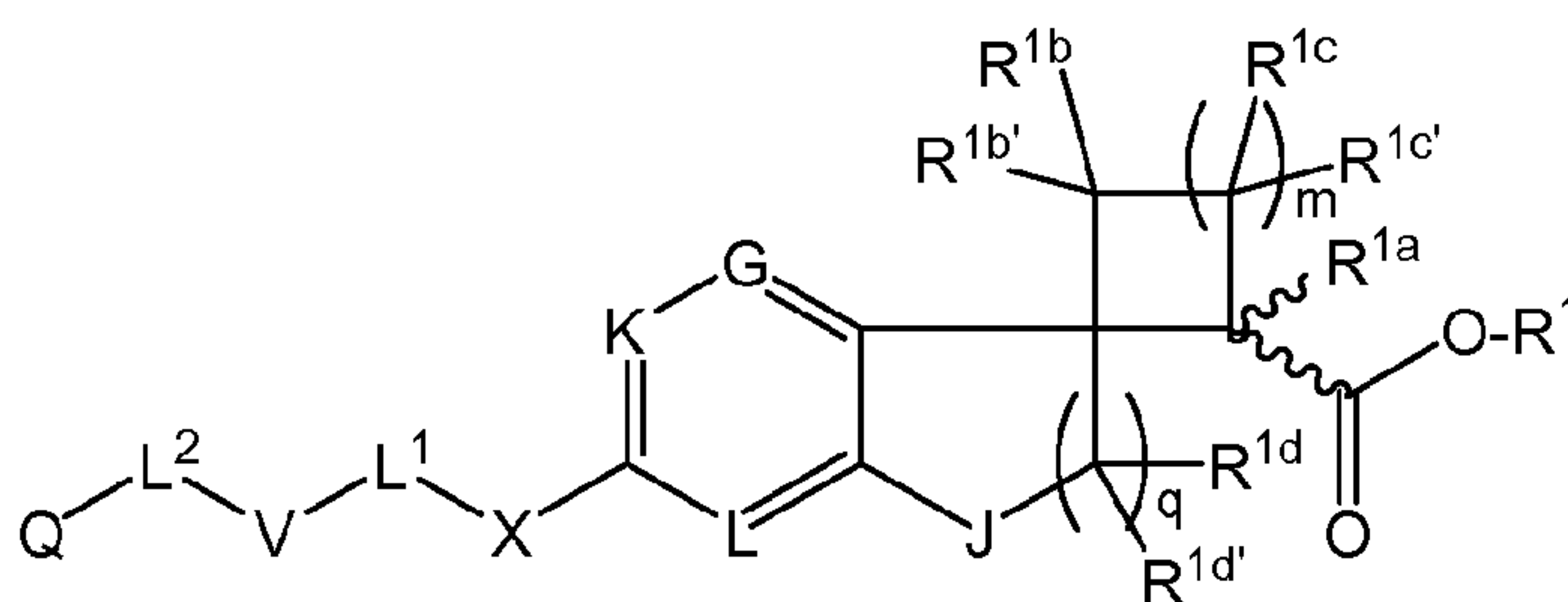
IX'B.

In some such embodiments, R^{1a} , R^{1b} , $R^{1b'}$, and each instance of R^{1d} and $R^{1d'}$ are H.

[0130] In another aspect, the invention provides a compound having the formula **IA** or **IB** or a pharmaceutically acceptable salt, stereoisomer, or mixture thereof. Compounds of formula **IA** and **IB** have the following structures:



IA



IB

or a pharmaceutically acceptable salt, stereoisomer, or a mixture thereof,
wherein

G is selected from N or CR^{11a};

K is selected from N or CR^{11b};

L is selected from N or CR^{11c};

wherein 0 or 1 of G, L, and K is N;

X is O, S, or NR^a wherein R^a is selected from -H or -(C₁-C₆) alkyl groups;

J is selected from O, S, NR^b, CR^cR^d, C(=O), or -C(=O)-NR^b-; wherein R^b is selected from H and (C₁-C₄)alkyl, and further wherein R^c and R^d are independently selected from H, F, and (C₁-C₄)alkyl;

L¹ is absent or is a (C₁-C₄) alkyl;

V is selected from a (C₄-C₈)cycloalkyl; a (C₆-C₁₀)aryl; a heteroaryl comprising from 5 to 10 ring members of which from 1 to 3 are heteroatoms selected from N, O, and S; a benzo-fused (C₅-C₈)cycloalkyl wherein the cycloalkyl group of the benzo-fused cycloalkyl is bonded to L¹, if present, or is bonded to X if L¹ is absent; a benzo-fused (C₅-C₈)cycloalkyl wherein the aromatic group of the benzo-fused cycloalkyl is bonded to L¹, if present, or is bonded to X if L¹ is absent; a heteroaryl-fused (C₅-C₈)cycloalkyl wherein the cycloalkyl group of the heteroaryl-fused cycloalkyl is bonded to L¹, if present, or is bonded to X if L¹ is absent; or a heteroaryl-fused (C₅-C₈)cycloalkyl wherein the heteroaryl group of the heteroaryl-fused cycloalkyl is bonded to L¹, if present, or is bonded to X if L¹ is absent; wherein the (C₆-C₁₀)aryl, heteroaryl, benzo-fused (C₅-C₈)cycloalkyl, and heteroaryl-fused (C₅-C₈)cycloalkyl group are optionally substituted with from 1 to 4 substituents independently selected from F, Cl, Br, OH, -O(C₁-C₆)alkyl groups, -S(C₁-C₆)alkyl groups (C₁-C₆)alkyl groups, -CF₃, or a group of formula A wherein A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-

C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, and -O-(C₁-C₄)alkyl-aryl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -(C₁-C₂)alkyl, or unsubstituted -O-(C₁-C₂)alkyl;

L² is absent or is selected from O, S, SO, SO₂, C(=O), (C₁-C₂)alkyl, or NR^x wherein R^x is selected from -H or -(C₁-C₆)alkyl groups;

Q is selected from H, a (C₄-C₈)cycloalkyl; a (C₆-C₁₀)aryl; or a heteroaryl comprising from 5 to 10 ring members of which from 1 to 3 are heteroatoms selected from N, O, and S; wherein the (C₄-C₈)cycloalkyl, (C₆-C₁₀)aryl, and heteroaryl groups are optionally substituted with from 1 to 5 substituents independently selected from F, Cl, Br, OH, -O(C₁-C₆)alkyl groups, -S(C₁-C₆)alkyl groups (C₁-C₆)alkyl groups, or -CF₃.

R¹ is H or -(C₁-C₆)alkyl;

R^{1a} is selected from -H and -(C₁-C₄)alkyl;

R^{1b} is selected from -H and -(C₁-C₄)alkyl;

R^{1b'} is selected from -H and -(C₁-C₄)alkyl;

R^{1c} is selected from -H and -(C₁-C₄)alkyl;

R^{1c'} is selected from -H and -(C₁-C₄)alkyl;

R^{1d} is in each instance independently selected from -H, -F, and -(C₁-C₄)alkyl;
 $R^{1d'}$ is in each instance independently selected from -H, -F and -(C₁-C₄)alkyl;
 R^{11a} , R^{11b} , and R^{11c} are independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or
 -O(C₁-C₄)alkyl;
 m is 0 or 1; and
 q is selected from 0, 1, 2, or 3,

wherein the  indicates that the R^{1a} and -C(=O)-O- R^1 may be attached to either side of the ring to which the  is attached and either R or S stereochemistry is allowed.

[0131] In some embodiments of the compound of formula **IA** or **IB**, L^1 is absent. In some such embodiments, X is O. In other embodiments L^1 is a (C₁-C₄) alkyl. In some such embodiments, X is O. In some embodiments L^1 is -CH₂-. In some embodiments L^1 is -CH₂- and X is O. In other embodiments, L^1 is -CH₂CH₂-. In still other embodiments, L^1 is -CH₂CH₂CH₂-.

[0132] In some embodiments of the compound of formula **IA** or **IB**, L^2 is absent or O. In some such embodiments, L^2 is absent. In other embodiments, L^2 is O.

[0133] In some embodiments of the compound of formula **IA** or **IB**, Q is H. In other embodiments, Q is an optionally substituted (C₆-C₁₀)aryl. In some such embodiments, Q is an optionally substituted benzene. In still other embodiments, Q is an optionally substituted heteroaryl comprising from 5 to 10 ring members of which from 1 to 3 are heteroatoms selected from N, O, and S. In some such embodiments Q is an optionally substituted pyridine.

[0134] In some embodiments of the compound of formula **IA** or **IB**, V is an optionally substituted (C₄-C₈)cycloalkyl such as a cyclopentyl, cyclohexyl, or cycloheptyl group. In other embodiments, V is an optionally substituted (C₆-C₁₀)aryl such as an optionally substituted benzene. In some such embodiments, V is a benzene that is substituted with an A group as described in any of the embodiments described herein. In yet other embodiments, V is an optionally substituted heteroaryl comprising from 5 to 10 ring members of which from 1 to 3 are heteroatoms selected from N, O, and S. For example, in some such embodiments, V is a methyl substituted thiazole group. In still other embodiments, V is an optionally substituted benzo-fused (C₅-C₈)cycloalkyl wherein the cycloalkyl group of the benzo-fused cycloalkyl is bonded to L^1 , if present, or is bonded to X if L^1 is absent. For example, in some such embodiments, V is a tetrahydronaphthalene or an indane in which the cycloalkyl group is bonded to the L^1 if

present or to the X if L^1 is absent. In still other embodiments, V is an optionally substituted benzo-fused (C_5 - C_8)cycloalkyl and the aromatic group of the benzo-fused cycloalkyl is bonded to L^1 , if present, or is bonded to X if L^1 is absent. For example, in some embodiments, V is an optionally substituted 1,2,3,4-tetrahydronaphthalene group. In some such embodiments, the cycloalkyl group of the tetrahydronaphthalene is substituted with 1 to 4 (C_1 - C_4)alkyl groups. In other embodiments, V is an optionally substituted heteroaryl-fused (C_5 - C_8)cycloalkyl and the cycloalkyl group of the heteroaryl-fused cycloalkyl is bonded to L^1 , if present, or is bonded to X if L^1 is absent. In still other embodiments, V is an optionally substituted heteroaryl-fused (C_5 - C_8)cycloalkyl and the heteroaryl group of the heteroaryl-fused cycloalkyl is bonded to L^1 , if present, or is bonded to X if L^1 is absent.

[0135] In some embodiments of the compound of formula **IA** or **IB**, G is CR^{11a} and R^{11a} is H.

[0136] In some embodiments of the compound of formula **IA** or **IB**, G is CR^{11a} and R^{11a} is F.

[0137] In some embodiments of the compound of formula **IA** or **IB**, K is CR^{11b} , L is CR^{11c} , and both R^{11b} and R^{11c} are H.

[0138] In some embodiments of the compound of formula **IA** or **IB**, R^{1a} is H or $-CH_3$. In some such embodiments, R^{1a} is H.

[0139] In some embodiments of the compound of formula **IA** or **IB**, R^{1b} is H or $-CH_3$. In some such embodiments R^{1b} is H.

[0140] In some embodiments of the compound of formula **IA** or **IB**, $R^{1b'}$ is H or $-CH_3$. In some such embodiments $R^{1b'}$ is H.

[0141] In some embodiments of the compound of formula **IA** or **IB**, R^{1c} is H or $-CH_3$. In some such embodiments R^{1c} is H.

[0142] In some embodiments of the compound of formula **IA** or **IB**, $R^{1c'}$ is H or $-CH_3$. In some such embodiments $R^{1c'}$ is H.

[0143] In some embodiments of the compound of formula **IA** or **IB**, R^{1d} is H or $-CH_3$. In some such embodiments R^{1d} is H.

[0144] In some embodiments of the compound of formula **IA** or **IB**, $R^{1d'}$ is H or $-CH_3$. In some such embodiments $R^{1d'}$ is H.

[0145] In some embodiments of the compound of formula **IA** or **IB**, q is 0, 1, or 2. In some such embodiments, q is 0. In other such embodiments, q is 1. In still other embodiments, q is 2.

[0146] In some embodiments of the compound of formula **IA** or **IB**, m is 0.

[0147] In some embodiments of the compound of formula **IA** or **IB**, J is O, NR^b , or S. In other embodiments, J is CR^cR^d . In some such embodiments, R^c and R^d are independently selected from H or $-\text{CH}_3$ and in some such embodiments R^c and R^d are both H.

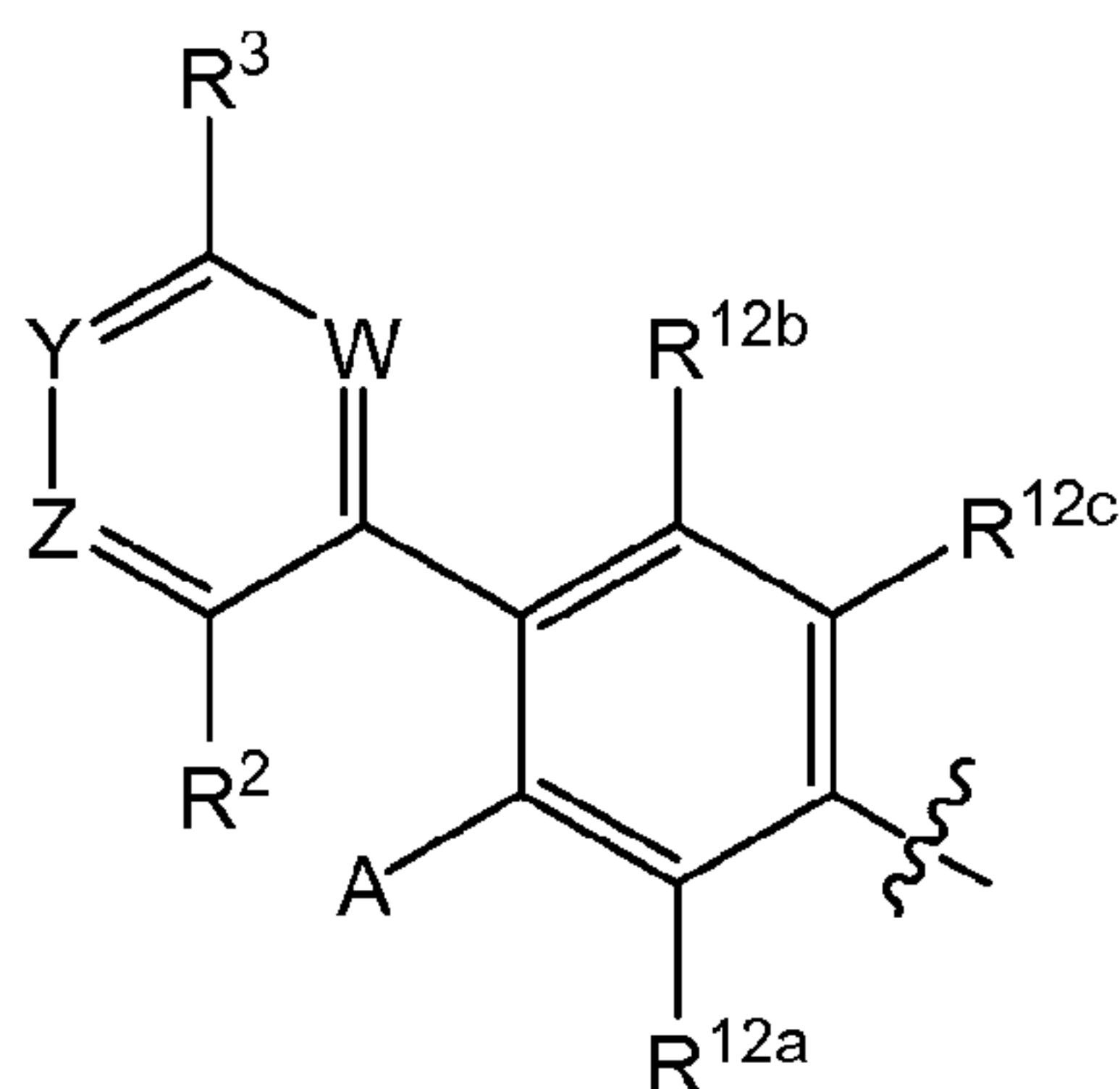
[0148] In some embodiments of the compound of formula **IA** or **IB**, the compound has the formula **IA**.

[0149] In some embodiments of the compound of formula **IA** or **IB**, the compound has the formula **IB**.

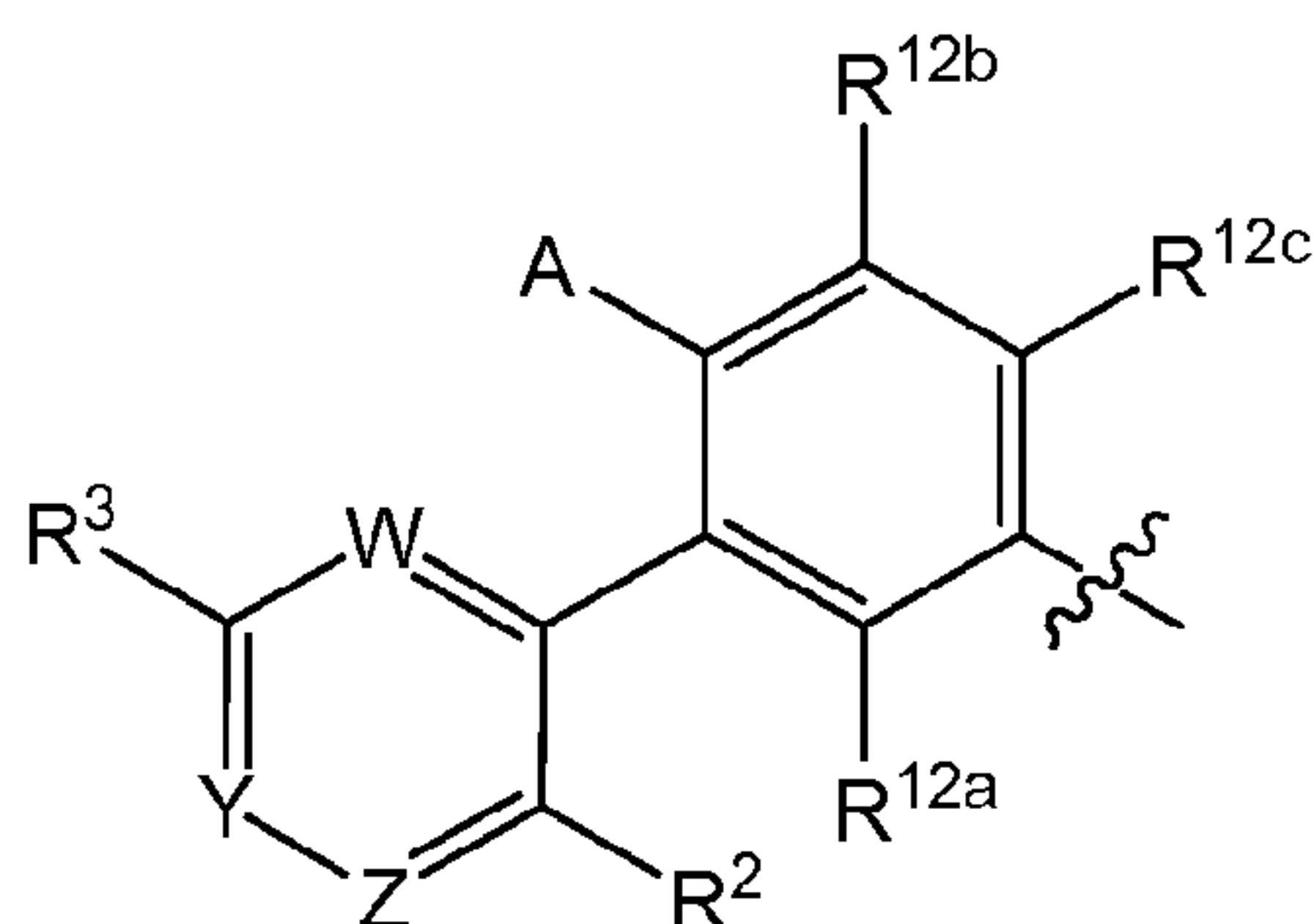
[0150] In some embodiments of the compound of formula **IA** or **IB**, X is O.

[0151] In some embodiments of the compound of formula **IA** or **IB**,

$\text{Q}-\text{L}^2-\text{V}-\begin{array}{c} \text{---} \\ \text{---} \\ \text{---} \end{array}$ has the formula



or



wherein

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N; and further wherein Z is not N if R² is -F;

A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, and -O-(C₁-C₄)alkyl-aryl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -(C₁-C₂)alkyl, or unsubstituted -O-(C₁-C₂)alkyl;

R² is selected from -H, -F, -CF₃, -Cl, or -O-(C₁-C₆)alkyl;

R^3 is -H, -F, -Cl, -OH, -(C₁-C₄)alkyl, -O-(C₁-C₃)alkyl, or -S-(C₁-C₂)alkyl;

R^{12a} , R^{12b} , and R^{12c} are independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl; and

R^{13} is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl, and

the  through the bond indicates the point of attachment to L¹ if present or X if L¹ is absent. In some such embodiments, X is O. In other embodiments, R^3 is selected from -OH, -O-(C₁-C₂)alkyl, or -S-(C₁-C₂)alkyl. In some such embodiments, R^3 is methoxy. In some embodiments, W, Y, and Z are all C-H whereas in other embodiments W and Z are C-H and Y is N. In some embodiments, R^{12c} is H whereas in other embodiments, R^{12c} is F. In some embodiments, R^{12a} and R^{12b} are both H. In some embodiments, G is CR^{11a} and R^{11a} is H. In other embodiments, G is CR^{11a} and R^{11a} is F. In some embodiments, K is CR^{11b}, L is CR^{11c}, and both R^{11b} and R^{11c} are H. In some embodiments, R^2 is selected from -H, -F, -CF₃, or -O-(C₁-C₆)alkyl. In some embodiments, R^2 is selected from F, CF₃, or (C₁-C₆)alkoxy. In some such embodiments, R^2 is selected from F, CF₃, or (C₄-C₆)alkoxy. Therefore, in some embodiments, R^2 is F. In some embodiments, R^2 is propoxy, butoxy, or pentoxy. In other embodiments, R^2 is -Cl. In some embodiments, G is CR^{11a}; K is CR^{11b}; L is CR^{11c}; R^{11b} , R^{11c} , R^{12a} , and R^{12b} are all H; J is CR^cR^d; R^c is H; R^d is H; R^{1a} is H; R^{1b} is H; $R^{1b'}$ is H; R^{1d} , if present, is H; $R^{1d'}$, if present, is H; W is C-H; Y is C-H or N; Z is C-H; R^2 is F; R^3 is methoxy; R^7 is H; R^8 is H; X is O; m is 0; and q is 0, 1, or 2. In some such embodiments Y is C-H whereas in other such embodiments, Y is N. In some such embodiments q is 0 whereas in other such embodiments q is 1 and in still other embodiments, q is 2. In some such embodiments, R^{12c} is F whereas in other embodiments, R^{12c} is H. In some such embodiments, R^{11a} is F whereas in other embodiments, R^{11a} is H. In some embodiments, A has the definitions of any of the embodiments described herein.

[0152] In some embodiments of the compound of formula **IA** or **IB**, R^1 is H

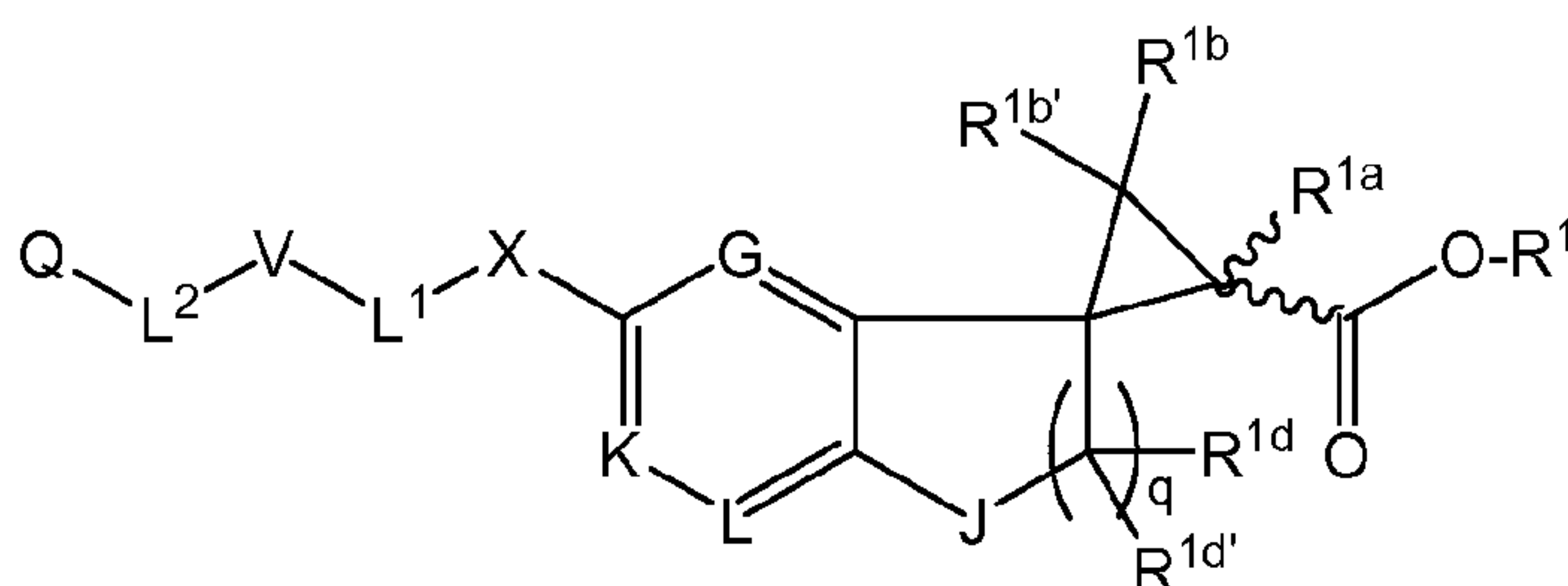
[0153] In some embodiments, the compound is selected from a group that includes each, all, or any one of the compounds in any of the tables or is a pharmaceutically acceptable salt thereof. In some such embodiments where the compound has a chiral center, the compound exists as a single enantiomer whereas in other embodiments, the compound is a mixture of enantiomers of the compounds shown above. In some such embodiments, the compound is one of the compounds in any of the tables or is a pharmaceutically acceptable salt thereof. In other embodiments, the

compound is an enantiomer or diastereomer of one of the compounds in any of the tables or is a pharmaceutically acceptable salt, or mixture thereof.

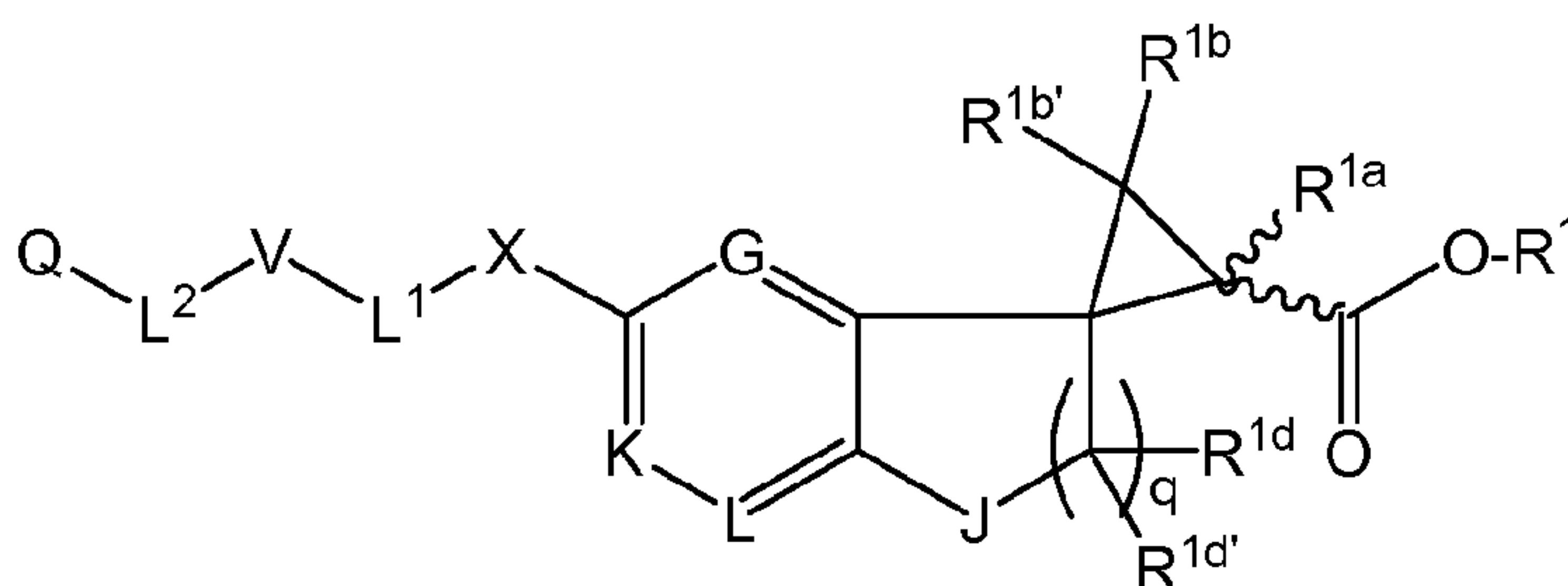
[0154] In some embodiments, the compound is selected from any of those in any of the tables. Furthermore, in some embodiments, the compound has a variable corresponding to any of the groups in the compounds of any of the tables. For example, if a compound in any of the tables has a group corresponding to the A group, then in some embodiments of the compound, the A group will correspond to that set forth in the compound(s) in any of the tables.

[0155] In some embodiments, R^1 is H such that the compound is a carboxylic acid. In other embodiments, R^1 is an unsubstituted $-(C_1-C_6)$ alkyl group such as a methyl, ethyl, propyl, butyl, pentyl, hexyl, or isopropyl group. Therefore, in some embodiments, R^1 is a $-CH_3$ or a $-CH_2CH_3$ group.

[0156] In some embodiments of the compound of formula **IA** or **IB**, the compound of formula **IA** or **IB** is a compound of formula **IIA** or **IIB**. The compounds of formula **IIA** and **IIB** have the following structures where each of the variables has any of the values of any of the embodiments described herein:



IIA



IIB.

In some such embodiments, the compound has the formula **IIA** whereas in other embodiments, the compound has the formula **IIB**.

[0157] In some embodiments, the compound of any of the embodiments is a salt.

[0158] In some embodiments, the compound comprises a stereomerically pure S-enantiomer. In other embodiments, the compound comprises a stereomerically pure R-enantiomer. In yet other embodiments, the compound comprises a mixture of S- and R-enantiomers.

[0159] In another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent, or excipient, and a compound of any of the embodiments of the invention.

[0160] In another aspect, a compound of any of the embodiments described herein is used to prepare a medicament.

[0161] In yet another aspect, the invention provides a therapeutic composition that includes a compound of any of the embodiments and a second therapeutic agent as a combined preparation for simultaneous, separate, or sequential use in the treatment of a disease or condition mediated by GPR40. In some such embodiments, the disease or condition is type II diabetes. In some embodiments, the second therapeutic agent is selected from metformin, a thiazolidinedione, or a DPP-IV inhibitor. In some embodiments, the compound of any of the embodiments described herein and the second therapeutic agent are provided as single composition. In other embodiments, the compound of any of the embodiments described herein and the second therapeutic agent are provided separately as parts of a kit.

[0162] In some embodiments, the invention provides a compound of any of the embodiments described herein for use as a medicament.

[0163] In some embodiments, the invention provides a compound of any of the embodiments described herein for use in modulating GPR40.

[0164] In some embodiments, the invention provides a compound of any of the embodiments described herein for use in treating a disease or condition selected from type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, or edema. In some such embodiments, the compound is used for treating type II diabetes.

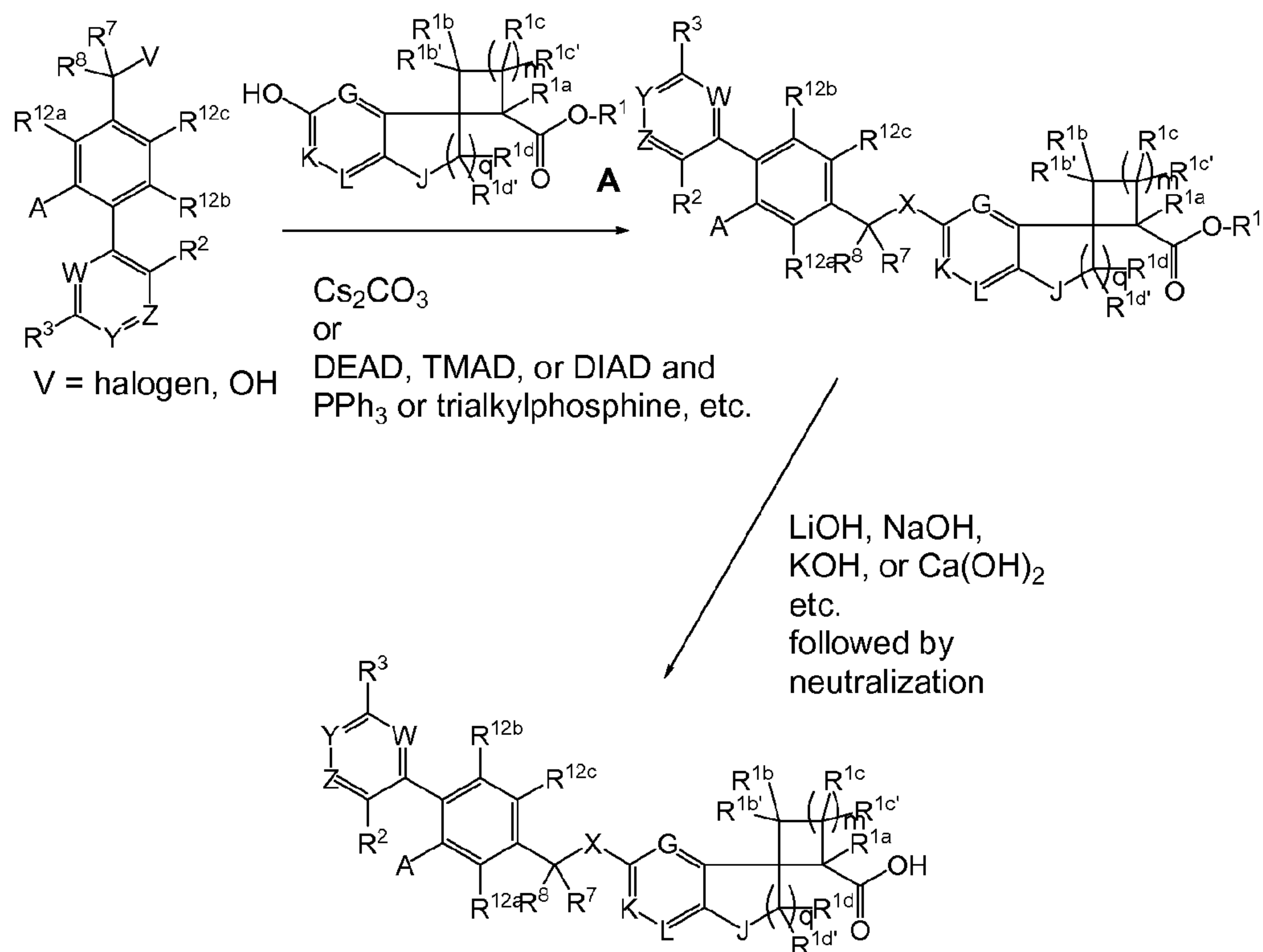
[0165] The compounds of the invention may stimulate GLP-secretion. Cells contacted with compounds of the invention may increase GLP-1 secretion. Therefore, in some embodiments, the invention provides a method of stimulating GLP-1 secretion by cells. Such methods typically include contacting a cell capable of producing GLP-1 with a compound of any of the embodiments set forth herein. Administration of the compounds of the invention to subjects may provide increased levels of GLP-1 in the blood plasma of such subjects. Therefore, in some embodiments, a compound of any of the embodiments described herein may be used to stimulate GLP-1 secretion and increase the blood plasma level of GLP-1 in a subject. In some such embodiments, the compounds of the invention both stimulate GLP-1 secretion and activate GPR40. Therefore, in some embodiments, the compounds of the invention both stimulate GLP-1 secretion and display incretin effect by activating GPR40.

[0166] In some embodiments, the invention further provides a method for increasing GLP-1 levels in the blood plasma of a subject. Such methods typically include administering a compound of any of the embodiments to a subject. In some such embodiments, the subject is a diabetic patient. In other such embodiments, the subject is an obese patient. In some embodiments, the invention provides a method for stimulating weight loss in a subject. In such embodiments, a compound of any of the embodiments is administered to a subject in an effective amount to stimulate weight loss in the subject. The compounds of the invention may be administered in the fasted or non-fasted state. Therefore, in some embodiments, a compound of any of the embodiments is administered to a subject prior to a meal. In some such embodiments, the compound is administered 2 hours, 1 hour, 30 minutes, or 15 minutes before a meal. In other embodiments, a compound of any of the embodiments set forth herein is administered to a subject during a meal. In other embodiments, a compound of any of the embodiments described herein is administered to a subject within 2 hours, within 1 hour, within 30 minutes, or within 15 minutes of a meal.

[0167] The compounds of the invention can be prepared by a variety of synthetic or semisynthetic techniques. Scheme 1 provides a general synthetic scheme for exemplary compounds of the invention of formula **I'A** utilizing ester **A** where the variables in Scheme 1 have any of the values described above with respect to any of the embodiments, V is a OH or a halogen such as, but not limited to a Cl, Br, or I, or sulfonate ester such as, but not limited to OTs (tosylate) or OTf (triflate); and Alk is a straight or branched chain alkyl group having from 1-8 carbon atoms. It will be

understood that the phenolic OH group of **A** can be replaced with an SH and reacted with a compound where V is a halogen to produce the analogous S-containing derivative (X = S) to the compounds shown. The synthesis of various chloromethyl, bromomethyl, and hydroxymethyl biphenyl tail group compounds and phenol carboxylic acid head group compounds is described herein. Appropriate starting materials can be prepared by techniques known or apparent to those of skill in the art or the starting materials may be commercially available. One of skill in the art will understand that the synthetic routes can be modified to use different starting materials or alternative reagents and that suitable adjustments in conditions (e.g., temperatures, solvents, etc.) can be made to accomplish the desired transformations. One of skill in the art will recognize that protecting groups may be necessary for the preparation of certain compounds and will be aware of those conditions compatible with a selected protecting group. Examples of such protecting groups include, for example, those set forth in *Protective Groups in Organic Synthesis*, Greene, T. W.; Wuts, P. G. M., John Wiley & Sons, New York, N.Y., (3rd Edition, 1999). Accordingly, the exemplary methods and the examples described herein are illustrative of the present invention and are not to be construed as limiting the scope thereof. One of skill in the art will recognize that compounds of formula **I'B** may be prepared using a similar scheme using the appropriately substituted tail group in place of that shown in Scheme 1. The same is true for compounds with tail groups different from that of the compounds of formula **I'A** and **I'B**.

Scheme 1



5.2.2 Compositions

[0168] In another aspect, the invention provides pharmaceutical compositions suitable for pharmaceutical use comprising one or more compounds of the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

[0169] The term “composition” as used herein is intended to encompass a product comprising the specified ingredients (and in the specified amounts, if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By “pharmaceutically acceptable” it is meant that the carrier, excipient, or diluent is compatible with the other ingredients of the formulation and is not deleterious to the recipient thereof.

[0170] Composition formulation may improve one or more pharmacokinetic properties (*e.g.*, oral bioavailability, membrane permeability) of a compound of the invention (herein referred to as the active ingredient).

[0171] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art. All methods include the step of

bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[0172] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,256,108, 4,160,452, and 4,265,874 to form osmotic therapeutic tablets for control release.

[0173] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0174] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose,

hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0175] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0176] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0177] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0178] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents.

[0179] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0180] The pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, for example, cocoa butter and polyethylene glycols.

[0181] For topical use, creams, ointments, jellies, solutions, or suspensions, *etc.*, containing the compounds of the invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.

[0182] The pharmaceutical compositions and methods of the invention may further comprise other therapeutically active compounds, as noted herein, useful in the treatment of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

5.2.3 Methods of Use

[0183] In another aspect, the invention provides methods of treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema. The methods comprise administering to a subject in need thereof, a therapeutically effective amount of a compound or composition of any of the embodiments of the invention.

[0184] In one embodiment, the disease or condition is type II diabetes.

[0185] In another aspect, the present invention provides a method for treating a disease or condition responsive to the modulation of GPR40. Such methods comprise administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

[0186] In some embodiments, the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

[0187] In certain embodiments, the disease or condition is type II diabetes.

[0188] In some embodiments, the disease or condition is obesity.

[0189] In some embodiments, the disease or condition is hypertension.

[0190] In some embodiments of administering the compounds or compositions of the invention, the compound or composition is administered orally, parenterally, or topically. In some embodiments, the compound or composition is administered orally. In other embodiments, the compound or composition is administered parenterally. In other embodiments, the compound or composition is administered topically.

[0191] The compounds of the invention may be administered alone or in combination with one or more other therapeutic agents. Therefore, in some embodiments,

the compound or composition of any of the embodiments is administered in combination with a second therapeutic agent. In some such embodiments, the second therapeutic agent is an insulin sensitizing agent, such as metformin or a thiazolidinedione, for example. In some embodiments, the second therapeutic agent is a GLP-1 analog. In some embodiments, the second therapeutic agent is an inhibitor of DPP-IV such as, but not limited to, sitagliptin.

[0192] In another aspect, the invention provides methods of treating a disease or disorder responsive to modulation of GPR40 comprising administering to a subject having such a disease or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions.

[0193] In yet another aspect, the invention provides methods of treating a GPR40-mediated condition, disease or disorder comprising administering to a subject having such a condition, disease or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions.

[0194] In yet another aspect, the invention provides methods of modulating GPR40 comprising contacting a cell with one or more of the subject compounds or compositions.

[0195] For example, in some embodiments, a cell that constitutively expresses GPR40 is contacted with one or more of the subject compounds or compositions.

[0196] In certain embodiments, a cell to be contacted can be made to express or overexpress GPR40, for example, by expressing GPR40 from heterologous nucleic acid introduced into the cell or, as another example, by upregulating the expression of GPR40 from nucleic acid endogenous to the cell.

[0197] Depending on the disease to be treated and the subject's condition, the compounds of the invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal, local) routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. The invention also contemplates administration of the compounds of the invention in a depot formulation, in which the active ingredient is released over a defined time period.

[0198] In the treatment of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema or other conditions or disorders associated with GPR40, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range, the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 3.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[0199] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0200] The compounds of the invention can be combined or used in combination with other agents useful in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds of the invention are useful, including type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema. Such other agents, or drugs,

may be administered, by a route and in an amount commonly used therefore, simultaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound of the invention.

[0201] The compounds of the invention may be used in combination with a second therapeutic agent such as those described herein. Thus, in some embodiments, therapeutic compositions are provided that include a compound of the invention and a second therapeutic agent as a combined preparation for simultaneous, separate or sequential use in the treatment of a subject with a disease or condition mediated by GPR40. In some embodiments, therapeutic compositions are provided that include a compound of the invention and a second therapeutic agent as a combined preparation for simultaneous, separate or sequential use in the prophylactic treatment of a subject at risk for a disease or condition mediated by GPR40. In some such embodiments, the components are provided as a single composition. In other embodiments, the compound and the second therapeutic agent are provided separately as parts of a kit.

[0202] Examples of other therapeutic agents that may be combined with a compound of the invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) cholesterol lowering agents such as HMG-CoA reductase inhibitors (*e.g.*, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and other statins), bile acid sequestrants (*e.g.*, cholestyramine and colestipol), vitamin B₃ (also known as nicotinic acid, or niacin), vitamin B₆ (pyridoxine), vitamin B₁₂ (cyanocobalamin), fibric acid derivatives (*e.g.*, gemfibrozil, clofibrate, fenofibrate and benzafibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (*e.g.*, beta-sitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (b) antithrombotic agents, such as thrombolytic agents (*e.g.*, streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β -blockers (*e.g.*, atenolol), β -adrenergic agonists (*e.g.*, isoproterenol), ACE inhibitors and vasodilators (*e.g.*, sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enalaprilat); and (c) anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (*e.g.*, glyburide, meglitinide), biguanides, *e.g.*, metformin

(GLUCOPHAGE[®]), α -glucosidase inhibitors (acarbose), insulin sensitizers, *e.g.*, thiazolidinone compounds, rosiglitazone (AVANDIA[®]), troglitazone (REZULIN[®]), ciglitazone, pioglitazone (ACTOS[®]) and englitazone, DPP-IV inhibitors, *e.g.*, vildagliptin (*Galvus*[®]), sitagliptin (*Januvia*[™]), and GLP-I analogs, *e.g.*, exenatide (*Byetta*[®]). In some embodiments, a compound of the invention may be administered along with a DPP-IV inhibitor or a GLP-I analog. In some embodiments, a compound of the invention is administered with any of the DPP-IV inhibitors set forth in U.S. Patent Publication No. 2006/0270701 which is hereby incorporated by reference in its entirety and for all purposes as if specifically set forth herein.

[0203] The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Combinations of a compound of the invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0204] In another aspect, the present invention provides a method for modulating circulating insulin concentration in a subject, comprising administering a compound or composition of the invention.

[0205] In some embodiments, the insulin concentration is increased after the compound is administered to the subject.

[0206] In other embodiments, the insulin concentration is decreased after the compound is administered to the subject.

[0207] The compounds and compositions described herein may be used to treat a variety of disease states and conditions. Therefore, in some embodiments, a compound of composition of any of the described embodiments is used for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema. In some such embodiments, the disease or condition is type II diabetes.

[0208] The compounds of the invention may also be used to modulate GPR 40. Therefore, in some embodiments, a compound or composition of any of the embodiments is used for modulating GPR40.

[0209] The compounds of any of the embodiments described herein may be used to prepare medicaments for treating the diseases or conditions described herein such as type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and/or edema. In some embodiment, the disease or condition is type II diabetes. The compounds of any of the embodiments may also be used to prepare medicaments for modulating GPR40 in a subject such as in a mammalian subject with type II diabetes.

[0210] The following examples are offered by way of illustration and are not intended to limit the scope of the invention. Those of skill in the art will readily recognize a variety of noncritical parameters that could be modified to yield essentially similar results.

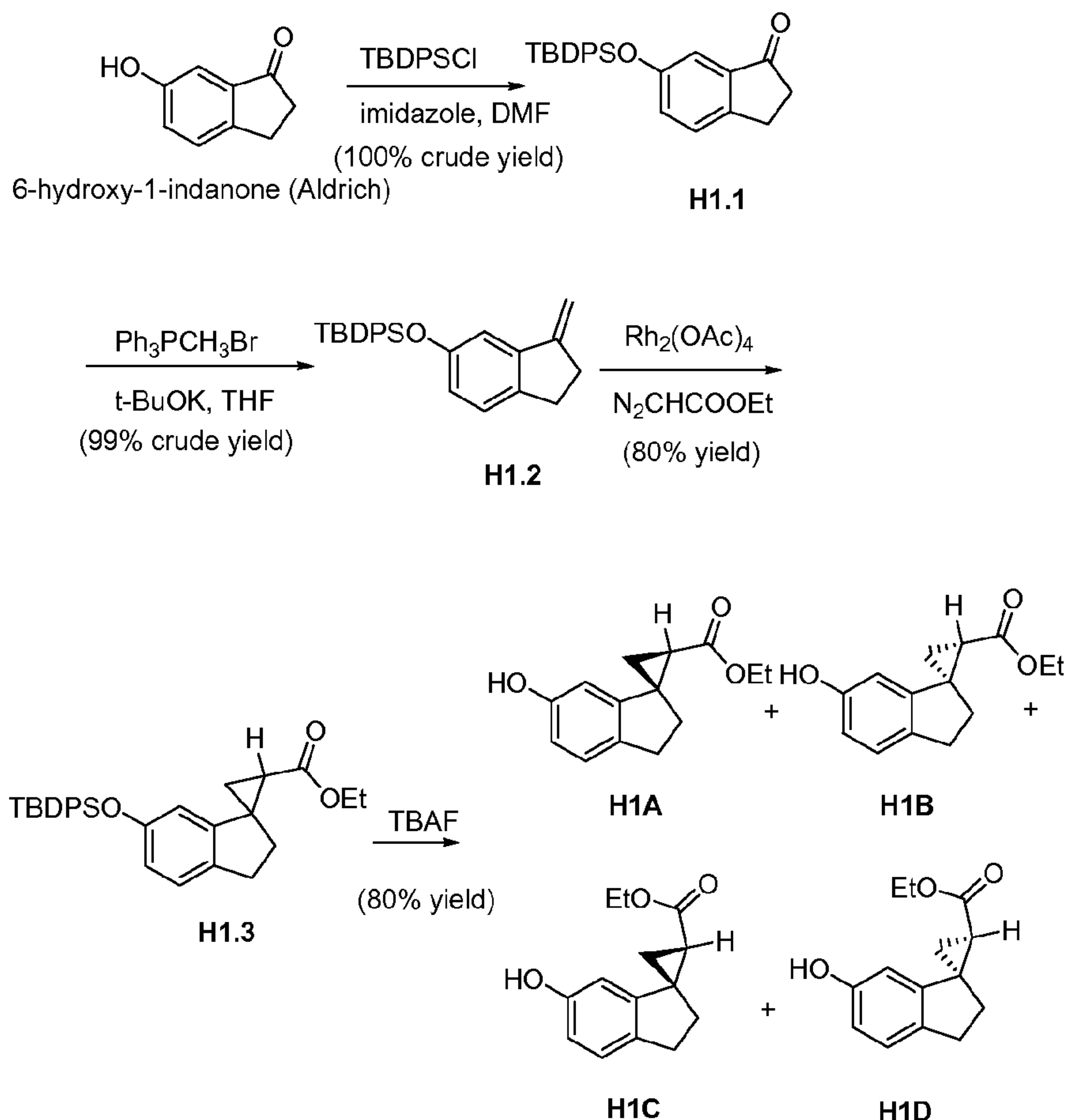
6. EXAMPLES

[0211] Unless otherwise stated, all compounds were obtained from commercial sources or were prepared using the methods and experimental procedures described herein. Various procedures are also set forth in published U.S. Patent Application No. 2006/0004012.

The following abbreviations are used to refer to various reagents, solvents, experimental procedures, or analytical techniques that are described in the examples:

ACN	Acetonitrile
AcOH	Acetic acid
DCM	Dichloromethane
DMF	N,N'-Dimethyl Formamide
DMAP	Dimethylaminopyridine
DME	Dimethoxyethane

DMSO	Dimethylsulfoxide
ESI	Electrospray Ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HSA	Human Serum Albumin
IPA	Isopropanol
LAH	Lithium Aluminum Hydride
LDA	Lithium Diisopropylamide
MeOH	Methanol
MS	Mass Spectrometry
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
PPTS	Pyridinium p-Toluenesulfonate
TBAF	Tetrabutylammonium fluoride
TBDPS	t-Butyldiphenylsilane
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
SPA	Scintillation Proximity Assay

Synthesis of Spiro Carboxylic Acid Intermediates**[0212]****Intermediates H1A, H1B, H1C and H1D****[0213]****6-(tert-Butyldiphenylsilyloxy)-2,3-dihydroinden-1-one (H1.1).**

A mixture of 6-hydroxy-1-indanone (250 g, 1687 mmol) (634549, commercially available from Sigma-Aldrich, St. Louis, MO, USA), t-butyldiphenylchlorosilane (487 g, 1772 mmol) and imidazole (138 g, 2025 mmol) in degassed DMF (900 mL) was heated at 60°C for 16 hours. The mixture was then concentrated to remove most of DMF, diluted with ether (3000 mL), filtered, and concentrated to give the initial product **H1.1** (674 g, 100% yield) which was used in the next step reaction without further purification. MS ESI (pos.) M/E: 409 (M+Na).

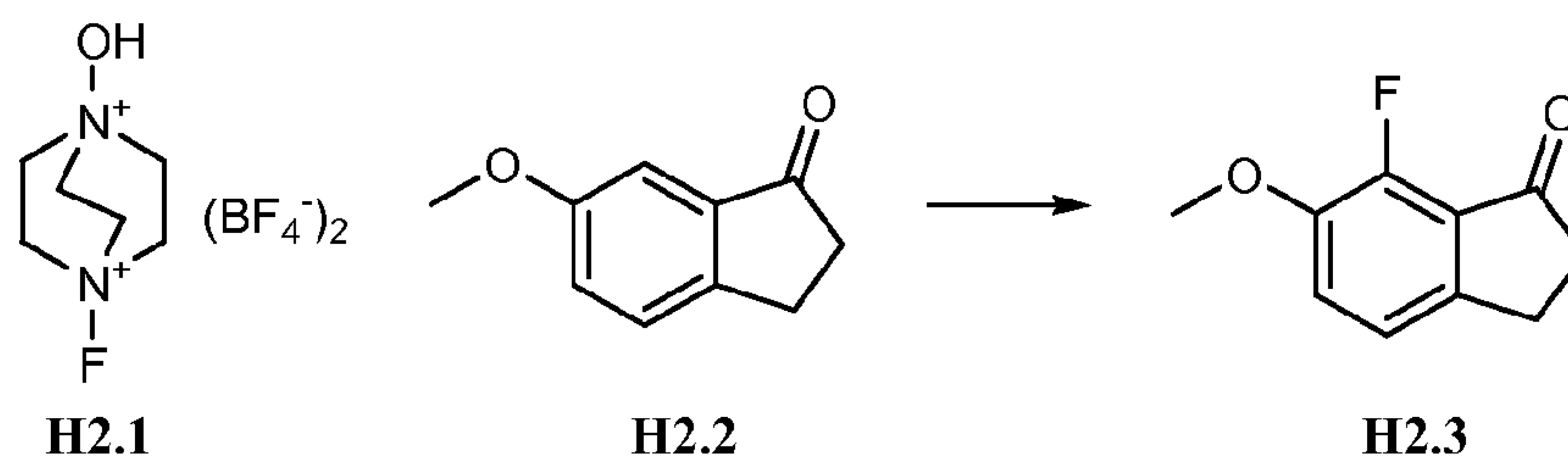
[0214]**tert-Butyl(3-methylene-2,3-dihydro-1H-inden-5-yloxy)diphenylsilane (H1.2).**

To a solution of **H1.1** (607 g, 1570 mmol) and triphenylmethylphosphonium bromide (673 g, 1884 mmol) in THF (1000 mL) was added potassium tert-butoxide 1.0 M

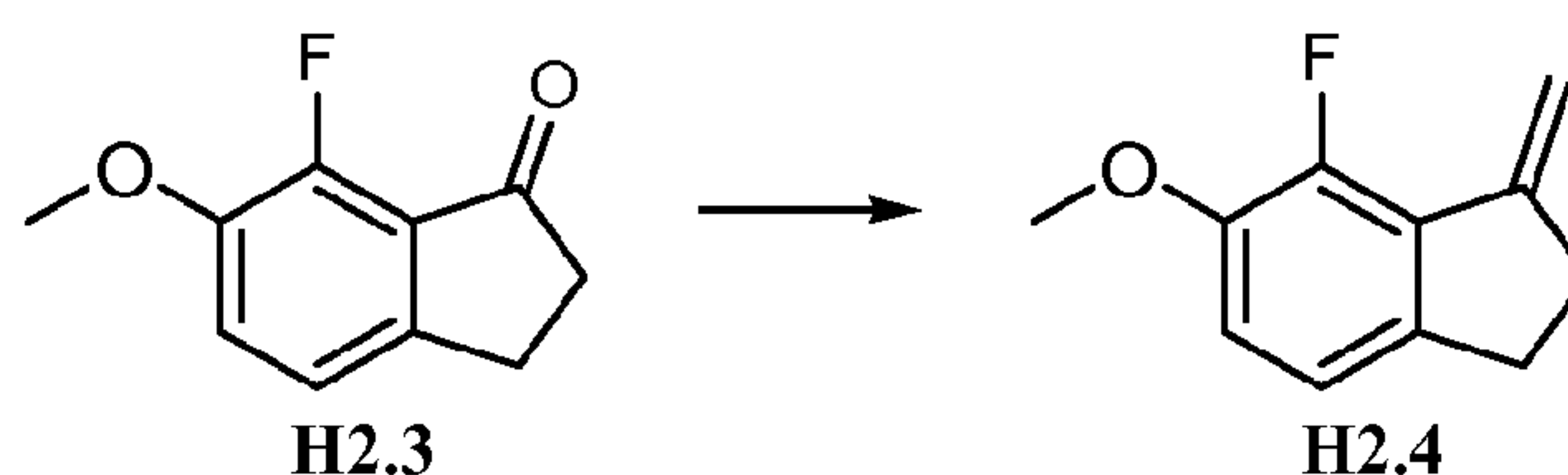
solution in THF) (1884 mL, 1884 mmol) via an addition funnel over 2 hours. The resulting mixture was stirred at room temperature for 16 hour and distilled to remove most of THF. The resulting mixture was suspended in hexanes, passed through a pad of silica gel (1 kg), rinsed with hexanes (total 8 L), and then with 10% EtOAc in hexanes (4L). The resulting mixture was concentrated to give **H1.2** (600 g, 99% yield). MS ESI (pos.) M/E: 385 (M+H).

[0215] Synthesis of H1.3. To a solution of tert-butyl(3-methylene-2,3-dihydro-1H-inden-5-yloxy)diphenylsilane **H1.2** (599.6 g, 1559 mmol) and rhodium (ii) acetate, dimer (2.8 g, 6.3 mmol) in refluxing DCM (1400 mL) was added ethyl diazoacetate (227 mL, 2191 mmol) in DCM via addition funnel over 2 hours. The resulting mixture was stirred at 45°C for 1 hour and then at room temperature for 2 hours. The reaction mixture was concentrated and passed through a short pad of silica gel (1 kg) with 5% EtOAc in hexanes (8L) to give **H1.3** (588 g, 80% yield) after removal of solvent.

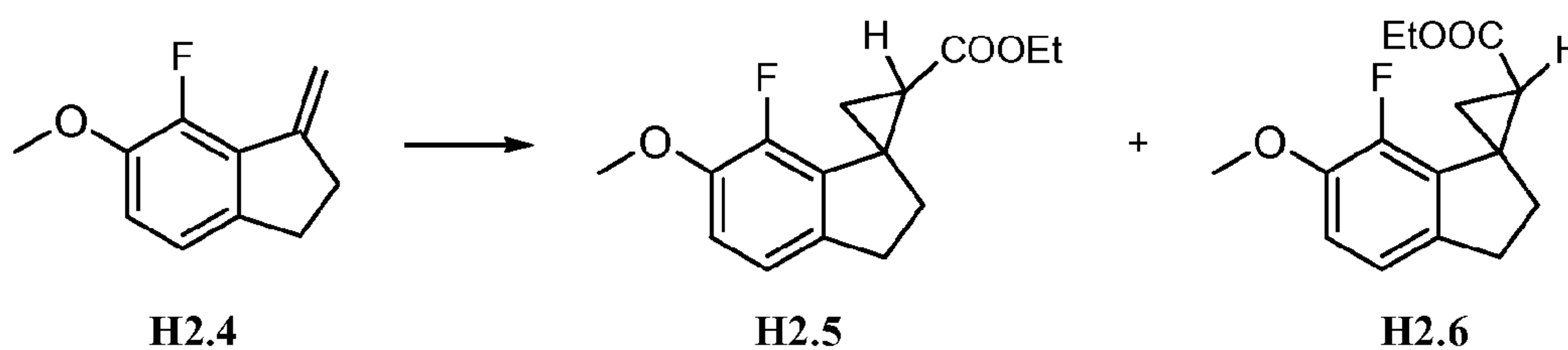
[0216] Synthesis of H1A, H1B, H1C and H1D. To a solution of **H1.3** (119 g, 253 mmol) in THF (500 mL) was added TBAF (303 mL, 303 mmol) in THF. The resulting mixture was stirred at room temperature for 1 hour. The mixture was then concentrated, redissolved in EtOAc, washed with saturated aqueous NH₄Cl, and concentrated with silica gel (300 g) to give a yellow solid after high vacuum. The solid was loaded into an empty solid load cartridge and purified by column chromatography (20% EtOAc in hexanes). The collected products were combined and separated by chiral column (ChiralPak® AD, 4% IPA/hexanes) to give **H1A** (8.3 g, 14% yield, 98%ee, retention time 34.5 min on AD-H with 5% IPA/hex, $\alpha_D = -346^\circ$, CDCl₃), **H1B** (8.3 g, 14% yield, 99%ee, retention time 23.9 min on AD-H with 5% IPA/hex, $\alpha_D = 370^\circ$, CDCl₃), **H1C** (10.0 g, 17% yield, 98%ee, retention time 17.6 min on AD-H with 5% IPA/hex, $\alpha_D = -0.5^\circ$, CDCl₃), **H1D** (10.0 g, 17% yield, 99%ee, retention time 13.2 min on AD-H with 5% IPA/hex, $\alpha_D = -5^\circ$, CDCl₃). MS ESI (pos.) M/E: 233 (M+H). The absolute stereochemistries were assigned based on the agreement of experimental values of optical rotations and vibrational circular dichroisms with theoretical calculations. The structure of **H1B** was further confirmed by X-ray analysis of a crystal derivatized from **H1B** (dibromination followed by hydrolysis).

[0217] Intermediates H2A and H2B

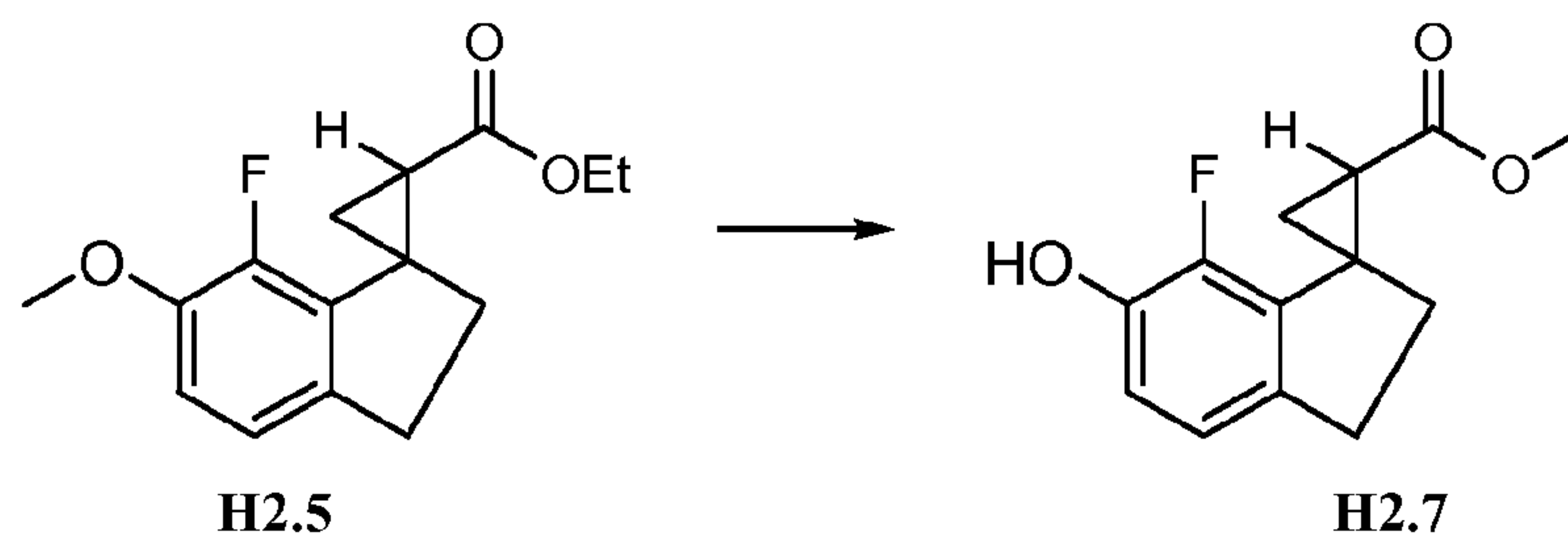
[0218] 7-Fluoro-6-methoxy-2,3-dihydroinden-1-one (H2.3). To a solution of **H2.2** (17.99 g, 111 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in ACN (600 mL) was added **H2.1** (37.5 g, 116 mmol) (commercially available from Alfa) (NFTh, 100g on alumina), and the suspension was heated under reflux for 2 hours. The solvent was removed and the resulting mixture was redissolved in DCM (600 mL). The mixture was filtered and the filtrate was concentrated to give a residue which was purified by CombiFlash® chromatography to give a yellow solid (5.22 g, 26%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.25 (d, *J* = 8 Hz, 1H), 7.17 (m, 1H), 3.94 (s, 3H), 3.10 (m, 2H), 2.75 (m, 2H).



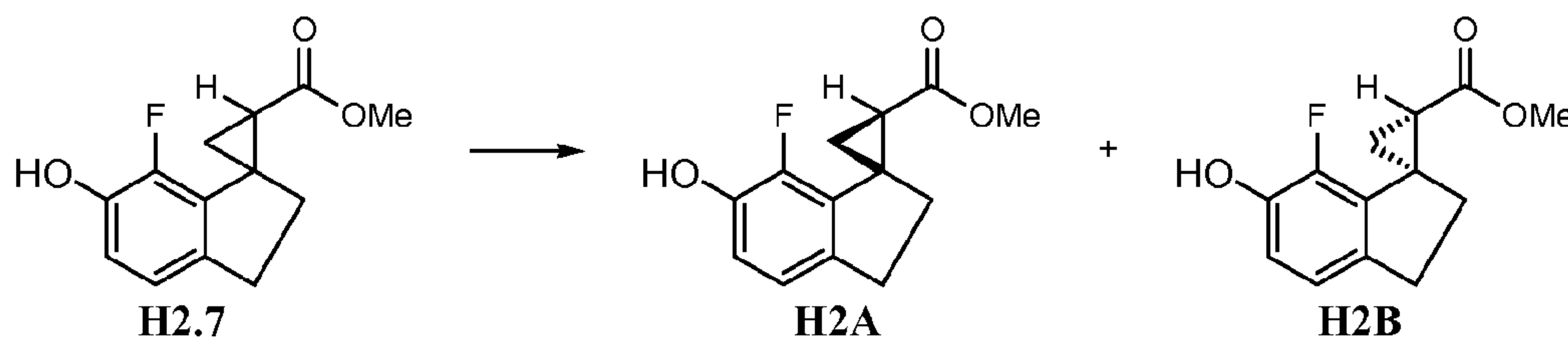
[0219] 7-Fluoro-6-methoxy-1-methylene-2,3-dihydro-1H-indene (H2.4). To a solution of **H2.3** (5.22 g, 29.0 mmol) and triphenylmethylphosphonium bromide (12.4 g, 34.8 mmol) in THF (100 mL) was added potassium tert-butoxide (1.0 M solution in THF) (34.8 mL, 34.8 mmol) via addition funnel over 15 minutes. The resulting mixture was stirred at room temperature for 30 minutes. The resulting mixture was then filtered, and the filtrate was concentrated to give a residue which was purified by CombiFlash® chromatography to give the product as a solid (3.85 g, 74.6%). ¹H NMR (400 MHz, CDCl₃) δ ppm 6.94 (d, *J* = 8 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 5.74 (s, 1H), 5.27 (s, 1H), 3.90 (s, 3H), 2.94 (m, 2H), 2.85 (m, 2H).



[0220] Synthesis of H2.5 and H2.6. To a solution of **H2.4** (3.90 g, 21.9 mmol) and rhodium (ii) acetate, dimer (0.145 g, 0.328 mmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (3.41 mL, 32.8 mmol)(commercially available from Sigma-Aldrich, St. Louis, MO, USA) in DCM via syringe pump over 40 minutes. The resulting mixture was stirred at 45°C for 1 hour and filtered. The filtrate was concentrated to give a residue which was purified by CombiFlash® chromatography to give two products: trans **H2.5** and cis **H2.6** (the structures of these compounds was confirmed by NMR analysis). **H2.5** ¹H NMR (400 MHz, CDCl₃) δ ppm 6.89 (d, *J* = 8Hz, 1H), 6.77 (m, 1H), 4.14 (q, *J* = 8Hz, 2H), 3.85 (s, 3H), 2.96 (m, 2H), 2.57 (m 1H), 2.27 (m, 2H), 1.89 (dd, *J* = 8Hz, *J* = 4Hz, 1H), 1.56 (m, 1H), 1.29 (t, *J* = 8Hz ,3H). **H2.6** ¹H NMR (400 MHz, CDCl₃) δ ppm 6.89 (d, *J* = 8Hz, 1H), 6.76 (m, 1H), 4.01 (m, 2H), 3.84 (s, 3H), 3.05 (m, 1H), 2.78 (dd, *J* = 16Hz, *J* = 8Hz, 1H), 2.45 (m, 2H), 2.01 (m, 1H), 1.71 (m, 1H), 1.42 (m, 1H) 1.14 (t, *J* = 8Hz ,3H).

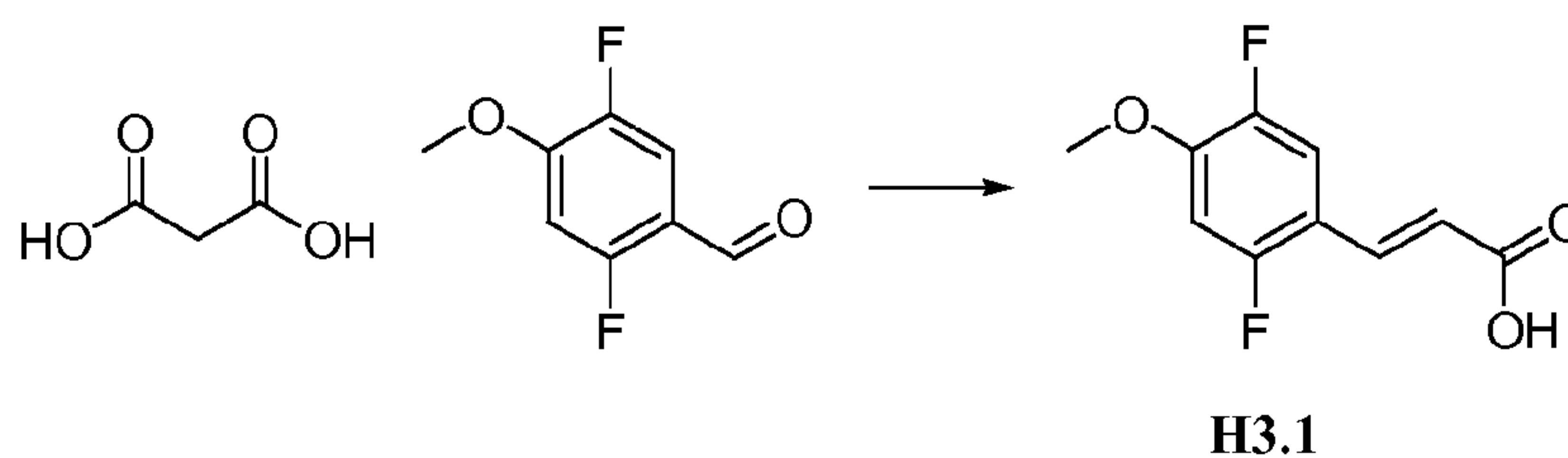


[0221] Synthesis of H2.7. To a solution of **H2.5** (2.50 g, 9.46 mmol) in 20 mL of NMP, was added NaOH (1.70 g, 42.6 mmol) and 1-dodecanethiol (7.94 mL, 33.1 mmol). The mixture was stirred at 125°C for 16 hours, cooled to room temperature, and diluted with 1 N HCl and ether. The organic layer was washed with water and brine, dried (MgSO₄) and concentrated to give a residue which was purified by CombiFlash® chromatography to give the desired acid (1.40 g). The solution of acid in 40 mL of benzene and 10 mL of MeOH was treated with (trimethylsilyl)diazomethane, 2.0 M in diethyl ether (9.46 mL, 18.9 mmol) at room temperature for 1 hour. Solvent was then removed to give **H2.7** (1.40g, 63%). MS ESI *m/e*: 237.10 (M+1)⁺.

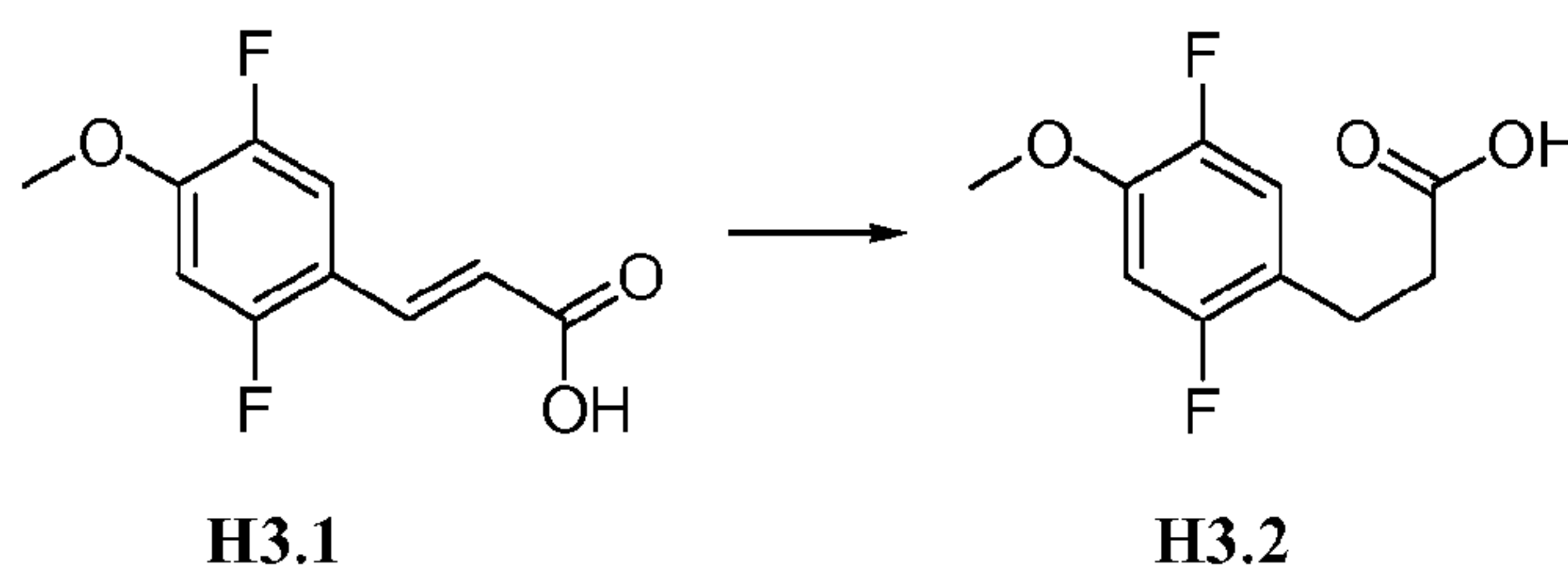


[0222] **Synthesis of H2A and H2B.** Chiral separation of **H2.7** was accomplished on a CHIRALCEL® OD column (3% IPA in hexane) to provide **H2A** and **H2B**. The stereochemistry of **H2A** and **H2B** was determined based on a comparison of their chiral HPLC retention times with those of **H1A** and **H1B**. However, absolute configurations are not known with certainty. Therefore, when **H2A** was used to synthesize a compound, both enantiomers are shown.

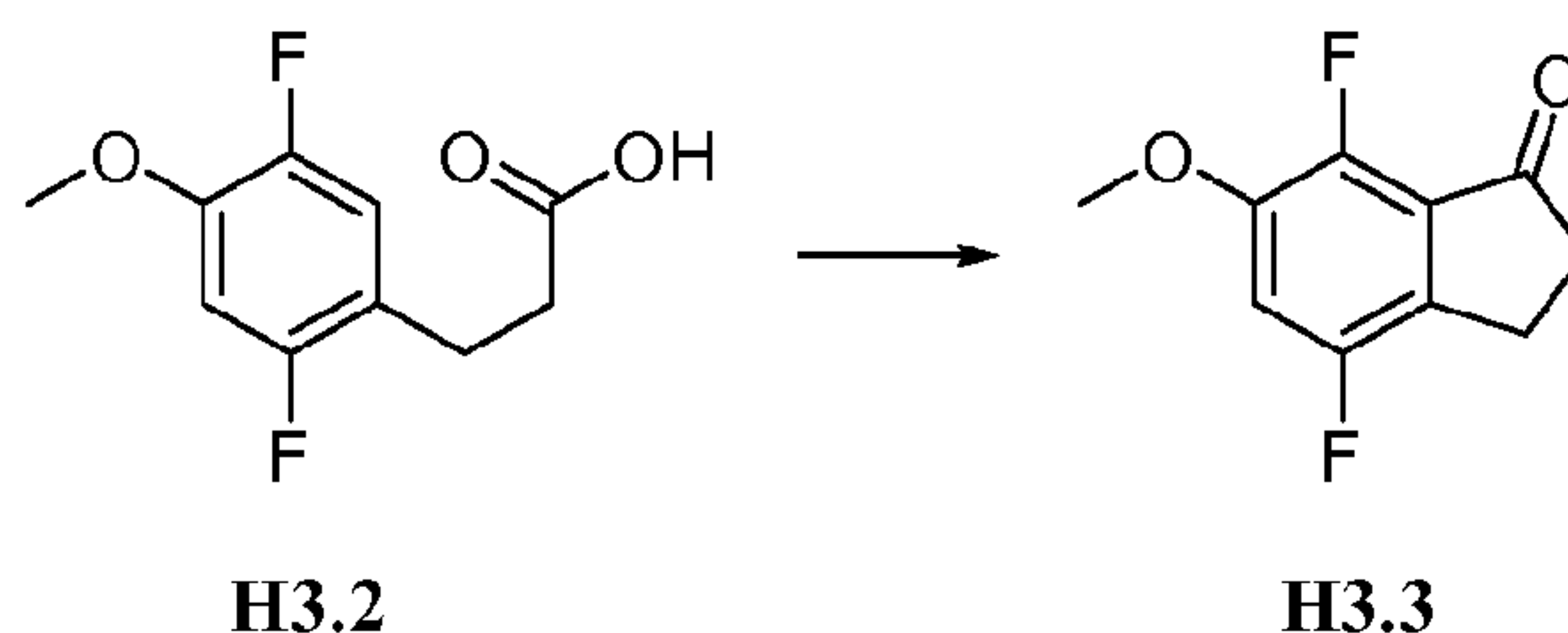
[0223] **Intermediates H3A, H3B, H3C and H3D**



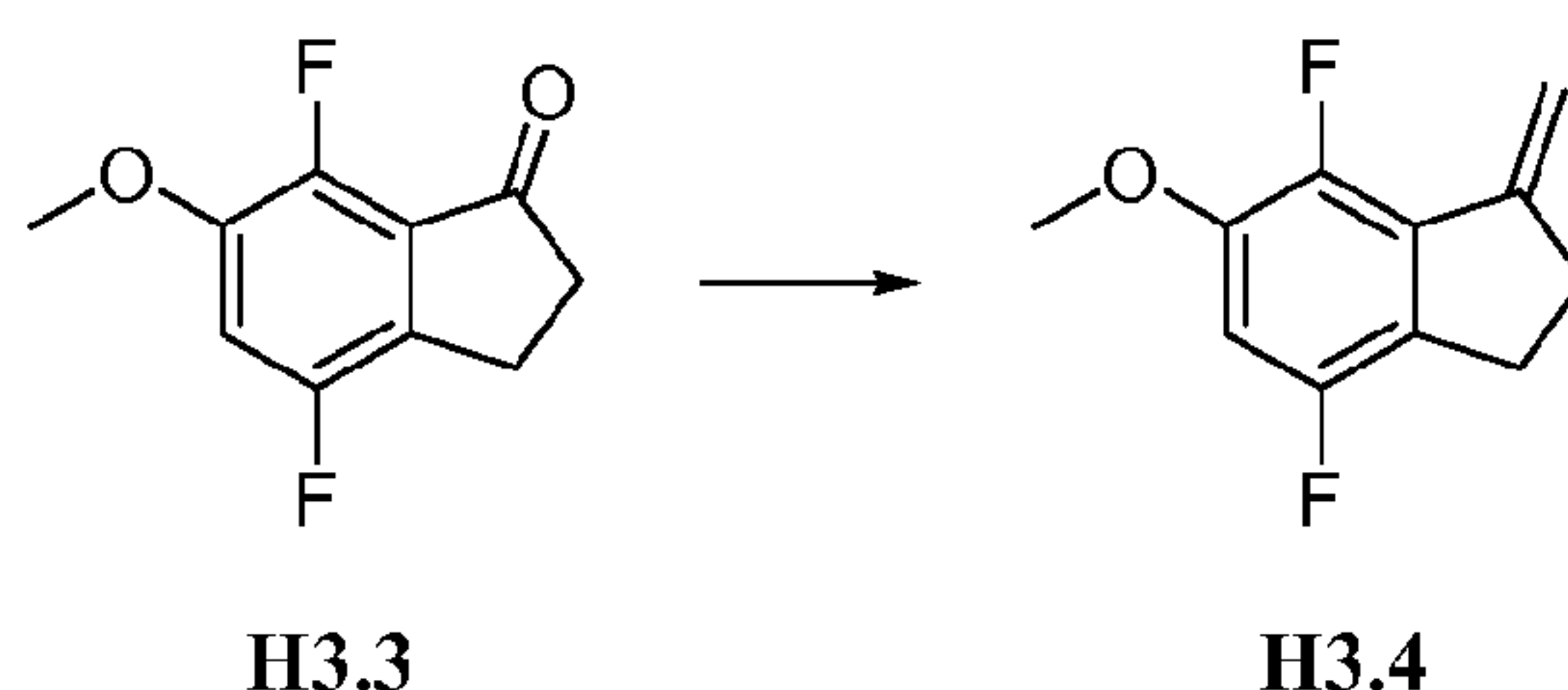
[0224] **(2E)-3-(2,5-Difluoro-4-(methoxy)phenyl)-2-propenoic acid (H3.1).** A 250 mL round bottom flask was charged with 2,5-difluoro-4-methoxybenzaldehyde (commercially available from Manchester Organics Ltd., UK) (18.45 g, 107.2 mmol), malonic acid (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (12.27 g, 117.9 mmol), and 10:1 EtOH/pyridine (27 mL). The mixture was stirred overnight at 70°C under a reflux condenser and cooled to 0°C for 2 hours. The precipitated solid was filtered, rinsed with ether, and dried in vacuo to afford **H3.1** (16.96 g, 74% yield) as a white powder.



[0225] **3-(2,5-Difluoro-4-methoxyphenyl)propanoic acid (H3.2).** To a homogeneous solution of **H3.1** (6.78 g, 32 mmol) in 1:1 EtOH/EtOAc (384 mL) was added wet palladium on carbon (10 wt. % (dry basis), water ca. 50%) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (0.67 g, 0.32 mmol). The mixture was subjected to 3 cycles of evacuation/back-filling with H₂ and stirred for 2 hours under a H₂ balloon. The mixture was filtered through Celite® filter aid (EtOAc) and concentrated to afford **H3.2** (6.81 g, 100% yield) as a white solid.

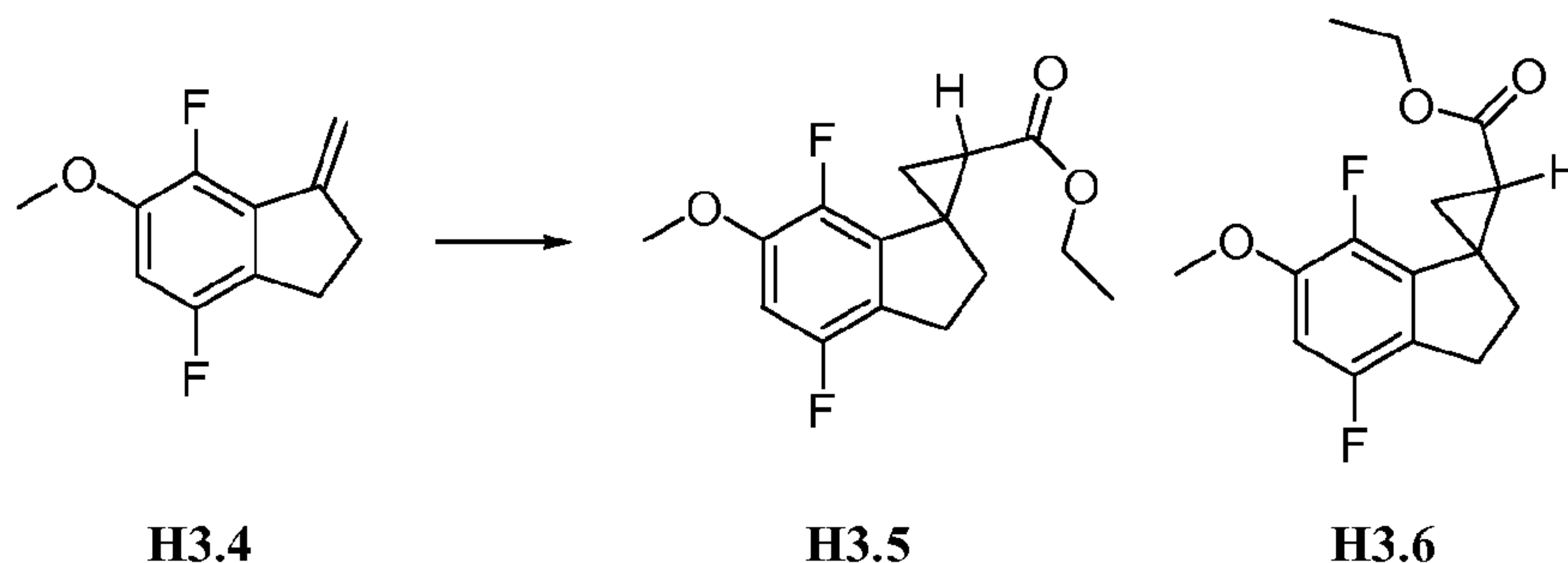


[0226] 4,7-Difluoro-6-methoxy-2,3-dihydroinden-1-one (H3.3). A 200 mL round bottom flask was charged with **H3.2** (6.75 g, 31.2 mmol), DCM (62 mL), oxalyl chloride (5.45 mL, 62.4 mmol), and a catalytic amount of DMF (0.0242 mL, 0.312 mmol) (vigorous gas evolution occurred). The solution was stirred for 30 minutes at room temperature and concentrated to afford the desired acid chloride as a yellow oil. A 500 mL round bottom flask was charged with aluminum(III) chloride (5.00 g, 37.5 mmol) and DCM (62 mL) and cooled to 0°C under N₂. To the cold slurry was added a solution of the above acid chloride in DCM (62 mL) dropwise. The resulting solution was stirred for 6 hours at 45°C (reflux). The mixture was carefully poured into ice-cold water (600 mL) with stirring and after 1 hour, was extracted with DCM (2 x 300 mL). The combined organic layers were washed with 1 N NaOH (1 x 300 mL) and brine (1 x 300 mL), dried (MgSO₄), and concentrated. The initially obtained product was purified by recrystallization from hot toluene to afford **H3.3** (0.968 g, 16% yield) as a flaky, light brown solid.

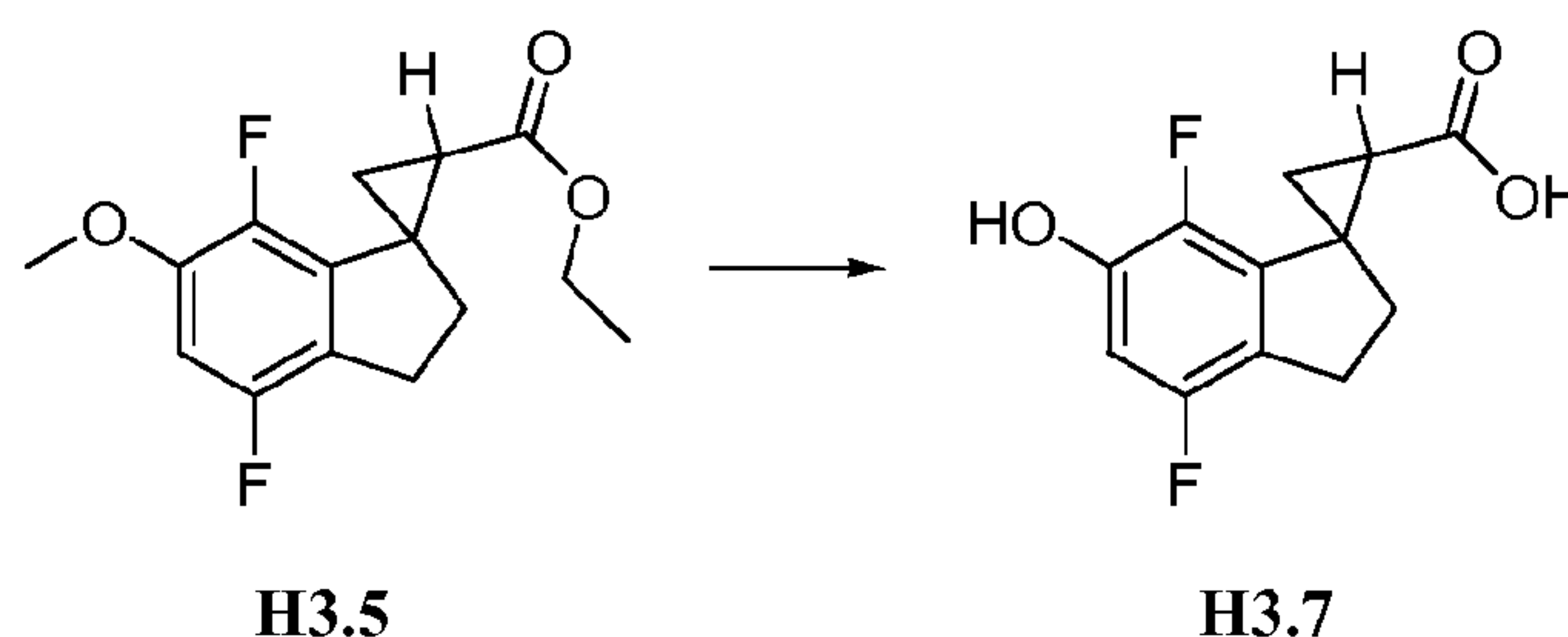


[0227] 4,7-Difluoro-6-methoxy-1-methylene-2,3-dihydro-1H-indene (H3.4). A screw-cap vial was charged with **H3.3** (0.962 g, 4.85 mmol), methyltriphenylphosphonium bromide (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (2.08 g, 5.83 mmol), and THF (20 mL). To the white slurry was added potassium *tert*-butoxide (1.0 M in THF) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (5.83 mL, 5.83 mmol) dropwise under N₂. The resulting brown mixture was stirred for 30 minutes at room temperature, quenched with acetone (1 mL) and saturated aqueous NH₄Cl, and diluted with EtOAc. The organic layer was washed with water and brine, dried (MgSO₄), and concentrated. The residue was suspended in

hexanes, filtered, and concentrated, and the initially obtained product was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **H3.4** (0.835 g, 88% yield) as a colorless oil.

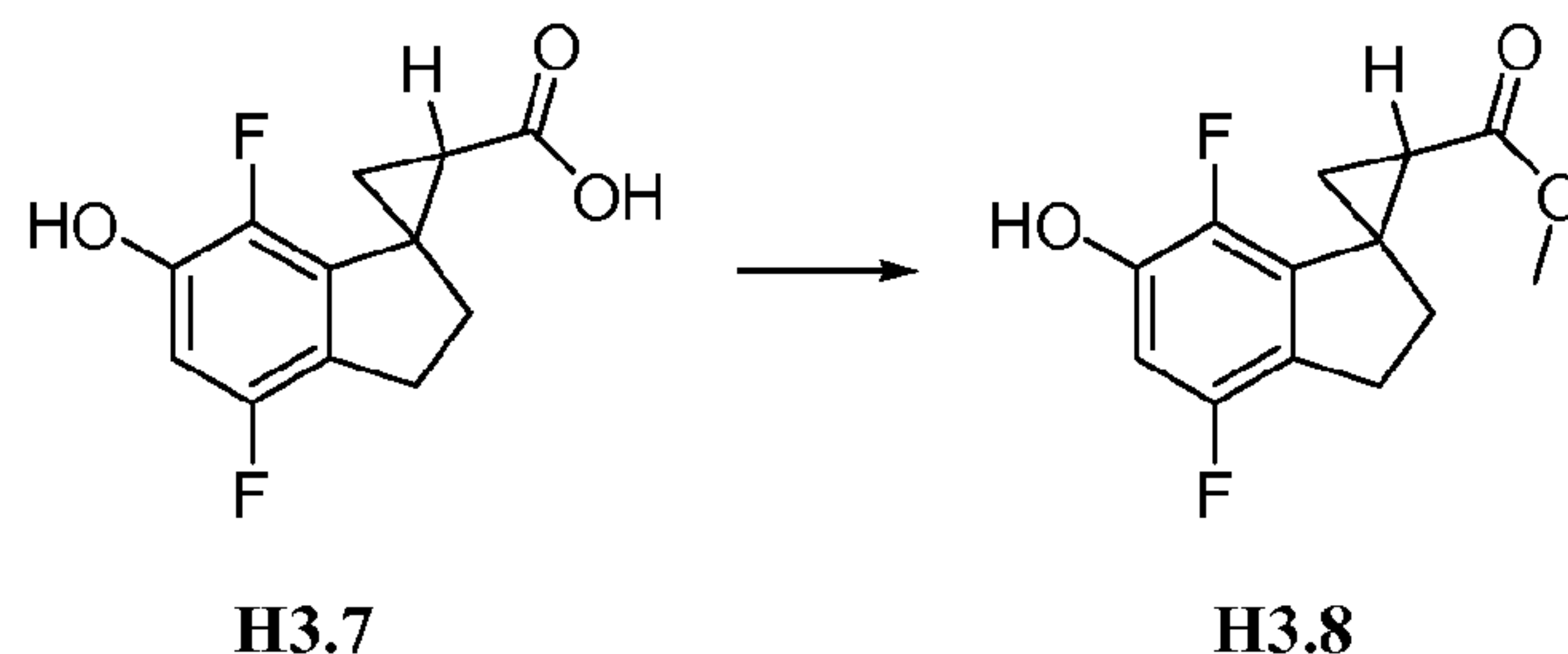


[0228] Synthesis of H3.5 and H3.6. A 250 mL 3-neck round bottom flask was charged with **H3.4** (0.835 g, 4.26 mmol), DCM (43 mL), and rhodium(II) acetate dimer (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (0.0188 g, 0.0426 mmol) and fitted with two septa and a reflux condenser. The green suspension was heated to reflux (45°C bath temperature) under a flaccid balloon, and to it was added a solution of ethyl diazoacetate (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (0.662 mL, 6.38 mmol) in DCM (6 mL) dropwise over 2 hours (syringe pump). The mixture was stirred for an additional 15 minutes, cooled to room temperature, filtered through Celite® filter aid (EtOAc), and concentrated. The initially obtained product was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford (in order of elution) **H3.5** (0.351 g, 29% yield) and **H3.6** (0.413 g, 34% yield). The *cis* and *trans* stereochemistries were determined by NMR.

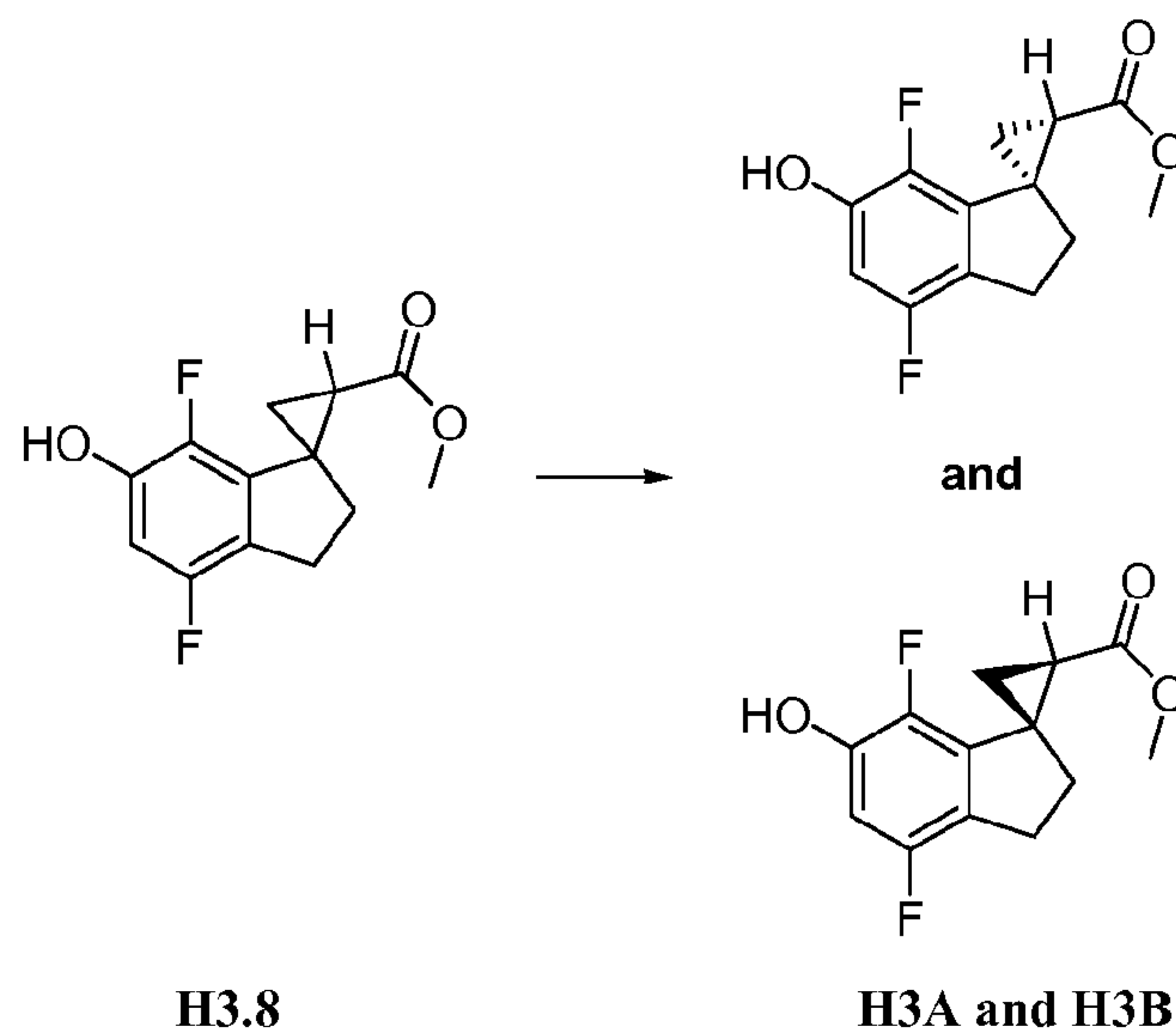


[0229] Synthesis of H3.7. A screw-cap vial was charged with **H3.5** (0.347 g, 1.23 mmol), N-methylpyrrolidone (NMP) (1.2 mL), NaOH (0.221 g, 5.53 mmol), and 1-dodecanethiol (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (1.03 mL, 4.30 mmol). The mixture was stirred overnight at 125°C (sealed vial) and cooled to room temperature. The solidified mixture was fractured with a spatula, quenched with 1 N HCl, and diluted with EtOAc. The organic layer was washed with water and brine,

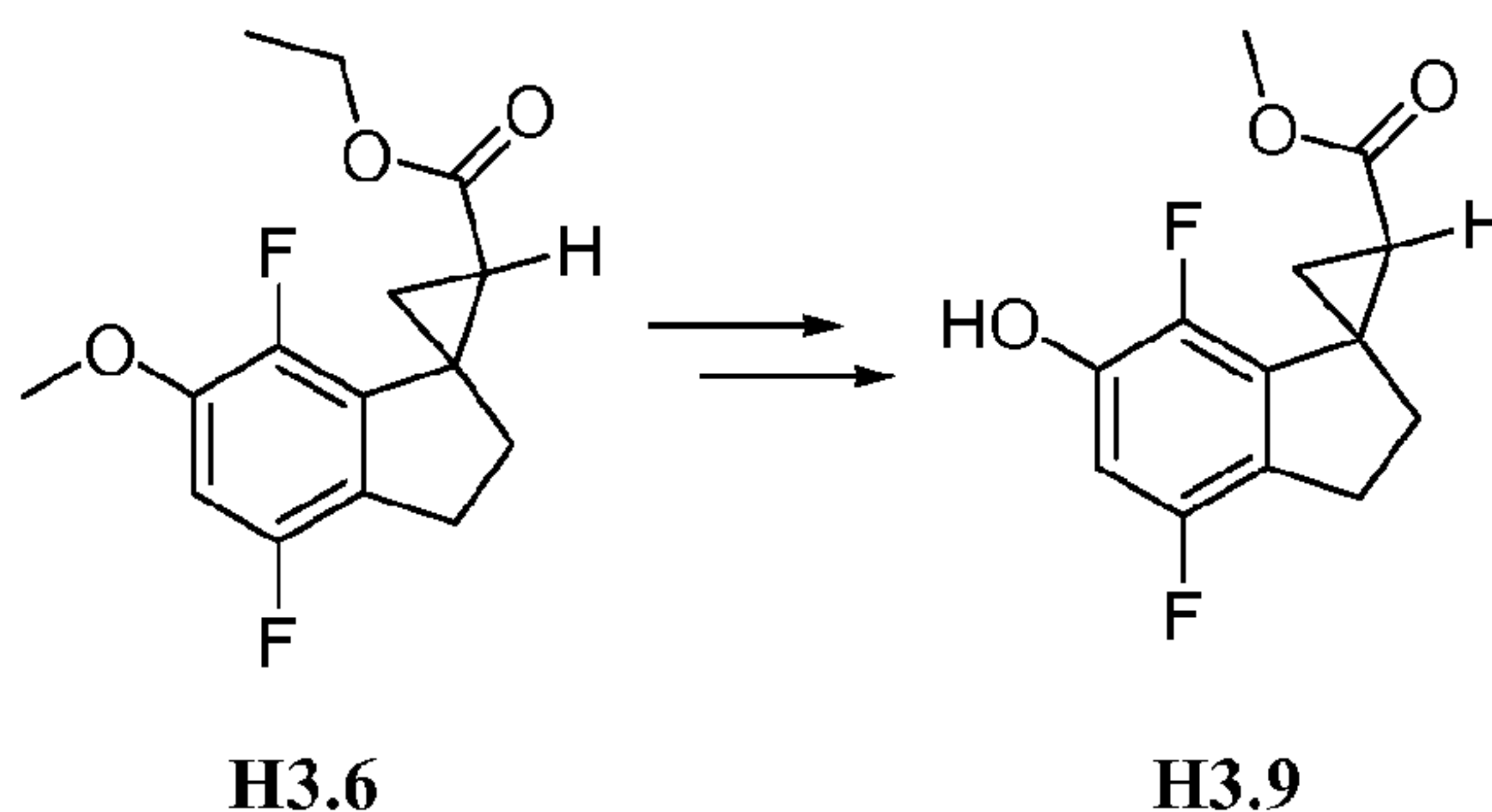
dried (MgSO_4), and concentrated. The initially obtained product was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **H3.7** (0.245 g, 83% yield) as a white solid.



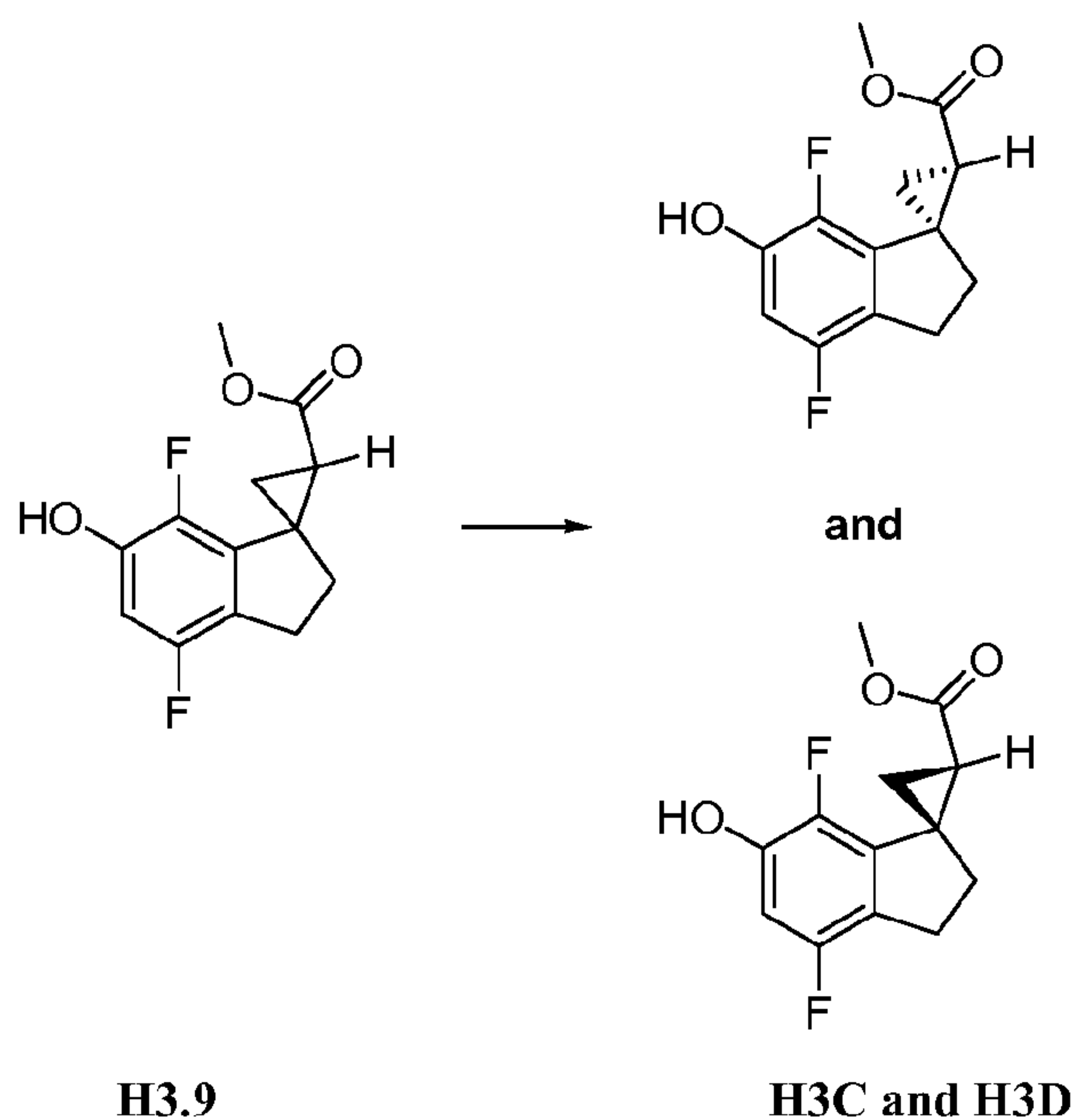
[0230] Synthesis of H3.8. A 100 mL round bottom flask was charged with **H3.7** (0.242 g, 1.01 mmol) and 10:1 DCM/MeOH (10 mL). To the colorless solution was added (trimethylsilyl)diazomethane (2.0 M in ether) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (0.604 mL, 1.21 mmol) dropwise (vigorous gas evolution occurred). The pale yellow solution was stirred for 15 minutes at room temperature, quenched with AcOH (0.0577 mL, 1.01 mmol), and concentrated. The initially obtained product was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford **H3.8** (0.207 g, 81% yield) as a crystalline, white solid.



[0231] Synthesis of H3B and H3A. Racemic **H3.8** (0.207 g, 0.81 mmol) was resolved by chiral HPLC (CHIRALCEL® OJ column, 4% IPA/hexane, detection at 220 nm) to afford (in order of elution) **H3B** (0.083 g, 80% yield, 99% e.e.) and **H3A** (0.089 g, 86% yield, 95% e.e.) as white solids. **H3B** was the first eluting enantiomer; **H3A** was the second eluting enantiomer.

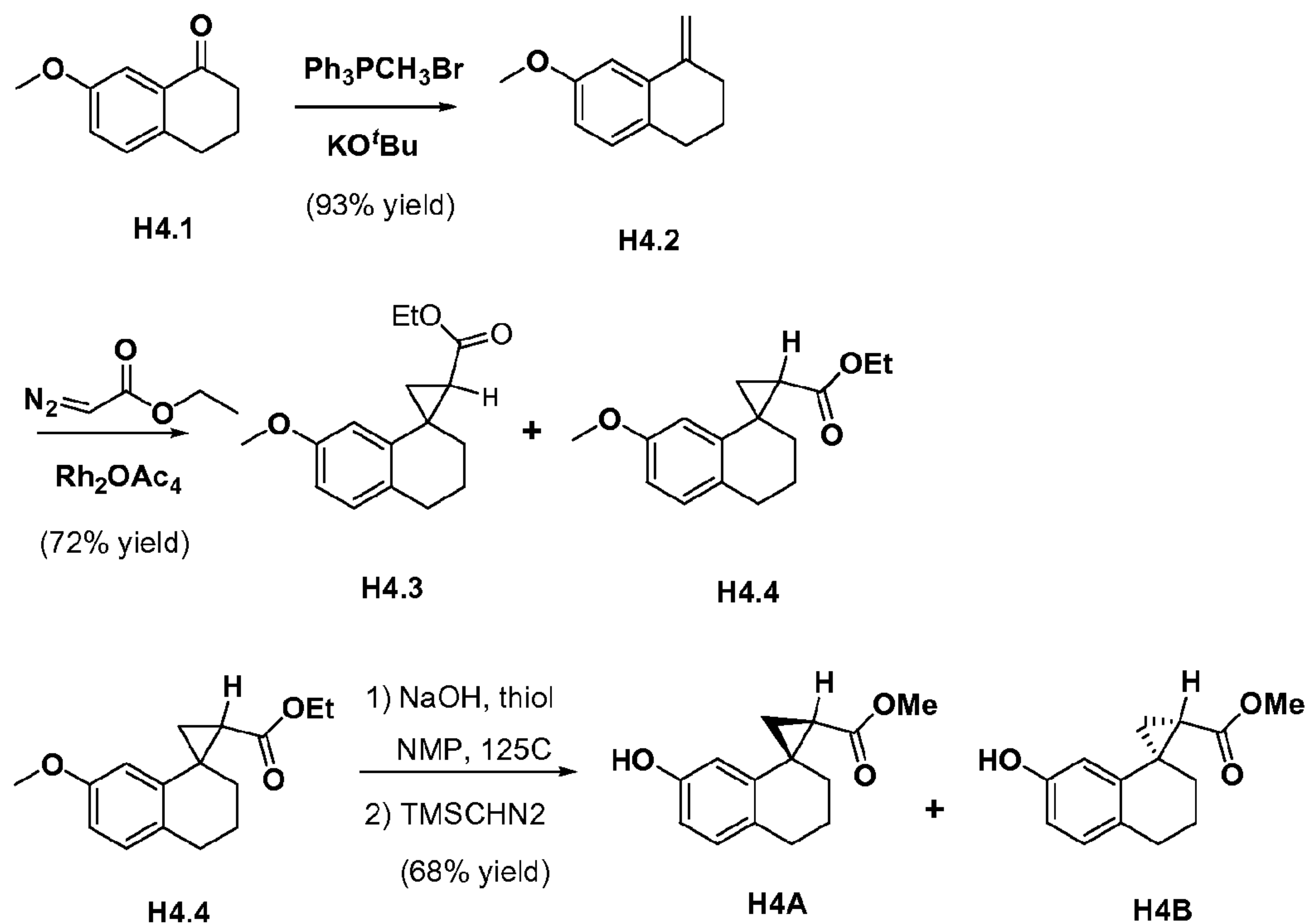


[0232] **Synthesis of H3.9.** **H3.9** was prepared from **H3.6** according to the analogous methods described for the synthesis of **H3.8**.



[0233] **Synthesis of H3D and H3C.** Racemic **H3.9** (0.156 g, 0.61 mmol) was resolved by chiral HPLC (CHIRALCEL® OJ column, 6% then 20% IPA/hexane, detection at 220 nm) to afford (in order of elution) **H3D** (0.069 g, 88% yield, 99% e.e.) and **H3C** (0.070 g, 90% yield, 99% e.e.) as white solids. **H3D** was the first eluting enantiomer; **H3C** was the second eluting enantiomer.

[0234]

Intermediates H4A and H4B

[0235]

7-Methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (H4.2).

To a solution of 7-methoxy-1-tetralone **H4.1** (26.9 g, 153 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and triphenylmethylphosphonium bromide (65.4 g, 183 mmol) in THF (550 mL) was added potassium tert-butoxide (1.0 M solution in THF) (183 mL, 183 mmol) via addition funnel over 1 hour. The resulting mixture was stirred at room temperature for 60 minutes after addition. The reaction was then concentrated and resuspended in hexanes (250 mL). The mixture was passed through a silica gel plug (25g silica) and rinsed with 250 mL of hexanes. Removal of solvent gave **H4.2** (24.5 g, 92 % yield). MS ESI (pos.) M/E: 175 (M+H).

[0236]

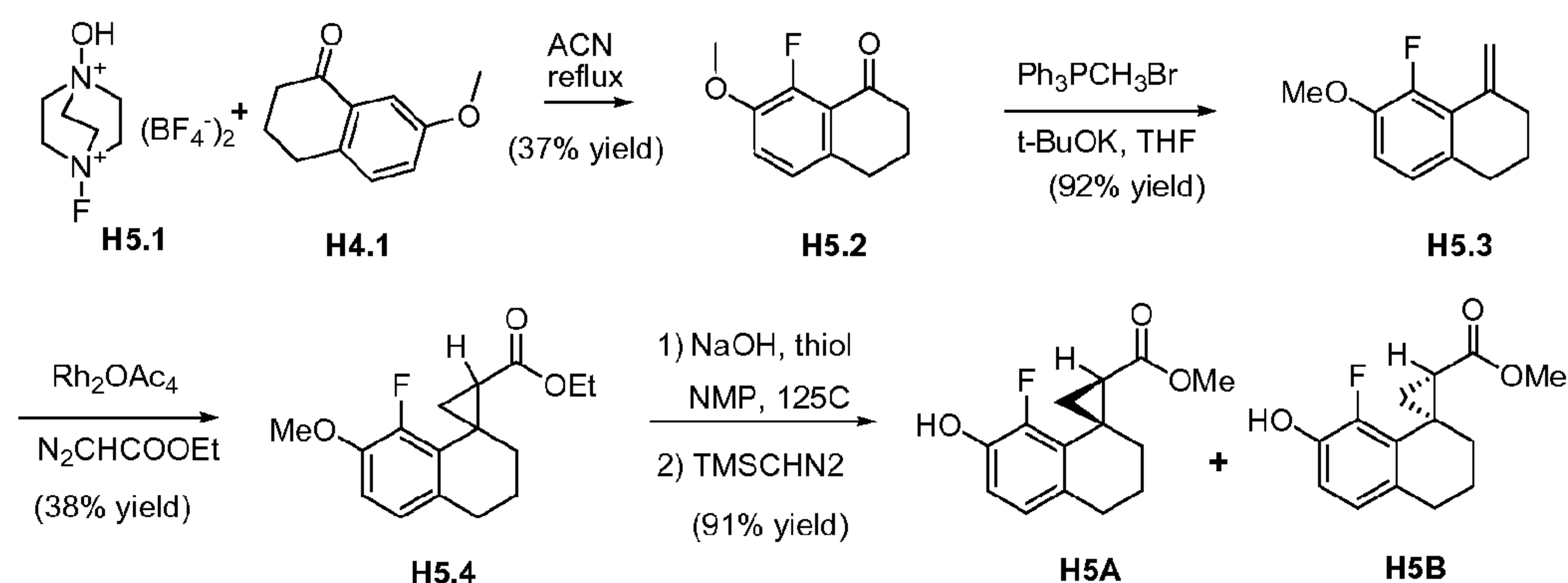
Ethyl 7'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-

naphthalene]-2-carboxylate (H4.3 and H4.4). To a solution of **H4.2** (5.23 g, 30.0 mmol) and rhodium (ii) acetate, dimer (0.133 g, 0.30 mmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (4.67 mL, 45.0 mmol) in DCM via syringe pump over 60 minutes. The resulting mixture was stirred at 45°C for 1 hour and then at room temperature for 2 hours. The reaction was concentrated and column purification (20% EtOAc in hexane) gave two products with the desired mass (**H4.3** and **H4.4**). **H4.3** (2.88

g) was obtained as oil which became a white solid after a few days, and NOE using ^1H NMR showed this to be the *cis* product. **H4.4** (3.04 g) was obtained as a colorless oil, and NOE using ^1H NMR showed this to be the *trans* product. MS ESI (pos.) M/E: 261 (M+H).

[0237] Synthesis of H4A and H4B. A 100 mL flask was charged with **H4.4** (2.56 g, 9.8 mmol), NMP (22 mL), NaOH (1.77 g, 44.3 mmol), and 1-dodecanethiol (8.25 mL, 34.4 mmol). The mixture was stirred for 24 hours at 125°C, cooled to room temperature, and diluted with 1 N HCl (200 mL) and ether (300mL). The organic layer was washed with water and brine, dried (MgSO_4), and concentrated. Column chromatography purification (10-40% EtOAc/hex) gave the desired acid (1.45 g, 68% yield), which was dissolved in 40 mL of benzene and 10 mL of MeOH, treated with (trimethylsilyl)diazomethane (2.0 M in diethyl ether)(8.3 mL, 16.6 mmol) at 0°C for 1 hour. The reaction mixture was concentrated to give methyl 7'-hydroxy-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylate (1.55 g, 100% yield), which was separated from CHIRALCEL® OJ column (15% IPA/hex) to give **H4A** (>99%ee, peak 2, 765 mg) and **H4B** (>99%ee, peak 1, 773 mg). MS ESI (pos.) M/E: 233 (M+H).

[0238] Intermediates H5A and H5B



[0239] 8-Fluoro-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (H5.2). To a solution of 7-methoxy-1-tetralone **H4.1** (199 g, 1130 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in ACN (1200 mL) was added **H5.1** (200.0 g, 622 mmol) (NFTh, 400 g on alumina), and the suspension was heated under reflux for 1.5 hours. The solvent was removed and the residue was redissolved in DCM (1500 mL). The resulting mixture was filtered, concentrated, and purified by column chromatography (0% to 20% then 40% EtOAc in Hexanes) to give 8-fluoro-7-methoxy-3,4-

dihydronaphthalen-1(2H)-one **H5.2** (43 g). (Reference: Stojan Stavber, Chemical Communication 2000, 1323). MS ESI (pos.) M/E: 195 (M+H).

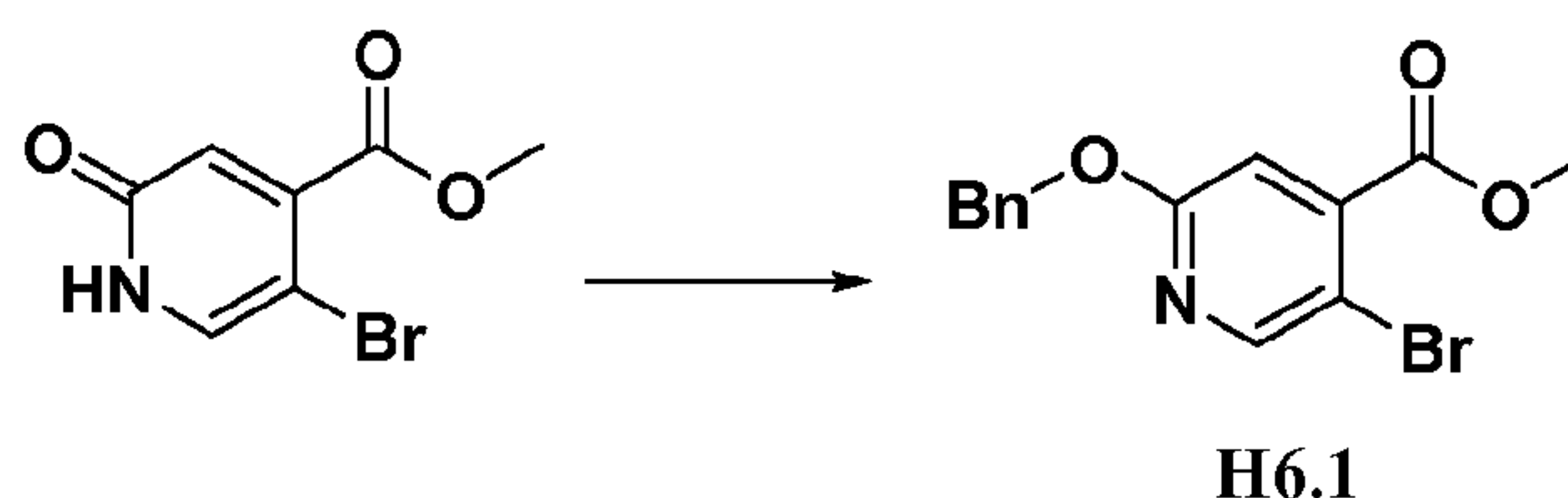
[0240] 8-Fluoro-7-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (H5.3). To a solution of **H5.2** (44.0 g, 227 mmol) and triphenylmethylphosphonium bromide (97.1 g, 272 mmol) in THF (1000 mL) was added potassium tert-butoxide (1.0 M solution in THF)(272 mL, 272 mmol) via addition funnel over 3 hours. The resulting mixture was stirred at room temperature for 30 minutes after addition. The solvent was removed and the residue was resuspended in hexanes (1L). The resulting mixture was passed through a silica gel plug (50 g silica) and rinsed with 1L of hexanes. Removal of solvent gave **H5.3** (40.1 g, 92.1% yield). MS ESI (pos.) M/E: 193 (M+H).

[0241] Ethyl 8'-fluoro-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylate (H5.4). To a solution of **H5.3** (4.18 g, 21.7 mmol) and rhodium (ii) acetate, dimer (0.0961 g, 0.217 mmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (3.38 mL, 32.6 mmol) in DCM via syringe pump over 40 minutes. The resulting mixture was stirred at 45°C for 1 hour and then at room temperature for 2 hours. Solvent was removed and the residue was purified by column chromatography (20% EtOAc in hexane) giving two products with the desired mass. The *cis* product (2.31 g) was obtained as an oil that became a white solid after a few days. A NOESY ¹ established this as the *cis* product. The *trans* product **H5.4** (2.31 g), was obtained as a colorless oil, and a NOESY ¹. MS ESI (pos.) M/E: 279 (M+H).

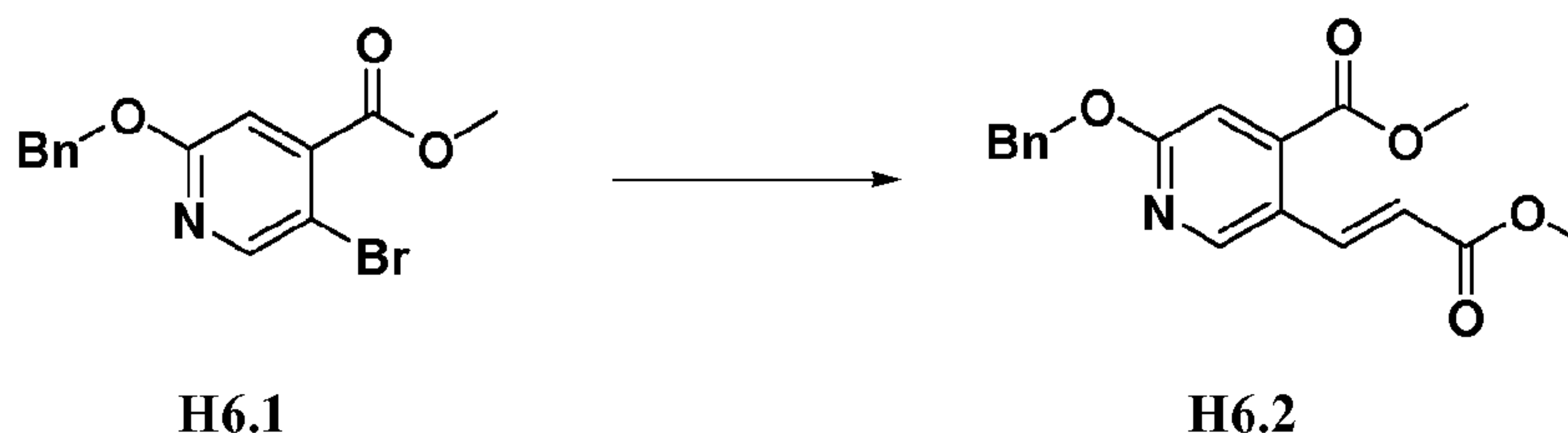
[0242] Synthesis of H5A and H5B. A 100 mL flask was charged with **H5.4** (2.30 g, 8.26 mmol), NMP (20mL), sodium hydroxide (1487 mg, 37.2 mmol), and 1-dodecanethiol (6936 µL, 28.9 mmol). The mixture was stirred for 16 hours at 125°C, cooled to room temperature, and diluted with 1 N HCl (200mL) and ether (300mL). The organic layer was washed with water and brine, dried (MgSO₄), and concentrated. Column purification (10-40% EtOAc/hex) gave desired the acid (1.77 g, 91% yield). The acid was then dissolved in 40 mL of benzene and 10 mL of MeOH, treated with (trimethylsilyl)diazomethane (2.0 M in diethyl ether)(8.3 mL, 16.6 mmol) at 0°C for 1 hour. Solvent was removed from the resulting mixture to give methyl 8'-fluoro-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylate (1.88 g, 99% yield), which was separated using a CHIRALCEL® OJ column (15% IPA/hex) to

give **H5A** (>99%ee, peak 2, 796 mg) and **H5B** (>99%ee, peak 1, 780 mg). MS ESI (pos.) M/E: 251 (M+H).

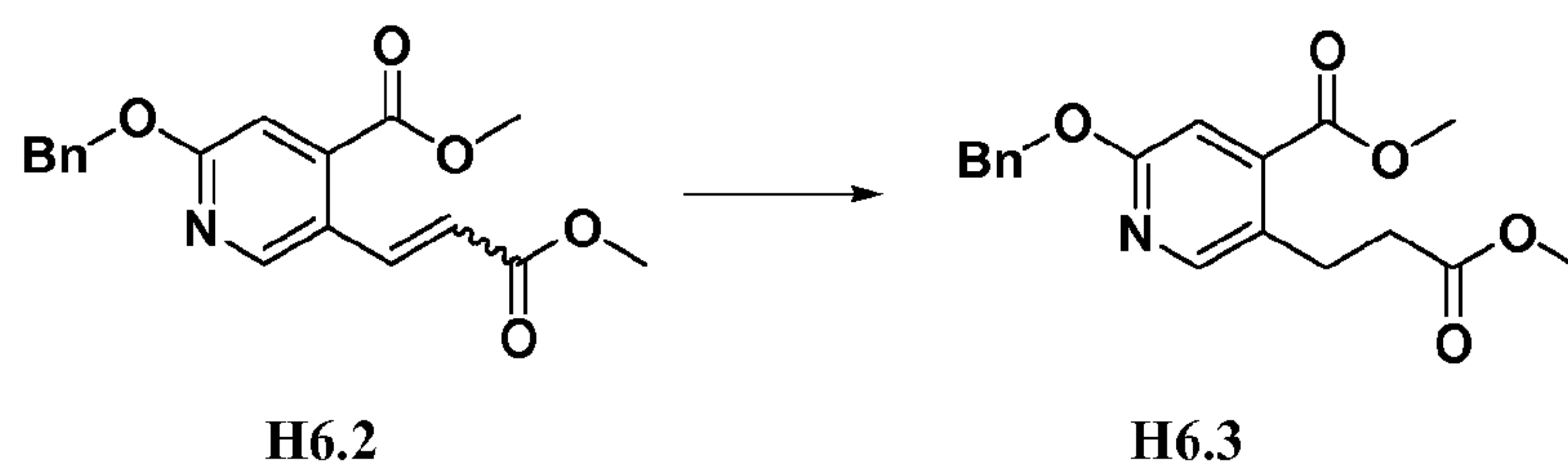
[0243] Intermediates H6A and H6B



[0244] Methyl 2-(benzyloxy)-5-bromoisonicotinate (H6.1) To 2 mL of methyl 5-bromo-2-oxo-1,2-dihydropyridine-4-carboxylate (232 mg, 1.00 mmol)(commercially available from Combi-Blocks) was added benzyl bromide (205 mg, 1.20 mmol) and silver carbonate (413 mg, 1.50 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA). The resulting mixture was stirred at 50°C overnight. After reaction completion, the mixture was loaded onto a solid silica gel cartridge and purified by chromatography with 10% EtOAc/hexane to afford the desired product **H6.1** (293 mg, 91%). MS ESI (pos.) m/e: 322.1 (M+H)⁺.

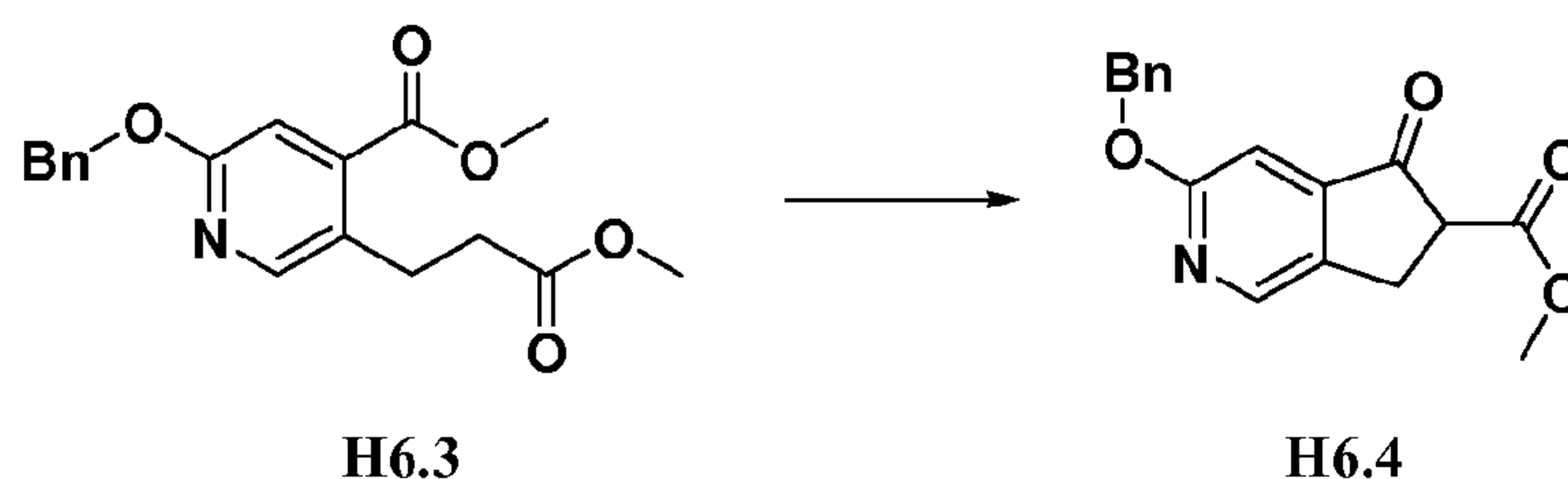


[0245] Methyl 2-(benzyloxy)-5-(3-methoxy-3-oxoprop-1-enyl)isonicotinate (H6.2). To NMP (1 mL) was added methyl acrylate (commercially available from Sigma-Aldrich, St. Louis, MO, USA), tri-*o*-tolylphosphine (8.5 mg, 28 μmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and palladium diacetate (2.5 mg, 11 μmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA). The solution was degassed three time with nitrogen. To this solution was then added a 1 mL NMP solution of methyl 2-(benzyloxy)-5-bromoisonicotinate (120 mg, 372 μmol). The reaction was stirred at 90°C overnight and then purified by column chromatography (silica gel ,10% EtOAc/hexane) to give desired product **H6.2** (50.2 mg, 41.4%). MS ESI (pos.) m/e: 328.1 (M+H)⁺.

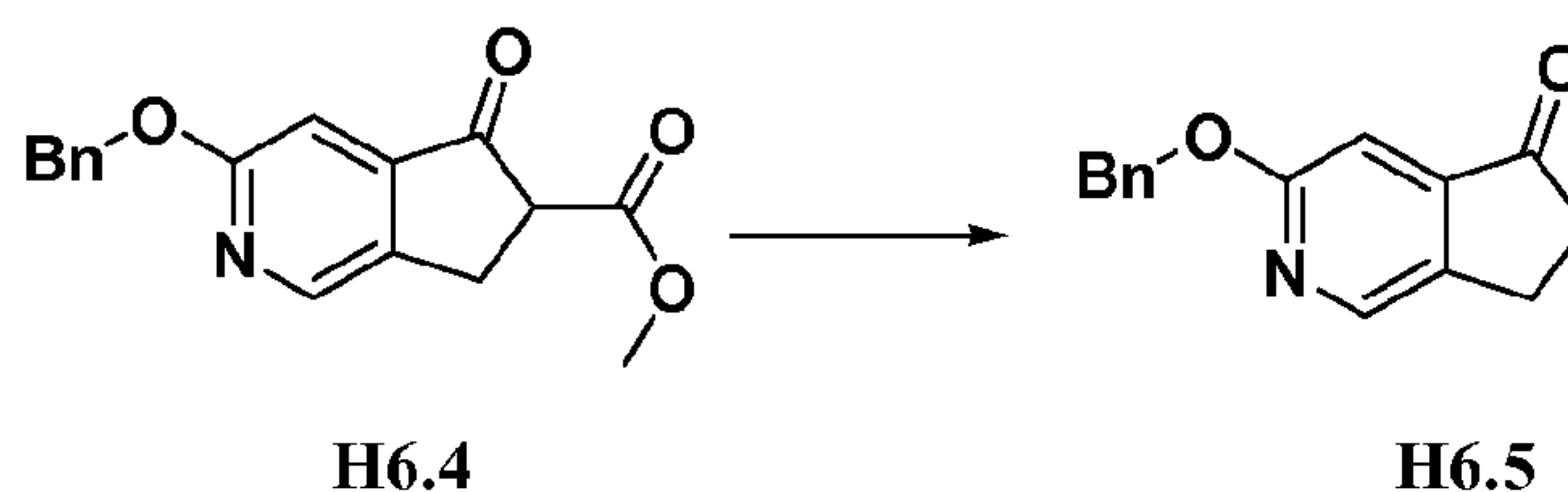


[0246] Methyl 2-(benzyloxy)-5-(3-methoxy-3-oxopropyl)isonicotinate (H6.3).

To 1 mL EtOH was added compound **H6.2** (50.0 mg, 152 μ mol) and palladium on carbon (16.2 mg, 15.2 μ mol). The resulting mixture was stirred under a balloon of H₂ for 4 hours. The catalyst was then filtered off, and the solvent was removed. The residue was redissolved in 1 mL toluene. To the resulting mixture was added silver carbonate (41.3 mg, 0.152 mmol) and benzyl bromide (20.5 mg, 0.120 mmol). The resulting mixture was stirred at 50°C overnight. After the reaction was done, the mixture was loaded onto silica gel and purified by column chromatography with 10% EtOAc/hexane to give desired product **F.3** (40.3 mg, 80.1%). MS ESI (pos.) m/e: 330.1 (M+H)⁺.

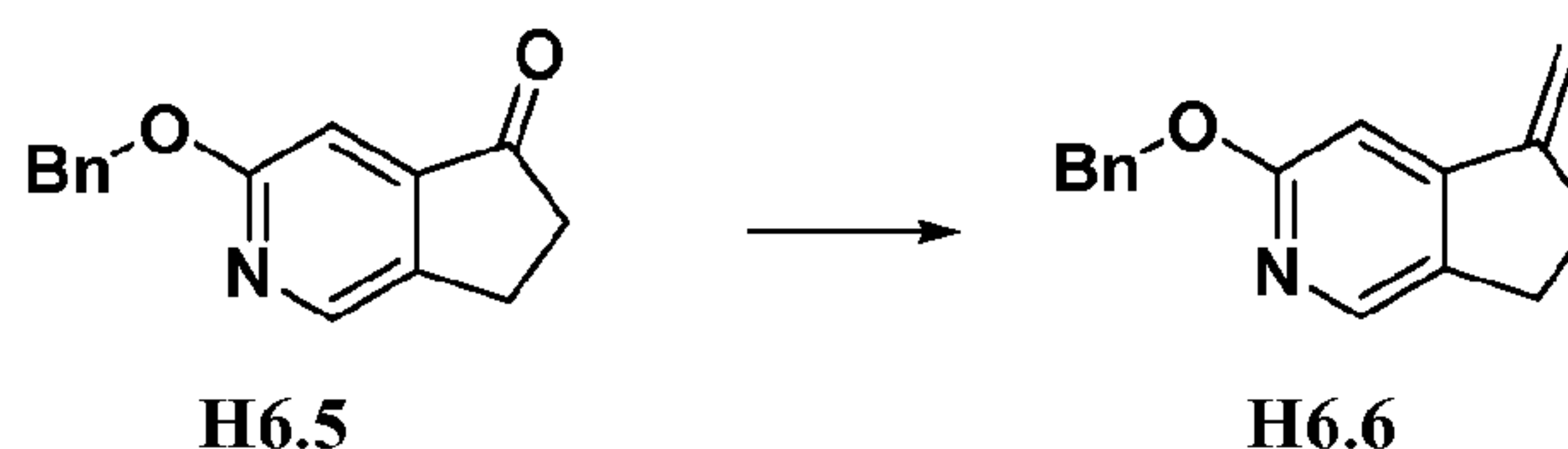


[0247] Methyl 3-(benzyloxy)-5-oxo-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylate (H6.4). To 75 mL dry THF was added methyl 2-(benzyloxy)-5-(3-methoxy-3-oxopropyl)isonicotinate (2.50 g, 7.59 mmol). The temperature of the solution was lowered to -78°C. To this solution was added 1N sodium bis(trimethylsilyl)amide (15.2 mL, 15.2 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) dropwise over 30 minutes. After completion, the reaction was stirred for an hour and then quenched by addition of 25 mL saturated NH₄Cl. The organic layer was extracted with EtOAc and washed with 150 mL water and 100 mL brine, and then dried over MgSO₄. The organic solvent was evaporated, and the residue was purified by column chromatography with 15% EtOAc/hexane to give desired product **H6.4** (1.90g, 84.1%). MS ESI (pos.) m/e: 298.1 (M+H)⁺.



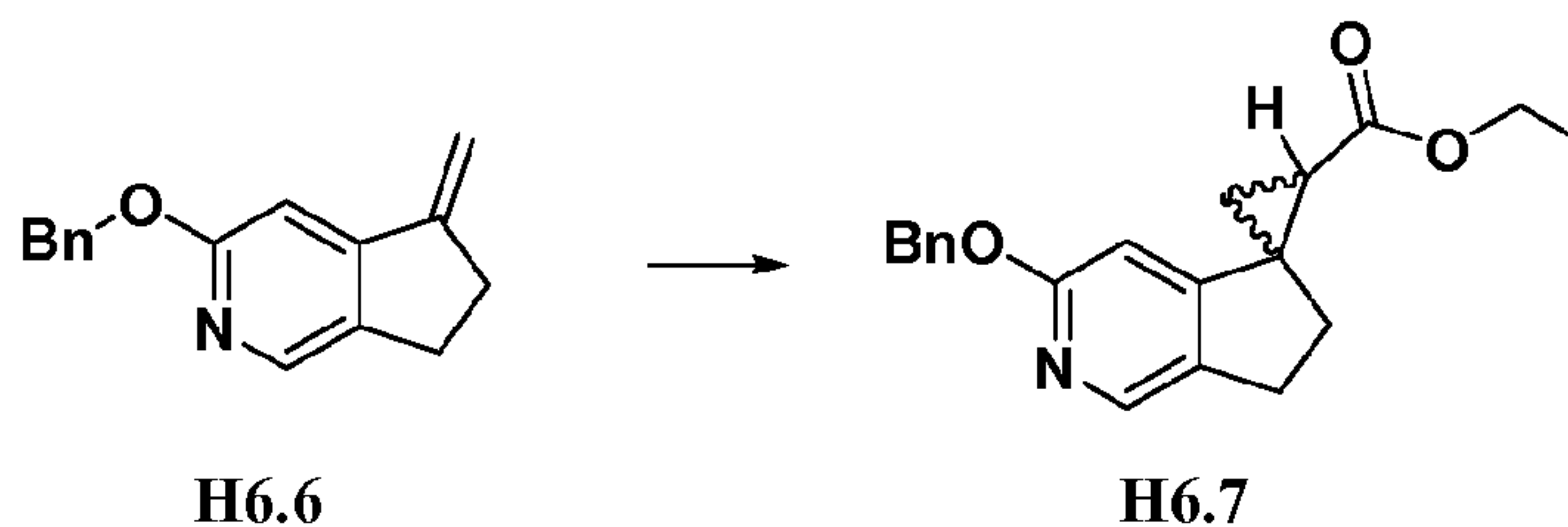
[0248] 3-(Benzyloxy)-6,7-dihydrocyclopenta[c]pyridin-5-one (H6.5).

Compound **H6.4** (2.50 g, 8.41 mmol) was dissolved in 27 mL DMSO and 3 mL water. The resulting mixture was heated to 150°C and stirred for 30 minutes. After the reaction was complete, the reaction was diluted with 120 mL water and extracted twice with 50 mL EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated onto silica gel. The resulting product was purified by column chromatography with 10% EtOAc/hexane to afford desired product **H6.5** (1.76 g, 87.5%). MS ESI (pos.) m/e: 240.1 (M+H)⁺.

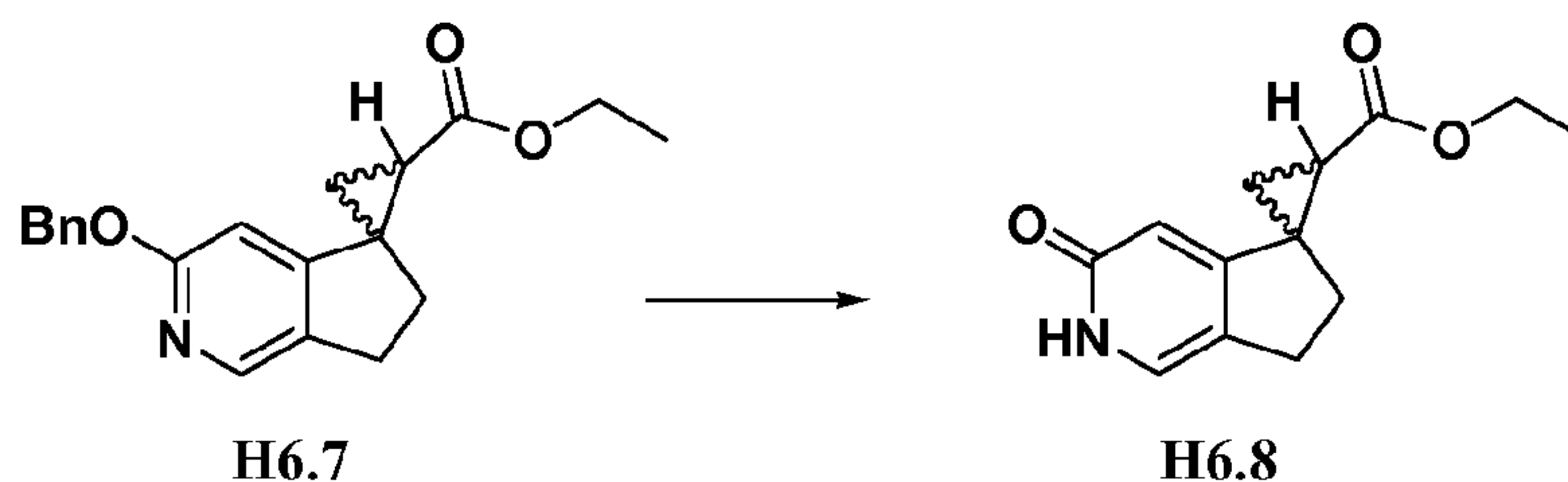


[0249] 3-(Benzyloxy)-5-methylene-6,7-dihydro-5H-cyclopenta [c]pyridine (H6.6).

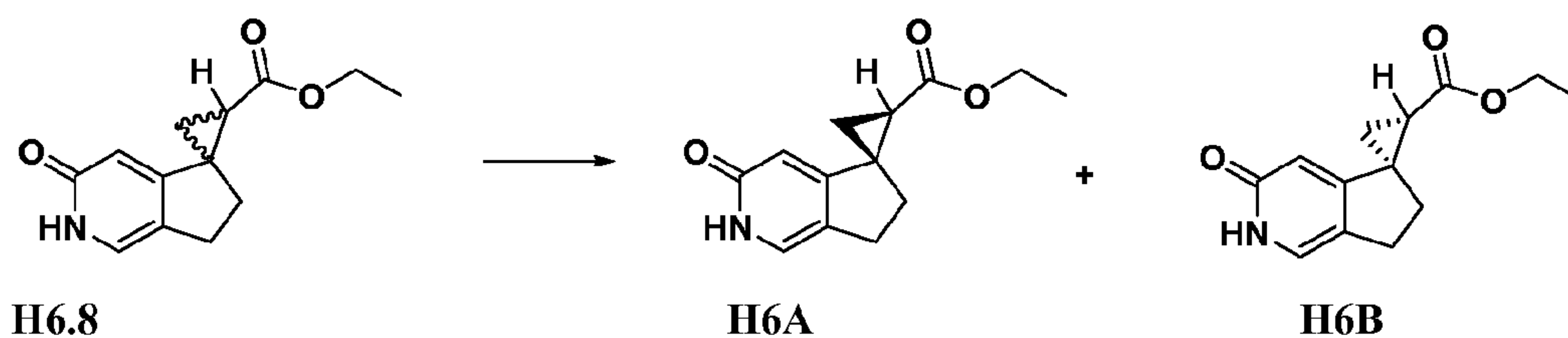
To a 100 mL round bottom flask were added compound **H6.5** (1.70 g, 7.10 mmol) and 35 mL THF. To this solution was added triphenylmethyl phosphonium bromide (3.05 g, 8.53 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and potassium tert-butoxide (8.53 mL, 8.53 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) dropwise. After completion, the reaction was stirred another hour and quenched with saturated NH₄Cl. The mixture was then extracted twice with EtOAc. The combined organic layers were washed with brine and then dried over MgSO₄. The solvent was removed and the residue was purified by column chromatography to give **H6.6** (1.25 g, 73.9%). MS ESI (pos.) m/e: 238.1 (M+H)⁺.



[0250] Ethyl 3-(benzyloxy)-6,7-dihydrospiro[cyclopenta[c]pyridine-5,1'-cyclopropane]-2'-carboxylate (H6.7). Compound **H6.6** (50.0 mg, 211 μ mol) and rhodium (ii) acetate, dimer (9.31 mg, 21.1 μ mol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) were mixed in 1.6 mL dry DCM. The resulting solution was refluxed at 45°C for 10 minutes. Ethyl diazoacetate (26.2 μ L, 253 μ mol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was then added to the mixture very slowly. After 1 hour, the reaction was cooled to room temperature. The catalyst was then filtered off, and the solvent was concentrated down with silica gel. The product was purified by column chromatography to give **H6.7** (25.1 mg, 36.9%). NMR confirmed that the product was the *trans* isomer. MS ESI (pos.) m/e : 324.2 ($M+H$)⁺. ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 7.55 - 7.60 (3 H, m), 7.37 - 7.47 (4 H, m), 4.90 (2 H, d, $J=3.7$ Hz), 4.12 (2 H, q, $J=7.1$ Hz), 2.92 (2 H, d, $J=19.3$ Hz), 2.82 (1 H, dd, $J=8.6, 6.4$ Hz), 2.31 (1 H, dd, $J=8.4, 5.0$ Hz), 2.19 (2 H, ddd, $J=8.7, 6.8, 2.8$ Hz), 1.36 (1 H, dd, $J=6.0, 5.5$ Hz), 1.21 (3 H, t, $J=7.1$ Hz).



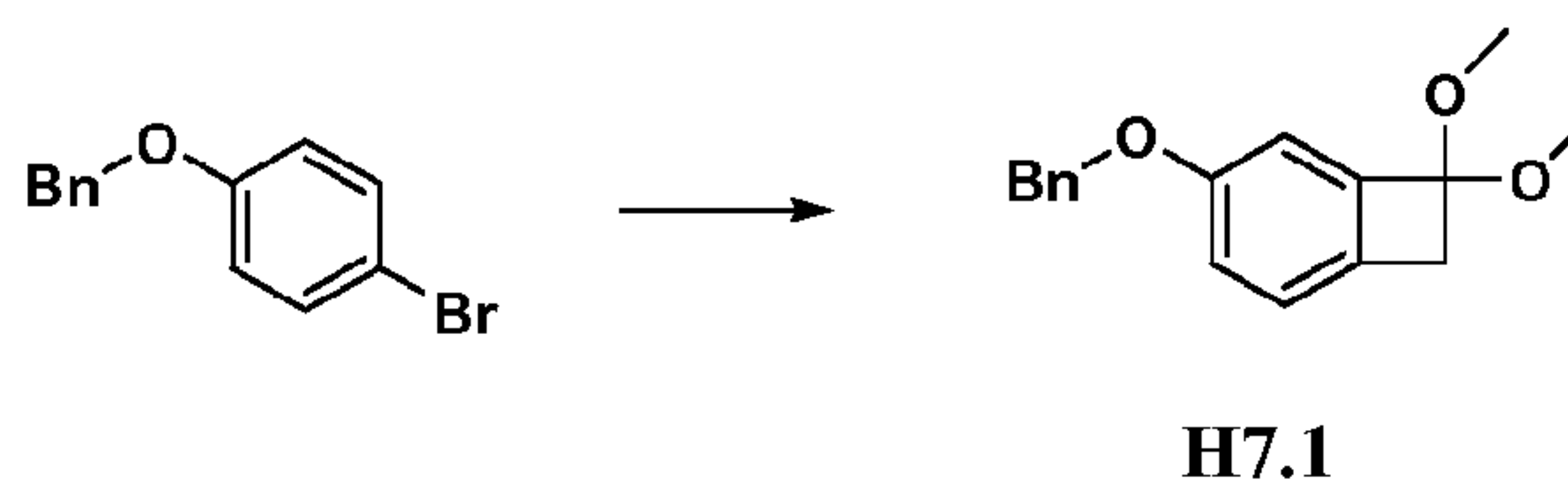
[0251] Ethyl 3-oxo-2,3,6,7-tetrahydrospiro[cyclopenta[c]pyridine-5,1'-cyclopropane]-2'-carboxylate (H6.8). Compound **H6.7** (200 mg, 618 μ mol) was dissolved in 5 mL EtOH. To this solution was added palladium on carbon (65.8 mg, 618 μ mol) and hydrogen was introduced by balloon. The reaction was stirred at room temperature for 1 hour. After the reaction was complete, the catalyst was filtered off and the solvent was removed to provide **H6.8** (135 mg, 93.6%). MS ESI (pos.) m/e : 234.2 ($M+H$)⁺.



[0252] Ethyl (2'*R*,5*R*)-3-oxo-2,3,6,7-tetrahydrospiro[cyclopenta[*c*]pyridine-5,1'-cyclopropane]-2'-carboxylate (**H6A**) and Ethyl (2'*S*,5*S*)-3-oxo-2,3,6,7-tetrahydrospiro[cyclopenta[*c*]pyridine-5,1'-cyclopropane]-2'-carboxylate (**H6B**).

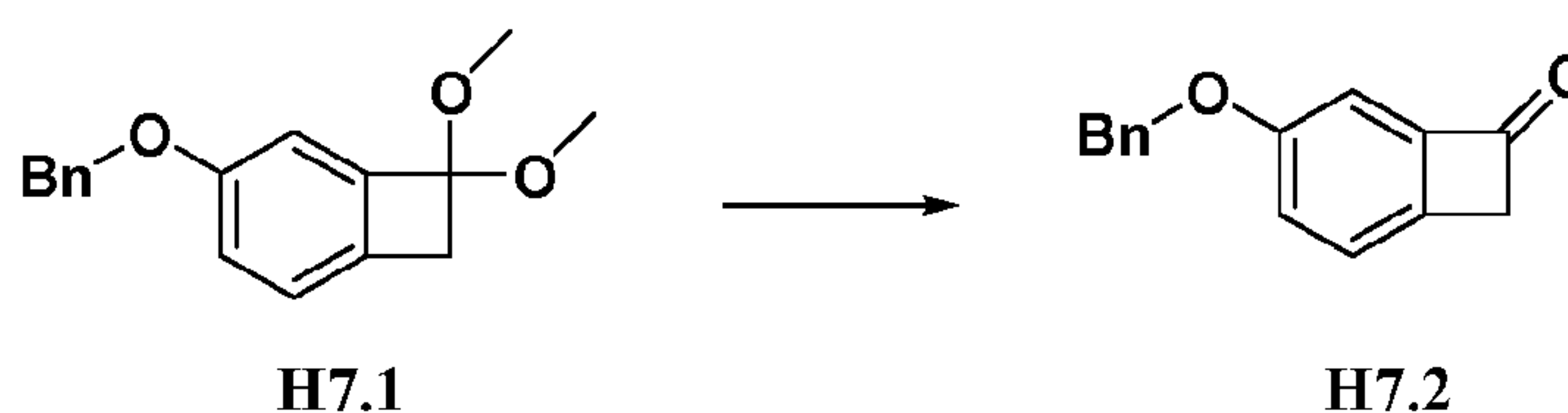
Racemate **H6.8** (120 mg, 0.537 mmol) was resolved by ChiralPak® AS-H chromatography (15 x 0.46 cm, 30% MeOH (0.1% DEA)/CO₂, 100 bar, 3 mL/min, 220 nm) to afford the two enantiomers represented by two peaks. The first peak is the compound **H6B** (55.0 mg, 45.8%) and the second peak is **H6A** (53.0 mg, 44.1%). The stereochemistry of **H6A** and **H6B** was determined by their chiral HPLC retention times compared to those of **H1A** and **H1B**.

[0253] Intermediates **H7A**, **H7B**, **H7C** and **H7D**



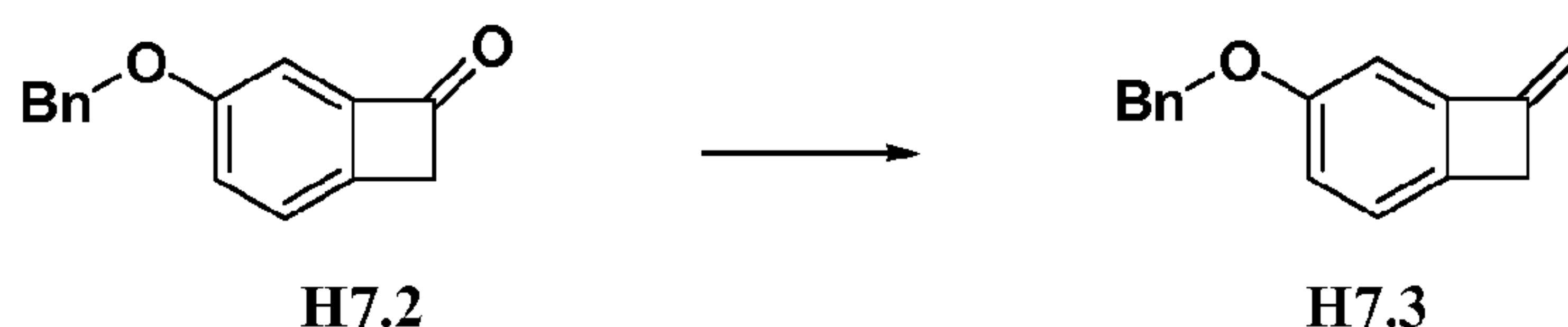
[0254] **5-(Benzyloxy)-1,1-dimethoxy-1,2-dihydrocyclobutabenzene (**H7.1**).**

To a 6 mL THF solution of 1-(benzyloxy)-4-bromobenzene (500 mg, 1900 μmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and ketene dimethyl acetal (359 μL, 3800 μmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added neat sodium amide (107 μL, 3800 μmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA). The resulting mixture was heated to 80°C and stirred for 48 hours. After the reaction was complete, it was quenched by slow addition of water. The resulting mixture was then extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄. Solvent was removed in the presence of silica gel, and the residue was purified by column chromatography with 20% EtOAc/hexane to afford desired product **H7.1** (274 mg, yield, 60%). MS ESI (pos.) *m/e*: 271.1 (M+H)⁺.



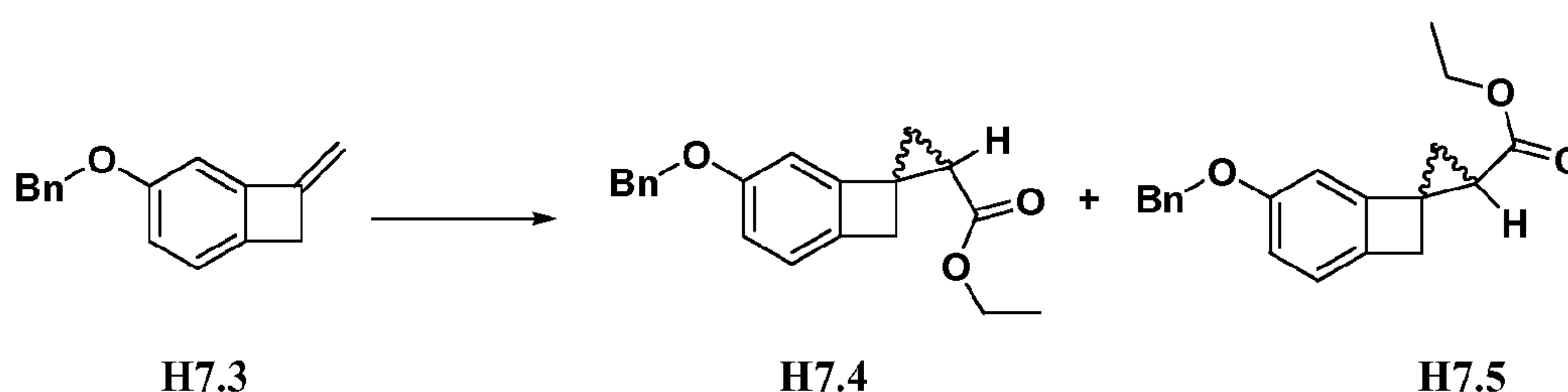
[0255] **5-(Benzyloxy)cyclobutabenzene-1(2H)-one (**H7.2**).** **H7.1** (270 mg, 1.00 mmol) was dissolved in 6 mL 5:1 THF and water. To this solution was added 0.5 mL 1N HCl, and the resulting mixture was stirred for 1 hour. The resulting mixture was then

diluted with 20 mL EtOAc and washed with saturated NaHCO_3 and brine. The organic layer was dried over MgSO_4 , filtered, and concentrated in the presence of silica gel. The residue was then purified by column chromatography with 10% EtOAc/hexane to afford **H7.2** (204 mg, yield, 91.1%). MS ESI (pos.) m/e: 225.1 ($\text{M}+\text{H}$)⁺.



[0256] 5-(Benzyloxy)-1-methylene-1,2-dihydrocyclobutabenzene (H7.3).

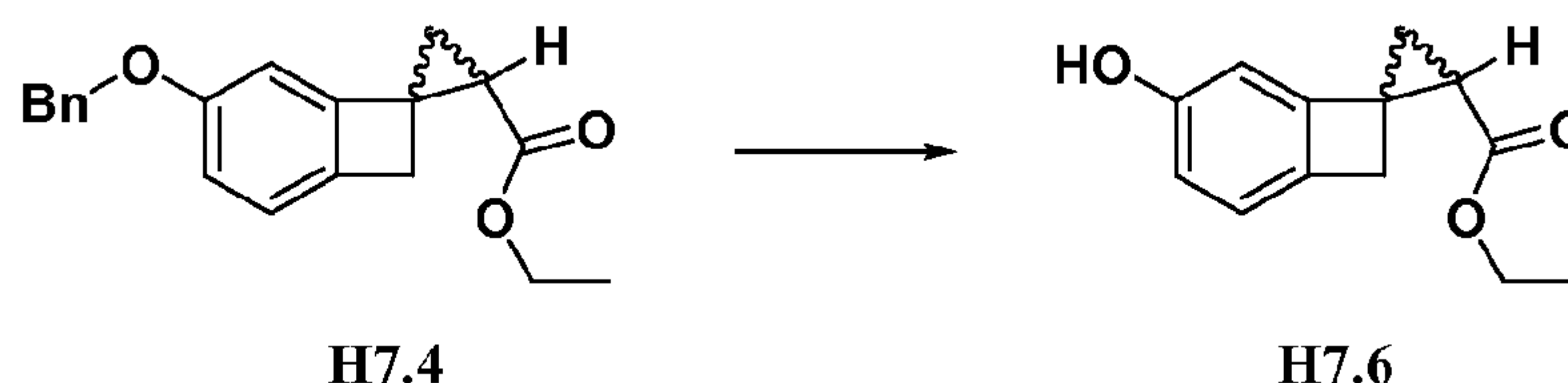
H7.2 (13.0 g, 58.0 mmol) was dissolved in 300 mL THF. The resulting solution was cooled to 0°C in an ice-water bath. Methyltriphenylphosphonium bromide (24.8 g, 69.6 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added and some yellow solid appeared. Potassium 2-methylpropan-2-olate (69.6 mL, 69.6 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was then added dropwise over an hour. The reaction was stirred at 0°C for another hour and then quenched by addition of 200 mL saturated NaHCO_3 . The THF solvent was evaporated by vacuum and the residue was extracted twice with 200 mL EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and then concentrated in the presence of silica gel. The residue was purified by column chromatography with 10% EtOAc/hexane to afford **H7.3** (4.1 g, 31.8%). MS ESI (pos.) m/e: 223.1 ($\text{M}+\text{H}$)⁺.



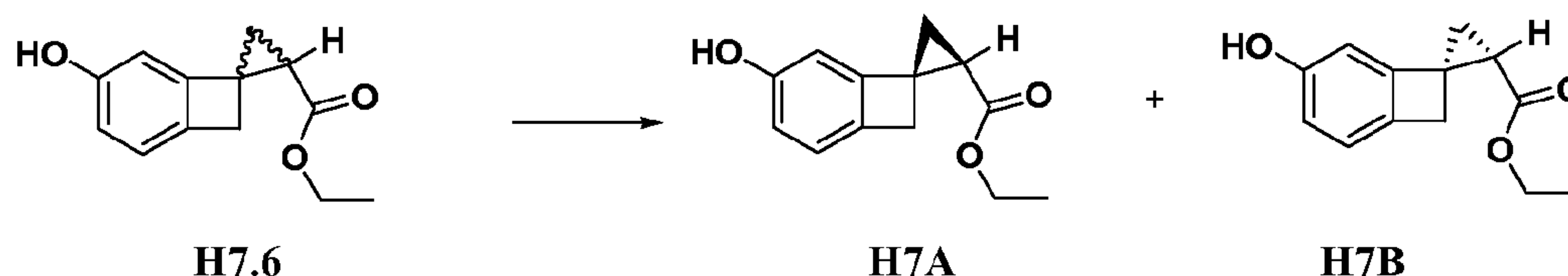
[0257] Ethyl 4-(benzyloxy)spiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H7.4 and H7.5).

H7.3 (1.77 g, 7.96 mmol) was dissolved in 64 mL DCM. To this solution was added rhodium (ii) acetate dimer (0.176 g, 0.398 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA). The resulting mixture was then refluxed at 45°C for 30 minutes. Ethyl diazoacetate (1.36 g, 11.9 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added to the refluxed solution via syringe pump over 1 hour. After completion, the reaction was

stirred for another hour. The solution was then filtered through Celite® filter aid, concentrated in the presence of silica gel and purified by column chromatography (5% EtOAc/hexane) to give compound **H7.4** (0.85g, 35%) and compound **H7.5** (0.85g, 35%). NMR confirmed that **H7.4** was the trans isomer and **H7.5** was the cis isomer. Compound **H7.4**: MS ESI (pos.) m/e: 309.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.28 - 7.44 (5 H, m), 7.01 (1 H, dd, *J*=8.0, 0.6 Hz), 6.84 (1 H, dd, *J*=7.9, 2.2 Hz), 6.66 (1 H, s), 5.02 (1 H, d, *J*=3.9 Hz), 4.98 - 5.06 (1 H, m), 4.05 (2 H, qd, *J*=7.1, 3.4 Hz), 3.15 - 3.29 (2 H, m), 2.30 (1 H, dd, *J*=8.4, 6.1 Hz), 1.64 (1 H, dd, *J*=8.5, 4.8 Hz), 1.55 - 1.60 (1 H, m), 1.13 - 1.18 (3 H, m). Compound **H7.5**: MS ESI (pos.) m/e: 309.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.30 - 7.46 (5 H, m), 7.02 (1 H, d, *J*=7.8 Hz), 6.83 (1 H, dd, *J*=8.0, 2.2 Hz), 6.72 (1 H, dd, *J*=1.9, 0.5 Hz), 5.03 (2 H, s), 4.10 (2 H, q, *J*=7.3 Hz), 3.20 - 3.26 (1 H, m), 3.08 - 3.14 (1 H, m), 2.25 (1 H, dd, *J*=8.5, 6.0 Hz), 1.56 - 1.66 (2 H, m), 1.15 - 1.27 (3 H, m).

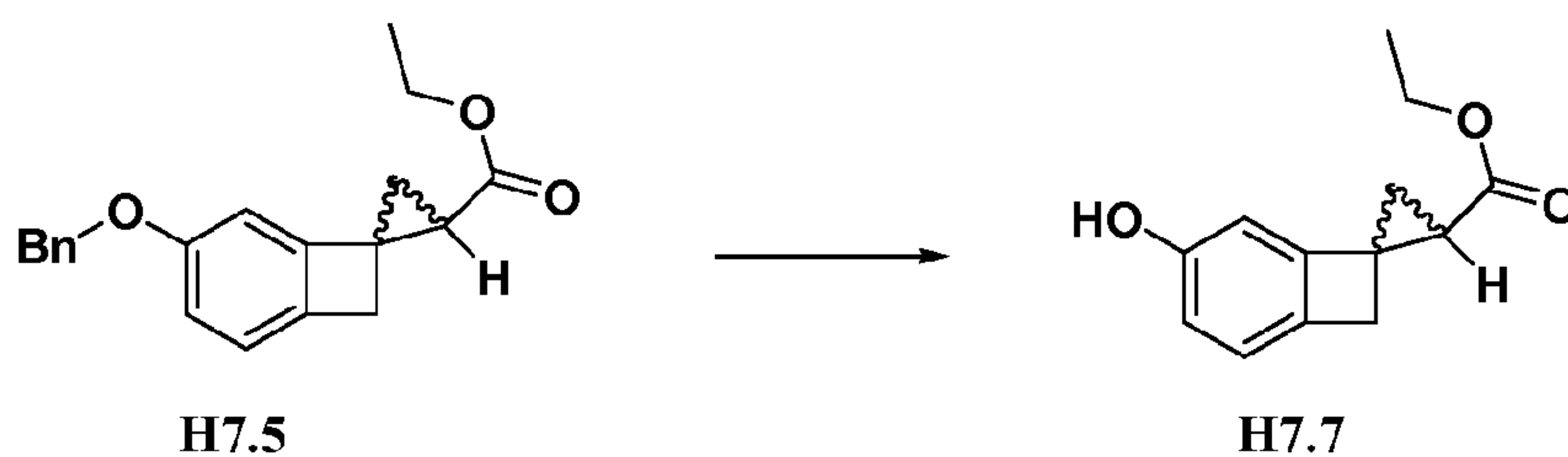


[0258] **Ethyl 4-hydroxyspiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H7.6).** **H7.4** (700 mg, 2.27 mmol) was dissolved in 5 mL MeOH. To this solution was added 10% palladium on carbon (242 mg, 0.227mmol) and a balloon of H₂ was placed over the reaction. The reaction mixture was stirred for 1 hour, and the catalyst was then removed by filtration. The filtrate was concentrated down in the presence of silica gel and purified by column chromatography with 30% EtOAc/hexane to give 250 mg compound **H7.6** (yield, 50.1%). MS ESI (pos.) m/e: 218.2 (M+H)⁺.

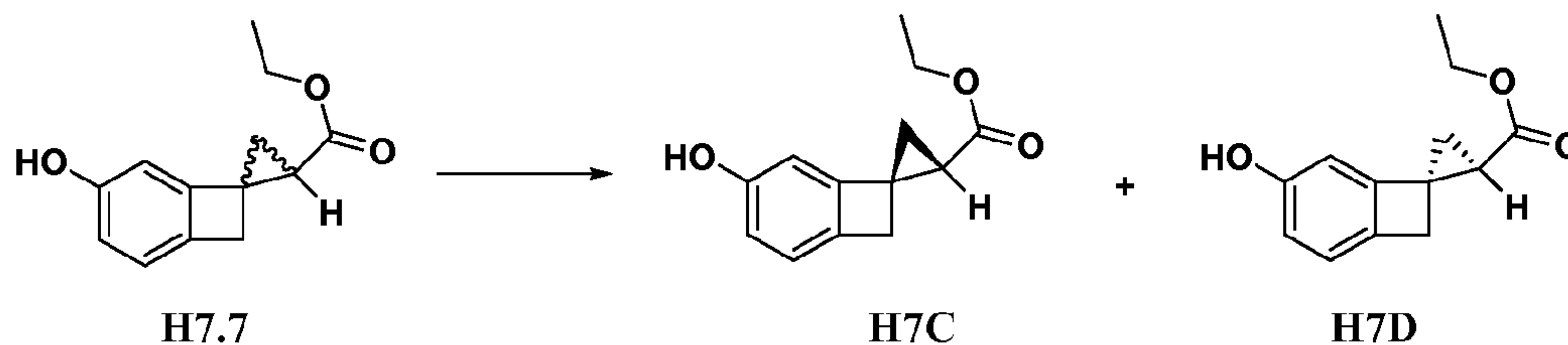


[0259] **Ethyl (2'*R*,7*S*)-4-hydroxyspiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H7A) and Ethyl (2'*S*,7*R*)-4-hydroxy spiro[bicycle[4.2.0] octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H7B).**

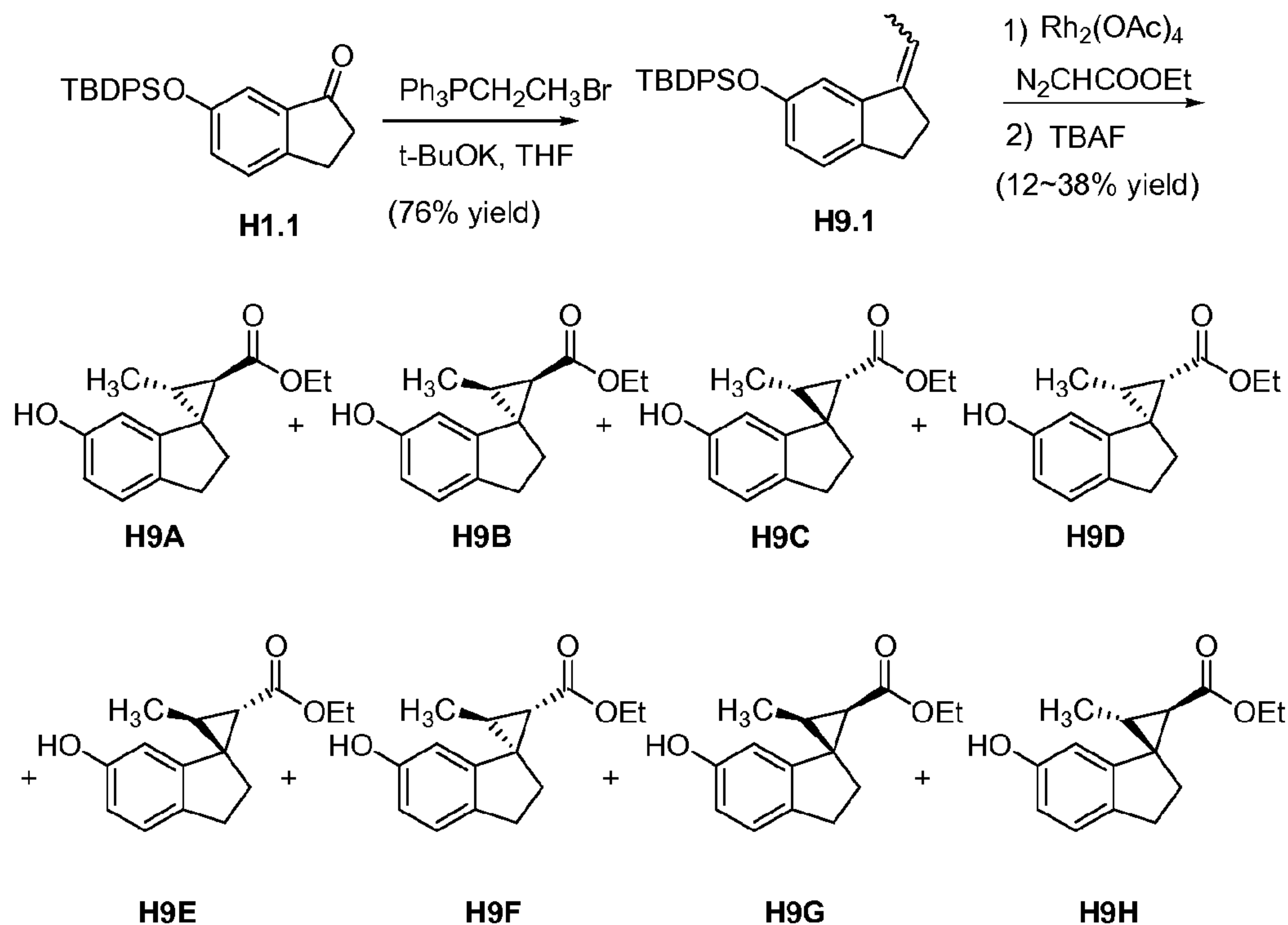
Racemate **H7.6** (350 mg, 1.60 mmol) was resolved by chiral HPLC (CHIRALCEL® OJ column, 10% IPA/hexane). The first peak corresponded to **H7B** (150 mg, 43%) and the second peak corresponded to **H7A** (152 mg, 43%). The stereochemistry of **H7A** and **H7B** was determined by their chiral HPLC retention times compared to those of **H1.A** and **H1.B**.



[0260] **Ethyl 4-hydroxyspiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H7.7)**. The hydrogenation of compound **H7.5** (700 mg, 2.27 mmol) using the method reported for preparation of the compound **H7.6** to afford **H7.7** (302 mg, 60.1%). MS ESI (pos.) m/e : 218.2 ($M+H$)⁺.



[0261] **Ethyl (2'*S*,7*S*)-4-hydroxyspiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H7C)** and **Ethyl (2'*R*,7*R*)-4-hydroxyspiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H7D)**. Racemate **H7.7** (300 mg, 1.37 mmol) was resolved by chiral HPLC (CHIRALCEL® OJ column, 10% IPA/hexane). The first peak corresponds to **H7C** (132 mg, 44%) and the second peak corresponded to **H7D** (130 mg, 44%). The stereochemistry of **H7C** and **H7D** was determined by their chiral HPLC retention times compared to those of **H1C** and **H1D**.

[0262] Intermediates H9A, H9B, H9C, H9D, H9E, H9F, H9G and H9H**[0263] *tert*-Butyl(3-ethylidene-2,3-dihydro-1H-inden-5-yloxy)diphenylsilane (H9.1).**

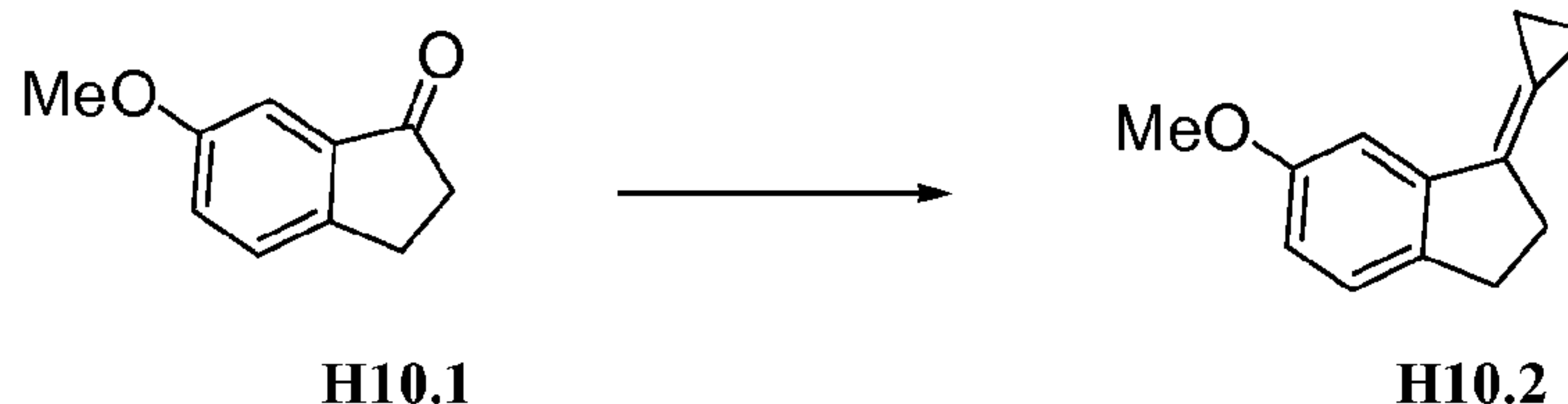
To a solution of **H1.1** (3.87 g, 10.0 mmol) and ethyltriphenylphosphonium bromide (4.46 g, 12.0 mmol) in THF (20 mL) was added potassium *tert*-butoxide, 1.0 M solution in THF (12.0 mL, 12.0 mmol). The resulting mixture was stirred at room temperature for 4 hours and concentrated to remove most of the THF. The resulting mixture was suspended in hexanes (50 mL), passed through a pad of silica gel (2027-U, 25 g), and rinsed with hexanes (250 mL) to give **H9.1** (3.02g, 76% yield) as a mixture of *cis/trans* isomers. MS ESI (pos.) M/E: 399 (M+H).

[0264] Synthesis of H9A, H9B, H9C, H9D, H9E, H9F, H9G and H9H.

To a solution of **H9.1** (2.61g, 6548 μmol) and rhodium (II) acetate, dimer (29 mg, 65 μmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (1019 μL , 9822 μmol) in refluxing DCM via syringe pump over 60 minutes. The resulting mixture was stirred at 45°C for 1 hour and then at room temperature for 16 hours. The resulting mixture was concentrated and purified by flash chromatography (0-10% EtOAc/hexane) to give several fractions of mixtures. These fractions were treated individually with 1 equivalent of TBAF in THF at room temperature for 1 hour. The mixtures were diluted with DCM,

washed with aqueous NH_4Cl , loaded onto a silica gel cartridge, and purified by flash chromatography (20% EtOAc/hexane) to give eight fractions. Most of the fractions were mixtures of two or three isomers. These eight fractions of mixtures were separated individually on an AD column (ChiralPak® AD, 4% IPA/hexanes) to give **H9A** (54 mg, 27% yield, 99%ee, retention time 11.7 minutes on AD-H with 4% IPA/hex.); **H9B** (34 mg, 17% yield, 99%ee, retention time 13.9 minutes on AD-H with 4% IPA/hex.); **H9C** (33 mg, 16% yield, 99%ee, retention time 20.2 minutes on AD-H with 4% IPA/hex.); **H9D** (61 mg, 30% yield, 99%ee, retention time 23.6 minutes on AD-H with 4% IPA/hex.); **H9E** (53 mg, 26% yield, 99%ee, retention time 28.6 minutes on AD-H with 4% IPA/hex.); **H9F** (28 mg, 14% yield, 95%ee, retention time 30.4 minutes on AD-H with 4% IPA/hex.); **H9G** (76 mg, 38% yield, 99%ee, retention time 31.9 minutes on AD-H with 4% IPA/hex.); and **H9H** (25 mg, 12% yield, 95%ee, retention time 35.4 minutes on AD-H with 4% IPA/hex.). MS ESI (pos.) M/E: 247 (M+H). Relative stereochemistry was assigned based on ^1H NMR and NOE studies. Absolute configuration was assigned based on their chiral HPLC retention times compared to those of **H1A**, **H1B**, **H1C**, and **H1D**. However, absolute configurations are not known with certainty. Therefore, when **H9A**, **H9B**, **H9C**, **H9D**, **H9E**, **H9F**, **H9G**, or **H9H** was used to synthesize an Example compound, all eight stereoisomers are shown.

[0265]

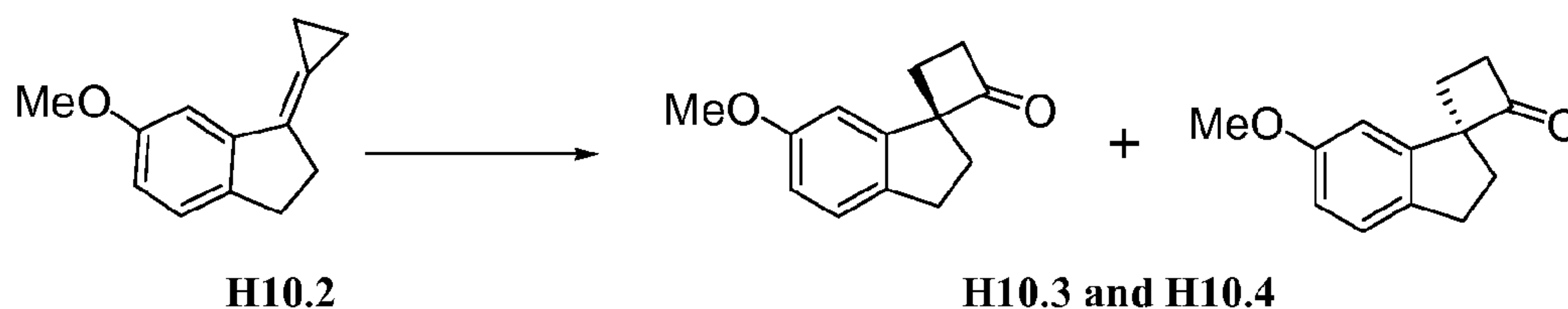
Intermediate H10

[0266]

1-Cyclopropylidene-6-methoxy-2,3-dihydro-1H-indene (H10.2).

NaH (1.5 g, 62 mmol) was added to a suspension of cyclopropyltriphenyl-phosphonium bromide (24 g, 62 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in THF (100 mL), and the resulting mixture was stirred at room temperature for 2 hours. Then, 6-methoxy-1-indanone (**H10.1**) (Oakwood Products, Inc.) (5.00 g, 31 mmol) and tris(2-(2-methoxyethoxy)ethyl)amine (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (1.1 mL, 3.1 mmol) were added slowly. The resulting mixture was stirred at room temperature for 10 minutes and then at 62°C for 4 hours. The reaction mixture was concentrated and purified by chromatography (silica gel, eluting

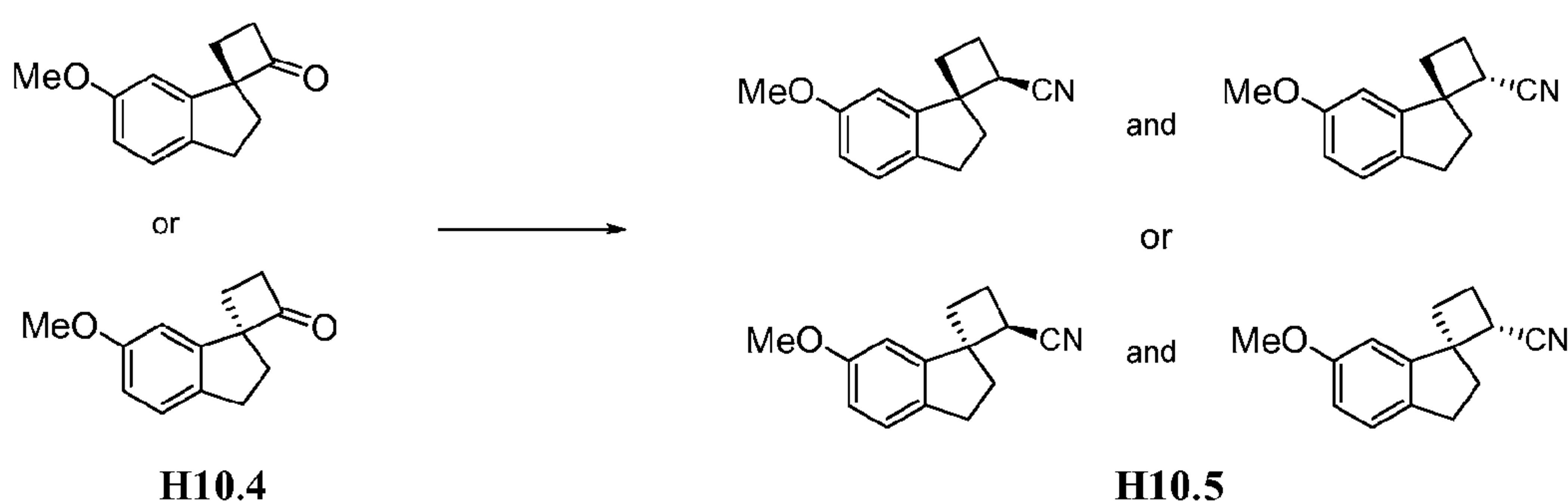
with 1:9 EtOAc/hexane) to provide **H10.2** (4.53 g, 79% yield) as a solid. MS ESI (pos.) M/E: 187.1 (M+H).



[0267] **(S)-6'-Methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-2-one and (R)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-2-one (H10.3 and H10.4).**

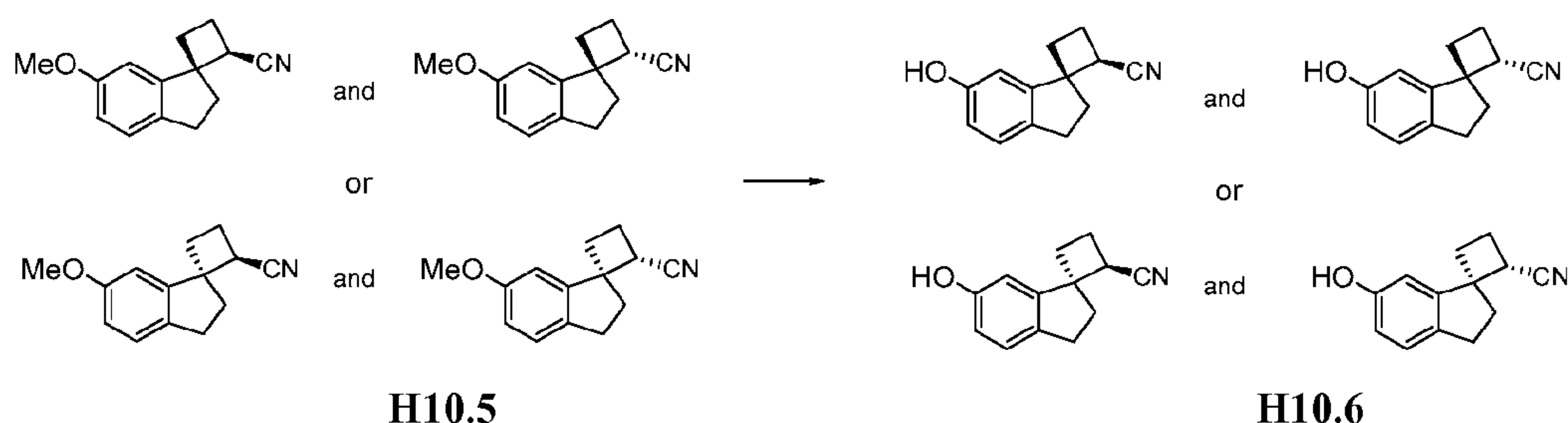
At 0-5 °C, 3-chloroperbenzoic acid (5.84 g, 33.8 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added portion by portion to a solution of 1-cyclopropylidene-6-methoxy-2,3-dihydro-1H-indene (**10.2**) (4.50g, 24.2 mmol) in DCM (70mL). The resulting mixture was stirred at 0-5 °C for 42 minutes and then at room temperature for 60 minutes. The mixture was then diluted with DCM (200 mL), washed with 10% NaOH solution and brine, and then dried over anhydrous sodium sulfate.

Solvent was removed, and the residue was purified by chromatography (silica gel, eluting with 1:9 EtOAc /hexane) to give the product ketone (1.95 g, 40% yield) as a pale yellow oil. MS ESI (pos.) M/E: 203.1 (M+H). Chiral separation was conducted on an OD column, eluting with 1% IPA/hexane. Pure enantiomer **H10.3** (0.896 g, oil) (first peak, retention time 8.4 minutes) and **H10.4** (1.01 g, oil) (second peak, retention time 10.5 min) were obtained. The absolute stereochemistry was not determined for either peak.

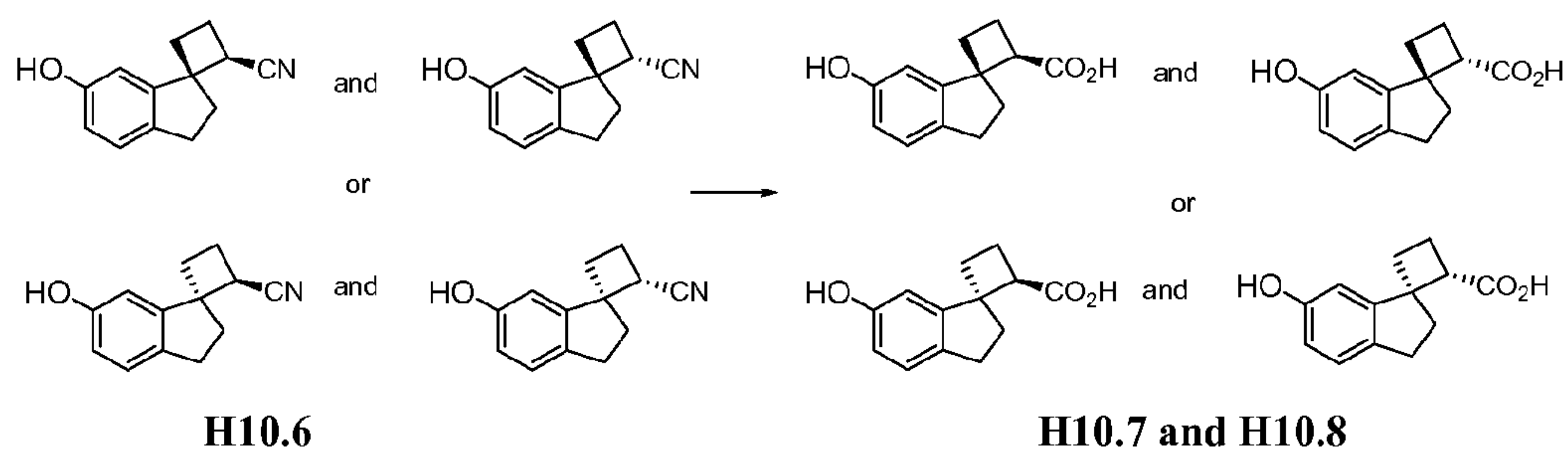


[0268] **(1S,2R)-6'-Methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-2-carbonitrile and (1S,2S)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-2-carbonitrile or (1R,2R)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-2-carbonitrile and (1R,2S)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-2-carbonitrile (H10.5).** At 0-5 °C, potassium 2-methylpropan-2-olate (2.41 g, 21.5 mmol)

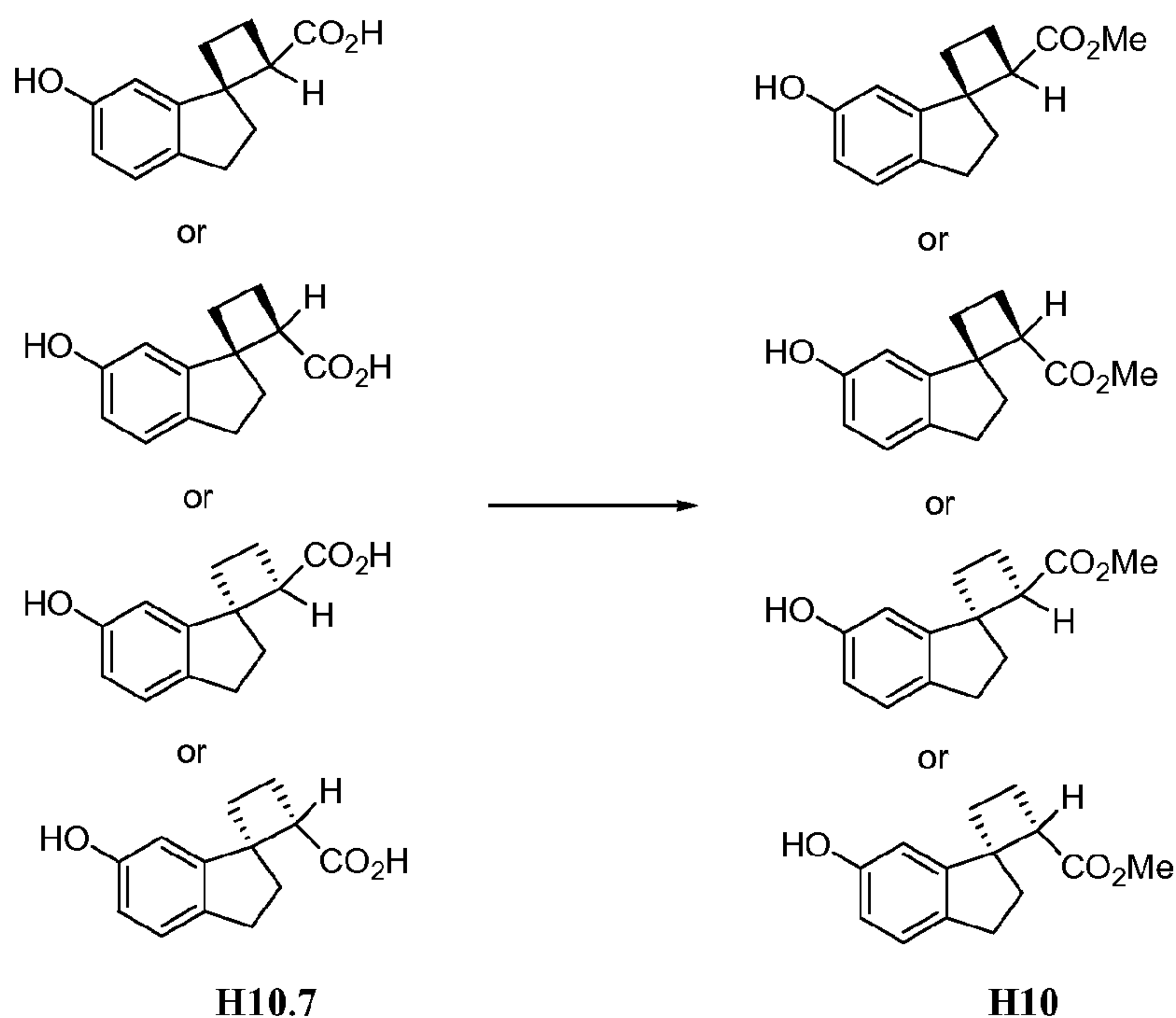
was added in one portion to a solution of **H10.4** (0.870 g, 4.30 mmol) and tosylmethyl isocyanide (1.68 g, 8.60 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in dimethoxyethane (30 mL) and MeOH (1.4 mL). The resulting mixture was stirred at room temperature for 2.4 hours and then the reaction mixture was poured into water (20 mL) and neutralized with 1N HCl to pH 6-7. The mixture was then extracted with EtOAc (3 x 100 mL) and the combined organic phase was washed with brine and dried over anhydrous sodium sulfate. After filtration, the solvent was removed and the residue was purified by chromatography (silica gel, eluting with 1:9 EtOAc /hexane) to give **H10.5**, pale yellow oil, in 24% yield. MS ESI (pos.) M/E: 214.1 (M+H).



[0269] (1S,2R)-6'-Hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1S,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile or (1R,2R)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1R,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile (**H10.6**). A mixture of **H10.5** (0.220 g, 1.0 mmol) and sodium methanethiolate (0.506 g, 7.22 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in DMF (27 mL) was stirred at 135°C for 3 hours. The reaction mixture was poured into NH₄Cl solution (20 mL). The resulting mixture was extracted with EtOAc (230 mL). The organic phase was then washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed and the residue was purified by chromatography (silica gel, eluting with 1:3 EtOAc /hexane) to give **H10.6** as a colorless oil, in 77% yield. MS ESI (pos.) M/E: 200.2 (M+H).



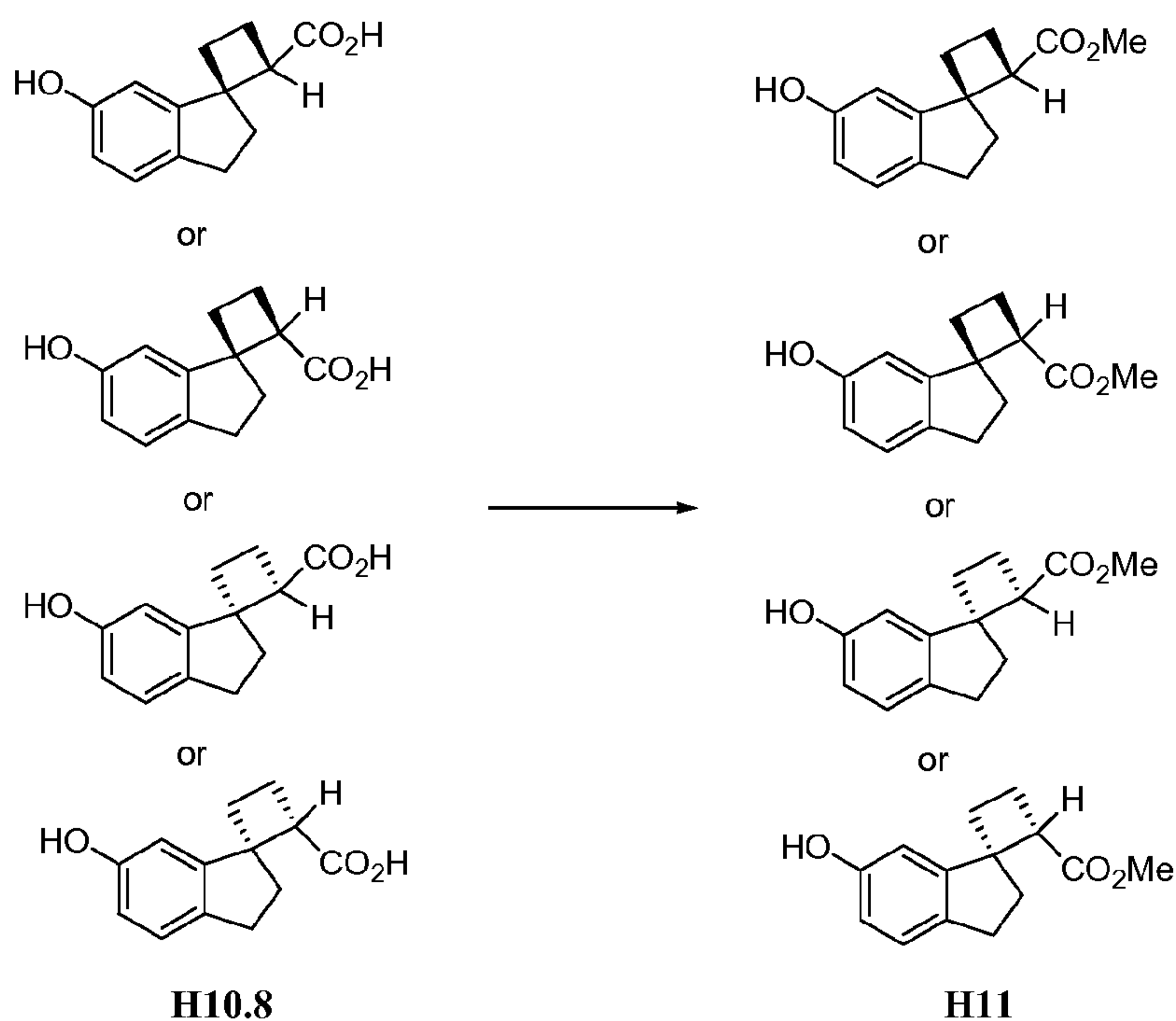
[0270] (1S,2R)-6'-Hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid and (1S,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid or (1R,2R)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid and (1R,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid (**H10.7 and H10.8**). A mixture of **H10.6** (0.154 g, 0.77 mmol) and NaOH (aq., 10%) (5 mL) in ethylene glycol (8 mL) was stirred at 135 °C for 2 hours. The resulting mixture was diluted with water (0.6 mL) and acidified with 1N HCl to pH 2-5. The resulting solution was purified by reverse phase HPLC to give **H10.7** (shorter retention time), 48 mg, white solid and **H10.8** (longer retention time), 18 mg. **H10.7**: MS ESI (pos.) M/E: 219.1 (M+H). **H10.8**: MS ESI (pos.) M/E: 219.1 (M+H).



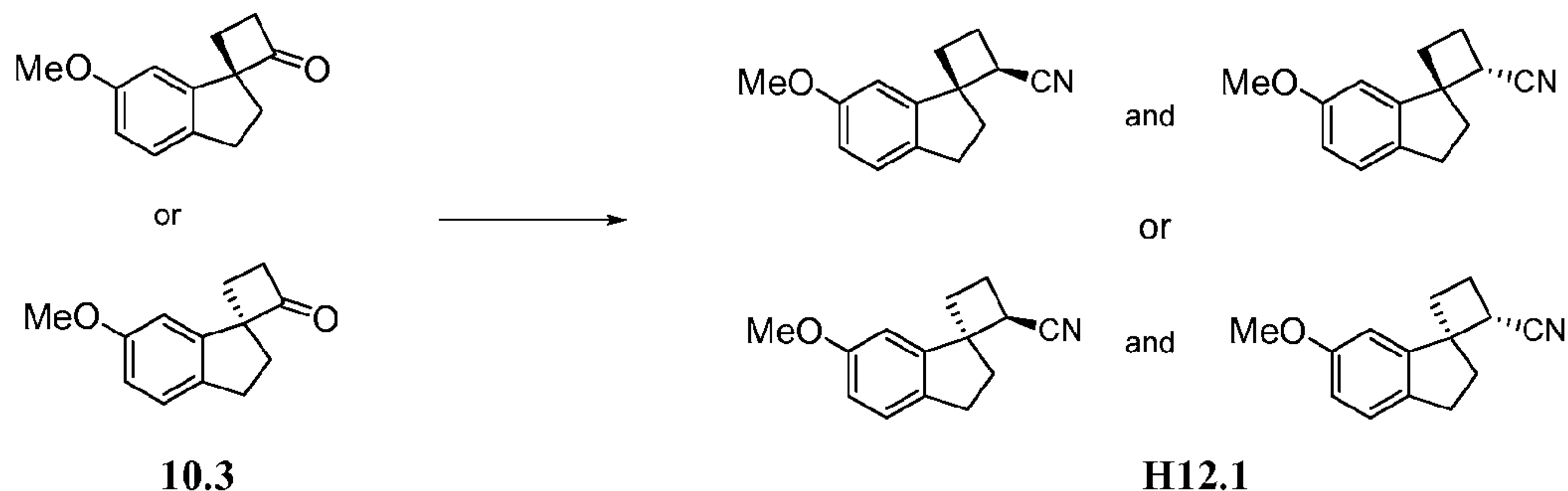
[0271] (1S,2R)-Methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate or (1S,2S)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-

1,1'-indene]-2-carboxylate or (1R,2R)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate or (1R,2S)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate (**H10**). A solution of **H10.7** (0.028 g, 0.13 mmol) in MeOH (7 mL) (containing 2 drops of concentrated H₂SO₄) was refluxed for 16 hours. The mixture was then cooled to room temperature and neutralized with NaHCO₃ solution. The mixture was concentrated and extracted with EtOAc (120 mL). The organic phase was dried over anhydrous sodium sulfate. After removal of solvent, **H10** (30 mg) was obtained. MS ESI (pos.) M/E: 250.1 (M+H₂O).

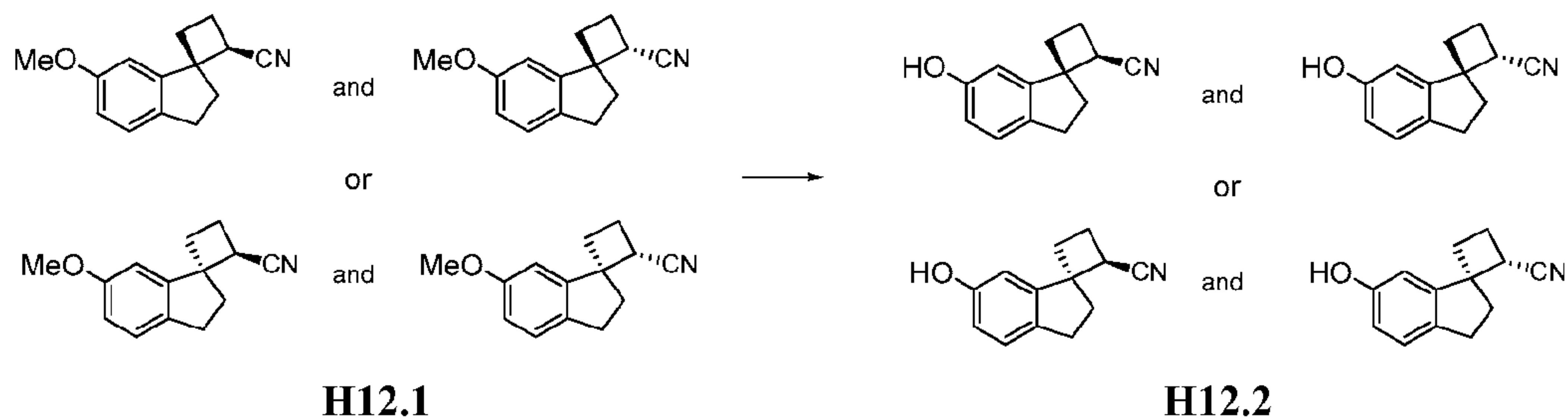
[0272] Intermediate H11



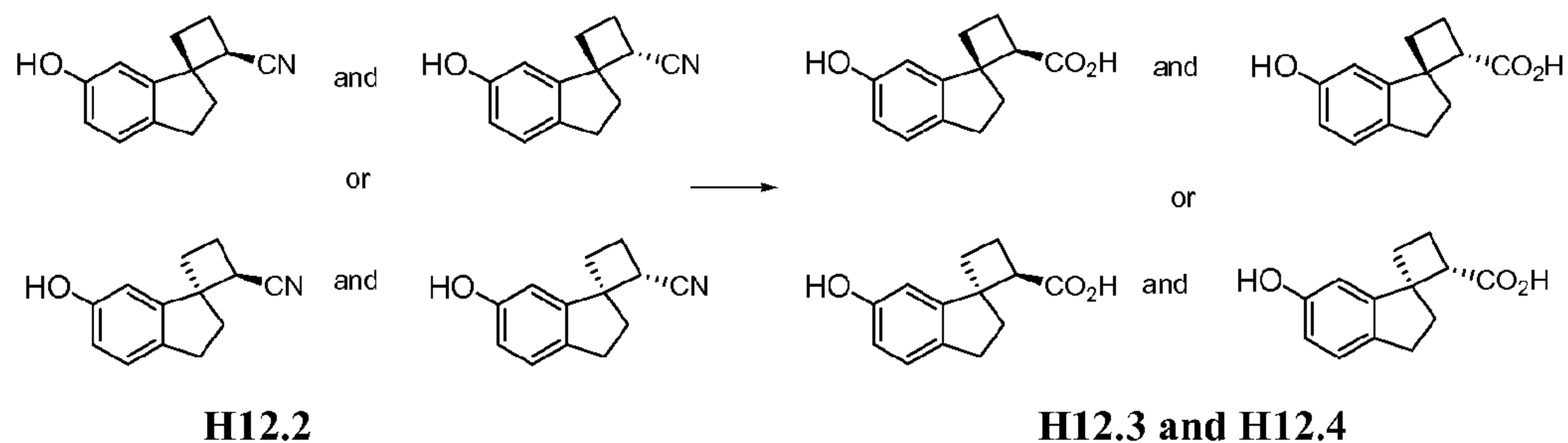
[0273] (1S,2R)-Methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate or (1S,2S)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate or (1R,2R)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate or (1R,2S)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate (**H11**). **H11** was synthesized from **H10.8** using a procedure similar to that used to prepare **H10** from **H10.7**.

[0274] Intermediate H12

[0275] (1S,2R)-6'-Methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1S,2S)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile or (1R,2R)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1R,2S)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile (H12.1). H12.1 was synthesized from H10.3 using the same procedure used to prepare H10.5 from H10.4.

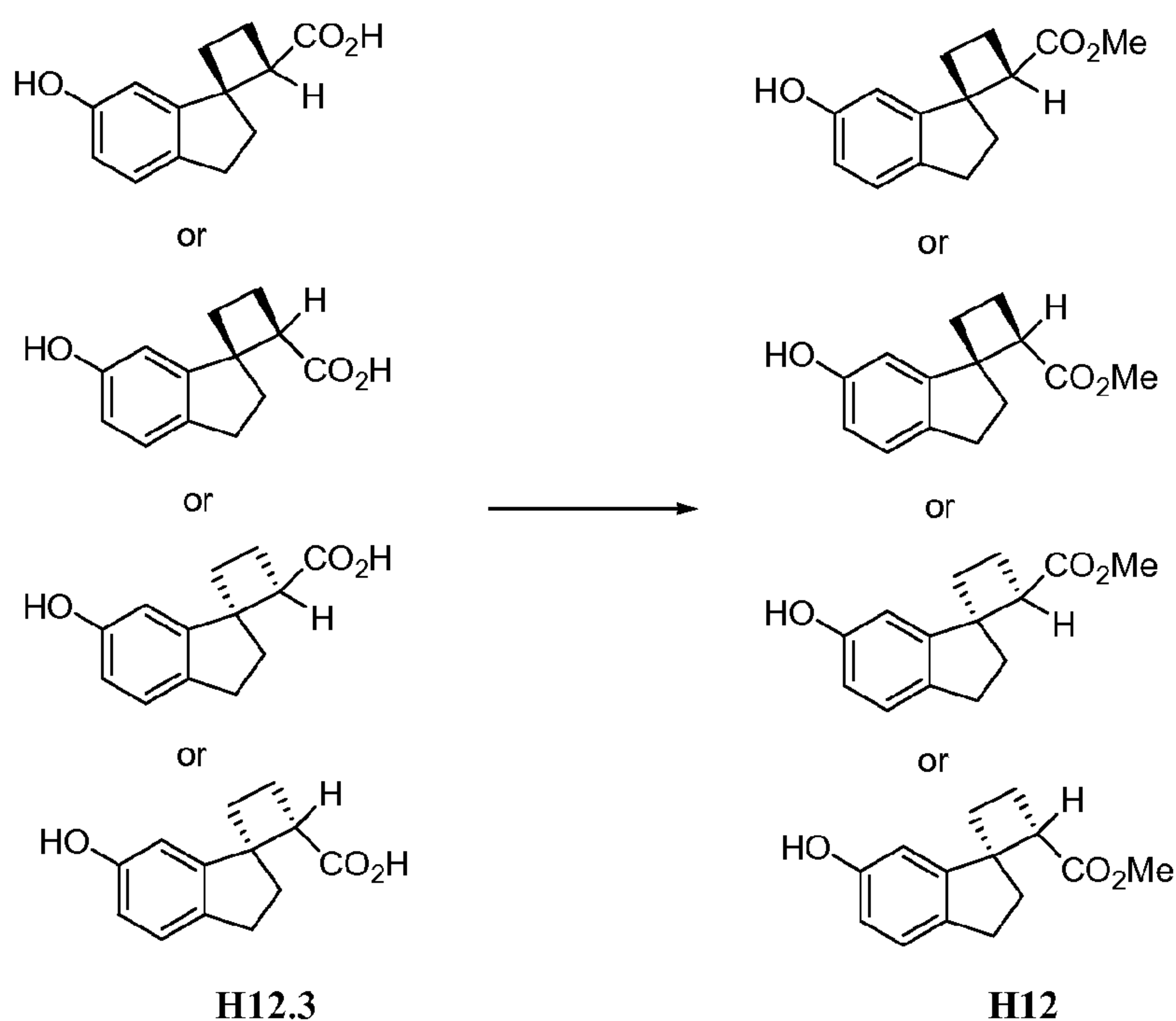


[0276] (1S,2R)-6'-Hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1S,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile or (1R,2R)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1R,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile (H12.2). H12.2 was synthesized from H12.1 using the same procedure used to prepare H10.6 from H10.5.



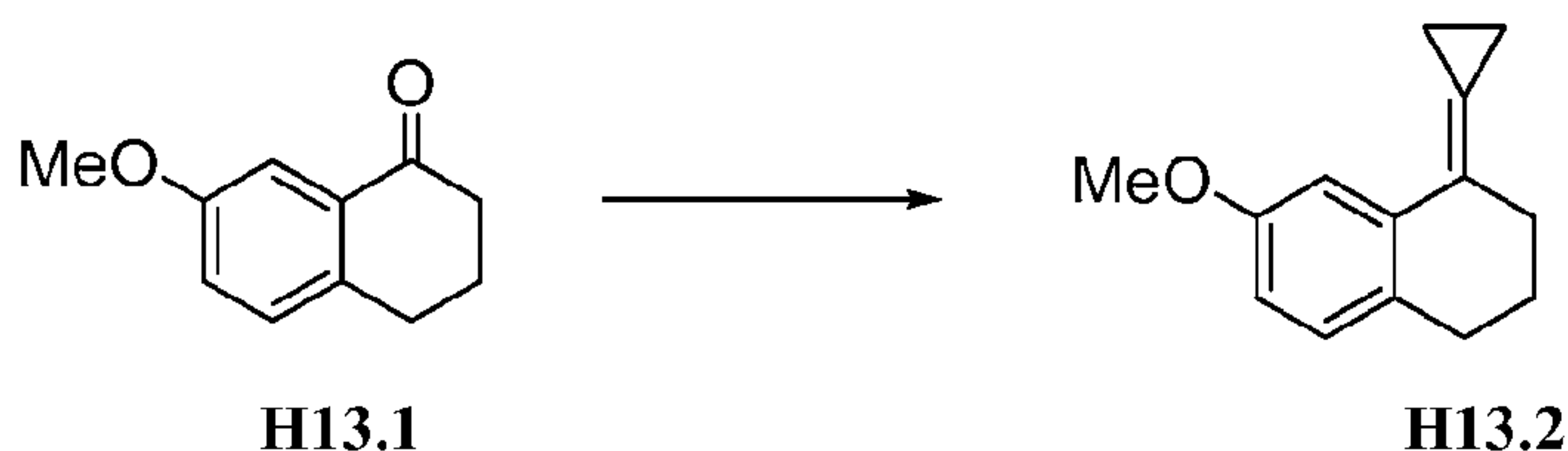
[0277] (1S,2R)-6'-Hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid and (1S,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-

2- carboxylic acid or (1R,2R)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2- carboxylic acid and (1R,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid (**H12.3** and **H12.4**). **H12.3** (first peak from reverse phase HPLC) and **H12.4** were synthesized from **H12.2** using the same procedure used to convert **H10.6** to **H10.7** and **H10.8**. MS ESI (pos.) M/E: 219.1 (M+H).

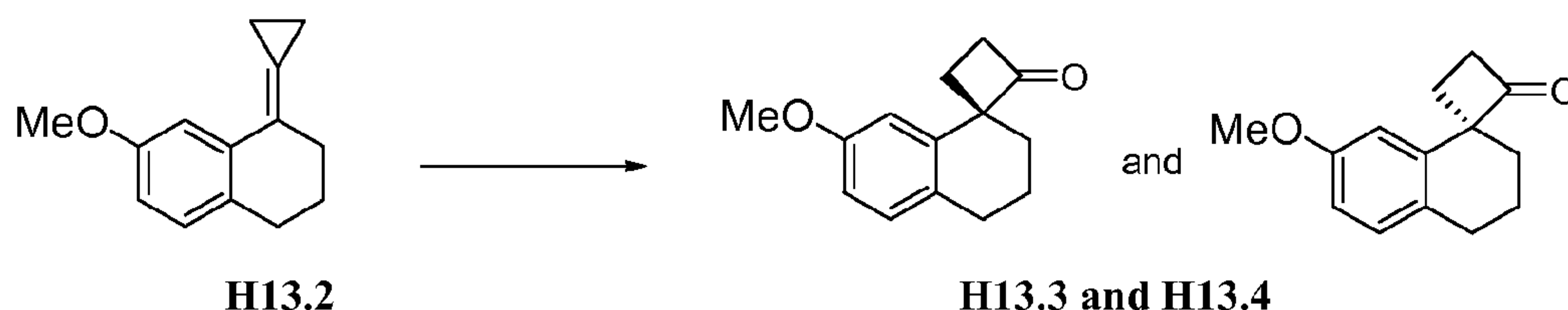


(1S,2R)-Methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate or (1S,2S)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2- carboxylate or (1R,2R)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate or (1R,2S)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate (**H12**). **H12** was synthesized from **H12.3** using the same procedure used to convert **H10.7** to **H10**. M/E: 250.1 (M+H₂O).

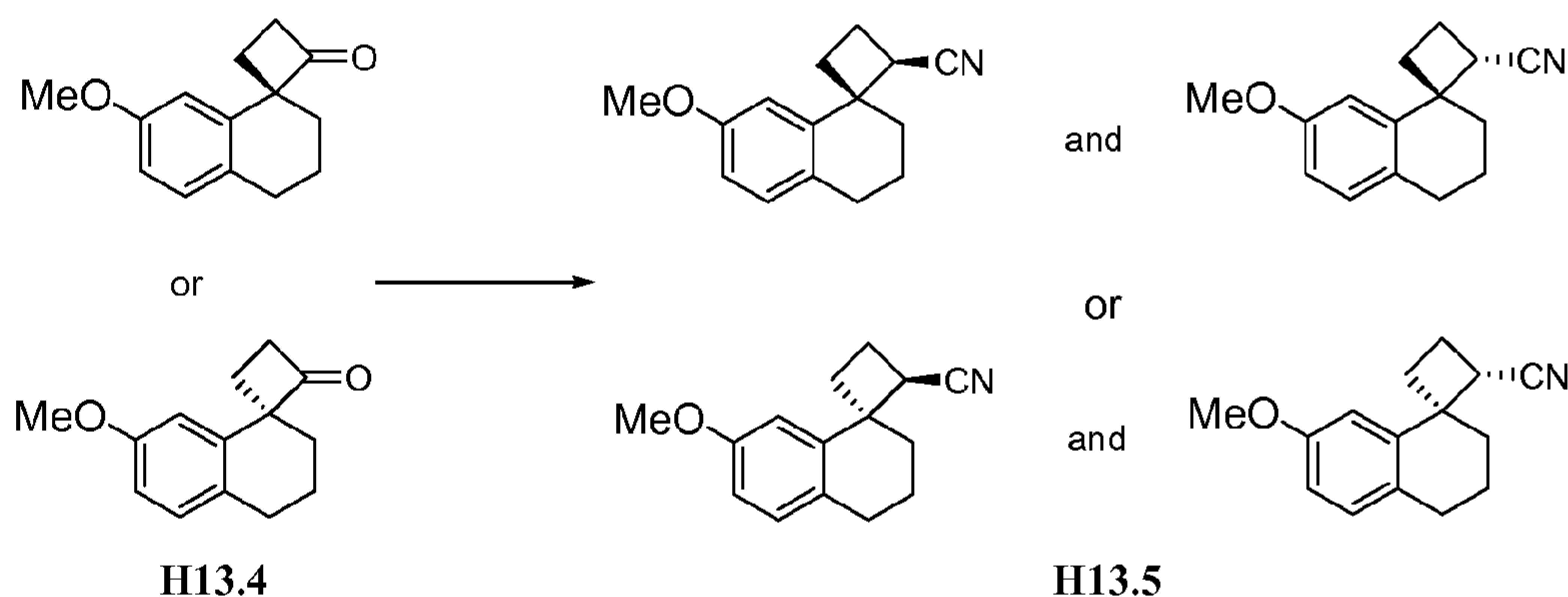
[0278]

Intermediate H13

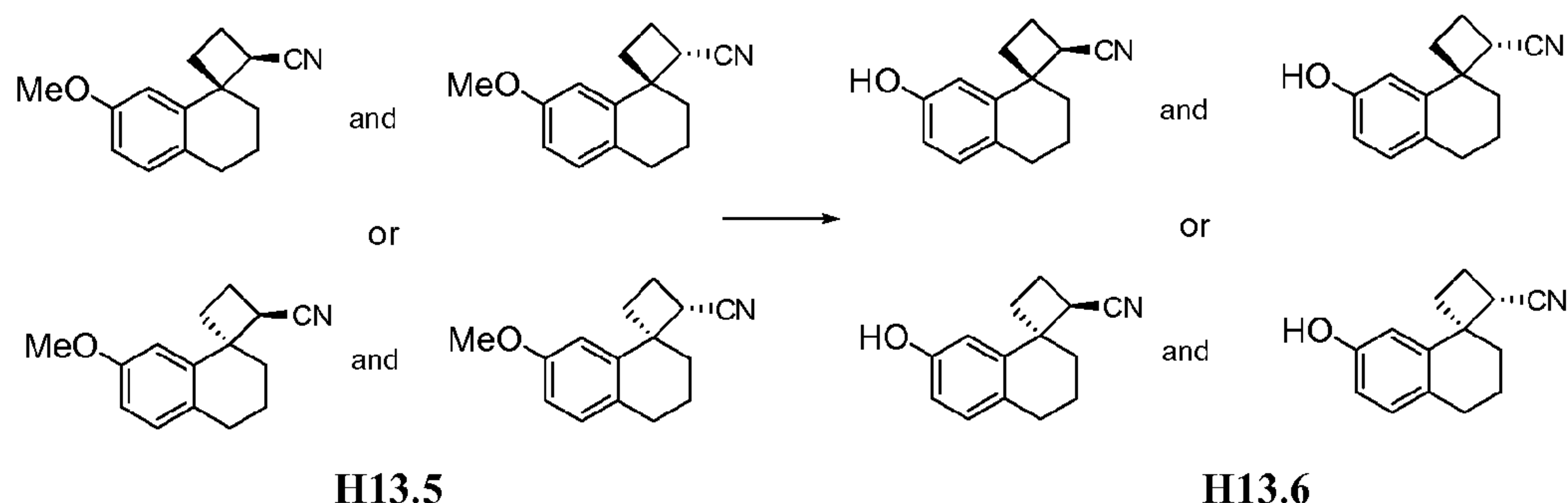
[0279] **1-Cyclopropylidene-7-methoxy-1,2,3,4-tetrahydronaphthalene (H13.1).** H13.2 was synthesized from 7-methoxy-3,4-dihydro-1(2H)-naphthalenone (H13.1, commercially available from Sigma-Aldrich, St. Louis, MO, USA) using the same procedure used to prepare H10.2 from H10.1.



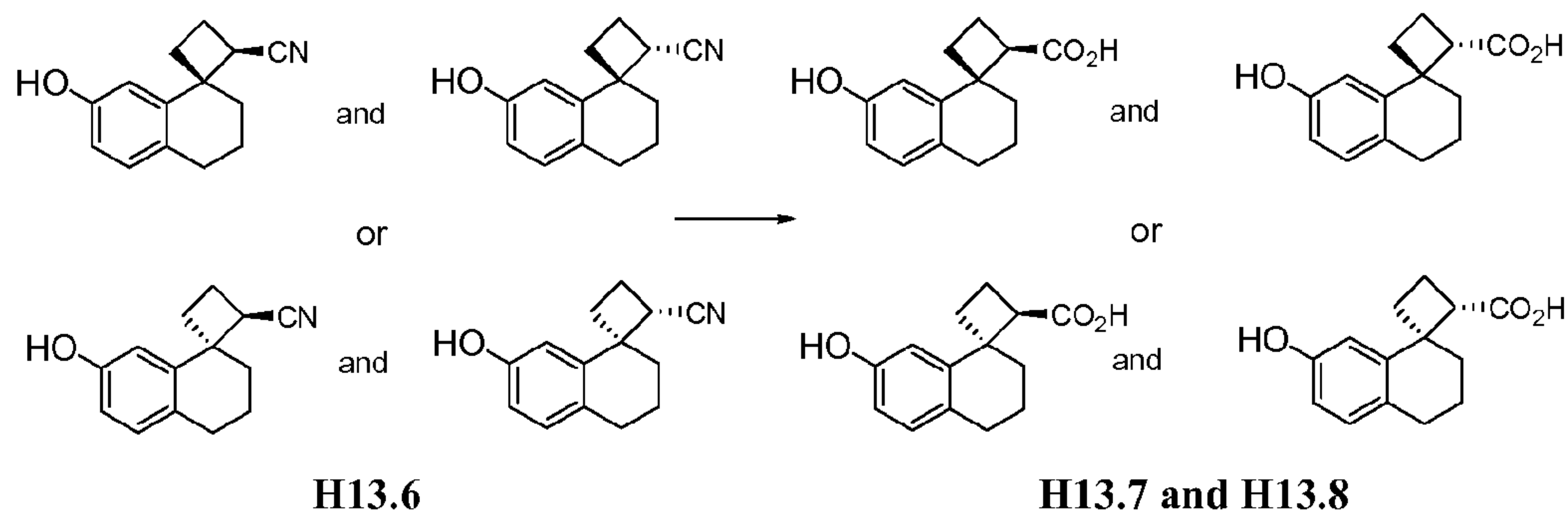
[0280] **(S)-7'-Methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalen]-2-one and (R)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalen]-2-one (H13.3 and H13.4).** H13.3 and H13.4 were synthesized from H13.2 using the same procedure used to prepare H10.3 and H10.4 from H10.2. The racemic product gave MS ESI (pos.) M/E: 217.1 (M+H). Chiral separation was conducted on a chiral OD column, eluting with 1% IPA/hexane. Pure enantiomer H13.3 (1.35 g, white solid) (first peak, retention time 8.06 minutes) and H13.4 (1.37 g, white solid) (second peak, retention time 101.6 minutes) were obtained. The absolute stereochemistry of the products associated with either was not determined.



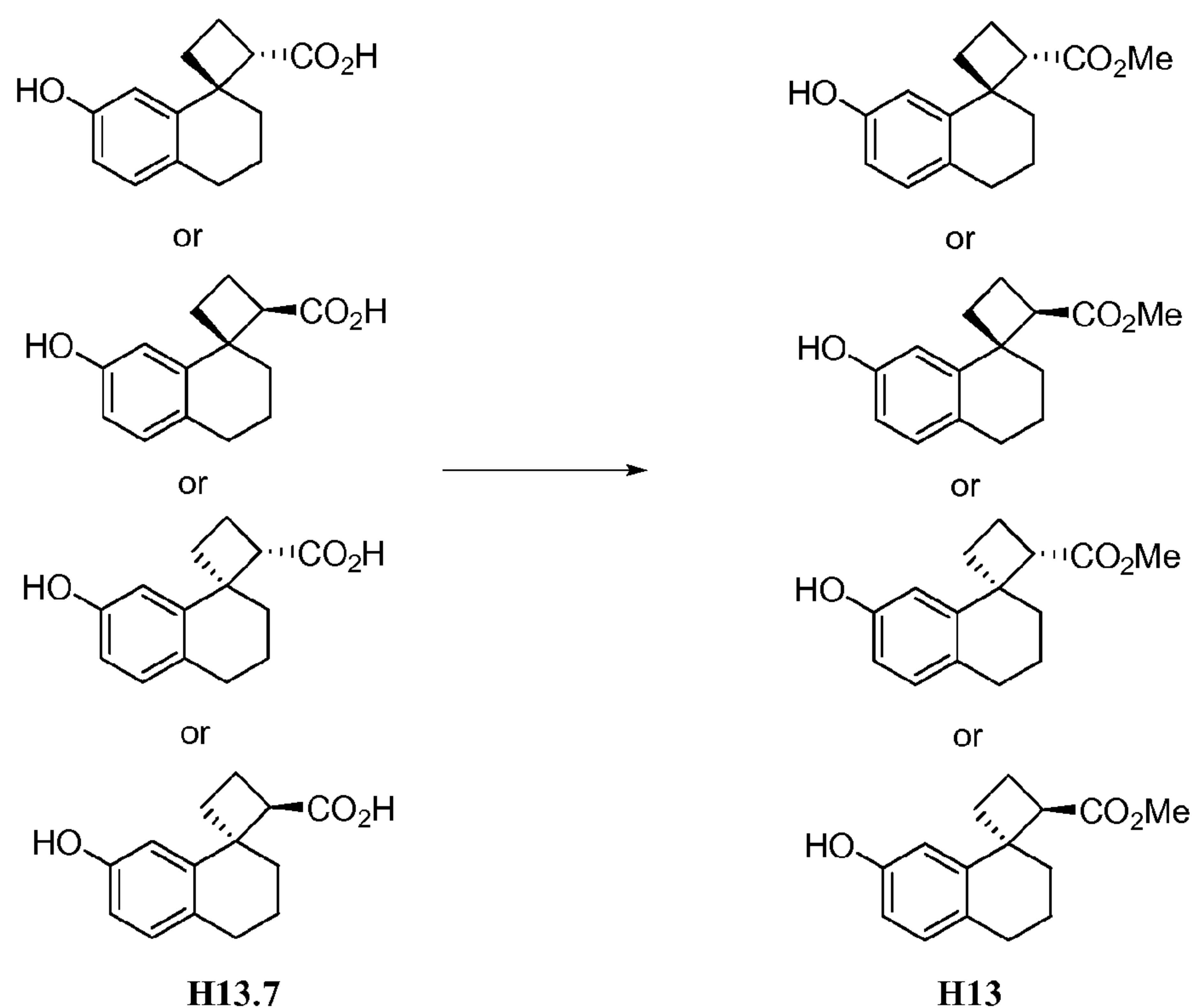
[0281] **(1R,2S)-7'-Methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1R,2R)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile or (1S,2S)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1S,2R)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile (H13.5).** H13.5 was synthesized from H13.4 using the same procedure used to prepare H10.5 from H10.4. MS ESI (pos.) M/E: 245.2 (M+H₂O).



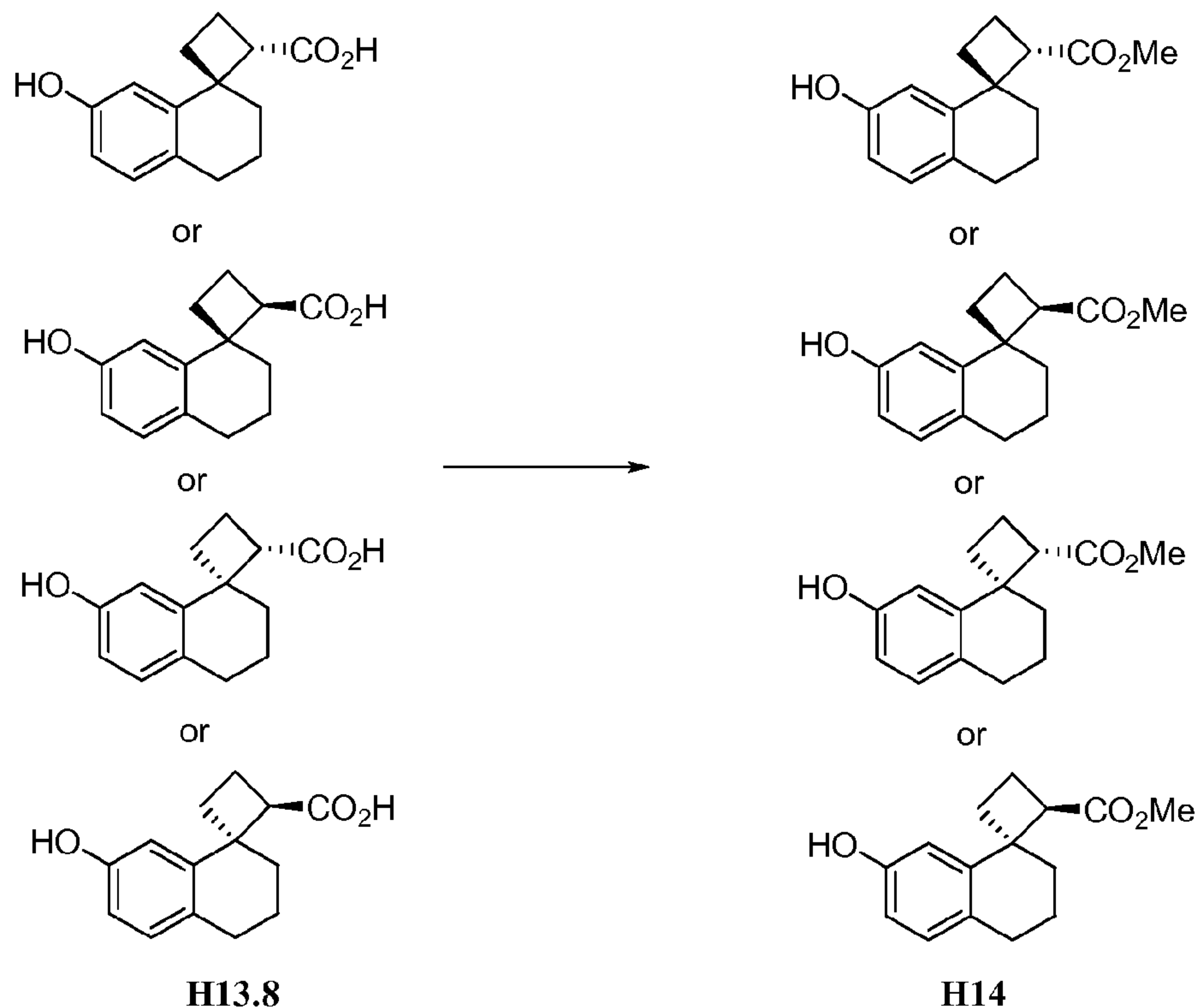
[0282] (1R,2S)-7'-Hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1R,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile or (1S,2S)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1S,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile (H13.6). H13.6 was synthesized from H13.5 using the same procedure used to prepare H10.6 from H10.5. MS ESI (pos.) M/E: 231.1 (M+H).



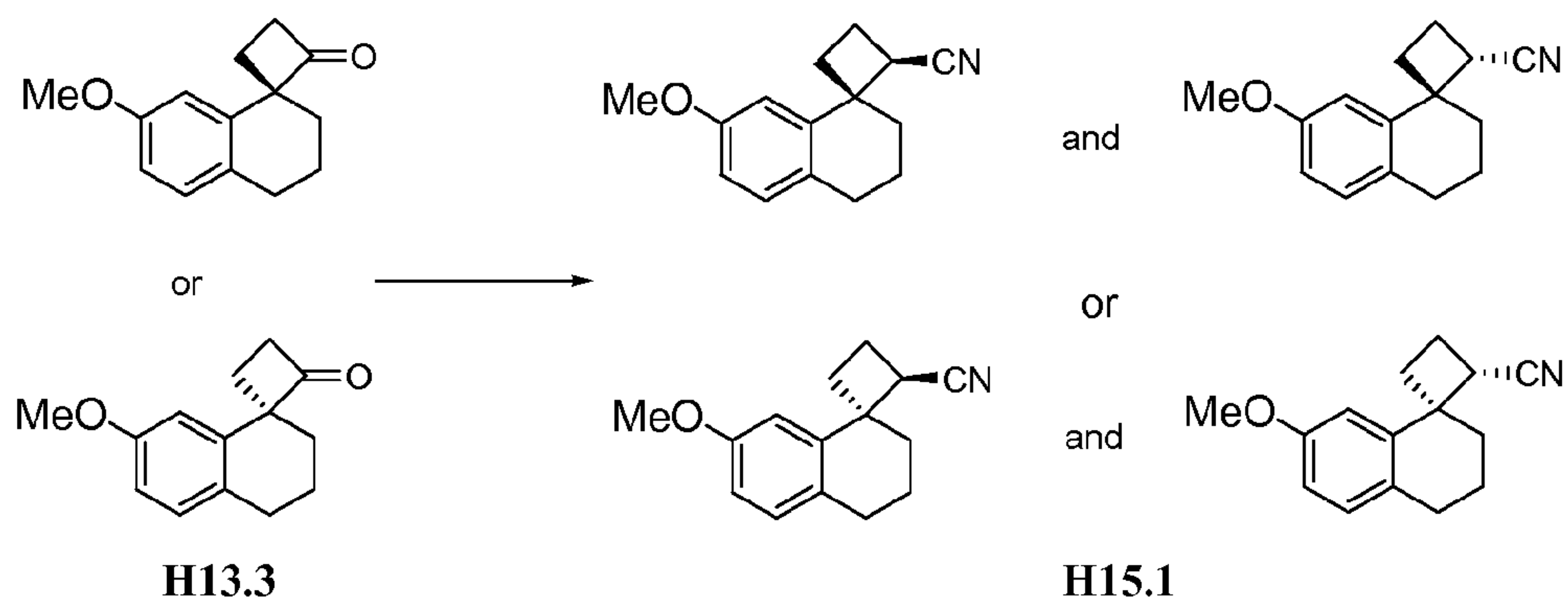
[0283] (1R,2S)-7'-Hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid and (1R,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid or (1S,2S)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid and (1S,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid and (1R,2S)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid (H13.7 and H13.8). H13.7 (first peak from reverse phase HPLC) and H13.8 (2ndnd peak from reverse phase HPLC) were synthesized from H13.6 using the same procedure used to prepare H10.7 and H10.8 from H10.6. MS ESI (neg.) M/E: 231.1 (M-H).



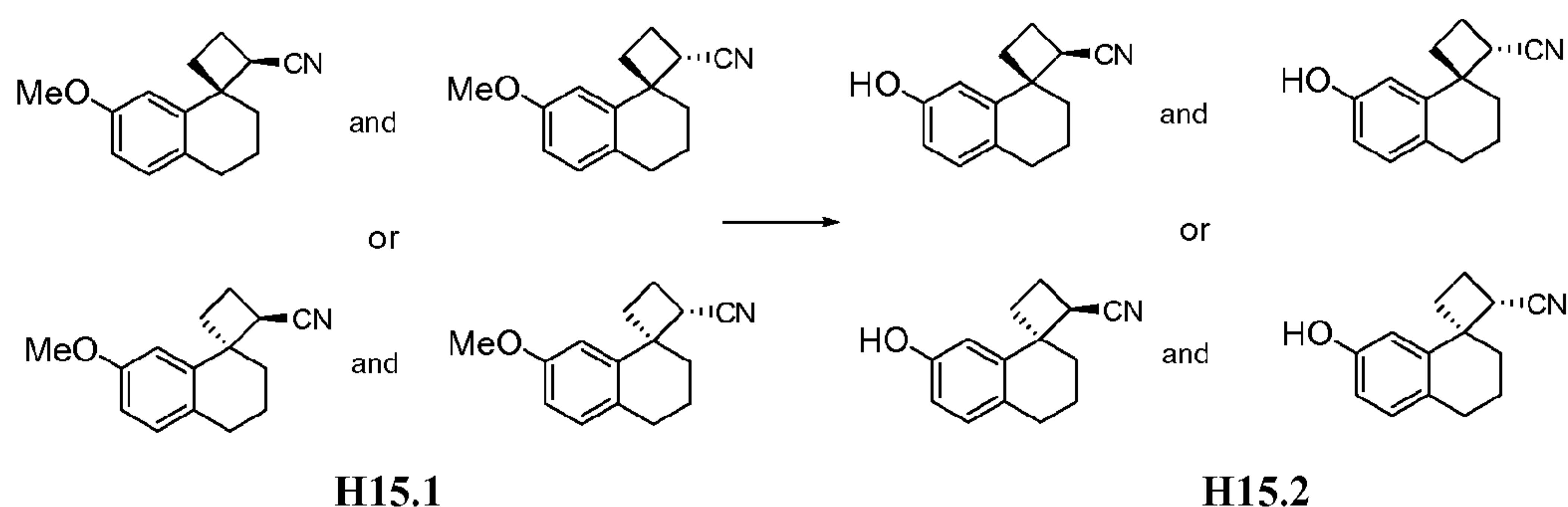
[0284] (1R,2S)-Methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1R,2R)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1S,2S)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1S,2R)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate (H13). H13 was synthesized from H13.7 using the same procedure used to prepare H10 from H10.7. MS ESI (pos.) M/E: 247.2 (M+H).

[0285] Intermediate H14

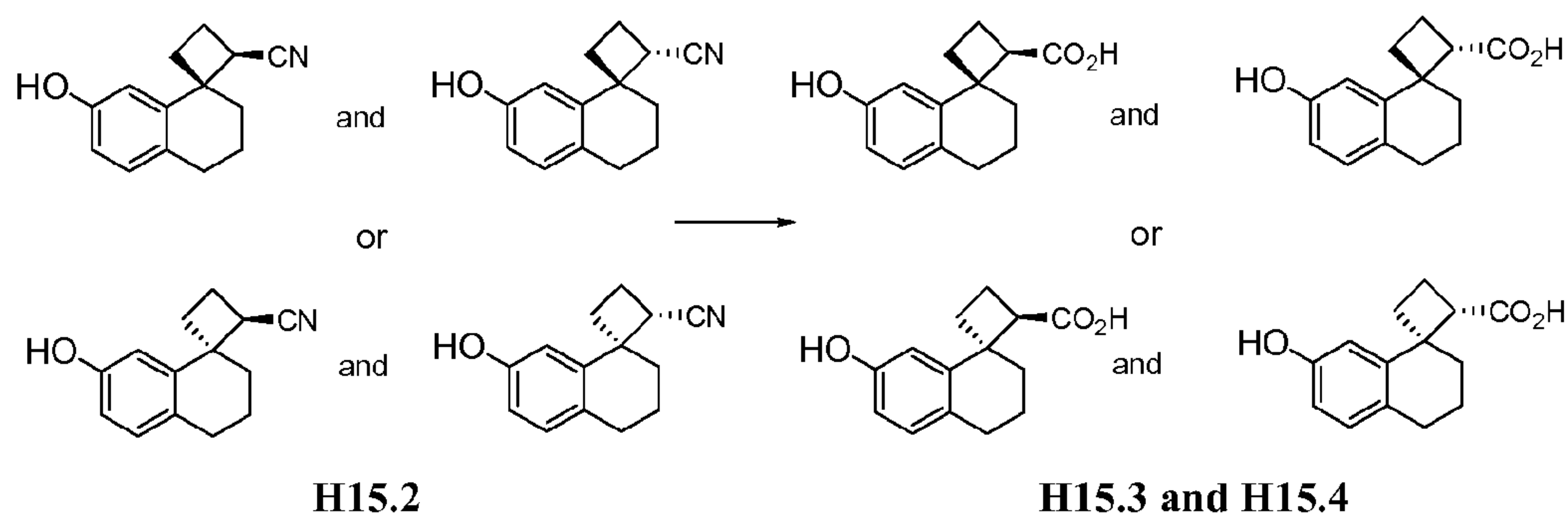
[0286] (1R,2S)-Methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1R,2R)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1S,2S)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1S,2R)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate (H14**). **H14** was synthesized from **H13.8** using the same procedure used to prepare **H10** from **H10.7**. MS ESI (pos.) M/E: 247.2 (M+H).**

[0287] Intermediate H15

[0288] (1R,2S)-7'-Methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1R,2R)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile or (1S,2S)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1S,2R)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile (H15.2). H15.2 was synthesized from H13.3 using the same procedure used to prepare H10.5 from H10.4. MS ESI (pos.) M/E: 245.2 (M+H₂O).

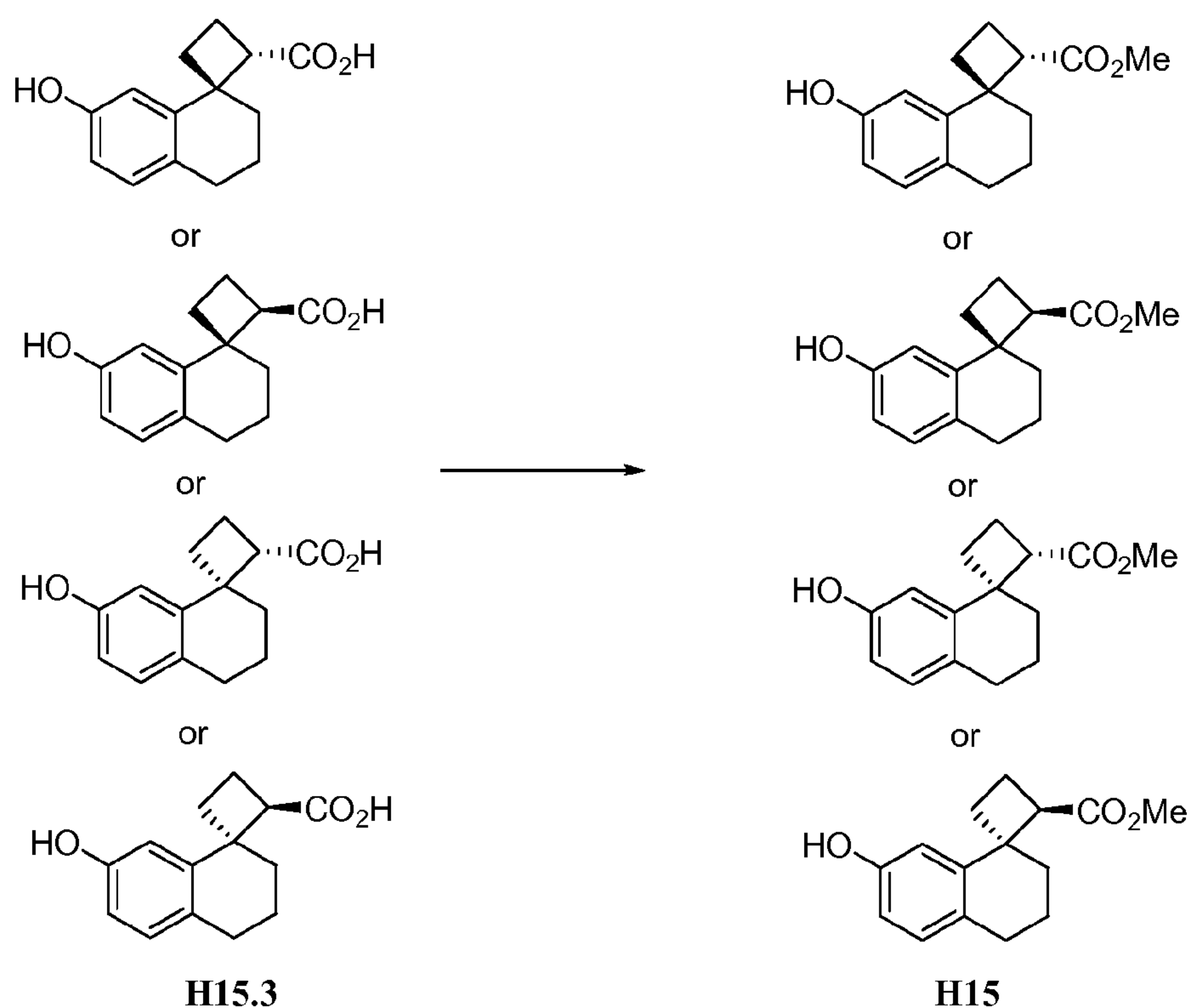


[0289] (1R,2S)-7'-Hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1R,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile or (1S,2S)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1S,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile (H15.2). H15.2 was synthesized from H15.1 using the same procedure used to prepare H10.6 from H10.5. MS ESI (pos.) M/E: 231.1 (M+H).



[0290] (1R,2S)-7'-Hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid and (1R,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid or (1S,2S)-7'-hydroxy-3',4'-

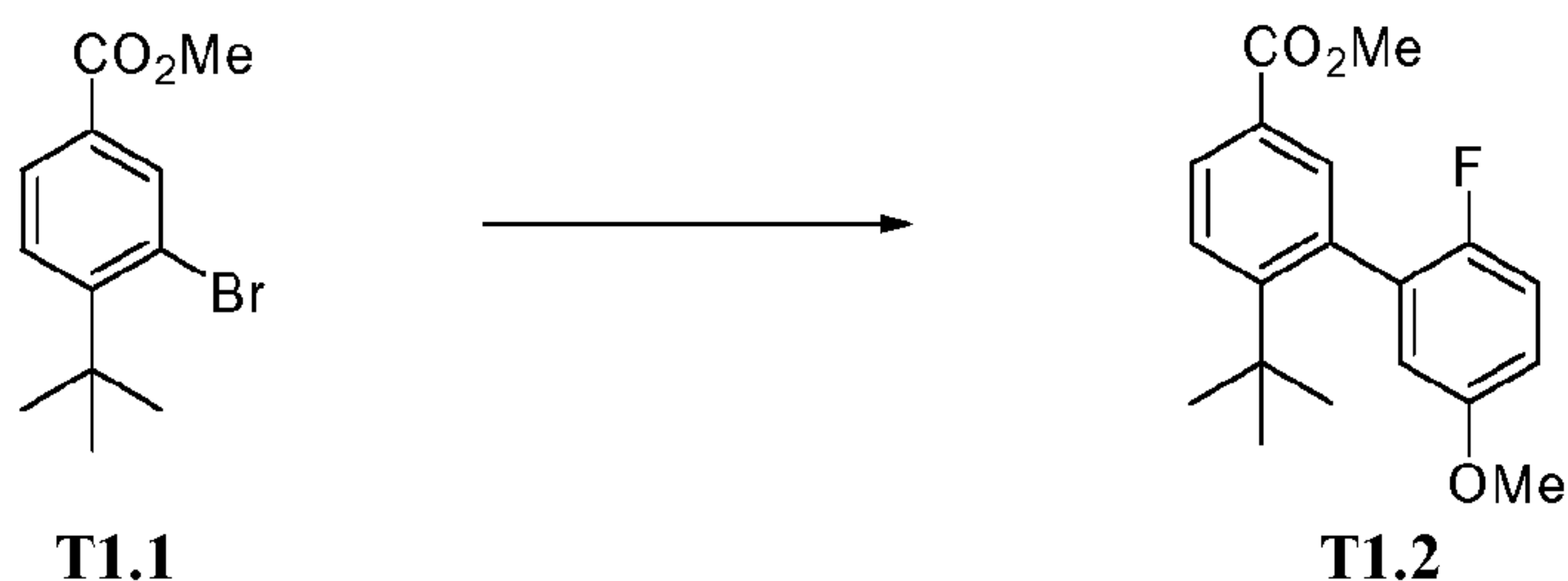
dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid and (1S,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid and (1R,2S)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid (**H15.3** and **H15.4**). **H15.3** (first peak from reverse phase HPLC) and **H15.4** (2nd⁺ peak from reverse phase HPLC) were synthesized from **H15.2** using the same procedure used to prepare **H10.7** and **H10.8** from **H10.6**. MS ESI (neg.) M/E: 231.1 (M-H).



[0291] (1R,2S)-Methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1R,2R)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1S,2S)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate or (1S,2R)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate (**H15**). **H15** was synthesized from **H15.3** using the same procedure used to prepare **H10** from **H10.7**. MS ESI (pos.) M/E: 247.2 (M+H).

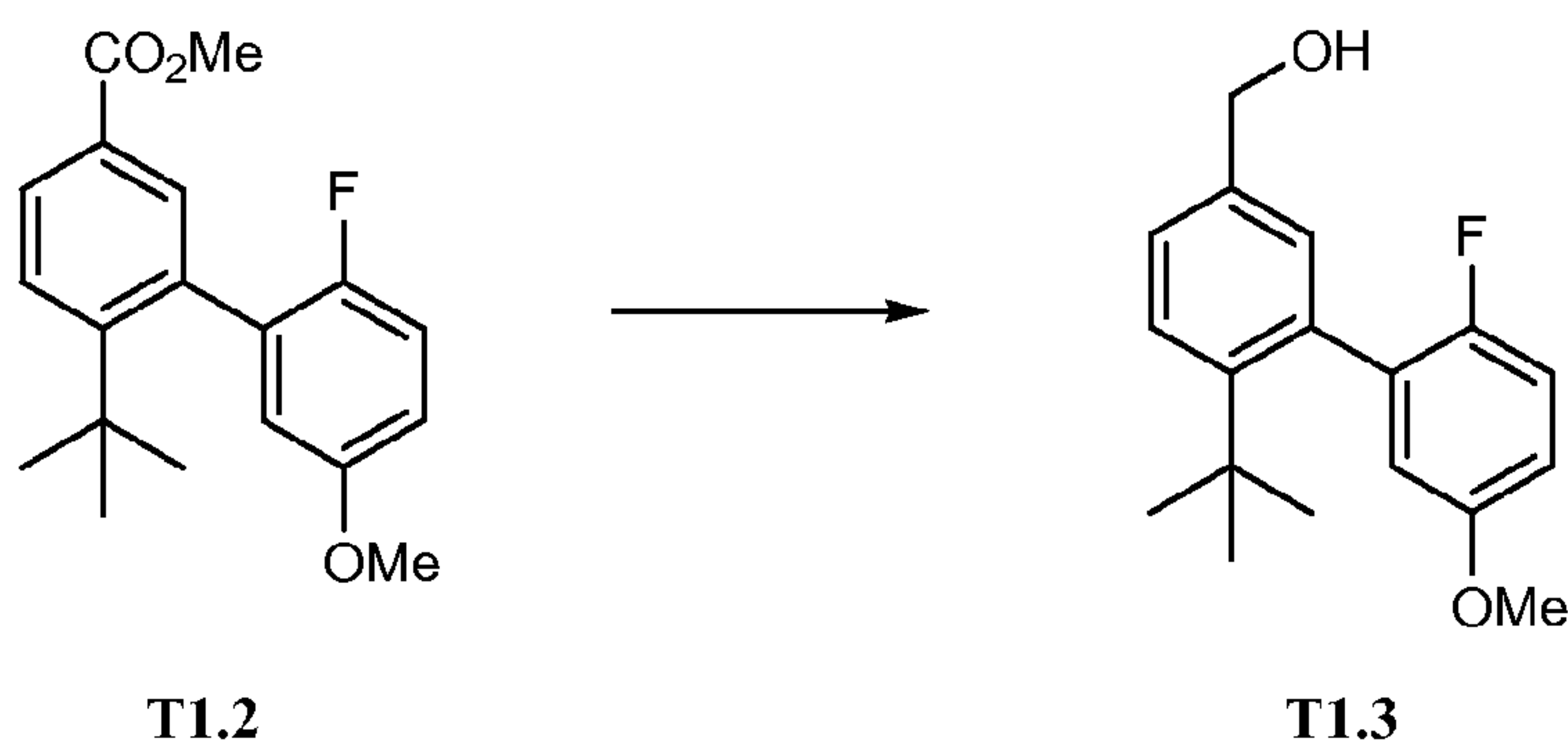
Synthesis of Biphenyl Intermediates

[0292]

Intermediate T1

[0293]

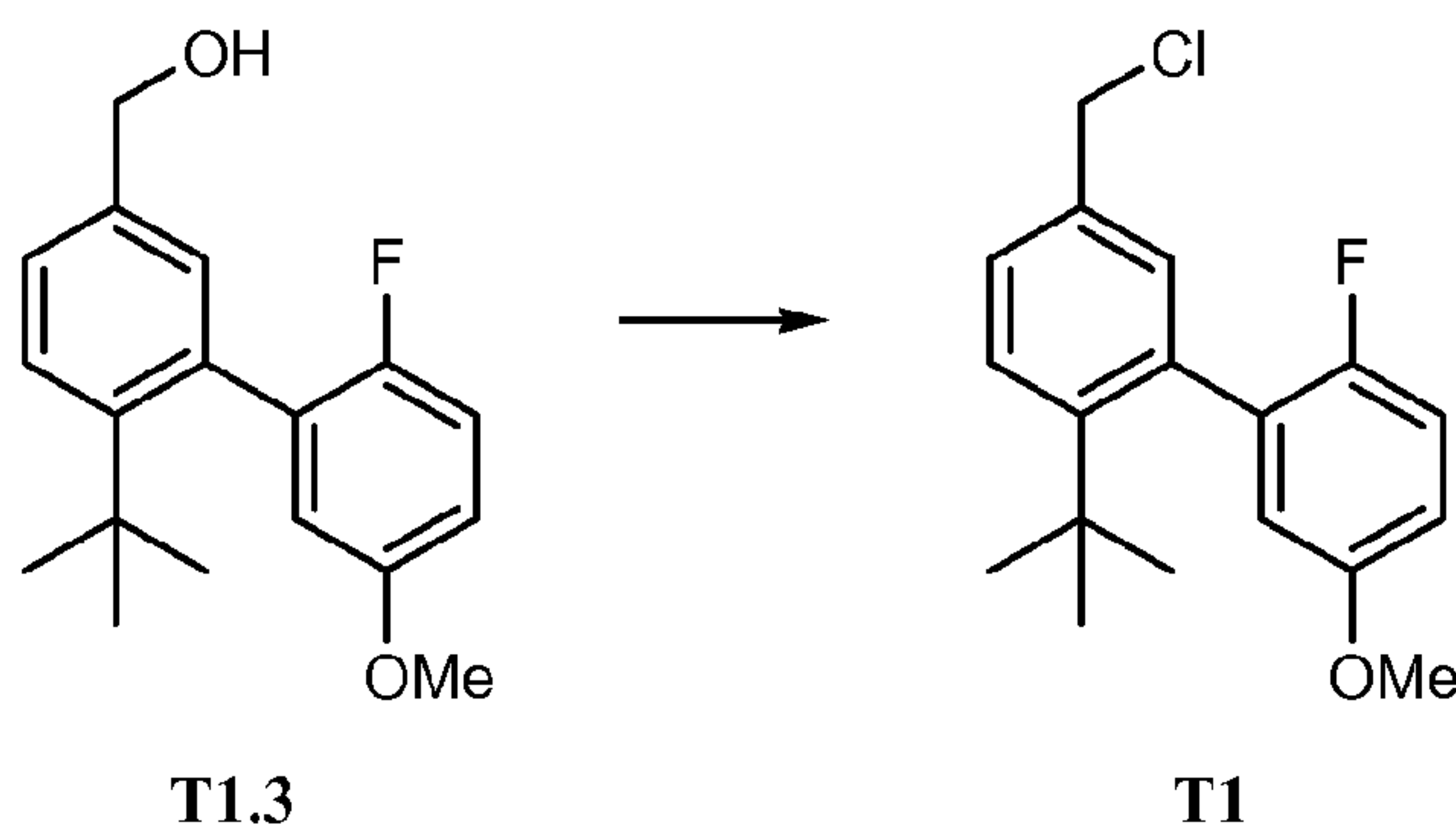
Methyl 6-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-3-carboxylate (T1.2). To a stirred solution of methyl 3-bromo-4-tert-butylbenzoate **T1.1** (*Australian Journal of Chemistry* **1990**, 43, 807-814) (1.00 g, 3.7 mmol) in toluene (4.00 mL, 4.0 mmol) and DMF (1.00 mL, 13.0 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (2.50 g, 15 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and potassium carbonate (1.50 g, 11 mmol), followed by tetrakis(triphenylphosphine)palladium (0.43 g, 0.37 mmol). The mixture was heated at 100°C for 21 hours and then cooled to room temperature. Water (30 mL) was added to the mixture, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-10% EtOAc in hexanes) to give a clear oil (2.3 g, 99% yield). MS ESI (pos.) m/e: 339.1 (M+Na)⁺, 334.1 (M+H₂O)⁺, 317.2 (M+H)⁺.



[0294]

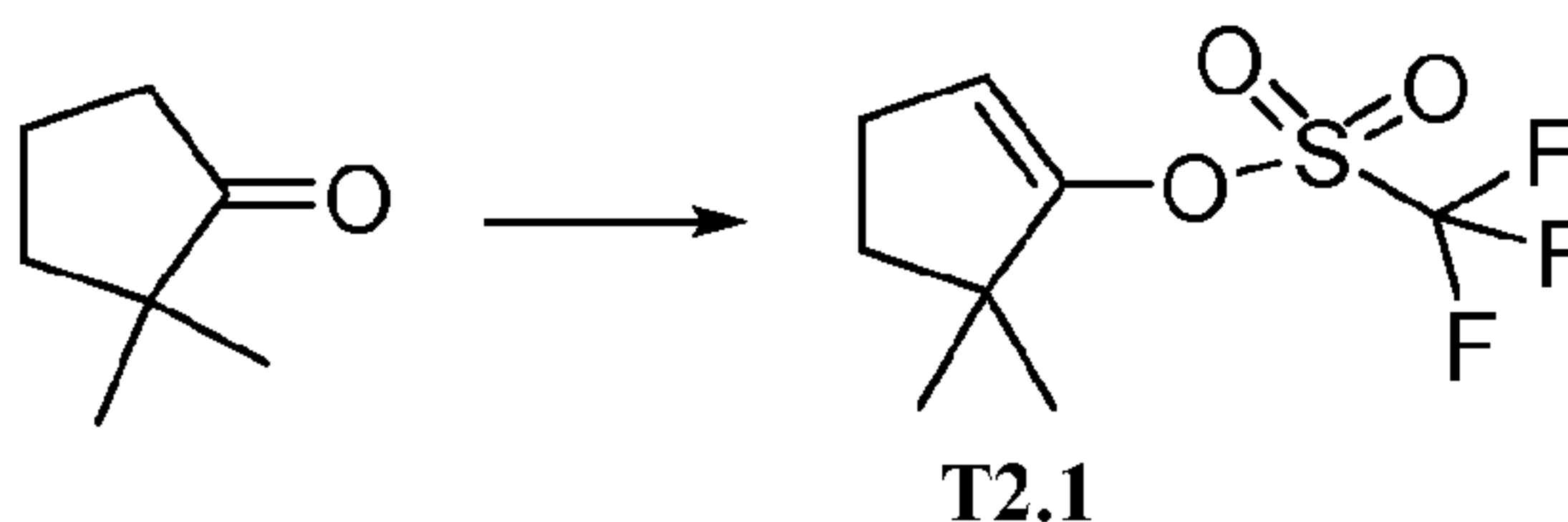
(6-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-3-yl)methanol (T1.3). To a stirred solution of **T1.2** (0.080 g, 0.3 mmol) in THF (10 mL, 3 mmol) at 0°C was added LAH (1.0M solution in THF (0.5 mL, 0.5 mmol)). The mixture was stirred for 15 minutes. 1N NaOH (5 mL) was then added to quench the reaction, and

the resulting solution was extracted with EtOAc (3×10 mL), dried over MgSO_4 , filtered and concentrated in vacuo. The residue was then purified by flash chromatography (SiO_2 gel 60, eluted with 0-30% EtOAc in hexanes) to give a clear oil (0.07 g, 96% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.57 (1 H, d, $J=8.2$ Hz), 7.44-7.31 (1 H, m), 7.04 (1 H, d, $J=4.0$ Hz), 7.00 (1 H, t, $J=8.0$ Hz), 6.86 (1 H, m), 6.78 (1 H, dd, $J=5.9, 3.1$ Hz), 4.68 (1 H, d, $J=5.9$ Hz), 3.79 (3 H, s), 1.63 (1 H, t, $J=5.9$ Hz), 1.23 (9 H, s).



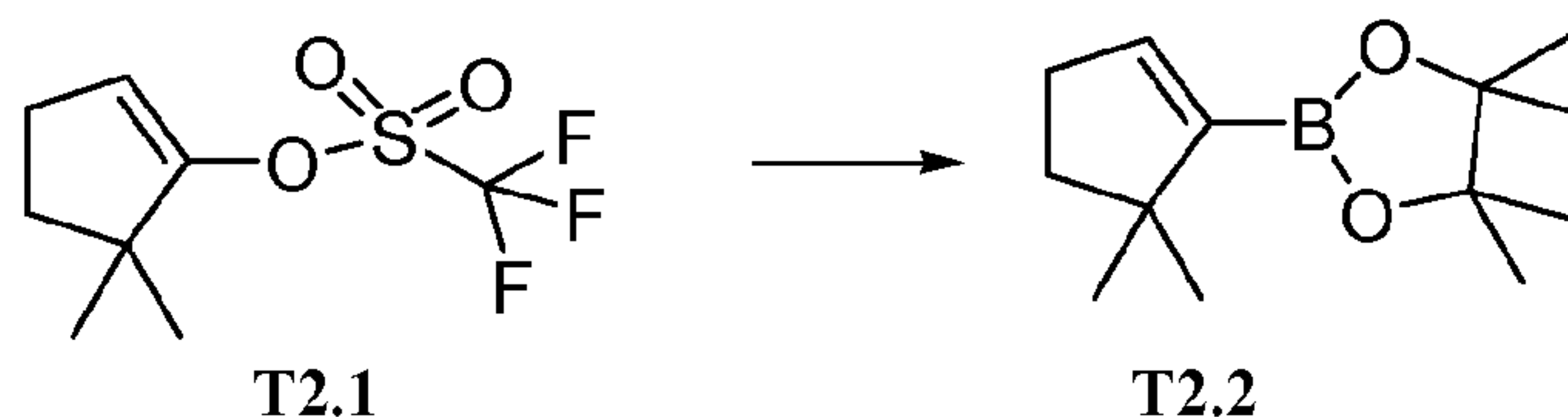
[0295] **5-(Chloromethyl)-2-(1,1-dimethylethyl)-2'-(methoxy)-[1,1'-biphenyl] (T1).** To a stirred solution of **T1.3** (0.07 g, 0.2 mmol) in DCM (10 mL, 155 mmol) at 23°C was added thionyl chloride (0.04 mL, 0.5 mmol). The resulting mixture was stirred for 16 hours and then concentrated in vacuo. The residue was purified by flash chromatography (SiO_2 gel 60, eluted with 0%-10% EtOAc in hexanes) to give a colorless oil (0.050 g, 67% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.56 (1 H, d, $J=8.2$ Hz), 7.37 (1 H, dd, $J=8.4, 2.2$ Hz), 7.05 (1 H, d, $J=1.6$ Hz), 7.01 (1 H, t, $J=9.2$ Hz), 6.87 (1 H, m), 6.79 (1 H, dd, $J=5.9, 3.1$ Hz), 4.57 (2 H, s), 3.80 (3 H, s), 1.23 (9 H, s).

[0296] **Intermediate T2**

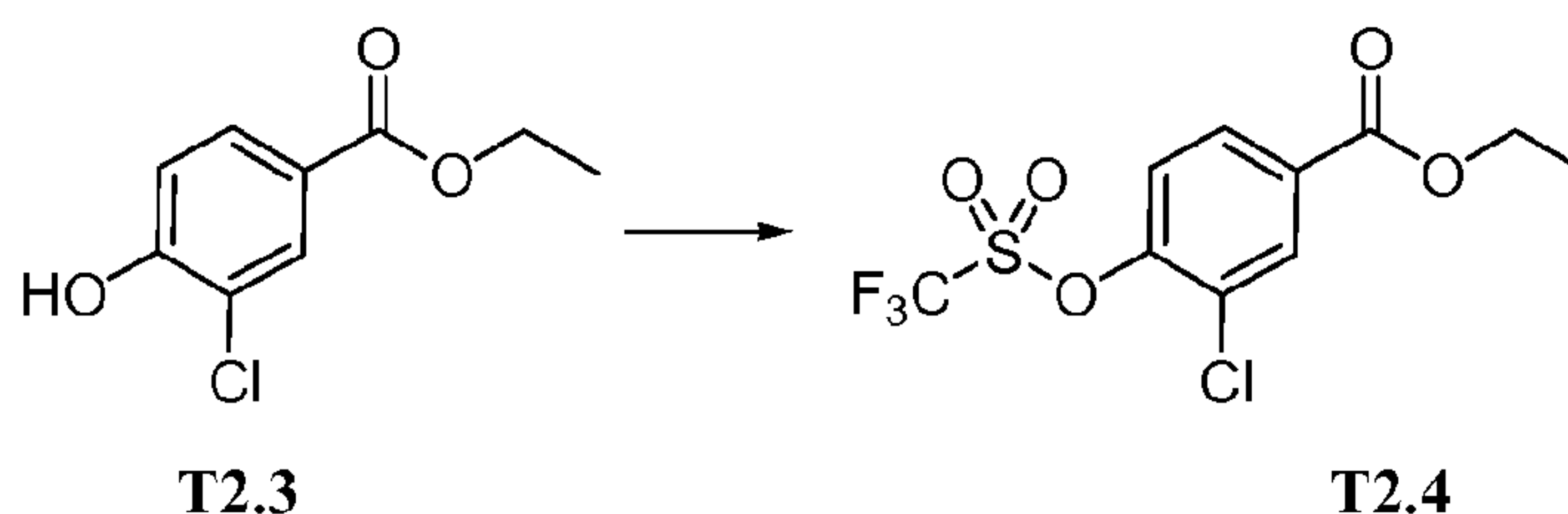


[0297] **5,5-Dimethylcyclopent-1-enyl trifluoromethanesulfonate (T2.1).** To a solution of 2,2-dimethylcyclopentanone (available from ChemSampCo) (3.00 g, 26.75 mmol) in THF (100 mL), was slowly added LDA (14.7 mL, 2.0 M, in heptane) at -78°C . The resulting mixture was stirred at -78°C for 1 hour. A solution of N-phenyltriflimide (10.00 g, 28.00 mmol) was added to the mixture at -78°C , and the resulting mixture was stirred at 0°C for 2 hours and then at room temperature overnight. The reaction mixture was extracted with hexane (80×2 mL). The combined organic layers were washed with

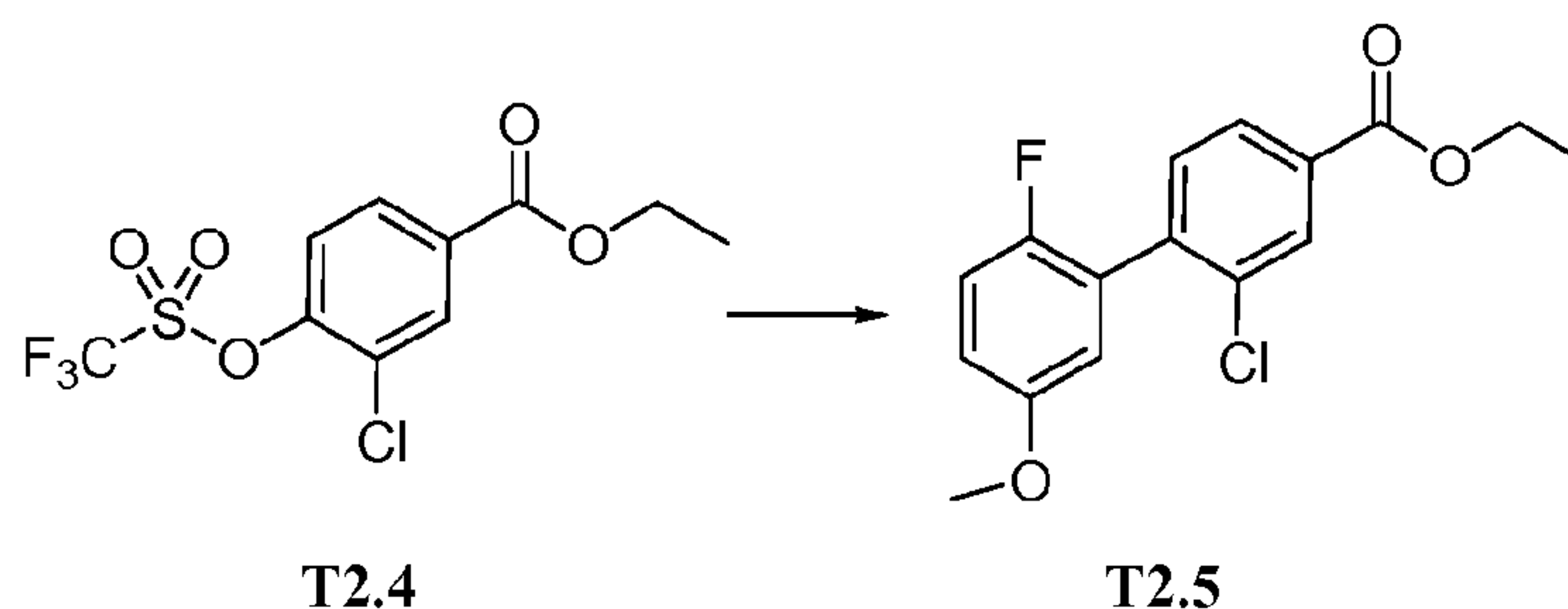
saturated Na_2CO_3 (30 mL), brine (20 mL), dried with MgSO_4 , and filtered. The solvent was removed, and the residue was purified by CombiFlash® chromatography (eluent was EtOAc and hexane) to give **T2.1**. ^1H NMR (CDCl_3) δ 1.16 (s, 6 H), 1.86 (t, $J = 7.1$ Hz, 2 H), 2.36 (t, $J = 7.1$ Hz, 2 H), 5.56 (m, 1 H).



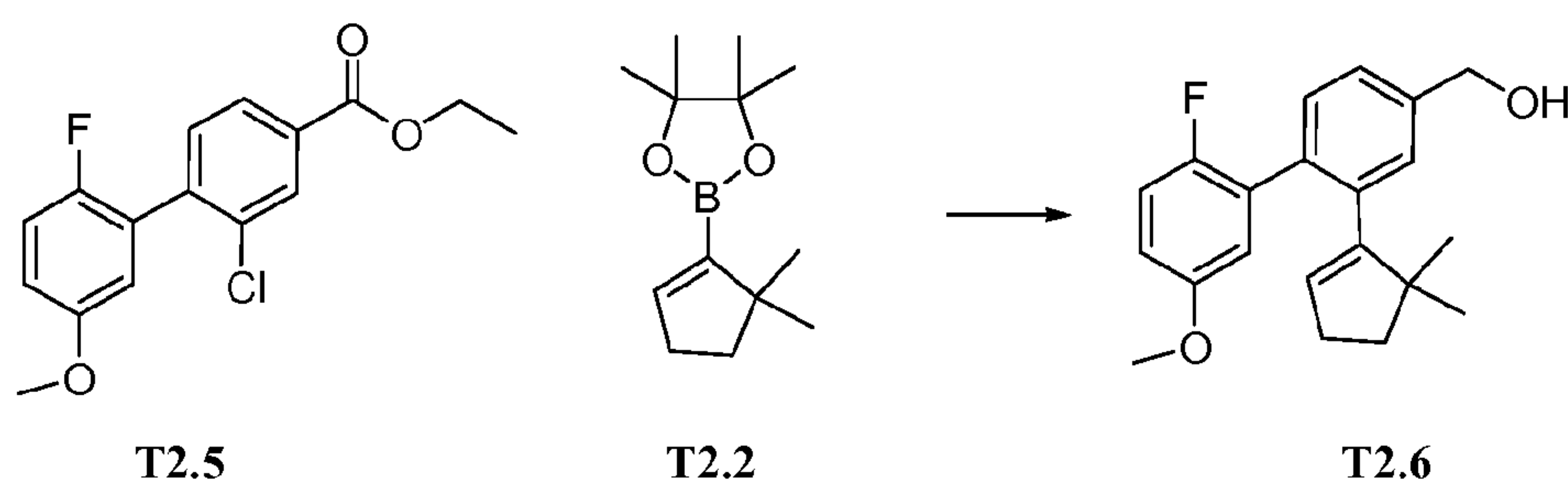
[0298] **2-(5,5-Dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (T2.2).** $\text{PdCl}_2(\text{PPh}_3)_2$ (0.56 g, 0.80 mmol), PPh_3 (0.63 g, 2.40 mmol), bis(pinacolato)diboron (6.80 g, 26.75 mmol) and KOPh (fine powder, 5.30 g, 40.10 mmol) were added to a flask. The flask was flushed with nitrogen and charged with toluene (100 mL) and with **T2.1** (6.53 g, 26.75 mmol). The mixture was stirred at 50°C for 2 hours. The reaction mixture was treated with water at room temperature and extracted with benzene (60×2 mL). The organic layer was dried over MgSO_4 . The product was then purified by CombiFlash® column chromatography to give intermediate **T2.2**. ^1H NMR (CDCl_3) δ 1.04 (s, 6 H), 1.18 (s, 12 H), 1.57 (t, $J = 7.1$ Hz, 2 H), 2.29 (t, $J = 7.1$ Hz, 2 H), 6.29 (m, 1 H).



[0299] **Ethyl 3-chloro-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (T2.4)** A mixture of ethyl 3-chloro-4-hydroxybenzoate (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (5.00 g, 25.0 mmol), *N*-phenyltriflimide (9.30 g, 26.0 mmol) and TEA (4.2 mL, 30.0 mmol) in DCM (40 mL) with a catalytic amount of DMAP, was stirred at ambient temperature overnight. DCM (150 mL) was added, and the reaction mixture was washed with brine (30×3 mL), dried over MgSO_4 , and the solvent was removed under reduced pressure. The product **T2.4** was used in the next step without further purification. MS ESI (pos.) m/e : 335.0 ($\text{M} + \text{Na}$) $^+$.

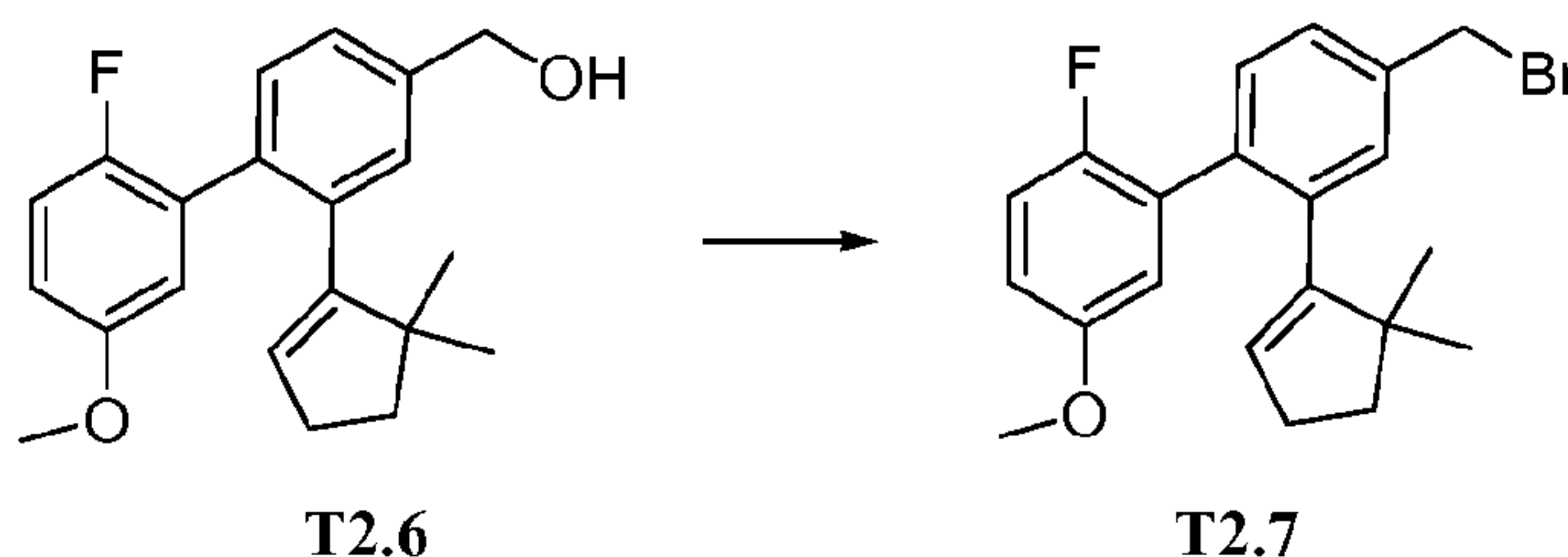


[0300] Ethyl 2-chloro-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T2.5) A mixture of ethyl 3-chloro-4-(trifluoromethylsulfonyloxy)benzoate **T2.4** (3.00 g, 9.02 mmol), 2-fluoro-5-methoxyphenylboronic acid (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (1.84 g, 10.8 mmol), tetrakis(triphenylphosphine)palladium (0.521 g, 0.451 mmol) and potassium carbonate (2.49 g, 18.0 mmol) in DMF (20 mL), was purged with N₂ three times and then heated at 100°C for 4 hours. The reaction was cooled to room temperature, and EtOAc (130 mL) was added. The mixture was then washed with brine (30 × 4 mL). The organic layer was dried over MgSO₄. The residue was purified by CombiFlash® silica gel column chromatography (eluent with hexane/EtOAc; 85/15) to give **T2.5**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.08 (d, 1H), 7.90 (d, 1H), 7.33 (dd, 1H), 6.96 - 7.02 (m, 1H), 6.82 - 6.85 (m, 1H), 6.74 (d, 1H), 4.33 (q, 2H), 4.31 (s, 3H), 1.34 (t, 3H). MS ESI (pos.) m/e: 309.1 (M+H)⁺.

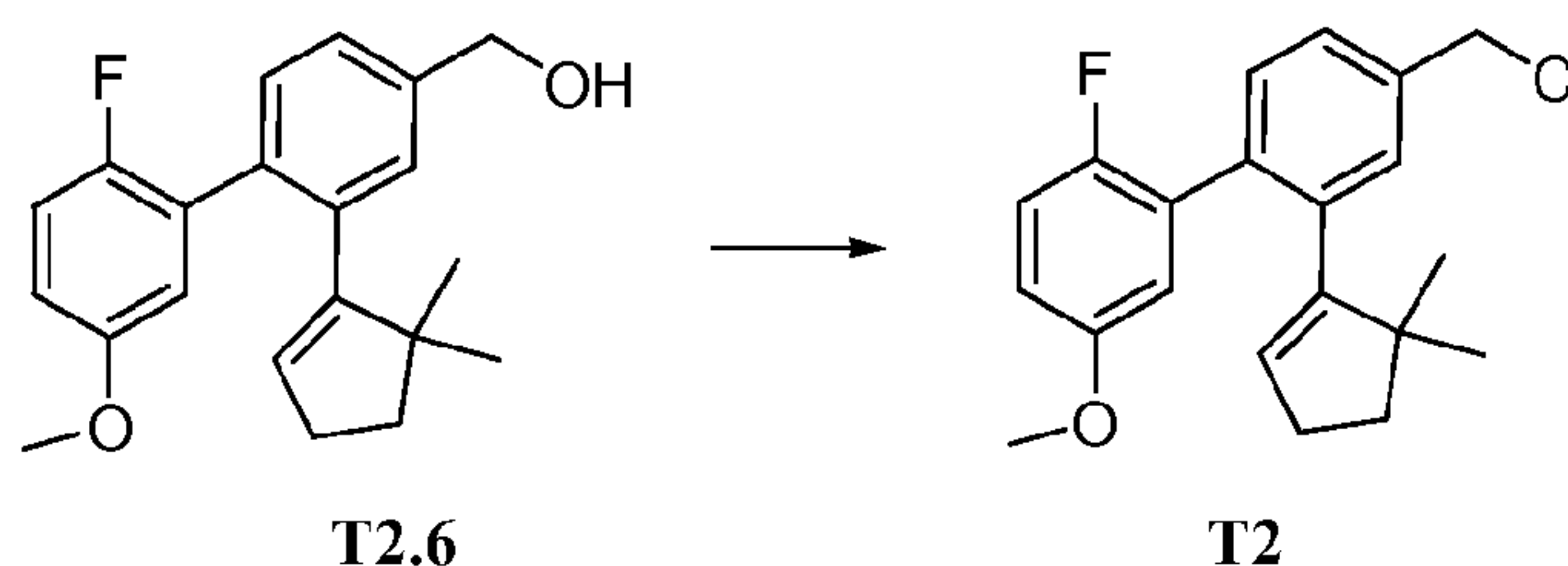


[0301] (2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T2.6) A mixture of compound **T2.5** (1.80 g, 5.80 mmol), 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**T2.2**) (1.40 g, 6.4 mmol), S-Phos (0.48 g, 1.20 mmol), tripotassium phosphate (3.10 g, 15.0 mmol) and palladium acetate (0.13 g, 0.58 mmol) in DMF (10.0 mL) and water (1.0 mL), was purged with N₂ three times. The resulting mixture was heated at 100 °C overnight. EtOAc (120 mL) was added, and the mixture was washed with brine (25 × 2 mL). The organic layer was dried with MgSO₄. The residue was purified by CombiFlash® silica gel column

chromatography, eluting with hexane/EtOAc, 9/1 to give the Suzuki coupling product as an intermediate, ethyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate. MS ESI (pos.) m/e: 369.1 (M+H)⁺. To a solution of ethyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (1.00 g, 3.0 mmol) in THF (10.0 mL), was slowly added LAH, (1.0M solution in diethyl ether, 4.0 mL, 4.0 mmol) at 0°C. After the addition, the reaction mixture was stirred at 40°C for 1.5 hours, and then at room temperature for 2 hours. A mixture of water (0.22 mL) in THF (2.0 mL) was slowly added and then 15% sodium hydroxide (0.22 mL) was added at 0°C. Finally, water (0.65 mL) was added at room temperature. The solid was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by CombiFlash® silica gel column chromatography, eluting with hexane/EtOAc, 90/10 to 70/30) to give the title compound **T2.6**. ¹H NMR (400 MHz, CDCl₃) δ ppm. 7.24 (s, 2H), 7.09 - 7.21 (m, 1H), 6.84 - 6.96 (m, 1H), 6.68-6.72 (m, 2H), 5.43 (s, 1H), 4.65 (s, 2H), 3.66 (s, 3H), 2.17 (td, 2H), 1.77 (b, 1H), 1.58 (t, 2H), 0.78 (s, 6H). MS ESI (pos.) m/e: 309.1 (M-HO)⁺, 345.2 (M+H₃O)⁺.

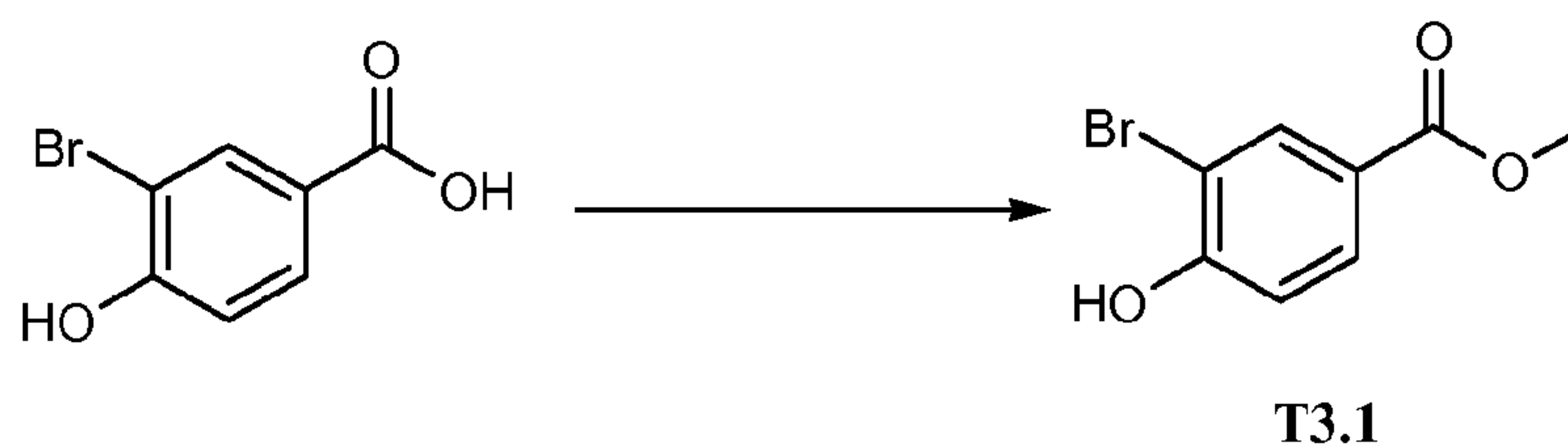


[0302] 4-(Bromomethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T2.7) To a solution of triphenylphosphine (0.13 g, 0.51 mmol) in DCM (1.0 mL), was slowly added bromine (0.081 g, 0.51 mmol, 0.25 mL, 2M in CCl₄) at 0°C. The resulting mixture was stirred at 0°C for 15 minutes and then a mixture of compound **T2.6** (0.15g, 0.46 mmol) and anhydrous pyridine (0.041 mL, 0.51 mmol) in DCM (3.0 mL) was added to the mixture. The reaction mixture was stirred at room temperature for 2 hours. DCM (80 mL) was added, and the mixture was washed with water (20 × 2 mL), and dried over Na₂SO₄. The solvent was removed under reduced pressure to provide product **T2.7**. ¹H NMR (400 MHz, CDCl₃) δ ppm. 7.16 - 7.29 (m, 3H), 6.88 (t, 1H), 6.72 (m, 2 H), 5.45 (s, 1H), 4.46 (s, 2 H), 3.68 (s, 3H), 2.16-2.19 (m, 2H), 1.59 (t, 2H), 0.78 (s, 6H).

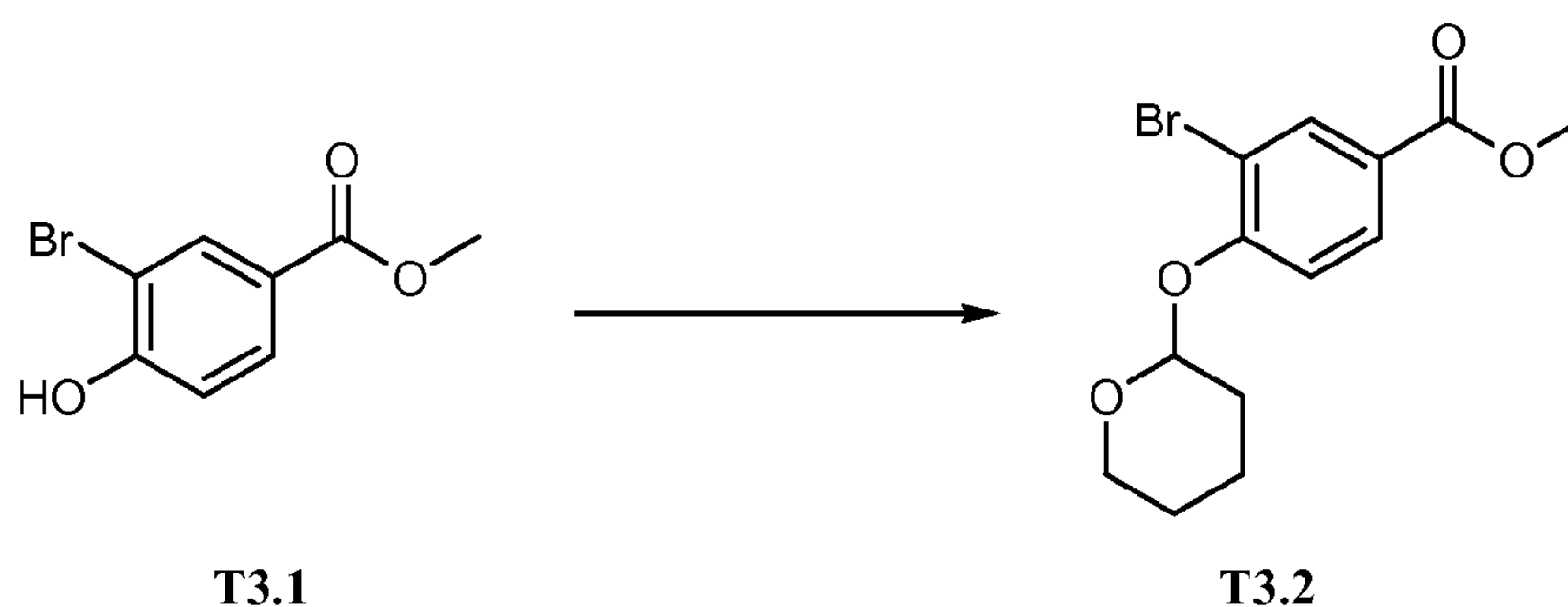


4-(Chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T2) To a solution of compound **T2.6** (1.10 g, 3.37 mmol) and a catalytic amount of DMF (0.10 mL) in DCM (12.0 mL), was slowly added thionyl chloride (0.802 g, 6.74 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, and the resulting residue was purified by CombiFlash® silica gel column chromatography eluting with hexane/EtOAc, 100/0 to 95/5) to give the title compound **T2** (1.15g). ¹H NMR (400 MHz, CDCl₃) δ ppm. 7.32 - 7.39 (m, 2H), 7.28-7.29 (m, 1H), 6.88 (t, 1H), 6.80-6.82 (m, 2 H), 5.56 (s, 1H), 4.66 (s, 2 H), 3.78 (s, 3H), 2.27-2.29 (m, 2H), 1.69 (t, 2H), 0.89 (s, 6H).

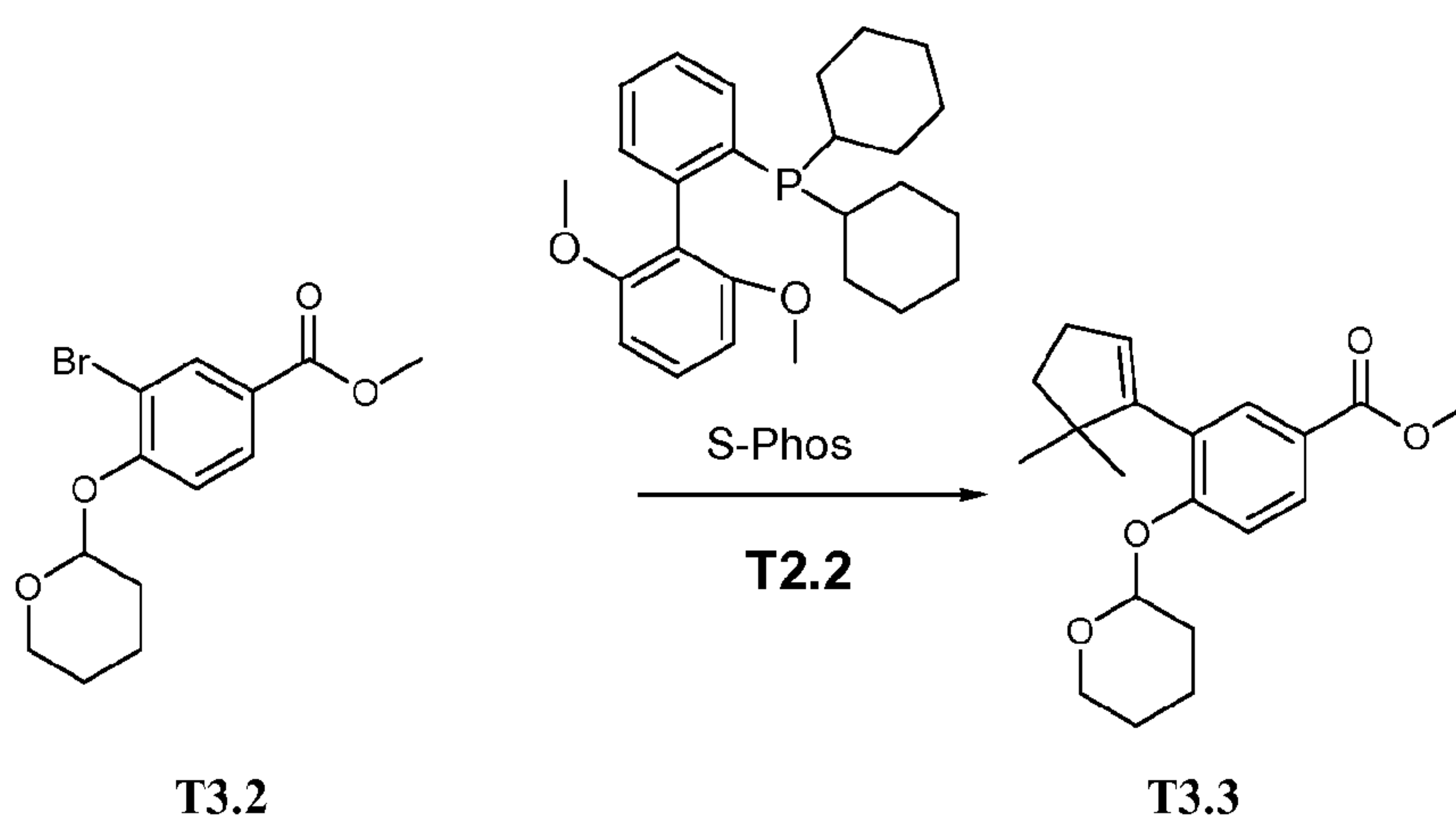
[0303] Intermediate T3



[0304] Methyl 3-bromo-4-hydroxybenzoate (T3.1). To a stirred solution of 3-bromo-4-hydroxybenzoic acid (available from Alfa Aesar, Avocado, Lancaster) (50.0 g, 231 mmol) in MeOH (300 mL) was added a cold solution of sulfuric acid (2.50 mL, 47 mmol). The mixture was heated to 80°C and monitored by TLC. After 16.5 hours, the solvent was removed and the reaction mixture was diluted with EtOAc. The organic phase was washed carefully two times with saturated aqueous NaHCO₃, once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed *in vacuo* to yield **T3.1** as a white solid (yield 100%) that was used without purification.

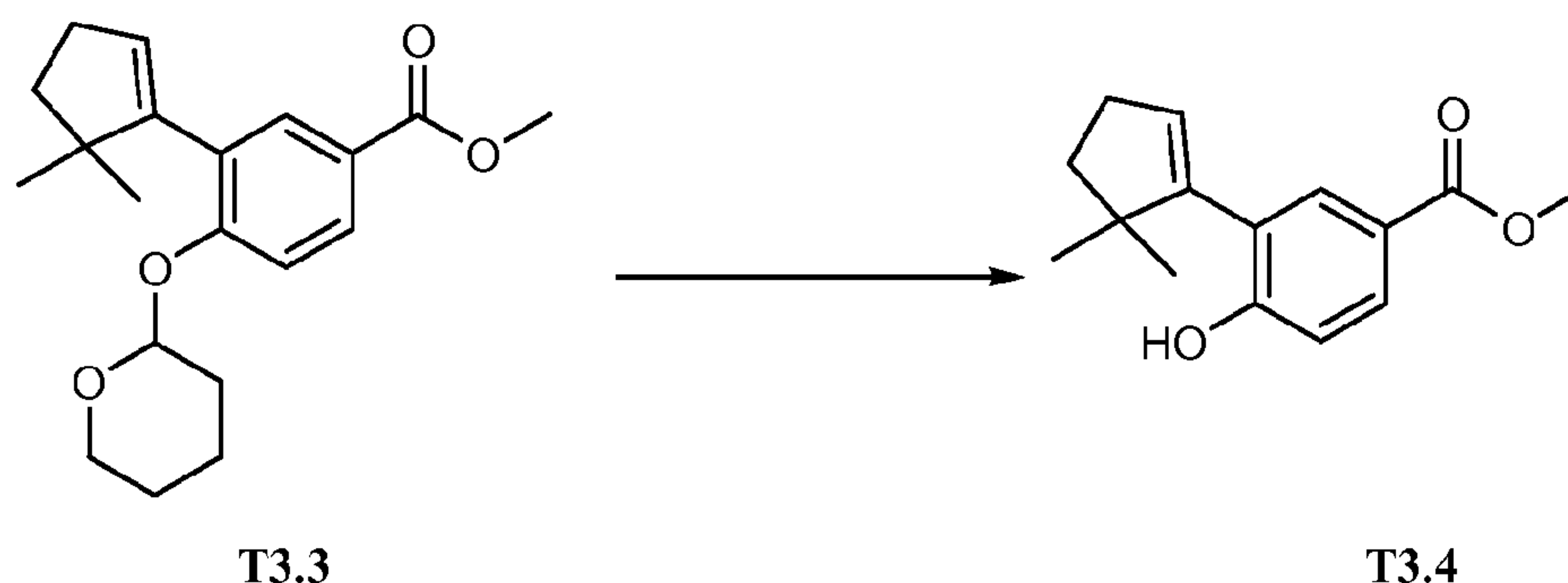


[0305] Methyl 3-bromo-4-(tetrahydro-2H-pyran-2-yloxy)benzoate(T3.2). To a stirred solution of **T3.1** (38 g, 164 mmol) and 3,4-dihydro-2H-pyran (45 mL, 493 mmol) in DCM (355 mL,) was added 4-methylbenzenesulfonic acid hydrate (0.63 g, 3.30 mmol). The mixture was stirred at room temperature and monitored by TLC. After 2 hours, the solution was washed with a mixed aqueous solution of saturated aqueous sodium bicarbonate/brine/water (1:1:2). The aqueous layer was extracted three times with ether. After drying over anhydrous sodium sulfate and then filtering, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-10% EtOAc in hexanes) to yield a white solid. The product was recrystallized from MeOH to provide **T3.2** (yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 8.24 (1 H, d, J=2.0 Hz), 7.93 (1 H, dd, J=8.6, 2.0 Hz), 7.17 (1 H, d, J=8.6 Hz), 5.62 (1 H, t, J=2.5 Hz), 3.90 (3 H, s), 3.83 (1 H, td, J=11.1, 2.9 Hz), 3.66 (1 H, m), 2.18 (1 H, m), 2.04 (1 H, m), 1.94 (1 H, m), 1.79 (2 H, m), 1.67 (1 H, m).)



[0306] Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (T3.3). A stirred mixture of **T3.2** (10.1 g, 31.9 mmol), ground S-Phos (2.62 g, 6.39 mmol), palladium acetate (0.72 g, 3.2 mmol), and potassium phosphate,

tribasic (17.0 g, 80.2 mmol) in DMF (70 mL) and water (3.5 mL) was purged three times with argon and placed under vacuum three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**T2.2**) (8.50 g, 38.3 mmol) was added via syringe. The resulting mixture was then heated to 75°C. After 21 hours, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtering, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **T3.3** as a colorless oil that solidified (yield 80%). ¹H NMR (400 MHz) (CDCl₃) δ 7.91 (1 H, dd, J=8.6, 2.3 Hz), 7.74 (1 H, d, J=2.3 Hz), 7.15 (1 H, d, J=8.6 Hz), 5.55 (1 H, t, J=2.3 Hz), 5.49 (1 H, t, J=2.9 Hz), 3.88 (3 H, s), 3.82 (1 H, td, J=11.1, 2.9 Hz), 3.64 (1 H, m), 2.43 (2 H, td, J=7.0, 2.3 Hz), 1.92 (5 H, m), 1.69 (1 H, m), 1.61 (2 H, m), 1.09 (6 H, d, J=13.7 Hz).

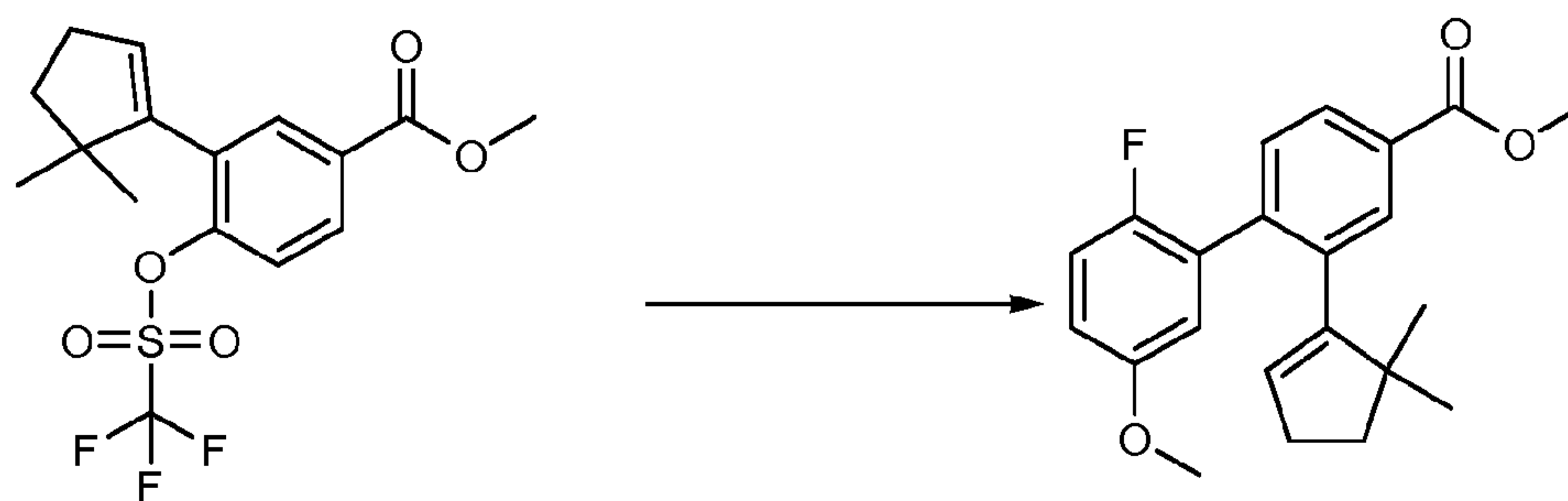


[0307] Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-hydroxybenzoate (T3.4).

To a stirred solution of **T3.3** (19.0 g, 57.6 mmol) in MeOH (150 mL) was added pyridinium para-toluenesulfonate (PPTS) (1.46 g, 5.80 mmol). The mixture was heated to 50°C and monitored with TLC. After 19 hours, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-15% EtOAc in hexanes) to yield **T3.4** as a white solid (yield 90%). ¹H NMR (400 MHz) (CDCl₃) δ 7.89 (1 H, dd, J=8.6, 2.0 Hz), 7.79 (1 H, d, J=2.3 Hz), 6.97 (1 H, d, J=8.6 Hz), 5.87 (1 H, s), 5.81 (1 H, t, J=2.3 Hz), 3.89 (3 H, s), 2.51 (2 H, td, J=7.1, 2.5 Hz), 1.94 (2 H, t, J=7.0 Hz), 1.12 (6 H, s).

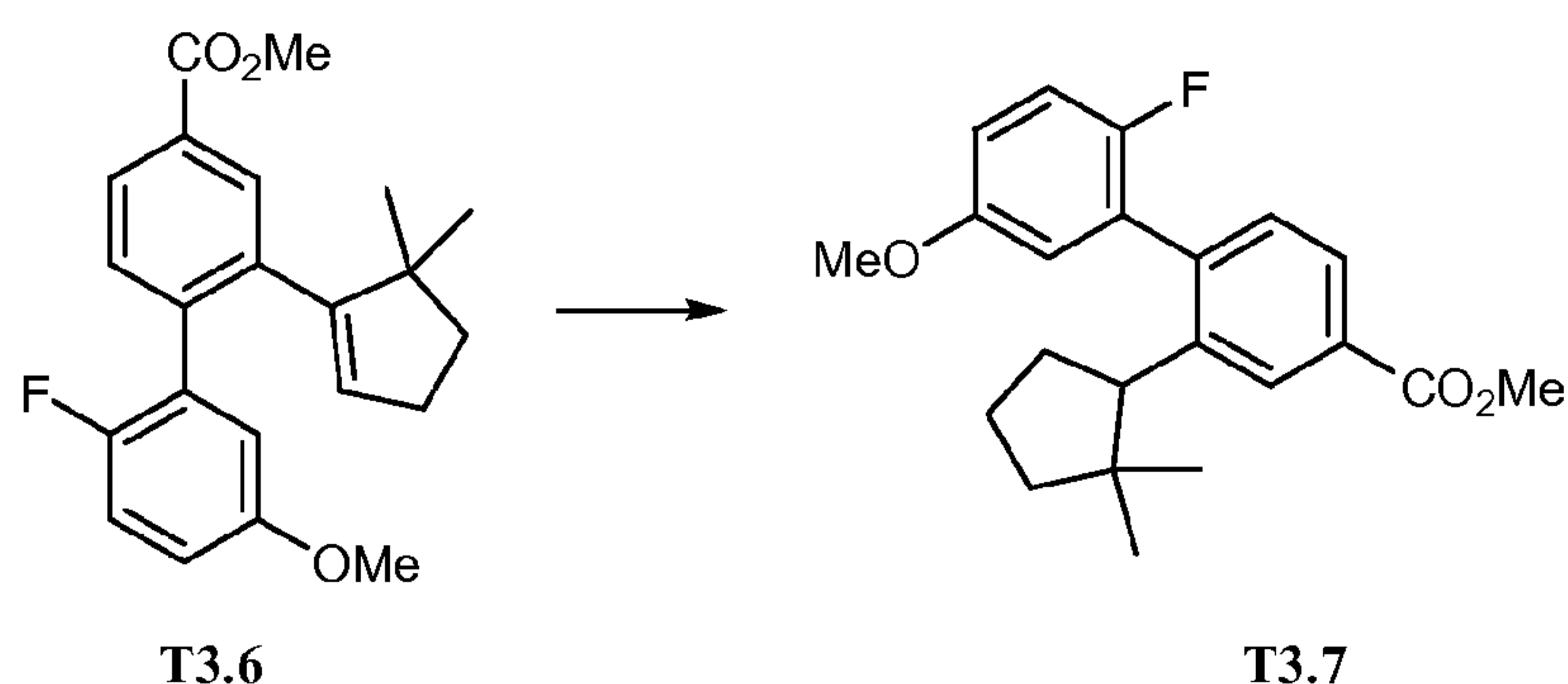
**T3.4****T3.5****[0308] Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-**

(trifluoromethylsulfonyloxy)benzoate (T3.5). To a stirred solution of **T3.4** (6.00 g, 24.4 mmol) in dry DCM (35 mL) was added TEA (6.80 mL, 48.9 mmol) and DMAP (0.30 g, 2.5 mmol). After about 20 minutes, N-phenyl bis-trifluoromethane sulfonimide (10.5 g, 29.3 mmol) was added in portion. Upon complete addition, the solution was stirred at room temperature and monitored with TLC. After 3 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T3.5** as a colorless oil (yield 88%). ¹H NMR (400 MHz, CDCl₃) δ 8.02 (1 H, dd, J=8.6, 2.0 Hz), 7.94 (1 H, d, J=2.0 Hz), 7.35 (1 H, d, J=8.6 Hz), 5.80 (1 H, t, J=2.5 Hz), 3.94 (3 H, s), 2.48 (2 H, td, J=7.0, 2.3 Hz), 1.91 (2 H, t, J=7.0 Hz), 1.09 (6 H, s).

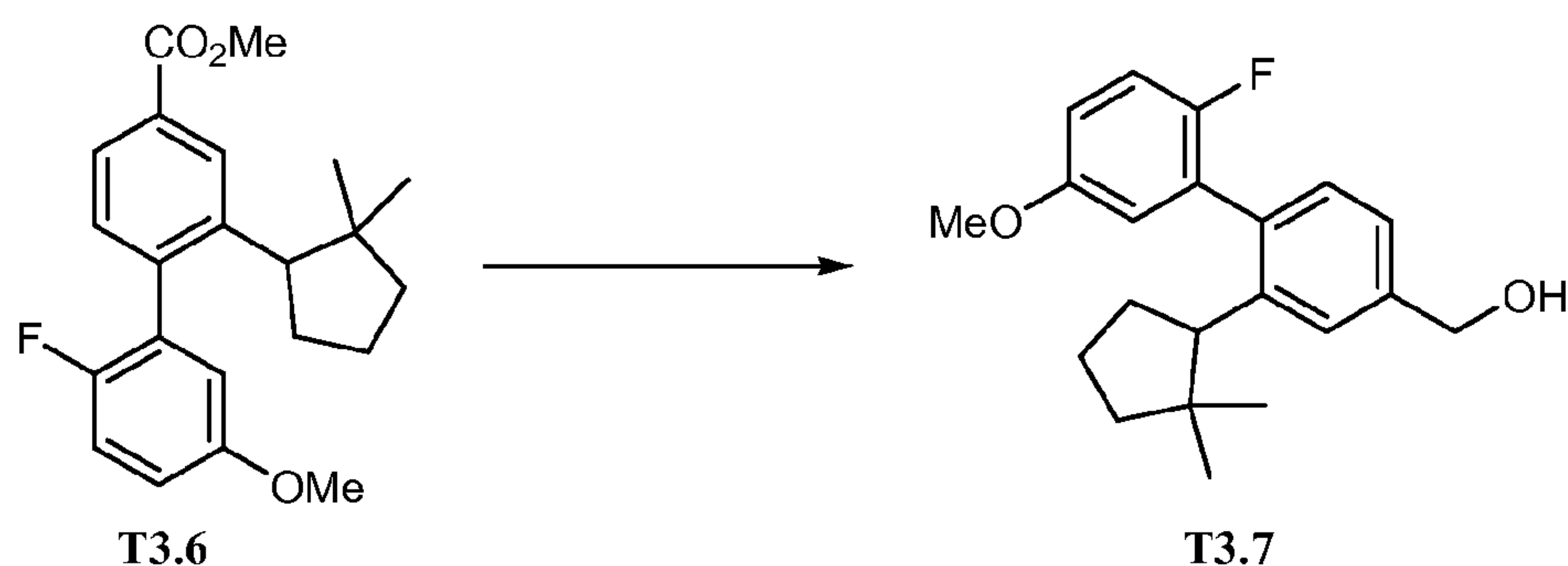
**T3.5****T3.6****[0309] Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-**

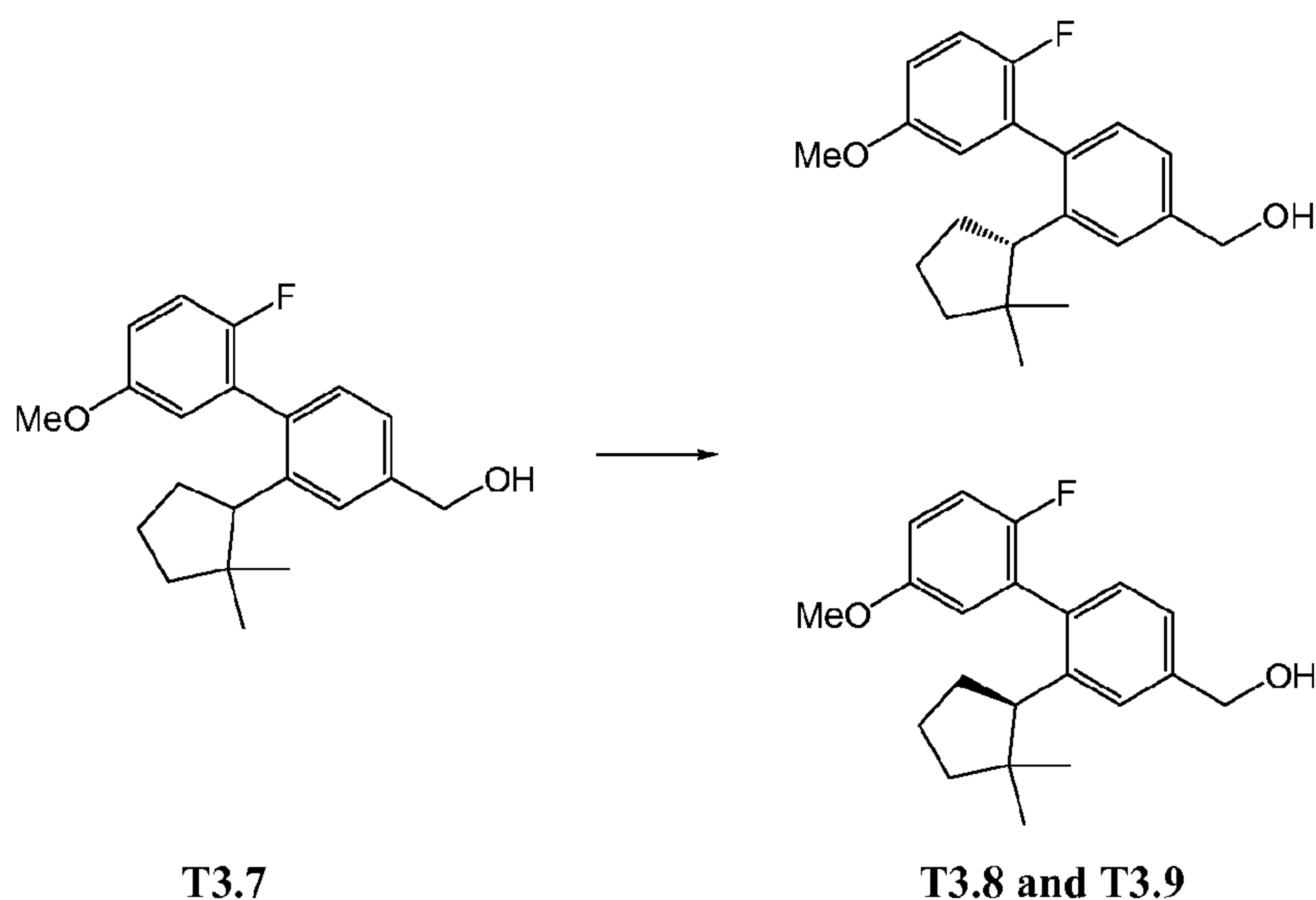
1,1'-biphenyl-4-carboxylate (T3.6). To a stirred solution of **T3.5** (8.71 g, 23.0 mmol) in DMF (20 mL) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (7.84 g, 46.1 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and potassium carbonate (9.56 g, 69.1 mmol) followed by tetrakis(triphenylphosphine)palladium (0) (2.67 g, 2.31 mmol). The mixture was heated to 90 °C. After 15 hours, LCMS-showed

that the reaction was complete. The mixture was then cooled to room temperature and diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to give **T3.6** as a clear oil that solidified (yield 91%). ^1H NMR (400 MHz, CDCl_3) δ 7.98 (1 H, dd, $J=8.0, 1.8$ Hz), 7.91 (1 H, d, $J=2.0$ Hz), 7.40 (1 H, d, $J=7.8$ Hz), 6.98 (1 H, t, $J=8.8$ Hz), 6.85 (2 H, m), 5.55 (1 H, s), 3.95 (3 H, s), 3.77 (3 H, s), 2.27 (2 H, td, $J=7.0, 2.7$ Hz), 1.68 (2 H, t, $J=7.0$ Hz), 0.87 (6 H, s).

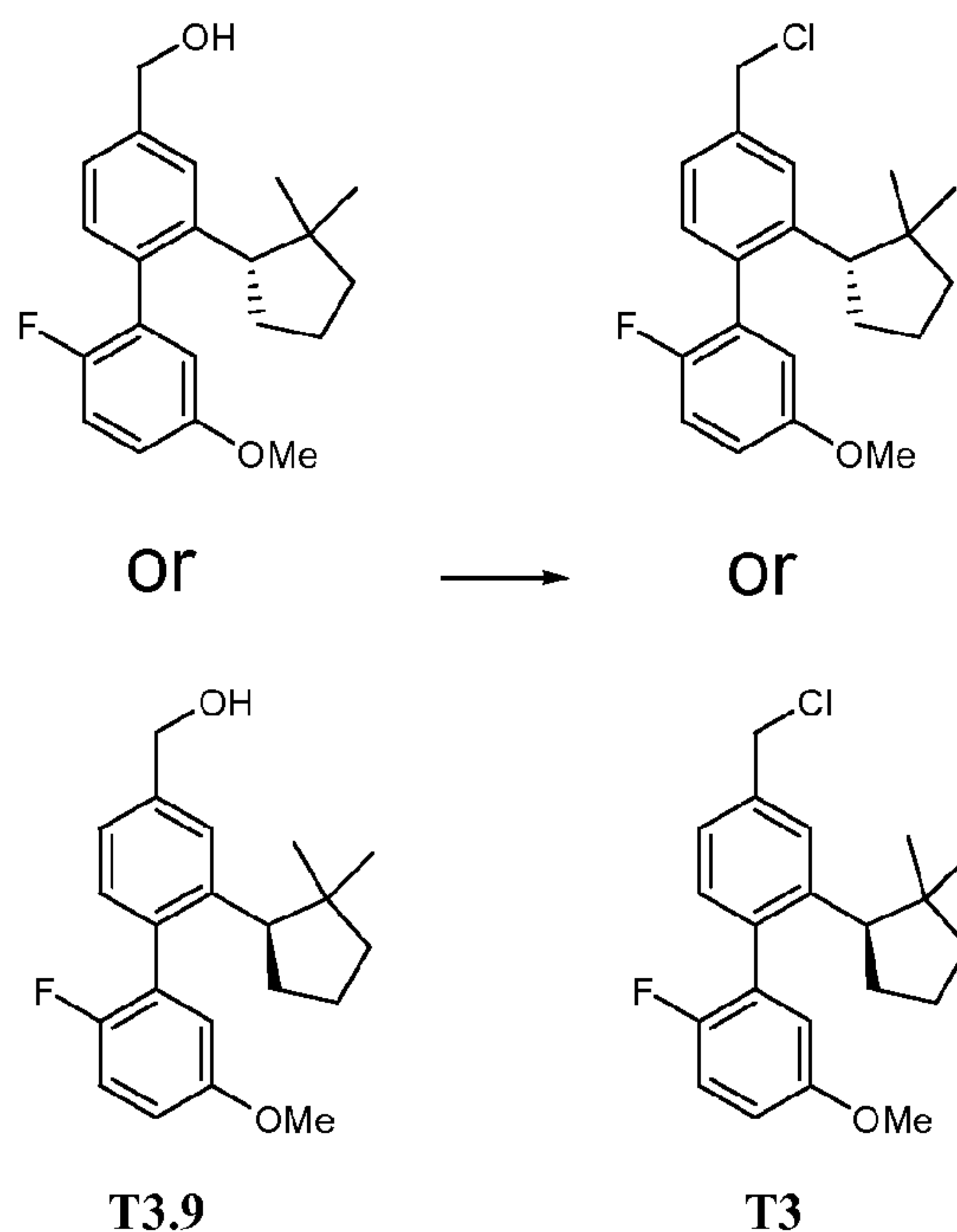


[0310] **Methyl 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T3.7).** To a stirred solution of **T3.6** (0.660 g, 1.86 mmol) in MeOH (20.00 mL, 1.86 mmol) at 23°C was added Pd/C (0.0198 g, 0.186 mmol). The resulting mixture was stirred under an atmosphere of hydrogen (0.00375 g, 1.86 mmol) for 16 hours. The reaction mixture was then filtered and concentrated in *vacuo* to give **T3.7** as a clear oil (0.600 g, 90.4% yield).



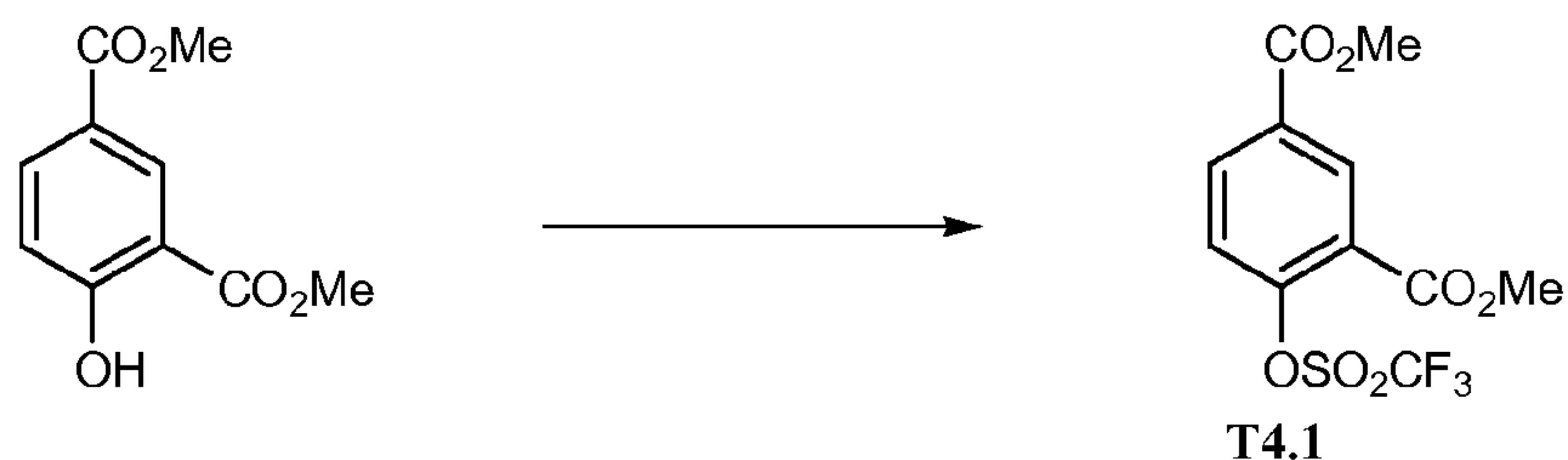


[0311] (2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T3.8 and T3.9). To a stirred solution of T3.6 (0.500 g, 1.4 mmol) in THF (7.0 mL, 1.4 mmol) at 0°C was added LAH (1.4 mL, 1.4 mmol). After addition, the reaction was stirred for 1.5 hours. 1N NaOH (aq) was then added to quench the reaction, and the mixture was extracted with EtOAc. The organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting product was then purified on silica gel (0%-20% EtOAc/hexane) to give T3.7 (0.442 g, 96% yield). Chiral separation of T3.7 was accomplished on a CHIRALCEL® OD column (3%IPA in hexane) to provide T3.8 and T3.9. Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. Analytical column (CHIRALCEL® OD column (2%IPA in hexane, 45 min run) Peak 1-15.5 mins, Peak 2-38.0 mins).¹



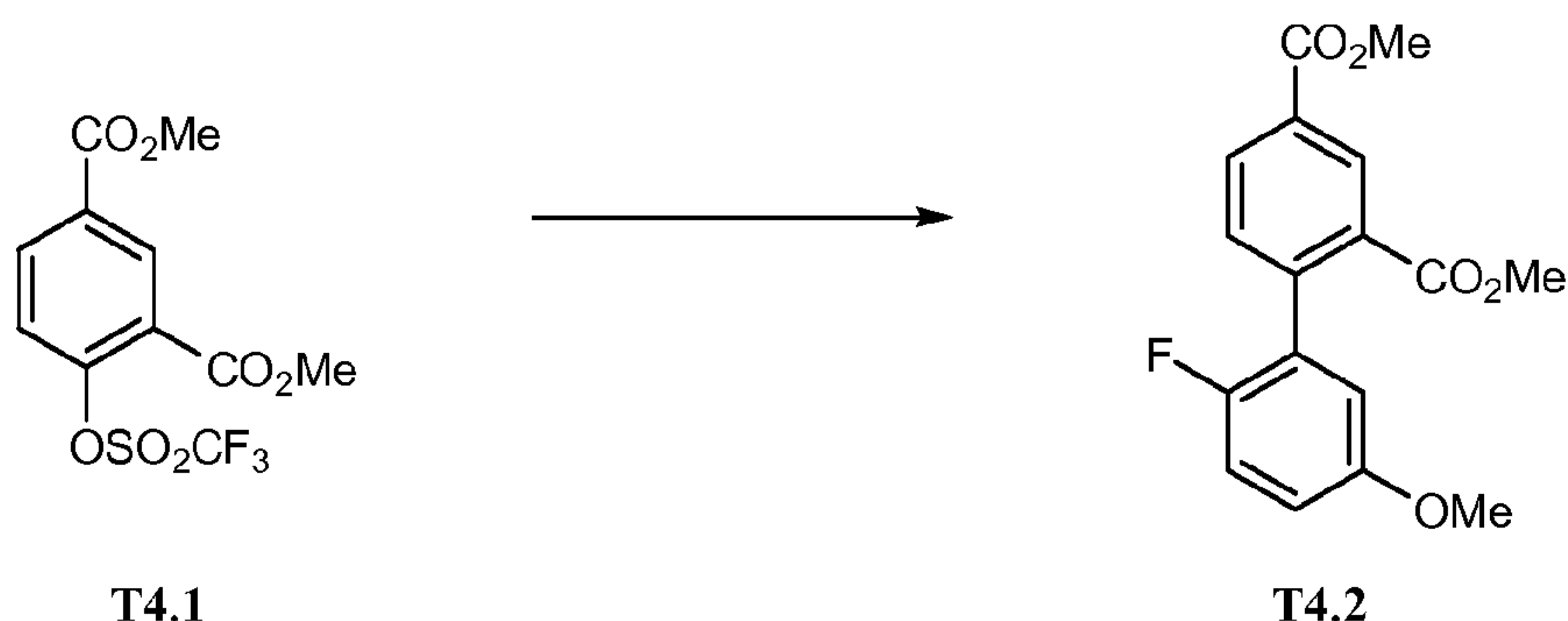
[0312] **4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl T3.** Thionyl chloride (1.5 mL, 20 mmol) was added to a stirred solution of **T3.9** (3.280 g, 10.0 mmol) (derived from peak two from the chiral separation of **T3.7**) in DCM (100 mL, 10.0 mmol) and DMF (0.77 mL, 10.0 mmol) at 0°C. Stirring was continued at room temperature for 2 hours. The reaction mixture was then concentrated in vacuo and purified on silica gel (0-10% EtOAc in hexane) to give the desired product **T3** (3.00 g, 87 % yield) as a clear oil.

[0313] **Intermediate T4**

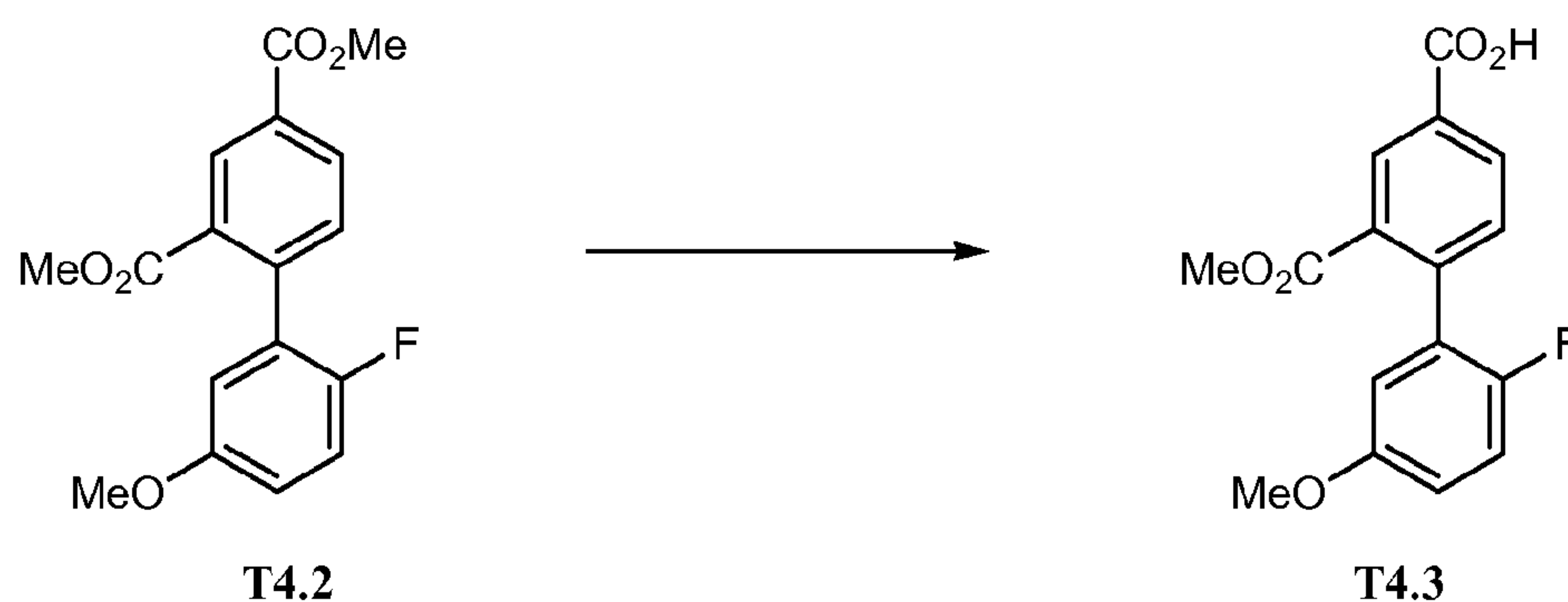


[0314] **Dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate (T4.1).** To a stirred solution of dimethyl 4-hydroxyisophthalate (commercially available from Chem Service)(37.7 g, 179 mmol) in DCM (256 mL, 179 mmol) at 23°C was added TEA (30 mL, 215 mmol), and a catalytic amount of DMAP. N-phenyltriflimide (70 g, 197 mmol)

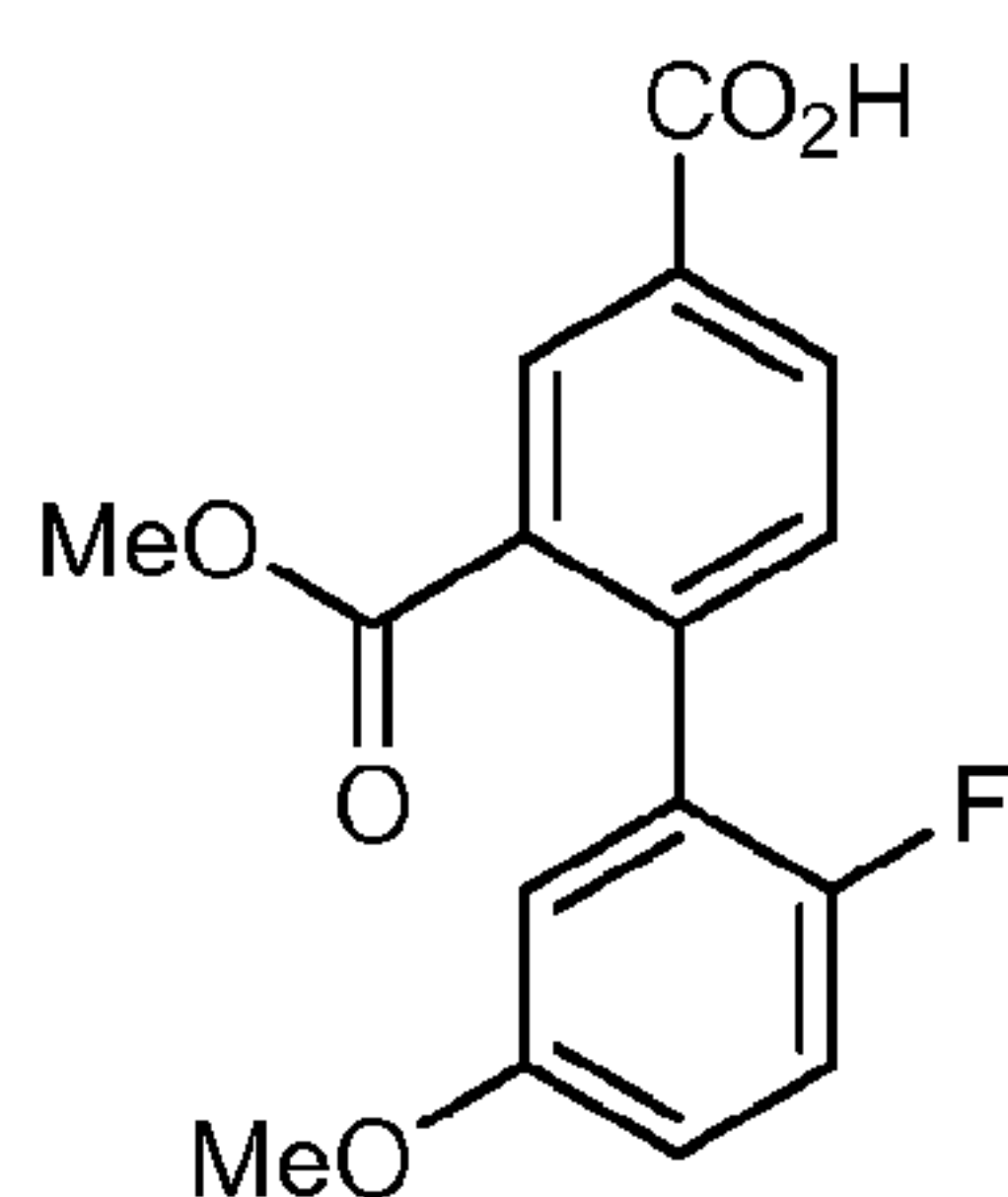
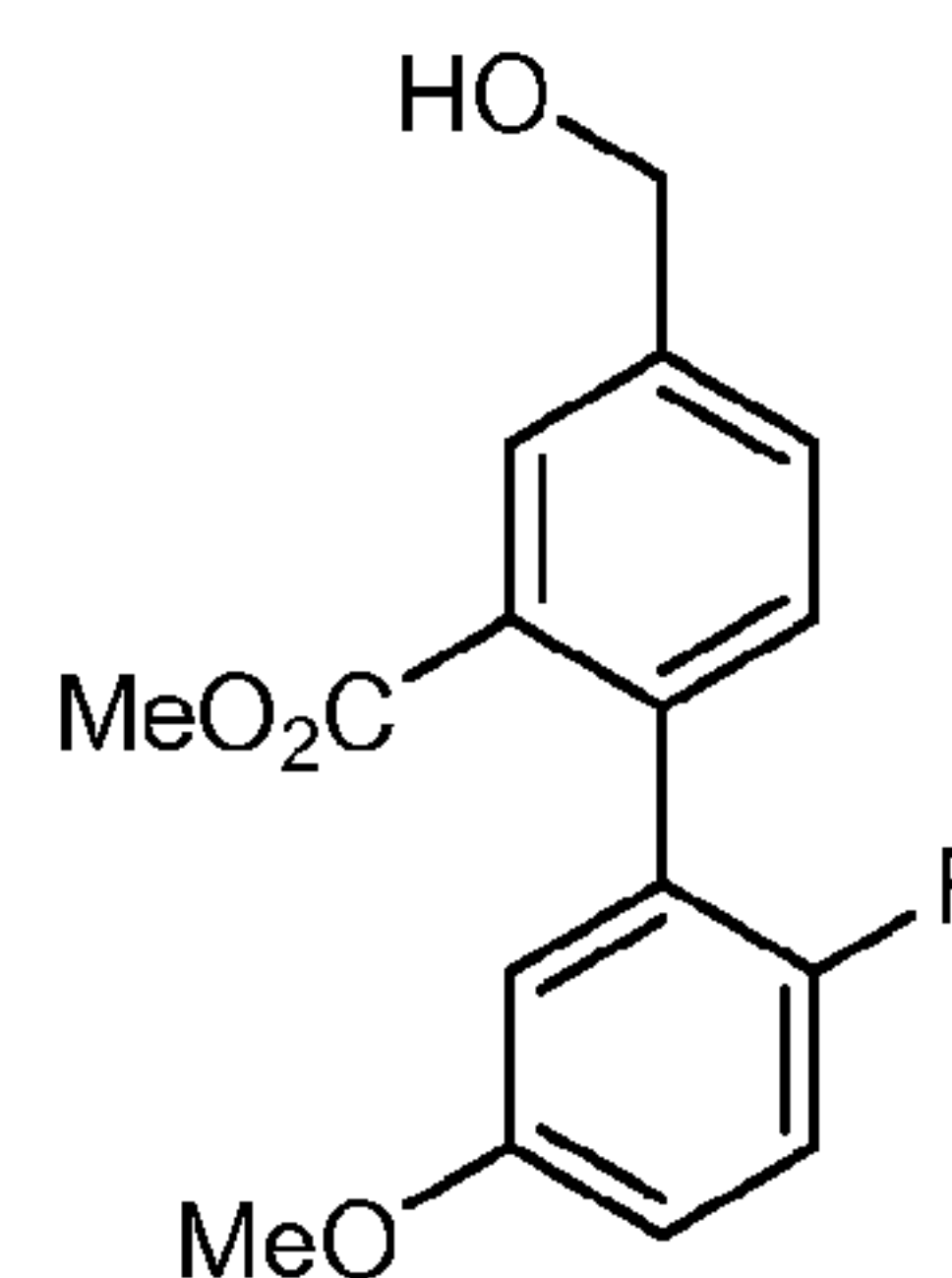
was then added to the mixture and the mixture was stirred at room temperature for 21 hours. The solvent was removed, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **T4.1** dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate as a colorless oil (59.00 g, 96% yield). MS ESI (pos.) m/e: 360.0 (M+H₂O)⁺, 343.0 (M+H)⁺.



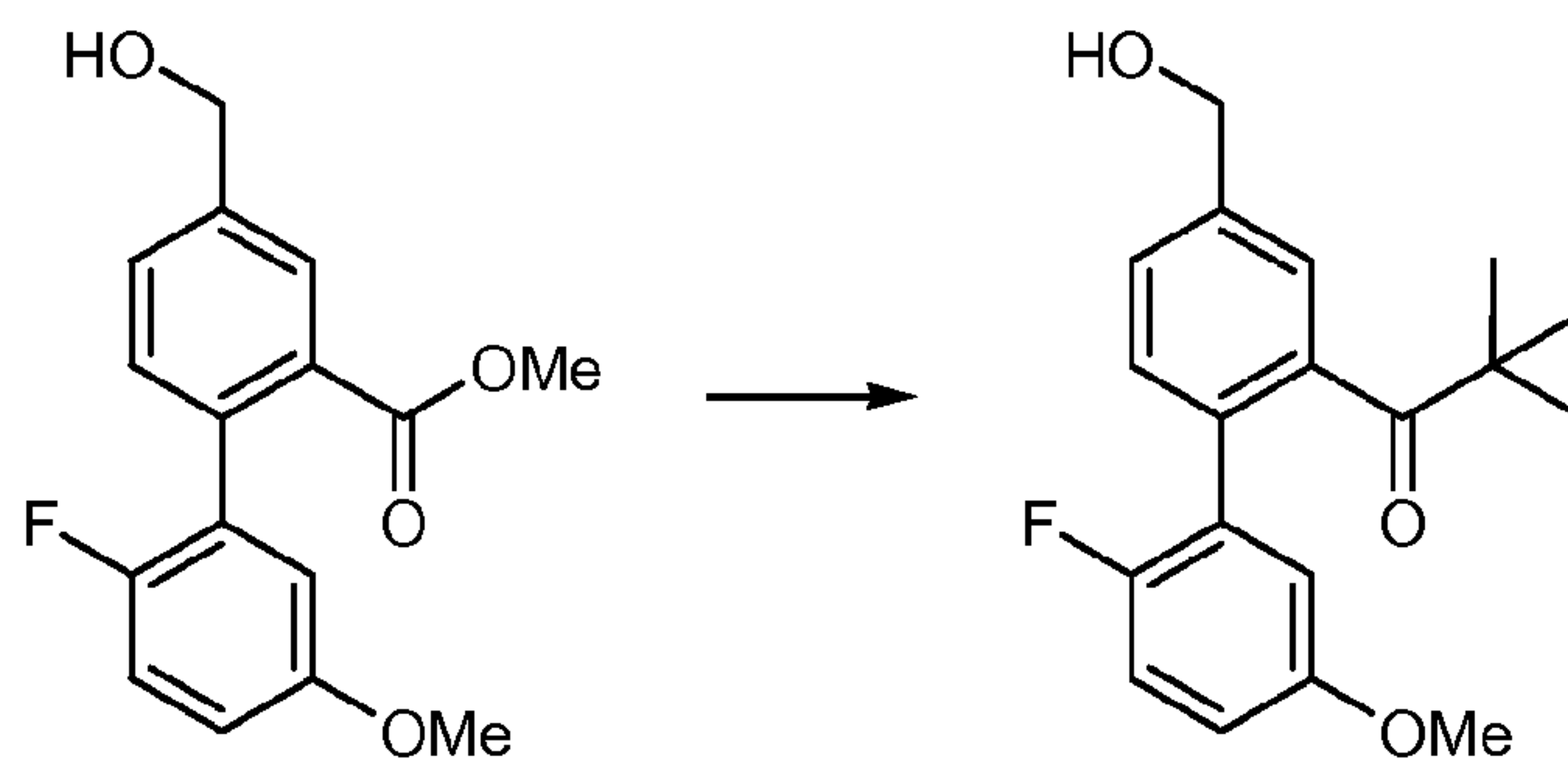
[0315] Dimethyl 2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2,4-dicarboxylate (T4.2). To a stirred solution of dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate **T4.1** (39.00 g, 114 mmol) in DMF (228 mL, 114 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (29 g, 171 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), and potassium carbonate (47 g, 342 mmol), followed by tetrakis(triphenylphosphine)palladium (9.2 g, 8.0 mmol). The mixture was heated to 90°C and stirred for 18 hours. The reaction was cooled to room temperature. Water was then added to the reaction, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over MgSO₄, and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford dimethyl 2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2,4-dicarboxylate **T4.2** as a clear oil (32.00 g, 88% yield). MS ESI (pos.) m/e: 319.1 (M+H)⁺.



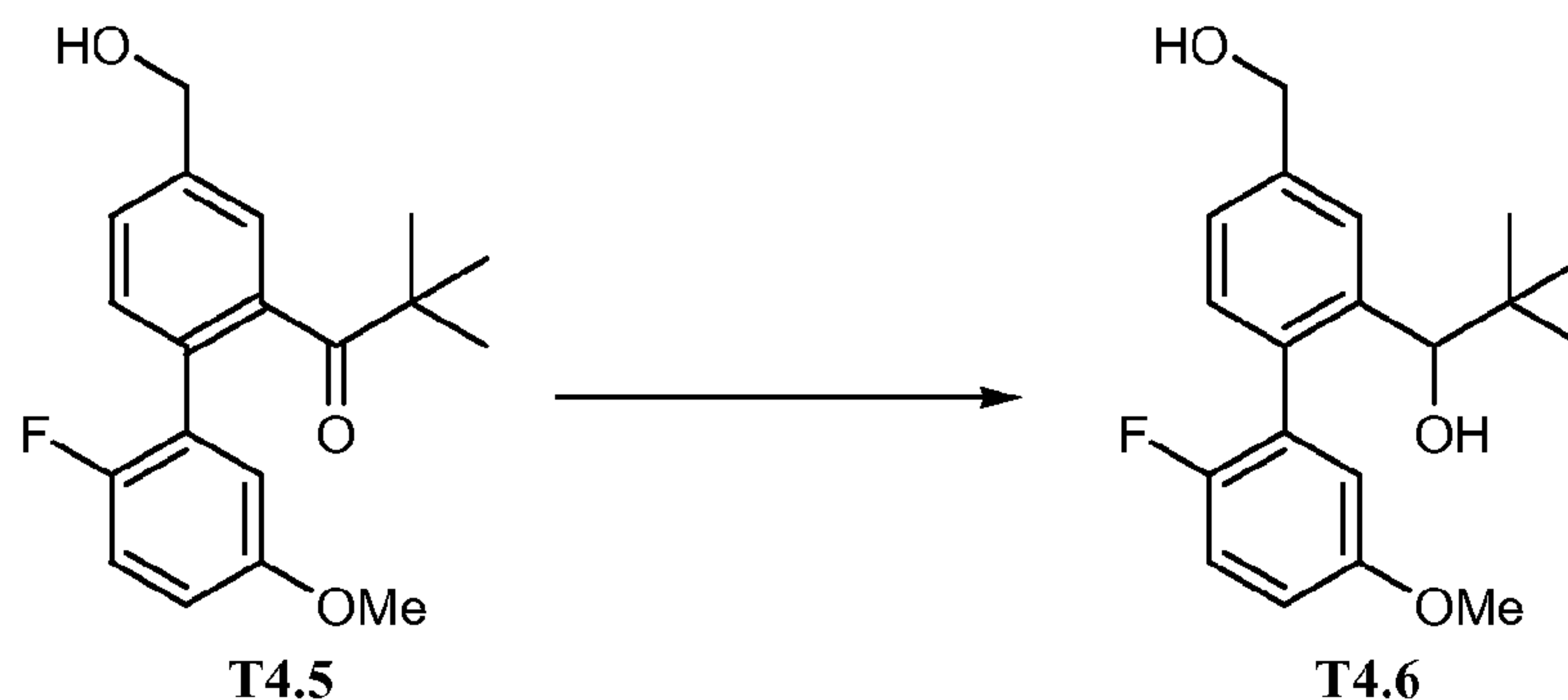
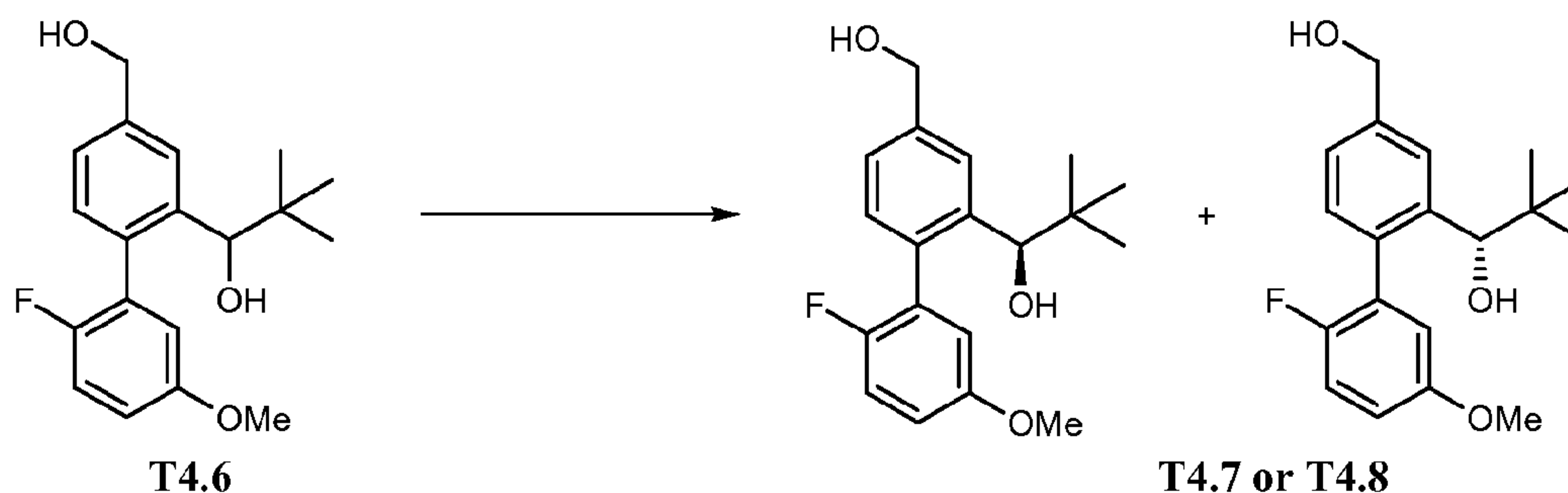
[0316] **2'-Fluoro-5'-(methyloxy)-2-((methyloxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid (T4.3).** To a stirred solution of **T4.2** (36.50 g, 115 mmol) in THF (70.0 mL, 854 mmol) and MeOH (70.0 mL, 1730 mmol) at 0°C was added potassium hydroxide (63 mL, 126 mmol) slowly to maintain the temperature below 6°C. The reaction mixture was allowed to warm to room temperature and was stirred for 15 hours. The reaction mixture was concentrated in vacuo. 1N HCl was added to the aqueous phase, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over MgSO₄, and concentrated in vacuo to give 2'-fluoro-5'-(methyloxy)-2-((methyloxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid **T4.3** as a white solid (35.00 g, 100% yield). MS ESI (pos.) m/e: 322.1 (M+H₂O)⁺, 305.0 (M+H)⁺.

**T4.3****T4.4**

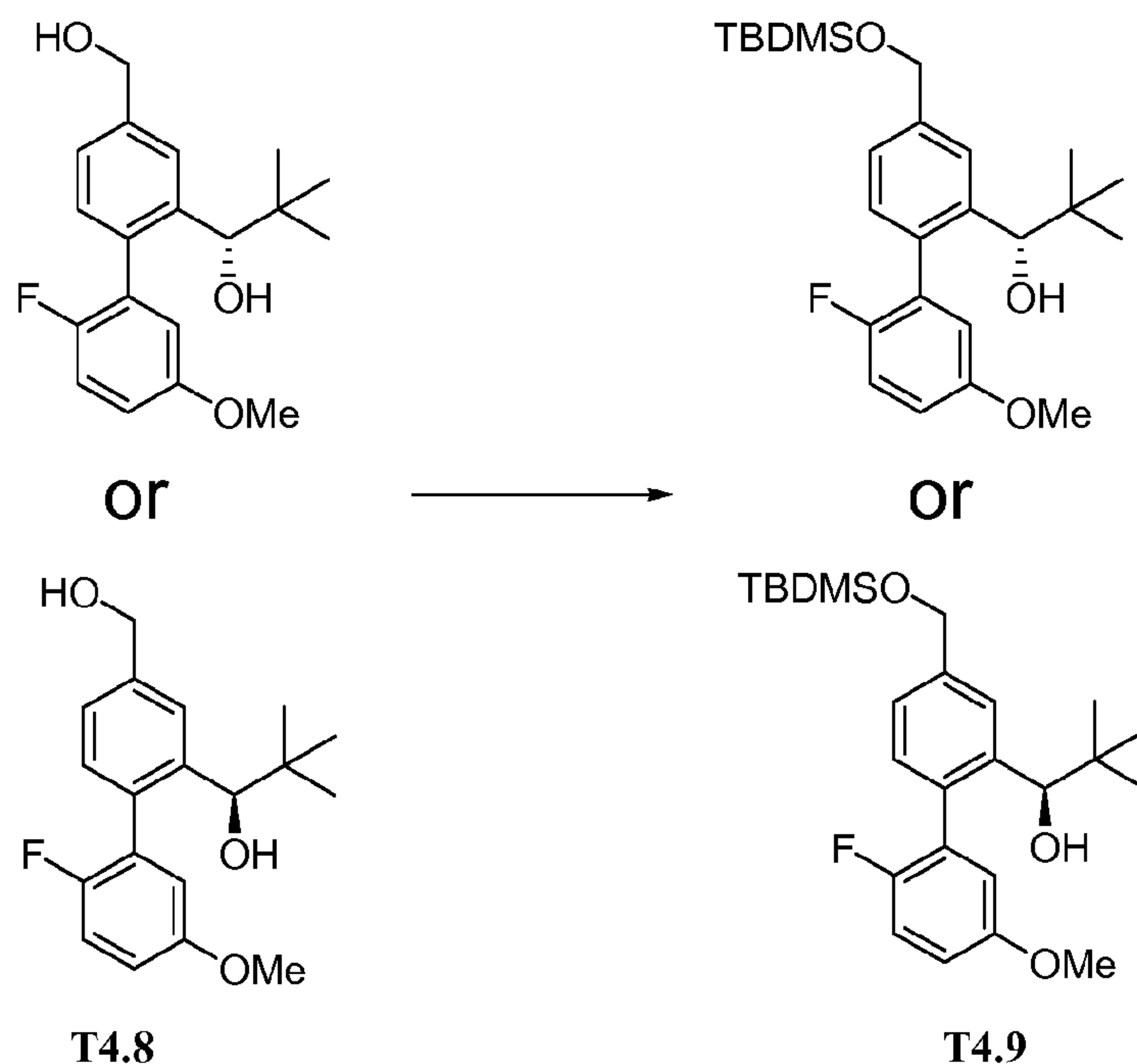
[0317] **Methyl 2'-fluoro-4-(hydroxymethyl)-5'-(methyloxy)-1,1'-biphenyl-2-carboxylate (T4.4).** To a stirred solution of 2'-fluoro-5'-(methyloxy)-2-((methyloxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid **T4.3** (35.60 g, 117 mmol) in THF (1170 mL, 117 mmol) at 0°C was added borane-THF (234 mL, 234 mmol). The reaction was warmed to 23°C, and the mixture was stirred for 6 hours. The mixture was then concentrated in vacuo. 1 N HCl was added, and the mixture was extracted with EtOAc. The organic layers were combined, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified on silica gel (0-40% EtOAc in hexane) to give methyl 2'-fluoro-4-(hydroxymethyl)-5'-(methyloxy)-1,1'-biphenyl-2-carboxylate **T4.4** as a clear oil (30.00 g, 88% yield). MS ESI (pos.) m/e: 308.0 (M+H₂O)⁺, 291.1 (M+H)⁺.

**T4.4****T4.5**

[0318] 1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone (T4.5). To a stirred solution of methyl 2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-carboxylate **T4.4** (2.00 g, 7 mmol) in THF (138 mL, 7 mmol) at -78°C was added t-butyllithium (1.7M in pentane, 9 mL, 14 mmol). The resulting mixture was then stirred for 3 hours. A saturated solution of ammonium chloride was added, to quench the reaction, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford 1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone **T4.5** as a clear oil (2.00 g, 92% yield). MS ESI (pos.) m/e: 334.1 (M+H₂O)⁺, 317.2 (M+H)⁺.

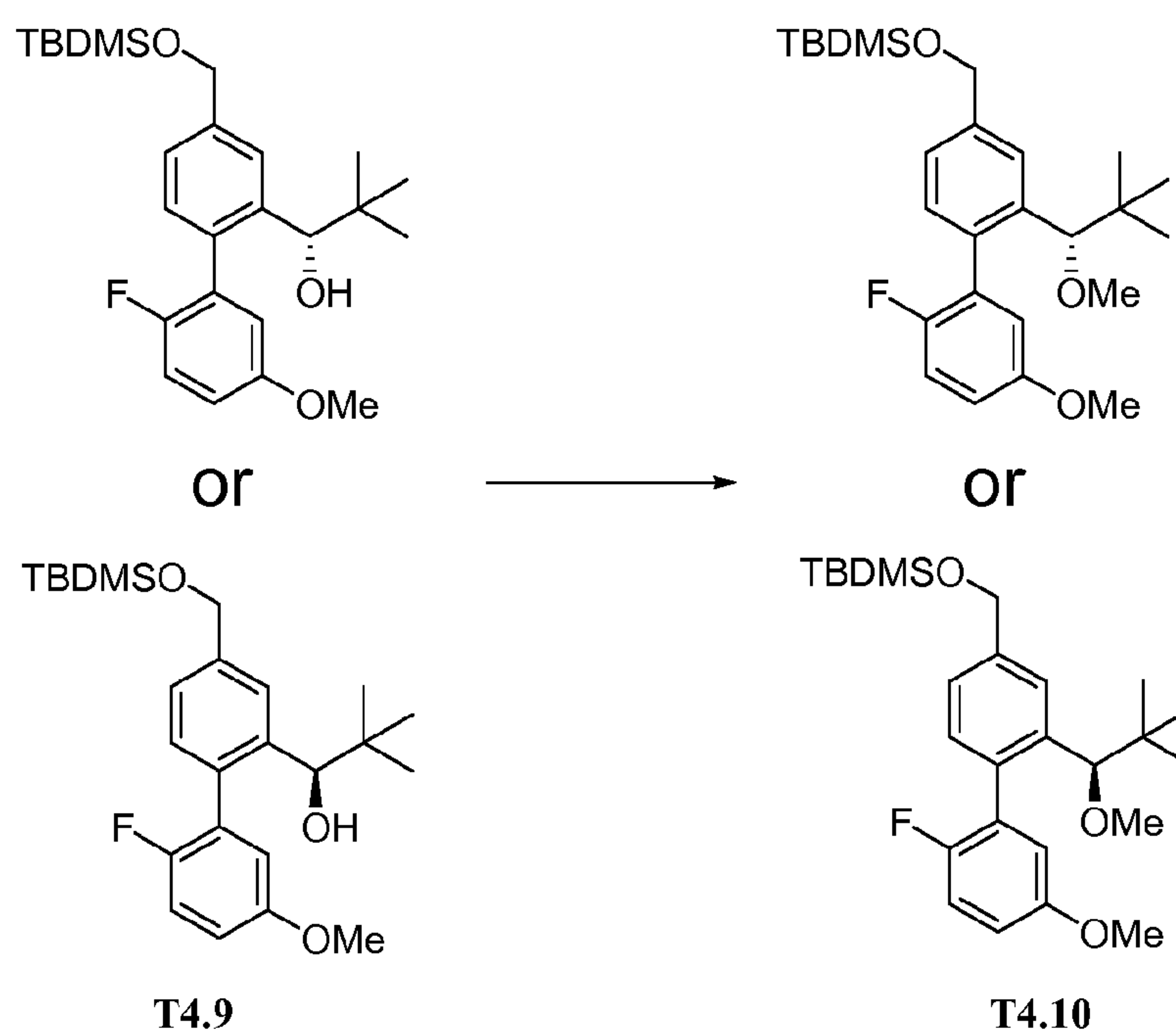
**T4.5****T4.6****T4.6****T4.7 or T4.8**

[0319] (1R)-1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol and (1S)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (T4.7 and T4.8). To a stirred solution of 1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone T4.5 (2.00 g, 6.3 mmol) in THF (63 mL, 6.3 mmol) at 0°C was added LAH (1.0 M in THF, 13 mL, 13 mmol). The reaction was then stirred for 2 hours. 1N NaOH (aq) was added to the mixture, and the resulting mixture was extracted with EtOAc. The organic layers were combined, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford 1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol T4.6 (1.50 g, 75% yield) as a white solid. MS ESI (pos.) m/e: 336.2 (M+H₂O)⁺. Chiral separation of T4.6 was accomplished on a CHIRALCEL® OD column (4%IPA in hexane) to provide T4.7 and T4.8. Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 (T4.8) provided the most active example compounds. Analytical column (CHIRALCEL® OD column (4%IPA in hexane, 45 min run) Peak 1-18.5 mins, Peak 2-24.5 mins).¹

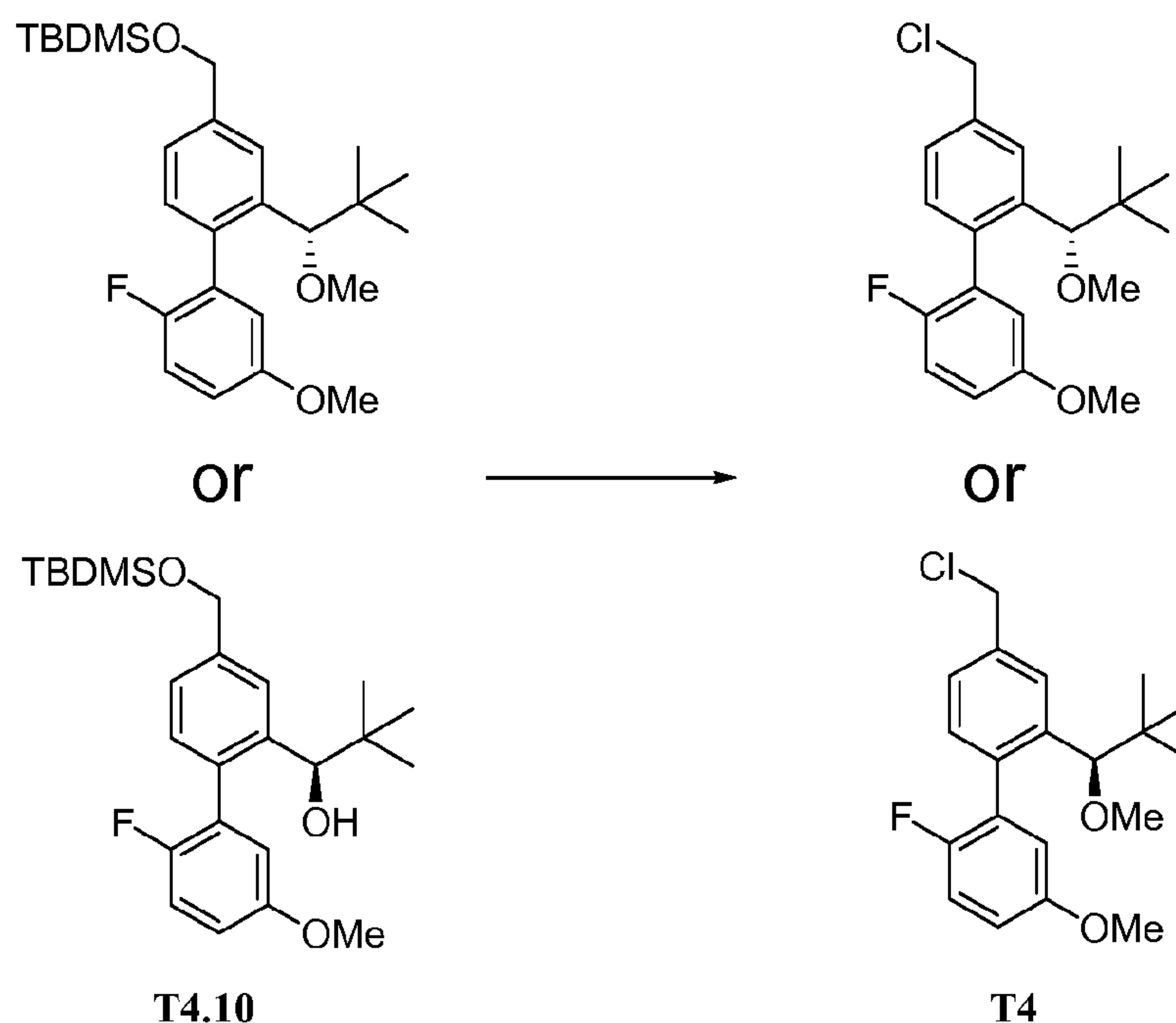


[0320] (1S)-1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1R)-1-(4-(((1,1-

dimethylethyl)(dimethyl)silyloxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (T4.9). To a stirred solution of **T4.9** (0.300 g, 0.9 mmol) (peak two from the chiral separation of **T4.6**) in DCM (10.00 mL, 155 mmol) at 23°C was added tert-butyldimethylsilyl chloride (0.2 mL, 1 mmol), followed by TEA (0.2 mL, 1 mmol) and DMAP (0.01 g, 0.09 mmol). The resulting mixture was stirred for 16 hours. The mixture was then concentrated in vacuo to give a residue which was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **T4.9** (0.375 g, 92% yield). MS ESI (pos.) m/e: 450.2 (M+H₂O)⁺.

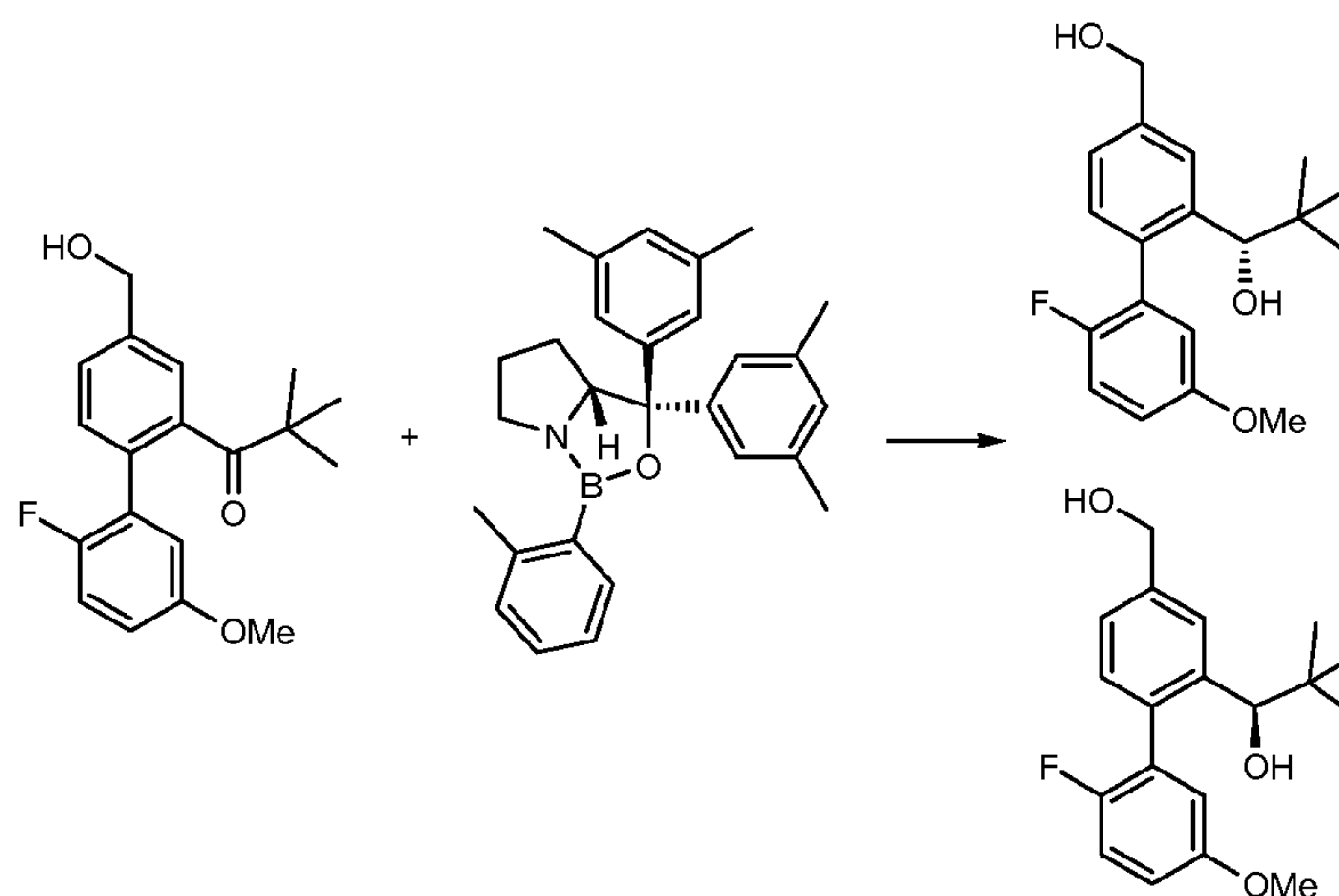


[0321] **(1,1-Dimethylethyl) (((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane or (1,1-dimethylethyl) (((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (T4.10).** To a stirred solution of **T4.9** (0.110 g, 0.25 mmol) in DMF (2.00 mL, 26 mmol) at 23°C was added iodomethane (0.069 g, 0.50 mmol), followed by sodium hydride (0.012 g, 0.50 mmol). The resulting mixture was stirred at 50°C for 21 hours. Water was added to the mixture, and the resulting mixture was extracted with EtOAc, dried over MgSO₄, filtered, and concentrated in vacuo. The residue thus obtained was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T4.10** (0.051 g, 45% yield).



[0322] **4-(Chloromethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T4).** To a stirred solution of **T4.10** (0.082 g, 0.18 mmol) in DCM (2.00 mL, 31 mmol) at 23°C was added DMF (0.0014 mL, 0.018 mmol) followed by thionyl chloride (0.027 mL, 0.37 mmol). The resulting mixture was stirred for one hour and then concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T4** (0.063 g, 98% yield).

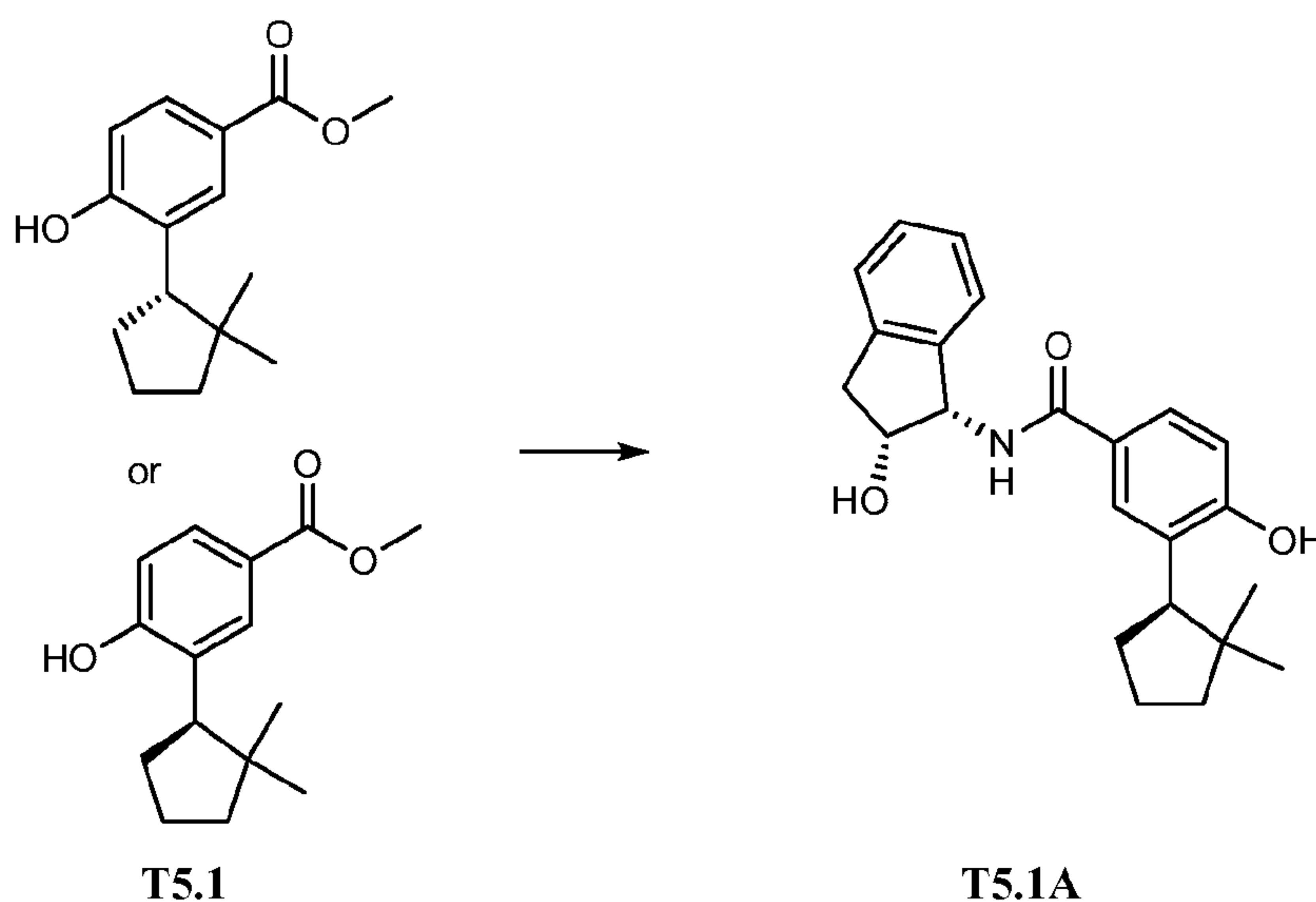
[0323] **Asymmetric Synthesis of T4.7 or T4.8**



T4.5**T4.7 or T4.8**

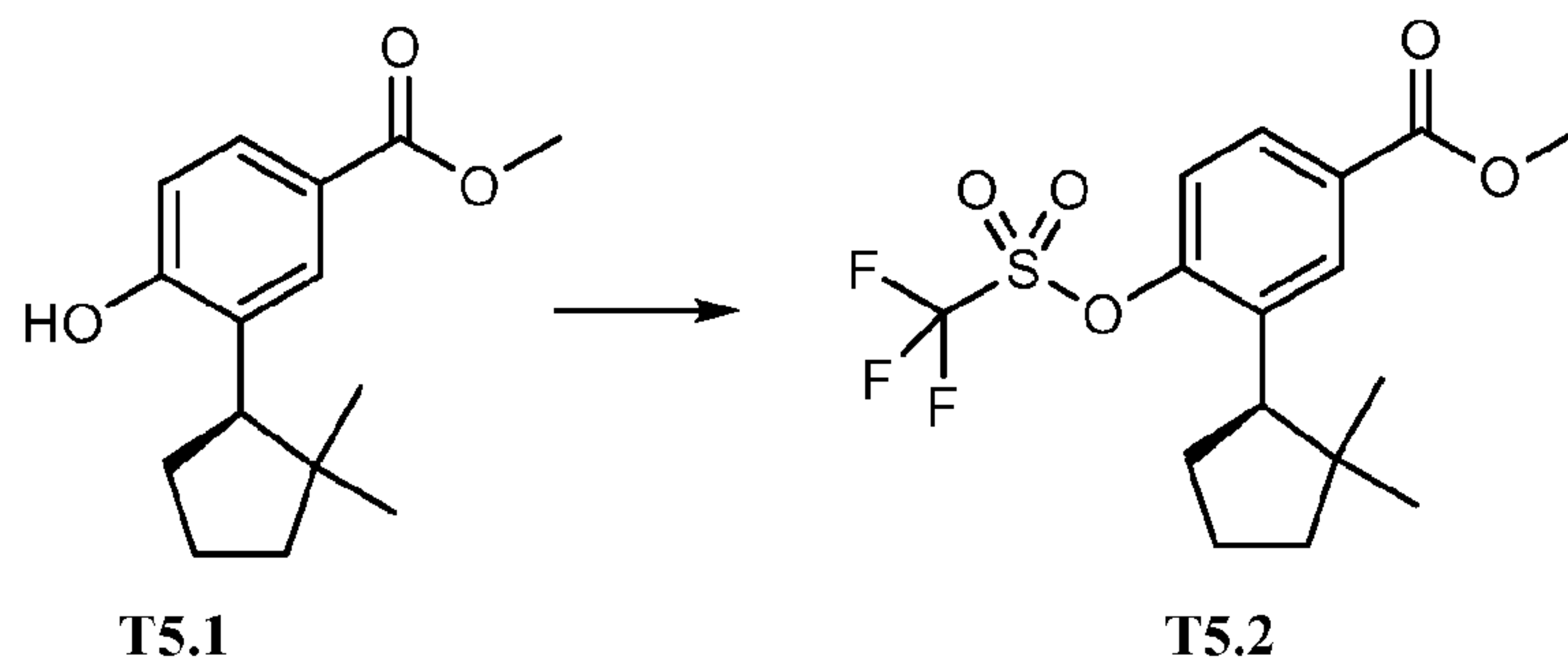
[0324] **(1R)-1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1S)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (T4.7 or T4.8).** To a stirred solution of **T4.5** (0.050 g, 0.2 mmol) in THF (2 mL, 0.2 mmol) at 0°C was added (R)-3,3-bis(3,5-dimethylphenyl)-1-o-tolyl-hexahydropyrrolo[1,2-c][1,3,2]oxazaborole in toluene (0.02 mL, 0.02 mmol, 1.0 M, commercially available from Sigma-Aldrich, St. Louis, MO, USA), followed by dropwise addition of borane in THF (0.2 mL, 0.2 mmol). The reaction was then stirred at 23°C for 4 hours. The reaction was quenched with 1N HCl (aq) and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified on silica gel (0%-20% EtOAc/hexane) to yield **T4.7 or T4.8** (0.045 g, 89% yield). Chiral HPLC determined that the major product was the desired more potent enantiomer with an enantiomeric excess of 85%.

[0325]

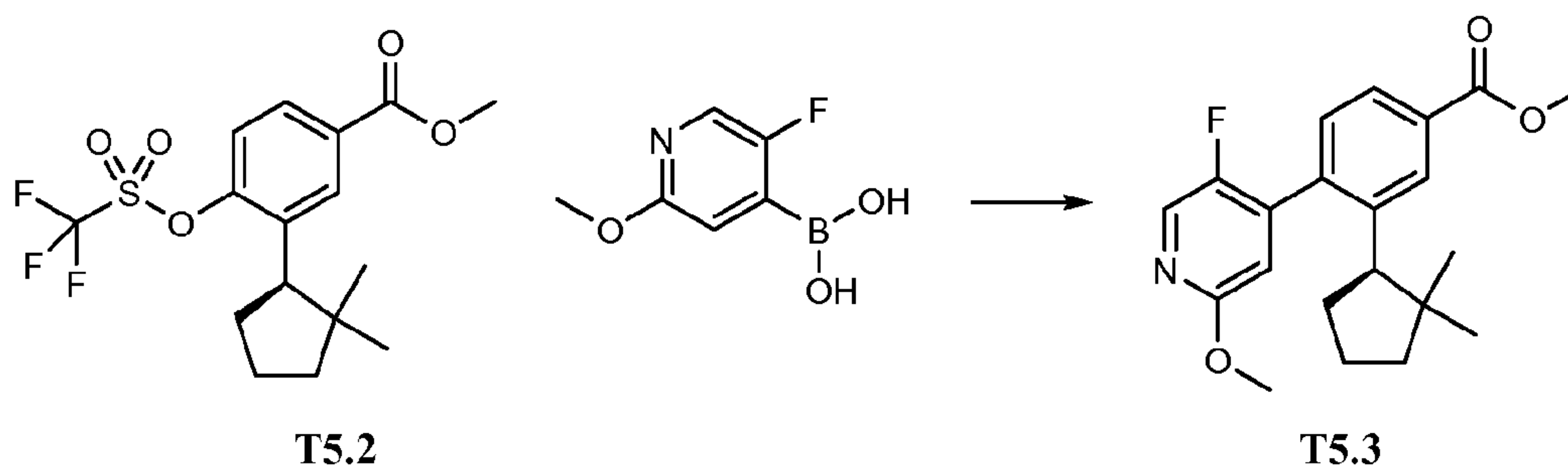
Intermediate T5

[0326] **3-((R)-2,2-Dimethylcyclopentyl)-4-hydroxy-N-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (T5.1A).** Intermediate **T5.1** was synthesized by a method analogous to that described for compound **T7.12**. Since the absolute configuration of intermediate **5.1** was initially unknown, it was derivatized with (1S,2R)-1-amino-2-indanol (commercially available from Sigma-Aldrich, St. Louis, MO) to obtain the amide. A single crystal was obtained by slow recrystallization from a

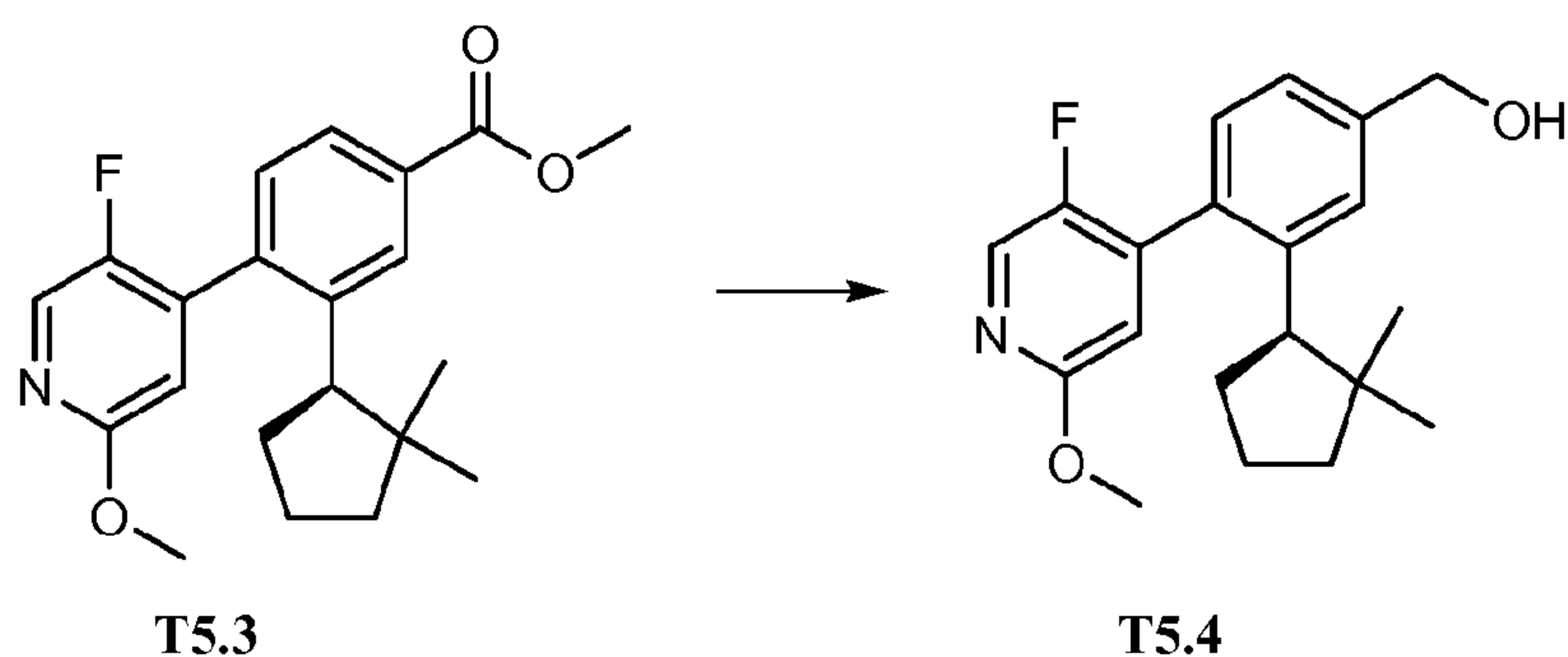
EtOAc/hexanes mixture and subjected to x-ray crystallographic structural determination. The crystal structure of intermediate **T5.1A** established that intermediate **T5.1** is in the *R* configuration at the chiral center in the cyclopentyl ring.



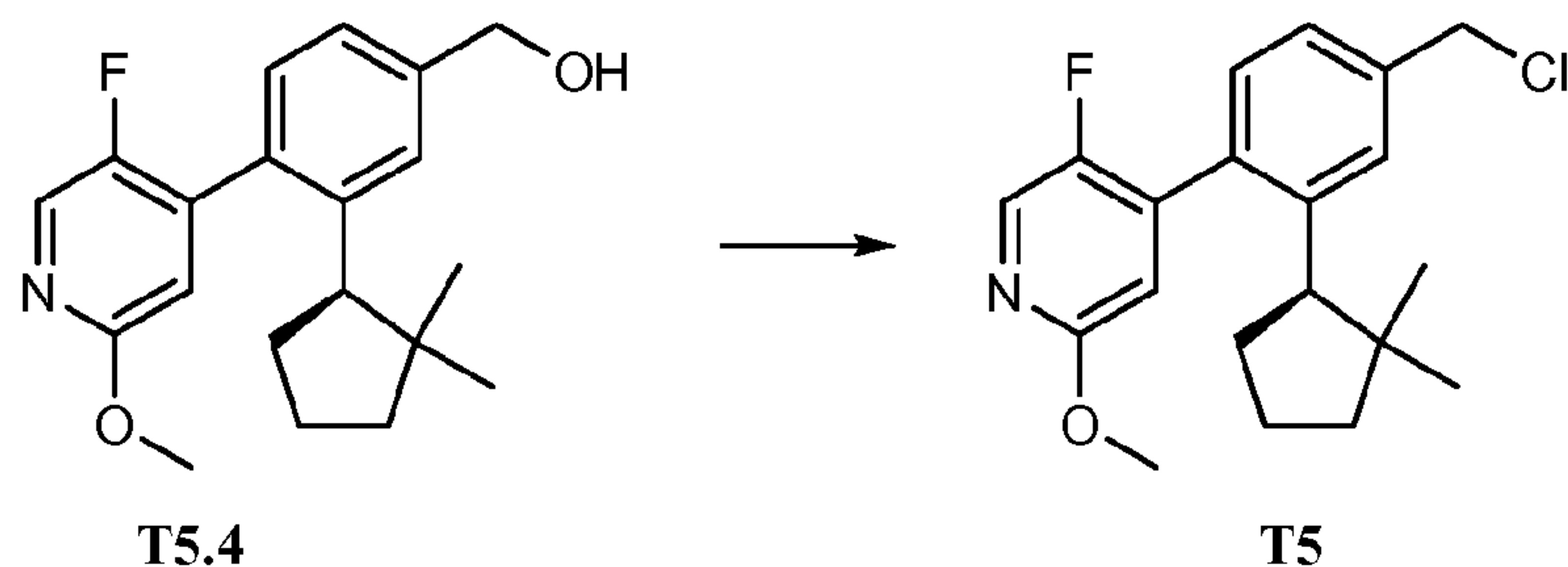
[0327] **(R)-Methyl 3-(2,2-dimethylcyclopentyl)-4-(trifluoromethylsulfonyloxy)benzoate (T5.2)**. DMAP (220 mg, 1804 μmol) was added to a flask containing (R)-methyl 3-(2,2-dimethylcyclopentyl)-4-hydroxybenzoate (**T5.1**) (8960 mg, 36083 μmol). The flask was flushed with nitrogen and DCM (87 mL, 36083 μmol) was added, followed by addition of TEA (7.5 mL, 54124 μmol). After 15 minutes, $\text{PhN}(\text{Tf})_2$ (14180 mg, 39691 μmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added. The reaction was stirred overnight and concentrated. Silica gel chromatography with EtOAc and hexanes as eluent afforded 13.7 g of **T5.2** (100%).



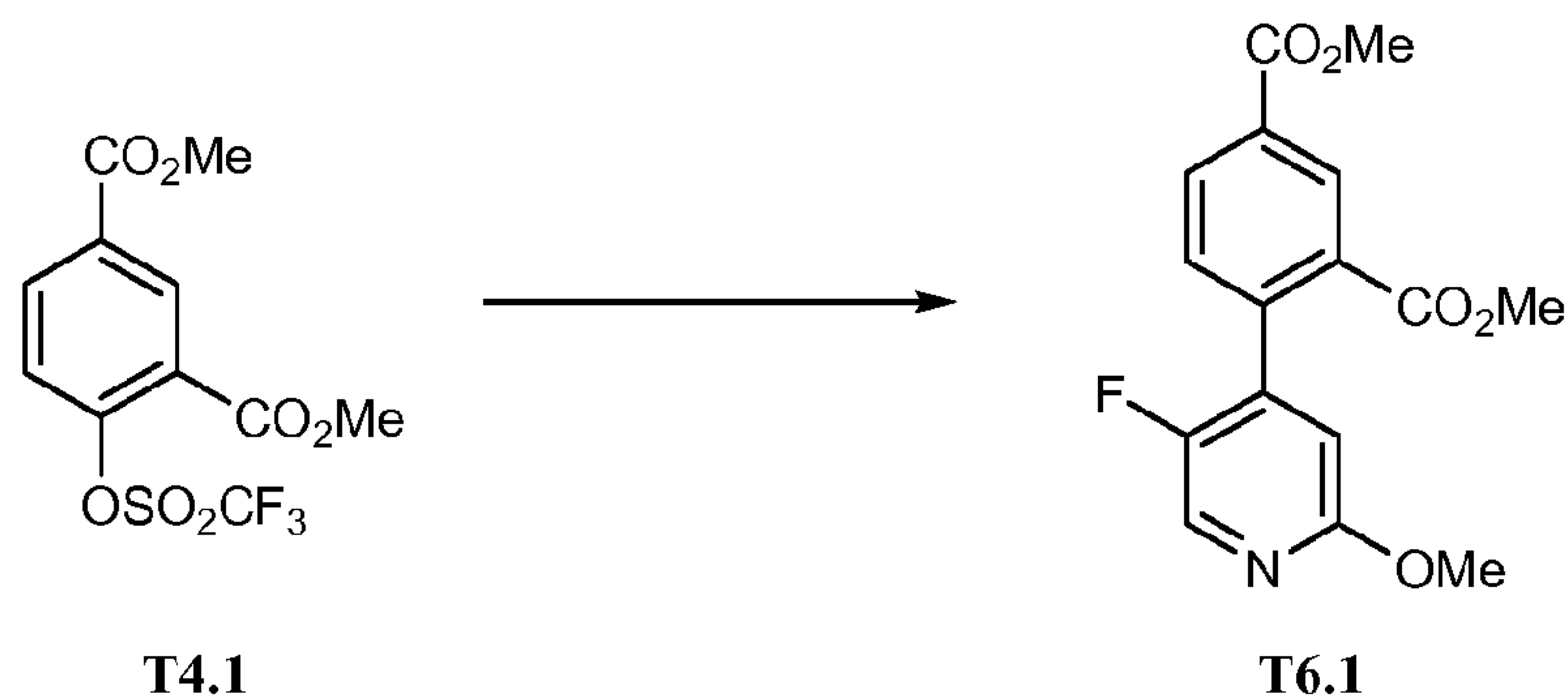
[0328] **Methyl 3-((R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzoate (T5.3)**. To a flask with **T5.2** (14.7 g, 38.6 mmol), was added 5-fluoro-2-methoxypyridin-4-ylboronic acid (12.7 g, 74.3 mmol, commercially available from Asymchem), potassium carbonate (15.6 g, 113 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (4.36 g, 3.77 mmol). The flask was flushed with nitrogen. Degassed DMF (106 mL) was then added. The reaction was heated overnight and partitioned between EtOAc and water. Silica gel chromatography with EtOAc and hexanes as eluents afforded 13.75 g of **T5.3** (100%). MS ESI (pos.) m/e : 358.1 ($\text{M}+\text{H}$)⁺.



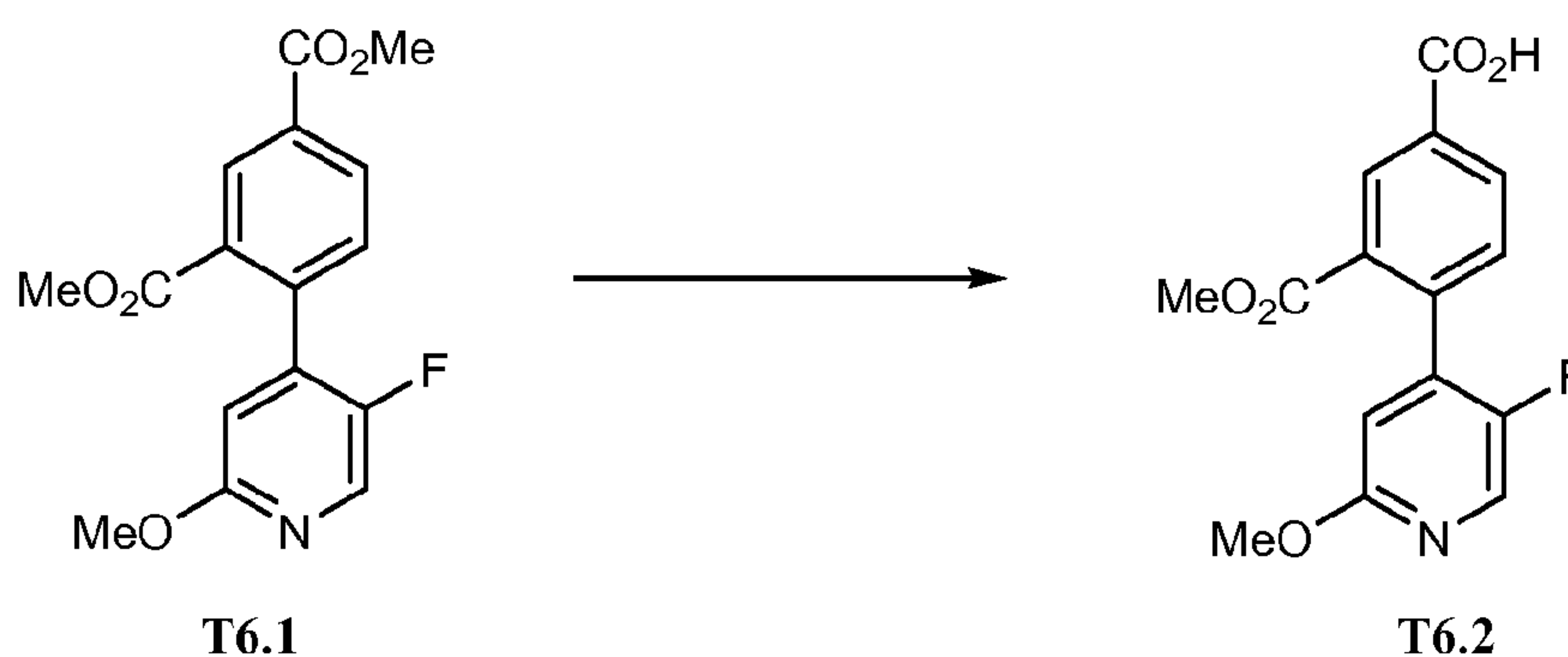
[0329] (3-((R)-2,2-Dimethylcyclopentyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol (T5.4). To a flask containing **T5.3** (14290 mg, 40 mmol) was added 200 mL anhydrous THF. The reaction vessel was then immersed in an ice-bath. LAH (60 mL, 60 mmol, 1 M solution in THF) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added slowly. The flask was kept in the ice-bath and the temperature of the bath was allowed to rise on its own. After 1.5 hours, the reaction was quenched with 1N NaOH, and water was added. The reaction mixture was then extracted with EtOAc and purified by silica gel chromatography with EtOAc/hexanes gradient elution to afford 12 g of **T5.4** (91%) as a colorless oil. MS ESI (pos.) m/e: 330.1 (M+H)⁺.



[0330] 4-(4-(Chloromethyl)-2-((R)-2,2-dimethylcyclopentyl)phenyl)-5-fluoro-2-methoxypyridine (T5). To a flask containing **T5.4** (10.7 g, 32 mmol) was added 160 mL of DCM. The resulting mixture was cooled in an ice-bath. Thionyl chloride (4.60 mL, 63 mmol) and DMF (0.5 mL, 6 mmol) were then added, and the mixture was stirred at room temperature for 1 hour. The reaction was concentrated and diluted with EtOAc. The resulting mixture was washed with NaHCO₃, brine, and the process repeated until the pH of the aqueous mixture was around 6. Silica gel chromatography with EtOAc/hexanes gradient elution afforded 9.44 g of the desired chloride **T5** (84%). MS ESI (pos.) m/e: 348.1 (M+H)⁺.

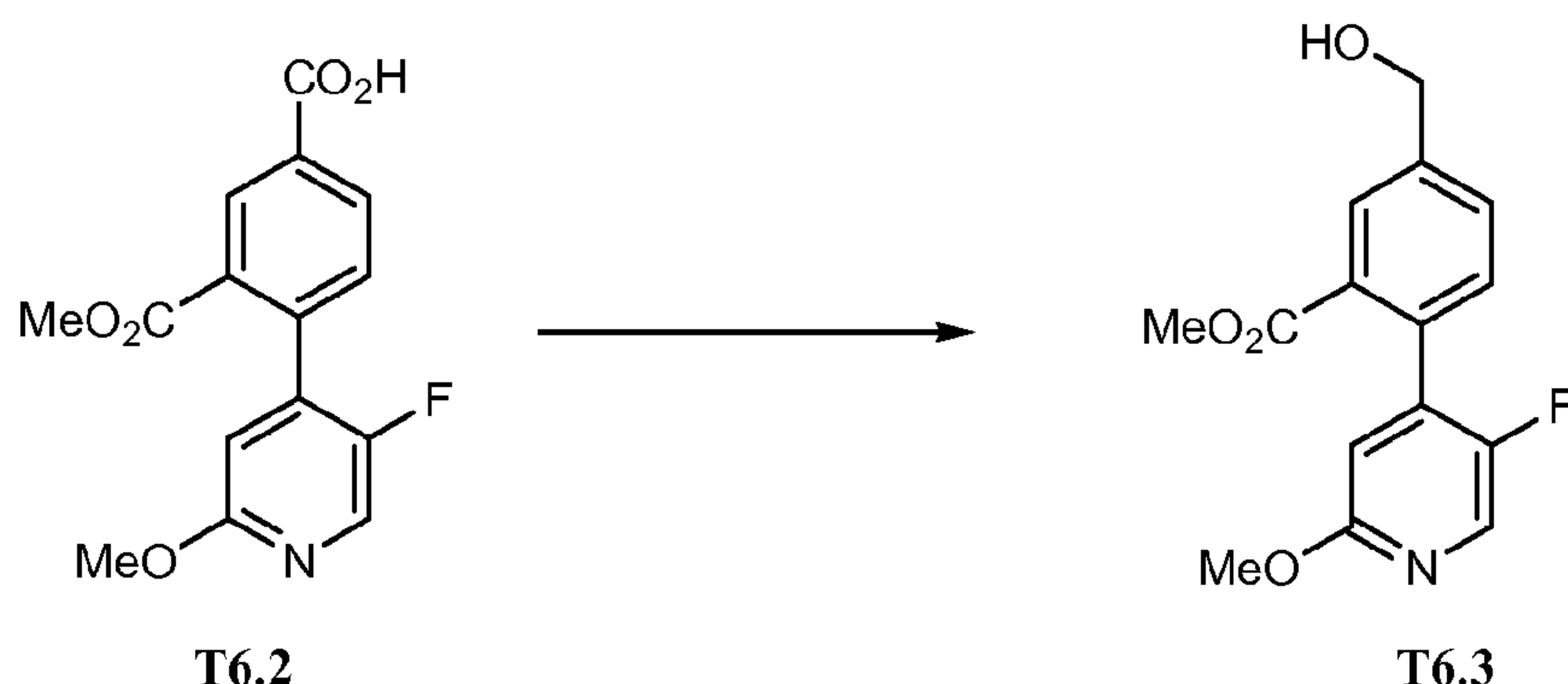
[0331] Intermediate T6**[0332] Dimethyl 4-(5-fluoro-2-(methoxy)-4-pyridinyl)-1,3-**

benzenedicarboxylate (T6.1). To a stirred solution of **T4.1** (1.00 g, 2.9 mmol) in DMF (12 mL) at 23°C was added 5-fluoro-2-methoxypyridin-4-ylboronic acid (0.75 g, 4.4 mmol, commercially available from Asymchem), potassium carbonate (1.2 g, 8.8 mmol), and tetrakis(triphenylphosphine)palladium (0.24 g, 0.20 mmol). The mixture was heated to 90°C and stirred for 17 hours. The mixture was then cooled to room temperature, diluted with brine and extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the organic solvent was removed under reduced pressure. The resulting residue was purified on silica gel (0-30% EtOAc in hexanes) to yield **T6.1** as a colorless solid (0.860 g, 92% yield).

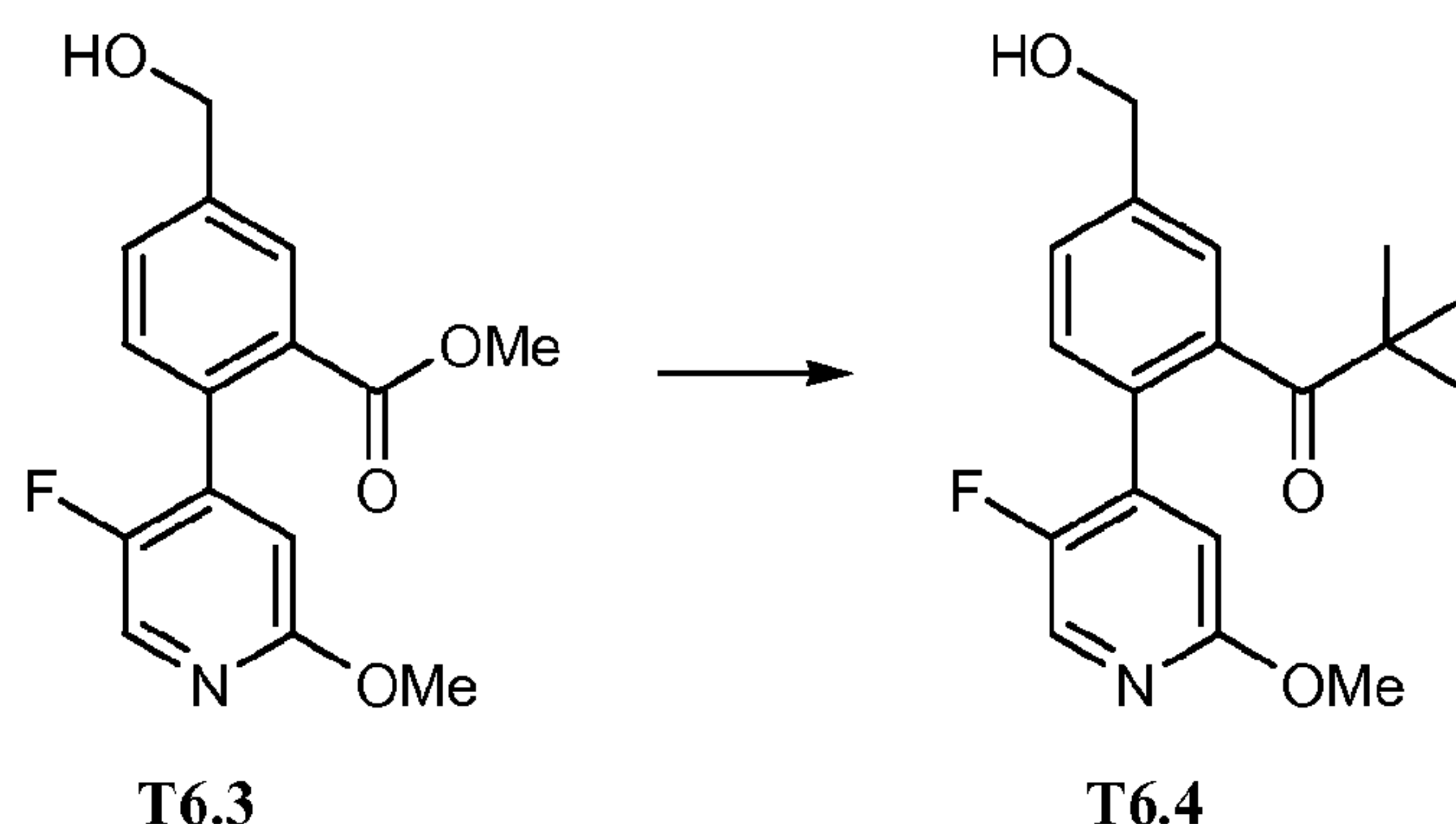
**[0333] 4-(5-Fluoro-2-(methoxy)-4-pyridinyl)-3-**

((methoxy)carbonyl)benzoic acid (T6.2). To a stirred solution of **T6.1** (0.860 g, 2.7 mmol) in THF (7.00 mL) and MeOH (7.00 mL) at 0°C was added potassium hydroxide (1.5 mL, 3.0 mmol) slowly maintaining the temperature below 6°C. The reaction mixture was allowed to warm to room temperature and stirred for 17 hours. The reaction was next acidified with 1N HCl and extracted three times with EtOAc. The organic layers were

combined, dried over anhydrous MgSO_4 , and filtered. The organic solvent was then removed under reduced pressure to yield **T6.2** as a colorless solid (0.82 g, 100% yield).

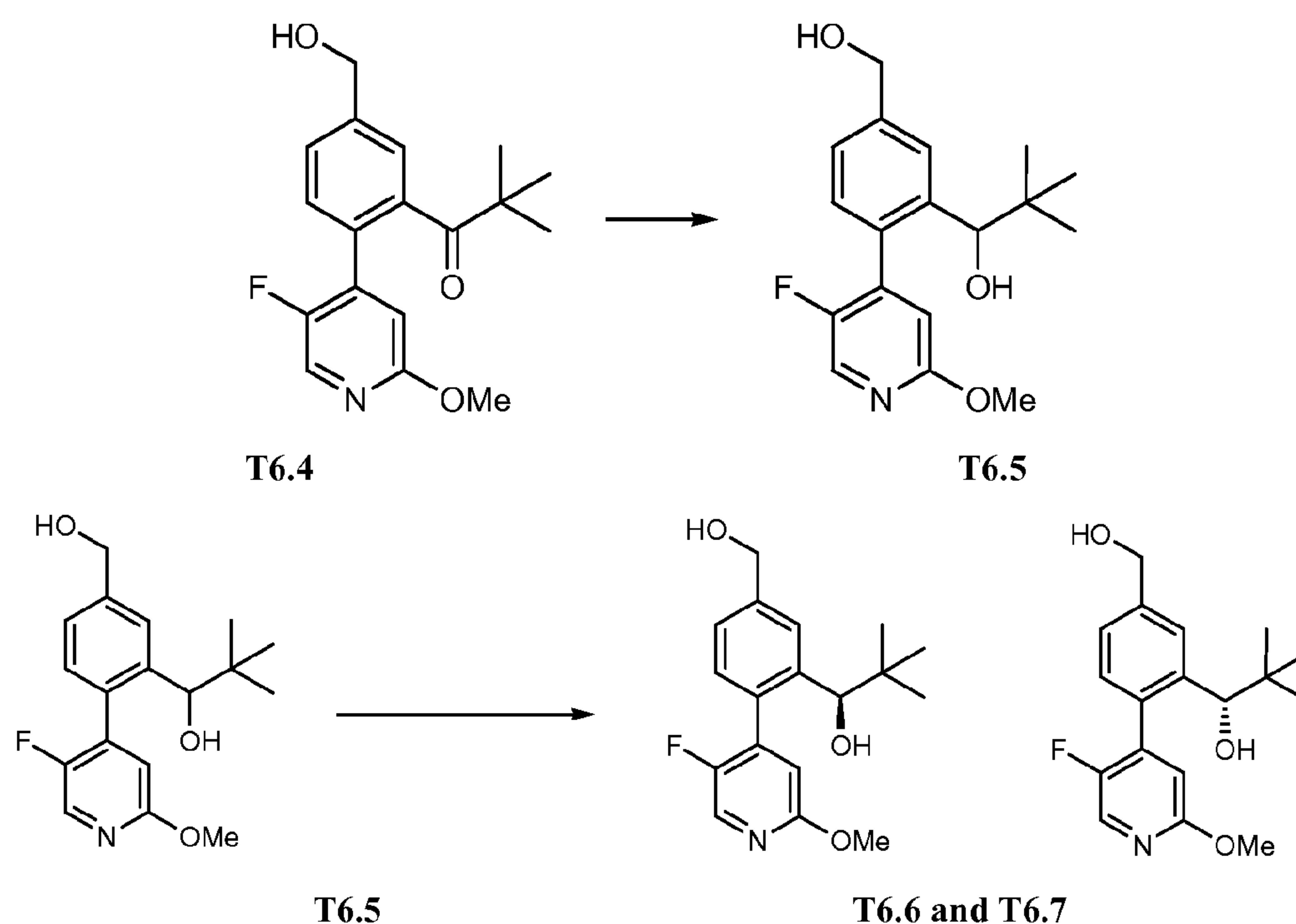


[0334] Methyl 2-(5-fluoro-2-(methoxy)-4-pyridinyl)-5-(hydroxymethyl)benzoate (T6.3). To a stirred solution of 4-(5-fluoro-2-methoxypyridin-4-yl)-3-(methoxycarbonyl)benzoic acid **T6.2** (0.416 g, 1 mmol) in THF (14 mL) at 0°C was added borane-THF (3 mL, 3 mmol, 1.0M). The reaction was warmed to 23°C and stirred for 46 hours. The reaction was then concentrated in vacuo, diluted with 1N HCl and extracted three times with EtOAc. The organic layers were combined, dried over anhydrous MgSO_4 , and filtered. The organic solvent was removed under reduced pressure, and the product was purified on silica gel (0-40% EtOAc in hexanes) to yield **T6.3** as a colorless solid (0.307 g, 77% yield).



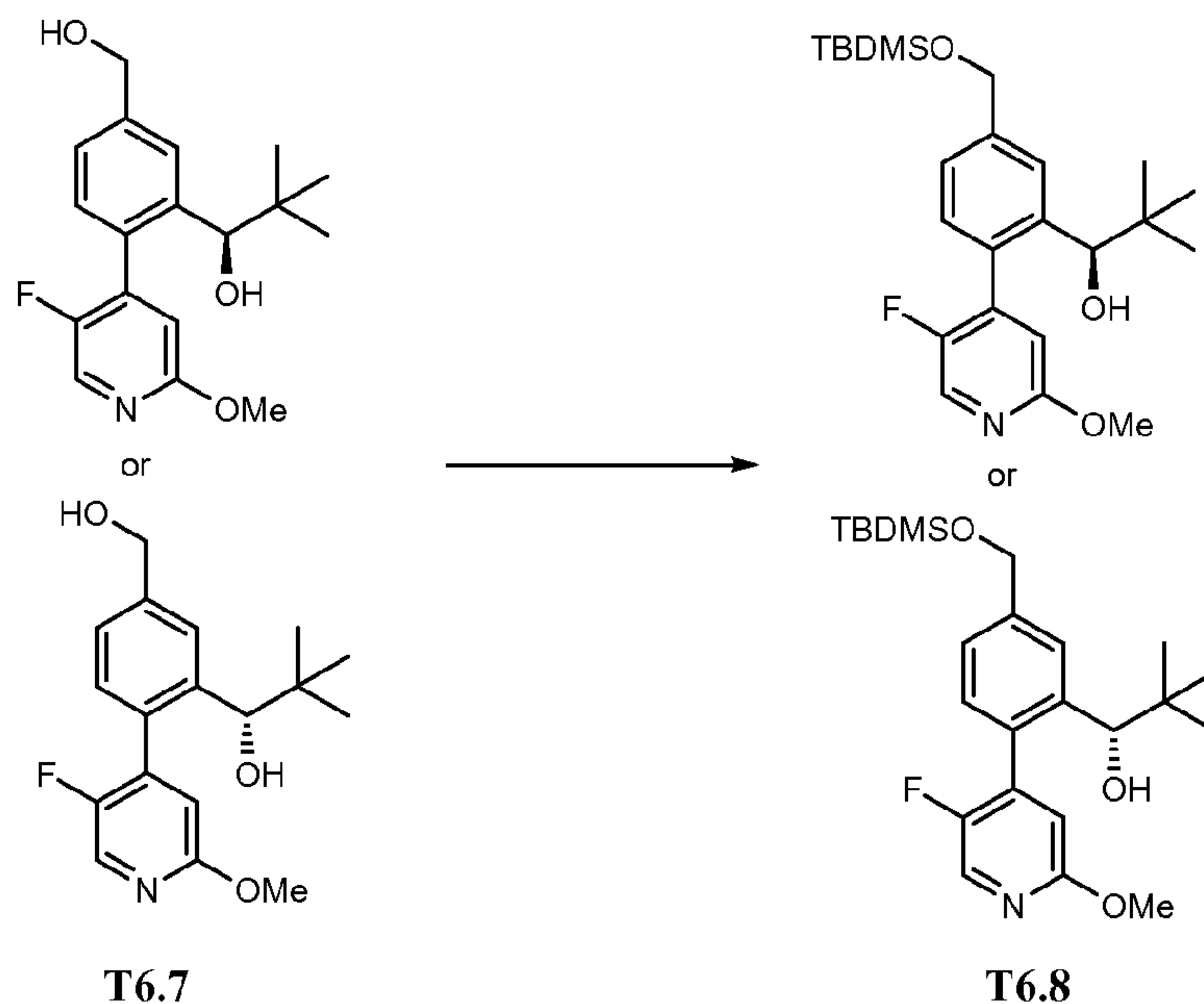
[0335] 1-(2-(5-Fluoro-2-(methoxy)-4-pyridinyl)-5-(hydroxymethyl)phenyl)-2,2-dimethyl-1-propanone (T6.4). To a stirred solution of methyl 2-(5-fluoro-2-methoxypyridin-4-yl)-5-(hydroxymethyl)benzoate **T6.3** (0.307 g, 1 mmol) in THF (11 mL) at -78°C was added tert-butyl lithium (2 mL, 3 mmol). The resulting mixture was stirred for one hour. The reaction was then quenched with a

saturated solution of ammonium chloride and extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the organic solvent was removed under reduced pressure. The residue was then purified on silica gel (0-40% EtOAc in hexanes) to yield **T6.4** as a colorless solid (0.28 g, 84% yield).

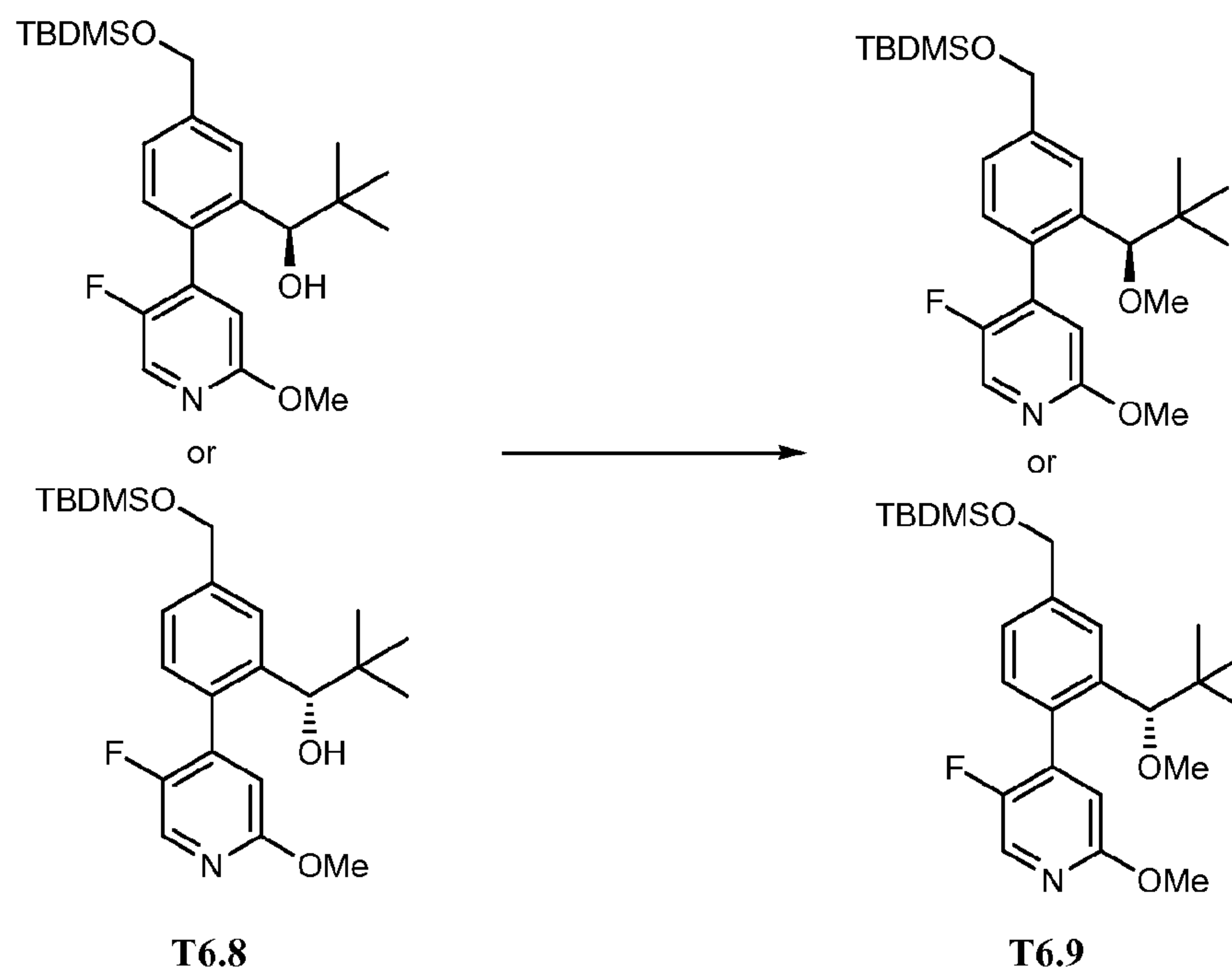


[0336] (1R)-1-(2-(5-Fluoro-2-methoxypyridin-4-yl)-5-(hydroxymethyl)phenyl)-2,2-dimethylpropan-1-ol or (1S)-1-(2-(5-fluoro-2-methoxypyridin-4-yl)-5-(hydroxymethyl)phenyl)-2,2-dimethylpropan-1-ol (T6.6 and T6.7). To a stirred solution of 1-(2-(5-fluoro-2-methoxypyridin-4-yl)-5-(hydroxymethyl)phenyl)-2,2-dimethylpropan-1-one **T6.4** (0.130 g, 0.4 mmol) in THF (2 mL) at 0°C was added LAH (0.6 mL, 0.6 mmol, 1.0M). The resulting mixture was stirred for 3 hours. Next, 1N NaOH(aq) was added to quench the reaction mixture. The reaction was extracted three times with EtOAc. The organic layers were combined, dried over MgSO₄, filtered, and the organic solvent was removed under reduced pressure. The residue was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T6.5** as a colorless solid (0.120 g, 92% yield). Chiral separation of **T6.5** was accomplished on a CHIRALCEL® OD column (4%IPA in hexane) to provide **T6.6** (peak one-23.87 mins) and **T6.7** (peak two-29.04 mins). Both enantiomers were used to synthesize example

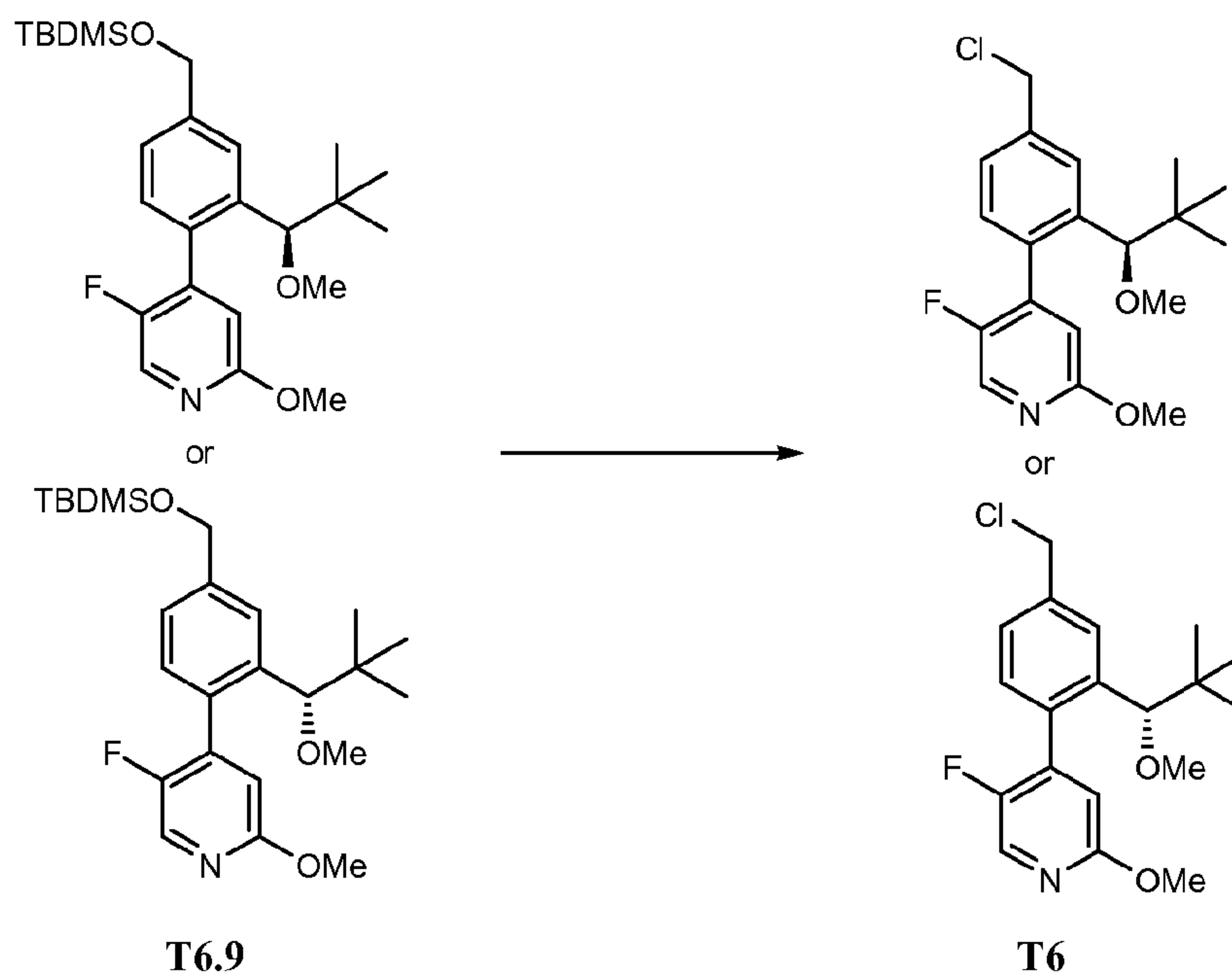
compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.¹



[0337] (1R)-1-(5-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)-2,2-dimethyl-1-propanol or (1S)-1-(5-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)-2,2-dimethyl-1-propanol (T6.8). To a stirred solution of T6.7 (0.050 g, 0.2 mmol) (from peak two from the chiral separation of T6.5) in DCM (2 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.03 mL, 0.2 mmol), followed by TEA (0.03 mL, 0.2 mmol) and DMAP (0.002 g, 0.02 mmol). The resulting mixture was stirred for 24 hours and then concentrated in vacuo. The reaction was extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ and filtered. The organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield T6.8 as a colorless oil (0.062 g, 91% yield).

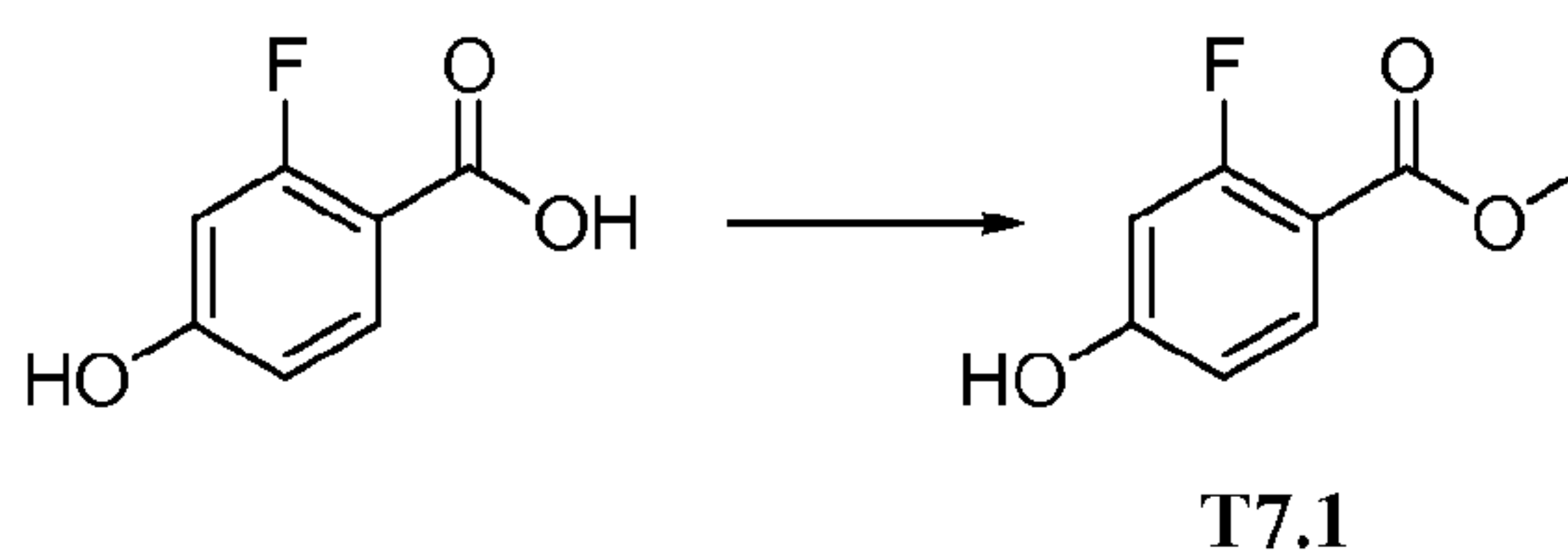


[0338] **4-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine or 4-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine (T6.9).** To a stirred solution of **T6.8** (0.062 g, 0.14 mmol) in DMF (1.4 mL) at 23°C was added iodomethane (0.018 mL, 0.29 mmol), followed by sodium hydride (0.0069 g, 0.29 mmol). The resulting mixture was stirred at 50°C for 15 hours and was then diluted with water and extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO₄, filtered, and the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-40% EtOAc in hexanes) to yield **T6.9** as a colorless oil (0.047 g, 73% yield).



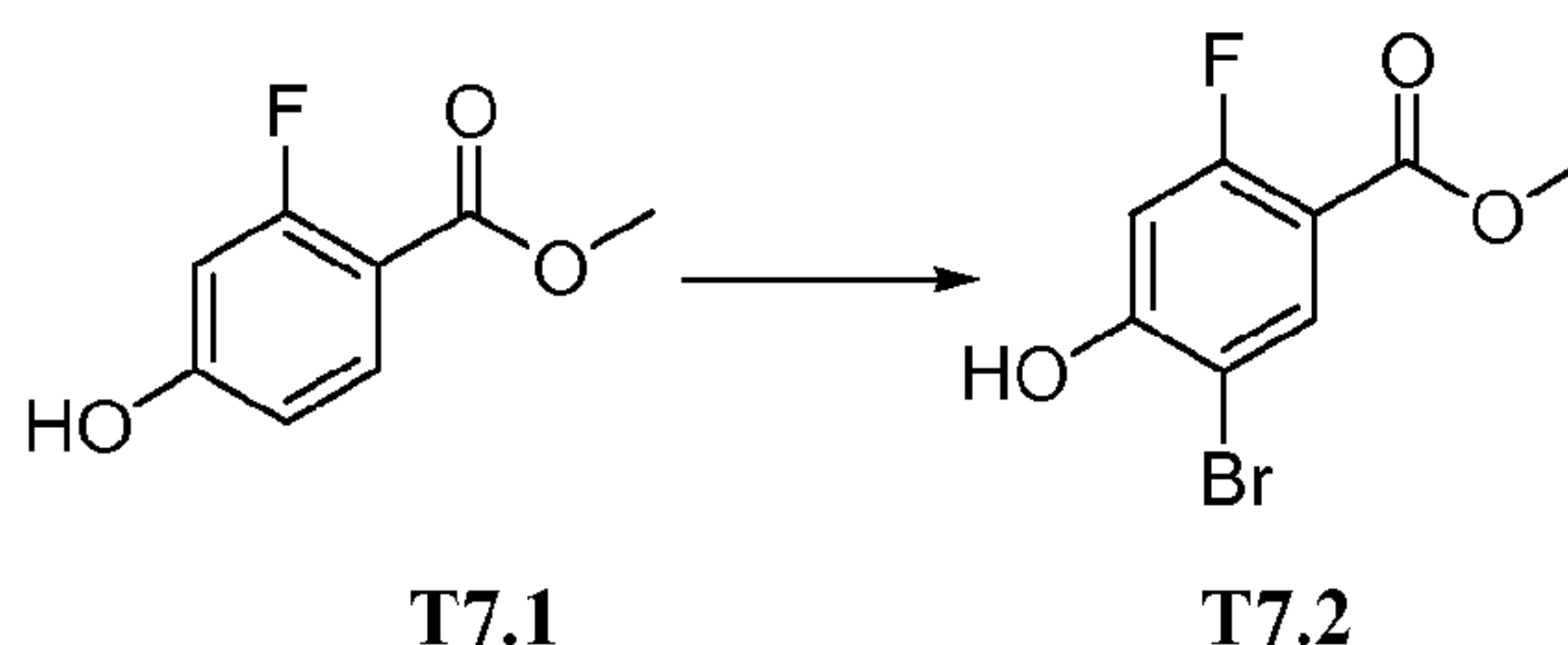
[0339] **4-(4-(Chloromethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine or 4-(4-(chloromethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine (T6).** To a stirred solution of T6.9 (0.047 g, 0.10 mmol) in DCM (1.0 mL) and DMF (0.0081 mL) at 0°C was added thionyl chloride (0.015 mL, 0.21 mmol). The mixture was stirred at room temperature for one hour and then the reaction mixture was concentrated in vacuo. The product thus obtained was purified on silica gel (0-10% EtOAc in hexanes) to yield T6 as a colorless solid (0.032 g, 87% yield).

[0340] **Intermediate T7**

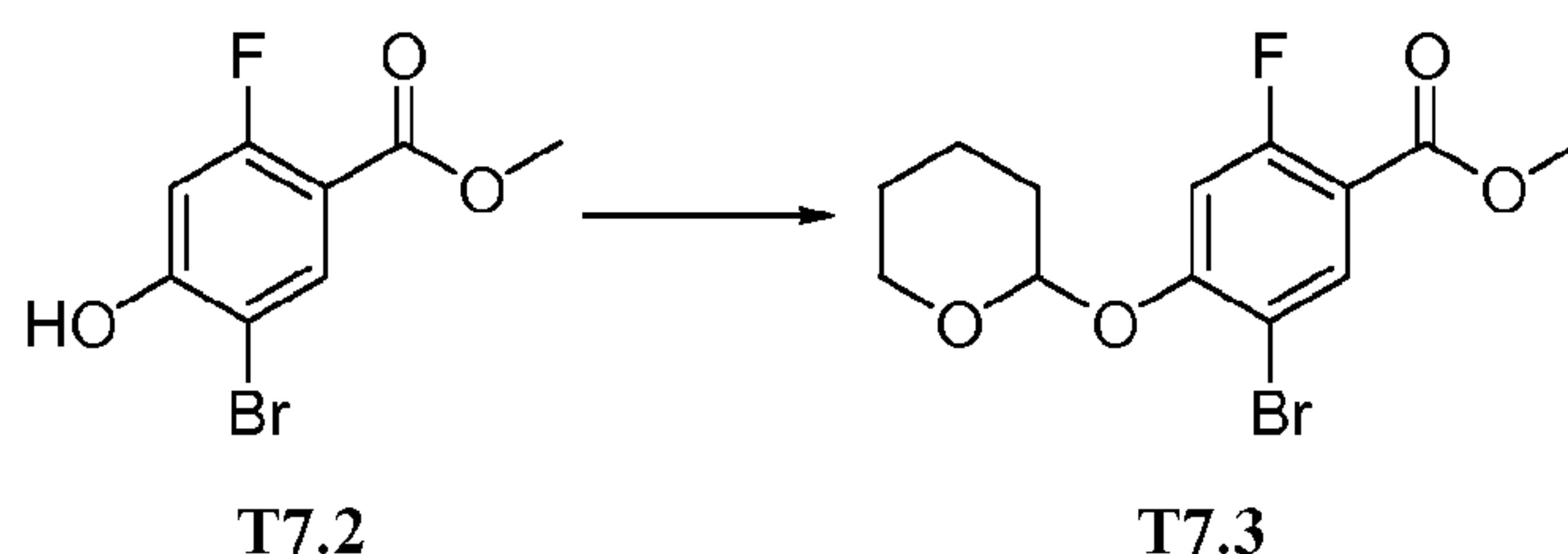


[0341] **Methyl 2-fluoro-4-hydroxybenzoate (T7.1).** To a round bottom containing 2-fluoro-4-hydroxybenzoic acid (Commercially available from TCI America) (5.34 g, 34.19 mmol) was added a cold solution of MeOH (50 mL) and sulfuric acid (2.0 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed and the residue was diluted with diethyl ether. The organic phase was washed carefully two times with saturated aqueous NaHCO₃, once with brine, and

then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to yield **T7.1** as a white solid (5.82, 85% yield). ^1H NMR (400 MHz, DMSO- d_6) 10.79 (1 H, s), 7.75 (1 H, t, $J=8.8$ Hz), 6.69 (1 H, dd, $J=8.6, 2.3$ Hz), 6.62 (1 H, dd, $J=13.1, 2.2$ Hz), 3.78 (3 H, s).

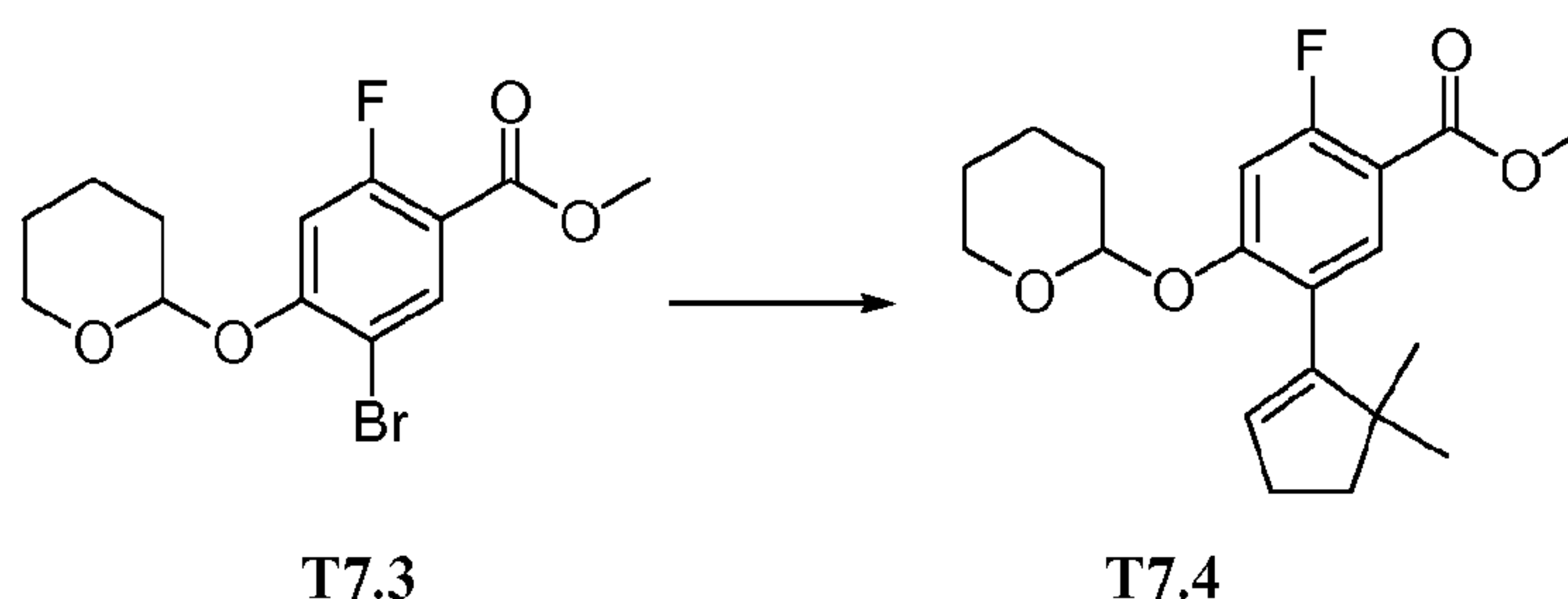


[0342] Methyl 5-bromo-2-fluoro-4-hydroxybenzoate (T7.2). To a solution of **T7.1** (2.03 g, 11.9 mmol) in AcOH (65 mL) was added a pre-mixed solution of bromine (0.67 mL, 13.1 mmol) in AcOH (10 mL). The mixture was stirred at 45°C and monitored with TLC and LC-MS. After 18 hours, the reaction mixture was concentrated under reduced pressure. Brine was added to the residue, and the mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and then concentrated to provide **T7.2** as a white solid (2.12 g, 71 % yield). ^1H NMR (400 MHz, CDCl_3) 8.13 (1 H, d, $J=7.4$ Hz), 6.82 (1 H, d, $J=11.3$ Hz), 6.04 (1 H, s), 3.92 (3 H, s).

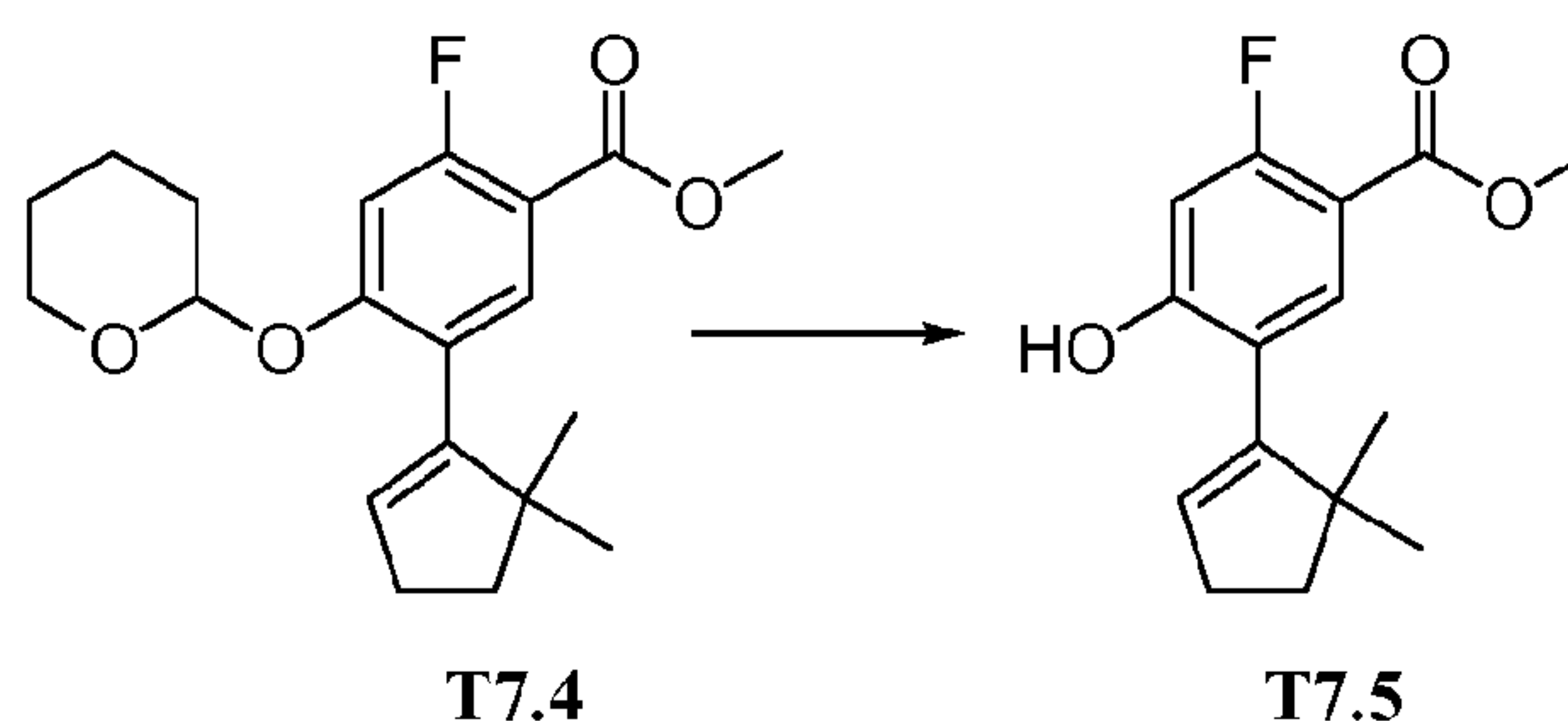


[0343] Methyl 5-bromo-2-fluoro-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (T7.3). To a round bottom containing **T7.2** (13.15 g, 52.8 mmol) in dry DCM (90 mL) was added 3,4-dihydro-2H-pyran (10 mL, 110 mmol) followed by PPTS (0.13 g, 0.53 mmol). The reaction mixture was heated at a gentle reflux (50°C) and monitored with TLC and LC-MS. After 24 hours, the reaction was concentrated under reduced pressure and then diluted with MeOH. After concentration, the residue was heated in a round bottom flask containing MeOH on a rotary evaporator (without vacuum) at 40 °C. After about 30 minutes, the solution was concentrated to a volume of about 5 mL. After cooling to room temperature, the white solid was filtered and rinsed once with MeOH to

yield **T7.3** (13.35 g, 76 % yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.25 (1 H, m), 6.96 (1 H, d, $J=12.5$ Hz), 5.56 (1 H, m), 3.91 (3 H, s), 3.79 (1 H, td, $J=11.1, 2.5$ Hz), 3.65 (1 H, d, $J=10.6$ Hz), 2.23 (2 H, m), 1.96 (3 H, m), 1.68 (1 H, m).

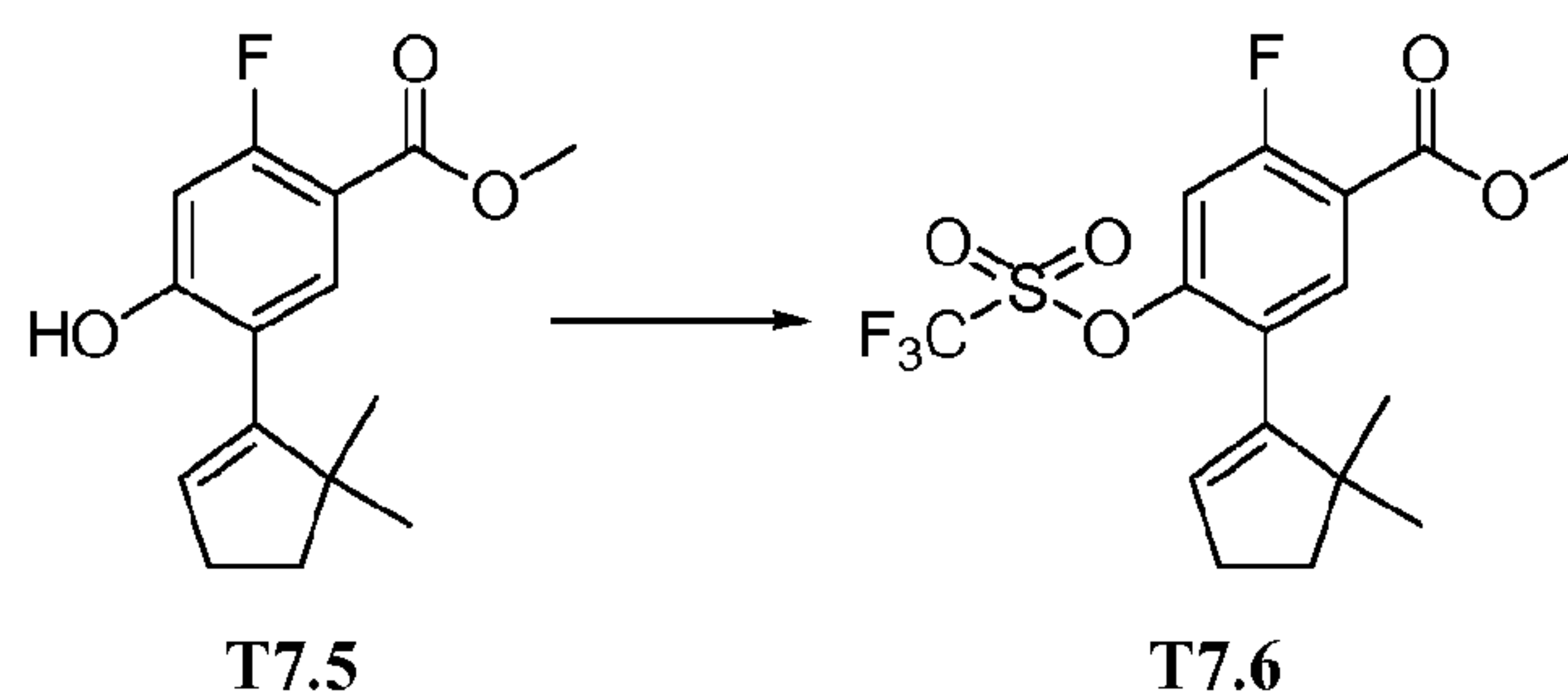


[0344] **Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (T7.4).** A stirred mixture of **T7.3** (10.33 g, 31.0 mmol), ground S-Phos (2.55 g, 6.21 mmol), palladium acetate (0.70 g, 3.11 mmol), and potassium phosphate, tribasic (16.49 g, 77.7 mmol) in DMF (75 mL) and water (4 mL) was purged three times with argon and placed under vacuum three times. 2-(5,5-Dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**T2.2**) (8.96 g, 40.4 mmol) was added via syringe, and then the mixture was heated to 75°C. After 21 hours, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The combined organic layers were washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to yield **T7.4** (5.65 g, 52 % yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.63 (1 H, d, $J=8.6$ Hz), 6.93 (1 H, d, $J=13.3$ Hz), 5.55 (1 H, t, $J=2.3$ Hz), 5.43 (1 H, t, $J=2.7$ Hz), 3.90 (3 H, s), 3.82 (1 H, m), 3.67 (1 H, m), 2.41 (2 H, td, $J=7.0, 2.3$ Hz), 1.97 (5 H, m), 1.79 (3 H, m), 1.07 (6 H, d, $J=13.7$ Hz).

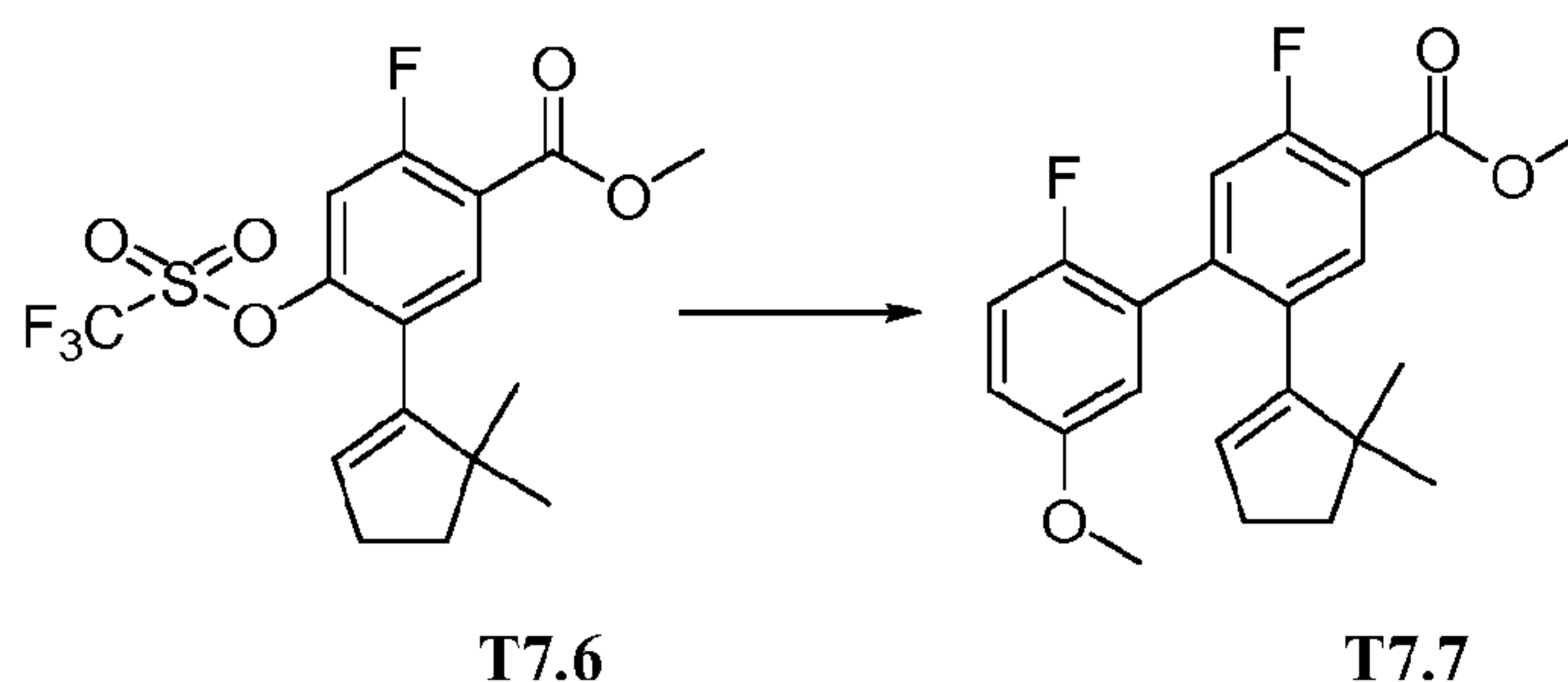


[0345] **Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-hydroxybenzoate (T7.5).** To a stirred mixture of **T7.4** (5.65 g, 16.2 mmol) in MeOH (60 mL) was added

PPTS (0.42 g, 1.69 mmol). The mixture was heated to 50°C and monitored with TLC and LCMS. After 19 hours, the organic solvent was removed under reduced pressure, and the residue was purified on silica gel (0-15% EtOAc in hexanes) to yield **T7.5** as a white solid (3.47g, 81% yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.69 (1 H, d, J=8.3 Hz), 6.71 (1 H, d, J=12.0 Hz), 5.93 (1 H, d, J=1.7 Hz), 5.80 (1 H, t, J=2.4 Hz), 3.90 (3 H, s), 2.54 (2 H, m), 1.93 (2 H, t, J=7.1 Hz), 1.11 (6 H, s).

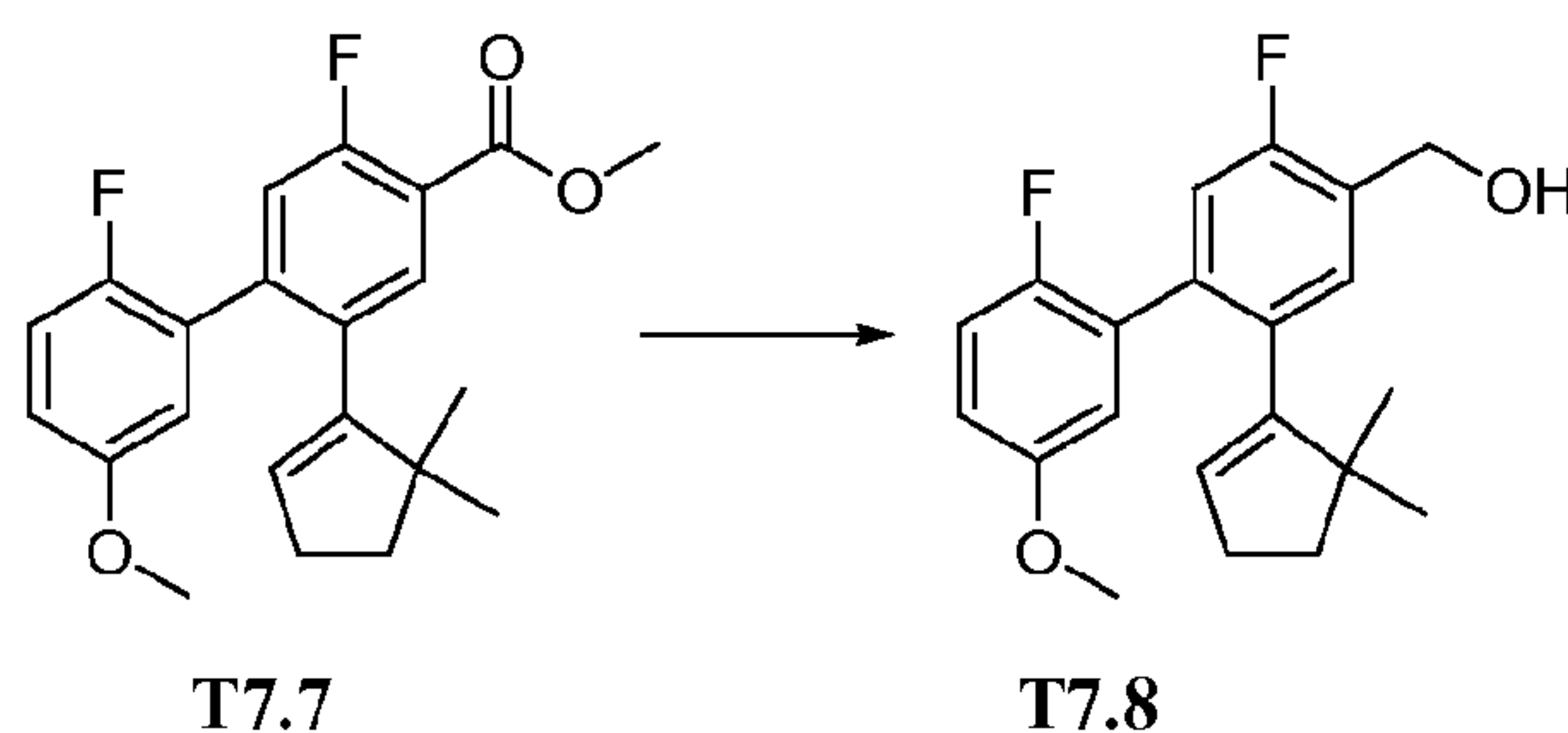


[0346] **Methyl 5-(5,5-dimethylcyclopent-1-en-1-yl)-2-fluoro-4-(trifluoromethanesulfonyloxy)benzoate (T7.6).** To a stirred solution of **T7.5** (0.80 g, 3.02 mmol) in dry DCM (15 mL) was added TEA (1.0 mL, 7.19 mmol) and DMAP (38.1 mg, 0.312 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonylimide) (1.30 g, 3.64 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 19 hours, the organic solvent was removed under reduced pressure, and the residue was then purified with silica gel chromatography using 0-10% EtOAc in hexanes to yield **T7.6** as a colorless oil (1.05 g, 88% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.84 (1 H, d, J=7.8 Hz), 7.13 (1 H, d, J=10.2 Hz), 5.79 (1 H, t, J=2.3 Hz), 3.96 (3 H, s), 2.47 (2 H, td, J=7.0, 2.3 Hz), 1.91 (2 H, t, J=7.0 Hz), 1.08 (6 H, s).

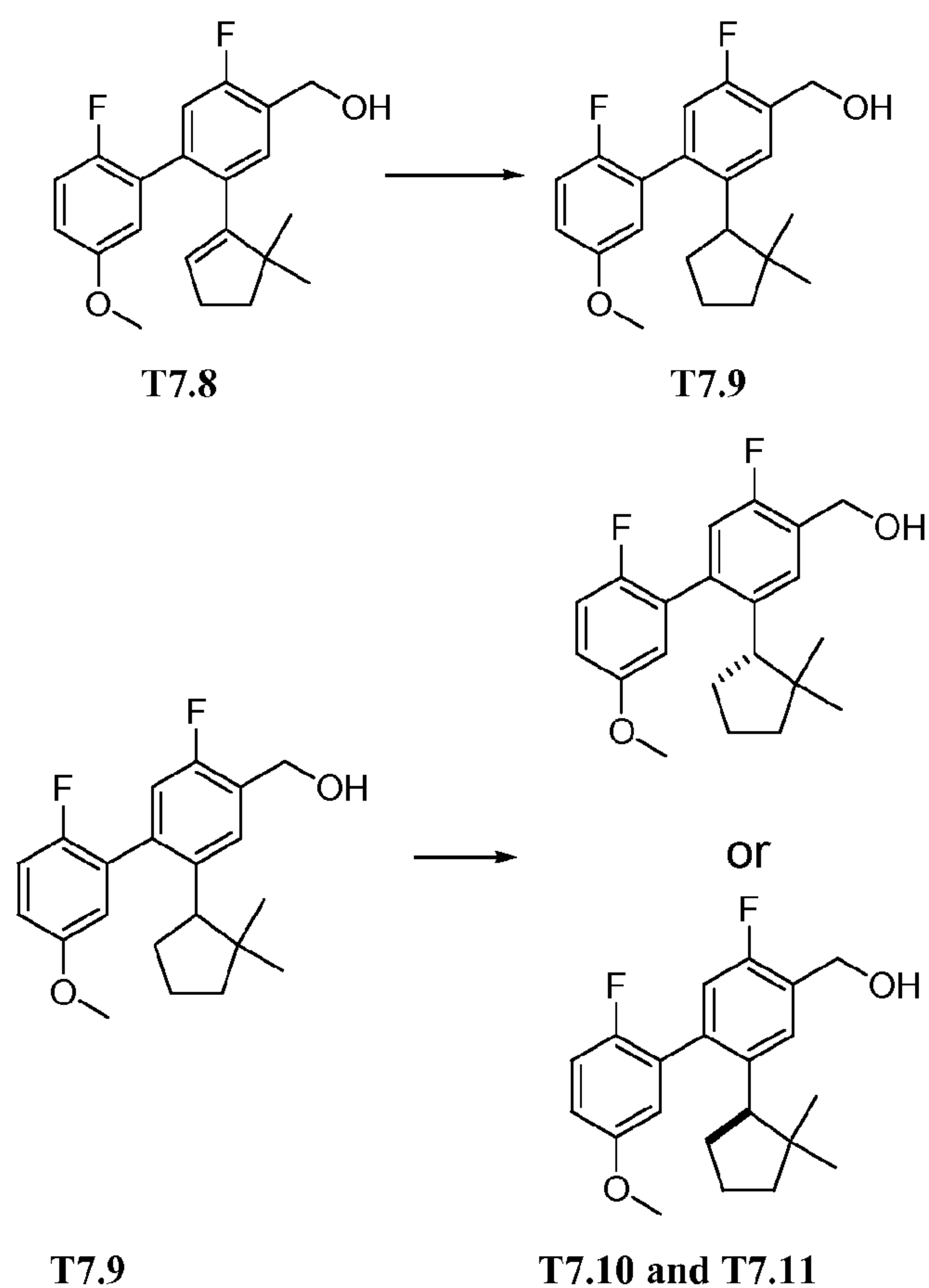


[0347] **Methyl 2-(5-(5,5-dimethylcyclopent-1-en-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T7.7).** To a stirred solution of **T7.6** (1.05 g, 2.65 mmol) in DMF (5 mL) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid

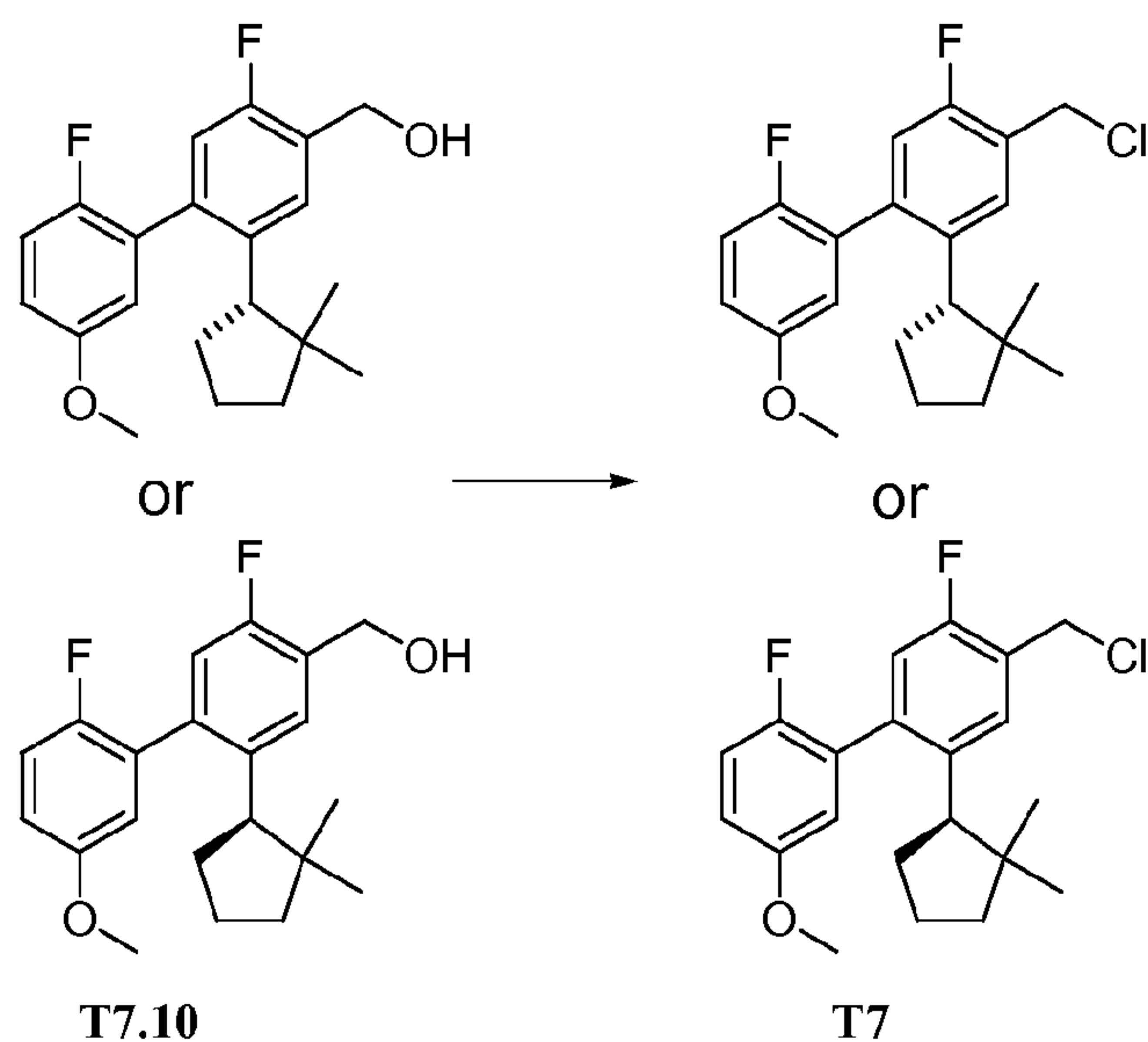
(0.90 g, 5.32 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and potassium carbonate (1.10 g, 7.96 mmol) followed by tetrakis(triphenylphosphine)palladium (0.31 g, 0.27 mmol). The mixture was heated to 90 °C. After 17 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to give **T7.7** as a clear oil that was used without further purification (0.92 g, 93 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.79 (1 H, d, J=7.4 Hz), 7.13 (1 H, d, J=11.3 Hz), 6.99 (1 H, t, J=9.0 Hz), 6.84 (1 H, dt, J=8.7, 3.7 Hz), 6.78 (1 H, dd, J=5.9, 3.1 Hz), 5.55 (1 H, s), 3.96 (3 H, s), 3.79 (3 H, s), 2.27 (2 H, td, J=7.1, 2.5 Hz), 1.67 (2 H, t, J=7.0 Hz), 0.84 (6 H, s).



[0348] (2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T7.8). To a cooled solution of **T7.7** (0.92 g, 2.47 mmol) in dry THF (15 mL) at 0°C was added LAH (1.0 M in THF)(5.0 mL, 5.0 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After combining the organic layers, drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T7.8** as a colorless oil (0.70 g, 82 % yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.30 (1 H, m), 7.05 (1 H, dd, J=10.6, 1.1 Hz), 6.97 (1 H, t, J=8.9 Hz), 6.83 (2 H, m), 5.52 (1 H, td, J=2.4, 0.9 Hz), 4.81 (2 H, s), 3.76 (3 H, s), 2.25 (2 H, td, J=7.1, 2.4 Hz), 1.76 (1 H, br. s.), 1.69(2 H, m), 0.85 (6 H, s).

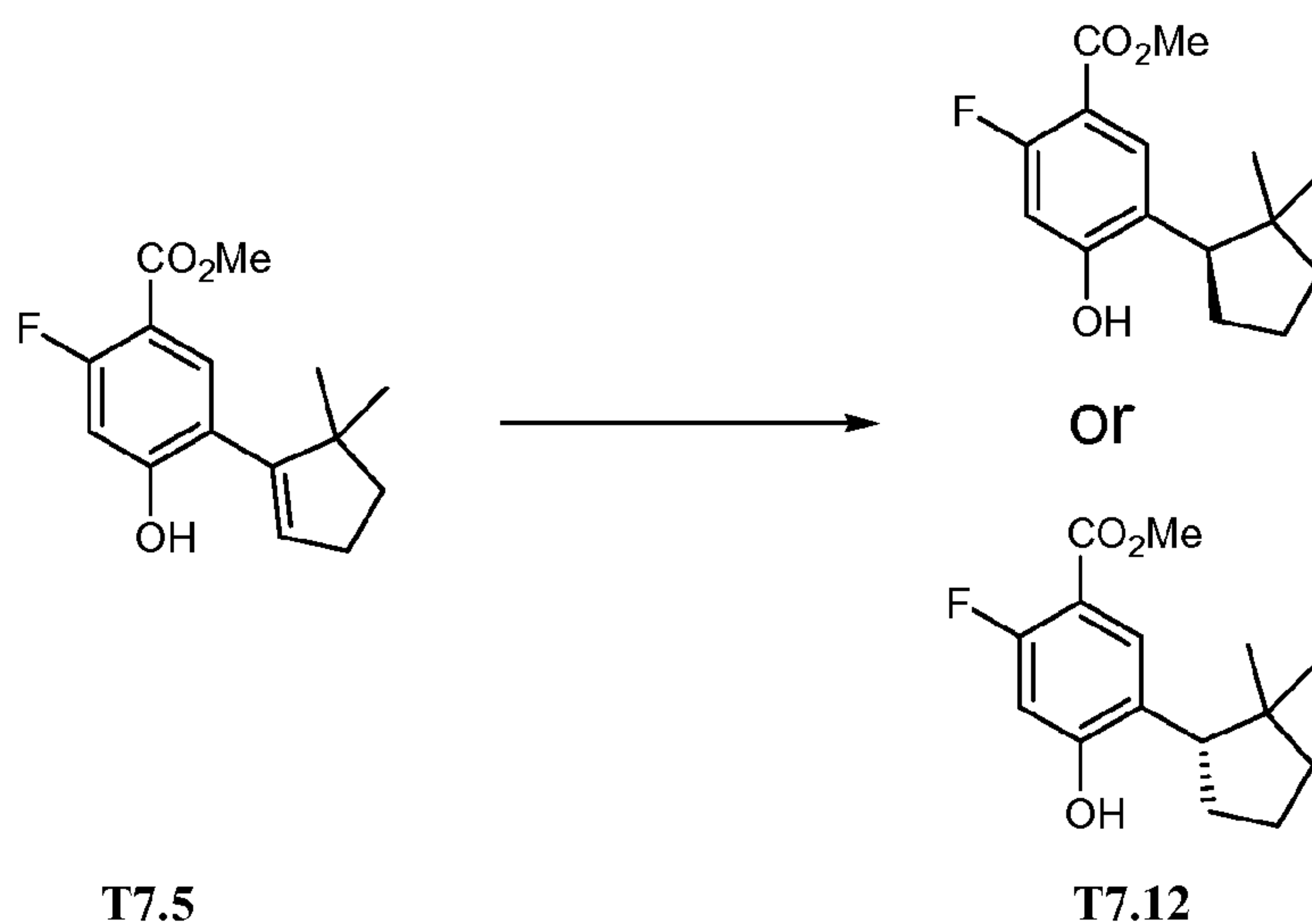


[0349] **(2-(2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T7.9).** To a dry flask containing T7.8 (0.70 g, 2.03 mmol) in dry MeOH (5 mL) and EtOAc (3 mL) was added Pd, 10 wt. % on activated carbon (77.2 mg). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. After 4.5 hours, the mixture was filtered through Celite® filter aid. After concentration, the residue was identified as T7.9 as a mixture of enantiomers and rotamers (0.31 g, 45 % yield). Chiral separation of T7.9 was accomplished on a CHIRALCEL® OJ column (2% IPA in hexane) to provide T7.10 (peak 1) and T7.11 (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.

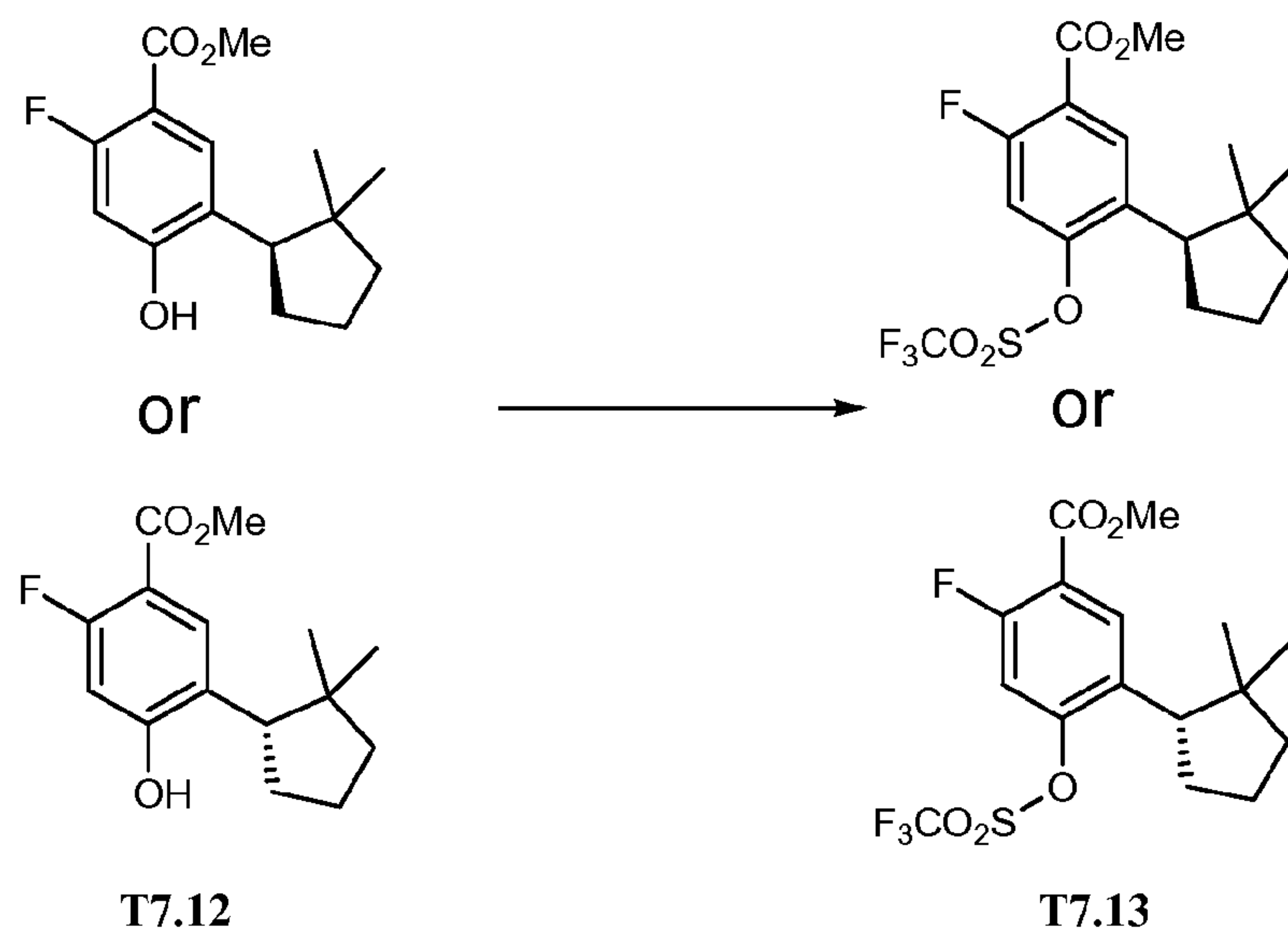


[0350] **4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl (T7).** To a solution of **T7.10** (0.71 g, 2.05 mmol) (derived from peak one from the chiral separation of **T7.9**) in dry DCM (23 mL) and dry DMF (0.18 mL) was added thionyl chloride (0.3 mL, 4.1 mmol) dropwise at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to yield **T7** as a colorless oil (0.73 g, 97 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.46 (1 H, m), 7.11 (3 H, m), 6.75 (1H, m), 4.78 (2 H, m), 3.80 (3 H, s), 2.91 (1 H, m), 2.20 (2 H, m), 1.87 (2 H, m), 1.59 (1 H, m), 1.43 (1 H, m), 0.77 (3 H, m), 0.64 (3 H, m).

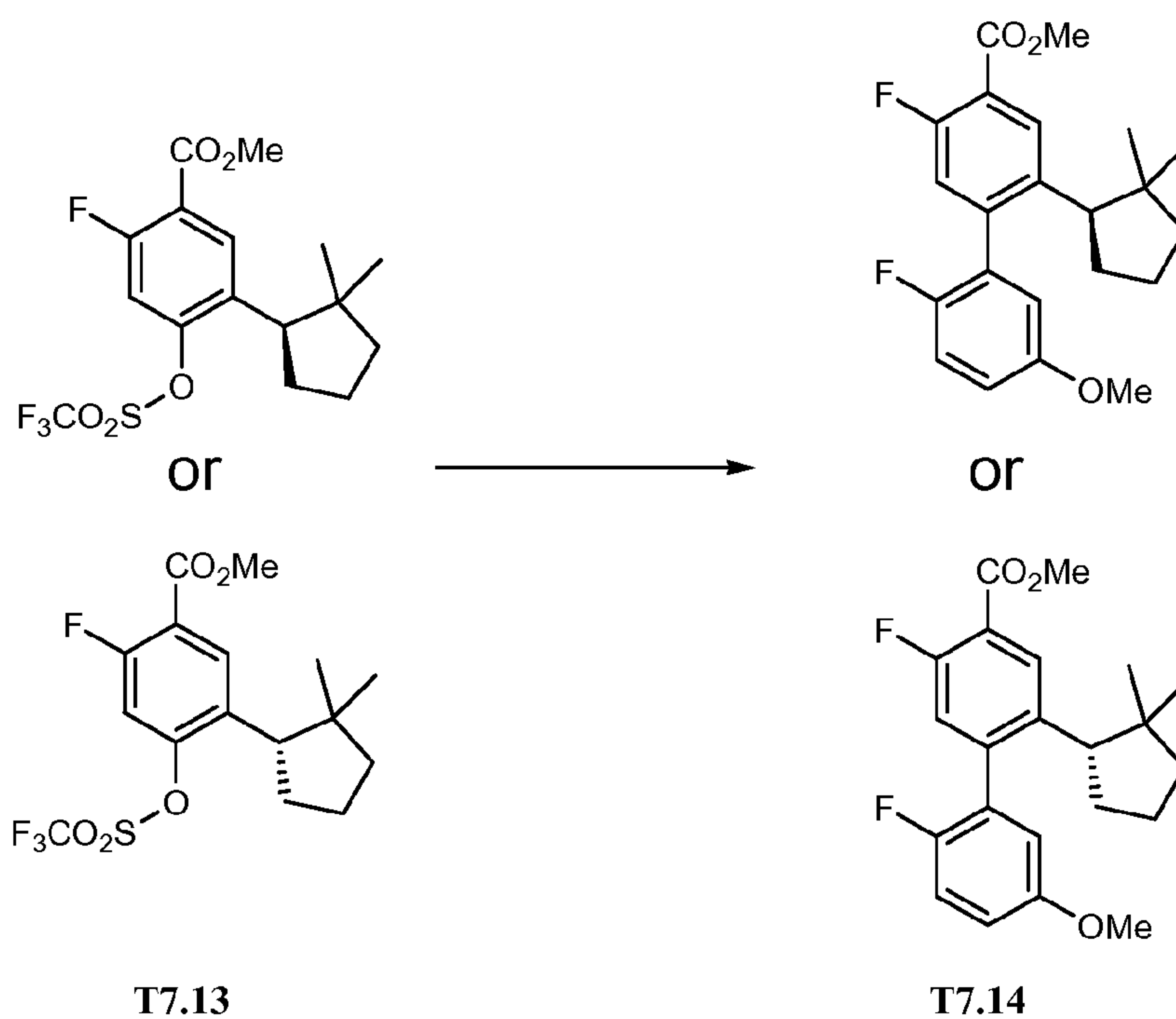
[0351] **Asymmetric synthesis of T7.** The following procedures were used to synthesize **T7.10** using a highly enantioselective procedure to hydrogenate **T7.5** to form **T7.11**.



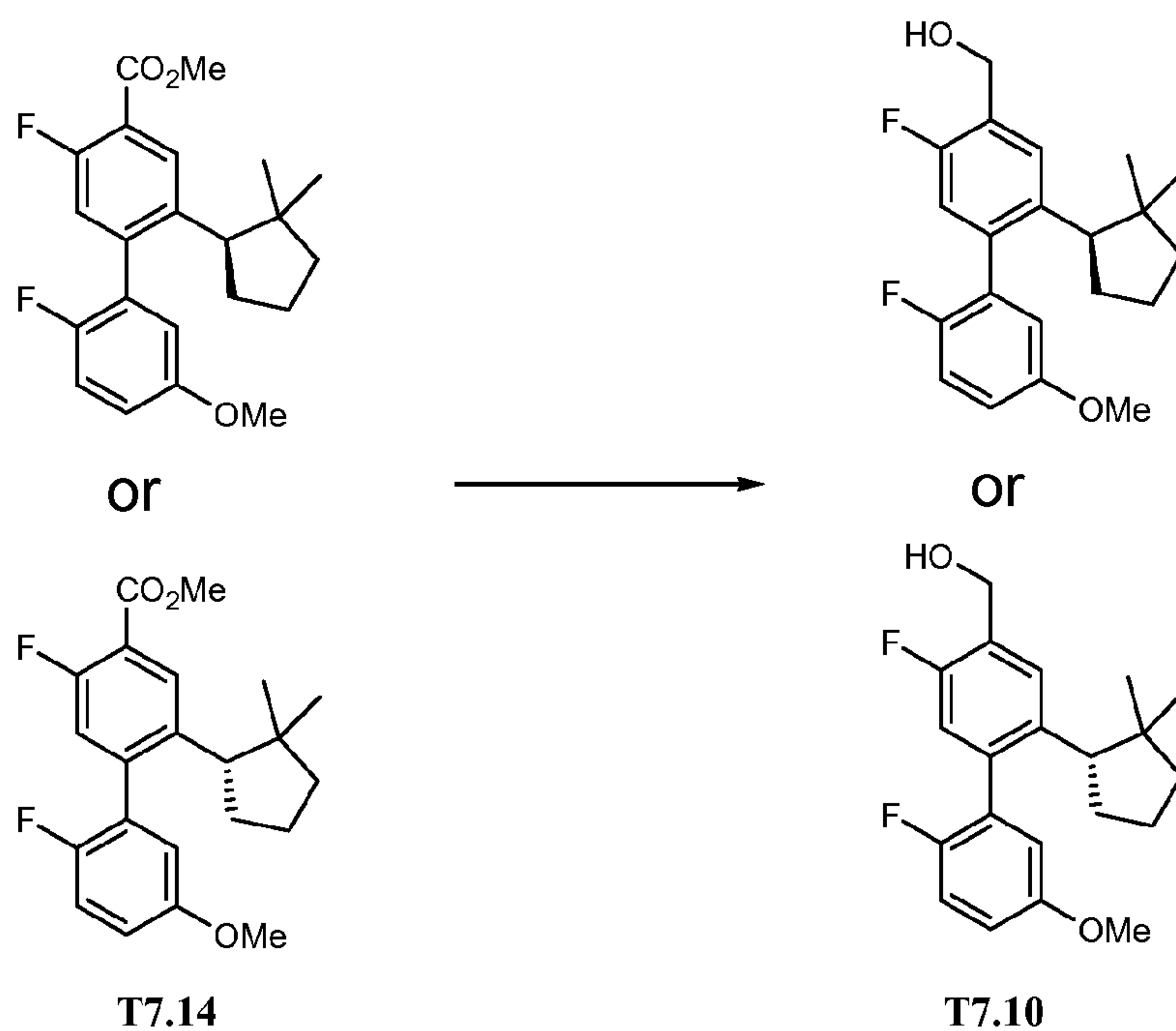
[0352] (R)-Methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-hydroxybenzoate or (S)-methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-hydroxybenzoate (T7.12). A mixture of Rh(COD)₂BF₄ (Stern Chemical, 35138-22-8, 36.95 mg, 0.091 mmol) and (R)-1-[(S)-2-(R)-(Ditertbutylphosphino)ferrocenyl]ethyl-bis-(3,5-bis(trifluoromethyl)phenyl)phosphine (Solvias, SL-J210-1, 81.5 mg, 0.100 mmol) in THF (75 mL) was stirred under N₂ for 60 minutes and a dark red solution formed. To the resulting solution was added methyl 5-(5,5-dimethylcyclopent-1-en-1-yl)-2-fluoro-4-hydroxybenzoate **T7.5** (8.2g, 45.4 mmol) and TEA (10mol%, 0.63 mL, 4.54 mmol). The resulting mixture was flushed with H₂ (200 psi) three times and stirred at room temperature under 200 psi H₂ for 2 hours. The resulting mixture was passed through a short plug of silica gel, eluting with 1:1 hexane/EtOAc. The mixture was then concentrated affording the desired product **T7.12** as a white solid (83% yield (6.8 g), 99.3% ee).



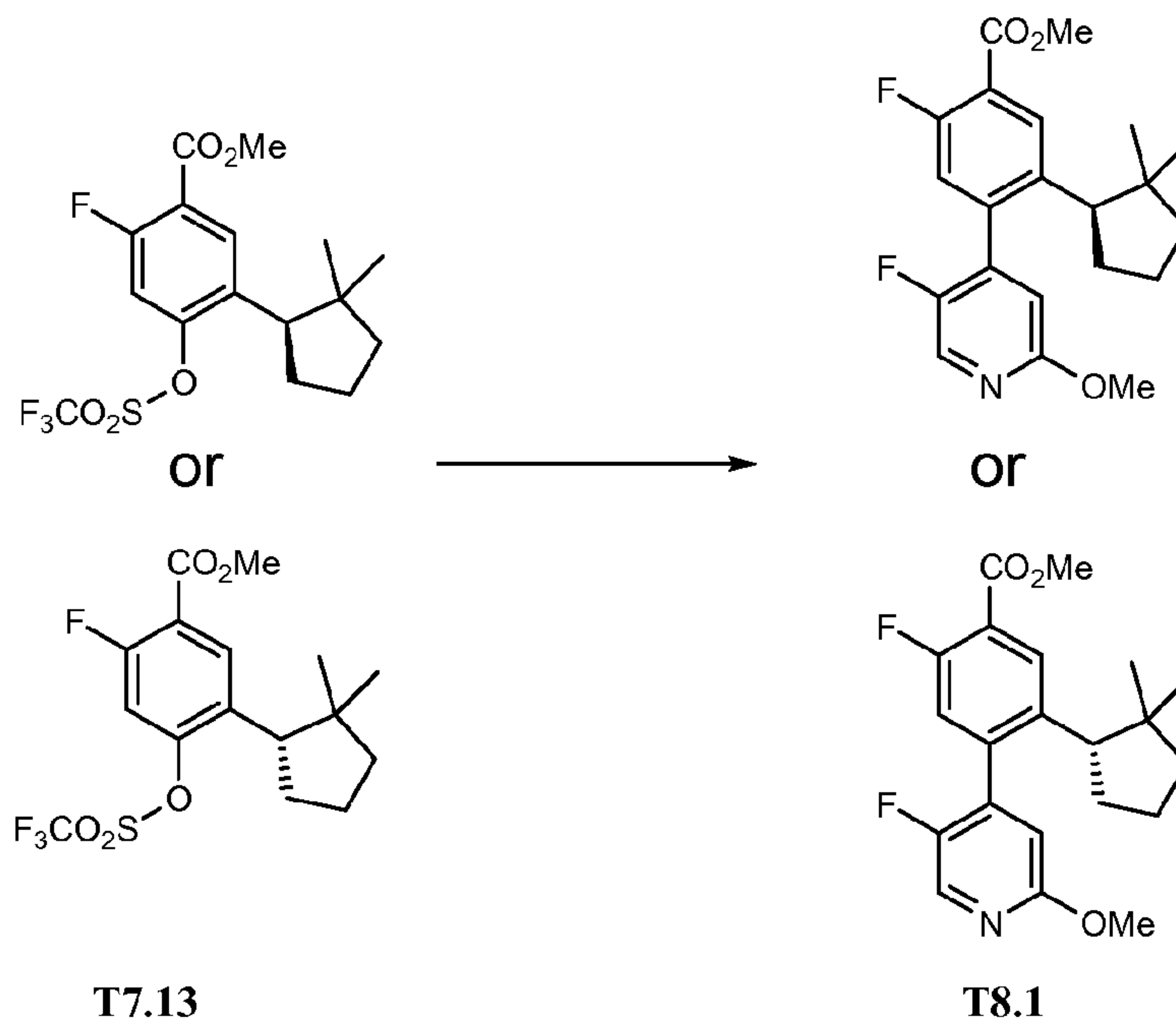
[0353] (R)-Methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate or (S)-methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate (T7.13). To a stirred solution of **T7.12** (4.02 g, 15.1 mmol) in dry DCM (50 mL) was added TEA (4.2 mL, 30.2 mmol) and DMAP (0.19 g, 1.52 mmol). After 20 minutes, N-phenyl-bis(trifluoromethanesulfonylimide) (5.94 g, 16.6 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 4 hours, the mixture was washed twice with brine and then dried over anhydrous MgSO_4 . After filtration and concentration, the residue was purified with silica gel chromatography (0-10% EtOAc in hexanes) to yield **T7.13** as a colorless oil (5.51, 92%). ^1H NMR (500 MHz, CDCl_3) δ ppm 7.97 (1 H, d, $J=7.8$ Hz), 7.14 (1 H, d, $J=10.0$ Hz), 3.96 (3 H, s), 3.13 (1 H, dd, $J=10.1, 8.2$ Hz), 2.14 (2 H, m), 1.96 (2 H, m), 1.70 (2 H, m), 1.00 (3 H, s), 0.69 (3 H, s).



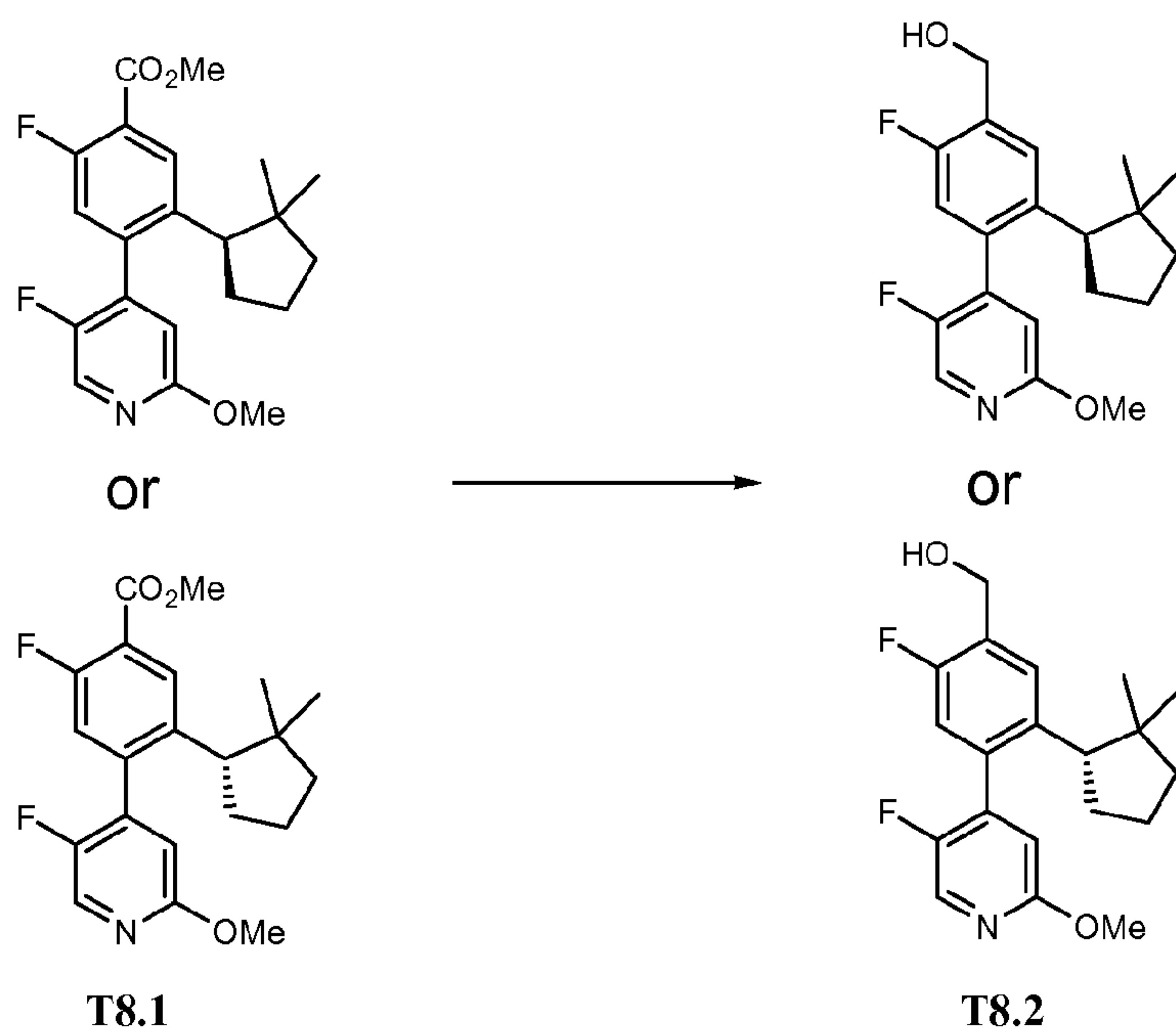
[0354] **Methyl 2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate or methyl 2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T7.14).** To a stirred solution of T7.13 (5.51 g, 13.8 mmol) in DMF (25 mL) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (4.71 g, 27.7 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and potassium carbonate (5.74 g, 41.6 mmol) followed by tetrakis(triphenylphosphine)palladium (1.60 g, 1.39 mmol). The mixture was heated to 90°C. After 3.5 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to yield T7.14 as an oil that solidified (5.11 g, 99%).



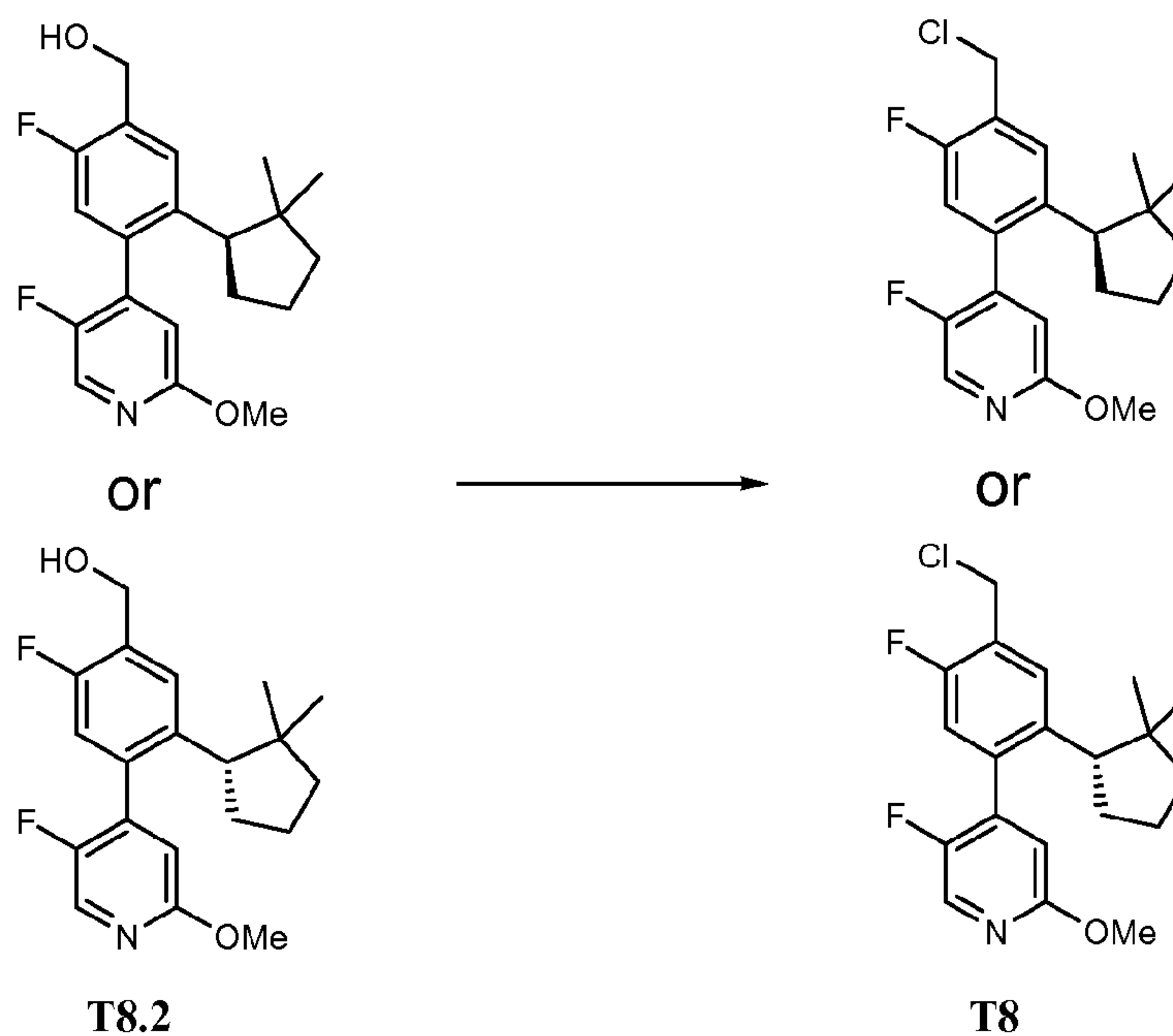
[0355] (2-((1R)-2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol or (2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**T7.10**). To a cooled solution of **T7.14** (5.11 g, 13.6 mmol) in dry THF (40 mL) at 0°C was added LAH (1.0 M in THF) (27.3 mL, 27.30 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by silica gel chromatography (0-25% EtOAc in hexanes) to yield **T7.10** as a colorless oil (3.94 g, 83 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.50 (1 H, m), 7.11 (3 H, m), 6.85 (1H, m), 4.81 (2 H, s), 3.80 (3 H, s), 2.92 (1H, m), 2.19 (2 H, m), 1.83 (1 H, m), 1.72 (1 H, m), 1.59 (2 H, m), 1.42 (1 H, m), 0.82 (3 H, m), 0.65 (3 H, m).

[0356] Intermediate T8

[0357] Methyl 5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methyloxy)-4-pyridinyl)benzoate or methyl 5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methyloxy)-4-pyridinyl)benzoate (T8.1). To a stirred solution of **T7.13** (0.7937 g, 1.992 mmol) in DMF (4 mL) at 23 °C was added 5-fluoro-2-methoxypyridine boronic acid (commercially available from Asymchem)(0.5115 g, 2.992 mmol) and potassium carbonate (0.8279 g, 5.990 mmol) followed by tetrakis(triphenylphosphine)palladium (0.2374 g, 0.2054 mmol). The mixture was heated to 90 °C. After 2 hours, LCMS-showed reaction was complete. The mixture was cooled to room temperature then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-20% EtOAc/hexane) to afford **T8.1** (601.2 mg, 80% yield). MS ESI (pos.) m/e: 376.1 (M+H)⁺.

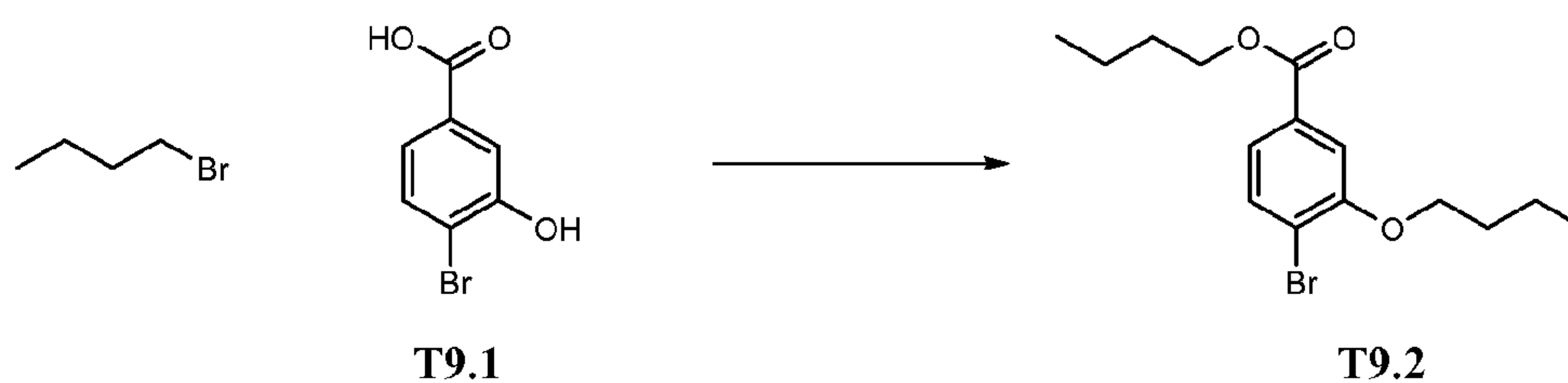


[0358] (5-((1S)-2,2-Dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methanol or (5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methanol (**T8.2**). To a cooled solution of **T8.1** (0.6012 g, 1.601 mmol) in dry THF (15 mL) at 0 °C was added LAH (1.0M in THF)(3.2 mL, 3.2 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified on silica gel (0%-20% EtOAc/hexane) to afford **T8.2** (449.9 mg, 81% yield). MS ESI (pos.) m/e: 348.1 (M+H)⁺.

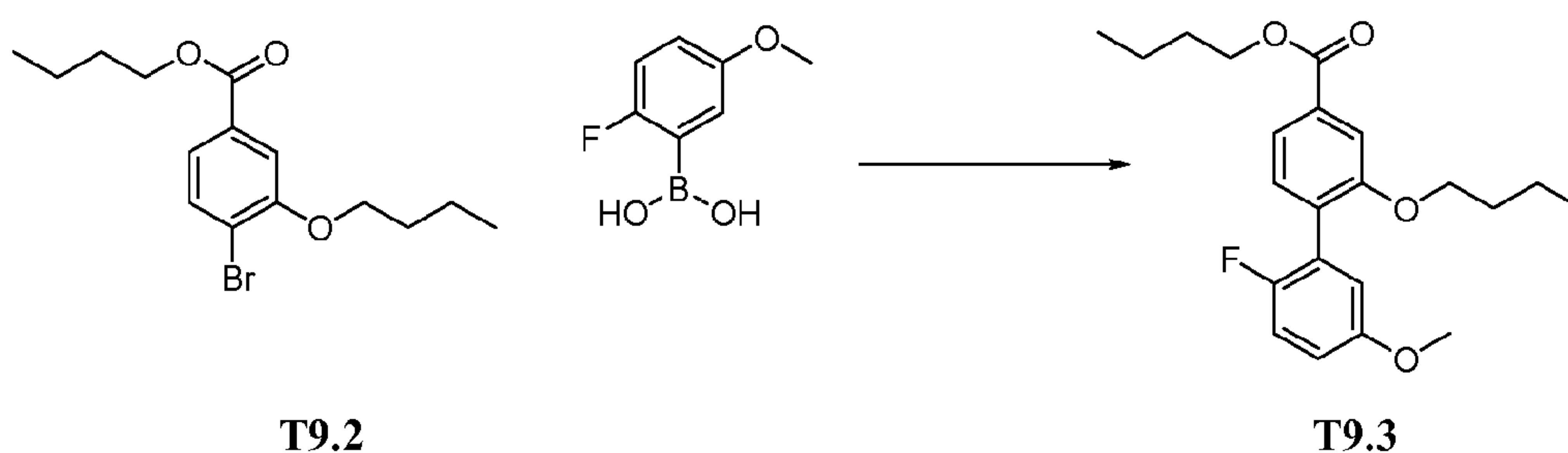


[0359] **4-(4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-5-fluorophenyl)-5-fluoro-2-(methyloxy)pyridine or 4-(4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-5-fluorophenyl)-5-fluoro-2-(methyloxy)pyridine (T8).** To a solution of **T8.2** (0.4463 g, 1.285 mmol) in dry DCM (17 mL) and dry DMF (0.12 mL) was added thionyl chloride (0.19 mL, 2.605 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 1.5 hours, the reaction was concentrated. The residue was diluted with EtOAc and washed once with saturated aqueous sodium bicarbonate solution and once with brine. The organic layer was subsequently dried over anhydrous sodium sulfate, filtered, concentrated, and purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford **T8** (446.9 mg, 95% yield). MS ESI (pos.) m/e: 366.1 (M+H)⁺.

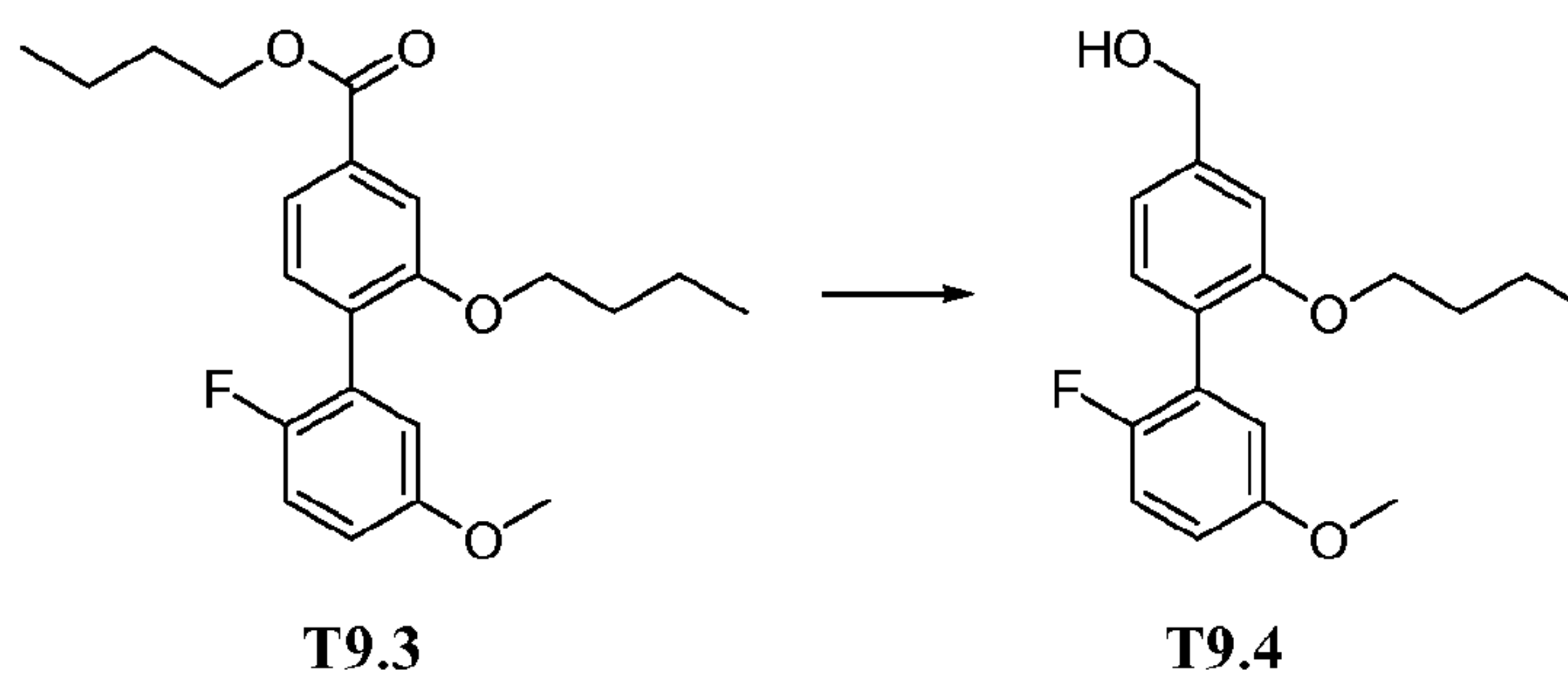
[0360] **Intermediate T9**



Butyl 4-bromo-3-(butyloxy)benzoate (T9.2). To a flask containing 4-bromo-3-hydroxybenzoic acid (T9.1)(available from Combi-Blocks Inc.)(2.40 g, 11.06 mmol) and Cs_2CO_3 (8.287 g, 25.44 mmol) in DMF (40 mL), was added 1-bromobutane (2.494 mL, 23.22 mmol), and the mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 , filtered, concentrated, and then purified by CombiFlash® column chromatography (0 to 20% EtOAc/ Hexanes) to provide **T9.2** (2.4326 g, 66.81% yield).

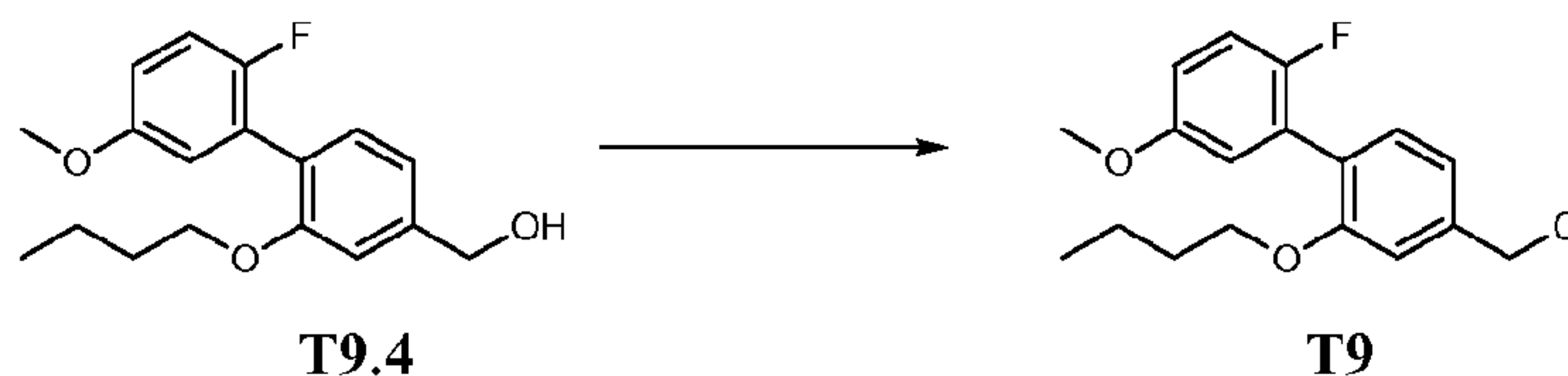


[0361] Butyl 2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T9.3). To a 2 dram vial charged with 2-fluoro-5-methoxyphenylboronic acid (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (2.323 g, 13.67 mmol), tetrakis(triphenylphosphine) palladium(0) (0.7897 g, 0.6834 mmol), cesium fluoride (0.8409 mL, 22.78 mmol), and **T9.2** (1.50 g, 4.556 mmol), was added DME (20 mL). The resulting mixture was heated at 90°C overnight. The reaction was allowed to cool and then filtered and concentrated. The residue was purified by CombiFlash® column chromatography (0 to 10% EtOAc/ hexanes) yielding **T9.3** (1.1530 g, 67.58% yield).



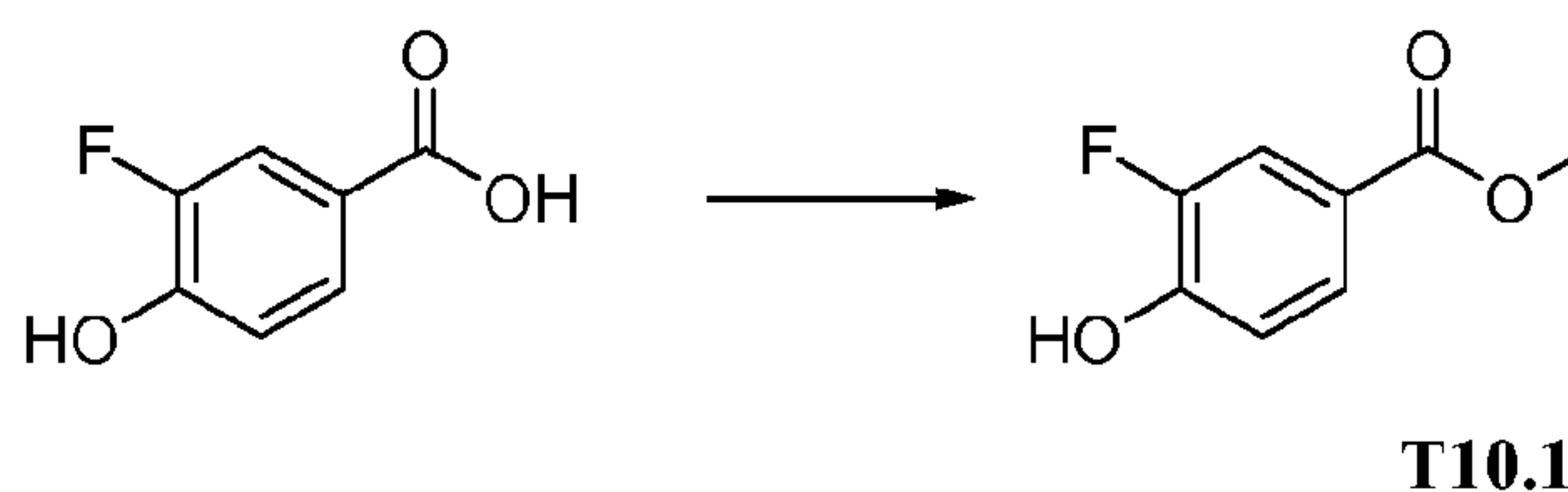
[0362] (2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T9.4). To a mixture of **T9.3** (1.1530 g, 3.079 mmol) and THF (10 mL) at 0°C was added LAH (1.0 M solution in THF (4.619 mL, 4.619 mmol)). The reaction was stirred for one

hour and then carefully diluted with water, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered, and concentrated to provide **T9.4** (0.9050 g, 96.57% yield).

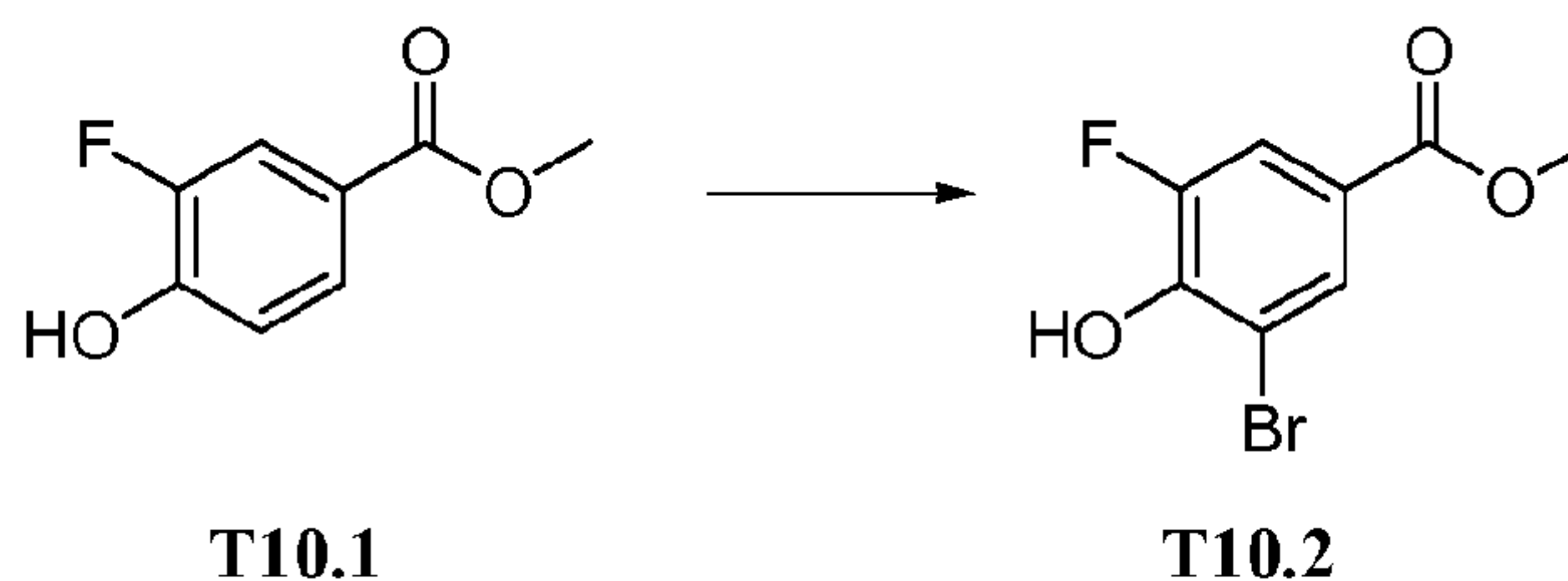


[0363] **2-(Butyloxy)-4-(chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T9).** To a stirred solution of **T9.4** (0.8800 g, 2.891 mmol) in DCM (15 mL) at 23 °C was added thionyl chloride (0.4218 mL, 5.783 mmol). The reaction mixture was stirred overnight and then concentrated and purified by CombiFlash® column chromatography (0 to 10% EtOAc/ Hexanes) to provide **T9** (0.7980 g, 85.50% yield).

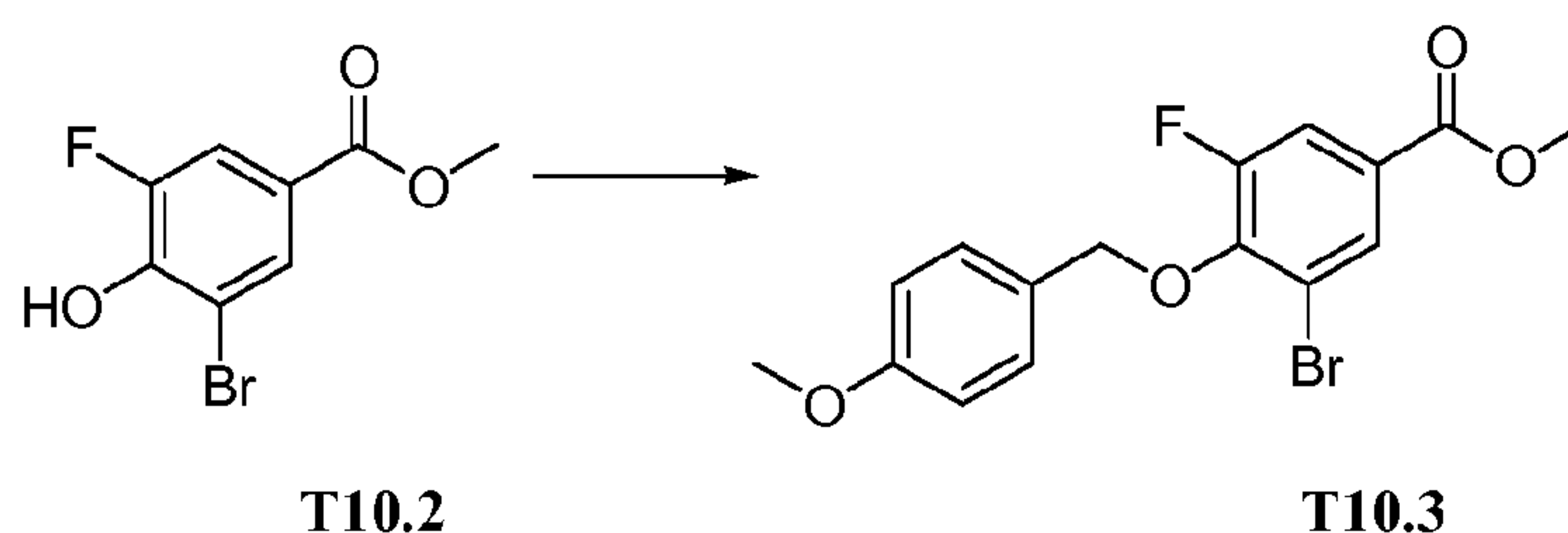
[0364] **Intermediate T10**



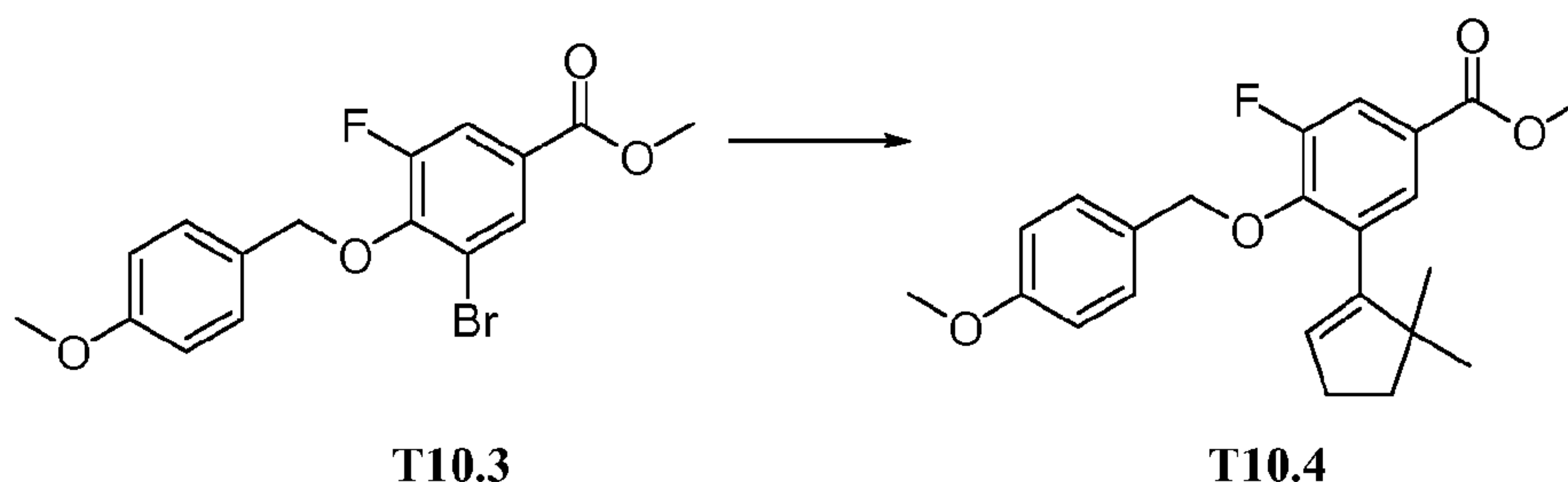
[0365] **Methyl 3-fluoro-4-hydroxybenzoate (T10.1).** To a round bottom flask containing 3-fluoro-4-hydroxybenzoic acid (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (5.03 g, 32.22 mmol) was added a cold solution of MeOH (50.0 mL) and sulfuric acid (2.0 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed and the resulting mixture was diluted with diethyl ether. The organic phase was washed carefully two times with saturated aqueous NaHCO₃, once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed *in vacuo* to afford **T10.1** as a white solid (4.79 g, 87% yield). ¹H NMR (400 MHz, CDCl₃) 7.81 (2 H, m), 7.06 (1 H, t, J=8.4 Hz), 5.62 (1 H, d, J=4.3 Hz), 3.91 (3 H, s).



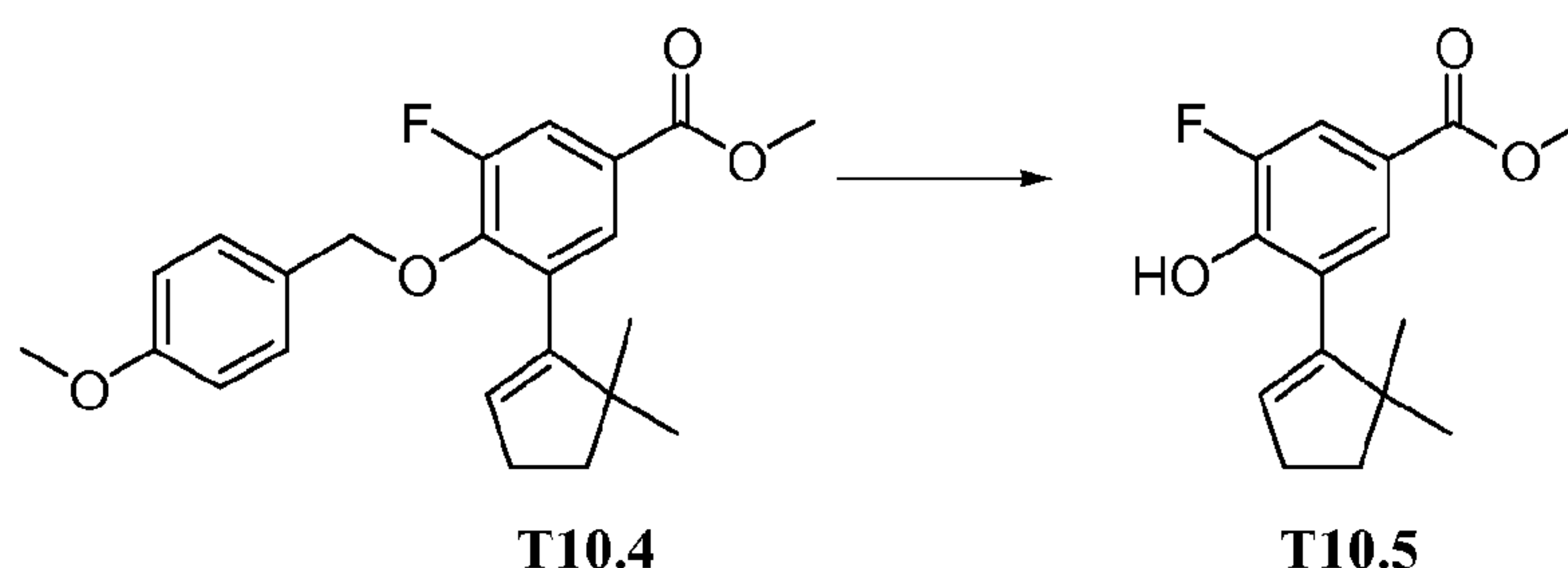
[0366] **Methyl 3-bromo-5-fluoro-4-hydroxybenzoate (T10.2).** Bromine (1.60 mL, 31.1 mmol) was added dropwise with stirring over 30 minutes to an ice-cooled solution of **T10.1** (4.79 g, 28.1 mmol) in a 1:1 mixture of DCM (20 mL) and AcOH (20 mL). Upon complete addition, the reaction mixture was allowed to warm to room temperature and monitored with TLC and LC-MS. After stirring at room temperature for 40 hours, the mixture was diluted with EtOAc. The resulting solution was washed twice with aqueous saturated Na₂SO₃, once with water, and once with brine. After drying over anhydrous MgSO₄, filtration, and concentration, the white solid was identified as **T10.2** (6.69 g, 95% yield). ¹H NMR (400 MHz, CDCl₃) 8.05 (1 H, m), 7.75 (1 H, dd, J=10.6, 2.0 Hz), 6.12 (1 H, s), 3.94 (3 H, s).



[0367] **Methyl 3-bromo-5-fluoro-4-(((4-(methyloxy)phenyl)methyl)oxy)benzoate (T10.3).** To a vial containing **T10.2** (0.64 g, 2.58 mmol) in 5.0 mL dry DMF was added Cs₂CO₃ (1.10 g, 3.36 mmol). The mixture was stirred at room temperature for 10 minutes and then 4-methoxybenzyl bromide (0.45 mL, 3.1 mmol) was added. After 4 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed once with brine and dried over anhydrous MgSO₄. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **T10.3** as a white solid (679.1 mg, 71% yield). ¹H NMR (400 MHz, CDCl₃) 8.02 (1 H, t, J=2.0 Hz), 7.72 (1 H, dd, J=11.5, 2.2 Hz), 7.42 (2 H, m, J=8.6 Hz), 6.90 (2 H, m), 5.20 (2 H, s), 3.91 (3 H, s), 3.82 (3 H, s).

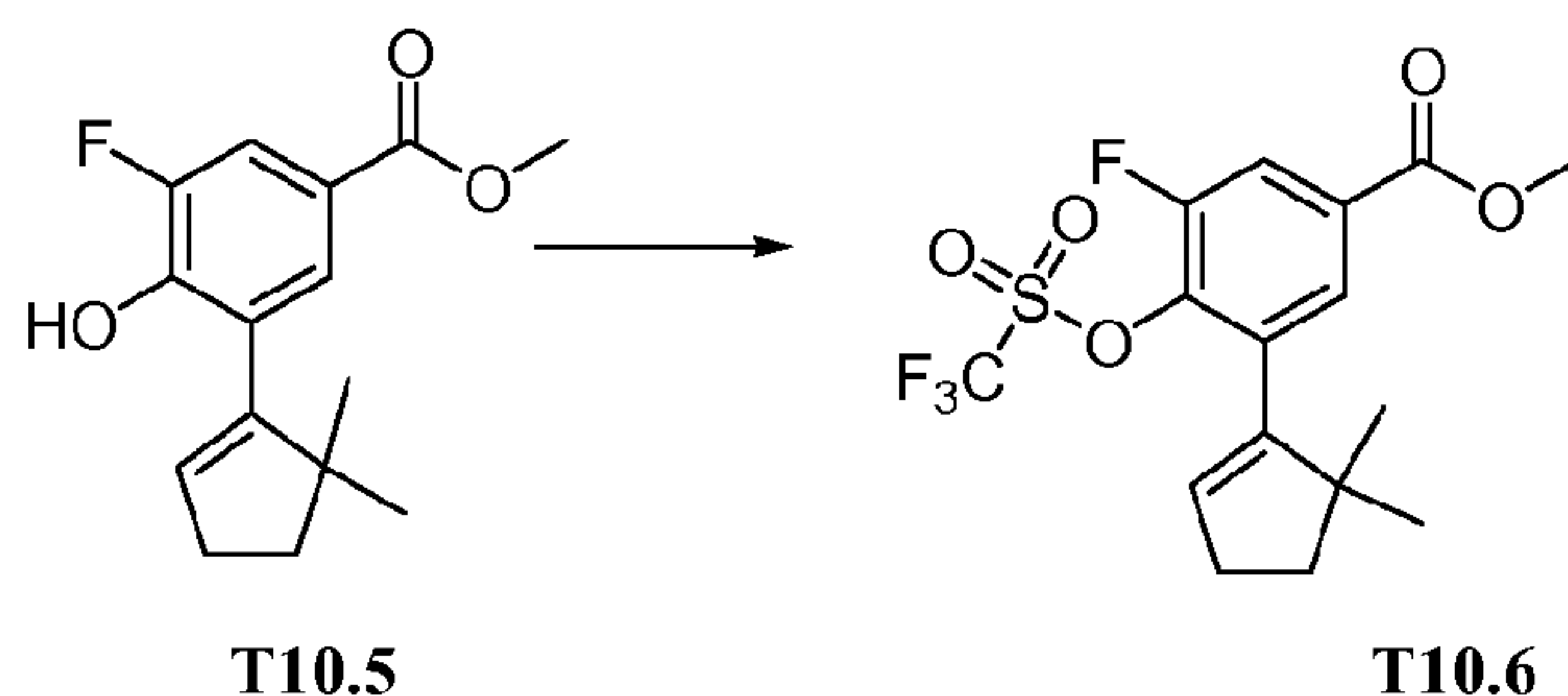


[0368] **Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-((4-methoxyphenyl)methyl)oxybenzoate (T10.4).** A stirred mixture of **T10.3** (1.63 g, 4.420 mmol), ground S-Phos (0.36 g, 0.88 mmol), palladium acetate (0.10 g, 0.45 mmol), and potassium phosphate tribasic (2.35 g, 11.06 mmol) in DMF (13 mL) and water (0.4 mL) was purged three times with argon and placed under vacuum three times. 2-(5,5-Dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**T2.2**) (1.47 g, 6.63 mmol) was added to the mixture via syringe, and the resulting mixture was heated to 75°C. After 18 hours (black solution), the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The combined organic layers were washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on a 40 g column of silica gel (0-10% EtOAc in hexanes) to afford **T10.4** as a white solid (1.12 g, 66% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.69 (1 H, dd, J=11.7, 2.3 Hz), 7.57 (1 H, dd, J=2.0, 1.2 Hz), 7.31 (2 H, m), 6.88 (2 H, m), 5.56 (1 H, t, J=2.5 Hz), 5.01 (2 H, s), 3.91 (3 H, s), 3.82 (3 H, s), 2.42 (2 H, td, J=7.0, 2.7 Hz), 1.86 (2 H, t, J=7.2 Hz), 1.06 (6 H, s).

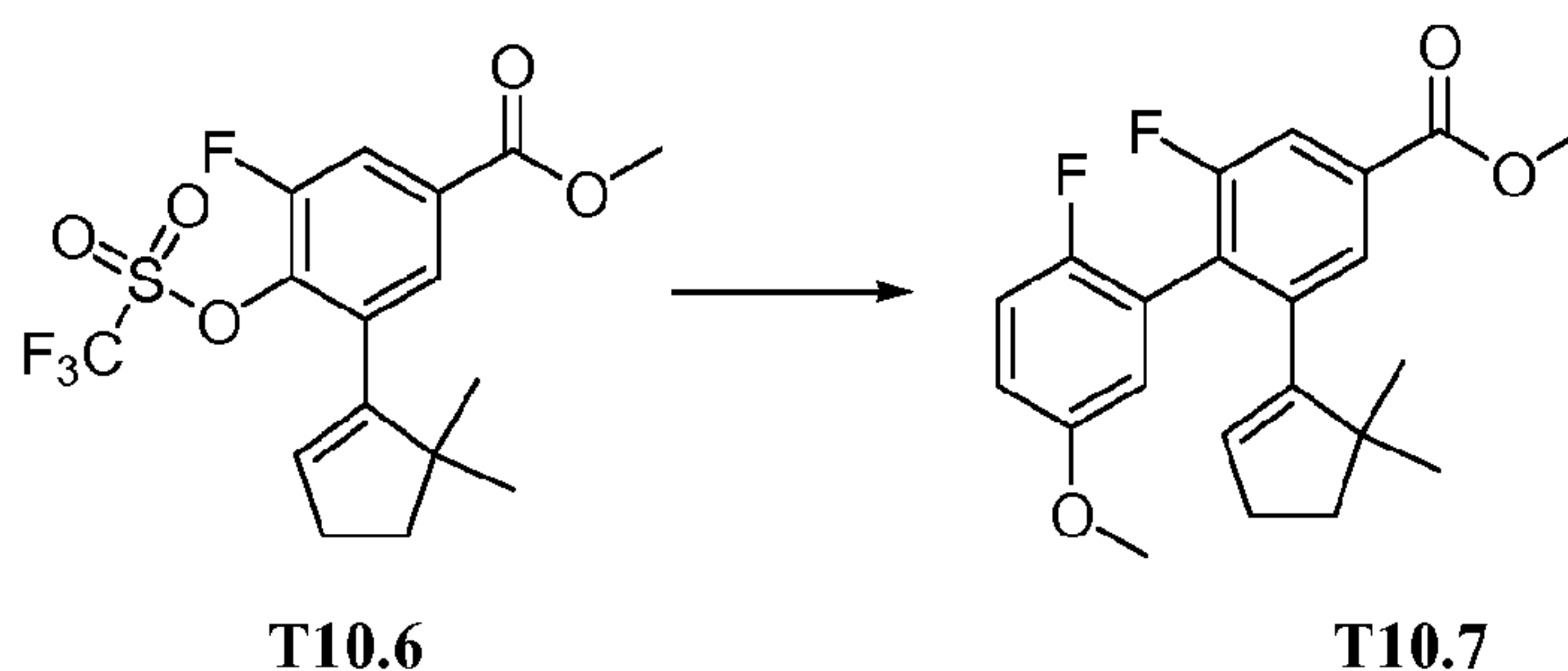


[0369] **Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-hydroxybenzoate (T10.5).** To a flask containing **T10.4** (1.12 g, 2.93 mmol) was added a premixed solution of DCM (14 mL) and TFA (1 mL). The mixture was stirred at room temperature and monitored with TLC and LC-MS. After 1 hour, the reaction was diluted with DCM and then washed once with a saturated aqueous sodium bicarbonate solution

and brine. The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide a colorless oil that solidified as **T10.5** and was used without further purification (732.6 mg, 95 % yield).

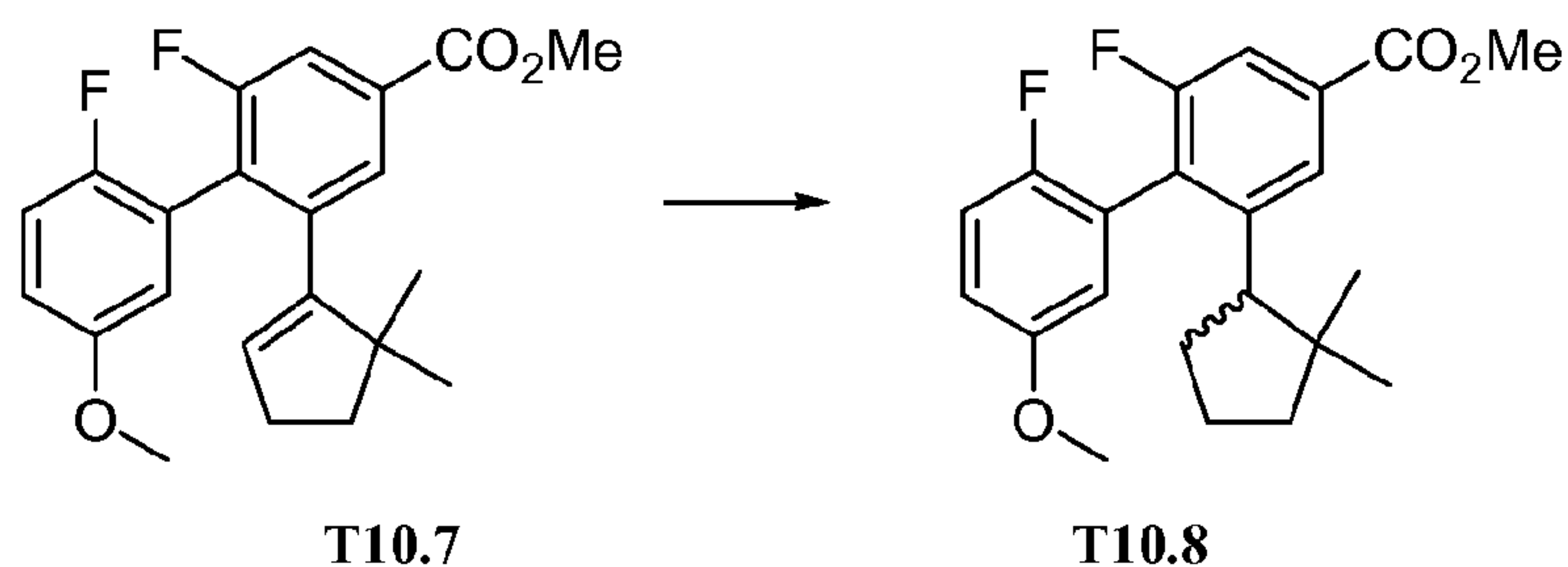


[0370] Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (T10.6). To a stirred solution of **T10.5** (0.7326 g, 2.77 mmol) in dry DCM (15 mL) was added TEA (0.78 mL, 5.60 mmol) and DMAP (0.0354 g, 0.29 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.20 g, 3.36 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 19 hours, the organic solvent was removed under reduced pressure and the residue was purified with silica gel chromatography using 0-10% EtOAc in hexanes to afford **T10.6** as a colorless oil (946.4 mg, 86 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.82 (1 H, dd, J=9.9, 2.1 Hz), 7.75 (1 H, m), 5.87 (1 H, t, J=2.4 Hz), 3.95 (3 H, s), 2.49 (2 H, td, J=7.1, 2.4 Hz), 1.92 (2 H, t, J=7.0 Hz), 1.11 (6 H, s).

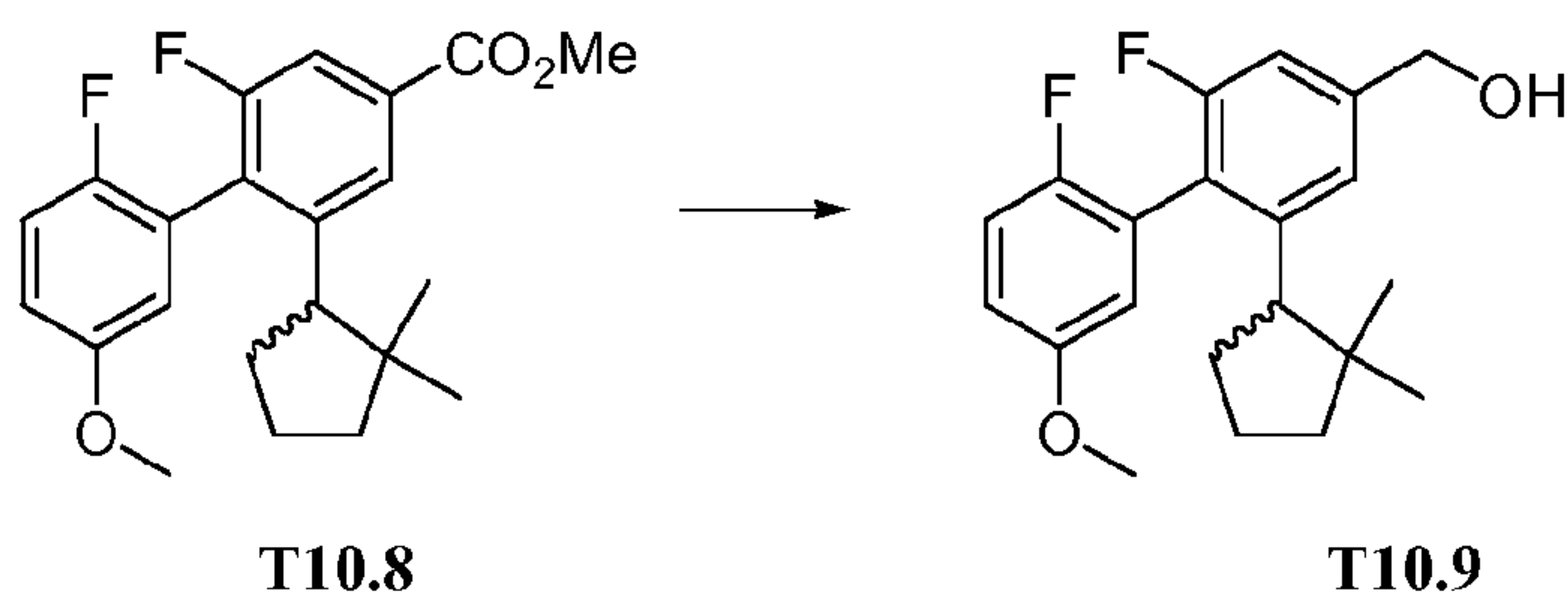


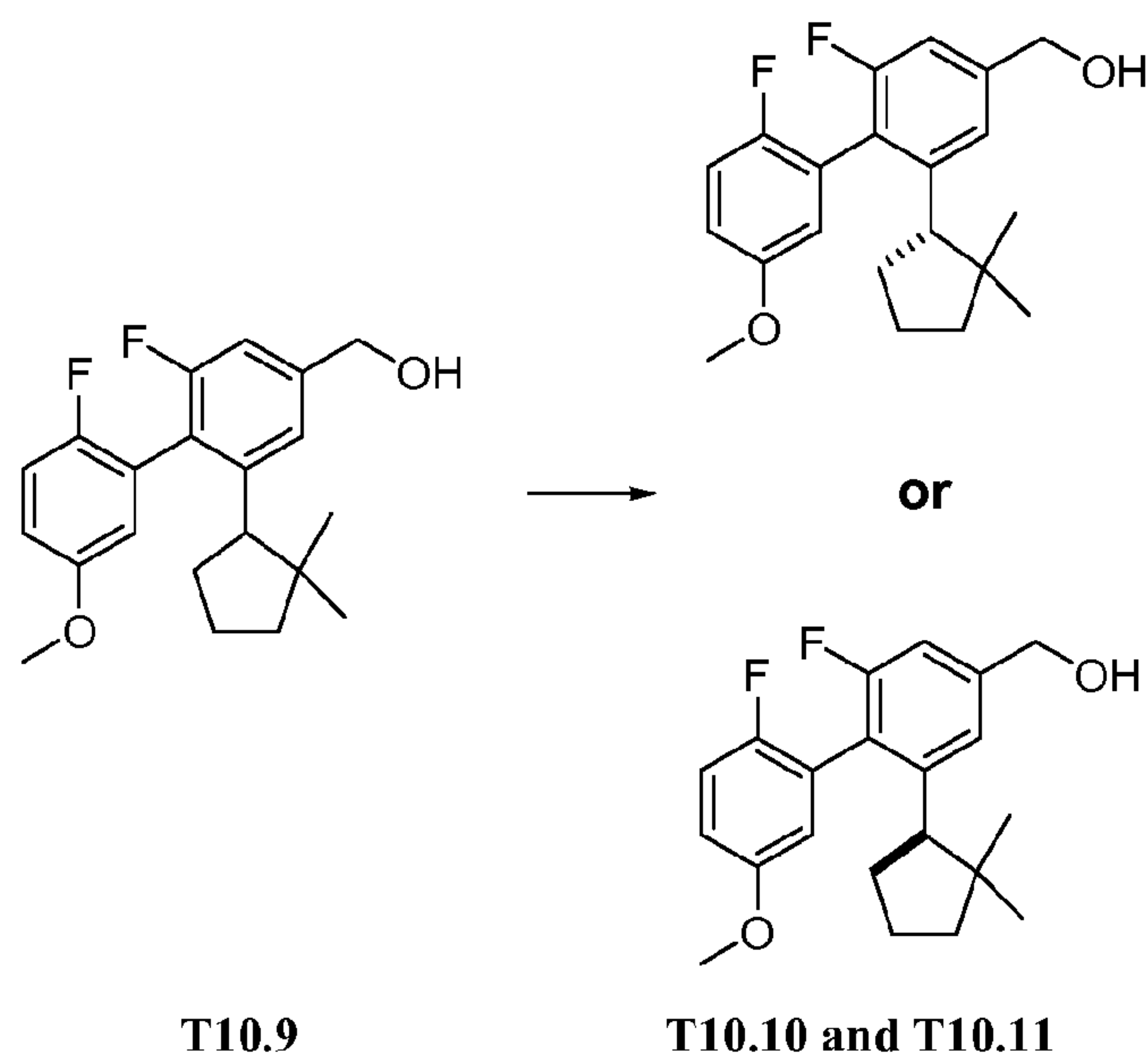
[0371] Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T10.7). A stirred mixture of **T10.6** (0.9464 g, 2.39 mmol), ground S-Phos (0.1977 g, 0.482 mmol), palladium acetate (0.0555 g,

0.247 mmol), 2-fluoro-5-methoxyphenylboronic acid (0.8114 g, 4.77 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), and potassium phosphate tribasic (1.2888 g, 6.072 mmol) in dry DMF (7.000 mL) was purged three times with argon and placed under vacuum three times. The mixture was heated to 75°C. After 21 hours, the reaction was cooled to room temperature, diluted with water and extracted three times with EtOAc. The combined organic layers were washed twice with brine. After drying over anhydrous sodium sulfate and filtering, the organic solvent was removed under reduced pressure. The residue was purified on an 80 g column of silica gel (0-20% EtOAc in hexanes) to afford **T10.7** as a colorless oil that was used as is without further purification (850.5 mg, 95% yield). MS ESI (pos.) m/e: 373.0 (M+H)⁺.

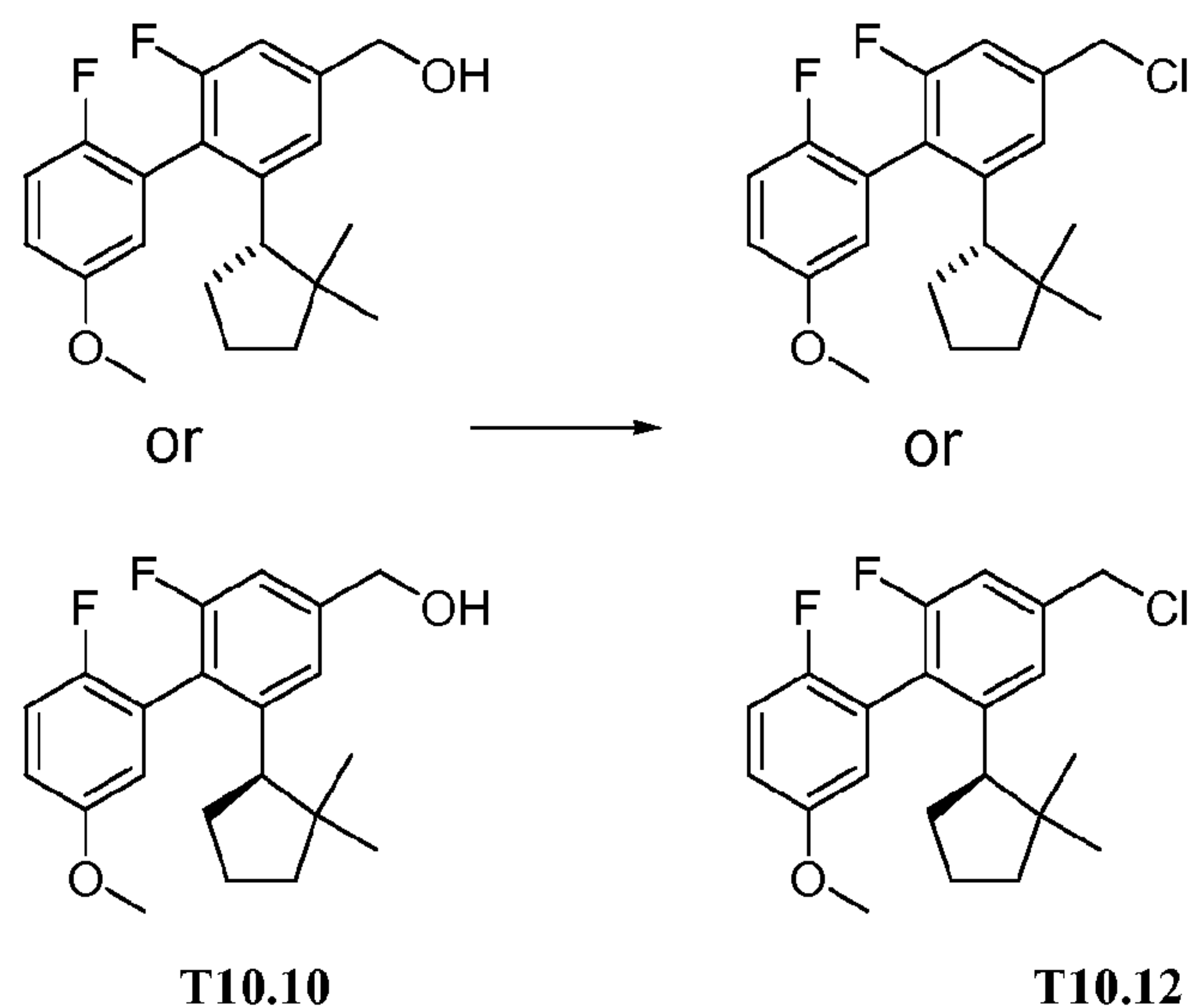


[0372] **Methyl 2-(2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T10.8).** To a flask containing **T10.7** (0.7168 g, 1.925 mmol) in dry MeOH (8 mL) and EtOAc (5 mL) was added palladium (10wt % on activated carbon, (0.2103 g, 0.1976 mmol)). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. After 18.5 hours, the mixture was filtered through Celite® filter aid. After concentration, the residue was identified **T10.8** (703.6 mg, 98% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.88 (1 H, s), 7.65 (1 H, dd, J=9.4, 1.6 Hz), 7.13 (2 H, m), 6.96 (2 H, m), 6.77 (1 H, dd, J=5.5, 3.1 Hz), 3.95 (3 H, s), 3.80 (3 H, s), 2.76 (1 H, ddd, J=10.3, 8.3, 1.8 Hz), 2.19 (1 H, m), 2.08 (1 H, m), 1.91 (1 H, m), 1.75 (2 H, m), 1.45 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s).



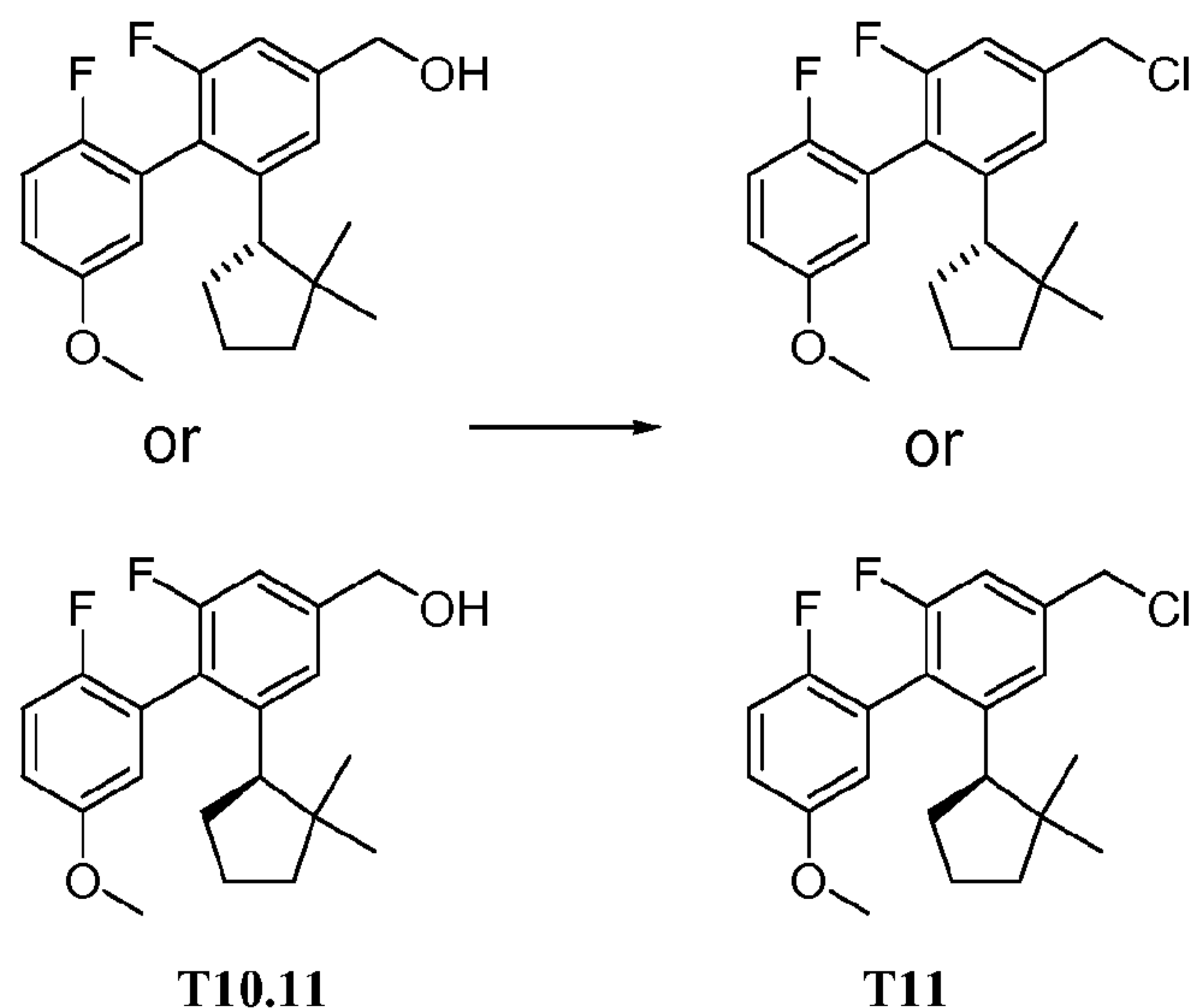


[0373] (2-((1S)-2,2-Dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**T10.10** and **T10.11**). To a cooled solution of **T10.8** (0.7036 g, 1.879 mmol) in dry THF (15 mL) at 0°C was added LAH (1.0 M in THF (4 mL, 4.0 mmol)) dropwise. Upon complete addition, the reaction was maintained at 0°C and monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide a colorless oil that solidified as **T10.9** (300.5 mg, 46 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.16 (1 H, s), 7.10 (2 H, m), 6.92 (1 H, m), 6.77 (1 H, dd, J=5.9, 3.1 Hz), 4.74 (2 H, s), 3.81 (3 H, m), 2.73 (1 H, ddd, J=10.3, 8.3, 1.8 Hz), 2.17 (1 H, m), 2.04 (1 H, m), 1.87 (1 H, m), 1.73 (3 H, m), 1.42 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s). Chiral separation of **T10.9** was accomplished on a CHIRALCEL®® OJ column (2% IPA in hexane) to provide **T10.10** (peak 1) and **T10.11** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.



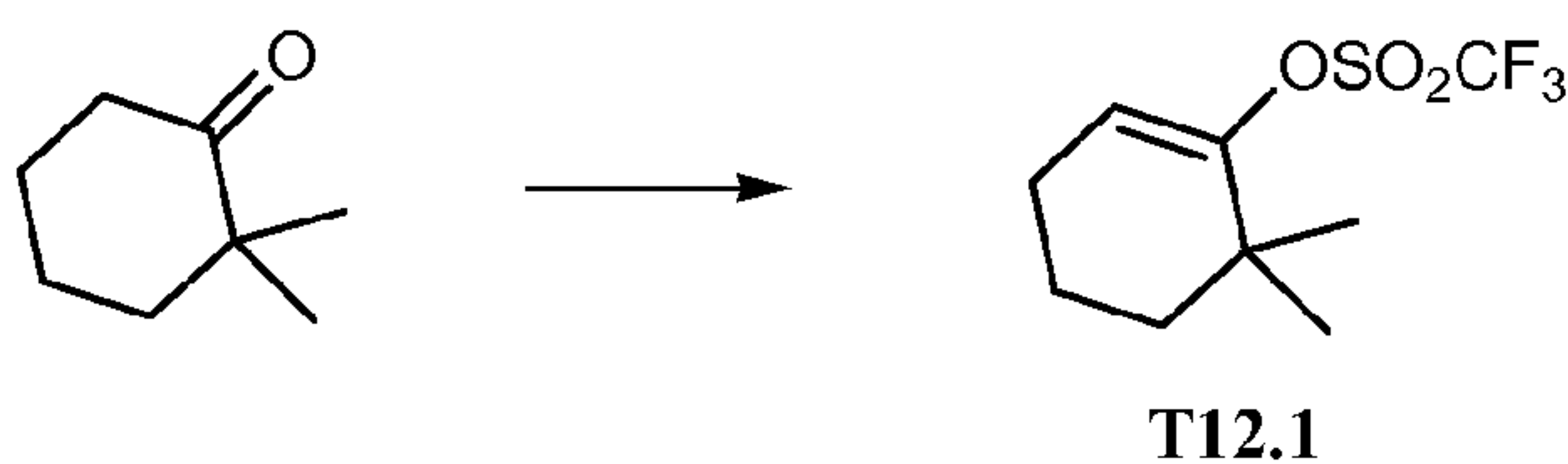
[0374] **4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl (T10.12).** To a solution of **T10.10** (0.1171 g, 0.338 mmol) (derived from peak one of the chiral separation of **T10.9**) in dry DCM (4.5 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.05 mL, 0.685 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 19 hours, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T10.12** (99.7 mg, 81% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.18 (1 H, d, J=1.6 Hz), 7.13 (2 H, m), 6.95 (1 H, m), 6.77 (1 H, dd, J=5.9, 3.1 Hz), 4.68 (2 H, m), 3.84 (3 H, m), 2.73 (1 H, ddd, J=10.3, 8.3, 1.8 Hz), 2.18 (1 H, m), 2.01 (1 H, m), 1.88 (1 H, m), 1.73 (3 H, m), 1.44 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s).

[0375]

Intermediate T11

[0376] 4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl (T11). To a solution of **T10.11** (0.1492 g, 0.431 mmol) (derived from peak two of the chiral separation of **T10.9**) in dry DCM (4.5 mL) and dry DMF (0.035 mL) was added thionyl chloride (0.063 mL, 0.864 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 20 hours, the reaction was concentrated then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T11** that was used as is without further purification (117.1 mg, 74% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.18 (1 H, d, J=1.6 Hz), 7.13 (2 H, m), 6.95 (1 H, m), 6.81 (1 H, m), 4.68 (2 H, m), 3.85 (3 H, m), 2.73 (1 H, ddd, J=10.3, 8.3, 1.8 Hz), 2.18 (1 H, m), 2.01 (1 H, m), 1.80 (1 H, d, J=4.3 Hz), 1.72 (3 H, m), 1.46 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s).

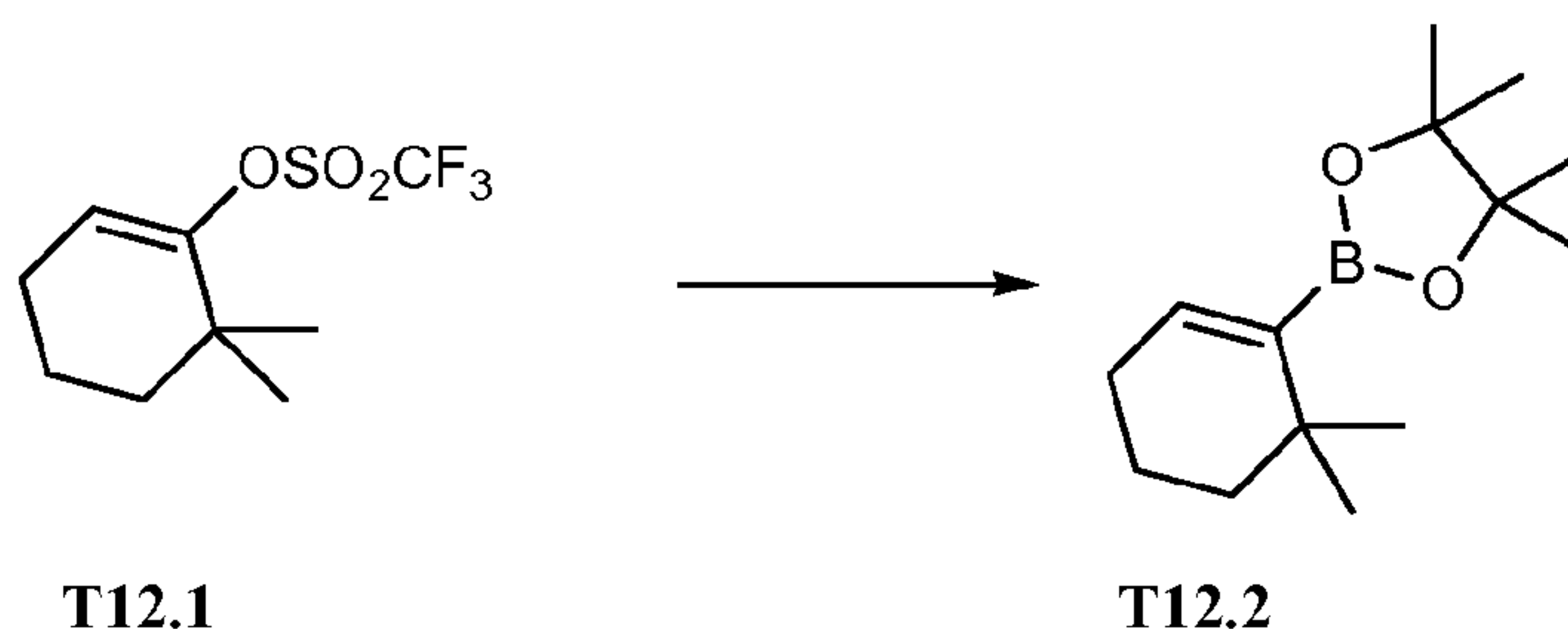
[0377]

Intermediate T12

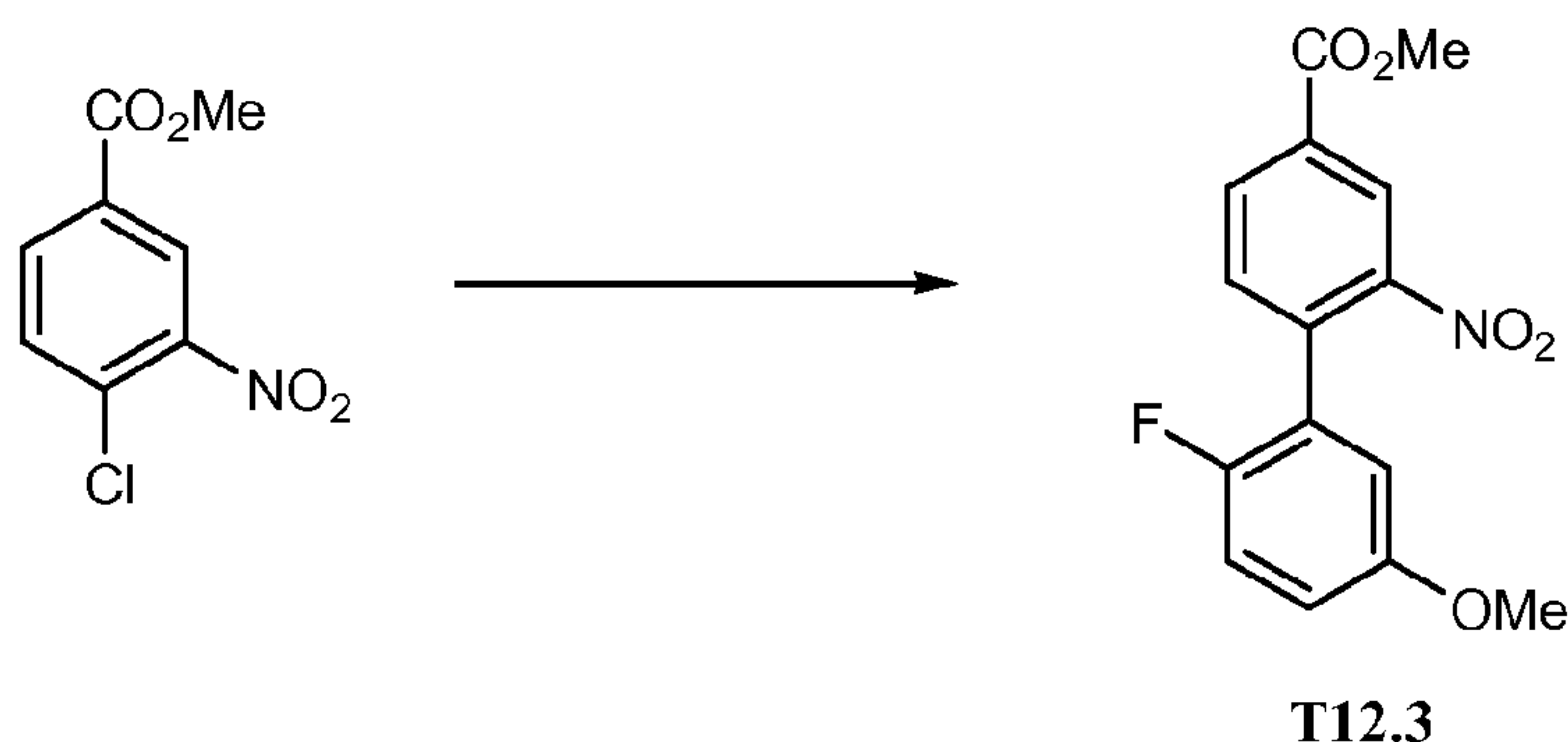
[0378] 6,6-Dimethyl-1-cyclohexen-1-yl trifluoromethanesulfonate (T12.1).

To a solution of 2,2-dimethylcyclohexanone (2.00 g, 16 mmol, commercially available

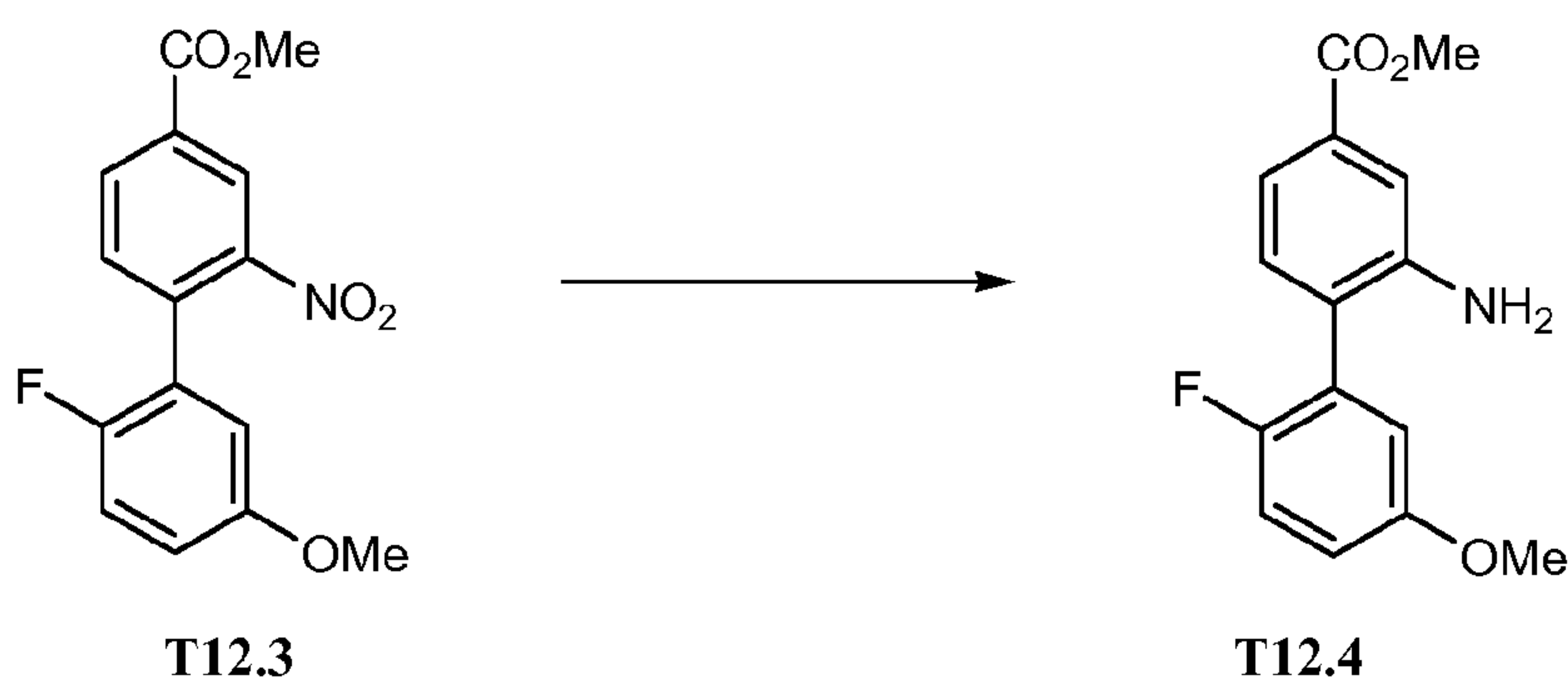
from Sigma-Aldrich, St. Louis, MO, USA) in THF (35 mL) at -78°C was added dropwise LDA (9 mL, 18 mmol, 2.0 M). The resulting solution was stirred at -78°C for 20 minutes. A solution of N-phenyl-bis(trifluoromethane sulfonimide) (6 g, 17 mmol) in THF (15 mL) was then slowly added at -78°C . The reaction mixture was then allowed to warm to 23°C over 3 hours. And then was concentrated in vacuo. The reaction was diluted with brine and extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 and filtered. The organic solvent was removed under reduced pressure, and the product was purified on silica gel (0-10% EtOAc in hexanes) to provide **T12.1** as a clear oil (4.1 g, 100%).



[0379] **2-(6,6-Dimethyl-1-cyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (T12.2).** A mixture of triphenylphosphine (0.4 g, 2 mmol), potassium phenolate (3 g, 22 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4 g, 16 mmol) and **T12.1** (4.1 g, 16 mmol) in toluene (79 mL, 16 mmol) was degassed using N_2 . Dichlorobis(triphenylphosphine)palladium(II) (0.6 g, 0.8 mmol) was then added, and the reaction mixture was further degassed with N_2 . The reaction was then stirred at 50°C for 3.5 hours. The reaction was then diluted with brine and extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and the organic solvent was removed under reduced pressure. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T12.2** as a colorless oil (3.00 g, 80% yield).

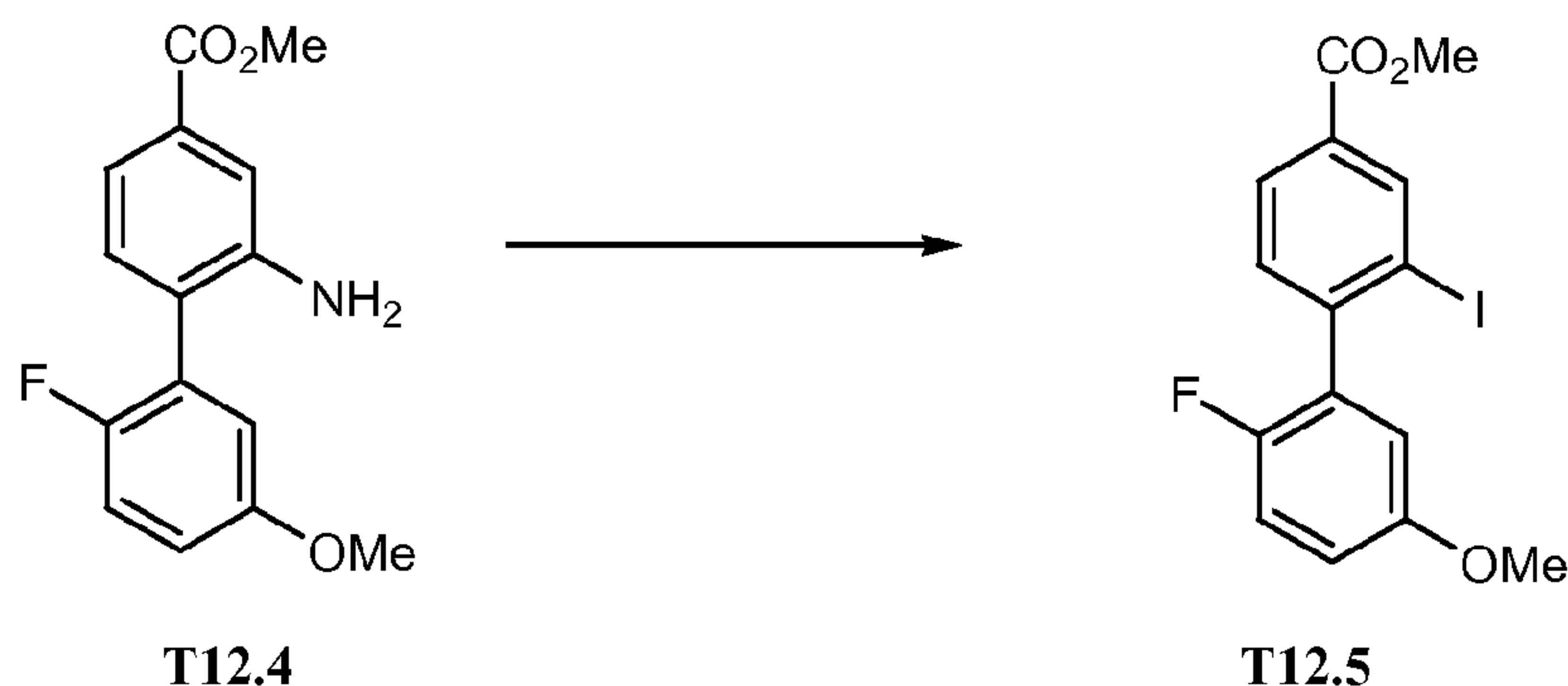


[0380] Methyl 2'-fluoro-5'-(methoxy)-2-nitro-1,1'-biphenyl-4-carboxylate (T12.3). To a stirred solution of methyl 4-chloro-3-nitrobenzoate (10.00 g, 46 mmol, commercially available from TCI) in DMF (15.00 mL, 194 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (12 g, 70 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), potassium carbonate (19 g, 139 mmol), and then tetrakis(triphenylphosphine)palladium (2.1 g, 1.9 mmol). The mixture was heated at 90°C for 18 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. The organic layers were combined, dried over anhydrous MgSO₄, and filtered. The organic solvent was removed under reduced pressure and the residue was purified on silica gel (0-40% EtOAc in hexanes) to yield **T12.3** as a colorless oil (14.00 g, 99% yield).

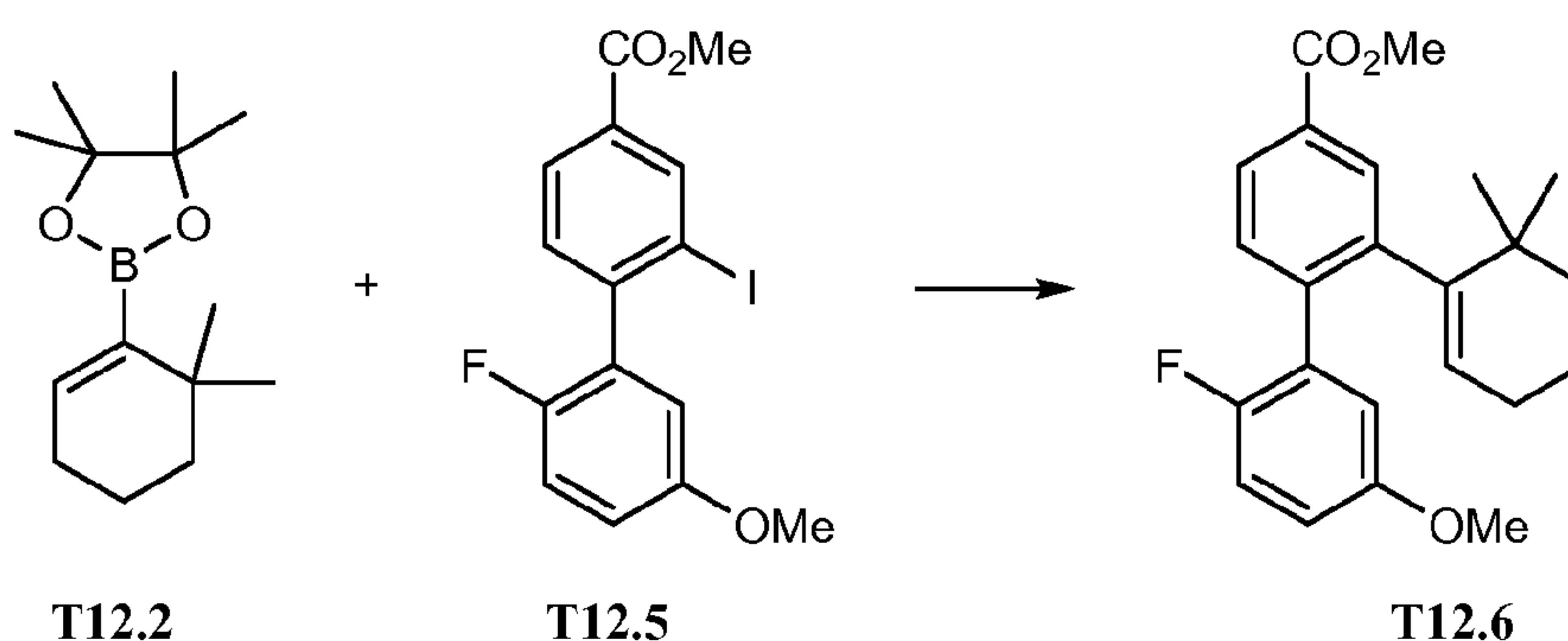


[0381] Methyl 2-amino-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T12.4). To a stirred solution of **T12.3** (1.00 g, 3.3 mmol) in AcOH (2.00 mL, 35 mmol) at 23°C was added DME (15.00 mL, 144 mmol), EtOH (10.00 mL), and then tin(II) chloride (4.7 g, 25 mmol). The mixture was heated at 60°C for 17 hours and then was cooled to room temperature. The reaction was diluted with water and extracted three times with EtOAc. The organic layers were combined, dried over anhydrous magnesium

sulfate, and filtered. The organic solvent was removed under reduced pressure to give the **T12.4** (0.90 g, 100% yield).

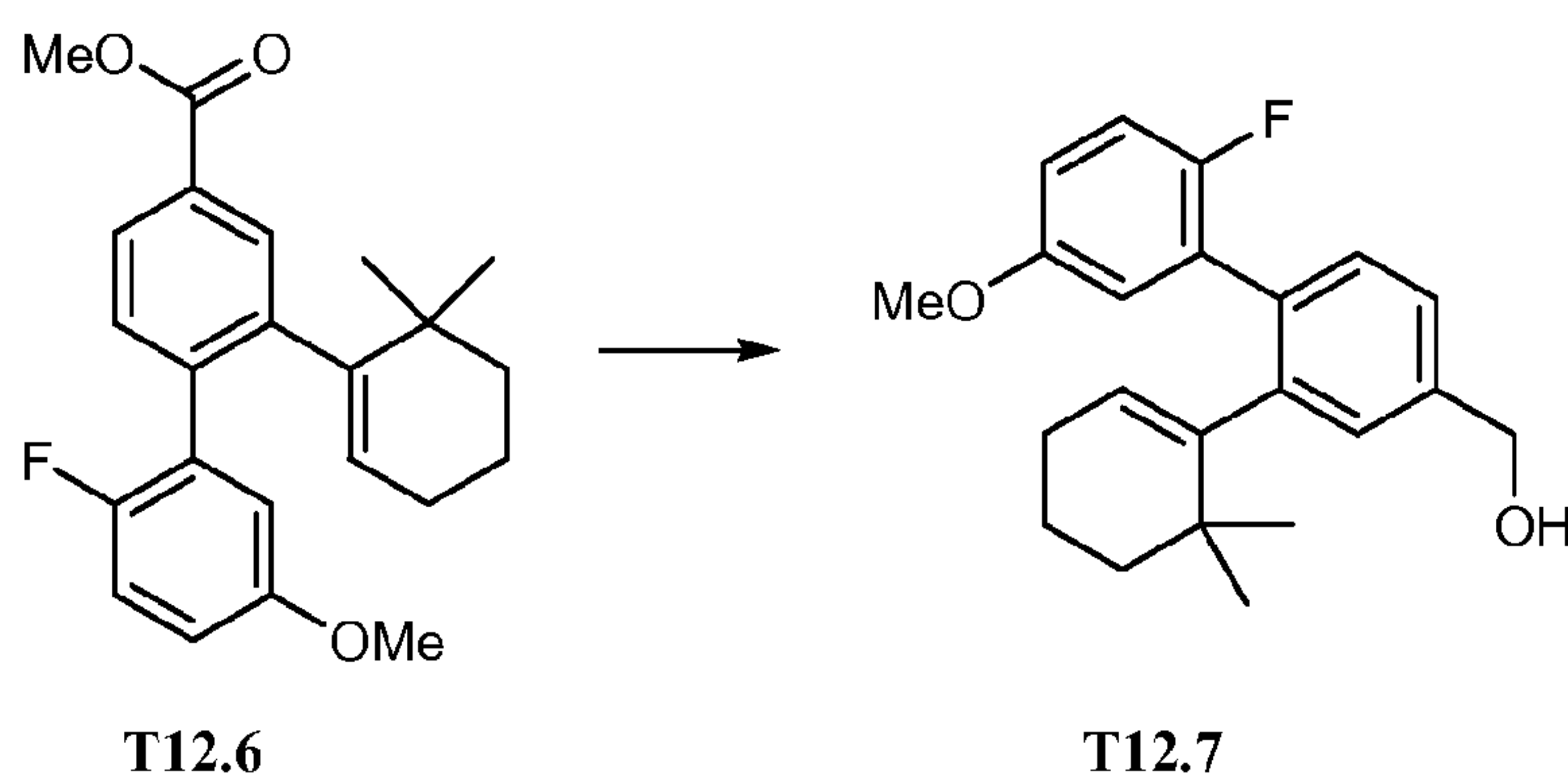


[0382] **Methyl 2'-fluoro-2'-iodo-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T12.5).** To a stirred solution of **T12.4** (1.00 g, 3.6 mmol) in DME (10.00 mL, 96 mmol) at 23°C was added sulfuric acid (0.19 mL, 3.6 mmol) in water (8 mL), followed by dropwise addition of a solution of sodium nitrite (0.38 g, 5.4 mmol) in water (2 mL) at 0°C over 30 minutes. The resulting mixture was stirred for 20 minutes and then a solution of sodium iodide (3.0 g, 20 mmol) in water (7 mL) was added at 0°C. The resulting mixture was stirred for 1 hour and then quenched with sodium thiosulfate and extracted three times with diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate and filtered. The organic solvent was removed under reduced pressure, and the product was purified on silica gel (0-40% EtOAc in hexanes) to yield a colorless solid **T12.5** (0.820 g, 58% yield).

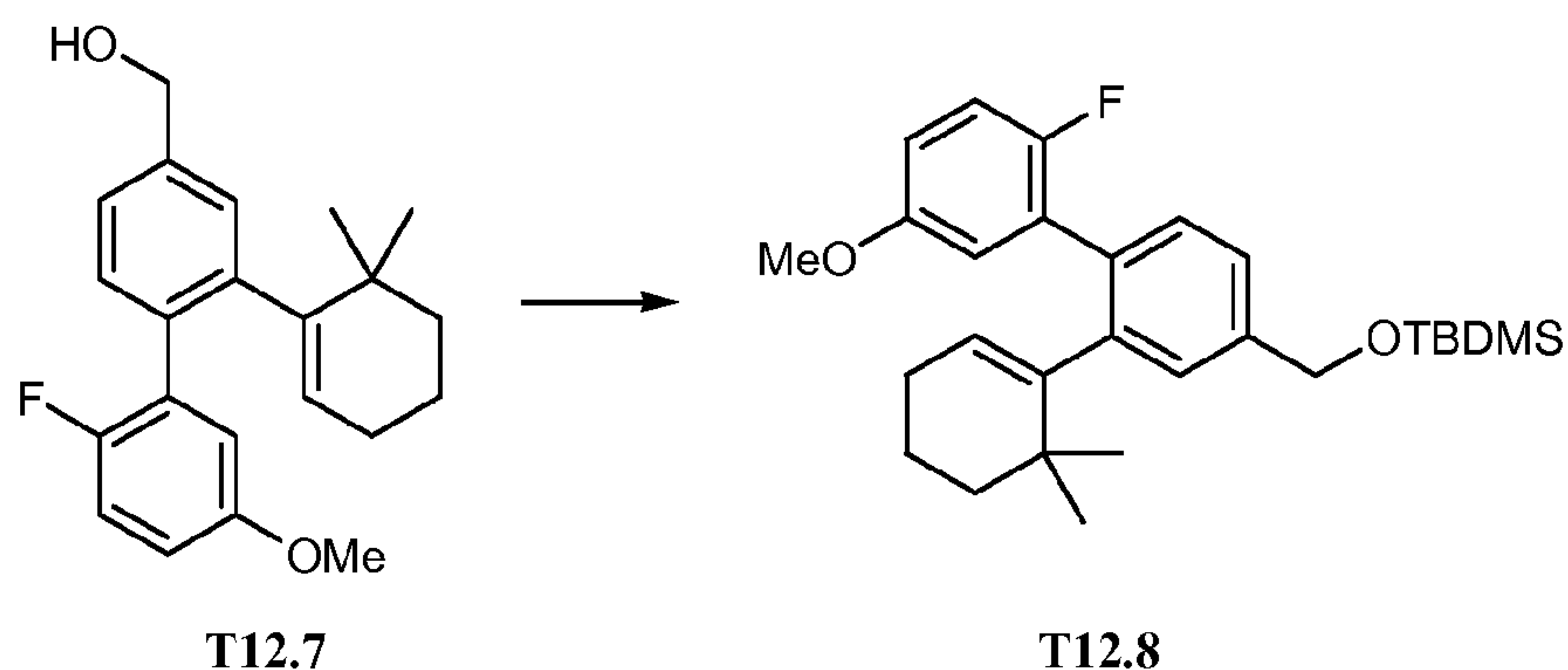


[0383] **Methyl 2-(6,6-dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T12.6).** To a stirred solution of **T12.5** (0.750 g, 1.9 mmol) in DMF (4.00 mL, 52 mmol) at 23°C was added **T12.2** (0.92 g, 3.9 mmol), potassium carbonate (0.81 g, 5.8 mmol), and then tetrakis(triphenylphosphine)palladium (0.22 g, 0.19 mmol). The mixture was heated to 90°C, stirred for 24 hours, and then cooled to

room temperature. The reaction was diluted with brine and extracted three times with EtOAc. The organic layers were combined, dried over anhydrous magnesium sulfate and filtered. The organic solvent was removed under reduced pressure, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **T12.6** as a colorless oil (0.34 g, 48% yield).

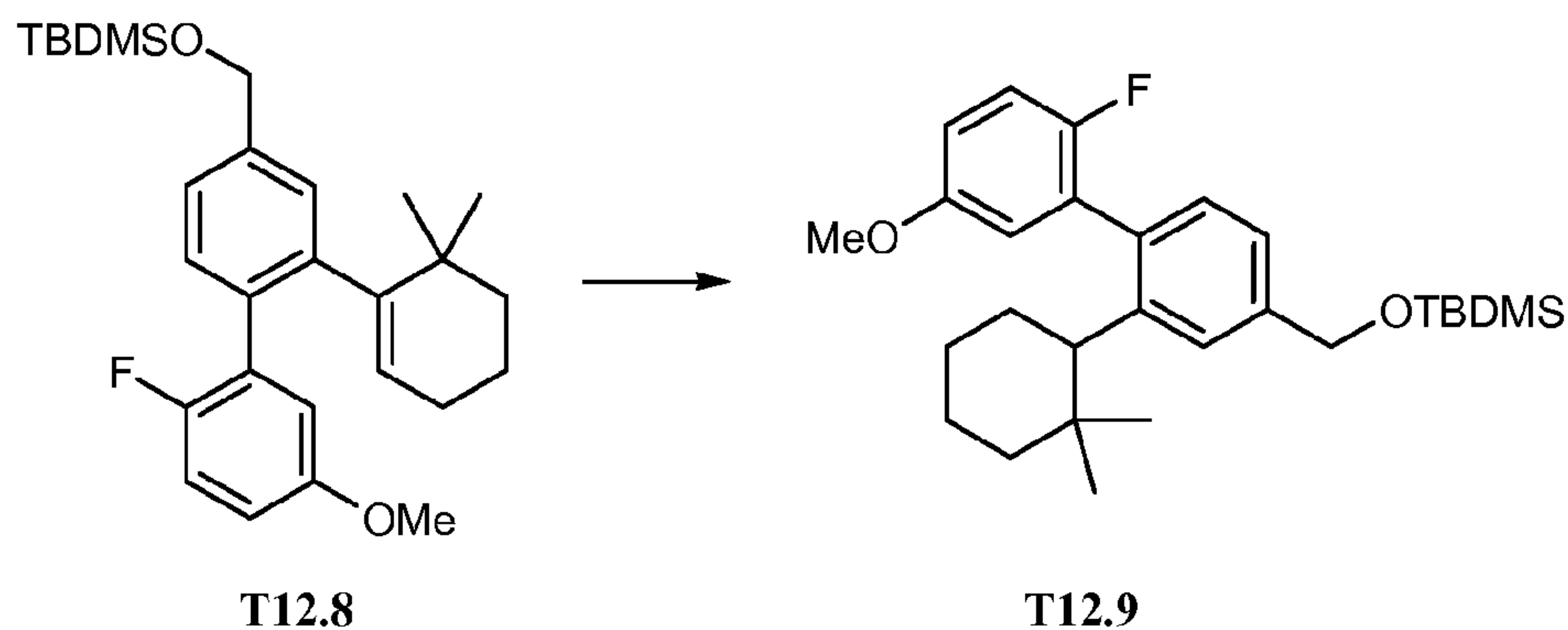


[0384] **(2-(6,6-Dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T12.7)**. To a stirred solution of **T12.6** (0.300 g, 0.814 mmol) in THF (0.0587 g, 0.814 mmol) at 0°C was added LAH (1.63 mL, 1.63 mmol, 1.0M). The resulting mixture was stirred for 4.5 hours. Next, 1N NaOH(aq) was added to quench the mixture. The reaction was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and filtered. The organic solvent was removed under reduced pressure, and the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **T12.7** as a colorless oil (0.250 g, 90.2% yield).

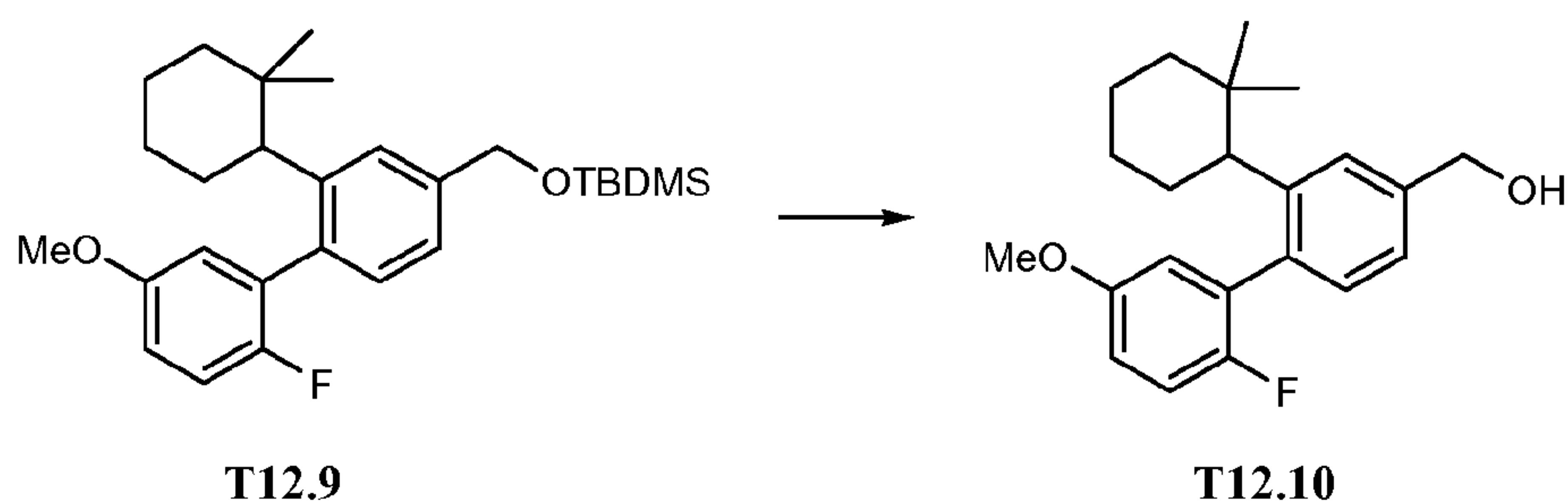


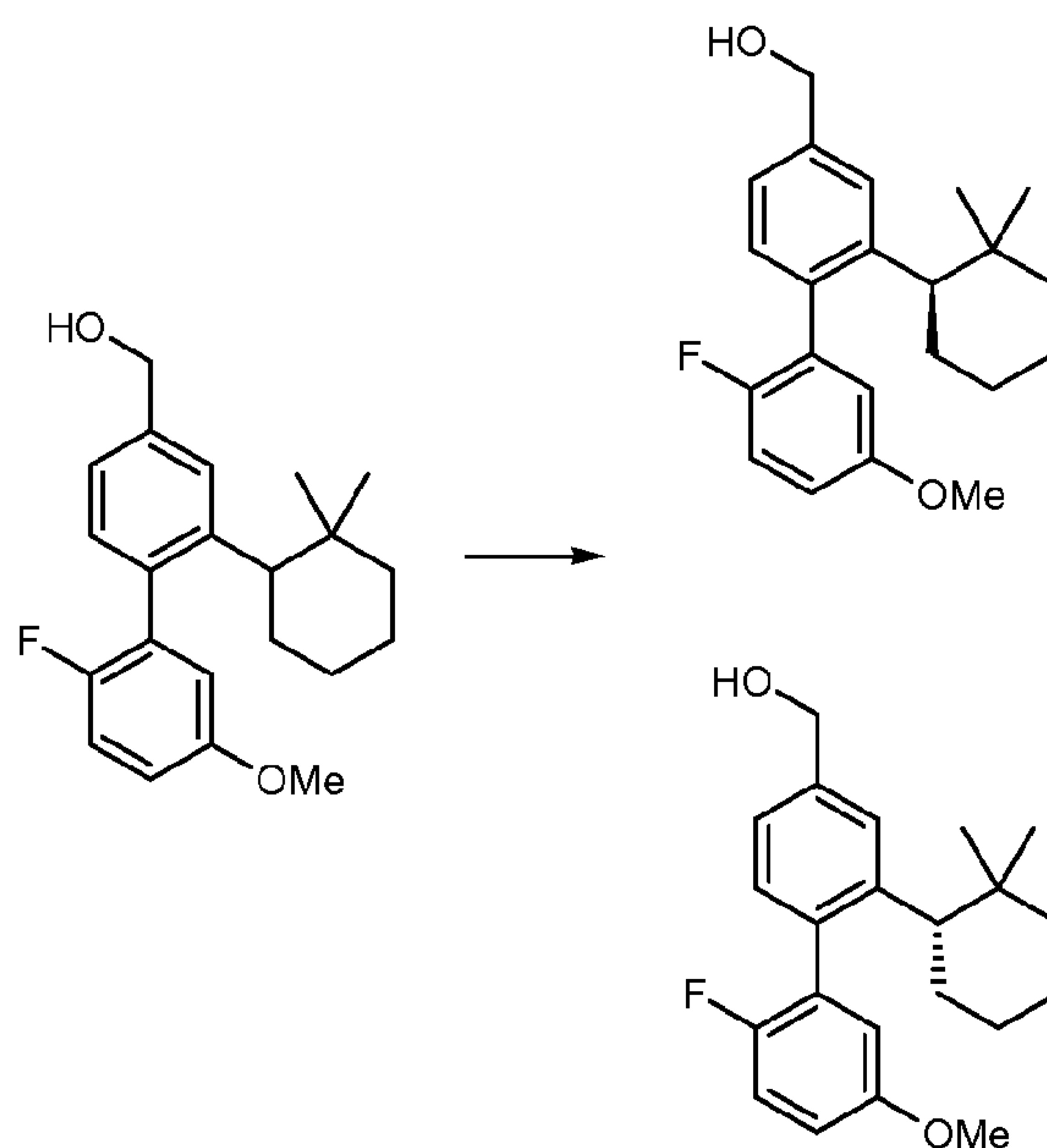
[0385] **(((2-(6,6-Dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)(1,1-dimethylethyl)dimethylsilane (T12.8)**. To a stirred solution of **T12.7** (0.160 g, 0.5 mmol) in DCM (10.00 mL, 155 mmol) at 23°C was added

tert-butyldimethylsilyl chloride (0.09 mL, 0.6 mmol), followed by TEA (0.08 mL, 0.6 mmol) and DMAP (0.006 g, 0.05 mmol). The mixture was stirred for one hour and then was concentrated in vacuo. The residue was purified on silica gel (0-5% EtOAc in hexanes) to yield **T12.8** as a colorless oil (0.198 g, 93% yield).

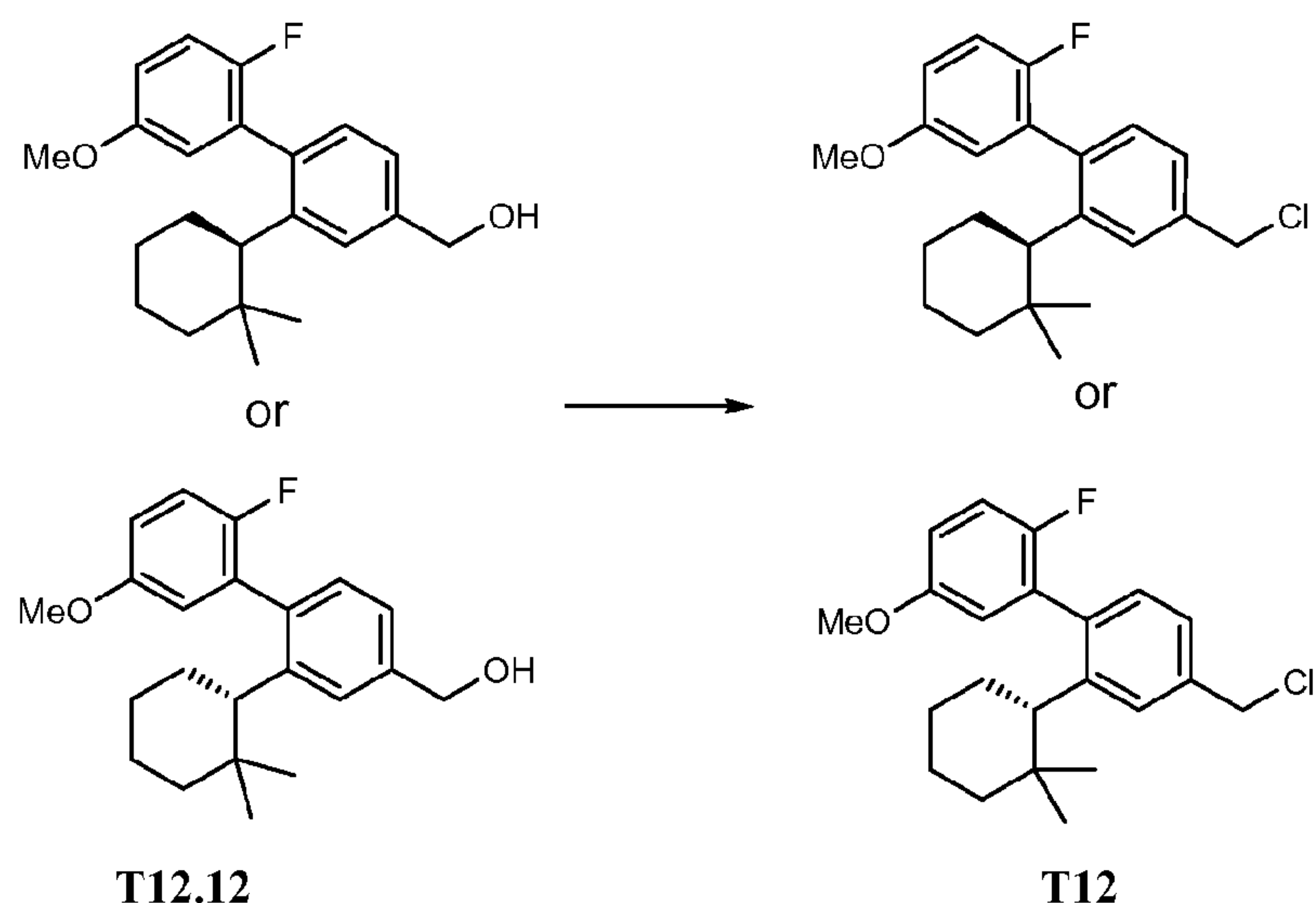


[0386] (((2-(2,2-Dimethylcyclohexyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)(1,1-dimethylethyl)dimethylsilane (**T12.9**). To a stirred solution of **T12.8** (0.090 g, 0.20 mmol) in EtOAc (2.00 mL, 20 mmol) at 23°C was added palladium on carbon (0.0021 g, 0.020 mmol). The mixture was stirred under an atmosphere of hydrogen (0.00040 g, 0.20 mmol) for 4 days. The reaction mixture was then filtered and the filtrate was concentrated in vacuo to yield **T12.9** as a colorless oil (0.090 g, 100% yield)



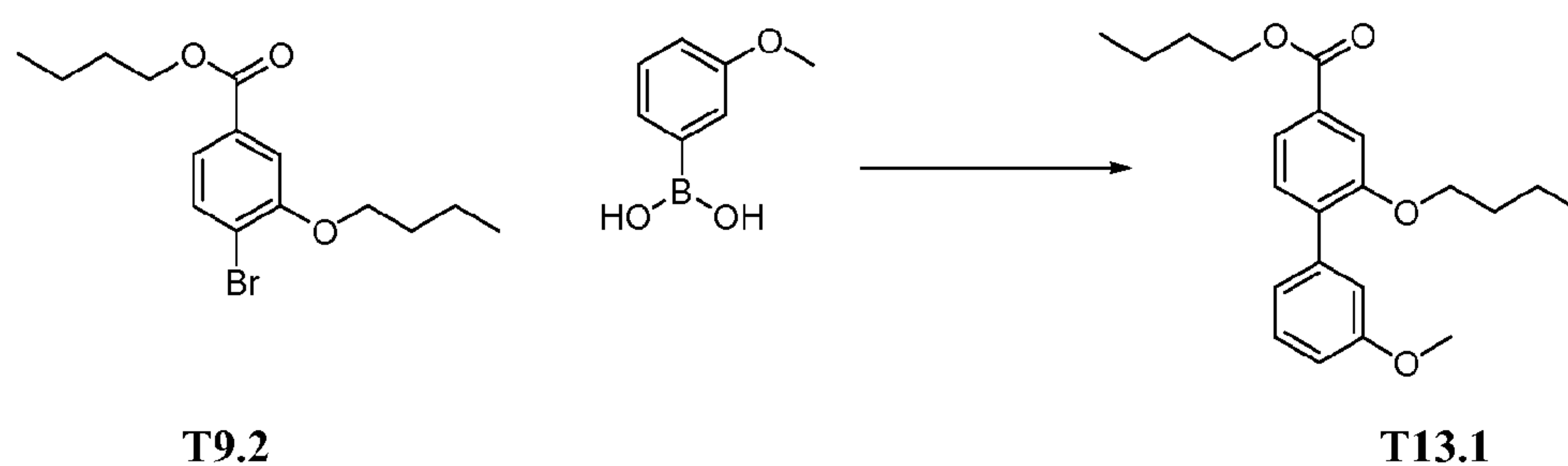
**T12.10****T12.11 and T12.12**

[0387] (2-((1R)-2,2-Dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**T12.11** and **T12.12**). To a stirred mixture of **T12.9** (0.090 g, 0.20 mmol) in MeOH (0.99 mL, 0.20 mmol) was added PPTS (0.0050 g, 0.020 mmol). The mixture was stirred for 4.5 hours and then was concentrated in vacuo. The residue was purified on silica gel (0-15% EtOAc in hexanes) to yield **T12.10** as a colorless oil (0.067 g, 99% yield). Chiral separation of **T12.10** was accomplished on CHIRALCEL® OD (3%IPA in hexane) to provide **T12.11** (peak one) and **T12.12** (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. ¹



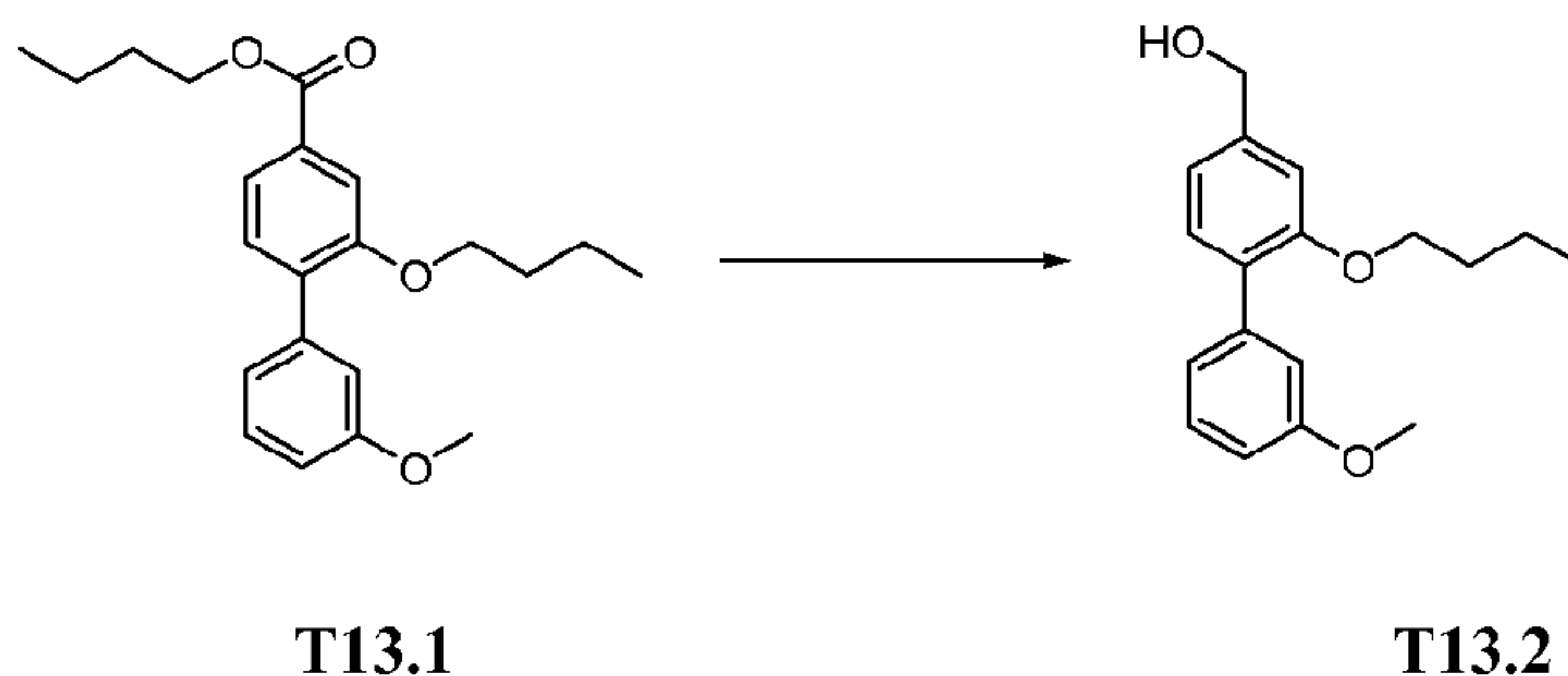
[0388] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T12).** To a stirred solution of **T12.12** (0.035 g, 0.10 mmol) (from peak two from the chiral separation of **T12.10**) in DCM (2.00 mL, 31 mmol) at 23°C was added DMF (0.00079 mL, 0.010 mmol) followed by thionyl chloride (0.015 mL, 0.20 mmol). The mixture was stirred for one hour and then concentrated in vacuo. The residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **T12** as a colorless oil (0.025 g, 68% yield).

[0389] **Intermediate T13**

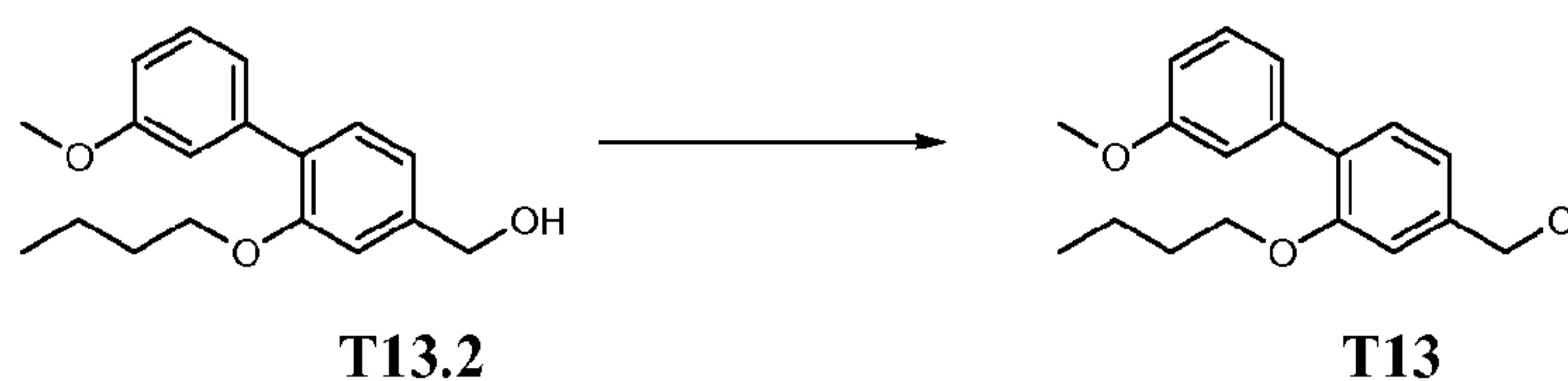


[0390] **Propyl 2-(butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-carboxylate (T13.1).** To a flask charged with 3-methoxyphenylboronic acid (1.02 g, 6.69 mmol, commercially available from Sigma-Aldrich, St. Louis, MO, USA), tetrakis(triphenylphosphine)palladium (0) (0.258 g, 0.223 mmol), cesium fluoride (0.411 mL, 11.1 mmol), and **T9.2** (0.734 g, 2.23 mmol), was added DME (20 mL). The resulting mixture was then heated at 90°C overnight. The reaction was allowed to cool

and was then filtered and concentrated. The residue was purified by silica gel column chromatography (0 to 10% EtOAc/ hexanes) yielding **T13.1** (795 mg, 99% yield).

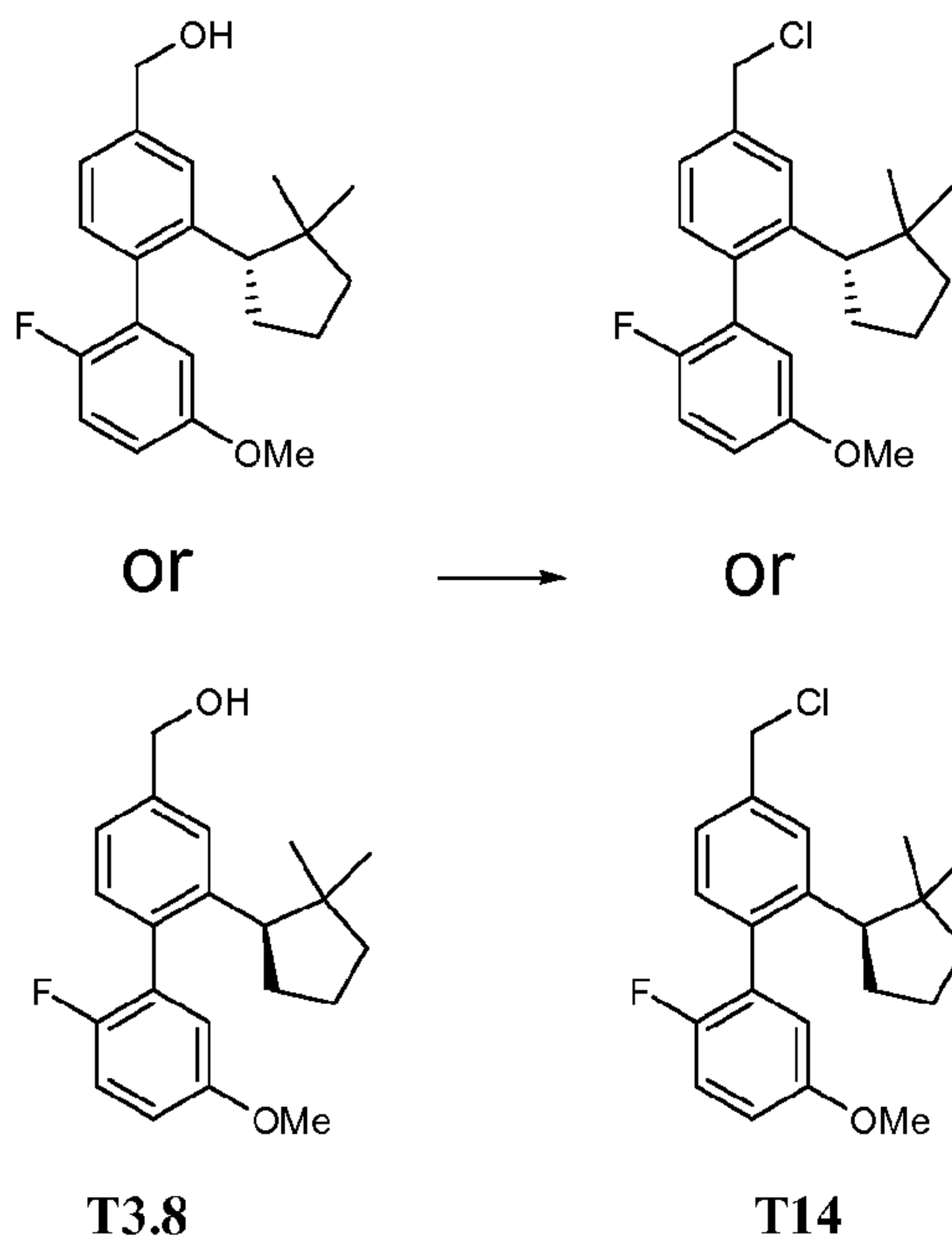


[0391] (2-(Butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T13.2) To a mixture of **T13.1** (795 mg, 2230 μmol) and THF (10 mL) at 0 °C was added LAH (1.0 M solution in THF (3345 μL , 3345 μmol)). The reaction was stirred for one hour and then carefully diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and then dried over sodium sulfate, filtered, and concentrated to provide **T13.2** (530 mg, 83.0% yield).



[0392] 2-(Butyloxy)-4-(chloromethyl)-3'-(methoxy)-1,1'-biphenyl (T13). To a stirred solution of **T13.2** (530 mg, 1851 μmol) in DCM (15 mL) at 23°C was added thionyl chloride (270 μL , 3702 μmol). The resulting mixture was stirred overnight and was then concentrated and then purified by silica gel chromatography (0 to 10% EtOAc/ hexanes) to provide **T13**.

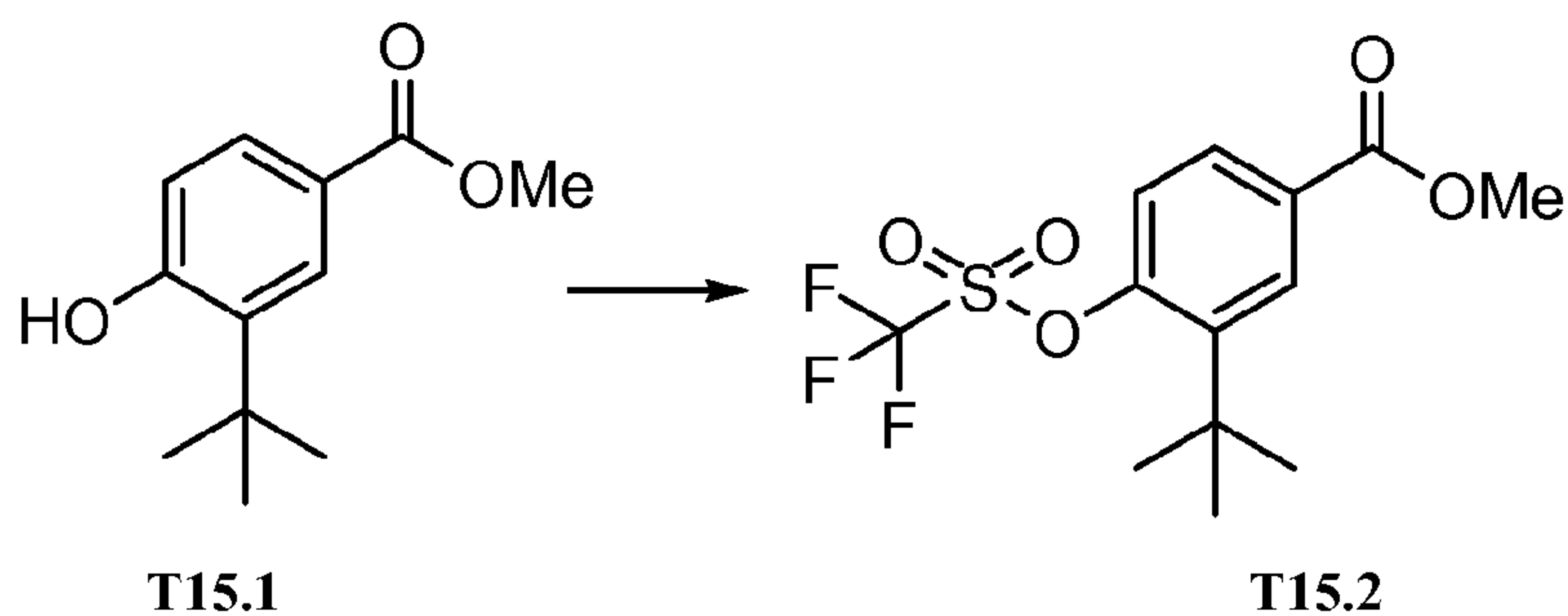
[0393]

Intermediate T14

[0394]

4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T14). Thionyl chloride (1.5 mL, 20 mmol) was added to a stirred solution of **T3.8** (3.280 g, 10.0 mmol) (derived from peak one from the chiral separation of **T3.7**) in DCM (100 mL, 10.0 mmol) and DMF (0.77 mL, 10.0 mmol) at 0°C. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was then concentrated in vacuo and purified on silica gel (0-10% EtOAc in hexane) to give the desired product **T14** (3.00 g, 87 % yield) as a clear oil.

[0395]

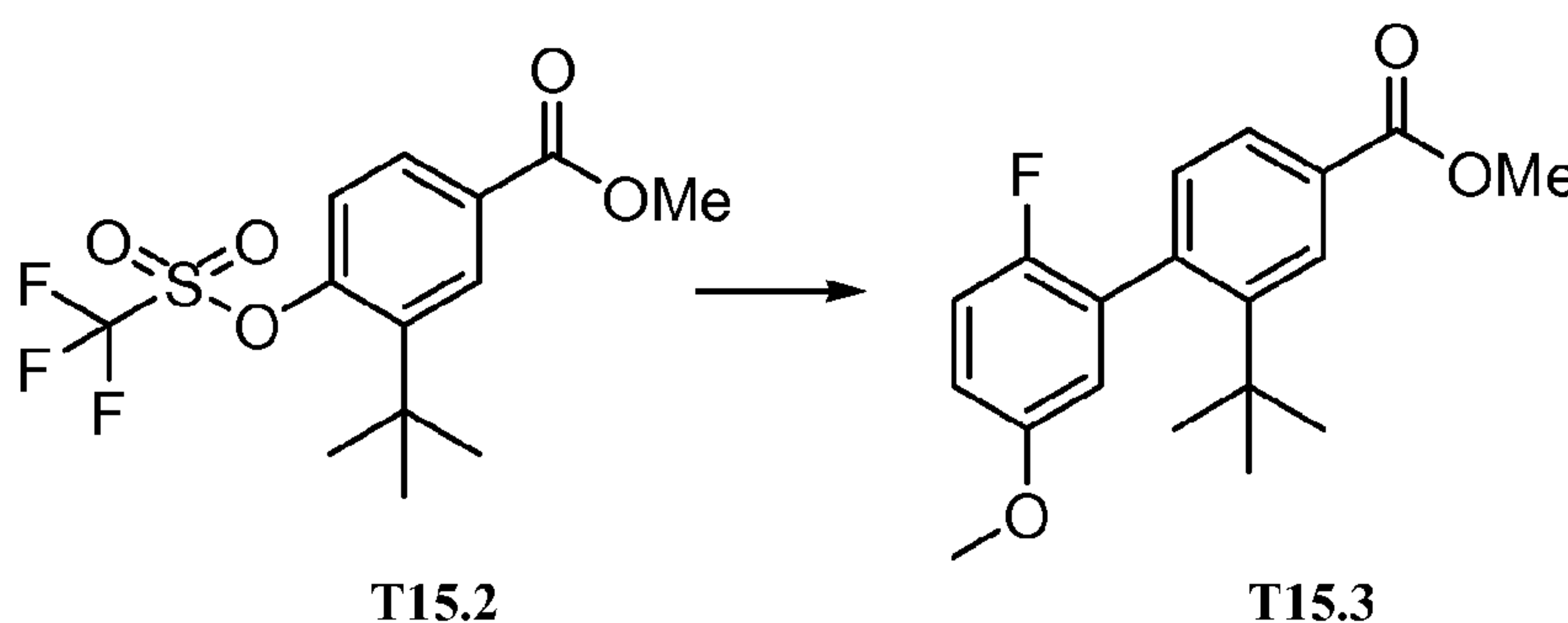
Intermediate T15

[0396]

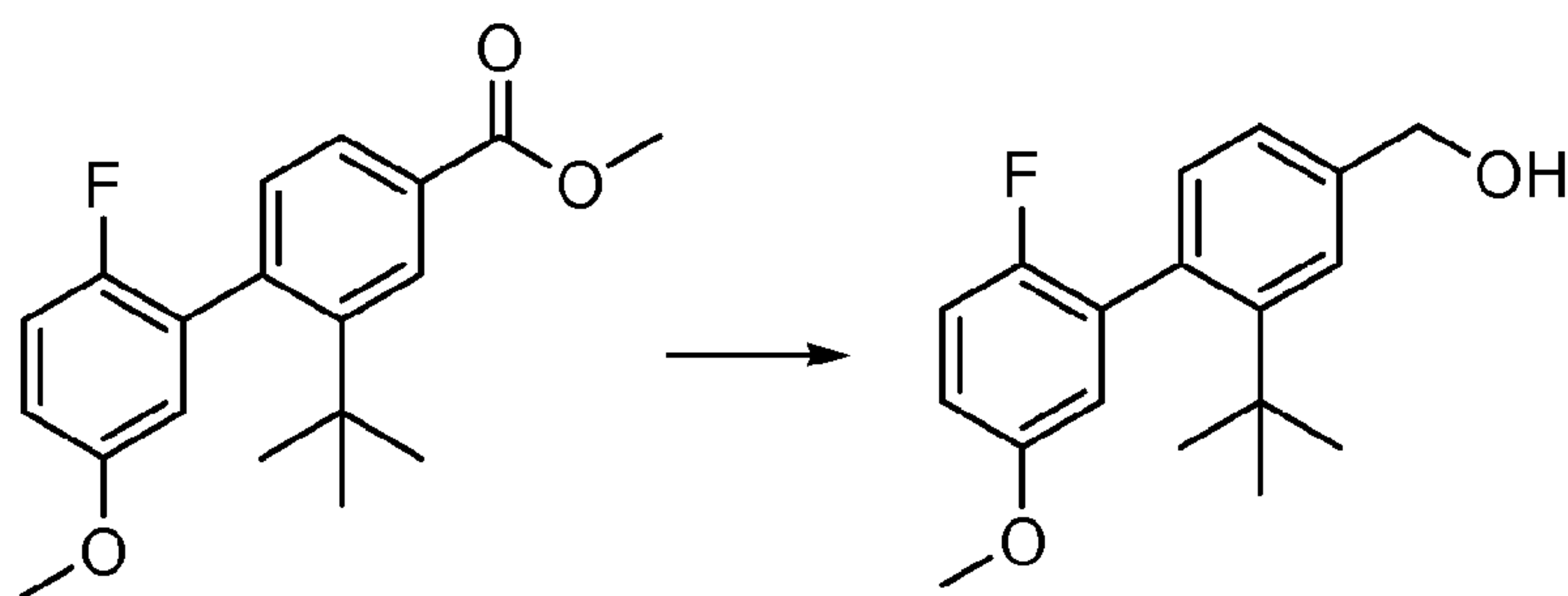
Methyl 3-tert-butyl-4-(trifluoromethylsulfonyloxy)benzoate (T15.2).

To a stirred solution of methyl 3-tert-butyl-4-hydroxybenzoate (**T15.1**)(available from

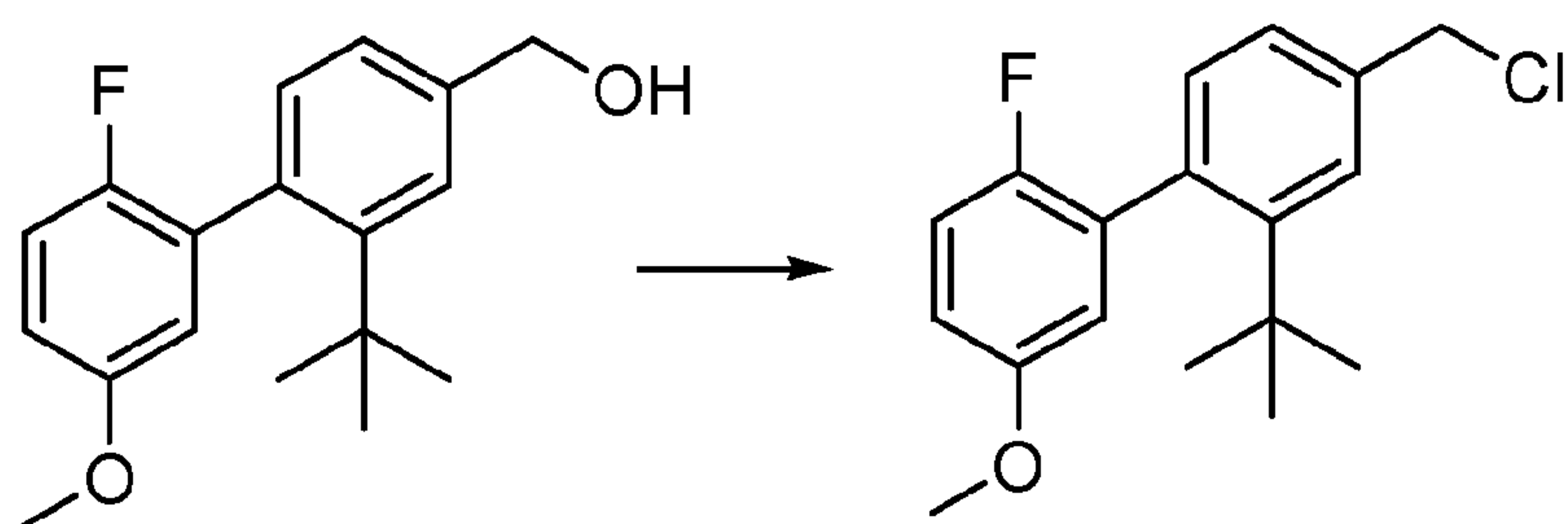
Apin Chemical Ltd, United Kingdom)(0.100 g, 0.48 mmol) in DCM (10 mL, 155 mmol) at 23°C, was added TEA (0.080 mL, 0.58 mmol) and DMAP (0.0059 g, 0.048 mmol), followed by triflic anhydride (0.097 mL, 0.58 mmol). The dark solution was stirred at room temperature and monitored by TLC and LC-MS. After 19 hours, the reaction was concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-10% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T15.2** as a colorless oil (0.16g, 98%). MS ESI (pos.) m/e: 341.0 (M+H)⁺.



[0397] **Methyl 2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T15.3).** To a stirred solution of **T15.2** (0.100 g, 0.29 mmol) in DMF (2.00 mL, 26 mmol) at 23°C, was added 2-fluoro-5-methoxyphenylboronic acid (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (0.100 g, 0.59 mmol), potassium carbonate (0.12 g, 0.88 mmol), followed by tetrakis(triphenylphosphine)palladium (0.034 g, 0.029 mmol). The mixture was heated to 100 °C. After 2 hours, the reaction was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (3 × 50mL) and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T15.3** as a colorless oil (0.85g, 71%). MS ESI (pos.) m/e: 317.2 (M+H)⁺.

**T15.3****T15.4**

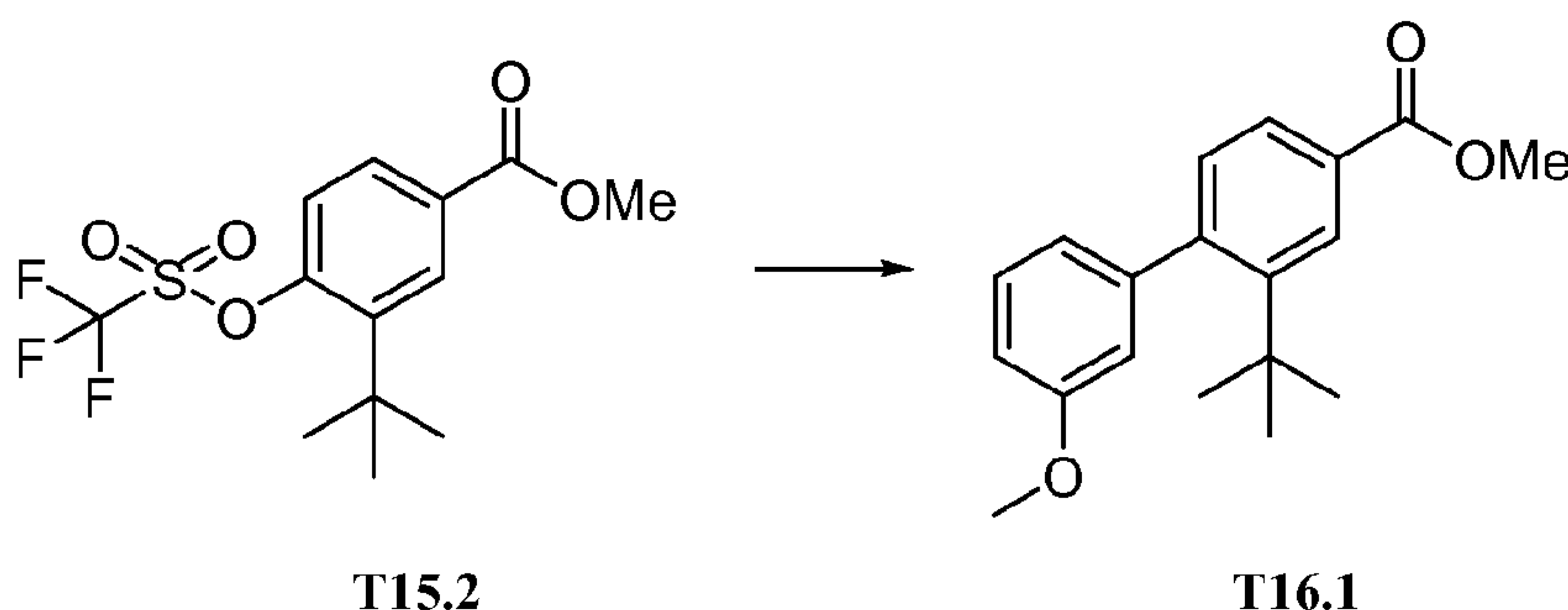
[0398] **(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T15.4).** To a cooled solution of **T15.3** (0.85 g, 2.69 mmol) in dry THF (10.0 mL, 2.69 mmol) at 0°C, was added LAH (1.0 M solution in THF (6.0 mL, 6.0 mmol)). Upon complete addition, the reaction was allowed to warm to room temperature and monitored by TLC and LCMS. Upon completion, 1N NaOH (5 mL) was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-40% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T15.4** as a colorless oil (0.56g, 72%). MS ESI (pos.) m/e: 311.2 (M+Na)⁺.

**T15.4****T15**

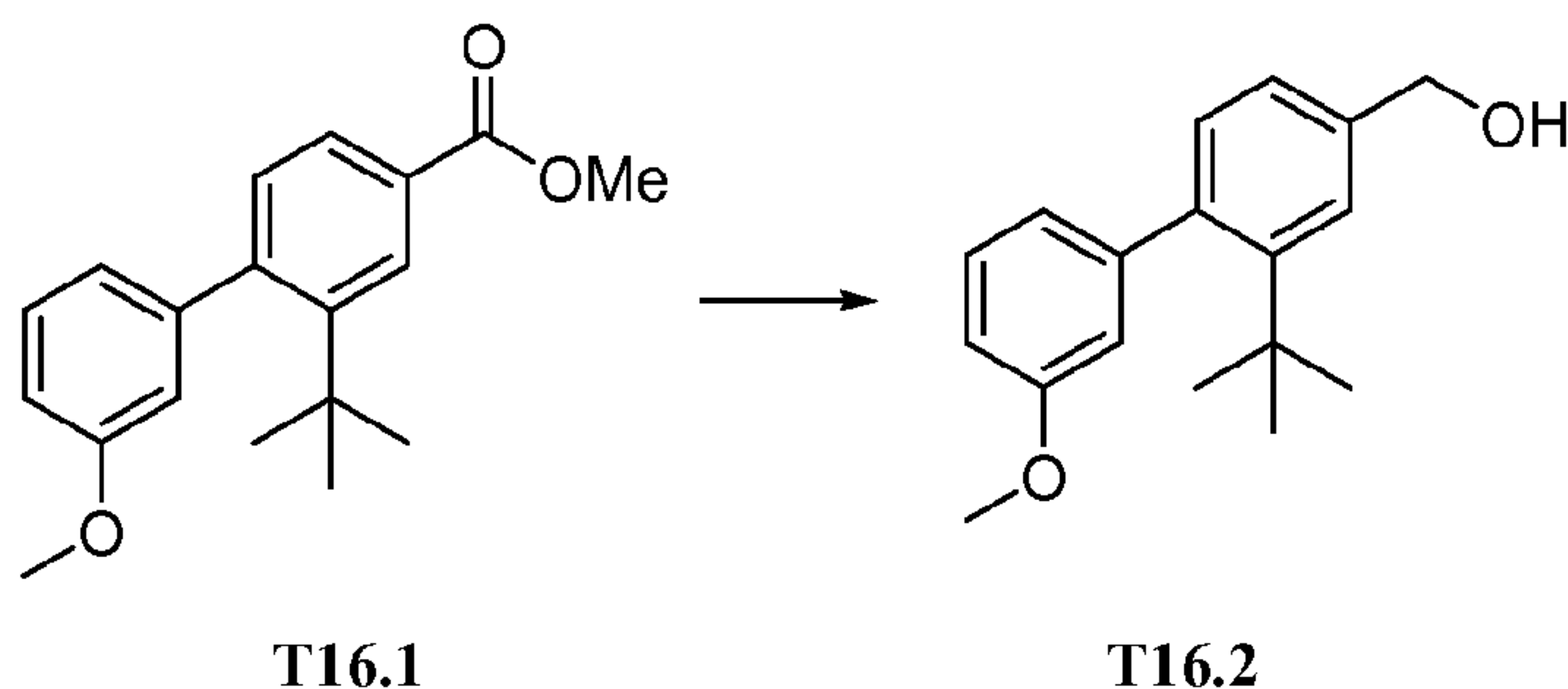
[0399] **4-(Chloromethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T15).** To a cooled solution of **T15.4** (0.56 g, 1.93 mmol) in dry DCM (3.60 mL, 1.93 mmol) at 0°C, was added thionyl chloride (0.40 mL, 5.48 mmol) dropwise. Upon complete addition of thionyl chloride, the mixture was allowed to warm to room temperature. After 18 hours, the reaction was concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T15** as a colorless solid (0.44g, 74%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.56

(1 H, s), 7.25 (5 H, dd, $J=7.7, 1.6$ Hz), 7.01 (2 H, m), 6.86 (1 H, dd, $J=9.0, 3.2$ Hz), 6.77 (1 H, dd, $J=5.9, 3.2$ Hz), 4.65 (3 H, s), 3.79 (3 H, s), 1.24 (9 H, s).

[0400] Intermediate T16

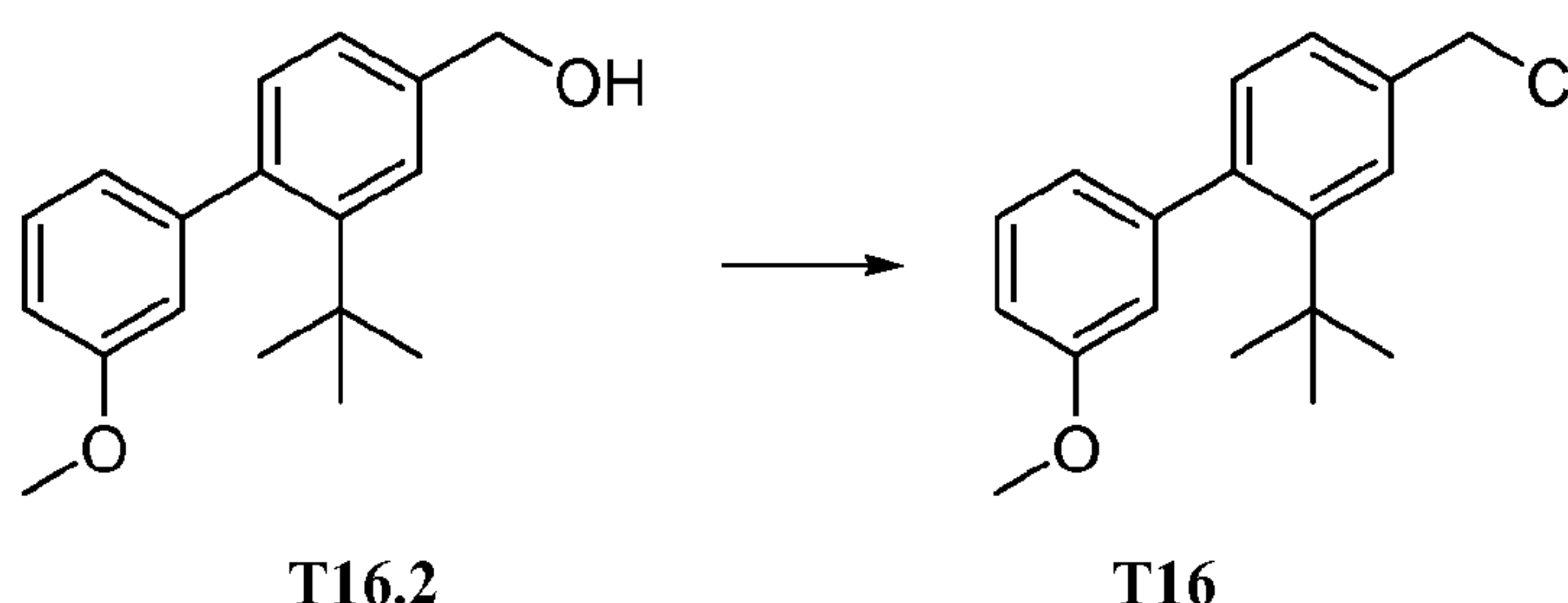


[0401] Methyl 2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-carboxylate (T16.1). A dry round bottom flask containing **T15.2** (1.40 g, 4.1 mmol), 3-methoxyphenylboronic acid (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (1.27 g, 8.34 mmol), tetrakis(triphenylphosphine)palladium (0.49 g, 0.42 mmol), and potassium carbonate (1.71 g, 12.36 mmol) was evacuated and backfilled three times with argon. Dry DMF (12.0 mL) was added via syringe under argon, and the mixture was then heated to 100 °C and monitored by TLC. After 2 hours, the reaction was cooled to room temperature and diluted with water. The mixture was extracted three times with EtOAc and then concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T16.1** as a colorless oil (1.01, 82%). MS ESI (pos.) m/e : 299.2 ($M+H$)⁺.



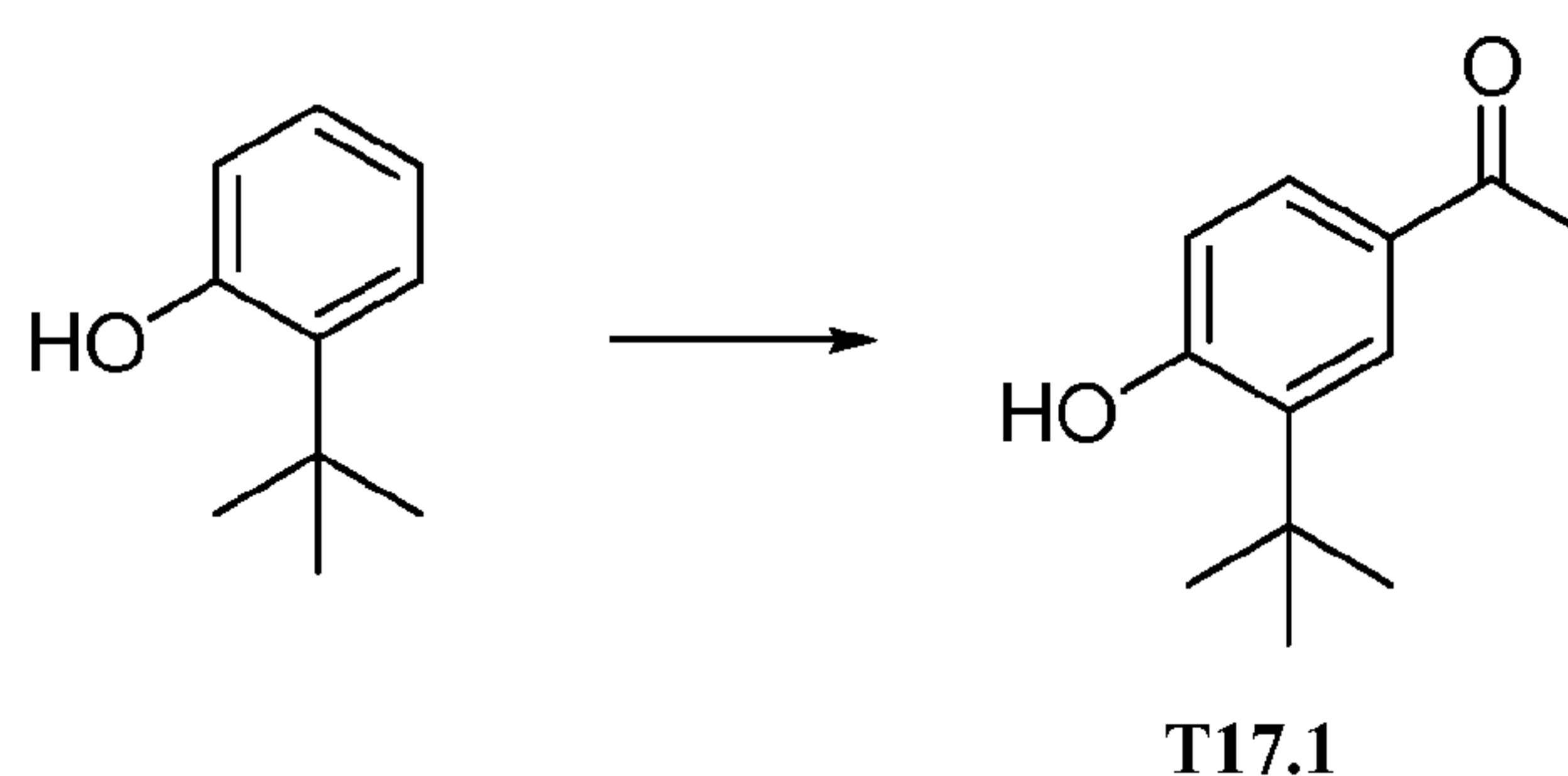
[0402] (2-(1,1-Dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T16.2). To a cooled solution of **T16.1** (1.01 g, 3.38 mmol) in dry THF (10.0 mL) at 0°C, was added LAH (1.0 M solution in THF (6.7 mL, 6.7 mmol)). Upon complete addition, the reaction was allowed to warm to room temperature and monitored by TLC and

LCMS. Upon completion, 1N NaOH (5 mL) was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3×10 mL), dried over MgSO_4 , filtered and concentrated in vacuo. The residue was then purified by flash chromatography (SiO_2 gel 60, eluted with 0%-40% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T16.2** as a colorless oil (0.82, 90%). ^1H NMR (500 MHz, CDCl_3) δ ppm 7.56 (1 H, s), 7.29 (1 H, t, $J=3.8$ Hz), 7.24 (1 H, m), 7.07 (1 H, d, $J=7.6$ Hz), 6.93 (2H, m), 6.86 (1H, d, $J=1.5$ Hz), 4.77 (2 H, s), 3.85 (3 H, s), 1.72 (1H, s), 1.26 (9 H, s).

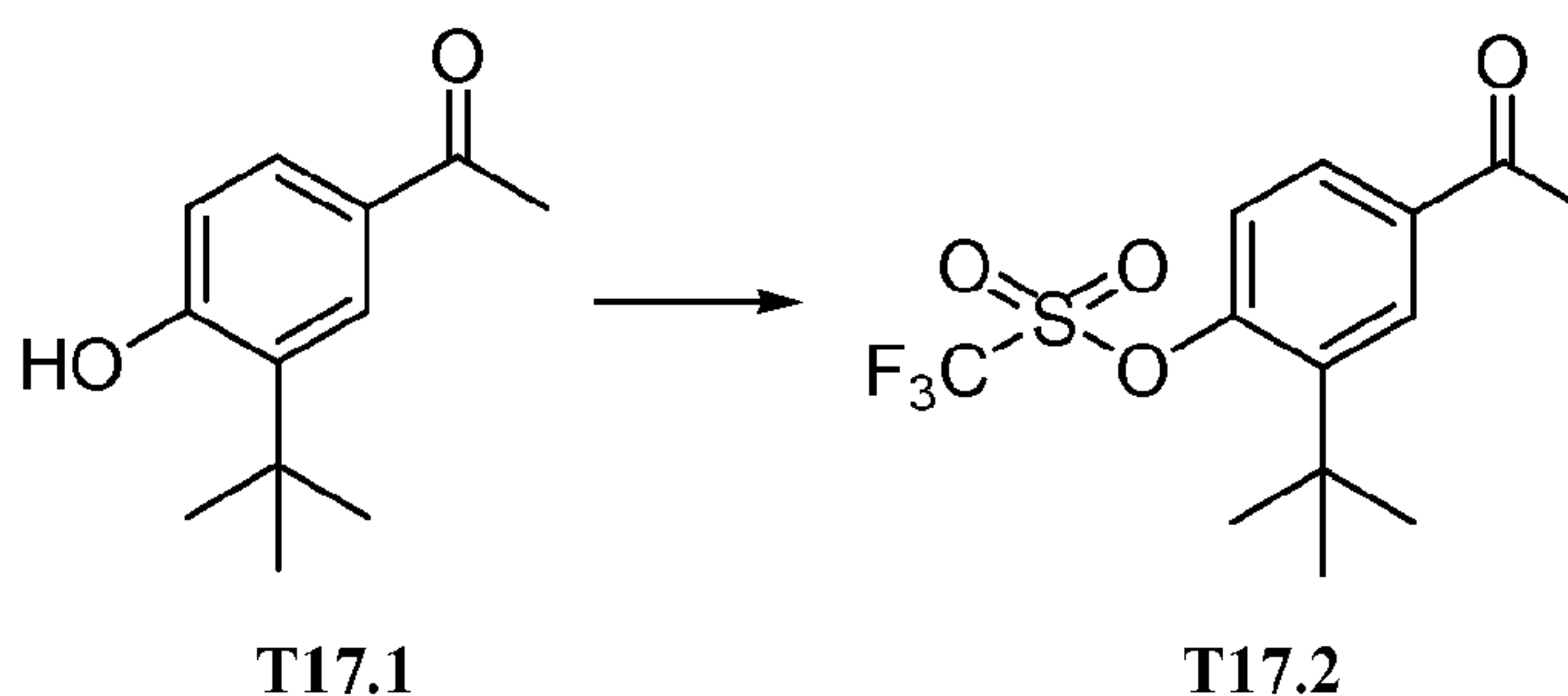


[0403] **4-(Chloromethyl)-2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl (T16).** A dry, round bottom flask containing **T16.2** (0.82 g, 3.04 mmol) and DCM (8.5 mL) was cooled to 0°C . After 15 minutes, thionyl chloride (1.50 mL, 20.56 mmol) was carefully added dropwise at 0°C . Upon complete addition of thionyl chloride, the mixture was allowed to warm to room temperature and stirred overnight. After 25 hours, the reaction was concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO_2 gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T16** as a colorless oil (0.82, 93%). ^1H NMR (500 MHz, CDCl_3) δ ppm 7.53 (1 H, d, $J=1.7$ Hz), 7.28 (3 H, m), 7.03 (1 H, d, $J=7.8$ Hz), 6.90 (3 H, m), 4.65 (2H, s), 3.82 (3 H, s), 1.23 (9H, s).

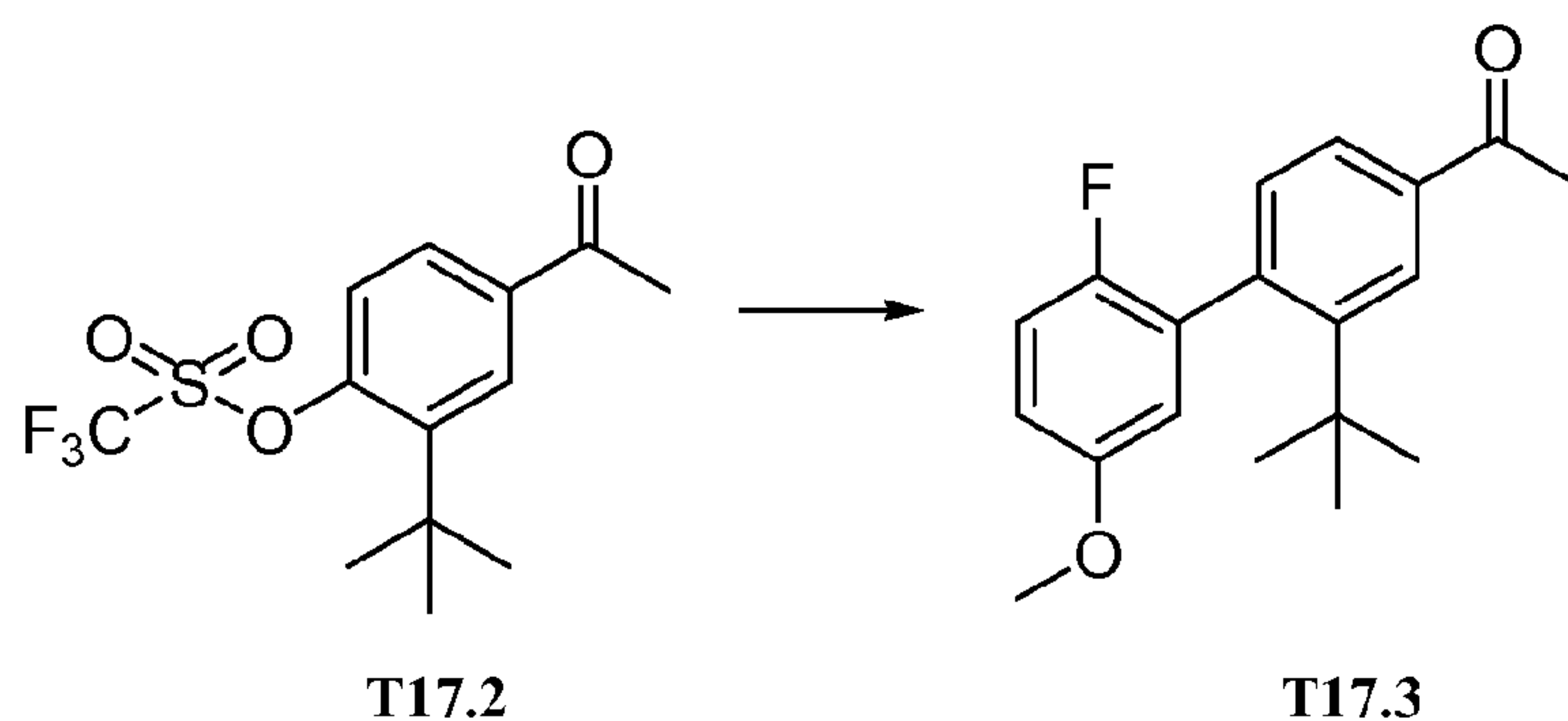
[0404] **Intermediates T17A and T17B**



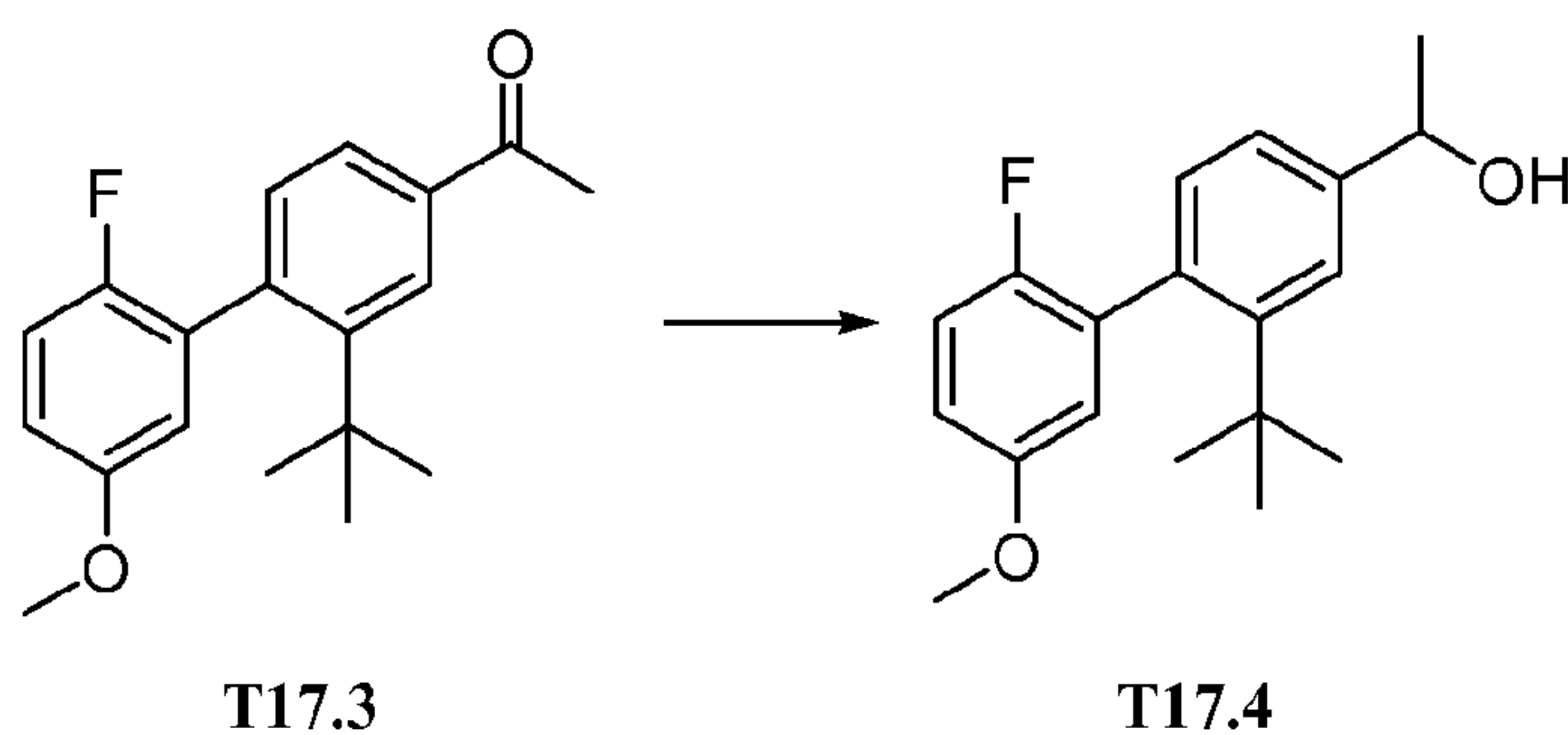
[0405] 1-(3-(1,1-Dimethylethyl)-4-hydroxyphenyl)ethanone (T17.1). To a dry, round bottom flask was added aluminum chloride (4.402g, 33.0 mmol). The flask was then cooled to -45°C. After 10 minutes, dry toluene (80 mL) was added followed by dropwise addition of 2-tert-butylphenol (5.00 mL, 32.7 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA). The mixture was stirred and maintained at -4°C. After 1.5 hours, acetyl chloride (2.40 mL, 33.8 mmol) was carefully added dropwise. The mixture was allowed to warm to room temperature and monitored with TLC and LC-MS. After 18 hours, the mixture was slowly poured onto crushed ice. This mixture was stirred at room temperature and the crystals were collected by filtration. The light yellow solid was identified as **T17.1** (4.2589 g, 68%). MS ESI (pos.) m/e: 193.1 (M+H)⁺.

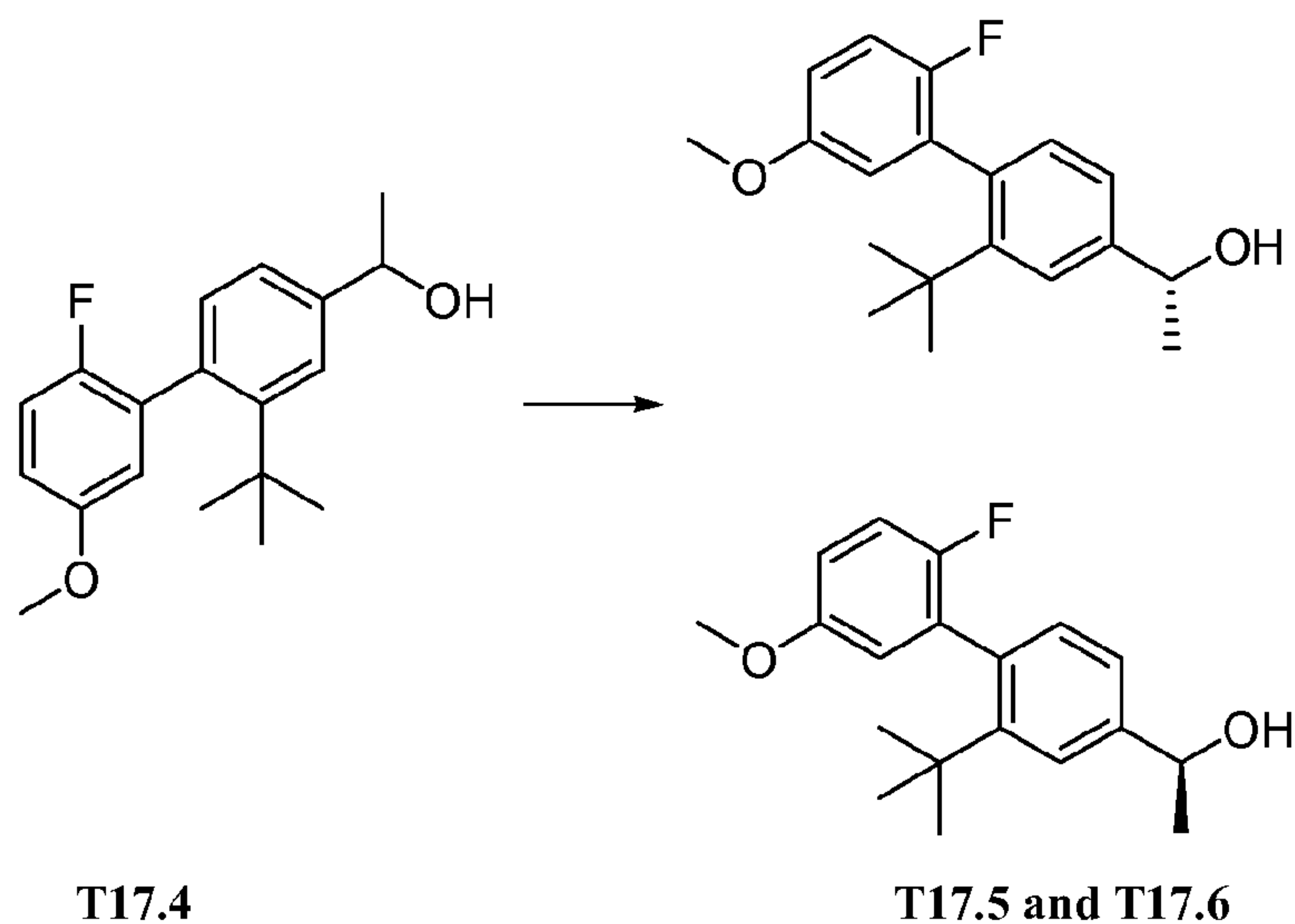


[0406] 4-Acetyl-2-(1,1-dimethylethyl)phenyl trifluoromethanesulfonate (T17.2). To a stirred solution of **T17.1** (2.0006 g, 10.41 mmol) in dry DCM (37 mL) was added TEA (3.0 mL, 21.57 mmol) and DMAP (0.1309 g, 1.071 mmol). After 20 minutes, N-phenyltrifluoromethanesulfonimide (5.5846 g, 15.63 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 4.5 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to yield **T17.2** (3.0227 g, 90 % yield). MS ESI (pos.) m/e: 325.1 (M+H)⁺.

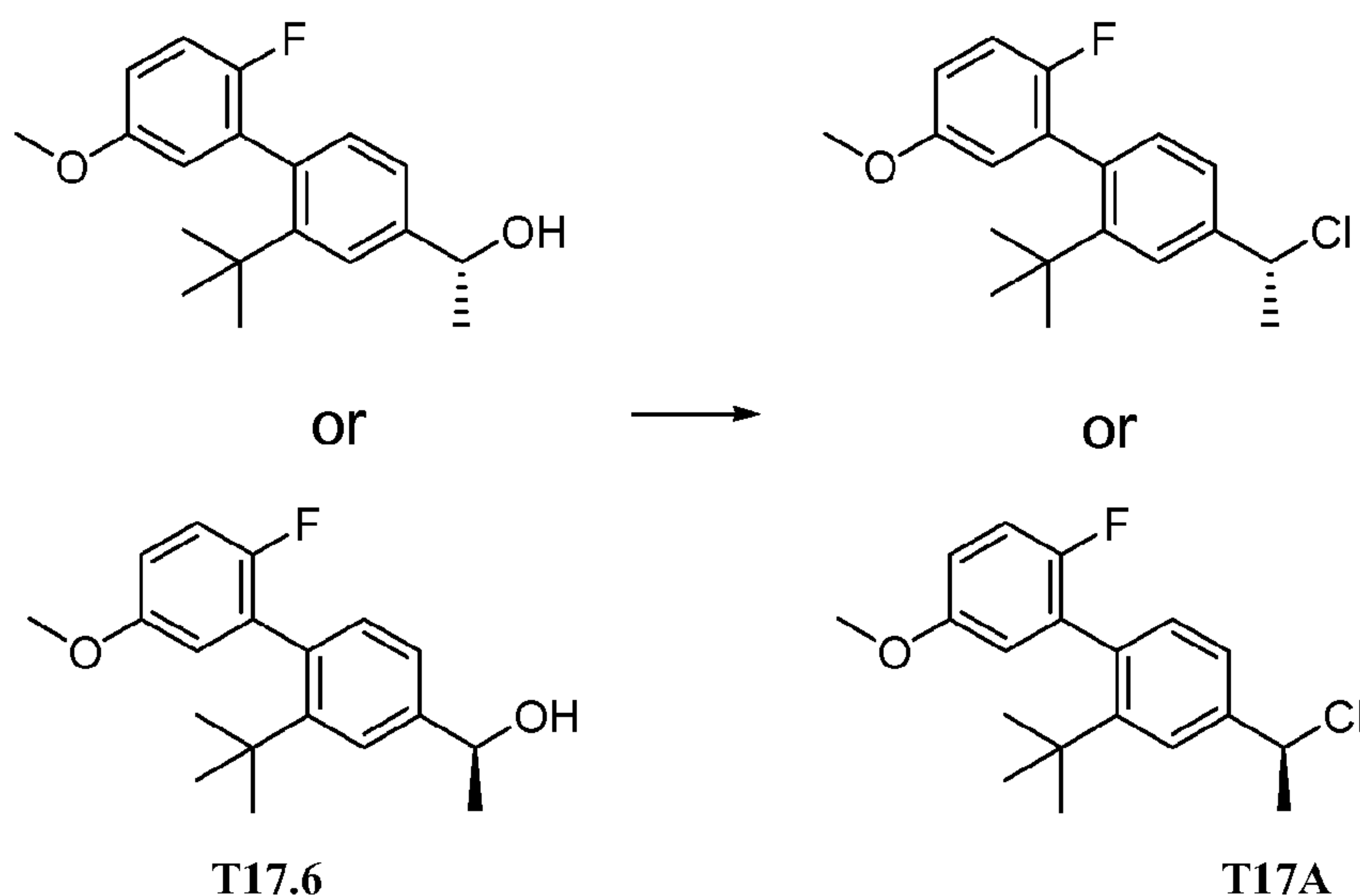


[0407] **1-(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethanone (T17.3).** A dry round bottom containing **T17.2** (3.0227 g, 9.3202 mmol), 2-fluoro-5-methoxyphenylboronic acid (2.4005 g, 14.125 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), tetrakis(triphenylphosphine)palladium (1.0853 g, 0.93920 mmol), and potassium carbonate (3.9996 g, 28.940 mmol) was evacuated and backfilled three times with argon. Dry DMF (25 mL) was added via syringe under argon, then the mixture was heated to 100 °C and monitored with TLC. After 3 hours, the reaction was cooled to room temperature, then diluted with water. The mixture was extracted three times with EtOAc then concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to yield **T17.3** (2.6053 g, 93 % yield). MS ESI (pos.) m/e: 301.1 (M+H)⁺.





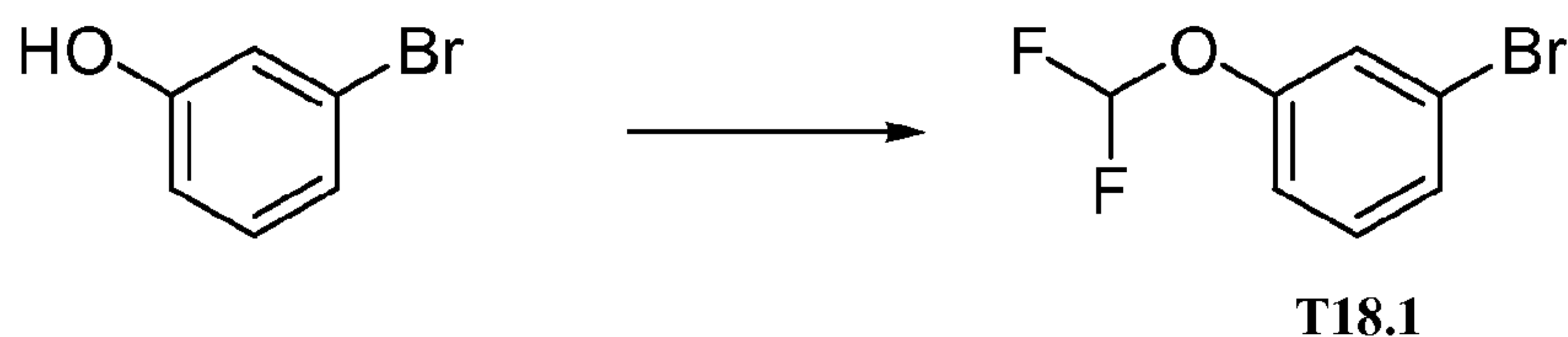
[0408] **1-(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethanol (T17.4).** To a dry round bottom flask containing **T17.3** (2.5921 g, 8.630 mmol) was added a premixed solution of dry MeOH (10 mL) and dry DCM (10 mL). After stirring at 0 °C for about 15 minutes, sodium borohydride (0.6632 g, 17.53 mmol) was carefully added at 0 °C. Upon complete addition, the reaction was allowed to warm to room temperature. After 2 hours, the reaction was cooled in an ice bath, then carefully quenched with water and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to yield **T17.4** (2.5329 g, 97 % yield). MS ESI (pos.) m/e: 285.1 (M-H₂O)⁺. Chiral separation of **T17.4** was accomplished using SFC with 9 g/min MeOH (0.6% DEA) + 81 g/min CO₂ on a 250 x 30 mm OD-H column. The outlet pressure of the system was set to 140 bar, temperature at 25 °C and detector wavelength was 220 nm. Sample was dissolved to 54 mg/mL in MeOH and separations on 13.5 mg injections were performed at a rate of one injection per 1.65 minutes to provide **T7.5** (peak 1) and **T17.6** (peak 2).



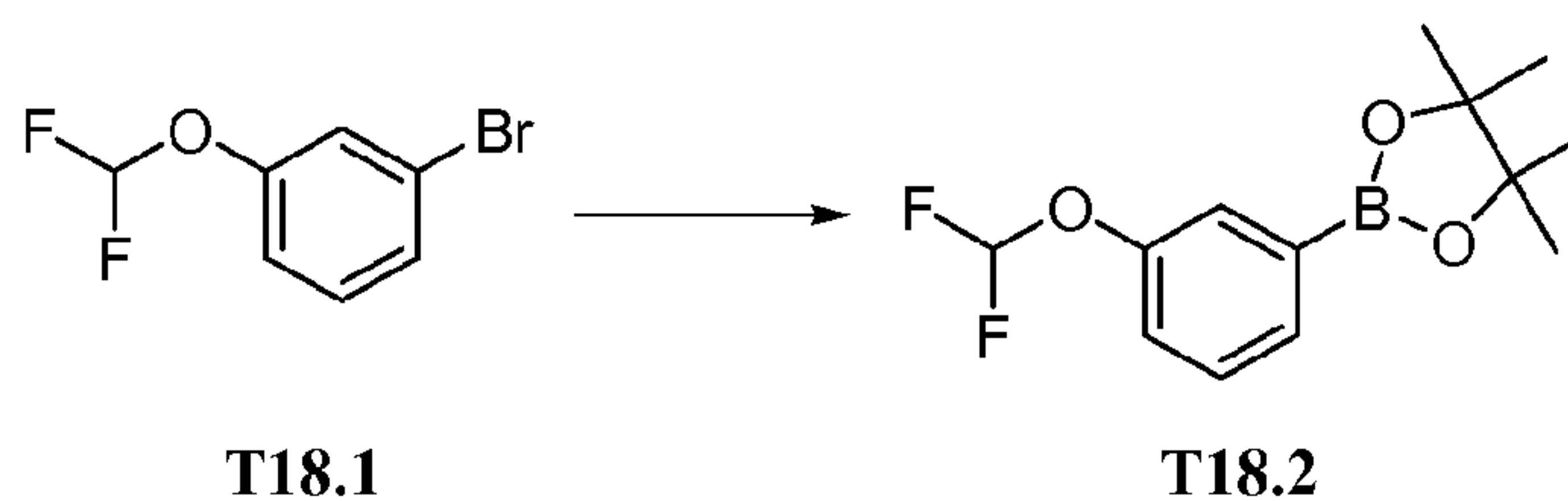
[0409] **4-((1S)-1-Chloroethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-((1R)-1-chloroethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T17A).** A dry, round bottom flask containing **T17.6** (1.0221 g, 3.380 mmol) was evacuated and backfilled with argon. Dry DCM (14 mL) was added under argon, and the homogeneous solution was cooled to 0 °C. After 15 minutes, thionyl chloride (1.0 mL, 13.71 mmol) was carefully added dropwise at 0 °C. Upon complete addition of thionyl chloride, the mixture was allowed to warm to room temperature and stirred overnight. After 2.5 hours, the reaction was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to yield **T17A** (744.7 mg, 69 % yield). MS ESI (pos.) m/e: 338.2 (M+H₂O)⁺.

[0410] **4-((1S)-1-Chloroethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-((1R)-1-chloroethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T17B).** This compound is prepared from **T17.5** using the same procedure described above with respect to **T17A**.

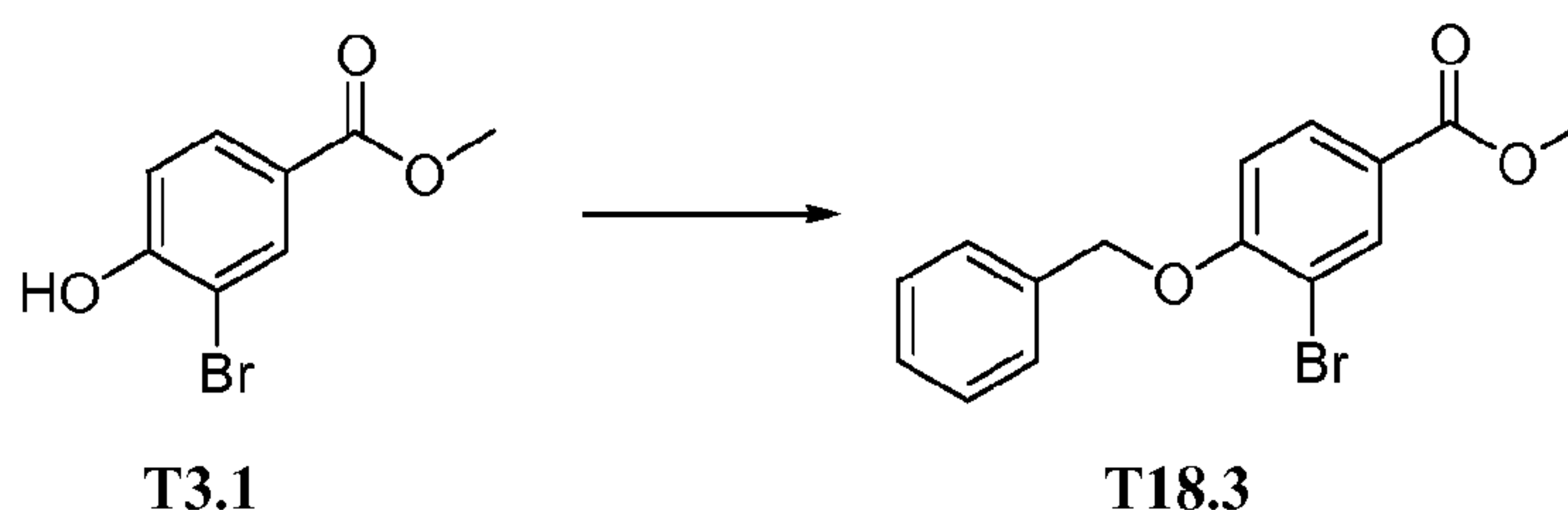
[0411] **Intermediates T18A and T18B**



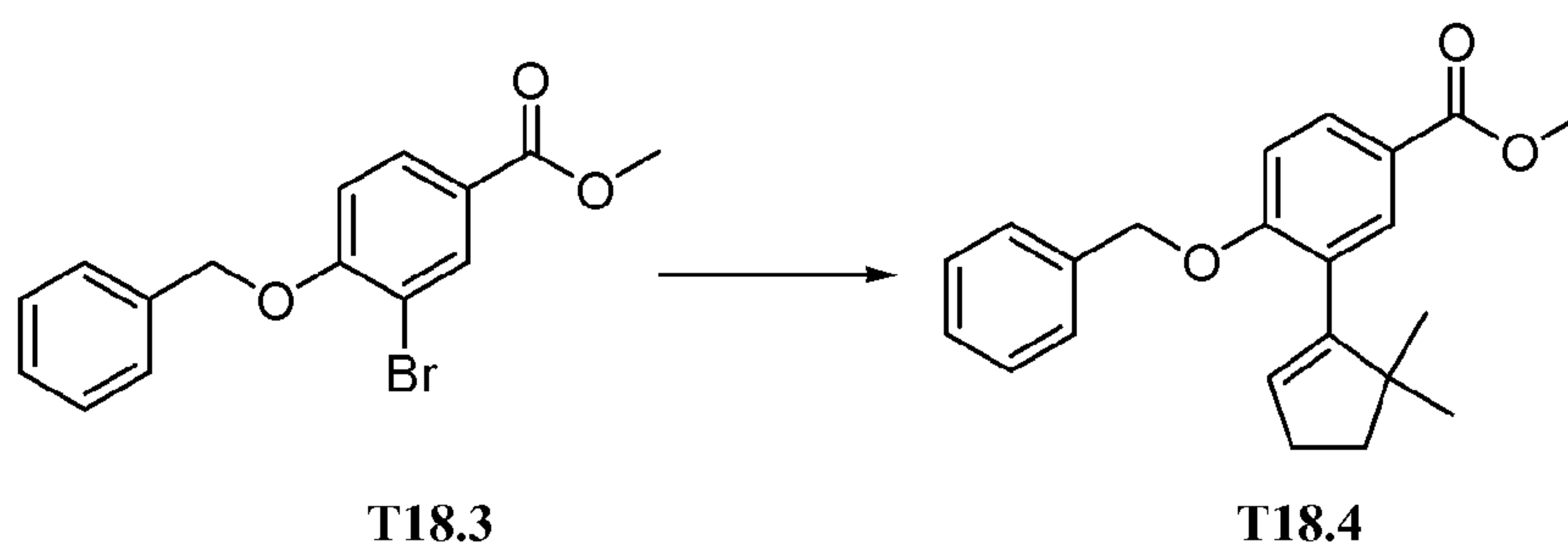
[0412] **1-Bromo-3-(difluoromethoxy)benzene (T18.1).** To a solution of 3-bromophenol (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (1.28 g, 7.39 mmol) in DMF (12.0 mL) was added sodium 2-chloro-2,2-difluoroacetate (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (2.82 g, 18.49 mmol) and Cs_2CO_3 (4.82 g, 14.79 mmol). The reaction mixture was heated at 100°C. Gas was released from the reaction so care should be taken. After 2 hours, the reaction was cooled to room temperature then diluted with EtOAc, washed with water and then brine and re-extracted three times with EtOAc. The combined organic layers were dried over magnesium sulfate and then filtered, concentrated, and purified with silica gel chromatography (0-5% EtOAc in hexanes) to yield **T18.1** as an oil that was used without further purification (yield 61%).



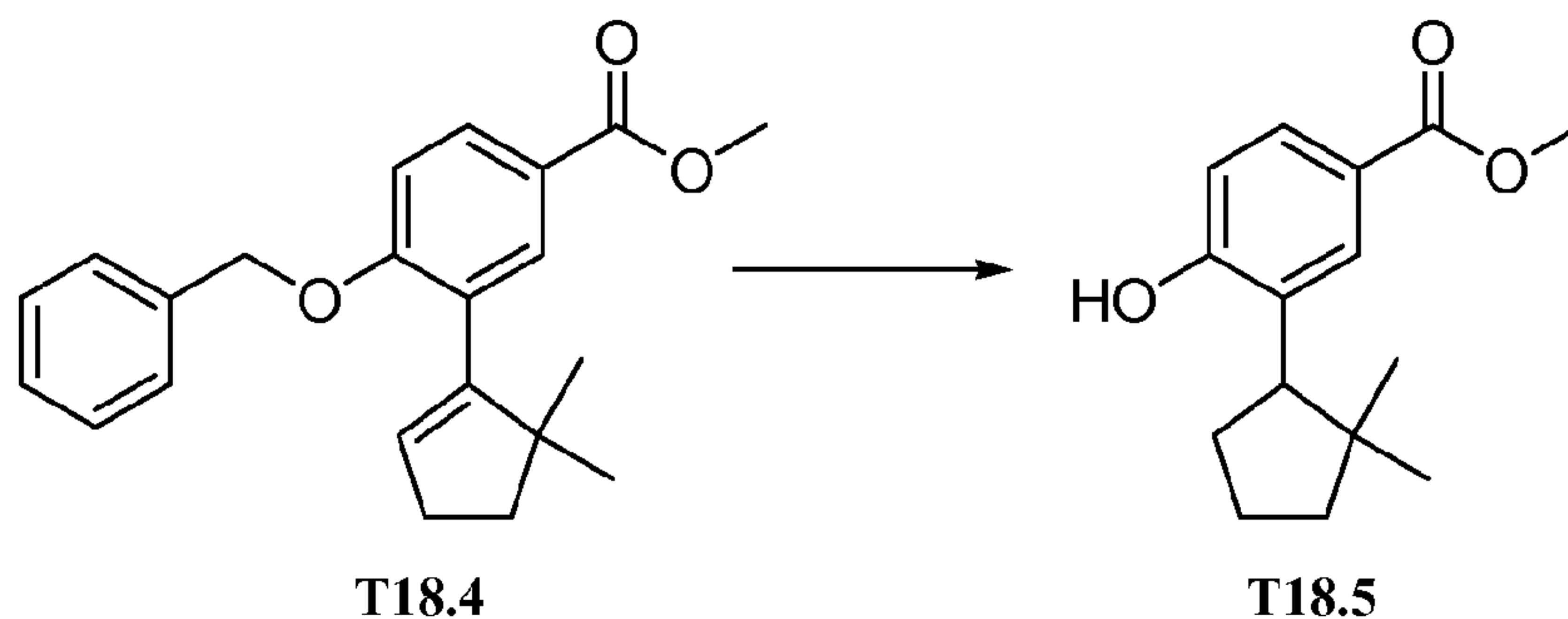
[0413] **2-(3-(Difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (T18.2).** A stirred mixture of **T18.1** (1.00 g, 4.50 mmol), bis(pinacolato)diboron (1.26 g, 4.95 mmol), potassium acetate (1.34 g, 13.70 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]dichloride palladium(II) DCM adduct (0.17 g, 0.23 mmol) in dry 1,4-dioxane (10.0 mL) was purged three times with argon and placed under vacuum three times. The mixture was heated to 100°C and monitored with LC-MS and TLC. After 21 hours, the reaction was cooled to room temperature and then filtered through Celite® filter aid. The organic solvent was removed under reduced pressure, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **T18.2** as a colorless oil (0.41 g, 34%). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.67 (1 H, d, $J=7.4$ Hz), 7.56 (1 H, d, $J=2.3$ Hz), 7.41 (1 H, m), 7.22 (1 H, dd, $J=7.8, 2.3$ Hz), 6.73 (1H, t, $J=7.4$ Hz), 1.36 (12 H, s).



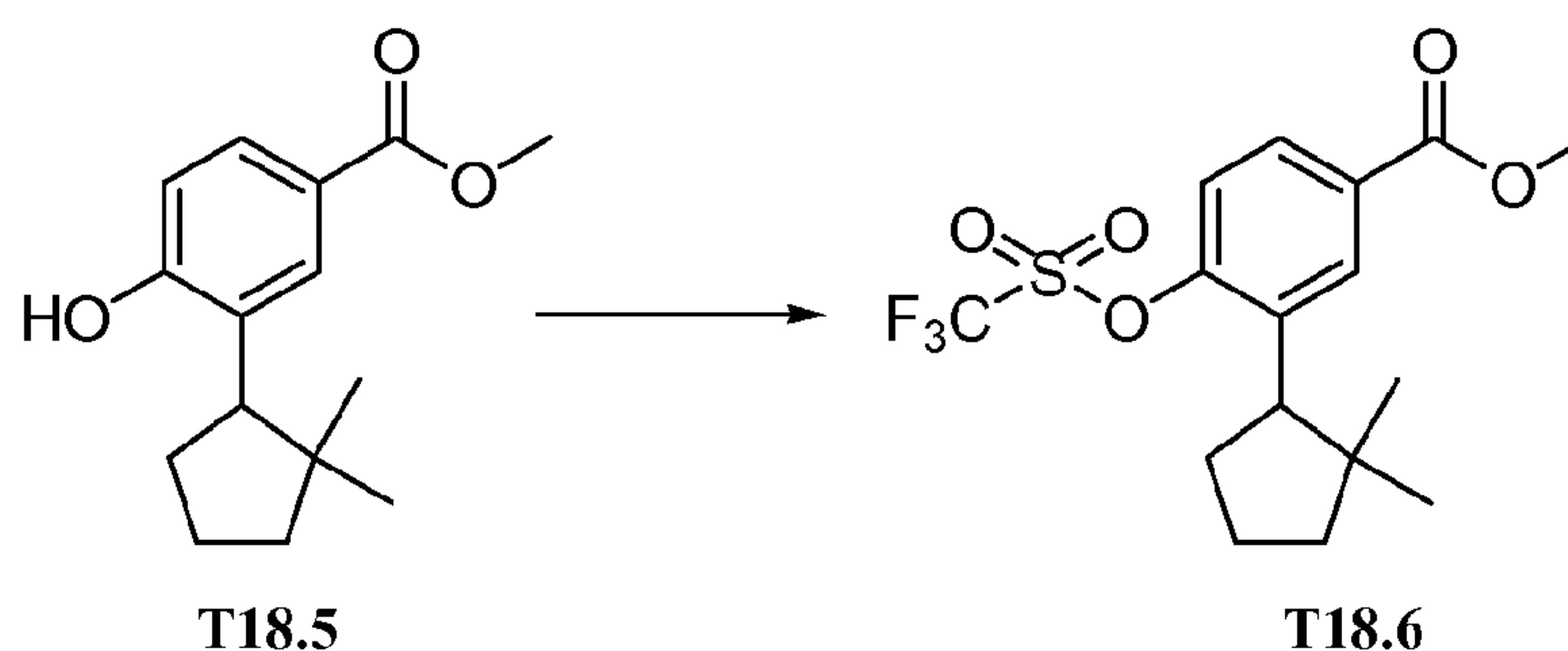
[0414] **Methyl 4-(benzyloxy)-3-bromobenzoate (T18.3).** To a solution of **T3.1** (53.2 g, 230 mmol) in DMSO (45.0 mL) was added 1-(bromomethyl)benzene (35.6 mL, 299 mmol). After cooling in an ice water bath, Cs_2CO_3 (128 g, 391 mmol) was carefully added to the mixture, and the mixture was allowed to warm to room temperature. After overnight stirring, the mixture was diluted with water and extracted three times with EtOAc. The organic layers were combined and then washed with brine. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure to yield **T18.3** as a white solid.



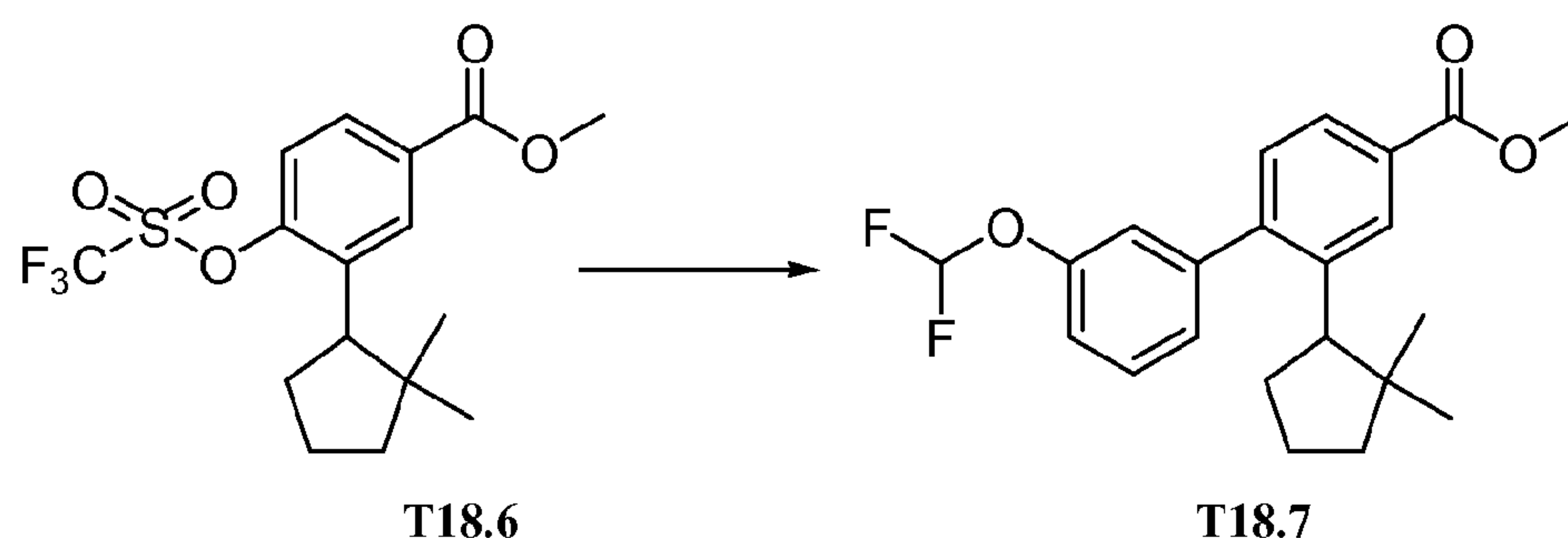
[0415] **Methyl 4-(benzyloxy)-3-(5,5-dimethylcyclopent-1-enyl)benzoate (T18.4).** A stirred mixture of **T18.3** (3.75 g, 11.66 mmol), ground S-Phos (0.96 g, 2.33 mmol), palladium acetate (0.26 g, 1.17 mmol), and potassium phosphate, tribasic (6.19 g, 29.17 mmol) in DMF (28.0 mL) and water (1.50 mL) was purged three times with argon and placed under vacuum three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**T2.2**) (3.11 g, 13.99 mmol) was added via syringe, then the mixture was heated to 75 °C. After 21 hours (black solution), the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The combined organic layers were washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **T18.4** as a colorless oil (3.03 g, 77%). MS ESI (pos.) m/e : 337.0 ($\text{M}+\text{H}$)⁺.



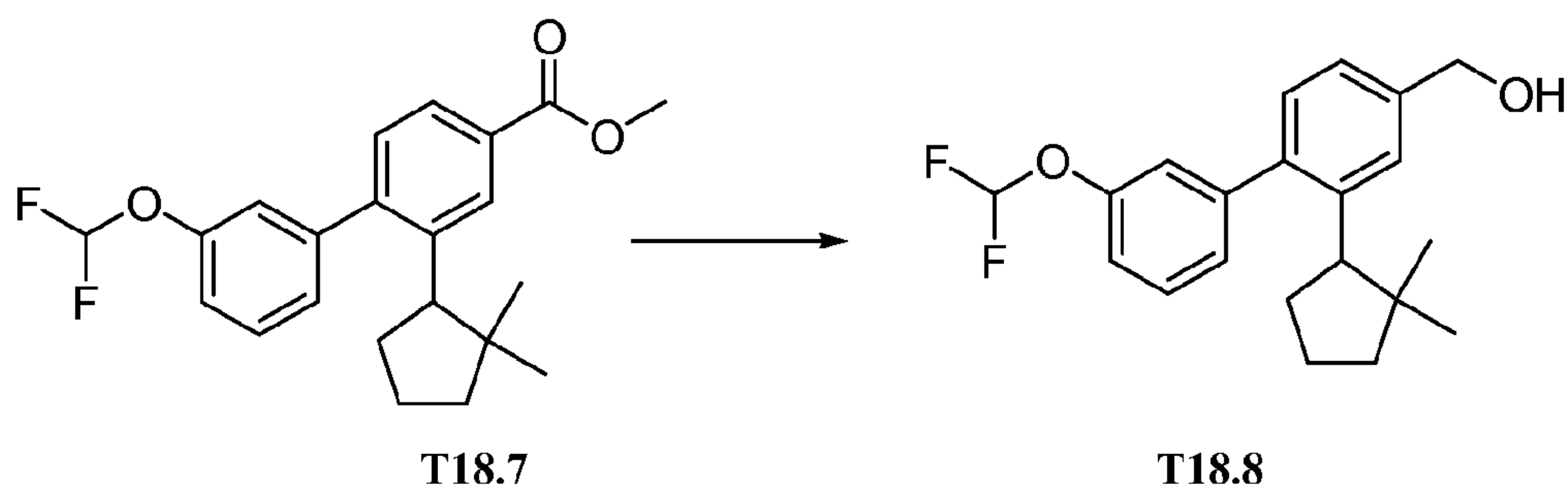
[0416] **Methyl 3-(2,2-dimethylcyclopentyl)-4-hydroxybenzoate (T18.5).** To a flask containing **T18.4** (3.03 g, 9.0 mmol) in MeOH (25.0 mL) was added palladium, 10% wt. on activated carbon (0.48 g, 0.45 mmol). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. The reaction was monitored with TLC and LC-MS. After 27.5 hours, the reaction was filtered through Celite® filter aid. After concentration, the residue was purified on silica gel using 0-50% EtOAc in hexanes to yield **T18.5** as a colorless oil that solidified (1.99 g, 89%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.91 (1 H, d, J=2.3 Hz), 7.79 (1 H, dd, J=8.4, 2.2 Hz), 6.82 (1 H, d, J=8.2 Hz), 5.54 (1 H, s), 3.90 (3 H, s), 3.17 (1 H, dd, J=10.4, 8.0 Hz), 2.17 (1 H, m), 2.04 (1 H, m), 1.92 (1 H, m), 1.81 (1 H, m), 1.68 (2 H, m), 1.06 (3 H, s), 0.72 (3 H, s).

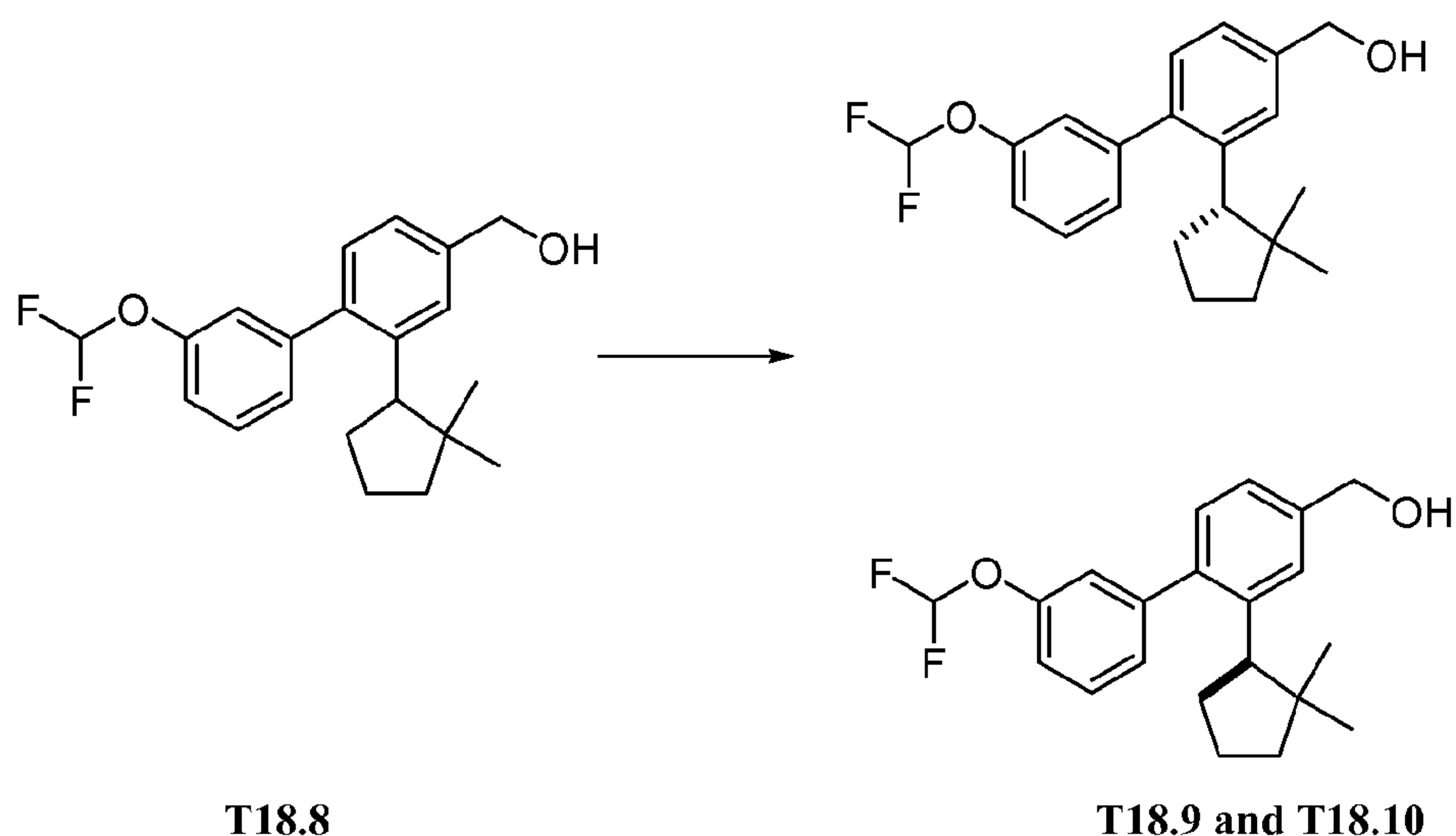


[0417] **Methyl 3-(2,2-dimethylcyclopentyl)-4-(trifluoromethylsulfonyloxy)benzoate (T18.6).** To a stirred solution of **T18.5** (0.93 g, 3.74 mmol) in dry DCM (10.0 mL) was added TEA (1.1 mL, 7.89 mmol) and 4-(dimethylamino)pyridine (46.2 mg, 0.378 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.61 g, 4.51 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 3.5 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure and the residue was purified with silica gel chromatography using 0-10% EtOAc in hexanes to yield **T18.6** as a colorless oil (1.21 g, 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.08 (1 H, d, J=2.2 Hz), 7.95 (1 H, dd, J=8.6, 2.2 Hz), 7.35 (1 H, d, J=8.6 Hz), 3.95 (3 H, s), 3.21 (1 H, dd, J=9.8, 8.4 Hz), 2.14 (2 H, m), 1.95 (1 H, m), 1.86 (1 H, m), 1.69 (2 H, m), 1.02 (3 H, s), 0.70 (3 H, s).

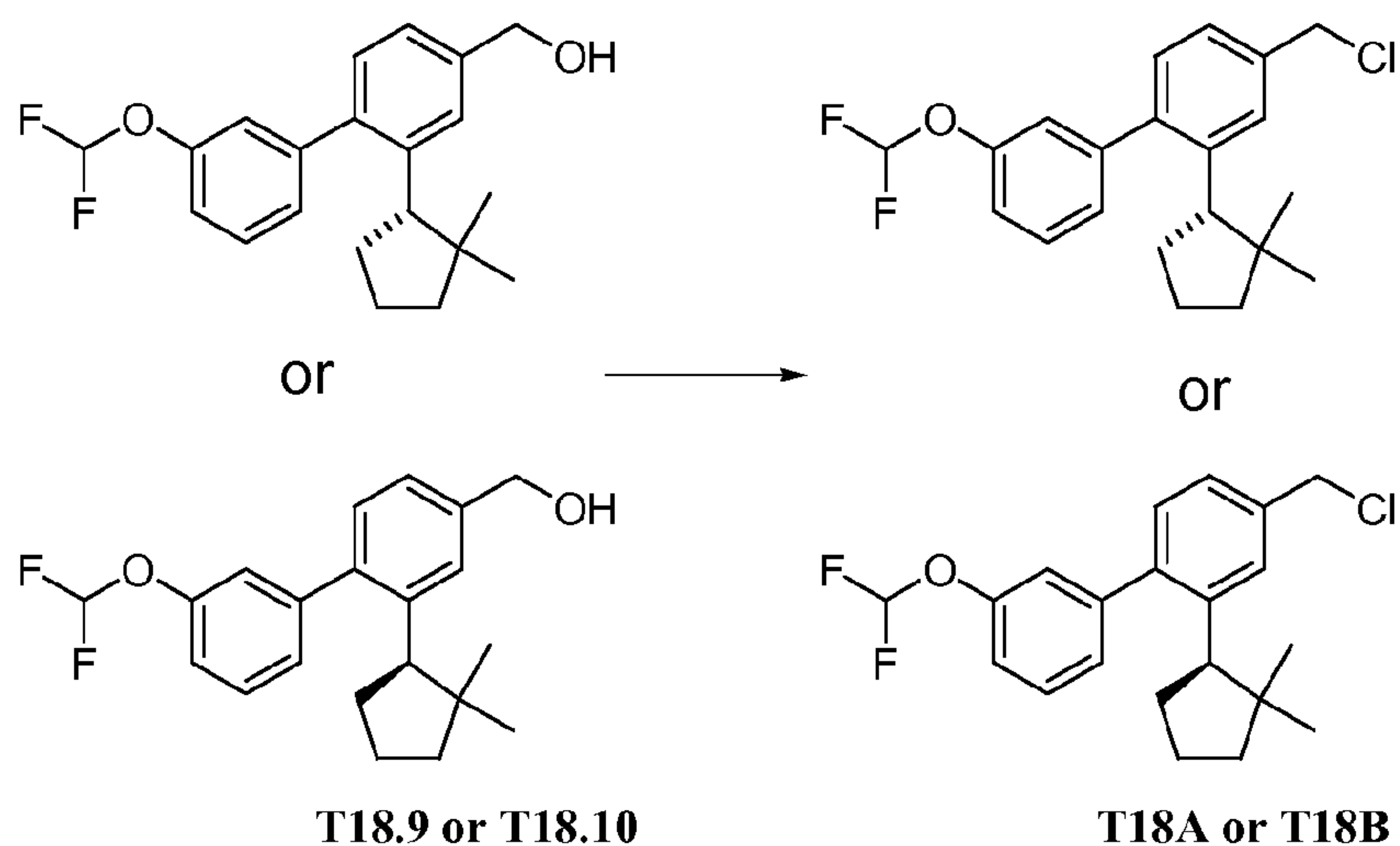


[0418] Methyl 3'-((difluoromethyl)oxy)-2-(2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-carboxylate (T18.7). A stirred mixture of **T18.6** (0.48 g, 1.26 mmol), ground S-Phos (104.8 mg, 0.255 mmol), palladium acetate (29.1 mg, 0.130 mmol), and potassium phosphate tribasic (0.6727 g, 3.17 mmol) in dry DMF (5.0 mL) was purged with argon and placed under vacuum (repeated three times). Before heating, **T18.2** (0.512 g, 1.89 mmol) was added via syringe, and then the mixture was heated to 75°C. After 16 hours, the reaction was cooled to room temperature, diluted with water and extracted three times with EtOAc. The combined organic layers were washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **T18.7** as a colorless oil (308.9 mg, 65%). ¹H NMR (500 MHz, CDCl₃) δ ppm 8.11 (1 H, d, J=1.7 Hz), 7.90 (1 H, dd, J=7.9, 1.8 Hz), 7.44 (1 H, m), 7.28 (1 H, m), 7.16 (2 H, m), 7.07 (1 H, s), 6.57 (1H, t, J = 75 Hz), 3.97 (3 H, s), 3.10 (1 H, t, J=9.4 Hz), 2.13 (2 H, m), 1.90 (1 H, m), 1.73 (1 H, m), 1.61 (1 H, m), 1.38 (1 H, ddd, J=12.6, 9.4, 7.6 Hz), 0.75 (3 H, s), 0.58 (3 H, s).



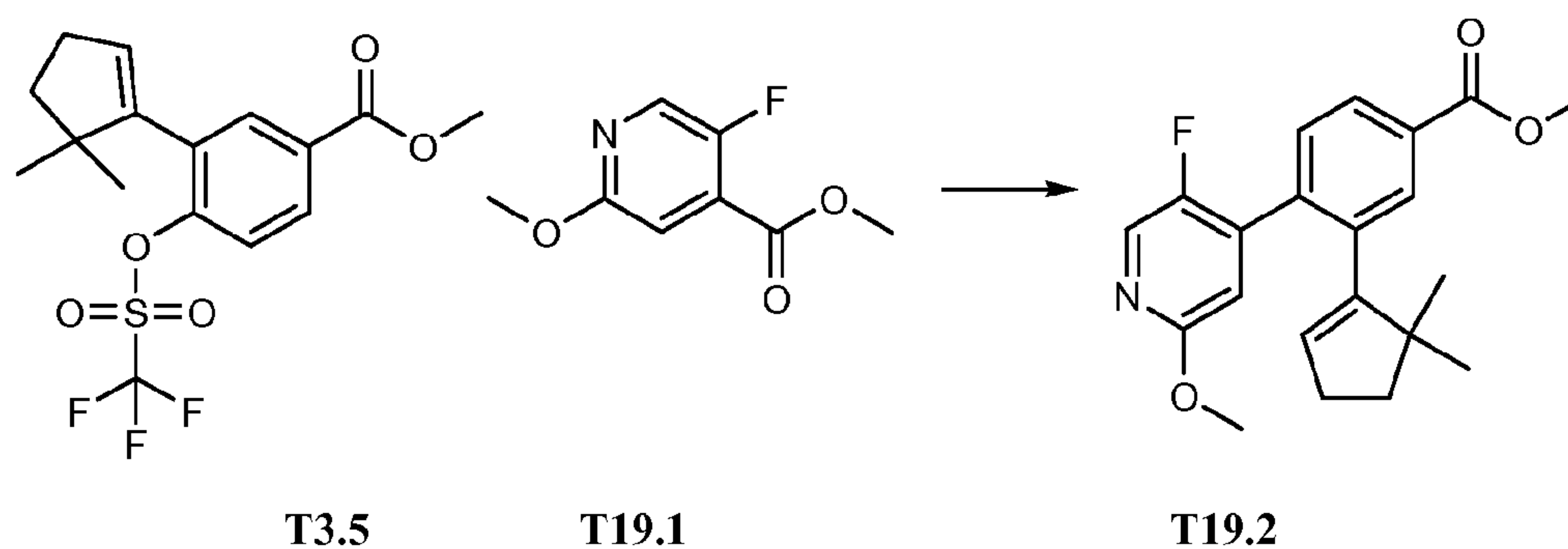
**T18.8****T18.9 and T18.10**

[0419] **(3'-((Difluoromethyl)oxy)-2-(2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methanol (T18.8).** To a cooled solution of **T18.7** (308.9 mg, 0.82 mmol) in dry THF (8.0 mL) at 0°C was added LAH, 1.0 M in THF (1.70 mL, 1.70 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction. The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to yield **T18.8** as a colorless oil (261.6 mg, 92%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.41 (2 H, m), 7.26 (1 H, m), 7.21 (1 H, m), 7.14 (2 H, m), 7.05 (1 H, s), 6.55 (1H, t, J = 75 Hz), 4.76 (2 H, m), 3.07 (1 H, dd, J=10.3, 8.6 Hz), 2.10 (2 H, m), 1.86 (1 H, m), 1.71 (1 H, m), 1.55 (1 H, ddd, J=12.7, 8.1, 4.9 Hz), 1.37 (1 H, ddd, J=12.5, 9.5, 7.6 Hz), 0.75 (3 H, s), 0.60 (3 H, s). Chiral separation of **T18.8** was accomplished on a CHIRALCEL® OD column (3% IPA in hexane) to provide **T18.9** (peak 1) and **T18.10** (peak 2).



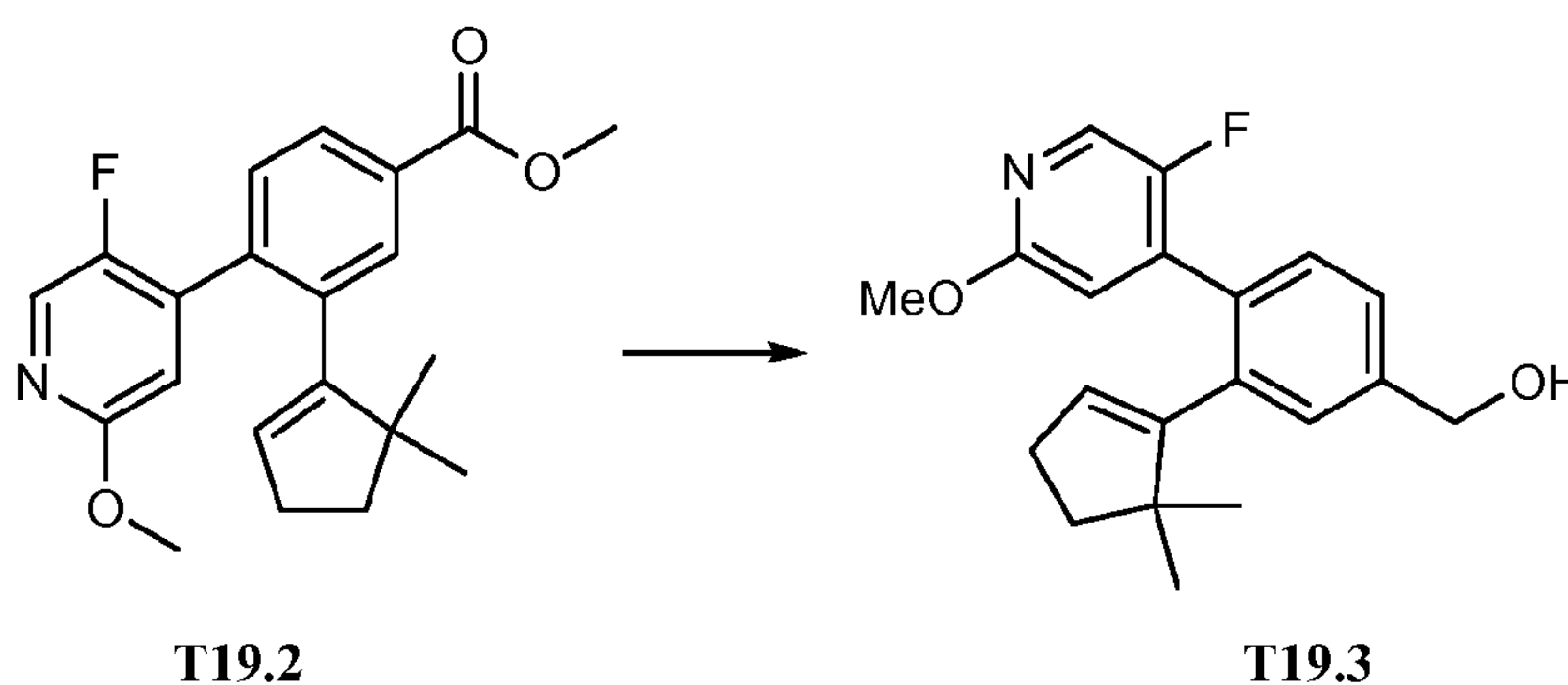
[0420] **4-(Chloromethyl)-3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl or 4-(chloromethyl)-3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl (T18A or T18B).** To a solution of **T18.9** or **T18.10** (112.7 mg, 0.325 mmol) in dry DCM (4.0 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.06 mL, 0.823 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to yield **T18A** or **T18B** (99.5 mg, 84 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.42 (2 H, m), 7.25 (1 H, d, J=2.0 Hz), 7.19 (1 H, m), 7.11 (2 H, dd, J=7.8, 2.0 Hz), 7.03 (1 H, s), 6.54 (1H, t, J= 74 Hz), 4.66 (2 H, m), 3.04 (1 H, dd, J=10.4, 8.4 Hz), 2.14 (2 H, m), 1.88 (1 H, m), 1.73 (1 H, m), 1.54 (2 H, ddd, J=12.7, 8.2, 4.9 Hz), 1.41 (1 H, m), 0.73 (3 H, s), 0.56 (3 H, s).

[0421] **Intermediate T19**

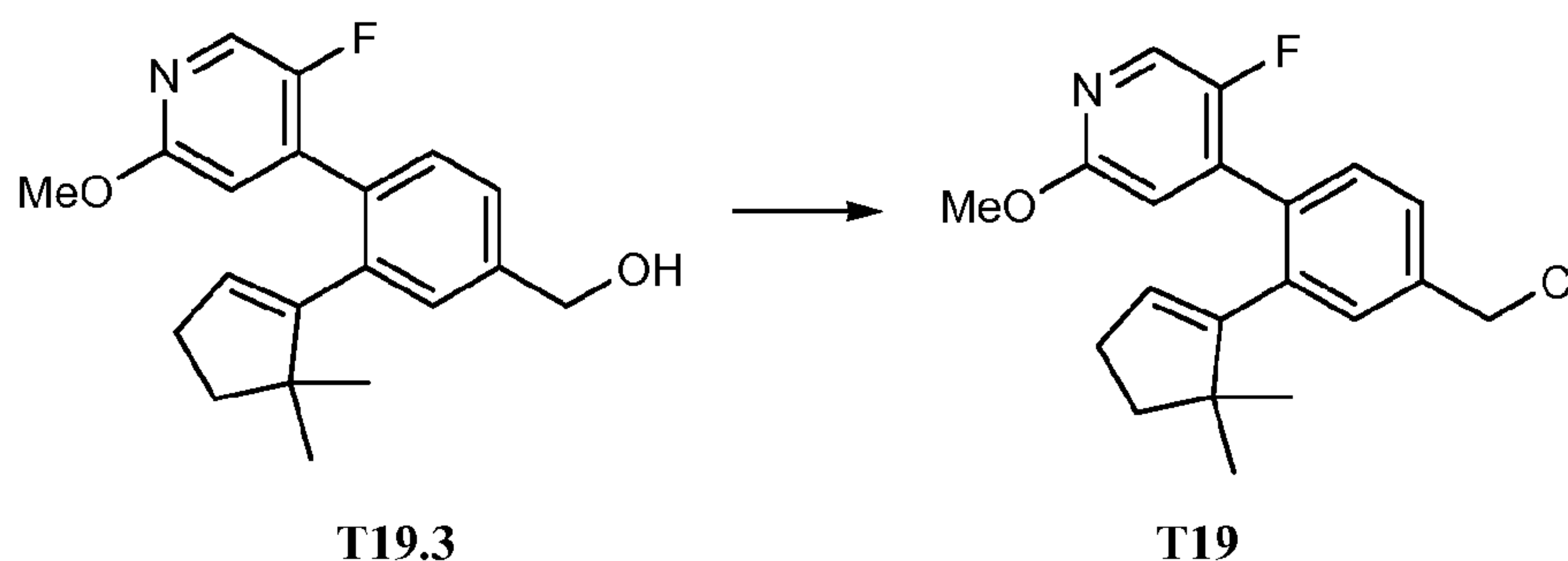


[0422] **Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzoate (T19.2).** To a flask with methyl 3-(5,5-

dimethylcyclopent-1-enyl)-4-(trifluoromethylsulfonyloxy)benzoate **T3.5** (404 mg, 1068 μmol) was added $\text{Pd}(\text{PPh}_3)_4$ (123 mg, 107 μmol), potassium carbonate (443 mg, 3203 μmol), 5-fluoro-2-methoxypyridin-4-ylboronic acid **T19.1** (456 mg, 2669 μmol , commercially available from Asymchem). The mixture was then degassed, and DMF (3 mL) was added. The reaction was stirred overnight at 87°C and worked up with EtOAc and water. Silica gel chromatography (0-50% EtOAc/Hexanes) afforded methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzoate **T19.2** (295 mg, 78%).



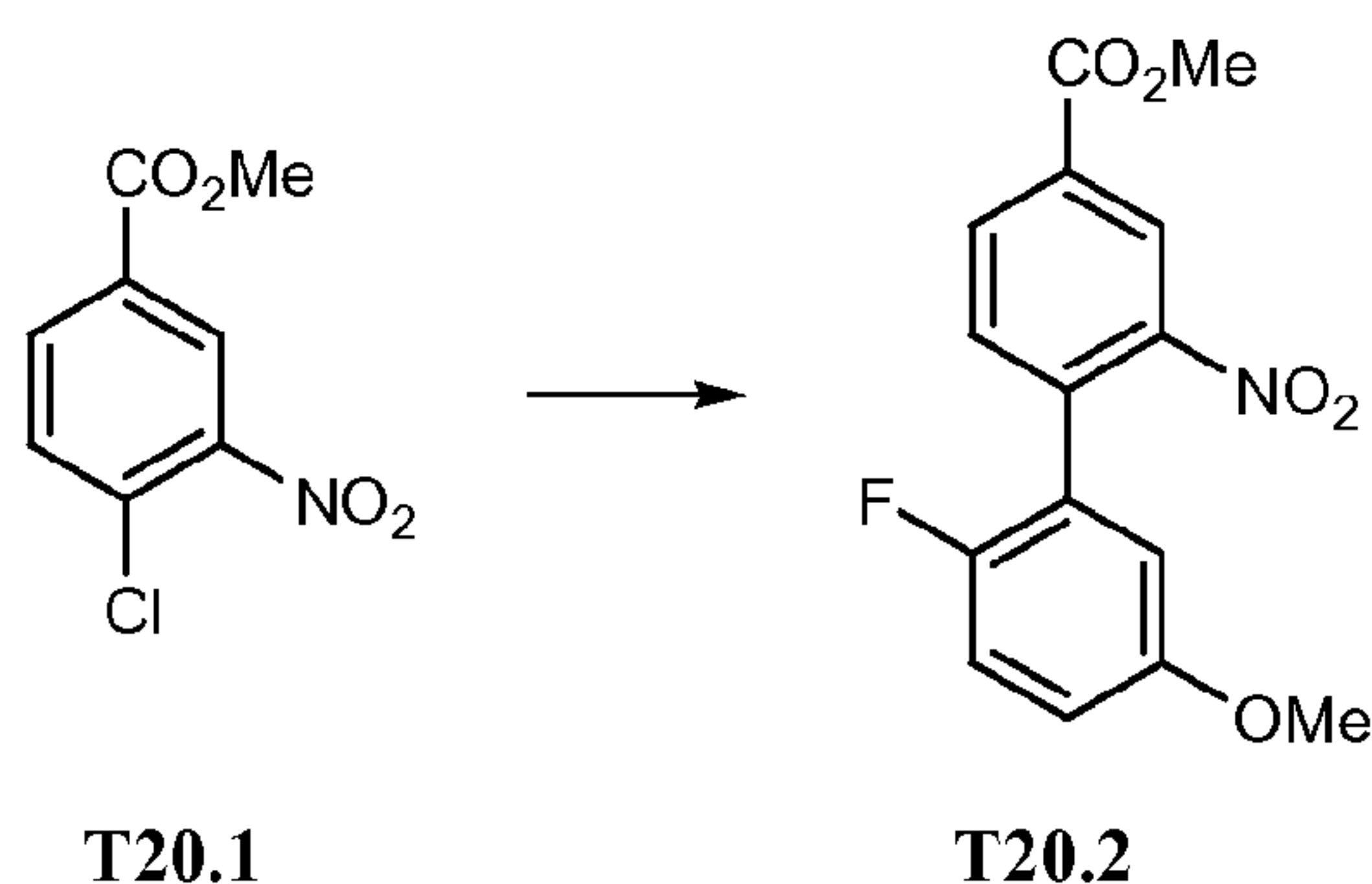
[0423] **(3-(5,5-Dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol (T19.3)**. To methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzoate **T19.2** (295 mg, 830 μmol) was added THF. The mixture was cooled to 0°C, and LAH (1660 μL , 1660 μmol) was added dropwise. The reaction was stirred at room temperature for 1 hour, and was quenched with water and a small amount of Rochelle's salt solution. Purification with silica gel chromatography afforded (3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol **T19.3** (201 mg) as an oil (74%).



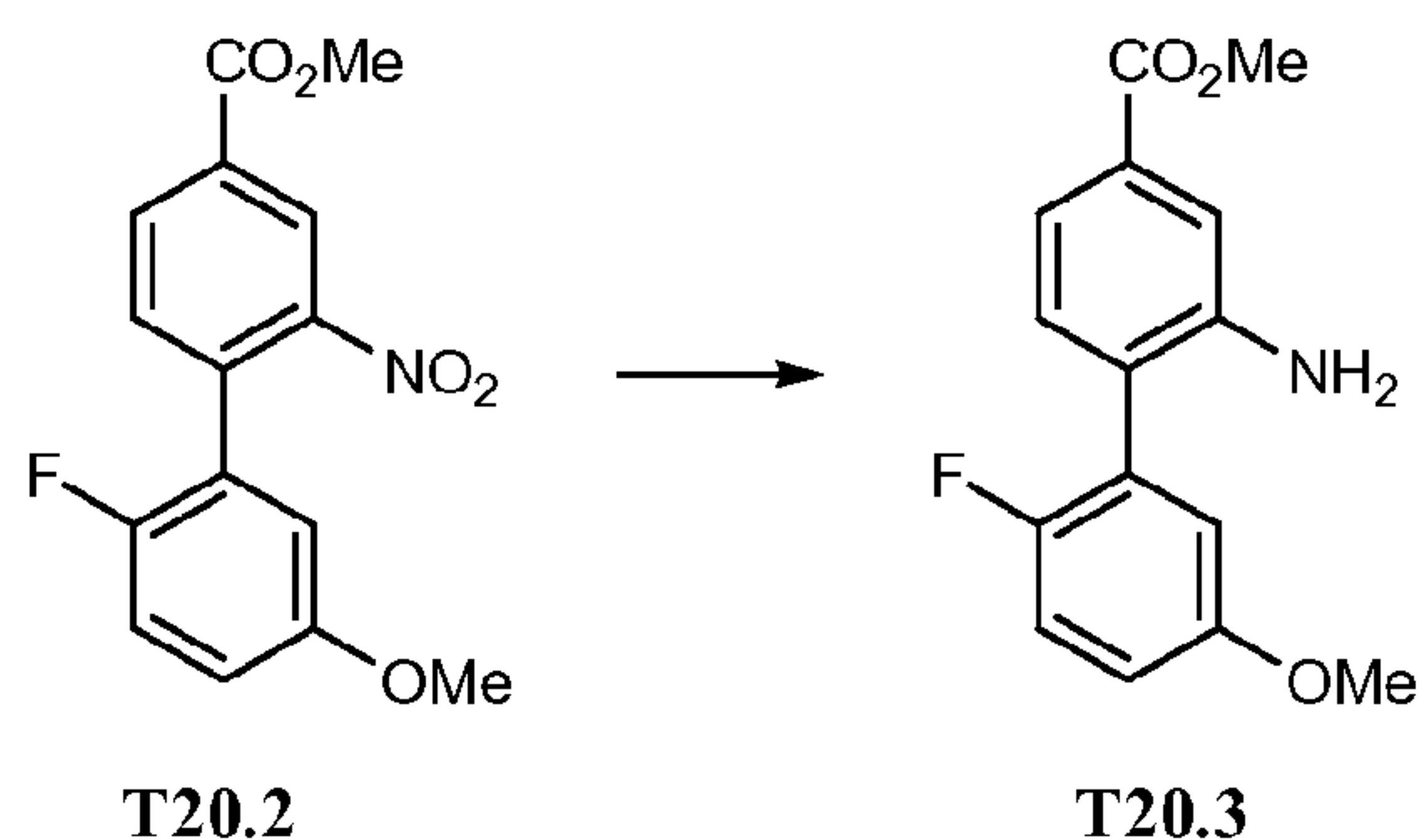
[0424] **4-(4-(Chloromethyl)-2-(5,5-dimethylcyclopent-1-enyl)phenyl)-5-fluoro-2-methoxypyridine (T19)**. To (3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol **T19.3** (34.5 mg, 105 μmol) was added DCM (1.1

mL) and DMF (8.2 μ L, 105 μ mol) followed by thionyl chloride (15 μ L, 211 μ mol) in an ice bath. The reaction was then stirred at room temperature for 1 hour. The reaction was concentrated and directly purified on silica gel to afford 4-(4-(chloromethyl)-2-(5,5-dimethylcyclopent-1-enyl)phenyl)-5-fluoro-2-methoxypyridine **T19** (36 mg) as an oil (99%).

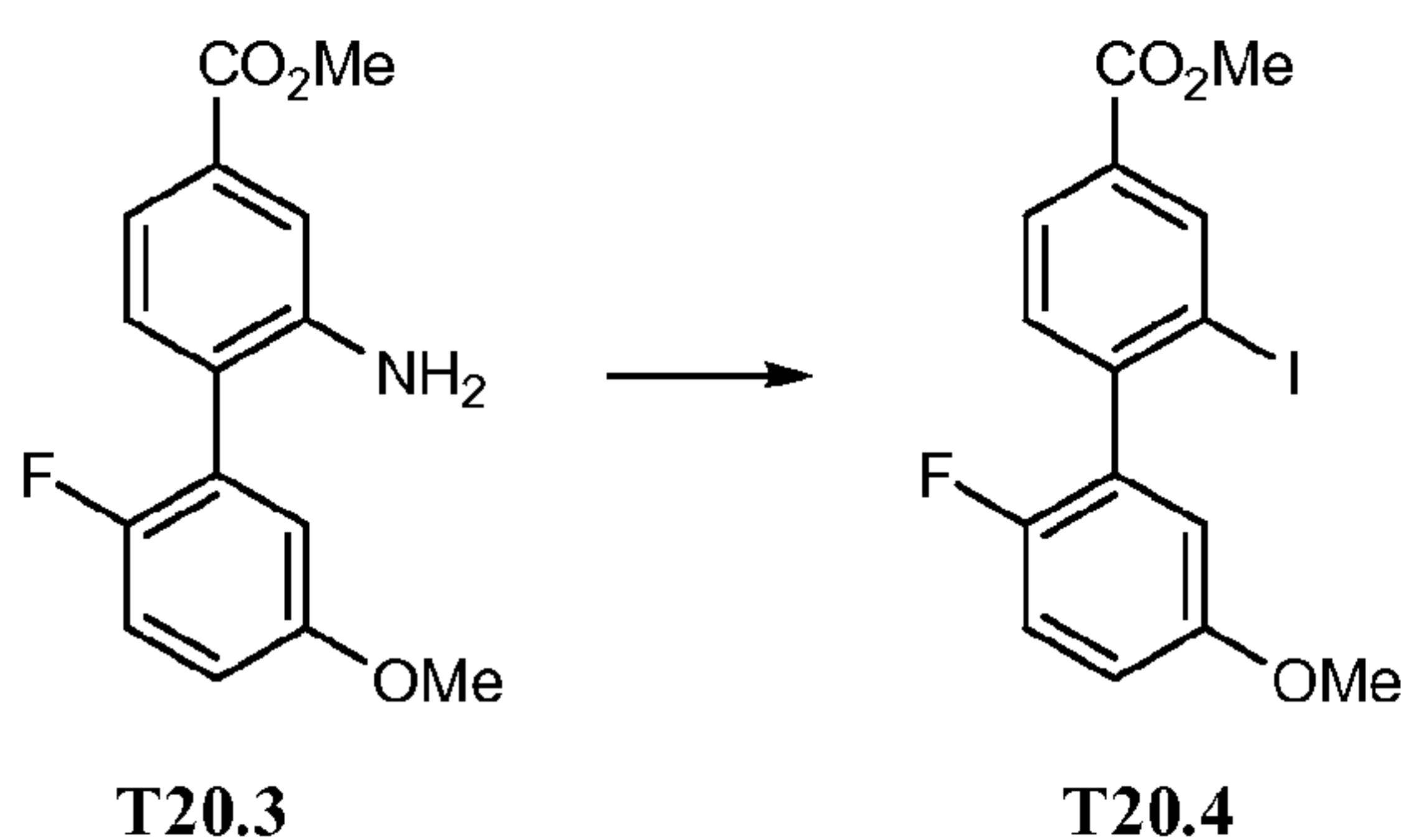
[0425] Intermediate T20



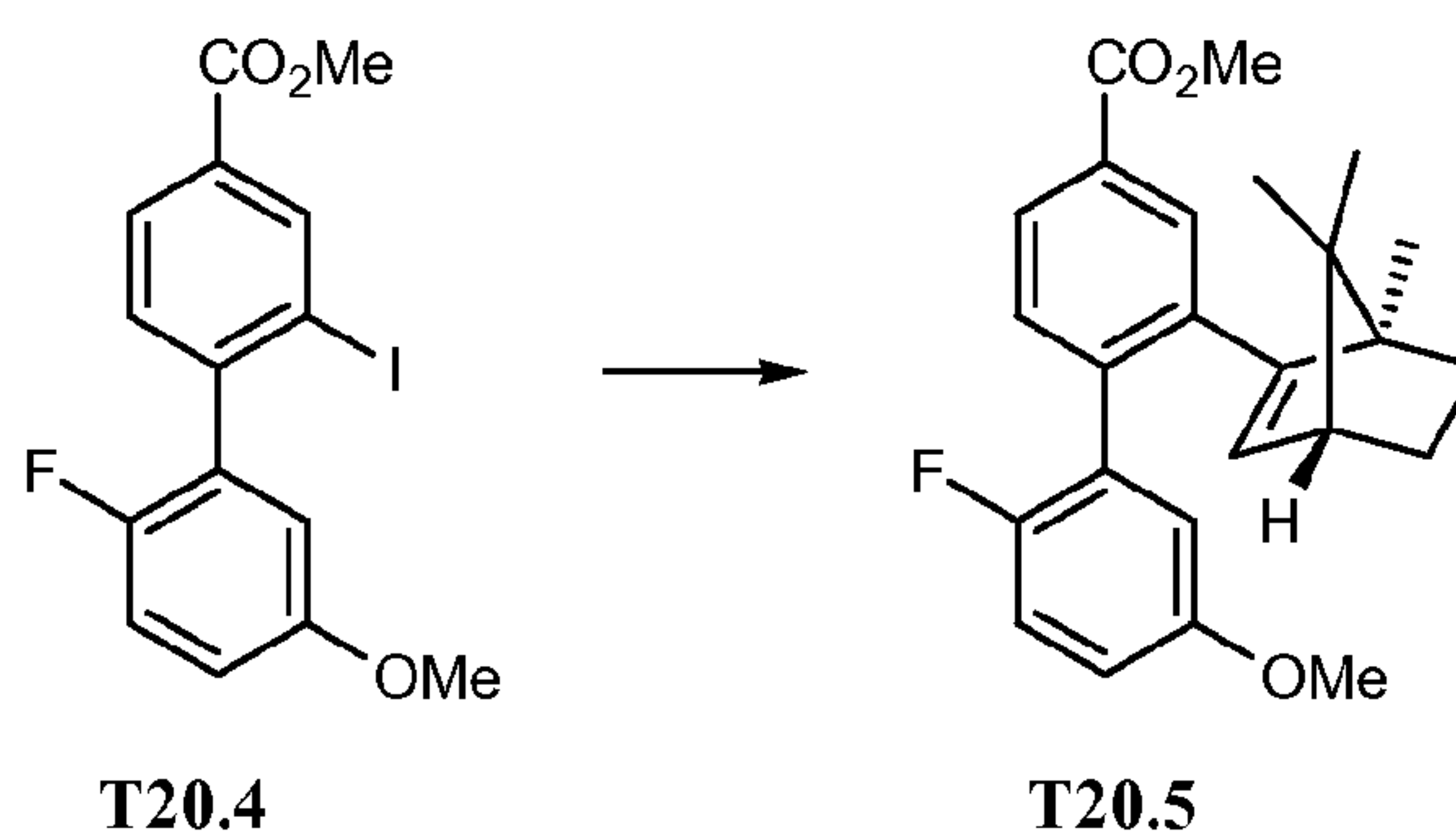
[0426] Methyl 2'-fluoro-5'-(methoxy)-2-nitro-1,1'-biphenyl-4-carboxylate (T20.2). To a stirred solution of methyl 4-chloro-3-nitrobenzoate **T20.1** (10.00 g, 46 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in DMF (15.00 mL, 194 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (12 g, 70 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), and potassium carbonate (19 g, 139 mmol). Tetrakis(triphenylphosphine)palladium (2.1 g, 1.9 mmol) was then added to the mixture, and the mixture was heated at 90°C for 18 hours. The mixture was then cooled to room temperature, diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-40% EtOAc in hexanes) to yield **T20.2** as a colorless oil (14.00 g, 99% yield).



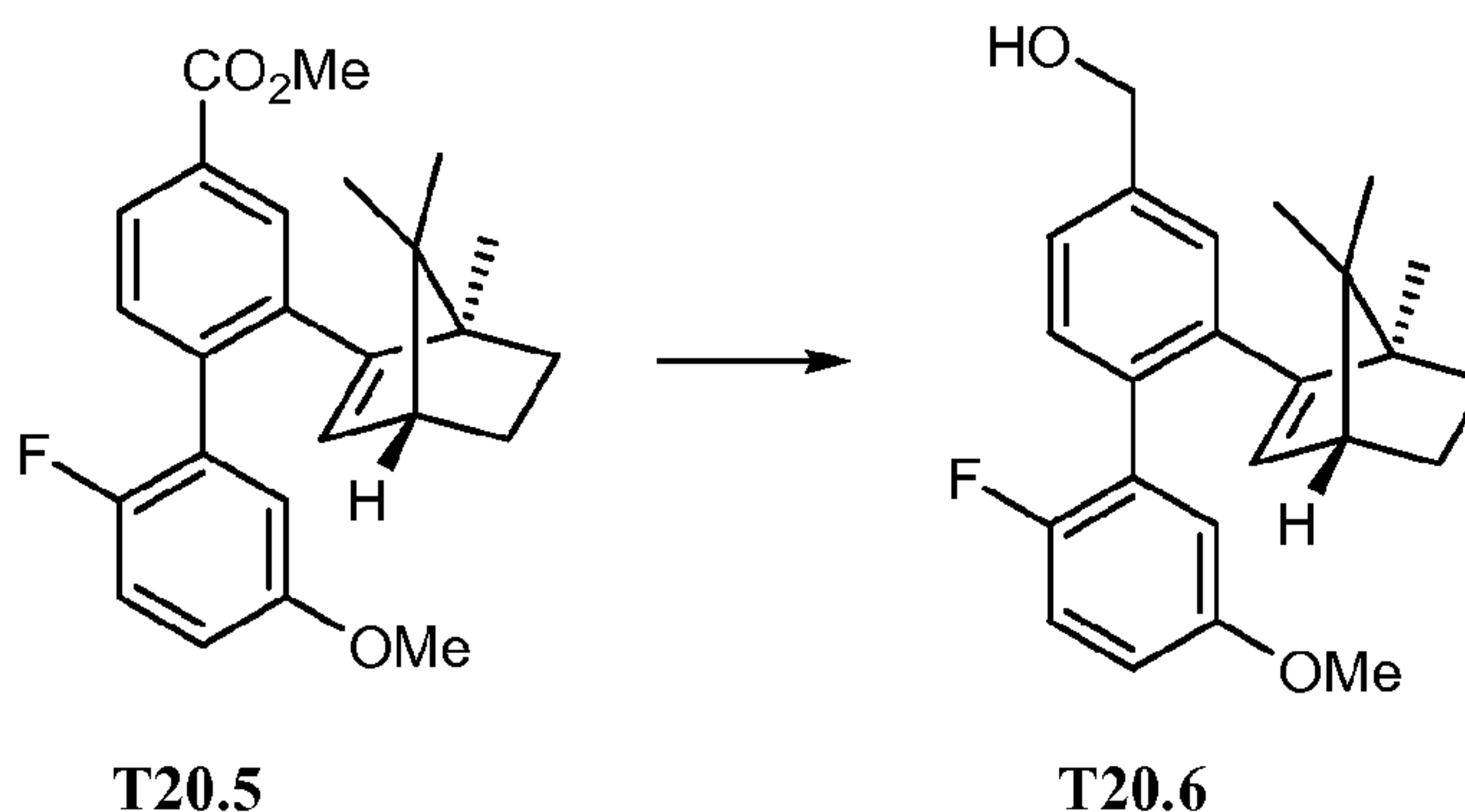
[0427] **Methyl 2-amino-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T20.3).** To a stirred solution of **T20.2** (1.00 g, 3.3 mmol) in acetic acid (2.00 mL, 35 mmol) at 23°C was added DME (15.00 mL, 144 mmol), EtOH (10.00 mL), followed by tin(II) chloride (4.7 g, 25 mmol). The mixture was heated at 60°C for 17 hours. After which, the reaction was cooled to room temperature. The reaction was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure to give the product **T20.3** (0.90 g, 100% yield).



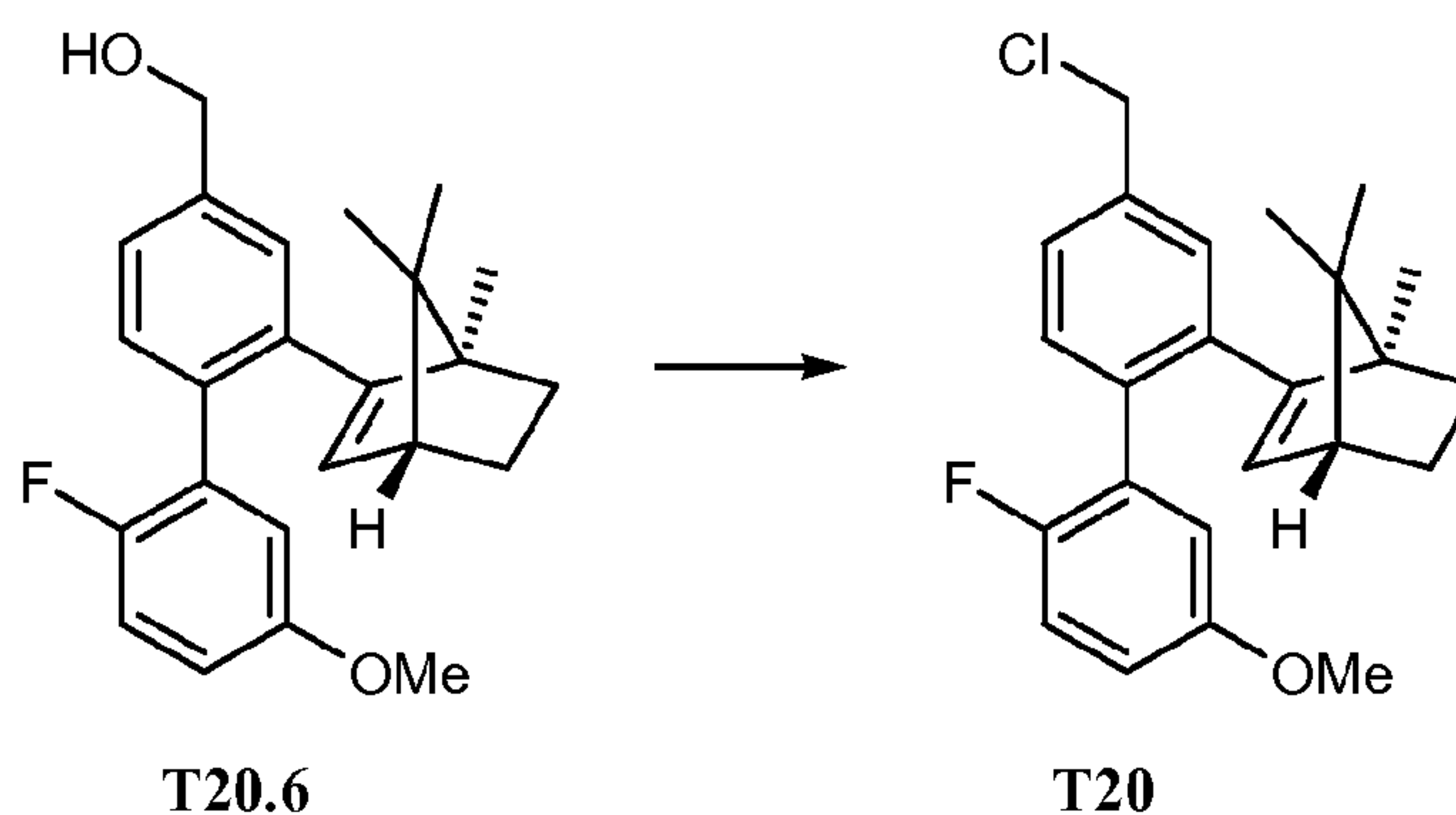
[0428] **Methyl 2'-fluoro-2-iodo-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T20.4).** To a stirred solution of **T20.3** (1.00 g, 3.6 mmol) in DME (10.00 mL, 96 mmol) at 23°C was added sulfuric acid (0.19 mL, 3.6 mmol) in water (8 mL), followed by dropwise addition of a solution of sodium nitrite (0.38 g, 5.4 mmol) in water (2 mL) at 0°C over 30 minutes. The reaction was then stirred for 20 minutes. To the mixture was added a solution of sodium iodide (3.0 g, 20 mmol) in water (7 mL) at 0°C. The resulting mixture was then stirred for 1 hour. The reaction was quenched with sodium thiosulfate and extracted three times with diethyl ether. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-40% EtOAc in hexanes) to yield a colorless solid **T20.4** (0.820 g, 58% yield).



[0429] **Methyl 2'-fluoro-5'-(methyloxy)-2-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-4-carboxylate (T20.5).** To a stirred solution of **T20.4** (0.200 g, 0.52 mmol) in DMF (4.00 mL, 52 mmol) at 23°C was added (1S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-ylboronic acid (0.19 g, 1.0 mmol, commercially available from Combi-Blocks, Cat. No. BB-2567), potassium carbonate (0.21 g, 1.6 mmol), and then tetrakis(triphenylphosphine)palladium (0.060 g, 0.052 mmol). The mixture was heated at 90°C for 19 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-10% EtOAc in hexanes) to yield **T20.5** as a colorless oil (0.165 g, 81% yield).

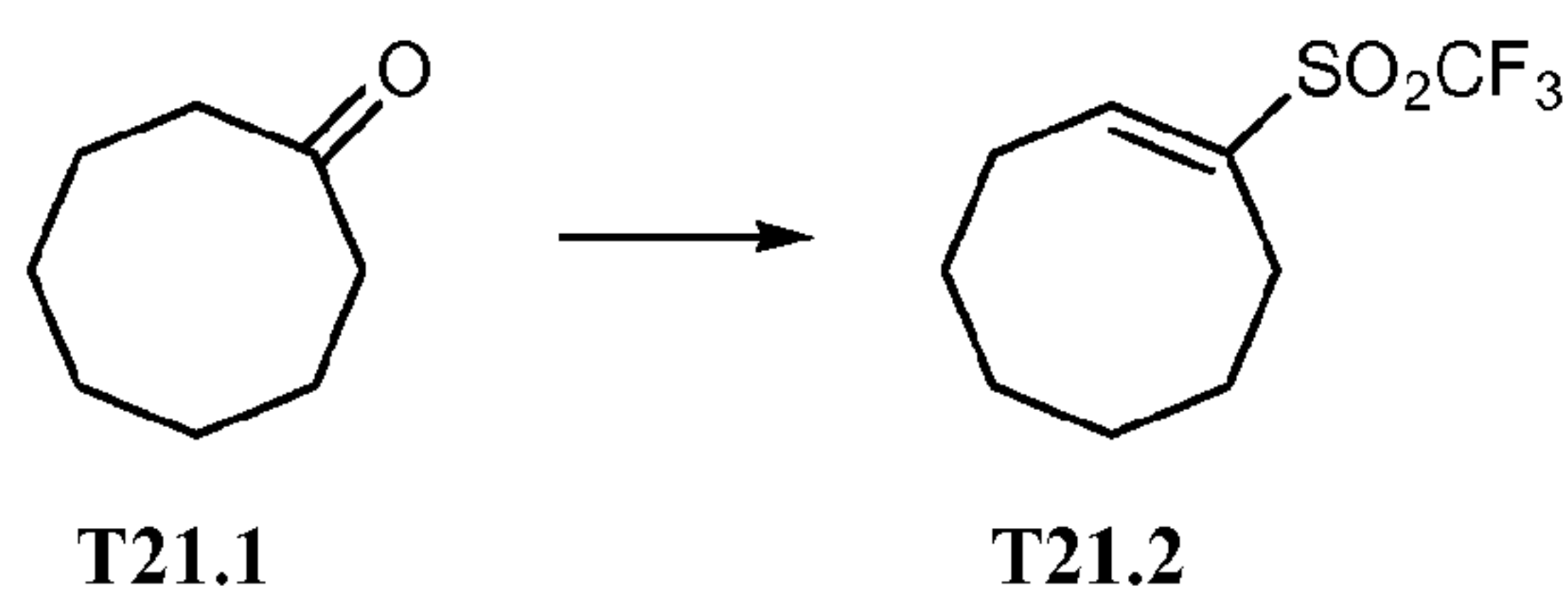


[0430] **(2'-Fluoro-5'-(methyloxy)-2-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-4-yl)methanol (T20.6).** To a stirred solution of **T20.5** (0.050 g, 0.1 mmol) in THF (4 mL) at 0°C was added LAH in THF (0.3 mL, 0.3 mmol, 1.0M). The resulting mixture was stirred for 2 hours. 1N NaOH(aq) was added to the mixture to quench it. The reaction was then extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **T20.6** as a colorless oil (0.035 g, 75% yield).

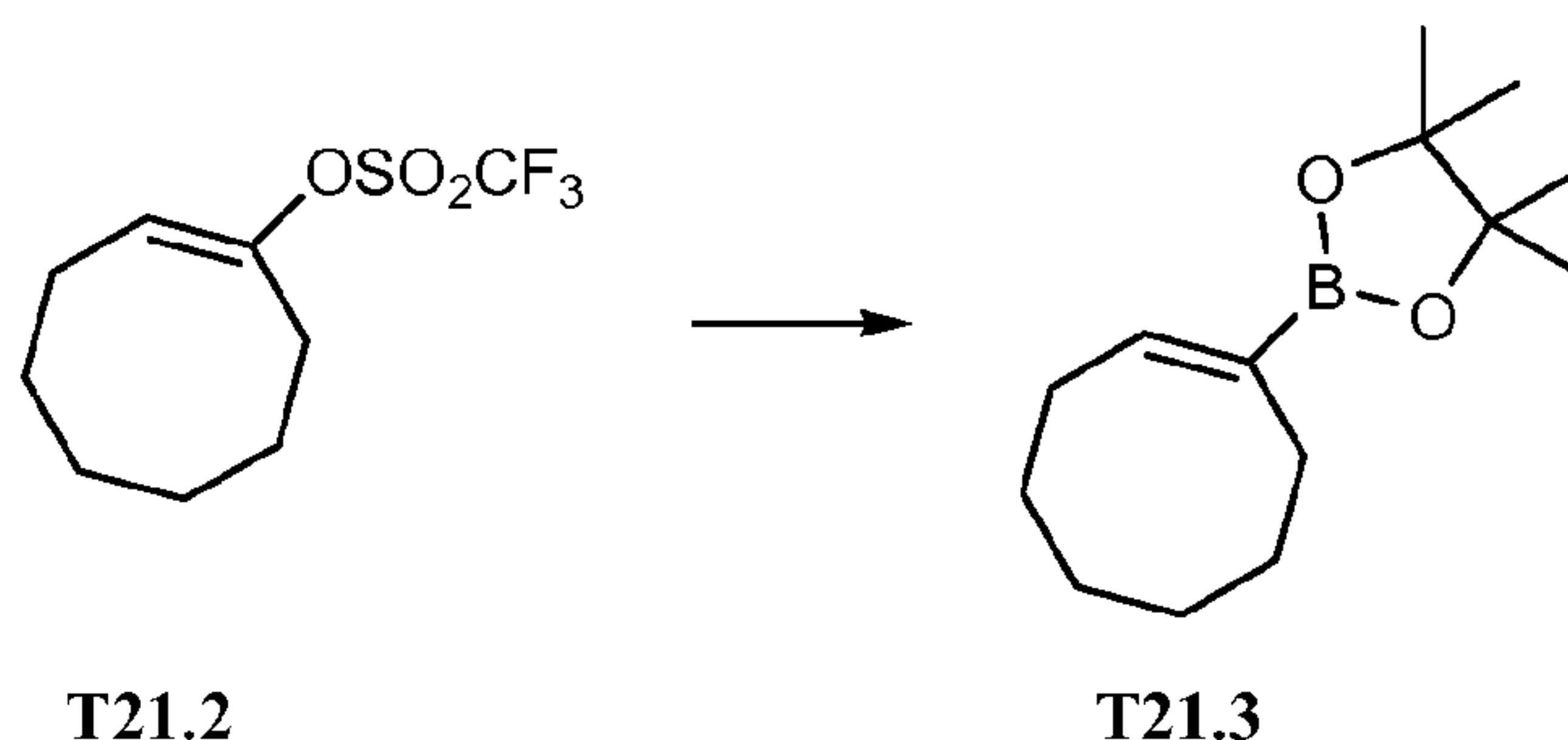


[0431] **4'-(Chloromethyl)-6-fluoro-2'-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-3-yl methyl ether (T20).** To a stirred solution of **T20.6** (0.035 g, 0.10 mmol) in DCM (2.00 mL) and DMF (0.01 mL) at 0°C was added thionyl chloride (0.01 g, 0.10 mmol). The reaction was then stirred at room temperature for 2 hours and was then concentrated in vacuo. The resulting product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T20** as a colorless oil (0.035 g, 95% yield).

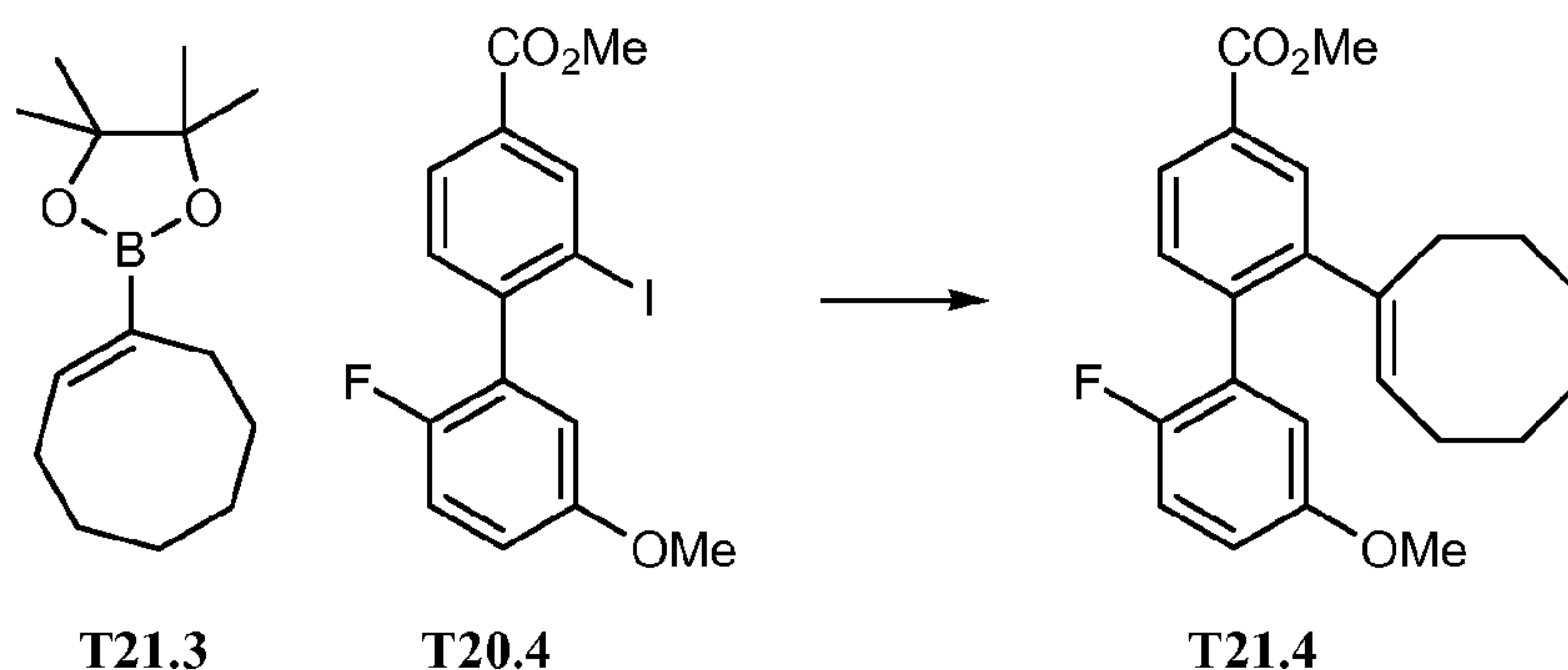
[0432] **Intermediate T21**



[0433] **1-Cycloocten-1-yl trifluoromethyl sulfone (T21.2).** To a stirred solution of cyclooctanone (**T21.1**) (5.00 g, 40 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in THF (35 mL) at -78°C was added LDA (22 mL, 44 mmol, 2.0M). The resulting solution was stirred at -78°C for 20 minutes. Then, a solution of N-phenyl-bis(trifluoromethane sulfonimide) (16 g, 44 mmol) in THF (15 mL) was added slowly at -78°C. The reaction mixture was allowed to warm to 23°C over 3 hours and then was concentrated in vacuo. The residue was diluted with water and extracted three times with hexanes. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **T21.2** as a colorless oil (10.00 g, 98% yield).

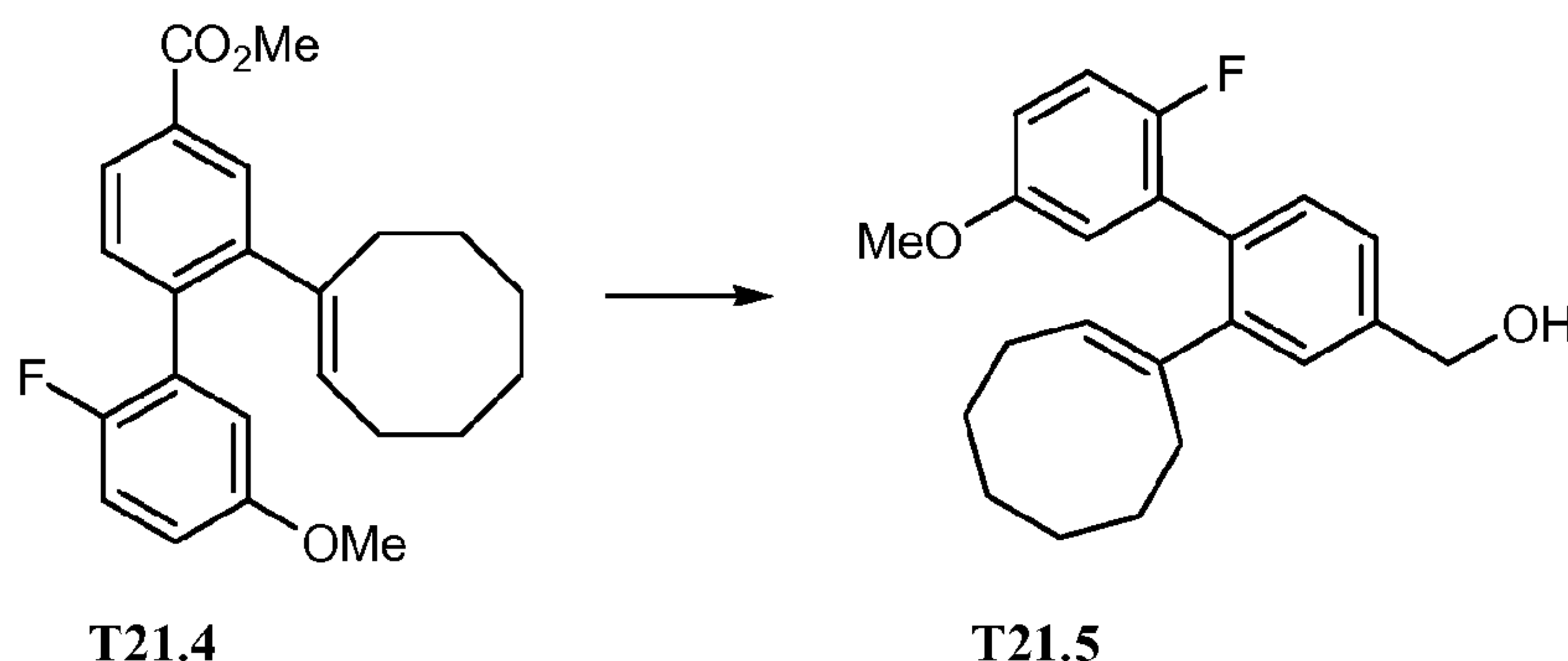


[0434] 2-(1-Cycloocten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (T21.3). A mixture of triphenylphosphine (1 g, 4 mmol), potassium phenolate (7 g, 54 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (10 g, 39 mmol) and **T21.2** (10.00 g, 39 mmol) in toluene (194 mL) was degassed with nitrogen. Then, dichlorobis(triphenylphosphine)palladium(II) (1 g, 2 mmol) was added and the mixture was further degassed with nitrogen. The reaction mixture was stirred at 50°C for 3.5 hours. The reaction mixture was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **T21.3** as a colorless oil (7.00 g, 77% yield).

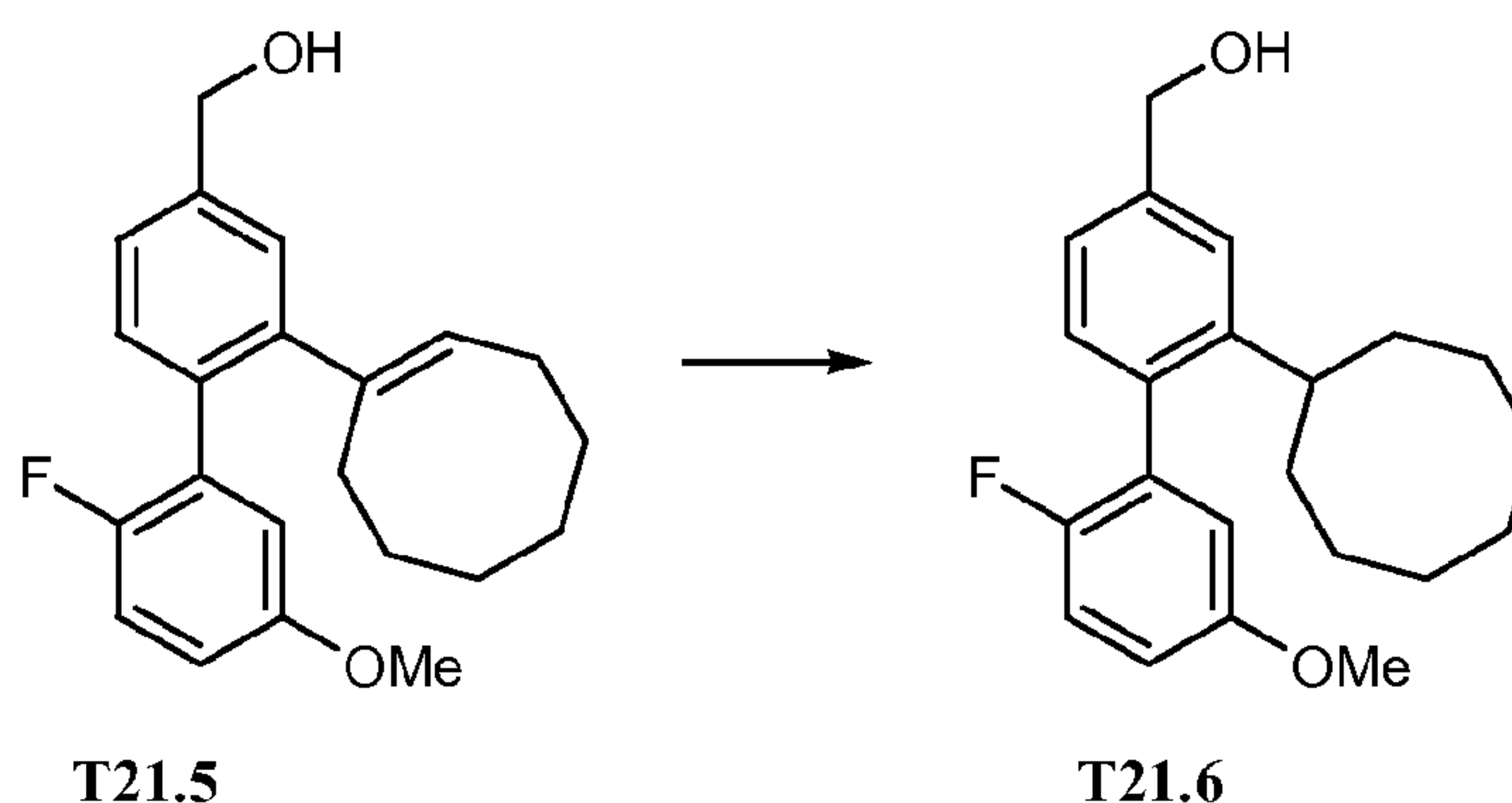


[0435] Methyl 2-(1-cycloocten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T21.4). To a stirred solution of **T20.4** (0.750 g, 1.9 mmol) in DMF (4.00 mL, 52 mmol) at 23°C was added (Z)-2-cyclooctenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **T21.3** (0.92 g, 3.9 mmol), potassium carbonate (0.81 g, 5.8 mmol), and then tetrakis(triphenylphosphine)palladium (0.22 g, 0.19 mmol). The mixture was heated at 90°C for 19 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the

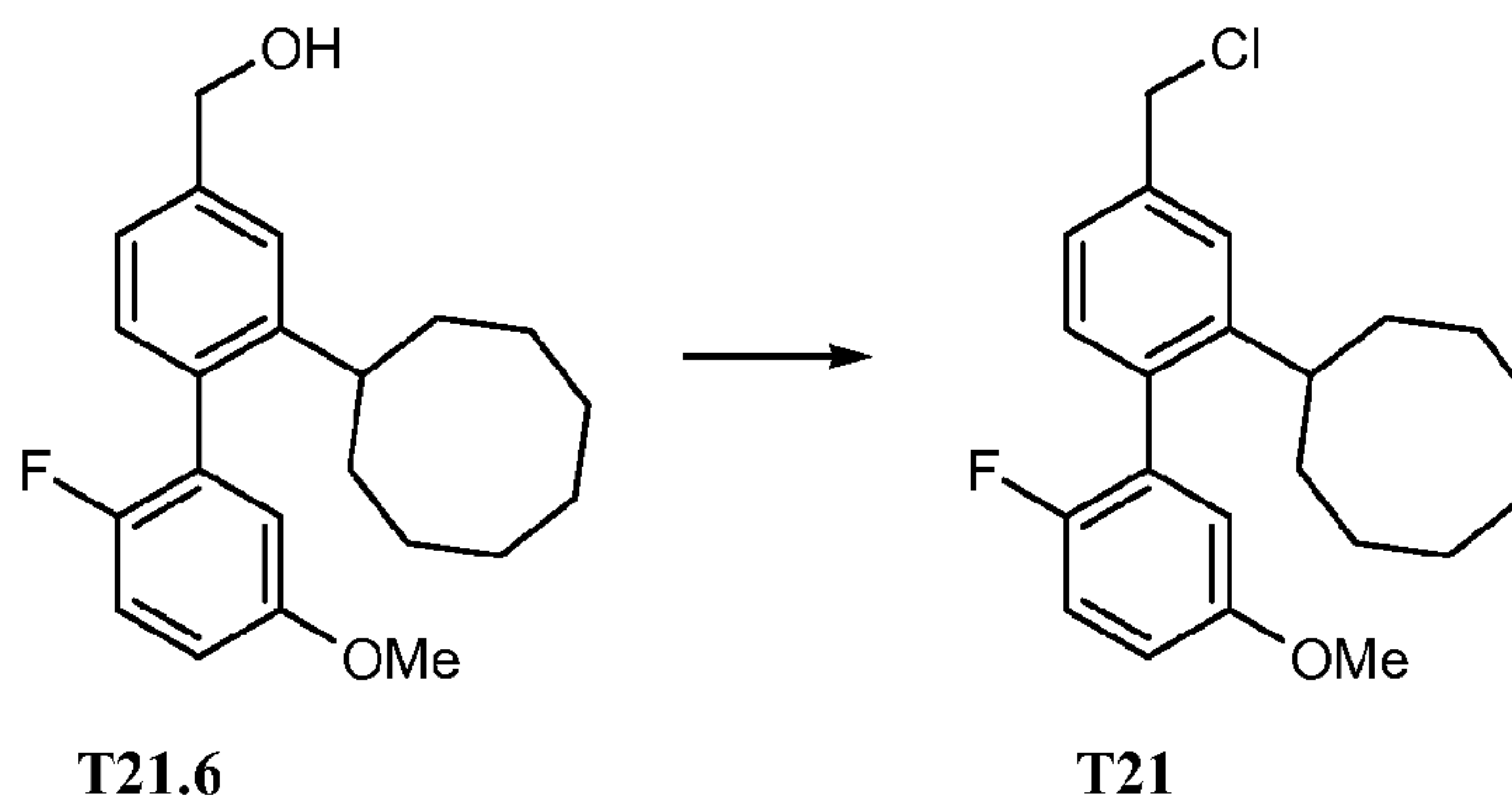
product was purified on silica gel (0-10% EtOAc in hexanes) to yield **T21.4** as a colorless oil (0.35 g, 49% yield).



[0436] **(2-(1-Cycloocten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T21.5)**. To a stirred solution of **T21.4** (0.350 g, 0.9 mmol) in THF (9 mL, 0.9 mmol) at 0°C was added LAH in THF (2 mL, 2 mmol, 1.0M). The reaction was stirred for 1 hour. 1N NaOH(aq) was then added to quench the reaction. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T21.5** as a colorless oil (0.387 g, 120% yield).

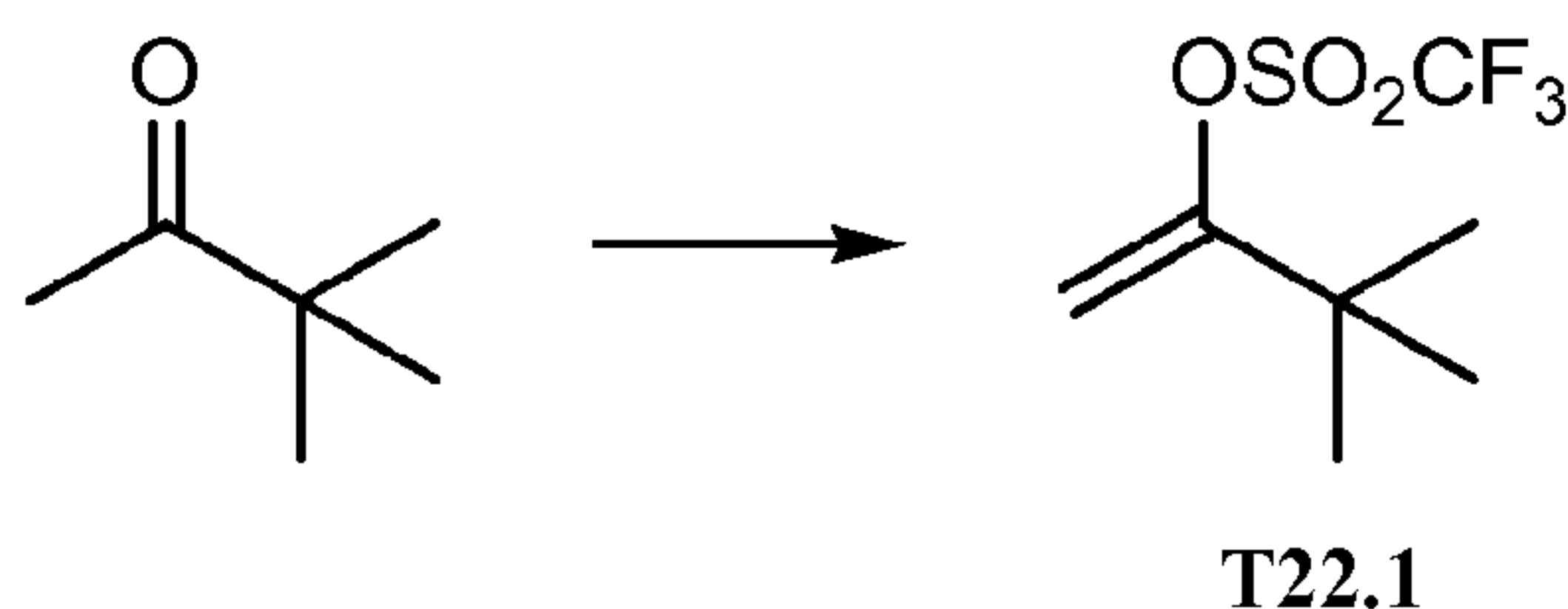


[0437] **(2-Cyclooctyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T21.6)**. To a stirred solution of **T21.5** (0.387 g, 1 mmol) in EtOAc (11 mL) at 23°C was added palladium on carbon (0.1 g, 1 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for 2 hours. The reaction mixture was then filtered and concentrated in vacuo. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **T21.6** as a colorless oil (0.13 g, 33% yield).

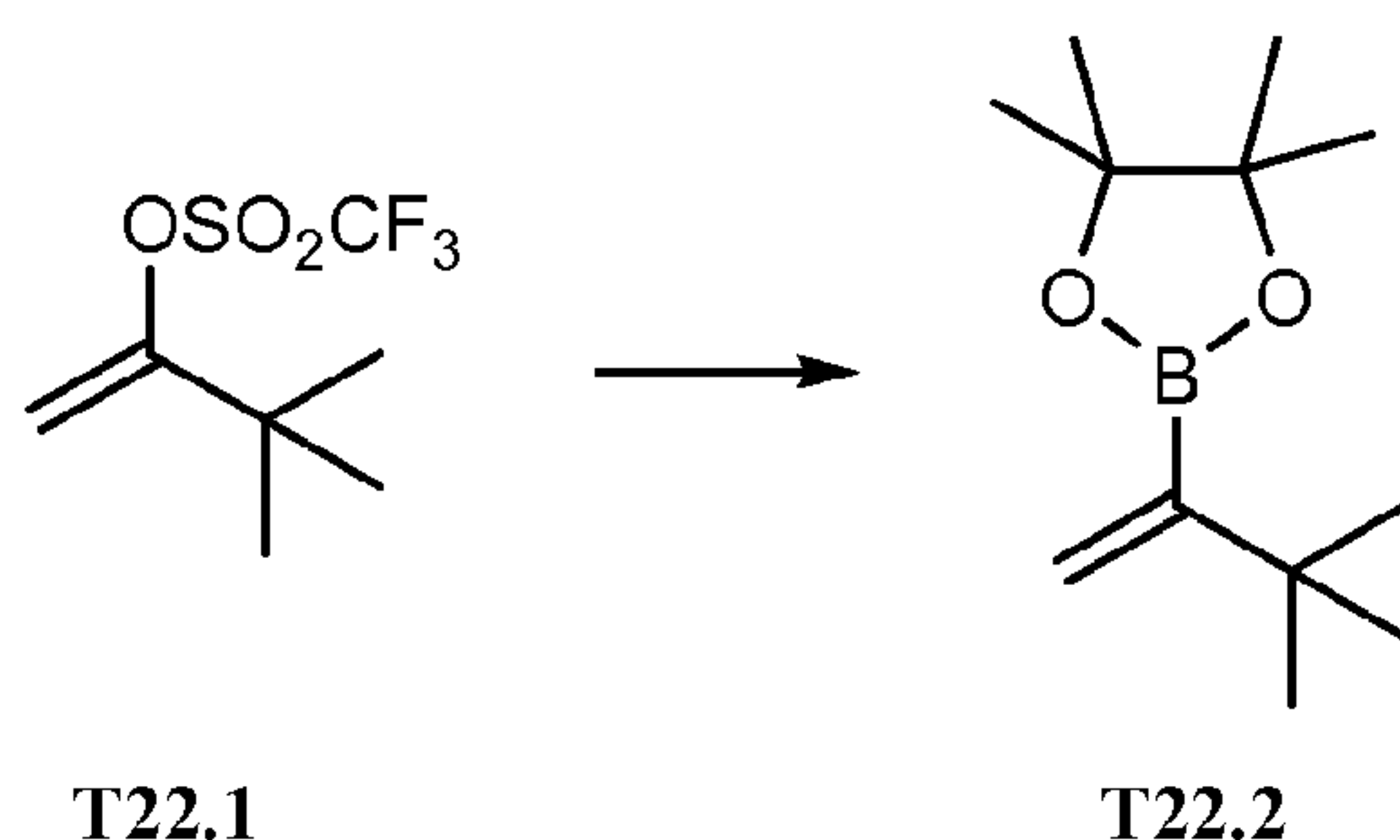


[0438] **4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-cyclooctyl-1,1'-biphenyl (T21).** To a stirred solution of **T21.6** (0.130 g, 0.4 mmol) in DCM (2.00 mL) and DMF (0.03 mL) at 0°C was added thionyl chloride (0.06 mL, 0.8 mmol). The reaction was stirred at room temperature for 2 hours. After which, the reaction was concentrated in vacuo and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T21** as a colorless oil (0.130 g, 95% yield).

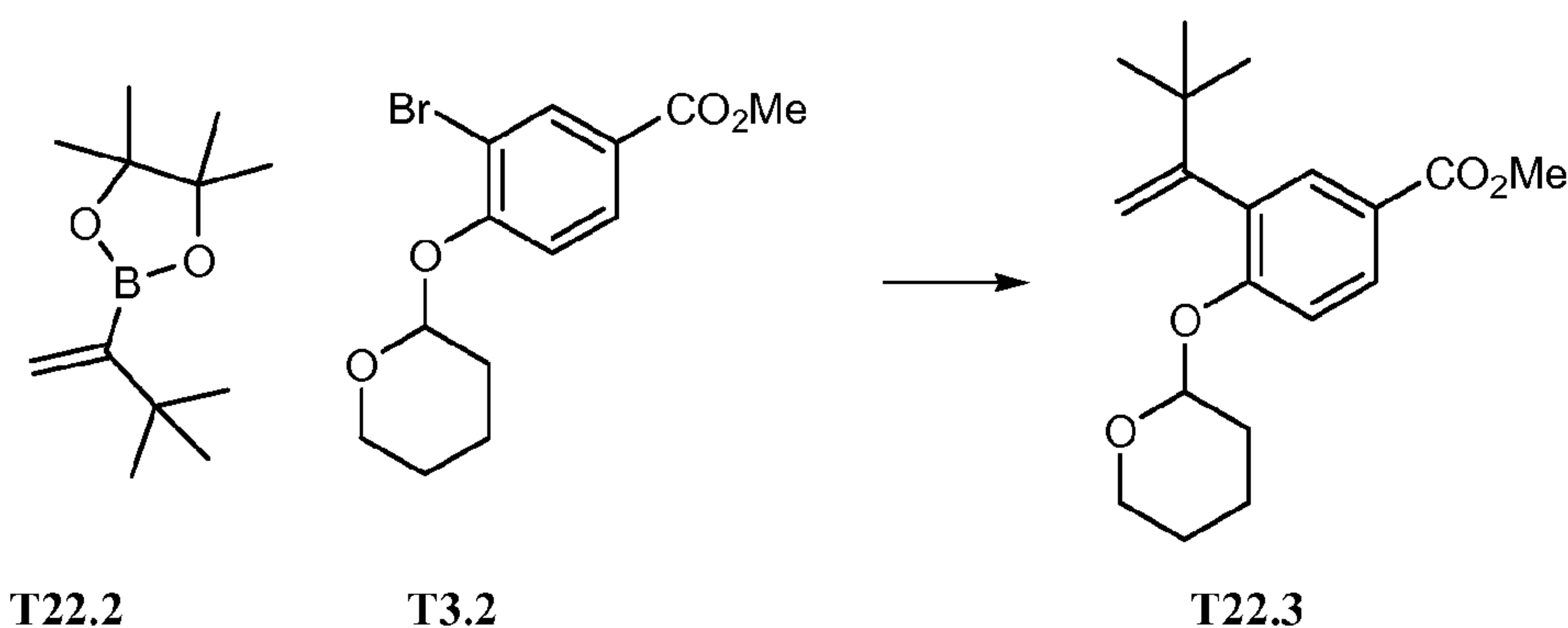
[0439] **Intermediates T22A and T22B**



[0440] **Synthesis of T22.1.** To a solution of 3,3-dimethylbutan-2-one (5.00 g, 50 mmol, commercially available from Sigma-Aldrich, St. Louis, MO, USA) in THF (71 mL) at -78°C was added dropwise a solution of LDA (28 mL, 56 mmol). The resulting solution was stirred at -78°C for 20 minutes. A solution of N-phenyl-bis(trifluoromethane sulfonimide) (20 g, 55 mmol) in THF (15 mL) was then added slowly at -78°C. The reaction mixture was allowed to room temperature over 3 hours. The reaction was concentrated in vacuo. The reaction was then diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-5% EtOAc in hexanes) to yield **T22.1** as a colorless oil (10.00 g, 86% yield).

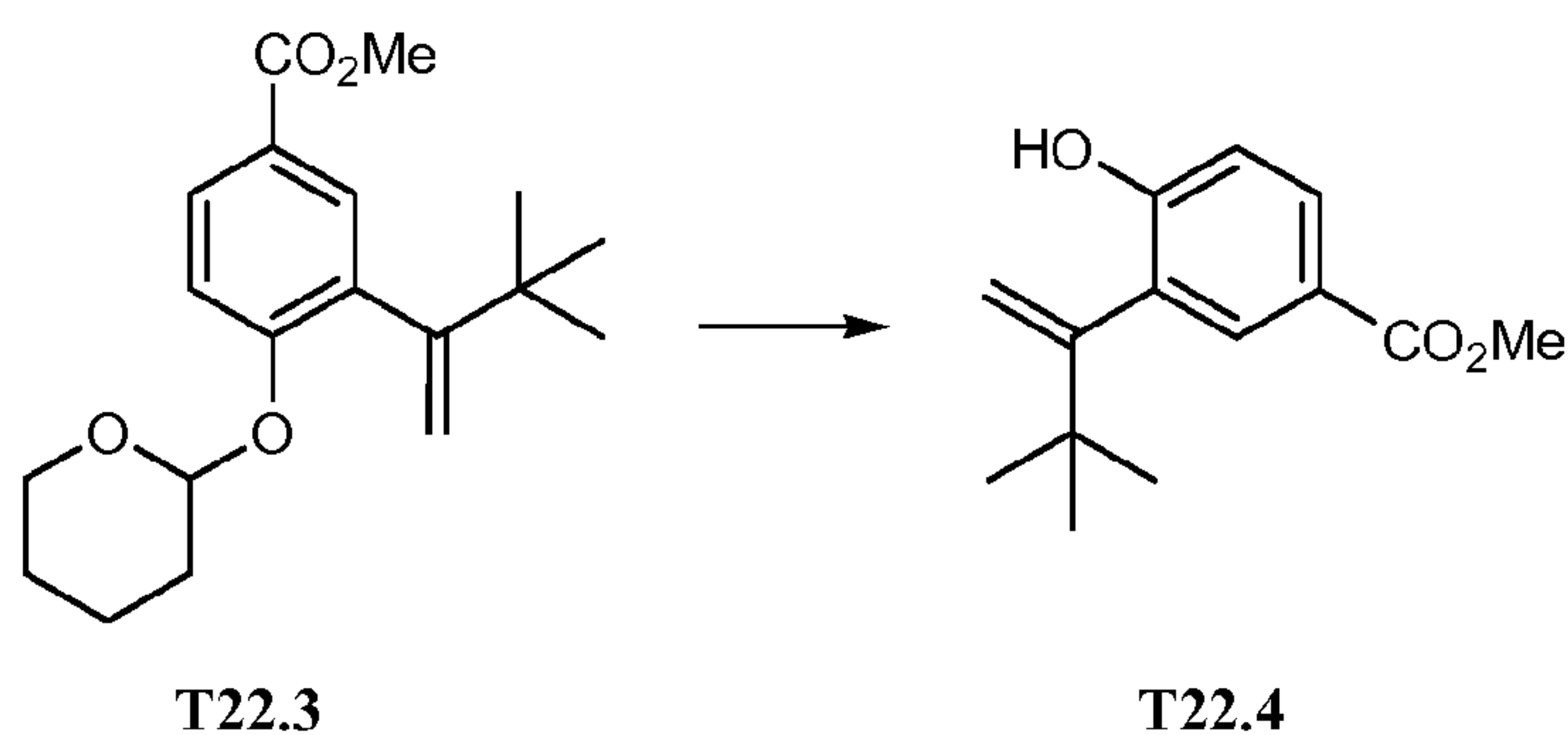


[0441] Synthesis of T22.2. A mixture of triphenylphosphine (0.90 g, 3.4 mmol), potassium phenolate (6.4 g, 48 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (8.7 g, 34 mmol) and **T22.1** (8.00 g, 34 mmol) in toluene (172 mL) was degassed by N₂. Then dichlorobis(triphenylphosphine)palladium(II) (1.2 g, 1.7 mmol) was added, and the reaction mixture was further degassed with N₂. The reaction was then stirred at 50°C for 3.5 hours. The reaction was then filtered and concentrated in vacuo. The product was purified on silica gel (0-5% EtOAc in hexanes) to yield **T22.2** as a colorless oil (5.0 g, 69% yield).



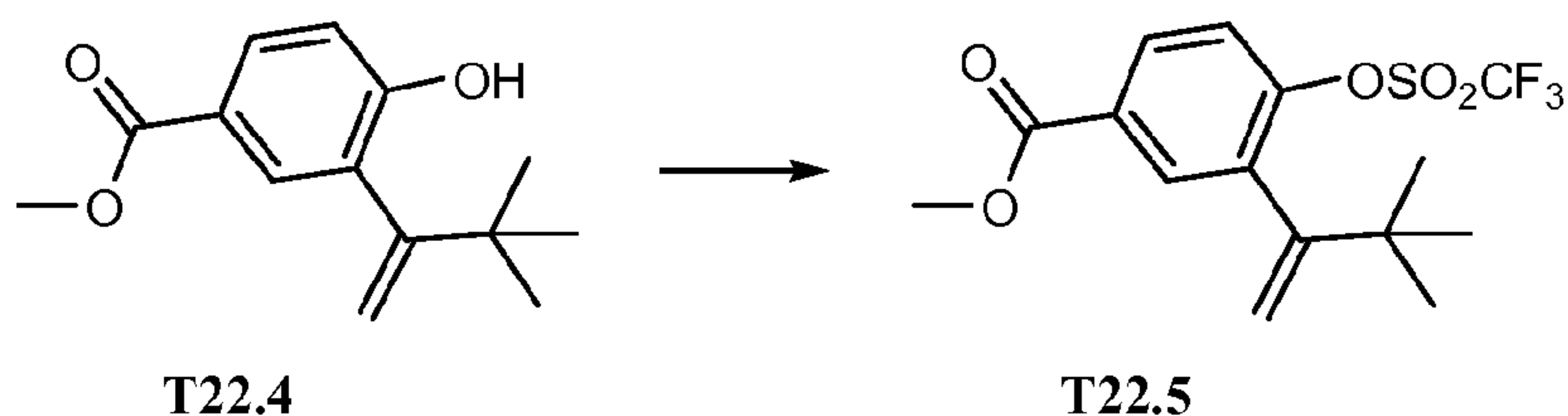
[0442] Methyl 3-(1-(1,1-dimethylethyl)ethenyl)-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (T22.3). A stirred solution of methyl 3-bromo-4-(tetrahydro-2H-pyran-2-yloxy)benzoate **T3.2** (2.50 g, 7.9 mmol), palladium acetate (0.18 g, 0.79 mmol), S-Phos (0.65 g, 1.6 mmol), tripotassium phosphate (1.6 mL, 20 mmol) in DMF (15.00 mL, 194 mmol) and water (0.600 mL, 33 mmol) was purged 3 times with nitrogen and placed under vacuum and the process repeated three times. Before heating, **T22.2** (2.0 g, 9.5 mmol) was added, and the mixture was heated to 70°C and stirred for 19 hours. The resulting mixture was then cooled to room temperature, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering,

the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T22.3** as a colorless oil (2.50 g, 99% yield).



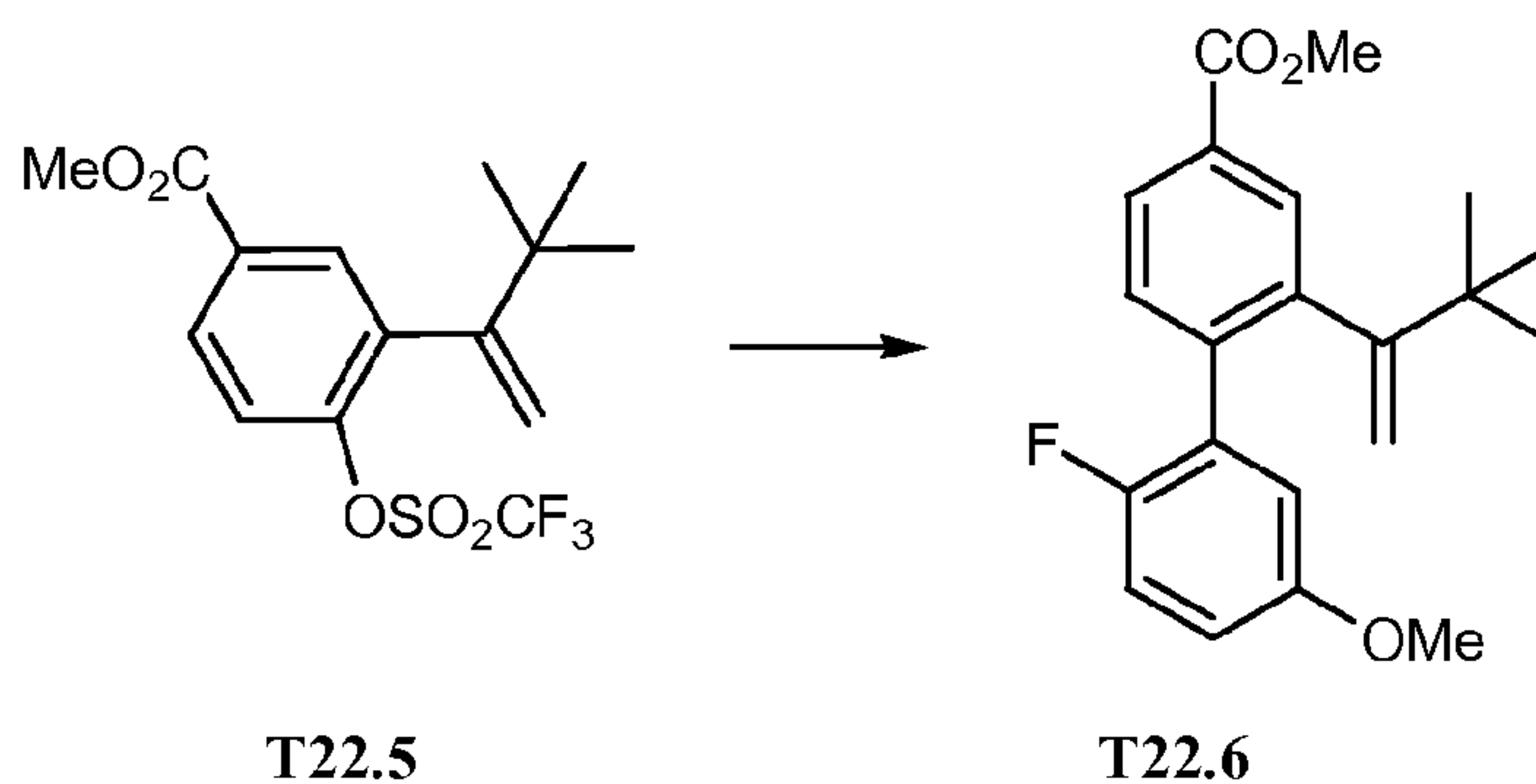
[0443] Methyl 3-(1-(1,1-dimethylethyl)ethenyl)-4-hydroxybenzoate (T22.4).

To a stirred solution of **T22.3** (2.500 g, 7.85 mmol) in MeOH (10.00 mL, 7.85 mmol) at 23°C was added PPTS (0.197 g, 0.785 mmol). The reaction was heated to 60°C and stirred for 19 hours. The reaction was then concentrated in vacuo to give a clear oil. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T22.4** as a colorless oil (1.50 g, 81.5% yield).

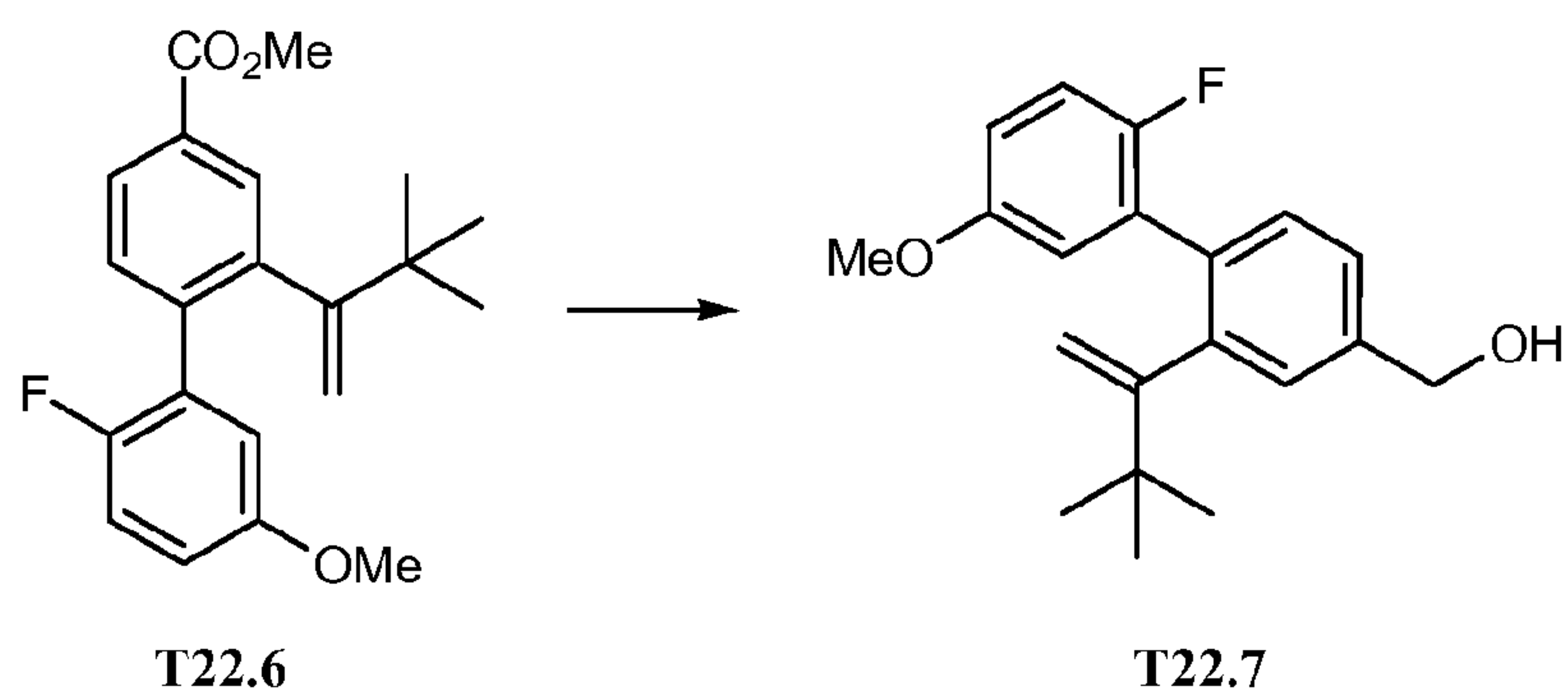


[0444] Methyl 3-(1-(1,1-dimethylethyl)ethenyl)-4-

(((trifluoromethyl)sulfonyl)oxy)benzoate (T22.5). To a stirred solution of **T22.4** (0.500 g, 2 mmol) in DCM (11 mL) at 23°C was added TEA (0.4 mL, 3 mmol), DMAP (catalytic), and then N-phenyltriflimide (0.8 g, 2 mmol). The reaction was further stirred for 19 hours and then concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **T22.5** as a colorless oil (0.1 g, 13% yield).

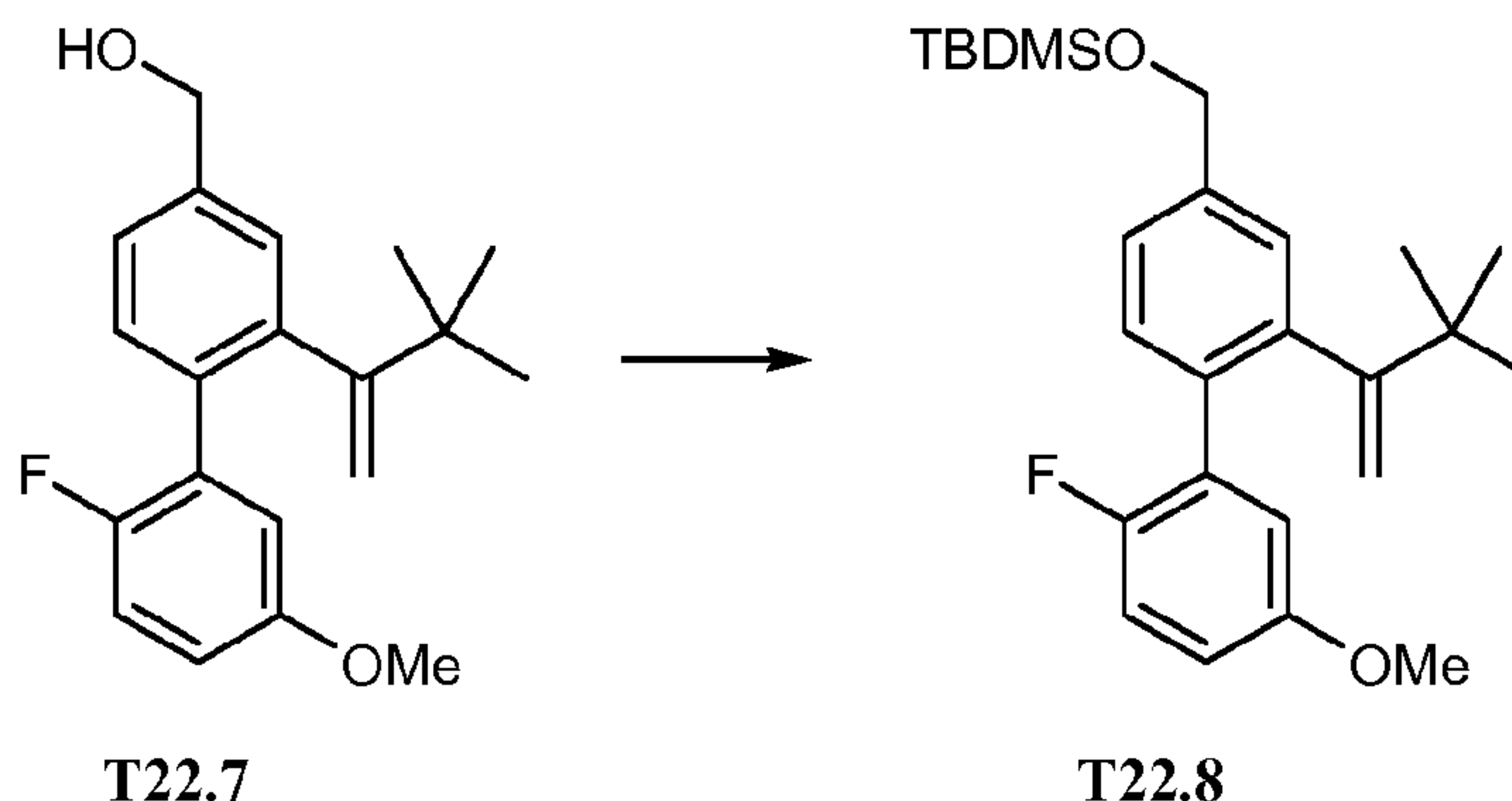


[0445] **Methyl 2-(1-(1,1-dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T22.6).** To a stirred solution of **T22.5** (0.550 g, 1.5 mmol) in DMF (3.0 mL, 1.5 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (0.38 g, 2.3 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), potassium carbonate (0.62 g, 4.5 mmol) and then tetrakis(triphenylphosphine)palladium (0.12 g, 0.11 mmol). The mixture was heated to 90 °C and stirred for 17 hours. The resulting mixture was then cooled to room temperature, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T22.6** as a colorless oil (0.100 g, 19% yield).

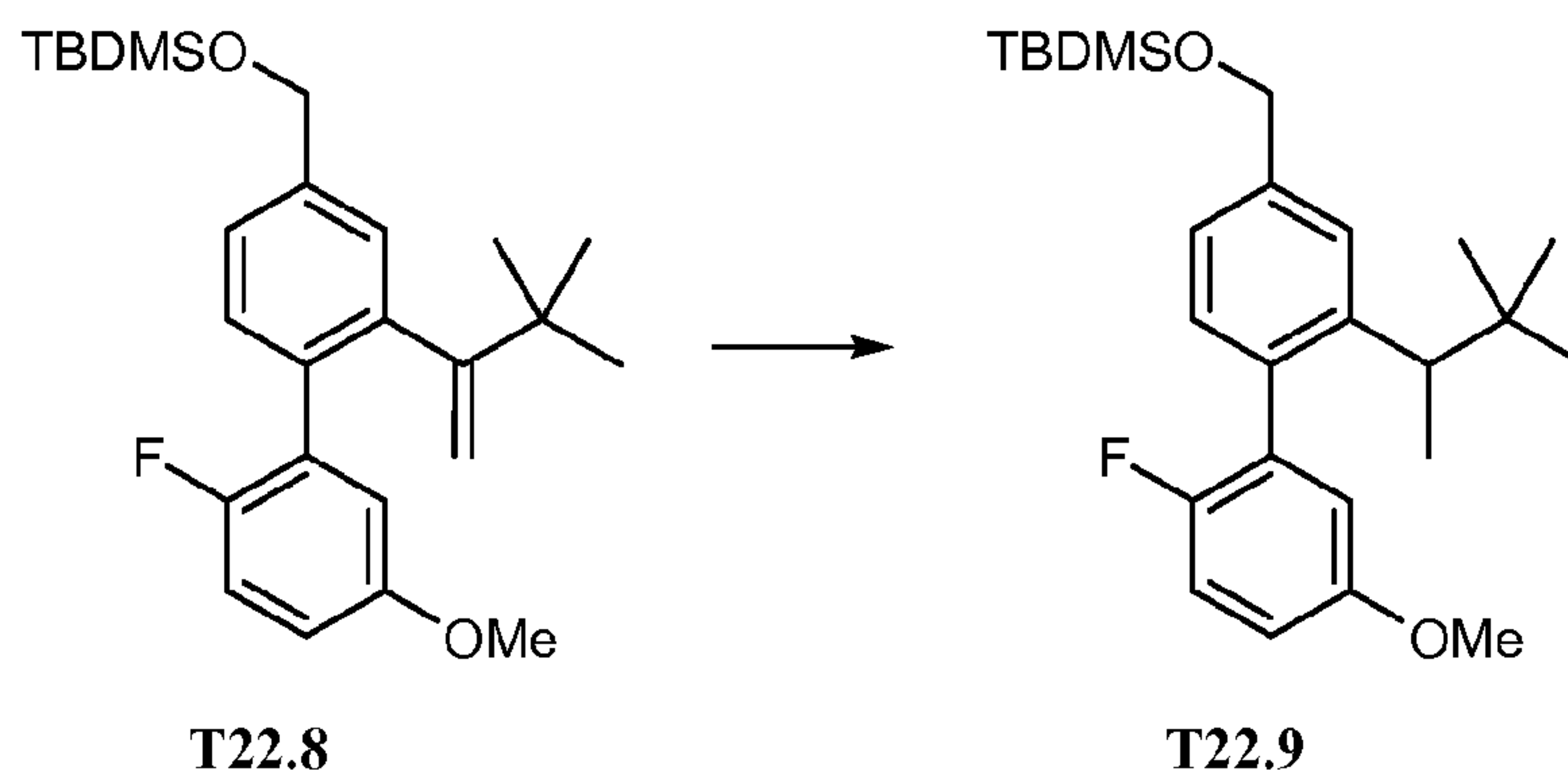


[0446] **(2-(1-(1,1-Dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T22.7).** To a stirred solution of **T22.6** (0.400 g, 1 mmol) in THF (6 mL) at 0°C was added LAH in THF (2 mL, 2 mmol, 1.0M). The resulting mixture was stirred for 2 hours. 1N NaOH(aq) was then added to the mixture, and the resulting mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure

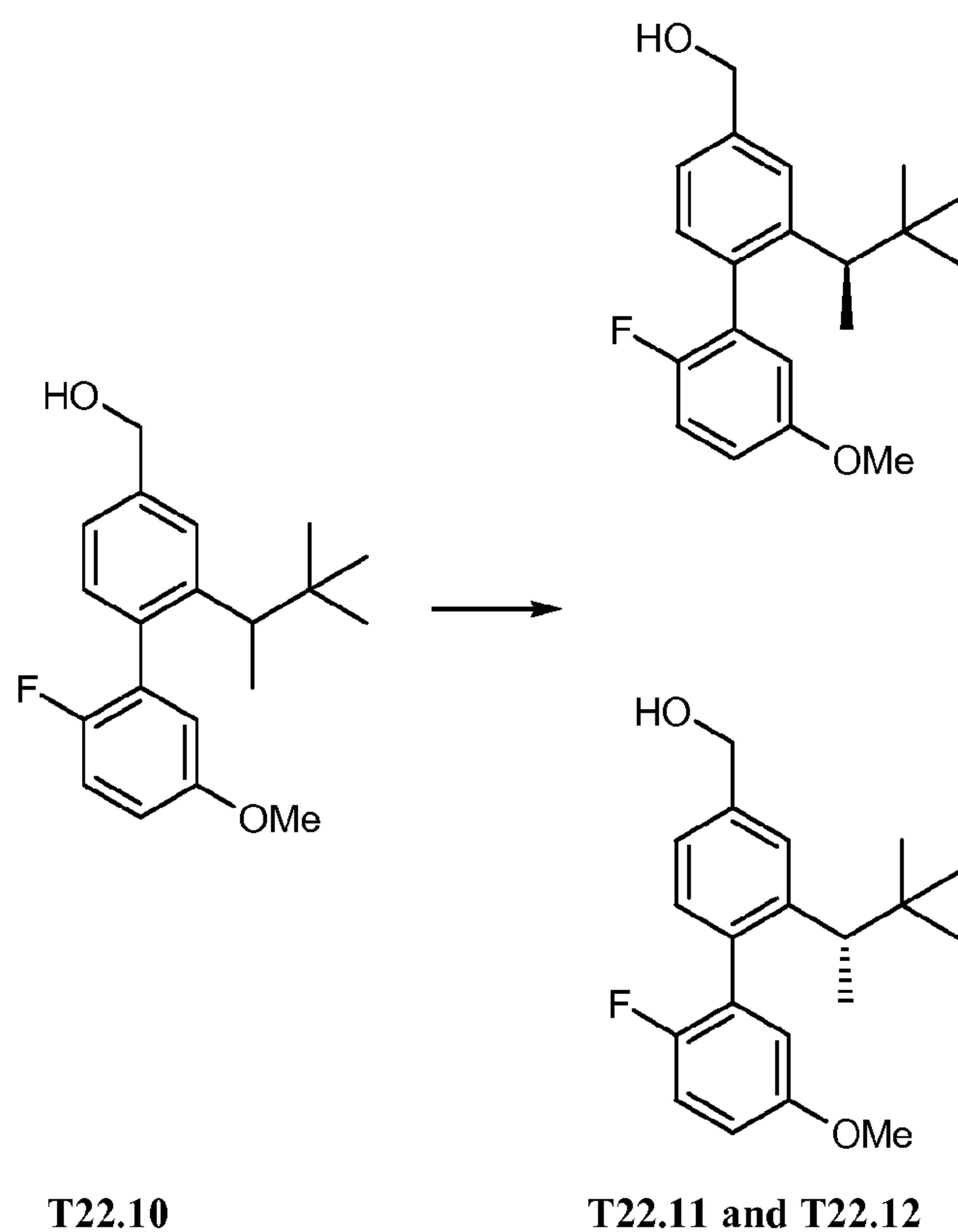
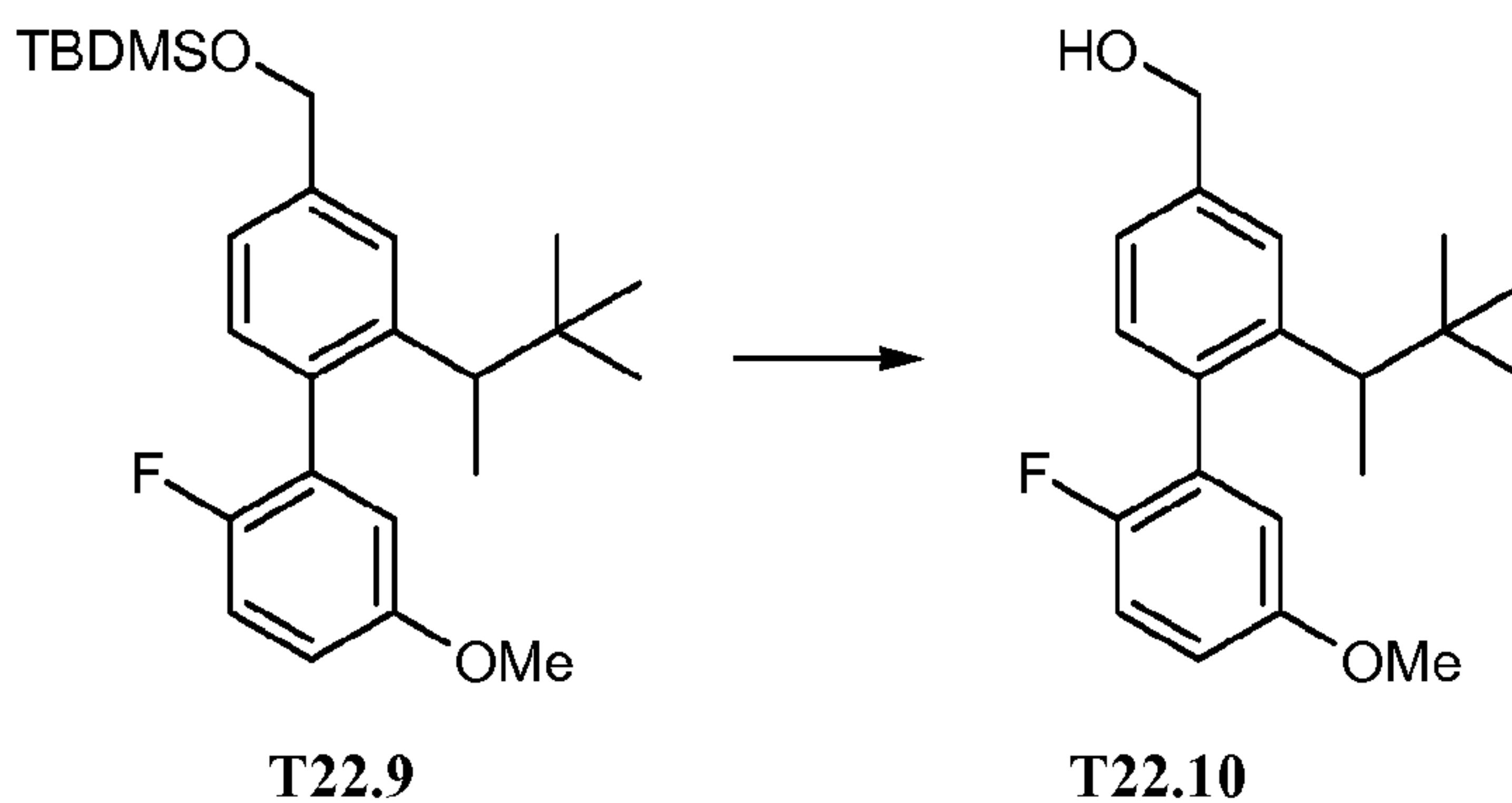
and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T22.7** as a colorless oil (0.273 g, 74% yield).



[0447] **(1,1-Dimethylethyl) (((2-(1-(1,1-dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (T22.8).** To a stirred solution of **T22.7** (0.273 g, 0.9 mmol) in DCM (2.00 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.2 mL, 1 mmol), followed by TEA (0.1 mL, 1 mmol) and DMAP (0.01 g, 0.09 mmol). The resulting mixture was then stirred for 16 hours and then was concentrated in vacuo to give the product. The product was purified on silica gel (0-5% EtOAc in hexanes) to yield **T22.8** as a colorless oil (0.374 g, 100% yield).

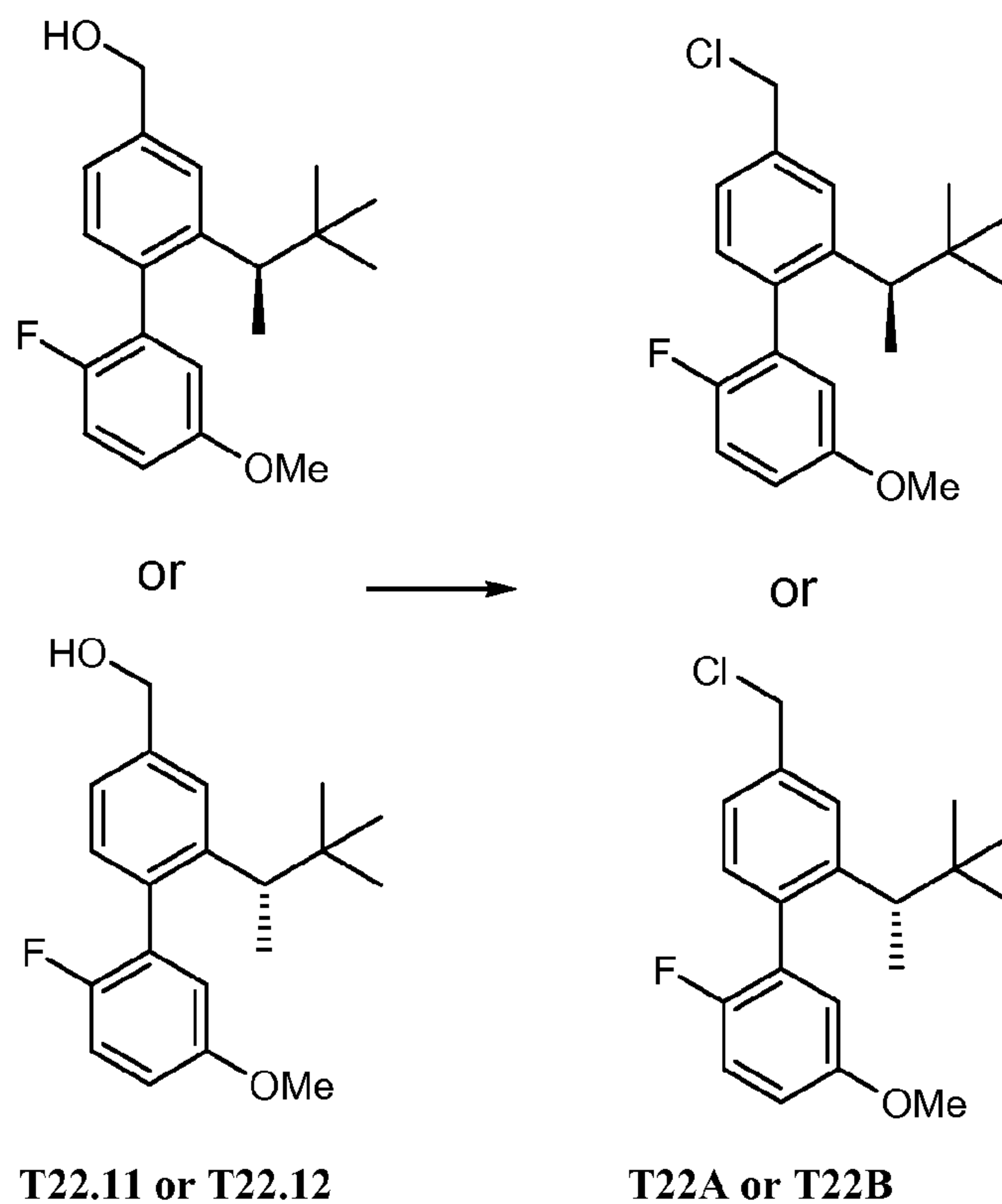


[0448] **(1,1-Dimethylethyl) (((2'-fluoro-5'-(methoxy)-2-(1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (T22.9).** To a stirred solution of **T22.8** (0.400 g, 0.93 mmol) in EtOAc (2.00 mL) at 23°C was added palladium on carbon (0.0099 g, 0.093 mmol). The resulting mixture was stirred under an atmosphere of hydrogen for 21 hours and then was filtered and concentrated in vacuo. The product was purified on silica gel (0-5% EtOAc in hexanes) to yield **T22.9** as a colorless oil (0.400 g, 100% yield).



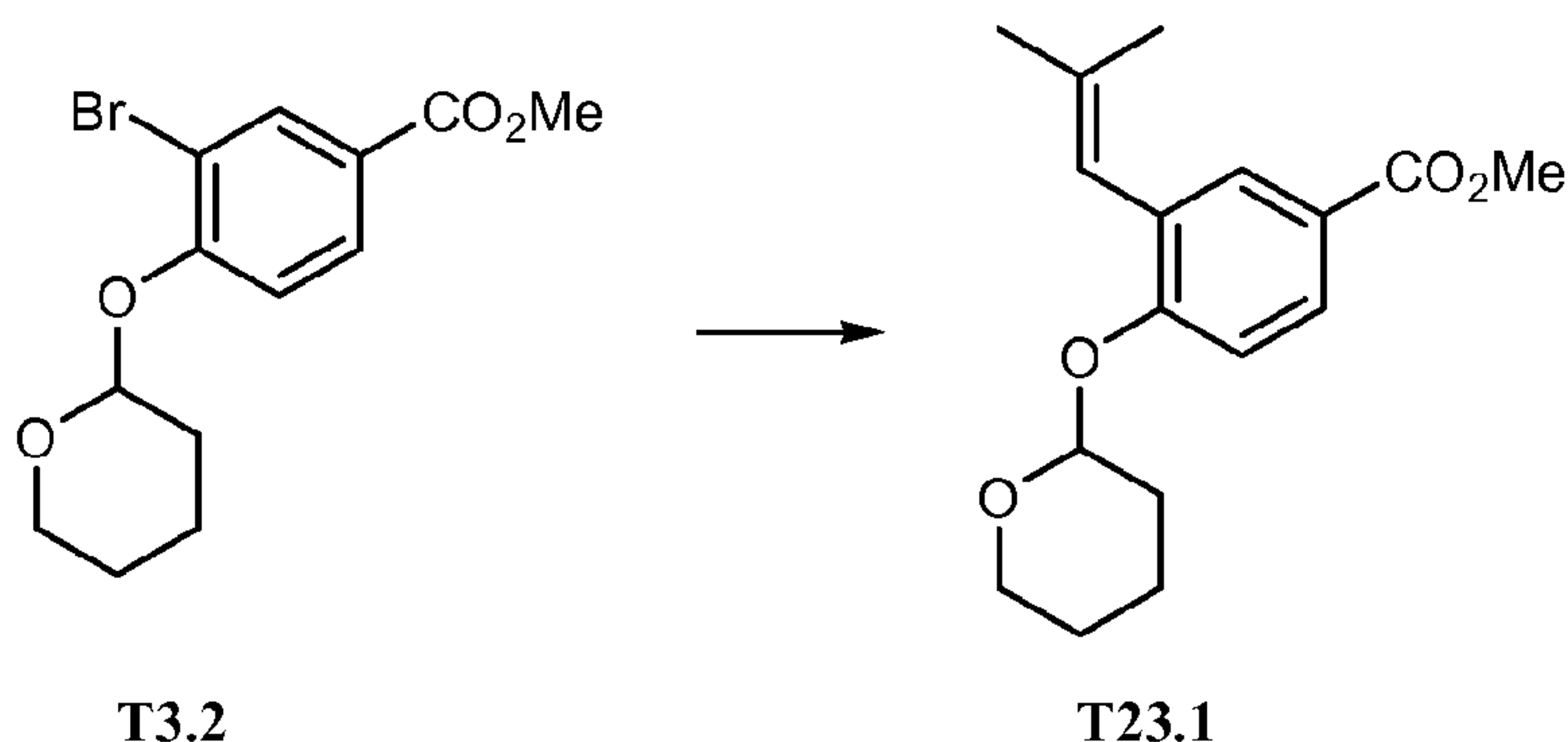
[0449] (2'-Fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methanol and (2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methanol (**T22.11** and **T22.12**). To a stirred solution of **T22.9** (0.400 g, 0.929 mmol) in MeOH (10.00 mL, 0.929 mmol) at 23°C was added PPTS (0.0233 g, 0.0929 mmol). The mixture was stirred for 19 hours and then was concentrated in vacuo to give a clear oil. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T22.10** as a colorless oil (0.250 g, 85% yield). Chiral

separation of **T22.10** was accomplished on a CHIRALCEL® OD column (3%IPA in hexane) to provide **T22.11** (peak one) and **T22.12** (peak two).¹



[0450] **4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl or 4-(chloromethyl)-2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl (T22A or T22B).** To a stirred solution of **T22.11** or **T22.12** (0.050 g, 0.16 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.0012 mL) followed by thionyl chloride (0.023 mL, 0.32 mmol). The mixture was stirred for one hour and then was concentrated in vacuo. The resulting product was purified on silica gel (0-10% EtOAc in hexanes) to yield **T22A** or **T22B** as a colorless oil (0.050 g, 94% yield).

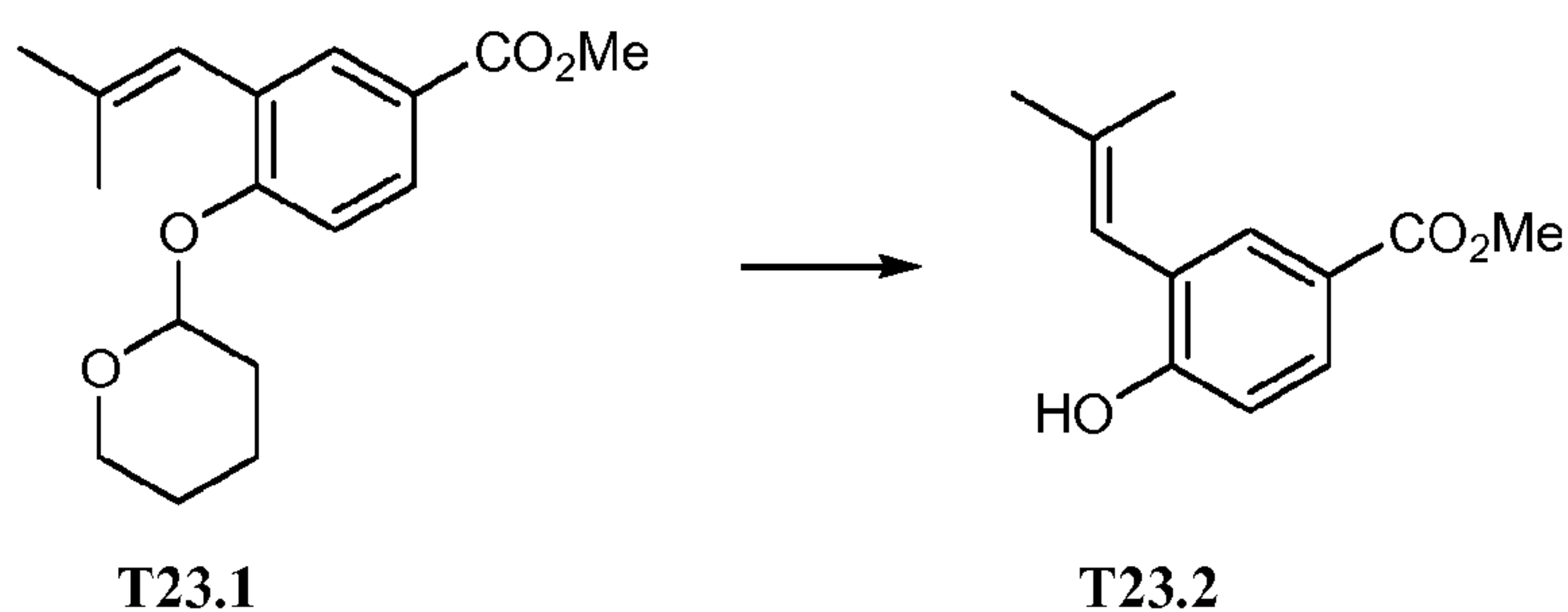
[0451]

Intermediate T23

[0452]

Methyl 3-(2-methyl-1-propenyl)-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (T23.1).

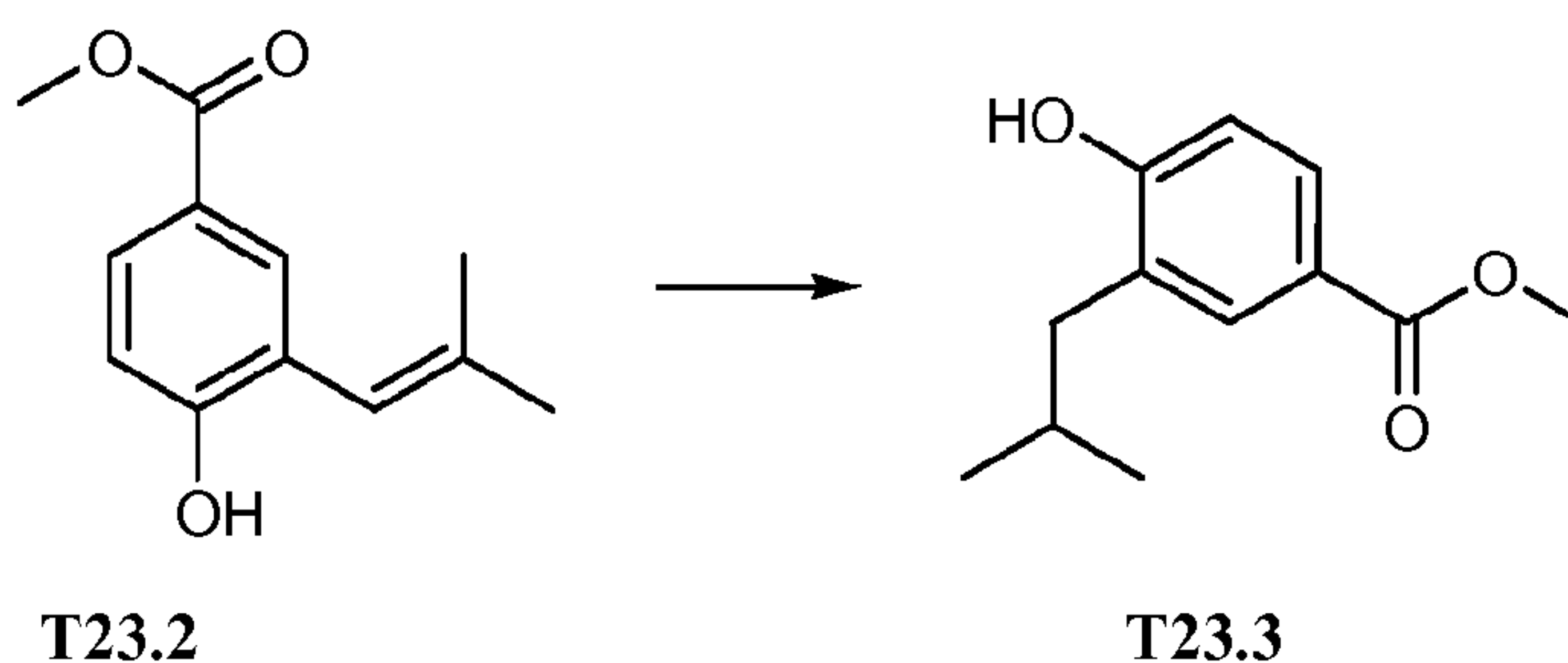
A mixture of methyl 3-bromo-4-(tetrahydro-2H-pyran-2-yloxy)benzoate **T3.2** (0.500 g, 1.6 mmol), palladium acetate (0.036 g, 0.16 mmol), S-Phos (0.13 g, 0.32 mmol) and tripotassium phosphate (0.32 mL, 4.0 mmol) in DMF (10.00 mL, 129 mmol) and water (0.40 mL, 22 mmol) was stirred. The mixture was purged with nitrogen and placed under vacuum and the process repeated three times. Before heating, 2-methylprop-1-enylboronic acid (0.24 g, 2.4 mmol, commercially available from Synthonix, Cat. No. D3007G1) was added, and the mixture was heated to 70°C and stirred for 23 hours. The mixture was then cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T23.1** as a colorless oil (0.460 g, 100% yield).



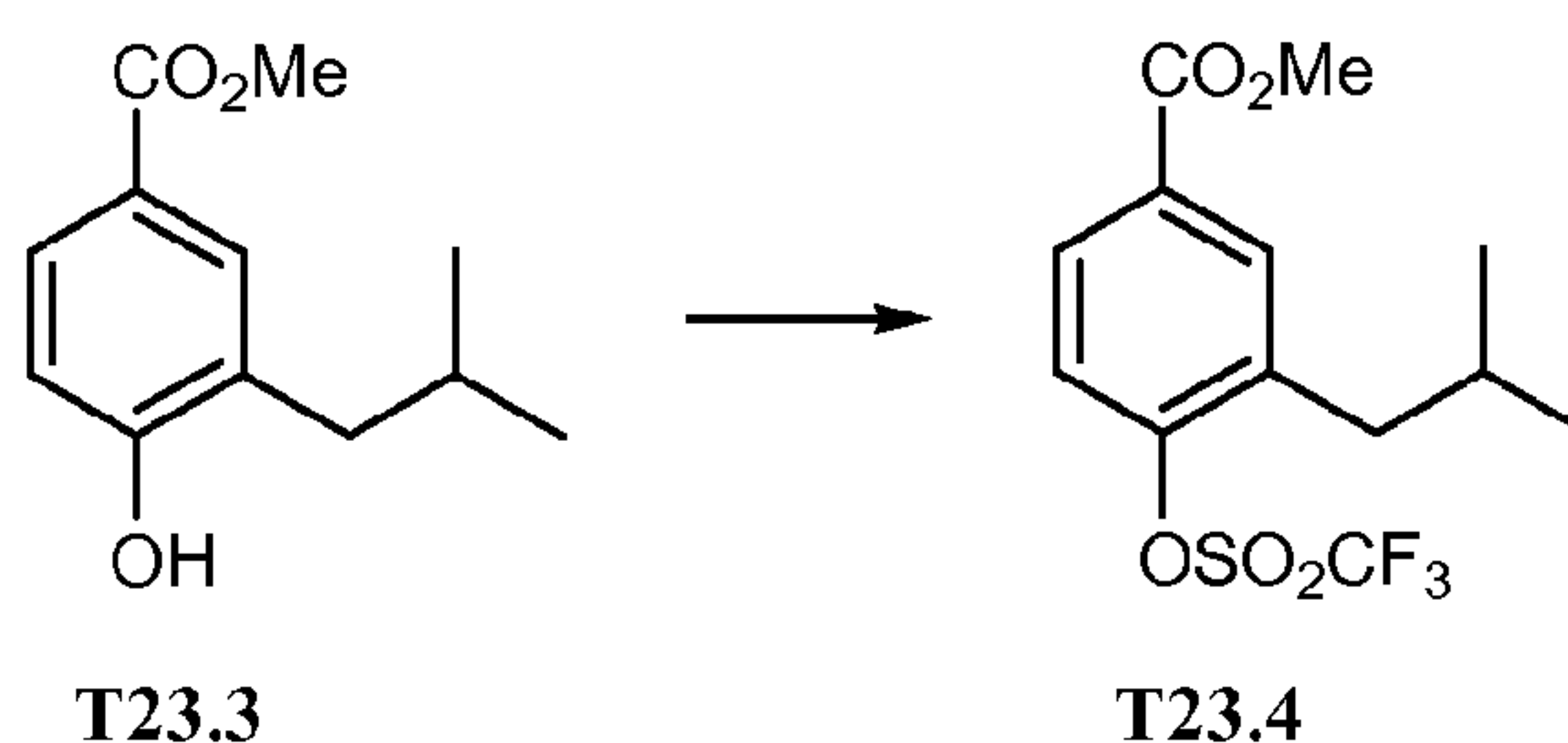
[0453]

Methyl 4-hydroxy-3-(2-methyl-1-propenyl)benzoate (T23.2).

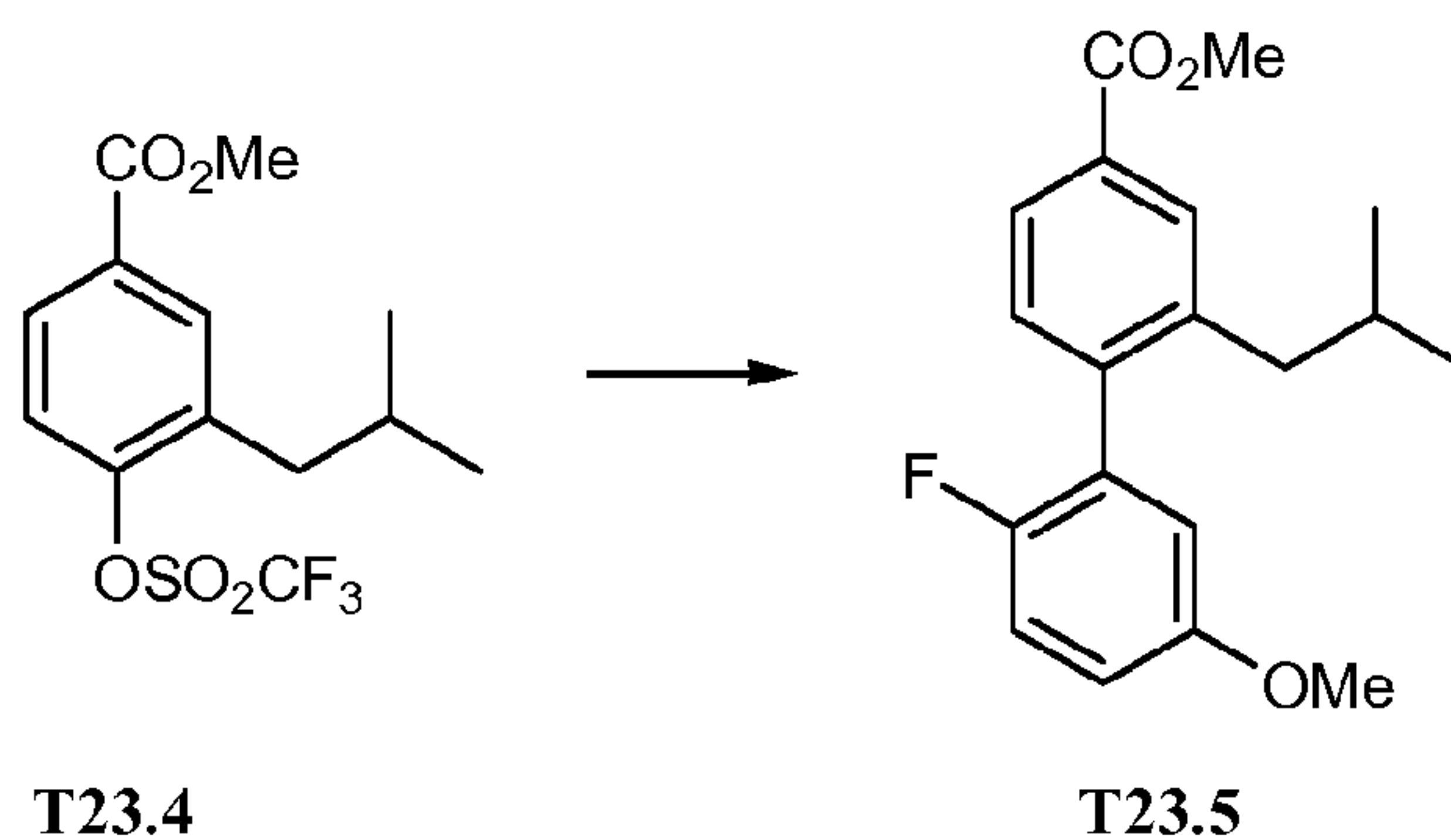
To a stirred mixture of **T23.1** (0.460 g, 2 mmol) in MeOH (8 mL) was added PPTS (0.04 g, 0.2 mmol). The reaction mixture was then stirred for 24 hours and then concentrated in vacuo. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **T23.2** as a colorless oil (0.320 g, 98% yield).



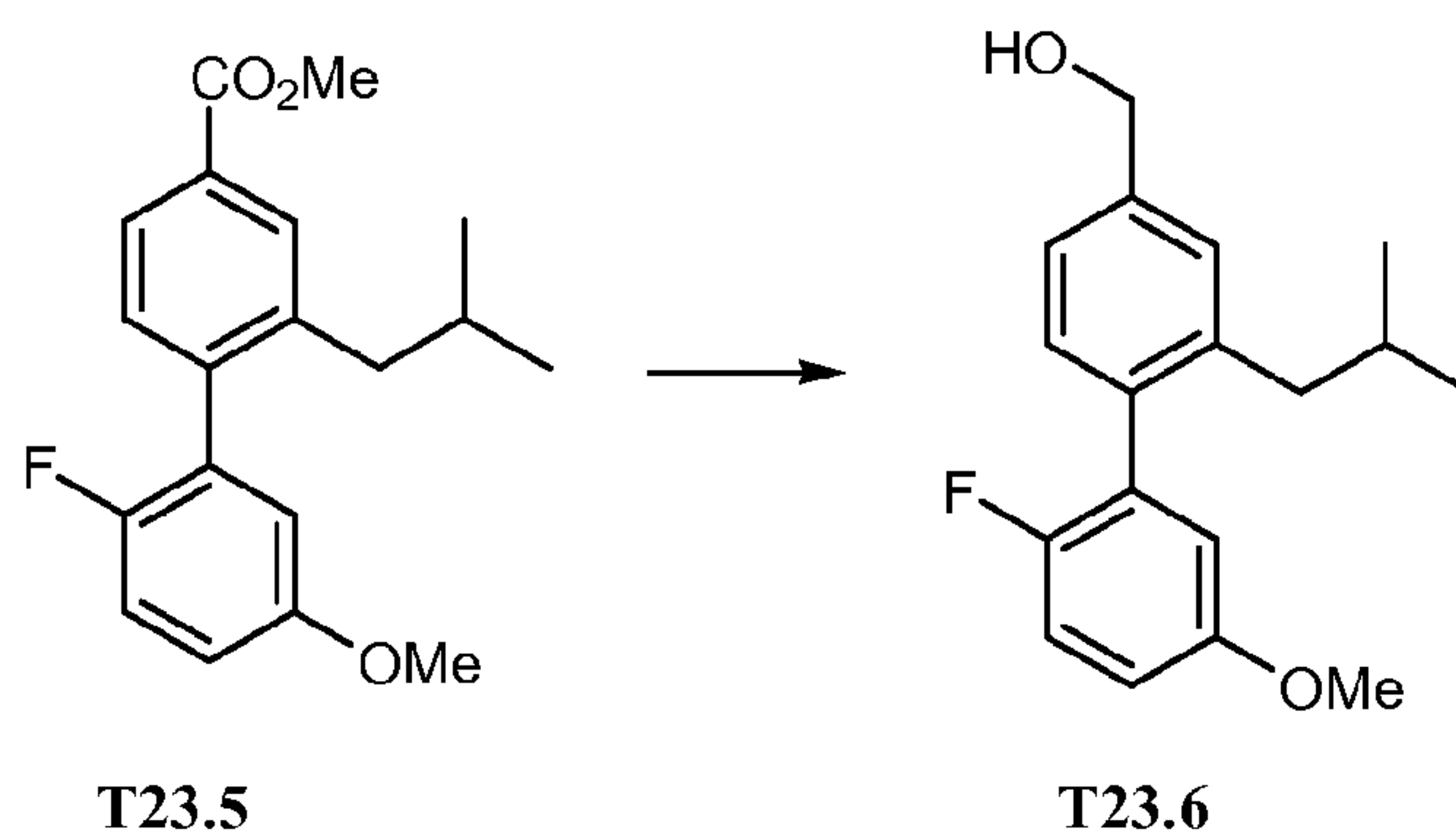
[0454] Methyl 4-hydroxy-3-(2-methylpropyl)benzoate (T23.3). To a stirred solution of methyl 4-hydroxy-3-(2-methylprop-1-enyl)benzoate **T23.2** (0.320 g, 1.6 mmol) in EtOAc (2.00 mL, 20 mmol) at 23°C was added palladium on carbon (0.017 g, 0.16 mmol). The reaction was stirred under an atmosphere of hydrogen (0.0031 g, 1.6 mmol) for 16 hours. The reaction mixture was then filtered and concentrated in vacuo to give a clear oil. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **T23.3** as a colorless oil (0.256 g, 79% yield)



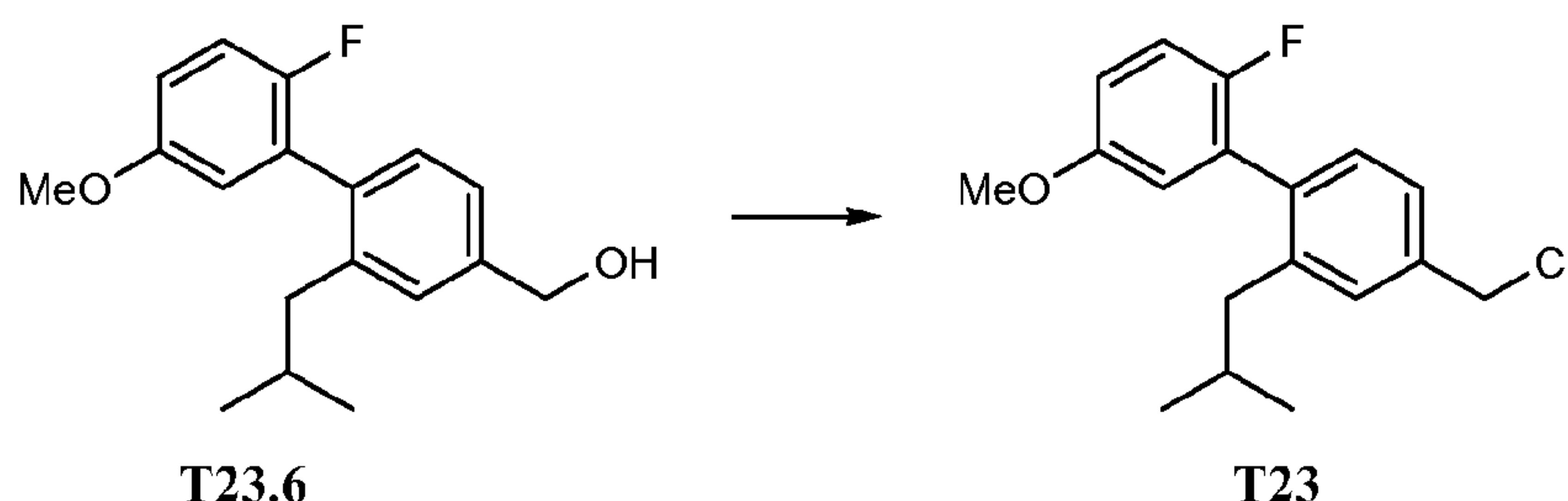
[0455] Methyl 3-(2-methylpropyl)-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (T23.4). To a stirred solution of **T23.3** (0.256 g, 1 mmol) in DCM (12 mL, 1 mmol) at 0°C was added TEA (0.2 mL, 1 mmol), and a catalytic amount of DMAP. N-phenyltriflimide (0.5 g, 1 mmol) was then added and the mixture was stirred at room temperature for 20 hours. The reaction was concentrated in vacuo, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **T23.4** as a colorless oil (0.400 g, 96% yield).



[0456] **Methyl 2'-fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl-4-carboxylate (T23.5).** To a stirred solution of **T23.4** (0.400 g, 1.2 mmol) in DMF (4.00 mL, 52 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (0.40 g, 2.4 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), potassium carbonate (0.49 g, 3.5 mmol), and then tetrakis(triphenylphosphine)palladium (0.14 g, 0.12 mmol). The mixture was heated to 90 °C and stirred for 22 hours. The mixture was cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T23.5** as a colorless oil (0.293 g, 79% yield).

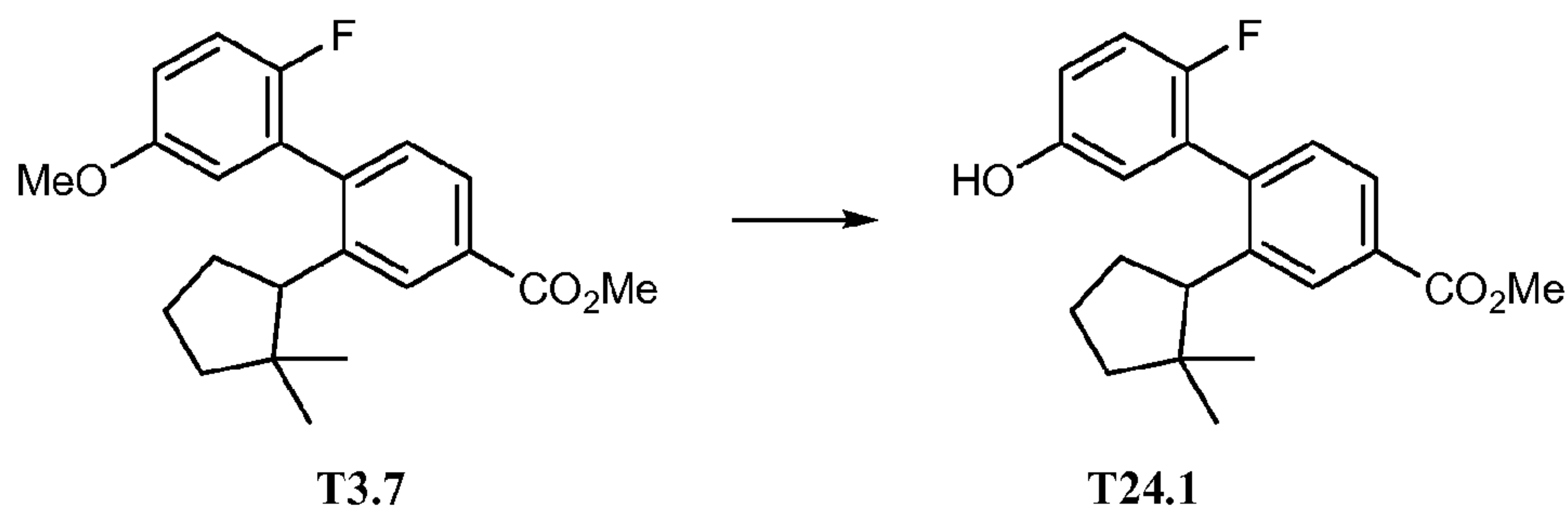


[0457] **(2'-Fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl-4-yl)methanol (T23.6).** To a stirred solution of **T23.5** (0.293 g, 0.9 mmol) in THF (5 mL, 0.9 mmol) at 0°C was added LAH in THF (2 mL, 2 mmol, 1.0M). The reaction was stirred for one hour and then 1N NaOH(aq) was added to quench the mixture. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T23.6** as a colorless oil (0.260 g, 97% yield).



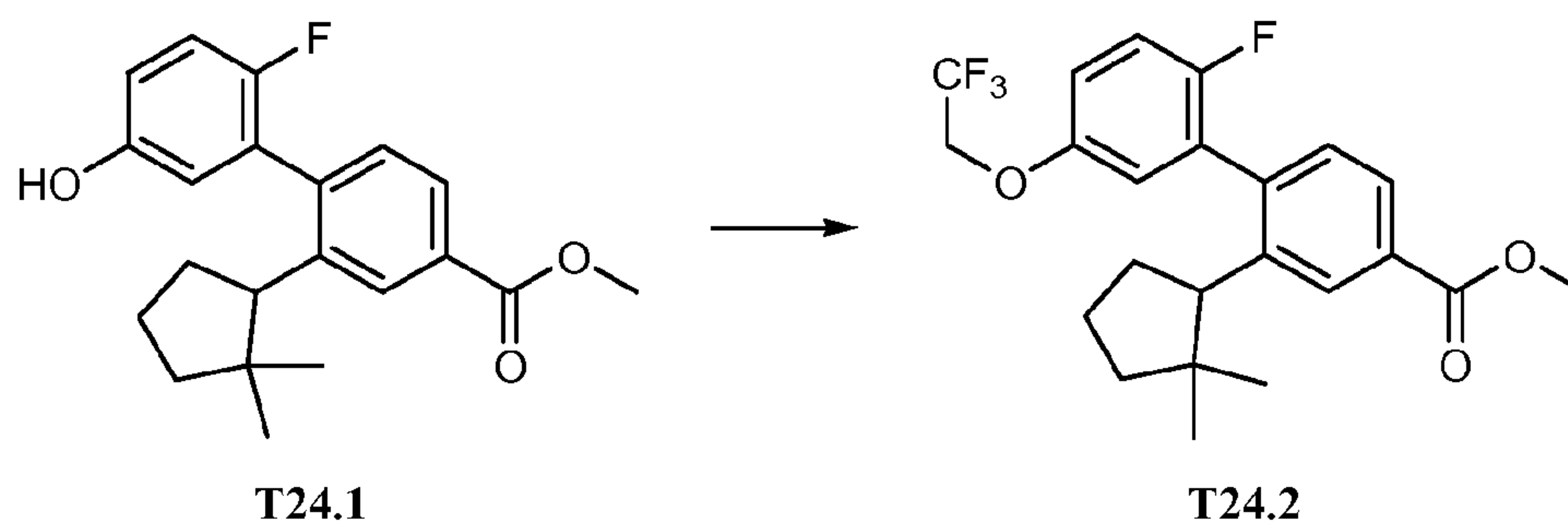
[0458] **4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl (T23).** To a stirred solution of **T23.6** (0.260 g, 0.90 mmol) in DCM (2.00 mL, 31 mmol) at 23°C was added DMF (0.0070 mL, 0.090 mmol) followed by thionyl chloride (0.13 mL, 1.8 mmol). The reaction was stirred for one hour and then the reaction was concentrated in vacuo. The residue was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T23** as a colorless oil (0.252 g, 91% yield).

[0459] **Intermediate T24**

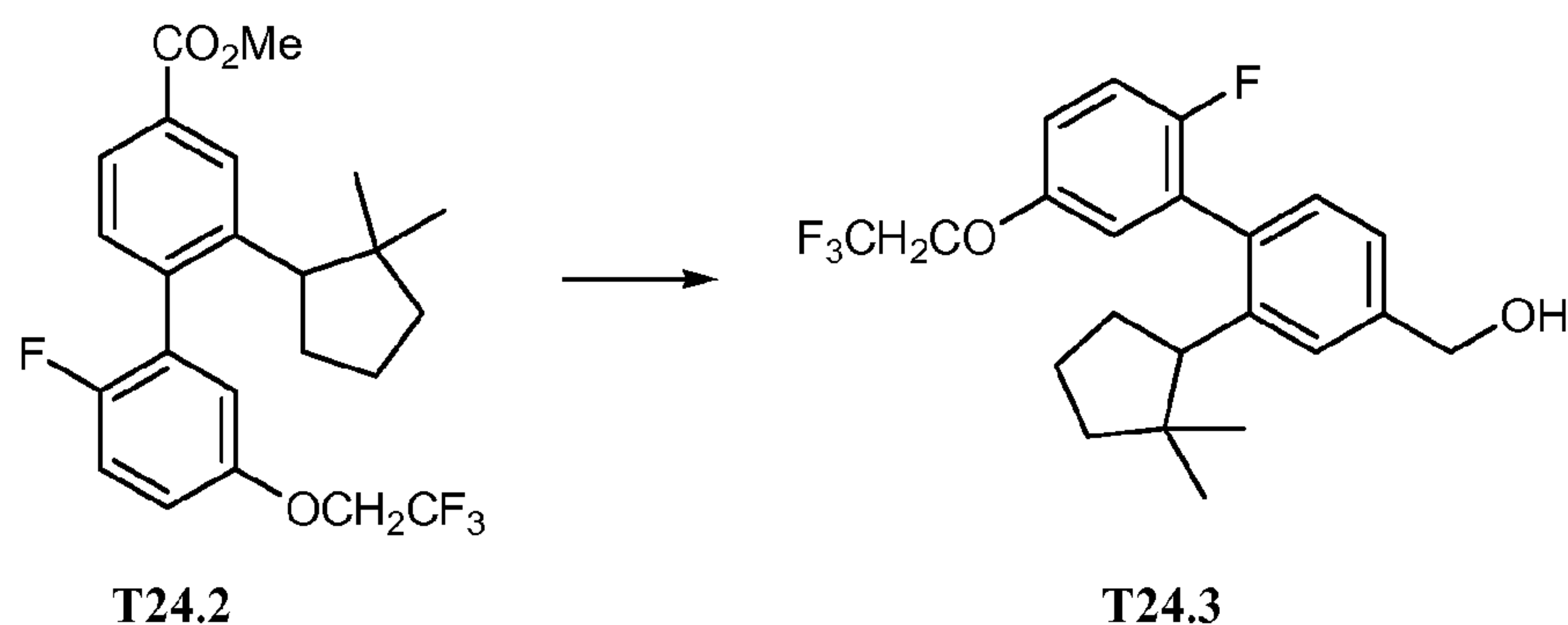


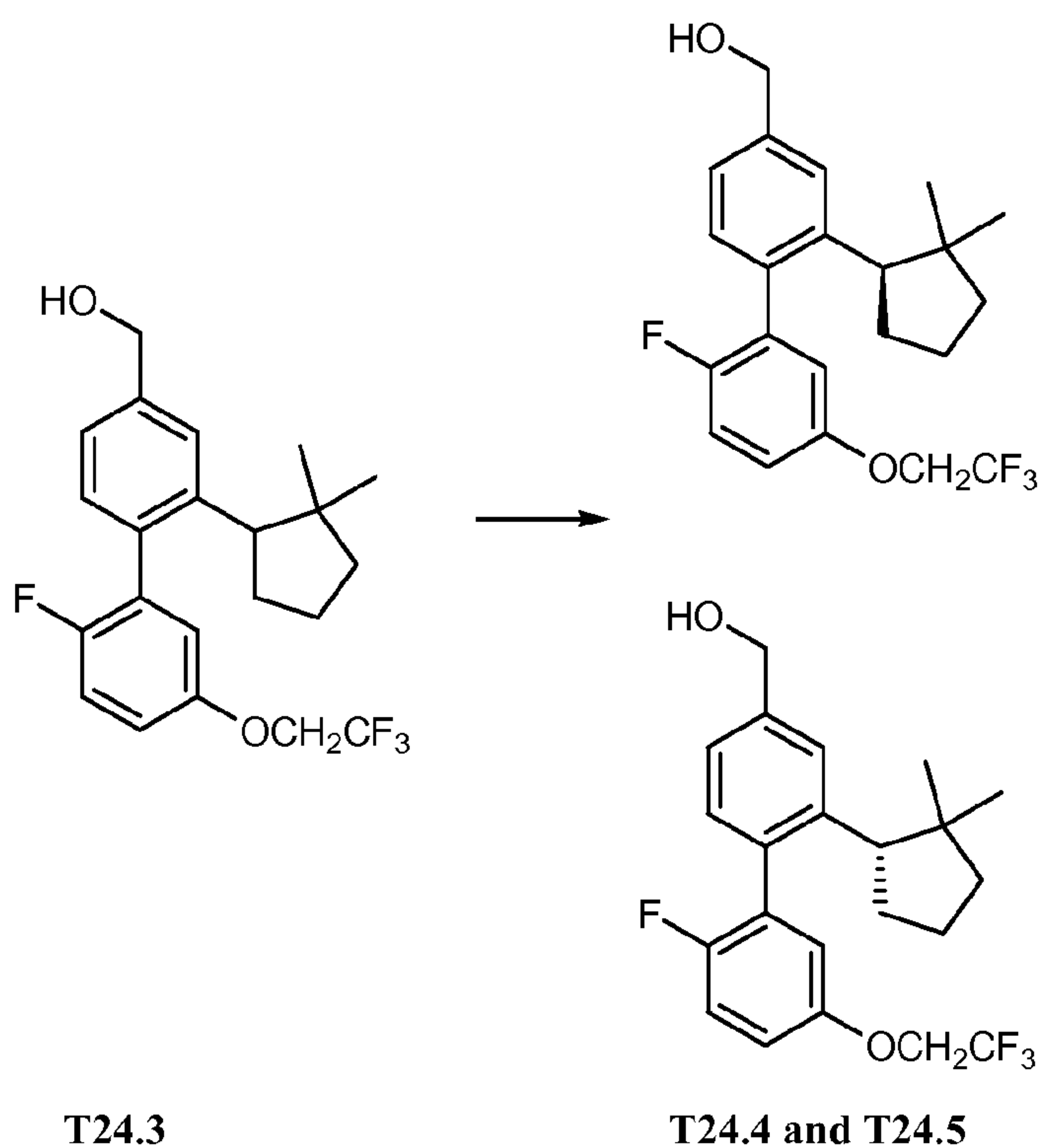
[0460] **Methyl 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-carboxylate (T24.1).** To a stirred solution of **T3.7** (0.400 g, 1.12 mmol) in DCM (10.00 mL) at 0°C was added boron tribromide (1.0M in DCM)(4.49 mL, 4.49 mmol). The reaction was stirred for one hour at 0°C. Water was then added, and the mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the desired product was isolated. The initial product was dissolved in a 1/1 mixture of THF/EtOH and to this was added 1N NaOH (aq), the resulting solution was stirred for 16 hours, after which it was concentrated in vacuo. The reaction was acidified with 1N HCl and the resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure. The resulting product was dissolved in MeOH and a drop of sulfuric

acid was added. The mixture was heated at 70°C for 16 hours. The reaction mixture was then concentrated in vacuo. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T24.1** as a colorless oil (0.250 g, 65% yield).

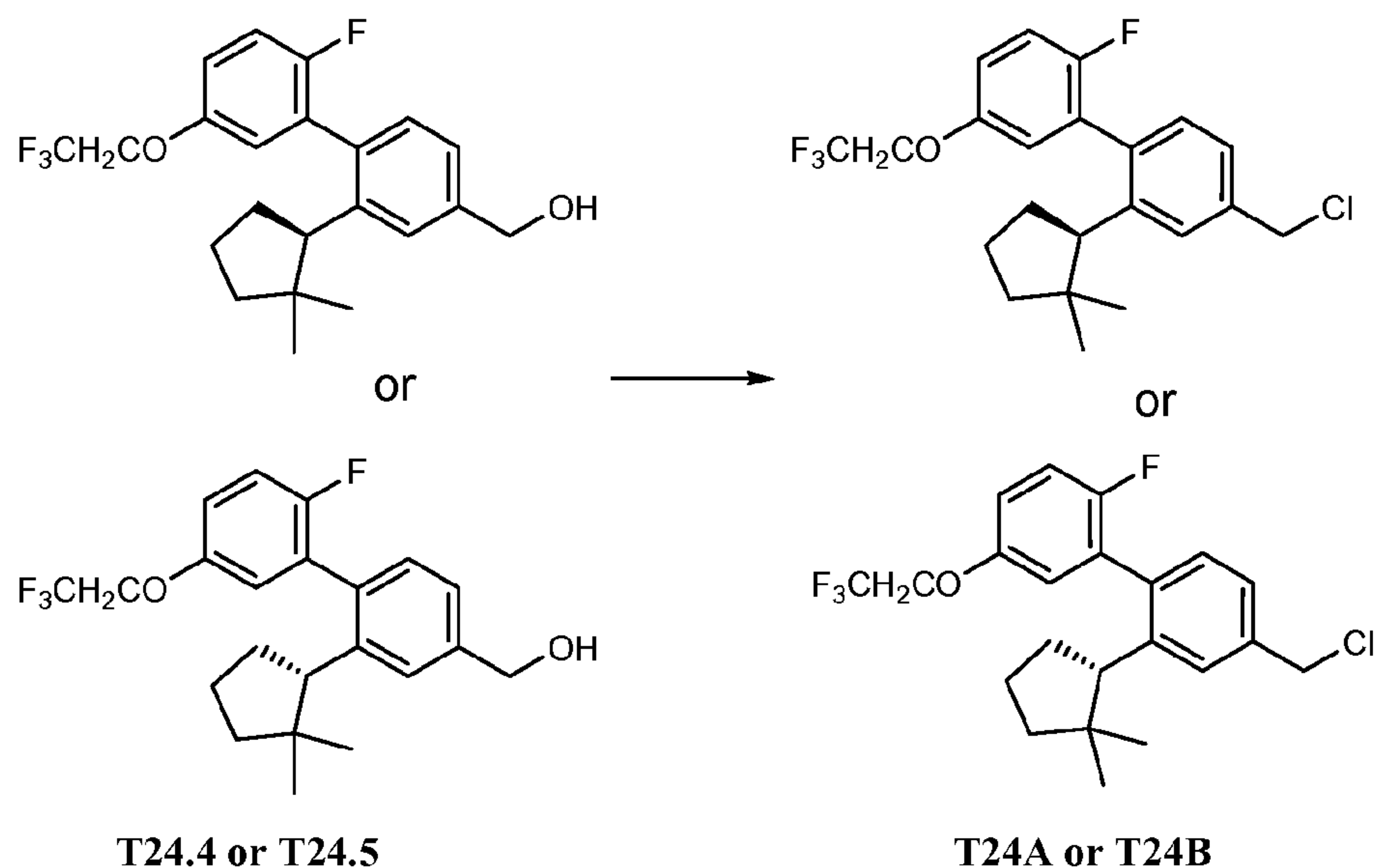


[0461] **Methyl 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-carboxylate (T24.2).** To a flask containing **T24.1** (0.100 g, 0.29 mmol) and Cs_2CO_3 (0.29 g, 0.88 mmol) in DMF (2 mL) was added 1,1,1-trifluoro-2-iodoethane (0.12 g, 0.58 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), and stirring was continued for 5 hours. The reaction was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T24.2** as a colorless oil (0.113 g, 91% yield).



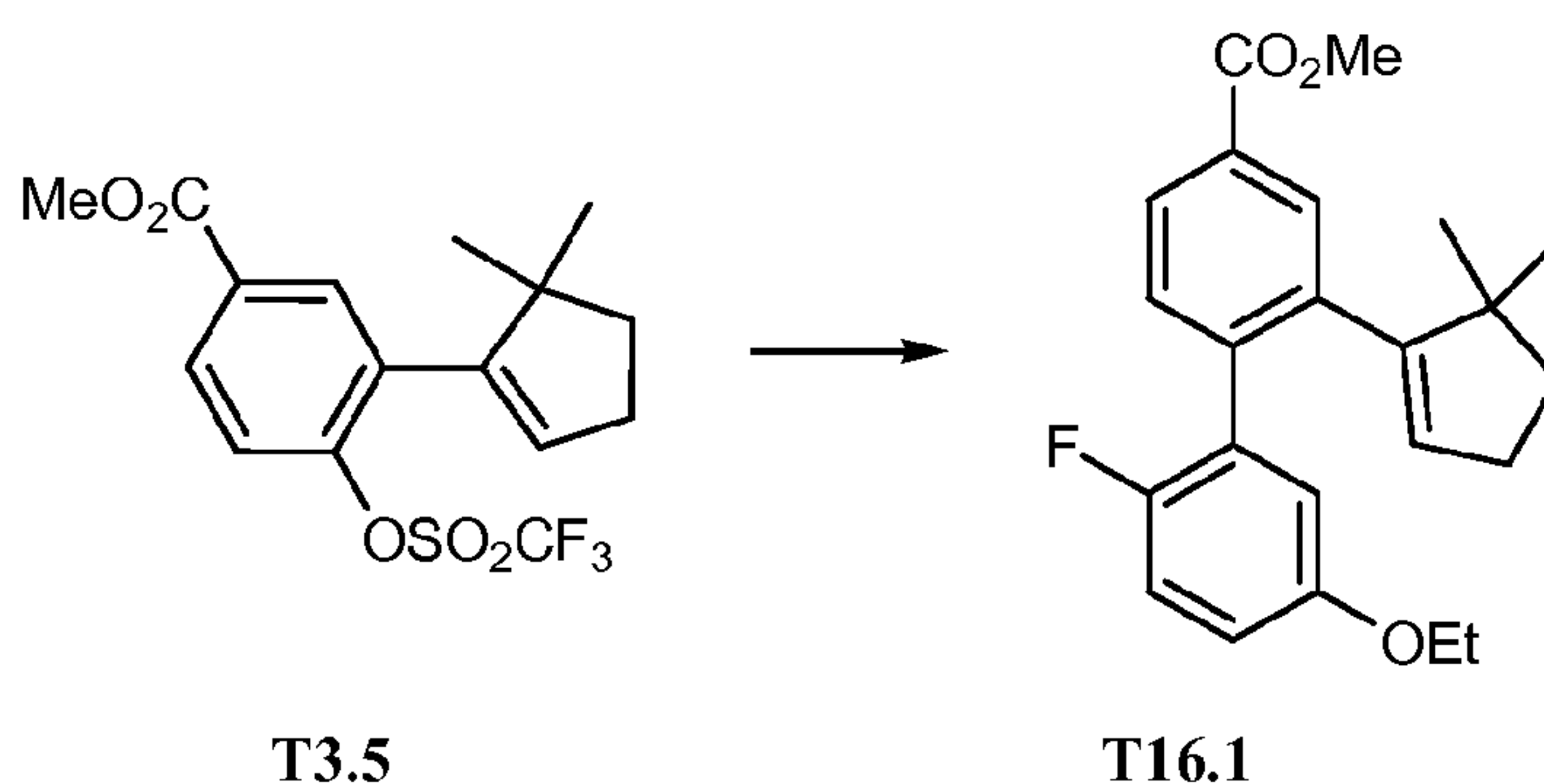


[0462] (2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methanol (**T24.4** and **T24.5**). To a stirred solution of **T24.2** (0.113 g, 0.3 mmol) in THF (5 mL) at 0°C was added LAH in THF (0.5 mL, 0.5 mmol, 1.0M). The mixture was stirred for one hour and then 1N NaOH(aq) was added to quench the reaction. The reaction mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T24.3** as a colorless oil (0.075 g, 71% yield). Chiral separation of **T24.3** was accomplished on CHIRALCEL® OD (3%IPA in hexane) to provide **T24.4** (peak one) and **T24.5** (peak two).¹



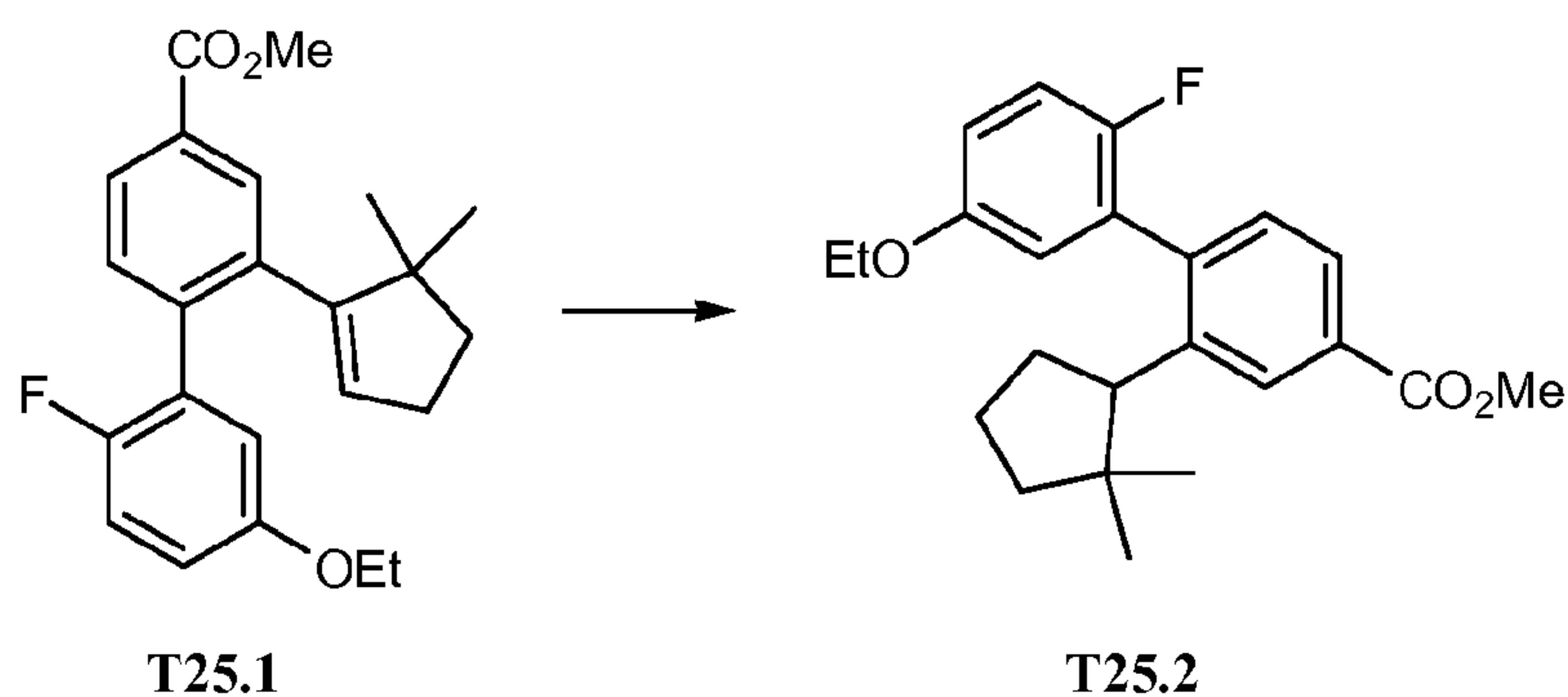
[0463] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethoxy)-1,1'-biphenyl (T24A or T24B).** To a stirred solution of **T24.4** or **T24.5** (0.022 g, 0.055 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.00043 mL) followed by thionyl chloride (0.0081 mL, 0.11 mmol). The reaction was stirred for two hours and then the reaction mixture was concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T24A** or **T24B** as a colorless oil (0.019 g, 83% yield).

[0464] **Intermediates T25A and T25B**

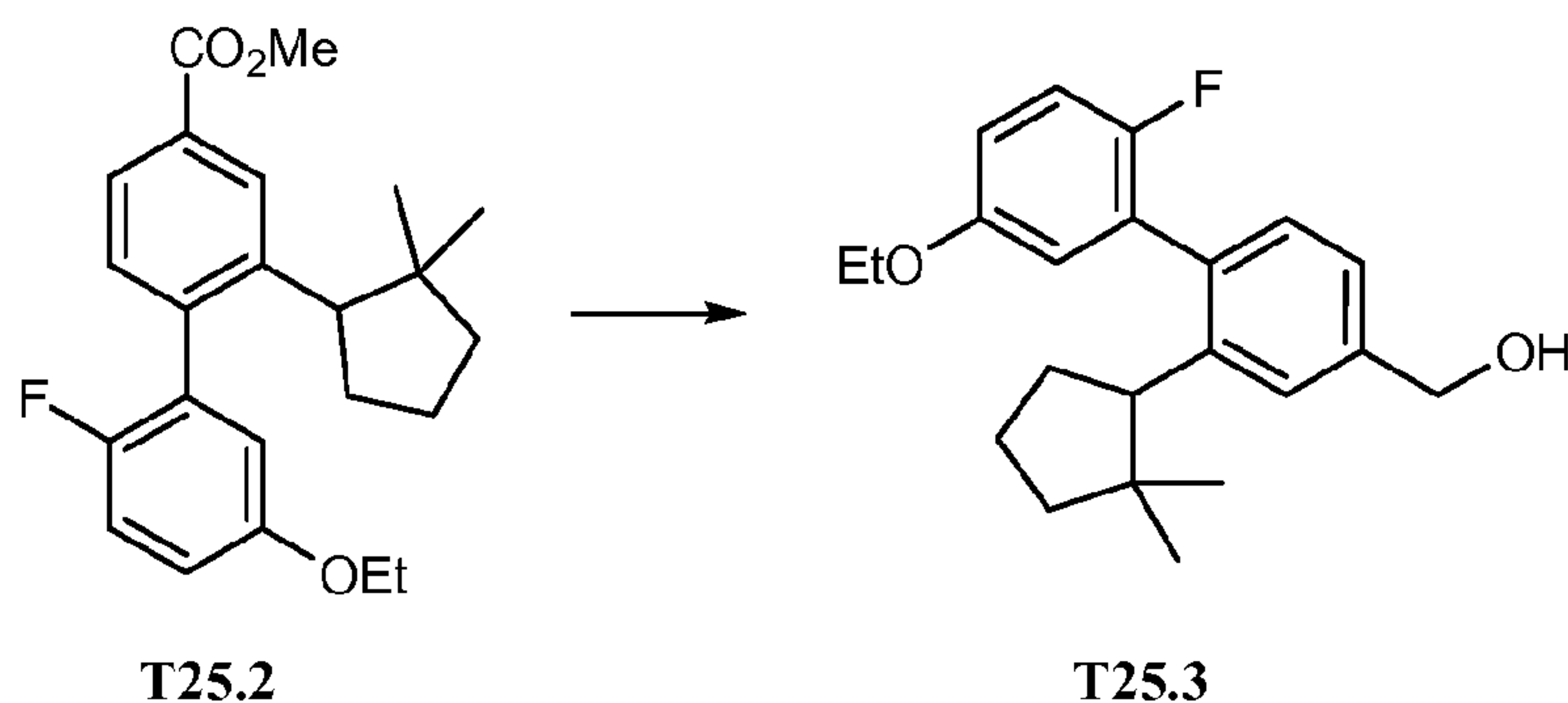


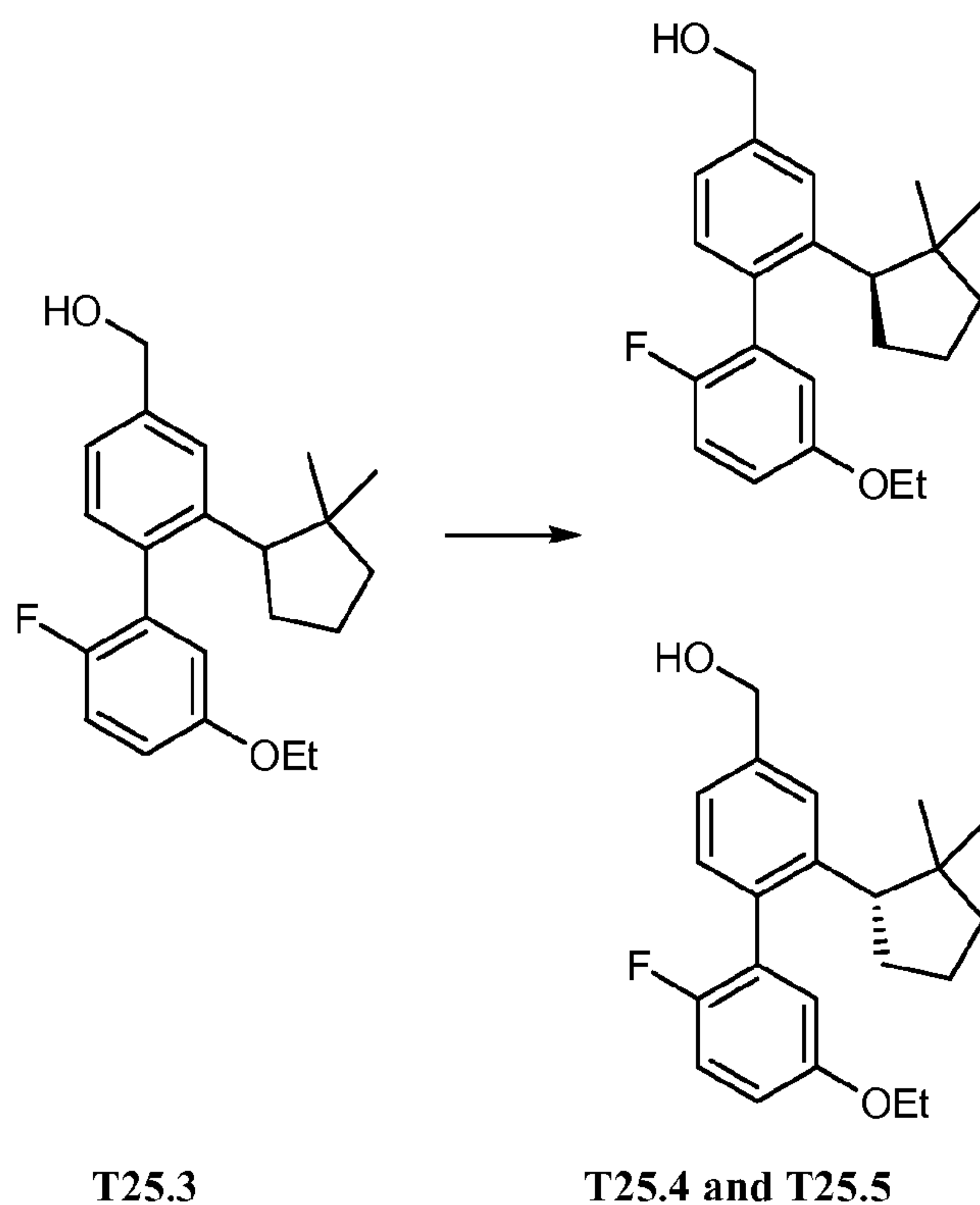
[0465] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-carboxylate (T25.1).** To a stirred solution of methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(trifluoromethylsulfonyloxy)benzoate **T3.5** (0.400 g, 1.1 mmol) in DMF (4.00 mL) at 23°C was added 5-ethoxy-2-fluorophenylboronic acid (0.29

g, 1.6 mmol, commercially available from Sigma-Aldrich, St. Louis, MO, USA), potassium carbonate (0.44 g, 3.2 mmol), and then tetrakis(triphenylphosphine)palladium (0.12 g, 0.11 mmol). The mixture was heated to 90 °C and stirred for 21 hours. The mixture was then cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T25.1** as a colorless oil (0.350 g, 90% yield).

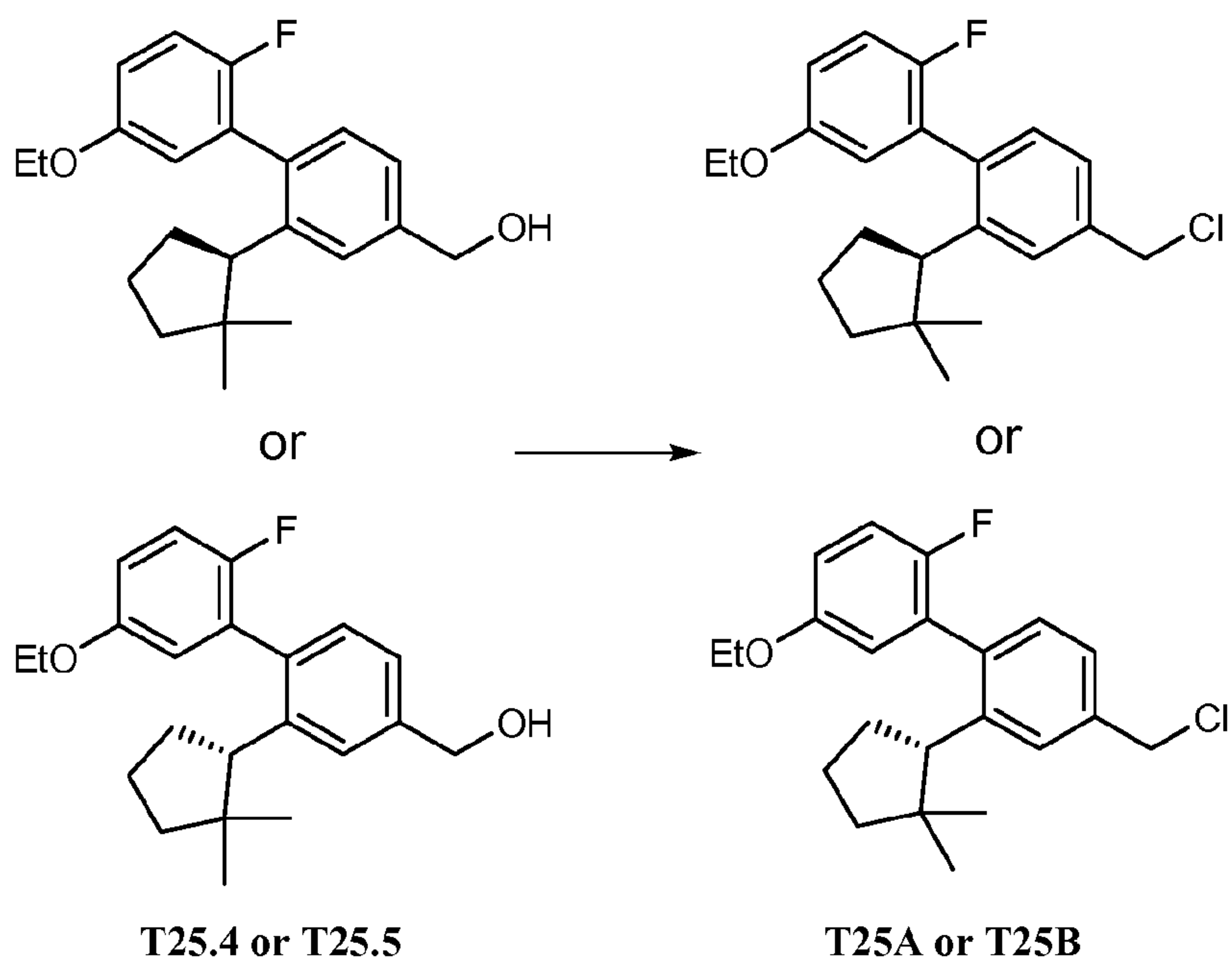


[0466] **Methyl 2-(2-(2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-carboxylate (T25.2).** To a stirred solution of **T25.1** (0.400 g, 1.09 mmol) in MeOH (10.00 mL, 1.09 mmol) at 23°C was added palladium on carbon (0.116 g, 1.09 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for 23 hours. The mixture was then filtered and concentrated in vacuo. The initial product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T25.2** as a colorless oil (0.400 g, 99.5% yield).



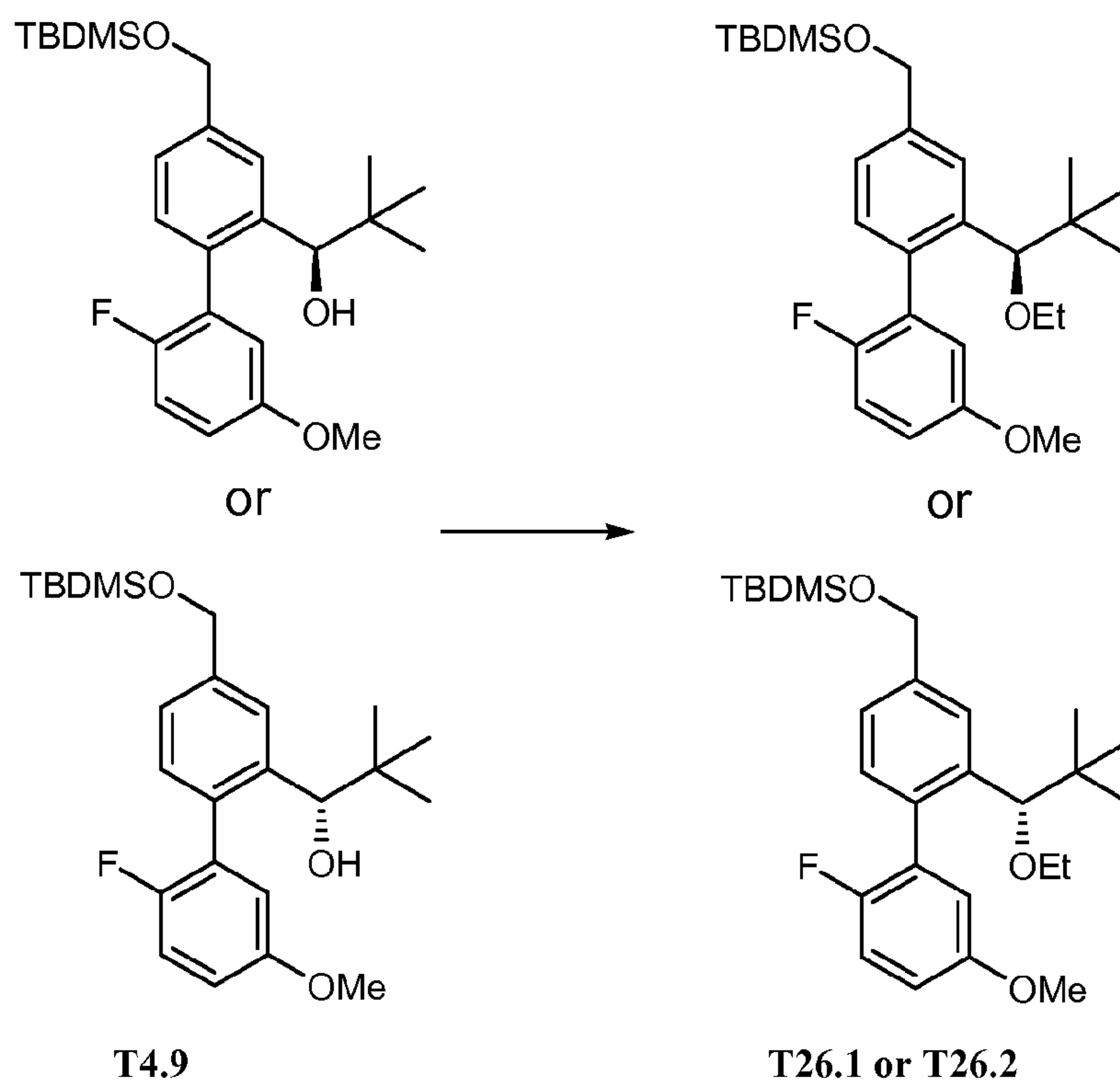


[0467] (2-((1R)-2,2-Dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (**T25.4** and **T25.5**). To a stirred solution of **T25.2** (0.400 g, 1.1 mmol) in THF (15.00 mL, 183 mmol) at 0°C was added LAH in THF (2.2 mL, 2.2 mmol, 1.0M). The mixture was stirred for one hour and then 1N NaOH(aq) was added to quench the reaction. The reaction mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **T25.3** as a colorless oil (0.320 g, 87% yield). Chiral separation of **T25.3** was accomplished on a CHIRALCEL® OD column (3%IPA in hexane) to provide **T25.4** (peak one) and **T25.5** (peak two).¹

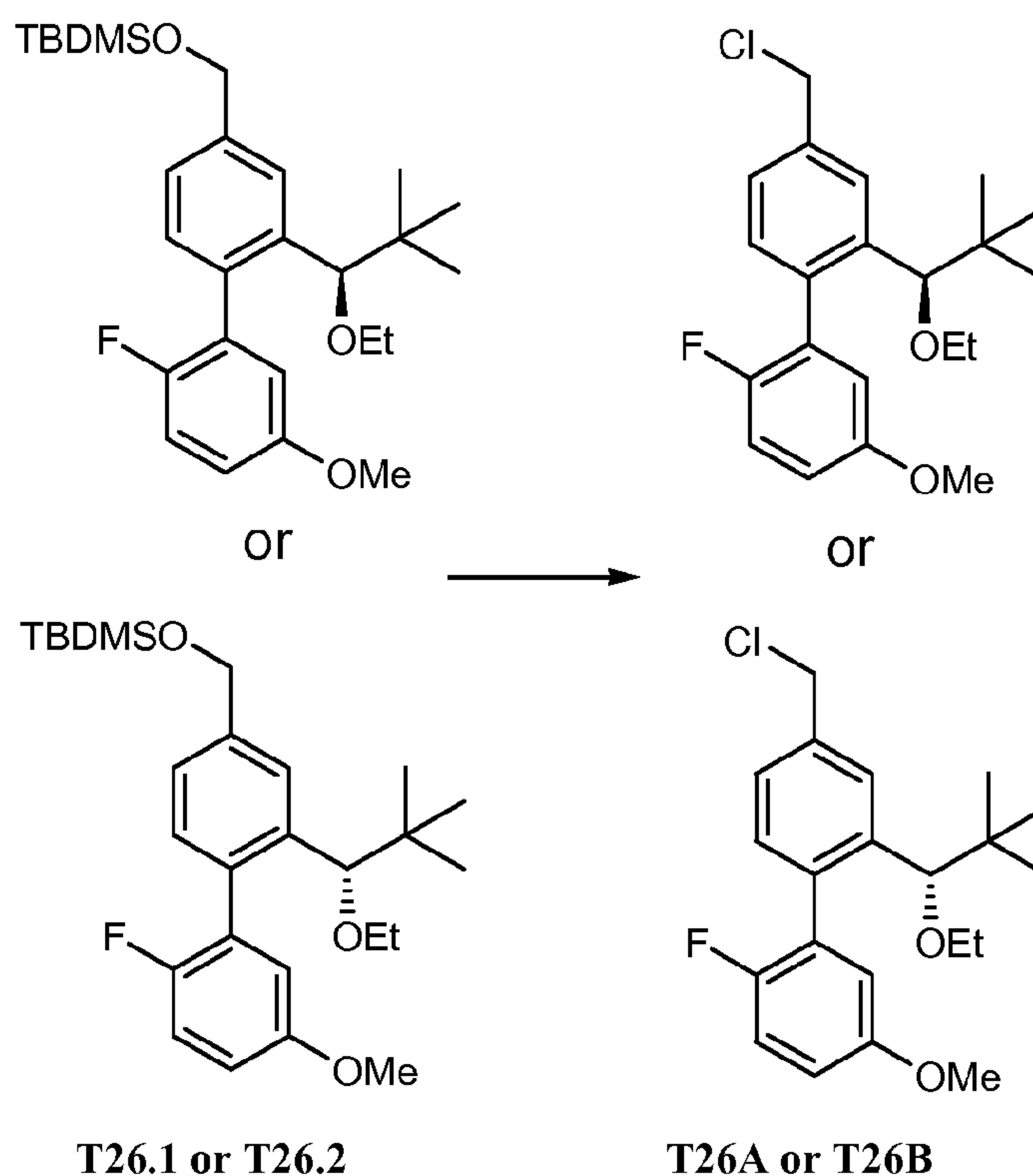


[0468] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-5'-(ethyloxy)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethyloxy)-2'-fluoro-1,1'-biphenyl (T25A or T25B).** To a stirred solution of **T25.4** or **T25.5** (0.147 g, 0.43 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.0033 mL) followed by thionyl chloride (0.063 mL, 0.86 mmol). The reaction was then stirred for 4 hours and then concentrated in vacuo. The initial product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T25A** or **T25B** as a colorless oil (0.120 g, 77% yield).

[0469] **Intermediates T26A and T26B**

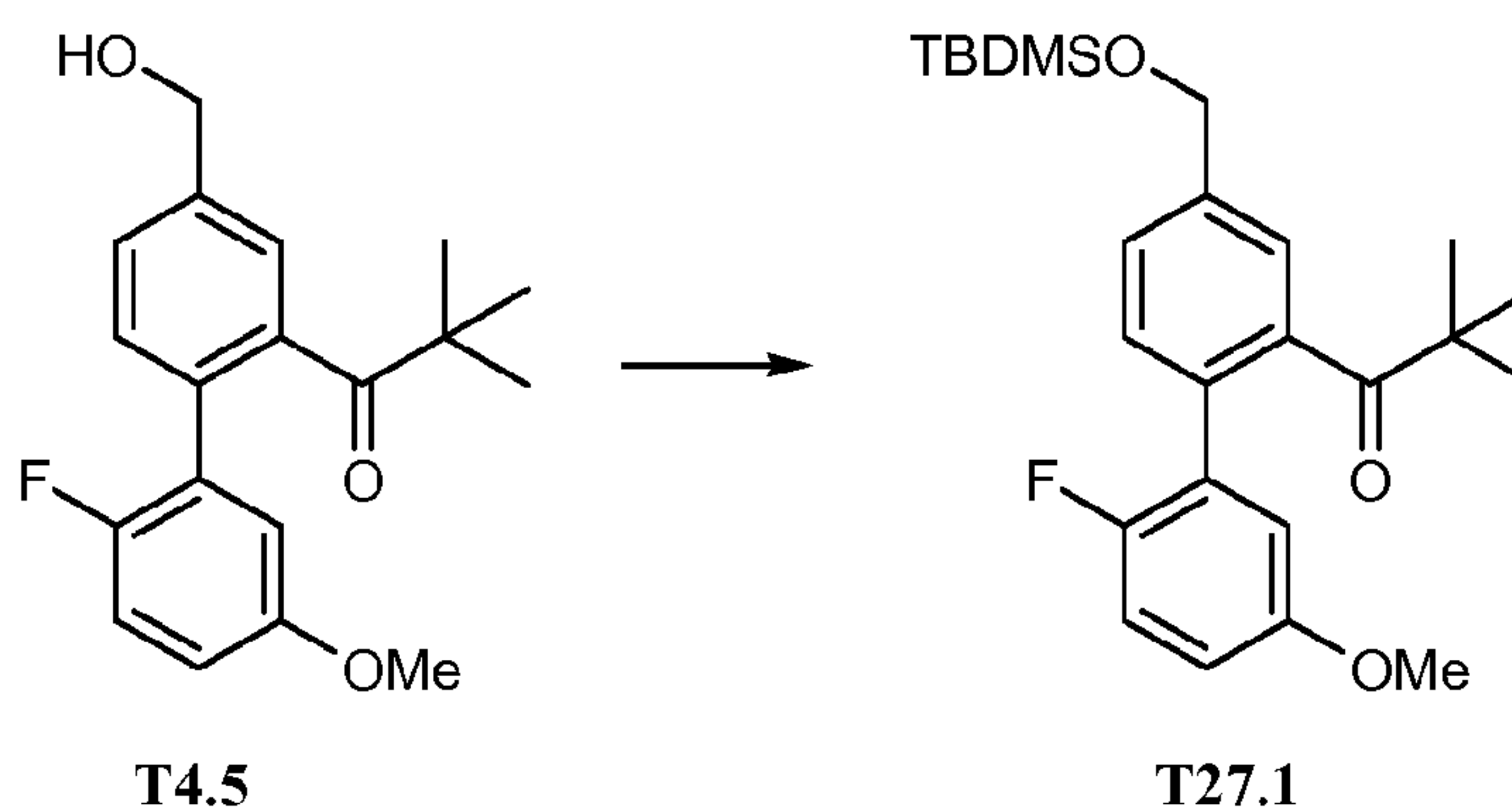


[0470] (1,1-Dimethylethyl) (((2-((1R)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methoxy)dimethylsilane or (1,1-dimethylethyl) (((2-((1S)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methoxy)dimethylsilane (T26.1 or T26.2). To a stirred solution of T4.9 (derived from peak two from chiral separation of T4.6) (0.110 g, 0.25 mmol) in DMF (2.00 mL) at 23°C was added iodoethane (0.048 g, 0.31 mmol), followed by sodium hydride (0.0073 g, 0.31 mmol). The mixture was stirred at 60°C for 21 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield T26.1 or T26.2 as a colorless oil (0.065 g, 55% yield).

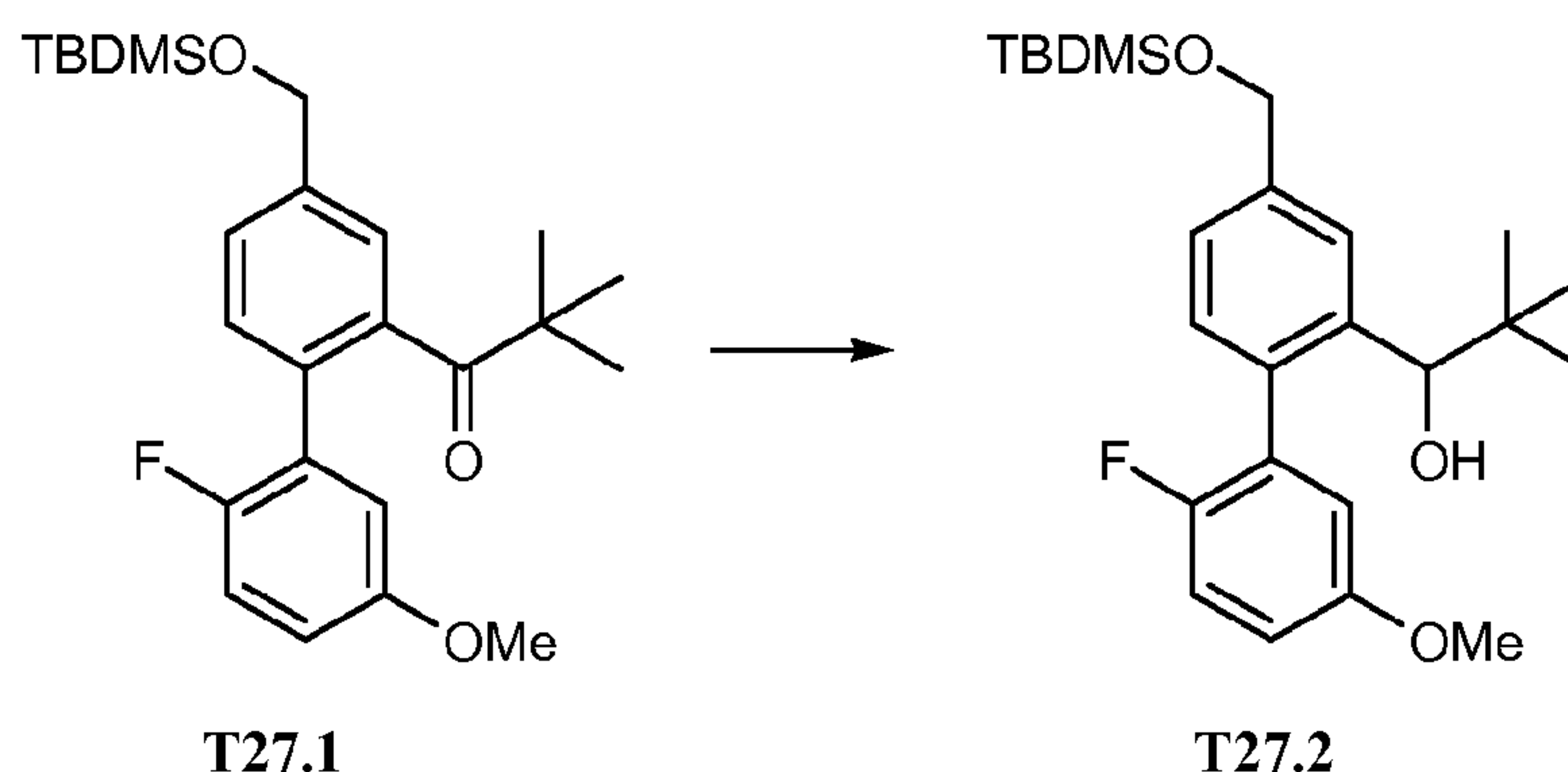


[0471] **4-(Chloromethyl)-2-((1R)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (T26A or T26B).** To a stirred solution of **T26.1** or **T26.2** (0.065 g, 0.1 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.001 mL) followed by thionyl chloride (0.02 mL, 0.3 mmol). The mixture was stirred for 2 hours and then concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T26A** or **T26B** as a colorless oil (0.04 g, 78% yield).

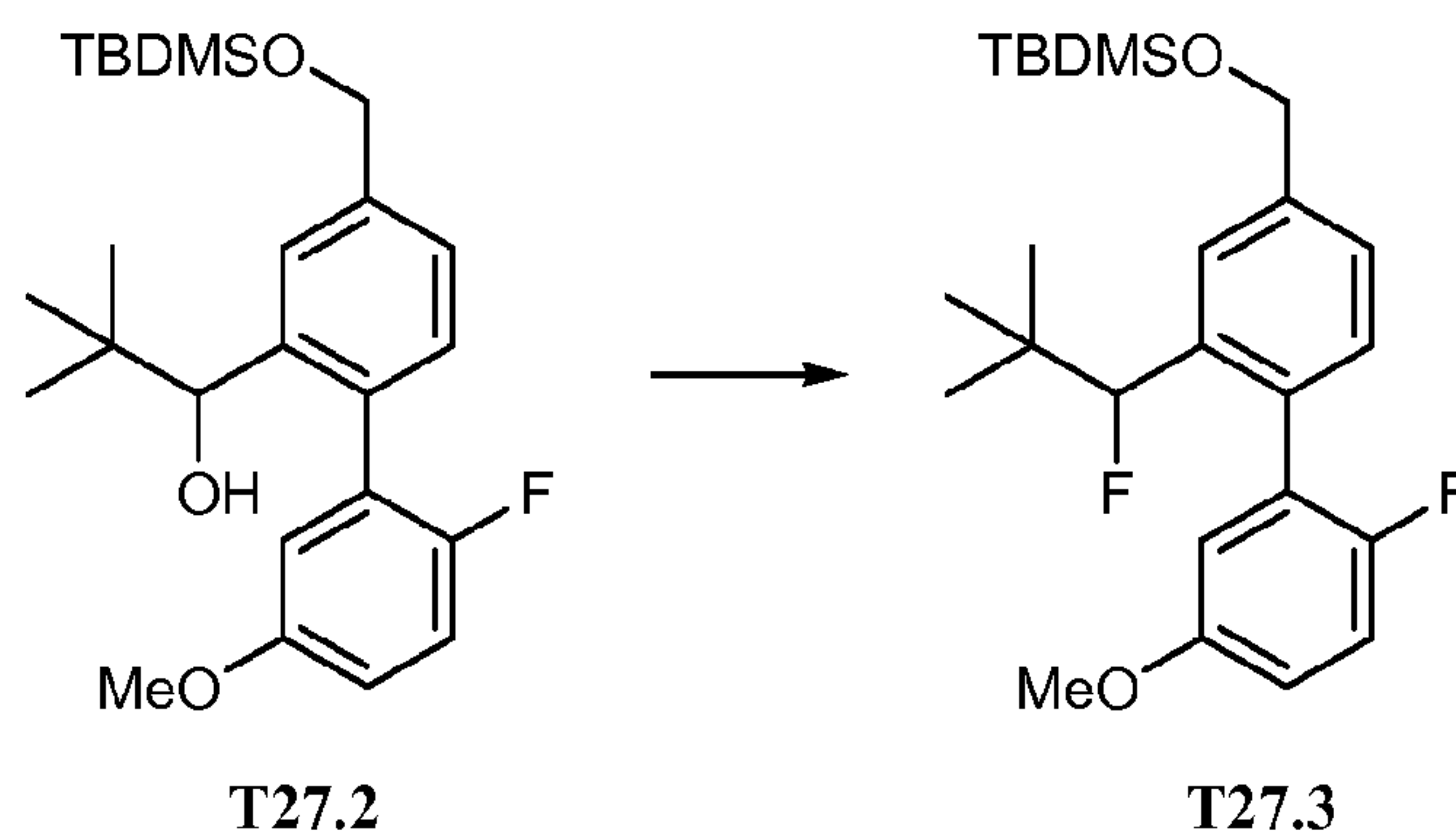
[0472] **Intermediates T27A and T27B**



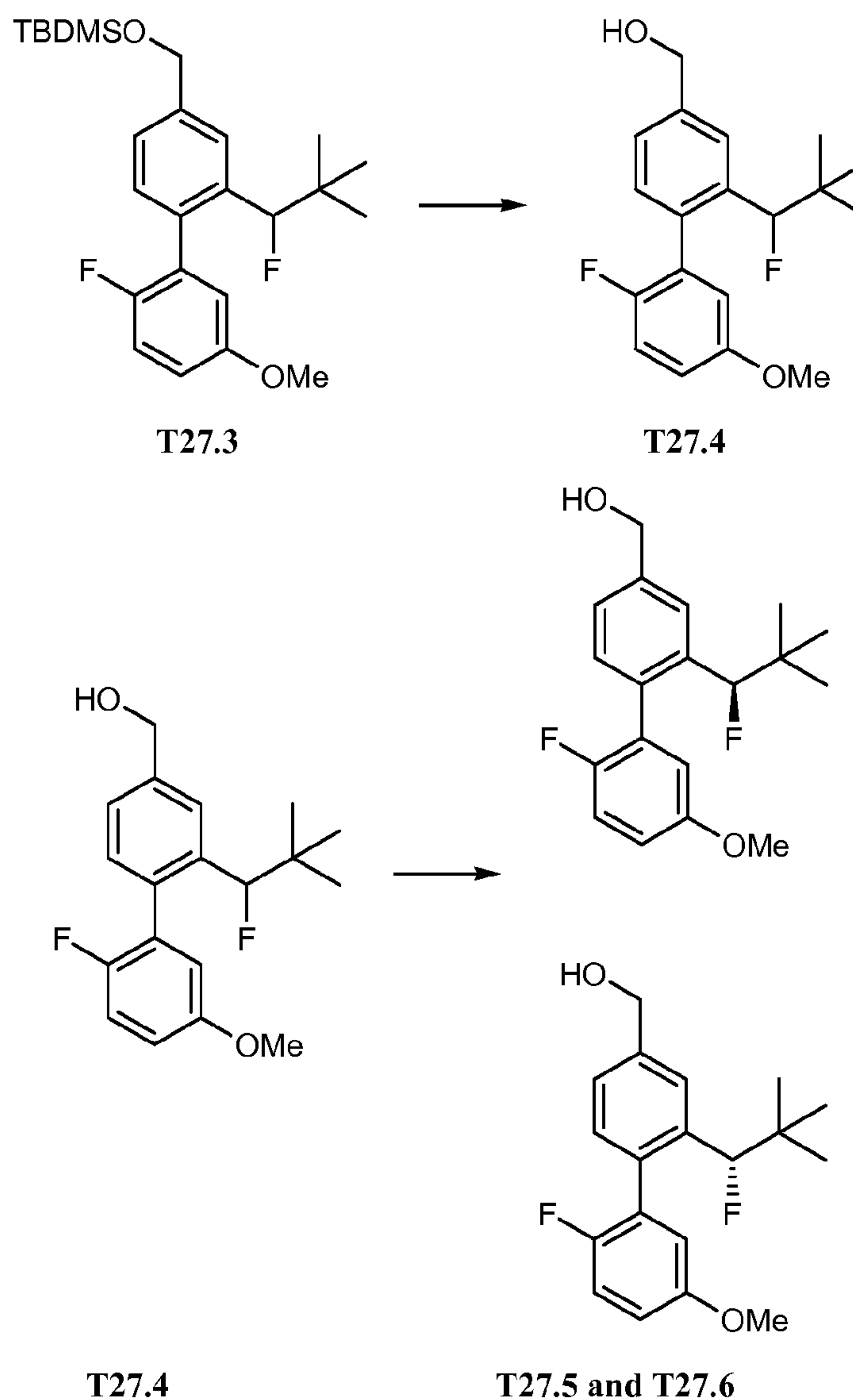
[0473] **1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone (T27.1).** To a stirred solution of **T4.5** (1.00 g, 3 mmol) in DCM (10.00 mL) at 23°C was added tert-butyltrimethylsilyl chloride (0.6 mL, 4 mmol), followed by TEA (0.5 mL, 4 mmol) and DMAP (0.04 g, 0.3 mmol). The reaction was stirred for 16 hours and then the reaction was concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **T27.1** as a colorless oil (1.30 g, 96% yield).



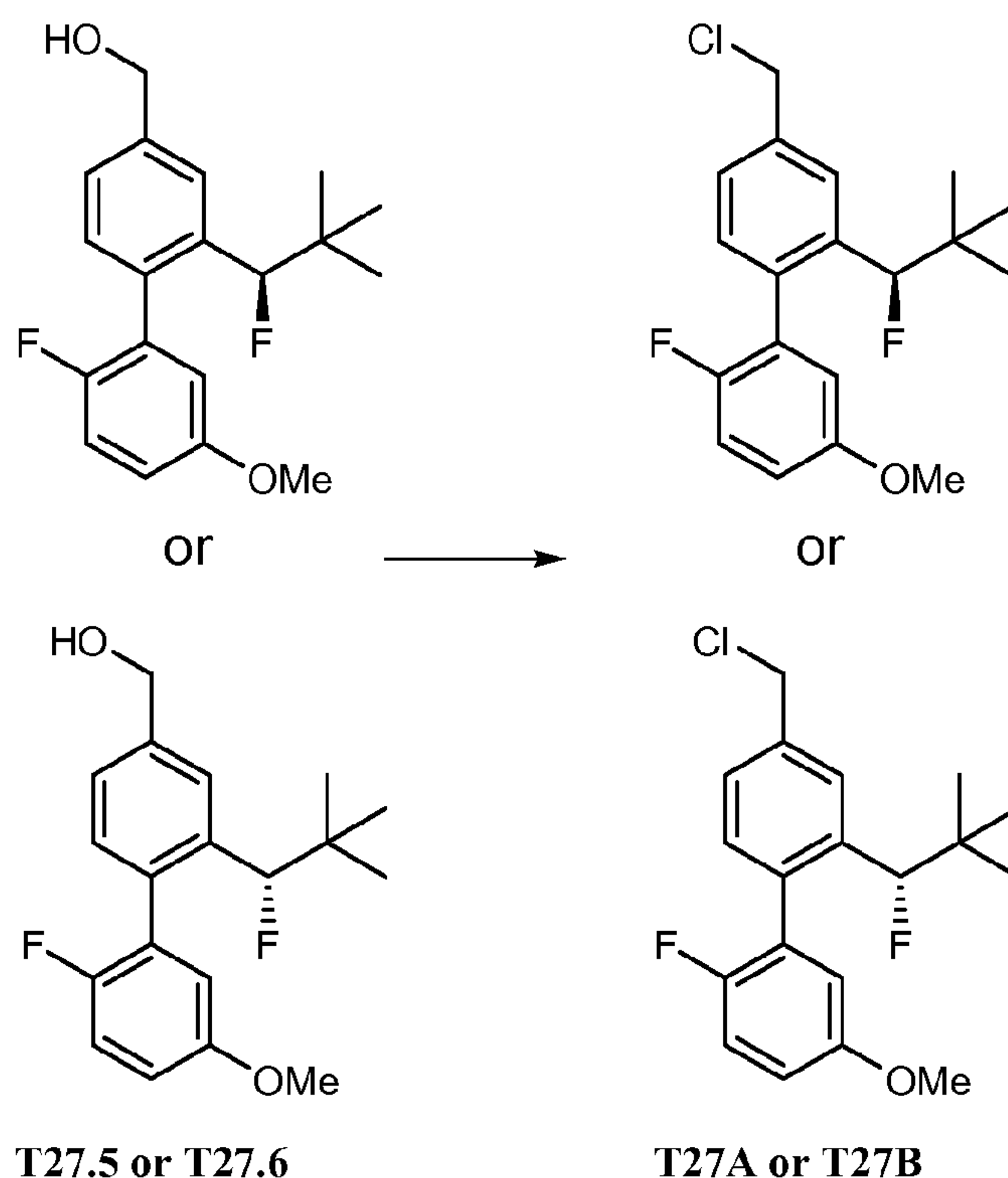
[0474] **1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (T27.2).** To a stirred solution of **T27.1** (0.500 g, 1.2 mmol) in THF (15.00 mL, 183 mmol) at 0°C was added LAH in THF (2.3 mL, 2.3 mmol, 1.0M). The reaction was stirred for two hours. 1N NaOH(aq) was added to quench the reaction mixture, and the reaction was then extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T27.2** as a colorless oil (0.400 g, 80% yield).



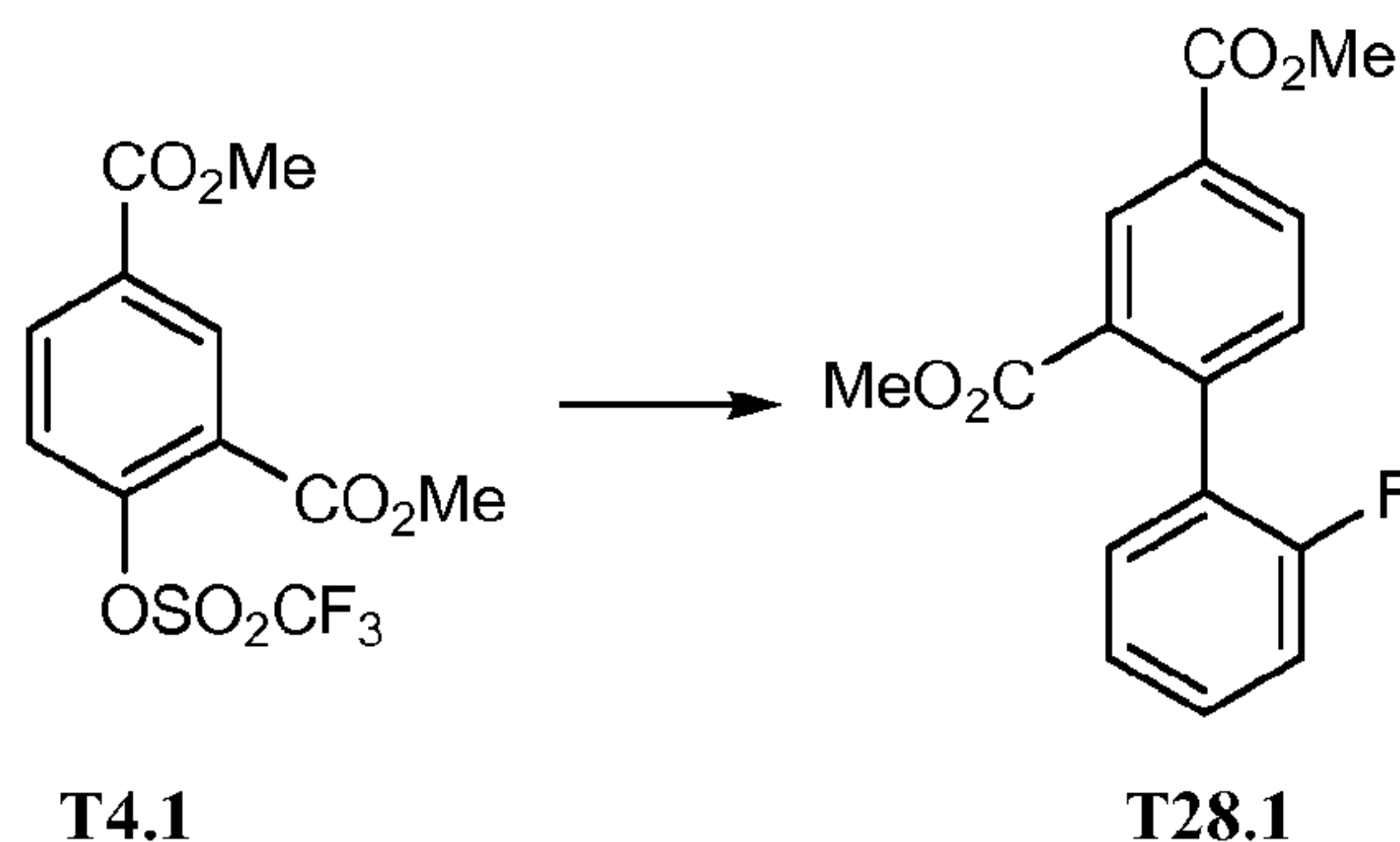
[0475] **(1,1-Dimethylethyl)(((2'-fluoro-2-(1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (T27.3).** To a solution of **T27.2** (0.400 g, 0.925 mmol) in toluene (10 mL) at -78°C was added DAST (0.209 g, 1.29 mmol) dropwise. The reaction was stirred at -78°C for 30 minutes and then warmed to 23°C and stirred for an additional 2 hours. Water was added to quench the reaction mixture. The reaction was then extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T27.3** as a colorless oil (0.400 g, 99% yield).



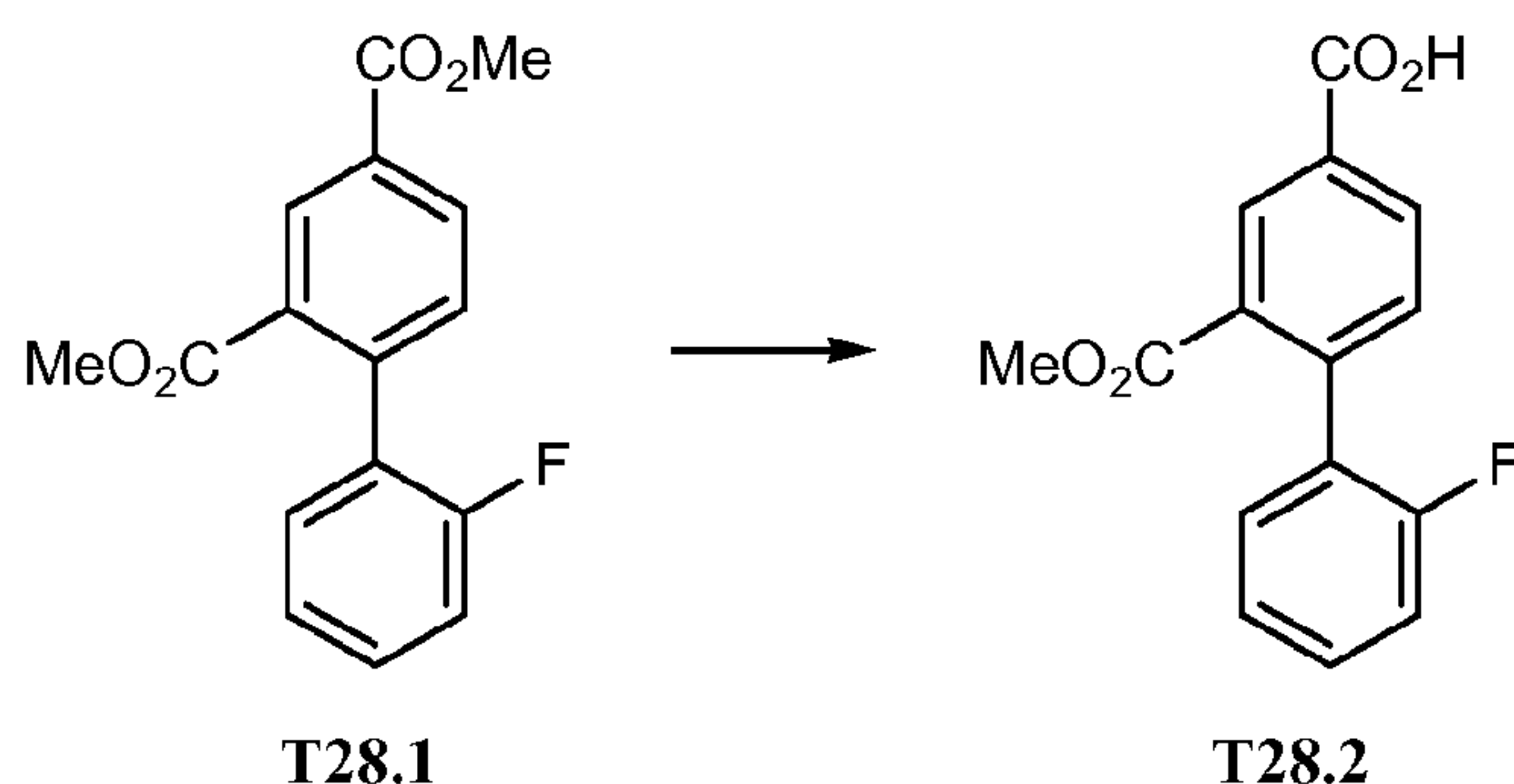
[0476] (2'-Fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T27.5 and T27.6). To a stirred solution of T27.3 (0.400 g, 0.920 mmol) in MeOH (10.00 mL) at 23°C was added PPTS (0.0231 g, 0.0920 mmol). The reaction was stirred for 19 hours and then concentrated in vacuo to give a clear oil. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield T27.4 as a colorless oil (0.272 g, 92% yield). Chiral separation of T27.4 was accomplished on a CHIRALCEL® OD column (3%IPA in hexane) to provide T27.5 and T27.6.



[0477] 4-(Chloromethyl)-2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl (T27A or T27B). To a stirred solution of T27.5 or T27.6 (0.102 g, 0.3 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.002 mL) followed by thionyl chloride (0.05 mL, 0.6 mmol). The reaction was stirred for 1.5 hours. The reaction was concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield T27A or T27B as a colorless oil (0.09 g, 83% yield).

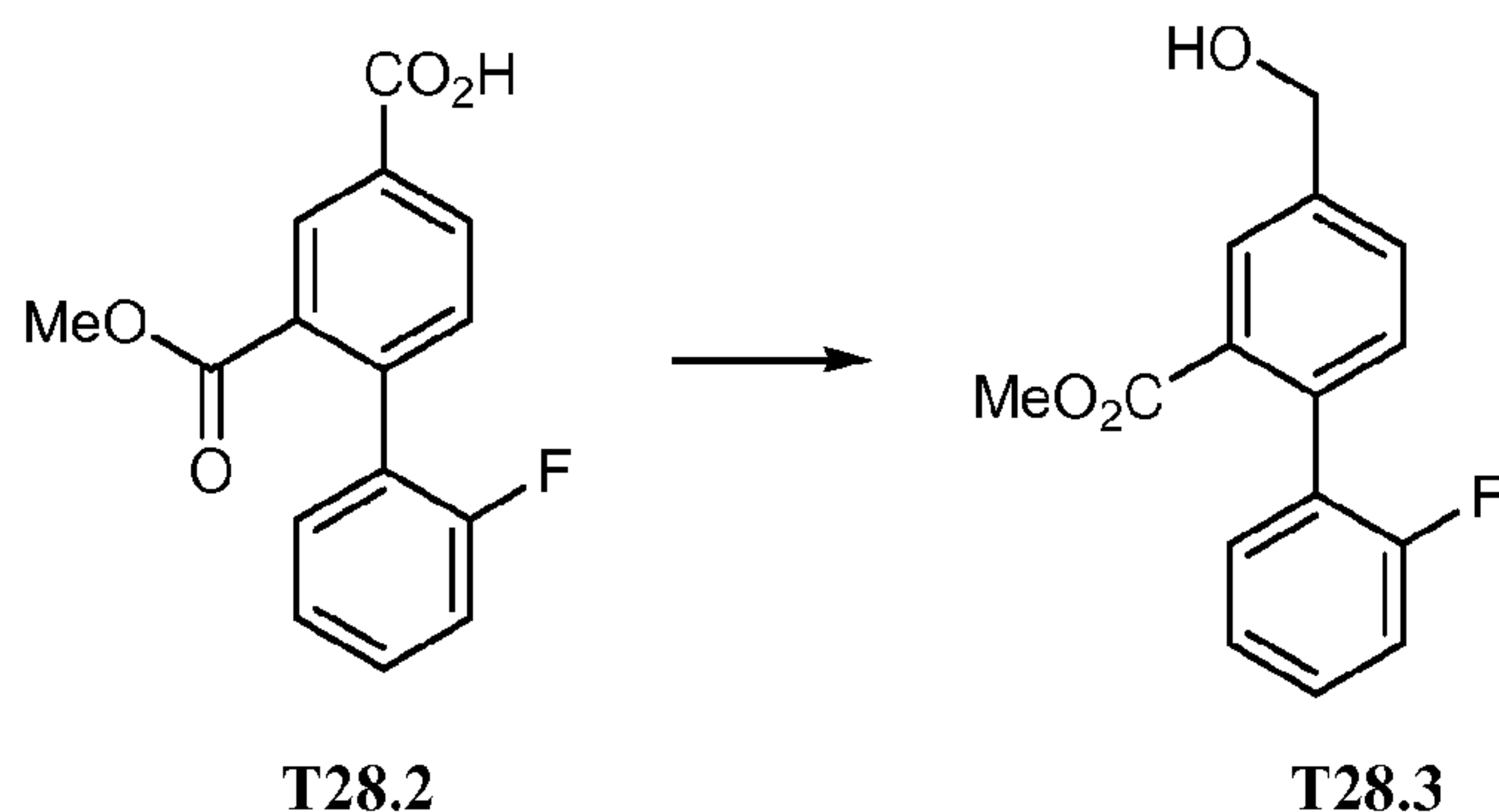
[0478] Intermediates T28A and T28B

[0479] Dimethyl 2'-fluoro-1,1'-biphenyl-2,4-dicarboxylate (T28.1). To a stirred solution of dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate **T4.1** (1.60 g, 4.7 mmol) in DMF (9.4 mL, 4.7 mmol) at 23°C was added 2-fluorophenylboronic acid (0.98 g, 7.0 mmol, commercially available from Sigma-Aldrich, St. Louis, MO, USA), potassium carbonate (1.9 g, 14 mmol), and then tetrakis(triphenylphosphine)palladium (0.54 g, 0.47 mmol). The reaction mixture was heated to 90°C and the reaction was stirred for 22 hours. The reaction was then cooled to room temperature, diluted with water, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T28.1** as a colorless oil (1.10 g, 82% yield).

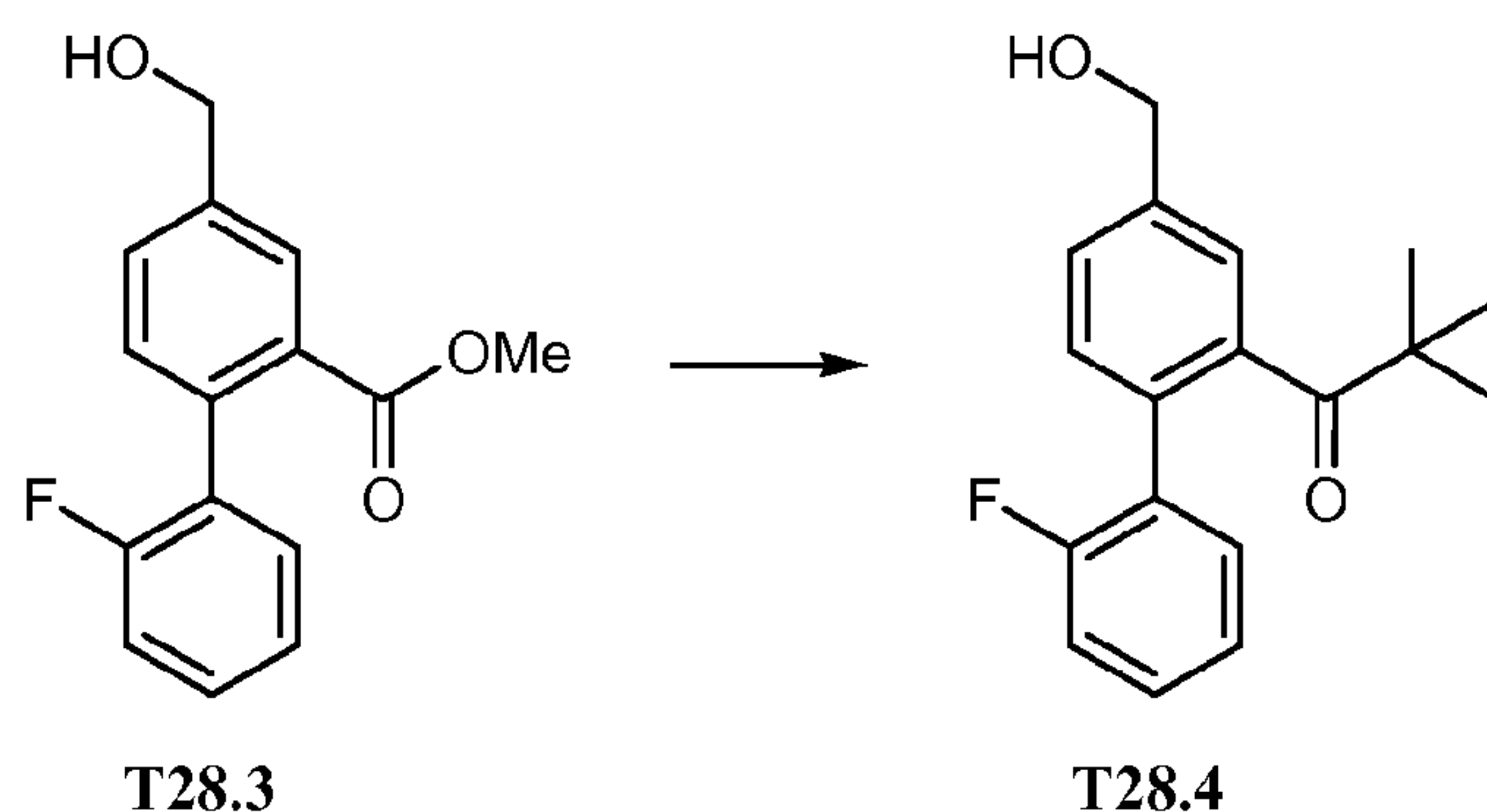


[0480] 2'-Fluoro-2-((methyloxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid (T28.2). To a stirred solution of **T28.1** (1.00 g, 3.5 mmol) in THF (70.0 mL) and MeOH (70.0 mL) at 0°C was slowly added potassium hydroxide (1.9 mL, 3.8 mmol) to maintain the temperature below 6°C. The reaction mixture was allowed to warm to room

temperature and stirred for 48 hours. The reaction mixture was then concentrated in vacuo, acidified with 1N HCl, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and to give a white solid **T28.2** (0.90 g, 95% yield).

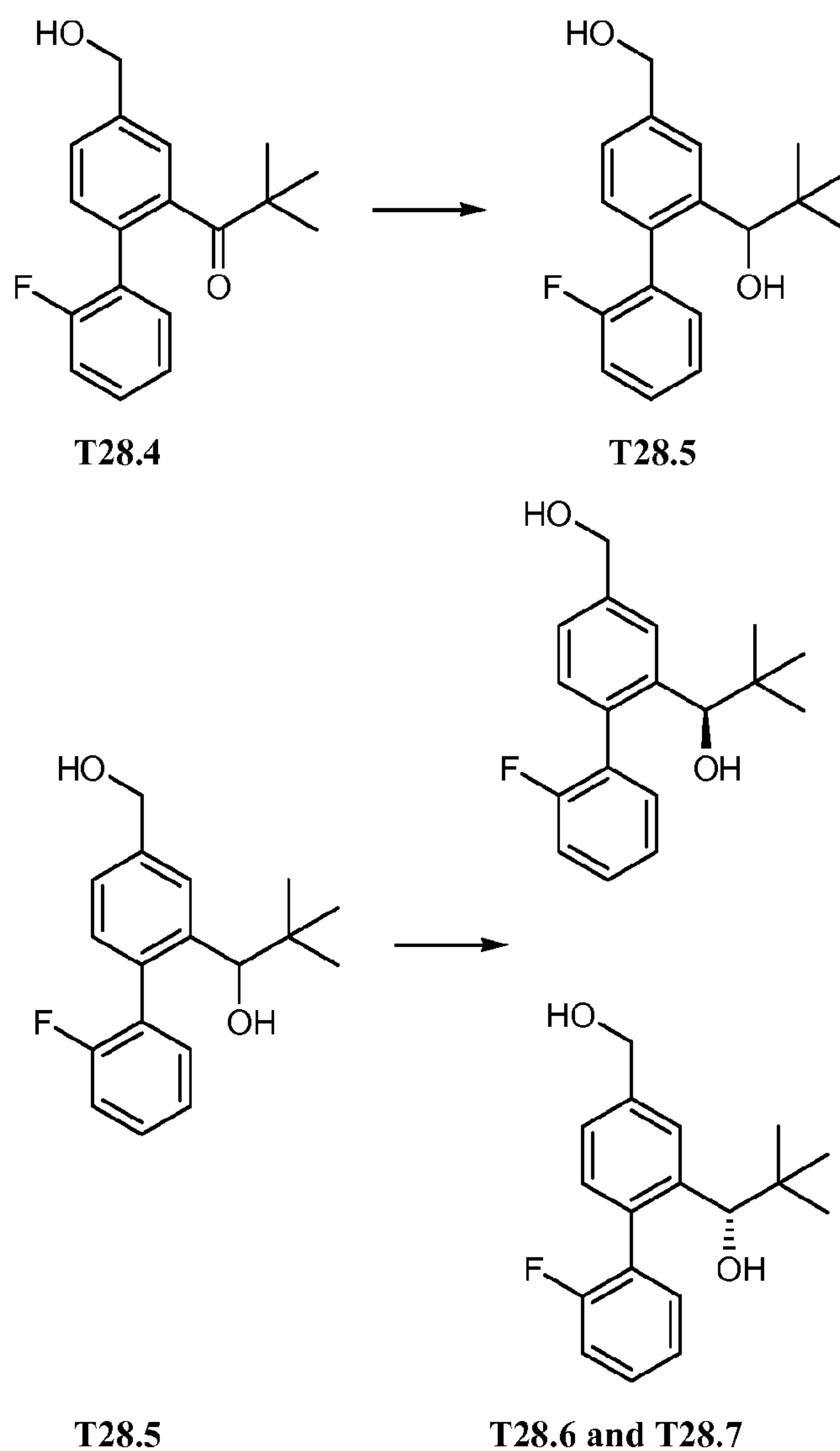


[0481] **Methyl 2'-fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-carboxylate (T28.3).** To a stirred solution of **T28.2** (0.90 g, 3 mmol) in THF (33 mL) at 0°C was added borane-THF complex (7 mL, 7 mmol, 1.0M). The reaction was allowed to warm to 23°C and stirred for 7 hours. The reaction mixture was then concentrated in vacuo. The reaction was diluted with 1N HCl and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **T28.3** as a colorless solid (0.850 g, 100% yield).



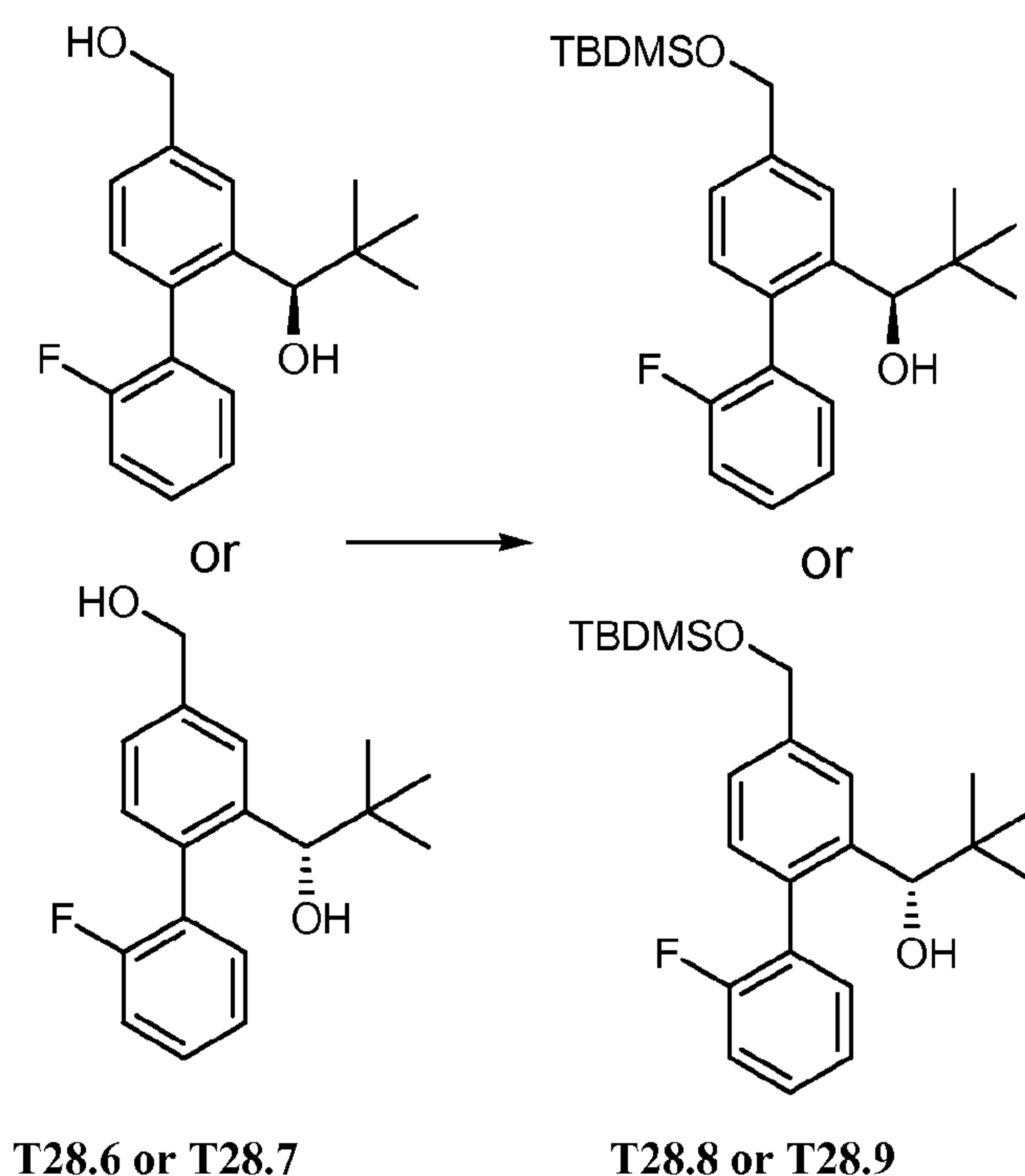
[0482] **1-(2'-Fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone (T28.4).** To a stirred solution of **T28.3** (0.850 g, 3 mmol) in THF (33 mL) at -78°C was added tert-butyllithium (6 mL, 10 mmol, 1.7M). The reaction was stirred for 5 hours and then a saturated solution of ammonium chloride was added and the mixture was

extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **T28.4** as a colorless oil (0.670 g, 72% yield).

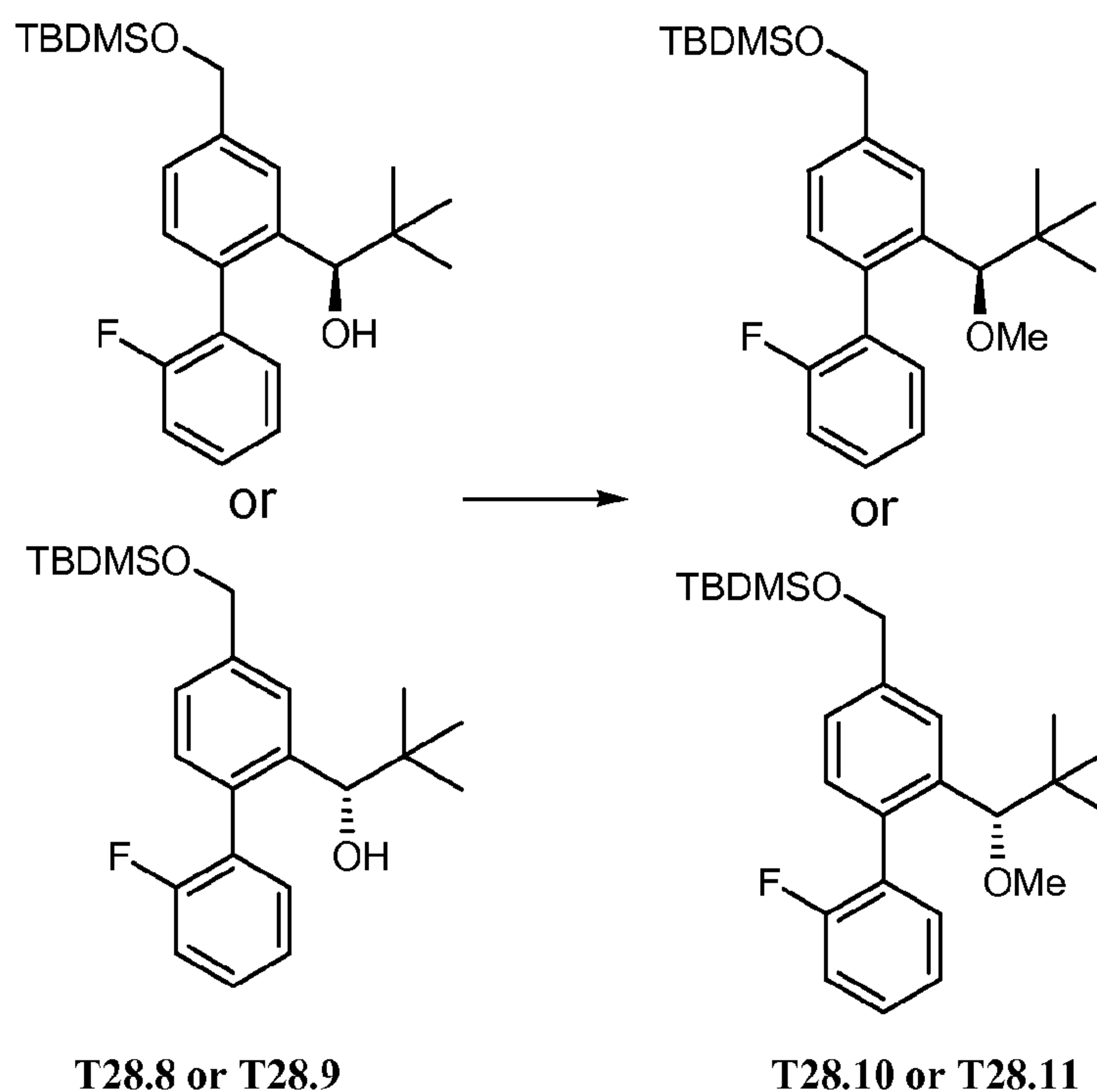


[0483] (1R)-1-(2'-Fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol and (1S)-1-(2'-fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (**T28.6** and **T28.7**). To a stirred solution of **T28.4** (0.670 g, 2 mmol) in THF (6 mL) at 0°C was added LAH in THF (5 mL, 5 mmol, 1.0M). The reaction was stirred for 1.5 hours and then 1N NaOH(aq) was added to quench the reaction mixture. The reaction was then extracted three times with EtOAc. After drying

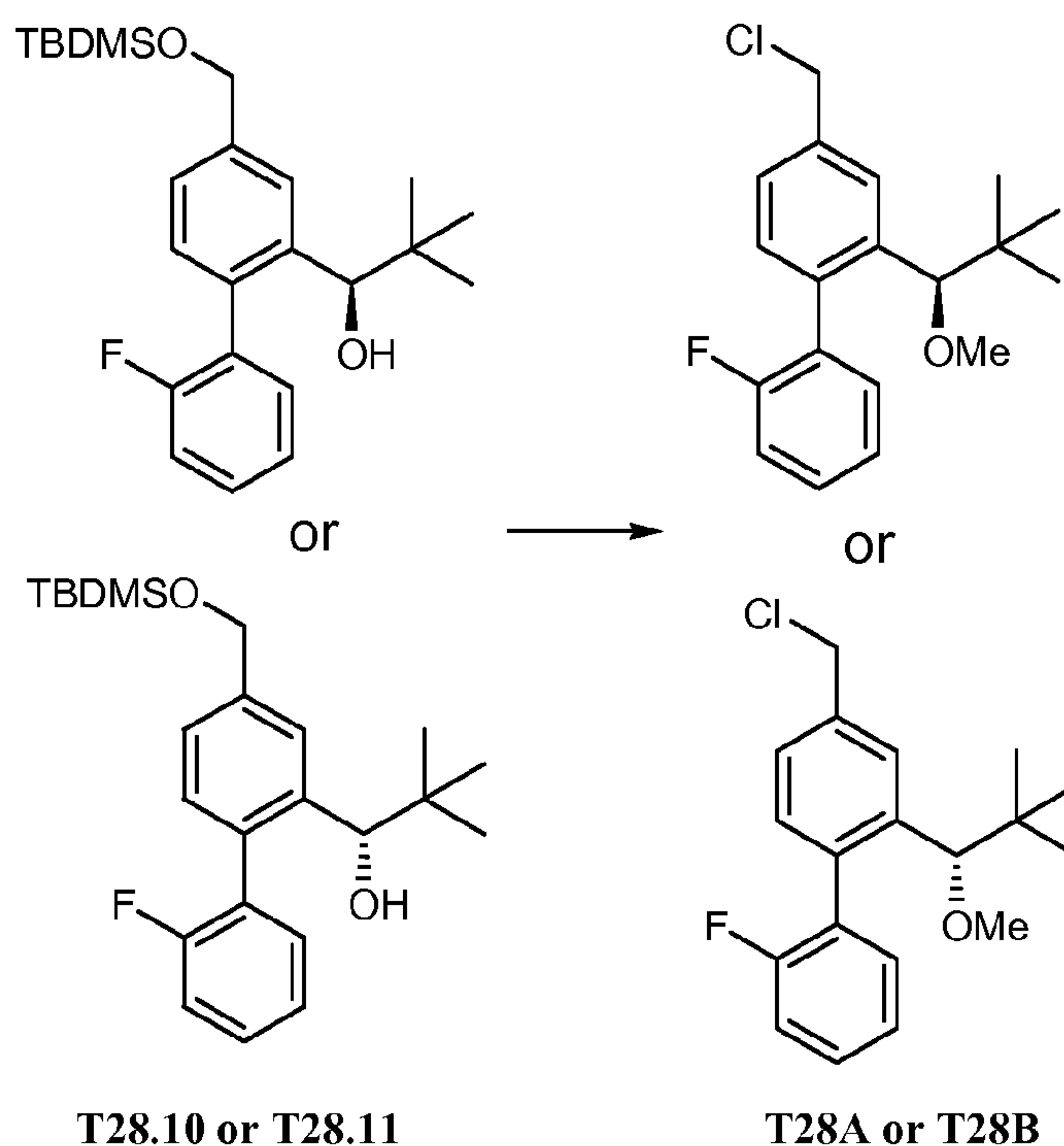
over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **T28.5** as a colorless oil (0.450 g, 67% yield). Chiral separation of **T28.5** was accomplished on a CHIRALCEL® OD column (3%IPA in hexane) to provide **T28.6** and **T28.7**.



[0484] (1R)-1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1S)-1-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (**T28.8 or T28.9**). To a stirred solution of **T28.6 or T28.7** (0.200 g, 0.7 mmol) in DCM (10.00 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.1 mL, 0.8 mmol), followed by TEA (0.1 mL, 0.8 mmol) and DMAP (0.008 g, 0.07 mmol). The reaction was stirred for 14 hours and then concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **T28.8 or T28.9** as a colorless oil (0.250 g, 90% yield).

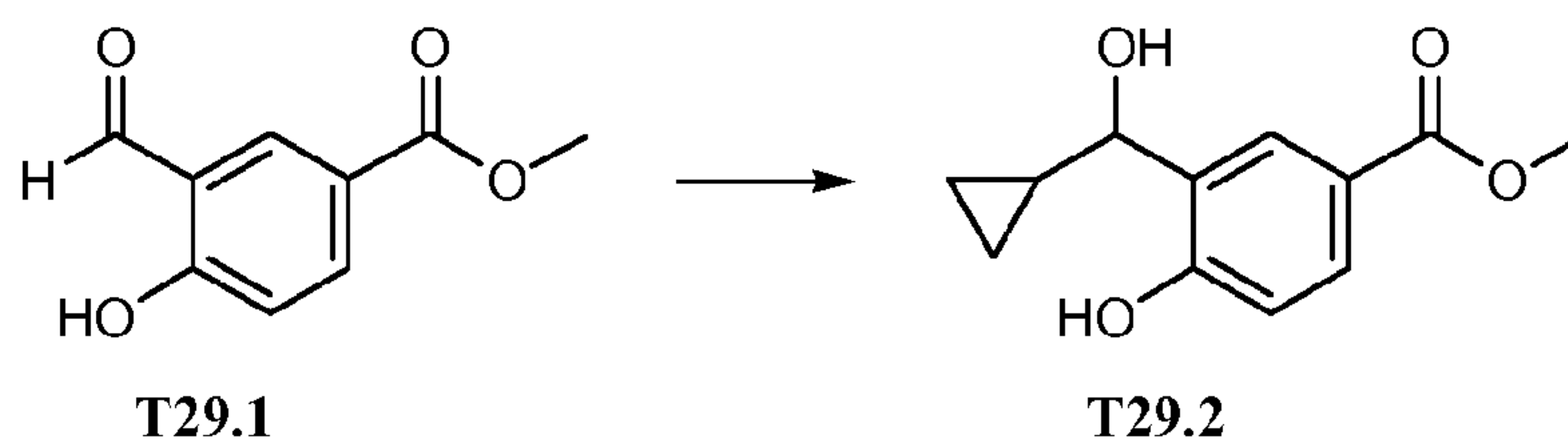


[0485] (1,1-Dimethylethyl)((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methoxy)dimethylsilane or (1,1-dimethylethyl)((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methoxy)dimethylsilane (**T28.10 or T28.11**). To a stirred solution of **T28.8** or **T28.9** (0.060 g, 0.15 mmol) in DMF (2.00 mL) at 23°C was added iodomethane (0.025 g, 0.18 mmol), followed by sodium hydride (0.0043 g, 0.18 mmol). The reaction was stirred at 60 °C for 19 hours, diluted with water, and the mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **T28.10** or **T28.11** as a colorless oil (0.062 g, 100% yield).



[0486] **4-(Chloromethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl (T28A or T28B).** To a stirred solution of **T28.10** or **T28.11** (0.071 g, 0.17 mmol) in DCM (1.7 mL) and DMF (0.013 mL) at 0°C was added thionyl chloride (0.025 mL, 0.34 mmol). The reaction was stirred at room temperature for 1.5 hours and then concentrated in vacuo. The product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **T28A** or **T28B** as a colorless oil (0.036 g, 66% yield).

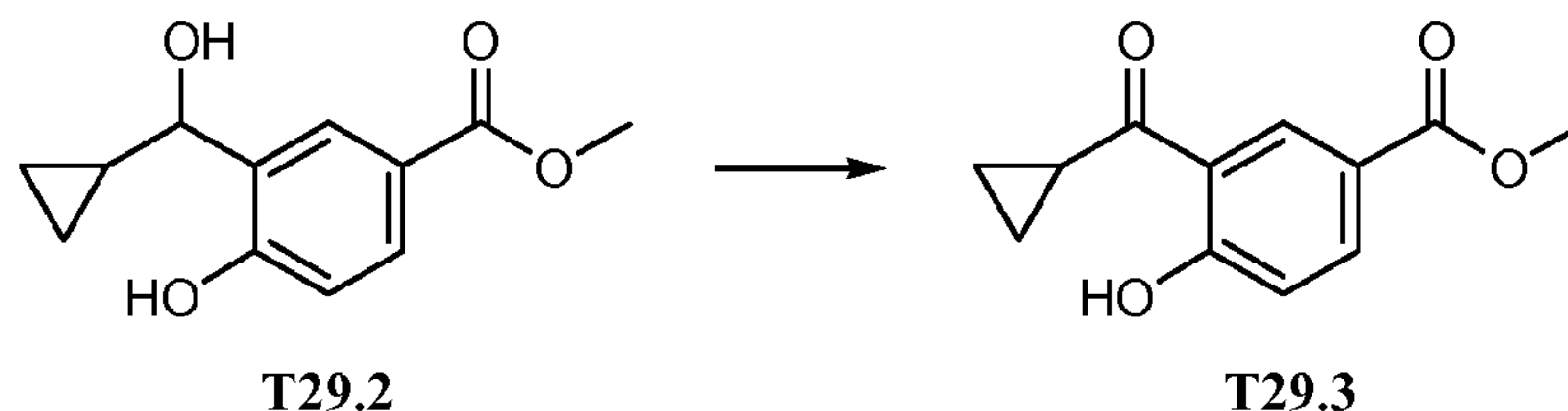
[0487] **Intermediate T29**



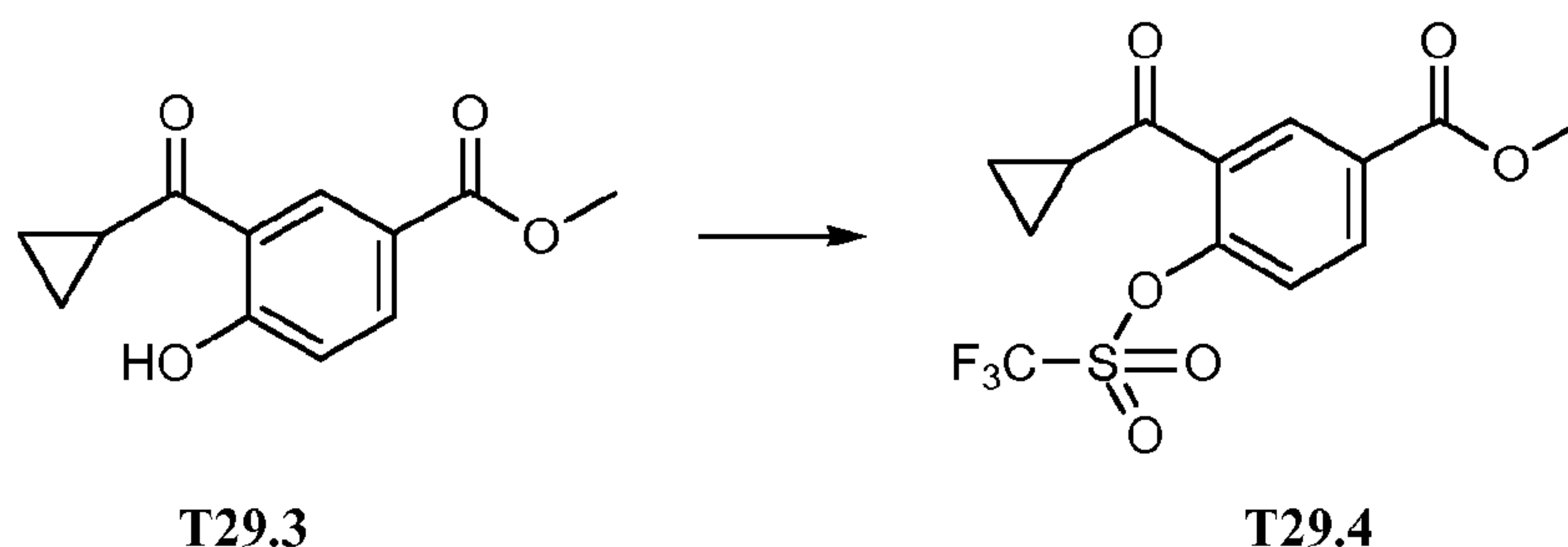
[0488] **Methyl 3-(cyclopropyl(hydroxy)methyl)-4-hydroxybenzoate (T29.2).**

In an ice-bath, methyl 3-formyl-4-hydroxybenzoate **T29.1** (900 mg, 5 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 5 mL THF. Then cyclopropylmagnesium bromide, 0.5 M in THF (22000 µL, 11 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added slowly.

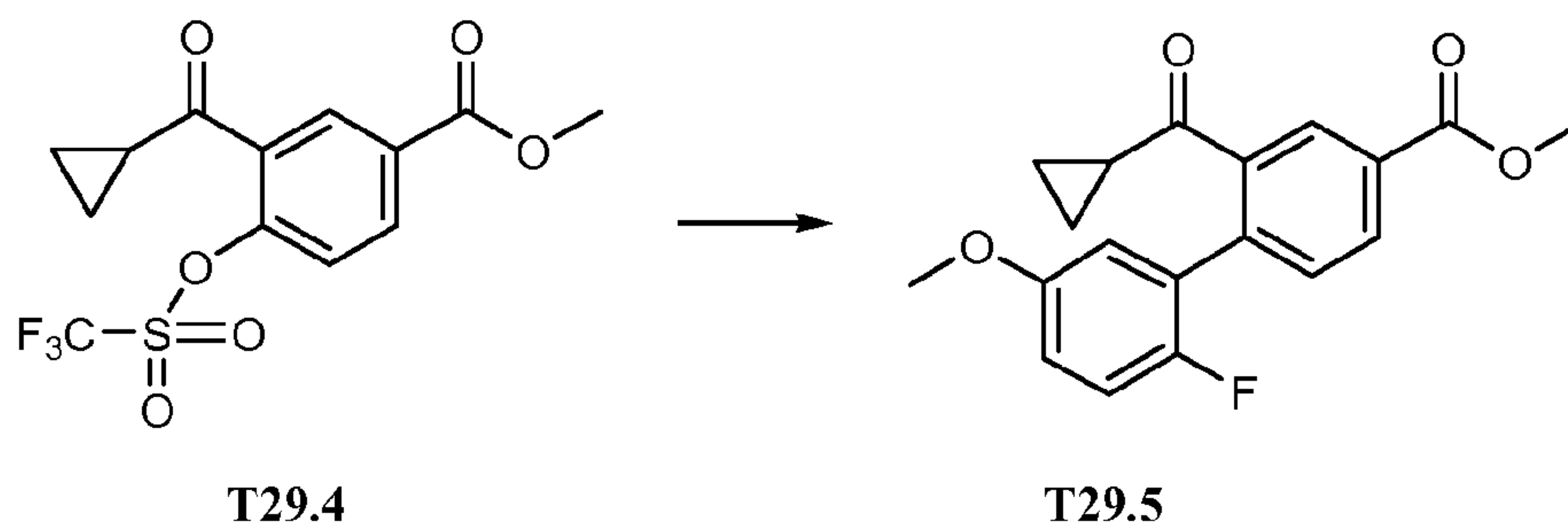
The reaction was raised to room temperature immediately and stirred at room temperature for 2 hours. After quenching with 1N HCl 11 mL, the reaction was extracted with EtOAc and dried. Silica gel chromatography afforded 950 mg of the product **T29.2** (85%).



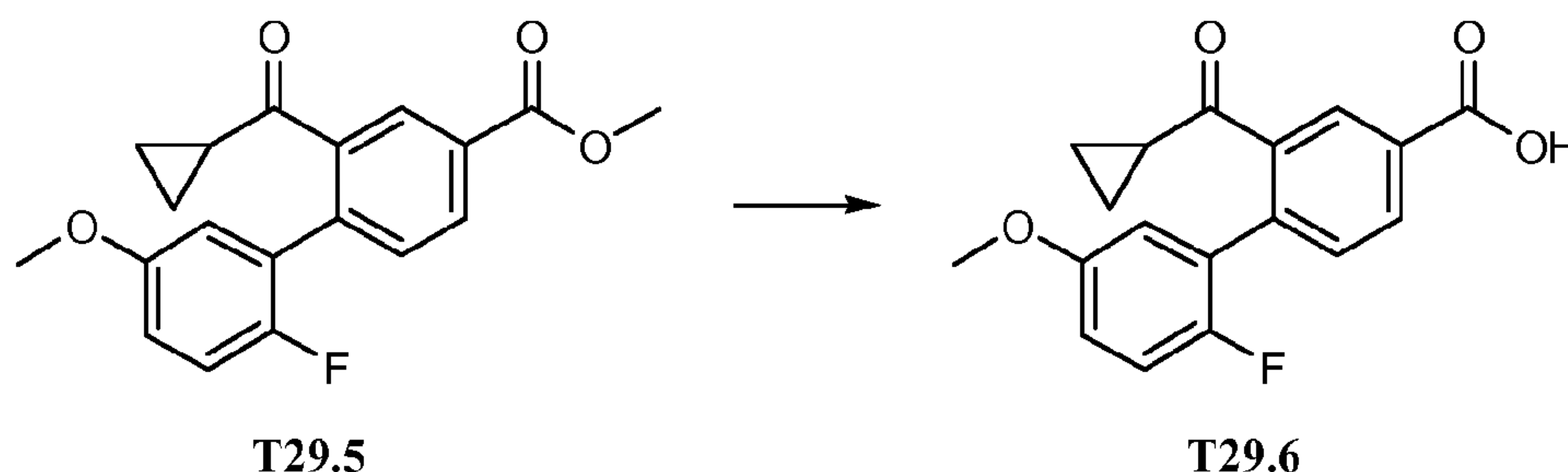
[0489] Methyl 3-(cyclopropanecarbonyl)-4-hydroxybenzoate (T29.3). To a flask with methyl 3-(cyclopropyl(hydroxy)methyl)-4-hydroxybenzoate (**T29.2**) (845 mg, 0.38 mmol) was added manganese (IV) oxide (1.65 g, 1.9 mmol). Then dioxane 3.5 mL was added and the reaction was heated at reflux for 4 hours. The reaction was filtered and concentrated and silica gel chromatography afforded 693 mg of **T29.3** (83%).



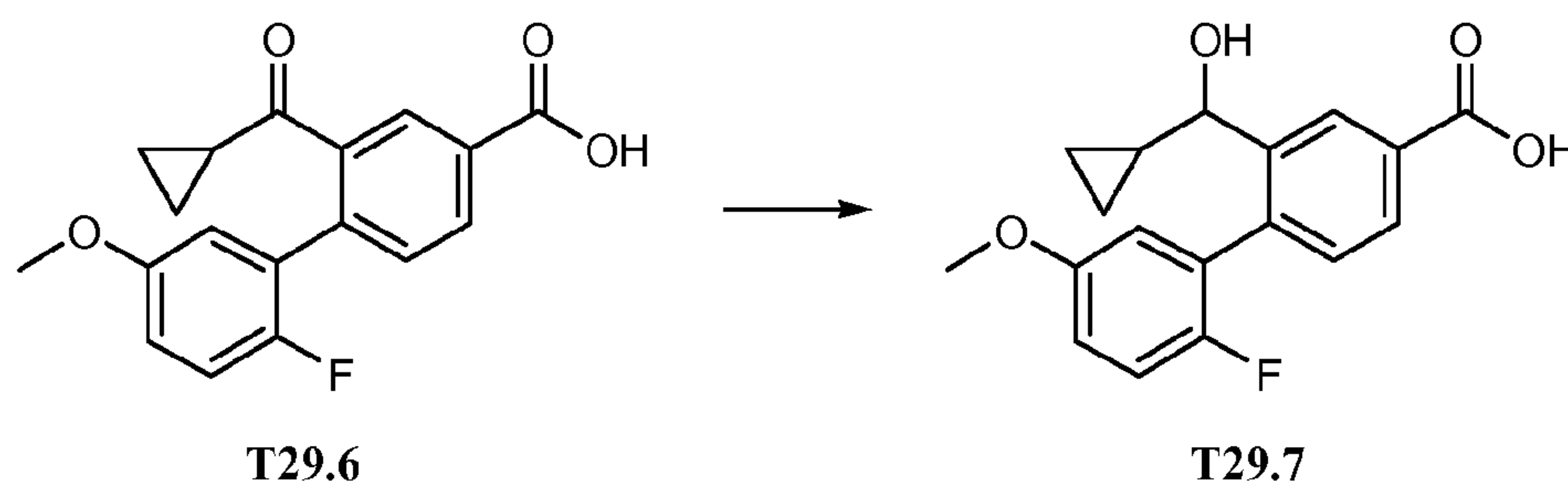
[0490] Methyl 3-(cyclopropanecarbonyl)-4-(trifluoromethylsulfonyloxy)benzoate (T29.4). To a flask with methyl 3-(cyclopropanecarbonyl)-4-hydroxybenzoate **T29.3** (693 mg, 3.1 mmol) was added DMAP (38mg, 0.31 mmol), and the mixture was flushed with nitrogen. DCM was then added followed by TEA (0.88 mL, 6.3 mmol). After stirring at room temperature for 20 minutes, PhN(Tf)₂ (1.2 g, 3.5 mmol) was added. The reaction gradually turned red and was stirred for another hour. The mixture was concentrated and purified by silica gel chromatography to afford 1.077g of **T29.4** as a colorless oil (97%).



[0491] **Methyl 3-(cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl))benzoate (T29.5).** Methyl 3-(cyclopropanecarbonyl)-4-(trifluoromethylsulfonyloxy)benzoate (**T29.4**) (1.077g, 3.1 mmol) was dried under vacuum. To a second flask was added 2-fluoro-5-methoxyphenylboronic acid (1.5 g, 8.9 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), Cs_2CO_3 (3.5 g, 11 mmol), and tetrakis(triphenylphosphine)Palladium (0) (0.35 g, 0.31 mmol). Both flasks were flushed with nitrogen followed by vacuum. Degassed DME was then added to the flask with **T29.4** (3 mL). Another 17 mL DME was added to the flask with the palladium catalyst followed by the DME solution of **T29.4**. The resulting slurry was stirred overnight in a 95°C oil-bath. The reaction was filtered, concentrated, and purified by silica gel chromatography to afford 0.94g of the desired product **T29.5** (94%).

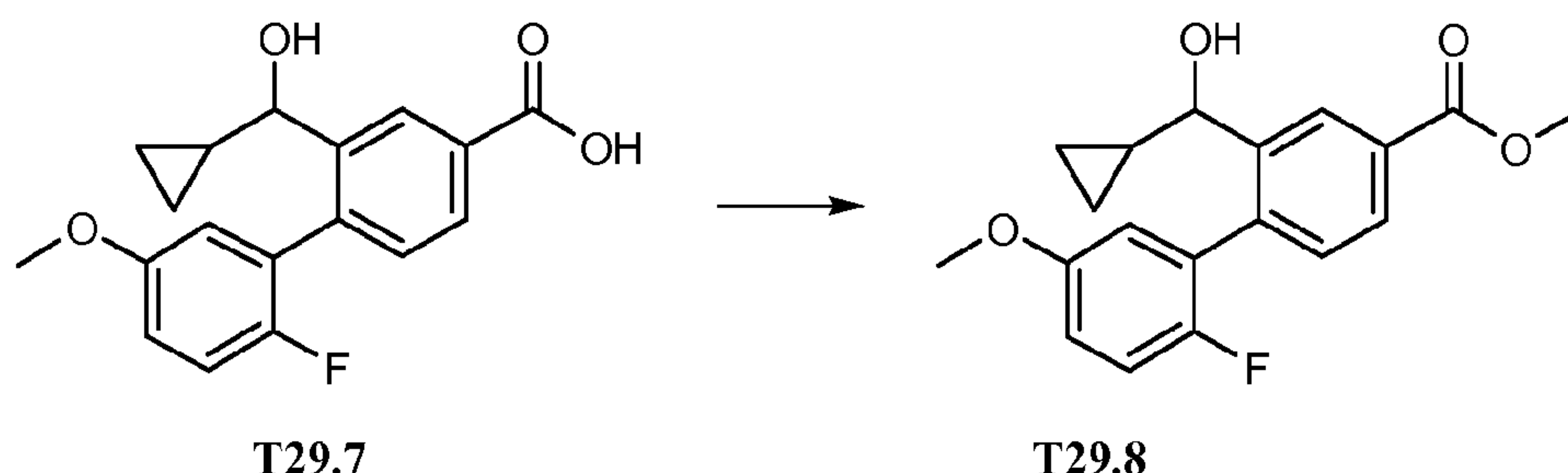


[0492] **3-(Cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (T29.6).** To a flask with methyl 3-(cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**T29.5**) (523 mg, 1593 μmol) was added 9.6 mL of MeOH and 1N NaOH (3186 μL , 3186 μmol). The reaction was heated to 55 C for 2 hours. The mixture was then acidified with 1N HCl, concentrated, and extracted with EtOAc. Removal of the solvent afforded 500 mg of **T29.6** (100%).

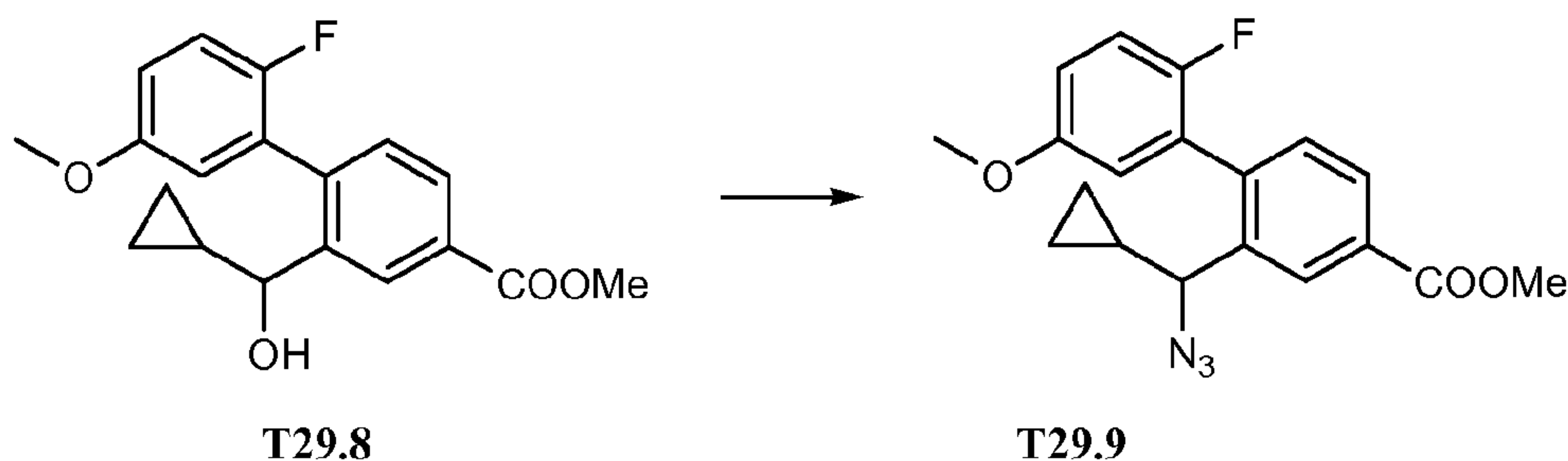


[0493] **3-(Cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (T29.7).** To a flask with 3-(cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (**T29.6**) (500 mg, 1591 μmol) was added anhydrous EtOH 10 mL, followed by addition of sodium borohydride (361 mg, 0.95

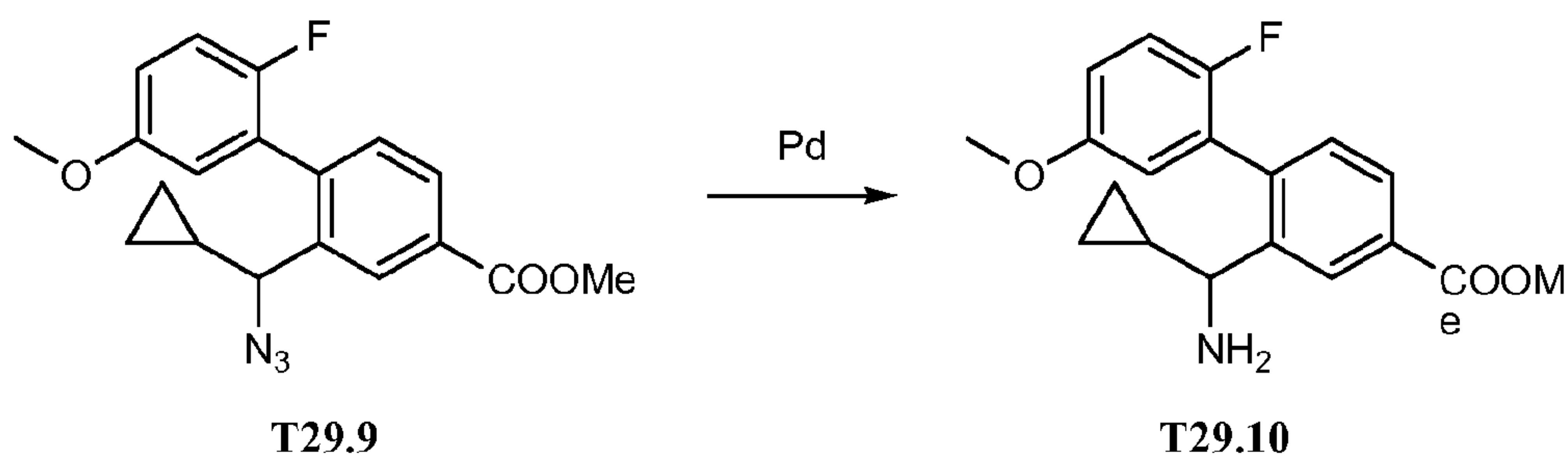
mmol). The reaction mixture was stirred overnight, quenched with water, and extracted with EtOAc. Removal of solvent gave 503 mg of **T29.7** in racemic form.



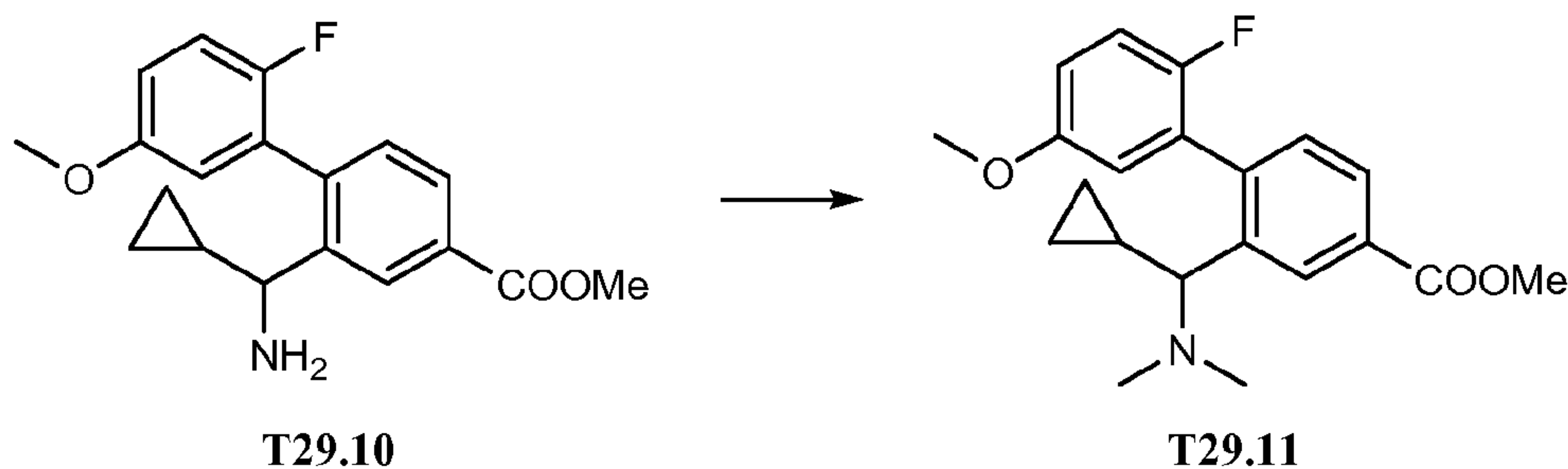
[0494] Methyl 3-(cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (T29.8). To a flask with 3-(cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (**T29.7**), (503 mg, 1.6 mmol) was added 10 mL DCM and 2 mL MeOH. TMSdiazomethane (795 μ L, 1590 μ mol) in ether was then added, and the reaction was stirred at room temperature for 1 hour, and then quenched with a acetic acid. Water was added, and the reaction was extracted with EtOAc. Purification by silica gel chromatography afforded 484 mg of **T29.8** (92%) in racemic form.



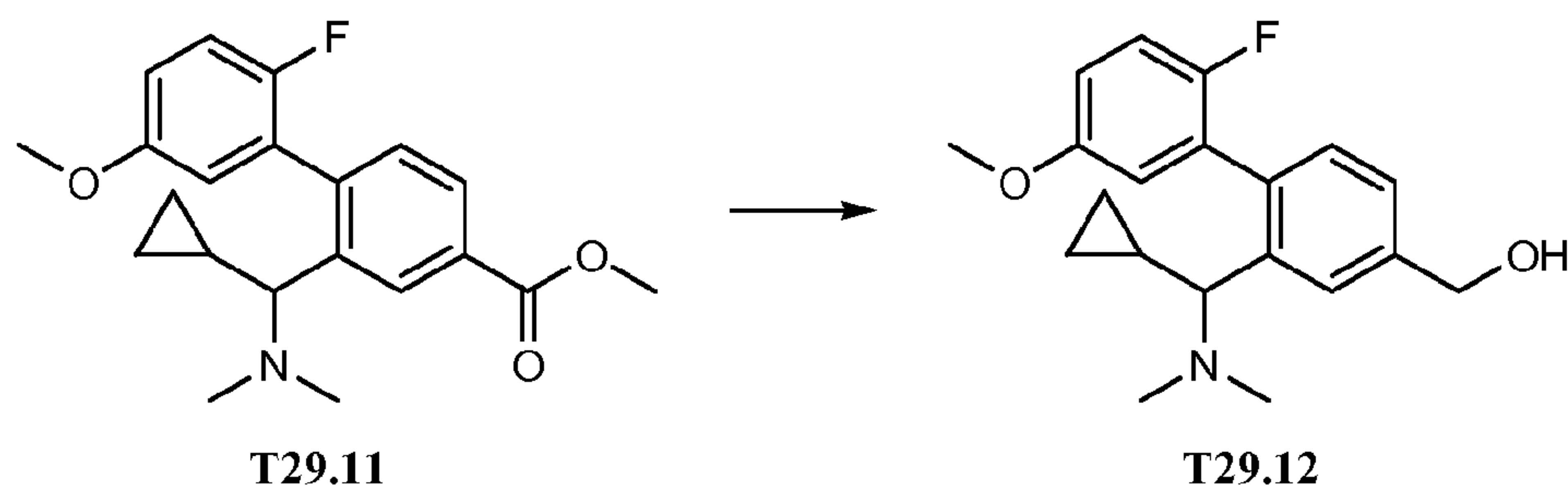
[0495] Methyl 3-(azido(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (T29.9). To methyl 3-(cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**T29.8**) (235 mg, 711 μ mol) was added DMF 4 mL, then 1,8-diazabicyclo[5.4.0]undec-7-ene (160 μ L, 1067 μ mol), and diphenylphosphoryl azide (231 μ L, 1067 μ mol). The mixture was heated to 80°C. After 3 hours, 1.5 equivalents more of each of the 1,8-diazabicyclo[5.4.0]undec-7-ene and diphenylphosphoryl azide were added. The reaction was heated for two more hours and water was then added followed by EtOAc extraction. Purification by silica gel chromatography afforded 260 mg of **T29.9** mixed with a non-polar side product. The product thus obtained was carried to the next step without further purification.



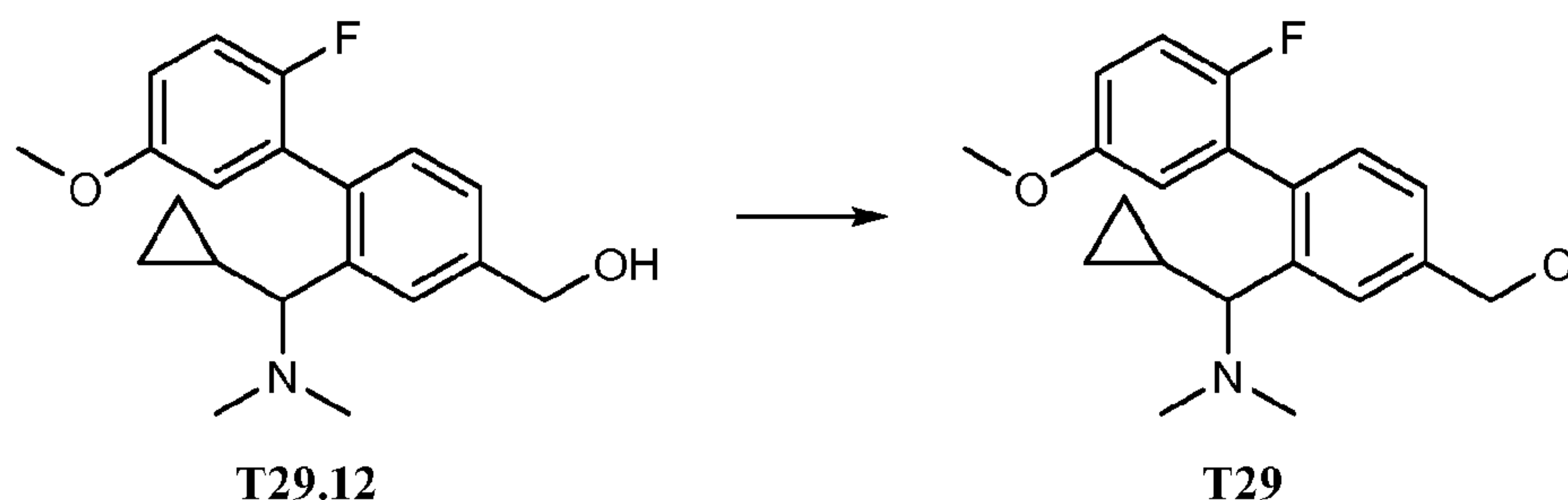
[0496] **Methyl 3-(amino(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (T29.10).** To a flask with methyl 3-(azido(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**T29.9**) (260 mg, 732 μmol) was added 10% Pd/C (78 mg, 732 μmol), and then 6 mL of MeOH was added. The reaction was purged with hydrogen and stirred under a hydrogen balloon for about 6 hours. The reaction was filtered through a pad of Celite® filter aid, concentrated, and purified by silica gel chromatography to afford 76 mg of the desired product **T29.10** (32% for 2 steps).



[0497] **Methyl 3-(cyclopropyl(dimethylamino)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (T29.11).** To a flask with methyl 3-(amino(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**T29.10**) (76 mg, 231 μmol) were added 2 mL DCM, formaldehyde (70 μL , 923 μmol), and acetic acid (26 μL , 461 μmol). Sodium triacetoxyborohydride (245 mg, 1154 μmol) was then added to the reaction mixture. The reaction was stirred for 1.5 hours and worked up with water and EtOAc. Silica gel chromatography afforded 35 mg of **T29.11** (43%).

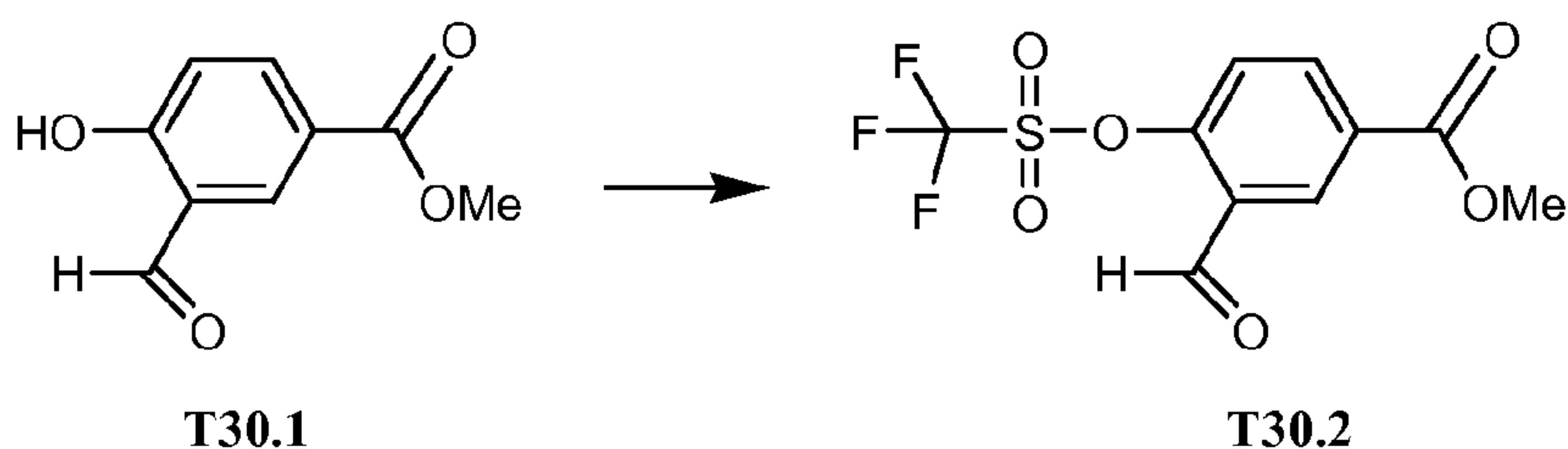


[0498] **(3-(Cyclopropyl(dimethylamino)methyl))-4-(2-fluoro-5-methoxyphenyl)phenyl)methanol (T29.12).** To a flask with methyl 3-(amino(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**T29.11**) (35 mg, 98 μ mol) was added THF (1.5 mL). The mixture was cooled to 0°C and then 1M LAH (196 μ L, 196 μ mol, 1M solution in THF) was added. The temperature was slowly raised to room temperature over 1 hour. Water and a small amount of Rochelle's salt solution were added to quench the reaction and it was then extracted with EtOAc. Silica gel chromatography afforded 26 mg of **T29.12** (81%).



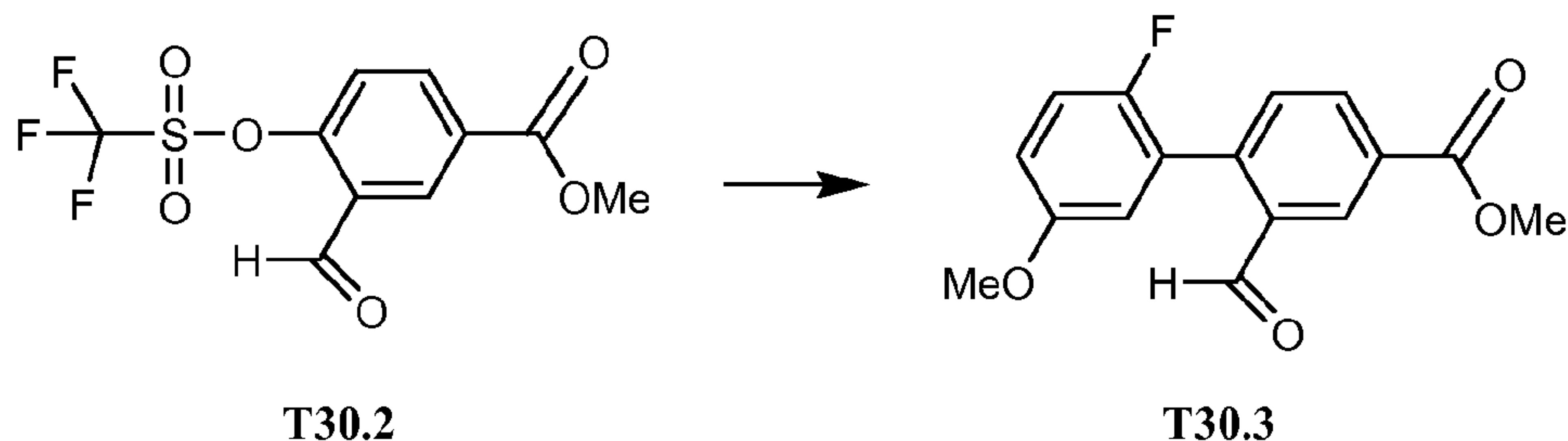
[0499] **(5-(Chloromethyl)-2-(2-fluoro-5-methoxyphenyl)phenyl)(cyclopropyl)-N,N-dimethylmethanamine (T29).** To a flask with (3-(cyclopropyl(dimethylamino)methyl))-4-(2-fluoro-5-methoxyphenyl)phenyl)methanol (**T29.12**) (26 mg, 79 μ mol) was added DCM. The mixture was cooled in an ice-bath and then thionyl chloride (12 μ L, 158 μ mol) and DMF (6 μ L, 79 μ mol) were added. The reaction was stirred at room temperature for 1 hour, and then it was concentrated and purified by silica gel chromatography to afford 28 mg of **T29** (102%).

[0500] **Intermediate T30**

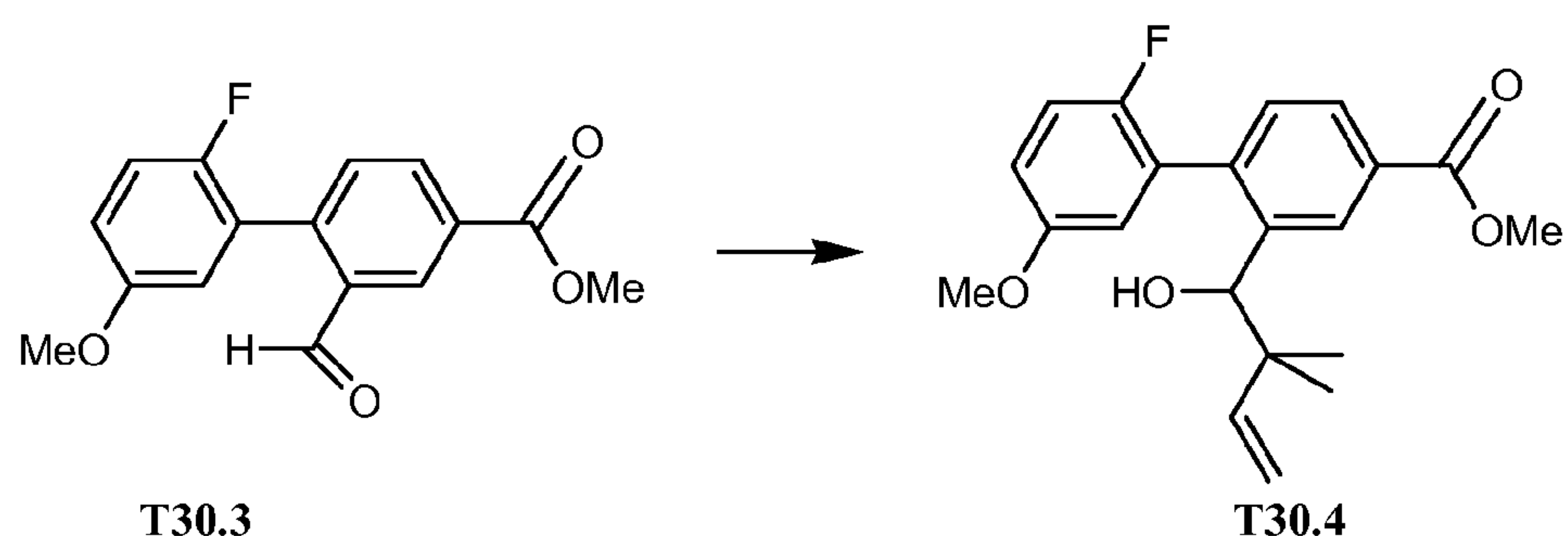


[0501] **Methyl 3-formyl-4-(trifluoromethylsulfonyloxy)benzoate (T30.2).** Compound **T30.2** was synthesized from methyl 3-formyl-4-hydroxybenzoate **T30.1** (commercially available from Sigma-Aldrich, St. Louis, MO, USA) using a method

analogous to the method used to prepare compound **T3.5** from **T3.4**. MS ESI m/e : 313.2 (M+H)⁺.

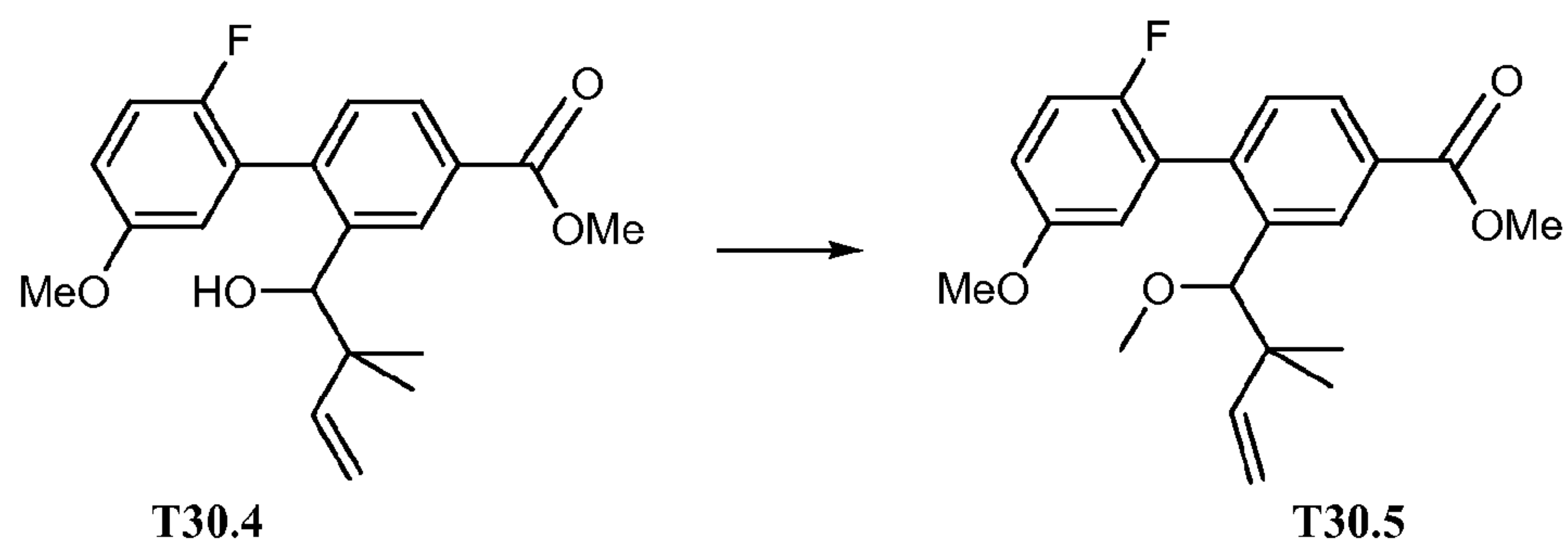


[0502] 2'-Fluoro-2-formyl-5'-methoxy-biphenyl-4-carboxylic acid methyl ester (T30.3). To a round bottle flask, was added methyl 3-formyl-4-(trifluoromethylsulfonyloxy)benzoate (6300 mg, 20 mmol), 2-fluoro-5-methoxyphenylboronic acid (10 g, 61 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), potassium phosphate tribasic (6.6 mL, 81 mmol) (granular) and tetrakis(triphenylphosphine)palladium (2.3 g, 2.0 mmol). The flask was flushed with nitrogen, DME was added, and the mixture was heated at 90°C for 6 hours. The reaction mixture was diluted with EtOAc and water. The organic phase was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to give a residue which was purified by chromatography to give the product as a yellow solid (5.80g, 100%). MS ESI m/e : 289.2 (M+H)⁺.

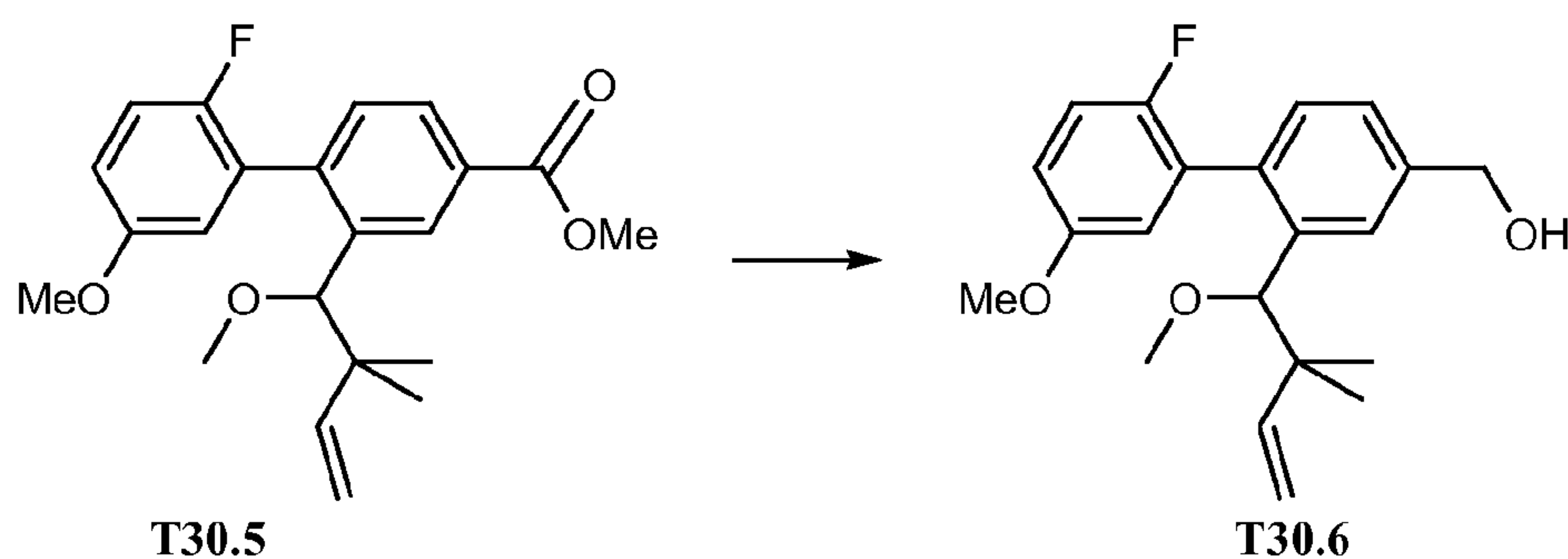


[0503] 2'-Fluoro-2-(1-hydroxy-2,2-dimethyl-but-3-enyl)-5'-methoxy-biphenyl-4-carboxylic acid methyl ester (T30.4). To a mixed solution of sodium iodide (2080 mg, 13876 μ mol), indium (2000mg, 6938 μ mol) and 1-bromo-3-methylbut-2-ene (1616 μ L, 13876 μ mol) in DMF(30 mL), was added **T30.3** (1593 mg, 13876 μ mol). The mixture was stirred at room temperature for 1 hour, and then was diluted with EtOAc and water. The organic phase was washed with water and brine and then dried over

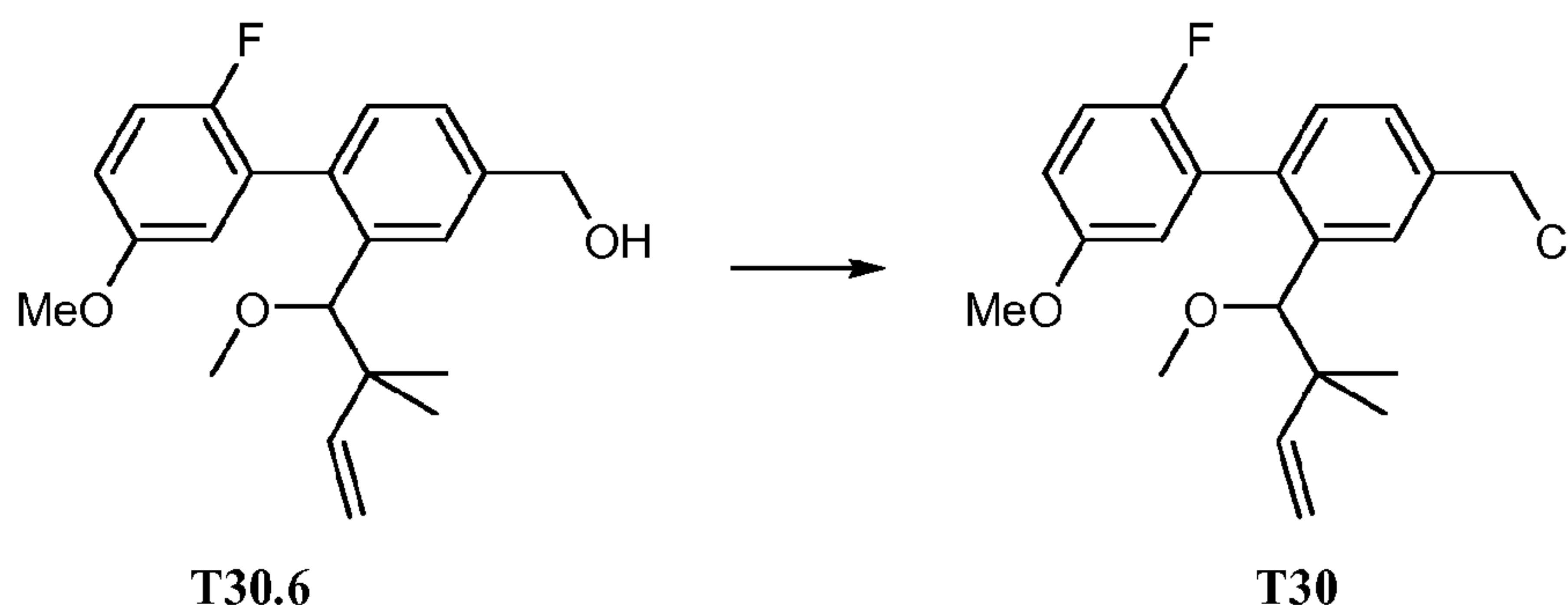
anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to give a residue which was purified by chromatography to give the product as an oil (2.30g, 92%). MS ESI m/e : 376.1 (M+18)⁺.



[0504] **2'-Fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethyl-but-3-enyl)-biphenyl-4-carboxylic acid methyl ester (T30.5).** To a solution of **T30.4** (1530 mg, 4269 μmol) in DMF (40 mL), was added sodium hydride (60% in oil)(213 μL , 8538 μmol). The mixture was stirred at room temperature for 10 minutes and then methyl iodide (530 μL , 8538 μmol) was added in one portion and the mixture was stirred at room temperature for 30 minutes. Water was added and the mixture was, extracted with EtOAc. The organic phase was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to give the product as a residue which was purified by chromatography to give the product as an oil (0.75g, 47%). MS ESI m/e : 373.2 (M+18)⁺.

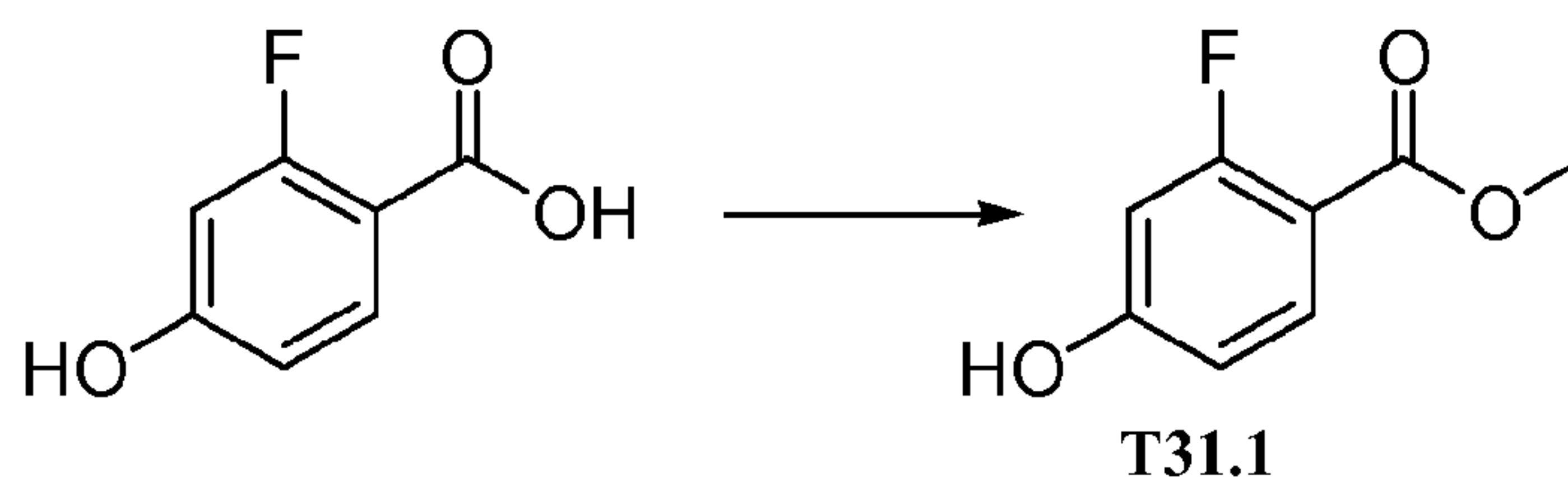


[0505] **[2'-Fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethyl-but-3-enyl)-biphenyl-4-yl]-methanol (T30.6).** Compound **T30.6** was synthesized from **T30.5** by a method analogous to that used to prepare compound **T15.4** from **T15.3**. MS ESI m/e : 345.2 (M+H)⁺.

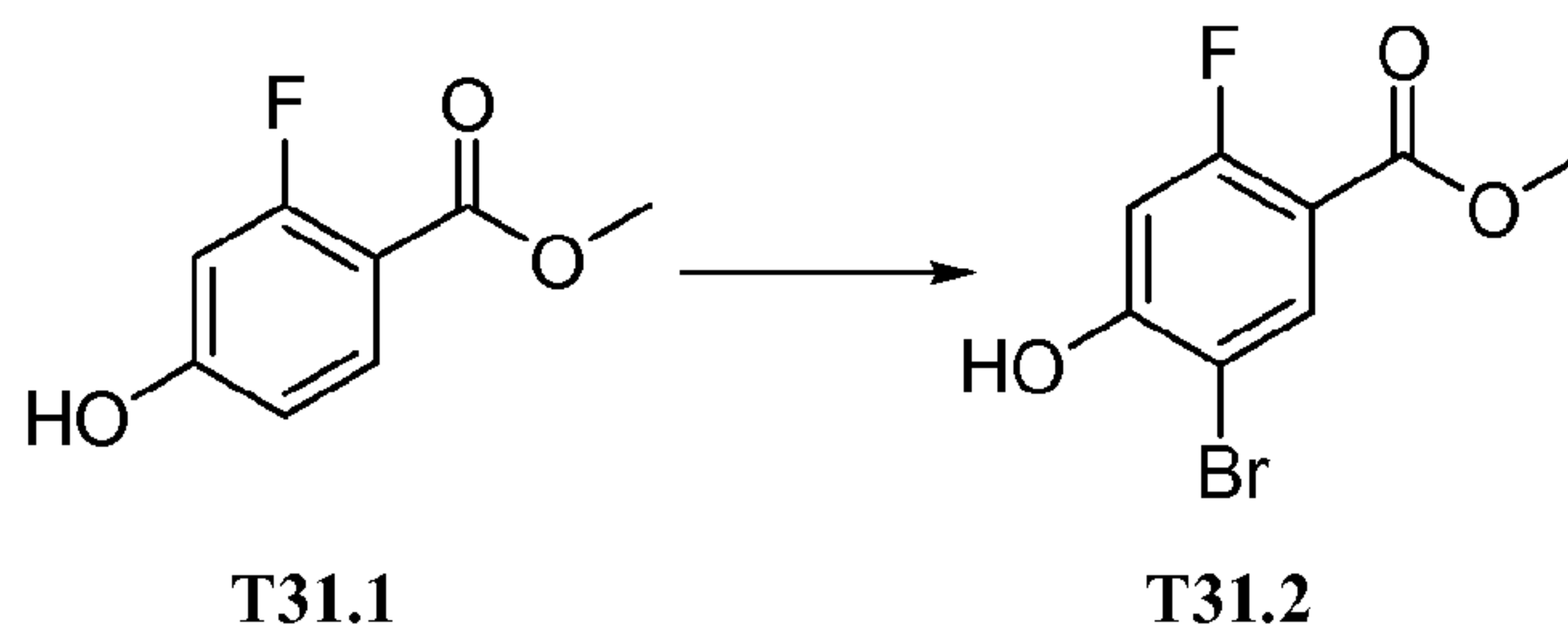


[0506] **4-Chloromethyl-2'-fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethylbut-3-enyl)-biphenyl (T30).** Compound T30 was synthesized from T30.6 by a method analogous to the method used to prepare compound T15 from T15.4. MS ESI m/e : 363.2 (M+H)⁺.

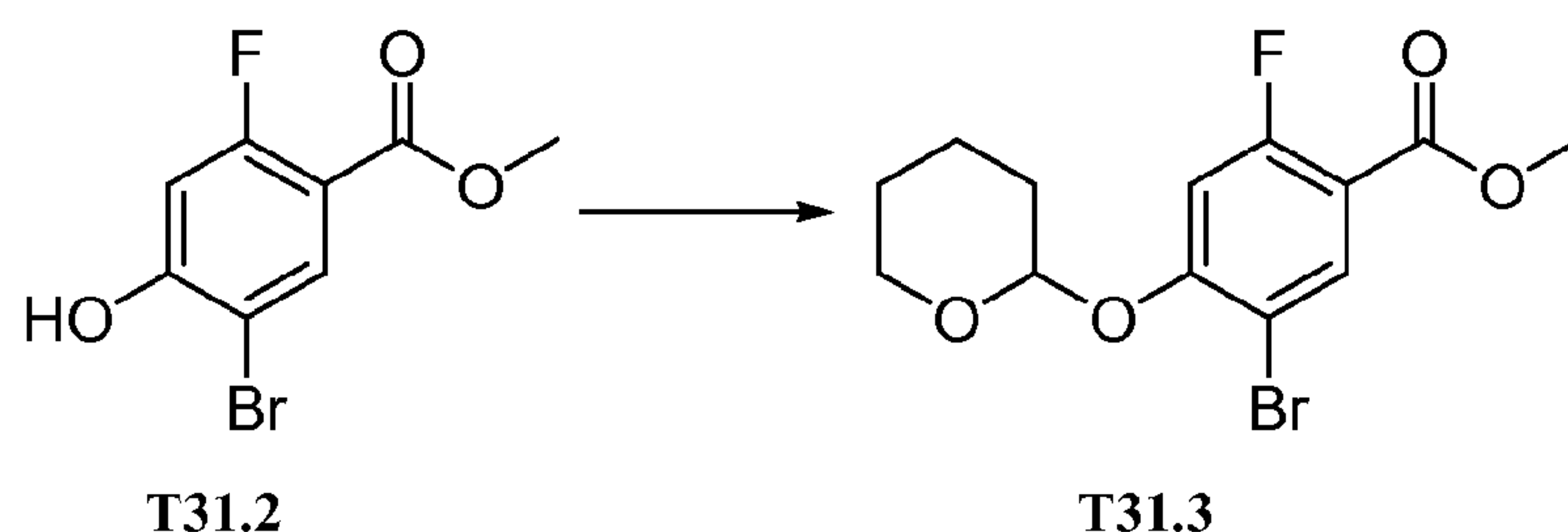
[0507] Intermediate T31



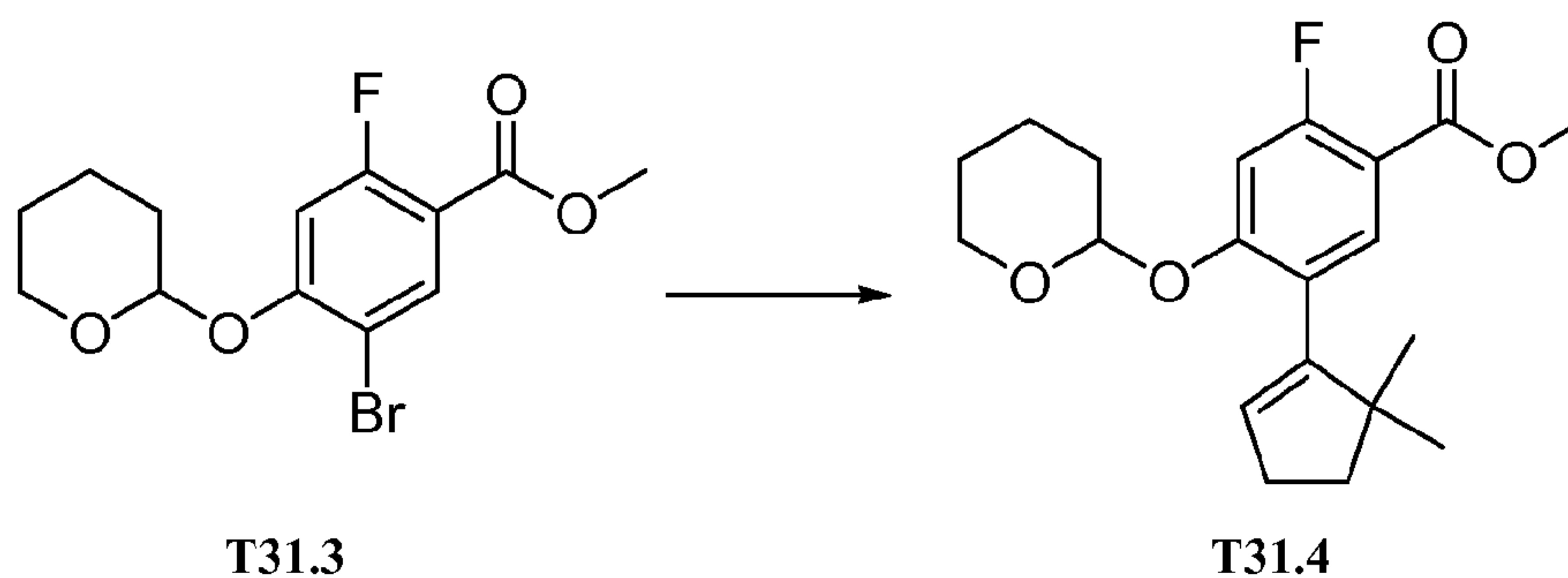
[0508] **Methyl 2-fluoro-4-hydroxybenzoate (T31.1).** To a round bottom containing 2-fluoro-4-hydroxybenzoic acid (5.34 g, 34.19 mmol) (commercially available from Matrix Scientific and TCI America) was added a cold solution of MeOH (50 mL) and sulfuric acid (2.0 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed, and the mixture was diluted with diethyl ether. The organic phase was washed carefully two times with saturated. aqueous NaHCO₃, once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to yield T31.1 as a white solid (5.82, 85% yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.79 (1 H, s), 7.75 (1 H, t, J=8.8 Hz), 6.69 (1 H, dd, J=8.6, 2.3 Hz), 6.62 (1 H, dd, J=13.1, 2.2 Hz), 3.78 (3 H, s).



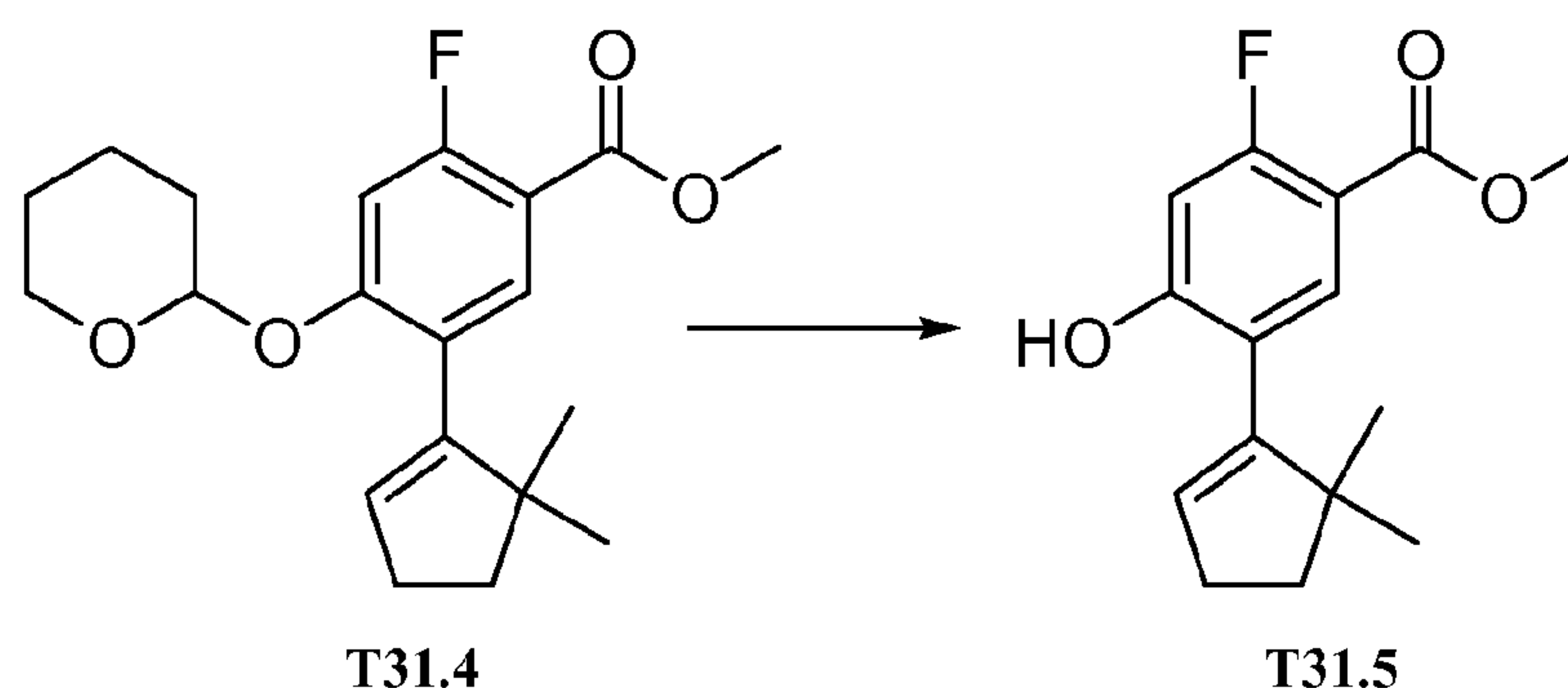
[0509] **Methyl 5-bromo-2-fluoro-4-hydroxybenzoate (T31.2).** To a solution of **T31.1** (2.03 g, 11.9 mmol) in acetic acid (65 mL) was added a pre-mixed solution of bromine (0.67 mL, 13.1 mmol) in acetic acid (10 mL). The mixture was stirred at 45°C and monitored with TLC and LC-MS. After 18 hours, the reaction mixture was concentrated under reduced pressure. Brine was added to the residue, and the mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to provide **T31.2** as a white solid (2.12 g, 71 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.13 (1 H, d, J=7.4 Hz), 6.82 (1 H, d, J=11.3 Hz), 6.04 (1 H, s), 3.92 (3 H, s).



[0510] **Methyl 5-bromo-2-fluoro-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (T31.3).** To a round bottom containing **T31.2** (13.15 g, 52.8 mmol) in dry DCM (90 mL) was added 3,4-dihydro-2H-pyran (10 mL, 110 mmol) followed by PPTS (0.13 g, 0.53 mmol). The reaction mixture was heated to a gentle reflux (50 °C) and monitored with TLC and LC-MS. After 24 hours, the reaction was concentrated under reduced pressure and then diluted with MeOH. After concentration, the residue was heated in a round bottom flask containing MeOH on the rotary evaporator (without vacuum.) at 40°C. After about 30 minutes, the solution was concentrated to a volume of about 5 mL. After cooling to room temperature, the white solid was filtered and rinsed once with MeOH to yield **T31.3** (13.35 g, 76 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.25 (1 H, m), 6.96 (1 H, d, J=12.5 Hz), 5.56 (1 H, m), 3.91 (3 H, s), 3.79 (1 H, td, J=11.1, 2.5 Hz), 3.65 (1 H, d, J=10.6 Hz), 2.23 (2 H, m), 1.96 (3 H, m), 1.68 (1 H, m).

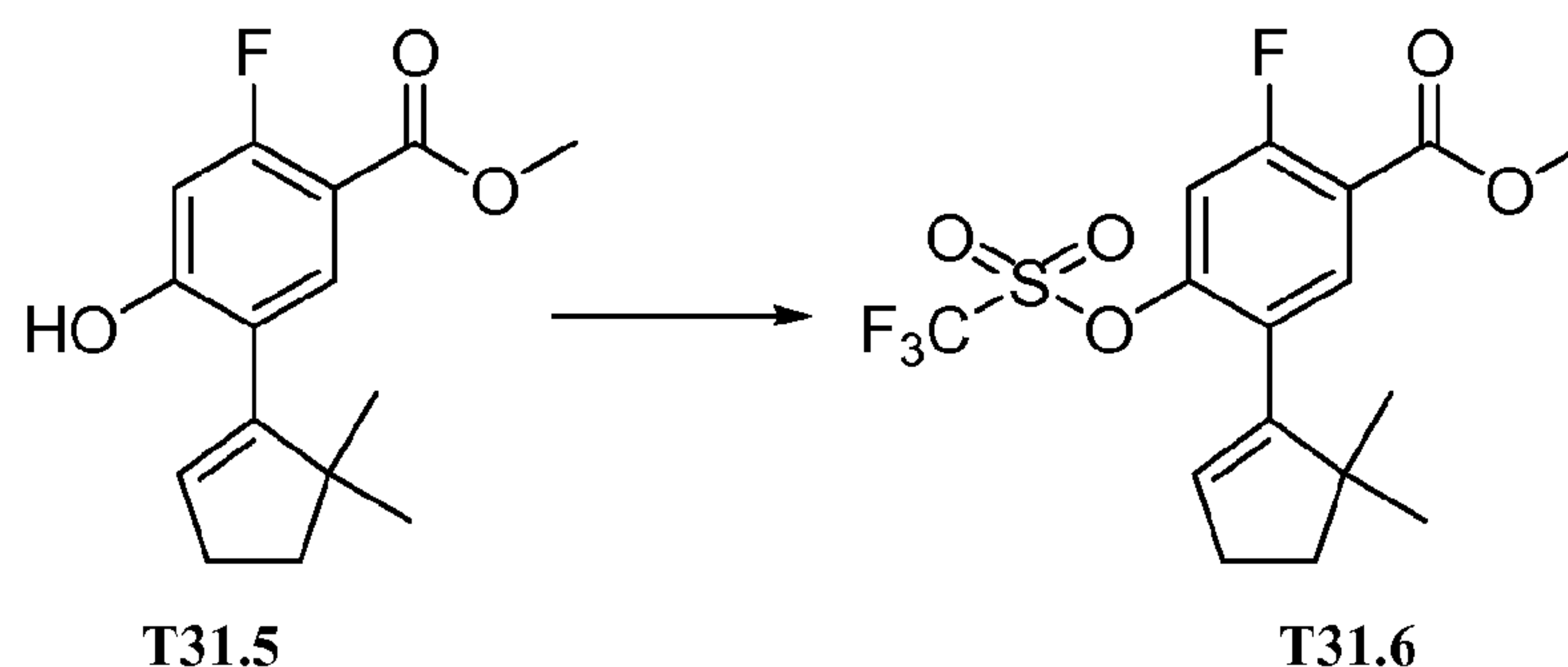


[0511] Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (T31.4). A stirred mixture of **T31.3** (10.33 g, 31.0 mmol), ground S-Phos (2.55 g, 6.21 mmol), palladium acetate (0.70 g, 3.11 mmol), and potassium phosphate, tribasic (16.49 g, 77.7 mmol) in DMF (75 mL) and water (4 mL) was purged with argon and placed under vacuum and the process repeated three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**T2.2**) (8.96 g, 40.4 mmol) was added via syringe. The mixture was then heated at 75°C. After 21 hours, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to yield **T31.4** (5.65 g, 52 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.63 (1 H, d, J=8.6 Hz), 6.93 (1 H, d, J=13.3 Hz), 5.55 (1 H, t, J=2.3 Hz), 5.43 (1 H, t, J=2.7 Hz), 3.90 (3 H, s), 3.82 (1 H, m), 3.67 (1 H, m), 2.41 (2 H, td, J=7.0, 2.3 Hz), 1.97 (5 H, m), 1.79 (3 H, m), 1.07 (6 H, d, J=13.7 Hz).

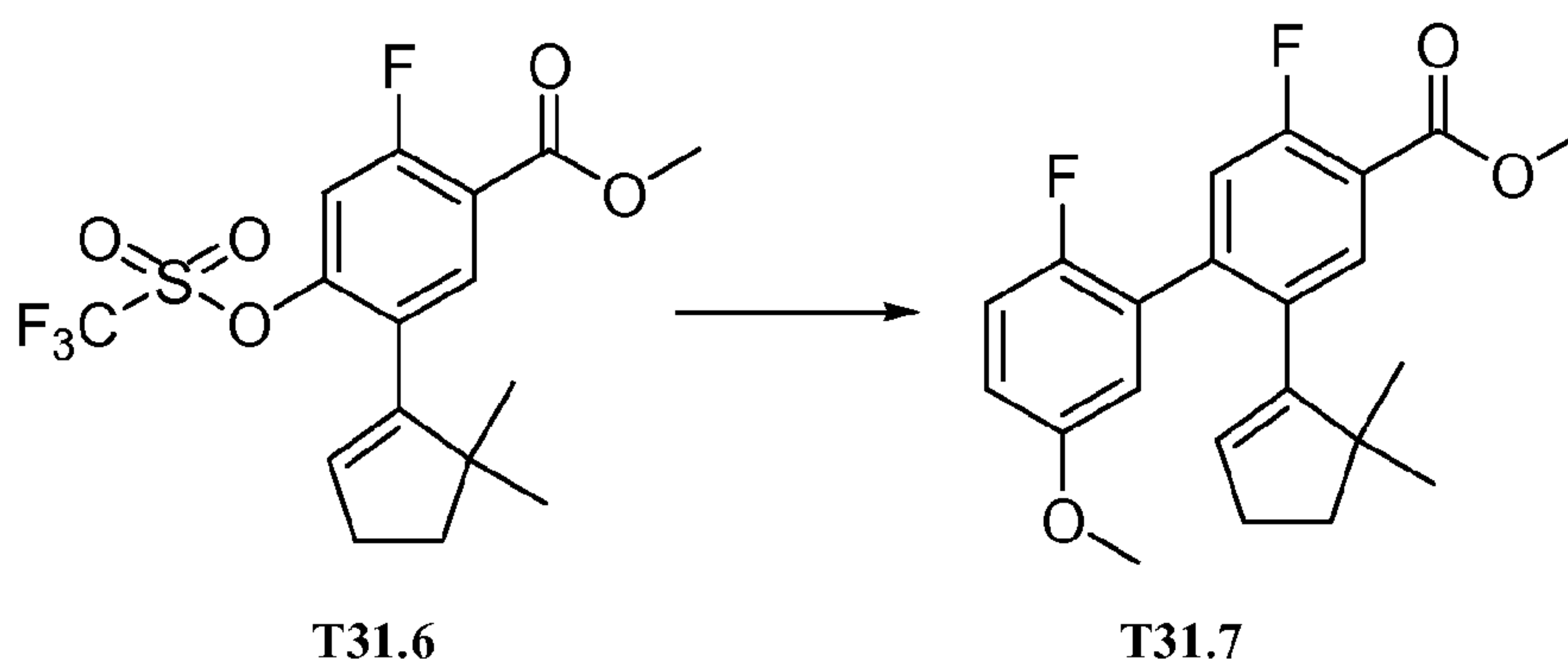


[0512] Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-hydroxybenzoate (T31.5). To a stirred mixture of **T31.4** (5.65 g, 16.2 mmol) in MeOH (60 mL) was added PPTS (0.42 g, 1.69 mmol). The mixture was heated to 50 °C and monitored with TLC

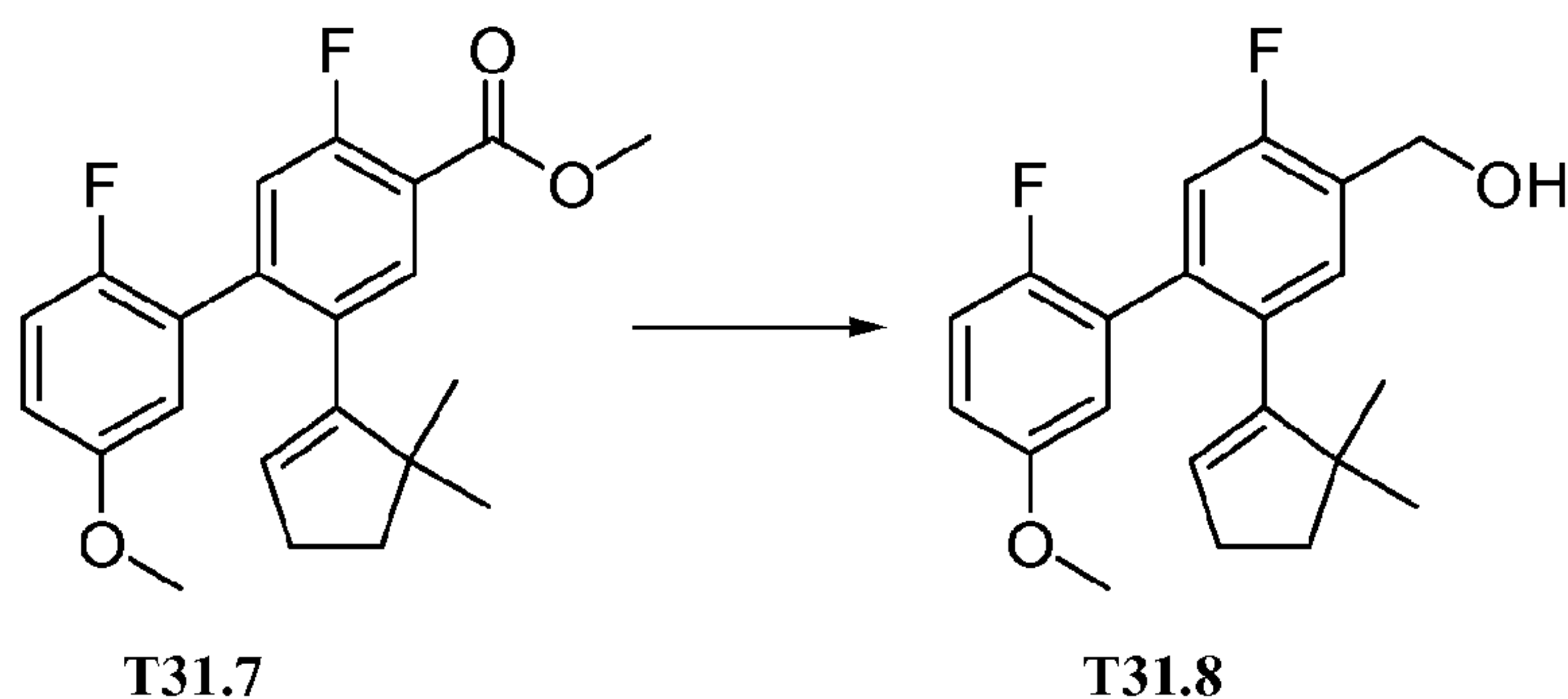
and LCMS. After 19 hours, the organic solvent was removed under reduced pressure, and the residue was then purified on silica gel (0-15% EtOAc in hexanes) to yield **T31.5** as a white solid (3.47g, 81% yield). ^1H NMR (500 MHz, CDCl_3) δ ppm 7.69 (1 H, d, $J=8.3$ Hz), 6.71 (1 H, d, $J=12.0$ Hz), 5.93 (1 H, d, $J=1.7$ Hz), 5.80 (1 H, t, $J=2.4$ Hz), 3.90 (3 H, s), 2.54 (2 H, m), 1.93 (2 H, t, $J=7.1$ Hz), 1.11 (6 H, s).



[0513] **Methyl 5-(5,5-dimethylcyclopent-1-en-1-yl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate (T31.6).** To a stirred solution of **T31.5** (0.80 g, 3.02 mmol) in dry DCM (15 mL) was added TEA (1.0 mL, 7.19 mmol) and 4-dimethylaminopyridine (38.1 mg, 0.312 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.30 g, 3.64 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 19 hours, the organic solvent was removed under reduced pressure and the resulting residue was purified with silica gel chromatography using 0-10% EtOAc in hexanes to yield **T31.6** as a colorless oil (1.05 g, 88% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.84 (1 H, d, $J=7.8$ Hz), 7.13 (1 H, d, $J=10.2$ Hz), 5.79 (1 H, t, $J=2.3$ Hz), 3.96 (3 H, s), 2.47 (2 H, td, $J=7.0, 2.3$ Hz), 1.91 (2 H, t, $J=7.0$ Hz), 1.08 (6 H, s).

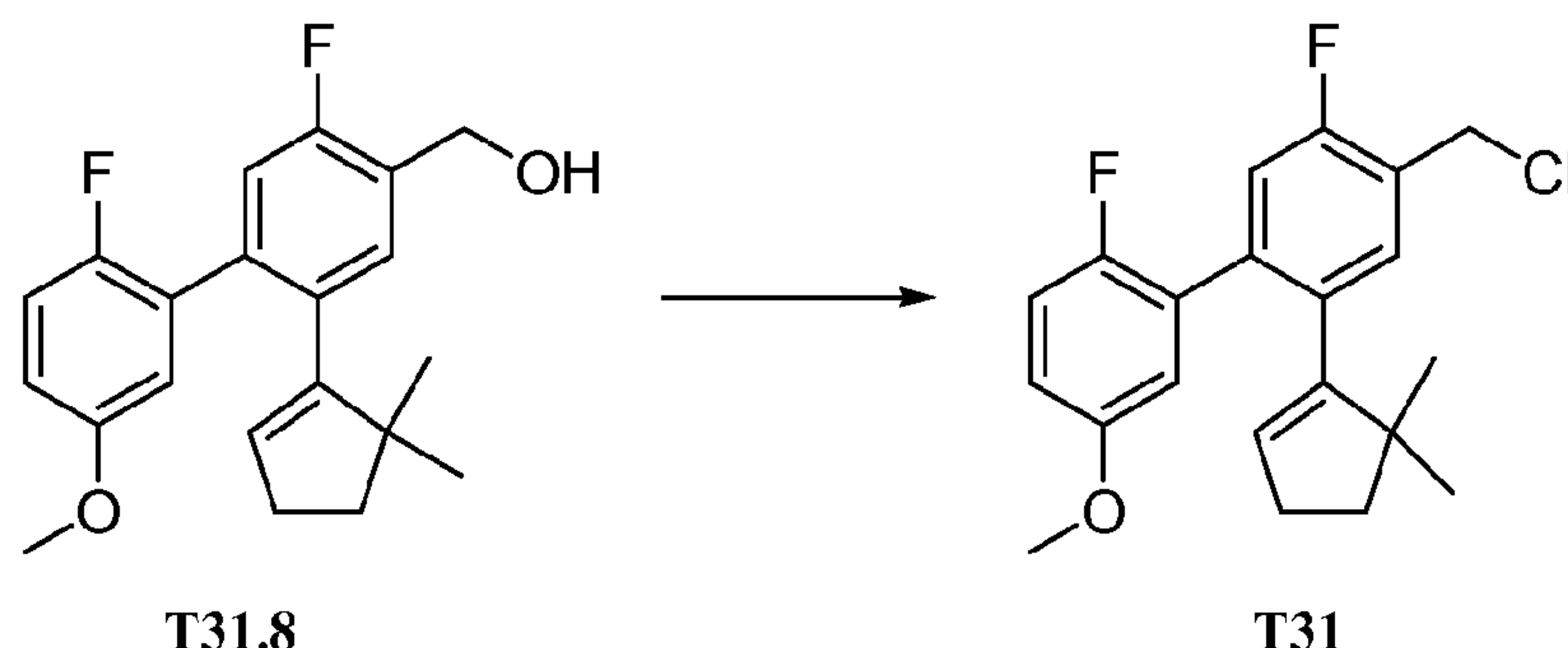


[0514] Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T31.7). To a stirred solution of **T31.6** (1.05 g, 2.65 mmol) in DMF (5 mL) at 23 °C was added 2-fluoro-5-methoxyphenylboronic acid (0.90 g, 5.32 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) and potassium carbonate (1.10 g, 7.96 mmol) followed by tetrakis(triphenylphosphine)palladium (0.31 g, 0.27 mmol). The mixture was heated to 90 °C. After 17 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to give **T31.7** as a clear oil that was used without further purification (0.92 g, 93 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.79 (1 H, d, J=7.4 Hz), 7.13 (1 H, d, J=11.3 Hz), 6.99 (1 H, t, J=9.0 Hz), 6.84 (1 H, dt, J=8.7, 3.7 Hz), 6.78 (1 H, dd, J=5.9, 3.1 Hz), 5.55 (1 H, s), 3.96 (3 H, s), 3.79 (3 H, s), 2.27 (2 H, td, J=7.1, 2.5 Hz), 1.67 (2 H, t, J=7.0 Hz), 0.84 (6 H, s).



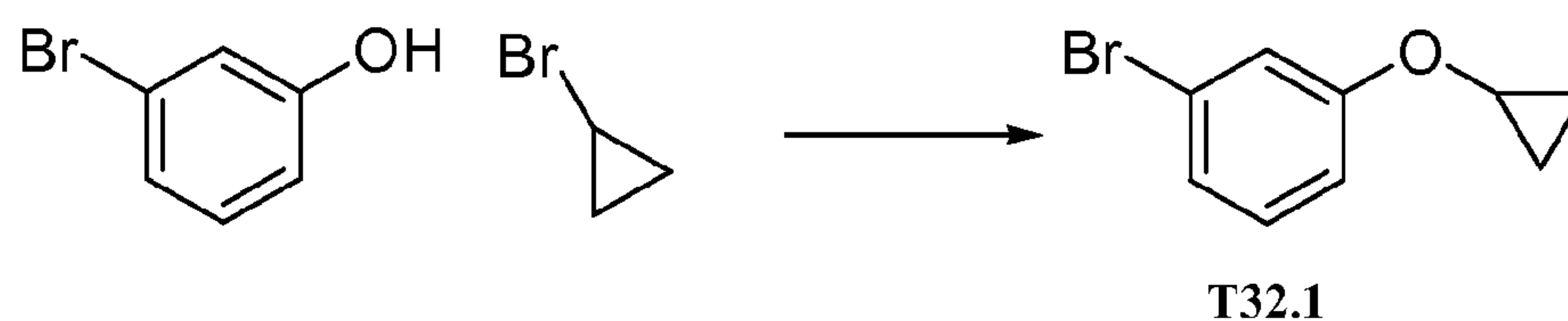
[0515] (2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T31.8). To a cooled solution of **T31.7** (0.92 g, 2.47 mmol) in dry THF (15 mL) at 0 °C was added LAH (1.0 M in THF)(5.0 mL, 5.0 mmol) dropwise. Upon complete addition, the reaction was maintained at 0 °C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (silica gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T31.8** as a colorless oil (0.70 g, 82 % yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.30 (1 H, m), 7.05 (1 H, dd, J=10.6, 1.1 Hz), 6.97 (1 H, t, J=8.9 Hz), 6.83 (2 H, m), 5.52

(1 H, td, J=2.4, 0.9 Hz), 4.81 (2 H, s), 3.76 (3 H, s), 2.25 (2 H, td, J=7.1, 2.4 Hz), 1.76 (1 H, br. s.), 1.69 (2 H, m), 0.85 (6 H, s).



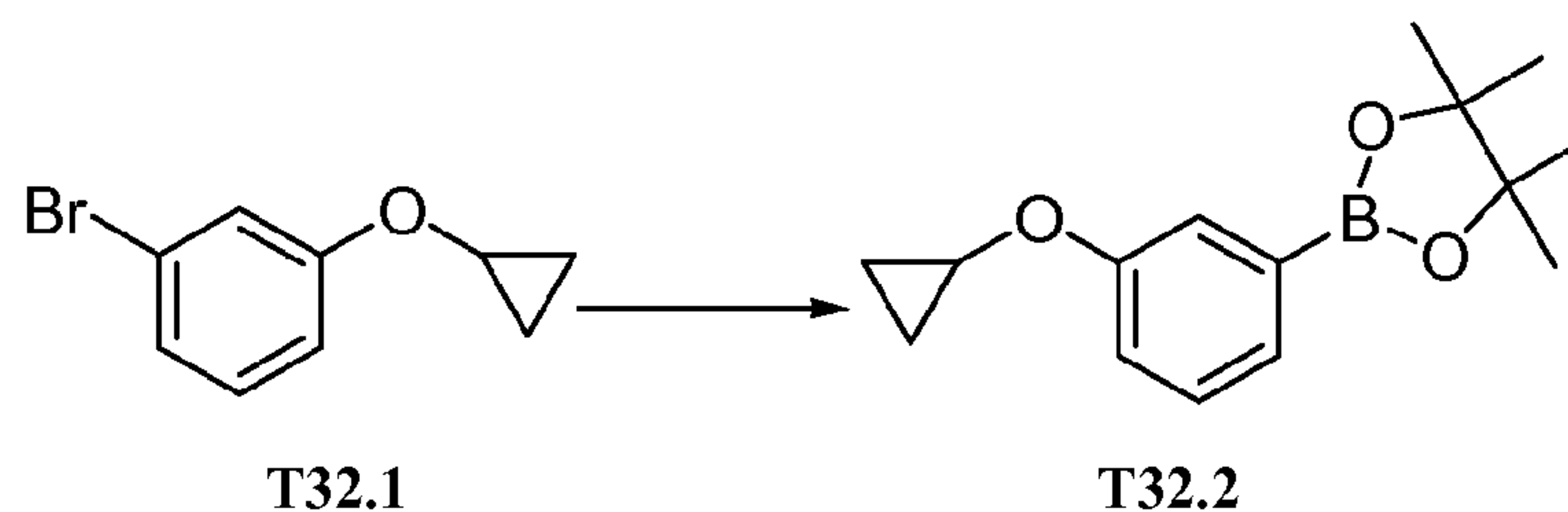
[0516] **4-(Chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl (T31).** To a solution of **T31.8** (0.17 g, 0.48 mmol) in dry DCM (2.0 mL) and dry DMF (0.020 mL) was added thionyl chloride (0.080 mL, 1.1 mmol) dropwise at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T31** as a colorless oil (0.16 g, 93% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.29 (1 H, d, J=7.8 Hz), 7.08 (1 H, d, J=10.2 Hz), 6.98 (1 H, t, J=9.0 Hz), 6.85 (2 H, m), 5.56 (1 H, s), 4.69 (2 H, s), 3.77 (3 H, s), 2.27 (2 H, td, J=7.0, 2.7 Hz), 1.68 (2 H, t, J=7.0 Hz), 0.86 (6 H, s).

[0517] **Intermediate T32**

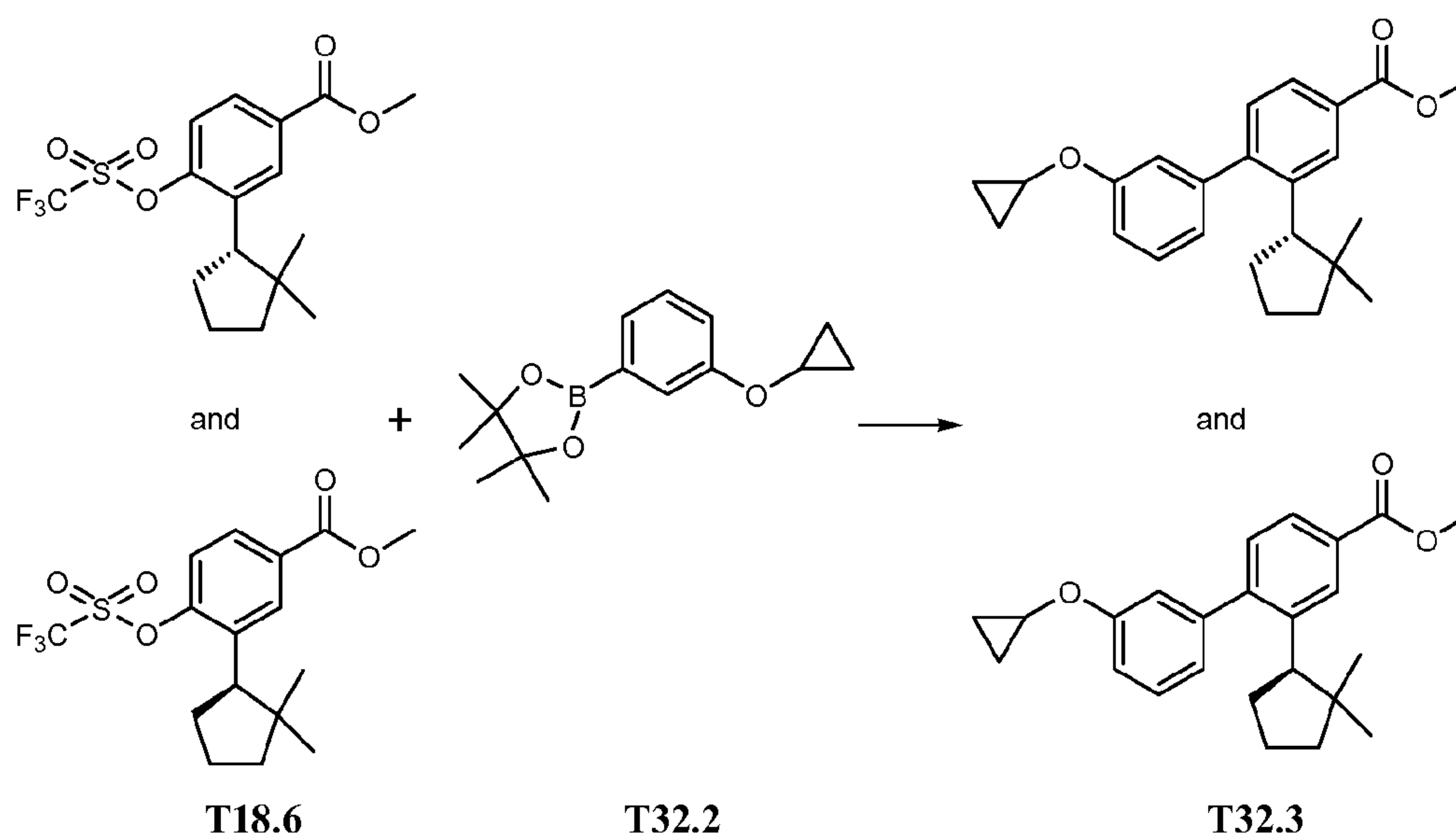


[0518] **3-Bromophenyl cyclopropyl ether (T32.1).** To a solution of 3-bromophenol (0.57 g, 3.29 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) in dry DMF (5.0 mL) was added cyclopropyl bromide (0.53 mL, 6.62 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), sodium iodide (50.1 mg, 0.334 mmol), and Cs₂CO₃ (3.2 g, 9.86 mmol). The reaction mixture was heated in a pressure tube to 150°C. After 19 hours, the reaction was cooled to room temperature then diluted with EtOAc, washed with water, and extracted three times with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and

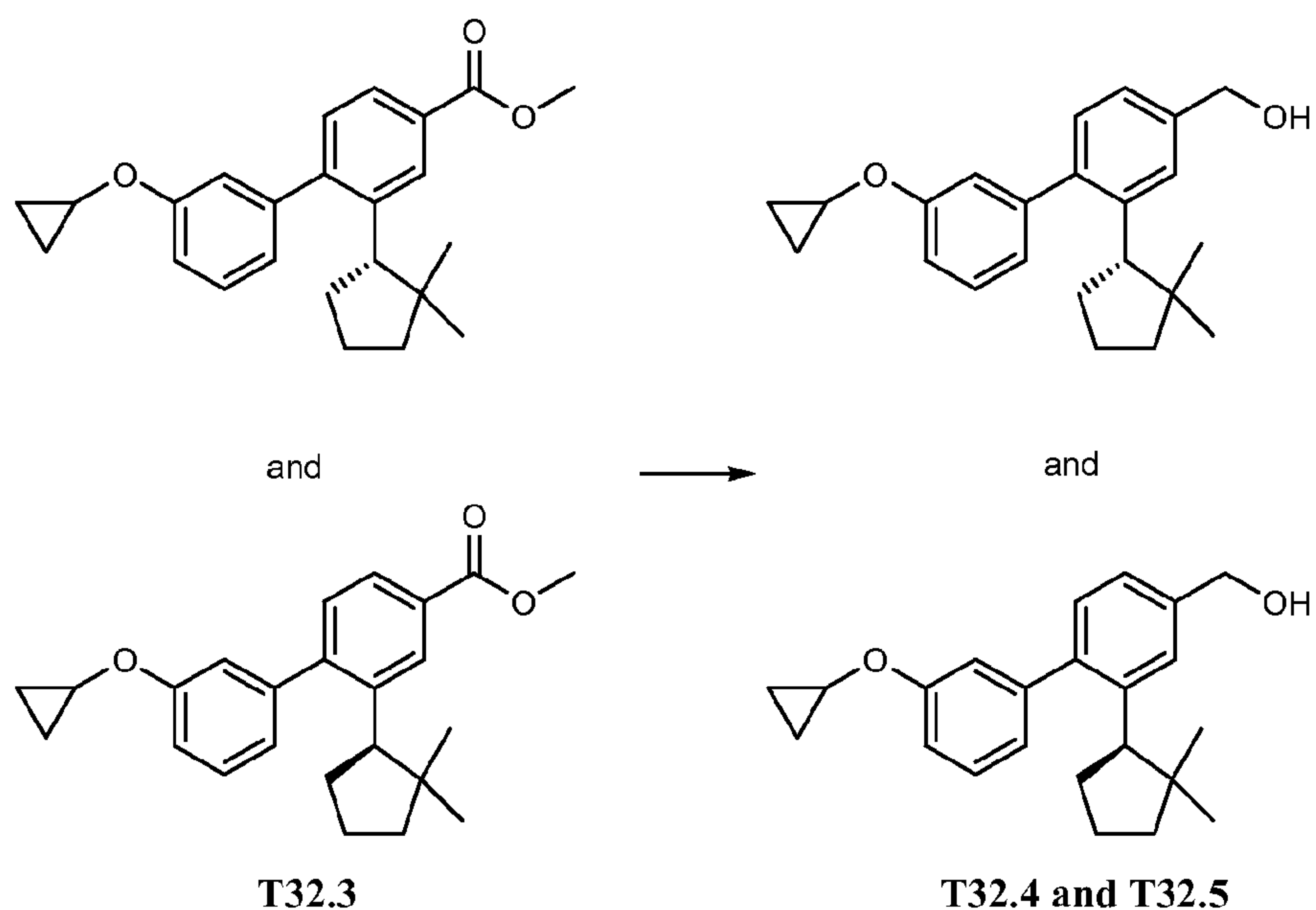
concentrated. The residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T32.1** as a colorless oil (144 mg, 21% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.29 (1 H, m), 7.19 (2 H, m), 6.99 (1 H, d, $J=7.8$ Hz), 3.74 (1 H, ddd, $J=8.9, 5.8, 3.3$ Hz), 0.81 (4 H, ddd, $J=11.2, 9.0, 8.8$ Hz.).



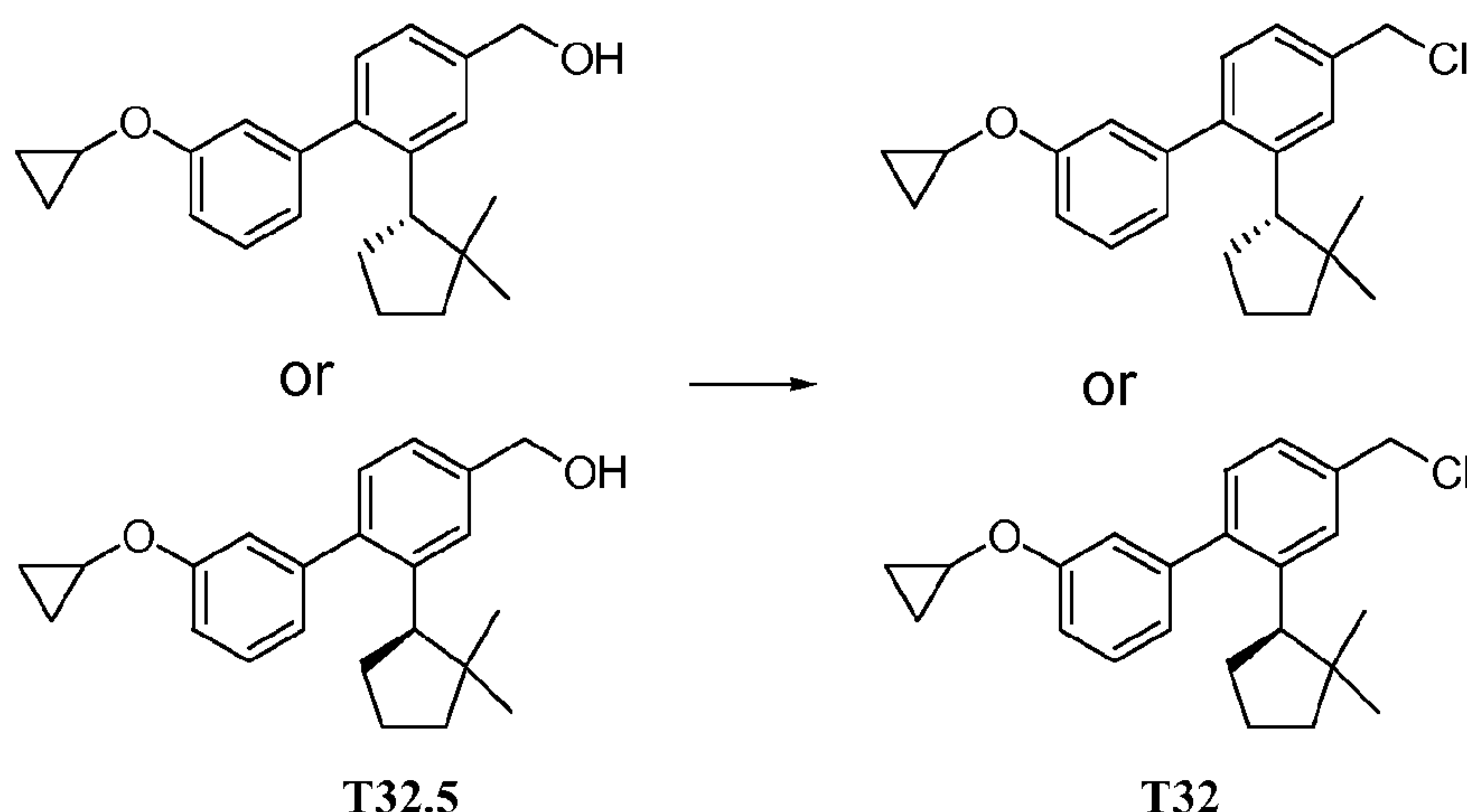
[0519] **2-(3-(Cyclopropyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (T32.2).** A stirred mixture of **T32.1** (0.144 g, 0.676 mmol), bis(pinacolato)diboron (0.189 g, 0.745 mmol), potassium acetate (0.2007 g, 2.04 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (25.3 mg, 0.0346 mmol) in dry 1,4-dioxane (3.0 mL) was purged three times with argon and placed under vacuum three times. The mixture was heated to 100°C, and monitored with LC-MS and TLC. After 21 hours, the reaction was cooled to room temperature and filtered through Celite® filter aid. The organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **T32.2** as a colorless oil (72 mg, 41% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.51 (1 H, d, $J=2.7$ Hz), 7.44 (1 H, d, $J=7.0$ Hz), 7.34 (1 H, m), 7.14 (1 H, dd, $J=7.6, 2.2$ Hz), 3.80 (1 H, ddd, $J=8.8, 5.9, 3.3$ Hz), 1.36 (12 H, s), 0.82 (4 H, m).



[0520] **Methyl 3'-(cyclopropyloxy)-2-(2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-carboxylate (T32.3).** To a stirred solution of **T18.6** (438.2 mg, 1.15 mmol) in dry DMF (5.0 mL) at 23 °C was added potassium carbonate (480.3 mg, 3.47 mmol) followed by tetrakis(triphenylphosphine)palladium (140.2 mg, 0.121 mmol). The mixture was purged three times with argon and placed under vacuum three times. Before heating, **T32.2** (523.1 mg, 2.01 mmol) was added via syringe and then the mixture was heated to 90°C. After 19 hours, LCMS showed that the reaction was complete. The mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to afford **T32.3** as a colorless oil that was used without further purification (411.5 mg, 98% yield). MS ESI (pos.) m/e: 365.0 (M+H)⁺.

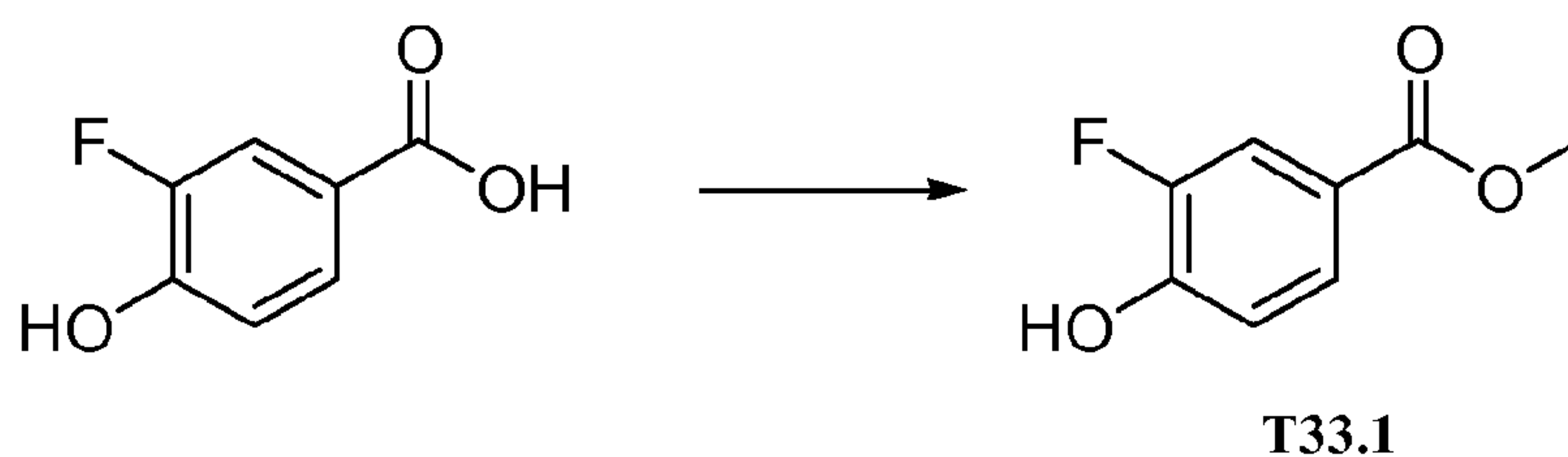


[0521] **(S)-(3'-Cyclopropoxy-2-(2,2-dimethylcyclopentyl)biphenyl-4-yl)methanol and (R)-(3'-cyclopropoxy-2-(2,2-dimethylcyclopentyl)biphenyl-4-yl)methanol (T32.4 and T32.5).** To a cooled solution of **T32.3** (0.4115 g, 1.129 mmol) in dry THF (10 mL) at 0 °C was added LAH (1.0 M in THF) (2.30 mL, 2.3 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction. The resulting mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide a colorless oil (317.1 mg, 83% yield, MS ESI (pos.) m/e: 319.0 (M-H₂O)⁺). The mixture of enantiomers was then separated by chiral chromatography on a CHIRALCEL® OD chromatography column (3% IPA in hexane) to provide **T32.4** (first peak) and **T32.5** (second peak).



[0522] **4-(Chloromethyl)-3'-(cyclopropyloxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl or 4-(chloromethyl)-3'-(cyclopropyloxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl (T32).** To a solution of **T32.5** (0.1335 g, 0.397 mmol) in dry DCM (4 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.07 mL, 0.96 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T32** as a colorless oil (118.3 mg, 84% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (1 H, d, J=1.6 Hz), 7.34 (1 H, d, J=1.6 Hz), 3.78 (1 H, m), 3.15 (1 H, dd, J=10.4, 3 H, m), 7.01 (1 H, dd, J=7.8, 3.1 Hz), 6.98 (1 H, m), 6.85 (1 H, d, J=7.4 Hz), 4.69 (2 H, m, 8.4 Hz), 2.13 (2 H, m), 1.88 (1 H, m), 1.72 (1 H, m), 1.59 (1 H, m), 1.41 (1 H, m), 0.82 (6 H, m), 0.58 (3 H, s).

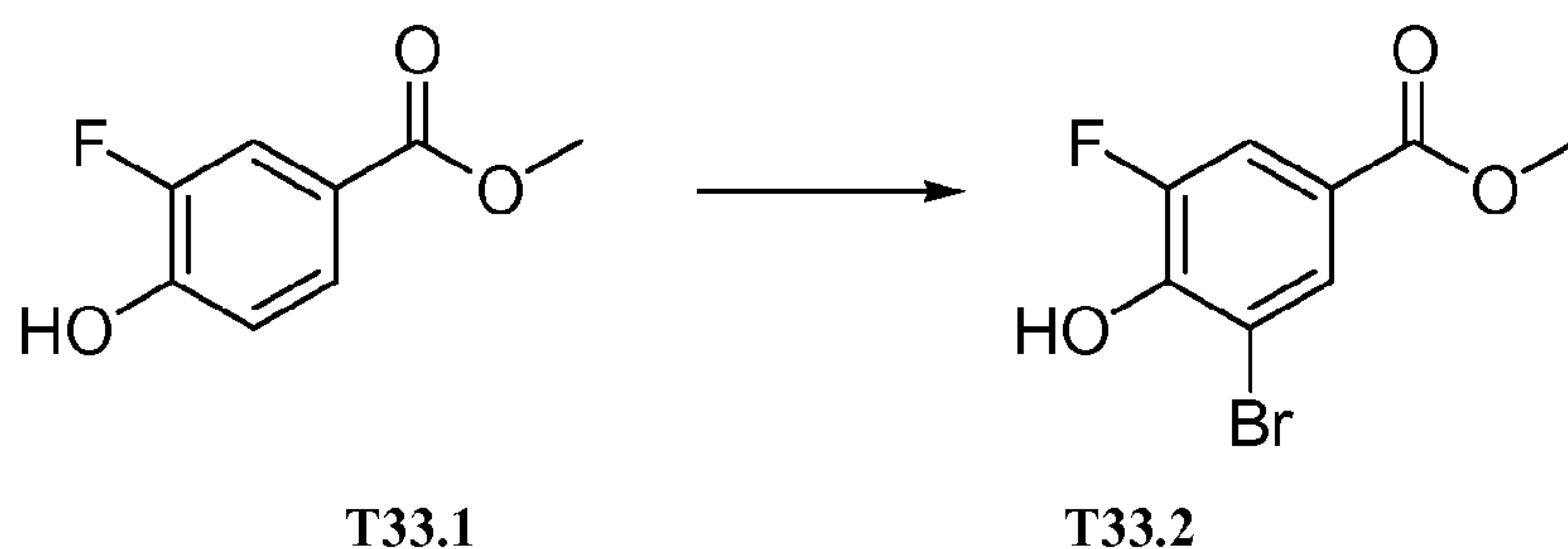
[0523] **Intermediate T33**



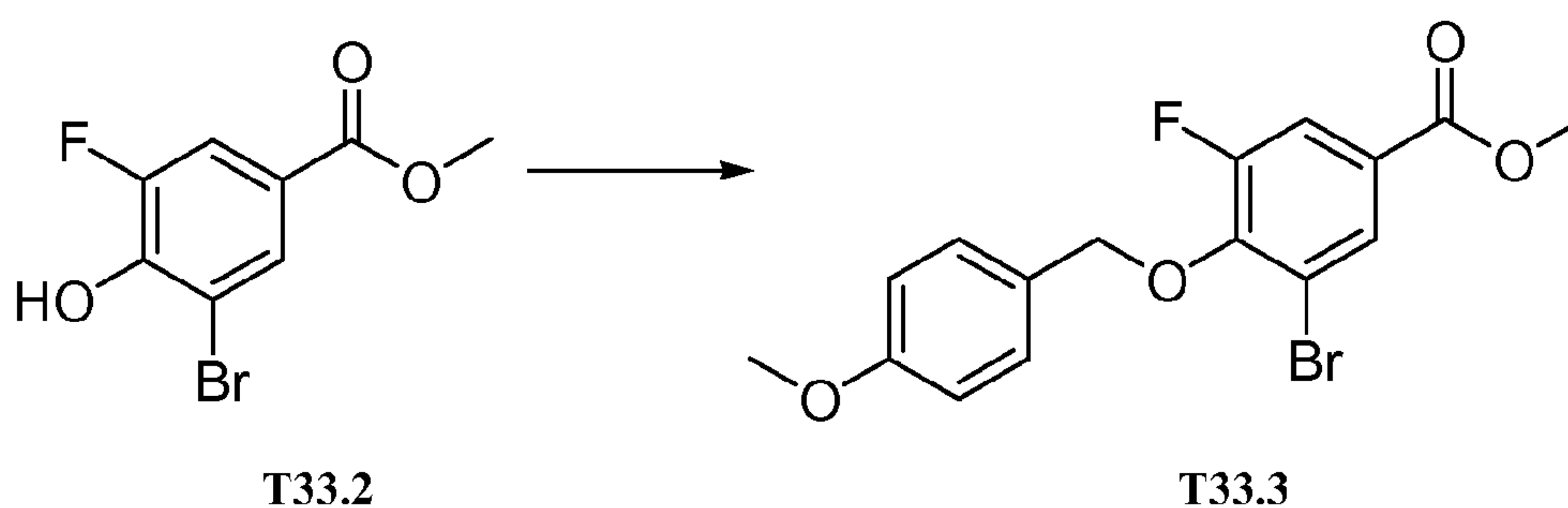
[0524] **Methyl 3-fluoro-4-hydroxybenzoate (T33.1).** To a round bottom flask containing 3-fluoro-4-hydroxybenzoic acid (5.03 g, 32.22 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA) was added a cold solution of MeOH (50.0 mL) and sulfuric acid (2.0 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed and the mixture was diluted with diethyl ether. The organic phase was washed carefully twice with saturated aqueous NaHCO₃.

and once with brine. The organic phase was then dried over anhydrous sodium sulfate.

After filtration, the organic solvent was removed in vacuo to afford **T33.1** as a white solid (4.79 g, 87% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.81 (2 H, m), 7.06 (1 H, t, $J=8.4$ Hz), 5.62 (1 H, d, $J=4.3$ Hz), 3.91 (3 H, s).

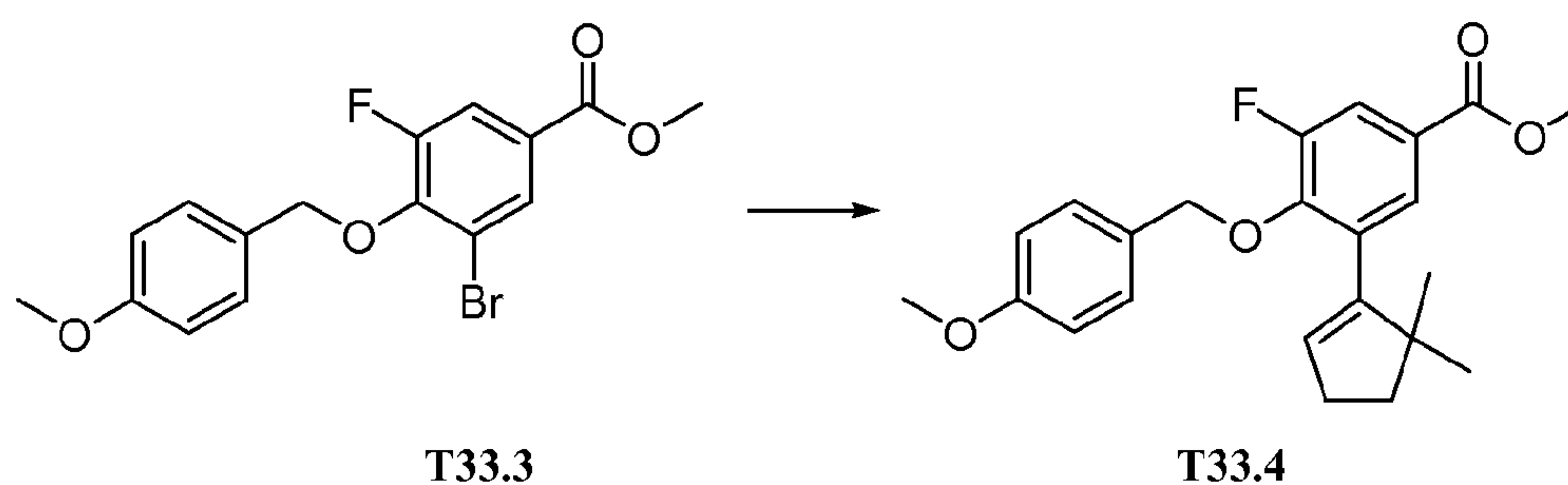


[0525] Methyl 3-bromo-5-fluoro-4-hydroxybenzoate (T33.2). Bromine (1.60 mL, 31.1 mmol) was added dropwise with stirring over 30 minutes to an ice-cooled solution of **T33.1** (4.79 g, 28.1 mmol) in a 1:1 mixture of DCM (20 mL) and acetic acid (20 mL). Upon complete addition, the reaction mixture was allowed to warm to room temperature and monitored with TLC and LC-MS. After stirring at room temperature for 40 hours, the mixture was diluted with EtOAc, and then the resulting solution was washed twice with aqueous saturated Na_2SO_3 , once with water, and once with brine. After drying over anhydrous magnesium sulfate, filtration, and concentration, the white solid **T33.2** was obtained 6.69 g, 95% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.05 (1 H, m), 7.75 (1 H, dd, $J=10.6, 2.0$ Hz), 6.12 (1 H, s), 3.94 (3 H, s).

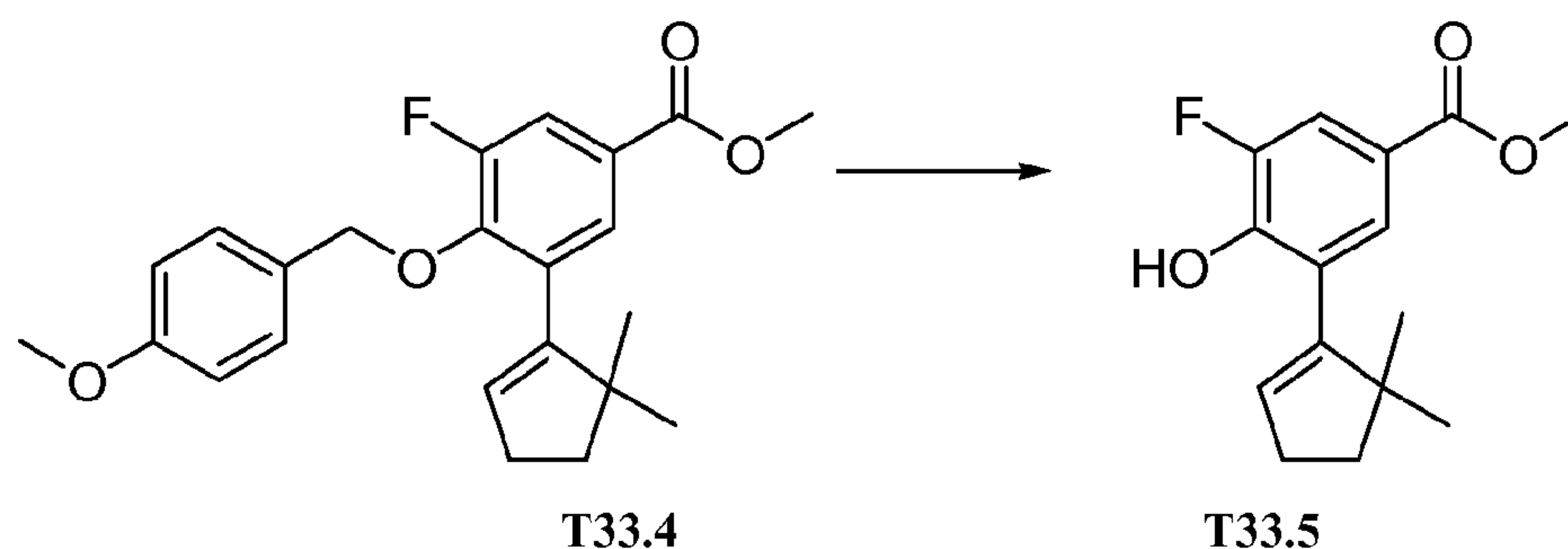


[0526] Methyl 3-bromo-5-fluoro-4-(((4-(methoxy)phenyl)methyl)oxy)benzoate (T33.3). To a vial containing **T33.2** (0.64 g, 2.58 mmol) in 5.0 mL dry DMF was added Cs_2CO_3 (1.10 g, 3.36 mmol). The mixture was stirred at room temperature for 10 minutes and then 4-methoxybenzyl bromide (0.45 mL, 3.1 mmol) was added. After 4 hours, the reaction was diluted with water and then extracted five times

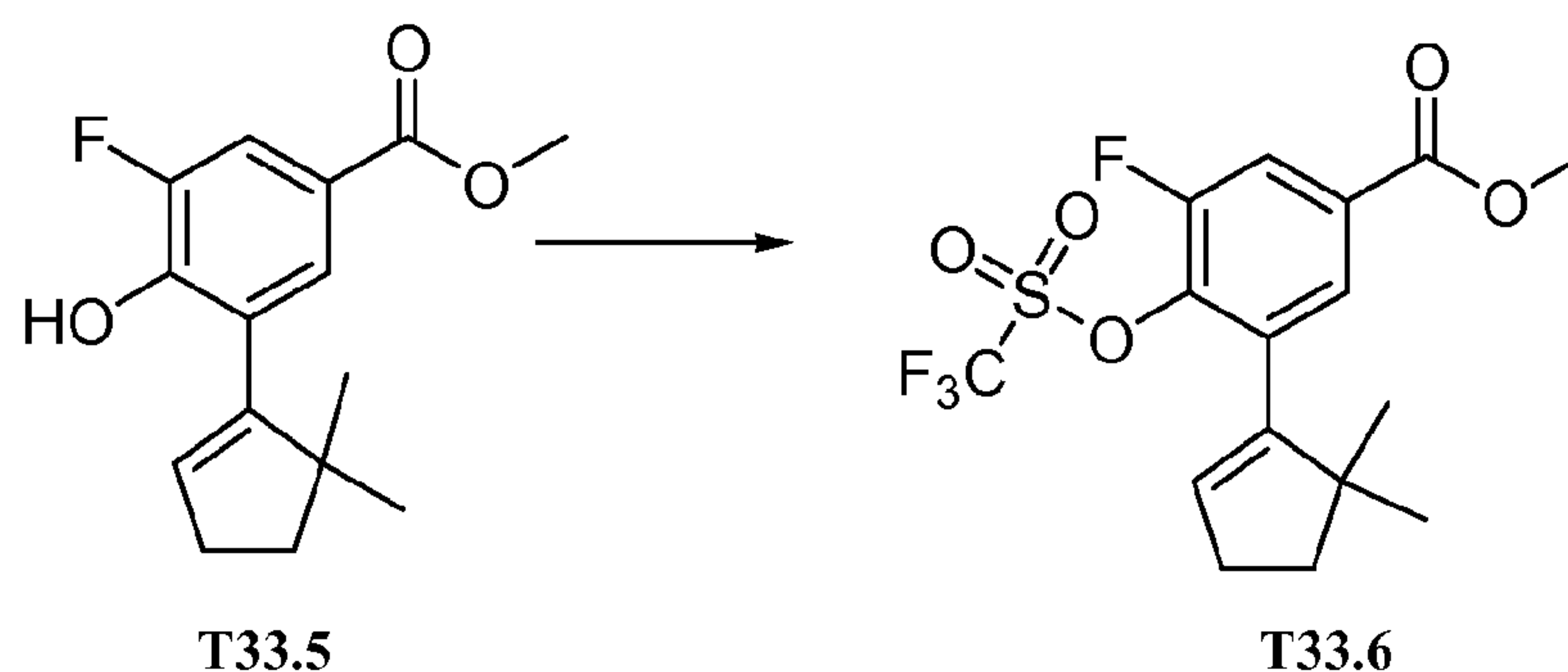
with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **T33.3** as a white solid (679.1 mg, 71% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.02 (1 H, t, $J=2.0$ Hz), 7.72 (1 H, dd, $J=11.5$, 2.2 Hz), 7.42 (2 H, m, $J=8.6$ Hz), 6.90 (2 H, m), 5.20 (2 H, s), 3.91 (3 H, s), 3.82 (3 H, s).



[0527] **Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-((4-methoxyphenyl)methyl)oxybenzoate (T33.4).** A stirred mixture of **T33.3** (1.63 g, 4.420 mmol), ground S-Phos (0.36 g, 0.88 mmol), palladium acetate (0.10 g, 0.45 mmol), and potassium phosphate tribasic (2.35 g, 11.06 mmol) in DMF (13 mL) and water (0.4 mL) was purged with argon and placed under vacuum and the process repeated three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**T2.2**) (1.47 g, 6.63 mmol) was added via syringe and then the mixture was heated to 75°C. After 18 hours, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on a 40 g column of silica gel (0-10% EtOAc in hexanes) to afford **T33.4** as a white solid (1.12 g, 66% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.69 (1 H, dd, $J=11.7$, 2.3 Hz), 7.57 (1 H, dd, $J=2.0$, 1.2 Hz), 7.31 (2 H, m), 6.88 (2 H, m), 5.56 (1 H, t, $J=2.5$ Hz), 5.01 (2 H, s), 3.91 (3 H, s), 3.82 (3 H, s), 2.42 (2 H, td, $J=7.0$, 2.7 Hz), 1.86 (2 H, t, $J=7.2$ Hz), 1.06 (6 H, s).

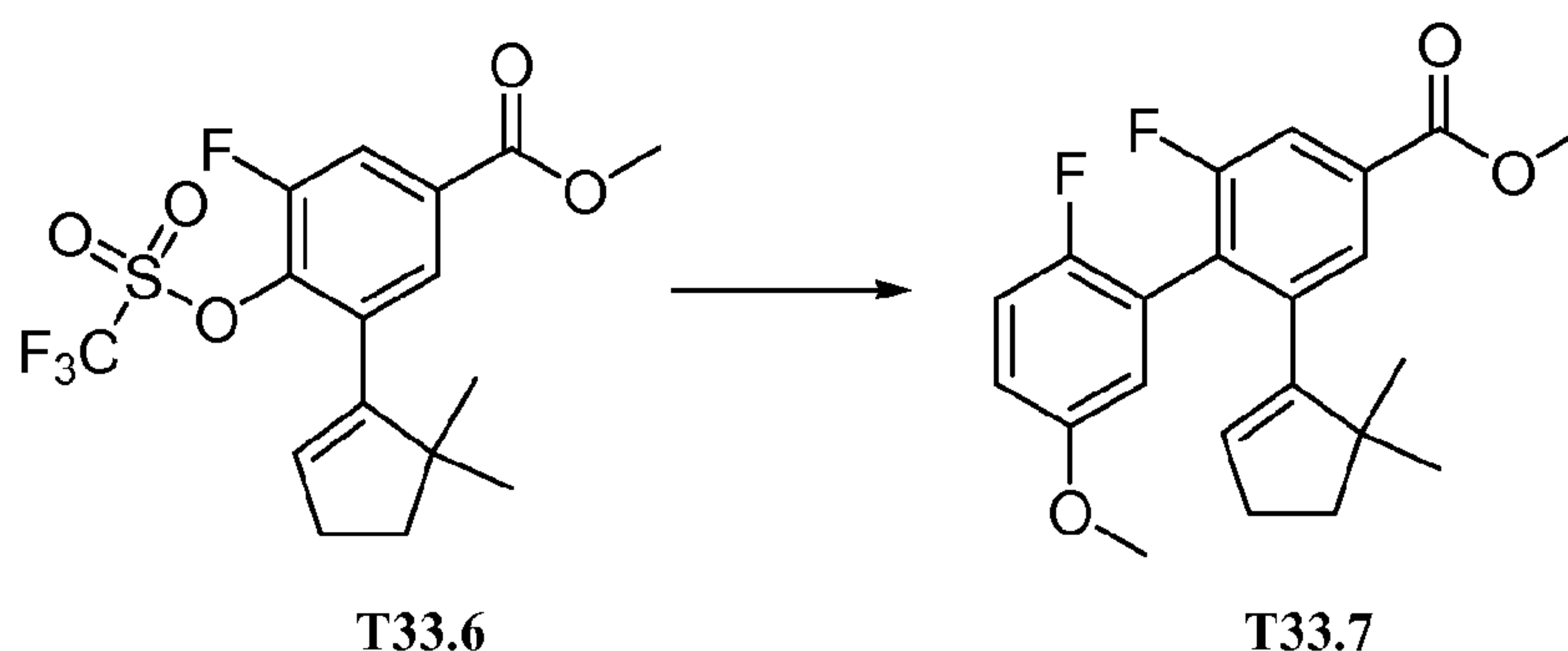


[0528] Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-hydroxybenzoate (T33.5). To a flask containing T33.4 (1.12 g, 2.93 mmol) was added a premixed solution of DCM (14 mL) and TFA (1 mL). The mixture was stirred at room temperature and monitored with TLC and LC-MS. After 1 hour, the reaction was diluted with DCM and then washed once with saturated aqueous sodium bicarbonate solution and brine. After washing, the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide a colorless oil that solidified as T33.5 and which was used without further purification (732.6 mg, 95 % yield).

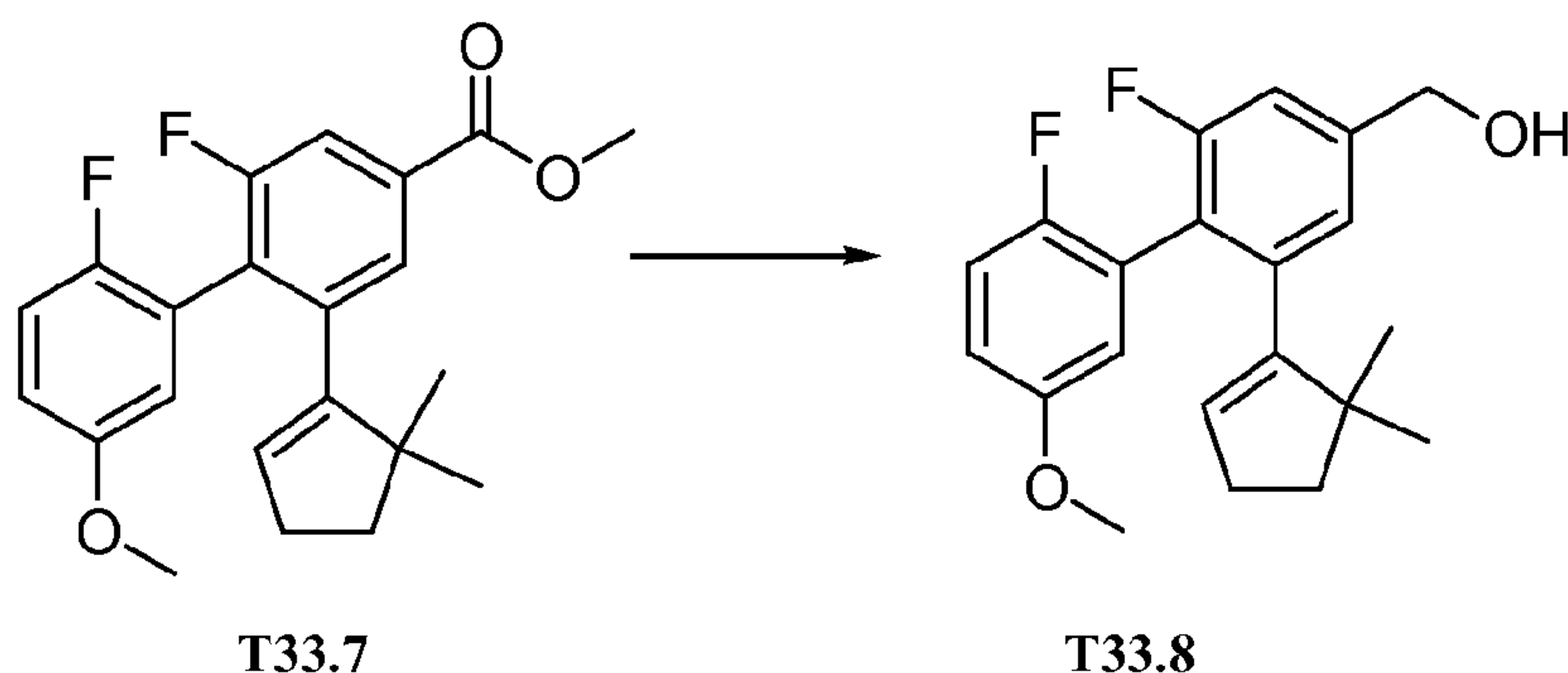


[0529] Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (T33.6). To a stirred solution of T33.5 (0.7326 g, 2.77 mmol) in dry DCM (15 mL) was added TEA (0.78 mL, 5.60 mmol) and 4-(dimethylamino)pyridine (0.0354 g, 0.29 mmol). After about 20 minutes, N-phenylbis(trifluoromethanesulfonimide) (1.20 g, 3.36 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 19 hours, the organic solvent was removed under reduced pressure and the product thus obtained was then purified with silica gel chromatography using 0-10% EtOAc in hexanes to afford T33.6 as a colorless oil (946.4 mg, 86 % yield). ¹H

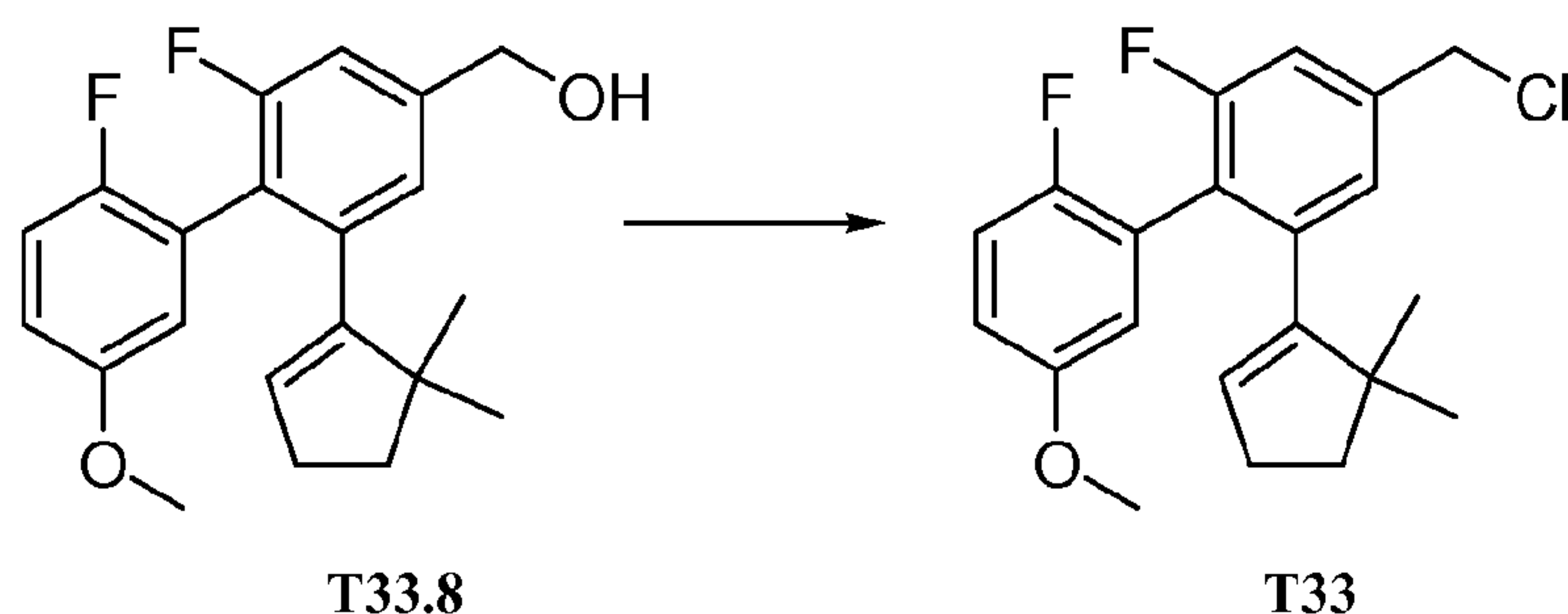
NMR (400 MHz, CDCl₃) δ ppm 7.82 (1 H, dd, J=9.9, 2.1 Hz), 7.75 (1 H, m), 5.87 (1 H, t, J=2.4 Hz), 3.95 (3 H, s), 2.49 (2 H, td, J=7.1, 2.4 Hz), 1.92 (2 H, t, J=7.0 Hz), 1.11 (6 H, s).



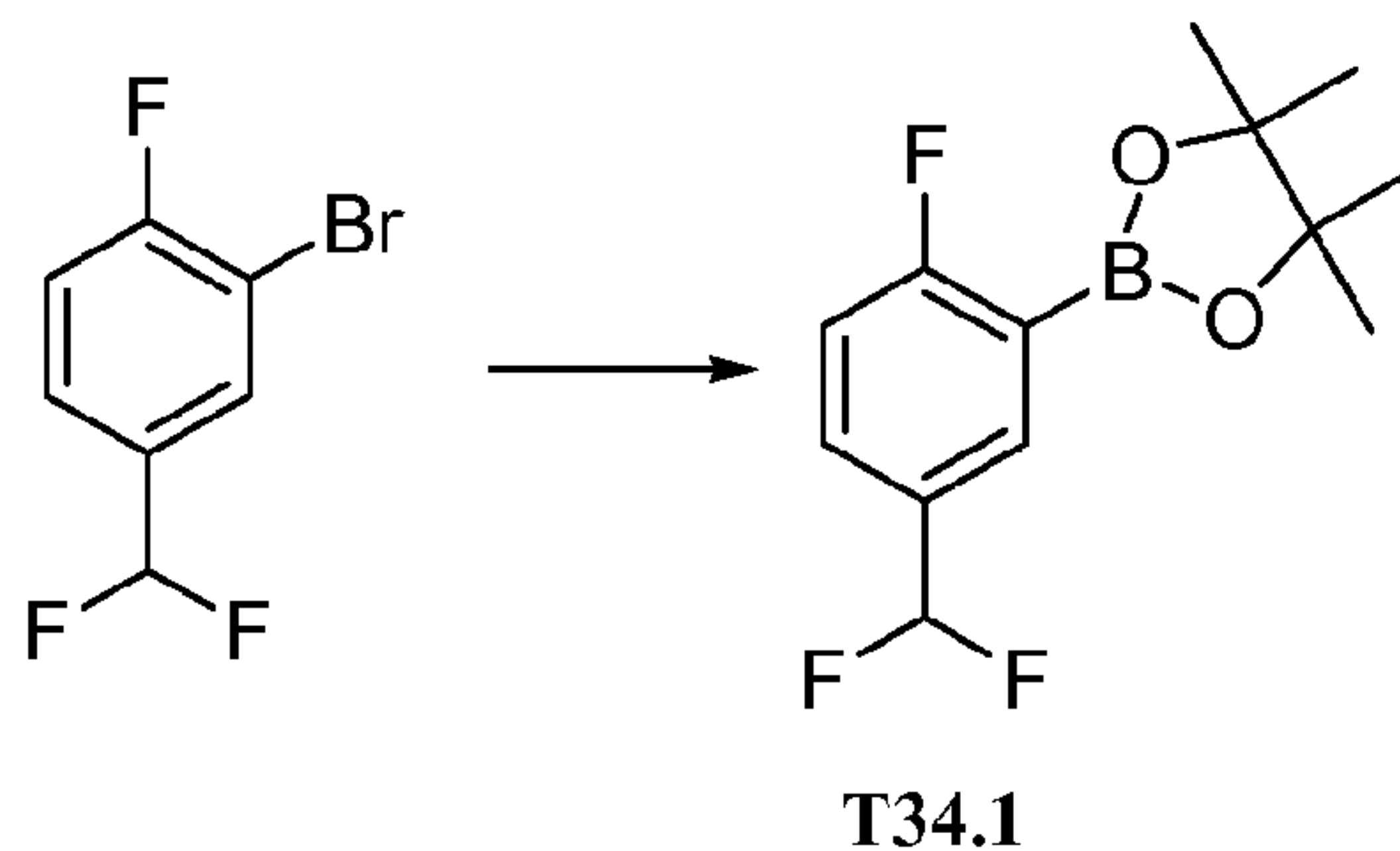
[0530] Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (T33.7). A stirred mixture of T33.6 (0.9464 g, 2.39 mmol), ground S-Phos (0.1977 g, 0.482 mmol), palladium acetate (0.0555 g, 0.247 mmol), 2-fluoro-5-methoxyphenylboronic acid (0.8114 g, 4.77 mmol) (commercially available from Sigma-Aldrich, St. Louis, MO, USA), and potassium phosphate tribasic (1.2888 g, 6.072 mmol) in dry DMF (7.000 mL) was purged with argon and placed under vacuum and the process repeated three times. The mixture was then heated to 75°C and the reaction was stirred for 21 hours. The reaction was then cooled to room temperature, diluted with water and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on an 80 g column of silica gel (0-20% EtOAc in hexanes) to afford T33.7 as a colorless oil that was used without further purification (850.5 mg, 95% yield). MS ESI (pos.) m/e: 373.0 (M+H)⁺.



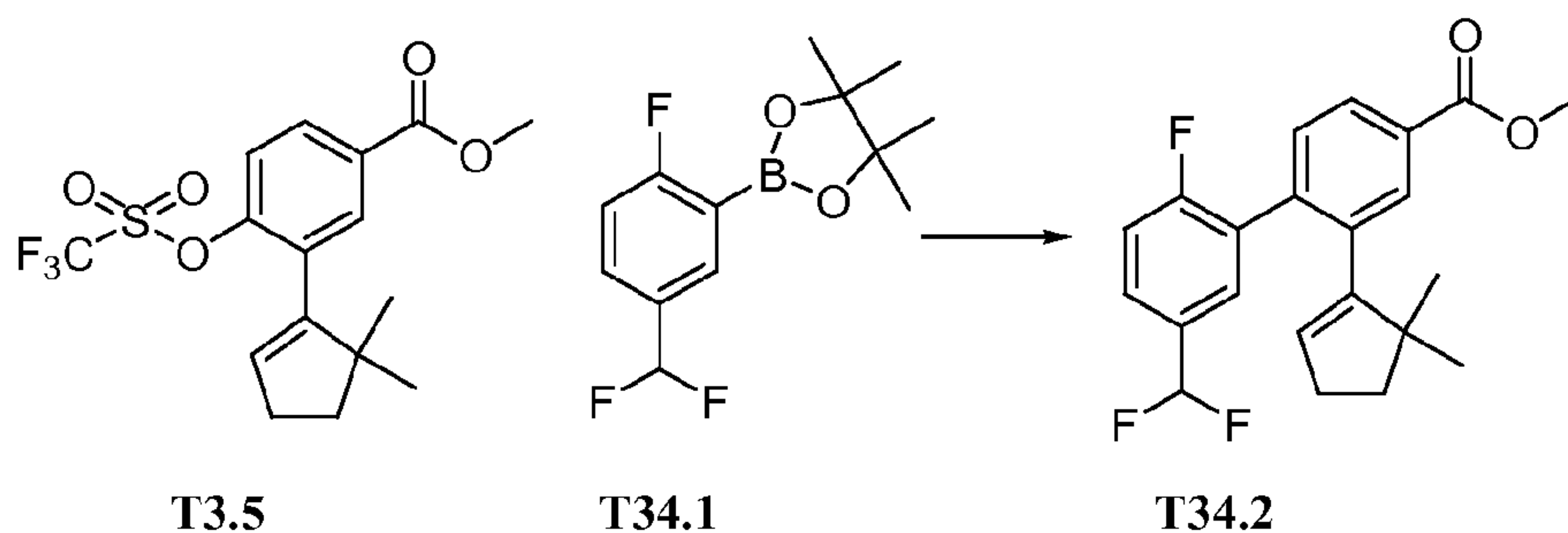
[0531] (2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (T33.8). To a cooled solution of **T33.7** (0.1435 g, 0.385 mmol) in dry THF (9 mL) at 0 °C was added LAH (1.0 M in THF)(0.8 mL, 0.80 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred), and the resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **T33.8** as a colorless oil (114.9 mg, 87% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.12 (1 H, dd, J=9.8, 1.6 Hz), 7.04 (2 H, m), 6.84 (1 H, dt, J=9.0, 3.5 Hz), 6.74 (1 H, dd, J=5.5, 3.1 Hz), 5.50 (1 H, t, J=2.3 Hz), 4.74 (2 H, s), 3.76 (3 H, s), 2.24 (2 H, td, J=7.0, 2.3 Hz), 1.75 (5 H, m), 0.97 (3 H, s), 0.78 (3 H, s).



[0532] 4-(Chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl (T33). To a solution of **T33.8** (0.1149 g, 0.334 mmol) in dry DCM (4 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.05 mL, 0.685 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T33** as a colorless oil (35.6 mg, 29% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.14 (1 H, dd, J=9.4, 1.6 Hz), 7.06 (1 H, s), 7.00 (1 H, t, J=9.0 Hz), 6.85 (1 H, dt, J=9.0, 3.7 Hz), 6.74 (1 H, dd, J=5.5, 3.1 Hz), 5.53 (1 H, t, J=2.3 Hz), 4.61 (2 H, s), 3.76 (3 H, s), 2.25 (2 H, td, J=7.1, 2.5 Hz), 1.73 (2 H, m), 0.97 (3 H, s), 0.78 (3 H, s).

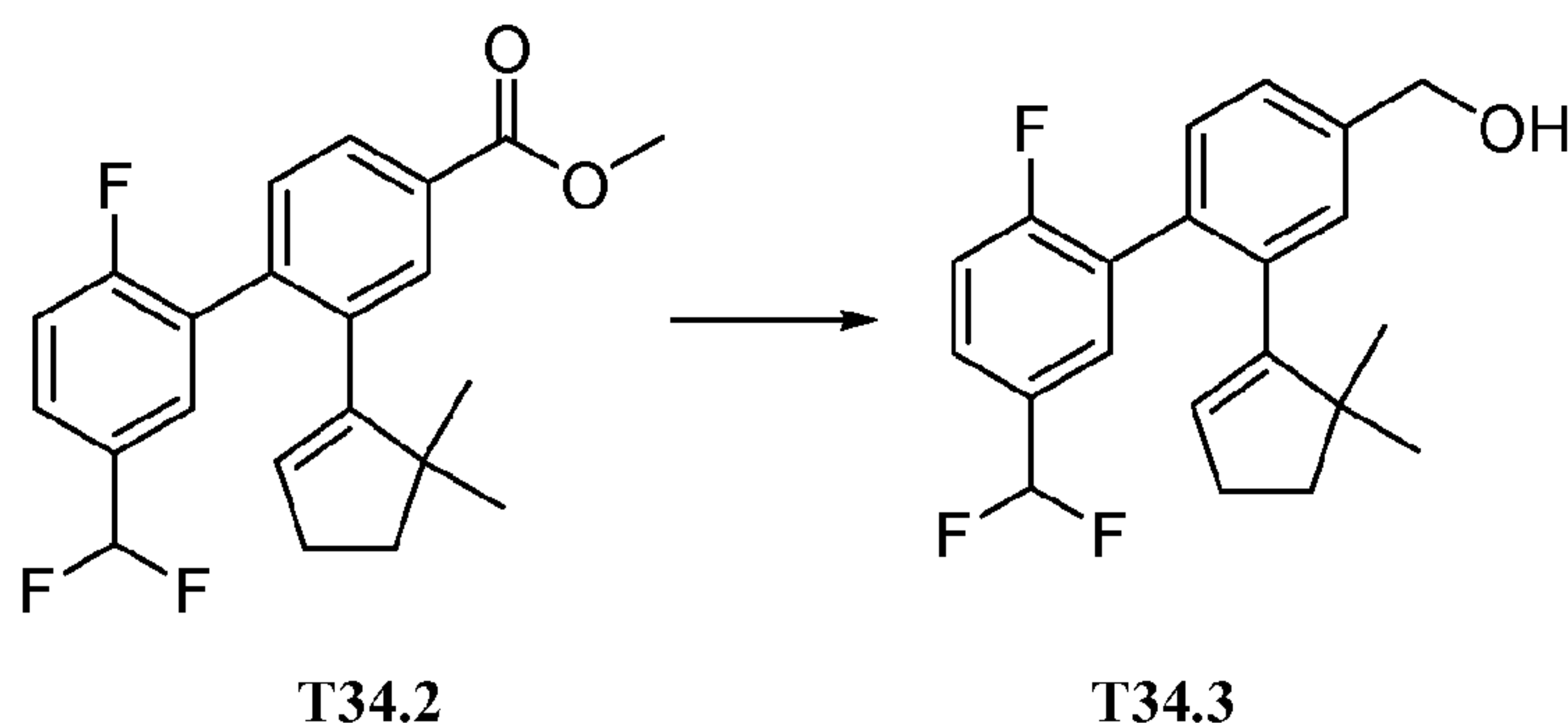
[0533] Intermediate T34

[0534] 2-(5-(Difluoromethyl)-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (T34.1). A stirred mixture of 1-bromo-5-difluoromethyl-2-fluorobenzene (commercially available from Oakwood Products, Inc.) (2.0231 g, 8.991 mmol), bis(pinacolato)diboron (2.5123 g, 9.893 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (0.3688 g, 0.4516 mmol), and potassium acetate (2.6504 g, 27.01 mmol) in dry 1,4-dioxane (35 mL) was purged with argon and placed under vacuum and the purging vacuum process repeated three times. The mixture was heated to 90°C and monitored with LC-MS and TLC. After 18 hours, the reaction was cooled to room temperature and then filtered through Celite® filter aid. The organic solvent was removed under reduced pressure, and the residue was purified on a 40 g column of silica gel (0-10% EtOAc in hexanes) to afford **T34.1** as a colorless oil that was used without further purification (1.6019 g, 65% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.89 (1 H, td, J=2.7, 1.2 Hz), 7.63 (1 H, m), 7.09 (1 H, t, J=8.6 Hz), 6.62 (1H, t), 1.35 (12 H, s).

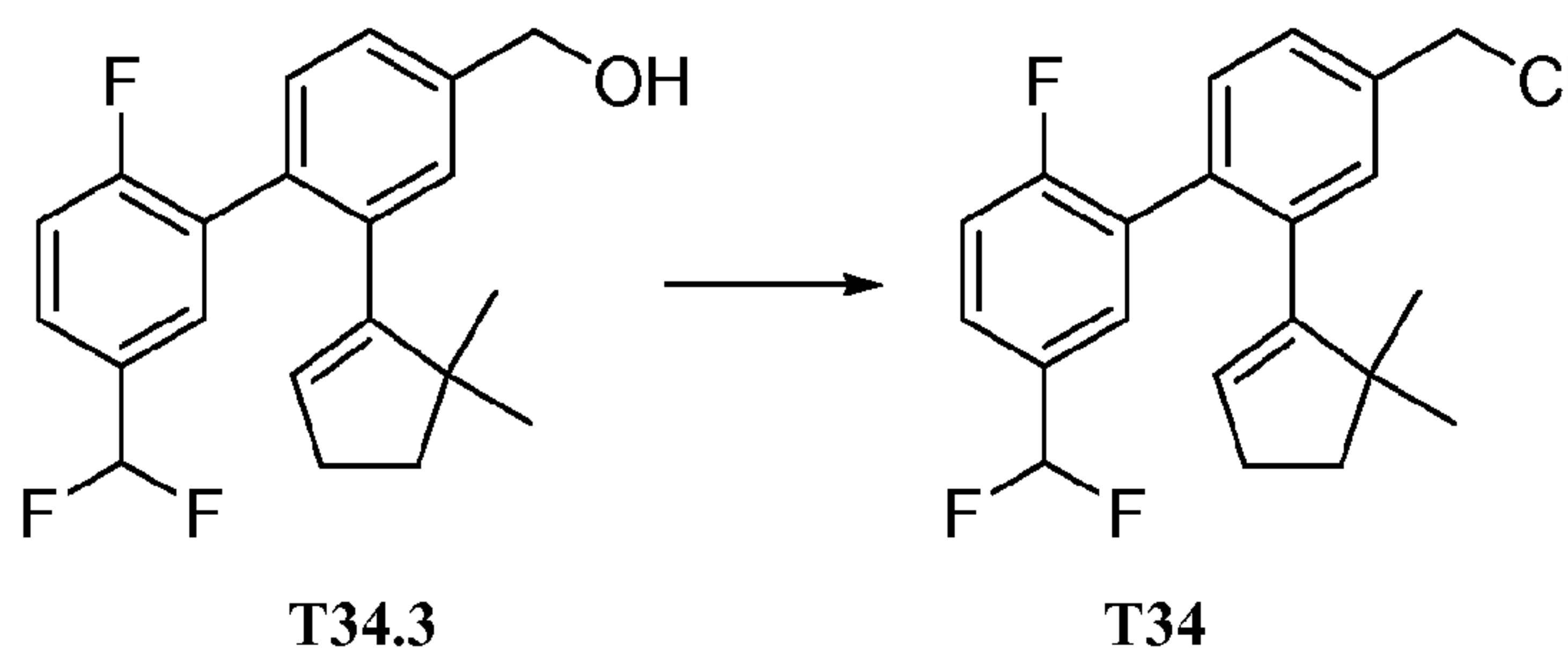


[0535] Methyl 5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-carboxylate (T34.2). To a stirred solution of **T3.5** (1.1209 g, 2.962 mmol) in dry DMF (10 mL) at 23°C was added potassium carbonate (1.2262 g, 8.872 mmol) and then tetrakis(triphenylphosphine)palladium (0.3408 g, 0.2949 mmol).

The mixture was purged with argon and placed under vacuum and the purging and vacuum process repeated three times. Before heating, **T34.1** (1.6019 g, 5.888 mmol) was added via syringe and then the mixture was heated to 90 °C. After 19 hours, LC-MS showed that the reaction was complete. The mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to afford **T34.2** as a clear oil (994.4 mg, 90% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.00 (1 H, dd, J=8.0, 1.8 Hz), 7.94 (1 H, d, J=1.6 Hz), 7.50 (3 H, m), 7.16 (1 H, t, J=9.0 Hz), 6.63 (1H, t), 5.53 (1 H, s), 3.96 (3 H, s), 2.25 (2 H, td, J=7.0, 2.3 Hz), 1.65 (2 H, t, J=7.0 Hz), 0.85 (6 H, s).

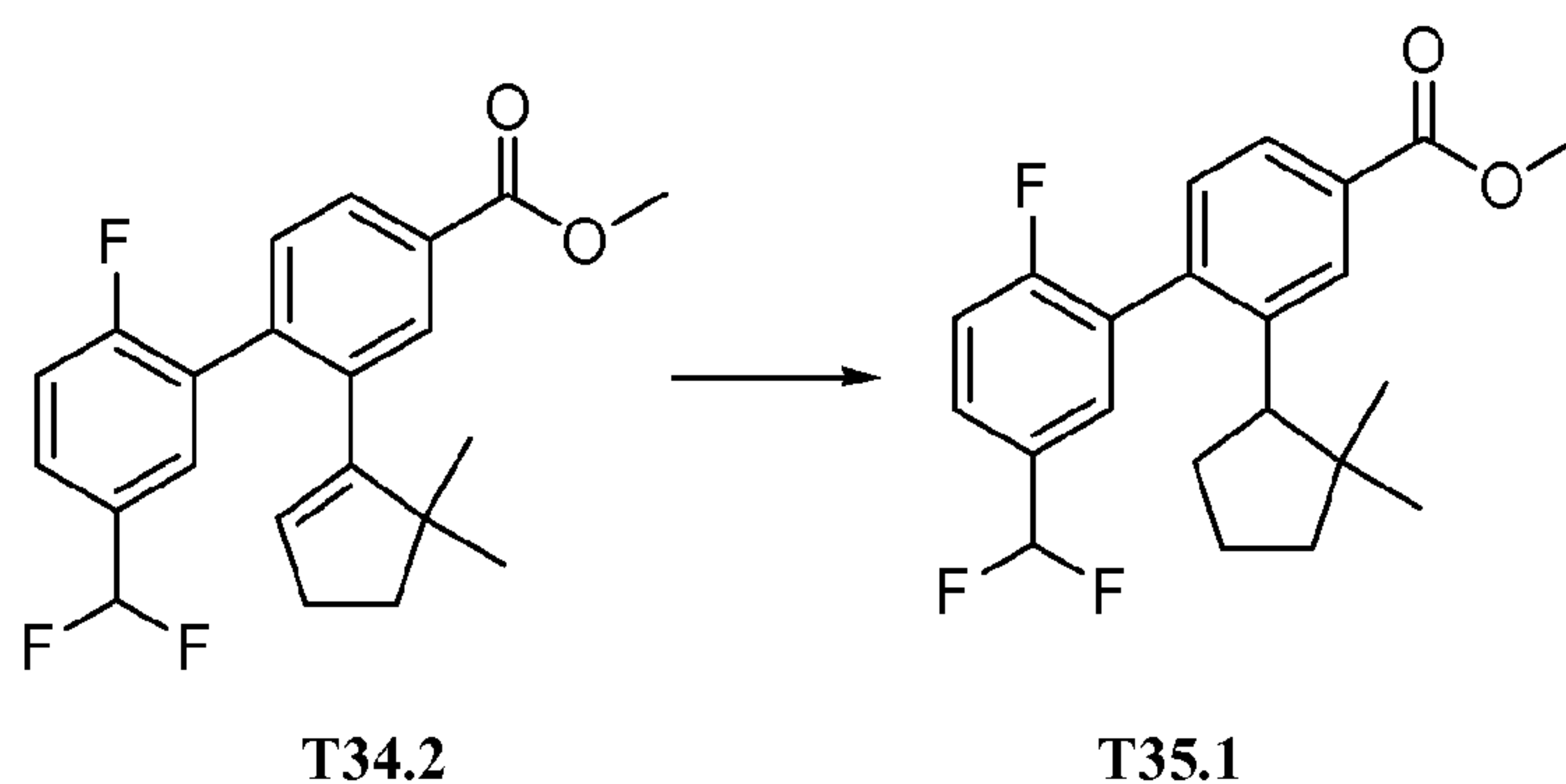


[0536] (5'-(Difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (T34.3). To a cooled solution of **T34.2** (0.2349 g, 0.6274 mmol) in dry THF (5 mL) at 0 °C was added LAH (1.0 M in THF)(1.3 mL, 1.3 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to a colorless oil as **T34.3** (166.6 mg, 77% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.47 (2 H, m), 7.38 (2 H, m), 7.14 (1 H, t, J=9.0 Hz), 6.62 (1H, t), 5.50 (1 H, td, J=2.4, 1.0 Hz), 4.76 (2 H, s), 2.23 (2 H, td, J=7.0, 2.3 Hz), 1.74 (3 H, m), 0.85 (6 H, s).

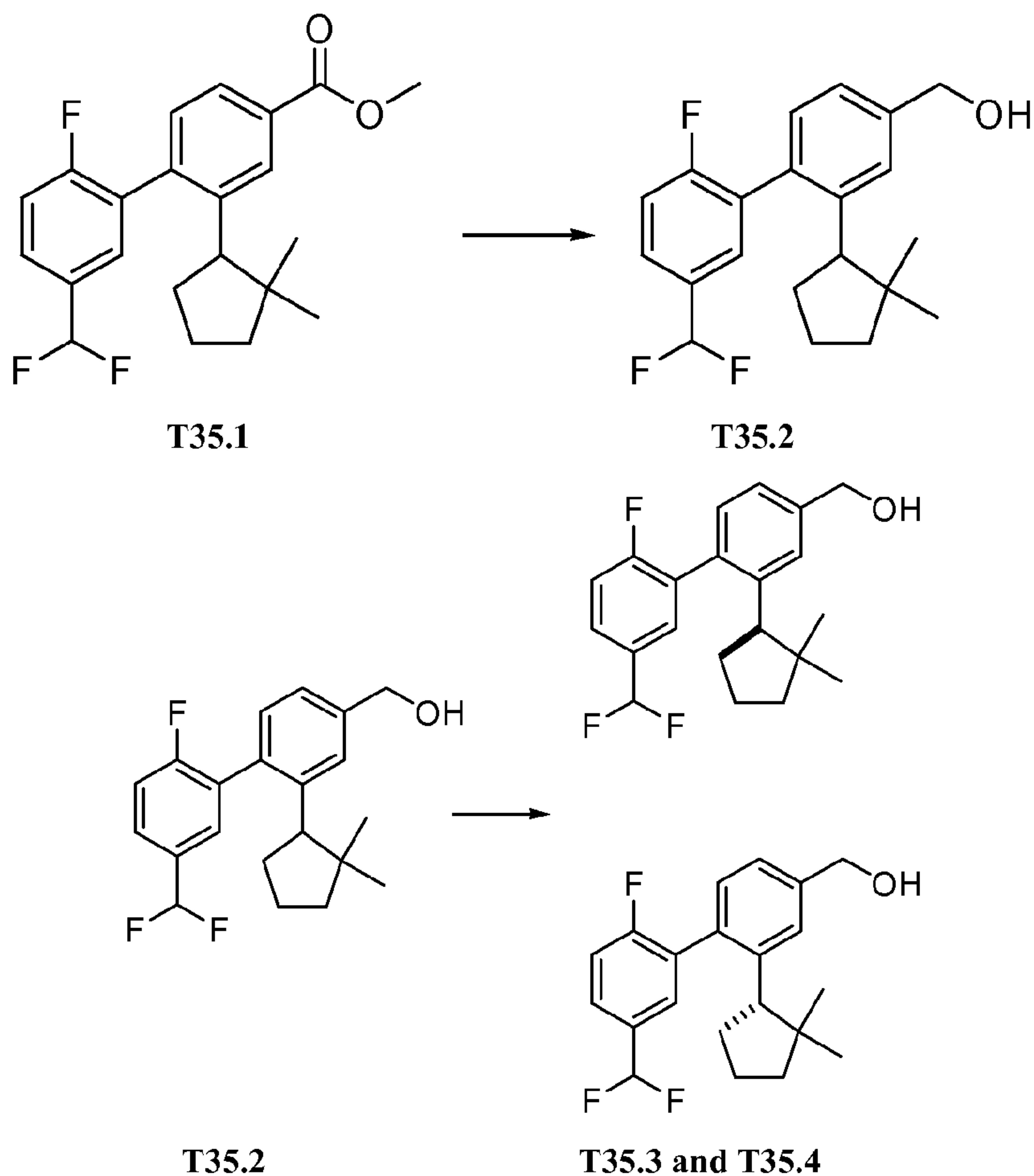


[0537] 4-(Chloromethyl)-5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl (T34). To a solution of **T34.3** (0.1666 g, 0.481 mmol) in dry DCM (3 mL) and dry DMF (0.06 mL) was added thionyl chloride (0.07 mL, 0.96 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T34** (172.1 mg, 98% yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.46 (2 H, m), 7.39 (1 H, m), 7.33 (1 H, m), 7.28 (1 H, d, J=1.7 Hz), 7.17 (1 H, m), 6.62 (1H, t), 5.51 (1 H, td, J=2.3, 1.0 Hz), 4.64 (2 H, s), 2.24 (2 H, td, J=7.1, 2.4 Hz), 1.68 (2 H, m), 0.85 (6 H, s).

[0538] Intermediates T35A and T35B

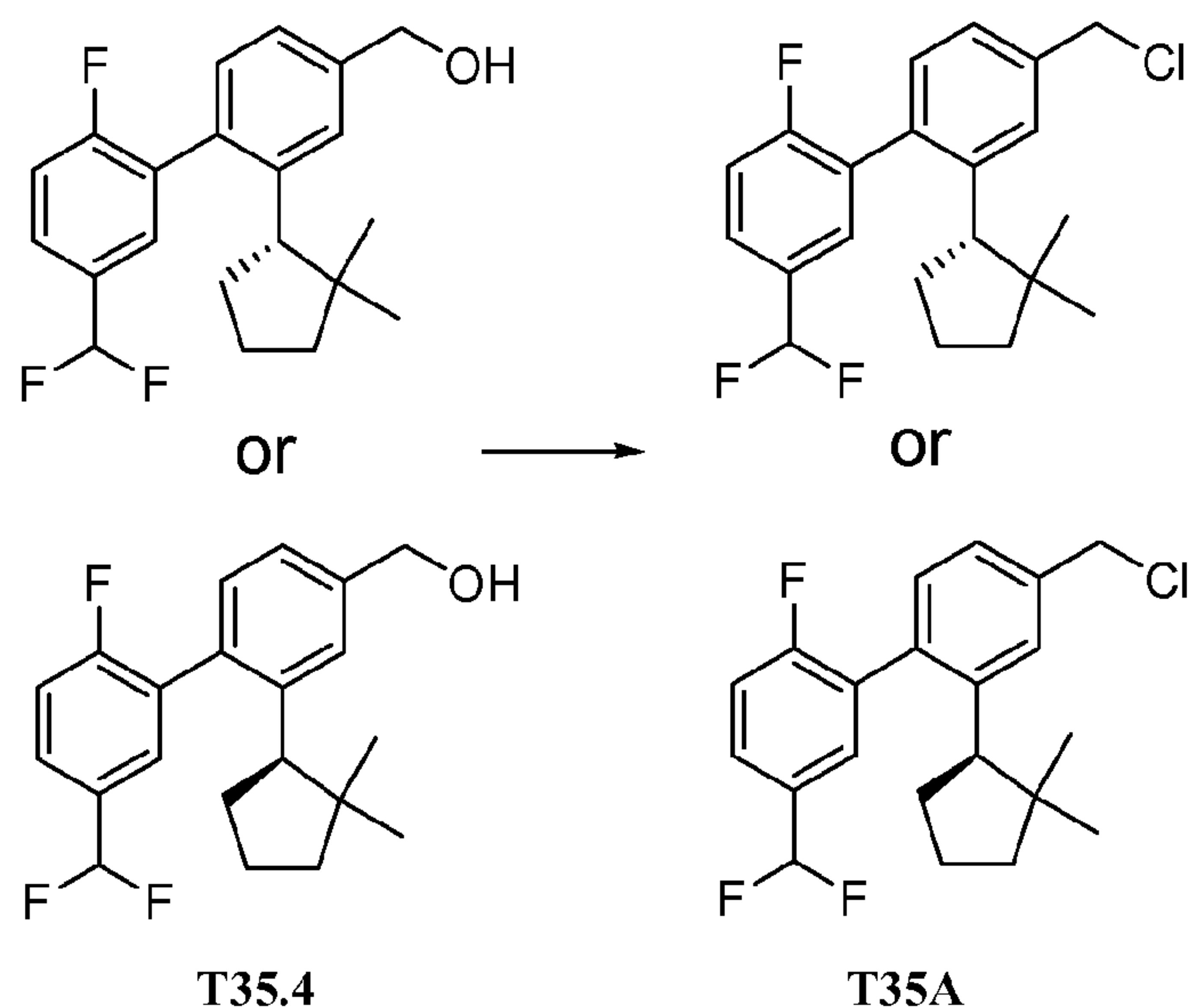


[0539] Methyl 5'-(difluoromethyl)-2-(2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-carboxylate (T35.1). To a dry flask containing **T34.2** (0.8621 g, 2.303 mmol) in dry MeOH (10 mL) and EtOAc (2 mL) was added palladium (10% wt. on activated carbon)(0.2455 g, 0.2307 mmol). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. The reaction was monitored with TLC and LC-MS. After 22.5 hours, the reaction was filtered through Celite® filter aid. After concentration, the residue was identified as **T35.1** and was used without purification (863 mg, 99% yield). MS ESI (pos.) m/e: 376.9 (M+H)⁺.



[0540] (5'-(Difluoromethyl)-2-(2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (T35.2). To a cooled solution of **T35.1** (0.8631 g, 2.293 mmol) in dry THF (15.4 mL) at 0 °C was added LAH (1.0 M in THF)(4.6 mL, 4.6 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-100% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to a colorless oil as **T35.2** (617.1 mg, 77% yield). MS ESI (pos.) m/e: 331.0 (M-H₂O)⁺. Chiral separation of **T35.2** was accomplished on a CHIRALCEL® OD column (4% IPA in hexane) to provide **T35.3** (peak 1) and **T35.4** (peak 2). Both

enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.

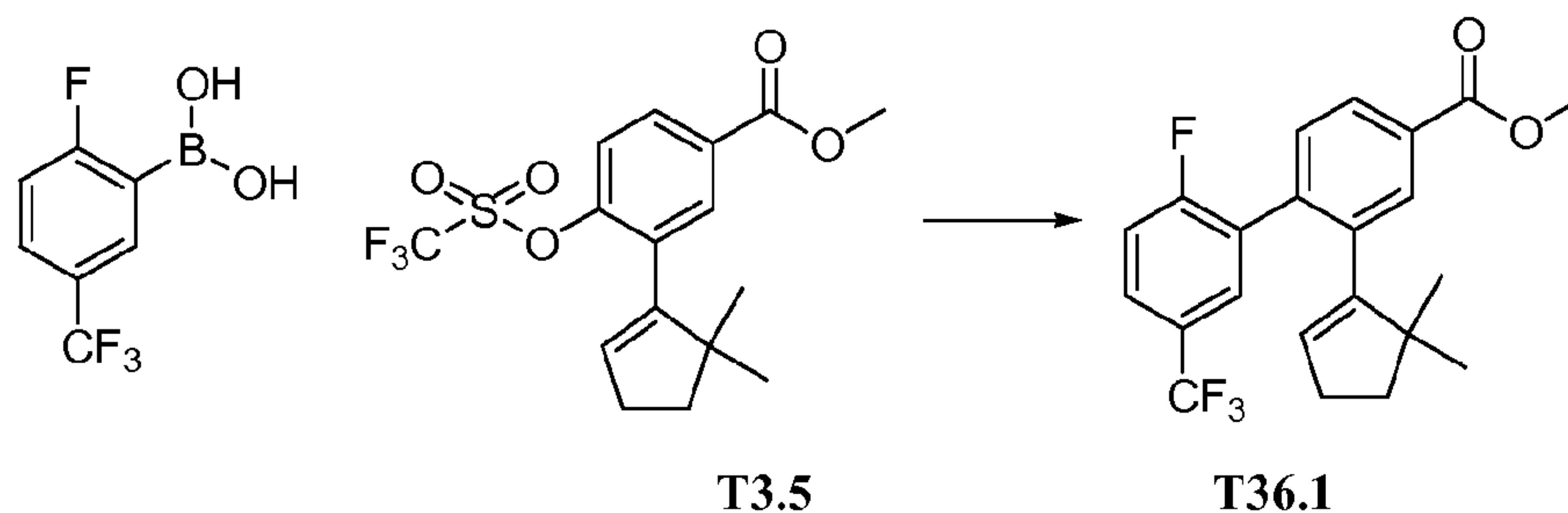


[0541] 4-(Chloromethyl)-5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl (T35A).

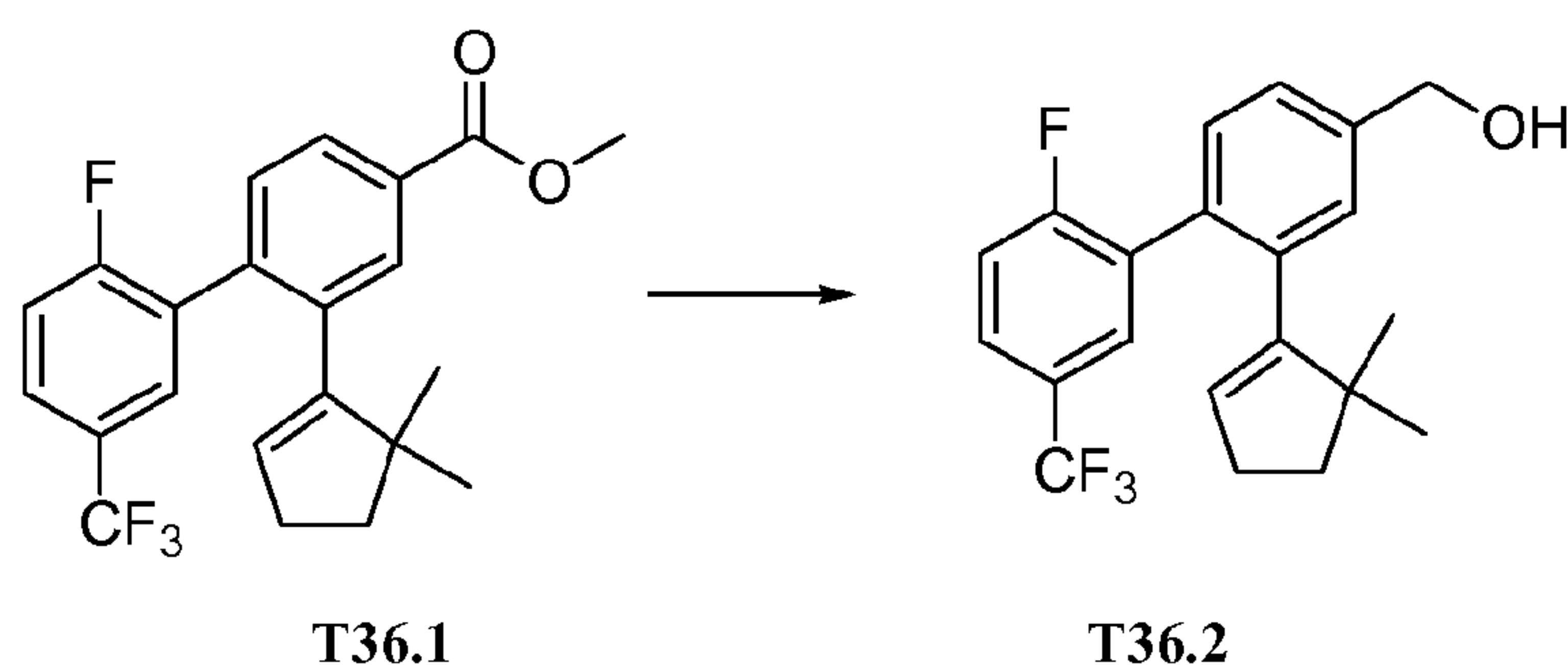
To a solution of **T35.4** (0.2882 g, 0.827 mmol) in dry DCM (10.5 mL) and dry DMF (0.08 mL) was added thionyl chloride (0.12 mL, 1.65 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T35A**. (272.1 mg, 90% yield).

[0542] 4-(Chloromethyl)-5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl (T35B).

To a solution of **T35.3** (0.2798 g, 0.803 mmol) in dry DCM (10 mL) and dry DMF (0.076 mL) was added thionyl chloride (0.12 mL, 1.65 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **T35B** (282.5 mg, 96% yield).

[0543] Intermediate T36

[0544] Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-carboxylate (T36.1). To a stirred solution of T3.5 (0.7595 g, 2.007 mmol) in DMF (5 mL) at 23 °C was added 2-fluoro-5-(trifluoromethyl)phenylboronic acid (commercially available from Sigma-Aldrich, St. Louis, MO, USA) (0.8352 g, 4.017 mmol) and potassium carbonate (0.8357 g, 6.047 mmol) followed by tetrakis(triphenylphosphine)palladium (0.2364 g, 0.2046 mmol). The mixture was heated to 90°C. After 17 hours, LCMS-showed that the reaction was complete. The mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to afford T36.1 as a clear oil that was used without further purification (414.2 mg, 53% yield).



[0545] (2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-yl)methanol (T36.2). To a cooled solution of T36.1 (0.4142 g, 1.056 mmol) in dry THF (7.8 mL) at 0 °C was added LAH (1.0 M in THF)(2.2 mL, 2.200 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-100% EtOAc

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

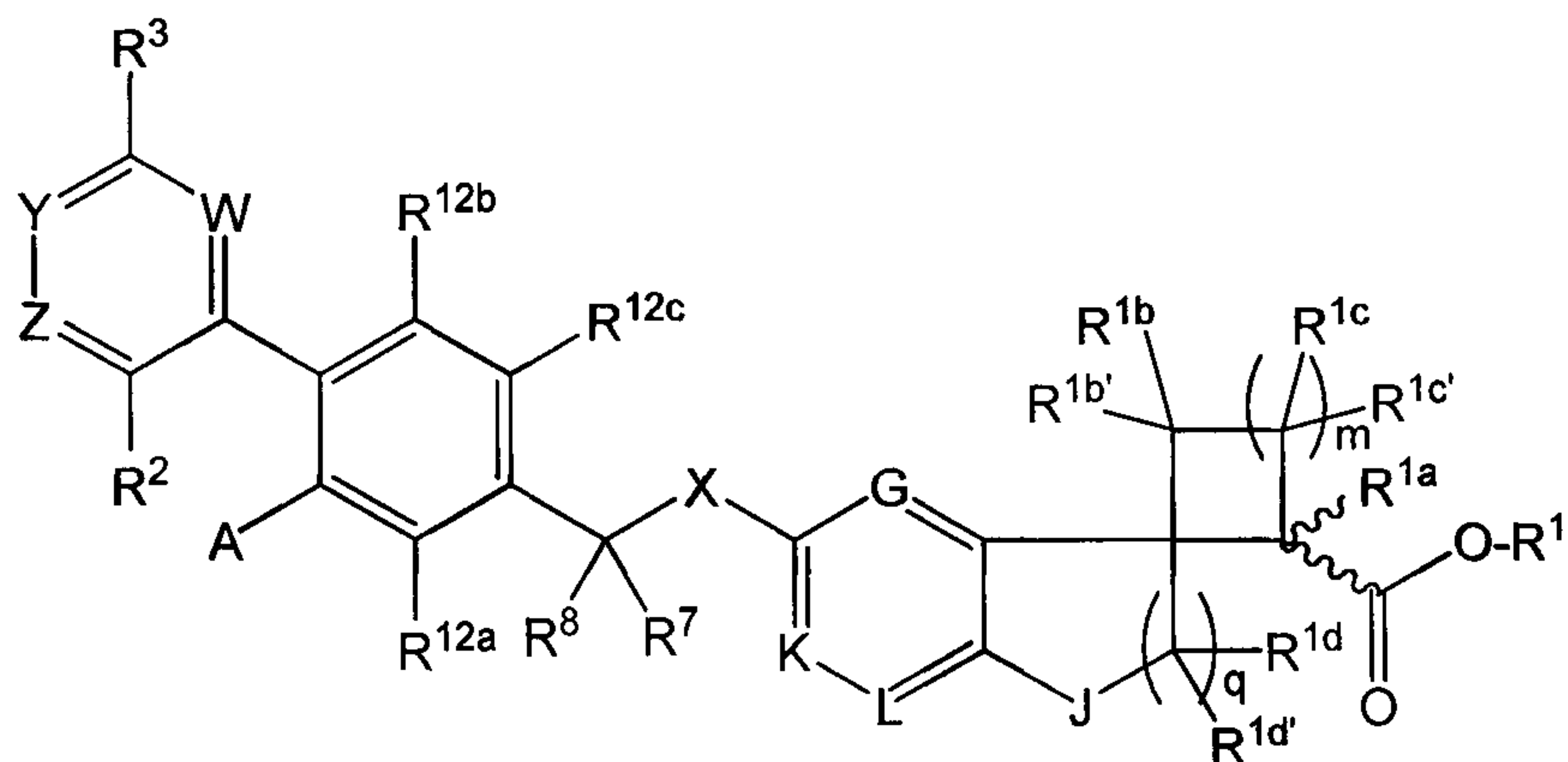
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

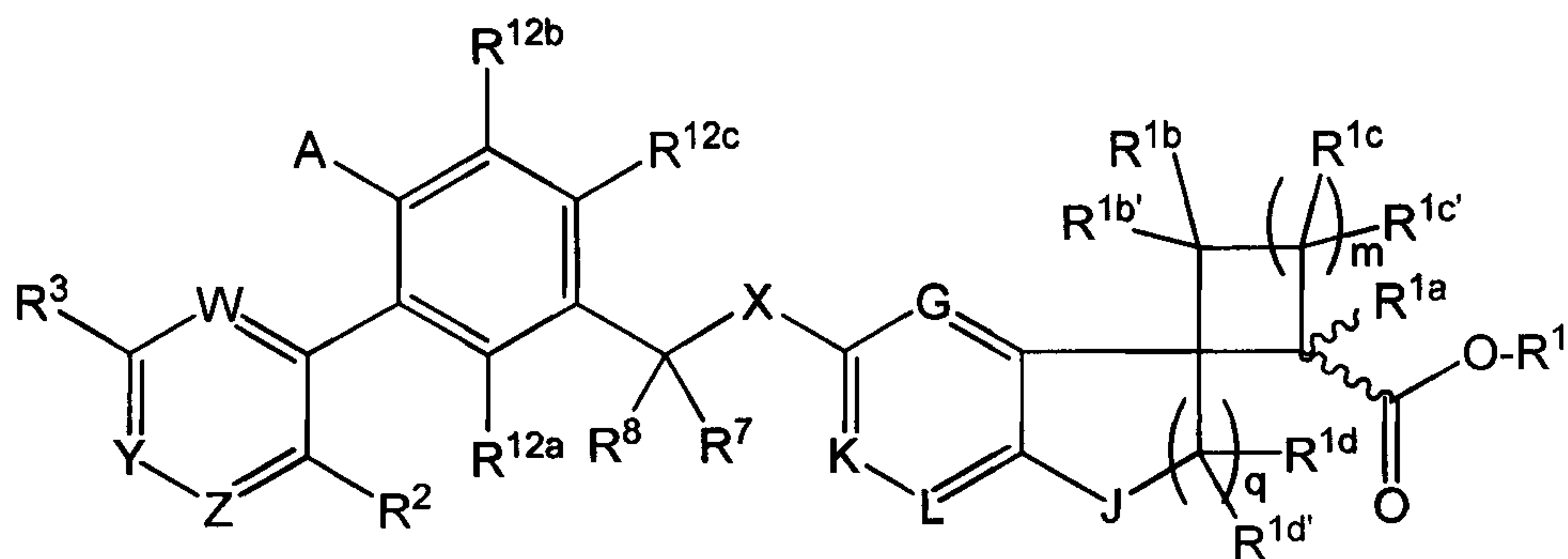
NOTE: For additional volumes please contact the Canadian Patent Office.

WHAT IS CLAIMED:

1. A compound of formula I'A or I'B:



I'A



I'B

or a pharmaceutically acceptable salt, stereoisomer, or a mixture thereof,

wherein

G is selected from N or CR^{11a};

K is selected from N or CR^{11b};

L is selected from N or CR^{11c};

wherein 0 or 1 of G, L, and K is N;

X is O;

J is CR^cR^d;

wherein R^c and R^d are both H;

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N; and further wherein Z is not N if R² is -F; and A and W, when W is C, may join together to form a ring having 5 to 7 ring members of which 0 or 1 is a heteroatom selected from N, O, or S, and further wherein the ring

having 5 to 7 ring members is optionally substituted with $-(C_1-C_8)alkyl$, $-(C_1-C_8)alkenyl$, $-OH$, $-O-(C_1-C_8)alkyl$, $-O-(C_1-C_8)alkenyl$, or halo;

A is selected from $-H$, $-(C_1-C_{12})alkyl$; $-(C_2-C_{12})alkenyl$; $-(C_1-C_{12})alkyl-O-(C_1-C_4)alkyl$; $-(C_1-C_{12})alkyl-OH$; $-(C_1-C_{12})alkyl-O-(C_2-C_4)alkenyl$; $-(C_2-C_{12})alkenyl-O-(C_1-C_4)alkyl$; $-(C_2-C_{12})alkenyl-OH$; $-(C_2-C_{12})alkenyl-O-(C_2-C_4)alkenyl$; $-O-(C_1-C_{12})alkyl$; $-O-(C_2-C_{12})alkenyl$; $-O-(C_1-C_4)alkyl-aryl$; $-S-(C_1-C_{12})alkyl$; $-S-(C_2-C_{12})alkenyl$; $-S(O)-(C_1-C_{12})alkyl$; $-S(O)-(C_2-C_{12})alkenyl$; $-S(O)_2-(C_1-C_{12})alkyl$; $-S(O)_2-(C_2-C_{12})alkenyl$; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)alkyl$ groups; a $-(C_1-C_4)alkyl-heterocyclyl$ wherein the heterocyclyl of the $-(C_1-C_4)alkyl-heterocyclyl$ comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)alkyl$ groups; or a $-O-heterocyclyl$ wherein the heterocyclyl of the $-O-heterocyclyl$ comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)alkyl$ groups; further wherein the alkyl and alkenyl groups of $-(C_1-C_{12})alkyl$, $-(C_2-C_{12})alkenyl$, $-(C_1-C_{12})alkyl-O-(C_1-C_4)alkyl$, $-(C_1-C_{12})alkyl-O-H$, $-(C_1-C_{12})alkyl-O-(C_2-C_4)alkenyl$, $-(C_2-C_{12})alkenyl-O-(C_1-C_4)alkyl$, $-(C_2-C_{12})alkenyl-OH$, $-(C_2-C_{12})alkenyl-O-(C_2-C_4)alkenyl$, $-O-(C_1-C_{12})alkyl$, $-O-(C_2-C_{12})alkenyl$, and $-O-(C_1-C_4)alkyl-aryl$ are unsubstituted or are substituted with from 1 to 4 substituents selected from $-F$, $-Cl$, $-OH$, $(=O)$, $-NH_2$, $NH(C_1-C_4)alkyl$, $-N((C_1-C_4)alkyl)_2$, aryl, unsubstituted $-(C_1-C_2)alkyl$, or unsubstituted $-O-(C_1-C_2)alkyl$;

R^1 is H or $-(C_1-C_6)alkyl$;

R^{1a} is selected from $-H$ and $-(C_1-C_4)alkyl$;

R^{1b} is selected from $-H$ and $-(C_1-C_4)alkyl$;

$R^{1b'}$ is selected from $-H$ and $-(C_1-C_4)alkyl$;

R^{1c} is selected from $-H$ and $-(C_1-C_4)alkyl$;

$R^{1c'}$ is selected from $-H$ and $-(C_1-C_4)alkyl$;

R^{1d} is in each instance independently selected from $-H$, $-F$, and $-(C_1-C_4)alkyl$;

$R^{1d'}$ is in each instance independently selected from $-H$, $-F$ and $-(C_1-C_4)alkyl$;

R^2 is selected from $-H$, $-F$, $-CF_3$, $-Cl$, or $-O-(C_1-C_6)alkyl$;

R^3 is $-H$, $-F$, $-Cl$, $-OH$, $-(C_1-C_4)alkyl$, $-O-(C_1-C_3)alkyl$, or $-S-(C_1-C_2)alkyl$;

R^7 and R^8 are independently selected from $-H$ and $-(C_1-C_4)alkyl$;

R^{11a} , R^{11b} , and R^{11c} are independently selected from $-H$, $-F$, $-Cl$, $-(C_1-C_4)alkyl$, or $-O(C_1-C_4)alkyl$;

R^{12a} , R^{12b} , and R^{12c} are independently selected from $-H$, $-F$, $-Cl$, $-(C_1-C_4)alkyl$, or $-O(C_1-C_4)alkyl$;

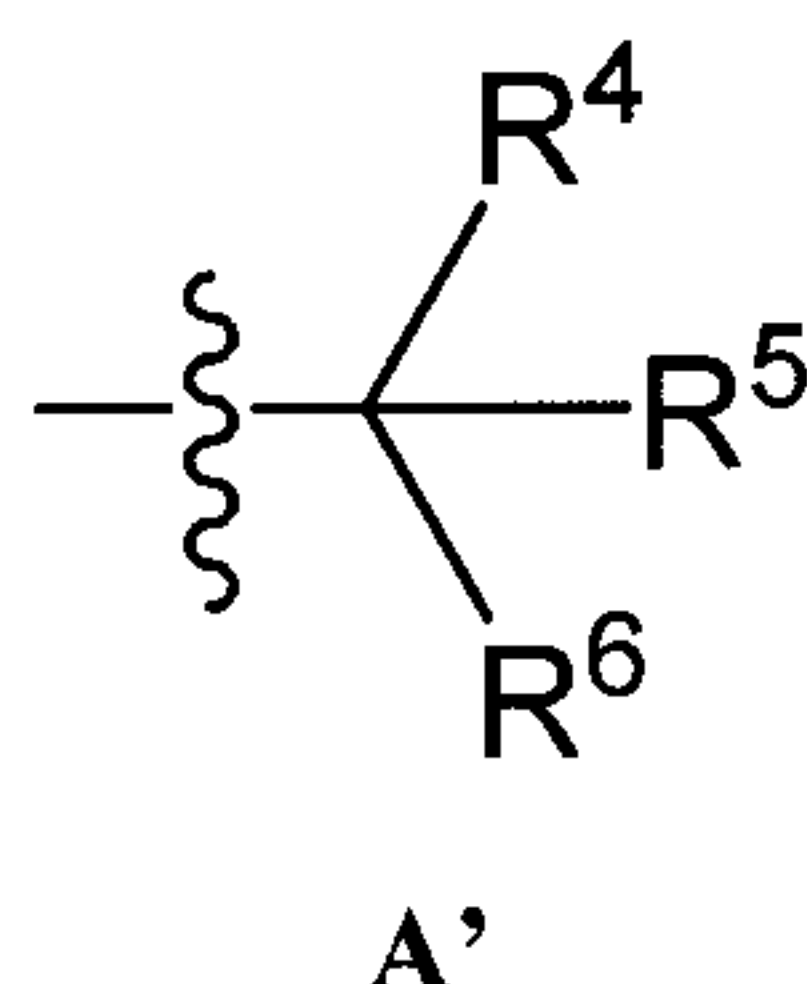
R^{13} is selected from $-H$, $-F$, $-(C_1-C_4)alkyl$, and $-O-(C_1-C_4)alkyl$;

m is 0 or 1; and

q is selected from 0, 1, 2, or 3,

wherein the $\sim$ indicates that the R^{1a} and $-C(=O)-O-R^1$ may be attached to either side of the ring to which the $\sim$ is attached and either R or S stereochemistry is allowed.

2. The compound of Claim 1, wherein R^3 is selected from -OH, $-O(C_1-C_2)\text{alkyl}$, or $-S(C_1-C_2)\text{alkyl}$.
3. The compound of Claim 2, wherein R^3 is methoxy.
4. The compound of any one of Claims 1-3, wherein A is selected from $(C_3-C_{10})\text{alkyl}$ or $(C_4-C_{10})\text{alkenyl}$.
5. The compound of any one of Claims 1-3, wherein A is a group of formula A'



where the wavy line indicates the point of attachment; and

R^4 , R^5 , and R^6 are independently selected from H, F, $(C_1-C_4)\text{alkyl}$, wherein at least two of R^4 , R^5 , and R^6 are other than H; or two or three of R^4 , R^5 , and R^6 join together to form an optionally substituted saturated or partially unsaturated 3-8 membered monocyclic or bicyclic ring.

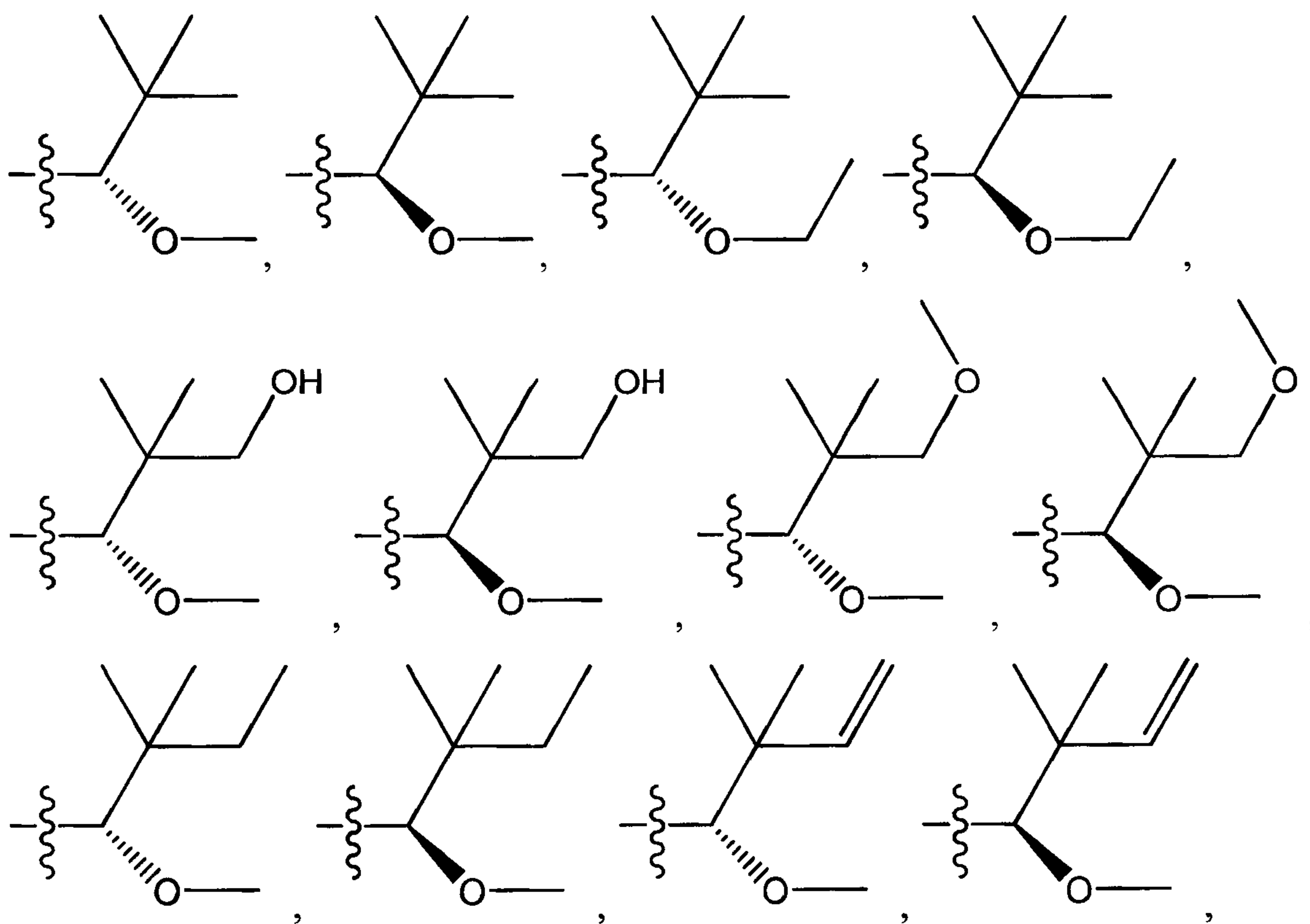
6. The compound of any one of Claims 1-3, wherein A is selected from $-(C_4-C_{12})\text{alkyl}$, $-(C_4-C_{12})\text{alkenyl}$, $-(C_3-C_{12})\text{alkyl-O-(C}_1\text{-C}_4\text{)alkyl}$, $-(C_3-C_{12})\text{alkyl-OH}$, $-(C_3-C_{12})\text{alkenyl-O-(C}_1\text{-C}_4\text{)alkyl}$, $-(C_3-C_{12})\text{alkenyl-OH}$, $-O-(C_4-C_{12})\text{alkyl}$, $-O-(C_4-C_{12})\text{alkenyl}$, a 4 to 7 membered heterocycle comprising 1 or 2 heteroatoms selected from N or O, wherein the heterocycle comprises 0 or 1 one double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)\text{alkyl}$ groups, a $-(C_1-C_4)\text{alkyl-heterocyclyl}$ wherein the heterocyclyl of the $-(C_1-C_4)\text{alkyl-heterocyclyl}$ is a 4 to 7 membered heterocycle comprising 1 or 2 heteroatoms selected from N or O, wherein the heterocycle comprises 0 or 1 one double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)\text{alkyl}$ groups, or a $-O\text{-heterocyclyl}$ wherein the heterocyclyl of the $-O\text{-heterocyclyl}$ is a 4 to 7 membered heterocycle comprising 1 or 2 heteroatoms selected from N or O, wherein the heterocycle comprises 0 or 1 one double bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-C_2)\text{alkyl}$ groups, further wherein the alkyl and alkenyl groups of $-(C_4-C_{12})\text{alkyl}$, $-(C_4-C_{12})\text{alkenyl}$, $-(C_3-C_{12})\text{alkyl-O-(C}_1\text{-C}_4\text{)alkyl}$, $-(C_3-C_{12})\text{alkyl-O-H}$, $-(C_3-C_{12})\text{alkenyl-O-(C}_1\text{-C}_4\text{)alkyl}$, $-(C_3-$

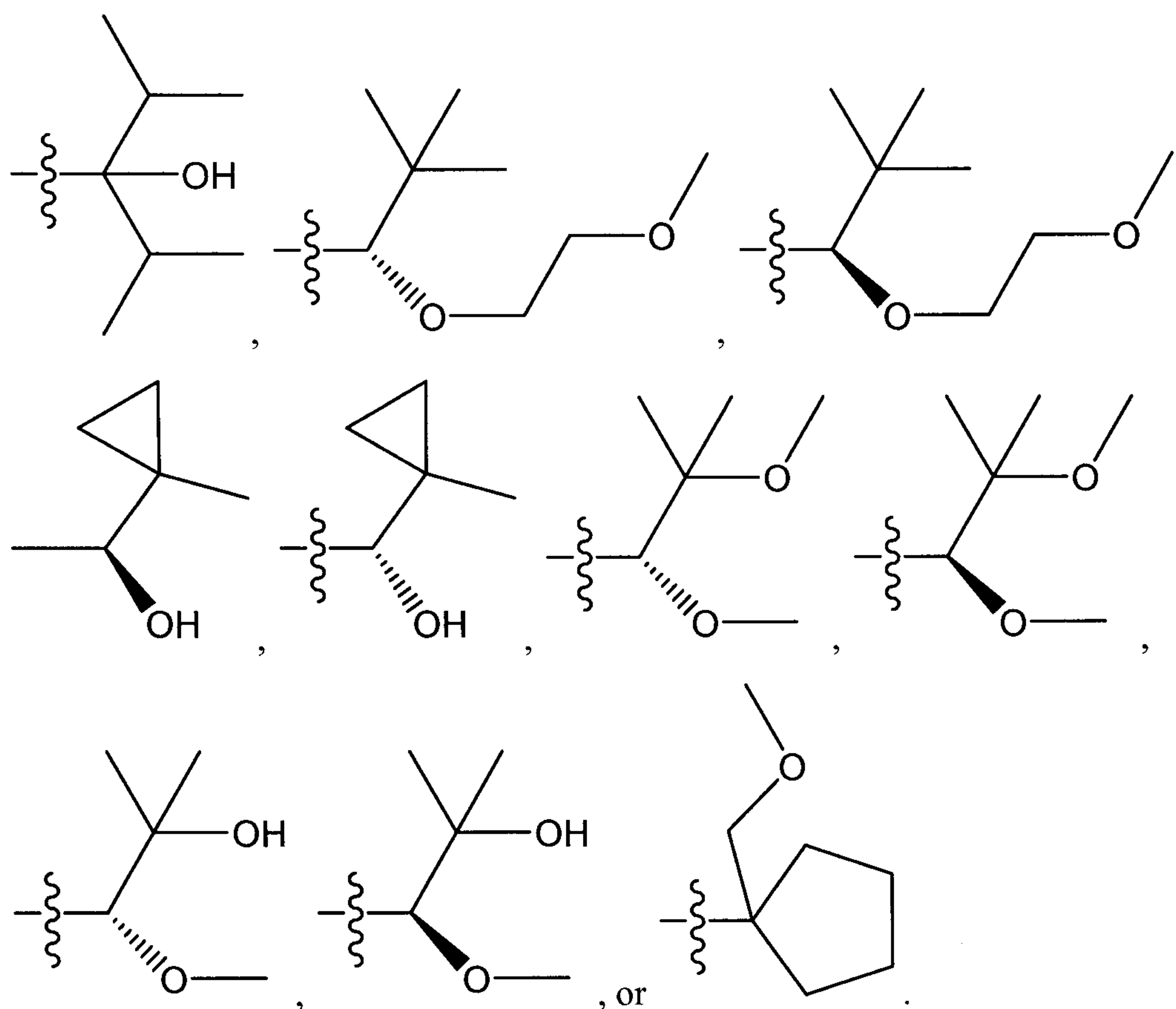
C_{12})alkenyl-OH, -O-(C_4 - C_{12})alkyl, or -O-(C_4 - C_{12})alkenyl are unsubstituted or are substituted with from 1 to 3 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C_1 - C_4)alkyl, -N((C_1 - C_4)alkyl)₂, aryl, or unsubstituted -O-(C_1 - C_2)alkyl.

7. The compound of Claim 6, wherein A is selected from -(C_4 - C_{12})alkyl, -(C_4 - C_{12})alkenyl, -(C_3 - C_{12})alkyl-O-(C_1 - C_4)alkyl, -(C_3 - C_{12})alkyl-OH, -(C_3 - C_{12})alkenyl-O-(C_1 - C_4)alkyl, -(C_3 - C_{12})alkenyl-OH, -O-(C_4 - C_{12})alkyl, or -O-(C_4 - C_{12})alkenyl, wherein the alkyl and alkenyl groups of -(C_4 - C_{12})alkyl, -(C_4 - C_{12})alkenyl, -(C_3 - C_{12})alkyl-O-(C_1 - C_4)alkyl, -(C_3 - C_{12})alkyl-OH, -(C_3 - C_{12})alkenyl-O-(C_1 - C_4)alkyl, -(C_3 - C_{12})alkenyl-OH, -O-(C_4 - C_{12})alkyl, or -O-(C_4 - C_{12})alkenyl are unsubstituted or are substituted with from 1 to 3 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C_1 - C_4)alkyl, -or N((C_1 - C_4)alkyl)₂, or unsubstituted -O-(C_1 - C_2)alkyl.

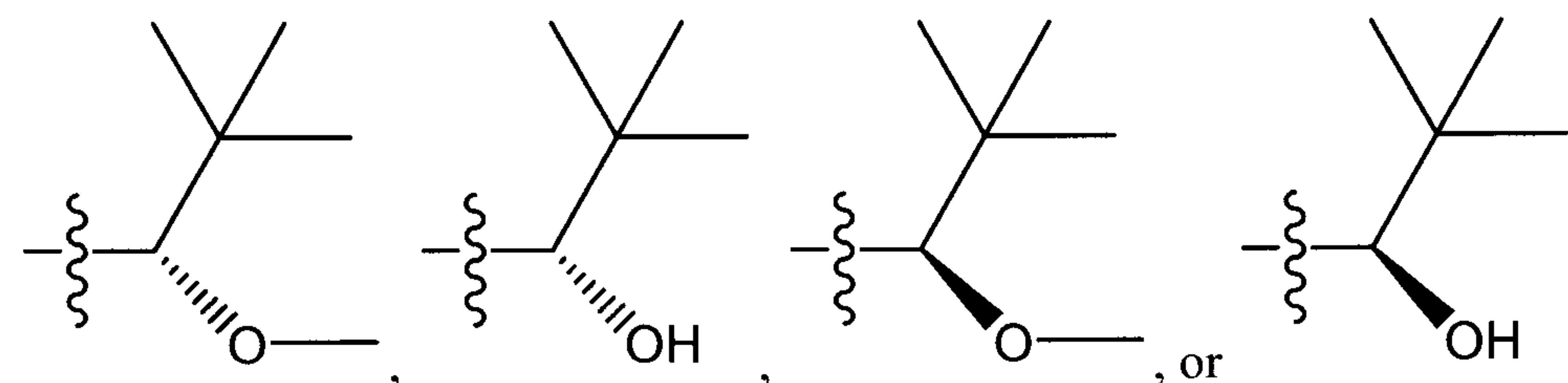
8. The compound of Claim 6, wherein A is a -(C_4 - C_8)alkyl-O-(C_1 - C_2)alkyl, -(C_4 - C_8)alkyl-OH, -(C_4 - C_8)alkenyl-O-(C_1 - C_2)alkyl, or -(C_4 - C_8)alkenyl-OH and each of the alkyl and alkenyl groups of -(C_4 - C_8)alkyl-O-(C_1 - C_2)alkyl, -(C_4 - C_8)alkyl-OH, -(C_4 - C_8)alkenyl-O-(C_1 - C_2)alkyl, or -(C_4 - C_8)alkenyl-OH are unsubstituted or are substituted with 1 substituent selected from -OH or unsubstituted -O-(C_1 - C_2)alkyl.

9. The compound of any one of Claims 1-3, wherein A is selected from



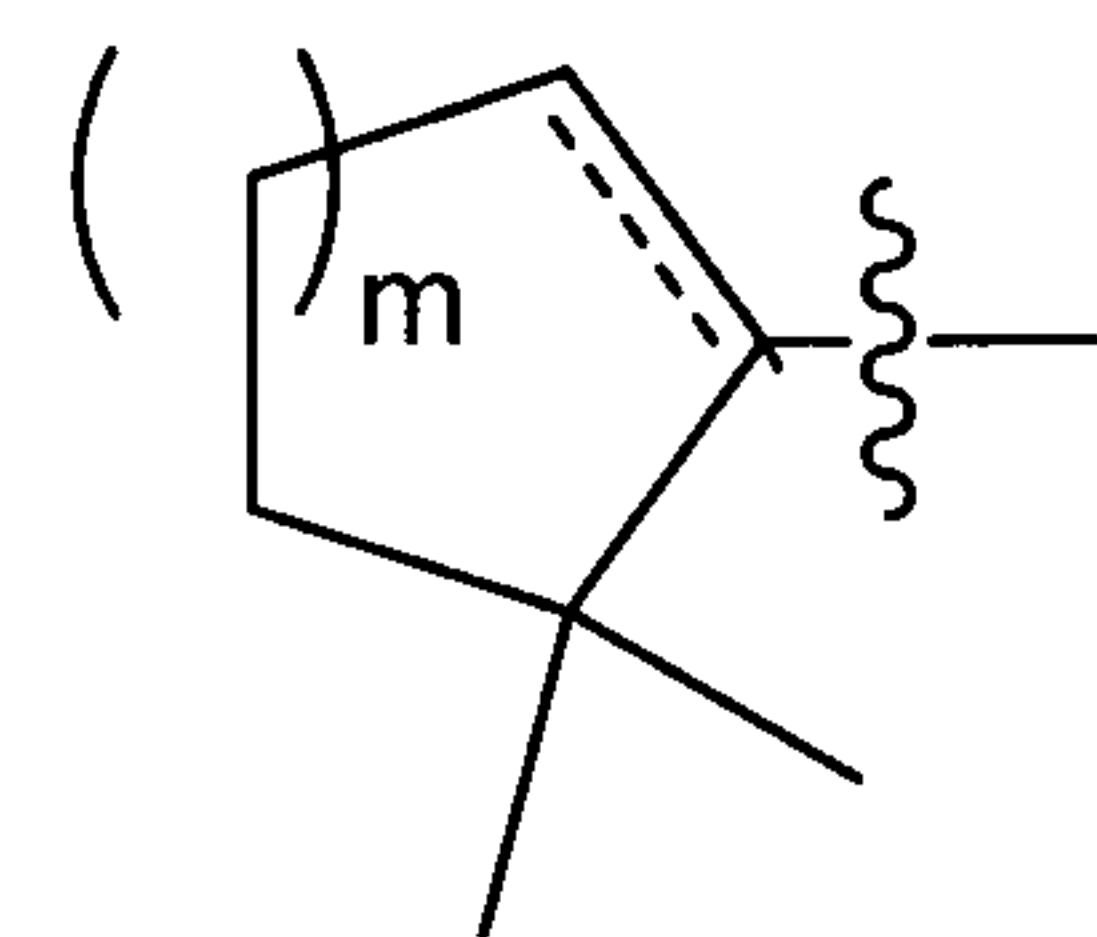


10. The compound of any one of Claims 1-3, wherein A is



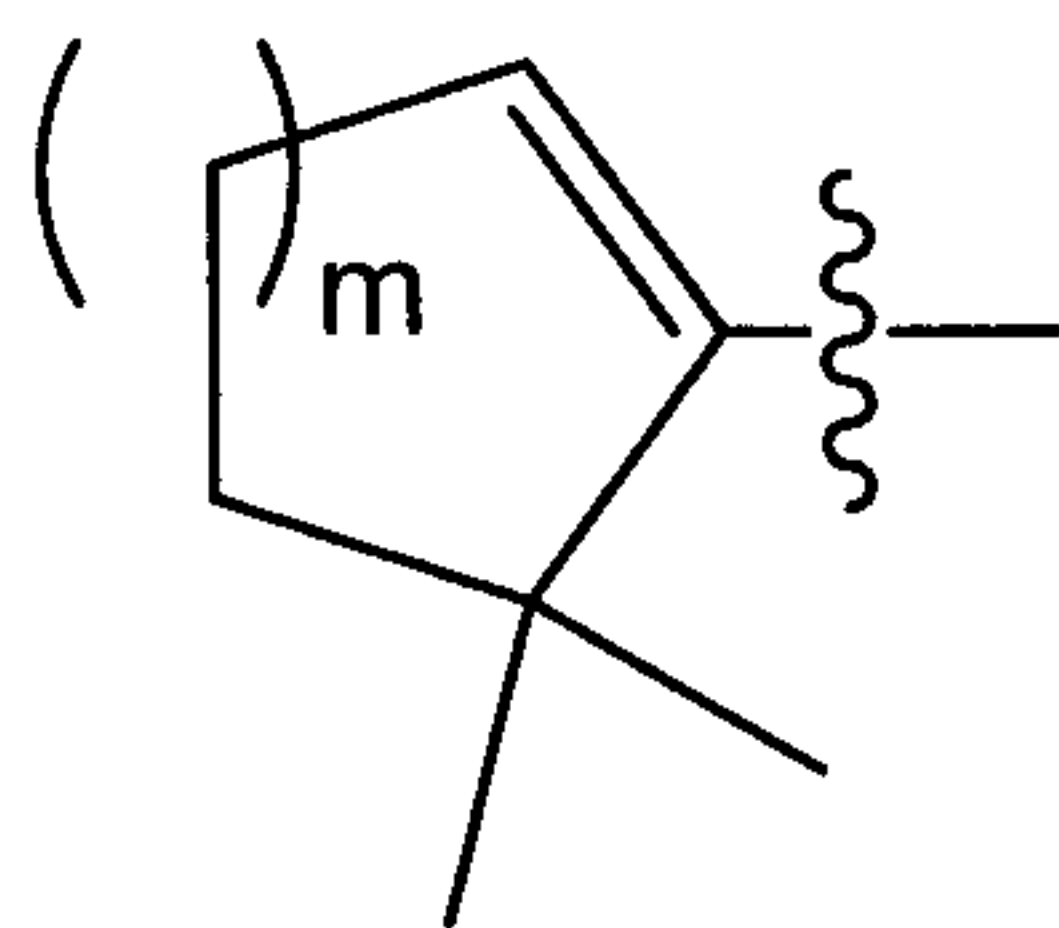
11. The compound of any one of Claims 1-3, wherein A is a (C₅-C₇)cycloalkyl group or a (C₅-C₇)cycloalkenyl group optionally substituted with 1, 2, 3, or 4 methyl groups.

12. The compound of Claim 11, wherein A has the formula



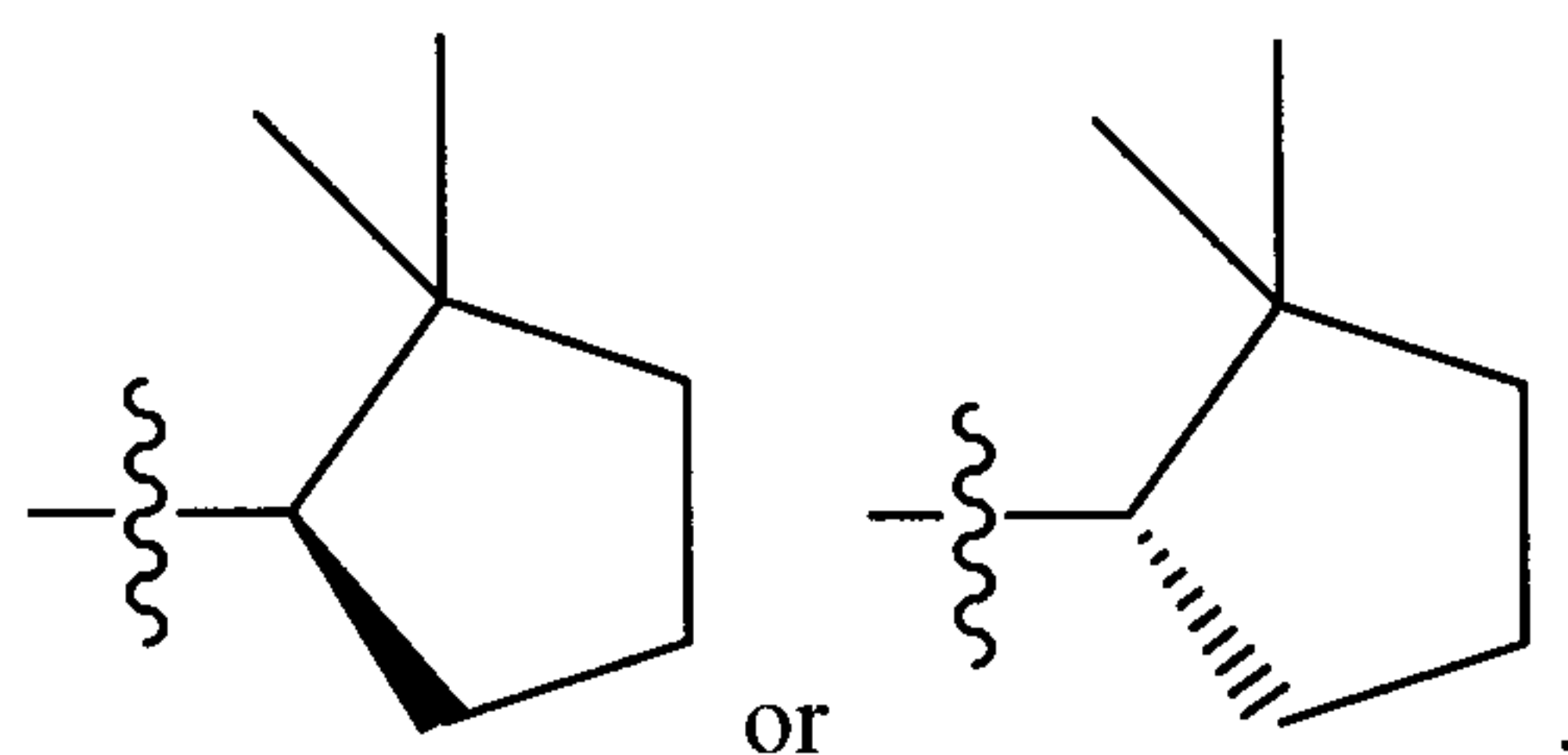
wherein m is 1, 2, or 3, and the dashed line indicates a single or double bond.

13. The compound of Claim 12, wherein A has the formula



wherein m is 1, 2, or 3.

14. The compound of Claim 12, wherein A is selected from



15. The compound of any one of Claims 1-14, wherein R^7 and R^8 are both H.

16. The compound of any one of Claims 1-15, wherein R^{1a} is H or $-CH_3$.

17. The compound of Claim 16, wherein R^{1a} is H.

18. The compound of any one of Claims 1-17, wherein R^{1b} is H or $-CH_3$.

19. The compound of Claim 18, wherein R^{1b} is H.

20. The compound of any one of Claims 1-19, wherein $R^{1b'}$ is H or $-CH_3$.

21. The compound of Claim 20, wherein $R^{1b'}$ is H.

22. The compound of any one of Claims 1-21, wherein R^{1c} , if present, is H or $-CH_3$.

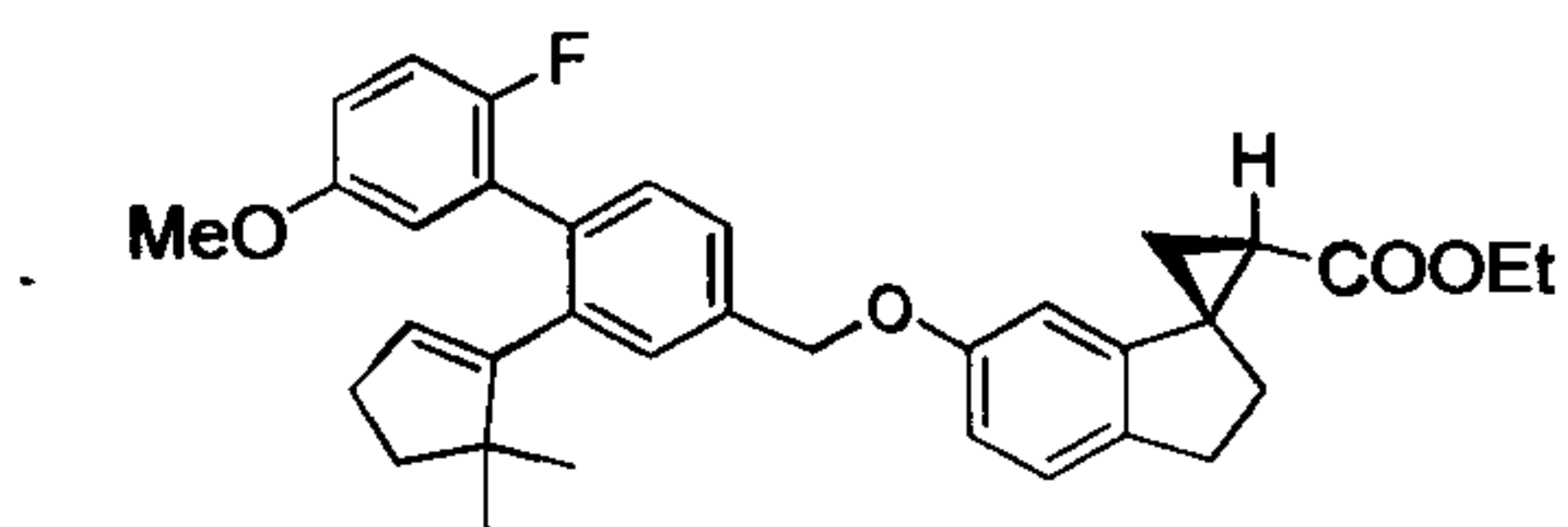
23. The compound of Claim 22, wherein R^{1c} , if present, is H.

24. The compound of any one of Claims 1-23, wherein $R^{1c'}$, if present, is H or $-CH_3$.

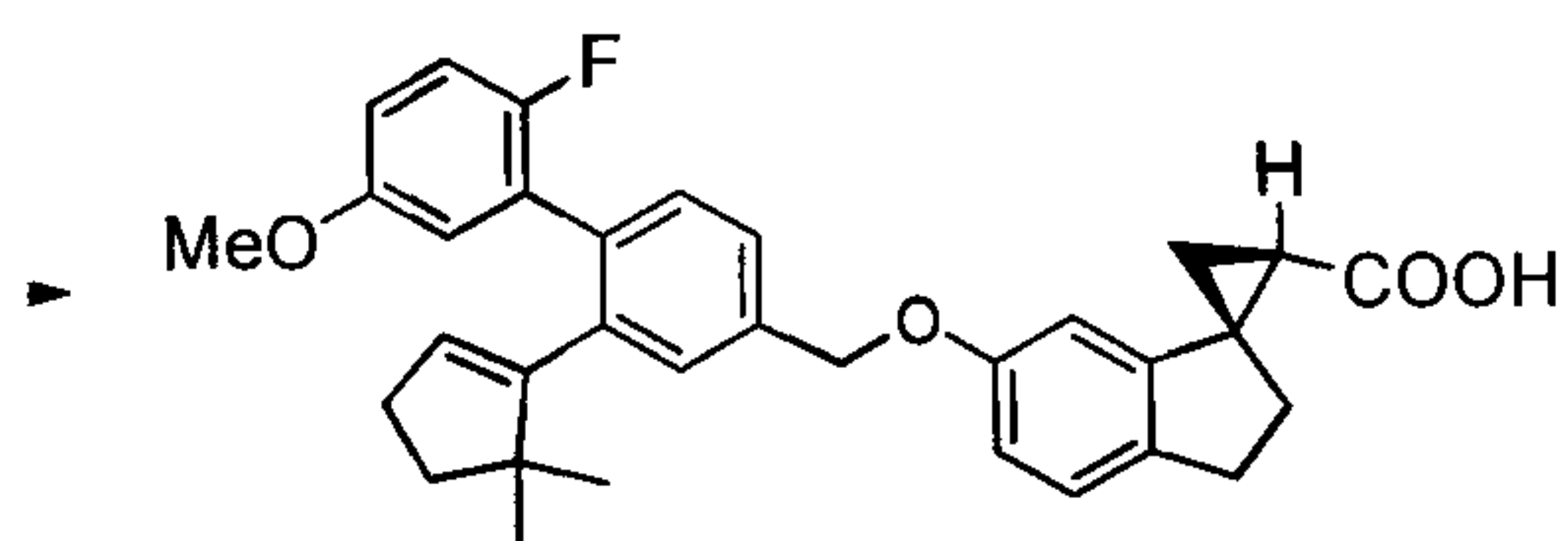
25. The compound of Claim 24, wherein R^{1c} , if present, is H.
26. The compound of any one of Claims 1-25, wherein R^{1d} , if present, is H or $-CH_3$.
27. The compound of Claim 26, wherein R^{1d} , if present is H.
28. The compound of any one of Claims 1-27, wherein $R^{1d'}$, if present, is H or $-CH_3$.
29. The compound of Claim 28, wherein $R^{1d'}$, if present, is H.
30. The compound of any one of Claims 1-29, wherein q is 0, 1, or 2.
31. The compound Claim 30, wherein q is 0.
32. The compound of Claim 30, wherein q is 1.
33. The compound of Claim 30, wherein q is 2.
34. The compound of any one of Claims 1-33, wherein m is 0.
35. The compound of any one of Claims 1-34, wherein the compound has the formula **I'A**.
36. The compound of any one of Claims 1-34, wherein the compound has the formula **I'B**.
37. The compound of any one of Claims 1-36, wherein W, Y, and Z are all C-H.
38. The compound of any one of Claims 1-36, wherein W and Z are C-H and Y is N.
39. The compound of any one of Claims 1-38, wherein R^{12c} is H.
40. The compound of any one of Claims 1-38, wherein R^{12c} is F.
41. The compound of any one of Claims 1-40, wherein R^{12a} and R^{12b} are both H.
42. The compound of any one of Claims 1-41, wherein G is CR^{11a} and R^{11a} is H.
43. The compound of any one of Claims 1-41, wherein G is CR^{11a} and R^{11a} is F.
44. The compound of any one of Claims 1-43, wherein K is CR^{11b} , L is CR^{11c} , and both R^{11b} and R^{11c} are H.

45. The compound of any one of Claims 1-44, wherein R^2 is selected from -H, -F, -CF₃, -or -O-(C₁-C₆)alkyl.
46. The compound of any one of Claims 1-45, wherein R^2 is selected from F, CF₃, or (C₁-C₆)alkoxy.
47. The compound of Claim 46, wherein R^2 is selected from F, CF₃, or (C₄-C₆)alkoxy.
48. The compound of Claim 46, wherein R^2 is F.
49. The compound of Claim 46, wherein R^2 is propoxy, butoxy, or pentoxy.
50. The compound of any one of Claims 1-44, wherein R^2 is -Cl.
51. The compound of Claim 1, wherein G is CR^{11a}; K is CR^{11b}; L is CR^{11c}; R^{11b}, R^{11c}, R^{12a}, and R^{12b} are all H; R^{1a} is H; R^{1b} is H; R^{1b'} is H; R^{1d}, if present, is H; R^{1d'}, if present, is H; W is C-H; Y is C-H or N; Z is C-H; R^2 is F; R³ is methoxy; R⁷ is H; R⁸ is H; m is 0; and q is 0, 1, or 2.
52. The compound of Claim 51, wherein Y is C-H.
53. The compound of Claim 51, wherein Y is N.
54. The compound of any one of Claims 51-53, wherein q is 0.
55. The compound of any one of Claims 51-53, wherein q is 1.
56. The compound of any one of Claims 51-53, wherein q is 2.
57. The compound of any one of Claims 51-56, wherein R^{12c} is H.
58. The compound of any one of Claims 51-56, wherein R^{12c} is F.
59. The compound of any one of Claims 51-58, wherein R^{11a} is H.
60. The compound of any one of Claims 51-58, wherein R^{11a} is F.
61. The compound of any one of Claims 1-60, wherein R¹ is H.
62. The compound of any one of Claims 1-60, wherein the compound is a salt.
63. The compound of any one of Claims 1-60, wherein R¹ is -CH₃ or -CH₂CH₃.

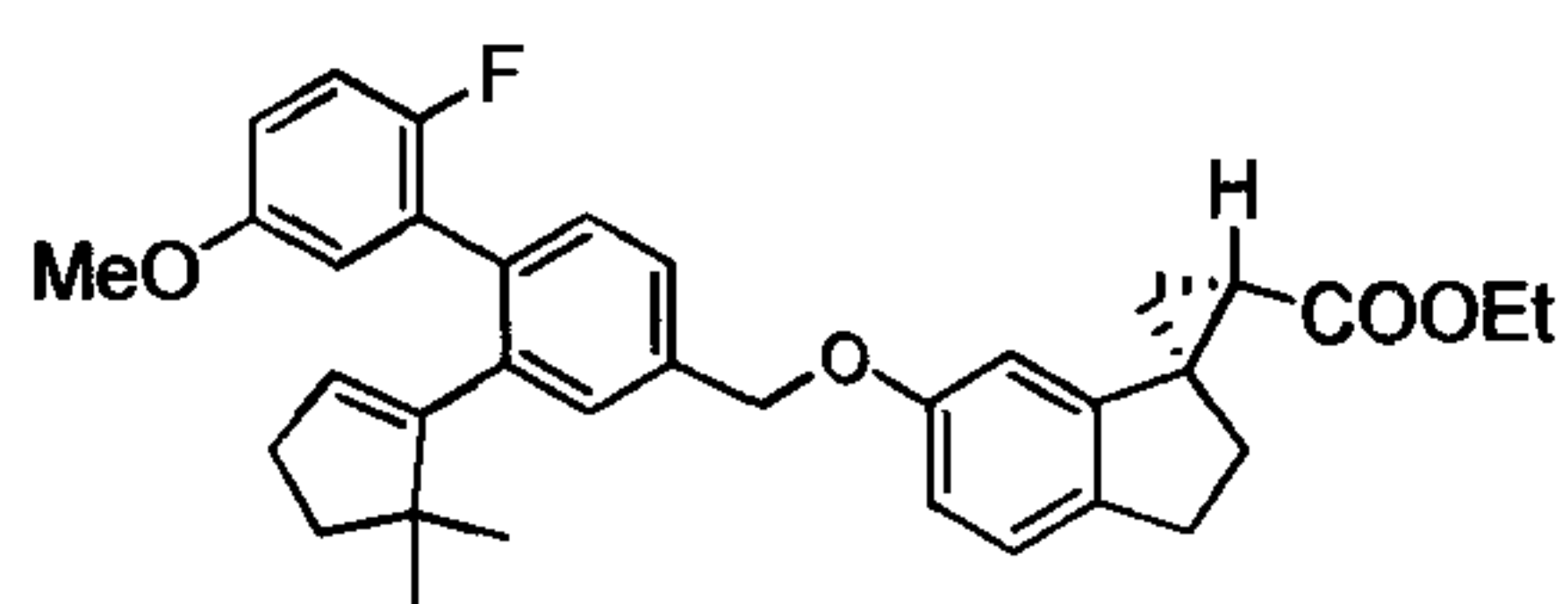
64. The compound



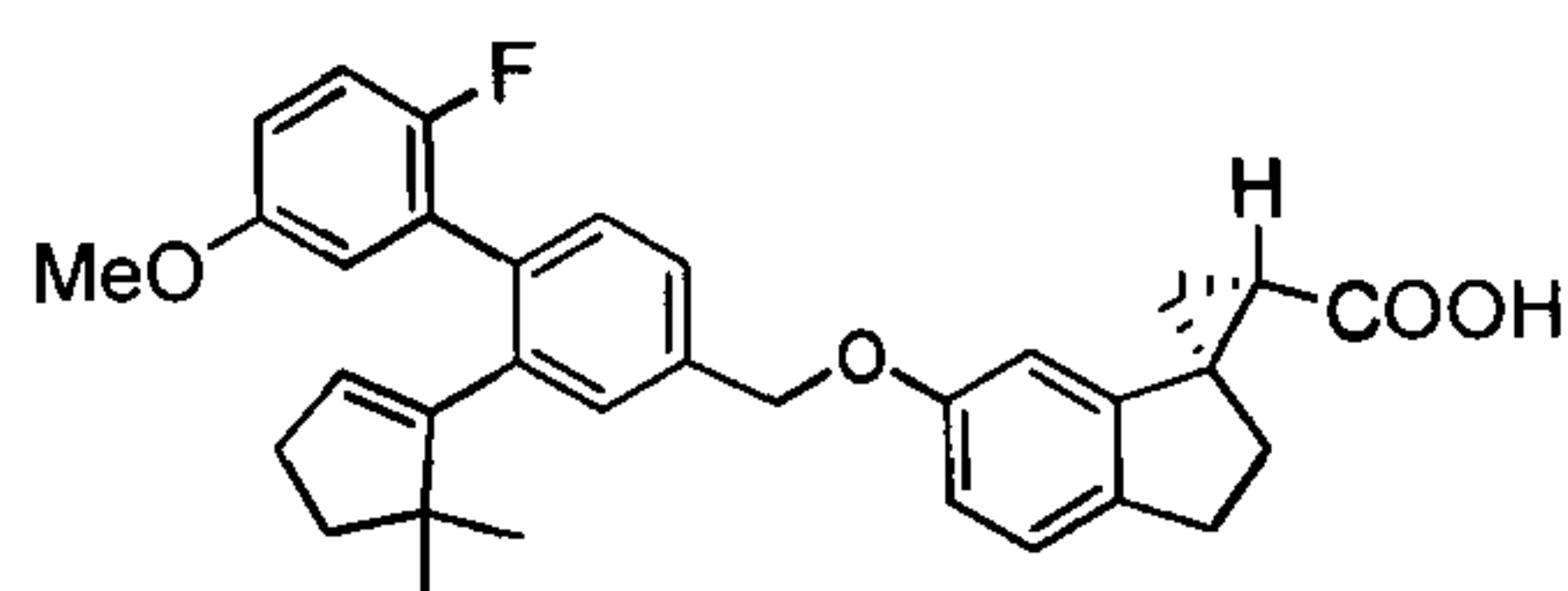
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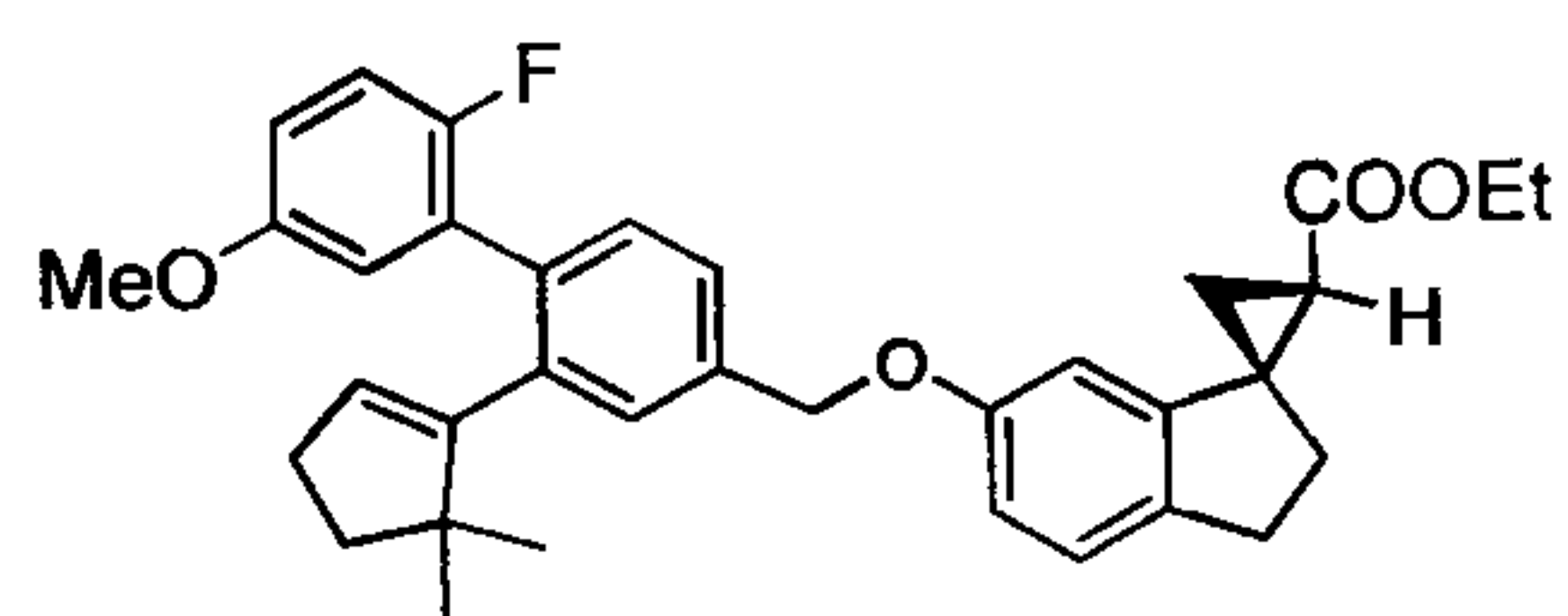
66. The compound



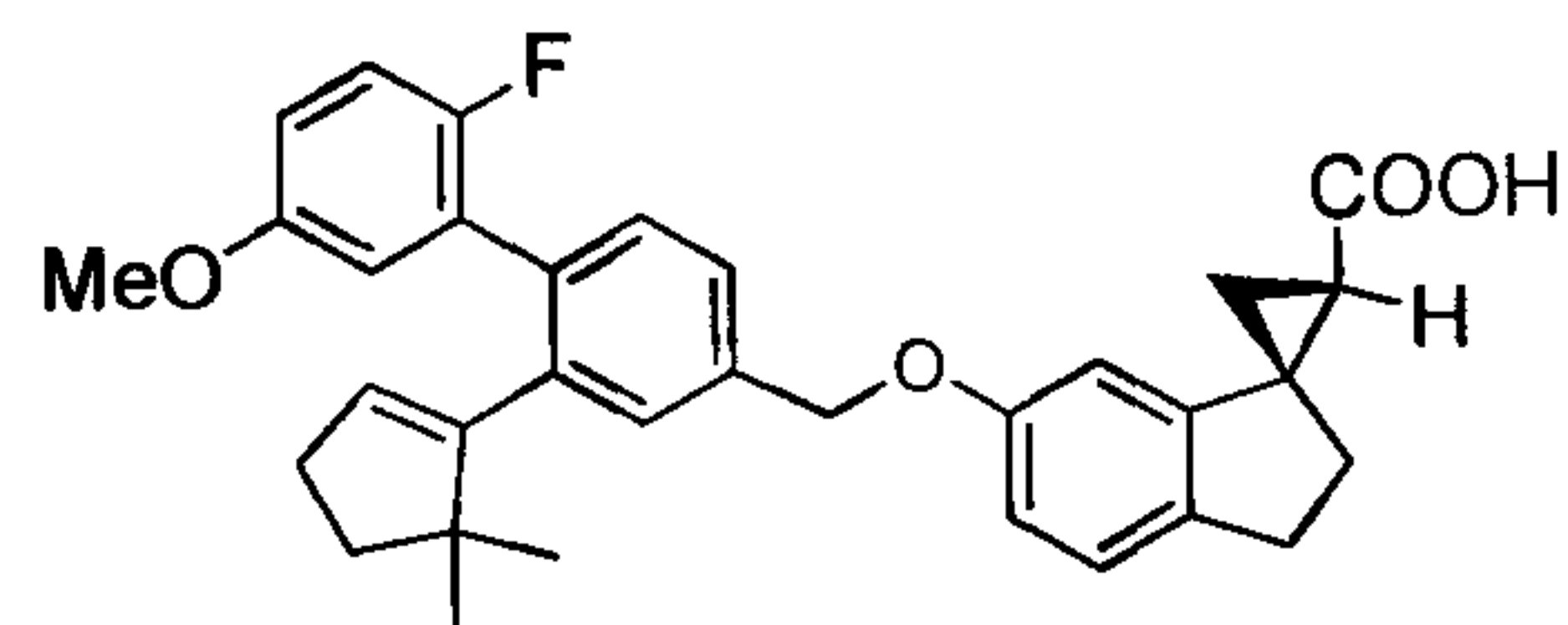
67. The compound



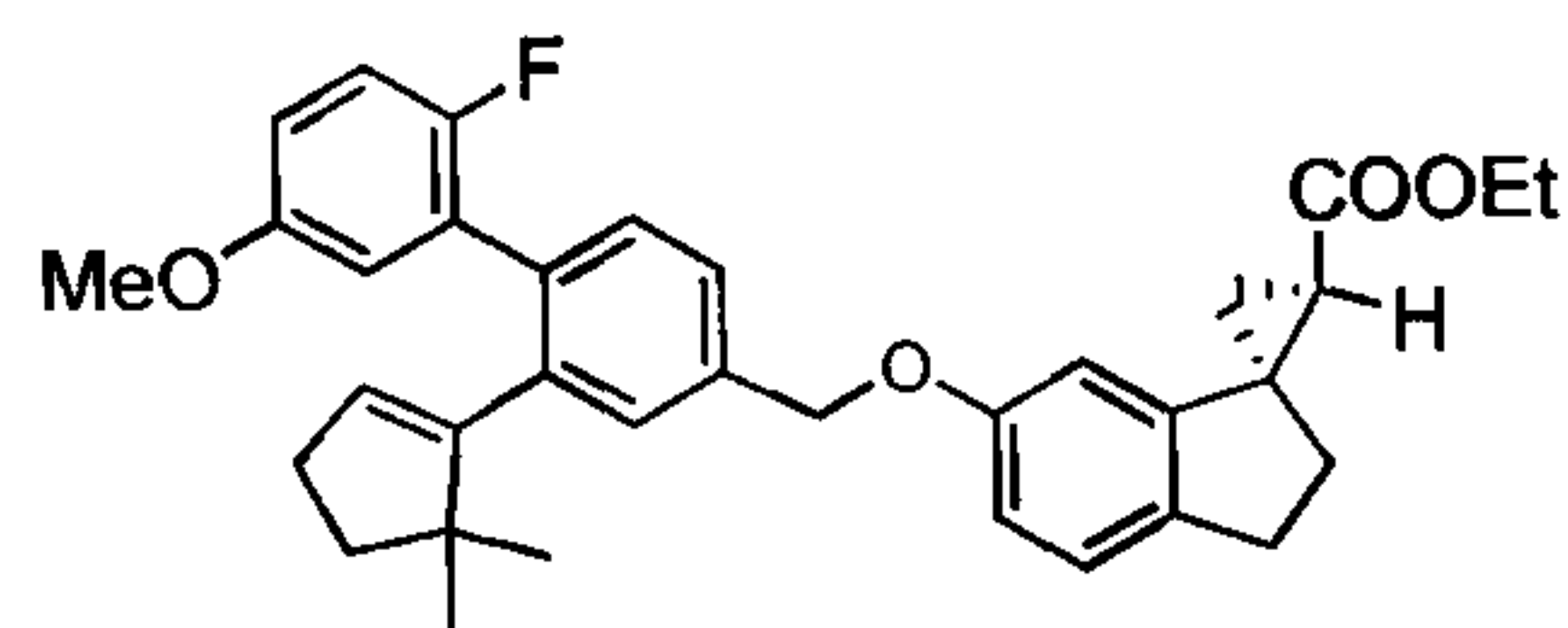
68. The compound



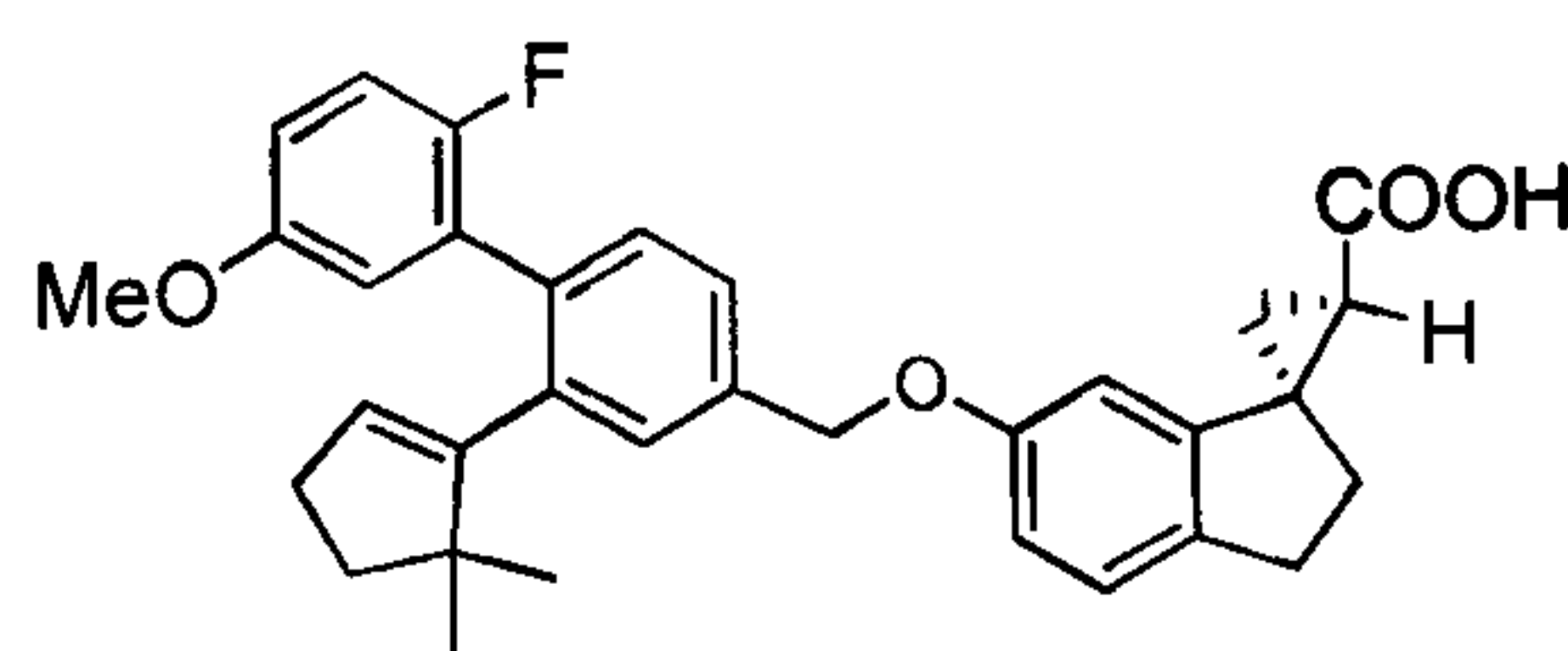
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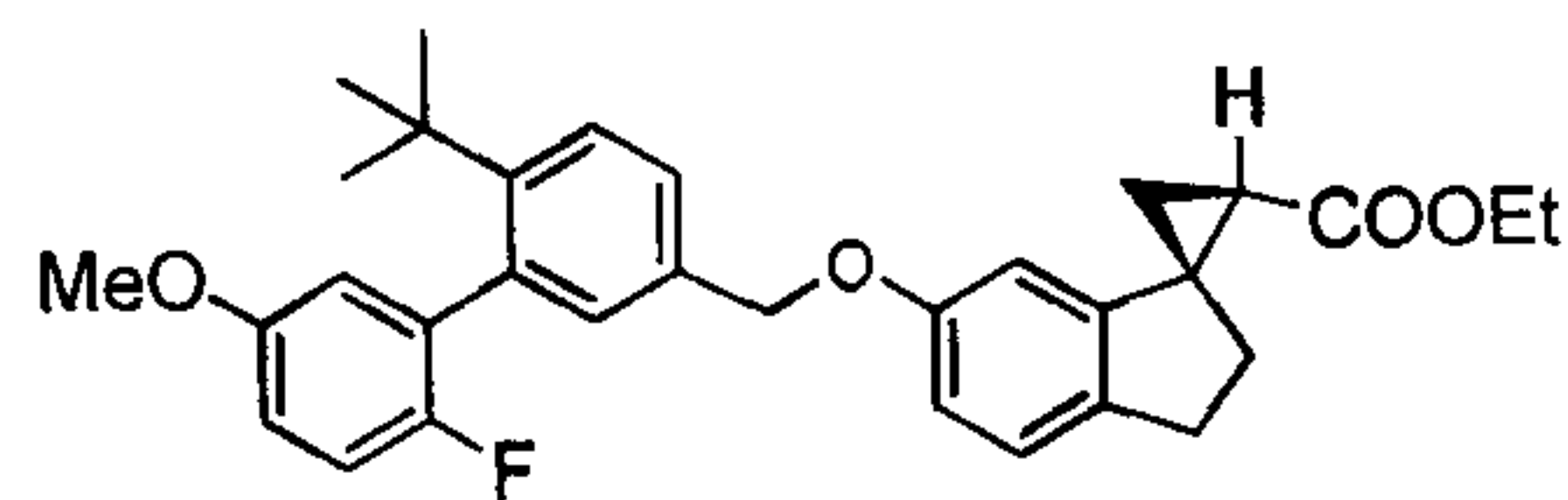
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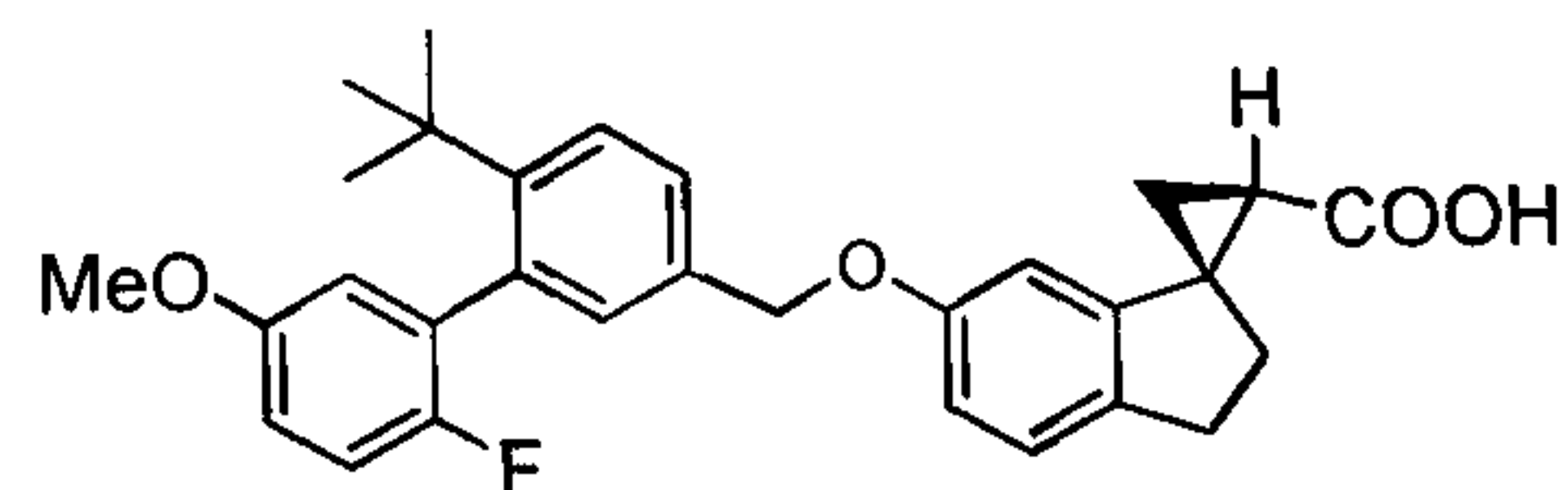
71. The compound



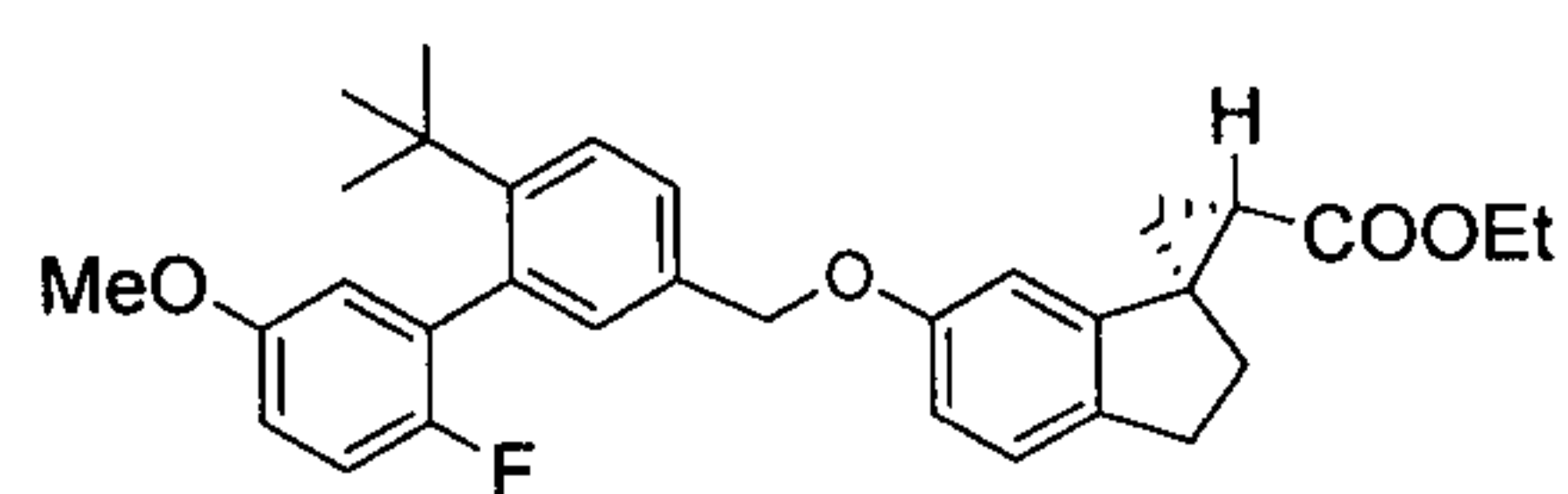
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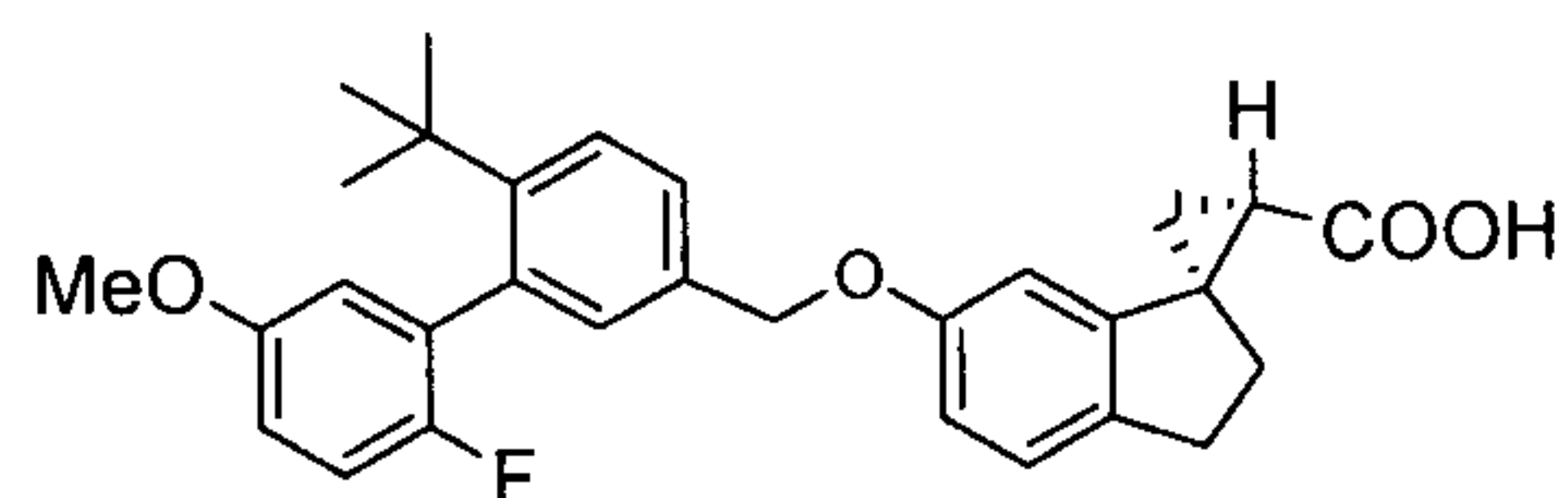
73. The compound



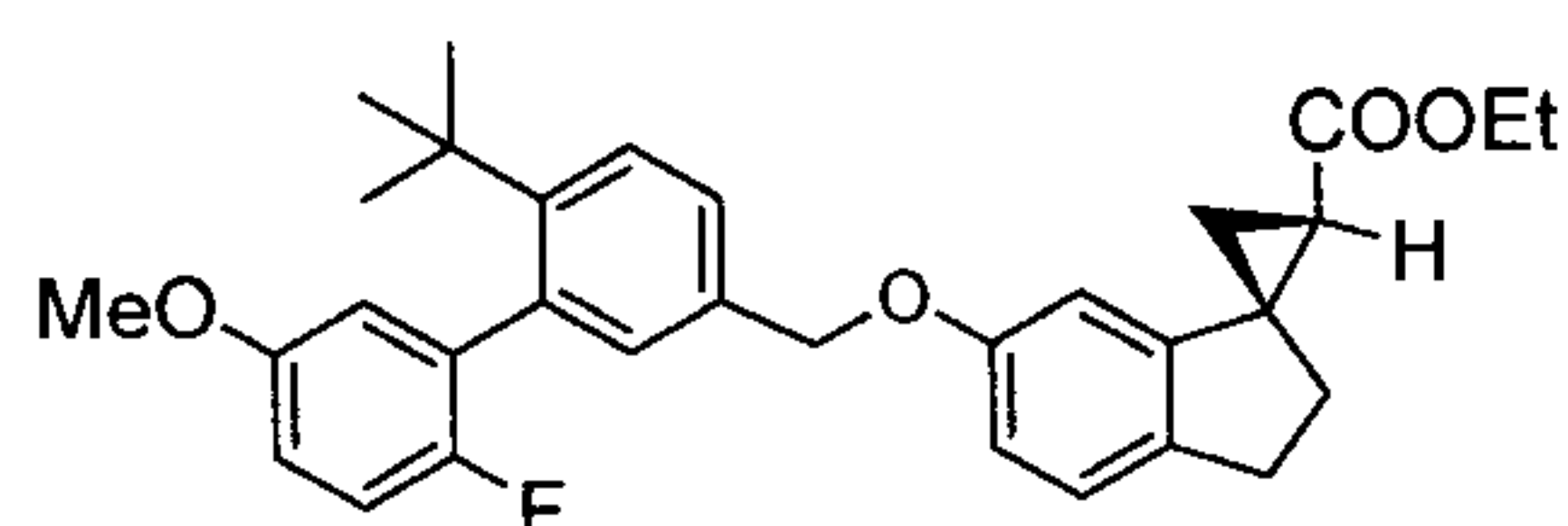
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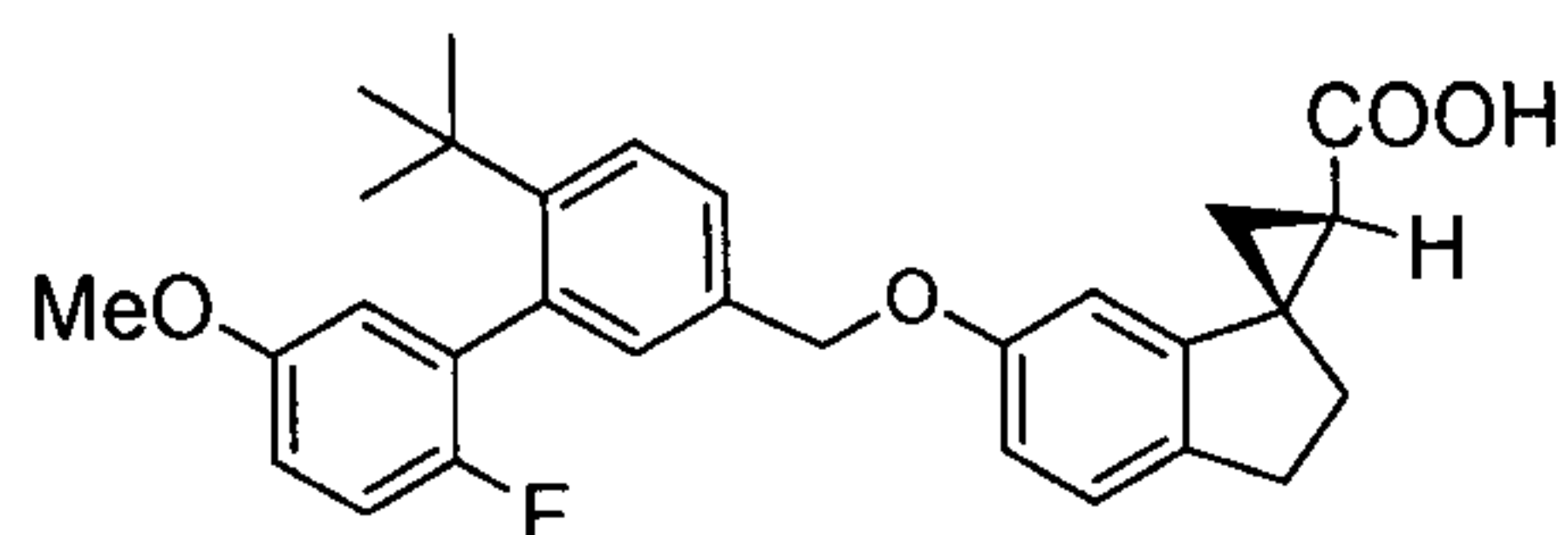
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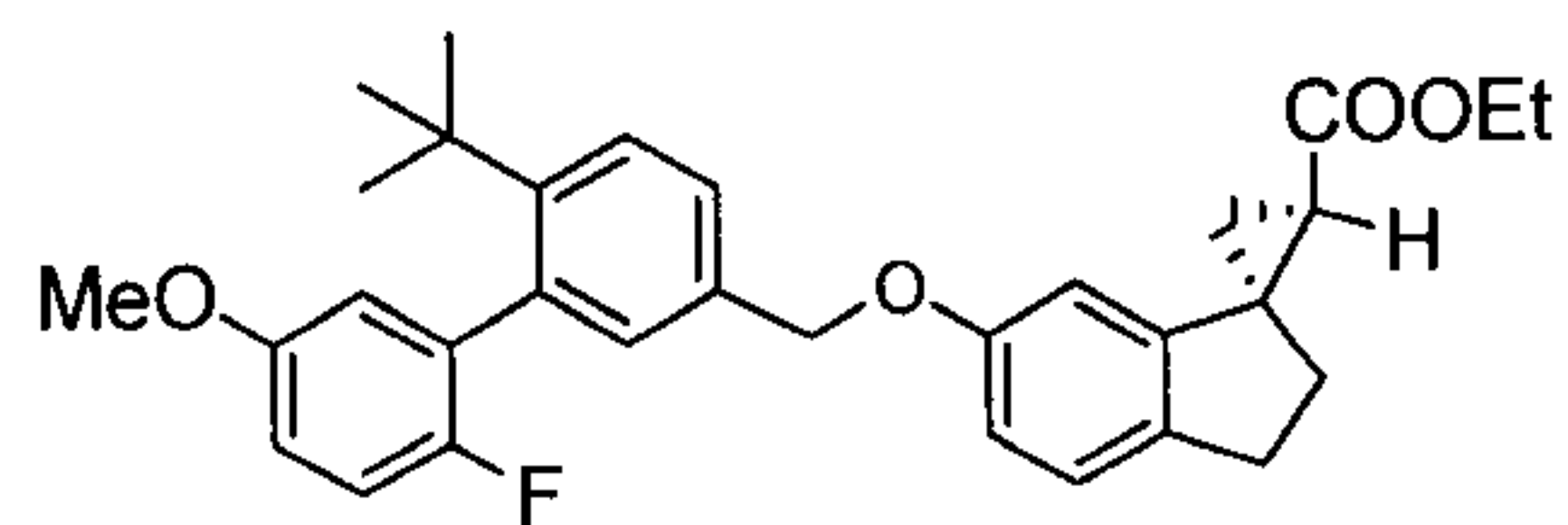
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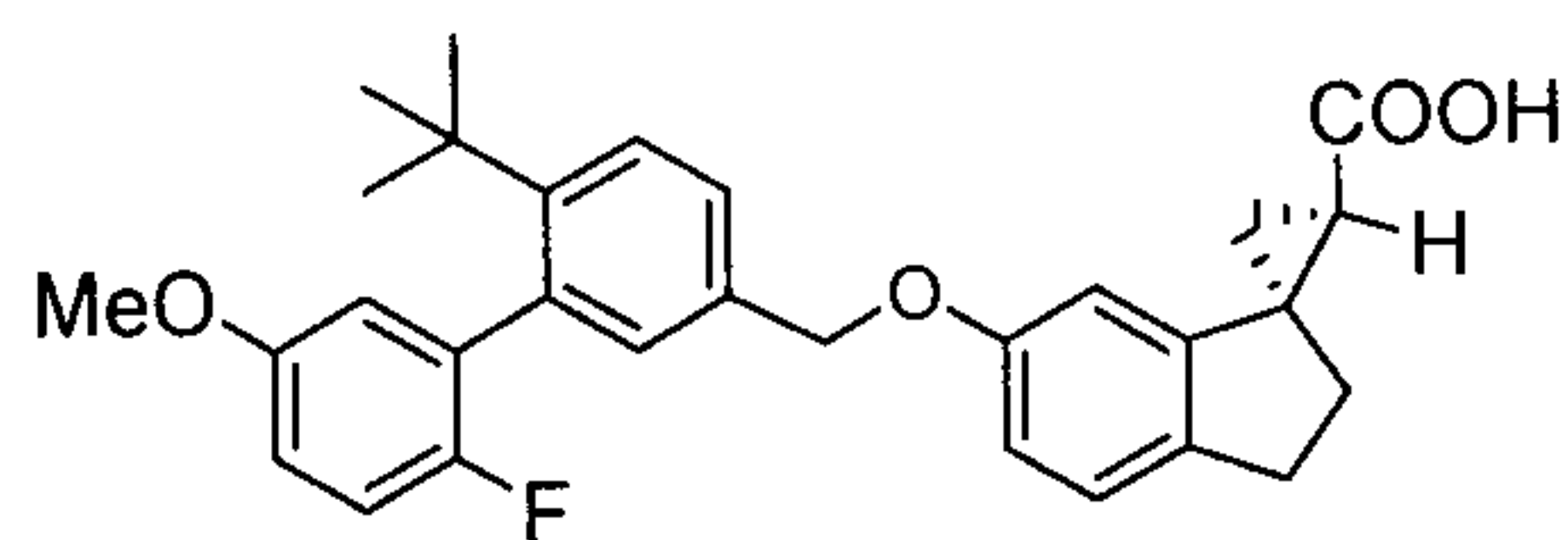
77. The compound



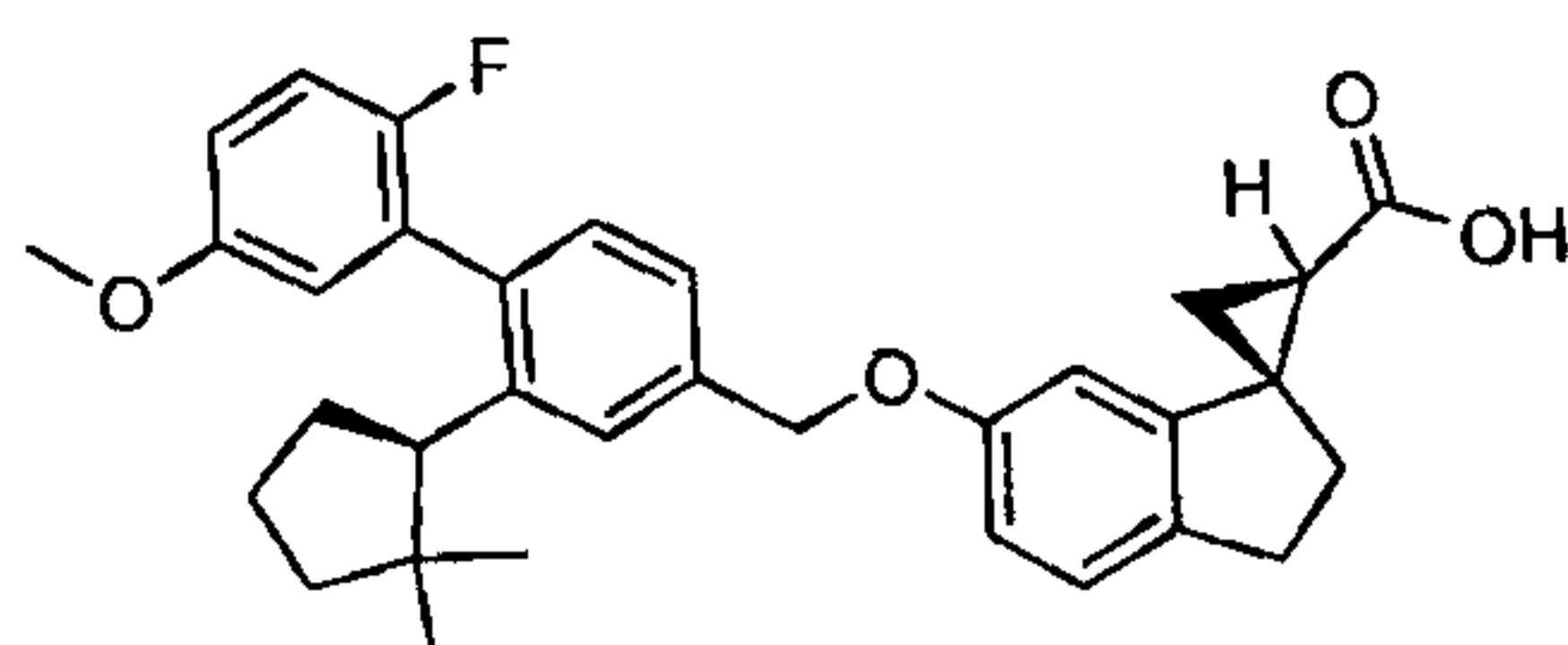
78. The compound



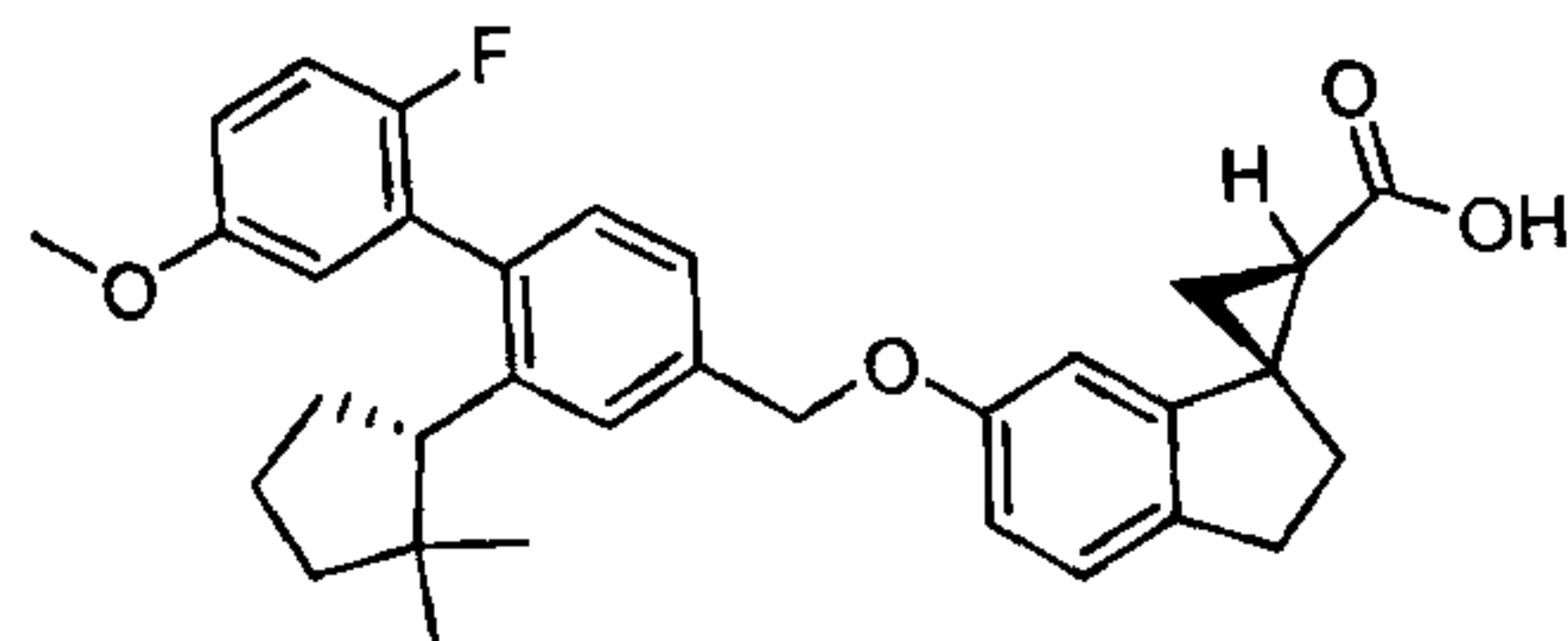
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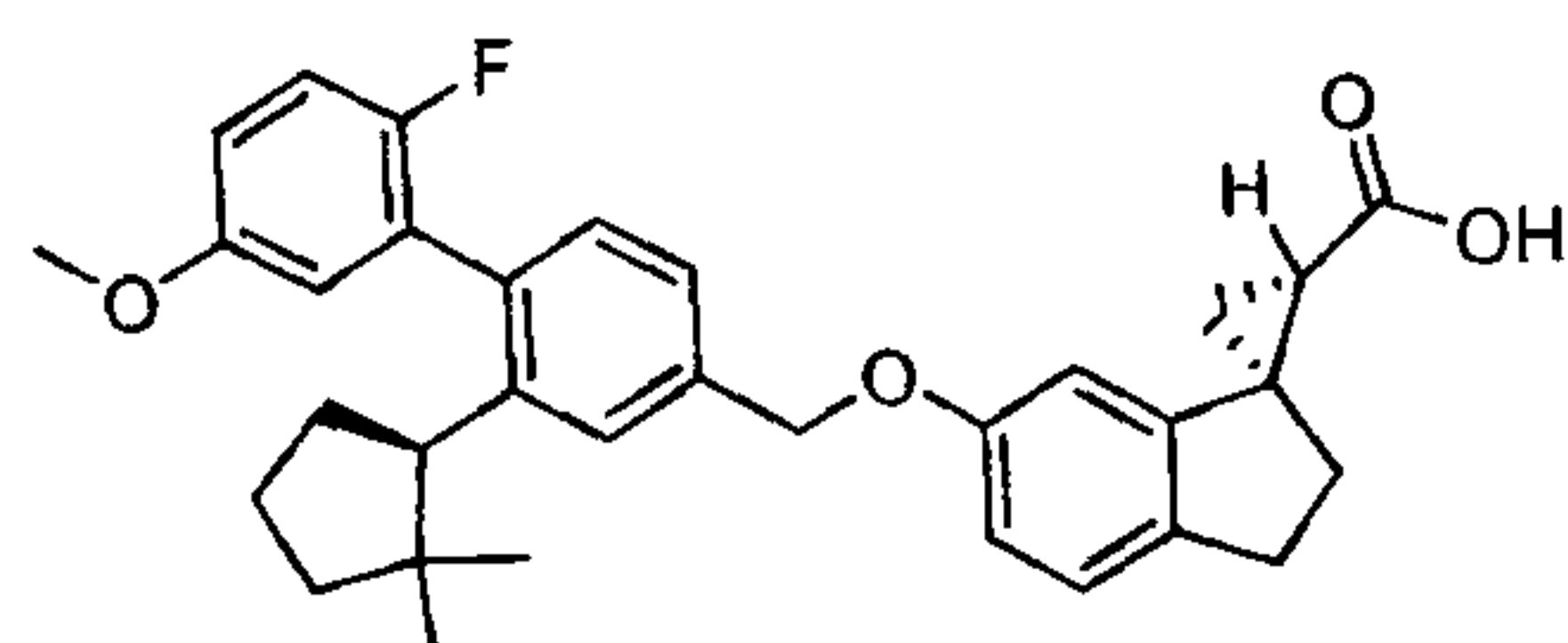
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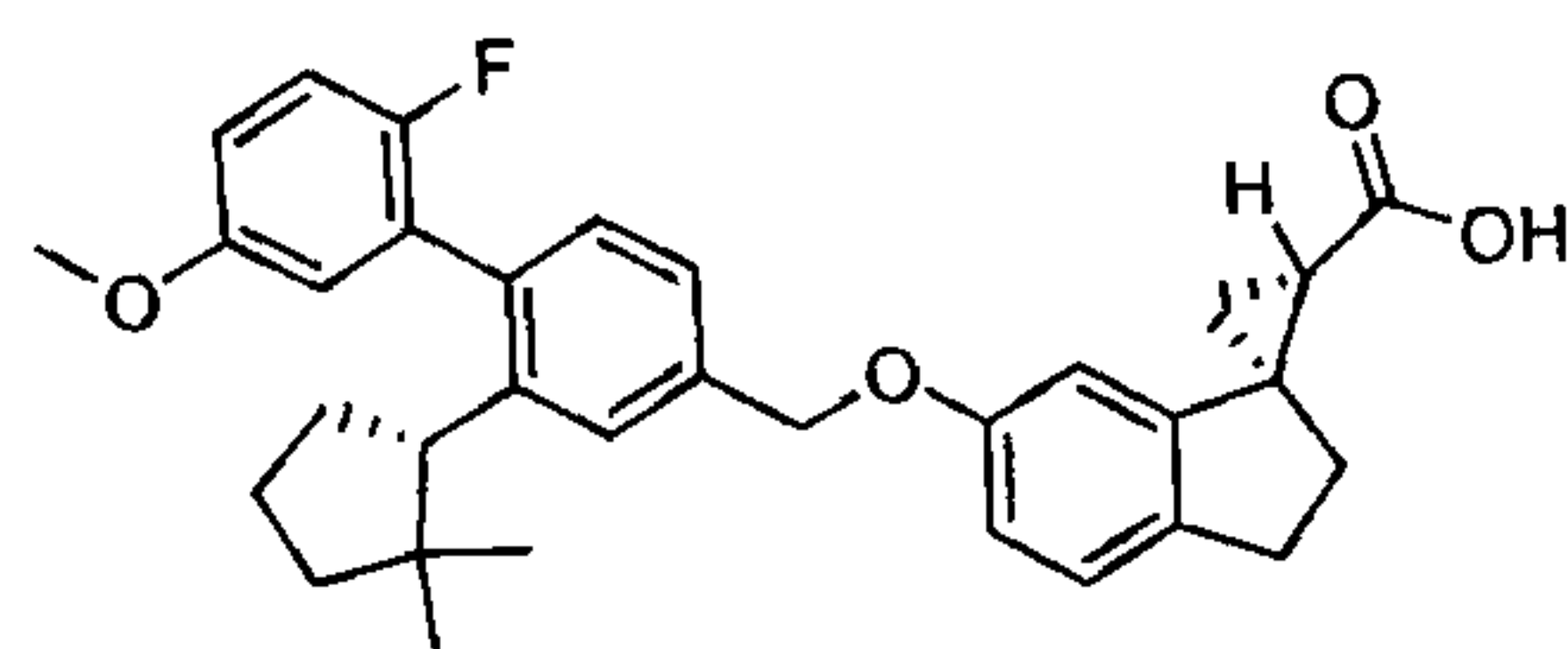
81. The compound



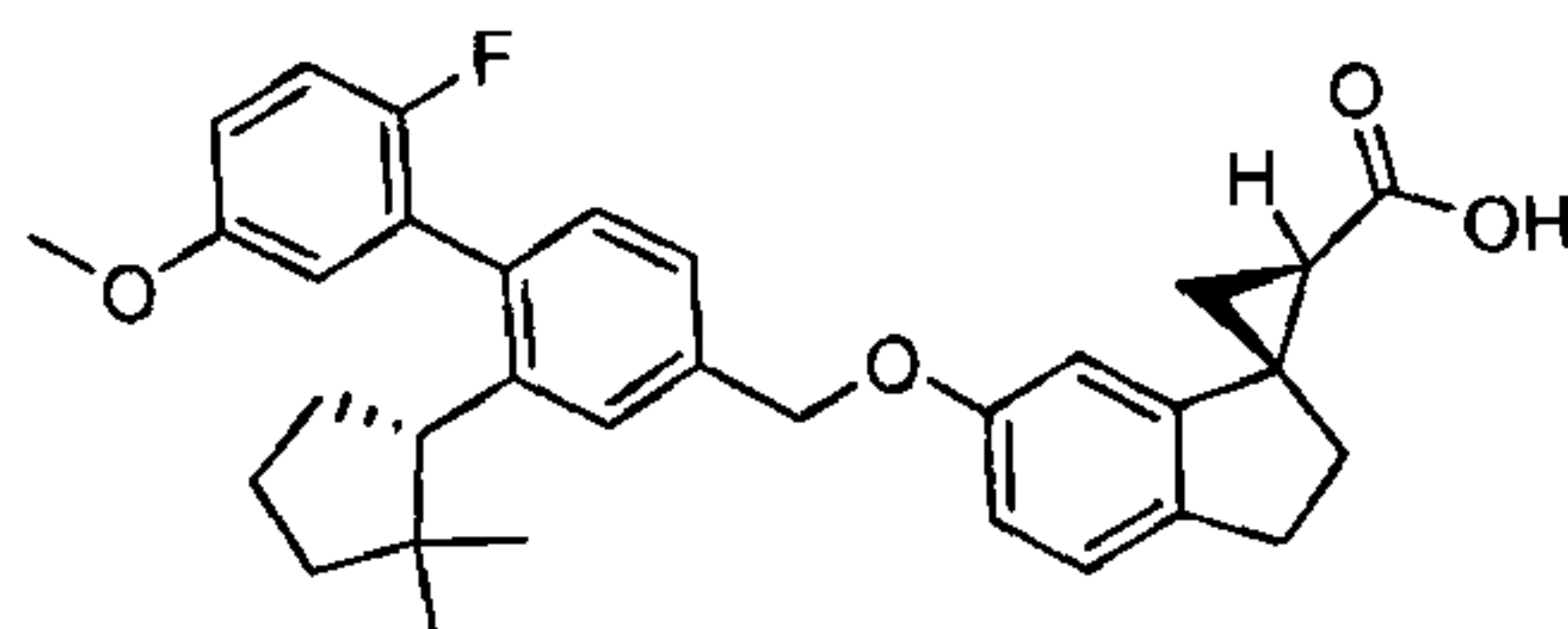
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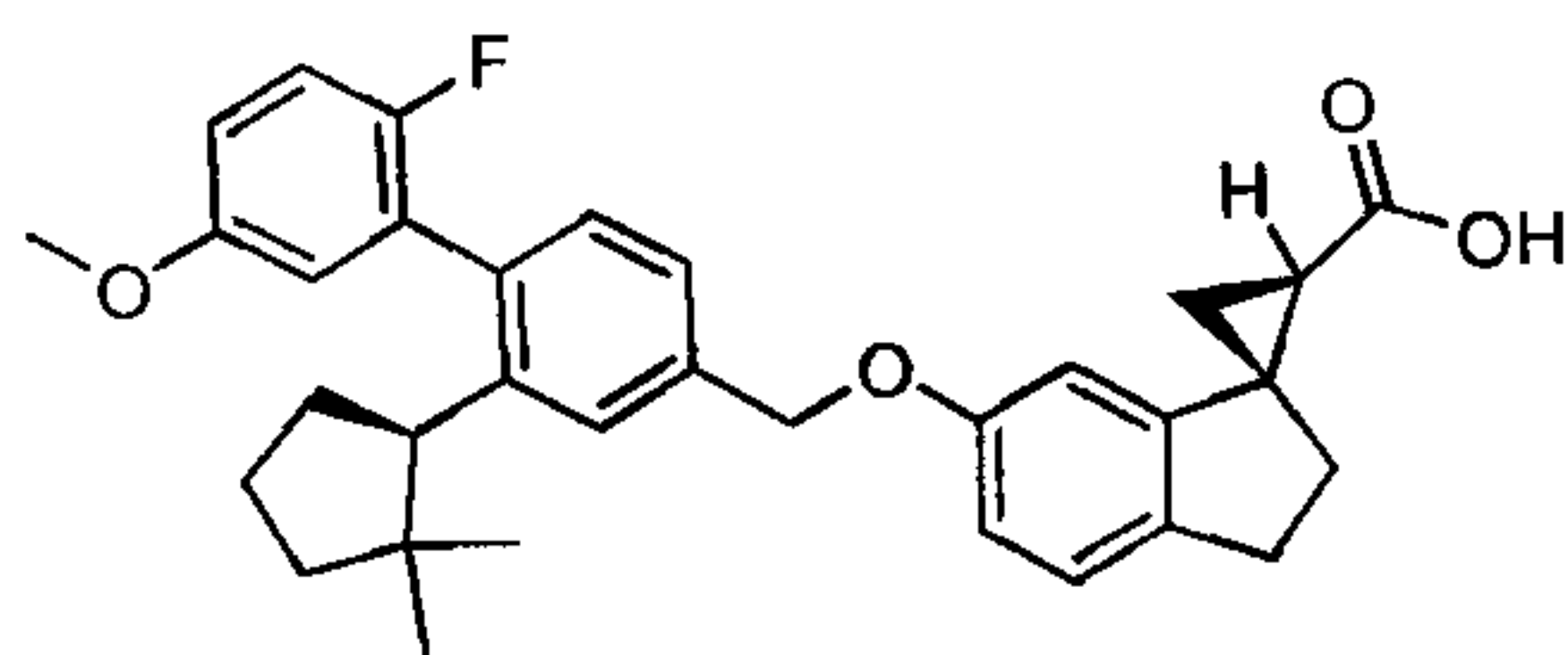
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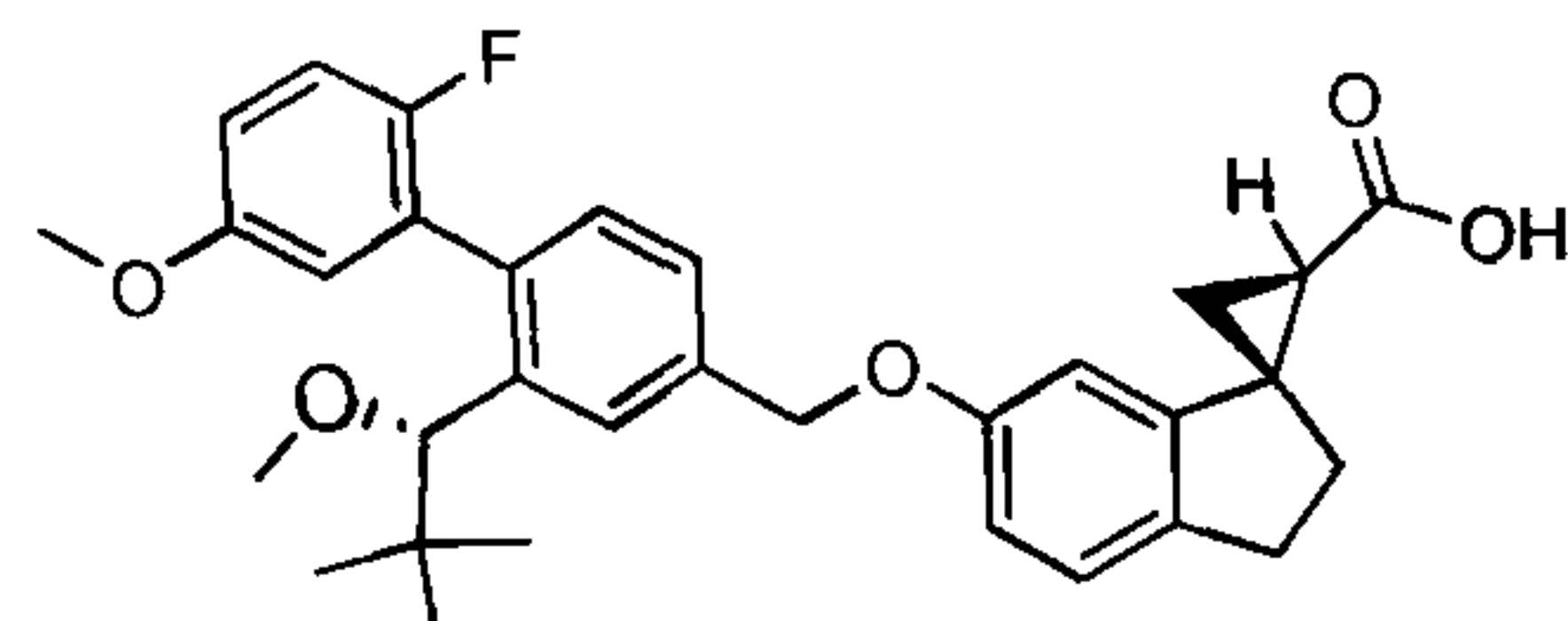
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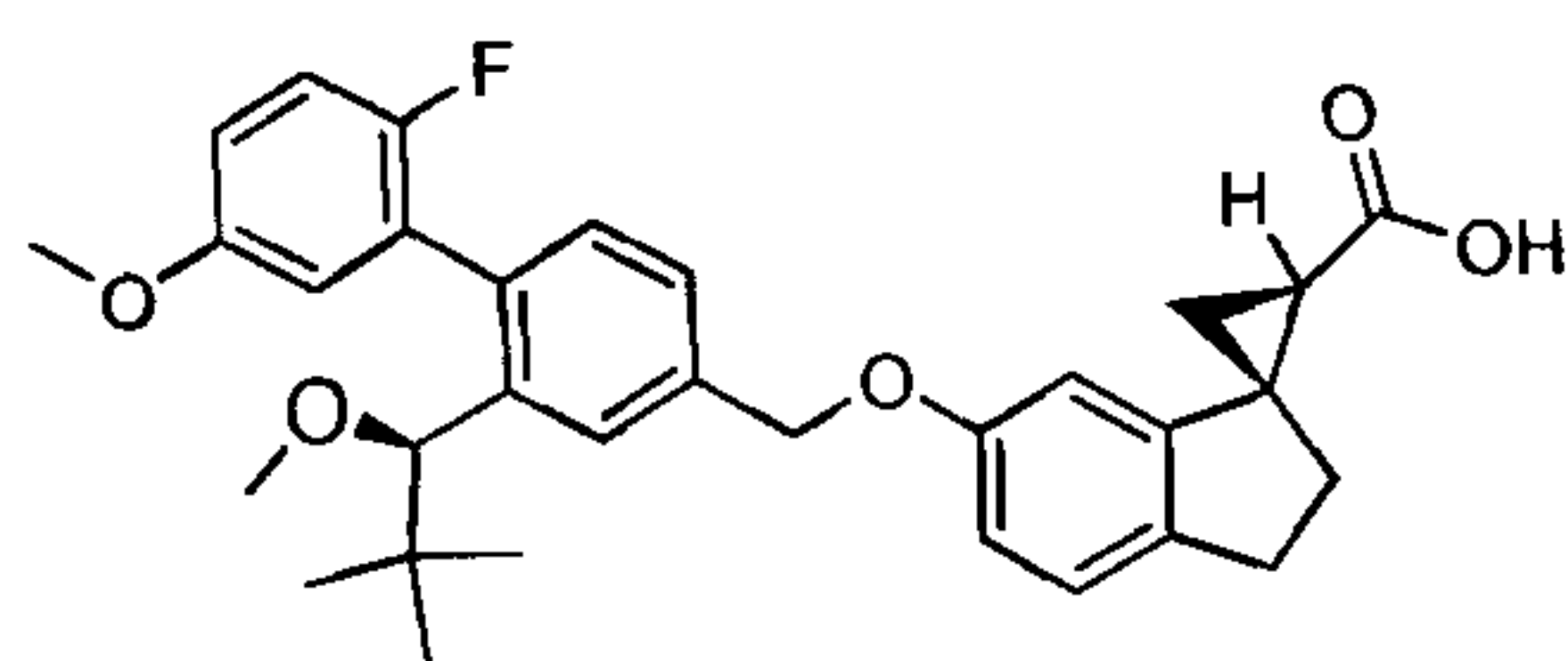
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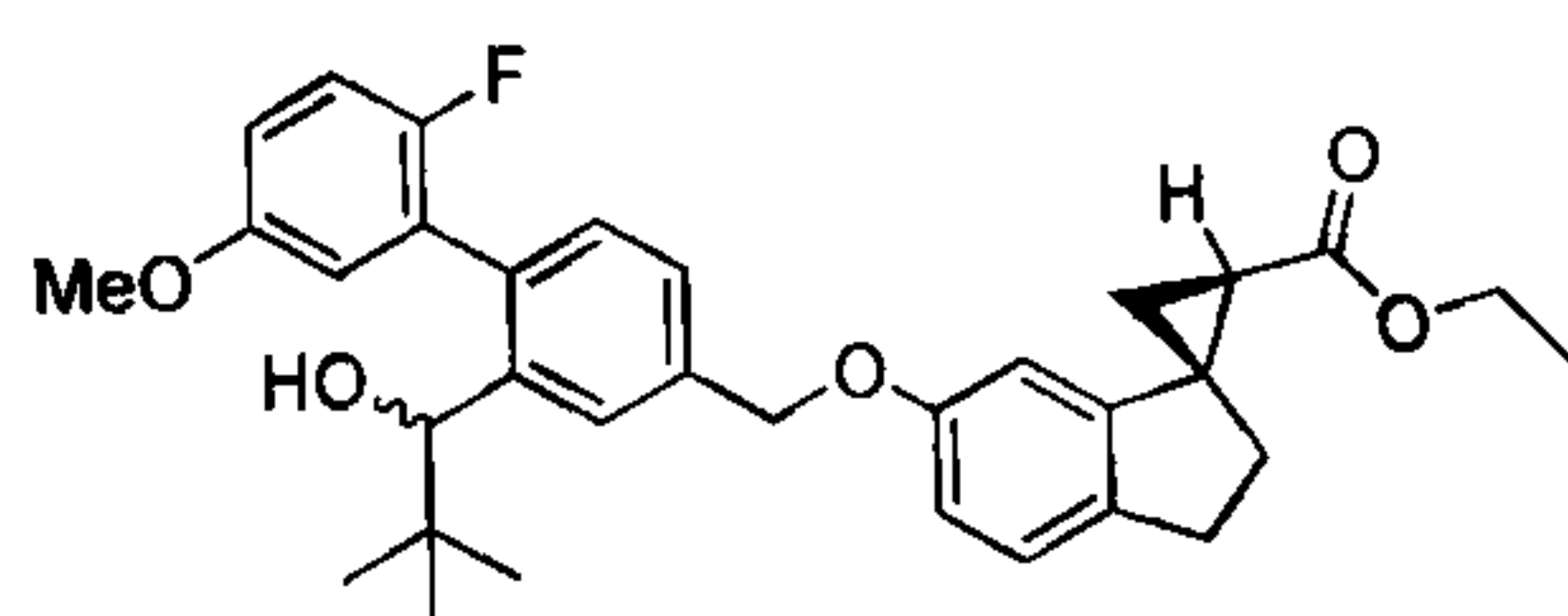
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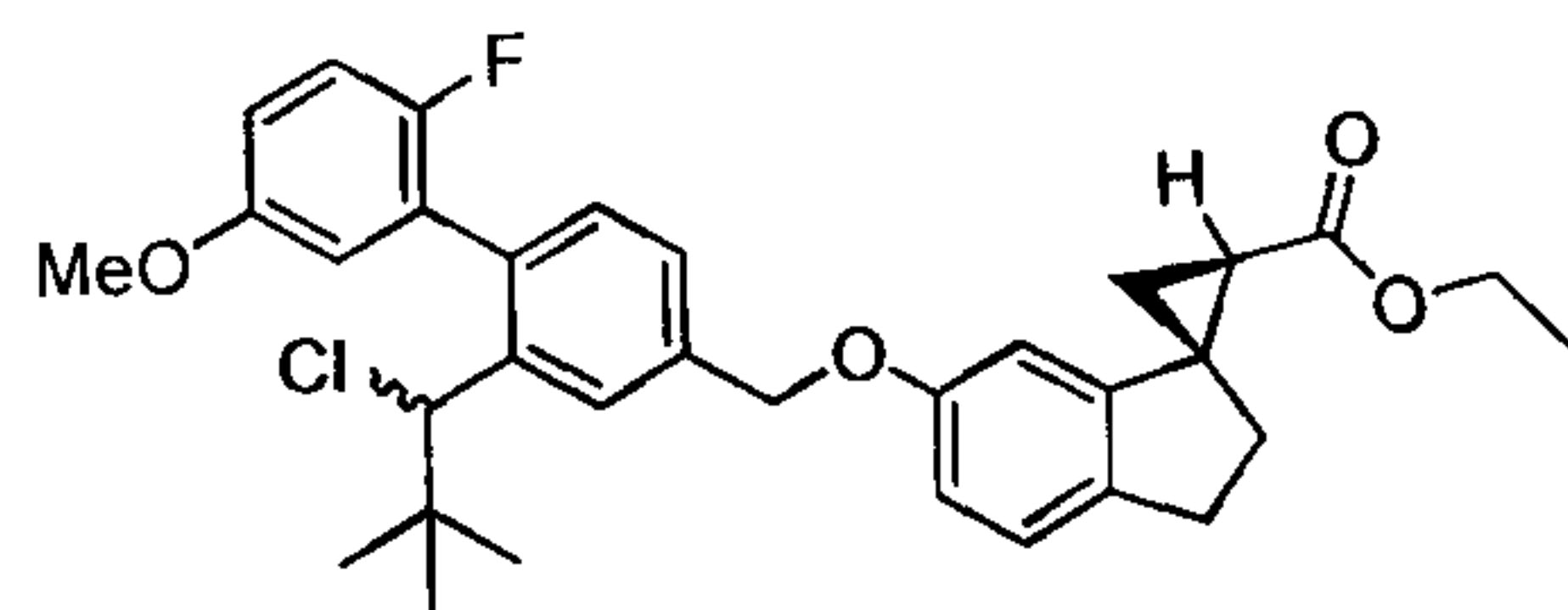
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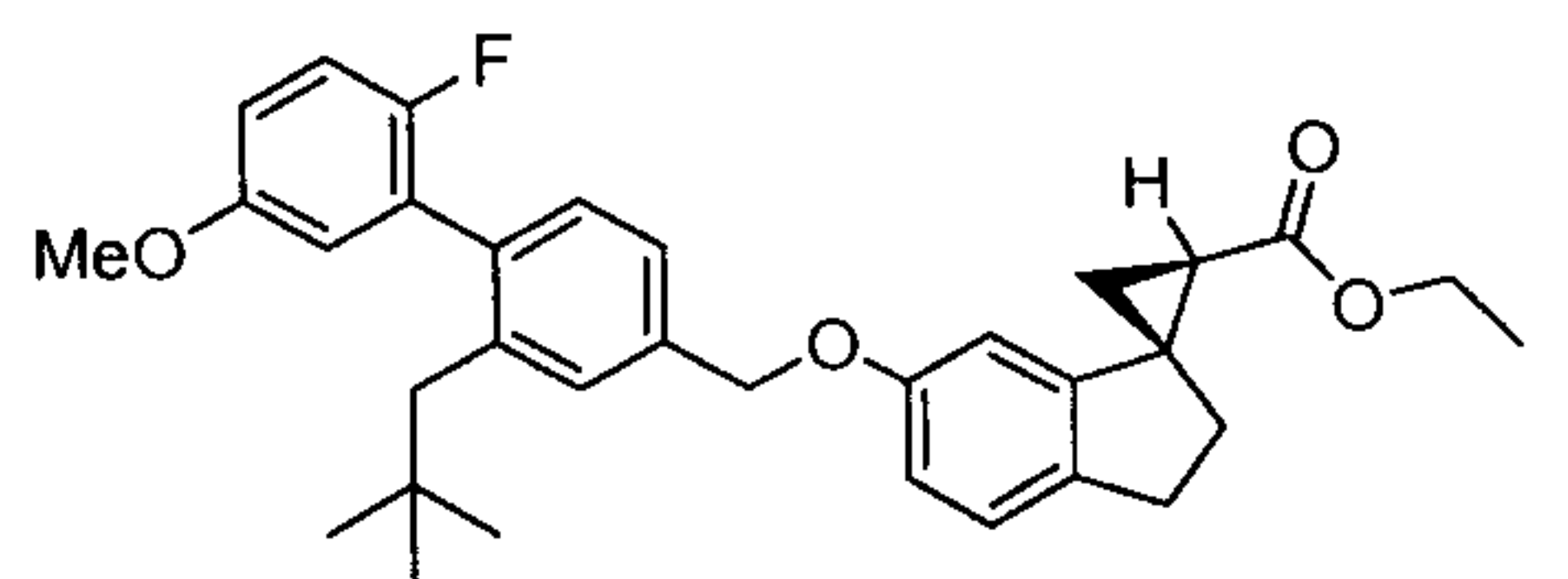
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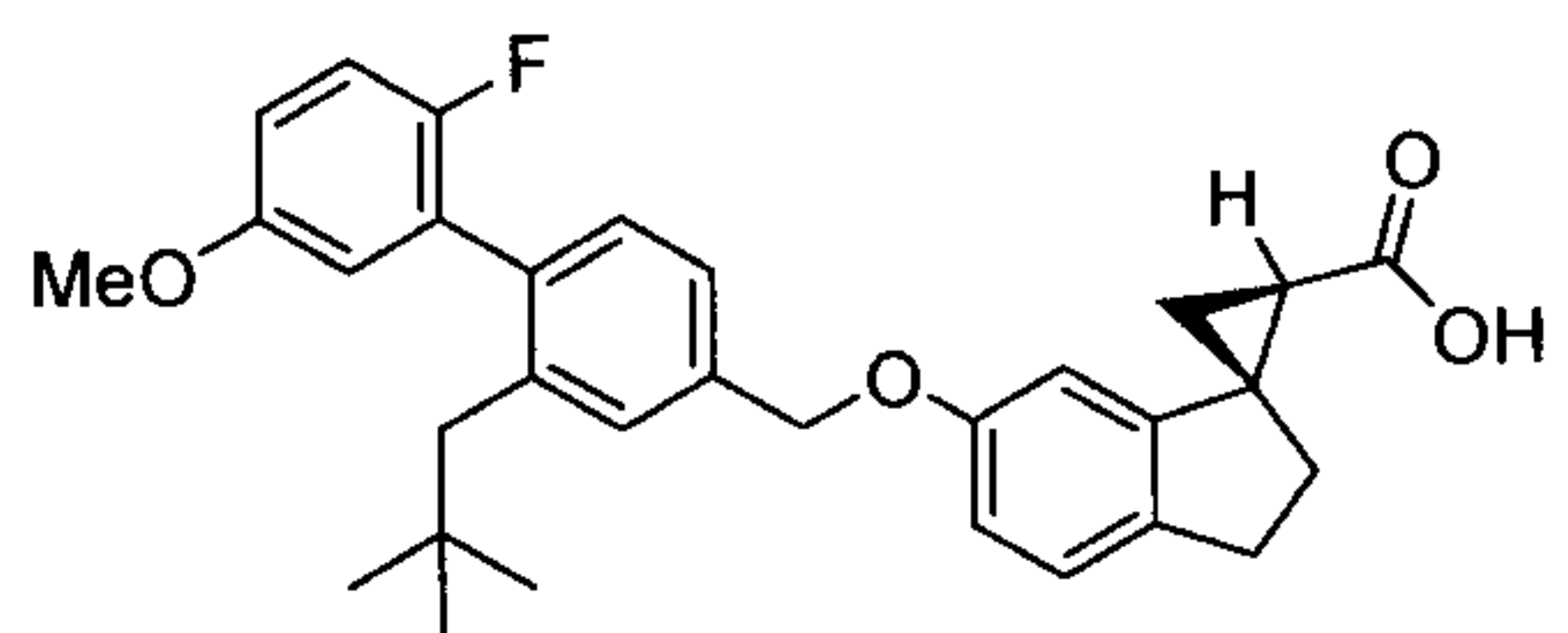
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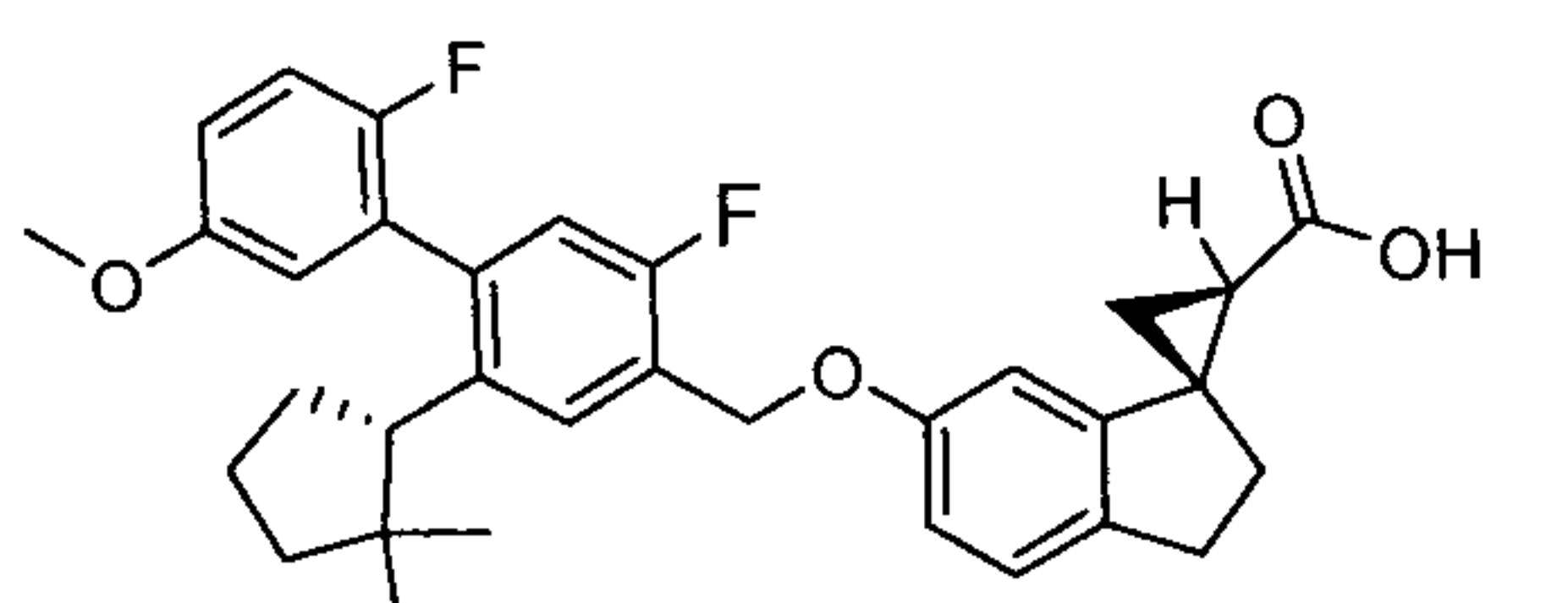
90. The compound



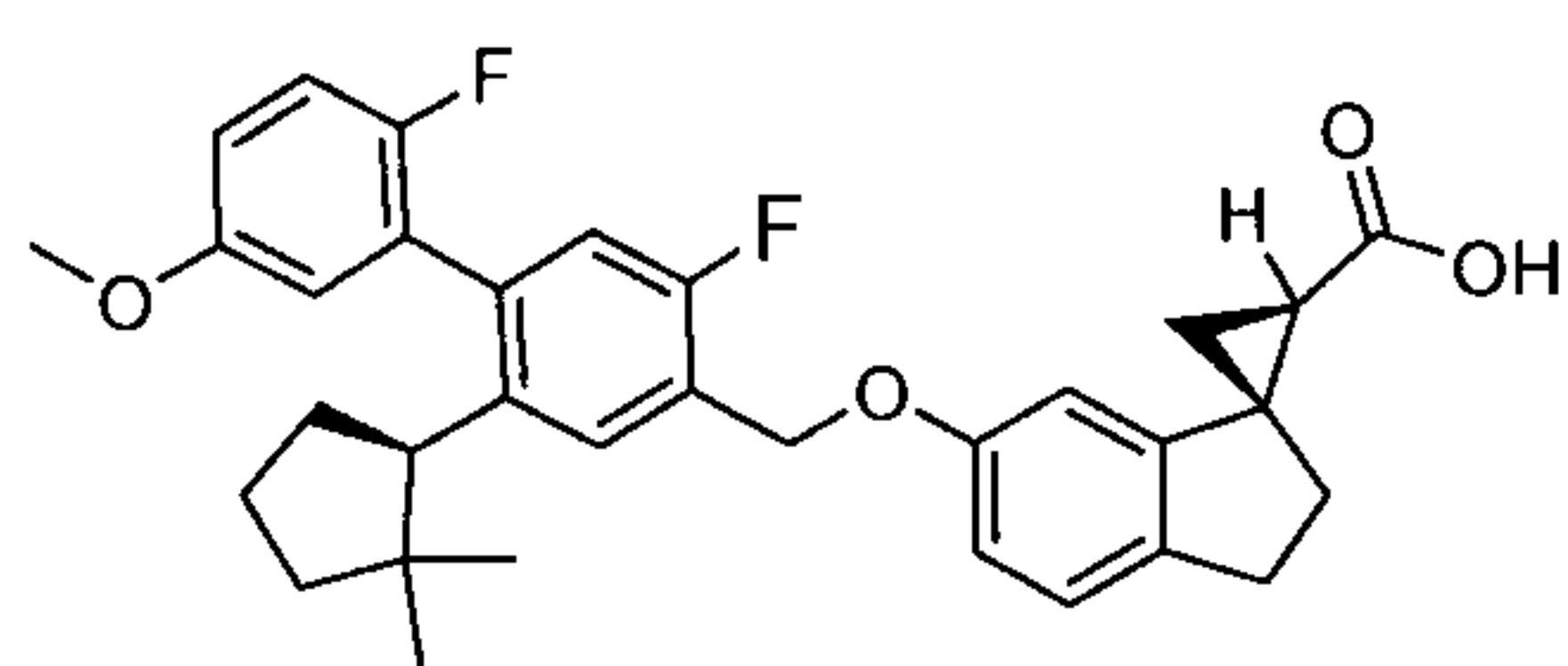
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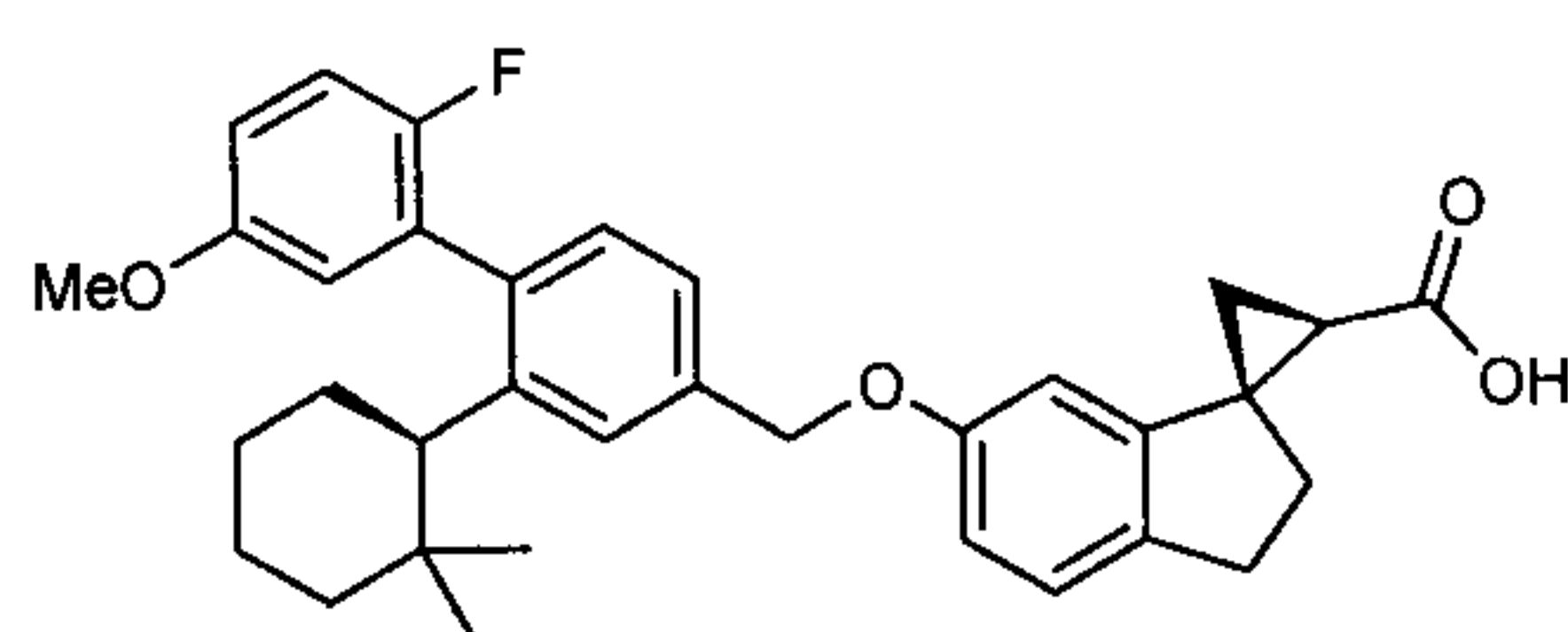
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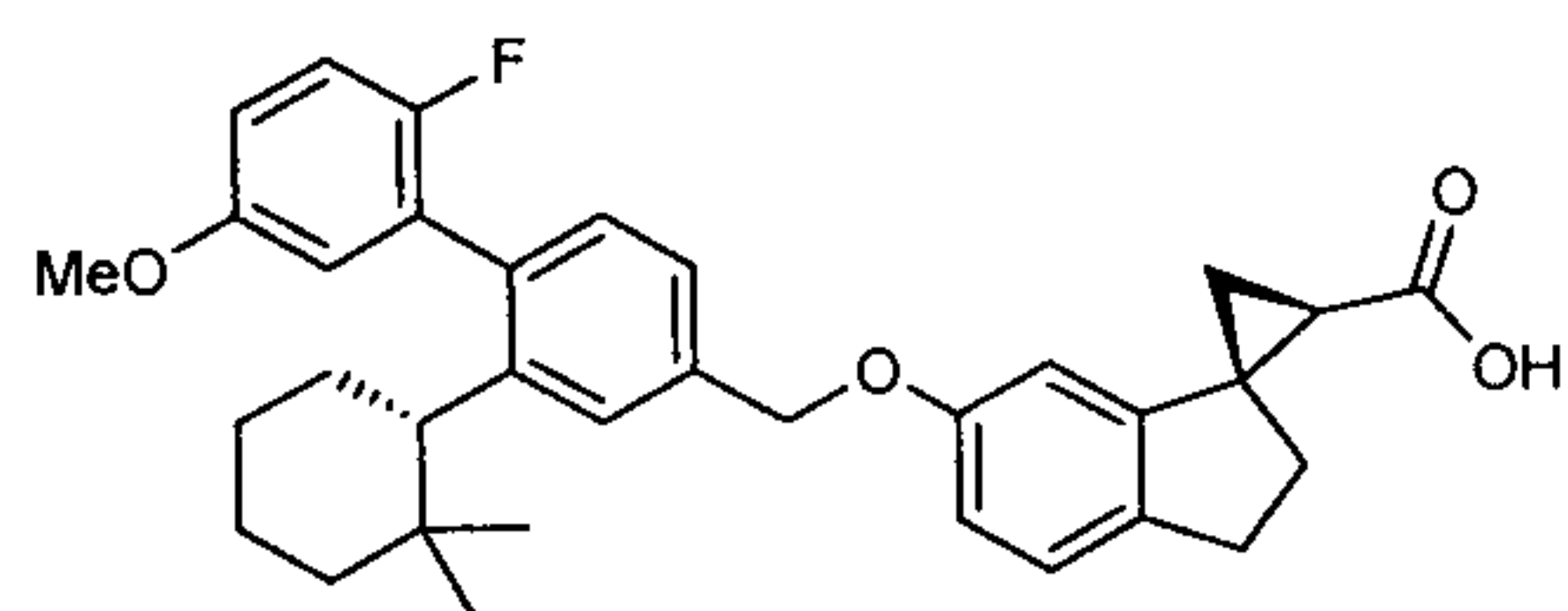
93. The compound



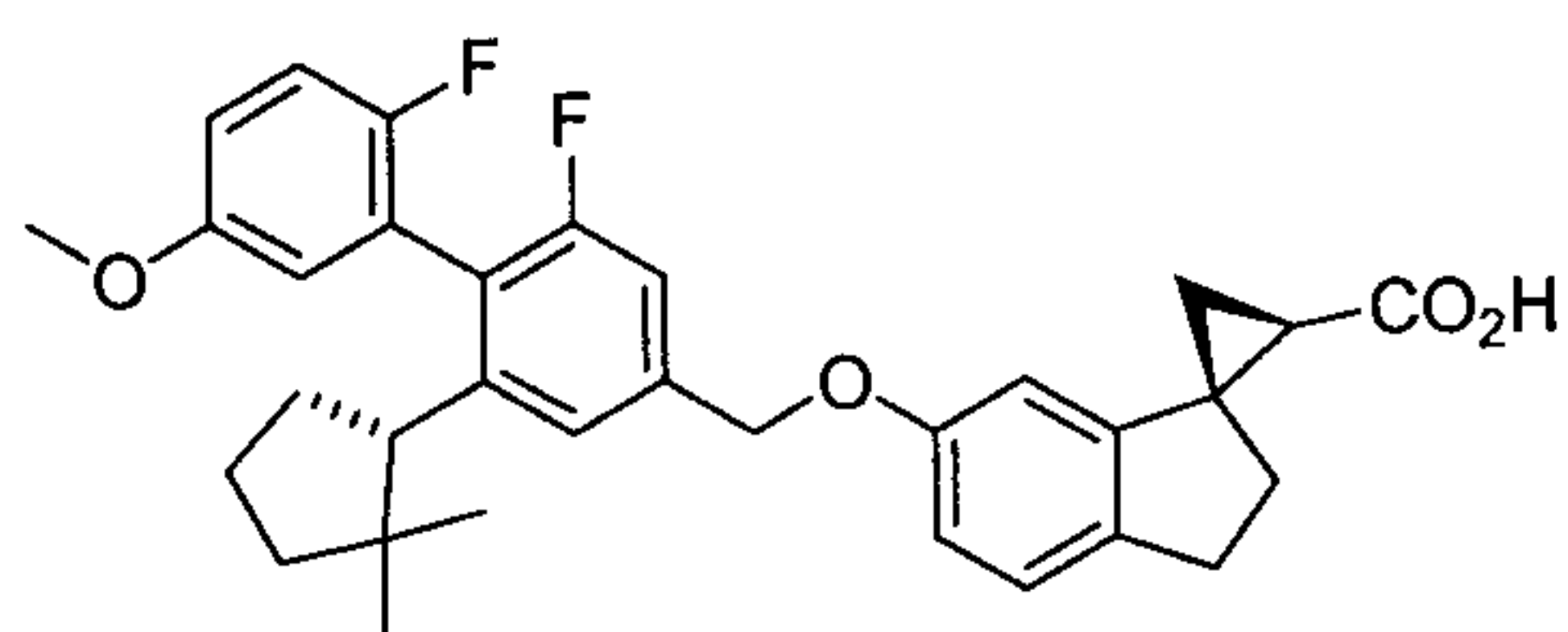
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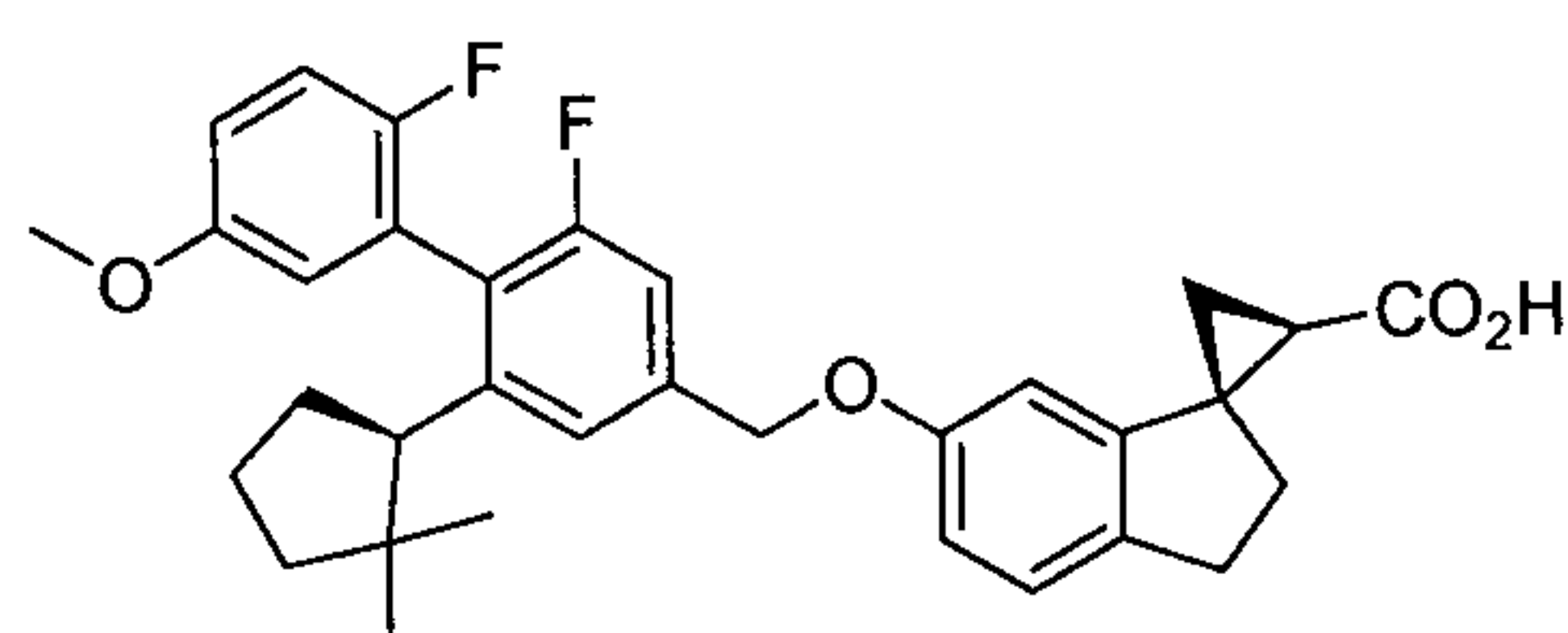
95. The compound



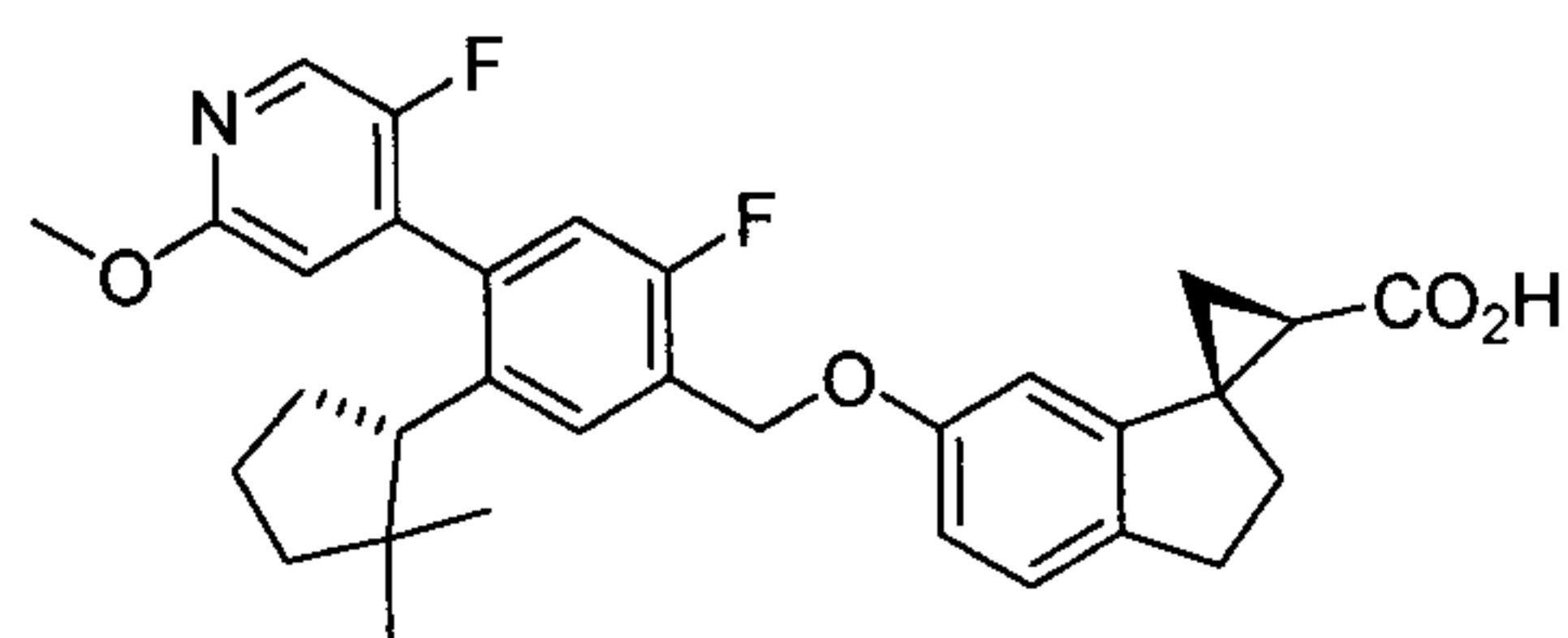
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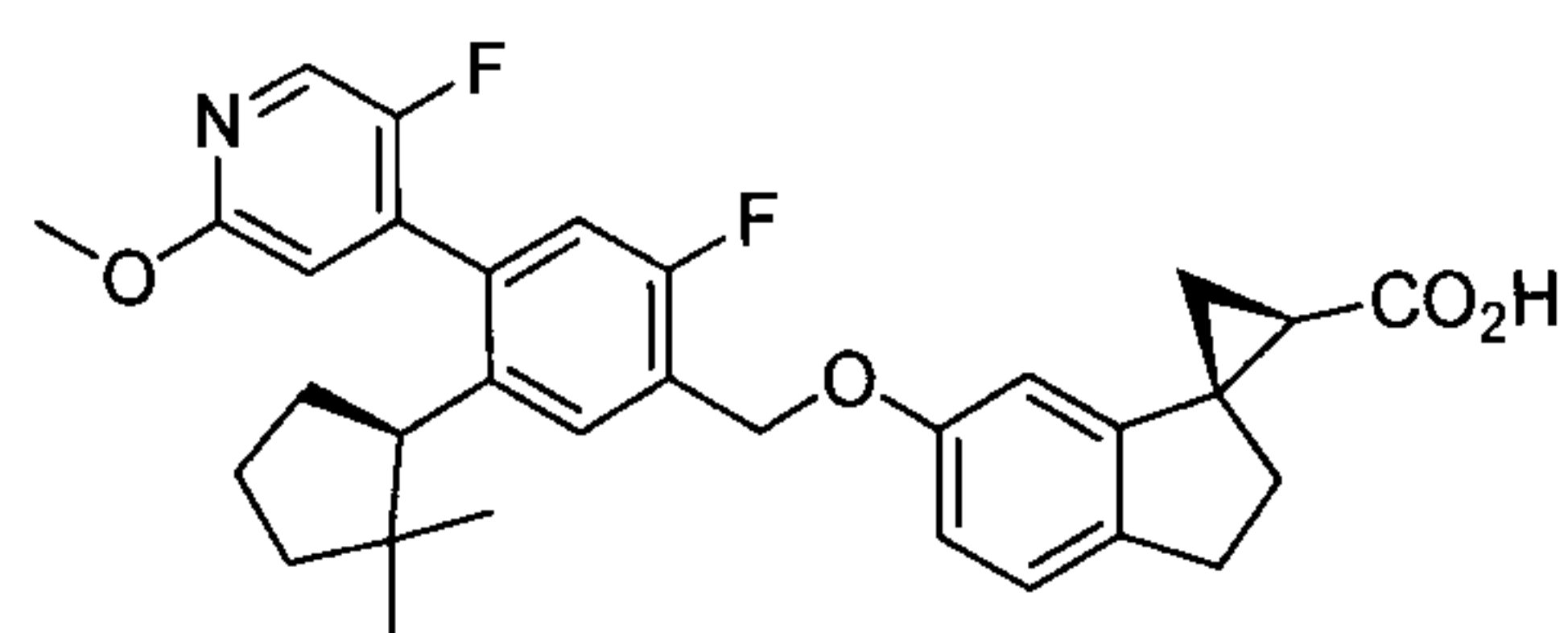
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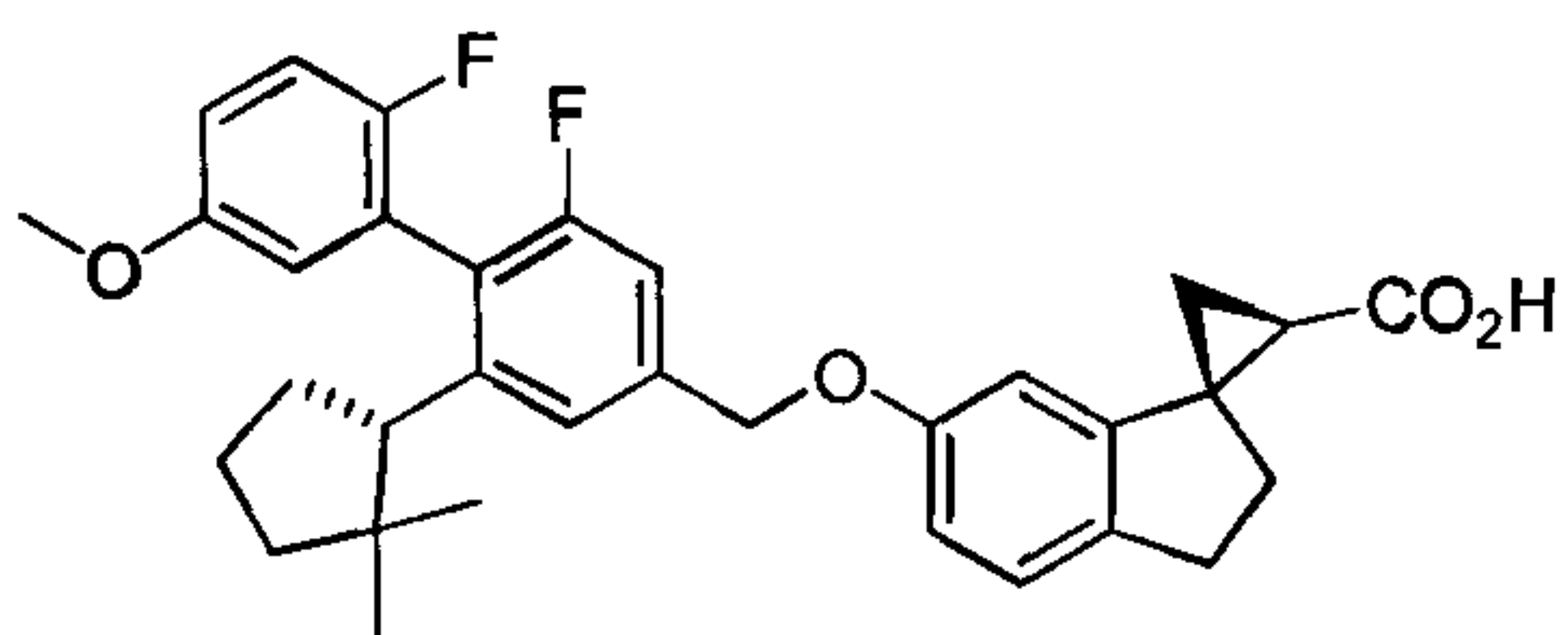
98. The compound



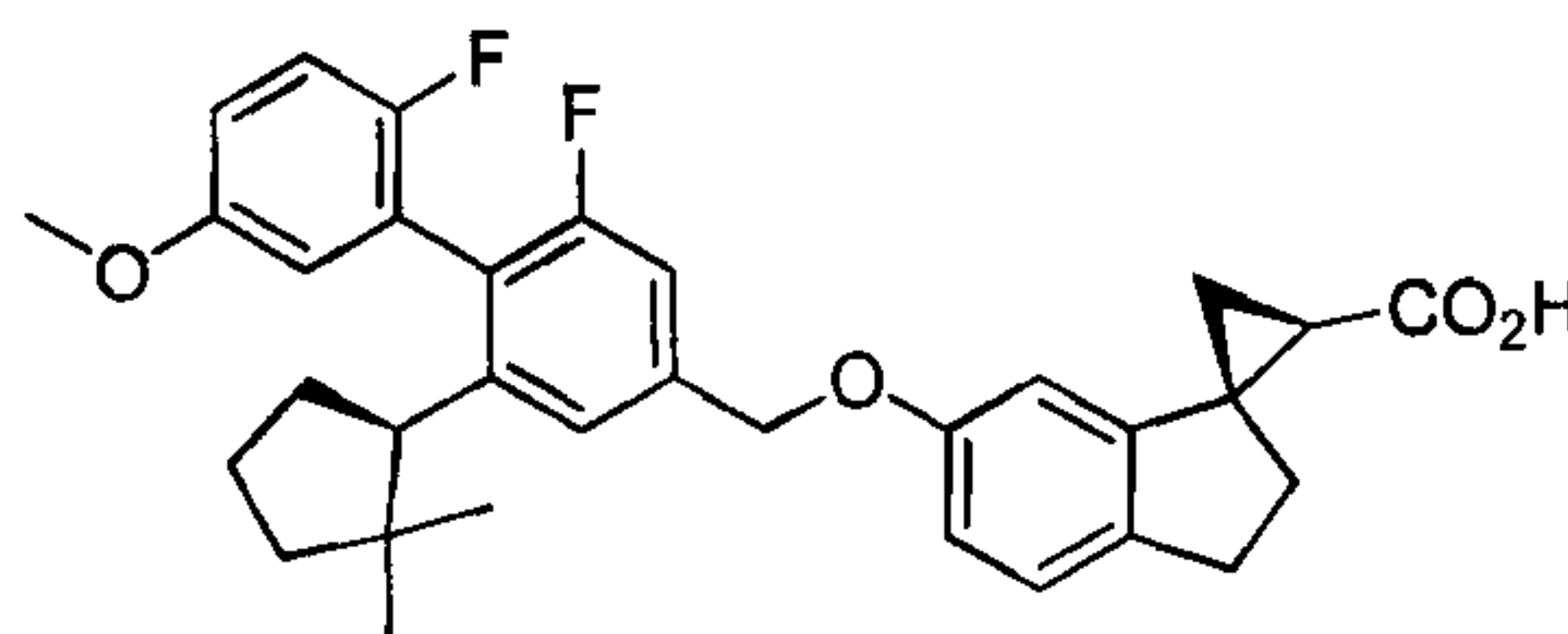
99. The compound



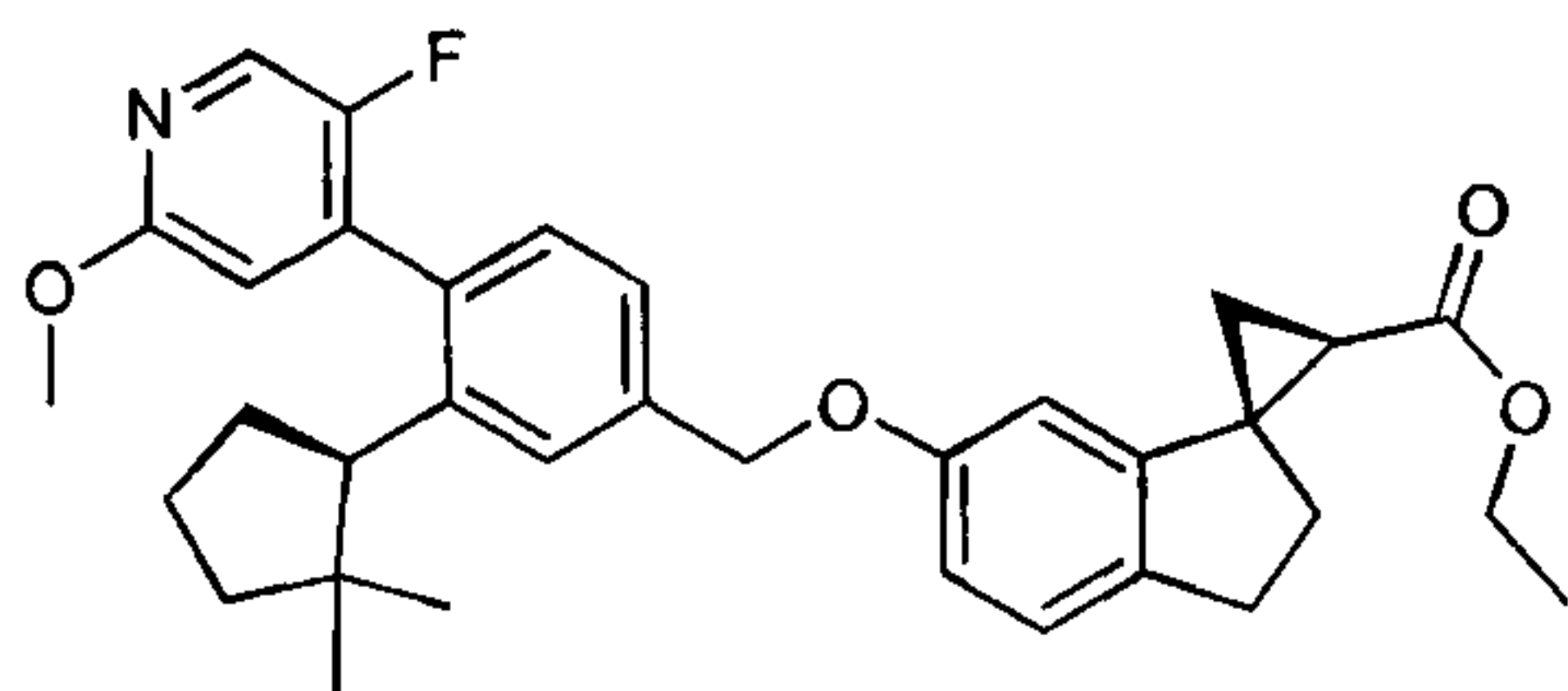
100. The compound



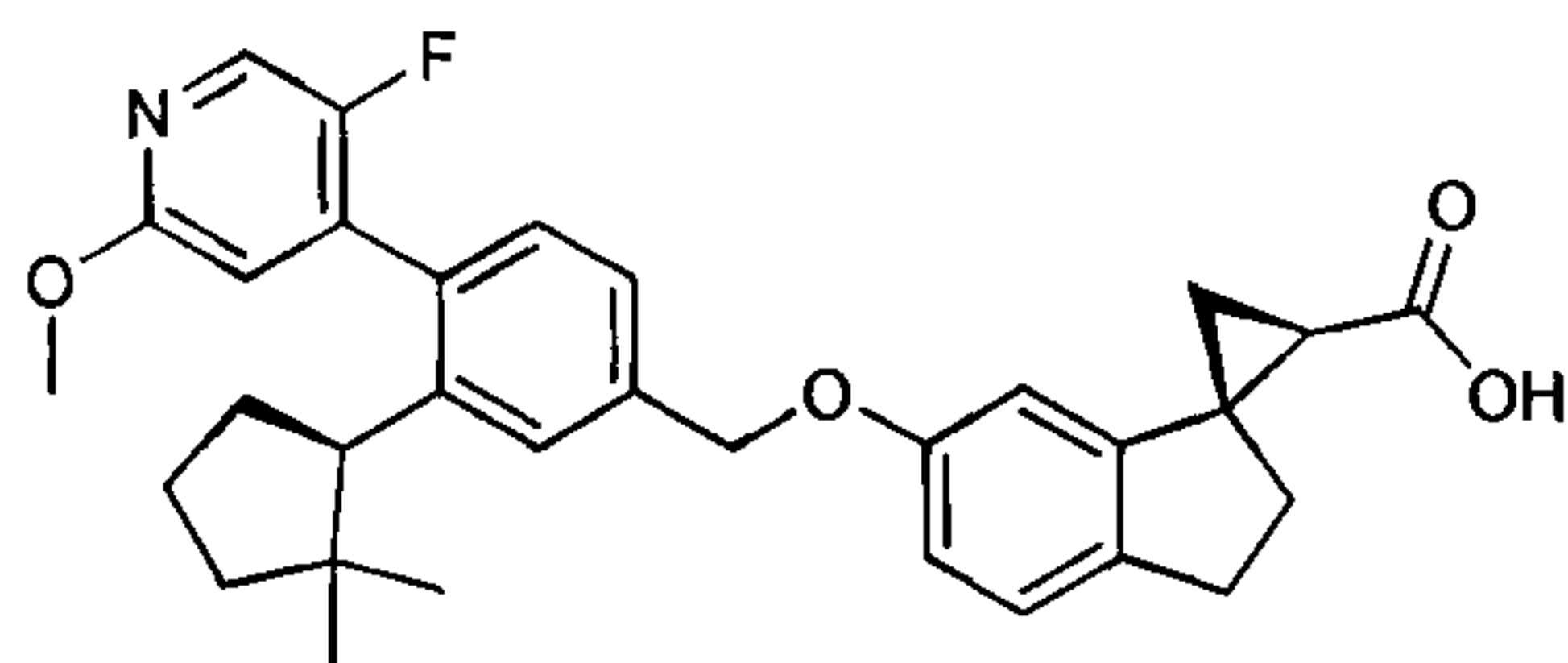
101. The compound



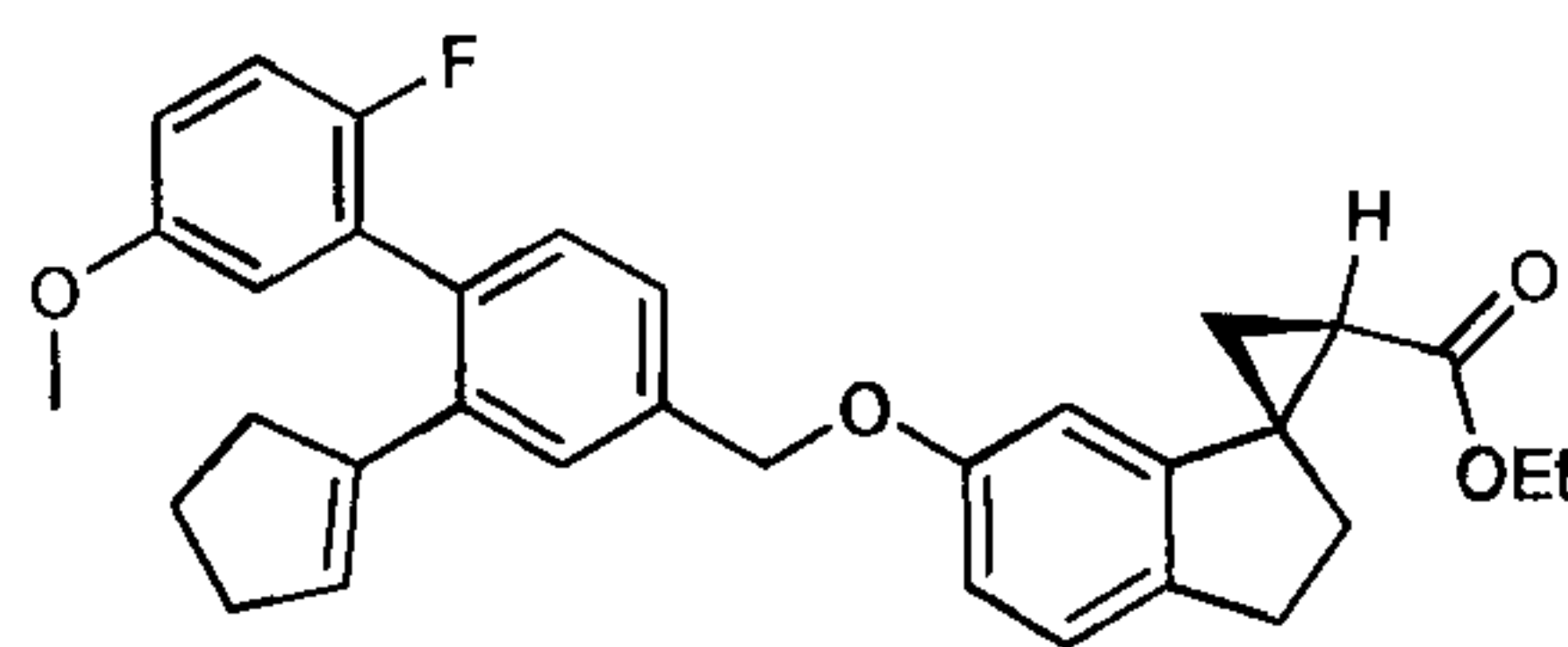
102. The compound



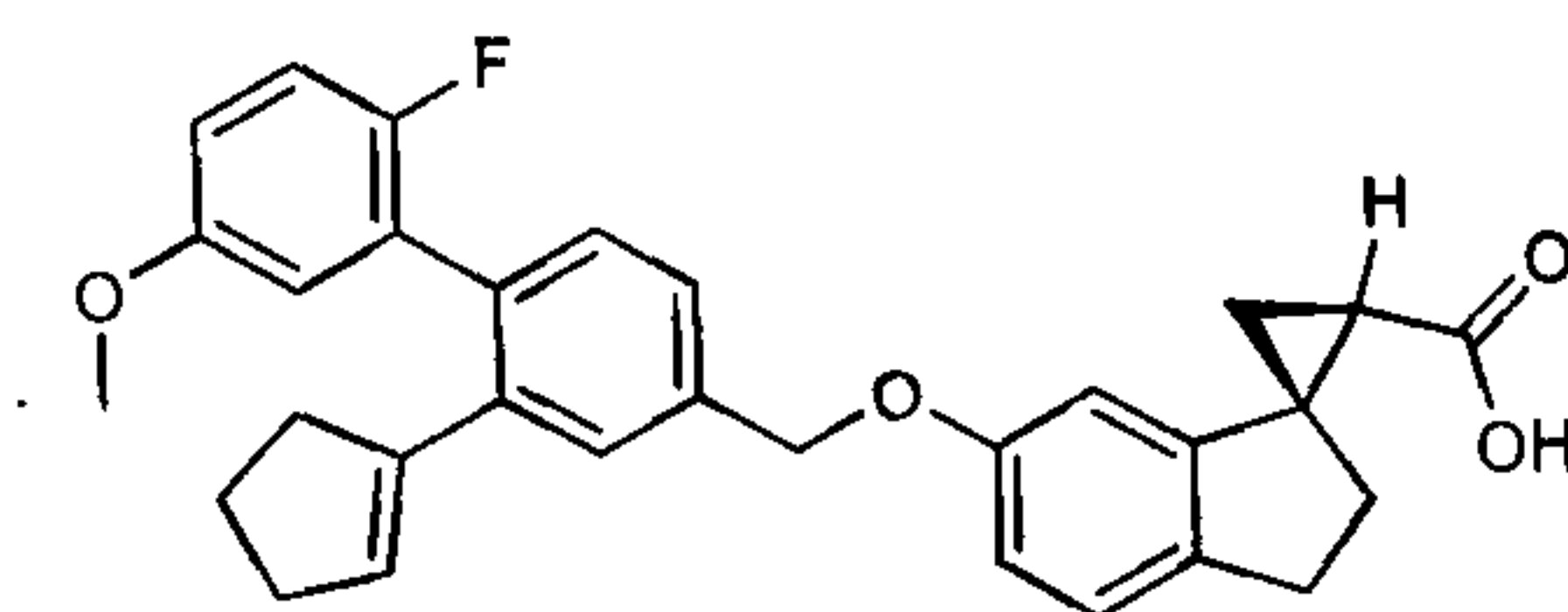
103. The compound



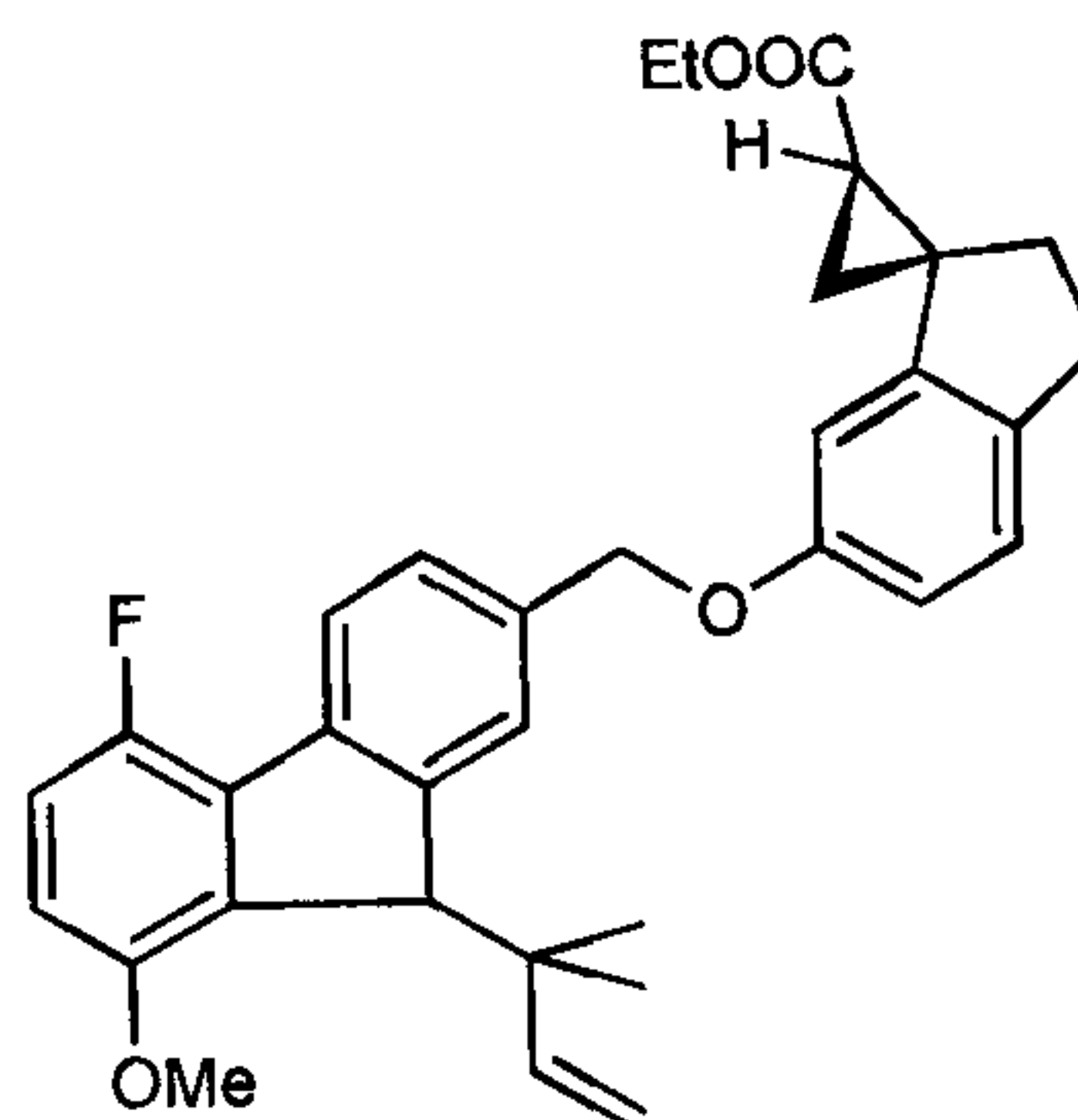
104. The compound



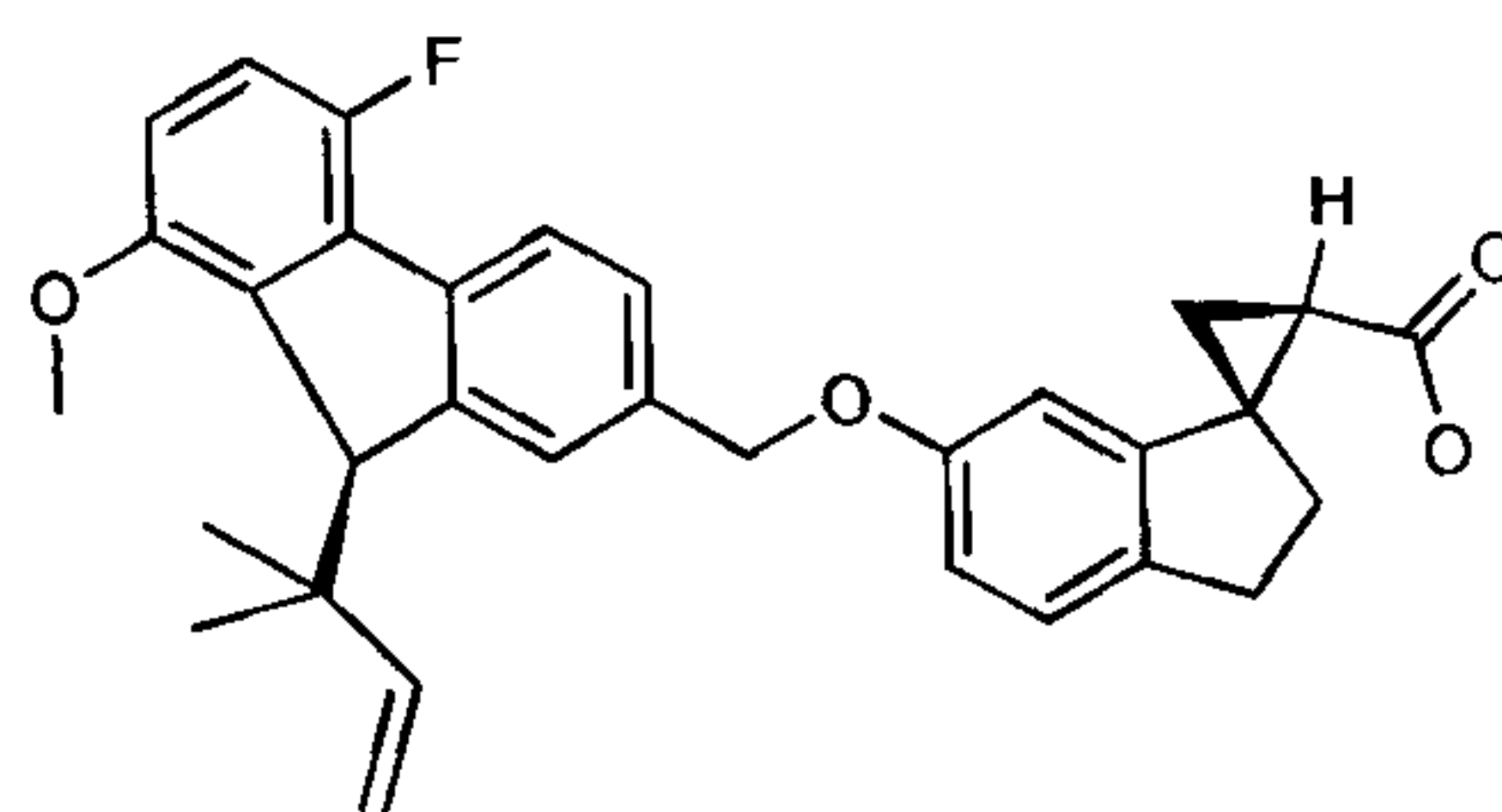
105. The compound



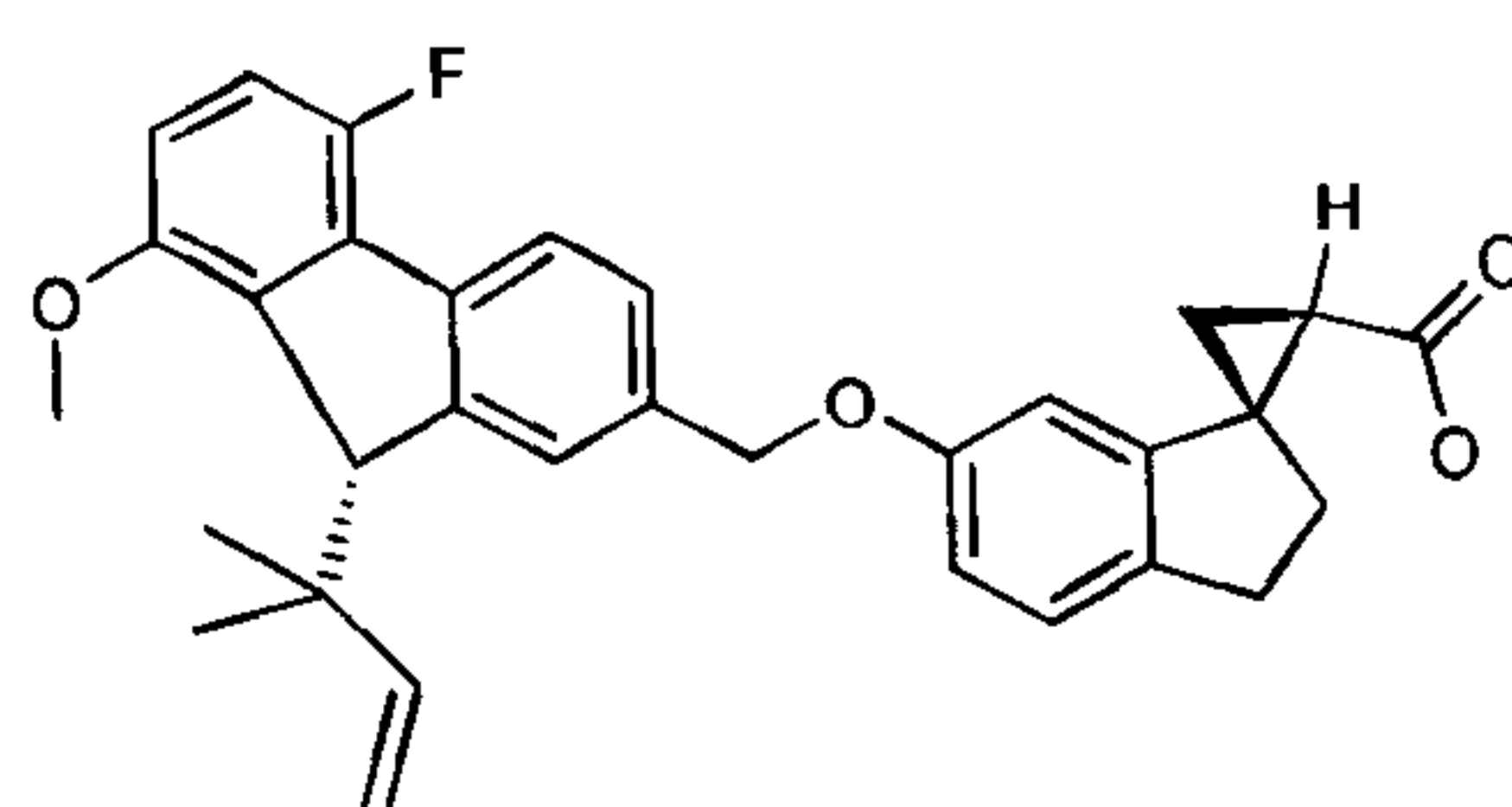
106. The compound



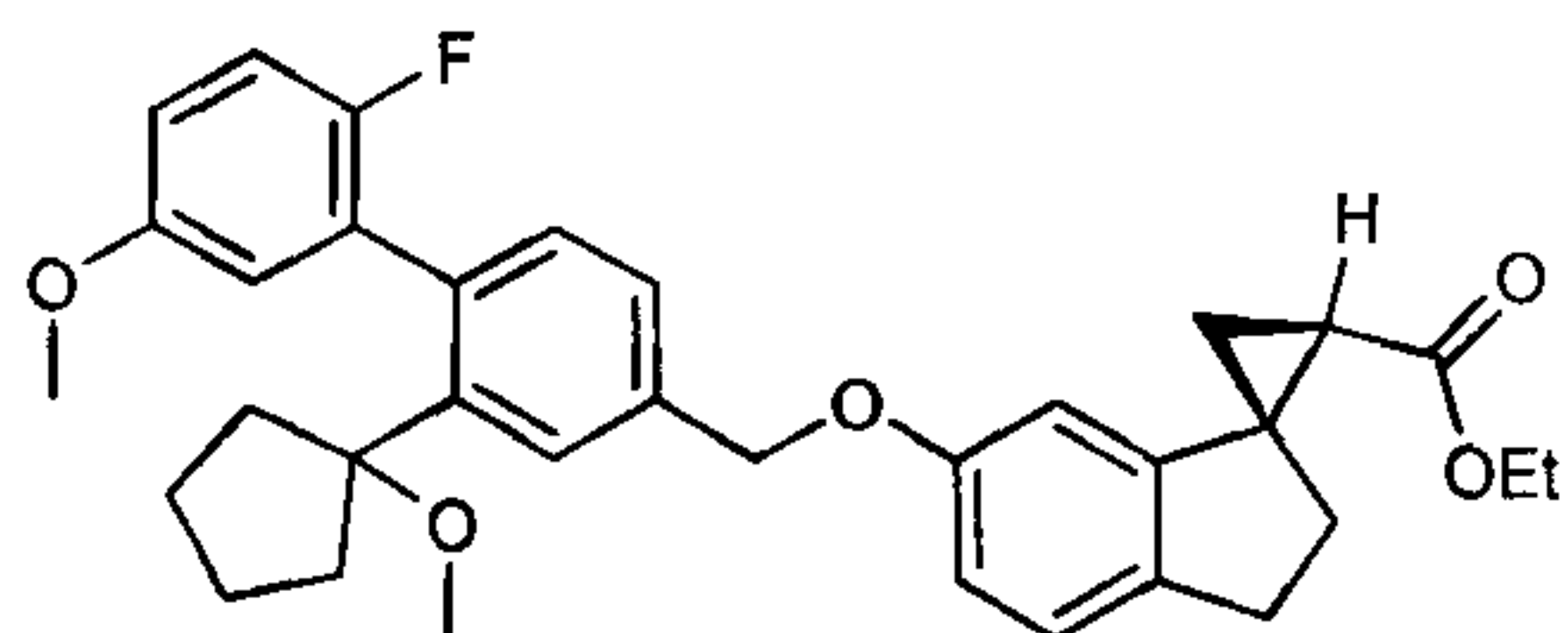
107. The compound



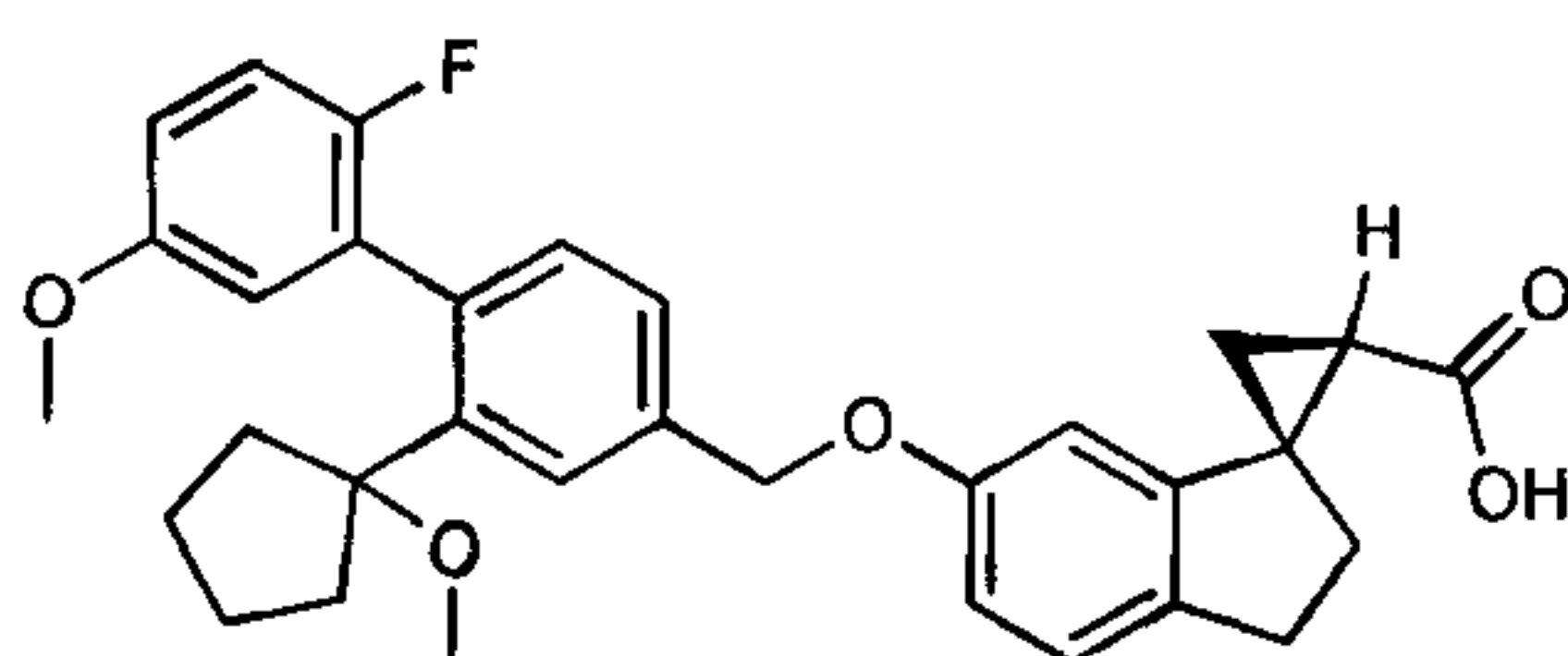
108. The compound



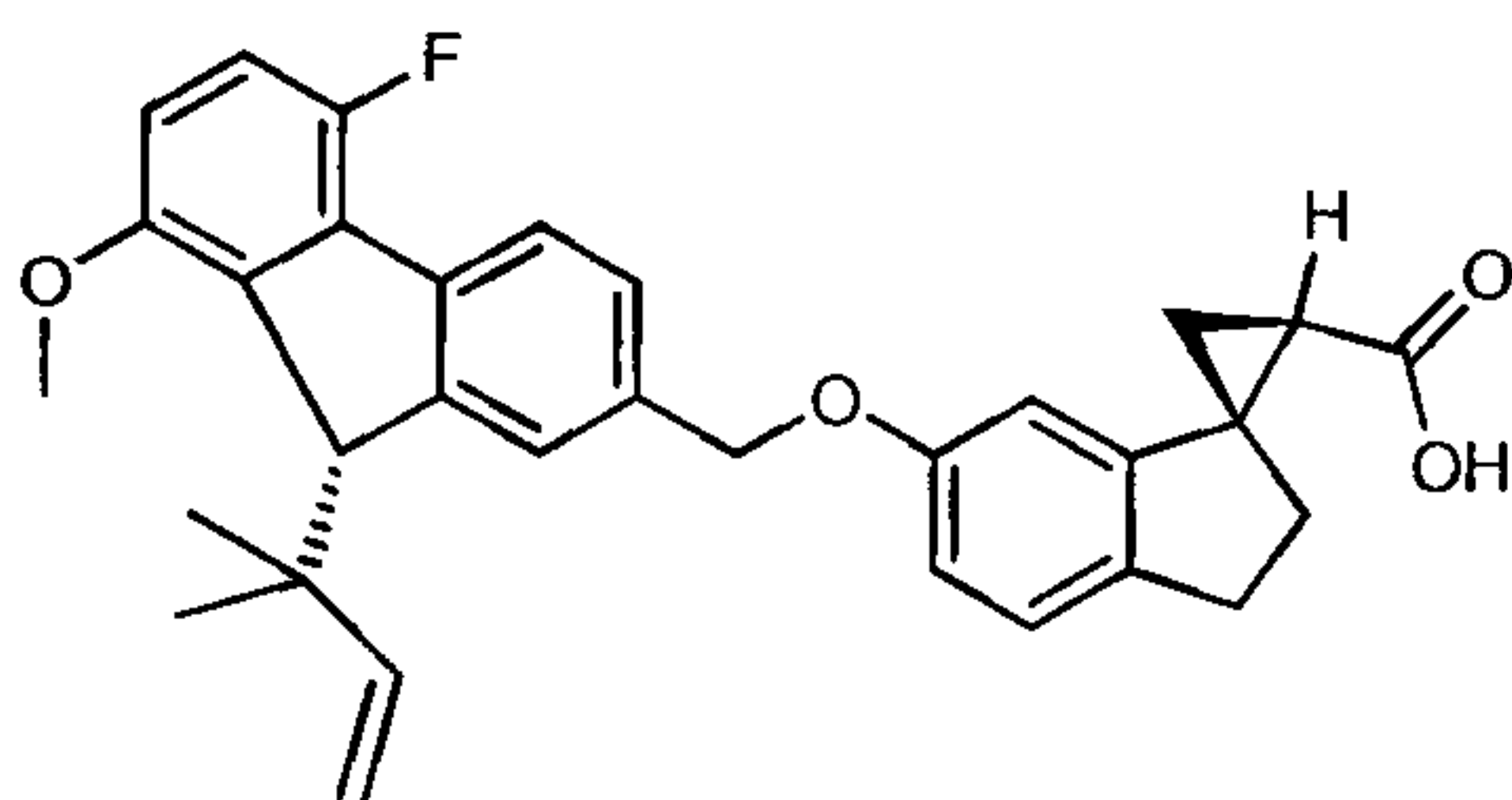
109. The compound



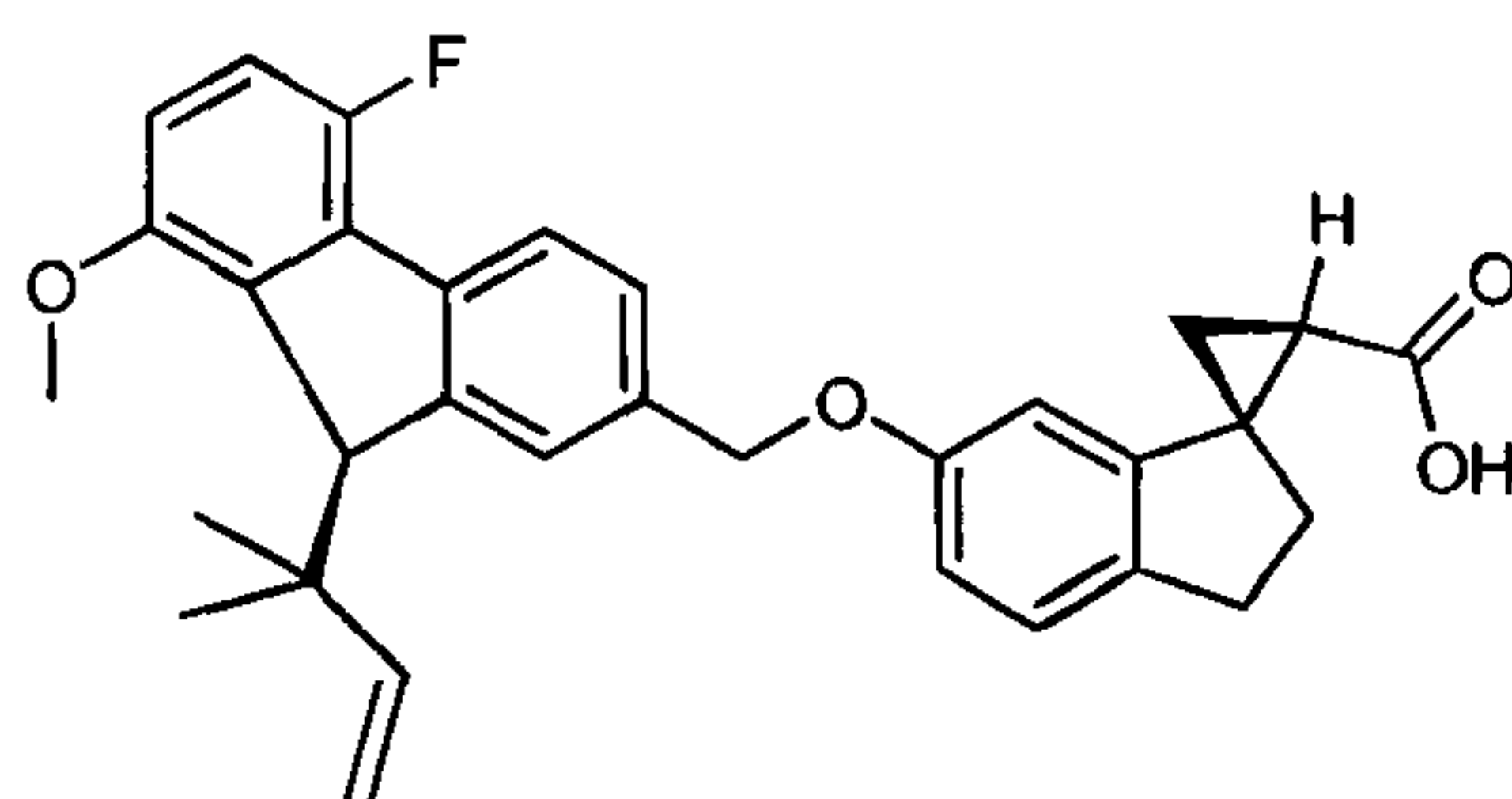
110. The compound



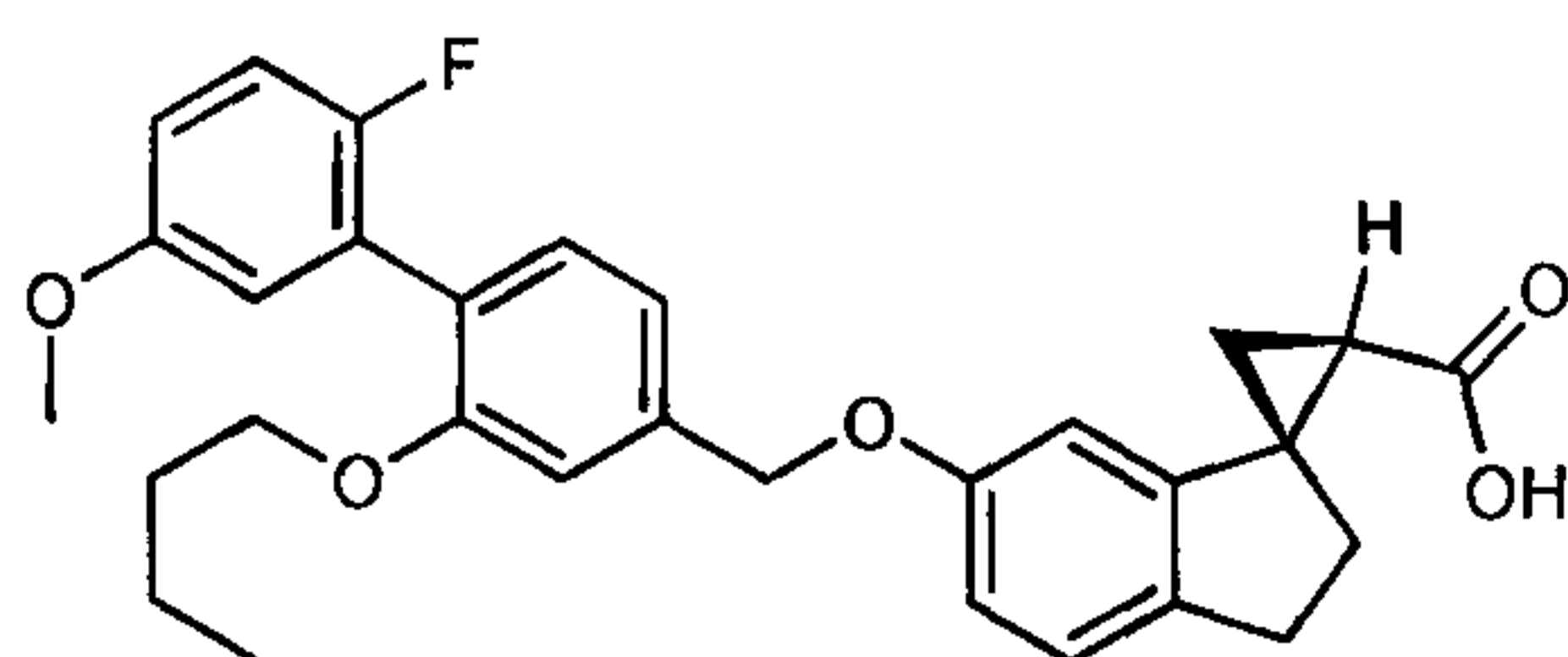
111. The compound

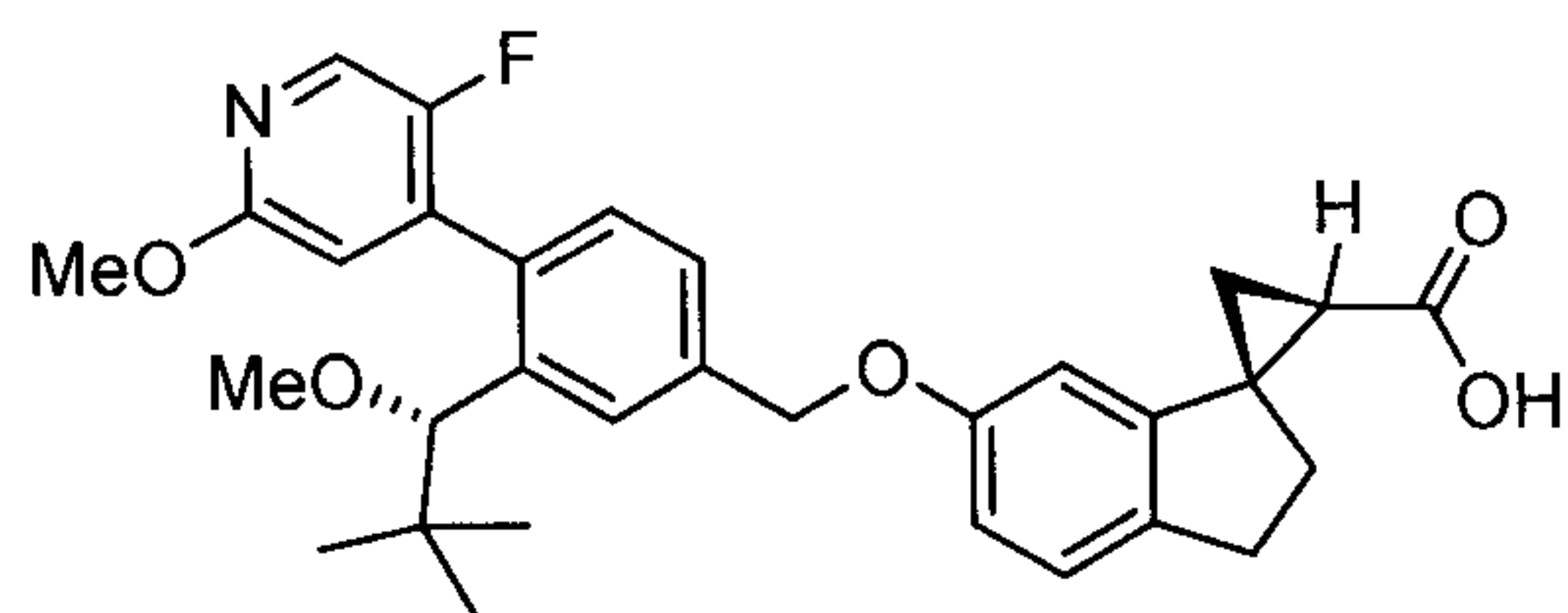


112. The compound

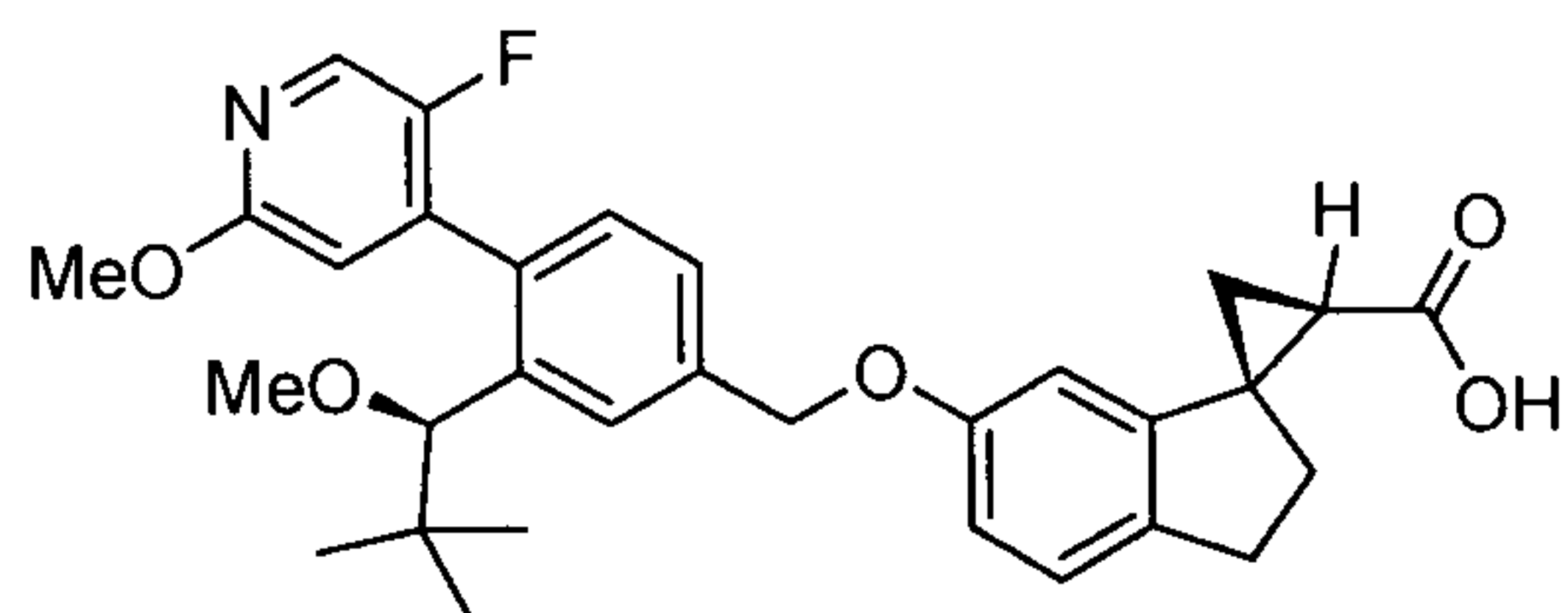


113. The compound

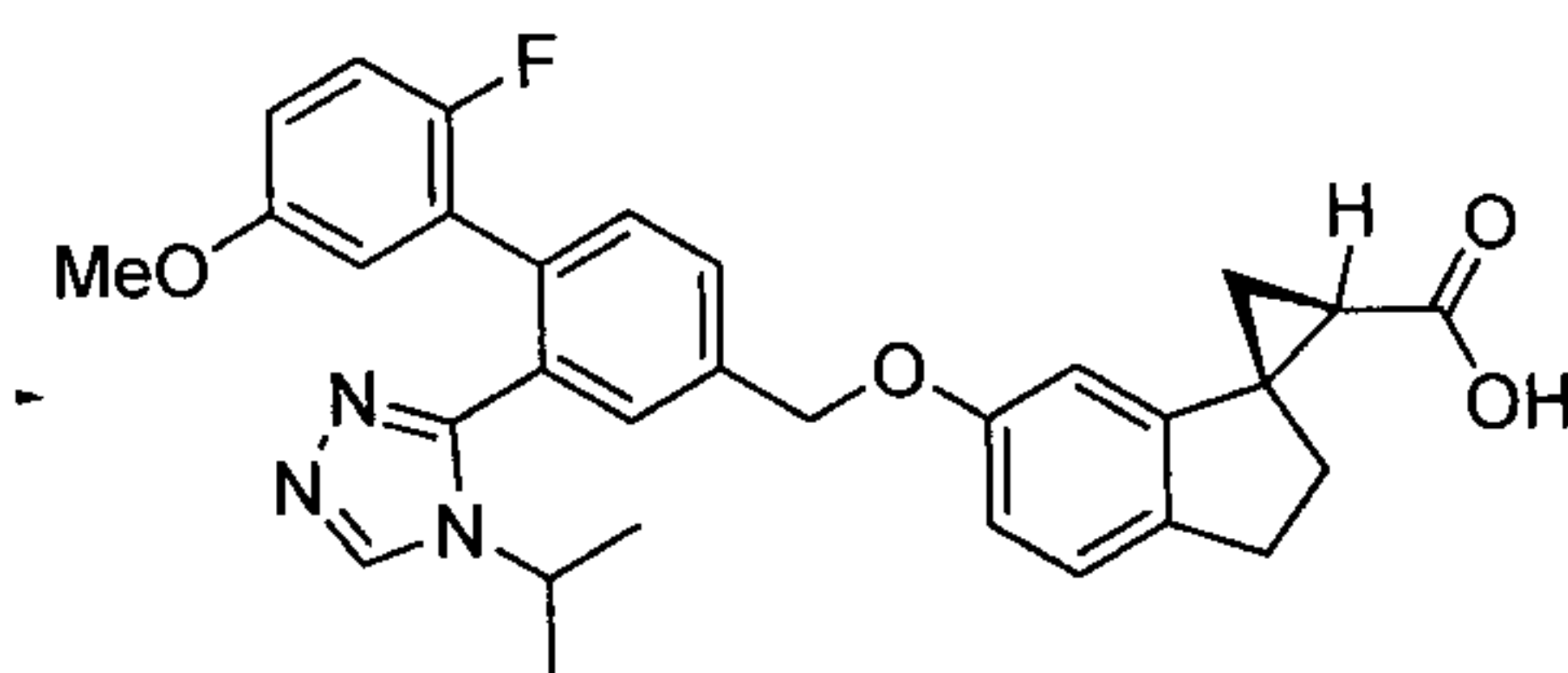




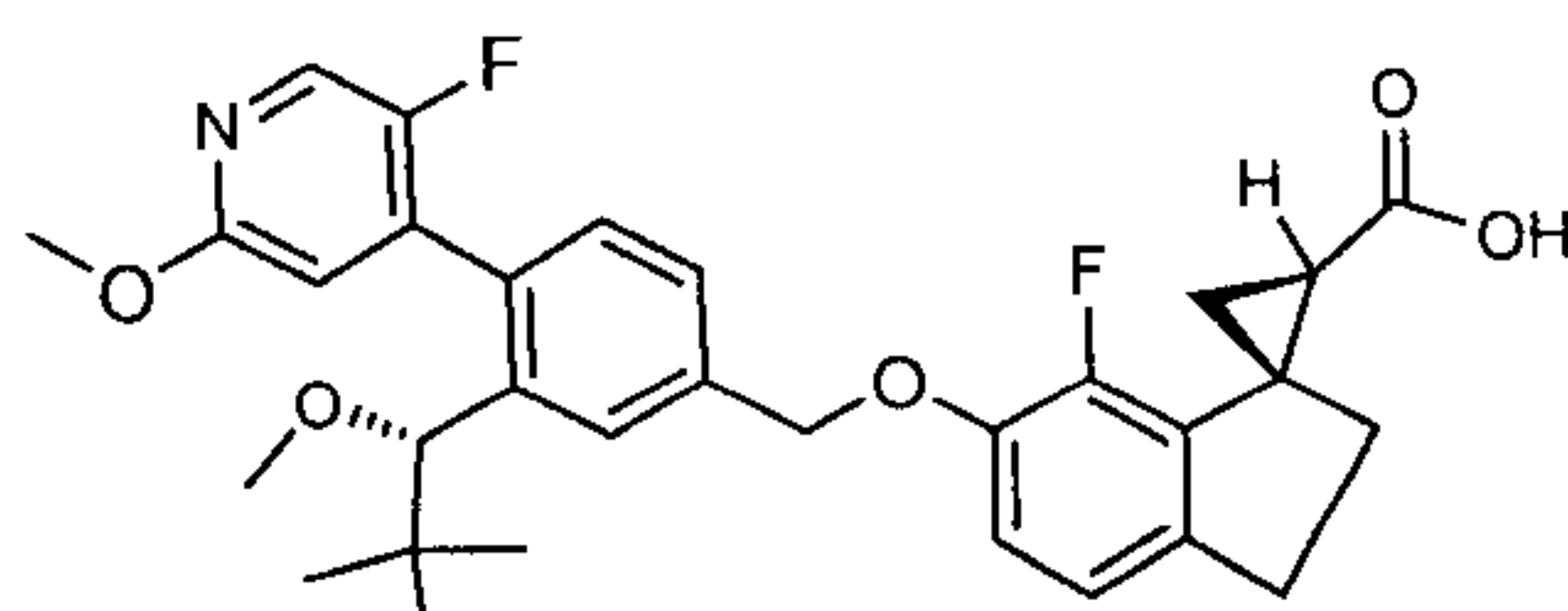
120. The compound



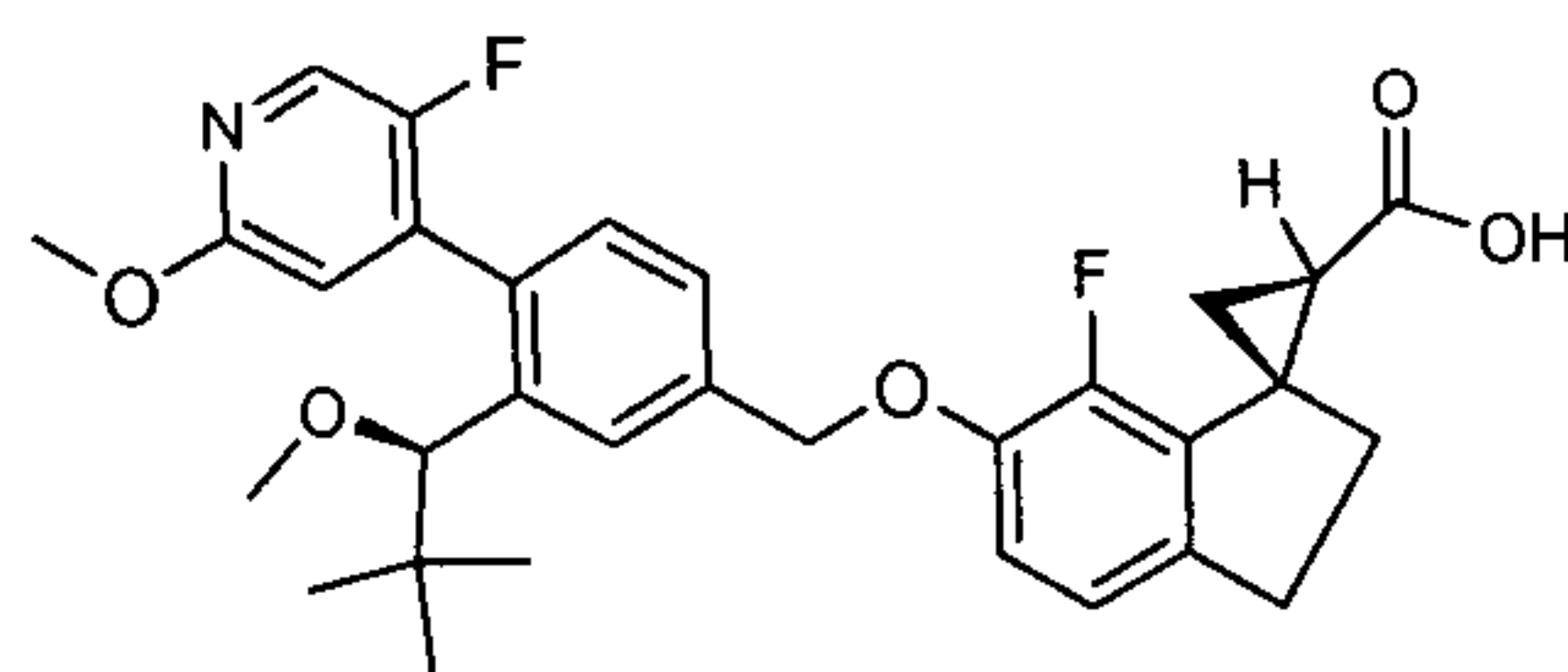
121. The compound



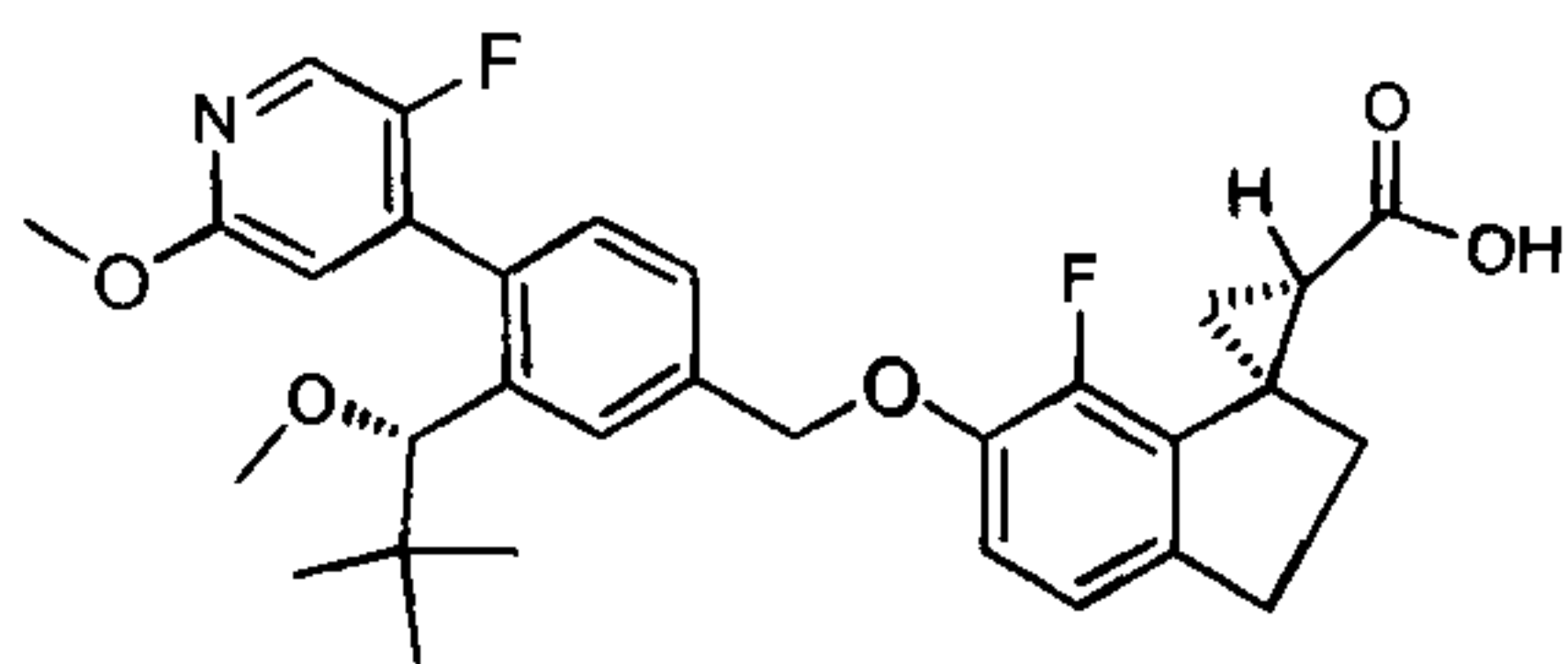
122. The compound



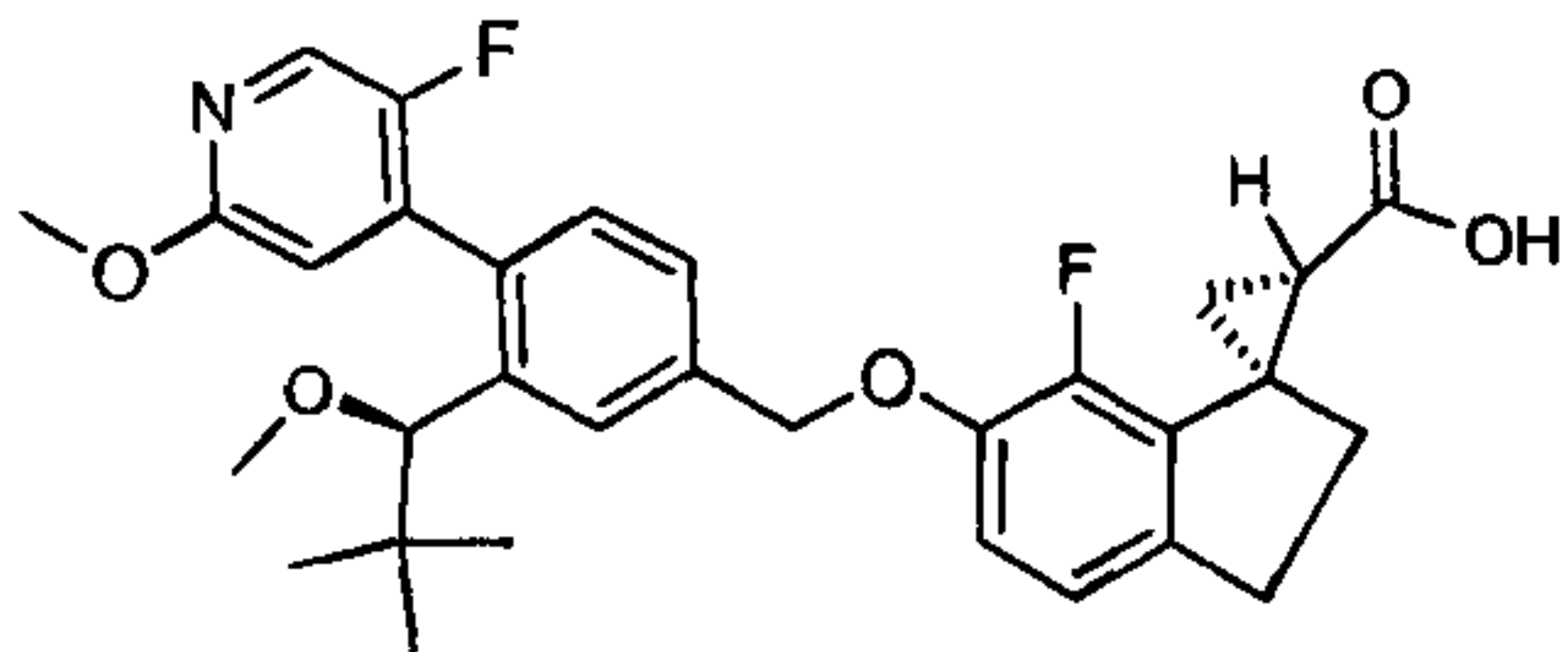
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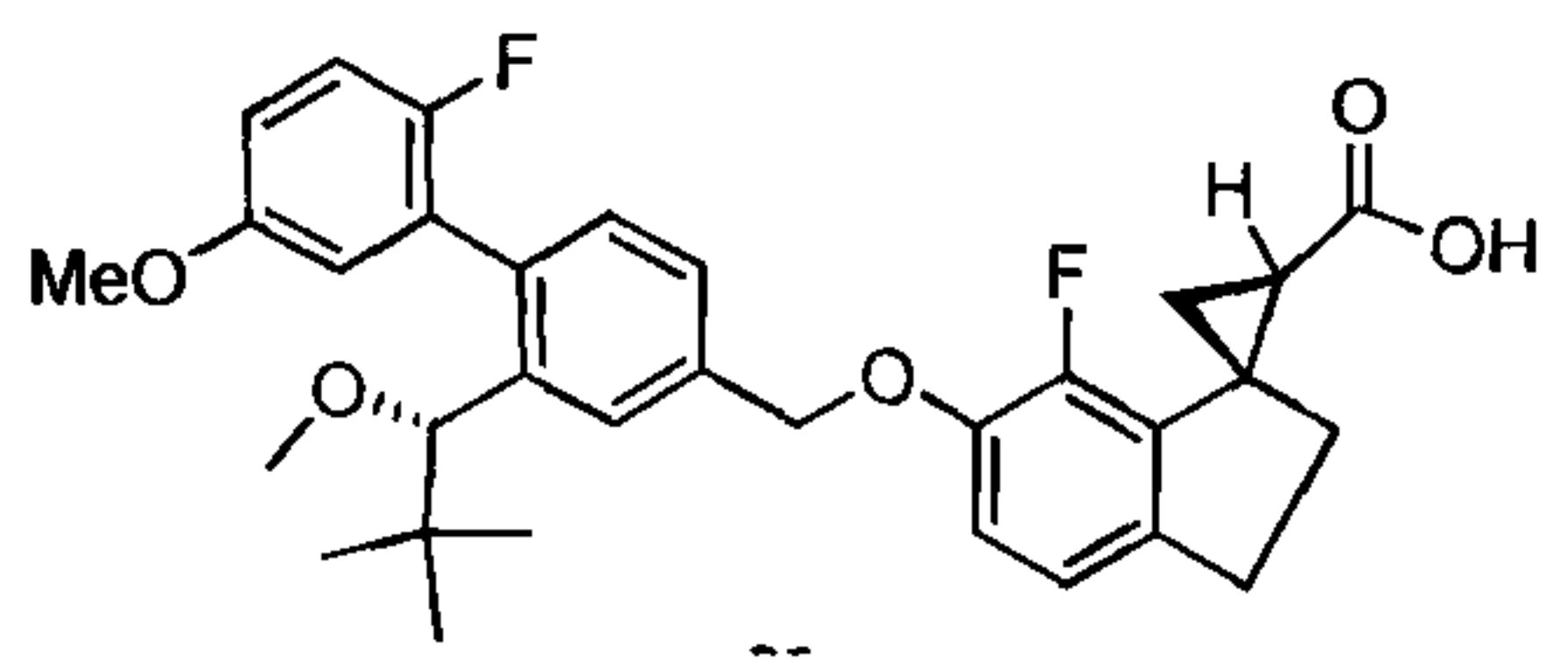
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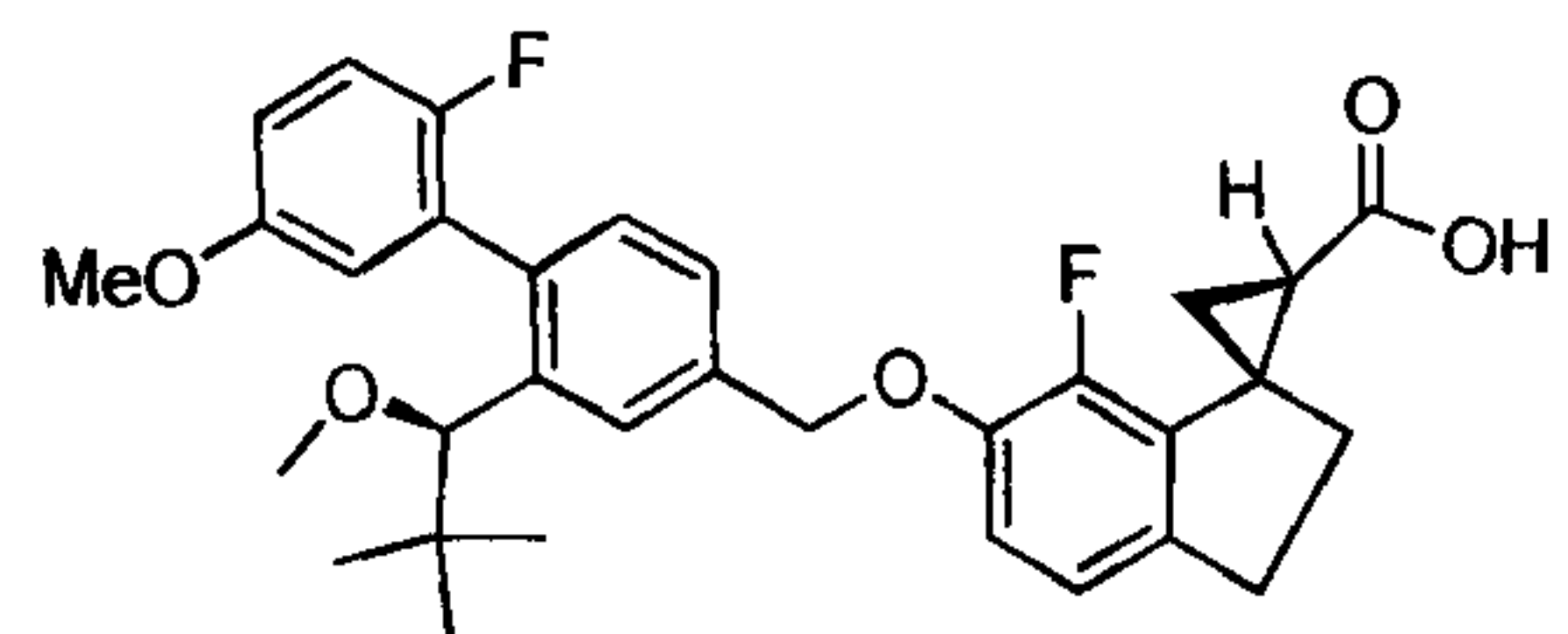
125. The compound



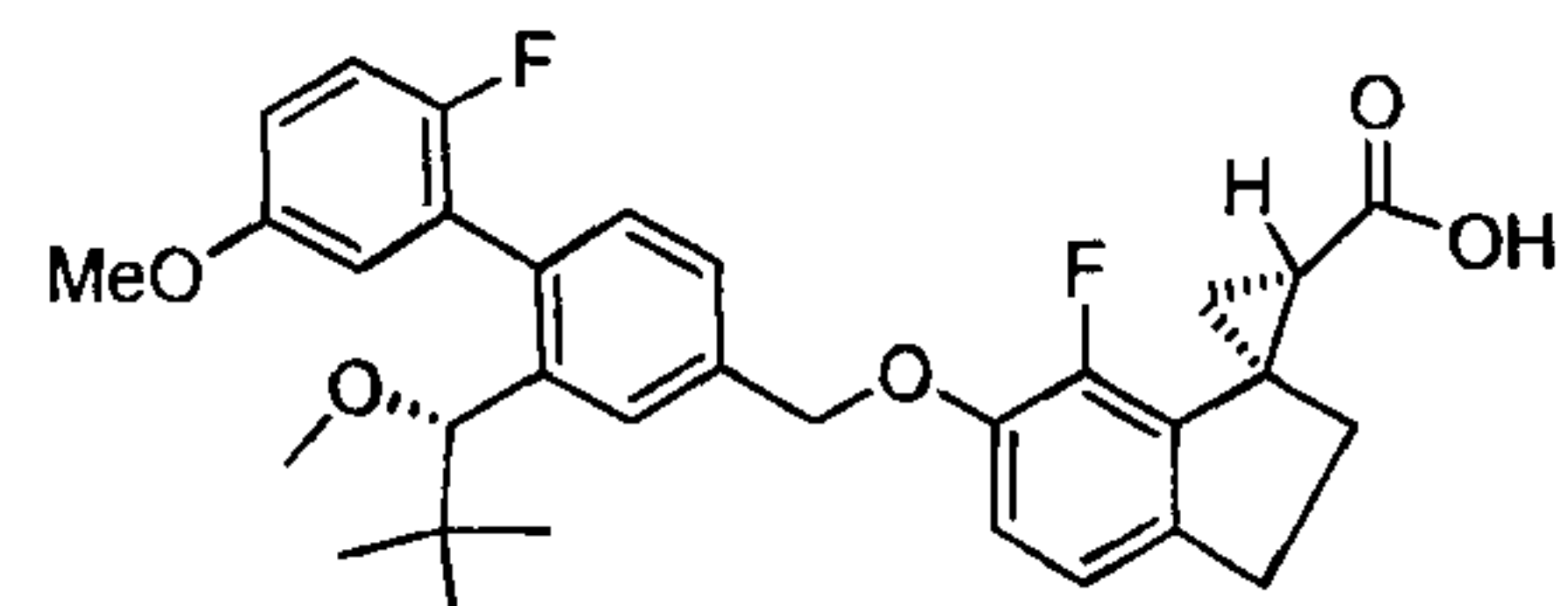
126. The compound



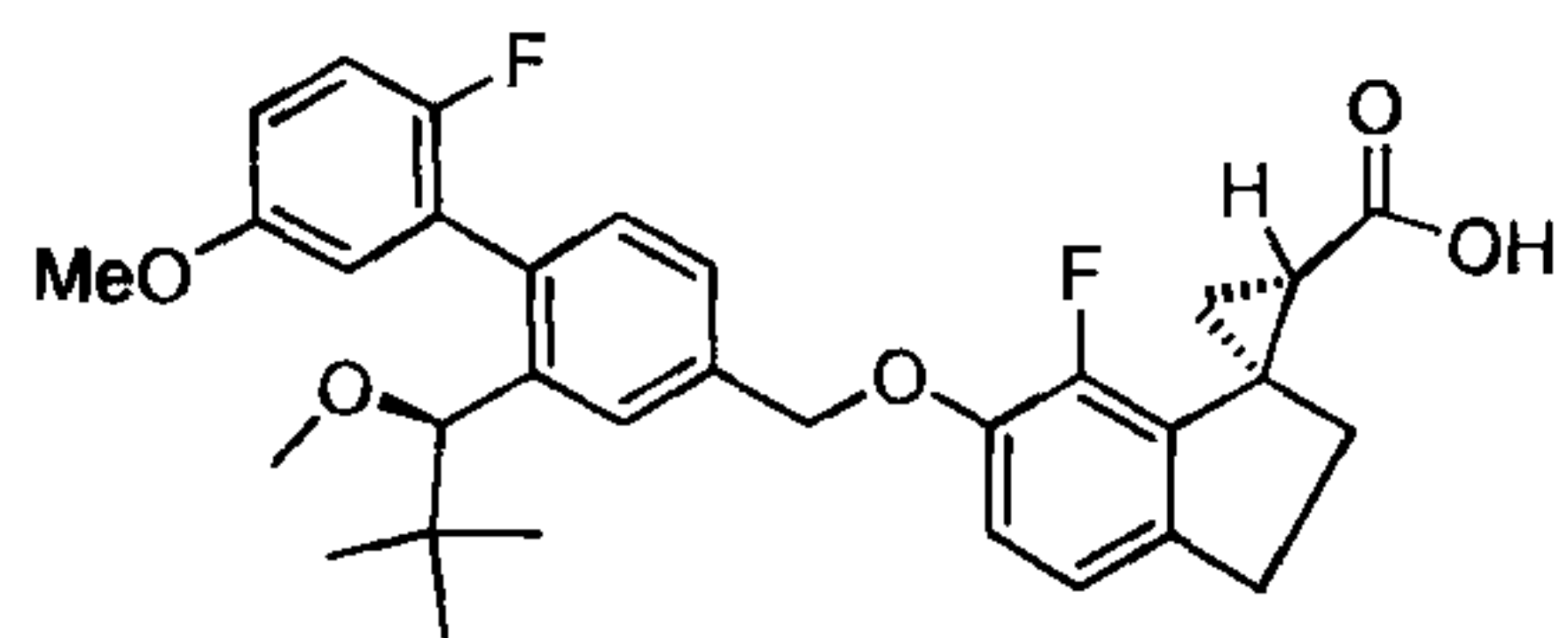
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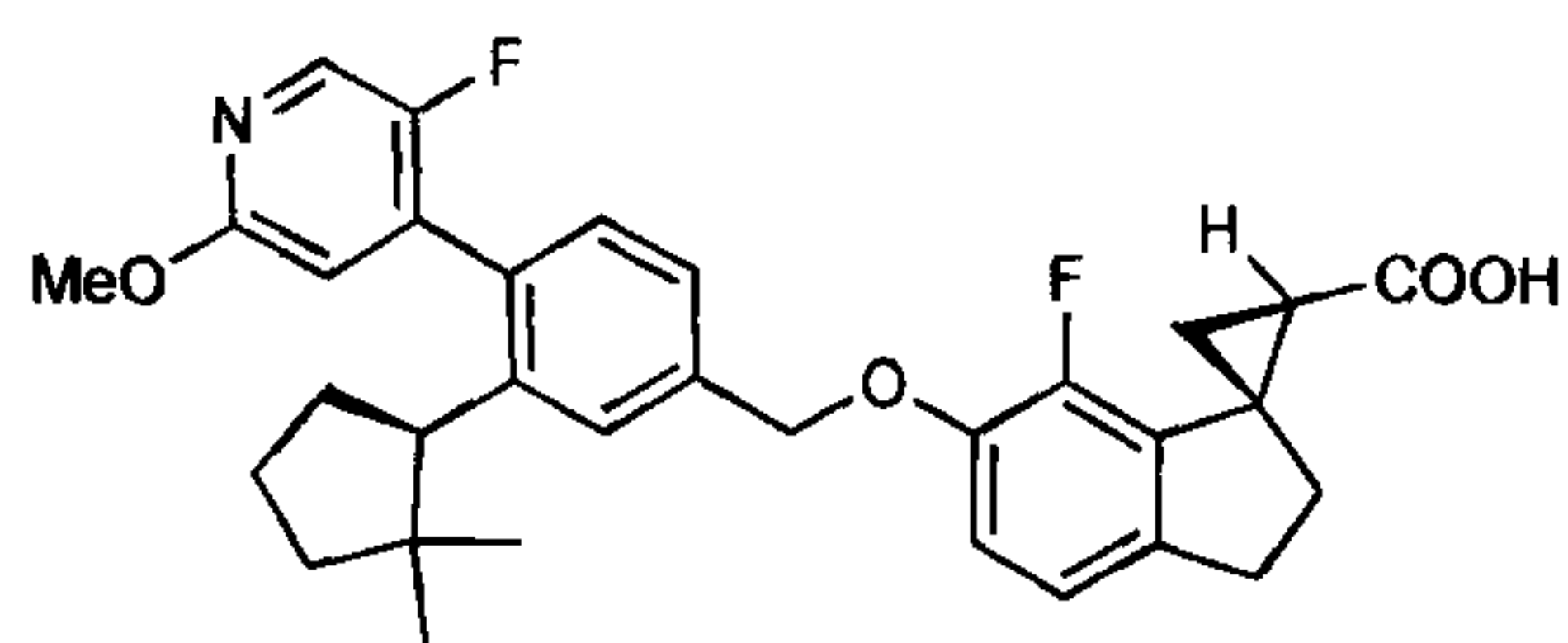
128. The compound



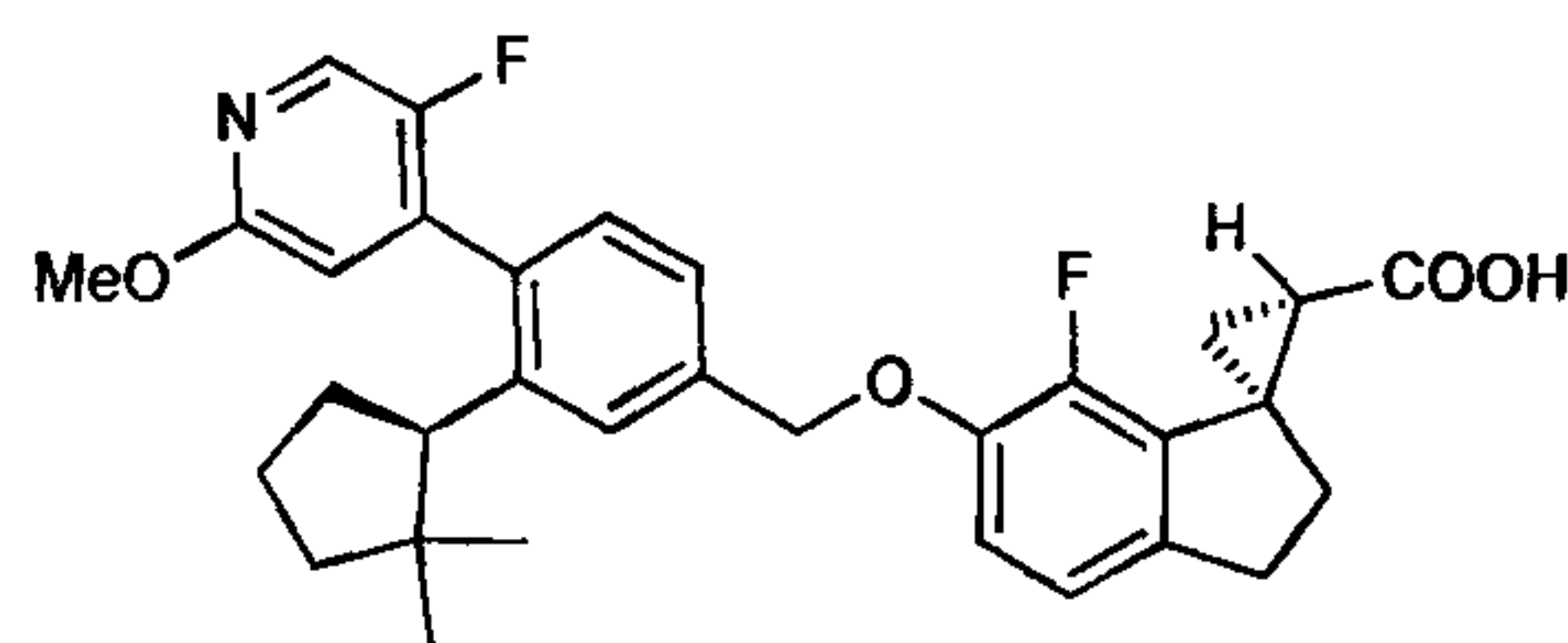
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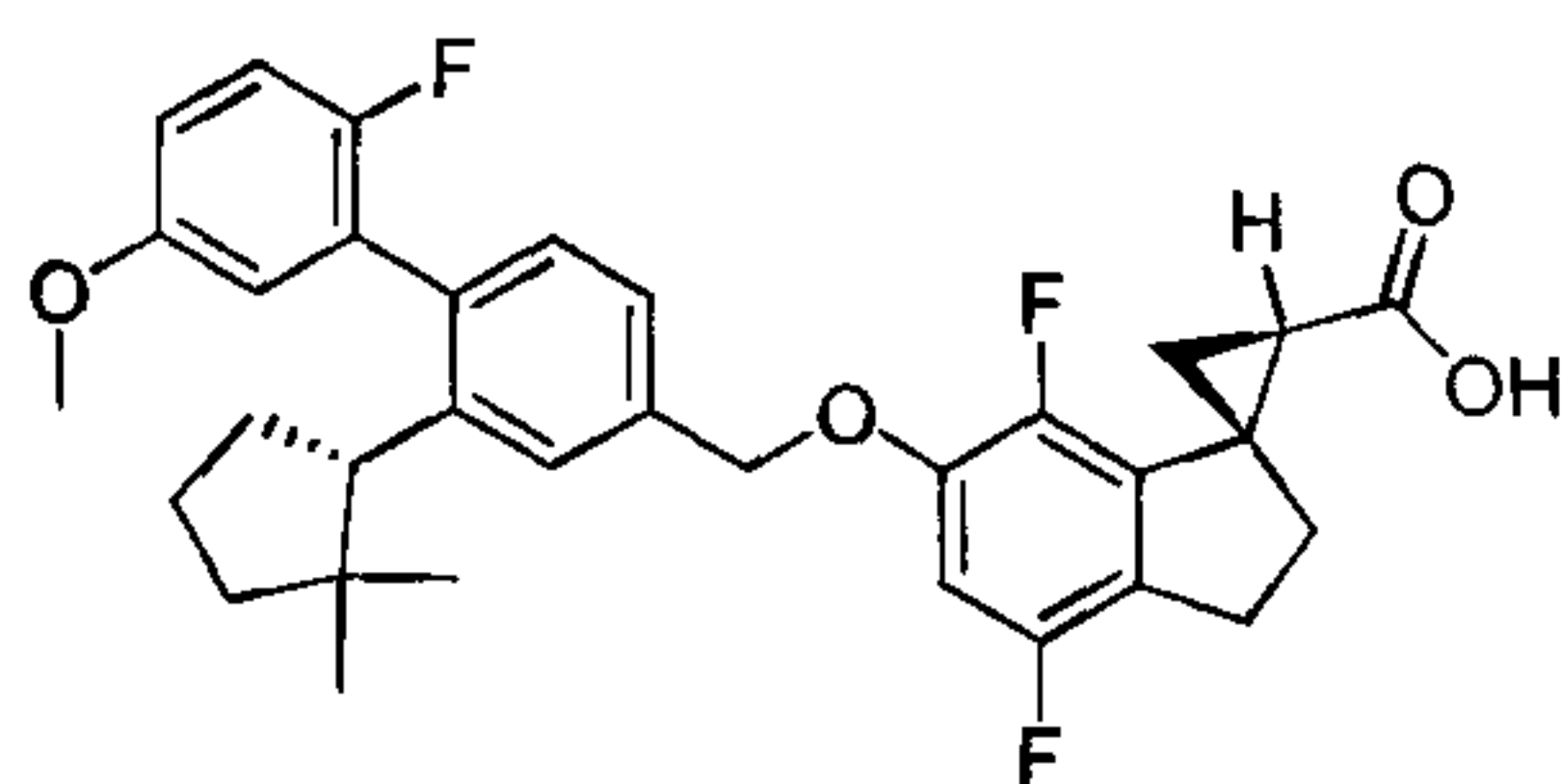
130. The compound



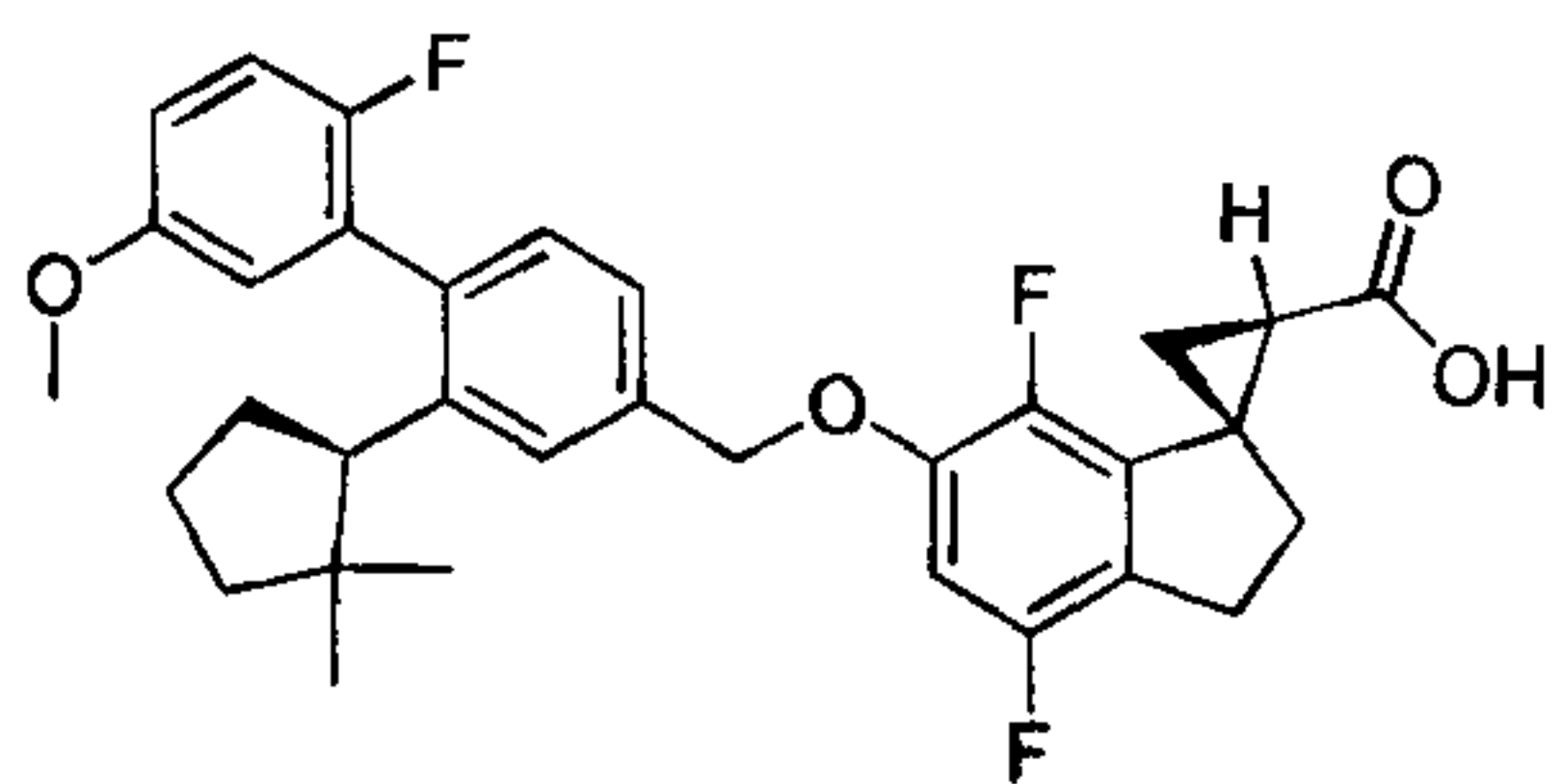
131. The compound



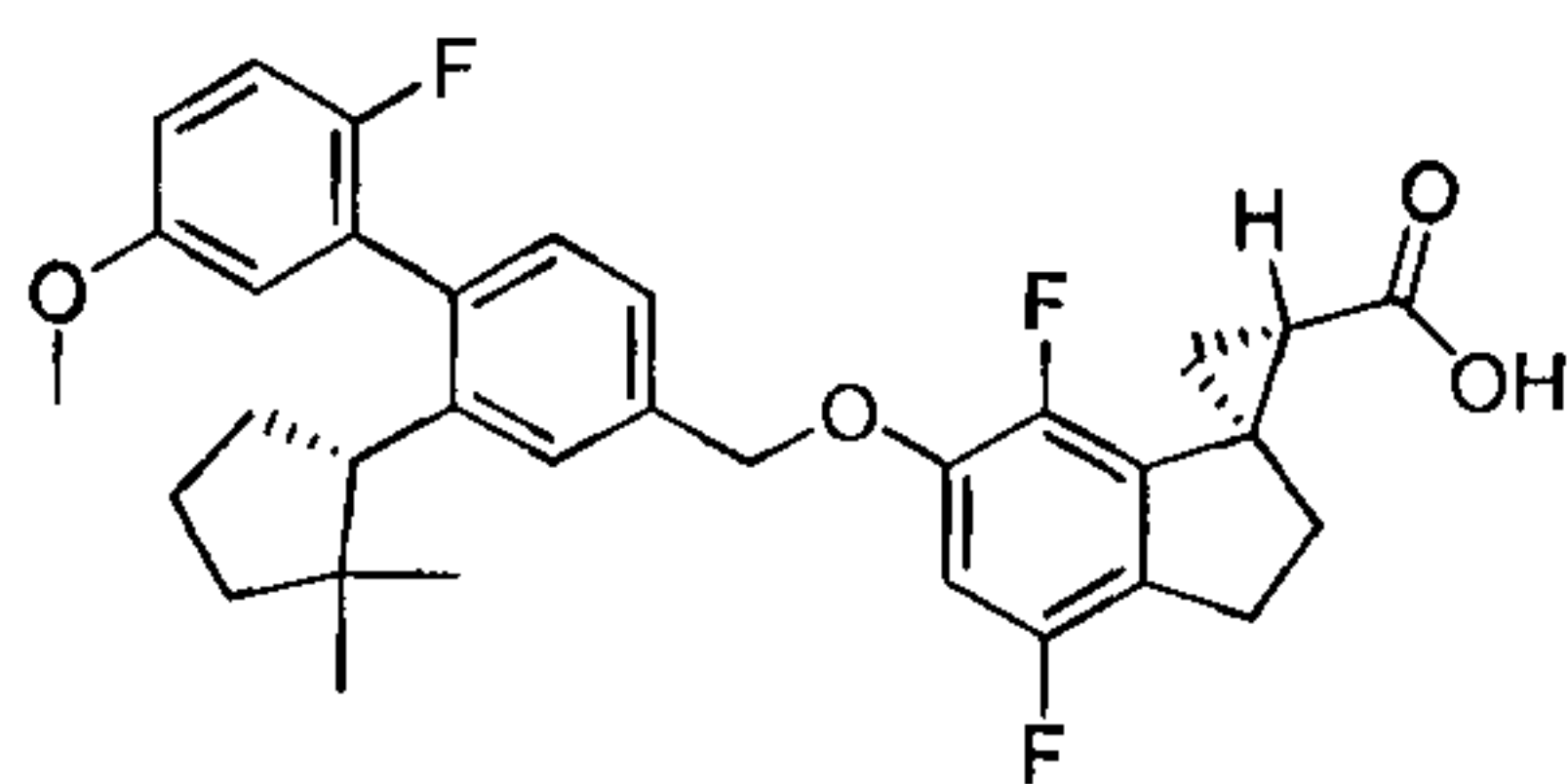
132. The compound



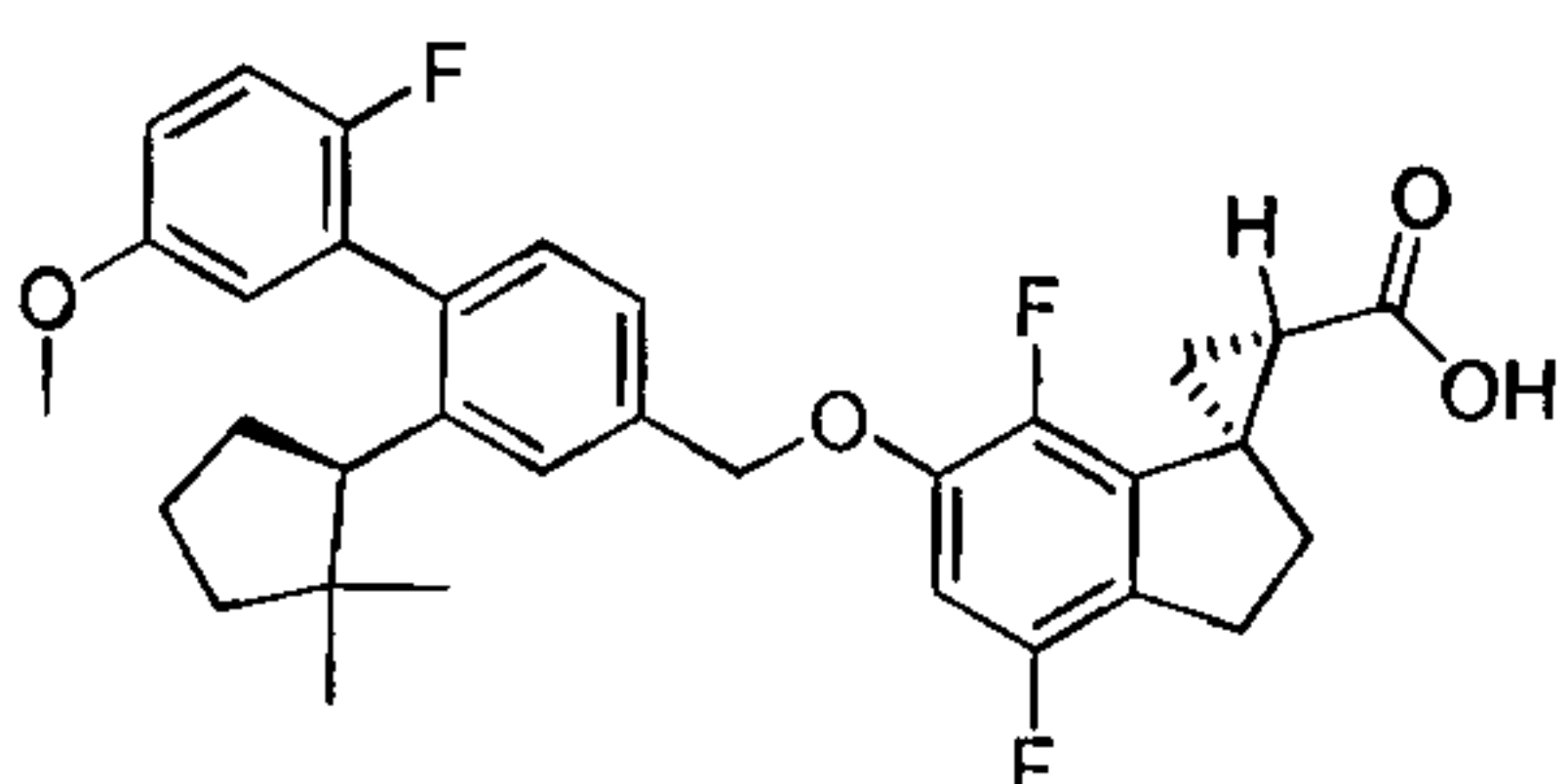
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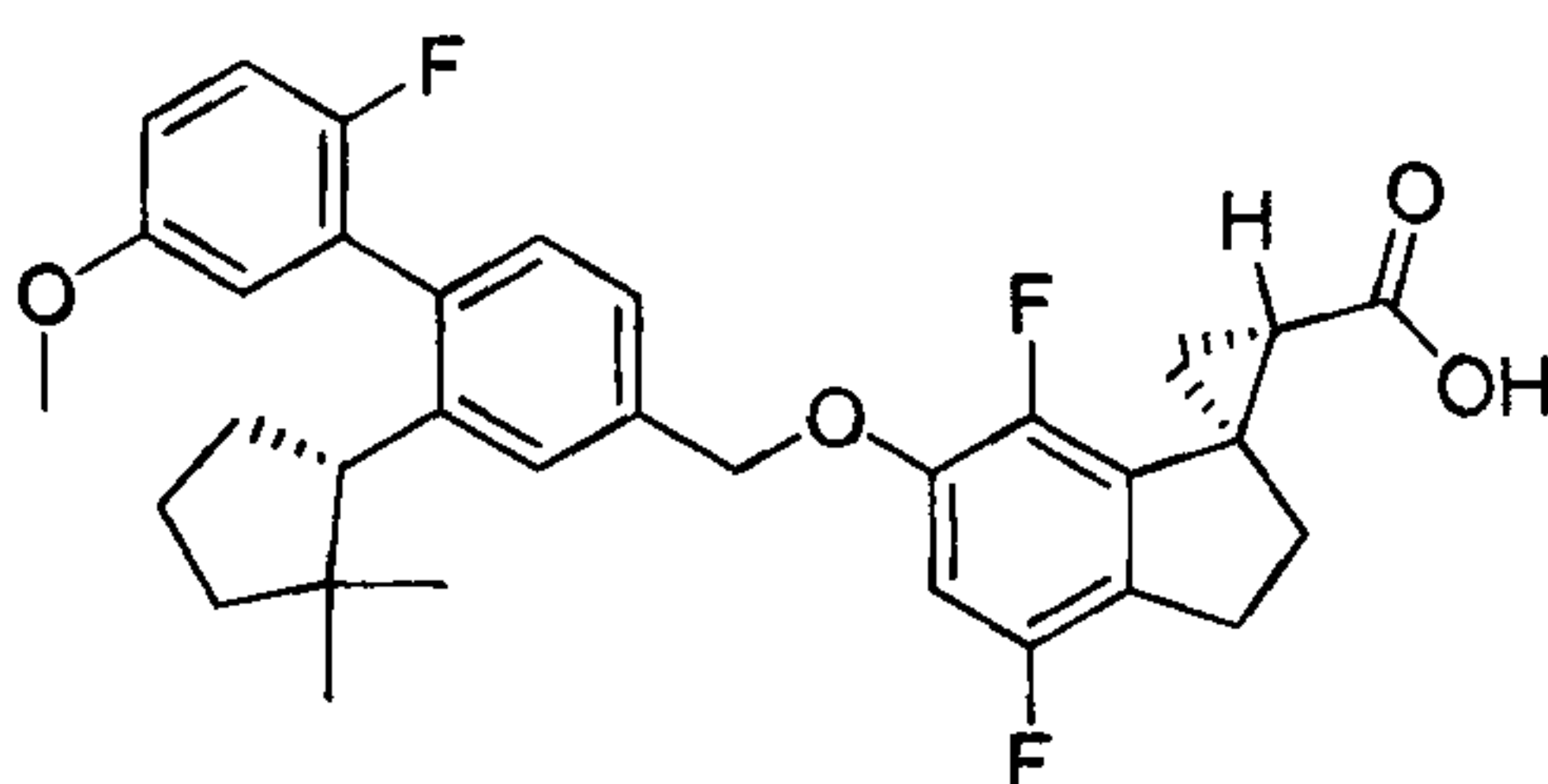
134. The compound



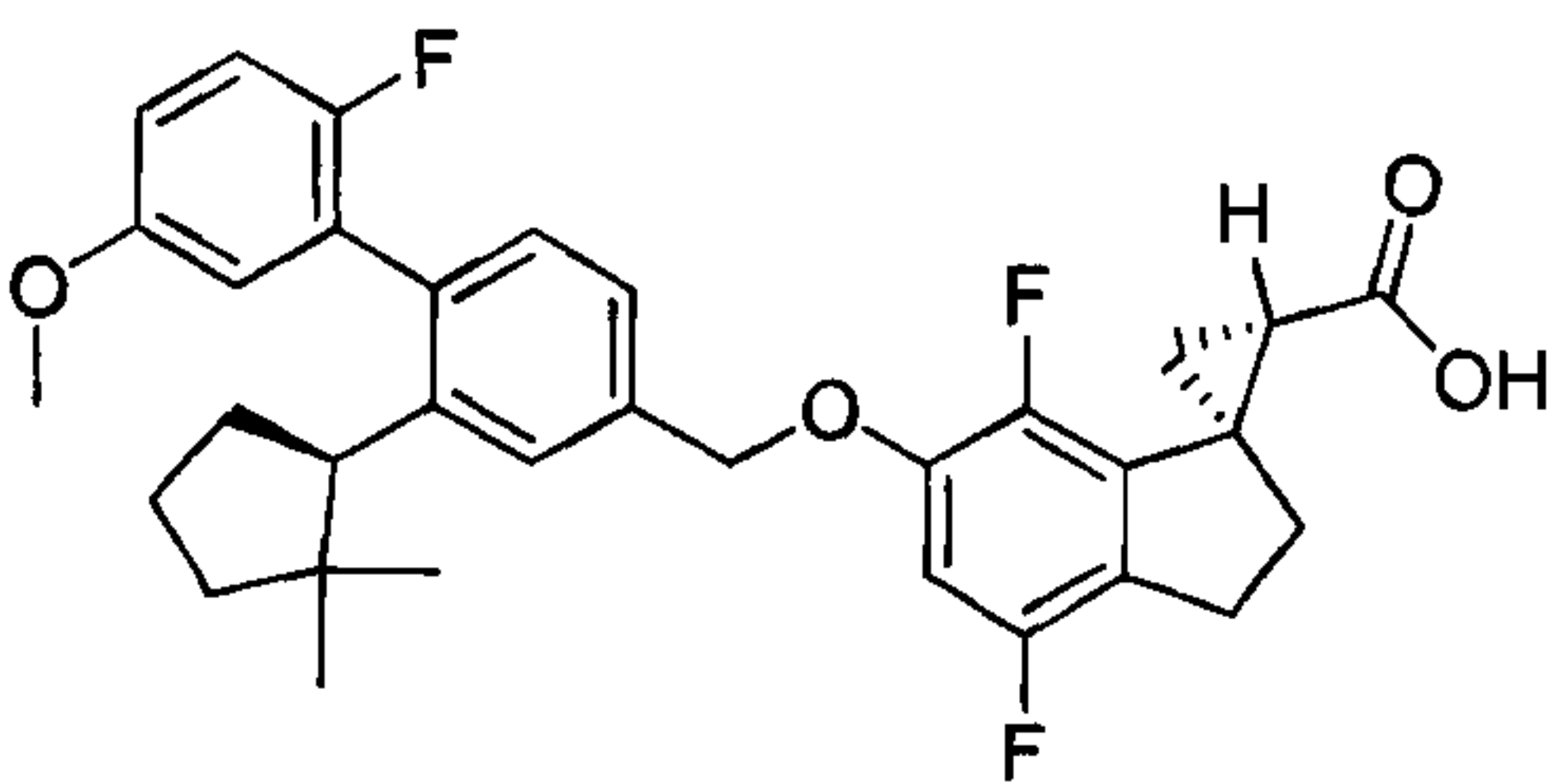
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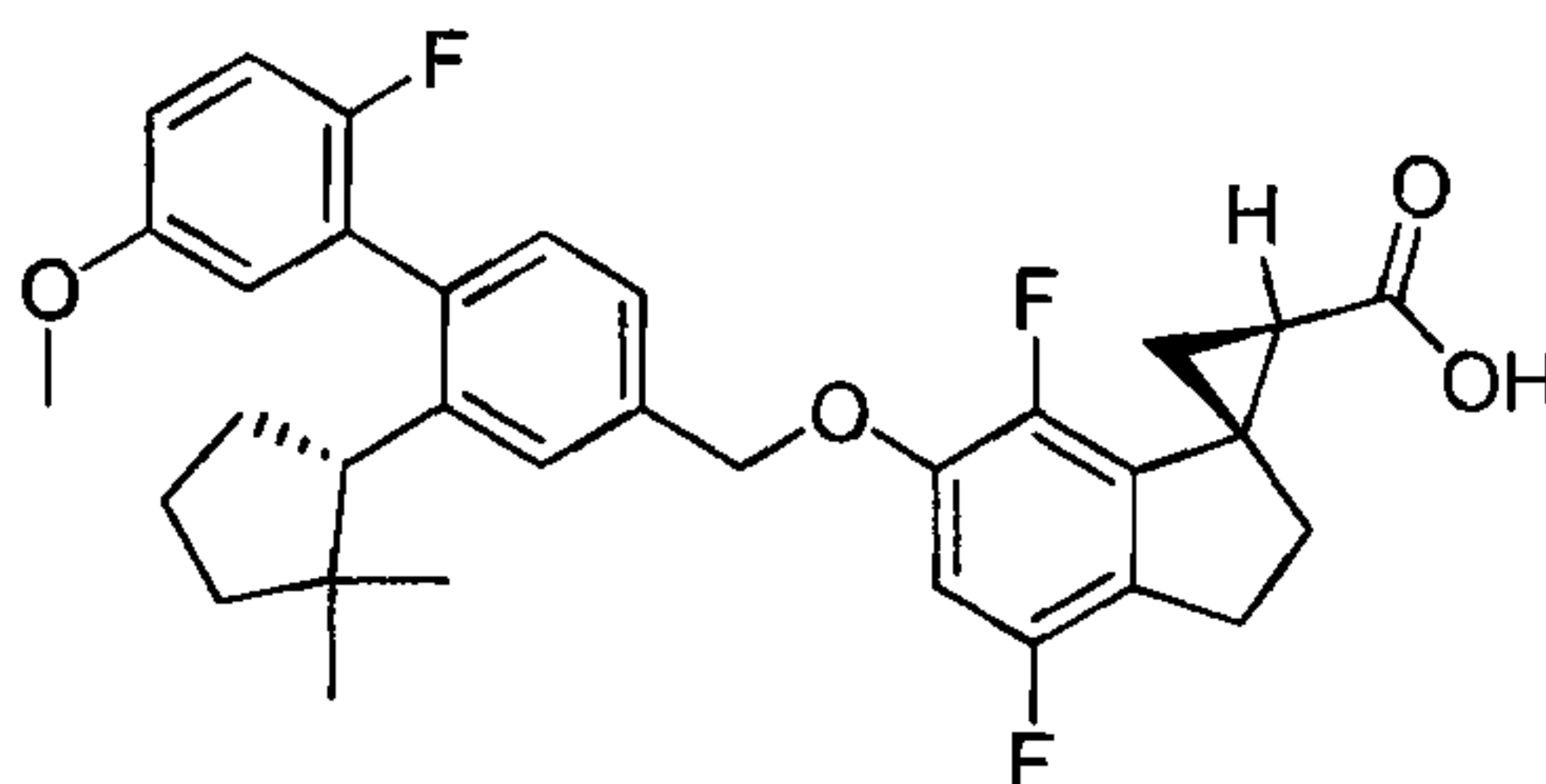
136. The compound



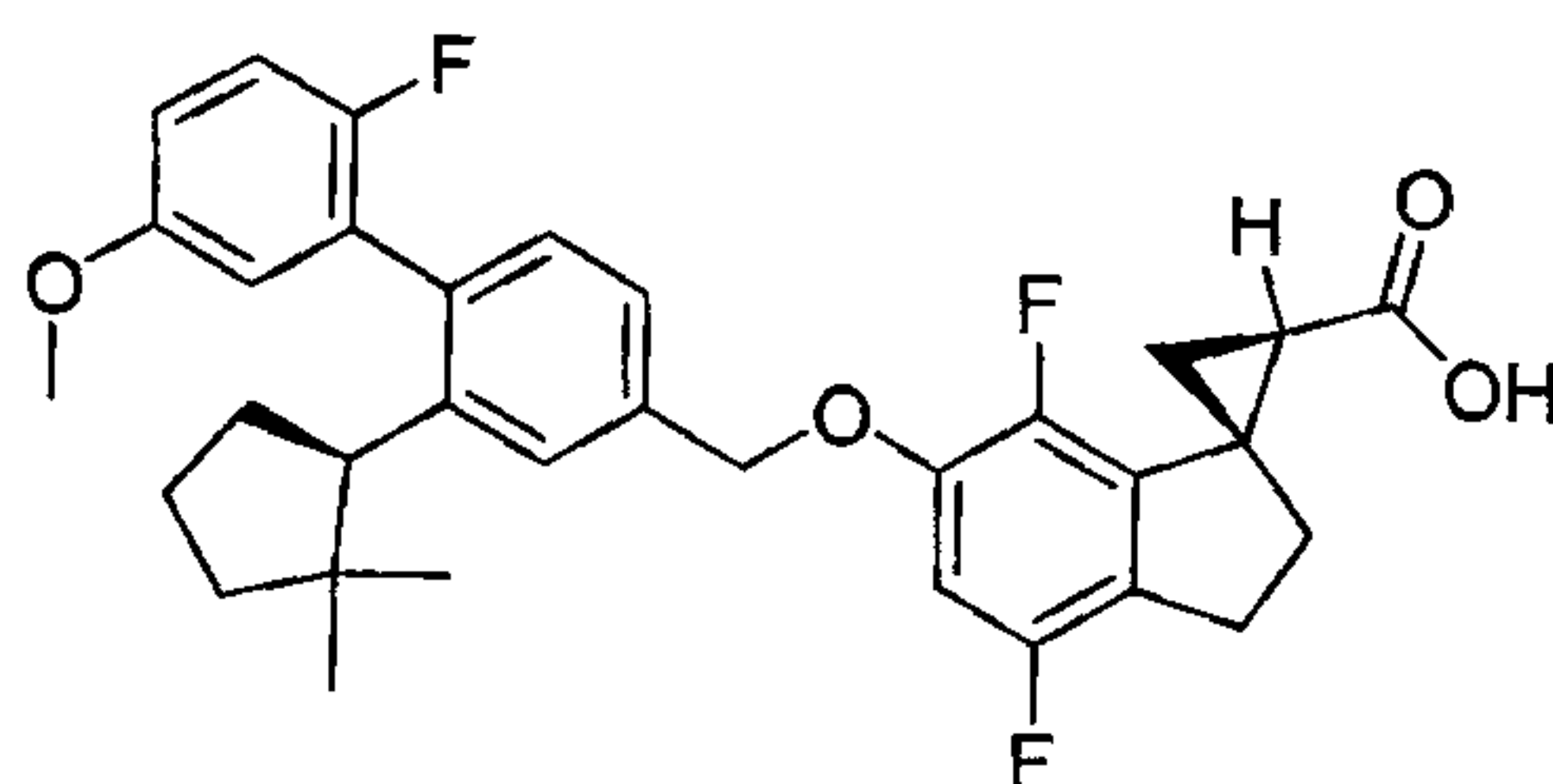
137. The compound



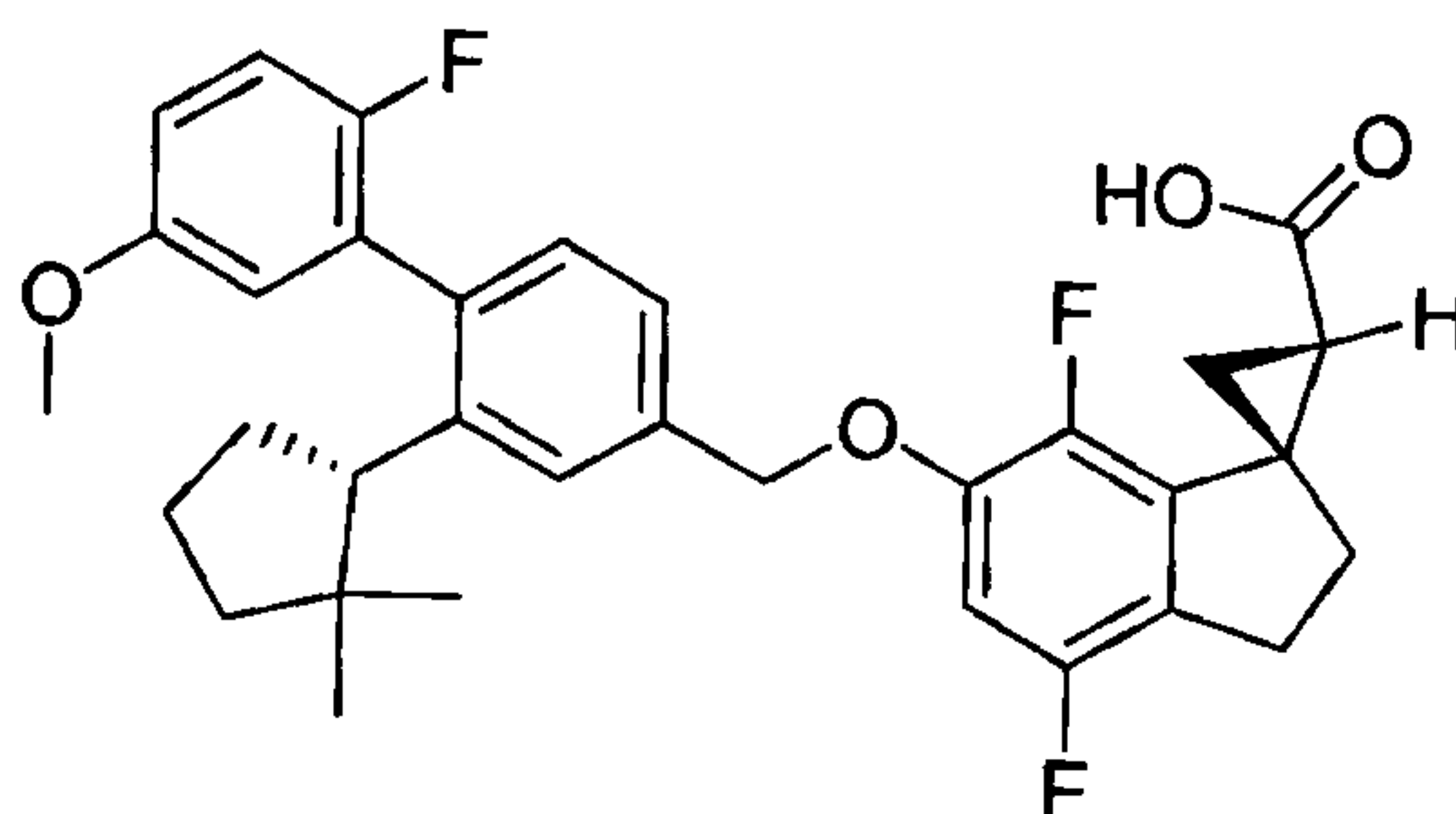
138. The compound



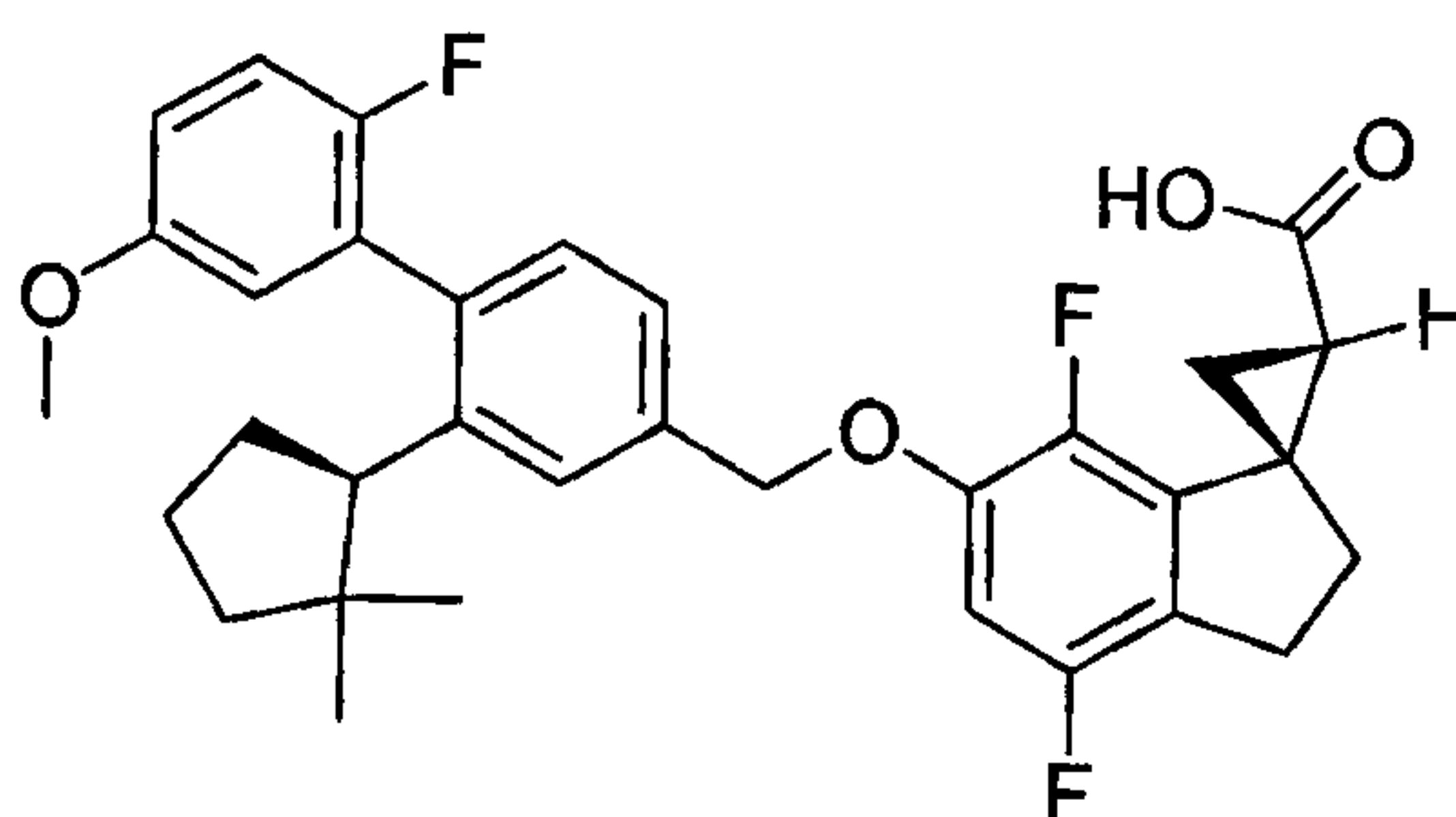
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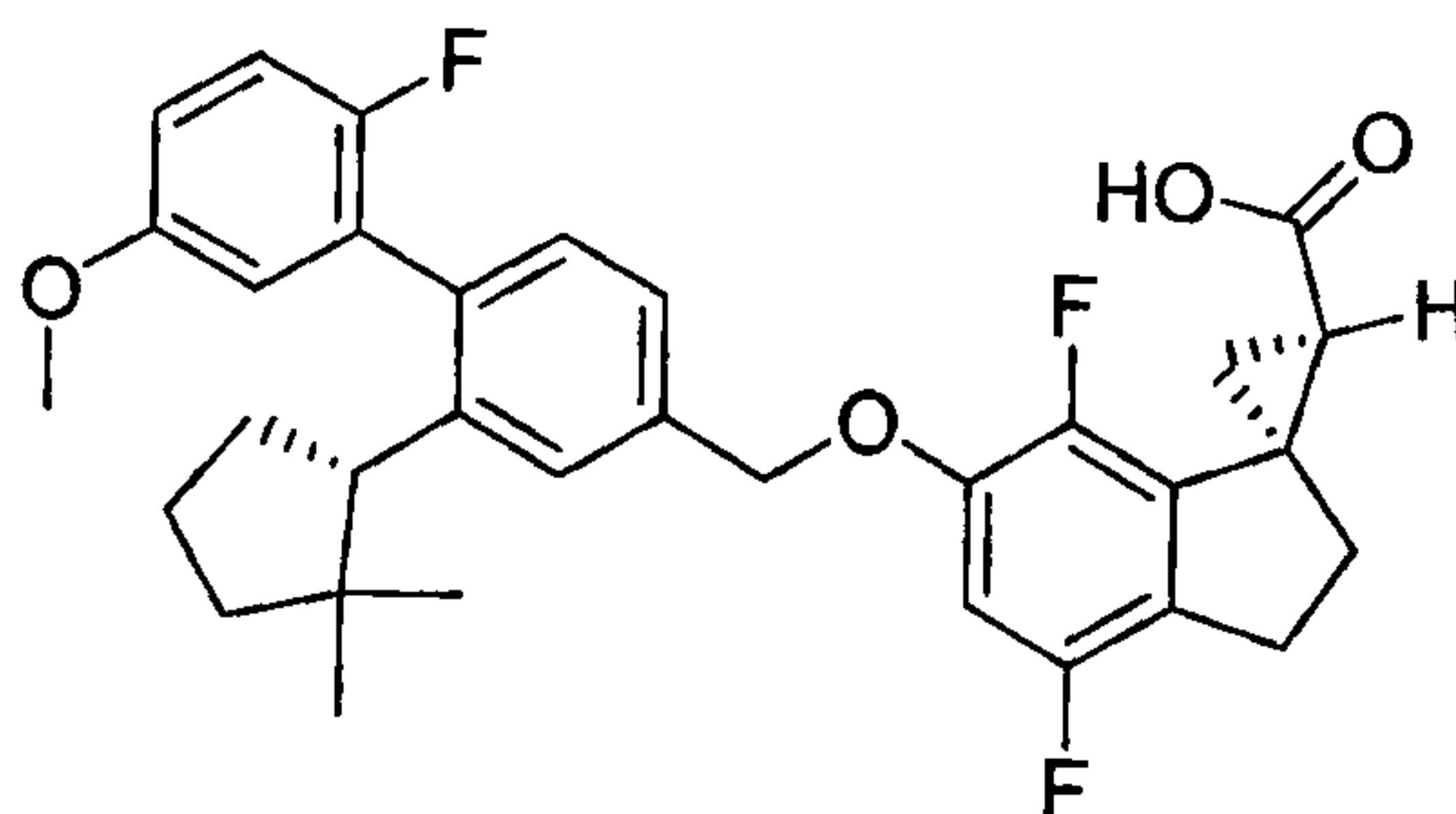
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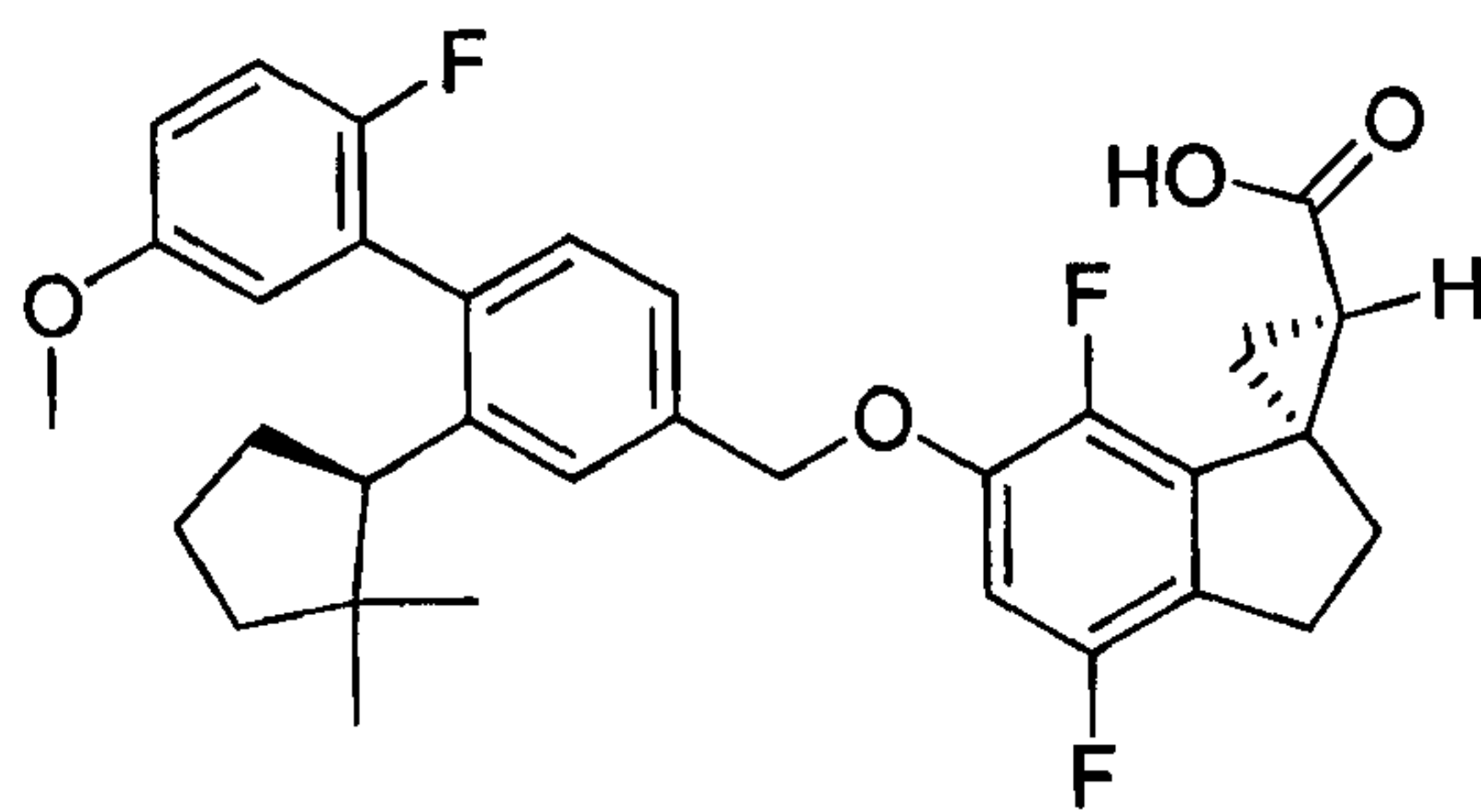
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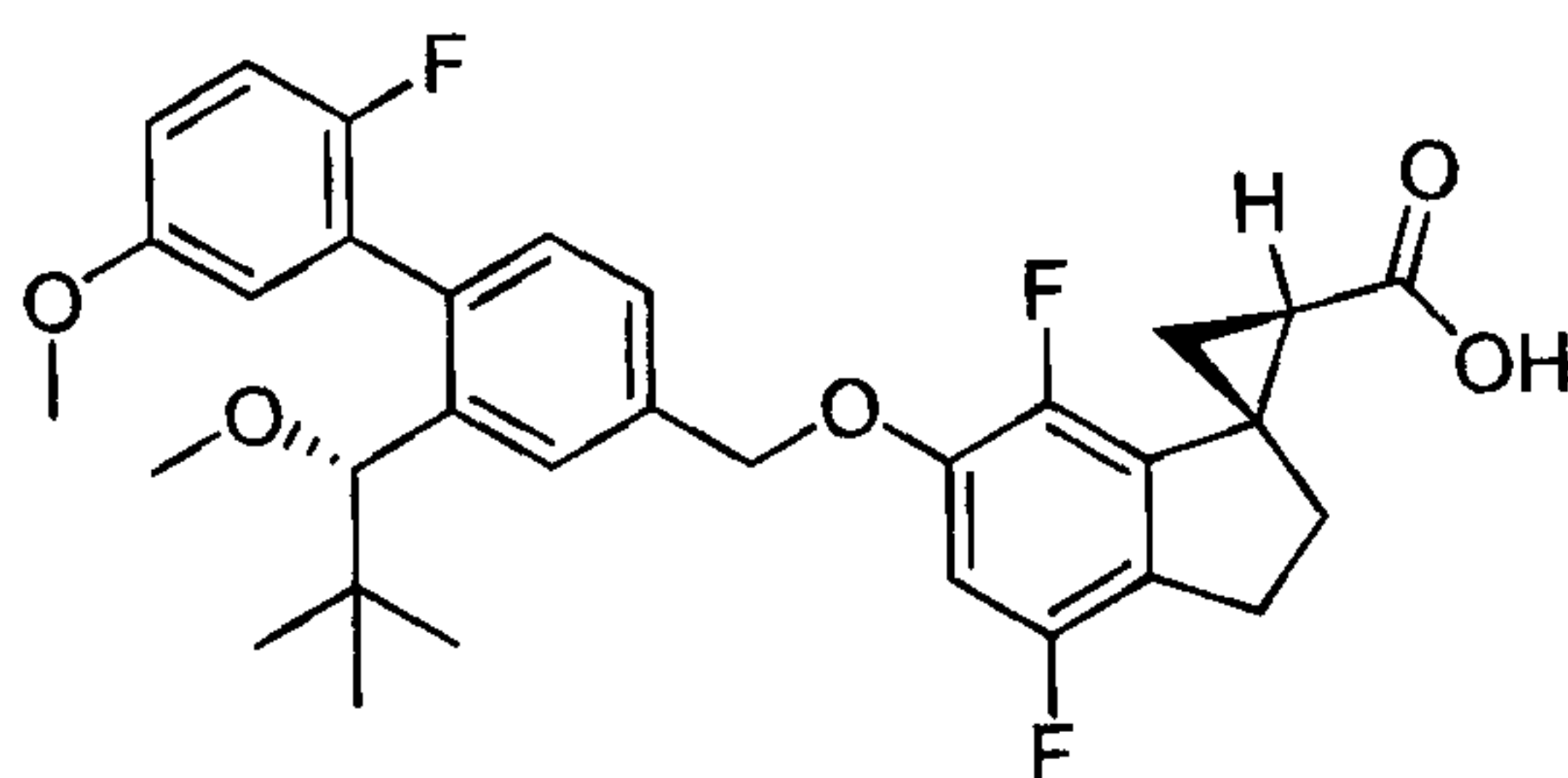
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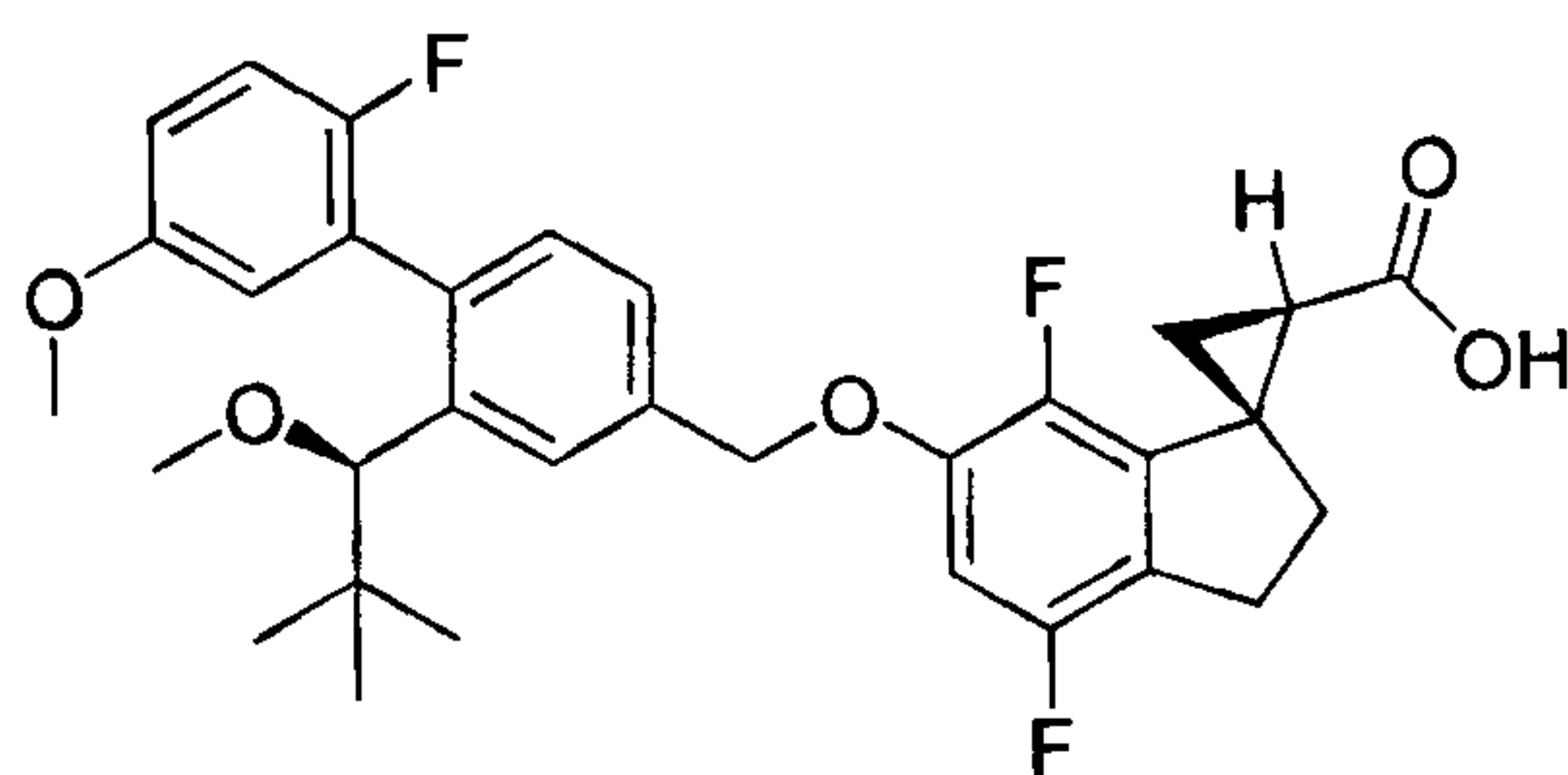
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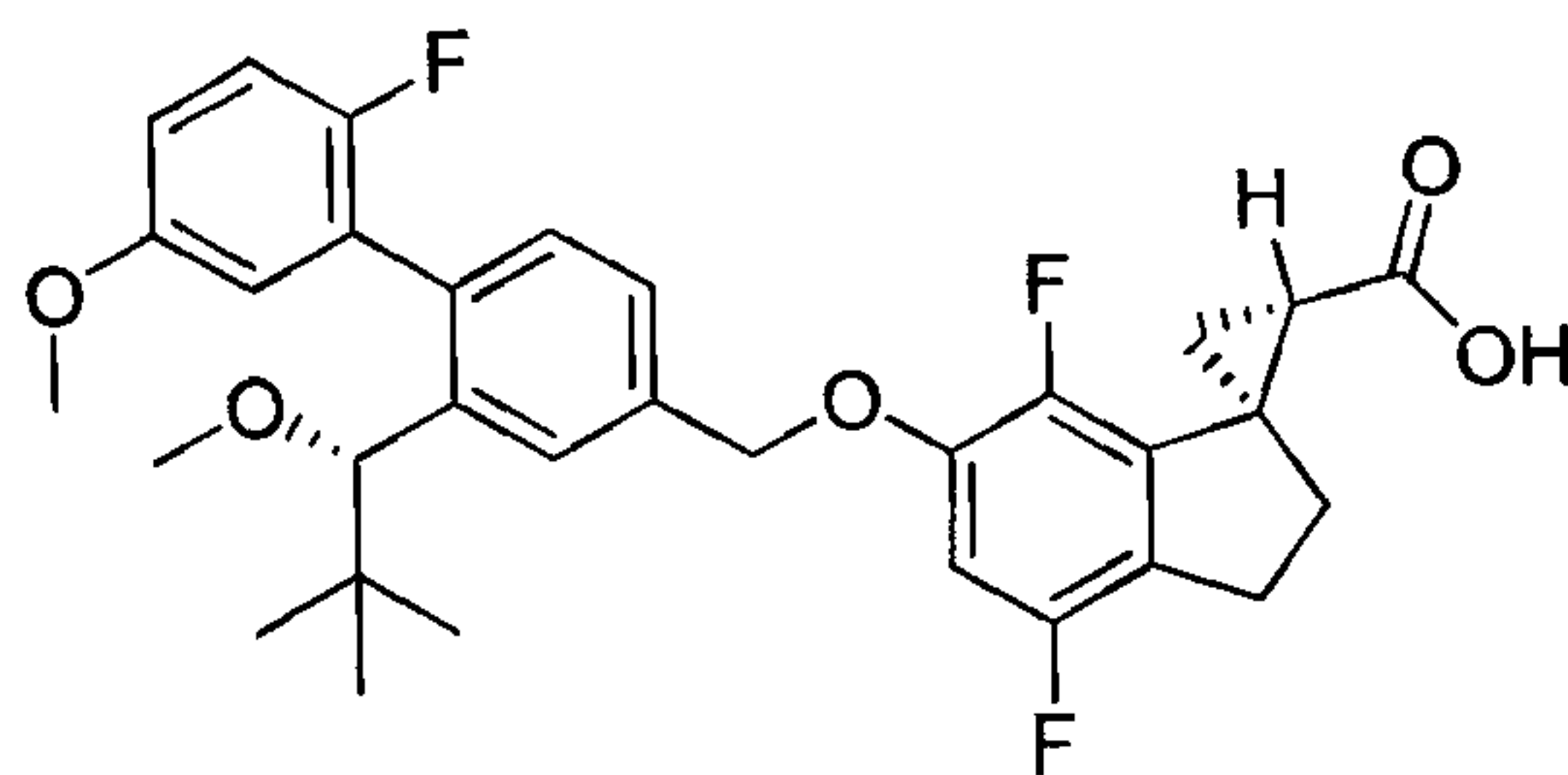
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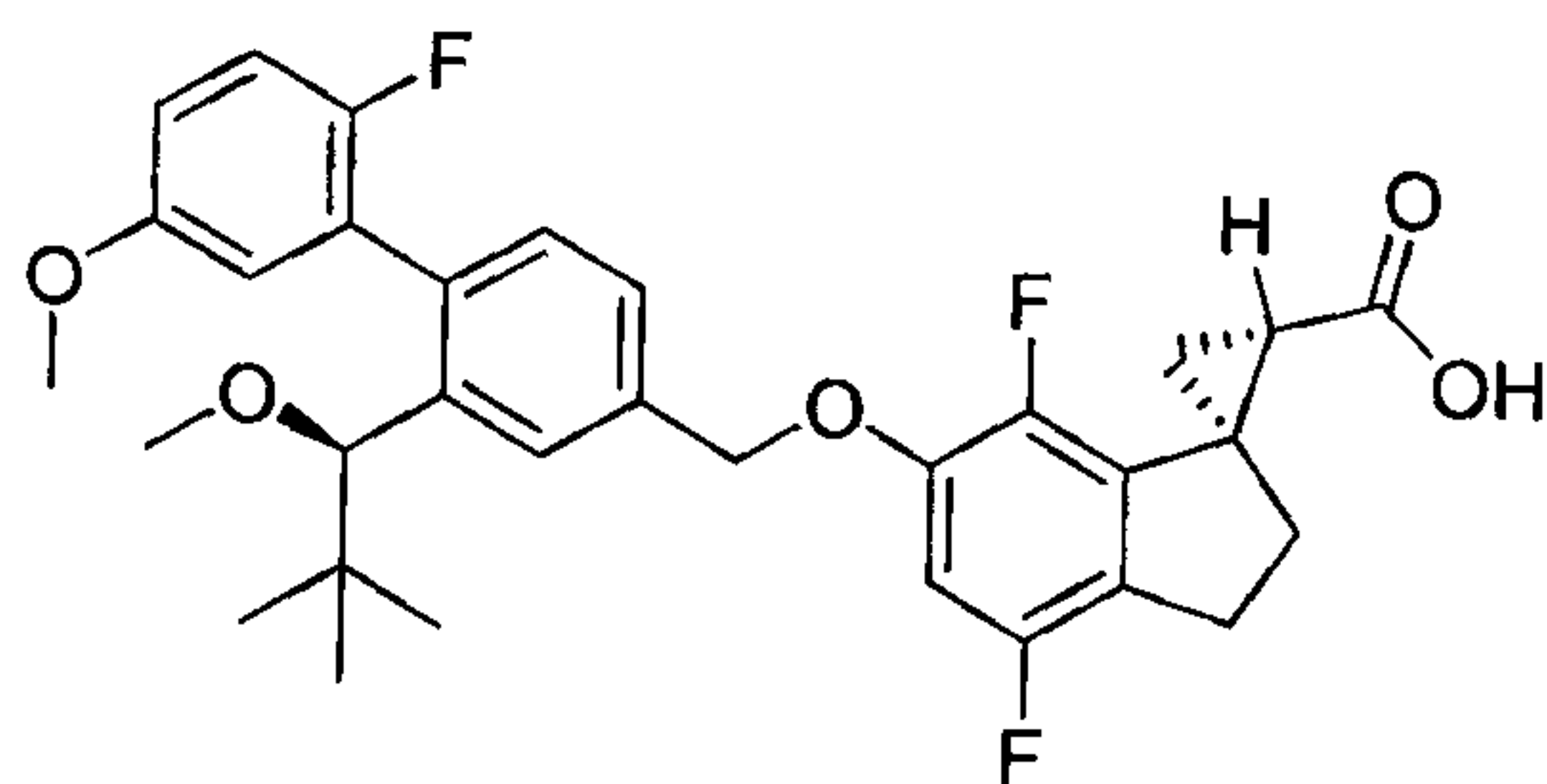
145. The compound



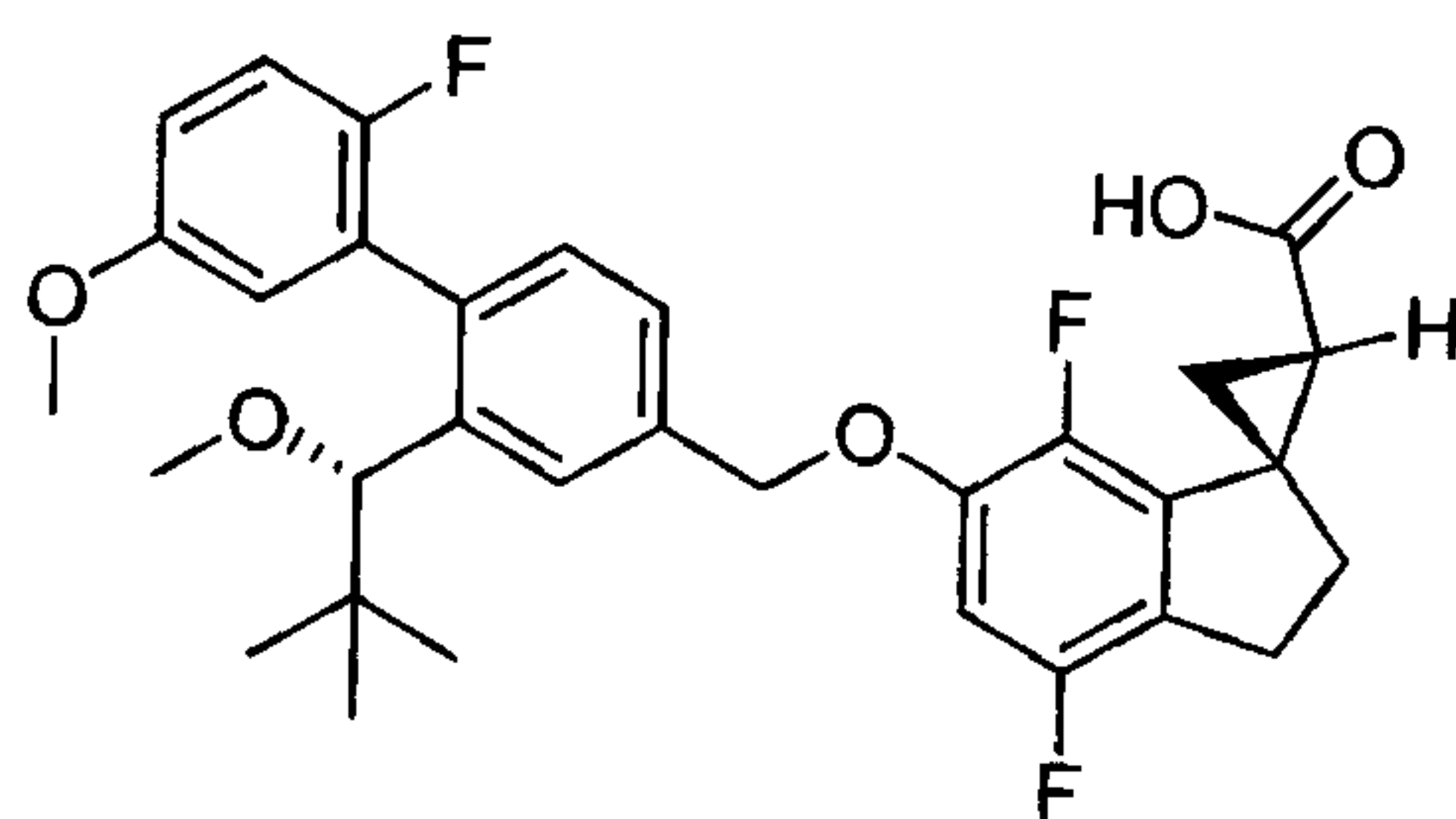
146. The compound



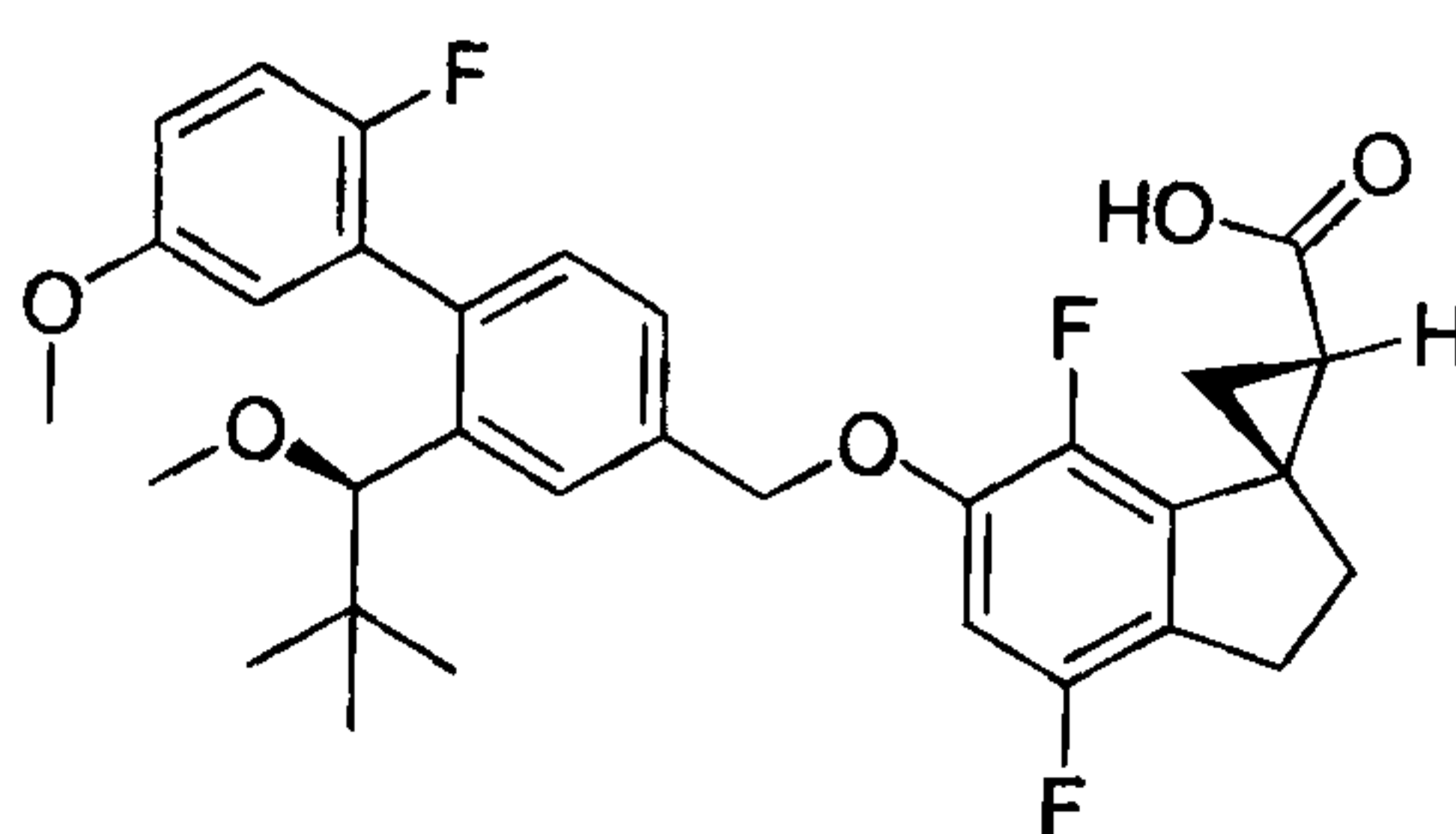
147. The compound



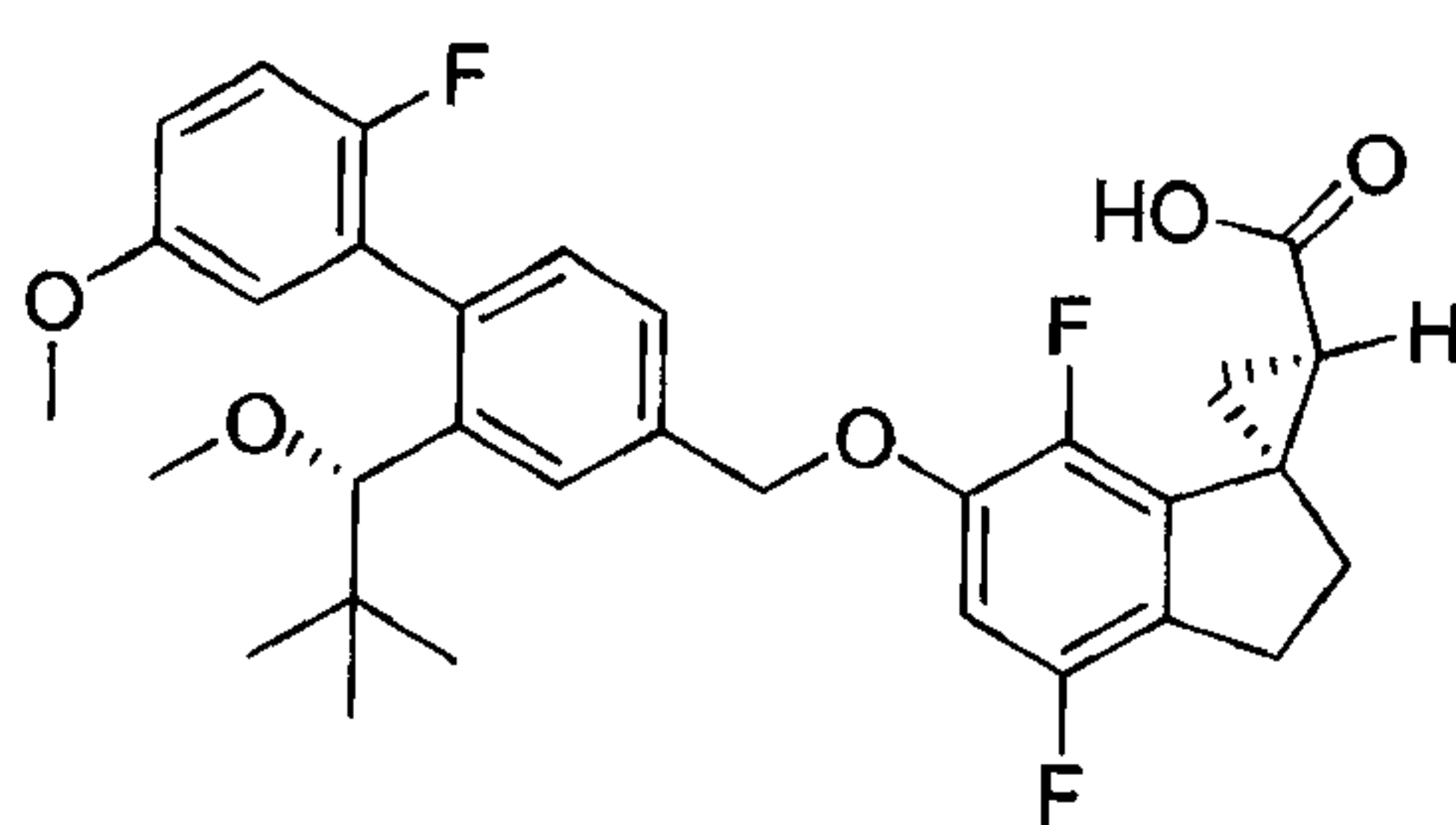
148. The compound



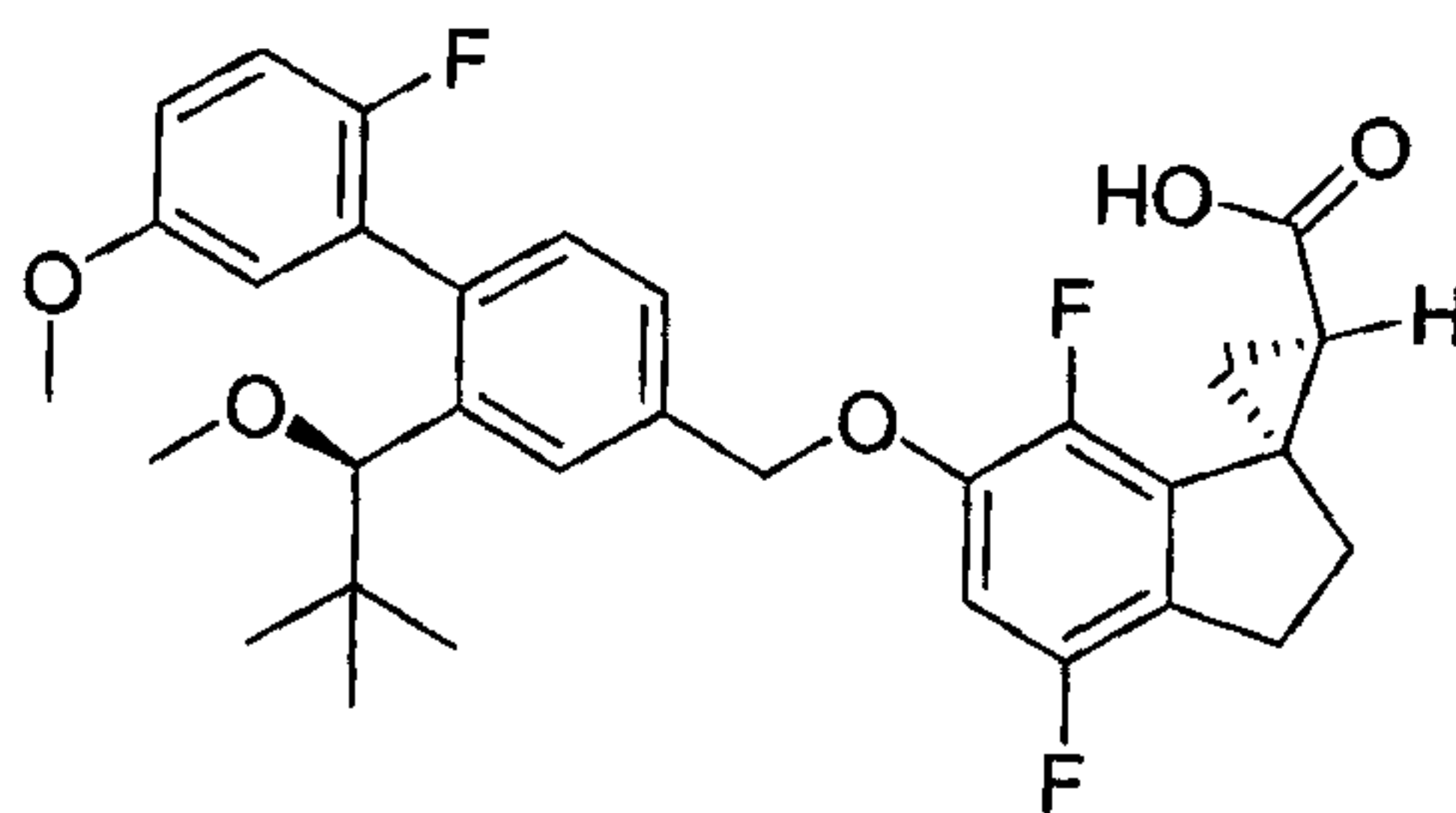
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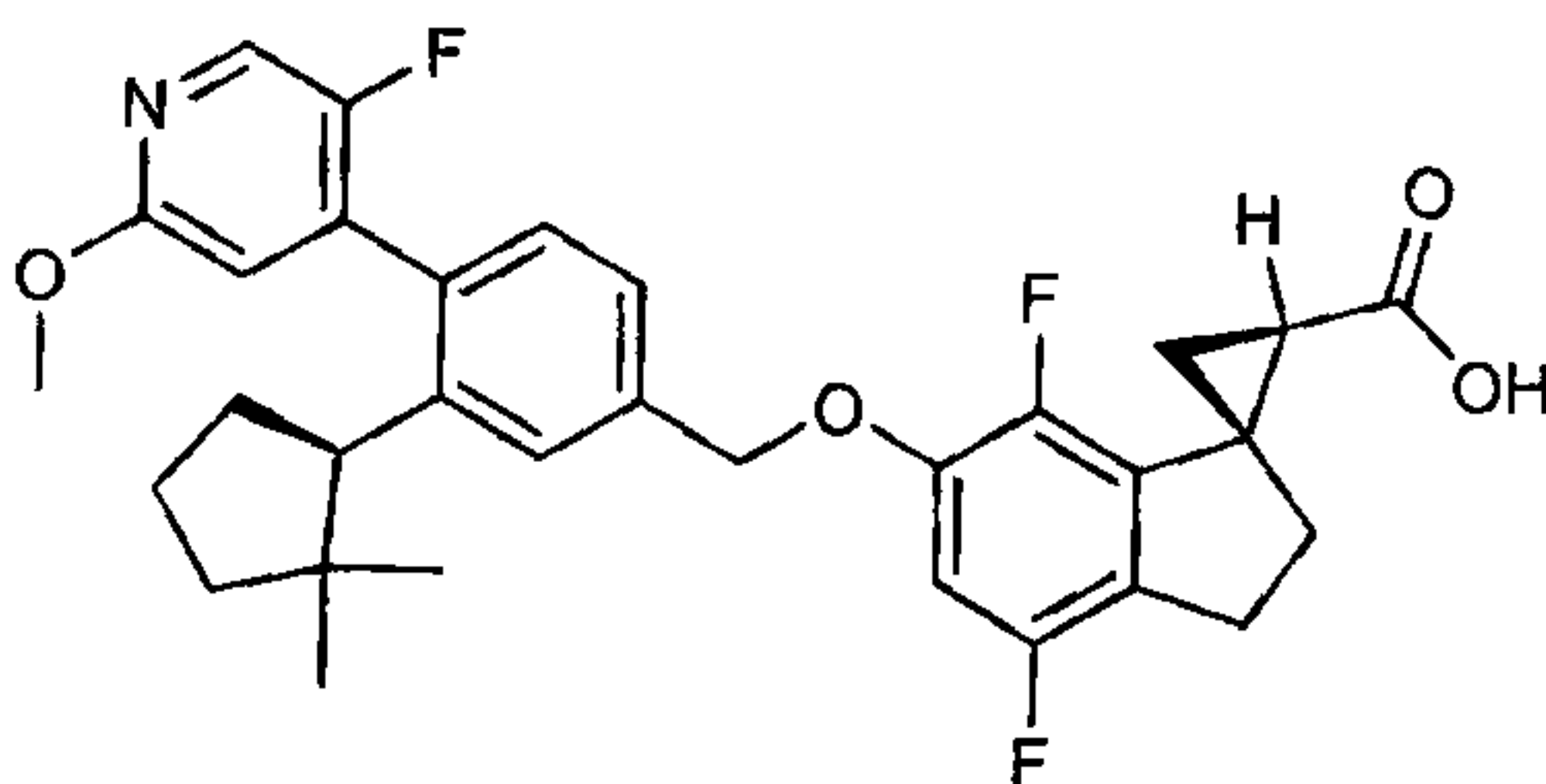
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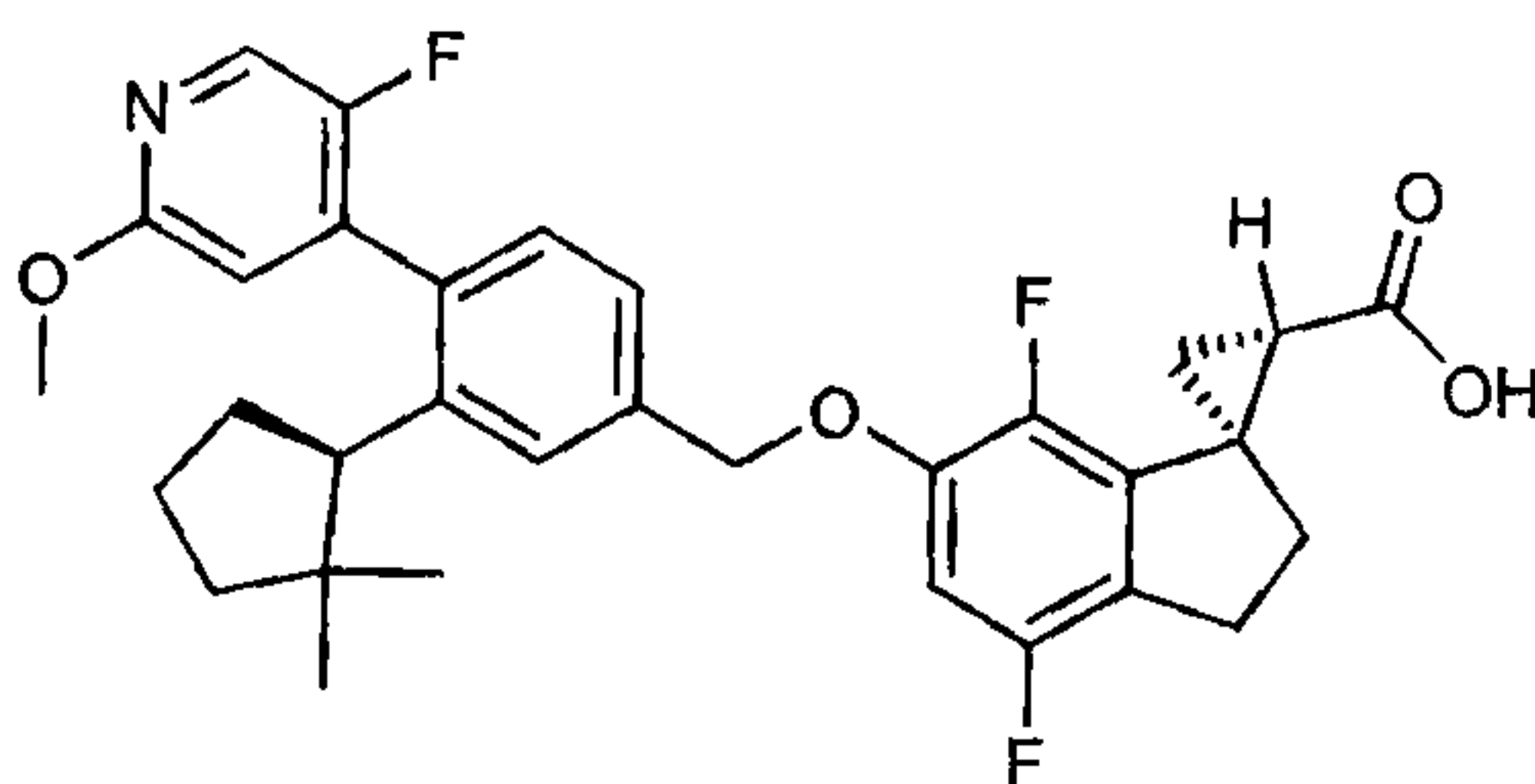
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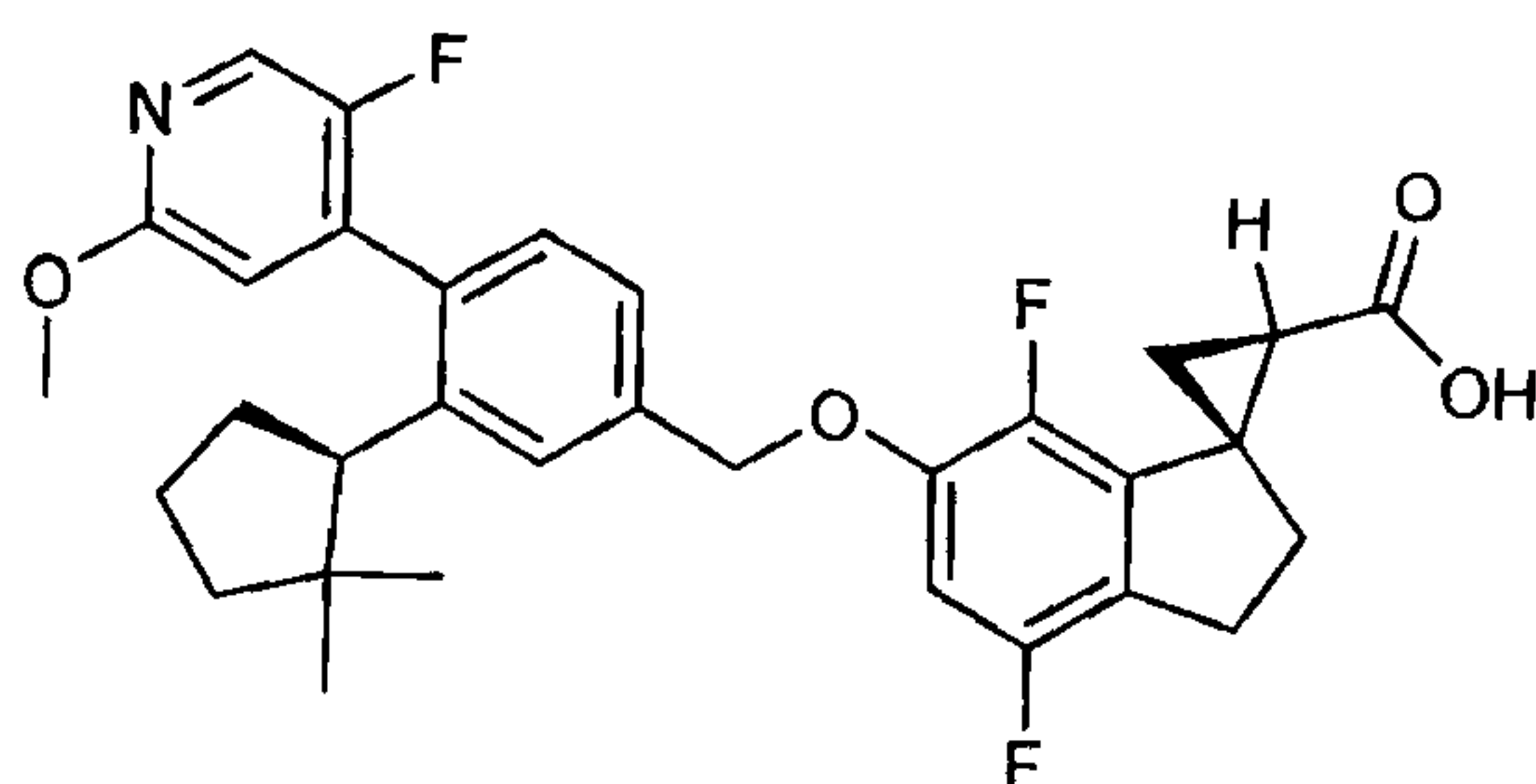
152. The compound



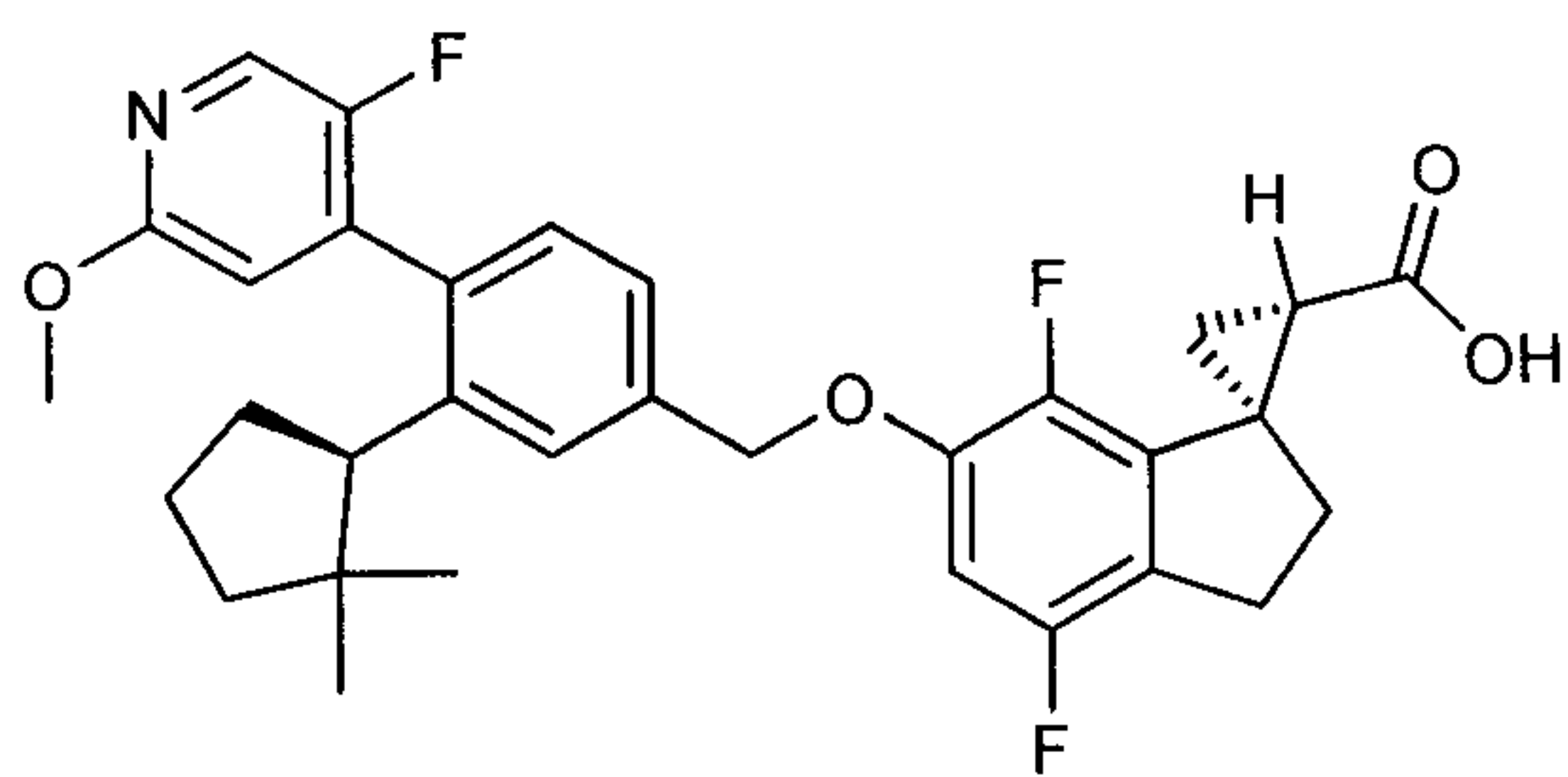
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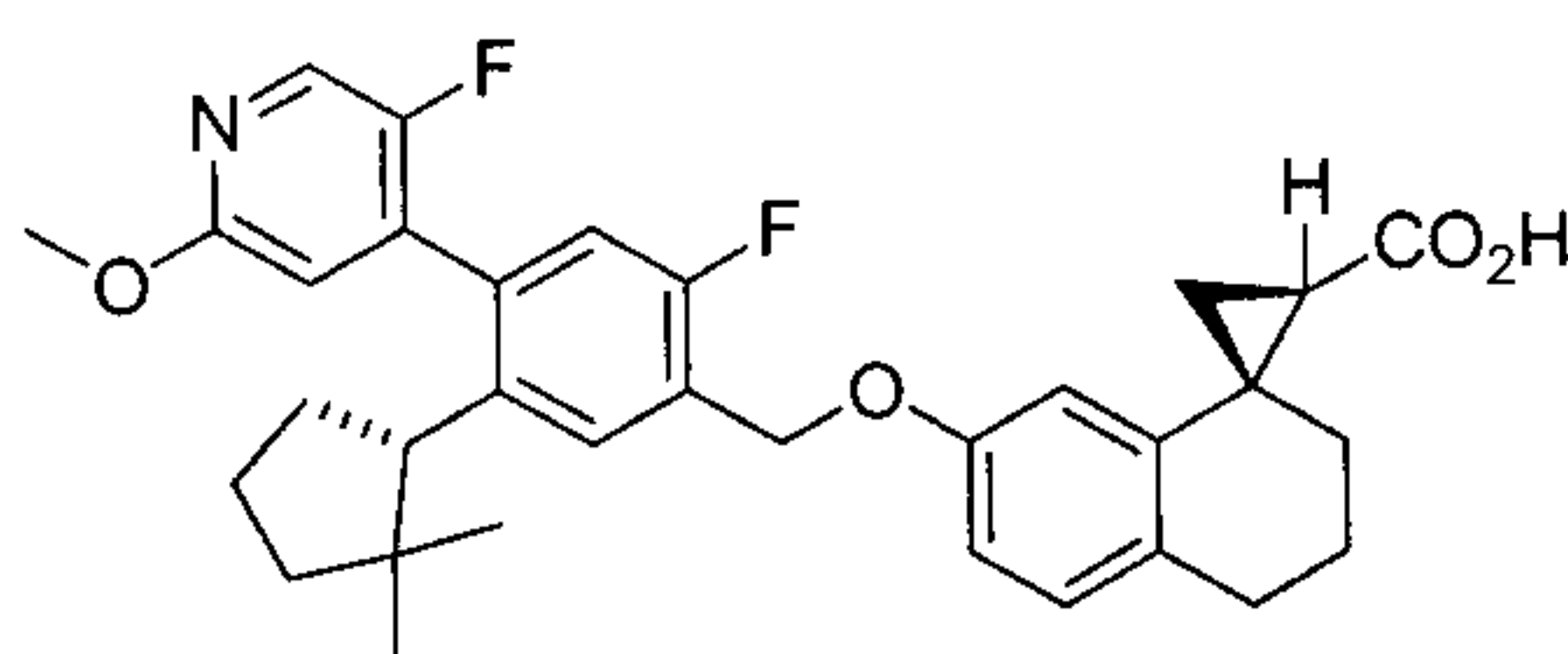
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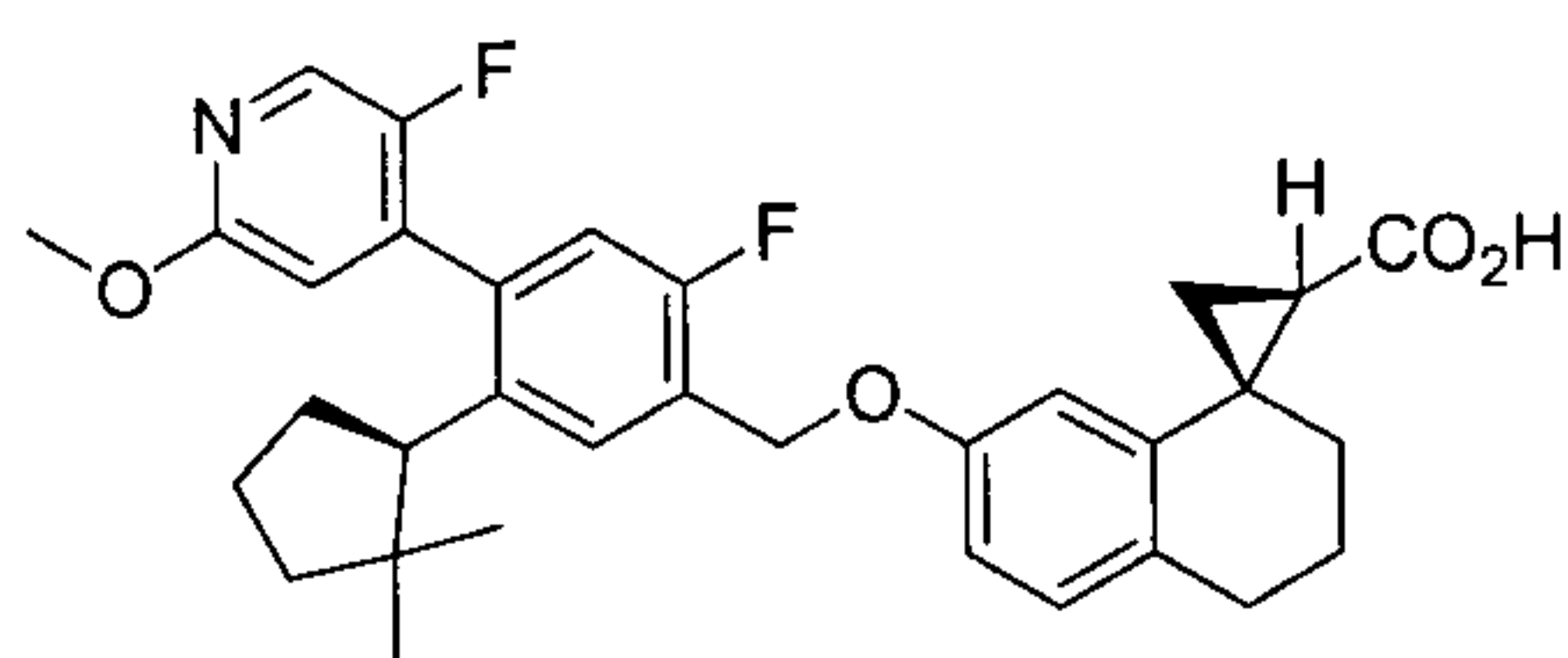
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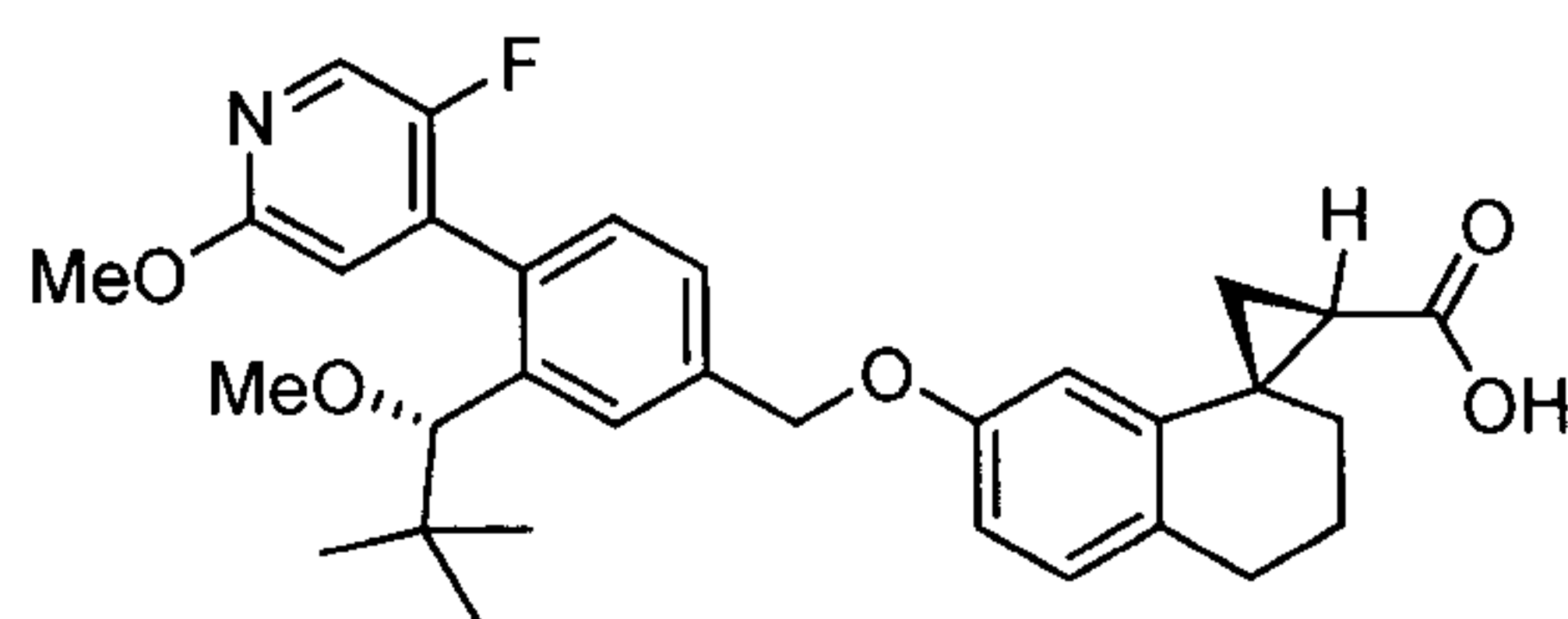
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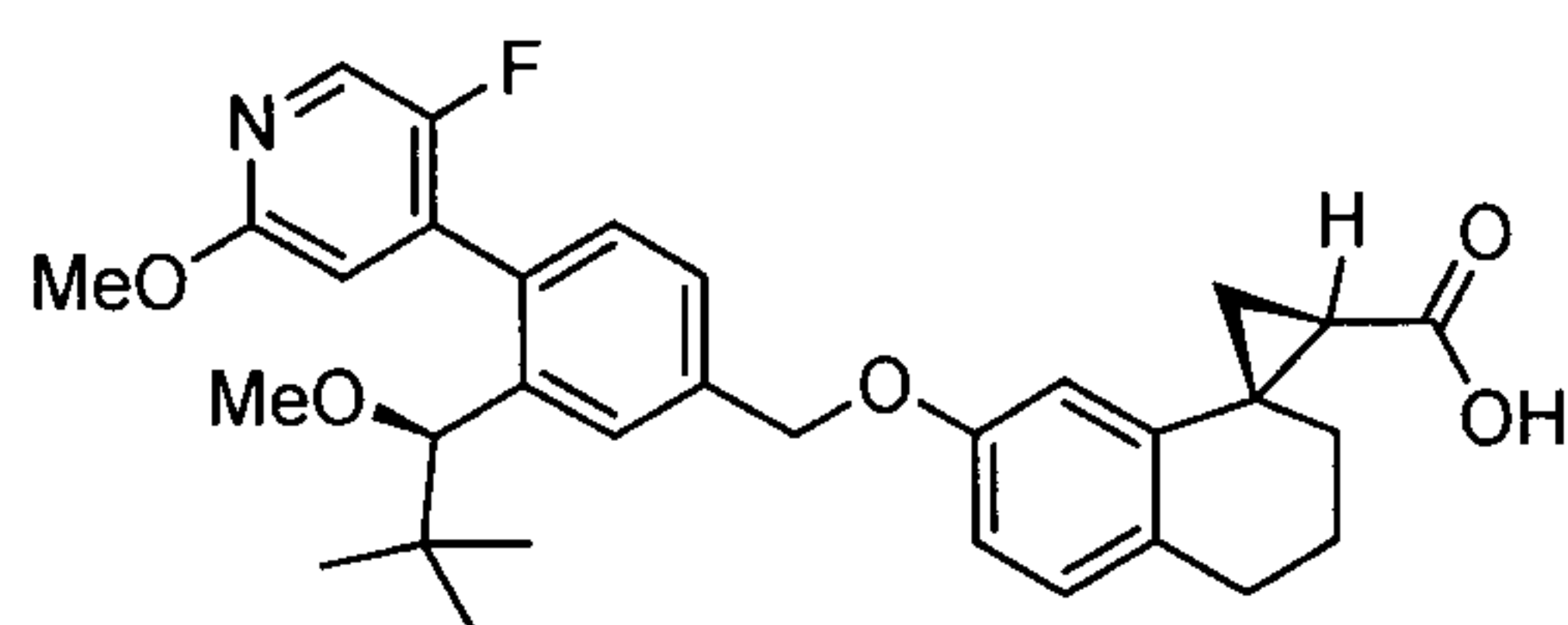
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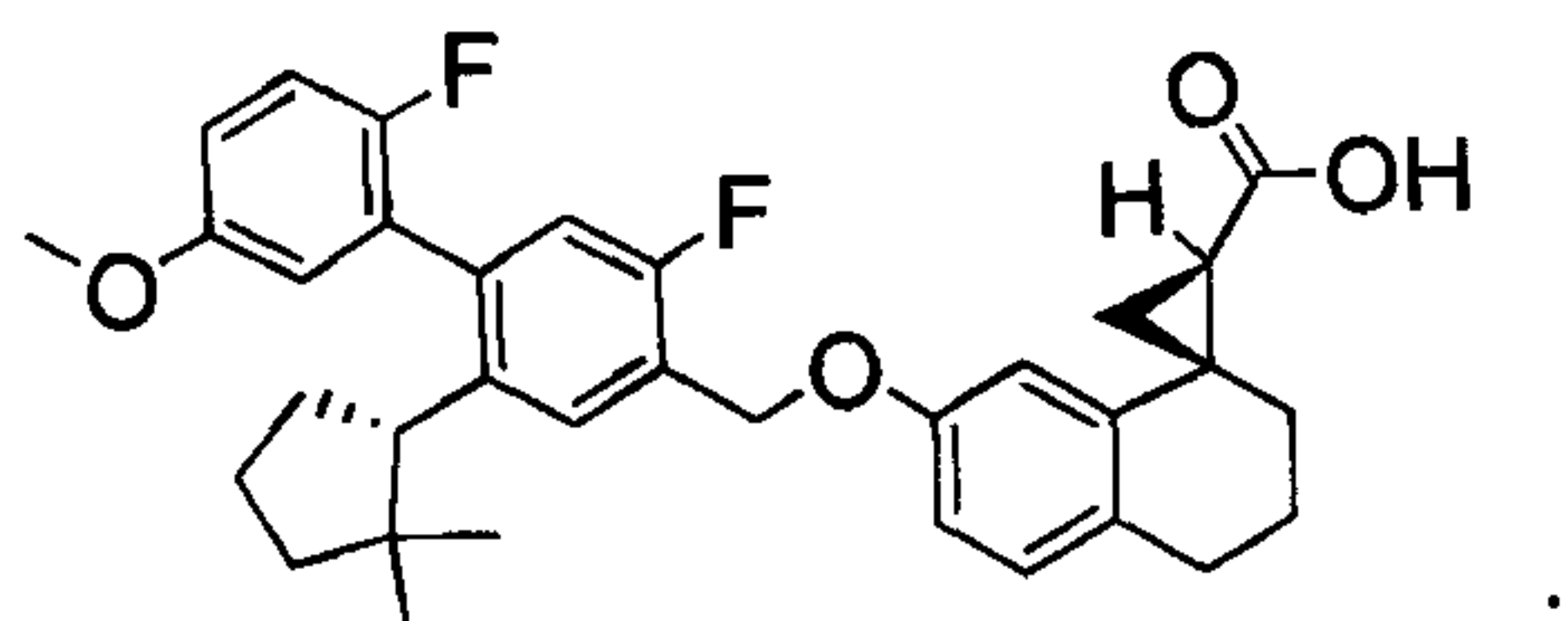
158. The compound



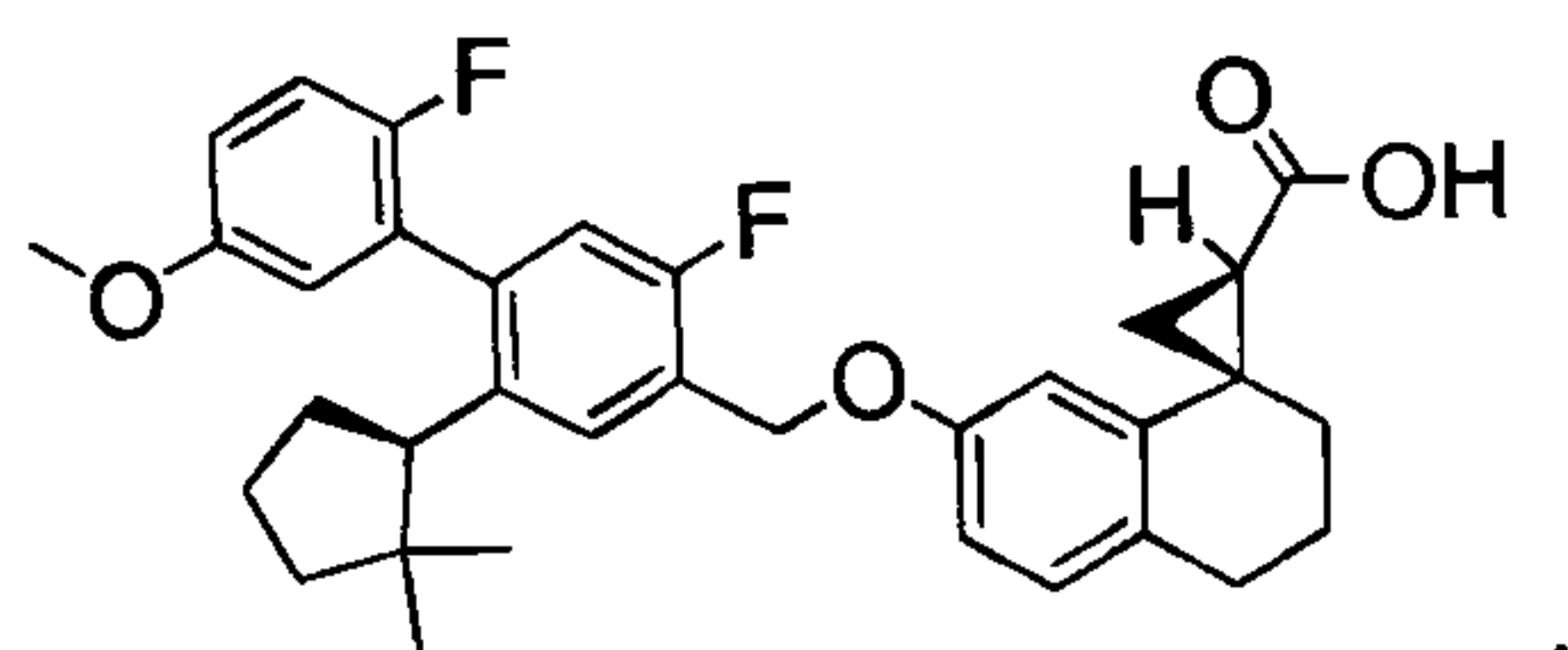
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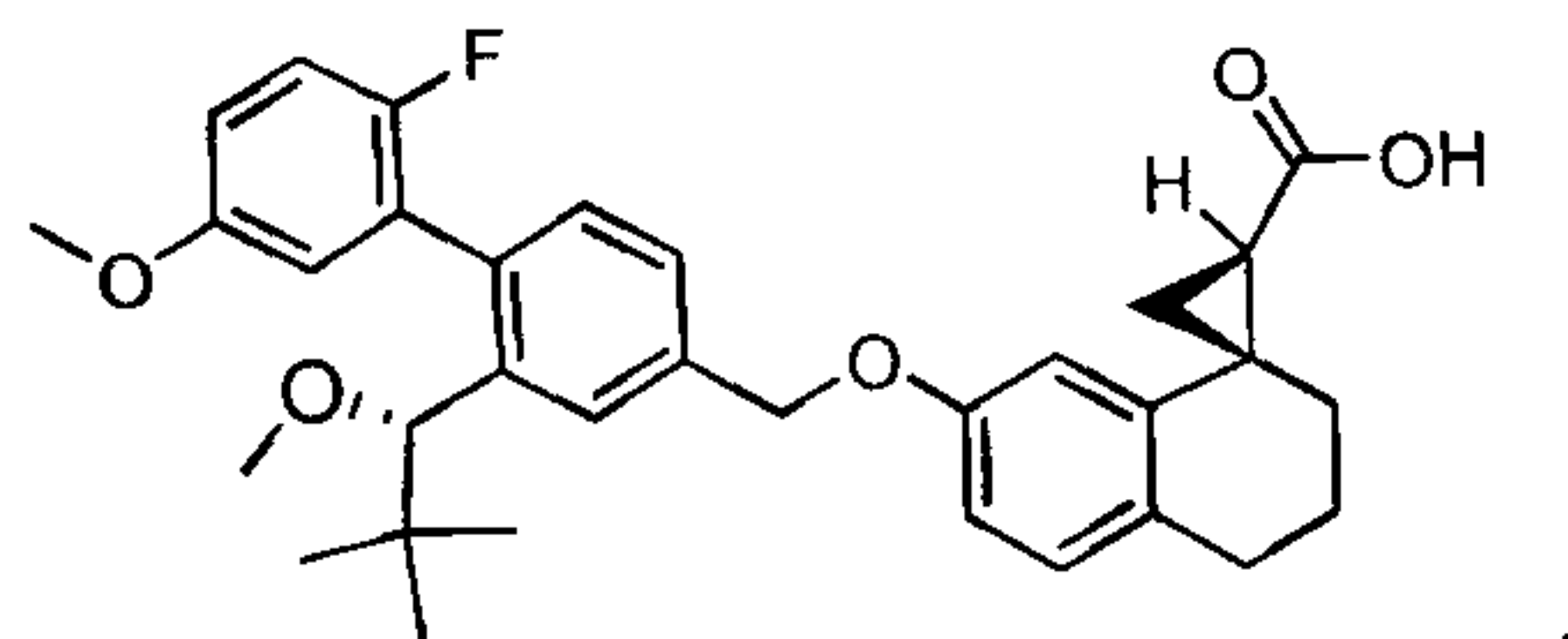
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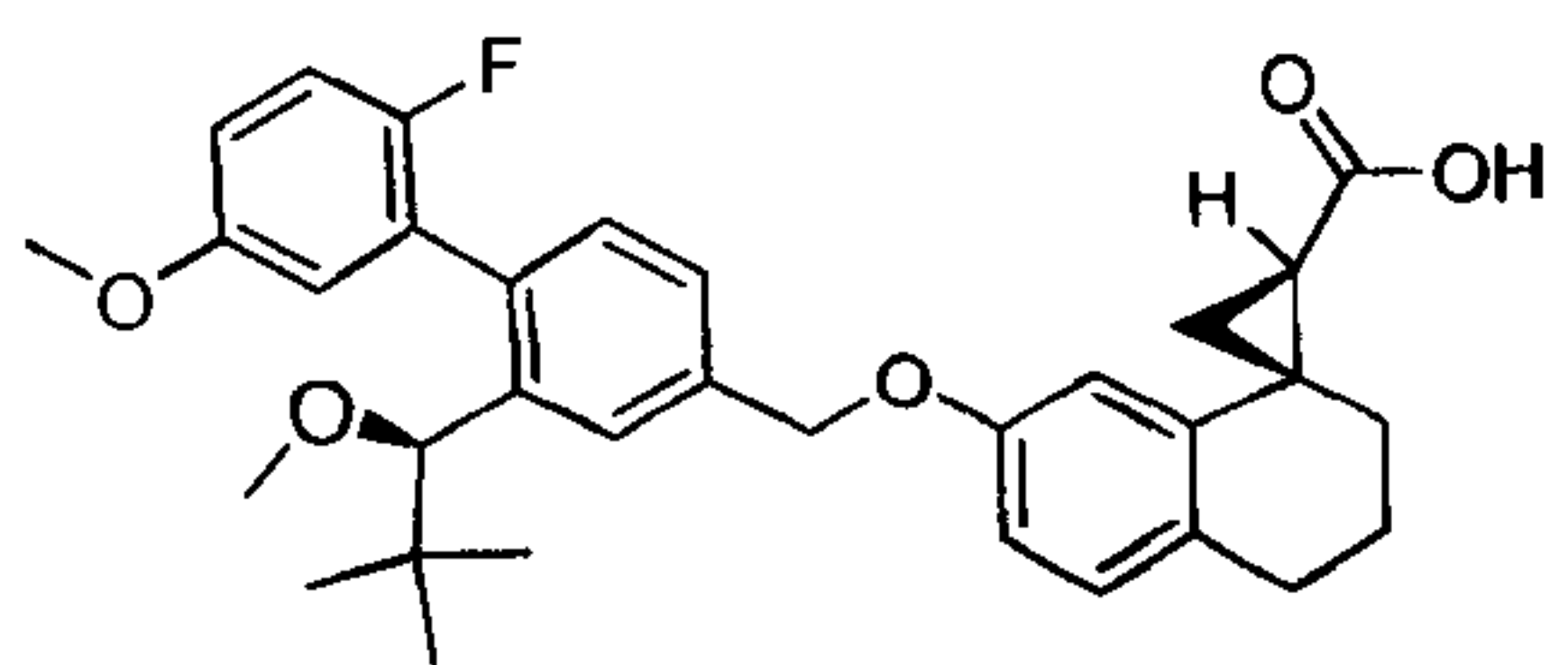
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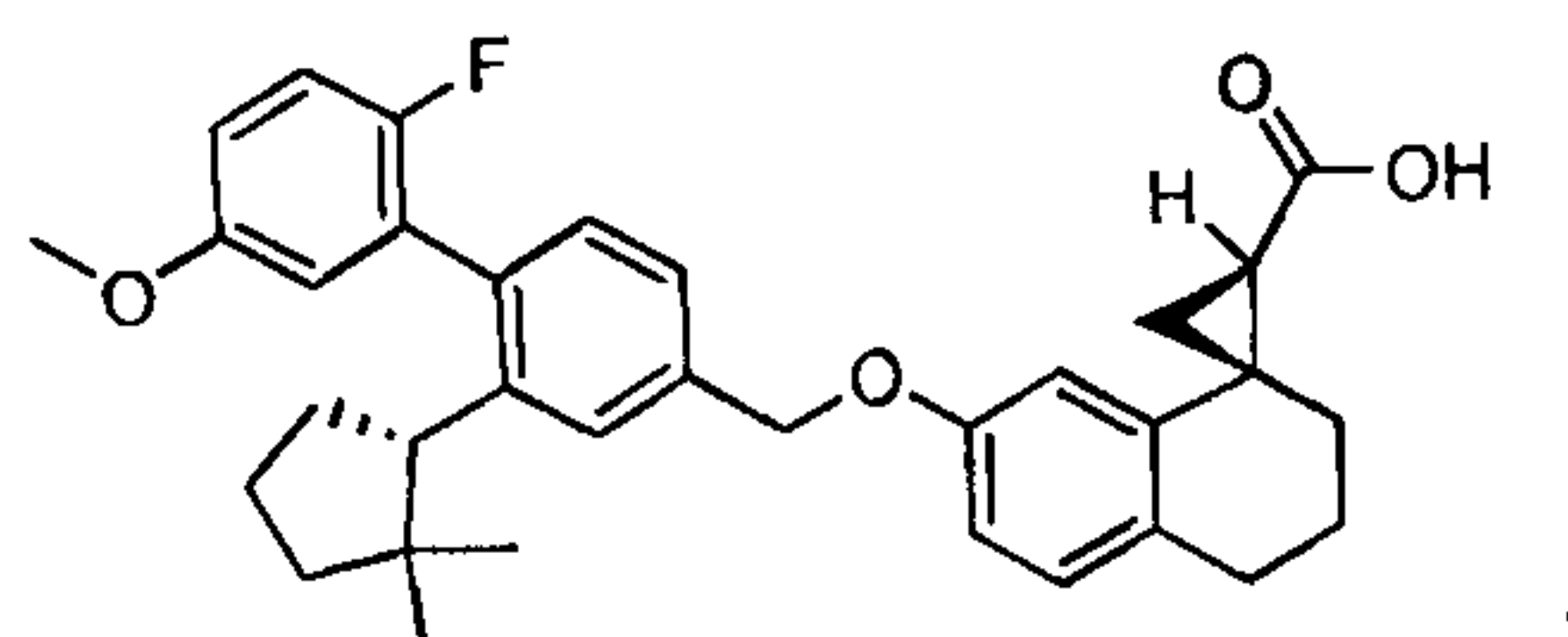
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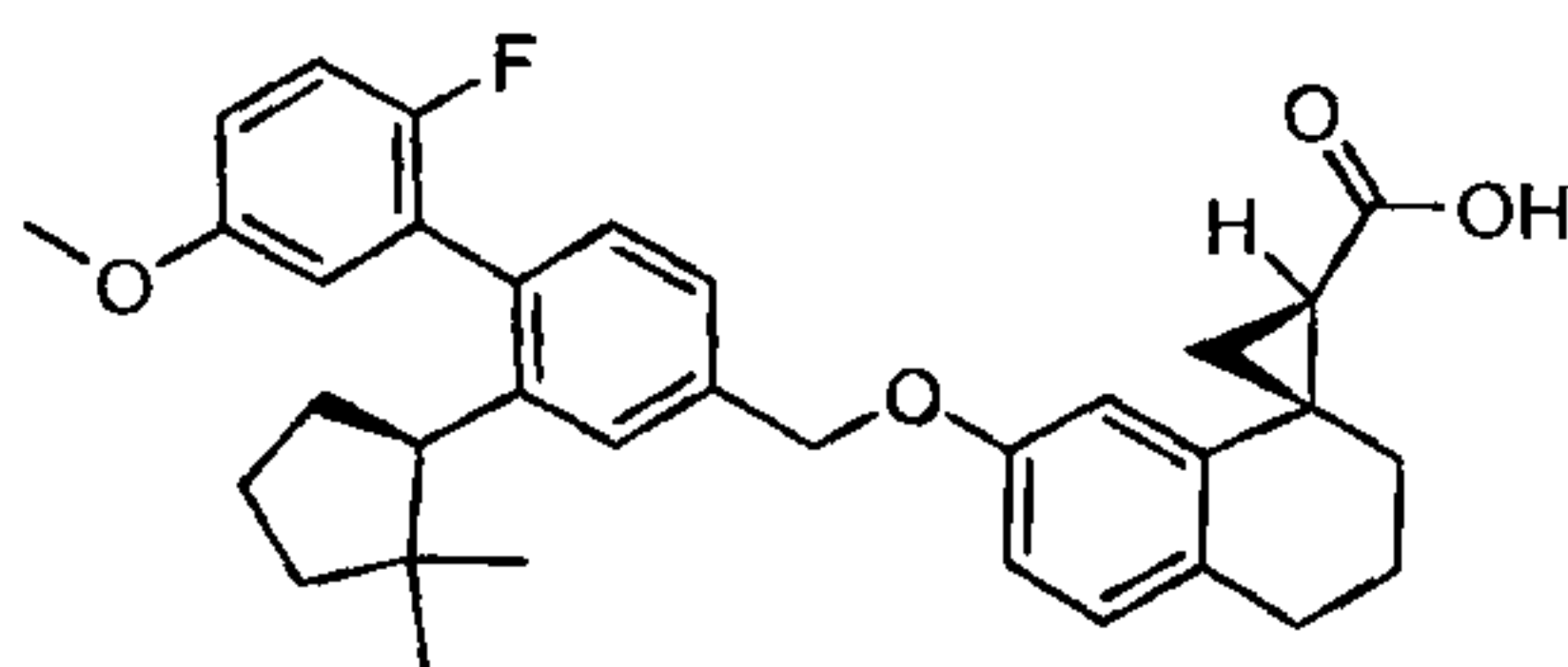
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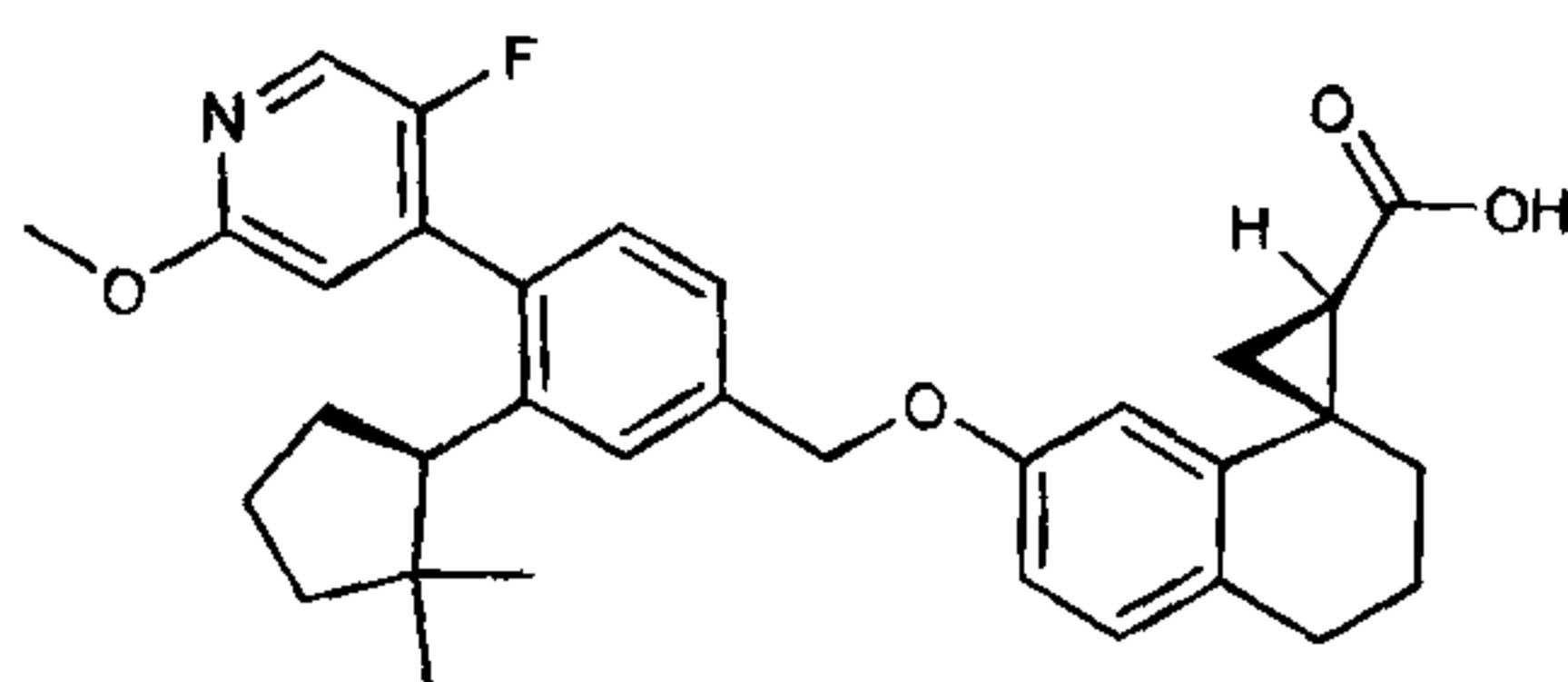
164. The compound



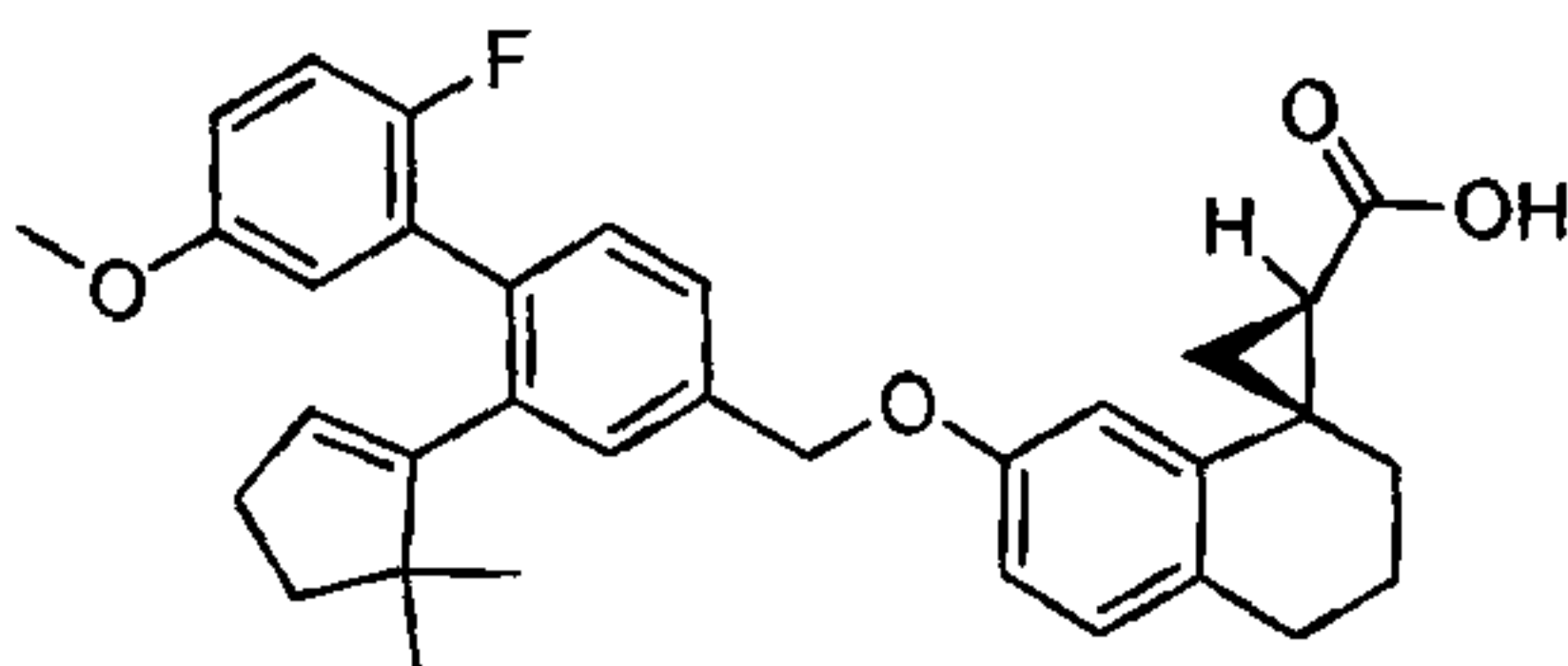
165. The compound



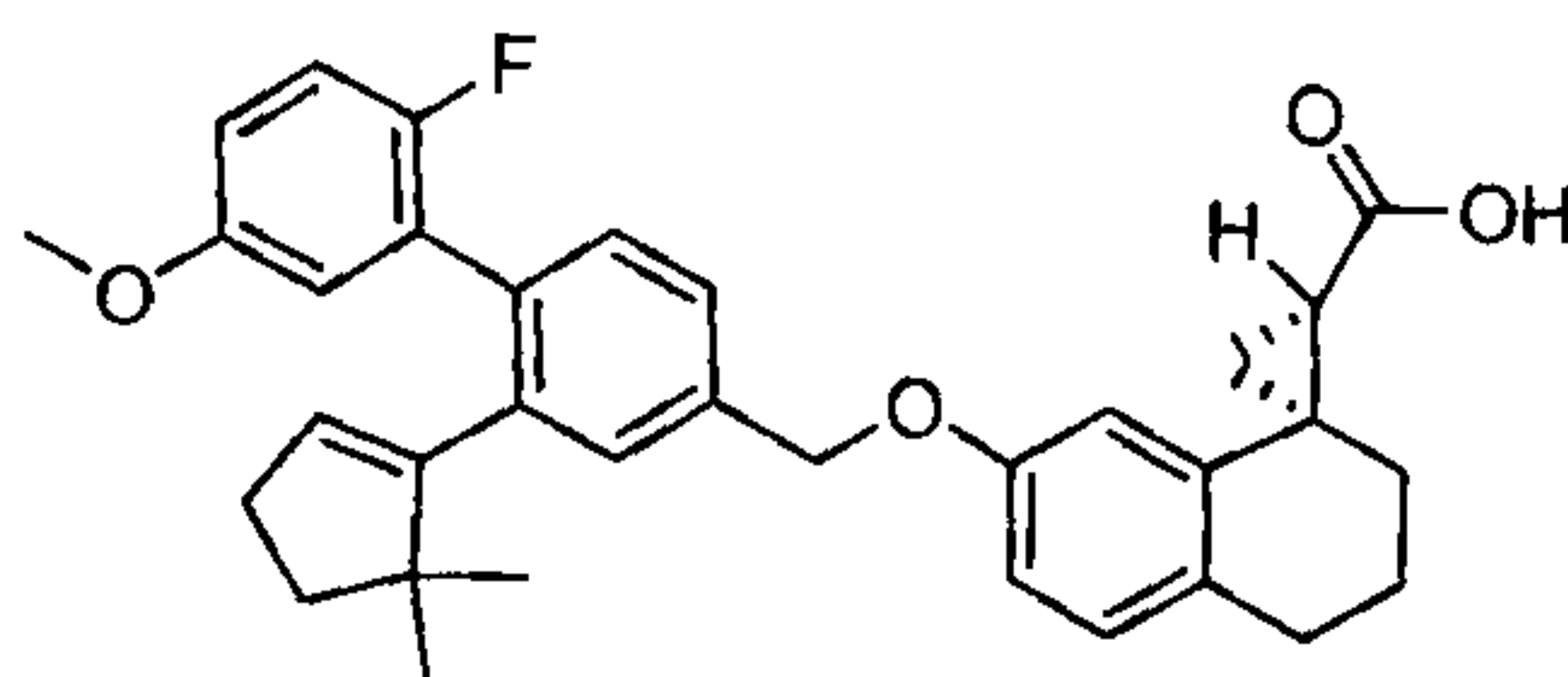
166. The compound



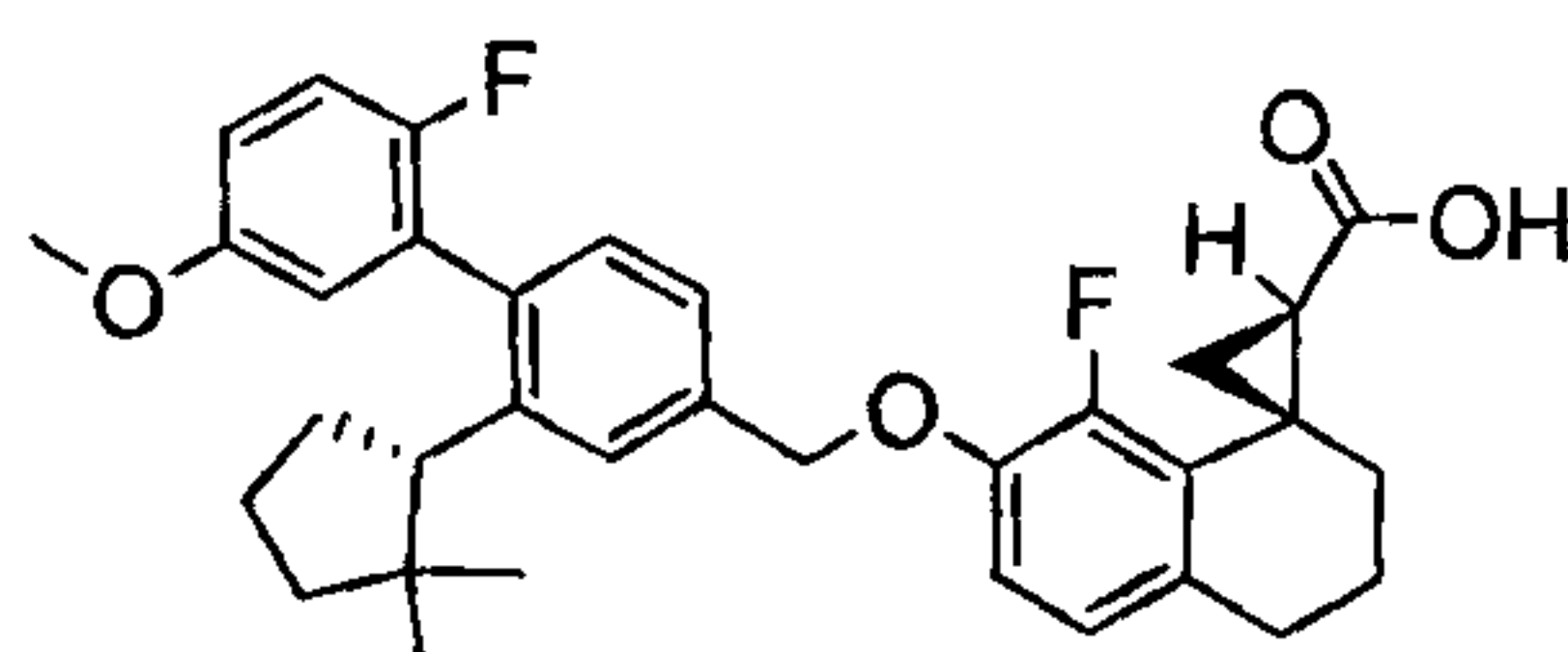
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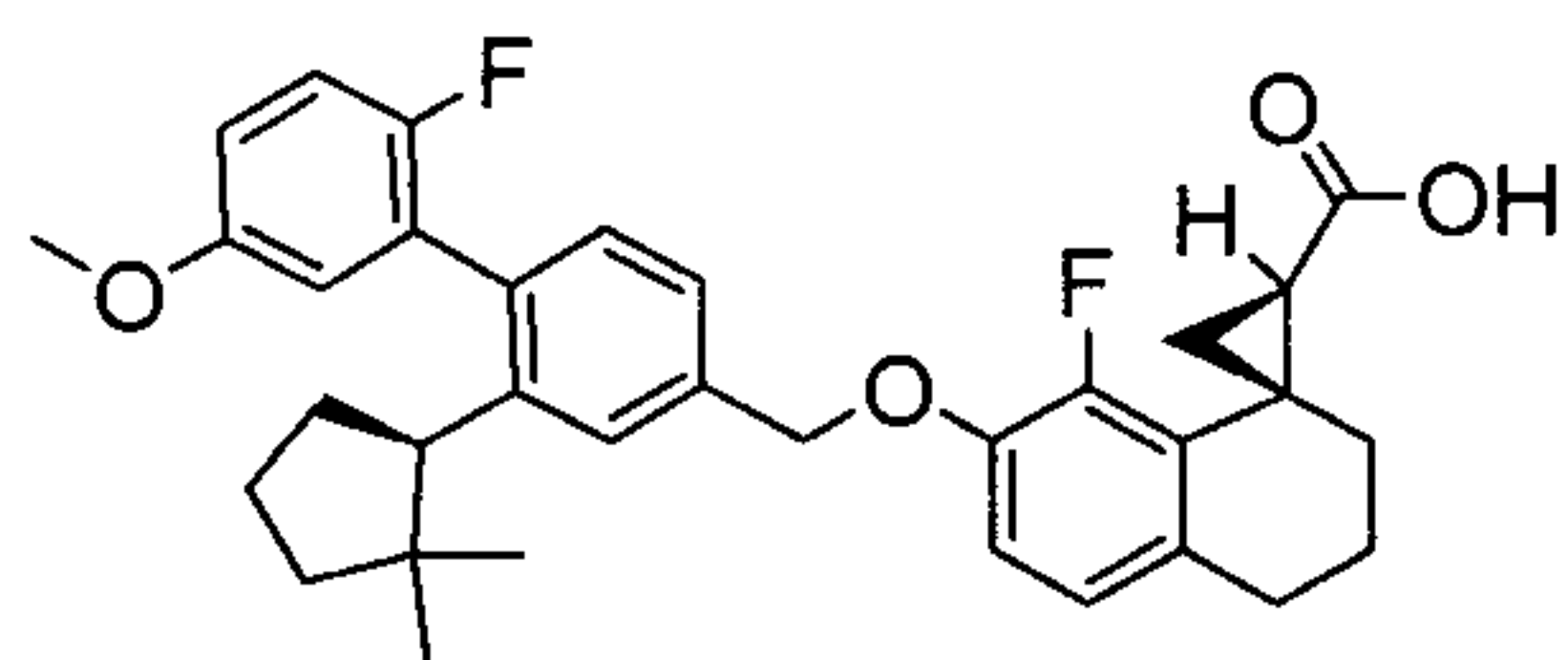
168. The compound



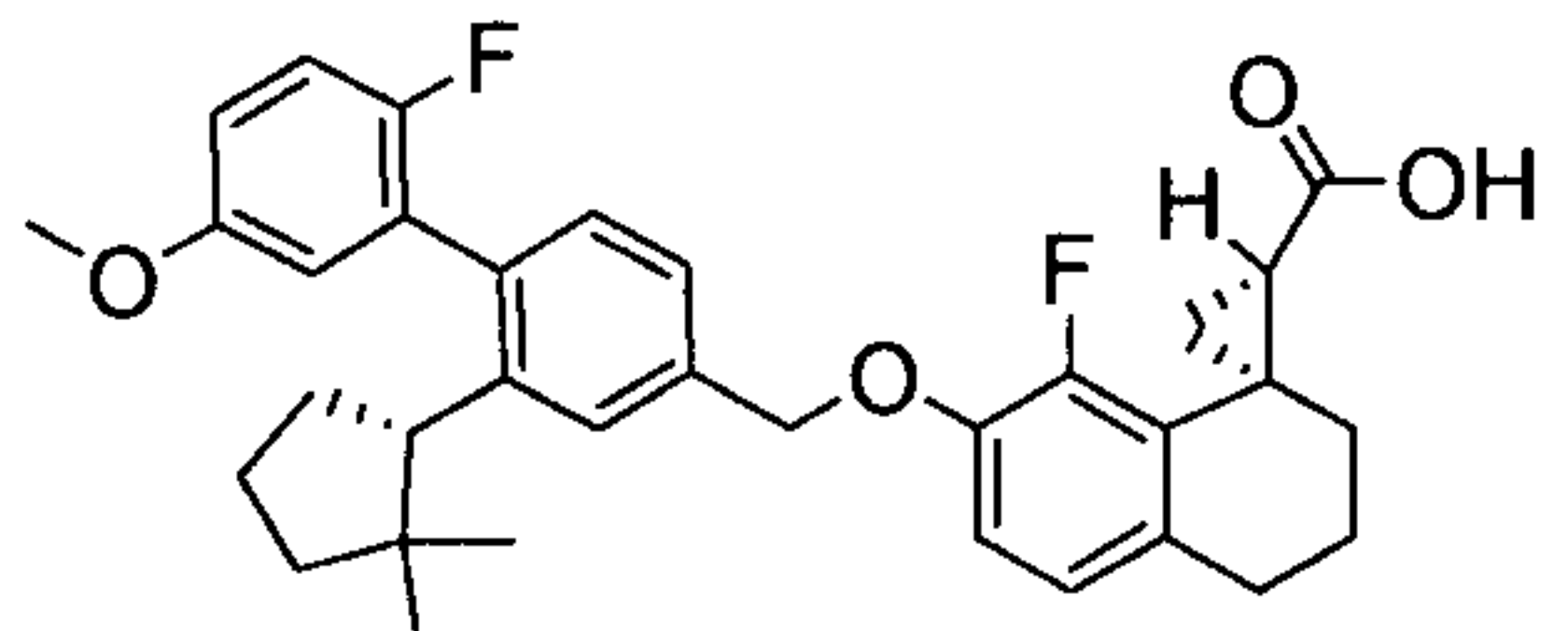
169. The compound



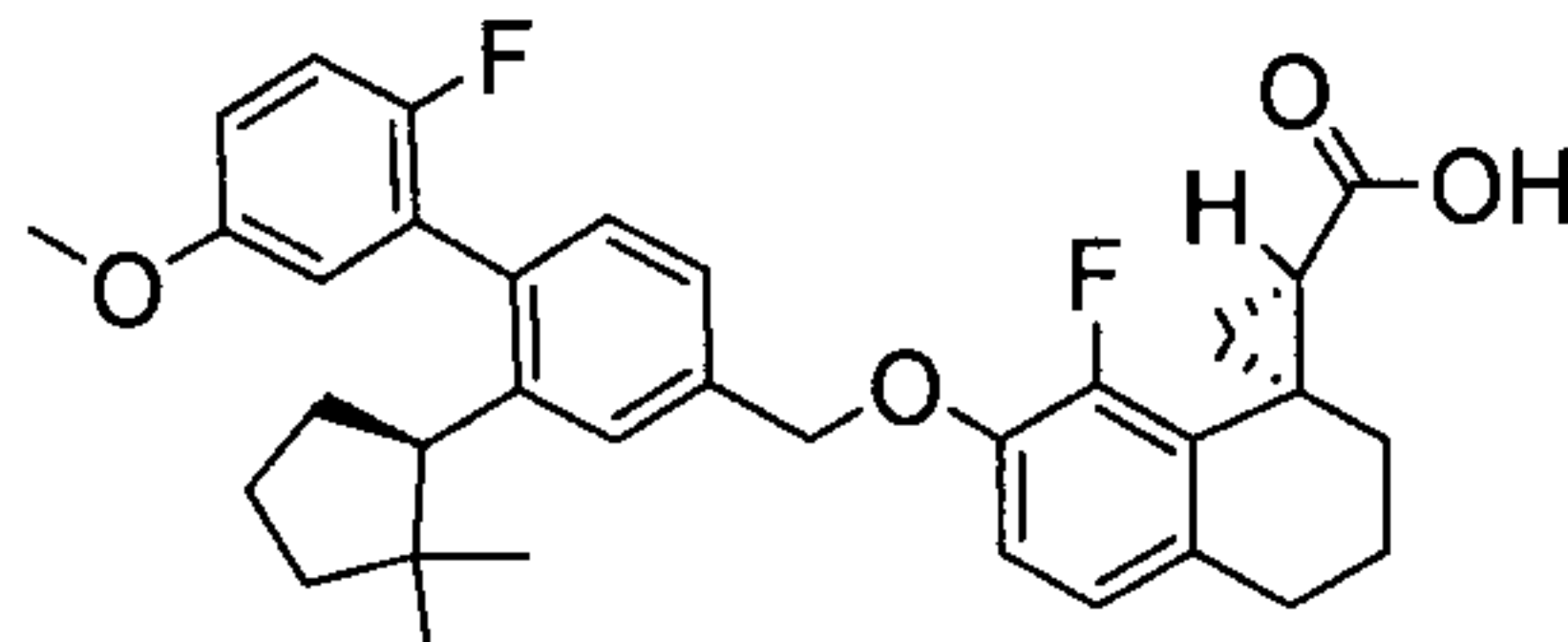
170. The compound



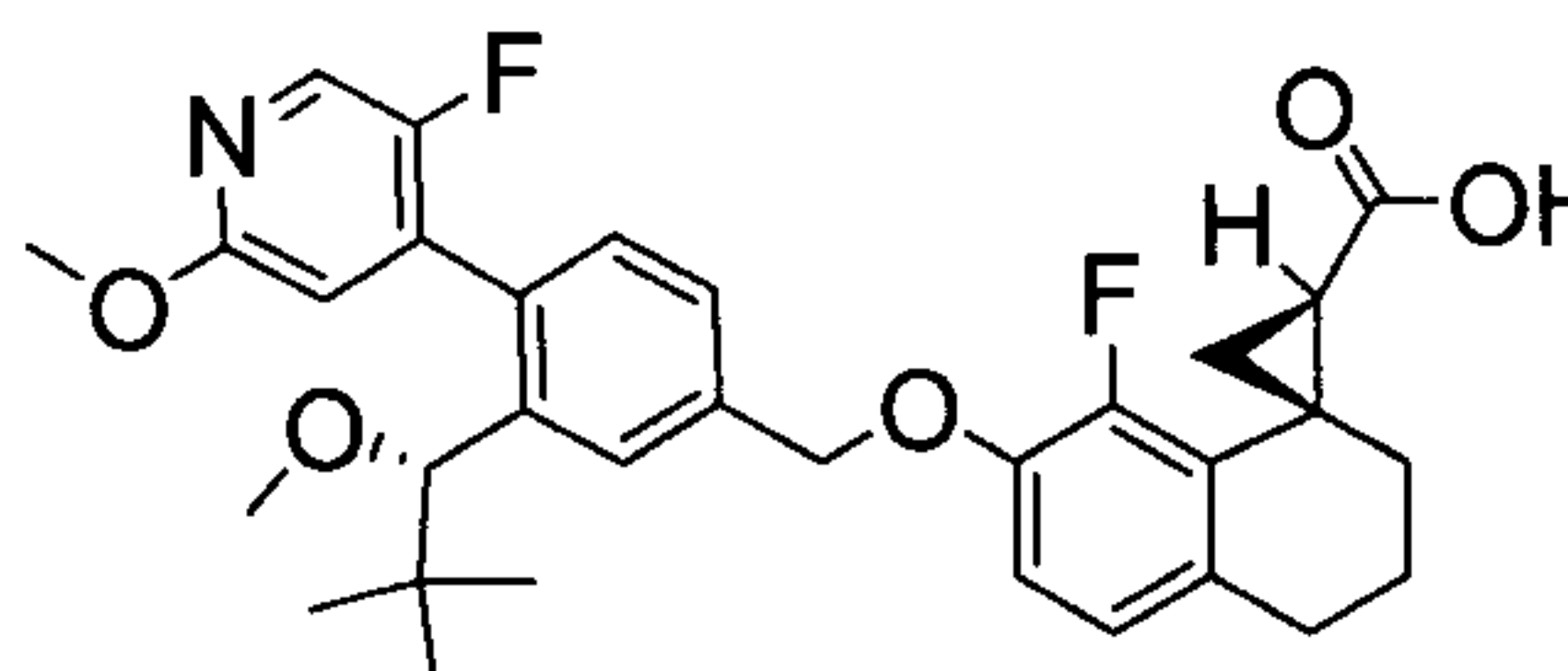
171. The compound



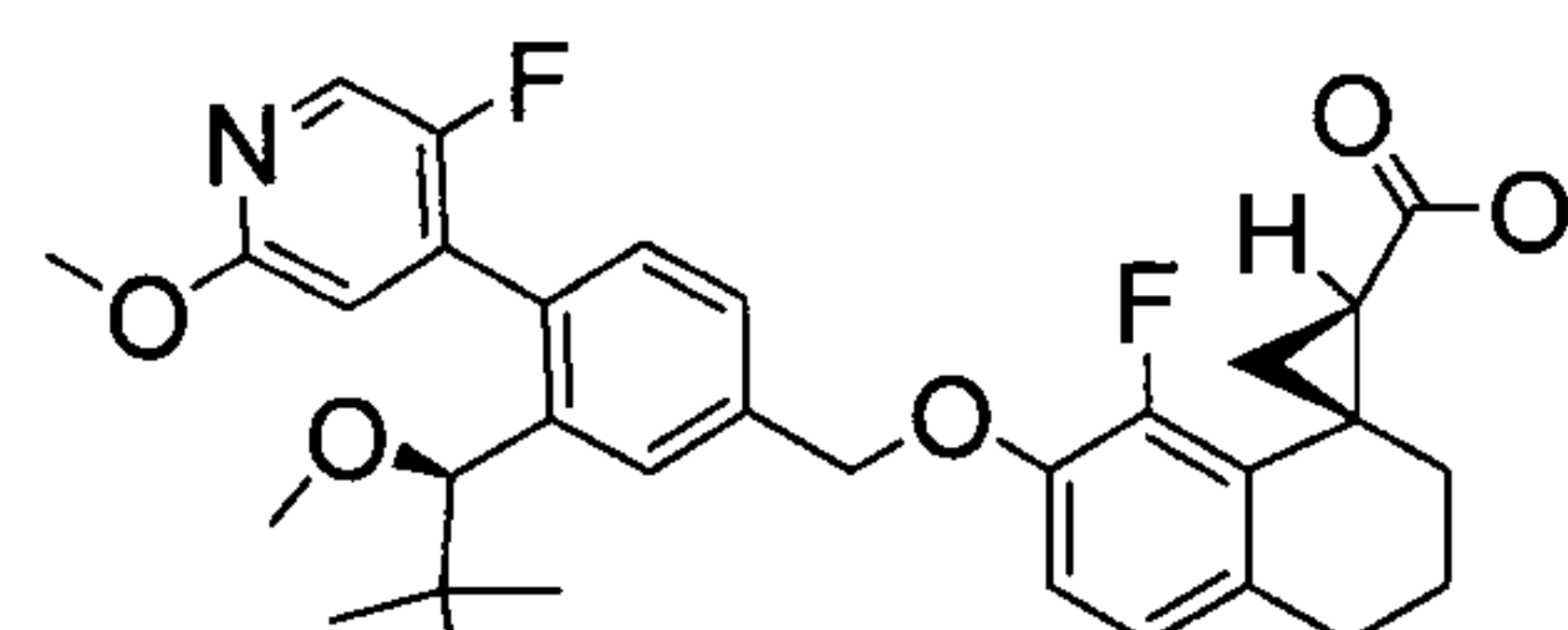
172. The compound



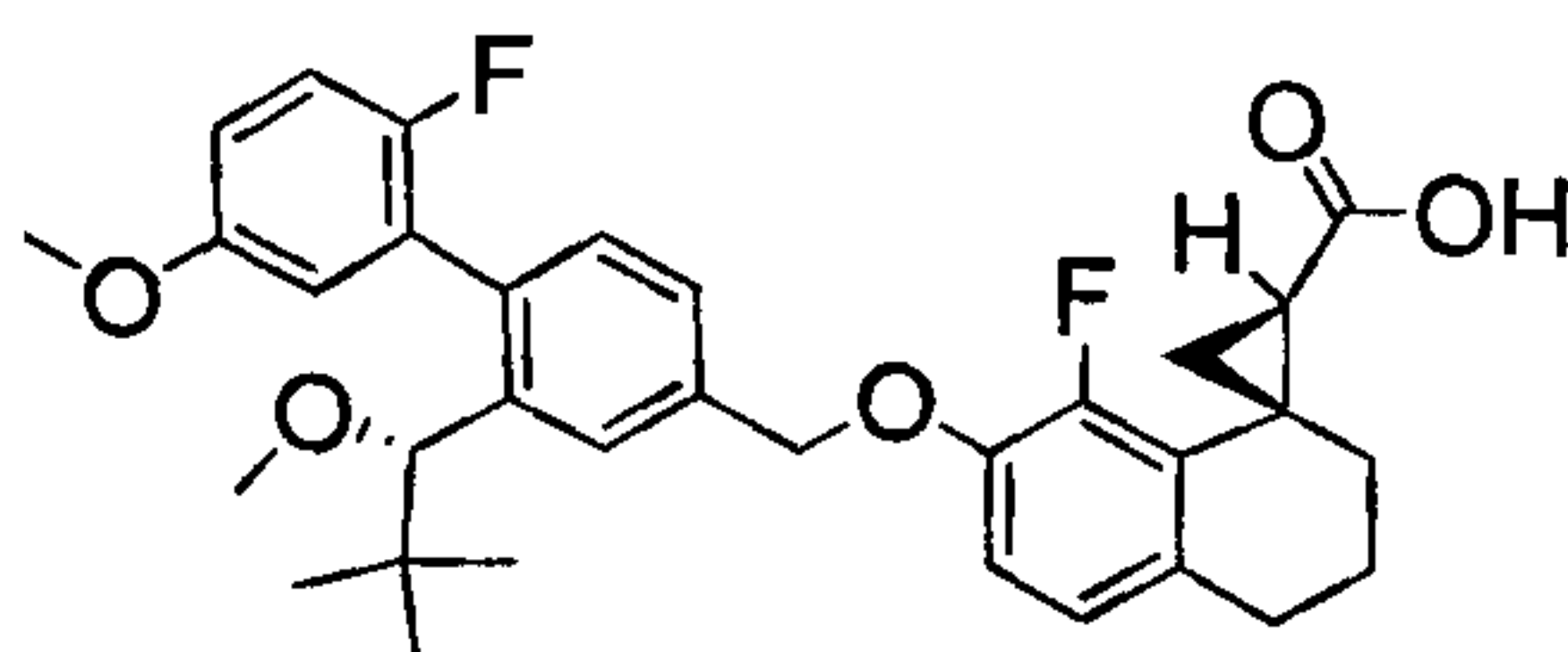
173. The compound



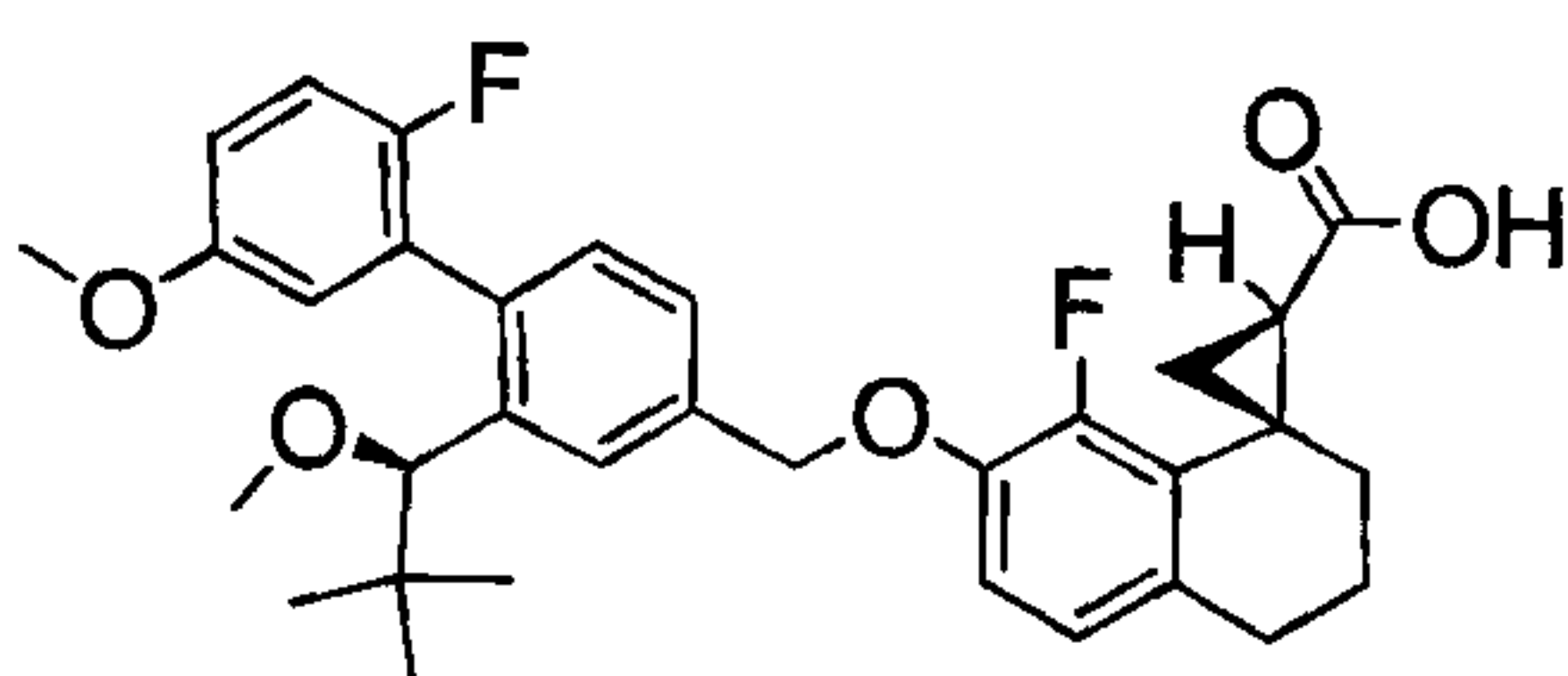
174. The compound



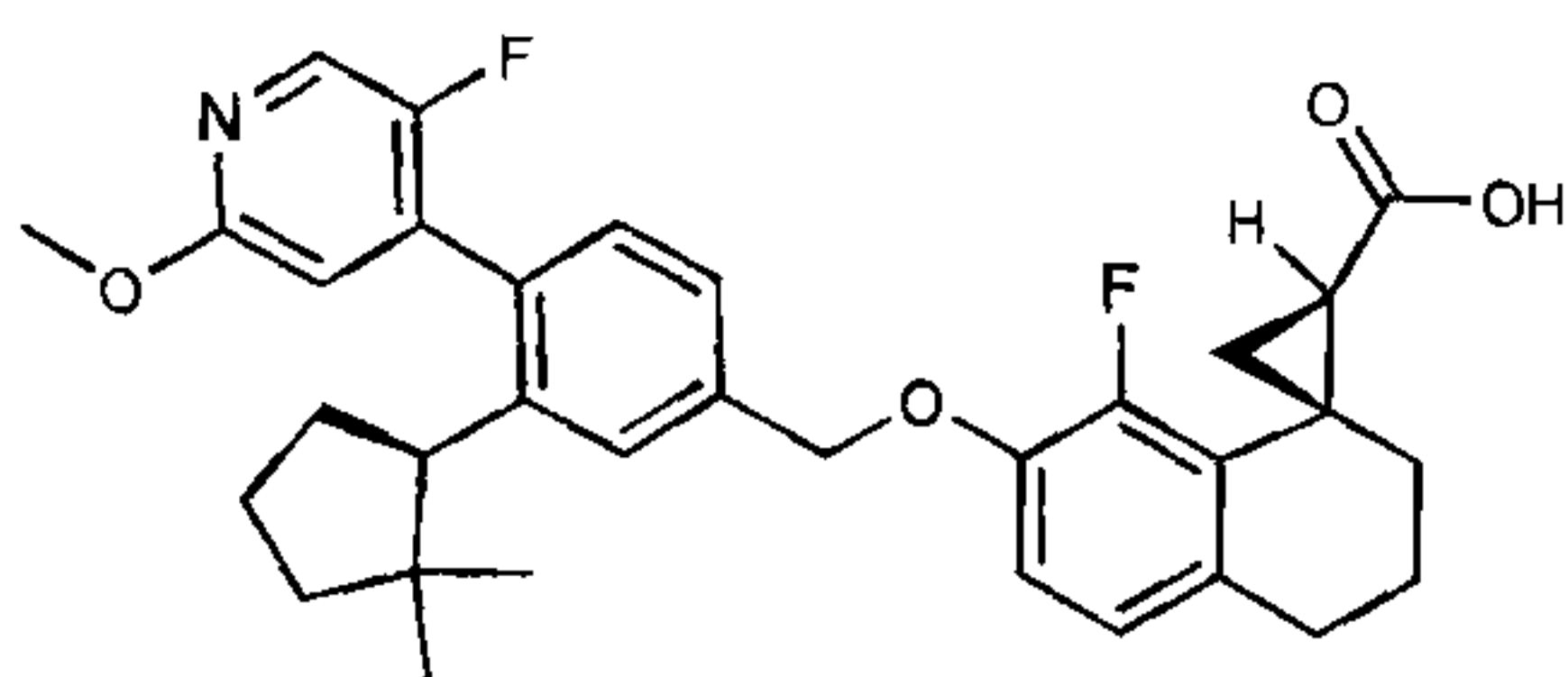
175. The compound



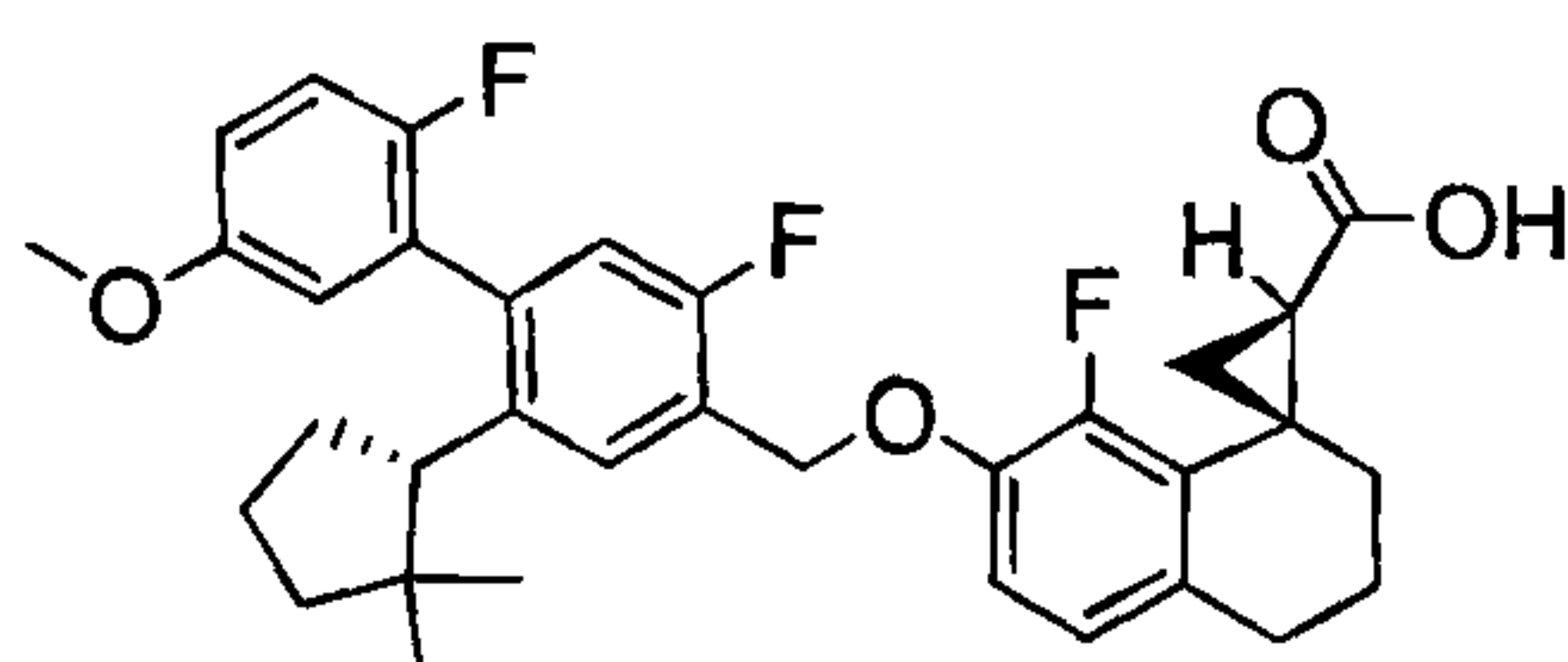
176. The compound



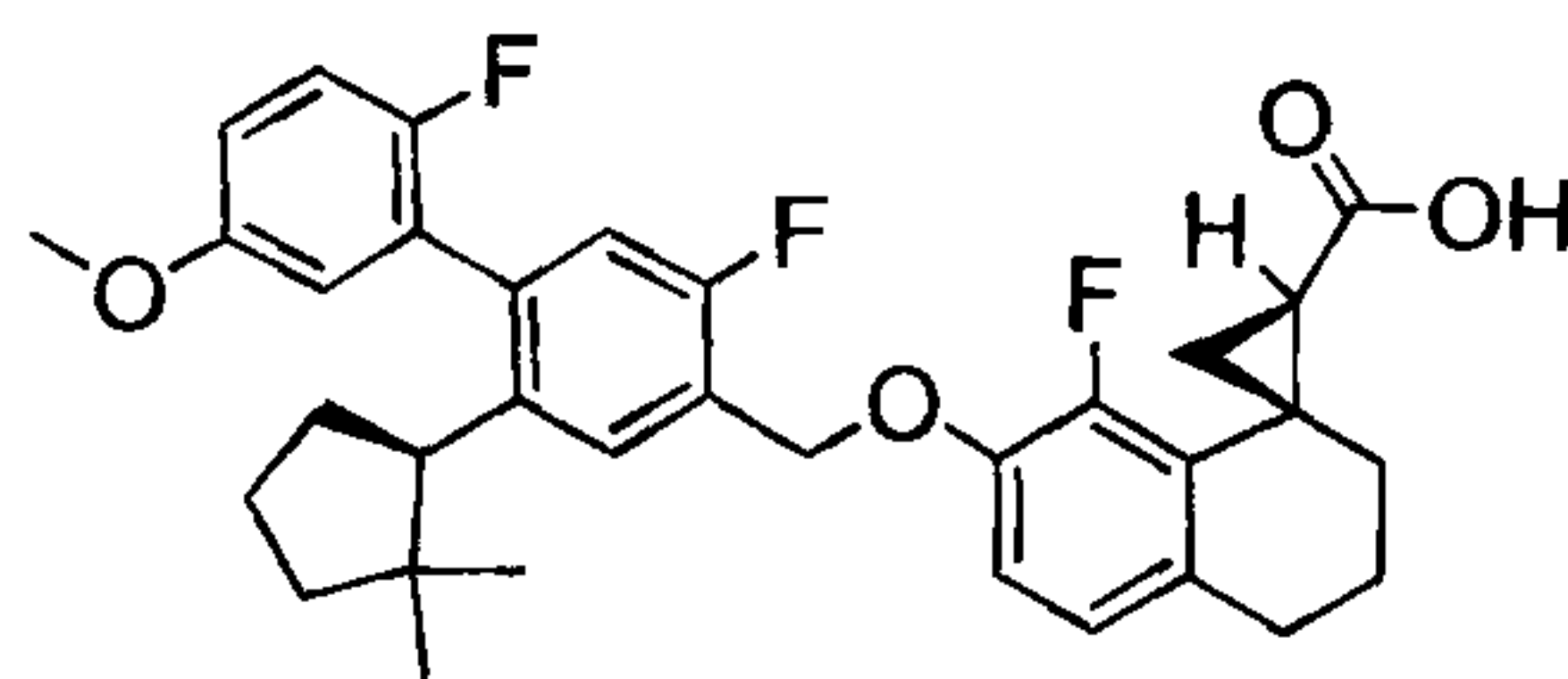
177. The compound



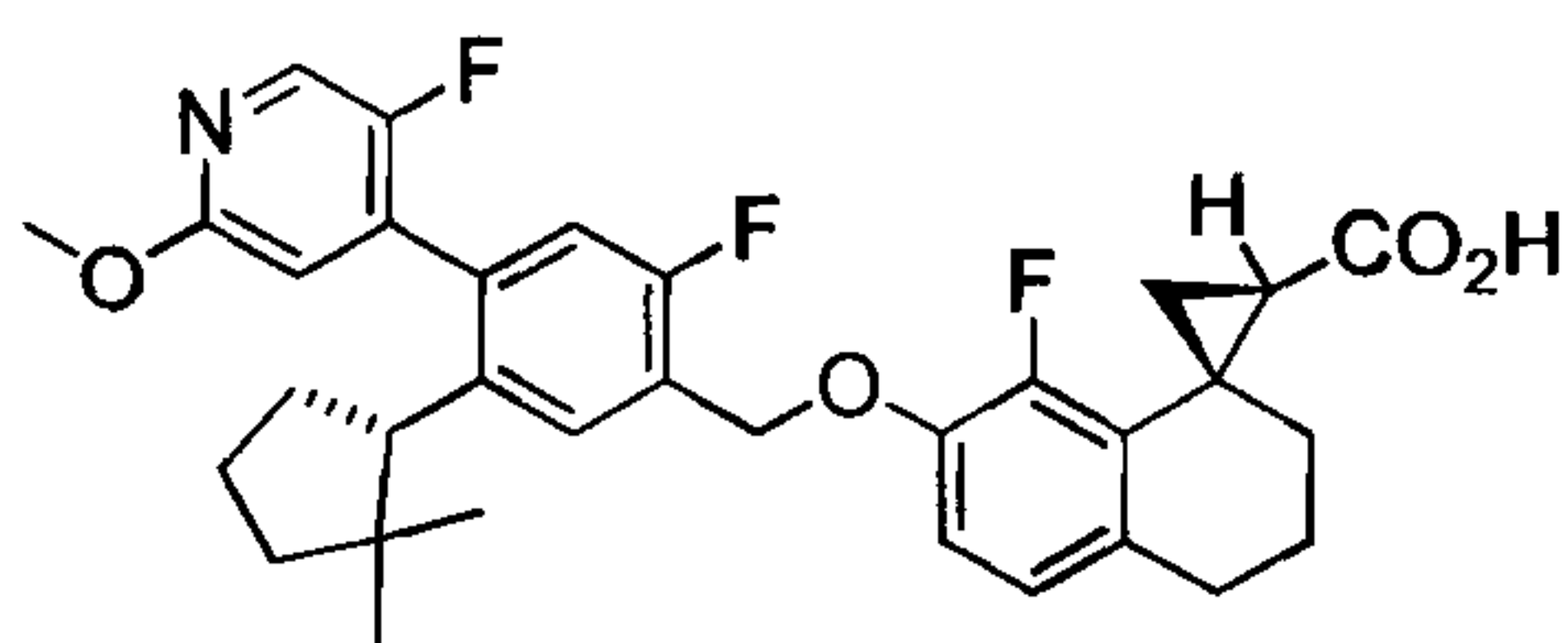
178. The compound



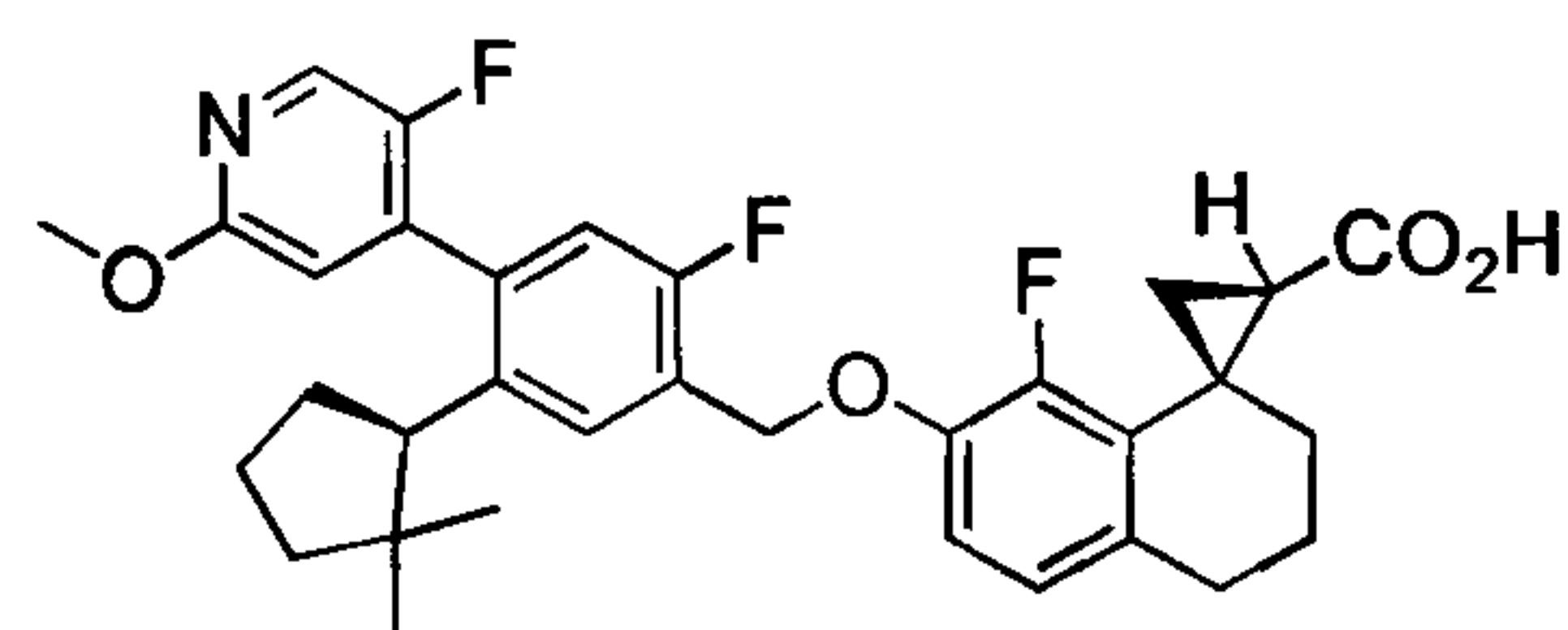
179. The compound



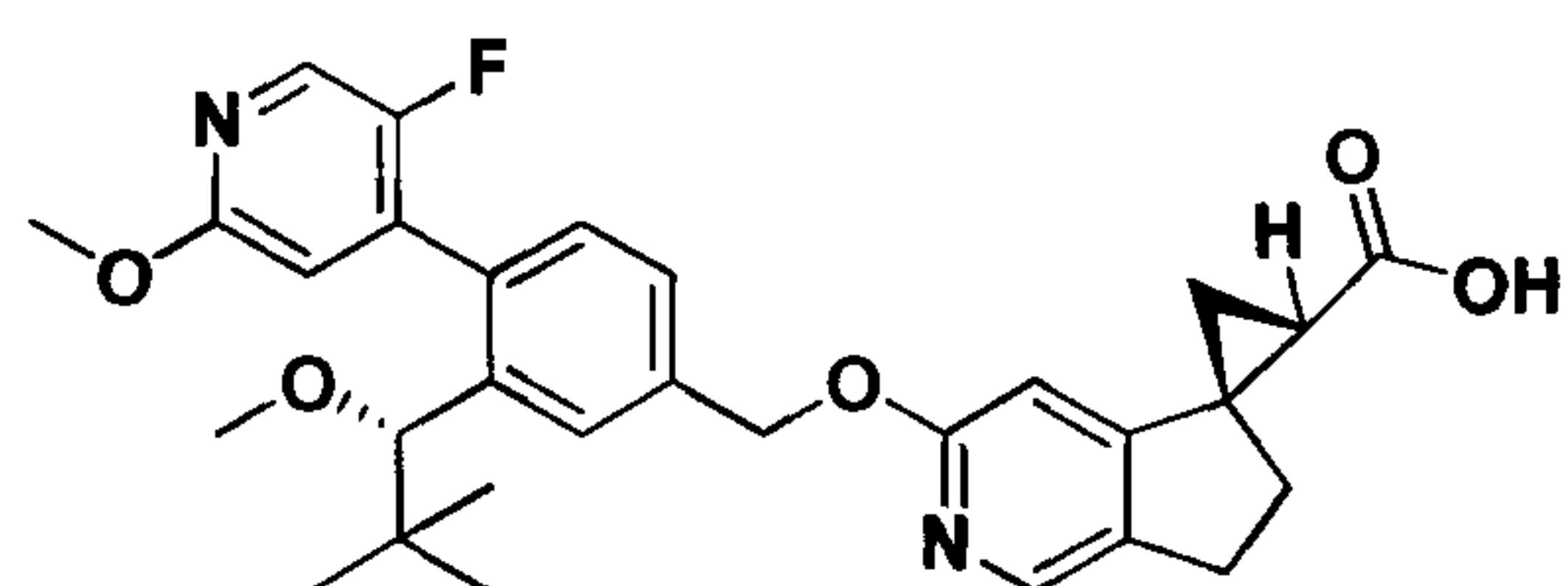
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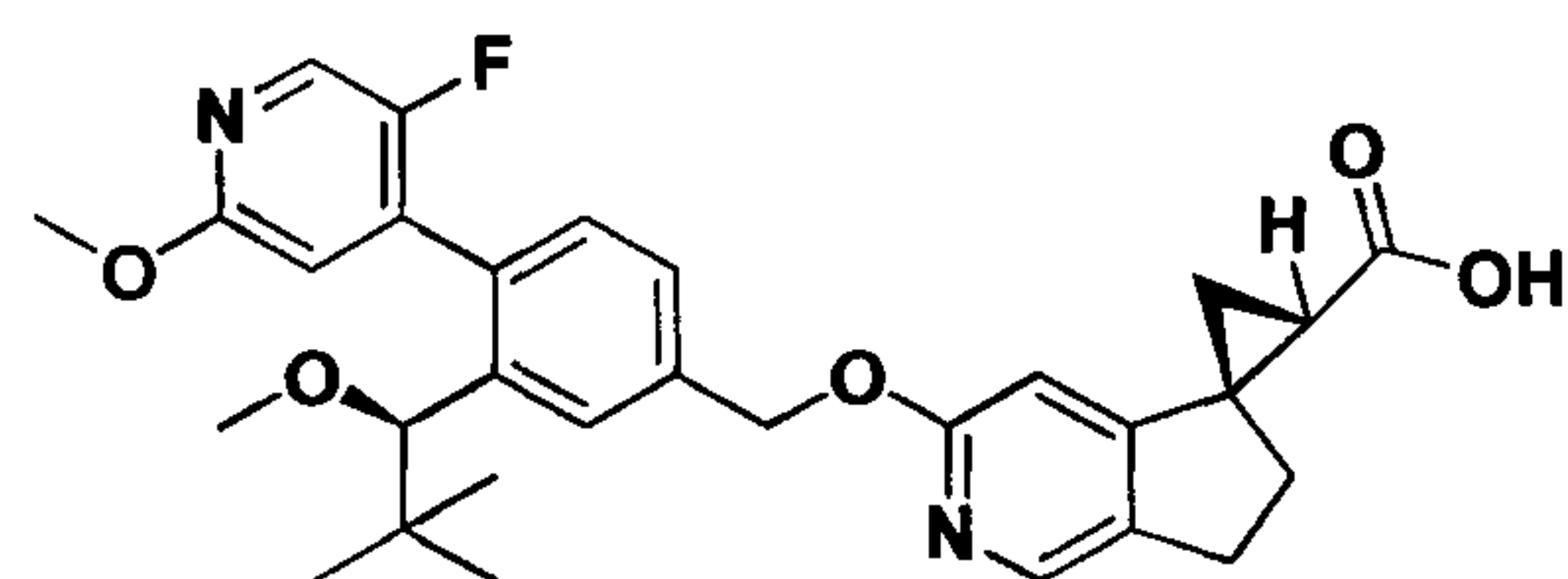
181. The compound



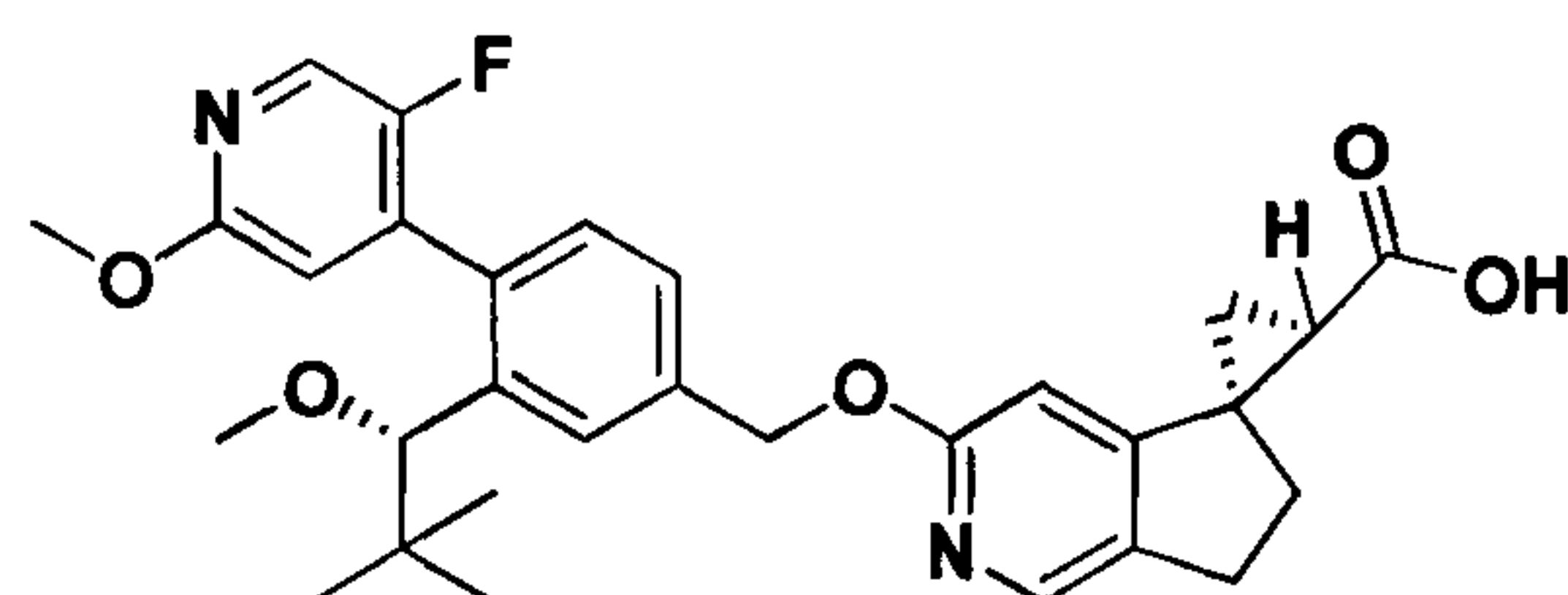
182. The compound



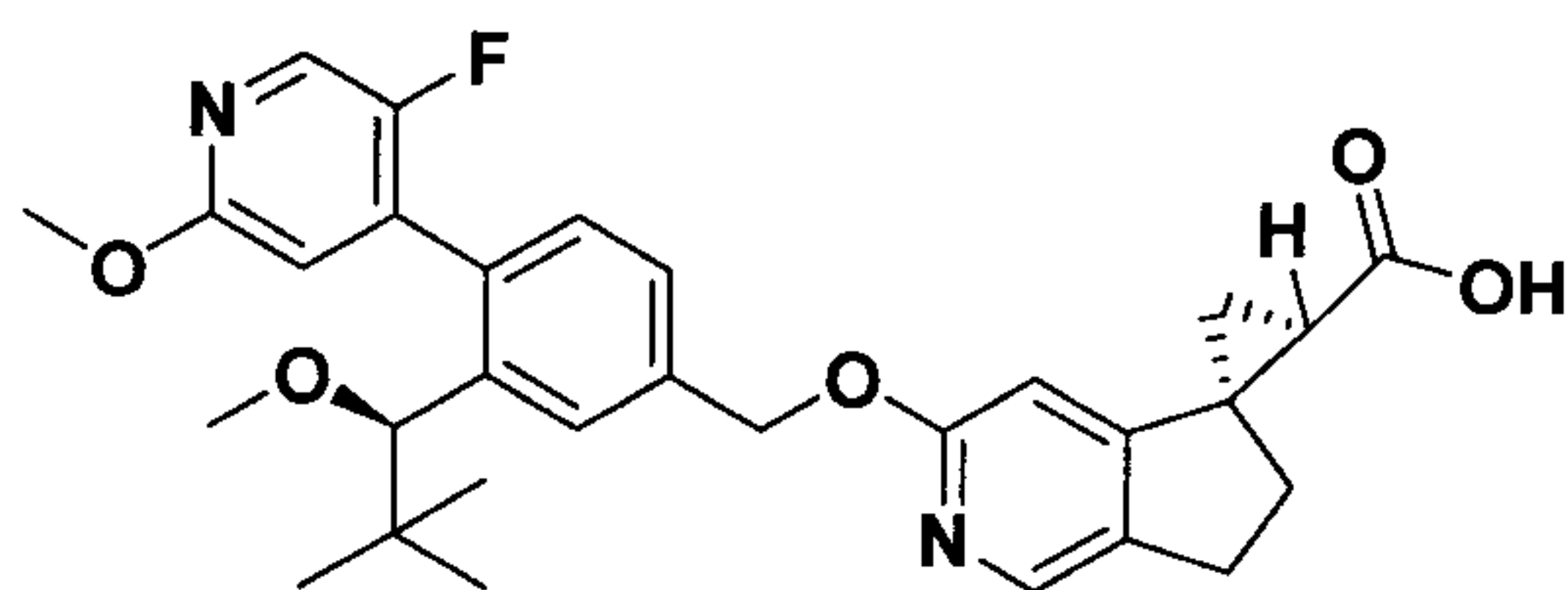
183. The compound



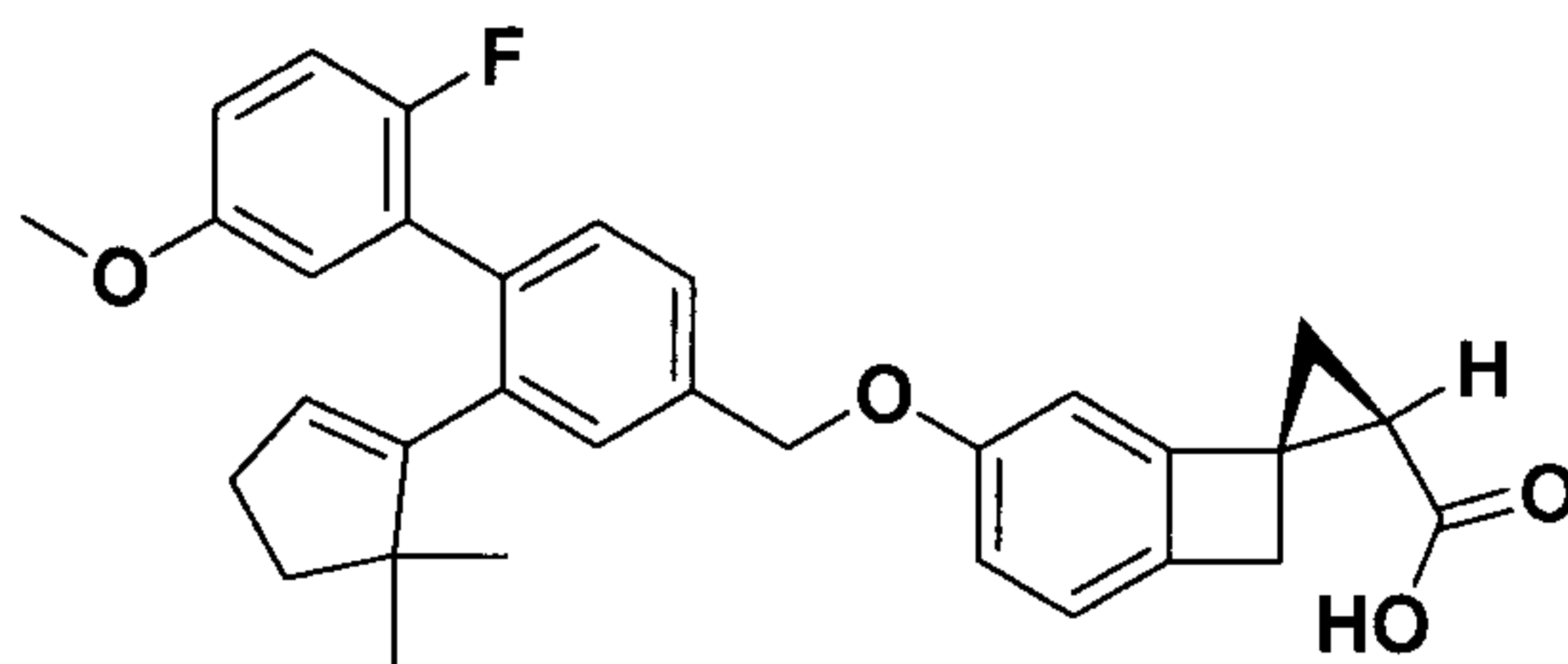
184. The compound



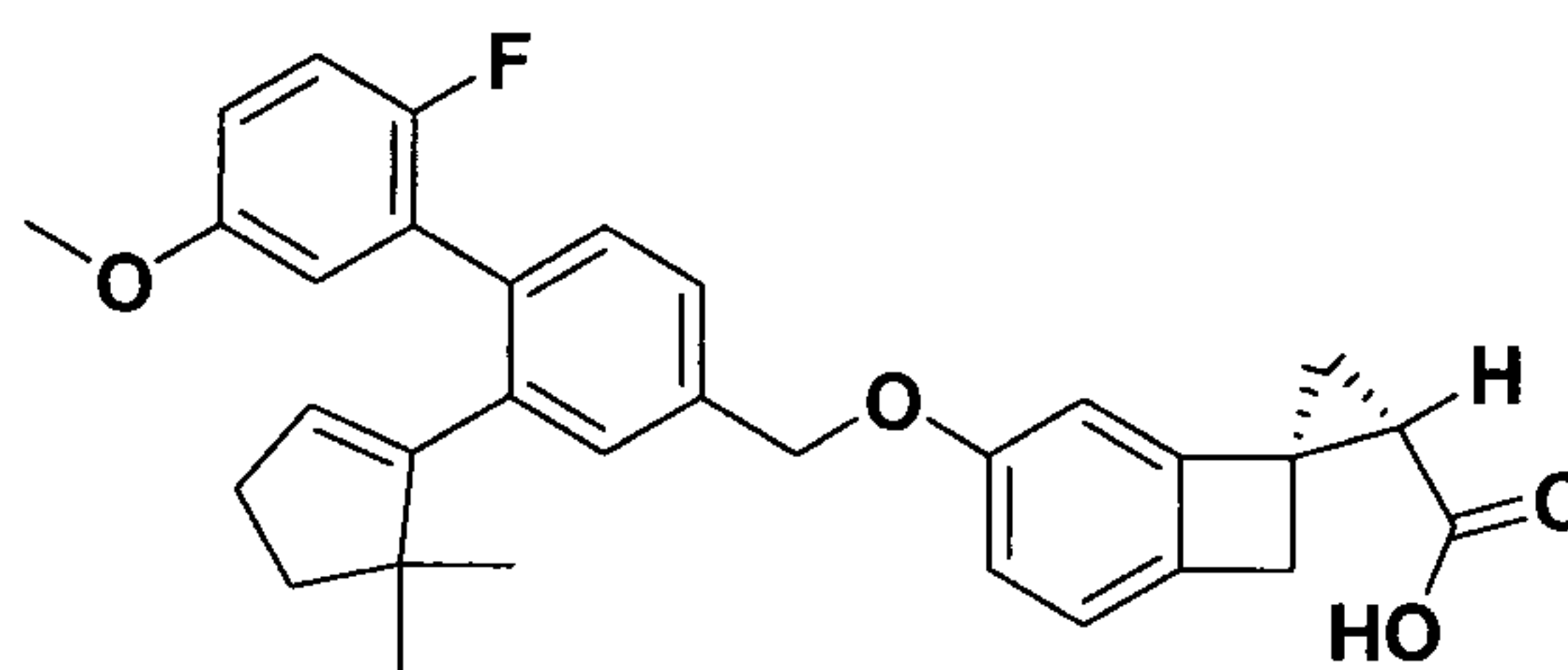
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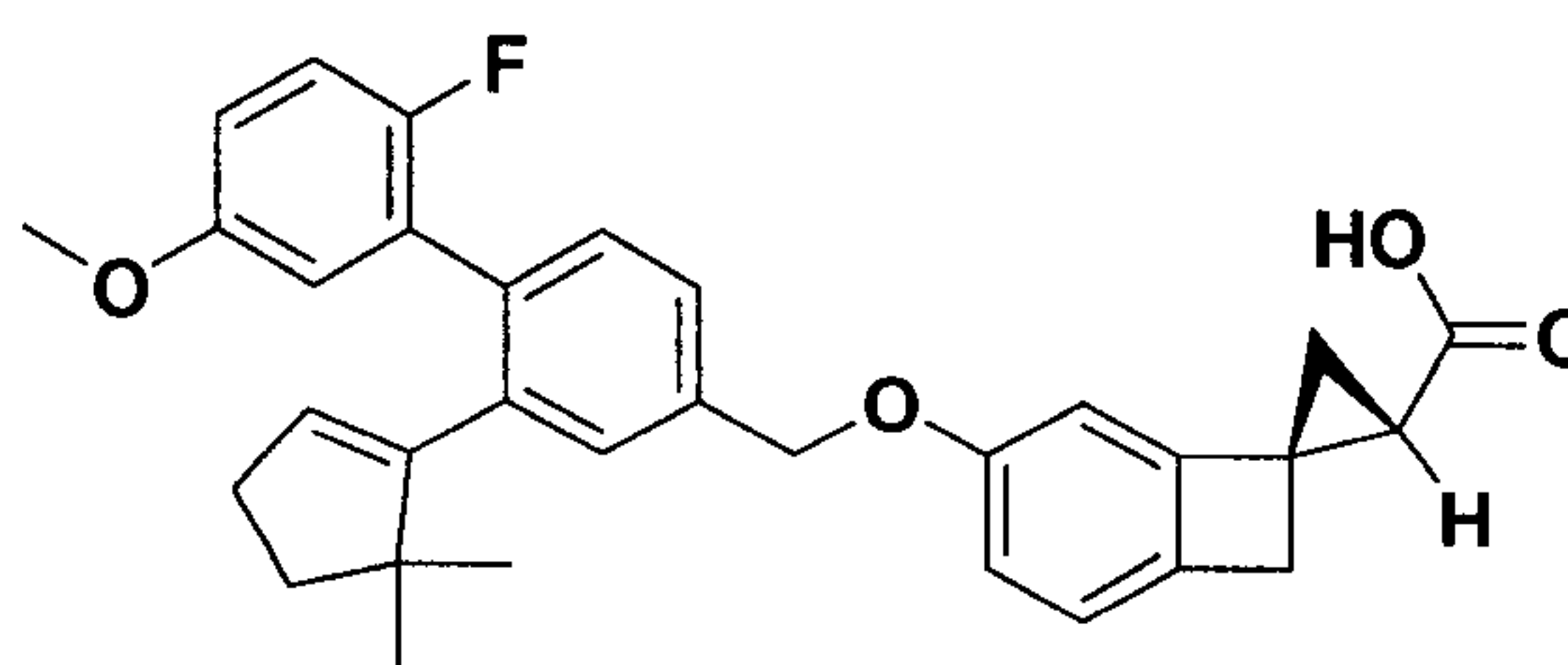
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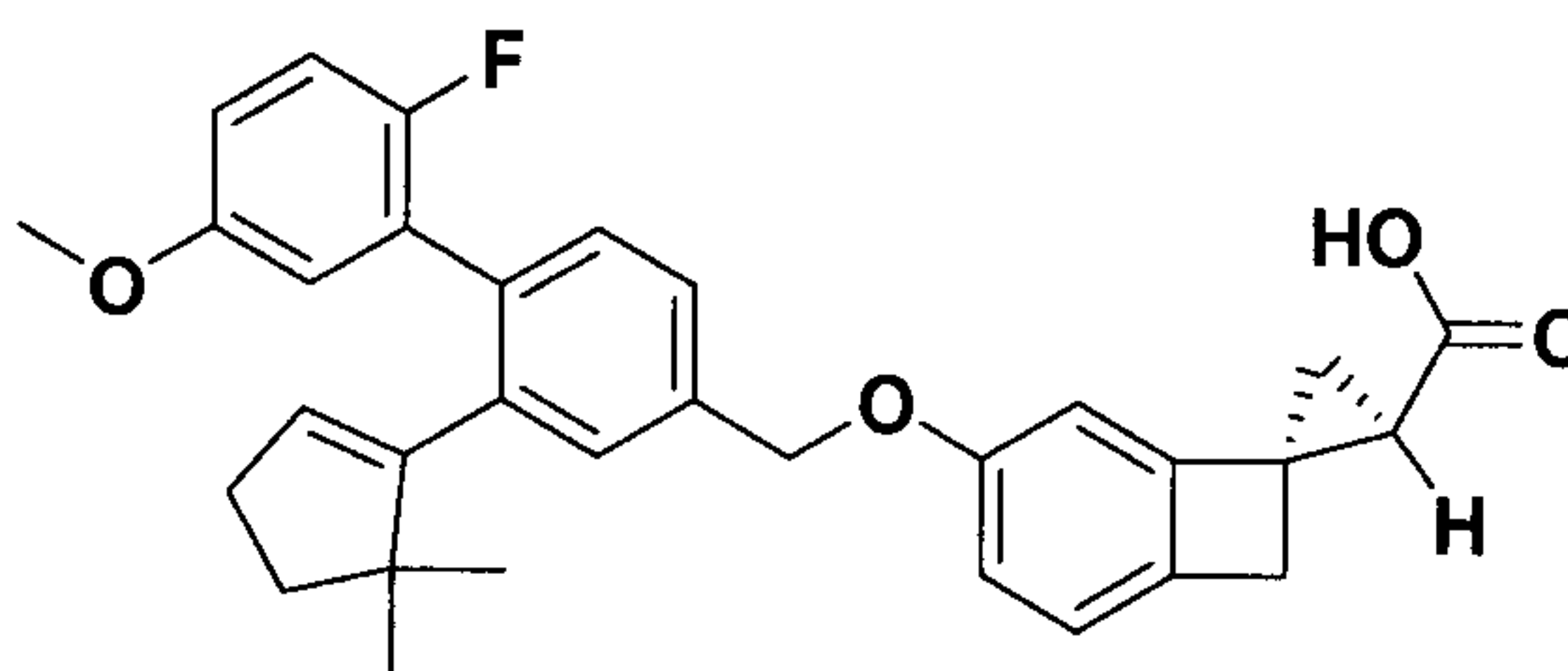
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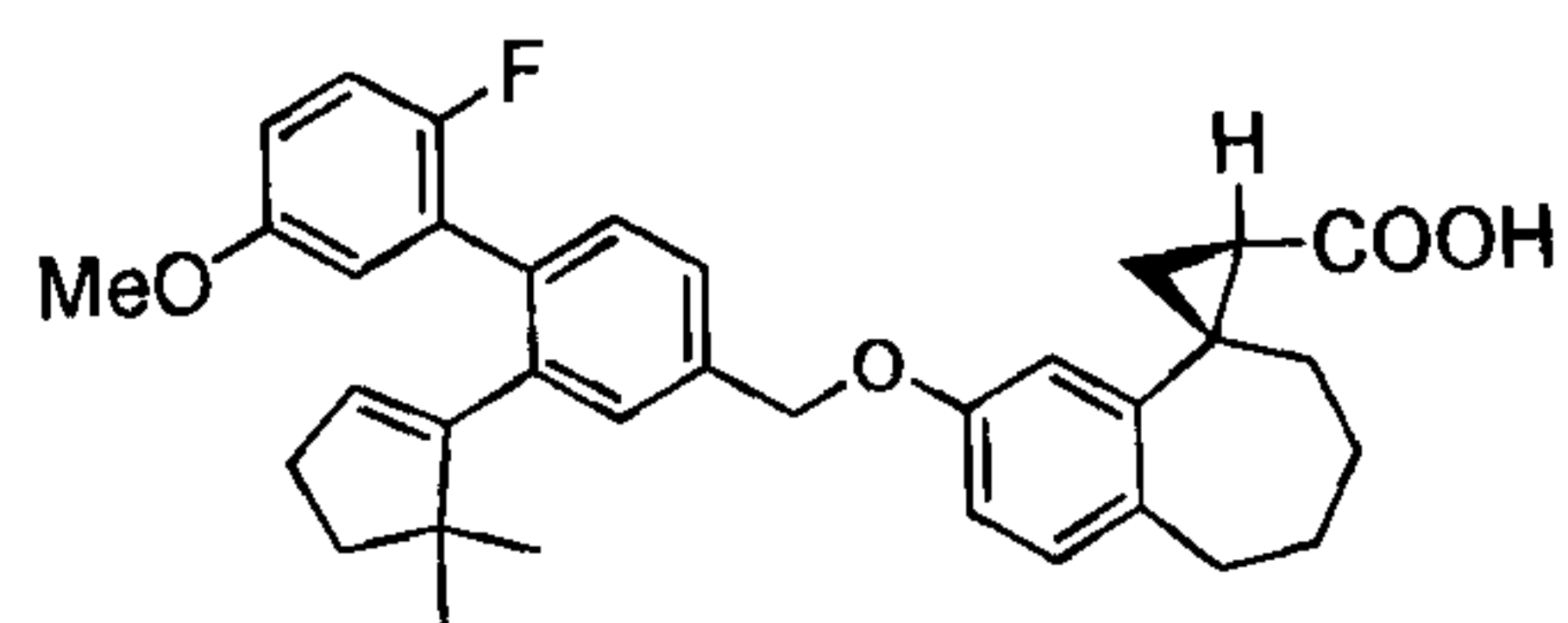
188. The compound



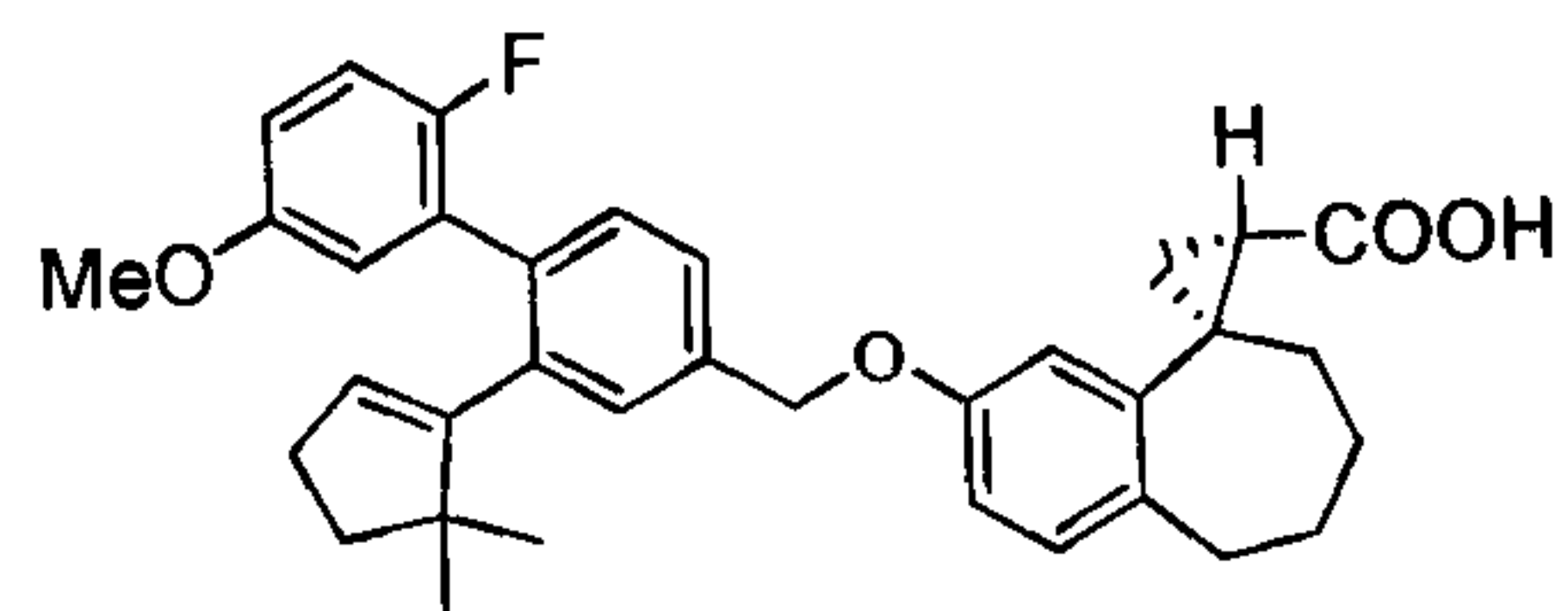
189. The compound



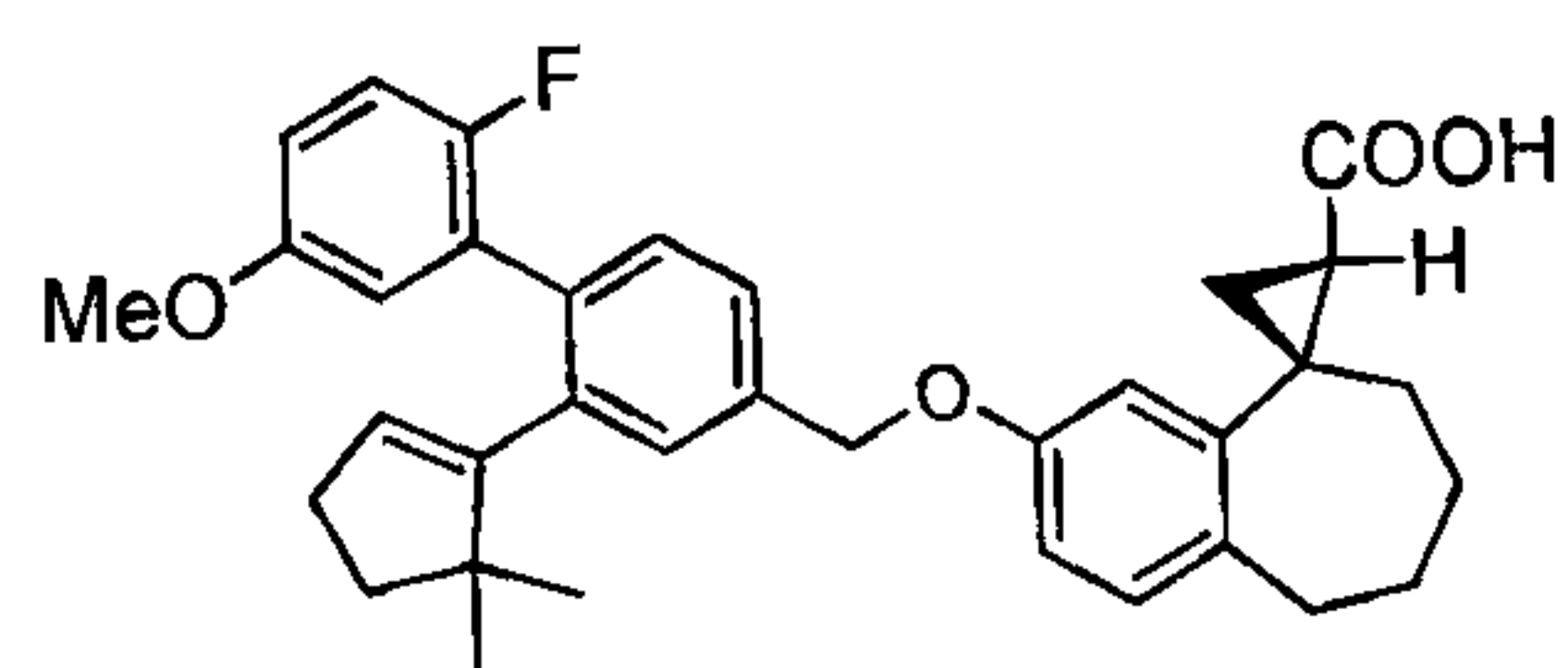
190. The compound



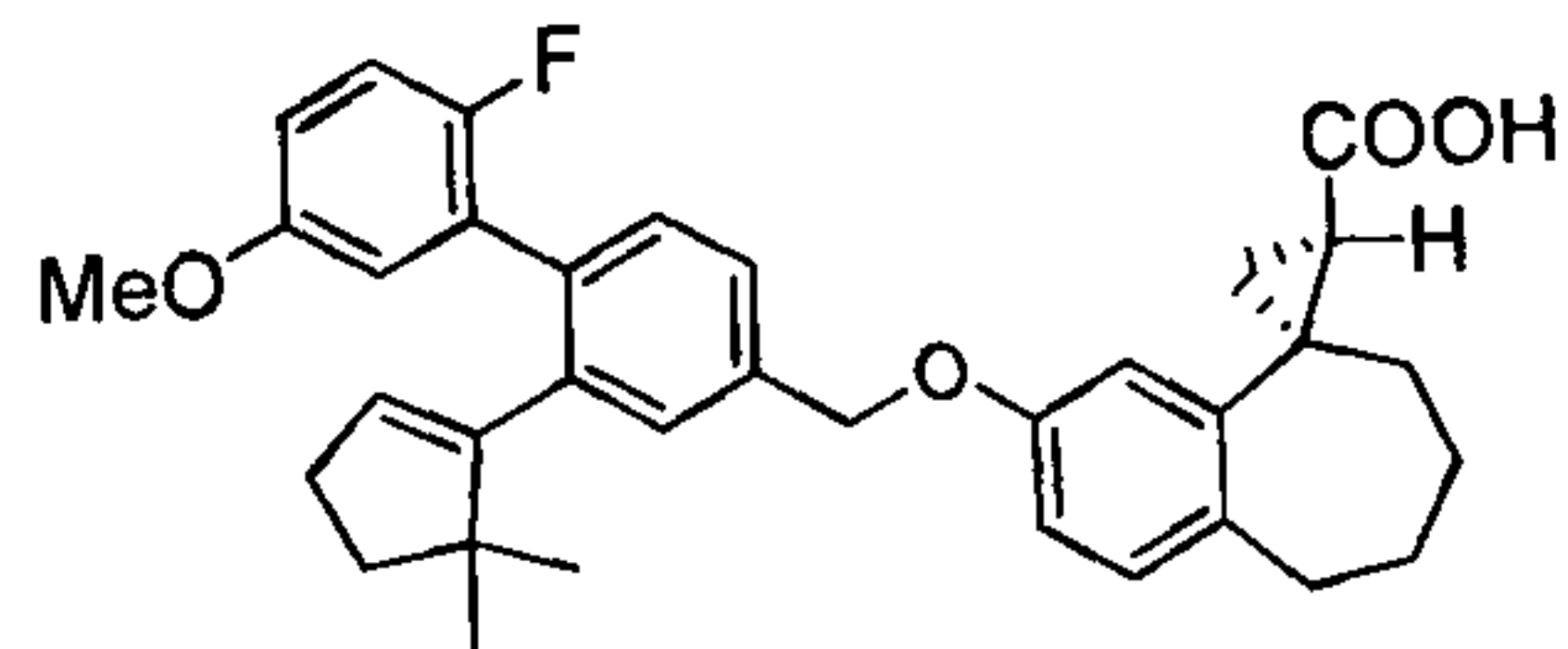
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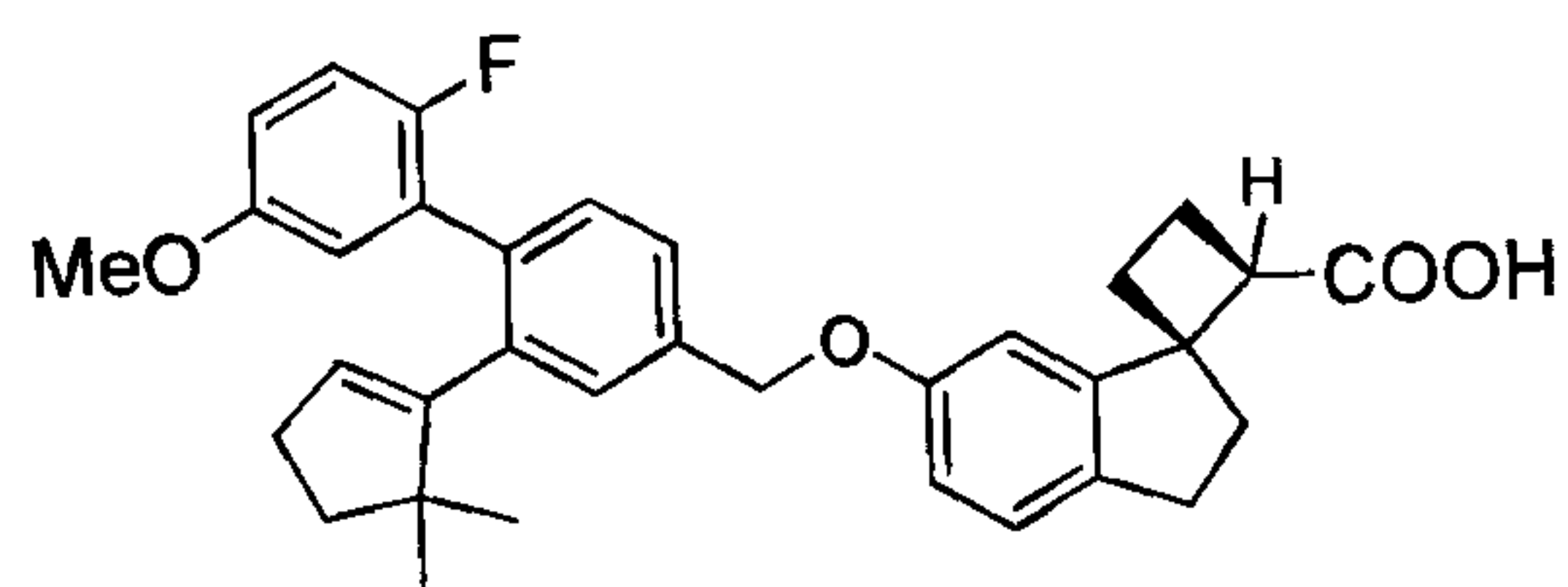
192. The compound



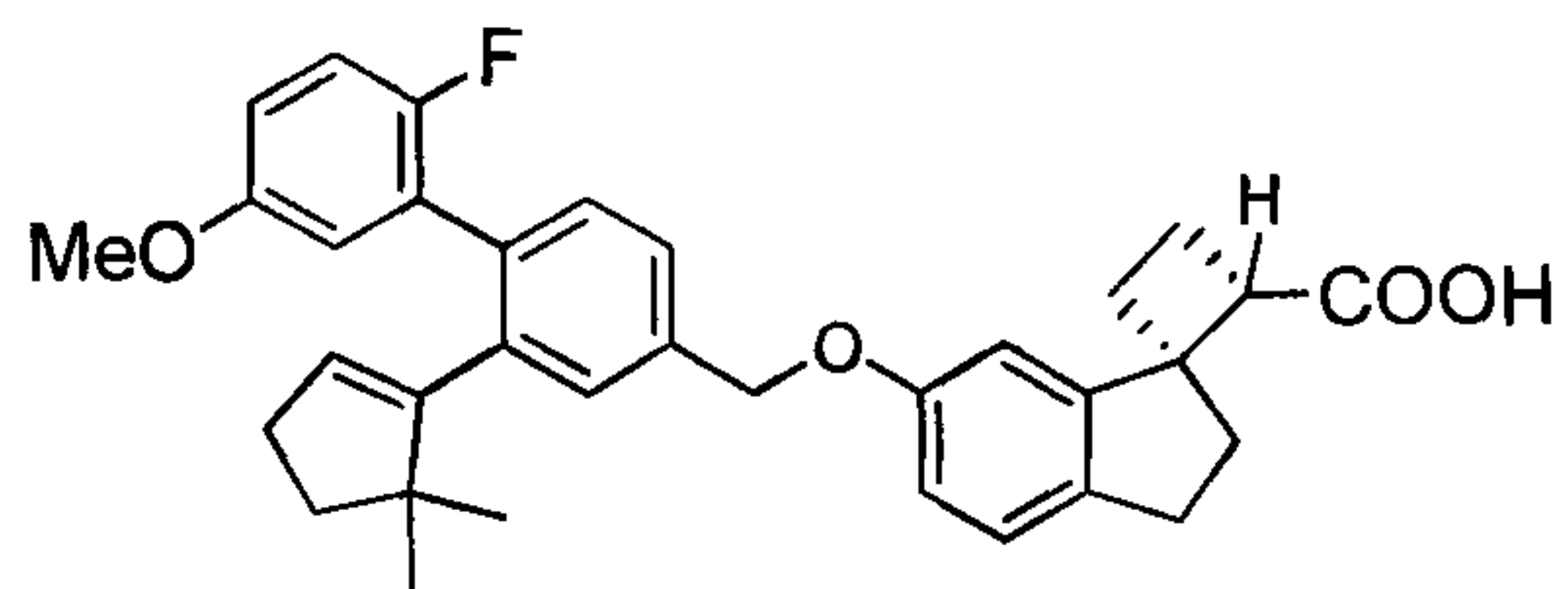
193. The compound



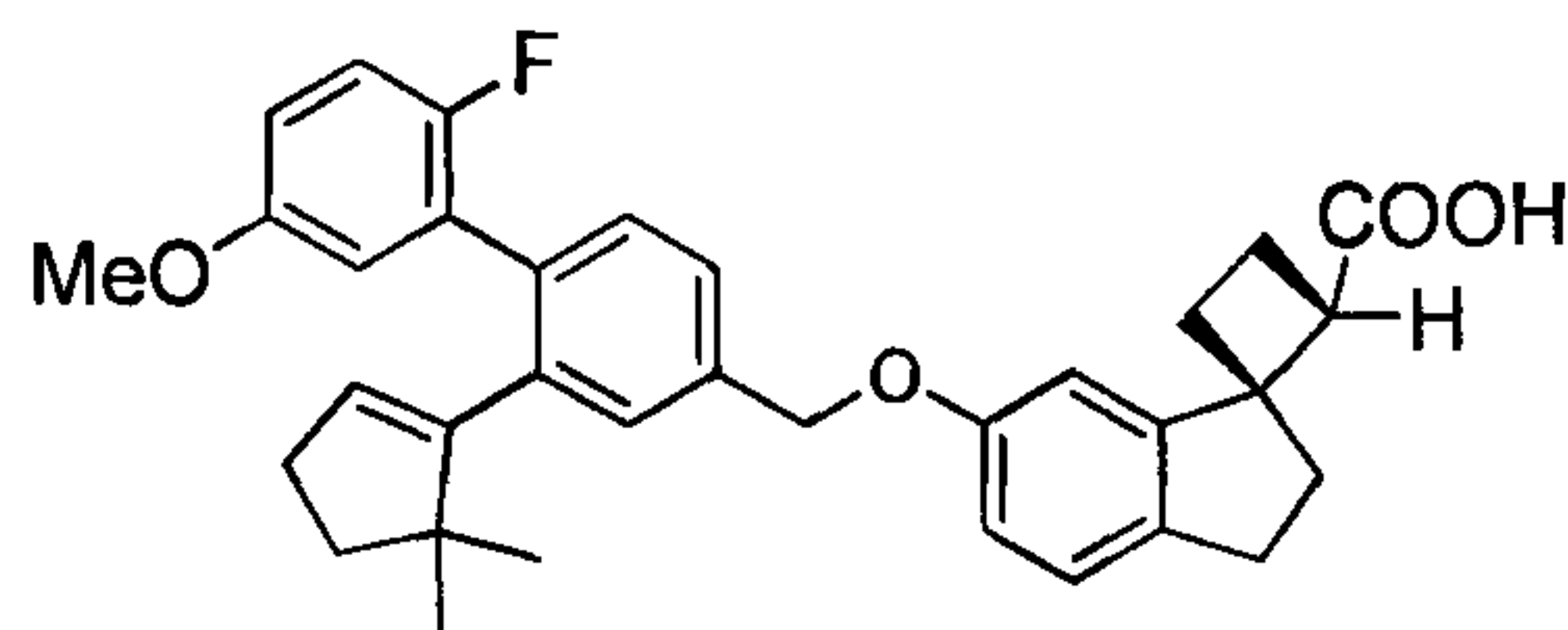
194. The compound



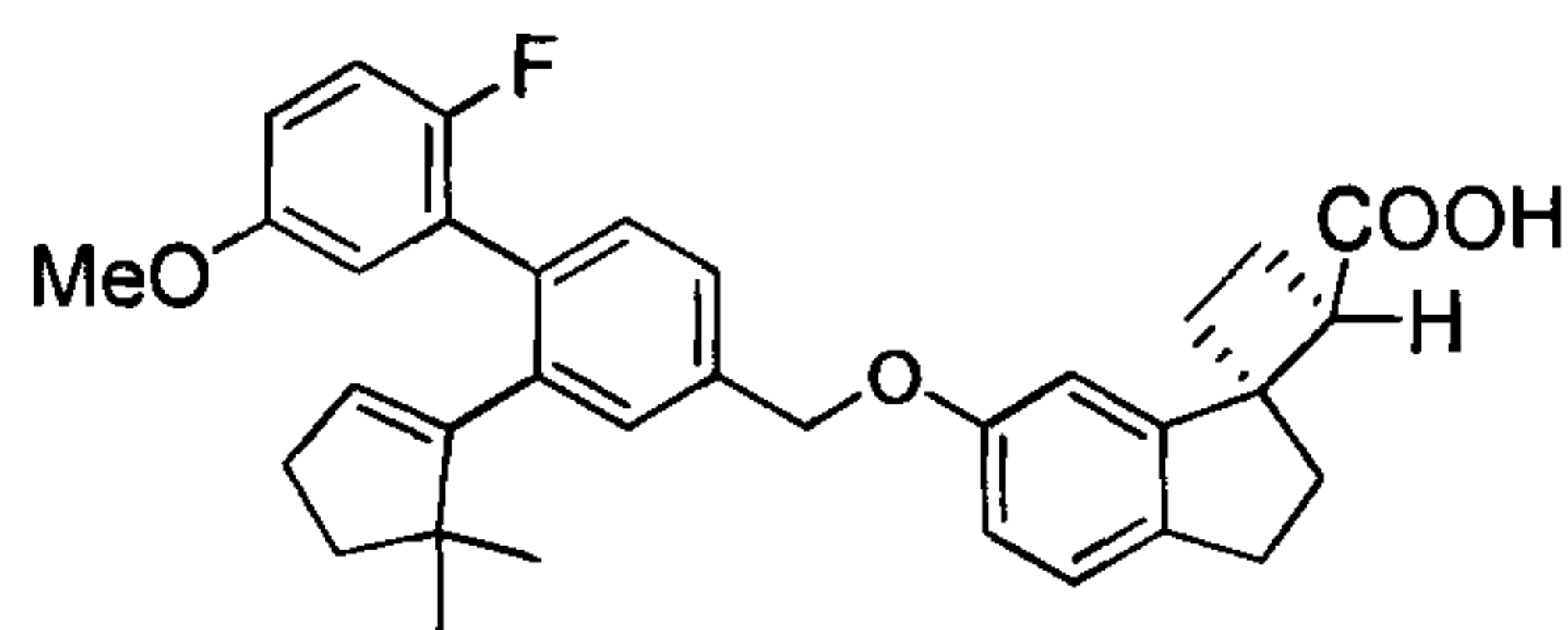
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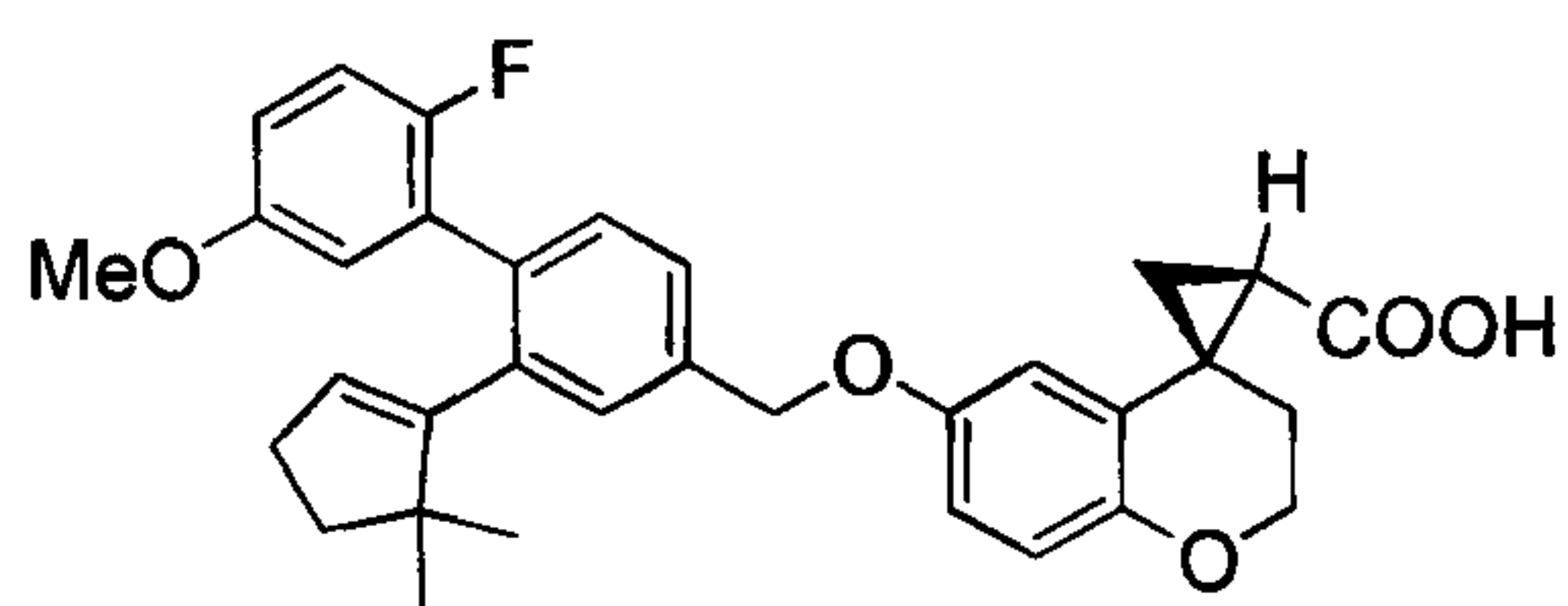
196. The compound



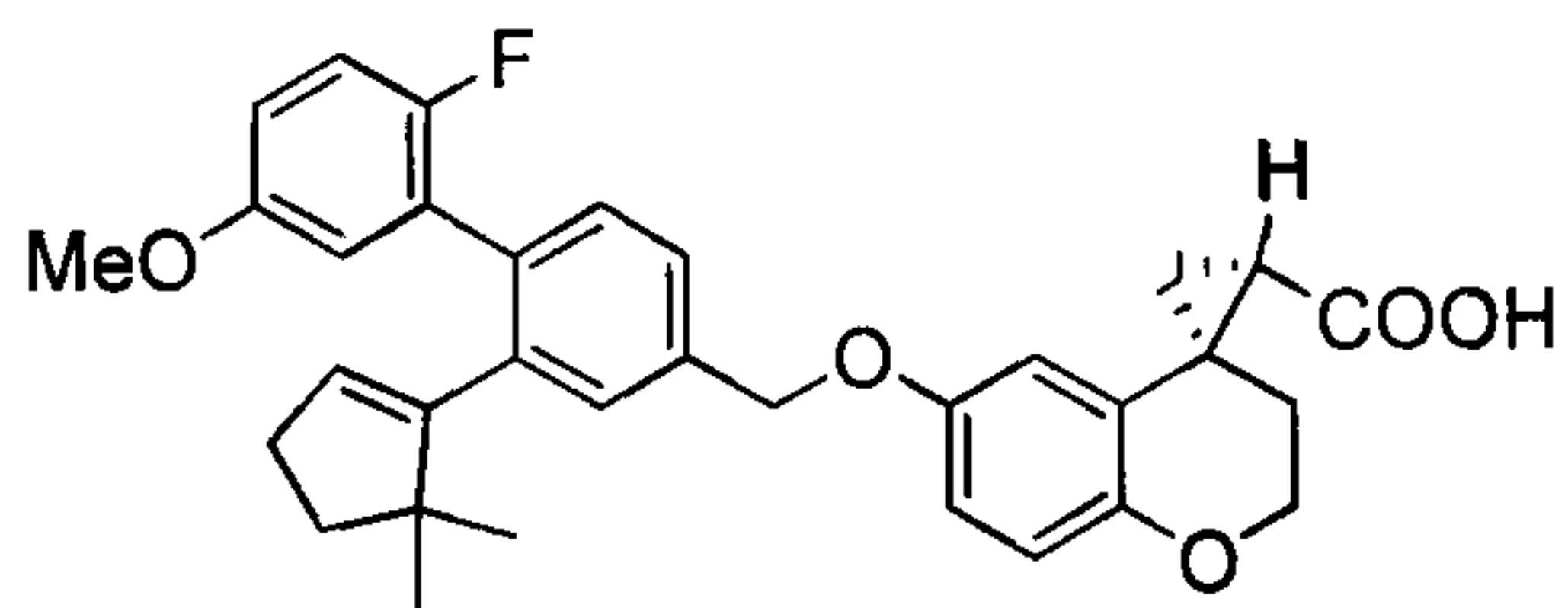
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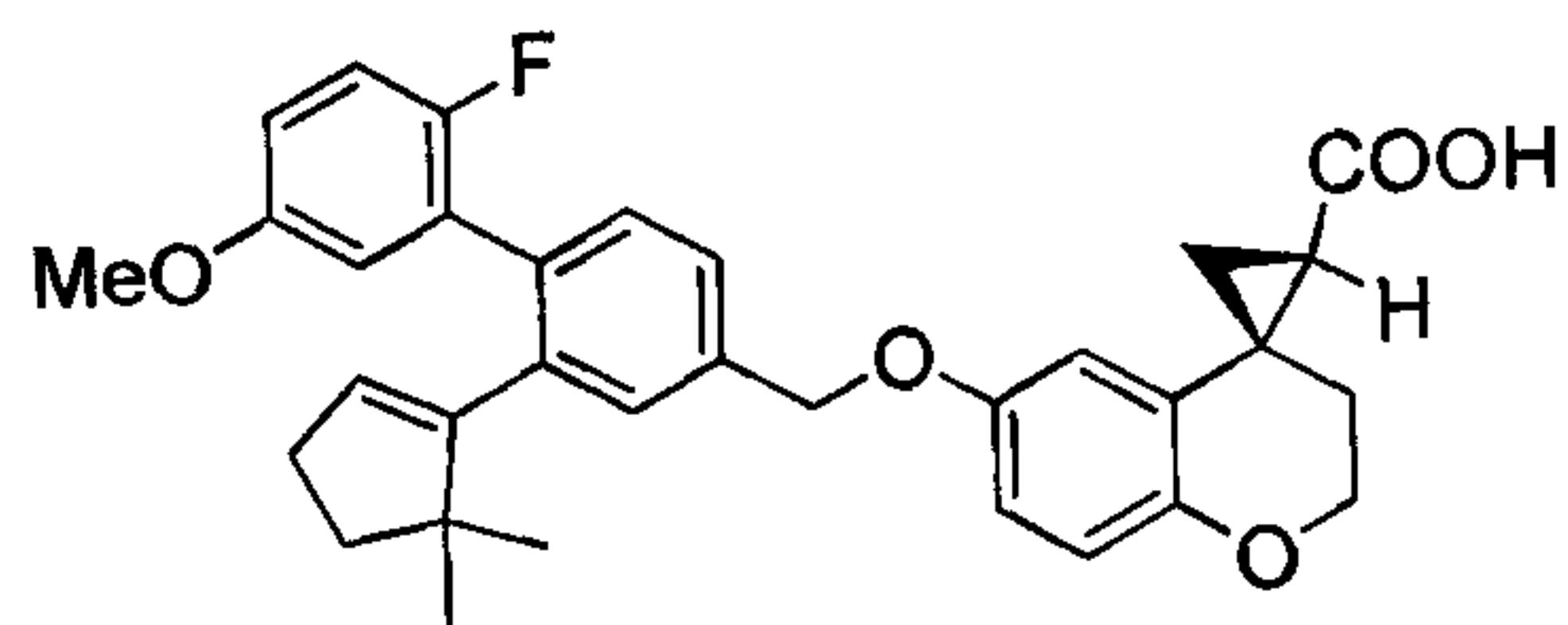
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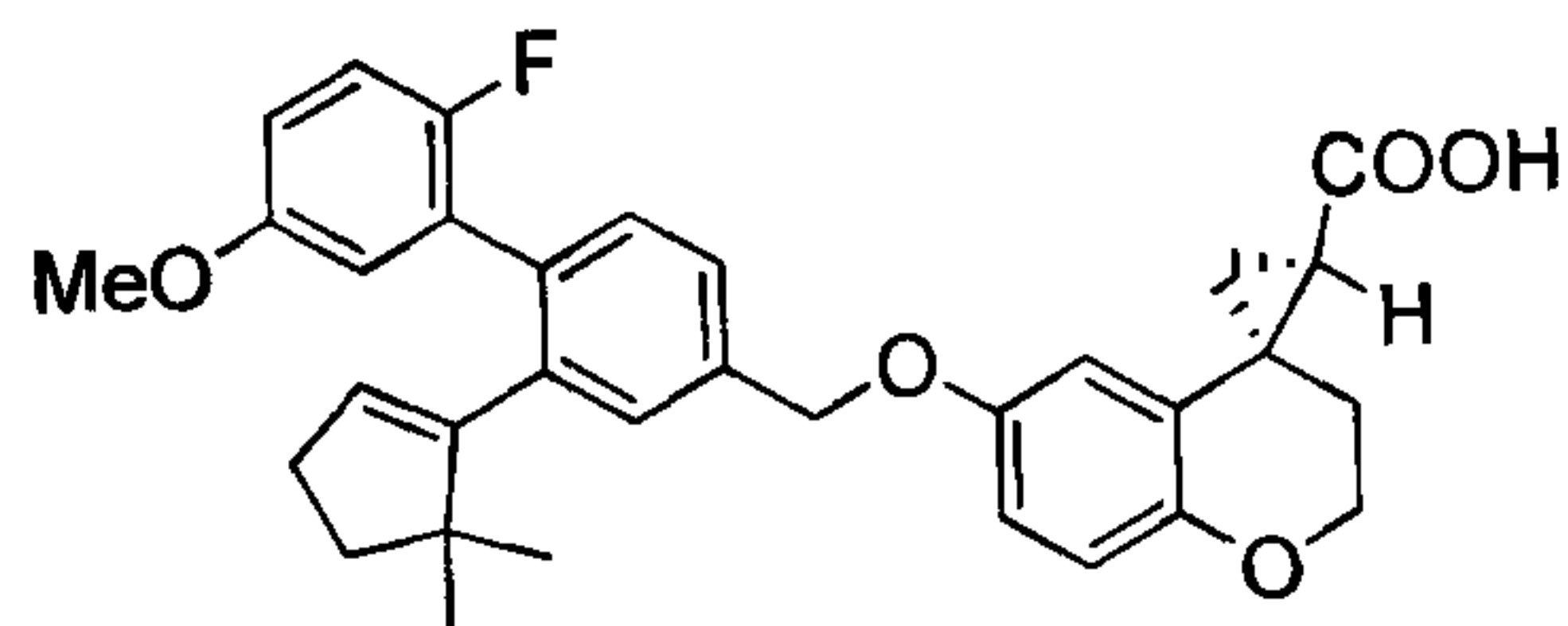
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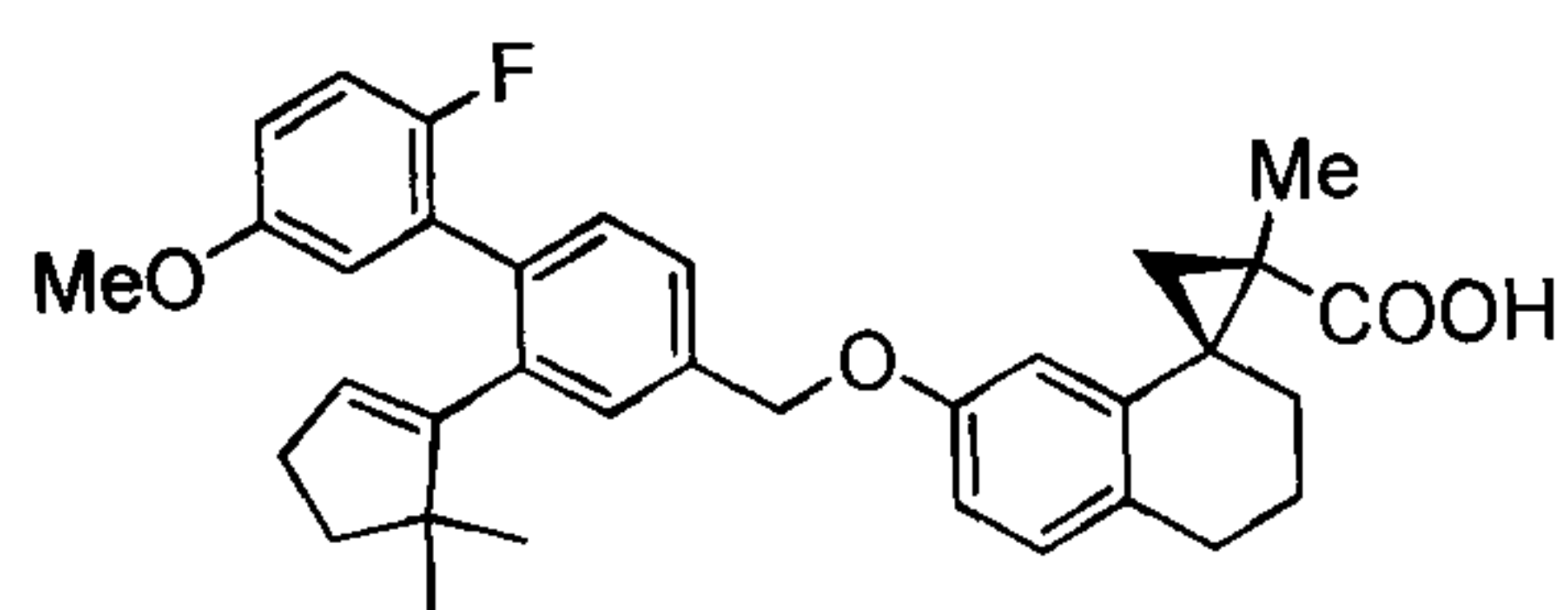
200. The compound



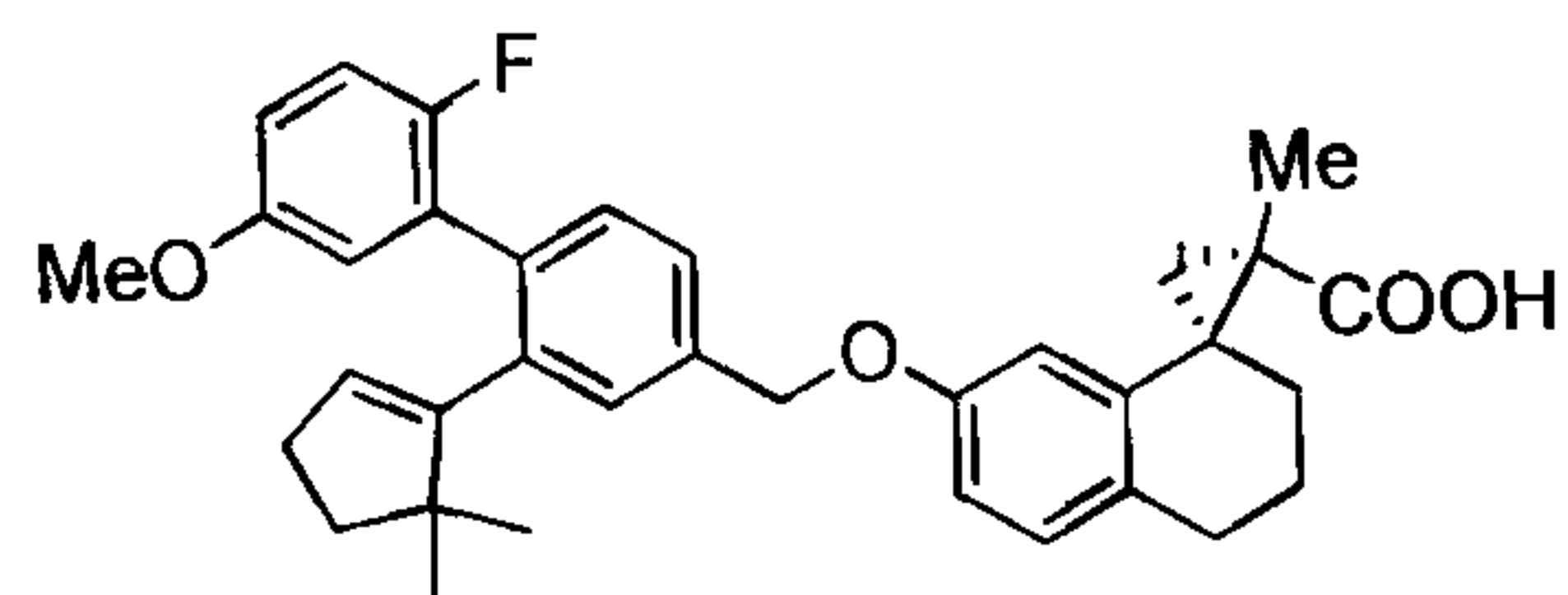
201. The compound



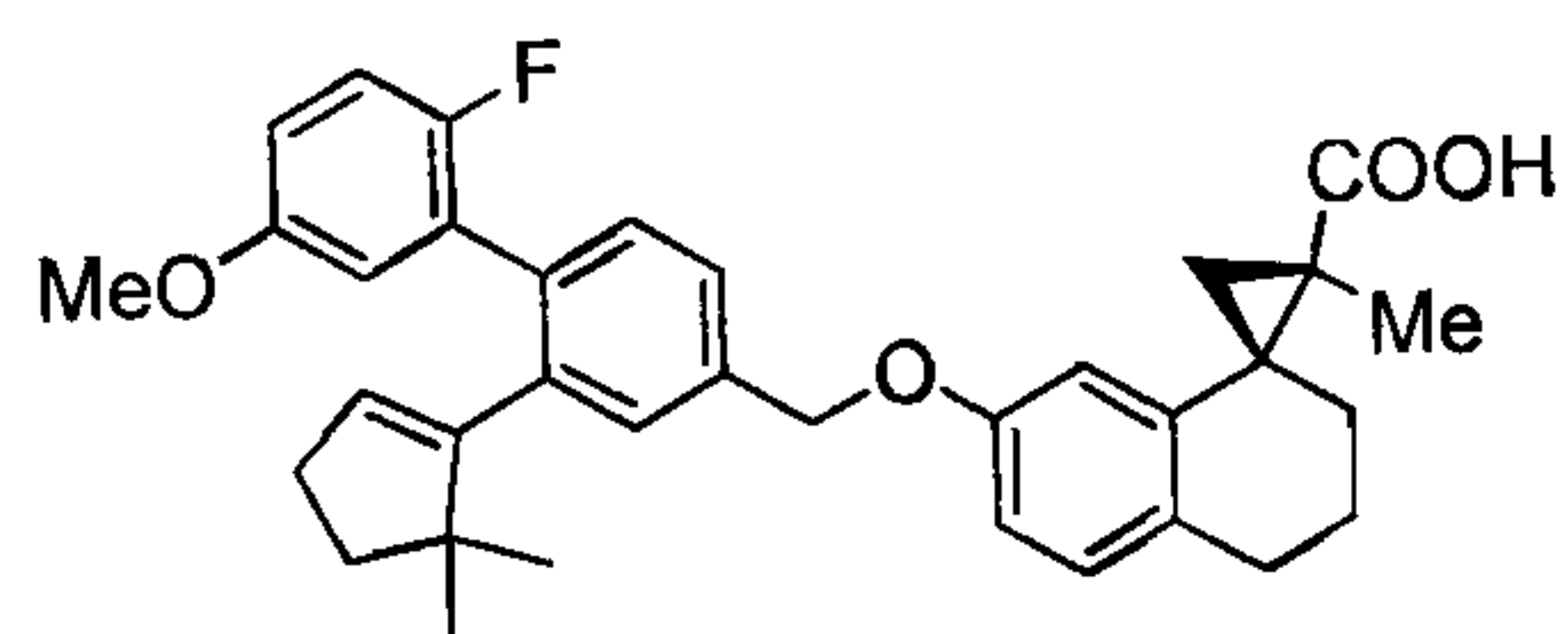
202. The compound



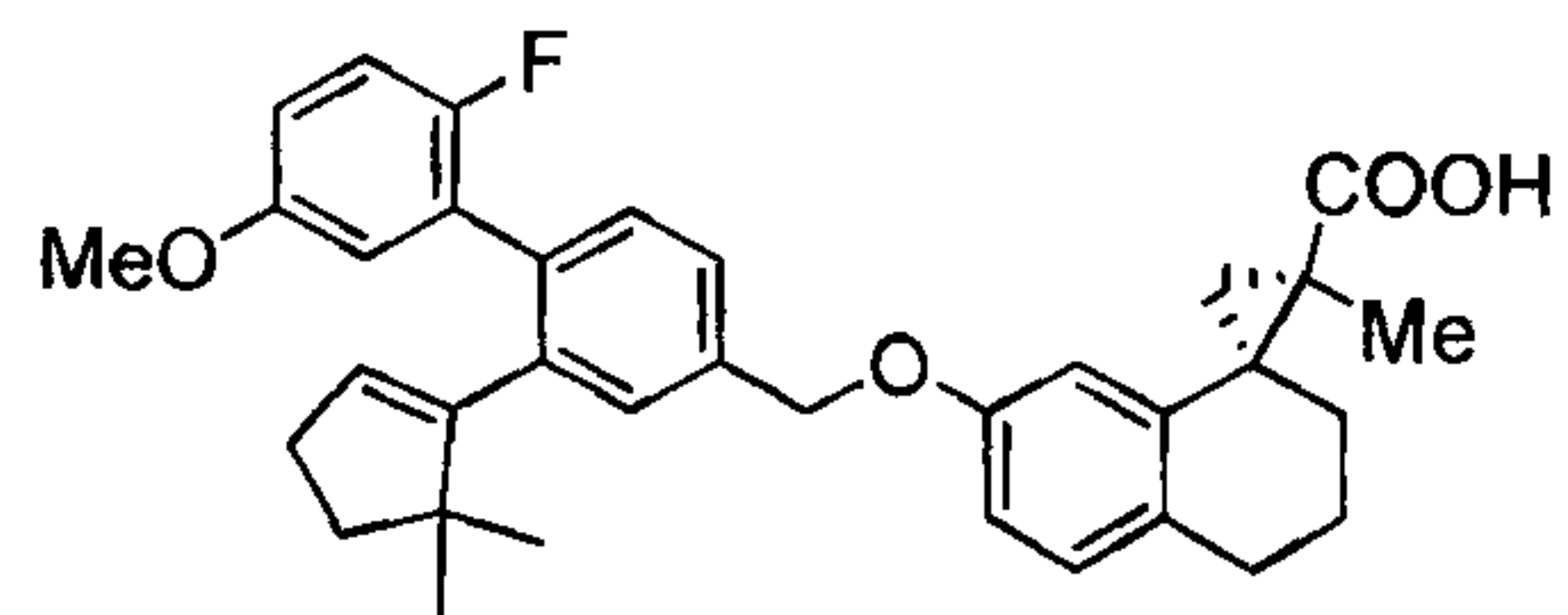
203. The compound



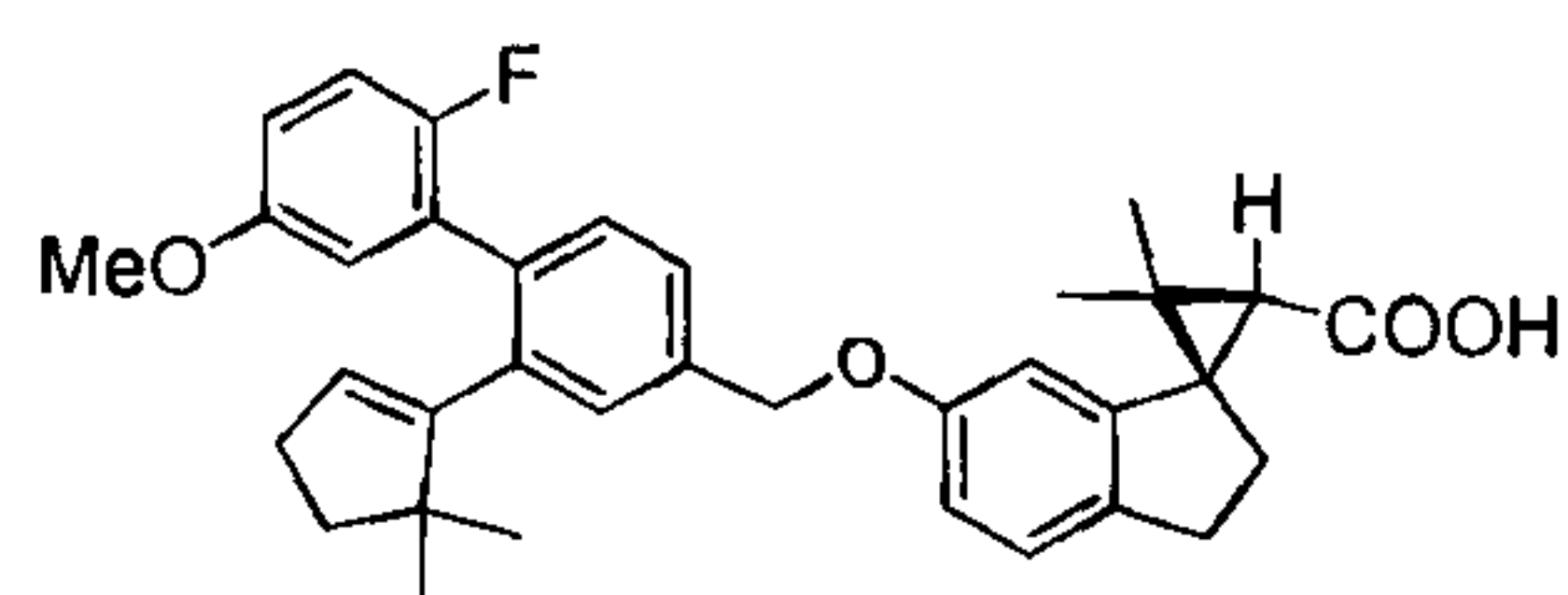
204. The compound



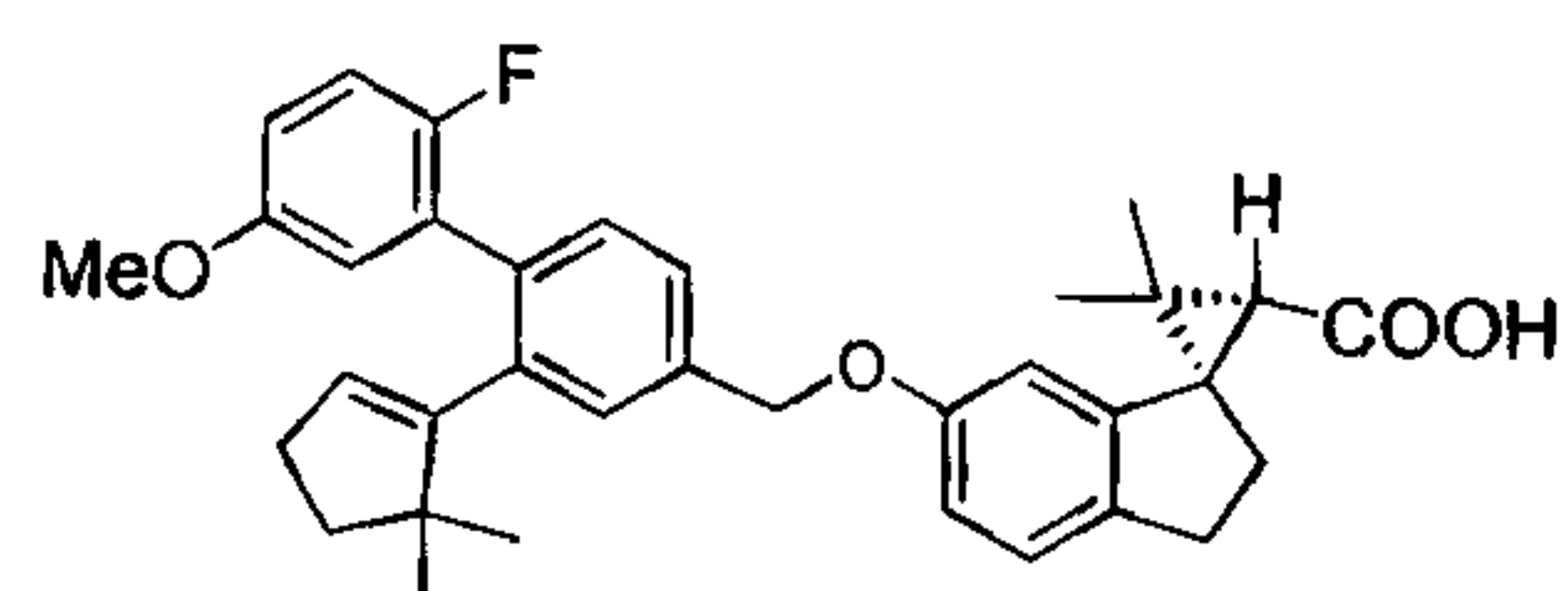
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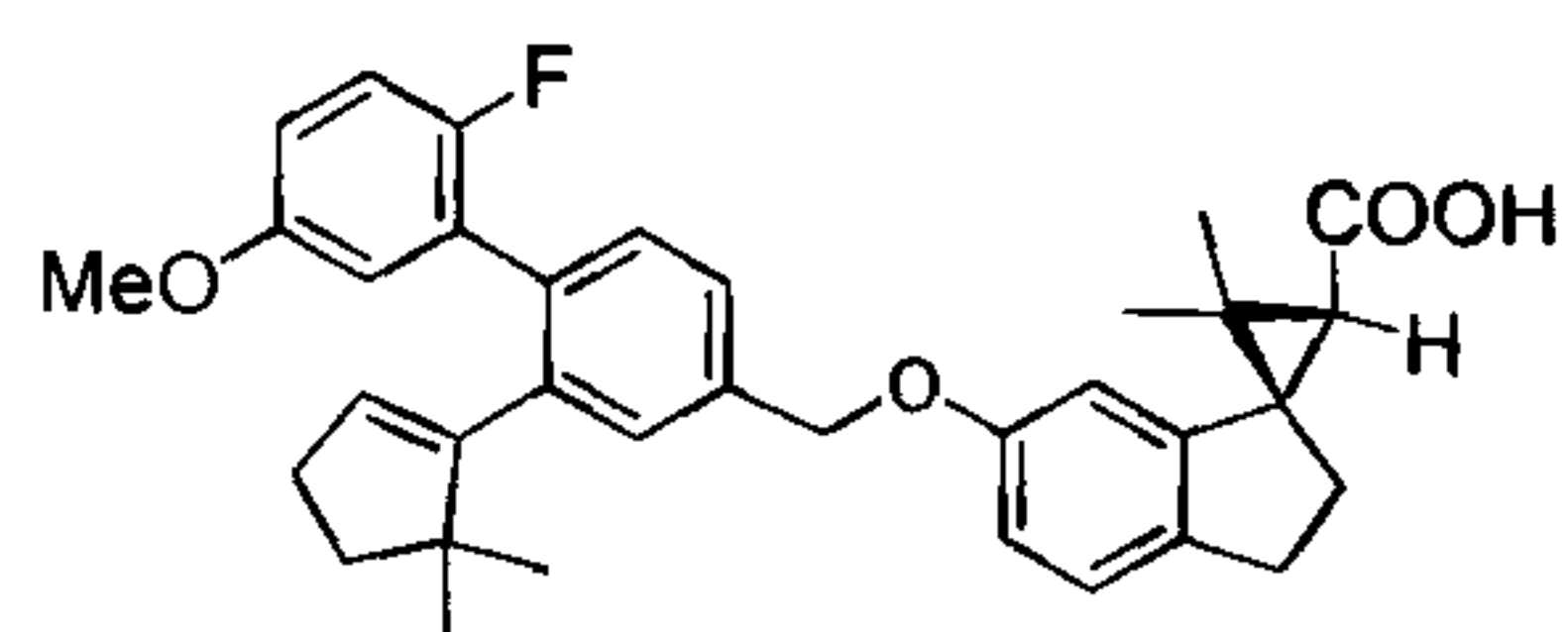
206. The compound



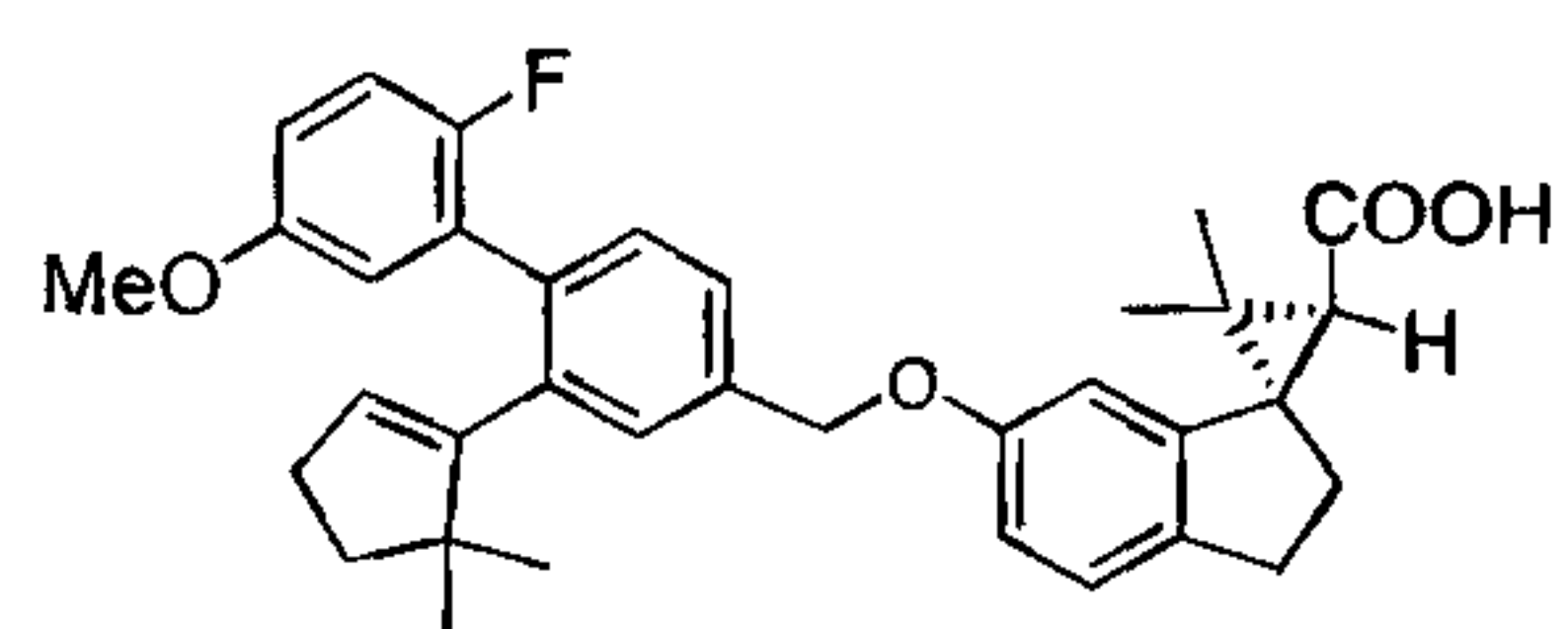
207. The compound



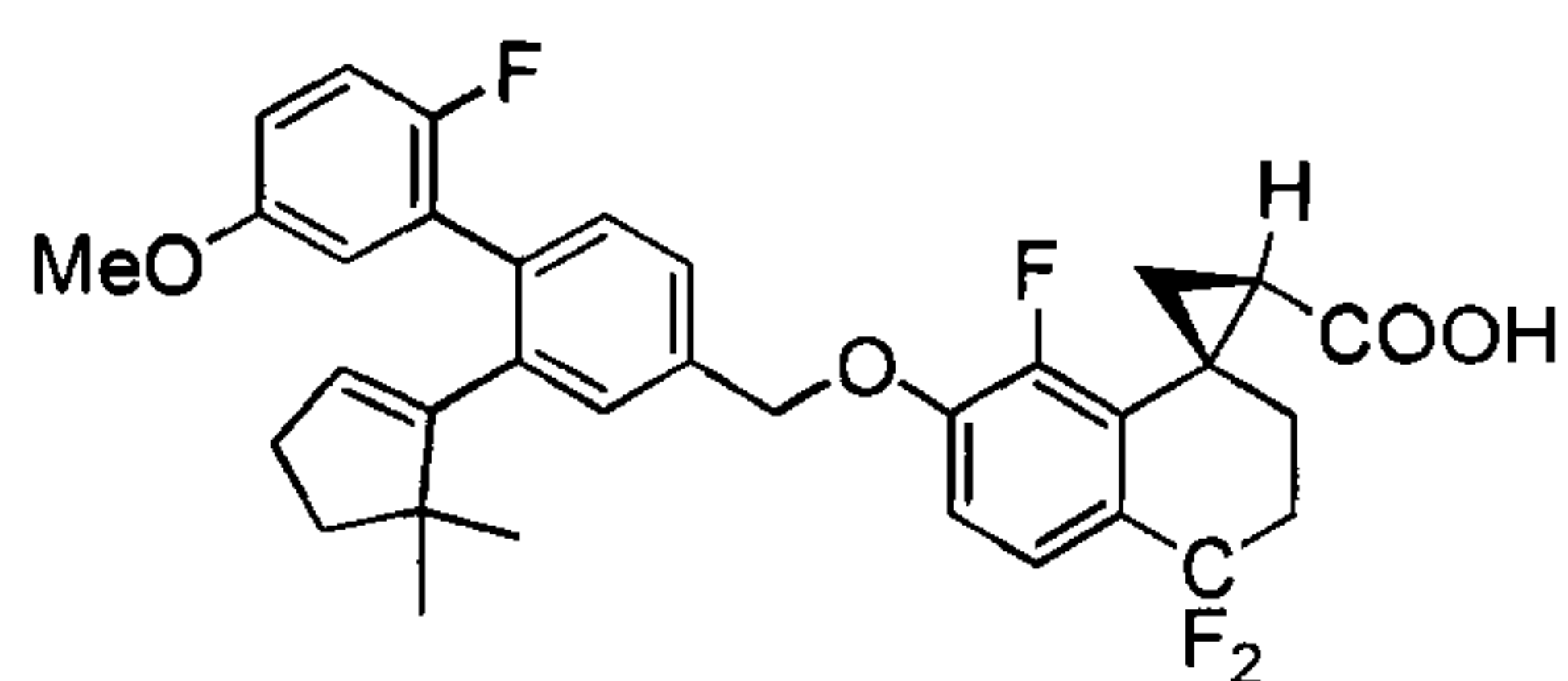
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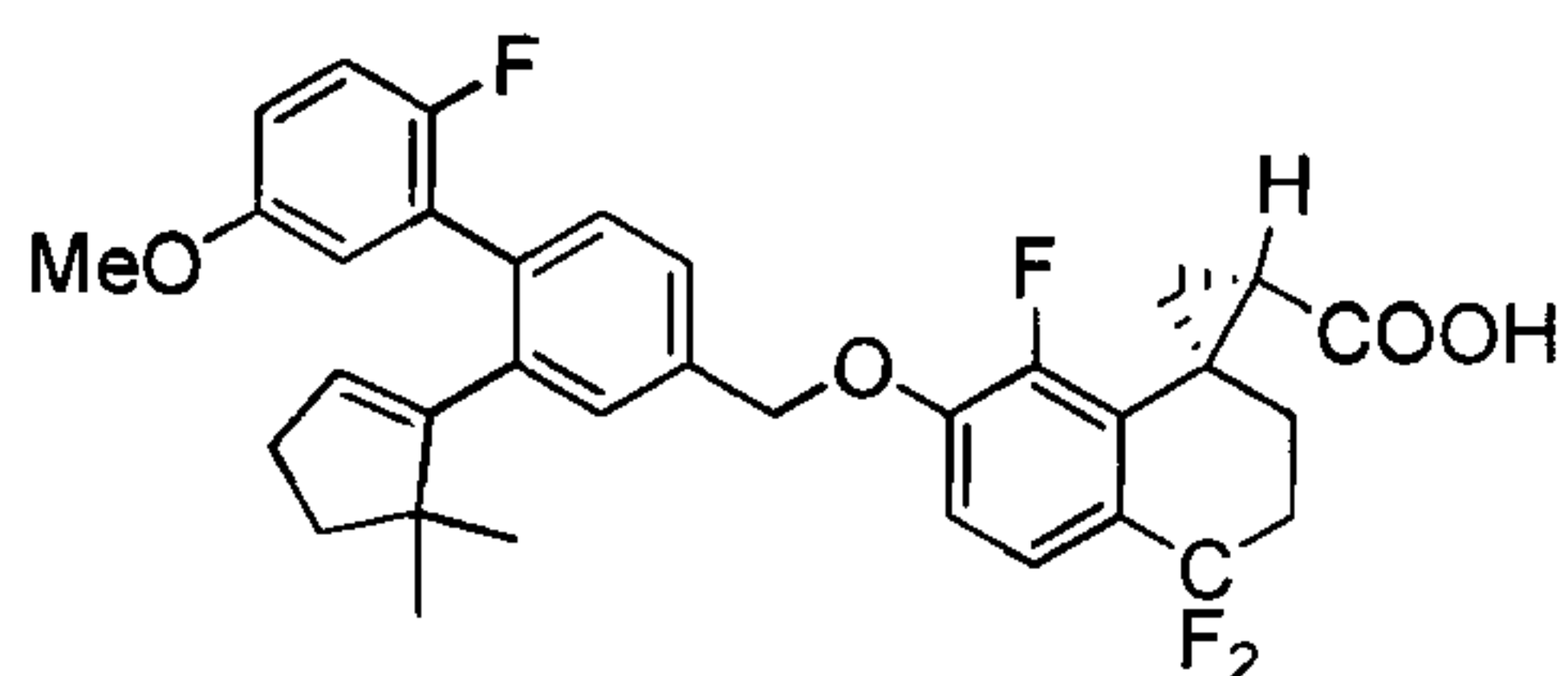
209. The compound



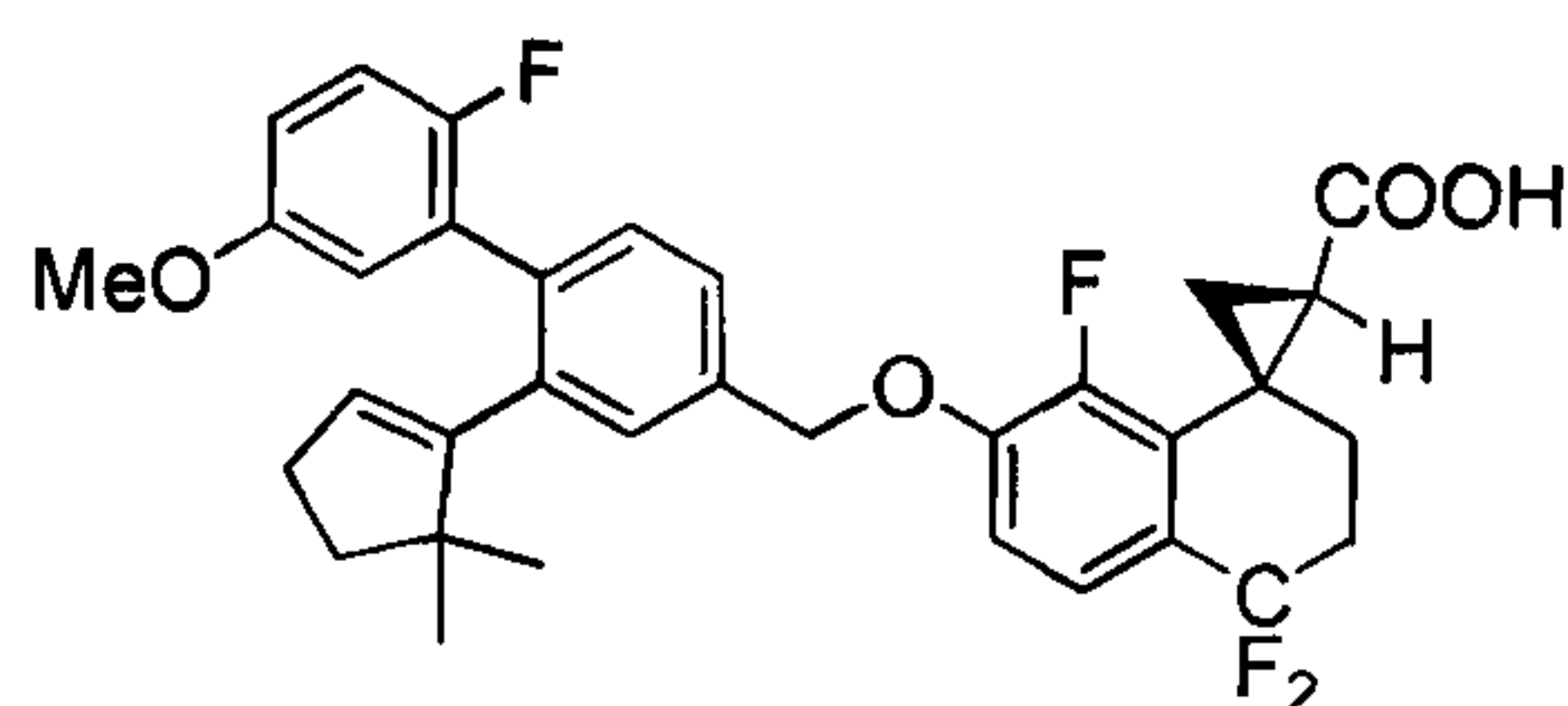
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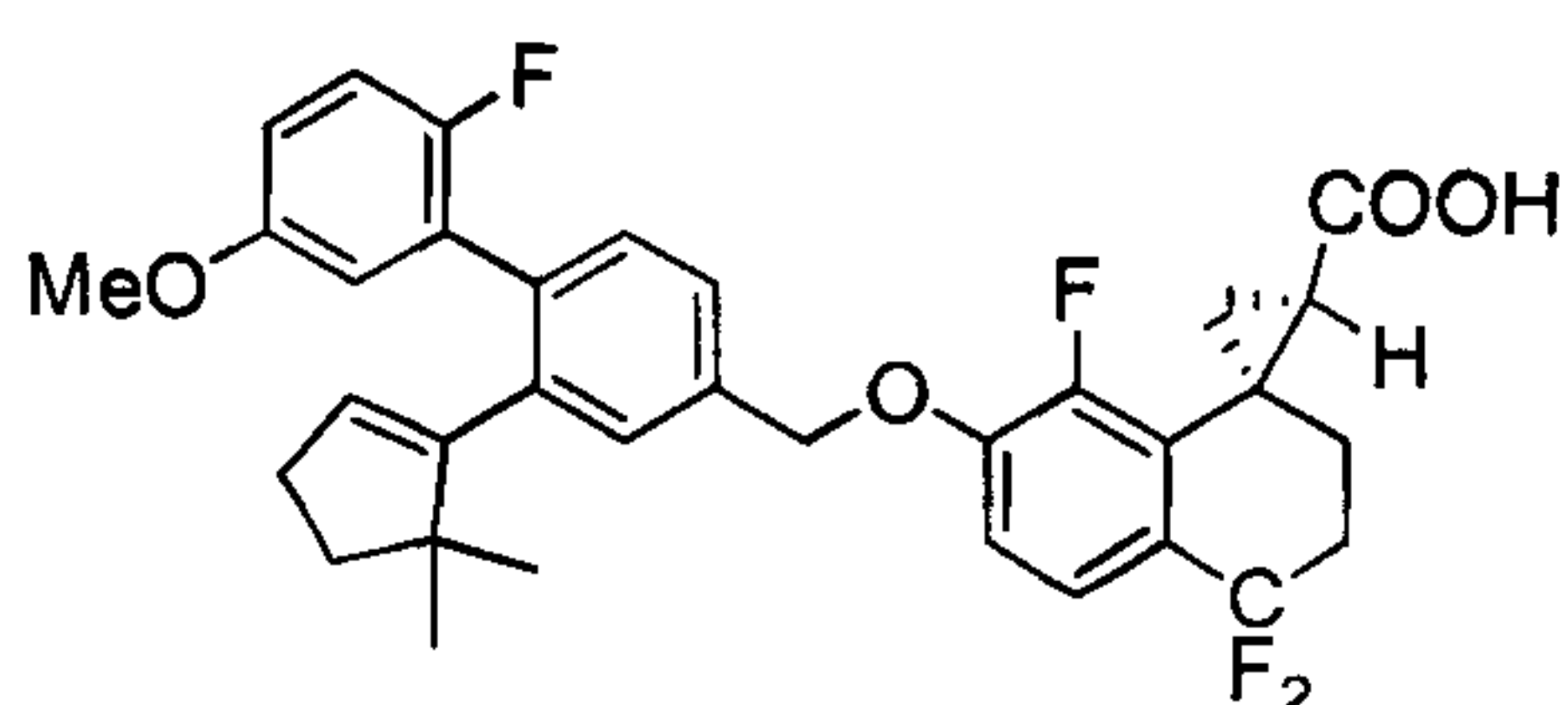
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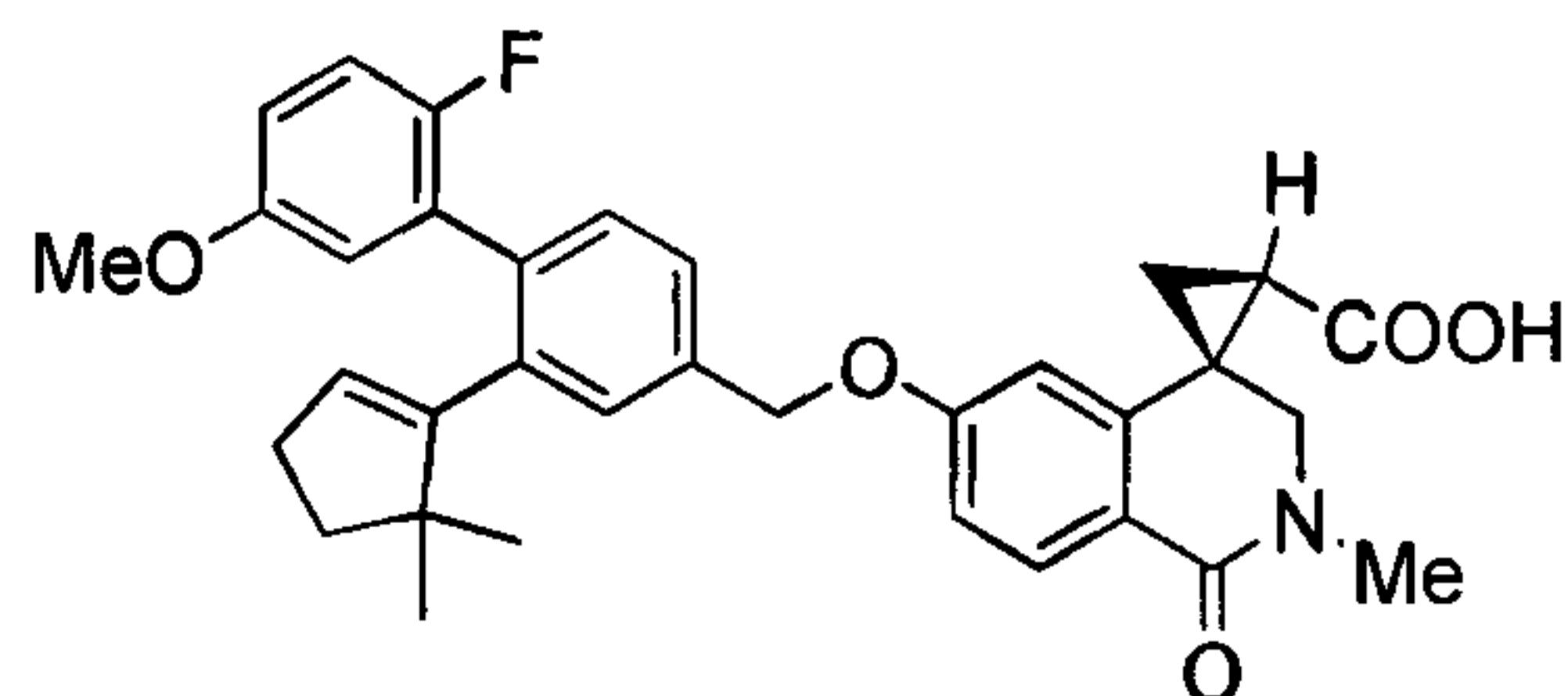
212. The compound



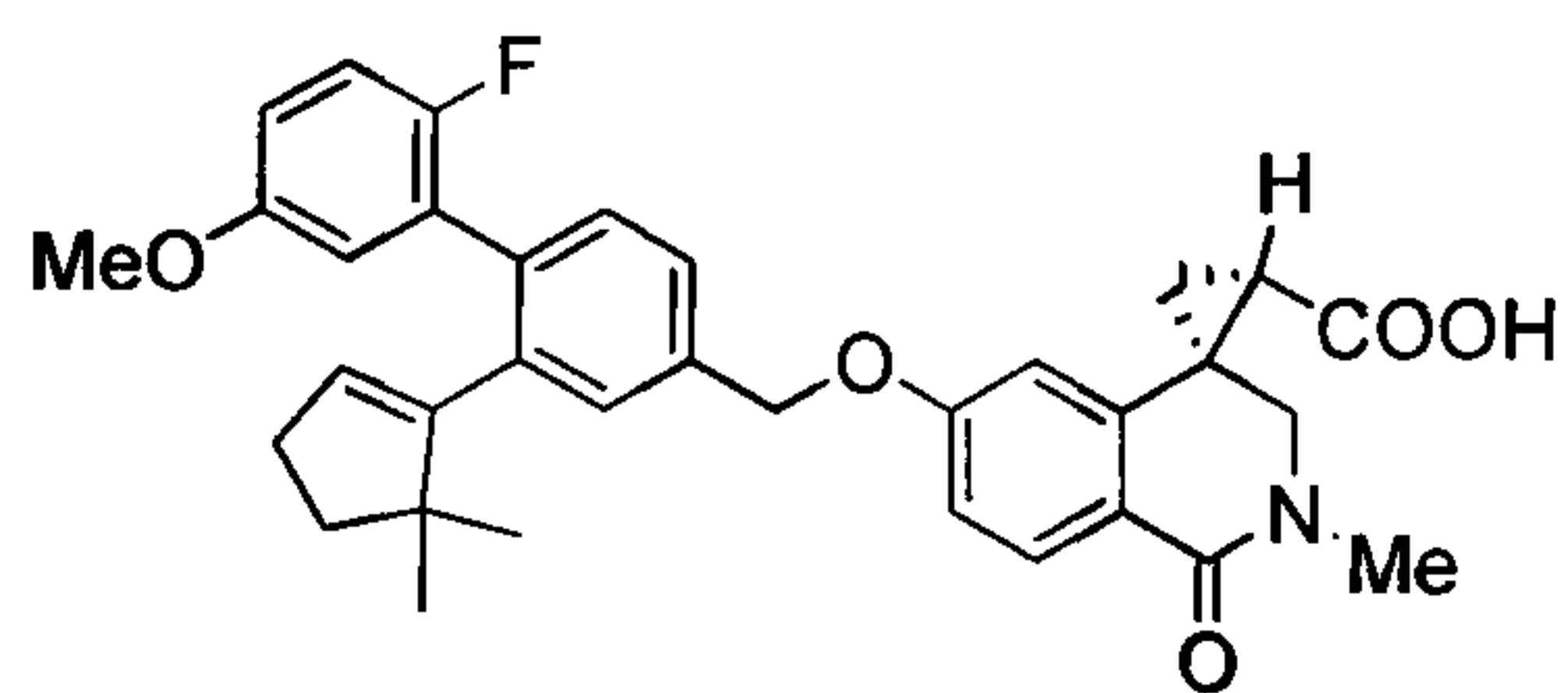
213. The compound



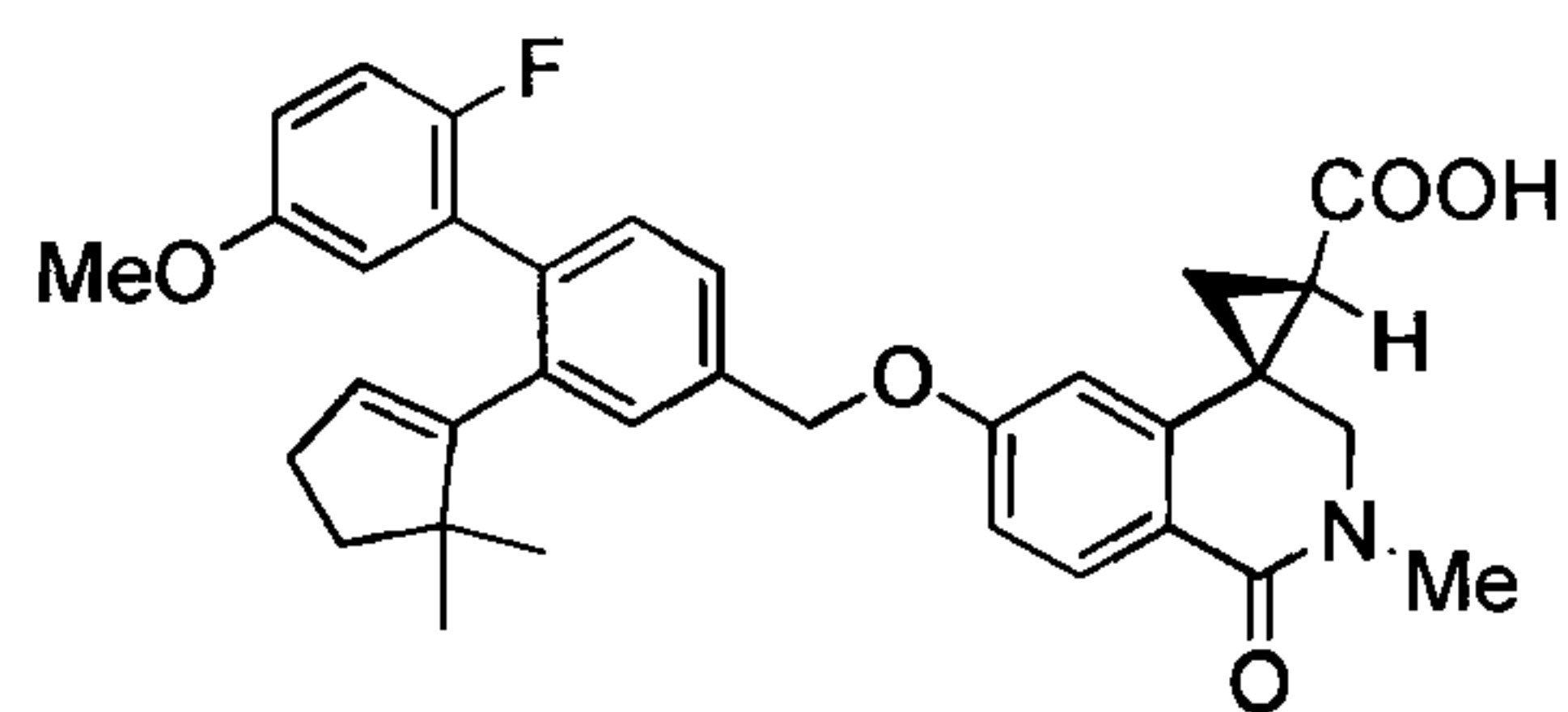
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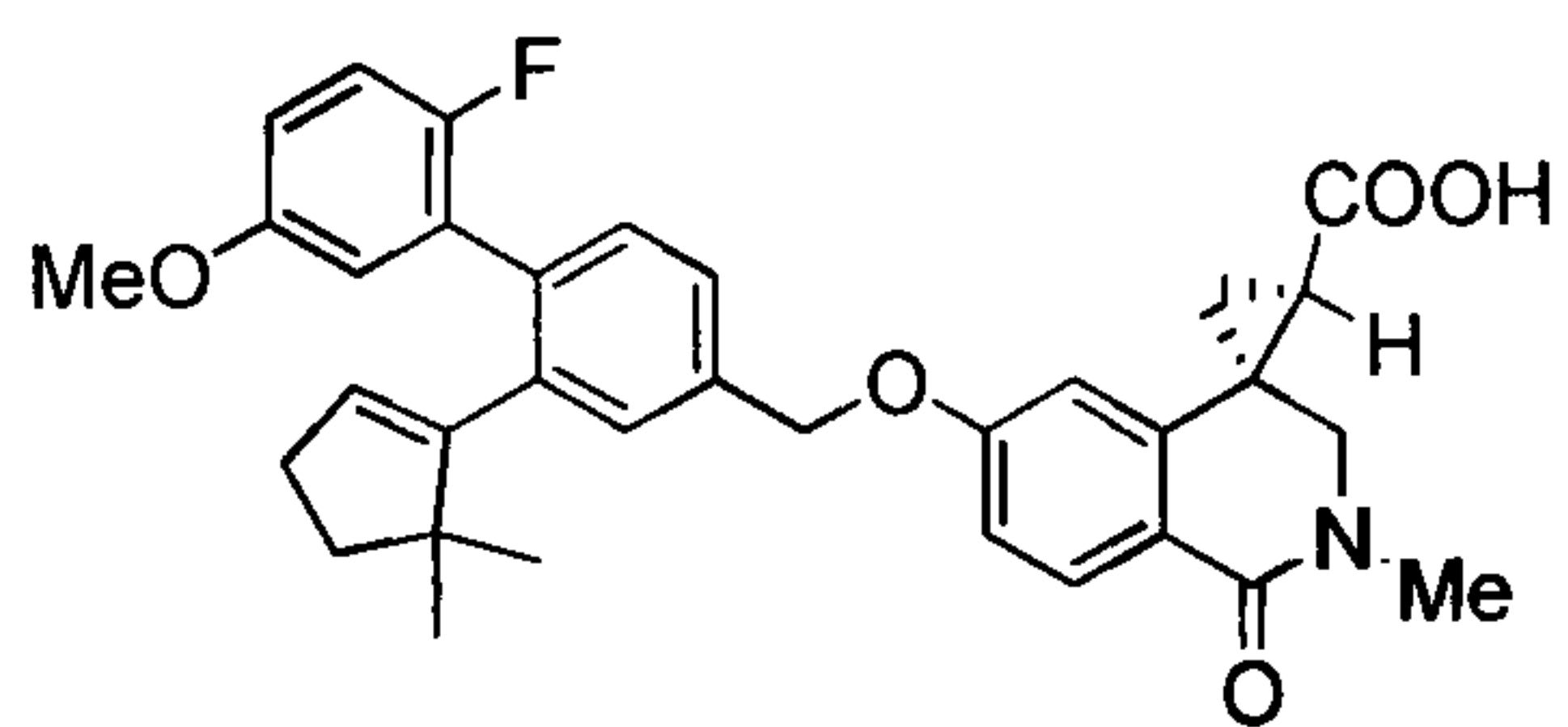
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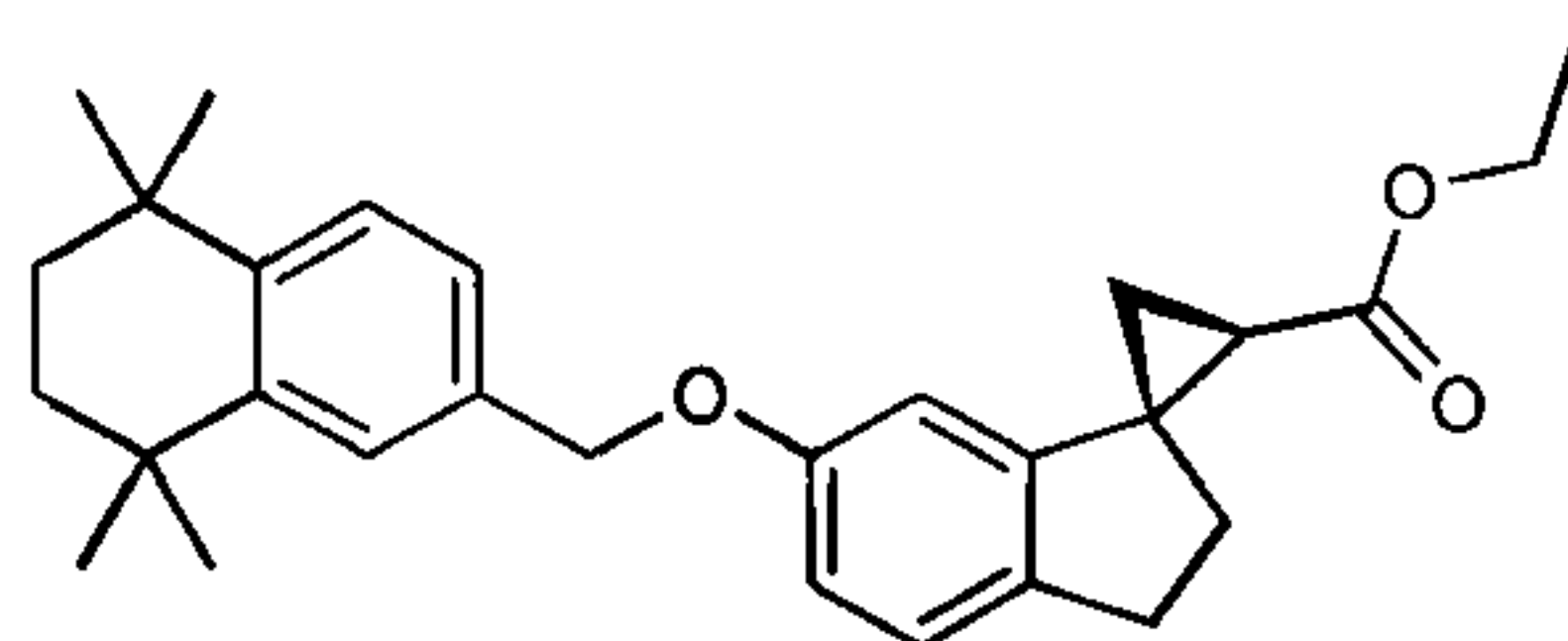
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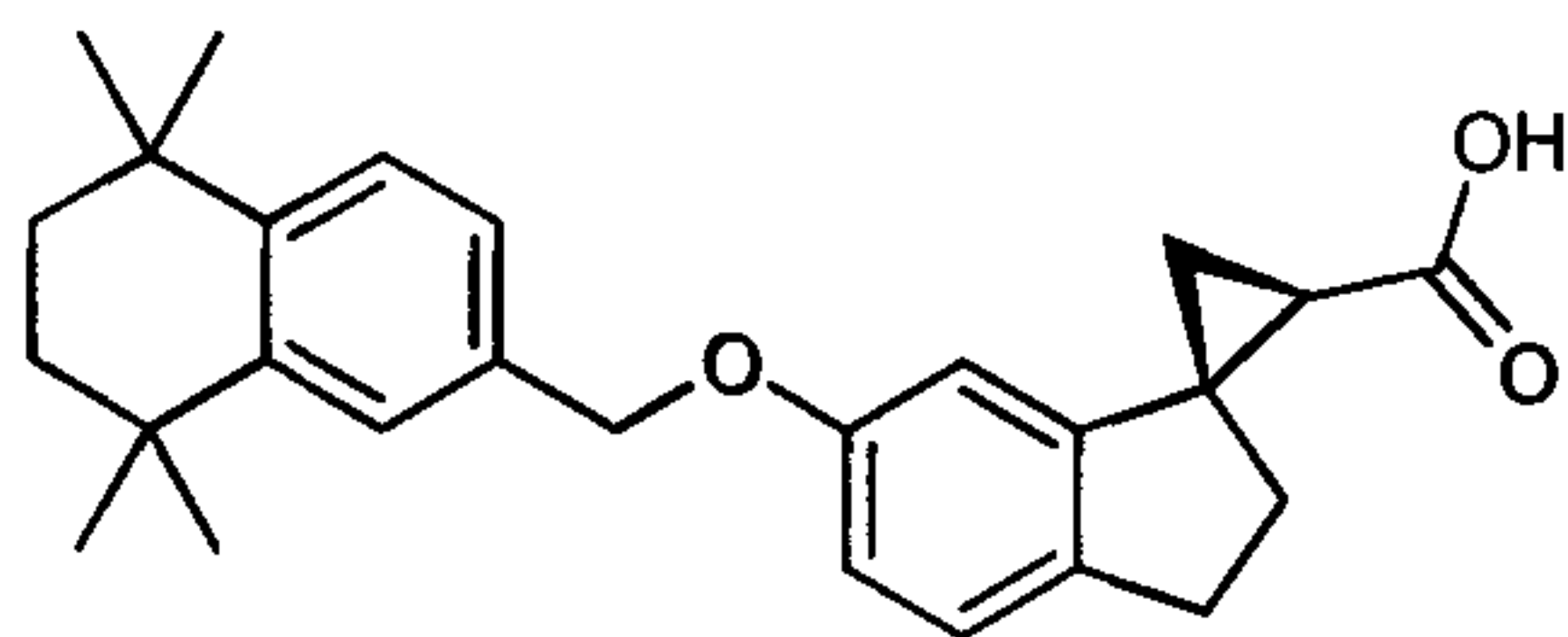
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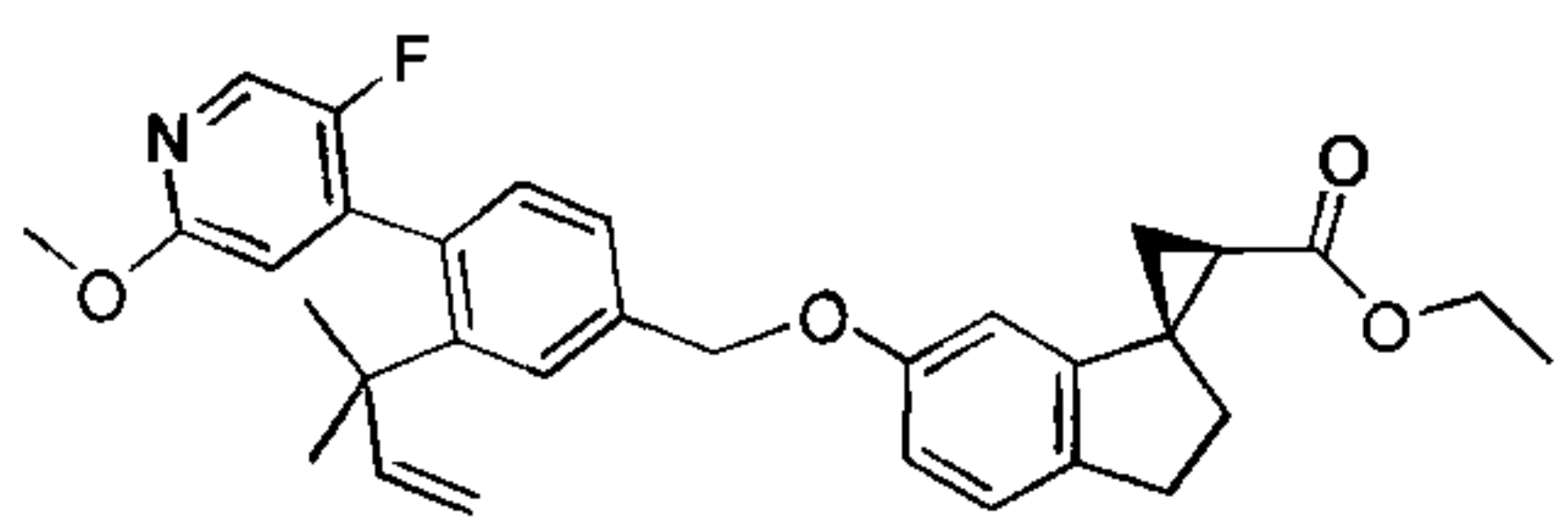
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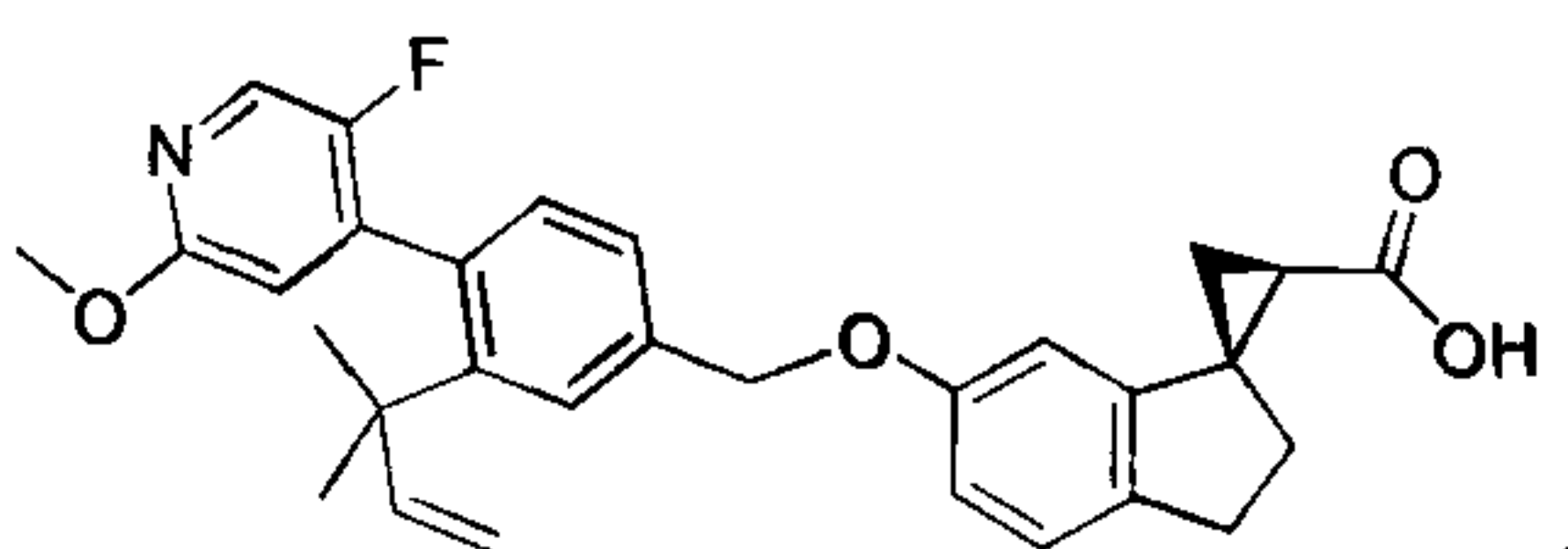
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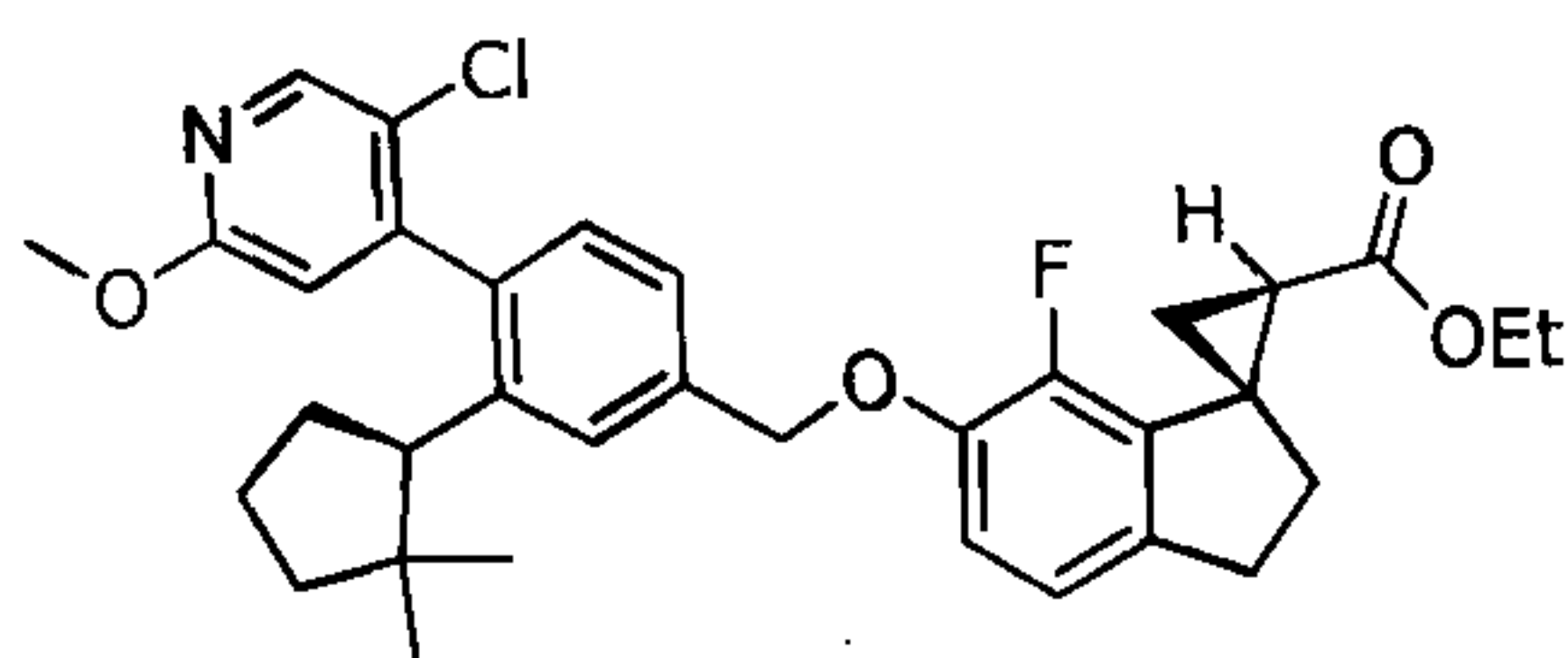
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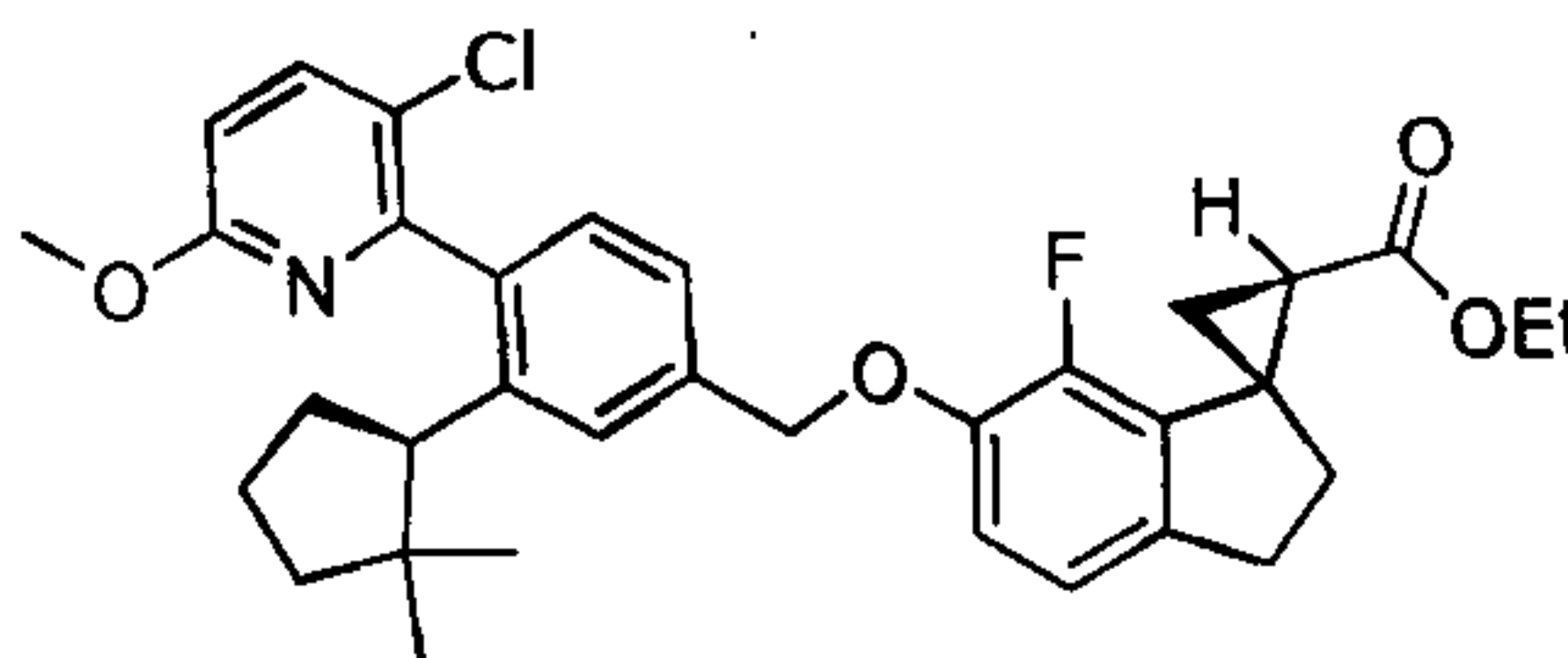
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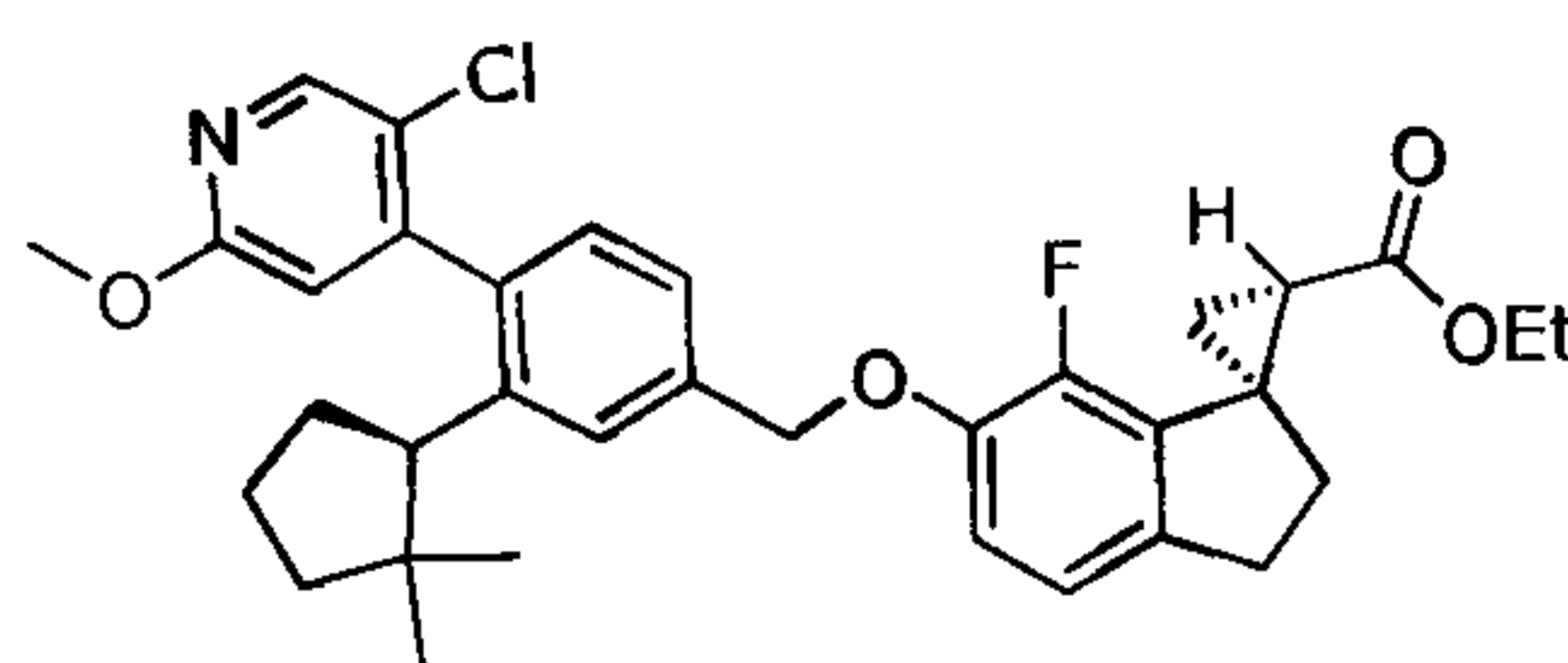
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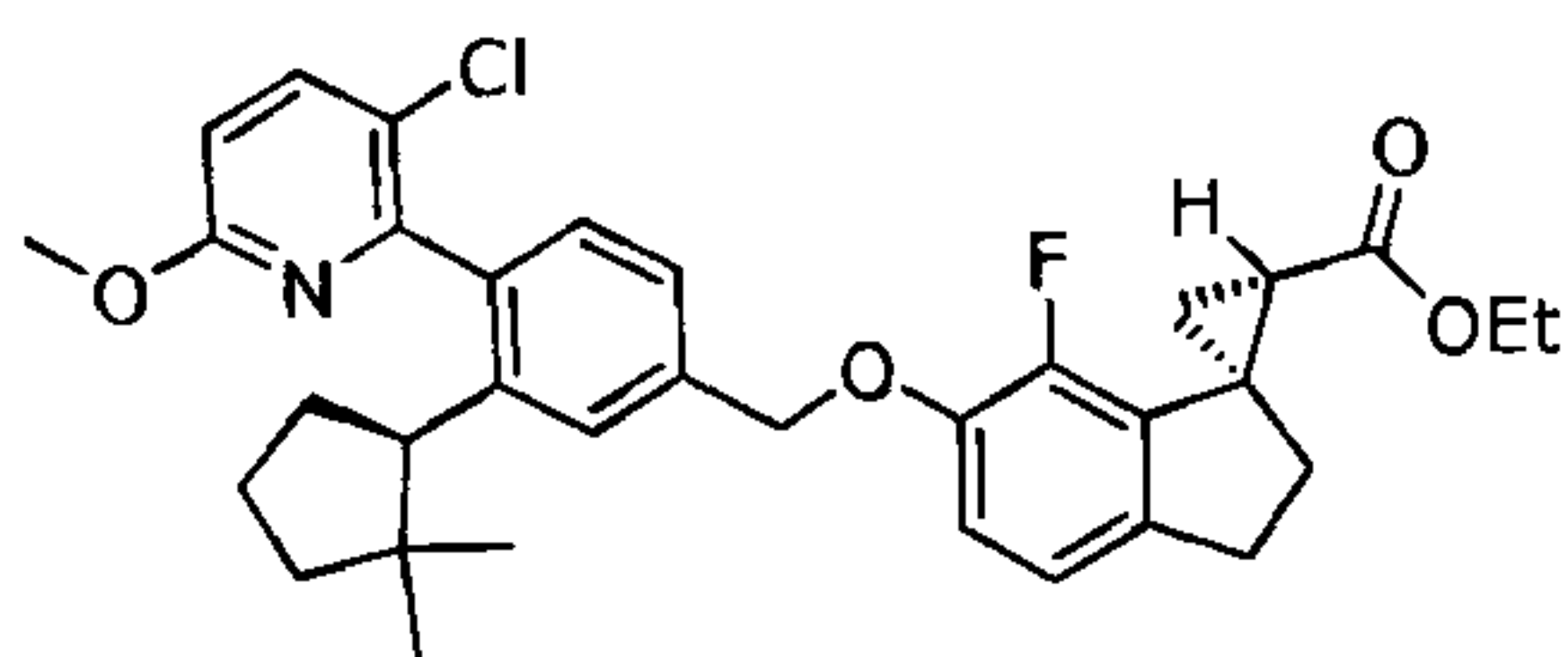
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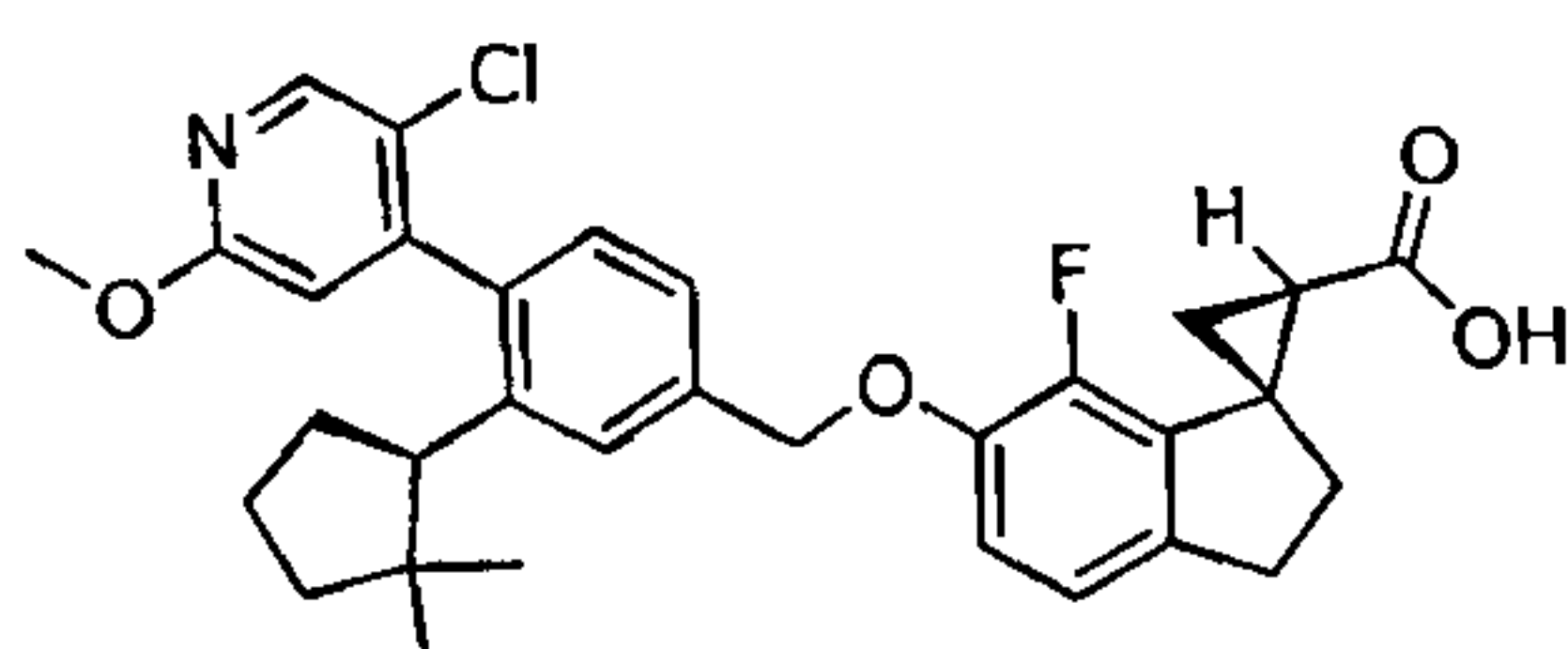
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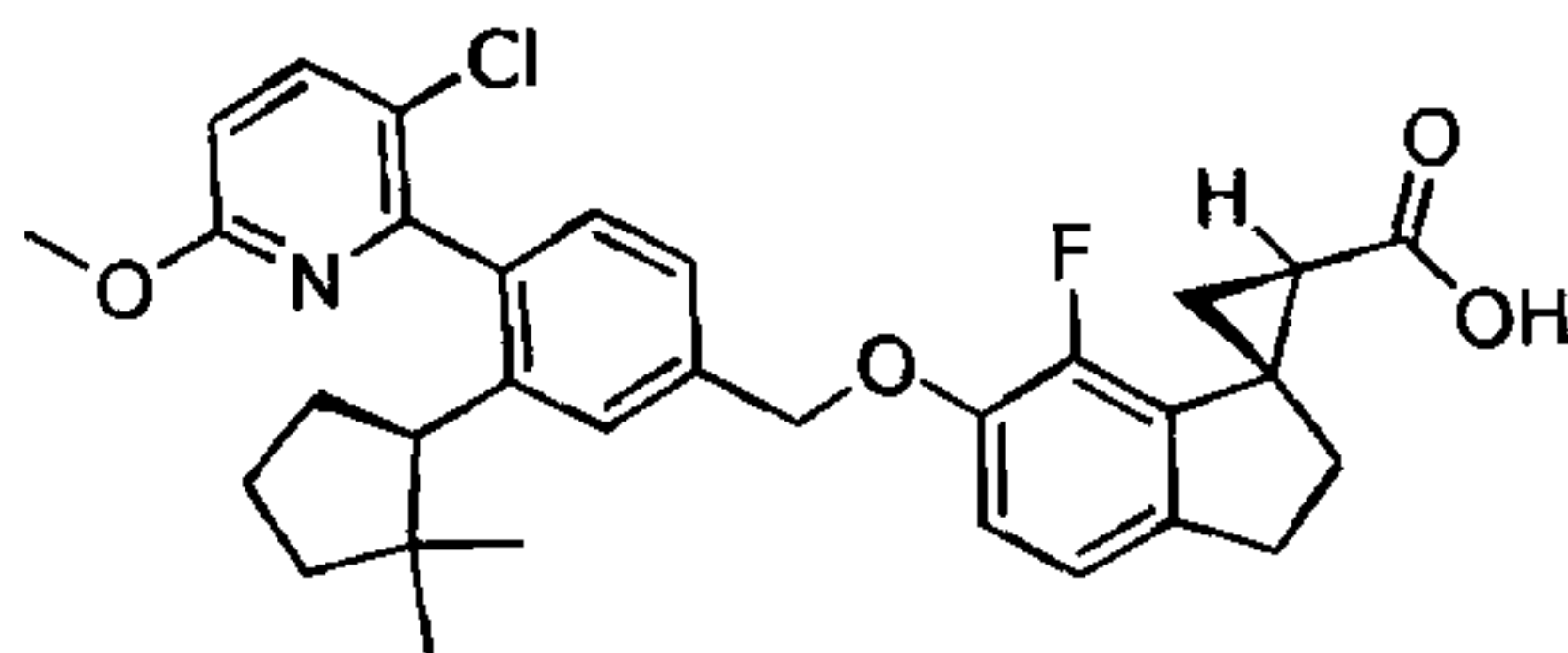
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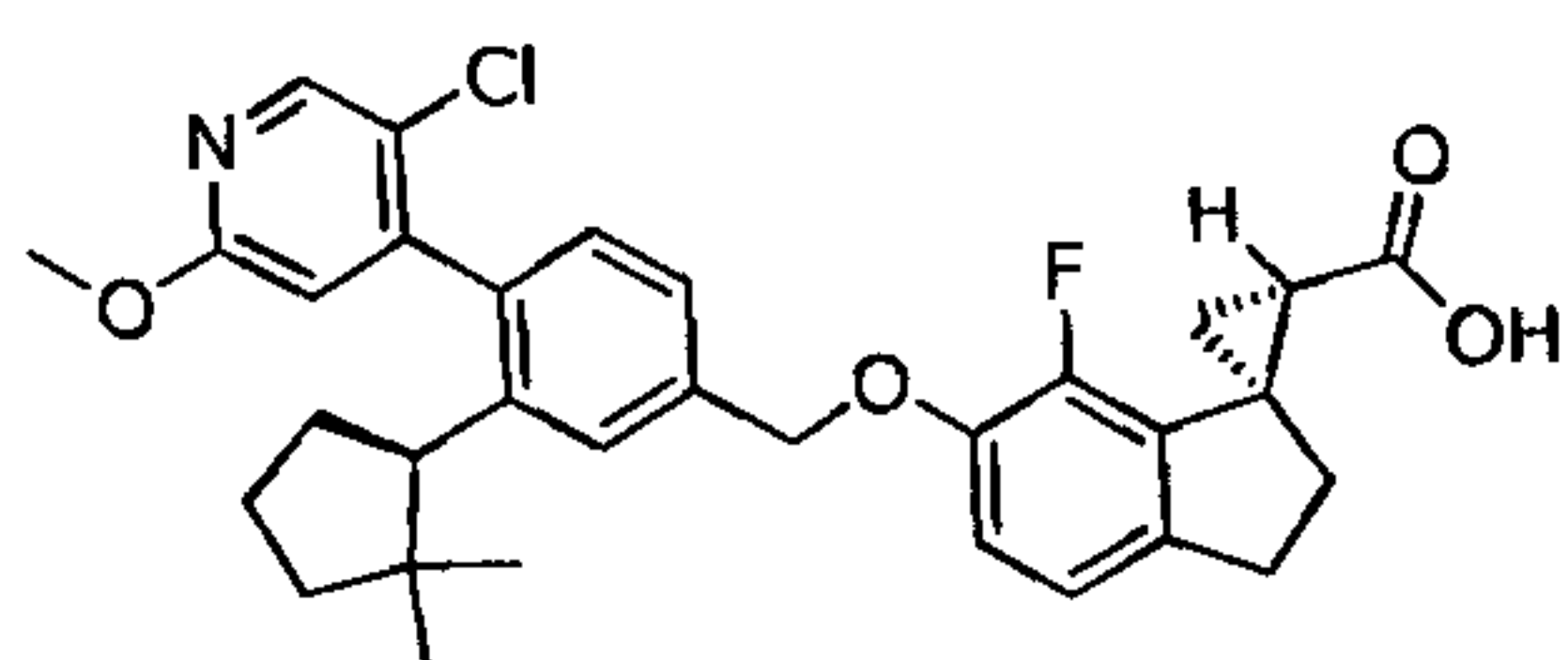
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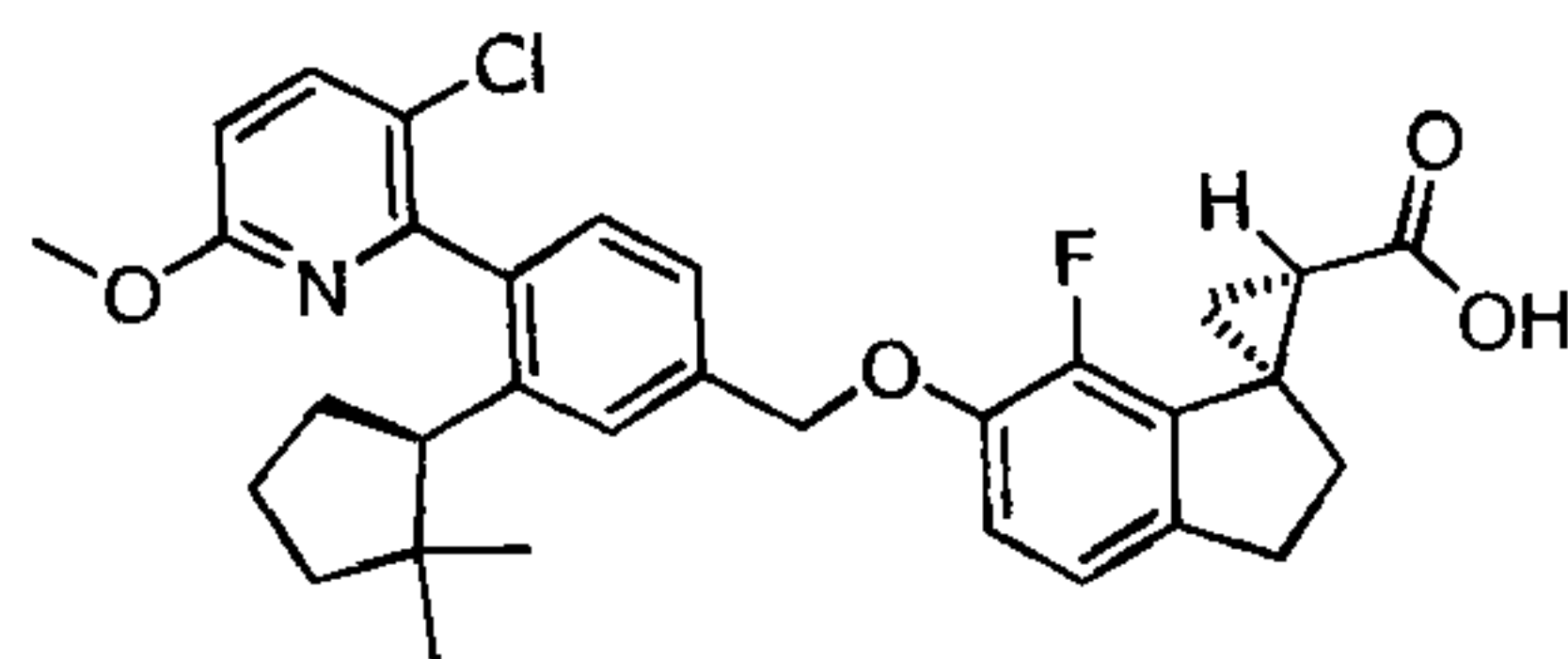
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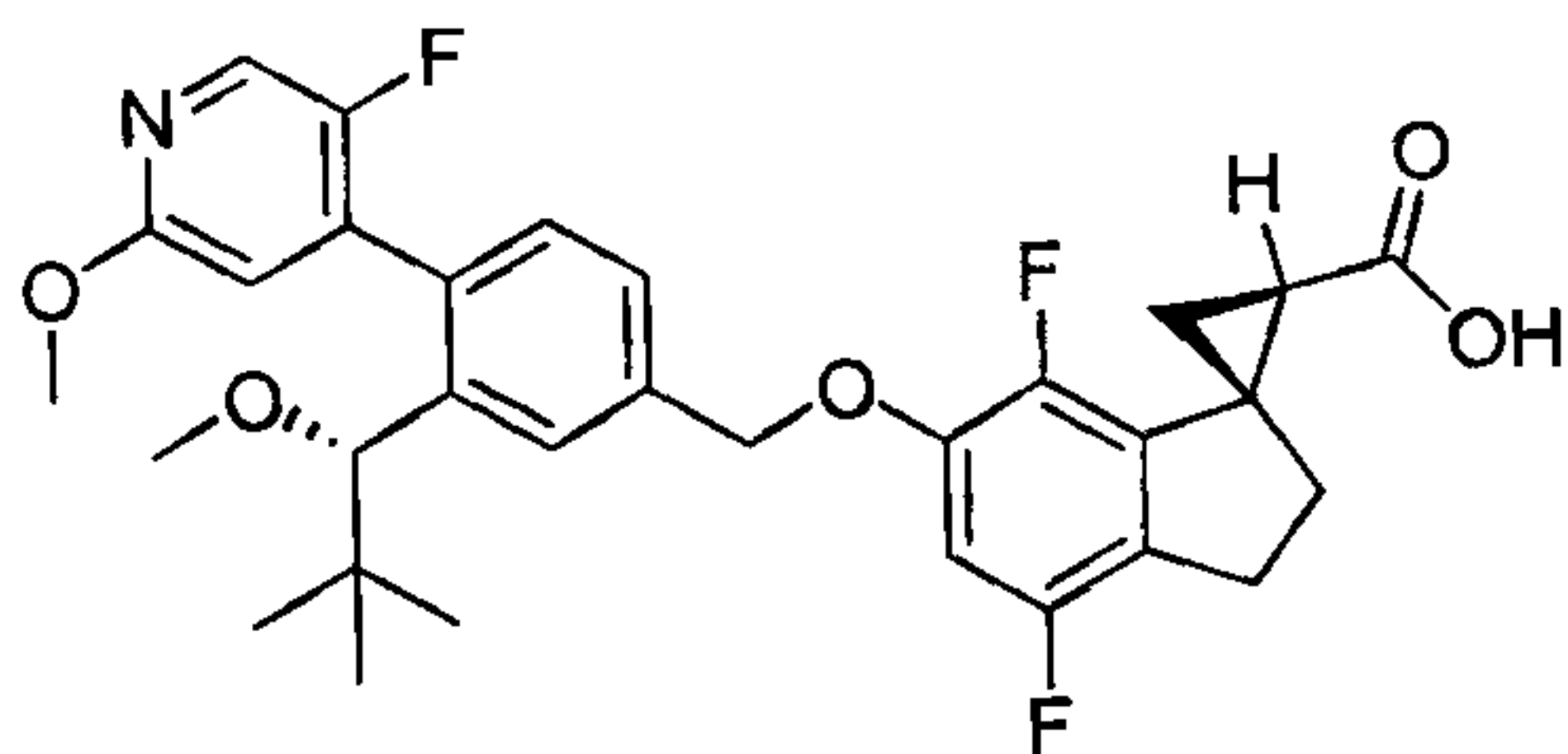
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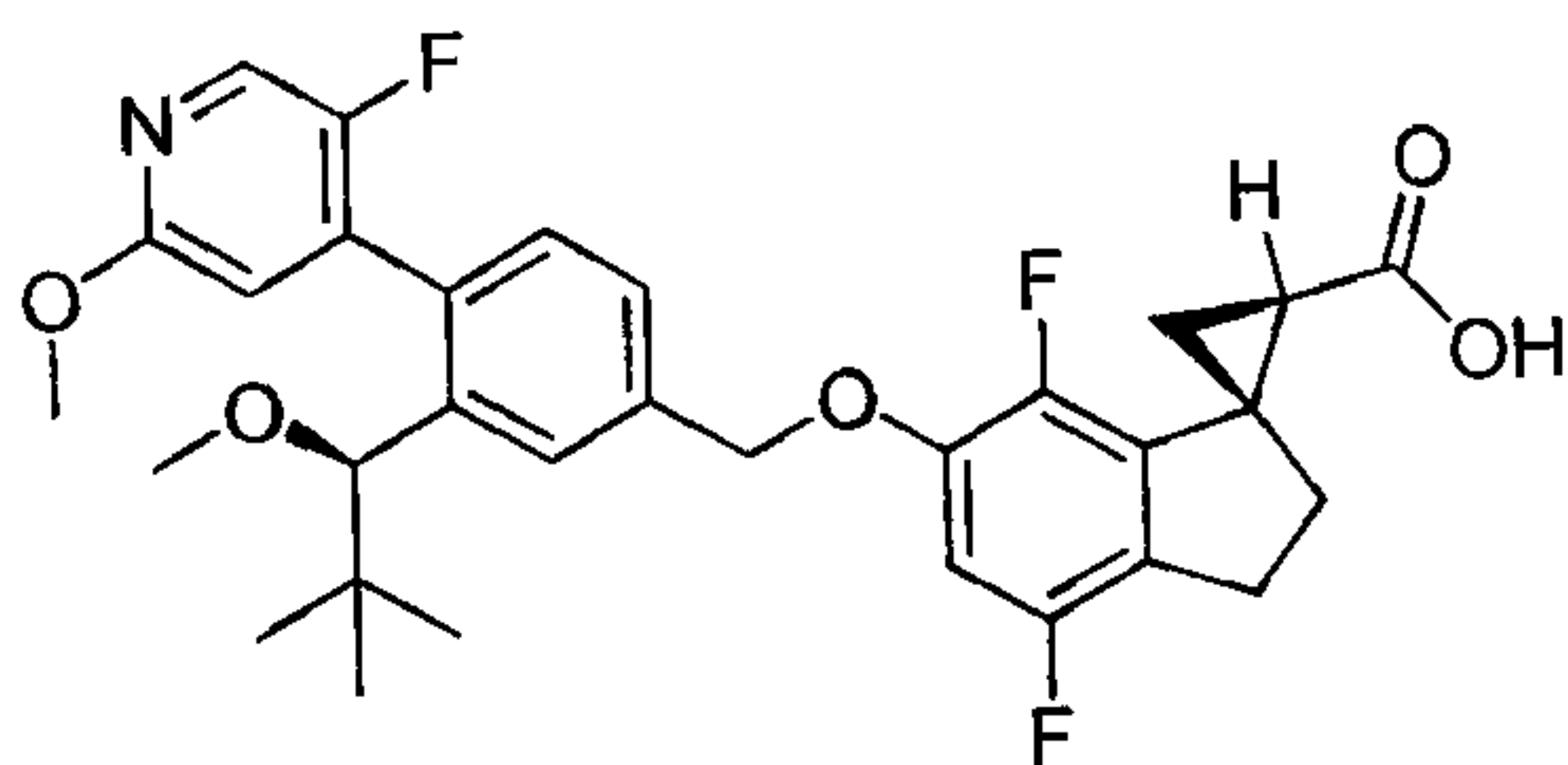
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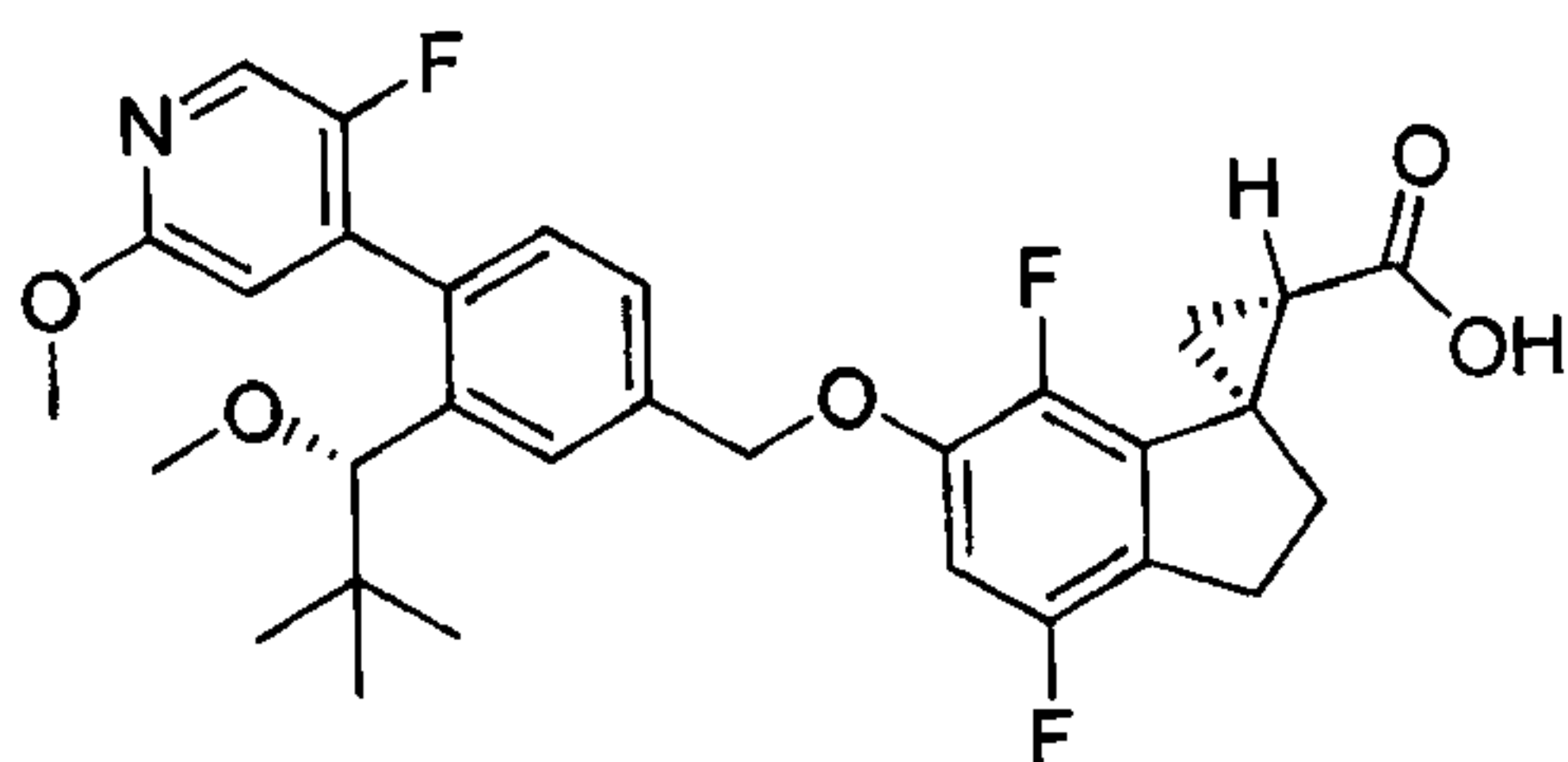
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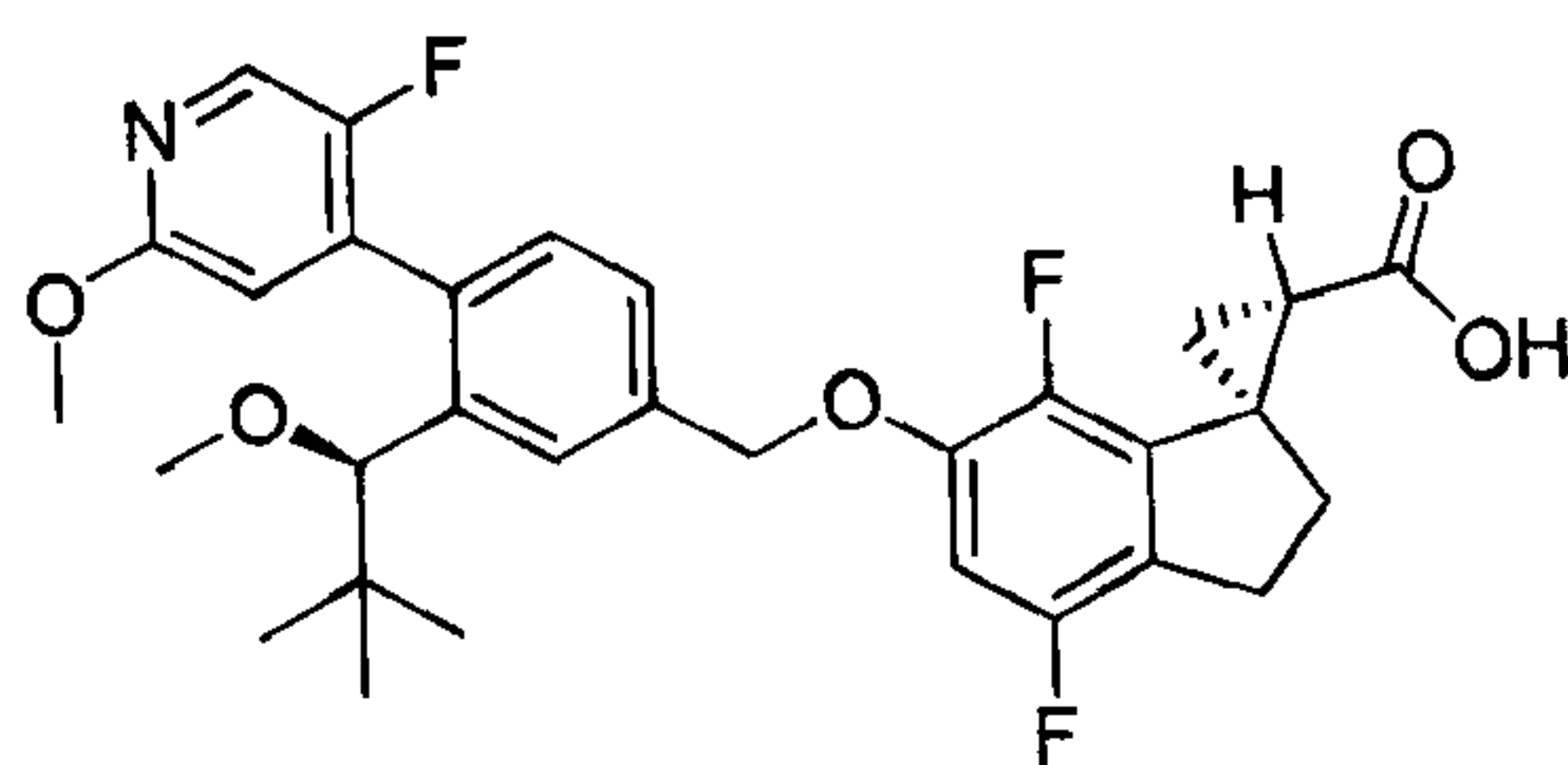
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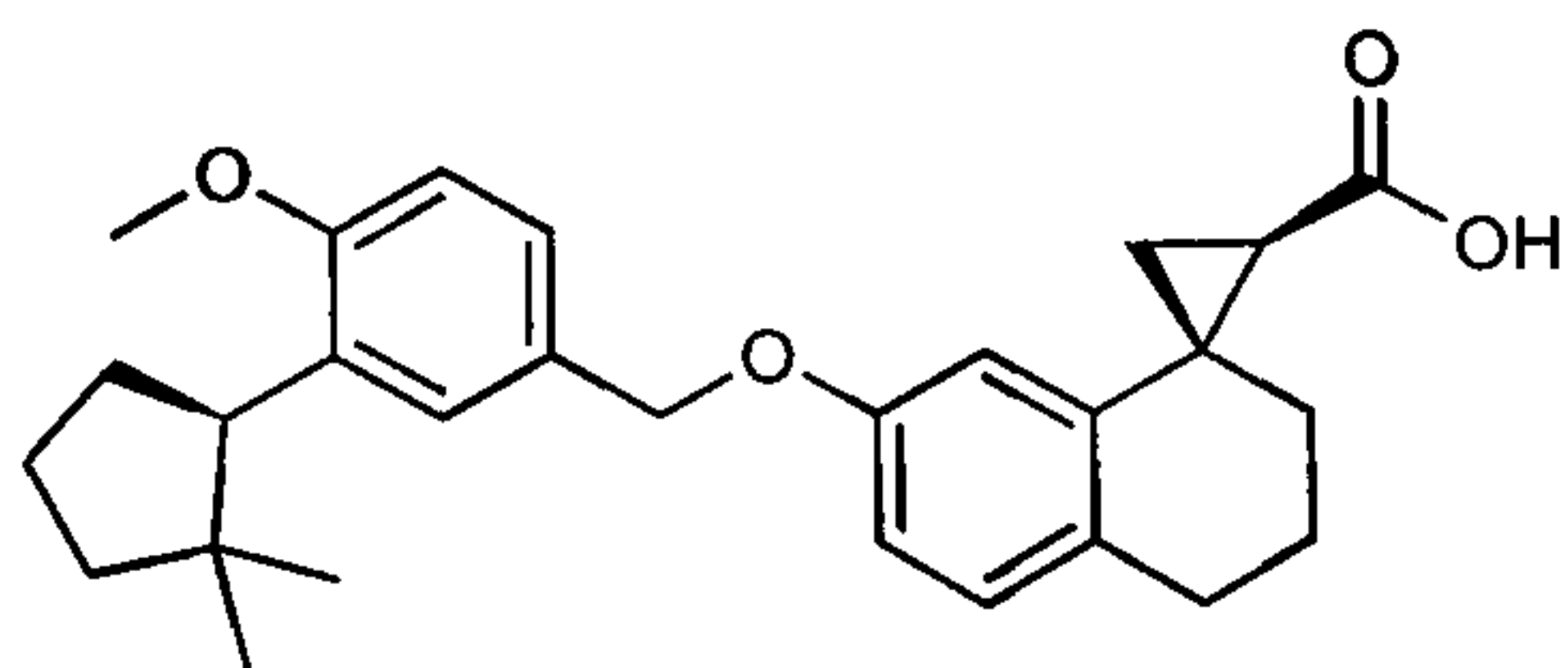
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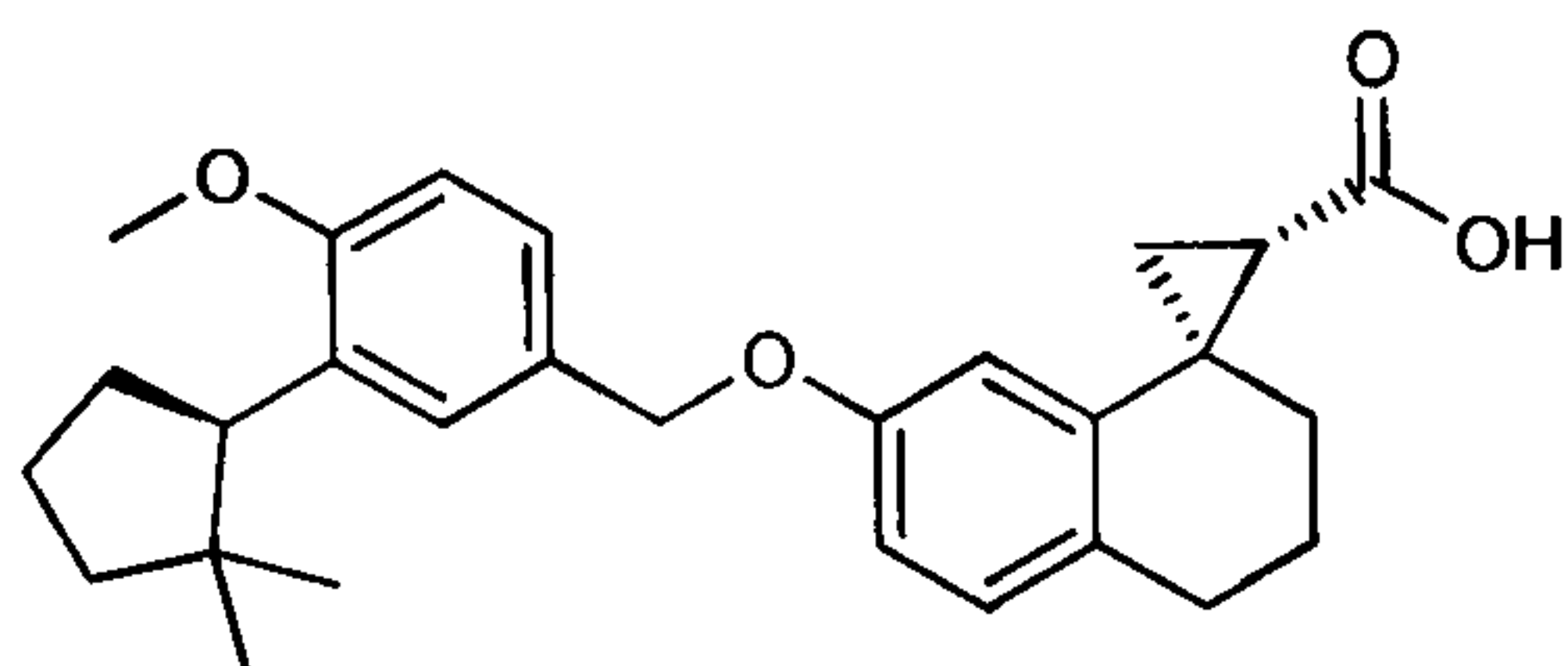
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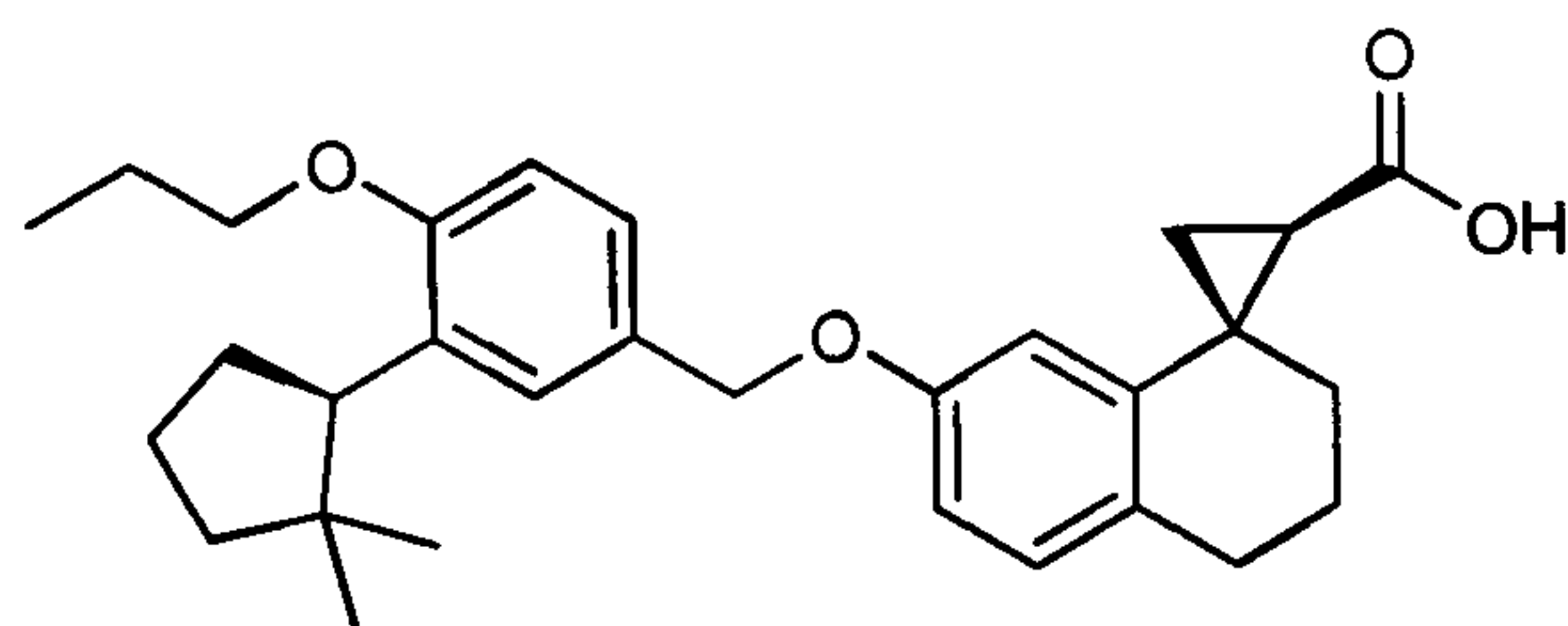
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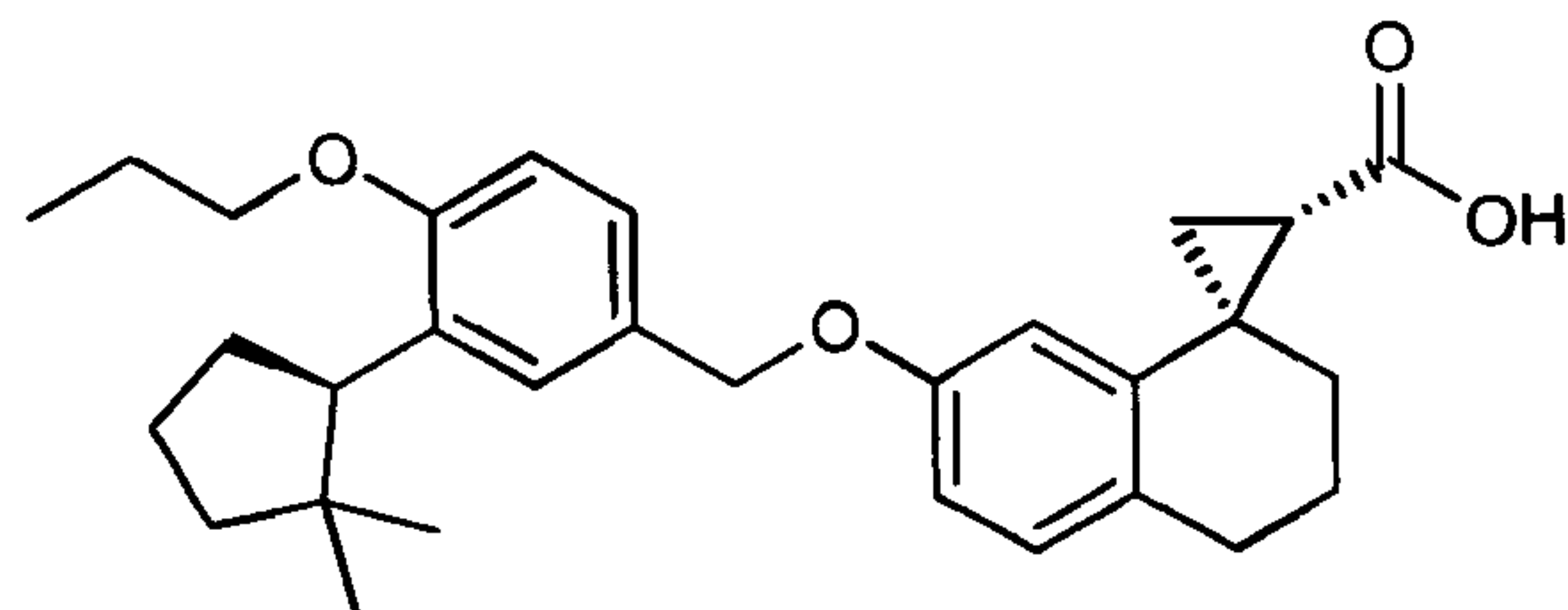
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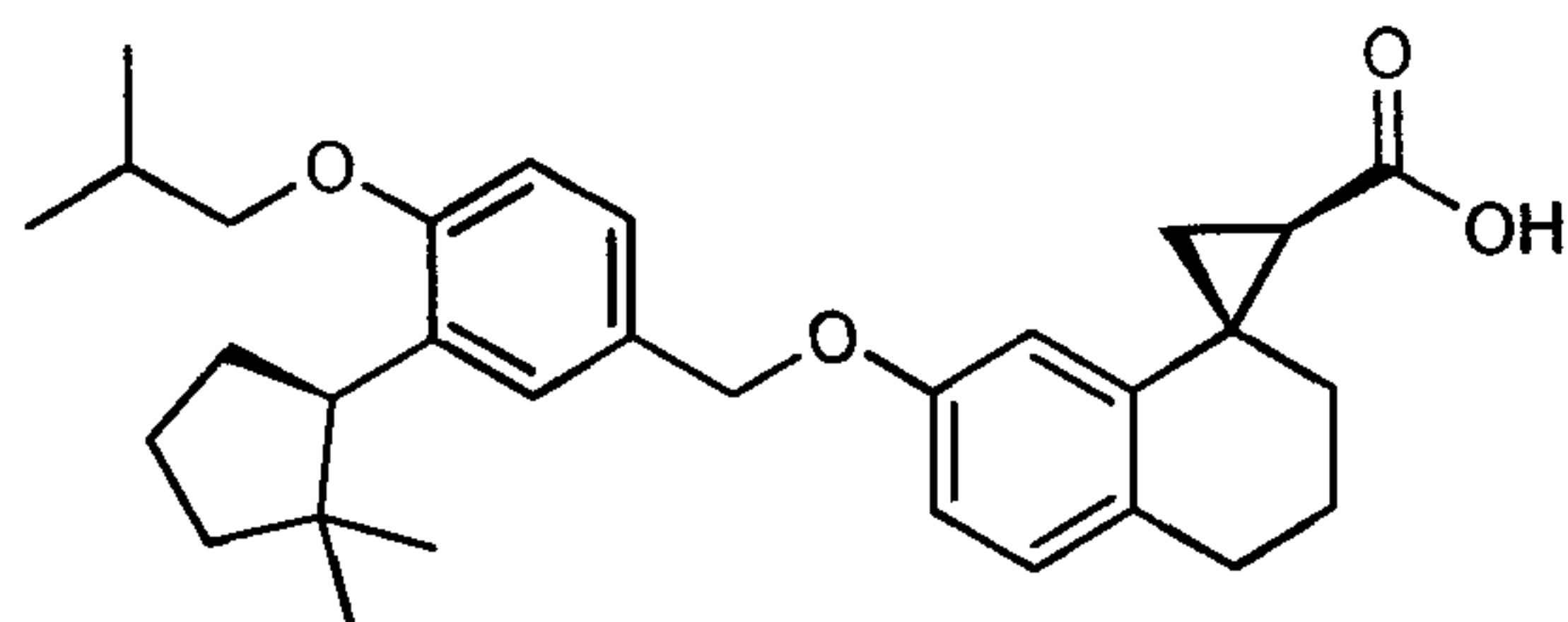
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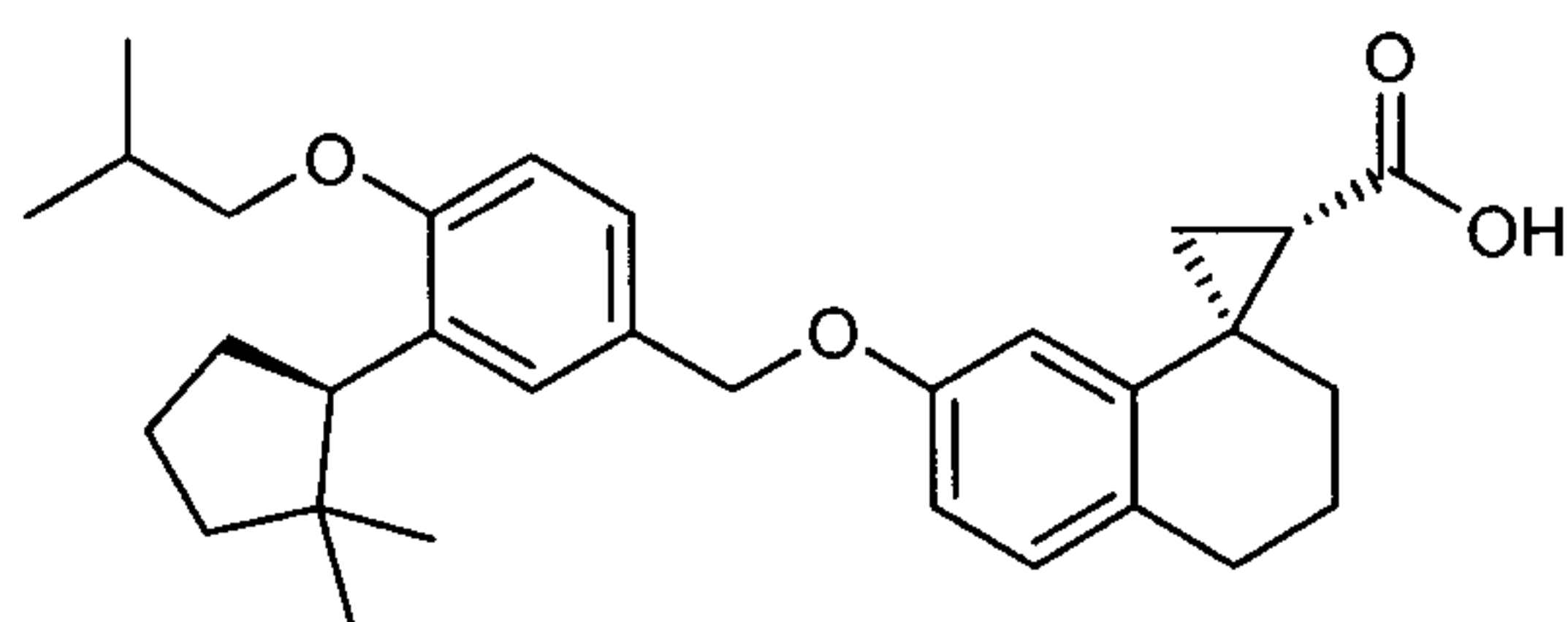
237. The compound



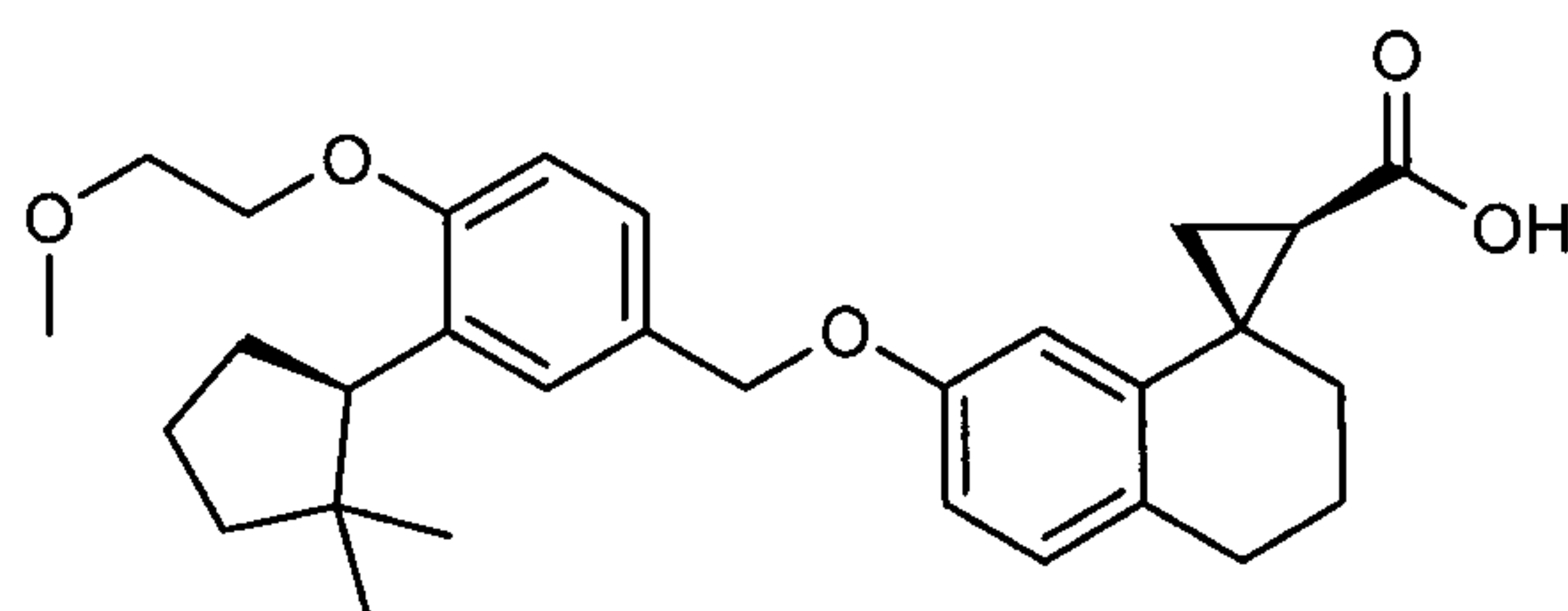
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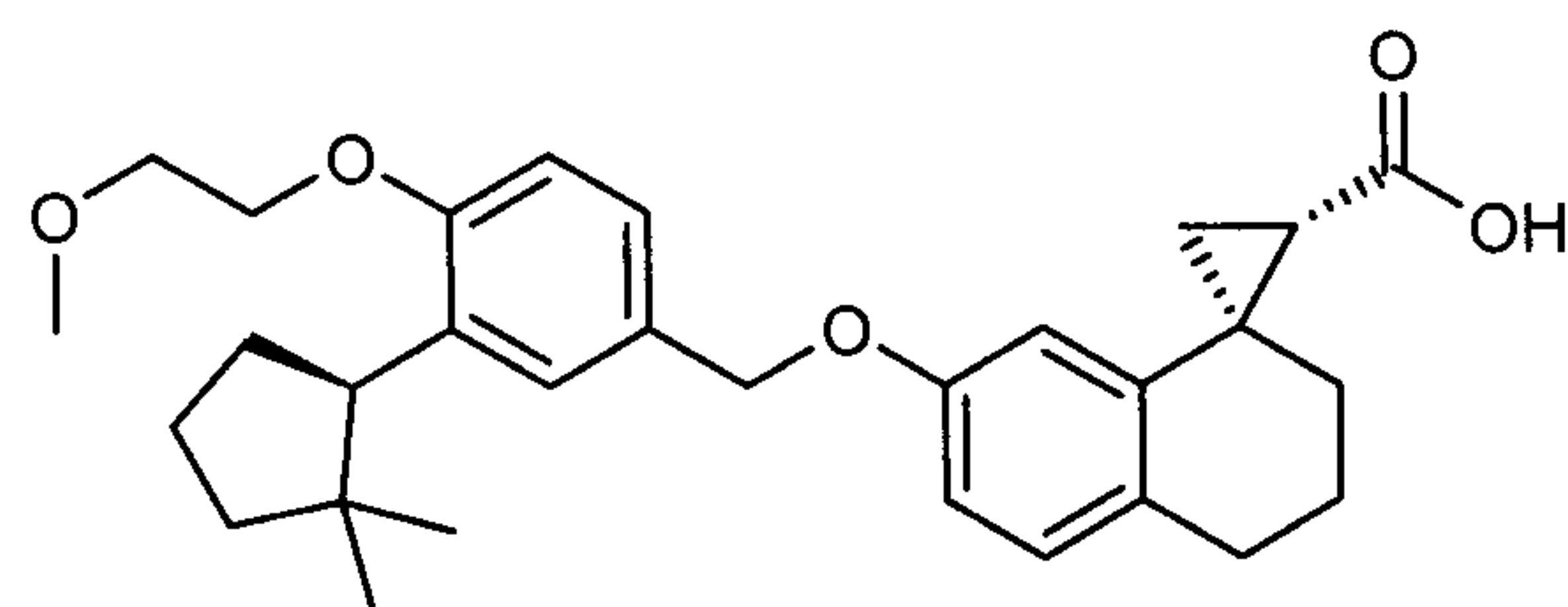
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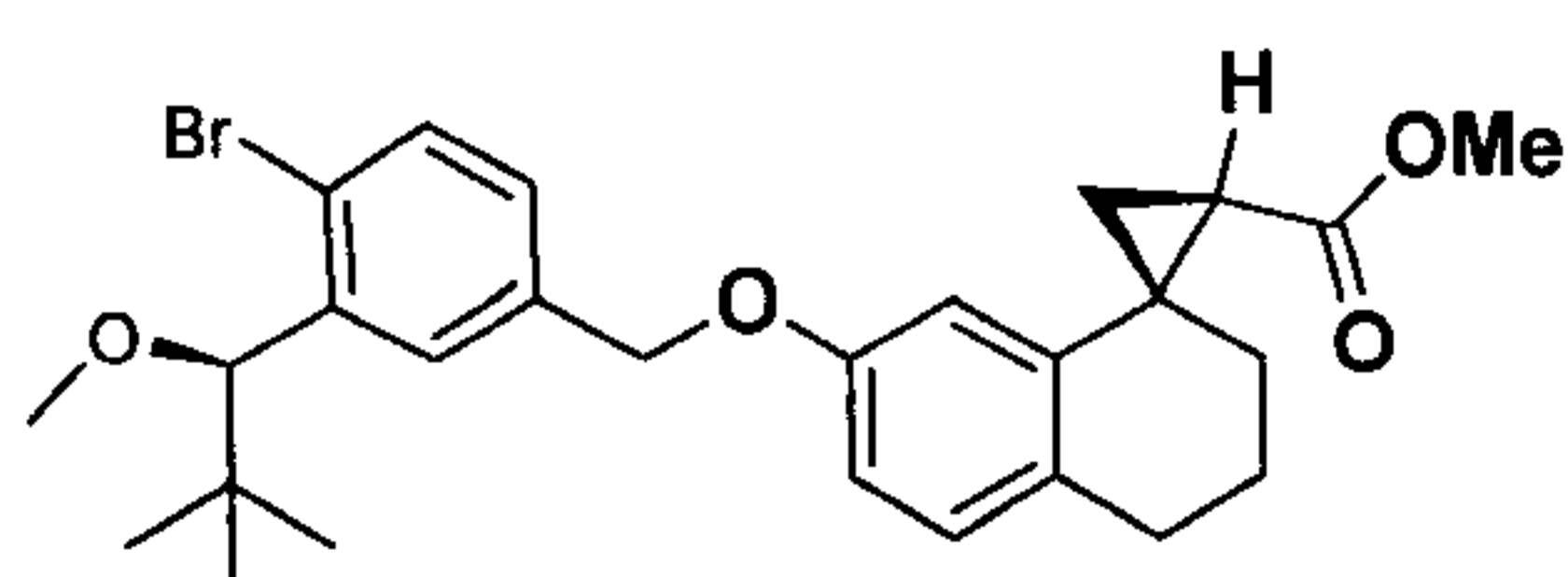
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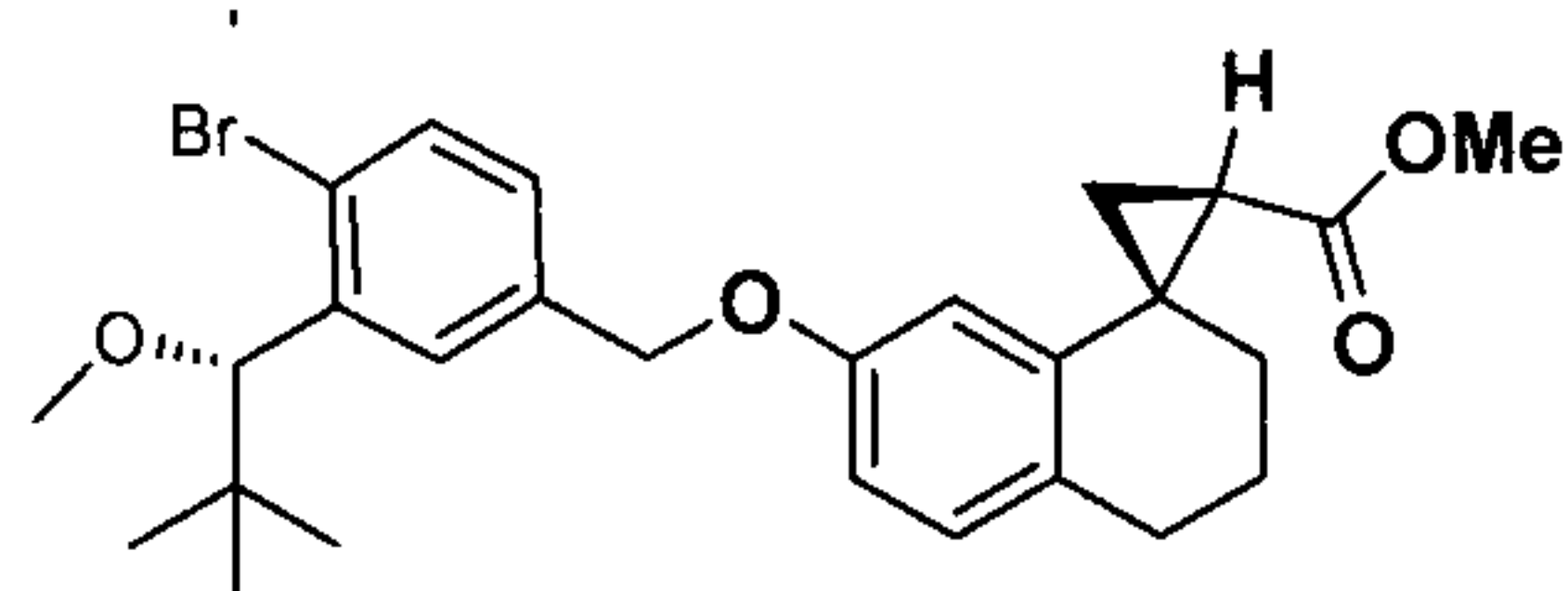
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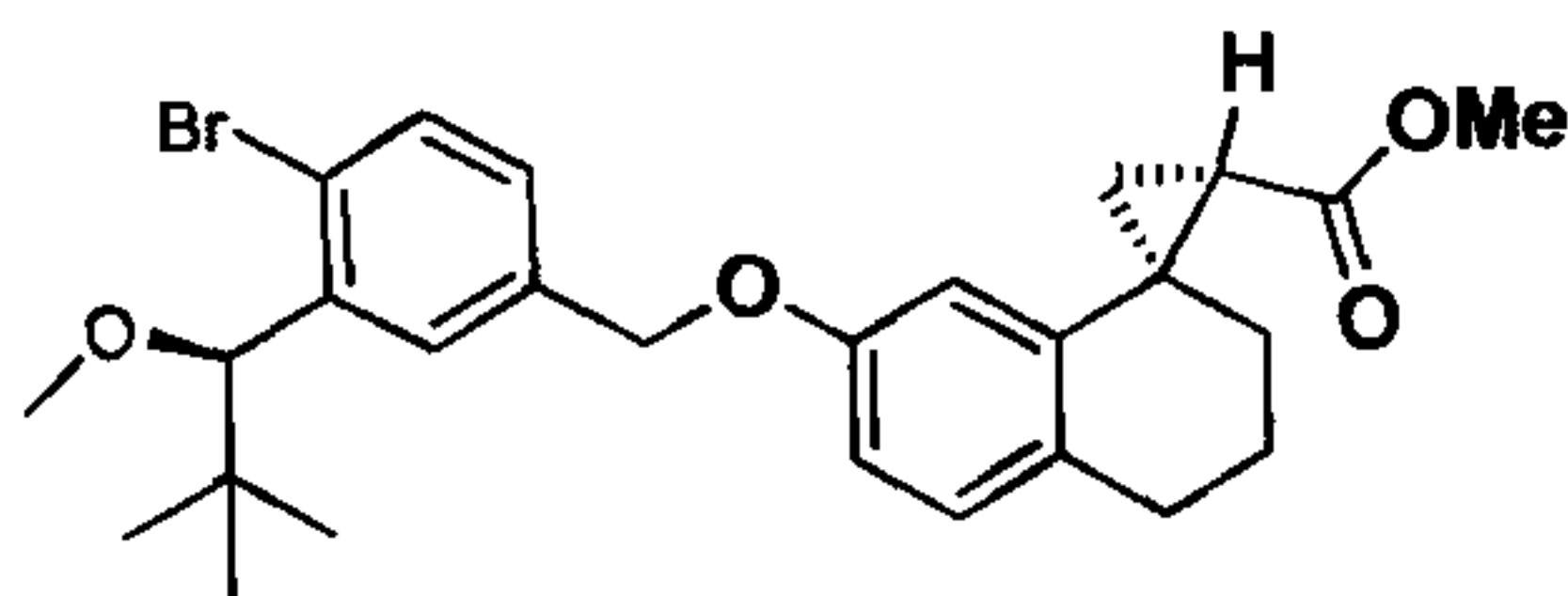
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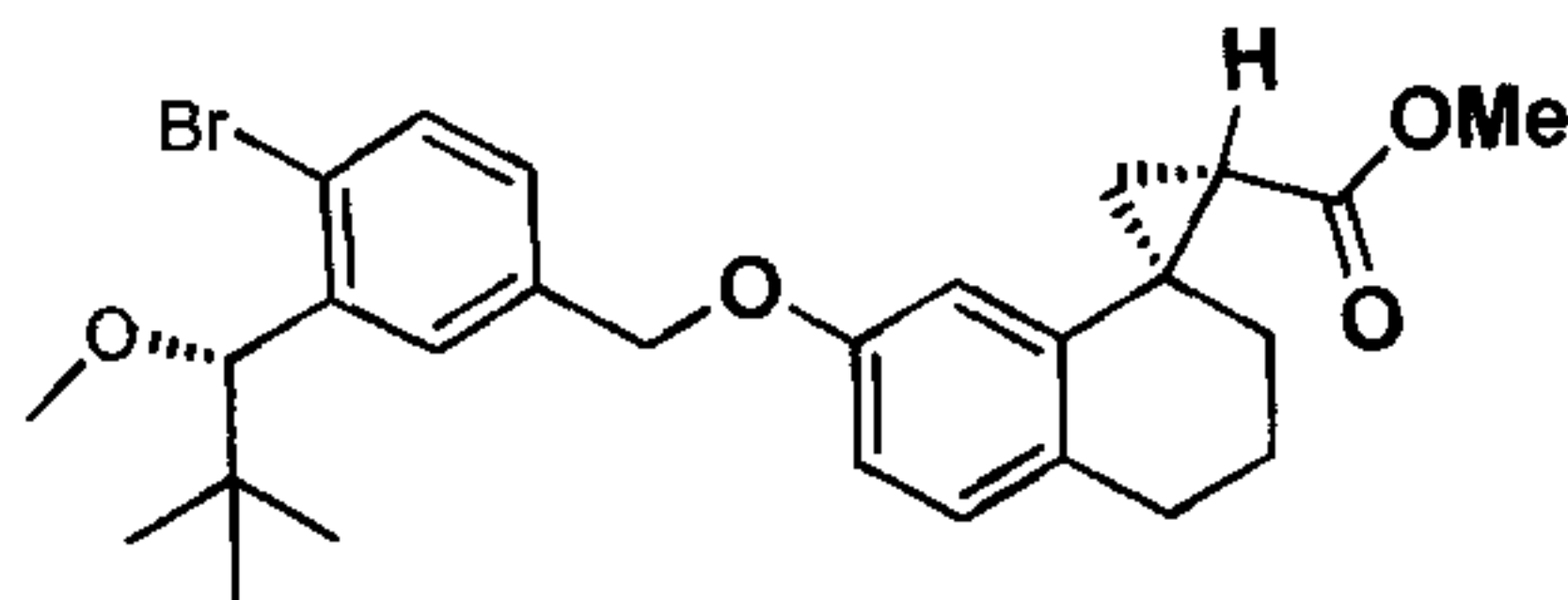
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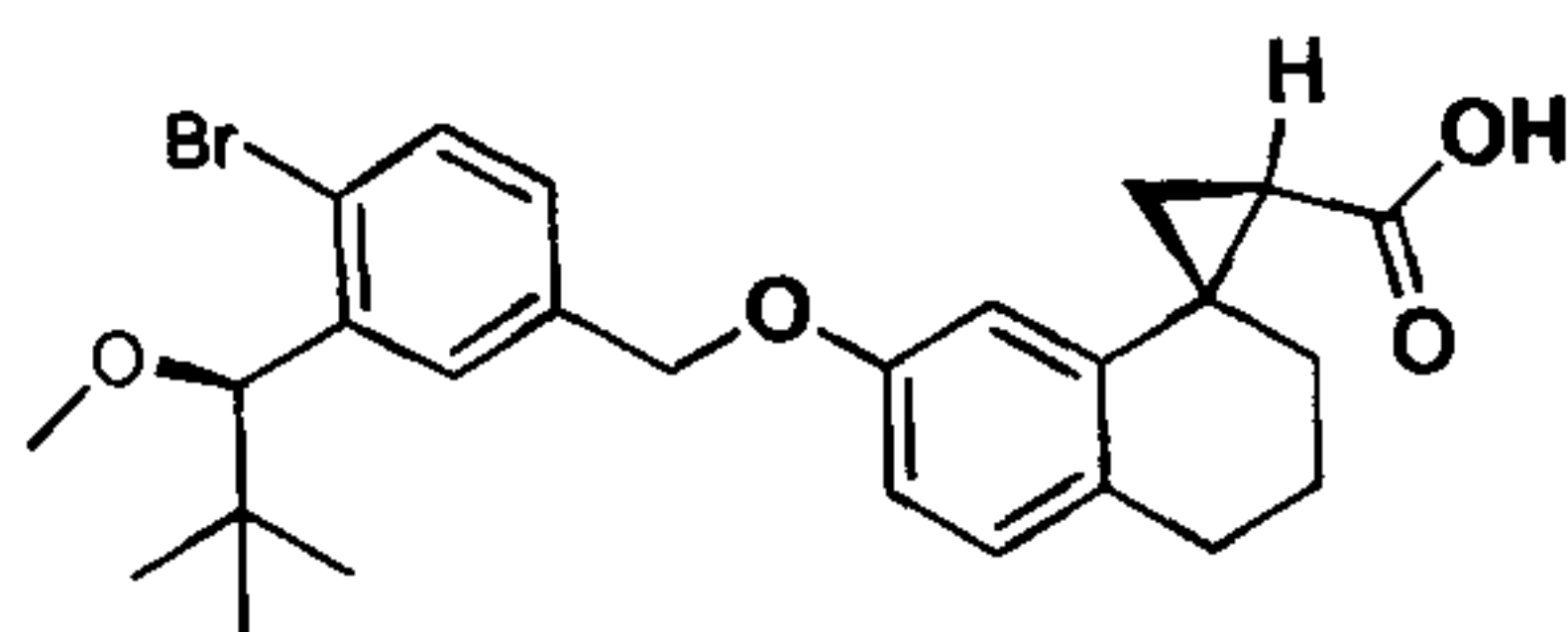
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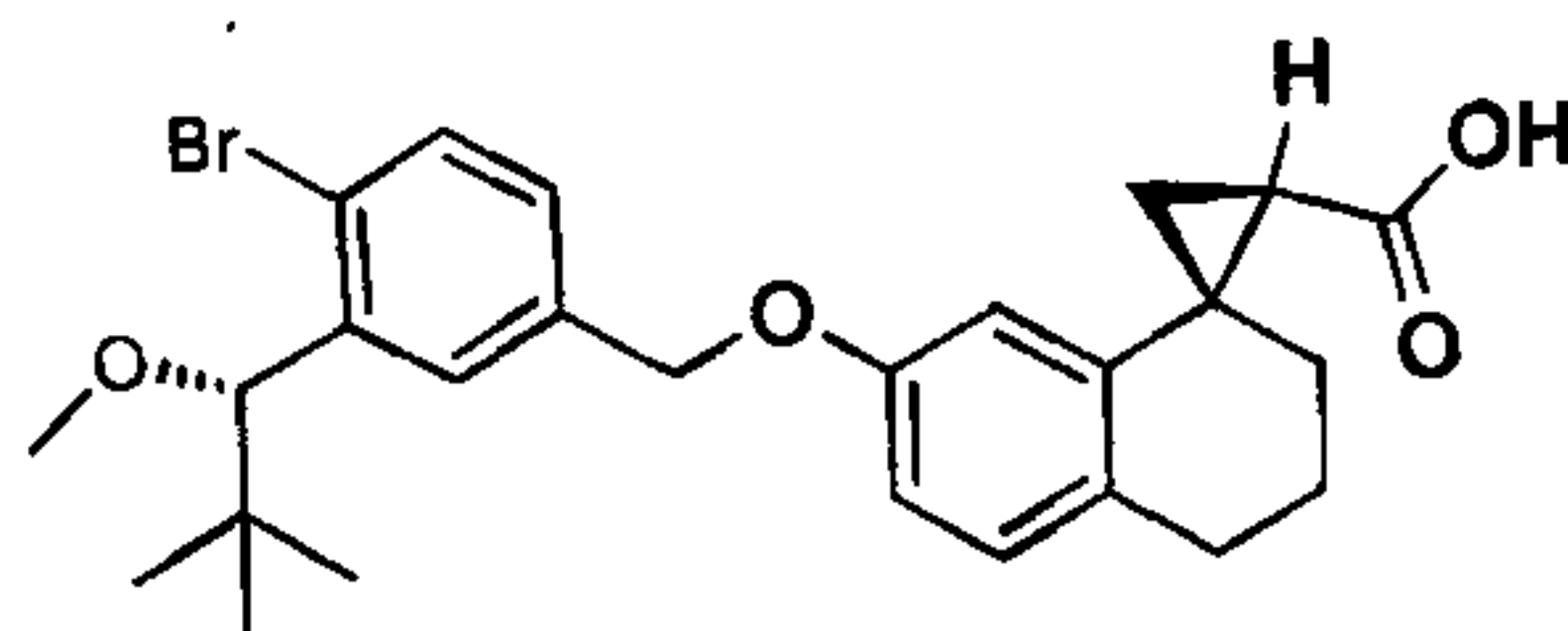
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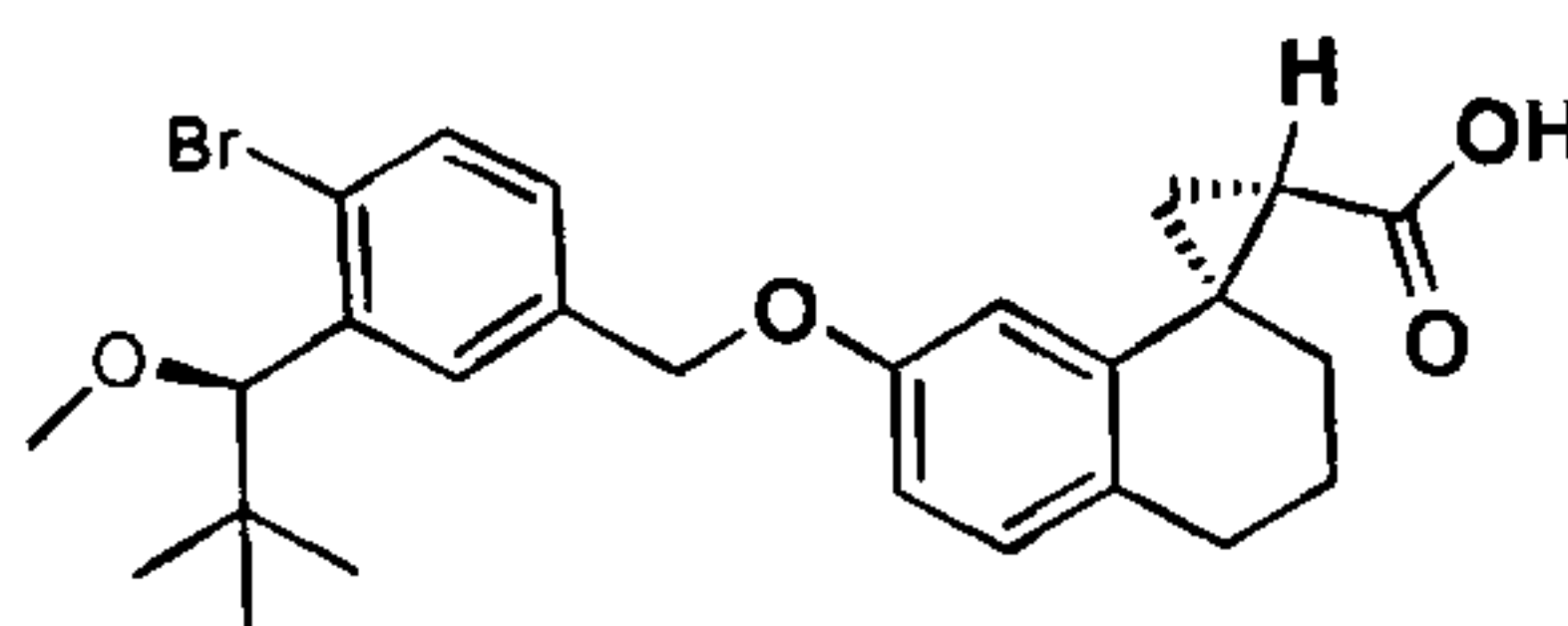
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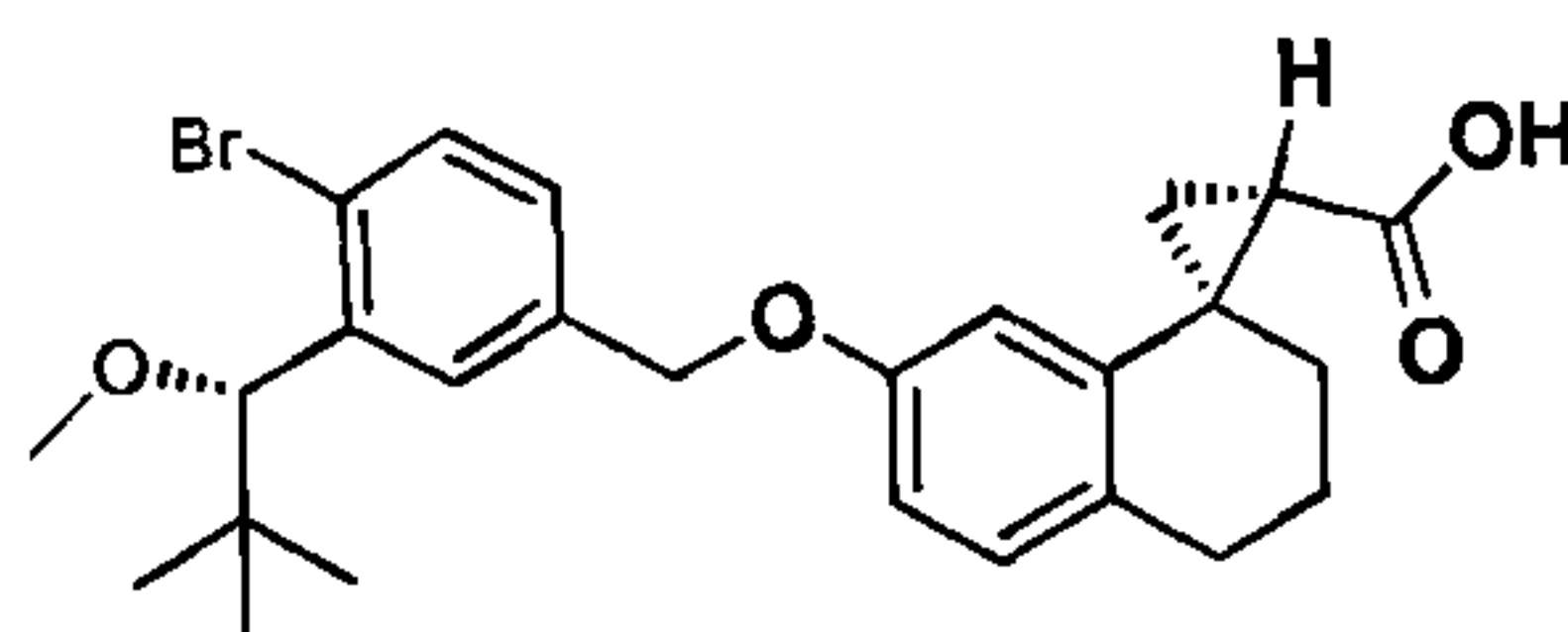
247. The compound



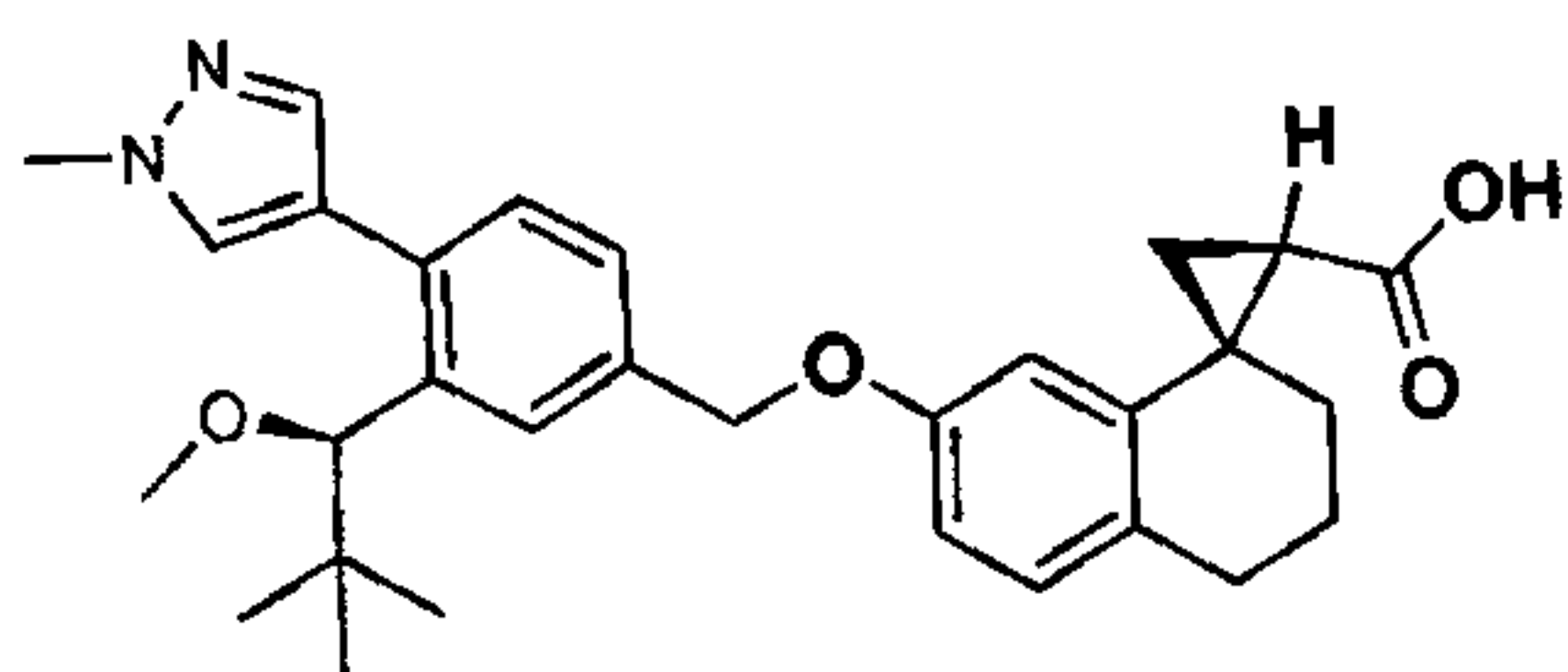
248. The compound



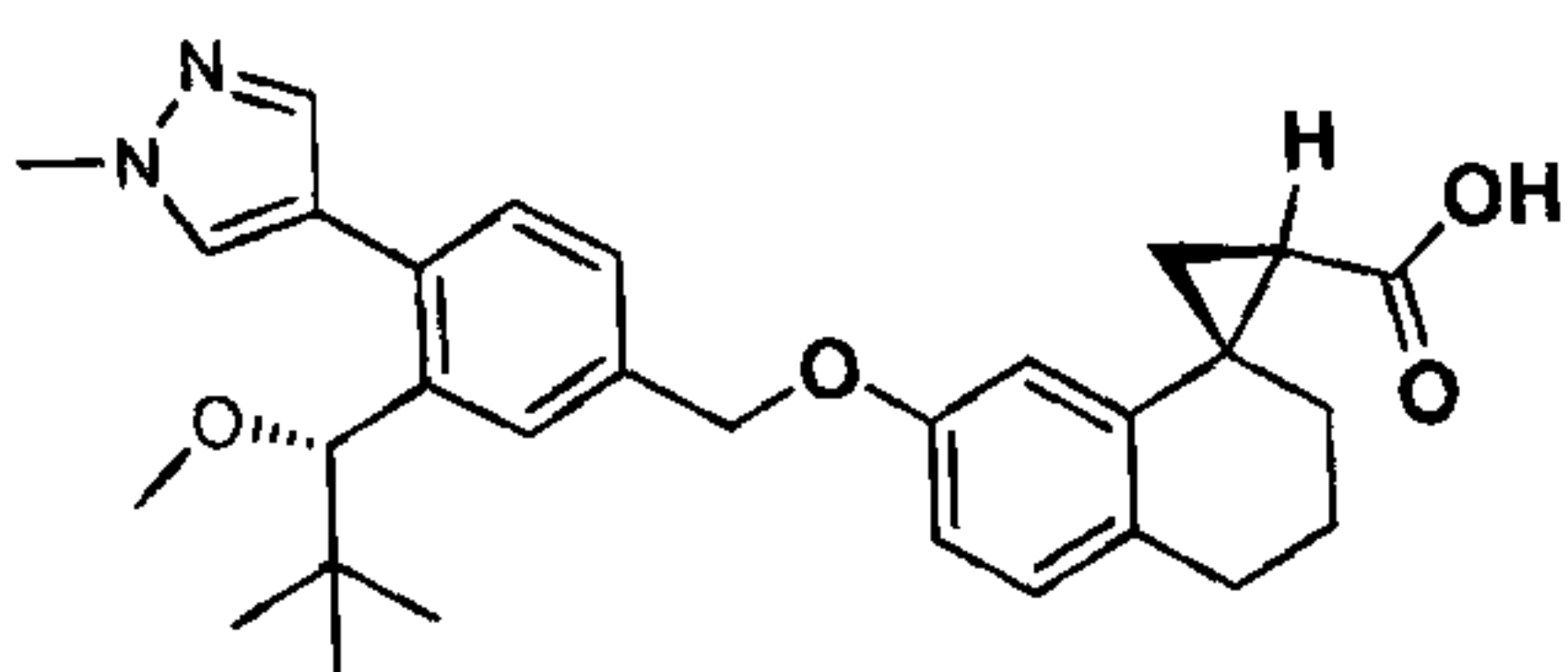
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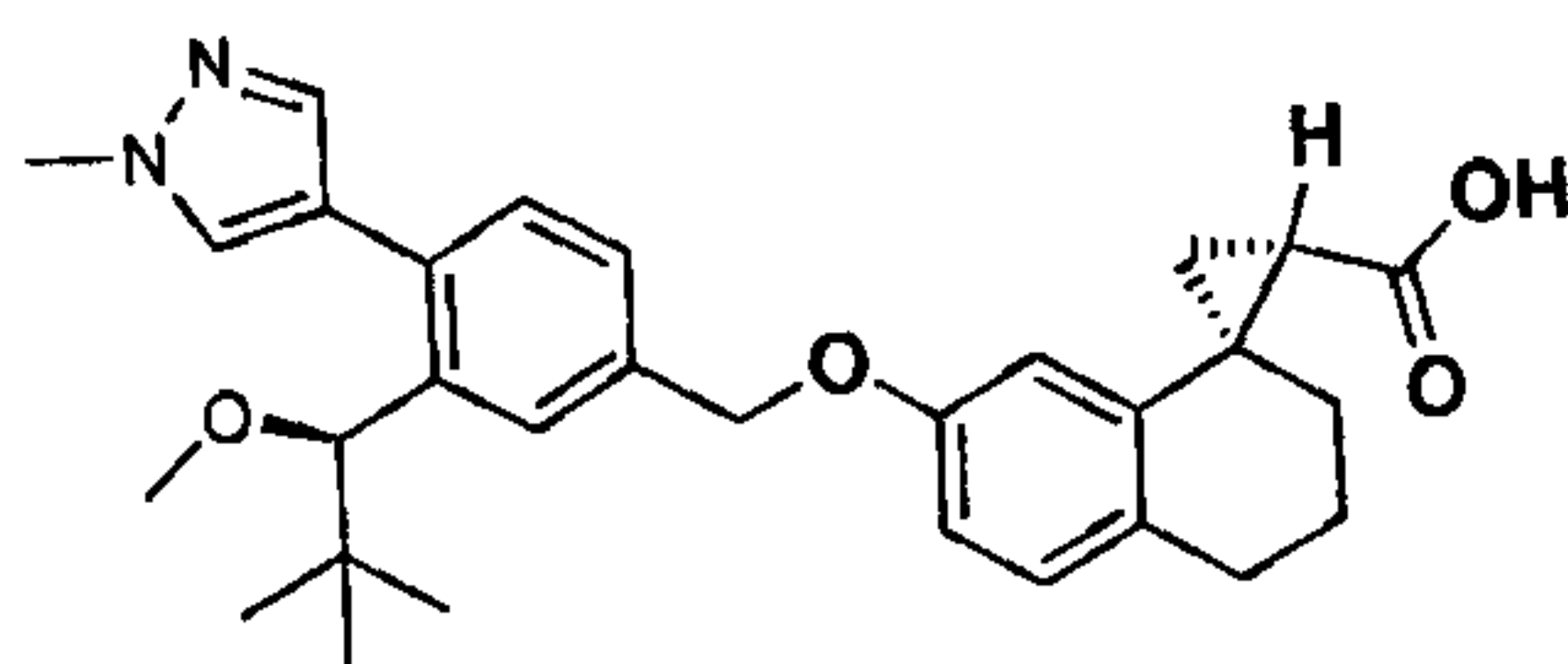
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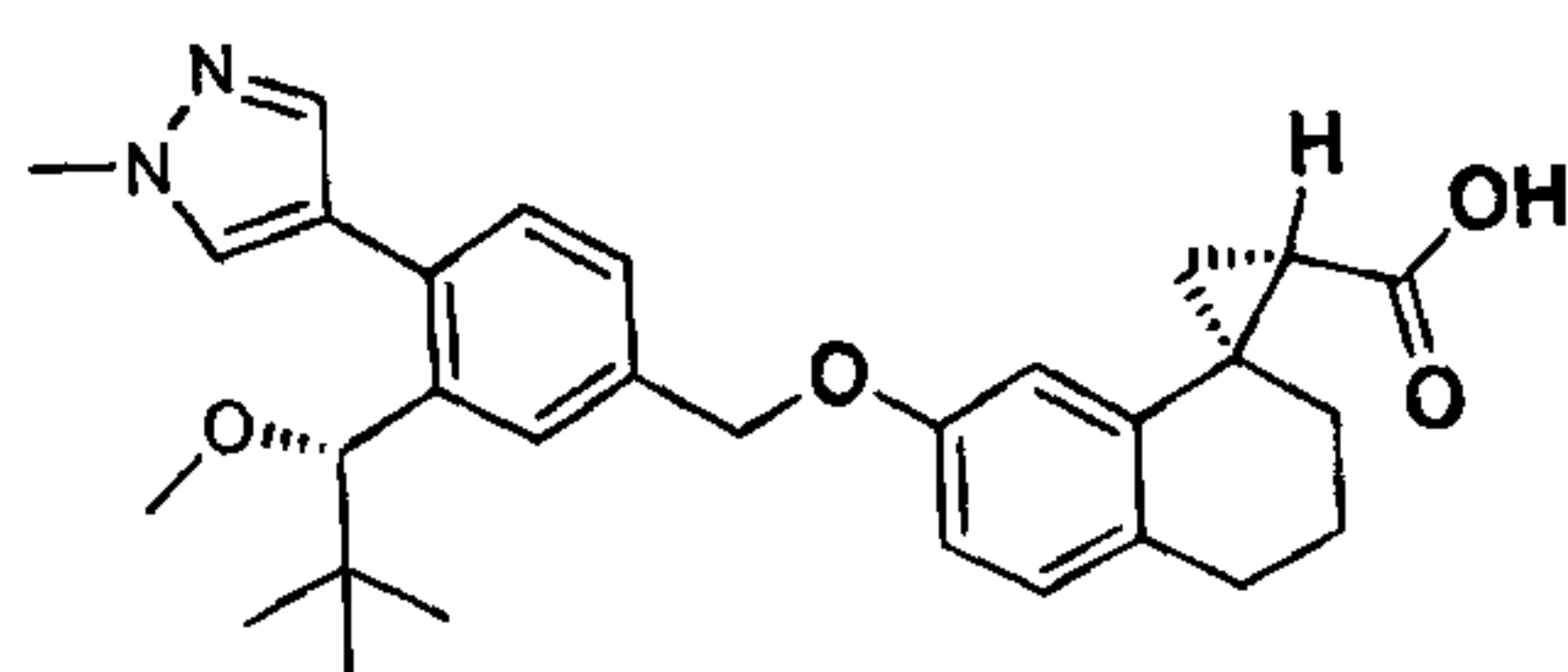
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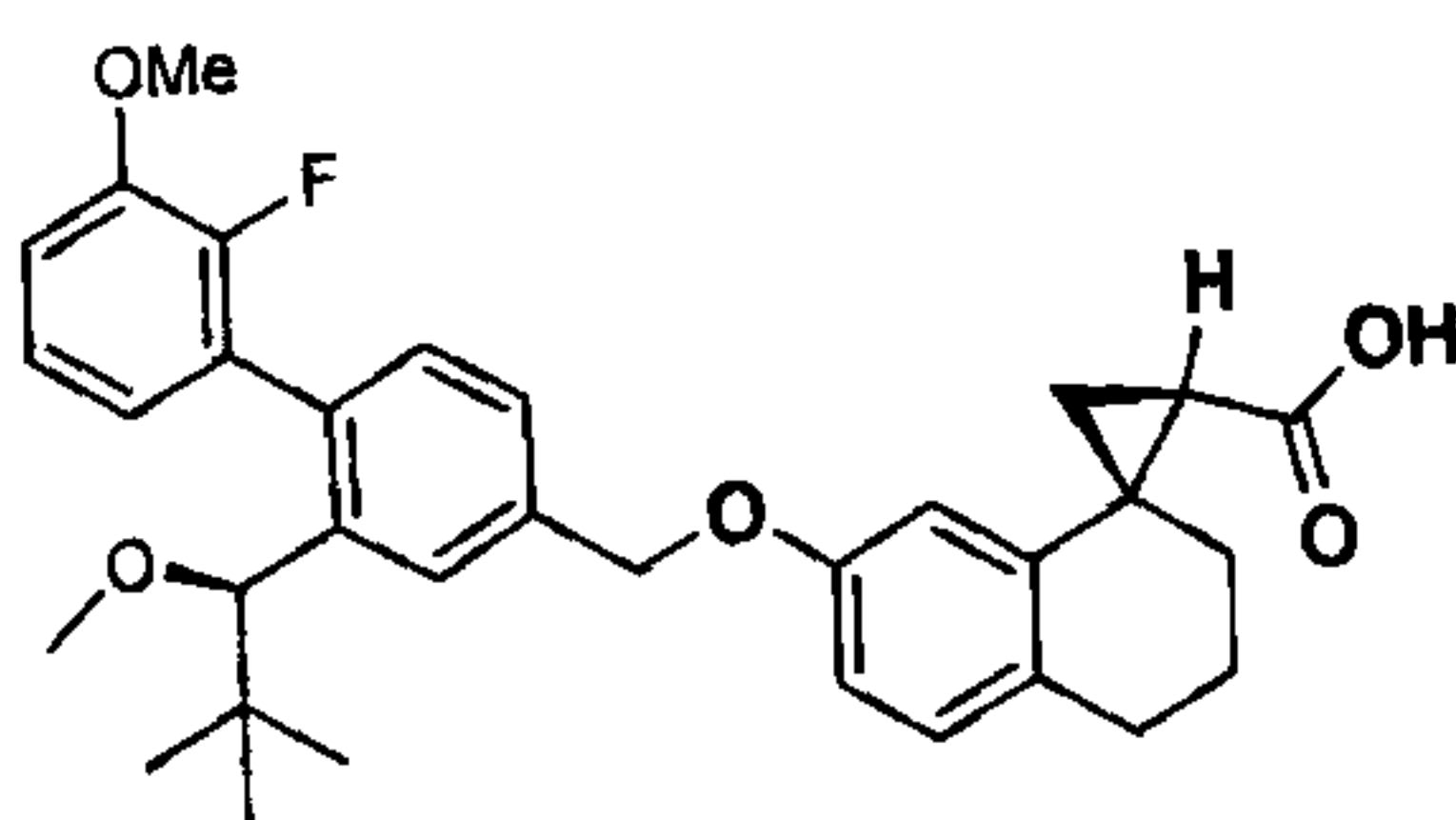
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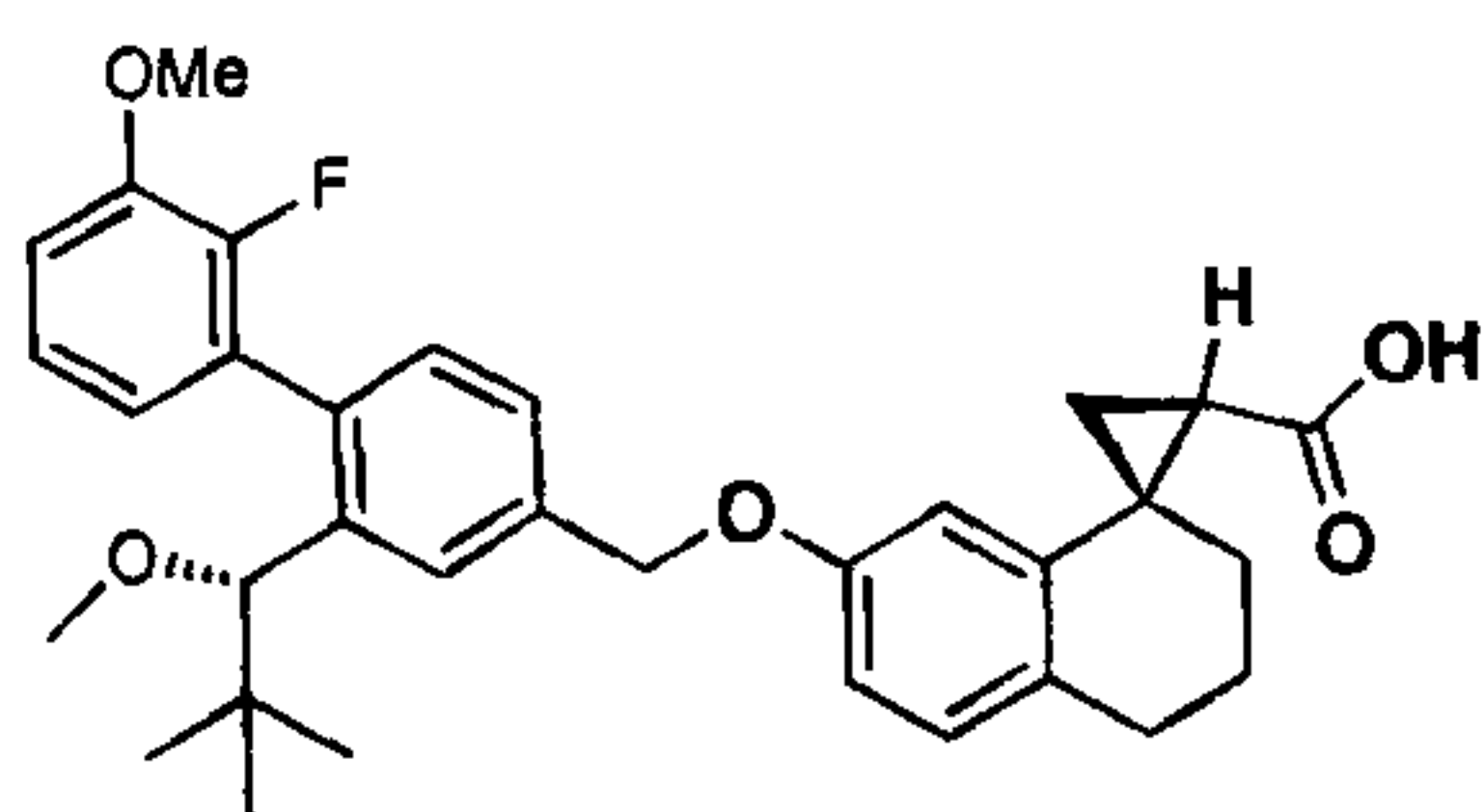
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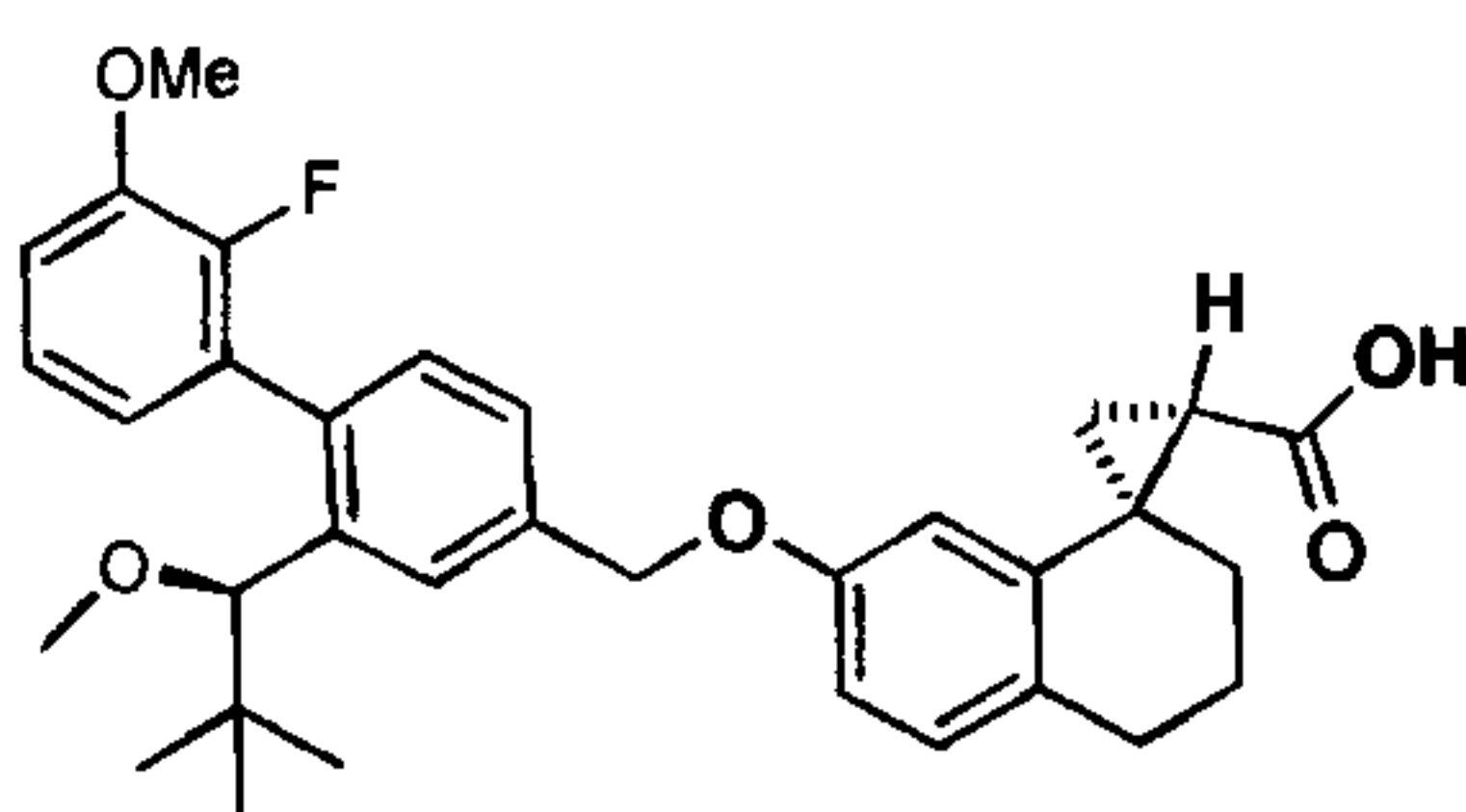
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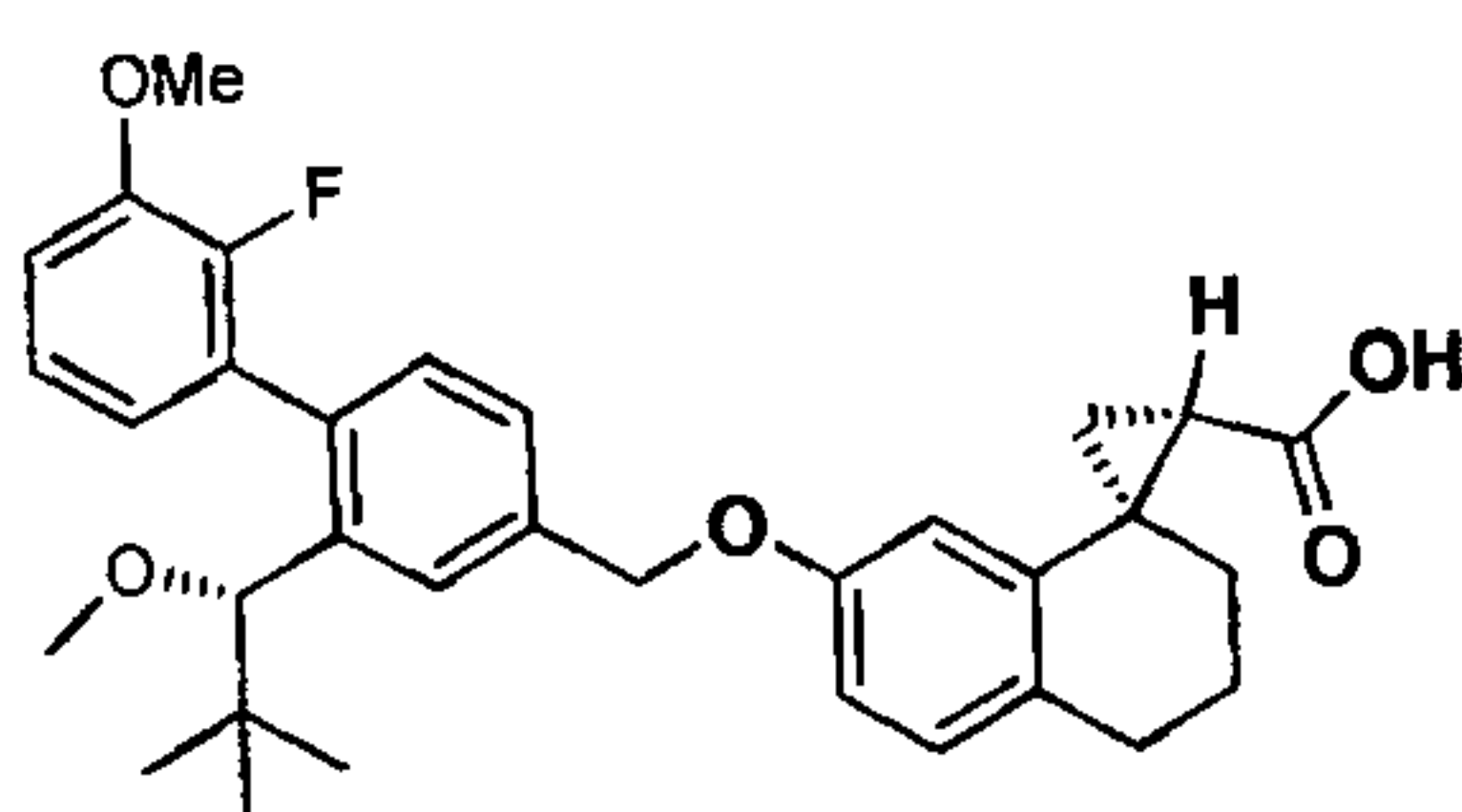
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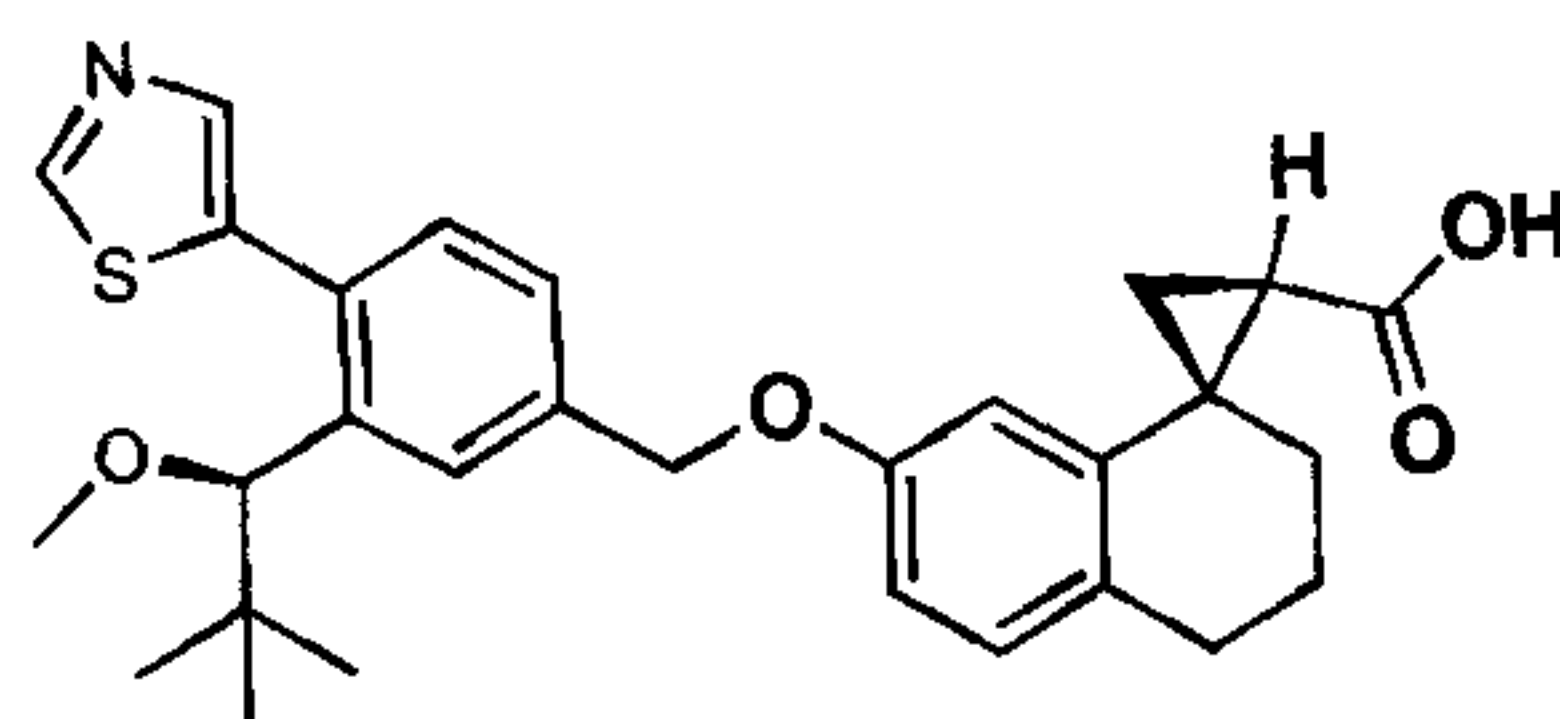
256. The compound



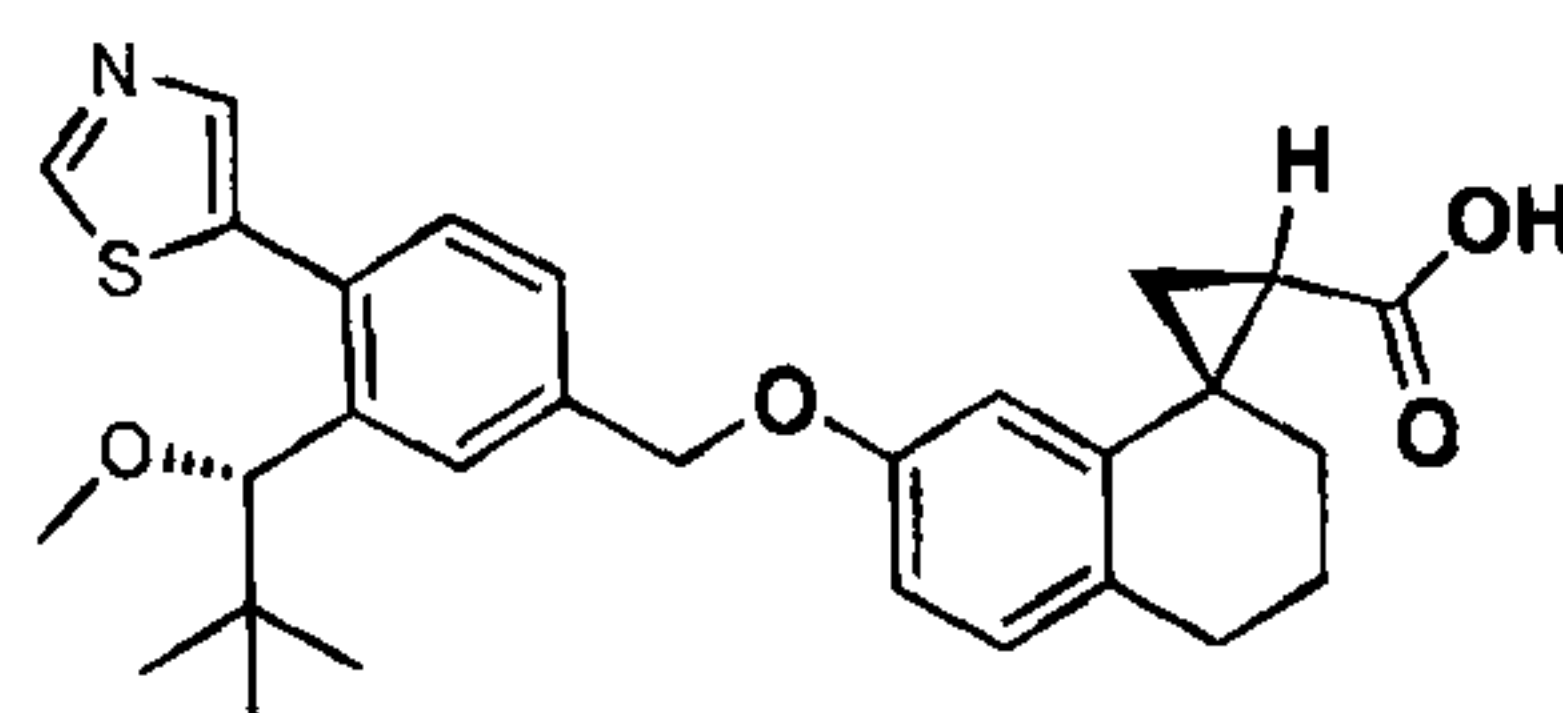
257. The compound



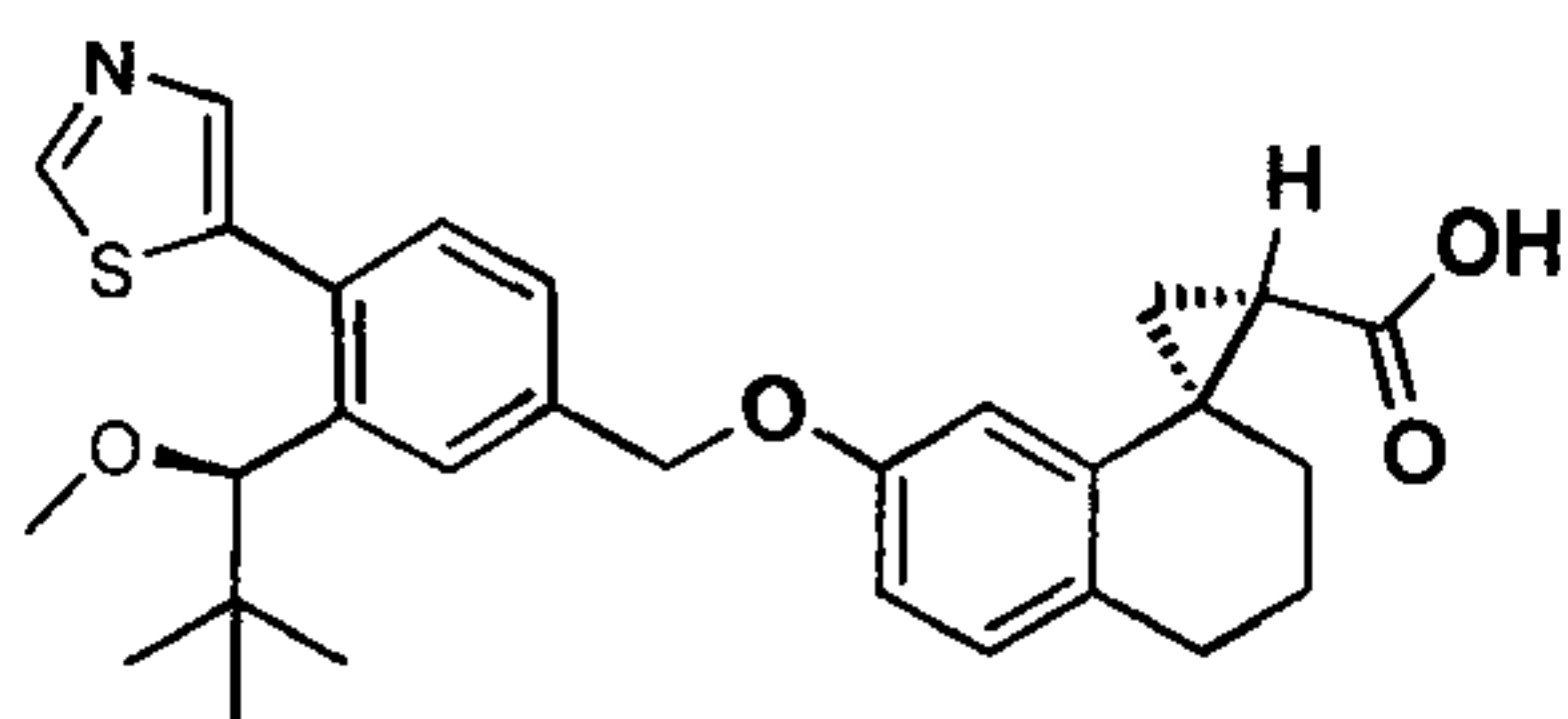
258. The compound



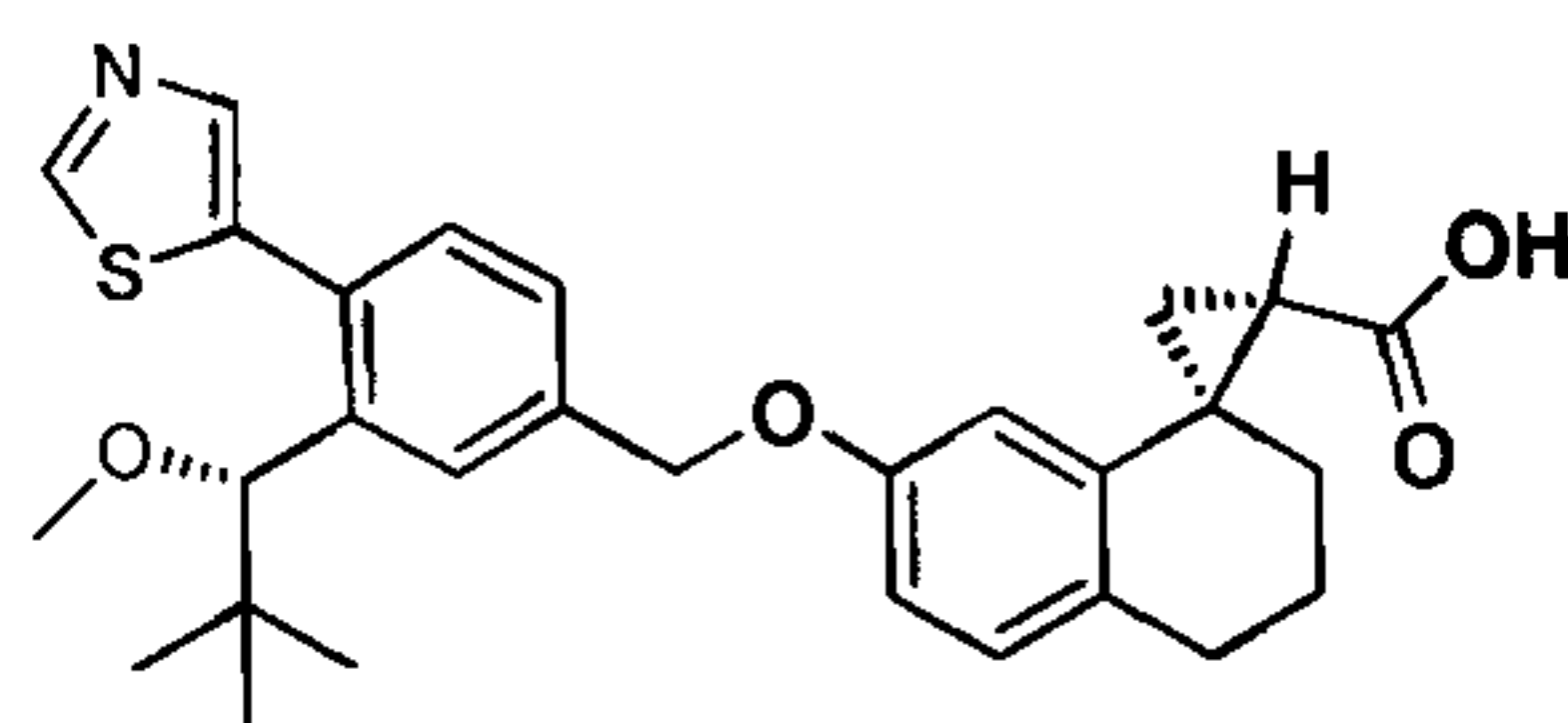
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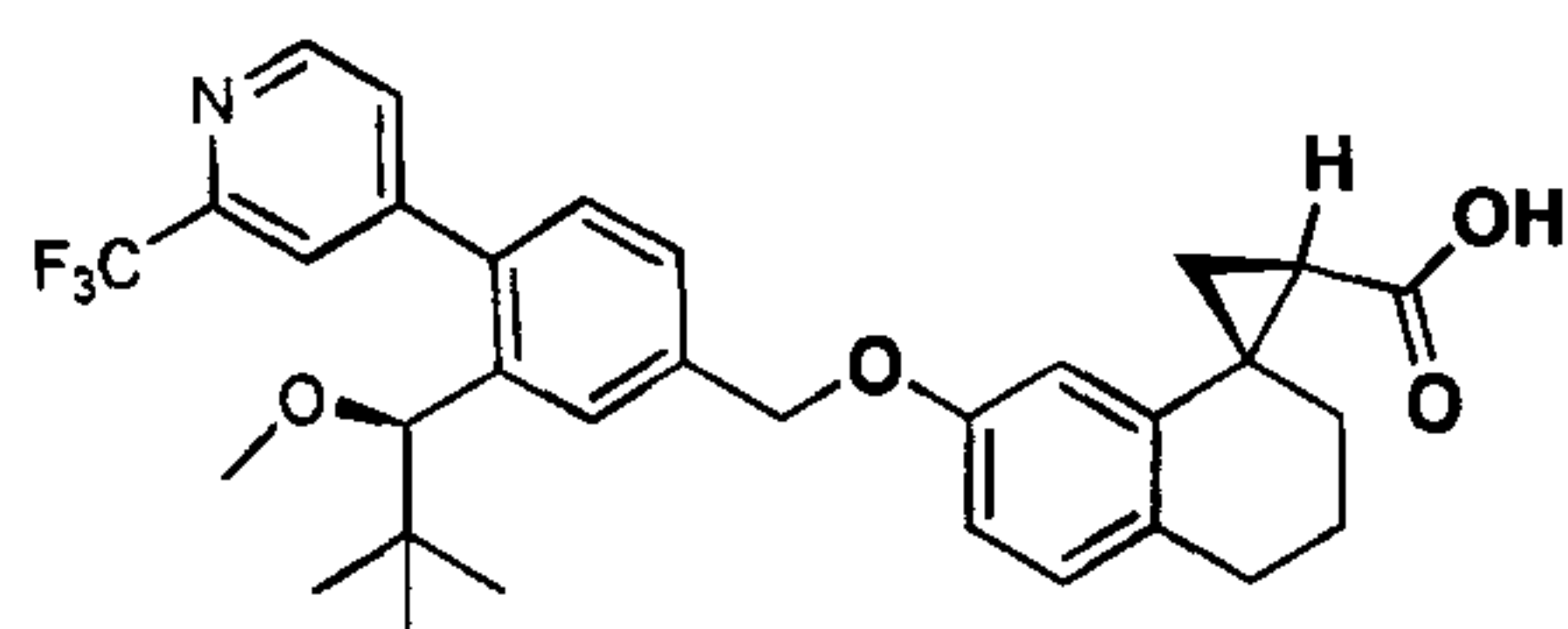
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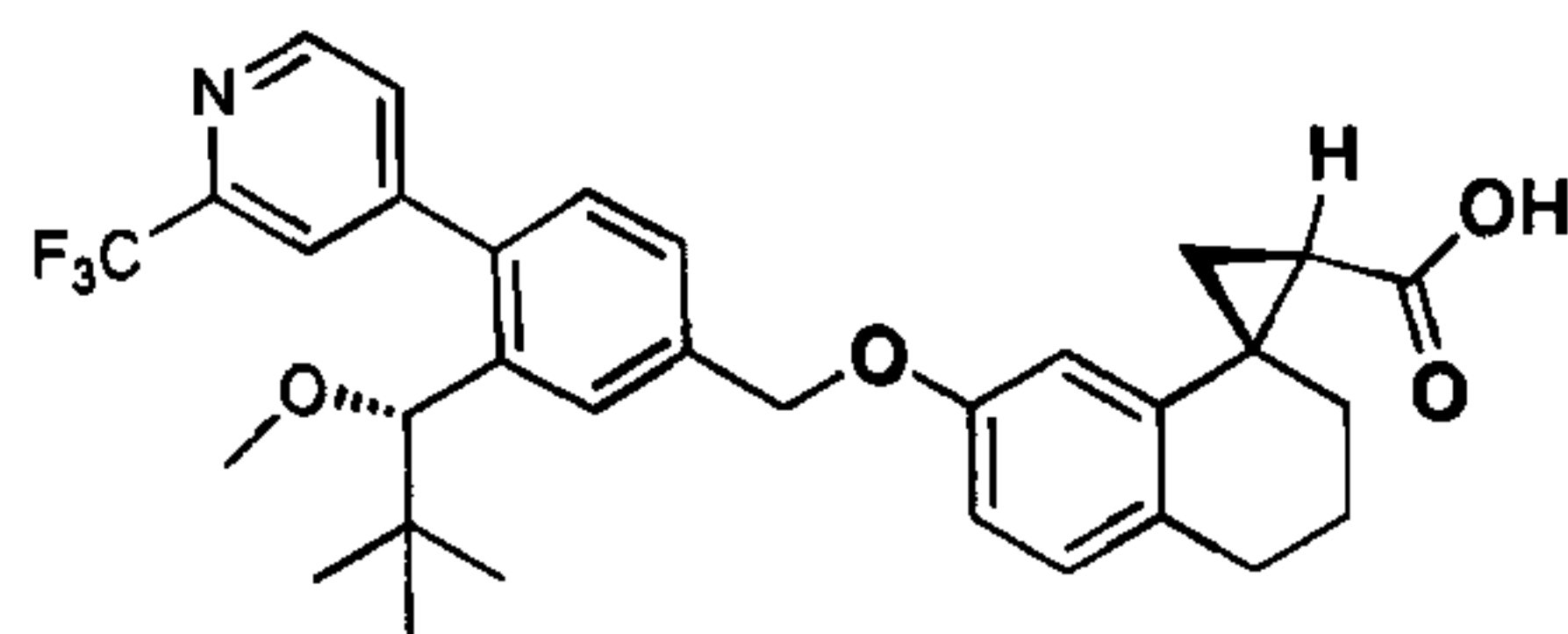
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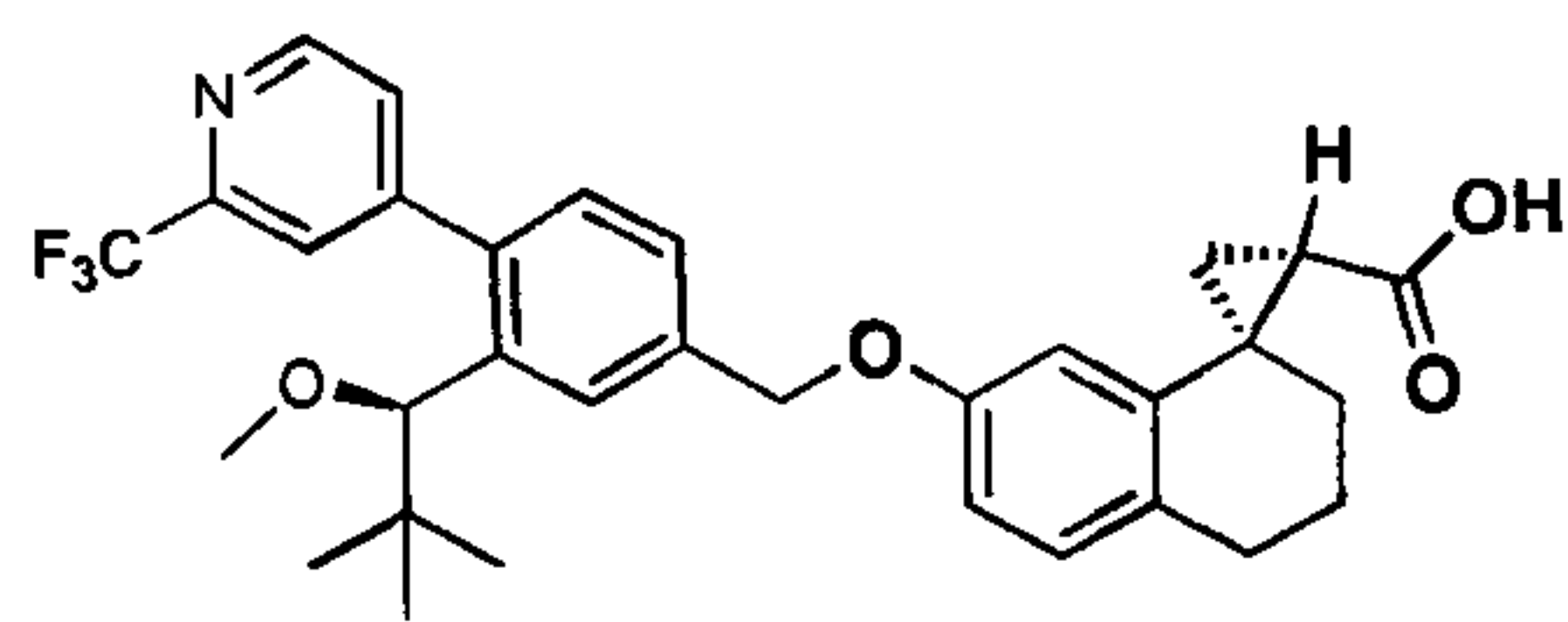
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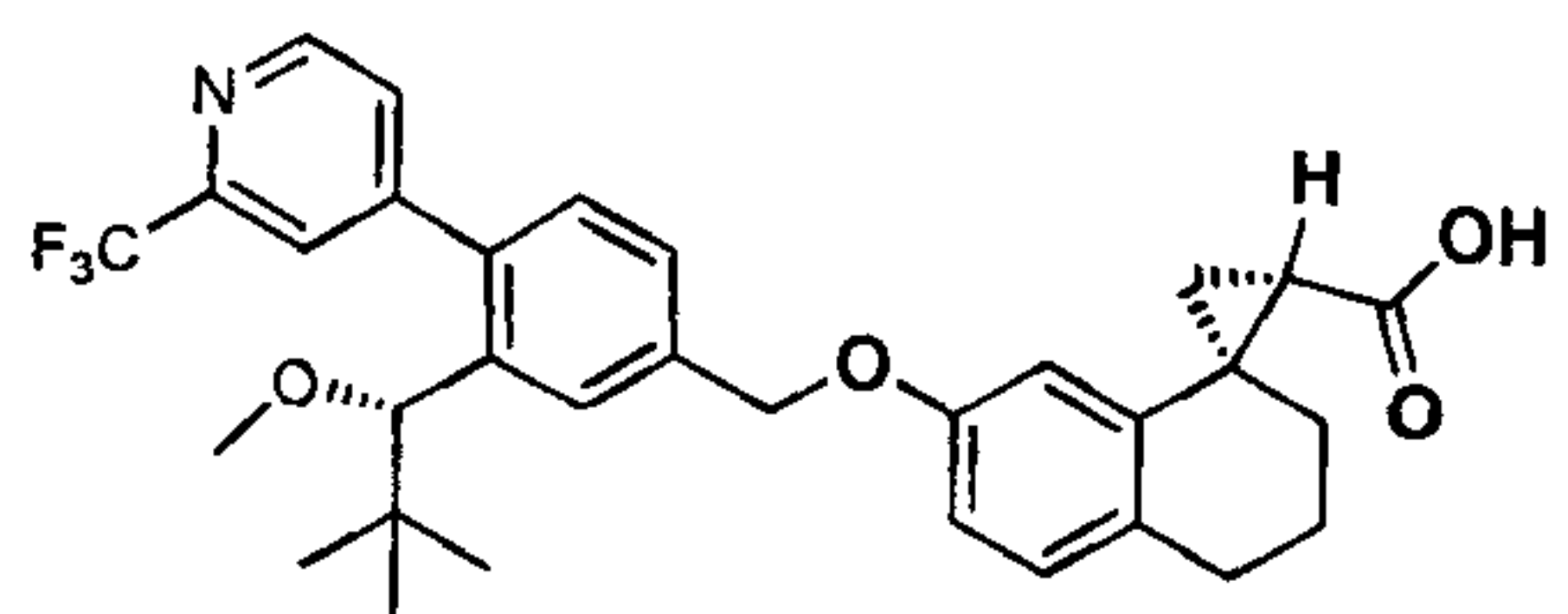
263. The compound



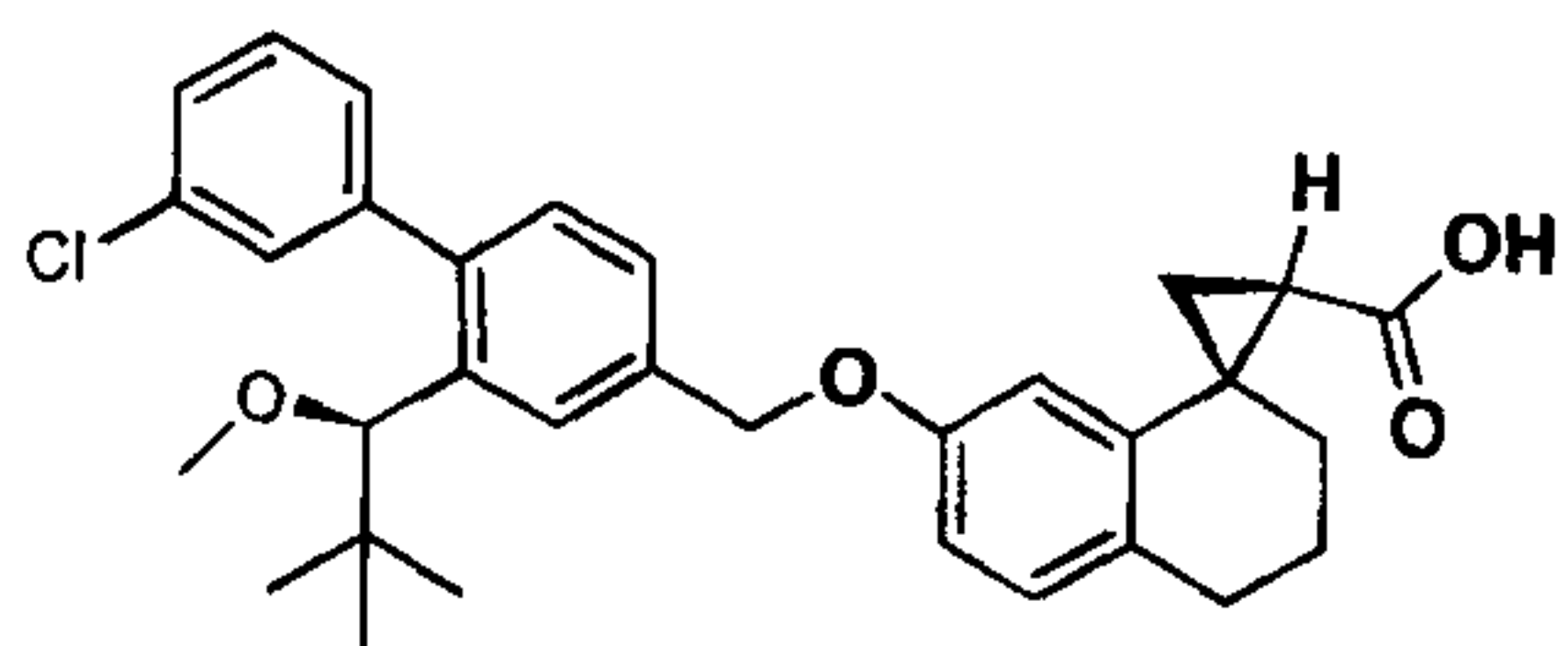
264. The compound



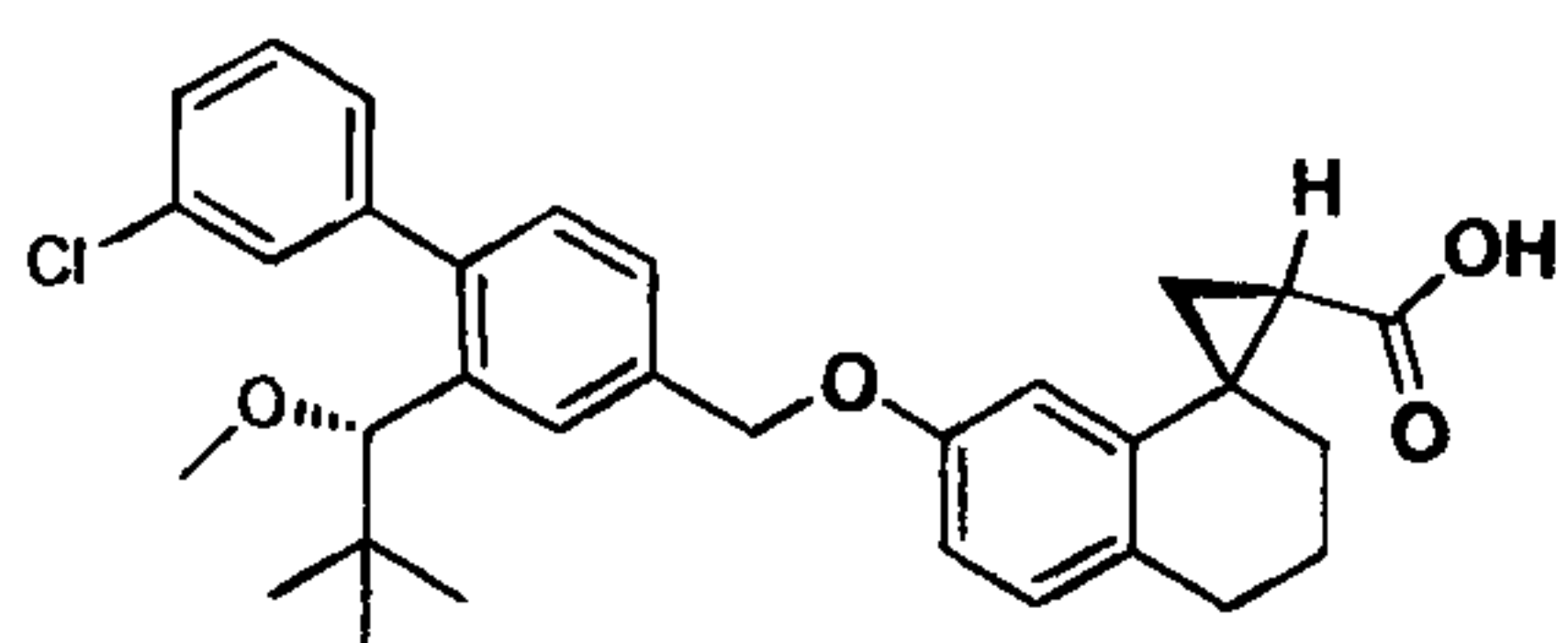
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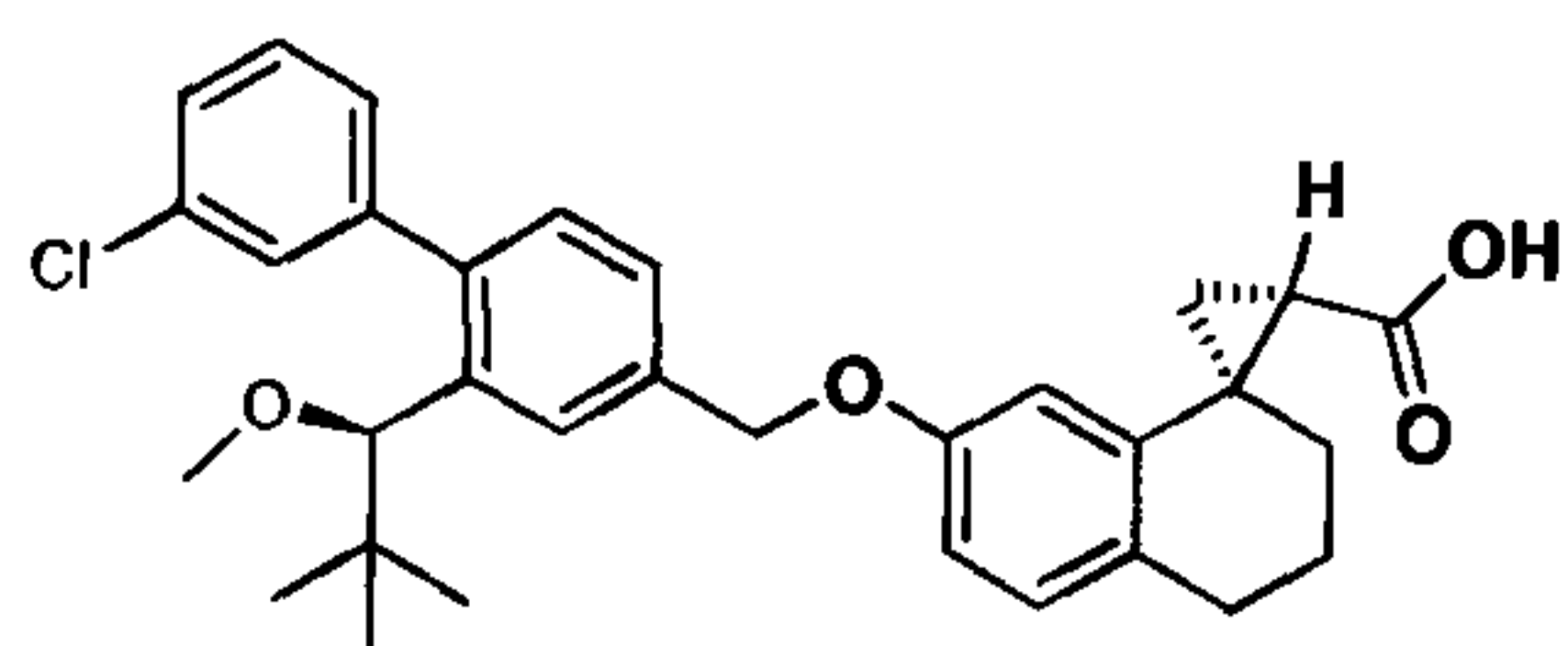
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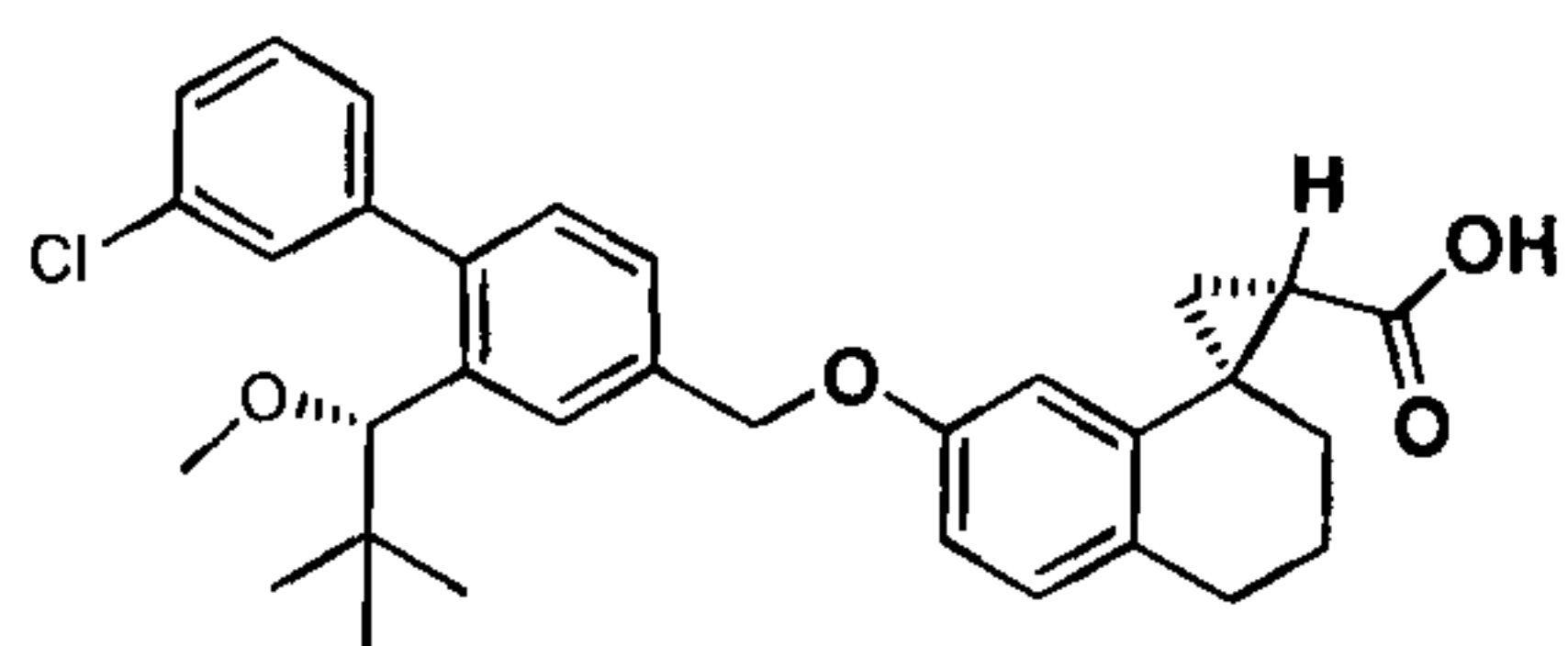
267. The compound



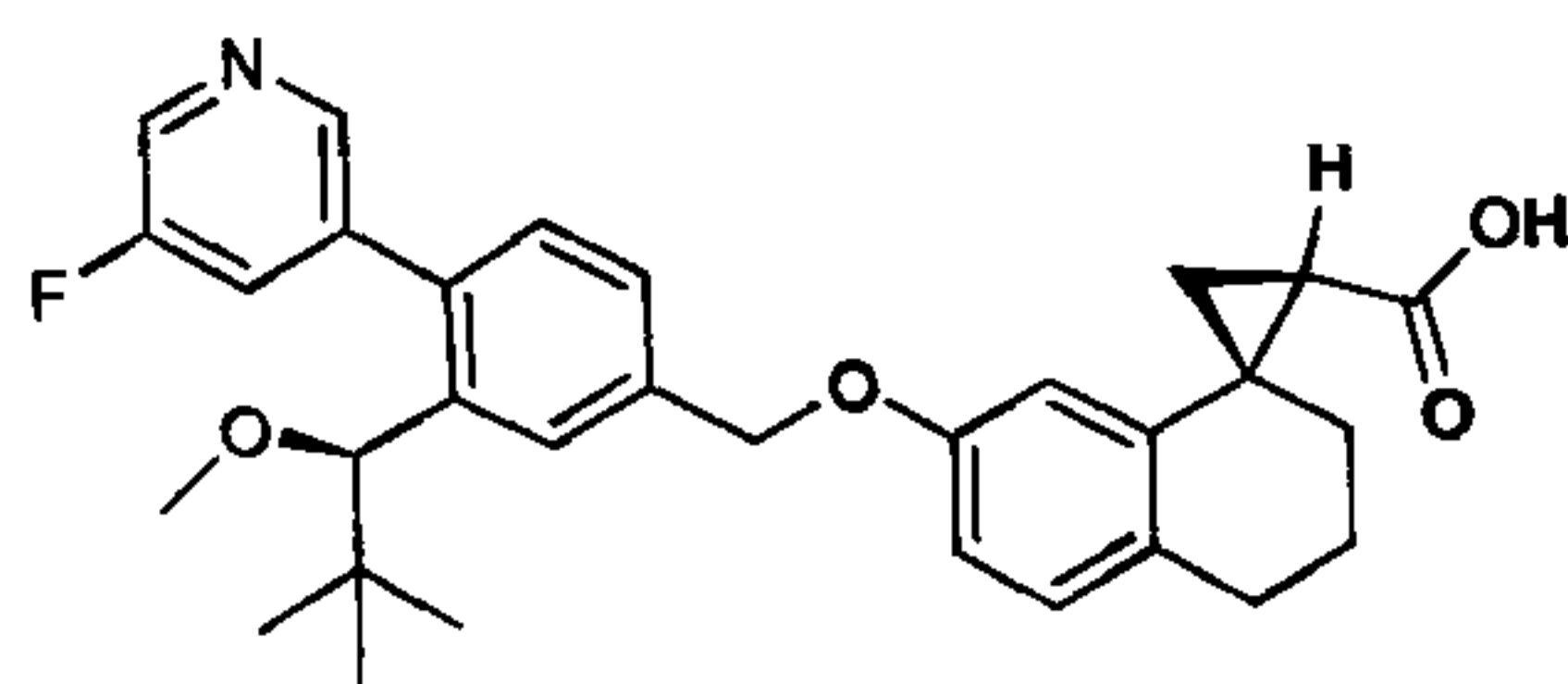
268. The compound



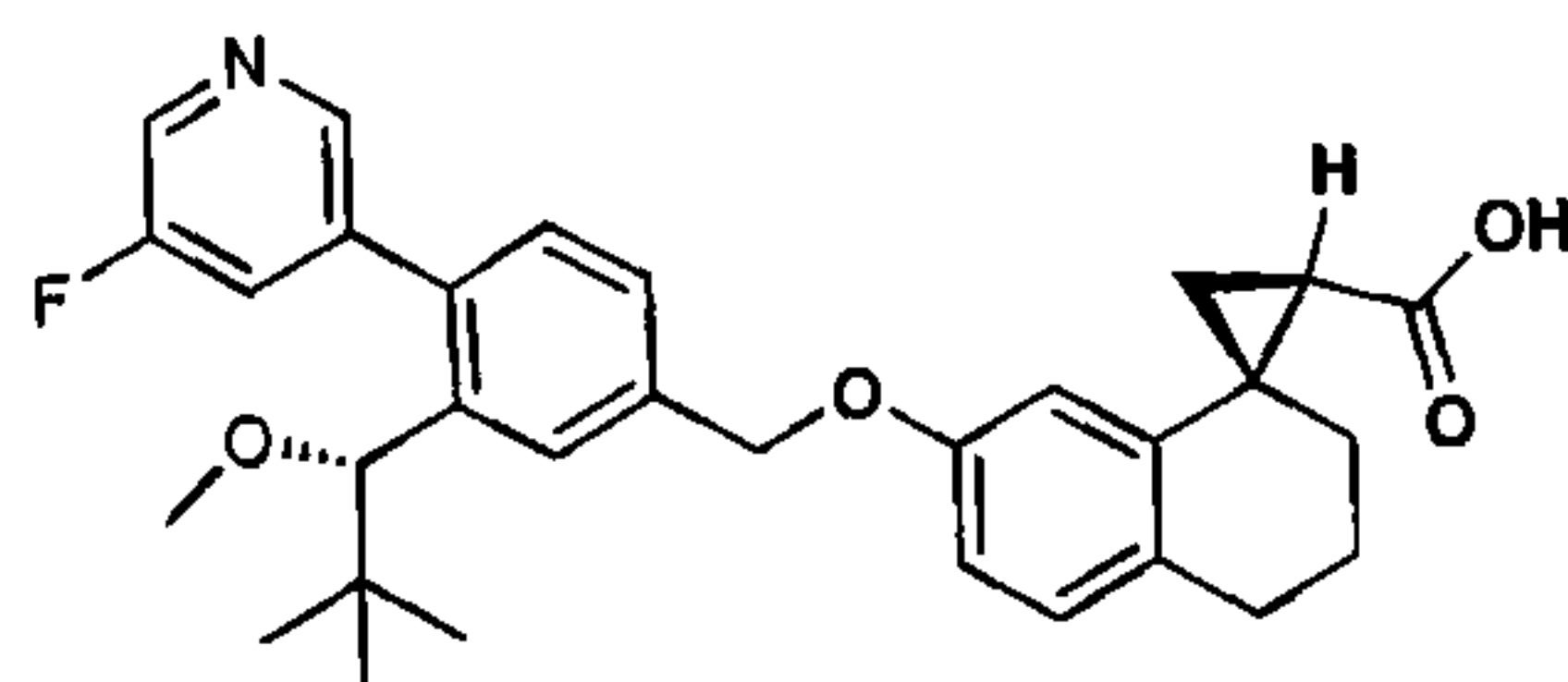
269. The compound



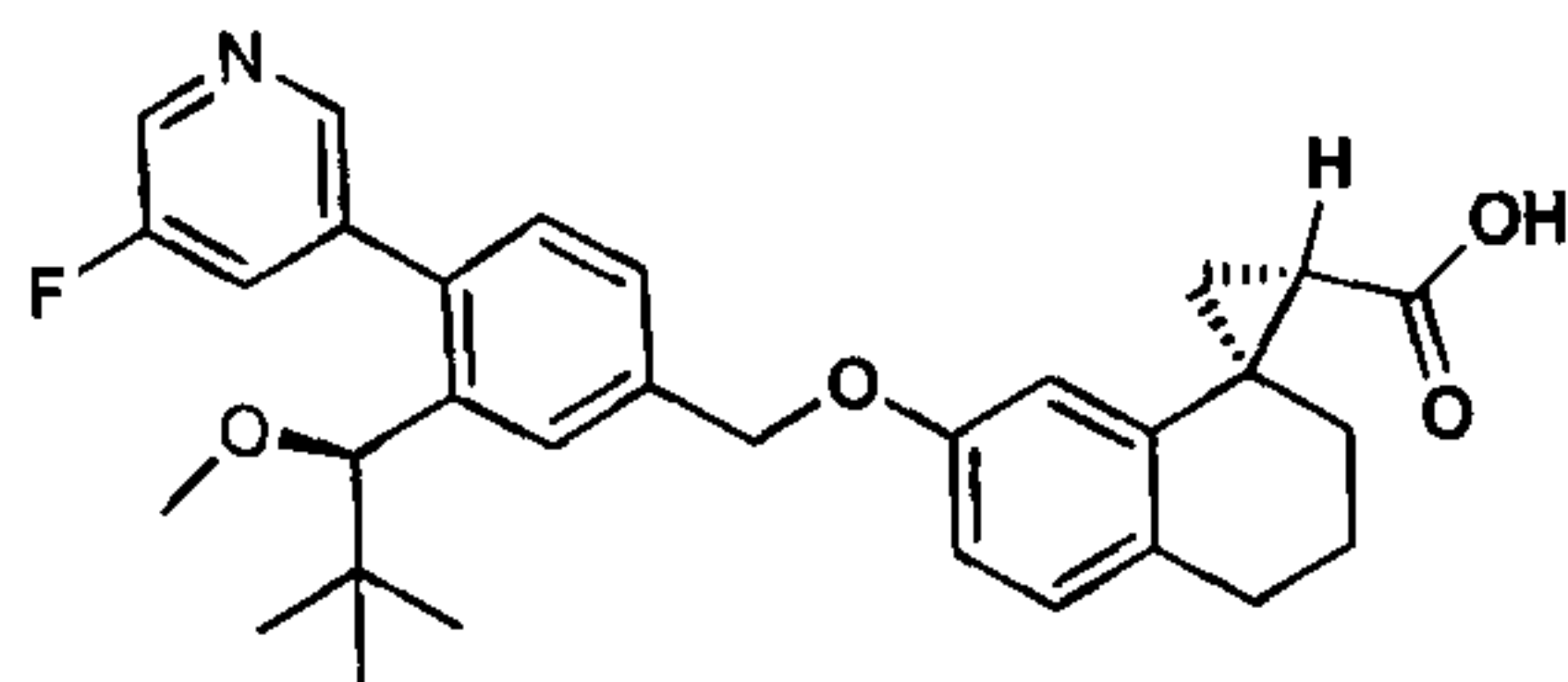
270. The compound



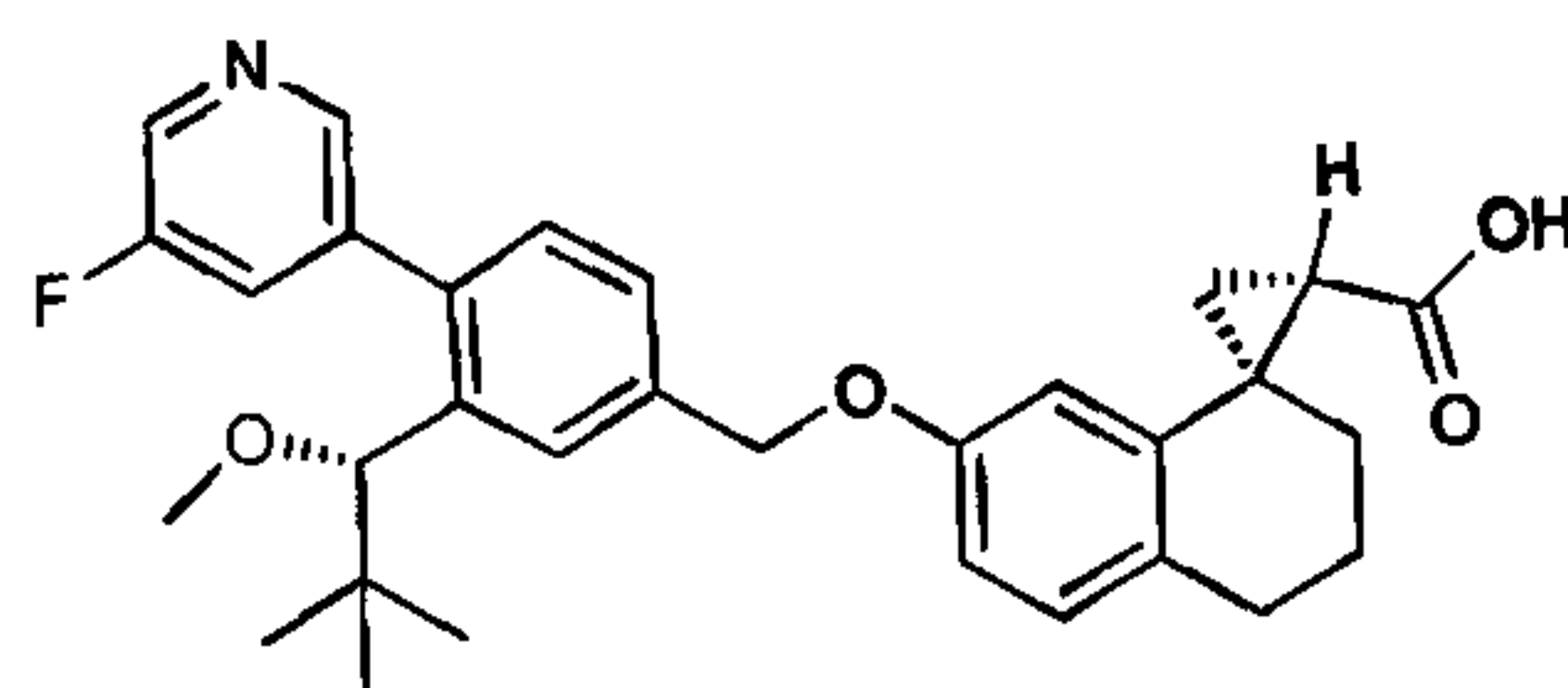
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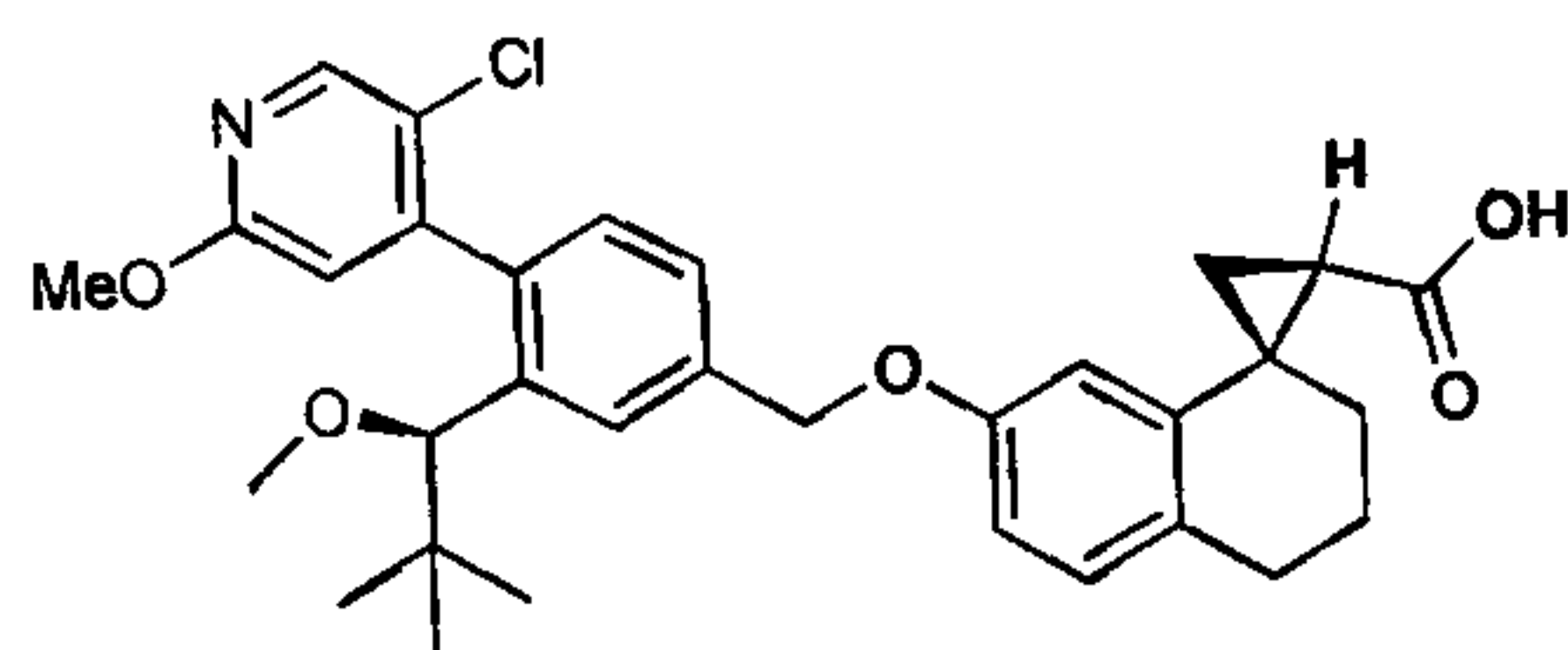
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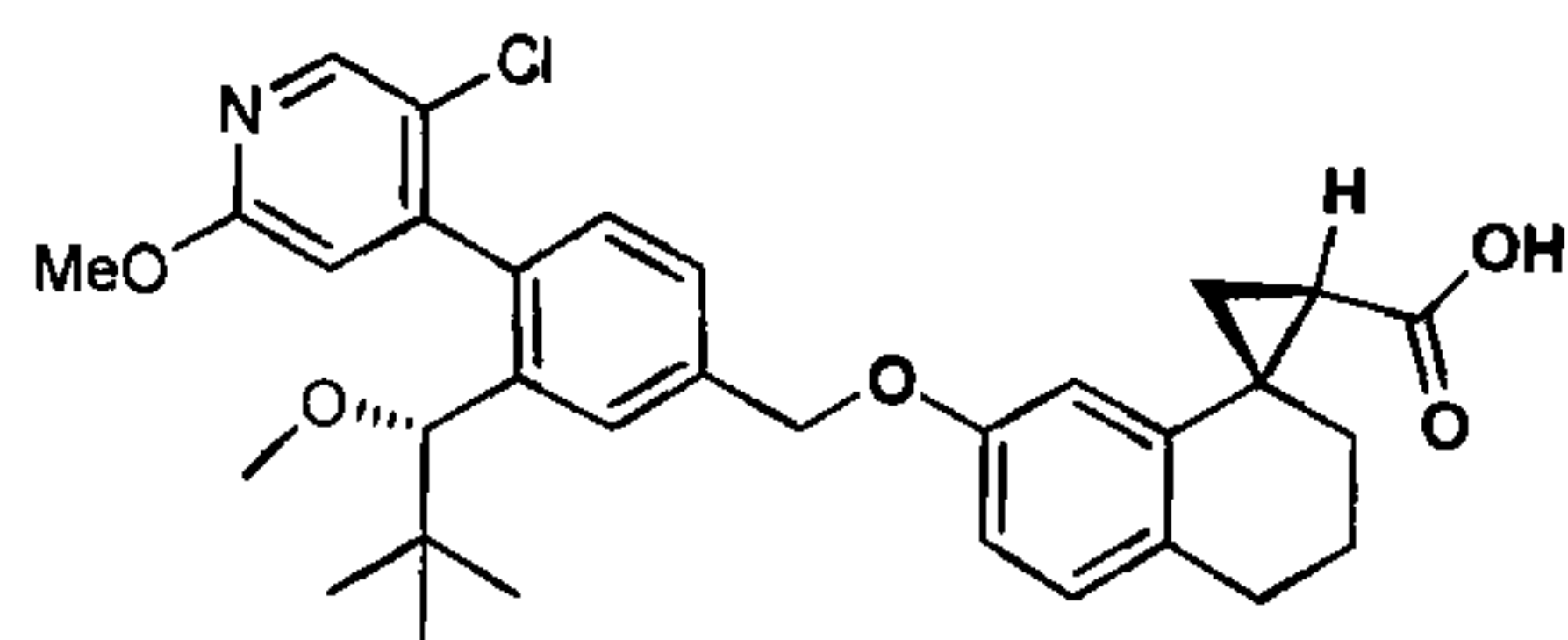
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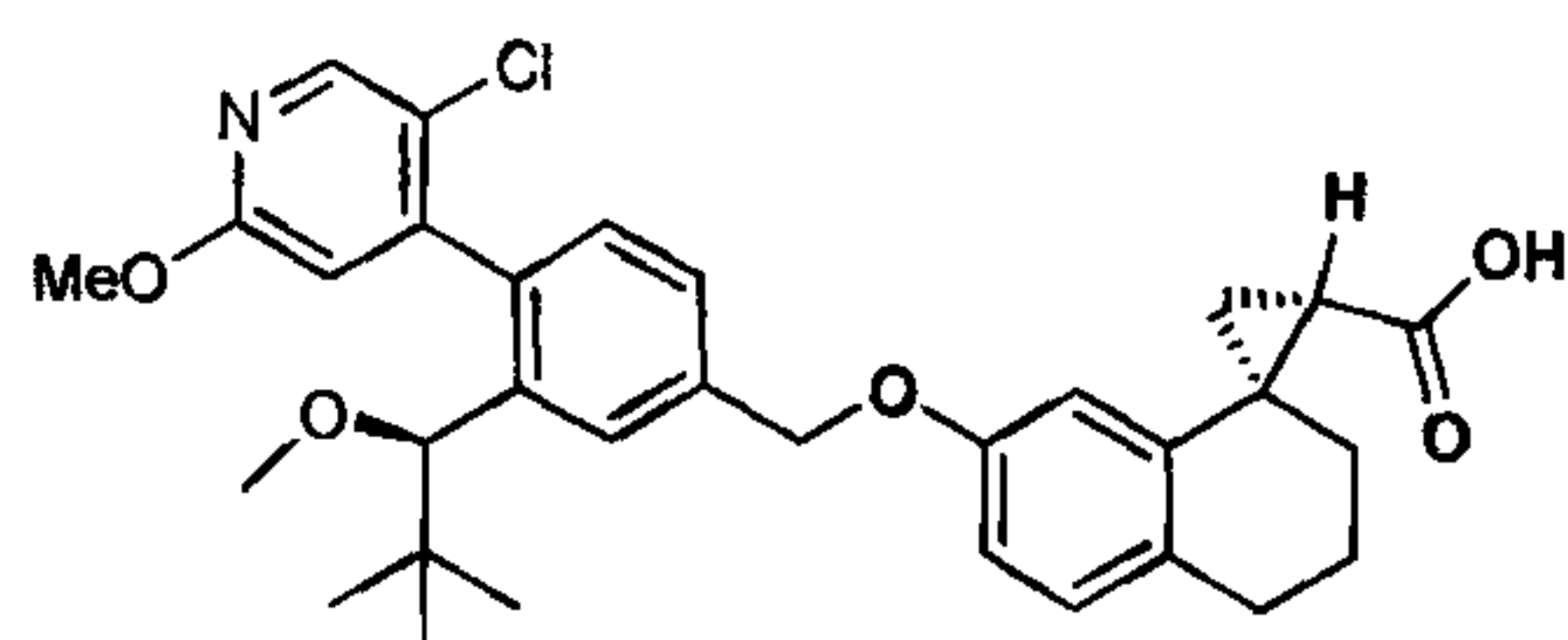
274. The compound



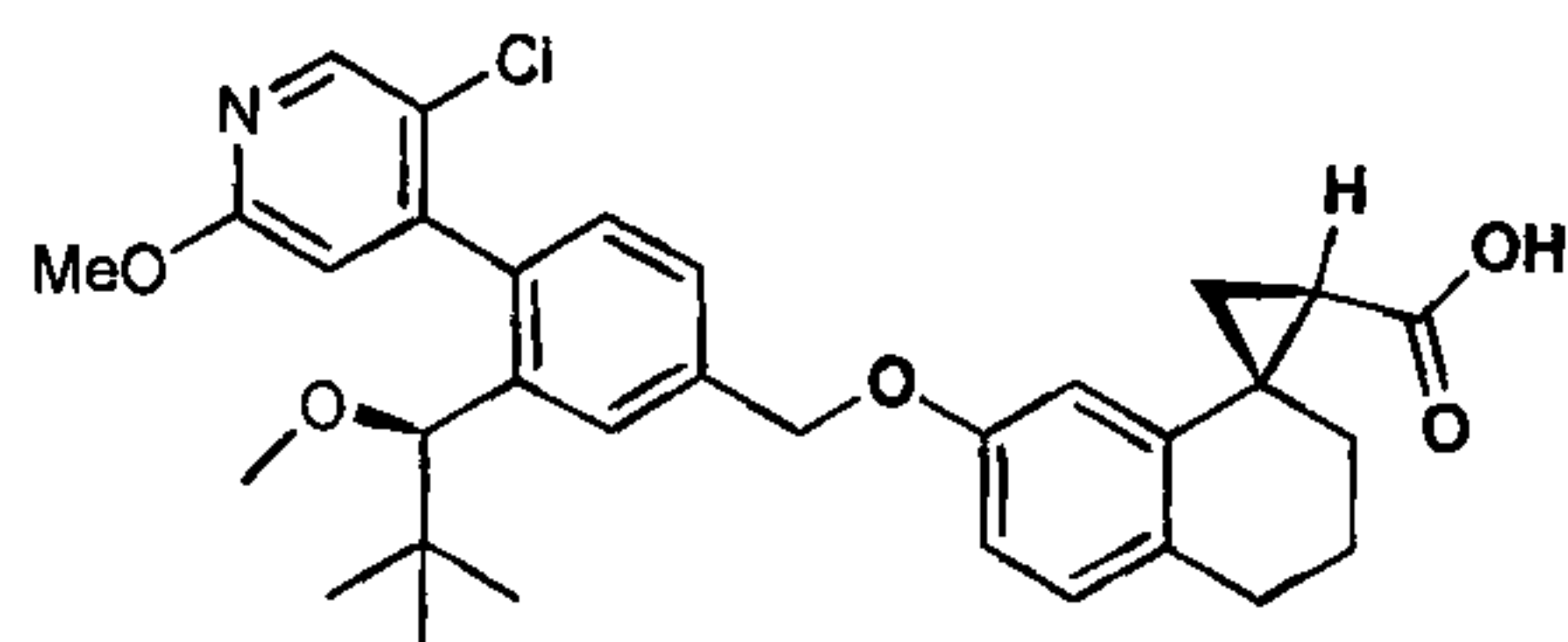
275. The compound



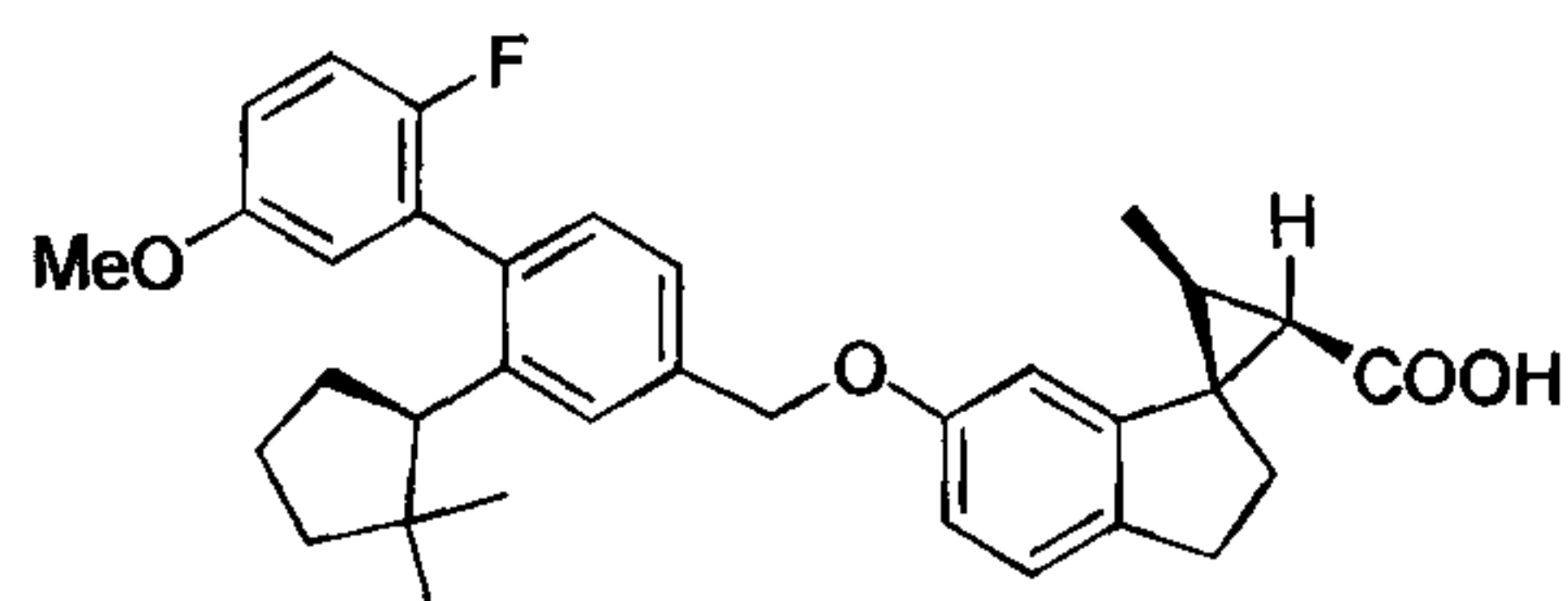
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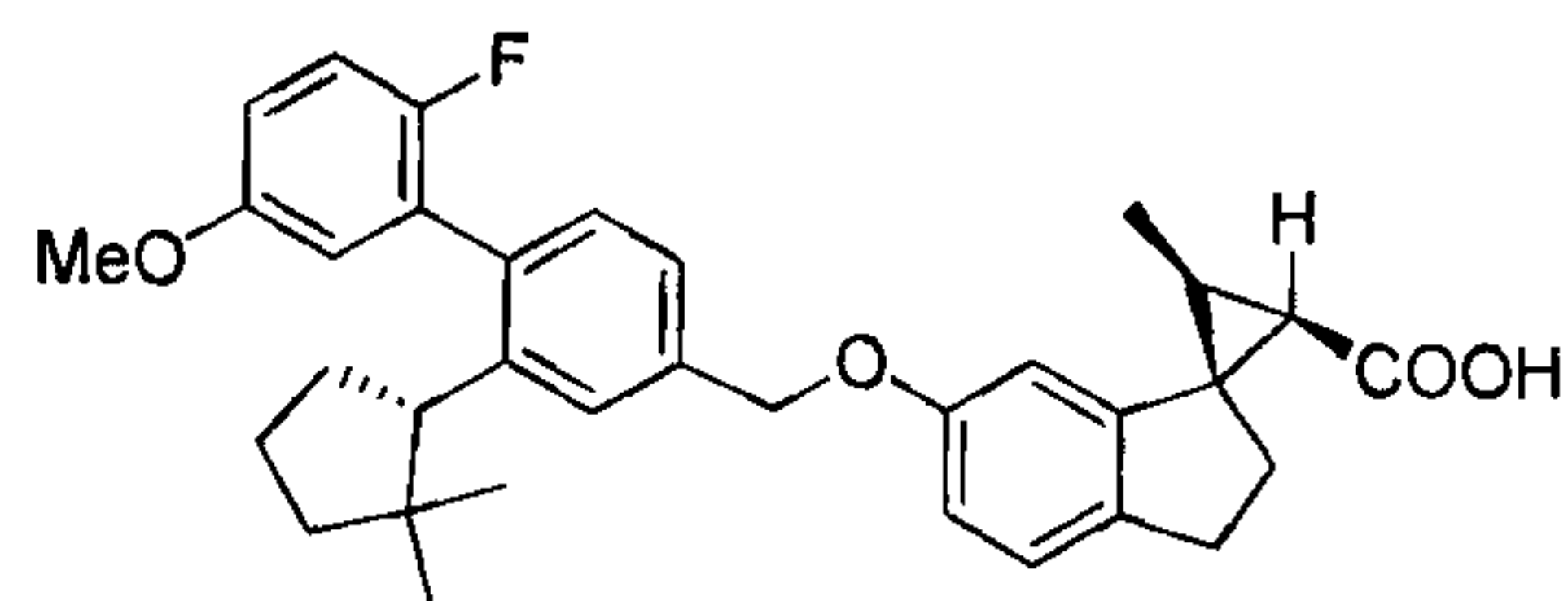
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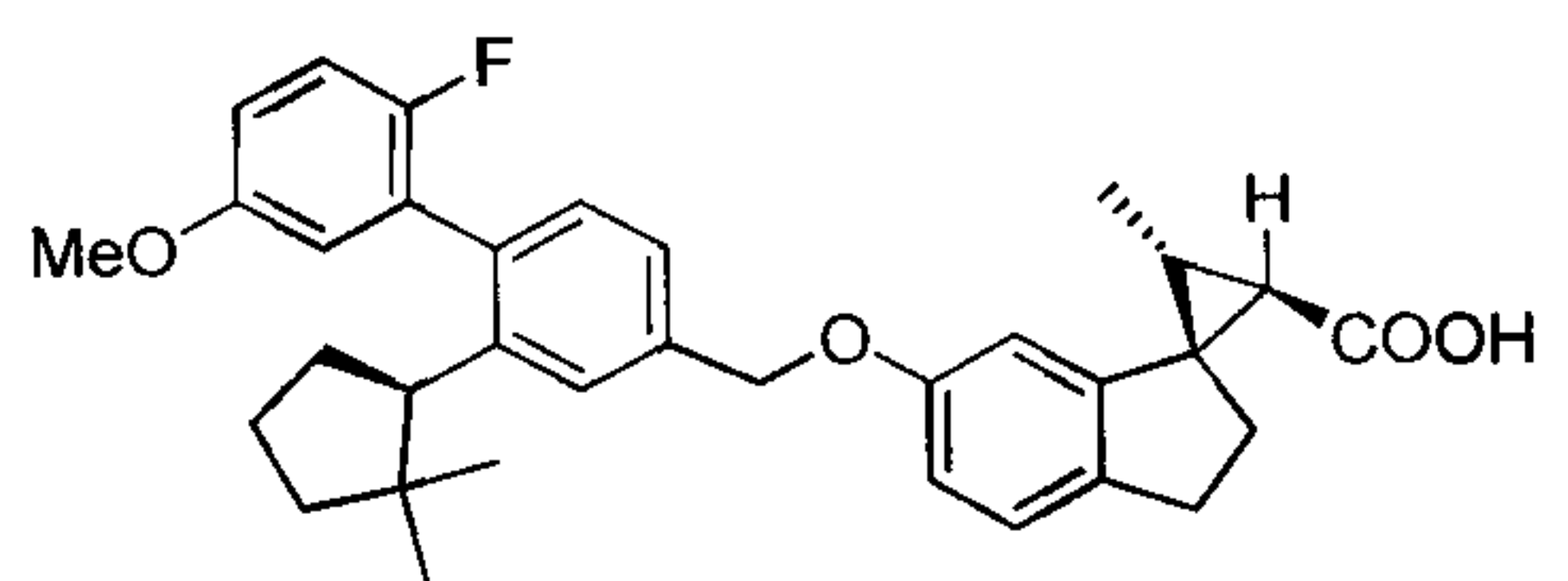
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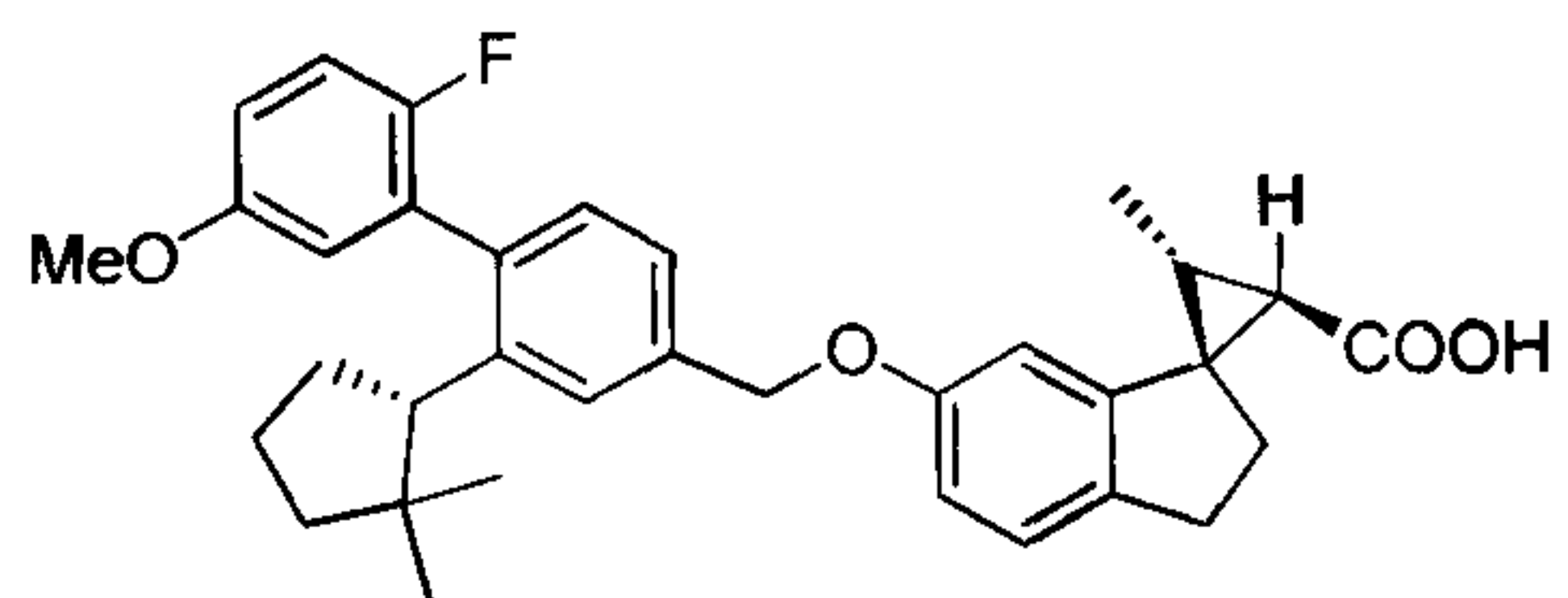
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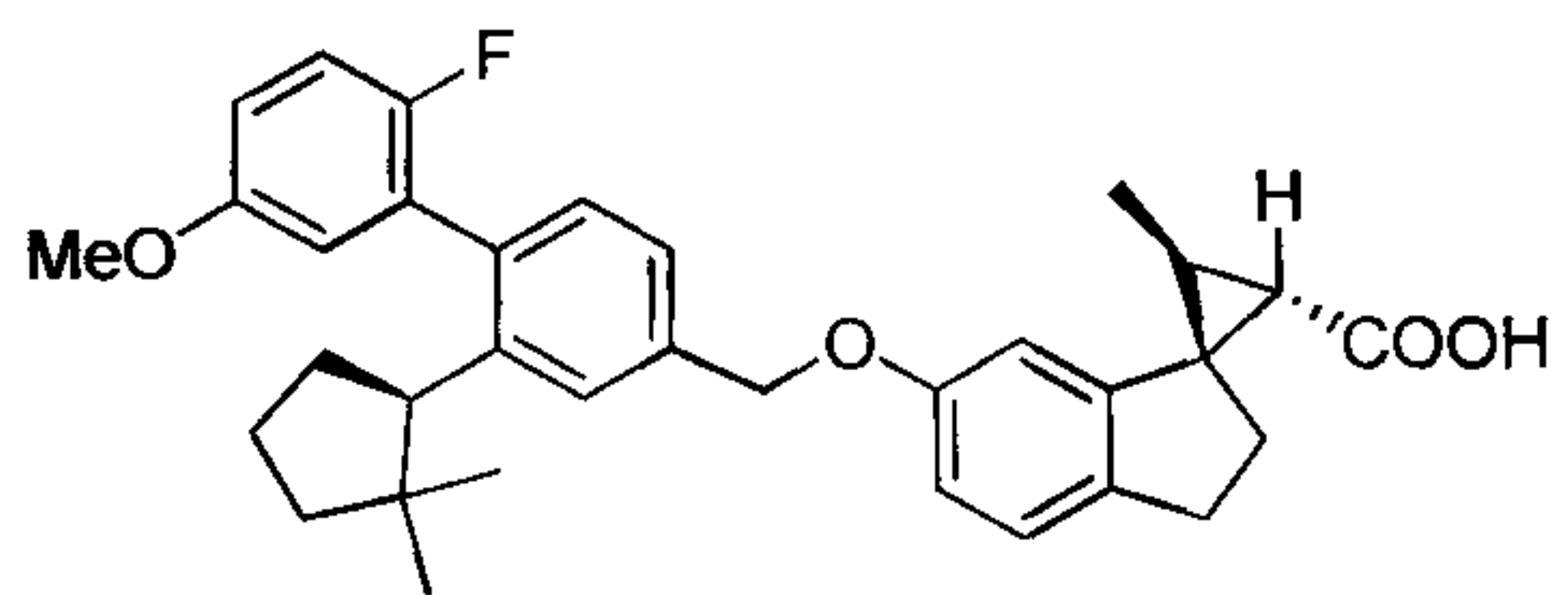
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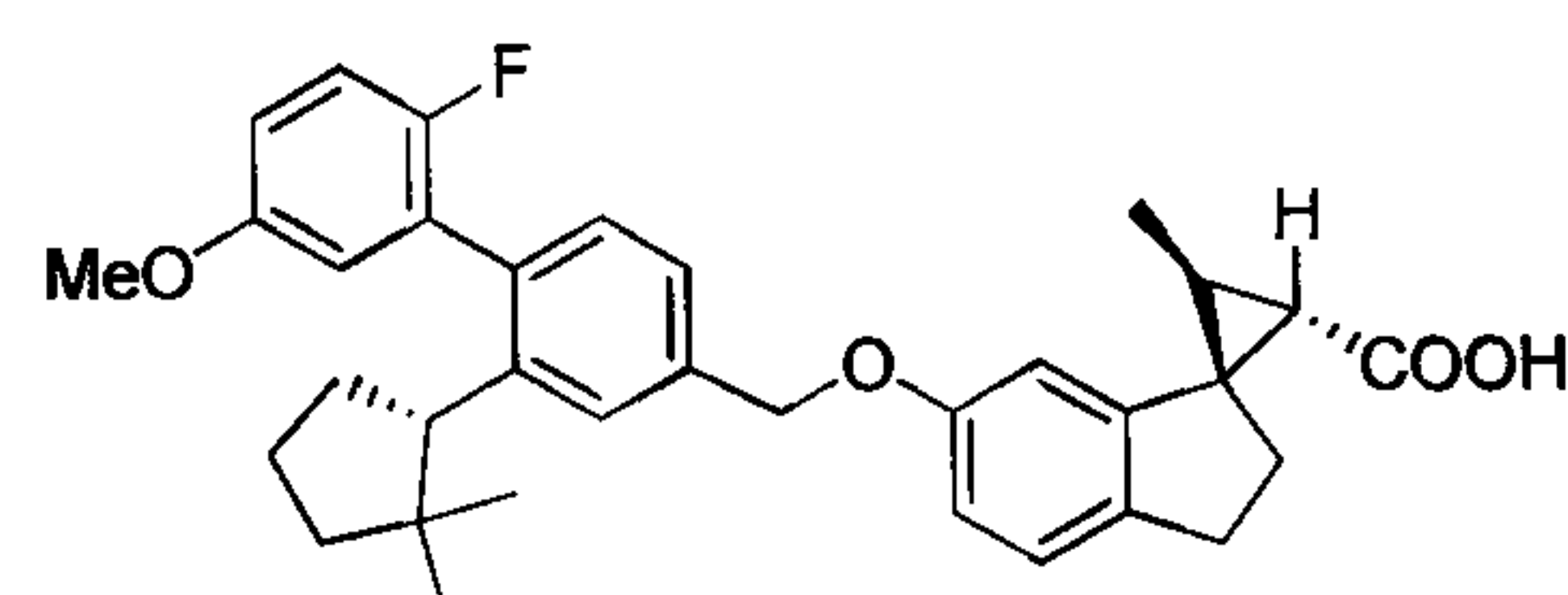
281. The compound



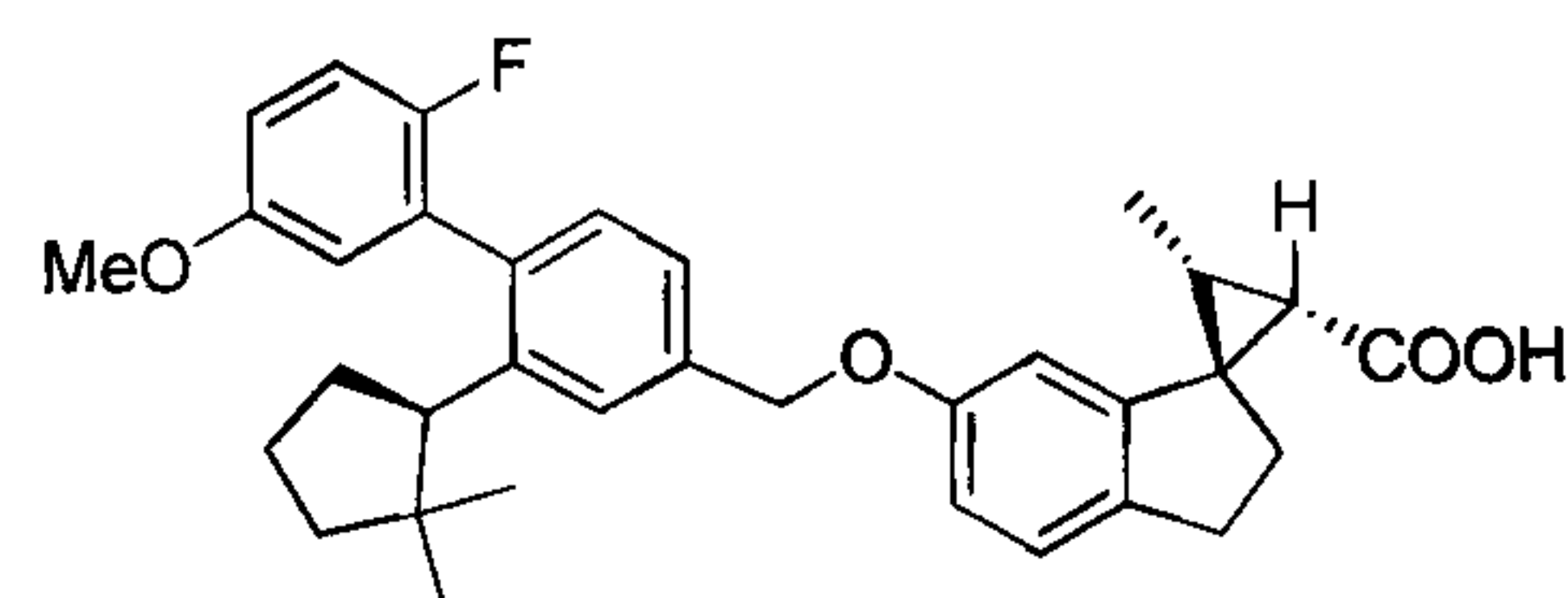
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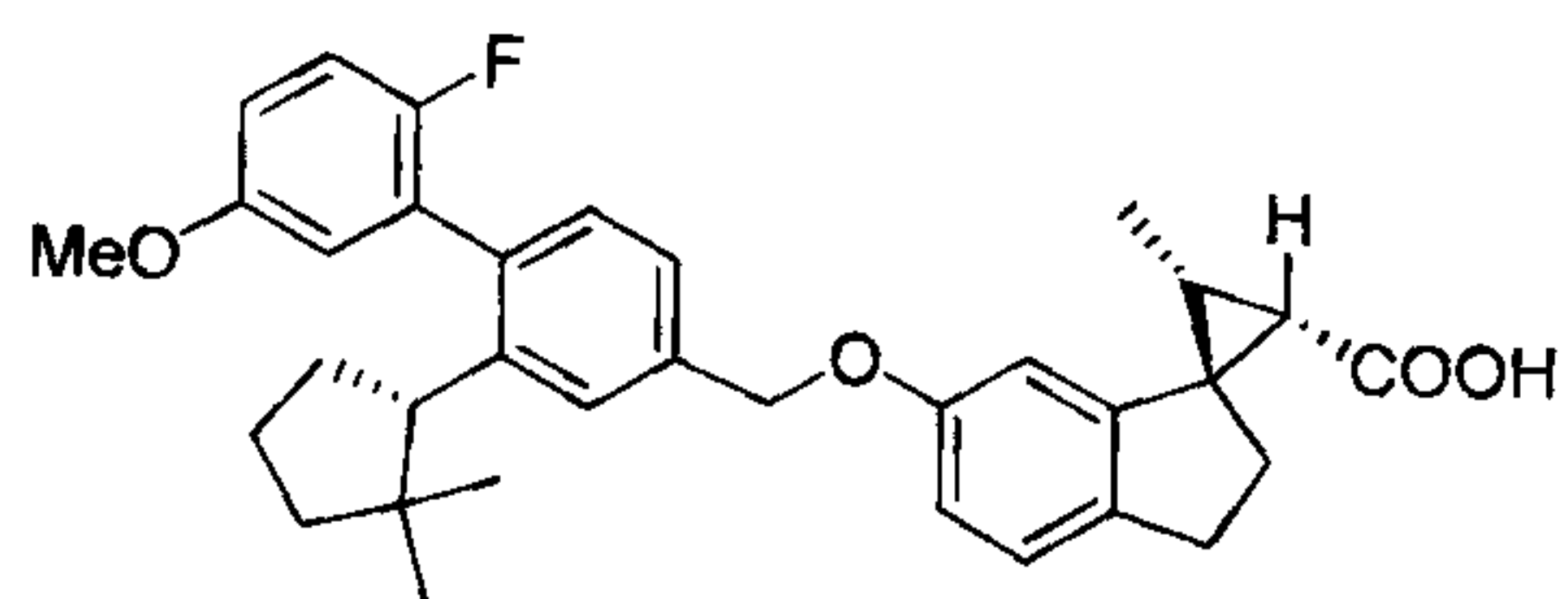
283. The compound



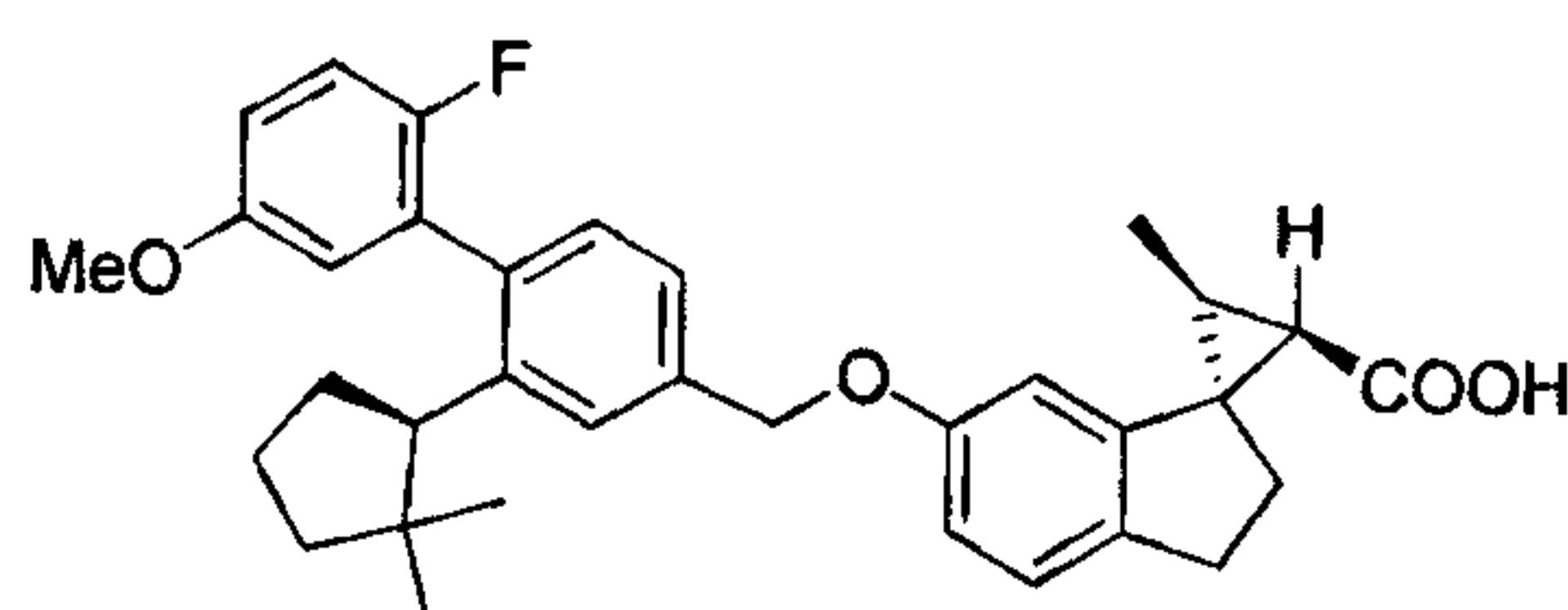
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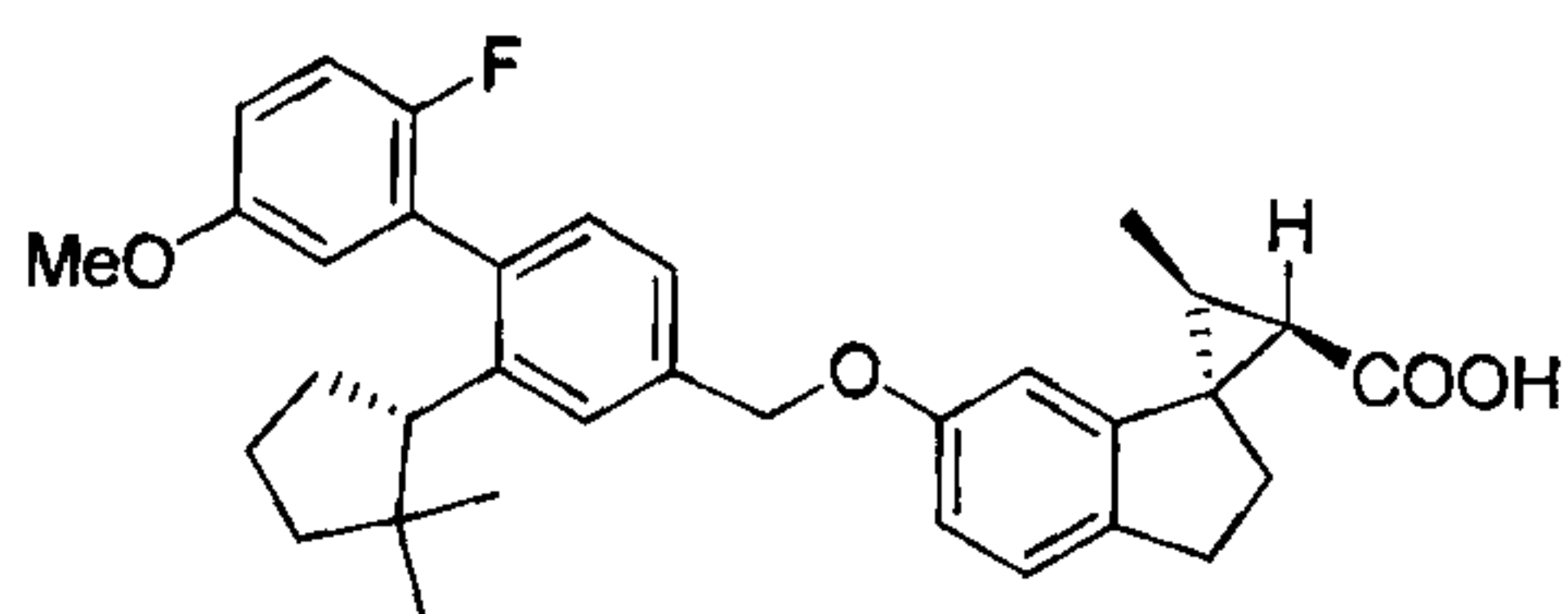
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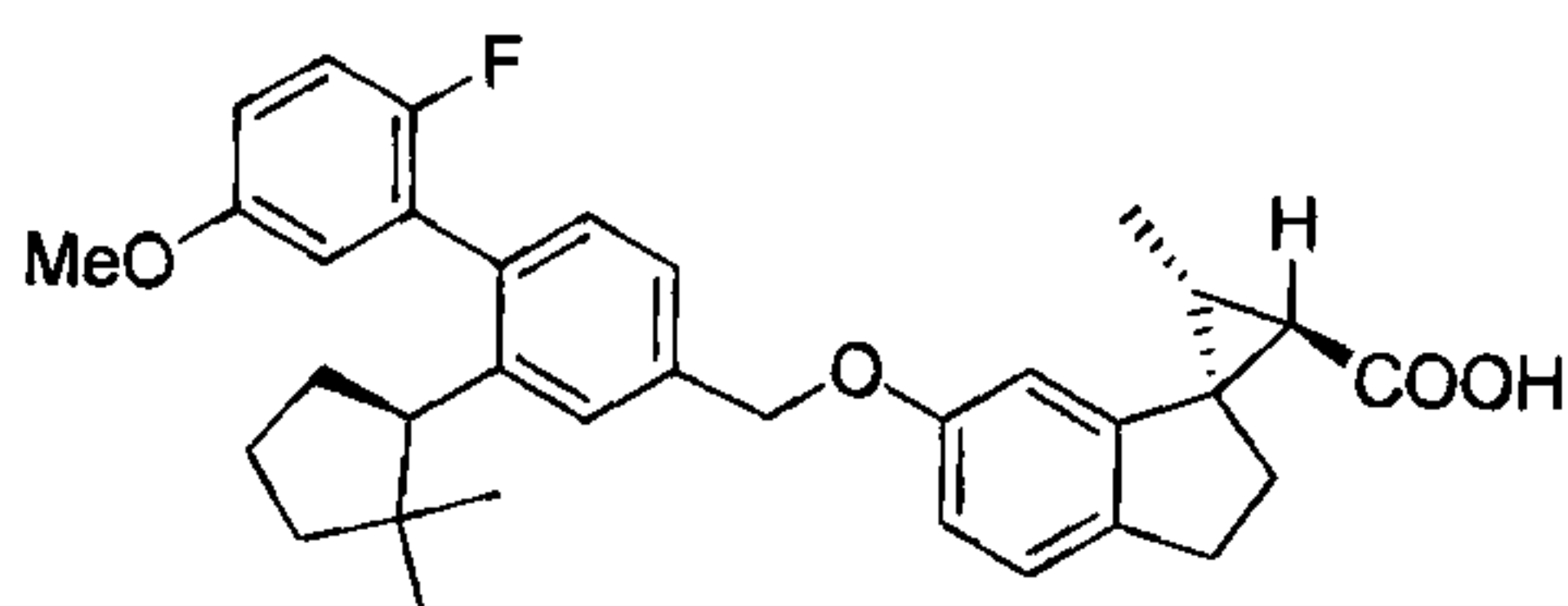
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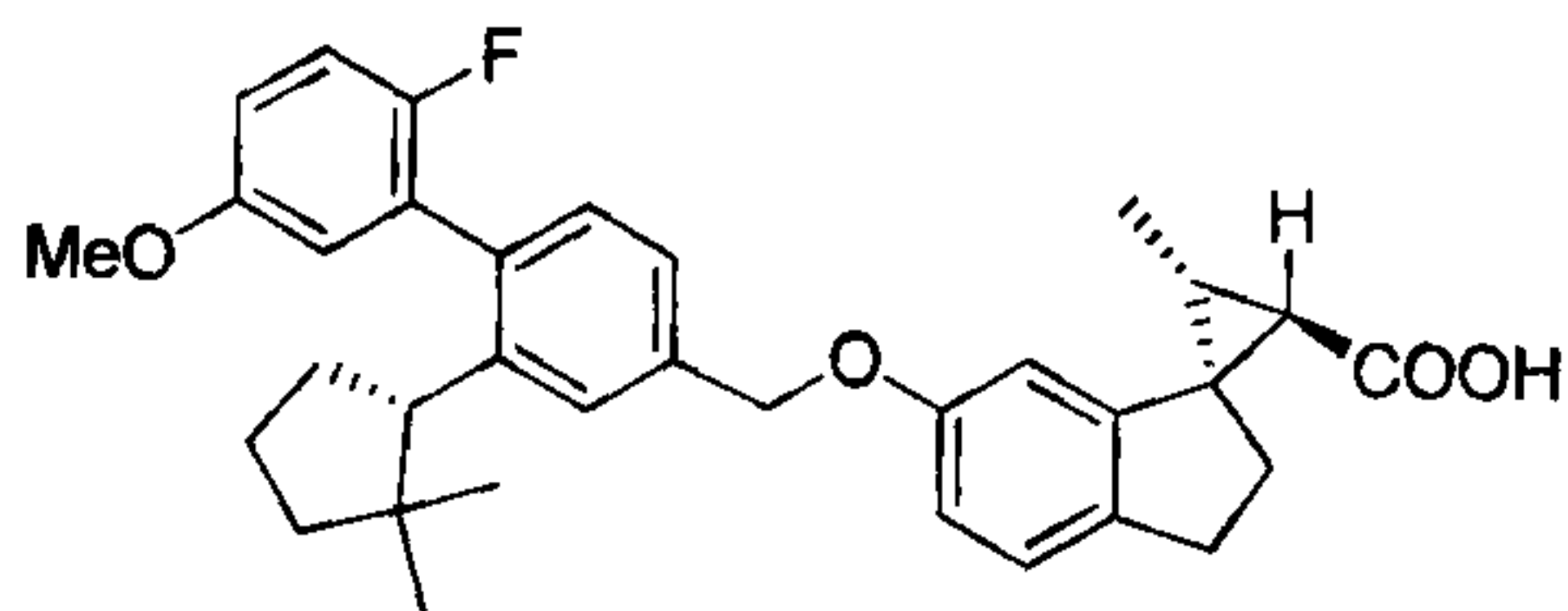
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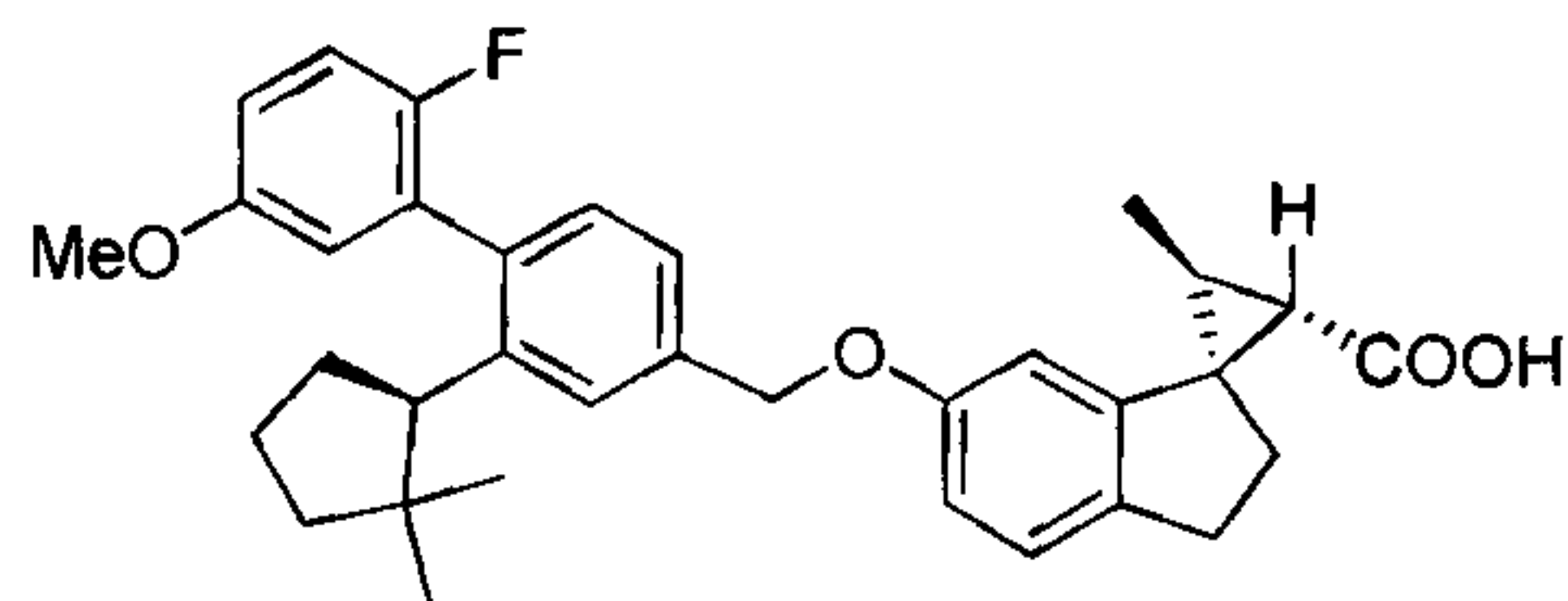
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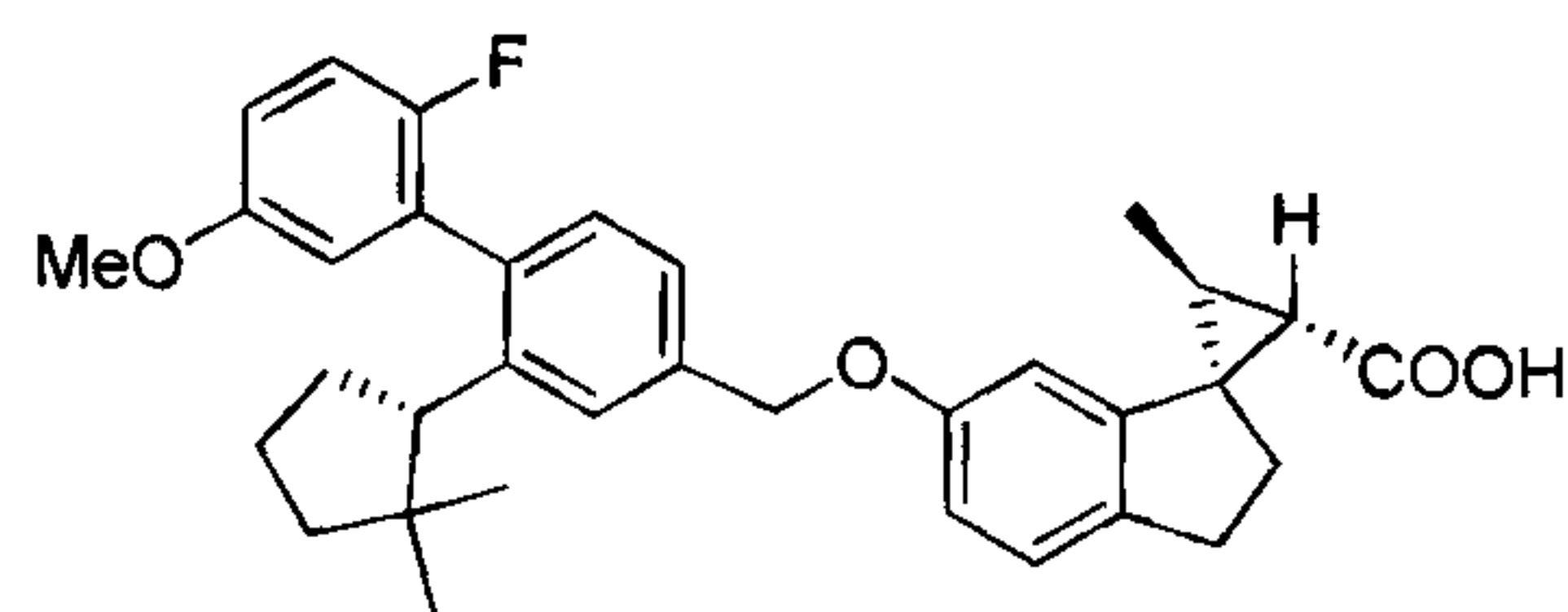
289. The compound



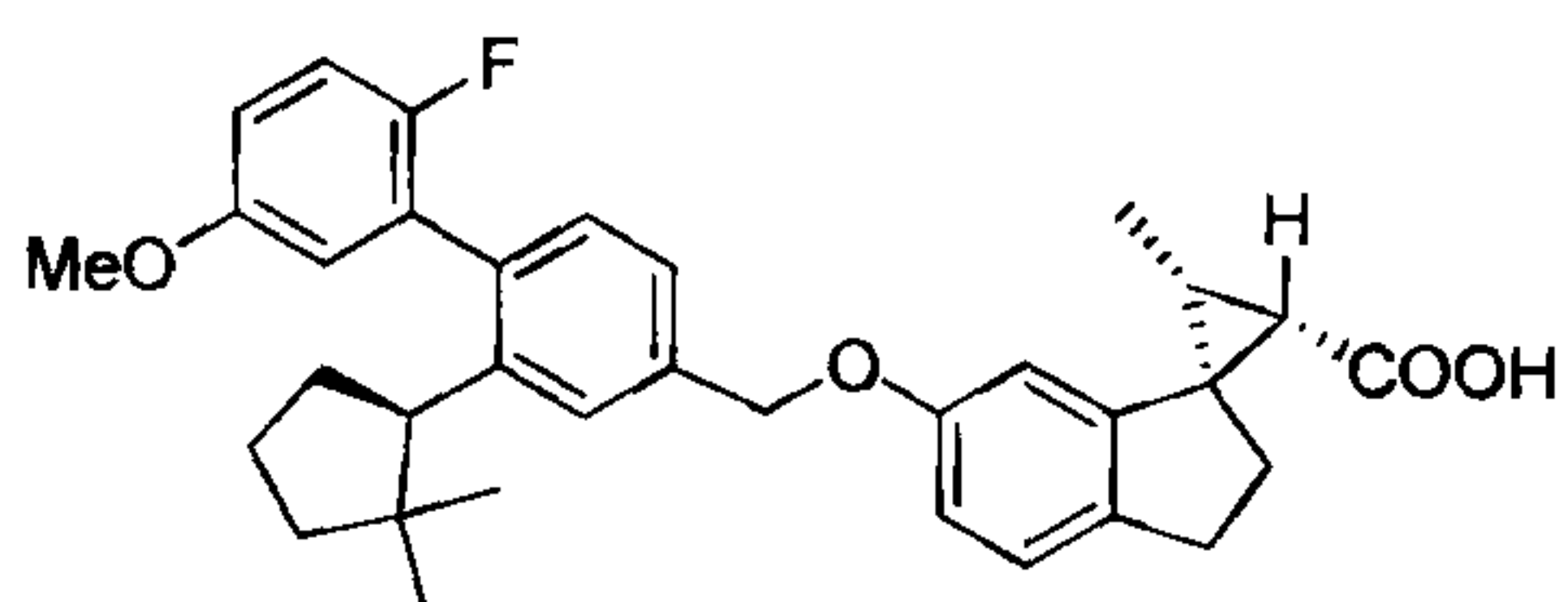
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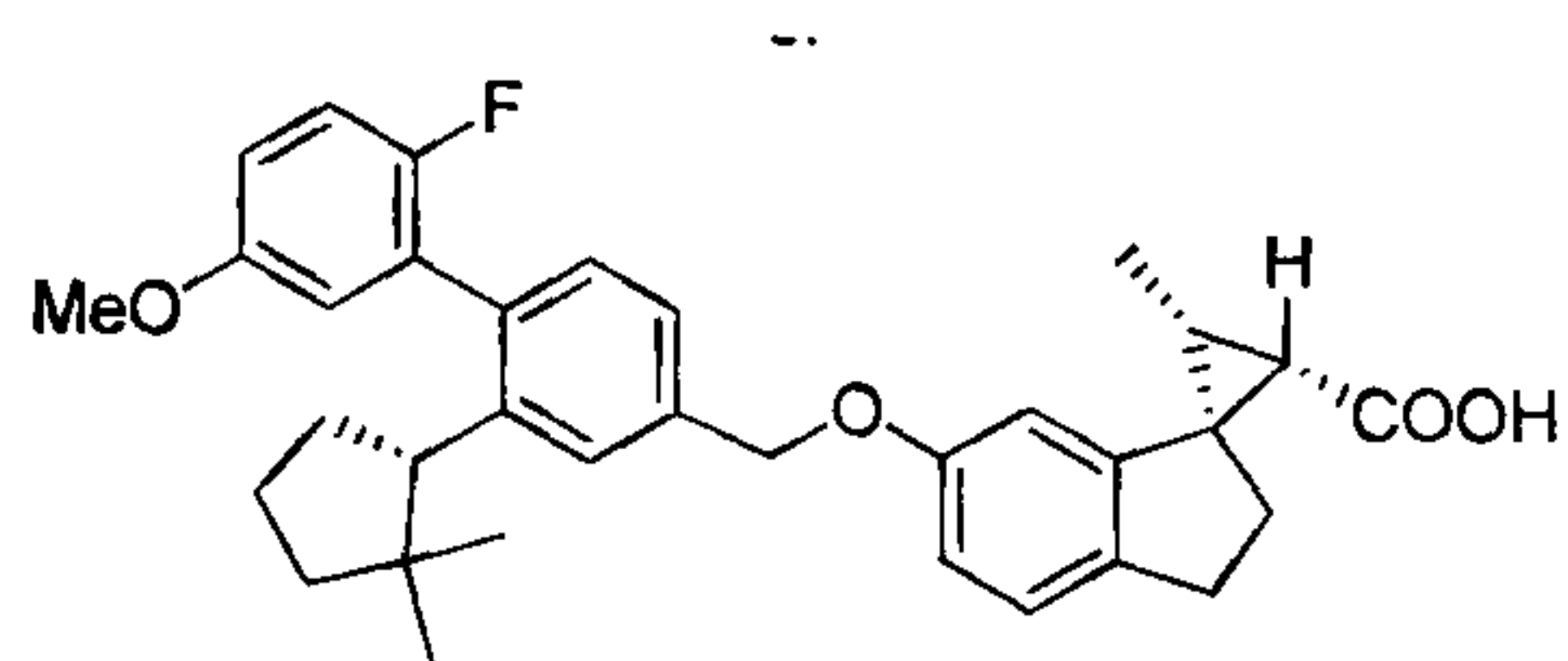
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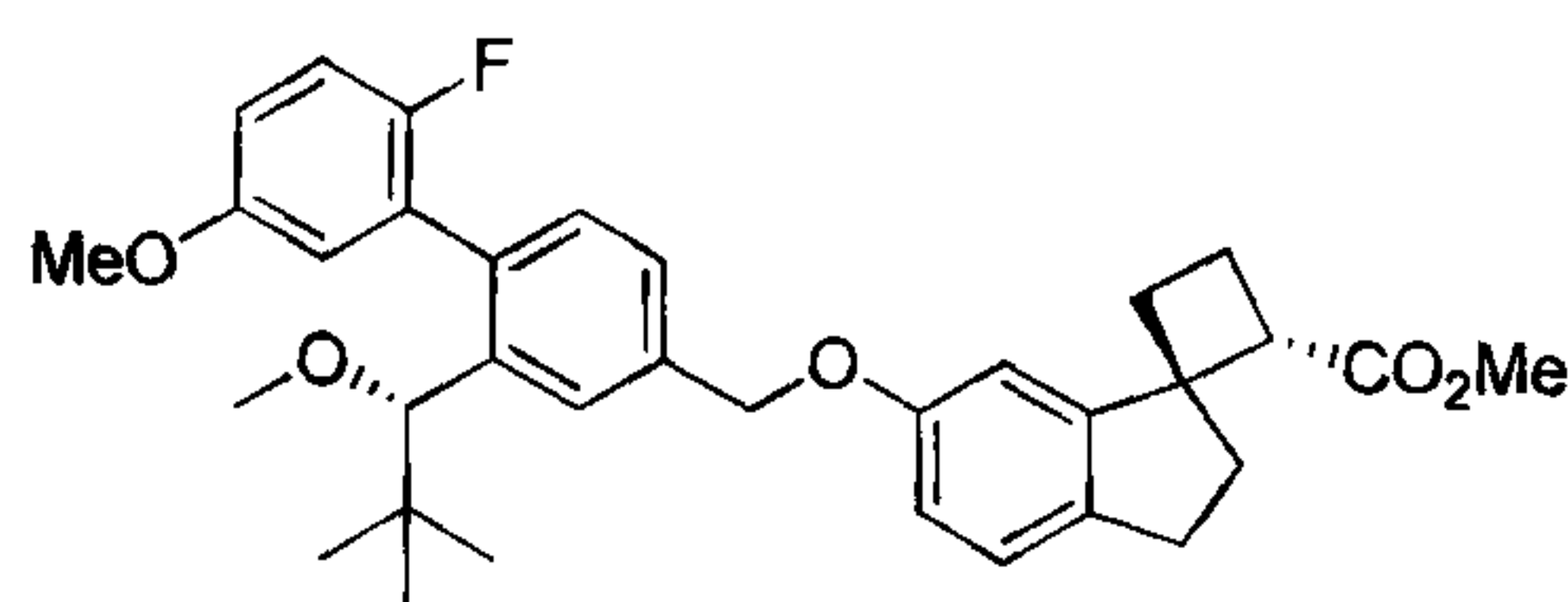
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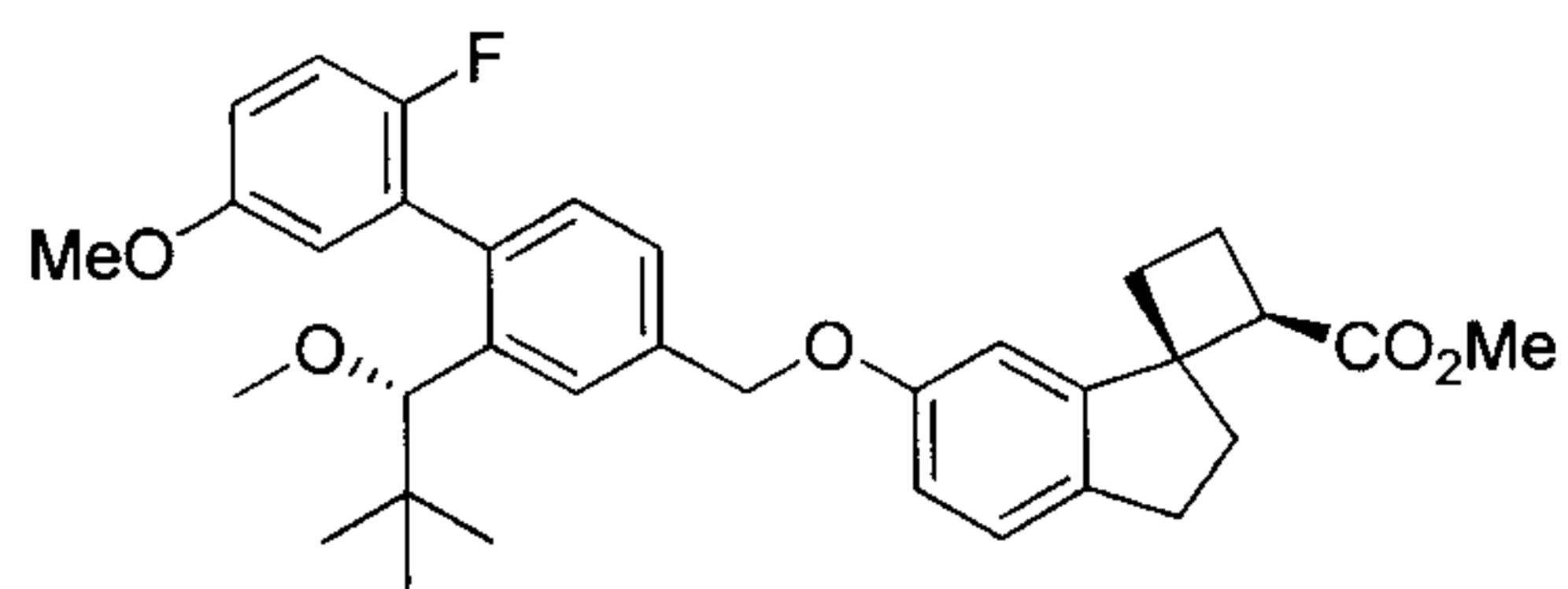
293. The compound



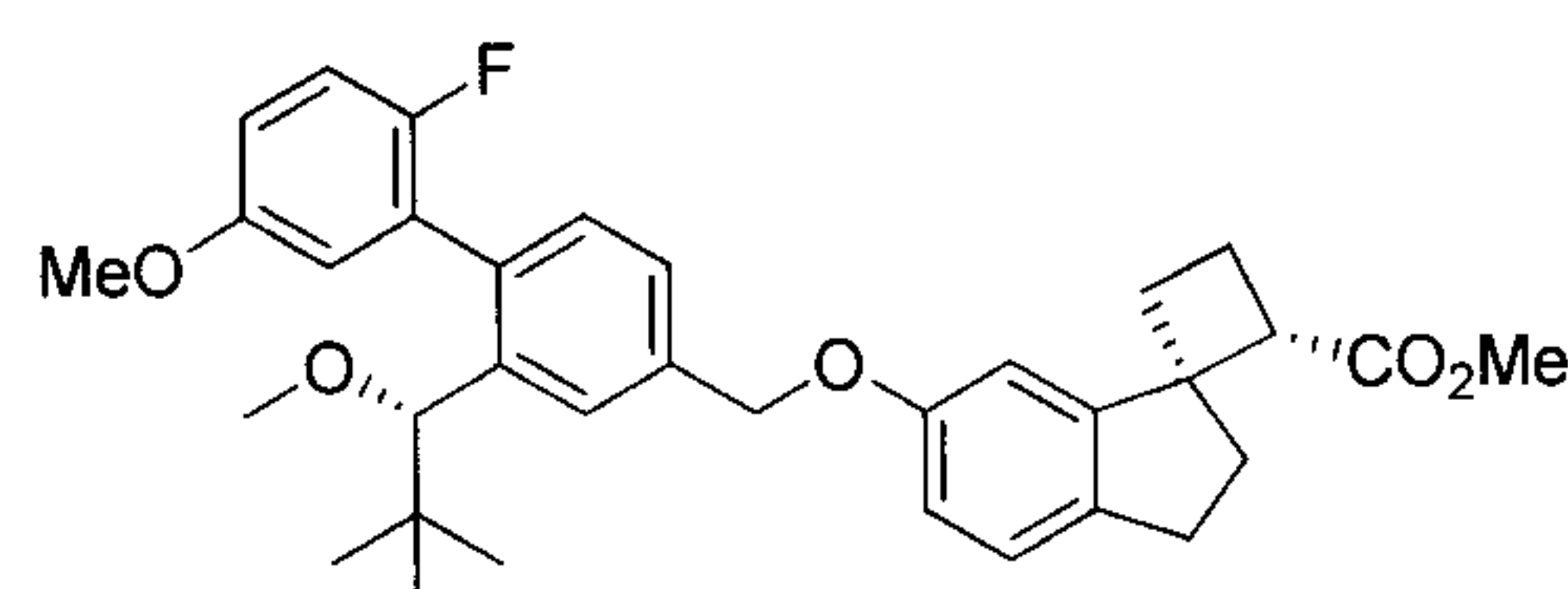
294. The compound



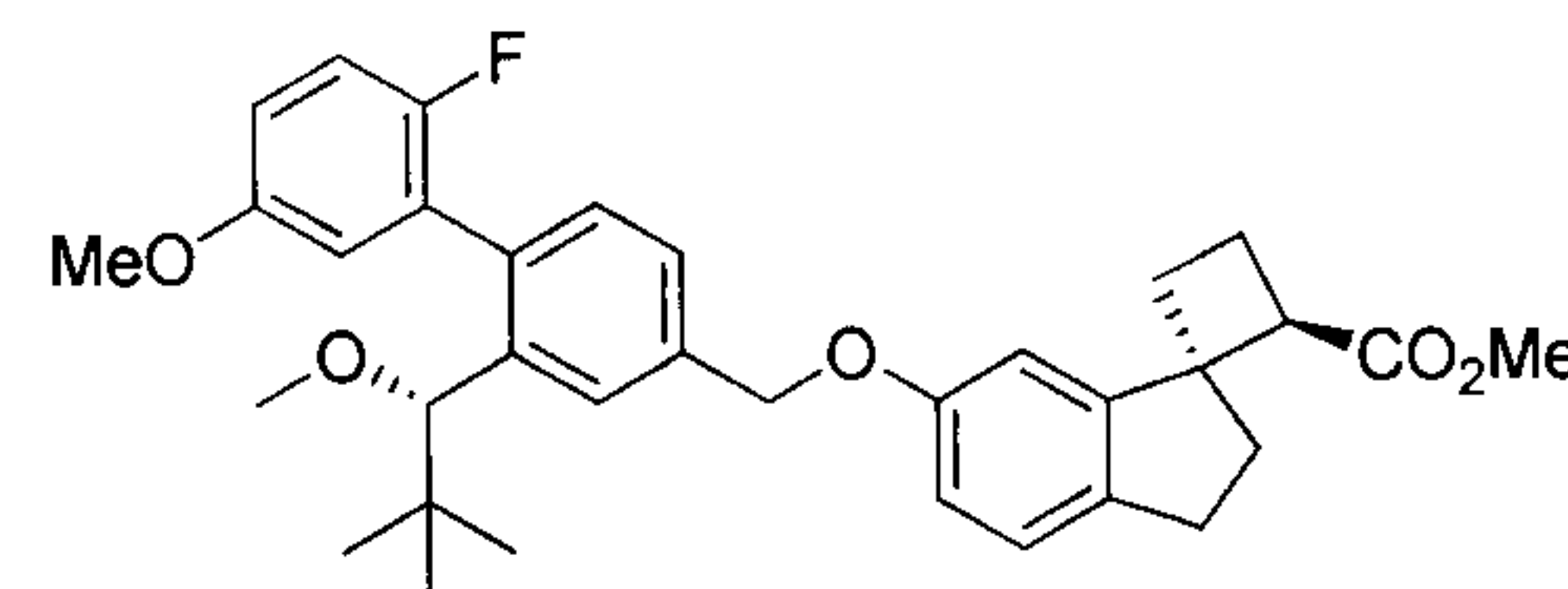
295. The compound



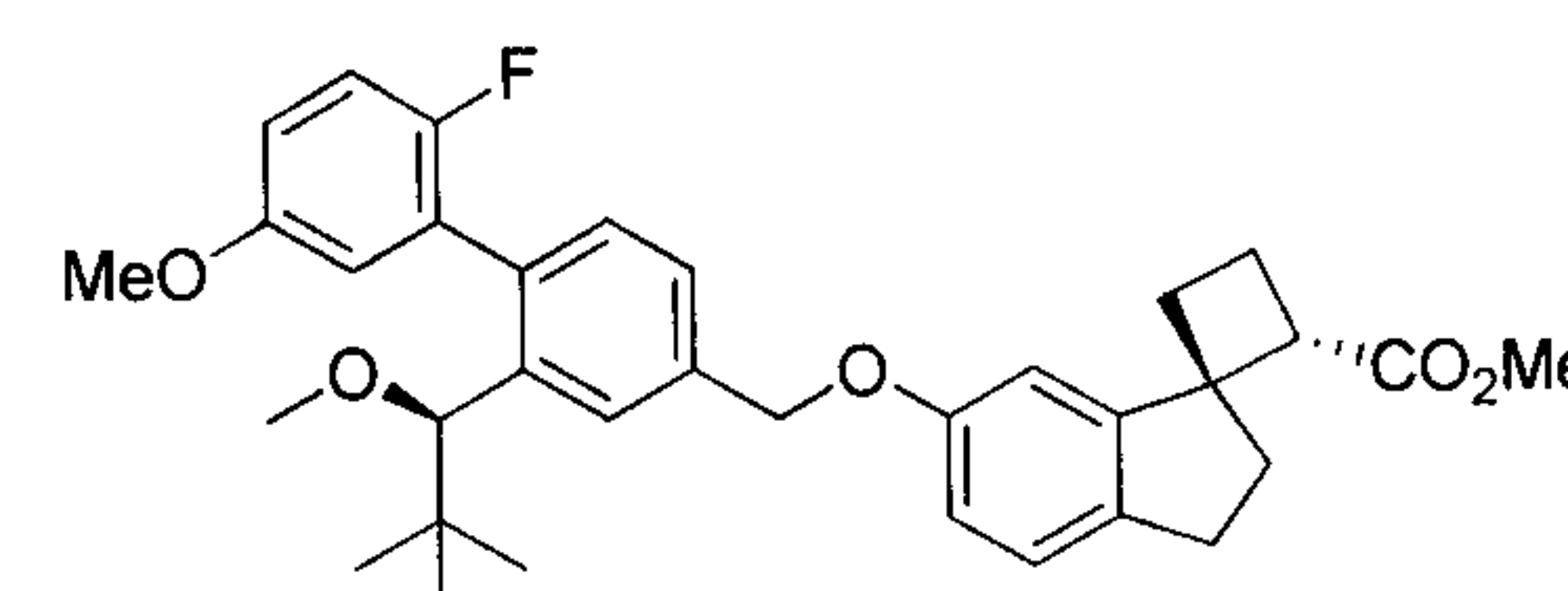
296. The compound



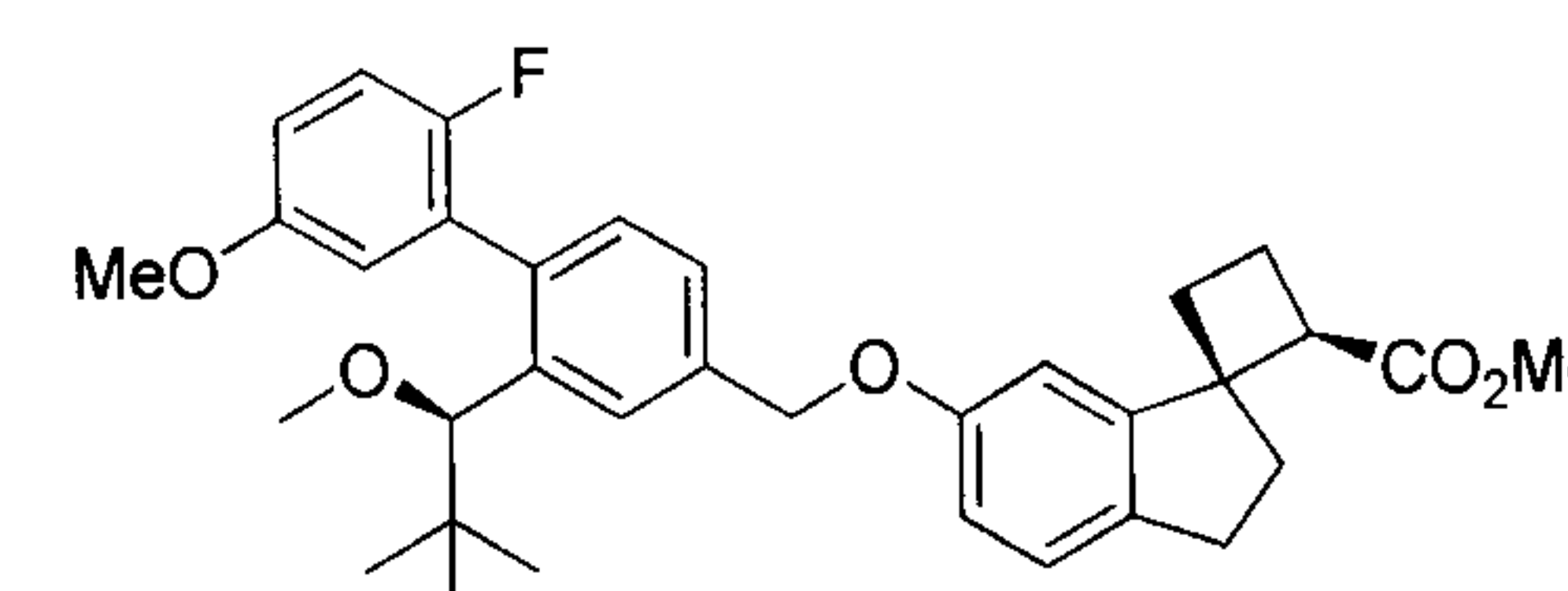
297. The compound



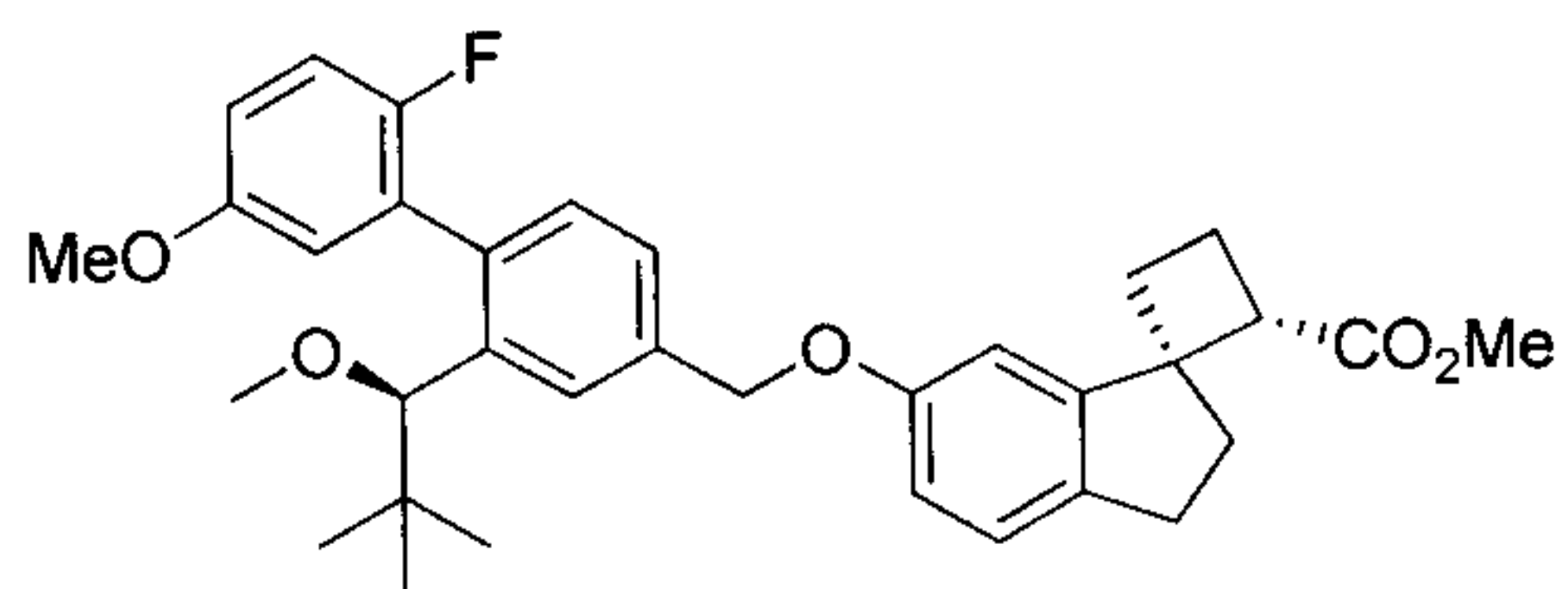
298. The compound



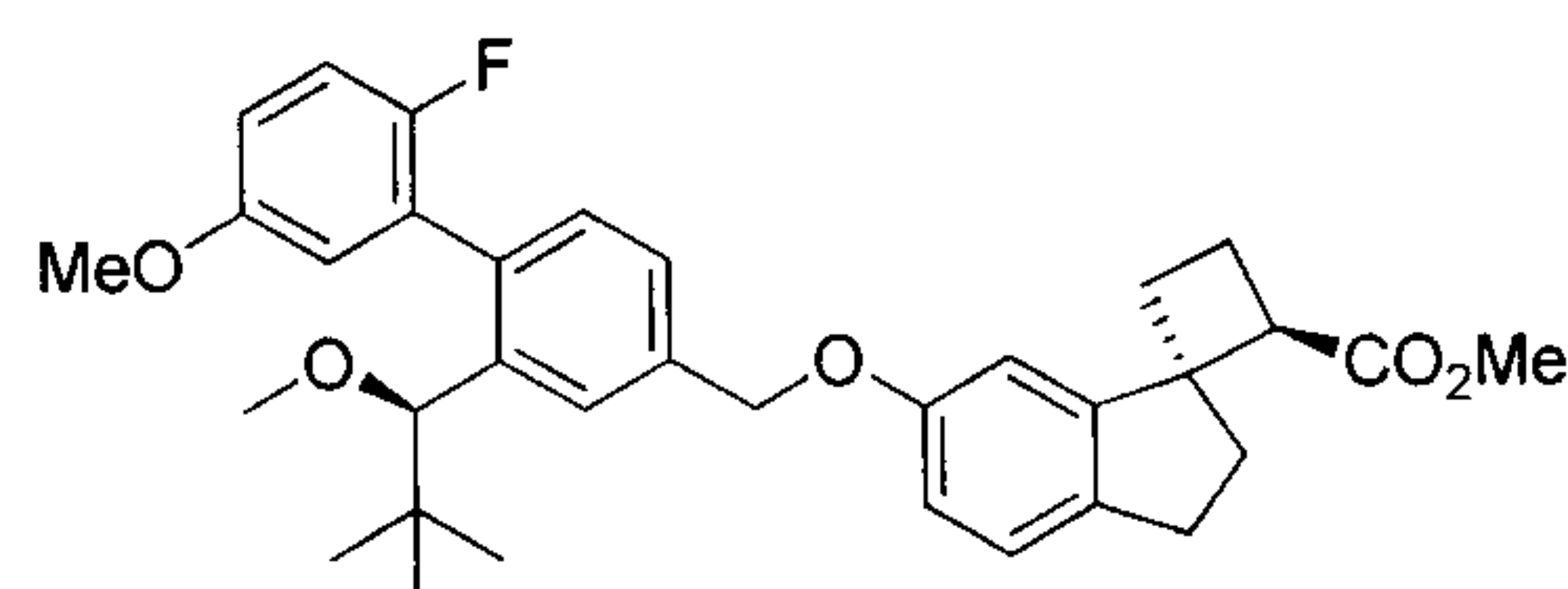
299. The compound



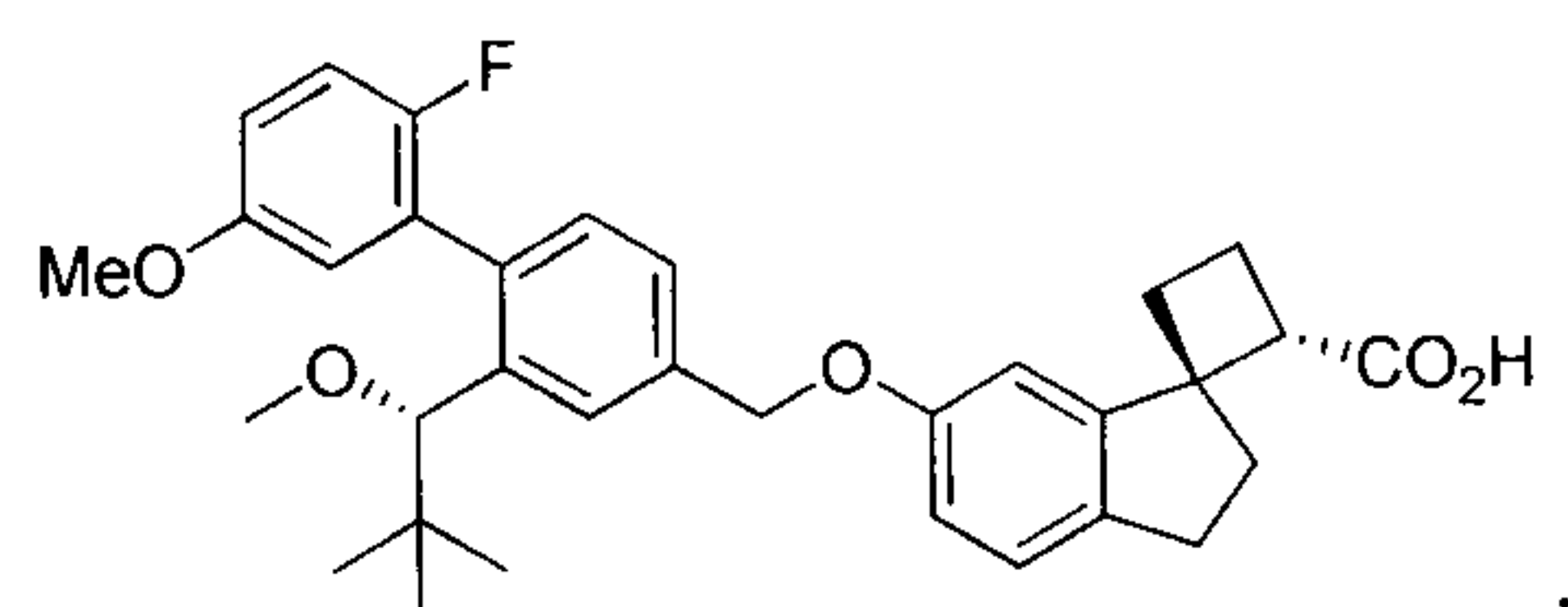
300. The compound



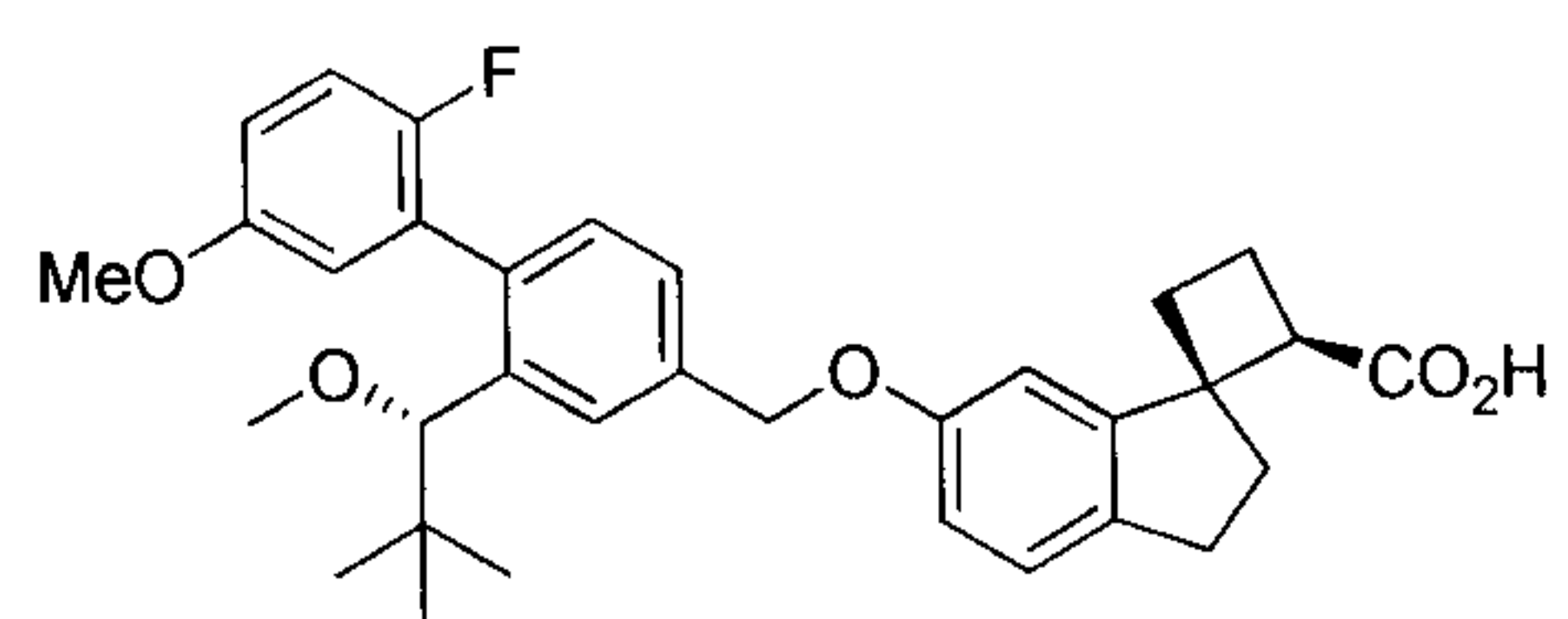
301. The compound



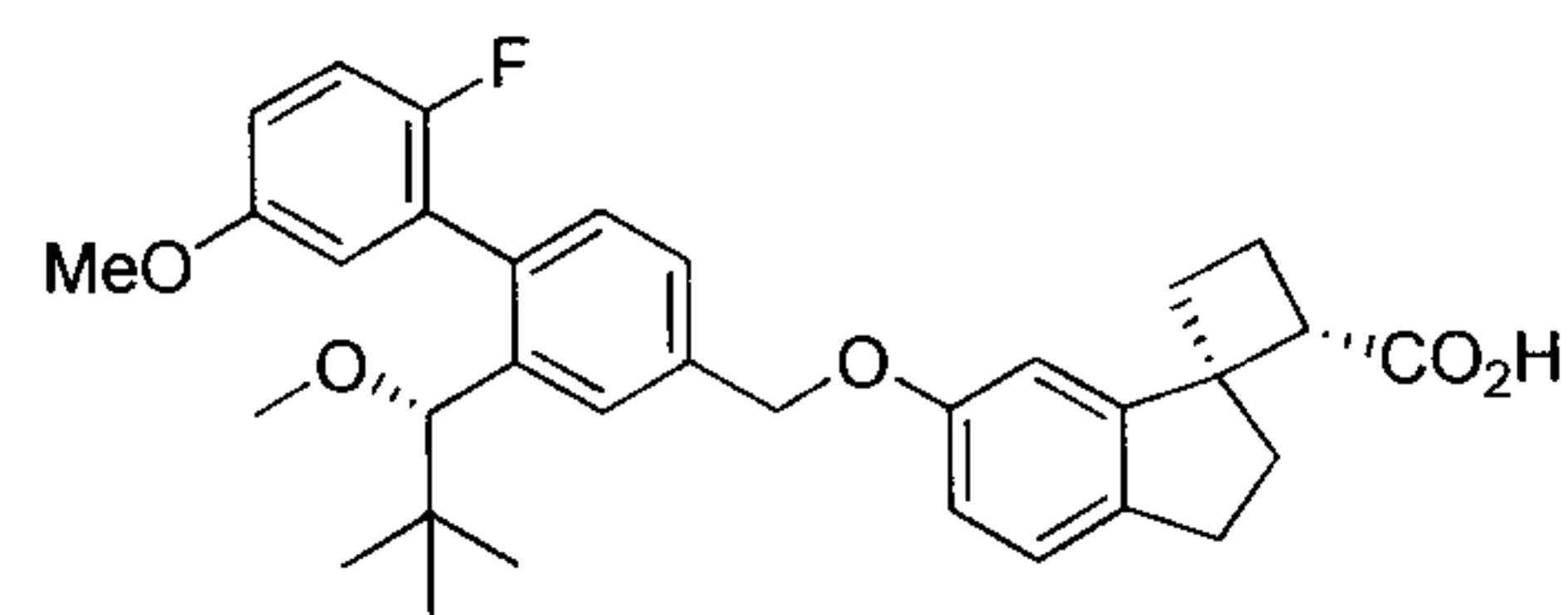
302. The compound



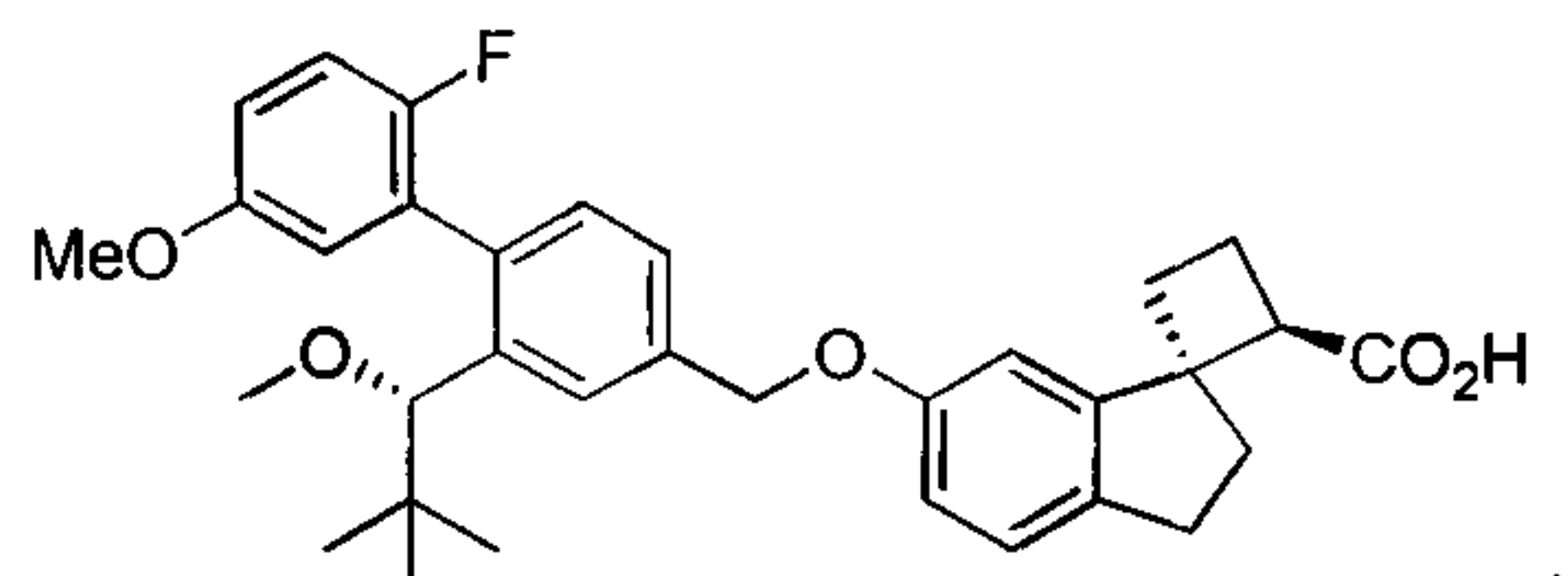
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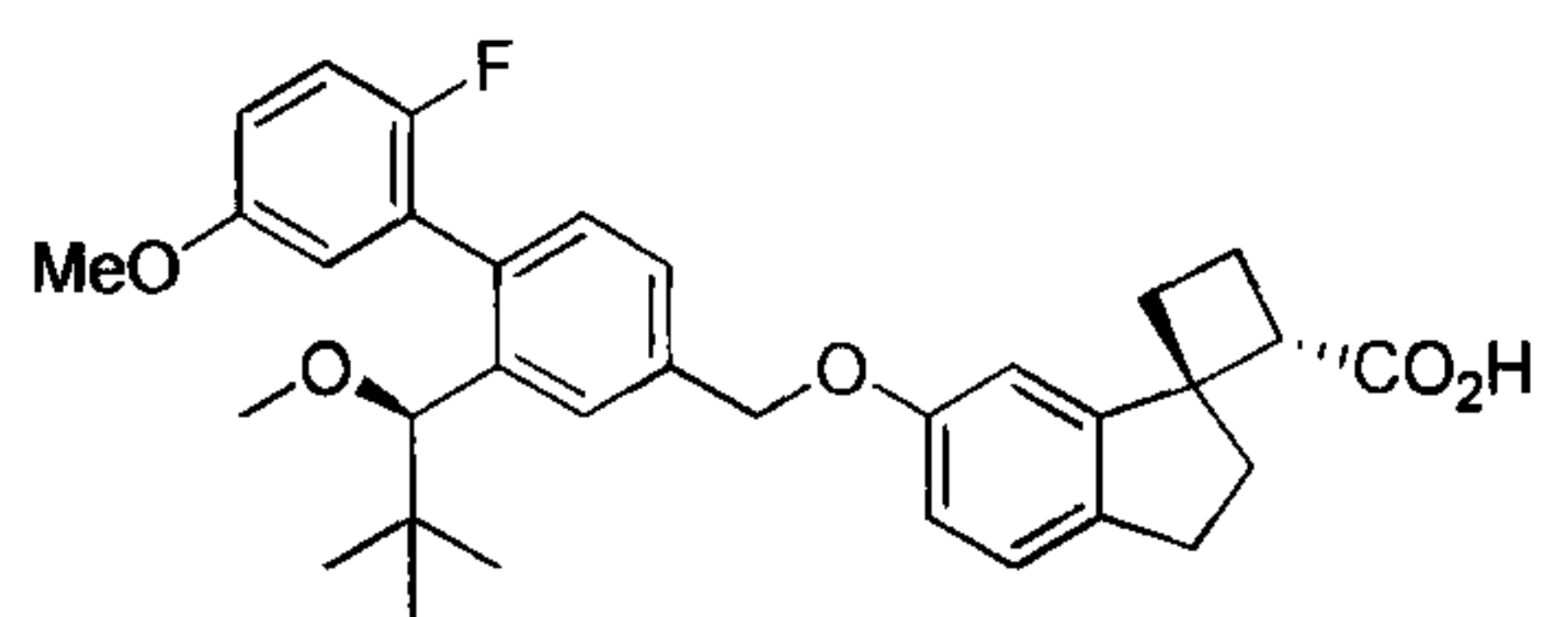
304. The compound



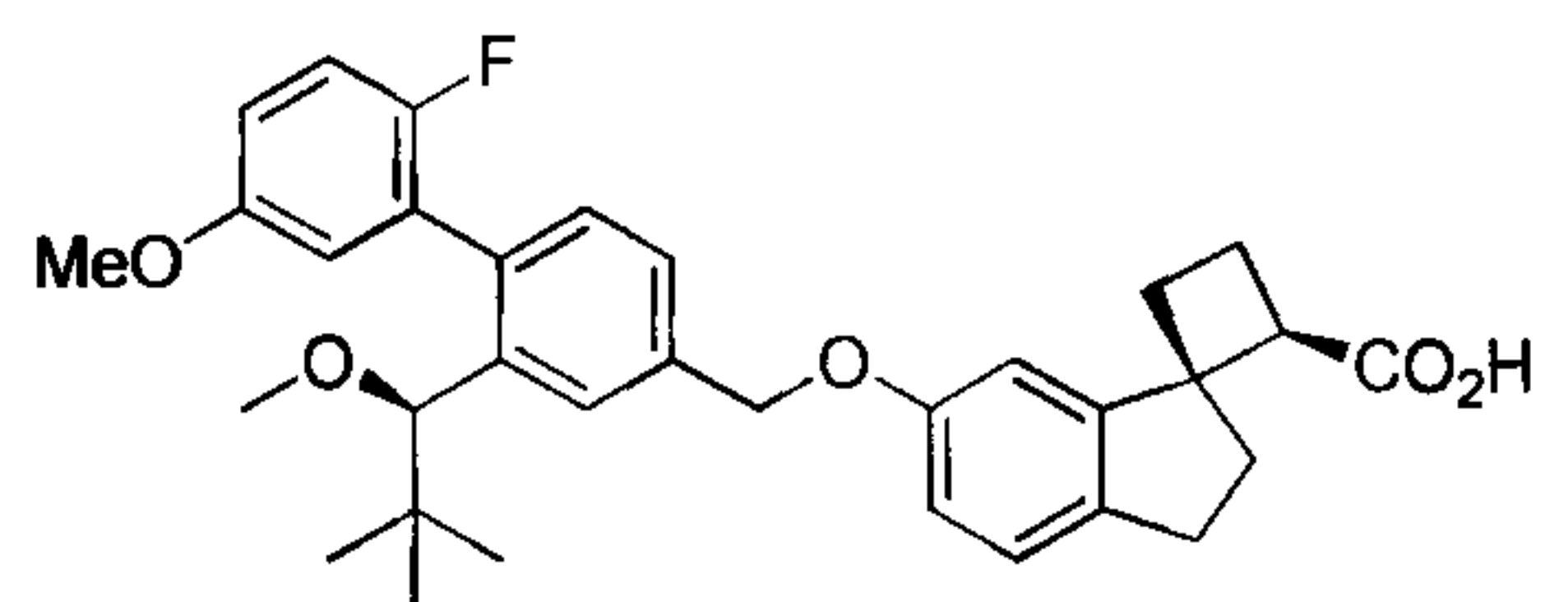
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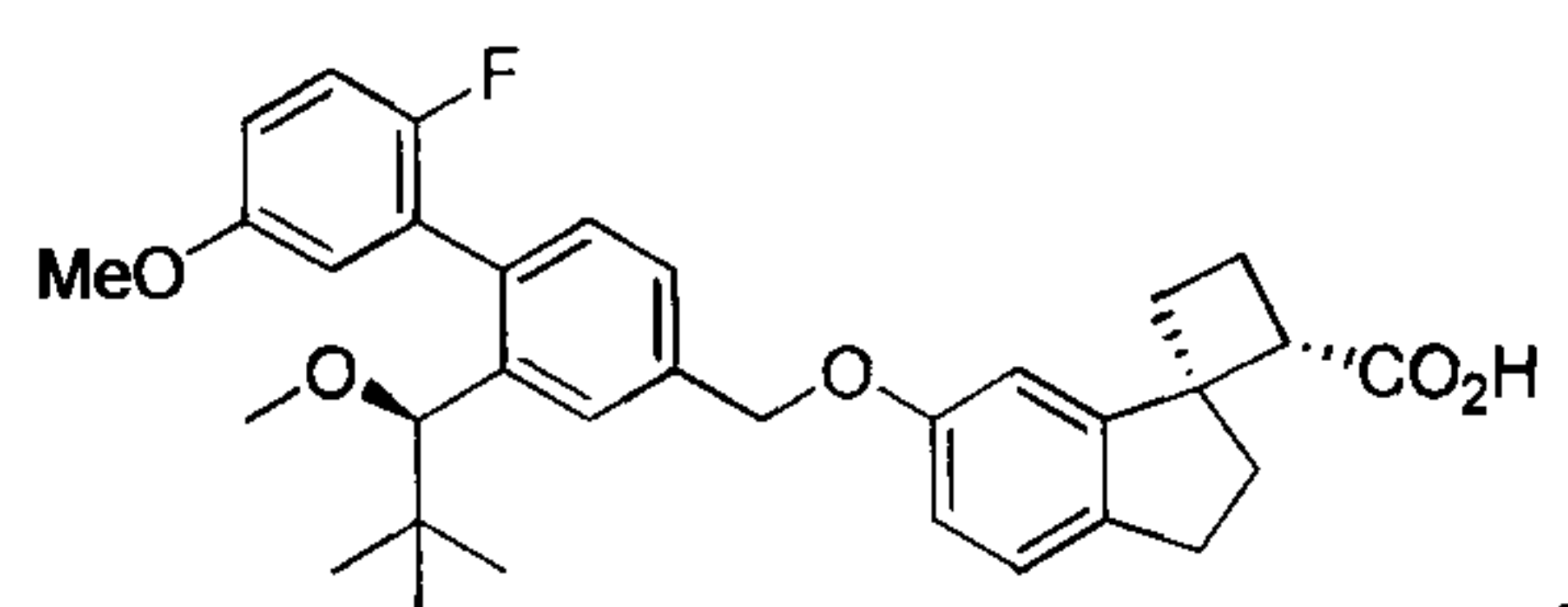
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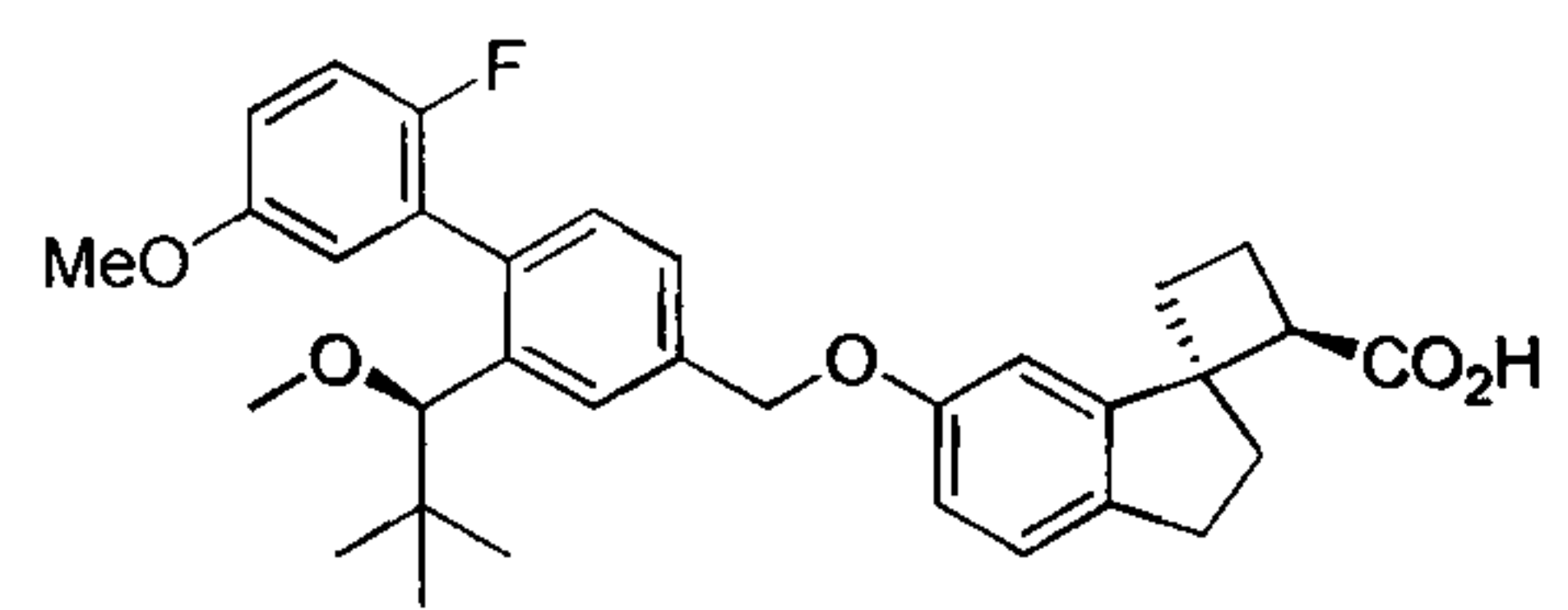
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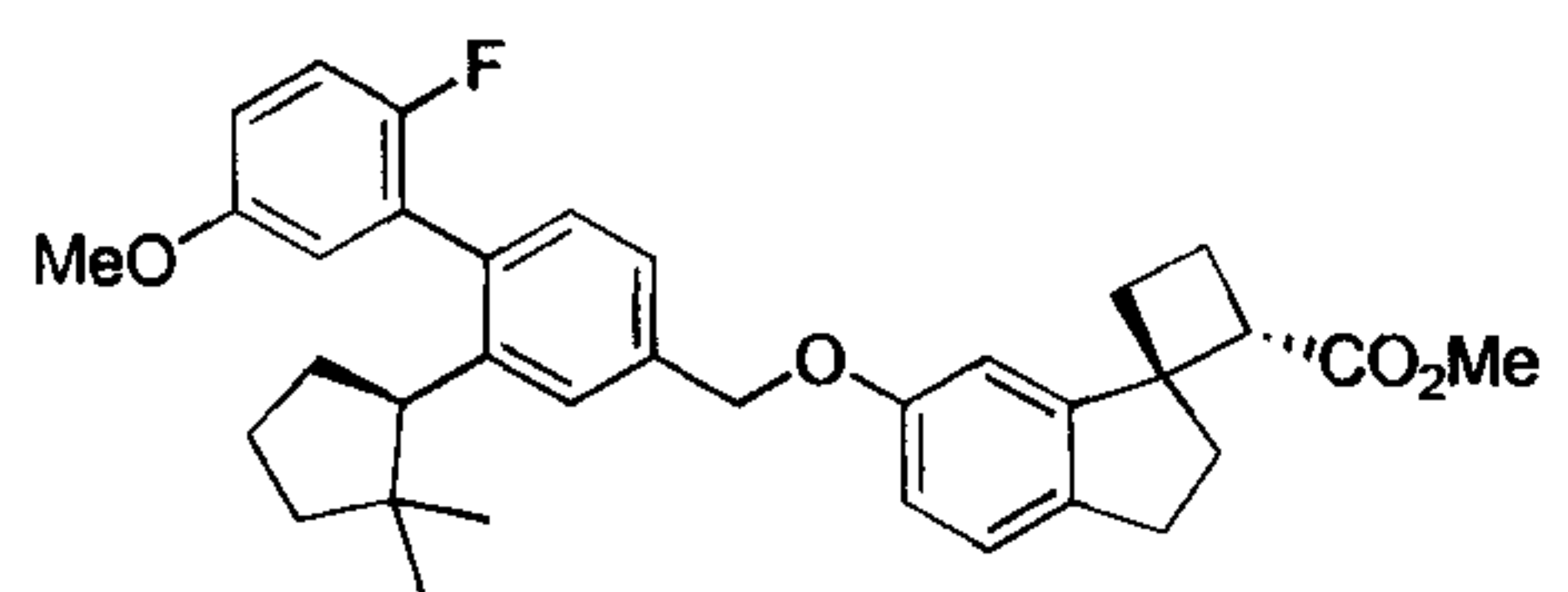
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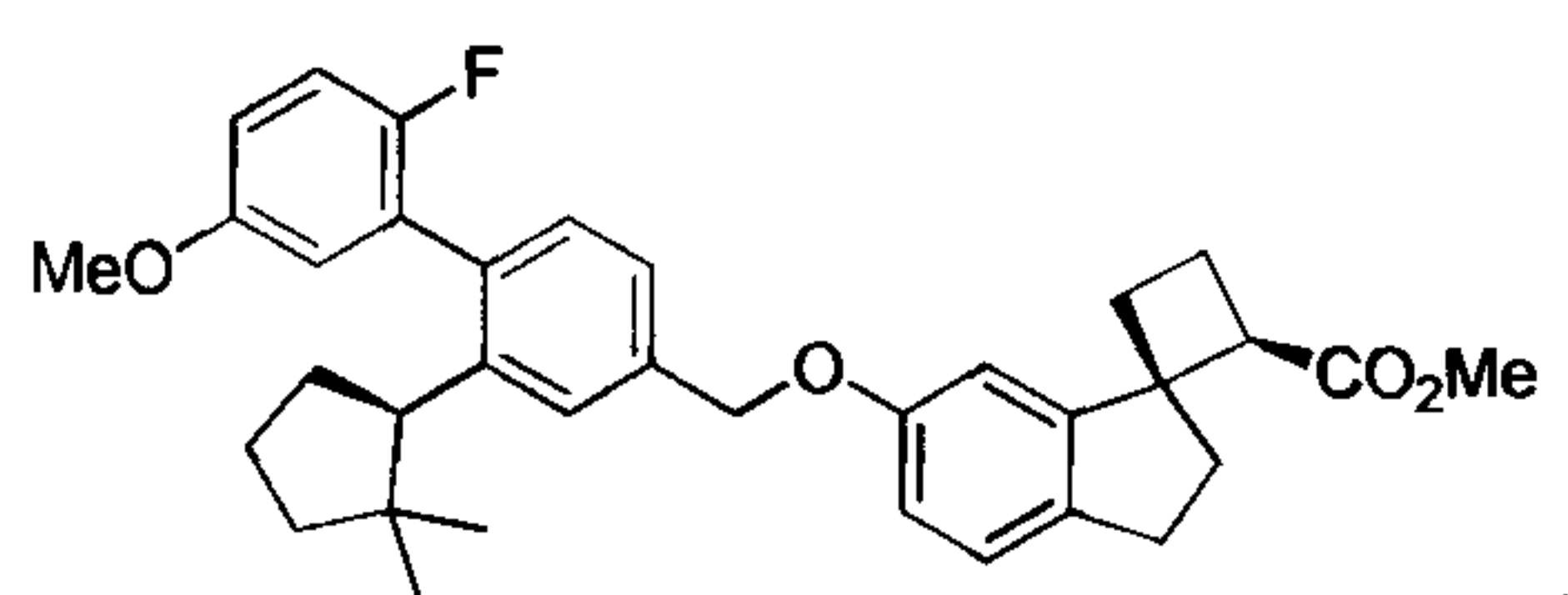
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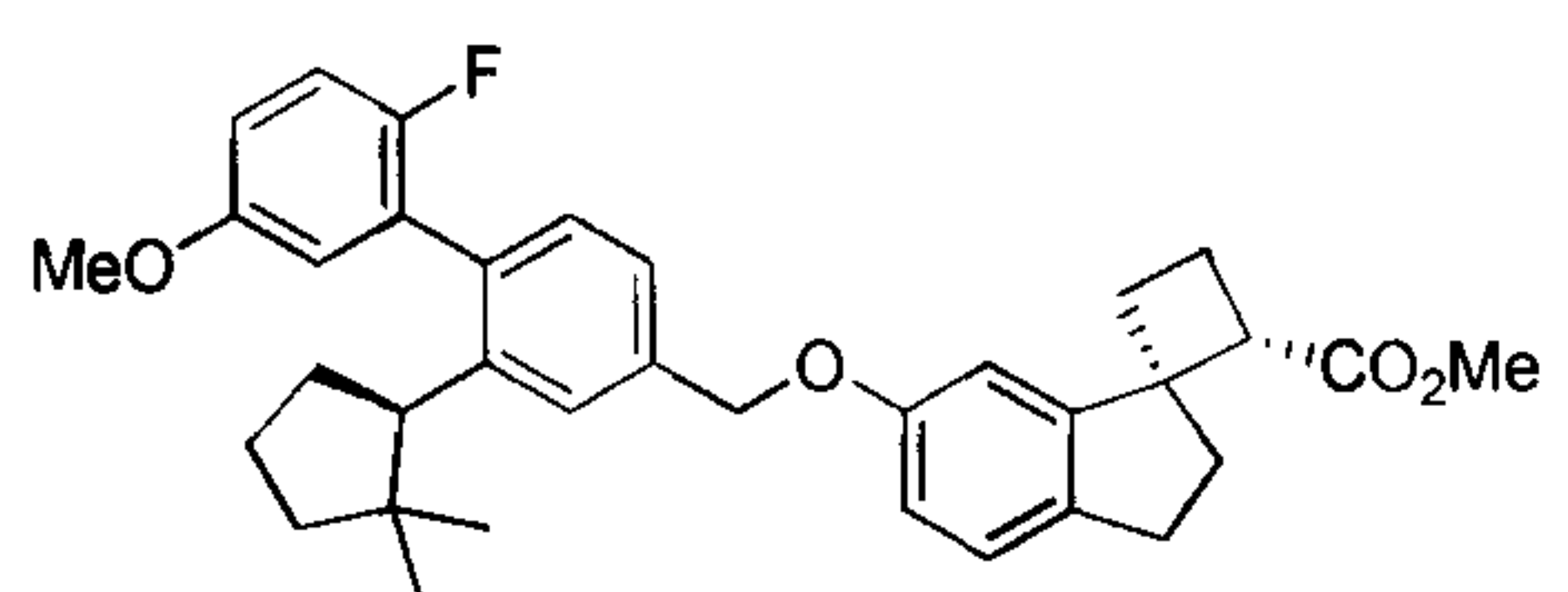
310. The compound



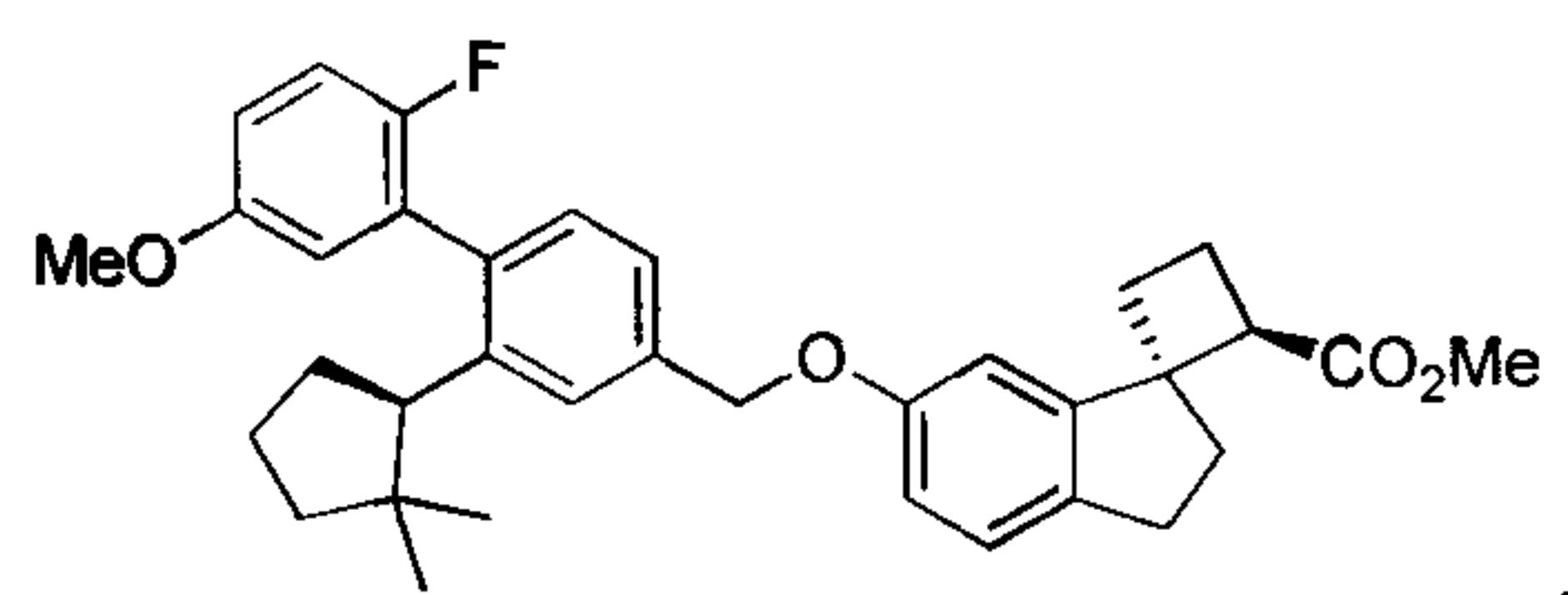
311. The compound



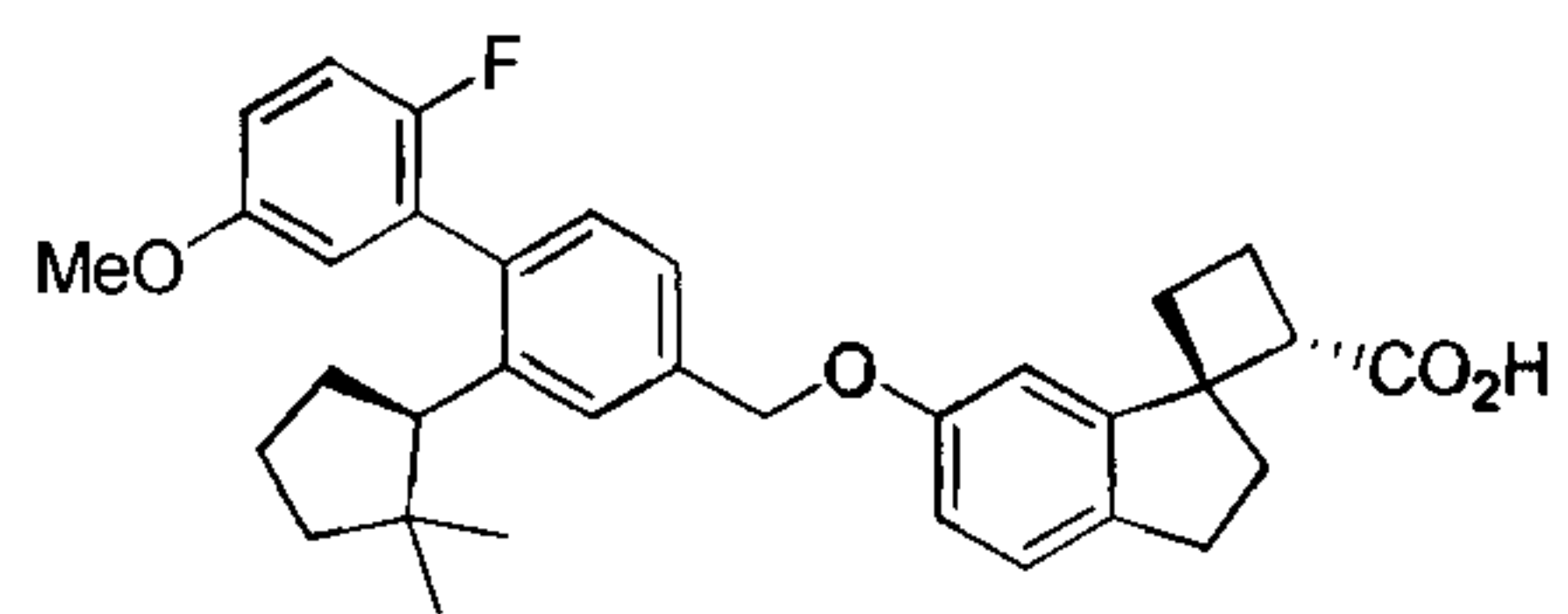
312. The compound



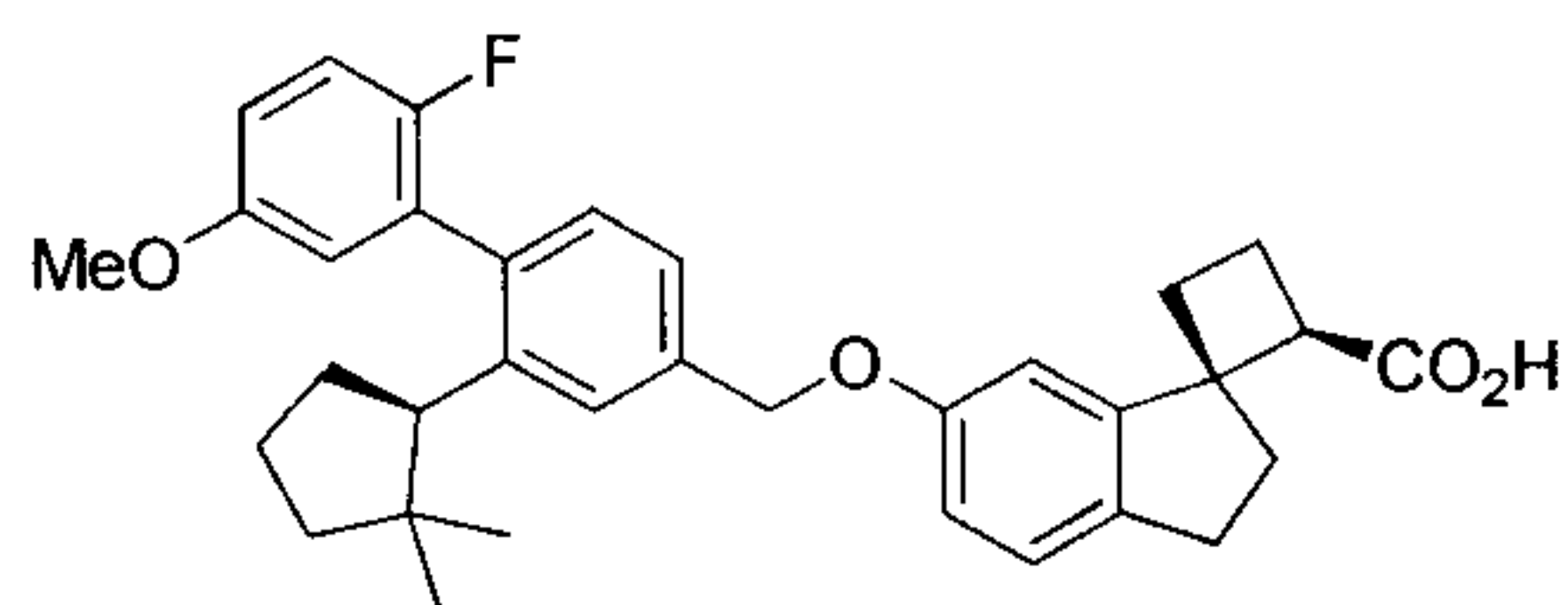
313. The compound



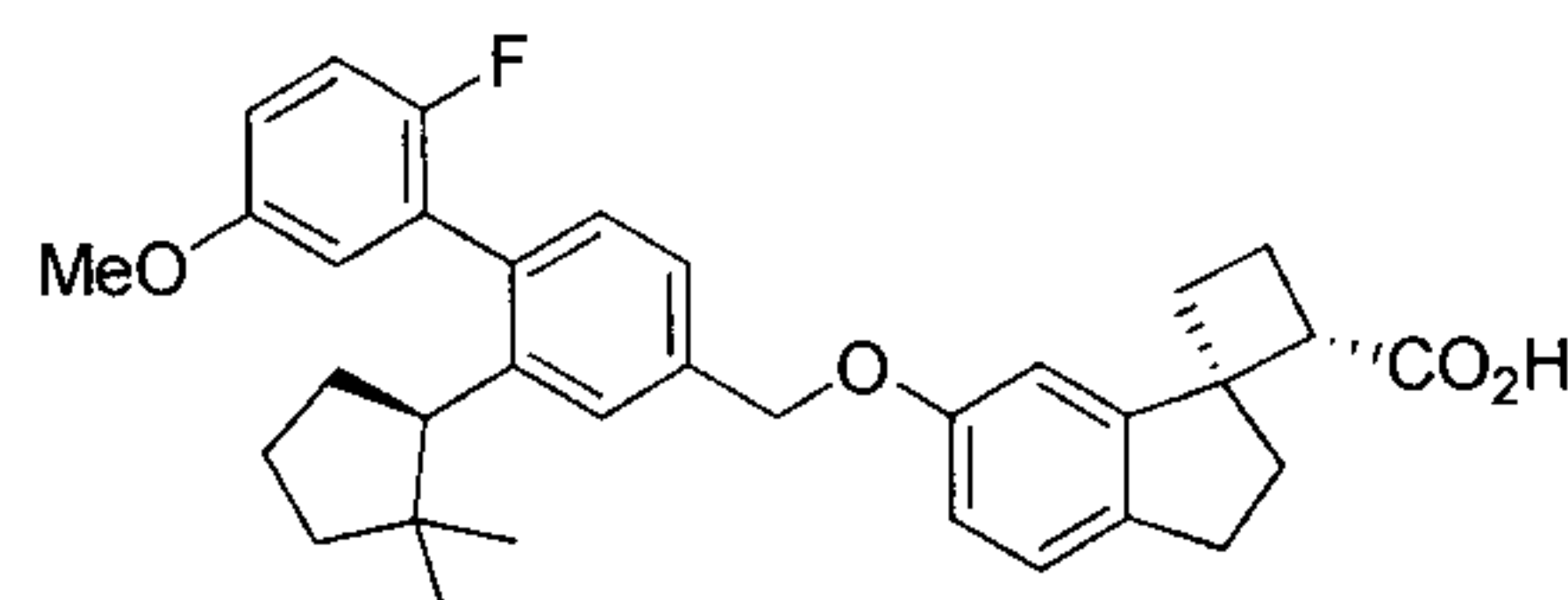
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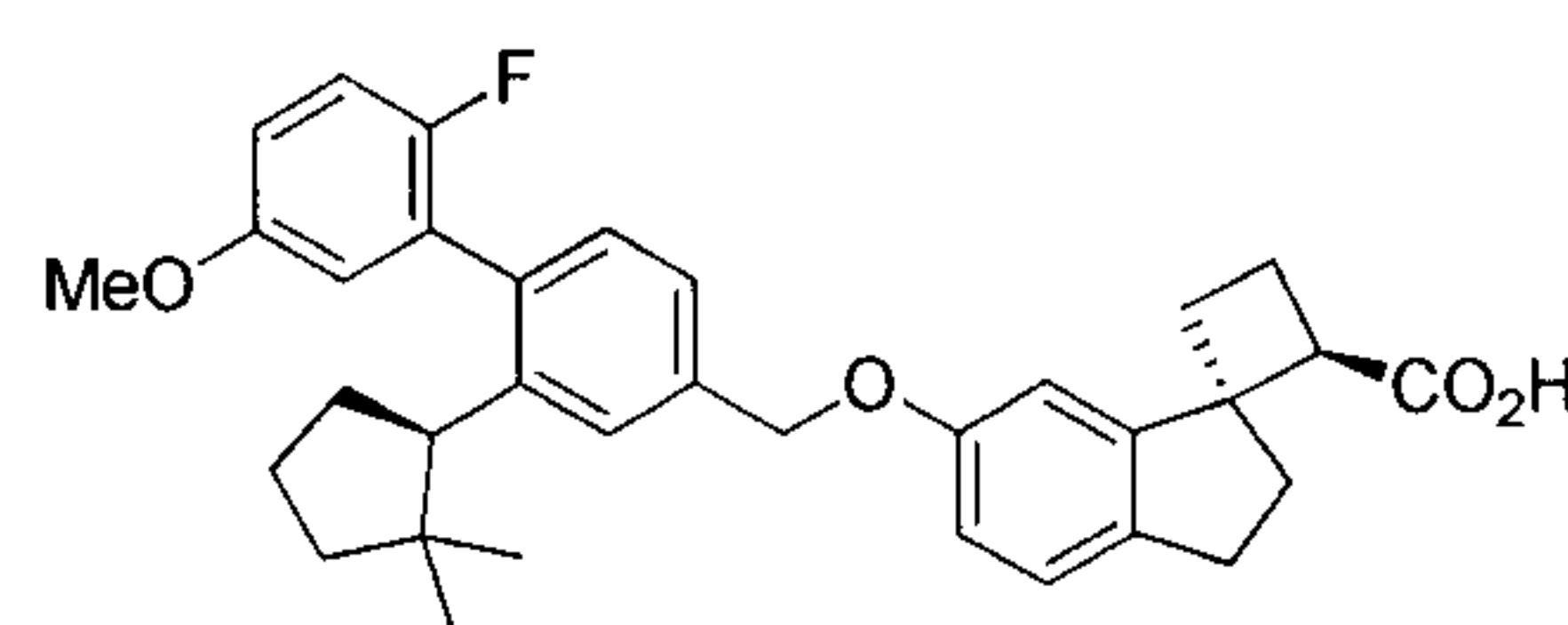
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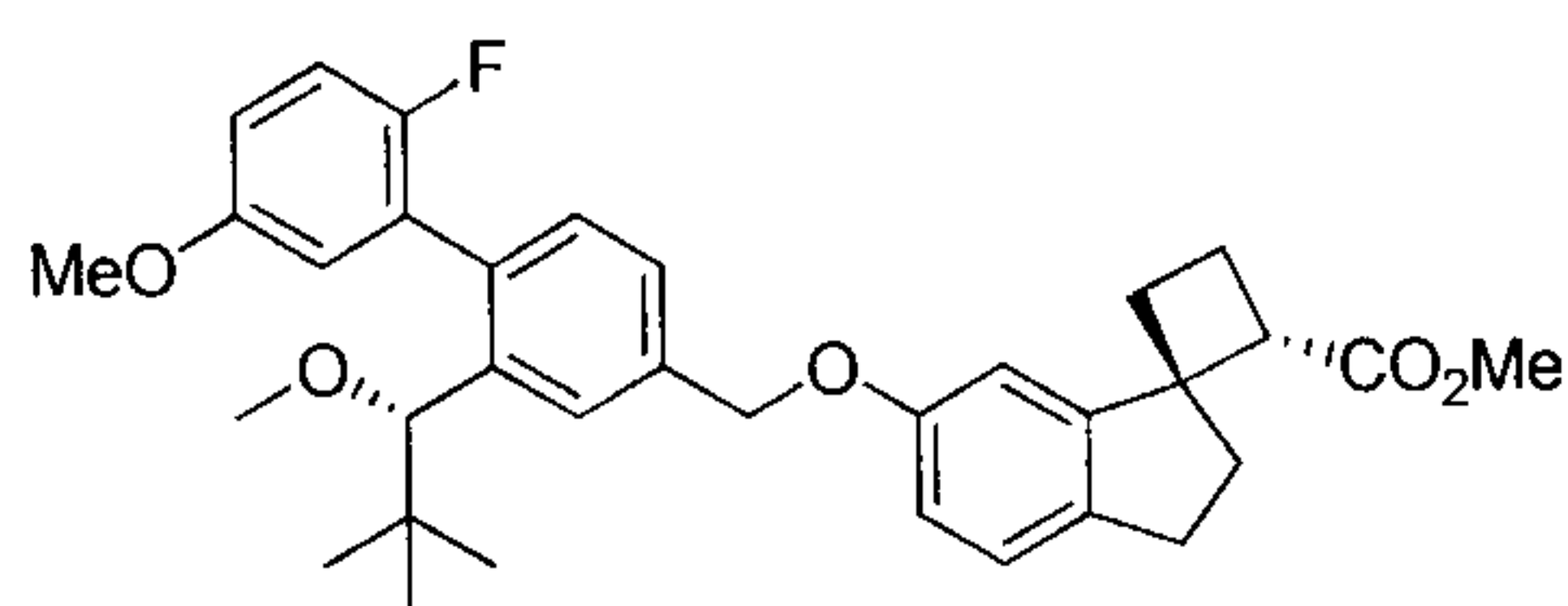
316. The compound



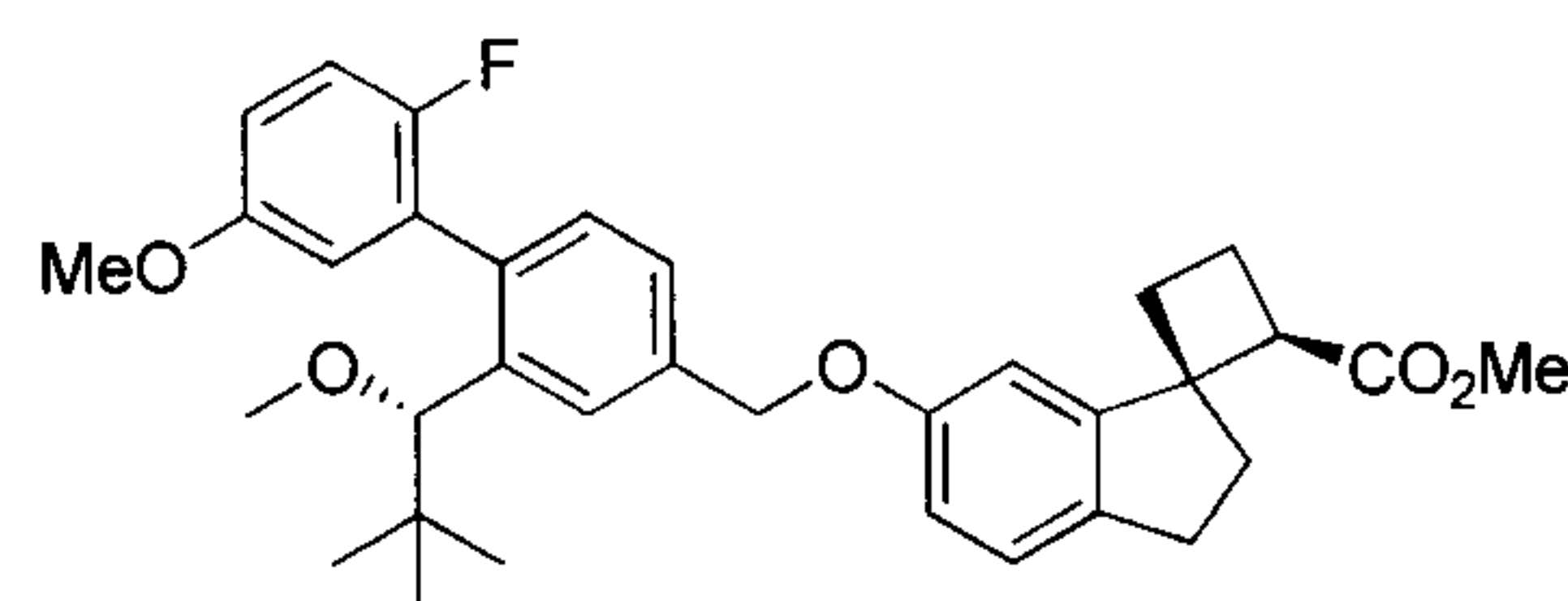
317. The compound



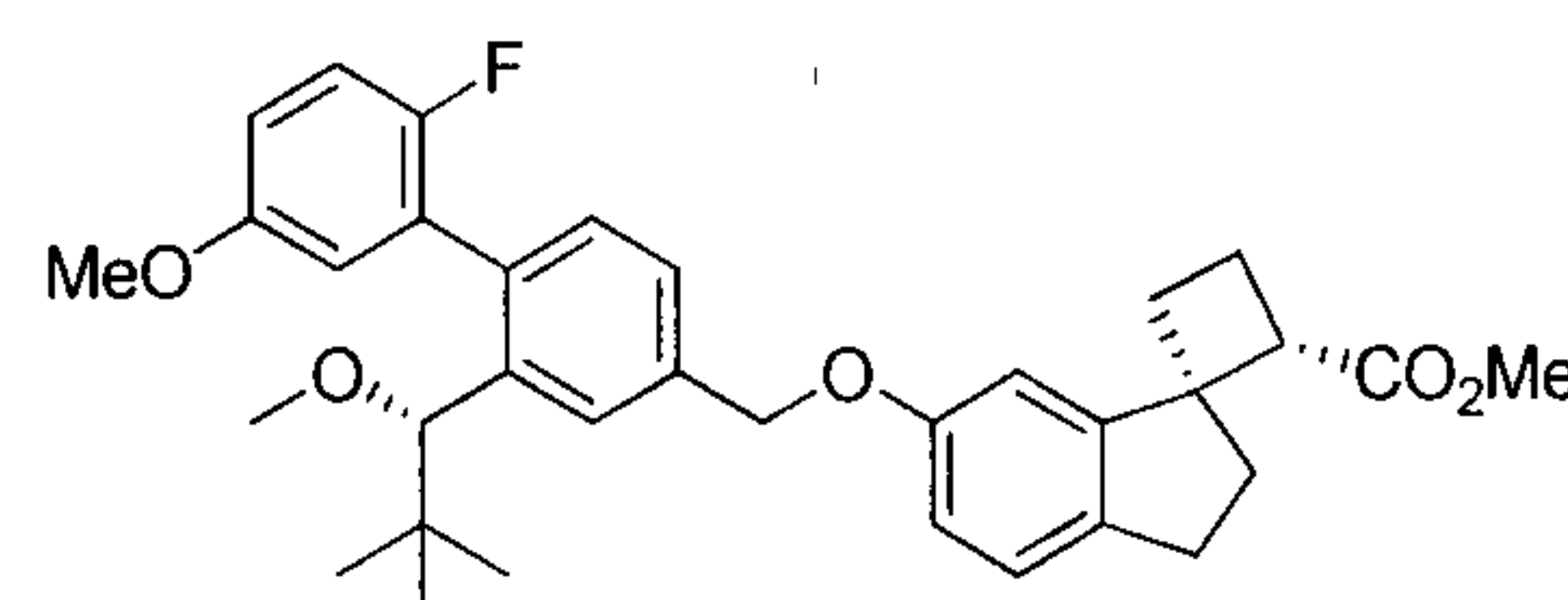
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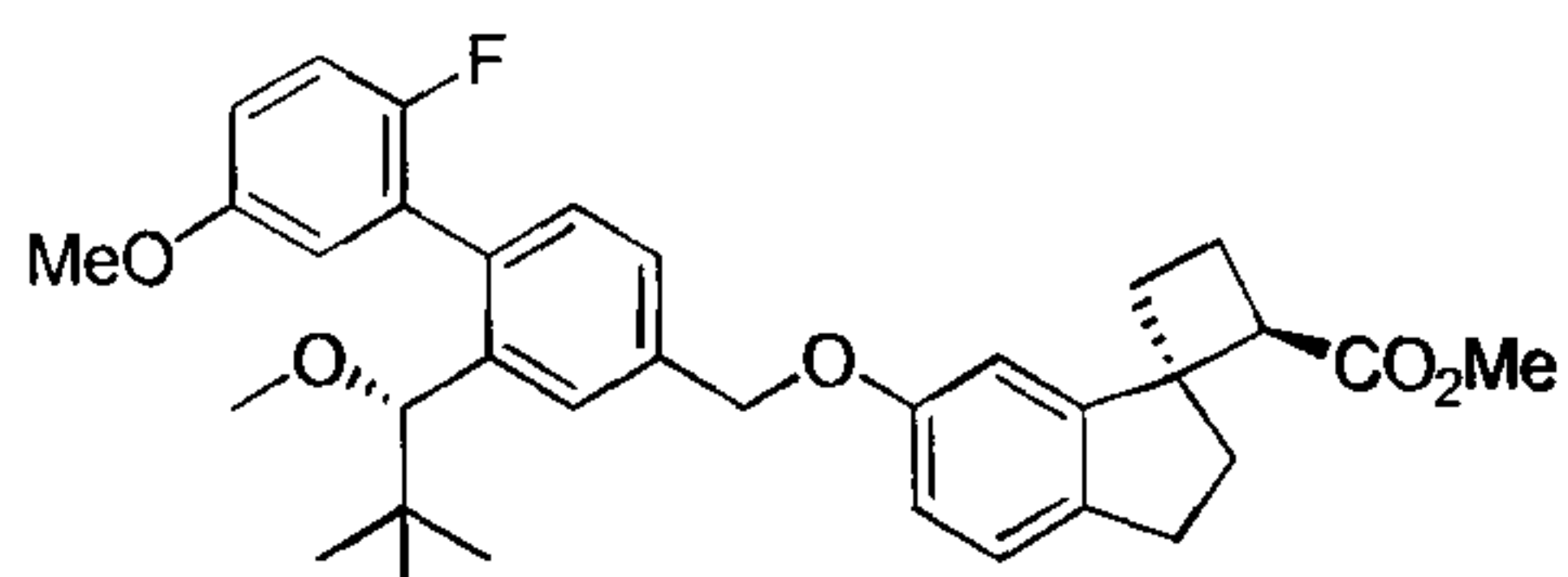
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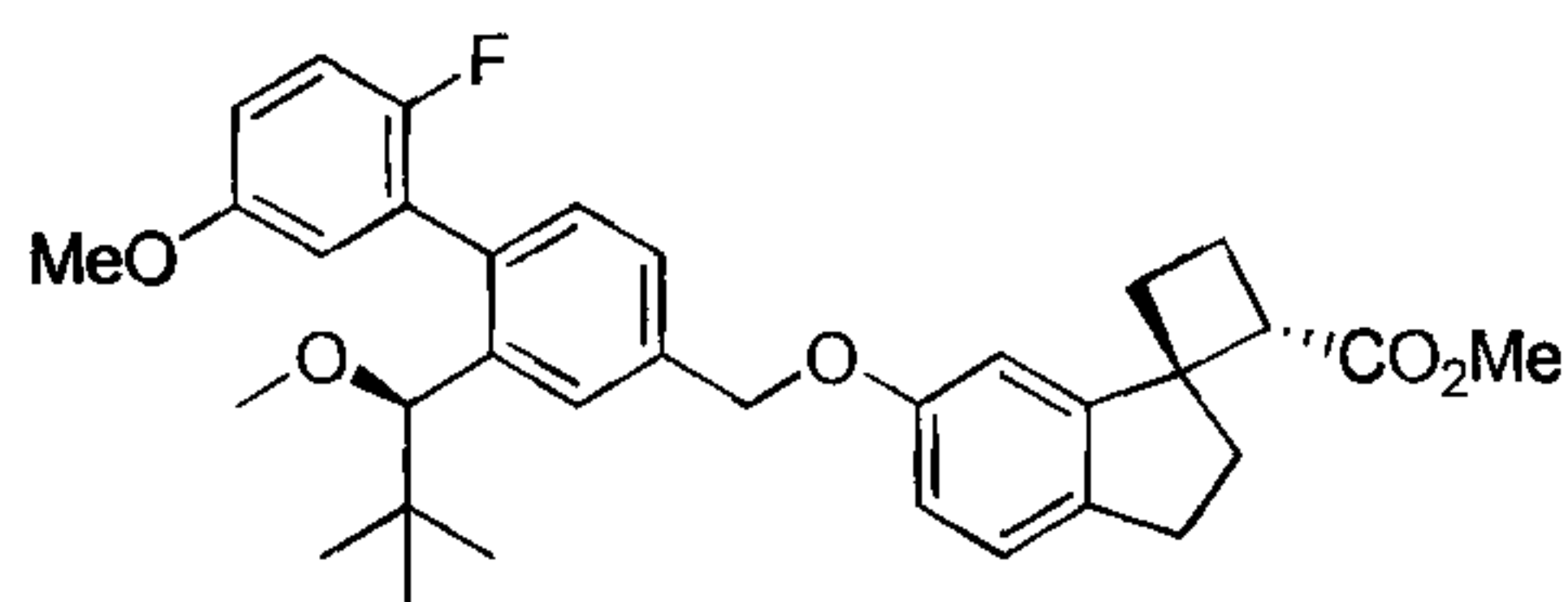
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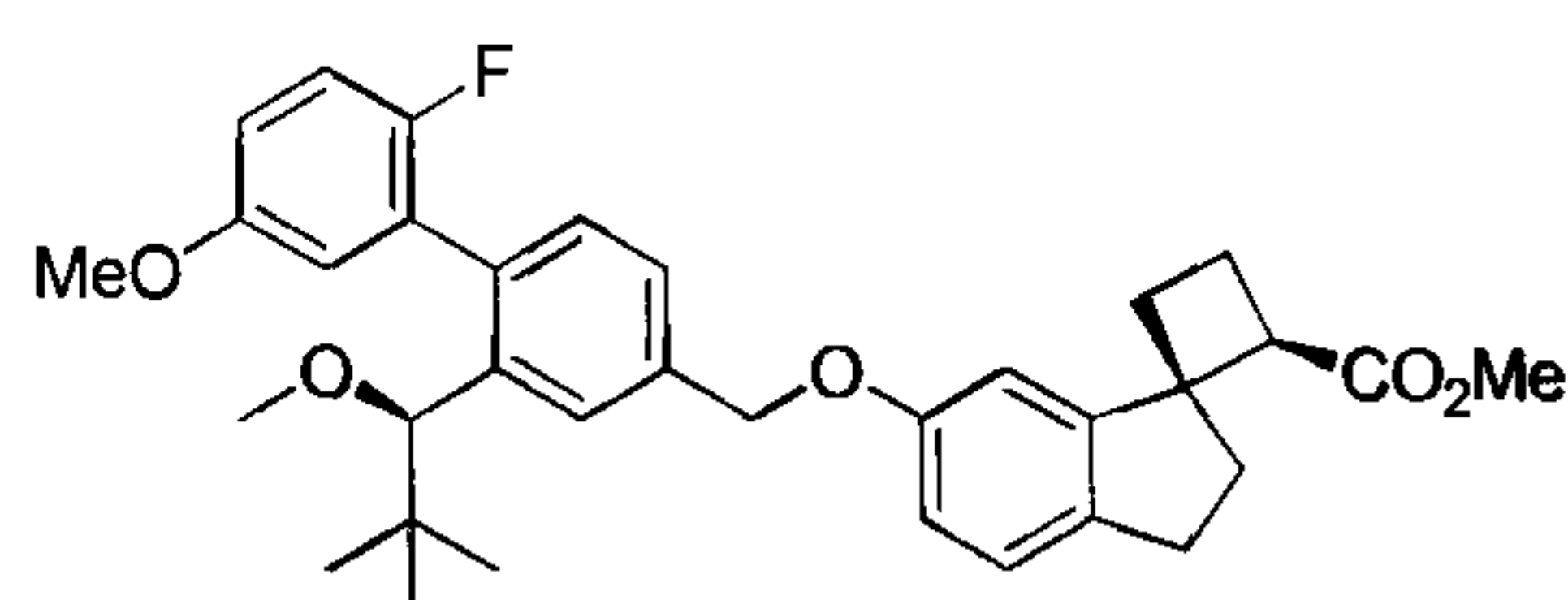
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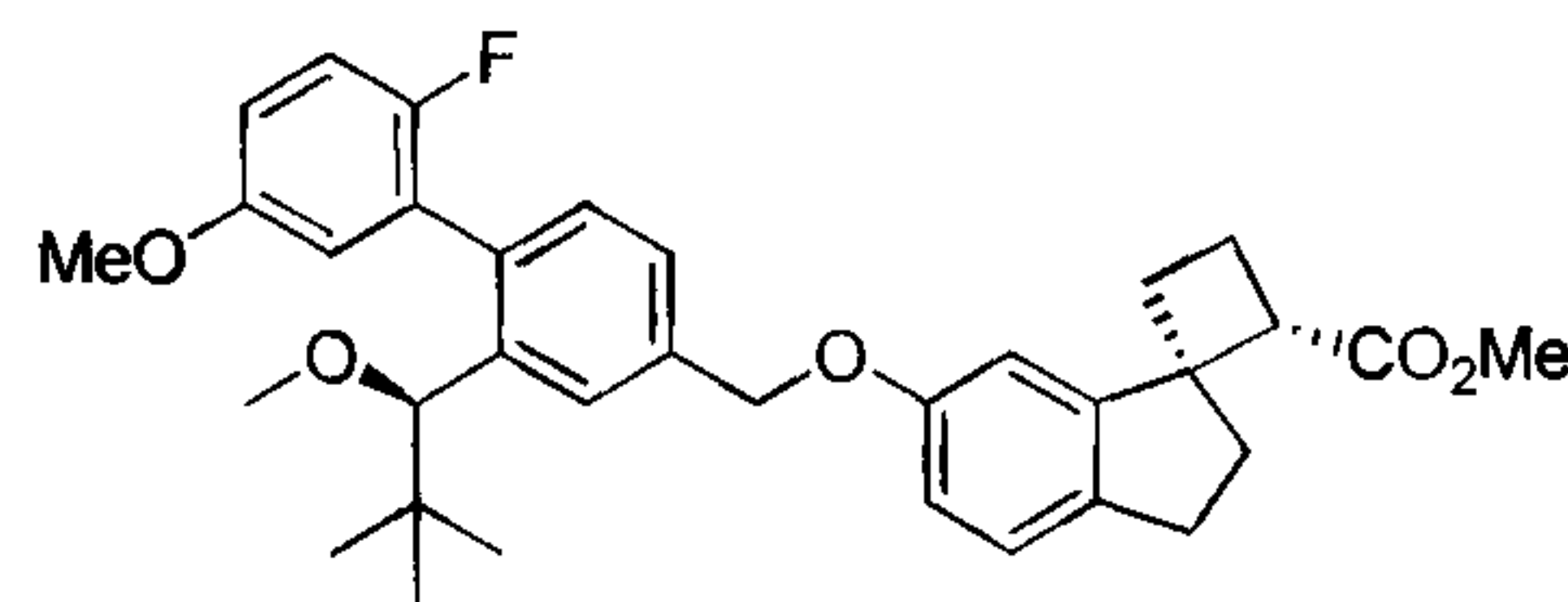
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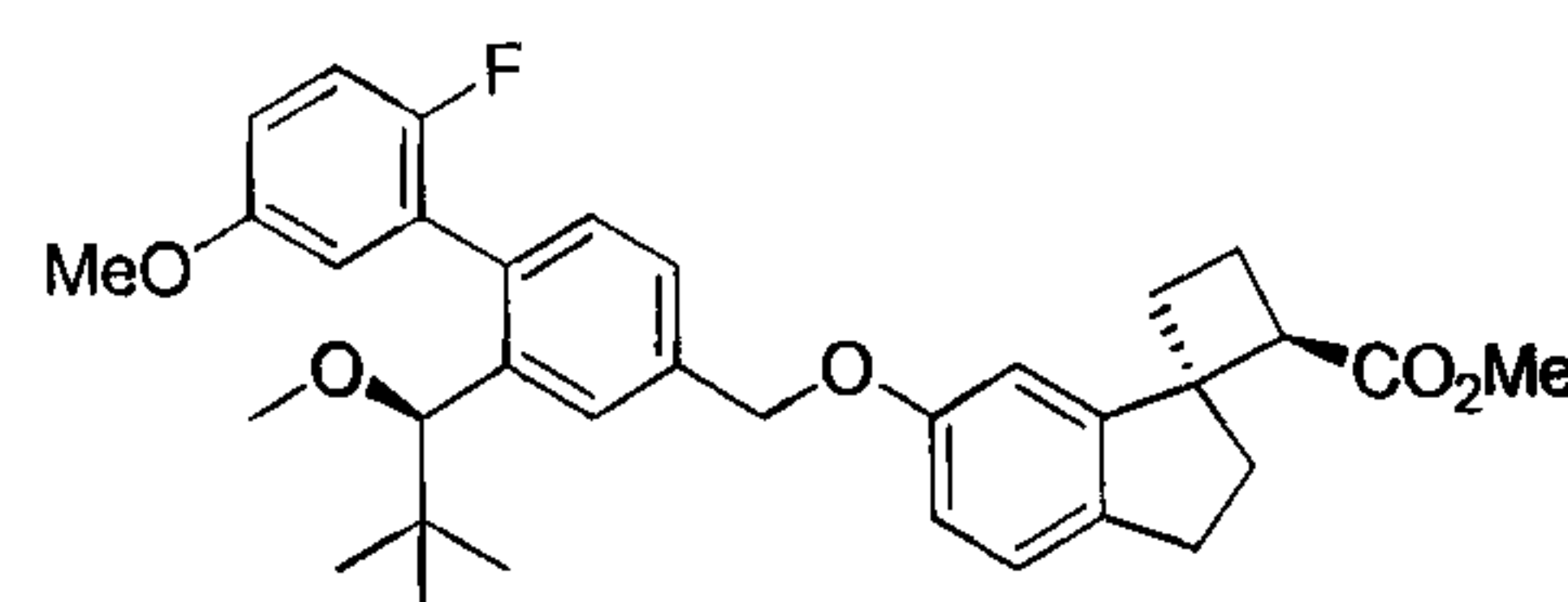
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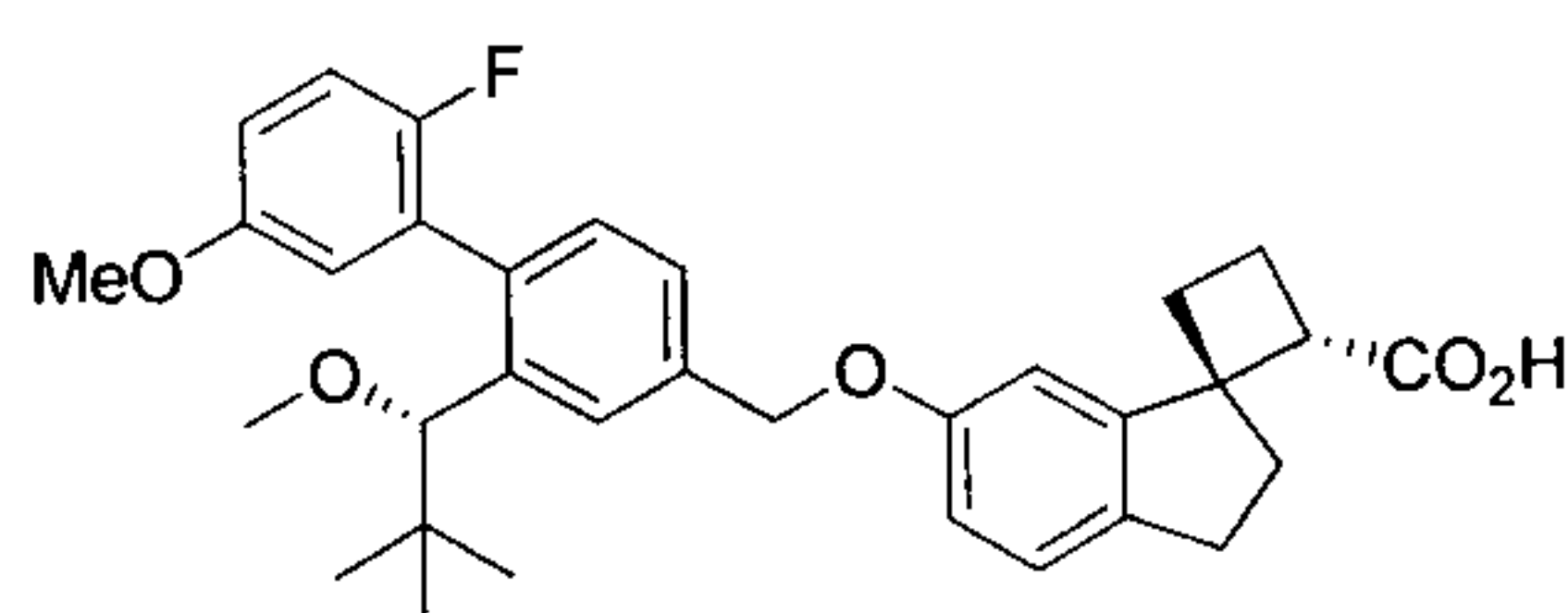
324. The compound



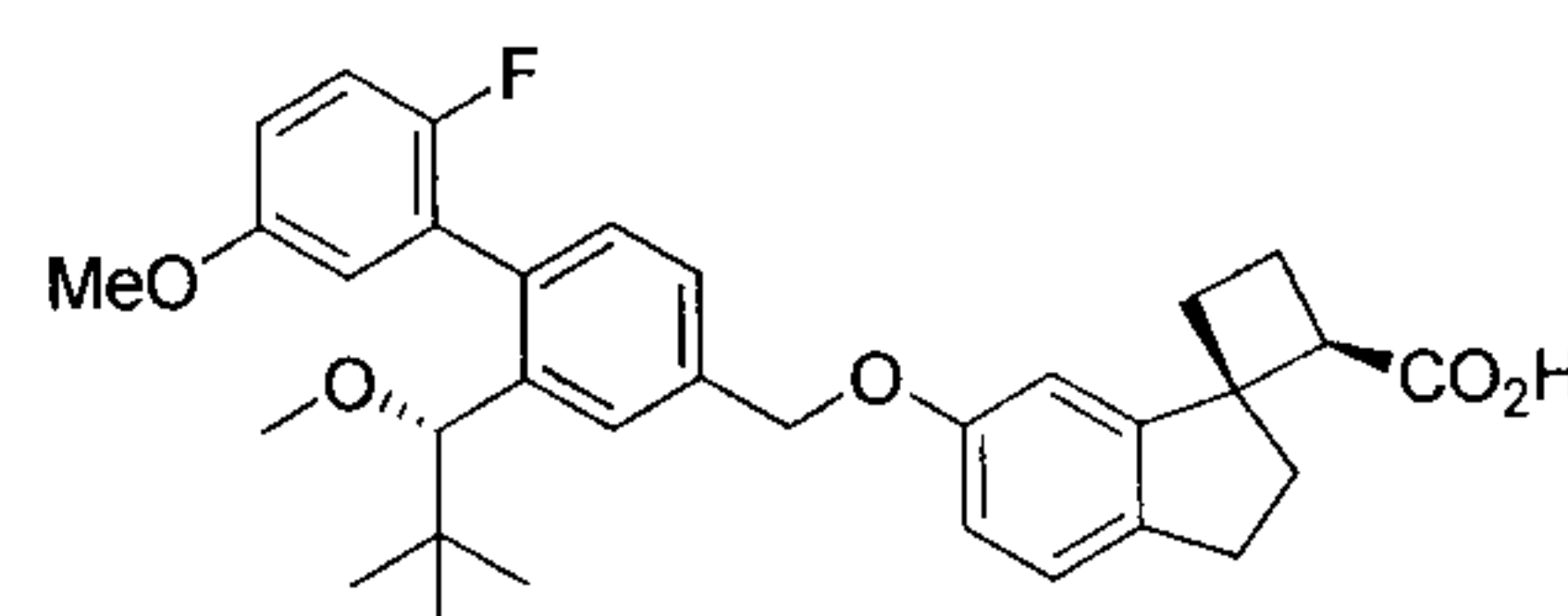
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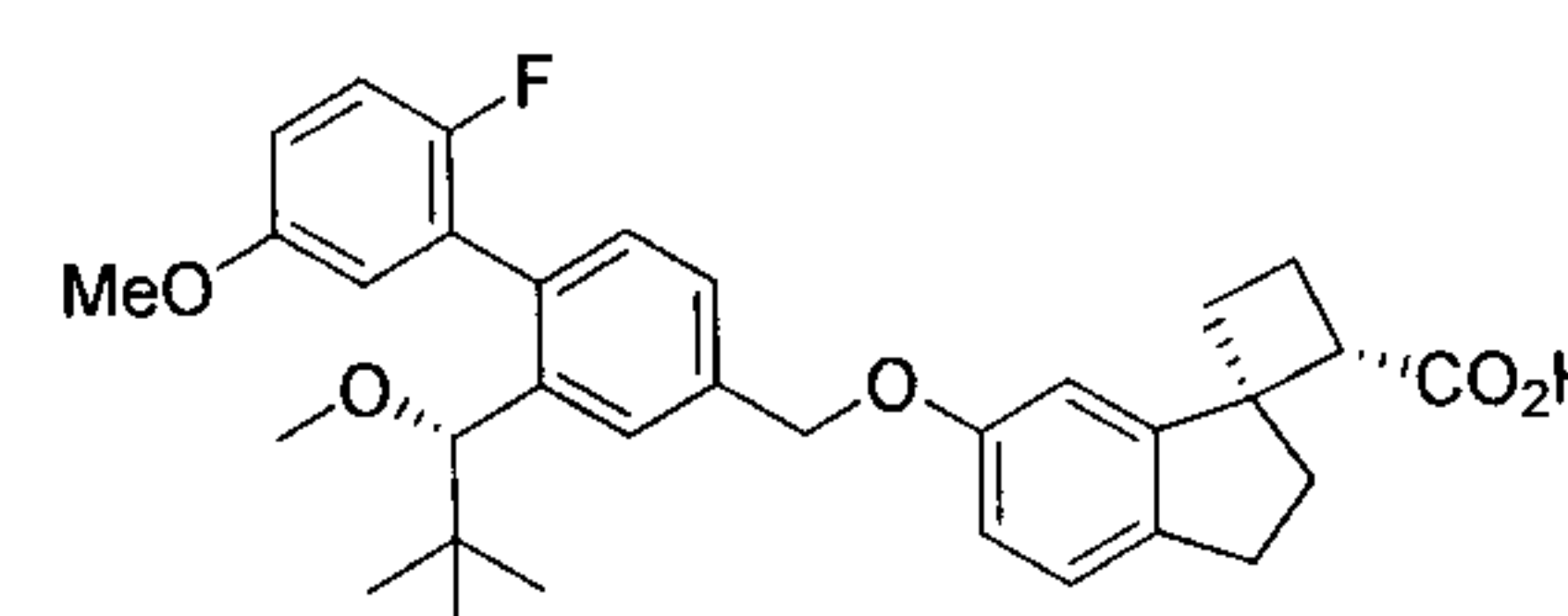
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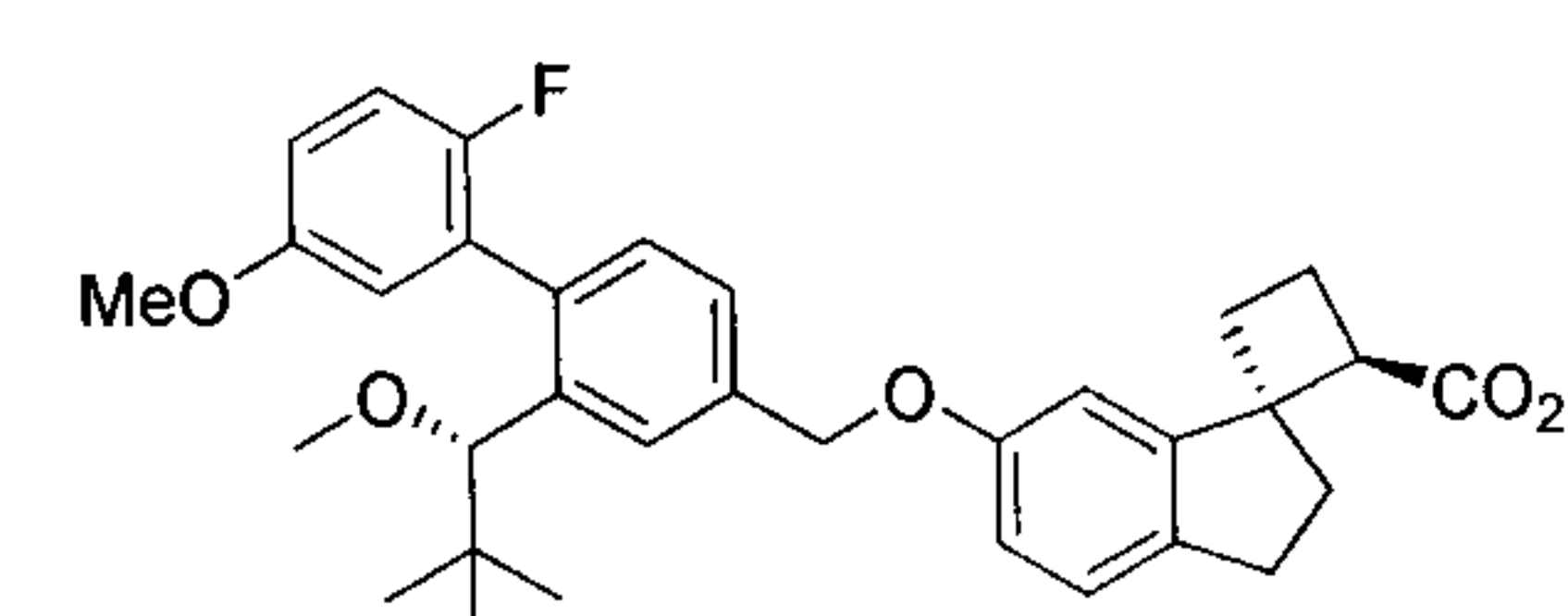
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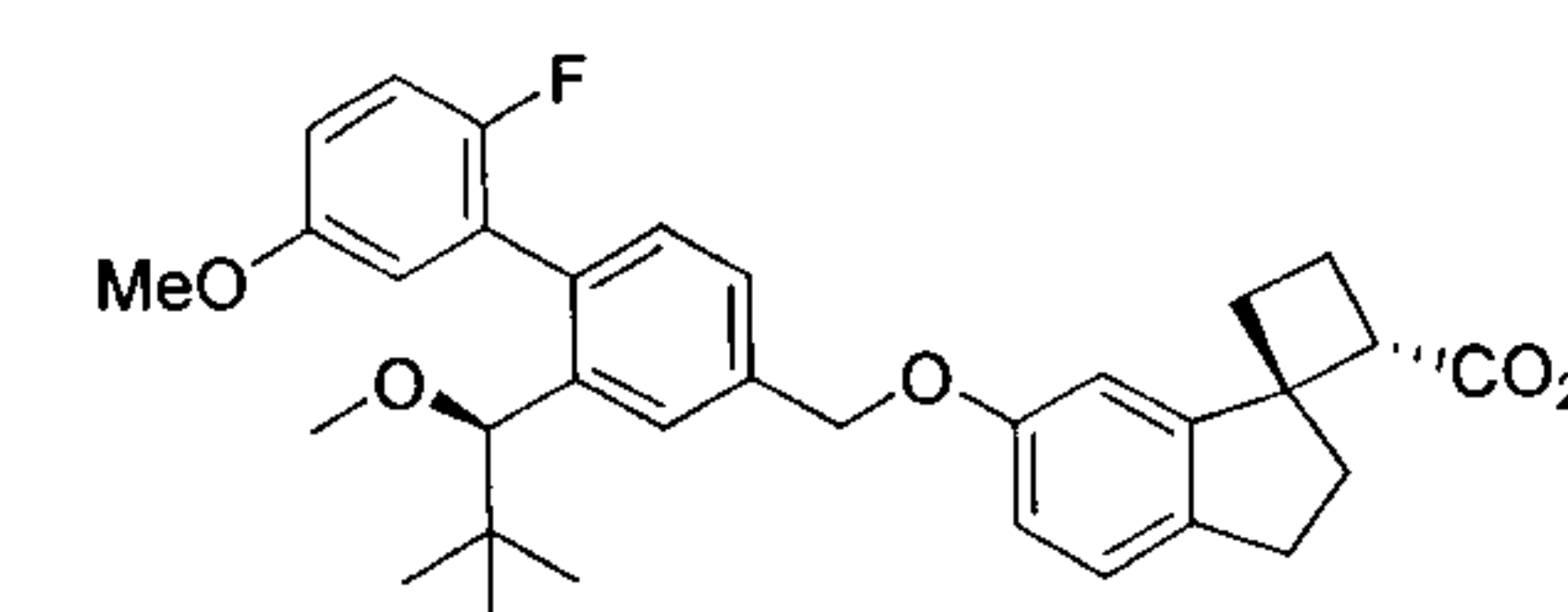
328. The compound



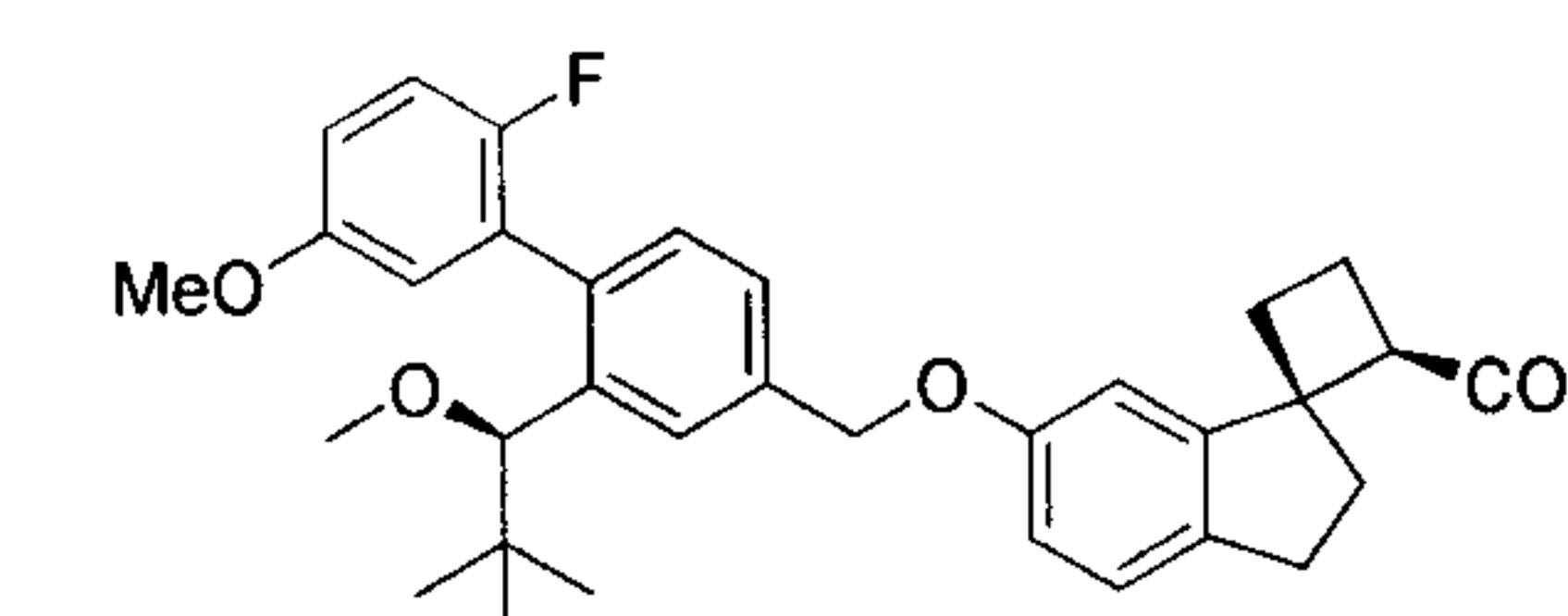
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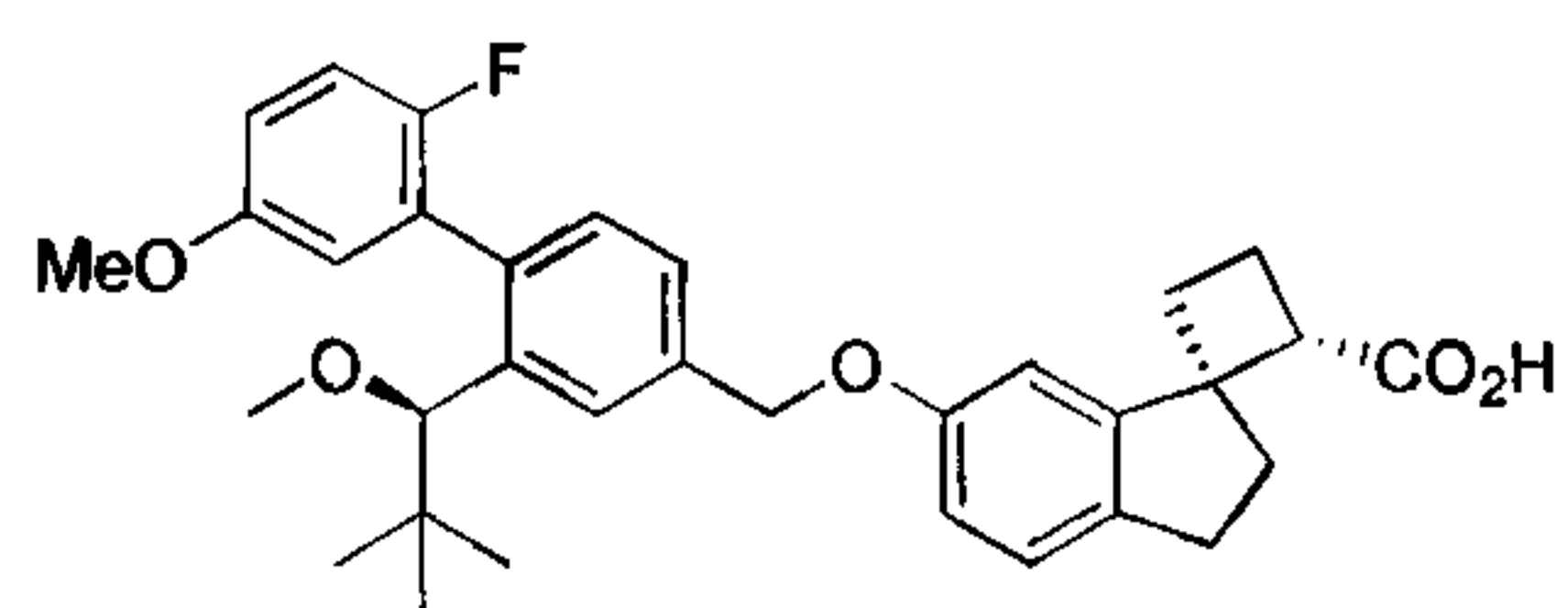
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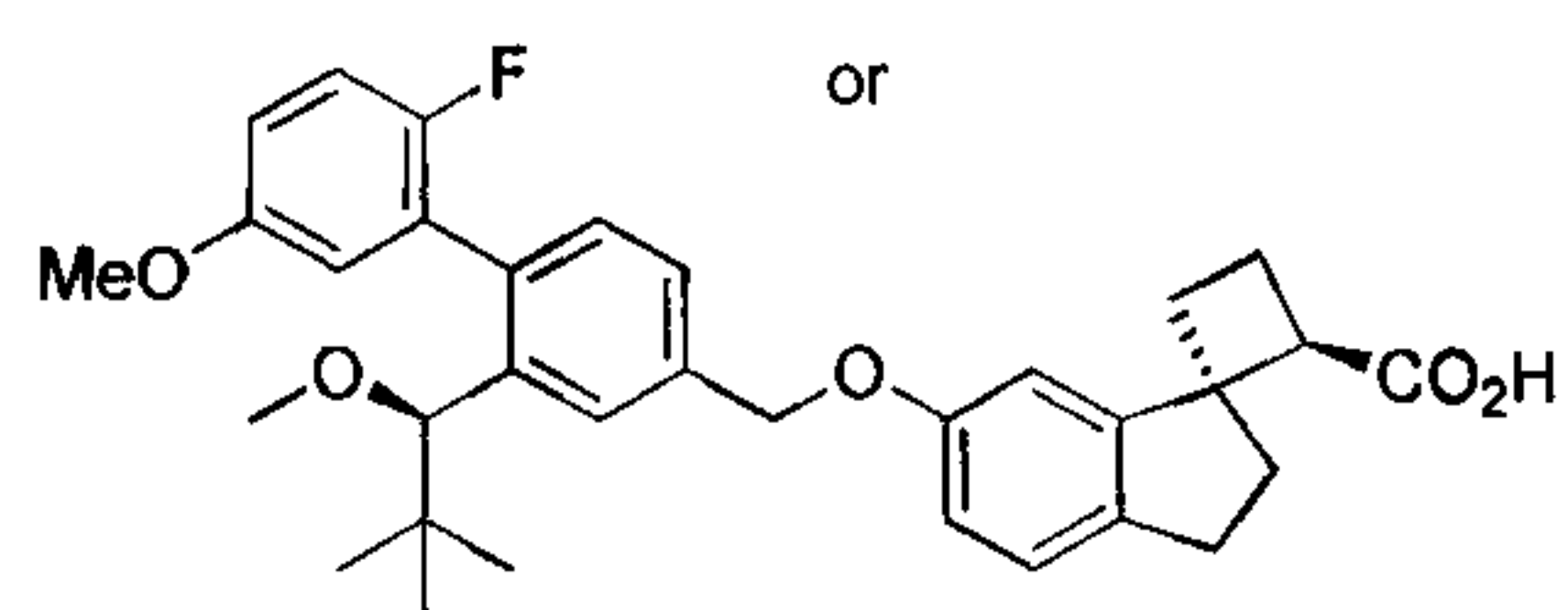
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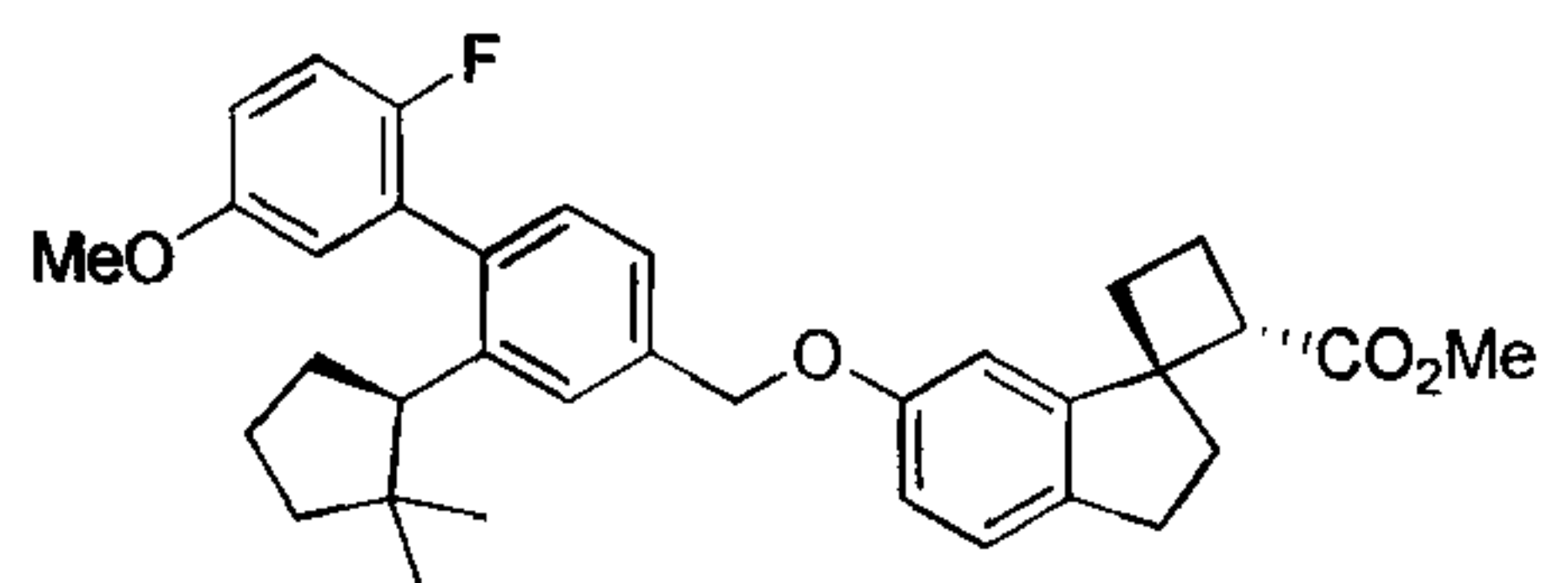
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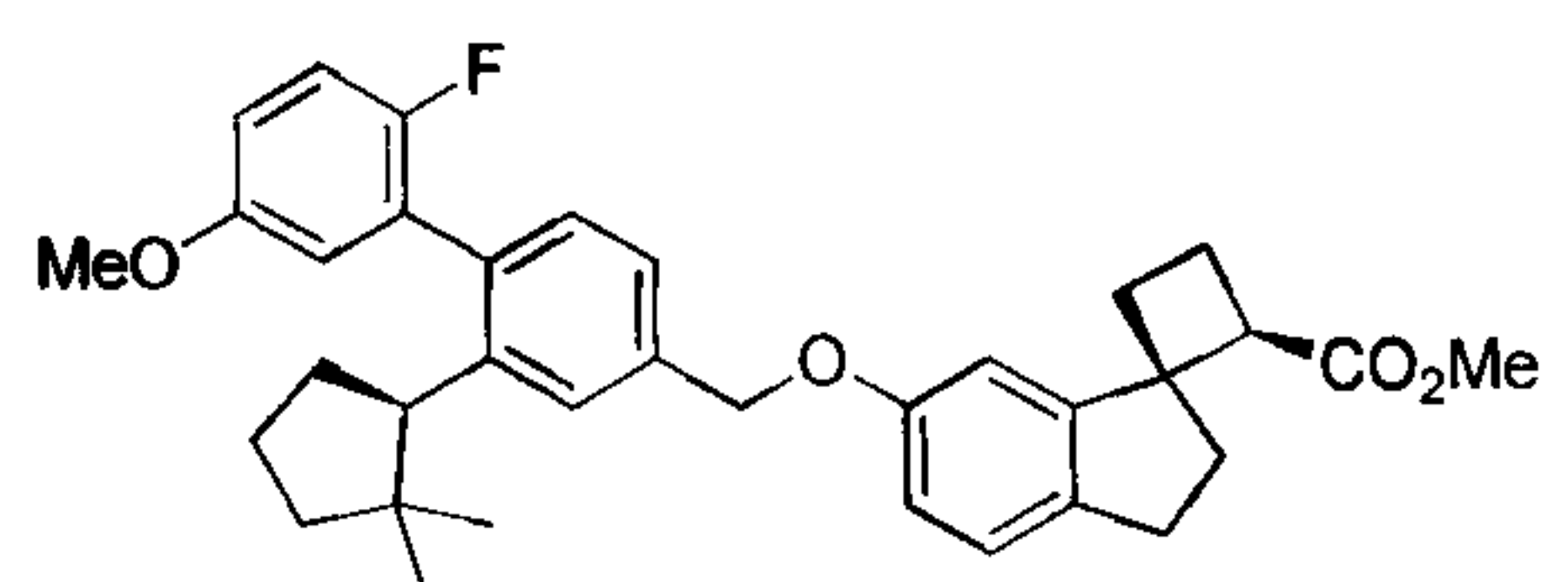
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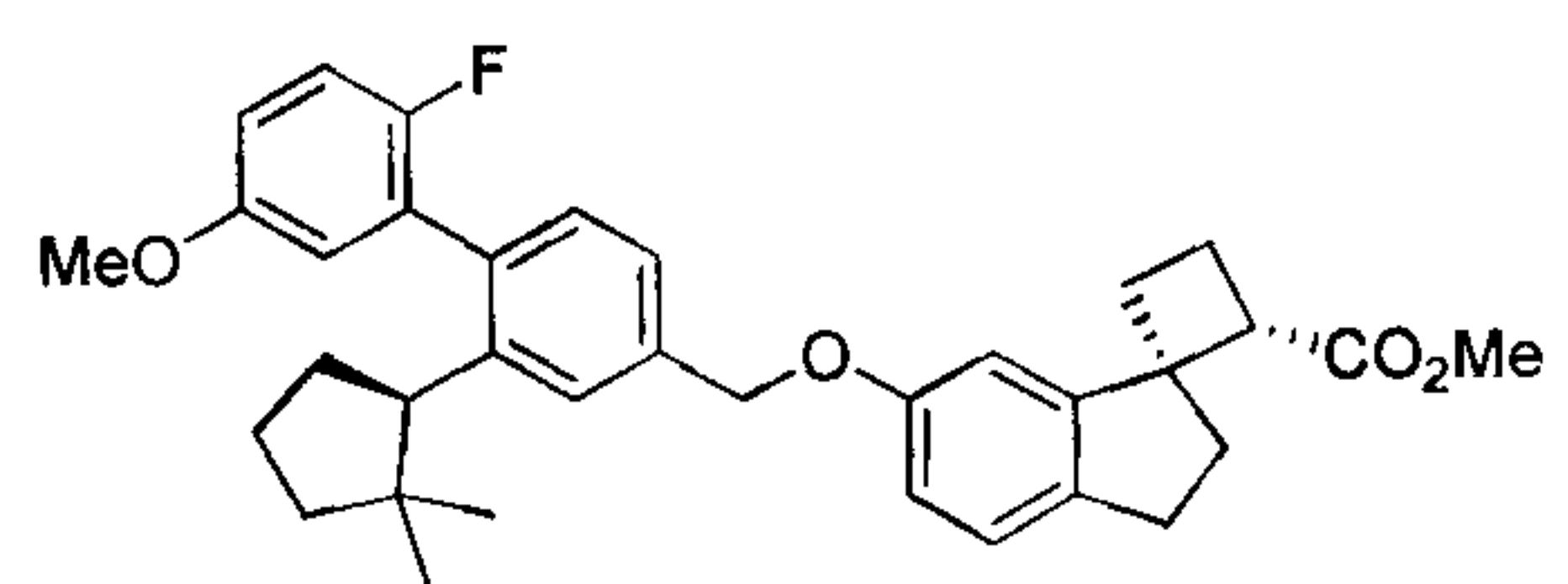
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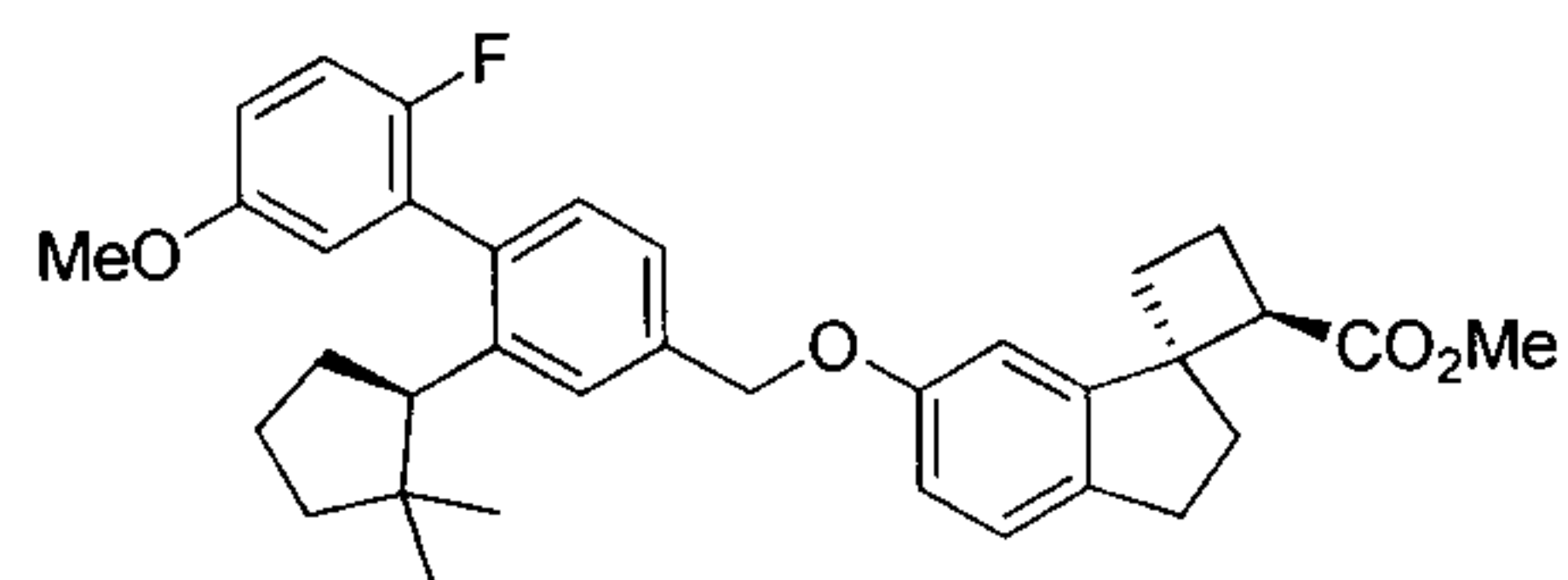
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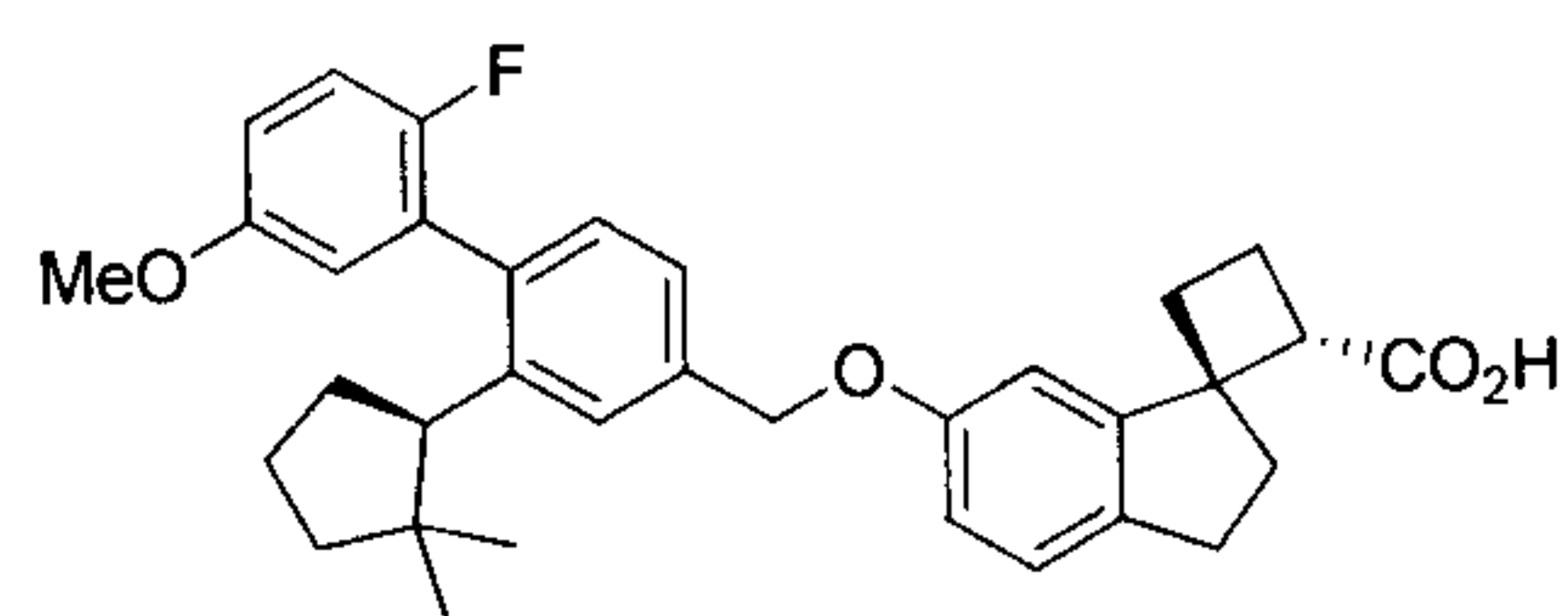
336. The compound



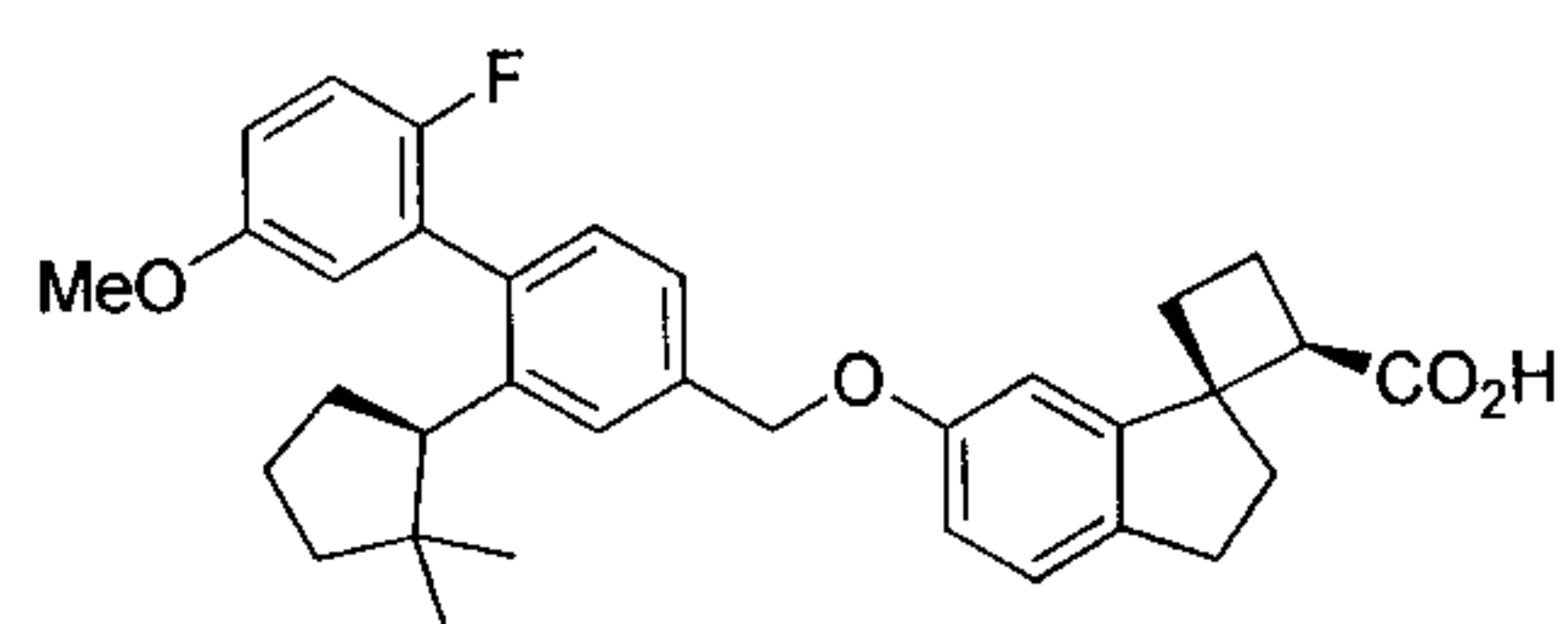
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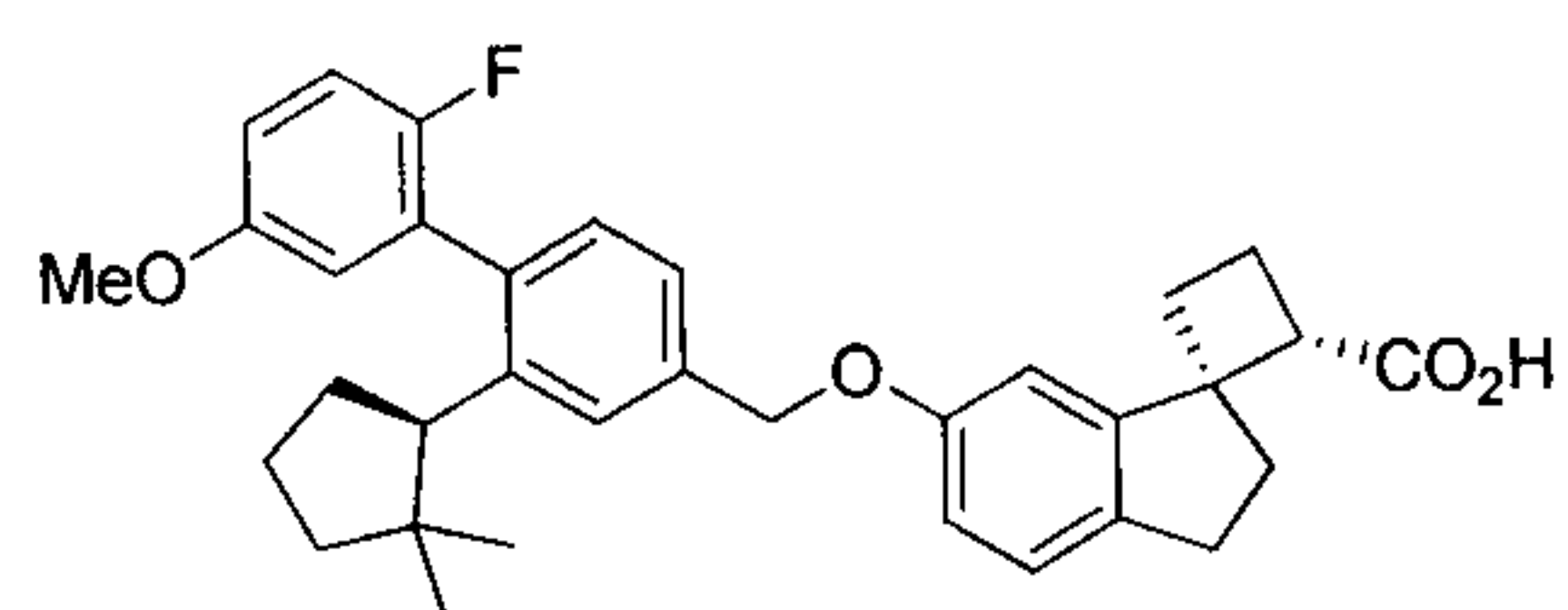
338. The compound



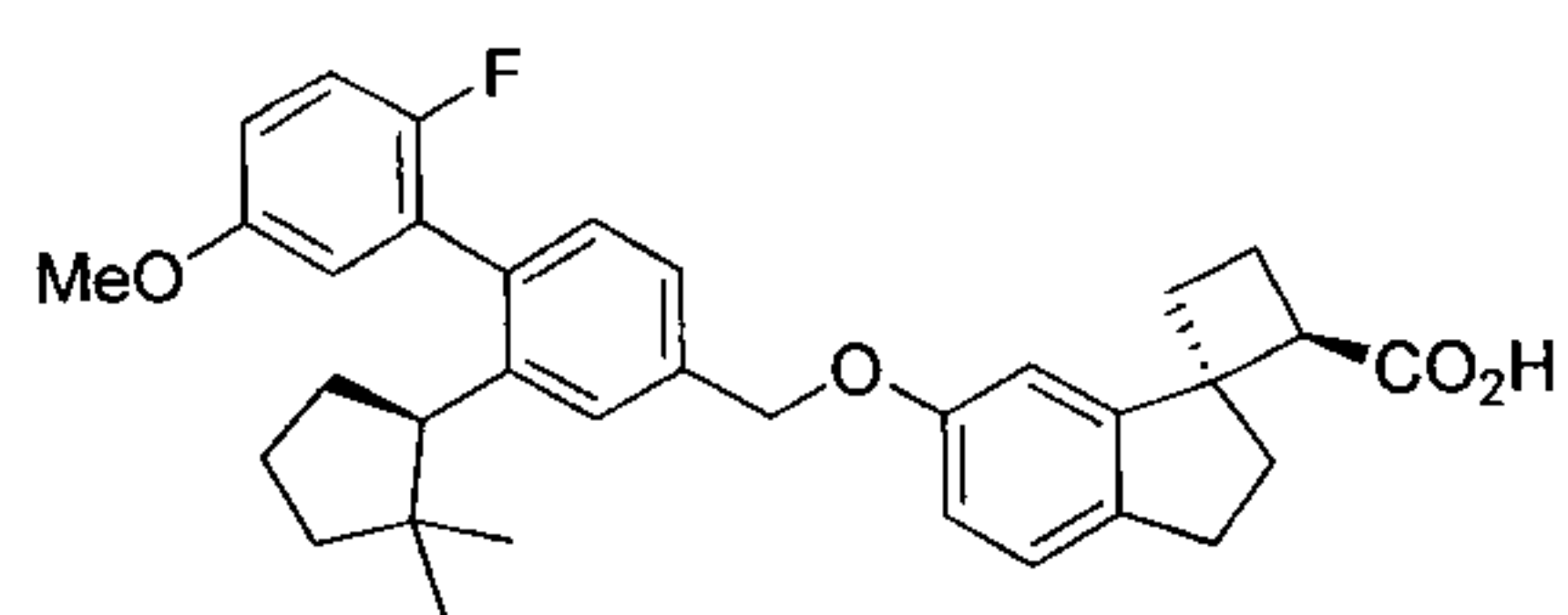
339. The compound



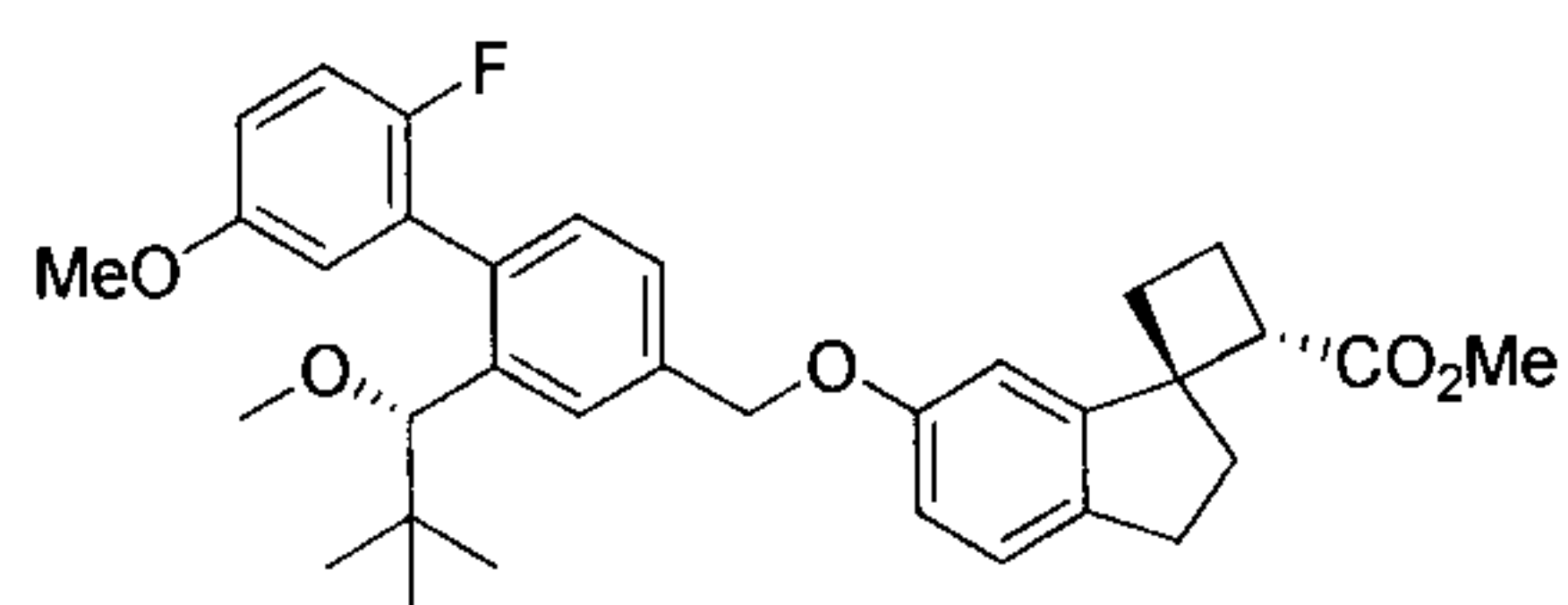
340. The compound



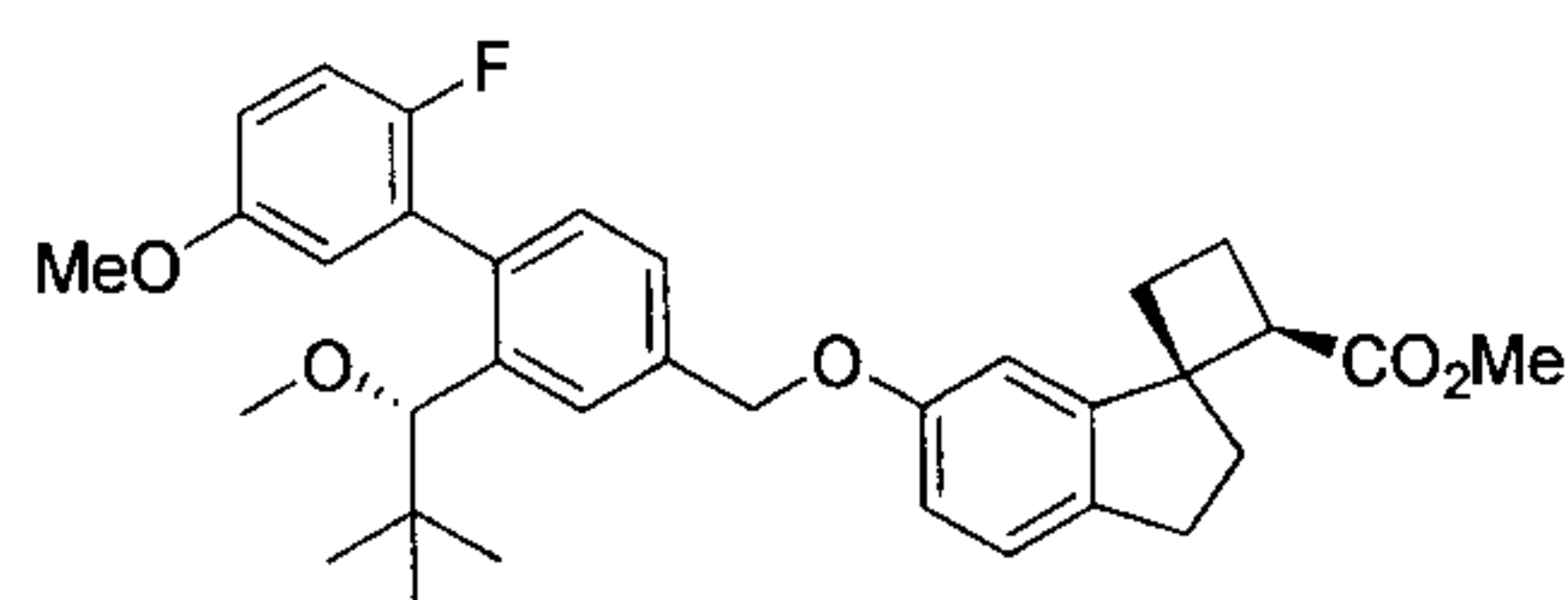
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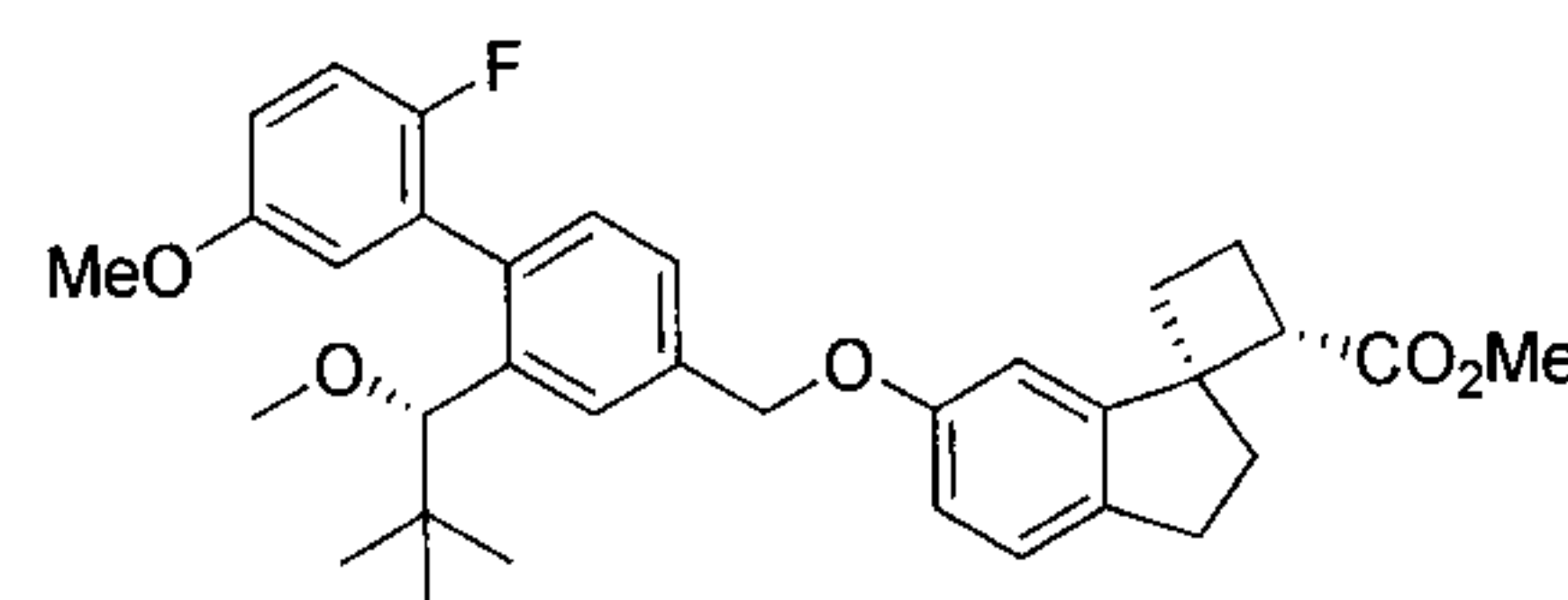
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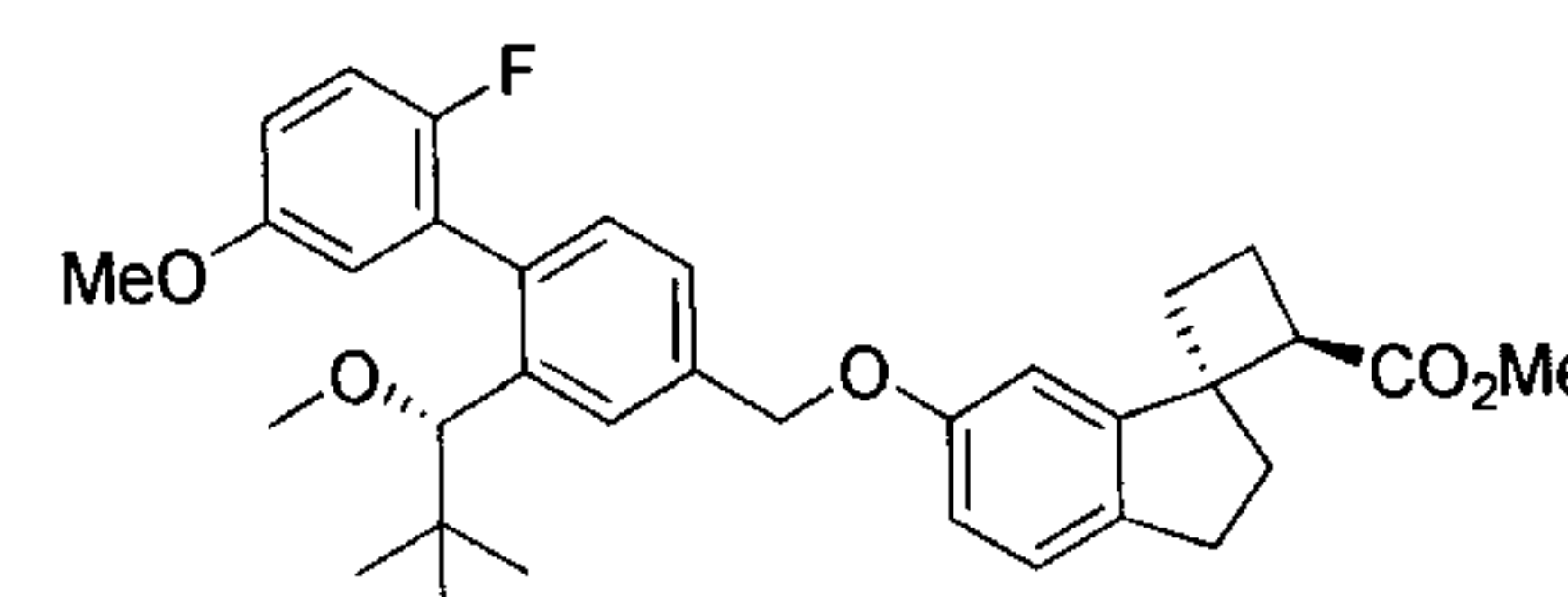
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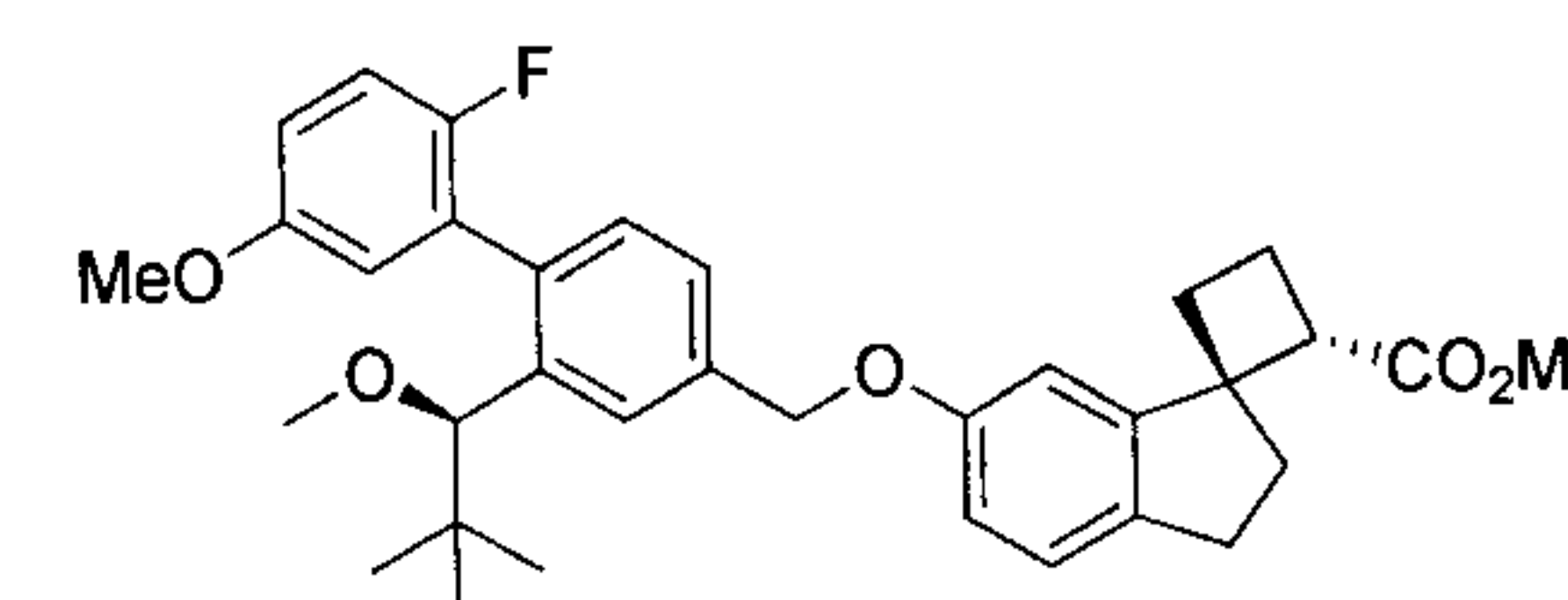
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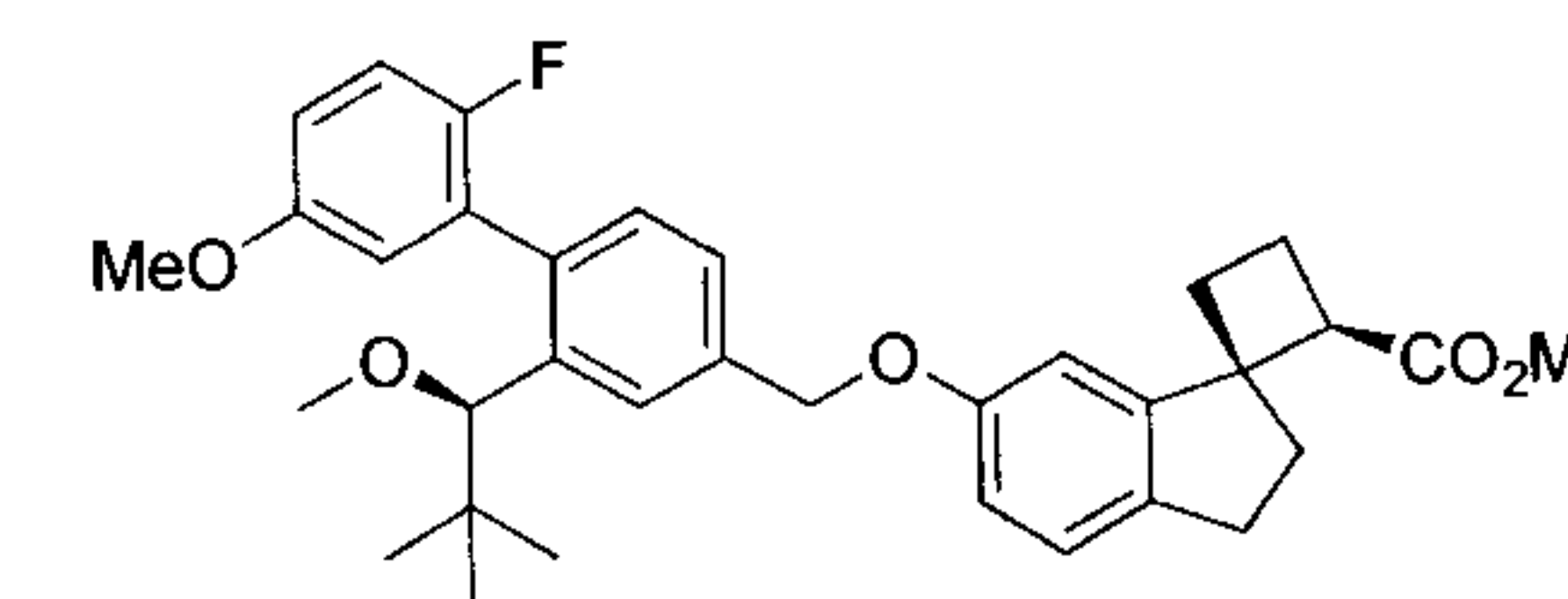
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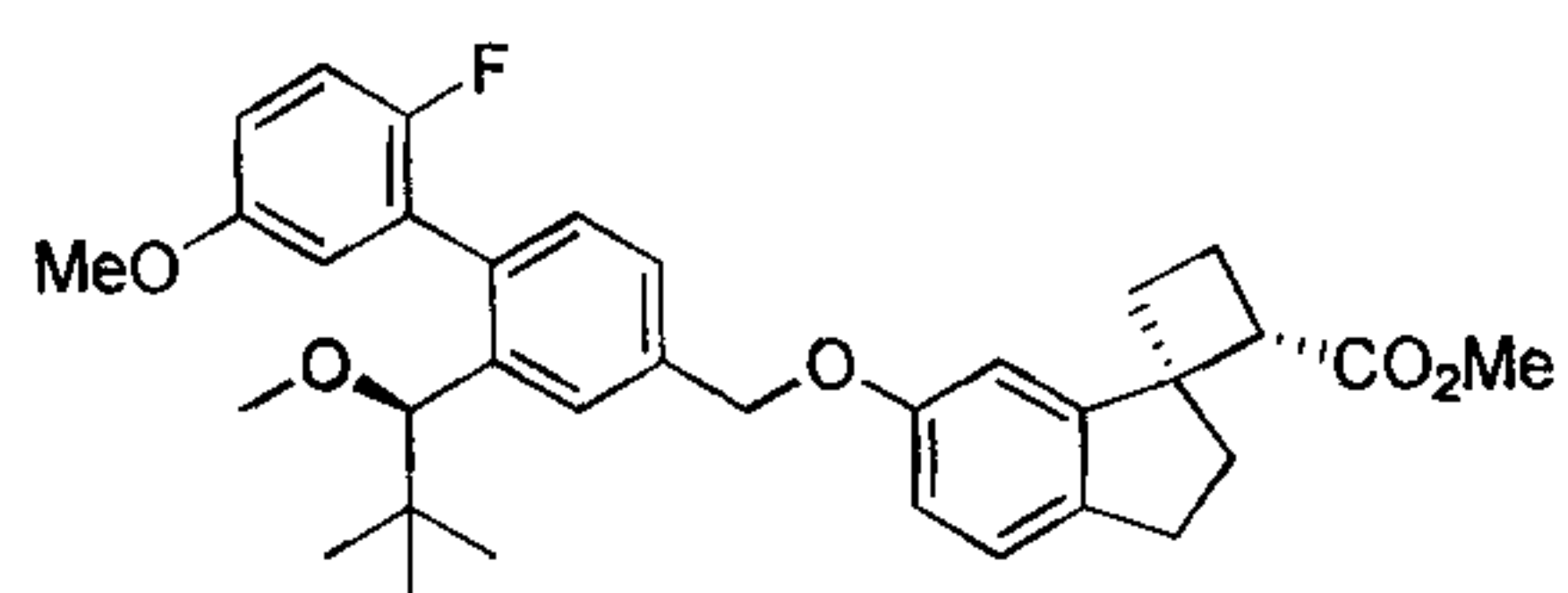
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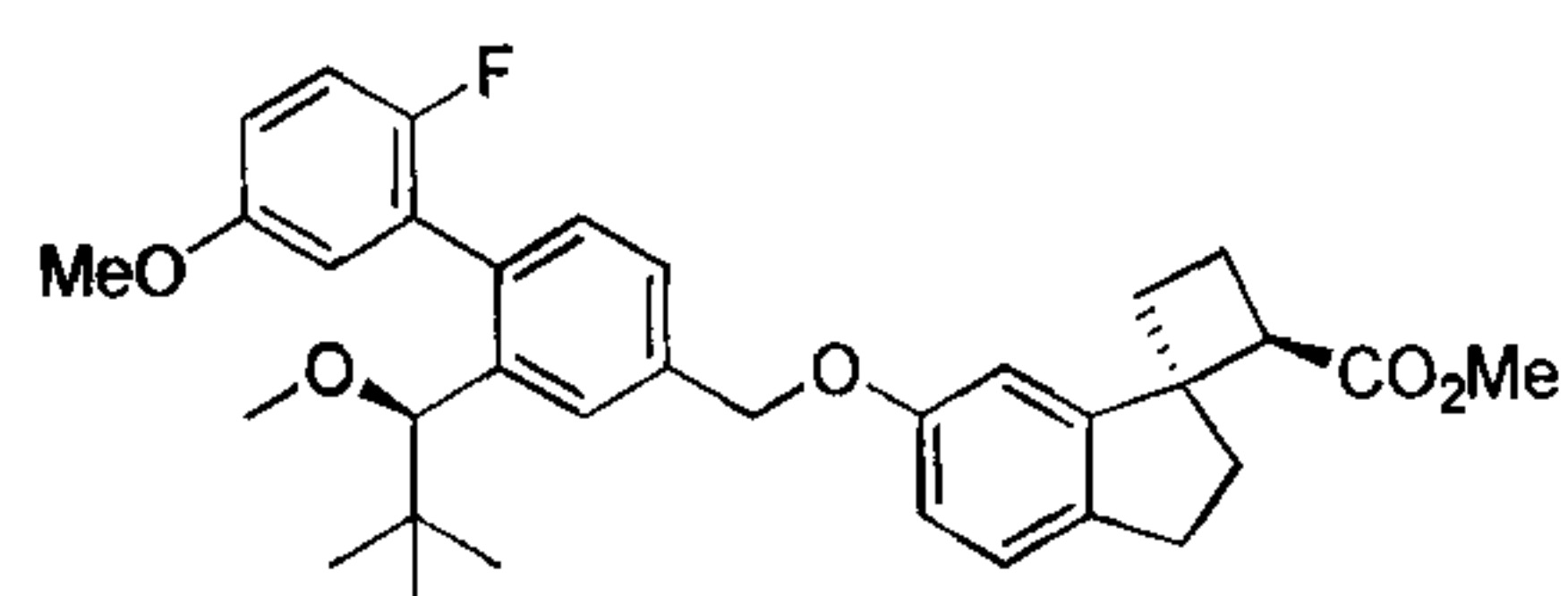
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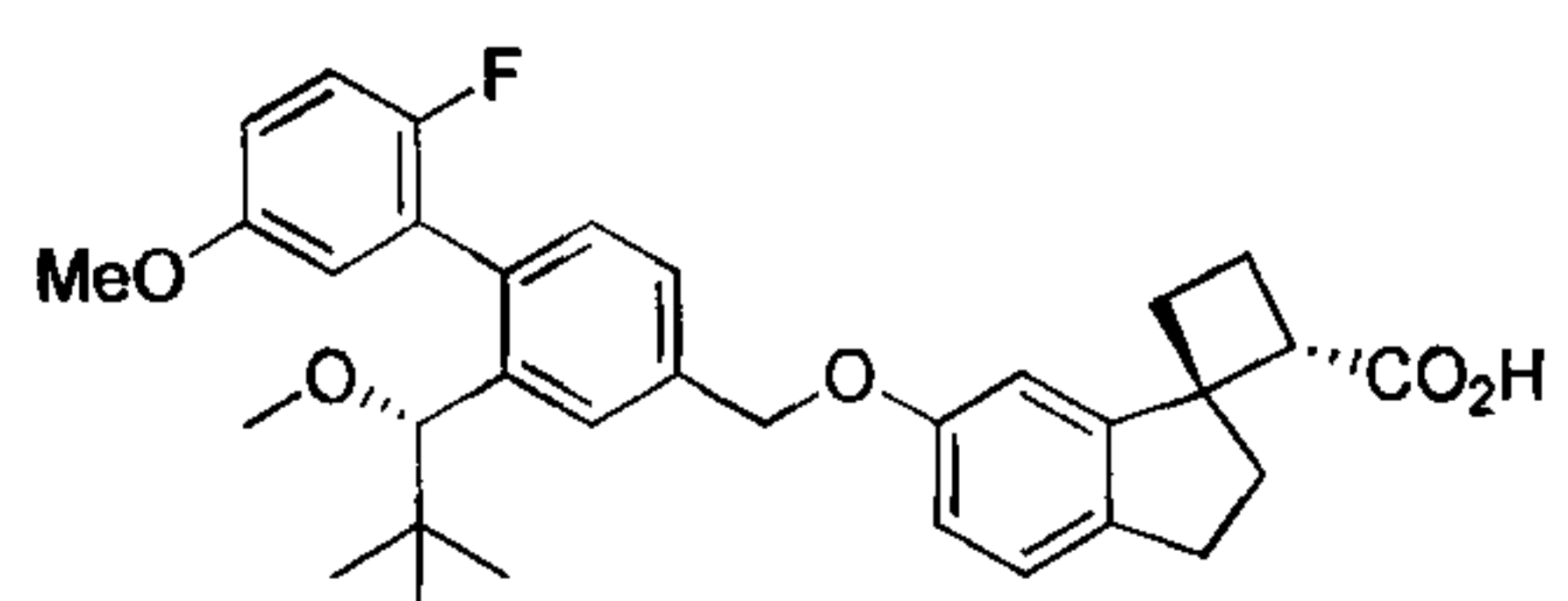
348. The compound



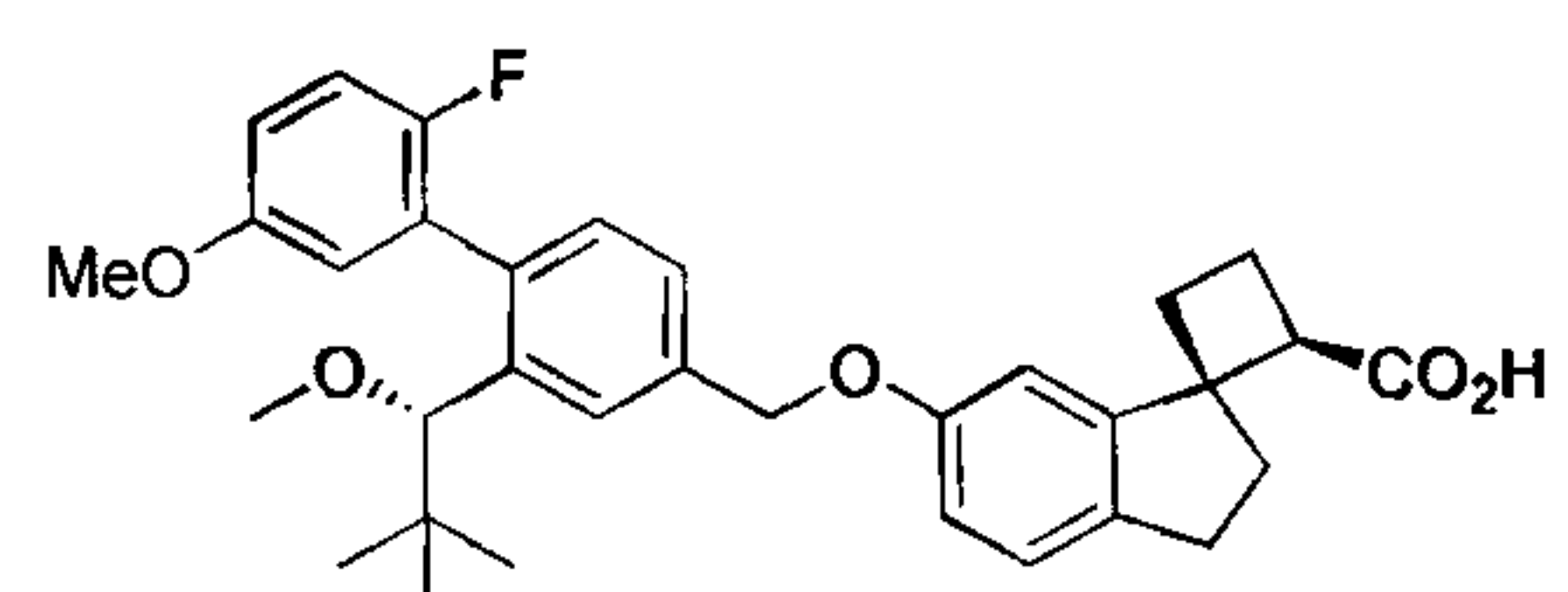
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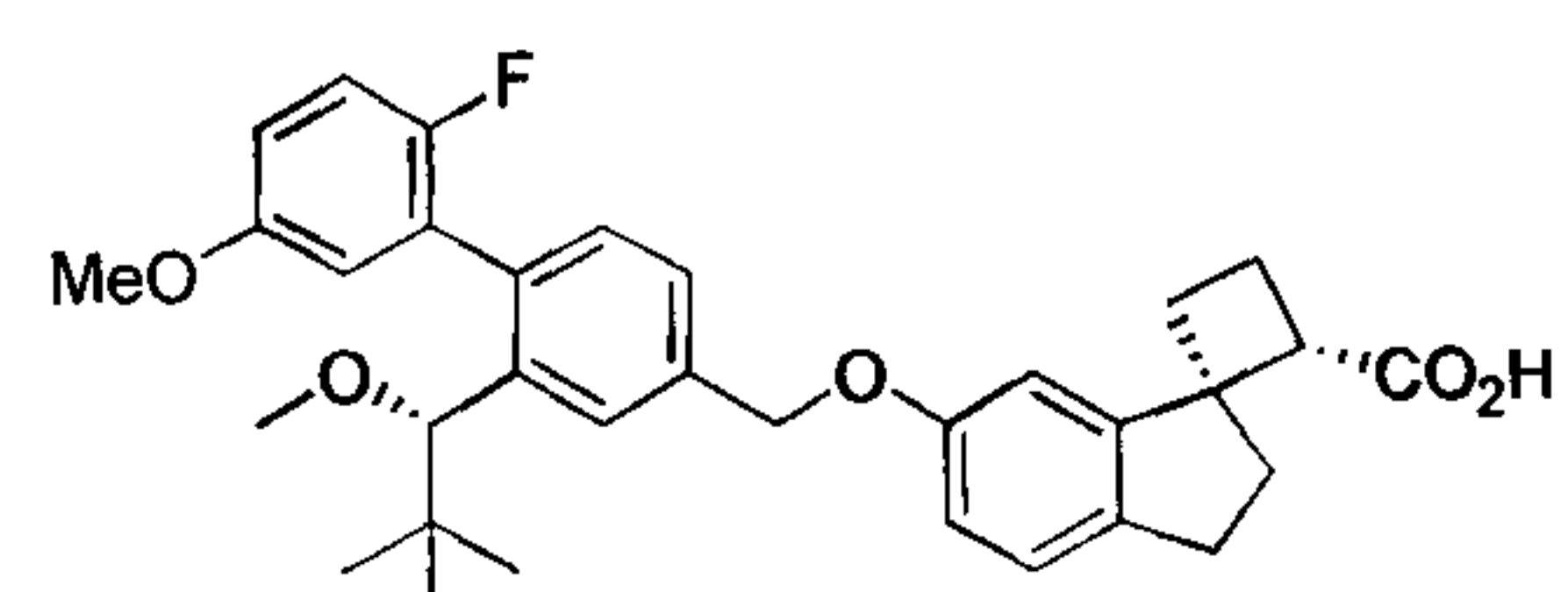
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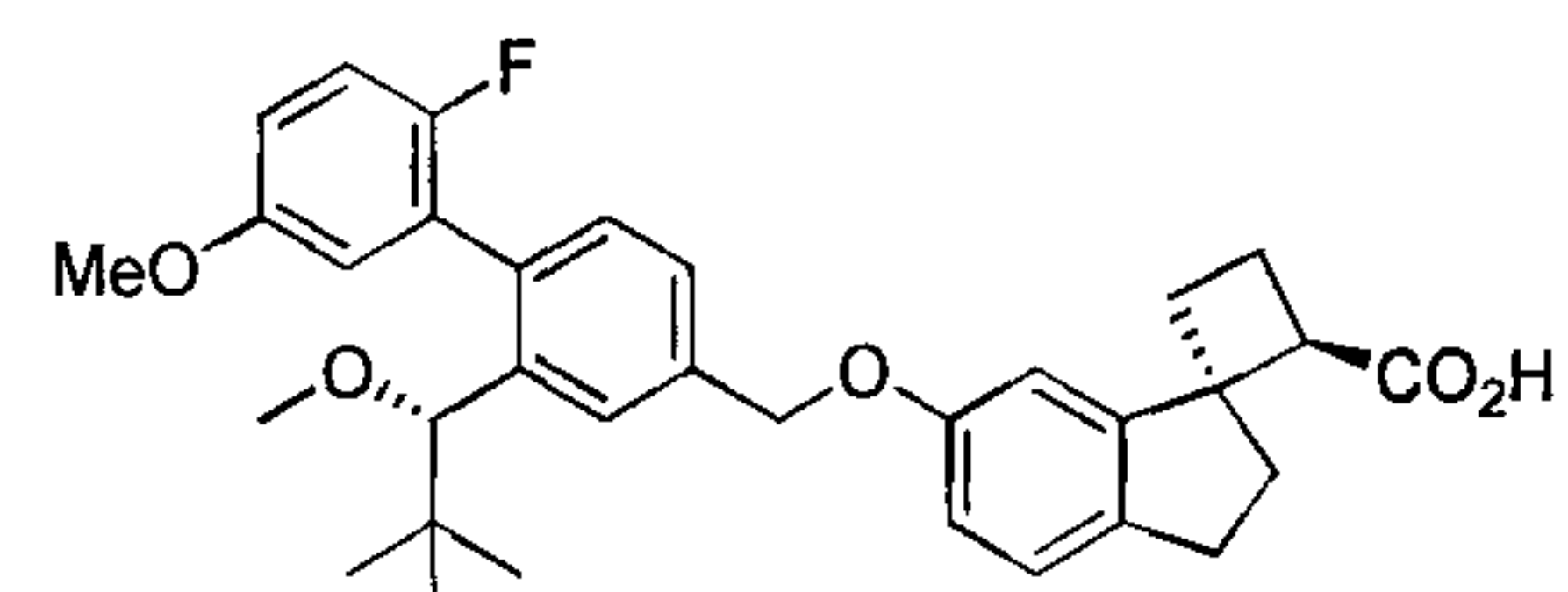
351. The compound



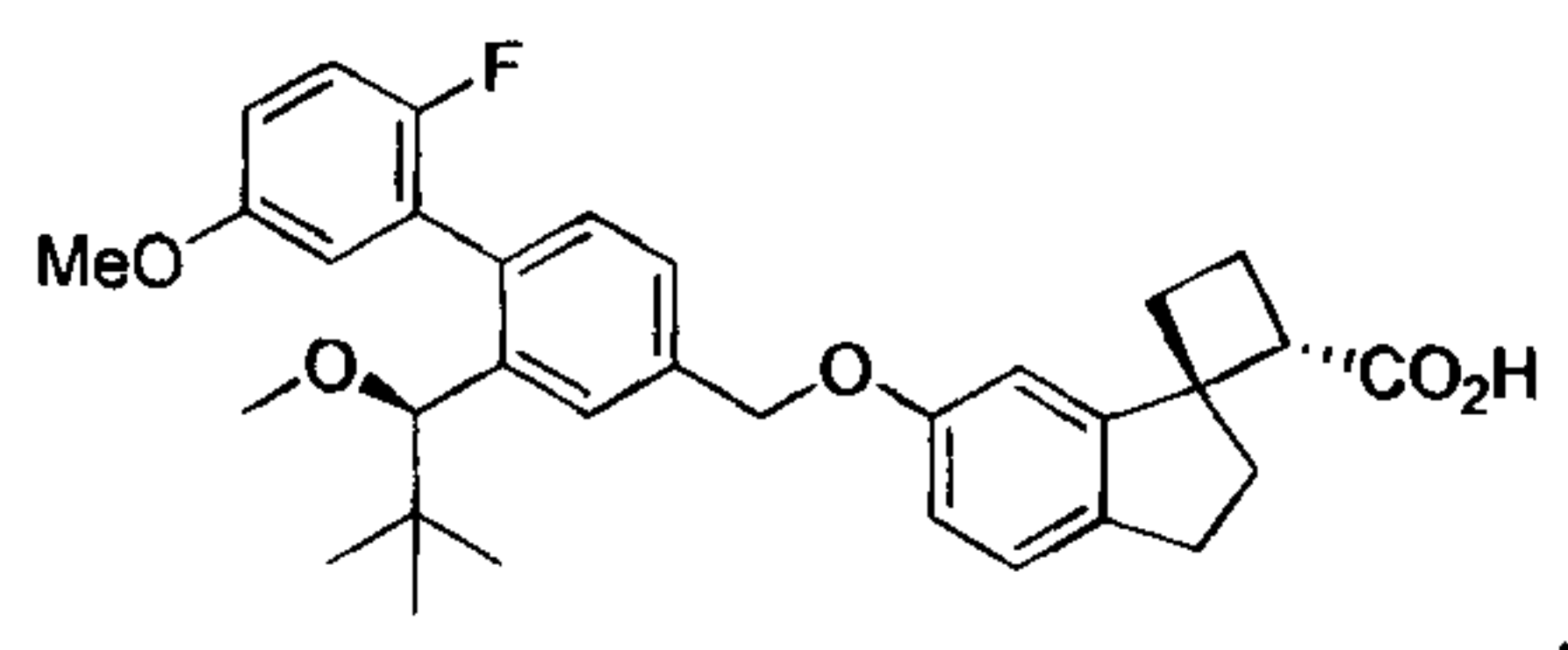
352. The compound



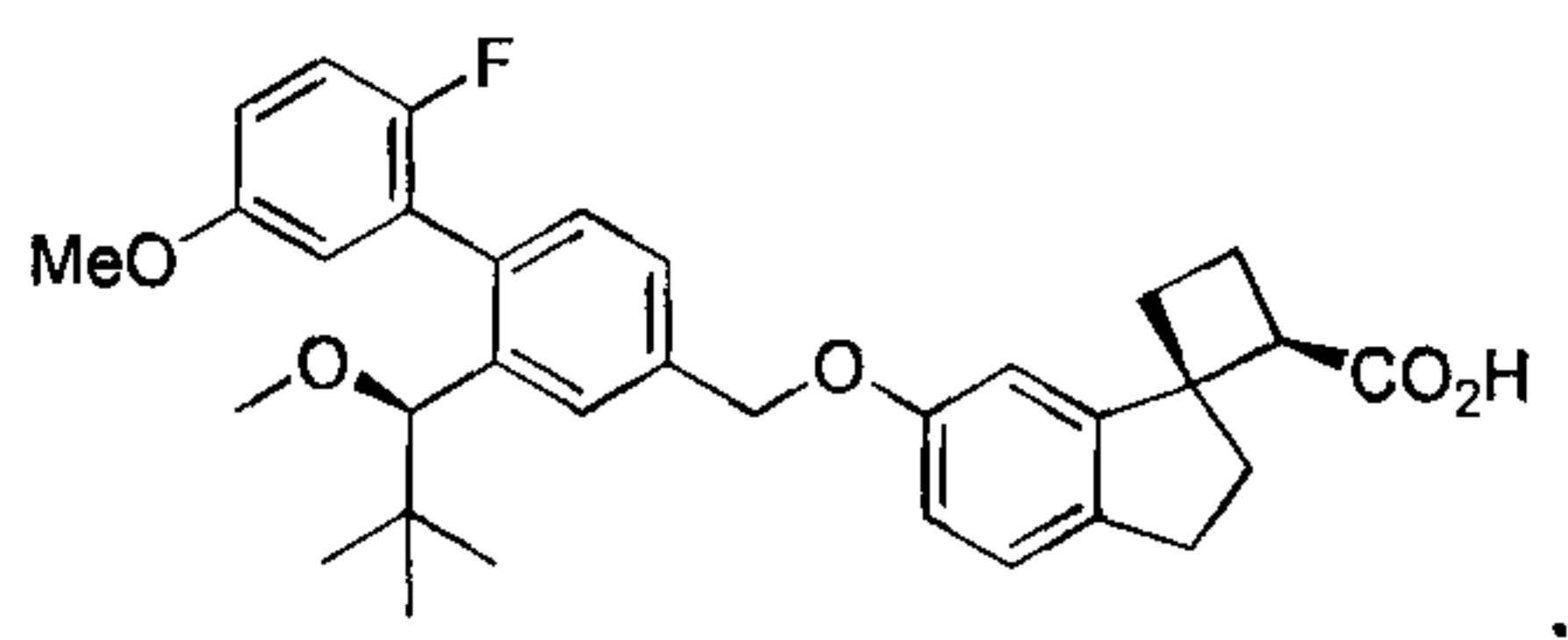
353. The compound



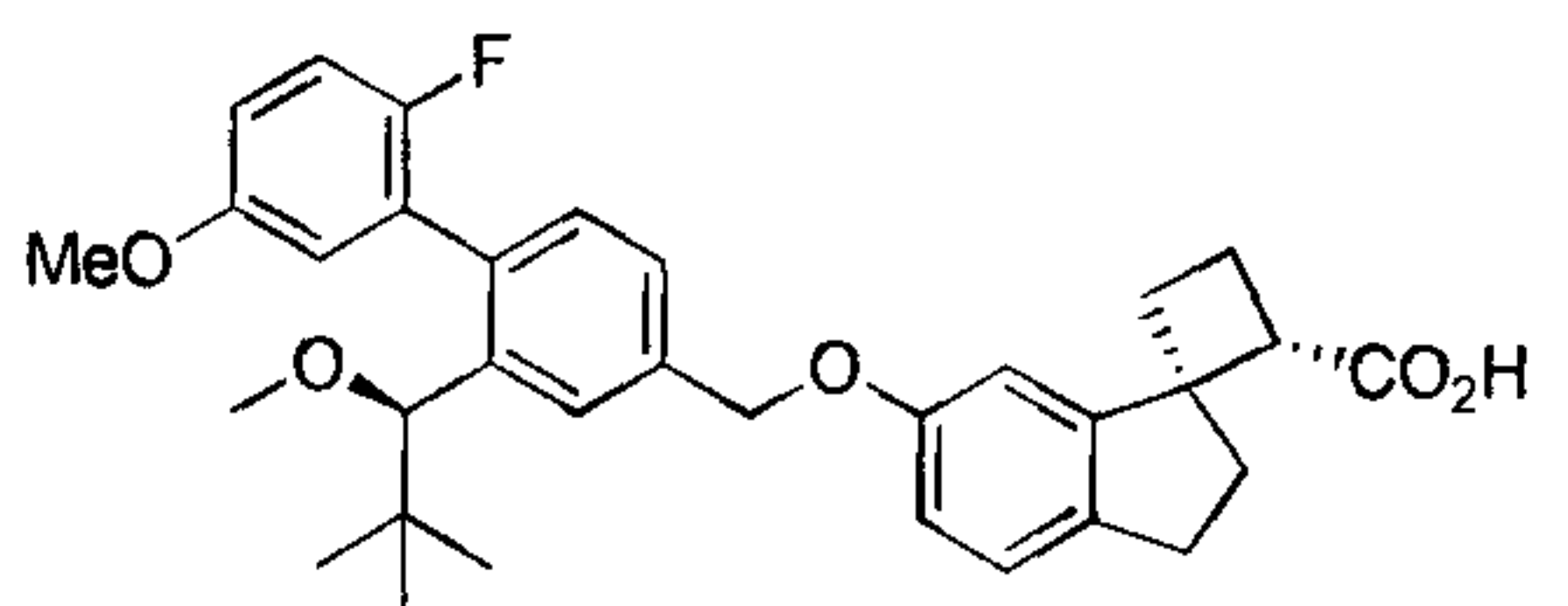
354. The compound



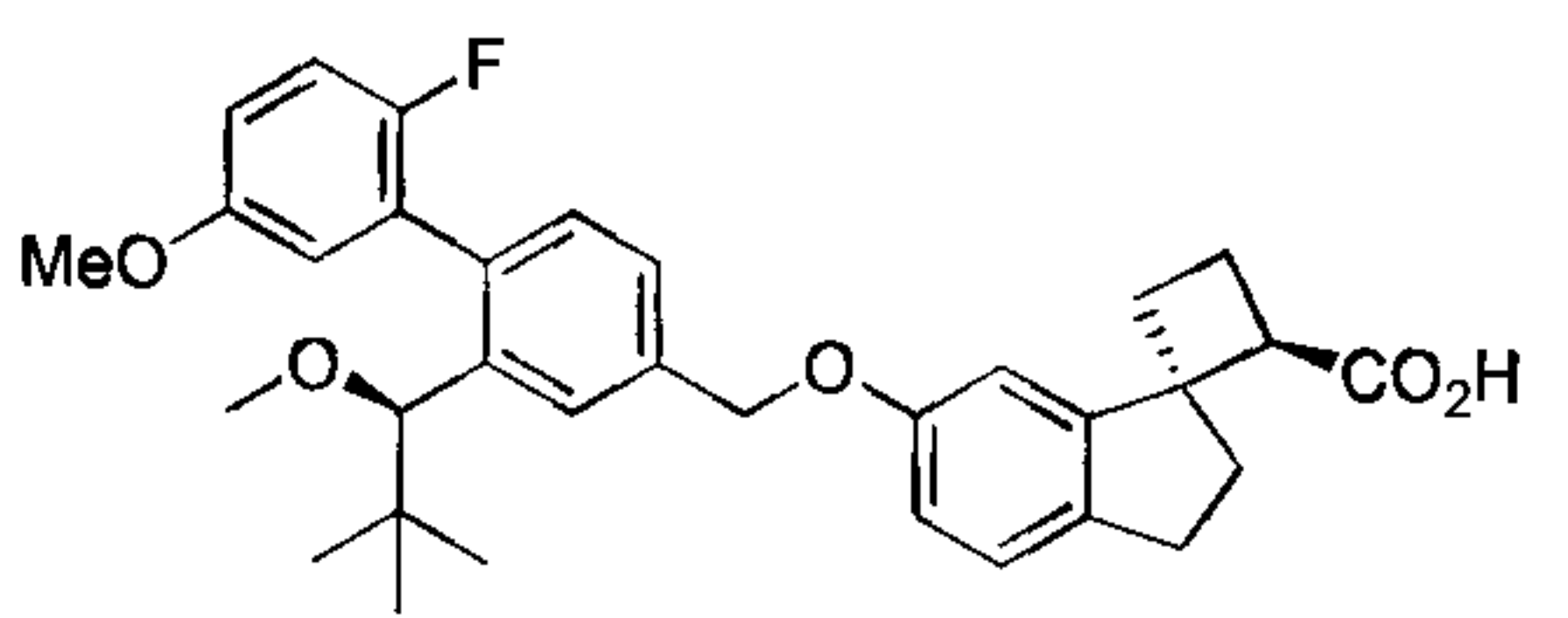
355. The compound



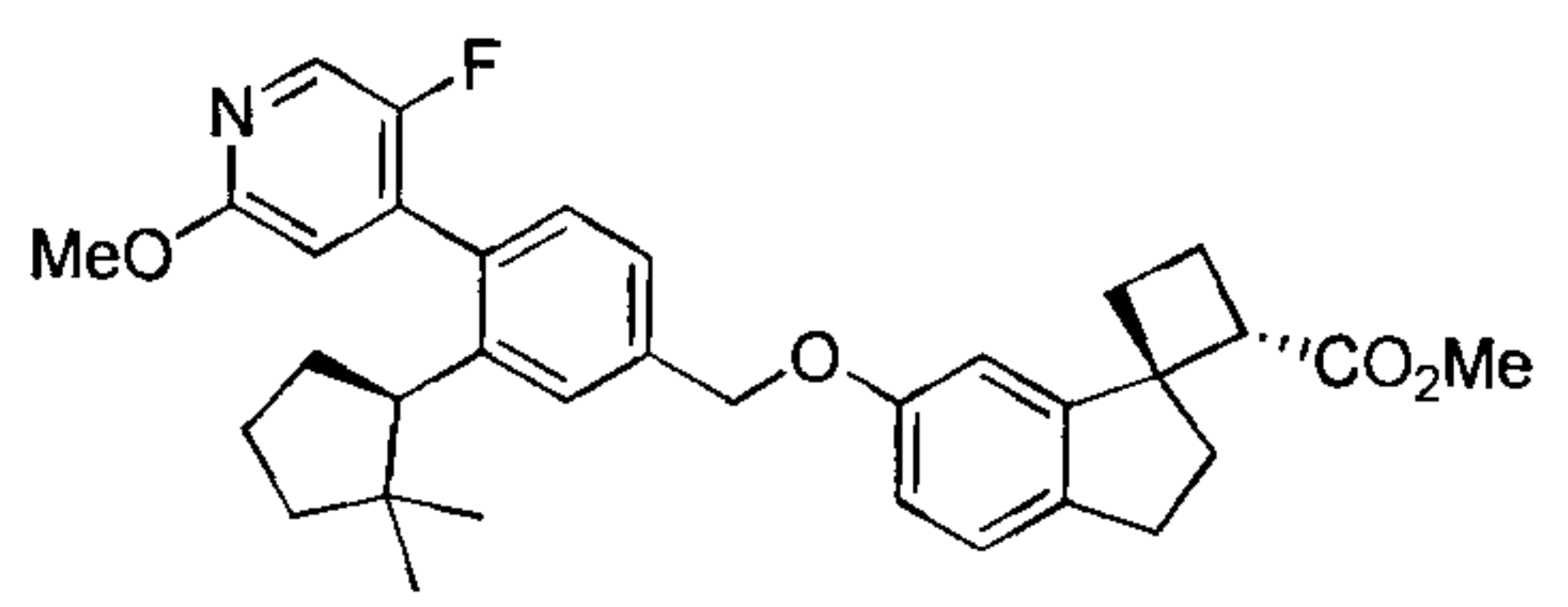
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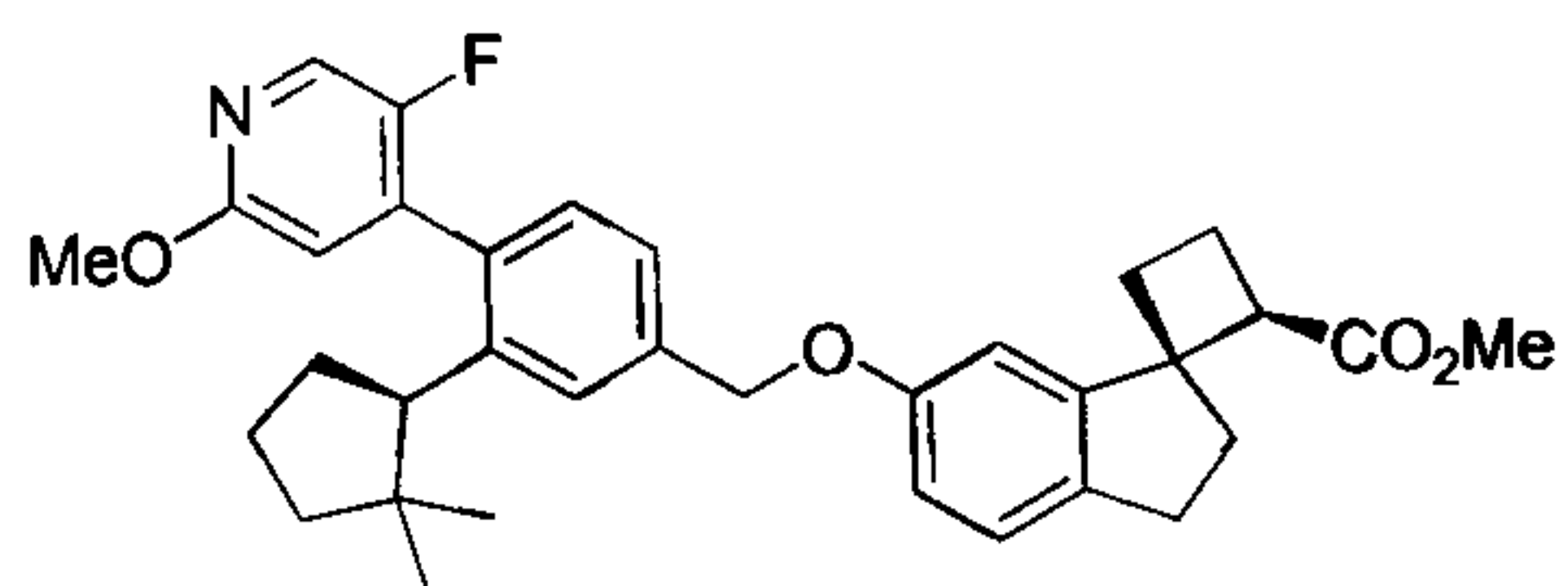
357. The compound



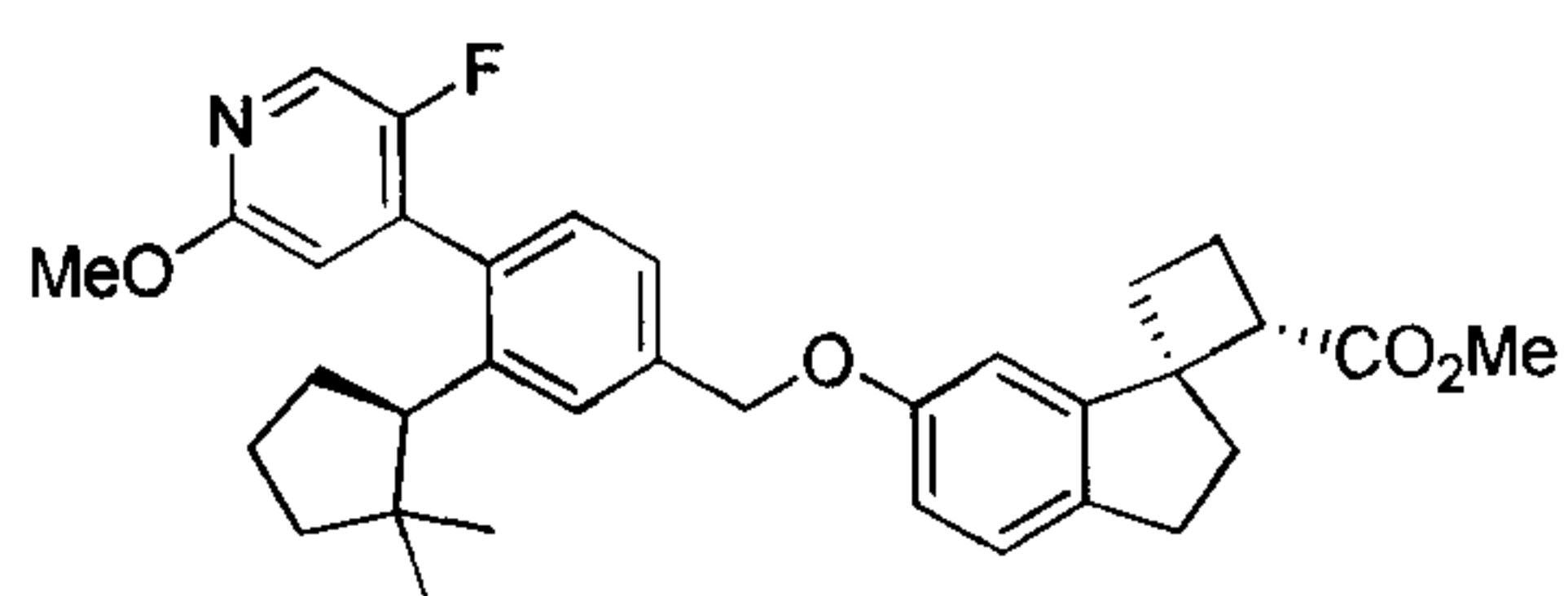
358. The compound



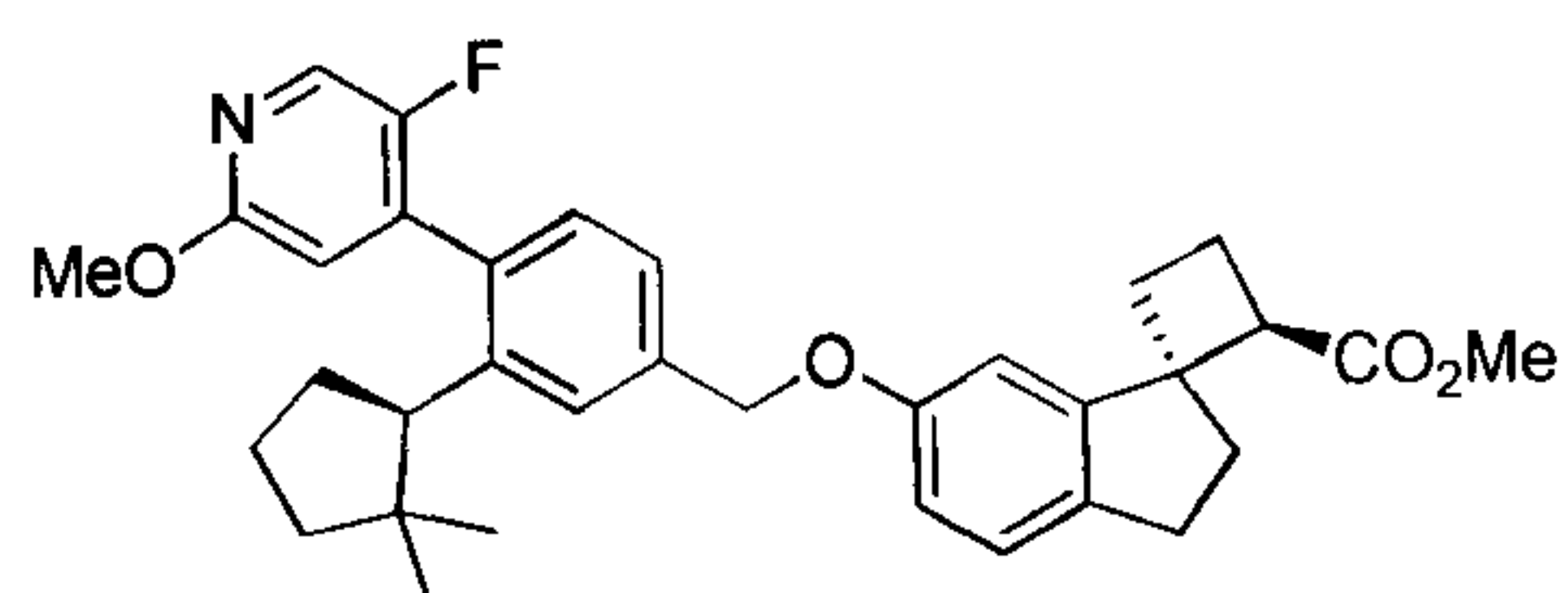
359. The compound



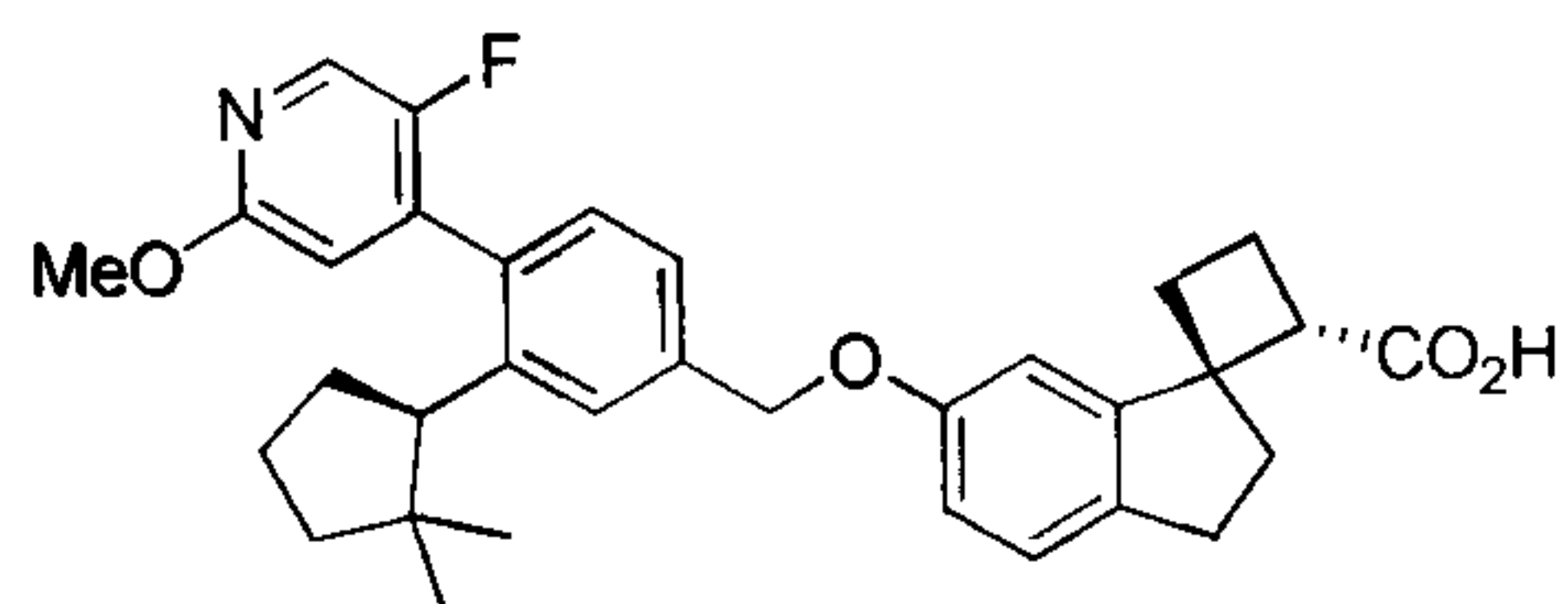
360. The compound



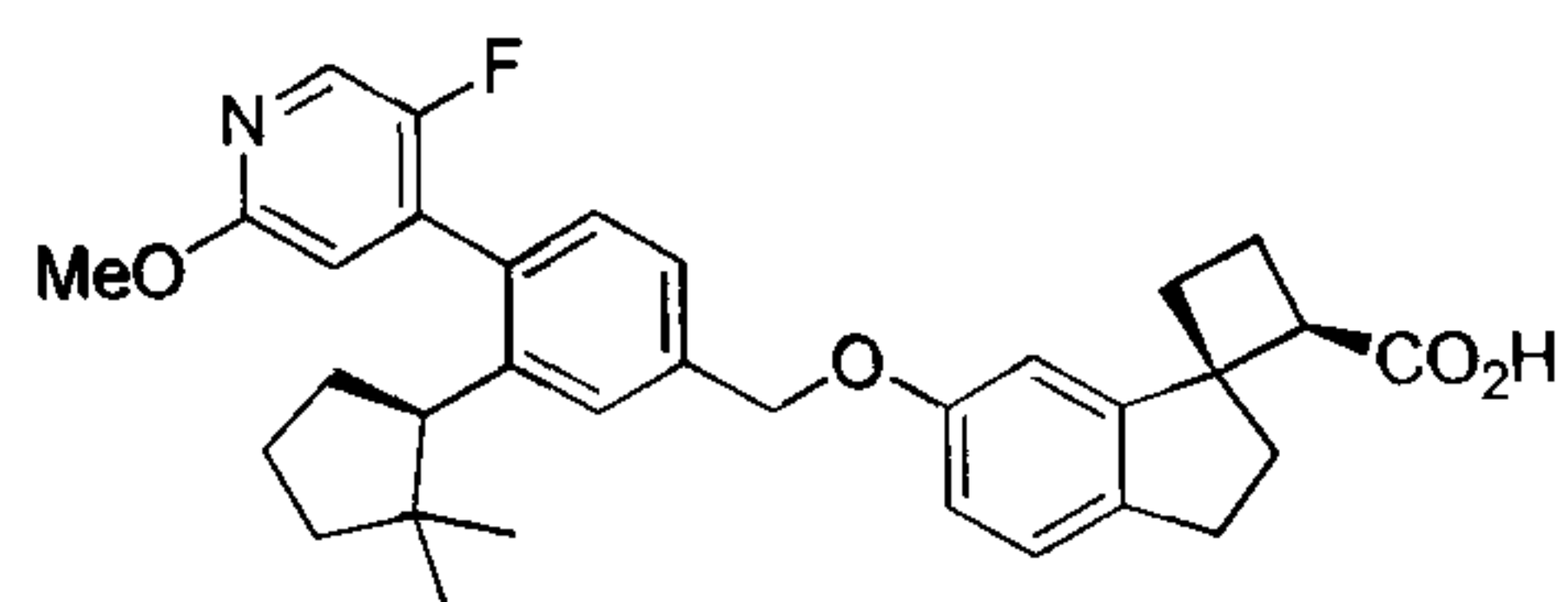
361. The compound



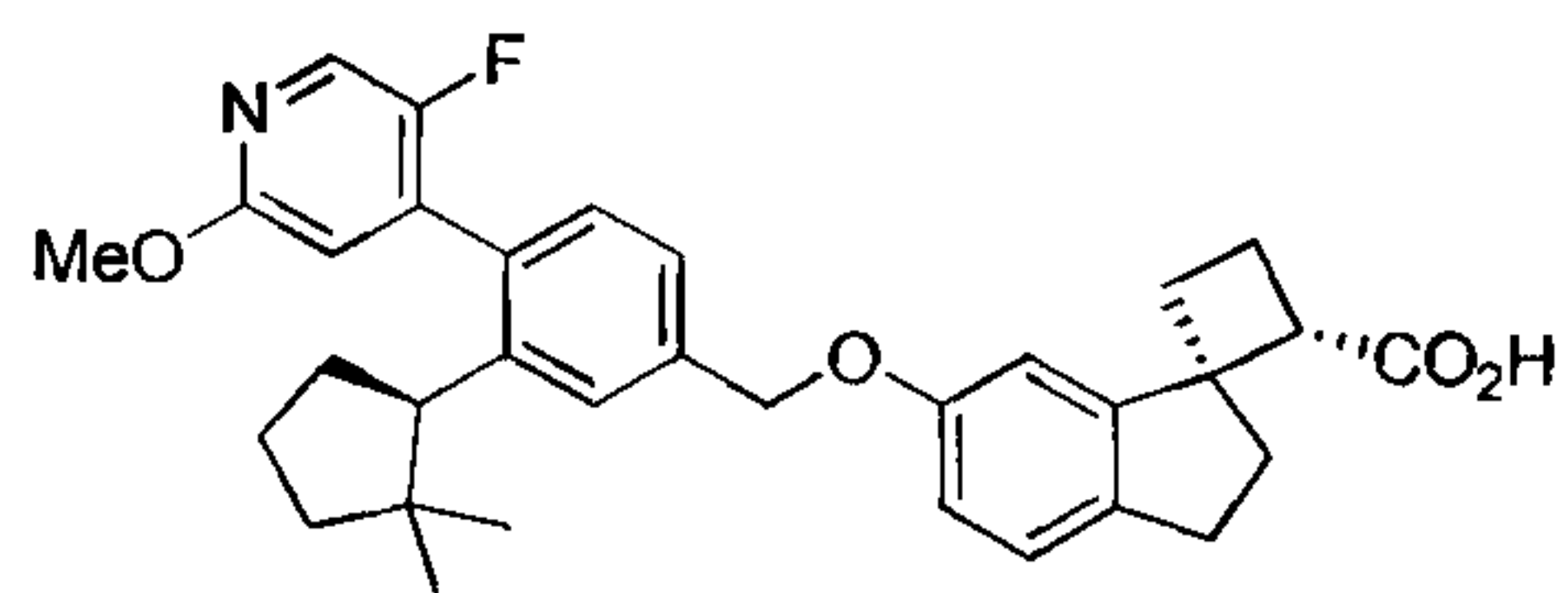
362. The compound



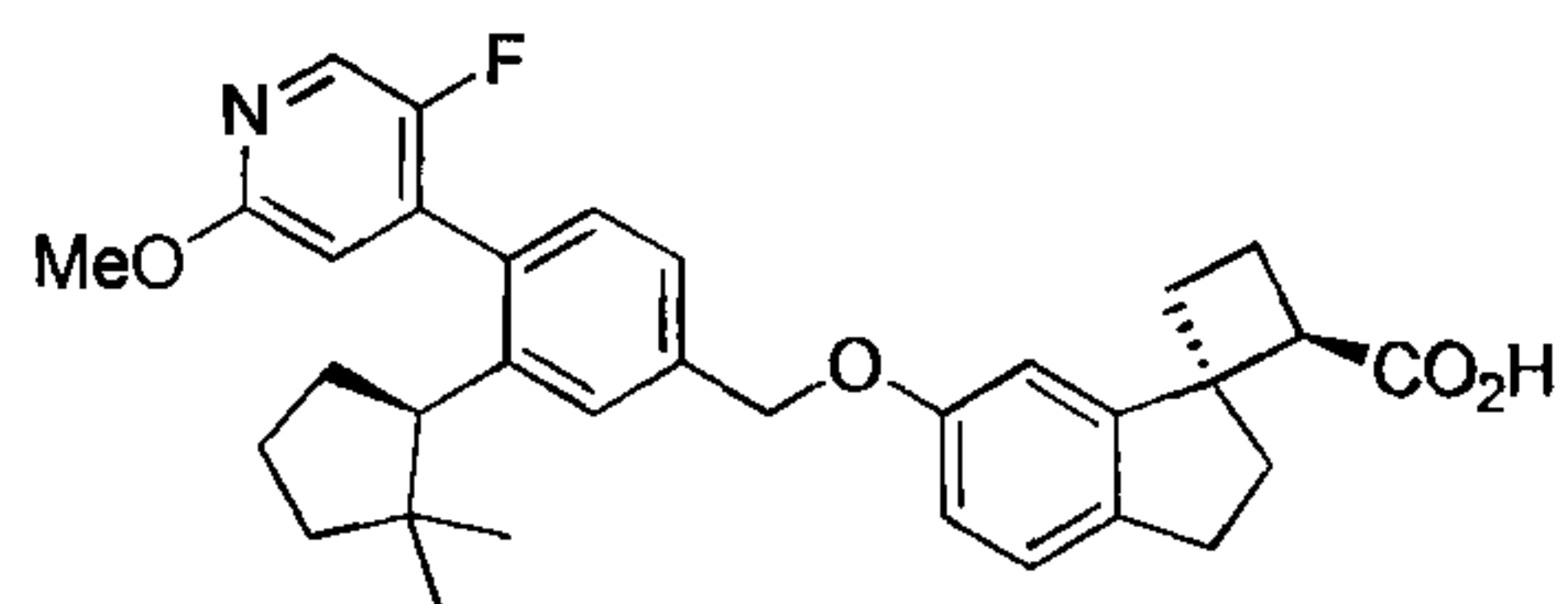
363. The compound



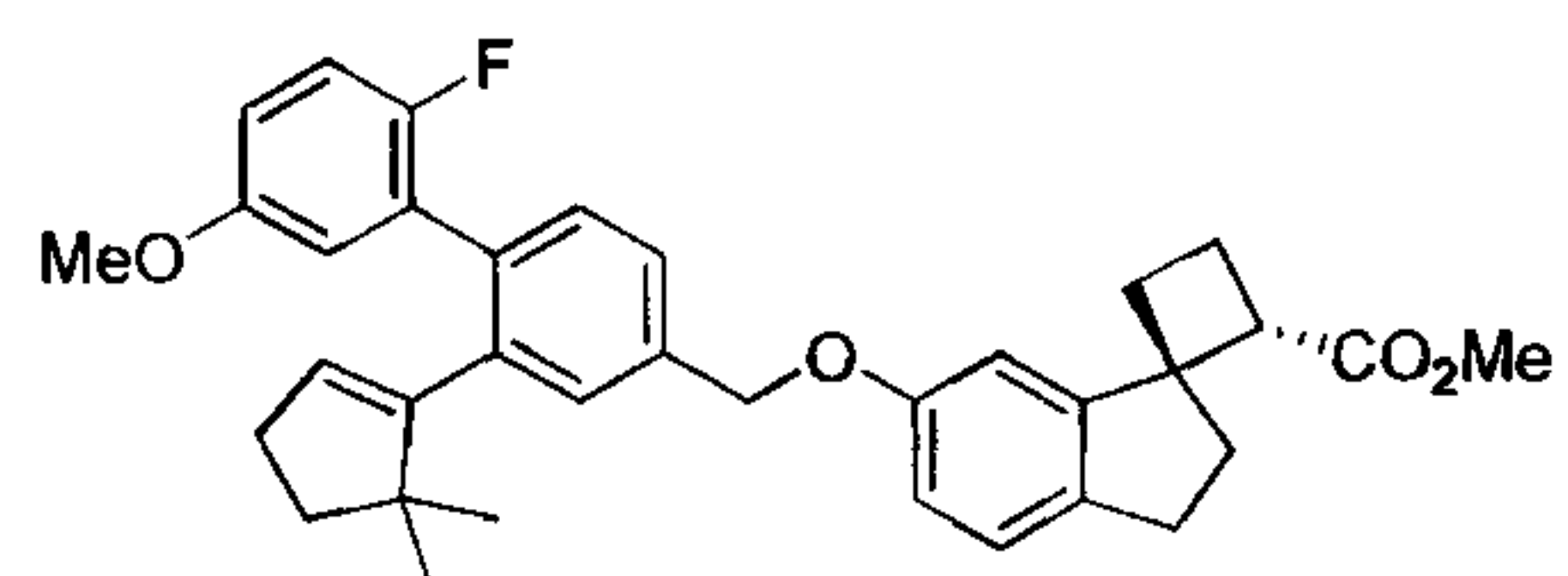
364. The compound



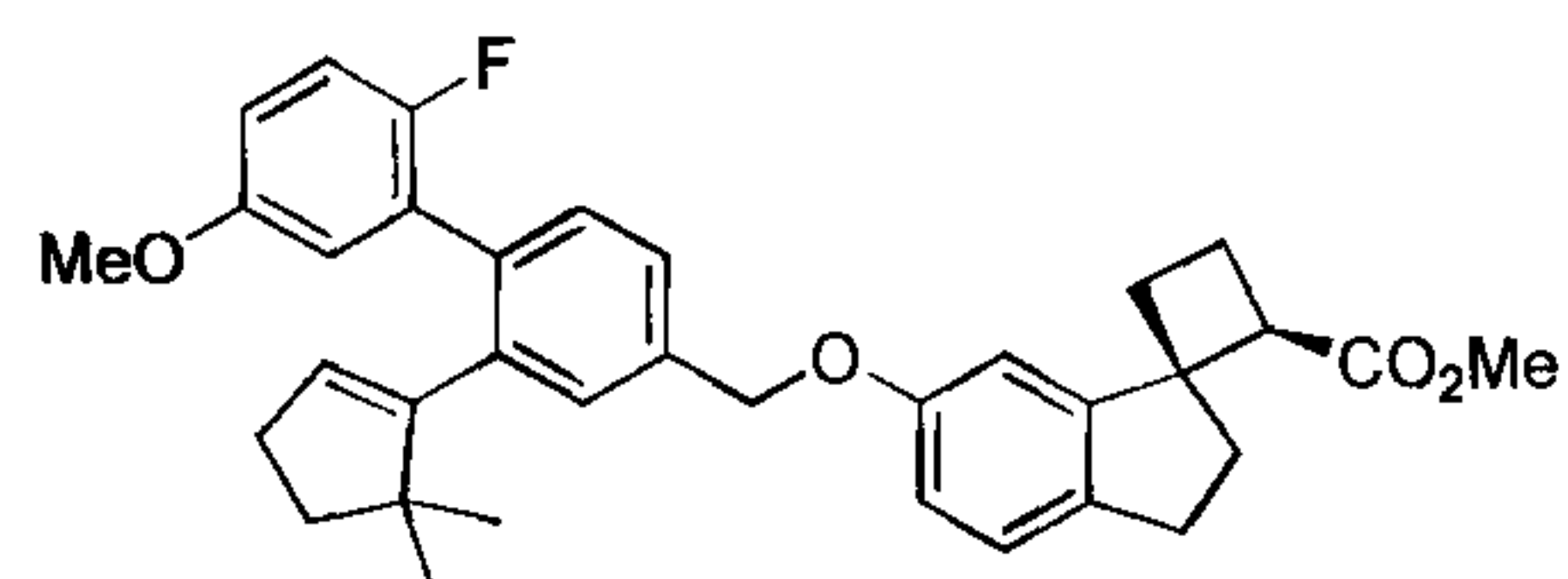
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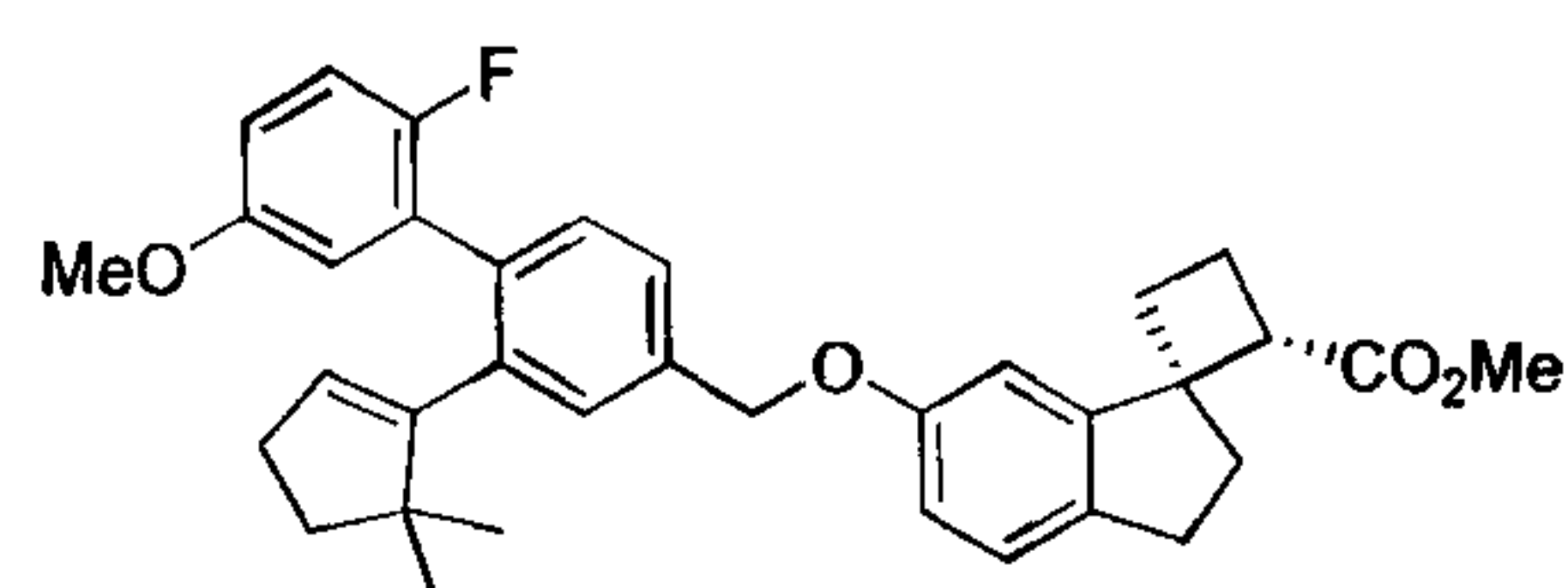
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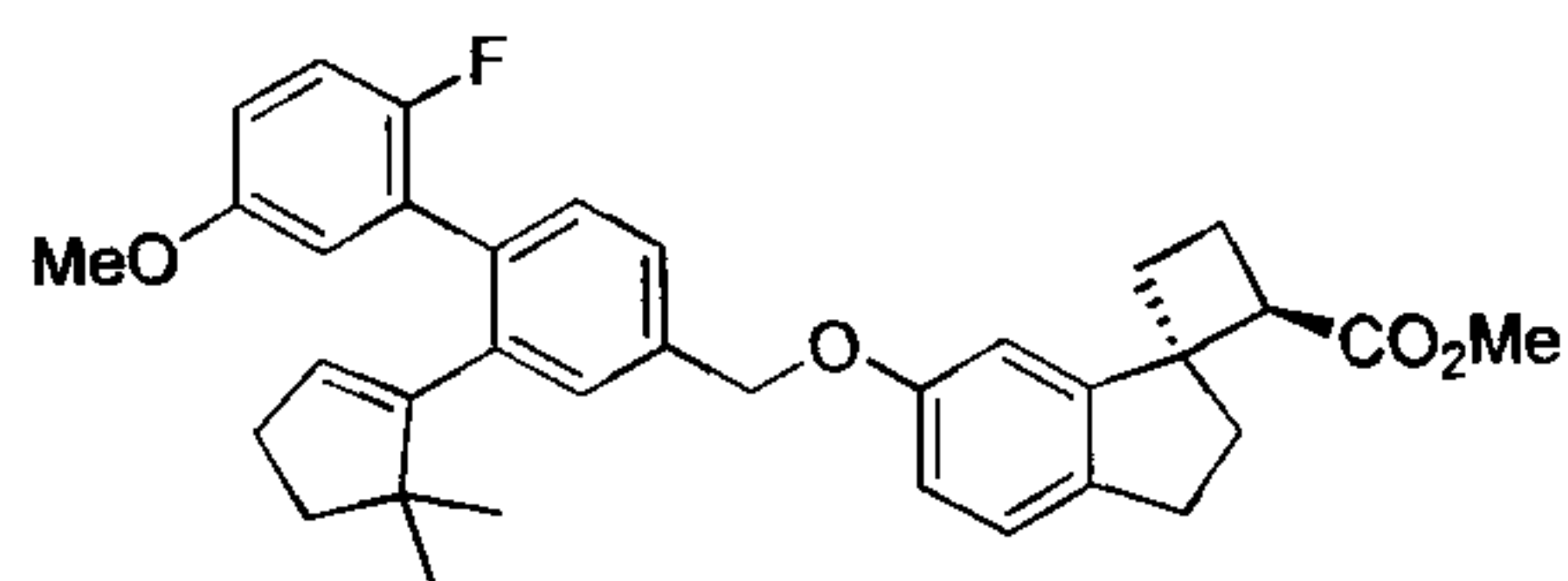
367. The compound



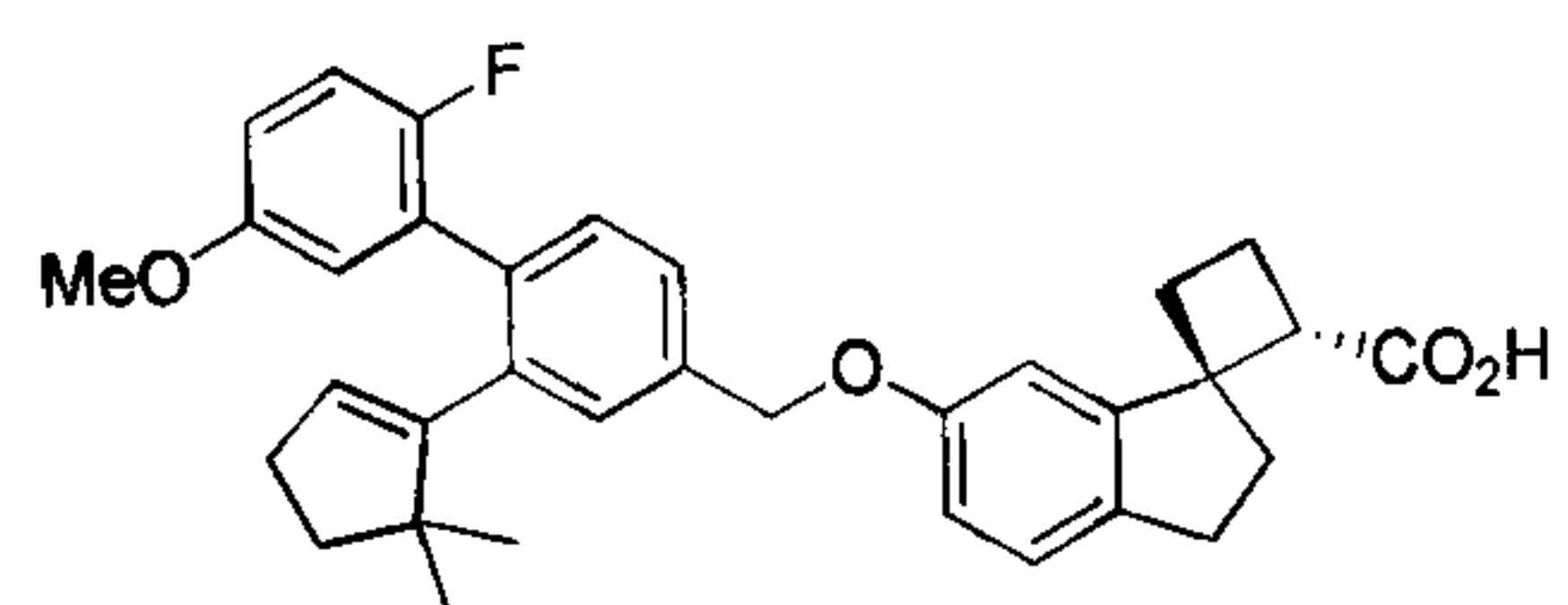
368. The compound



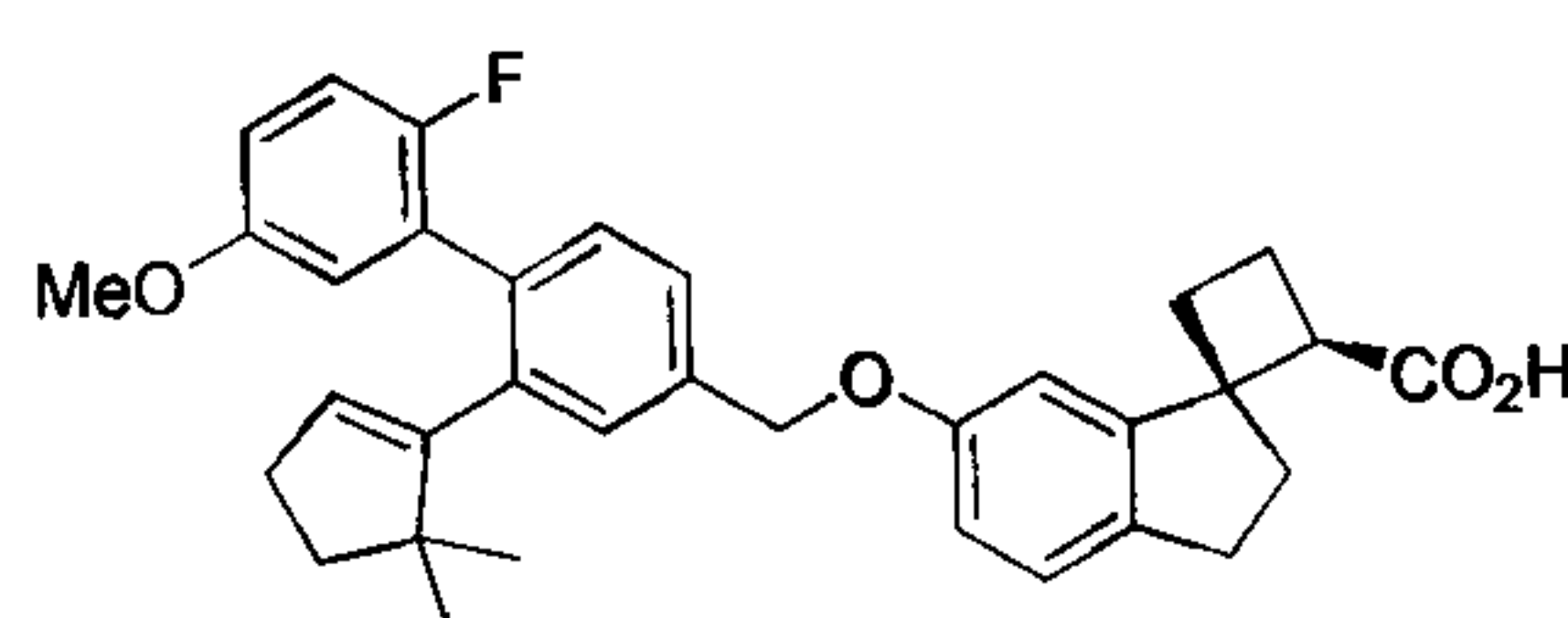
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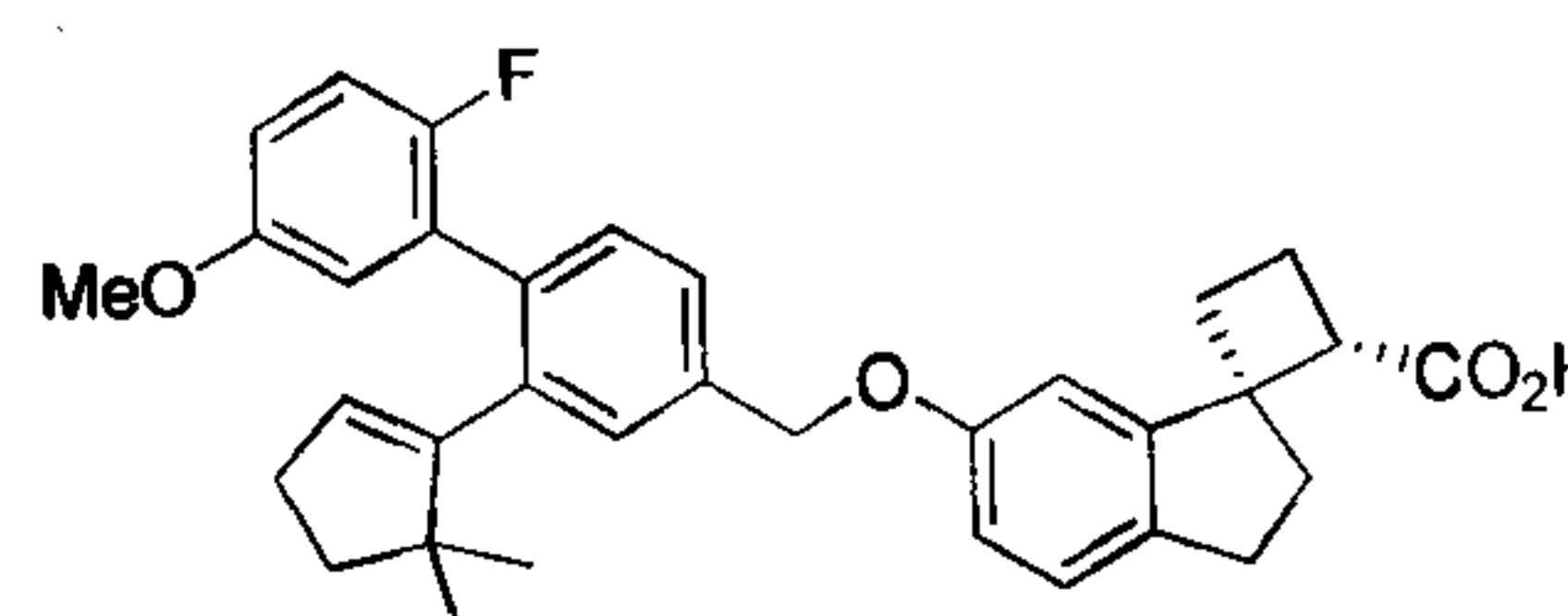
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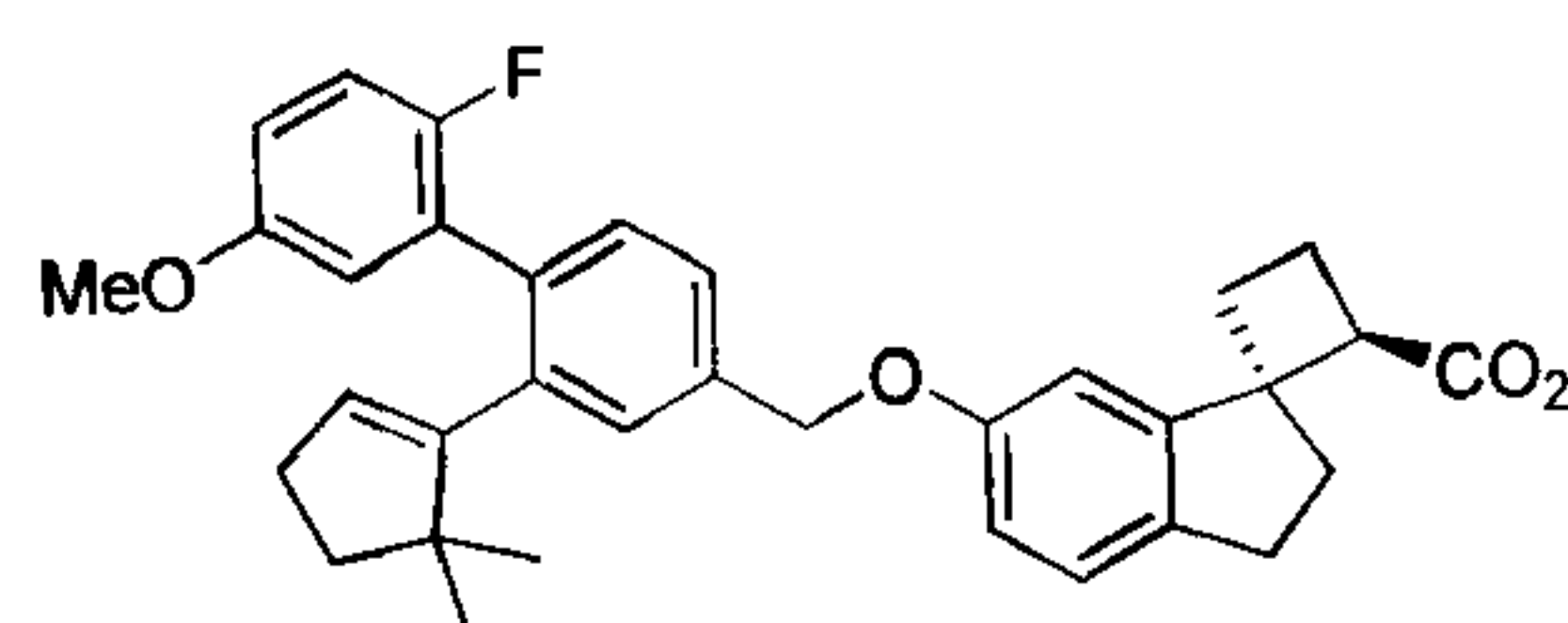
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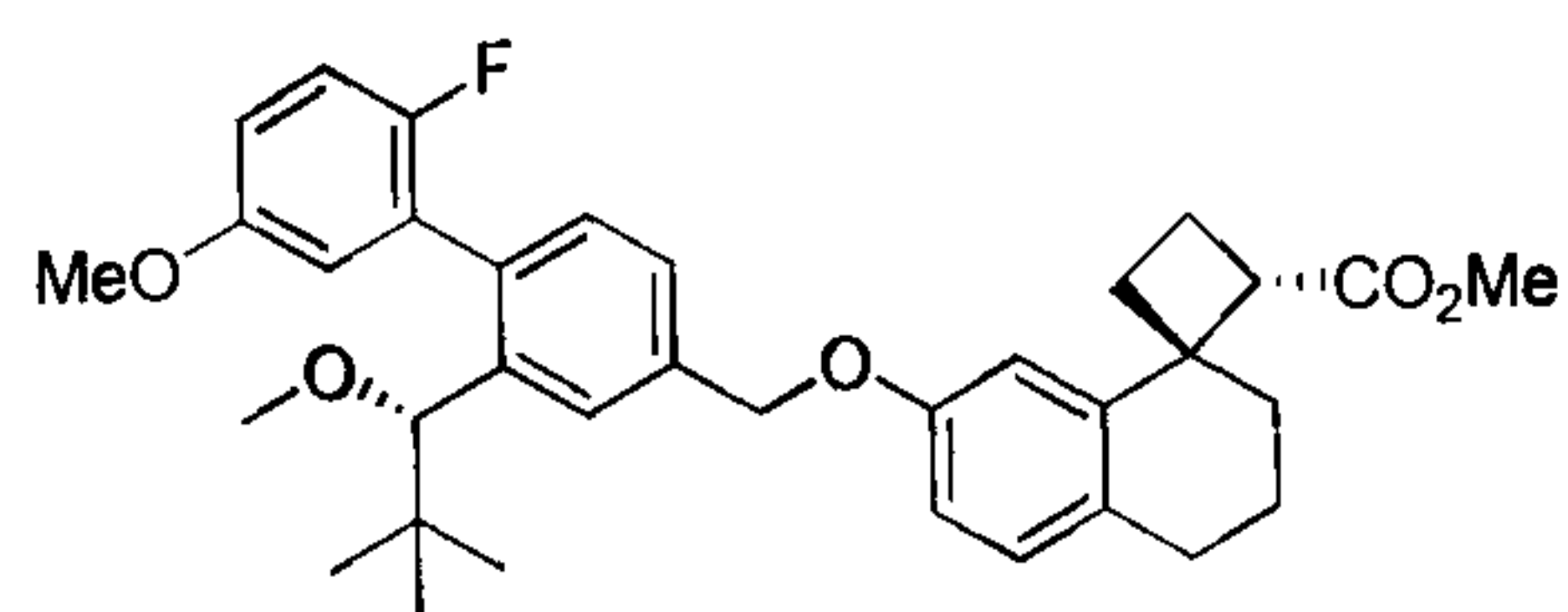
372. The compound



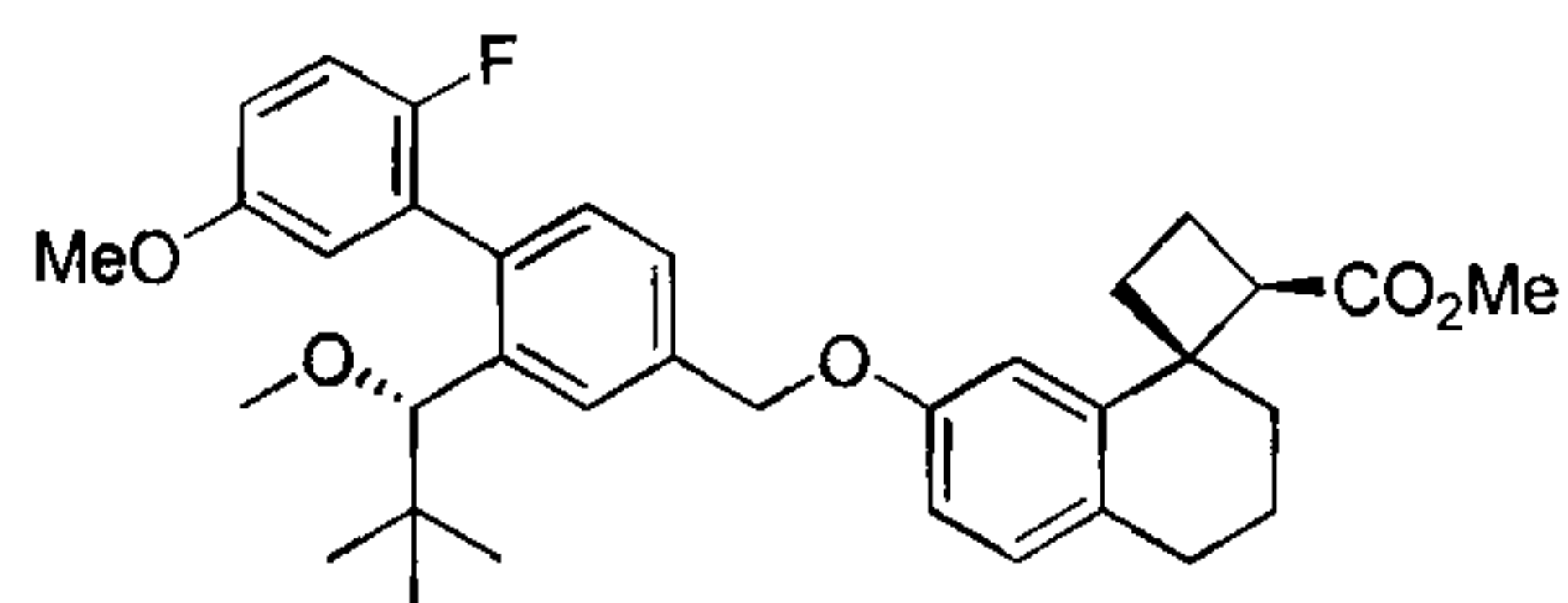
373. The compound



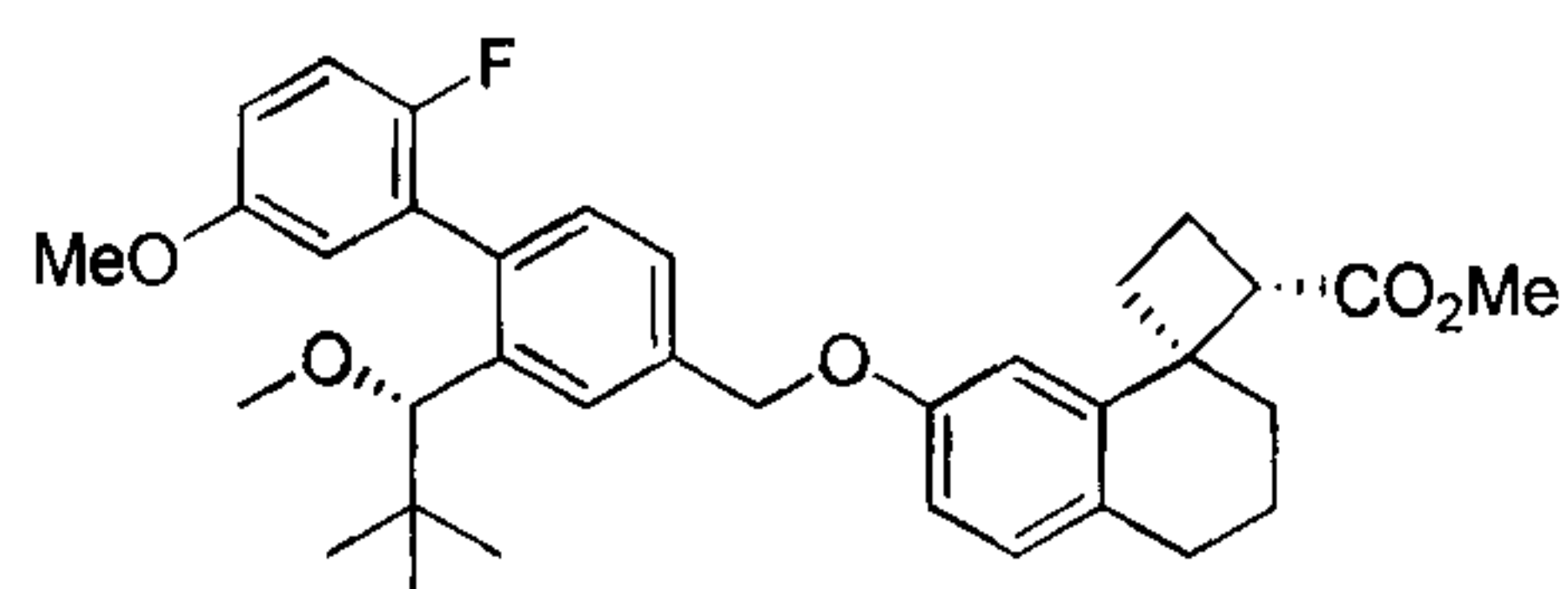
374. The compound



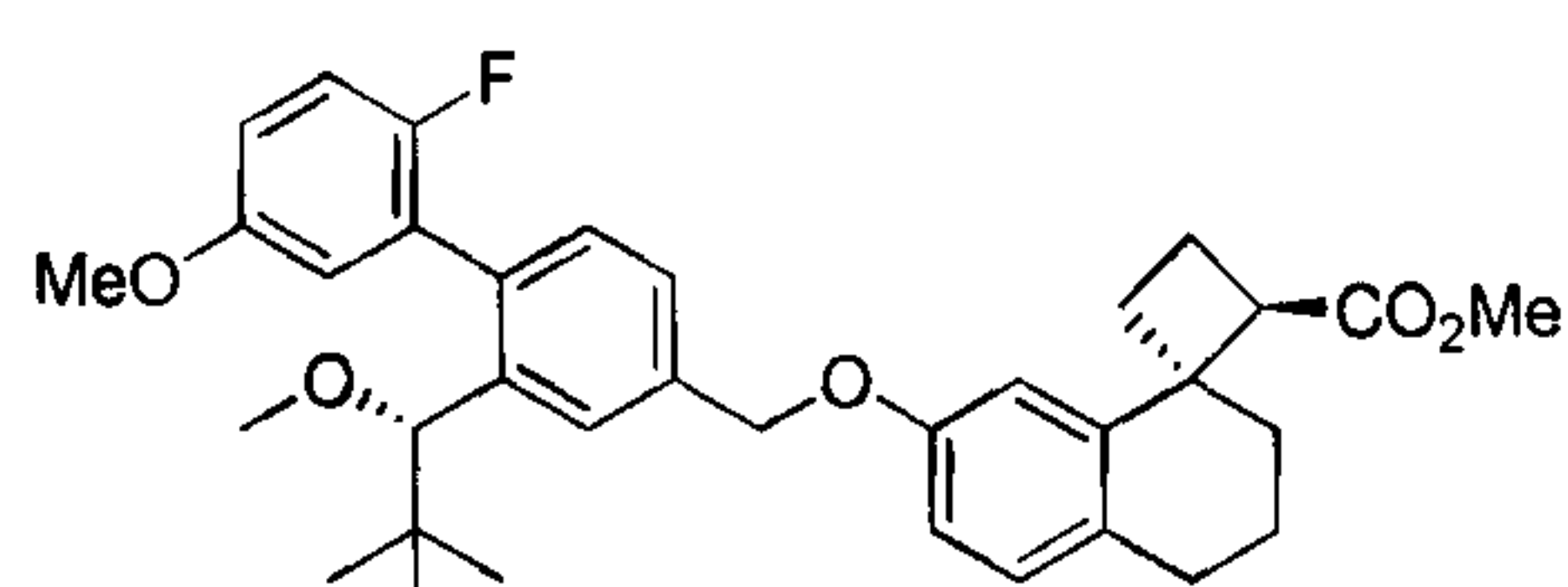
375. The compound



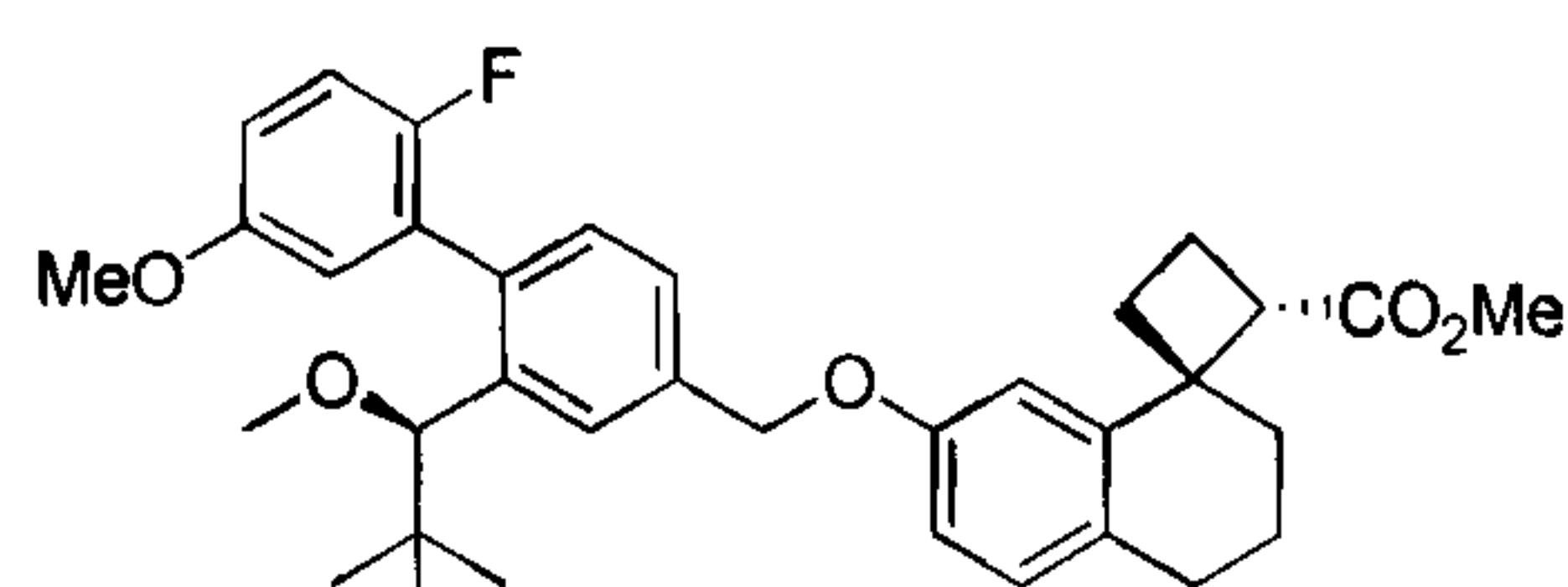
376. The compound



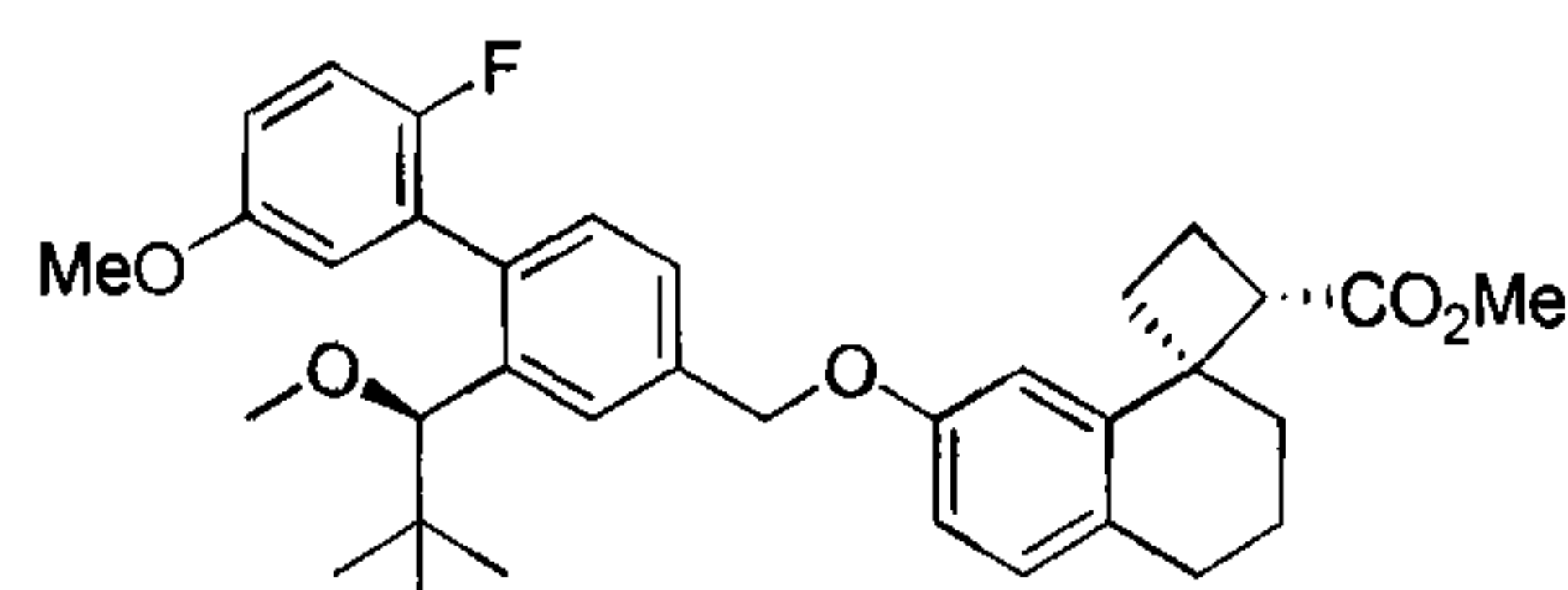
377. The compound



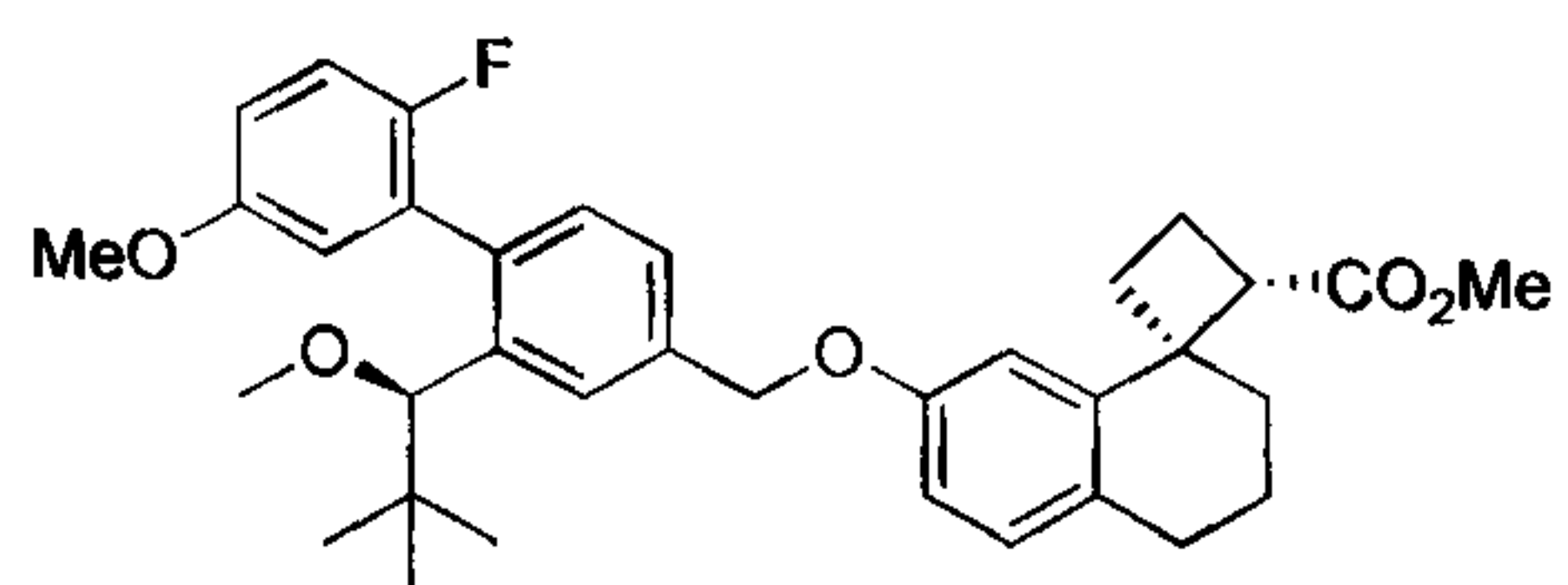
378. The compound



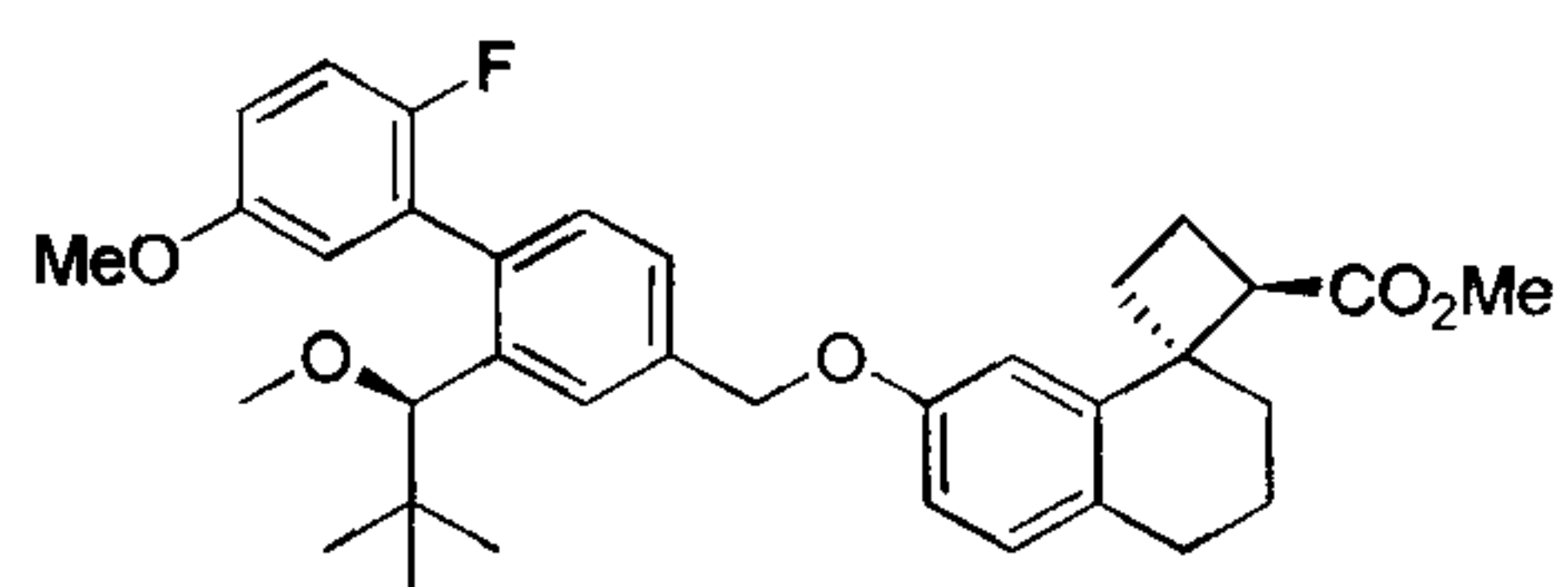
379. The compound



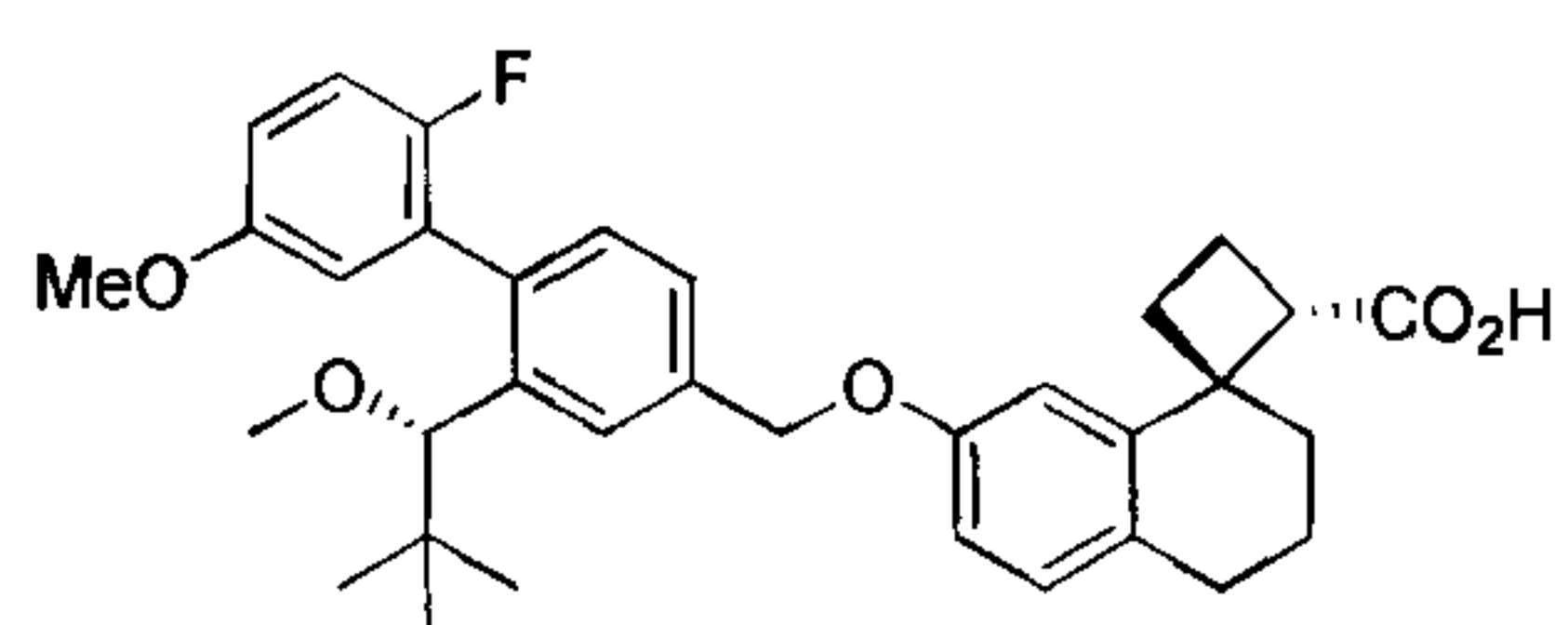
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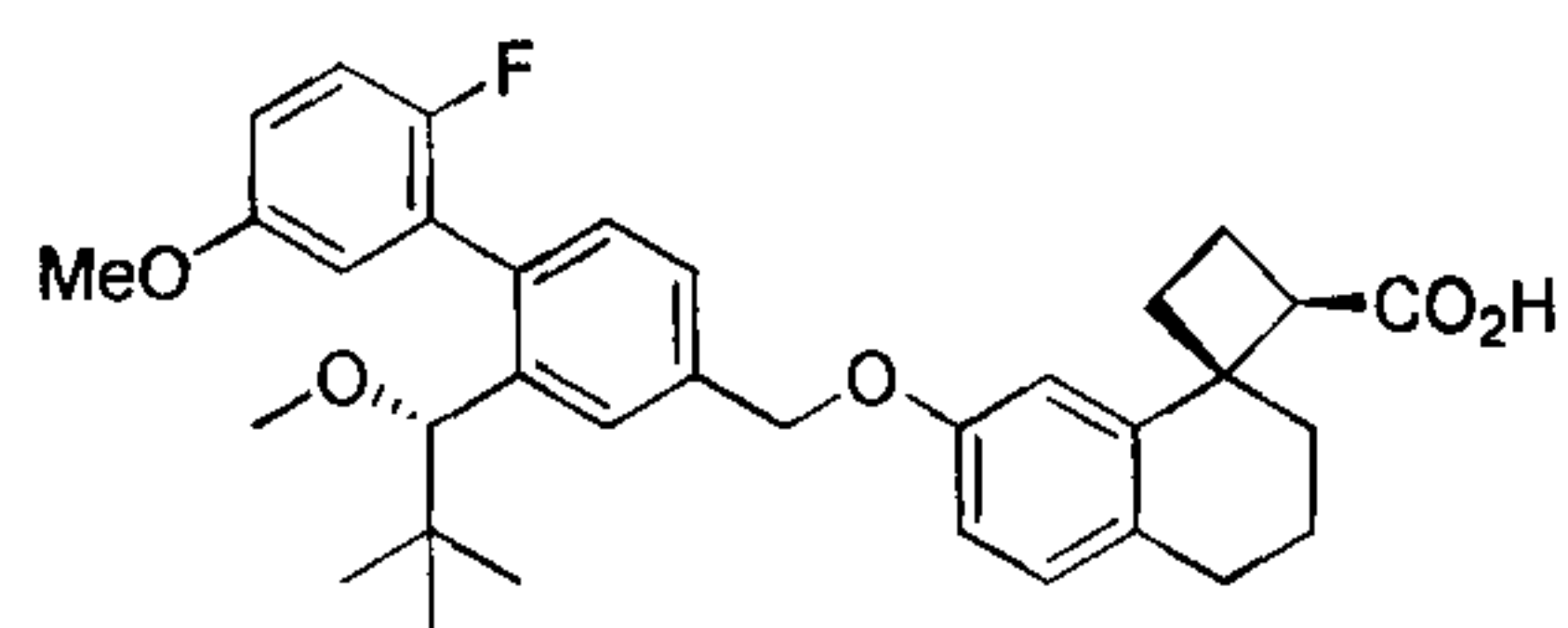
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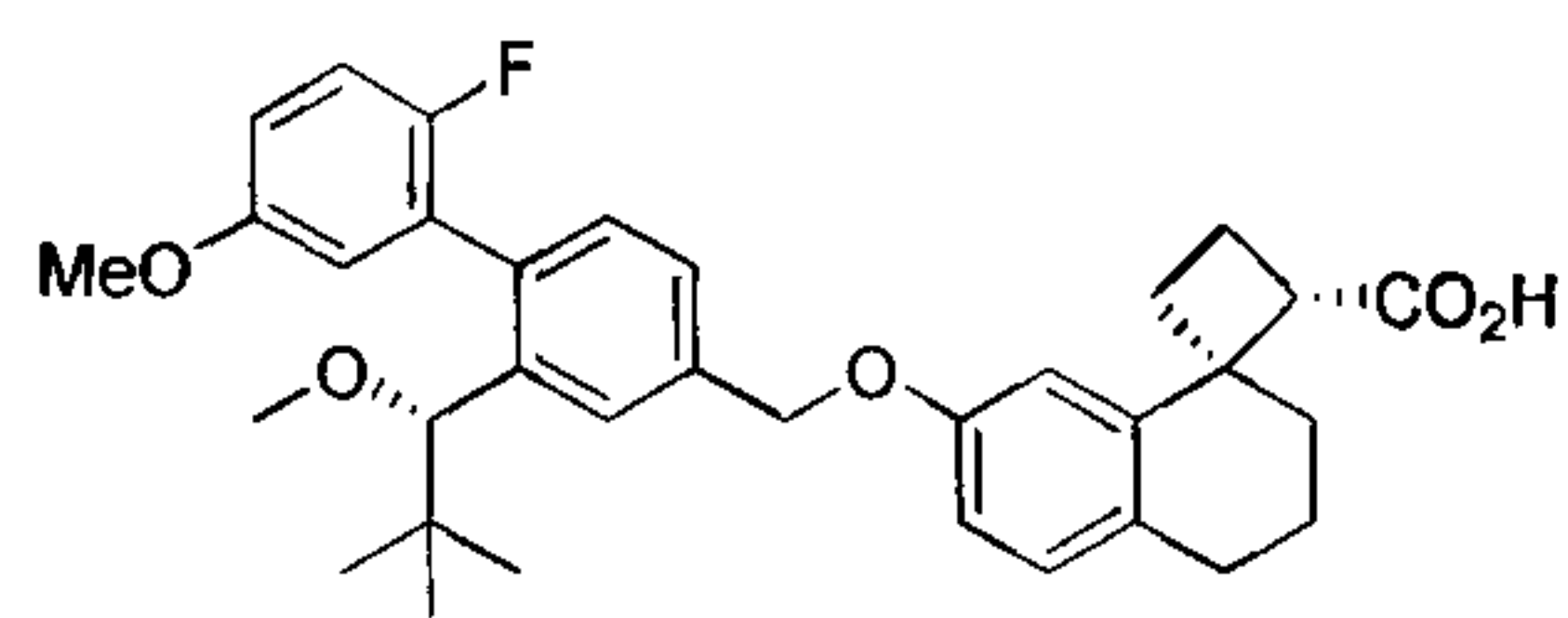
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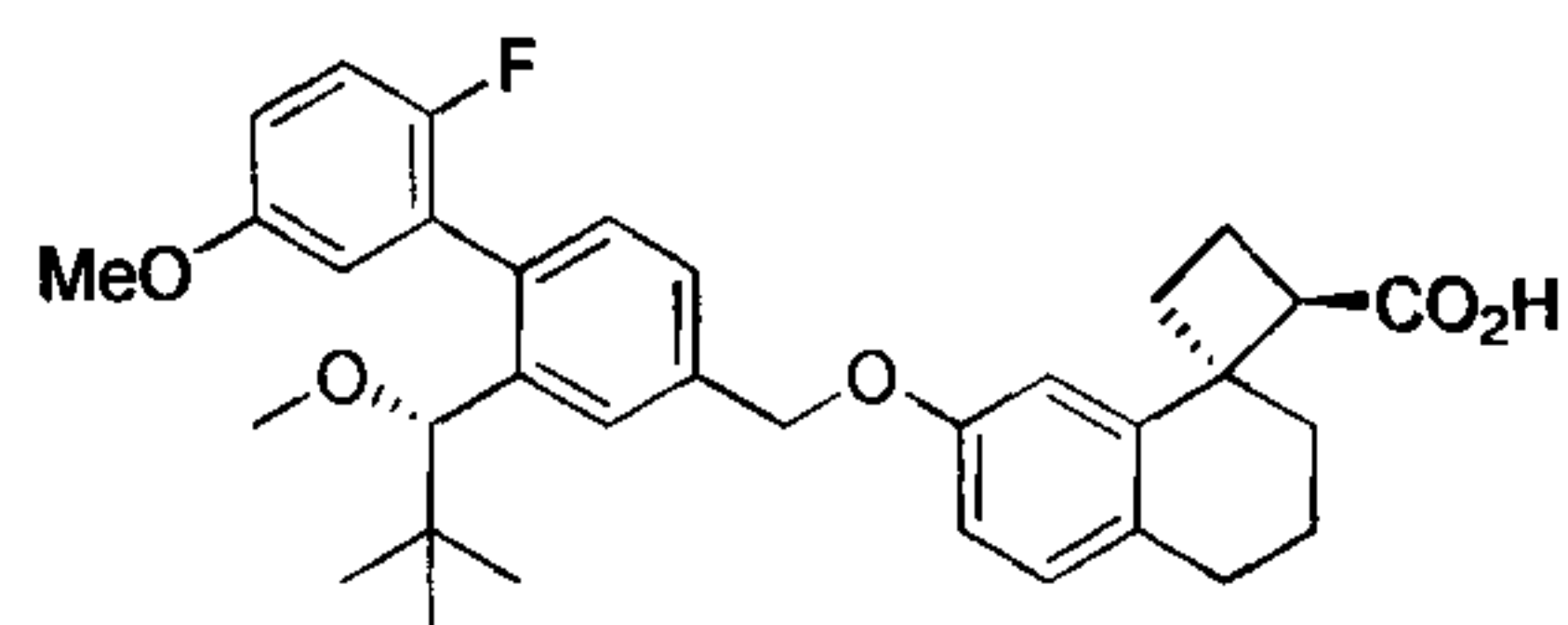
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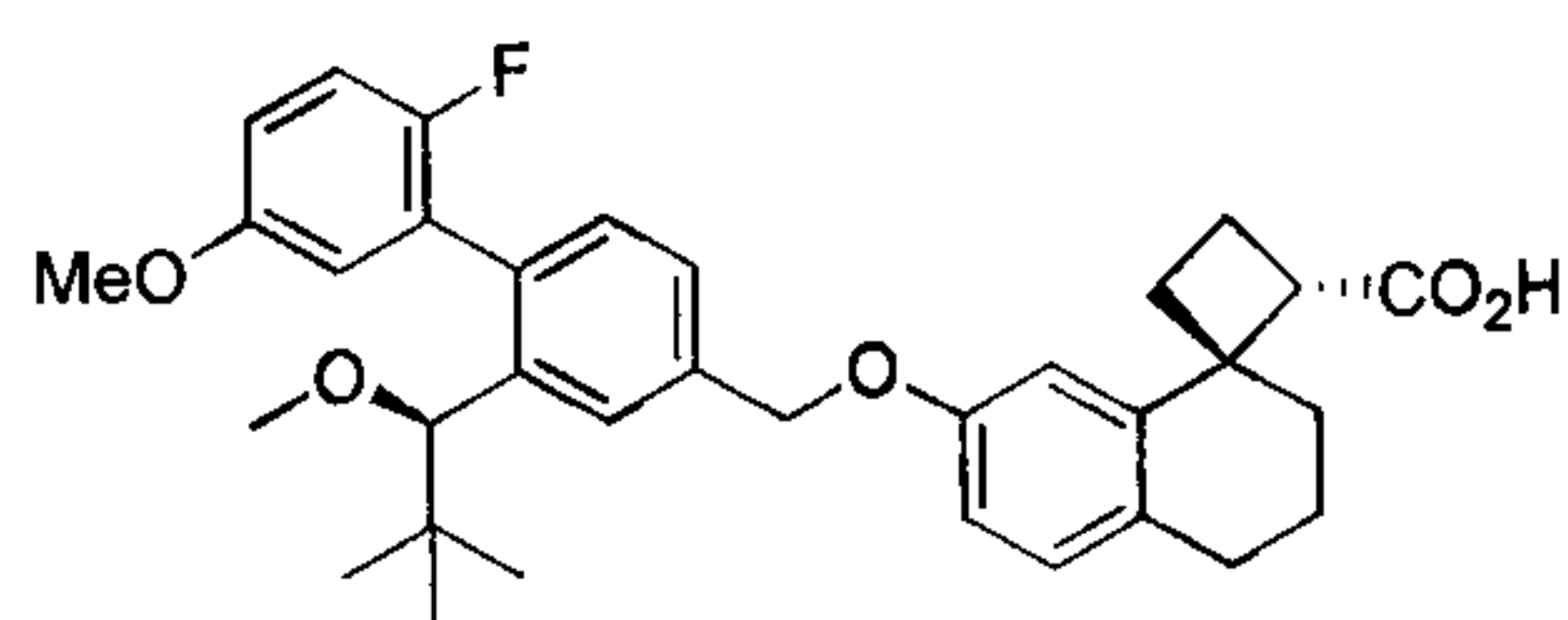
384. The compound



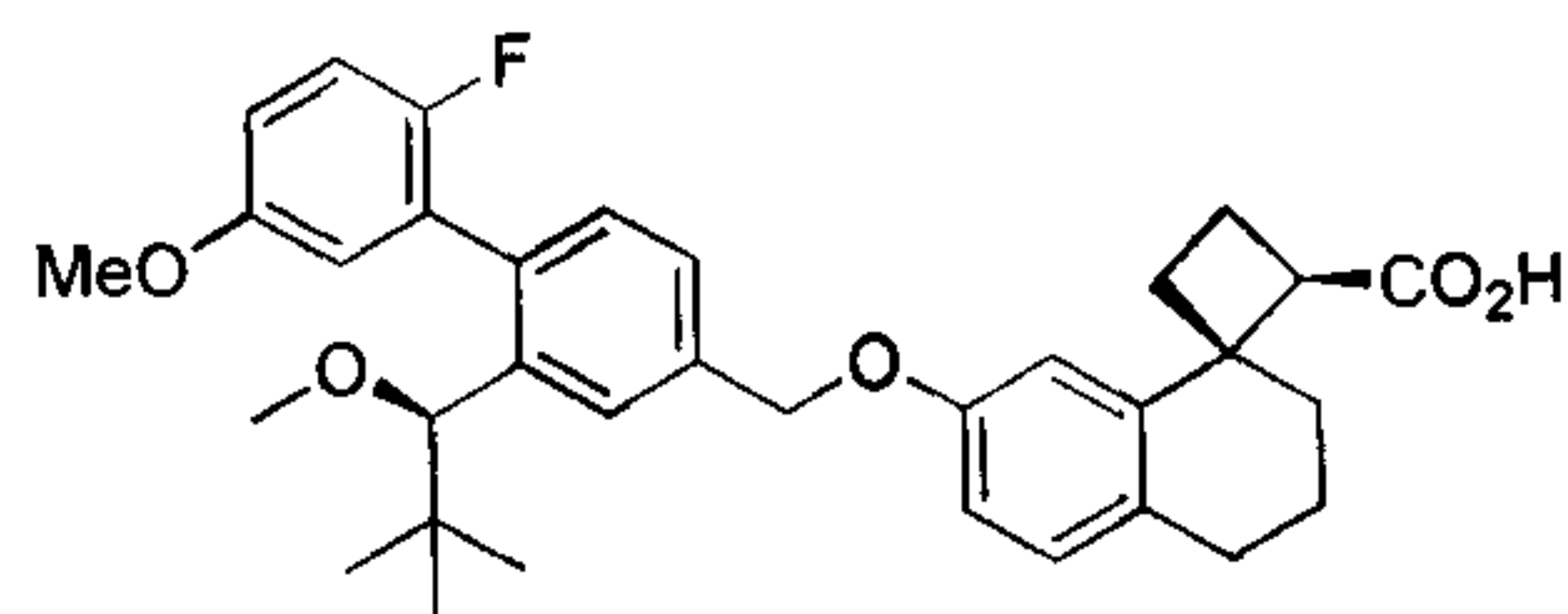
385. The compound



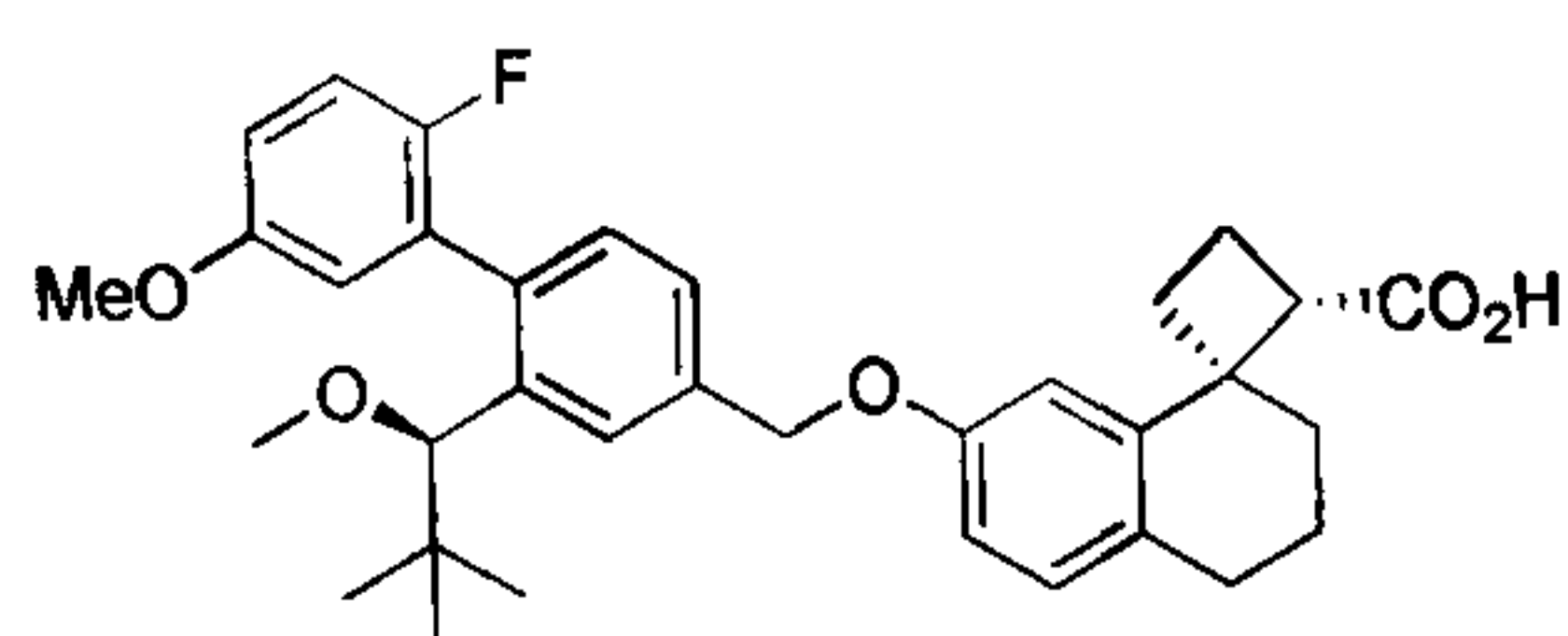
386. The compound



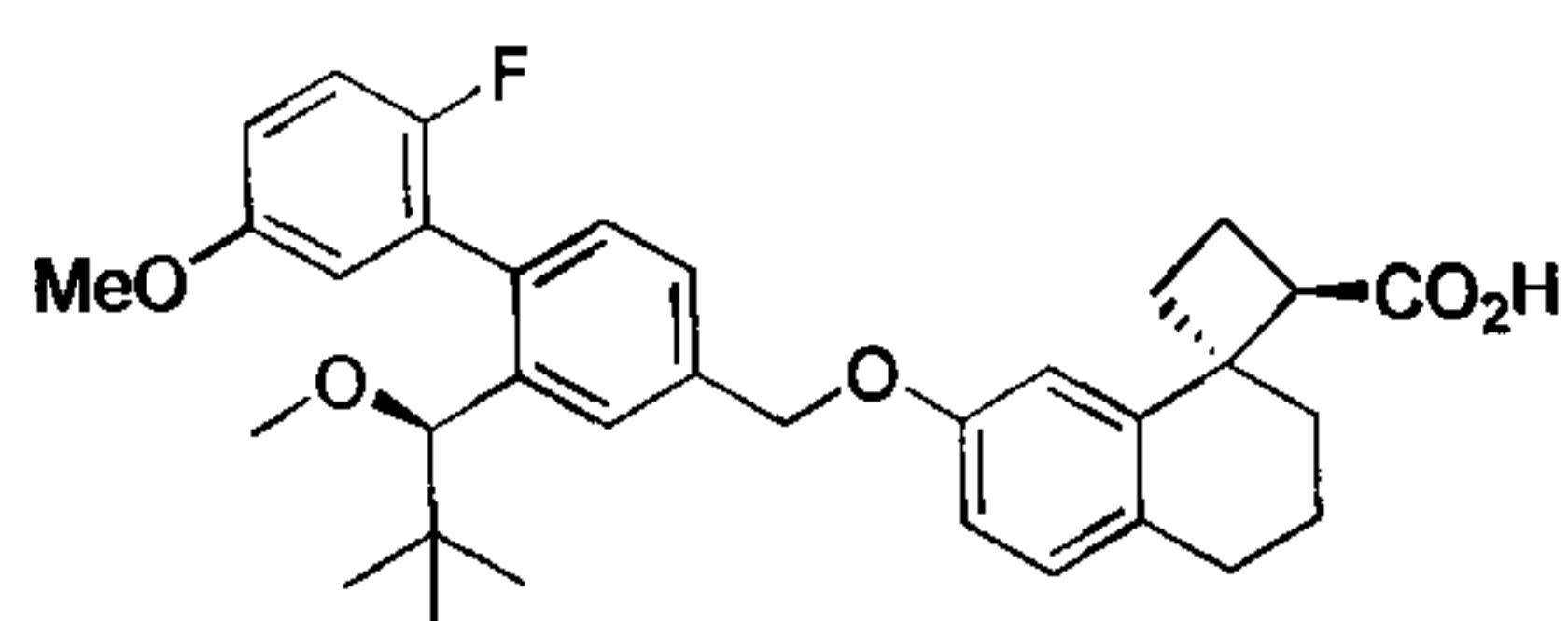
387. The compound



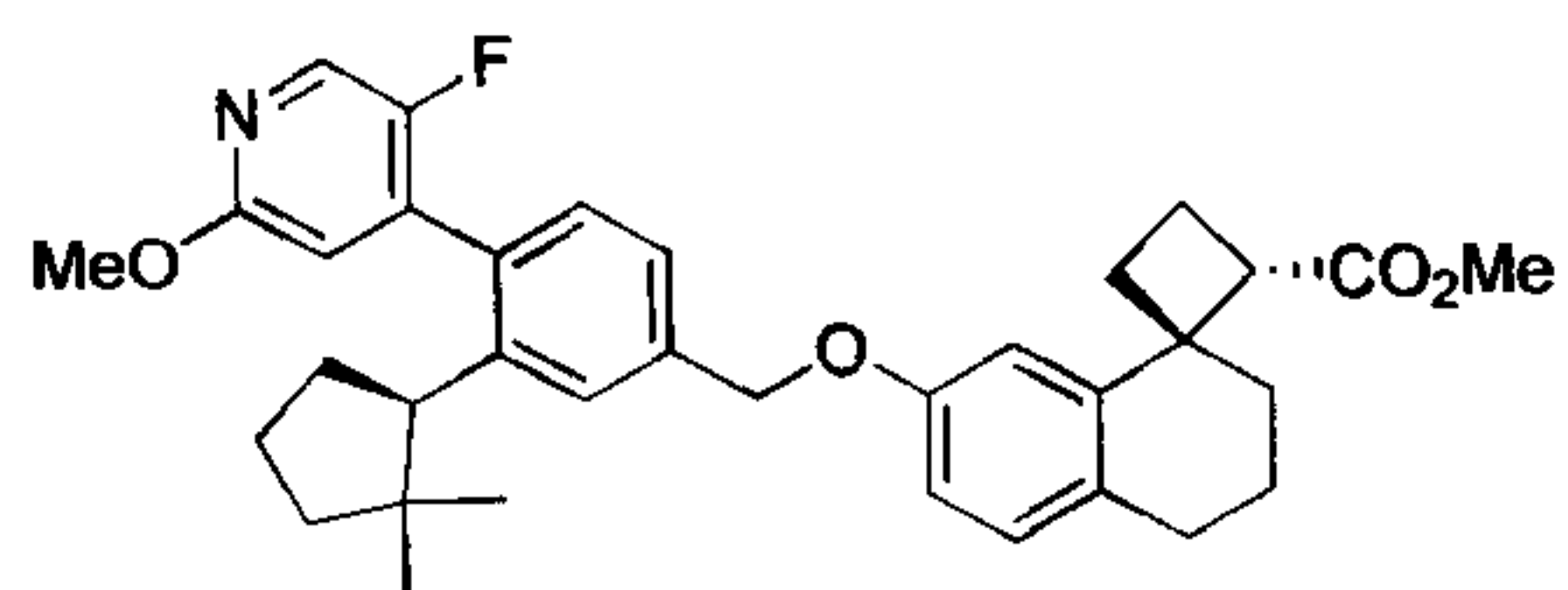
388. The compound



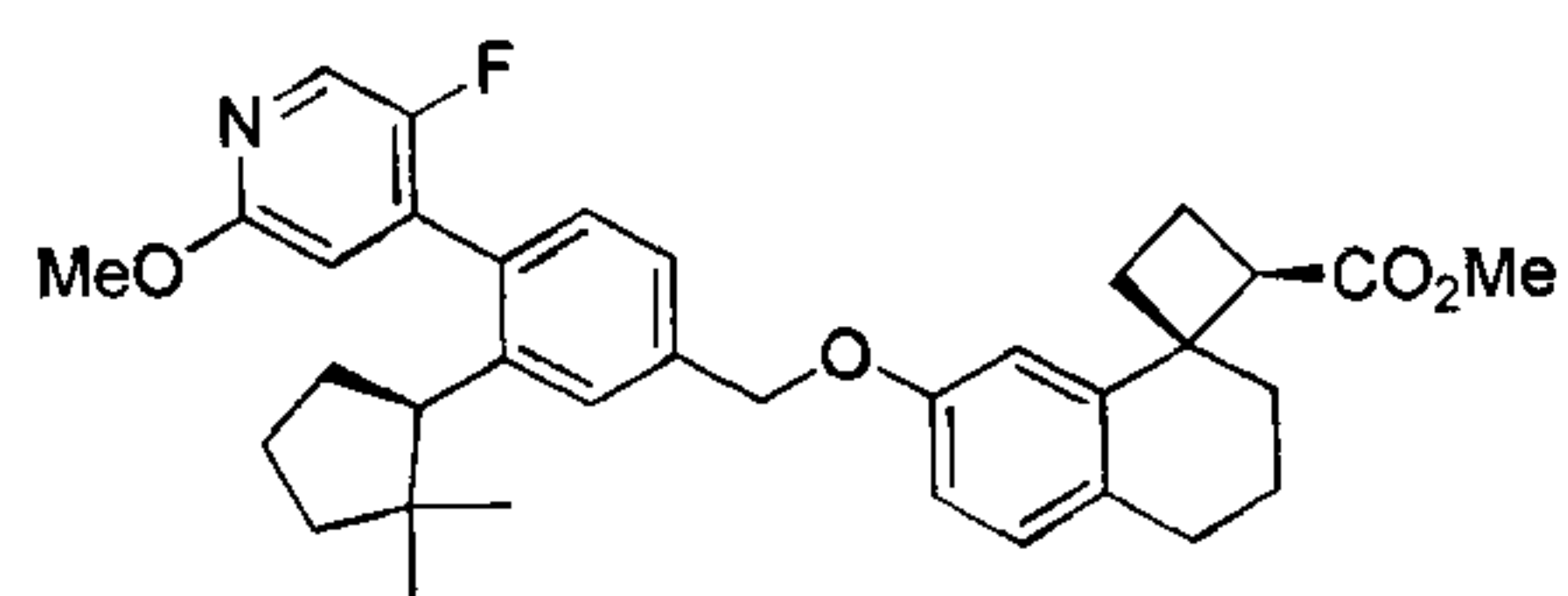
389. The compound



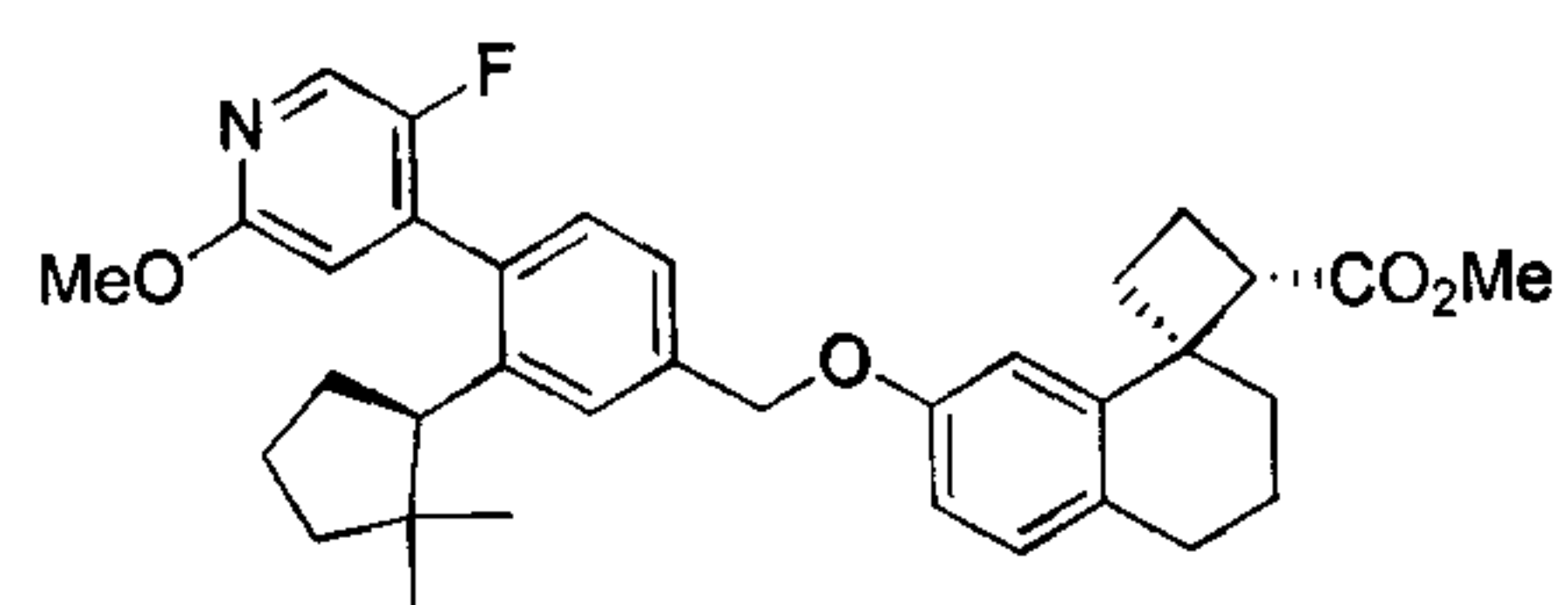
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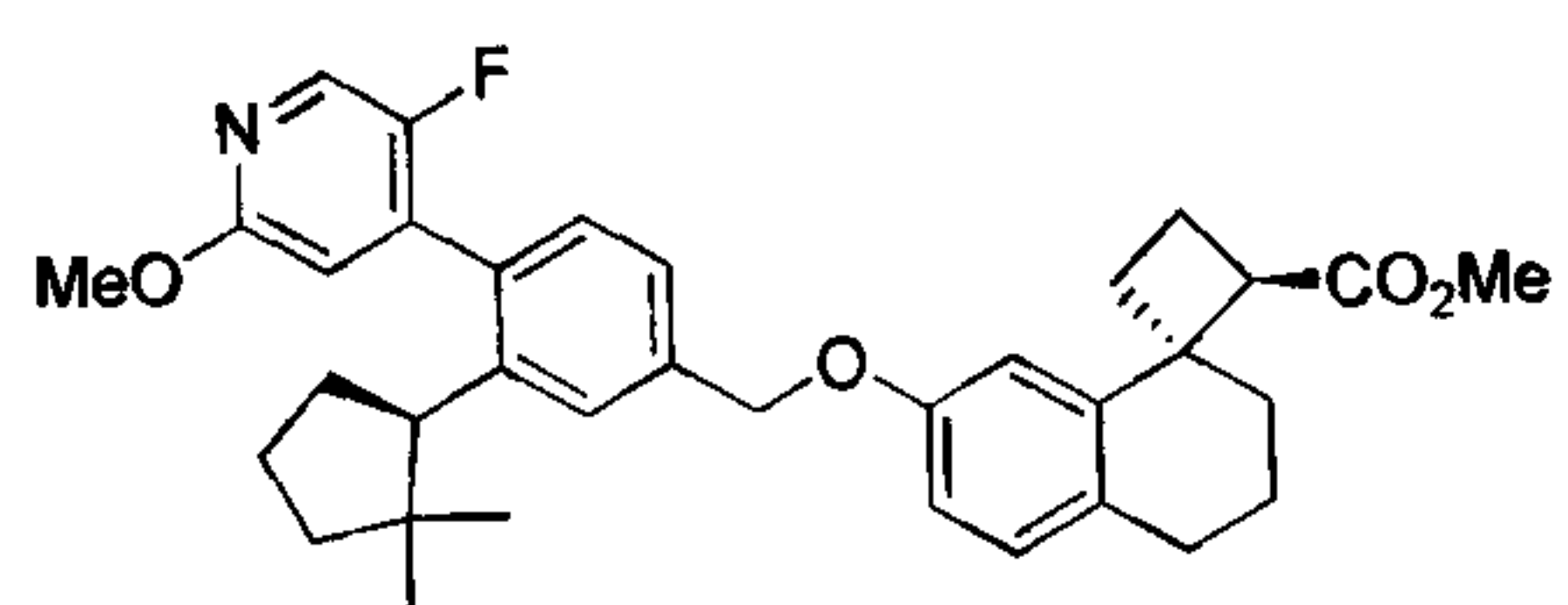
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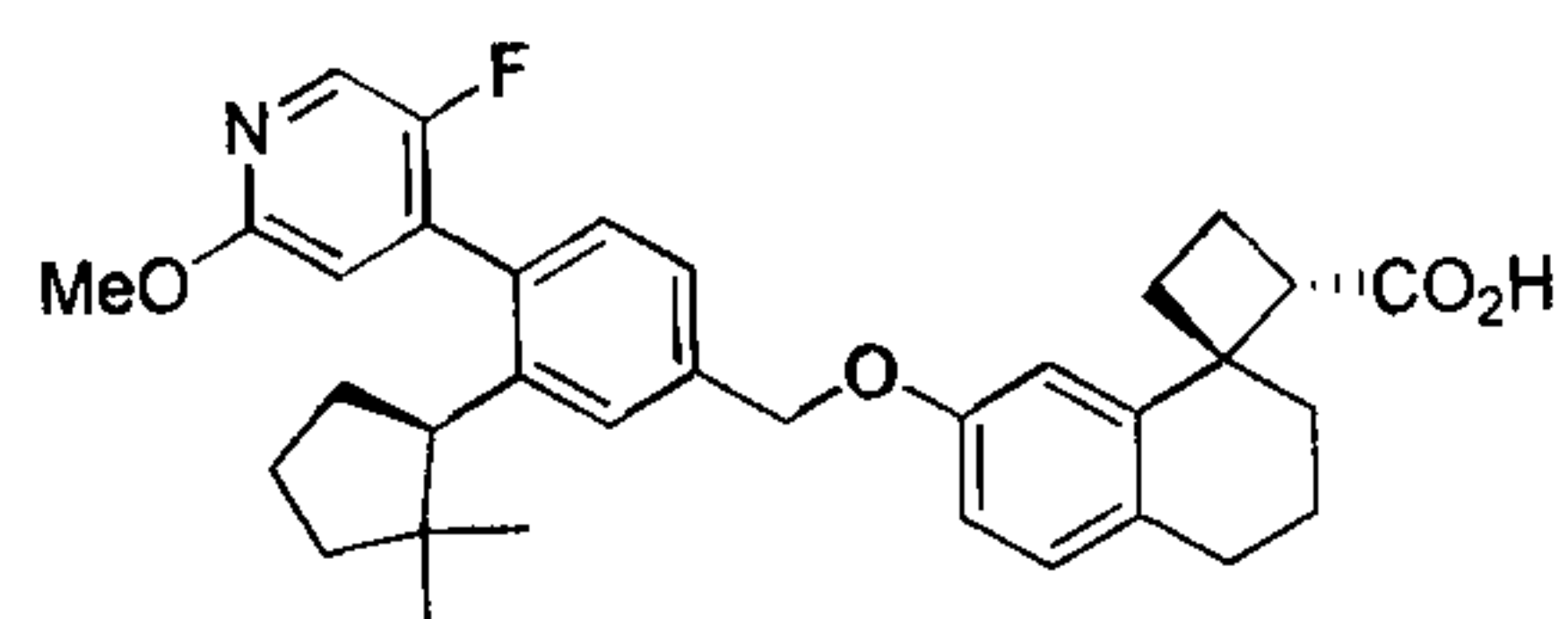
392. The compound



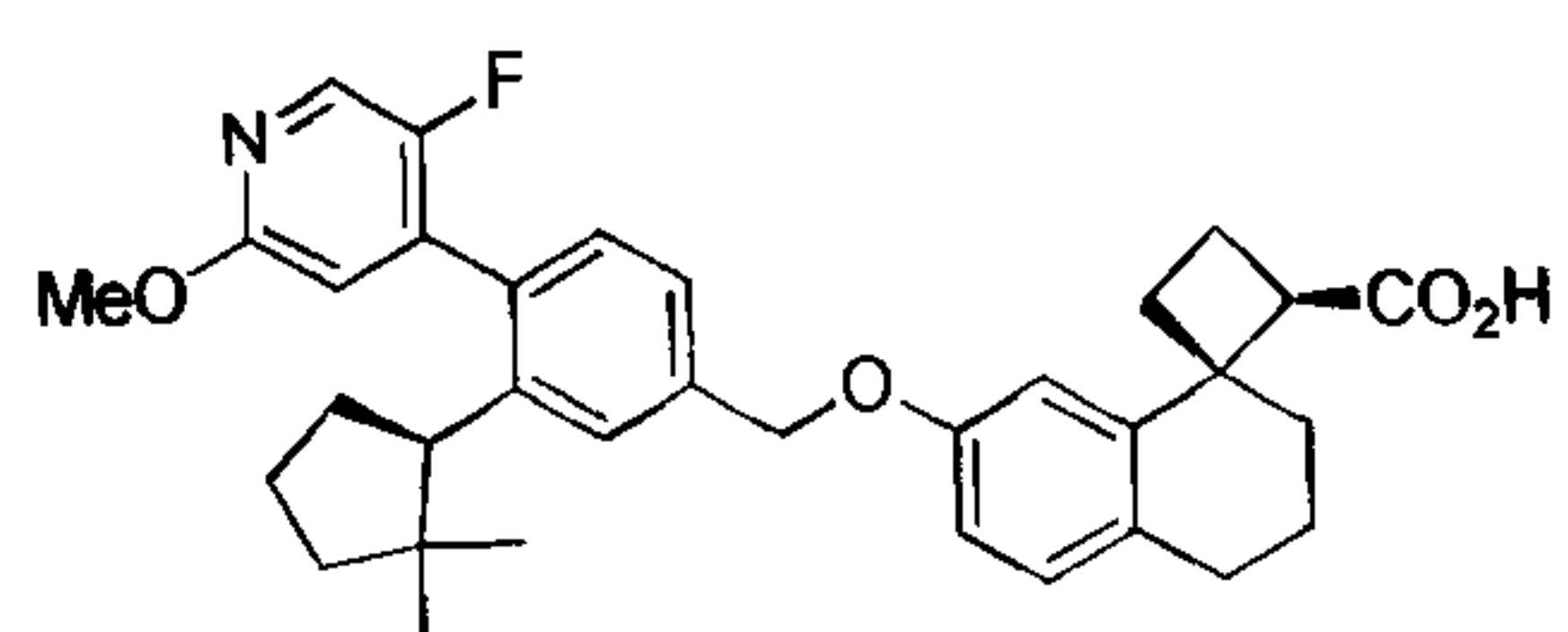
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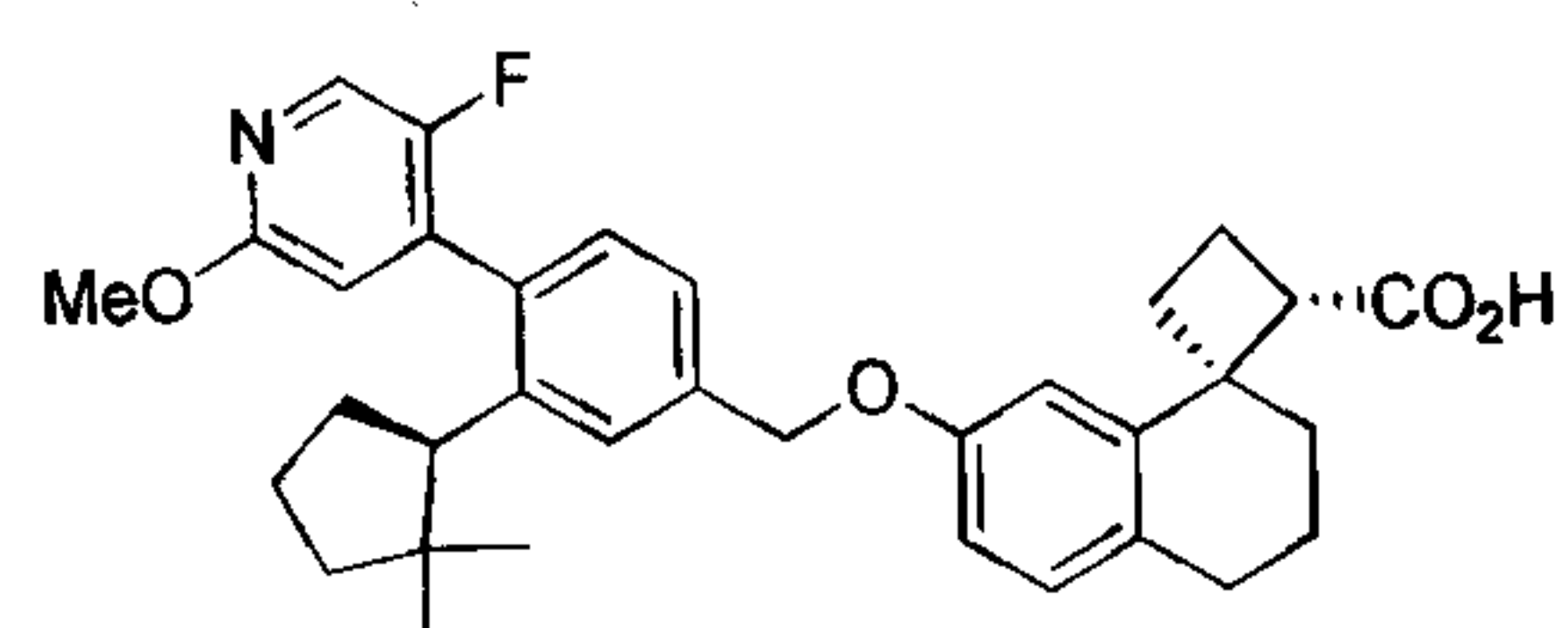
394. The compound



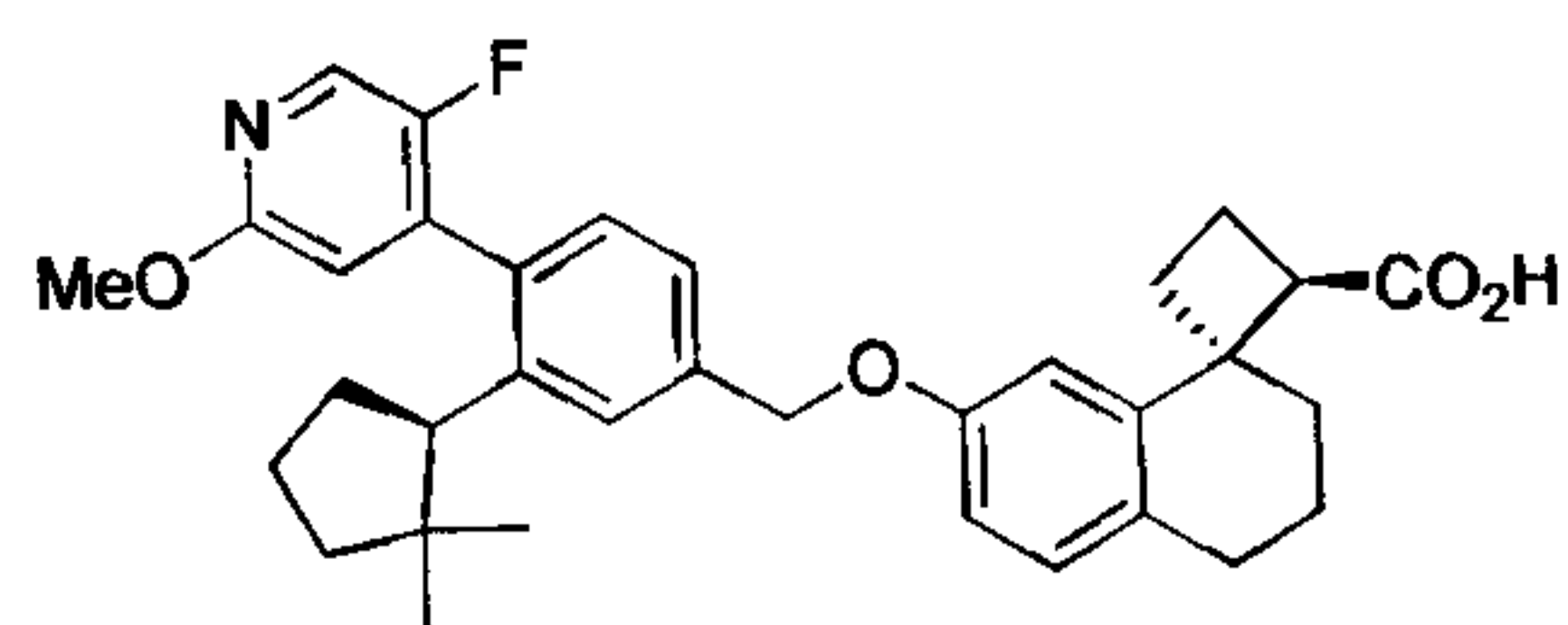
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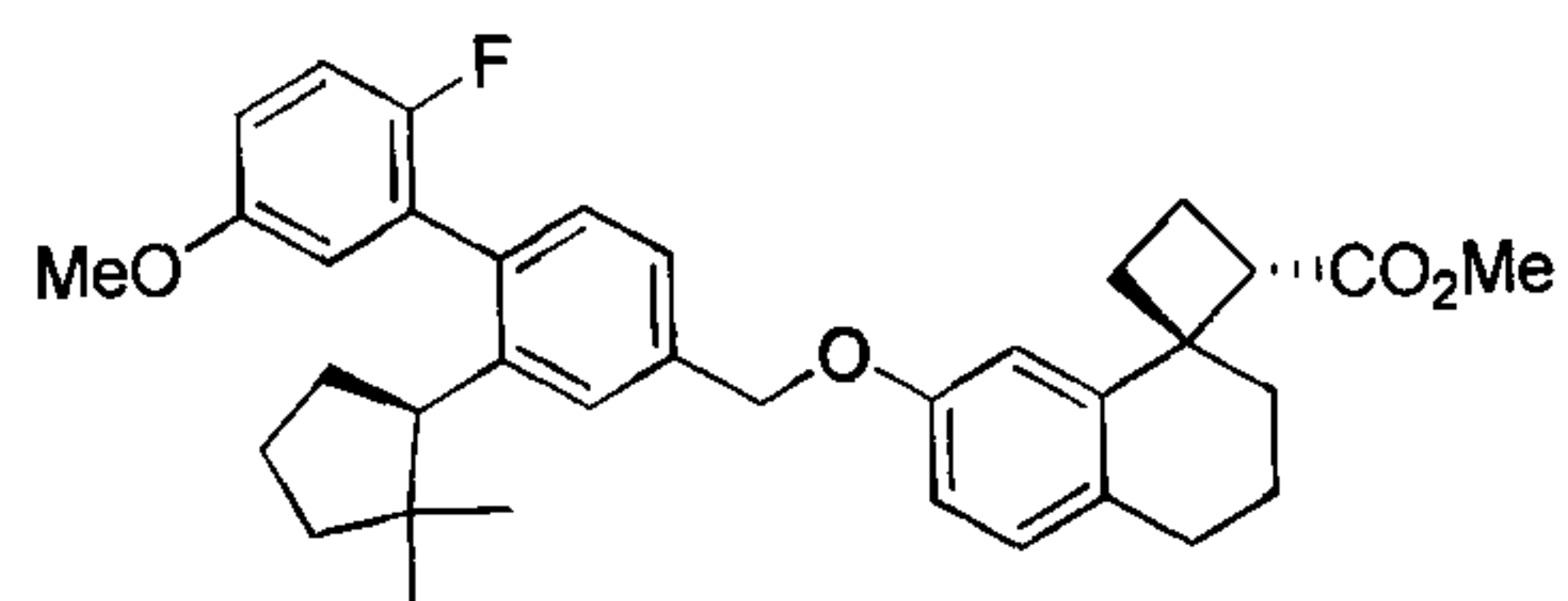
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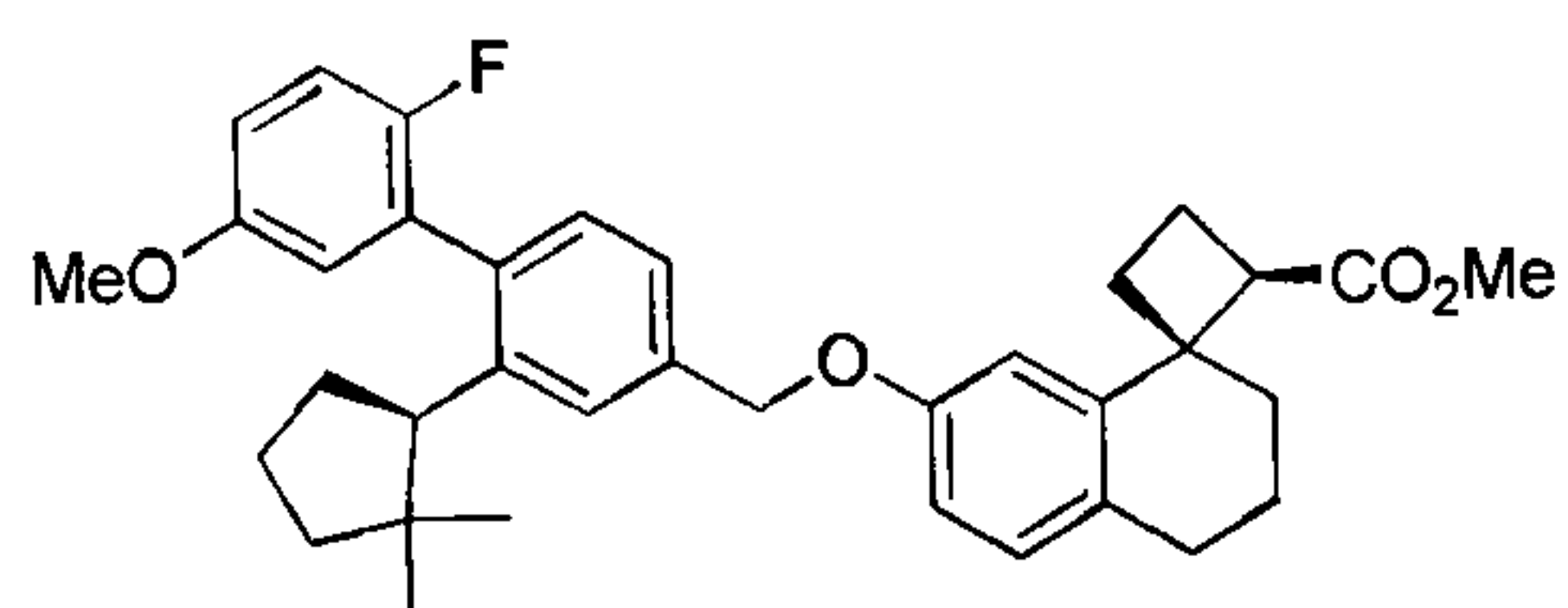
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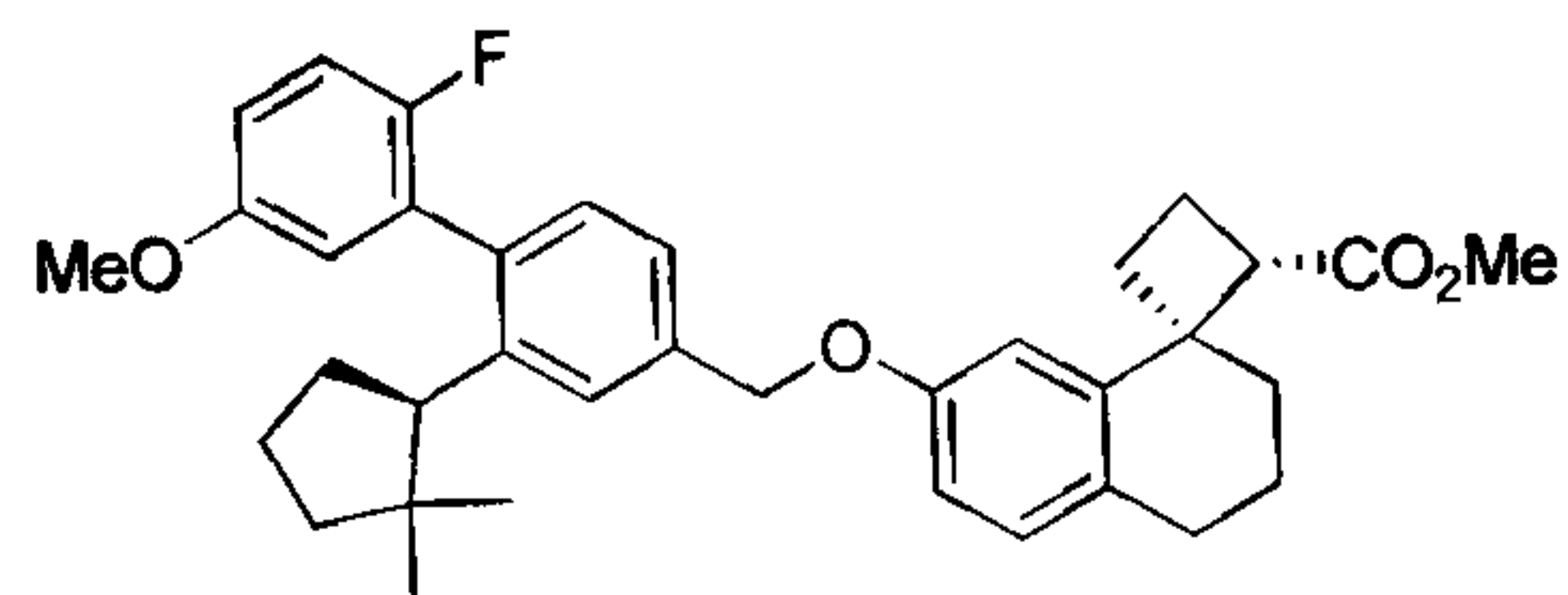
398. The compound



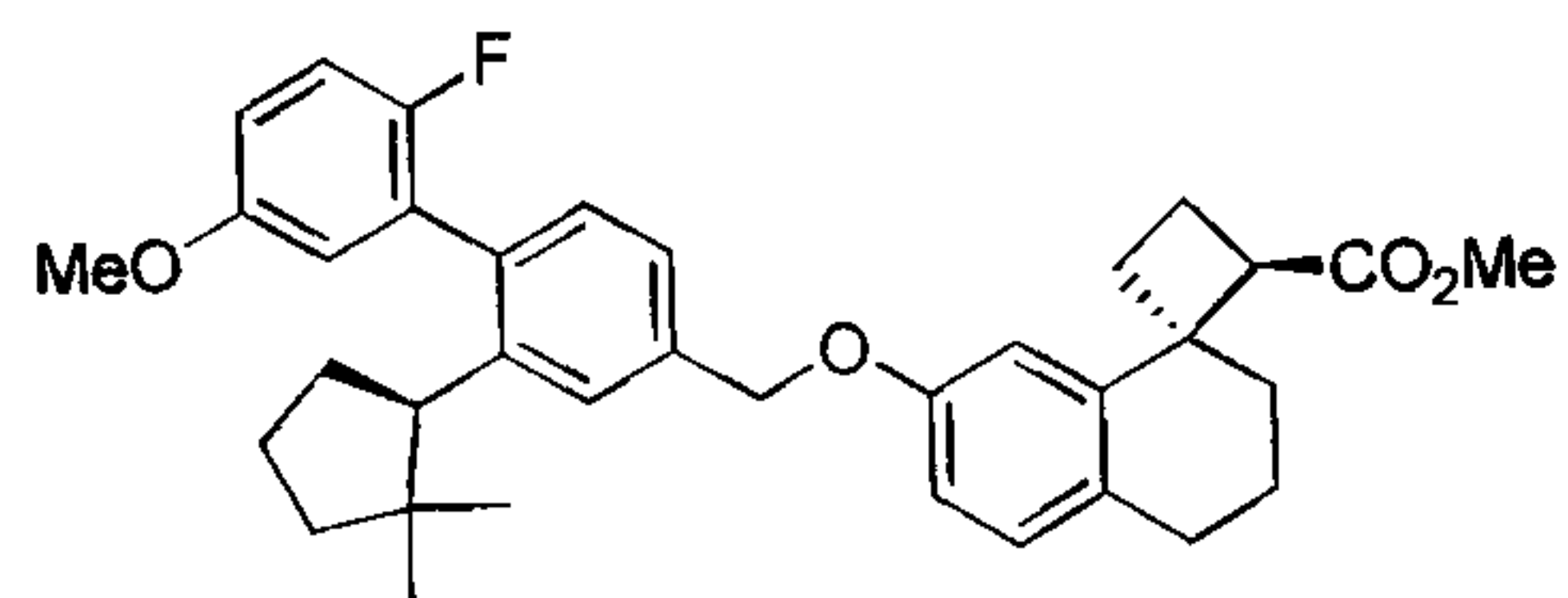
399. The compound



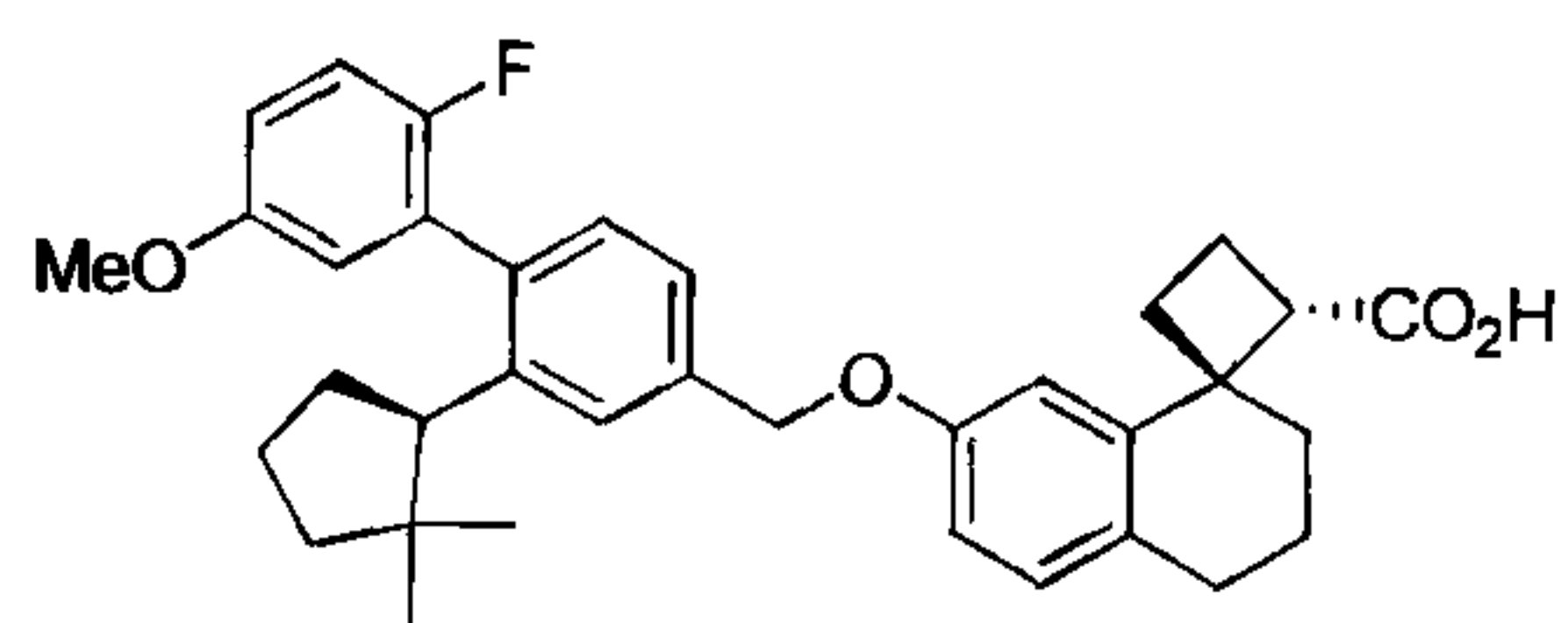
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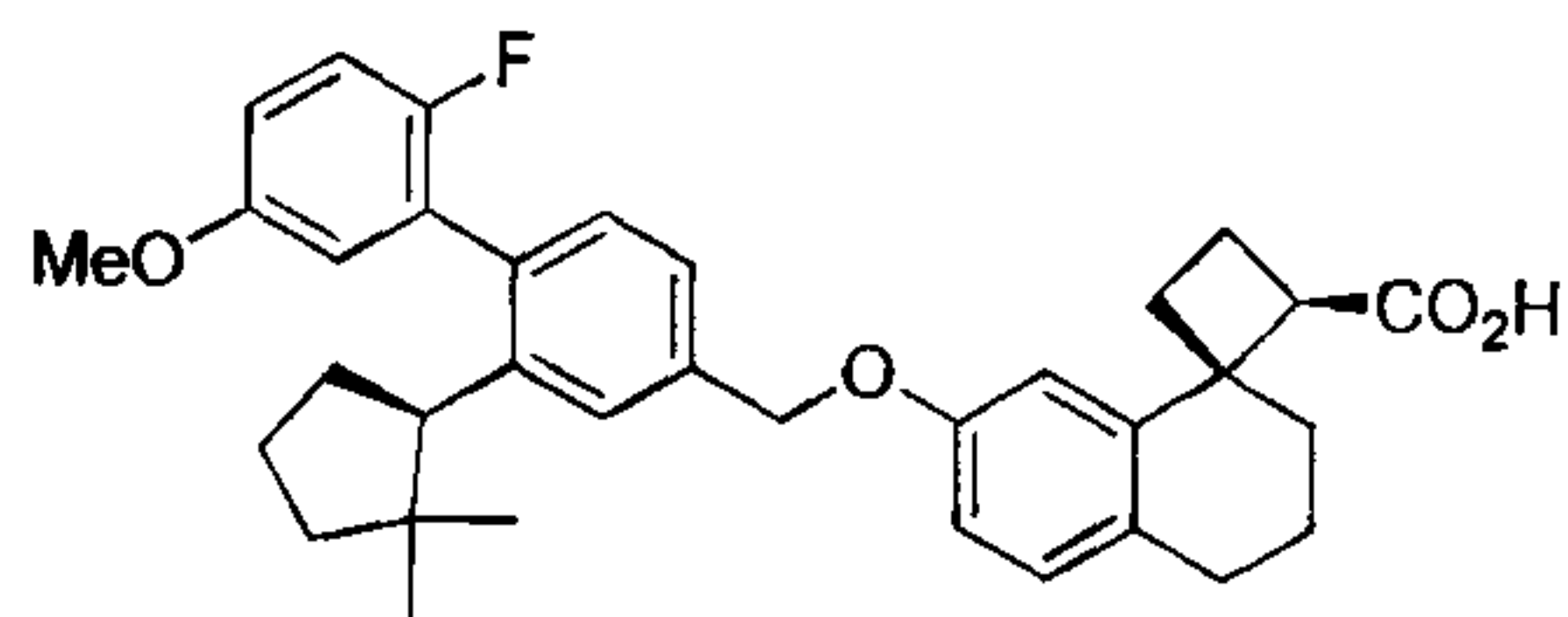
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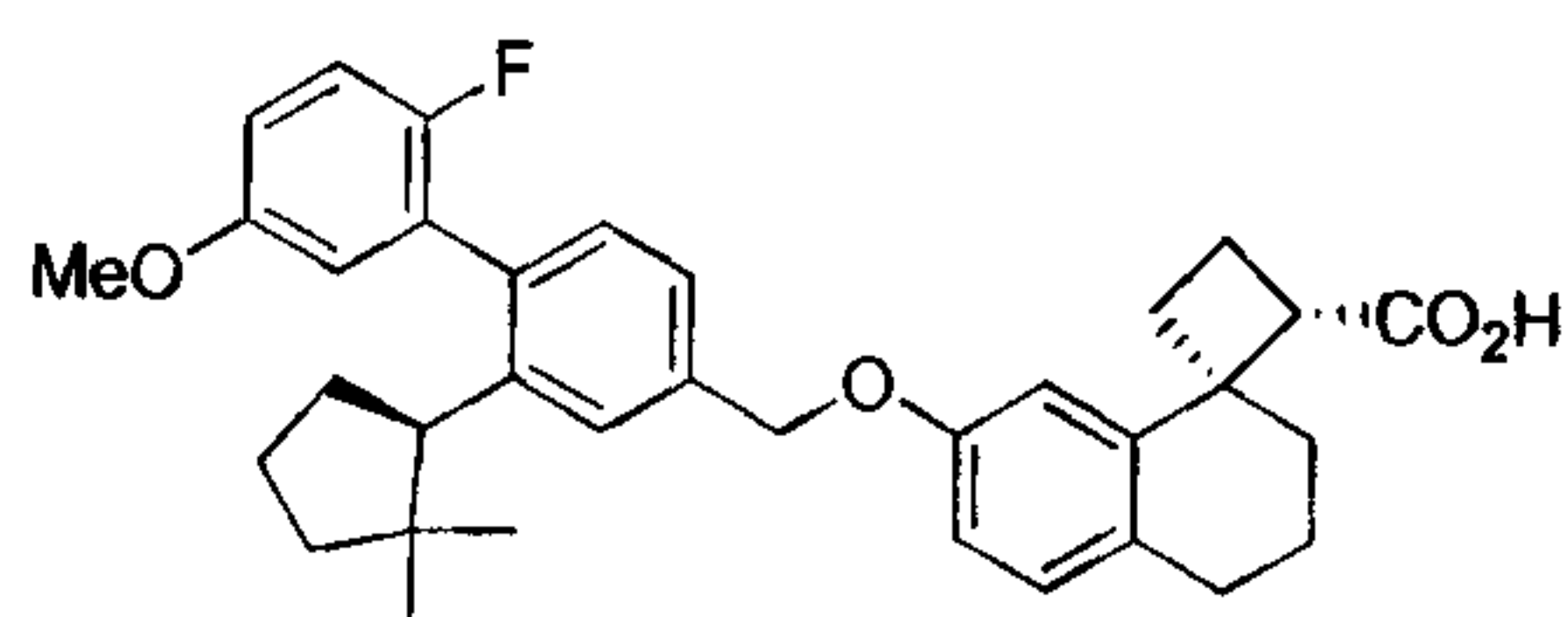
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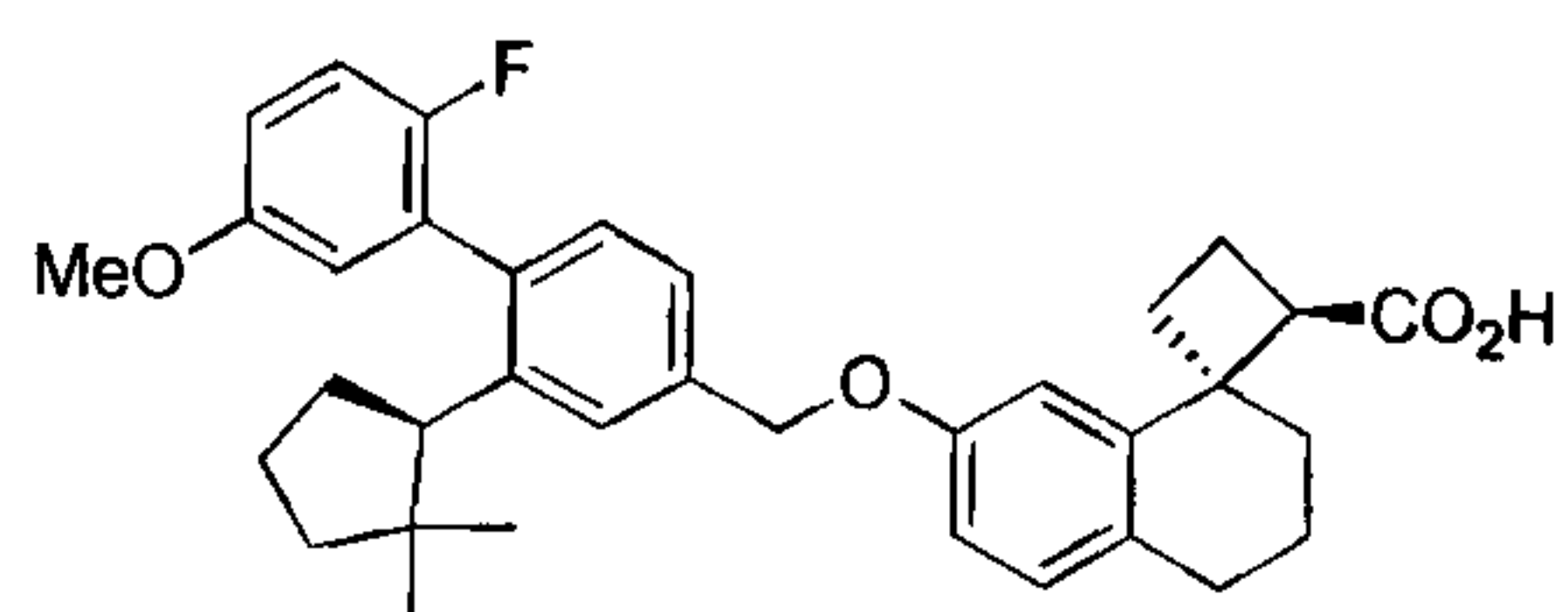
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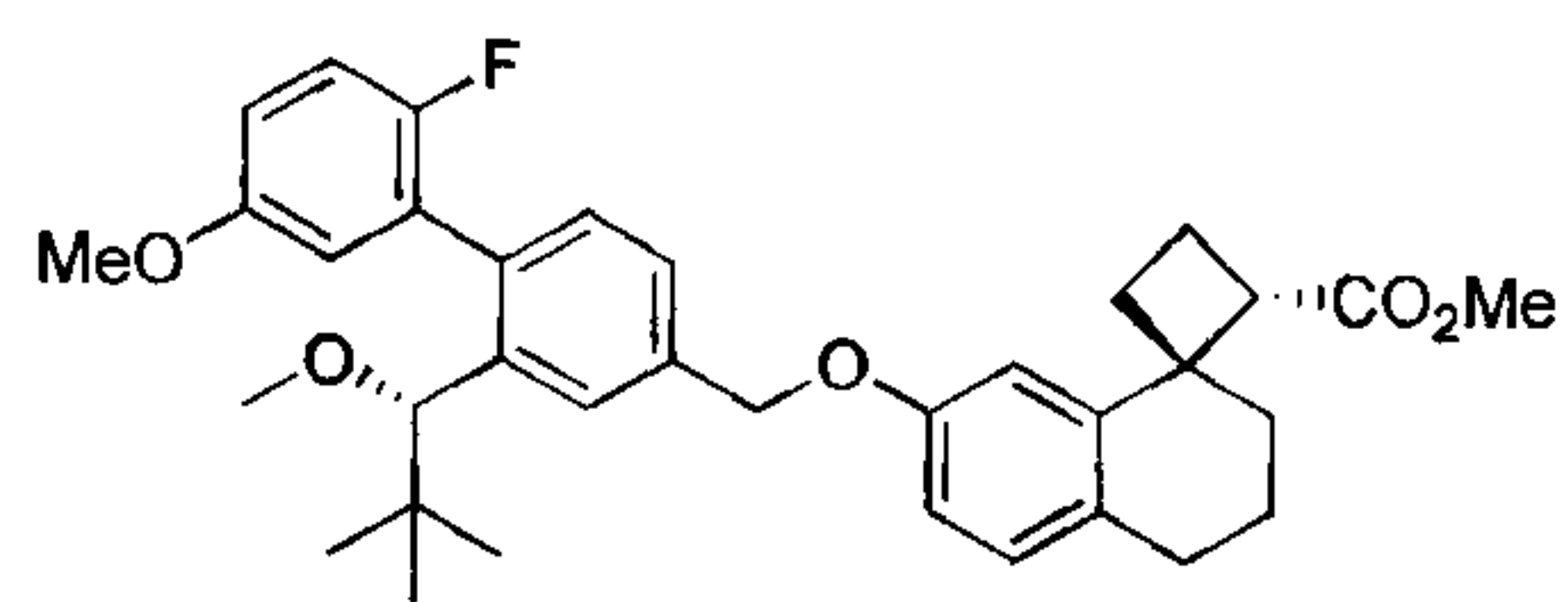
404. The compound



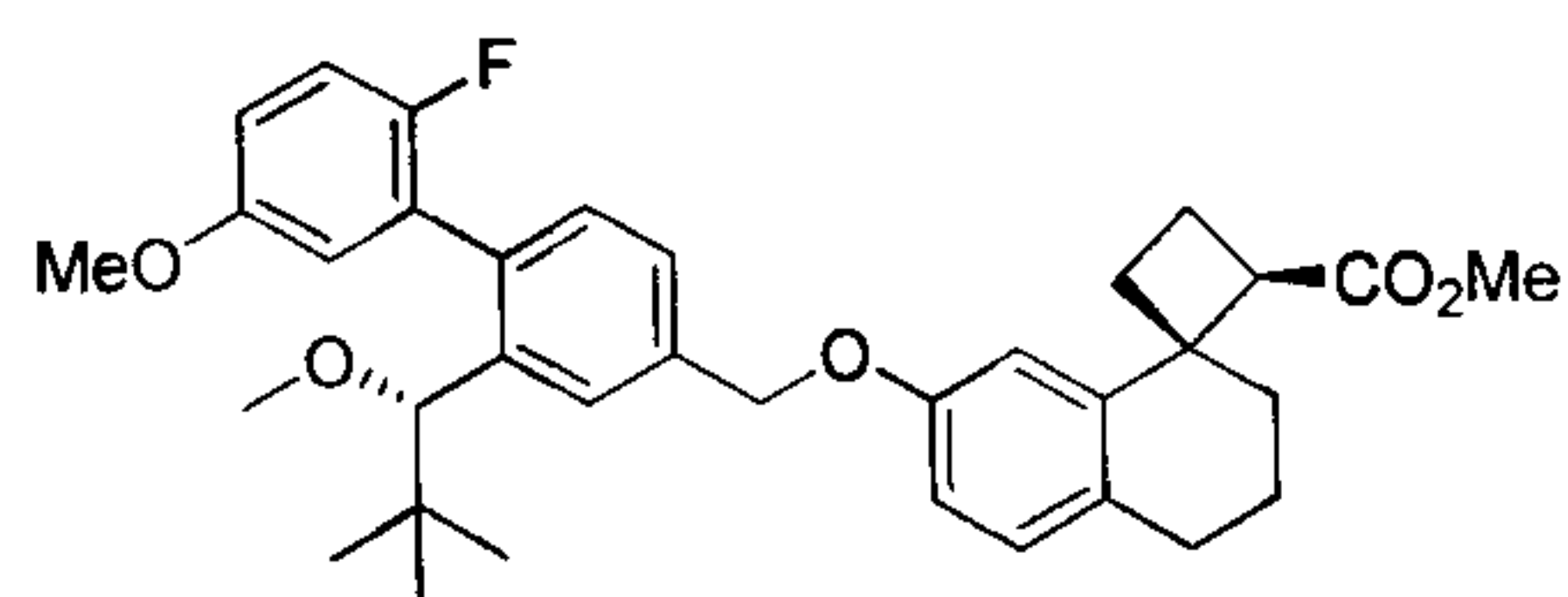
405. The compound



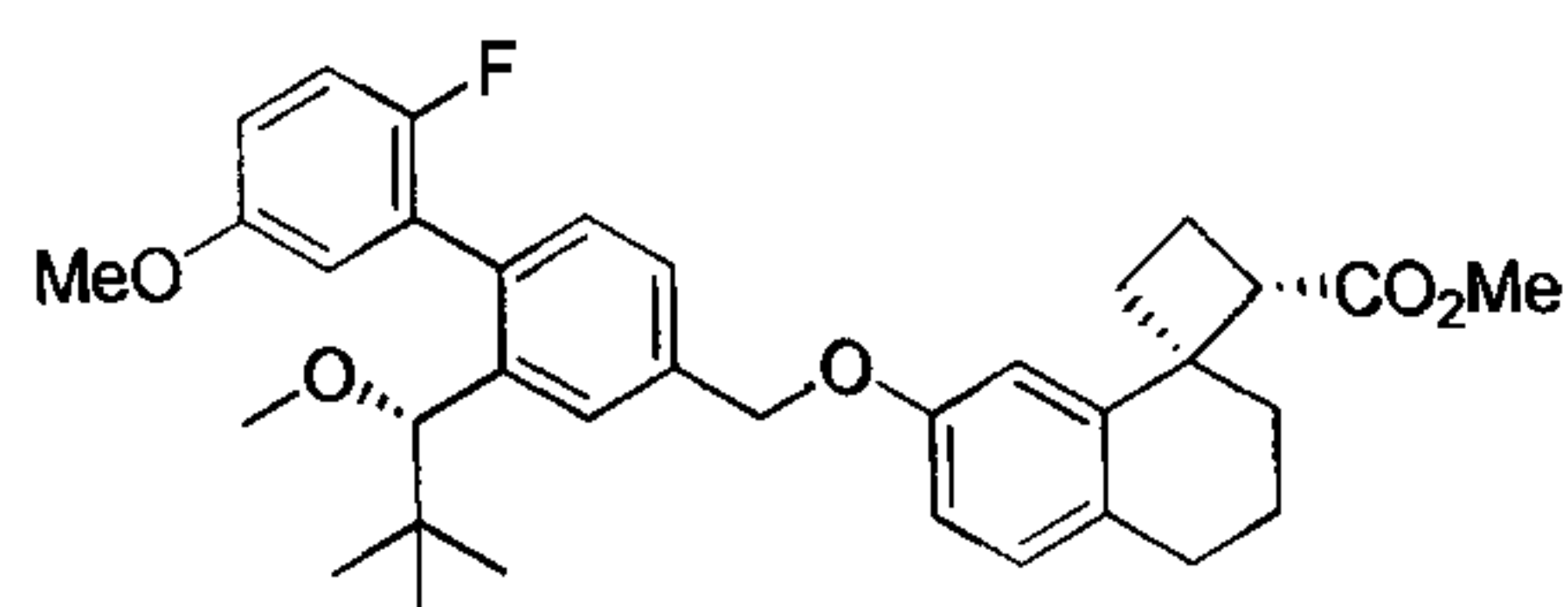
406. The compound



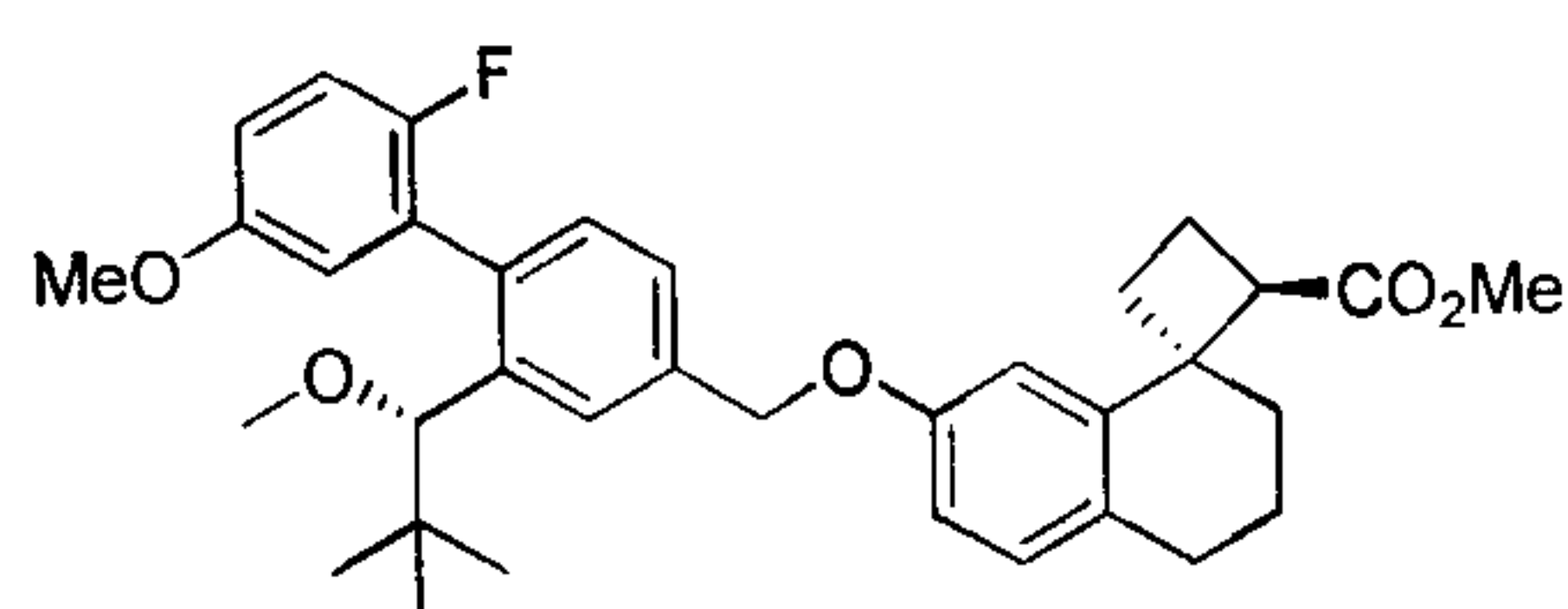
407. The compound



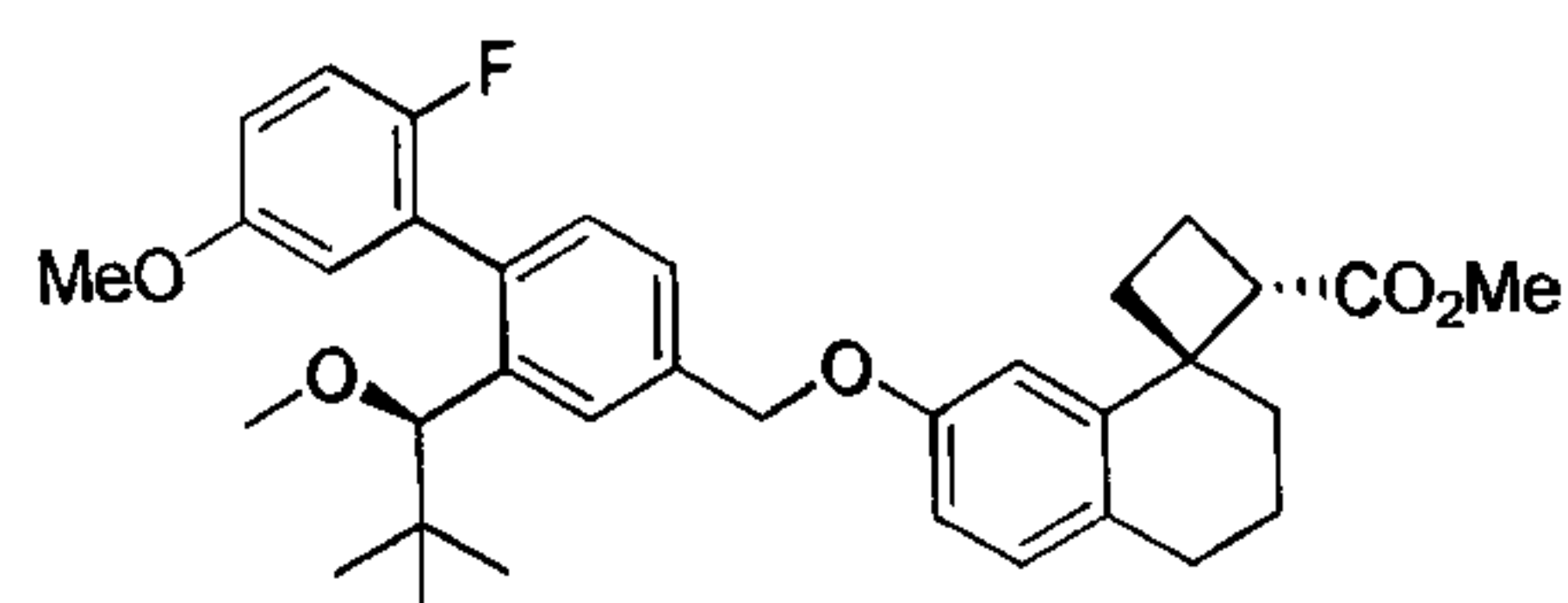
408. The compound



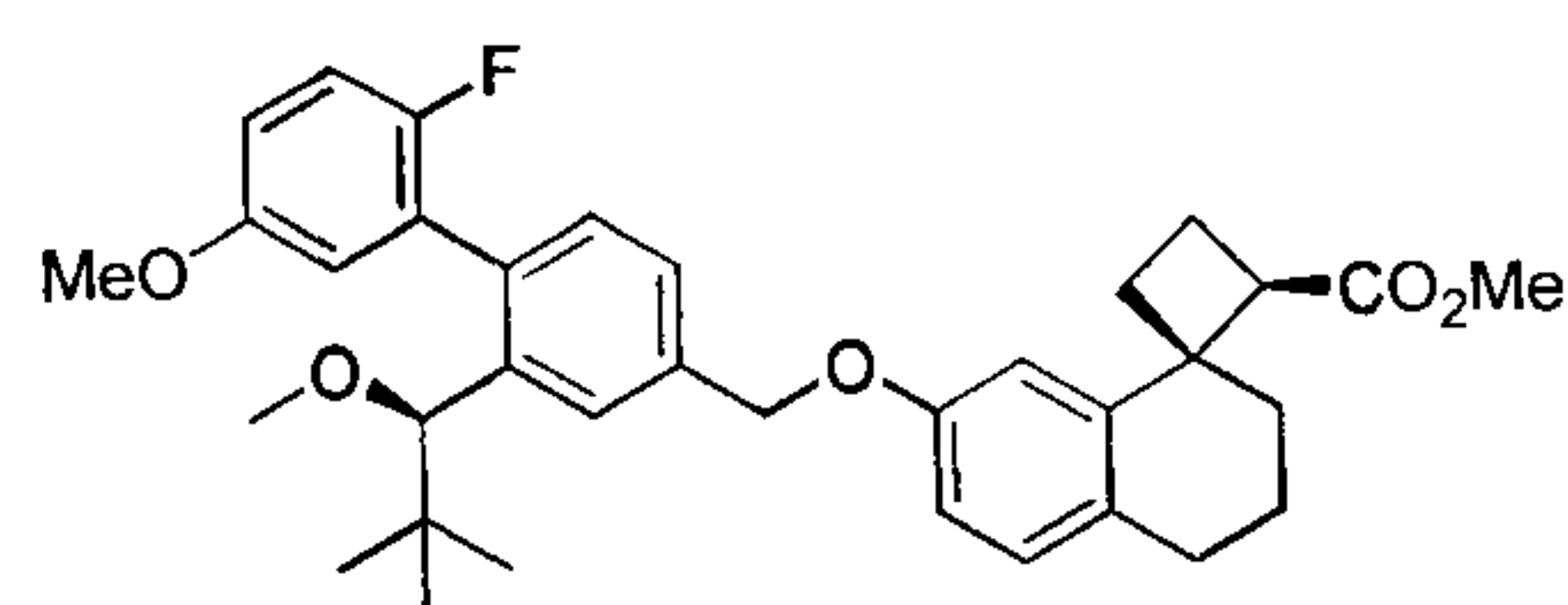
409. The compound



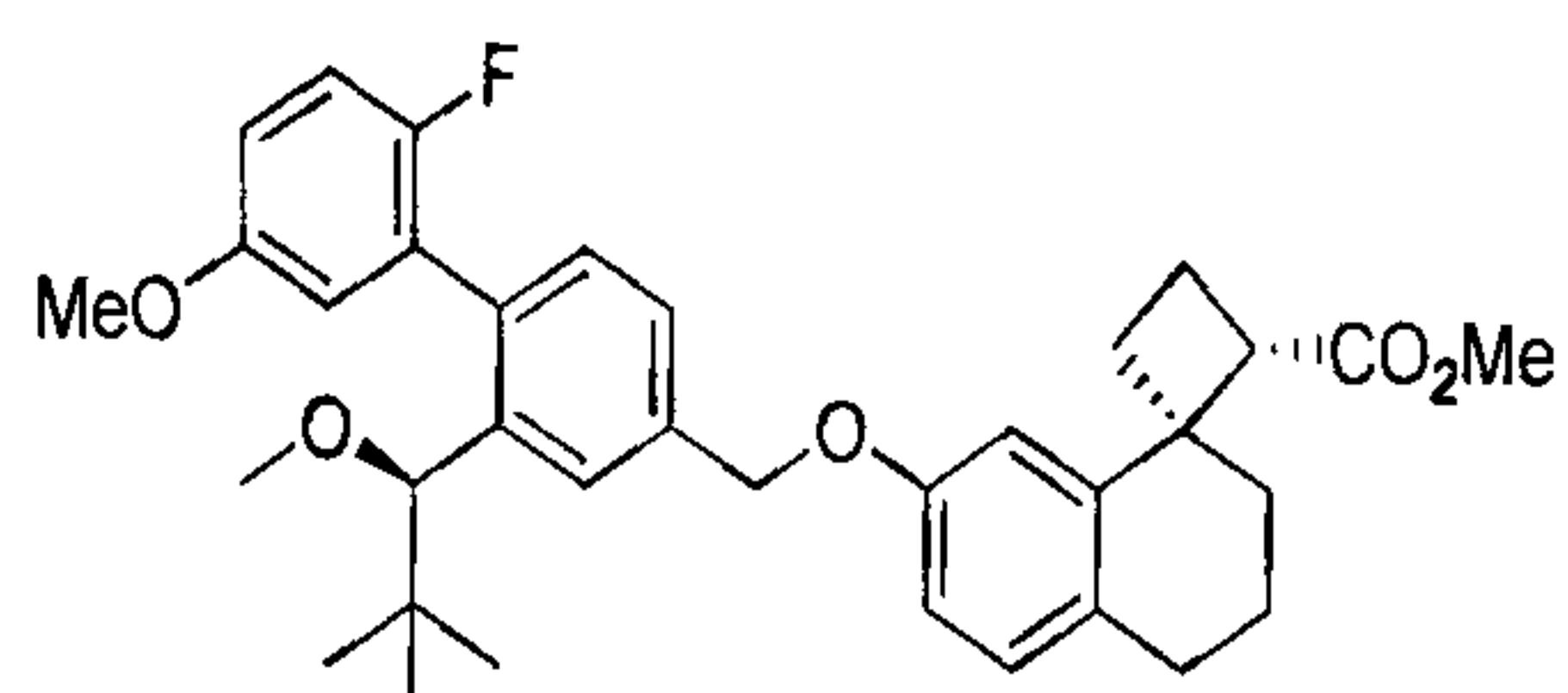
410. The compound



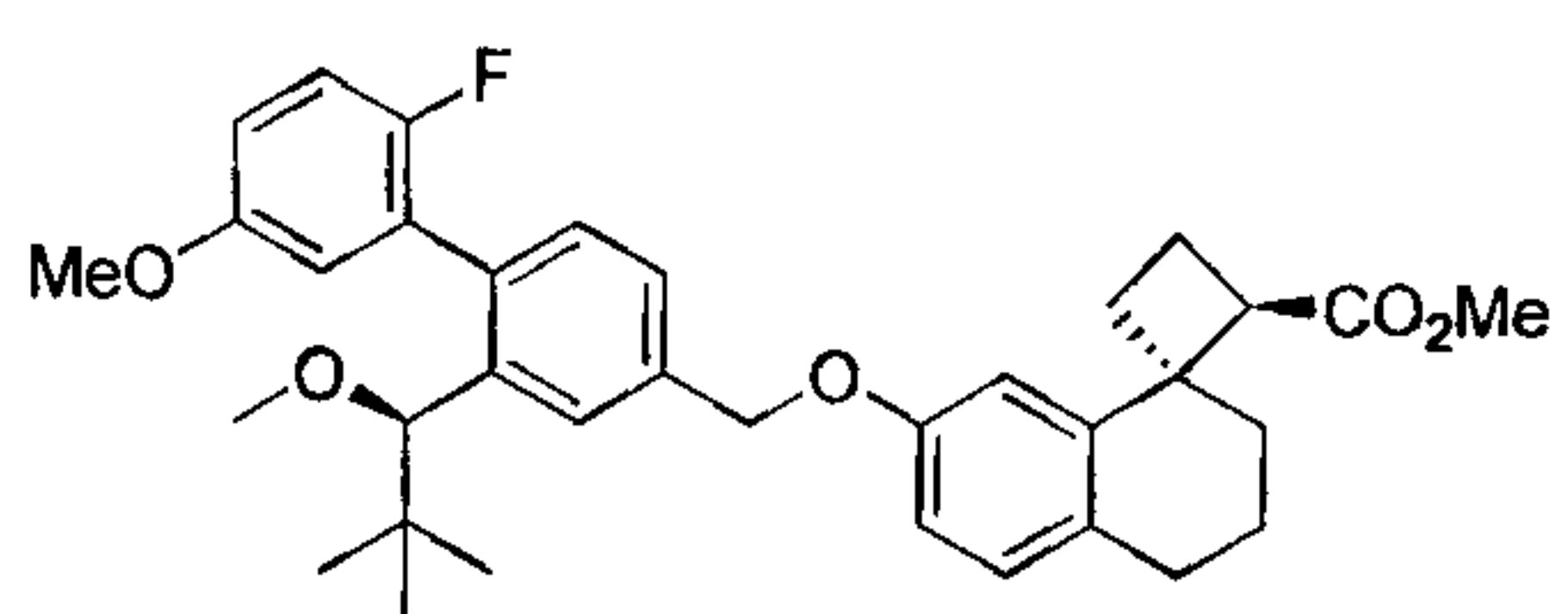
411. The compound



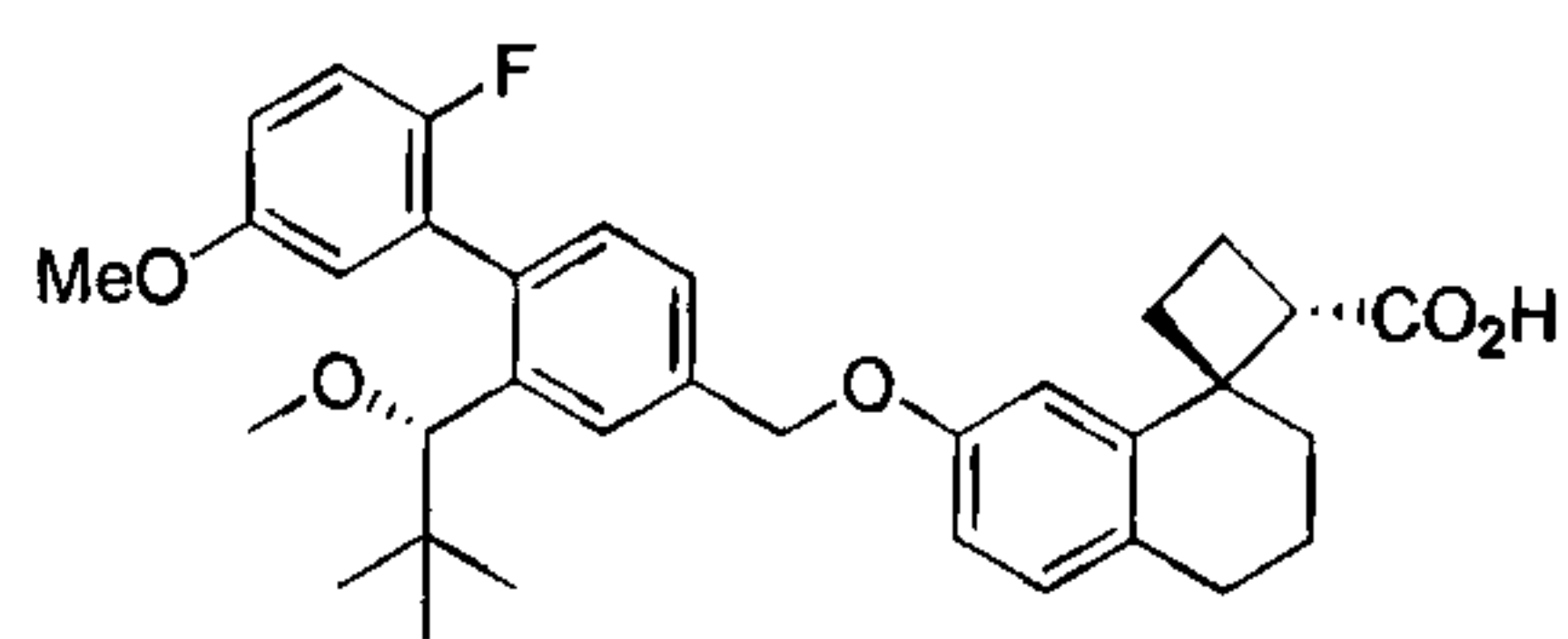
412. The compound



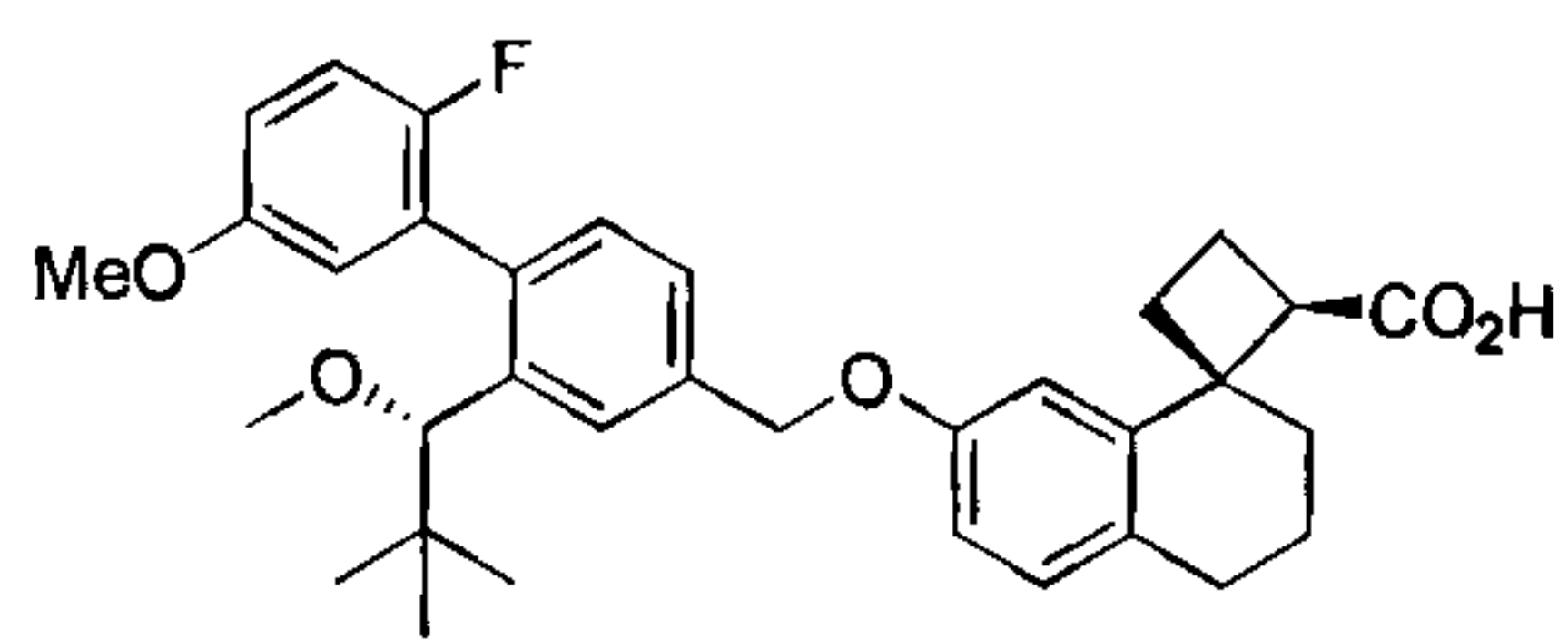
413. The compound



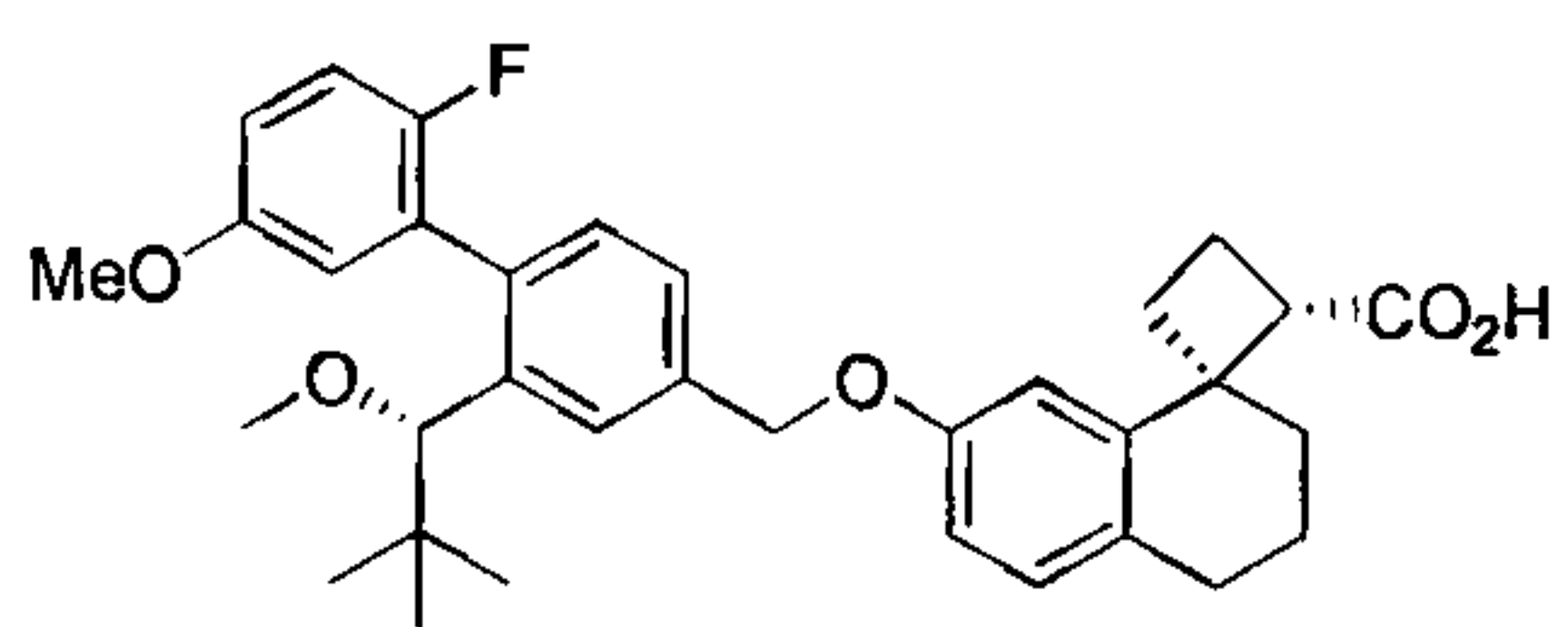
414. The compound



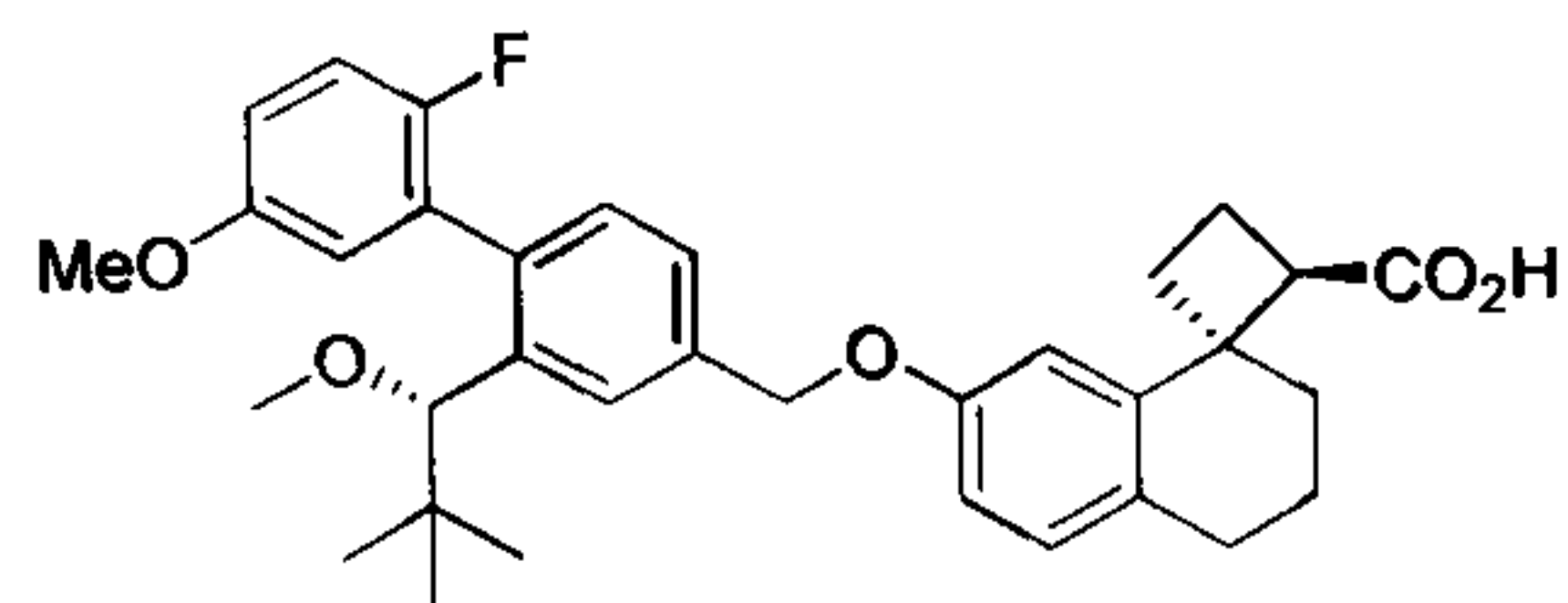
415. The compound



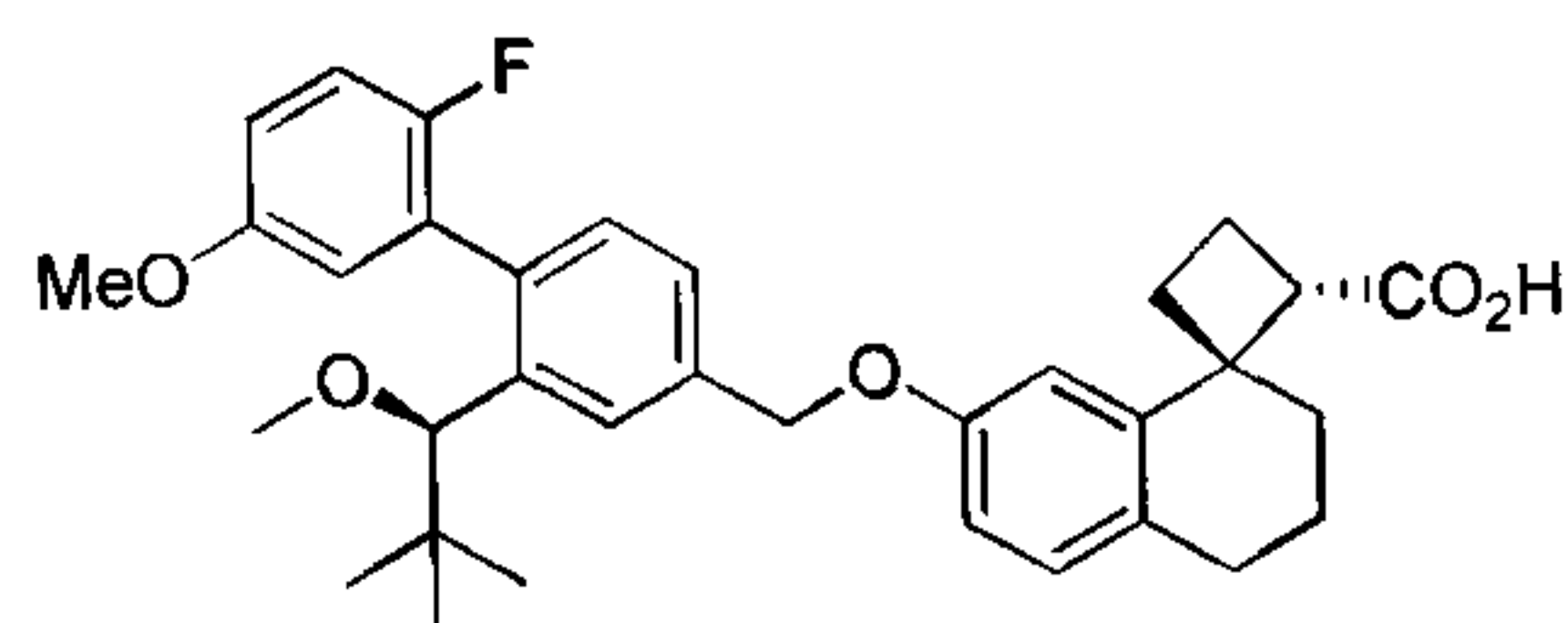
416. The compound



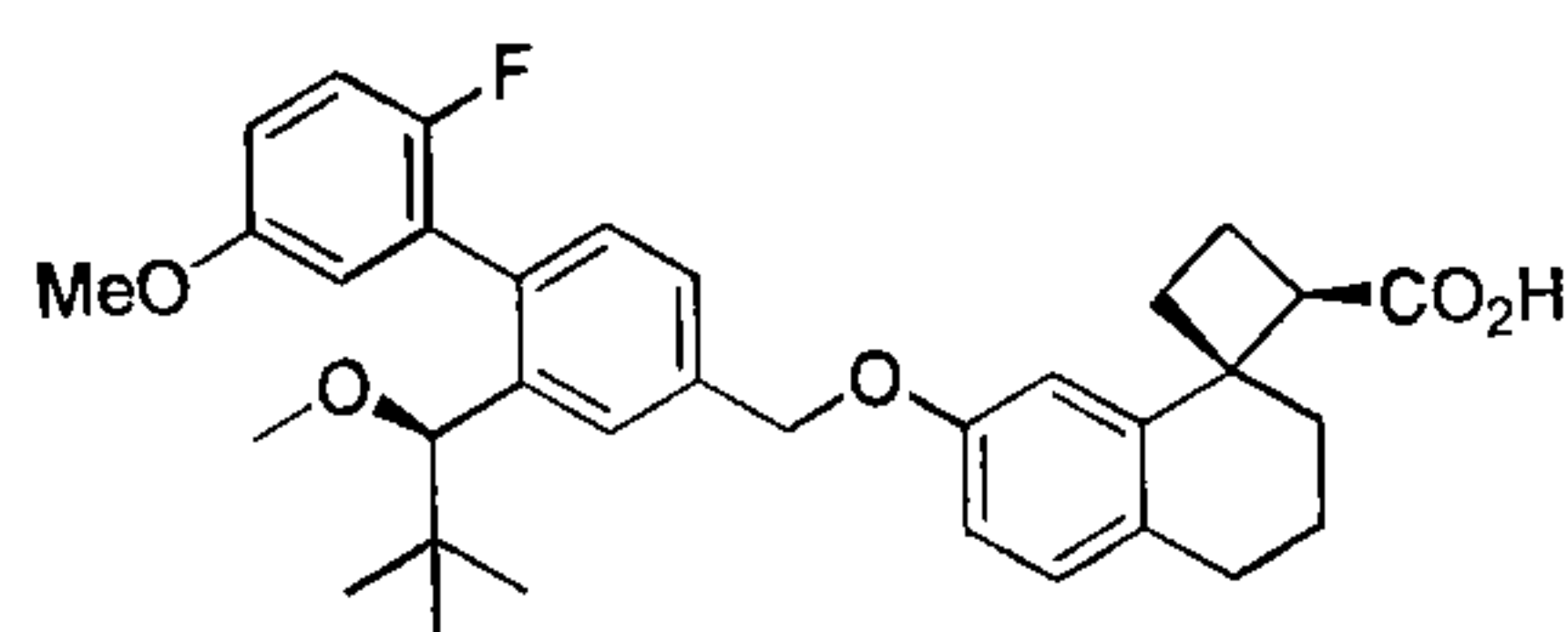
417. The compound



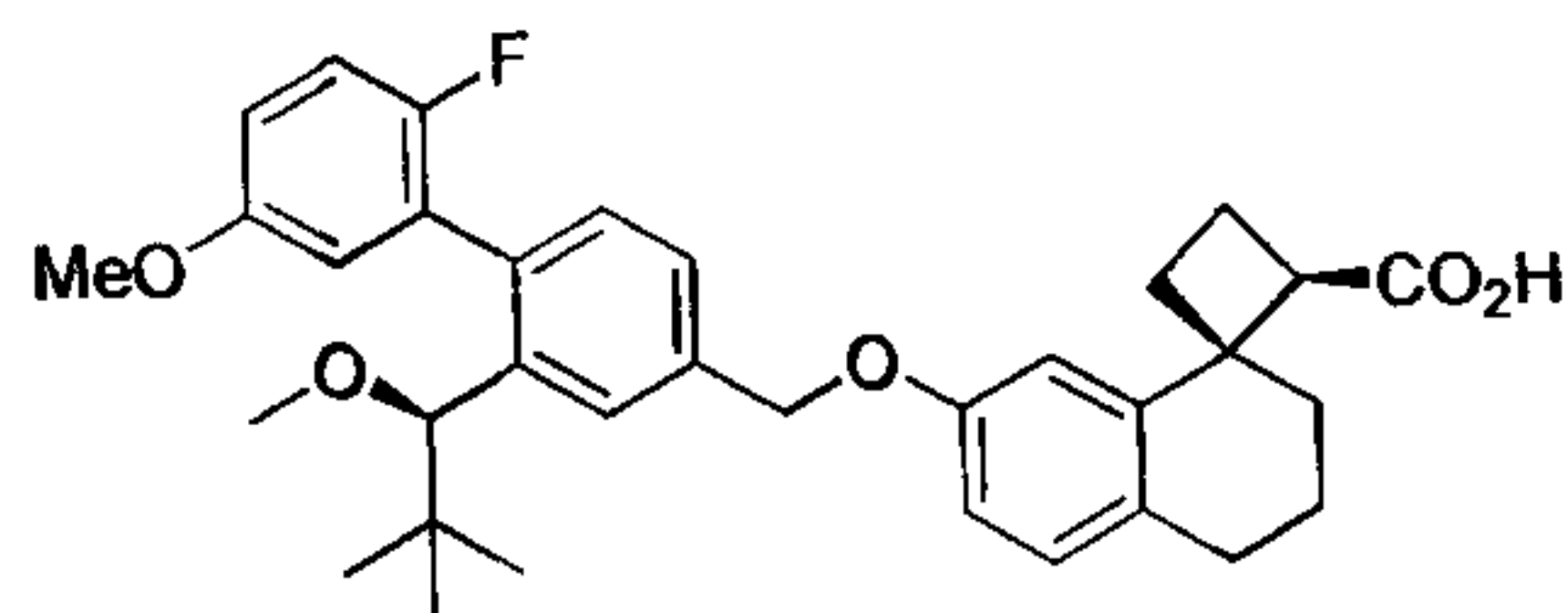
418. The compound



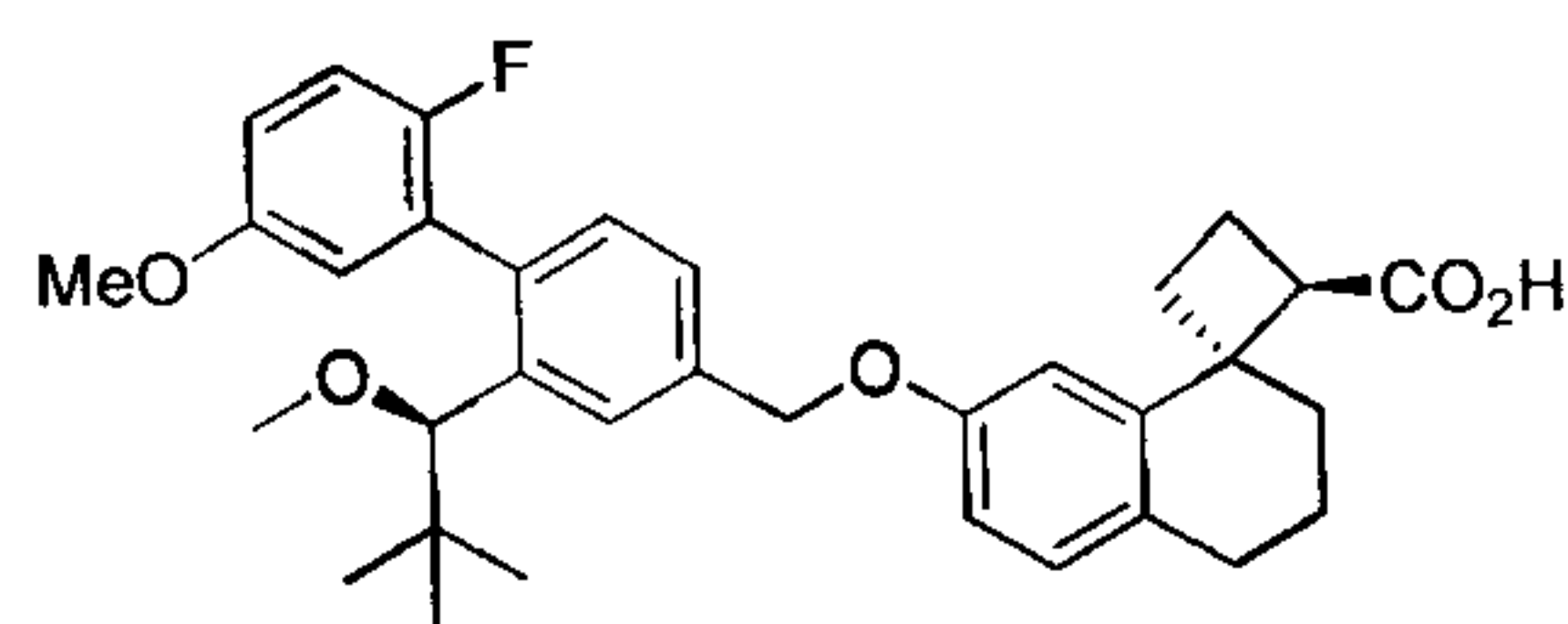
419. The compound



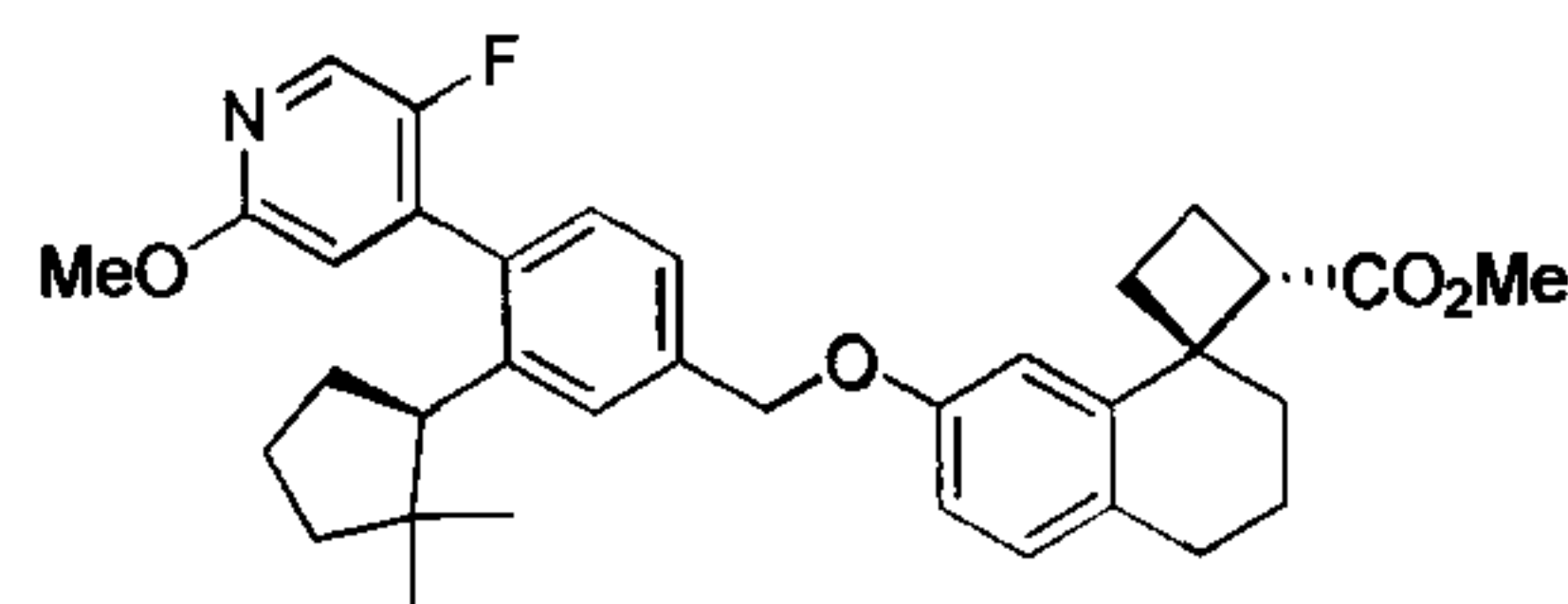
420. The compound



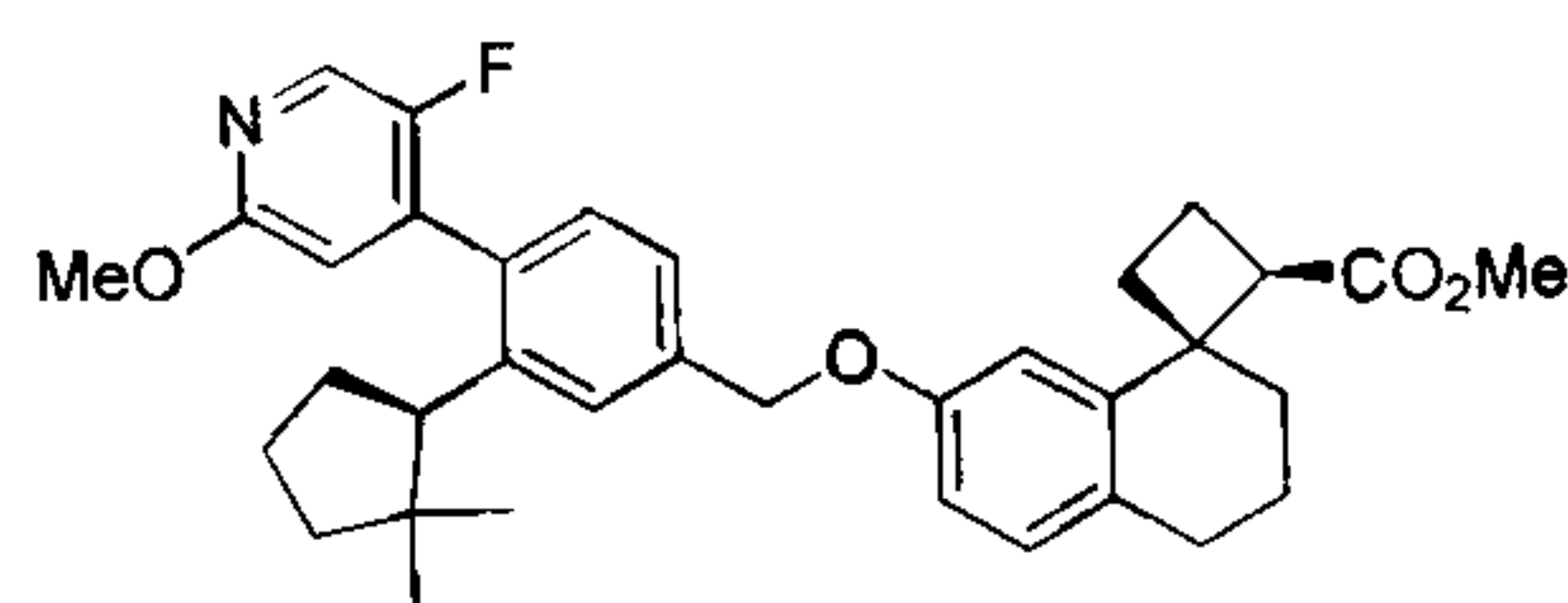
421. The compound



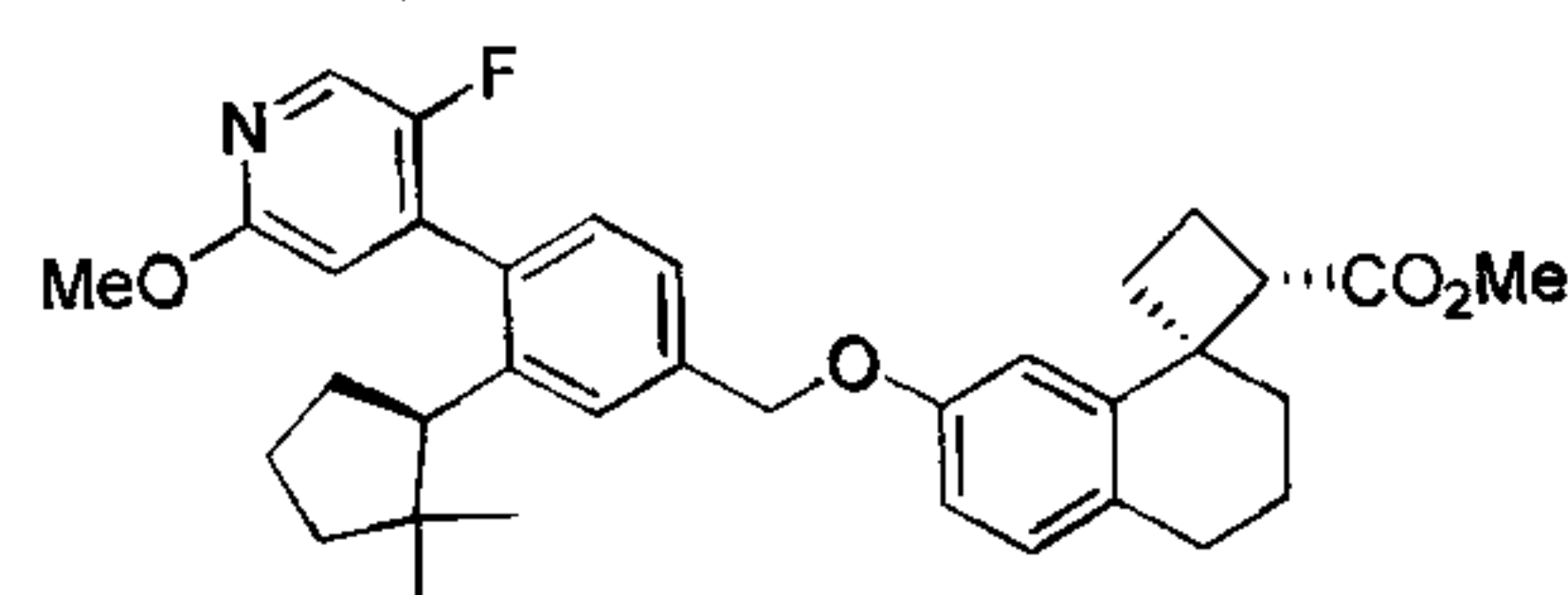
422. The compound



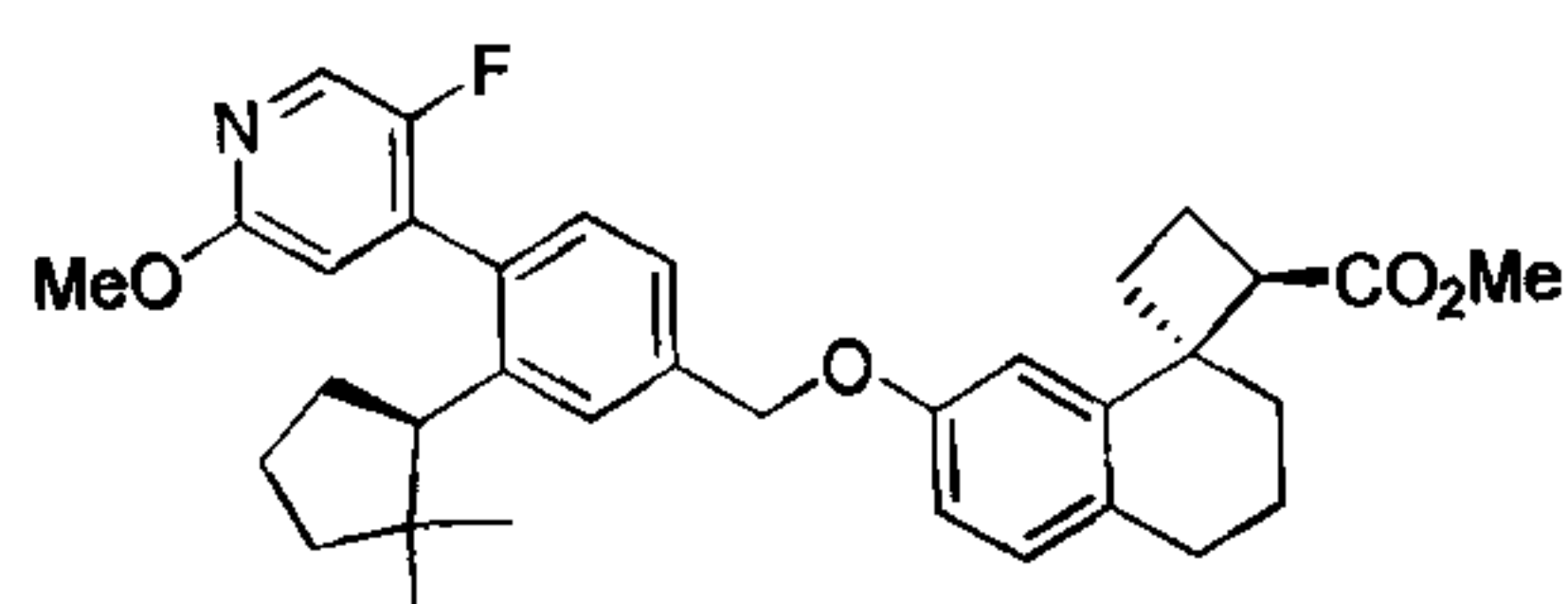
423. The compound



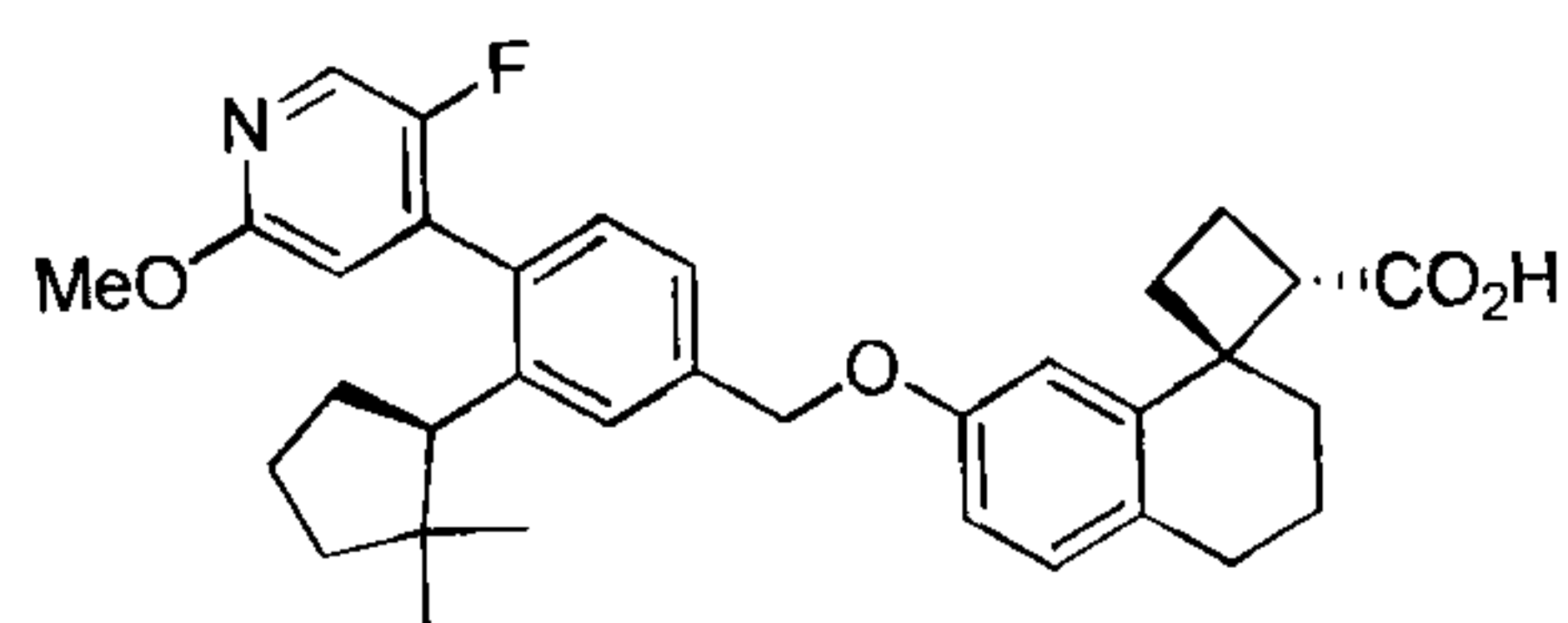
424. The compound



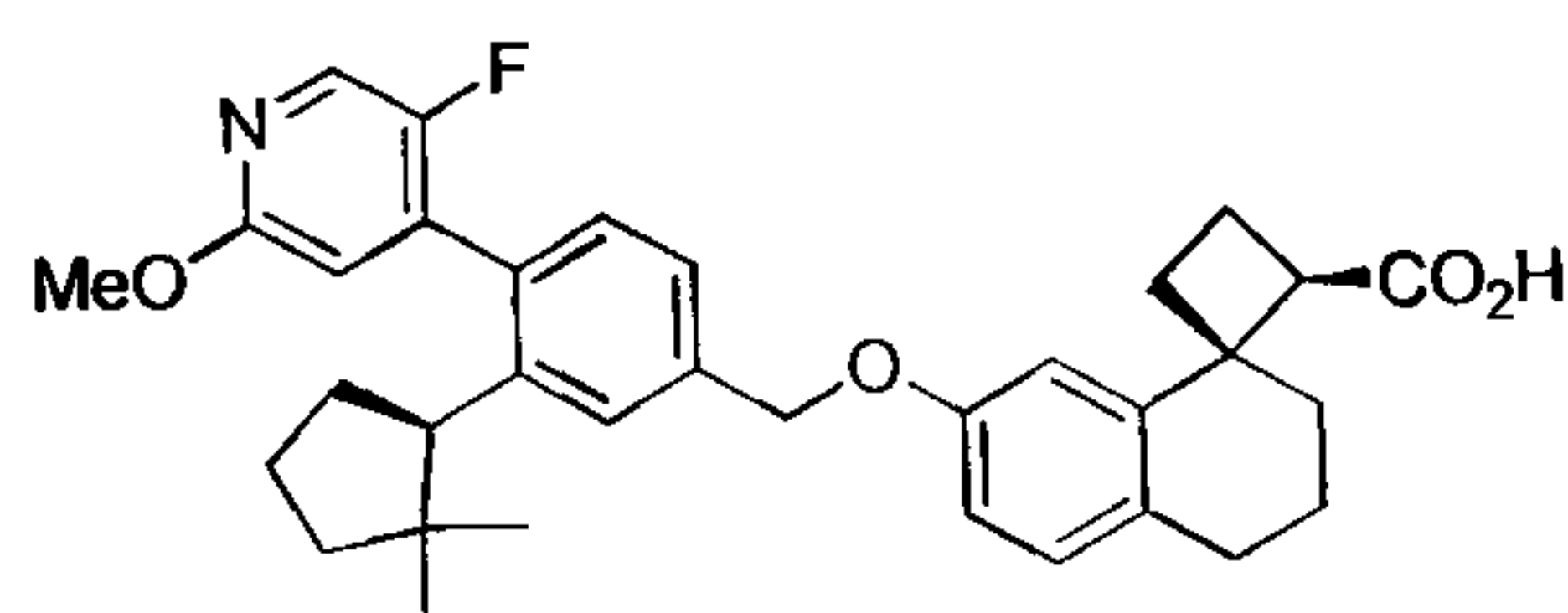
425. The compound



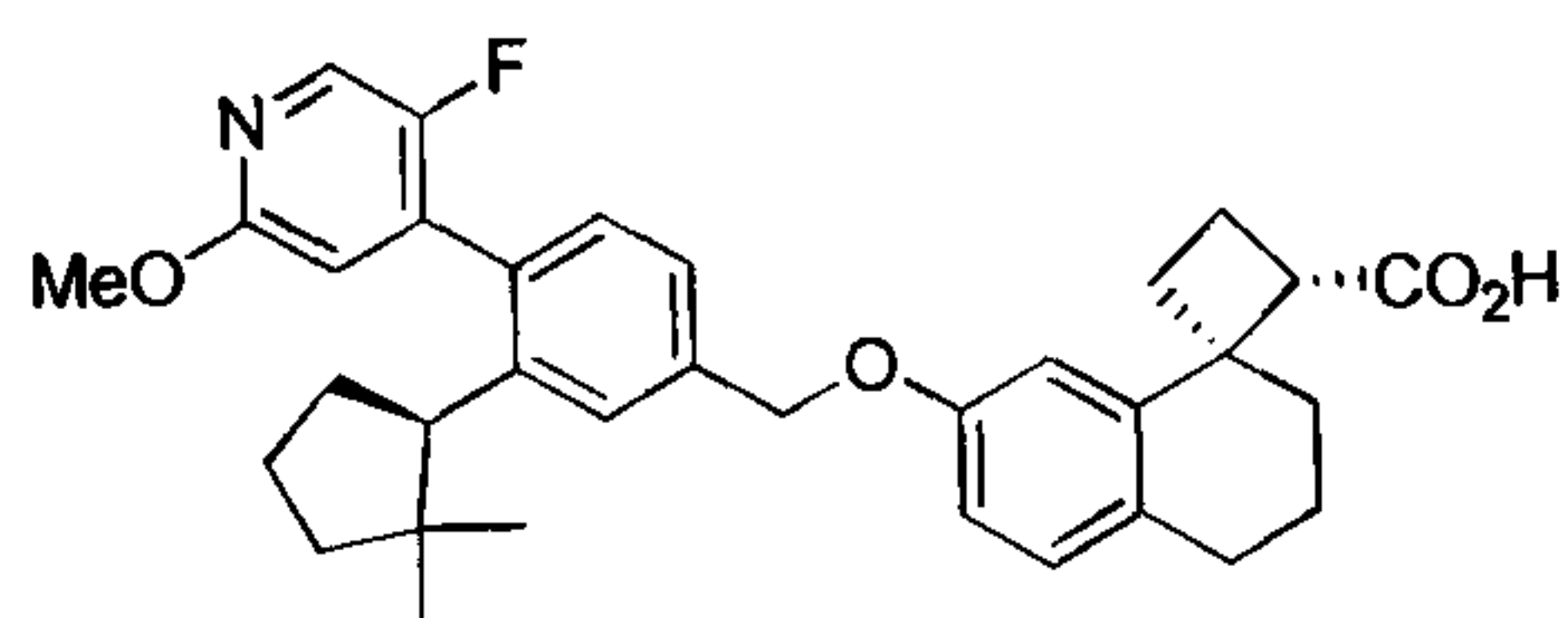
426. The compound



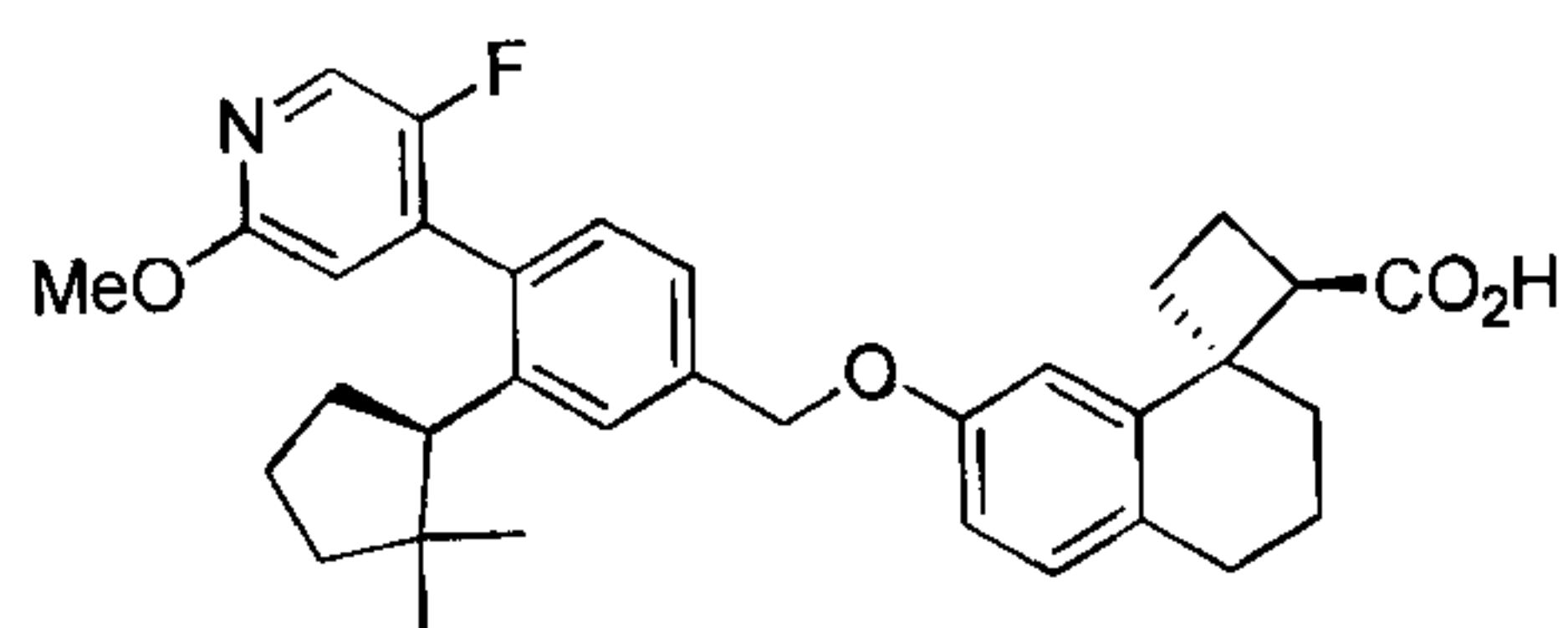
427. The compound



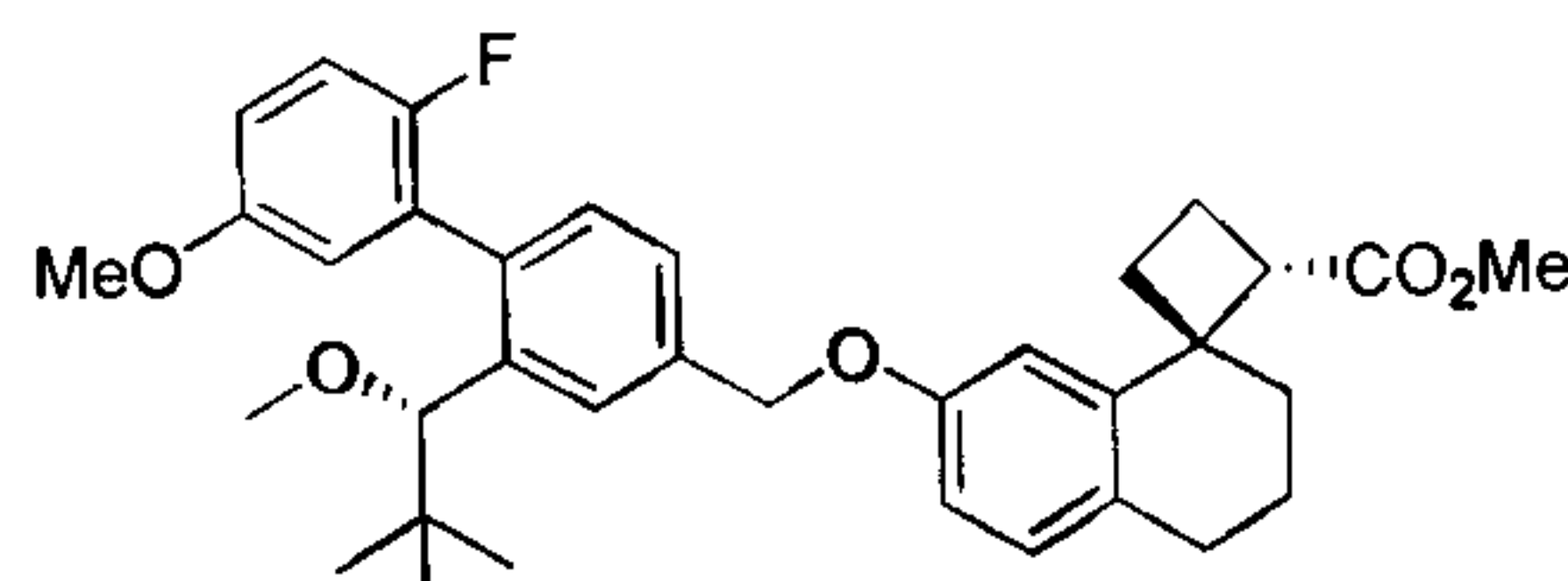
428. The compound



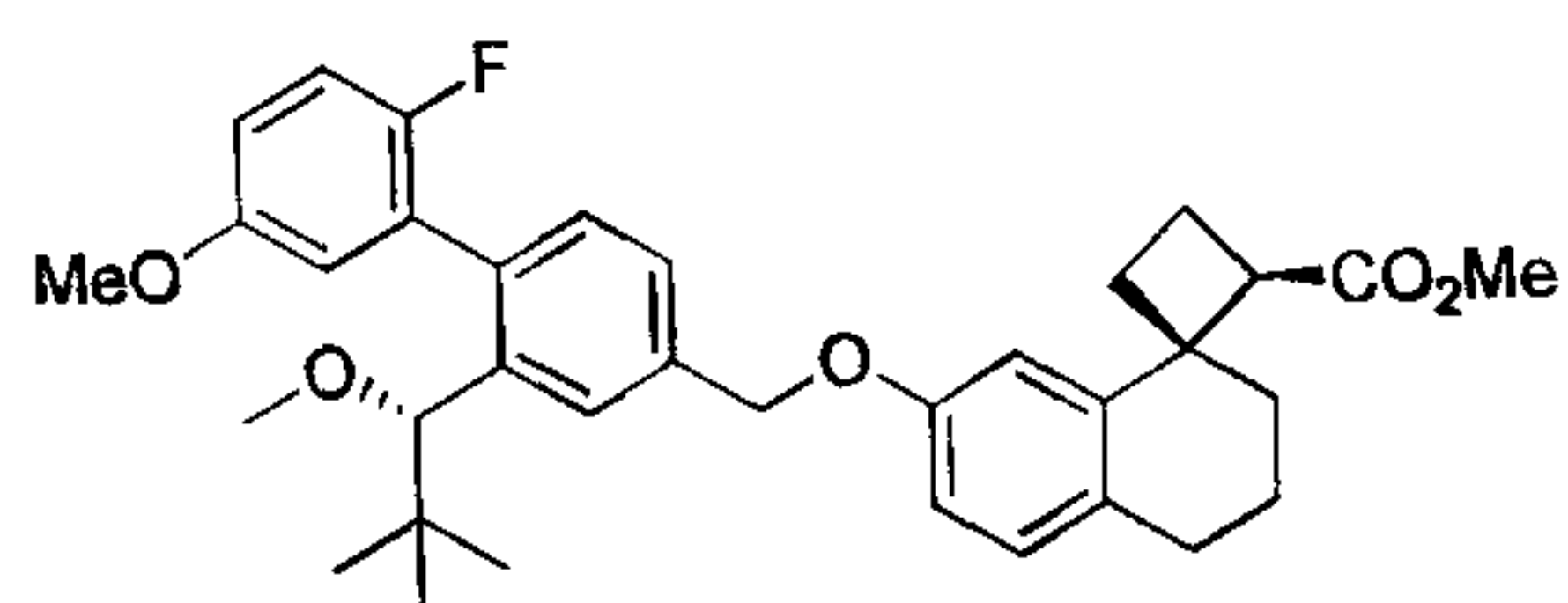
429. The compound



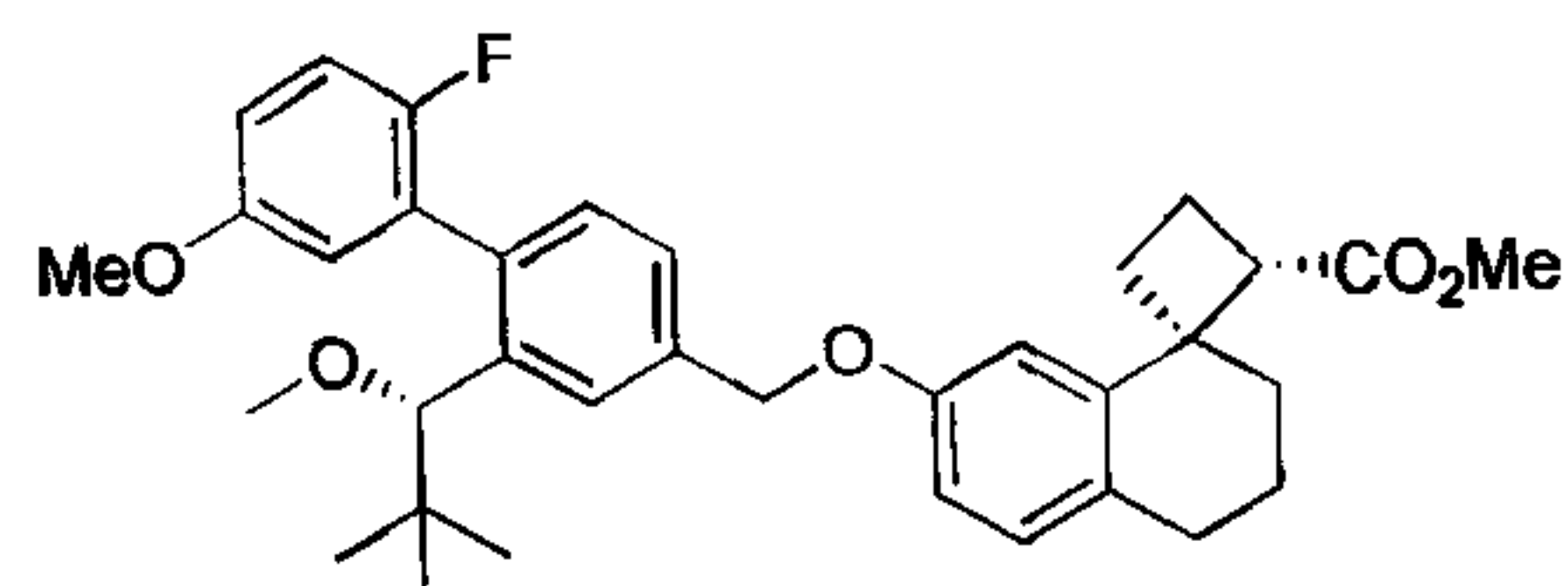
430. The compound



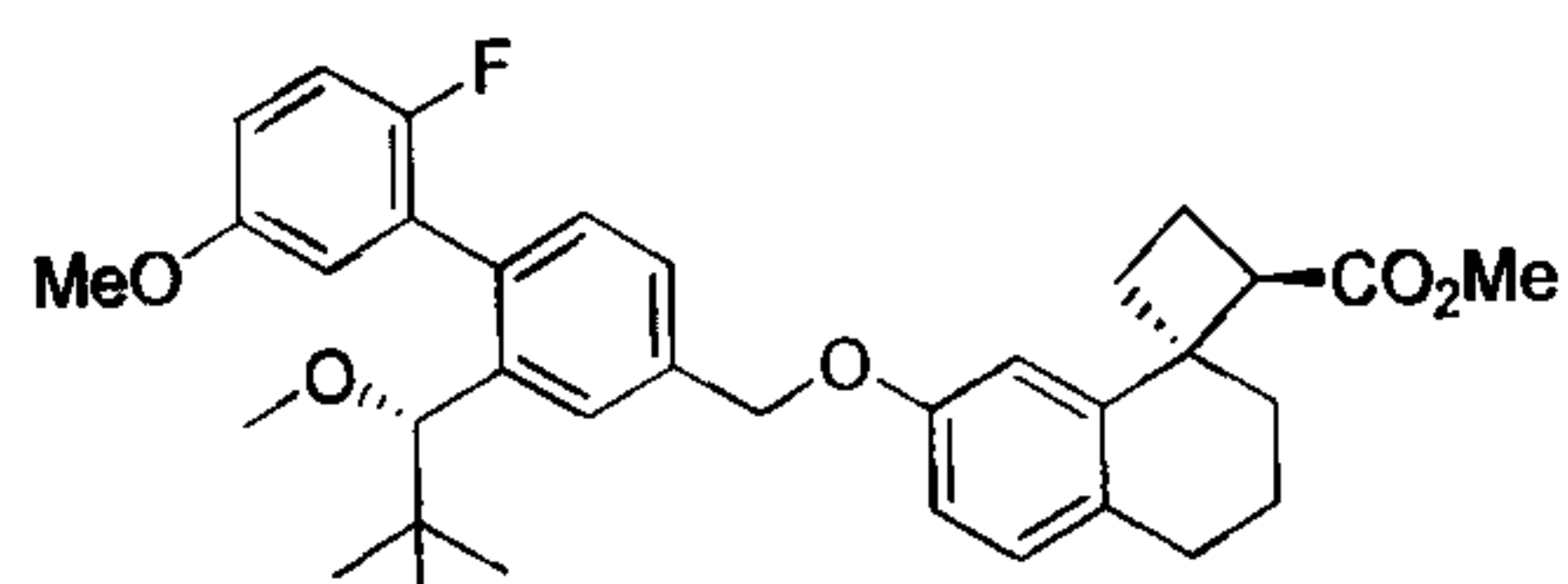
431. The compound



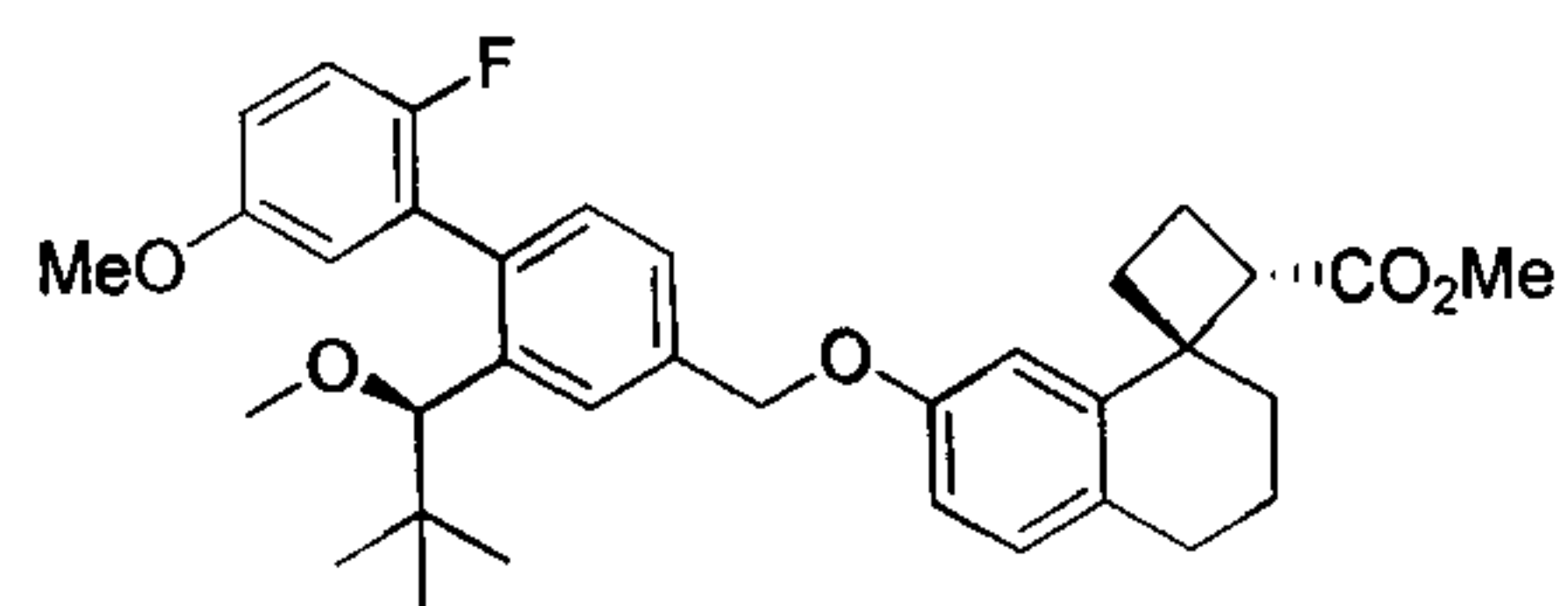
432. The compound



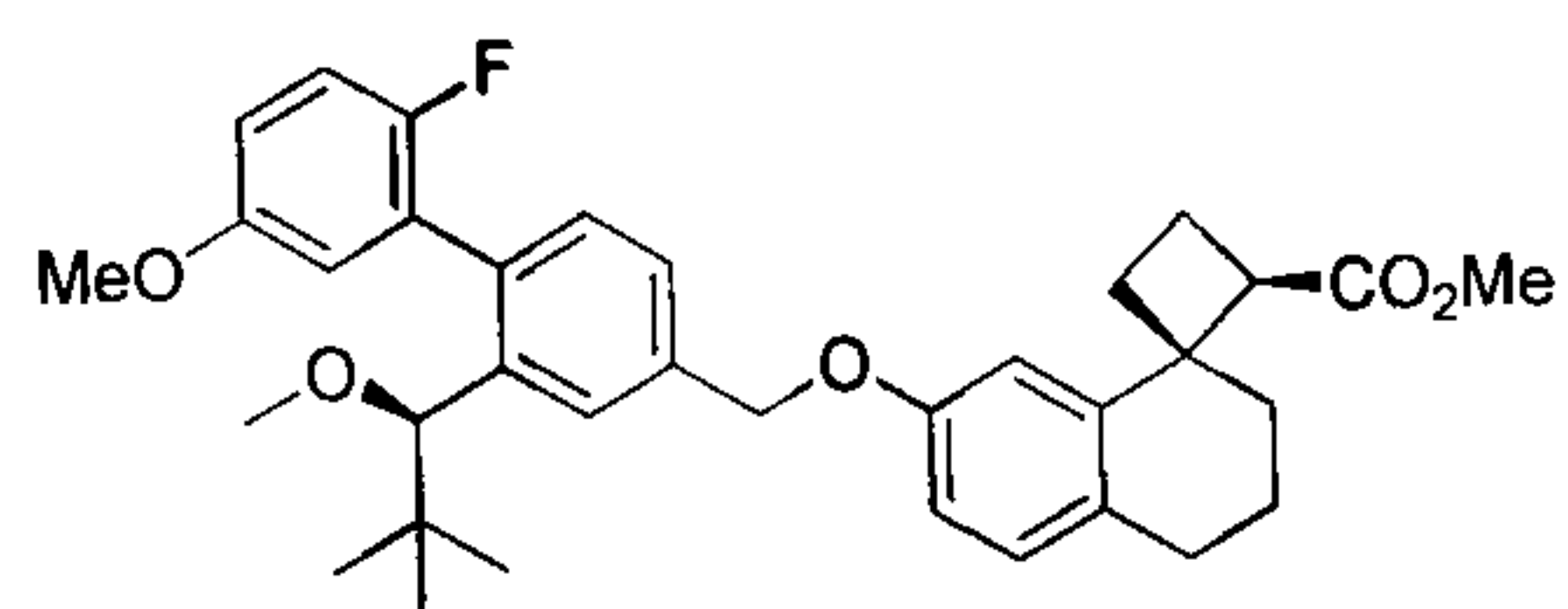
433. The compound



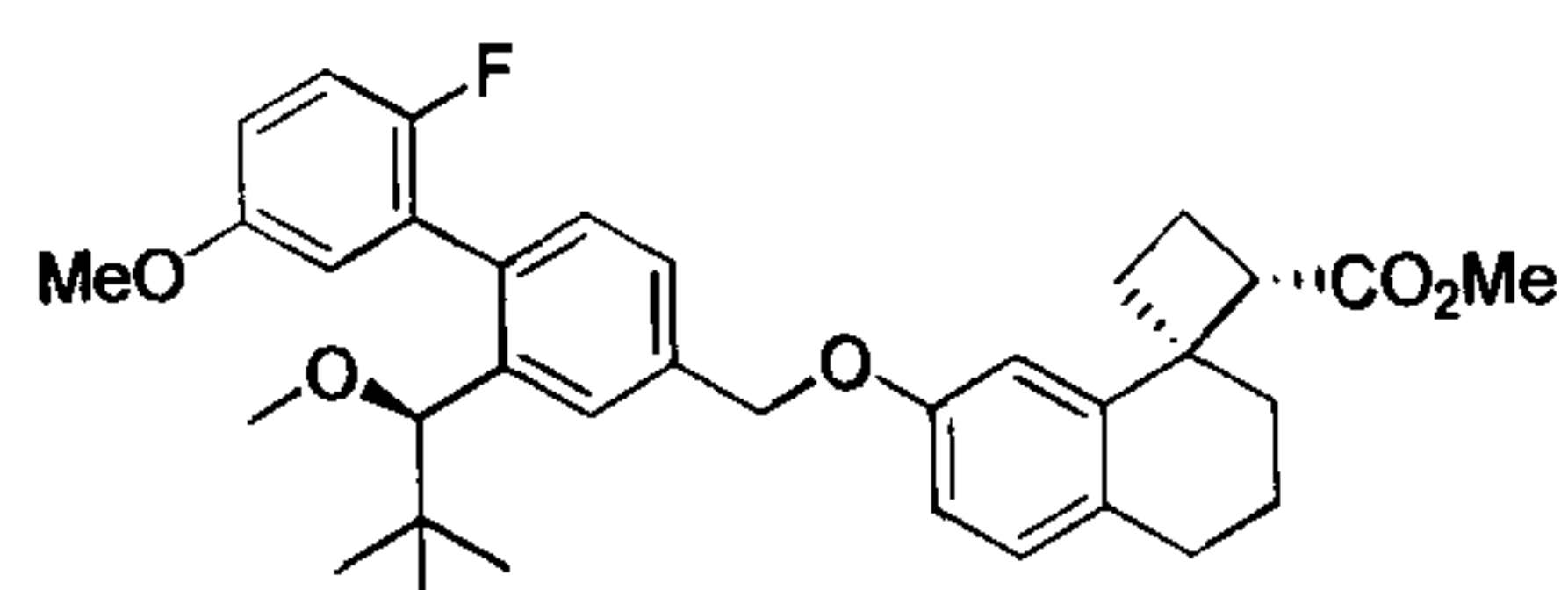
434. The compound



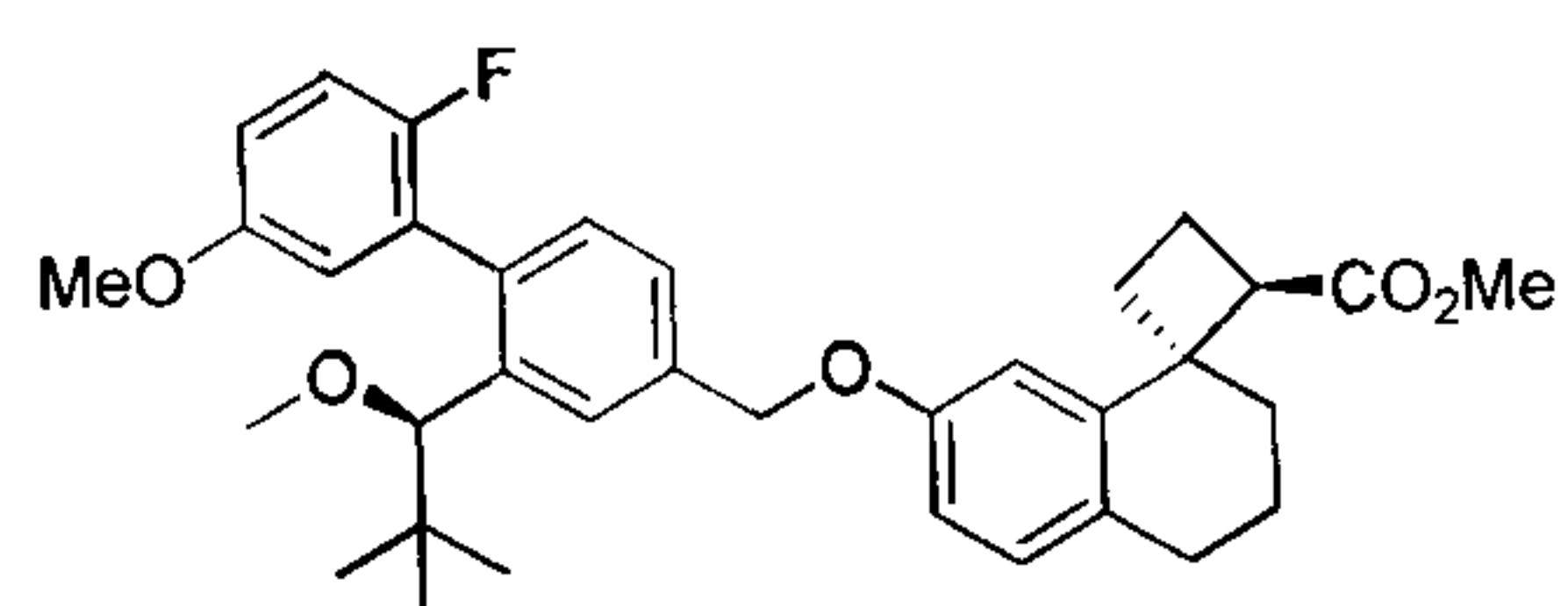
435. The compound



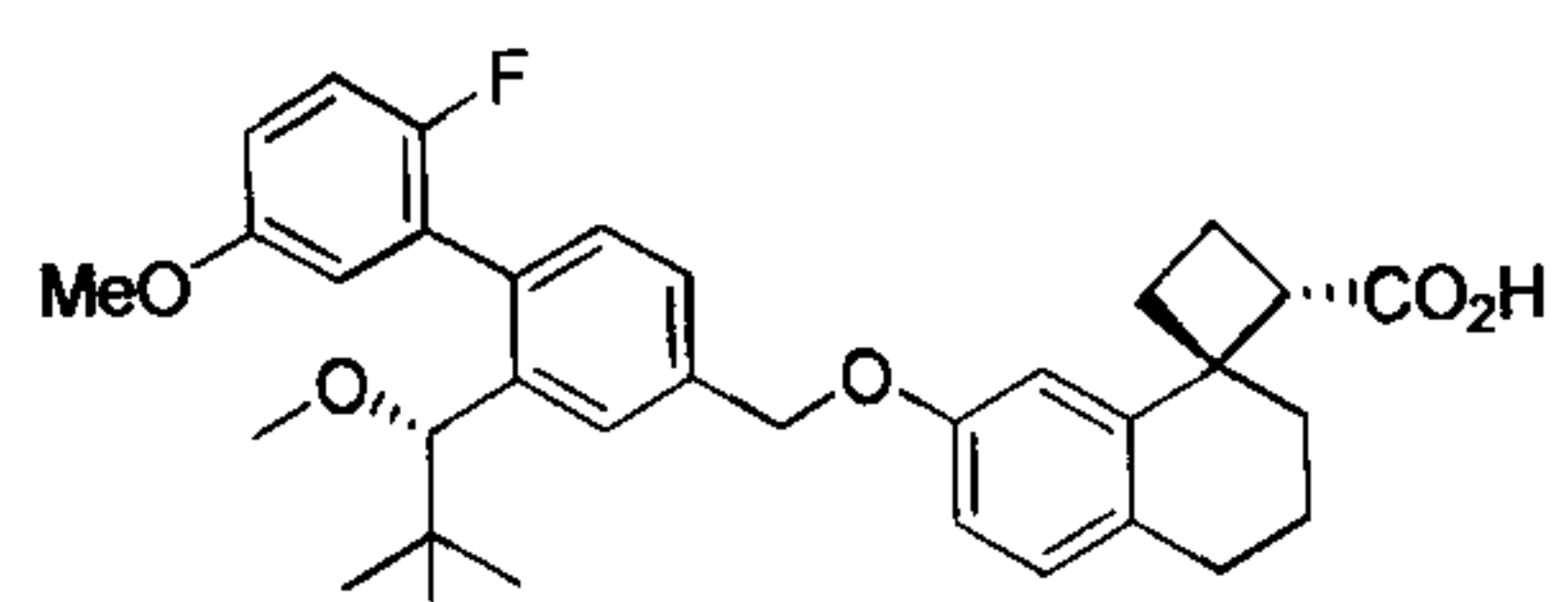
436. The compound



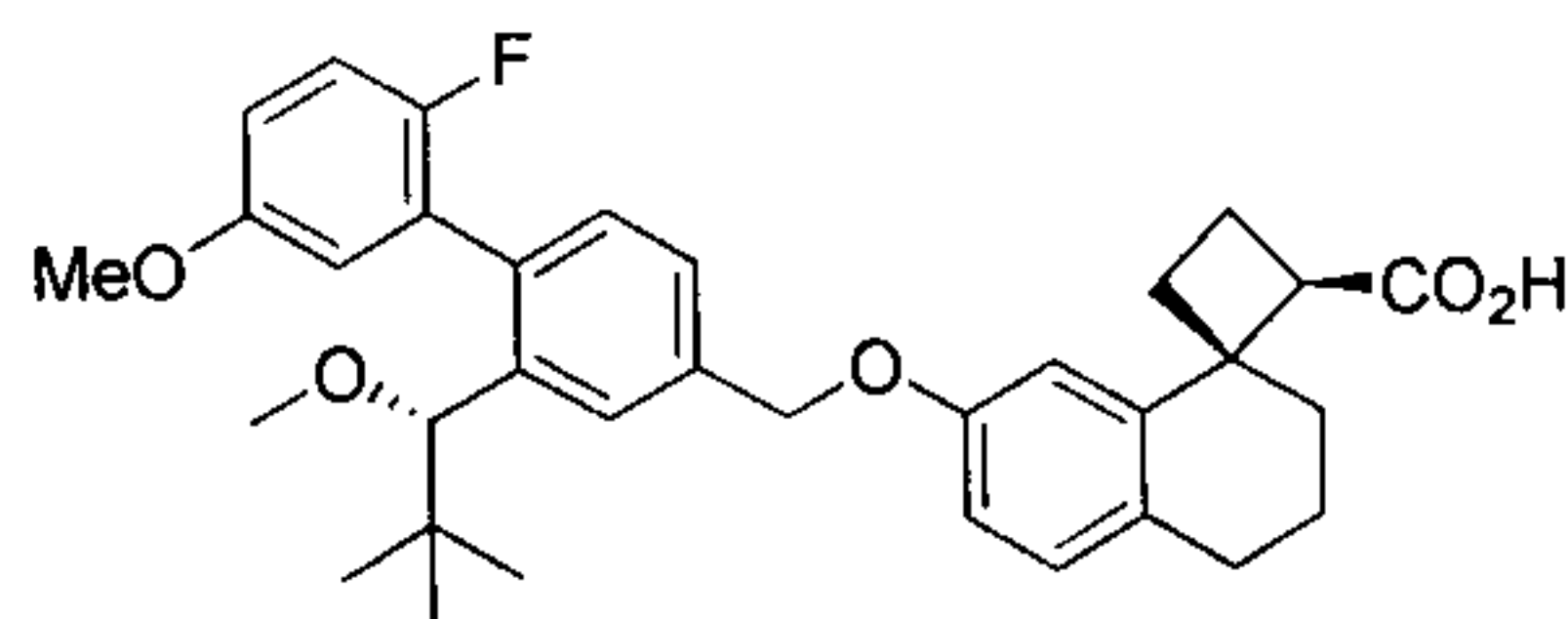
437. The compound



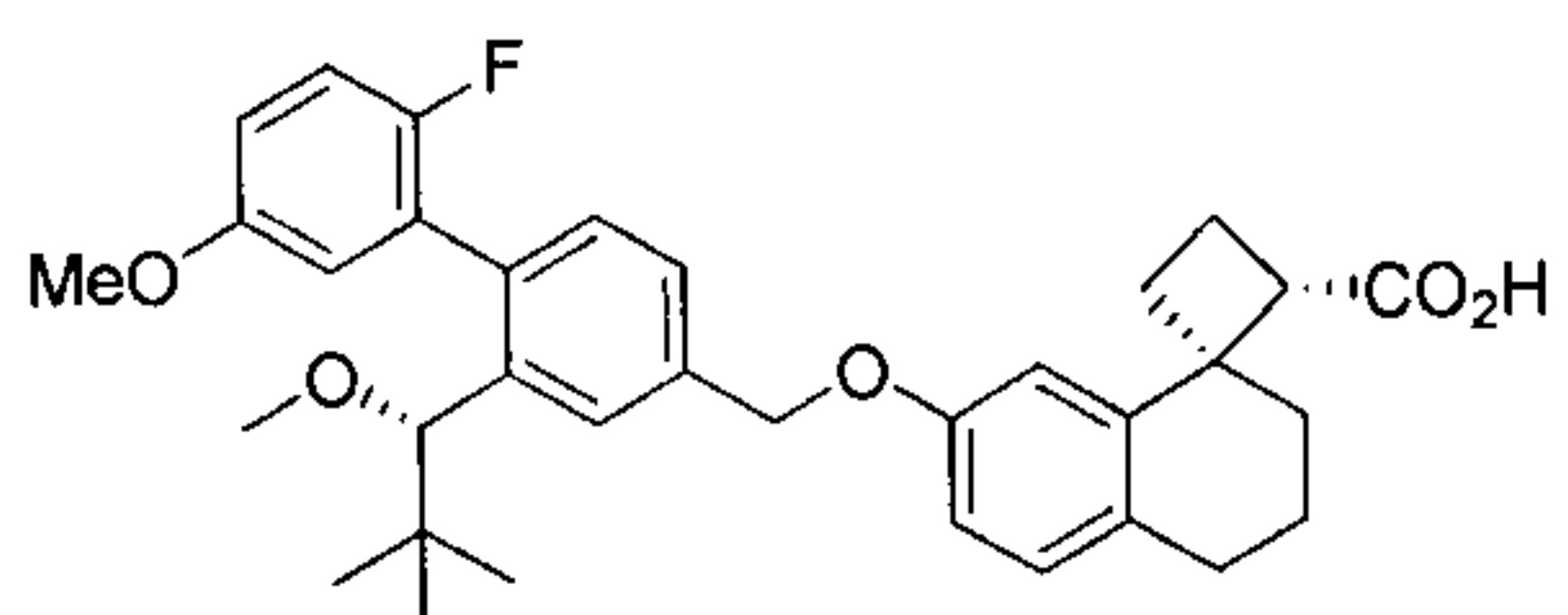
438. The compound



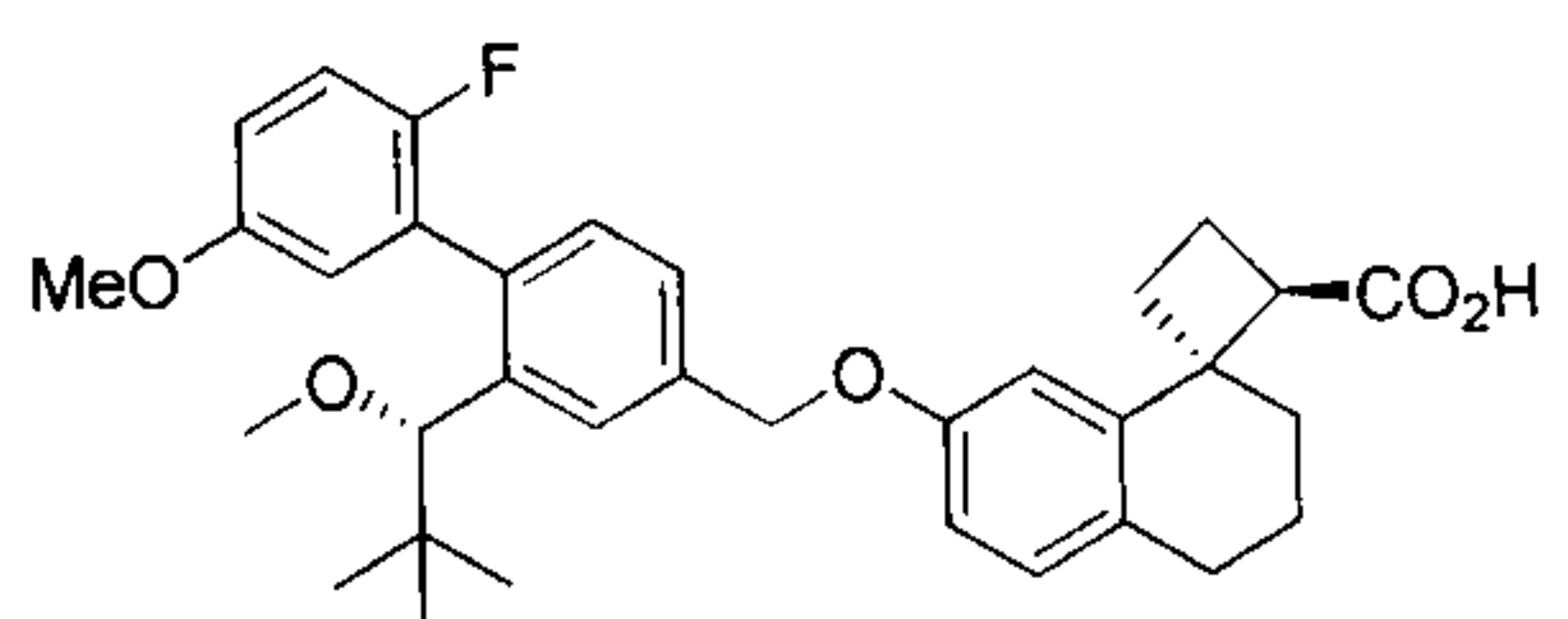
439. The compound



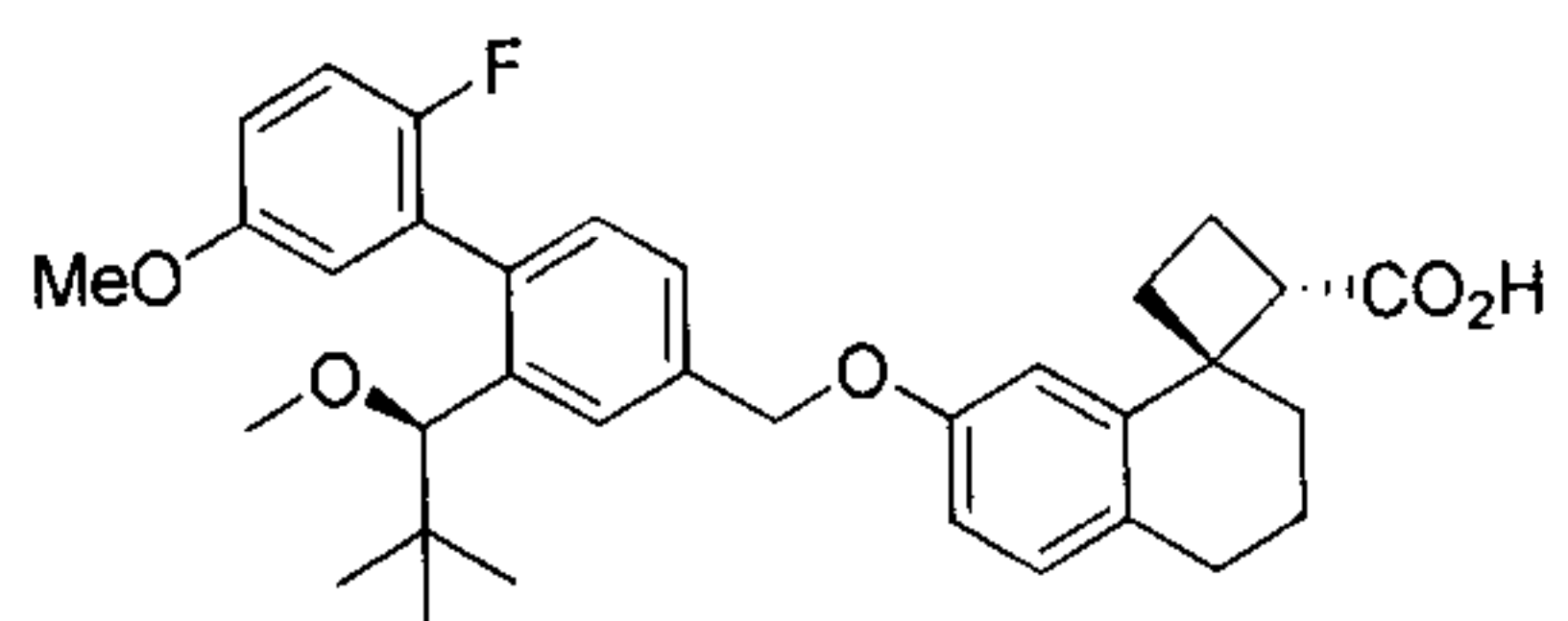
440. The compound



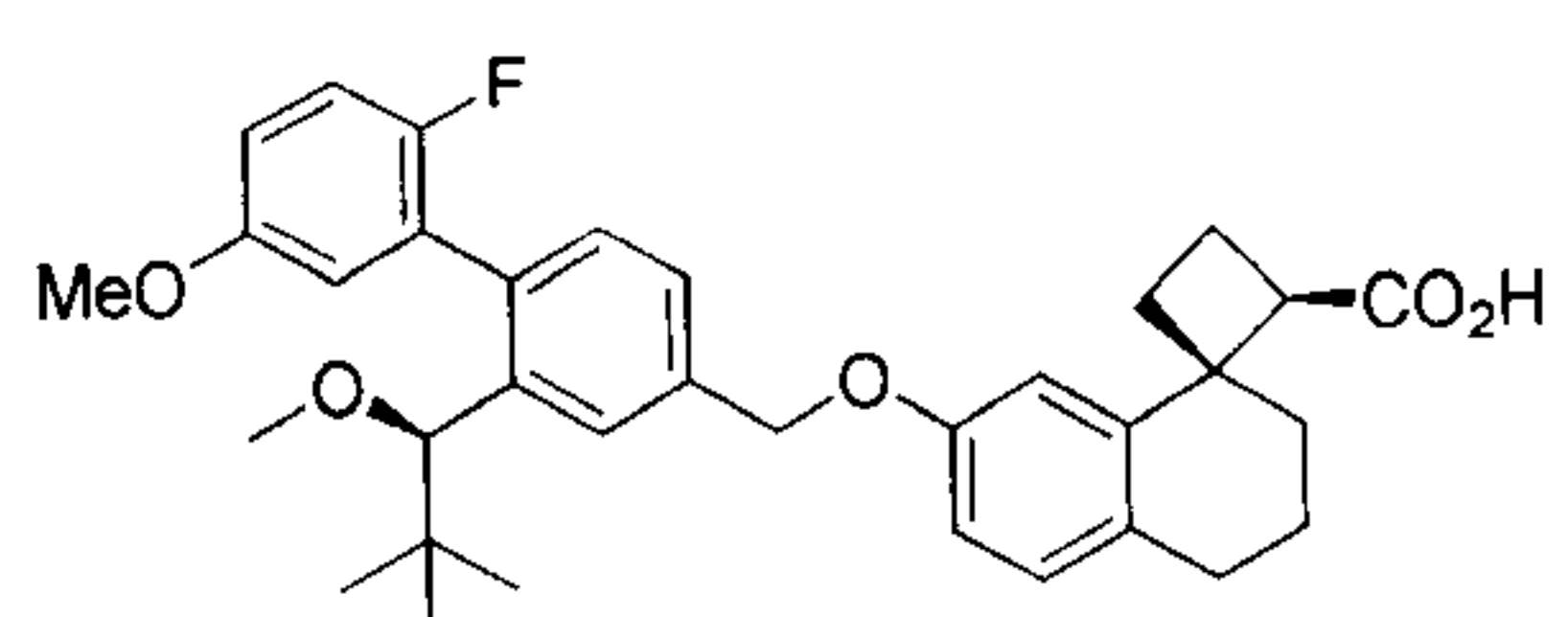
441. The compound



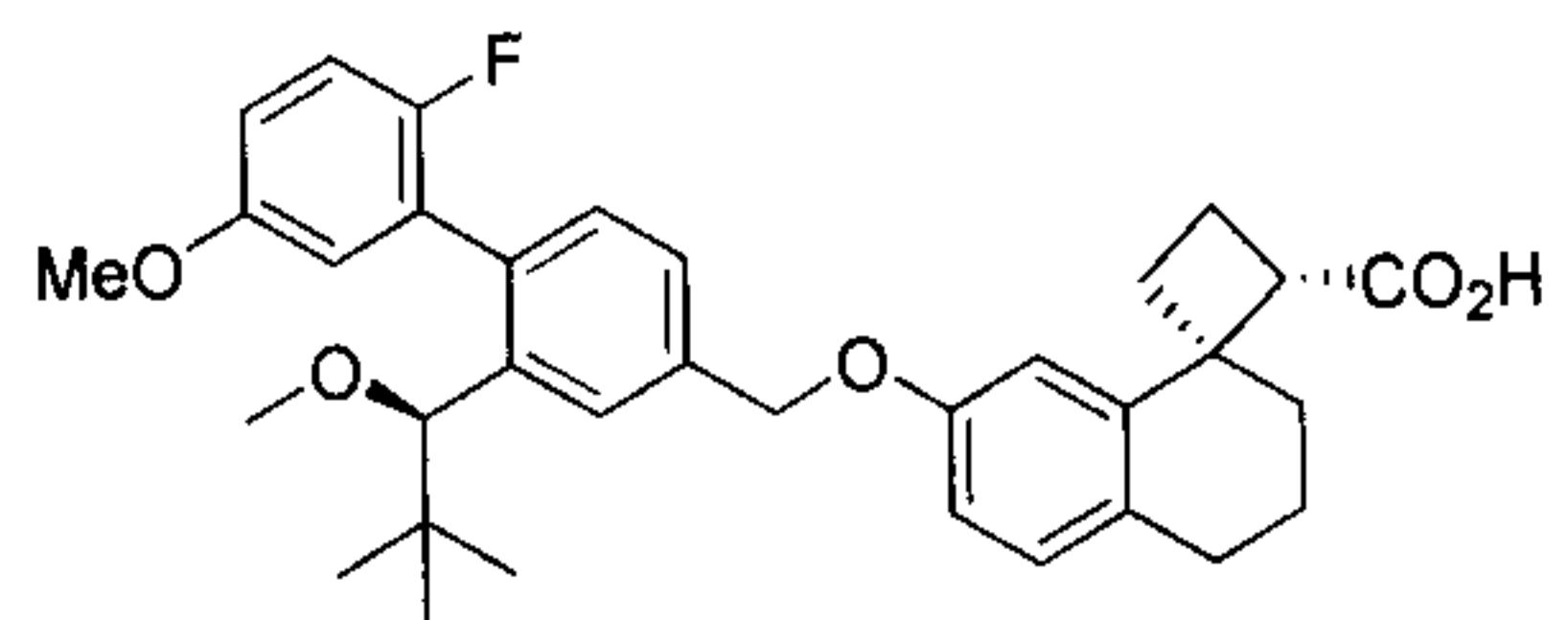
442. The compound



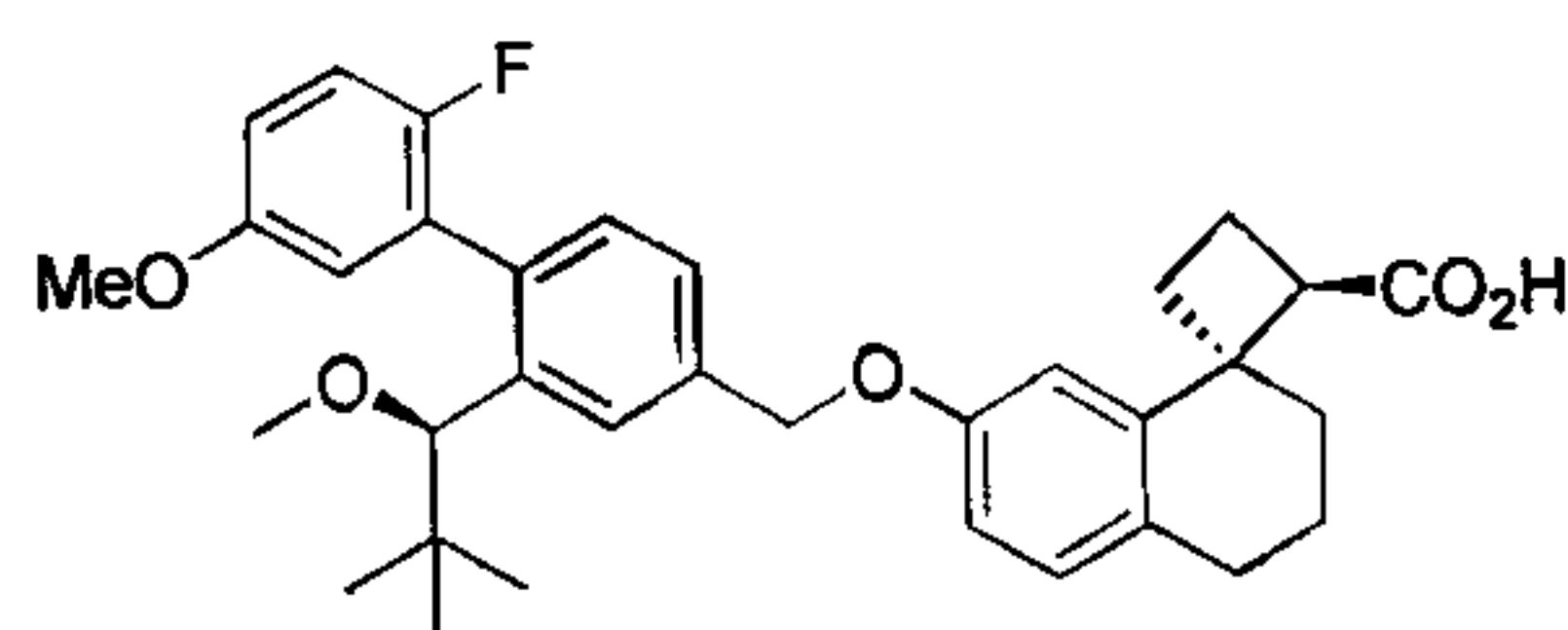
443. The compound



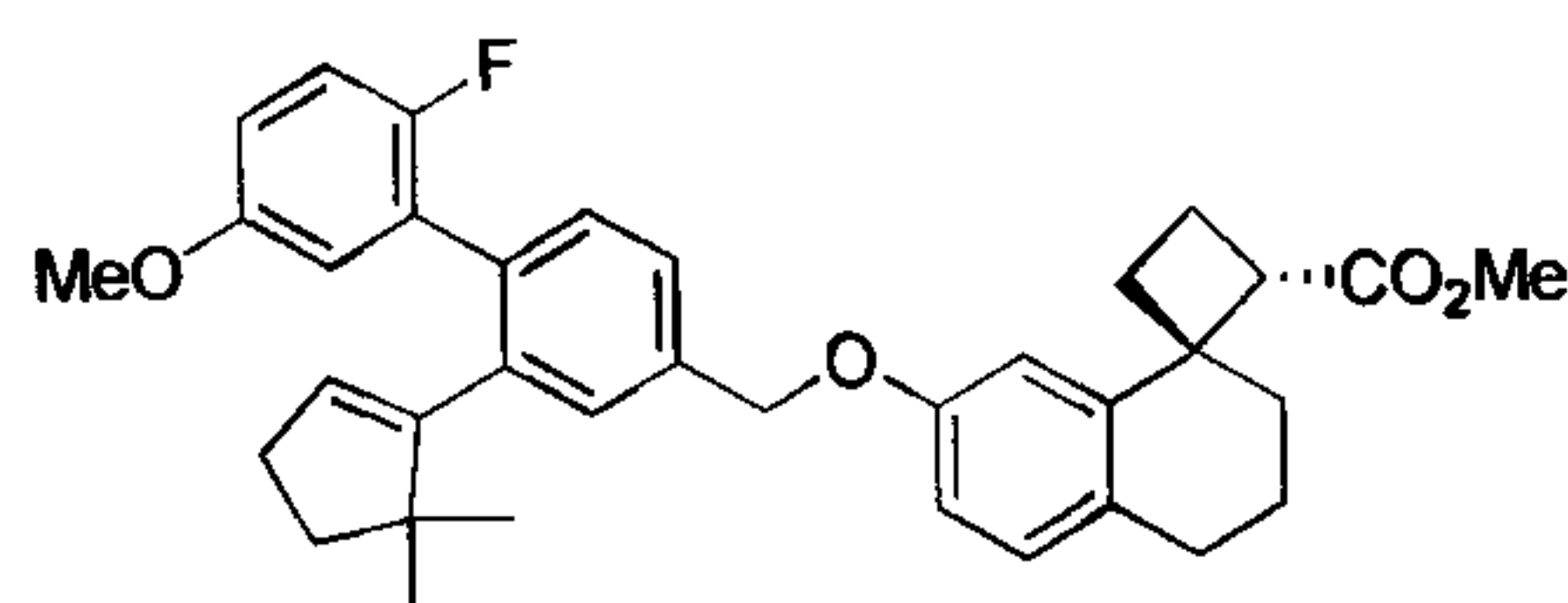
444. The compound



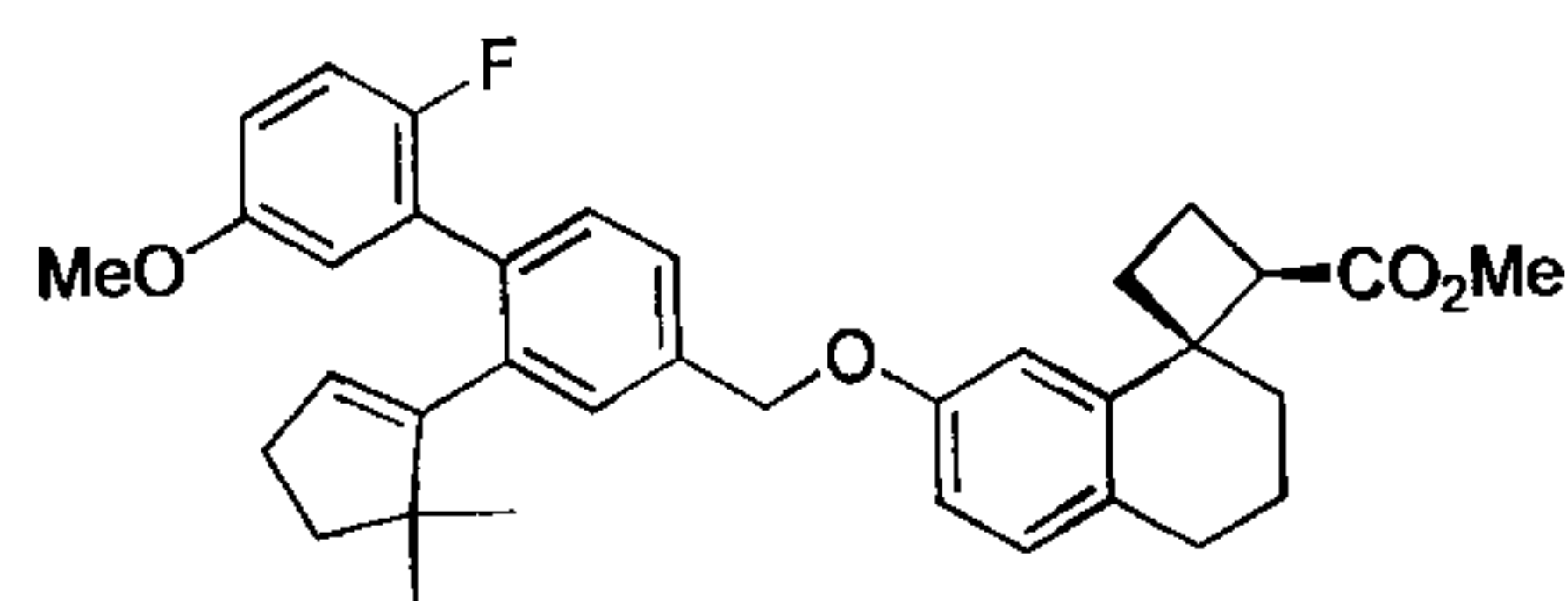
445. The compound



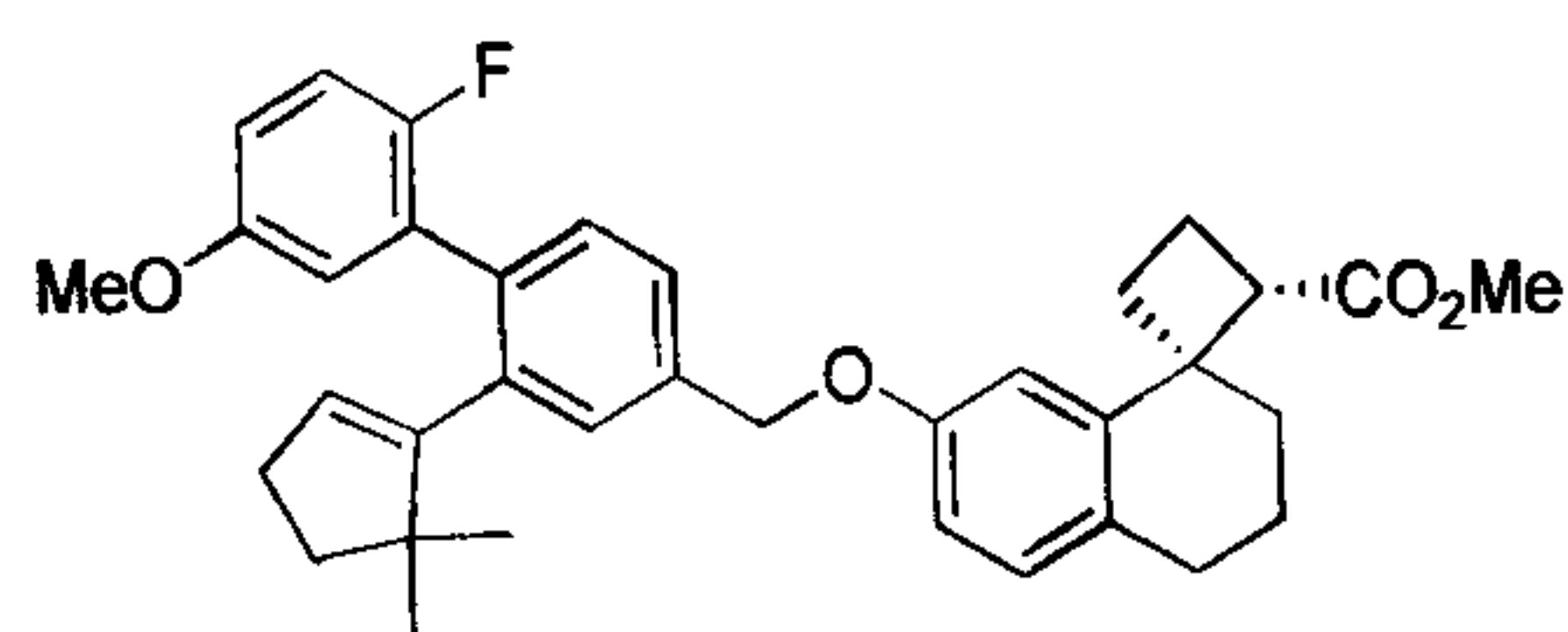
446. The compound



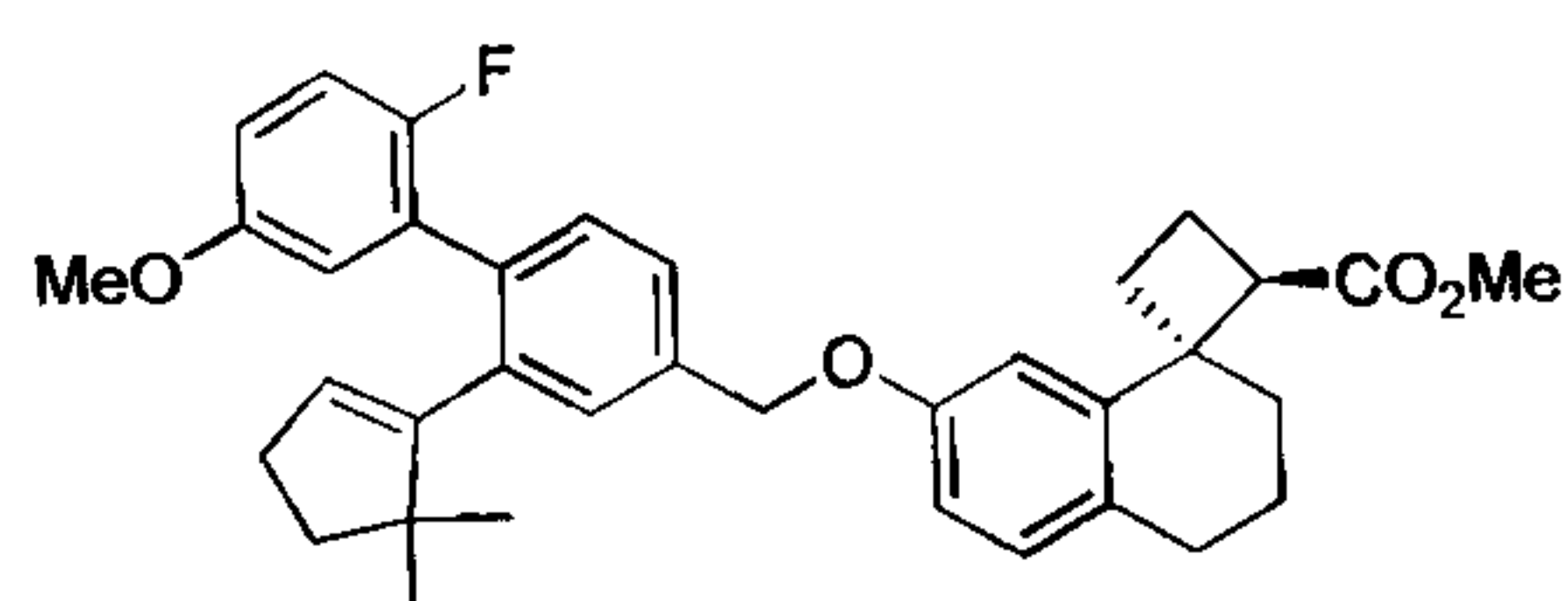
447. The compound



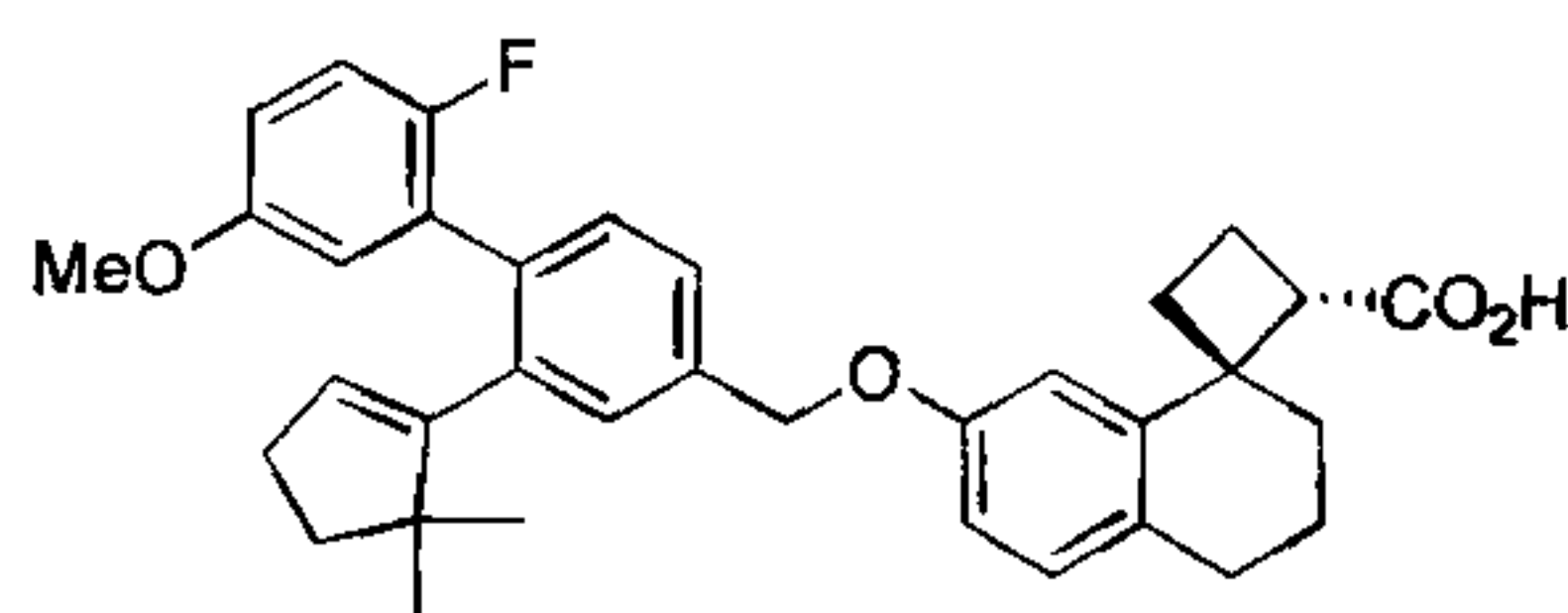
448. The compound



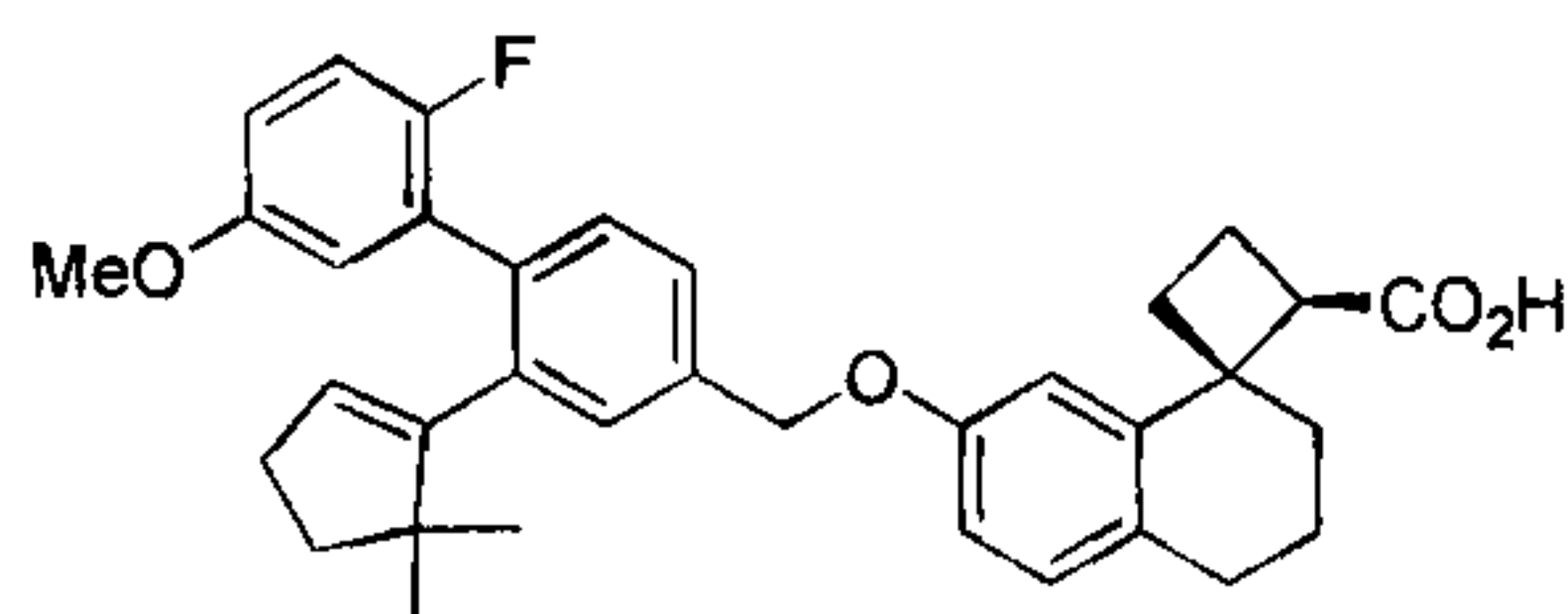
449. The compound



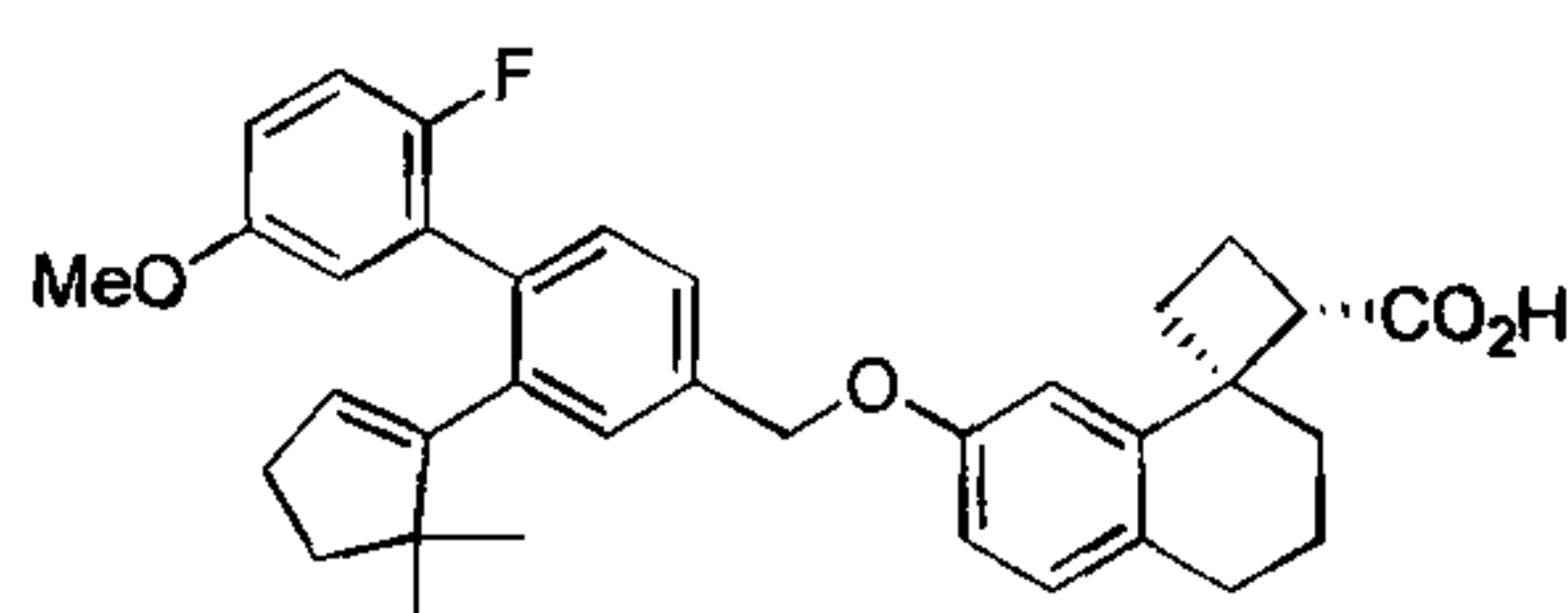
450. The compound



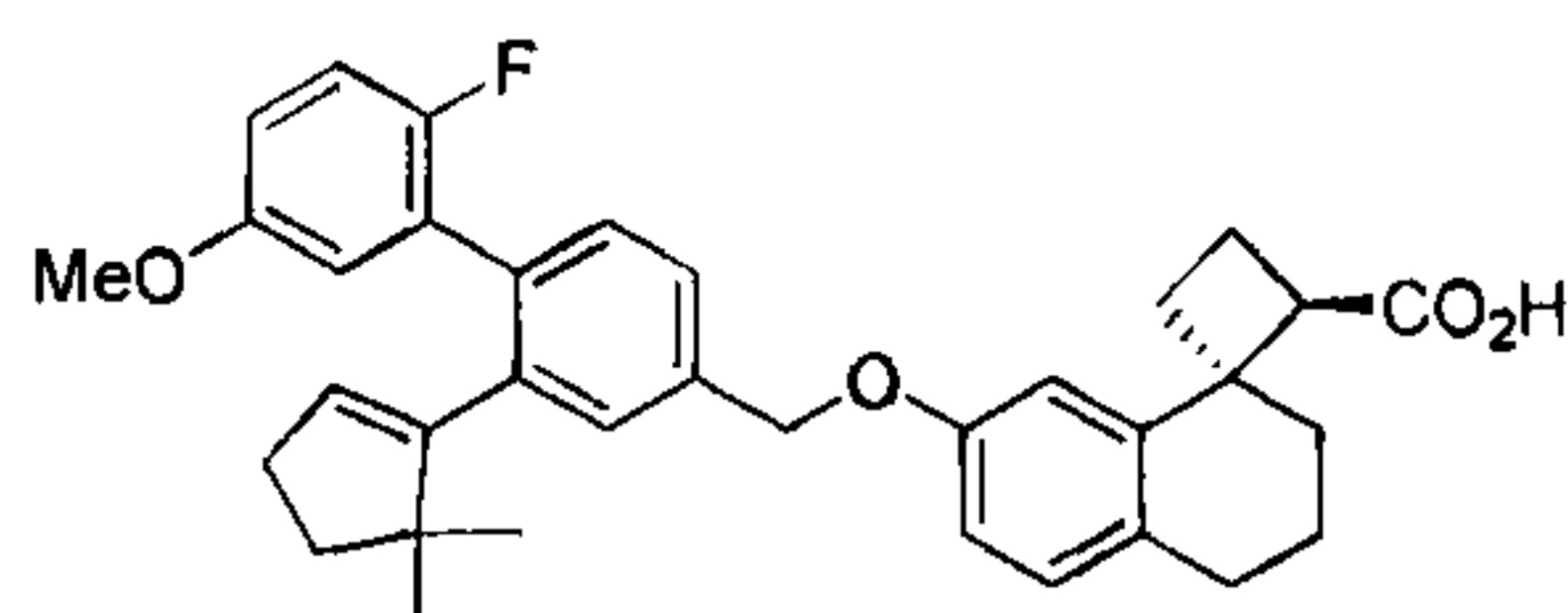
451. The compound



452. The compound



453. The compound

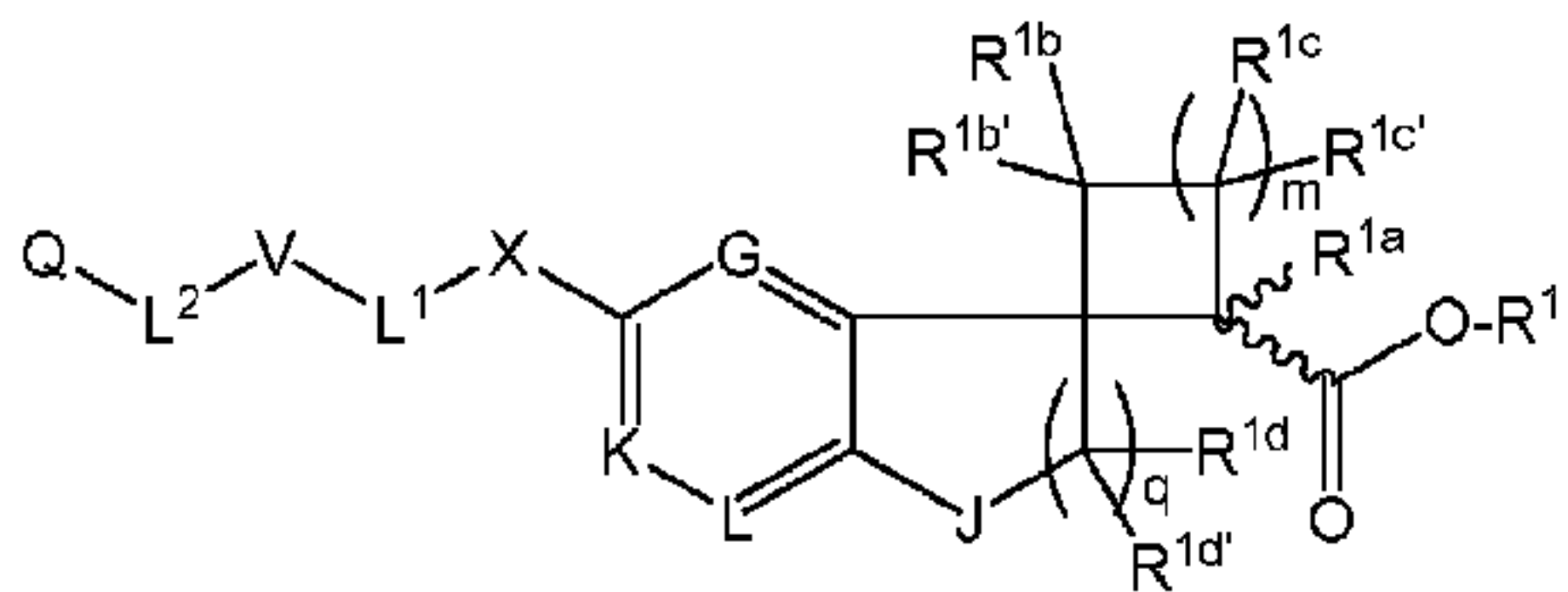


454. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier, diluent, or excipient, and the compound of any one of Claims 1-453.

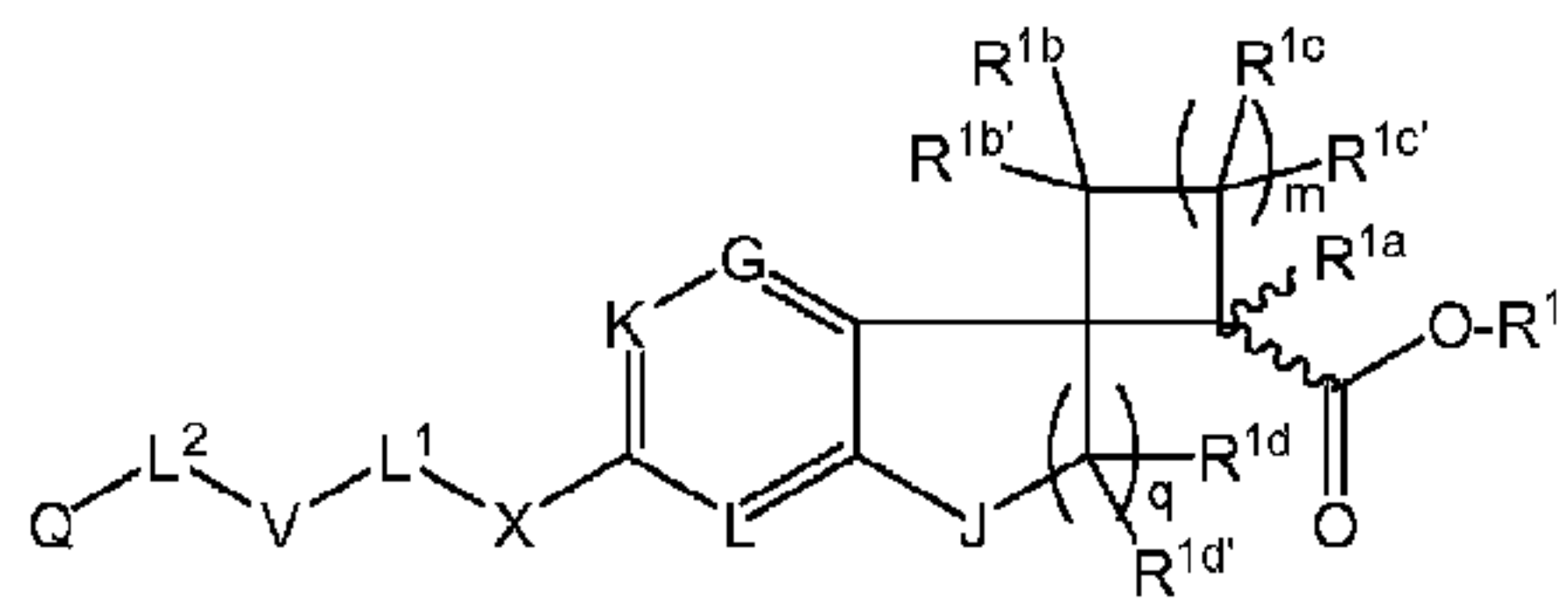
455. A use of the compound of any one of Claims 1-453 in the preparation of a medicament for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

456. The use of Claim 455, wherein the disease or condition is type II diabetes.

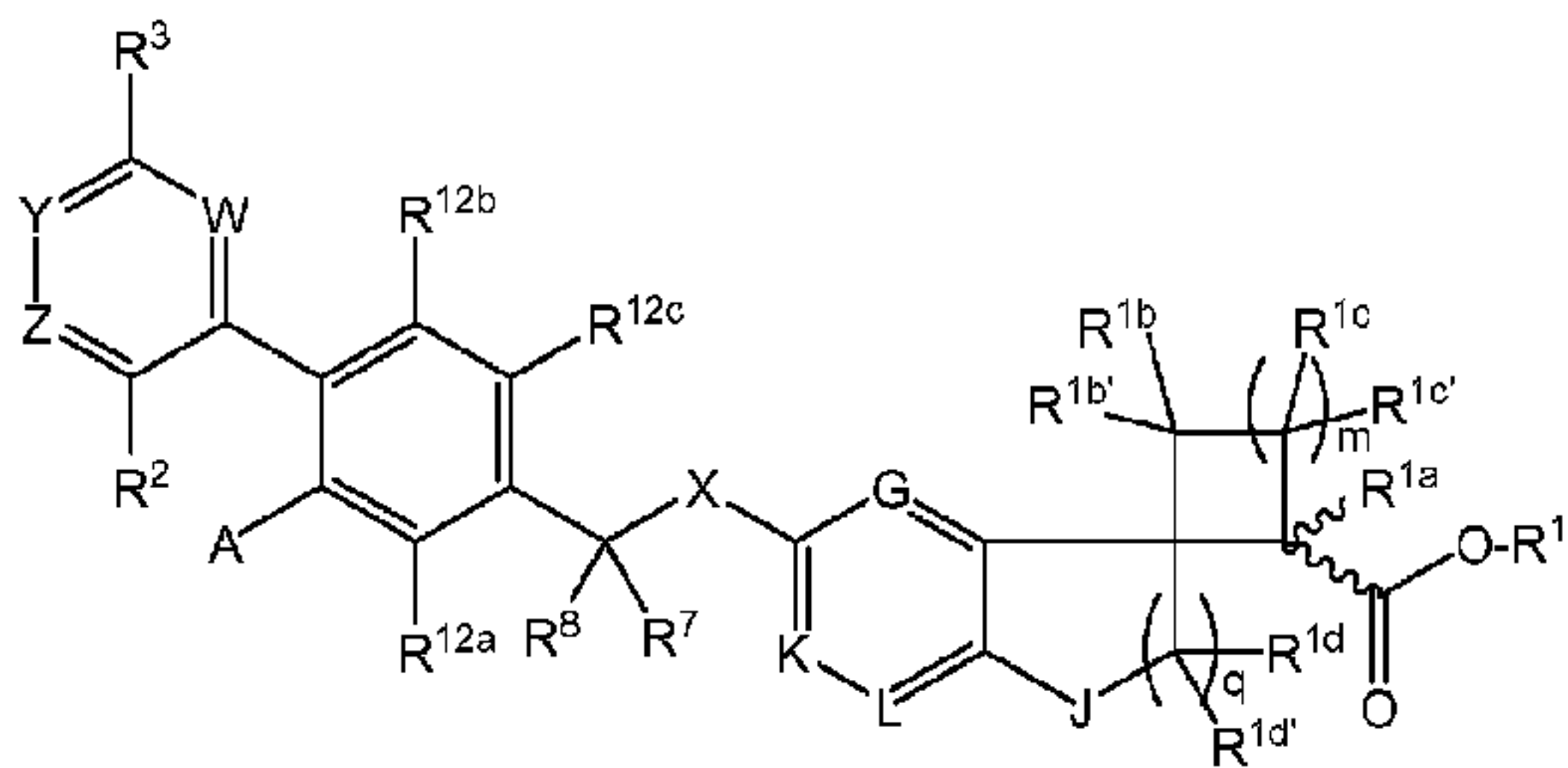
457. A compound of any one of Claims 1-453 for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.
458. The compound of Claim 457, wherein the disease or condition is type II diabetes.



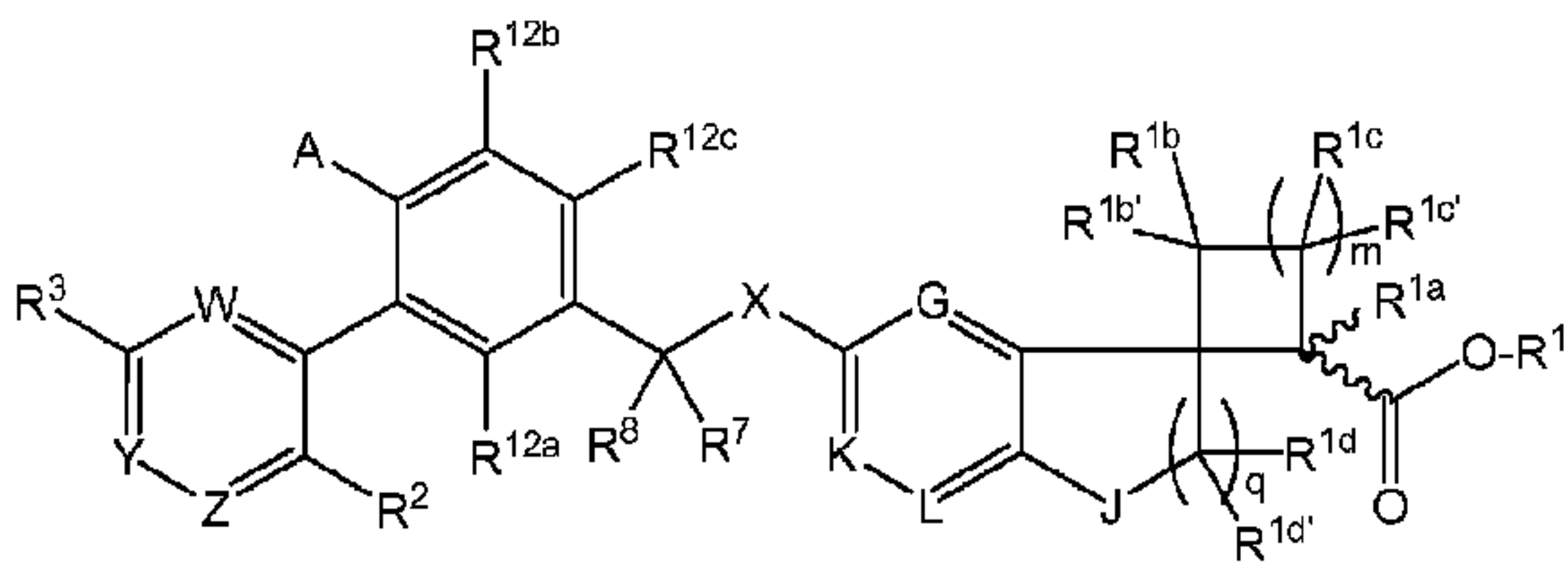
IA



IB



I'A



I'B