PYRROLIDINE AND PIPERIDINE DERIVATES AS NK1 ANTAGONISTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to an antagonist of the neuropeptide neurokinin-1 (NK_1 or NK-1) receptor.

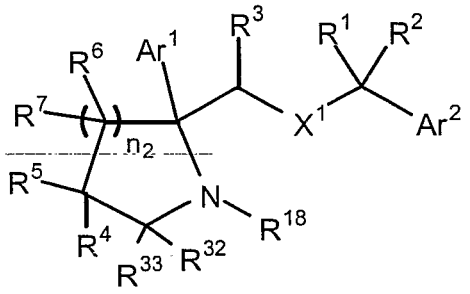
2. Description of Related Art

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. 5,760,018 (1998) (pain, inflammation, migraine and emesis), U.S. 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).

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

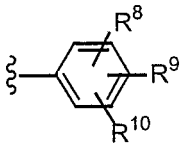
In one aspect of the invention, a compound is provided having the formula (I):



(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 chemically feasible 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 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;

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;

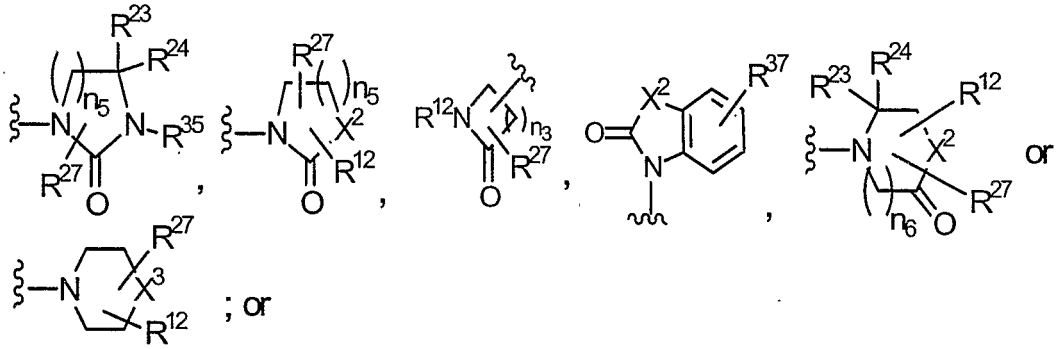
n_2 is 1 to 4;

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

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 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};

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_8 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, $-CH_2CF_3$, aryl and heteroaryl; or

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 $-NR^{34}$-;

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_6)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 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 $-NR^{34}$-;

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.

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.

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

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.

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.

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.

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.

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

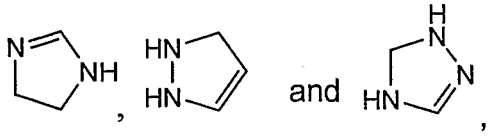
The term "aryl," as used herein, means an aromatic, mono- or bicyclic, carbocyclic ring system having from one to two aromatic rings. The aryl moiety will generally have from 6 to 14 carbon atoms with all available substitutable carbon atoms of the aryl moiety being intended as possible points of attachment.

Representative examples include phenyl, cumenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

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.

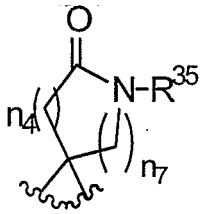
The term "heterocycloalkyl" as used herein means a saturated cyclic ring having from 3 to 8 members, preferably 5 or 6 members, and comprising 2 to 7 carbon atoms and 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S-, -S(O)-, $-SO_2-$ and $-NR^{35}-$. Typical heterocycloalkyl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

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:

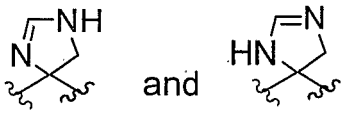


, wherein the ring can be attached to the rest of the structure through either a substitutable ring carbon or a substitutable ring nitrogen (e.g., in R^4, when G is heterocycloalkenyl, it can be joined to the $(CR^{28}R^{29})_{n1}$ group through either a substitutable ring carbon or a substitutable ring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

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^2 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



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



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.

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.

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

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).

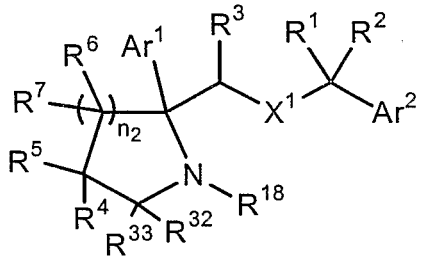
When a variable appears more than once in a structural formula, for example, R^8, its definition at each occurrence is independent of its definition at every other occurrence.

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.

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.

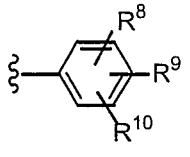
Other than as shown in the operating examples or where is otherwise indicated, all numbers used in the specification and claims expressing quantities of ingredients, reaction conditions, and so forth, are understood as being modified in all instances by the term "about."

Referring to the compound having the formula (I):



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

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.

X^1 is, preferably -O- or $-NR^{34}$-. More preferably, X^1 is -O-.

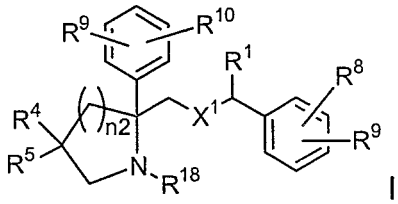
R^1 and R^2 are each, preferably, independently selected from the group consisting of H and C_1-C_6 alkyl. More preferably, R' and R^2 are each independently selected from the group consisting of H and CH_3.

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

Each R^6 is preferably independently selected from the group consisting of H and C_1-C_6 alkyl. Even more preferably, each R^6 is H.

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.

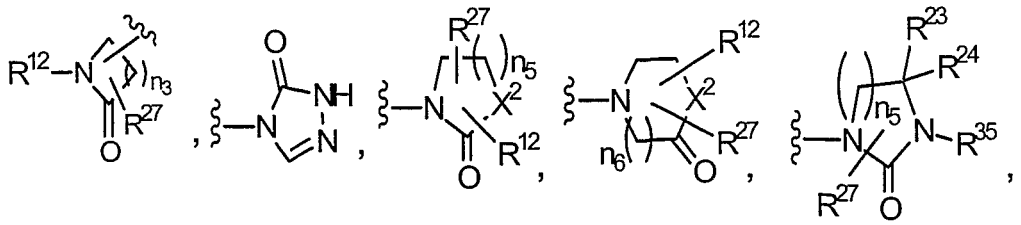
More preferred are compounds of the structure II

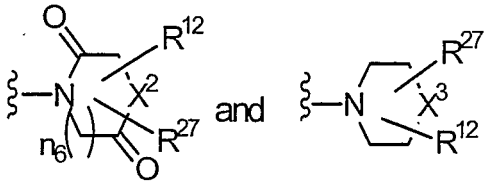


II

wherein X^1 is –O- or $-NR^{34}$-; 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.

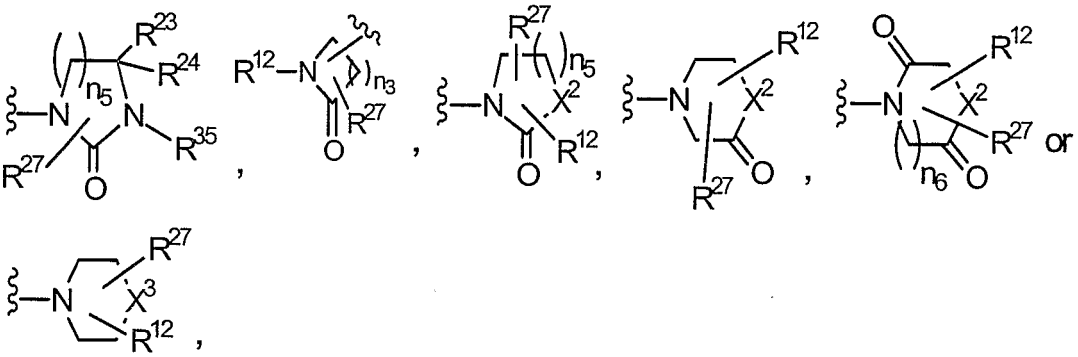
Preferred compounds of formula I and formula II are those wherein one of R^4 and R^5 is H and the other is $-C(R^{28}R^{29})_{n1}$-G, wherein n_1 is 0, 1 or 2. More preferred are compounds wherein one of R^4 and R^5 is H and the other is selected from the group consisting of $-NR^{13}R^{14}$, $-NR^{12}C(O)R^{14}$,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





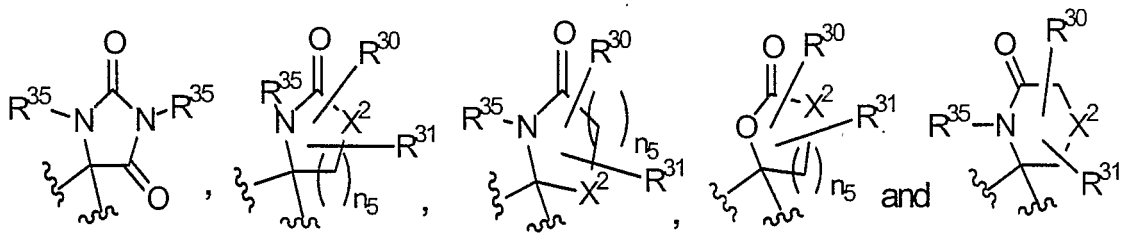
Even more preferred are such compounds wherein R^{12} and R^{27} are independently selected from the group consisting of H and C_1-C_6 alkyl, especially H and $-CH_3$, and more especially, both are H; n_3 is 2 or 3; and n_5 is 1 or 2.

In another embodiment, preferred compounds of formula I and formula II are those wherein R^4 is $-NR^{13}R^{14}$, $-NR^{12}C(O)R^{14}$, $NR^{12}C(O)OR^{13}$, $-NR^{12}(C(O)NR^{13}R^{14})$, -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,

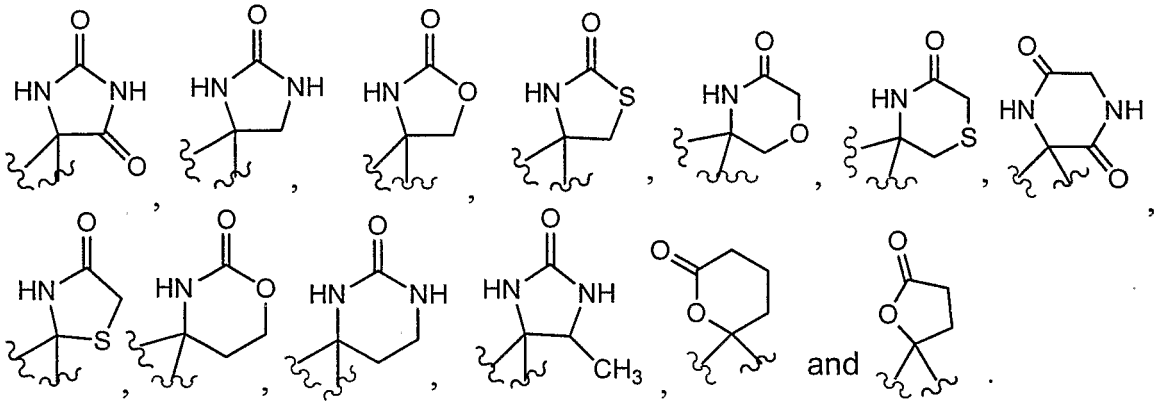


wherein X_2 is –O-, -S-, $-CH_2-$ or $-NR^{35}-$; and R^5 is $-C(O)OR^{13}$ or $-C(O)N\ R^{13}R^{14}$. More preferred are compounds wherein R^{12} is independently selected from the group consisting of H, C_1-C_6 alkyl and C_3-C_8 cycloalkyl; R^{27} is H; n_3 is 2 or 3; and n_5 is 1 or 2.

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 8-membered ring is selected from the group consisting of:

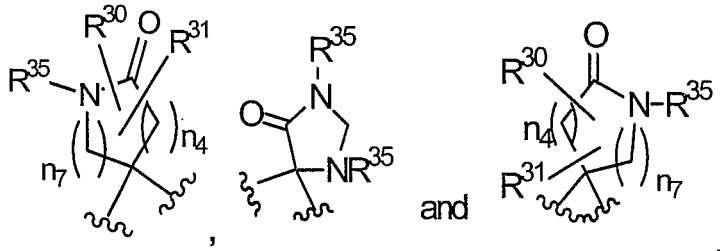


wherein R^{35} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl; n_5 is 1, 2 or 3; X^2 is $-NR^{35}$-, $-CH_2$-, -O- or –S-; R^{30} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and R^{31} is H, -OH or C_1-C_6 alkyl. Especially preferred are 4- to 8-membered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

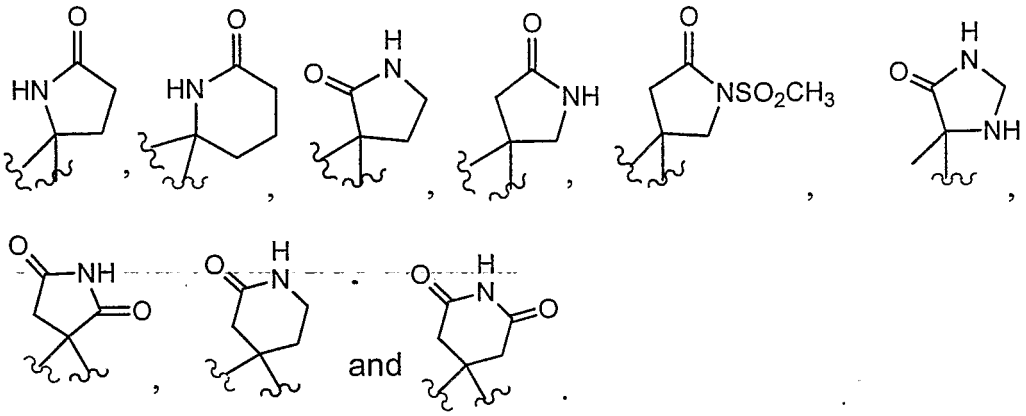


The rings are optionally substituted with R^{30} and R^{31}.

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



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_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. Especially preferred are 4- to 8-membered rings selected from the group consisting of



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

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.

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

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.

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.

Preferably, r is 1 or 2. More preferably, r is 1.

R^{21} and R^{22} 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.

R^{23} and R^{24} are each, preferably, independently selected from the group consisting of H and C_1-C_6 alky, 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.

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

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.

R^{32} and R^{33} are preferably independently selected from the group consisting of H and -CH_3. Even more preferably, R^{32} and R^{33} are each H.

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

R^{37} is preferably 1 or 2 substituents selected from the group consisting of H, $-CH_3$ and halogen.

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.

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":

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

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.

In vivo activity may be measured by inhibition of an agonist-induced foot tapping in a gerbil, as descibed 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.

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

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.

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.

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 migraines, 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.

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).

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. 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.

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.

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.

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.

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).

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, ET_A antagonists, renin inhibitors, serotonin 5-HT_{2c} receptor agonists, nociceptin receptor agonists, rho kinase inhibitors, potassium channel modulators and/or inhibitors of multidrug resistance protein 5. 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.

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, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

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.

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.

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.

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.

Preferably the compound is administered orally.

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.

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.

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.

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.

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_3in 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.

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.

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.

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.

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.

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.

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

RBF is a round bottom flask;
RT is room temperature;
Me is methyl;
Bu is butyl;
Ac is acetyl;
Et is ethyl;
Ph is phenyl;
THF is tetrahydrofuran;
OAc is acetate;
$(Boc)_2O$ is di-tert-butyl dicarbonate;
(Boc) is tert-butoxy carbonyl;
TLC is thin layer chromatography;
LAH is lithium aluminum hydride;
LDA is lithium diisopropyl amine;
CDI is 1,1-carbonyl diimidazole;

HOBT is hydroxybenzotriazole;

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

TFA is trifluoroacetic acid;

MTBE is *t*-butyl methyl ether;

DIEA or i-Pr_2EtN is diisopropylethyl amine;

Prep plate is preparative thin layer chromatography;

DMF is dimethyl formamide

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

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

BuLi is butyl lithium;

KHMDS is potasium bis(trimethylo silyl)amide; and

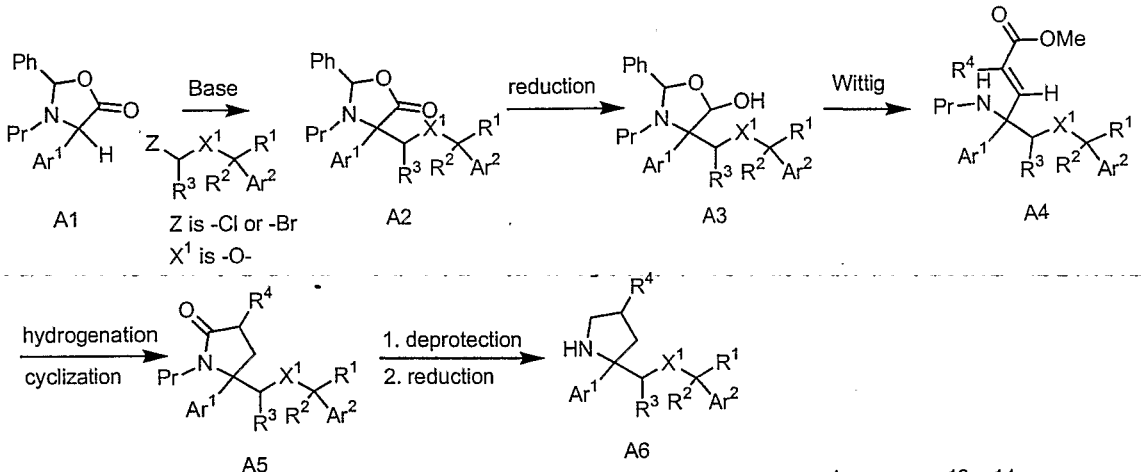
DBU is 1, 8-diazabicyclo[5.4.0]un dec-7-ene.

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).

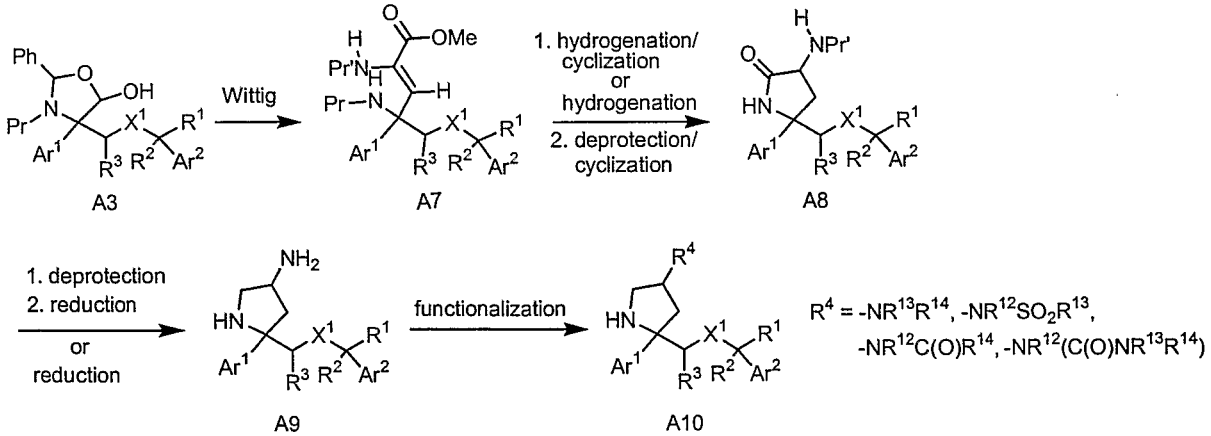
General Methods of Preparation

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.

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.

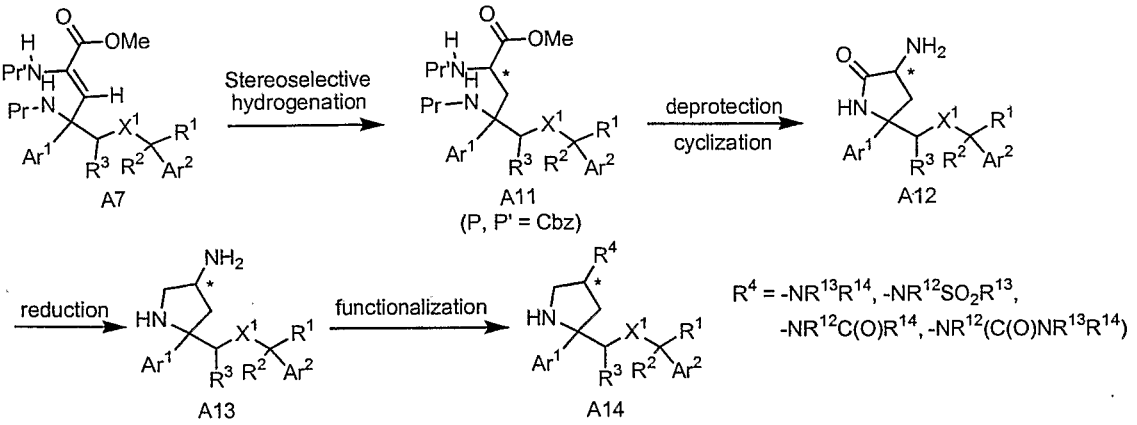


Compounds having the formula I, where n_2 is 1 and R^4 is $-NR^{13}R^{14}$, $-NR^{12}SO_2R^{13}$, $-NR^{12}C(O)R^{14}$, or $-NR^{12}(C(O)NR^{13}R^{14})$ can also be prepared by conversion of lactol A3 to olefin A7 via Wittig reaction using a nitrogen protected (NPr') glycine ester Wittig reagent where 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.

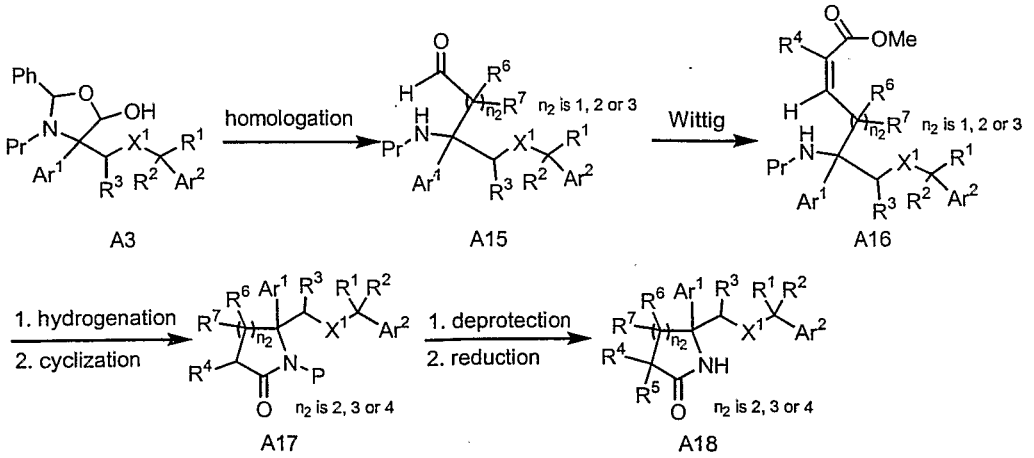


Those skilled in the art will appreciate that the stereoselective hydrogenation of the double bond of olefin A7 are can also be performed using a chiral hydrogenation catalyst such as chiral Rhodium catalyst which can provide chiral

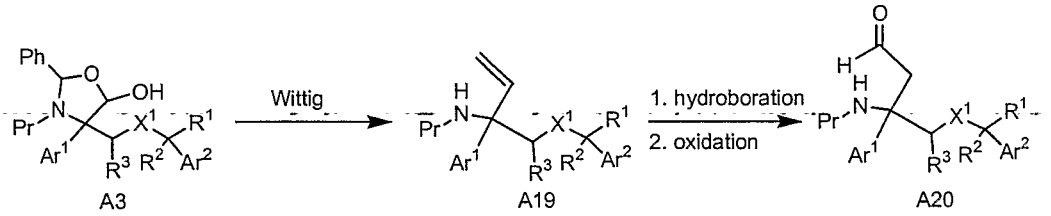
ester A11. Deprotection of the protecting group (if Pr, Pr' are Cbz groups) under standard hydrogenation conditions followed by spontaneous cyclization will provide chiral amino-lactam A12. The reduction of the chiral amino-lactam A12 with reducing agents as LAH or LAH/$AlCl_3$, preferably, LAH/$AlCl_3$, provides chiral amino-pyrrolidines A13 which can further be functionalized using standard conditions to give N-substituted pyrrolidines A14.



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 Horner-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.

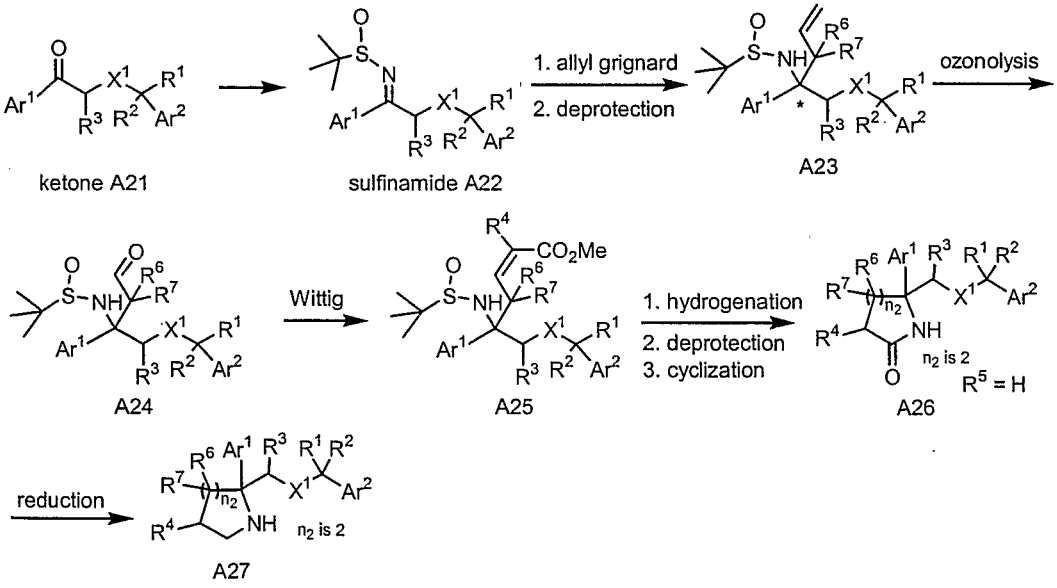


Another method for preparing aldehyde A15 where R^6, R^7 = H involves Wittig homologation of lactol A3 to ethylene derivative A19 which upon hydroboration, preferably with 9-BBN, and subsequent oxidation provides aldehyde A20.



A3 A19 A20

Alternatively, compounds having the formula I, where n_2 is 2, and X^1 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.



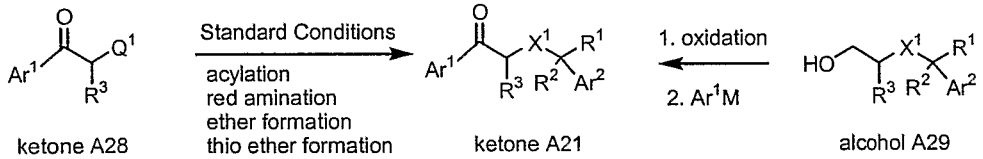
ketone A21 sulfinamide A22 A23

A24 A25 A26

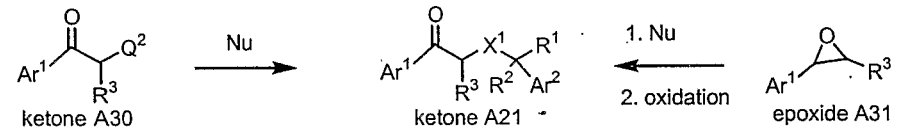
A27

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

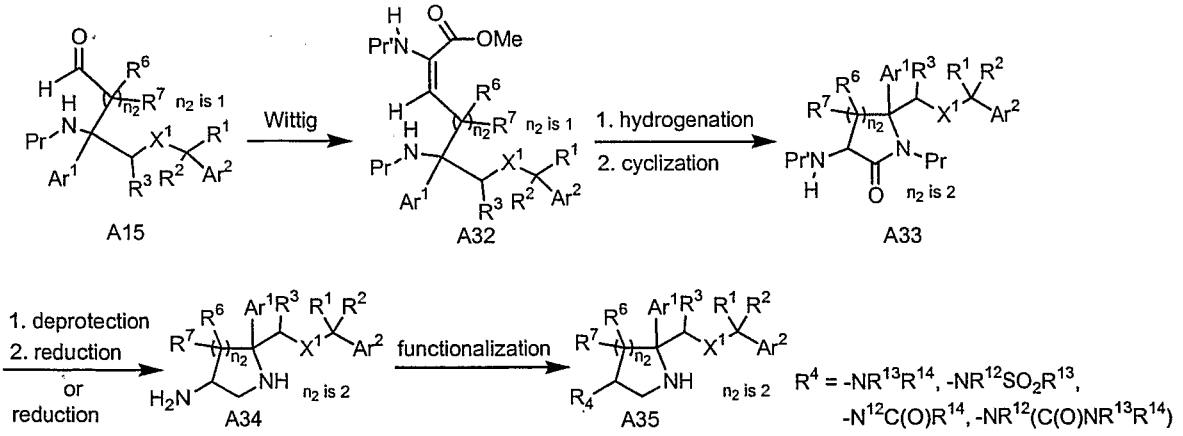
methods employing commercially available materials. Ketone A28 can be subjected to acylation (Q^1 is $-NH_2$, -OH or -SH), reductive amination (Q^1 is $-NH_2$), ether formation (Q^1 is -OH) by standard alkylation methods, thio ether formation (Q^1 is -SH) by standard alkylation methods, or esterification (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.



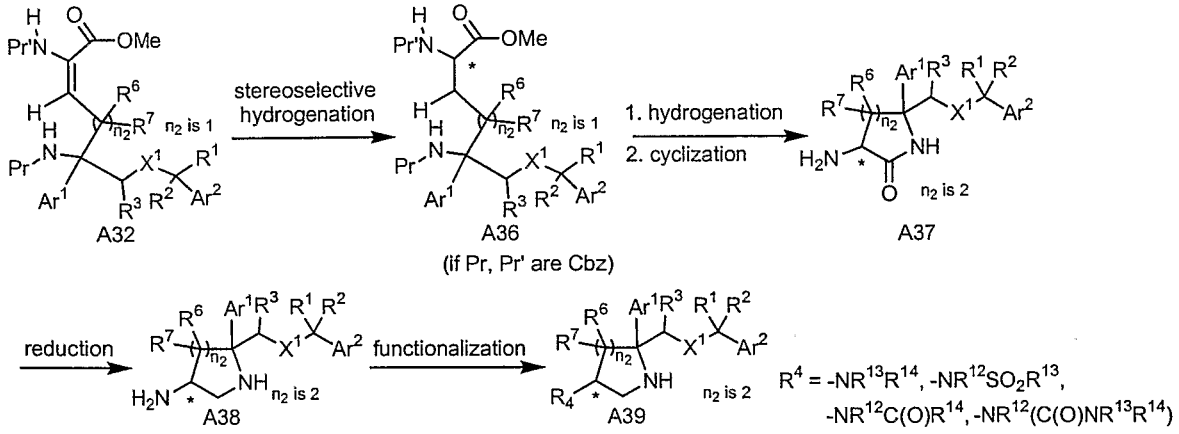
Another method for preparing ketone A21 involves nucleophilic displacement of a leaving group, such as -Cl, -Br, -I, -OMs and -OTf, adjacent to the aryl or heteroaryl ketone, for example, see WO 01/44200 (2001), which is incorporated herein in its entirety by reference. Accordingly, a suitable substituted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



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).

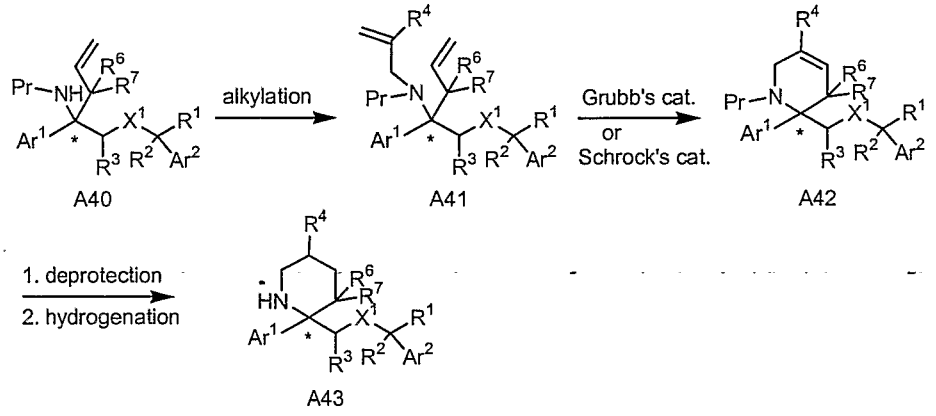


Those skilled in the art will appreciate that the stereoselective hydrogenation of the double bond of olefin A32 can also be performed using a chiral hydrogenation catalyst such as chiral Rhodium catalyst which can provide chiral ester A36. The chiral ester A36 can be converted to chiral functionalized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

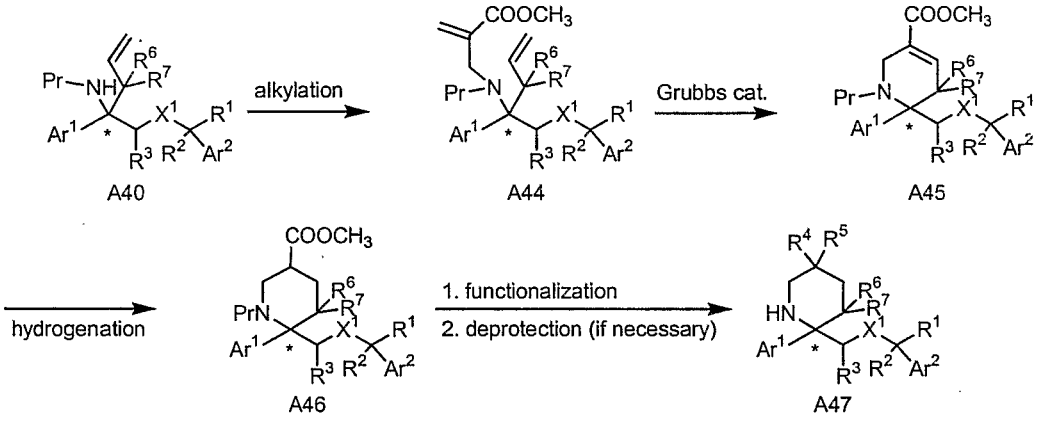


Those skilled in the art will appreciate that homologation of the aldehyde A15 followed by subsequent synthetic operations as described above will result in the cyclic reduced lactams, where n_2 is 3 or 4.

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.

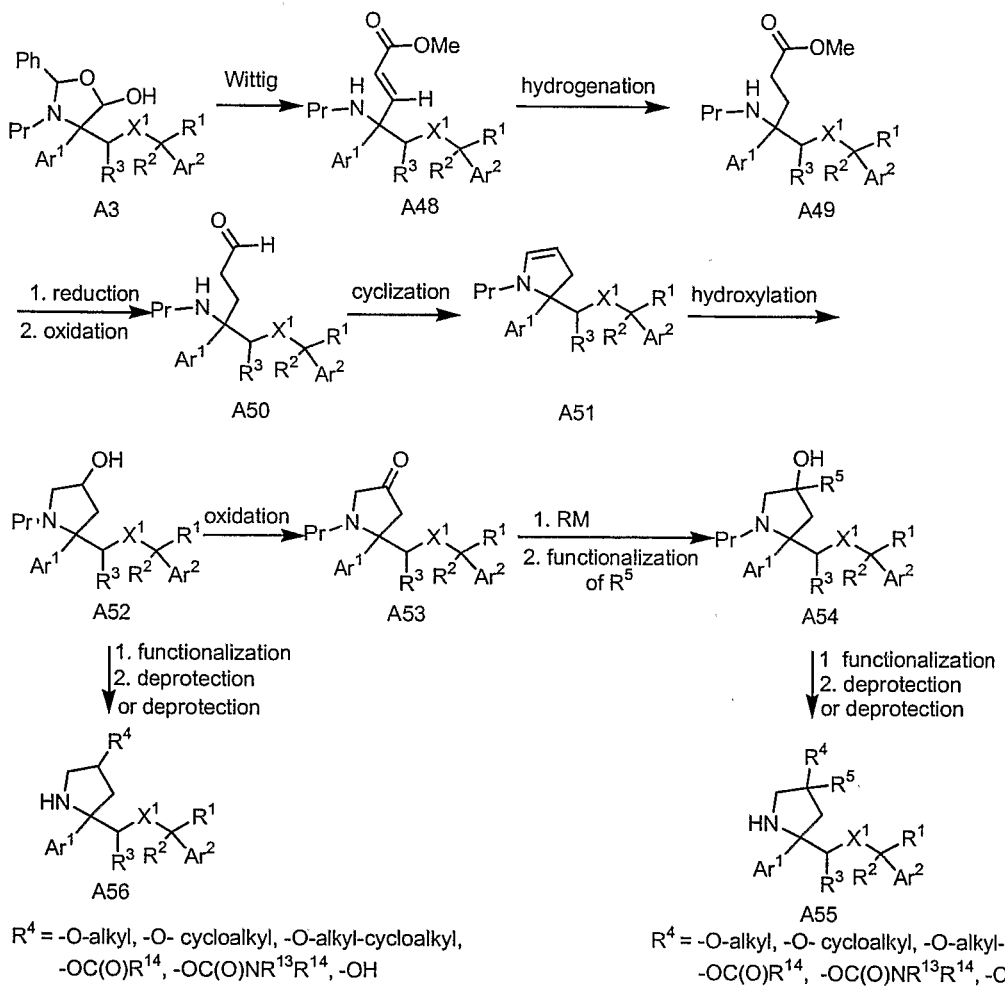


When R^4 = $COOCH_3$, the chemistry as described above provides A46 where ester group could be further transformed to other functional groups such as amide (R^4 = $CONR^{13}R^{14}$) and alcohol (R^4 = CH_2OH) using standard chemistry. In addition, the piperidine A46 can be further functionalized using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

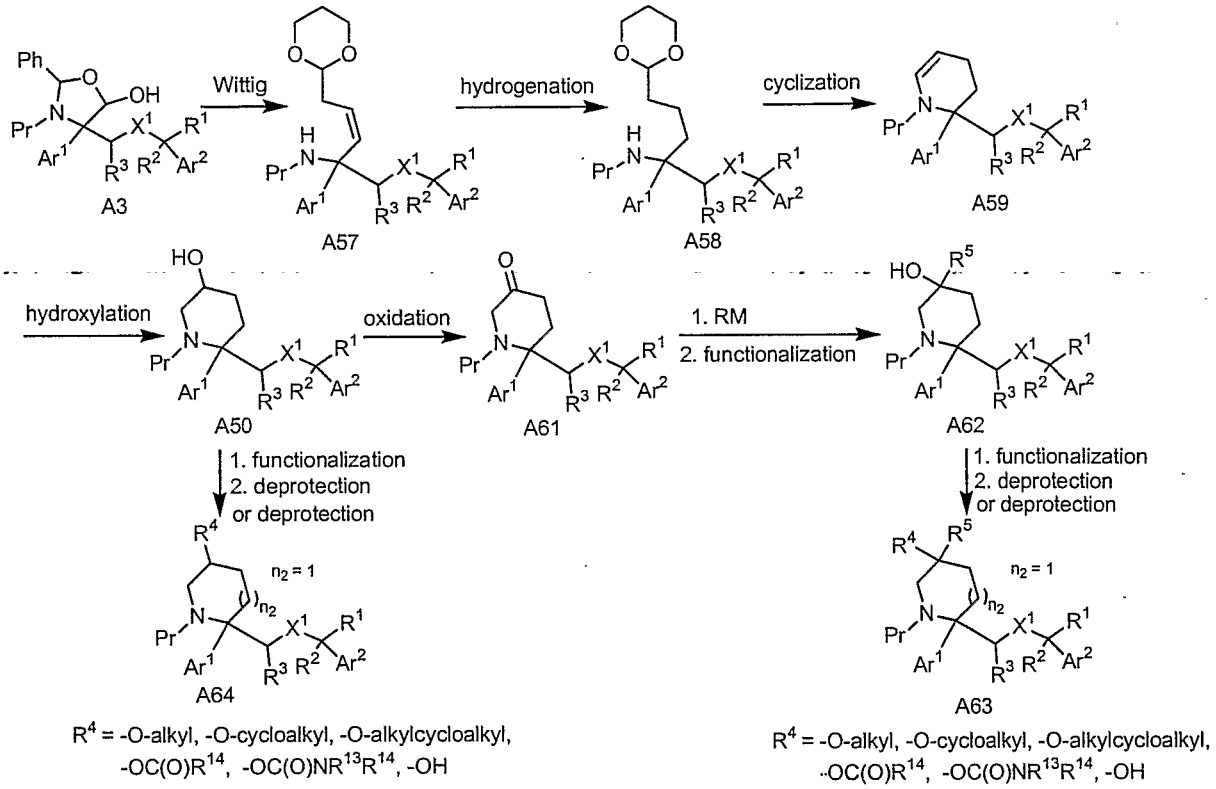


Another method of preparing compounds having the formula (I), where n_2 is 1, X^1 is -O- and R^4 is -OH, -O-(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl), -O-(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), $-OC(O)R^{14}$, or $-OCONR^{13}R^{14}$, from lactol A3 involves Wittig chemistry to provide the corresponding 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.



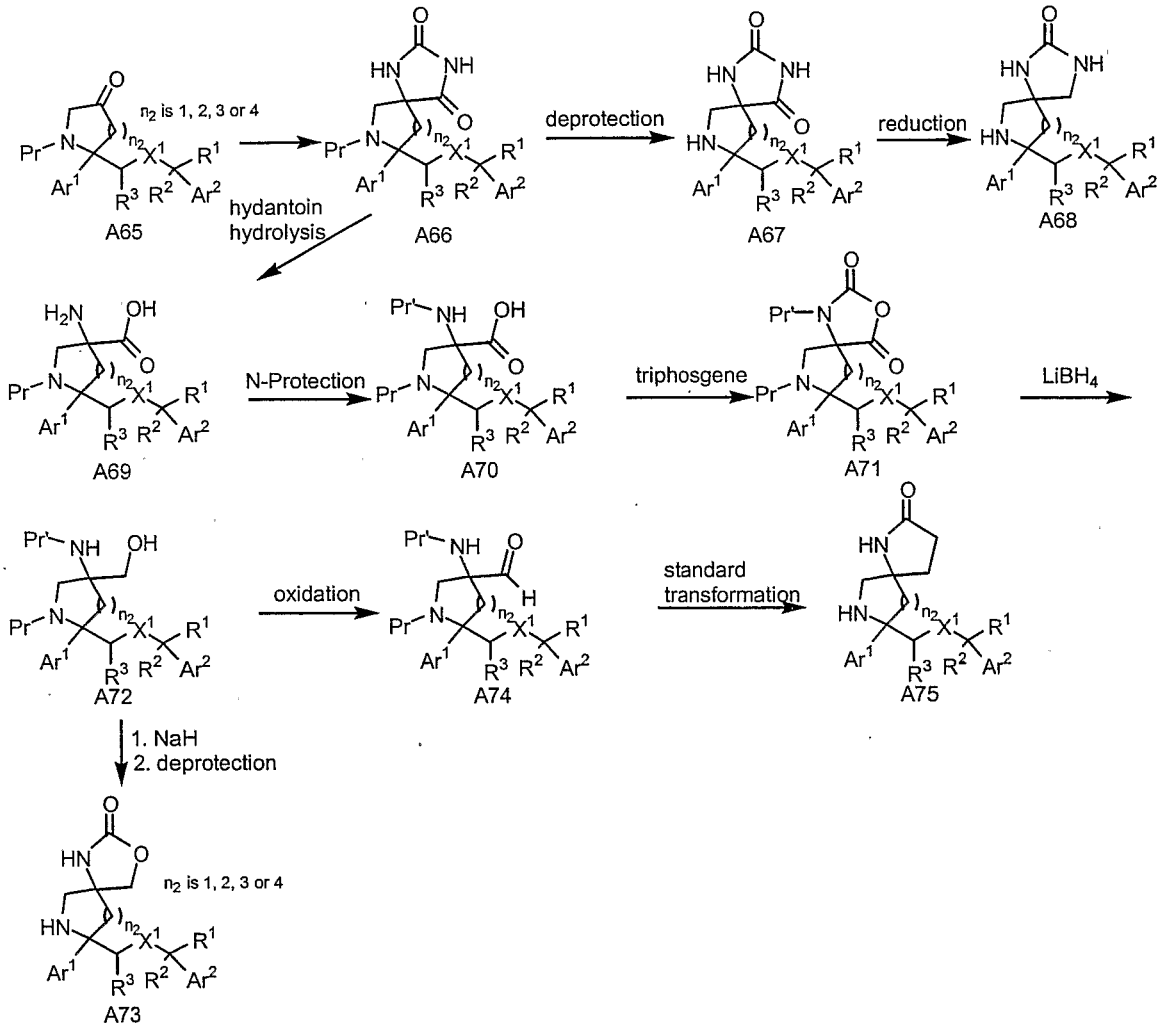
Compounds having the formula I, where n_2 is 2, X^1 is -O- and R^4 is -OH, -O-(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl),), -O-(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), -OC(O)R^{14} or -OCONR^{13}R^{14}, can be prepared from lactol A3. Wittig chemistry followed by hydrogenation and cyclization in weakly acidic conditions such as p-toluenesulfonic 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.



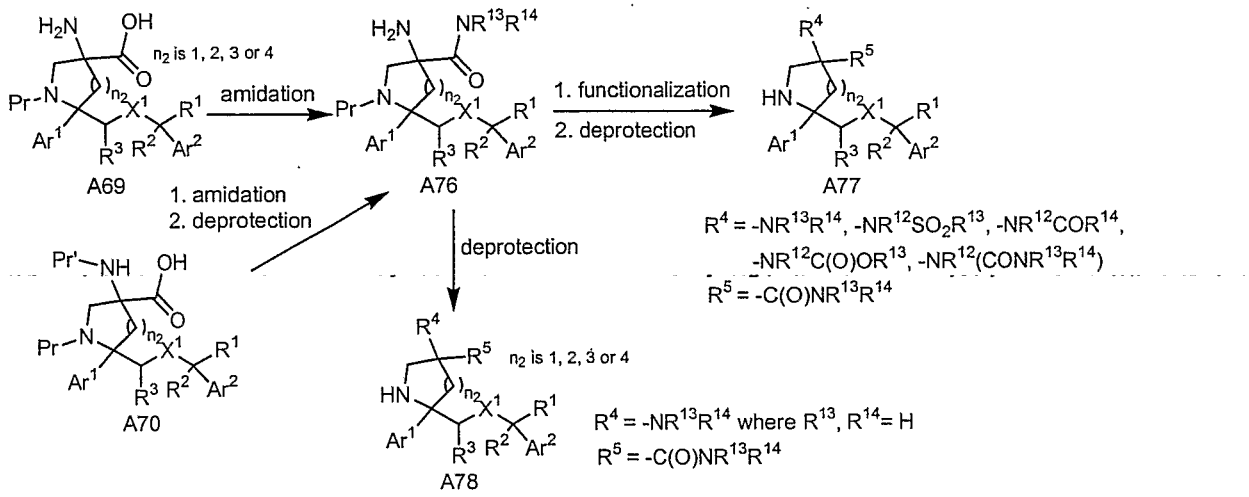
Those skilled in the art will appreciate that homologation of the lactol A3 to the aldehyde A15 where n_2 is 2 or 3 followed by subsequent synthetic operations as described above will result in the monosubstituted cyclic amines A64 or disubstituted cyclic amines A63 where n_2 is 2 or 3.

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

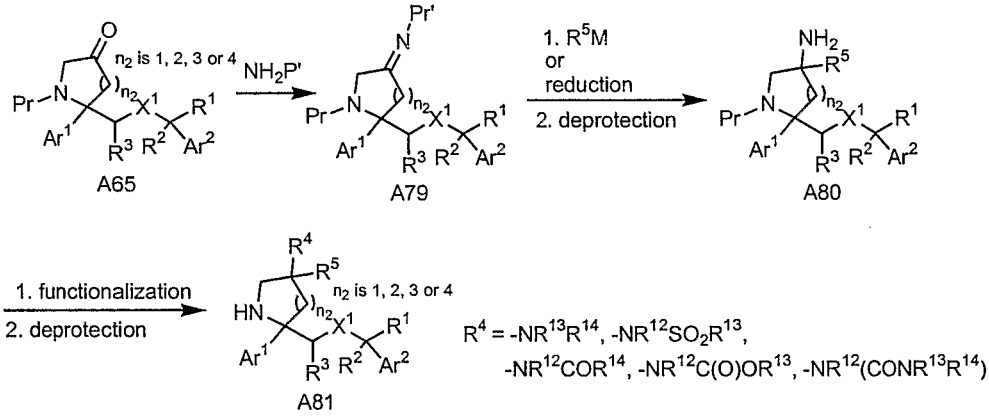
membered cyclic compounds such as carbamate A73 by intramolecular cyclization (if Pr' is carbamate protecting group such as Boc) using base, preferably NaH, followed by deprotection. Alternatively, alcohol A72 can be oxidized to NBoc-aldehyde A74 by standard oxidation conditions such as Swern oxidation 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 γ-lactam A75.



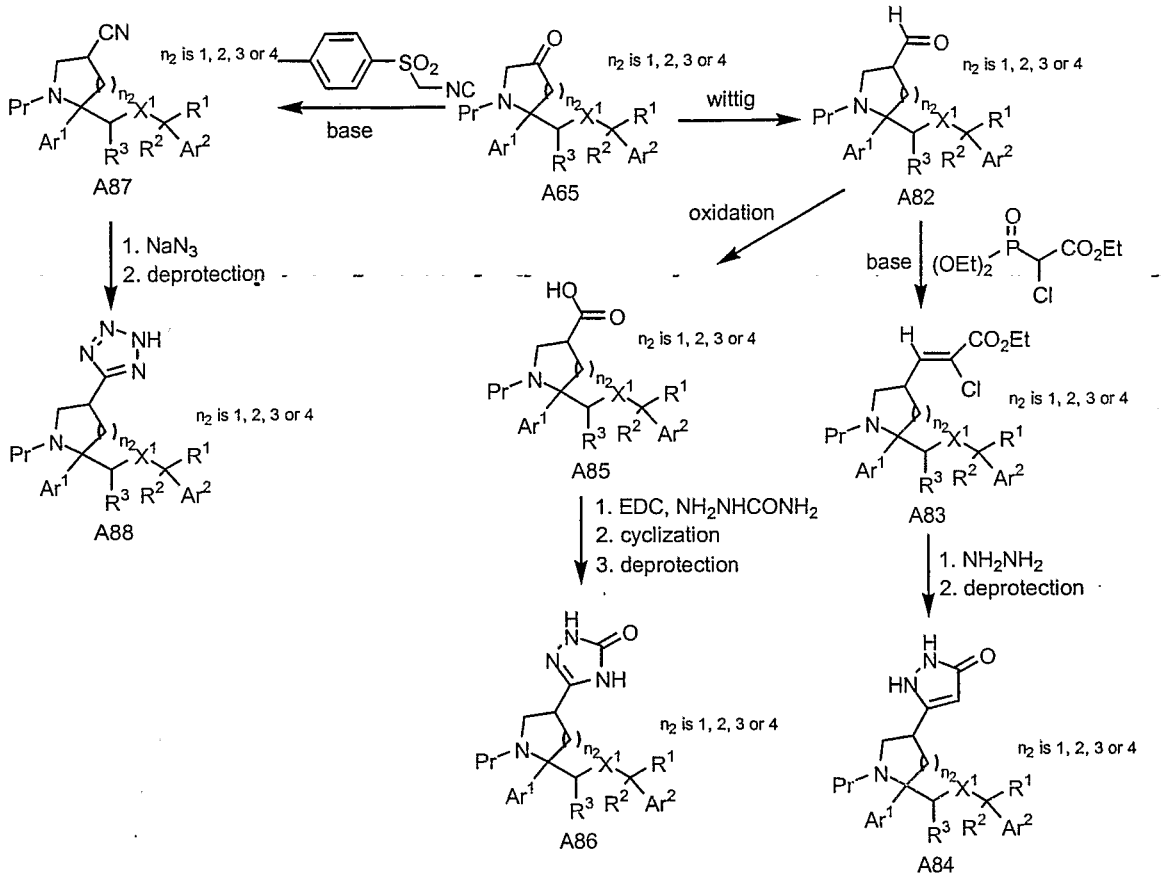
The compounds having the formula I, where n_2 is 1, 2, 3, or 4, X^1 is -O- and R^4 is $-NR^{13}R^{14}$, $-NR^{12}SO_2R^{13}$, $-NR^{12}COR^{14}$, $-NR^{12}C(O)OR^{13}$, or $-NR^{12}(CONR^{13}R^{14})$, and R^5 is $-C(O)NR^{13}R^{14}$ can be prepared by amidation of amino-acid A69 to give amino-amide A76 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.



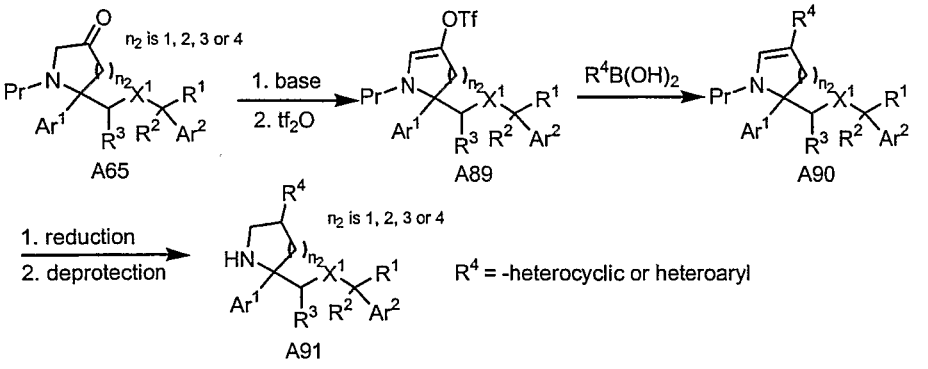
Another method of preparing compounds having the formula I, where n_2 is 1, 2, 3 or 4, X^1 is -O- and R^4 is $-NR^{13}R^{14}$, $-NR^{12}SO_2R^{13}$, $-NR^{12}COR^{14}$, $-NR^{12}C(O)OR^{13}$, or $-NR^{12}(CONR^{13}R^{14})$, involves treatment of ketone A65 with a protected amine under appropriate conditions 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.



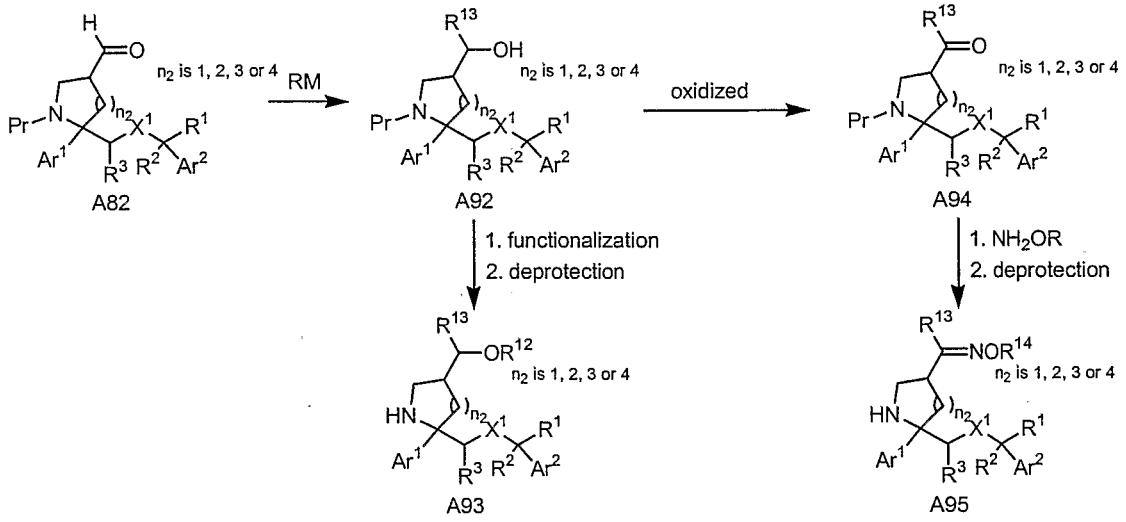
The compounds having the formula I, where n_2 is 1, 2, 3 or 4, X^1 is -O-, R^5 is H, and R^4 is a heterocyclic or heteroaryl group can be prepared by conversion of ketone A65 to nitrile A87, aldehyde A82 and a carboxylic acid A85 via aldehyde A82 using the standard oxidation conditions. Those who are 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.



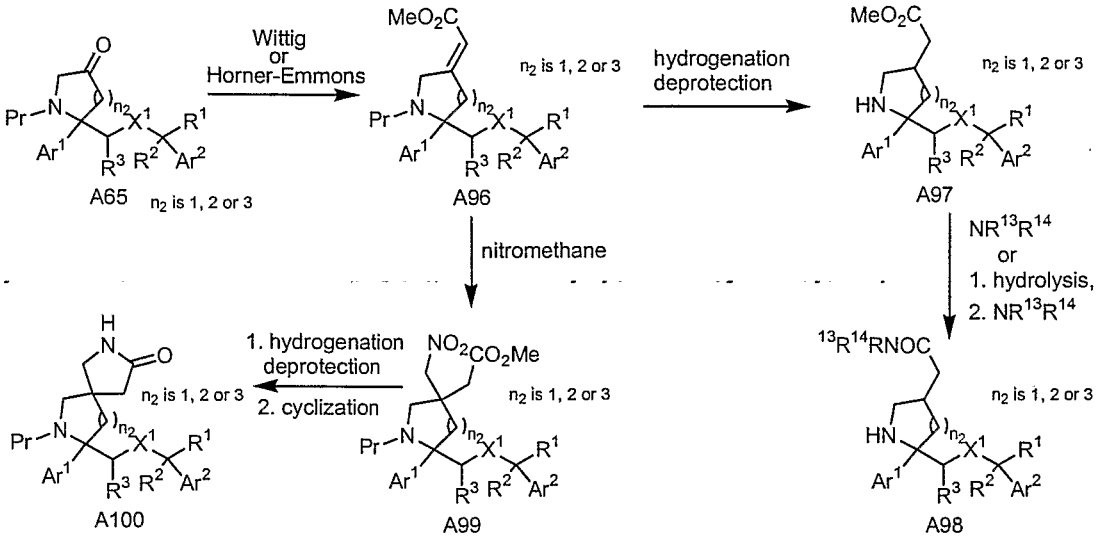
Another method of preparing the compounds having the formula I, where n_2 is 1, 2, 3, or 4, X^1 is -O-, R^5 is H, and R^4 is a heterocyclic or heteroaryl group involves conversion of the ketone A65 to a vinyl triflate A89 by using a base such as LDA and triflic anhydride as an electrophile. The triflate A89 could be coupled with suitable organometalic 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.



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.

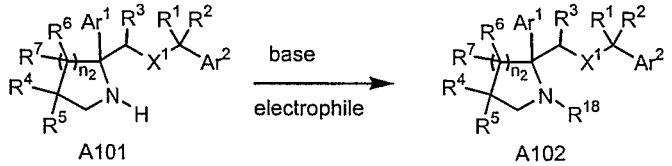


The compounds having the formula I, where n_2 is 1, 2, 3 or 4, X^1 is -O-, R^5 is H, and R^4 is $-C(R^{28}R^{29})CONR^{13}R^{14}$, where R^{28}, R^{29} = H or methyl, can be prepared by conversion of ketone A65 to unsaturated ester A96 using Wittig chemistry. Hydrogenation of the double bond and deprotection 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.



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)$_2$.

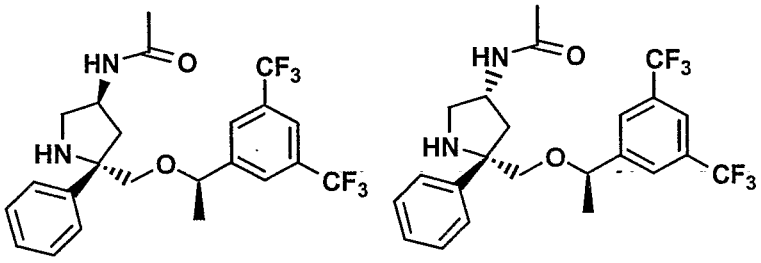
Functionalization of the reduced lactam nitrogen can be performed at an appropriate point in the synthesis by deprotonation with a suitable base and reaction of the necessary electrophile to provide the substitutents defined for R^{18}. Those skilled in the art will appreciate that a substituted alkyl 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)$_2$.



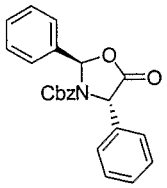
Those skilled in the art will recognize that certain additional protection and deprotection steps may be needed in order to accommodate different functional groups. Accordingly, the order of synthetic operations may be different in order to maintain functional group compatibility with the operational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

Specific Methods Of Preparation – Examples

Example 1a **Example 1b**



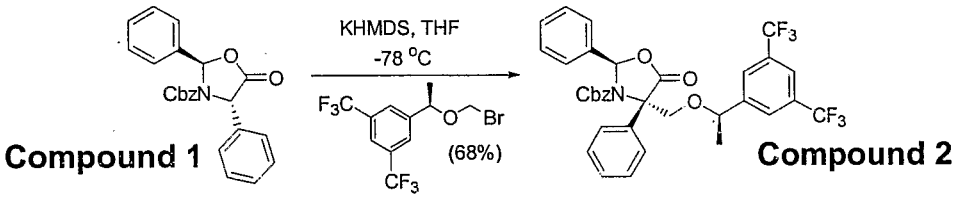
Step 1:



Compound 1

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:

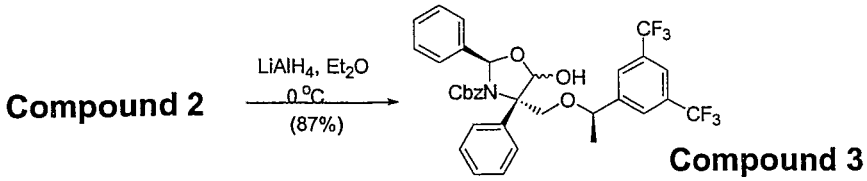


Compound 1 **Compound 2**

To a nitrogen purged solution of oxazolidinone **Compound 1** (10.0g, 0.027mol, 1equiv) in THF (500ml) at -78 °C, a solution of KHMDS (0.5M in toluene, 64ml, 0.032mol, 1.18equiv) was added. After stirring at -78 °C for 30 min, a solution of bromomethyl ether (11.3g, 0.032mol, 1.18equiv) in THF (100ml) 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 (200ml x 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** (11.7g, 68%) as a colorless oil.

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

Step 3:

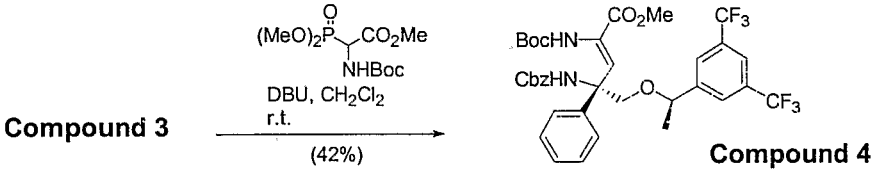


Compound 2 **Compound 3**

To a solution of lactone **Compound 2** (35.2g, 0.055mol, 1equiv) in Et_2O at 0°C, a 1M solution of LAH (17.8ml, 0.018mol, 0.32equiv) 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 (300ml x 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 (240ml) at RT, and water (60ml) 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** (23g) 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** (3g). 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 (4g). The combined yield for **Compound 3** was 30g, 87%.

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

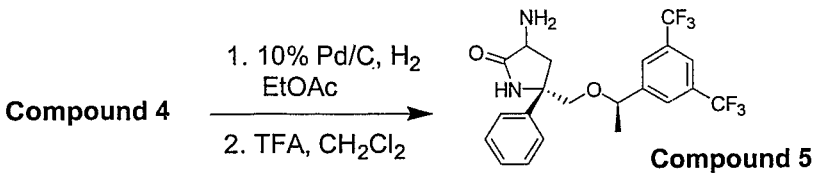
Step 4:



To a solution of **Compound 3** (0.98g, 1.52mmol, 1equiv) and NBoc-□-phosphonoglycine trimethylester (1.26g, 3.80mmol, 2.5equiv) in CH_2Cl_2 (5ml) at 23°C, DBU (0.57ml, 3.80mmol, 2.5equiv) 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 (250ml x 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** (587mg, 52%) as white foam.

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

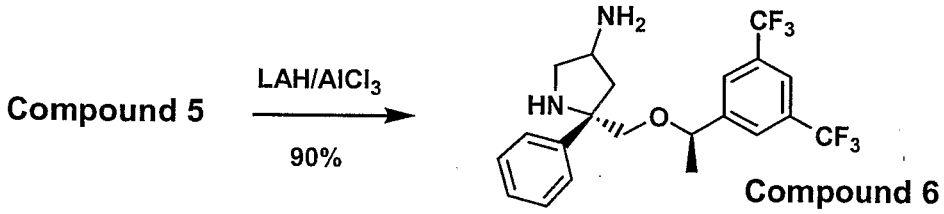
Step 5:



A solution of **Compound 4** (1.4g, 1.88mmol, 1.0equiv.) in EtOAc (30ml) was flushed with N_2. After the addition of Palladium on carbon (10%, 2g) 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 (45ml), cooled to 0°C, then treated with TFA solution (4.5ml, 0.059mmol, 30.0equiv). 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 (300ml) washed with saturated $NaHCO_3$ solution (100ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to give **Compound 5** (0.8g, 95%).

Step 6:

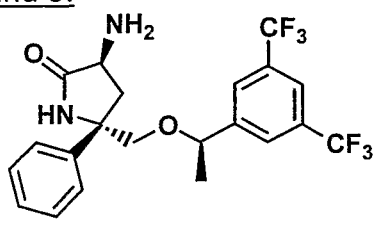


In a flame dry 25ml RBF was placed $AlCl_3$ (0.089g, 0.67mmol, 1.5equiv). The reaction flask was cooled to 0°C and 1M solution of LAH in Et_2O (2ml, 1.98mmol, 4.5equiv) was carefully added. The reaction mixture was cooled to -78°C and a solution of **Compound 5** (0.2g, 0.44mmol, 1.0equiv) in dry THF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

Step 7:

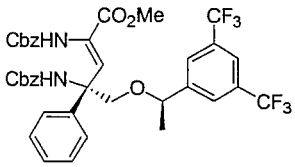
To a solution of **Compound 6** (0.21g, 0.486mmol, 1.0equiv) in MeOH (3ml) at 0°C was added 2-trifluoromethyl-*N,N*-diacetylaniline (0.131g, 0.535mmol, 1.1equiv). The mixture was stirred at 0°C for 1h, then warmed to 23°C and stirred for 18 h. The reaction mixture was then concentrated and purified using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

Preparation of Compound 9:



Compound 9

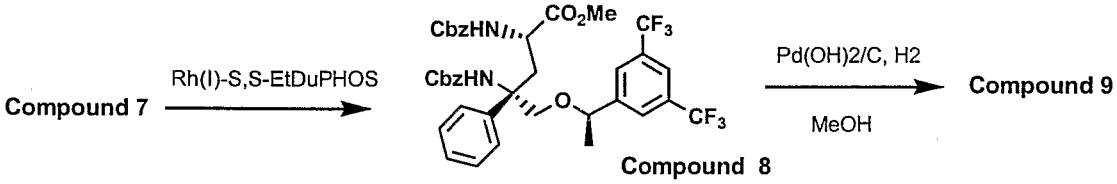
Step 1:



Compound 7

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.

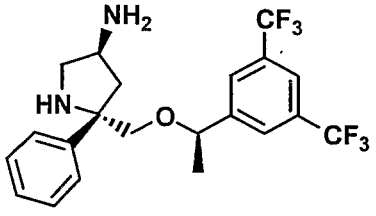
Step 2:



Compound 7 (3.0g, 4.03mmol, 1.0equiv) was taken in MeOH (30ml) 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 (0.12g, 0.16mmol, 0.04equiv) 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 ml RBF. 20% of $Pd(OH)_2/C$ (1g) 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** (1.3g, 72%).

Electronspray MS $[M+1]^+$ 447.1.

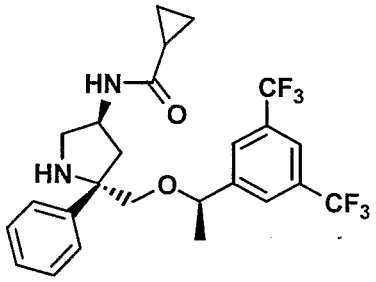
Preparation of Compound 10:



Compound 10

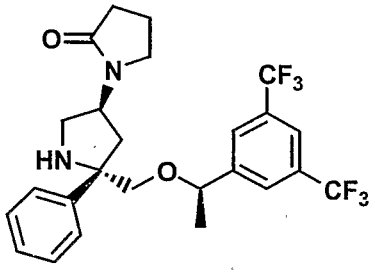
Compound 10 was prepared using similar procedure to **Compound 6**, using **Compound 9** instead of **Compound 5**.

Example 2

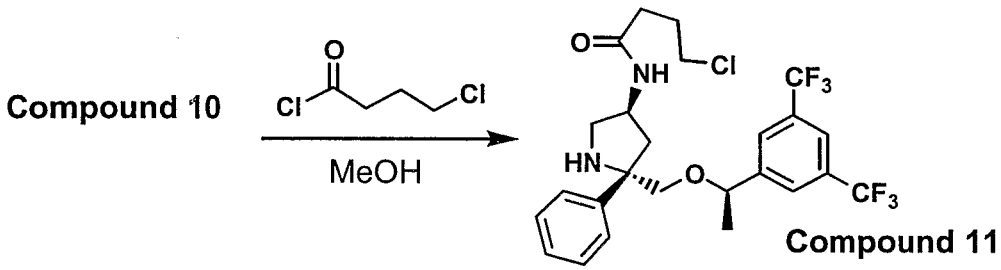


To a solution of **Compound 10** (0.05g, 0.116mmol, 1.0equiv) in MeOH (2ml) at -78°C was added cyclopropanecarbonyl chloride (12□l, 0.127mmol, 1.1equiv). The mixture was stirred at -78°C for 5 min, then warmed to 23°C and stirred for 18 h. The reaction mixture was then concentrated and taken up in EtOAc (200 ml) and washed with sat. aq. $NaHCO_3$ (1 x 100ml). 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** (0.04g, 69%). Electrospray MS $[M+1]^+$ 501.

Example 3



Step 1:



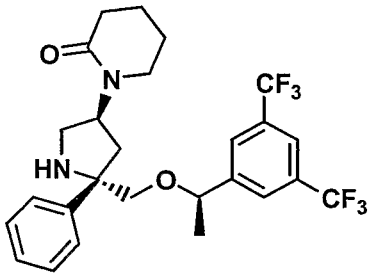
To a solution of **Compound 10** (0.05g, 0.116mmol, 1.0equiv) in MeOH (2ml) at -78°C was added 4-chlorobutyryl chloride (14μl, 0.127mmol, 1.1equiv). The mixture was stirred at -78°C for 5 min, then warmed to 23°C and stirred for 18 h. The reaction mixture was then concentrated and taken up in EtOAc (200ml) and washed with sat. aq. $NaHCO_3$(1 x 100ml). 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:

To a solution of crude **Compound 11** in dry THF (2ml) was added NaH (60% dispersion in mineral oil, 0.014g, 0.347mmol, 3equiv) at 0°C and stirred for 5 min,

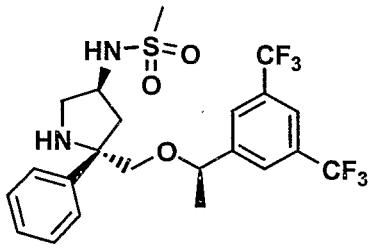
then heated at 60°C for 2 h. The reaction mixture was cooled to 0°C and quenched carefully with water (3ml). The mixture was poured into EtOAc (100 ml) and washed with saturated aqueous $NaHCO_3$ (100ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the resulting mixture on Biotage with 5%MeOH/EtOAc gave **Example 3** (0.20g, 34%). Electrospray MS $[M+1]^+$ 501.1.

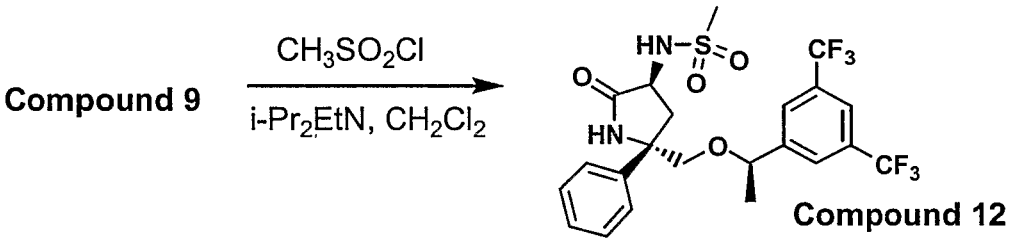
Example 4



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

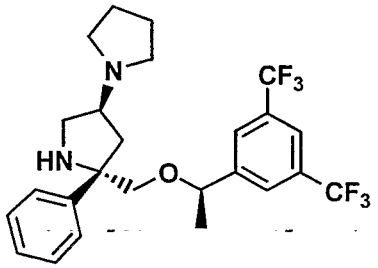




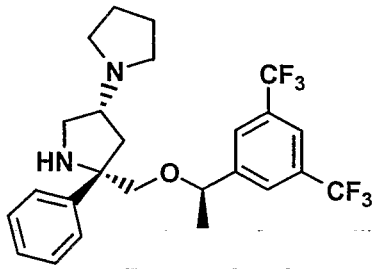
To a solution of **Compound 9** (0.13g, 0.29mmol, 1.0equiv) in CH_2Cl_2 (3ml) at 0°C was added DIEA (0.11ml, 0.61mmol, 2.1equiv) and CH_3SO_2Cl (34µl, 0.435mmol, 1.5equiv). The mixture was stirred at 0°C for 30 min, then poured into EtOAc (150ml) and washed with saturated aqueous $NaHCO_3$ (100ml). The 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.

The crude **Compound 12** was converted to **Example 5** (80mg, 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

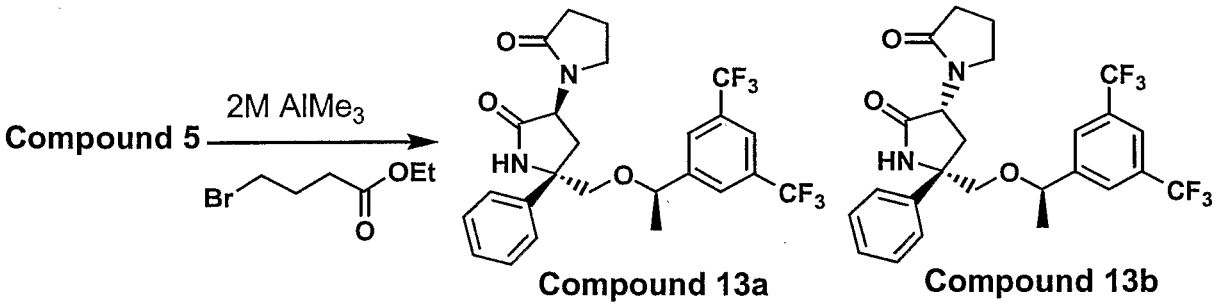


Example 6a



Example 6b

Step 1:



To a solution of amino-lactam **Compound 5** (0.100g, 0.224mmol, 1equiv) in toluene (7ml) at 0°C, was added a solution of 2M $AlMe_3$ in toluene (0.14ml, 0.28mmol, 1.25equiv). 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 (20ml), and washed with of saturated aqueous $NaHCO_3$ (100ml) and saturated aqueous NaCl (100ml) 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** (40mg, 35%), and the **Compound 13b** (20mg, 18%).

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

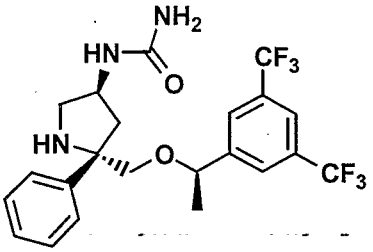
Electrospray MS $[M+1]^+$ 515.1 for the **Compound 13b.**

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

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

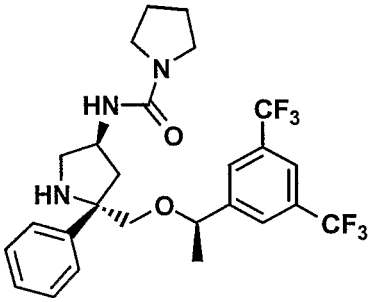
Electrospray MS $[M+1]^+$ 487.11 for the **Example 6b.**

Example 7



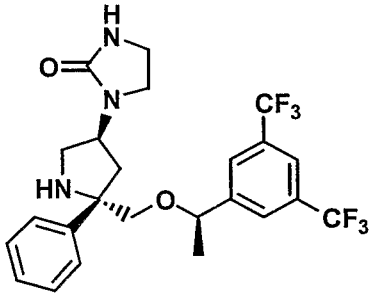
Example 7 (74% overall yield) was prepared from **Compound 10** in a manner similar to that used to prepare **Example 29** from **Example 13.** Electrospray MS $[M+1]^+$ 476.1.

Example 8



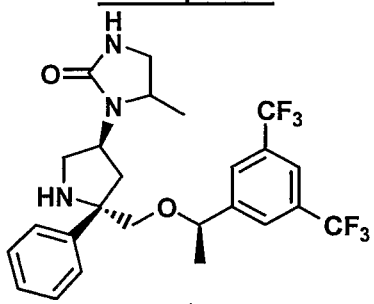
Example 8 (94% overall yield) was prepared from **Compound 10** in a manner similar to that used to prepare **Example 33** from **Example 13.** Electrospray MS $[M+1]^+$ 430.1.

Example 9



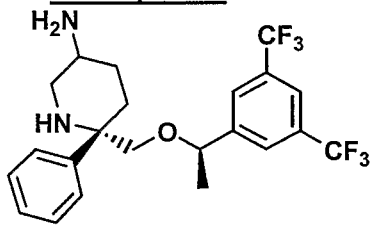
Example 9 (50% overall yield) was prepared from **Compound 10** in a manner similar to that used to prepare **Example 36** from **Example 13.** Electrospray MS $[M+1]^+$ 502.1.

Example 10

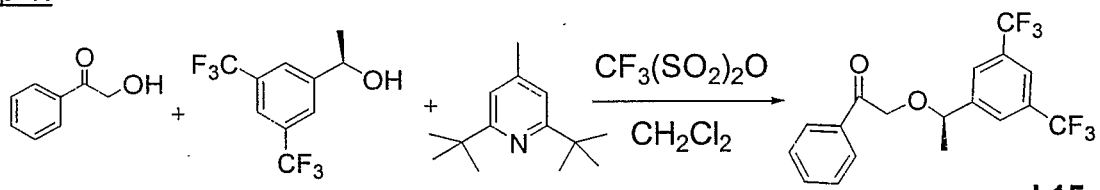


To a solution of **Compound 10** (0.15g, 0.3mmol, 1equiv) in CH_2Cl_2 (2ml) was added methyl levulinate (0.041ml, 0.33mmol, 1.1equiv) followed by sodium triacetoxyborohydride (0.127g, 0.6mmol, 2equiv.) and the reaction mixture was stirred at 23°C and stirred for 72 h. The reaction was quenched with saturated aq. $NaHCO_3$ (100ml) and extracted with EtOAc (200ml). 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 (0.070g, 47%). (Electrospray MS $[M+1]^+$ 515.1.

Example 11



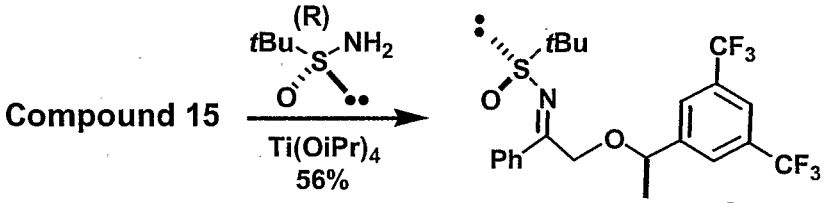
Step 1:



compound 14 **compound 15**

Procedures for preparing **Compound 14** and **Compound 15** are shown in WO 01/44200.

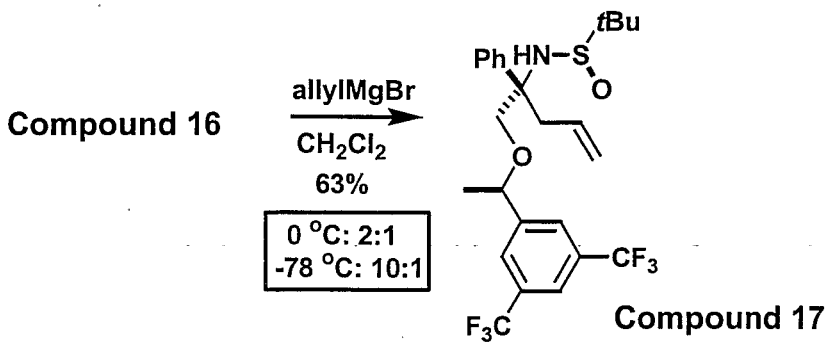
Step 2:



Compound 16

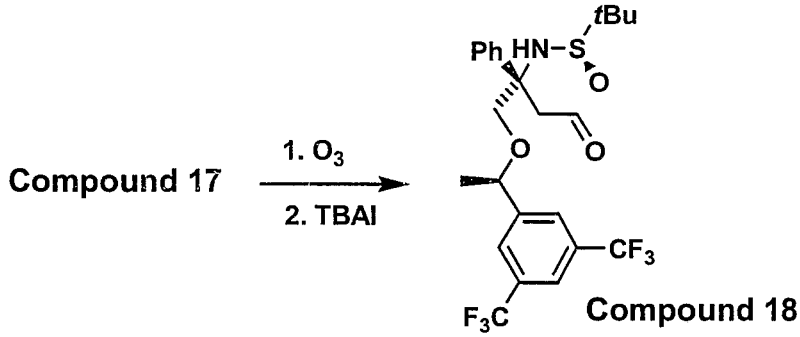
To a flask containing ketone **Compound 15** (1.05g, 2.8mmol, 1equiv) and (R)-t-butylsulfinamide (0.4g, 3.3mmol, 1.8equiv), was applied a vacuum for 5 min. Then, the flask was filled with N_2. $Ti(OiPr)_4$ (1ml) was added through a syringe dropwise to the reaction mixture. The reaction mixture was stirred at 23°C for 36 h. The reaction mixture was then poured into brine (10ml) and EtOAc (20ml) 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** (0.75g, 56%).

Step 3:



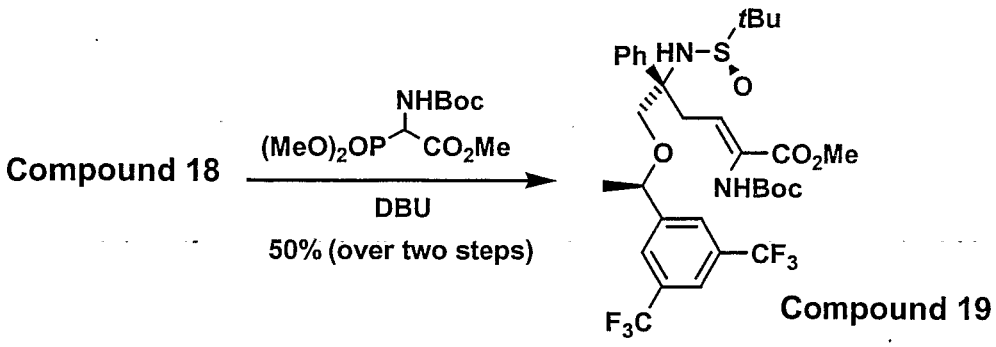
To a solution of sulfinimine **Compound 16** (2.44g, 5.1mmol, 1equiv) in CH_2Cl_2 at -78°C, was added dropwise allylmagnesium bromide (6.1ml, 6.1mmol, 1.2equiv, 1M in Et_2O) through a syringe. After stirring for 3 h at -78°C, the reaction mixture was quenched with a saturated aqueous NH_4Cl and allowed 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** (1.672g, 63%).

Step 4:



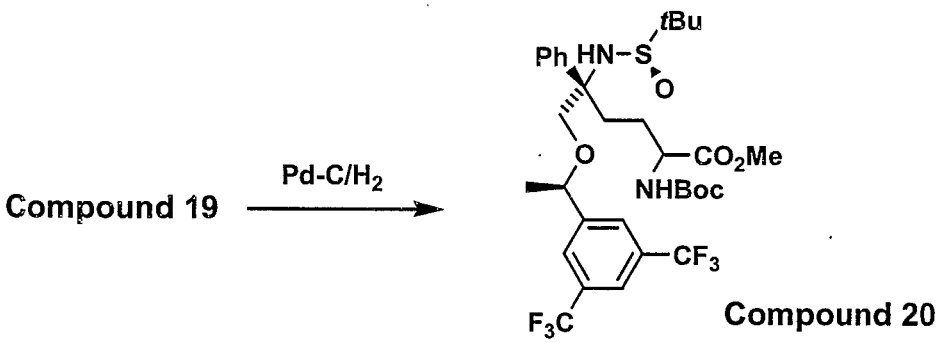
A 15ml RBF was charged with **Compound 17** (245mg, 0.47mmol, 1.0equiv) and CH_2Cl_2 (2ml). This pale orange solution was cooled to -78°C, and then O_3 was bubbled in at 1.0 ml/min. After the solution turned pale blue, the reaction solution was stirred at -78°C for 10 min. Then it was flushed with N_2 to get rid of O_3. Tetrabutylammonium iodide (177mg, 0.47mmol, 1.0equiv) 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** (243.5mg, 99%). Electrospray MS $[M+1]^+$ 524.1.

Step 5:



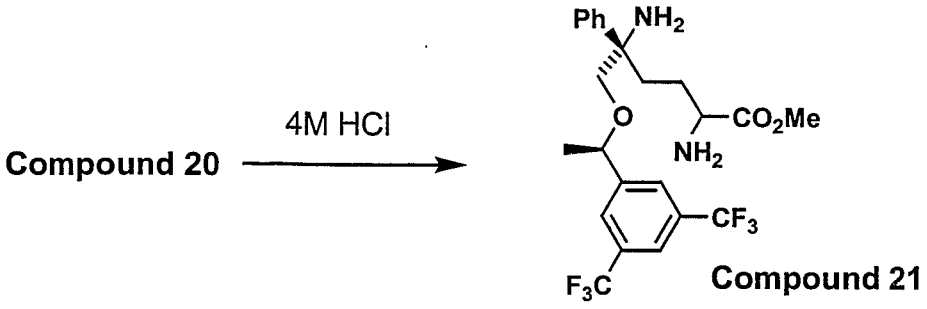
To a solution of **Compound 18** (1.2g, 2.29mmol, 1.0equiv) Boc-Phosphonate (818mg, 2.75mmol, 1.2equiv) in DMF (20ml) was added Cs_2CO_3 (2.24g, 6.87mmol, 3.0equiv). After stirring at RT for 3h, the mixture was diluted with Et_2O, and washed with water (100ml 2 x), and brine. The combined aqueous layer 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** (830mg, 55%). Electrospray MS $[M+1]^+$ 695.2.

Step 6:



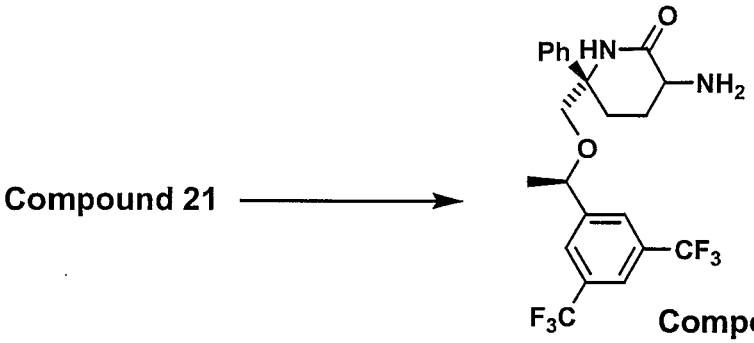
A solution of **Compound 19** (830mg, 1.19mmol, 1.0equiv) in EtOH (20ml) was flushed with N_2. After the addition of Palladium on carbon (10%, 1.27g, 1.19mmol, 1.0equiv), a H_2 balloon was attached to the reaction flask. The reaction mixture was stirred for almost 24 h until TLC showed completion of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

Step 7:



A solution of **Compound 20** (400mg, 0.57mmmol, 1.0equiv) in anhydrous MeOH (4ml) was cooled to 0°C, then treated with 4 M solution of HCl in 1,4-dioxane (16ml). 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:



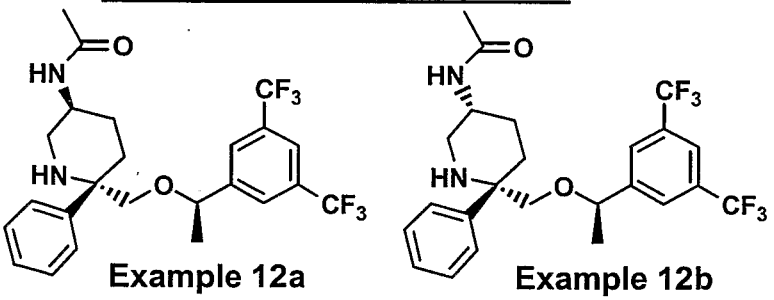
Compound 22

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

Step 9:

A flame-dried 500ml RBF was charged with $ALCl_3$ (37.4mg, 0.28mmol, 1.5 equiv). The reaction flask was cooled to 0°C and anhydrous THF (1ml) was syringed in. After stirred for 5 min, 1M solution of LAH in Et_2O (0.84ml, 0.84mmol, 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** (50mg, 0.187mmol, 1.0equiv) in dry THF (1ml) 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** (34mg, 41%). Electrospray MS $[M+1]^+$ 447.1.

Example 12a and Example 12b

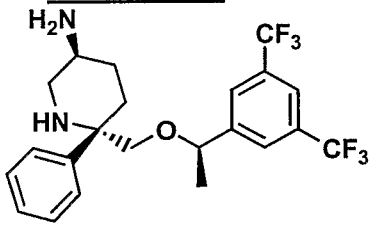


Example 12a **Example 12b**

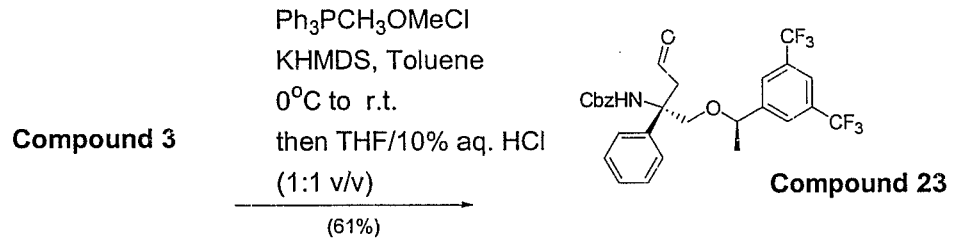
Step 1:

To a solution of **Example 11** (30mg, 0.067mmol, 1.0equiv) in CH_2Cl_2 (10ml) at 0°C was added DIEA(17.5µl, 0.10mmol, 1.5equiv) and Ac_2O (6.3µl, 0.067mmol, 1.0equiv). The mixture was stirred at 0°C for 30 min. It was quenched with saturated aqueous $NaHCO_3$ solution (4ml) and extracted with CH_2Cl_2. The combined organic layers were dried, filtered and concentrated to give the crude product (39mg). 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



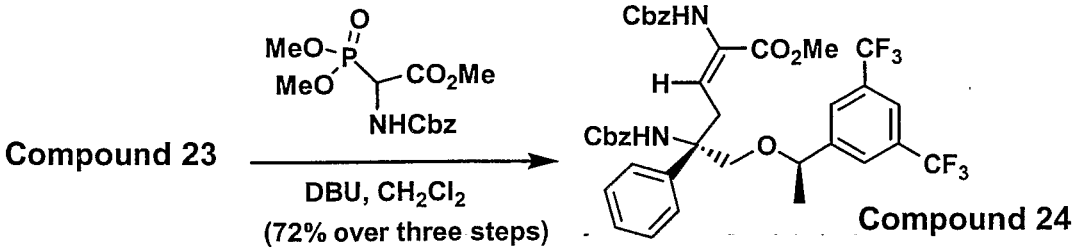
Step 1:



To a suspension of (methoxymethyl)triphenylphosphonium chloride (21.3g, 0.062mmol, 2.95equiv) in toluene (300ml) at 0°C under N_2, a solution of potassium bis(trimethylsilyl)amide (125ml, 0.062mmol, 2.95equiv) was added. After being stirred at 0°C for 1 h, a solution of **Compound 3** (13.4g, 0.021mmol, 1equiv) in toluene (100ml) 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 (400ml x 2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give crude enol ether as yellow oil.

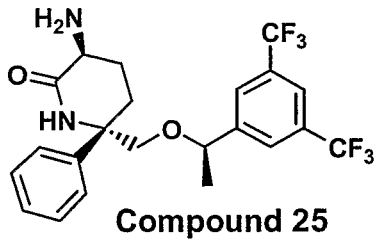
The crude enol ether was dissolved in THF (100ml) at 23°C and aqueous HCl (100ml, 10% in water) was added. The mixture was stirred overnight and was quenched with saturated $KHCO_3$ solution. Et_2O was added and layers were separated. The separated aqueous layer was extracted with Et_2O (300ml x 2). 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** (6.97g, 61%) as yellow oil.

Step 2:



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:

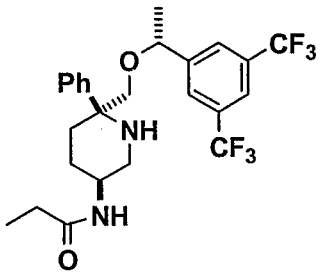


Compound 25 was prepared using a procedure similar to that for **Compound 9** using **Compound 24** instead of **Compound 7**. Electrospray MS $[M+1]^+$461.1.

Step 4:

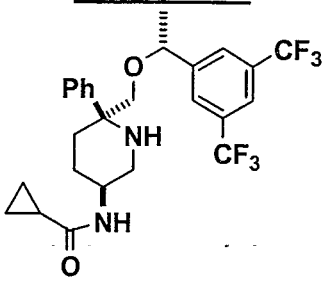
Example 13 (6.84g, 73%) was prepared using similar procedure to **Compound 6** using **Compound 25** instead of **Compound 5**. Electrospray MS $[M+1]^+$447.1.

Example 14



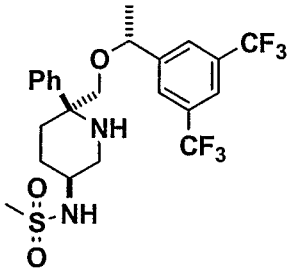
To a solution of **Example 13** (275mg, 0.60mmol, 1.0equiv) in anhydrous CH_2Cl_2 (10ml) at -78°C was added propionyl chloride (52µl, 0.60mmol, 1.0equiv). The reaction was completed within 30 min. Reaction mixture was quenched with 7N ammonia in MeOH (0.5ml), then loaded directly onto silica column and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

Example 15



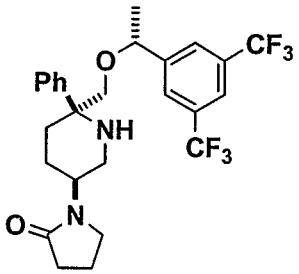
Example 15 (yield 89%) was prepared using similar procedure as for **Example 14** using cyclopropanecarbonyl chloride in place of propionyl chloride. Electrospray MS $[M+1]^+$ 515.1.

Example 16



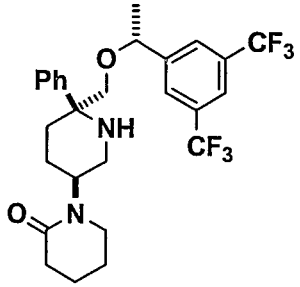
Example 16 (yield 89%) was prepared using similar procedure as for **Example 14** using **Example 13** and CH_3SO_2Cl in place of propionyl chloride. Electrospray MS $[M+1]^+$ 52.1.

Example 17



Example 17 (overall yield 23%) was prepared using similar procedure as for **Example 3** using **Example 13** in place of **Compound 10**. Electrospray MS $[M+1]^+$ 515.1.

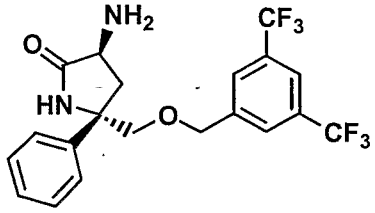
Example 18



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

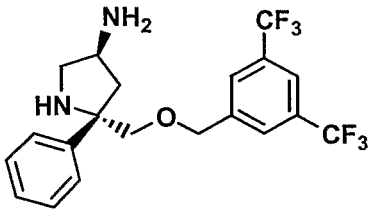
Electrospray MS $[M+1]^+$ 529.1.

Preparation of Compounds 26, 27, 28 and 29:



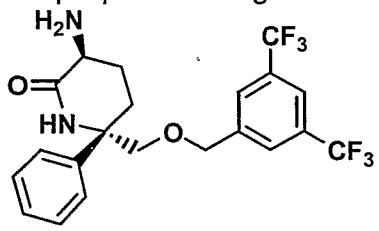
Compound 26

Compound 26 was prepared from **Compound 1** using similar procedure as for **Compound 9**.



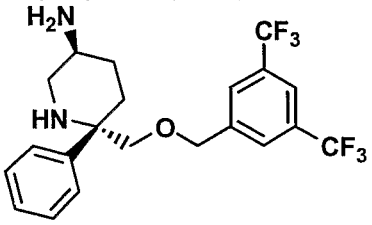
Compound 27

Compound 27 was prepared using similar procedure as for **Compound 10**.



Compound 28

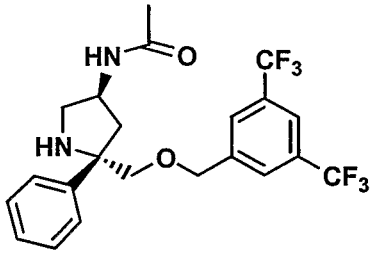
Compound 28 (90% yield) was prepared using the similar procedure for **Compound 25**. Electrospray MS $[M+1]^+$ 447.1.



Compound 29

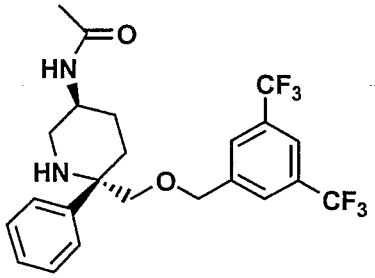
Compound 29 was prepared using similar procedure as for **Example 13**. Electrospray MS $[M+1]^+$ 433.1.

Example 19



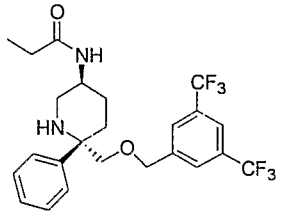
Example 19 (40mg, 70% yield) was prepared using a procedure similar to **Example 1a** using **Compound 27** instead of **Compound 6**.
Electrospray MS $[M+1]^+$ 461.1.

Example 20



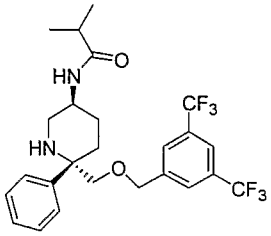
Example 20 (99mg, 72%) was prepared using similar procedure as for **Example 1a** using **Compound 29** instead of **Compound 6**.
Electrospray MS $[M+1]^+$ 475.1.

Example 21



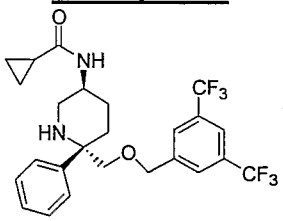
Example 21 (74mg, 66%) was prepared from **Compound 29** using similar procedure as for **Example 2** from **Compound 10** using propionic anhydride in place of cyclopropanecarbonyl chloride. Electrospray MS $[M+1]^+$ 489.1.

Example 22



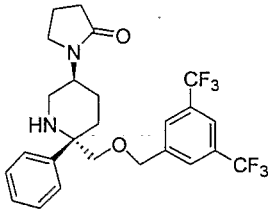
Example 22 (75mg, 78%) was prepared from **Compound 29** using similar procedure as for **Example 2** from **Compound 10** using isobutyryl chloride in place of cyclopropanecarbonyl chloride. Electrospray MS $[M+1]^+$ 503.1.

Example 23



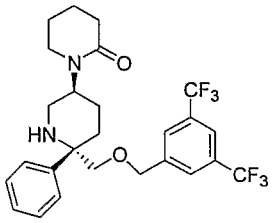
Example 23 (9mg, 35%) was prepared from **Compound 29** using similar procedure as for **Example 2** from **Compound 10**. Electrospray MS $[M+1]^+$ 501.1.

Example 24



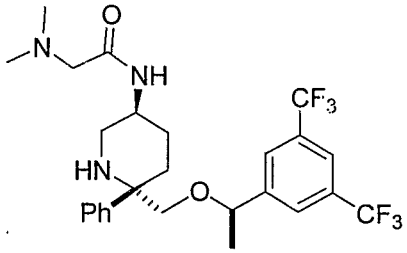
Example 24 (31mg, 71%) was prepared from **Compound 29** using similar procedure as for **Example 3** from **Compound 10**. Electrospray MS $[M+1]^+$ 501.1.

Example 25



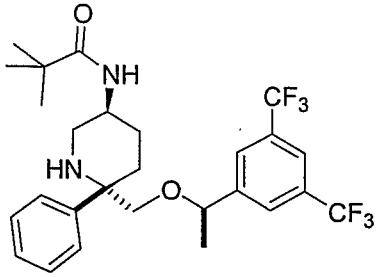
Example 25 (68mg, 68%) was prepared from **Compound 29** using similar procedure as for **Example 4** from **Compound 10**. Electrospray MS $[M+1]^+$ 515.1.

Example 26



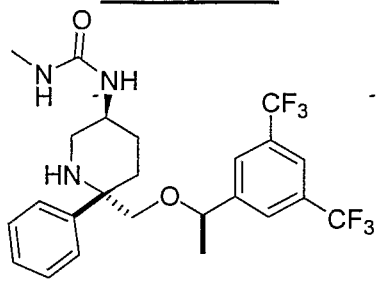
To a solution of **Example 13** (0.14g, 0.314mmol, 1equiv) in anhydrous DMF (1.6ml) at 23°C was added N,N-dimethyl glycine (33.95mg, 0.329mmol, 1.05equiv) followed by EDC.HCl (66.13mg, 0.345mmol, 1.1equiv) and the reaction mixture was stirred at 23°C for 18 h. The reaction mixture was diluted with DMF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

Example 27



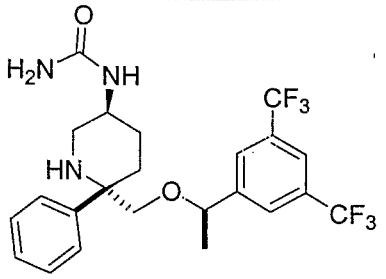
Example 27 (yield 62%) was prepared using similar procedure as for **Example 14** using trimethylacetyl chloride in place of propionyl chloride. Electrospray MS $[M+1]^+$ 531.1

Example 28



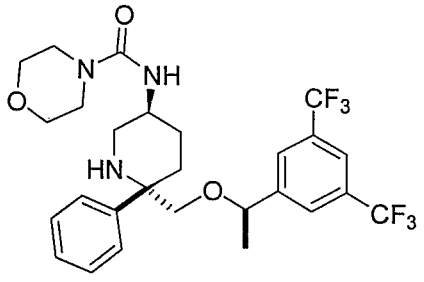
Example 28 (105mg, 74%) was prepared using similar procedure as for **Example 14** using methyl isocyanate in place of propionyl chloride. Electrospray MS $[M+1]^+$ 504.1

Example 29



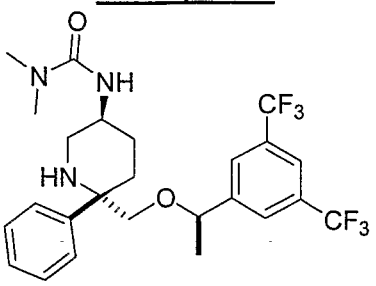
Example 29 (146mg, 754%) was prepared using similar procedure as for **Example 14** using trimethylsilyl isocyanate in place of propionyl chloride. Electrospray MS $[M+1]^+$ 490.1

Example 30



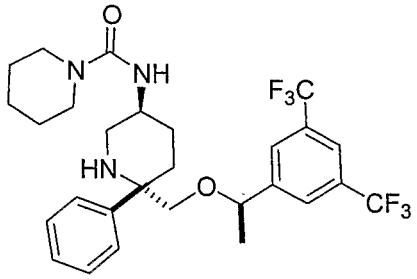
To a solution of **Example 13** (100mg, 0.224mmol, 1equiv) in anhydrous CH_2Cl_2 (2ml) was added 4-morpholinylcarbonyl chloride (28.7μl, 0.246mmol, 1.1equiv) and DIEA (39μl, 0.223mmol, 1equiv). The reaction mixture was stirred at RT overnight. Aqueous work-up and purification by using silica column to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

Example 31



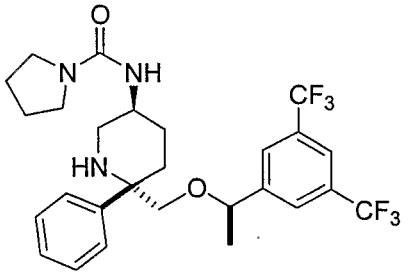
Example 31 (40% yield) was prepared using similar procedure as for **Example 30** using dimethylcarbamyl chloride in place of 4-morpholinylcarbonyl chloride. Electrospray MS $[M+1]^+$ 518.1

Example 32



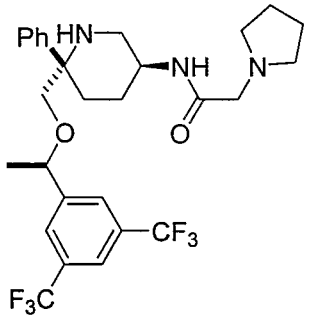
Example 32 (42% yield) was prepared using similar procedure as for **Example 30** using 1-piperidinecarbonyl chloride in place of 4-morpholinylcarbonyl chloride. Electrospray MS $[M+1]^+$ 558.1

Example 33

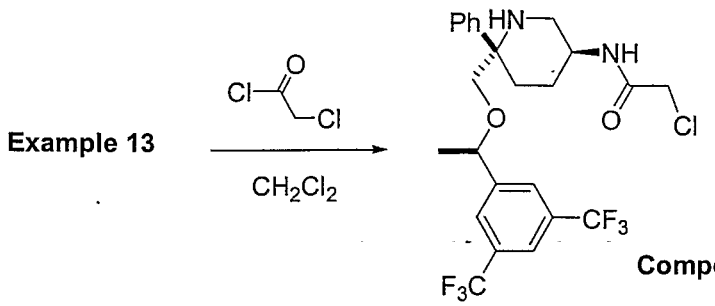


Example 33 (40% yield) was prepared using similar procedure as for **Example 30** using 1-pyrrolidinecarbonyl chloride in place of 4-morpholinylcarbonyl chloride. Electrospray MS $[M+1]^+$ 544.1

Example 34



Step 1:



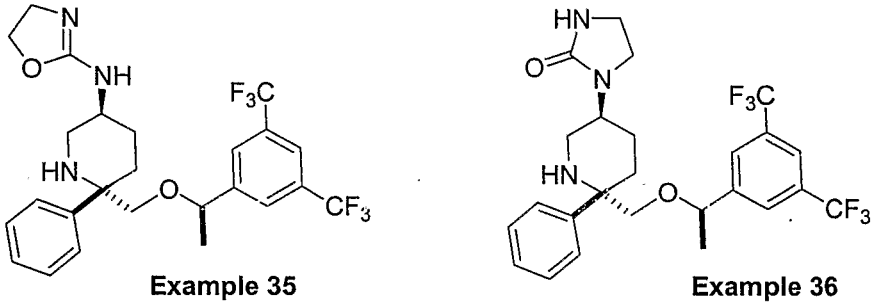
Compound 30

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

Step 2:

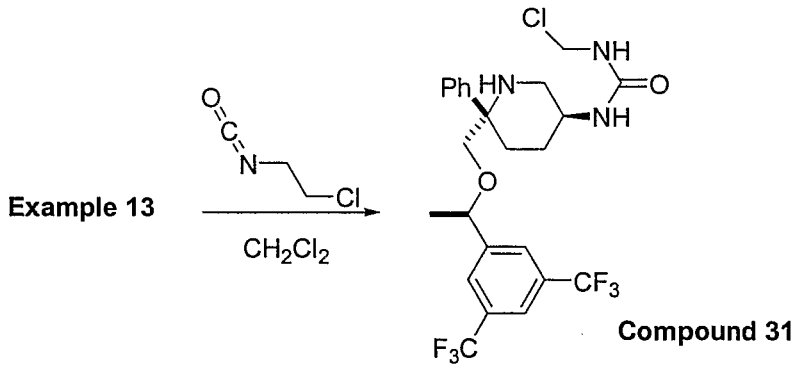
To a solution of **Compound 30** (90mg, 0.17mmol, 1equiv) in anhydrous CH_2Cl_2 (0.5ml) was added pyrrolidine (17.2µl, 0.206mmol, 1.2equiv) and DIEA (30µl, 0.17mmol, 1equiv). The reaction mixture was stirred at RT overnight. Aqueous work-up and purification by using silica column to afford **Example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

Example 35 **Example 36**



Example 35 Example 36

Step 1:



Compound 31

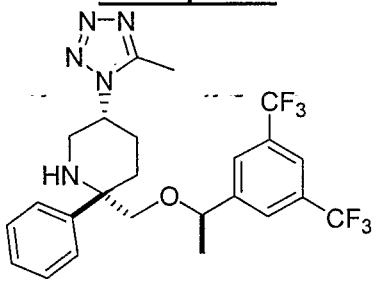
Compound 31 was prepared using similar procedure as for **Example 14** using 2-chloroethyl isocyanate in place of propionyl chloride.

Step 2:

To a solution of **Compound 31** in anhydrous THF (7ml), was added NaH (25mg, 0.625mmol, 1.7equiv, 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

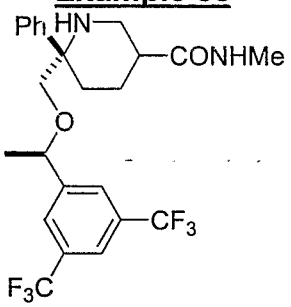
product which was purified by silica gel column to give the less polar title compound **Example 35** (10mg, 5.4%), Electrospray MS $[M+1]^+$ 516.1; and the more polar title compound **Example 36** (122mg, 66%), Electrospray MS $[M+1]^+$516.1

Example 37

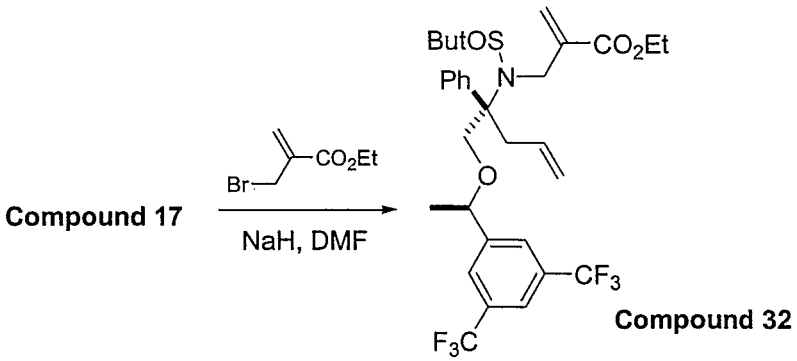


To a solution of **Example 12b** (200mg, 0.41mmol, 1equiv) in anhydrous CH_2Cl_2 (1ml) at 0°C, was added trifluoromethanesulfonic anhydride (69µl, 0.41mmol, 1equiv). The reaction mixture was stirred for 40 min before NaN_3 (26.6mg, 0.41mmol, 1equiv) was added. The mixture was warmed up to RT for 2 h.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

Example 38



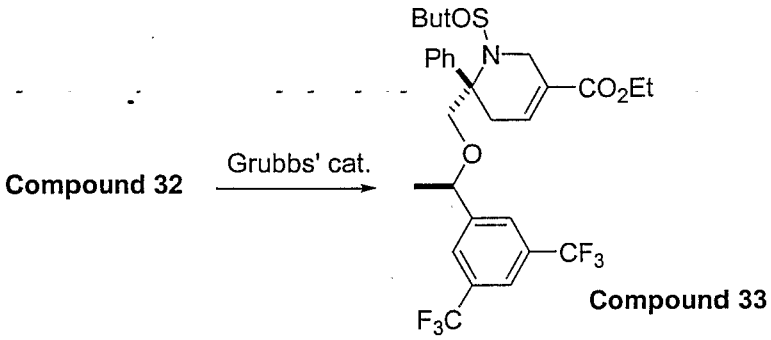
Step 1:



To **Compound 17** (0.3g, 0.575mmol, 1equiv) under N_2 in anhydrous DMF (3ml) at 0°C was added NaH (27.6mg, 0.69mmol, 1.2equiv, 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 (0.088ml, 0.629mmol, 1.1equiv). 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

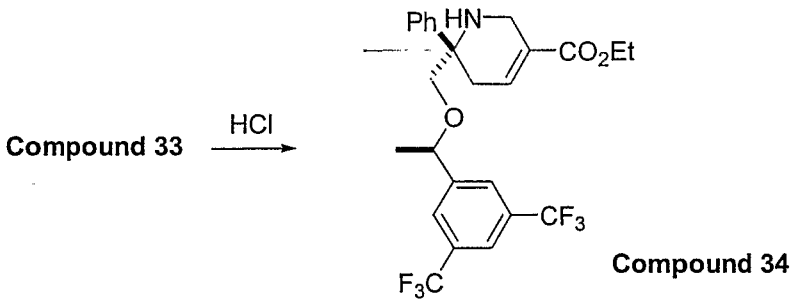
with Et_2O. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. The crude product was purified using flash silica gel column to give titled **Compound 32** (0.199g, 55%).

Step 2:



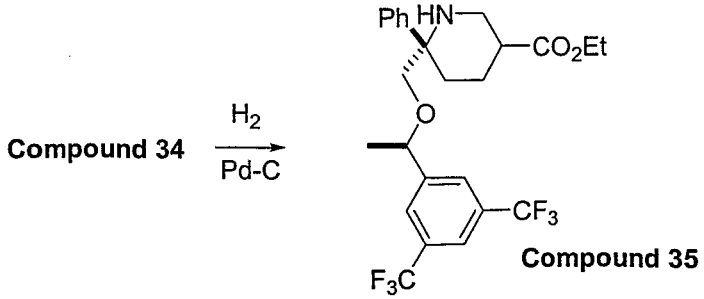
To a solution of **Compound 32** (50mg, 0.078mmol, 1equiv) in anhydrous CH_2Cl_2 (0.8ml) under N_2 was added Grubbs' catalyst tricyclohexylphosphine [1,3-bis(2,4,6-trimethyl-phenyl)-4,5-dihydro-imidazol-2-ylidene][benzylidine]ruthenium(IV) dichloride (6.7mg, 0.0079mmol, 0.1equiv). The resulting brown 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** (60mg, 63%). Electrospray MS $[M+1]^+$ 502.1.

Step 3:



To a solution of **Compound 33** (30mg, 0.05mmol, 1equiv) in absolute MeOH (0.5ml) at 0°C was added a solution of 4N HCl in dioxane (0.5ml). 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:

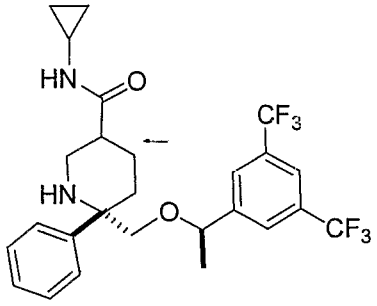


A solution of **Compound 34** (30mg, 0.06mmol) in EtOH (5ml) was treated with 10% Pd-C (32mg, 0.03mmol) and was hydrogenated at 60 psig for 18 h. The catalyst was filtered and washed with EtOAc. The filtrate was concentrated and the resulting residue of **Compound 35** was taken directly to the next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

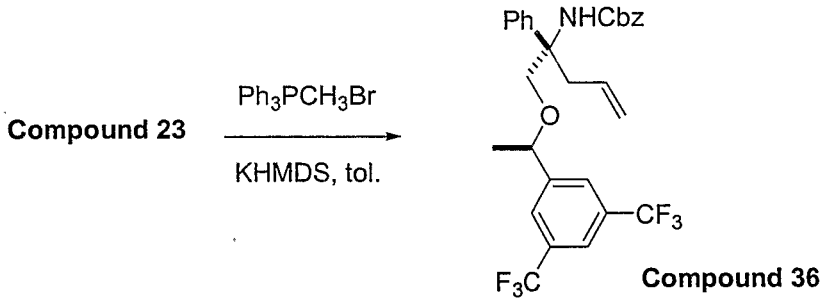
Step 5:

To a mixture of methylamine HCl salt (52mg, 0.77mmol, 12.8 equiv) in toluene (0.2 ml) was added Me_3Al (2M in toluene, 0.36ml, 0.72mmol) and the resulting mixture stirred for 30 min. A solution of **Compound 35** (30mg, 0.06mmol) in toluene (0.5ml) 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 (10ml), stirred for 10 min and extracted with EtOAc (4 x 10ml). 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



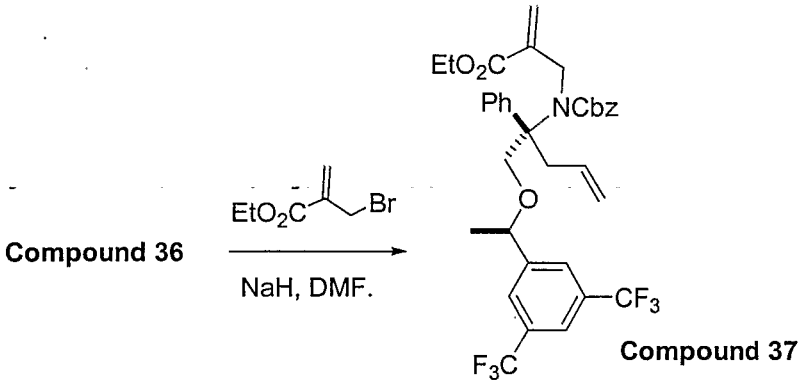
Step 1:



Compound 36

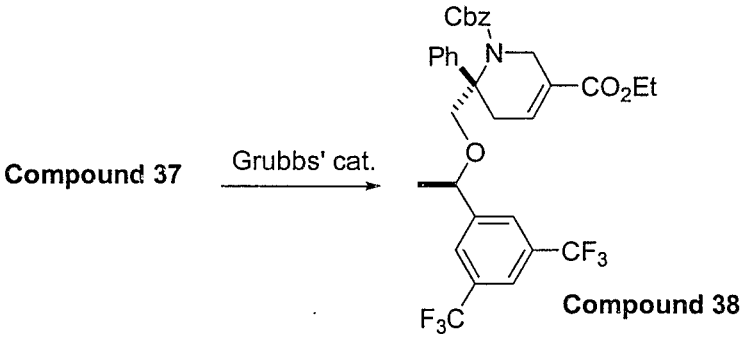
Compound 36 (yield 63%) was prepared from **Compound 23** using the procedure similar to the preparation of **Compound 23** from **Compound 3** and using methyltriphenyl-phosphonium bromide in place of (methoxymethyl)triphenylphosphonium chloride.

Step 2:



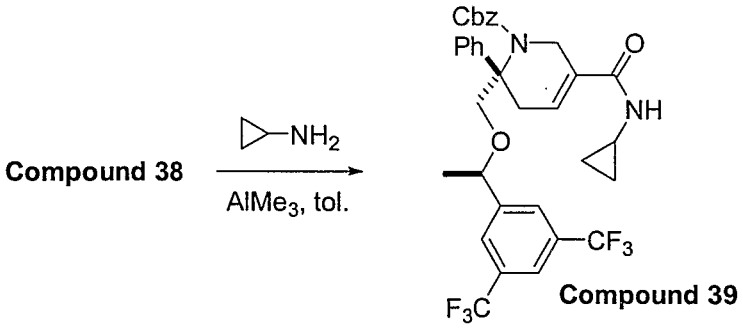
Compound 37 (50% yield) was prepared using similar procedure as for **Compound 32** using **Compound 36** in place of **Compound 17**.

Step 3:



To a solution of **Compound 37** (2.46g, 3.71mmol, 1equiv) in anhydrous CH_2Cl_2 (50ml) under N_2 was added Grubbs' catalyst (327mg, 0.385mmol, 0.1equiv). 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** (2.1g, 89%).

Step 4:



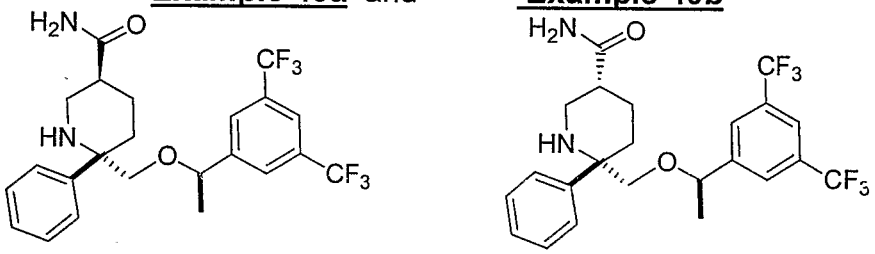
To a mixture of cyclopropylamine (0.24ml, 3.45mmol, 4.2equiv) in toluene (1.0 ml) was added Me_3Al (2M in toluene, 1.71ml, 3.41mmol, 4.2 equiv) and the resulting mixture stirred for 30 min. A solution of **Compound 38** (516mg, 0.82mmol, 1 equiv) in toluene (2.5ml) was added to the reaction mixture via 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 (10ml x 4). The combined organic layers were washed with brine and concentrated. The residue was purified on silica column to afford **Compound 39** (360mg, 68%).

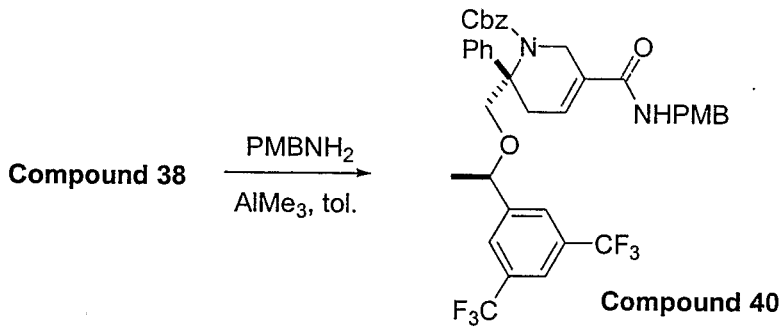
Step 5:

A solution of **Compound 39** (360mg, 0.556mmol, 1equiv) in EtOH (25ml) was treated with 10% Pd-C (641mg, 0.613mmol, 1.1equiv) 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** (54mg, 19%) Electrospray MS $[M+1]^+$ 515.1, and the more polar isomer, **Example 39b** (22mg, 8%) Electrospray MS $[M+1]^+$ 515.1

Example 40a and **Example 40b**

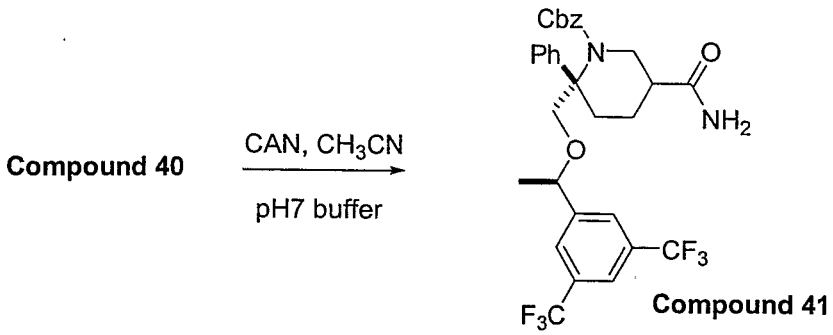


Step 1:



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

Step 2:



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

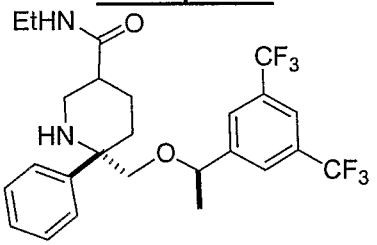
Step 3:

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.**

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

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

Example 41

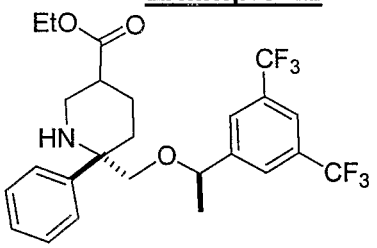


Example 41a and **Example 41b** were prepared using a similar procedure as for **Example 38a** and **Example 38b** using ethylamine instead of methylamine.

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

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

Example 42

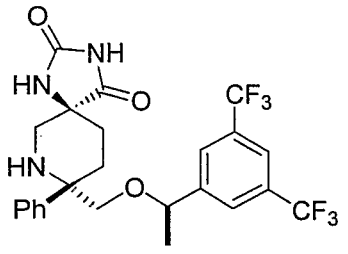


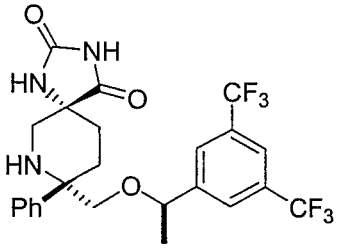
The mixture of two isomers of **Compound 35** was separated by column chromatography to give pure **Example 42a** and **Example 42b**

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

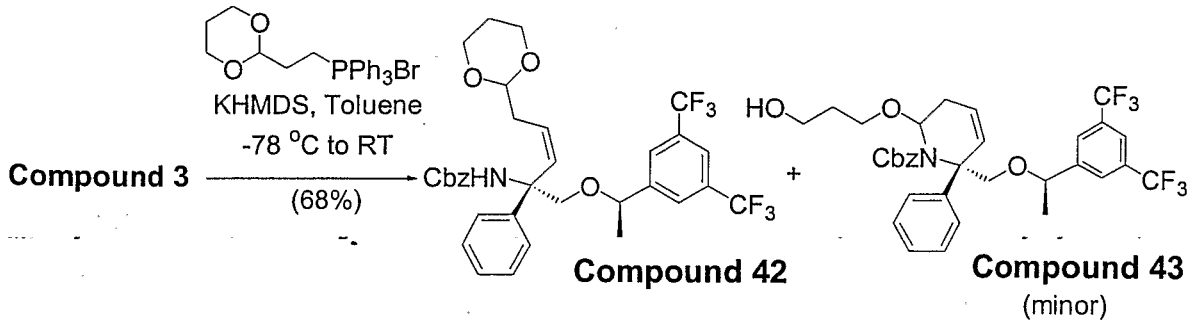
Electrospray MS $[M+1]^+$ 504.1 for the **Example 42b** (more polar isomer).

Example 43a **Example 43b**



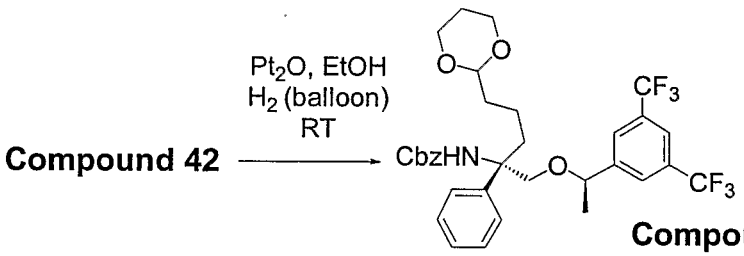


Step 1:



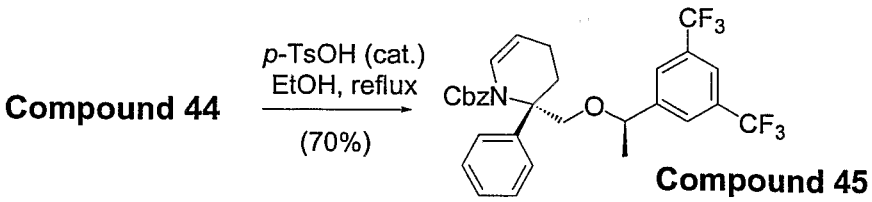
To a suspension of lactol **Compound 3** (60g, 93.0mmol, 1equiv.) and Wittig Reagent (93.5g, 200.0mmol, 2.15equiv.) in toluene (800ml) stirred at -78°C under N_2, a solution of KHMDS (0.5M in toluene, 558ml, 280.0mmol, 3equiv.) was added dropwise at -78°C. The cooling bath was removed and the yellow 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 x 500ml). 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 (40.5g, 68%), Electrospray MS $[M+1]^+$ 638.1. Continuous elution gave an impure cyclized product **Compound 43**.

Step 2:



A suspension of alkene **Compound 42** (40.5g, 64mmol, 1equiv.) and PtO_2 (1.44g, 6.4mmol, 0.1equiv.) in EtOH (400ml) were stirred under a H_2 balloon at 23°C for 24 h. Another batch of PtO_2 (1.44g, 6.4mmol, 0.1equiv) 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:



p-TsOH.H_2O (2.42g, 13.0mmol) 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 (300ml x 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 10mol% *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** (25g, 70%), Electrospray MS $[M+1]^+$ 564.1, was obtained as yellow oil.

Step 4:

Compound 45 $\xrightarrow[(74\%)]{BH_3.DMS,\ THF,\ r.t.\ \text{then}\ NaOH,\ H_2O_2}$ **Compound 46**

$BH_3.Me_2S$ (13.6ml, 133mmo, 3.02 equiv) was added to a solution of enamide **Compound 45** (25g, 44.0mmol, 1equiv.) 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 (500ml, 2N) was added slowly followed by a solution of H_2O_2 (500ml, 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 (500ml x 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 (19g, 74%), Electrospray MS $[M+1]^+$ 582.1.

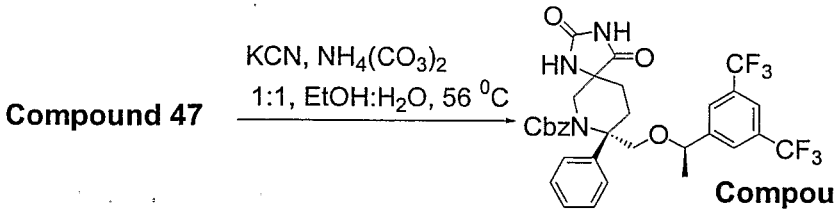
Step 5:

Compound 46 $\xrightarrow[(80\%)]{(COCl)_2,\ DMSO\ CH_2Cl_2,\ -78\ ^oC\ \text{then}\ Et_3N}$ **Compound 47**

Oxalyl chloride (5.7ml, 65.3mmol, 2equiv.) was added to a solution of DMSO (9.3ml, 131.0mmol, 4equiv.) in CH_2Cl_2 (300ml) at -78°C under N_2. The mixture was stirred at -78°C for 15 min before a solution of alcohol **Compound 46** (19g,

32.7mmol. 1equiv.) in CH_2Cl_2 (50ml) was added. The mixture was stirred at -78°C for a further 1 h and Et_3N (32ml, 228.9mmol, 7equiv.) 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 (300ml x 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 (15g, 80%), Electrospray MS $[M+1]^+$ 580.1.

Step 6:



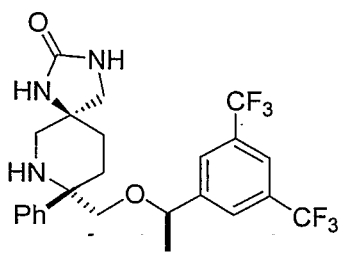
Compound 48

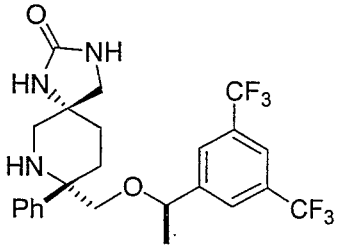
EtOH (150ml) was added to Cbz-ketone **Compound 47** (15g, 25.88mmol, 1equiv.), followed by $NH_4(CO_3)_2$ (9.95g, 103.5mmol, 4equiv.) and a solution of KCN (3.4g, 51.77mmol, 2equiv.). The resulting mixture was heated at 58°C under N_2 for 72 h. TLC (1:1 EtOAc:hexane) revealed complete consumption of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

Step 7:

The crude Cbz-hydantoin **Compound 48** (16.5g, 25.4mmol, 1equiv.) was dissolved in MeOH (220ml) and 20% $Pd(OH)_2$-C (3.6g) 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), Electrospray MS $[M+1]^+$ 516.1.

Examples 44a and 44b





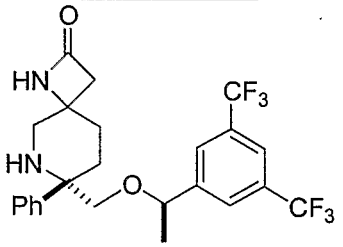
Example 44a **Example 44b**

A flame-dried 25ml RBF was charged with $AlCl_3$ (0.01g, 0.776mmol, 4equiv). The reaction flask was cooled to 0°C and 1M solution of LAH in Et_2O (0.58ml, 0.58mmol, 3equiv) was added. The mixture was stirred at 0°C for 10 min and then a solution of **Example 43b** (0.1g, 0.194mmol, 1equiv.) in dry THF (3ml) 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 x 200ml). 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** (0.066g, 68%), Electrospray MS $[M+1]^+$ 502.1.

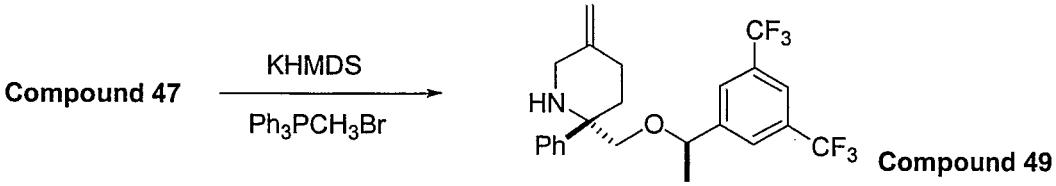
Example 44a was prepared from **Example 43a** using the procedure described for the preparation of **Example 44b** from **Example 43b.**

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

Example 45



Step 1:



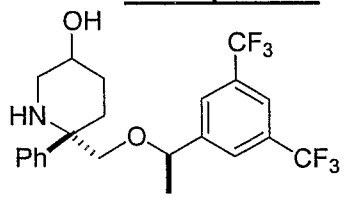
To a suspension of (methyl)triphenylphosphonium bromide (0.37g, 1.04mmol, 3equiv) in toluene (5ml) at 0°C under N_2, a solution of KHMDS (1.73ml, 0.863mmol, 2.5equiv) was added. After being stirred at 0°C for 1 h, a solution of **Compound 47** (0.2g, 0.35mmol, 1equiv) in toluene (7ml) was added. The mixture

was stirred at 0°C for 1.5 h and then quenched with saturated $NaHCO_3$ (150ml). The mixture was extracted with EtOAc (100ml x 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** (0.196g, 98%).

Step 2:

To a solution of **Compound 49** (0.196g, 0.34mmol, 1equiv) in dry Et_2O (3ml) at 0°C was added chlorosulfonylisocyanate (0.045ml, 0.51mmol, 1.5equiv). 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 (12ml), 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 (20mg) 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** (0.006g, 3.5% over four steps), Electrospray MS $[M+1]^+$ 487.1 and the more polar isomer, **Example 45b** (0.003g, 1.79% over four steps), Electrospray MS $[M+1]^+$ 487.1.

Examples 46

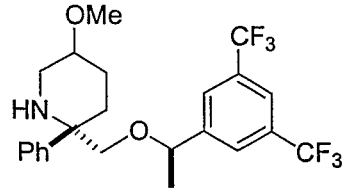


Example 46a and **Example 46b** were prepared from **Compound 46** using a procedure similar to the preparation of **Example 43a** and **Example 43b** from **Compound 48.**

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

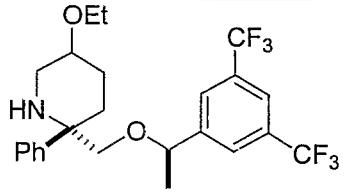
Electrospray MS $[M+1]^+$ 448.1 for the **Example 46b** (more polar isomer).

Example 47



To a solution of NCbz-alcohol **Compound 46** (0.125g, 0.215mmol, 1equiv) in dry DMF (3ml) at 0°C was added NaH (60% in mineral oil, 0.017g, 0.43mmol, 2equiv). The reaction mixture was stirred at 0°C for 20 min and then CH_3I (0.04ml, 0.645mmol, 3equiv) added and the mixture was stirred at 23°C for 18 h. The crude was poured into CH_2Cl_2 (100ml) and washed with brine (100ml x 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 (69mg) 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

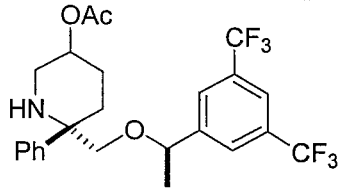


Example 48a and **Example 48b** were prepared from **Compound 46** using the procedure similar to the preparation of **Example 47a** and **Example 47b** and using ethyl iodide in place of methyl iodide.

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

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

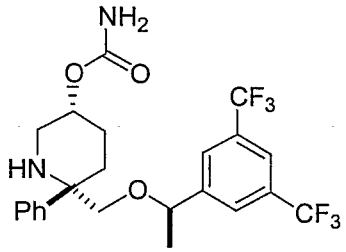
Example 49



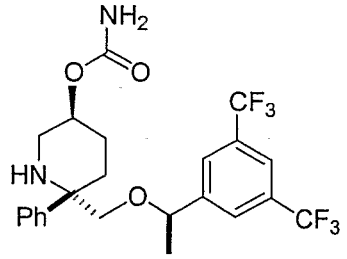
To a solution of NCbz-alcohol **Compound 46** (0.118g, 0.20mmol, 1equiv) in dry CH_2Cl_2 (3ml) at 0°C was added dry pyridine (0.026ml, 0.325mmol, 1.6equiv), followed by acetyl chloride (0.023ml, 0.325mmol, 1.6equiv). The reaction mixture was warmed to 23°C for and stirred for 18 h. The mixture was then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

Examples 50a and 50b



Example 50a



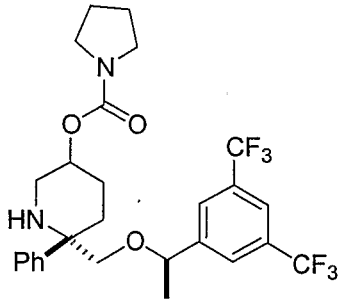
Example 50b

To a solution of NCbz-alcohol **Compound 46** (0.223g, 0.385mmol, 1equiv) in CH_2Cl_2 (8ml) at 0°C was added trichloroacetyl isocyanate (0.055ml, 0.46mmol, 1.2equiv). The reaction mixture was stirred at 0°C for 15 min and then concentrated in vacuo. The residue was dissolved in CH_3OH (7ml) and water (5 ml) was added. The mixture was cooled to 0°C and K_2CO_3 (0.16g, 1.16mmol, 3equiv) 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 (100ml) was added to the residue and the mixture was extracted with CH_2Cl_2 (100ml x 2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford the crude NCbz-carbamate product (232mg) 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**.

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

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

Example 51



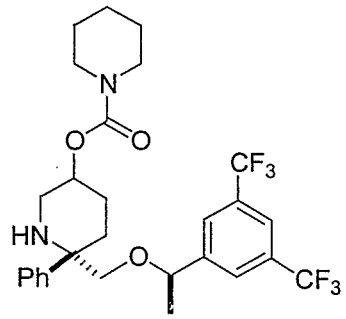
A mixture of NCbz-alcohol **Compound 46** (0.2g, 0.344mmol, 1equiv.), 1,4-dioxane (3ml), 1-pyrrolidine carbonyl chloride (0.076ml, 0.69mmol, 2equiv.) and dry pyridine (0.084ml, 1.03mmol, 3equiv.) was heated in a sealed tube at 100°C for 18 h. The reaction mixture was cooled to 23°C and diluted with EtOAc (150ml). The

mixture was washed with water (100ml) and the organic layer was dried (Na_2SO_4), filtered and concentrated to afford the crude NCbz-carbamate product (232mg) which was hydrogenated to the mixture of desired products **Example 51a** and **51b** 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.**

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

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

Example 52

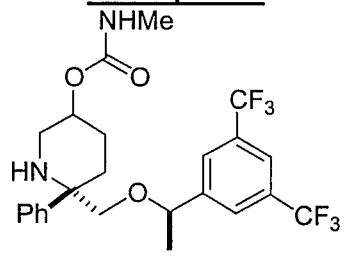


Example 52a and **Example 52b** were prepared from **Compound 46** using the procedure similar to that used for the preparation of **Example 51a** and **Example 51b** and using 1-piperidine carbonyl chloride in place of 1-pyrrolidine carbonyl chloride.

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

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

Example 53

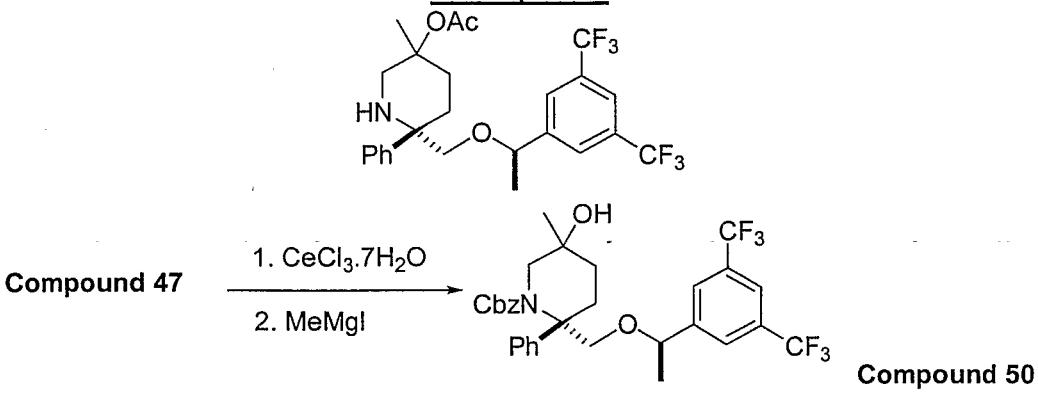


Example 53a and **Example 53b** were prepared from **Compound 46** using the procedure similar to that used for the preparation of **Example 51a** and **Example 51b** and using methylisocyanate in place of 1-pyrrolidine carbonyl chloride.

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

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

Example 54

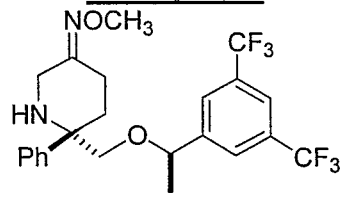


$CeCl_3$ (0.186g, 0.5mmol, 2.1equiv) was added to a 25ml RBF and heated in vacuo at 140°C for two h. The flask was cooled to 23°C under N_2, dry THF (2ml) was added and the resulting suspension was stirred at 23°C for 18 h. The mixture was then cooled to 140°C and CH_3MgI (0.159ml, 0.476mmol, 2equiv.) was added and stirred at 0°C for 1 h. A solution of **Compound 47** (0.138g, 0.238mmol, 1equiv) in dry THF (2.5ml) 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 (50ml) and extracted with EtOAc (100ml x 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** (0.115g, 80%).

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.**

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

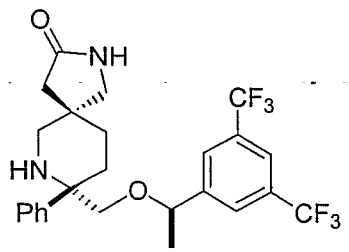
Example 55



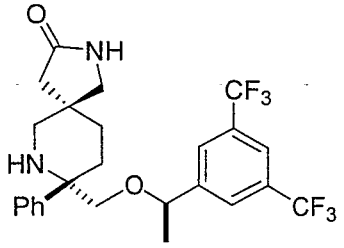
To a solution of **Compound 47** (0.1g, 0.173mmol, 1equiv) in dry pyridine (1ml) was added methoxylamine hydrochloride (0.058g, 0.69mmol, 4equiv) and the reaction mixture was stirred 23°C for 18 h. The mixture was quenched with water (50ml) and extracted with CH_2Cl_2 (100ml x 2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give NCbz-oxime (0.102g, 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 40psi. The crude product was purified by column chromatography over Biotage (4:1, EtOAc:hexane) to afford **Example 55** (0.063g, 79%), Electrospray MS $[M+1]^+$ 475.1.

Examples 56a and 56b

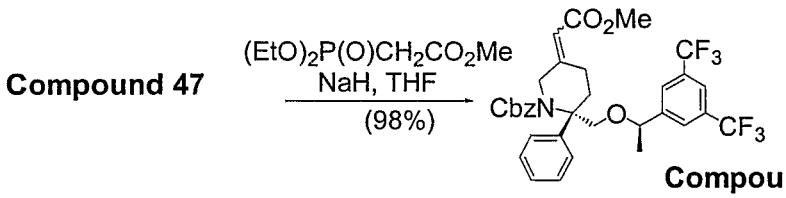


Example 56a



Example 56b

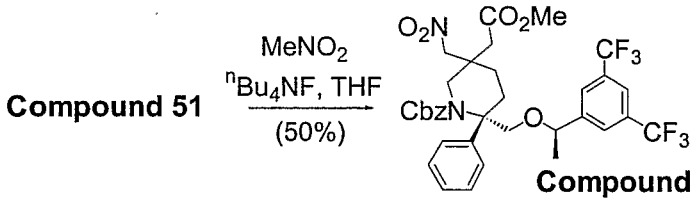
Step 1:



Compound 51

To a suspension of NaH (1.8g, 44.5mmol, 60% in oil) in THF (200ml) at 0°C under N_2, methyl diethylphosphonoacetate (8.2ml, 44.5mmol) was added. The mixture was stirred at 0°C for 15 min and a solution of ketone **Compound 47** (8.6g, 14.8mol) in THF (50ml) 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 (200ml x 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** (9.2g, 98%) as colorless oil. Electrospray MS $[M+1]^+$=636.1.

Step 2:



Compound 52

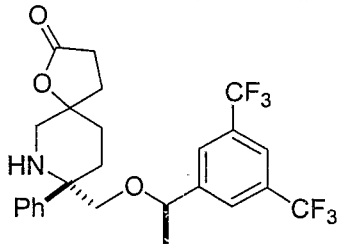
A mixture of unsaturated ester **Compound 51** (9.2g, 14.5mmol) and tetrabutylammonium fluoride (145ml, 1.0M in THF) in CH_3NO_2 were heated to reflux for 2 h. The mixture was cooled to RT and quenched with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and 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 (4.1g, 45%) as colorless oil. Continuous elution with the same solvent system gave the more polar nitroester **Compound 52** (5.1g, 50%) as colorless oil. Electrospray MS $[M+1]^+$=670.1.

Step 3:

A mixture of **Compound 52** (5.1g, 7.32mmol), 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 (3.5g, 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.

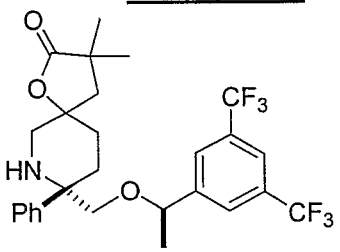
Example 57



To a solution of ethyl propiolate (0.27ml, 2.69mmol) in THF (10ml) at -78°C under N_2, *t*-butyllithium (1.6ml, 2.69mmol, 1.7M in pentane) was added. The mixture was stirred at -78°C for 10 min and a solution of **Compound 47** (519mg, 0.90mmol) in THF (5ml) 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. Layers were separated and the aqueous layer was extracted with EtOAc (200ml x 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 (250ml x 2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed

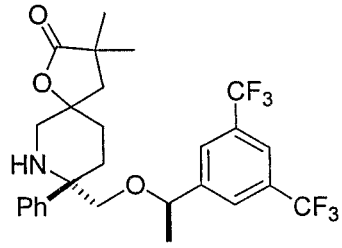
in vacuum to give a mixture of **Example 57a** and **57b** as colorless oil. Separation by column chromatography [hexane-ether, 1:2(v/v)] gave the less polar minor isomer **Example 57a** (67mg, 15%) as white foam. Electrospray MS $[M+1]^+$=502.1. Continuous elution with the same solvent system gave the more polar major isomer **Example 57b** (134mg, 30%) as white solid. Electrospray MS $[M+1]^+$=502.1.

Example 58



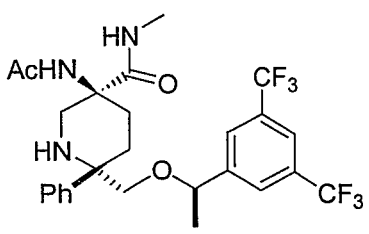
To a solution of **Example 57a** (112mg, 0.22mmol) in THF (5ml) at –78°C under N_2, lithium bis(trimethylsilyl)amide (1.1ml, 1.12mmol, 1.0M in THF) was added. The mixture was stirred at –78°C for 1 h and CH_3I (70µl, 1.12mmol) was added. The mixture was stirred at –78°C for 1 h before quenched with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (100ml x 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** (92mg, 78%) as colorless oil. Electrospray MS $[M+1]^+$=530.1.

Example 59

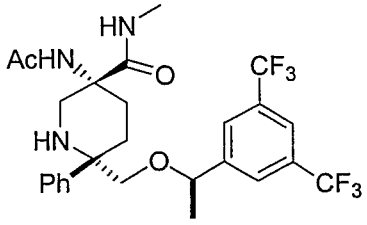


Example 59 (75%) was prepared from **Example 57b** in a manner similar to that used to prepare **Example 58** from **Example 57a**. Electrospray MS $[M+1]^+$=530.1.

Examples 60a and **60b**

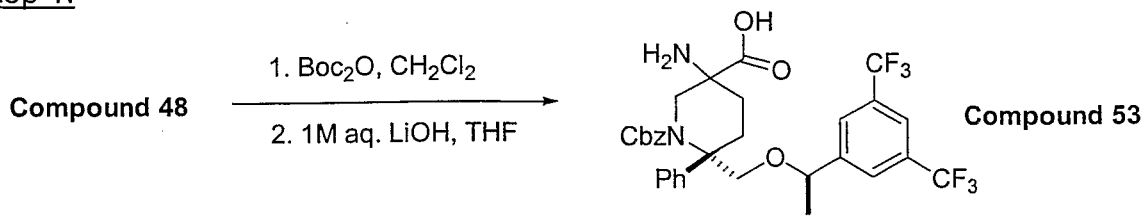


Example 60a



Example 60b

Step 1:

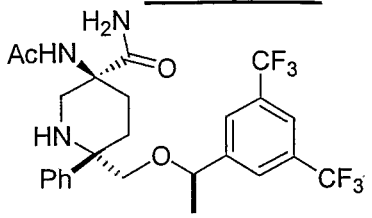


To a solution of **Compound 48** (0.5g, 0.77mmol, 1equiv) in CH_2Cl_2 (30ml) was added di *tert*-butyl dicarbonate (0.37g, 1.69mmol, 2.2equiv) followed by DMAP (0.035g, 0.286mmol, 0.37equiv) and the reaction mixture was stirred at 23°C for 18 h. The reaction mixture was then filtered through a short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

Step 2:

To a mixture of crude **Compound 53** (0.52g) in pyridine (3ml) and THF (2ml) at 0°C was added acetyl chloride (0.072ml, 1mmol, 1.2equiv) 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 (0.31g, 0.456mmol, 1equiv.) which was dissolved in THF (10ml). A 2M solution of CH_3NH_2 in THF (2.3ml, 4.6mmol, 10equiv) was added and the reaction mixture was stirred at 23°C for 18 h. The mixture was diluted with EtOAc (100ml) and washed with saturated aq. $NaHCO_3$ (100ml). 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.

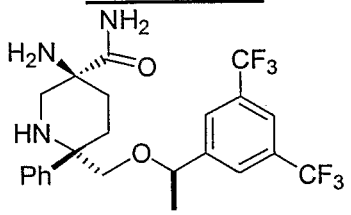
Example 61



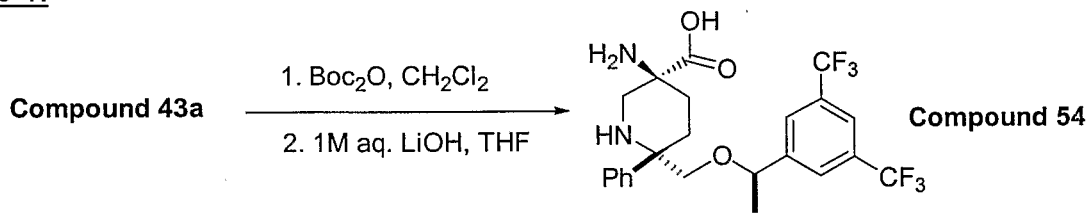
Example 61 was prepared from **Example 43a** using the procedure similar to the preparation of **Examples 60a** and **60b** from **Compound 48**, but using a solution of ammonia (0.5M in 1,4-dioxane) in place of CH_3NH_2 solution (2M in THF).

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

Example 62

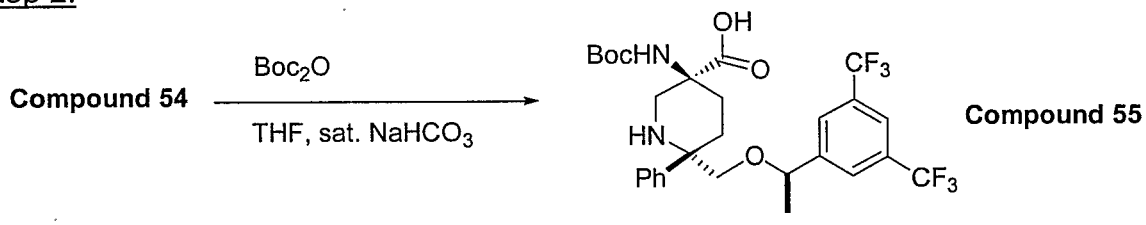


Step 1:



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:

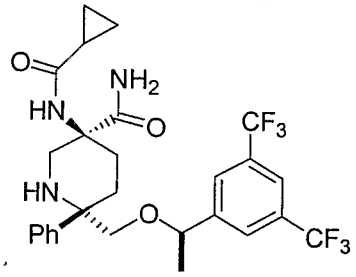


To a mixture of **Compound 54** (0.5g, 1.02mmol, 1equiv) in THF (30ml) was added sat. aq. $NaHCO_3$ followed by di *tert*-butyl dicarbonate (0.58g, 2.65mmol, 2.6equiv). The reaction mixture was stirred at 23°C for 18 h. The mixture was cooled to 0°C and 10% aq. citric acid (20ml) was added and the resulting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

Step 3:

To a solution of **Compound 55** (0.93g, 1.57mmol, 1equiv) in CH_2Cl_2 (15ml) was added DIEA(0.83ml, 4.72mmol, 3equiv) followed by PyBOP (1.23g, 2.4mmol, 1.3equiv). After 15 min, 0.5M solution of ammonia in 1,4-dioxane (31.5ml, 15.75mmol, 10equiv) was added to the reaction mixture and stirred at for 23°C for 18 h. The reaction mixture was quenched with water (100ml) and extracted with EtOAc (100ml x 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 (10ml) and cooled to 0°C. TFA (6ml) was added and the reaction mixture was warmed to 23°C and stirred for 2 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ (100ml) and diluted with CH_2Cl_2 (100ml). 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** (0.18g, 35% over three steps), Electrospray MS $[M+1]^+$=490.1.

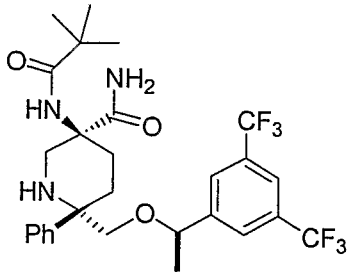
Example 63



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 (1.3equiv).

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

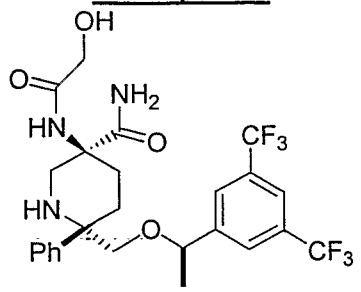
Example 64



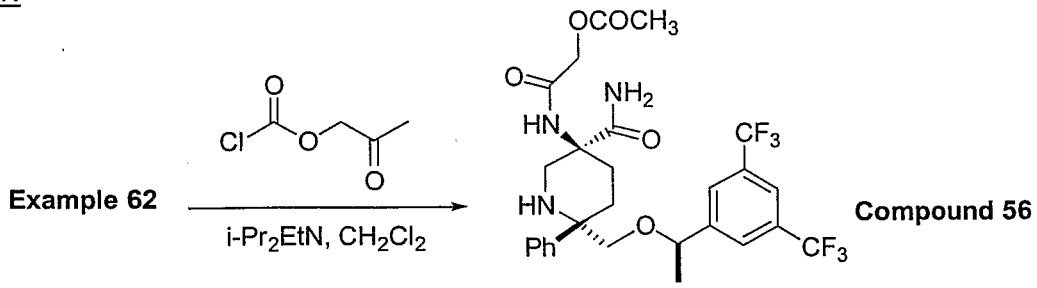
Example 64 was prepared from **Example 62** using the procedure similar to the preparation of **Example 14** from **Example 13** and using *t*-butyl chloride in place of propionyl chloride.

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

Example 65



Step 1:

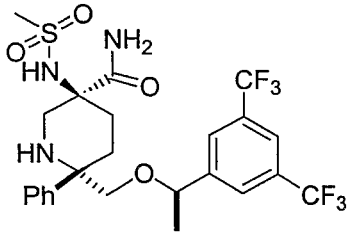


Compound 56 was prepared from **Example 62** using the procedure similar to the preparation of **Example 14** from **Example 13** but using acetoxyacetyl chloride in place of propionyl chloride. The crude **Compound 56** was used in the next reaction without further purification.

Step 2:

The crude **Compound 56** was dissolved in MeOH (5ml), $KHCO_3$ (3equiv) 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.

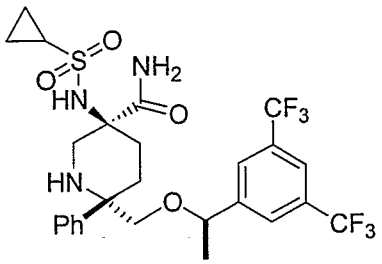
Example 66



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.

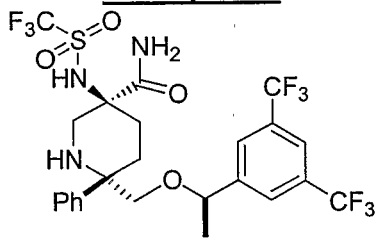
Electrospray MS $[M+1]^+$=568.1 for the **Example 66.**

Example 67



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.

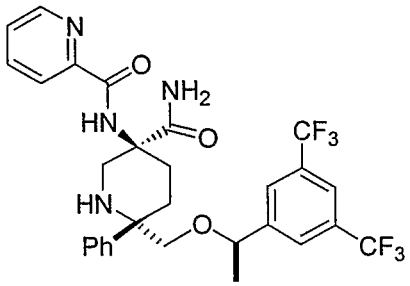
Example 68



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.

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

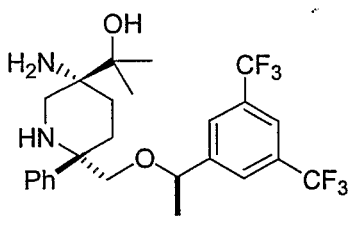
Example 69



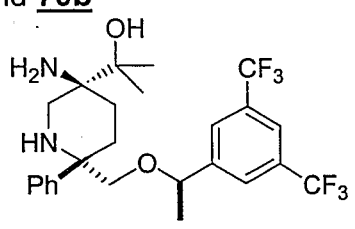
Example 69 was prepared from **Example 62** using the procedure similar to the preparation of **Example 14** from **Example 13** and using nicotinoyl chloride in place of propionyl chloride.

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

Examples 70a and **70b**

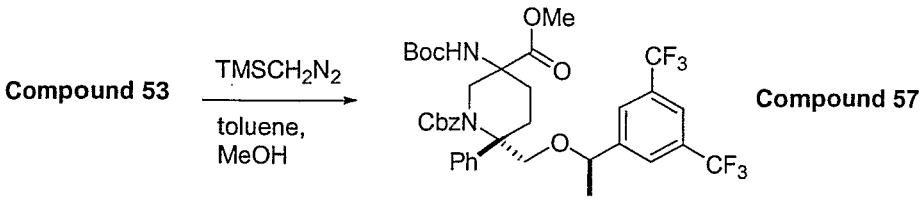


Example 70a



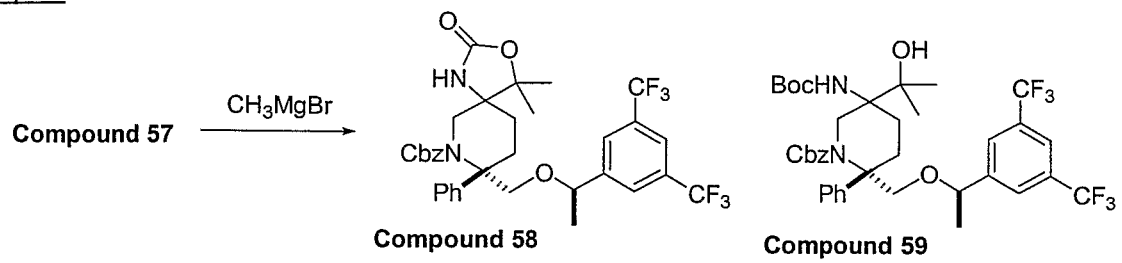
Example 70b

Step 1:



To a mixture of **Compound 53** (4g, 5.52mmol, 1equiv), toluene (46ml) and MeOH (18ml) at 0°C was added $TMSCH_2N_2$ (2M solution in hexane, 13.8ml, 27.6mmol, 5equiv) and the resulting solution was stirred at 0°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** (1.8g, 44%).

Step 2:

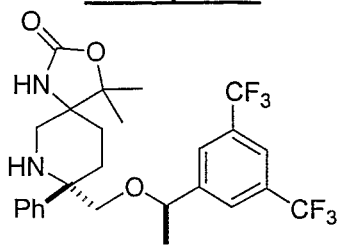


To a mixture of **Compound 57** (1g, 1.35mmol, 1equiv) in dry THF (18ml) at 0°C was added CH_3MgBr (1M solution in n-butylether, 3.24ml, 3.24mmol, 2.4equiv.) and the resulting solution was stirred at 0°C for 30 min. The reaction mixture was then warmed to 23°C and stirred for 18 h. The reaction was quenched with saturated aq. $NaHCO_3$ (100ml) and extracted with EtOAc (200ml). 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** (0.52g, 56%) and less polar **Compound 59** (0.31g, 34%).

Step 3:

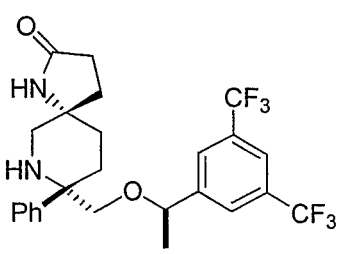
Compound 59 was deprotected with TFA using the procedure described in the preparation of **Example 62**. The resulting NCbz-aminoalcohol compound was hydrogenated to afford the mixture of two isomers **Example 70a** and **70b** using a procedure similar to the preparation of **Examples 43a** and **43b** 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

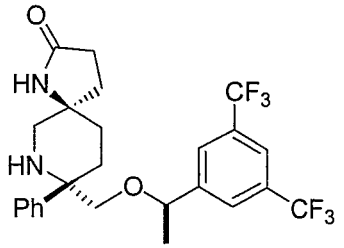


Compound 58 was hydrogenated to a mixture of desired products **Example 71a** and **71b** using a procedure similar to the preparation of **Examples 43a** and **43b** from **Compound 48.** The mixture of two products was purified by column chromatography over Biotage (1:1, hexane:EtOAc) to afford pure 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

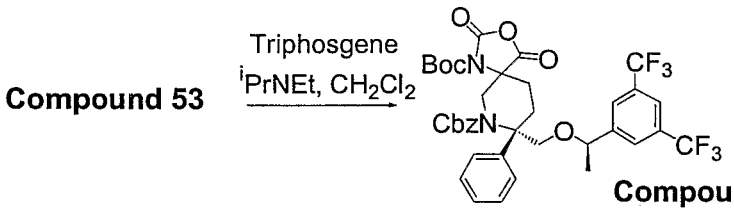


Example 72a



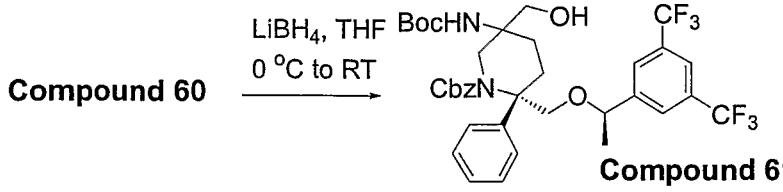
Example 72b

Step 1:



To a solution of crude **Compound 53** (19g) in CH_2Cl_2 (300ml) at RT, DIEA (15ml, 0.087mol) was added, followed by triphosgene (4.34g, 0.015mol). 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:



To the crude **Compound 60** in THF (200ml) at 0°C, $LiBH_4$ (1.26g, 0.058mol) was added in small portions. The mixture was stirred at RT for 18 h before

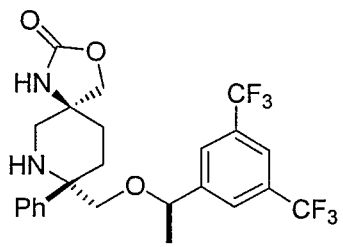
quenching with saturated NH_4Cl solution. Water and EtOAc were added to the mixture. Layers were separated and the aqueous layer was extracted with EtOAc (100 x 2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-EtOAc, 4:1 (v/v)] gave **Compound 61** (12.9g, 62% overall) as white foam.

Step 3:

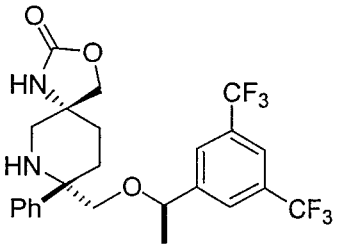
Oxalyl chloride (4.2ml, 0.048mol) was added to a solution of DMSO (6.8ml, 0.096) in CH_2Cl_2 (300ml) at –78°C under N_2. The mixture was stirred at –78°C for 15 min before a solution of **Compound 61** (8.5g, 0.012mol) in CH_2Cl_2 (100ml) was added. The mixture was stirred at –78°C for a further 1 h and Et_3N (23.5ml) 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 (150ml x 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 (1.44g, 0.036mol) in THF at 0°C, methyl diethylphosphonoacetate (6.6ml, 0.036mol) was added. The mixture was stirred at 0°C for 15 min and a solution of aldehyde in THF (100ml) 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 (200ml x 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 (100ml) and a catalytic amount of palladium (1.28g, 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 (200ml) and TFA (8.9ml, 0.12mol) 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 (200ml x 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 (50ml) and a catalytic amount of K_2CO_3 (166mg, 0.0012mol) 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** (2.3g, 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. Electrospray MS $[M+1]^+$=501.1.

Examples 73a and **73b**



Example 73a



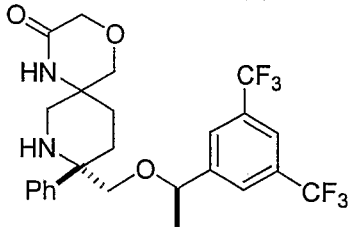
Example 73b

To a solution of **Compound 61** (3g, 4.22mmol, 1equiv) in DMF (60ml) at 0°C was added NaH (60% in mineral oil, 0.122g, 5.07mmol, 1.2equiv) and the mixture was allowed to warm to 23°C and stirred for 45 min. The reaction was quenched with water (100ml) and extracted with EtOAc (100ml x 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.**

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

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

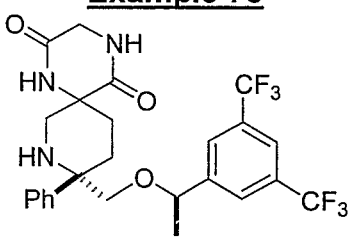
Example 74



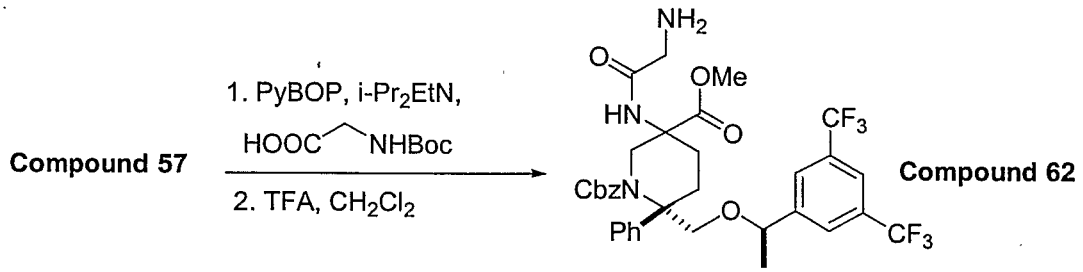
Compound 61 (1.68g, 2.36mmol, 1equiv) was dissolved in CH_2Cl_2 (50ml), TFA (5.46ml, 70.9mmol, 30equiv) was added and the reaction mixture was stirred at 23°C for 2.5 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ (150ml) and diluted with CH_2Cl_2 (100ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to give crude amino-alcohol product (1.4g, 97%). The

product (0.32g, 0.524mmol, 1equiv) was dissolved in dry THF (10ml) and NaH (60% in mineral oil, 0.025g, 0.63mmol, 1.2equiv.) was added. The reaction mixture was stirred at 23°C for 5 min and then ethyl chloroacetate (0.062ml, 0.576mmol, 1.1equiv) was added and the reaction mixture was stirred for 2.5 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ (100ml) and diluted with EtOAc (200ml). 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 (0.1g, 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



Step 1:



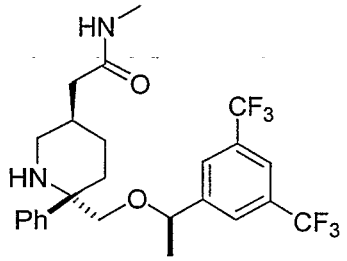
Compound 57 was converted to **Compound 62** (72% yield over two steps) using the PyBOP coupling followed by TFA deprotection procedures as described in the preparation of **Example 62** from **Compound 55** but using **Compound 57** (1equiv.) in place of ammonia and NH-Boc-glycine (2equiv.) in place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

Step 2:

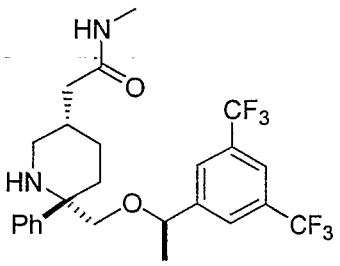
Compound 62 (0.5g, 0.72mmol, 1equiv) was dissolved in MeOH (10ml) and Et_3N (1ml, 7.2mmol, 10equiv) was added. The resulting mixture was heated at 23°C for 18 h. The reaction mixture was then concentrated and purified by column chromatography over Biotage (EtOAc) to give NCbz-diketopiperazine (0.33g) 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** (0.03g, 8% over two steps), Electrospray MS $[M+1]^+$ 530.1, and more polar isomer **Example 75b,** (0.04g, 11% over two steps), Electrospray MS $[M+1]^+$ 530.1.

Examples 76a and **76b**



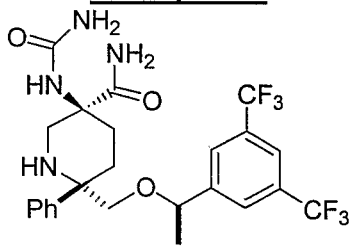
Example 76a



Example 76b

Compound 51 (3.66g, 5.76mmol, 1equiv.) was hydrogenated using a procedure similar to the preparation of **Examples 43a** and **43b** from **Compound 48** and the hydrogenated product (2.85g) was treated with CH_3NH_2 (2M solution in CH_3OH, 200ml) 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 $[M+1]^+$ 503.1, and more polar isomer **Example 76a,** Electrospray MS $[M+1]^+$ 503.1.

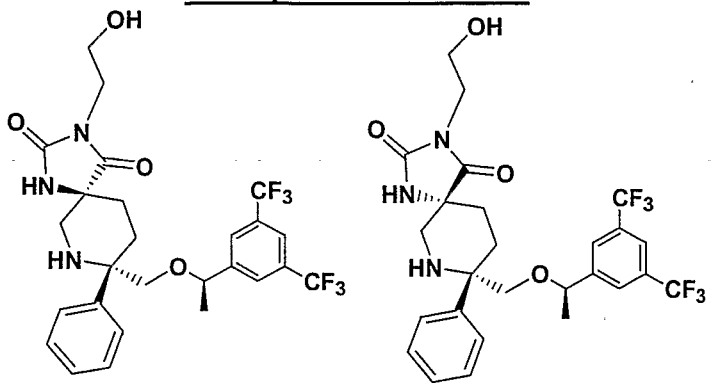
Example 77



Example 62 (0.07g, 0.133mmol, 1equiv) was dissolved in CH_2Cl_2 (3ml) and DIEA (0.03ml, 0.147mmol, 1.1equiv) was added followed by 4-methoxyphenyl (pmb)-isocyanate (0.021ml, 0.147mmol, 1.1equiv) and the reaction mixture was stirred at 23°C for 18 h. The reaction mixture was then concentrated and treated with CH_3CN (3ml) and water (1ml) and the mixture was cooled to 0°C. Ammonium cerium nitrate (0.24g, 0.44mmol, 4equiv) was added and the reaction mixture was stirred at 0°C for 45 min. The reaction was quenched with saturated aq. $NaHCO_3$ (100ml) and extracted with EtOAc (200ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The mixture was purified by column

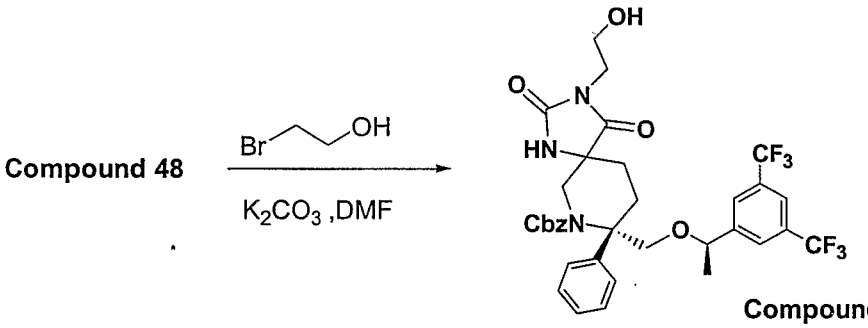
chromatography over Biotage (15:85, MeOH:EtOAc) to give **Example 77** (0.03g, 42%), Electrospray MS $[M+1]^+$ 533.1.

Examples 78a and 76b



Example 78a **Example 78b**

Step 1:



Compound 63

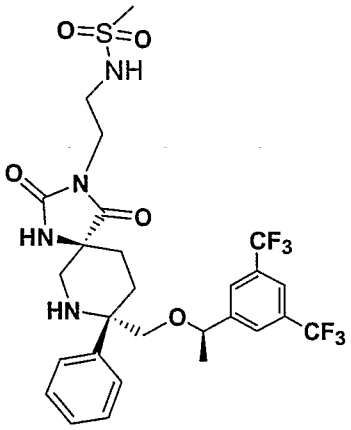
In a flame dry 15ml RBF **Compound 48** (0.25g, 0.385mmol, 1equiv) in DMF (1ml) was added to K_2CO_3 (0.106g, 0.77mmol, 2equiv) followed by 2-bromoethanol (0.033ml, 0.46mmol, 1.2equiv) and the mixture was stirred for 2h at RT, then heated to 50 °C for 6 h. The reaction was monitored by TLC (60/40 EtOAc/Hexane). 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 (0.258g, 97%), Electrospray MS $[M+1]^+$ 694.1.

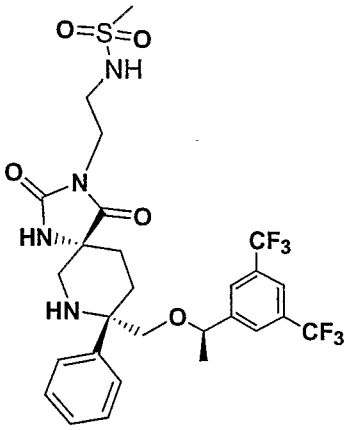
Step 2:

To a solution of **Compound 63** (0.25g, 0.36mmol, 1equiv) in anhydrous MeOH was added (5.5ml) 20% $Pd(OH)_2/C$ (0.08g). 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** (0.13g, 63%).

Electrospray MS $[M+1]^+$ 560.1 for **Example 78a** (less polar isomer);
Electrospray MS $[M+1]^+$ 560.1 for **Example 78b** (more polar isomer).

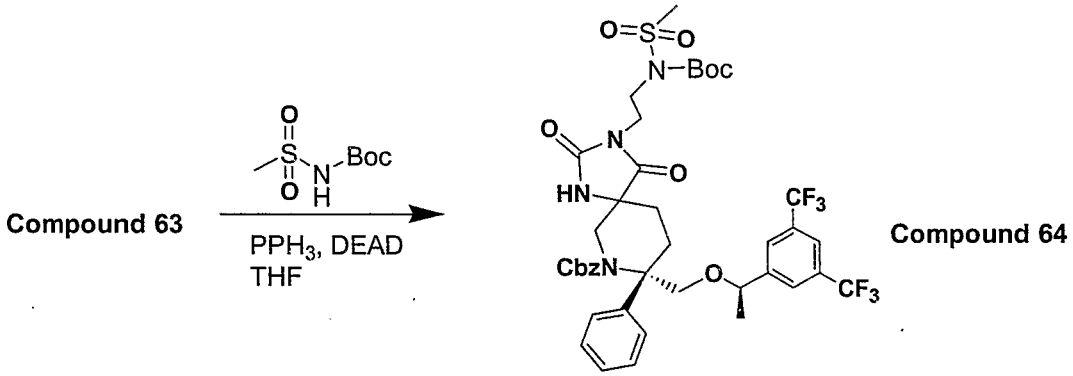
Examples 79a and 79b





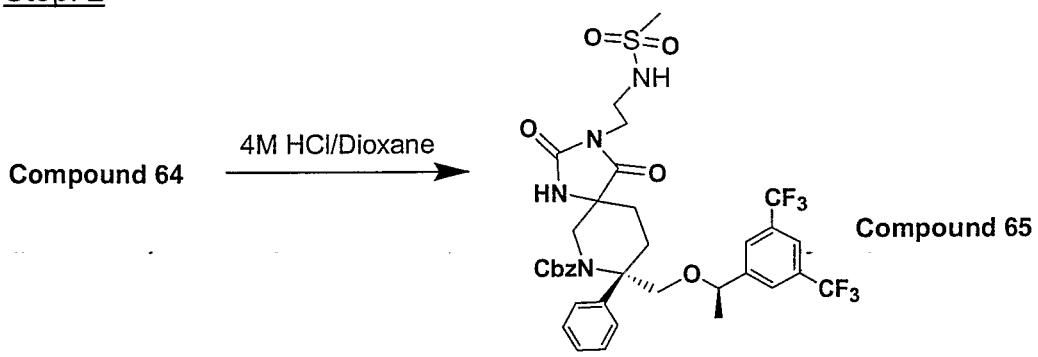
Example 79a **Example 79b**

Step 1:



N-(Boc)-methanesulfonamide (0.041g, 0.43mmol, 1.5equiv) was dissolved in dry THF (1ml) and triphenyl phosphine (0.228g, 0.43mmol, 3equiv) was added. The resulting solution was stirred under N_2 and a solution of **Compound 63** (0.2g, 0.29mmol, 1equiv) in THF followed by diethyl azodicarboxylate (DEAD) (0.12ml, 0.26mmol, 2.5equiv) 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 (0.24g, 95%), Electrospray MS $[M+1]^+$ 871.1.

Step: 2



To a solution of **Compound 64** (0.25g, 0.29mmol, 1equiv) in dry CH_2Cl_2 (10ml) at 0°C was added 4M HCl in dioxane (0.755ml, 2.9mmol, 10equiv). 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 (0.2g, 89%). The crude material was carried forward without any purification.

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

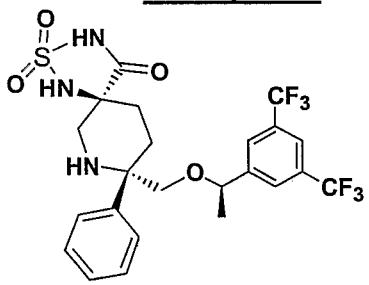
Step: 3

To a solution of **Compound 65** (0.2g, 0.26mmol, 1equiv) in MeOH (5ml) was added10% Pd/C followed by ammonium formate (0.082g, 1.3mmol, 5equiv). 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** (0.06g, 36% total for both isomers).

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

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

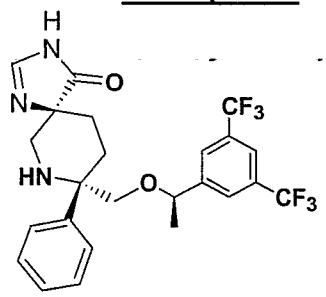
Example 80



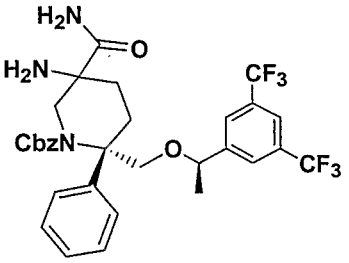
To a solution of **Example 62** (0.079g, 0.127mmol, 1equiv) in dry CH_2Cl_2 (1ml) was added Et_3N (0.108ml, 0.76mmol, 6equiv). The reaction mixture was cooled to 0°C and stirred for 15 min. SO_2Cl_2 (0.011ml, 0.133mmol, 1.05equiv) was added very slowly to the reaction over 5 min. The reaction stirred 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** (0.015g, 20%), Electrospray MS $[M+1]^+$ 552.1.

Example 81



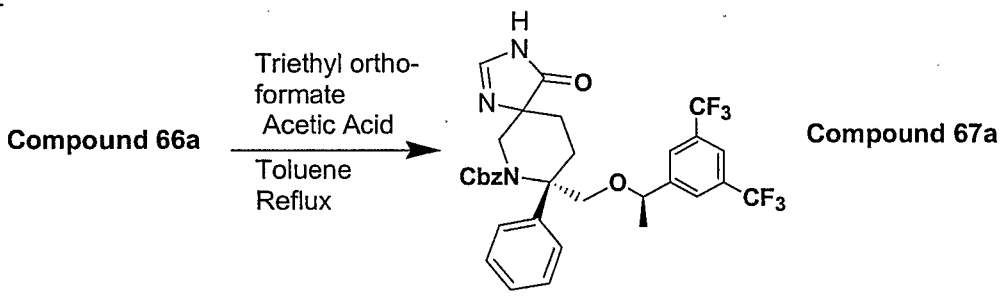
Step 1:



Compound 66a and 66b

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

Step 2:



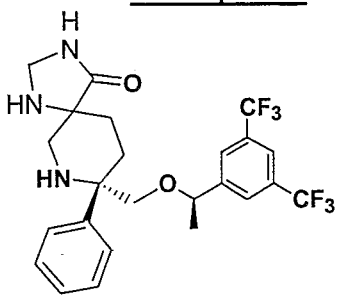
To a solution of **Compound 66a** (0.34g, 0.545mmol, 1equiv) in dry toluene (14ml) was added HOAc (0.17ml) followed by triethyl orthoformate (0.363ml, 2.18mmol, 4equiv). The solution was refluxed for 12 h and monitored by TLC (9:1 EtOAc/CH_3OH). The reaction was cooled to 0 °C, quenched with H_2O, diluted 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** (0.272g, 79%), Electrospray MS $[M+1]^+$ 634.1.

Step3:

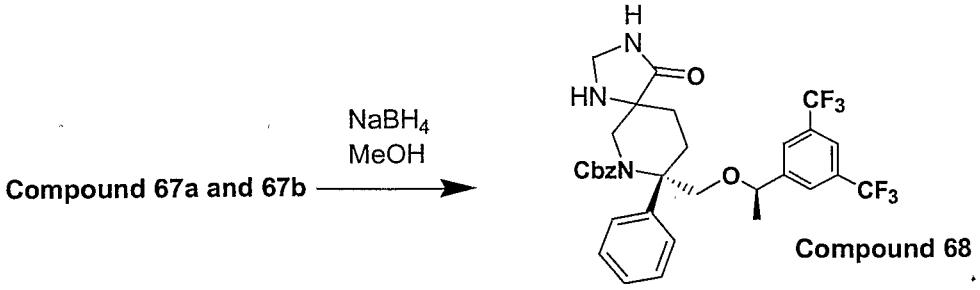
Example 81 was prepared from **Compound 67a** using a similar procedure as for **Examples 79a** and **79b** from **Compound 65.**

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

Example 82



Step 1:



To a solution of a mixture of the two isomers of **Compound 67** (0.27g, 0.426mmol, 1equiv) in dry CH_3OH (3ml) was added $NaBH_4$ (0.048g, 1.28mmol, 3equiv). 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**, (0.25g, 92%) and was carried forward without any purification.

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

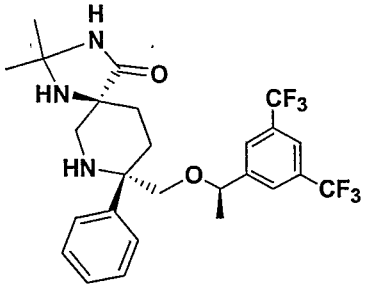
Step2:

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

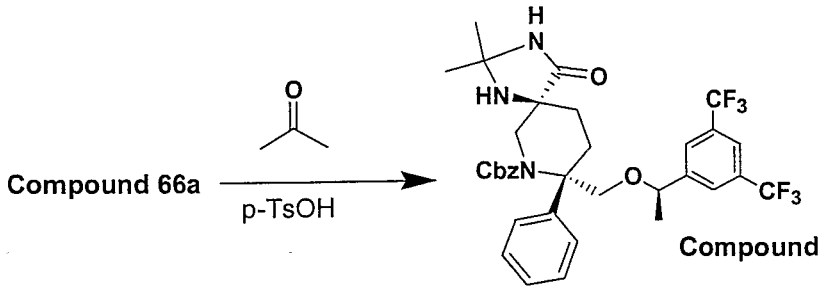
Electrospray MS $[M+1]^+$ 502.1 for **Example 82a,**

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

Example 83



Step 1:



Compound 69

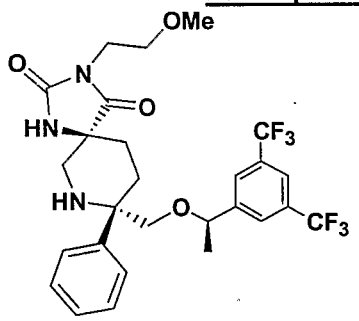
To a solution of **Compound 66a** (0.1g, 0.16mmol, 1equiv) in a 25ml RBF in MeOH (0.5ml) was added acetone (0.352ml, 0.48mmol, 3equiv) and p-TsOH (0.06g, 0.32mmol, 2equiv). The reaction mixture was refluxed for 12 h and was monitored by mass spectrum analysis. Reaction upon completion was concentrated,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

Step 2:

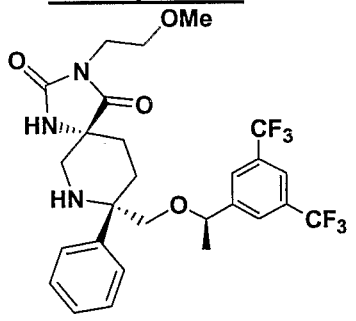
Example 83 (0.026g, 33%) was prepared from **Compound 69** using a similar procedure as forpreparing **Examples 79a** and **79b** from **Compound 65.**

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

Examples 84a and **Example 84b**



Example 84a



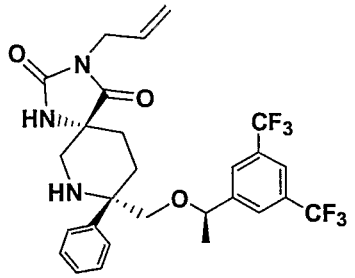
Example 84b

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.

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

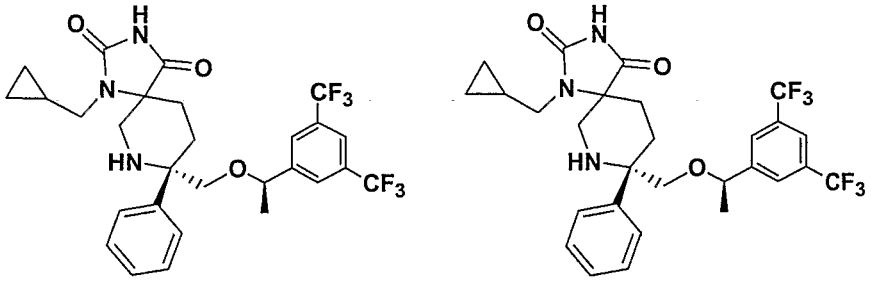
Electrospray MS $[M+1]^+$ 574.1 for **Example 84b.**

Example 85



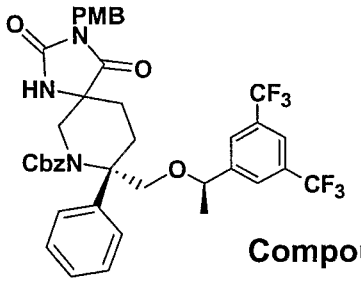
Example 85 (46mg, 88%) was prepared from **Example 43b** using a similar procedure as for **Compound 63**, but using allyl bromide instead of 2-bromoethanol. Electrospray MS $[M+1]^+$ 556.1.

Examples 86a and Example 86b



Example 86a **Example 86b**

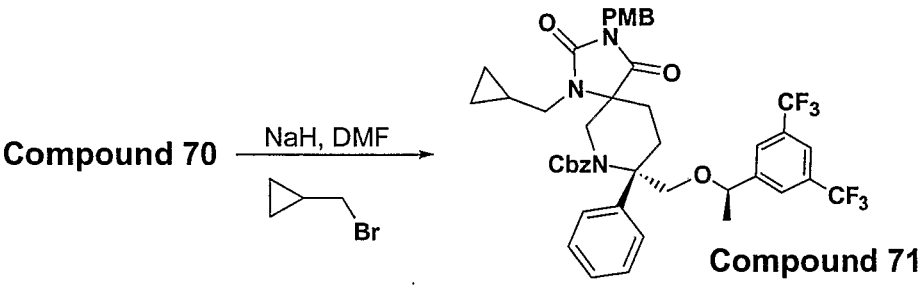
Step 1:



Compound 70

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.

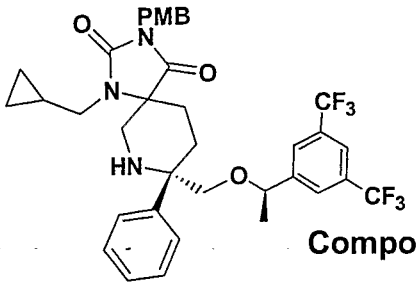
Step 2:



Compound 71

To a solution of **Compound 70** (0.19g, 0.25mmol, 1equiv) in 1.0ml of anhydrous DMF at 0°C was added NaH (60% dispersion in mineral oil, 0.012g, 0.30mmol, 1.2equiv). 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 (0.029ml, 0.30mmol, 1.2equiv). 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** (0.11g, 99%) Electrospray MS $[M+1]^+$ 824.2.

Step 3:



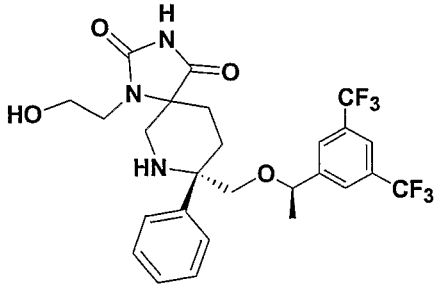
Compound 72

Compound 72 (0.24g, 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.

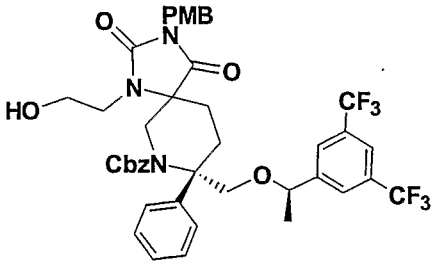
Step 4:

To a solution of **Compound 72** (0.24g, 0.34mmol, 1equiv) in 5.0ml of CH_3CN and 1.7ml of water at 0°C was added ammonium cerium nitrate (0.79g, 1.4mmol, 4equiv). 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 (100ml x 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** (15mg, 8%), isomerically pureless polar **Example 86a** (14mg, 7%) Electrospray MS $[M+1]^+$ 570.1, and isomerically pure more polar **Example 86b** (16mg, 9%) Electrospray MS $[M+1]^+$ 570.1.

Example 87



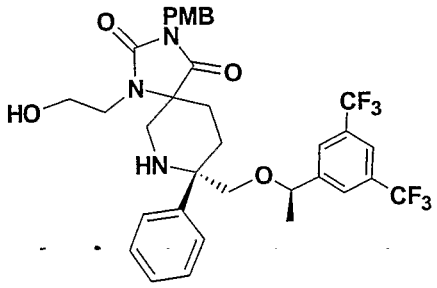
Step 1:



Compound 73

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:



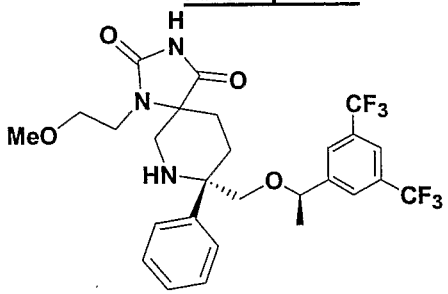
Compound 74

Compound 74 (0.16g, 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.

Step3:

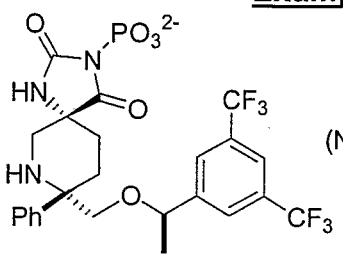
Examples 87a and **87b** were prepared from **Compound 74** using a similar procedure as for **Example 86a and 86b** from **Compound 72**, but purification using a Gilson with water/CH_3CN was used instead of chromatography on a Biotage to isolate a diastereomeric mixture of **Examples 87a** and **87b**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

Example 88



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 50mg 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** (16mg) Electrospray MS $[M+1]^+$ 574.3, and isomerically pure second-eluted product **Example 88b** (29mg) Electrospray MS $[M+1]^+$ 574.3.

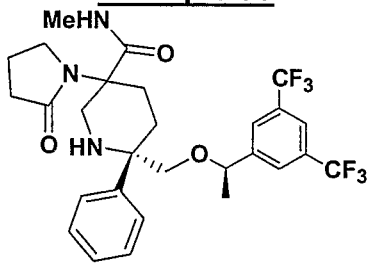
Example 89



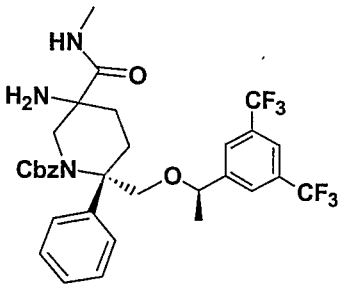
(N-Me-D-glucamine)$_2$

To a solution of **Example 43b** (0.68g, 1.32mmol, 1equiv) in DMF (7ml) at 0°C was added NaH (60% in mineral oil, 0.105g, 2.64mmol, 2equiv) and the mixture was stirred at 0°C for 15 min. Tetravbenzyl pyrophosphate (1.42g, 2.64mmol, 2equiv) 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. $NaHCO_3$ (100ml) and extracted with EtOAc (100ml x 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 (0.24g) which was dissolved in MeOH (10ml); N-Me-D-glucamine (0.119, 0.619mmol, 2equiv) was added, followed by 10% Pd-C (0.021g). 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 (100ml) and extracted with water (100ml) and the aqueous layer was lyophilized to give the desired product **Example 89** as N-Me-D-glucamine salt (0.22g, 21% over two steps).

Example 90



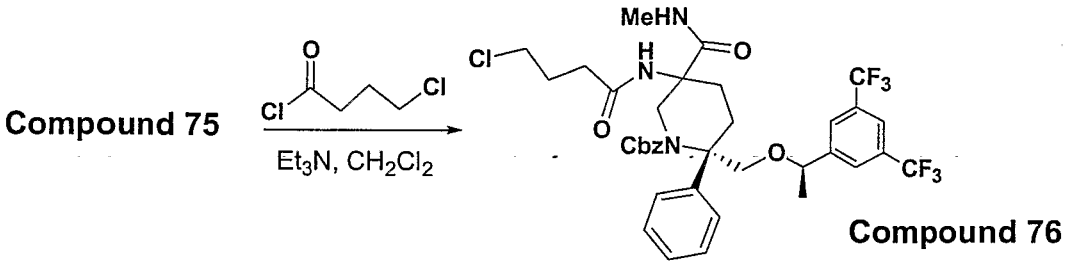
Step 1:



Compound 75

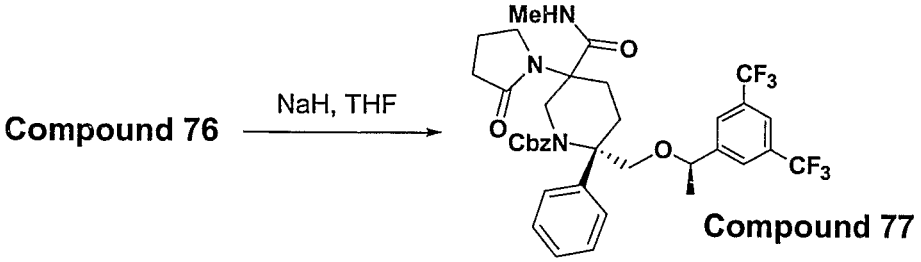
Compound 75 was prepared from **Compound 48** using a procedure similar to the preparation of **Compound 66** from **Compound 48.**

Step 2:



To a solution of the diastereomeric **Compound 75** (0.10g, 0.16mmol, 1equiv) in 2.0ml of anhydrous CH_2Cl_2 at 0°C was added Et_3N (0.033ml, 0.24mmol, 1.5equiv) and 4-chlorobutyrylchloride (0.017ml, 0.17mmol, 1.1equiv). 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 (0.12g, 100%) Electrospray MS $[M+1]^+$ 742.2.

Step3:

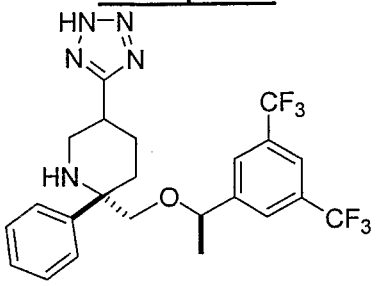


To a solution of **Compound 76** (0.12g, 0.16mmol, 1equiv) in 1.0ml of anhydrous THF at RT was added NaH (60% dispersion in mineral oil, 0.010g, 0.24mmol, 1.5equiv). After 3 h, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with EtOAc. The layers were separated and the organic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

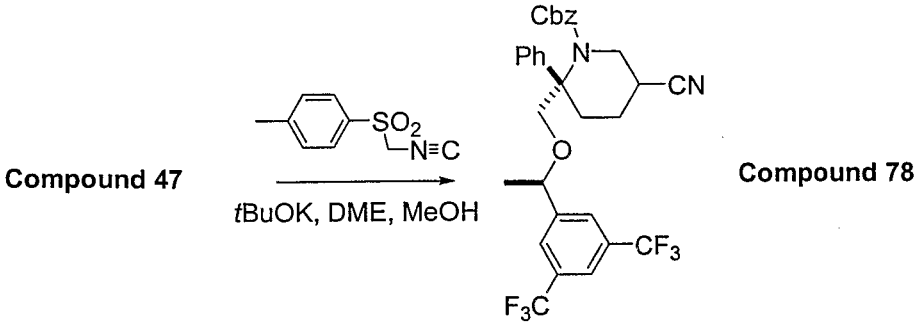
Step 4:

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** (26mg, 32%)was obtained: less polar product **Example 90a** (20mg, 25%) Electrospray MS $[M+1]^+$ 572.1, more polar product **Example 90b** (14mg, 17%) Electrospray MS $[M+1]^+$ 572.1.

Example 91

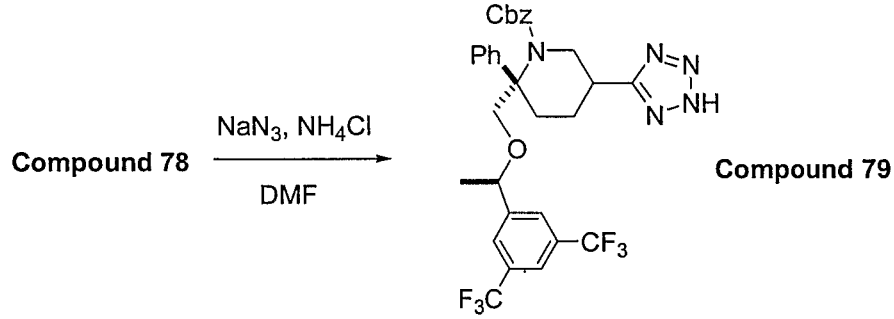


Step 1:



To a solution of **Compound 47** (1g, 1.73mmol, 1equiv) and tosylmethyl-isocyanide (374mg, 1.9mmol, 1.1equiv) in anhydrous ethylene glycol dimethylether (11ml) at –30 °C, was added anhydrous MeOH (0.15ml) followed by addition of potassium *tert*-butoxide (426mg, 3.8mmol, 2.2equiv). 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** (470mg, 46%).

Step 2:

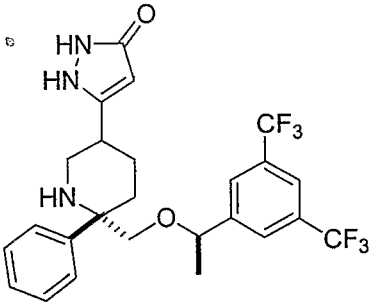


A solution of **Compound 78** (125.7mg, 0.21mmol, 1equiv) and NH_4Cl (68.3mg, 1/28mmol, 6equiv) and NaN_3 (69.2mg, 1.06mmol, 5equiv) in anhydrous DMF (1.2ml) under N_2 was heated at 115°C overnight. The mixture was concentrated, then acidified with HCl (6N, 10ml) and extracted with EtOAc (15ml x 3). 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** (67mg, 50%).

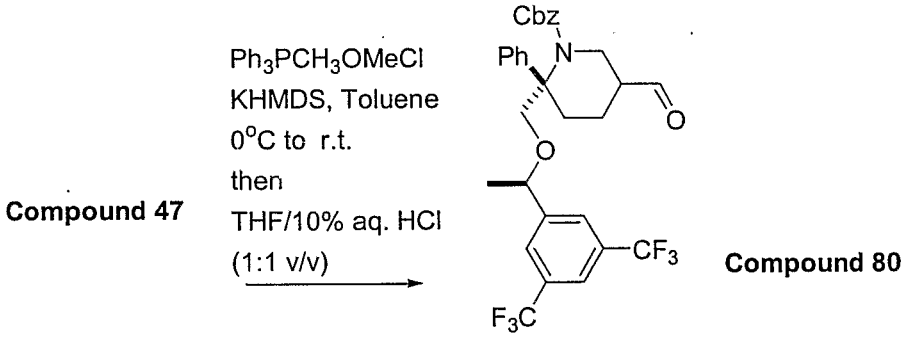
Step 3:

A solution of **Compound 79** (65mg, 0.103mmol, 1equiv) in EtOH (1.5ml) was treated with 10% Pd-C (107mg, 0.1mmol, 1.equiv) and 1,4-cyclohexadiene (0.5ml, 5.29mmol, 50equiv). 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** (11mg, 21%) Electrospray MS $[M+1]^+$ 500.1.

Example 92

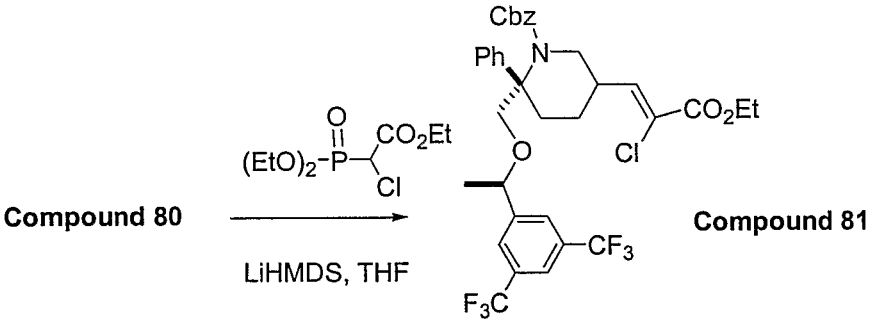


Step 1:



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

Step 2:



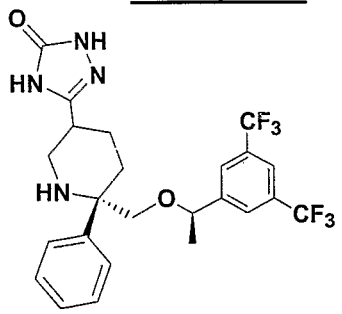
To a solution of triethyl 2-chloro-2-phophonoacetate (73µl, 0.34mmol, 1.05equiv) in anhydrous THF (1.5ml) at -78°C, was added dropwise of LiHMDS (0.35ml, 0.35mmol, 1.1equiv, 1N solution in THF). The solution was stirred for 20 min before a solution of **Compound 80** (192mg, 0.32mmol, 1equiv) in dry THF (1ml)

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** (127mg, 57%).

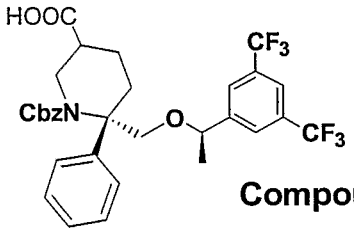
Step 3:

To a solution of **Compound 81** (127mg, 0.18mmol, 1.0equiv) in EtOH (1ml) was added H_2NNH_2 (35µl, 1.1mmol, 6equiv). It was stirred for 3 h and then concentrated in vacuum. The crude product was retaken up into EtOH (3ml) and treated with 10% Pd/C (40mg, 0.036mmol, 0.2equiv) 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** (14.2mg, 15%), Electrospray MS $[M+1]^+$514.1; and more polar isomer **Example 92b** (28.1mg, 30%), Electrospray MS $[M+1]^+$514.1

Example 93



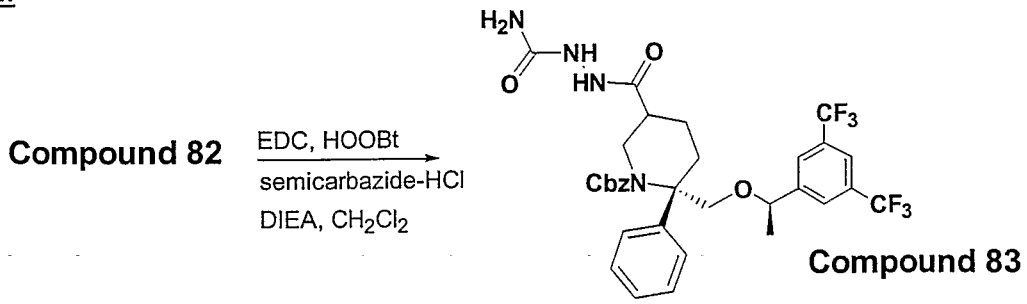
Step 1:

Compound 80 → (EDC, HOOBt; semicarbazide-HCl; DIEA, CH_2Cl_2) → 

Compound 82

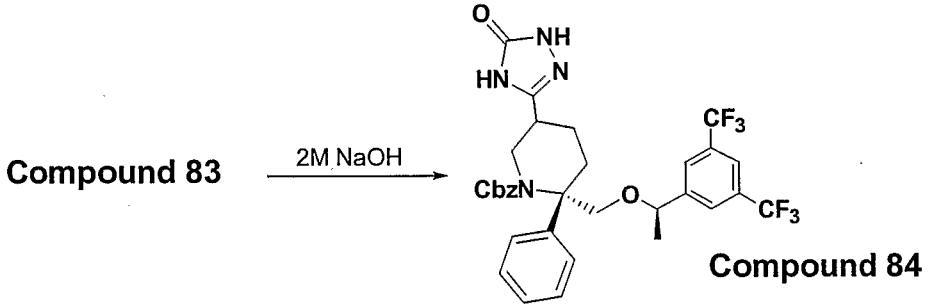
Compound 80 (0.74g, 1.25mmol, 1equiv), was dissolved in t-BuOH (20ml) and 2-methyl-2-butadiene (7ml). To this solution was added a fresh solution of $NaClO_2$ (1.13g, 12.5mmol, 10equiv.) in 20% (v/w) aq. NaH_2PO_4 solution. The reaction mixture was stirred at RT for 2 h. It was then diluted with EtOAc (200ml) 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:



To a solution of the diastereomeric **Compound 82** (0.33g, 0.54mmol, 1equiv) in 2 ml of anhydrous CH_2Cl_2 at RT was sequentially added DIEA (0.11ml, 0.65mmol, 1.2equiv), DEC (0.21g, 1.1mmol, 2equiv), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (0.18g, 1.1mmol, 2equiv), and semicarbazide hydrochloride (0.072g, 0.65mmol, 1.2equiv). After 3 h, the starting carboxylic acid was present by TLC [Hexane-EtOAc 1:1(v/v)] and an additional amount of DIEA (0.11mL, 0.65mmol, 1.2equiv) 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 (0.19g, 54%) Electrospray MS $[M+1]^+$ 667.07.

Step 3:



A solution of **Compound 83** (0.17g, 0.26mmol, 1equiv) in 8ml 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 (0.16g). Purification by chromatography on a Biotage eluting with 3% MeOH/EtOAc gave **Compound 84** as a diastereomeric mixture (0.12g, 71%) Electrospray MS $[M+1]^+$ 649.2.

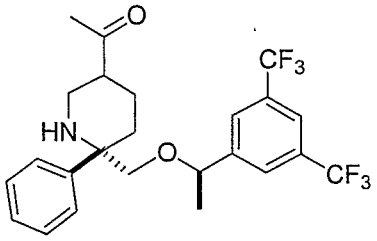
Step 4:

Less polar product **Example 93a** and more polar product **Example 93b** (32mg and 44mg, 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.

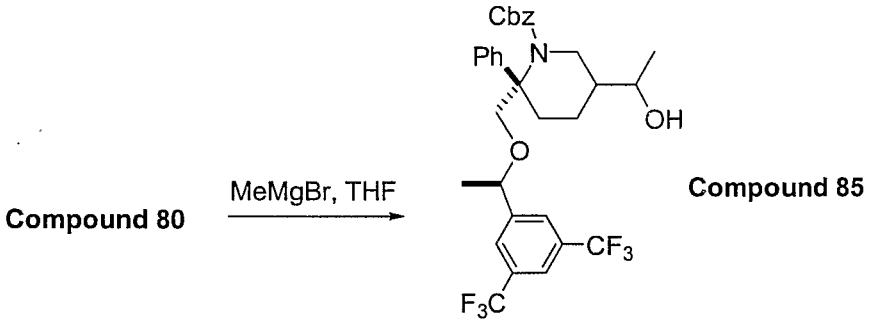
Electrospray MS $[M+1]^+$ 515.3 for **Example 93a**.

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

Example 94

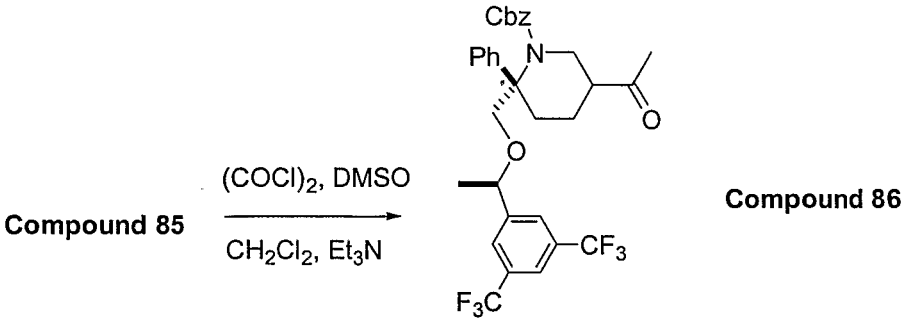


Step 1:



To a solution of **Compound 80** (550mg, 0.98mmol, 1equiv) in anhydrous THF (6ml) at -10°C, was added dropwise CH_3MgBr (1.24ml, 3.7mmol, 4equiv, 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** (236mg, 42%).

Step 2:



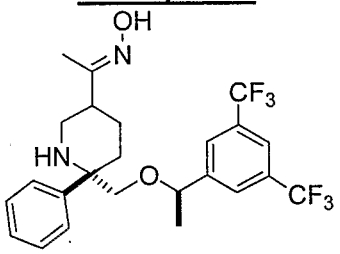
To a solution of DMSO (0.11ml, 1.55mmol, 4equiv) in anhydrous CH_2Cl_2 (5ml) at -78°C, was added dropwise oxalyl chloride (0.067ml, 0.78mmol, 2equiv). The solution was stirred for 15 min before a solution of **Compound 85** (236mg, 0.387mmol, 1equiv) in dry CH_2Cl_2 (1ml) was cannulated in. It was stirred at -78°C

for 1 h, then Et_3N (0.37ml, 2.71mmol, 7equiv) 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** (140mg, 60%).

Step 3:

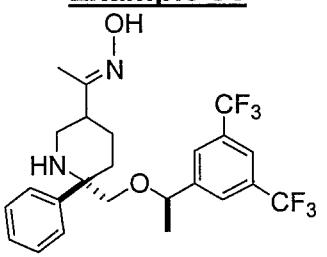
To a solution of **Compound 86** (1.0equiv) in EtOH (3ml) was added 10% Pd/C (0.4equiv) and the mixture hydrogenated overnight in a H_2 balloon atmosphere. The catalyst was filtered off and washed with MeOH. The filtrate was concentrated to give the crude residue which was purified on silica gel column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

Example 95



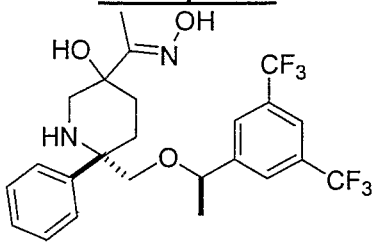
To a solution of **Example 94a** (16mg, 0.033mmol, 1equiv) in anhydrous EtOH (1ml) was added hydroxylamine hydrochloride salt (18mg, 0.26mmol, 7.7equiv), and NaOAc (5mg, 0.061mmol, 1.8equiv). The reaction mixture was stirred at RT overnight, then concentrated to dryness. The residue was retaken up with Et_2O, and washed with saturated $NaHCO_3$ aqueous solution. The organic layers were dried over MgSO4, filtered and concentrated in vacuum. The crude product was purified on silica gel column to afford **Example 95** (12mg, 74%), Electrospray MS $[M+1]^+$ 489.1

Example 96

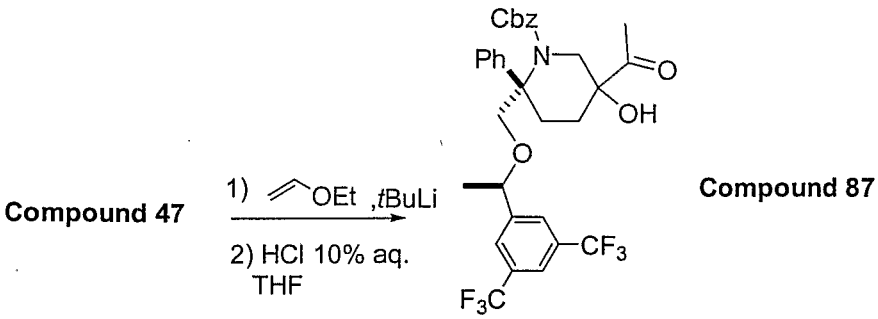


Example 96 (13mg, 50%) was prepared by similar procedure as for **Example 95** but using **Example 94b** in place of **Example 94a**. Electrospray MS $[M+1]^+$ 489.1.

Example 97

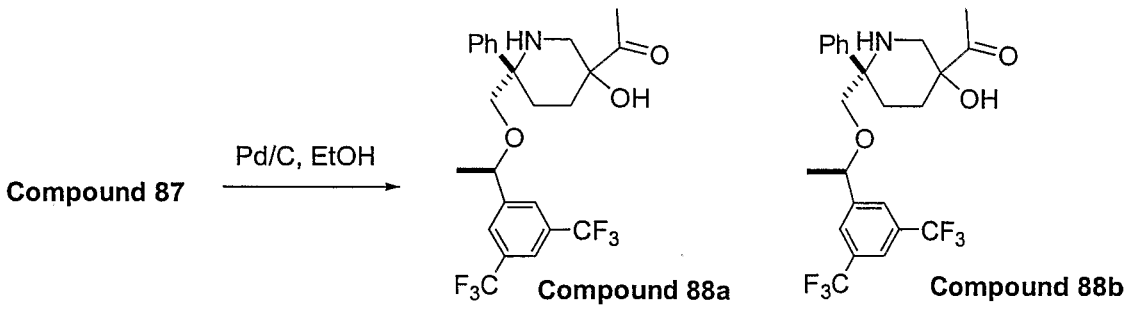


Step 1:



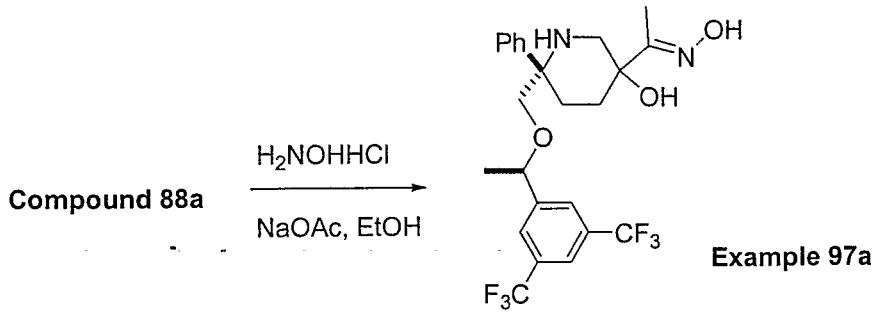
To a solution of ethyl vinylether (0.5ml, 4.83mmol, 12equiv) in anhydrous THF (6ml) at -78°C, was added dropwise *t*BuLi (0.73ml, 1.24mmol, 3equiv, 1.7N solution in pentane). The solution was stirred at -10°C bath until the orange color faded away. It was cooled to -78°C again, and a solution of **Compound 47**(240mg, 0.41mmol, 1equiv) in dry THF (1ml) 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 (6ml) and treated with 10% HCl aqueous solution (0.8ml). 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** (100mg, 39%).

Step 2:



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** (13mg, 18%), and **Compound 88b** (10mg, 14%).

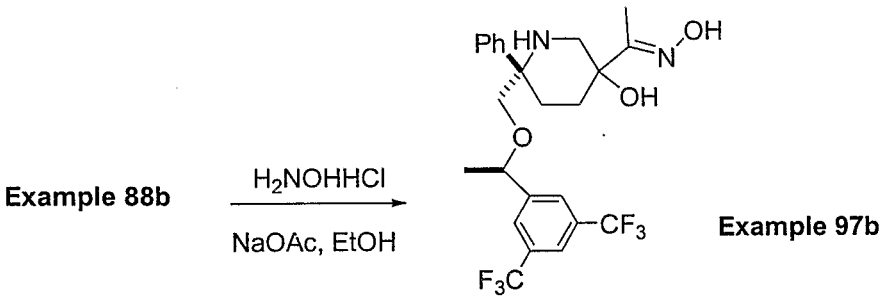
Step 3 :



Example 97a

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

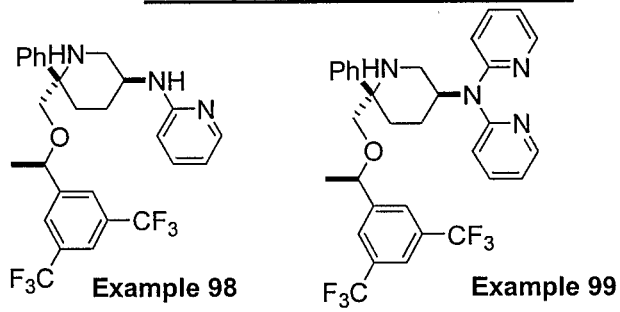
Step 4:



Example 97b

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

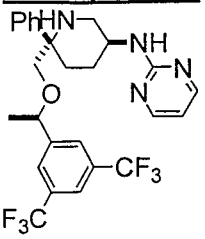
Example 98 and Example 99



Example 98 Example 99

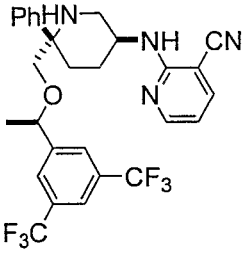
To **Example 13** (340mg, 0.76mmol) in 1ml toluene was added $Pd_2(dba)_3$ (27.8 mg, 0.03mmol), BINAP (37.8 mg, 0.06mmol), 2-bromopyridine (73µl, 0.76mmol) and NaO*t*Bu (102mg, 1.065mmol). The mixture was concentrated in vacuo and the flask filled with N_2. The process was repeated once. The dark-brown solution was heated at 90°C for 16h. It was cooled to 23°C and quenched with 2ml pH7 buffer. The solution was extracted with EtOAc (10ml x 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



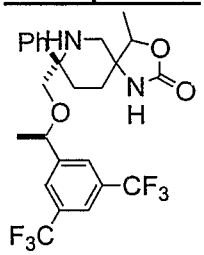
Example 100 was prepared using a similar procedure to **Example 98**, using 2-bromopyrimidine in place of 2-bromopyridine. Electrospray MS $[M+1]^+$ 525.1.

Example 101

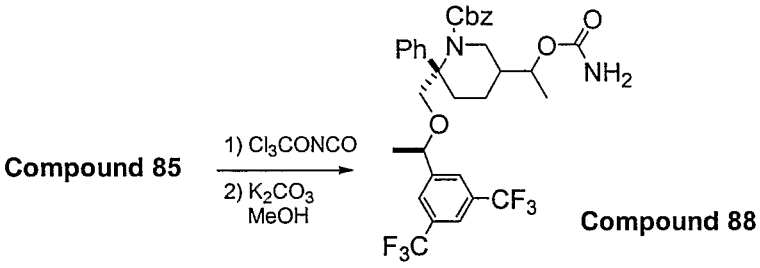


Example 101 was prepared using a similar procedure to **Example 98,** using 2-chloro-3-cyanopyridine in place of 2-bromopyridine. Electrospray MS $[M+1]^+$ 549.1.

Example 102



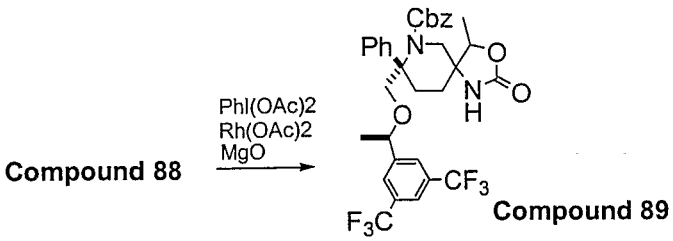
Step 1:



To **Compound 85** (429mg, 0.704mmol) in CH_2Cl_2 (3.5ml) at 0°C was added Cl_3CONCO (100ml, 0.844mmol) dropwise. The solution was stirred at 0°C for 2 h. The solvent was then removed and the residue was dissolved in MeOH (4ml) and H_2O (1ml). K_2CO_3(1.0g) was added and the suspension was stirred for 14 h. The mixture was then diluted with 3ml of water, concentrated to remove MeOH. The residue was extracted with EtOAc (10ml x 3). The combined organic layers were

concentrated and passed through a short silica gel column to give product **Compound 88** (420mg, 91%).

Step 2:

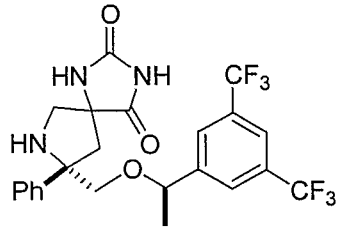


To **Compound 88** (290mg, 0.446mmol) in CH_2Cl_2 (3ml) was added $PhI(OAc)_2$ (131mg, 0.625mmol), $Rh_2(OAc)_4$ (12.9mg, 0.022mmol) and MgO (26.4mg, 1.0mmol). The suspension was heated at 40°C for 16 h then cooled to 23°C. Celite (0.5g) was added and the suspension was stirred for 5 min. The mixture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

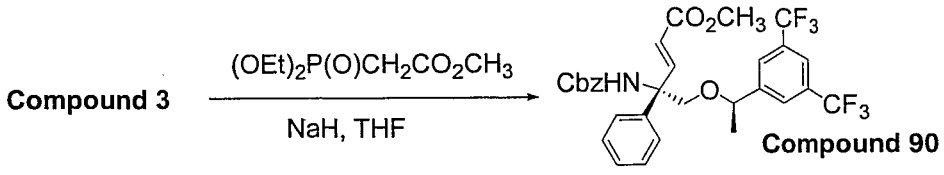
Step 3:

Compound 89 transferred to a Parr shaker using 5ml EtOH. 10%Pd-C (10%, 60mg) was added and the suspension was hydrogenated at 40psi overnight. The reaction mixture was filtered and concentrated. The residue was separated using HPLC on OD column eluted with 1:9 IPA/hexane 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



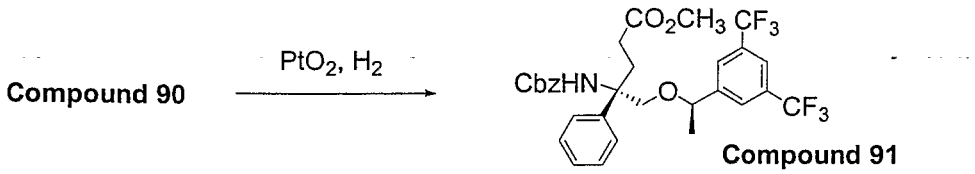
Step 1:



To a mixture of methyl diethylphosphonoacetate (9.5ml, 51.77mmol, 3equiv) in dry THF (100ml) at 0°C under N_2 was added NaH (60% in mineral oil, 1.24g, 51.77ml, 3equiv.). After being stirred at 0°C for 15 min, a solution of **Compound 3** (10g, 17.26mmol, 1equiv) in THF (250ml) was added. The mixture was warmed to 23°C and stirred for 1 h and then quenched with saturated aq. $NaHCO_3$ solution

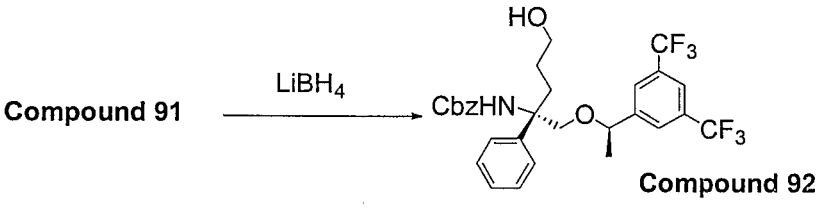
(100ml). The mixture was extracted with EtOAc (100ml x 3). The combined organic layers were dried ($MgSO_4$) and filtered. The crude product was purified by column chromatography over Biotage (4:1, hexane:EtOAc then 1:1, hexane:EtOAc) to afford the **Compound 90** (8.88g, 86%), Electrospray MS $[M+1]^+$ 596.1.

Step 2:



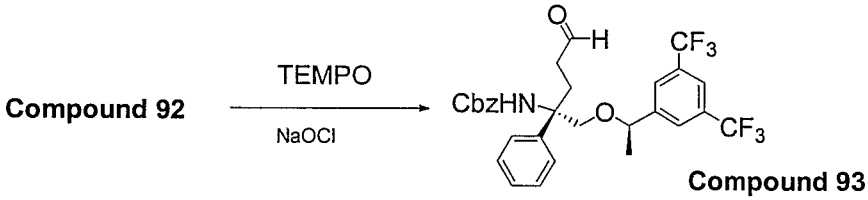
Compound 91 was prepared from **Compound 90** using the procedure similar to the preparation of **Compound 44** from **Compound 42**. The crude **Compound 91** was used in the next reaction without further purification.

Step 3:



To a solution of **Compound 91** (8.8g, 14.73mmol, 1equiv.) in dry THF (150ml) was added $LiBH_4$ (0.58g, 26.51mmol, 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 $NaHCO_3$ (50ml). The reaction mixture was extracted with EtOAc (3x100 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give crude **Compound 92** (8.2g), Electrospray MS $[M+1]^+$ 570.1, which was used in the next reaction without further purification.

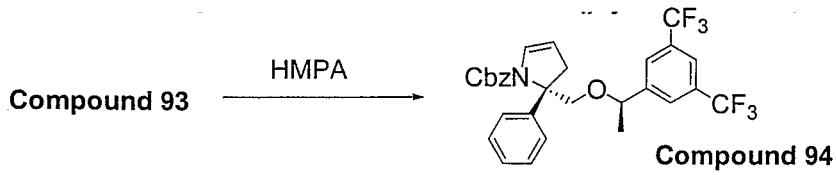
Step 4:



To a solution of **Compound 92** (8.2g, 14.4mmol, 1.0equiv.) in EtOAc (150ml) at 0°C was added saturated aq. $NaHCO_3$ (150ml) and the reaction mixture was stirred for 10 min at 0°C. NaBr (1.5g, 14.4mmol, 0.01equiv.) was added to the reaction mixture, followed by TEMPO (0.0225g, 0.144mmol, 0.1 equiv), and bleach (5.25% in H_2O, 20.4ml, 14.4mmol, 1.0equiv.). 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 (2ml) was added to the

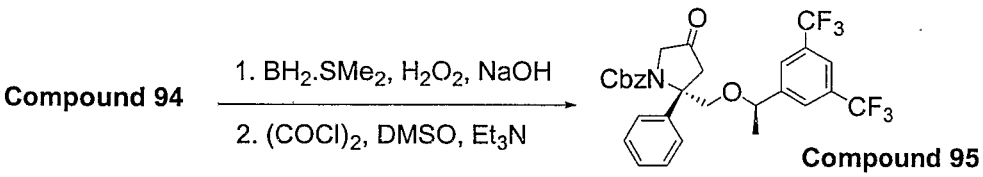
reaction mixture and was stirred for 15 min at 0°C and then it was quenched with saturated $Na_2S_2O_3$ (20ml). The reaction mixture was extracted with EtOAc (150ml x 3). The combined organic layers were dried over ($MgSO_4$), filtered and concentrated to give crude **Compound 93** (8g) which was used in the next reaction without further purification.

Step 4:



A mixture of **Compound 93** (8g, 14.1mmol, 1.0equiv.) and HMPA (50ml) was heated at 170°C for two h. The reaction mixture was cooled to 23°C and quenched with water (50ml). The reaction mixture was extracted with Et_2O (150ml x 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** (3.8g, 40% over three steps), Electrospray MS $[M+1]^+$ 550.1.

Step 5:

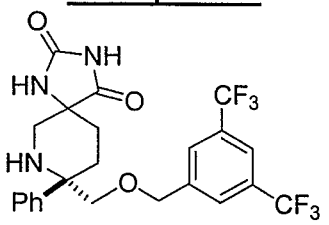


Compound 95 was prepared from **Compound 94** using the procedure similar to the preparation of **Compound 47** from **Compound 45**. Electrospray MS $[M+1]^+$ 566.1.

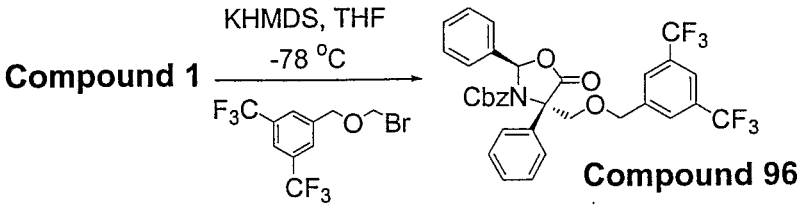
Step 6:

Compound 95 was converted toless polar isomer **Example 103a,** Electrospray MS $[M+1]^+$ 502.1, andmore 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



Step 1:



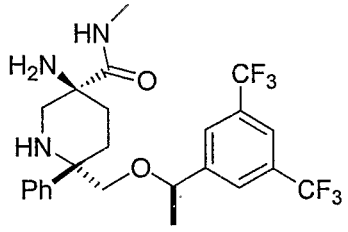
Compound 96

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:

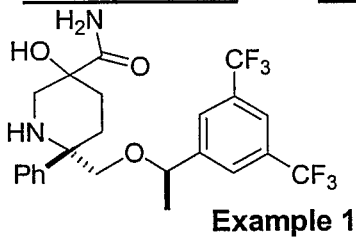
Compound 96 was converted to a mixture of **Example 104a** and **Example 104b** using the procedure similar to the preparation of **Examples 43a** and **44b** from **Compound 2**. The mixture of two isomers was separated on HPLC "ChiralPak AD column" using (5:95, IPA:hexane) to afford pure less polar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

Example 105

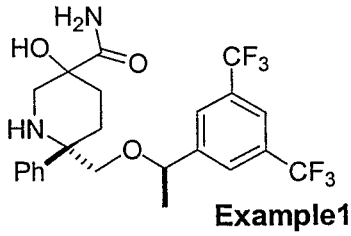


Example 105 was prepared from **Compound 54** using the procedure similar to the preparation of **Compound 62** from **Compound 54,** but using CH_3NH_2 (2M in THF) in place of ammonia (0.5M in 1,4-dioxane). Electrospray MS $[M+1]^+$ 504.1.

Example 106a and **Example 106b**

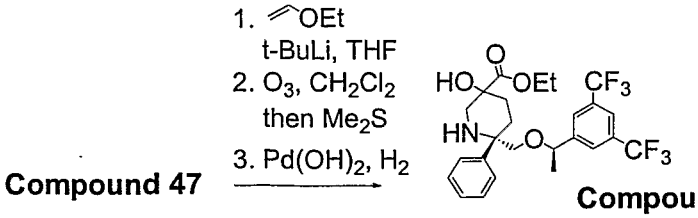


Example 106a



Example106b

Step1:



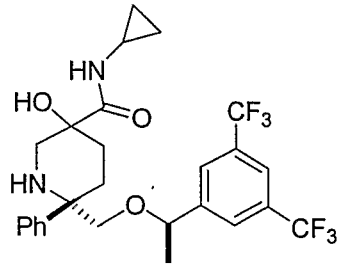
Compound 97

To a solution of ethyl vinyl ether (2.51ml, 26.1mmol) in THF (50ml) at -78°C underN_2, *t*-BuLi (6.6ml, 11.2mmol, 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**(2.16g, 3.73mmol) in THF (20ml) 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 (200ml x 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 (20ml) and ozone was bubbled through the solution at -78°C until pale blue color persisted. $(CH_3)_2S$ (2.7ml, 37.3mmol) 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 (20ml) 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:

Compound 97 was dissolved in CH_3OH (10ml) 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.

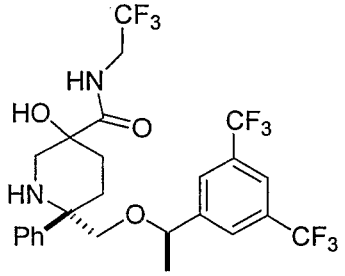
Example 107



To a solution of cyclopropylamine (17μl, 0.20mmol) in toluene (1ml) at RT under N_2, $Al(CH_3)_3$(0.1ml, 0.20mmol, 2.0M in toluene) was added. The mixture was allowed to stir at RT for 20 min. and a solution of **Compound 97** (20mg, 0.040mmol) in toluene (1ml) was added. The mixture was heated at 60°C overnight and was cooled to RT. EtOAc was added and the mixture was quenched with

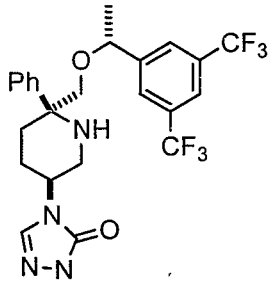
saturated potassium sodium tartarate solution. The layers were separated and the aqueous layer was extracted with EtOAc (100ml x 2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum and purification by column chromatography [hexane-EtOAc, 2:1 (v/v)] gave **Example 107** (11mg, 56%) as colorless oil. Electrospray MS $[M+1]^+$=531.

Example 108

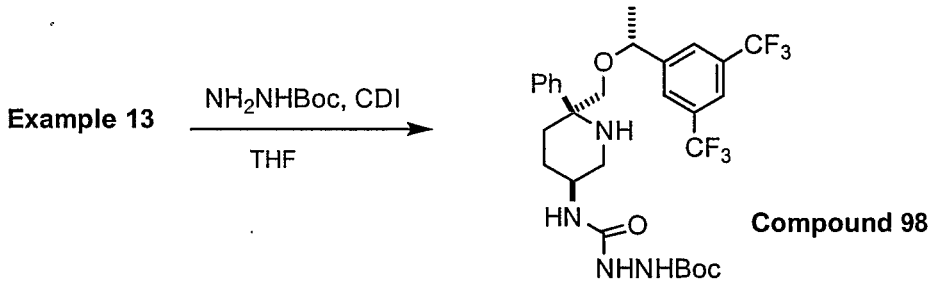


Example 108a and **Example 108b** were prepared from **Compound 97** using the procedure similar to the preparation of **Example 107** from **Compound 97** but using 2,2,2-trifluoroethylamine in place of cyclopropylamine. Electrospray MS $[M+1]^+$ 573.1 for the less polar isomer **Example 108a** and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

Example 109

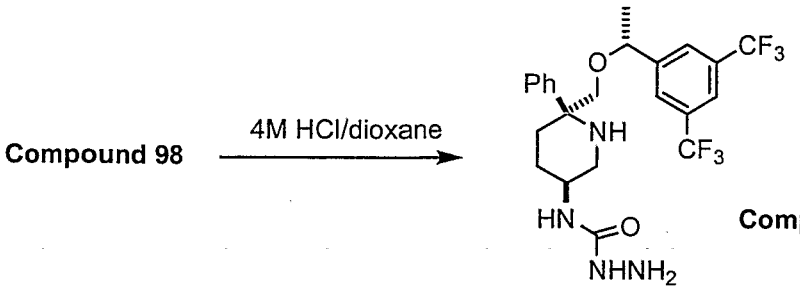


Step 1:



To a solution of diamine **Example 13** (150mg, 0.336mmol, 1equiv) in anhydrous THF (5ml) at 0°C was added *tert*-butylcarbazine (44.4mg, 0.336mmol, 1equiv) followed by CDI (65.4mg, 0.404mmol, 1.2equiv). 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** (170mg, 84%), Electrospray MS $[M+1]^+$ 605.3.

Step 2:

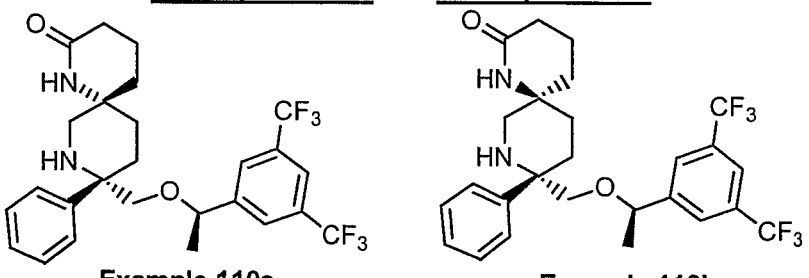


To a solution of **Compound 98** (170mg, 0.281mmol, 1equiv) in anhydrous CH_2Cl_2 (15ml) at 0°C was added a 4M HCl solution in 1,4-dioxane (0.7ml, 2.81mmol, 10equiv). The reaction mixture was warmed to RT and stirred for 18 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (100ml) and extracted with EtOAc (2 x 150ml). 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.

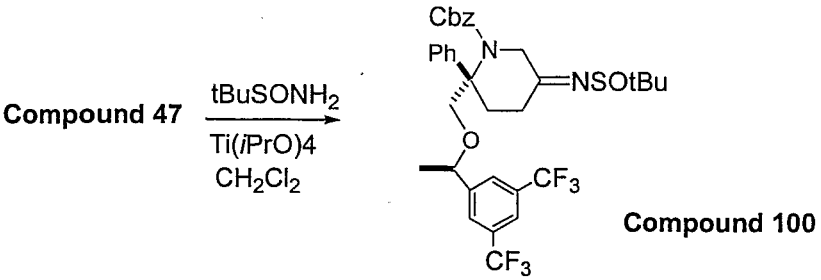
Step 3:

To a solution of **Compound 99** (160mg, 0.317mmol, 1equiv) in anhydrous DMF (5ml) was added formaimidine acetate (165mg, 1.6mmol, 5equiv) and the reaction mixture was stirred at RT for 30 min. HOAc (0.091ml, 1.6mmol, 5equiv) 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 (200ml) and washed with water (3 x 100ml). 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** (50mg, 35%), Electrospray MS $[M+1]^+$ 515.3.

Example 110a and **Example 110b**

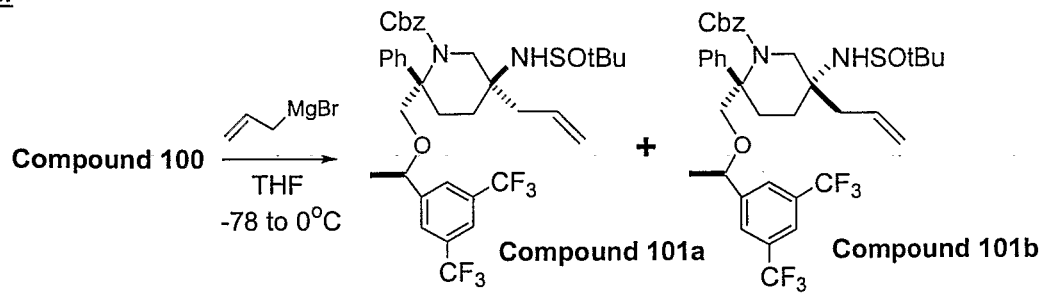


Step 1:



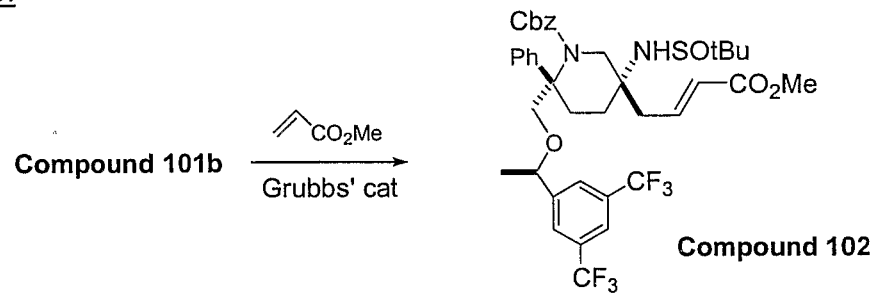
Using a procedure similar to **Example 11,** step 2, **Compound 47** was converted to the corresponding sulfinimine, **Compound 100.**

Step 2:



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

Step 3:



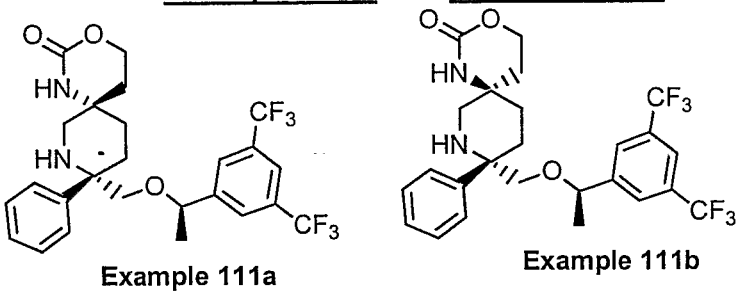
A 15ml pear-shaped flask was charged with **Compound 101b** (140mg, 0.193mmol, 1equiv) and CH_2Cl_2 (1ml). To this pale yellow solution was added Grubbs' catalyst (13.7mg, 0.016 mmol, 0.084 equiv), and methyl acrylate (21μl, 0.232 mmol, 1.2 equiv). The resulting reddish solution was heated at 40 °C overnight and quenched with methylsulfoxide (0.2ml). 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** (100mg, 66%).

Step 4:

A RBF was charged with **Compound 102** (100mg, 0.128mmol, 1 equiv) in EtOH (3ml), and $Pd(OH)_2$ on carbon (90mg, 0.128 mmol, 1equiv, 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 (2ml), treated with HCl (2ml, 4.0M in 1,4-dioxane), stirred at RT for 2 h, then concentrated again, retaken up again into MeOH (5ml), 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** (42mg, 64%), Electrospray MS $[M+1]^+$ 515.1

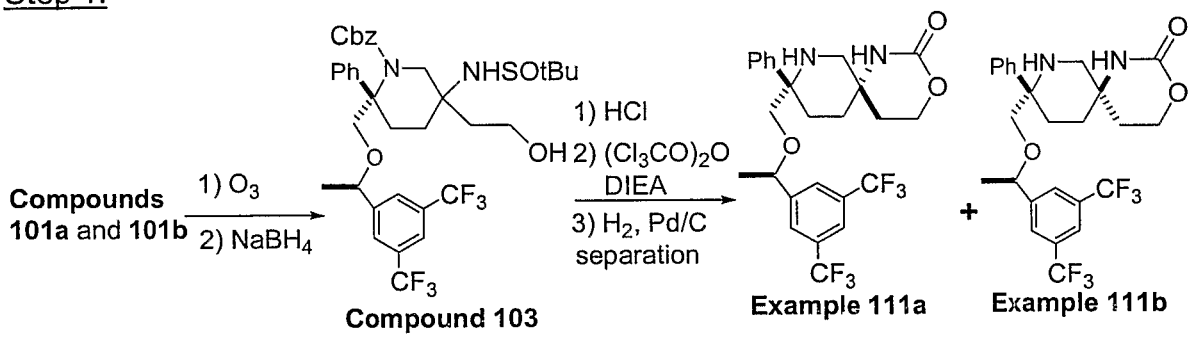
Example 110b (49%) was prepared by a similar procedure, but using **Compound 101a**. Electrospray MS $[M+1]^+$ 515.1

Example 111a and **Example 111b**



Example 111a **Example 111b**

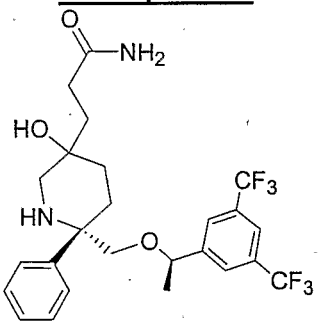
Step 1:



An RBF was charged with a mixture of **Compound 101a** and **101b** (180mg, 0.248mmol, 1.0equiv) and CH_2Cl_2 (2ml). 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 $NaBH_4$ (120mg). The solution was stirred at RT for 12h. It was quenched with NH_4Cl solution. The reaction was extracted with EtOAc (3 x 10ml). The organic solution was washed with brine, dried and concentrated to give **Compound 103,** which was used in the next reaction without further purification.

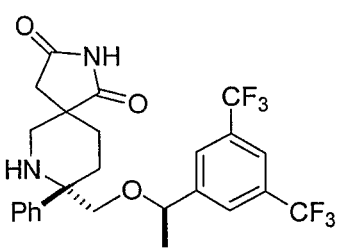
The crude **Compound 103** was dissolved in MeOH (2ml) and cooled to 0°C, followed by the addition of HCl (6ml, 4N in dioxane). After stirring for 3 h, the solvent was removed and the residue was redissolved in 3ml CH_2Cl_2, followed by the addition of DIEA (178µl). The solution was cooled to 0°C, triphosgene (36mg) was added, and the reaction was allowed to warm to RT and stirred for 3h. 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

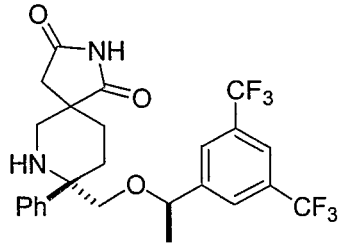


To a solution of ethyl propiolate (83µl, 0.82mmol) in THF (2ml) at -78°C under N_2, *t*-butyllithium (0.48ml, 0.82mmol, 1.7M in pentane) was added. The mixture was stirred at -78°C for 10 min and a solution of **Compound 47** (158mg, 0.27mmol) in THF (1ml) was added. The mixture was stirred at –78°C 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 (200ml x 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 (112mg, 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 (10ml) 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 (54mg, 61%). Electrospray MS $[M+1]^+$=519.1.

Examples 113a and 113b



Example 113a



Example 113b

To a solution of **Compound 51** (1.97g, 3.10mmol) in CH_2Cl_2 (50ml) at -78°C, DIBAL-H (9.3ml, 9.3mmol, 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 x 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 (1.6g, 85%) as colorless oil.

The allylic alcohol (1.6g, 2.63mmol) was dissolved in triethylorthoacetate (30ml) 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 (891mg, 50%) as colorless oil.

The alkene (891mg, 1.31mmol) was dissolved in CH_2Cl_2 (20ml) 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 (1ml) 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 (800mg, 90%) as colorless oil.

The aldehyde (280mg, 0.41mmol) was dissolved in isoprene (2.4ml) and t-butyl alcohol (7ml) at RT. A solution of sodium chlorite (414mg, 4.12mmol) in sodium dihydrogenphosphate (4ml, 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 (250ml x 2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give a crude acid as yellow oil.

The crude acid was dissolved in CH_2Cl_2 (10ml) at RT and diisopropylamine (0.22ml, 1.24mmol), followed by PyBOP (322mg, 0.62mmol) were added. The mixture was stirred at RT for 20 min. before a solution of ammonia in dioxane (8ml, 4.12mmol) 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 (250ml x 2). The combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed in vacuum to give the crude amide as yellow oil.

The crude amide was dissolved in CH_3OH (10ml) 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.

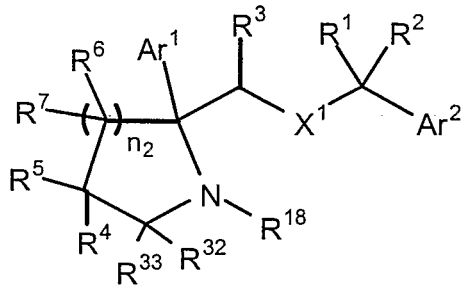
The crude amino-amide was dissolved in CH_3OH and excess $NaOCH_3$ was added. The mixture was heated at 60°C for 1 h before it was quenched with saturated with saturated NH_4Cl solution. Water and EtOAc were added. Layers were separated and the aqueous layer was extracted with EtOAc (250ml x 2). The 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** (20mg, 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** (25mg, 12%, 4 steps overall) as colorless oil. Electrospray MS $[M+1]^+$=515.1.

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:

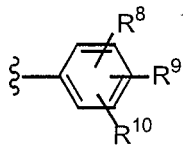
1. A compound having the formula (I):



(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;

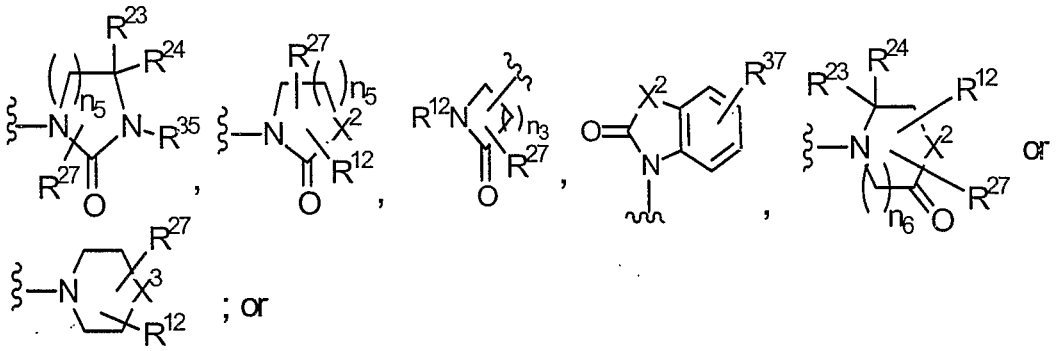
n_2 is 1 to 4;

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

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_8 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, $-CH_2CF_3$, 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 $-OR^{12}$, where one of the carbon atoms in the ring is optionally replaced by a heteroatom selected from the group consisting of -O-, -S- and $-NR^{34}$-;

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_6)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 -$CR^{12}F$-;

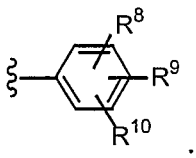
n_3 is 1 to 5; and

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-.

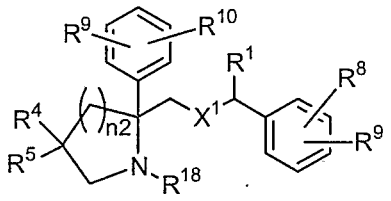
3. The compound or salt according to claim 1, where Ar^1 and Ar^2 are each



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.

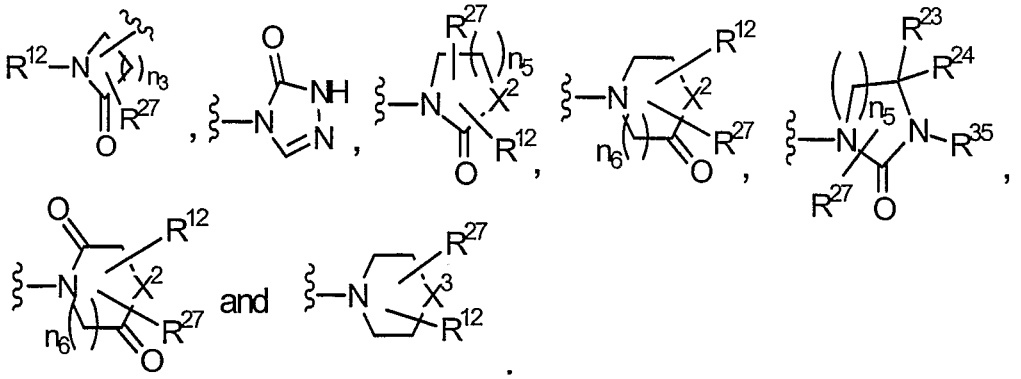
6. The compound or salt according to claim 1 represented by the formula



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.

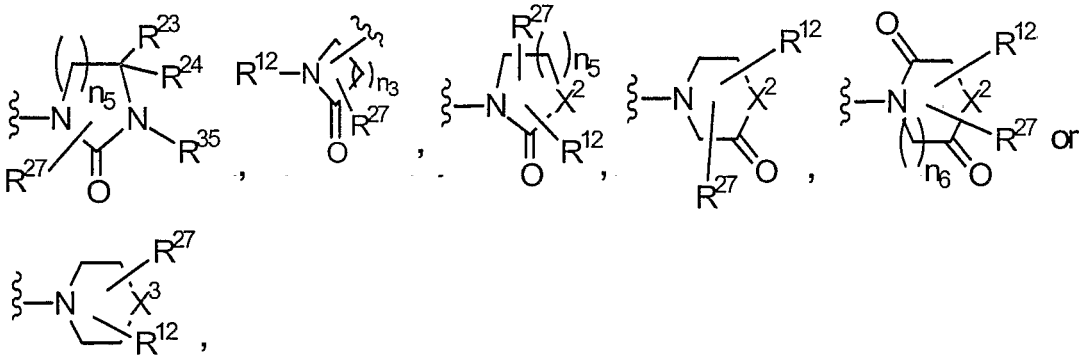
7. The compound according to claim 6 wherein one of R^4 and R^5 is H and the other is $-C(R^{28}R^{29})_{n1}$-G, wherein n_1 is 0, 1 or 2.

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,



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,



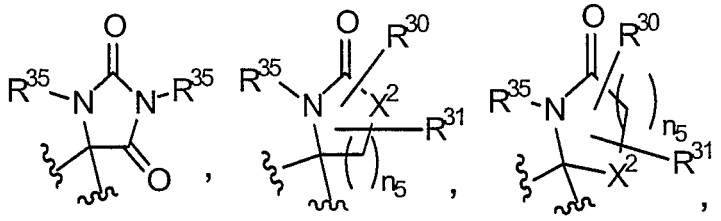
wherein X_2 is –O-, -S-, -CH_2- or –NR^{35}-; and R^5 is –C(O)OR^{13} or –C(O)N $R^{13}R^{14}$.

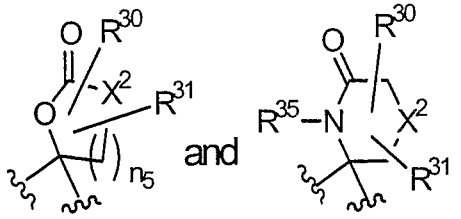
10. The compound or salt according to claim 8, where R^{12} and R^{27} are independently selected from the group consisting of H and –CH_3; n_3 is 2 or 3; and n_5 is 1 or 2.

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}.

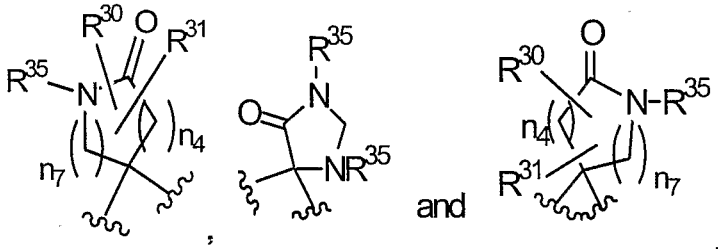
13. The compound or salt according to claim 12, where the 4- to 8-membered ring is selected from the group consisting of:





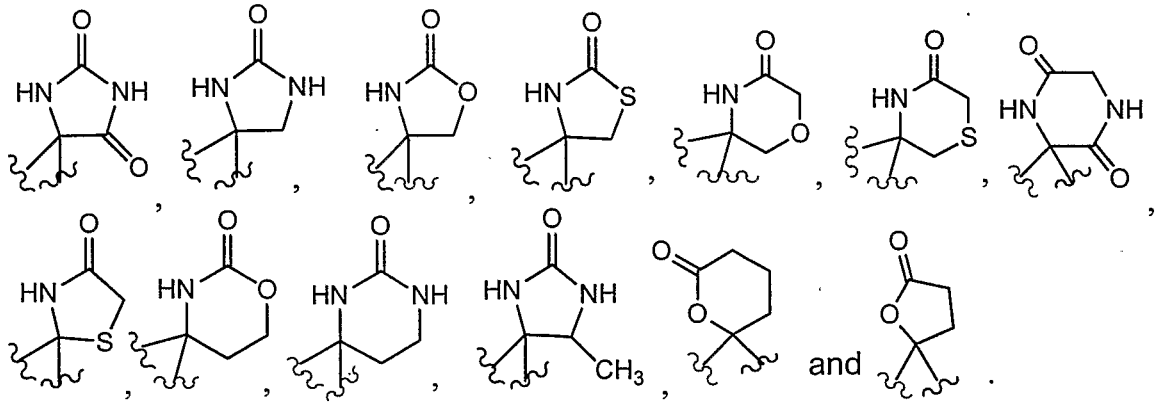
wherein R^{35} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl; n_5 is 1, 2 or 3; X^2 is $-NR^{35}$-, $-CH_2$-, -O- or –S-; R^{30} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and R^{31} is H, -OH or C_1-C_6 alkyl.

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

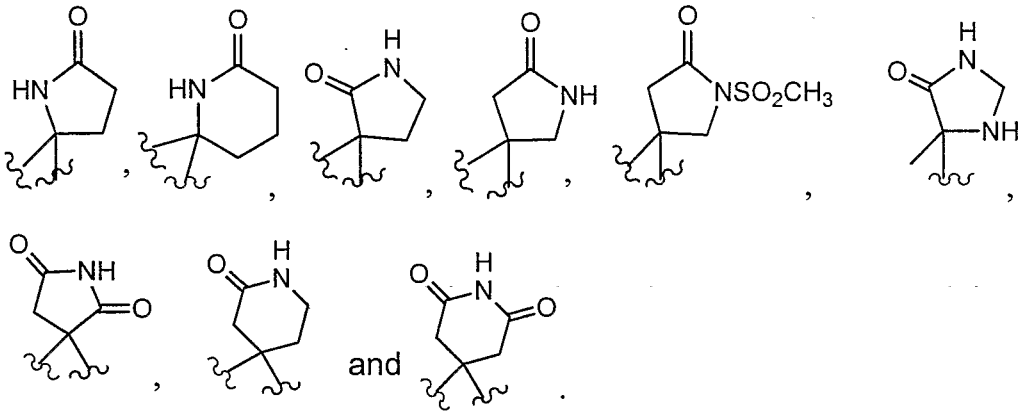


wherein R^{30} is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; R^{31} is H, -OH or C_1-C_6 alkyl; each R^{35} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl and hydroxy(C_1-C_6)alkyl; n_4 and n_7 are independently 0-5, provided 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

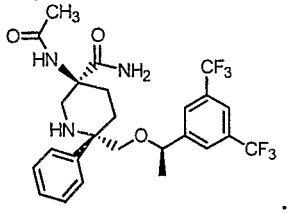


16. The compound according to claim 14, wherein the 4- to 8-membered ring is selected from the group consisting of

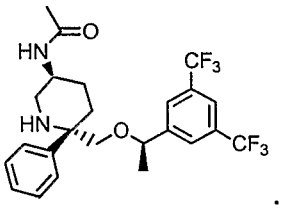


17. The compound or salt according to claim 1, wherein the compound is selected from the group consisting of Examples 3, 9, 12a, 13, 14, 15, 20, 23, 29, 36, 40, 43b, 44b, 45, 50, 53, 56b, 57, 60a, 61, 62, 63, 72a, 73b, 74a, 75b, 76a, 82a, 82b, 90, 96, 105, 106b, 109, 110a, 111a, 112 and 113, and the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

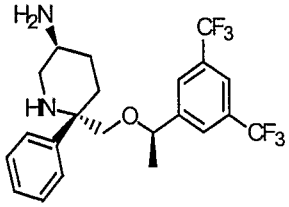
18. The compound or salt according to claim 17, wherein the compound is:



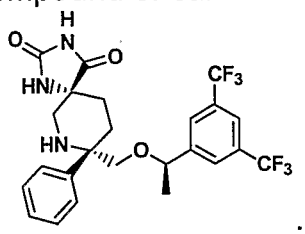
19. The compound or salt according to claim 17, wherein the compound is:



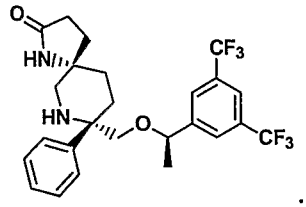
20. The compound or salt according to claim 17, wherein the compound is:



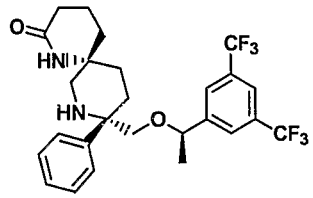
21. The compound or salt according to claim 17, wherein the compound is:



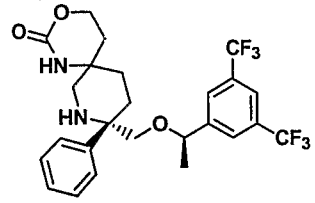
22. The compound or salt according to claim 17, wherein the compound is:



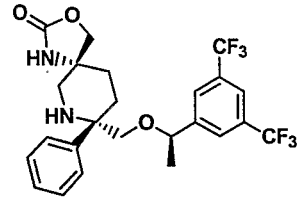
23. The compound or salt according to claim 17, wherein the compound is:



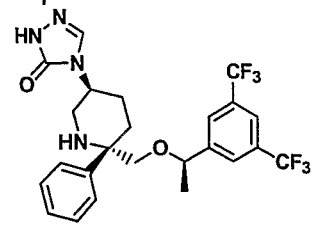
24. The compound or salt according to claim 17, wherein the compound is:



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. The use of a compound of claim 1 for the preparation of a medicament for treating a physiological disorder, symptom or disease in a patient, 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 use according to claim 32 for treating asthma, emesis, nausea, depression, anxiety, cough or migraine.

34. The use of claim 33 for treating depression or anxiety further comprising at least one selective serotonin reuptake inhibitor.

35. The use of claim 33 for treating emesis further comprising at least one serotonin 5-HT_3 receptor antagonist or at least one corticosteroid or at least one substituted benzamide.

36. The use of claim 33 for treating emesis further comprising at least one serotonin 5-HT_3 receptor antagonist and at least one corticosteroid.

37. The use of claim 33 for treating emesis further comprising at least one corticosteroid and at least one substituted benzamide.

38. The use of a compoind of claim 1 for the preparation of a medicament for antagonizing an effect of a Substance P at a neurokinin-1 receptor site or for blocking at least one neurokinin-1 receptor.