

PROCESS FOR THE PREPARATION OF OPIOID MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

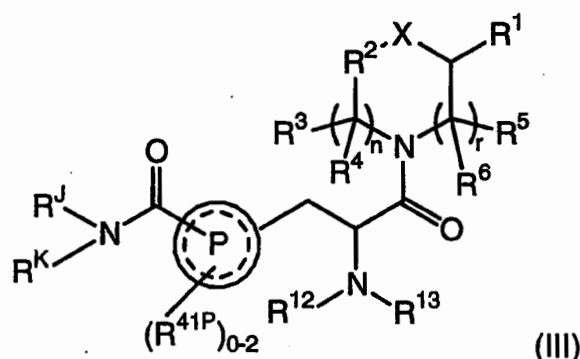
This application claims the benefit of U. S. Provisional Application
 5 60/661,784, filed on March 14, 2005, which is incorporated by reference herein
 in its entirety.

FIELD OF THE INVENTION

The present invention is directed to a novel process for the preparation
 10 of opioid modulators (agonists and antagonists), and intermediates in their
 synthesis. The opioid modulators are useful in the treatment and prevention of
 such disorders as pain, visceral pain including post-operative pain,
 gastrointestinal disorders including diarrheic syndromes, motility disorders
 including post-operative ileus, constipation, irritable bowel syndrome and
 15 inflammatory bowel disorders.

BACKGROUND OF THE INVENTION

The present invention is directed to the preparation of novel opioid
 receptor modulators and intermediates in their synthesis. More specifically, the
 20 present invention is further directed to processes for the preparation of
 compounds of formula (III),

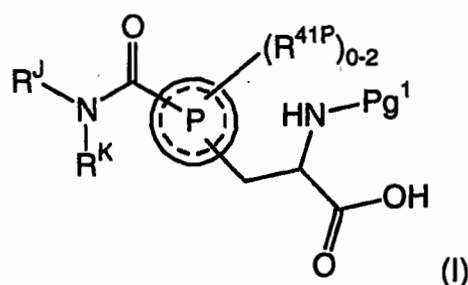


wherein all variables are as hereinafter defined, disclosed in United
 States Application No. 10/400,006, filed March 26, 2003, and published as US
 25 Patent Publication US-2004-0010014-A1, September 26, 2004, which is hereby
 incorporated by reference.

Known methods for the preparation of compounds of formula (III) and compounds of formula (I), as herein defined, require the use of dimethyl-tyrosine, which is expensive and thus not suitable for large scale syntheses. Thus there remains a need for a process for the preparation of compounds of
 5 formula (I) and compounds of formula (III) which is suitable for large scale production.

SUMMARY OF THE INVENTION

The present invention is directed to a process for the preparation of
 10 compounds of formula (I)



wherein



is C₆₋₁₀aryl or a heteroaryl selected from the group consisting of
 furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl,
 15 pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl,
 benzimidazolyl, benzthiazolyl, benzoxazolyl, quinoliziny, quinolinyl,
 isoquinolinyl and quinazolinyl;

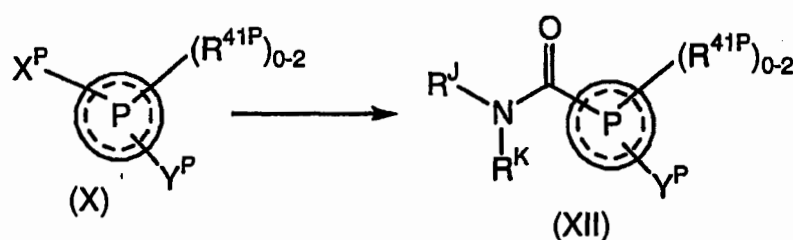
each R^{41P} is independently selected from C₁₋₆alkyl, C₁₋₆alkoxy or fluoro;

R^J and R^K are each independently selected from hydrogen or C₁₋₄alkyl;

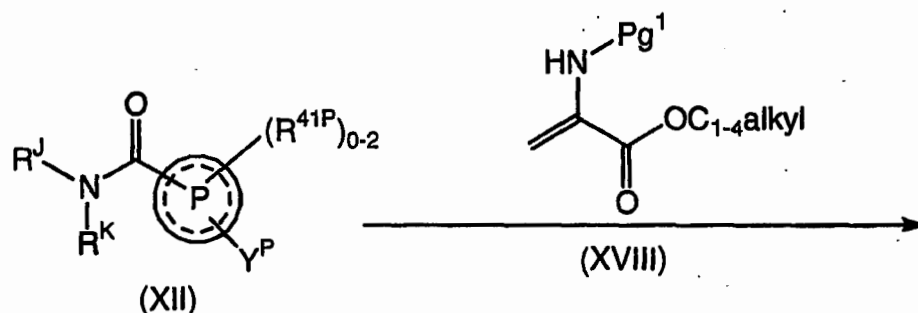
20 alternatively, R^J and R^K are taken together with the nitrogen atom to which they
 are bound to form a five to seven membered heterocyclyl;

Pg¹ is a nitrogen protecting group;

comprising



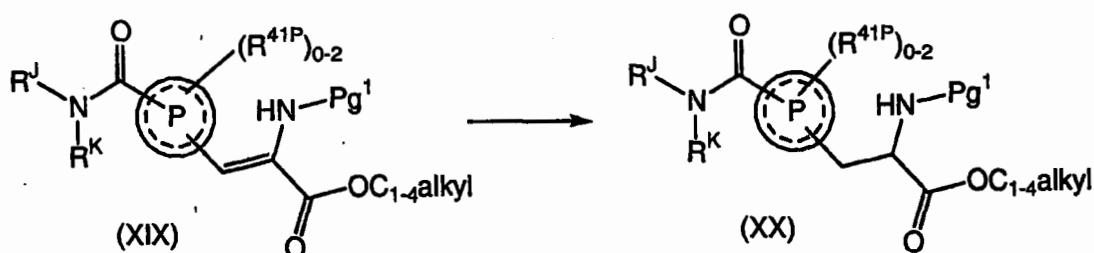
reacting a compound of formula (X), wherein X^P is selected from OH, CN, $-\text{CO}_2\text{H}$, $-\text{C}(\text{O})-\text{Cl}$ or $-\text{C}(\text{O})-\text{OC}_{1-4}\text{alkyl}$ and wherein Y^P is selected from Br, Cl or I, to yield the corresponding compound of formula (XII);



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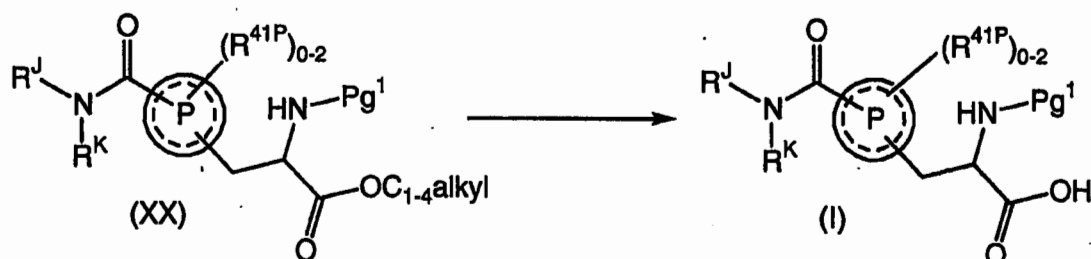
reacting the compound of formula (XII) with a suitably substituted compound of formula (XVIII); in the presence of palladium catalyst; in the presence of an organic or inorganic base; in an organic solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula (XIX);

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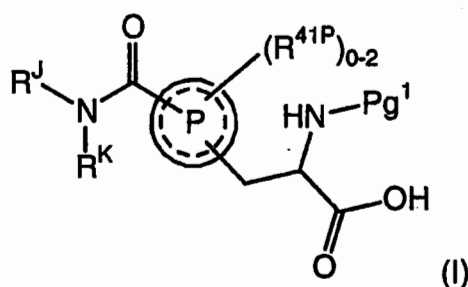
reacting the compound of formula (XIX) with hydrogen or a source of hydrogen; in the presence of a catalyst; in a solvent; at a temperature greater

than about room temperature; to yield the corresponding compound of formula (XX);



reacting the compound of formula (XX) with an aqueous base; in an
5 organic solvent; to yield the corresponding compound of formula (I).

The present invention is further directed to a process for the preparation of a compound of formula (I)



10

wherein



is C₆₋₁₀aryl or a heteroaryl selected from the group consisting of
furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl,
pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl,
benzimidazolyl, benzthiazolyl, benzoxazolyl, quinoliziny, quinollinyl,

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isoquinolinyl and quinazolinyl;

each R^{41P} is independently selected from C₁₋₆alkyl, C₁₋₆alkoxy or fluoro;

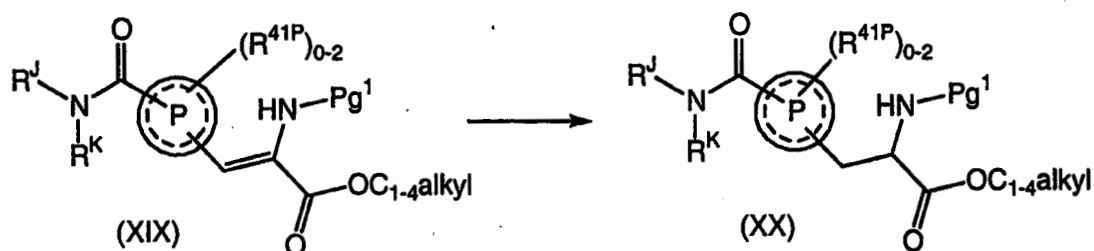
R^J and R^K are each independently selected from hydrogen or C₁₋₄alkyl;

alternatively, R^J and R^K are taken together with the nitrogen atom to which they
are bound to form a five to seven membered heterocyclyl;

20

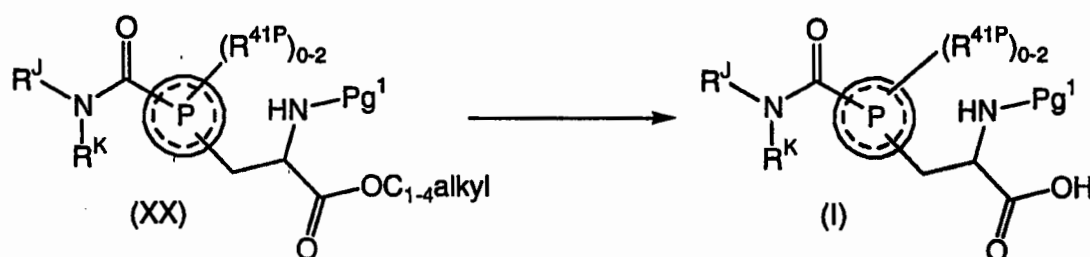
Pg¹ is a nitrogen protecting group;

comprising



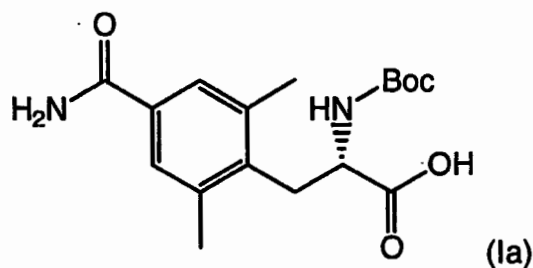
reacting the compound of formula (XIX) with hydrogen or a source of hydrogen; in the presence of a catalyst; in a solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula

5 (XX);

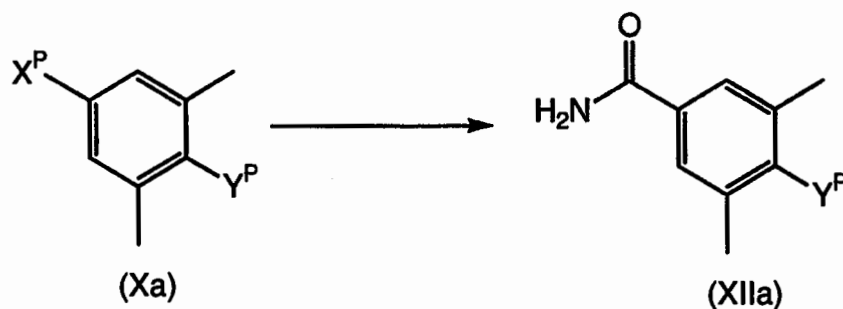


reacting the compound of formula (XX) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (I).

10 The present invention is further directed to a process for the preparation of a compound of formula (Ia) (also known as, 4-(aminocarbonyl)-*N*-[(1,1-dimethylethoxy)carbonyl]-2,6-dimethyl-L-phenylalanine)

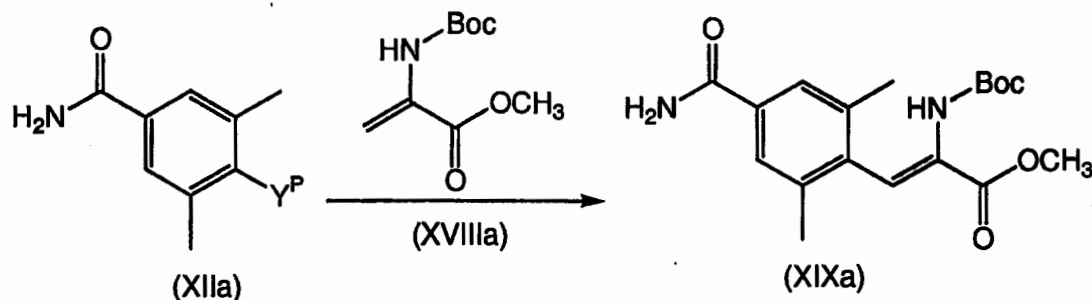


comprising

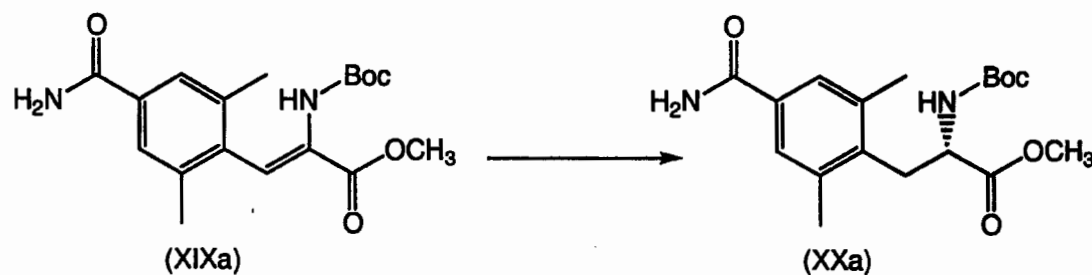


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reacting a compound of formula (Xa), wherein X^P is selected from OH, CN, $-\text{CO}_2\text{H}$, $-\text{C}(\text{O})-\text{Cl}$ or $-\text{C}(\text{O})-\text{OC}_{1-4}\text{alkyl}$ and wherein Y^P is selected from Br, Cl or I, to yield the corresponding compound of formula (XIIa);

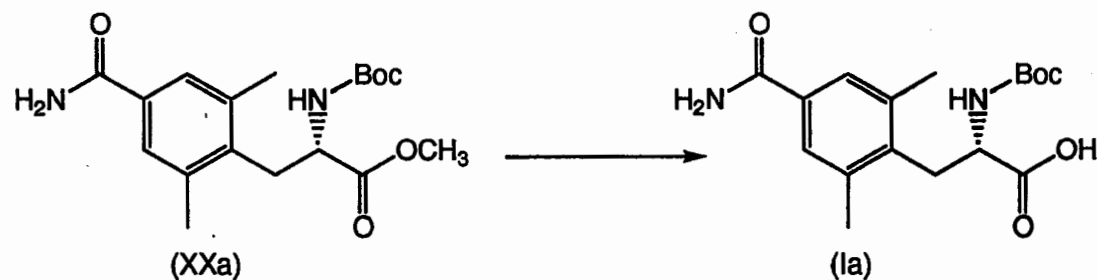


- 5 reacting the compound of formula (XIIa) with a suitably substituted compound of formula (XVIIIa); in the presence of palladium catalyst; in the presence of an organic or inorganic base; in an organic solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula (XIXa);



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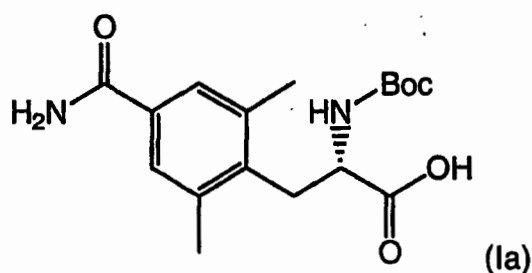
reacting compound of formula (XIXa) with hydrogen gas, at a pressure sufficient to hydrogenate; in the presence of a suitable chiral catalyst; at a temperature greater than about room temperature; in an organic solvent; to yield the corresponding compound of formula (XXa);



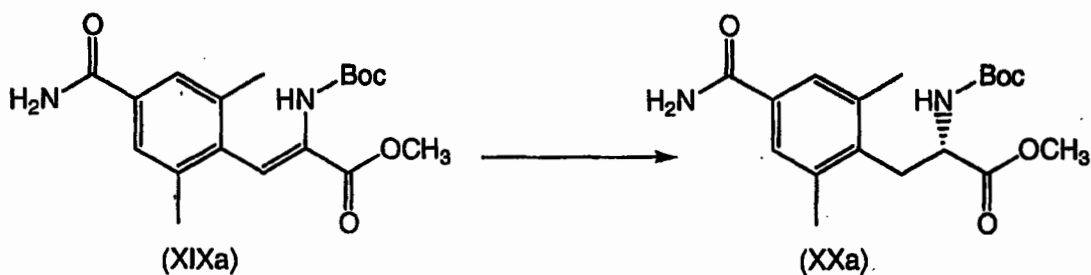
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reacting the compound of formula (XXa) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (Ia).

The present invention is further directed to a process for the preparation of the compound of formula (Ia)

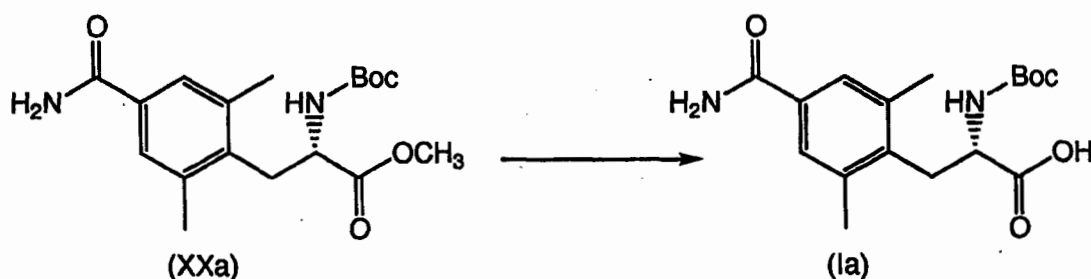


comprising



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reacting compound of formula (XIXa) with hydrogen gas, at a pressure sufficient to hydrogenate; in the presence of a suitable chiral catalyst; at a temperature greater than about room temperature; in an organic solvent; to yield the corresponding compound of formula (XXa);

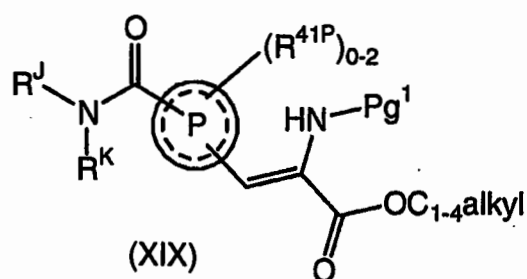


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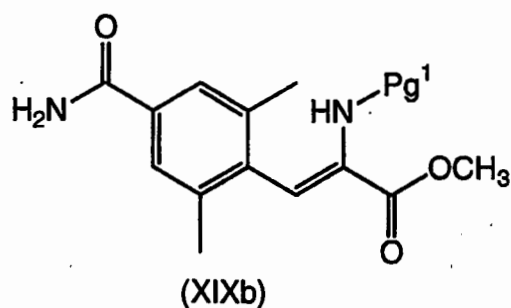
reacting the compound of formula (XXa) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (Ia).

The present invention is further directed to processes for the preparation of compounds of formula (XIX)

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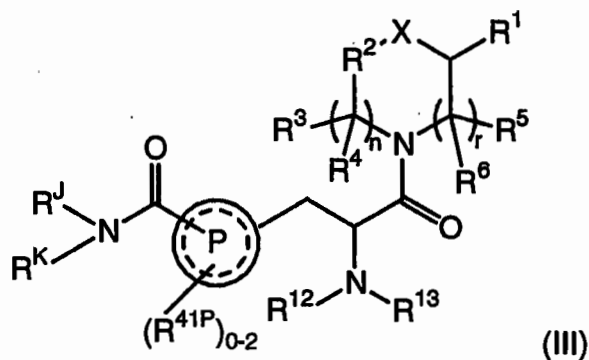


The present invention is further directed to processes for the preparation of the compound of formula (XIXb)



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The present invention is further directed to a process for the preparation of compounds of formula (III)



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wherein



is C₆₋₁₀aryl or a heteroaryl selected from the group consisting of
 furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl,
 pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl,
 15 benzimidazolyl, benzthiazolyl, benzoxazolyl, quinoliziny, quinolinyl,
 isoquinolinyl and quinazolinyl;

each R^{41P} is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy or fluoro;
 R^J and R^K are each independently selected from hydrogen or C_{1-4} alkyl;
 alternatively, R^J and R^K are taken together with the nitrogen atom to which they
 are bound to form a five to seven membered heterocyclyl;

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X is selected from a group consisting of O; S; $N(R^{14})$; and $-(CR^{15}R^{16})_m$,
 wherein:

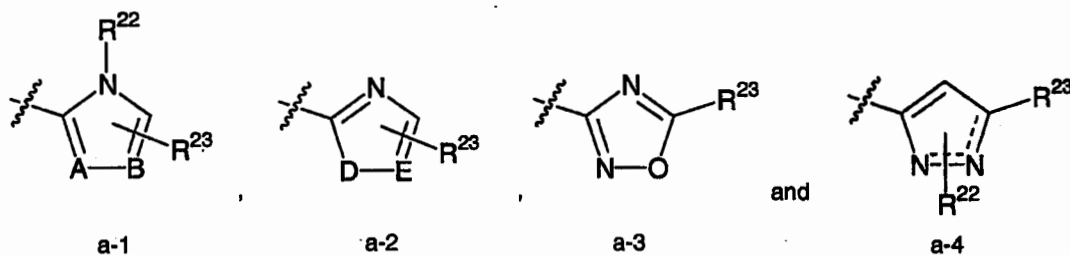
m is an integer from 0 to 2, and

R^{14} , R^{15} , and R^{16} are independently selected from the group
 consisting of hydrogen, C_{1-4} alkyl, and aryl; provided that only one
 of R^{15} or R^{16} can be C_{1-4} alkyl, or aryl;

10

and the total core ring size of the ring containing X will not be greater
 than an eight membered ring;

15 R^1 is selected from the group consisting of benzimidazole, benzoxazole,
 benzothiazole, indole, phenyl,



a-1

a-2

a-3

a-4

wherein

A-B is selected from the group consisting of N-C, C-N, N-N and C-C;

20

D-E is selected from the group consisting of O-C, S-C, and O-N;

R^{22} is a substituent attached to a ring nitrogen and is selected from
 the group consisting of hydrogen, C_{1-4} alkyl and aryl;

25

R^{23} is one to two substituents independently selected from the group
 consisting of hydrogen, halogen, amino, aryl, arylamino,
 heteroaryl amino, hydroxy, aryloxy, heteroaryloxy, an amino acid
 residue such as $-C(O)-NH-CH(-R^{40})-C(O)-NH_2$ and C_{1-6} alkyl
 {wherein said alkyl is optionally substituted with a substituent
 selected from the group consisting of hydroxy, hydroxycarbonyl,
 C_{1-4} alkoxycarbonyl, aminocarbonyl, amino, aryl,

(C₁₋₄)alkylaminocarbonyl, di(C₁₋₄)alkylaminocarbonyl, heteroaryl-amino, heteroaryloxy, aryl(C₁₋₄)alkoxy, and heteroaryl};

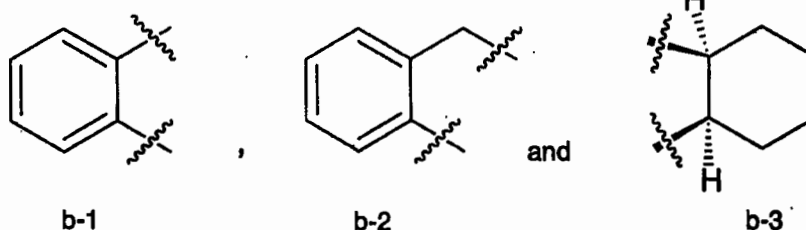
5 R^{40} is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonylamino, diC₁₋₆alkylcarbonylamino, aryl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkyl, aryl, and heteroaryl;

10 wherein when R¹ is benzimidazole, said benzimidazole is optionally substituted with one to two substituents independently selected from the group consisting of halogen, C₁₋₄alkyl, hydroxy, hydroxycarbonyl and aryl, with the proviso that when R¹ is benzimidazole, r, s and p are 0, n is 0 or 1, L is O and R³, R⁴, R⁹, R¹² and R¹³ are all hydrogen,



15 is not (4-OH)Phenyl or (4-OH-2,6-diMe)Phenyl;

R² is a divalent radical -CH₂-CH₂- optionally substituted with a substituent selected from the group consisting of halogen and phenylmethyl, or is selected from the group of divalent radicals of the formula



20 wherein said radicals -CH₂CH₂-, b-1 and b-2 are optionally substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, nitro, amino, cyano, trifluoromethyl and aryl; and the radical b-3 is unsubstituted;

25 R³ and R⁴ are each independently selected from the group consisting of hydrogen, C₁₋₆alkyl, aryl, and heteroaryl; provided that only one of R³ or R⁴ can be C₁₋₆alkyl, aryl, or heteroaryl;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, aryl, and heteroaryl; provided that only one of R^5 or R^6 can be C_{1-6} alkyl, aryl, or heteroaryl;

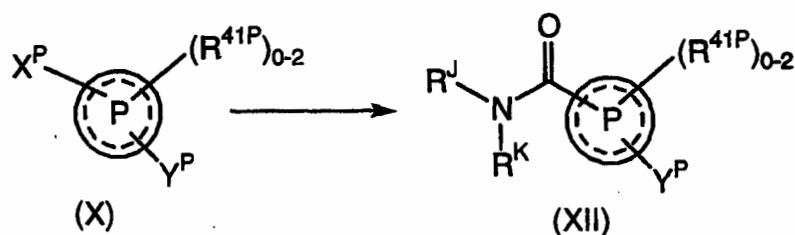
5 n and r are integers from 0 to 2;

R^{12} and R^{13} are each independently selected from the group consisting of hydrogen; C_{1-6} alkyl, formyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, di- C_{1-6} alkylcarbonylamino, aryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl, aryl, and heteroaryl, wherein when R^{12} and R^{13} are

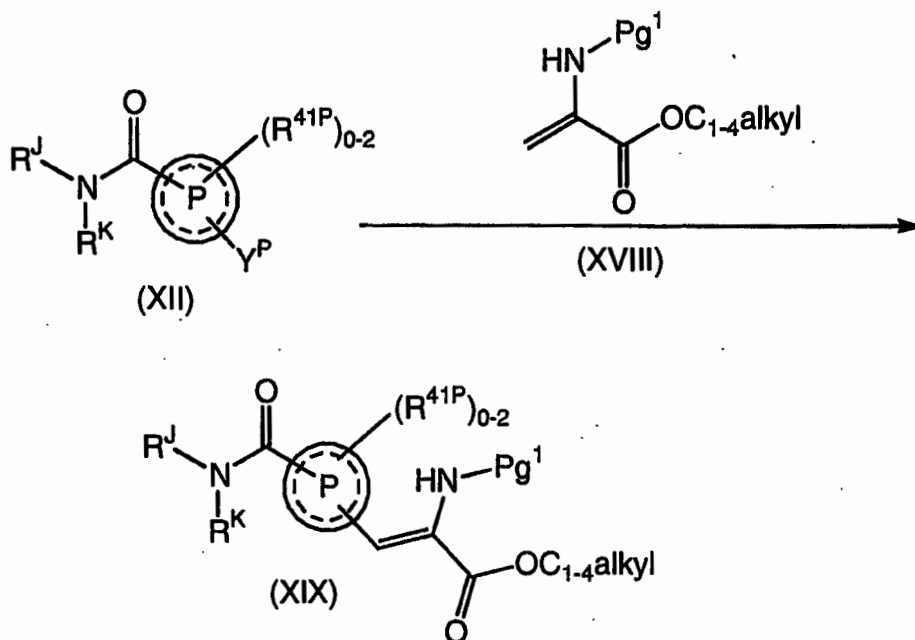
selected from C_{1-6} alkyl, R^{12} and R^{13} may be optionally fused to ;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof;

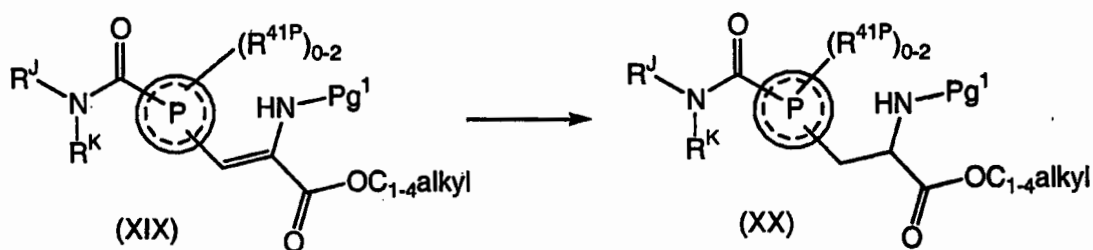
15 comprising



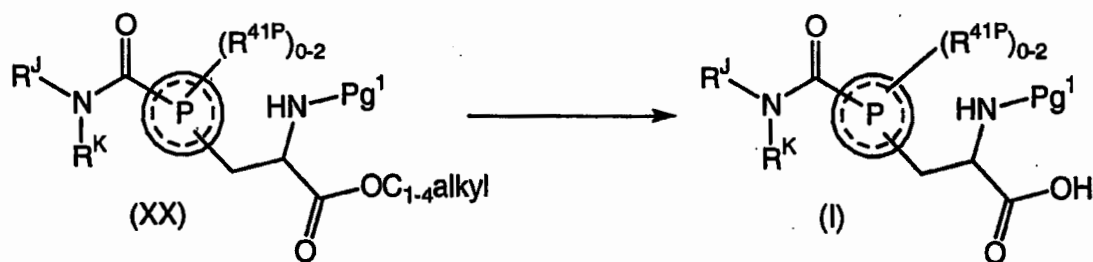
reacting a compound of formula (X), wherein X^P is selected from OH, CN, $-CO_2H$, $-C(O)-Cl$ or $-C(O)-OC_{1-4}alkyl$ and wherein Y^P is selected from Br, Cl or I, to yield the corresponding compound of formula (XII);



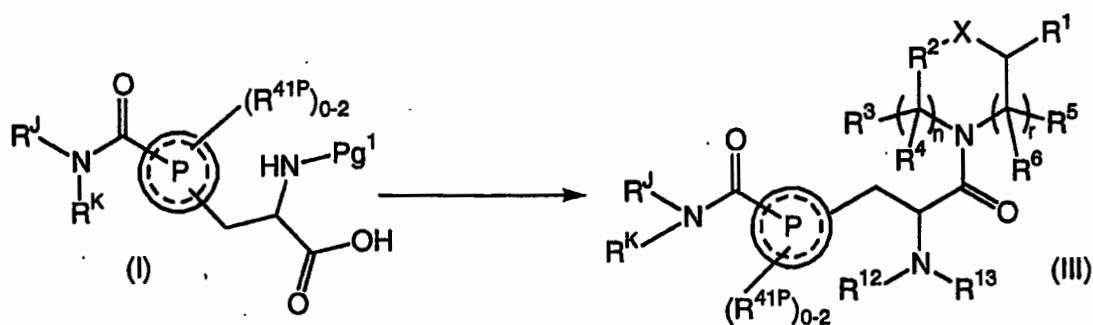
- reacting the compound of formula (XII) with a suitably substituted compound of formula (XVIII) wherein Pg^1 is a nitrogen protecting group; in the presence of palladium catalyst; in the presence of an organic or inorganic base;
- 5 in an organic solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula (XIX);



- reacting the compound of formula (XIX) with hydrogen or a source of hydrogen; in the presence of a catalyst; in a solvent; at a temperature greater
- 10 than about room temperature; to yield the corresponding compound of formula (XX);



- reacting the compound of formula (XX) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (I);



reacting the compound of formula (I) to yield the corresponding compound of formula (III).

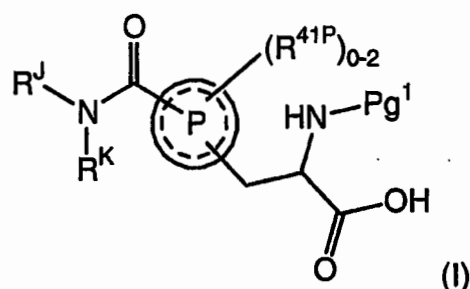
5 The present invention is further directed to a product prepared according to any of the processes described herein.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at a product prepared according to the process described herein. An illustration of the invention is a pharmaceutical composition made by mixing a product prepared according to the process described herein and a pharmaceutically acceptable carrier. Illustrating the invention is a process for making a pharmaceutical composition comprising mixing a product prepared according to the process described herein and a pharmaceutically acceptable carrier.

Exemplifying the invention are methods of treating or preventing a disorder mediated by at least one opioid receptor, preferably the δ or μ opioid receptor selected from the group consisting of pain and gastrointestinal disorders, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions prepared as described above.

DETAILED DESCRIPTION OF THE INVENTION

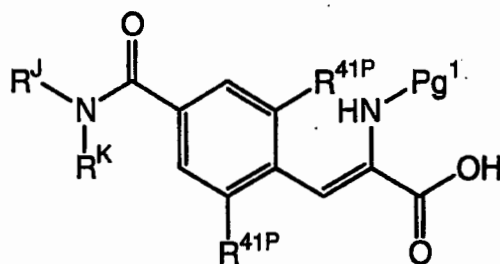
25 The present invention is directed to processes for the preparation of compounds of formula (I)



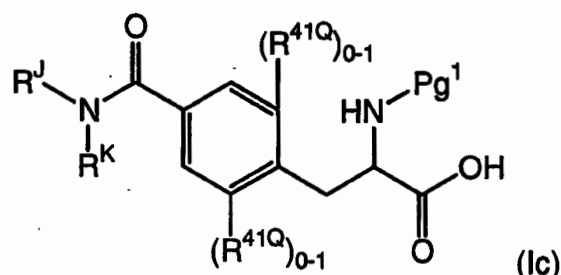
wherein Pg^1 , , R^J , R^K and $\text{R}^{41\text{P}}$ are as herein defined. The compounds of formula (I) are useful in the preparation of opioid receptor modulators - compounds of formula (II) and compounds of formula (III). The present invention is further directed to processes for the preparation of the compound of formula (Ia) as herein defined, useful as intermediates in the synthesis of opioid receptor modulators.

In an embodiment, the present invention is directed to processes for the preparation of compounds wherein the  ring is unsubstituted. In an embodiment of the present invention, the  ring is substituted with one $\text{R}^{41\text{P}}$ group, which is bound at the 2- or 6-position. In another embodiment, the present invention is directed to processes for the preparation of compounds

wherein the  ring is substituted with two $\text{R}^{41\text{P}}$ groups, which are bound at the 2- and 6-positions. For example, processes wherein  is phenyl, the compound of formula (I) is of the following structure:

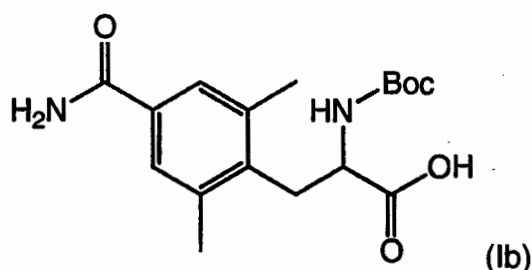


In an embodiment, the present invention is directed to processes for the preparation of compounds of formula (Ic)



- 5 wherein R^{41Q} is selected from methyl, ethyl, methoxy, ethoxy or fluoro and wherein R^J , R^K and Pg^1 are as herein defined.

In another embodiment, the present invention is directed to processes for the preparation of the compound of formula (Ib)

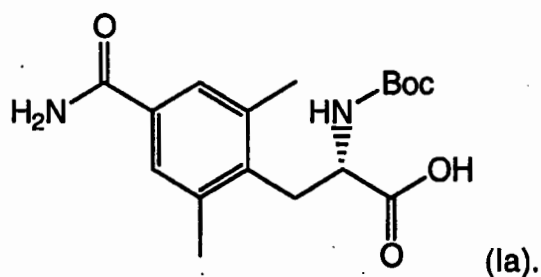


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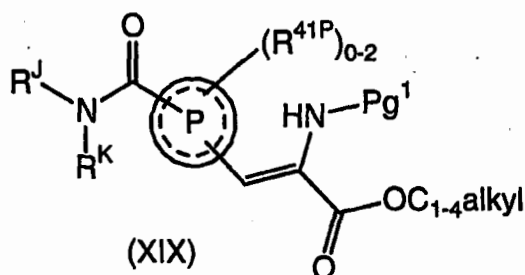
(i.e. a compound of formula (I) wherein  is phenyl; R^J and R^K are each hydrogen; the phenyl ring is further substituted with two R^{41P} groups, which are each methyl and Pg^1 is Boc), also known as 2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionic acid.

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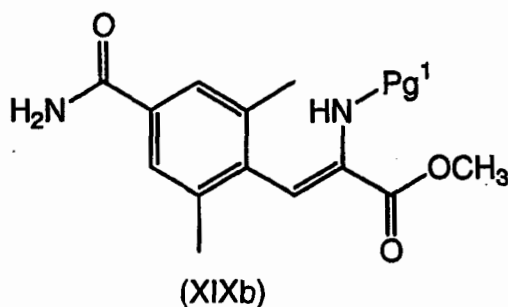
In another embodiment, the present invention is directed to processes for the preparation of the compound of formula (Ia)



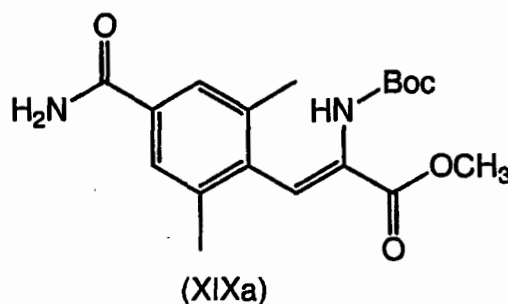
The present invention is further directed to processes for the preparation of compounds of formula (XIX)



In an embodiment, the present invention is directed to processes for the preparation of the compound of formula (XIXb),



Preferably, the present invention is directed to processes for the preparation of the compound of formula (XIXa)



The compounds of formula (XIX) are useful as intermediates in the synthesis of compounds of formula (III).

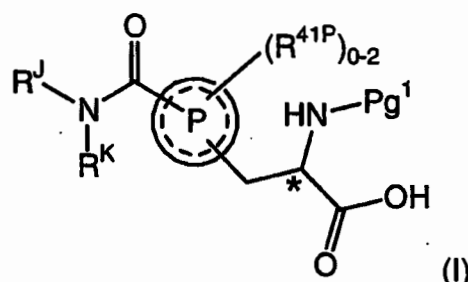
Embodiments of the present invention include processes for the

preparation of compounds wherein  is C₆₋₁₀aryl. Embodiments of the present invention further include processes for the preparation of compounds

wherein  is phenyl.

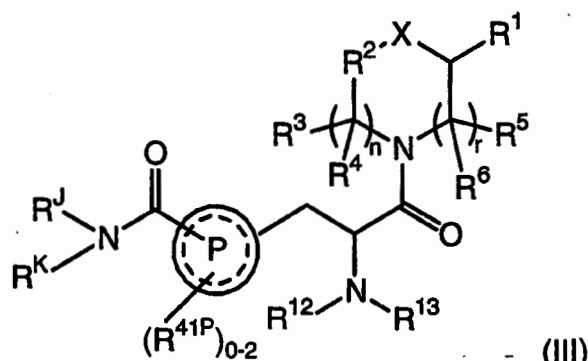
Embodiments of the present invention include processes for the preparation of compounds wherein R^{41P} is selected from C_{1-3} alkyl, C_{1-6} alkoxy or fluoro. Embodiments of the present invention further include processes for the preparation of compounds wherein R^{41P} is selected from C_{1-3} alkyl or C_{1-3} alkoxy. Embodiments of the present invention further include processes for the preparation of compounds wherein R^{41P} is selected from methyl, ethyl, methoxy, ethoxy or fluoro. Embodiments of the present invention further include processes for the preparation of compounds wherein R^{41P} is selected from methyl or methoxy.

Embodiments of the present invention include processes for the preparation of compounds of formula (I) wherein the stereo-center denoted with a "*" as shown below,



is in the S-configuration. In another embodiment are processes for the preparation of compounds of formula (I) wherein the stereo-center denoted with a "*" on the compound of formula (I) is in the R-configuration.

The present invention is further directed to processes for the preparation of compounds of formula (III)





wherein $R^J, R^K, R^{41P}, X, R^1, R^2, R^3, R^4, R^5, R^6, R^{12}, R^{13}, n$ and r are as herein defined. The compounds of the present invention are opioid receptor modulators, useful in the treatment of disorders mediated by at least one opioid receptor, including, but not limited to pain and gastrointestinal disorders.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, X is –
 $(CR^{15}R^{16})_{m-}$.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, m is an integer from 1 to 2. More preferably, m is 1.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R^{15} and R^{16} are each hydrogen.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R^1 is a-1.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, A-B is N-C.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R^{22} is hydrogen.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R^{23} is phenyl.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R^2 is selected from the group consisting of $-CH_2CH_2-$ and b-1.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R^3 is hydrogen.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R^4 is hydrogen.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, n is an integer from 0 to 1. More preferably, n is 1.

5 Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, r is 0.

Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R¹² is selected from the group consisting of hydrogen and methyl. More preferably, R¹² is hydrogen.

10 Embodiments of the present invention further include processes for the preparation of compounds of formula (III) wherein, preferably, R¹³ is selected from the group consisting of hydrogen and methyl. More preferably, R¹³ is hydrogen.

15 Additional embodiments of the present invention, include processes for the preparation of compounds wherein the substituents for one or more of the

variables defined herein (i.e. , R^J, R^K, R^{41P}, Pg¹, etc.) are independently selected to be any individual substituent or any subset of substituents selected from the complete list as defined herein.

20

Divalent substituents drawn or named herein are read into the base structure from left to right.

25 The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are hereinafter defined. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

30 Unless specified otherwise, the term "alkyl" refers to a saturated straight or branched chain consisting solely of 1-8 hydrogen substituted carbon atoms or a mixture of hydrogen substituted and fluoro substituted carbon atoms

wherein there may be 1-3 fluorine atoms on each carbon atom provided that the total number of fluorine atoms does not exceed 3 and the total number of carbon atoms does not exceed 8; preferably, 1-6 hydrogen substituted carbon atoms or a mixture of hydrogen substituted and fluoro substituted carbon atoms

5 wherein there may be 1-3 fluorine atoms on each carbon atom provided that the total number of fluorine atoms does not exceed 3 and the total number of carbon atoms does not exceed 6; and, most preferably, 1-4 hydrogen substituted carbon atoms or a mixture of hydrogen substituted and fluoro substituted carbon atoms wherein there may be 1-3 fluorine atoms on each

10 carbon atom provided that the total number of fluorine atoms does not exceed 3 and the total number of carbon atoms does not exceed 4. The term "alkoxy" refers to -O-alkyl, where alkyl is as defined *supra*. The term "hydroxyalkyl" refers to radicals wherein the alkyl chain terminates with a hydroxy radical of the formula HO-alkyl, where alkyl is as defined *supra*. Alkyl chains are

15 optionally substituted within the alkyl chain or on a terminal carbon atom.

The term "heterocyclyl" refers to a saturated or partially unsaturated ring having five or six members of which at least one member is a N, O or S atom and which optionally contains additional N, O or S atoms; a saturated or

20 partially unsaturated bicyclic ring having nine or ten members of which at least one member is a N, O or S atom and which optionally contains additional N, O, or S atoms. Examples include, and are not limited to, pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, imidazolanyl, imidazolidinyl, pyrazolanyl, pyrazolidinyl, piperidinyl, morpholinyl or piperazinyl.

25

The term "aryl" refers to a phenyl or naphthyl group.

The term "heteroaryl" refers to an aromatic monocyclic ring system containing five or six members of which at least one member is a N, O or S

30 atom and which optionally contains additional N, S or O atoms; an aromatic bicyclic ring having nine or ten members of which at least one member is a N, O or S atom and which optionally contains additional N, S or O atoms. Examples include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl,

thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, indazolyl, benzo[b]thienyl, quinoliny, isoquinolinyl or quinazolinyl.

5 Wherein the terms "aryl" and "heteroaryl" are used either alone or as part of a substituent term (Ex. aryloxy, heteroaryloxy, etc.) the said aryl or heteroaryl may be optionally substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, cyano, C₁₋₆alkyl, C₁₋₆alkoxy, and nitro; additionally, the aryl or heteroaryl may also be
10 optionally substituted with one phenyl group (which may optionally be substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, cyano, C₁₋₆alkyl, C₁₋₆alkoxy, and nitro), where the substituents on the aryl or heteroaryl group are not otherwise specified.

15 Whenever the term "alkyl", "aryl" or "heteroaryl" or either of their prefix roots appear in a name of a substituent (e.g., heteroaryl(C₁₋₆)alkyl) it shall be interpreted as including those limitations given above for "alkyl", "aryl" and "heteroaryl." Designated numbers of carbon atoms (e.g., C₁₋₆) shall refer
20 independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

25 The term "halogen" shall include iodine, bromine, chlorine and fluorine.

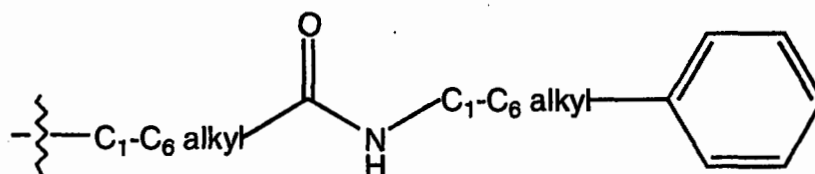
30 Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e.,

hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

An "Independently" selected substituent refers to a group of substituents, wherein the substituents may be different. Therefore, designated numbers of carbon atoms (e.g., C₁₋₈) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

5 It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily
10 synthesized by techniques known in the art as well as those methods set forth herein.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the
15 adjacent functionality toward the point of attachment. Thus, for example, a "phenylC₁-C₆alkylaminocarbonylC₁-C₆alkyl" substituent refers to a group of the formula



20

Abbreviations used in the specification, particularly the Schemes and Examples, are as follows:

Ac	=	Acetyl group (-C(O)-CH ₃)
Ac ₂ O	=	Acetic anhydride
Cbz or CBZ	=	Benzyloxy-carbonyl-

Cpd	=	Compound
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	=	Dichloromethane
DIPEA or DIEA	=	Diisopropylethylamine
DMF	=	N,N-Dimethylformamide
DPPE	=	1,2-Bis(diphenylphosphino)ethane
DPPF	=	1,1'-Bis(diphenylphosphino)ferrocene
DPPP	=	1,3-Bis(diphenylphosphino)propane
EDCI or EDC	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et ₂ O	=	Diethyl ether
EtOAc	=	Ethyl acetate
Fmoc	=	9-fluorenyl-methoxy-carbonyl-
HOAc	=	Acetic acid
HOBT	=	1-Hydroxybenzotriazole
Me		Methyl
MeOH	=	Methanol
MeO	=	Methoxy
MTBE	=	Methyl- <i>tert</i> -butyl ether
NaBH(OAc) ₃	=	Sodium triacetoxymethylborohydride
Pd-C	=	Palladium on Carbon Catalyst
Pd ₂ (OAc) ₂	=	Palladium(II)acetate
Pd ₂ (dba) ₃	=	Tris(dibenzylidene acetone)dipalladium(0)
Pd(PPh ₃) ₄	=	Tetrakis(triphenylphosphine)palladium (0)
Ph	=	Phenyl
P(Ph) ₃	=	Triphenylphosphine
PyBop	=	Benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate
PyBrop	=	Bromotri(pyrrolidino)phosphonium hexafluorophosphate

[Rh(cod)(R,R-DIPAMP)] ⁺ BF ₄ ⁻		(R,R)-(-)-Bis[(o-methoxyphenyl)(phenyl)phosphino]ethane(1,5-cyclo-octadiene)rhodium (I) tetrafluoroborate
rt or RT	=	Room temperature
t-BOC or Boc	=	<i>tert</i> -Butoxycarbonyl
TEA	=	Triethylamine
Tf	=	Trifluoromethyl-sulfonyl- (-SO ₂ -CF ₃)
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
Tyr	=	Tyrosine

As used herein, the term "pain" shall include centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, pain related to inflammation, progressive disease related pain, neuropathic pain, acute pain and chronic pain. Further, the term "**chronic pain**" shall include neuropathic pain conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes and cluster or migraine headaches.

As used herein, the term "**gastrointestinal disorder**" shall include diarrheic syndromes, motility disorders such as diarrhea-predominant, constipation-predominant, alternating irritable bowel syndrome, post-operative ileus and constipation, and inflammatory bowel disease. Further, the term "**inflammatory bowel disease**" shall include ulcerative colitis and Crohn's disease.

The term "**subject**" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "**therapeutically effective amount**" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a

researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

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 combinations of the specified ingredients in the specified amounts.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "**about**". It is understood that whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value.

As used herein, unless otherwise noted, the term "**aprotic solvent**" shall mean any solvent that does not yield a proton. Suitable examples include, but are not limited to DMF, dioxane, THF, acetonitrile, pyridine, dichloroethane, dichloromethane, MTBE, toluene, and the like.

One skilled in the art will recognize that wherein a reaction step of the present invention may be carried out in a variety of solvents or solvent systems, said reaction step may also be carried out in a mixture of the suitable solvents or solvent systems.

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt

formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

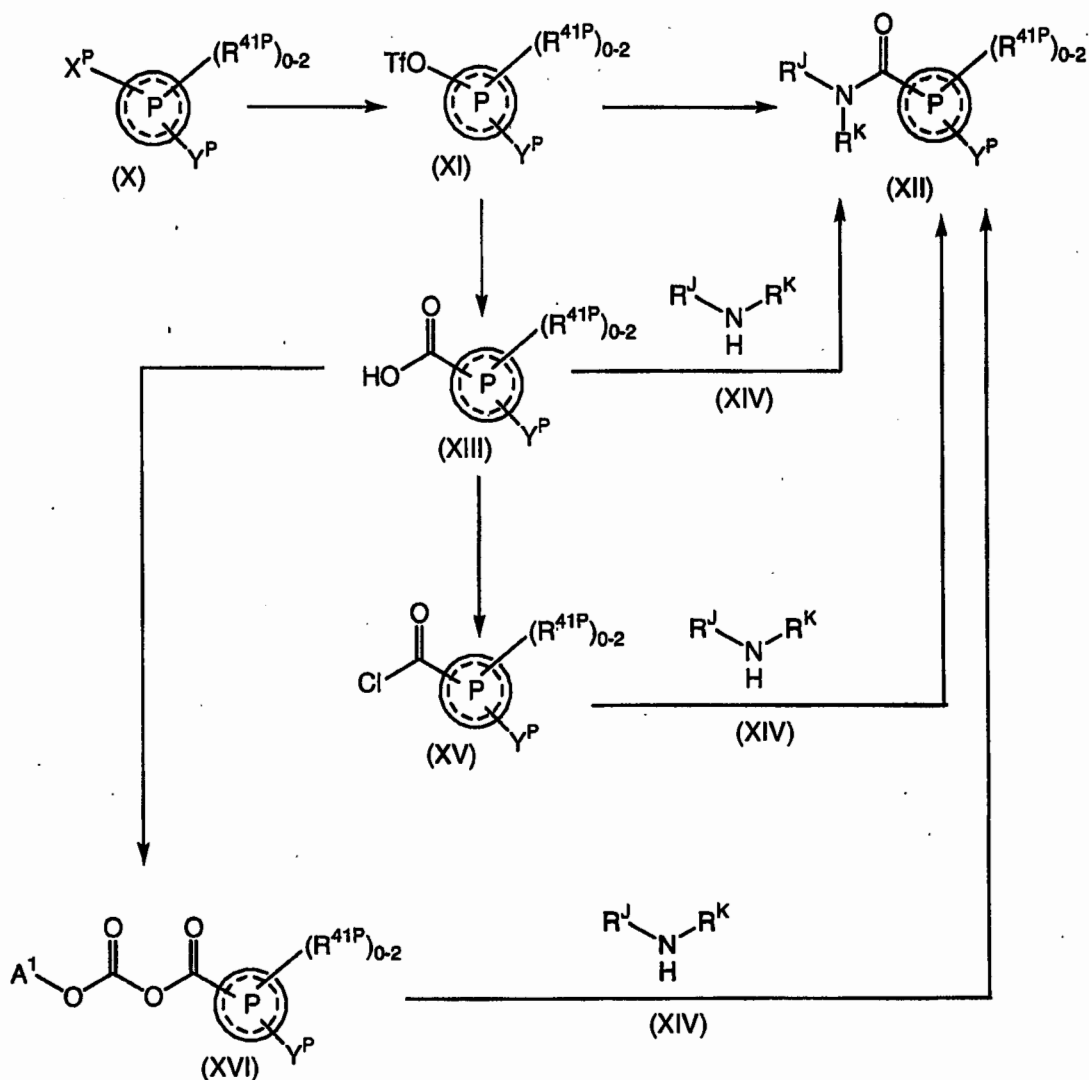
During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

As used herein, unless otherwise noted, the term "**nitrogen protecting group**" shall mean a group which may be attached to a nitrogen atom to protect said nitrogen atom from participating in a reaction and which may be readily removed following the reaction. Suitable nitrogen protecting groups include, but are not limited to carbamates – groups of the formula $-C(O)O-R$ wherein R is for example methyl, ethyl, t-butyl, benzyl, phenylethyl, $CH_2=CH-CH_2-$, and the like; amides – groups of the formula $-C(O)-R'$ wherein R' is for example methyl, phenyl, trifluoromethyl, and the like; N-sulfonyl derivatives – groups of the formula $-SO_2-R''$ wherein R'' is for example tolyl, phenyl, trifluoromethyl, 2,2,5,7,8-pentamethylchroman-6-yl-, 2,3,6-trimethyl-4-methoxybenzene, and the like. Other suitable nitrogen protecting groups may be found in texts such as T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

For use in medicine, the salts of the compounds of this invention refer to nontoxic pharmaceutically acceptable salts.

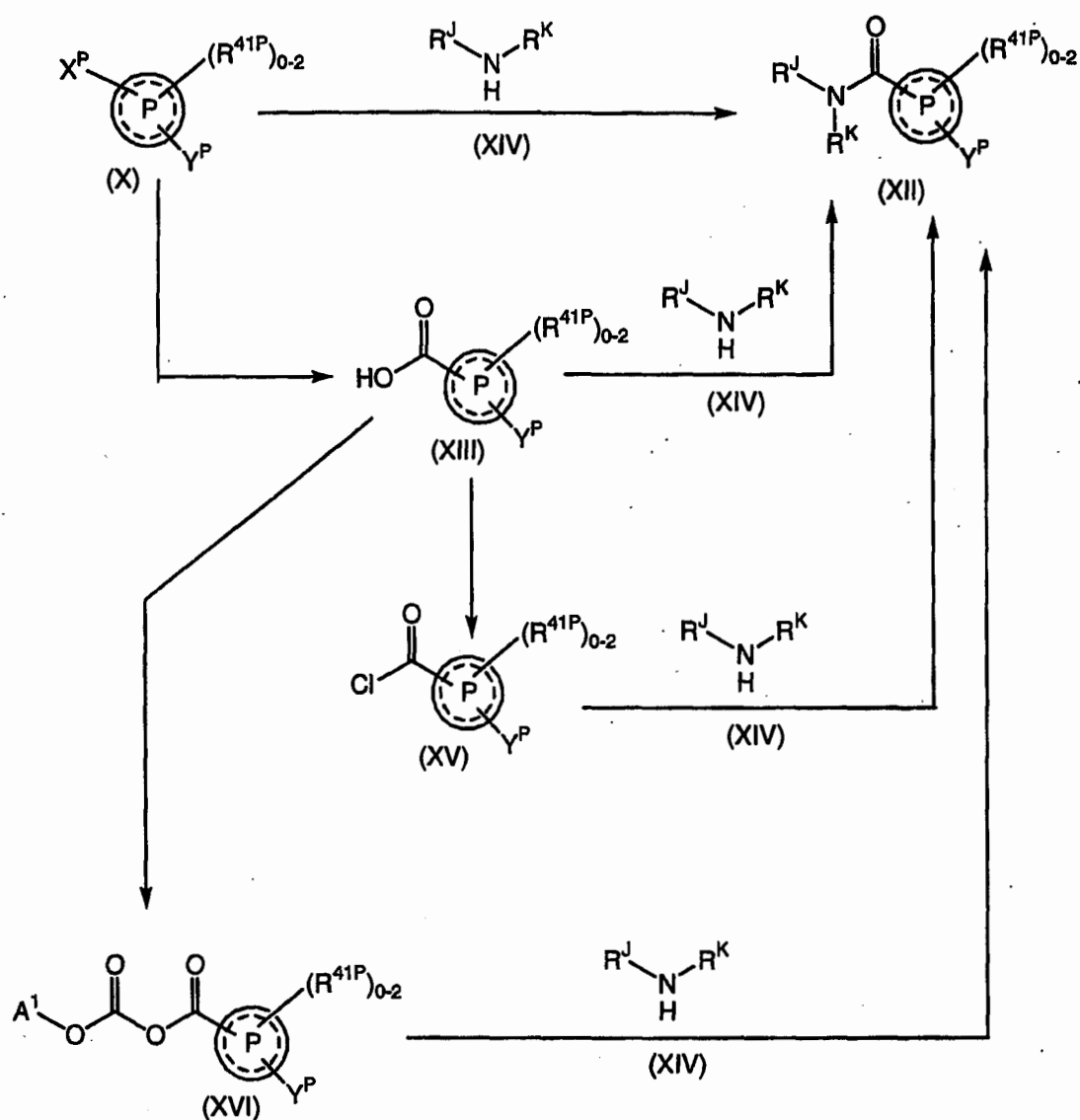
The present invention is directed to processes for the preparation of compounds of formula (I) as outlined in Scheme 1 below.

- 5 STEP 1: Preparation of Compounds of Formula (XII), wherein X is -OH and Y is selected from Br or Cl



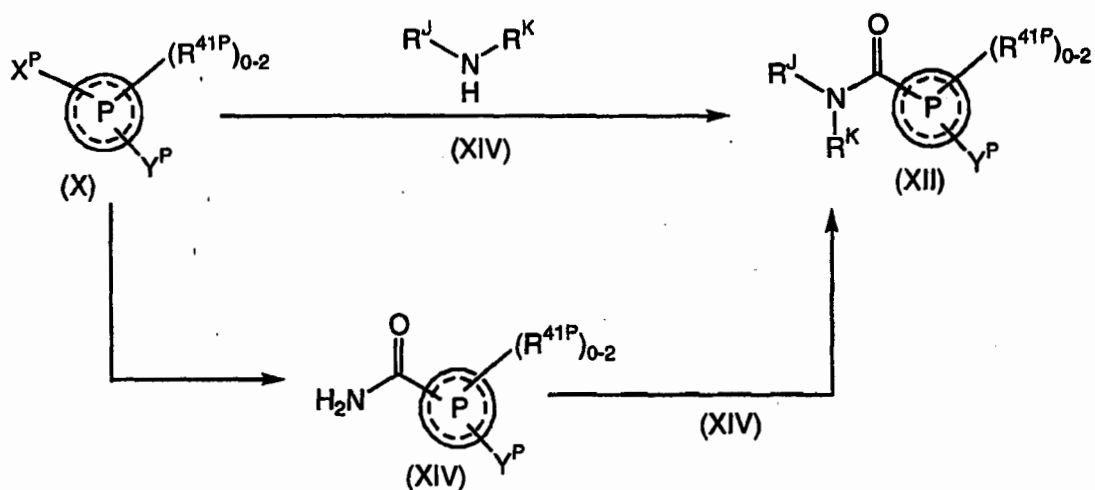
STEP 1: Preparation of Compounds of Formula (XII), wherein X is -OC(O)-C₁-

- 10 alkyl and Y is selected from Br, Cl or I

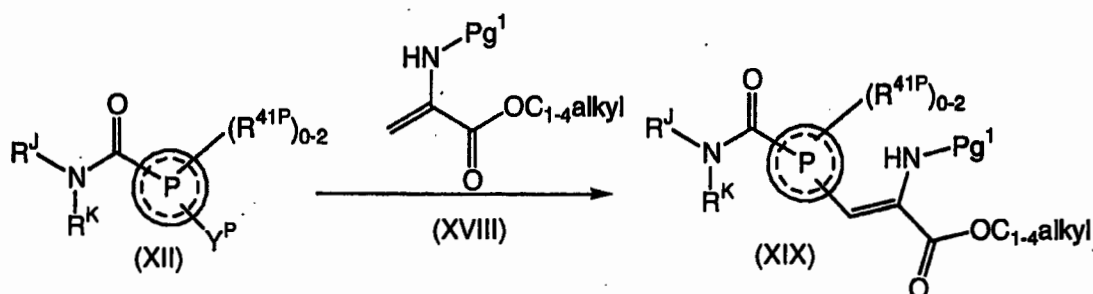


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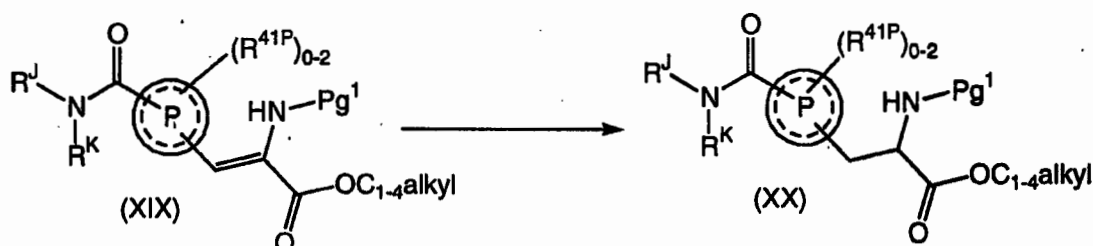
STEP 1: Preparation of Compounds of Formula (XII), wherein X is -CN and Y is selected from Br, Cl or I



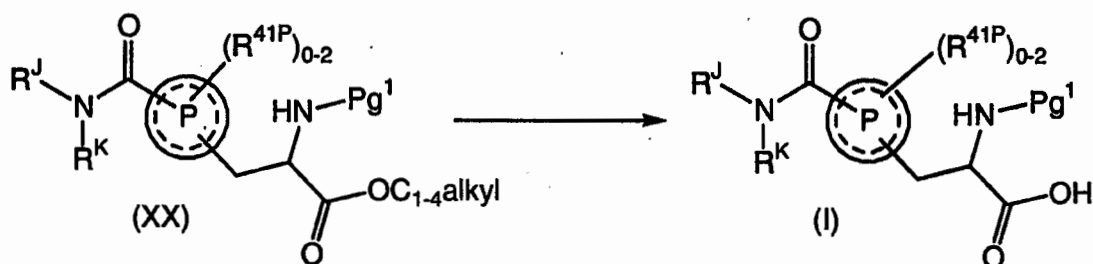
STEP 2: Preparation of Compound of Formula (XIX)



5 STEP 3: Preparation of Compounds of Formula (XX)



STEP 4: Preparation of Compounds of Formula (I)



10

Scheme 1

STEP 1: Wherein X is OH and Y is selected from Br or Cl

Accordingly, a suitably substituted compound of formula (X), wherein X^P is OH and wherein Y^P is Br or Cl, preferably Y^P is Br, a known compound or
 15 compound prepared by known methods; is reacted with a triflating reagent such as triflic anhydride, N-phenyltrifluoromethanesulfonimide, and the like; in the presence of an organic or inorganic base such as pyridine, TEA, DIPEA, K₃PO₄, K₂CO₃, and the like; optionally in an organic solvent such as DCM, chloroform, THF, and the like; to yield the corresponding compound of formula
 20 (XI).

The compound of formula (XI) is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* (2003), 5(23), pp4269-4272) and a suitably substituted amine, a compound of formula $\text{NR}^{\text{J}}\text{R}^{\text{K}}$ (a compound of formula (XIV)) or when R^{J} and R^{K} are each hydrogen, with a suitable source of ammonia such as HMDS, ammonia gas, and the like; in the presence of a palladium catalyst such as PdCl_2 , $\text{Pd}_2(\text{OAc})_2$, and the like, in combination with a suitable ligand, such as DPPP, DPPF, $\text{P}(\text{Ph})_3$, and the like; or in the presence of a palladium:ligand complex such as $\text{Pd}(\text{PPh}_3)_4$, and the like; in an organic solvent such as DMF, THF, dioxane, and the like, preferably DMF; at a temperature in the range of from about 50°C to about 160°C , preferably at a temperature in the range of from about 60°C to about 120°C ; to yield the corresponding compound of formula (XII).

Alternatively, the compound of formula (XI) is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K_2CO_3 , Na_2CO_3 , and the like, in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about 160°C , preferably at a temperature in the range of from about 60°C to about 80°C ; to yield the corresponding compound of formula (XIII).

The compound of formula (XIII) is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^{J} and R^{K} are each hydrogen, with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBT, PyBop, PyBrop, and the like; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or an amount of the compound of formula (XIV) or source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XII).

Alternatively, the compound of formula (XI) is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Gogglamani, *Org. Lett.* (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as
5 K_2CO_3 , Na_2CO_3 , and the like, in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about 160°C , preferably at a temperature in the range of from about 60°C to about 80°C ; to yield the corresponding compound of formula (XIII).

The compound of formula (XIII) is reacted with a suitably source of
10 chlorine such as thionyl chloride, PCl_3 , PCl_5 , oxalyl chloride, oxalyl chloride in DMF, and the like; in an organic solvent such as DCM, chloroform, and the like, preferably at a temperature greater than about room temperature, more preferably at a temperature in the range of about 35°C to about 60°C ; to yield the corresponding compound of formula (XV).

15 The compound of formula (XV) is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as ammonium chloride, NH_4OH , HMDS, ammonia gas, and the like, preferably ammonium chloride; preferably in the presence of an
20 organic base such as TEA, DIPEA, pyridine, the like, or an amount of the compound of formula (XIV) or source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XII).

25

Alternatively, the compound of formula (XIII) is reacted with C_{1-4} alkyl-chloroformate, preferably, methylchloroformate; in the presence of a organic base such as TEA, DIPEA, pyridine and the like; preferably at a temperature less than about room temperature, more preferably at a temperature in the
30 range of from about 0°C ; in an organic solvent such as DMF, DCM, chloroform, THF, and the like; to yield the corresponding compound of formula (XVI), wherein A^1 is the corresponding C_{1-4} alkyl, preferably methyl.

The compound of formula (XVI) is reacted with a suitably substituted compound of formula (XIV) or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as NH_4OH , HMDS, ammonia gas, and the like, preferably NH_4OH ; in the presence of a palladium catalyst such $PdCl_2$, $Pd_2(OAc)_2$, and the like, in combination with a suitable ligand, such DPPP, DPPF, $P(Ph)_3$, and the like; or in the presence of a palladium:ligand complex such as $Pd(PPh_3)_4$, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XII).

10

One skilled in the art will further recognize that the compound of formula (XI) may be reacted according to known methods, to yield the corresponding compound of formula (X) wherein X^P is $-C(O)-OC_{1-4}alkyl$ or CN.

15 STEP 1: Wherein X is $-C(O)-OC_{1-4}alkyl$ and wherein Y^P is Br, Cl or I

Alternatively, a suitably substituted compound of formula (X), wherein X^P is $-C(O)-OC_{1-4}alkyl$ and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as NH_4OH , HMDS, ammonia gas, and the like; at a temperature greater than room temperature, preferably at about reflux temperature; to yield the corresponding compound of formula (XII).

Alternatively, a suitably substituted compound of formula (X), wherein X^P is $-C(O)-OC_{1-4}alkyl$ and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as NH_4OH , HMDS, ammonia gas, and the like; in the presence of an activating agent such as trimethylaluminum, triisopropylaluminum, and the like; in an aprotic organic solvent such as THF, dioxane, toluene, DCM, and the like; preferably at a temperature in the range of

about 0°C to about reflux temperature; to yield the corresponding compound of formula (XII).

Alternatively, a suitably substituted compound of formula (X), wherein X^P is $-\text{C}(\text{O})-\text{OC}_{1-4}\text{alkyl}$ and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is hydrolyzed according to known methods, for example by reacting with a base such as NaOH, LiOH, KOH, and the like, or by reacting with an acid such as HCl, H_2SO_4 , and the like; preferably, the compound of formula (X) is reacted with an acid at a temperature greater than about room temperature, preferably at a temperature in the range of from about 60° to about 120°C, more preferably at a temperature of about 100°C; to yield the corresponding compound of formula (XIII).

The compound of formula (XIII) is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBt, PyBop, PyBrop, and the like; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or in the presence of an amount of the compound of formula (XIV) or source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like, to yield the corresponding compound of formula (XII).

Alternatively, the compound of formula (X), wherein X^P is $-\text{C}(\text{O})-\text{OC}_{1-4}\text{alkyl}$ and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, Org. Lett. (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K_2CO_3 , Na_2CO_3 , and the like, in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a

temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XIII).

The compound of formula (XIII) is reacted with a suitably source of chlorine such as thionyl chloride, PCl_3 , PCl_5 , oxalyl chloride, oxalyl chloride in DMF, and the like; in an organic solvent such as DCM, chloroform, and the like, preferably at a temperature greater than about room temperature, more preferably at a temperature in the range of about 35°C to about 60°C, to yield the corresponding compound of formula (XV).

The compound of formula (XV) is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as ammonium chloride, NH_4OH , HMDS, ammonia gas, and the like, preferably ammonium chloride; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or in the presence of an amount of the compound of formula (XIV) or source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XII).

Alternatively, the compound of formula (X), wherein X^P is $-\text{C}(\text{O})-\text{OC}_{1-4}\text{alkyl}$ and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, Org. Lett. (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K_2CO_3 , Na_2CO_3 , and the like, in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XIII).

Alternatively, the compound of formula (XIII) is reacted with $\text{C}_{1-4}\text{alkyl-chloroformate}$, preferably, methylchloroformate; in the presence of a organic base such as TEA, DIPEA, pyridine and the like; preferably at a temperature less than about room temperature, more preferably at a temperature of about

0°C; in an organic solvent such as DMF, DCM, chloroform, THF, and the like; to yield the corresponding compound of formula (XVI), wherein A¹ is the corresponding C₁₋₄alkyl, preferably methyl.

5 The compound of formula (XVI) is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as NH₄OH, HMDS, ammonia gas, and the like, preferably NH₄OH; in the presence of a palladium catalyst such PdCl₂, Pd₂(OAc)₂, and the like, in combination with a ligand, such DPPP, DPPF, P(Ph)₃, and the like; or in
10 the presence of a palladium:ligand complex such as Pd(PPh₃)₄, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XII).

15 STEP 1: Wherein X is -CN and wherein Y^P is Br, Cl or I

Alternatively, a suitably substituted compound of formula (X), wherein X^P is CN and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known
20 methods, according to known methods (for example as described in Parris, C.L., Org. Syn. Coll., (1973), 5, p73; Lin, S., Synthesis, (April 1978), p.330; Murahashi, S., Takeshi Naota, T., and Eiichiro Saito, E., JACS, (1986), 108(24), p7846), to yield the corresponding compound of formula (XII).

25 Alternatively, a suitably substituted compound of formula (X), wherein X^P is CN and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with an acid such as concentrated sulfuric acid, and the like; at a temperature greater than about room temperature, preferably at reflux temperature; to yield the corresponding
30 compound of formula (XVI).

Alternatively, a suitably substituted compound of formula (X), wherein X^P is CN and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with an inorganic base such

as NaOH, KOH, and the like; at a temperature greater than about room temperature, preferably at about reflux temperature; to yield the corresponding compound of formula (XVI).

- 5 The compound of formula (XVI) is reacted according to known methods, for example, by alkylating in the presence of a base, to yield the corresponding compound of formula (XII).

STEP 2:

- 10 The compound of formula (XII) is reacted with a suitably substituted compound of formula (XVII), wherein Pg^1 is a suitable nitrogen protecting group such as Boc, Cbz, Fmoc, acetyl, and the like, preferably Pg^1 is Boc, a known compound or compound prepared by known methods; in the presence of palladium catalyst such as $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2$, and the like, preferably $Pd_2(dba)_3$; and preferably in the presence of a phosphorous ligand such as P(o-toluenes)₃, P(Ph)₃, P(t-butyl)₃, DPPE, and the like, preferably P(t-butyl)₃ or P(o-toluenes)₃; or in the presence of a palladium:ligand complex such as $Pd(PPh_3)_4$, and the like; in the presence of an organic or inorganic base such as dicyclohexylmethylamine, Na_2CO_3 , K_2CO_3 , TEA, DIPEA, pyridine, and the like, preferably TEA; in an organic solvent such as DMF, dioxane, and the like; at a
15 temperature greater than about room temperature, preferably at a temperature in the range of about 60°C to about 120°C; to yield the corresponding compound of formula (XIX).
20

STEP 3:

- 25 The compound of formula (XIX) is hydrogenated according to known methods; for example by reacting with hydrogen or a source of hydrogen (such as cyclohexadiene, and the like); in the presence of a catalyst such as platinum oxide, palladium on carbon, nickel, $ClRh(PPh_3)_3$, $RuCl_2$, and the like, preferably palladium on carbon; in an organic solvent such as methanol, ethanol, THF,
30 ethyl acetate, and the like, preferably methanol; at a temperature greater than room temperature, preferably at a temperature in the range of about 60°C to about 120°C, to yield the corresponding compound of formula (XX).

One skilled in the art will recognize that the compound of formula (XIX) may be optionally reacted in the presence of a chiral catalyst, to yield the corresponding compound of formula (XX), wherein one stereo-isomer is present in an enantiomeric excess.

5

STEP 4:

The compound of formula (XX) is reacted with an aqueous base such as NaOH, LiOH, KOH, and the like; in an organic solvent such as methanol, THF, ethanol, and the like; to yield the corresponding compound of formula (I).

10

In an embodiment, the present invention is directed to processes for the preparation of compounds of formula (Ic).

In an embodiment, the present invention is directed to processes for the preparation of a compound of formula (Ib), a compound of formula (I) wherein



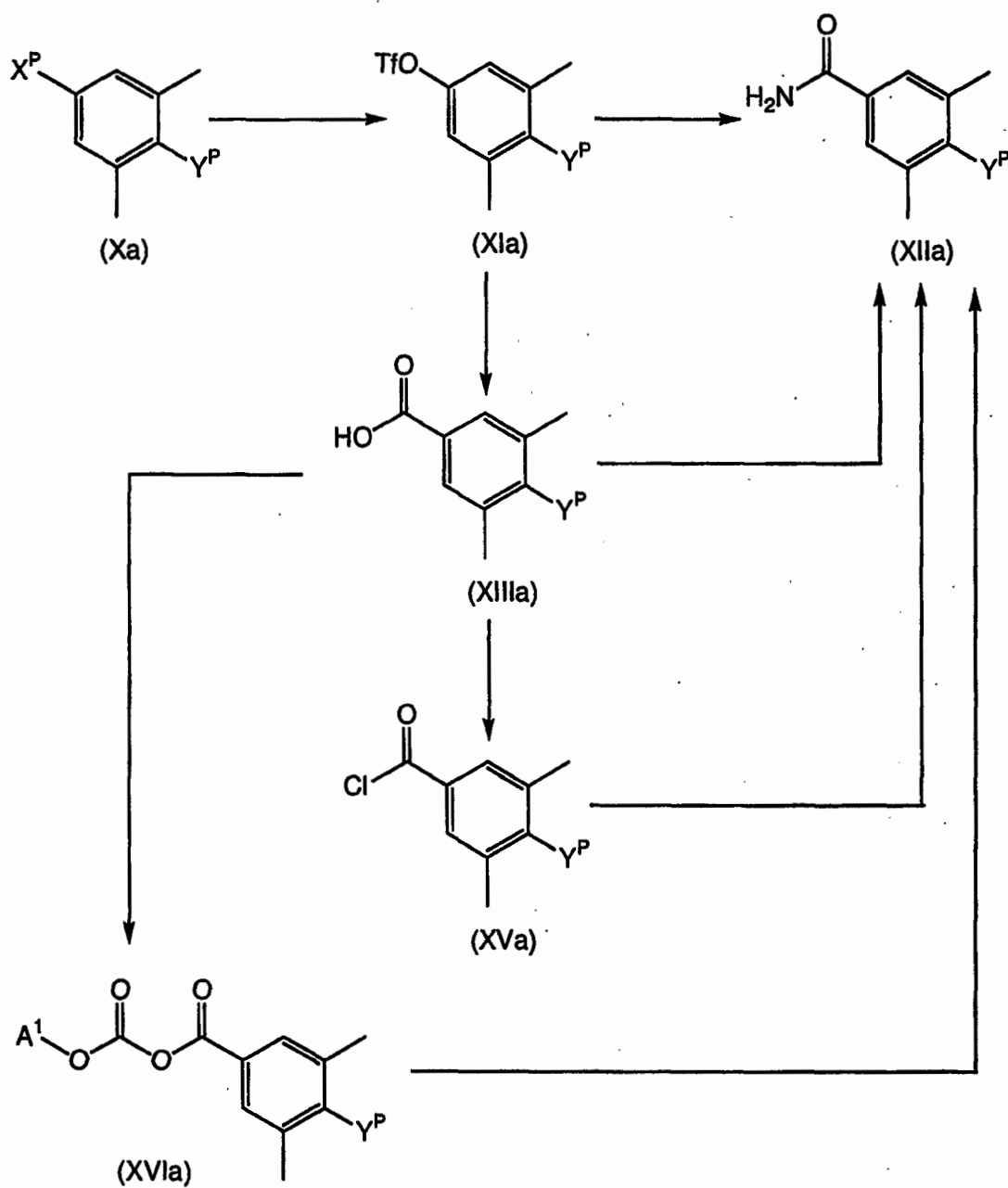
is phenyl; R^J and R^K are each hydrogen; the phenyl ring is further substituted with two R^{41P} groups, which are each methyl and Pg^1 is Boc, also known as 2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionic acid, as described in Scheme 1 above.

20

The present invention is further directed to processes for the preparation of the compound of formula (Ia) as outlined in Scheme 2 below.

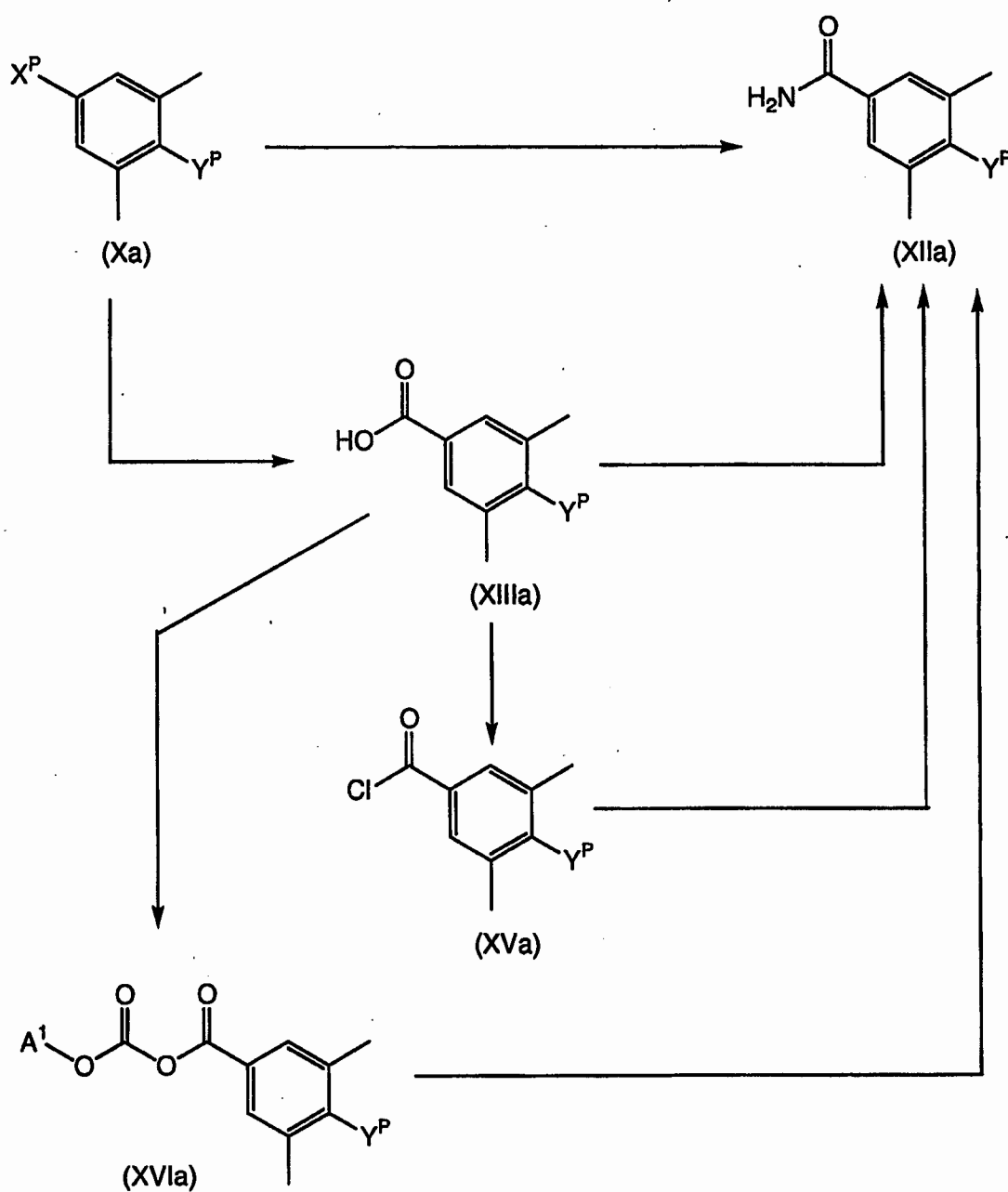
STEP 1a: Preparation of the Compound of Formula (XIa), wherein X is -OH

25 and Y is selected from Br or Cl



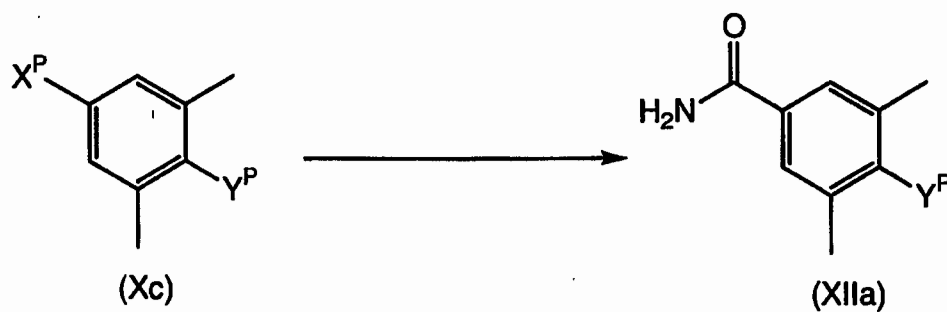
or

STEP 1a: Preparation of the Compound of Formula (XIIa), wherein X is –OC(O)-C₁₋₄alkyl and Y is selected from Br, Cl or I

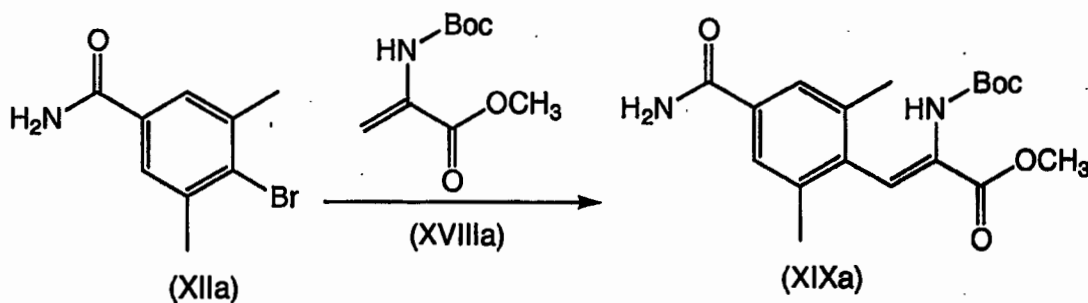


or

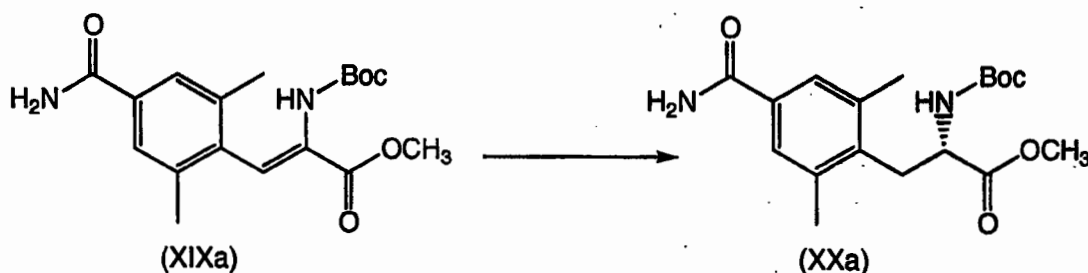
STEP 1a: Preparation of the Compound of Formula (XIIa), wherein X is $-CN$ and Y is selected from Br, Cl or I



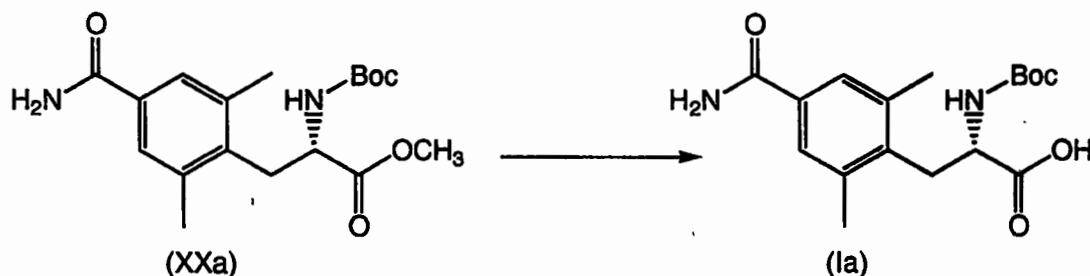
STEP 2a: Preparation of the Compound of Formula (XIXa)



STEP 3a: Preparation of the Compound of Formula (XXa)



5 STEP 4a: Preparation of the Compound of Formula (Ia)



Scheme 2

STEP1a: Wherein X is -OH and Y is selected from Br or Cl

- 10 Accordingly, a suitably substituted compound of formula (Xa), wherein X^P is OH and wherein Y^P is Br or Cl, preferably Y^P is Br, a known compound or compound prepared by known methods, is reacted with a triflating reagent such as triflic anhydride, N-phenyltrifluoromethanesulfonimide, and the like; in the presence of an organic or inorganic base such as pyridine, TEA, DIPEA,
- 15 K_3PO_4 , K_2CO_3 , and the like, preferably pyridine; optionally in an organic solvent such as DCM, chloroform, THF, and the like, to yield the corresponding compound of formula (XIa).

The compound of formula (XIa) is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with $HCOONa$ (see

for example, S. Cacchi, G. Fabrizi, A. Goggiamani, Org. Lett. (2003), 5(23), pp4269-4272) and a suitable source of ammonia such as HMDS, ammonia gas, and the like; in the presence of a palladium catalyst such PdCl₂, Pd₂(OAc)₂, and the like, in combination with a ligand, such DPPP, DPPF, P(Ph)₃, and the like; or in the presence of a palladium:ligand complex such as Pd(PPh₃)₄, and the like; in an organic solvent such as DMF, THF, dioxane, and the like, preferably DMF; at a temperature in the range of from about 50°C to about 160°C; preferably at a temperature in the range of from about 60°C to about 120°C; to yield the corresponding compound of formula (XIa).

10

Alternatively, the compound of formula (XIa) is reacted with carbon monoxide or a source of carbon monoxide such as Ac₂O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, Org. Lett. (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K₂CO₃, Na₂CO₃, and the like; in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XIIIa).

The compound of formula (XIIIa) is reacted with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBT, PyBop, PyBrop, and the like; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or in the presence of an amount of the source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like, to yield the corresponding compound of formula (XIa).

Alternatively, the compound of formula (XIa) is reacted with carbon monoxide or a source of carbon monoxide such as Ac₂O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, Org. Lett. (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K₂CO₃, Na₂CO₃, and the like; in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about

160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XIIIa).

The compound of formula (XIIIa) is reacted with a suitable source of chlorine such as thionyl chloride, PCl_3 , PCl_5 , oxalyl chloride, oxalyl chloride in
5 DMF, and the like; in an organic solvent such as DCM, chloroform, and the like; preferably at a temperature greater than about room temperature, more preferably at a temperature in the range of about 35°C to about 60°C; to yield the corresponding compound of formula (XVa).

The compound of formula (XVa) is reacted with a suitable source of
10 ammonia such as ammonium chloride, NH_4OH , HMDS, ammonia gas, and the like, preferably ammonium chloride; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or in the presence of an amount of the source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the
15 like; to yield the corresponding compound of formula (XIIa).

Alternatively, the compound of formula (XIa) is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with HCOONa (see for example, S. Cacchi, G. Fabrizi, A. Goggiani, *Org. Lett.*
20 (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K_2CO_3 , Na_2CO_3 , and the like; in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XIIIa).

25 Alternatively, the compound of formula (XIIIa) is reacted with C_{1-4} alkylchloroformate, preferably, methylchloroformate; in the presence of an organic base such as TEA, DIPEA, pyridine and the like; preferably at a temperature less than about room temperature, more preferably at a temperature of about 0°C; in an organic solvent such as DMF, DCM, chloroform, THF, and the like;
30 to yield the corresponding compound of formula (XVIa), wherein A^1 is the corresponding C_{1-4} alkyl, preferably methyl.

The compound of formula (XVIa) is reacted with a suitable source of ammonia such as NH_4OH , HMDS, ammonia gas, and the like, preferably

NH₄OH; in the presence of a palladium catalyst such PdCl₂, Pd₂(OAc)₂, and the like, in combination with a ligand, such DPPP, DPPF, P(Ph)₃, and the like; or in the presence of a palladium:ligand complex such as Pd(PPh₃)₄, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XIla).

One skilled in the art will further recognize that the compound of formula (XIa) may be reacted according to known methods, to yield the corresponding compound of formula (Xa) wherein X^P is -C(O)-OC₁₋₄alkyl or CN.

STEP 1a: Wherein X is -C(O)-OC₁₋₄alkyl and wherein Y^P is Br, Cl or I

Alternatively, a suitably substituted compound of formula (Xa), wherein X^P is -C(O)-OC₁₋₄alkyl and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with a suitable source of ammonia such as NH₄OH, HMDS, ammonia gas, and the like; at a temperature greater than room temperature, preferably at about reflux temperature; to yield the corresponding compound of formula (XIIa).

Alternatively, a suitably substituted compound of formula (Xa), wherein X^P is -C(O)-OC₁₋₄alkyl and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with a suitable source of ammonia such as NH₄OH, HMDS, ammonia gas, and the like; in the presence of a activating agent such as trimethylaluminum, triisopropylaluminum, and the like; in an aprotic organic solvent such as THF, dioxane, toluene, DCM, and the like; preferably, at a temperature in the range of about 0°C to reflux temperature; to yield the corresponding compound of formula (XIIa).

Alternatively, a suitably substituted compound of formula (Xa), wherein X^P is -C(O)-OC₁₋₄alkyl and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is hydrolyzed according to known methods; for example by reacting with a base such as NaOH, LiOH, KOH, and the like, or by reacting with an acid such as HCl, H₂SO₄, and the like;

preferably, the compound of formula (Xa) is reacted with an acid at a temperature greater than about room temperature, preferably at a temperature in the range of from about 60° to about 120°C, preferably at a temperature of about 100°C; to yield the corresponding compound of formula (XIIIa).

- 5 The compound of formula (XIIIa) is reacted with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBT, PyBop, PyBrop, and the like; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or in the presence of an amount of the source of ammonia
10 sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like, to yield the corresponding compound of formula (XIIa).

- Alternatively, the compound of formula (Xa), wherein X^P is $-C(O)-OC_{1-4}$
15 alkyl and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with $HCOONa$ (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, Org. Lett. (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K_2CO_3 , Na_2CO_3 ,
20 and the like; in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to about 80°C; to yield the corresponding compound of formula (XIIIa).

- The compound of formula (XIIIa) is reacted with a suitable source of
25 chlorine such as thionyl chloride, PCl_3 , PCl_5 , oxalyl chloride, and the like; in an organic solvent such as DCM, chloroform, and the like; preferably at a temperature greater than about room temperature, more preferably at a temperature in the range of about 35°C to about 60°C, to yield the corresponding compound of formula (XVa).

- 30 The compound of formula (XVa) is reacted with a suitable source of ammonia such as ammonium chloride, NH_4OH , HMDS, ammonia gas, and the like, preferably ammonium chloride; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like; or in the presence of an amount

of the source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XIla).

5 Alternatively, the compound of formula (Xa), wherein X^P is $-C(O)-OC_{1-4}$ alkyl and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with carbon monoxide or a source of carbon monoxide such as Ac_2O in combination with $HCOONa$ (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* (2003), 5(23), pp4269-4272); in the presence of an inorganic base such as K_2CO_3 , Na_2CO_3 , and the like; in an organic solvent such as DMF, dioxane, THF, and the like; at a temperature in the range of from about $50^\circ C$ to about $160^\circ C$, preferably at a temperature in the range of from about $60^\circ C$ to about $80^\circ C$; to yield the corresponding compound of formula (XIIIa).

15 Alternatively, the compound of formula (XIIIa) is reacted with C_{1-4} alkylchloroformate, preferably, methylchloroformate; in the presence of a organic base such as TEA, DIPEA, pyridine and the like; preferably at a temperature less than about room temperature, more preferably at a temperature of about $0^\circ C$; in an organic solvent such as DMF, DCM, chloroform, THF, and the like; to yield the corresponding compound of formula (XVIa), wherein A^1 is the corresponding C_{1-4} alkyl, preferably methyl.

20 The compound of formula (XVIa) is reacted with a suitable source of ammonia such as NH_4OH , HMDS, ammonia gas, and the like, preferably NH_4OH ; in the presence of a palladium catalyst such $PdCl_2$, $Pd_2(OAc)_2$, and the like, in combination with a ligand, such DPPP, DPPF, $P(Ph)_3$, and the like, or in the presence of a palladium:ligand complex such as $Pd(PPh_3)_4$, and the like; at a temperature in the range of from about $50^\circ C$ to about $160^\circ C$, preferably at a temperature in the range of from about $60^\circ C$ to about $80^\circ C$; to yield the corresponding compound of formula (XIIa).

30

STEP 1a: Wherein X is $-CN$ and wherein Y^P is Br, Cl or I

Alternatively, a suitably substituted compound of formula (Xa), wherein X^P is CN and wherein Y^P is selected from Br, Cl or I, a known compound or

compound prepared by known methods, is reacted with an acid such as concentrated sulfuric acid, and the like; at a temperature greater than about room temperature, preferably at about reflux temperature; to yield the corresponding compound of formula (XVIa).

- 5 Alternatively, a suitably substituted compound of formula (Xa), wherein X^P is CN and wherein Y^P is selected from Br, Cl or I, a known compound or compound prepared by known methods, is reacted with an inorganic base such as NaOH, KOH, and the like; at a temperature greater than about room temperature, preferably at about reflux temperature; to yield the corresponding
10 compound of formula (XVIa).

- Preferably, a suitably substituted compound of formula (Xa), a known compound or compound prepared by known methods, is reacted with a triflating reagent such as triflic anhydride, N-phenyltrifluoromethanesulfonimide,
15 and the like, preferably triflic anhydride; in the presence of an organic or inorganic base such as pyridine, TEA, DIPEA, K_3PO_4 , K_2CO_3 , and the like, preferably pyridine; optionally in an organic solvent such as DCM, chloroform, THF, and the like; to yield the corresponding compound of formula (XIa).

- The compound of formula (XIa) is reacted with carbon monoxide or a
20 source of carbon monoxide such as Ac_2O in combination with $HCOONa$ (see for example, S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* (2003), 5(23), pp4269-4272) and a suitable source of ammonia such as HMDS, ammonia gas, and the like; preferably the compound of formula (XIa) is reacted with carbon monoxide and HMDS; in the presence of a palladium catalyst such
25 $PdCl_2$, $Pd_2(OAc)_2$, and the like, in combination with a suitable ligand, such as DPPP, DPPF, $P(Ph)_3$, and the like; or in the presence of a palladium:ligand complex such as $Pd(PPh_3)_4$, and the like; preferably, in the presence of $PdCl_2$ in combination with DPPP; at a temperature in the range of from about 50°C to about 160°C, preferably at a temperature in the range of from about 60°C to
30 about 120°C, more preferably, at a temperature of about 100°C; in an organic solvent such as DMF, THF, dioxane, and the like, preferably, in DMF; to yield the corresponding compound of formula (XII).

STEP 2a:

The compound of formula (XIIa) is reacted with a suitably substituted compound of formula (XVIIIa), a known compound or compound prepared by known methods, in the presence of palladium catalyst such as $\text{Pd}_2(\text{dba})_3$, $\text{Pd}(\text{OAc})_2$, PdCl_2 , and the like, preferably $\text{Pd}_2(\text{dba})_3$; and preferably in the presence of a phosphorous ligand such as $\text{P}(\text{o-toluene})_3$, $\text{P}(\text{Ph})_3$, $\text{P}(\text{t-butyl})_3$, DPPE, and the like, preferably $\text{P}(\text{o-toluene})_3$; or in the presence of a palladium:ligand complex such as $\text{Pd}(\text{PPh}_3)_4$, and the like; in the presence of an organic or inorganic base such as dicyclohexylmethylamine, Na_2CO_3 , K_2CO_3 , TEA, DIPEA, pyridine, and the like, preferably TEA; in an organic solvent such as DMF, dioxane, and the like, preferably DMF; at a temperature greater than about room temperature, preferably at a temperature in the range of about 60°C to about 120°C , preferably at about 120°C ; to yield the corresponding compound of formula (XIXa).

15

STEP 3a:

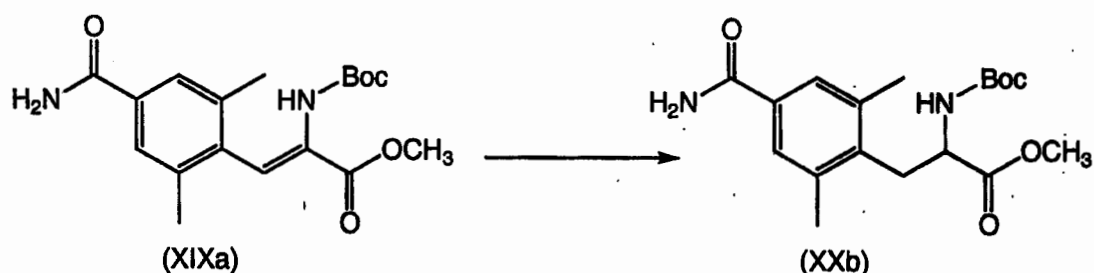
The compound of formula (XIXa) is reacted with hydrogen gas, at a pressure sufficient to hydrogenate, preferably at a pressure greater than about 500 psi, more preferably, at a pressure greater than about 800 psi, more preferably still, at a pressure about 1000 psi; in the presence of a suitable chiral catalyst such as $[\text{Rh}(\text{cod})(\text{R,R-DIPAMP})]^+\text{BF}_4^-$, $[\text{Rh}(\text{cod})(\text{R,R-DIPAMP})]^+\text{SO}_2\text{CF}_3^-$, and the like; wherein the chiral catalyst is preferably present in an amount greater than about 0.01 equivalents, more preferably, in an amount of about 0.04 equivalents; at a temperature greater than about room temperature, preferably at a temperature in the range of about 60°C to about 100°C , more preferably, at a temperature of about 60°C ; in an organic solvent such as methanol, ethanol, THF, ethyl acetate, and the like, preferably methanol; preferably not under vacuum; to yield the corresponding compound of formula (XXa), wherein the S-enantiomer is present in an enantiomeric excess of greater than about 80%, preferably, in an enantiomeric excess of greater than about 90%, more preferably, in an enantiomeric excess of greater than about 95%, more preferably, in an enantiomeric excess of greater than

30

about 98%, most preferably, in an enantiomeric excess of greater than about 99%.

One skilled in the art will recognize that if the chiral catalyst is oxygen sensitive, then the hydrogenation reaction vessel is purged with an inert gas such as argon, nitrogen, and the like, prior to charging the vessel with the
5 oxygen sensitive catalyst reagents and hydrogen gas.

One skilled in the art will recognize that the compound of formula (XIXa) may be optionally reacted to yield the corresponding racemic compound of
10 formula (XXb), as outlined in the scheme below,



by hydrogenating the compound of formula (XIXa) according to known methods, for example, by reacting with hydrogen or a source of hydrogen (such as cyclohexadiene, and the like); in the presence of a catalyst such as platinum oxide, palladium on carbon, nickel, $\text{CIRh(PPh}_3)_3$, RuCl_2 , and the like, preferably
15 palladium on carbon; in a solvent such as methanol, ethanol, THF, ethyl acetate, and the like; in an organic solvent such as methanol, ethanol, THF, ethyl acetate, and the like, preferably methanol; at a temperature greater than room temperature, preferably at a temperature in the range of about 60°C to
20 about 120°C.

Preferably, for the preparation of the compound of formula (Ib), the compound of formula (XIXa) is reacted with hydrogen gas; at a pressure sufficient to hydrogenate, preferably at a pressure greater than about 40 psi,
25 more preferably at a pressure of about 51 psi; in a solvent such as methanol, ethanol, THF, and the like, preferably methanol; preferably, at about room temperature; to yield the corresponding compound of formula (XXb).

The compound of formula (XXb) is then reacted according to the process described in Step 4a below, to yield the corresponding compound of formula (Ib).

5 **STEP 4a:**

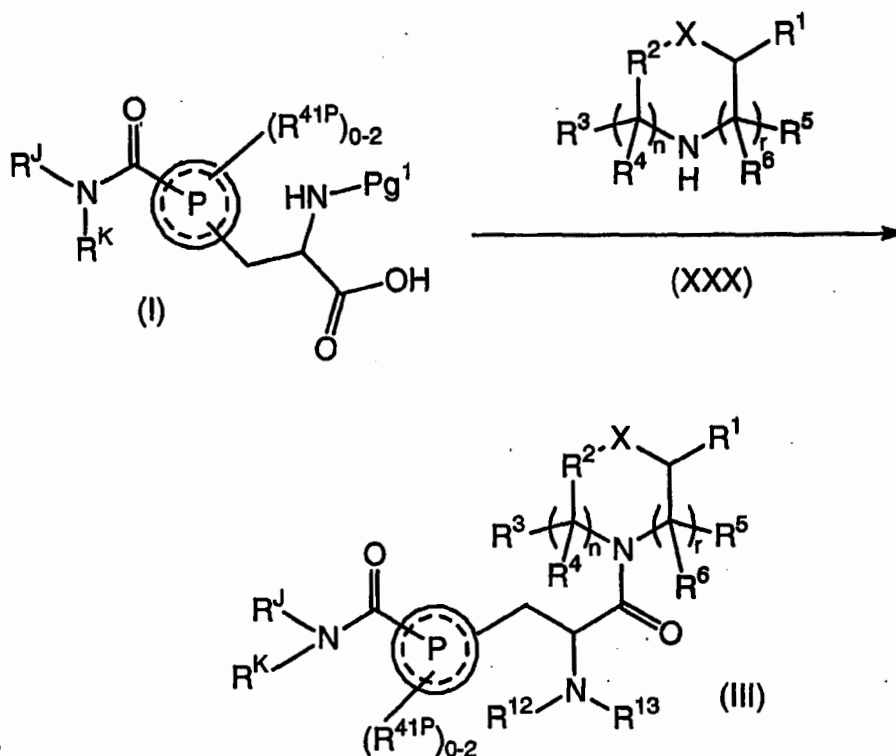
The compound of formula (XXa) is reacted with an aqueous base such as NaOH, LiOH, KOH, and the like, preferably LiOH; in an organic solvent such as methanol, THF, ethanol, and the like, preferably THF; to yield the corresponding compound of formula (Ia).

10

The present invention is further directed to processes for the preparation of compounds of formula (III).

15 The compounds of formula (I), prepared according to any of the processes as disclosed herein, may be further reacted according to known processes, for example as disclosed in disclosed in United States Application No. 10/400,006, filed March 26, 2003 and published as US Patent Publication US-2004-0010014-A1, September 26, 2004, to yield the corresponding compounds of

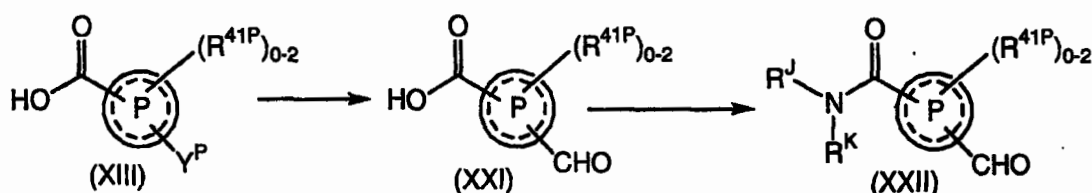
formula (III), as shown in Scheme 3

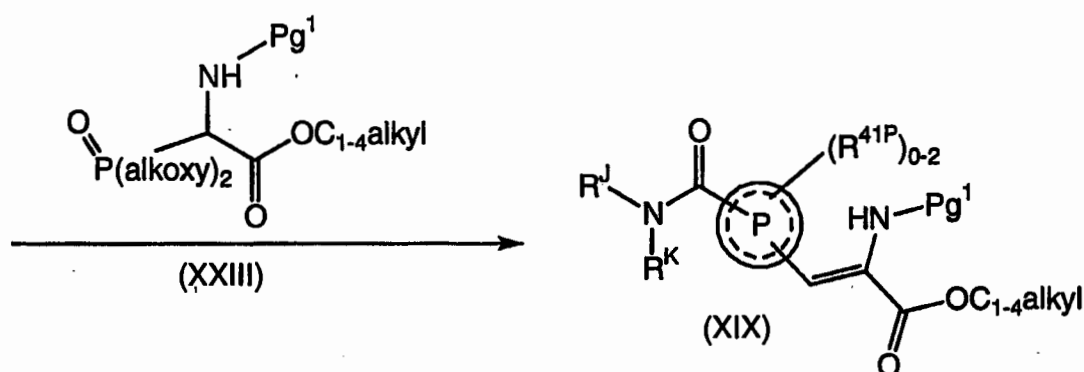


below.

Accordingly, a suitably substituted compound of formula (I), is coupled with a suitably substituted compound of formula (XXX), a known compound or compound prepared by known methods (for example according to Scheme A-G in United States Application No. 10/400,006, filed March 26, 2003 and published as US Patent Publication US-2004-0010014-A1, September 26, 2004), under standard peptide coupling conditions, for example in the presence of a coupling reagent such as EDC, PyBop, and the like, also in the presence of a coupling additive such as HOBT, and the like, to yield the corresponding compound of formula (III).

The present invention is further directed to processes for the preparation of compounds of formula (XIX). More specifically, in an embodiment, the present invention is directed to a process for the preparation of compounds of formula (XIX) as outlined in Scheme 4.





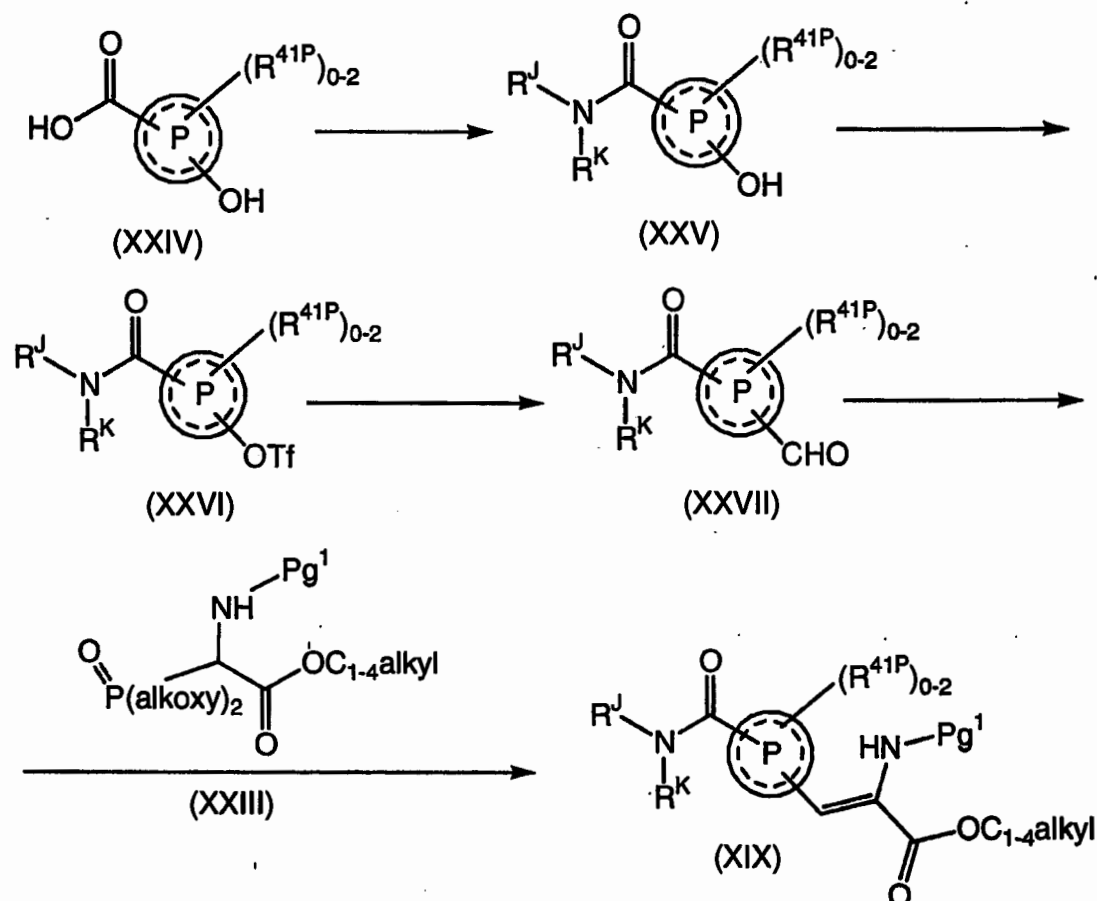
Scheme 4

Accordingly, a suitably substituted compound of formula (XIII), wherein Y^P is Br or Cl, is reacted with a formylating reagent such as a DMF, $HC(O)-$
 5 $N(CH_3)(OCH_3)$, and the like; in the presence of a base such as n-butyl lithium, NaH, and the like; in an organic solvent such as THF, dioxane, and the like; at a temperature less than about room temperature, preferably at a temperature in the range of about $-130^\circ C$ to about $0^\circ C$, more preferably, at about $-100^\circ C$; to yield the corresponding compound of formula (XXI).

10 The compound of formula (XXI) is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBT, PyBop, PyBrop, and
 15 the like; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or an amount of the compound of formula (XIV) or source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XXII).

20 The compound of formula (XXII) is reacted with a suitably selected compound of formula (XXIII), a known compound or compound prepared by known methods; in the presence of a base such as DBU, potassium t-butoxide, NaH, and the like; in an organic solvent such as THF, dioxane, and the like; preferably at about room temperature, to yield the corresponding compound of
 25 formula (XIX).

In another embodiment, the present invention is directed to a process for the preparation of compounds of formula (XIX) as outlined in Scheme 5.



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Scheme 5

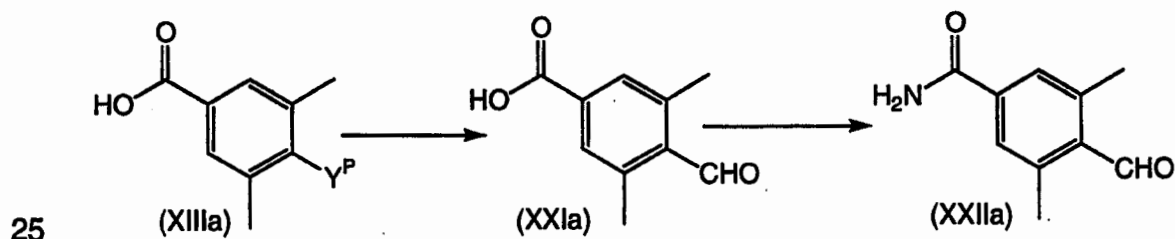
Accordingly, a suitably substituted compound of formula (XXIV), a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, or when R^J and R^K are each hydrogen, with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBT, PyBop, PyBrop, and the like; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or an amount of the compound of formula (XIV) or source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XXV).

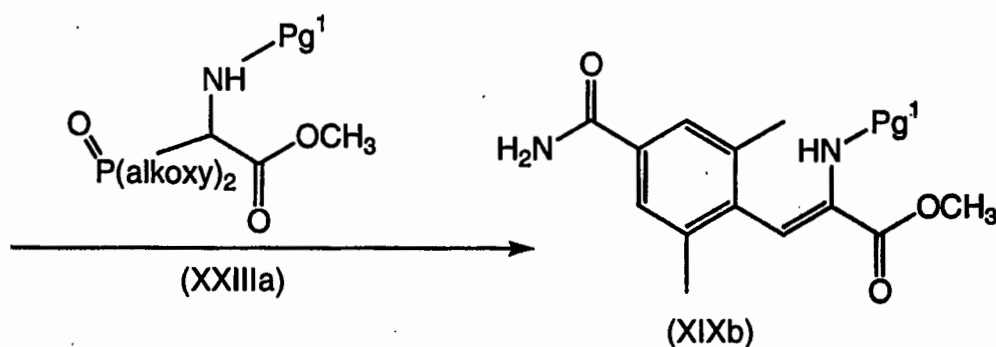
The compound of formula (XXV) is reacted with triflating reagent such as triflic anhydride, N-phenyltrifluoromethanesulfonimide, and the like; in the presence of an organic or inorganic base such as pyridine, TEA, DIPEA, K_3PO_4 , K_2CO_3 , and the like; optionally in an organic solvent such as DCM, chloroform, THF, and the like; to yield the corresponding compound of formula (XXVI).

The compound of formula (XXVI) is reacted with carbon monoxide; in the presence of a palladium catalyst such $PdCl_2$, $Pd_2(OAc)_2$, and the like, in combination with a suitable ligand, such DPPP, DPPF, $P(Ph)_3$, and the like; or in the presence of a palladium:ligand complex such as $Pd(PPh_3)_4$, and the like; in the presence of an organic base such as TEA, DIPEA, pyridine, and the like; in the presence of $(alkyl)_3SiH$; in an organic solvent such as DMF, THF, dioxane, and the like; to yield the corresponding compound of formula (XXVII).

The compound of formula (XXVII) is reacted with a suitably selected compound of formula (XXIII), a known compound or compound prepared by known methods; in the presence of a base such as DBU, potassium t-butoxide, NaH, and the like; in an organic solvent such as THF, dioxane, and the like; preferably at about room temperature, to yield the corresponding compound of formula (XIX).

In an embodiment, the present invention is directed to processes for the preparation of the compound of formula (XIX). More specifically, in an embodiment, the present invention is directed to a process for the preparation of compounds of formula (XIXa) as outlined in Scheme 6.





Scheme 6

Accordingly, a suitably substituted compound of formula (XIIIa), wherein Y^P is Br or Cl, is reacted with a formylating reagent such as a DMF, $HC(O)-$

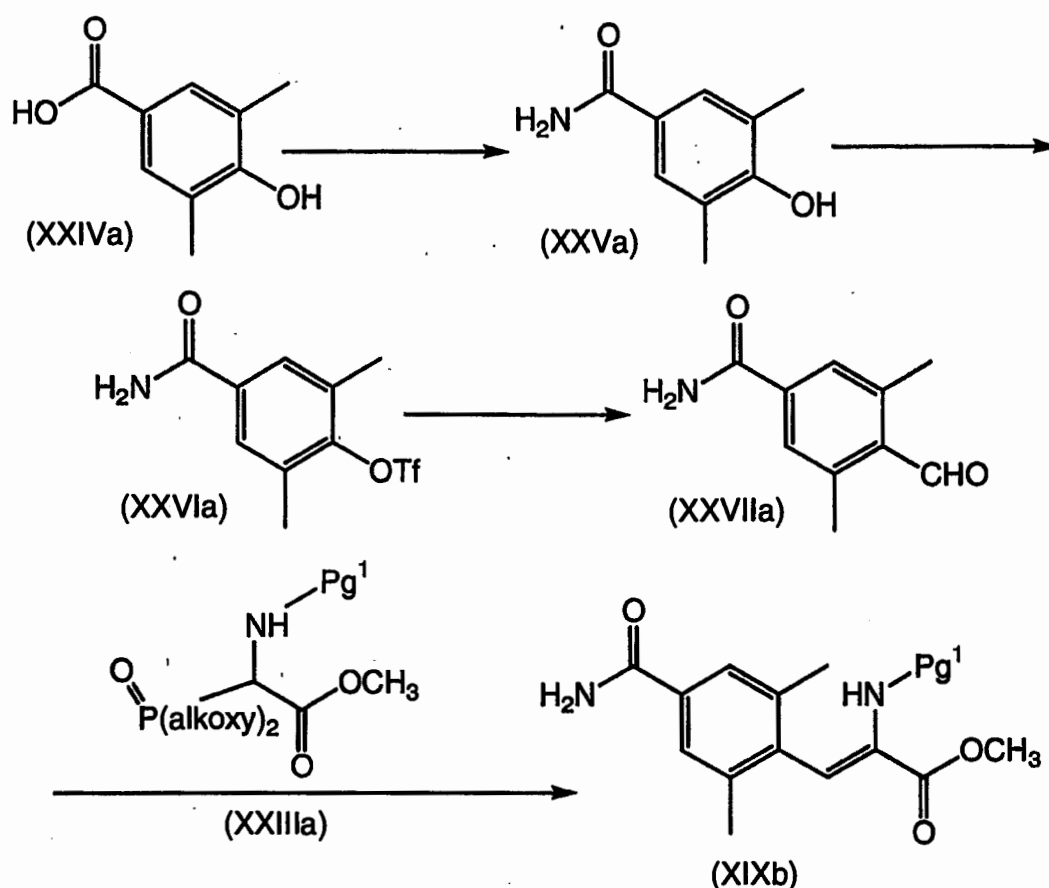
- 5 $N(CH_3)(OCH_3)$, and the like; in the presence of a base such as *n*-butyl lithium, NaH, and the like; in an organic solvent such as THF, dioxane, and the like; at a temperature less than about room temperature, preferably at a temperature in the range of about -130°C to about 0°C , more preferably, at about -100°C ; to yield the corresponding compound of formula (XXIa).

- 10 The compound of formula (XXIa) is reacted with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBT, PyBop, PyBrop, and the like; preferably in the presence of an organic base such as TEA, DIPEA, pyridine, the like, or an amount of the source of ammonia sufficient to act as the
- 15 base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XXIIa).

- The compound of formula (XXIIa) is reacted with a suitably selected compound of formula (XXIIIa), wherein Pg^1 is a suitable nitrogen protecting
- 20 group such as Boc, Cbz, and the like, a known compound or compound prepared by known methods; in the presence of a base such as DBU, potassium *t*-butoxide, NaH, and the like; in an organic solvent such as THF, dioxane, and the like; preferably at about room temperature, to yield the corresponding compound of formula (XIXb).

25

In another embodiment, the present invention is directed a process for the preparation of compounds of formula (XIXa) as outlined in Scheme 7.



Scheme 7

- 5 Accordingly, a suitably substituted compound of formula (XXIVa), a known compound or compound prepared by known methods, is reacted with a suitable source of ammonia such as HMDS, ammonia gas, and the like, preferably HMDS; in the presence of a coupling agent such as EDCI, HOBT, PyBop, PyBrop, and the like; preferably in the presence of an organic base
- 10 such as TEA, DIPEA, pyridine, the like, or in the presence of an amount of the source of ammonia sufficient to act as the base, preferably greater than about 2 equivalents; in an organic solvent such as THF, dioxane, DMF, and the like; to yield the corresponding compound of formula (XXVa).

- The compound of formula (XXVa) is reacted with triflating reagent such
- 15 as triflic anhydride, N-phenyltrifluoromethanesulfonimide, and the like; in the presence of an organic or inorganic base such as pyridine, TEA, DIPEA, K₃PO₄, K₂CO₃, and the like; optionally in an organic solvent such as DCM, chloroform, THF, and the like; to yield the corresponding compound of formula (XXVIa).

The compound of formula (XXVIa) is reacted with carbon monoxide; in the presence of a palladium catalyst such PdCl₂, Pd₂(OAc)₂, and the like, in combination with a suitable ligand, such DPPP, DPPF, P(Ph)₃, and the like; or in the presence of a palladium:ligand complex such as Pd(PPh₃)₄, and the like;
5 in the presence of an organic base such as TEA, DIPEA, pyrldine, and the like; in the presence of (alkyl)₃SiH; in an organic solvent such as DMF, THF, dioxane, and the like; to yield the corresponding compound of formula (XXVIIa).

The compound of formula (XXVIIa) is reacted with a suitably selected compound of formula (XXIIIa), wherein Pg1 is a suitable nitrogen protecting
10 group such as Boc, Cbz, abd the like, a known compound or compound prepared by known methods; in the presence of a base such as DBU, potassium t-butoxide, NaH, and the like; in an organic solvent such as THF, dioxane, and the like; preferably at about room temperature, to yield the corresponding compound of formula (XIXb).

15

The present invention further comprises pharmaceutical compositions containing one or more compounds prepared according to any of the processes described herein with a pharmaceutically acceptable carrier. Pharmaceutical compositions containing one or more of the compounds of the invention
20 described herein as the active ingredient can be prepared by intimately mixing the compound or compounds with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral). Thus for liquid oral preparations such as suspensions, elixirs
25 and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations
30 may also be coated with substances such as sugars or be enteric-coated so as to modulate major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients may be added to

increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives.

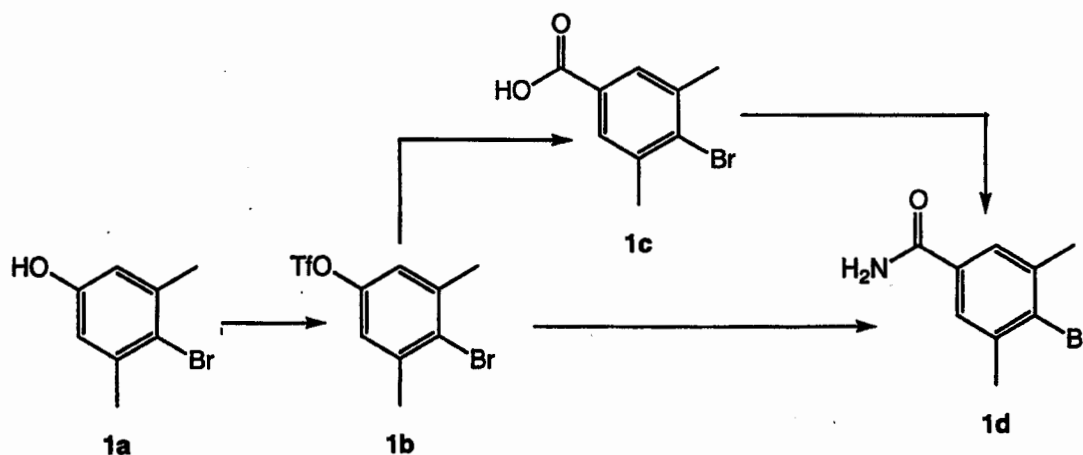
Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

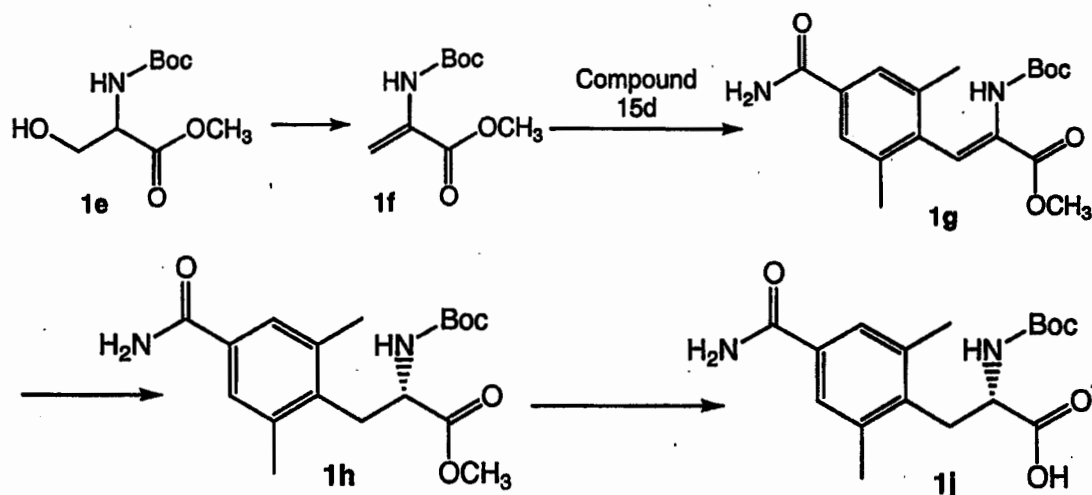
The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

In the Examples which follow, some synthesis products are listed as having been isolated as a residue. It will be understood by one of ordinary skill in the art that the term "residue" does not limit the physical state in which the product was isolated and may include, for example, a solid, an oil, a foam, a gum, a syrup, and the like.

Example 1

(S)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propanoic acid





STEP A: Trifluoromethanesulfonic acid 4-bromo-3,5-dimethyl-phenyl ester

- 5 To a cooled (0°C) solution of 4-bromo-3,5-dimethylphenol (3.05 g, 15.2 mmol) in pyridine (8 mL) was added trifluoromethanesulfonic anhydride (5.0 g, 17.7 mmol) dropwise. After completion of addition, the resulting mixture was stirred at 0°C for 15 min, and then at room temperature overnight. The reaction was quenched by addition of water, and then extracted with EtOAc. The organic extracts were washed sequentially with water, 2N HCl (2x), brine, and then dried over MgSO₄. Filtration and evaporation to dryness yielded compound **1b** as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 2.45 (6H, s), 7.00 (2H, s).

15 Step B: 4-Bromo-3,5-dimethylbenzoic acid

- Into a solution of compound **1b** (6.57 g, 19.7 mmol) in DMF (65 mL) were added K₂CO₃ (13.1 g, 94.7 mmol), Pd(OAc)₂ (0.44 g, 1.97 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (2.29 g, 4.14 mmol). The resulting mixture was bubbled in gaseous CO for 10 min and was heated to 60°C for 7.5h with a CO(g) balloon. The cooled mixture was partitioned between aqueous NaHCO₃ and EtOAc, and filtered. The aqueous phase was separated, acidified with aqueous 6N HCl, extracted with EtOAc, and then dried over Na₂SO₄. Filtration and concentration of the filtrate yielded crude compound **1c** as a brown residue, which was used in the next step without further purification.

STEP C: Method A: 4-Bromo-3,5-dimethyl-benzamide

Into a suspension of compound **1c** in DCM (40 mL) was added SOCl₂ (3.1 mL, 42 mmol) and the mixture was heated at reflux for 2 h. Upon removal
5 of the solvent by evaporation, the residue was dissolved in DCM (40 mL) and then ammonium hydroxide (28% NH₃ in water, 2.8 mL) was added. The reaction mixture was heated at 50°C for 2 h and concentrated. The residue was diluted with H₂O, extracted with EtOAc, and the organic portion was dried over Na₂SO₄. After filtration and evaporation, the residue was purified by flash
10 column chromatography (eluent: EtOAc) to yield compound **1d** as an off-white solid.

¹H NMR (300 MHz, CD₃CN): δ 2.45 (6H, s), 5.94 (1H, br s), 6.71 (1H, br s), 7.57 (2H, s)

MS(ES⁺)(relative intensity): 228.0 (100%) (M+1).

15

Step C: Method B: 4-Bromo-3,5-dimethyl-benzamide

A mixture of compound **1b** (3.33 g, 10 mmol), PdCl₂ (0.053 g, 0.3 mmol), hexamethyldisilazane (HMDS, 8.4 mL, 40 mmol), and DPPP (0.12 g, 0.3 mmol) was bubbled with a gaseous CO for 5 min and then stirred in a CO balloon at
20 80°C for 4 h. To the reaction mixture was added MeOH (5 mL). The reaction mixture was stirred for 10 min, diluted with 2N H₂SO₄ (200 mL), and then extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaHCO₃, brine, and then dried over Na₂SO₄. Filtration and evaporation of the resultant filtrate yielded a residue, which was purified by flash column
25 chromatography (eluent: EtOAc) to yield compound **1d** as a white solid.

Step D: 2-tert-Butoxycarbonylaminoacrylic acid methyl ester

To a suspension of *N*-Boc-serine methyl ester (Compound **1e**, 2.19 g, 10 mmol) and EDCI (2.01 g, 10.5 mmol) in DCM (70 mL) was added CuCl (1.04 g,
30 10.5 mmol). The reaction mixture was stirred at room temperature for 72 h. Upon removal of the solvent, the residue was diluted with EtOAc, washed sequentially with water and brine and then dried over MgSO₄. The crude

product was purified by flash column chromatography (eluent: EtOAc:hexane ~1:4) to yield compound **1f** as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 1.49 (9H, s), 3.83 (3H, s), 5.73 (1H, d, *J* = 1.5 Hz), 6.16 (1H, s), 7.02 (1H, s).

5

STEP E: (Z)-2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)acrylic acid methyl ester

A flask charged with compound **1d** (0.46 g, 2.0 mmol), compound **1f** (0.80 g, 4.0 mmol), tri-*o*-tolylphosphine (0.098 g, 0.32 mmol) and DMF (8 mL) was purged with N_{2(g)} 3 times. After the addition of tris(dibenzylideneacetone)dipalladium (0) (0.074 g, 0.08 mmol) and TEA (0.31 mL, 2.2 mol), the reaction mixture was heated at 110°C for 24 h. At that time, the reaction was quenched by addition of water, and then extracted with EtOAc. The organic phase was washed with 1N HCl, saturated aqueous NaHCO₃, brine, and dried over MgSO₄. The mixture was concentrated to a residue, which was purified by flash column chromatography (eluent: EtOAc:hexane~1:1 to EtOAc only) to yield compound **1g** as a white solid.

¹H NMR (300 MHz, CD₃OD): δ 1.36 (9H, s), 2.26 (6H, s), 3.83 (3H, s), 7.10 (1H, s), 7.56 (2H, s);

¹³C NMR (75 MHz, DMSO-*d*₆): δ 17.6, 25.7, 50.2, 78.7, 124.9, 126.4, 128.3, 131.2, 135.2, 135.5, 152.8, 164.3, 169.6;

MS (ES⁺) (relative intensity): 349.1 (38%)(M+1).

STEP F: (S)-2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid methyl ester

Into a reactor charged with a solution of compound **1g** (0.56 g, 1.6 mmol) in degassed MeOH (80 mL) was added [Rh(cod)(*R,R*-DIPAMP)]⁺BF₄⁻ under a stream of argon. The reactor was sealed and flushed with H₂, stirred at 60°C under 1000 psi of H₂ for 14 days. The crude product was purified by flash column chromatography (eluent: EtOAc:hexane ~1:1) to yield compound **1h** as a white solid.

ee: >99%;

^1H NMR (300 MHz, CDCl_3): δ 1.36 (9H, s), 2.39 (6H, s), 3.11 (2H, $J = 7.2$ Hz), 3.65 (3H, s), 4.53-4.56 (1H, m), 5.12 (1H, d, $J = 8.7$ Hz), 5.65 (1H, br s), 6.09 (1H, br s), 7.46 (2H, s);

MS(ES^+) (relative intensity): 250.9 (100) (M-Boc) $^+$.

5

STEP G: (*S*)-2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid

Into an ice-cooled solution of compound **1h** (0.22 g, 0.63 mmol) in THF (3.5 mL) was added an aqueous LiOH solution (1 N, 3.5 mL) and the reaction mixture stirred at 0°C. Upon completion of the reaction, the reaction mixture was concentrated and the aqueous phase was neutralized with cooled aqueous 1 N HCl at 0°C, and then extracted with EtOAc. The combined extracts were dried over Na_2SO_4 overnight. Filtration and evaporation of the filtrate to dryness yielded compound **1j** as a white solid.

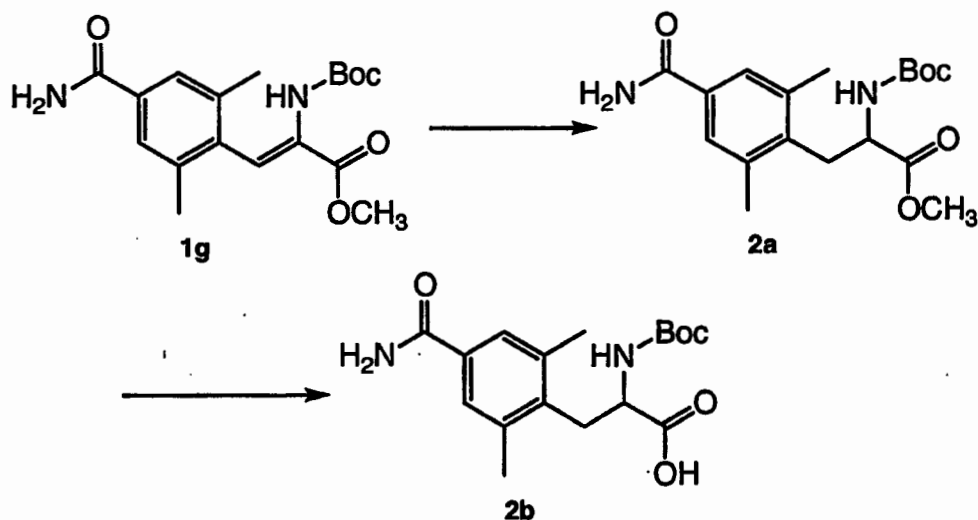
^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.30 (9H, s), 2.32 (6H, s), 2.95 (1H, dd, $J = 8.8, 13.9$ Hz), 3.10 (1H, dd, $J = 6.2, 14.0$ Hz), 4.02-4.12 (1H, m), 7.18-7.23 (2H, m), 7.48 (2H, s), 7.80 (1H, s);

MS(ES^+) (relative intensity): 236.9 (6) (M-Boc) $^+$.

20

Example 2

Racemic 2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionic acid



STEP A: Racemic 2-*tert*-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid methyl ester

To a reactor charged with a solution of compound **1g** (0.68 g, 1.95 mmol) in MeOH (80 mL) was added 10% Pd-C (0.5 g). The reactor was
5 connected to a hydrogenator and shaken under 51 psi of H₂ overnight. The mixture was filtered through a pad of Celite and the filtrate was concentrated to dryness to yield compound **2a** as a white solid.

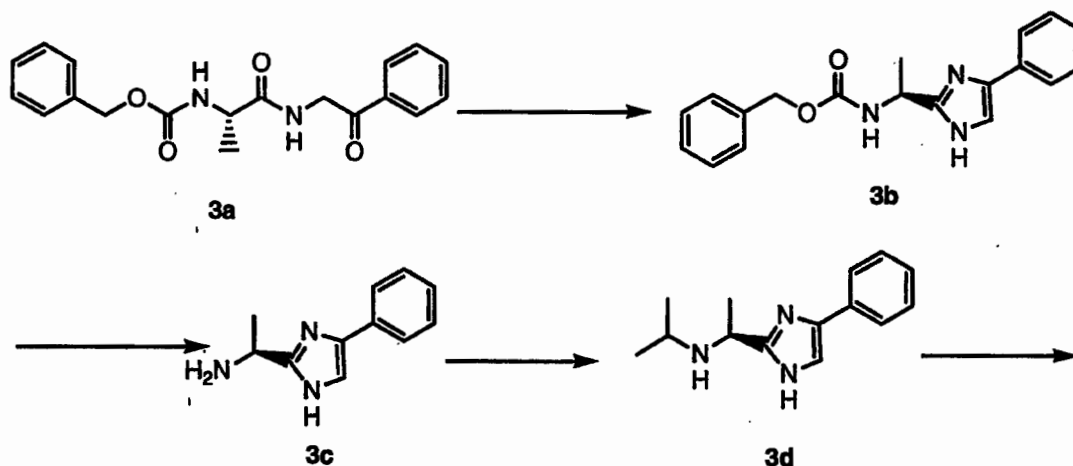
The ¹H NMR spectrum was identical to that of (*S*)-2-*tert*-
butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid
10 methyl ester, compound **1h**.

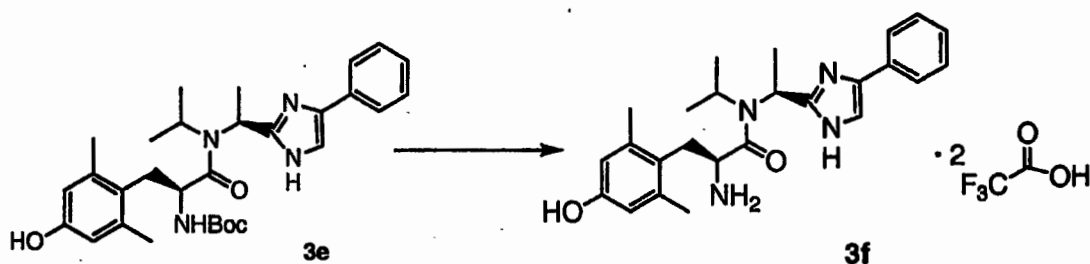
STEP B: Racemic 2-*tert*-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid

Following the procedure described for Example 1, STEP G (preparation
15 of (*S*)-2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid), compound **2b** - racemic 2-*tert*-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid - was prepared.

Example 3

20 **2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-N-isopropyl-N-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-propionamide**





STEP A. [1-(2-Oxo-2-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzyl ester.

5 To a solution of commercially available N- α -CBZ-L-alanine (2.11 g, 9.5 mmol) in dichloromethane (50 mL) was added 2-aminoacetophenone hydrochloride (1.62g, 9.5 mmol). The resulting solution was cooled to 0°C and N-methylmorpholine (1.15 g, 11 mmol), 1-hydroxybenzotriazole (2.55 g, 18.9 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.35

10 g, 12.3 mmol), in that order, were added under an Argon atmosphere. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by addition of saturated aqueous NaHCO₃ solution; the separated organic phase was washed with 2N citric acid, saturated NaHCO₃ solution and brine, then dried over MgSO₄ overnight. After filtration and

15 concentration, the residue was purified by column chromatography on silica gel (eluent, EtOAc:hexane-1:1) to yield the title compound, [1-(2-oxo-2-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzyl ester.

¹H NMR (300 MHz, CDCl₃): δ 1.46 (3H, d), 4.39 (1H, m), 4.75 (2H, d), 5.13 (2H, d), 5.40 (1H, m), 7.03 (1H, m), 7.36 (5H, m), 7.50 (2H, m), 7.63 (1H,

20 m), 7.97(2H, m)

MS(ES⁺): 341.1 (100%).

step B. [1-(4-Phenyl-1H-Imidazol-2-yl)-ethyl]-carbamic acid benzyl ester.

To a suspension of [1-(2-oxo-2-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzyl ester (2.60 g, 7.64 mmol) in xylene (60 mL) was added NH₄OAc (10.3 g, 134 mmol) and HOAc (5 mL). The resulting mixture was heated at

25 reflux for 7 h. After being cooled to room temperature, brine was added and the mixture was separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over Na₂SO₄ overnight. After

filtration and concentration, the residue was purified by column chromatography on silica gel (eluent, EtOAc:hexane-1:1) to yield the title compound.

¹H NMR (300 MHz, CDCl₃): δ 1.65 (3H, d), 5.06 (1H, m), 5.14 (2H, q), 5.94 (1H, d), 7.32 (10H, m), 7.59 (2H, d)

5 MS(ES⁺): 322.2 (100%).

Step C. 1-(4-Phenyl-1H-imidazol-2-yl)-ethylamine

To a solution of [1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamic acid benzyl ester (1.5 g, 4.67 mmol) in methanol (25 mL) was added 10% palladium on carbon (0.16 g). The mixture was shaken in a hydrogenation apparatus at rt under a hydrogen atmosphere (10 psi) for 8 h. Filtration followed by evaporation to dryness under reduced pressure yielded the crude product 1-(4-phenyl-1H-imidazol-2-yl)-ethylamine.

¹H NMR (300 MHz, CDCl₃): δ 1.53 (3H, d), 4.33 (1H, q), 7.23 (3H, m), 7.37 (2H, m), 7.67 (2H, m)

15 MS(ES⁺): 188.1 (38%).

STEP D. Isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine

1-(4-Phenyl-1H-imidazol-2-yl)-ethylamine (0.20 g, 1.07 mmol) and acetone (0.062 g, 1.07 mmol) were mixed in 1,2-dichloroethane (4 mL), followed by the addition of NaBH(OAc)₃ (0.34 g, 1.61 mmol). The resulting mixture was stirred at rt for 3 h. The reaction was quenched with saturated NaHCO₃ solution. The mixture was extracted with EtOAc and the combined extracts were dried over Na₂SO₄. Filtration followed by evaporation to dryness under reduced pressure yielded crude isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine, which was used for the next reaction without further purification.

¹H NMR (300 MHz, CDCl₃): δ 1.10 (3H, d), 1.18 (3H, d), 1.57 (3H, d), 2.86 (1H, m), 4.32 (1H, m), 7.24 (2H, m), 7.36 (2H, m), 7.69 (2H, m)

25 MS(ES⁺): 230.2 (100%).

30

STEP E. (2-(4-Hydroxy-2,6-dimethyl-phenyl)-1-[isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl]-ethyl)-carbamic acid *tert*-butyl ester

Into a solution of 2-*tert*-Butoxycarbonylamino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid (0.18 g, 0.6 mmol) in DMF (7 mL) was added isopropyl-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-amine (0.11 g, 0.5 mmol), 1-hydroxybenzotriazole (0.22 g, 1.6 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.12 g, 0.6 mmol). The resulting mixture was stirred under an Argon atmosphere at room temperature overnight. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed sequentially with saturated aqueous NaHCO₃ solution, 1N HCl, saturated aqueous NaHCO₃ solution, and brine. The organic phase was then dried over MgSO₄, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (eluent: EtOAc) to yield the product (2-(4-hydroxy-2,6-dimethyl-phenyl)-1-{isopropyl-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-carbamoyl}-ethyl)-carbamic acid *tert*-butyl ester.

MS(ES⁺): 521.5 (100%).

Step F. 2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-N-isopropyl-N-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-propanamide

A solution of (2-(4-hydroxy-2,6-dimethyl-phenyl)-1-{isopropyl-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-carbamoyl}-ethyl)-carbamic acid *tert*-butyl ester (0.13 g, 0.25 mmol) in trifluoroacetic acid (5 mL) was stirred at room temperature for 2 h. Upon removal of the solvents, the residue was purified by preparative LC and lyophilized to yield the TFA salt of the title compound as a white powder.

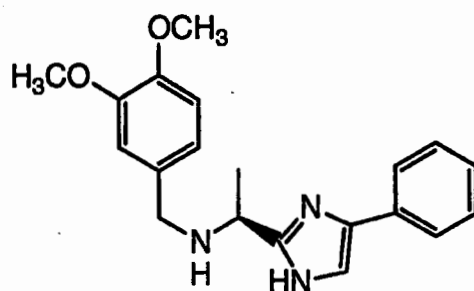
¹H NMR (300 MHz, CDCl₃): δ 0.48 (3H, d), 1.17 (3H, d), 1.76 (3H, d), 2.28 (6H, s), 3.19 (2H, m), 3.74 (1H, m), 4.70 (1H, m), 4.82 (1H, q), 6.56 (2H, s), 7.45 (4H, m), 7.74 (2H, m)

MS(ES⁺): 421.2 (100%).

30

Example 4

(3,4-Dimethoxy-benzyl)-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-amine



A solution of 1-(4-phenyl-1H-imidazol-2-yl)-ethylamine (0.061 g, 0.33 mmol) of Example 3, and 0.55 g (0.33 mmol) of 3,4-dimethoxybenzaldehyde in 5 mL of anhydrous methanol was stirred at room temperature for 1 h and then cooled to about 0-10°C in an ice bath for 1 h. The reaction was treated carefully with 0.019 g (0.49 mmol) of sodium borohydride in one portion and maintained at about 0-10°C for 21 h. Cold 2M aqueous HCl was added dropwise (30 drops), the mixture was stirred for 5 min, and then partially concentrated *in vacuo* unheated. The residual material was taken up in EtOAc to yield a suspension that was treated with 5 mL of cold 3M aqueous NaOH and stirred vigorously until clear. The phases were separated and the aqueous layer was extracted three times additional with EtOAc. The combined extracts were dried over MgSO₄, filtered, and concentrated to yield (3,4-dimethoxybenzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine as a light yellow oil (HPLC: 87% @ 254nm and 66% @ 214 nm).

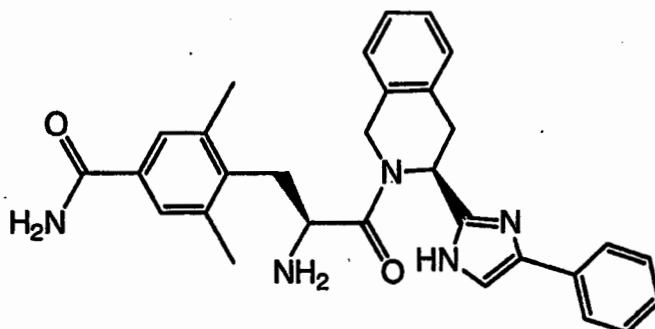
MS (ES⁺) (relative intensity): 338.1 (100) (M+1)

This sample was of sufficient quality to use in the next reaction without further purification.

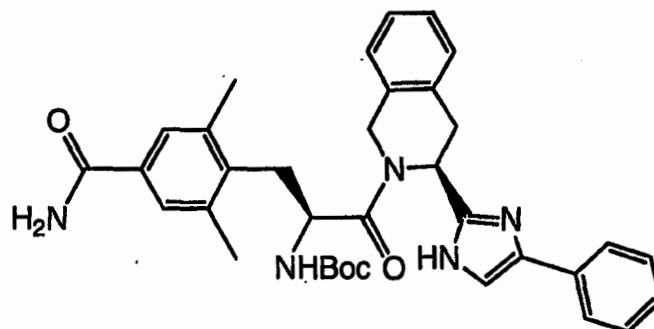
20

Example 5

S,S isomer of 4-{2-amino-3-oxo-3-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-propyl}-3,5-dimethyl-benzamide

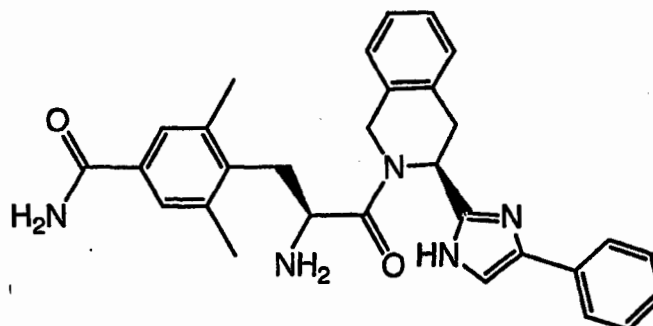


Step A: {1-(4-carbamoyl-2,6-dimethyl-benzyl)-2-oxo-2-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl}-carbamic acid tert-butyl ester



- 5 To a mixture of 220mg (0.8 mmol) of 3-(4-phenyl-1H-imidazol-2-yl)-1,2,3,4-tetrahydro-isoquinoline, 269mg (0.8 mmol) of 2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionic acid, 216mg (1.6 mmol) of hydroxybenzotriazole hydrate and 184mg (0.96 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride may be added 3 mL
- 10 of dimethylformamide. The resulting mixture may then be allowed to stir overnight at room temperature under argon. The resulting mixture may then be partitioned between ethyl acetate and water. The organic layer may be separated, dried over magnesium sulfate and concentrated to yield {1-(4-carbamoyl-2,6-dimethyl-benzyl)-2-oxo-2-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-
- 15 dihydro-1H-isoquinolin-2-yl]-ethyl}-carbamic acid tert-butyl.

Step B. S,S Isomer of 4-{2-amino-3-oxo-3-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-propyl}-3,5-dimethyl-benzamide



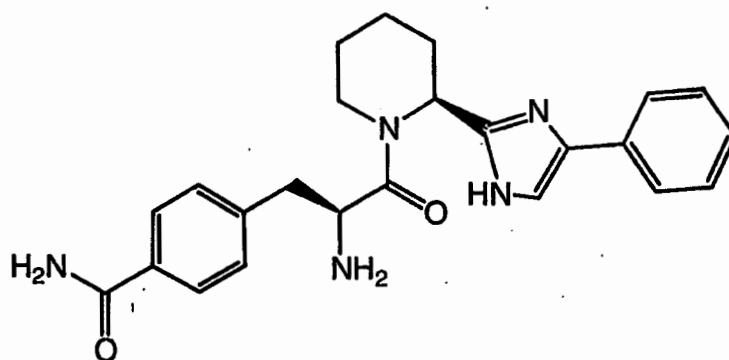
- 20 To 0.8 mmol of {1-(4-carbamoyl-2,6-dimethyl-benzyl)-2-oxo-2-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl}-carbamic acid tert-butyl ester cooled in an ice bath under argon, may be added 3 mL of

trifluoroacetic acid. After stirring for 3 hours, the reaction mixture may be concentrated and purified on a Gilson prep LC system to yield the S,S isomer of 4-{2-amino-3-oxo-3-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-propyl}-3,5-dimethyl-benzamide in a mixture of diastereomers.

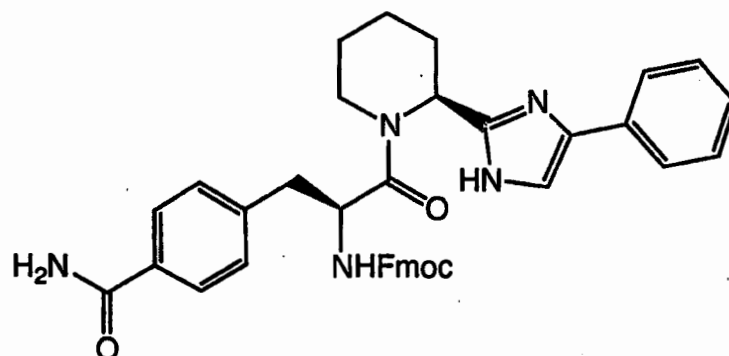
5

Example 6

4-{2-Amino-3-oxo-3-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-propyl}-benzamide



10 STEP A: {1-(4-Carbamoyl-benzyl)-2-oxo-2-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester



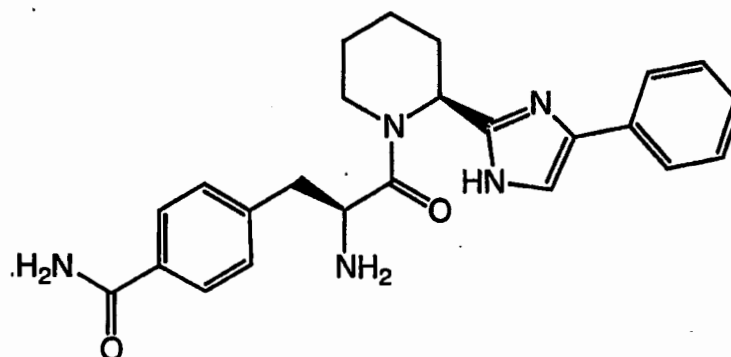
To a mixture of 138 mg (0.5 mmol) of 2-(4-Phenyl-1H-imidazol-2-yl)-piperidine, 215 mg (0.5 mmol) of 3-(4-Carbamoyl-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-propionic acid, 135 mg (1.0 mmol) of hydroxybenzotriazole hydrate, 115 mg (0.6 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride may be added 2 mL of dimethylformamide. The resulting mixture may then be allowed to stir at room temperature under argon overnight. The resulting mixture may then be partitioned between ethyl acetate and water. The organic layer may be separated, dried over MgSO₄ and concentrated to yield {1-(4-carbamoyl-

20

benzyl)-2-oxo-2-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester.

Step B: 4-{2-Amino-3-oxo-3-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-propyl}-benzamide

5



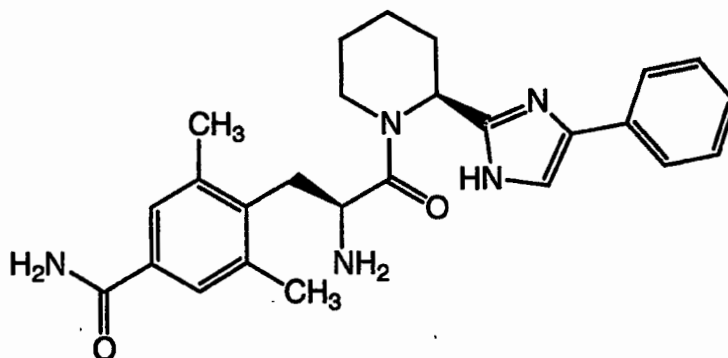
To a solution of the product from step A (assumed to be 0.5 mmol based on the previous step), in 4 mL of chloroform may be added 1 mL of piperidine. The mixture may then be allowed to stir overnight at room temperature under argon. The mixture may then be concentrated and the residue purified on a Gilson prep LC system to yield 4-{2-Amino-3-oxo-3-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-propyl}-benzamide in a mixture of diastereomers.

10

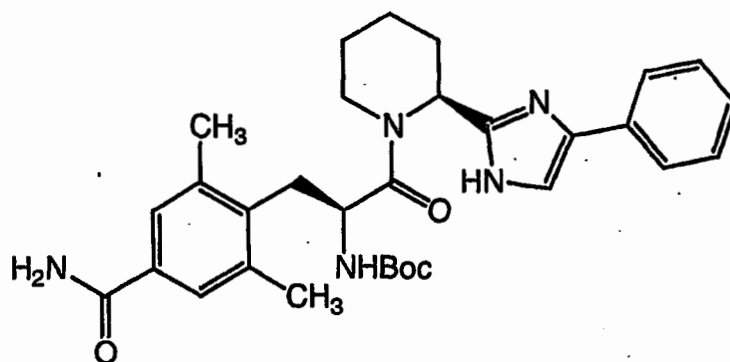
Example 7

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4-{2-amino-3-oxo-3-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-propyl}-3,5-dimethyl-benzamide

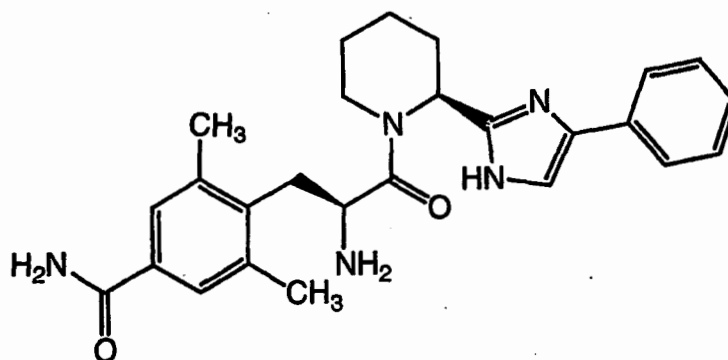


Step A: {1-(4-carbamoyl-2,6-dimethyl-benzyl)-2-oxo-2-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-ethyl}-carbamic acid tert-butyl ester



2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionic acid (0.42 g, 1.25 mmol) may be dissolved in DMF (5 mL) followed by 1-hydroxybenzotriazole (0.34 g, 1.75 mmol), and the resulting solution may then be cooled to 0°C. To the resulting may then be added 2-(4-phenyl-1H-imidazol-2-yl)-piperidine (0.31 g, 1.75 mmol) followed by (4-dimethylamino-butyl)-ethyl-carbodiimide (0.34 g, 1.75 mmol). The reaction may then be warmed to room temperature and stirred for 16 hours. The reaction mixture may then be combined with 2N citric acid and washed multiple times with ethyl acetate. The combined organics may be washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to {1-(4-carbamoyl-2,6-dimethyl-benzyl)-2-oxo-2-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-ethyl}-carbamic acid tert-butyl ester.

Step B: 4-{2-amino-3-oxo-3-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-propyl}-3,5-dimethyl-benzamide

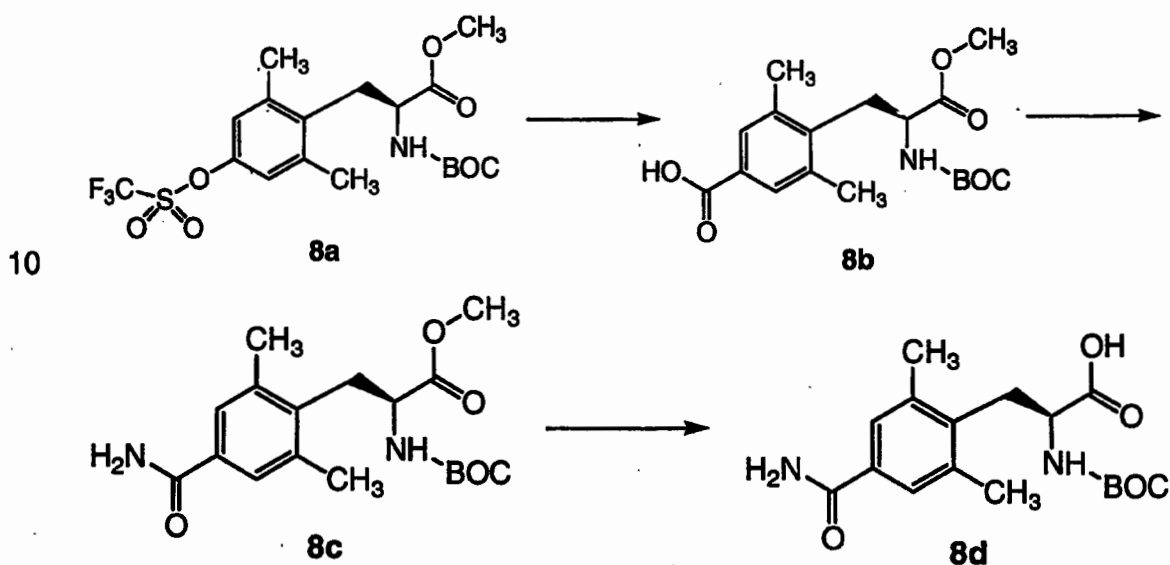


To {1-(4-carbamoyl-2,6-dimethyl-benzyl)-2-oxo-2-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-ethyl}-carbamic acid tert-butyl ester (0.60 g, 1.10 mmol) may be added 0°C trifluoroacetic acid (4 mL). The resulting solution may

then be warmed to room temperature, and after 30 minutes the excess trifluoroacetic acid may be removed under a stream of nitrogen. The resulting material may then be purified via a Gilson preparative HPLC to yield 4-{2-amino-3-oxo-3-[2-(4-phenyl-1H-imidazol-2-yl)-piperidin-1-yl]-propyl}-3,5-dimethyl-benzamide.

Example 8

(S)-2-tert-Butoxycarbonylamino-3-(2,6-dimethyl-4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester



STEP A. (S)-2-tert-Butoxycarbonylamino-3-(2,6-dimethyl-4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester

15 Into a cool solution of Boc-L-(2,6-diMe)Tyr-OMe (7.0 g, 21.6 mmol; Sources: Chiramer or RSP AminoAcidAnalogues) and *N*-phenyltrifluoromethanesulfonimide (7.9 g, 22.0 mmol) in dichloromethane (60 mL) was added triethylamine (3.25 mL, 23.3 mmol). The resulting solution was stirred at 0°C for 1 h and slowly warmed to room temperature. Upon

20 completion, the reaction was quenched by addition of water. The separated organic phase was washed with 1N NaOH aqueous solution, water and dried over Na₂SO₄ overnight. After filtration and evaporation, the residue was purified by flash column chromatography (eluent: EtOAc-hexane: 3:7) to yield the desired product as a clear oil.

^1H NMR (300 MHz, CDCl_3): δ 1.36 (9H, s), 2.39 (6H, s), 3.06 (2H, d, $J = 7.7$ Hz), 3.64 (3H, s), 4.51-4.59 (1H, m), 5.12 (1H, d, $J = 8.5$ Hz), 6.92 (2H, s)

MS (ES+) (relative intensity): 355.8 (100) (M-Boc) $^+$.

5 **STEP B. (S)-4-(2-*tert*-Butoxycarbonylamino-2-methoxycarbonylethyl)-3,5-dimethylbenzoic acid**

To a suspension of (S)-2-*tert*-butoxycarbonylamino-3-(2,6-dimethyl-4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester (9.68 g, 21.3 mmol), K_2CO_3 (14.1 g, 0.102 mol), $\text{Pd}(\text{OAc})_2$ (0.48 g, 2.13 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (2.56 g, 4.47 mmol) in DMF (48 mL) was bubbled in gaseous CO for 15 min. The mixture was heated to 60°C for 8 h with a CO balloon. The cool mixture was partitioned between NaHCO_3 and EtOAc, and filtered. The aqueous layer was separated, acidified with 10% citric acid aqueous solution, extracted with EtOAc, and finally dried over Na_2SO_4 .
10
15 Filtration and concentration of the filtrate resulted in a residue. The residue was recrystallized from EtOAc-hexanes to yield the desired product.

^1H NMR (300 MHz, CDCl_3): δ 1.36 (9H, s), 2.42 (6H, s), 3.14 (2H, $J = 7.4$ Hz), 3.65 (3H, s), 4.57-4.59 (1H, m), 5.14 (1H, d, $J = 8.6$ Hz), 7.75 (2H, s)

MS(ES+) (relative intensity): 251.9 (100) (M-Boc) $^+$.

20

STEP C. (S)-2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethylphenyl)propionic acid methyl ester

Into a stirring solution of (S)-4-(2-*tert*-butoxycarbonylamino-2-methoxycarbonylethyl)-3,5-dimethylbenzoic acid (3.00 g, 8.54 mmol), PyBOP (6.68 g, 12.8 mmol) and HOBt (1.74 g, 12.8 mmol) in DMF (36 mL) was added DIPEA (5.96 mL, 34.2 mmol) and NH_4Cl (0.92 g, 17.1 mmol). The resulting mixture was stirred at rt for 40 min before being partitioned between aqueous NH_4Cl solution and EtOAc. The separated organic phase was washed sequentially with 2N citric acid aqueous solution, saturated aqueous NaHCO_3
25
30 solution, and brine, then dried over Na_2SO_4 overnight. After filtration and concentration, the residue was purified by flash column chromatography (eluent: EtOAc) to yield the product.

^1H NMR (300 MHz, CDCl_3): δ 1.36 (9H, s), 2.39 (6H, s), 3.11 (2H, $J = 7.2$ Hz), 3.65 (3H, s), 4.53-4.56 (1H, m), 5.12 (1H, d, $J = 8.7$ Hz), 5.65 (1H, br s), 6.09 (1H, br s), 7.46 (2H, s)

MS(ES+) (relative intensity): 250.9 (100) (M-Boc) $^+$.

5

STEP D. (*S*)-2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethylphenyl)propionic acid

Into an ice-cooled solution of methyl ester from Step C (2.99 g, 8.54 mmol) in THF (50 mL) was added an aqueous LiOH solution (1N, 50 mL) and stirred at 0°C. Upon consumption of the starting materials, the organic solvents were removed and the aqueous phase was neutralized with cooled 1N HCl at 0°C, and extracted with EtOAc, and dried over Na_2SO_4 overnight. Filtration and evaporation to dryness yielded the title acid (*S*)-2-*tert*-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethylphenyl)propionic acid.

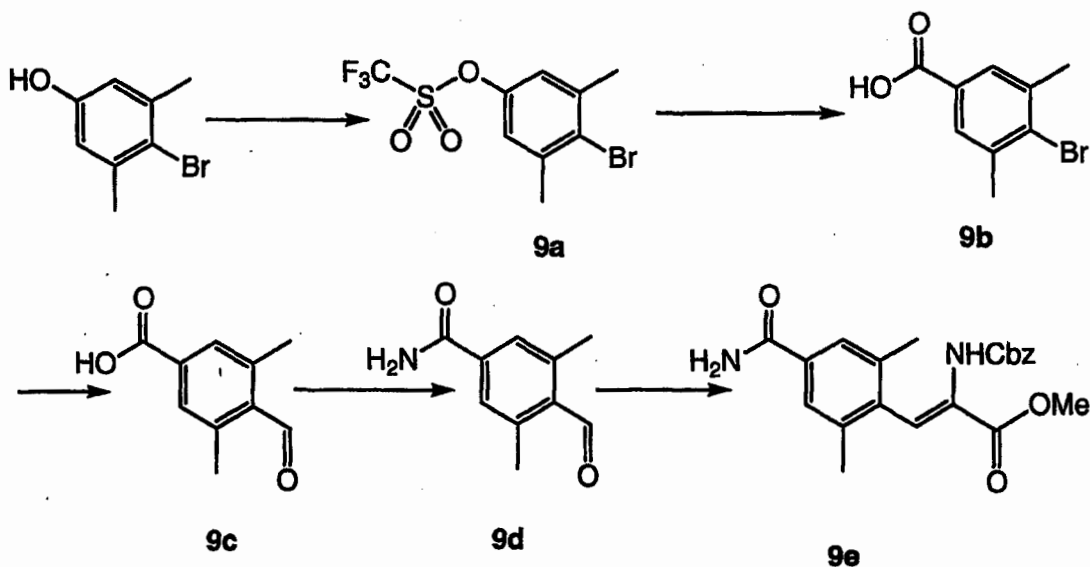
^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.30 (9H, s), 2.32 (6H, s), 2.95 (1H, dd, $J = 8.8, 13.9$ Hz), 3.10 (1H, dd, $J = 6.2, 14.0$ Hz), 4.02-4.12 (1H, m), 7.18-7.23 (2H, m), 7.48 (2H, s), 7.80 (1H, s)

MS(ES+) (relative intensity): 236.9 (6) (M-Boc) $^+$.

20

Example 9

(*Z*)-2-Benzylloxycarbonylamino-3-(4-carbamoyl-2,6-dimethylphenyl)acrylic acid methyl ester



STEP A. Trifluoromethanesulfonic acid 4-bromo-3,5-dimethyl-phenyl ester

To a cooled (0°C) solution of 4-bromo-3,5-dimethylphenol (3.05 g, 15.2 mmol) in pyridine (8 mL) was added trifluoromethanesulfonic anhydride (5.0 g, 17.7 mmol) dropwise. After completion of addition, the resulting mixture was stirred at 0°C for 15 min and at room temperature overnight. The reaction was then quenched by addition of water, then extracted with EtOAc. The EtOAc extracts were washed with water, 2N HCl (2 x), brine and dried over MgSO₄. Filtration and evaporation to dryness yield the product (9a) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 2.45 (6H, s), 7.00 (2H, s).

STEP B. 4-Bromo-3,5-dimethylbenzoic acid

Into a solution of trifluoro-methanesulfonic acid 4-bromo-3,5-dimethyl-phenyl ester (6.57 g, 19.7 mmol) in DMF (65 mL) were added K₂CO₃ (13.1 g, 94.7 mmol), Pd(OAc)₂ (0.44 g, 1.97 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (2.29 g, 4.14 mmol). The resulting mixture was bubbled in gaseous CO for 10 min and was then heated to 60°C for 7.5 h with a CO balloon. The cooled mixture was partitioned between aqueous NaHCO₃ and EtOAc, and filtered. The aqueous phase layer was separated, acidified with aqueous 6N HCl, extracted with EtOAc, and then dried over Na₂SO₄. Filtration and concentration of the filtrate resulted in the crude product (9b) as a brown residue, which was used in the next step without further purification.

STEP C. 4-Formyl-3,5-dimethyl-benzoic acid

A solution of 4-bromo-3,5-dimethylbenzoic acid (0.92 g, 4 mmol) in THF (10 mL) was cooled down to -100°C with N₂(l)-Et₂O bath and added n-butyllithium (1.6 M in hexanes, 5 mL, 8 mmol) slowly. After completion of addition, the reaction mixture was warmed to -78°C and DMF (0.74 mL, 8 mmol) was added dropwise. The resulting mixture was stirred at -78°C for 1.5 h and allowed to warm to -20°C, followed by the addition of 2N aqueous HCl (30 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc, the combined organic phases were dried over MgSO₄.

The solvent was removed and the resulting residue was purified by flash column chromatography (eluent: EtOAc-hexanes~1:1) to yield 4-formyl-3,5-dimethyl-benzoic acid (**9c**).

^1H NMR (300 MHz, CDCl_3): δ 2.65 (6H, s), 7.82 (2H, s), 10.67 (1H, s).

5

STEP D. 4-Formyl-3,5-dimethyl-benzamide

To a solution of 4-formyl-3,5-dimethyl-benzoic acid (0.15 g, 0.85 mmol) in DMF (6 mL) were added PyBOP (1.0 g, 1.92 mmol), HOBt (0.26 g, 1.92 mmol), DIPEA (0.89 mL, 5.12 mmol) and NH_4Cl (0.14 g, 2.56 mmol). The resulting mixture was stirred at room temperature for 1 h, and quenched by addition of brine, then extracted with EtOAc. The organic phase was washed with 2N aqueous HCl, saturated NaHCO_3 , brine and then dried over MgSO_4 . The solvent was removed to yield the crude product (**9d**), which was used in the next step without further purification.

15

STEP E. (Z)-2-Benzyloxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)acrylic acid methyl ester

Into a solution of N-(benzyloxycarbonyl)- α -phosphinoglycine trimethyl ester (0.46 g, 1.4 mmol) in DCM (5 mL) was added DBU (0.21 mL, 1.4 mmol). After stirring for 10 min, a solution of the above made 4-formyl-3,5-dimethyl-benzamide in DCM (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 5.5 h and the solvent was removed by rotary evaporation. The residue was dissolved in EtOAc and washed with 1N aqueous HCl, brine and then dried over MgSO_4 . The solvent was removed and the residue purified by flash column chromatography (eluent: EtOAc-hexanes~1:1) to yield (Z)-2-*tert*-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)acrylic acid methyl ester (**9e**) as a white solid.

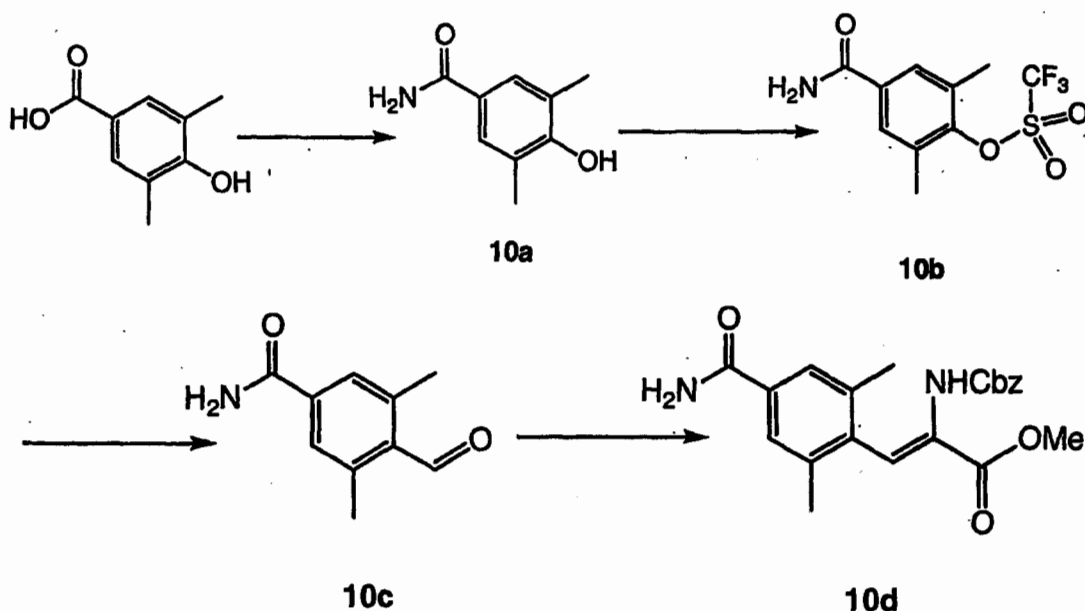
25

MS(ES^+) (relative intensity): 383.4 (10%)($\text{M}+1$).

30

Example 10

(Z)-2-Benzyloxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)acrylic acid methyl ester



STEP A. 4-Hydroxy-3,5-dimethyl-benzamide

5 Using the procedure described in Example 9, Step D, 4-hydroxy-3,5-dimethyl-benzamide (**10a**) was prepared as a yellowish solid.

^1H NMR (300 MHz, CDCl_3): δ 2.82 (6H, s), 5.51 (1H, br s), 5.90 (1H, br s), 7.48 (2H, s);

MS(ES^+) (relative intensity): 166.2 (8%)(M+1).

10

STEP B. Trifluoromethanesulfonic acid 4-carbamoyl-2,6-dimethyl-phenyl ester

Into a solution of 4-hydroxy-3,5-dimethyl-benzamide (3.72 g, 22.5 mmol) and N-phenyltrifluoromethanesulfoniunimide (9.4 g, 25 mmol) in DCM (80 mL) was added TEA (3.48 mL, 25 mmol) at room temperature, then the resulting mixture was stirred at room temperature overnight. After the reaction was quenched by addition of water, the separated organic phase was washed with 1N NaOH, water and then dried over MgSO_4 . The solvent was removed and the residue purified by flash column chromatography (eluent: EtOAc-hexanes~1:1) to yield trifluoromethanesulfonic acid 4-carbamoyl-2,6-dimethyl-phenyl ester (**10b**) as a white solid.

15

20

^1H NMR (300 MHz, CDCl_3): δ 2.42 (6H, s), 6.28 (2H, br s), 7.57 (2H, s)

MS(ES^+) (relative intensity): 298.1 (63%)(M+1).

STEP C. 4-Formyl-3,5-dimethyl-benzamide

Into a solution of trifluoro-methanesulfonic acid 4-carbamoyl-2,6-dimethyl-phenyl ester (1.49 g, 5 mmol), Pd(OAc)₂ (0.037 g, 0.15 mmol), DPPP (0.062 g, 0.15 mmol) and TEA (1.74 mL, 12.5 mmol) in DMF (25 mL) was bubbled CO (gas) for 10 min, then triethylsilane (1.6 mL, 10 mmol) was added. The resulting mixture was stirred at 75°C under a CO gas balloon for 6.5 hr. After cooling to room temperature, the reaction was quenched by addition of water, then extracted with EtOAc. The EtOAc extracts were washed with water, brine and then dried over MgSO₄. After filtration and evaporation, the residue was purified by column chromatography (eluent, EtOAc-hexanes~1:1) to yield 4-formyl-3,5-dimethyl-benzamide (**10c**) as a yellowish solid.

¹H NMR (300 MHz, CDCl₃): δ 2.65 (6H, s), 5.75 (1H, br s), 6.13 (1H, br s), 7.52 (2H, s), 10.64 (1H, s).

STEP D. (Z)-2-Benzylloxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)acrylic acid methyl ester

The title compound was prepared as described in Example 9, Step E.

Example 11 Optical Rotation Measurements

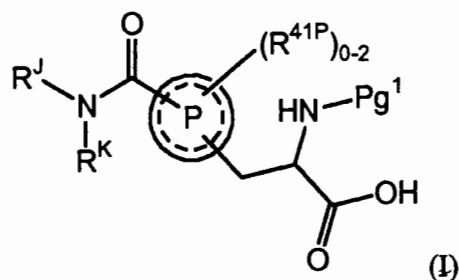
The optical rotation of a representative sample of the compound of formula (Ia), prepared as in Example 1, was measured as [α]_D = -12 (c 1.5, MeOH).

The optical rotation of a representative sample of the compound of formula (Ia), prepared as in Example 8, from commercially purchased (S)-N-BOC-Tyr-OMe was measured as [α]_D = -10.8 (c 1.7, MeOH).

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

We claim:

1. A process for the preparation of a compound of formula (I)



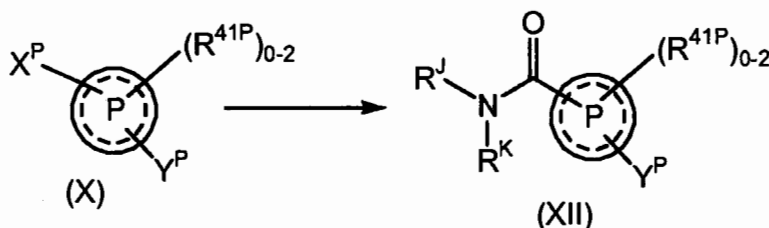
wherein



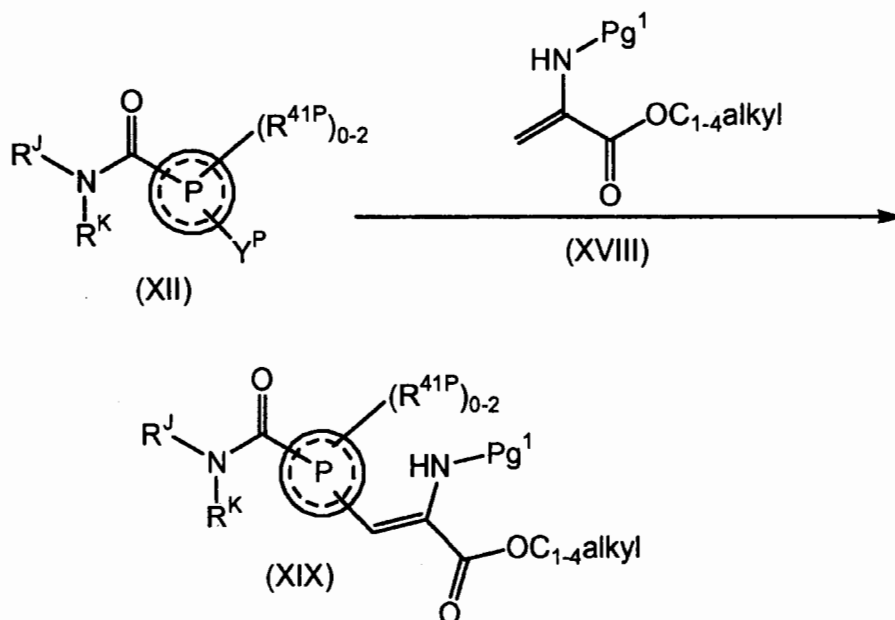
is phenyl;

each R^{41P} is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy or fluoro;
 R^J and R^K are each independently selected from hydrogen or C_{1-4} alkyl; alternatively, R^J and R^K are taken together with the nitrogen atom to which they are bound to form a five to seven membered heterocyclyl;
 Pg^1 is a nitrogen protecting group;

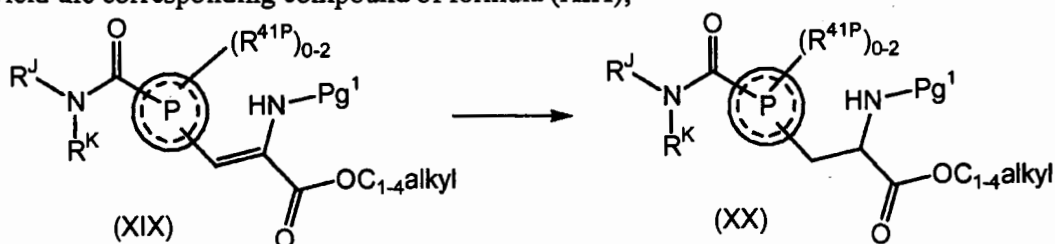
comprising



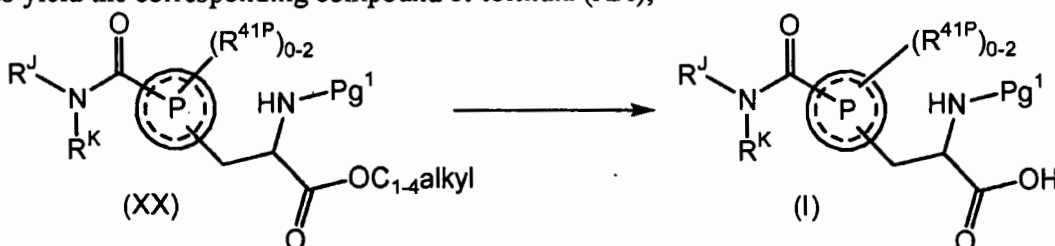
reacting a compound of formula (X), wherein X^P is selected from OH, CN, $-CO_2H$, $-C(O)-Cl$ or $-C(O)-OC_{1-4}alkyl$ and wherein Y^P is selected from Br, Cl or I, to yield the corresponding compound of formula (XII);



reacting the compound of formula (XII) with a compound of formula (XVIII); in the presence of palladium catalyst; in the presence of an organic or inorganic base; in an organic solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula (XIX);



reacting the compound of formula (XIX) with hydrogen or a source of hydrogen; in the presence of a catalyst; in a solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula (XX);



reacting the compound of formula (XX) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (I).

2. The process as in claim 1, wherein

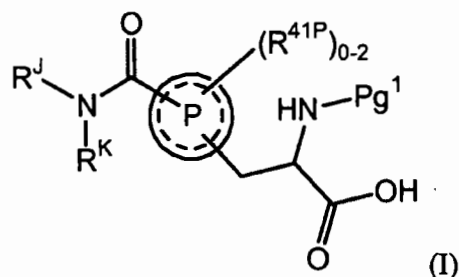


is substituted with a R^{41P} group at 2-position and a second R^{41P} group at the 4- position;
each R^{41P} is independently selected from C_{1-2} alkyl, C_{1-2} alkoxy or fluoro;
 R^J and R^K are each independently selected from hydrogen or C_{1-4} alkyl; alternatively, R^J and R^K are taken together with the nitrogen atom to which they are bound to form a five to seven membered heterocyclyl; and
 Pg^1 is a nitrogen protecting group.



3. The process as in Claim 1, wherein
is substituted with a R^{41P} group at the 2-position and a second R^{41P} group at the 4- position; each R^{41P} is methyl; R^J and R^K are each hydrogen; and Pg^1 is a t-butoxycarbonyl.

4. A process for the preparation of a compound of formula (I)



wherein



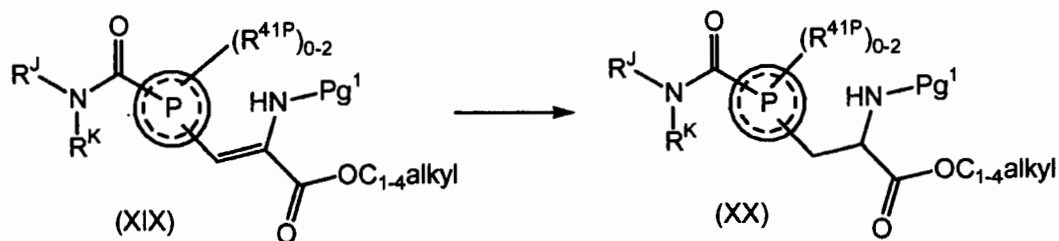
is phenyl;

each R^{41P} is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy or fluoro;

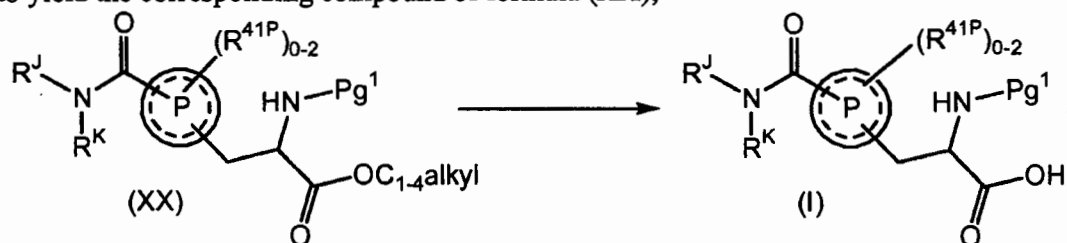
R^J and R^K are each independently selected from hydrogen or C_{1-4} alkyl; alternatively, R^J and R^K are taken together with the nitrogen atom to which they are bound to form a five to seven membered heterocyclyl;

Pg^1 is a nitrogen protecting group;

comprising

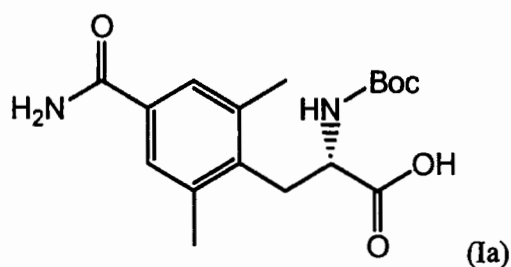


reacting the compound of formula (XIX) with hydrogen or a source of hydrogen; in the presence of a catalyst; in a solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula (XX);

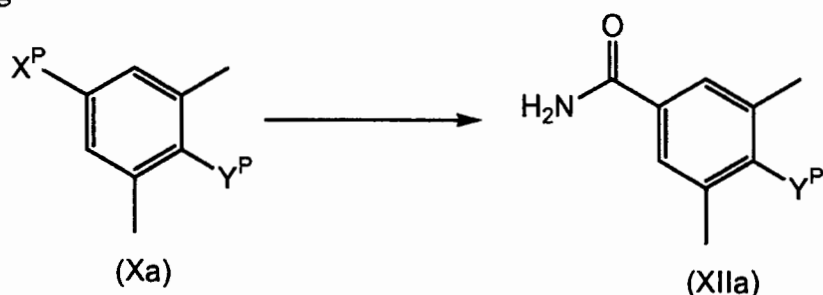


reacting the compound of formula (XX) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (I).

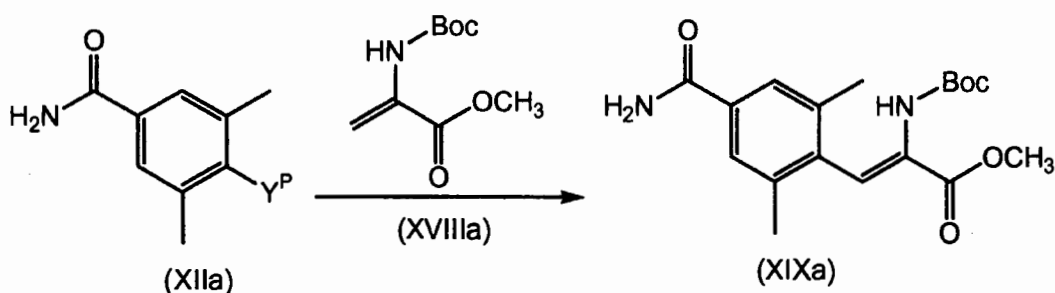
5. A process for the preparation of a compound of formula (Ia)



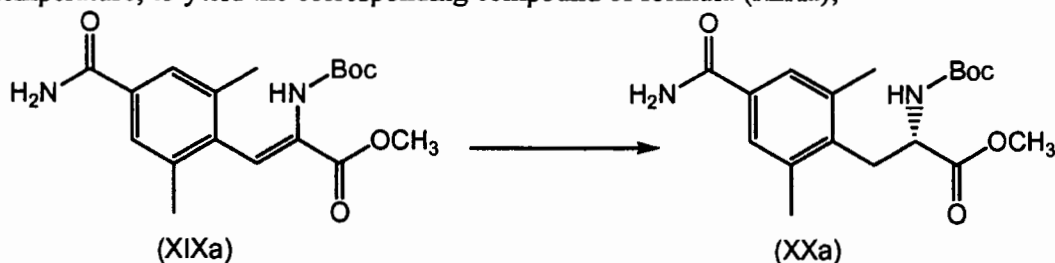
comprising



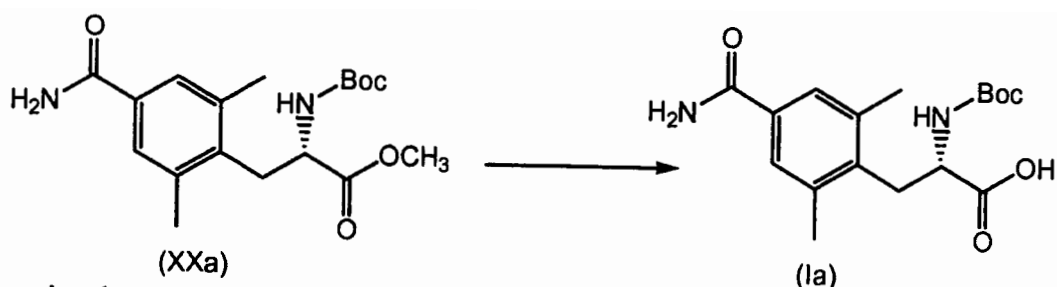
reacting a compound of formula (Xa), wherein X^P is selected from OH, CN, $-\text{CO}_2\text{H}$, $-\text{C}(\text{O})-\text{Cl}$ or $-\text{C}(\text{O})-\text{OC}_{1-4}\text{alkyl}$ and wherein Y^P is selected from Br, Cl or I, to yield the corresponding compound of formula (XIIa);



reacting the compound of formula (XIIa) with a compound of formula (XVIIIa); in the presence of palladium catalyst; in the presence of an organic or inorganic base; in an organic solvent; at a temperature greater than about room temperature; to yield the corresponding compound of formula (XIXa);



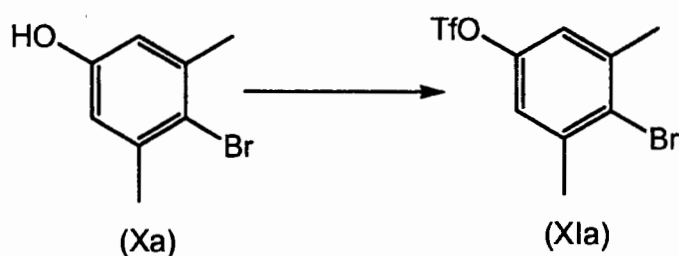
reacting compound of formula (XIXa) with hydrogen gas, at a pressure greater than about 500 psi; in the presence of a chiral catalyst; at a temperature greater than about room temperature; in an organic solvent; to yield the corresponding compound of formula (XXa);



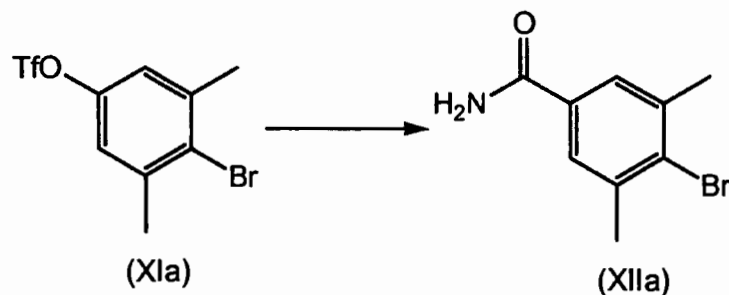
reacting the compound of formula (XXa) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (Ia).

6. The process as in claim 5, wherein X^P is -OH and wherein X^P is Br.

7. The process as in claim 6, further comprising



reacting the compound of formula (Xa), with a triflating reagent; in the presence of an organic or inorganic base; to yield the corresponding compound of formula (XIa);

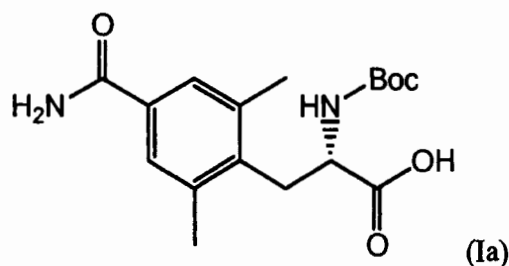


reacting the compound of formula (XIa) with carbon monoxide and a source of ammonia; in the presence of a palladium catalyst in combination with a ligand; or in the presence of a palladium:ligand complex; at a temperature in the range of from about 50°C to about 160°C; in an organic solvent; to yield the corresponding compound of formula (XII).

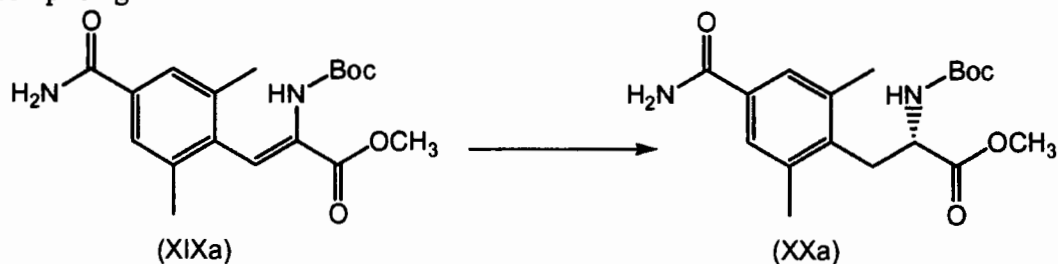
8. The process as in claim 5, wherein the compound of formula (XIIa) is reacted with the compound of formula (XVIIIa) in the presence of $\text{Pd}_2(\text{dba})_3$ and $\text{P}(\text{o-toluene})_3$.

9. The process as in claim 5, wherein the chiral catalyst is $[\text{Rh}(\text{cod})(\text{R},\text{R}\text{-DIPAMP})]^+\text{BF}_4^-$.

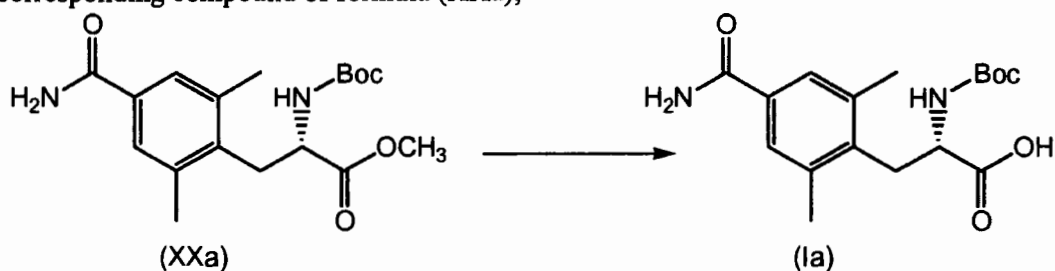
10. A process for the preparation of the compound of formula (Ia)



comprising



reacting compound of formula (XIXa) with hydrogen gas, at a pressure greater than about 500 psi; in the presence of a chiral catalyst; at a temperature greater than about room temperature; in an organic solvent; to yield the corresponding compound of formula (XXa);



reacting the compound of formula (XXa) with an aqueous base; in an organic solvent; to yield the corresponding compound of formula (Ia).