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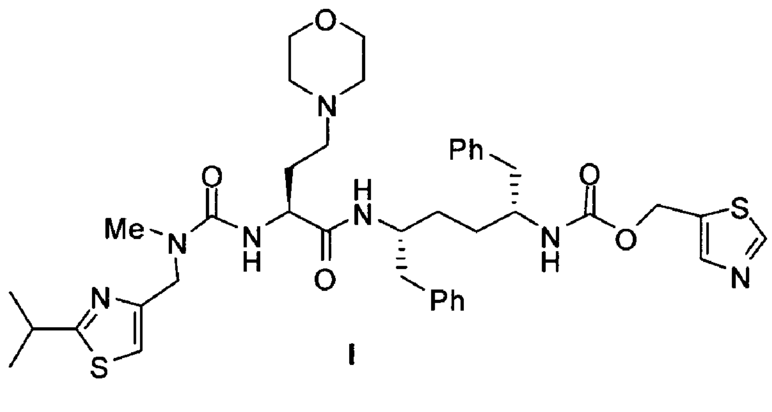

I

(57) Abstract: The invention provides methods and intermediates that are useful for preparing a compound of formula I.

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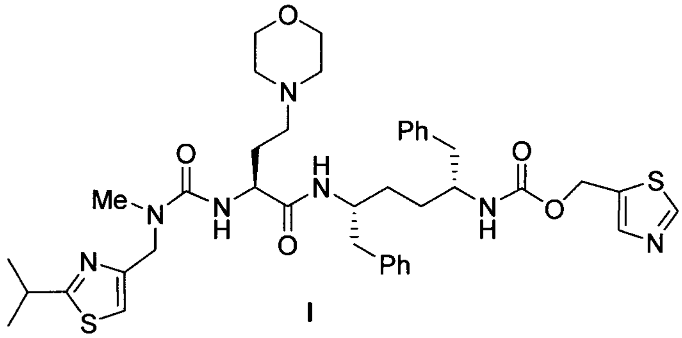
METHODS AND INTERMEDIATES FOR PREPARING PHARMACEUTICAL AGENTS

Priority of Invention

This application claims priority to United States Provisional Patent Application Number 61/166,498 filed 03 April 2009. The entire content of this application is hereby incorporated herein by reference.

Background of the Invention

International Patent Application Publication Number WO 2008/010921 and International Patent Application Publication Number WO 2008/103949 disclose certain compounds that are reported to be useful to modify the pharmacokinetics of a co-administered drug, e.g. by inhibiting cytochrome P450 monooxygenase. One specific compound identified therein is a compound of the following formula **I**:



I

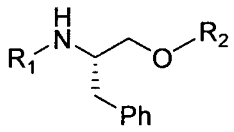
There is currently a need for improved synthetic methods and intermediates that can be used to prepare the compound of formula **I** and its salts. There is also a need for improved methods for preparing intermediate compounds that can be used to prepare the compound of formula **I** and its salts. The improved methods and intermediates may reduce the cost, time, and/or the amount of waste associated with the existing methods for preparing the compound of formula **I** and its salts.

Summary of the Invention

An improved synthetic route for preparing the compound of formula **I** and its salts has been identified. This improved synthetic route utilizes novel intermediates of formulae **IV**, **V**, **XIV**, **XVI**, **XVII**, and **XVIII**, identified herein below.

This route reduces the cost, the time, and the amount of waste associated with the preparation of the compound of formula **I** and its salts.

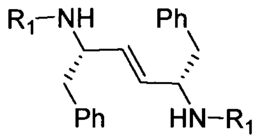
Accordingly in one embodiment, the invention provides a compound of formula **IV**:



IV

wherein R_1 and R_2 are each independently a suitable protecting group; or a salt thereof.

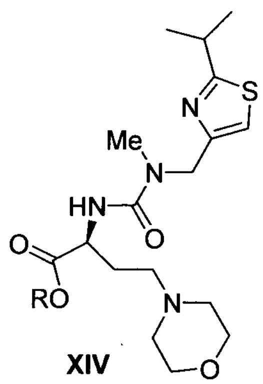
In another embodiment, the invention provides a compound of formula **V**:



V

wherein each R_1 is a suitable protecting group other than *tert*-butylsulfonyl; or a salt thereof.

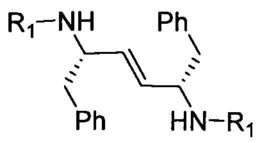
In another embodiment, the invention provides a compound of formula **XIV**:



XIV

wherein R is $(C_2\text{-}C_8)$alkyl, or a salt thereof.

In another embodiment, the invention provides a method for preparing a compound of formula **V**:



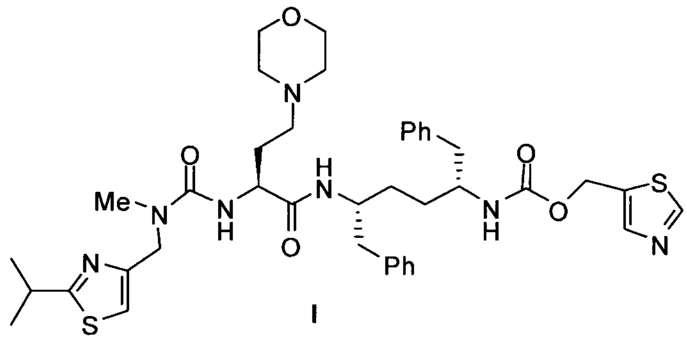
V

wherein each R_1 is a suitable protecting group other than *tert*-butylsulfonyl, or a salt thereof, comprising dimerizing a corresponding compound of formula **II**:

II

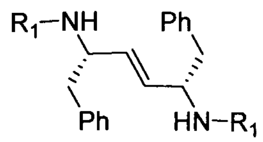
to provide the compound of formula **V**, or the salt thereof.

In another embodiment, the invention provides a method for preparing a compound of formula **I**:



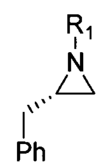
I

or a salt thereof, wherein a compound of formula **V**:



V

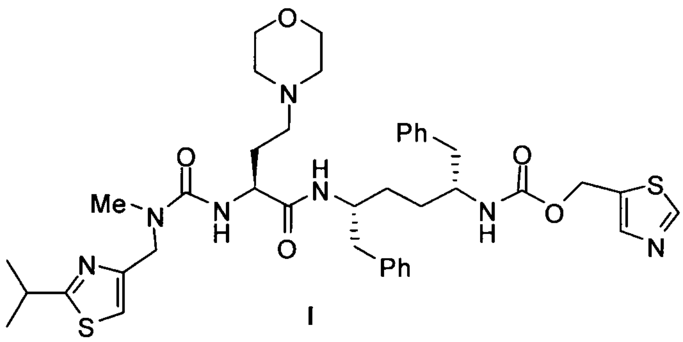
wherein R_1 is a suitable protecting group, or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **V** is prepared from a corresponding compound of formula **II**:



II

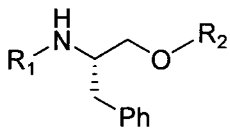
or a salt thereof, by dimerizing the compound of formula **II**.

In another embodiment, the invention provides a method for preparing a compound of formula **I**:



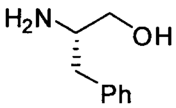
I

or a salt thereof, wherein a compound of formula **IV**:



IV

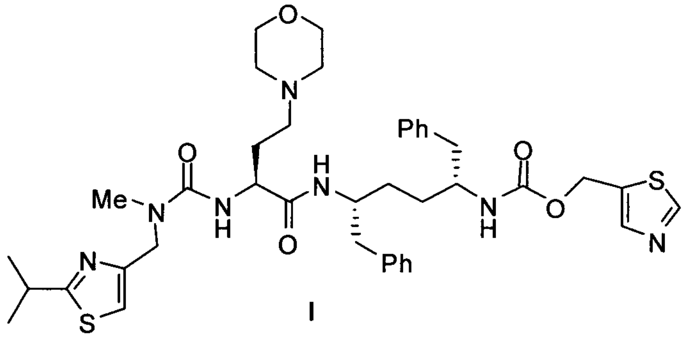
wherein R_1 and R_2 are each independently a suitable protecting group, or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **IV** is prepared from a compound of formula **III**:



III

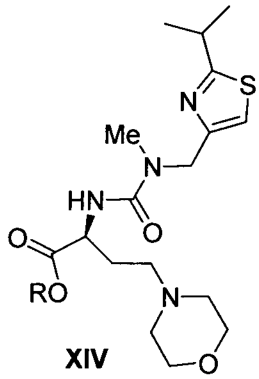
or a salt thereof, by protecting the compound of formula **III**.

In another embodiment, the invention provides a method for preparing a compound of formula **I**:



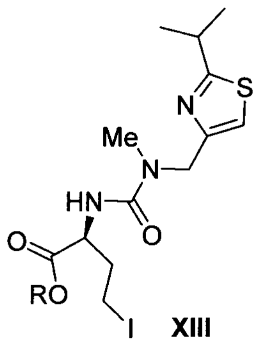
I

or a salt thereof, wherein a compound of formula **XIV**:



XIV

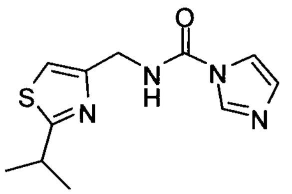
wherein R is H or (C_1-C_8)alkyl, or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XIV** or the salt thereof is prepared from a compound of formula **XIII**:



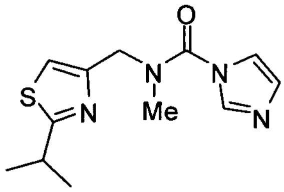
XIII

wherein R is H or (C_1-C_8)alkyl or a salt thereof, by displacing the iodide with a suitable morpholine reagent. In a further embodiment of this method of the invention R is (C_2-C_8)alkyl in the compound of formula XIII and XIV.

In another embodiment, the invention provides a compound of formula **XVI** or **XVII**:



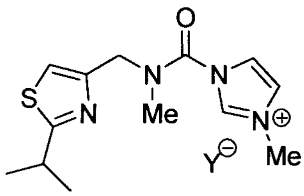
XVI



XVII

or a salt thereof.

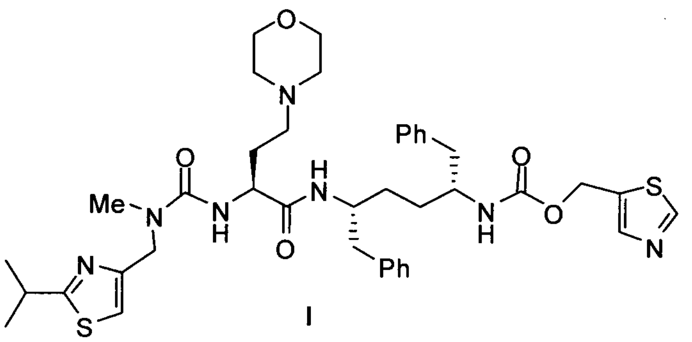
In another embodiment, the invention provides a salt of formula **XVIII**:



XVIII

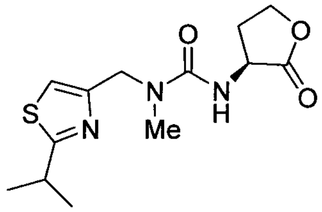
wherein Y^- is a suitable counterion.

In another embodiment, the invention provides a method for preparing a compound of formula **I**:



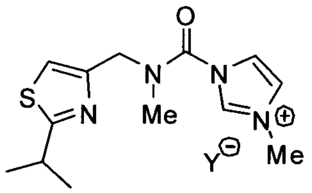
I

or a salt thereof, wherein a compound of formula **XII**:



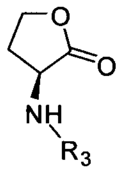
XII

or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XII** is prepared from a corresponding compound of formula **XVIII**:



XVIII

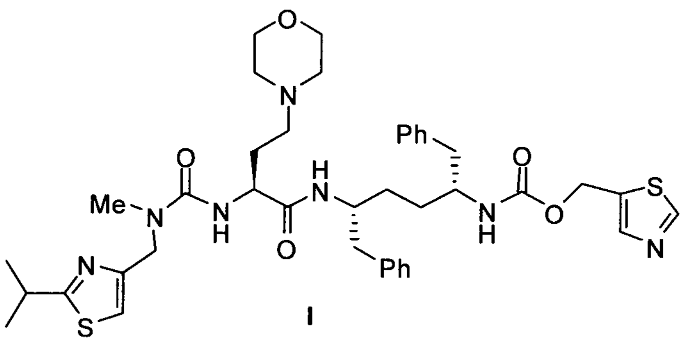
wherein Y^- is a suitable counterion, by treatment with a compound of formula **XI**:



XI

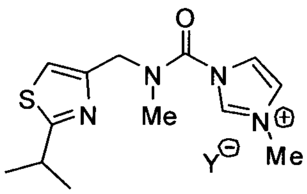
wherein R_3 is H or a protecting group in the presence of a base and optionally removing R_3 if it is a protecting group to provide the compound of formula **XII**.

In another embodiment, the invention provides a method for preparing a compound of formula **I**:



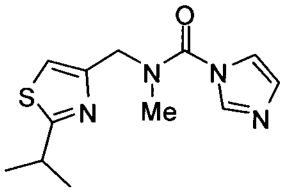
I

or a salt thereof, wherein a salt of formula **XVIII**:



XVIII

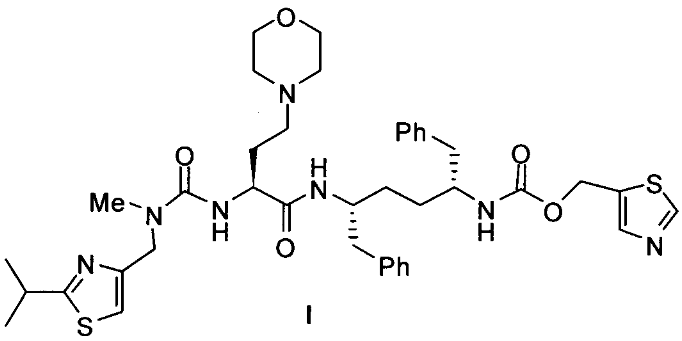
wherein Y^- is a suitable counterion is prepared and converted into a compound of formula **I**, characterized in that the salt of formula **XVIII** is prepared from a compound of formula **XVII**:



XVII

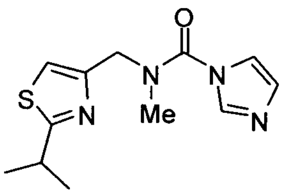
or a salt thereof by treatment with a methylating agent to provide the salt of formula **XVIII**.

In another embodiment, the invention provides a method for preparing a compound of formula **I**:



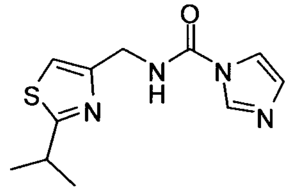
I

or a salt thereof, wherein a compound of formula **XVII**:



XVII

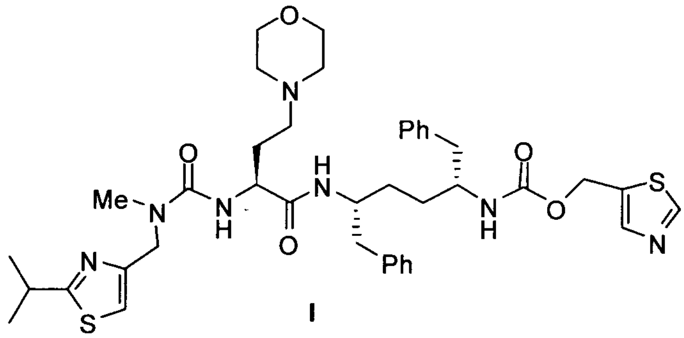
or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XVII** is prepared from a corresponding compound of formula **XVI**:



XVI

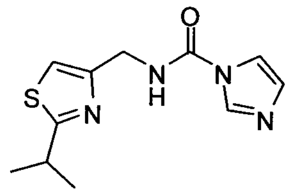
or a salt thereof by treatment with a methylating agent to provide the compound of formula **XVII** or the salt thereof.

In another embodiment, the invention provides a method for preparing a compound of formula **I**:



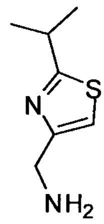
I

or a salt thereof, wherein a compound of formula **XVI**:



XVI

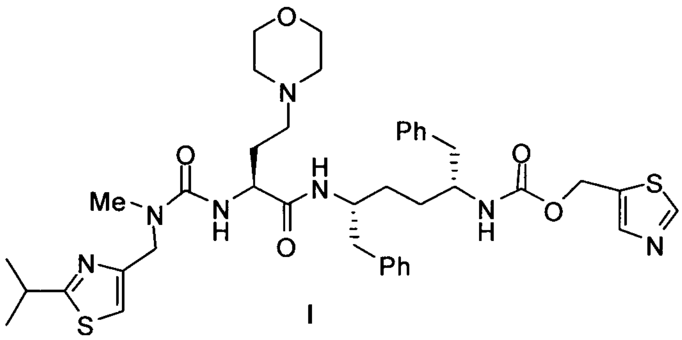
or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XVI** is prepared from a corresponding compound of formula **XV**:



XV

or a salt thereof by treatment with carbonyldiimidazole in the presence of a base to provide the compound of formula **XVI**.

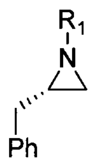
In another embodiment, the invention provides a method (Method A) for preparing a compound of formula **I**:



I

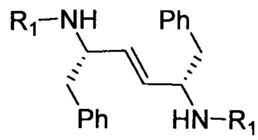
or a salt thereof comprising:

a) dimerizing a corresponding compound of formula **II**:



II

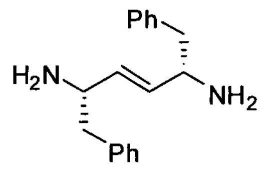
wherein R_1 is a suitable protecting group to provide a corresponding compound of formula **V**:



V

or a salt thereof;

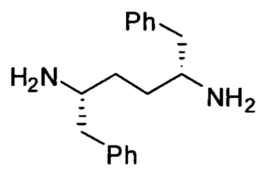
b) deprotecting the compound of formula **V** or the salt thereof to provide a compound of formula **VI**:



VI

or a salt thereof;

c) reducing the compound of formula **VI** or the salt thereof to a compound of formula **VII:**

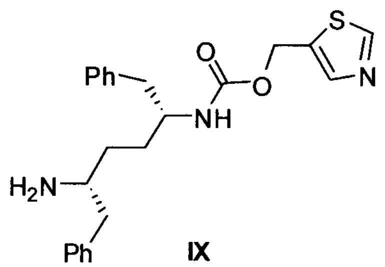


VII

or a salt thereof;

d) converting the compound of formula **VII** to a corresponding salt by treatment with an acid in an organic solvent;

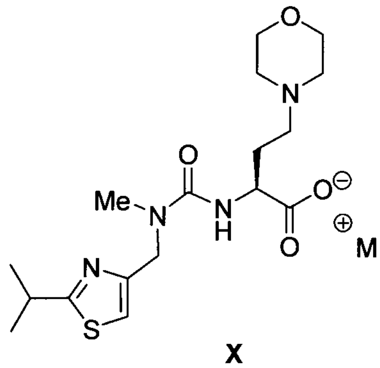
e) converting the corresponding salt from d) to a compound of formula **IX:**



IX

or a salt thereof (e.g. a mineral acid salt such as an HCl salt); and

f) coupling the compound of formula **IX** or the salt thereof with a salt of formula **X**:



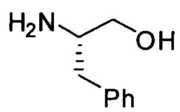
X

wherein M^+ is a suitable counterion to provide the compound of formula **I.** In one specific embodiment of the invention a salt of the compound of formula **IX** (e.g. an HCl salt) can be coupled with a salt of formula **X** to provide the compound of formula **I.**

In another embodiment, Method A can further comprise preparing the compound of formula **II** by reacting (*S*)-2-benzylaziridine with a corresponding compound R_1-X, wherein X is a leaving group (e.g. Cl) to provide the compound of formula **II.**

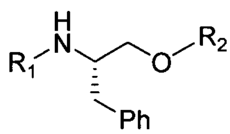
In another embodiment, Method A can further comprise preparing the compound of formula **II** by:

a) protecting a compound of formula **III**:



III

or a salt thereof to provide a corresponding compound of formula **IV**:



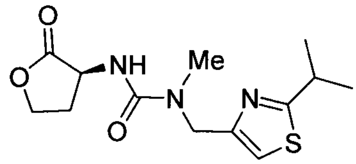
IV

wherein R_1 and R_2 are each independently a suitable protecting group, or a salt thereof; and

b) treating the compound of formula **IV** or the salt thereof with a suitable base to provide the compound of formula **II.**

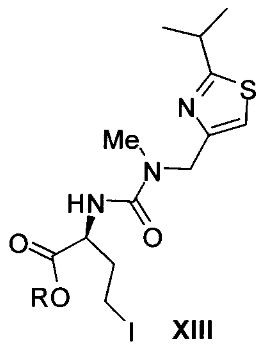
In another embodiment, Method A can further comprise preparing the salt of formula **X** by:

a) treating a compound of formula **XII**:



XII

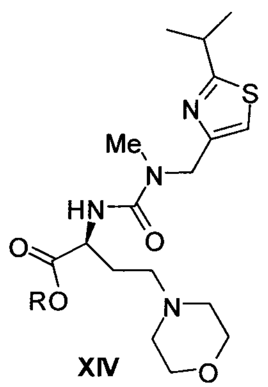
or a salt thereof with a suitable iodide source in the presence of an alcohol ROH to provide a compound of formula **XIII**:



XIII

wherein R is $(C_1\text{-}C_8)$alkyl, or a salt thereof;

b) treating the compound of formula **XIII** or the salt thereof with morpholine to provide an ester of formula **XIV**:



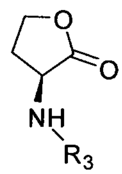
XIV

or a salt thereof; and

c) hydrolyzing the ester of formula **XIV** to provide the salt of formula **X**.

In another embodiment, Method A can further comprise preparing the compound of formula **XII** or the salt thereof by:

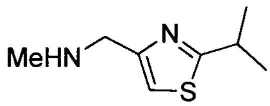
a) treating L-methionine with an alkylating agent and optionally protecting the resulting amine to provide an amine of formula **XI**:



XI

wherein R_3 is H or a protecting group, or a salt thereof; and

b) treating the amine of formula **XI** or the salt thereof with a compound of formula **XIX**:

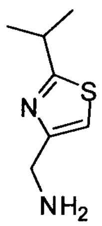


XIX

or a salt thereof to provide the compound of formula **XII** or the salt thereof.

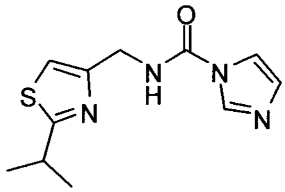
In another embodiment, Method A can further comprise preparing the compound of formula **XII** or the salt thereof by:

a) treating a compound of formula **XV**:



XV

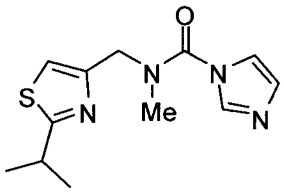
or a salt thereof with carbonyldiimidazole in the presence of a base to provide a compound of formula **XVI**:



XVI

or a salt thereof;

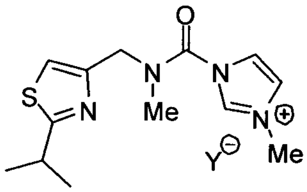
b) treating the compound of formula **XVI** or the salt thereof with a suitable methylating agent in the presence of a base to provide a compound of formula **XVII**:



XVII

or a salt thereof;

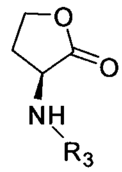
c) methylating the compound of formula **XVII** or the salt thereof to provide a salt of formula **XVIII**:



XVIII

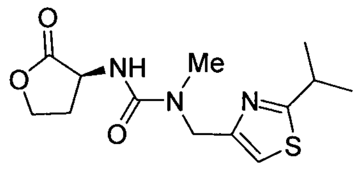
wherein Y^- is a suitable counterion; and

d) treating the salt of formula **XVIII** with an amine of formula **XI**:



XI

wherein R_3 is H or a protecting group, or a salt thereof with a suitable base, and deprotecting to remove R_3 if it is a protecting group, to provide the compound of formula **XII** or the salt thereof.



XII

The invention also provides novel synthetic intermediates described herein as well as methods for preparing such intermediates.

Detailed Description

As used herein alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such as propyl embraces only the straight chain radical, a branched chain isomer such as isopropyl being specifically referred to. Haloalkyl denotes an alkyl group that is substituted with one or more (e.g. 1, 2, 3, 4, etc.) halo groups. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

Specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, $(C_1\text{-}C_8)$alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, heptyl, or octyl; $(C_1\text{-}C_8)$alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, hexyloxy, heptyloxy, or octyloxy; halo$(C_1\text{-}C_8)$alkyl can be fluoromethyl, difluoromethyl, and trifluoromethyl; aryl-$(C_1\text{-}C_8)$alkoxy can be benzyloxy; and aryl can be phenyl, indenyl, or naphthyl.

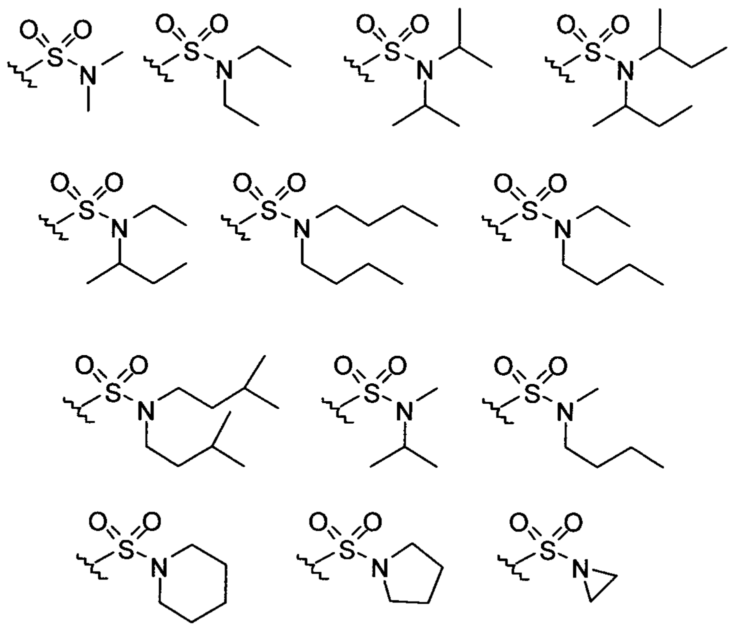
A specific value for R_1 is an *N,N*-disubstituted aminosulfonyl group.

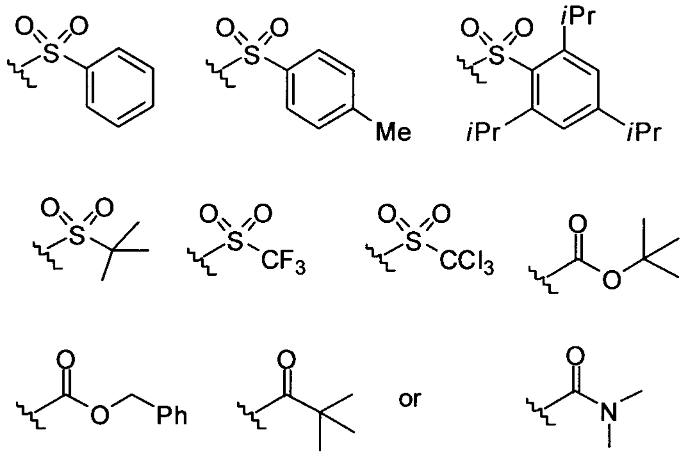
Another specific value for R_1 is an *N,N*-dialkyl aminosulfonyl group.

Another specific value for R_1 is $-S(=O)_2NR_aR_b$, $-S(=O)_2R_c$, $-C(=O)R_c$, or $-C(=O)NR_aR_b$ wherein each of R_a and R_b is independently $(C_1\text{-}C_8)$alkyl; or R_a and R_b together with the nitrogen to which they are attached form a 3 or 4 membered saturated ring or a 5, 6, or 7 membered saturated or partially unsaturated ring comprising 1 or 2 heteroatoms (e.g. aziridine, azetidine, piperidine, morpholine, thiomorpholine, pyrrolidine, homopiperazine, homopiperidine, or piperazine); and R_c is aryl, $(C_1\text{-}C_8)$alkyl, halo$(C_1\text{-}C_8)$alkyl $(C_1\text{-}C_8)$alkoxy, or aryl-$(C_1\text{-}C_8)$alkoxy, wherein any aryl can optionally be substituted with one or more $(C_1\text{-}C_8)$alkyl. In one embodiment of the invention R_1 is not *tert*-butylsulfonyl (e.g. for a compound of formula **V**).

Another specific value for R_1 is $-S(=O)_2NR_aR_b$ wherein each of R_a and R_b is independently $(C_1\text{-}C_8)$alkyl; or R_a and R_b together with the nitrogen to which they are attached form a 3 or 4 membered saturated ring or a 5, 6, or 7 membered saturated or partially unsaturated ring comprising 1 or 2 heteroatoms (e.g. aziridine, azetidine, piperidine, morpholine, thiomorpholine, pyrrolidine, homopiperazine, homopiperidine, or piperazine.)

Another specific value for R_1 is:





Another specific value for R_1 is $-S(O)_2N(CH_3)_2$.

Another specific value for R_1 is benzyloxycarbonyl.

A specific value for R_2 is an *N,N*-disubstituted aminosulfonyl group.

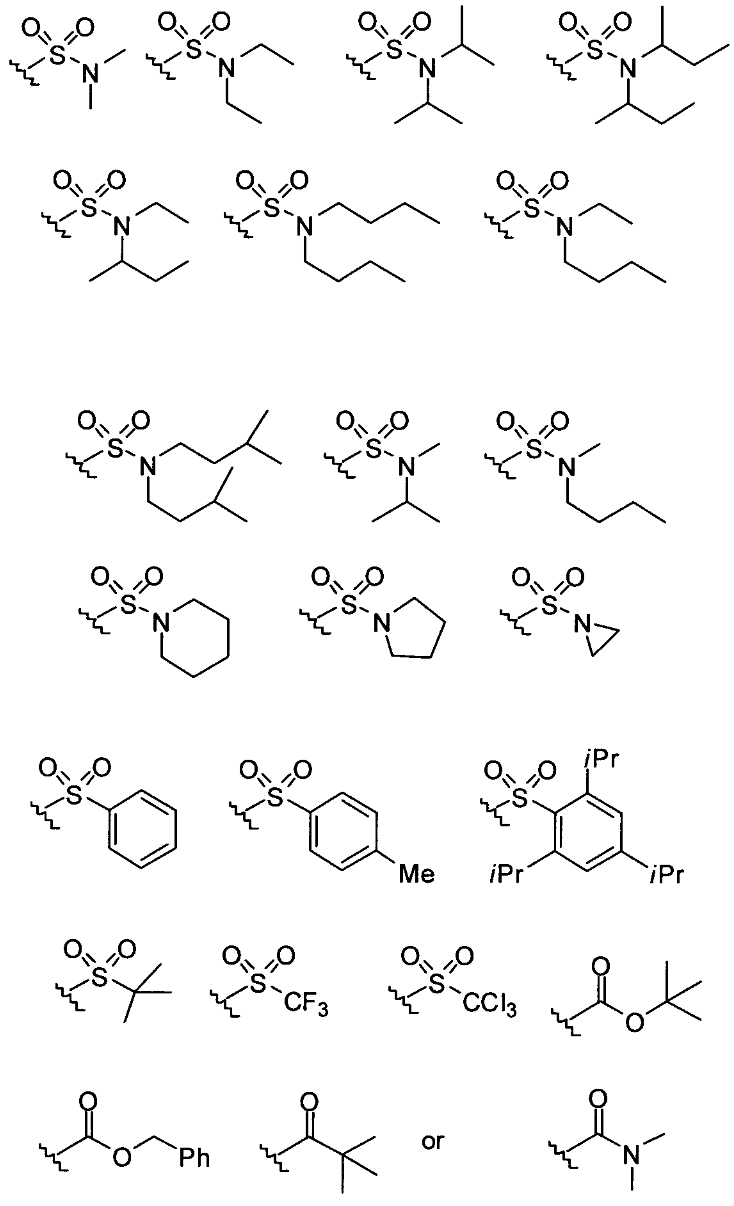
Another specific value for R_2 is an *N,N*-dialkyl aminosulfonyl group.

Another specific value for R_2 is $-S(=O)_2NR_aR_b$, $-S(=O)_2R_c$, $-C(=O)R_c$, or $-C(=O)NR_aR_b$ wherein each of R_a and R_b is independently $(C_1\text{-}C_8)$alkyl; or R_a and R_b together with the nitrogen to which they are attached form a 3 or 4 membered saturated ring or a 5, 6, or 7 membered saturated or partially unsaturated ring comprising 1 or 2 heteroatoms (e.g. aziridine, azetidine, piperidine, morpholine, thiomorpholine, pyrrolidine, homopiperazine, homopiperidine, or piperazine); and R_c is aryl, $(C_1\text{-}C_8)$alkyl, halo$(C_1\text{-}C_8)$alkyl $(C_1\text{-}C_8)$alkoxy, or aryl-$(C_1\text{-}C_8)$alkoxy, wherein any aryl can optionally be substituted with one or more $(C_1\text{-}C_8)$alkyl.

Another specific value for R_2 is $-S(=O)_2NR_dR_e$ wherein each of R_d and R_e is independently $(C_1\text{-}C_8)$alkyl; or R_d and R_e together with the nitrogen to which they are attached form a 3 or 4 membered saturated ring or a 5, 6, or 7 membered saturated or partially unsaturated ring comprising 1 or 2 heteroatoms (e.g. aziridine, azetidine, piperidine, morpholine, thiomorpholine, pyrrolidine, homopiperazine, homopiperidine, or piperazine.

Another specific value for R_2 is a leaving group such as 4-methylphenyl-sulfonyl, methylsulfonyl, trifluoromethylsulfonyl.

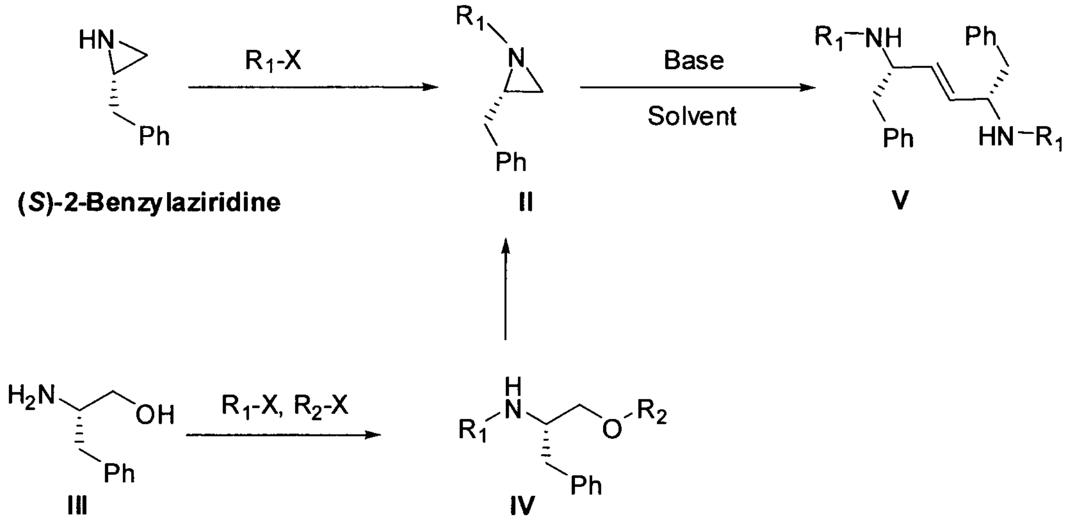
Another specific value for R_2 is:



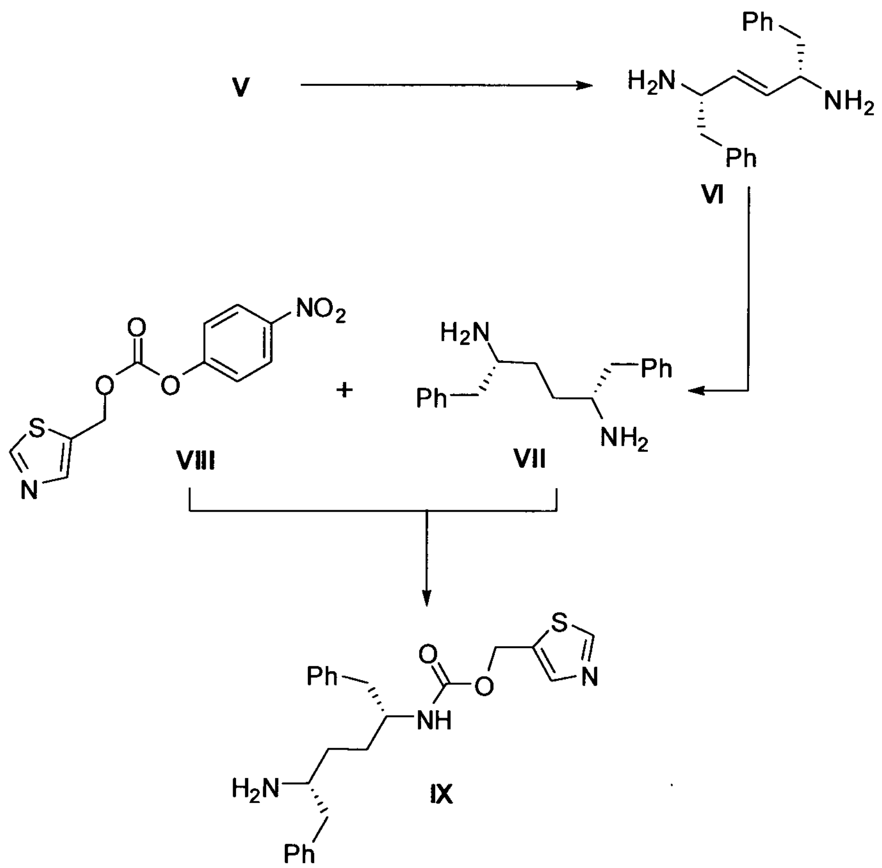
A specific value for R^3 is H.

A compound of formula **I** or a salt thereof can be prepared as illustrated in Schemes 1-4 below.

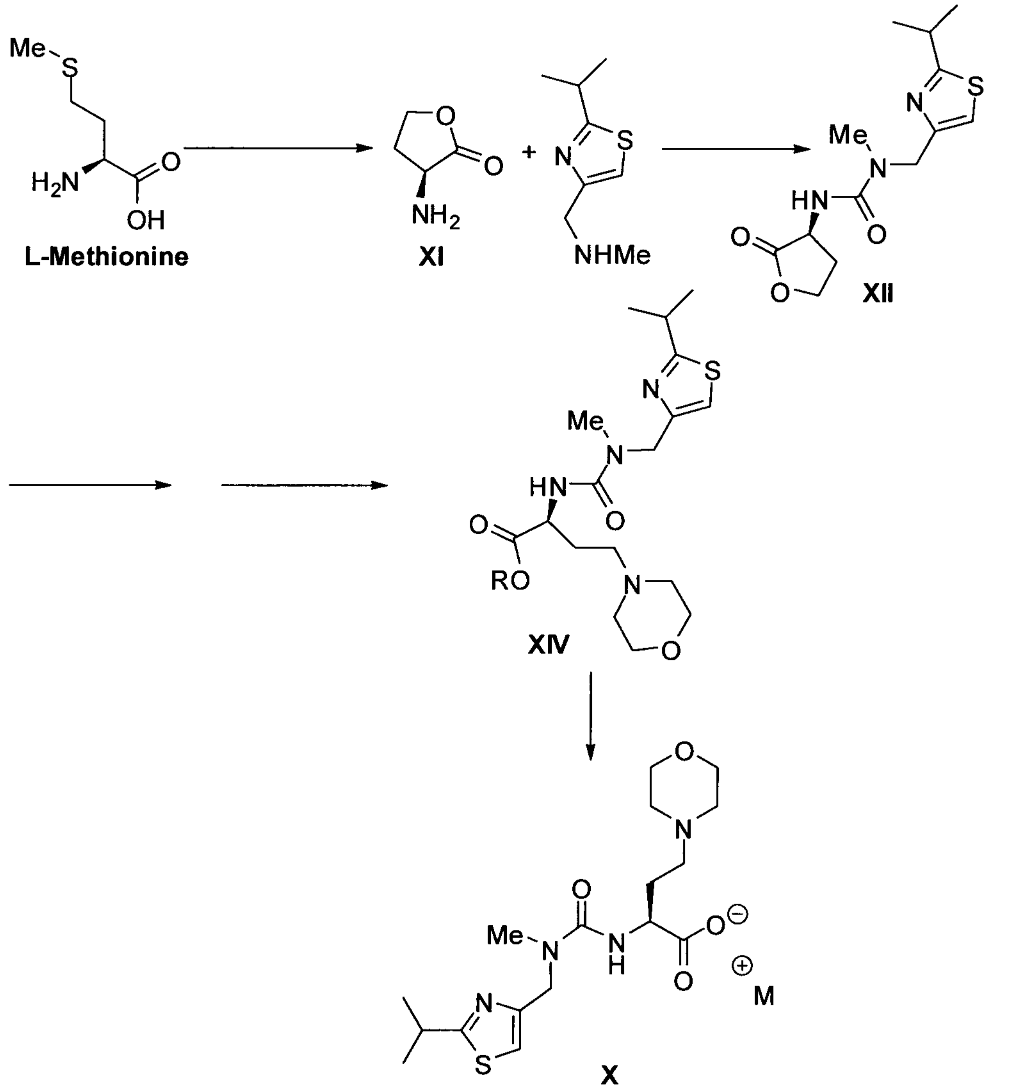
Scheme 1



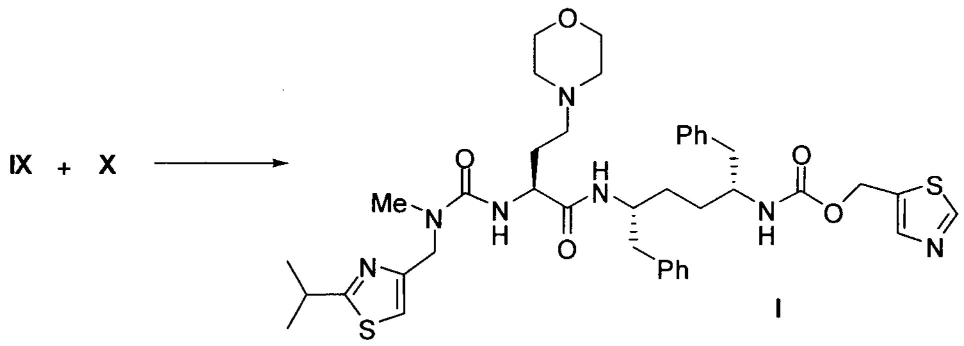
Scheme 2



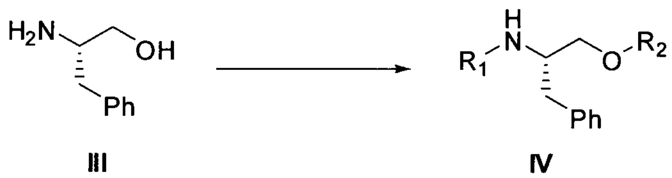
Scheme 3



Scheme 4



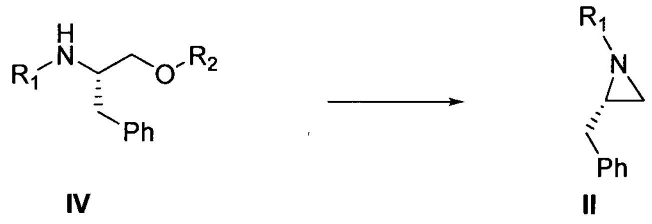
Preparation of a compound of formula **IV**



A compound of formula **III** can be protected with any suitable protecting groups (R_1 and R_2, which can be the same or different) under standard conditions to provide the corresponding compound of formula **IV**. For example, the reaction(s) can be carried out in a suitable solvent in the presence of a base. Suitable solvents include aprotic solvents such as, dichloromethane, tetrahydrofuran, and 2-methyltetrahydrofuran, as well as other aprotic organic solvents, and mixtures thereof. Suitable bases include trialkylamines, such as triethylamine, diisopropylethylamine, and *N*-methyl morpholine, as well as hydride bases, such as sodium hydride. The reaction can conveniently be carried out at a temperature from about -20 °C to 40 °C.

Suitable protecting groups include a *tert*-butylsulfonyl (Bus) group, *N,N*-dialkylsulfamoyl groups such as *N,N*-diisopropylsulfamoyl , *N*-aziridinylsulfamoyl and other sulfamoyl groups containing an *N*-heterocycle (such as pyrrolidine or piperidine), as well as *N*-ethyl and *N*-methylsulfamoyl groups and other mixed *N*-alkylsulfamoyl groups.

Preparation of a compound of formula **II**



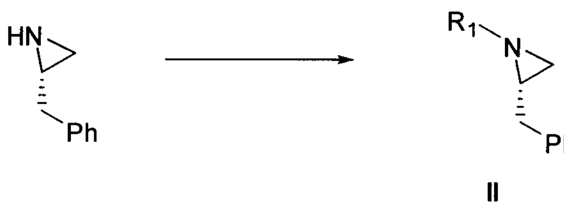
A compound of formula **II** can be prepared from a compound of formula **IV** by treatment with a base in a suitable solvent. Suitable bases include metal hydrides such as sodium hydride and potassium hydride; lithium 2,2,6,6-tetramethylpiperidide; the alkoxides, such as sodium *tert*-butoxide or lithium *tert*-butoxide, the hexamethyldisilazides, such as lithium hexamethyldisilazide, and carbonate bases, such as potassium carbonate or cesium carbonate.

Suitable solvents include aprotic solvents such as dichloromethane, tetrahydrofuran, and 2-methyltetrahydrofuran, as well as other aprotic organic solvents, and mixtures thereof. The reaction can conveniently be carried out at a temperature from about 0 °C to 22 °C.

Suitable R_1 groups include a *tert*-butylsulfonyl (Bus) group, *N,N*-dialkylsulfamoyl groups such as *N,N*-diisopropylsulfamoyl , *N*-aziridinylsulfamoyl and other sulfamoyl groups containing an *N*-heterocycle (such as pyrrolidine or piperidine), as well as *N*-ethyl and *N*-methylsulfamoyl groups and other mixed *N*-alkylsulfamoyl groups.

The resulting compound of formula **II** can be purified by recrystallization from a suitable solvent or mixture of solvents. For example, combinations of ethereal and non-polar solvents, such as isopropyl ether/heptane as well as crystallization out of concentrated solutions of purely ethereal solvents such as *tert*-butyl methyl ether can be carried out.

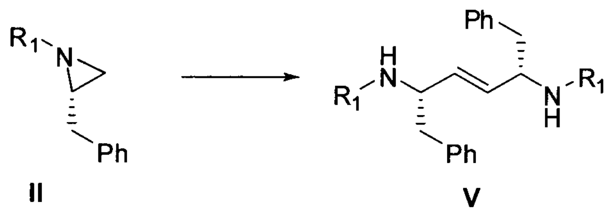
Alternative preparation of a compound of formula **II**



The starting aziridine can be protected with any suitable protecting group (R_1), for example, by treatment with a compound R_1-X wherein X is a leaving group, under standard conditions to provide the corresponding compound of formula **II**. For example, the reaction can be carried out in a suitable solvent in the presence of a base. Suitable solvents include aprotic solvents such as dichloromethane, tetrahydrofuran, ethyl ether, *tert*-butyl methyl ether, tetrahydropyran, 1,4-dioxane, 1,2-dichloroethane, and mixtures thereof. Suitable bases include trialkylamines such as triethylamine, *N*-methyl morpholine, quinuclidine, *N*-methylpiperidine, *N,N*-diisopropylethylamine, and *N*-methyl pyrrolidine; as well as other weak, non-nucleophilic bases such as, potassium carbonate and sodium bicarbonate. The reaction can conveniently be carried out at a temperature from about -10 °C to 40 °C.

The resulting compound of formula **II** can be purified by recrystallization from a suitable solvent or mixture of solvents. For example, combinations of ethereal and non-polar solvents, such as ethyl ether, *n*-butyl ether, tetrahydrofuran, tetrahydropyran, 1,2-dimethoxyethane, hexanes, *tert*-butyl methyl ether, heptane, pentane, cyclohexane, toluene can be used.

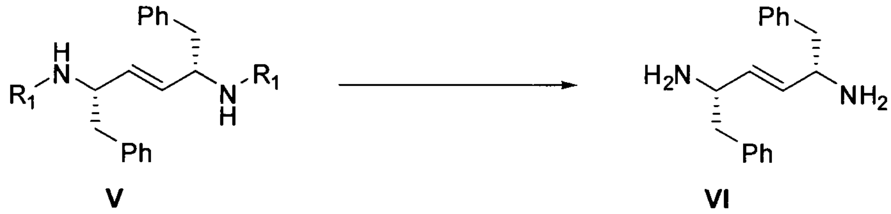
<u>Preparation of a compound of formula **V**:</u>



The starting aziridine can be dimerized by treatment with a non-nucleophilic amide base in a suitable solvent. Suitable solvents include ethers such as ethyl ether, *tert*-butyl methyl ether, *n*-butyl ether, tetrahydropyran, and tetrahydrofuran, as well as hydrocarbons such as hexanes and heptane, and mixtures thereof. Suitable non-nucleophilic amide base include lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium di-*t*-butylamide, and lithium isopropylcyclohexylamide. The reaction can conveniently be carried out at a temperature from about -78 °C to 22 °C.

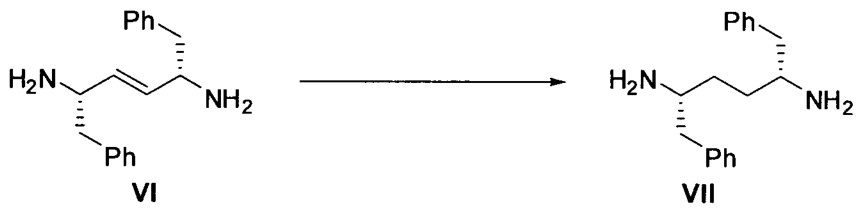
The resulting compound of formula **V** can be purified by recrystallization from a suitable solvent or mixture of solvents. For example, combinations of ethereal and non-polar solvents, such as ethyl ether, *n*-butyl ether, tetrahydrofuran, tetrahydropyran, 1,2-dimethoxyethane, and *tert*-butyl methyl ether can be used.

Preparation of a compound of formula **VI**:



The starting compound of formula **V** can be deprotected under standard conditions to provide the corresponding compound of formula **VI**. The reaction can be carried out in a solvent that comprises an amine; for example, a monoamine such as ethanolamine, a diamine such as 1,3-diaminopropane, ethylenediamine, 1,2-diaminocyclohexane, 1,2-phenylenediamine, putrescene, or cadaverine, or a polyamine such as diethylenetriamine, triethylenetriamine, or polyethyleneimine. The solvent can also comprise toluene, anisole, or the like, or mixtures thereof. The reaction can conveniently be carried out at a temperature from about 100 °C to about 140 °C.

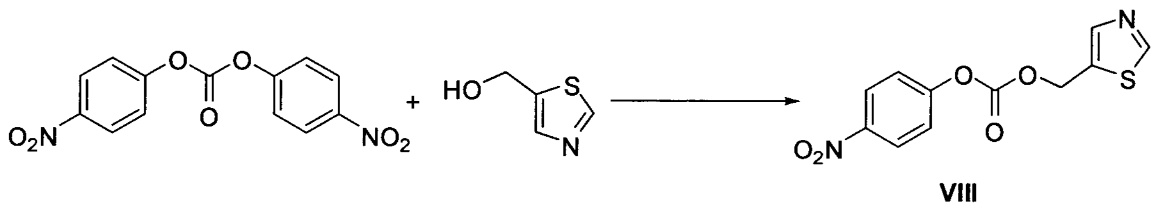
Hydrogenation to provide a compound of formula **VII**



The starting alkene **VI** can be hydrogenated under standard conditions. For example, the hydrogenation can be carried out using a metal containing catalyst in an alcoholic solvent. Suitable solvents include methanol, ethanol, isopropanol, *n*-propanol, butanol, ethyl acetate, toluene, dioxane, and anisole, and mixtures thereof. Suitable catalysts include palladium on carbon, platinum on carbon, Raney nickel, Wilkinson's catalyst, and palladium hydroxide. The reaction can conveniently be carried out at a pressure from about ambient pressure to about 60 psi.

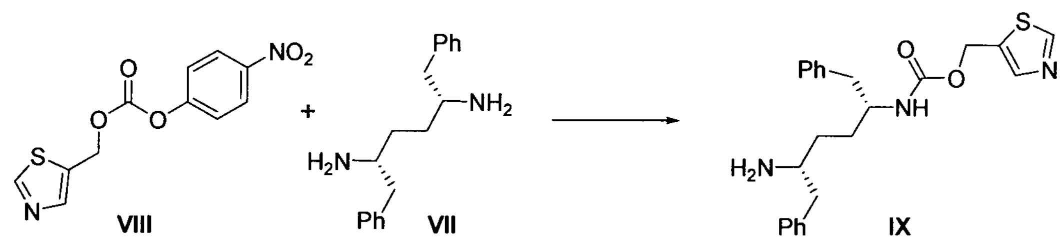
The compound of formula **VII** can conveniently be isolated by treatment with an acid in an organic solvent to provide a corresponding salt. Suitable acids include hydrochloric acid, hydrobromic acid, hydroiodic acid, and sulfuric acid. Suitable solvents include dichloromethane, ethyl ether, tetrahydrofuran, *tert*-butyl methyl ether, 1,4-dioxane, 1,2-dimethoxyethane, chloroform, 1,2-dichloroethane, toluene, and anisole, and mixtures thereof. The conversion to the salt can conveniently be carried out at a temperature from about -10 °C to about 40 °C.

<u>Preparation of a compound of formula **VIII**:</u>



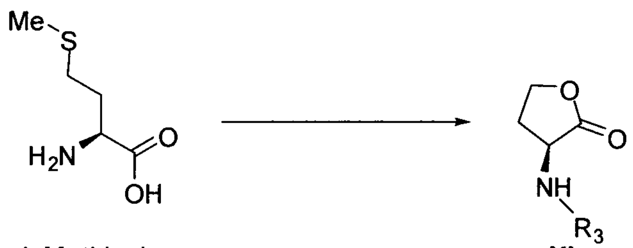
The mixed carbonate of formula **VIII** can be prepared by treating 5-hydroxymethylthiazole with a suitable carbonate or carbonate equivalent having a leaving group adjacent to the carbonyl carbon, such as phosgene in the presence of a base. For example, suitable carbonates include bis-(4-nitrophenyl)carbonate and disuccinimidyl carbonate. The reaction can conveniently be carried out in a suitable aprotic organic solvent, such as dichloromethane, tetrahydrofuran, 1,2-dichloroethane, or diethylether, or a mixture thereof. Suitable bases include trialkylamine bases, such as diisopropylethylamine, *N*-methyl morpholine, and triethylamine.

<u>Preparation of a compound of formula **IX** or a salt thereof</u>



A compound of formula **IX** or a salt thereof can be prepared from a compound of formula **VII** or a salt thereof by treatment with a carbonate of formula **VIII** or a salt thereof in the presence of a suitable base in a suitable solvent. Suitable bases include carbonate bases (e.g. potassium carbonate) and trialkylamines (e.g. diisopropylethylamine, or *N*-methyl morpholine). Suitable solvents include solvents such as dichloromethane, tetrahydrofuran, 1,2-dichloroethane, isopropylacetate, and diethylether, and mixtures thereof.

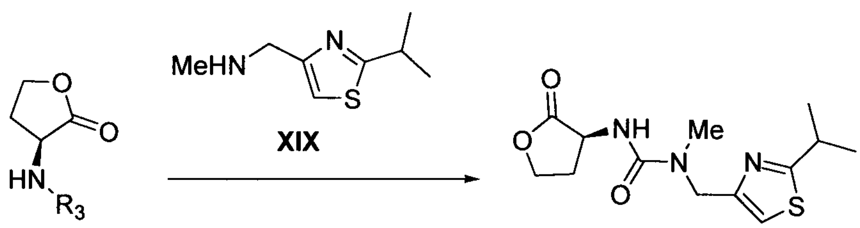
Preparation of a compound of formula **XI:**



L-Methionine **XI**

A compound of formula **XI** wherein R_3 is H or a salt thereof can be prepared by treating L-methionine with an alkylating agent in the presence of water and acetic acid. Suitable alkylating agents include alkyl bromides (bromoacetic acid), alkyl iodides, alkyl chlorides, and dimethyl sulfate. The reaction can conveniently be carried out in a solvent that comprises an alcohol (e.g. isopropanol), water, and acetic acid. The reaction can be carried out at a temperature from about 22 °C to about 90 °C. A compound of formula **XI** wherein R_3 is a protecting group (e.g. a carbamate , amide, or benzyl protecting group) or a salt thereof can be prepared by protecting a corresponding compound of formula **XI** wherein R_3 is hydrogen to provide the compound of formula **XI** wherein R_3 is a protecting group or the salt thereof.

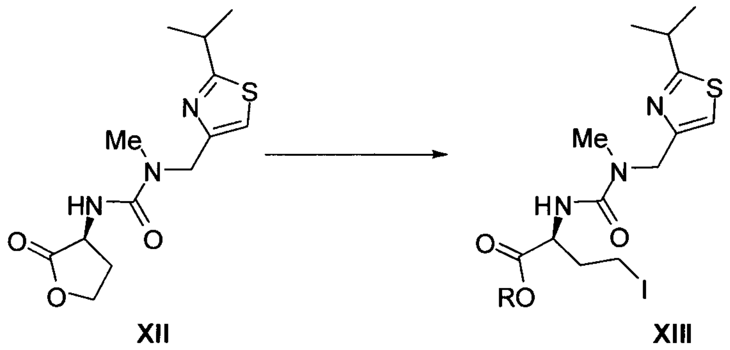
Preparation of a compound of formula **XII:**



XI **XII**

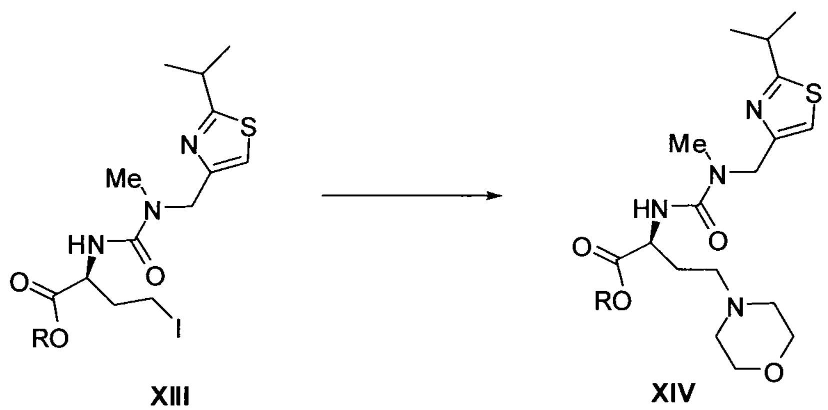
A compound of formula **XII** can be prepared by treating a compound of formula **XI** wherein R_3 is H or a protecting group (e.g. a carbamate, amide, or benzyl protecting group), or a salt thereof with a compound of formula **XIX** or a salt thereof, in an aprotic solvent at a temperature from about 0 °C to about 30 °C in the presence of a suitable base and a carbonyl source, such as CDI. When R_3 is a protecting group it can subsequently be removed to provide the compound of formula **XII** or the salt thereof. Suitable bases include metal hydrides (e.g. sodium hydride), and trialkylamines (e.g. diisopropylethylamine, triethylamine, *N*-methyl morpholine or DBU). Suitable aprotic solvents include tetrahydrofuran, 2-methyltetrahydrofuran, and dichloromethane, and mixtures thereof.

<u>Preparation of a compound of formula **XIII**:</u>



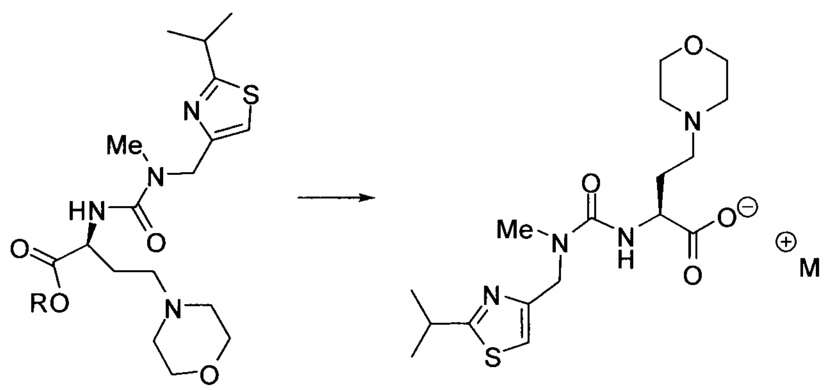
A compound of formula **XIII** can be prepared by treating a compound of formula **XII** or a salt thereof with a suitable iodide source (e.g. trimethylsilyl iodide, hydrogen iodide, or sodium iodide and trimethylsilyl chloride) in an aprotic solvent in the presence of an alcohol ROH to provide the compound of formula **XIII** wherein R is $(C_1$-$C_8)$alkyl. Suitable aprotic solvents include tetrahydrofuran, 2-methyltetrahydrofuran, dichloromethane, and acetonitrile, and mixtures thereof. The reaction can typically be carried out at a temperature from about 0 °C to about 22 °C.

<u>Preparation of a compound of formula **XIV** or a salt thereof:</u>



A compound of formula **XIV** or a salt thereof can be prepared by treating a compound of formula **XIII** wherein R is (C_1-C_8)alkyl with morpholine to provide the compound of formula **XIV** or the salt thereof. The resulting compound of formula **XIV** can be converted to a corresponding salt by treatment with an acid (e.g. an organic acid such as oxalic acid, citric acid, or fumaric acid, or a mineral acid) in an organic solvent. Suitable solvents include *tert*-butyl methyl ether, methylene chloride, tetrahydrofuran, acetone, acetonitrile, toluene, heptanes, isopropyl acetate, ethyl acetate and alcohols, and mixtures thereof. The salt formation can typically be carried out at a temperature from about 22 °C to about 60 °C.

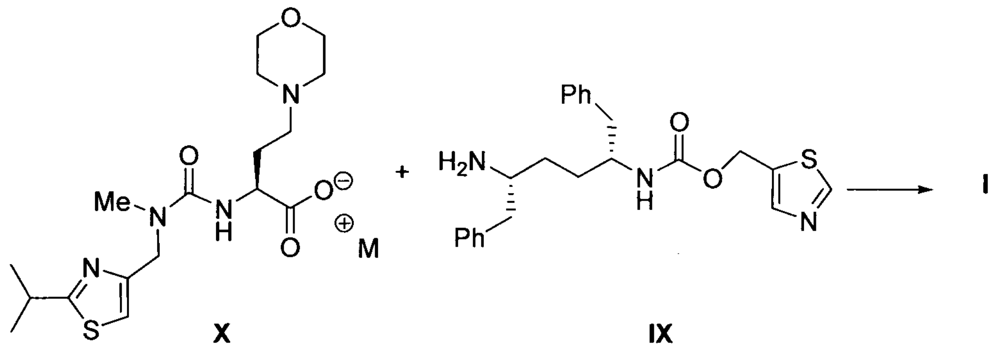
Preparation of a compound of formula **X:**



XIV X

A compound of formula **X** wherein $M^+$is a counterion, or a salt thereof, can be prepared by hydrolyzing an ester of formula **XIV** wherein R is (C_1-C_8)alkyl or a salt thereof under standard conditions. For example, the hydrolysis can be carried out in an aqueous solvent (e.g. water and dichloromethane) in the presence of a base (e.g. potassium hydroxide or lithium hydroxide) at a temperature from about -10 °C to about 28 °C.

Preparation of a compound of formula **I:**

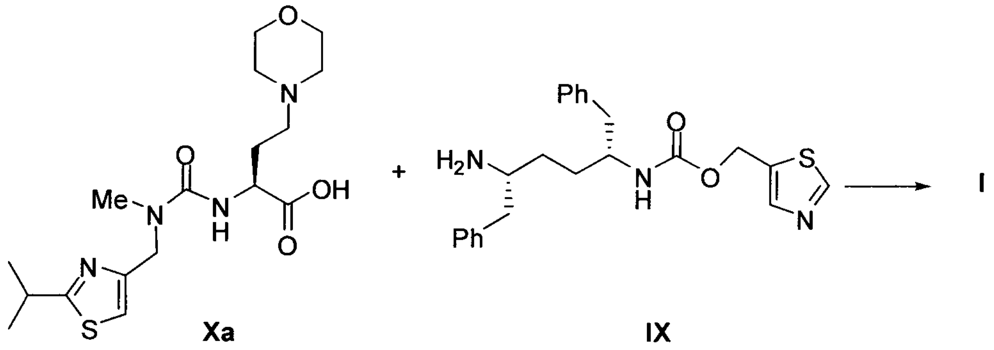


A compound of formula **I** or a salt thereof can be prepared by coupling an acid salt of formula **X** wherein M^+ is a counterion with an amine of formula **IX** to form the corresponding amide. This amide forming reaction can be carried out under standard conditions. For example, it can be carried out in a suitable organic solvent (e.g. dichloromethane) in the presence of a suitable coupling agent (e.g. EDC•HCl and HOBt). Other suitable amide coupling reagents and conditions are known in the field. The reaction can typically be carried out at a temperature from about -30 °C to about 20 °C.

When carried out in dichloromethane or toluene or a mixture thereof, this coupling reaction unexpectedly provides improved results compared to the coupling in tetrahydrofuran that is described on page 254 of international patent application publication number WO 2008/103949. Accordingly, in one embodiment, the invention provides a process for preparing a compound of formula **I** comprising coupling an acid salt of formula **X** with an amine of formula **IX** or a salt thereof in dichloromethane or toluene or a mixture thereof. This reaction can conveniently be carried out in the presence of a coupling agent (e.g. EDC•HCl and HOBt) at a temperature from about -30 °C to about 20 °C.

The resulting compound of formula **I** can be isolated using standard techniques. The compound of formula **I** can be isolated employing a solid support material as described in International Patent Application Publication Number WO 2009/135179

Alternative Preparation of a compound of formula **I:**

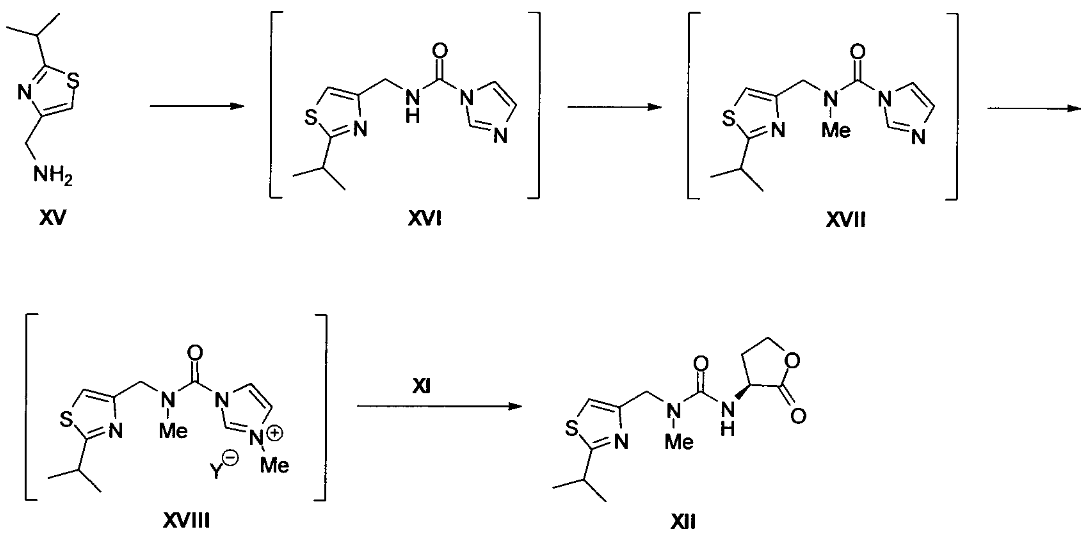


A compound of formula **I** or a salt thereof can be prepared by coupling an acid of formula **Xa** or a salt thereof with an amine of formula **IX** or a salt thereof to form the corresponding amide. This amide forming reaction can be carried out under standard conditions. For example, it can be carried out in a suitable organic solvent (e.g. dichloromethane) in the presence of a suitable coupling agent (e.g. EDC•HCl and HOBt). Other suitable amide coupling reagents and conditions are known in the field. The reaction can typically be carried out at a temperature from about -30 °C to about 20 °C.

Alternative preparation of a compound of formula **XII**

The compound of formula **XII** shown in Scheme III above can also be prepared as illustrated in Scheme V.

Scheme V

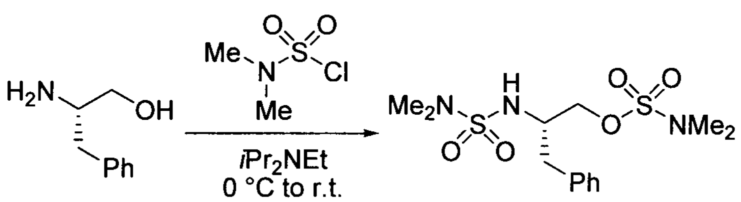


Preparation of a compound of formula **XII**

The amine of formula **XV** or a salt thereof can be treated with carbonyldiimidazole, in the presence of a suitable base (e.g. a trialkylamine, such as triethylamine, N-methyl morpholine, diisopropylethylamine, or DBU; a hydride base, such as sodium hydride; or an amide base, such as LiHMDS) in an aprotic solvent (e.g. tetrahydrofuran, or 2-methyltetrahydrofuran) to provide the urea of formula **XVI**. Alkylation of the urea of formula **XVI** with a suitable methylating agent (e.g. methyl iodide) in the presence of a base in an aprotic solvent provides a compound of formula **XVII**. Further alkylation with a suitable methylating agent (e.g. methyl iodide) provides a salt of formula **XVIII**. Treatment of the salt of formula **XVIII** with an *N*-unprotected amino γ-lactone of formula **XI** or with a corresponding *N*-protected amino γ-lactone (e.g. a carbamate, amide or benzylamine) in a suitable aprotic solvent (e.g. tetrahydrofuran, or 2-methyltetrahydrofuran) in the presence of a suitable base (e.g. a trialkylamine, such as triethylamine, N-methyl morpholine, diisopropylethylamine, or DBU) provides the compound of formula **XII**. If an *N*-protected amino γ-lactone is utilized in the previously described step (i.e. R_3 is a protecting group), the resulting protected product can be deprotected to provide the compound of formula **XII**.

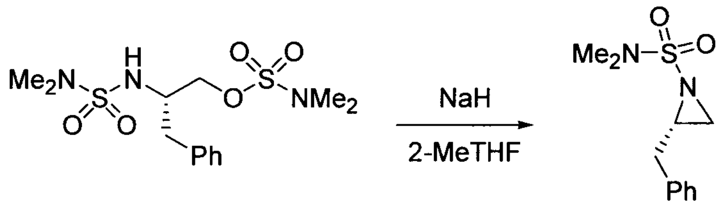
The invention will now be illustrated by the following non-limiting examples.

Example 1. Preparation of *protected(L)-phenylalaninol* ***IVa***:



L-phenylalaninol **III** (5.0 g) was dissolved in dichloromethane (150 mL). The resulting solution was cooled to 0 °C and diisopropylethylamine (21.4 g) was charged to the reaction mixture, followed by *N,N*-dimethylsulfamoyl chloride (10 g). The reaction was warmed to room temperature and allowed to stir. After 20 hours, the reaction was quenched with saturated aqueous ammonium chloride (100 mL) and water (50 mL). The layers were then separated and the organic phase was washed with 1 M HCl (2 x 10 volumes) and water (2 x 50 mL). The organics were then dried over sodium sulfate. The solids were filtered off and the liquors were concentrated in vacuo to yield 97% of compound **IVa** as a yellow-orange oil. Compound **IVa** was then typically used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H), 4.94 (d, 1H, J = 8 Hz), 3.75 (m, 1H), 3.57 (m, 2H), 2.94 (s, 6H), 2.85 (m, 2H), 2.54 (s, 6H).

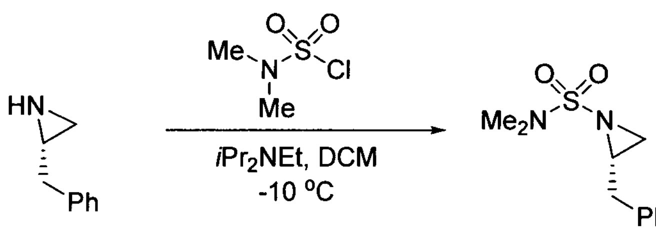
<u>Example 2</u>. Preparation of *(S)-2-benzyl-N,N-dimethylaziridine-1-sulfonamide* ***IIa***



IVa **IIa**

Protected amino alcohol **IVa** (10 g) was dissolved in 2-MeTHF (300 mL). The resulting solution was cooled to 0 °C. Sodium hydride (2.0 g) was then charged portion-wise. The reaction was then warmed to room temperature and allowed to stir. After 4.5 hours, the reaction was cooled to 0 °C and quenched with saturated aqueous ammonium chloride solution (150 mL) and water (100 mL). The layers were separated and the organic layer was washed with 1M HCl (150 mL) followed by saturated aqueous NaCl (150 mL). The organics were dried over sodium sulfate. The solids were filtered off and the filtrate concentrated. Further purification can be done either by column chromatography eluting with 100% dichloromethane, or by recrystallization from MTBE/hexanes, ultimately yielding 64% of compound **IIa** as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 2.94 (dd, 1H, J = 14, 5 Hz), 2.83 (m, 1H), 2.71 (dd, 1H, J = 14, 7 Hz), 2.66 (s, 6H), 2.56 (d, 1H, J = 7Hz), 2.14 (d, 1H, J = 4 Hz); ^{13}C NMR ($CDCl_3$) δ 137.4, 129.3, 128.9, 127.2, 77.6, 77.3, 77.0, 40.6, 38.3, 38.1, 33.0.

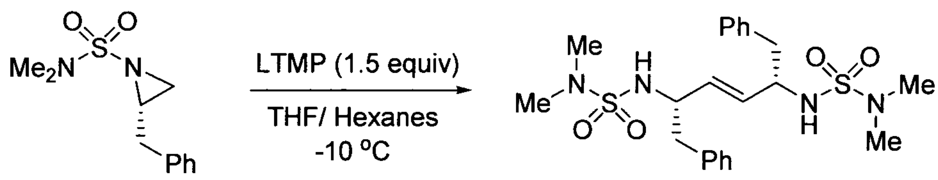
<u>Example 3</u>. Alternative Preparation of *(S)-2-benzyl-N,N-dimethylaziridine-1-sulfonamide* ***IIa**:*



IIa

To a cooled (-10 °C) solution of (*S*)-2-benzylaziridine (100 g, 0.751 mol) and *N,N*-dimethylsulfamoyl chloride (84.5 mL, 0.787 mol) in dichloromethane (100 mL) was added *N,N*-diisopropylethylamine (131 mL, 0.751 mol) . The resulting yellow solution was stirred at -10 °C for a minimum of 16 hours. After this period, a 0.5M solution of citric acid (500 mL) was added and the phases were separated. The organic phase was then washed with 1.0 M sodium bicarbonate solution (500 mL). The organic phase was then solvent exchanged into *tert*-butyl methyl ether (500 mL). The solution was then cooled to 0 °C, and heptane (100 mL) was added dropwise over a period of 2 hours. The mixture was then aged for an additional 2hours at 0 °C , and then cooled (-10 °C), to allowed compound **IIa** to precipitate out as a white, crystalline solid (27.8 g, 77%). Tlc assay: R_f: 0.53 (SiO_2; 1:1 heptane:ethyl acetate, $KMnO_4$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.20-7.29 (m, 5H), 2.94 (dd, *J* = 14, 5 Hz, 1H), 2.80-2.88 (m, 1H), 2.70 (dd, *J* = 14, 7 Hz, 1H), 2.66 (s, 6H), 2.56 (d, *J* = 7 Hz, 1H), 2.14 (d, *J* = 4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 129.3, 128.9, 127.2, 40.6, 38.3, 38.1, 33.0.

<u>Example 4</u>. Preparation of *Protected Diamine **Va**:*

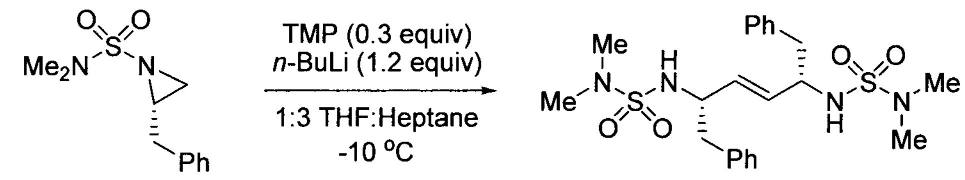


IIa **Va**

To a cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (5.5 mL) in tetrahydrofuran (14 mL) was added *n*-butyllithium (10M in hexanes, 3.1 mL). The resulting cloudy, yellow solution was warmed to 22 °C and allowed to stir at that temperature for 20 minutes.

To a cooled (-10 °C) cloudy solution of **IIa** (5.0 g) in tetrahydrofuran (7 mL) was added the preformed lithium tetramethylpiperidide (LTMP) dropwise by syringe pump (addition rate: 40 mL/hr, LTMP temperature: 22 °C). During the addition, the reaction gradually turns to a purple-brown solution. The reaction was then allowed to slowly warm to 0 °C over the course of 45 minutes. A 10% (w/v) solution of citric acid (15 mL) was then added to the cold reaction and the resulting bright-yellow solution was stirred vigorously at 0 °C for several minutes. The biphasic mixture was then diluted with ethyl acetate (75 mL) and the phases were separated. The organic phase was washed with 10% (w/v) citric acid (1 x 15 mL), saturated sodium bicarbonate (2 x 15 mL) and brine (1 x 15 mL). The organic phase was subsequently dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a bright yellow solid. The crude mixture was suspended in hot *tert*-butyl methyl ether, cooled to -16 °C, and filtered to give **Va** as a white powder (3.2 g, 64%). Tlc assay: R_f: 0.32 (SiO_2, 1:1 heptane:ethyl acetate, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.35 (m, 10H), 5.59 (s, 2H), 3.95-4.10 (m, 4H), 2.80 (ddd, J = 22, 13, 6 Hz, 4H), 2.59 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 132.0, 129.9, 128.9, 127.2, 57.0, 42.4, 38.1.

Example 5. Alternative Preparation of *Protected Diamine **Va**:*

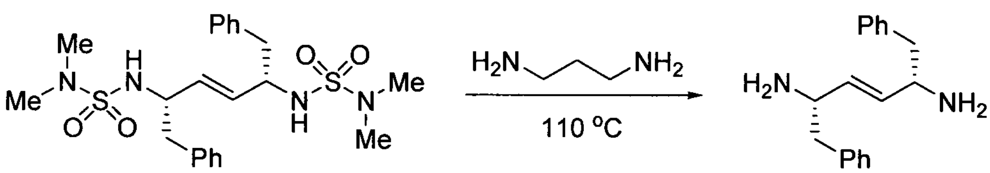


IIa **Va**

To a cooled (-10 °C) slurry of **IIa** (10.0 g) and 2,2,6,6-tetramethylpiperidine (2.1 mL) in 1:3 tetrahydrofuran:heptane (30 mL) was slowly added *n*-butyllithium (2.6M in hexanes, 19 mL) over the course of 3 hr. During the addition, the reaction gradually turned to a purple-brown solution; upon completion the resulting was stirred at that temperature for an additional 20 minutes.

Glacial acetic acid (4.0 mL) was then added to the cold reaction and the resulting bright-yellow suspension was stirred vigorously at 5 °C for several minutes. The mixture was then filtered and the solid material was washed with 3:1 *t*-butyl methyl ether : heptane (2 x 30 mL), water (3 x 30 mL), and again with 3:1 *t*-butyl methyl ether : heptane (2 x 30 mL). The wet cake was then thoroughly dried to give **Va** as a white powder (7.22 g, 72%). Tlc assay: R_f: 0.32 (SiO_2, 1:1 heptane:ethyl acetate, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.35 (m, 10H), 5.59 (s, 2H), 3.95-4.10 (m, 4H), 2.80 (ddd, J = 22, 13, 6 Hz, 4H), 2.59 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 132.0, 129.9, 128.9, 127.2, 57.0, 42.4, 38.1.

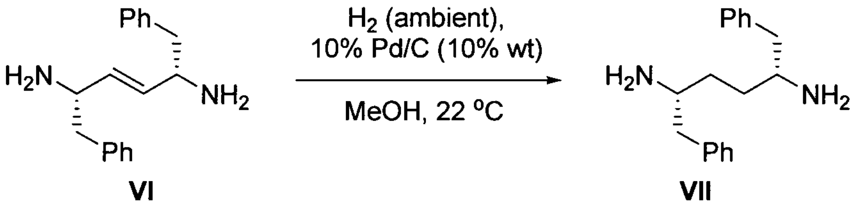
Example 6. Preparation of *unsaturated diamine **VI**:*



Va **VI**

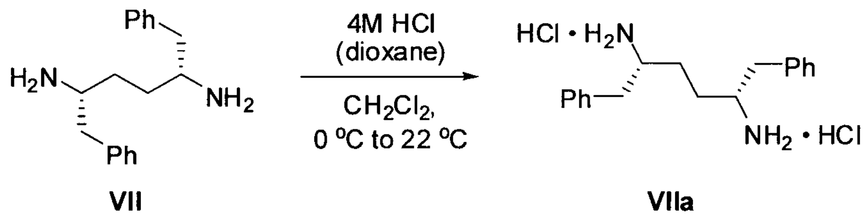
A solution of the protected diamine **Va** (2.0 g) in 1,3-diaminopropane (4 mL) was heated to 110 °C and stirred at that temperature for 90 minutes. After cooling the yellow solution to 22 °C, water (16 mL) was added followed by dichloromethane (20 mL). The phases were separated and the aqueous phase was washed with an additional portion of dichloromethane (1 x 10 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give **VI** as a thick, yellow oil (1.1 g, 100%). This material was used directly in the next reaction without further purification. Tlc assay: R_f: 0.61 (SiO_2, 4:1 CH_2Cl_2:CH_3OH w/ 5% Et_3N, $KMnO_4$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.10-7.35 (m, 10H), 5.60 (dd, J = 4, 2 Hz, 2H), 3.50-3.60 (br, 2H), 2.85 (dd, J = 13, 5 Hz, 2H), 2.60 (13, 8 Hz, 2H), 1.15 (br, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 134.1, 129.7, 128.6, 126.5, 54.9, 44.9.

Example 7. Preparation of *compound VII:*



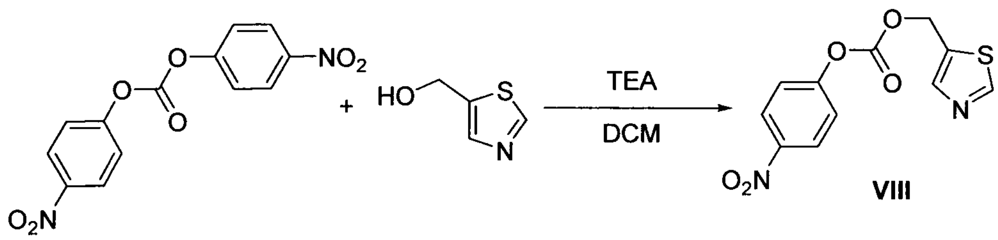
To a solution of unsaturated diamine **VI** (1.1g) in methanol (8.2 mL) was added 10% palladium on carbon (110 mg, 10 wt%). The resulting black suspension was purged with hydrogen gas and held under a hydrogen atmosphere (balloon) for 16 hours. The reaction was then filtered through celite and concentrated under reduced pressure to provide **VII** as a thick, yellow oil (1.11 g, 100%). This material was carried on to the next reaction without further purification. Tlc assay: R_f: 0.60 (SiO_2, 4:1 CH_2Cl_2:CH_3OH w/ 5% Et_3N, $KMnO_4$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.15-7.35 (m, 10H), 2.95-3.05 (m, 2H), 2.82 (dd, J = 13, 5 Hz, 2H), 2.50 (dd, J = 13, 9 Hz, 2H), 1.45-1.66 (m, 4H), 1.36 (br, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 129.5, 128.7, 126.5, 53.2, 45.1, 34.6.

Example 8. Preparation of *diamine-dihydrogen chloride **VIIa**:*



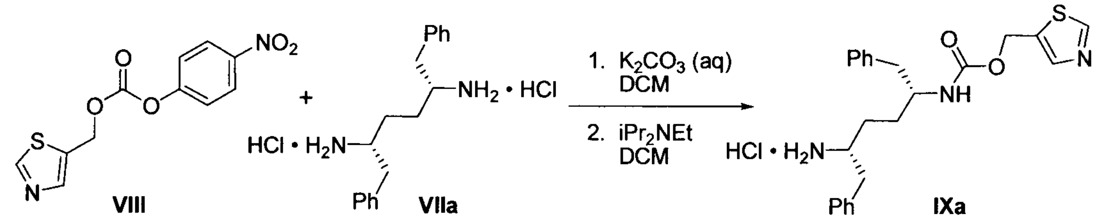
To a cooled (0 °C) solution of **VII** (1.11 g) in dichloromethane (14 mL) was added a solution of 4M hydrochloric acid in dioxane (2.6 mL). The resulting pale-pink suspension was allowed to warm to 22 °C and was stirred at that temperature for 90 minutes. The mixture was then filtered; the precipitate was washed with copious amounts of dichloromethane and dried *in vacuo* to provide **VIIa** as a pale-pink powder (1.32 g, 94% from **V**). ^{1}H NMR (400 MHz, D_2O): δ 7.10-7.35 (m, 10H), 3.38-3.48 (m, 2H), 2.92 (dd, J = 14, 7 Hz, 2H), 2.76 (dd, J = 14, 8 Hz, 2H), 1.58-1.74 (m, 4H).

Example 9. Preparation of *Carbonate VIII.*



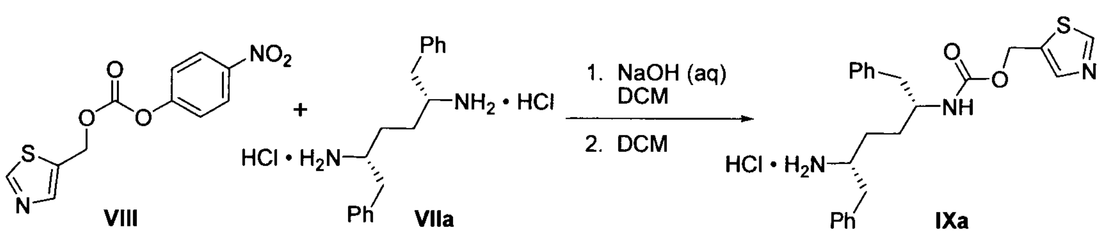
5-Hydroxymethylthiazole (5 kg) was dissolved in dichloromethane (210 kg). To this solution was added bis-(4-nitrophenyl)carbonate (15 kg) and triethylamine (7.5 kg). The reaction mixture was allowed to stir overnight. Upon reaction completion, the reaction mixture was washed with 1.0 M aqueous K_2CO_3 solution (50 kg) to fully remove 4-nitrophenol. The organic layer was then washed with 1.0 M aqueous citric acid until the pH of the organic solution was less than 8. The organic layer was dried over Na_2SO_4. The solids were then filtered off and the organic layer was solvent exchanged into isopropyl acetate and concentrated to a volume of approximately 4 volumes. To this solution was slowly added n-heptane (100 L) and allowed to age over a period of 5 or more hours. This affords **VIII** as a solid which can subsequently be isolated via filtration. ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.26 (d, 2H), 7.99 (s, 1H), 7.37 (d, 2H), 5.51 (s, 2H).

Example 10a. Preparation of *mono-carbamate hydrochloride* ***IXa***.



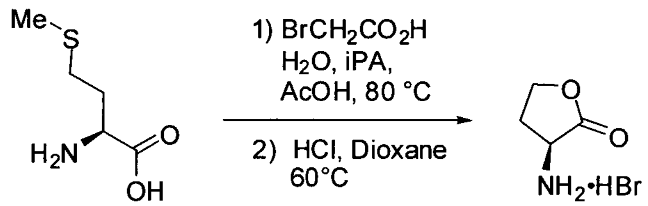
Diamine-dihydrochloride **VIIa** (2.37 kg), aqueous potassium carbonate (1M, 27 kg), and dichloromethane (68 kg) were agitated for 1 hour at 20 °C. The dichloromethane layer was separated, dried over sodium sulfate (7.1 kg), and filtered to afford the diamine freebase. To this solution was charged additional dichloromethane (66 kg) and mixed-carbonate **VIII** (1.95 kg). Once all solids had dissolved, diisopropylethylamine (1.1 kg, 8.3 mol) was added and the reaction monitored by tlc assay (SiO_2, 80% ethyl dichloromethane in methanol as eluant, product $R_f = 0.73$, visualization by UV). The reaction contents were washed with 0.25N aqueous NaOH until the presence of residual **VIII** and 4-nitrophenol were not detected by tlc assay. The organic layer was washed with water, dried over sodium sulfate (7 kg), filtered, concentrated and dissolved into isopropyl acetate (about 50 L) and diluted with dichloromethane (47 kg). To this solution was charged HCl (1.88 kg 4N HCl in dioxane, about 8.2 mol HCl) to induce precipitation. The product **IXa** was filtered and rinsed with isopropyl acetate (21 kg) and dried under vacuum to afford a white powder (2.57 kg, 83% yield). ^{1}H NMR (CD_3OD) δ 9.0 (s, 1H), 7.8 (s, 1H), 7.4-7.14 (m, 10H), 5.2 (d, 1H), 4.8 (s, 5 H) 3.7 (m, 1H), 3.6 (m, 1H), 3.3 (s, 1H), 2.6-2.8 (m, 2H), 1.8-1.4 (m, 4H). ^{13}C NMR (CD_3OD) δ 154.4, 143.2, 129.6, 128.0, 126.0, 58.0, 52.4, 44.3, 41.6, 33.8, 30.5.

Example 10b. Preparation of *mono-carbamate hydrochloride* ***IXa***.



Diamine-dihydrochloride **VIIa** (2.0 g), aqueous sodium hydroxide (3M, 4.1 g), and dichloromethane (13.3 g) were agitated for 1 hour at 20 °C. The dichloromethane layer was separated and subsequently washed with water (10 g) to afford the diamine freebase. To this solution was charged additional dichloromethane (26.6 g) and mixed-carbonate **VIII** (1.72 g). The resulting solution was heated to 40 °C and held at that temperature until the reaction was deemed complete by HPLC. The solvent was then removed *in vacuo*, co-distilled with tetrahydrofuran (17.8 g) and then rediluted with tetrahydrofuran (35.6 g). To this solution was then added concentrated hydrochloric acid (12M, 0.588 g) to induce precipitation. The product **IXa** was filtered, rinsed with 1% H_2O in 1:1 THF:CH_2Cl_2 (2 x 40mL) and dried under vacuum to afford a white powder (2.15 g, 82% yield). ^{1}H NMR (CD_3OD) δ 9.0 (s, 1H), 7.8 (s, 1H), 7.4-7.14 (m, 10H), 5.2 (d, 1H), 4.8 (s, 5 H) 3.7 (m, 1H), 3.6 (m, 1H), 3.3 (s, 1H), 2.6-2.8 (m, 2H), 1.8-1.4 (m, 4H). ^{13}C NMR (CD_3OD) δ 154.4, 143.2, 129.6, 128.0, 126.0, 58.0, 52.4, 44.3, 41.6, 33.8, 30.5.

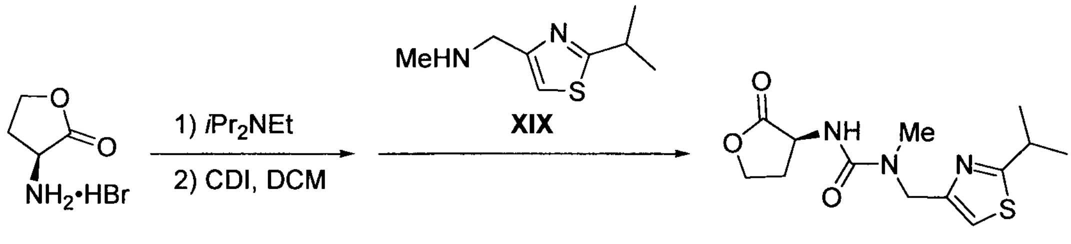
Example 11. Preparation of *amino lactone XIa:*



L-Methionine **XIa**

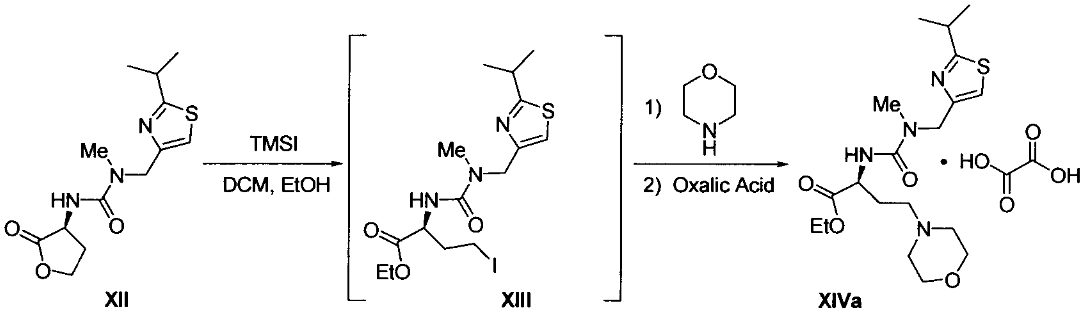
To a solution of *L*-methionine (46 kg) in water (69 kg, at ambient temperature was charged bromoacetic acid (46.0 kg), 2-propanol (69.0 kg) and acetic acid (69.0 kg). The resulting mixture was heated to reflux (85 °C to 95 °C) and agitated at this temperature until the reaction was judged complete by ^{1}H NMR. The mixture was concentrated under reduced pressure and co-evaporated with 2-propanol. 2-Propanol (161.0 kg) was charged to the concentrated mixture, followed by a slow addition of 10 wt% HCl/dioxane solution (102 kg) at ambient temperature. The resulting slurry was heated to about 60 °C and agitated for about 4 hours. The pot temperature was adjusted to about 22 °C and agitated for about 2 hours. The product **XIa** was filtered, washed with two portions of 2-propanol (28 kg each portion) and dried under vacuum at 40 °C to afford white to off-white solid (39.3 kg, 70% yield). ^{1}H NMR (D_2O) δ 4.79 (s, 2H), 4.61 (dd, 1H), 4.49-4.41 (m, 2H), 2.80 (m, 1H), 2.42 (m, 1H).

Example 12. Preparation of *urea XII:*



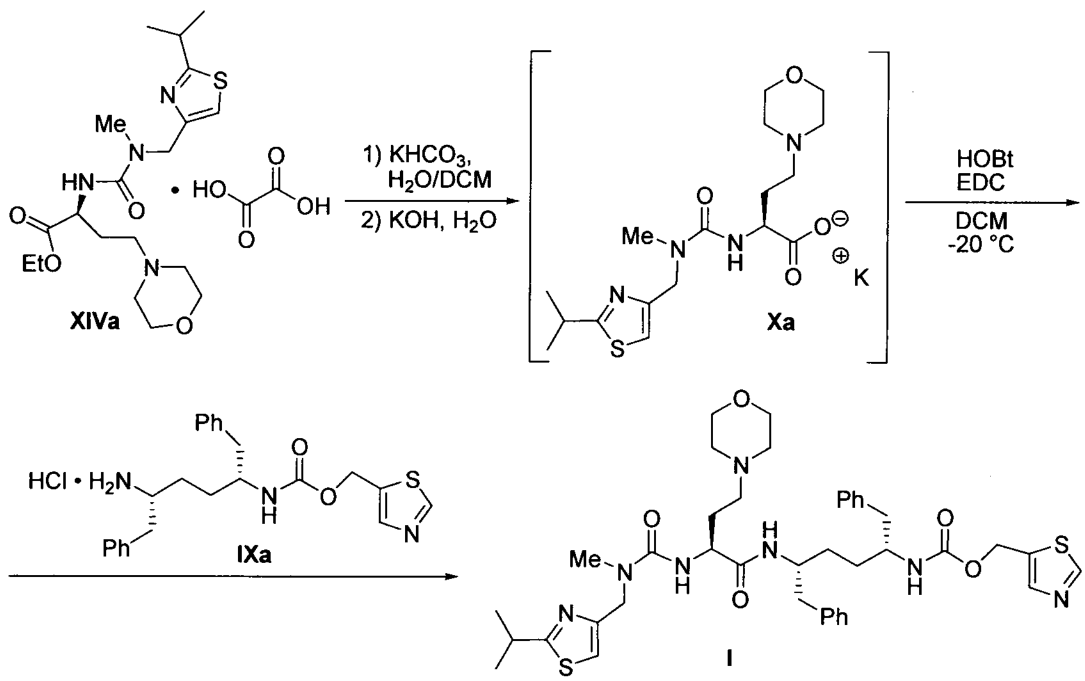
To a slurry of (*L*)-amino lactone **XIa** 31.5 kg) in dichloromethane (105 kg) was charged diisopropylethylamine (28.8 kg). The reaction mixture was cooled to about 10 °C and carbonyldiimidazole (27.1 kg) was added portion-wise while the content temperature was maintained at less than or equal to 25 °C. The resulting mixture was agitated until the reaction was judged complete. Methyl aminomethyl thiazole **XIX** (21.0 kg) was charged maintaining content temperature at less than or equal to 25 °C and agitated. Once complete, the reaction mixture was washed with water (63.0 kg), then two times with 20 wt% aqueous citric acid solution (63.0 kg). All the aqueous layers were combined and extracted with dichloromethane (63.0 kg). The organic layers were combined and washed once with 8 wt% aqueous sodium bicarbonate solution (63.0 kg) and once with water (63.0 kg). The organic layer was concentrated under reduced pressure to 3 volumes and co-evaporated with dichloromethane. The product **XII** was discharged as a stock solution in dichloromethane (33.4 kg, 91% yield). ^{1}H NMR ($CDCl_3$) δ 7.02 (s, 1H), 4.55-4.41 (m, 4H), 4.27 (m, 1H), 3.29 (septets, 1H), 2.98 (s, 3H), 2.78 (m, 1H), 2.20 (m, 1H), 1.38 (d, 6H).

Example 13. Preparation of *L-thiazole morpholine ethyl ester oxalate salt XIVa:*



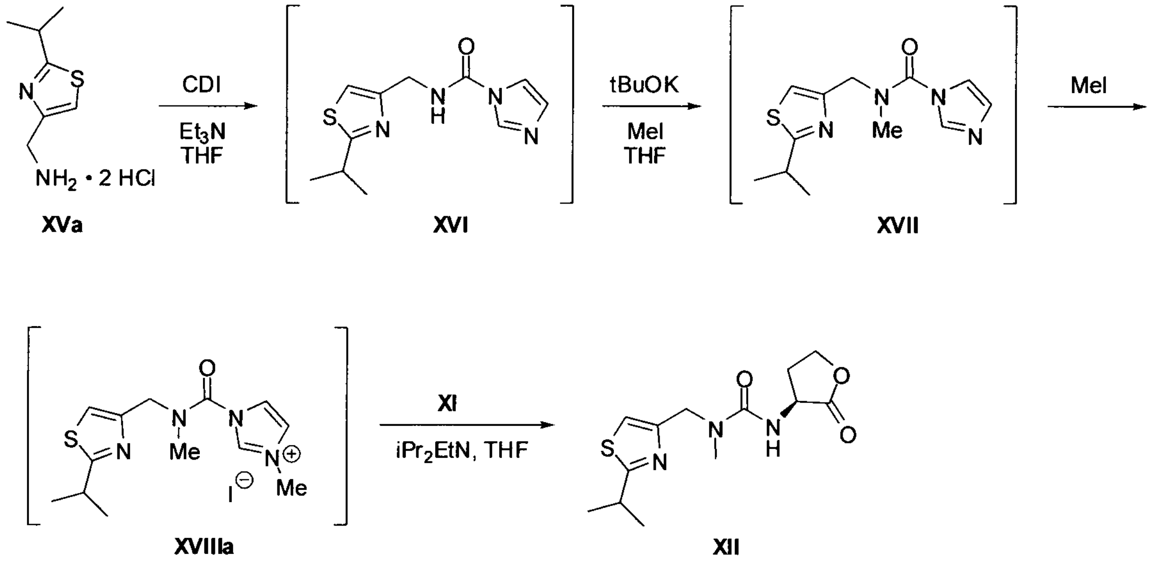
To a solution of (*L*)-thiazole amino lactone **XII** (33.4 kg) in dichloromethane (89.5 kg) was charged dichloromethane (150 kg) and absolute ethanol (33.4 kg). The content temperature was then adjusted to about 10 °C, followed by slow addition of TMSI (78.8 kg) while the content temperature was maintained at less than or equal to 22 °C and agitated until the reaction was judged complete. The content temperature was adjusted to about 10 °C, followed by a slow addition of morpholine (49.1 kg) while the content temperature was maintained at less than or equal to 22 °C. Once complete, the reaction mixture was filtered to remove morpholine•HI salt and the filter cake was rinsed with two portions of dichloromethane (33.4 kg). The filtrate was washed twice with water (100 kg). The organic layer was concentrated under vacuum to dryness. Acetone (100 kg) was then charged to the concentrate and the solution was concentrated under reduced pressure to dryness. Acetone (233.8 kg) was charged to the concentrate, followed by a slow addition of the solution of oxalic acid (10 kg) in acetone (100 kg). The resulting slurry was refluxed for about 1 hour before cooling down to about 3 °C for isolation. The product **XIVa** was filtered and rinsed with acetone (66.8 kg) and dried under vacuum at 40 °C to afford a white to off-white solid (40 kg, 71% yield). ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 1H), 6.35 (broad s, 1H), 4.60-4.40 (m, 3H), 4.19 (quartets, 2H), 4.00-3.90 (m, 4H), 3.35-3.10 (m, 7H), 3.00 (s, 3H), 2.40-2.30 (m, 1H), 2.15-2.05 (m, 1H), 1.38 (d, 6H), 1.25 (triplets, 3H).

Example 14. Preparation of *compound I*:



To the solution of *L*-thiazole morpholine ethyl ester oxalate salt **XIVa** (35.6 kg) in water (66.0 kg) was charged dichloromethane (264 kg), followed by a slow addition of 15 wt% $KHCO_3$ solution (184.8 kg). The resulting mixture was agitated for about 1 hour. The layers were separated and the organic layer was washed with water (132 kg). The organic layer was concentrated under vacuum to dryness. Water (26.5 kg) was charged and the content temperature was adjusted to about 10 °C, followed by slow addition of 45% KOH solution (9.8 kg) while maintaining the content temperature at less than or equal to 20 °C. The mixture was agitated at less than or equal to 20 °C until the reaction was judged complete by HPLC. The reaction mixture was concentrated under vacuum to dryness and co-evaporated five times with dichloromethane (132 kg each time) under reduced pressure to dryness. Co-evaporation with dichloromethane (132 kg) was continued until the water content was < 4% by Karl Fischer titration. Additional dichloromethane (264 kg) was charged and the content temperature was adjusted to -18 °C to -20 °C, followed by addition of monocarbamate•HCl salt **IXa** (26.4 kg). The resulting mixture was agitated at -18 °C to -20 °C for about 1 hour. HOBt (11.4 kg) was charged and the reaction mixture was again agitated at -18 °C to -20 °C for about 1 hour. A pre-cooled solution (-20 °C) of EDC•HCl (21.4 kg) in dichloromethane (396 kg) was added to the reaction mixture while the content temperature was maintained at less than or equal to -20 °C. The reaction mixture was agitated at -18 °C to -20 °C until the reaction was judged complete. The content temperature was adjusted to about 3 °C and the reaction mixture quenched with a 10 wt% aqueous citric acid solution (290 kg). The layers were separated and the organic layer was washed once with 15 wt% potassium bicarbonate solution (467 kg) and water (132 kg). The organic layer was concentrated under reduced pressure and then co-evaporated with absolute ethanol. The product **I** was isolated as the stock solution in ethanol (35.0 kg product, 76.1% yield). ^1H NMR (^dDMSO) δ 9.05 (s, 1H), 7.85 (s, 1H), 7.52 (d, 1H), 7.25-7.02 (m, 12H), 6.60 (d, 1H), 5.16 (s, 2H), 4.45 (s, 2H), 4.12-4.05 (m, 1H), 3.97-3.85 (m, 1H), 3.68-3.59 (m, 1H), 3.57-3.45 (m, 4H), 3.22 (septets, 1H), 2.88 (s, 3H), 2.70-2.55 (m, 4H), 2.35-2.10 (m, 6H), 1.75 (m, 1H), 1.62 (m, 1H), 1.50-1.30 (m, 4H), 1.32 (d, 6H). ^{13}C NMR (CD_3OD) δ 180.54, 174., 160.1, 157.7, 156.9, 153.8, 143.8, 140.1, 140.0, 136.0, 130.53, 130.49, 129.4, 127.4, 127.3, 115.5, 67.7, 58.8, 56.9, 55.9, 54.9, 53.9, 51.6, 49.8, 42.7, 42.0, 35.4, 34.5, 32.4, 32.1, 29.1, 23.7.

Example 15. Alternative preparation of *urea XII*:



A urea of formula **XII** can also be prepared as described in steps a-d below.

a. To a slurry of carbonyldiimidazole (8.5 g, 0.052 mol, 1.2 eq.) in tetrahydrofuran (100 g) at about 10°C was charged triethylamine (6.6 g, 0.065 mol, 1.5 eq.) while the reaction temperature was maintained at about 10 °C. The resulting slurry was charged in portions with starting amino isopropylthiazole diHCl, (**XVa**, 10 g, 0.044 mol) with the pot temperature maintained at about 10 °C. Once the addition was complete, the pot temperature was allowed to warm to ambient temperature and the reaction mixture was agitated at this temperature until the reaction was judged complete by HPLC (target: starting material ≤ 1%). Once complete, the triethylamine HCl salt was filtered off. The wet filter cake was washed with THF (80 kg) and the filtrate was concentrated under vacuum at about 40 °C and co-evaporated with ethyl acetate (50 kg). To the resulting slurry was charged with ethyl acetate (20 kg), then cooled to about 0 °C and agitated at this temperature for about 1 hour. The product was filtered off and washed with heptane (20 kg). The filter cake was pulled dry in the filter under vacuum.

b. The above wet filter cake was slurried up in tetrahydrofuran (80 g) and the pot temperature was adjusted to about 0 °C. To this slurry, *tert*-BuOK (6.9 g, 0.061 mol, 1.4 eq.) was slowly charged while the reaction temperature was maintained at about 0°C, followed by addition of methyl iodide (8.7 g, 0.061 mol, 1.4 eq.) at about 0°C. Once the addition was complete, the reaction mixture was allowed to warm to ambient temperature and agitated at this temperature until the reaction was judged complete by HPLC (target: product $\geq$ 70%). Once complete, the reaction mixture was adjusted to about 3 °C and agitated at this temperature for about 1 hour. The potassium iodide salt was filtered off and the filter cake was washed with THF (20 g). The mother-liquor containing product was collected and carried forward to the next step.

c. To the above mother-liquor, methyl iodide was charged (18.6 g, 0.131 mol, 3 eq.) and the reaction mixture was warmed to about 35 °C and agitated at this temperature until the reaction was judged complete by HPLC (target: starting material $\leq$ 1%, approximately 24 hours). Once complete, the reaction mixture was adjusted to ambient temperature and filtered. The product filter cake was washed with THF (20 g). The filter cake was pulled dry in the filter under vacuum.

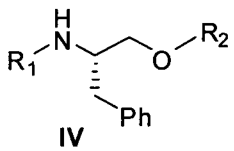
d. To the above wet filter cake was charged THF (80 g), followed by portion-wise addition of L-amino lactone, **XI** (7 g, 0.038 mol, 0.9 eq.). To the resulting mixture, diisopropylethylamine (8.5 g, 0.066 mol, 1.5 eq.) was charged slowly while the reaction temperature was maintained below 30 °C. Once the addition was complete the reaction temperature was adjusted to ambient and agitated until the reaction was judged complete by HPLC (*target*: starting material $\leq$ 1%, approximately 48 hours). Once complete, the reaction mixture was concentrated under vacuum to approximately 3 volumes with the bath temperature set at maximum (40 °C). The concentrate was then adjusted to ambient and charged with methylene chloride (50 g). The resulting organic solution was washed with 20% citric acid solution (30 g) and then water (30 g). The aqueous layers were combined and back extracted with methylene chloride (50 g). The organic layers were combined and concentrated under reduced pressure to about 3 volumes with bath temperature set at $\leq$ 40 °C. The concentration was repeated until KF limit was met (target: KF $\leq$ 0.5%). Once KF limit was met, the product **XII** was discharged as a stock solution in methylene chloride (5.8 g, 45% yield). ^{1}H NMR ($CDCl_3$) δ7.02 (s, 1H), 4.55-4.41 (m, 4H), 4.27 (m, 1H), 3.29 (septets, 1H), 2.98 (s, 3H), 2.78 (m, 1H), 2.20 (m, 1H), 1.38 (d, 6H).

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A compound of formula **IV**:

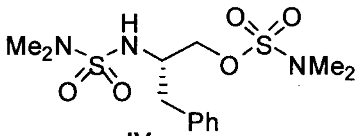


IV

wherein R_1 and R_2 are each independently a suitable protecting group; or a salt thereof.

2. The compound of claim 1 wherein R_1 and R_2 are each the same protecting group.

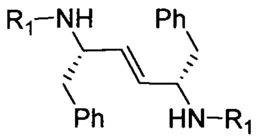
3. The compound of claim 1 which is a compound of formula **IVa**:



IVa

or a salt thereof.

4. A compound of formula **V**:

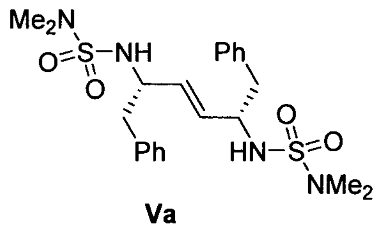


V

wherein each R_1 is a suitable protecting group other than *tert*-butylsulfonyl; or a salt thereof.

5. The compound of claim 4 wherein each R_1 is $-S(=O)_2NR_aR_b$, wherein each of R_a and R_b is independently $(C_1\text{-}C_8)$alkyl; or R_a and R_b together with the nitrogen to which they are attached form a 3 or 4 membered saturated ring or a 5, 6, or 7 membered saturated or partially unsaturated ring comprising 1 or 2 heteroatoms.

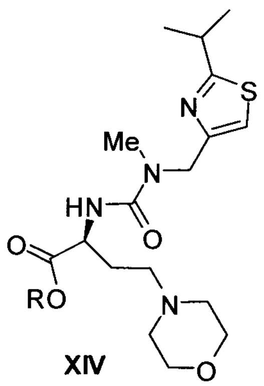
6. The compound of claim 4 which is a compound of formula **Va**:



Va

or a salt thereof.

7. A compound of formula **XIV**:

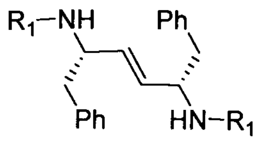


XIV

wherein R is (C_2-C_8)alkyl or a salt thereof.

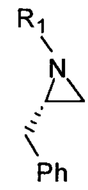
8. The compound of claim 7 which is an oxalate salt of the compound of formula **XIV**.

9. A method for preparing a compound of formula **V**:



V

wherein R_1 is a suitable protecting group other than *tert*-butylsulfonyl, or a salt thereof, comprising dimerizing a corresponding compound of formula **II**:



II

to provide the compound of formula **V** or the salt thereof.

10. The method of claim 9 wherein R_1 is an *N,N*-disubstituted sulfamoyl group.

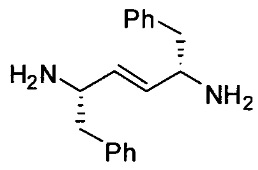
11. The method of claim 9 or 10 wherein the compound of formula **II** is dimerized by treatment with a non-nucleophilic amide base in a suitable solvent at a temperature from about -78 °C to about 22 °C.

12. The method of claim 11 wherein the non-nucleophilic amide base is selected from lithium diisopropylamide, lithium hexamethyldisilazide, lithium 2,2,6,6-tetramethylpiperidide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium di-*t*-butylamide, and lithium isopropylcyclohexylamide.

13. The method of claim 11 wherein the non-nucleophilic amide base is lithium 2,2,6,6-tetramethylpiperidide.

14. The method of claim 11 or 12 wherein the solvent comprises ethyl ether, *t*-butyl methyl ether, *n*-butyl ether, tetrahydrofuran, hexanes, tetrahydropyran, or 1,2-dimethoxyethane,or a mixture thereof.

15. The method of any one of claims 9-14 further comprising deprotecting the compound of formula **V** or the salt thereof to provide a compound of formula **VI**:



VI

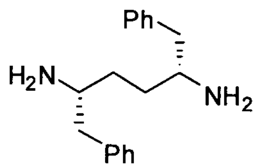
or a salt thereof.

16. The method of claim 15 wherein the deprotecting is carried out in a solvent at a temperature from about 100 °C to about 140 °C.

17. The method of claim 16 wherein the deprotecting is carried out in a solvent that comprises ethanolamine, 1,3-diaminopropane, ethylenediamine, 1,2-diaminocyclohexane, 1,2-phenylenediamine, putrescene, cadaverine, diethylenetriamine, triethylenetriamine, or polyethyleneimine.

18. The method of claim 17 wherein the deprotecting is carried out in 1,3-diaminopropane, at a temperature of about 110 °C.

19. The method of any one of claims 15-18 further comprising reducing the compound of formula **VI** or the salt thereof to a compound of formula **VII:**



VII

.

20. The method of claim 19 wherein the reduction is carried out by hydrogenation in an alcoholic solvent.

21. The method of claim 20 wherein the hydrogenation is carried out with a hydrogenation catalyst that comprises palladium on carbon, platinum on carbon, Raney nickel, Wilkinson's catalyst, or palladium hydroxide.

22. The method of claim 20 or 21 wherein the alcoholic solvent comprises methanol, ethanol, *i*-propanol, *n*-propanol, butanol, ethyl acetate, toluene, or anisole, or a mixture thereof.

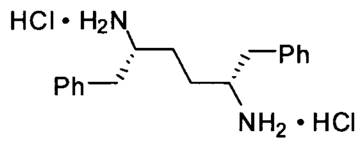
23. The method of claim 21 wherein the hydrogenation catalyst comprises 10% palladium on carbon and the alcoholic solvent comprises methanol.

24. The method of any one of claims 19-23 further comprising converting the compound of formula **VII** to a corresponding salt by treatment with an acid in an organic solvent at a temperature from about -10 °C to about 40 °C.

25. The method of claim 24 wherein the acid is hydrochloric acid, hydrobromic acid, hydroiodic acid, or sulfuric acid.

26. The method of claim 24 or 25 wherein the organic solvent comprises dichloromethane, ethyl ether, tetrahydrofuran, *t*-butyl methyl ether, 1,4-dioxane, 1,2-dimethoxyethane, chloroform, 1,2-dichloroethane, toluene, or anisole, or a mixture thereof.

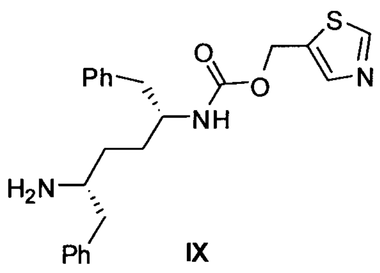
27. The method of claim 24 wherein the compound of formula **VII** is converted into a salt of formula **VIIa**:



VIIa

by treatment with HCl in dioxane, methanol, ethanol, isopropanol, or methyl tert-butylether, or a mixture thereof at a temperature from about 0 °C to about 22 °C.

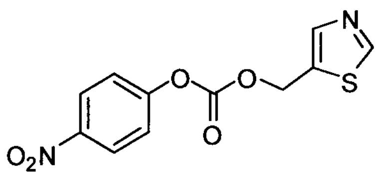
28. The method of any one of claims 19-27 further comprising converting the compound of formula **VII** or the salt thereof to a compound of formula **IX**:



IX

or a salt thereof.

29. The method of claim 28 wherein the compound of formula **VII** or the salt thereof is converted to the compound of formula **IX** or the salt thereof by treatment with a carbonate of formula **VIII**:

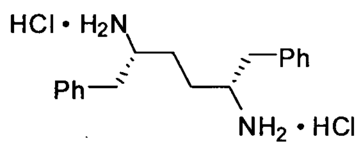


VIII

in the presence of a suitable base in a suitable solvent.

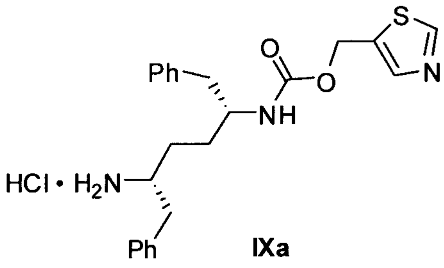
30. The method of claim 29 wherein the base is a carbonate base or a trialkyl amine and the solvent comprises dichloromethane, tetrahydrofuran, 1,2-dichloroethane, or diethylether, or a mixture thereof.

31. The method of claim 29 wherein a salt of formula **VIIa**:



VIIa

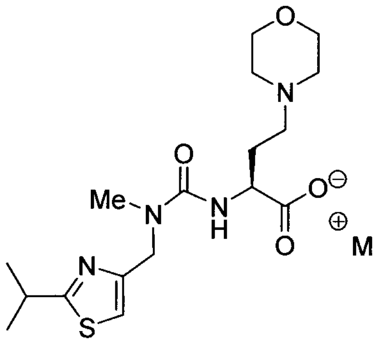
is treated with the carbonate of formula **VIII** in dichloromethane in the presence of a base (e.g. potassium carbonate or sodium hydroxide) to provide a salt of formula **IXa**:



IXa

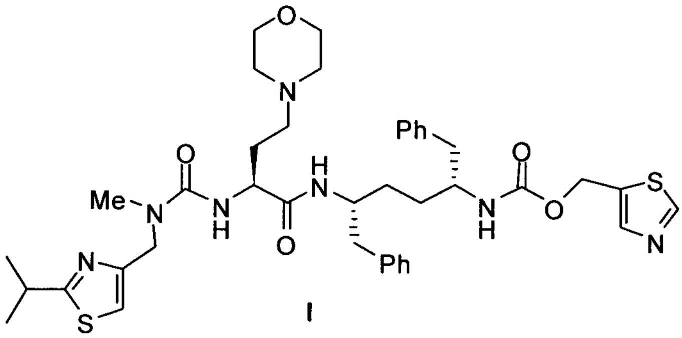
.

32. The method of any one of claims 28-31 further comprising coupling the compound of formula **IX** or the salt thereof with a salt of formula **X**:



X

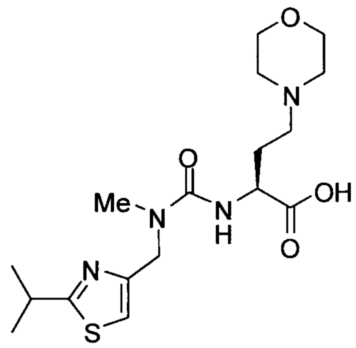
wherein M^+ is a suitable counterion to provide a compound of formula **I**:



I

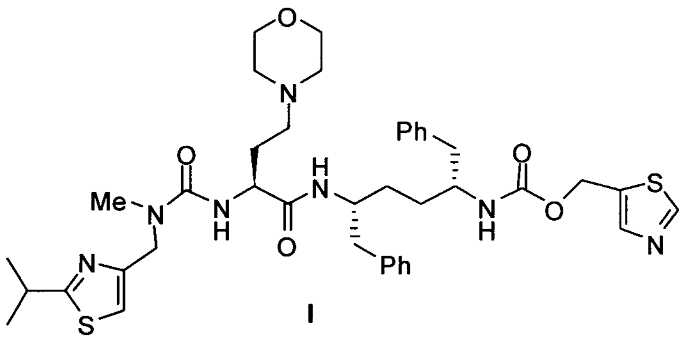
or a salt thereof.

33. The method of any one of claims 28-31 further comprising coupling the compound of formula **IX** or the salt thereof with an acid of formula **Xa**:



Xa

or a salt thereof to provide a compound of formula **I**:



I

or a salt thereof.

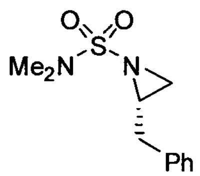
34. The method of claim 33 wherein the coupling is carried out in dichloromethane at a temperature from about -30 °C to about 20 °C in the presence of a coupling reagent (e.g. EDC•HCl and HOBt or n-propanephosphonic acid cyclic anhydride).

35. The method of any one of claims 9-34 further comprising preparing the compound of formula **II** by reacting (*S*)-2-benzylaziridine with a compound R_1-X, wherein X is a leaving group in a suitable solvent, in the presence of a base at a temperature from about -10 °C to about 40 °C.

36. The method of claim 35 wherein R_1 is $-S(=O)_2NR_aR_b$ wherein each of R_a and R_b is independently $(C_1\text{-}C_8)$alkyl; or R_a and R_b together with the nitrogen to which they are attached form a 3 or 4 membered saturated ring or a 5, 6, or 7 membered saturated or partially unsaturated ring comprising 1 or 2 heteroatoms.

37. The method of claim 35 wherein the (*S*)-2-benzylaziridine is reacted with the compound R_1-X in a solvent comprises tetrahydrofuran, ethyl ether, *tert*-butyl methyl ether, tetrahydropyran, 1,4-dioxane, or 1,2-dichloroethane or a mixture thereof; the base is selected from a trialkylamine, potassium carbonate, and sodium bicarbonate and mixtures thereof; and the temperature is from about 0 °C to about 22 °C.

38. The method of claim 35 wherein (*S*)-2-benzylaziridine is reacted with $(CH_3)_2NS(O)_2$-Cl in the presence of diisopropylethylamine in dichloromethane at a temperature from about 0 °C to about 22 °C to provide a compound of formula **IIa**:



IIa

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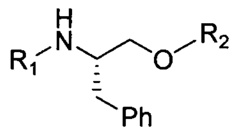
39. The method of any one of claims 9-34 further comprising preparing the compound of formula **II** by treating a corresponding compound of formula **IV**:



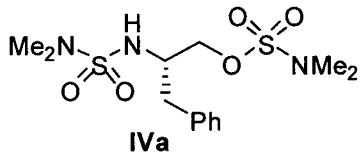
IV

wherein R_1 and R_2 are each independently a suitable protecting group, or a salt thereof with a suitable base, in a suitable aprotic solvent, at a temperature from about 0 °C to about 22 °C.

40. The method of claim 39 wherein the base is selected from a metal hydride, a tetramethylpiperidine, an alkoxide, a hexamethyldisilazide, and a carbonate base, and mixtures thereof.

41. The method of claim 39 or 40 wherein the aprotic solvent is selected from tetrahydrofuran and dichloromethane, and mixtures thereof.

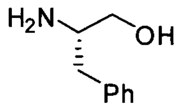
42. The method of claim 39 wherein a compound of formula **IVa**:



IVa

or a salt thereof is treated with sodium hydride in 2-methyltetrahydrofuran at a temperature from about 0 °C to about 22 °C to provide the corresponding compound of formula **II**.

43. The method of any one of claims 39-42 further comprising preparing the compound of formula **IV** or the salt thereof by protecting a compound of formula **III**:



III

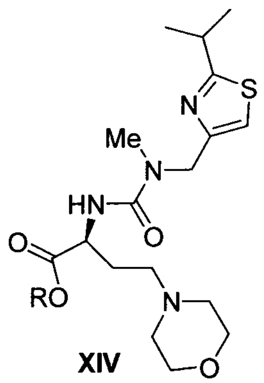
or a salt thereof to provide the compound of formula IV.

44. The method of claim 43 wherein the compound of formula **III** is protected by treatment with a compound of formula $(CH_3)_2NS(O)_2Cl$ in a solvent selected from dichloromethane, tetrahydrofuran, and 2-methyltetrahydrofuran, and mixtures thereof, in the presence of a base.

45. The method of claim 44 wherein the base is a trialkylamine or a hydride.

46. The method of claim 44 wherein the compound of formula **III** is protected by treatment with a compound of formula $(CH_3)_2NS(O)_2Cl$ in dichloromethane in the presence of diisopropylethylamine at a temperature of about 0 °C.

47. The method of any one of claims 32-46 further comprising preparing the salt of formula **X** by hydrolyzing a corresponding ester of formula **XIV**:



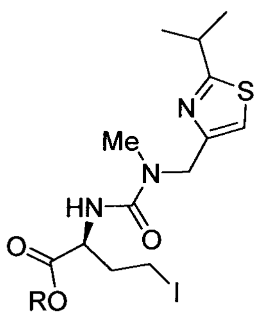
XIV

wherein R is (C_1-C_8)alkyl or a salt thereof to provide the salt of formula **X**.

48. The method of claim 47 wherein the ethyl ester of the oxalate salt of the compound of formula **XIV** is hydrolyzed to provide the salt of formula **X**.

49. The method of claim 48 wherein the ethyl ester of the oxalate salt of the compound of formula **XIV** is hydrolyzed by treatment with potassium hydroxide in methylene chloride and water to provide the salt of formula **X**.

50. The method of claim 47 further comprising preparing the ester of formula **XIV** or the salt thereof by treating a compound of formula **XIII**:



XIII

wherein R is (C_1-C_8)alkyl with morpholine in the presence of an alcohol ROH to provide the corresponding compound of formula **XIV** or the salt thereof.

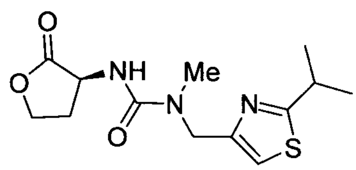
51. The method of claim 50 wherein the compound of formula **XIII** is treated with morpholine in a solvent that comprises dichloromethane and absolute ethanol.

52. The method of claim 50 wherein the compound of formula **XIII** is treated with morpholine at about 10 °C in a suitable solvent to provide the compound of formula **XIV**.

53. The method of any one of claims 50-52 comprising forming a salt of the compound of formula **XIV** by treatment with an acid in an organic solvent to provide the salt thereof.

54. The method of claim 53 wherein an oxalate salt of the compound of formula **XIV** is formed by treating the compound of formula **XIV** with oxalic acid in acetone.

55. The method of any one of claims 50-54 further comprising preparing the compound of formula **XIII** by treating a corresponding compound of formula **XII**:



XII

or a salt thereof with a suitable iodide source in an aprotic solvent in the presence of an alcohol ROH to provide the compound of formula **XIII**.

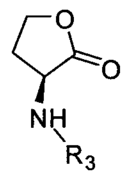
56. The method of claim 55 wherein the iodide source is trimethylsilyl iodide, hydrogen iodide, or sodium iodide and trimethylsilyl chloride.

57. The method of claim 55 wherein the iodide source is trimethylsilyl iodide.

58. The method of any one of claims 55-57 wherein the aprotic solvent comprises tetrahydrofuran, 2-methyltetrahydrofuran, dichloromethane, or acetonitrile, or a mixture thereof.

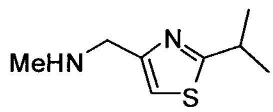
59. The method of any one of claims 55-57 wherein the aprotic solvent comprises dichloromethane.

60. The method of any one of claims 55-59 further comprising preparing the compound of formula **XII** or the salt thereof by treating an amine of formula **XI**:



XI

wherein R_3 is H or a protecting group, with a compound of formula **XIX**:



XIX

or a salt thereof, and a suitable base, in an aprotic solvent, at a temperature from about 0 °C to about 30 °C, and optionally removing any protecting group to provide the compound of formula **XII** or the salt thereof.

61. The method of claim 60 wherein R_3 is H.

62. The method of claim 60 wherein R_3 is a carbamate, amide, or benzyl protecting group and wherein R_3 is removed following the reaction of the compound of formula **XI** and the compound of formula **XIX** to provide the compound of formula **XII**.

63 . The method of any one of claims 60-62 wherein the base is a metal hydride or a trialkylamine.

64. The method of any one of claims 60-63 wherein the aprotic solvent is selected from tetrahydrofuran, 2-methyltetrahydrofuran, and dichloromethane, and mixtures thereof.

65. The method of any one of claims 60-64 wherein the base is diisopropylethyl amine and the solvent comprises dichloromethane.

66. The method of any one of claims 60-65 further comprising preparing the compound of formula **XI** by treating L-methionine with a corresponding alkylating agent in the presence of water and acetic acid and optionally protecting the resulting amine.

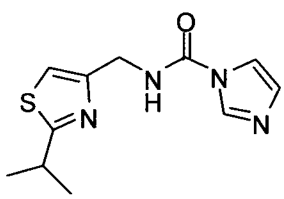
67. The method of claim 66 wherein the alkylating agent is an alkyl bromide, an alkyl iodide, an alkyl chloride, or dimethyl sulfate.

68. The method of claim 66 wherein the alkylating agent is bromoacetic acid.

69. The method of any one of claims 66-68 wherein the L-methionine is treated with the alkylating agent in a solvent that comprises an alcohol, water, and acetic acid.

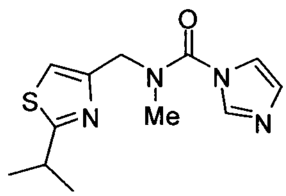
70. The method of claim 69 wherein the solvent comprises an isopropanol, water, and acetic acid.

71. A compound of formula **XVI** or **XVII**:



XVI

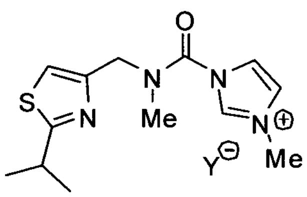
or



XVII

or a salt thereof.

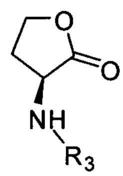
72. A salt of formula **XVIII**:



XVIII

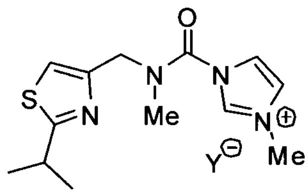
wherein Y^- is a suitable counterion.

73. The method of any one of claims 55-59 further comprising preparing the compound of formula **XII** or the salt thereof by treating an amine of formula **XI**:



XI

wherein R_3 is H or a protecting group, with a salt of formula **XVIII**:



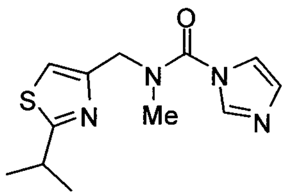
XVIII

wherein Y^- is a counterion or a salt thereof, with a suitable base, in an aprotic solvent and optionally removing any protecting group to provide the compound of formula **XII** or the salt thereof.

74. The method of claim 73 wherein R_3 is H.

75. The method of claim 73 wherein R_3 is a carbamate, amide, or benzyl protecting group and wherein R_3 is removed following the reaction of the compound of formula **XI** and the compound of formula **XVIII** to provide the compound of formula **XII**.

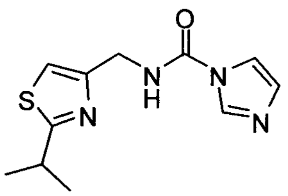
76. The method of any one of claims 73-75 further comprising preparing the salt of formula **XVIII** by treating a compound of formula **XVII**:



XVII

or a salt thereof with a methylating agent to provide the salt of formula **XVIII**.

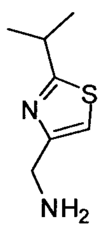
77. The method of claim 76 further comprising preparing the compound of formula **XVII** by treating a compound of formula **XVI**:



XVI

or a salt thereof with a suitable methylating agent in the presence of a base to provide the salt of formula **XVII**.

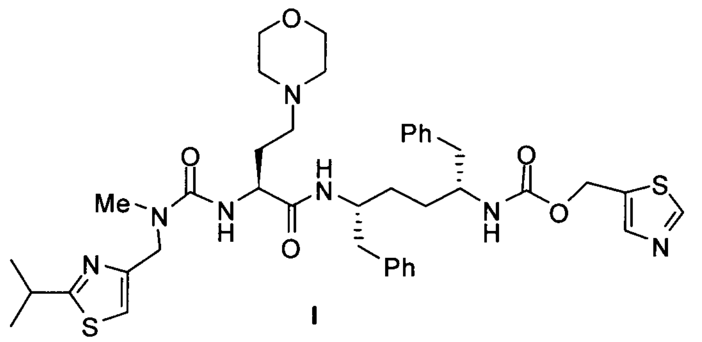
78. The method of claim 77 further comprising preparing the compound of formula **XVI** by treating a compound of formula **XV**:



XV

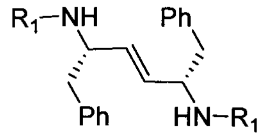
or a salt thereof with carbonyldiimidazole, in the presence of a base, to provide the compound of formula **XVI**.

79. A method for preparing a compound of formula **I**:



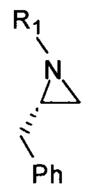
I

or a salt thereof, wherein a compound of formula **V**:



V

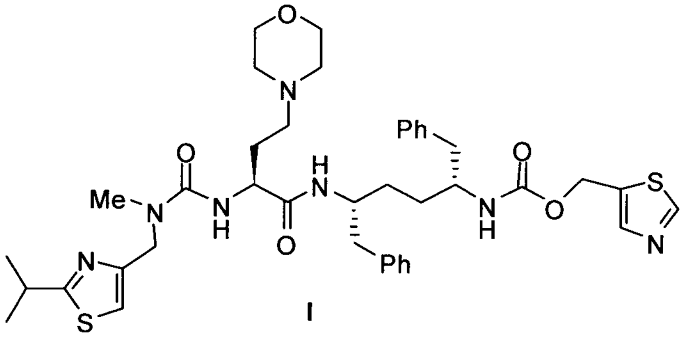
wherein R_1 is a suitable protecting group, or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **V** is prepared from a corresponding compound of formula **II**:



II

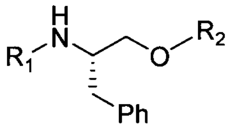
or a salt thereof, by dimerizing the compound of formula **II**.

80. A method for preparing a compound of formula **I**:



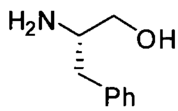
I

or a salt thereof, wherein a compound of formula **IV**:



IV

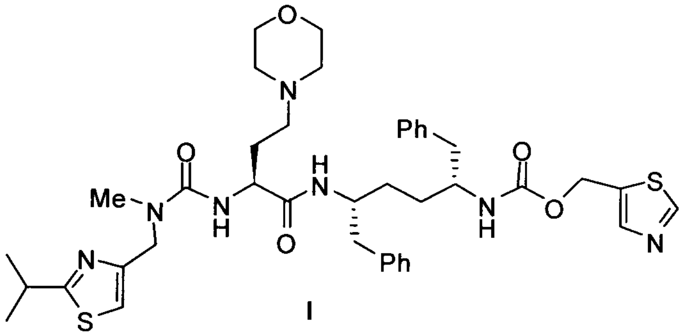
wherein R_1 and R_2 are each independently a suitable protecting group, or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **IV** is prepared from a compound of formula **III**:



III

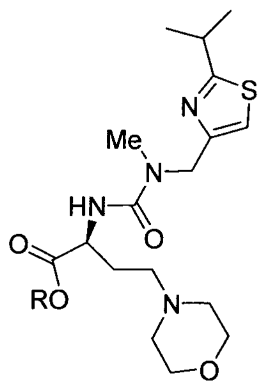
or a salt thereof, by protecting the compound of formula **III**.

81. A method for preparing a compound of formula **I**:



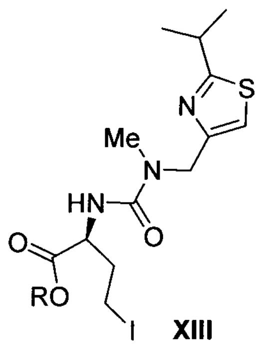
I

or a salt thereof, wherein a compound of formula **XIV**:



XIV

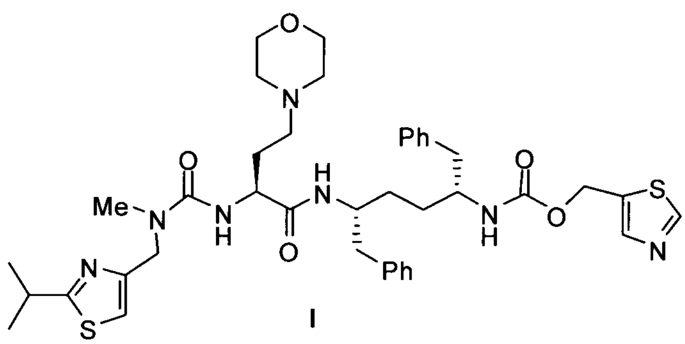
wherein R is $(C_1\text{-}C_8)$alkyl, or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XIV** or the salt thereof is prepared from a corresponding compound of formula **XIII**:



XIII

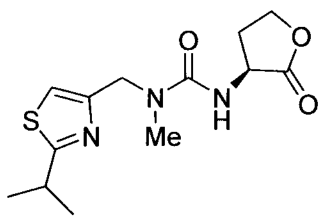
or a salt thereof, by displacing the iodide with a suitable morpholine reagent.

82. A method for preparing a compound of formula **I**:



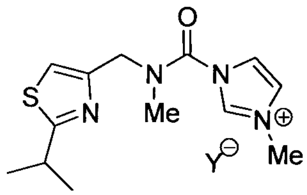
I

or a salt thereof, wherein a compound of formula **XII**:



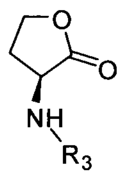
XII

or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XII** is prepared from a corresponding compound of formula **XVIII**:



XVIII

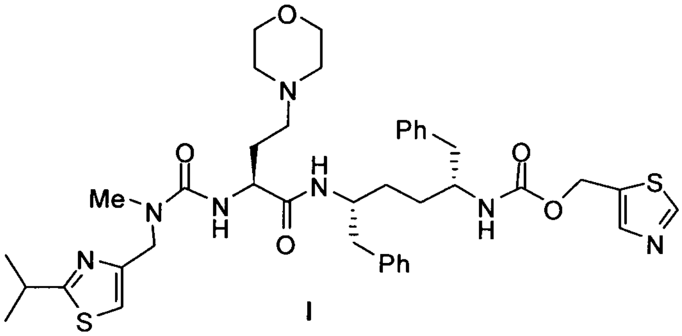
wherein Y^- is a suitable counterion, by treatment with a compound of formula **XI**:



XI

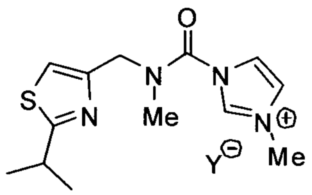
wherein R_3 is H or a protecting group in the presence of a base and optionally removing R_3 if it is a protecting group to provide the compound of formula **XII**.

83. A method for preparing a compound of formula **I**:



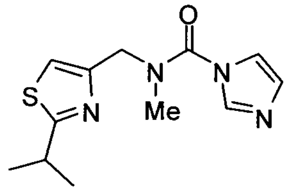
I

or a salt thereof, wherein a salt of formula **XVIII**:



XVIII

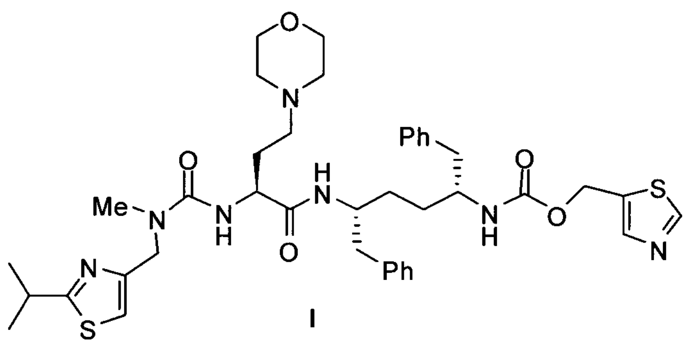
wherein Y⁻ is a suitable counterion is prepared and converted into a compound of formula **I**, characterized in that the salt of formula **XVIII** is prepared from a corresponding compound of formula **XVII**:



XVII

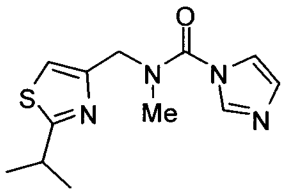
or a salt thereof by treatment with a methylating agent to provide the salt of formula **XVIII**.

84. A method for preparing a compound of formula **I**:



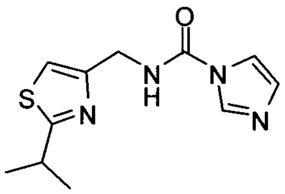
I

or a salt thereof, wherein a compound of formula **XVII**:



XVII

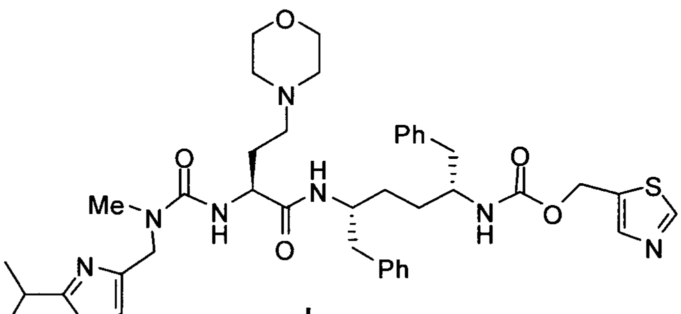
or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XII** is prepared from a corresponding compound of formula **XVI**:



XVI

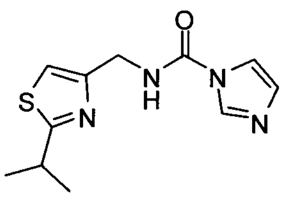
or a salt thereof by treatment with a methylating agent to provide the compound of formula **XVII** or the salt thereof.

85. A method for preparing a compound of formula **I**:



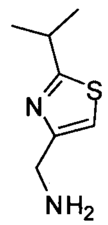
I

or a salt thereof, wherein a compound of formula **XVI:**



XVI

or a salt thereof is prepared and converted into a compound of formula **I**, characterized in that the compound of formula **XVI** is prepared from a corresponding compound of formula **XV**:



XV

or a salt thereof by treatment with carbonyldiimidazole, in the presence of a base to provide the compound of formula **XVI**.