US 20170283434A1

(19) United States
(12) Patent Application Publication
Paliwal et al.
(10) Pub. No.: US 2017/0283434 A1
(43) Pub. Date: Oct. 5, 2017

(54) **NK1 ANTAGONISTS**

(71) Applicant: **OPKO Health, Inc.**, Miami, FL (US)

(72) Inventors: **Sunil Paliwal**, Monroe Township, NJ (US); **Gregory A. Reichard**, Ann Arbor, MI (US); **Cheng Wang**, Summit, NJ (US); **Dong Xiao**, Warren, NJ (US); **Hon-Chung Tsui**, East Brunswick, NJ (US); **Neng-Yang Shih**, Warren, NJ (US); **Juan D. Arredondo**, Montclair, NJ (US); **Michelle Laci Wrobleski**, Whitehouse Station, NJ (US); **Anandan Palani**, Bridgewater, NJ (US)

(21) Appl. No.: **15/631,613**

(22) Filed: **Jun. 23, 2017**

Related U.S. Application Data

(60) Division of application No. 14/341,097, filed on Jul. 25, 2014, now Pat. No. 9,688,693, which is a continuation of application No. 13/625,799, filed on Sep. 24, 2012, now Pat. No. 8,796,299, which is a continuation of application No. 12/967,132, filed on Dec. 14, 2010, now Pat. No. 8,273,895, which is a continuation of application No. 11/358,827, filed on Feb. 21, 2006, now Pat. No. 7,902,366, which is a division of application No. 10/321,687, filed on Dec. 17, 2002, now Pat. No. 7,049,320.

(60) Provisional application No. 60/341,452, filed on Dec. 18, 2001.

Publication Classification

(51) **Int. Cl.**

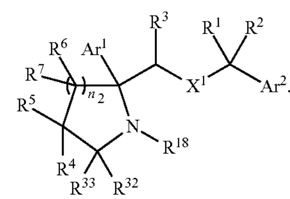
C07D 498/10	(2006.01)
C07D 211/56	(2006.01)
C07D 487/10	(2006.01)
C07D 401/04	(2006.01)
A61K 31/454	(2006.01)
A61K 31/166	(2006.01)
A61K 31/451	(2006.01)
A61K 31/437	(2006.01)
A61K 31/4375	(2006.01)
A61K 31/537	(2006.01)
C07D 211/60	(2006.01)
A61K 31/573	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 498/10*** (2013.01); ***C07D 211/60*** (2013.01); ***C07D 211/56*** (2013.01); ***C07D 487/10*** (2013.01); ***C07D 401/04*** (2013.01); ***A61K 31/573*** (2013.01); ***A61K 31/166*** (2013.01); ***A61K 31/451*** (2013.01); ***A61K 31/437*** (2013.01); ***A61K 31/4375*** (2013.01); ***A61K 31/537*** (2013.01); ***A61K 31/454*** (2013.01)

(57) **ABSTRACT**

A NK_1 antagonist having the formula (I),



(I)

wherein Ar^1 and Ar^2 are optionally substituted phenyl or heteroaryl, X^1 is an ether, thio or imino linkage, R^4 and R^5 are not both H or alkyl, and the remaining variables are as defined in the specification, useful for treating a number of disorders, including emesis, depression, anxiety and cough. Pharmaceutical compositions. Methods of treatment and combinations with other agents are also disclosed.

NK1 ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation of U.S. application Ser. No. 11/358,827, filed Feb. 21, 2006, which is a divisional of U.S. application Ser. No. 10/321,687, filed Dec. 17, 2002, and claims the benefit of U.S. Provisional Application 60/341,452, filed Dec. 18, 2001.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0002] The invention relates to an altagonist of the neuropeptide neurokinin-1 (NK_1 or NK-1) receptor.

2. Description of Related Art

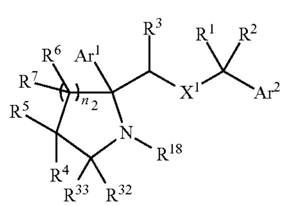
[0003] Tachykinins are peptide ligands for neurokinin receptors. Neurokinin receptors, such as NK_1, NK_2 and NK_3, are involved in a variety of biological processes. They can be found in a mammal's nervous and circulatory systems, as well as in peripheral tissues. Consequently, the modulation of these types of receptors have been studied to potentially treat or prevent various mammalian disease states. For instance, NK_1 receptors have been reported to be involved in microvascular leakage and mucus secretion. Representative types of neurokinin receptor antagonists and their uses can be found in: U.S. Pat. No. 5,760,018 (1998) (pain, inflammation, migraine and emesis), U.S. Pat. No. 5,620,989 (1997) (pain, nociception and inflammation), WO 95/19344 (1995) (same), WO 94/13639 (1994) (same) and WO 94/10165 (1994) (same). Further types of NK_1 receptor antagonists can be found in Wu et al, *Tetrahedron* 56, 3043-3051 (2000); Rombouts et al, *Tetrahedron Letters* 42, 7397-7399 (2001); and Rogiers et al, *Tetrahedron* 57, 8971-8981 (2001).

[0004] It would be beneficial to provide a NK_1 antagonist that is potent, selective, and possesses beneficial therapeutic and pharmacological properties, and good metabolic stability. It would further be beneficial to provide a NK_1 antagonist that is effective for treating a variety of physiological disorders, symptoms and diseases while minimizing side effects. The invention seeks to provide these and other benefits, which will become apparent as the description progresses.

SUMMARY OF THE INVENTION

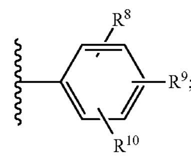
[0005] In one aspect of the invention, a compound is provided having the formula (I):

(I)



[0006] or a pharmaceutically-acceptable salt thereof, wherein

[0007] Ar^1 and Ar^2 are each independently selected from the group consisting of R^{17}-heteroaryl and



[0008] X^1 is —O—, —S—, —SO—, —SO_2—, —NR^{34}—, —$N(COR^{12})$— or —$N(SO_2R^{15})$—;

[0009] when X^1 is —SO—, —SO_2—, —$N(COR^{12})$— or —$N(SO_2R^{15})$—, then:

[0010] R^1 and R^2 are each independently selected from the group consisting of H, C_1-C_6 alkyl, hydroxy(C_1-C_3alkyl), C_3-C_8 cycloalkyl, —CH_2F, —CHF_2 and —CF_3; or R^1 and R^2, together with the carbon atom to which they are both attached, form a chemically feasible C_3 to C_6 alkylene ring; or

[0011] when X^1 is —O—, —S— or —NR^{34}—, then:

[0012] R^1 and R^2 are each independently selected from the group consisting of H. C_1-C_6 alkyl, hydroxy(C_1-C_3alkyl), C_3-C_8 cycloalkyl, —CH_2F, —CHF_2 and —CF_3; or R^1 and R^2, together with the carbon atom to which they are both attached, form a chemically feasible C_3 to C_6 alkylene ring; or R^1 and R^2, together with one another and the carbon atom to which they are both attached, form a C═O group;

[0013] R^3 is selected from the group consisting of H, C_1-C_6 alkyl, hydroxy(C_1-C_3 alkyl), C_3-C_8 cycloalkyl, —CH_2F, —CHF_2 and —CF_3;

[0014] each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl and —OH;

[0015] each R^7 is independently selected from the group consisting of H and C_1-C_6 alkyl;

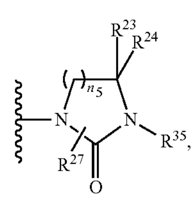
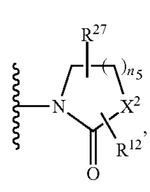
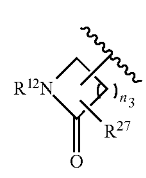
[0016] n_2 is 1 to 4;

[0017] R^4 and R^5 are each independently selected from the group consisting of —$(CR^{28}R^{29})_{n1}$-G,

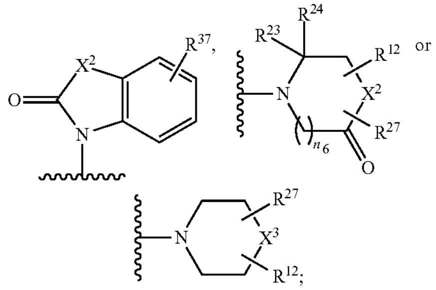
[0018] where,

[0019] n_1 is 0 to 5; and

[0020] G is H, —CF_3, —CHF_2, —CH_2F, —OH, —O—(C_1-C_6 alkyl), —OCH_2F, —$OCHF_2$, —OCF_3, —OCH_2CF_3, —O—(C_3-C_6 cycloalkyl), —O—(C_1-C_6) alkyl(C_3-C_6 cycloalkyl), —$NR^{13}R^{14}$, —$SO_2NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$NR^{12}C(O)R^{14}$, —$NR^{12}C(O)OR^{13}$, —$NR^{12}(C(O)NR^{13}R^{14})$, —$C(O)NR^{13}R^{14}$, —C(O)$OR^{13}$, —$C_3$-$C_8$ cycloalkyl, $(R^{19})_r$-aryl, (R^{19})-heteroaryl, —$OC(O)R^{14}$, —$OC(O)NR^{13}R^{14}$, —$C(=NOR^{14})(R^{13})$, —$C(O)R^{13}$, —$C(OR^{12})(R^{13})(R^{14})$, heterocycloalkenyl optionally substituted by 1 to 4 substituents independently selected from the group consisting of R^{30} and R^{31},

-continued



or

[0021] R^4 and R^5 together are =O, =NOR^{12}; or

[0022] R^4 and R^5, together with the carbon atom to which they are both attached, form a chemically feasible 4- to 8-membered heterocycloalkyl or heterocycloalkenyl ring containing 1 to 3 groups independently selected from X^2, provided that at least one X^2 is —NR^{35}—, —O—, —S—, —S(O)— or —SO$_2$—, the chemically feasible ring being optionally substituted with from 1 to 6 substituents independently selected from the group consisting of R^{30} and R^{31};

[0023] provided that R^4 and R^5 are not both selected from the group consisting of H, alkyl and cycloalkyl;

[0024] further provided that, when one of R^4 and R^5 is —OH, then the other one of R^4 and R^5 is not alkyl or $(R^{19})_r$-aryl;

[0025] R^8, R^9 and R^{10} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, —OR^{12}, halogen, —CN, —NO$_2$, —CF$_3$, —CHF$_2$, —CH$_2$F, —CH$_2$CF$_3$, —OCF$_3$, —OCHF$_2$, —OCH$_2$F, —OCH$_2$CF$_3$, —COOR^{12}, —CONR^{21}R^{22}, —OC(O)NR^{21}R^{22}, —OC(O)R^{12}, —NR^{21}COR^{12}, —NR^{21}CO$_2$R^{15}, —NR^{21}CONR^{21}R^{22}, —NR^{21}SO$_2$R^{15}, —NR^{21}R^{22}, —SO$_2$NR^{21}R^{22}, —S(O)$_{n6}$R^{15}, $(R^{19})_r$-aryl and $(R^{19})_r$-heteroaryl;

[0026] R^{12} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

[0027] R^{13} and R^{14} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, —CH$_2$CF$_3$, aryl and heteroaryl; or

[0028] R^{13} and R^{14}, together with the nitrogen atom to which they are both attached, form a chemically feasible 4- to 7-membered saturated or unsaturated ring that is optionally substituted with —OR^{12}, where one of the carbon atoms in the ring is optionally replaced by a heteroatom selected from the group consisting of —O—, —S— and —NR^{34}—;

[0029] n_6 is 0, 1 or 2;

[0030] R^{15} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, —CF$_3$ or —CH$_2$CF$_3$;

[0031] R^{18} is H. C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, hydroxy(C_2-C_6)alkyl or —P(O)(OH)$_2$;

[0032] each R^{19} is a substituent on the aryl or heteroaryl ring to which it is attached, and is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, —OH, halogen, —CN, —NO$_2$, —CF$_3$, —CHF$_2$, —CH$_2$F, —OCF$_3$, —OCHF$_2$, —OCH$_2$F, —O—(C_1-C_6 alkyl), —O—(C_3-C_8 cycloalkyl), —COOR^{12}, —CONR^{21}R^{22}, —OC(O)NR^{21}R^{22}, —OC(O)R^{12}, —NR^{21}R^{22}, —NR^{21}COR^{22}, —NR^{21}CO$_2$R^{12}, —NR^{21}CONR^{21}R^{22}, —NR^{21}SO$_2$R^5 and —S(O)$_{n6}$R^{15};

[0033] R^{21} and R^{22} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl and benzyl; or

[0034] R^{21} and R^{22}, together with the nitrogen atom to which they are both attached, form a chemically feasible 4- to 7-membered saturated or unsaturated ring, where one of the carbon atoms in the ring is optionally replaced by a heteroatom selected from the group consisting of —O—, —S— and —NR^{34}—;

[0035] R^{23} and R^{24} are each independently selected from the group consisting of H and C_1-C_6 alkyl; or

[0036] R^{23} and R^{24}, together with the carbon atom to which they are both attached, form a C=O or cyclopropyl group;

[0037] R^{27} is H, —OH or C_1-C_6 alkyl:

[0038] R^{28} and R^{29} are each independently selected from the group consisting of H and C_1-C_2 alkyl;

[0039] R^{30} and R^{31} are each independently selected from the group consisting of H, —OH, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl and —C(O)NR^{13}R^{14}; or

[0040] R^{30} and R^{31}, together with the carbon atom to which they are both attached, form =O, =S, a cyclopropyl ring or =NR^{36};

[0041] R^{32} and R^{33} are each independently selected from the group consisting of H and C_1-C_6 alkyl;

[0042] R^{34} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl or hydroxy(C_2-C_6)alkyl;

[0043] R^{35} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, —P(O)(OH)$_2$, allyl, hydroxy(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_5)alkyl, —SO$_2$R^{15}, or —(CH$_2$)$_2$—N(R^{12})—SO$_2$—R^{15};

[0044] R^{36} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, —NO$_2$, —CN or OR^{12};

[0045] R^{37} is 1 to 3 substituents independently selected from the group consisting of H, C_1-C_6 alkyl, —OH, C_1-C_6 alkoxy and halogen;

[0046] r is 1 to 3;

[0047] X^2 is —NR^{35}—, —O—, —S—, —S(O)—, —SO$_2$—, —CH$_2$—, —CF$_2$— or —CR^{12}F—;

[0048] X^3 is —NR^{34}—, —N(CONR^{13}R^{14})—, —N(CO$_2$R^{13})—, —N(SO$_2$R^{15})—, —N(COR^{12})—, —N(SO$_2$NHR^{13})—, —O—, —S—, —S(O)—, —SO$_2$—, —CH$_2$—, —CF$_2$— or —CR^{12}F—;

[0049] n_3 is 1 to 5; and

[0050] n_5 is 1 to 3.

[0051] The invention comprises at least one compound having the formula (I), including any and all diastereomers, enantiomers, stereoisomers, regiostereomers, rotomers, tautomers and prodrugs of the compounds having the formula (I) and their corresponding salts, solvates (e.g., hydrates), esters, and the like. The compounds having the formula (I) can be useful for treating a variety of diseases, symptoms and physiological disorders, such as emesis, depression, anxiety and cough.

[0052] Another aspect of the invention comprises a pharmaceutical composition comprising a compound of formula (I), alone or with another active agent, and a pharmaceutically acceptable carrier or excipient therefor. The inventive compounds and compositions can be used alone or in combination with other active agents and/or methods of treatment for treating a variety of diseases, symptoms and physiological disorders, such as the ones disclosed herein.

DETAILED DESCRIPTION

[0053] The following definitions and terms are used herein or are otherwise known to a skilled artisan. Except where stated otherwise, the following definitions apply throughout the specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "alkoxy," etc.

[0054] The term "substituted," as used herein, means the replacement of one or more atoms, usually hydrogen atoms, in a given structure with an atom or radical selected from a specified group. In the situations where more than one atom may be replaced with a substituent selected from the same specified group, the substituents may be, unless otherwise specified, either the same or different at every position.

[0055] The term "heteroatom," as used herein, means a nitrogen, sulfur, or oxygen atom. Multiple heteroatoms in the same group may be the same or different.

[0056] The term "alkyl," as used herein, means a straight or branched, hydrocarbon chain having the designated number of carbon atoms. If the number of carbon atoms is not designated, the carbon chain is from one to twenty-four carbon atoms, more preferably, from one to twelve carbon atoms, and most preferably, from one to six carbon atoms.

[0057] The term "cycloalkyl" as used herein, means a saturated, stable, non-aromatic carbocyclic ring having from three to eight carbon atoms. The cycloalkyl may be attached at any endocyclic carbon atom that results in a stable structure.

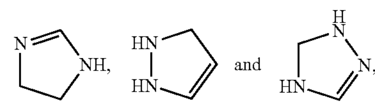
[0058] Preferred carbocyclic rings have from three to six carbons. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

[0059] The term "aryl," as used herein, means an aromatic, mono- or bicyclic, carbocyclic ring system having from one to two aromatic rings. The aryl moiety will generally have from 6 to 14 carbon atoms with all available substitutable carbon atoms of the aryl moiety being intended as possible points of attachment. Representative examples include phenyl, cumenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

[0060] The term "heteroaryl," as used herein, means a mono- or bicyclic, chemically feasible ring system containing one or two aromatic rings and 1 to 4 nitrogen, oxygen or sulfur atoms in the aromatic ring. Typically, a heteroaryl group represents a cyclic group of five or six atoms, or a bicyclic group of nine or ten atoms, at least one of which is carbon, and having at least one oxygen, sulfur or nitrogen atom interrupting a carbocyclic ring having a sufficient number of pi (π) electrons to provide aromatic character. Representative heteroaryl (heteroaromatic) groups are pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furanyl, benzofuranyl, thienyl, benzothienyl, thiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isothiazolyl, benzothiazolyl, benzoxazolyl, oxazolyl, pyrrolyl, isoxazolyl, 1,3,5-triazinyl and indolyl groups. The heteroaryl group can be joined to the rest of the molecule through a bond at any substitutable carbon or nitrogen.

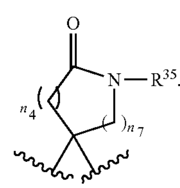
[0061] The term "heterocycloalkyl" as used herein means a saturated cyclic ring having from 3 to 8 members, preferably 5 or 6 members, and comprising 2 to 7 carbon atoms and 1 to 3 heteroatoms independently selected from the group consisting of —O—, —S—, —S(O)—, —SO_2— and —NR^{35}—. Typical heterocycloalkyl rings are pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, and the like. The heterocycloalkyl ring can be attached to the rest of the structure through either a substitutable ring carbon or a substitutable ring nitrogen.

[0062] The term "heterocycloalkenyl" as used herein means a cyclic ring having from 3 to 8 members, preferably 5 or 6 members, and comprising 2 to 7 carbon atoms and 1 to 3 heteroatoms independently selected from the group consisting of —O—, —S—, —S(O)—, —SO_2— and —NR^{35}—, and having at least one double bond in the ring, but not having aromatic characteristics. Examples of such rings are:

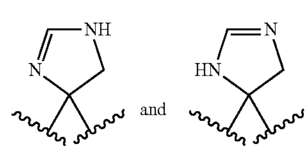


wherein the ring can be attached to the rest of the structure through either a substitutable ring carbon or a substitutable ring nitrogen (e.g., in R^4, when G is heterocycloalkenyl, it can be joined to the $(CR^{28}R^{29})_{n1}$ group through either a substitutable ring carbon or a substitutable ring nitrogen).

[0063] When R^4 and R^5 form a ring with 1, 2 or 3 groups independently selected from X^2, and 1 or 2 of X^Z are carbon, the variable size of the ring can be defined by n_4 and n_7, which are independently selected from 0-5, provided that the sum of n_4 and n_7 is 1 to 5. A typical structure wherein the heteroatom is —NR^{35}—, X^2 is —CH_2—, and R^{30} and R^{31} together form a carbonyl group is represented by the formula



[0064] When R^4 and R^5, together with the carbon to which they are attached, form a heterocycloalkenyl ring, examples of such rings are



[0065] The term "alkoxy," as used herein, means an oxygen atom bonded to a hydrocarbon chain, such as an alkyl or alkenyl group (e.g., —O-alkyl or —O-alkenyl). Representative alkoxy groups include methoxy, ethoxy; and isopropoxy groups.

[0066] The term "hydroxyalkyl," as used herein, means a substituted hydrocarbon chain, preferably, an alkyl group, having at least one hydroxy substituent (i.e., —OH). Representative hydroxyalkyl groups include hydroxymethyl, hydroxyethyl and hydroxypropyl groups.

[0067] The term "halo" or "halogen" as used herein means a chloro, bromo, fluoro or iodo atom radical.

[0068] Unless otherwise known, stated or shown to be to the contrary, the point of attachment for a multiple term substituent (multiple terms that are combined to identify a single moiety) to a subject structure is through the last named term of the multiple term. For example, an "arylalkyl" substituent attaches to a targeted structure through the "alkyl" portion of the substituent. Conversely, when the substituent is "alkylaryl", it attaches to a targeted structure through the "aryl" portion of the substituent. Similarly, a cycloalkylalkyl substituent attaches to a targeted through the latter "alkyl" portion of the substituent (e.g., Structure-alkyl-cycloalkyl).

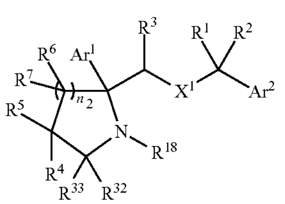
[0069] When a variable appears more than once in a structural formula, for example, R^8, its definition at each occurrence is independent of its definition at every other occurrence.

[0070] The term "prodrug," as used herein, represents compounds that are drug precursors which, following administration to a patient, release the drug in vivo via a chemical or physiological process (e.g., a prodrug on being brought to a physiological pH or through an enzyme action is converted to the desired drug form). A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of A.C.S. Symposium Series (1987), and in Bioreversible Carriers in Drug Design, E. B. Roche, ed., American Pharmaceutical Association and Pergamon Press (1987), each of which is incorporated herein by reference in its entirety.

[0071] As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

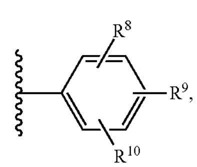
[0072] Other than as shown in the operating examples or where is otherwise indicated, all numbers used in the specification and claims expressing quantities of ingredients, reaction conditions, and so forth, are understood as being modified in all instances by the term "about."

[0073] Referring to the compound having the formula (I):



[0074] or a pharmaceutically-acceptable salt thereof, preferred are compounds wherein

[0075] Ar^1 and Ar^2 are each, preferably,



where R^8, R^9 and R^{10} are each independently defined as above in the summary of the invention. More preferably, for Ar^2, R^{10} is H, and R^8 and R^9 are independently selected from the group consisting of —CF_3, —CHF_2, —CH_2F, halogen, C_1-C_6 alkyl, —OCF_3 and —OR^{12}; for Ar^1, R^9 and R^{10} are independently selected from the group consisting of H. —OH and halogen. The variable n_2 is preferably 1 or 2.

[0076] X^1 is, preferably —O— or —NR^{34}—. More preferably, X^1 is —O—.

[0077] R^1 and R^2 are each, preferably, independently selected from the group consisting of H and C_1-C_6 alkyl. More preferably, R^1 and R^2 are each independently selected from the group consisting of H and CH_3.

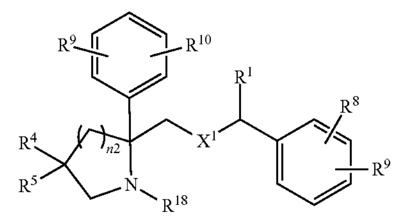
[0078] R^3 is preferably selected from the group consisting of H and C_1-C_6 alkyl. More preferably, R^3 is H.

[0079] Each R^6 is preferably independently selected from the group consisting of H and C_1-C_5 alkyl. Even more preferably, each R^6 is H.

[0080] Each R^7 is preferably independently selected from the group consisting of H and C_1-C_6 alkyl. Even more preferably, each R^7 is H.

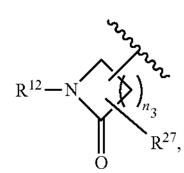
[0081] More preferred are compounds of the structure II

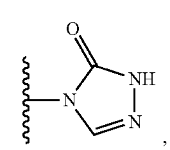
II

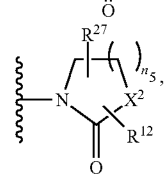


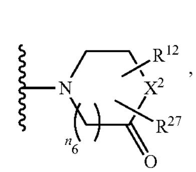
wherein X^1 is —O— or —NR^{14}—; R^8 and R^9 are independently selected from the group consisting of —CF_3, —CHF_2, —CH_2F, halogen, C_1-C_6 alkyl, —OCF_3 and —OR^{12}; R^9 and R^{10} are independently selected from the group consisting of H, —OH and halogen; and n_2 is 1 or 2.

[0082] Preferred compounds of formula I and formula II are those wherein one of R^4 and R^5 is H and the other is —$C(R^{28}R^{29})_{n1}$-G, wherein n_1 is 0, 1 or 2. More preferred are compounds wherein one of R^4 and R^5 is H and the other is selected from the group consisting of —$NR^{13}R^{14}$, —$NR^{12}C(O)R^{14}$, —$C(O)NR^{13}R^{14}$, —$OC(O)R^{14}$, —$OC(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{13}$, —$C(O)OR^{13}$, —$NR^{12}(C(O)NR^{13}R^{14})$, —$NR^{12}SO_2R^{13}$, —$SO_2NR^{13}R^{14}$, R^{19}-heteroaryl,

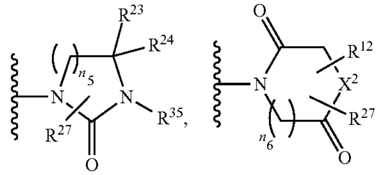




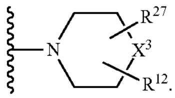




-continued

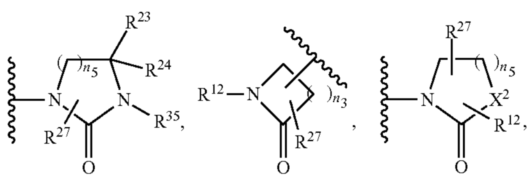


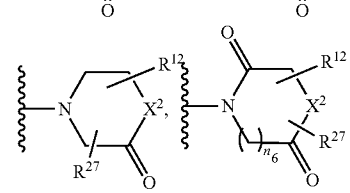
and



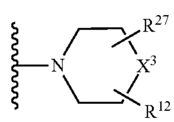
Even more preferred are such compounds wherein R^{12} and R^{27} are independently selected from the group consisting of H and C_1-C_6 alkyl, especially H and —CH_3, and more especially, both are H; n_3 is 2 or 3; and n_5 is 1 or 2.

[0083] In another embodiment, preferred compounds of formula I and formula II are those wherein R^4 is —$NR^{13}R^{14}$, —$NR^{12}C(O)R$, $NR^{12}C(O)OR^{13}$, —$NR^{12}(C(O)NR^{13}R^{14})$, —OH, —O—($C_1$-$C_6$)alkyl, —O—($C_3$-$C_8$)cycloalkyl, —$OC(O)R^{14}$, —$OC(O)NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$SO_2NR^{13}R^{14}$, R^{19}-heteroaryl,



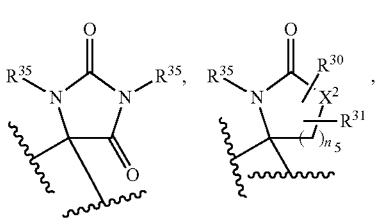


or

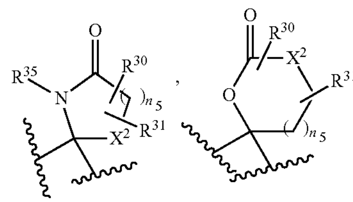


wherein X_2 is —O—, —S—, —CH_2— or —NR^{35}—; and R^5 is —$C(O)OR^{13}$ or —$C(O)NR^{13}R^{14}$. More preferred are compounds wherein R^{12} is independently selected from the group consisting of H, C_1-C_6 alkyl and C_3-C_6 cycloalkyl; R^{27} is H; n_3 is 2 or 3; and n_5 is 1 or 2.

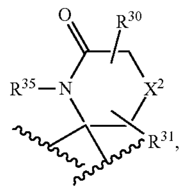
[0084] Still another preferred embodiment of compounds of formula I and II is that wherein R^4 and R^5, together with the carbon atom to which they are both attached, form a 4- to 8-membered heterocycloalkyl or heterocycloalkenyl ring containing 1 to 3 groups independently selected from X^2, provided that at least one X^2 is —NR^{35}—, —O—, —S—, —S(O)— or —SO_2—, the ring being optionally substituted with from 1 to 6 substituents independently selected from the group consisting of R^{30} and R^{31}. More preferred are compounds wherein the 4- to 3-membered ring is selected from the group consisting of:



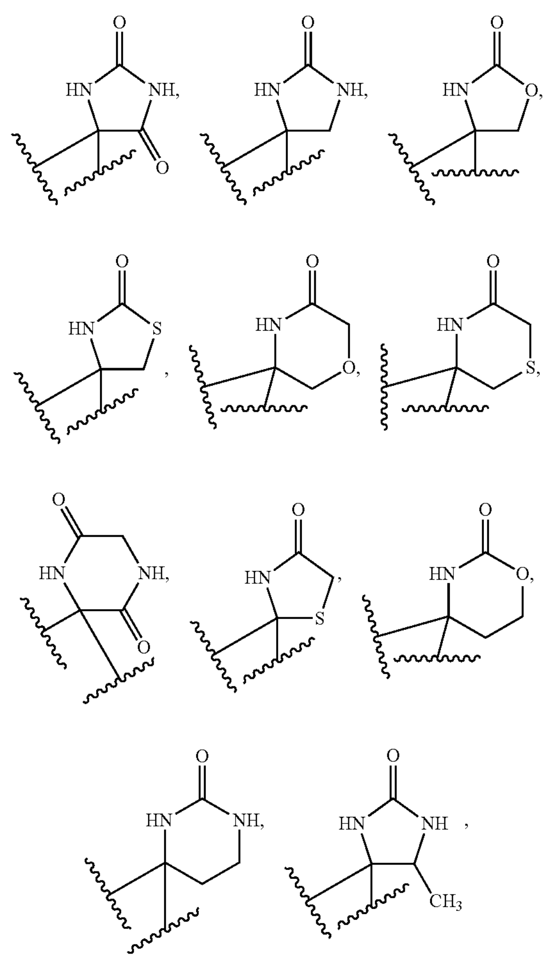
-continued



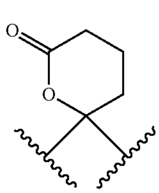
and



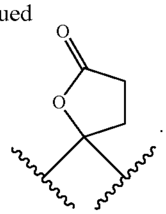
wherein R^{35} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8) cycloalkyl(C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl; n_5 is 1, 2 or 3; X^2 is —NR^{35}—, —CH_2—, —O— or —S—; R^{30} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and R^{31} is H, —OH or C_1-C_6 alkyl. Especially preferred are 4- to 8-membered rings selected from the group consisting of



-continued

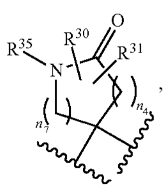


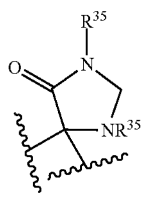
and



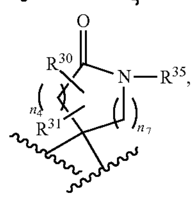
The rings are optionally substituted with R^{30} and R^{31}.

[0085] Yet another group of preferred compounds wherein R^4 and R^5 form a ring is that wherein the ring is selected from the group consisting of

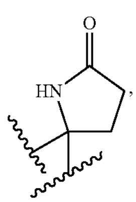


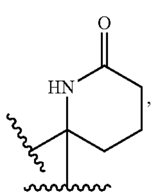


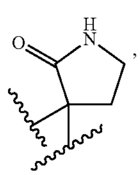
and

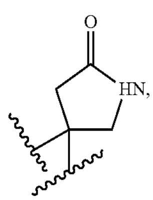


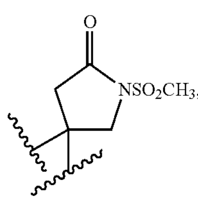
wherein R^{30} is H. C_1-C_6 alkyl or C_3-C_8 cycloalkyl; R^{31} is H, —OH or C_1-C_6 alkyl; each R^{35} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_5)alkyl and hydroxy(C_1-C_6)alkyl; n_4 and n_7 are independently 0-5, provided that the sum of n_4 and n_7 is 1-5. Especially preferred are 4- to 8-membered rings selected from the group consisting of

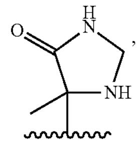


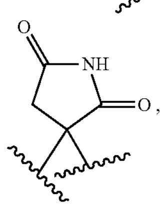


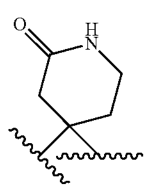






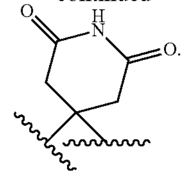






and

-continued



The rings are optionally substituted with R^{30} and R^{31}.

[0086] In still another embodiment of the invention, it is preferable for at least one of R^4 and R^5 to be in a cis orientation to the Ar^1 substituent.

[0087] R^{15} is preferably C_1-C_6 alkyl or —CF_3. More preferably, R^{15} is C_1-C_6 alkyl.

[0088] R^{18} is preferably H or —C_1-C_6 alkyl. More preferably, R^{18} is H or CH_3. Even more preferably, R^{18} is H.

[0089] Each R^{19} is a substituent on the aryl or heteroaryl ring to which it is attached, and is, preferably, independently selected from the group consisting of H, C_1-C_6 alkyl, —CF_3. —CHF_2, —CH_2F, —OCF_3, —$OCHF_2$ and —OCH_2F. More preferably, each R^{19} is selected from the group consisting of H and C_1-C_6 alkyl.

[0090] Preferably, r is 1 or 2. More preferably, r is 1.

[0091] R^{21} and R^{22} preferably are each, preferably, independently selected from the group consisting of H and C_1-C_6 alkyl. More preferably, R^{21} and R^{22} are each independently selected from the group H and CH_3.

[0092] R^{23} and R^{24} is are each, preferably, independently selected from the group consisting of H and C_1-C_6 alkyl, or R^{23} and R^{24} together are =O. More preferably, R^{23} and R^{24} are each independently selected from the group H and CH_3.

[0093] R^{28} and R^{29} are preferably, independently selected from the group consisting of H and —CH_3.

[0094] R^{30} and R^{31} are preferably independently selected from the group consisting of H and C_1-C_2 alkyl, or R^{30} and R^{31} together are =O. More preferably, R^{30} and R^{31} are each independently selected from the group consisting of H and —CH_3.

[0095] R^{32} and R^{31} are preferably independently selected from the group consisting of H and —CH_3. Even more preferably, R^{32} and R^{33} are each H.

[0096] R^{36} is preferably H or C_1-C_6 alkyl. More preferably, R^{36} is H or —CH_3.

[0097] R^{37} is preferably 1 or 2 substituents selected from the group consisting of H, —CH_3 and halogen.

[0098] Preferred compounds of the invention are those shown below in Examples 3, 9, 12a, 13, 14, 15, 20, 23, 29, 36, 40, 43b, 44b, 45, 50, 53, 56b, 57, 60a, 61, 62, 63, 72a, 73b, 74a, 75b, 76a, 82a, 82b, 90, 96, 105, 106b, 109, 110a, 111a, 112 and 113. More preferred are compounds of Examples 12a, 43b, 72a, 73b, 109, 110a and 111a.

[0099] Compounds having the formula (I) can be effective antagonists of the NK_1 receptor, and of an effect of its endogenous agonist, Substance P, at the NK_1 receptor site, and therefore, can be useful in treating conditions caused or aggravated by the activity of said receptor. The in vitro and in vivo NK_1, NK_2 and NK_3 activities of the compounds having the formula (I) can be determined by various procedures known in the art, such as a test for their ability to inhibit the activity of the NK_1 agonist Substance P. The percent inhibition of neurokinin agonist activity is the difference between the percent of maximum specific binding

("MSB") and 100%. The percent of MSB is defined by the following equation, wherein "dpm" represents "disintegrations per minute":

$$\% \ MSB = \frac{(dpm \text{ of unknown}) - (dpm \text{ of nonspecific binding})}{(dpm \text{ of total binding}) - (dpm \text{ of nonspecific binding})} \times 100.$$

The concentration at which the compound produces 50% inhibition of binding is then used to determine an inhibition constant ("Ki") using the Chang-Prusoff equation.

[0100] In vivo activity may be measured by inhibition of an agonist-induced foot tapping in a gerbil, as described in *Science,* 281, 1640-1695 (1998), which is herein incorporated by reference in its entirety. It will be recognized that compounds having the formula (I) can exhibit NK_1 antagonist activities of varying degrees. For instance, certain compounds can exhibit stronger NK_1 antagonist activities than others.

[0101] The compounds of the invention exhibit potent affinities for the NK_1 receptor as measured by Ki values (in nM). The activities (potencies) for the compounds of the invention are determined by measuring their Ki values. The smaller the Ki value, the more active is a compound for antagonizing the NK_1 receptor. Compounds of the invention exhibit a wide range of activities. The NK_1 average Ki values for compounds having the formula (I) generally range from 0.01 nM to about 1000 nM, preferably, from about 0.01 nM to about 500 nM, with values of from about 0.01 nM to about 100 nM being more preferred. Even more preferred are compounds having average Ki values of from 0.01 nM to about 10 nM for the NK_1 receptor. The most preferred compounds have NK_1 average Ki values of from 0.01 nM to about 3 nM.

[0102] The preferred compounds noted above have the following Ki values: Example 43b: 0.77 nM; 72a: 0.66 nM; 73b: 0.2 nM; 109: 0.1 nM; 110a: 0.41 nM; and 111a: 0.38 nM.

[0103] The inventive compounds are also highly selective for antagonizing a NK_1 receptor as opposed to antagonizing (i) NK_2 and/or (ii) NK_3 receptors. When a compound's selection ratio is greater than about 100 for the Ki of the NK_1 receptor to the Ki of the NK_2 receptor, and/or, independently, the Ki of the NK_3 receptor, then the compound is defined herein as a selective antagonist of the NK_1 receptor, as opposed to the NK_2 and/or NK_3 receptors, respectively.

[0104] Compounds having the formula (I) may have at least one asymmetrical carbon atom. All isomers, including stereoisomers, diastereomers, enantiomers, regiostereomers, tautomers and rotational isomers, are contemplated as being part of the invention. Prodrugs, salts, solvates, esters, etc., derived from the compounds having the formula (I) or precursors thereof are also within the scope of the invention. The invention includes d- and l-isomers in pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound having the formula (I). Those skilled in the art will appreciate that for some compounds having the formula (I), particular isomers can show greater pharmacological activity than other isomers.

[0105] There are many uses for the compounds having the formula (I). For instance, compounds having the formula (I) can be useful as antagonists of neurokinin receptors, particularly, NK_1 receptors in a mammal, such as a human. As such, they may be useful in treating and preventing one or more of a variety of mammalian (human and animal) disease states (physiolgical disorders, symptoms and diseases), for instance, respiratory diseases (e.g., chronic lung disease, bronchitis, pneumonia, asthma, allergy, cough and bronchospasm), inflammatory diseases (e.g., arthritis and psoriasis), skin disorders (e.g., atopic dermatitis and contact dermatitis), ophthalmalogical disorders (e.g., retinitis, ocular hypertension and cataracts), central nervous system conditions, such as depressions (e.g., neurotic depression), anxieties (e.g., general anxiety, social anxiety and panic anxiety disorders), phobias (e.g., social phobia), and bipolar disorder, addictions (e.g., alcohol dependence and psychoactive substance abuse), epilepsy, nociception, psychosis, schizophrenia, Alzheimer's disease, AIDs related dementia, Towne's disease, stress related disorders (e.g., post tramautic stress disorder), obsessive/compulsive disorders, eating disorders (e.g., bulemia, anorexia nervosa and binge eating), mania, premenstrual syndrome, gastrointestinal disorders (e.g., irritable bowel syndrome, Crohn's disease, colitis, and emesis), atherosclerosis, fibrosing disorders (e.g., pulmonary fibrosis), obesity, Type II diabetes, pain related disorders (e.g., headaches, such as migraires, neuropathic pain, post-operative pain, and chronic pain syndromes), bladder and genitourinary disorders (e.g., interstitial cystitis and urinary incontinence), and nausea. In particular, the compounds having the formula (I) are useful for treating disease states related to microvascular leakage and mucus secretion. Consequently, the compounds of the invention are especially useful in the treatment and prevention of asthma, emesis, nausea, depressions, anxieties, cough and pain related disorders.

[0106] In still another aspect of the invention, a method is provided for antagonizing an effect of a Substance P at a neurokinin-1 receptor site or for the blockade of one or more neurokinin-1 receptors in a mammal in need of such treatment, comprising administering to the mammal an effective amount of at least one compound having the formula (I).

[0107] In another embodiment of the invention, an effective amount of one or more of the inventive NK_1 receptor antagonists may be combined with an effective amount of one or more selective serotonin reuptake inhibitors ("SSRIs") to treat depression or anxiety. SSRIs alter the synaptic availability of serotonin through their inhibition of presynaptic reaccumulation of neuronally released serotonin. U.S. Pat. No. 6,162,805, which is incorporated herein by reference in its entirety, discloses a method for treating obesity with a combination therapy of a NK_1 receptor antagonist and an SSRI. An inventive compound(s) having the formula (I) can be combined together with an SSRI(s) in a single pharmaceutical composition or it can be administered simultaneously, concurrently or sequentially with an SSRI.

[0108] Numerous chemical substances are known to alter the synaptic availability of serotonin through their inhibition of presynaptic reaccumulation of neuronally released serotonin. Representative SSRIs include, without limitation, the following: fluoxetine, fluvoxamine, paroxetine, sertaline, and pharmaceutically-acceptable salts thereof. Other compounds can readily be evaluated to determine their ability to selectively inhibit serotonin reuptake. Thus, the invention relates to a pharmaceutical composition comprising at least one NK_1 receptor antagonist having the formula (I) and at least one SSRI, and a method of treating the above identified mammalian disease states, the method comprising administering to a patient in need of such treatment an effective amount of the pharmaceutical composition comprising at least one NK_1 receptor antagonist having the formula (I) in combination with at least one SSRI, such as one of those recited above.

[0109] In another aspect, the invention relates to a method of treating emesis, comprising administering to a patient in need of such treatment an effective amount of at least one NK_1 receptor antagonist having the formula (I). Compounds of the present invention are particularly useful in treating delayed onset emesis such as that experienced 24 hours to several days after the administration of chemotherapy. See Gonzales et al, *Oncology Special Edition, Vol.* 5 (2002), p. 53-58. Combinations of at least one NK_1 receptor antagonist and at least one other anti-emetic agent such as a serotonin 5-HT_3 receptor antagonist, a corticosteroid or a substituted benzamide can be used to treat other forms of emesis, e.g., acute emesis induced by chemotherapy, radiation, motion and alcohol (e.g., ethanol), and post-operative nausea and vomiting. Examples of serotonin 5-HT_3 receptor antagonists are palonsetron, dolasetron, ondansetron and granisetron, or a pharmaceutically-acceptable salts thereof. An examples of a suitable corticosteroid is dexamethasone. An example of a substituted benzamide is metoclopramide.

[0110] Preferred combinations for the treatment of emesis include a compound of formula I and a serotonin 5-HT_3 receptor antagonist; a compound of formula I and a corticosteroid; a compound of formula I and a substituted benzamide; a compound of formula I, a serotonin 5-HT_3 receptor antagonist and a corticosteroid; and a compound of formula I, a substituted benzamide and a corticosteroid.

[0111] When an inventive NK_1 receptor antagonist is combined with an SSRI, a serotonin 5-HT_3 receptor antagonist, a corticosteroid or a substituted benzamide for administration to a patient in need of such treatment, the two or more active ingredients can be administered simultaneously, consecutively (one after the other within a relatively short period of time), or sequentially (first one and then the other over a period of time).

[0112] Thus, the compounds of the invention may be employed alone or in combination with other agents. In addition to the above described NK_1 receptor antagonist/SSRI or serotonin 5-HT_3 receptor antagonist combination therapy, the compounds having the formula (I) may be combined with other active agents, such as other types of NK_1 receptor antagonists, prostanoids, H_1 receptor antagonists, α-adrenergic receptor agonists, dopamine receptor agonists, melanocortin receptor agonists, endothelin receptor antagonists, endothelin converting enzyme inhibitors, angiotensin II receptor antagonists, angiotensin converting enzyme inhibitors, neutral metalloendopeptidase inhibitors, ETA antagonists, renin inhibitors, serotonin 5-HT_{2c} receptor agonists, nociceptin receptor agonists, rho kinase inhibitors, potassium channel modulators and/or inhibitors of multi-drug resistance-protein 5.

[0113] Preferable therapeutic agents for combination therapy with compounds of the invention are the following: prostanoids, such as prostaglandin E_1; α-adrenergic agonists, such as phentolamine mesylate; dopamine receptor agonists, such as apomorphine; angiotensin II antagonists, such as losartan, irbesartan, valsartan and candesartan; and ET_A antagonists, such as bosentan and ABT-627. Dosage ranges for the other agent can be determined from the literature.

[0114] For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20^{th} Edition, (2000), Lippincott Williams & Wilkins. Baltimore, Md.

[0115] Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

[0116] Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

[0117] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

[0118] The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

[0119] Preferably the compound is administered orally.

[0120] Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparations subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

[0121] The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 4,000 mg, preferably from about 0.02 mg to about 1000 mg, more preferably from about 0.03 mg to about 500 mg, and most preferably from about 0.04 mg to about 250 mg according to the particular application.

[0122] The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill in the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

[0123] The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.02 mg/day to about 2000 mg/day, in two to four divided doses.

[0124] The quantity of NK_1 receptor antagonist in combination with a SSRI or serotonin 5-HT_3 receptor antagonist (5-HT_3) in a unit dose of preparation may be varied or adjusted from about 10 to about 300 mg of NK_1 receptor antagonist combined with from about 10 to about 100 mg of SSRI or 5-HT_3. A further quantity of NK_1 receptor antagonist in combination with a SSRI or 5-HT_3 in a unit dose of preparation may be varied or adjusted from about 50 to about 300 mg of NK_1 receptor antagonist combined with from about 10 to about 100 mg of SSRI or 5-HT_3. An even further quantity of NK_1 receptor antagonist in combination with SSRI or 5-HT_3 in a unit dose of preparation may be varied or adjusted from about 50 to about 300 mg of NK_1 receptor antagonist combined with from about 20 to about 50 mg of SSRI or 5-HT_3, depending on the particular application. Dosage levels for the corticosteroids and substituted benzamides can be determined form the literature.

[0125] Alternatively, separate dosage forms of the compounds of formula I and the other agents can be provided in a single package as a kit for the convenience of the patient. This is particularly useful when the separate components must be administered in different dosage forms (e.g., a tablet and a capsule) or at different dosage schedules.

[0126] Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of the invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained. When the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

[0127] The inventive compounds can exist in unsolvated as well as solvated forms, Including hydrated forms. In general, the solvated forms, with pharmaceutically-acceptable solvents, such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

[0128] The inventive compounds may form pharmaceutically-acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in a conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution, such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms may differ somewhat from their respective salt forms in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

[0129] Acidic compounds of the invention (e.g., those compounds which possess a carboxyl group) form pharmaceutically-acceptable salts with inorganic and organic bases. Representative examples of such types of salts are sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically-acceptable amines, such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine, and the like.

[0130] Following are general and specific methods of preparing compounds having the formula (I). As used herein, the following abbreviations are defined as follows:

[0131] RBF is a round bottom flask;

[0132] RT is room temperature;

[0133] Me is methyl;

[0134] Bu is butyl;

[0135] Ac is acetyl;

[0136] Et is ethyl;

[0137] Ph is phenyl;

[0138] THF is tetrahydrofuran;

[0139] OAc is acetate;

[0140] $(Boc)_2O$ is di-tert-butyl dicarbonate;

[0141] (Boc) is tert-butoxy carbonyl;

[0142] TLC is thin layer chromatography;

[0143] LAH is lithium aluminum hydride;

[0144] LDA is lithium diisopropyl amine;

[0145] CDI is 1,1-carbonyl diimidazole;

[0146] HOBT is hydroxybenzotriazole;

[0147] DEC is 1[3-(dimethylamino)propyl]-3-ethylcarbodlimide hydrochloride;

[0148] TFA is trifluoroacetic acid;

[0149] MTBE is t-butyl methyl ether,

[0150] DIEA or i-Pr_2EtN is diisopropylethyl amine;

[0151] Prep plate is preparative thin layer chromatography;

[0152] DMF is dimethyl formamide

[0153] DMPU is 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

[0154] TEMPO is a free radical of 2, 2, 6, 6-tetra methyl-1-piperidinyloxy;

[0155] BuLi is butyl lithium;

[0156] KHMDS is potassium bis(trimethylo silyl)amide; and

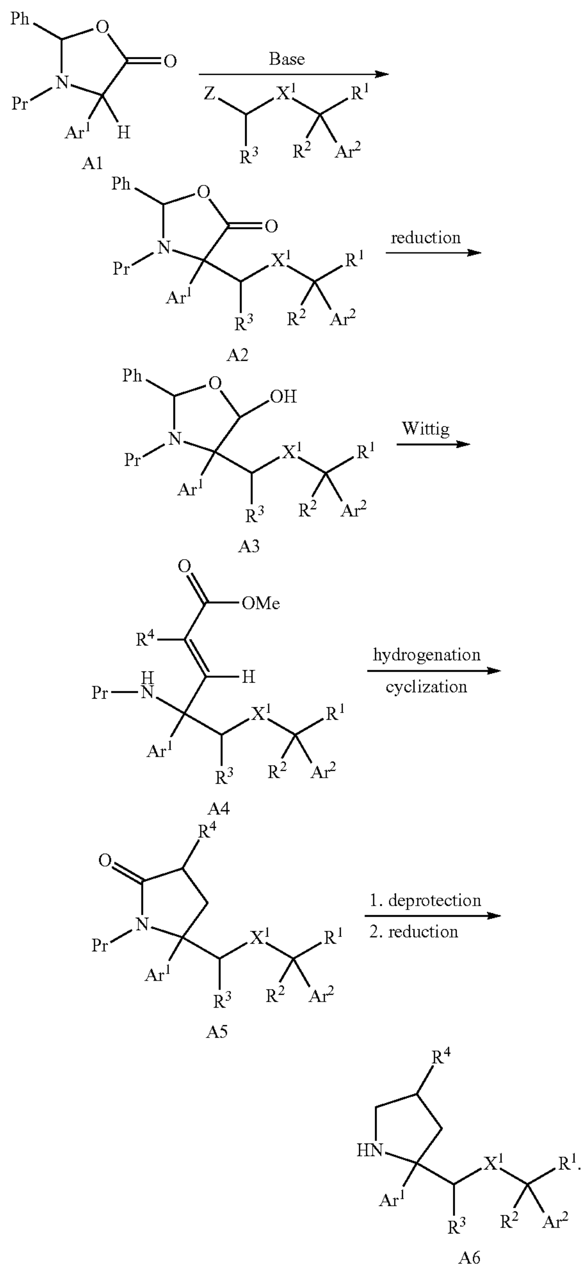
[0157] DBU is 1, 8-diazabicyclo[5.4.]un dec-7-ene.

[0158] Compounds having the formula (I) can be prepared using methods known to those skilled in the art. Typical procedures are described below, although a skilled artisan will recognize that other procedures may be applicable, and that the procedure may be suitably modified to prepare other compounds within the scope of formula (I).

General Methods of Preparation

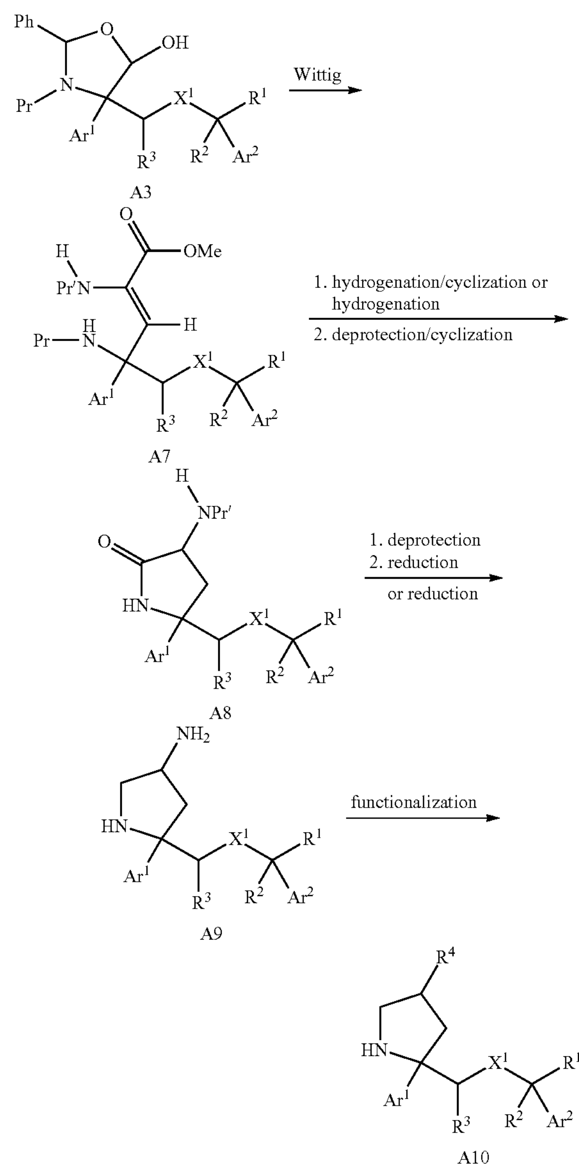
[0159] Compounds having the formula (I) may be generally prepared from the corresponding protected oxazolidinone derivative A1 as shown under the following conditions, where Ar^1 and Ar^2 are each defined as in the summary of the invention; X^1 is —O—; R^1 through R^{33}, independently of one another, are each defined as in the summary of the invention; and n_2 is 1.

[0160] The stereoselective alkylation of a protected oxazolidinone A1 provides the protected oxazolidinone A2. Partial reduction with a reducing agent, such as LAH, provides the lactol A3. A Wittig reaction provides the corresponding olefin A4. Hydrogenation of the olefin A4 and cyclization provides the lactam A5. If the protecting group (Pr) on the nitrogen is Cbz then it might cleave under hydrogenation conditions. The deprotection of the nitrogen of the lactam A5, if necessary, followed by reduction of the lactam with reducing agents such as LAH or $LAH/AlCl_3$, preferably $LAH/AlCl_3$, provides substituted pyrrolidines A6.



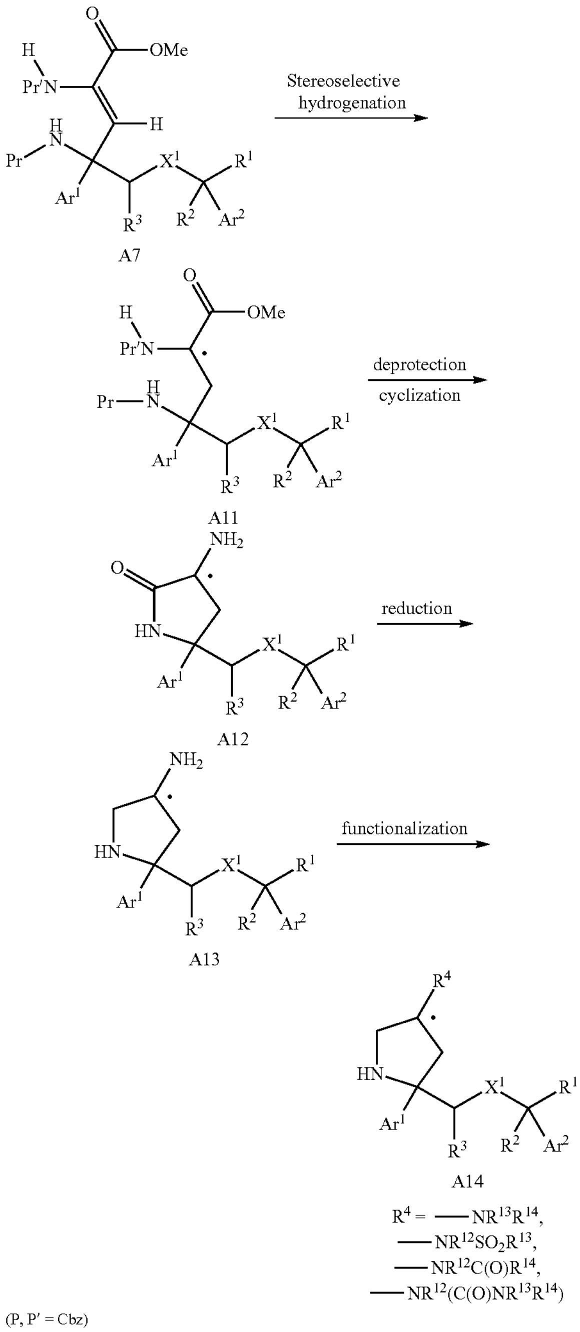
Z is —Cl or —Br
X^1 is —O—

[0161] Compounds having the formula I, where n_2 is 1 and R^4 is —$NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$NR^{12}C(O)R^{14}$, or —$NR^{12}(C(O)NR^{13}R^{14})$ can also be prepared by conversion of lactol A3 to olefin A7 via Wittig reaction using a nitrogen protected (NPr') glycine ester Wittig reagent where Pr' can be a Boc or Cbz protecting group and Pr is preferably a Cbz protecting group. Palladium catalyzed hydrogenation and deprotection (if Pr is a Cbz group) of olefin A7, followed by spontaneous cyclization will provide lactam A8. When Pr is not Cbz or a protecting group readily cleaved under standard hydrogenation conditions, then hydrogenation of the olefin A7 is followed by deprotection of —NHPr and subsequent cyclization to provide lactam A8. The deprotection of the N—Pr' group, if necessary, followed by the reduction of the lactam with reducing agents as LAH or $LAH/AlCl_3$, preferably $LAH/AlCl_3$, provides amino-pyrrolidines A9 which can further be functionalized using standard conditions to give N-substituted pyrrolidines A10.

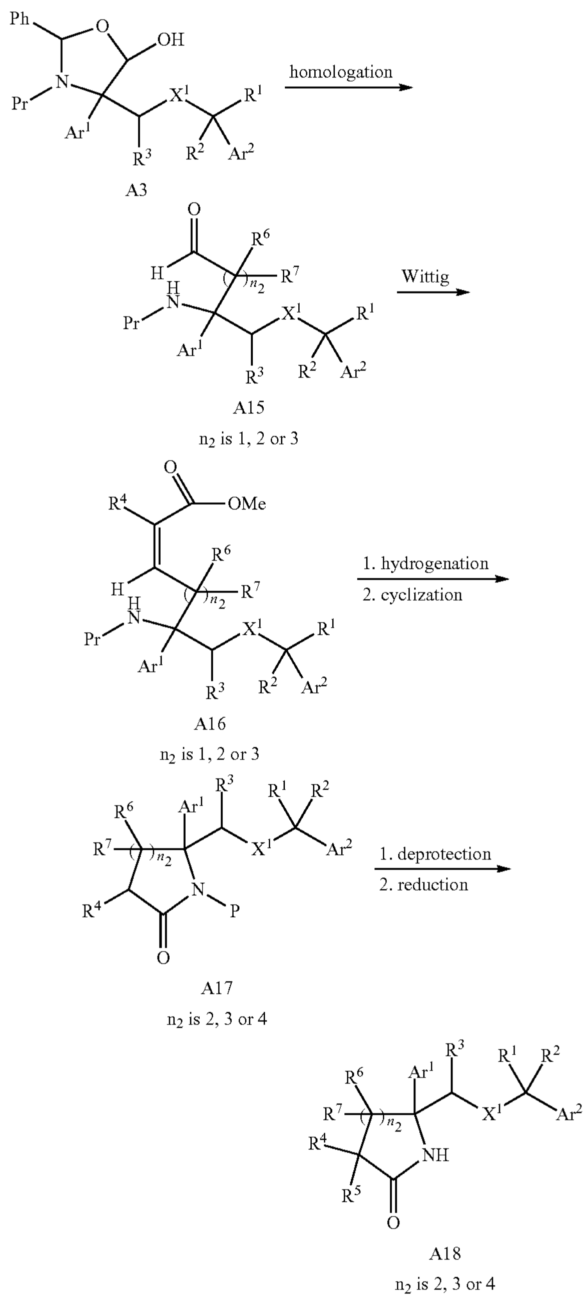


R^4 = —$NR^{13}R^{14}$,
—$NR^{12}SO_2R^{13}$,
—$NR^{12}C(O)R^{14}$,
—$NR^{12}(C(O)NR^{13}R^{14})$

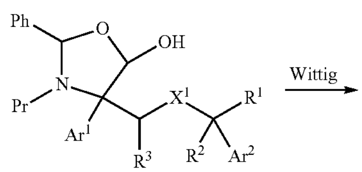
[0162] Those skilled in the art will appreciate that the stereoselective hydrogenation of the double bond of olefin A7 are can also be performed using a chiral hydrogenation catalyst such as chiral Rhodium catalyst which can provide chiral ester A11. Deprotection of the protecting group (if Pr, Pr' are Cbz groups) under standard hydrogenation conditions followed by spontaneous cyclization will provide chiral amino-lactam A12. The reduction of the chiral amino-lactam A12 with reducing agents as LAH or LAH/$AlCl_3$, preferably, LAH/$AlCl_3$, provides chiral amino-pyrrolidines A13 which can further be functionalized using standard conditions to give N-substituted pyrrolidines A14.



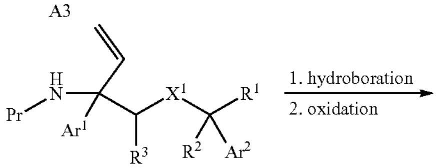
[0163] Compounds having the formula I, where n_2 is 2, 3 or 4, may be prepared by conversion of the lactol A3 to carbon homologated derivatives A15 (n is 1, 2 or 3) using routine chemistry known to those skilled in the art. Particularly useful reagents for this carbon chain homologation include: Wittig chemistry using methoxymethyl triphenylphosphonium bromide or an analogous reagent, cyanomethyl triphenylphosphonium bromide and Homer-Emmons protocols, and aldol chemistry. Hydrogenation and cyclization to the 6-, 7- and 8-membered lactams A17, respectively, and deprotection and reduction to the 6-, 7- and 8-membered substituted reduced lactams A18, are analogous to the previously described procedures.



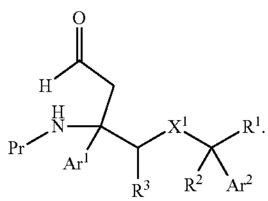
[0164] Another method for preparing aldehyde A15 where R^6, R^7=H involves Wittig homologation of lactol A3 to ethylene derivative A19 which upon hydroboration, preferably with 9-BBN, and subsequent oxidation provides aldehyde A20.



A3

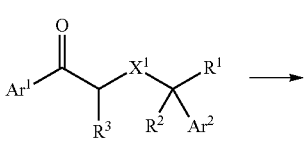


A19

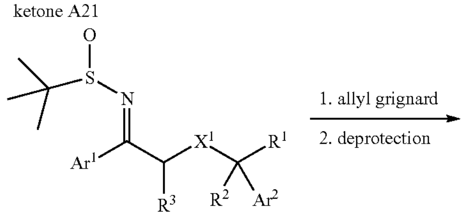


A20

[0165] Alternatively, compounds having the formula I, where n_2 is 2, and X is —O— can be prepared by means of transformation of ketone A21 to the sulfinamide using the appropriate sulfinamide (racemic or chiral) and titaniumisopropoxide, according to the protocol described in Cogan et al, *Tetrahedron,* 55, 8883 (1999). The sulfinamide A22 is then treated with a suitable allyl grignard reagent, followed by ozonolysis to provide the aldehyde A24. Those skilled in the art will recognize that addition of allyl grignard will provide A23 where R^6, R^7=H which can be further modified at the allylic position to incorporate functionalities from the definition of R^6 and R^7 using routine chemistry such as alkylation and hydroxylation. Wittig chemistry on aldehyde A24, followed by hydrogenation, deprotection and cyclization provides the lactam A26. Standard reduction of the lactam A26 provides the substituted piperidines A27, where n_2 is 2.

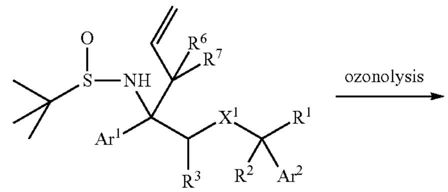


ketone A21

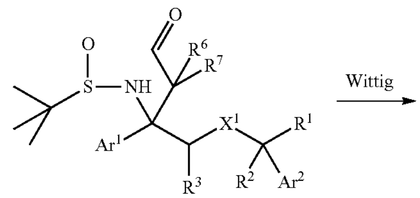


sulfinamide A22

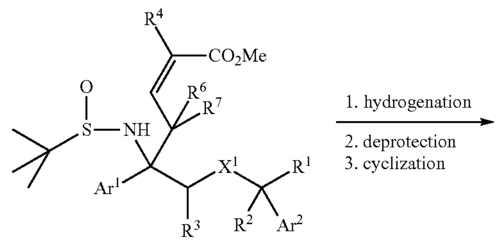
-continued



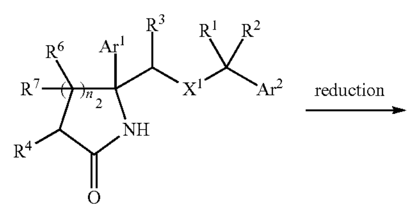
A23



A24



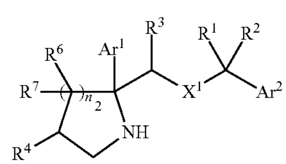
A25



A26

n_2 is 2

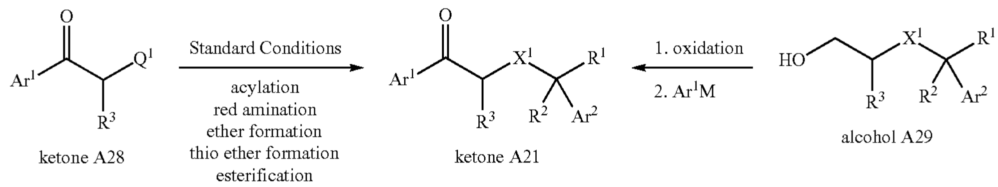
R^5 = H



A27

n_2 is 2

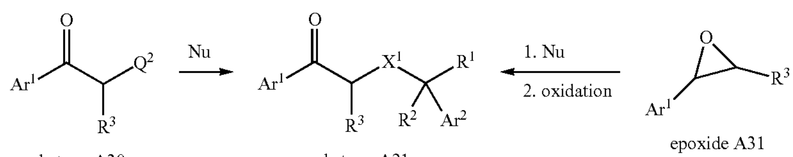
[0166] When X^1 is as defined in the summary of the invention, the ketone A21 wherein X^1 is an ether, thio or imino group may be prepared using several different methods employing commercially available materials. Ketone A28 can be subjected to acylation (Q^1 is —NH_2. —OH or —SH), reductive amination (Q^1 is —NH_2), ether formation (Q^1 is —OH) by standard alkylation methods, thio ether formation (Q^1 is —SH) by standard alkylation methods, or esterification (Q^1 is —OH or —SH). Alternatively, the corresponding alcohol A29 can be oxidized to an aldehyde and treated with an aryl or heteroaryl organometallic reagent, followed by oxidation to give ketone A21.



ketone A28 ketone A21 alcohol A29

Q^1 is —OH, —SH or —NH_2

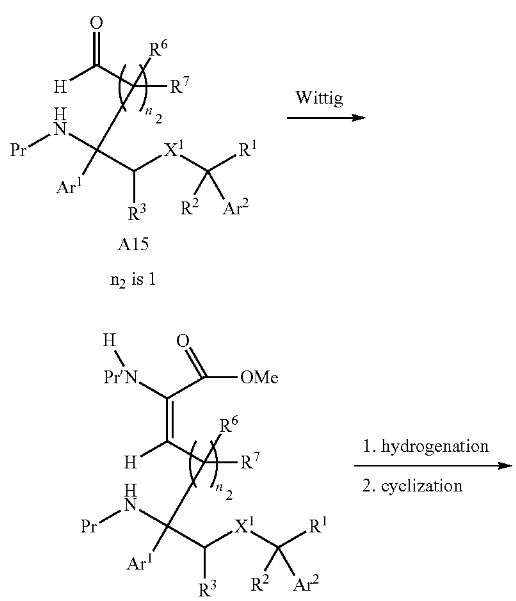
[0167] Another method for preparing ketone A21 involves nucleophilic displacement of a leaving group, such as —Cl, —Br, —I, —OMs and —OTf, adjacent to the aryl or heteroaryl ketone, for example, see WO 01/44200 (2001), which is incorporated herein in its entirety by reference. Accordingly, a suitable substituted styrene or heteroaryl epoxide may be opened with the appropriate nucleophile to give the desired X^1:



ketone A30 ketone A21 epoxide A31

Q^2 is a leaving group, such as —Cl, —Br, —I, —OMs and —OTf

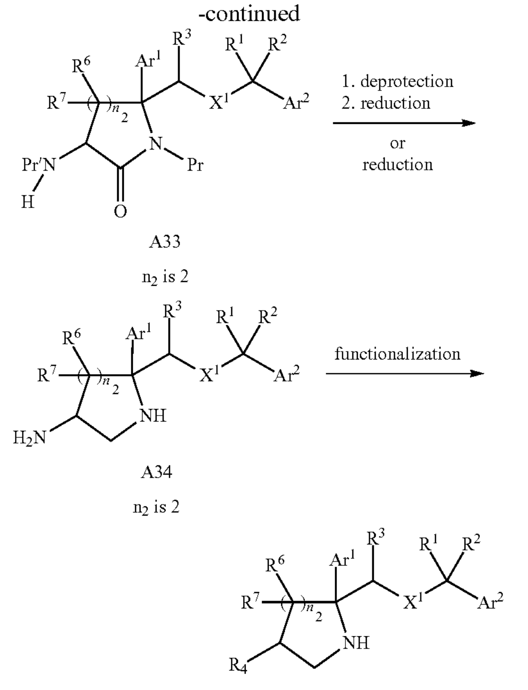
[0168] Compounds having the formula I where n_2 is 2 and R^4 or R^5 is —$NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$NR^{12}C(O)R^{14}$, or —$NR^{12}(C(O)NR^{13}R^{14})$ can also be prepared from aldehyde A15 using the chemistry as described earlier for the pyrrolidine compounds (n_2=1).



A15 n_2 is 1

A32 n_2 is 1

-continued



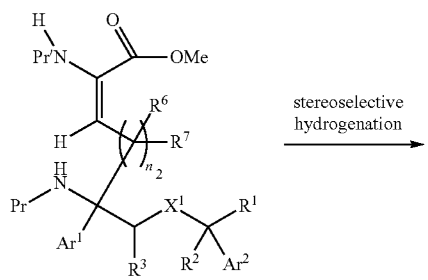
A33 n_2 is 2

A34 n_2 is 2

A35 n_2 is 2

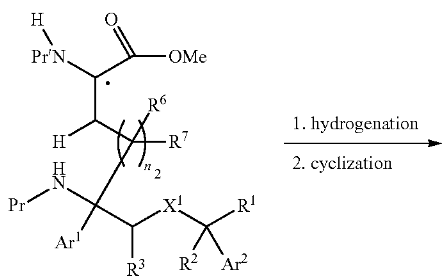
R^4 = —$NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$N^{12}C(O)R^{14}$, —$NR^{12}C(O)NR^{13}R^{14}$)

[0169] Those skilled in the art will appreciate that the stereoselective hydrogenation of the double bond of olefin A32 can also be performed using a chiral hydrogenation catalyst such as chiral Rhodium catalyst which can provide chiral ester A36. The chiral ester A36 can be converted to chiral functionalized amino-piperidine compounds A39 using the chemistry as described earlier for the chiral functionalized amino-pyrrolidine compounds (n_2=1).



A32

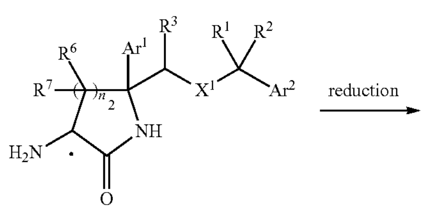
n_2 is 1



A36

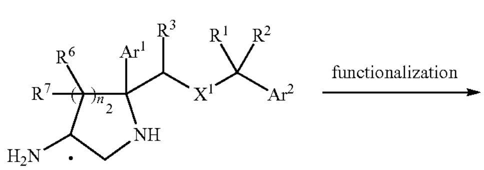
n_2 is 1

(if Pr, Pr′ are Cbz)



A37

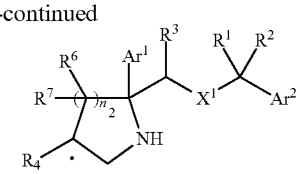
n_2 is 2



A38

n_2 is 2

-continued



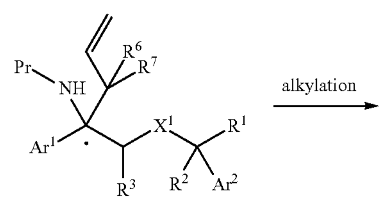
A39

n_2 is 2

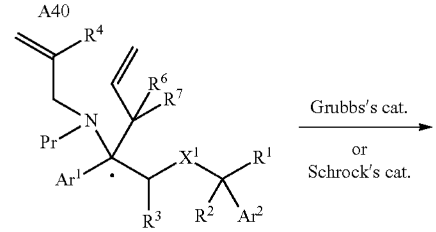
R^4 = —$NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$N^{12}C(O)R^{14}$, —$NR^{12}(C(O)NR^{13}R^{14})$

[0170] Those skilled in the art will appreciate that hortiologation of the aldehyde A15 followed by subsequent synthetic operations as described above will result in the cyclic reduced lactams, where n_2 is 3 or 4.

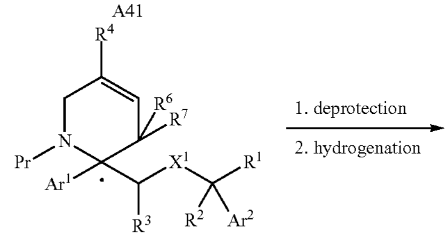
[0171] Another method of preparing compounds having the formula I, where n_2 is 2, and X^1 is —O—, involves the alkyation of amine derivative A40 with a suitable substituted allylic halide, preferably a 2-substituted allylic bromide, to bis olefin A41. Treatment of the bis olefin A41 with Grubb's or Schrock's catalyst using standard olefin metathesis conditions provides the unsaturated piperidine derivative A42. Deprotection of the nitrogen and hydrogenation provides the six-membered cyclic reduced lactams or substituted piperidines A43. If the protecting group (Pr) on the nitrogen is Cbz, then it might cleave under hydrogenation conditions. Those skilled in the art will appreciate that alkylation of amine A40 with an appropriate substituted alkyl halide of 4 to 5 carbon atoms in length containing a terminal olefin, followed by subsequent synthetic operations as described above will result in the substituted cyclic reduced lactams, where n_2 is 3 or 4.



A40

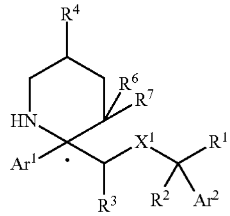


A41



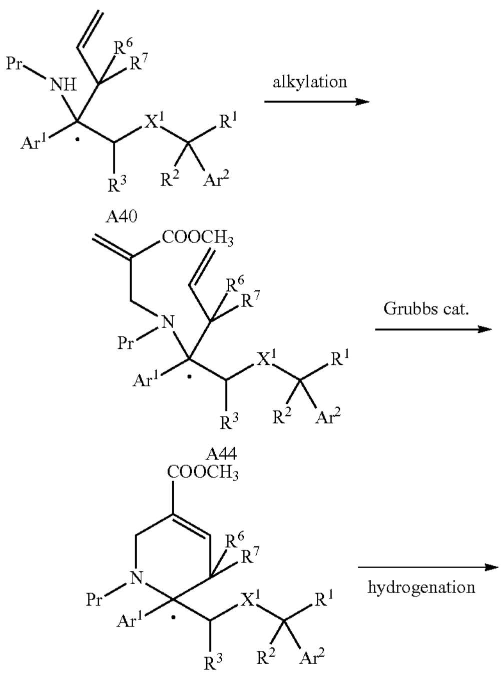
A42

-continued



A43

[0172] When R^4=$COOCH_3$, the chemistry as described above provides A46 where ester group could be further transformed to other functional groups such as amide (R^4=$CONR^{13}R^{14}$) and alcohol (R^4=CH_2OH) using standard chemistry. In addition, the piperidine A46 can be further functionalized using chemistry such as alkylation followed by deprotection of the nitrogen, if necessary, to provide substituted piperidines A47.

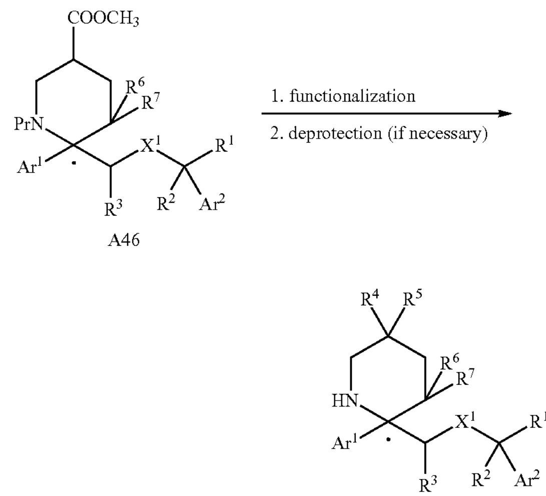


A40

A44

A45

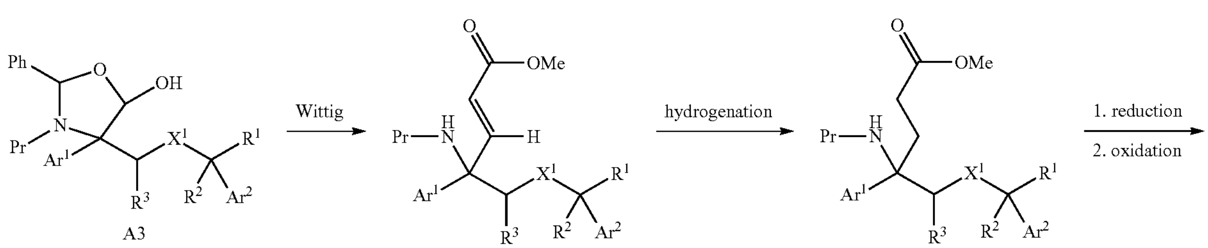
-continued



A46

A47

[0173] Another method of preparing compounds having the formula (I), where n_2 is 1, X^1 is —O— and R^4 is —OH, —O—(C_1-C_6 alkyl), —O—(C_3-C_8 cycloalkyl), —O—(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), —OC(O)R^{14}, or —OCON$R^{13}R^{14}$, from lactol A3 involves Wittig chemistry to provide the corresponding olefin ester A48. Hydrogenation of the olefin ester A48, followed by reduction to the alcohol using metal hydride reducing agents, preferably $LiBH_4$, and subsequent oxidation, such as Swern or bleach, gives aldehyde A50. The cyclization of aldehyde A50 provides enamide A51 which upon hydroxylation, preferably using a borane gives alcohol A52. The alcohol A52 can be oxidized under standard oxidation conditions such as Swern oxidation to give ketone A53. Treatment of the ketone with a suitable organometallic reagent provides the tertiary alcohol A54. For instances where the desired R^5 substituent cannot be incorporated directly with an organometallic reagent, further functionalization at the R^5 position may be necessary. The hydroxyl group of alcohol A54 can be further functionalized using standard chemistry followed by deprotection to give disubstituted pyrrolidines A55. Alternatively, the further modification of the secondary alcohol A52 under standard conditions and deprotection of the nitrogen provides the monosubstituted pyrrolidines A56.

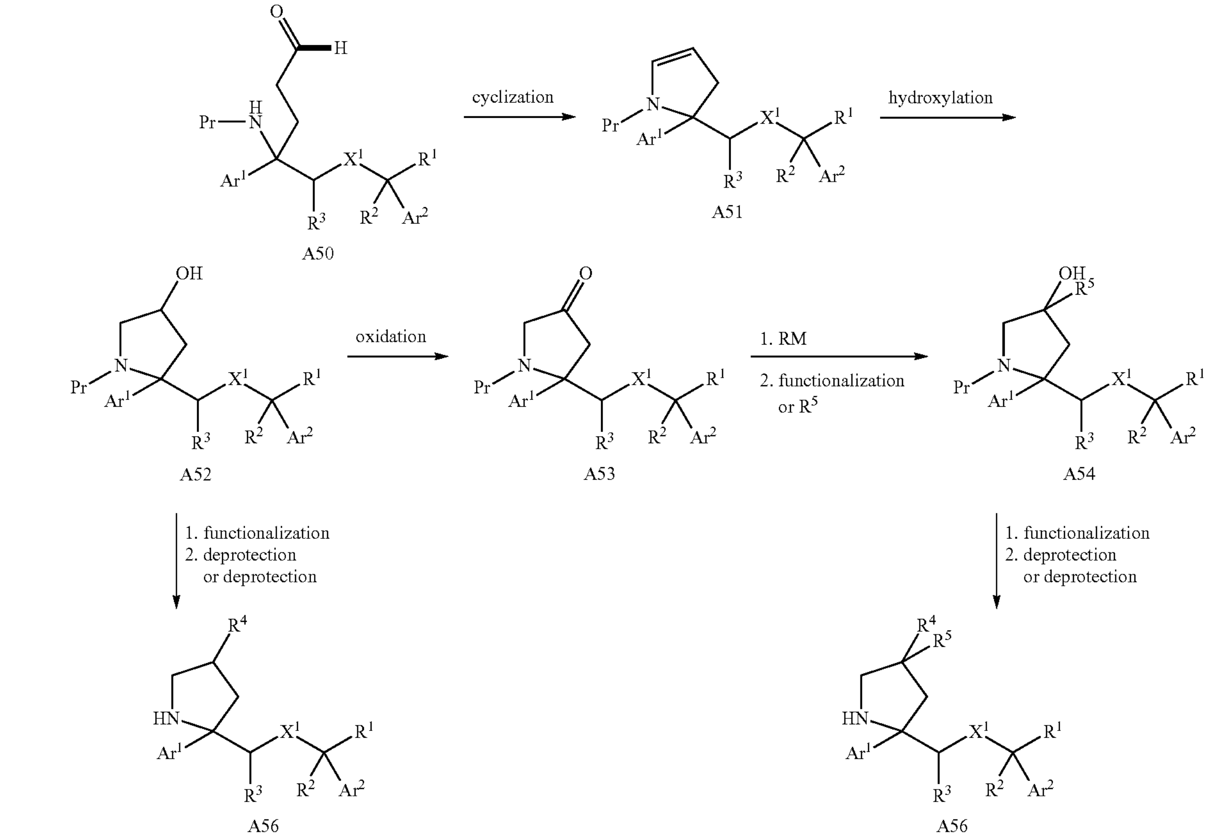


A3

A48

A49

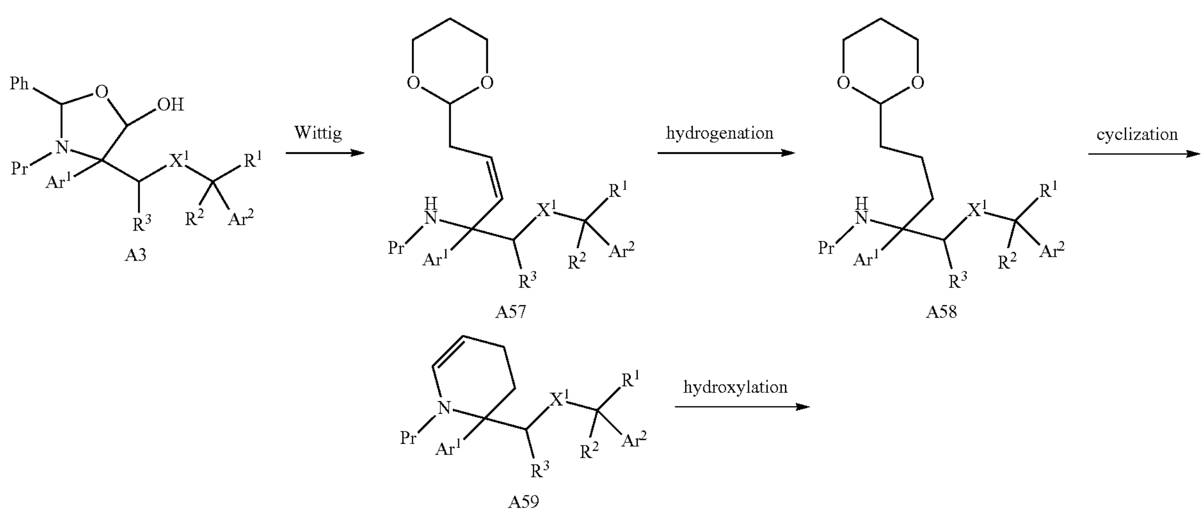
-continued



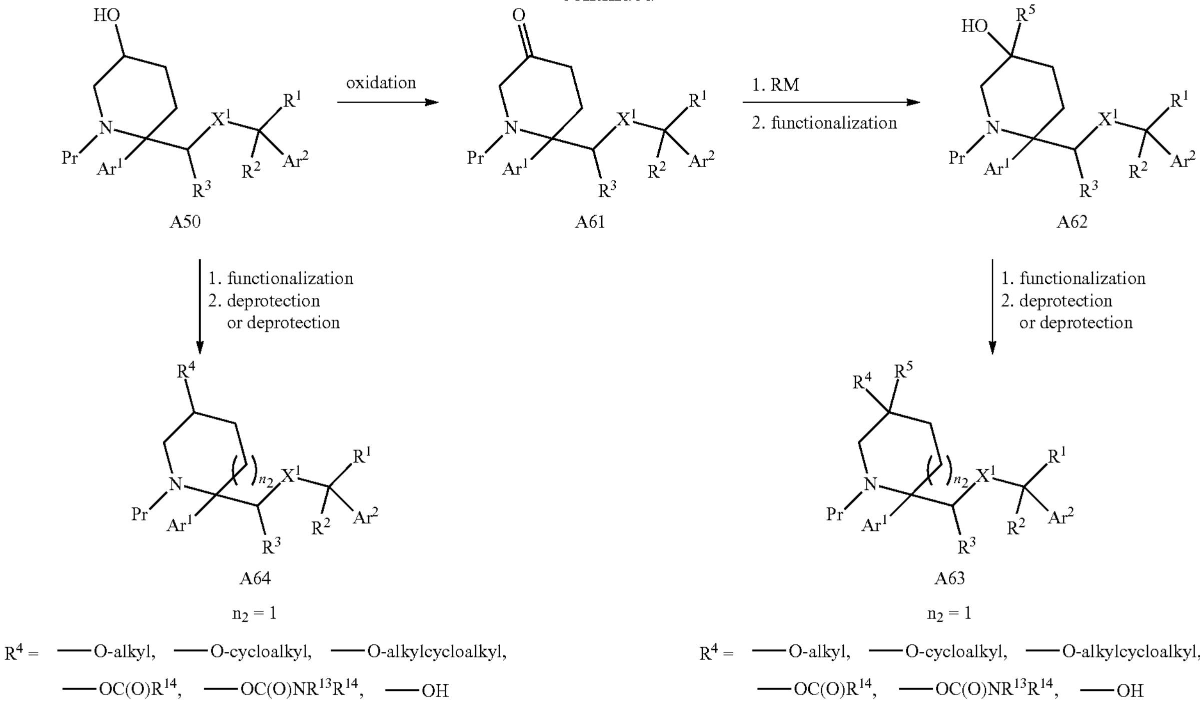
R^4 = —O-alkyl, —O-cycloalkyl, —O-alkyl-cycloalkyl, —OC(O)R^{14}, —OC(O)$NR^{13}R^{14}$, —OH

R^4 = —O-alkyl, —O-cycloalkyl, —O-alkyl-cycloalkyl, —OC(O)R^{14}, —OC(O)$NR^{13}R^{14}$, —OH

[0174] Compounds having the formula I, where n_2 is 2, X^1 is —O— and R^4 is —OH, —O—(C_1-C_6 alkyl), —O—(C_3-C_8 cycloalkyl), —O—(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), —OC(O)R^{14} or —OCONR^{13}R^{14}, can be prepared from lactol A3. Wittig chemistry followed by hydrogenation and cyclization in weakly acidic conditions such as p-toluene-sulfonic acid provides the enamide A59. Using the synthetic operations as described above from the enamide A51, the enamide A59 will result in the disubstituted piperidines A63 and monosubstituted piperidines A64.

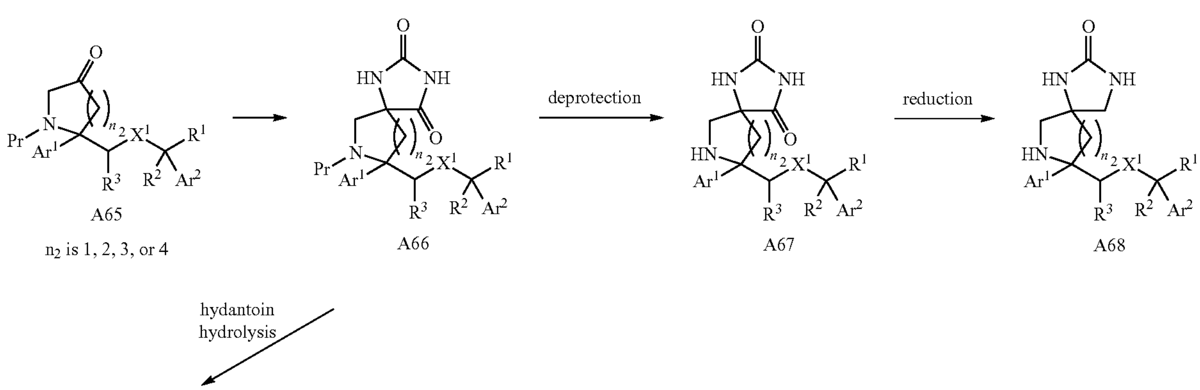


-continued

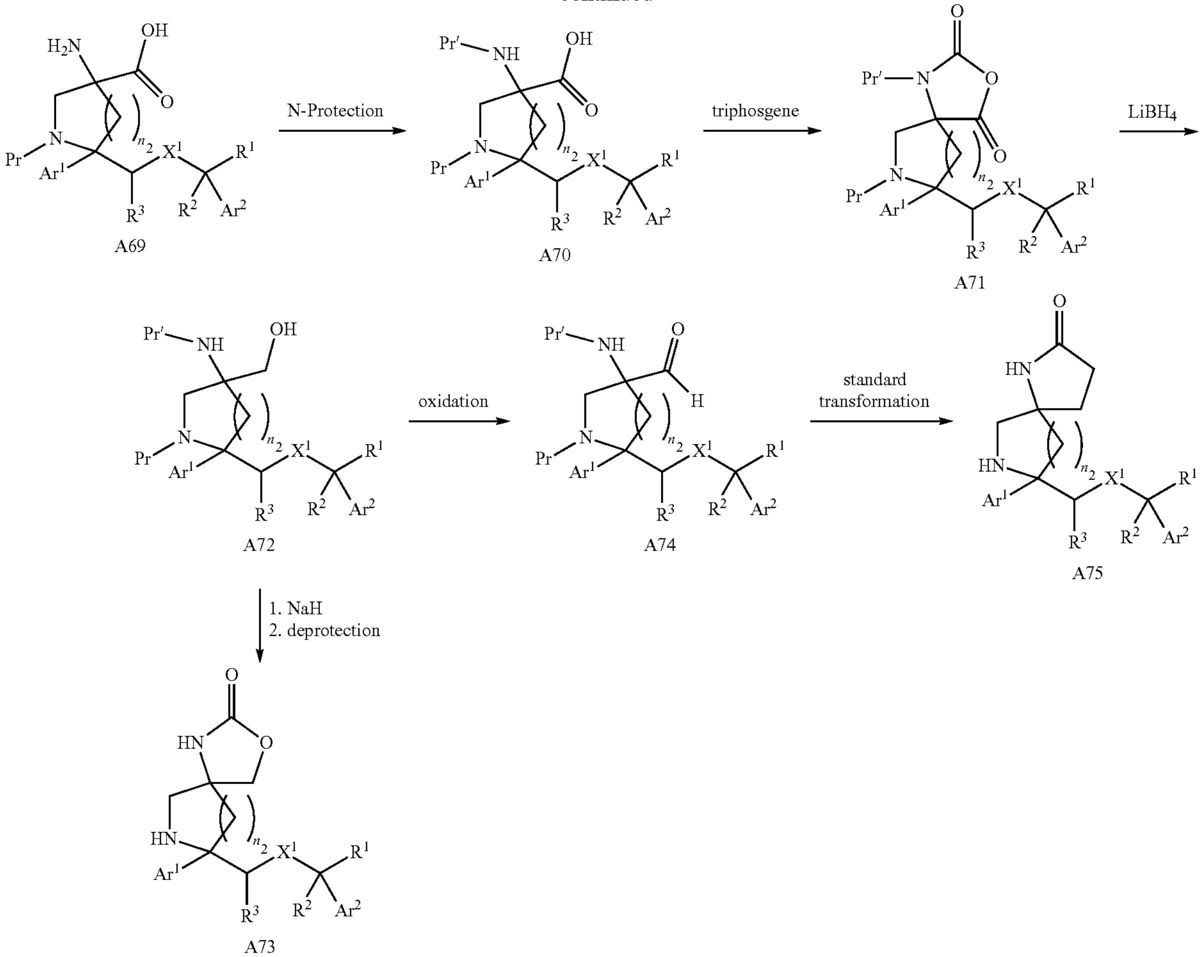


[0175] Those skilled in the art will appreciate that homologation of the lactol A3 to the aldehyde A15 where n_2 is 2 or 3 followed by subsequent synthetic operations as described above will result in the monosubstituted cyclic amines A64 or disubstituted cyclic amines A63 where n_2 is 2 or 3.

[0176] The compounds having the formula I, where n_2 is 1, 2, 3 or 4, X^1 is —O— and, R^4 and R^5, together with the carbon to which they are both attached, form a chemically feasible 5 membered ring can be prepared from corresponding ketones. The ketone A65 is transformed into the corresponding hydantoin A66 by heating with KCN/ammonium carbonate in ethanol/water mixture or by using alternate standard conditions known to those skilled in the art. The amine is deprotected to give hydanotin A67 which can be converted to corresponding urea analogs A68 by reduction preferably with LAH/$AlCl_3$. Alternatively hydanotin A66 can be cleaved to amino-acid A69 using the protocol described in Kubik, S.; Meissner, R. S.; Rebek, J. *Tetrahedron Lett.* 35, 6635 (1994). Standard protection of the amino-acid A69 as a carbamate derivative (Pr') is followed by activation of the carboxylic acid. Treatment with phosgene or a phosgene equivalent, preferably triphosgene, is one such method for acid activation. The reduction of NBoc-UNCA A71 with reducing agents, preferably lithium borohydride, gives alcohol A72 which can be converted to five membered cyclic compounds such as carbamate A73 by intramolecular cyclization (if Pr' is carbamate protecting group such as Boc) using base, preferably NaH, followed by deprotection. Alternatively, alcohol A72 can be oxidized to NBoc-aldehyde A74 by standard oxidation conditions such as Swern oxidation and using the routine chemistry known to those skilled in the art. The NBoc-aldehyde A74 can be converted to cyclic analogs such as the r-lactam A75.

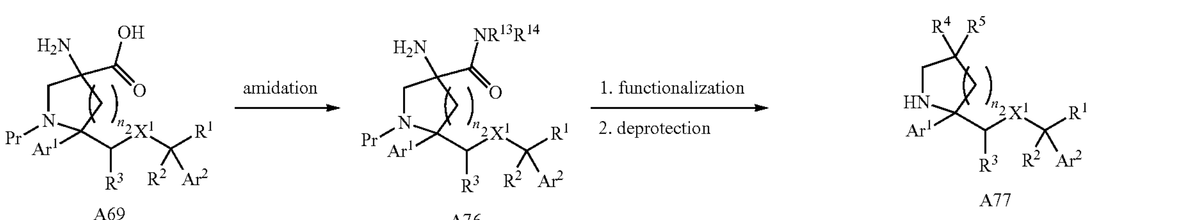


-continued



n_2 is 1, 2, 3, or 4

[0177] The compounds having the formula I, where n_2 is 1, 2, 3, or 4, X^1 is —O— and R^4 is $—NR^{13}R^{14}$, $—NR^{12}SO_2R^{13}$, $—NR^{12}COR^{14}$, $—NR^{12}C(O)OR^{13}$, or $—NR^{12}(CONR^{13}R^{14})$, and R^5 is $—C(O)NR^{13}R^{14}$ can be prepared by amidation of amino-acid A69 to give amino-amide A76 followed by functionalization of amino group and deprotection to provide disubstituted analogs A77. Alternatively, the NBoc-amino-acid A70 can be reacted with an amine, followed by deprotection of N—Pr' group to give amino-amide A76. The amino-amide A76 can also be deprotected to give analogs A78 where R^4 is $—NR^{13}R^{14}$ and R^{13}, R^{14}═H.

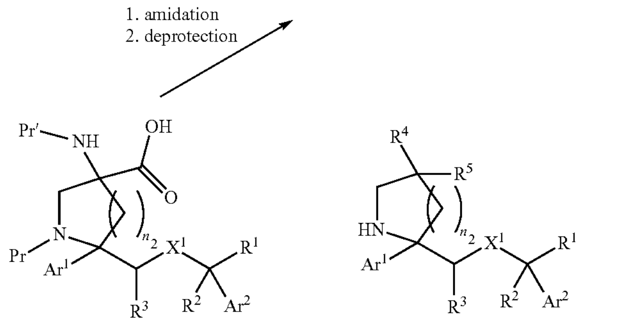


n_2 is 1, 2, 3, or 4

R^4 = $—NR^{13}R^{14}$, $—NR^{12}SO_2R^{13}$, $—NR^{12}COR^{14}$, $—NR^{12}C(O)OR^{13}$, $—NR^{12}(CONR^{13}R^{14})$

R^5 = $—C(O)NR^{13}R^{14}$

-continued



A70

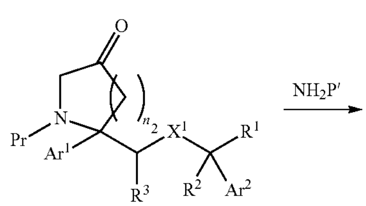
A78

n_2 is 1, 2, 3, or 4

R^4 = —$NR^{13}R^{14}$ where R^{13}, R^{14} = H

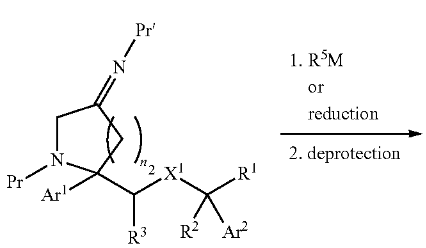
R^5 = —$C(O)NR^{13}R^{14}$

[0178] Another method of preparing compounds having the formula I, where n_2 is 1, 2, 3 or 4, X^1 is —O— and R^4 is —$NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —NR^2COR^{14}, —$NR^{12}C(O)OR^{13}$, or —$NR^{12}(CONR^{13}R^{14})$, involves treatment of ketone A65 with a protected amine under appropriate conditions to provide imine A79. Nucleophilic addition of compatible organometallic reagents such as grignard or reduction (if R^5═H) of imine A79 followed by deprotection of nitrogen (N—Pr') provides amine A80. The functionalization of amine A80 under standard conditions and deprotection of nitrogen provides the substituted pyrrolidines A81.



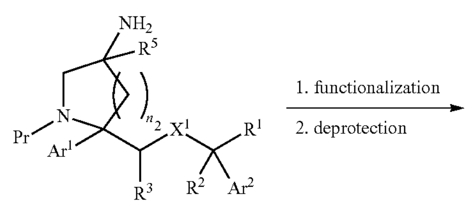
A65

n_2 is 1, 2, 3, or 4

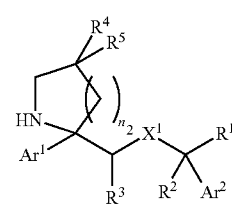


A79

-continued



A80

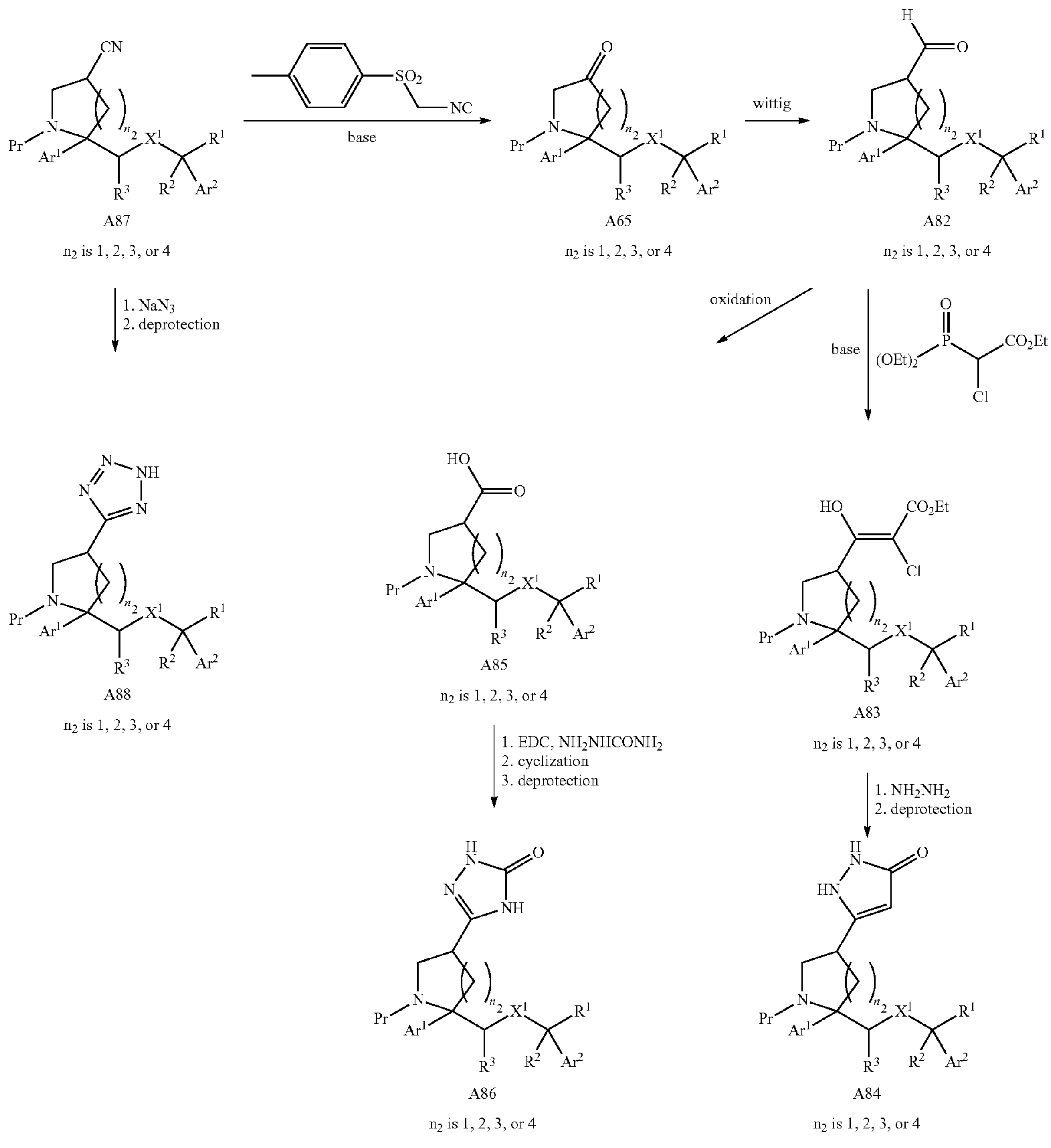


A81

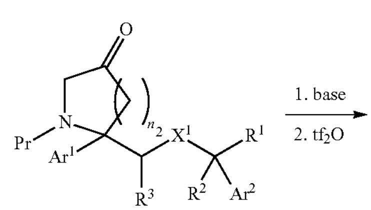
n_2 is 1, 2, 3, or 4

R^4 = —$NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$NR^{12}COR^{14}$, —$NR^{12}C(O)OR^{13}$, —$NR^{12}(CONR^{13}R^{14})$

[0179] The compounds having the formula I, where n_2 is 1, 2, 3 or 4, X is —O—, R^5 is H, and R^4 is a heterocyclic or heteroaryl group can be prepared by conversion of ketone A65 to nitrile A87, aldehyde A82 and a carboxylic acid A85 via aldehyde A82 using the standard oxidation conditions. Those who are skilled in the art will appreciate that the cyano, aldehyde and carboxylic acid compounds can provide the appropriate heterocyclic or heteroaryl functionality using standard chemistry.



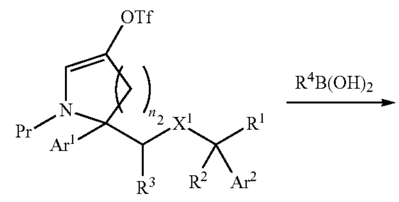
[0180] Another method of preparing the compounds having the formula I, where n_2 is 1, 2, 3, or 4, X^1 is —O—, R^5 is H, and R^4 is a heterocyclic or heteroaryl group involves conversion of the ketone A65 to a vinyl triflate A89 by using a base such as LDA and triflic anhydride as an electrophile. The triflate A89 could be coupled with suitable organometallic reagents, preferably boronic acid, to give heterocyclic or heteroaryl unsaturated compound A90. The reduction of the double bond followed by deprotection of the amine (if necessary) provides heterocyclic or heteroaryl substituted cyclic amines A91.



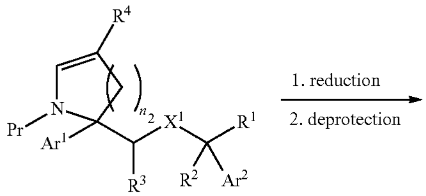
A65

n_2 is 1, 2, 3, or 4

-continued

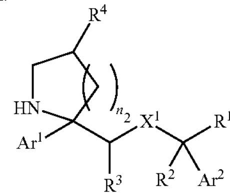


A89



A90

-continued

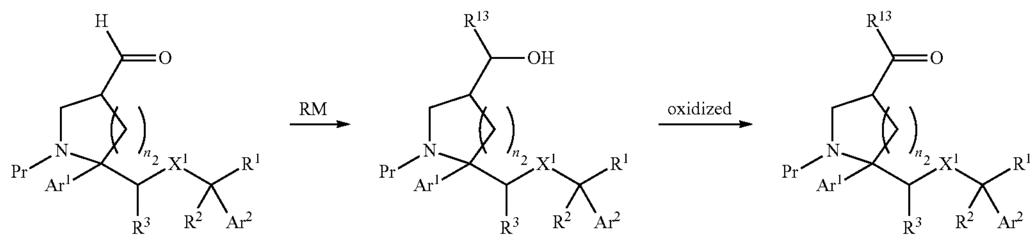


A91

n_2 is 1, 2, 3, or 4

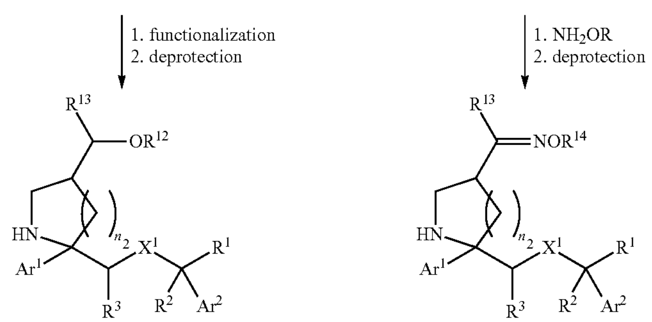
R^4 = -heterocyclic or heteroaryl

[0181] The compounds having the formula I, where n_2 is 1, 2, 3, or 4, X^1 is —O— and R^4 is —C(OR^{12})(R^{13})(R^{14}), where R^{14} is H, or —C(=NOR^{14})(R^{13}) can be prepared by conversion of aldehyde A82 to an alcohol A92 via addition of an organometallic reagent. The alcohol A92 can be transformed to analogs such as A93 or it can be oxidized to ketone A94 which can provided analogs such as oxime A95 using the standard conditions.



A82 A92 A94

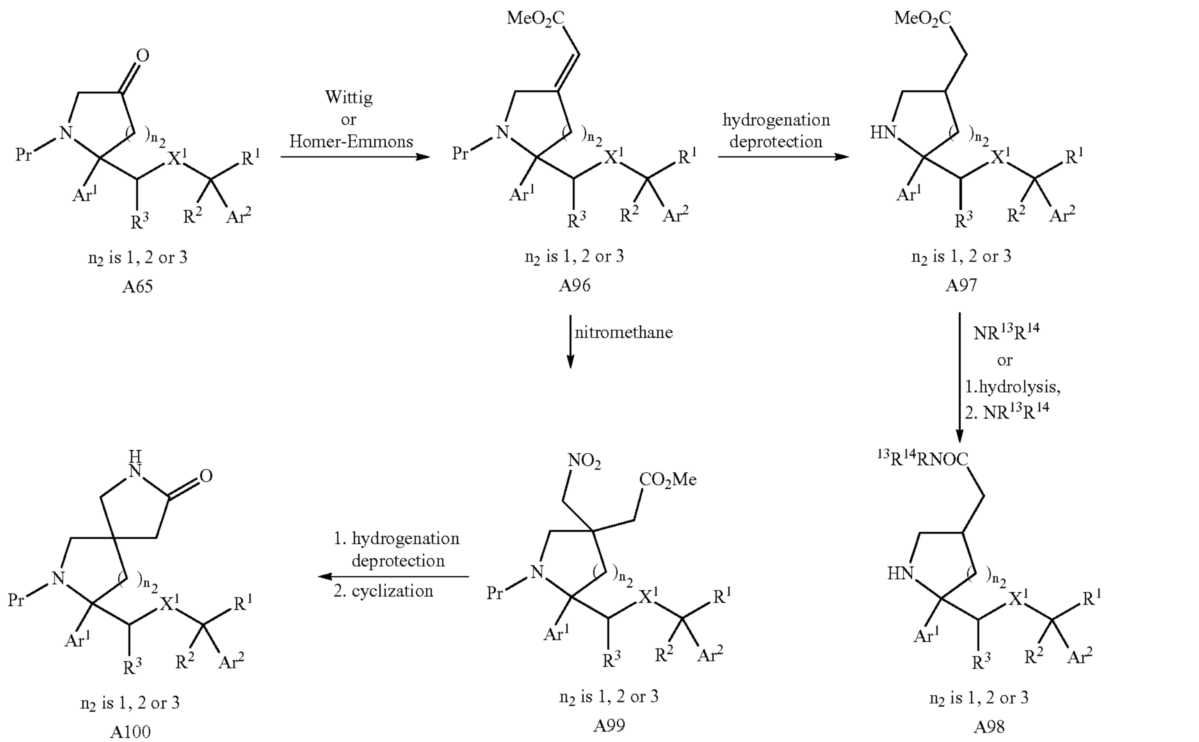
n_2 is 1, 2, 3, or 4 n_2 is 1, 2, 3, or 4 n_2 is 1, 2, 3, or 4



A93 A95

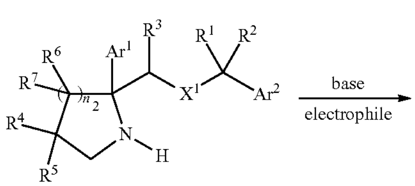
n_2 is 1, 2, 3, or 4 n_2 is 1, 2, 3, or 4

[0182] The compounds having the formula I, where n_2 is 1, 2, 3 or 4, X^1 is —O—, R^5 is H, and R^4 is —C($R^{28}R^{29}$)$CONR^{13}R^{14}$, where R^{28}, R^{29}=H or methyl, can be prepared by conversion of ketone A65 to unsaturated ester A96 using Wittig chemistry. Hydrogenation of the double bond and deprotection of the protecting group, if necessary, provides the ester A97. Conversion of the ester to amides A98 can be realized through treatment with amines, or transformation to the acid and subsequent coupling with amines using standard methods. In addition, the unsaturated ester A96 can also provide compounds where R^4 and R^5, together with the carbon to which they are attached, form a five membered cyclic ring such as lactam A100.



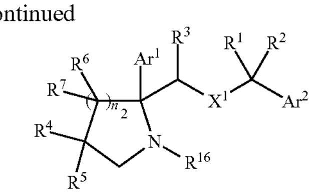
[0183] Those skilled in the art will appreciate that functionalization of the nitrogen of cyclic ring formed by R^4 and R^5 when R^4 and R^5 together and to the carbon to which they are attached form cyclic rings such as hydantoin A67, urea A68 and lactam A100 may be performed at an appropriate point in the synthesis by deprotonation with a suitable base and reaction of the necessary electrophile to provide the substitutents defined for R^{35}. Those skilled in the art will appreciate that a substituted alkyl halide will afford the corresponding substituted C_1-C_6 alkyl group and treatment with tetrabenzylpyrophosphate, followed by hydrogenation will serve to provide for R^{35}=—P(O)(OH)$_2$.

[0184] Functionalization of the reduced lactam nitrogen can be performed at an appropriate point in the synthesis by deprotonation with a suitable base and reaction of the necessary electrophile to provide the substitutents defined for R^{18}. Those skilled in the art will appreciate that a substituted alkyl halide will afford the corresponding substituted C_1-C_6 alkyl group and treatment with tetrabenzylpyrophosphate, followed by hydrogenation will serve to provide for R^{18}=—P(O)(OH)$_2$.



A101

-continued



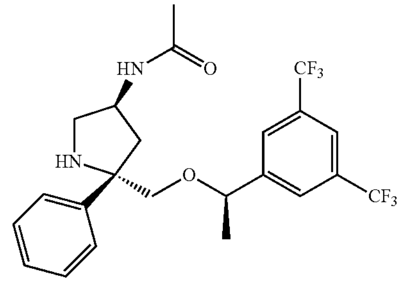
A102

[0185] Those skilled in the art will recognize that certain additional protection and deprotection steps may be needed in order to accommodate different functional groups. Accordingly, the order of synthetic operations may be different in order to maintain functional group compatibility with the operational steps in the synthesis.

Specific Methods Of Preparation—Examples

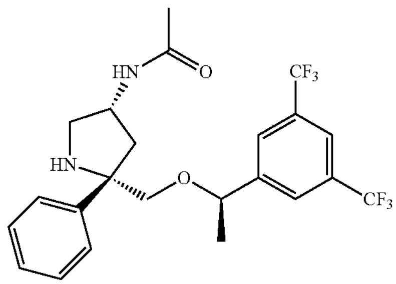
[0186]

Example 1a



-continued

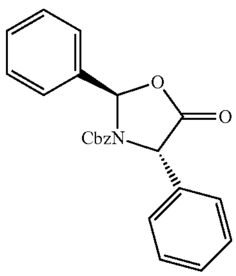
Example 1b



Step 1

[0187]

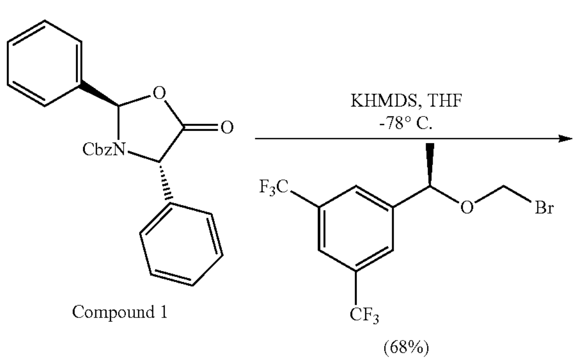
Compound 1



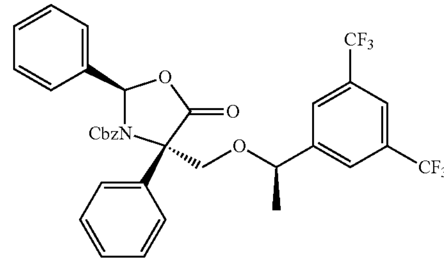
[0188] Compound 1 was prepared using a synthetic procedure reported by M. J. O'Donnell, Z. Fang, X. Ma and J. C. Huffman, *J. Am. Chem. Soc.,* 1997, 46, 617.

Step 2

[0189]



-continued



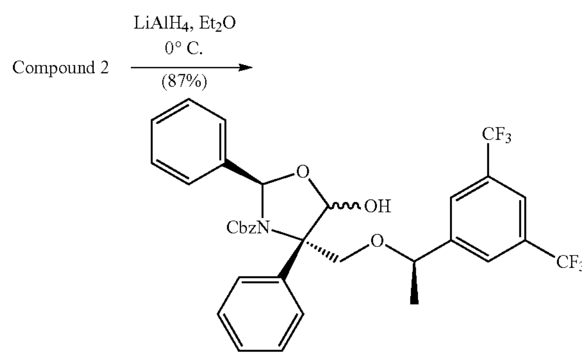
Compound 2

[0190] To a nitrogen purged solution of oxazolidinone Compound 1 (10.0 g, 0.027 mol, 1 equiv) in THF (500 ml) at −78° C., a solution of KHMDS (0.5M in toluene, 64 ml, 0.032 mol, 1.18 equiv) was added. After stirring at −78° C. for 30 min, a solution of bromomethyl ether (11.3 g, 0.032 mol, 1.18 equiv) in THF (100 ml) at −78° C. was cannulated into the reaction mixture. The solution was stirred at −78° C. for 1 h before being quenched with a saturated NH_4Cl solution at −78° C. The reaction mixture was warmed to RT, and water and EtOAc were added. The aqueous layer was extracted with EtOAc (200 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered, and solvents in the filtrate were removed by vacuum. Purification using column chromatography [hexane-toluene, 1:1 (v/v)] gave Compound 2 (11.7 g. 68%) as a colorless oil.

[0191] Electrospray MS $[M+1]^+$ 644.1.

Step 3

[0192]



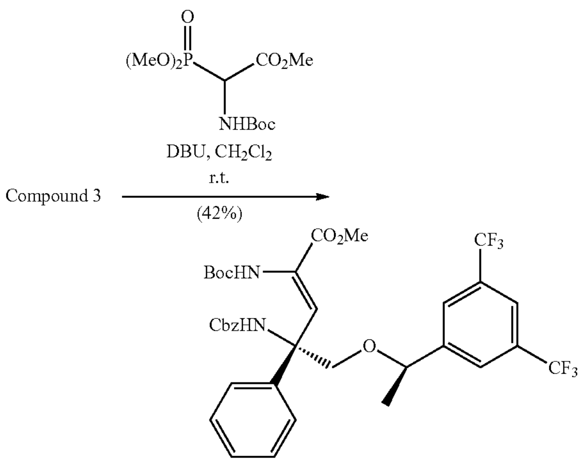
Compound 3

[0193] To a solution of lactone Compound 2 (35.2 g, 0.055 mol, 1 equiv) in Et_2O at 0° C., a 1M solution of LAH (17.8 ml, 0.018 mol, 0.32 equiv) in Et_2O was added. The reaction mixture was stirred at 0° C. for 30 min before being quenched with saturated NH_4Cl solution. Water was added and the resulting layers were separated. The separated aqueous layer was extracted with EtOAc (300 ml×2), and the combined organic layers were dried ($MgSO_4$), and filtered. Solvents in the filtrate were removed in a vacuum to give a colorless oil. The oil was dissolved in HOAc (240 ml) at RT, and water (60 ml) was added. After being stirred at RT for 1 h, the white solid was filtered, washed with water and dried under a high vacuum. Recrystallization [hexane-toluene] gave Compound 3 (23 g) as a white powder. All filtrates were combined, and the solvents removed in a vacuum to give a yellow oil. The above procedure [HOAc—H_2O, followed by recrystallization] was repeated to give another batch of lactol Compound 3 (3 g). Solvents in the filtrate were removed in a vacuum, and the resulting oil was subjected to column chromatography [hexane-EtOAc, 6:1 (v/v)] to give a third batch (4 g). The combined yield for Compound 3 was 30 g, 87%.

[0194] Electrospray MS $[M+1]^+$ 646.2.

Step 4

[0195]



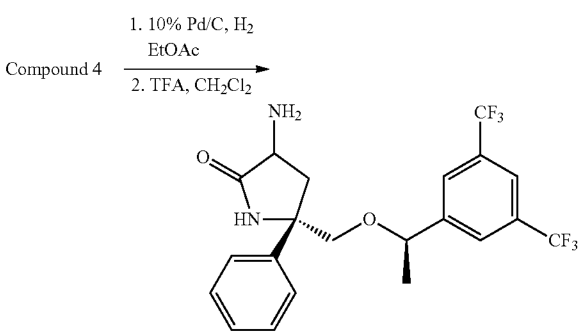
Compound 4

[0196] To a solution of Compound 3 (0.98 g, 1.52 mmol, 1 equiv) and NBoc-O-phosphonoglycine trimethylester (1.26 g, 3.80 mmol, 2.5 equiv) in CH_2Cl_2 (5 ml) at 23° C., DBU (0.57 ml, 3.80 mmol, 2.5 equiv) was added dropwise. The mixture was stirred at 23° C. for 4 h before it was quenched with saturated NH_4Cl solution. Et_2O was added and layers were separated. The separated aqueous layer was extracted with Et_2O (250 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Removal of solvents in vacuum followed by chromatographic purification [hexane:ether, 3:1 (v/v)] gave Compound 4 (587 mg, 52%) as white foam.

[0197] Electrospray MS $[M+1]^+$ 745.1.

Step 5

[0198]

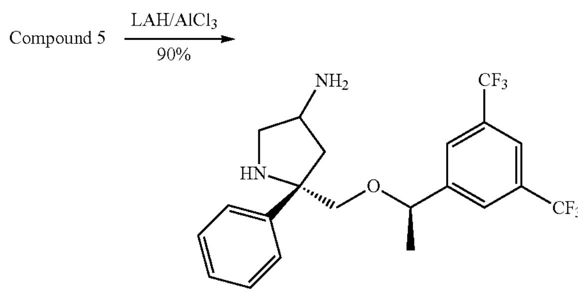


Compound 5

[0199] A solution of Compound 4 (1.4 g, 1.88 mmol, 1.0 equiv.) in EtOAc (30 ml) was flushed with N_2. After the addition of Palladium on carbon (10%, 2 g) a H_2 balloon was attached to the reaction flask. The reaction mixture was stirred for 18 h at 23° C. under H_2 atmosphere and then filtered and concentrated. The residue was dissolved in anhydrous CH_2Cl_2 (45 ml), cooled to 0° C., then treated with TFA solution (4.5 ml, 0.059 mmol, 30.0 equiv). The reaction mixture was stirred at 0° C. for 30 min and then at 23° C. for another 4 h. Reaction mixture was diluted with CH_2Cl_2 (300 ml) washed with saturated $NaHCO_3$ solution (100 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to give Compound 5 (0.8 g, 95%).

Step 6

[0200]



Compound 6

[0201] In a flame dry 25 ml RBF was placed $AlCl_3$ (0.089 g. 0.67 mmol, 1.5 equiv). The reaction flask was cooled to 0° C. and 1M solution of LAH in Et_2O (2 ml, 1.98 mmol, 4.5 equiv) was carefully added. The reaction mixture was cooled to −78° C. and a solution of Compound 5 (0.2 g, 0.44 mmol, 1.0 equiv) in dry THF (4 ml) was slowly added. The reaction mixture was stirred at −78° C. for 2 h, then slowly warmed to 23° C. and stirred for 18 h. The reaction was then cooled to 0° C. and quenched carefully with saturated aqueous sodium potassium tartrate solution. Reaction mixture was taken up in EtOAc (200 ml) and extracted with saturated aqueous $NaHCO_3$(100 ml). Aqueous layer was extracted with EtOAc (150 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give Compound 6 (180 mg, 95%). Electrospray MS $[M+1]^+$ 433.1.

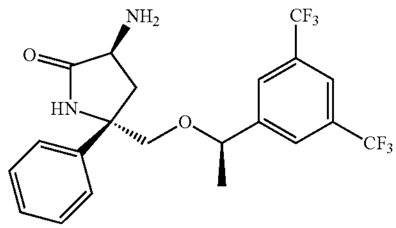
Step 7

[0202] To a solution of Compound 6 (0.21 g, 0.486 mmol, 1.0 equiv) in MeOH (3 ml) at 0° C. was added 2-trifluoromethyl-N,N-diacetylaniline (0.131 g, 0.535 mmol, 1.1 equiv). The mixture was stirred at 0° C. for 1 h, then warmed to 23° C. and stirred for 18 h. The reaction mixture was then concentrated and purified using a Gilson with water/CH_3CN to give a mixture of two compounds (0.16 g). Purification of the mixture by HPLC using ChiralPak column (98:2, hexane:IPA) gave less polar isomer Example 1a (0.050 g, 22%), Electrospray MS $[M+1]^+$ 475.1, and more polar isomer Example 1b (0.015 g, 7%), Electrospray MS $[M+1]^+$ 475.1.

Preparation of Compound 9

[0203]

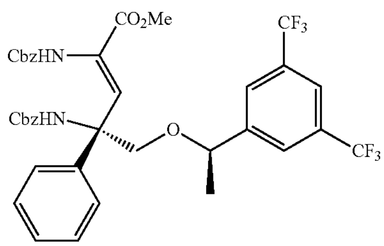
Compound 9



Step 1

[0204]

Compound 7

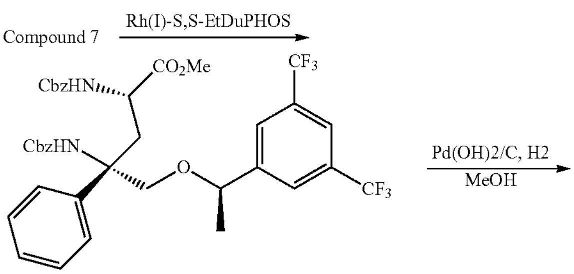


[0205] Compound 7 was prepared using a procedure similar to that for Compound 4, using Compound 3 and $PO(OEt)_2CH(NHCbz)CO_2Me$ in place of $PO(OMe)_2CH(NHBoc)CO_2Me$. Electrospray MS $[M+1]^+$ 745.1.

Step 2

[0206]

Compound 7



Compound 8

Compound 9

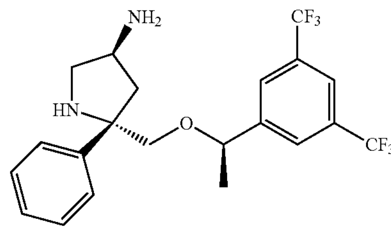
[0207] Compound 7 (3.0 g, 4.03 mmol, 1.0 equiv) was taken in MeOH (30 ml) in a parr reaction bottle. The reaction bottle was degassed using N_2 for 15 min. (+)-1,2-Bis-((2S,5S)-2,5-diethylphospholano) benzene (cyclooctadiene)rhodium(I) trifluoro-methanesulfonate (0.12 g, 0.16 mmol, 0.04 equiv) was added to the reaction mixture in a glove box, and shaken under H_2 at 60 psi for 96 h. The reaction mixture was transferred to a 200 mil RBF. 20% of $Pd(OH)_2/C$ (1 g) was added to the reaction mixture, which was stirred under H_2 at 23° C. for 18 h. The reaction was monitored by TLC 9/1 $EtOAc/CH_3OH$. Once the reaction was completed it was filtered through celite and concentrated. Purification was carried out using a silica plug 9:1 $EtOAc/MeOH(NH_3)$ to give the Compound 9 (1.3 g, 72%).

[0208] Electrospray MS $[M+1]^+$ 447.1.

Preparation of Compound 10

[0209]

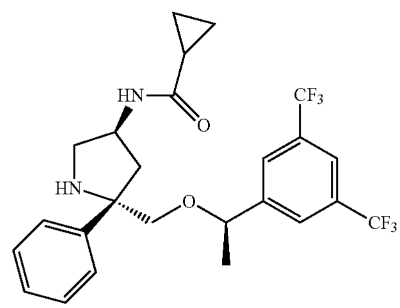
Compound 10



[0210] Compound 10 was prepared using similar procedure to Compound 6, using Compound 9 instead of Compound 5.

Example 2

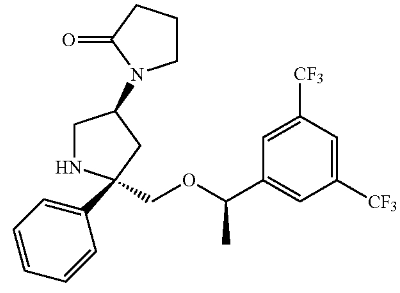
[0211]



[0212] To a solution of Compound 10 (0.059, 0.116 mmol, 1.0 equiv) in MeOH (2 ml) at −78° C. was added cyclopropanecarbonyl chloride (1201, 0.127 mmol, 1.1 equiv). The mixture was stirred at −78° C. for 5 min, then warmed to 23° C. and stirred for 18 h. The reaction mixture was then concentrated and taken up in EtOAc (200 ml) and washed with sat. aq. $NaHCO_3$ (1×100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification of the resulting mixture on a Biotage with 5% MeOH/EtOAc gave Example 2 (0.04 g, 69%). Electrospray MS $[M+1]^+$ 501.

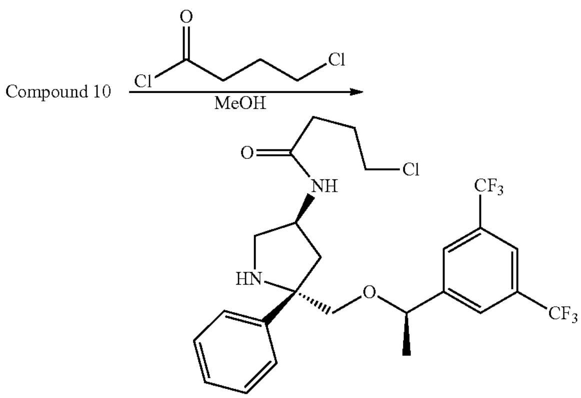
Example 3

[0213]



Step 1

[0214]



Compound 11

[0215] To a solution of Compound 10 (0.05 g, 0.116 mmol, 1.0 equiv) in MeOH (2 ml) at −78° C. was added 4-chlorobutyryl chloride (14 μl, 0.127 mmol, 1.1 equiv). The mixture was stirred at −78° C. for 5 min, then warmed to 23° C. and stirred for 18 h. The reaction mixture was then concentrated and taken up in EtOAc (200 ml) and washed with sat. aq. $NaHCO_3$(1×100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated to provide the crude Compound 11, which was used in the next reaction without further purification.

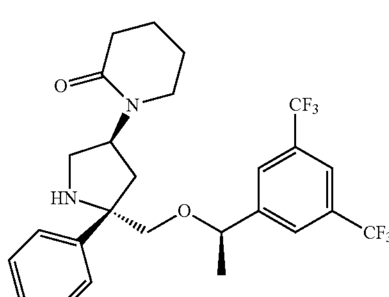
Step 2

[0216] To a solution of crude Compound 11 in dry THF (2 ml) was added NaH (60% dispersion in mineral oil, 0.014 g, 0.347 mmol, 3 equiv) at 0° C. and stirred for 5 min, then heated at 60° C. for 2 h. The reaction mixture was cooled to 0° C. and quenched carefully with water (3 ml). The mixture was poured into EtOAc (100 ml) and washed with saturated aqueous $NaHCO_3$ (100 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the resulting mixture on Biotage with 5% MeOH/EtOAc gave Example 3 (0.20 g, 34%).

[0217] Electrospray MS $[M+1]^+$ 501.1.

Example 4

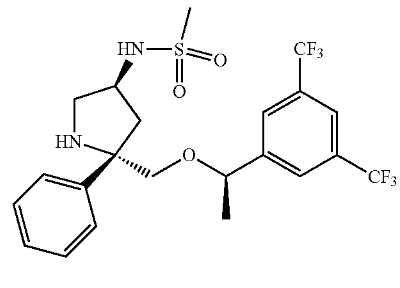
[0218]

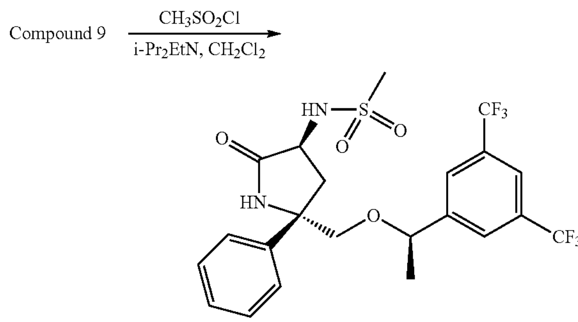


[0219] Example 4 (53% overall yield) was prepared from Compound 10 in a manner similar to that used to prepare the Example 3, but using 5-chlorovaleryl chloride in place of 4-chlorobutyryl chloride. Electrospray MS $[M+1]^+$ 515.1.

Example 5

[0220]





Compound 12

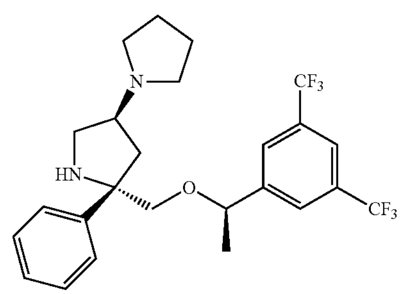
[0221] To a solution of Compound 9 (0.13 g, 0.29 mmol, 1.0 equiv) in CH_2Cl_2 (3 ml) at 0° C. was added DIEA (0.11 ml, 0.61 mmol, 2.1 equiv) and CH_3SO_2Cl (34 μl, 0.435 mmol, 1.5 equiv). The mixture was stirred at 0° C. for 30 min, then poured into EtOAc (150 ml) and washed with saturated aqueous $NaHCO_3$ (100 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to provide the crude Compound 12, which was used in the next reaction without further purification.

[0222] The crude Compound 12 was converted to Example 5 (80 mg, 54% yield, two steps from Compound 9) using a method similar to the preparation Compound 6 from Compound 5. Electrospray MS $[M+1]^+$ 511.1.

Example 6a and Example 6b

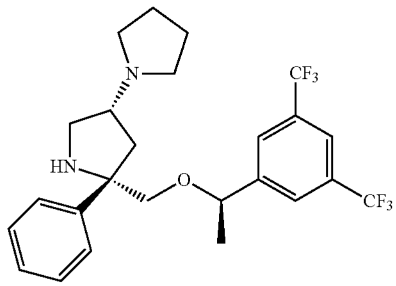
[0223]

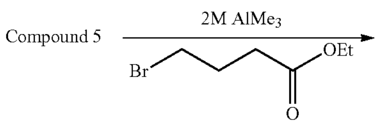
Example 6a

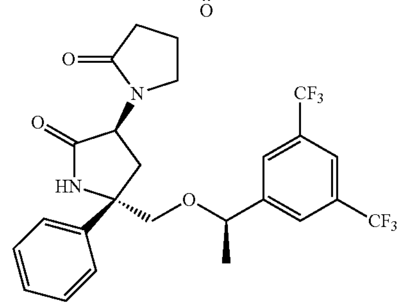


-continued

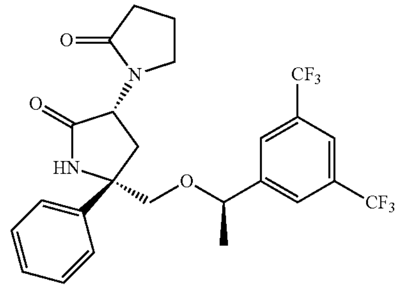
Example 6b







Compound 13a



Compound 13b

[0224] To a solution of amino-lactam Compound 5 (0.100 g. 0.224 mmol, 1 equiv) in toluene (7 ml) at 0° C., was added a solution of 2M $AlMe_3$ in toluene (0.14 ml, 0.28 mmol, 1.25 equiv). The reaction mixture was warmed to RT and stirred for 15 min. Ethyl 4-bromobutyrate was added, and the resulting mixture was heated at 100° C. for 18 h. The reaction mixture was cooled to RT, poured into EtOAc (20 ml), and washed with of saturated aqueous $NaHCO_3$ (100 ml) and saturated aqueous NaCl (100 ml) successively. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. HPLC separation on ChiralCel OD column using a (90/10) hexane/IPA mixture gave the Compound 13a (40 mg, 35%), and the Compound 13b (20 mg, 18%).

[0225] Electrospray MS $[M+1]^+$ 515.1 for the Compound 13a.

[0226] Electrospray MS $[M+1]^+$ 515.1 for the Compound 13b.

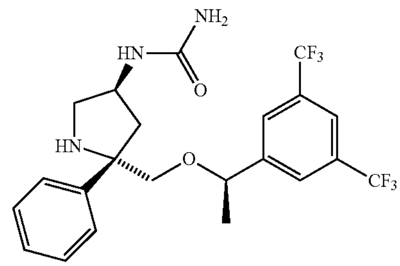
[0227] Example 6a and Example 6b were prepared using a procedure similar to Compound 6, using Compound 13a and 13b instead of Compound 5.

[0228] Electrospray MS $[M+1]^+$ 487.11 for the Example 6a.

[0229] Electrospray MS $[M+1]^+$ 487.11 for the Example 6b.

Example 7

[0230]

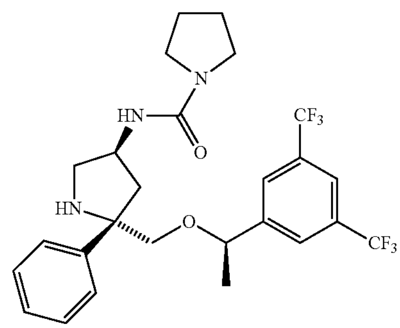


[0231] Example 7 (74% overall yield) was prepared from Compound 10 in a manner similar to that used to prepare Example 29 from Example 13.

[0232] Electrospray MS $[M+1]^+$ 476.1.

Example 8

[0233]

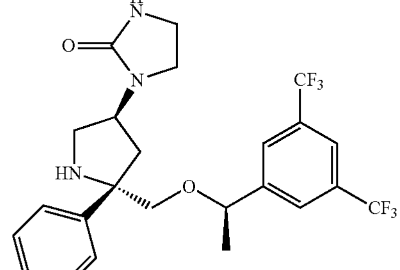


[0234] Example 8 (94% overall-yield) was prepared from Compound 10 in a manner similar to that used to prepare Example 33 from Example 13.

[0235] Electrospray MS $[M+1]^+$ 430.1.

Example 9

[0236]

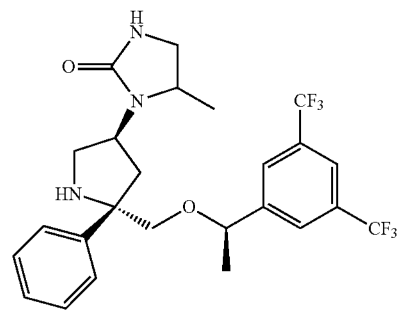


[0237] Example 9 (50% overall yield) was prepared from Compound 10 in a manner similar to that used to prepare Example 36 from Example 13.

[0238] Electrospray MS $[M+1]^+$ 502.1.

Example 10

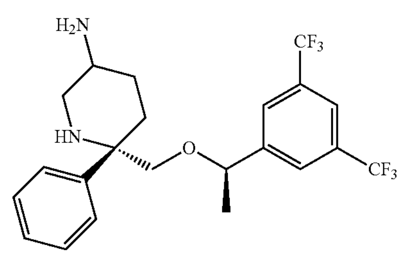
[0239]



[0240] To a solution of Compound 10 (0.15 g, 0.3 mmol, 1 equiv) in CH_2Cl_2 (2 ml) was added methyl levulinate (0.041 ml, 0.33 mmol, 1.1 equiv) followed by sodium triacetoxyborohydride (0.127 g, 0.6 mmol, 2 equiv.) and the reaction mixture was stirred at 23° C. and stirred for 72 h. The reaction was quenched with saturated aq. $NaHCO_3$ (100 ml) and extracted with EtOAc (200 ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The mixture was purified by chromatography over Gilson (1:9, water:CH_3CN) to give the title compound (0.070 g, 47%). (Electrospray MS $[M+1]^+$ 515.1.

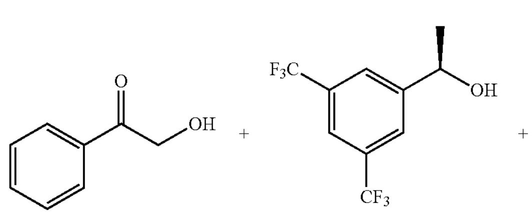
Example 11

[0241]



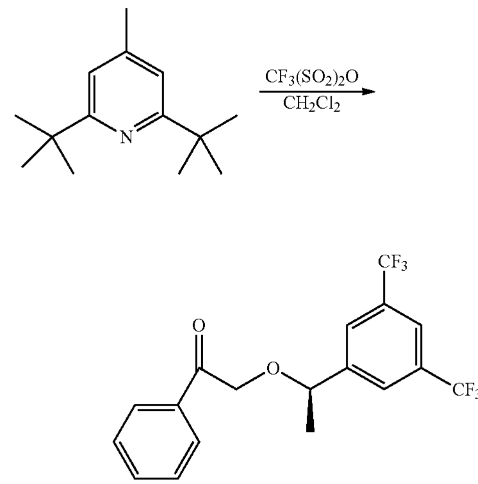
Step 1:

[0242]



compound 14

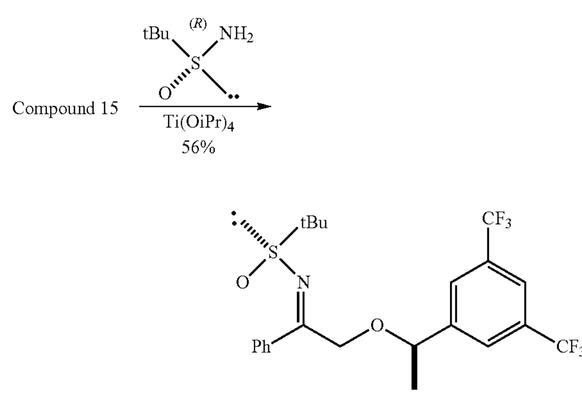
-continued



compound 15

Step 2

[0243]



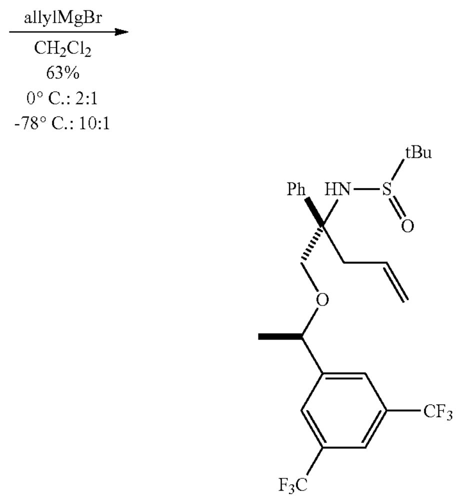
Compound 16

[0244] To a flask containing ketone Compound 15 (1.05 g, 2.8 mmol, 1 equiv) and (R)-t-butylsulfinamide (0.4 g, 3.3 mmol, 1.8 equiv), was applied a vacuum for 5 min. Then, the flask was filled with N_2. $Ti(OiPr)_4$ (1 ml) was added through a syringe dropwise to the reaction mixture. The reaction mixture was stirred at 23° C. for 36 h. The reaction mixture was then poured into brine (10 ml) and EtOAc (20 ml) and stirred vigorously for 10 min. The resulting suspension was passed through a pad of celite 545. The celite pad was washed with EtOAc several times. The combined organic solution was dried and concentrated under reduced pressure. Flash column chromatography afforded Compound 16 (0.75 g, 56%).

Step 3

[0245]

Compound 16



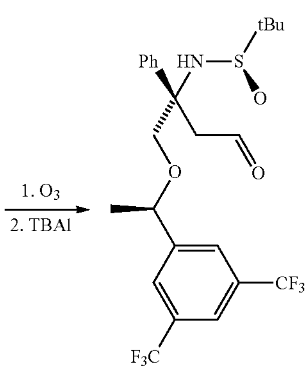
Compound 17

[0246] To a solution of sulfinimine Compound 16 (2.44 g, 5.1 mmol, 1 equiv) in CH_2Cl_2 at −78° C., was added dropwise allylmagnesium bromide (6.1 ml, 6.1 mmol, 1.2 equiv, 1M in Et_2O) through a syringe. After stirring for 3 h at −78° C., the reaction mixture was quenched with a saturated aqueous NH_4Cl and allowed to warm to 23° C. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried and concentrated. Flash column chromatography gave Compound 17 (1.672 g, 63%).

Step 4

[0247]

Compound 17



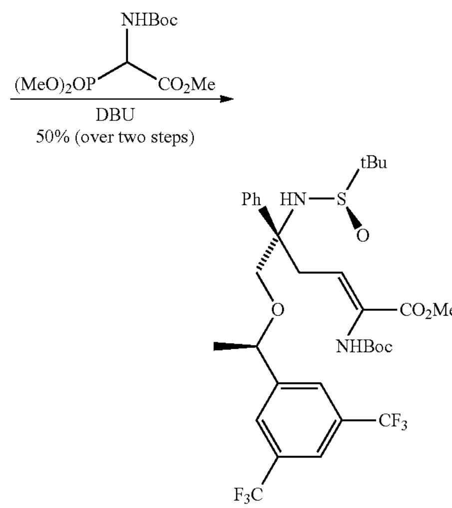
Compound 18

[0248] A 15 ml RBF was charged with Compound 17 (245 mg, 0.47 mmol, 1.0 equiv) and CH_2Cl_2 (2 ml). This pale orange solution was cooled to −78° C., and then O_3 was bubbled in at 1.0 ml/min. After the solution turned pale blue, the reaction solution was stirred at −78° C. for 10 min. Then it was flushed with N_2 to get rid of O_3. Tetrabutylammonium iodide (177 mg, 0.47 mmol, 1.0 equiv) was added to break the complex. Then it was quenched with saturated $Na_2S_2O_3$, and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated, then re-taken up with Et_2O and filtered. The residue on the filter was dissolved in water and extracted with Et_2O. The combined Et_2O layer was dried, filtered and concentrated to give Compound 18 (243.5 mg, 99%). Electrospray MS $[M+1]^+$ 524.1.

Step 5

[0249]

Compound 18



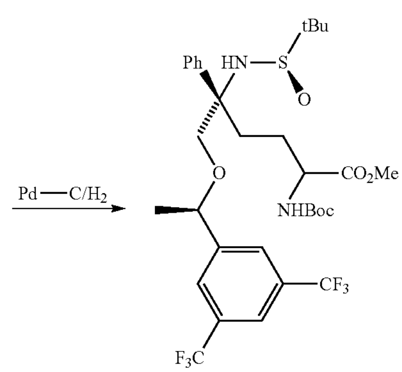
Compound 19

[0250] To a solution of Compound 18 (1.2 g, 2.29 mmol, 1.0 equiv) Boc-Phosphonate (818 mg, 2.75 mmol, 1.2 equiv) in DMF (20 ml) was added Cs_2CO_3 (2.24 g, 6.87 mmol, 3.0 equiv). After stirring at RT for 3 h, the mixture was diluted with Et_2O, and washed with water (100 ml 2×), and brine. The combined aqueous layer was further extracted with Et_2O. The combined organic layer was dried, filtered and concentrated to give crude brownish oil, which was purified by column to give Compound 19 (830 mg, 55%). Electrospray MS $[M+1]^+$ 695.2.

Step 6

[0251]

Compound 19

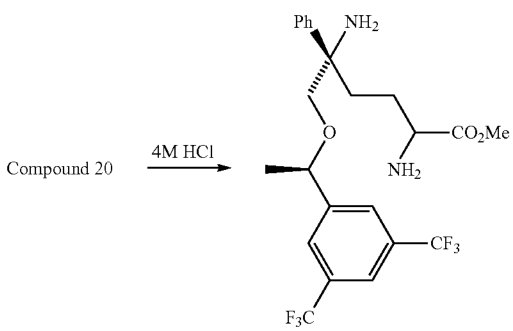


Compound 20

[0252] A solution of Compound 19 (830 mg, 1.19 mmol, 1.0 equiv) in EtOH (20 ml) was flushed with N_2. After the addition of Palladium on carbon (10%. 1.27 g. 1.19 mmol, 1.0 equiv), a H_2 balloon was attached to the reaction flask. The reaction mixture was stirred for almost 24 h until TLC showed completion of the reaction. The mixture was filtered and concentrated to give Compound 20 as white solid (790 mg, 95%). Electrospray MS $[M+1]^+$ 697.2.

Step 7

[0253]

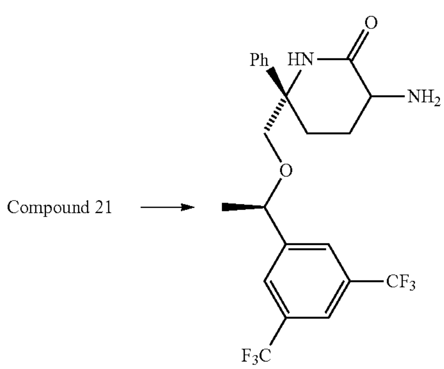


Compound 21

[0254] A solution of Compound 20 (400 mg, 0.57 mmol, 1.0 equiv) in anhydrous MeOH (4 ml) was cooled to 0° C., then treated with 4 M solution of HCl in 1,4-dioxane (16 ml). After 30 min at 0° C., it was stirred at RT for another 3 h. The solvent was evaporated under vacuum to give Compound 21 as pale brown solid. Electrospray MS $[M+1]^+$ 493.1.

Step 8

[0255]



Compound 22

[0256] To a solution of Compound 21 in MeOH (50 ml) was added K_2CO_3 (4.5 g). The mixture was stirred for 30 min, then filtered and concentrated to give Compound 22 (199 mg, 76%). Electrospray MS $[M+1]^+$ 461.1.

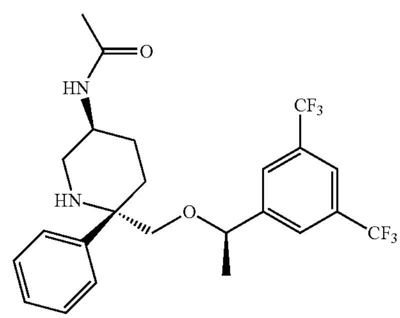
Step 9

[0257] A flame-dried 500 ml RBF was charged with $ALCl_3$ (37.4 mg, 0.28 mmol, 1.5 equiv). The reaction flask was cooled to 0° C. and anhydrous THF (1 ml) was syringed in. After stirred for 5 min, 1M solution of LAH in Et_2O (0.84 ml, 0.84 mmol, 4.5 equiv) was cannulated in. The ice-bath was removed and the solution was stirred at RT for 30 min. Then the reaction mixture was cooled to −78° C. and a solution of Compound 22 (50 mg, 0.187 mmol, 1.0 equiv) in dry THF (1 ml) was slowly added. The reaction mixture was stirred at −78° C., and allowed to warm up to RT overnight. After TLC ($MeOH/CH_2Cl_2$=1/9) indicated the reaction was completed, the reaction was then cooled to 0° C. and diluted with EtOAc and quenched carefully with saturated aqueous sodium potassium tartarate solution. It was stirred at RT for over 30 min to get separation of the two layers. The aqueous layer was further extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give Example 11 (34 mg, 41%). Electrospray MS $[M+1]^+$ 447.1.

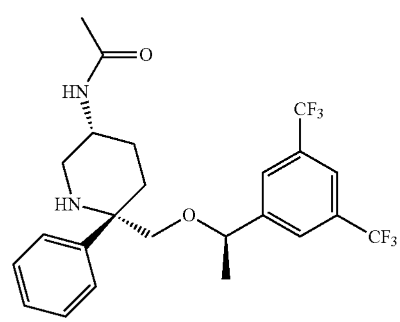
Example 12a and Example 12b

[0258]

Example 12a



Example 12b

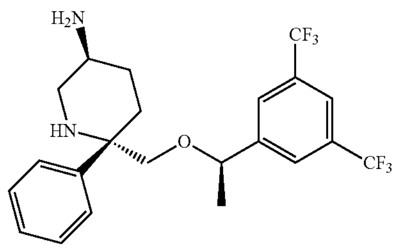


Step 1

[0259] To a solution of Example 11 (30 mg, 0.067 mmol, 1.0 equiv) in CH_2Cl_2 (10 ml) at 0° C. was added DIEA (17.5 µl, 0.10 mmol, 1.5 equiv) and Ac_2O (6.3 µl, 0.067 mmol, 1.0 equiv). The mixture was stirred at 0° C. for 30 min. It was quenched with saturated aqueous $NaHCO_3$ solution (4 ml) and extracted with CH_2Cl_2. The combined organic layers were dried, filtered and concentrated to give the crude product (39 mg). Purification of the mixture by HPLC using ChiralPak AD column (2:98, IPA:hexane) gave more polar isomer Example 12a, Electrospray MS $[M+1]^+$ 489.1, and less polar isomer Example 12b, Electrospray MS $[M+1]^+$ 489.1.

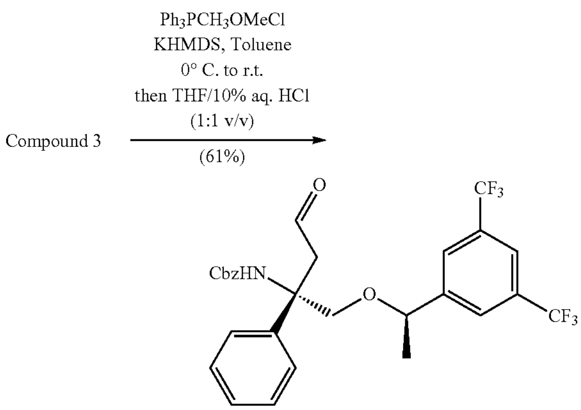
Example 13

[0260]



Step 1

[0261]



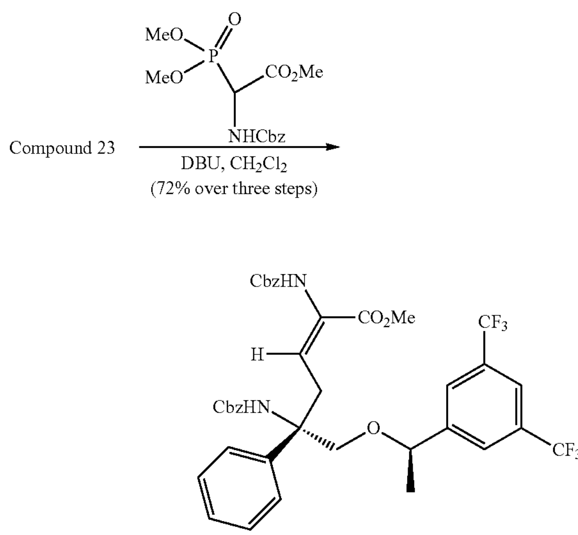
Compound 23

[0262] To a suspension of (methoxymethyl)triphenylphosphonium chloride (21.3 g, 0.062 mmol, 2.95 equiv) in toluene (300 ml) at 0° C. under N_2, a solution of potassium bis(trimethylsilyl)amide (125 ml, 0.062 mmol, 2.95 equiv) was added. After being stirred at 0° C. for 1 h, a solution of Compound 3 (13.4 g, 0.021 mmol, 1 equiv) in toluene (100 ml) was added. The mixture was allowed to stir from 0° C. to 23° C. in 1 h and then was quenched with saturated NH_4Cl solution. Et_2O was added and layers were separated. The separated aqueous layer was extracted with Et_2O (400 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give crude enol ether as yellow oil.

[0263] The crude enol ether was dissolved in THF (100 ml) at 23° C. and aqueous HCl (100 ml, 10% in water) was added. The mixture was stirred overnight and was quenched with saturated $KHCO_3$ solution. Et_2O was added and layers were separated. The separated aqueous layer was extracted with Et_2O (300 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Removal of solvents in vacuum followed by chromatographic purification [hexane:EtOAc, 4:1 (v/v)] gave Compound 23 (6.97 g, 61%) as yellow oil.

Step 2

[0264]



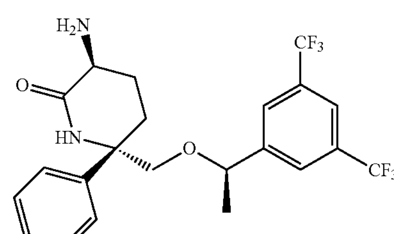
Compound 24

[0265] Compound 24 was prepared from Compound 23 using a procedure similar to the preparation of Compound 4 from Compound 3 and using $PO(OEt)_2CH(NHCbz)CO_2Me$ in place of $PO(OMe)_2CH(NHBoc)CO_2Me$.

Step 3

[0266]

Compound 25



[0267] Compound 25 was prepared using a procedure similar to that for Compound 9 using Compound 24 instead of Compound 7. Electrospray MS $[M+1]^+$461.1.

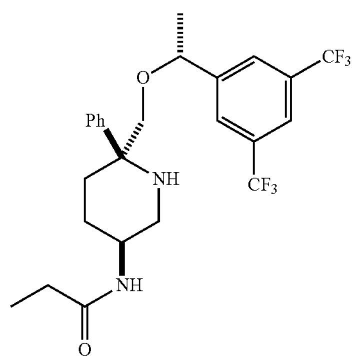
Step 4

[0268] Example 13 (6.84 g, 73%) was prepared using similar procedure to Compound 6 using Compound 25 instead of Compound 5.

[0269] Electrospray MS $[M+1]^+$ 447.1.

Example 14

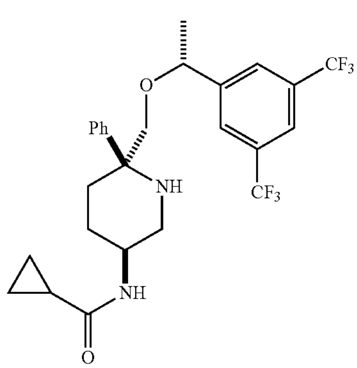
[0270]



[0271] To a solution of Example 13 (275 mg, 0.60 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 ml) at −78° C. was added propionyl chloride (52 μl, 0.60 mmol, 1.0 equiv). The reaction was completed within 30 min. Reaction mixture was quenched with 7N ammonia in MeOH (0.5 ml), then loaded directly onto silica column and purified to give Example 14. (241.3 mg, 80%). Electrospray MS $[M+1]^+$ 503.1.

Example 15

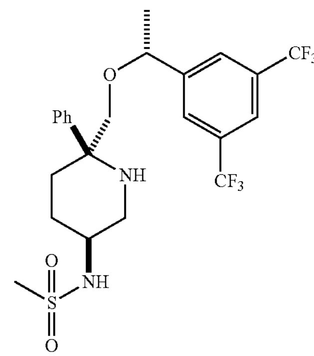
[0272]



[0273] Example 15 (yield 89%) was prepared using similar procedure as for Example 14 using cyclopropanecarbonyl chloride in place of propionyl chloride. Electrospray MS $[M+1]^+$ 515.1.

Example 16

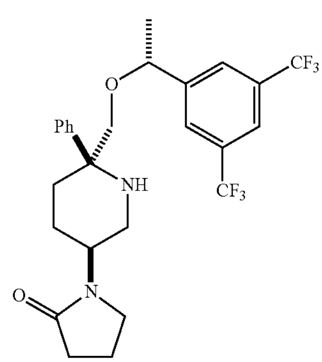
[0274]



[0275] Example 16 (yield 89%) was prepared using similar procedure as for Example 14 using Example 13 and CH_3SO_2Cl in place of propionyl chloride. Electrospray MS $[M+1]^+$ 52.1.

Example 17

[0276]

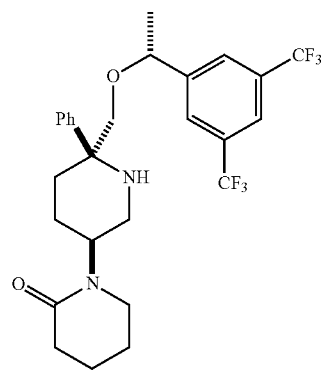


[0277] Example 17 (overall yield 23%) was prepared using similar procedure as for Example 3 using Example 13 in place of Compound 10.

[0278] Electrospray MS $[M+1]^+$ 515.1.

Example 18

[0279]



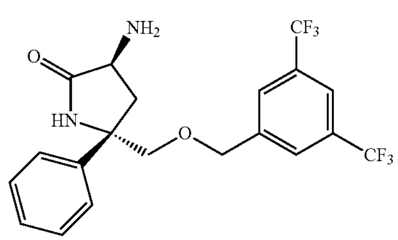
[0280] Example 18 (overall yield 42%) was prepared using similar procedure as for Example 4 using Example 13 in place of Compound 10.

[0281] Electrospray MS $[M+1]^+$ 529.1.

Preparation of Compounds 26, 27, 28 and 29

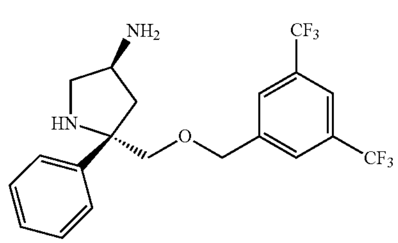
[0282]

Compound 26



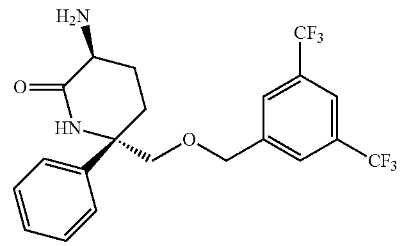
[0283] Compound 26 was prepared from Compound 1 using similar procedure as for Compound 9.

Compound 27



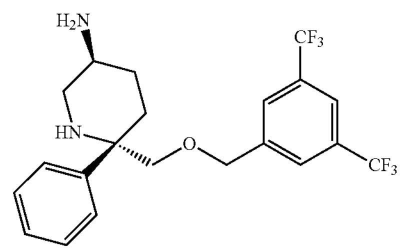
[0284] Compound 27 was prepared using similar procedure as for Compound 10.

Compound 28



[0285] Compound 28 (90% yield) was prepared using the similar procedure for Compound 25. Electrospray MS $[M+1]^+$ 447.1.

Compound 29

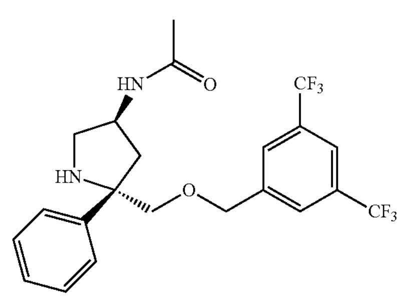


[0286] Compound 29 was prepared using similar procedure as for Example 13.

[0287] Electrospray MS $[M+1]^+$ 433.1.

Example 19

[0288]

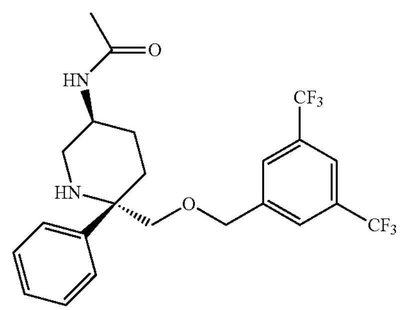


[0289] Example 19 (40 mg, 70% yield) was prepared using a procedure similar to Example 1a using Compound 27 instead of Compound 6.

[0290] Electrospray MS $[M+1]^+$ 461.1.

Example 20

[0291]

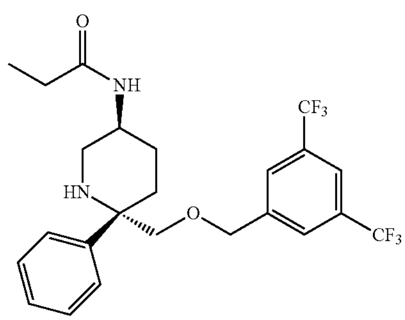


[0292] Example 20 (99 mg, 72%) was prepared using similar procedure as for Example 1a using Compound 29 instead of Compound 6.

[0293] Electrospray MS $[M+1]^+$ 475.1.

Example 21

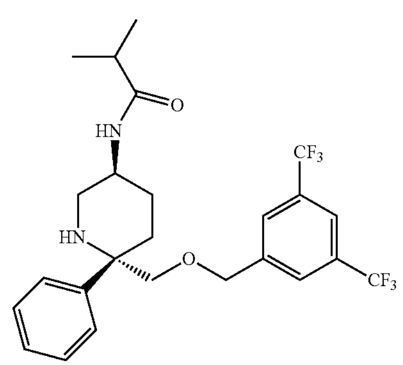
[0294]



[0295] Example 21 (74 mg, 66%) was prepared from Compound 29 using similar procedure as for Example 2 from Compound 10 using propionic anhydride in place of cyclopropanecarbonyl chloride. Electrospray MS $[M+1]^+$ 489.1.

Example 22

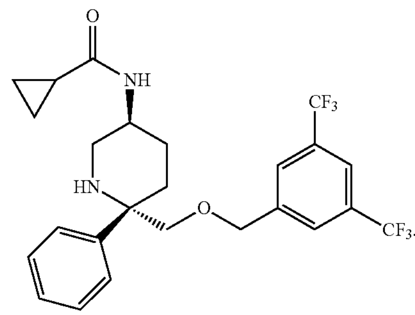
[0296]



[0297] Example 22 (75 mg. 78%) was prepared from Compound 29 using similar procedure as for Example 2 from Compound 10 using isobutyryl chloride in place of cyclopropanecarbonyl chloride. Electrospray MS $[M+1]^+$ 503.1.

Example 23

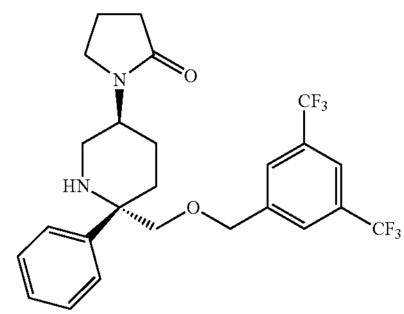
[0298]



[0299] Example 23 (9 mg, 35%) was prepared from Compound 29 using similar procedure as for Example 2 from Compound 10. Electrospray MS $[M+1]^+$ 501.1.

Example 24

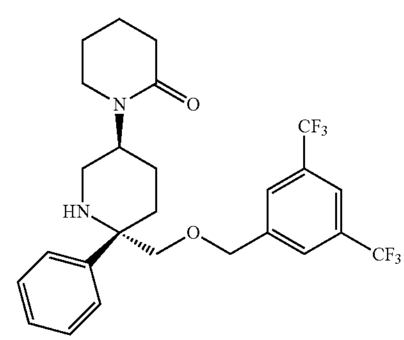
[0300]



[0301] Example 24 (31 mg, 71%) was prepared from Compound 29 using similar procedure as for Example 3 from Compound 10. Electrospray MS $[M+1]^+$ 501.1.

Example 25

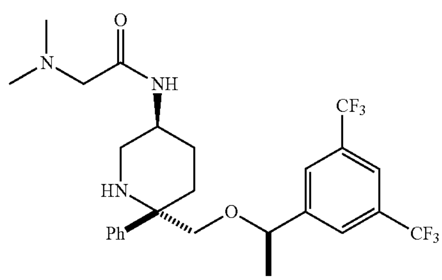
[0302]



[0303] Example 25 (68 mg, 68%) was prepared from Compound 29 using similar procedure as for Example 4 from Compound 10. Electrospray MS $[M+1]^+$ 515.1.

Example 26

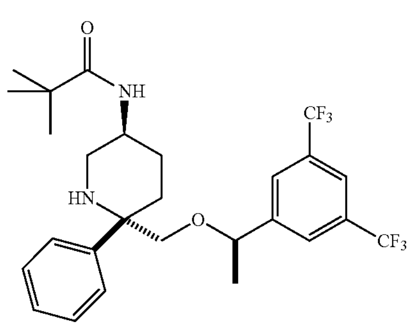
[0304]



[0305] To a solution of Example 13 (0.14 g, 0.314 mmol, 1 equiv) in anhydrous DMF (1.6 ml) at 23° C. was added N,N-dimethyl glycine (33.95 mg. 0.329 mmol, 1.05 equiv) followed by EDC.HCl (66.13 mg, 0.345 mmol, 1.1 equiv) and the reaction mixture was stirred at 23° C. for 18 h. The reaction mixture was diluted with DMF (2.4 ml) and purified using Gilson to give Example 26 (66 mg, 40%). Electrospray MS $[M+1]^+$ 532.1.

Example 27

[0306]

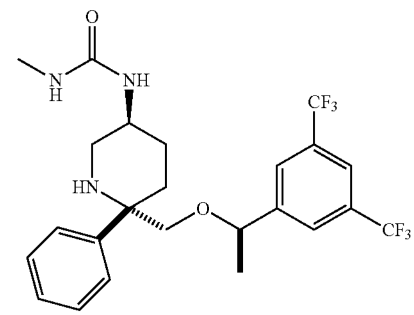


[0307] Example 27 (yield 62%) was prepared using similar procedure as for Example 14 using trimethylacetyl chloride in place of propionyl chloride.

[0308] Electrospray MS $[M+1]^+$ 531.1

Example 28

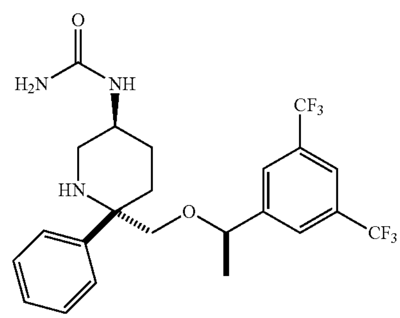
[0309]



[0310] Example 28 (105 mg, 74%) was prepared using similar procedure as for Example 14 using methyl isocyanate, in place of propionyl chloride. Electrospray MS $[M+1]^+$ 504.1

Example 29

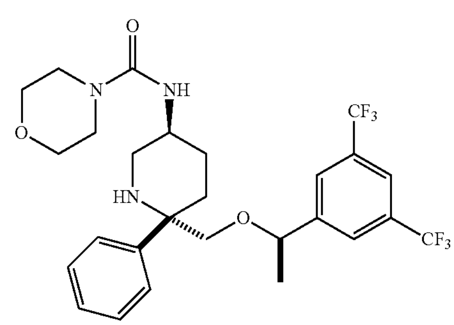
[0311]



[0312] Example 29 (146 mg, 754%) was prepared using similar procedure as for Example 14 using trimethylsilyl isocyanate in place of propionyl chloride. Electrospray MS $[M+1]^+$ 490.1

Example 30

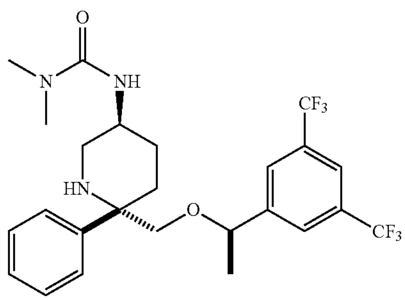
[0313]



[0314] To a solution of Example 13 (100 mg, 0.224 mmol, 1 equiv) in anhydrous CH_2Cl_2 (2 ml) was added 4-morpholinylcarbonyl chloride (28.7 μl, 0.246 mmol, 1.1 equiv) and DIEA (39 μl, 0.223 mmol, 1 equiv). The reaction mixture was stirred at RT overnight. Aqueous work-up and purification by using silica column to afford Example 30 (53 mg, 42%). Electrospray MS $[M+1]^+$ 560.1

Example 31

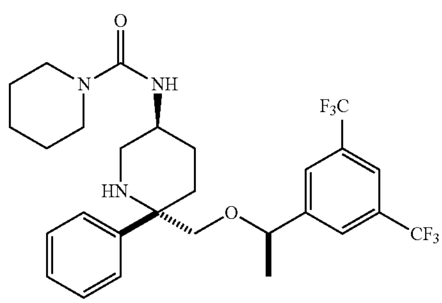
[0315]



[0316] Example 31 (40% yield) was prepared using similar procedure as for Example 30 using dimethylcarbamyl chloride in place of 4-morpholinylcarbonyl chloride. Electrospray MS $[M+1]^+$ 518.1

Example 32

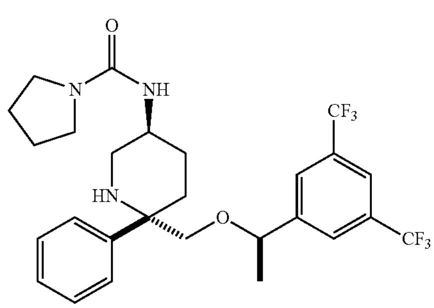
[0317]



[0318] Example 32 (42% yield) was prepared using similar procedure as for Example 30 using 1-piperidinecarbonyl chloride in place of 4-morpholinylcarbonyl chloride. Electrospray MS $[M+1]^+$ 558.1

Example 33

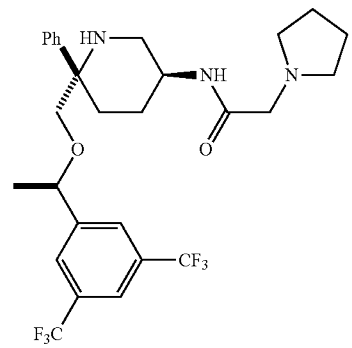
[0319]



[0320] Example 33 (40% yield) was prepared using similar procedure as for Example 30 using 1-pyrrolidinecarbonyl chloride in place of 4-morpholinylcarbonyl chloride. Electrospray MS $[M+1]^+$ 544.1

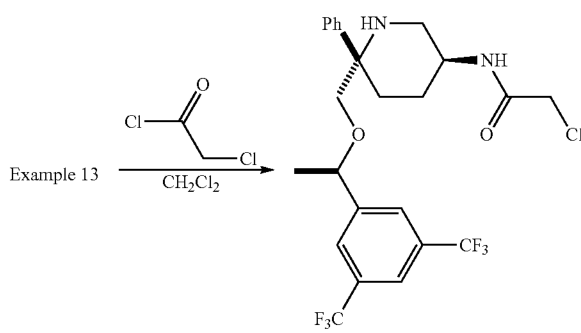
Example 34

[0321]



Step 1

[0322]



Compound 30

[0323] Compound 30 (43% yield) was prepared using similar procedure as for Example 10 using chloroacetyl chloride in place of propionyl chloride.

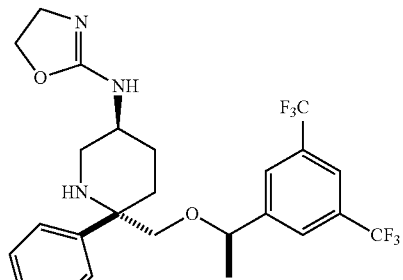
Step 2

[0324] To a solution of Compound 30 (90 mg, 0.17 mmol, 1 equiv) in anhydrous CH_2Cl_2 (0.5 ml) was added pyrrolidine (17.2 μl; 0.206 mmol, 1.2 equiv) and DIEA (30 μl, 0.17 mmol, 1 equiv). The reaction mixture was stirred at RT overnight. Aqueous work-up and purification by using silica column to afford Example 34 (45 mg, 47%). Electrospray MS $[M+1]^+$ 558.1.

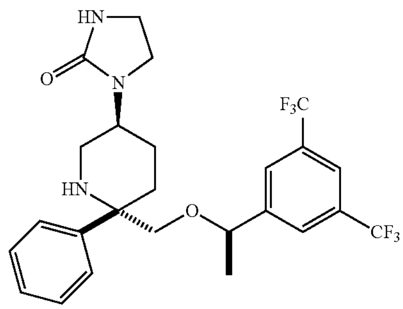
Example 35 Example 36

[0325]

Example 35

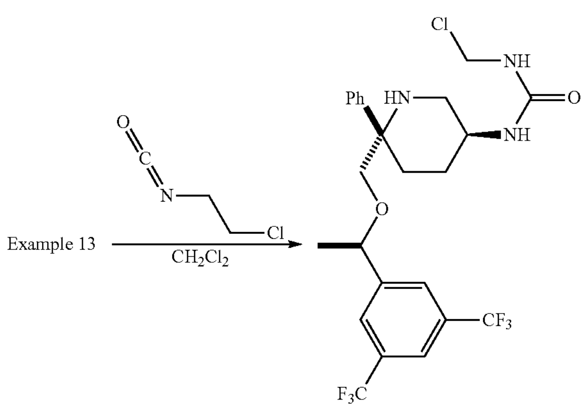


Example 36



Step 1

[0326]



Compound 31

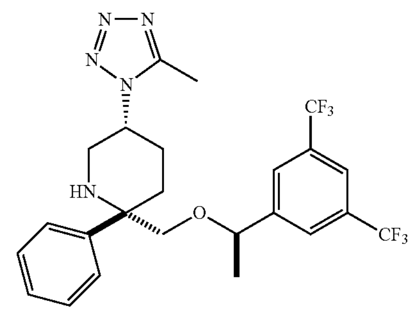
[0327] Compound 31 was prepared using similar procedure as for Example 14 using 2-chloroethyl isocyanate in place of propionyl chloride.

Step 2

[0328] To a solution of Compound 31 in anhydrous THF (7 ml), was added NaH (25 mg, 0.625 mmol, 1.7 equiv, 60% dispersion in mineral oil) at 0° C. The resulting cloudy solution was heated at 60° C. for 2 h. Aqueous work-up to give the crude product which was purified by silica gel column to give the less polar title compound Example 35 (10 mg, 5.4%), Electrospray MS $[M+1]^+$ 516.1; and the more polar title compound Example 36 (122 mg, 66%), Electrospray MS $[M+1]^+$516.1

Example 37

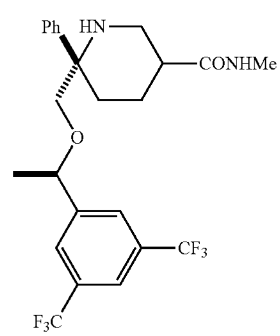
[0329]



[0330] To a solution of Example 12b (200 mg, 0.41 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1 ml) at 0° C., was added trifluoromethanesulfonic anhydride (69 μl, 0.41 mmol, 1 equiv). The reaction mixture was stirred for 40 min before NaN_3 (26.6 mg, 0.41 mmol, 1 equiv) was added. The mixture was warmed up to RT for 2 h. The solvent was removed in vacuum. The residue was purified with prep-TLC (silica) to obtain Example 37 (4.5 mg, 2%). Electrospray MS $[M+1]^+$ 514.1

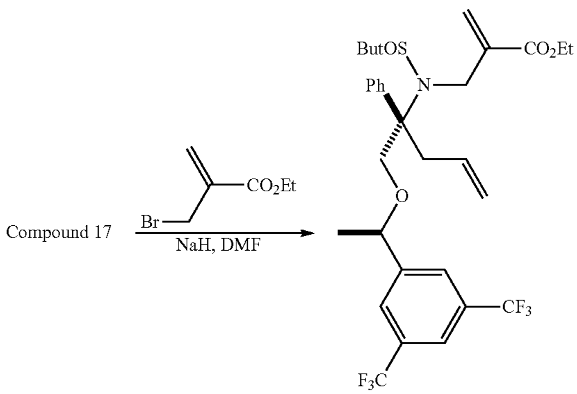
Example 38

[0331]



Step 1

[0332]

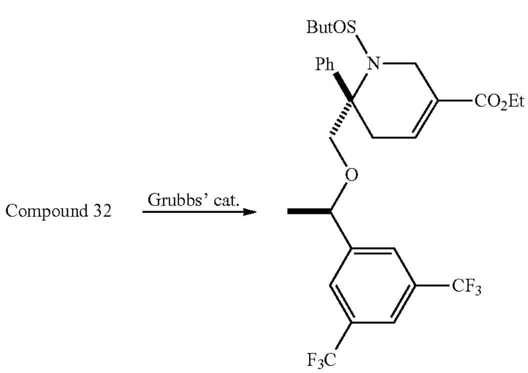


Compound 32

[0333] To Compound 17 (0.3 g, 0.575 mmol, 1 equiv) under N_2 in anhydrous DMF (3 ml) at 0° C. was added NaH (27.6 mg, 0.69 mmol, 1.2 equiv, 60% in mineral oil) and the reaction mixture was stirred for 1 h. To the resulting suspension under vigorous stirring was dropwise added ethyl-2-bromomethylacrylate (0.088 ml, 0.629 mmol, 1.1 equiv). The reaction mixture was allowed to warm to 23° C. and stirred for 18 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. The crude product was purified using flash silica gel column to give titled Compound 32 (0.199 g, 55%).

Step 2

[0334]

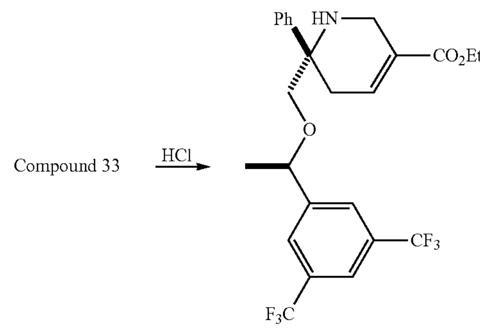


Compound 33

[0335] To a solution of Compound 32 (50 mg, 0.078 mmol, 1 equiv) in anhydrous CH_2Cl_2 (0.8 ml) under N_2 was added Grubbs' catalyst tricyclohexylphosphine [1,3-bis(2,4,6-trimethyl-phenyl)-4,5-dihydro-imidazol-2-ylidene][benzytidine]ruthenium(IV) dichloride (6.7 mg, 0.0079 mmol, 0.1 equiv). The resulting brown solution was heated at 40-45° C. for 2 h. The solvent was then removed and the residue was purified on a silica gel column to afford the titled Compound 33 (60 mg, 63%). Electrospray MS $[M+1]^+$ 502.1.

Step 3

[0336]

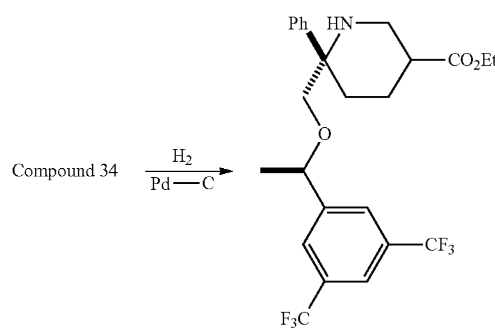


Compound 34

[0337] To a solution of Compound 33 (30 mg, 0.05 mmol, 1 equiv) in absolute MeOH (0.5 ml) at 0° C. was added a solution of 4N HCl in dioxane (0.5 ml). The resulting solution was stirred at 0° C. for 4 h. The solvent was then removed and the residue was dissolved in CH_2Cl_2 and passed through a short K_2CO_3 column. The residue of Compound 34 was taken directly to the next step without further purification.

Step 4

[0338]



Compound 35

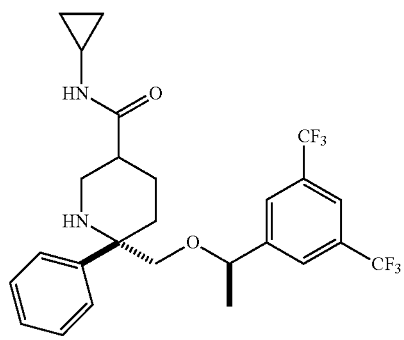
[0339] A solution of Compound 34 (30 mg, 0.06 mmol) in EtOH (5 ml) was treated with 10% Pd—C (32 mg, 0.03 mmol) and was hydrogenated at 60 psig for 18 h. The catalyst was filtered and washed with EtOAc. The filtrate was concentrated and the resulting residue of Compound 35 was taken directly to the next step without further purification.

Step 5

[0340] To a mixture of methylamine HCl salt (52 mg, 0.77 mmol, 12.8 equiv) in toluene (0.2 ml) was added Me_3Al (2M in toluene, 0.36 ml, 0.72 mmol) and the resulting mixture stirred for 30 min. A solution of Compound 35 (30 mg, 0.06 mmol) in toluene (0.5 ml) was added to the reaction mixture via syringe. The resulting solution was heated at 100° C. for 18 h. The reaction mixture was then poured into saturated aq. Na/K tartarate solution (10 ml), stirred for 10 min and extracted with EtOAc (4×10 ml). The combined organic layers were washed with brine and concentrated. The residue was subjected to prep TLC to afford the less polar isomer, Example 38a, Electrospray MS $[M+1]^+$ 489.1 and the more polar isomer, Example 38b, Electrospray MS $[M+1]^+$ 489.1.

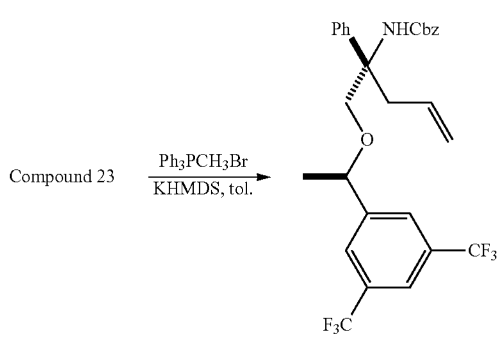
Example 39

[0341]



Step 1

[0342]

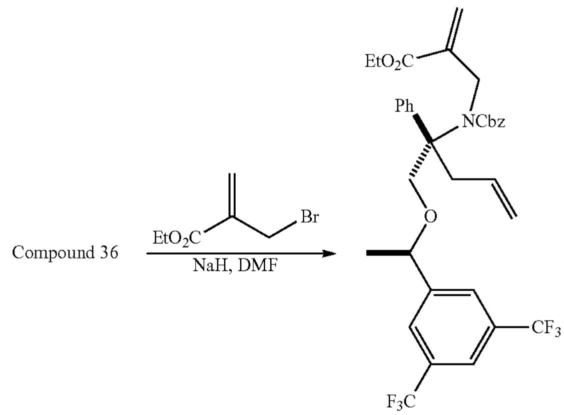


Compound 36

[0343] Compound 36 (yield 63%) was prepared from Compound 23 using the procedure similar to the preparation of Compound 23 from Compound 3 and using methyltriphenyl-phosphonium bromide in place of (methoxymethyl) triphenylphosphonium chloride.

Step 2

[0344]

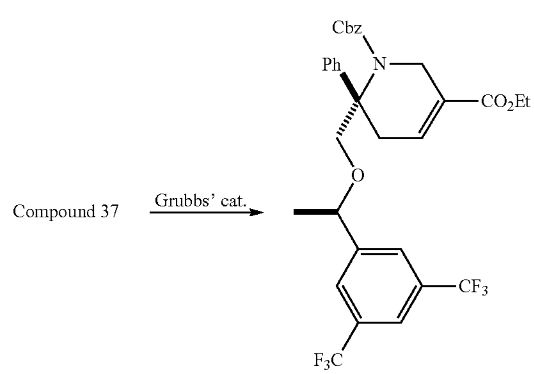


Compound 37

[0345] Compound 37 (50% yield) was prepared using similar procedure as for Compound 32 using Compound 36 in place of Compound 17.

Step 3

[0346]

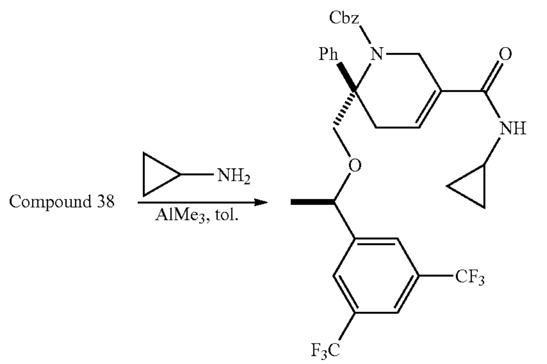


Compound 38

[0347] To a solution of Compound 37 (2.46 g. 3.71 mmol, 1 equiv) in anhydrous CH_2Cl_2 (50 ml) under N_2 was added Grubbs' catalyst (327 mg, 0.385 mmol, 0.1 equiv). The resulting brown solution was heated at 40-45° C. overnight. The solvent was then removed and the residue was purified on a silica gel column to afford Compound 38 (2.1 g, 89%).

Step 4

[0348]



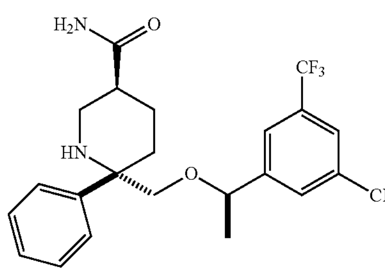
Compound 39

[0349] To a mixture of cyclopropylamine (0.24 ml, 3.45 mmol, 4.2 equiv) in toluene (1.0 ml) was added Me_3Al (2M in toluene, 1.71 ml, 3.41 mmol, 4.2 equiv) and the resulting mixture stirred for 30 min. A solution of Compound 38 (516 mg, 0.82 mmol, 1 equiv) in toluene (2.5 ml) was added to the reaction mixture via syringe. The resulting solution was heated at 60° C. for 18 h. The reaction mixture was then poured into saturated aq. Na,K tartarate solution, stirred for 10 min and extracted with EtOAc (10 ml×4). The combined organic layers were washed with brine and concentrated. The residue was purified on silica column to afford Compound 39 (360 mg, 68%).

Step 5

[0350] A solution of Compound 39 (360 mg, 0.556 mmol, 1 equiv) in EtOH (25 ml) was treated with 10% Pd—C (641 mg, 0.613 mmol, 1.1 equiv) and was hydrogenated at 50 psi for 6 h. The catalyst was filtered and washed with EtOAc. The residue was purified by silica gel column to afford the less polar isomer, Example 39a (54 mg, 19%) Electrospray MS $[M+1]^+$ 515.1, and the more polar Isomer, Example 39b (22 mg, 8%) Electrospray MS $[M+1]^+$ 515.1

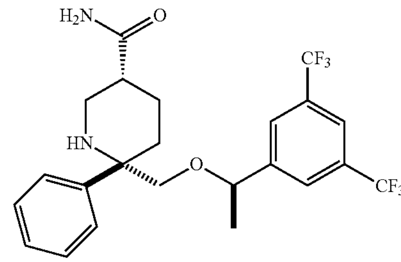
Example 40a



and

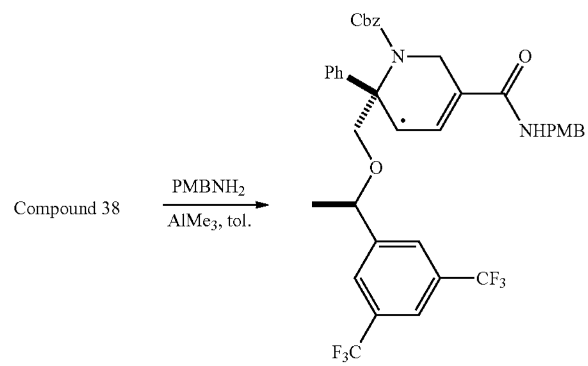
-continued

Example 40b



Step 1

[0351]

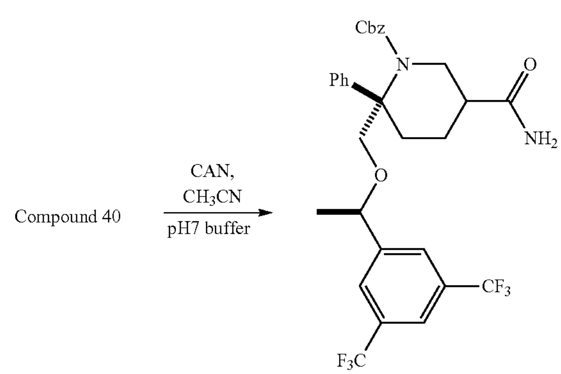


Compound 40

[0352] Compound 40 (yield 55%) was prepared using similar procedure as for Compound 39 using para-methoxylbenzylamine in place of cyclopropylamine.

Step 2

[0353]



Compound 41

[0354] A solution of Compound 40 (1 g, 1.38 mmol, 1 equiv) in CH_3CN (10 ml) and pH7 buffer (3 ml) was treated with ammonium cerium(IV) nitrate (2.17 g, 3.96 mmol, 2.9 equiv) at RT for 2 h. Aqueous work-up gave the crude product which was purified by silica gel column to give Compound 41 (760 mg, 91%).

Step 3

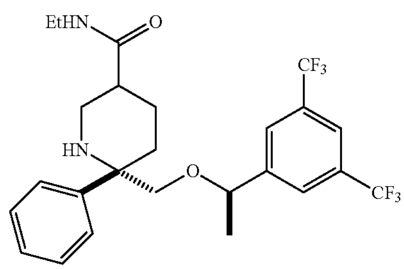
[0355] Example 40a and Example 40b were prepared using a similar procedure as for Example 39a and Example 39b using Compound 41 instead of Compound 39.

[0356] Electrospray MS $[M+1]^+$ 475.1 for the Example 40a (less polar isomer);

[0357] Electrospray MS $[M+1]^+$ 475.1 for the Example 40b (more polar isomer).

Example 41

[0358]



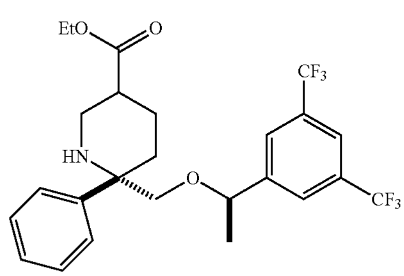
Example 41a and Example 41b were prepared using a similar procedure as for Example 38a and Example 38b using ethylamine instead of methylamine.

[0359] Electrospray MS $[M+1]^+$ 503.1 for the Example 41a (less polar isomer);

[0360] Electrospray MS $[M+1]^+$ 503.1 for the Example 41b (more polar isomer).

Example 42

[0361]

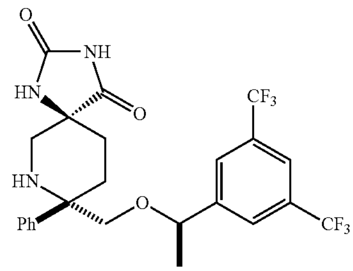


[0362] The mixture of two isomers of Compound 35 was separated by column chromatography to give pure Example 42a and Example 42b

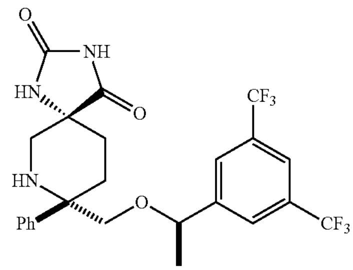
[0363] Electrospray MS $[M+1]^+$ 504.1 for the Example 42a (less polar isomer);

[0364] Electrospray MS $[M+1]^+$ 504.1 for the Example 42b (more polar isomer).

Example 43a

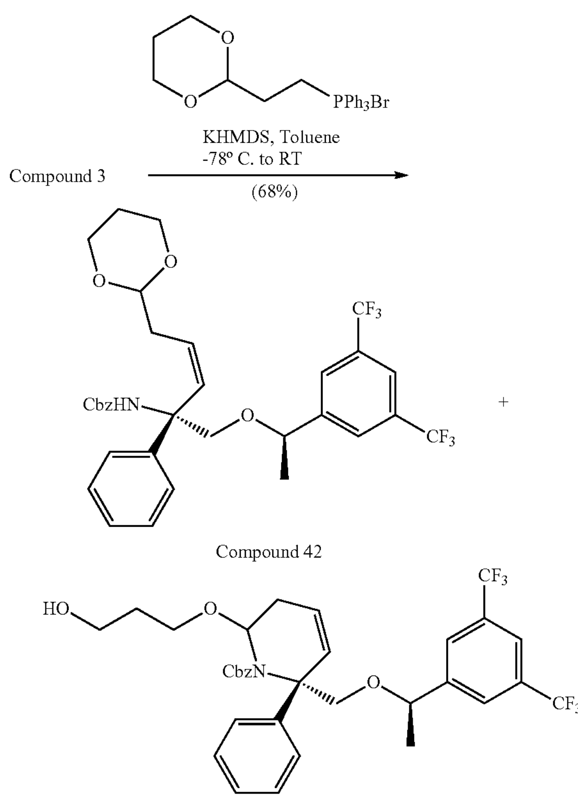


Example 43b



Step 1

[0365]



Compound 42

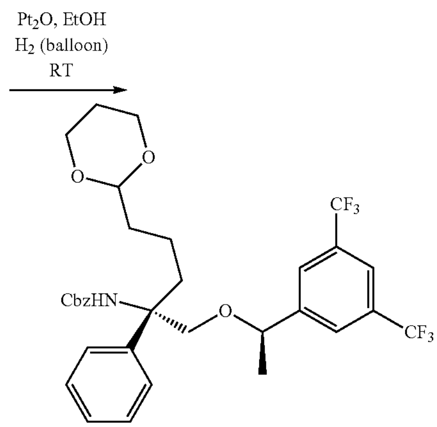
Compound 43
(minor)

[0366] To a suspension of lactol Compound 3 (60 g, 93.0 mmol, 1 equiv.) and Wittig Reagent (93.5 g, 200.0 mmol, 2.15 equiv.) in toluene (800 ml) stirred at −78° C. under N_2, a solution of KHMDS (0.5M in toluene, 558 ml, 280.0 mmol, 3 equiv.) was added dropwise at −78° C. The cooling bath was removed and the yellow mixture was warmed to RT to form a red solution. The mixture was allowed to stir at 23° C. for further 1 h before being quenched with saturated NH_4Cl solution. EtOAc was added and layers were separated. The separated aqueous layer was extracted with EtOAc (2×500 ml). The combined organic layers were dried ($MgSO_4$) and filtered. Removal of solvents in vacuum followed by Biotage column chromatography [5% EtOAc-hexane to 10% EtOAc-hexane] gave alkene Compound 42 as white solid (40.5 g, 68%), Electrospray MS $[M+1]^+$ 638.1. Continuous elution gave an impure cyclized product Compound 43.

Step 2

[0367]

Compound 42



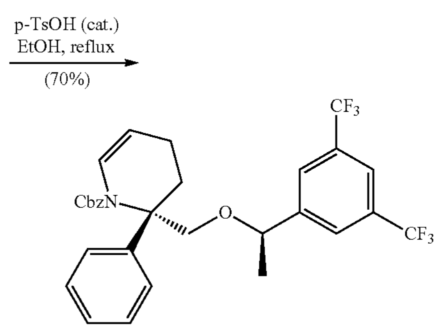
Compound 44

[0368] A suspension of alkene Compound 42 (40.5 g, 64 mmol, 1 equiv.) and PtO_2 (1.44 g, 6.4 mmol, 0.1 equiv.) in EtOH (400 ml) were stirred under a H_2 balloon at 23° C. for 24 h. Another batch of PtO_2 (1.44 g, 6.4 mmol, 0.1 equiv) was added and the mixture was stirred for another 24 h at 23° C. The catalyst was filtered via a pad of Celite. This solution of alkane Compound 44 was used in the next step without further purification.

Step 3

[0369]

Compound 44



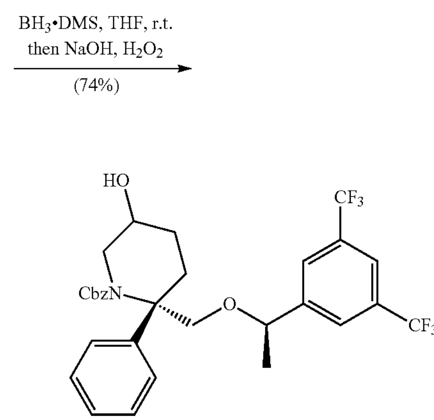
Compound 45

[0370] p-TsOH.H_2O (2.42 g, 13.0 mmol) was added to the ethanolic solution of alkane Compound 44 from above and the solution was heated to reflux for 4 h. The solution was cooled to RT and neutralized with Et_3N. Solvents were removed in vacuum and EtOAc was added. Saturated $NaHCO_3$ solution was added and layers were separated. The separated aqueous layer was extracted with EtOAc (300 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Removal of solvents in vacuum followed by Biotage column chromatography [10% ether-hexane] gave enamide Compound 45 (first batch) as yellow oil. Some intermediate and starting material were recovered as yellow oil by continuous elution with [50% EtOAc-hexane]. The yellow oil was dissolved in toluene and 10 mol % p-TsOH was added. The mixture was heated to reflux for 2 h and cooled to RT. Work up was as above and the combined enamide Compound 45 (25 g, 70%), Electrospray MS $[M+1]^+$ 564.1, was obtained as yellow oil.

Step 4

[0371]

Compound 45



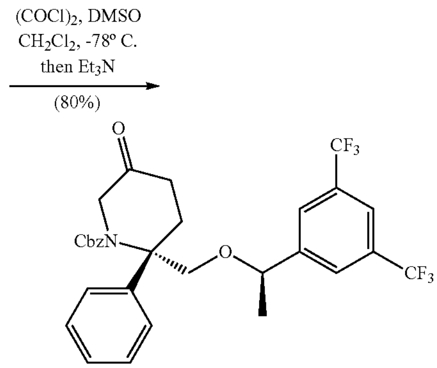
Compound 46

[0372] $BH_3.Me_2S$ (13.6 ml, 133 mmol, 3.02 equiv) was added to a solution of enamide Compound 45 (25 g, 44.0 mmol, 1 equiv.) in THF at 23° C. under N_2. The mixture was stirred at 23° C. for 18 h and then cooled over an ice-water bath. A solution of NaOH (500 ml, 2N) was added slowly followed by a solution of H_2O_2(500 ml, 30% aqueous). The mixture was allowed to stir from 0° C. to 23° C. for 18 h. Layers were separated and the separated aqueous layer was extracted with Et_2O (500 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Removal of solvents in vacuum followed by Biotage column chromatography [hexane-EtOAc, 3:1 (v/v)] gave alcohol Compound 46 as colorless oil (19 g. 74%), Electrospray MS [M+1]j 582.1.

Step 5

[0373]

Compound 46



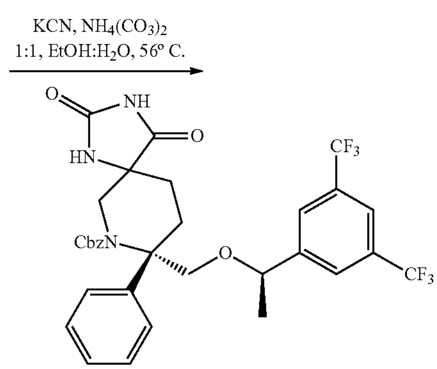
Compound 47

[0374] Oxalyl chloride (5.7 ml, 65.3 mmol, 2 equiv.) was added to a solution of DMSO (9.3 ml, 131.0 mmol, 4 equiv.) in CH_2C_2(300 ml) at −78° C. under N_2. The mixture was stirred at −78° C. for 15 min before a solution of alcohol Compound 46 (19 g, 32.7 mmol. 1 equiv.) in CH_2Cl_2 (50 ml) was added. The mixture was stirred at −78° C. for a further 1 h and Et_3N (32 ml, 228.9 mmol, 7 equiv.) was added. The cooling bath was removed and the mixture was warmed to RT before it was quenched with saturated $NaHCO_3$ solution. Layers were separated and the aqueous was extracted with CH_2Cl_2 (300 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Removal of solvents in vacuum followed by Biotage column chromatography [hexane-ether, 4:1 (v/v)] gave ketone Compound 47 as colorless oil (15 g, 80%), Electrospray MS $[M+1]^+$580.1.

Step 6

[0375]

Compound 47



Compound 48

[0376] EtOH (150 ml) was added to Cbz-ketone Compound 47 (15 g, 25.88 mmol, 1 equiv.), followed by $NH_4(CO_3)_2$(9.95 g, 103.5 mmol, 4 equiv.) and a solution of KCN (3.4 g, 51.77 mmol, 2 equiv.). The resulting mixture was heated at 58° C. under N_2 for 72 h. TLC (1:1 EtOAc:hexane) revealed complete consumption of the starting material. The reaction mixture was cooled to RT and poured into sat. aq. $NaHCO_3$ (200 ml) and extracted with EtOAc (3×200 ml). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford crude Cbz-hydantoin Compound 48 (16.5 g, 98%). Electrospray MS $[M+1]^+$ 650.1. The crude material was used in the next reaction without further purification.

Step 7

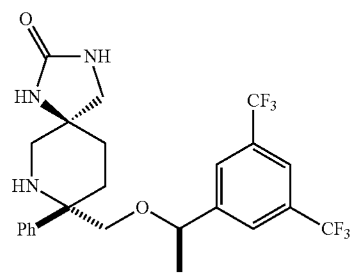
[0377] The crude Cbz-hydantoin Compound 48 (16.5 g, 25.4 mmol, 1 equiv.) was dissolved in MeOH (220 ml) and 20% $Pd(OH)_2$—C (3.6 g) was added. The reaction mixture was shaken in a parr shaker under H_2 atmosphere at 40 psi for 18 h. TLC (1:1 EtOAc:hexane) revealed complete consumption of the starting material. The reaction mixture was filtered through a pad of celite and the celite was washed with MeOH. The resulting solution was concentrated in vacuo. The crude product was purified by column chromatography on a Biotage (3:2, EtOAc:hex). Two major spots were collected. The less-polar spot corresponds to the isomer Example 43a (3 g. overall 20% over two steps), Electrospray MS $[M+1]^+$ 516.1. The more polar spot corresponds to the isomer Example 43b (4.5 g, overall 30% over two steps),

[0378] Electrospray MS $[M+1]^+$ 516.1.

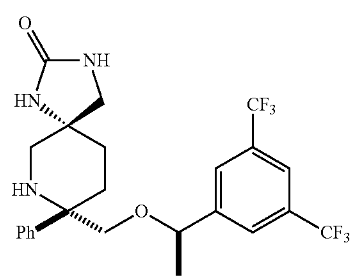
Examples 44a and 44b

[0379]

Example 44a



Example 44b



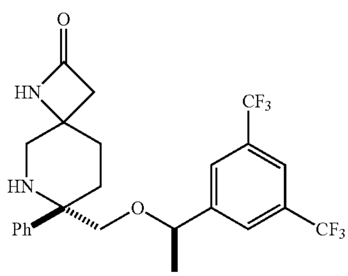
[0380] A flame-dried 25 ml RBF was charged with $AlCl_3$ (0.01 g, 0.776 mmol, 4 equiv). The reaction flask was cooled to 0° C. and 1M solution of LAH in Et_2O (0.58 ml, 0.58 mmol, 3 equiv) was added. The mixture was stirred at 0° C. for 10 min and then a solution of Example 43b (0.1 g, 0.194 mmol, 1 equiv.) in dry THF (3 ml) was slowly added via cannula. The reaction mixture was stirred at 0° C. for 1 h and then allowed to warm up to RT stirred for 18 h. The reaction was then cooled to 0° C. and quenched carefully with saturated aqueous sodium potassium tartarate solution. It was then stirred at 0° C. for over 30 min. The mixture was extracted with EtOAc (2×200 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on a Biotage (1:9, MeOH:EtOAc) to afford Example 44b (0.066 g, 68%). Electrospray MS $[M+1]^+$ 502.1.

[0381] Example 44a was prepared from Example 43a using the procedure described for the preparation of Example 44b from Example 43b.

[0382] Electrospray MS $[M+1]^+$ 502.1 for the Example 44a.

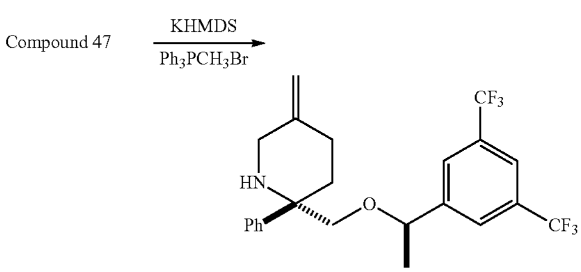
Example 45

[0383]



Step 1

[0384]



Compound 49

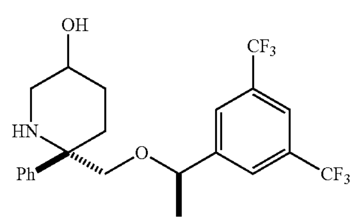
[0385] To a suspension of (methyl)triphenylphosphonium bromide (0.37 g, 1.04 mmol, 3 equiv) in toluene (5 ml) at 0° C. under N_2, a solution of KHMDS (1.73 ml, 0.863 mmol. 2.5 equiv) was added. After being stirred at 0° C. for 1 h, a solution of Compound 47 (0.2 g. 0.35 mmol, 1 equiv) in toluene (7 ml) was added. The mixture was stirred at 0° C. for 1.5 h and then quenched with saturated $NaHCO_3$ (150 ml). The mixture was extracted with EtOAc (100 ml×3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography on a Biotage (4:1, hexane:EtOAc) to afford Compound 49 (0.196 g, 98%).

Step 2

[0386] To a solution of Compound 49 (0.196 g, 0.34 mmol, 1 equiv) in dry Et_2O (3 ml) at 0° C. was added chlorosulfonylisocyanate (0.045 ml, 0.51 mmol, 1.5 equiv). The reaction mixture was stirred at 0° C. for 1 h and then warmed to 23° C. Another equivalent of chlorosulfonylisocyanate was added and the mixture was stirred 23° C. for 18 h. The reaction mixture was diluted with Et_2O (12 ml), 10% aqueous Na_2SO_3 solution was added and pH of the reaction mixture was adjusted to 8 using 2M aqueous KOH solution. The mixture was stirred for 1.5 h and then washed with brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography on a Biotage (2:1, hexane:EtOAc) to afford the crude NCbz-lactam product (20 mg) which was converted to mixture of desired products Example 45a and 45b using a procedure similar to the preparation of Example 43a and Example 43b from Compound 48. The mixture of two products was separated on prep. plate (5:95, MeOH:EtOAc) to afford the less polar isomer. Example 45a (0.006 g, 3.5% over four steps), Electrospray MS $[M+1]^+$ 487.1 and the more polar isomer, Example 45b (0.003 g, 1.79% over four steps), Electrospray MS $[M+1]^+$ 487.1.

Examples 46

[0387]



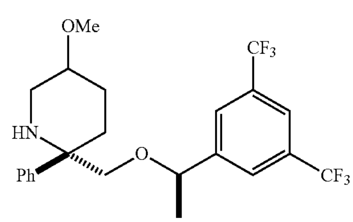
[0388] Example 46a and Example 46b were prepared from Compound 46 using a procedure similar to the preparation of Example 43a and Example 43b from Compound 48.

[0389] Electrospray MS $[M+1]^+$ 448.1 for the Example 46a (less polar isomer);

[0390] Electrospray MS $[M+1]^+$ 448.1 for the Example 46b (more polar isomer).

Example 47

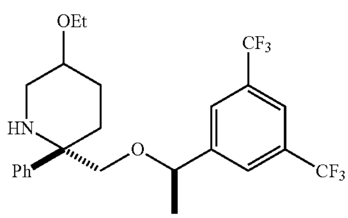
[0391]



[0392] To a solution of NCbz-alcohol Compound 46 (0.125 g, 0.215 mmol, 1 equiv) in dry DMF (3 ml) at 0° C. was added NaH (60% in mineral oil, 0.017 g, 0.43 mmol, 2 equiv). The reaction mixture was stirred at 0° C. for 20 min and then CH_3I (0.04 ml, 0.645 mmol, 3 equiv) added and the mixture was stirred at 23° C. for 18 h. The crude was poured into CH_2Cl_2 (100 ml) and washed with brine (100 ml×2). The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography over Biotage (4:1, hexane:EtOAc) to afford the crude NCbz-methylether product (69 mg) which was hydrogenated to the mixture of desired products Example 47a and 47b using a procedure similar to the preparation of Example 43a and Example 43b from Compound 48. The mixture of two products was purified by column chromatography over Biotage (1:4, hexane:EtOAc) to afford the less polar isomer, Example 47a, Electrospray MS $[M+1]^+$ 462.1 and the more polar isomer, Example 47b, Electrospray MS $[M+1]^+$ 462.1.

Example 48

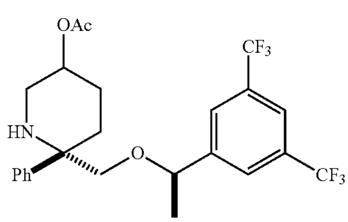
[0393]



[0394] Example 48a and Example 48b were prepared from Compound 46 using the procedure similar to the preparation of Example 47a and Example 47b and using ethyl iodide in place of methyl iodide.

[0395] Electrospray MS $[M+1]^+$ 476.1 for the Example 48a (less polar isomer);

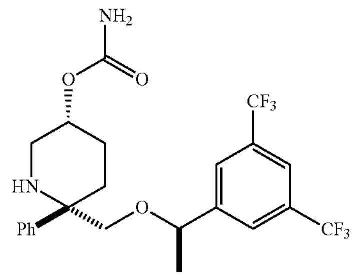
[0396] Electrospray MS $[M+1]^+$ 476.1 for the Example 48b (more polar isomer) Example 49



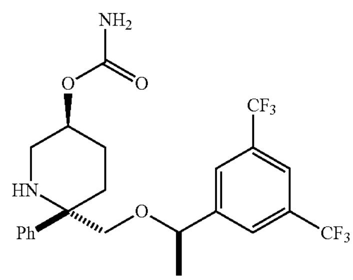
[0397] To a solution of NCbz-alcohol Compound 46 (0.118 g, 0.20 mmol, 1 equiv) in dry CH_2Cl_2 (3 ml) at 0° C. was added dry pyridine (0.026 ml, 0.325 mmol, 1.6 equiv), followed by acetyl chloride (0.023 ml, 0.325 mmol, 1.6 equiv). The reaction mixture was warmed to 23° C. for and stirred for 18 h. The mixture was then concentrated and purified by column chromatography on a Biotage (4:1, hexane:EtOAc) to afford the crude NCbz-acetate product (108 mg) which was hydrogenated to the crude desired product using a procedure similar to the preparation of Example 23a and Example 23b from Compound 48. The crude product was purified by column chromatography on a Biotage (5:95 MeOH:EtOAc) to afford Example 49 (0.079 g, 79% over two steps), Electrospray MS $[M+1]^+$ 490.1.

Examples 50a and 50b

[0398]



Example 50a



Example 50b

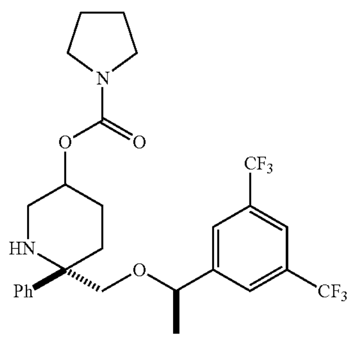
[0399] To a solution of NCbz-alcohol Compound 46 (0.223 g, 0.385 mmol, 1 equiv) in CH_2Cl_2 (8 ml) at 0° C. was added trichloroacetyl isocyanate (0.055 ml, 0.46 mmol, 1.2 equiv). The reaction mixture was stirred at 0° C. for 15 min and then concentrated in vacuo. The residue was dissolved in CH_3OH (7 ml) and water (5 ml) was added. The mixture was cooled to 0° C. and K_2CO_3 (0.16 g. 1.16 mmol, 3 equiv) was added. The reaction mixture was stirred at 0° C. for 1 h and then warmed to 23° C. and stirred for 18 h. The reaction mixture was then concentrated in vacuo and water (100 ml) was added to the residue and the mixture was extracted with CH_2Cl_2 (100 ml×2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford the crude NCbz-carbamate product (232 mg) which was hydrogenated to the mixture of desired products Example 50a and 50b using a procedure similar to the preparation of Example 43a and Example 43b from Compound 48. The mixture of two products was purified by column chromatography over Biotage (1:4, hexane:EtOAc) to afford pure Example 50a and pure Example 50b.

[0400] Electrospray MS $[M+1]^+$ 491.1 for the Example 50a (less polar isomer);

[0401] Electrospray MS $[M+1]^+$ 491.1 for the Example 50b (more polar isomer)

Example 51

[0402]



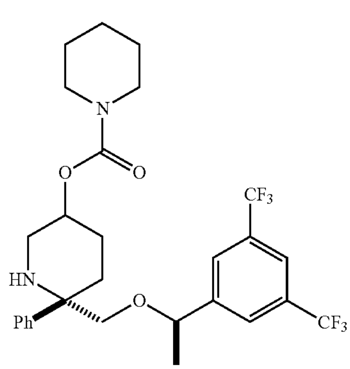
[0403] A mixture of NCbz-alcohol Compound 46 (0.2 g, 0.344 mmol, 1 equiv.), 1,4-dioxane (3 ml), 1-pyrrolidine carbonyl chloride (0.076 ml, 0.69 mmol, 2 equiv.) and dry pyridine (0.084 ml, 1.03 mmol, 3 equiv.) was heated in a sealed tube at 100° C. for 18 h. The reaction mixture was cooled to 23° C. and diluted with EtOAc (150 ml). The mixture was washed with water (l00 ml) and the organic layer was dried (Na_2SO_4), filtered and concentrated to afford the crude NCbz-carbamate product (232 mg) which was hydrogenated to the mixture of desired products Example 51a and 51 b using a procedure similar to the preparation of Example 43a and Example 43b from Compound 48. The mixture of two products was purified by column chromatography over Biotage (2:3, hexane:EtOAc) to afford the less polar isomer, Example 51a and the more polar isomer, Example 51b.

[0404] Electrospray MS $[M+1]^+$ 545.1 for the Example 51a;

[0405] Electrospray MS $[M+1]^+$ 545.1 for the Example 51b.

Example 52

[0406]



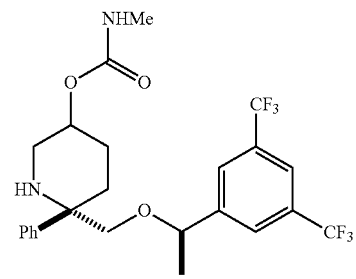
[0407] Example 52a and Example 52b were prepared from Compound 46 using the procedure similar to that used for the preparation of Example 51a and Example 51b and using 1-piperidine carbonyl chloride in place of 1-pyrrolidine carbonyl chloride.

[0408] Electrospray MS $[M+1]^+$ 559.1 for the Example 52a (less polar isomer);

[0409] Electrospray MS $[M+1]^+$ 559.1 for the Example 52b (more polar isomer).

Example 53

[0410]



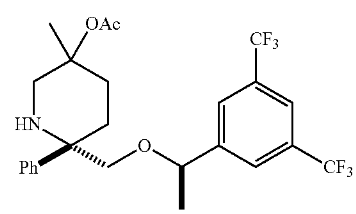
[0411] Example 53a and Example 53b were prepared from Compound 46 using the procedure similar to that used for the preparation of Example 51a and Example 51b and using methylisocyanate in place of 1-pyrrolidine carbonyl chloride.

[0412] Electrospray MS $[M+1]^+$ 505.1 for the Example 53a (less polar isomer);

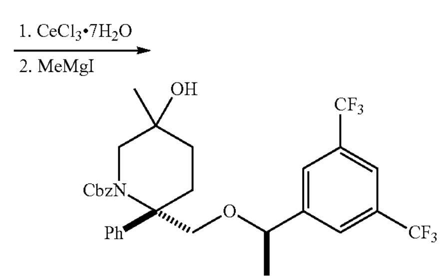
[0413] Electrospray MS $[M+1]^+$ 505.1 for the Example 53b (more polar isomer).

Example 54

[0414]



Compound 47



Compound 50

[0415] $CeCl_3$ (0.186 g, 0.5 mmol, 2.1 equiv) was added to a 25 ml RBF and heated in vacuo at 140° C. for two h. The flask was cooled to 23° C. under N_2, dry THF (2 ml) was added and the resulting suspension was stirred at 23° C. for 18 h. The mixture was then cooled to 140° C. and CH_3MgI

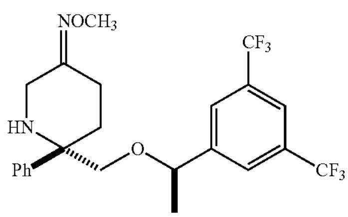
(0.159 ml, 0.476 mmol, 2 equiv.) was added and stirred at 0° C. for 1 h. A solution of Compound 47 (0.138 g, 0.238 mmol, 1 equiv) in dry THF (2.5 ml) was added dropwise and the reaction mixture was stirred under N_2 at 0° C. for 0.5 h. The mixture was quenched with saturated aq. NH_4Cl solution (50 ml) and extracted with EtOAc (100 ml×2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The mixture was purified by column chromatography over Biotage (4:1, hexane:Et_2O) to afford the NCbz-alcohol Compound 50 (0.115 g, 80%).

[0416] The NCbz-alcohol Compound 50 was converted to the desired product Example 54 (63% yield over two steps) using a procedure similar to the preparation of Example 49 from Compound 46.

[0417] Electrospray MS $[M+1]^+$ 504.1 for the Example 54.

Example 55

[0418]

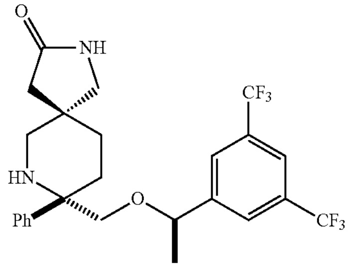


[0419] To a solution of Compound 47 (0.1 g, 0.173 mmol, 1 equiv) in dry pyridine (1 ml) was added methoxylamine hydrochloride (0.058 g, 0.69 mmol, 4 equiv) and the reaction mixture was stirred 23° C. for 18 h. The mixture was quenched with water (50 ml) and extracted with CH_2Cl_2 (100 ml×2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give NCbz-oxime (0.102 g, 97%) which was hydrogenated to afford the crude product Example 55 using a procedure similar to the preparation of Example 43a and Example 43b from Compound 48, except that the reaction was carried out in a H_2 balloon atmosphere at RT instead of a parr shaker at 40 psi. The crude product was purified by column chromatography over Biotage (4:1, EtOAc:hexane) to afford Example 55 (0.063 g, 79%), Electrospray MS $[M+1]^+$ 475.1.

Examples 56a and 56b

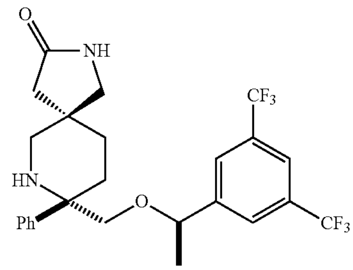
[0420]

Example 56a



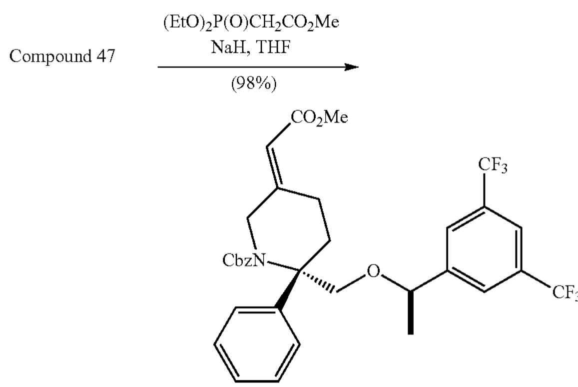
-continued

Example 56b



Step 1

[0421]

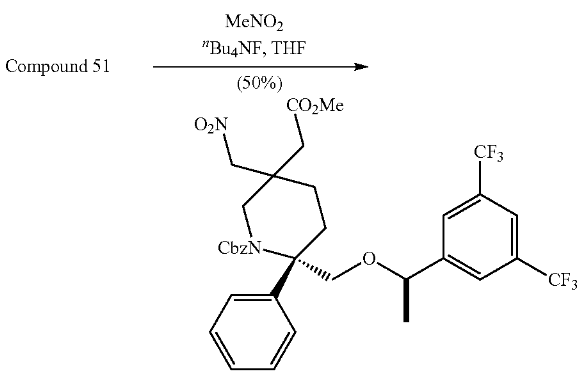


Compound 51

[0422] To a suspension of NaH (1.8 g, 44.5 mmol, 60% in oil) in THF (200 ml) at 0° C. under N_2, methyl diethylphosphonoacetate (8.2 ml, 44.5 mmol) was added. The mixture was stirred at 0° C. for 15 min and a solution of ketone Compound 47 (8.6 g, 14.8 mol) in THF (50 ml) was added. The mixture was allowed to warm to RT and stirred for 1 h before it was quenched with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (200 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-EtOAc, 4:1 (v/v)] gave unsaturated ester Compound 51 (9.2 g, 98%) as colorless oil. Electrospray MS $[M+1]^{+=}$636.1.

Step 2

[0423]



Compound 52

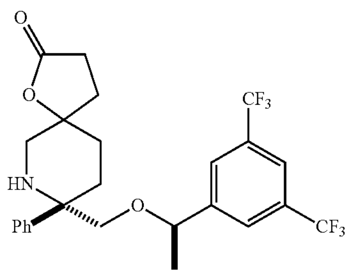
[0424] A mixture of unsaturated ester Compound 51 (9.2 g, 14.5 mmol) and tetrabutylammonium fluoride (145 ml, 1.0M in THF) in CH_3NO_2 were heated to reflux for 2 h. The mixture was cooled to RT and quenched with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (X2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-acetone, 9:1 (v/v)] gave the less polar alkene (4.1 g, 45%) as colorless oil. Continuous elution with the same solvent system gave the more polar nitroester Compound 52 (5.1 g, 50%) as colorless oil. Electrospray MS $[M+1]^{+}$=670.1.

Step 3

[0425] A mixture of Compound 52 (5.1 g, 7.32 mmol), a catalytic amount of $Pd(OH)_2$ (20% on carbon) and a catalytic amount of Raney Ni (50% slurry in water) were shaken in a Parr hydrogenator at 50 psi overnight. The mixture was filtered through a pad of Celite and solvents were removed in vacuum to give a mixture of Example 56a and 56b as colorless oil (3.5 g. 95%). Separation by HPLC using Chiralcel OD [hexane-isopropanol, 9:1 (v/v)] gave less polar isomer Example 56a as white foam. Electrospray MS $[M+1]^{+}$=501.1. Continuous elution with the same solvent system gave the more polar isomer Example 56b as colorless oil. Electrospray MS $[M+1]^{+}$=501.1.

Example 57

[0426]

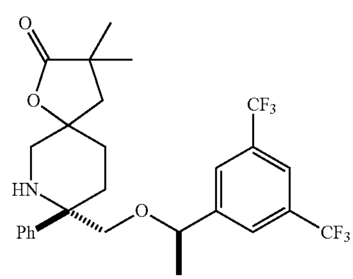


[0427] To a solution of ethyl propiolate (0.27 ml, 2.69 mmol) in THF (10 ml) at −78° C. under N_2, t-butyllithium (1.6 ml, 2.69 mmol, 1.7M in pentane) was added. The mixture was stirred at −78° C. for 10 min and a solution of Compound 47 (519 mg, 0.90 mmol) in THF (5 ml) was added. The mixture was stirred at −78° C. for 1 h, then quenched with HOAc at −78° C. Water and EtOAc were added to the mixture.

[0428] Layers were separated and the aqueous layer was extracted with EtOAc (200 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-EtOAc, 4:1 (v/v)] gave a colorless oil. The oil was dissolved in EtOH and a catalytic amount of palladium (10% on carbon) was added. The mixture was shaken in a Parr hydrogenator at 45 psi overnight. The mixture was filtered through a pad of Celite and solvents were removed in vacuum to give a colorless oil. The oil was dissolved in toluene and catalytic amount of p-TsOH was added. The mixture was heat to reflux overnight. After being cooled to RT, the mixture was quenched with saturated $NaHCO_3$ solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (250 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give a mixture of Example 57a and 57b as colorless oil. Separation by column chromatography [hexane-ether, 1:2(v/v)] gave the less polar minor isomer Example 57a (67 mg, 15%) as white foam. Electrospray MS $[M+1]^{+}$=502.1. Continuous elution with the same solvent system gave the more polar major isomer Example 57b (134 mg, 30%) as white solid. Electrospray MS $[M+1]^{+}$=502.1.

Example 58

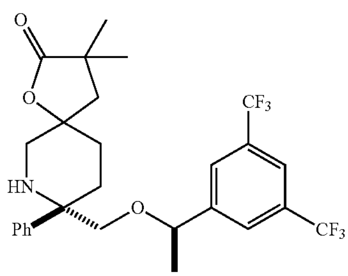
[0429]



[0430] To a solution of Example 57a (112 mg, 0.22 mmol) in THF (5 ml) at −78° C. under N_2, lithium bis(trimethylsilyl)amide (1.1 ml, 1.12 mmol, 1.0M in THF) was added. The mixture was stirred at −78° C. for 1 h and CH_3I (70 μl, 1.12 mmol) was added. The mixture was stirred at −78° C. for 1 h before quenched with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (100 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-ether, 3:1 (v/v)] gave Example 58 (92 mg, 78%) as colorless oil. Electrospray MS $[M+1]^{+}$=530.1.

Example 59

[0431]

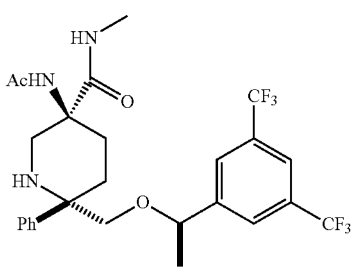


[0432] Example 59 (75%) was prepared from Example 57b in a manner similar to that used to prepare Example 58 from Example 57a. Electrospray MS $[M+1]^+=530.1$.

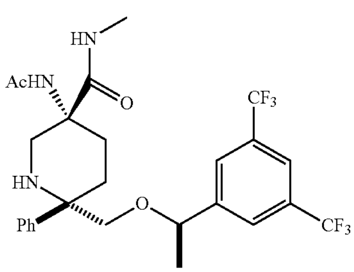
Examples 60a and 60b

[0433]

Example 60a

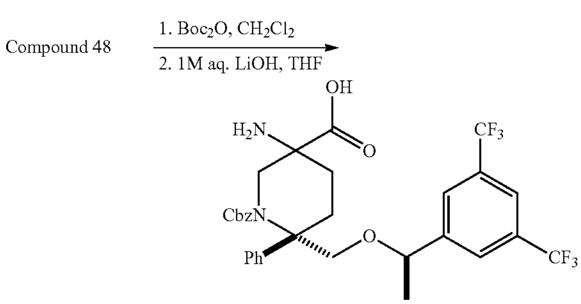


Example 60b



Step 1

[0434]



Compound 53

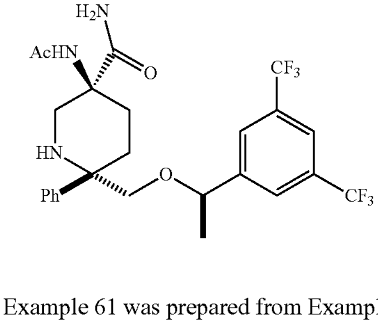
[0435] To a solution of Compound 48 (0.5 g, 0.77 mmol, 1 equiv) in CH_2Cl_2 (30 ml) was added di tert-butyl dicarbonate (0.37 g, 1.69 mmol, 2.2 equiv) followed by DMAP (0.035 g, 0.286 mmol, 0.37 equiv) and the reaction mixture was stirred at 23° C. for 18 h. The reaction mixture was then filtered through a short pad of silica using (1:1 hexane: EtOAc) and concentrated in vacuo to afford diBoc-hydantoin (0.59 g. 90%). The diBoc-hydantoin (0.59 g, 0.7 mmol, 1 equiv) was dissolved in THF (30 ml) and 1 M aq. LiOH solution (5.56 ml, 5.56 mmol, 8 equiv) was added. The reaction mixture was stirred at 23° C. for 18 h. Saturated aq. $NaHCO_3$ was added to the reaction mixture and extracted with EtOAc (100 ml×3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give crude Compound 53 (0.52 g) which was used in the next reaction without further purification.

Step 2

[0436] To a mixture of crude Compound 53 (0.52 g) in pyridine (3 ml) and THF (2 ml) at 0° C. was added acetyl chloride (0.072 ml, 1 mmol, 1.2 equiv) and the reaction mixture was warmed to 23° C. and stirred for 18 h. The reaction mixture was then concentrated and purified by column chromatography over Biotage (5:95, MeOH:EtOAc) to afford a yellow oil of N-acelyated product (0.31 g, 0.456 mmol, 1 equiv.) which was dissolved in THF (10 ml). A 2M solution of CH_3NH_2 in THF (2.3 ml, 4.6 mmol, 10 equiv) was added and the reaction mixture was stirred at 23° C. for 18 h. The mixture was diluted with EtOAc (100 ml) and washed with saturated aq. $NaHCO_3$ (100 ml). The organic layer was were dried (Na_2SO_4), filtered and concentrated to give crude NCbz-amide which was hydrogenated to afford the mixture of two isomers Example 60a and 60b using a procedure similar to the preparation of Example 43a and Example 43b from Compound 48. The mixture of two products was separated on HPLC "ChiralPak AD column" using (1:9, IPA:hexane) to afford the more polar isomer pure Example 60a, Electrospray MS $[M+1]^+=546.1$ and less polar isomer pure Example 60b, Electrospray MS $[M+1]^{+=}546.1$.

Example 61

[0437]

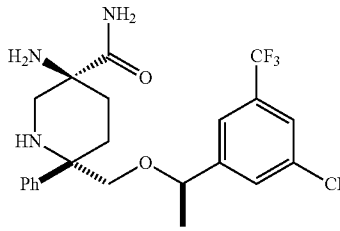


[0438] Example 61 was prepared from Example 43a using the procedure similar to the preparation of Examples 60a and 60b from Compound 48, but using a solution of ammonia (0.5M in 1,4-dioxane) in place of CH_3NH_2 solution (2M in THF).

[0439] Electrospray MS $[M+1]^+=532.1$.

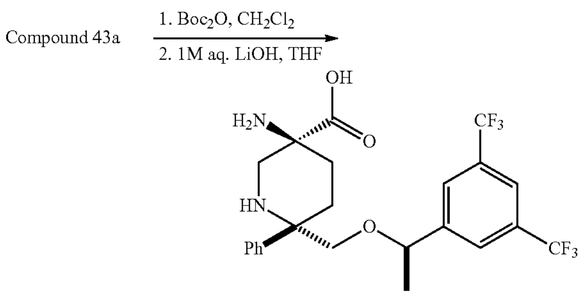
Example 62

[0440]



Step 1

[0441]

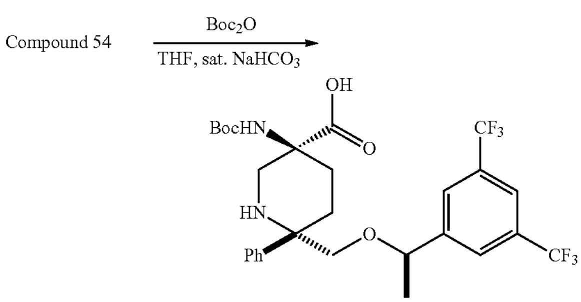


Compound 54

[0442] Compound 54 was prepared from Example 43a using the procedure similar to the preparation of Compound 53 from Compound 48. Compound 54 was used in the next reaction without further purification.

Step 2

[0443]



Compound 55

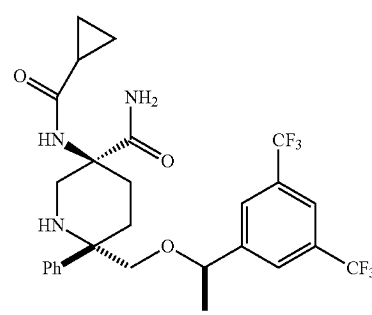
[0444] To a mixture of Compound 54 (0.5 g, 1.02 mmol, 1 equiv) in THF (30 ml) was added sat. aq. $NaHCO_3$ followed by di tert-butyl dicarbonate (0.58 g, 2.65 mmol, 2.6 equiv). The reaction mixture was stirred at 23° C. for 18 h. The mixture was cooled to 0° C. and 10% aq. citric acid (20 ml) was added and the resulting mixture was extracted with EtOAc (100 ml×3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give crude Compound 55 (0.93 g) which was used in the next reaction without further purification.

Step 3

[0445] To a solution of Compound 55 (0.93 g, 1.57 mmol, 1 equiv) in CH_2Cl_2 (15 ml) was added DIEA (0.83 ml, 4.72 mmol, 3 equiv) followed by PyBOP (1.23 g, 2.4 mmol, 1.3 equiv). After 15 min, 0.5M solution of ammonia in 1,4-dioxane (31.5 ml, 15.75 mmol, 10 equiv) was added to the reaction mixture and stirred at for 23° C. for 18 h. The reaction mixture was quenched with water (100 ml) and extracted with EtOAc (100 ml×3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography over Biotage (1:10:89, Et_3N:MeOH:EtOAc) to afford NBoc-amide which was dissolved in CH_2Cl_2 (10 ml) and cooled to 0° C. TFA (6 ml) was added and the reaction mixture was warmed to 23° C. and stirred for 2 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ (100 ml) and diluted with CH_2Cl_2 (100 ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography over Biotage (10:90, MeOH:EtOAc) to afford the desired product Example 62 (0.18 g, 35% over three steps), Electrospray MS $[M+1]^+$=490.1.

Example 63

[0446]

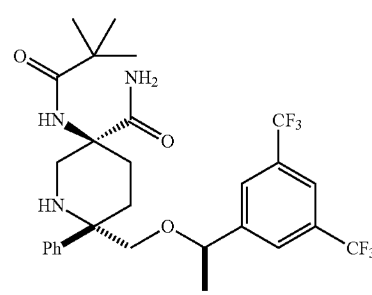


[0447] Example 63 was prepared from Example 62 using the procedure similar to the preparation of Example 14 from Example 13 and using cyclopropyl acid chloride in place of propionyl chloride and also using DIEA (1.3 equiv).

[0448] Electrospray MS $[M+1]^{+=}$558.1.

Example 64

[0449]

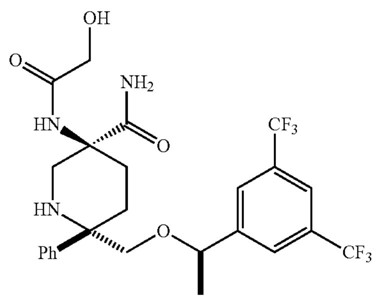


[0450] Example 64 was prepared from Example 62 using the procedure similar to the preparation of Example 14 from Example 13 and using t-butyl chloride in place of propionyl chloride.

[0451] Electrospray MS $[M+1]^{+}$=574.1.

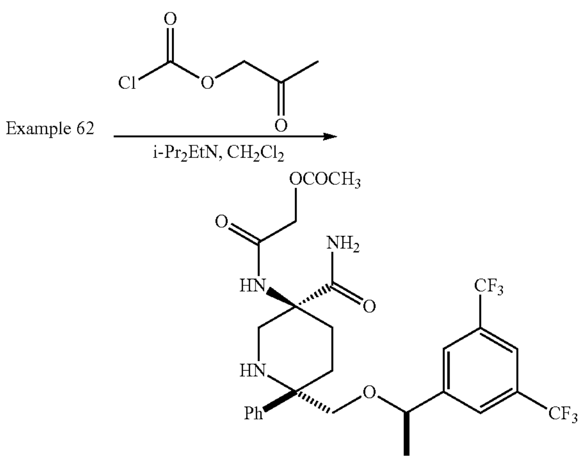
Example 65

[0452]



Step 1

[0453]



Compound 56

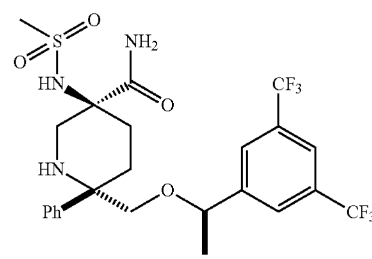
[0454] Compound 56 was prepared from Example 62 using the procedure similar to the preparation of Example 14 from Example 13 but using acetoxyacetyl chloride in place of propionyl chloride. The crude Compound 56 was used in the next reaction without further purification.

Step 2

[0455] The crude Compound 56 was dissolved in MeOH (5 ml), $KHCO_3$ (3 equiv) was added and the reaction mixture was stirred at 23° C. for 18 h. The reaction mixture was concentrated and purified by column chromatography over Biotage (10:90, MeOH:EtOAc) to afford the desired product Example 65, Electrospray MS $[M+1]^{+}$=548.1.

Example 66

[0456]

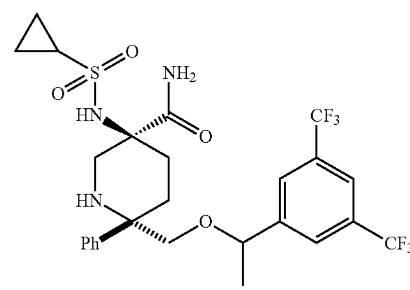


[0457] Example 66 was prepared from Example 62 using the procedure similar to the preparation of Example 14 from Example 13 and using CH_3SO_2Cl in place of propionyl chloride.

[0458] Electrospray MS $[M+1]^{+}$=568.1 for the Example 66.

Example 67

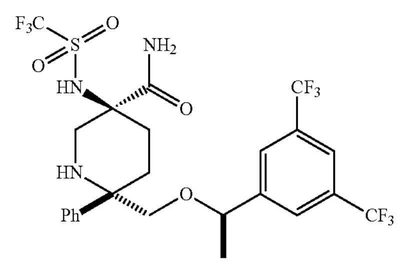
[0459]



[0460] Example 67 was prepared from Example 62 using the procedure similar to the preparation of Example 14 from Example 13 but using cyclopropylsulfonyl chloride in place of propionyl chloride. Electrospray MS $[M+1]^{+}$=594.1.

Example 68

[0461]

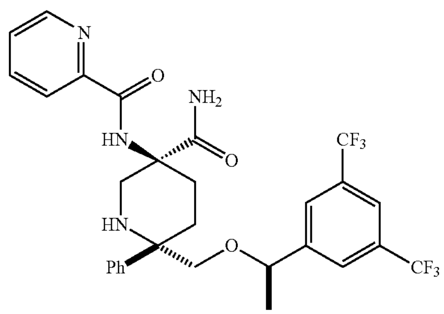


[0462] Example 68 was prepared from Example 62 using the procedure similar to the preparation of Example 14 from Example 13 but using trifluoromethanesulfonic anhydride in place of propionyl chloride.

[0463] Electrospray MS $[M+1]^{+}$=622.1 for the Example 68.

Example 69

[0464]



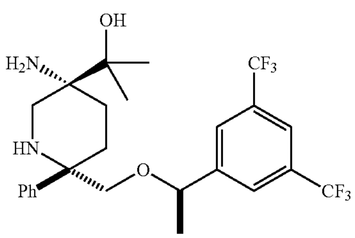
[0465] Example 69 was prepared from Example 62 using the procedure similar to the preparation of Example 14 from Example 13 and using nicotinoyl chloride in place of propionyl chloride.

[0466] Electrospray MS $[M+1]^+$=595.1 for the Example 69.

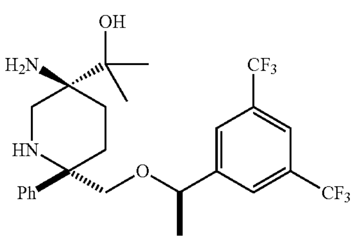
Examples 70a and 70b

[0467]

Example 70a

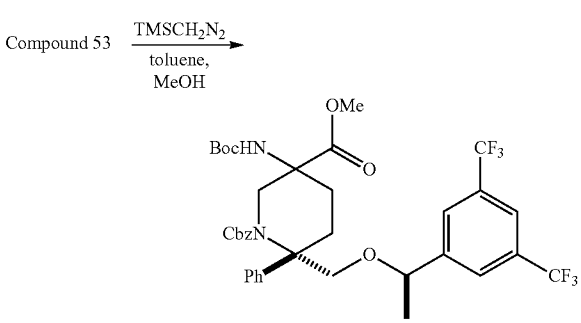


Example 70b



Step 1

[0468]

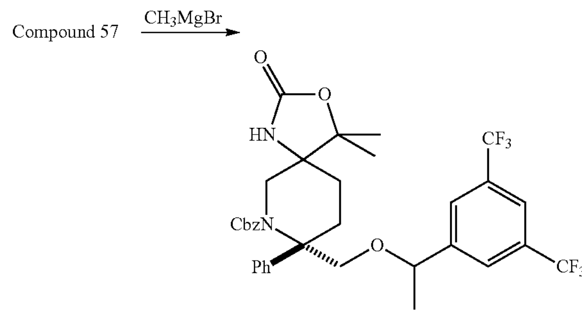


Compound 57

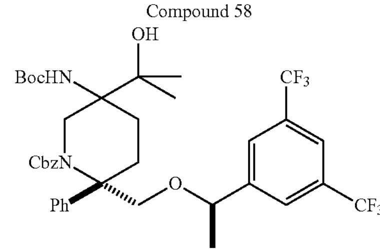
[0469] To a mixture of Compound 53 (4 g, 5.52 mmol, 1 equiv), toluene (46 ml) and MeOH (18 ml) at 0° C. was added $TMSCH_2N_2$(2M solution in hexane, 13.8 ml, 27.6 mmol, 5 equiv) and the resulting solution was stirred at 000° C. for 30 min. The reaction mixture was then concentrated and purified by column chromatography over Biotage (2:1, hexane:EtOAc) to give Compound 57 (1.8 g, 44%).

Step 2

[0470]



Compound 58



Compound 59

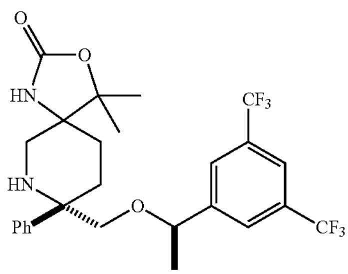
[0471] To a mixture of Compound 57 (1 g, 1.35 mmol, 1 equiv) in dry THF (18 ml) at 0° C. was added CH_3MgBr (1 M solution in n-butylether, 3.24 ml, 3.24 mmol, 2.4 equiv.) and the resulting solution was stirred at 0° C. for 30 min., The reaction mixture was then warmed to 23° C. and stirred for 18 h. The reaction was quenched with saturated aq. $NaHCO_3$ (100 ml) and extracted with EtOAc (200 ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The mixture was purified by column chromatography over Biotage (2:1, hexane:EtOAc) to give more polar Compound 58 (0.52 g, 56%) and less polar Compound 59 (0.31 g. 34%).

Step 3

[0472] Compound 59 was deprotected with TFA using the procedure described in the preparation of Example 62. The resulting NCbz-aminoalcohol compound was hydrogenated to afford the mixture of two isomers Example 70a and 70b using a procedure similar to the preparation of Examples 43a and 43b from Compound 48. The mixture of two products was separated on HPLC "ChiralCel OD column" using (1:9, IPA:hexane) to afford less polar isomer Example 70a, Electrospray MS $[M+1]^+$ 505.1, and more polar isomer Example 70b, Electrospray MS $[M+1]^+$ 505.1.

Example 71

[0473]

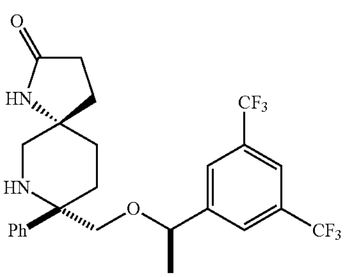


[0474] Compound 58 was hydrogenated to a mixture of desired products Example 71a and 71b using a procedure similar to the preparation of Examples 43a and 43b from Compound 48. The mixture of two products was purified by column chromatography over Biotage (1:1, hexane:EtOAc) to afford pure less polar isomer Example 71a, Electrospray MS $[M+1]^+$ 531.1 and pure more polar isomer Example 71b, Electrospray MS $[M+1]^+$ 531.1.

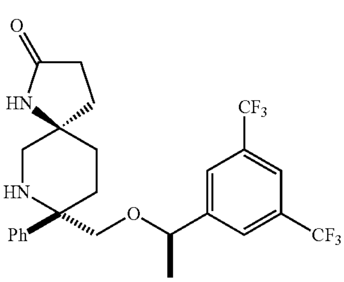
Examples 72a and 72b

[0475]

Example 72a

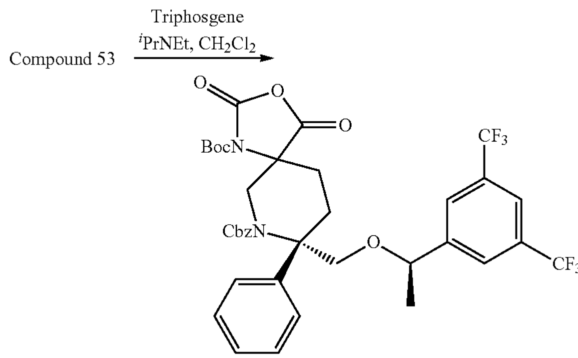


Example 72b



Step 1

[0476]

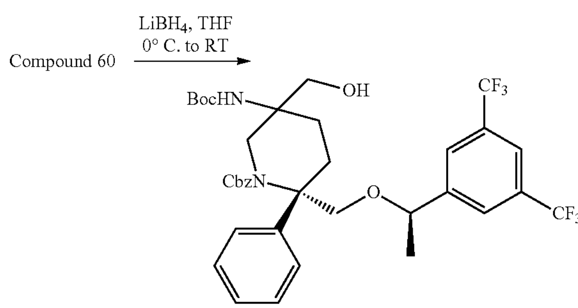


Compound 60

[0477] To a solution of crude Compound 53 (19 g) in CH_2Cl_2 (300 ml) at RT, DIEA (15 ml, 0:087 mol) was added, followed by triphosgene (4.34 g, 0.015 mol). The mixture was stirred at RT for 18 h and was filtered through a pad of silica. Solvents were removed in vacuum to give crude Compound 60 as yellow oil which was used in the next reaction without further purifications.

Step 2

[0478]



Compound 61

[0479] To the crude Compound 60 in THF (200 ml) at 0° C., $LiBH_4$ (1.26 g, 0.058 mol) was added in small portions. The mixture was stirred at RT for 18 h before quenching with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (100×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-EtOAc, 4:1 (v/v)] gave Compound 61 (12.9 g, 62% overall) as white foam.

Step 3

[0480] Oxalyl chloride (4.2 ml, 0.048 mol) was added to a solution of DMSO (6.8 ml, 0.096) in CH_2Cl_2 (300 ml) at −78° C. under N_2. The mixture was stirred at −78° C. for 15 min before a solution of Compound 61 (8.5 g. 0.012 mol) in

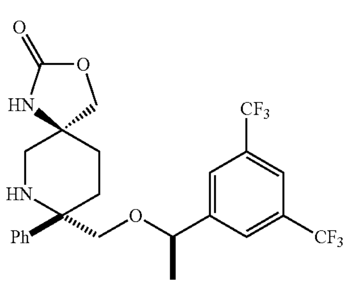
CH_2Cl_2 (100 ml) was added. The mixture was stirred at −78° C. for a further 1 h and Et_3N (23.5 ml) was added. The cooling bath was removed and the mixture was warmed to RT before it was quenched with saturated $NaHCO_3$ solution. Layers were separated and the aqueous was extracted with CH_2Cl_2 (150 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Removal of solvents in vacuum gave an aldehyde as yellow oil. To a mixture of NaH (1.44 g, 0.036 mol) in THF at 0° C., methyl diethylphosphonoacetate (6.6 ml, 0.036 mol) was added. The mixture was stirred at 0° C. for 15 min and a solution of aldehyde in THF (100 ml) was added. The cooling bath was removed and the mixture was stirred at RT for 1 h. The reaction was quenched with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (200 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-EtOAc, 4:1 (v/v)] gave an ester as white foam. The ester was dissolved in EtOH (100 ml) and a catalytic amount of palladium (1.28 g, 10% on carbon) was added. The mixture was shaken under H_2 (50 psi) for 2 days. Catalytic amount of $Pd(OH)_2$ (20% on carbon) was then added to the mixture and the mixture was again shaken under H_2 (50 psi) for 5 h. The mixture was filtered through a pad of Celite and solvents were removed in vacuum to give a white foam. The foam was then dissolved in CH_2Cl_2 (200 ml) and TFA (8.9 ml, 0.12 mol) was added. The mixture was stirred at RT for 18 h and was cooled at 0° C. before it was neutralized with saturated $NaHCO_3$ solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (200 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give a yellow oil. The oil was dissolved in CH_3OH (50 ml) and a catalytic amount of K_2CO_3 (166 mg, 0.0012 mol) was added. The mixture was heated at 60° C. for 2 h. After being cooled to RT, the mixture was filtered through a pad of silica and solvents were removed in vacuum. Purification by column chromatography (EtOAc) gave the mixture of two isomers Example 72a and 72b (2.3 g, 38% overall) as white foam. Separation by HPLC using Chiralcel OD [hexane-isopropanol, 95:5 (v/v)] gave the less polar major isomer Example 72a as white foam. Electrospray MS $[M+1]^{+}$=501.1. Continuous elution with the same solvent system gave the more polar minor isomer Example 72b as colorless oil.

[0481] Electrospray MS $[M+1]^{+}$=501.1.

Examples 73a and 73b

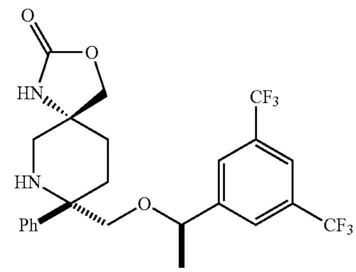
[0482]

Example 73a



-continued

Example 73b



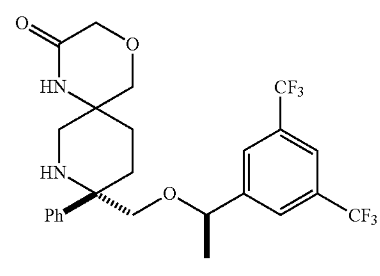
[0483] To a solution of Compound 61 (3 g, 4.22 mmol, 1 equiv) in DMF (60 ml) at 0° C. was added NaH (60% in mineral oil, 0.122 g, 5.07 mmol, 1.2 equiv) and the mixture was allowed to warm to 23° C. and stirred for 45 min. The reaction was quenched with water (100 ml) and extracted with EtOAc (100 ml×3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude product purified by column chromatography over Biotage (2:1, hexane:EtOAc) to afford the desired product which was hydrogenated to afford the mixture of two isomers Example 73a and 73b using a procedure similar to the preparation of Examples 43a and 43b from Compound 48. The mixture of two products was separated on HPLC "ChiralPak AD column" using (5:95, IPA:hexane) to afford pure less polar isomer Example 73a and more polar isomer Example 73b.

[0484] Electrospray MS $[M+1]^{+}$=503.1 for Example 73a.

[0485] Electrospray MS $[M+1]^{+}$=503.1 for Example 73b.

Example 74

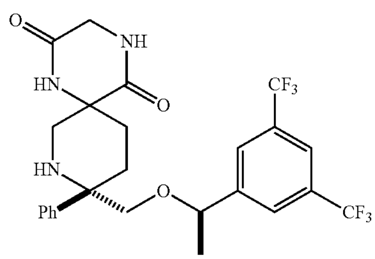
[0486]



[0487] Compound 61 (1.68 g, 2.36 mmol, 1 equiv) was dissolved in CH_2Cl_2 (50 ml), TFA (5.46 ml, 70.9 mmol, 30 equiv) was added and the reaction mixture was stirred at 23° C. for 2.5 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ (150 ml) and diluted with CH_2Cl_2 (100 ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to give crude amino-alcohol product (1.4 g, 97%). The product (0.32 g, 0.524 mmol, 1 equiv) was dissolved in dry THF (10 ml) and NaH (60% in mineral oil, 0.025 g, 0.63 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at 23° C. for 5 min and then ethyl chloroacetate (0.062 ml, 0.576 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 2.5 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ (100 ml) and diluted with EtOAc (200 ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography over Biotage (2:3, hexane:EtOAc) to give the product (0.1 g, 32%) which was hydrogenated to afford the mixture of two isomers Example 74a and 74b using a procedure similar to the preparation of Examples 43a and 43b from Compound 48. The mixture of two products was separated on HPLC "ChiralCel OD column" using (1:9, IPA:hexane) to afford pure Example 74a, Electrospray MS $[M+1]^+$ 517.1, and pure Example 74b, Electrospray MS $[M+1]^+$ 517.1.

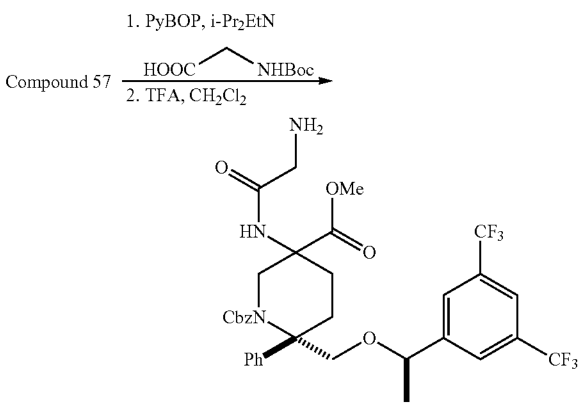
Example 75

[0488]



Step 1

[0489]



Compound 62

[0490] Compound 57 was converted to Compound 62 (72% yield over two steps) using the PyBOP coupling followed by TFA deprotection procedures as described in the preparation of Example 62 from Compound 55 but using Compound 57 (1 equiv.) in place of ammonia and NH-Boc-glycine (2 equiv.) in place of Compound 55.

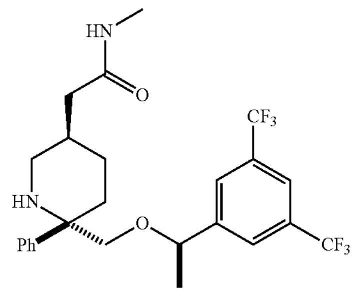
Step 2

[0491] Compound 62 (0.5 g, 0.72 mmol, 1 equiv) was dissolved in MeOH (10 ml) and Et_3N (1 ml, 7.2 mmol, 10 equiv) was added. The resulting mixture was heated at 23° C. for 18 h. The reaction mixture was then concentrated and purified by column chromatography over Biotage (EtOAc) to give NCbz-diketopiperazine (0.33 g) which was hydrogenated to afford the mixture of two isomers Example 75a and 75b using a procedure similar to the preparation of Examples 43a and 43b from Compound 48. The mixture of two products was separated on HPLC "ChiralPak AD column" using (5:95, IPA:hexane) to afford pure less polar isomer Example 75a (0.03 g. 8% over two steps), Electrospray MS $[M+1]^+$ 530.1, and more polar isomer Example 75b, (0.04 g, 11% over two steps), Electrospray MS $[M+1]^+$ 530.1.

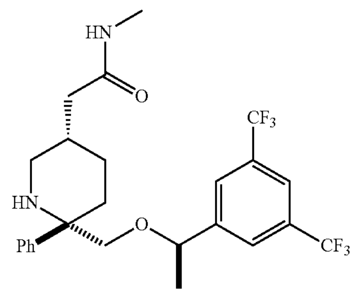
Examples 76a and 76b

[0492]

Example 76a



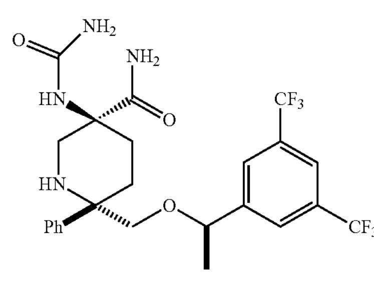
Example 76b



[0493] Compound 51 (3.66 g, 5.76 mmol, 1 equiv.) was hydrogenated using a procedure similar to the preparation of Examples 43a and 43b from Compound 48 and the hydrogenated product (2.85 g) was treated with CH_3NH_2 (2M solution in CH_3OH, 200 ml) and stirred at 23° C. for 18 h. The reaction mixture was then concentrated and purified by column chromatography over Biotage (1:9, MeOH:EtOAc) to give the mixture of two isomers Example 76a and 76b. The mixture of two isomers was separated on HPLC "ChiralPak AD column" using (5:95, IPA:hexane) to afford less polar isomer Example 76b, Electrospray MS [M+1]f 503.1, and more polar isomer Example 76a, Electrospray MS $[M+1]^+$ 503.1.

Example 77

[0494]

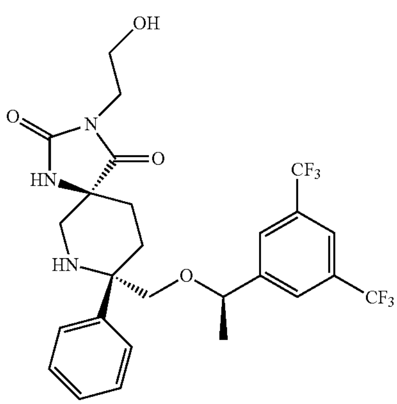


[0495] Example 62 (0.07 g, 0.133 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3 ml) and DIEA (0.03 ml, 0.147 mmol, 1.1 equiv) was added followed by 4-methoxyphenyl (pmb)-isocyanate (0.021 ml, 0.147 mmol, 1.1 equiv) and the reaction mixture was stirred at 23° C. for 18 h. The reaction mixture was then concentrated and treated with CH_3CN (3 ml) and water (1 ml) and the mixture was cooled to 0° C. Ammonium cerium nitrate (0.24 g, 0.44 mmol, 4 equiv) was added and the reaction mixture was stirred at 0° C. for 45 min. The reaction was quenched with saturated aq. $NaHCO_3$ (100 ml) and extracted with EtOAc (200 ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The mixture was purified by column chromatography over Biotage (15:85, MeOH:EtOAc) to give Example 77 (0.03 g, 42%), Electrospray MS $[M+1]^+$ 533.1.

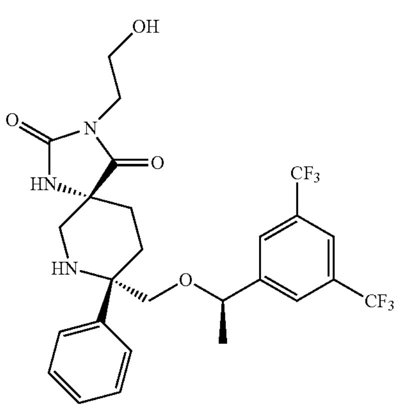
Examples 78a and 76b

[0496]

Example 78a

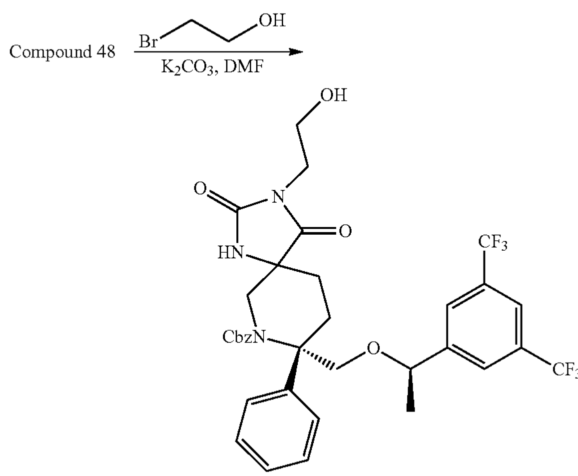


Example 78b



Step 1

[0497]



Compound 63

[0498] In a flamedry 15 ml RBF Compound 48 (0.25 g, 0.385 mmol, 1 equiv) in DMF (1 ml) was added to K_2CO_3 (0.106 g, 0.77 mmol, 2 equiv) followed by 2-bromoethanol (0.033 ml, 0.46 mmol, 1.2 equiv) and the mixture was stirred for 2 h at RT, then heated to 50° C. for 6 h. The reaction was monitored by TLC (60/40 EtOAc/Hexane). The reaction mixture was cooled to 0° C., quenched with H_2O, diluted with EtOAc and washed with brine. The organic layer was combined and dried over Na_2SO_4, filtered and concentrated. The reaction mixture was purified using Biotage using 2:3 EtOAc/Hexane to 3:2 EtOAc/Hexane to elute Compound 63 as a mixture of two isomers (0.258 g, 97%), Electrospray MS $[M+1]^+$ 694.1.

Step 2

[0499] To a solution of Compound 63 (0.25 g, 0.36 mmol, 1 equiv) in anhydrous MeOH was added (5.5 ml) 20% $Pd(OH)_2/C$ (0.08 g). The reaction mixture was purged with N_2 followed by H_2 and stirred for 18 h under H_2. The reaction was monitored by TLC (60/40 EtOAc/Hexane). The catalyst was filtered through a plug of celite and the solution was concentrated to give crude product. The material was subjected to flash chromatography using a Biotage (80:20 EtOAc/Hexane). The isomers were separated to give Example 78a and Example 78b (0.13 g, 63%).

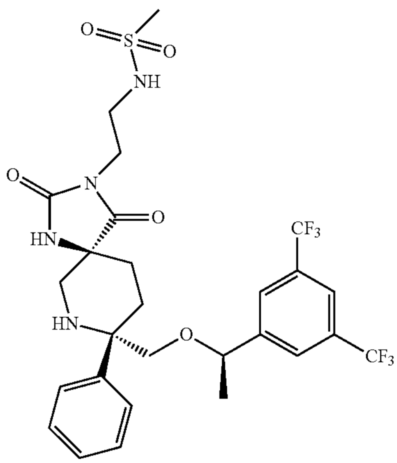
[0500] Electrospray MS $[M+1]^+$ 560.1 for Example 7878a (less polar isomer)

[0501] Electrospray MS $[M+1]^+$ 560.1 for Example 78b (more polar isomer)

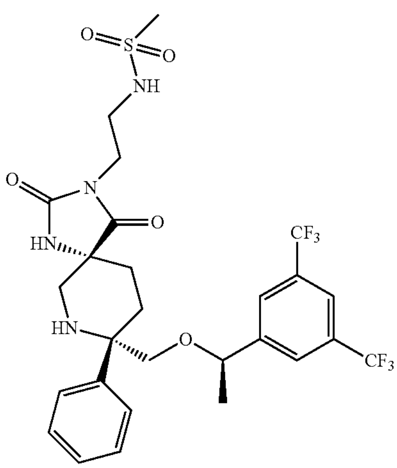
Examples 79a and 79b

[0502]

Example 79a

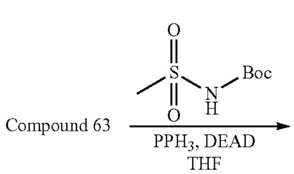


Example 79b

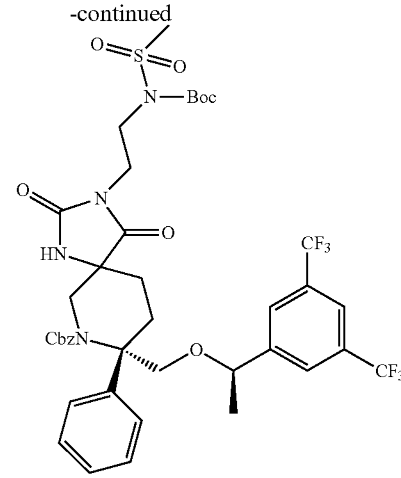


Step 1

[0503]



-continued

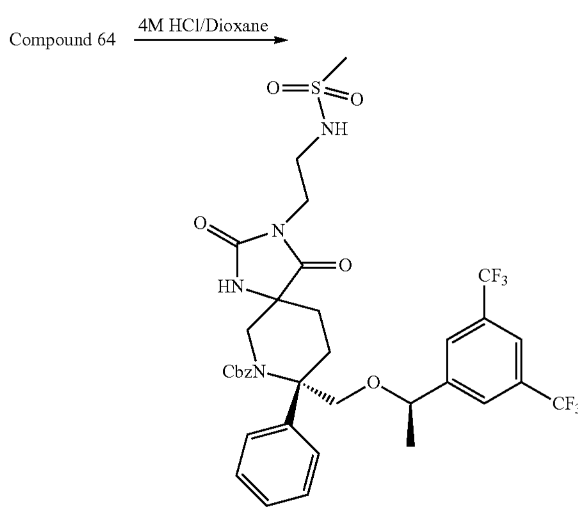


Compound 64

[0504] N-(Boc)-methanesulfonamide (0.041 g, 0.43 mmol, 1.5 equiv) was dissolved in dry THF (1 ml) and triphenyl phosphine (0.228 g, 0.43 mmol, 3 equiv) was added. The resulting solution was stirred under N_2 and a solution of Compound 63 (0.2 g, 0.29 mmol, 1 equiv) in THF followed by diethyl azodicarboxylate (DEAD) (0.12 ml, 0.26 mmol, 2.5 equiv) were added. The reaction monitored by TLC (60/40 EtOAc/Hexane). Upon completion, the reaction mixture was concentrated to give a yellow oil which was subjected to flash chromatography using a Biotage (1:1 EtOAc/Hexane) to elute the product, Compound 64, as a mixture of two isomers (0.24 g, 95%), Electrospray MS $[M+1]^+$ 871.1.

Step: 2

[0505]



Compound 65

[0506] To a solution of Compound 64 (0.25 g, 0.29 mmol, 1 equiv) in dry CH_2Cl_2 (10 ml) at 0° C. was added 4M HCl in dioxane (0.755 ml, 2.9 mmol, 10 equiv). The reaction was warmed to RT and monitored by TLC (60/40 EtOAc/Hexane). Upon completion the reaction was quenched with water, diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, and dried over Na_2SO_4 to give crude Compound 65 as a mixture of two isomers (0.2 g, 89%). The crude material was carried forward without any purification.

[0507] Electrospray MS $[M+1]^+$ 771.1 for Compound 65.

Step: 3

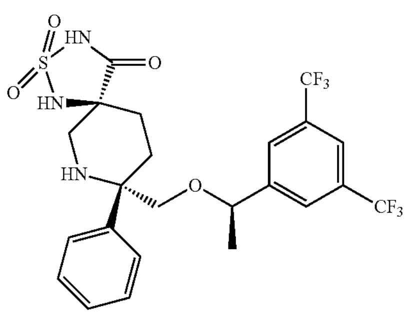
[0508] To a solution of Compound 65 (0.2 g, 0.26 mmol, 1 equiv) in MeOH (5 ml) was added 10% Pd/C followed by ammonium formate (0.082 g, 1.3 mmol, 5 equiv). The reaction was refluxed under N_2 for 3 h, then cooled to RT, filtered through celite, and concentrated. The residue was dissolved in EtOAc, washed with $NaHCO_3$ and dried over Na_2SO_4. The crude material was subjected to prep plate chromatography. Both of the isomers were isolated to give pure Example 79a and Example 79b (0.06 g, 36% total for both isomers).

[0509] Electrospray MS $[M+1]^+$ 637.1 for Example 79a (less polar isomer);

[0510] Electrospray MS $[M+1]^+$ 637.1 for Example 79b (more polar isomer).

Example 80

[0511]

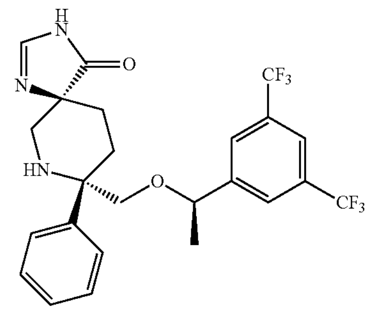


[0512] To a solution of Example 62 (0.079 g, 0.127 mmol, 1 equiv) in dry CH_2Cl_2 (1 ml) was added Et_3N (0.108 ml, 0.76 mmol, 6 equiv). The reaction mixture was cooled to 0° C. and stirred for 15 min. SO_2Cl_2 (0.011 ml, 0.133 mmol, 1.05 equiv) was added very slowly to the reaction over 5 min. The reaction stirred for 10 h and was monitored by TLC (9:1 $EtOAc/CH_3OH$). The reaction mixture was diluted with EtOAc, washed with $NaHCO_3$, and dried over Na_2SO_4. The crude product was subjected to prep plate chromatography to isolate Example 80 (0.015 g, 20%),

[0513] Electrospray MS $[M+1]^+$ 552.1.

Example 81

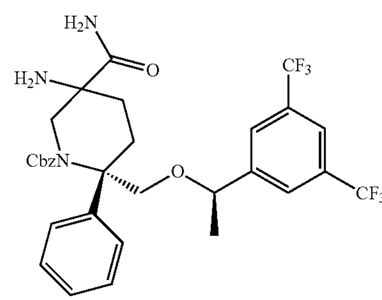
[0514]



Step 1

[0515]

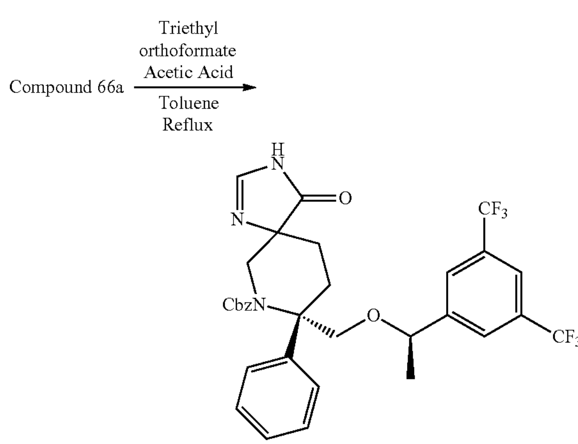
Compound 66a and 66b



[0516] Compounds 66a and 66b were prepared from Compound 48 using a procedure similar to the preparation of Example 62 from Example 43a.

Step 2

[0517]



Compound 67a

[0518] To a solution of Compound 66a (0.34 g, 0.545 mmol, 1 equiv) in dry toluene (14 ml) was added HOAc (0.17 ml) followed by triethyl orthoformate (0.363 ml, 2.18 mmol, 4 equiv). The solution was refluxed for 12 h and monitored by TLC (9:1 EtOAc/CH_3OH). The reaction was cooled to 0° C., quenched with H_2O, diluted with EtOAc, washed with $NaHCO_3$, and dried over Na_2SO_4. The crude was subjected to flash chromatography using a Biotage (60:40 EtOAc/Hexane) to elute Compound 67a (0.272 g. 79%), Electrospray MS $[M+1]^+$ 634.1.

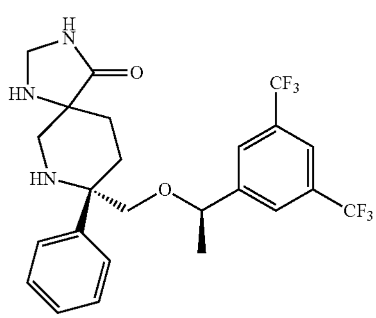
Step 3

[0519] Example 81 was prepared from Compound 67a using a similar procedure as for Examples 79a and 79b from Compound 65.

[0520] Electrospray MS $[M+1]^+$ 500.1 for Example 81.

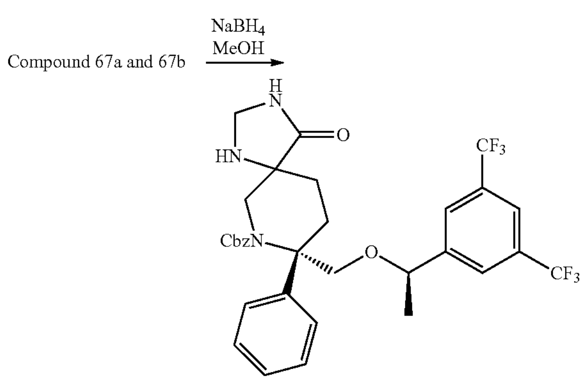
Example 82

[0521]



Step 1

[0522]



Compound 68

[0523] To a solution of a mixture of the two isomers of Compound 67 (0.27 g, 0.426 mmol, 1 equiv) in dry CH_3OH (3 ml) was added $NaBH_4$ (0.048 g, 1.28 mmol, 3 equiv). The reaction mixture bubbled upon the addition of the reagent, and was stirred for 5 h under N_2. The reaction was monitored by TLC (60/40 EtOAc/Hexane), and upon completion was quenched with HOAc, concentrated, diluted with EtOAc, washed with $NaHCO_3$ and dried over Na_2SO_4. The crude product was a mixture of two isomers, Compound 68, (0.25 g. 92%) and was carried forward without any purification.

[0524] Electrospray MS $[M+1]^+$ 636.1 for the Compound 68.

Step 2

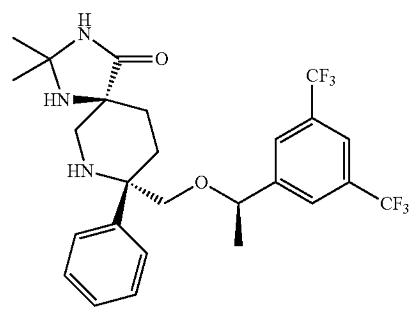
[0525] Example 82a (less polar isomer) and Example 82b (more polar isomer) (0.12 g, 61%) were prepared from Compound 68 using a similar procedure as for preparing Examples 79a and 79b from Compound 65.

[0526] Electrospray MS $[M+1]^+$ 502.1 for Example 82a,

[0527] Electrospray MS $[M+1]^+$ 502.1 for Example 82b.

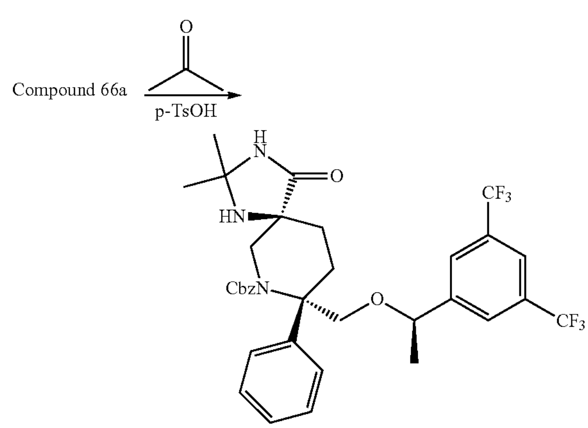
Example 83

[0528]



Step 1

[0529]



Compound 69

[0530] To a solution of Compound 66a (0.1 g, 0.16 mmol. 1 equiv) in a 25 ml in MeOH (0.5 ml) was added acetone (0.352 ml, 0.48 mmol, 3 equiv) and p-TsOH (0.06 g. 0.32 mmol, 2 equiv). The reaction mixture was refluxed for 12 h and was monitored by mass spectrum analysis. Reaction upon completion was concentrated, diluted with EtOAc, washed with $NaHCO_3$, and dried over Na_2SO_4 to give Compound 69 (0.1 g, 94%). The crude product was carried forward without any purification.

Step 2

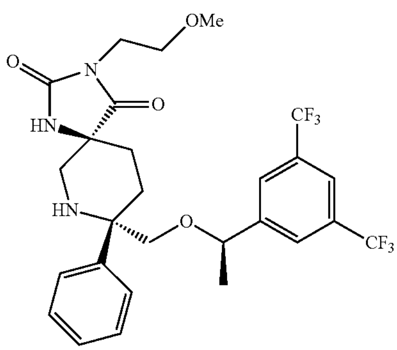
[0531] Example 83 (0.026 g, 33%) was prepared from Compound 69 using a similar procedure as for preparing Examples 79a and 79b from Compound 65.

[0532] Electrospray MS $[M+1]^+$ 530.1 for Example 83.

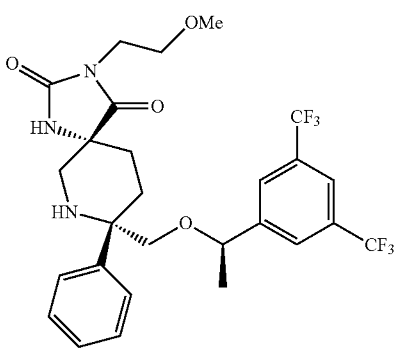
Examples 84a and Example 84b

[0533]

Example 84a



Example 84b



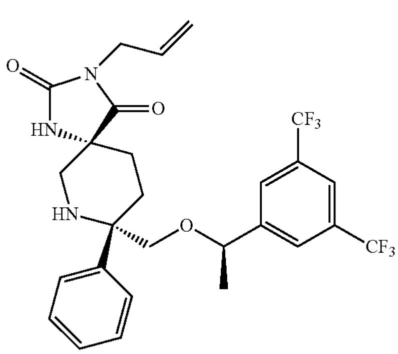
[0534] Examples 84a and Example 84b were prepared using a similar procedure as for Examples 78a and 78b, but using 2-bromoethyl methyl ether instead of 2-bromoethanol.

[0535] Electrospray MS $[M+1]^+$ 574.1 for Example 84a,

[0536] Electrospray MS $[M+1]^+$ 574.1 for Example 84b.

Example 85

[0537]

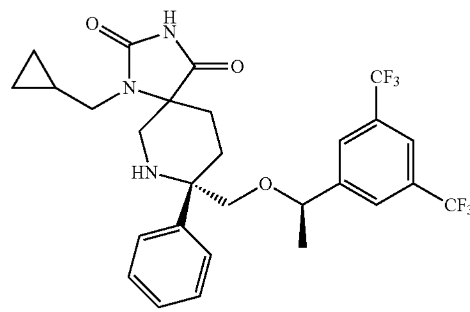


[0538] Example 85 (46 mg, 88%) was prepared from Example 43b using a similar procedure as for Compound 63, but using allyl bromide instead of 2-bromoethanol. Electrospray MS $[M+1]^+$ 556.1.

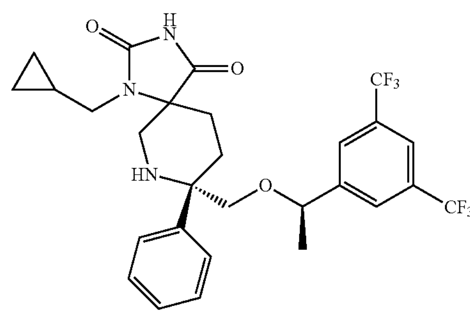
Examples 86a and Example 86b

[0539]

Example 86a



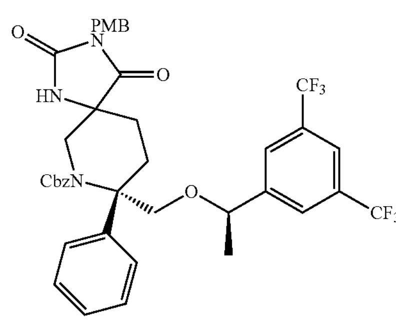
Example 86b



Step 1

[0540]

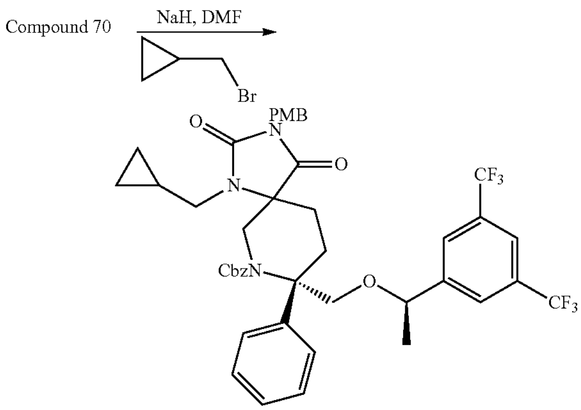
Compound 70



[0541] Compound 70 (1.14, 99%) was prepared from Compound 48 using a similar procedure as for Compound 63 but using para-methoxybenzyl chloride instead of 2-bromoethanol. Electrospray MS $[M+1]^+$ 770.2.

Step 2

[0542]



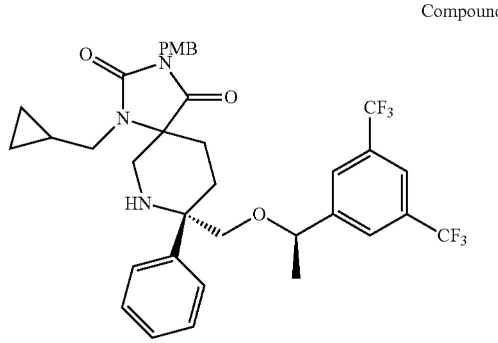
Compound 71

[0543] To a solution of Compound 70 (0.19 g, 0.25 mmol, 1 equiv) in 1.0 ml of anhydrous DMF at 0° C. was added NaH (60% dispersion in mineral oil, 0.012 g, 0.30 mmol, 1.2 equiv). After 5 min, the ice bath was removed and the reaction mixture was allowed to stir for 30 min before the addition of bromomethyl cyclopropane (0.029 ml, 0.30 mmol, 1.2 equiv). After 20 h, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with EtOAc. The layers were separated and the organic layer was washed once with brine, dried over Na_2SO_4, filtered and concentrated to give Compound 71 (0.11 g, 99%) Electrospray MS $[M+1]^+$ 824.2.

Step 3

[0544]

Compound 72



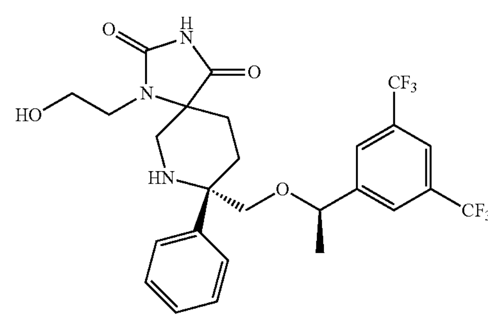
[0545] Compound 72 (0.24 g. 90%) was prepared from Compound 71 using a similar procedure as for Examples 78a and 78b from Compounds 63. Electrospray MS [M+1]+ 690.1.

Step 4

[0546] To a solution of Compound 72 (0.24 g, 0.34 mmol, 1 equiv) in 5.0 ml of CH_3CN and 1.7 ml of water at 0° C. was added ammonium cerium nitrate (0.79 g, 1.4 mmol, 4 equiv). After 5 min the ice bath was removed and the reaction mixture was allowed to stir at RT for 17 h. The reaction mixture was quenched with water and diluted with EtOAc. The layers were separated and the organic layer was washed with water (100 ml×2), dried over Na_2SO_4, filtered and concentrated to give a yellow oil. Purification by chromatography on a Biotage eluting with the solvent gradient 20% EtOAc/hexane to 30% EtOAc/hexane to 50% EtOAc/hexane gave a diastereomeric mixture of Examples 86a and 86b (15 mg, 8%), isomerically pureless polar Example 86a (14 mg, 7%) Electrospray MS $[M+1]^+$ 570.1, and isomerically pure more polar Example 86b (16 mg, 9%) Electrospray MS $[M+1]^+$ 570.1.

Example 87

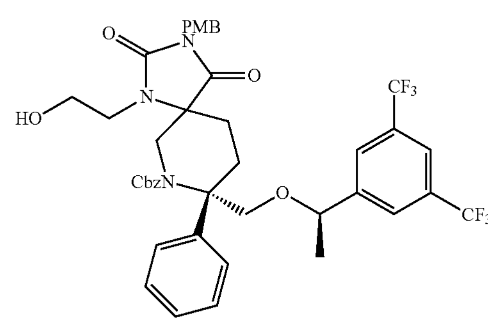
[0547]



Step 1

[0548]

Compound 73

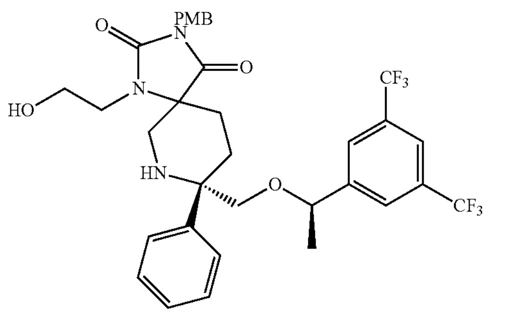


[0549] Compound 73 (0.20, 64%) was prepared from Compound 48 using a similar procedure as for Compound 63. Electrospray MS $[M+1]^+$ 814.19.

Step 2

[0550]

Compound 74



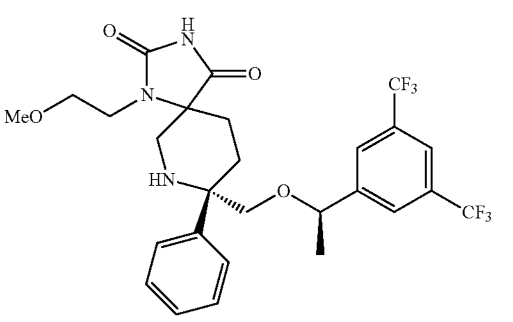
[0551] Compound 74 (0.16 g, 96%) was prepared from Compound 73 using a similar procedure as for Examples 78a and 78b from Compound 63. Electrospray MS $[M+1]^+$ 680.1.

Step 3

[0552] Examples 87a and 87b were prepared from Compound 74 using a similar procedure as for Example 86a and 86b from Compound 72, but purification using a Gilson with water/CH_3CN was used instead of chromatography on a Biotage to isolate a diastereomeric mixture of Examples 87a and 87b (92 mg, 71%). HPLC separation on 50 mg of the mixture on a ChiralCel OD column using a (90/10) hexane/IPA as the eluent gave a diastereomeric mixture of Example 87a and 87b (11 mg), isomerically pure first-eluted product Example 87a (10 mg) Electrospray MS $[M+1]^+$ 560.1, and isomerically pure second-eluted product Example 87b (11 mg) Electrospray MS $[M+1]^+$ 570.1.

Example 88

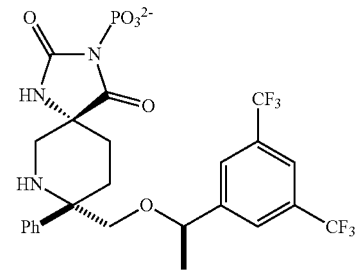
[0553]



[0554] A diastereomeric mixture of Example 88a and 88b (22% overall yield in three steps from Compound 70) was prepared using a similar procedure as for Example 86a and 86b, but using 2-bromoethyl methyl ether instead of bromomethyl cyclopropane. HPLC separation on 50 mg of the diastereomeric mixture on a ChiralCel OD column using a (90/10) hexane/IPA as the eluent gave isomerically pure first-eluted product Example 88a (16 mg) Electrospray MS $[M+1]^+$ 574.3, and isomerically pure second-eluted product Example 88b (29 mg) Electrospray MS $[M+1]^+$ 574.3.

Example 89

[0555]

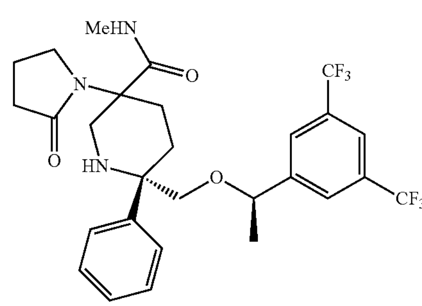


(N-Me-D-glucamine)$_2$

[0556] To a solution of Example 43b (0.68 g, 1.32 mmol, 1 equiv) in DMF (7 ml) at 0° C. was added NaH (60% in mineral oil, 0.105 g, 2.64 mmol, 2 equiv) and the mixture was stirred at 0° C. for 15 min. Tetrabenzyl pyrophosphate (1.42 g, 2.64 mmol, 2 equiv) was added and the reaction mixture stirred at 0° C. for 15 min, then warmed to 23° C. and stirred for 1 h. The reaction was quenched with saturated aq. $NaHCO_3$ (100 ml) and extracted with EtOAc (100 ml×3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product purified by column chromatography over Biotage (2:1, hexane:EtOAc) to afford the N-phosphorated hydantoin product (0.24 g) which was dissolved in MeOH (10 ml): N-Me-D-glucamine (0.119, 0.619 mmol, 2 equiv) was added, followed by 10% Pd—C (0.021 g). The resulting mixture was shaken in a parr shaker under H_2 atmosphere at 40 psi for 18 h. The reaction mixture was filtered through a pad of celite and the celite was washed with MeOH. The resulting solution was concentrated in vacuo. The residue was dissolved in EtOAc (100 ml) and extracted with water (100 ml) and the aqueous layer was lyophilized to give the desired product Example 89 as N-Me-D-glucamine salt (0.22 g, 21% over two steps).

Example 90

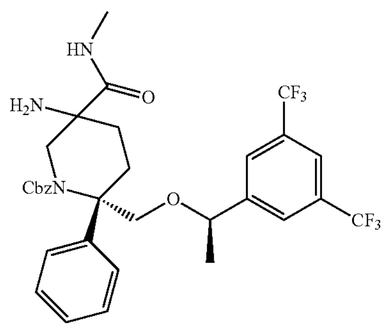
[0557]



Step 1

[0558]

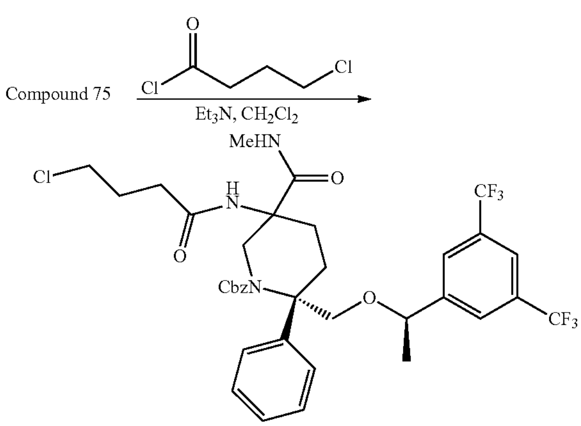
Compound 75



[0559] Compound 75 was prepared from Compound 48 using a procedure similar to the preparation of Compound 66 from Compound 48.

Step 2

[0560]

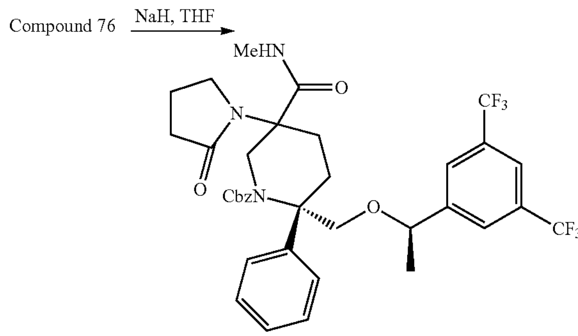


Compound 76

[0561] To a solution of the diastereomeric Compound 75 (0.10 g, 0.16 mmol, 1 equiv) in 2.0 ml of anhydrous CH_2Cl_2 at 0*C was added Et_3N (0.033 ml, 0.24 mmol, 1.5 equiv) and 4-chlorobutyrylchloride (0.017 ml, 0.17 mmol, 1.1 equiv). After 6 h, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with EtOAc. The layers were separated and the organic layer was washed once with brine, dried over Na_2SO_4, filtered and concentrated to give Compound 76 as a diastereomeric mixture (0.12 g, 100%) Electrospray MS $[M+1]^+$ 742.2.

Step 3

[0562]



Compound 77

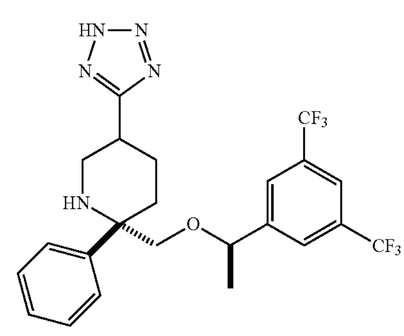
[0563] To a solution of Compound 76 (0.12 g, 0.16 mmol, 1 equiv) in 1.0 ml of anhydrous THF at RT was added NaH (60% dispersion in mineral oil, 0.010 g, 0.24 mmol, 1.5 equiv). After 3 h, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with EtOAc. The layers were separated and the organic layer was washed once with brine, dried over Na_2SO_4, filtered and concentrated to give Compound 77 (0.10 g, 88%) Electrospray MS $[M+1]^+$ 706.2.

Step 4

[0564] Examples 90a and 90b were prepared from Compound 77 using a similar procedure as for preparing Example 83 from Compound 69, but purification used chromatography on a Biotage instead of a Prep plate. A diastereomeric mixture of Examples 90a and 90b (26 mg, 32%) was obtained: less polar product Example 90a (20 mg, 25%) Electrospray MS $[M+1]^+$ 572.1, more polar product Example 90b (14 mg, 17%) Electrospray MS $[M+1]^+$ 572.1.

Example 91

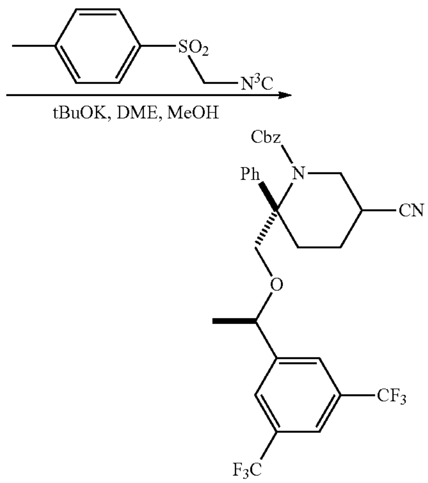
[0565]



Step 1

[0566]

Compound 47



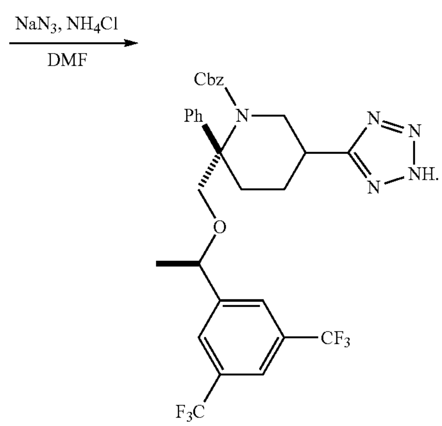
Compound 78

[0567] To a solution of Compound 47 (1 g, 1.73 mmol, 1 equiv) and tosylmethyl-isocyanide (374 mg, 1.9 mmol, 1.1 equiv) in anhydrous ethylene glycol dimethylether (1 ml) at −30° C., was added anhydrous MeOH (0.15 ml) followed by addition of potassium tert-butoxide (426 mg, 3.8 mmol, 2.2 equiv). After stirring at −30° C. to 10° C. for 7 h, the reaction mixture was passed through celite. The celite pad was thoroughly washed with Et_2O. The filtrate was concentrated and the residue was purified on silica gel column to afford the titled Compound 78 (470 mg, 46%).

Step 2

[0568]

Compound 78



Compound 79

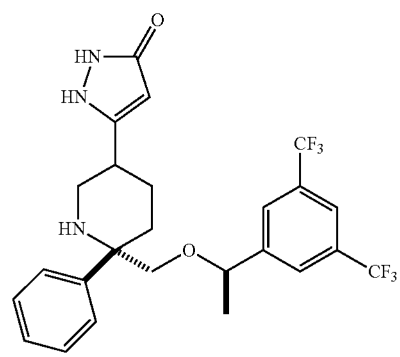
[0569] A solution of Compound 78 (125.7 mg, 0.21 mmol, 1 equiv) and NH_4Cl (68.3 mg, 1/28 mmol, 6 equiv) and NaN_3 (69.2 mg, 1.06 mmol, 5 equiv) in anhydrous DMF (1.2 ml) under N_2 was heated at 115° C. overnight. The mixture was concentrated, then acidified with HCl (6N, 10 ml) and extracted with EtOAc (15 ml×3). The combined organic solvent was dried over Na_2SO_4, filtered and evaporated in vacuum. The residue was purified on a silica gel column to afford Compound 79 (67 mg, 50%).

Step 3

[0570] A solution of Compound 79 (65 mg, 0.103 mmol, 1 equiv) in EtOH (1.5 ml) was treated with 10% Pd—C (107 mg, 0.1 mmol, 1 equiv) and 1,4-cyclohexadiene (0.5 ml, 5.29 mmol, 50 equiv). The mixture was heated at 85° C. for 10 min, then passed through celite. The celite pad was washed with MeOH. The filtrate was concentrated in vacuum and the residue was purified by silica gel column to afford Example 91 (11 mg, 21%) Electrospray MS $[M+1]^+$ 500.1.

Example 92

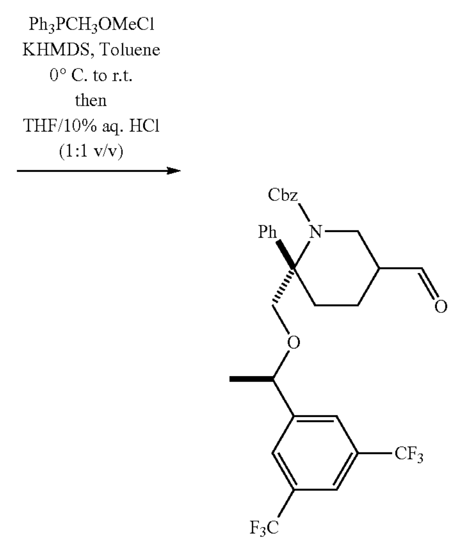
[0571]



Step 1

[0572]

Compound 47

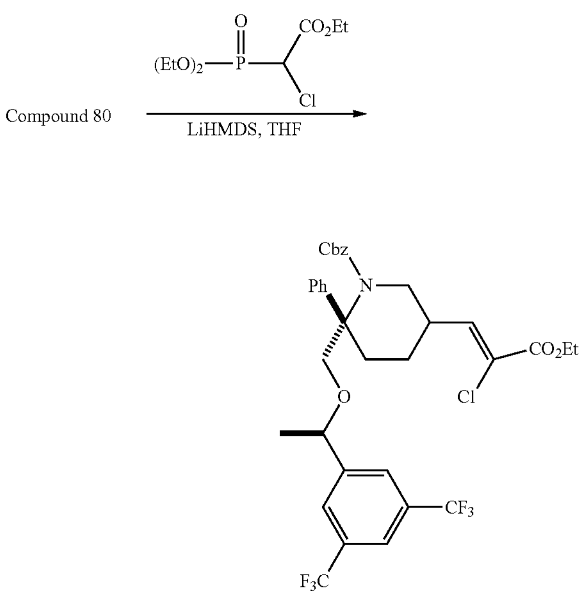


Compound 80

[0573] Compound 80 (72% yield) was prepared by similar procedure as for Compound 23 using Compound 47 in place of Compound 3.

Step 2

[0574]



Compound 81

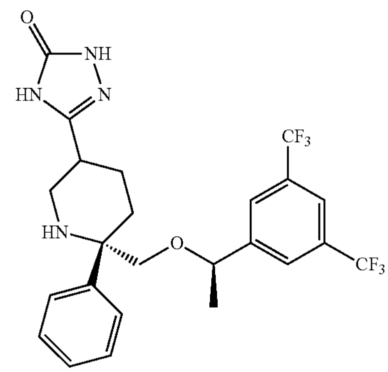
[0575] To a solution of triethyl 2-chloro-2-phophonoacetate (73 μl, 0.34 mmol, 1.05 equiv) in anhydrous THF (1.5 ml) at −78° C., was added dropwise of LiHMDS (0.35 ml, 0.35 mmol, 1.1 equiv, 1N solution in THF). The solution was stirred for 20 min before a solution of Compound 80 (192 mg, 0.32 mmol, 1 equiv) in dry THF (1 ml) was cannulated in. It was stirred at −78° C. for 2 h then quenched with saturated NH_4Cl aqueous solution, and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product which was purified by silica gel column to give Compound 81 (127 mg, 57%).

Step 3

[0576] To a solution of Compound 81 (127 mg, 0.18 mmol, 1.0 equiv) in EtOH (1 ml) was added H_2NNH_2 (35 μl, 1.1 mmol, 6 equiv). It was stirred for 3 h and then concentrated in vacuum. The crude product was retaken up into EtOH (3 ml) and treated with 10% Pd/C (40 mg, 0.036 mmol, 0.2 equiv) and hydrogenated overnight. The catalyst was filtered off and washed with MeOH. The filtrate was concentrated to give the crude residue which was purified on silica gel column to afford less polar isomer Example 92a (14.2 mg, 15%), Electrospray MS $[M+1]^+514.1$; and more polar isomer Example 92b (28.1 mg, 30%), Electrospray MS $[M+1]^+514.1$

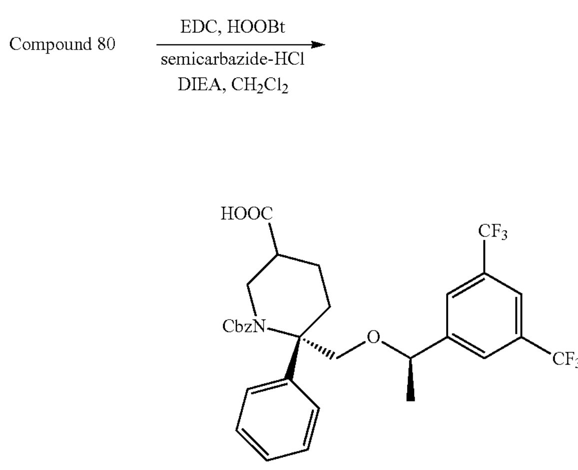
Example 93

[0577]



Step 1

[0578]

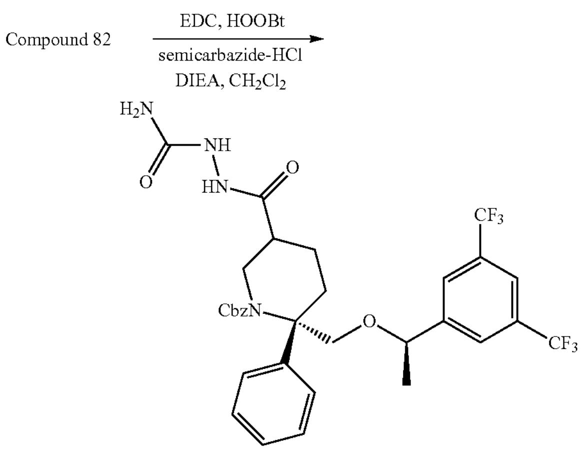


Compound 82

[0579] Compound 80 (0.74 g, 1.25 mmol, 1 equiv), was dissolved in t-BuOH (20 ml) and 2-methyl-2-butadiene (7 ml). To this solution was added a fresh solution of $NaClO_2$ (1.13 g, 12.5 mmol, 10 equiv.) in 20% (v/w) aq. NaH_2PO_4 solution. The reaction mixture was stirred at RT for 2 h. It was then diluted with EtOAc (200 ml) and the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to give the crude Compound 82 which was used in the next reaction without further purification.

Step 2

[0580]

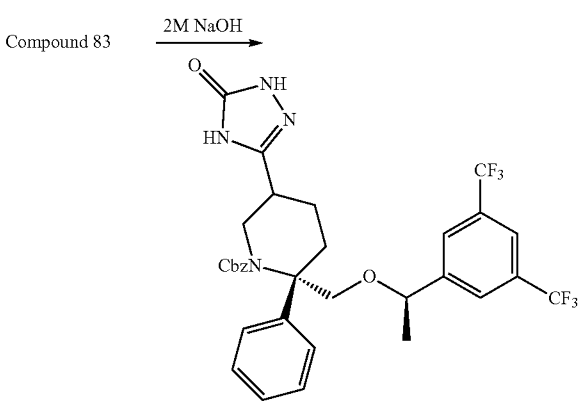


Compound 83

[0581] To a solution of the diastereomeric Compound 82 (0.33 g, 0.54 mmol, 1 equiv) in 2 ml of anhydrous CH_2Cl_2 at RT was sequentially added DIEA (0.11 ml, 0.65 mmol, 1.2 equiv), DEC (0.21 g, 1.1 mmol, 2 equiv), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (0.18 g, 1.1 mmol, 2 equiv), and semicarbazide hydrochloride (0.072 g, 0.65 mmol, 1.2 equiv). After 3 h, the starting carboxylic acid was present by TLC [Hexane-EtOAc 1:1(v/v)] and an additional amount of DIEA (0.11 mL, 0.65 mmol, 1.2 equiv) was added. After 2 days, the reaction mixture was quenched with saturated $NaHCO_3$ solution and diluted with EtOAc. The layers were separated and the organic layer was washed once with water and brine, dried over Na_2SO_4, filtered and concentrated to give an orange oil. Purification by chromatography on a Biotage eluting with the solvent gradient 50% EtOAc/hexane to 80% EtOAc/hexane to EtOAc to 5% MeOH/EtOAc gave Compound 83 as a diastereomeric mixture (0.19 g, 54%) Electrospray MS $[M+1]^+$ 667.07.

Step 3

[0582]



Compound 84

[0583] A solution of Compound 83 (0.17 g, 0.26 mmol, 1 equiv) in 8 ml of 2.0M NaOH solution was heated to reflux. After 15 h, the mixture was allowed to cool to RT and was neutralized with 1.0M HCl to pH6. The aqueous solution was diluted with EtOAc and the layers were separated. The organic layer was washed once with brine, dried over Na_2SO_4, filtered and concentrated to give a yellow oil (0.16 g). Purification by chromatography on a Biotage eluting with 3% MeOH/EtOAc gave Compound 84 as a diastereomeric mixture (0.12 g, 71%) Electrospray MS $[M+1]^+$ 649.2.

Step 4

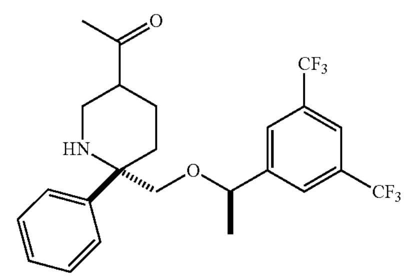
[0584] Less polar product Example 93a and more polar product Example 93b (32 mg and 44 mg, total 88% for both isomers) were prepared from Compound 84 using a similar procedure as for preparing Examples 79a and 79b from Compound 65, but purification used chromatography on a Biotage instead of a Prep plate.

[0585] Electrospray MS $[M+1]^+$ 515.3 for Example 93a.

[0586] Electrospray MS $[M+1]^+$ 515.3 for Example 93b.

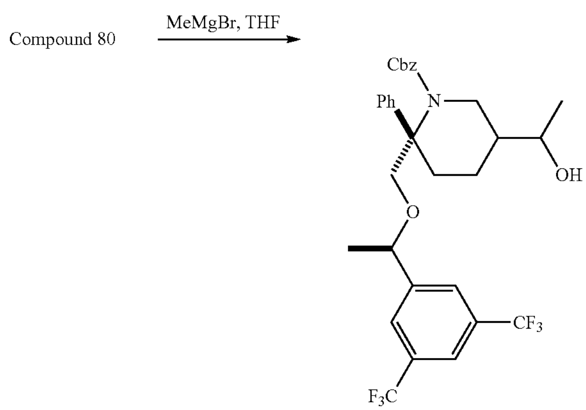
Example 94

[0587]



Step 1

[0588]



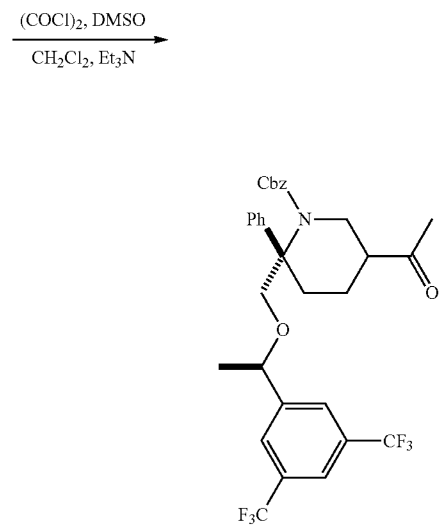
Compound 85

[0589] To a solution of Compound 80 (550 mg, 0.98 mmol, 1 equiv) in anhydrous THF (6 ml) at −10° C., was added dropwise CH_3MgBr (1.24 ml, 3.7 mmol, 4 equiv, 3.0M solution in Et_2O). The solution was stirred at −10° C. to 10° C. for 30 min. Aqueous work-up gave the crude product which was purified on silica gel column to afford Compound 85 (236 mg. 42%).

Step 2

[0590]

Compound 85



Compound 86

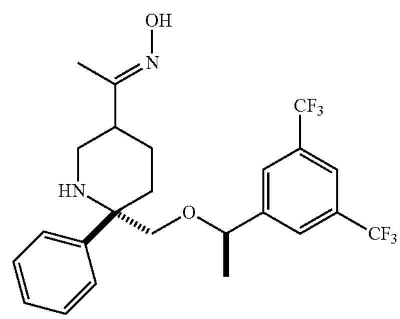
[0591] To a solution of DMSO (0.11 m, 1.55 mmol, 4 equiv) in anhydrous CH_2Cl_2 (5 ml) at −78° C., was added dropwise oxalyl chloride (0.067 ml, 0.78 mmol, 2 equiv). The solution was stirred for 15 min before a solution of Compound 85 (236 mg, 0.387 mmol, 1 equiv) in dry CH_2Cl_2 (1 ml) was cannulated in. It was stirred at −78° C. for 1 h, then Et_3N (0.37 ml, 2.71 mmol, 7 equiv) was added dropwise, After stirring at −78° C. for 30 min, the cooling bath was removed and the reaction was warmed up to RT. It was quenched with saturated NH_4Cl aqueous solution, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by silica gel column to give Compound 86 (140 mg, 60%).

Step 3

[0592] To a solution of Compound 86 (1.0 equiv) in EtOH (3 ml) was added 10% Pd/C (0.4 equiv) and the mixture hydrogenated overnight in a H_2 balloon atmosphere. The catalyst was filtered off and washed with MeOH. The filtrate was concentrated to give the crude residue which was purified on silica gel column to affordless polar isomer Example 94a (24 mg, 22%), Electrospray MS $[M+1]^+$ 474.1; and more polar isomer Example 94b (32 mg, 29%). Electrospray MS $[M+1]^+$ 474.1

Example 95

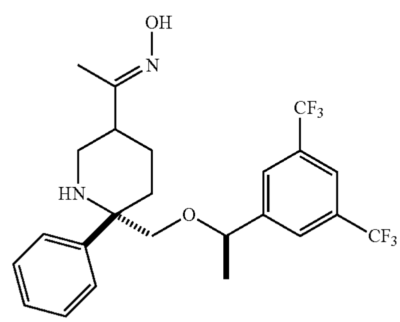
[0593]



[0594] To a solution of Example 94a (16 mg. 0.033 mmol, 1 equiv) in anhydrous EtOH (1 ml) was added hydroxylamine hydrochloride salt (18 mg, 0.26 mmol, 7.7 equiv), and NaOAc (5 mg. 0.061 mmol. 1.8 equiv). The reaction mixture was stirred at RT overnight, then concentrated to dryness. The residue was retaken up with Et_2O, and washed with saturated $NaHCO_3$ aqueous solution. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. The crude product was purified on silica gel column to afford Example 95 (12 mg, 74%), Electrospray MS $[M+1]^+$ 489.1

Example 96

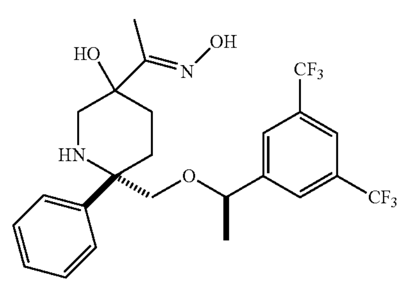
[0595]



[0596] Example 96 (13 mg, 50%) was prepared by similar procedure as for Example 95 but using Example 94b in place of Example 94a. Electrospray MS $[M+1]^+$ 489.1.

Example 97

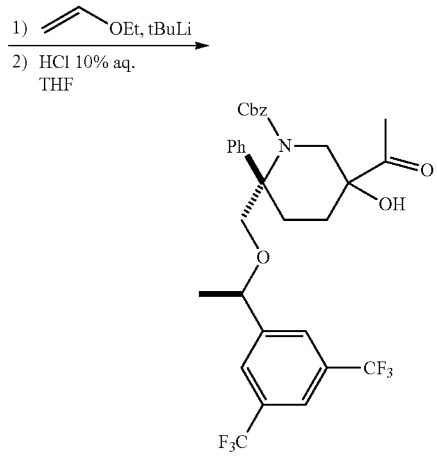
[0597]



Step 1

[0598]

Compound 47



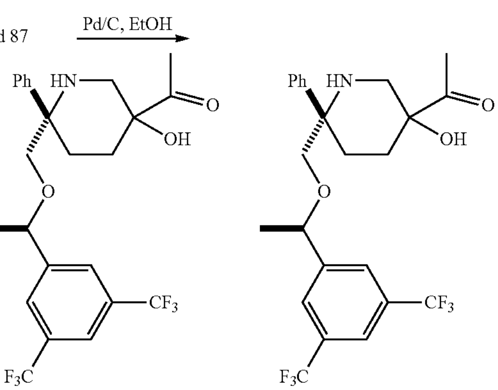
Compound 87

[0599] To a solution of ethyl vinylether (0.5 ml, 4.83 mmol, 12 equiv) in anhydrous THF (6 ml) at −78° C., was added dropwise tBuLi (0.73 ml, 1.24 mmol, 3 equiv, 1.7N solution in pentane). The solution was stirred at −10° C. bath until the orange color faded away. It was cooled to −78° C. again, and a solution of Compound 47(240 mg, 0.41 mmol, 1 equiv) in dry THF (1 ml) was cannulated in. It was stirred at −78° C. for 1.5 h then was quenched with saturated NH_4Cl aqueous solution and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product, which was retaken up into THF (6 ml) and treated with 10% HCl aqueous solution (0.8 ml). It was stirred at RT overnight. Alkaline aqueous work-up gave the crude product which was purified on silica gel column to afford Compound 87 (100 mg, 39%).

Step 2

[0600]

Compound 87



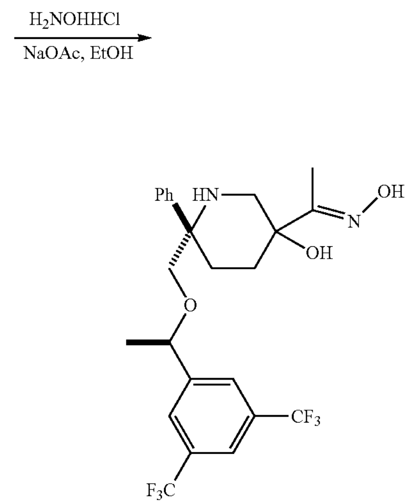
Compound 88a Compound 88b

[0601] Compound 88a and Compound 88b were prepared using a similar procedure as for Examples 94a and 94b using Compound 87 instead of Compound 86. Separation by chiral HPLC column afforded Compound 88a (13 mg, 18%), and Compound 88b (10 mg, 14%).

Step 3

[0602]

Compound 88a



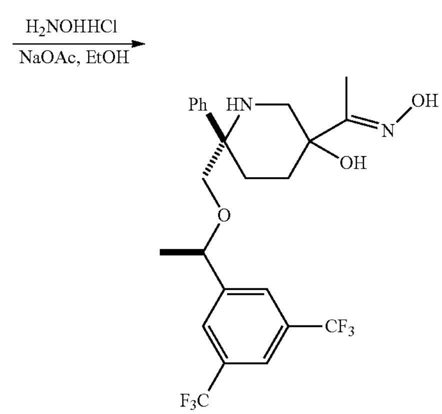
Example 97a

[0603] Example 97a (9.7 mg, 71%) was prepared using similar procedure as for Example 95 using Compound 88a in place of Example 94a. Electrospray MS $[M+1]^+$ 505.1

Step 4

[0604]

Example 88b



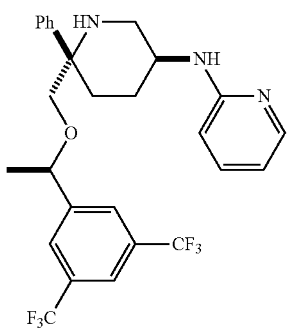
Example 97b

[0605] Example 97b (10.7 mg, 100%) was prepared using similar procedure as for Example 95 using Compound 88b in place of Example 94a. Electrospray MS $[M+1]^+$ 505.1

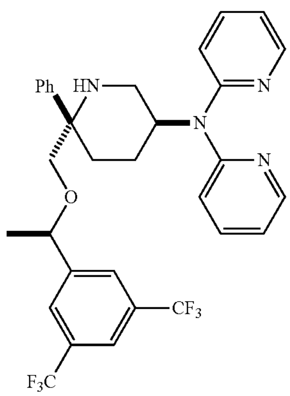
Example 98 and Example 99

[0606]

Example 98



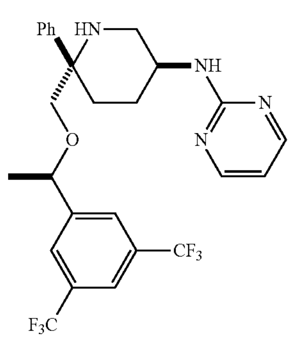
Example 99



[0607] To Example 13 (340 mg, 0.76 mmol) in 1 ml toluene was added $Pd_2(dba)_3$ (27.8 mg, 0.03 mmol), BINAP (37.8 mg, 0.06 mmol), 2-bromopyridine (73 μl, 0.76 mmol) and NaOtBu (102 mg, 1.065 mmol). The mixture was concentrated in vacuo and the flask filled with N_2. The process was repeated once. The dark-brown solution was heated at 90° C. for 16 h. It was cooled to 23° C. and quenched with 2 ml pH7 buffer. The solution was extracted with EtOAc (10 ml×2). The organic layers were dried over Na_2SO_4 and concentrated. HPLC separation give Example 98, Electrospray MS M+1]$^+$ 524.1; and Example 99, Electrospray MS [M+1]$^+$601.1.

Example 100

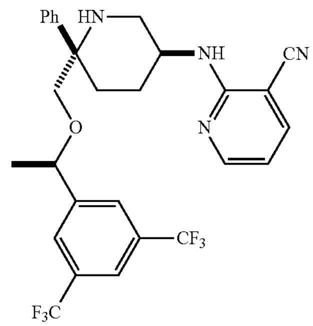
[0608]



[0609] Example 100 was prepared using a similar procedure to Example 98, using 2-bromopyrimidine in place of 2-bromopyridine. Electrospray MS [M+1]$^+$ 525.1.

Example 101

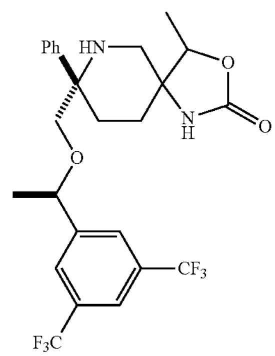
[0610]



[0611] Example 101 was prepared using a similar procedure to Example 98, using 2-chloro-3-cyanopyridine in place of 2-bromopyridine. Electrospray MS [M+1]$^+$ 549.1.

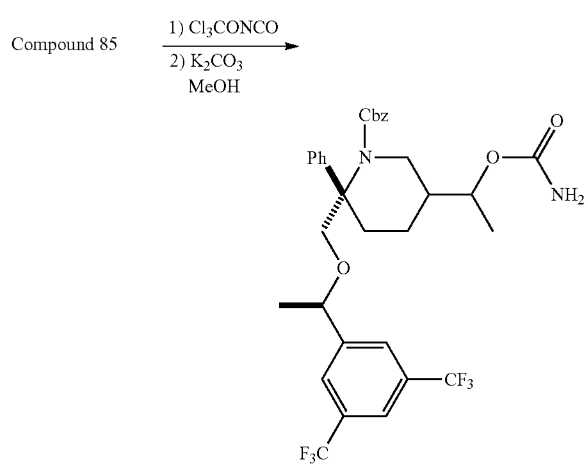
Example 102

[0612]



Step 1

[0613]

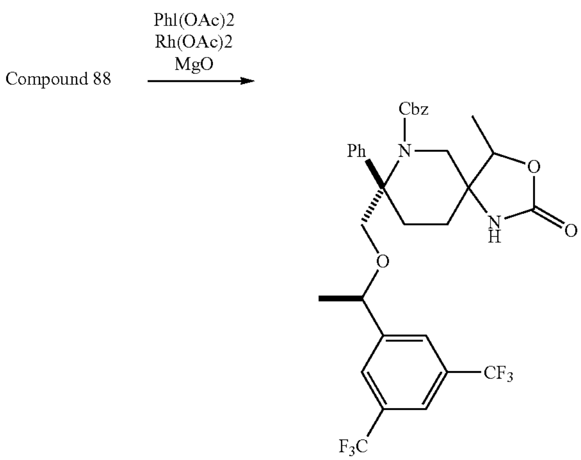


Compound 88

[0614] To Compound 85 (429 mg, 0.704 mmol) in CH_2Cl_2 (3.5 ml) at 0° C. was added Cl_3CONCO (100 ml, 0.844 mmol) dropwise. The solution was stirred at 0° C. for 2 h. The solvent was then removed and the residue was dissolved in MeOH (4 ml) and H_2O (1 ml). K_2CO_3(1.0 g) was added and the suspension was stirred for 14 h. The mixture was then diluted with 3 ml of water, concentrated to remove MeOH. The residue was extracted with EtOAc (10 ml×3). The combined organic layers were concentrated and passed through a short silica gel column to give product Compound 88 (420 mg, 91%).

Step 2

[0615]



Compound 89

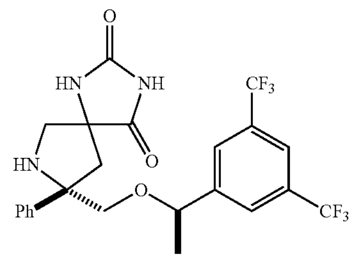
[0616] To Compound 88 (290 mg, 0.446 mmol) in CH_2Cl_2 (3 ml) was added $PhI(OAc)_2$ (131 mg, 0.625 mmol), $Rh_2(OAc)_4$ (12.9 mg, 0.022 mmol) and MgO (26.4 mg, 1.0 mmol). The suspension was heated at 40° C. for 16 h then cooled to 23° C. Celite (0.5 g) was added and the suspension was stirred for 5 min. The mixture was filtered and washed with EtOAC. The combined filtrate was concentrated and purified by chromatography on silica gel to give Compound 89 (60 mg, 31%).

Step 3

[0617] Compound 89 transferred to a Parr shaker using 5 ml EtOH. 10% Pd—C (10%, 60 mg) was added and the suspension was hydrogenated at 40 psi overnight. The reaction mixture was filtered and concentrated. The residue was separated using HPLC on OD column eluted with 1:9 IPANhexane to give two isomers, less polar isomer Example 102a, Electrospray MS $[M+1]^+$ 517.1 and more polar isomer Example 102b, Electrospray MS $[M+1]^+$ 517.1.

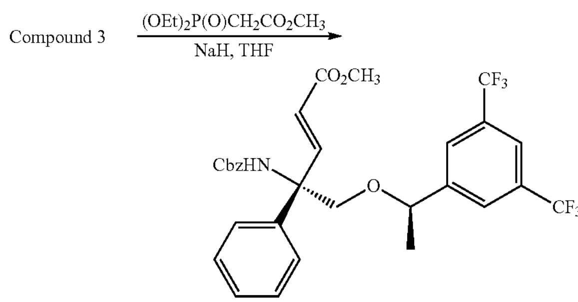
Example 103

[0618]



Step 1

[0619]

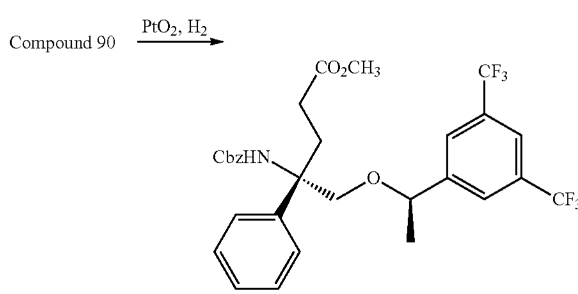


Compound 90

[0620] To a mixture of methyl diethylphosphonoacetate (9.5 ml. 51.77 mmol, 3 equiv) in dry THF (100 ml) at 0° C. under N_2 was added NaH (60% in mineral oil, 1.24 g, 51.77 ml, 3 equiv.). After being stirred at 0° C. for 15 min, a solution of Compound 3 (109, 17.26 mmol, 1 equiv) in THF (250 ml) was added. The mixture was warmed to 23° C. and stirred for 1 h and then quenched with saturated aq. $NaHCO_3$ solution (100 ml). The mixture was extracted with EtOAc (100 ml×3). The combined organic layers were dried ($MgSO_4$) and filtered. The crude product was purified by column chromatography over Biotage (4:1, hexane:EtOAc then 1:1, hexane:EtOAc) to afford the Compound 90 (8.88 g, 86%), Electrospray MS $[M+1]^+$ 596.1.

Step 2

[0621]

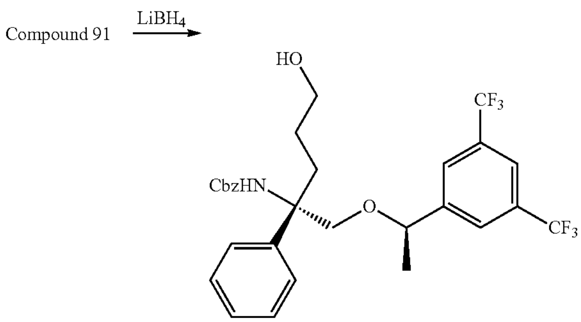


Compound 91

[0622] Compound 91 was prepared from Compound 90 using the procedure similar to the preparation of Compound 44 from Compound 42. The crude Compound 91 was used in the next reaction without further purification.

Step 3

[0623]

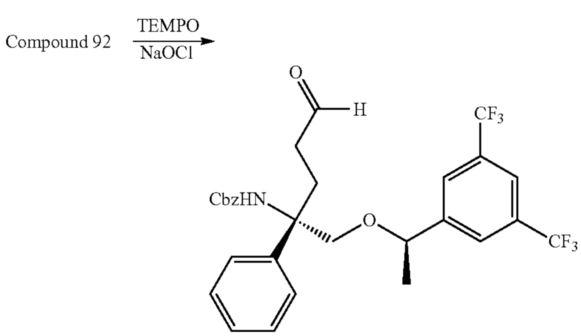


Compound 92

[0624] To a solution of Compound 91 (8.8 g, 14.73 mmol, 1 equiv.) in dry THF (150 ml) was added $LiBH_4$ (0.58 g, 26.51 mmol, 1.8 equiv.) and the reaction mixture was stirred at 0° C. for two h. The reaction mixture was cooled to 0° C. over an ice bath and quenched with saturated $NaHCO_3$ (50 ml). The reaction mixture was extracted with EtOAc (3×100 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give crude Compound 92 (8.2 g), Electrospray MS $[M+1]^+$ 570.1, which was used in the next reaction without further purification.

Step 4

[0625]

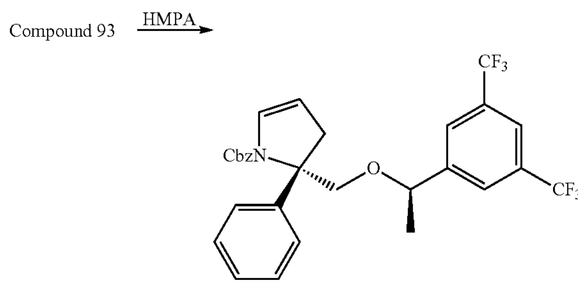


Compound 93

[0626] To a solution of Compound 92 (8.2 g, 14.4 mmol, 1.0 equiv.) in EtOAc (150 ml) at 0° C. was added saturated aq. $NaHCO_3$ (150 ml) and the reaction mixture was stirred for 10 min at 0° C. NaBr (1.5 g, 14.4 mmol, 0.01 equiv.) was added to the reaction mixture, followed by TEMPO (0.0225 g, 0.144 mmol, 0.1 equiv), and bleach (5.25% in H_2O, 20.4 ml, 14.4 mmol, 1.0 equiv). The reaction mixture was stirred for 15 min at 0° C. The reaction was monitored by TLC in 1:2 EtOAc/hexane which indicted presence of starting material. Additional NaOCl (2 ml) was added to the reaction mixture and was stirred for 15 min at 0° C. and then it was quenched with saturated $Na_2S_2O_3$ (20 ml). The reaction mixture was extracted with EtOAc (150 ml×3). The combined organic layers were dried over ($MgSO_4$), filtered and concentrated to give crude Compound 93 (8 g) which was used in the next reaction without further purification.

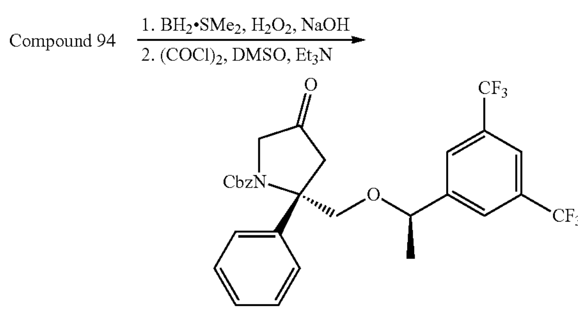
Step 4

[0627]



Compound 94

[0628] A mixture of Compound 93 (8 g, 14.1 mmol, 1.0 equiv.) and HMPA (50 ml) was heated at 170° C. for two h. The reaction mixture was cooled to 23° C. and quenched with water (50 ml). The reaction mixture was extracted with Et_2O (150 ml×3). The combined organic layers were dried over ($MgSO_4$), filtered and concentrated. The crude product purified by column chromatography over Biotage (7:3, hexane:EtOAc) to afford Compound 94 (3.8 g, 40% over three steps), Electrospray MS [M+1]+550.1.



Compound 95

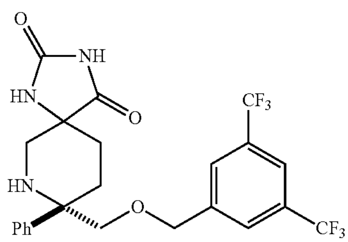
[0629] Compound 95 was prepared from Compound 94 using the procedure similar to the preparation of Compound 47 from Compound 45. Electrospray MS $[M+1]^+$ 566.1.

Step 6

[0630] Compound 95 was converted to less polar isomer Example 103a, Electrospray MS $[M+1]^+$ 502.1, and more polar isomer Example 103b, Electrospray MS $[M+1]^+$ 502.1, using the procedure similar to the preparation of Example 43a and Example 44b from Compound 47.

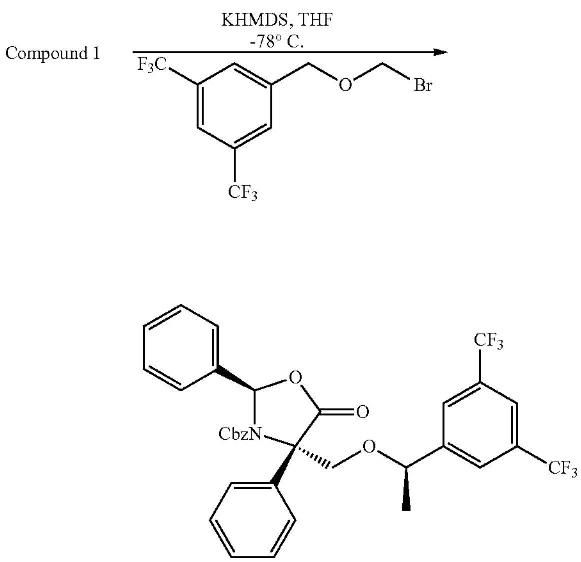
Example 104

[0631]



Step 1

[0632]



Compound 96

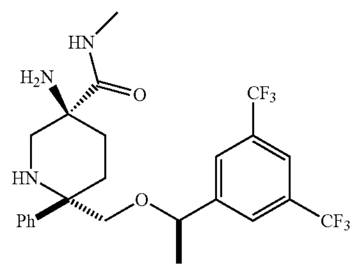
[0633] Compound 96 was prepared from Compound 1 using the procedure similar to the preparation of Compound 3 from Compound 1. Electrospray MS $[M+1]^+$ 566.1 for the Compound 106.

Step 2

[0634] Compound 96 was converted to a mixture of Example 104a and Example 104b using the procedure similar to the preparation of Examples 43a and 44b from Compound 2. The mixture of two isomers was separated on HPLC "ChiralPak AD column" using (5:95, IPA:hexane) to afford pure less polar isomer Example 104a, Electrospray MS $[M+1]^+$ 502.1 and more polar isomer Example 104b, Electrospray MS $[M+1]^+$ 502.1.

Example 105

[0635]

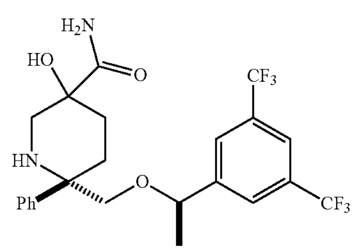


[0636] Example 105 was prepared from Compound 54 using the procedure similar to the preparation of Compound 62 from Compound 54, but using CH_3NH_2 (2M in THF) in place of ammonia (0.5M in 1,4-dioxane). Electrospray MS $[M+1]^+$ 504.1.

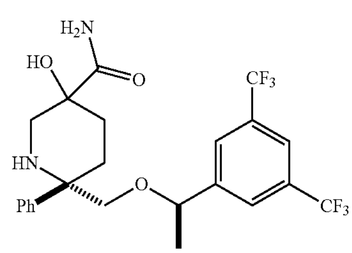
Example 106a and Example 106b

[0637]

Example 106a

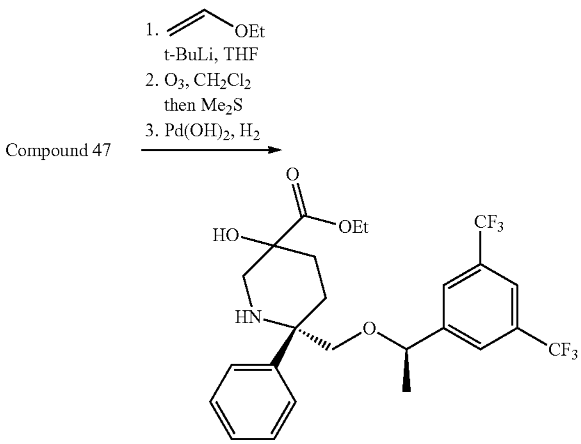


Example 106b



Step 1

[0638]



Compound 97

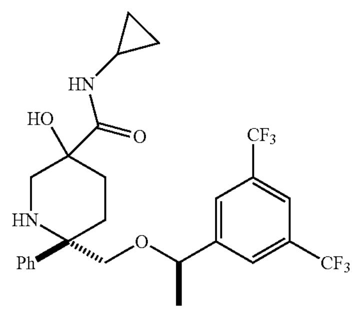
[0639] To a solution of ethyl vinyl ether (2.51 ml, 26.1 mmol) in THF (50 ml) at −78° C. under N_2, t-BuLi (6.6 ml, 11.2 mmol, 1.7M in pentane) was added. The mixture was warmed to 0° C. and stirred until the color of the solution turned pale yellow. The mixture was then re-cooled at −78° C. and a solution of Compound 47(2.16 g, 3.73 mmol) in THF (20 ml) was added. The mixture was stirred at −78° C. for 1 h before quenched with saturated $NaHCO_3$ solution. Water and Et_2O were added to the mixture. Layers were separated and the aqueous layer was extracted with Et_2O (200 ml×2). The combined organic layers were dried (K_2CO_3, Na_2SO_4) and filtered. Solvents were removed in vacuum to give an alcohol as yellow oil. The alcohol was dissolved in CH_2Cl_2 (20 ml) and ozone was bubbled through the solution at −78° C. until pale blue color persisted. $(CH_3)_2S$ (2.7 ml, 37.3 mmol) was added and the mixture was warmed to RT. Solvents were removed in vacuum and purification by column chromatography [CH_2Cl_2] gave an ester as colorless oil. The ester was dissolved in EtOH (20 ml) and a catalytic amount of $Pd(OH)_2$ (20% on carbon) was added. The mixture was shaken in a Parr hydrogenator at 45 psi overnight. The mixture was filtered through a pad of Celite and solvents were removed in vacuum to give a colorless oil. Separation by column chromatography [hexane-EtOAc, 4:1(v/v)] gave Compound 97 as colorless oil.

Step 2

[0640] Compound 97 was dissolved in CH_3OH (10 ml) and ammonia was bubbled through the solution for 30 min. The mixture was stirred at RT overnight and solvents were removed in vacuum to give a yellow oil. Separation by HPLC using Chiralcel OD [hexane-isopropanol, 9:1 (v/v)] gave the less polar major isomer Example 106a (15% overall) as white foam. Electrospray MS $[M+1]^{+}$=491.1. Continuous elution with the same solvent system gave the more polar minor isomer Example 106b (10% overall) as white foam. Electrospray MS $[M+1]^{+}$=491.1.

Example 107

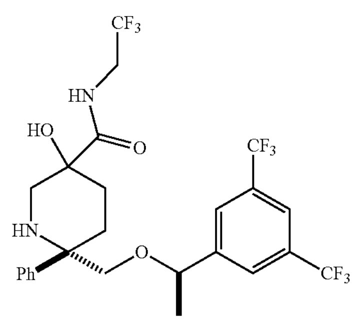
[0641]



[0642] To a solution of cyclopropylamine (17 μl, 0.20 mmol) in toluene (1 ml) at RT under N_2, $Al(CH_3)_3$(0.1 ml, 0.20 mmol, 2.0M in toluene) was added. The mixture was allowed to stir at RT for 20 min. and a solution of Compound 97 (20 mg, 0.040 mmol) in toluene (1 ml) was added. The mixture was heated at 60° C. overnight and was cooled to RT. EtOAc was added and the mixture was quenched with saturated potassium sodium tartarate solution. The layers were separated and the aqueous layer was extracted with EtOAc (100 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-EtOAc, 2:1 (v/v)] gave Example 107 (11 mg, 56%) as colorless oil. Electrospray MS (M+1)=531.

Example 108

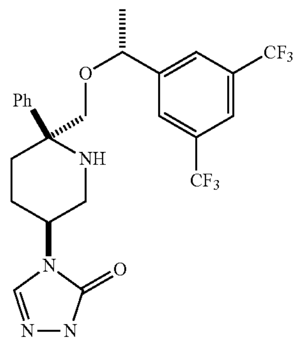
[0643]



[0644] Example 108a and Example 108b were prepared from Compound 97 using the procedure similar to the preparation of Example 107 from Compound 97 but using 2,2,2-trifluoroethylamine in place of cyclopropylamine. Electrospray MS $[M+1]^{+}$ 573.1 for the less polar isomer Example 108a and Electrospray MS [M+1]+573.1 for the more polar isomer Example 108b.

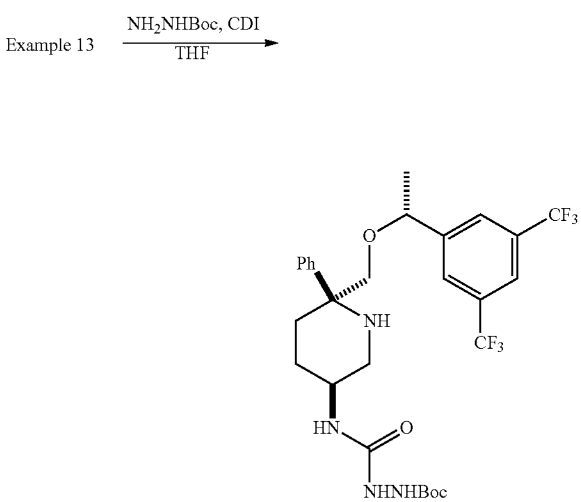
Example 109

[0645]



Step 1

[0646]

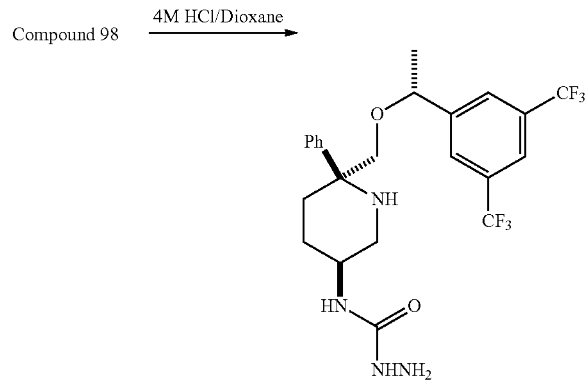


Compound 98

[0647] To a solution of diamine Example 13 (150 mg, 0.336 mmol, 1 equiv) in anhydrous THF (5 ml) at 0° C. was added tert-butylcarbazine (44.4 mg, 0.336 mmol, 1 equiv) followed by CDI (65.4 mg, 0.404 mmol, 1.2 equiv). The reaction mixture was warmed to RT and stirred for 2 h. The reaction mixture was then concentrated and purified on a biotage (5:95 MeOH/EtOAc) to give Compound 98 (170 mg, 84%), Electrospray MS $[M+1]^+$ 605.3.

Step 2

[0648]



Compound 99

[0649] To a solution of Compound 98 (170 mg, 0.281 mmol, 1 equiv) in anhydrous CH_2Cl_2 (15 ml) at 0° C. was added a 4M HCl solution in 1,4-dioxane (0.7 ml, 2.81 mmol, 10 equiv). The reaction mixture was warmed to RT and stirred for 18 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (100 ml) and extracted with EtOAc (2×150 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product Compound 99 was used in the next reaction without further purification.

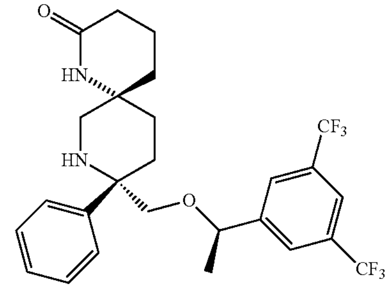
Step 3

[0650] To a solution of Compound 99 (160 mg, 0.317 mmol, 1 equiv) in anhydrous DMF (5 ml) was added formamidine acetate (165 mg, 1.6 mmol, 5 equiv) and the reaction mixture was stirred at RT for 30 min. HOAc (0.091 ml, 1.6 mmol, 5 equiv) was added and the reaction mixture was heated at 80° C. for 6 h. The reaction mixture was then cooled to RT, poured into EtOAc (200 ml) and washed with water (3×100 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified on Gilson (1:9 H_2O/CH_3CN) to give Example 109 (50 mg, 35%), Electrospray MS $[M+1]^+$ 515.3.

Example 110a and Example 110b

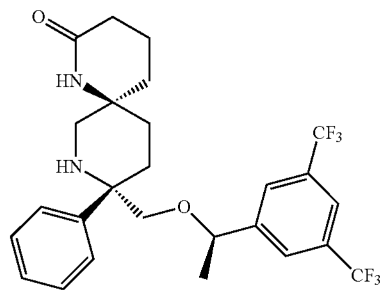
[0651]

Example 110a



-continued

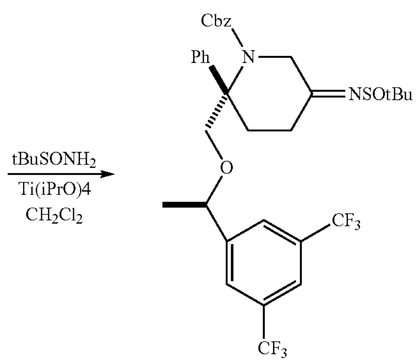
Example 110b



Step 1

[0652]

Compound 47



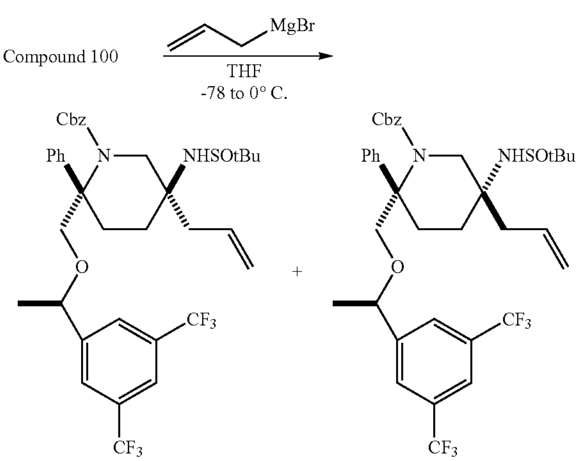
Compound 100

[0653] Using a procedure similar to Example 11, step 2. Compound 47 was converted to the corresponding sulfinimine, Compound 100.

Step 2

[0654]

Compound 100



Compound 101a

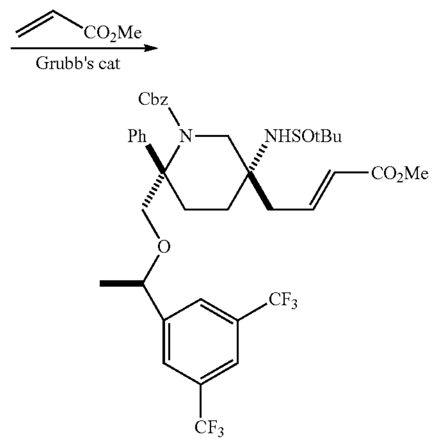
Compound 101b

[0655] Following a procedure similar to Example 11, Step 3, Compound 100 was converted to sulfinamide Compounds 101a and 101b.

Step 3

[0656]

Compound 101b



Compound 102

[0657] A 15 ml pear-shaped flask was charged with Compound 101b (140 mg, 0.193 mmol, 1 equiv) and CH_2Cl_2(1 ml). To this pale yellow solution was added Grubbs' catalyst (13.7 mg, 0.016 mmol, 0.084 equiv), and methyl acrylate (21 μl, 0.232 mmol, 1.2 equiv). The resulting reddish solution was heated at 40° C. overnight and quenched with methylsulfoxide (0.2 ml). After stirring at RT for 20 h, it was diluted with Et_2O and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica column to give Compound 102 (100 mg, 66%).

Step 4

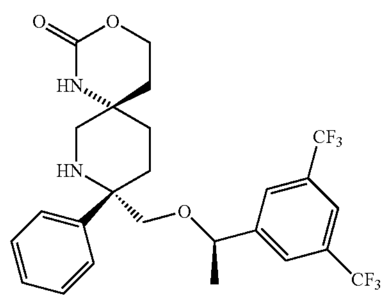
[0658] A RBF was charged with Compound 102 (100 mg, 0.128 mmol, 1 equiv) in EtOH (3 ml), and $Pd(OH)_2$ on carbon (90 mg, 0.128 mmol, 1 equiv, 20% wt). A hydrogen balloon was attached on the top and the mixture was hydrogenated overnight. The reaction mixture was carefully passed through a celited funnel and the celite pad was washed thoroughly with MeOH. The filtrate was concentrated, then re-taken up into MeOH (2 ml), treated with HCl (2 ml, 4.0M in 1,4-dioxane), stirred at RT for 2 h, then concentrated again, retaken up again into MeOH (5 ml), treated with an excess amount of K_2CO_3, and heated at 50° C. for 3 h, filtered, concentrated, and the resulted residue was purified on a silica column to afford Example 110a (42 mg, 64%). Electrospray MS $[M+1]^+$ 515.1

[0659] Example 110b (49%) was prepared by a similar procedure, but using Compound 101a. Electrospray MS $[M+1]^+$ 515.1

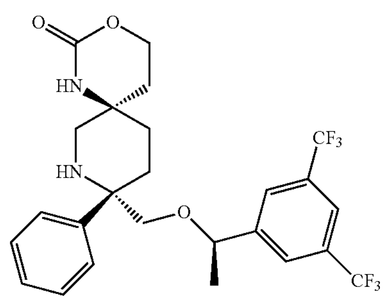
Example 11a and Example 111b

[0660]

Example 111a

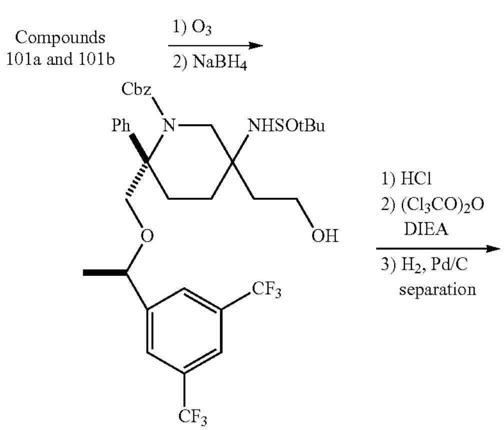


Example 111b



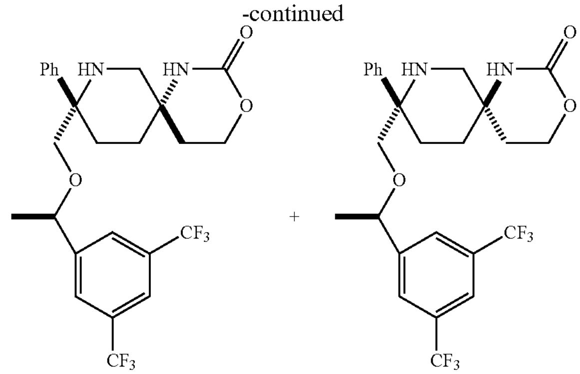
Step 1

[0661]



Compound 103

-continued



Example 111a

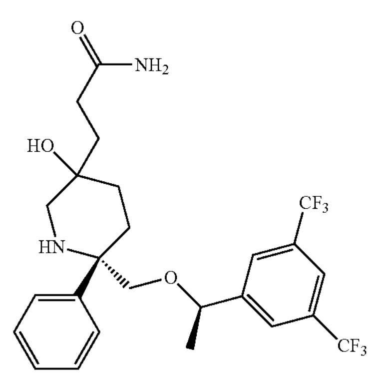
Example 111b

[0662] An RBF was charged with a mixture of Compound 101a and 101b (180 mg, 0.248 mmol, 1.0 equiv) and CH_2Cl_2 (2 ml). This pale orange solution was cooled to −78° C., and then O_3 was bubbled in. After the solution turned pale blue, the reaction solution was stirred at −78° C. for 10 min, then it was flushed with N_2 to get rid of O_3. The solvent was then removed carefully. The residue was dissolved in EtOH followed by addition of $NaBH_4$ (120 mg). The solution was stirred at RT for 12 h. It was quenched with NH_4Cl solution. The reaction was extracted with EtOAc (3×10 ml). The organic solution was washed with brine, dried and concentrated to give Compound 103, which was used in the next reaction without further purification.

[0663] The crude Compound 103 was dissolved in MeOH (2 ml) and cooled to 0° C., followed by the addition of HCl (6 ml, 4N in dioxane). After stirring for 3 h, the solvent was removed and the residue was redissolved in 3 ml CH_2Cl_2, followed by the addition of DIEA (178 μl). The solution was cooled to 0° C., triphosgene (36 mg) was added, and the reaction was allowed to warm to RT and stirred for 3 h. It was then diluted with EtOAc, washed with 5% HCl, $NaHCO_3$ (aq.) and brine. The organic layers were dried with Na_2SO_4, filtered and concentrated. The crude product was hydrogenated to give a mixture of Example 111a and 111b. The mixture was separated using prep TLC (5% MeOH in CH_2Cl_2) to give Example 111a (less polar) and Example 111b (more polar). Electrospray MS Example 111a $[M+1]^+$ 517.1; Example 111a $[M+1]^+$ 517.1.

Example 112

[0664]

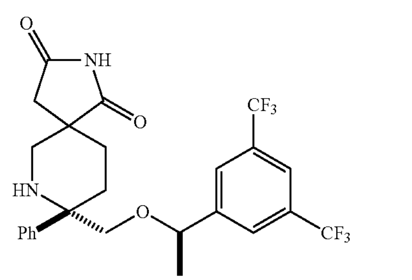


[0665] To a solution of ethyl propioiate (83 μl, 0.82 mmol) in THF (2 ml) at −78° C. under N_2, t-butyllithium (0.48 ml, 0.82 mmol, 1.7M in pentane) was added. The mixture was stirred at −78° C. for 10 min and a solution of Compound 47 (158 mg, 0.27 mmol) in THF (1 ml) was added. The mixture was stirred at −78° C. for 1 h before quenching with HOAc at −78° C. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (200 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexanes-EtOAc, 4:1 (v/v)] gave a colorless oil (112 mg, 61%). The oil was dissolved in EtOH and catalytic amount of palladium (10% on charcoal) was added. The mixture was shaken in a Parr hydrogenator at 45 psi overnight. The mixture was filtered through a pad of celite and solvents were removed in vacuum to give an ester as a colorless oil. The oil was dissolved in CH_3OH (10 ml) and ammonia was bubbled through the solution for 30 min. The mixture was stirred at RT overnight and solvents were removed in vacuum. Purification by column chromatography [CH_3OH-EtOAc, 1:9 (v/v)] gave Example 112 as a colorless oil (54 mg, 61%). Electrospray MS $[M+1]^+$=519.1.

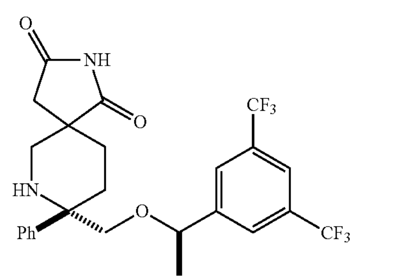
Examples 113a and 113b

[0666]

Example 113a



Example 113b



[0667] To a solution of Compound 51 (1.97 g, 3.10 mmol) in CH_2Cl_2 (50 ml) at −78° C., P DIBAL-H (9.3 ml, 9.3 mmol, 1.0M in toluene) was added. The mixture was stirred at −78° C. for 1 h before it was quenched with saturated potassium sodium tartrate solution. The mixture was warmed to RT and water and EtOAc were added. Layers were separated and the aqueous layer was extracted with EtOAc (200 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and column chromatography [hexane-EtOAc, 3:1(v/v)] gave the allylic alcohol (1.6 g, 85%) as colorless oil.

[0668] The allylic alcohol (1.6 g, 2.63 mmol) was dissolved in triethylorthoacetate (30 ml) and catalytic amount of propanoic acid was added. The mixture was heated in a sealed-tube at 130° C. overnight. Solvents were removed in vacuum and column chromatography [hexane-Et_2O, 5:1(v/v)] gave the alkene (891 mg, 50%) as colorless oil.

[0669] The alkene (891 mg, 1.31 mmol) was dissolved in CH_2Cl_2 (20 ml) and was cooled at −78° C. O_3 was bubbled through the solution until a pale blue color persisted in the solution. The mixture was purged with N_2 until a colorless solution was obtained. Methyl sulfide (1 ml) was added and the mixture was warmed to RT. Solvents were removed in vacuum and column chromatography [Hexanes-EtOAc, 5:1 (v/v)] gave the aldehyde (800 mg, 90%) as colorless oil.

[0670] The aldehyde (280 mg. 0.41 mmol) was dissolved in isoprene (2.4 ml) and t-butyl alcohol (7 ml) at RT. A solution of sodium chlorite (414 mg, 4.12 mmol) in sodium dihydrogenphosphate (4 ml, 20% wt. in water) was added. The mixture was stirred at RT vigorously for 2 h. Water and EtOAc were added. Layers were separated and the aqueous layer was extracted with EtOAc (250 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give a crude acid as yellow oil.

[0671] The crude acid was dissolved in CH_2Cl_2 (10 mil) at RT and diisopropylamine (0.22 ml, 1.24 mmol), followed by PyBOP (322 mg, 0.62 mmol) were added. The mixture was stirred at RT for 20 min. before a solution of ammonia in dioxane (8 ml, 4.12 mmol) was added. The mixture was stirred at RT overnight before it was quenched with saturated $NaHCO_3$ solution. Water and EtOAc were added. Layers were separated and the aqueous layer was extracted with EtOAc (250 ml×2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give the crude amide as yellow oil.

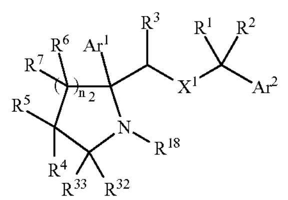
[0672] The crude amide was dissolved in CH_3OH (10 ml) and $Pd(OH)_2$ (20% on carbon) was added. The mixture was stirred under H_2 (balloon) for 4 h. Solid was filtered through a pad of celite and solvents were removed in vacuum to give the crude amino-amide as yellow oil.

[0673] The crude amino-amide was dissolved in CH_3OH and excess $NaOCH_3$ was added. The mixture was heated at 60° C. for 1 h before it was quenched with saturated with saturated NH_4Cl solution. Water and EtOAc were added. Layers were separated and the aqueous layer was extracted with EtOAc (250 ml×2): The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and column chromatography [hexane-EtOAc, 2:1 (v/v)] gave the less polar isomer Example 113a (20 mg, 9%, 4 steps overall) as white foam. Electrospray MS $[M+1]^+$ =515.1. Continuous elution with the same solvent system gave the more polar isomer Example 113b (25 mg, 12%, 4 steps overall) as colorless oil. Electrospray MS $[M+1]^+$ =515.1.

[0674] The above description is not intended to detail all modifications and variations of the invention. It will be appreciated by those skilled in the art that changes can be made to the embodiments described above without departing from the inventive concept. It is understood, therefore, that the invention is not limited to the particular embodiments described above, but is intended to cover modifications that are within the spirit and scope of the invention, as defined by the language of the following claims.

What is claimed is:

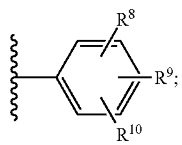
1. A compound having the formula (I):



(I)

or a pharmaceutically-acceptable salt thereof, wherein

Ar^1 and Ar^2 are each independently selected from the group consisting of R^{17}-heteroaryl and



X^1 is —O—, —S—, —SO—, —SO_2—, —NR^{34}—, —$N(COR^{12})$— or —$N(SO_2R^{15})$—;

when X^1 is —SO—, —SO_2—, —$N(COR^{12})$— or —$N(SO_2R^{15})$—, then:

R^1 and R^2 are each independently selected from the group consisting of H, C_1-C_6 alkyl, hydroxy(C_1-C_3alkyl), C_3-C_8 cycloalkyl, —CH_2F, —CHF_2 and —CF_3; or R^1 and R^2, together with the carbon atom to which they are both attached, form a C_3 to C_6 alkylene ring; or

when X^1 is —O—, —S— or —NR^{34}—, then:

R^1 and R^2 are each independently selected from the group consisting of H, C_1-C_6 alkyl, hydroxy(C_1-C_3alkyl), C_3-C_8 cycloalkyl, —CH_2F, —CHF_2 and —CF_3; or R^1 and R^2, together with the carbon atom to which they are both attached, form a C_3 to C_6 alkylene ring; or R^1 and R^2, together with the carbon atom to which they are both attached, form a C═O group;

R^3 is selected from the group consisting of H, C_1-C_6 alkyl, hydroxy(C_1-C_3 alkyl), C_3-C_8 cycloalkyl, —CH_2F, —CHF_2 and —CF_3;

each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl and —OH;

each R^7 is independently selected from the group consisting of H and C_1-C_6 alkyl;

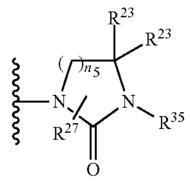
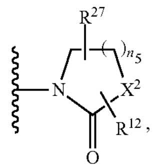
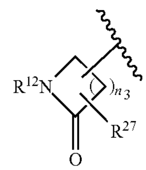
n_2 is 1 to 4;

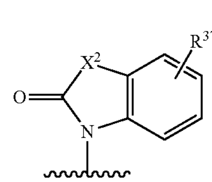
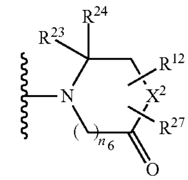
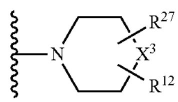
R^4 and R^5 are each independently selected from the group consisting of —$(CR^{28}R^{29})_{n1}$-G,

where,

n_1 is 0 to 5; and

G is H, —CF_3, —CHF_2, —CH_2F, —OH, —O—(C_1-C_6 alkyl), —OCH_2F, —$OCHF_2$, —OCF_3, —OCH_2CF_3, —O—(C_3-C_8 cycloalkyl), —O—(C_1-C_6)alkyl(C_3-C_8 cycloalkyl), —$NR^{13}R^{14}$, —$SO_2NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$NR^{12}C(O)R^{14}$, —$NR^{12}C(O)OR^{13}$, —$NR^{12}(C(O)NR^{13}R^{14})$, —$C(O)NR^{13}R^{14}$, —$C(O)OR^{13}$, —$C_3$-$C_8$ cycloalkyl, $(R^{19})_r$-aryl, $(R^{19})_r$-heteroaryl, —$OC(O)R^{14}$, —$OC(O)NR^{13}R^{14}$, —$C(=NOR^{14})(R^{13})$, —$C(O)R^{13}$, —$C(OR^{12})(R^{13})(R^{14})$, heterocycloalkenyl optionally substituted by 1 to 4 substituents independently selected from the group consisting of R^{30} and R^{31},



or

; or

R^4 and R^5 together are ═O, ═NOR^{12}; or

R^4 and R^5, together with the carbon atom to which they are both attached, form a 4- to 8-membered heterocycloalkyl or heterocycloalkenyl ring containing 1 to 3 groups Independently selected from X^2, provided that at least one X^2 is —NR^{35}—, —O—, —S—, —S(O)— or —SO_2—, the ring being optionally substituted with from 1 to 6 substituents independently selected from the group consisting of R^{30} and R^{31};

provided that R^4 and R^5 are not both selected from the group consisting of H, alkyl and cycloalkyl;

further provided that, when one of R^4 and R^5 is —OH, then the other one of R^4 and R^5 is not alkyl or $(R^{19})_r$-aryl;

R^8, R^9 and R^{10} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, —OR^{12}, halogen, —CN, —NO_2, —CF_3, —CHF_2, —CH_2F, —CH_2CF_3, —OCF_3, —$OCHF_2$, —OCH_2F, —OCH_2CF_3, —$COOR^{12}$, —$CONR^{21}R^{22}$, —$OC(O)NR^{21}R^{22}$, —$OC(O)R^{12}$, —$NR^{21}COR^{12}$, —$NR^{21}CO_2R^{15}$, —$NR^{21}CONR^{21}R^{22}$, —$NR^{21}SO_2R^{15}$, —$NR^{21}R^{22}$, —$SO_2NR^{21}R^{22}$, —$S(O)_{n6}R^{15}$, $(R^{19})_r$-aryl and $(R^{19})_r$-heteroaryl;

R^{12} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

R^{13} and R^{14} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, —CH_2CF, aryl and heteroaryl; or

R^{13} and R^{14}, together with the nitrogen atom to which they are both attached, form a 4- to 7-membered saturated or unsaturated ring that is optionally substituted with —OR^{17}, where one of the carbon atoms In the ring is optionally replaced by a heteroatom selected from the group consisting of —O—, —S— and —NR^{34}—;

n_6 is 0, 1 or 2;

R^{15} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, —CF_3 or —CH_2CF_3;

R^{18} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, hydroxy(C_2-C_8)alkyl or —P(O)$(OH)_2$;

each R^{19} is a substituent on the aryl or heteroaryl ring to which it is attached, and is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, —OH, halogen, —CN, —NO_2, —CF_3—CHF_2, —CH_2F, —OCF_3, —$OCHF_2$, —OCH_2F, —O—(C_1-C_6 alkyl), —O—(C_3-C_8 cycloalkyl), —$COOR^{12}$, —$CONR^{21}R^{22}$, —OC(O)$NR^{21}R^{22}$, —OC(O)R^{12}, —$NR^{21}R^{22}$, —$NR^{21}COR^{12}$, —$NR^{21}CO_2R^{12}$, —$NR^{21}CONR^{21}R^{22}$, —$NR^{21}SO_2R^{15}$ and —$S(O)_{n6}R^{15}$;

R^{21} and R^{22} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl and benzyl; or

R^{21} and R^{22}, together with the nitrogen atom to which they are both attached, form a 4- to 7-membered saturated or unsaturated ring, where one of the carbon atoms in the ring is optionally replaced by a heteroatom selected from the group consisting of —O—, —S— and —NR^{34}—;

R^{23} and R^{24} are each independently selected from the group consisting of H and C_1-C_6 alkyl; or

R^{23} and R^{24}, together with the carbon atom to which they are both attached, form a C═O or cyclopropyl group;

R^{27} is H, —OH or C_1-C_6 alkyl;

R^{28} and R^{29} are each independently selected from the group consisting of H and C_1-C_2 alkyl;

R^{30} and R^{31} are each independently selected from the group consisting of H, —OH, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl and —C(O)$NR^{13}R^{14}$; or

R^{30} and R^{31}, together with the carbon atom to which they are both attached, form ═O, ═S, a cyclopropyl ring or ═NR^{36};

R^{32} and R^{33} are each independently selected from the group consisting of H and C_1-C_6 alkyl;

R^{34} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl or hydroxy(C_2-C_6)alkyl;

R^{35} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, —P(O)$(OH)_2$, allyl, hydroxy(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, —SO_2R^{15} or —$(CH_2)_2$—N(R^{12})—SO_2—R^{15};

R^{36} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, —NO_2, —CN or OR^{12};

R^{37} is 1 to 3 substituents independently selected from the group consisting of H, C_1-C_6 alkyl, —OH, C_1-C_6 alkoxy and halogen;

r is 1 to 3;

X^2 is —NR^{35}—, —O—, —S—, —S(O)—, —SO_2—, —CH_2—, —CF_2— or —$CR^{12}F$—;

X^3 is —NR^{34}—, —N($CONR^{13}R^{14}$)—, —N(CO_2R^{13})—, —N(SO_2R^{15})—, —N(COR^{12})—, —N(SO_2NHR^{13})—, —O—, —S—, —S(O)—, —SO_2—, —CH_2—, —CF_2— or —$CR^{12}F$—;

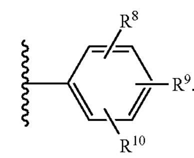
n_3 is 1 to 5; and

n_5 is 1 to 3;

or a diastereomer, enantiomer, stereoisomer, regiostereomer, rotomer, tautomer or prodrug thereof.

2. The compound or salt according to claim **1**, where X^1 is —O—.

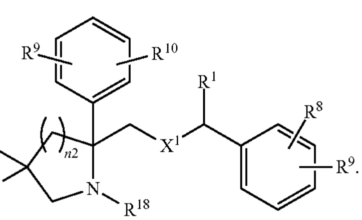
3. The compound or salt according to claim **1**, where Ar^1 and Ar^2 are each



4. The compound or salt according to claim **3**, where for Ar^2, at least two of R^8, R^9 and R^{10} are each —CF_3.

5. The compound or salt according to claim **3**, where for Ar^1, R^8, R^9 and R^{10} are each independently selected from the group consisting of H, —OH and halogen.

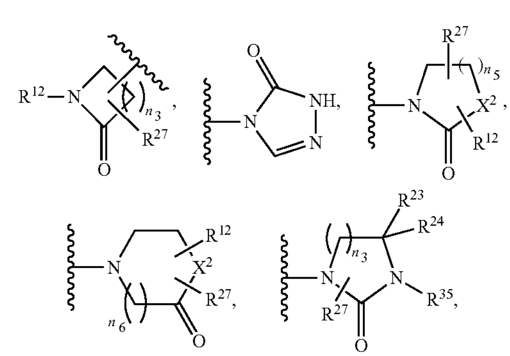
6. The compound or salt according to claim **1** represented by the formula



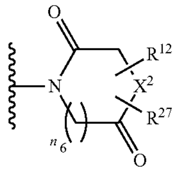
wherein X^1 is —O— or —NR^{34}—; for Ar^2, R^8 and R^9 are independently selected from the group consisting of —CF_3, —CHF_2, —CH_2F, halogen, C_1-C_6 alkyl, —OCF_3 and —OR^{12}; for Ar^1, R^9 and R^{10} are independently selected from the group consisting of H, —OH and halogen; and n_2 is 1 or 2.

7. The compound according to claim **6** wherein one of R^4 and R^5 is H and the other is —C($R^{28}R^{29}$)$_{n1}$-G, wherein n_1 is 0, 1 or 2.

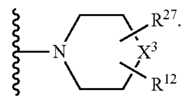
8. The compound according to claim **7** wherein one of R^4 and R^5 is H and the other is selected from the group consisting of —$NR^{13}R^{14}$, —$NR^{12}C(O)R^{14}$, —C(O)$NR^{13}R^{14}$, —OC(O)R^{14}, —OC(O)$NR^{13}R^{14}$, $NR^{12}C(O)OR^{13}$, —C(O)OR^{13}, —NR^{12}(C(O)$NR^{13}R^{14}$), —$NR^{12}SO_2R^{13}$, —$SO_2NR^{13}R^{14}$, R^{19}-heteroaryl,



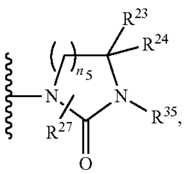
-continued

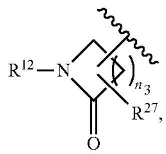


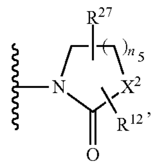
and

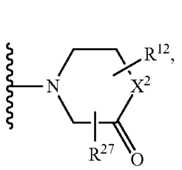


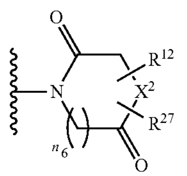
9. The compound or salt according to claim **6** wherein R^4 is —$NR^{13}R^{14}$, —$NR^{12}C(O)R^{14}$, $NR^{12}C(O)OR^{13}$, —$NR^{12}(C(O)NR^{13}R^{14})$, —OH, —O—($C_1$-$C_6$)alkyl, —O—($C_3$-$C_8$)cycloalkyl, —$OC(O)R^{14}$, —$OC(O)NR^{13}R^{14}$, —$NR^{12}SO_2R^{13}$, —$SO_2NR^{13}R^{14}$, R^{19}-heteroaryl,



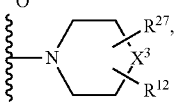








or



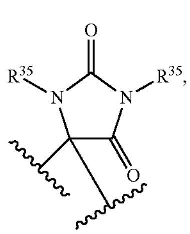
wherein X_2 is —O—, —S—, —CH_2— or —NR^{35}—; and R^5 is —$C(O)OR^{13}$ or —$C(O)NR^{13}R^{14}$.

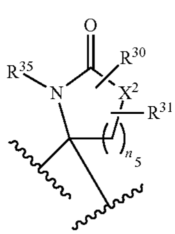
10. The compound or salt according to claim **8**, where R^{12} and R^{27} are independently selected from the group consisting of H and —CH_3; n_3 is 2 or 3; and n_5 is 1 or 2.

11. The compound or salt according to claim **9**, wherein R^{12} and R^{27} are H; n_3 is 2 or 3; and n_5 is 1 or 2.

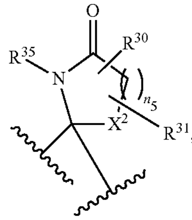
12. The compound or salt according to claim **6**, wherein R^4 and R^5, together with the carbon atom to which they are both attached, form a 4- to 8-membered heterocycloalkyl or heterocycloalkenyl ring containing 1 to 3 groups independently selected from X^2, provided that at least one X^2 is —NR^{35}—, —O—, —S—, —S(O)— or —SO_2—, the ring being optionally substituted with from 1 to 6 substituents independently selected from the group consisting of R^{30} and R^{31}.

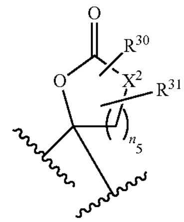
13. The compound or salt according to claim **12**, where the 4- to 8-membered ring is selected from the group consisting of:



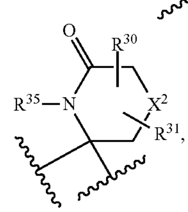


-continued



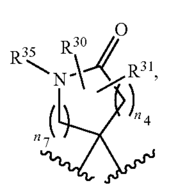


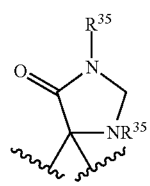
and



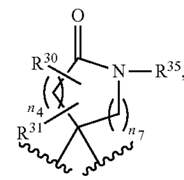
wherein R^{35} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl; n_5 is 1, 2 or 3; X^2 is —NR^{35}—, —CH_2—, —O— or —S—; R^{30} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and R^{31} is H, —OH or C_1-C_6 alkyl.

14. The compound or salt according to claim **12**, where the 4- to 8-membered ring is selected from the group consisting of:



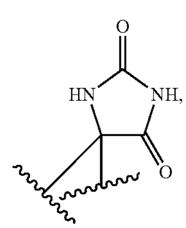


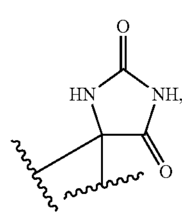
and

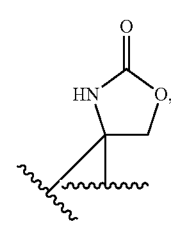


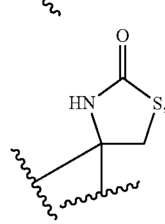
wherein R^{30} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; R^3 is H, —OH or C_1-C_6 alkyl; each R^{35} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl and hydroxy(C_1-C_6)alkyl; n_4 and n_7 are independently 0-5, provided that the sum of n_4 and n_7 is 1-5.

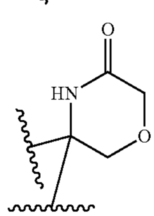
15. The compound or salt according to claim **13** wherein the 4- to 8-membered ring is selected from the group consisting of

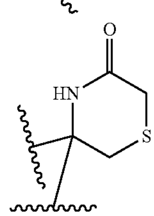




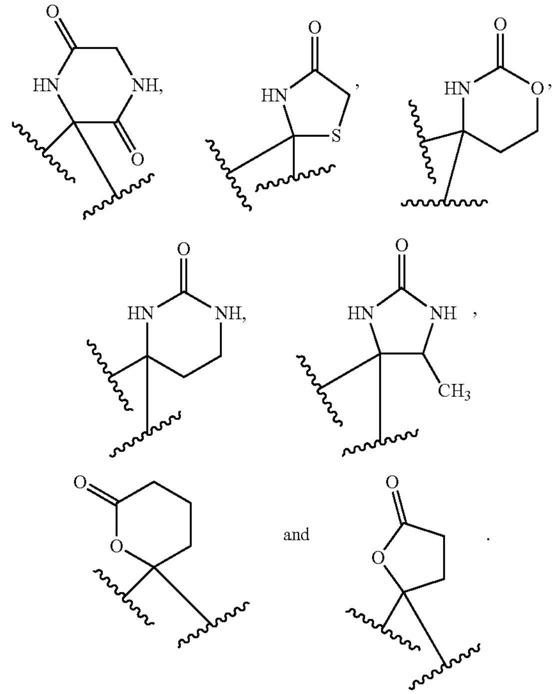




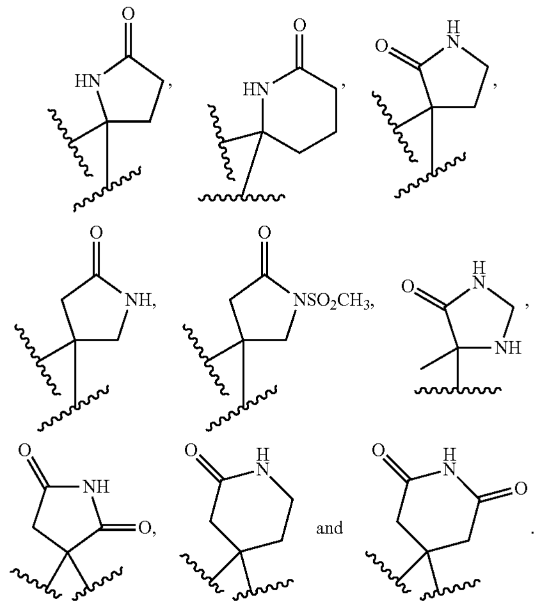
,

,

-continued

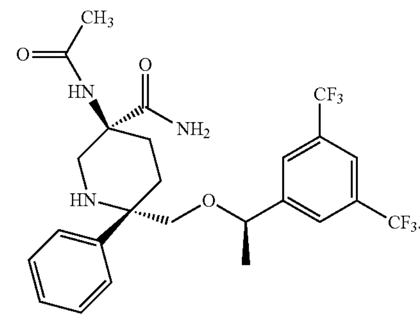


16. The compound according to claim 14, wherein the 4- to 8-membered ring is selected from the group consisting of

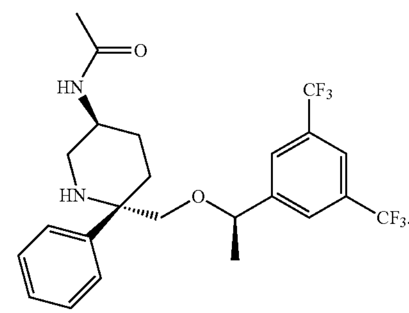


17. The compound or salt according to claim 1, wherein the compound is selected from the group consisting of Examples 3, 9, 12a, 13, 14, 15, 20, 23, 29, 36, 40, 43b, 44b, 45, 50, 53, 56b, 57, 60a, 61, 62, 63, 72a, 73b, 74a, 75b, 76a, 82a, 82b, 90, 96, 105, 106b, 109, 110a, 111a, 112 and 113, and the stereoisomers thereof.

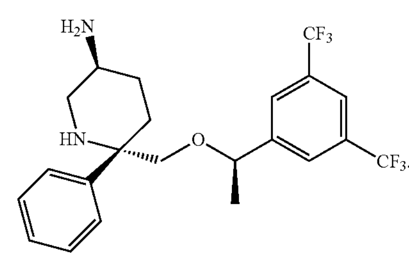
18. The compound or salt according to claim 17, wherein the compound is:



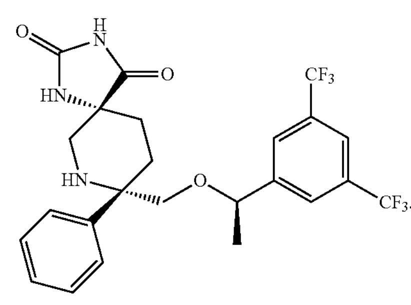
19. The compound or salt according to claim 17, wherein the compound is:



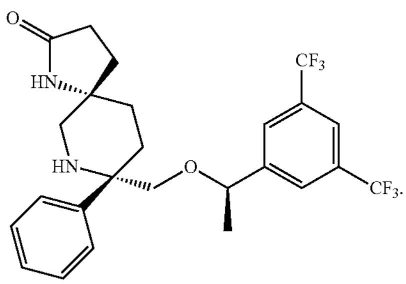
20. The compound or salt according to claim 17, wherein the compound is:



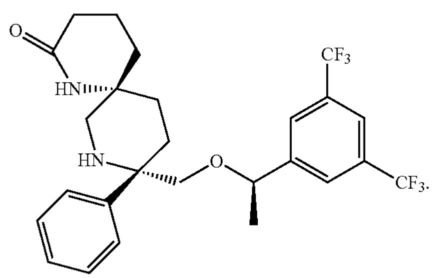
21. The compound or salt according to claim 17, wherein the compound is:



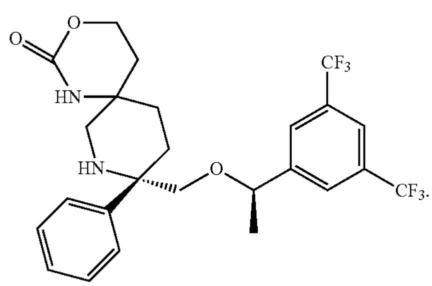
22. The compound or salt according to claim **17**, wherein the compound is:



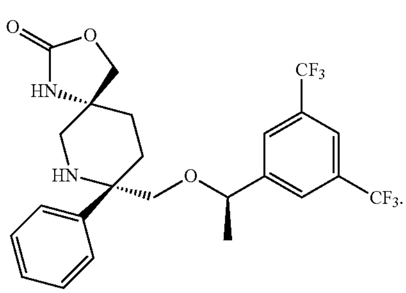
23. The compound or salt according to claim **17**, wherein the compound is:



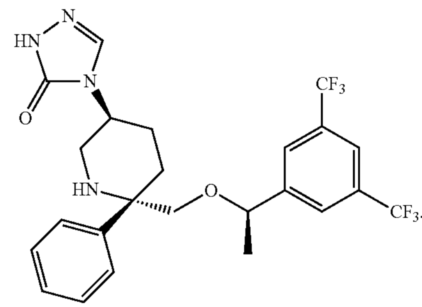
24. The compound or salt according to claim **17**, herein the compound is:



25. The compound or salt according to claim **17**, wherein the compound is:



26. The compound or salt according to claim **17**, wherein the compound is:



27. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim **1** in a pharmaceutically acceptable carrier.

28. The pharmaceutical composition according to claim **27**, further comprising at least one selective serotonin reuptake inhibitor.

29. The pharmaceutical composition according to claim **27**, further comprising at least one serotonin 5-HT_3 receptor antagonist, or at least one corticosteroid or at least one substituted benzamide.

30. The pharmaceutical composition according to claim **27**, further comprising at least one serotonin 5-HT_3 receptor antagonist and at least one corticosteroid.

31. The pharmaceutical composition according to claim **27**, further comprising at least one substituted benzamide and at least one corticosteroid.

32. A method for treating a physiological disorder, symptom or disease in a patient, comprising administering to the patient an effective amount of at least one compound or salt according to claim **1**, or a pharmaceutical composition thereof, where the physiological disorder, symptom or disease is a respiratory disease, cough, inflammatory disease, skin disorder, ophthalmalogical disorder, depression, anxiety, phobia, bipolar disorder, alcohol dependence, psychoactive substance abuse, epilepsy, nociception, psychosis, schizophrenia, Alzheimer's disease, AIDs related dementia, Towne's disease, stress related disorder, obsessive/compulsive disorder, bulemia, anorexia nervosa, binge eating, mania, premenstrual syndrome, gastrointestinal disorder, atherosclerosis, fibrosing disorder, obesity, Type II diabetes, headache, neuropathic pain, post-operative pain, chronic pain syndrome, bladder disorder, genitourinary disorder, emesis or nausea.

33. The method according to claim **32** for treating asthma, emesis, nausea, depression, anxiety, cough or migraine.

34. The method of claim **33** for treating depression or anxiety further comprising administering to the patient an effective amount of at least one selective serotonin reuptake inhibitor.

35. The method according to claim **34**, where the selective serotonin reuptake inhibitor is fluoxetine, fluvoxamine, paroxetine, sertaline, or a pharmaceutically-acceptable salt thereof.

36. The method of claim **33** for treating emesis further comprising administering to the patient an effective amount of at least one serotonin 5-HT_3 receptor antagonist or at least one corticosteroid or at least one substituted benzamide.

37. The method of claim **33** for treating emesis further comprising administering to the patient an effective amount of at least one serotonin 5-HT_3 receptor antagonist and at least one corticosteroid.

38. The method of claim **33** for treating emesis further comprising administering to the patient an effective amount of at least one corticosteroid and at least one substituted benzamide.

39. The method according to claim **36**, where the serotonin 5-HT_3 receptor antagonist is ondansetron, dolasetron, palonsetron or granisetron, the corticosteroid is dexamethasone, and the substituted benzamide is metoclopramide.

40. A method for antagonizing an effect of a Substance P at a neurokinin-1 receptor site or for blocking at least one neurokinin-1 receptor, in a mammal in need of such treatment, comprising administering to the mammal an effective amount of at least the compound or salt according to claim **1**, or a pharmaceutical composition thereof.

* * * * *