

SYNTHESIS OF SALINOSPORAMIDE A ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims priority to U.S. Provisional Patent Application
Nos. 60/790,168, entitled "Total Synthesis of Salinosporamide A and Analogs
Thereof," filed April 6, 2006; 60/816,968, entitled "Total Synthesis of Salinosporamide
A and Analogs Thereof," filed June 27, 2006; 60/836,155, entitled "Total Synthesis of
Salinosporamide A and Analogs Thereof," filed August 7, 2006; 60/844,132, entitled
10 "Total Synthesis of Salinosporamide A and Analogs Thereof," filed September 12, 2006;
and 60/885,379, entitled "Total Synthesis of Salinosporamide A and Analogs Thereof,"
filed January 17, 2007.

BACKGROUND OF THE INVENTION

15 Field of the Invention

The present invention relates to certain compounds and to methods for
the preparation of certain compounds that can be used in the fields of chemistry and
medicine.

20 Description of the Related Art

Cancer is a leading cause of death in the United States. Despite
significant efforts to find new approaches for treating cancer, the primary treatment
options remain surgery, chemotherapy and radiation therapy, either alone or in
combination. Surgery and radiation therapy, however, are generally useful only for
25 fairly defined types of cancer, and are of limited use for treating patients with
disseminated disease. Chemotherapy is the method that is generally useful in treating
patients with metastatic cancer or diffuse cancers such as leukemias. Although
chemotherapy can provide a therapeutic benefit, it often fails to result in cure of the
disease due to the patient's cancer cells becoming resistant to the chemotherapeutic
30 agent. Due, in part, to the likelihood of cancer cells becoming resistant to a
chemotherapeutic agent, such agents are commonly used in combination to treat
patients.

Similarly, infectious diseases caused, for example, by bacteria, fungi and protozoa are becoming increasingly difficult to treat and cure. For example, more and more bacteria, fungi and protozoa are developing resistance to current antibiotics and chemotherapeutic agents. Examples of such microbes include *Bacillus*, *Leishmania*, *Plasmodium* and *Trypanosoma*.

Furthermore, a growing number of diseases and medical conditions are classified as inflammatory diseases. Such diseases include conditions such as asthma to cardiovascular diseases. These diseases continue to affect larger and larger numbers of people worldwide despite new therapies and medical advances.

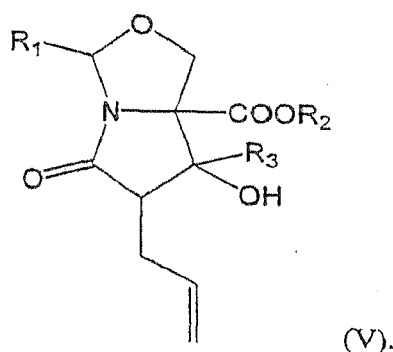
Therefore, a need exists for additional chemotherapeutics, anti-microbial agents, and anti-inflammatory agents to treat cancer, inflammatory diseases and infectious disease. A continuing effort is being made by individual investigators, academia and companies to identify new, potentially useful chemotherapeutic and anti-microbial agents.

Marine-derived natural products are a rich source of potential new anti-cancer agents and anti-microbial agents. The oceans are massively complex and house a diverse assemblage of microbes that occur in environments of extreme variations in pressure, salinity, and temperature. Marine microorganisms have therefore developed unique metabolic and physiological capabilities that not only ensure survival in extreme and varied habitats, but also offer the potential to produce metabolites that would not be observed from terrestrial microorganisms (Okami, Y. 1993 *J Mar Biotechnol* 1:59). Representative structural classes of such metabolites include terpenes, peptides, polyketides, and compounds with mixed biosynthetic origins. Many of these molecules have demonstrable anti-tumor, anti-bacterial, anti-fungal, anti-inflammatory or immunosuppressive activities (Bull, A.T. *et al.* 2000 *Microbiol Mol Biol Rev* 64:573; Cragg, G.M. & D.J. Newman 2002 *Trends Pharmacol Sci* 23:404; Kerr, R.G. & S.S. Kerr 1999 *Exp Opin Ther Patents* 9:1207; Moore, B.S 1999 *Nat Prod Rep* 16:653; Faulkner, D.J. 2001 *Nat Prod Rep* 18:1; Mayer, A. M. & V.K. Lehmann 2001 *Anticancer Res* 21:2489), validating the utility of this source for isolating invaluable therapeutic agents. Further, the isolation of novel anti-cancer and anti-microbial agents that represent alternative mechanistic classes to those currently on the market will help to address resistance concerns, including any mechanism-based resistance that may have been engineered into pathogens for bioterrorism purposes.

SUMMARY OF THE INVENTION

The embodiments disclosed herein generally relate to the total synthesis of chemical compounds, including heterocyclic compounds and analogs thereof. Some embodiments are directed to the chemical compound and intermediate compounds. Other embodiments are directed to the individual methods of synthesizing the chemical compound and intermediate compounds.

An embodiment disclosed herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (V):



One embodiment described herein relates to a method for synthesizing an intermediate compound of formula (V).

Another embodiment described herein relates to a method for synthesizing an intermediate compound of formula (X).

Still another embodiment described herein relates to a method for synthesizing an intermediate compound of formula (XV).

Yet still another embodiment described herein relates to a method for synthesizing an intermediate compound of formula (XVII).

One embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (V).

Another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (VI).

Still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (X).

Still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (Xp).

Yet still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (XI).

One embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (XV).

Another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (XVII).

Still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (XVIIp).

Yet still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (XVIII).

One embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (XXIII).

Some embodiments described herein relate to the individual methods of synthesizing compounds of formula (III), (IV), (VI), (VI), (VII), (VIII), (IX), (X), (XV), (XVI), (XXII), (XXIII), (XXIV), (XXV), (XXVI), (XXVII), (XXVIII) and protected derivatives thereof.

Other embodiments described herein relate to the individual compounds of formula (III), (IV), (VI), (VI), (VII), (VIII), (IX), (X), (XV), (XVI), (XXII), (XXIII), (XXIV), (XXV), (XXVI), (XXVII), (XXVIII) and protected derivatives thereof.

One embodiment described herein relates to a method of forming a compound of formula (X) from a compound of formula (V) comprising the steps of: cleaving the carbon-carbon double bond of the compound of formula (V) and cyclizing the cleaved double bond with the tertiary hydroxy group; transforming $-\text{COOR}_2$ to an aldehyde; and adding R_4 to the aldehyde using an organometallic moiety containing at least one R_4 , wherein R_2 and R_4 are described herein

An embodiment described herein relates to a method of forming a compound of formula (XV) from a compound of formula (X) comprising the steps of: cleaving an aminal group; removing PG₁ and reductively opening the hemiacetal; and forming a four membered lactone ring, wherein PG₁ can be a protecting group moiety described herein. In some embodiments, the cleaving of the aminal group can occur before the removal of PG₁ and reductively opening the hemiacetal, and before the formation of the four membered lactone ring. In other embodiments, the cleaving of the aminal group can occur after the removal of PG₁ and reductively opening the hemiacetal, but before the formation of the four membered ring.

Another embodiment described herein relates to a method of forming a compound of formula (XVII) from a compound of formula (V) comprising the steps of: cleaving the carbon-carbon double bond of the compound of formula (V) and cyclizing the cleaved double bond with the tertiary hydroxy group; and adding R₄ after cyclization with the tertiary hydroxy group using an organometallic moiety containing at least one R₄, wherein R₄ is described herein;

On embodiment described herein relates to a method of forming a compound of formula (XXII) from a compound of formula (XVII) comprising the steps of: cleaving an aminal group; removing PG₁ and reductively opening the hemiacetal; forming a four membered ring via a lactonization reaction; and removing any protecting groups on a ketone, wherein PG₁ can be a protecting group moiety described herein. In some embodiments, the cleaving of the aminal group can occur before the removal of PG₁ and reductively opening the hemiacetal, and before the formation of the four membered ring via a lactonization reaction. In other embodiments, the cleaving of the aminal group is after the removal of PG₁ and reductively opening the hemiacetal, but before the formation of the four membered ring via a lactonization reaction.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and form part of the specification, merely illustrate certain preferred embodiments of the present invention. Together with the remainder of the specification, they are meant to serve to explain preferred modes of making certain compounds of the invention to those of skilled in the art. In the drawings:

Figure 1 shows the chemical structure of Salinosporamide A.

Figure 2 shows a ^1H NMR spectrum of the compound of formula (I-1) in CDCl_3 .

Figure 3 shows a ^1H NMR spectrum of the ester precursor to the compound of formula (II-1) in CDCl_3 .

Figure 4 shows a ^1H NMR spectrum of the protected ester precursor of the compound of formula (II-1) in CDCl_3 .

Figure 5 shows a ^1H NMR spectrum of the compound of formula (II-1) in CDCl_3 .

Figure 6a shows a ^1H NMR spectrum of the compound of formula (III-1) in CDCl_3 .

Figure 6b shows a LC-MS of the compound of formula (III-1).

Figure 7a shows a ^1H NMR spectrum of the compound of formula (IV-1) in CDCl_3 .

Figure 7b shows a NOESY spectrum of the compound of formula (IV-1) in CDCl_3 .

Figure 7c shows a ^1H NMR spectrum of the compound of formula (IV-1A) in CDCl_3 .

Figure 7d shows a ^1H NMR spectrum of the compound of formula (IV-1B) in CDCl_3 .

Figure 7e shows a LC-MS of the compound of formula (IV-1).

Figure 8 shows a ^1H NMR spectrum of the compound of formula (V-1A) in CDCl_3 .

Figure 9 shows a ^{13}C NMR spectrum of the compound of formula (V-1A) in CDCl_3 .

Figure 10 shows a ^1H - ^1H COSY NMR spectrum of the compound of formula (V-1A) in CDCl_3 .

Figure 11 shows the crystal structure of the compound of formula (V-1A).

Figure 12 shows a ^1H NMR spectrum of the compound of formula (VI-1) in CDCl_3 .

Figure 13 shows a ^1H NMR spectrum of the compound of formula (VII-1a) in CDCl_3 .

Figure 14 shows a ^1H NMR spectrum of the compound of formula (VII-1b) in CDCl_3 .

Figure 15 shows the crystal structure of the compound of formula (VII-1_b).

Figure 16 shows a ¹H NMR spectrum of the compound of formula (VIII-1_b) in CDCl₃.

Figure 17 shows a ¹H NMR of the compound of formula (VIII-1_a) in CDCl₃.

Figure 18 shows a ¹H NMR spectrum of the compound of formula (IX-1_b) in CDCl₃.

Figure 19 shows a ¹H NMR spectrum of the compound of formula (IX-1_a) in CDCl₃.

Figure 20 shows a ¹H NMR spectrum of the compound of formula (X-1_bB) in CDCl₃.

Figure 21 shows a ¹³C NMR spectrum of the compound of formula (X-1_bB) in CDCl₃.

Figure 22 shows the crystal structure of the compound of formula (X-1_bB).

Figure 23 shows a ¹H NMR spectrum of the compound of formula (X-1_aB) in CDCl₃.

Figure 24 shows a ¹³C NMR spectrum of the compound of formula (X-1_aB) in CDCl₃.

Figure 25 shows a ¹H NMR spectrum of the compound of formula (V-1B) in CDCl₃.

Figure 26 shows the crystal structure of the compound of formula (V-1B).

Figure 27 shows a ¹H NMR spectrum of the compound of formula (V-1C) in CDCl₃.

Figure 28 shows a ¹³C NMR spectrum of the compound of formula (V-1C) in CDCl₃.

Figure 29 shows a NOESY spectrum of the compound of formula (V-1C) in CDCl₃.

Figure 30 shows a ¹H NMR spectrum of the compound of formula (XXIX-1) in CDCl₃.

Figure 31 shows a ¹³C NMR spectrum of the compound of formula (XXIX-1) in CDCl₃.

Figure 32 shows a ^1H NMR spectrum of the compound of formula (XXIII-1B) in CDCl_3 .

Figure 33 shows a ^{13}C NMR spectrum of the compound of formula (XXIII-1B) in CDCl_3 .

Figure 34 shows a ^1H NMR spectrum of the compound of formula (XXIV-1B-Bz) in CDCl_3 .

Figure 35 shows a ^1H NMR spectrum of the compound of formula (XXV-1B-Bz) in CDCl_3 .

Figure 36 shows a ^{13}C NMR spectrum of the compound of formula (XXV-1B-Bz) in CDCl_3 .

Figure 37 shows a ^1H NMR spectrum of the compound of formula (XXVp-1B-Bz-TMS) in CDCl_3 .

Figure 38 shows a ^{13}C NMR spectrum of the compound of formula (XXVp-1B-Bz-TMS) in CDCl_3 .

Figure 39 shows a ^1H NMR spectrum of the compound of formula (XXVI-1B-Bz) in CD_3OD .

Figure 40 shows a ^{13}C NMR spectrum of the compound of formula (XXVI-1B-Bz) in CD_3OD .

Figure 41 shows a ^1H NMR spectrum of the compound of formula (XXVIII-1B-TBS) in CDCl_3 .

Figure 42 shows a ^1H NMR spectrum of the compound of formula (XV-1B) in acetone- d_6 .

Figure 43 shows a ^{13}C NMR spectrum of the compound of formula (XV-1B) in acetone- d_6 .

Figure 44 shows a ^1H NMR spectrum of the compound of formula (XVI-1B) produced from the compound of formula (XV-1B) produced synthetically in CDCl_3 .

Figure 45 shows a ^{13}C NMR spectrum of the compound of formula (XVI-1B) produced from the compound of formula (XV-1B) produced synthetically in CDCl_3 .

Figure 46 shows a ^1H NMR spectrum of the compound of formula (XXII-1) produced from the compound of formula (XVI-1B) obtained synthetically in CDCl_3 .

Figure 47 shows ^1H NMR spectrum of the compound of formula (XVI-1A) produced from the compound of formula (XXII-1) obtained synthetically in DMSO-d_6 .

Figure 48 shows a comparison of ^1H NMR spectra of compound (XVI-1A) produced synthetically and from fermentation.

Figure 49 shows a ^{13}C NMR spectrum of the compound of formula (XVI-1A) produced from the compound of formula (XXII-1) obtained synthetically in DMSO-d_6 .

Figure 50 shows a comparison of ^{13}C NMR spectra of compound (XVI-1A) produced synthetically and from fermentation.

Figure 51 shows a ^1H NMR spectrum of cyclohexenyltributyltin in CDCl_3 .

Figure 52 shows a ^1H NMR spectrum of the compound of formula (X-1_a) in CDCl_3 .

Figure 53 s shows a ^{13}C NMR spectrum of the compound of formula (X-1_a) in CDCl_3 .

Figure 54 shows a ^1H NMR spectrum of the compound of formula (X-1_b) in CDCl_3 .

Figure 55 shows a ^{13}C NMR spectrum of the compound of formula (X-1_b) in CDCl_3 .

Figure 56 shows the crystal structure of the compound of formula (X-1_b).

Figure 57 shows a plot of the inhibition of the chymotrypsin-like activity of 20S proteasomes by the synthetic and fermentation compounds of formula (XVI-1A).

Figure 58 shows a plot of the inhibition of the trypsin-like activity of 20S proteasomes by the synthetic and fermentation compounds of formula (XVI-1A).

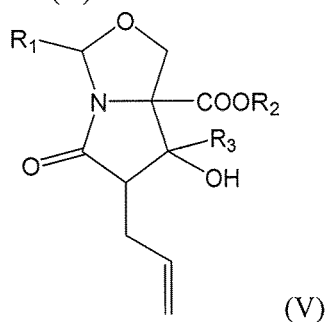
Figure 59 shows a plot of the inhibition of the caspase-like activity of 20S proteasomes by the synthetic and fermentation compounds of formula (XVI-1A).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Embodiments of the invention include methods for the preparation of various compounds and intermediates, and the compounds and intermediates themselves. In some embodiments, one or more substituents, one or more compounds, or groups of compounds can be specifically excluded in any one or more of the methods or compounds as described more fully below.

5 Salinosporamide A and its analogs thereof have various biological activities. For example, the compounds have chemosensitizing activity, anti-microbial, anti-inflammation, radiosensitizing, and anti-cancer activity. Studies have been conducted that show Salinosporamide A and its analogs have proteasome inhibitory activity, effect NF- κ B / I κ B signaling pathway, and have anti-anthrax activity. Salinosporamide A and several analogs, as well as biological activity of the same, are described in U.S. Provisional Patent Applications Nos., 60/480270, filed June 20, 2003; 60/566952, filed April 30, 2004; 60/627461, filed 10 November 12, 2004; 60/633379, filed December 3, 2004; 60/643922, filed January 13, 2005; 60/658884, filed March 4, 2005; 60/676533, filed April 29, 2005; 60/567336, filed April 30, 2004; 60/580838, filed June 18, 2004; 60/591190, filed July 26, 2004; 60/627462, filed 15 November 12, 2004; 60/644132, filed January 13, 2005; and 60/659385, filed March 4, 2005; U.S. Patent Applications Nos., 10/871368, filed June 18, 2004; 11/118260, filed April 29, 2005; 11/412,476, filed April 27, 2006; and 11/453374, filed June 15, 2006; and International Patent Applications Nos., PCT/US2004/019543, filed June 18, 2004; PCT/US2005/044091, filed December 2, 2005; PCT/US2005/014846, filed April 29, 2005; and PCT/US2006/016104, filed 20 April 27, 2006. Endo et al. *J. Am. Chem. Soc.* (2005) 123, 8298-8299 provides a synthetic route for obtaining Salinosporamide A. International Patent Application No. PCT/US2005/014846, corresponding to PCT Publication No. WO 2006/028525, also provide a fermentation method for obtaining Salinosporamide A and semi-synthetic procedures for obtaining analogs of Salinosporamide A.

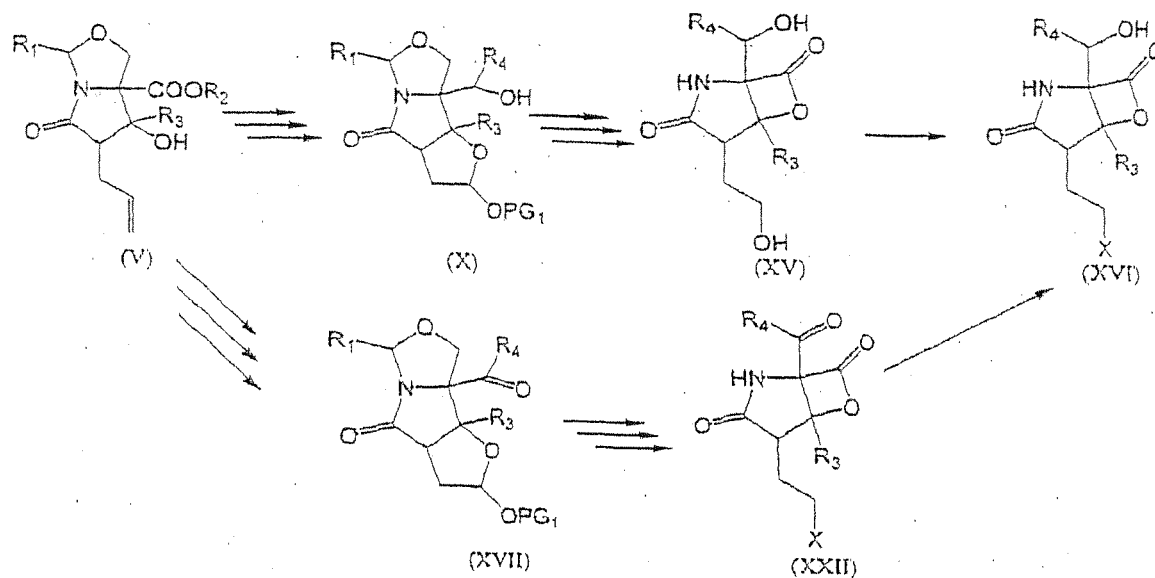
25 Provided herein are methods for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (V):



The compound of formula (V) can be synthesized from readily available starting materials, as described herein. The compound of formula (V) may be

subsequently converted to Salinosporamide A or analogs thereof. For example Salinosporamide A or analogs thereof may be synthesized according to Scheme A.

Scheme A



For the compounds described herein, each stereogenic carbon can be of R or S configuration. Although the specific compounds exemplified in this application can be depicted in a particular configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned unless otherwise specified. When chiral centers are found in the derivatives of this invention, it is to be understood that the compounds encompasses all possible stereoisomers unless otherwise indicated.

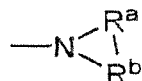
The term "substituted" has its ordinary meaning, as found in numerous contemporary patents from the related art. See, for example, U.S. Patent Nos. 6,509,331; 6,506,787; 6,500,825; 5,922,683; 5,886,210; 5,874,443; and 6,350,759.

Examples of suitable substituents include hydrogen, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, alkyl amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxy, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-H, -SO₂-OH, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl, heteroaryl, boronate alkyl, boronic acid, (OH)₂B-alkyl, phosphate and phosphate esters, phosphonooxy,

phosphonooxyalkyl, azido, azidoalkyl, ammonium, carboxyalkyl, a salt of a carboxyalkyl, alkylamino, a salt of an alkylamino, dialkylamino, a salt of a dialkylamino, alkylthio, arylthio, carboxy, cyano, alkanesulfonyl, alkanesulfinyl, alkoxysulfinyl, thiocyno, boronic acidalkyl, boronic esteralkyl, sulfoalkyl, a salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, a salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, a salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, a salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, a salt of a pyridinylalkyl, a salt of a heteroarylalkyl guanidino, a salt of a guanidino, and guanidinoalkyl. Each of the substituents can be further substituted. The other above-listed patents also provide standard definitions for the term "substituted" that are well-understood by those of skill in the art.

Whenever a group is described as "optionally substituted" the group may be unsubstituted or substituted with one or more substituents as described herein.

As used herein, any "R" group(s) such as, without limitation, R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R_A and R_B represent substituents that can be attached to the indicated atom. An R group may be substituted or unsubstituted. If two "R" groups are covalently bonded to the same atom or to adjacent atoms, then they may be "taken together" as defined herein to form a cycloalkyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R_{1a} and R_{1b} of an NR_{1a}R_{1b} group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



The term "alkyl," as used herein, means any unbranched or branched, substituted or unsubstituted, saturated hydrocarbon, with C₁-C₂₄ preferred, and C₁-C₆ hydrocarbons being preferred, with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl, and pentyl being most preferred.

The term "alkenyl," as used herein, means any unbranched or branched, substituted or unsubstituted, unsaturated hydrocarbon containing one or more double bonds. Some examples of alkenyl groups include allyl, homo-allyl, vinyl, crotyl, butenyl, pentenyl, hexenyl, heptenyl and octenyl.

The term "alkynyl" as used herein, means any unbranched or branched, substituted or unsubstituted, unsaturated hydrocarbon with one or more triple bonds

The term "cycloalkyl" refers to any non-aromatic, substituted or unsubstituted, hydrocarbon ring, preferably having five to twelve atoms comprising the ring. Furthermore, in the present context, the term "cycloalkyl" comprises fused ring systems such that the definition covers bicyclic and tricyclic structures.

The term "cycloalkenyl" refers to any non-aromatic, substituted or unsubstituted, hydrocarbon ring that includes a double bond, preferably having five to twelve atoms comprising the ring. Furthermore, in the present context, the term "cycloalkenyl" comprises fused ring systems such that the definition covers bicyclic and tricyclic structures.

The term "cycloalkynyl" refers to any non-aromatic, substituted or unsubstituted, hydrocarbon ring that includes a triple bond, preferably having five to twelve atoms comprising the ring. Furthermore, in the present context, the term "cycloalkynyl" comprises fused ring systems such that the definition covers bicyclic and tricyclic structures.

The term "acyl" refers to hydrogen, lower alkyl, lower alkenyl, or aryl connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted or unsubstituted.

In the present context the term "aryl" is intended to mean a carbocyclic aromatic ring or ring system. Moreover, the term "aryl" includes fused ring systems wherein at least two aryl rings, or at least one aryl and at least one C₃₋₈-cycloalkyl share at least one chemical bond. Some examples of "aryl" rings include optionally substituted phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl. An aryl group may be substituted or unsubstituted.

In the present context, the term "heteroaryl" is intended to mean a heterocyclic aromatic group where one or more carbon atoms in an aromatic ring have been replaced with one or more heteroatoms selected from the group comprising nitrogen, sulfur, phosphorous, and oxygen. Furthermore, in the present context, the term "heteroaryl" comprises fused ring systems wherein at least one aryl ring and at least one heteroaryl ring, at least two heteroaryl rings, at least one heteroaryl ring and at least one heterocyclyl ring, or at least one heteroaryl ring and at least one C₃₋₈-cycloalkyl ring share at least one chemical bond. A heteroaryl can be substituted or unsubstituted.

The terms "heterocycle" and "heterocyclyl" are intended to mean three-, four-, five-, six-, seven-, and eight-membered rings wherein carbon atoms together with from 1 to 3 heteroatoms constitute said ring. A heterocycle may optionally contain

one or more unsaturated bonds situated in such a way, however, that an aromatic π -electron system does not arise. The heteroatoms are independently selected from oxygen, sulfur, and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides, and cyclic carbamates. Heterocyclyl rings may optionally also be fused to at least other heterocyclyl ring, at least one C₃₋₈-cycloalkyl ring, at least one C₃₋₈-cycloalkenyl ring and/or at least one C₃₋₈-cycloalkynyl ring such that the definition includes bicyclic and tricyclic structures. Examples of benzo-fused heterocyclyl groups include benzimidazolidinone, tetrahydroquinoline, and methylenedioxybenzene ring structures. Some examples of "heterocycles" include tetrahydrothiopyran, 4*H*-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2*H*-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyridine, pyridinium, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane. A heterocycle group of this invention may be substituted or unsubstituted.

The term "alkoxy" refers to any unbranched, or branched, substituted or unsubstituted, saturated or unsaturated ether, with C₁-C₆ unbranched, saturated, unsubstituted ethers being preferred, with methoxy being preferred, and also with dimethyl, diethyl, methyl-isobutyl, and methyl-tert-butyl ethers also being preferred.

The term "cycloalkoxy" refers to any non-aromatic hydrocarbon ring comprising an oxygen heteroatom, preferably having five to twelve atoms comprising the ring. A cycloalkoxy can be substituted or unsubstituted.

The term "alkoxy carbonyl" refers to any linear, branched, cyclic, saturated, unsaturated, aliphatic or aromatic alkoxy attached to a carbonyl group. The examples include methoxycarbonyl group, ethoxycarbonyl group, propyloxycarbonyl group, isopropyloxycarbonyl group, butoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, cyclopentyloxycarbonyl group, cyclohexyloxycarbonyl group, benzyloxycarbonyl group, allyloxycarbonyl group, phenyloxycarbonyl group, and pyridyloxycarbonyl group. An alkoxy carbonyl may be substituted or unsubstituted.

The term “(cycloalkyl)alkyl” is understood as a cycloalkyl group connected, as a substituent, via a lower alkylene. The (cycloalkyl)alkyl group and lower alkylene of a (cycloalkyl)alkyl group may be substituted or unsubstituted.

5 The terms “(heterocycle)alkyl” and “(heterocyclyl)alkyl” are understood as a heterocycle group connected, as a substituent, via a lower alkylene. The heterocycle group and the lower alkylene of a (heterocycle)alkyl group may be substituted or unsubstituted.

10 The term “arylalkyl” is intended to mean an aryl group connected, as a substituent, via a lower alkylene, each as defined herein. The aryl group and lower alkylene of an arylalkyl may be substituted or unsubstituted. Examples include benzyl, substituted benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl.

15 The term “heteroarylalkyl” is understood as heteroaryl groups connected, as substituents, via a lower alkylene, each as defined herein. The heteroaryl and lower alkylene of a heteroarylalkyl group may be substituted or unsubstituted. Examples include 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, imidazolylalkyl, and their substituted as well as benzo-fused analogs.

20 The term “halogen atom,” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, i.e., fluorine, chlorine, bromine, or iodine, with bromine and chlorine being preferred.

As employed herein, the following terms have their accepted meaning in the chemical literature.

	9-BBN	: 9-borabicyclo[3.3.1]nonane
	BF ₃ .Et ₂ O	: borontrifluoride diethyl etherate
25	Bn	: benzyl
	BnOH	: benzyl alcohol
	BOPCl	: bis(2-oxo-3-oxazolidinyl)phosphinic chloride
	t-BuOH	: <i>tert</i> -butanol/ <i>tert</i> -butyl alcohol
	t-BuOK	: potassium <i>tert</i> -butoxide
30	Bz	: benzoyl
	DMIPS	: Dimethyl <i>iso</i> -propylsilyl
	ESI	: electrospray ionization

EtOAc	:ethyl acetate
FDH	:formate dehydrogenase
GDH	:glucose dehydrogenase
ID	:internal diameter
IPA	:isopropyl alcohol
LC-MS	:liquid chromatography – mass spectrometry
LDA	:lithium diisopropylamide
MS	:mass spectrum
MsCl	:methanesulfonyl chloride
NaOMe	:sodium methoxide
NaOEt	:sodium ethoxide
NMO	:N-methylmorpholine N-oxide
NMR	:nuclear magnetic resonance
Pb(OAc) ₄	:lead tetraacetate
PCC	:pyridinium chlorochromate
PDC	:pyridinium dicromate
PPTS	:pyridinium p-toluene sulfonate
PTSA	:p-toluene sulfonic acid
RT	:room temperature
SAR	:structure-activity relationship
TMS	:trimethylsilyl
TBS	: <i>t</i> -butyldimethylsilyl
TES	:triethylsilyl
THF	:tetrahydrofuran
TFA	:trifluoroacetic acid
TPAP	:tetrapropylammonium perruthenate

The terms “organometallic moiety” and “organometallic moieties” as used herein refer to any chemical compound that contains a metal-element bond(s) of a largely covalent character. The term “metal” as used herein include those elements traditionally classified as metals (e.g., lithium, magnesium, zinc, and tin) and those elements classified as metalloids (e.g., boron).

The terms “protecting group moiety” and “protecting group moieties” as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions.

Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3. Ed. John Wiley & Sons, 1999, and in J.F.W. McOmie, *Protective Groups in Organic Chemistry* Plenum Press, 1973.

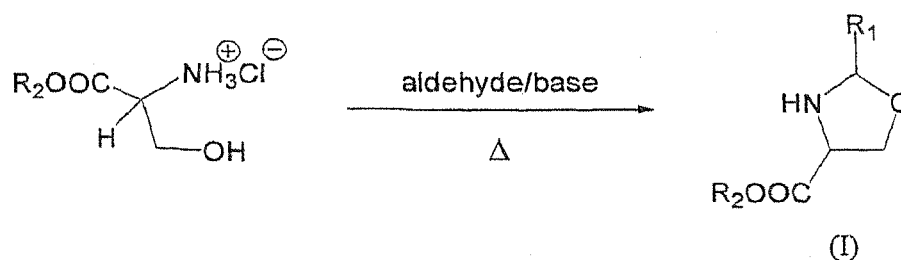
The protecting group moiety may be chosen in such a way, that they are stable to the reaction conditions applied and readily removed at a convenient stage using methodology known from the art. A non-limiting list of protecting groups include benzyl; substituted benzyl; alkylcarbonyls (e.g., t-butoxycarbonyl (BOC)); arylalkylcarbonyls (e.g., benzyloxycarbonyl, benzoyl); substituted methyl ether (e.g. methoxymethyl ether); substituted ethyl ether; a substituted benzyl ether; tetrahydropyranyl ether; silyl ethers (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, or t-butyldiphenylsilyl); esters (e.g. benzoate ester); carbonates (e.g. methoxymethylcarbonate); sulfonates (e.g. tosylate, mesylate); acyclic ketal (e.g. dimethyl acetal); cyclic ketals (e.g., 1,3-dioxane or 1,3-dioxolanes); acyclic acetal; cyclic acetal; acyclic hemiacetal; cyclic hemiacetal; and cyclic dithioketals (e.g., 1,3-dithiane or 1,3-dithiolane). As used herein, any "PG" group(s) such as, without limitation, PG₁, PG₂ and PG₃ represent a protecting group moiety.

The terms "pure," "purified," "substantially purified," and "isolated" as used herein refer to the compound of the embodiment being free of other, dissimilar compounds with which the compound, if found in its natural state, would be associated in its natural state. In certain embodiments described as "pure," "purified," "substantially purified," or "isolated" herein, the compound may comprise at least 0.5%, 1%, 5%, 10%, or 20%, and most preferably at least 50% or 75% of the mass, by weight, of a given sample.

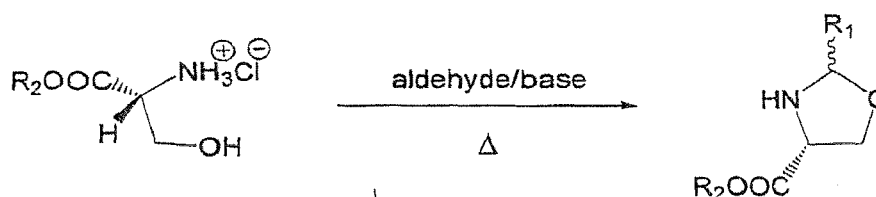
The terms "derivative," "variant," or other similar term refers to a compound that is an analog of the other compound.

As shown in Schemes 1-4, the starting compounds of formulae (I) and (II) may be synthesized from readily available materials. As shown in Scheme 1-1, a compound of formula (I) can be synthesized from a serine ester salt, an aldehyde (e.g. t-butyl aldehyde) and a base (e.g., triethylamine) at elevated temperatures. In some embodiments, the serine ester salt can be a D-serine methylester salt which can form a compound of formula (I) with the stereochemistry shown in Scheme 1-2.

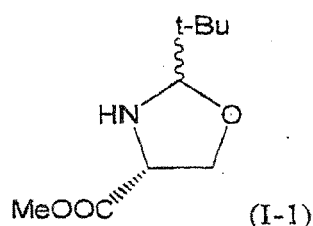
Scheme 1-1



Scheme 1-2

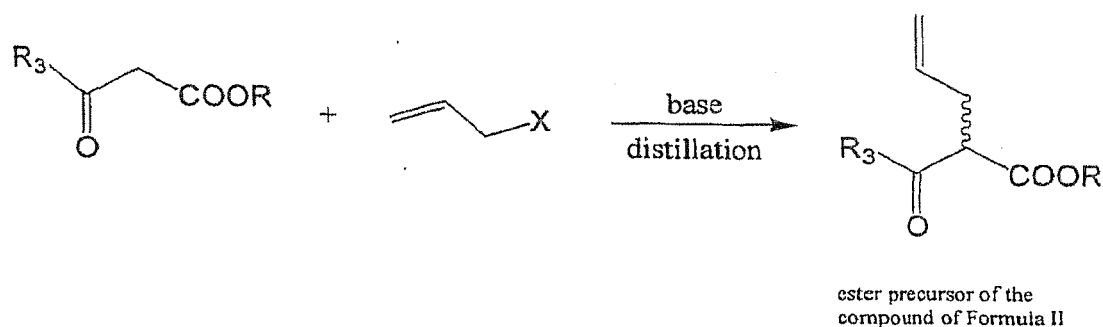


In some embodiments, a compound of formula (I) can have the structure shown above wherein R_1 can be hydrogen or unsubstituted or substituted C_{1-6} alkyl; and R_2 can be hydrogen, or substituted or unsubstituted variants of the following: C_{1-6} alkyl, aryl or arylalkyl. In an embodiment when R_1 is hydrogen, one skilled in the art would recognize that the stereochemistry at C-4 may not be retained upon conversion of a compound of formula (IV) to a compound of formula (V) shown below. In an embodiment when R_1 is an unsubstituted or substituted C_{1-6} alkyl, one skilled in the art would recognize that the stereochemistry at C-4 would be retained upon conversion of a compound of formula (IV) to a compound of formula (V) shown below. As an example, a compound of formula (I) can have the following structure and stereochemistry:

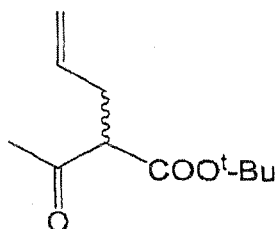


A compound of formula (II) can be synthesized according to Schemes 2, 3 and 4. The ester precursor of the compound of Formula II can be prepared according to Scheme 2, starting with a β -ketoester and a base (e.g., t-BuOK or NaH) and then adding an allyl halide.

Scheme 2

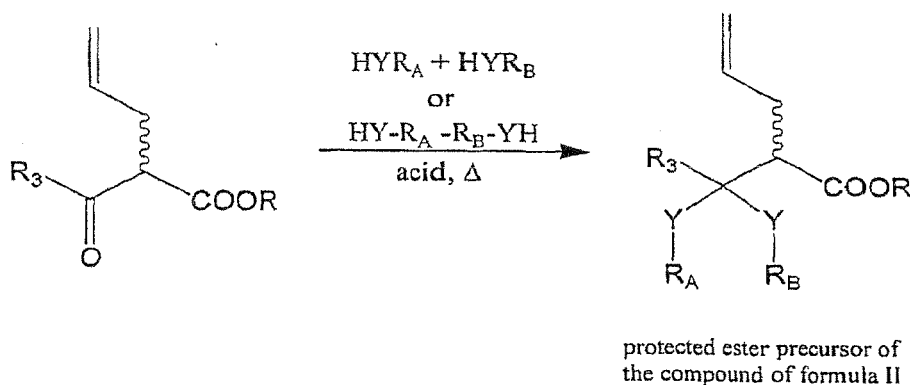


In some embodiments, the ester precursor of the compound of formula (II) can have the structure shown above wherein R can be hydrogen or substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl or arylalkyl; and R₃ can be substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, or arylalkyl. An exemplary ester precursor is the compound having the following structure:



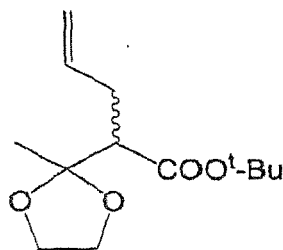
The protected ester precursor of the compound of formula (II) can be prepared according to Scheme 3. The ketone carbonyl of the ester precursor can be protected using a suitable protecting group moiety/moieties, as described herein. One method for protecting the ketone carbonyl is shown in Scheme 3.

Scheme 3



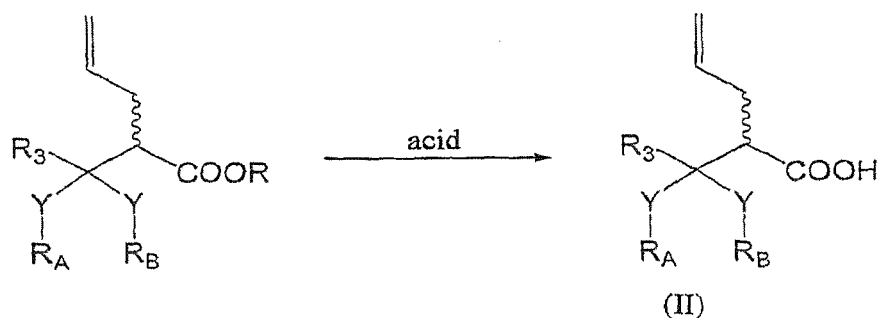
In some embodiments, the protected ester precursor of the compound of formula (II) can have structure shown in Scheme 3 wherein R can be hydrogen or substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl or arylalkyl; R₃ can be substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, or arylalkyl; each Y can be an oxygen or sulfur; and R_A and R_B can be each independently selected from the group consisting of substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl, wherein R_A and R_B can be optionally bound together to form an optionally substituted 5, 6, 7, or 8 membered heterocyclyl.

For example, the ketone carbonyl may be protected by reacting the ester precursor with 1,2 dihydroxyethane to form a 1,3-dioxolane heterocyclic ring as shown below:



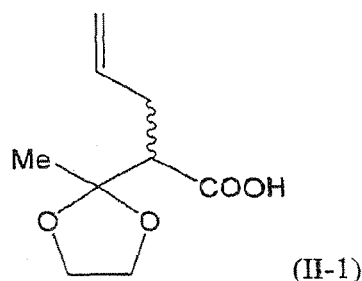
As shown in Scheme 4, the protected ester precursor of a compound of formula (II) can then be hydrolyzed to the carboxylic acid equivalent using an appropriate acid such as TFA or PTSA to form a compound of formula (II).

Scheme 4



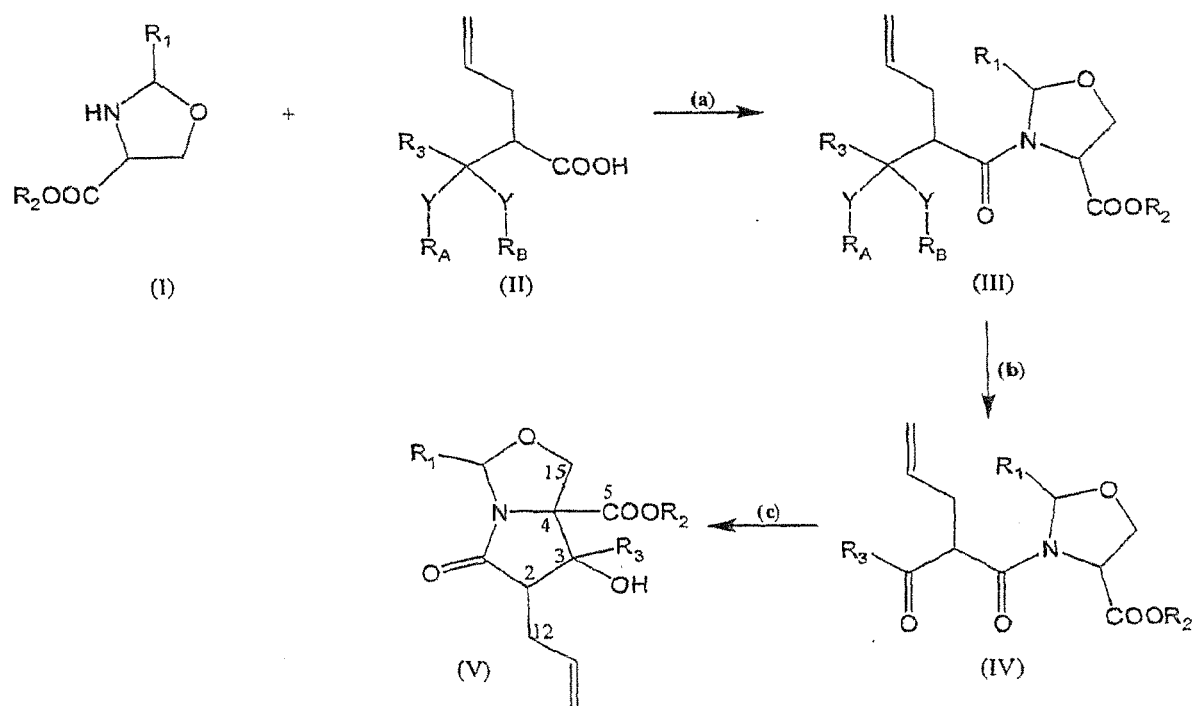
In some embodiments, a compound of formula (II) can have the structure shown in Scheme 4 wherein R₃ can be substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, or arylalkyl; each Y can be an oxygen or sulfur; and R_A and R_B can be each independently selected from the group consisting of substituted or unsubstituted variants of the following: C₁₋₆

alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl, wherein R_A and R_B can be optionally bound together to form an optionally substituted 5, 6, 7, or 8 membered heterocyclyl. As an example, the compound of formula (II) can have the following structure:



A method of preparing a compound of formula (V) from the starting compounds of formulae (I) and (II) is shown below in Scheme 5.

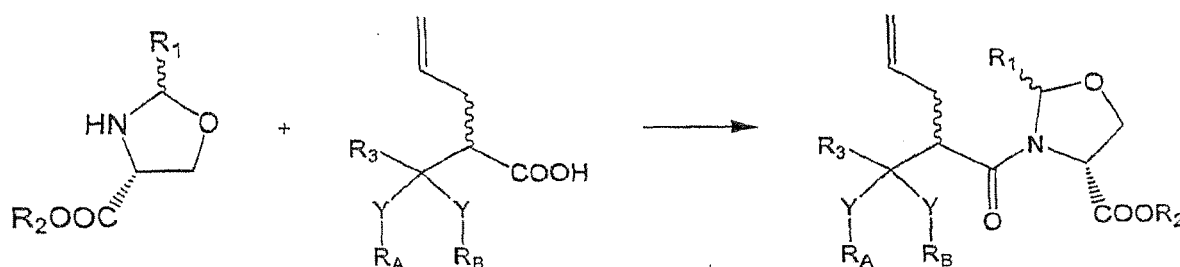
Scheme 5



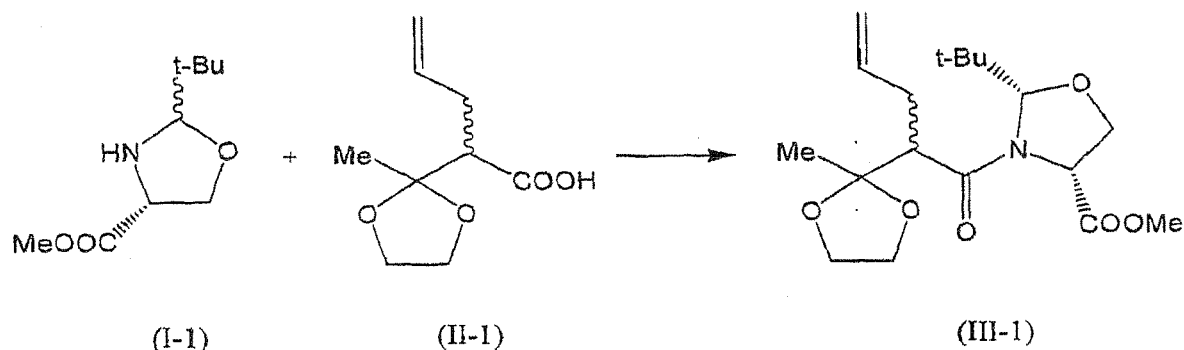
In step (a) of Scheme 5, a compound of formula (III) can be formed by reacting a compound of formula (I) with a compound of formula (II) under suitable conditions wherein R₁ can be hydrogen or unsubstituted or substituted C₁₋₆ alkyl; R₂ can be hydrogen, or substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl or arylalkyl; R₃ can be substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl, wherein R_A and R_B can be optionally bound together to form an optionally substituted 5, 6, 7, or 8 membered heterocyclyl. As an example, the compound of formula (II) can have the following structure:

sulfur; and R_A and R_B can be each independently selected from the group consisting of substituted or unsubstituted variants of the following: C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, wherein R_A and R_B can be optionally bound together to form an optionally substituted 5, 6, 7, or 8 membered heterocyclyl. For example, a compound of formula (I) can be added to a mixture containing a compound of formula (II), a mild base (e.g., triethylamine or N-methyl piperidine) and an acylating agent such as methanesulfonyl chloride, trifluoromethanesulfonyl chloride or chloromethylformate.

As an example, the compounds of formulae (I), (II) and (III) may have the following structures and stereochemistry:



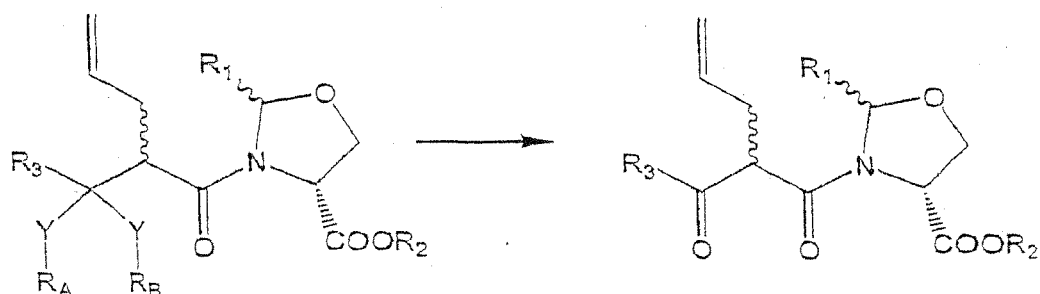
In one embodiment, the compounds of formulae (I), (II) and (III) can have the following structures:



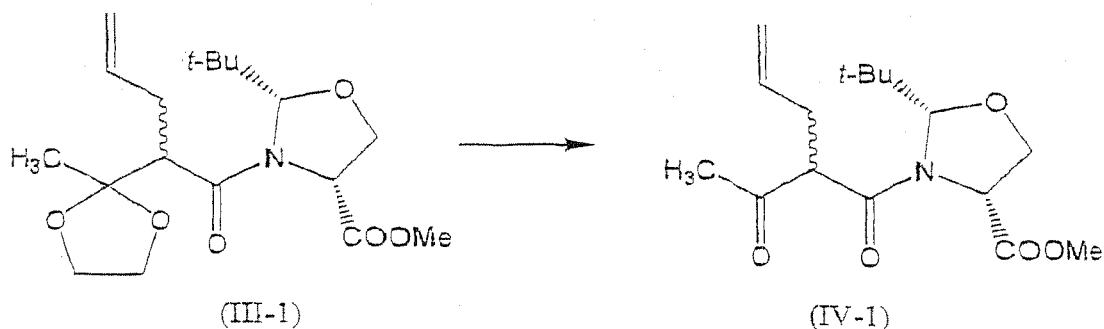
The compound of formula (III) can be deprotected to form a compound of formula (IV), as shown in step (b) of Scheme 5, wherein: R_1 can be hydrogen or unsubstituted or substituted C_{1-6} alkyl; R_2 can be hydrogen, or substituted or unsubstituted variants of the following: C_{1-6} alkyl, aryl or arylalkyl; R_3 can be substituted or unsubstituted variants of the following: C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{3-6} cycloalkenyl, aryl, or arylalkyl; each Y can be an oxygen or sulfur; and R_A and R_B can be each independently selected from the group consisting of substituted or unsubstituted variants of the following: C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, wherein R_A and R_B can be optionally bound together to form an optionally substituted 5, 6, 7, or 8 membered

heterocyclyl. One method for removing the ketone carbonyl protecting group (e.g., 1,3-dioxolane) includes reacting a compound of formula (III) with sodium iodide and a Lewis base such as cerium (III) chloride heptahydrate. A second method includes reacting a compound of formula (III) with iodine in acetone at an elevated temperature. Alternatively, a compound of formula (III) can be reacted with lithium tetrafluoroborate at an elevated temperature to form a compound of formula (IV). If Y is sulfur, the ketone carbonyl protecting group can be removed using various hydrolytic, oxidative and/or solid-state methods such as those described and cited in Habibi et al., *Molecules*, (2003) 8, 663-9.

Exemplary structures and stereochemistry of compounds of formulae (III) and (IV) are shown below:

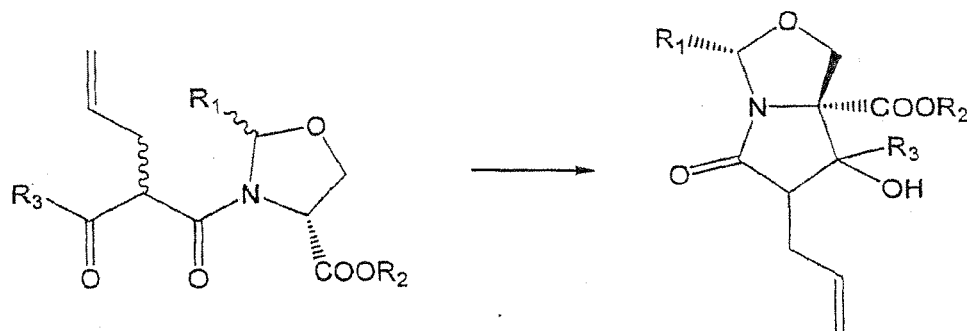


For example, the compounds of formulae (III) and (IV) can have the following structures:

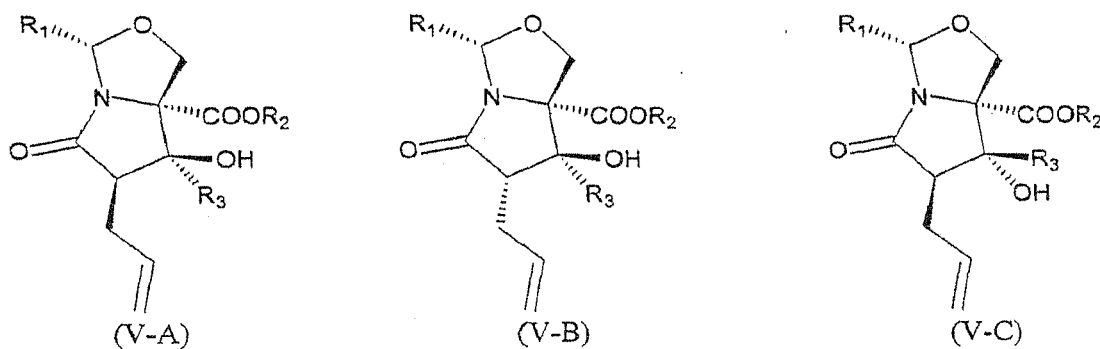


As shown in step (c) of Scheme 5, treatment of a compound of formula (IV) with an appropriate base (e.g., *t*-BuOK, NaOMe, NaOEt or LDA) can induce an intramolecular aldol reaction to form a compound of formula (V) wherein R₁ can be hydrogen or unsubstituted or substituted C₁₋₆ alkyl; R₂ can be hydrogen, or substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl or arylalkyl; and R₃ can be substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, or arylalkyl.

As an example, the compounds of formulae (IV) and (V) may have the following structures and stereochemistry:

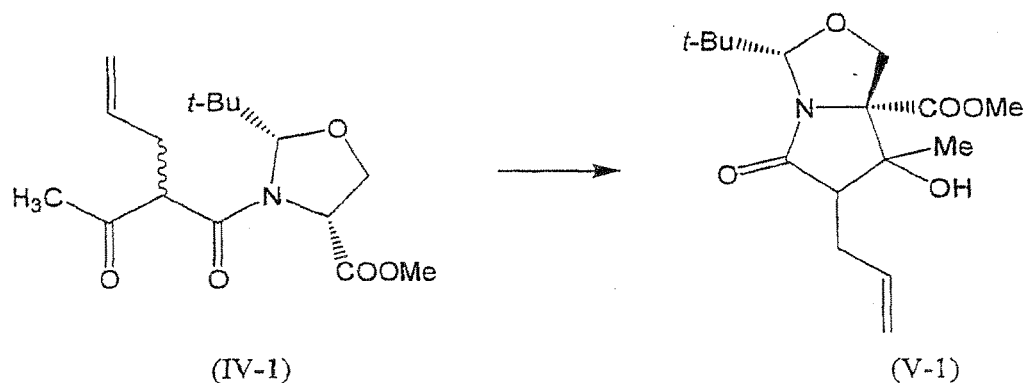


More specifically, compounds of formula (V) may adopt one of the following stereochemical structures:

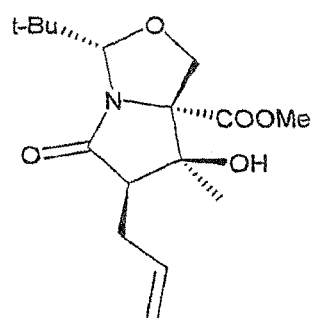


Exemplary structures of compounds formulae (IV) and (V) are shown

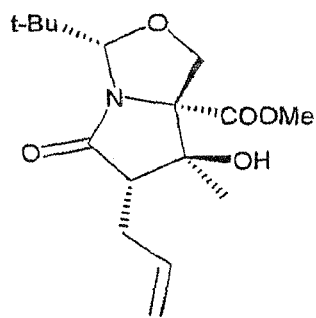
below:



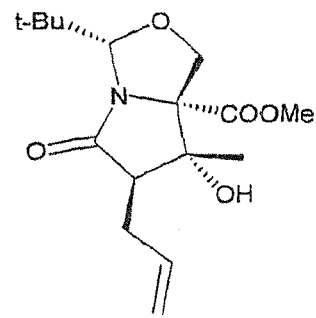
More specifically, a compound of formula (V) may adopt one of the following stereochemical structures:



(V-1A)



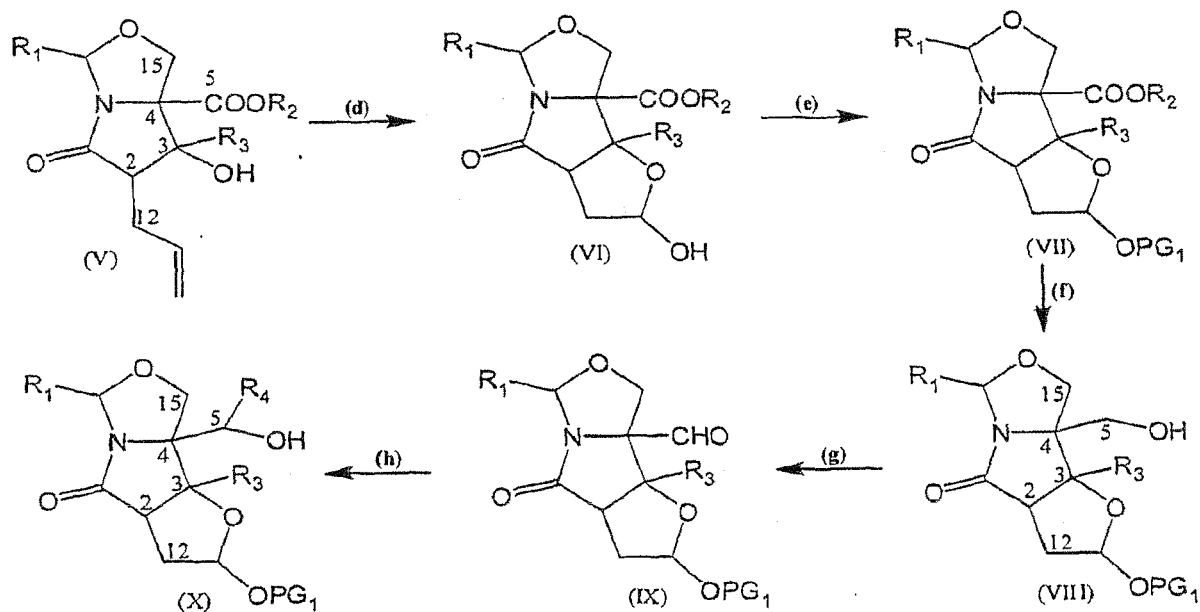
(V-1B)



(V-1C)

A compound of formula (V) can be used to synthesize heterocyclic compounds such as Salinosporamide A and analogs thereof. One method can proceed through a compound of formula (X), which can then be transformed to Salinosporamide A and analogs thereof, as shown in the schemes herein. In an embodiment, a compound of formula (X) can be produced from a compound of formula (V) as shown in Scheme 6.

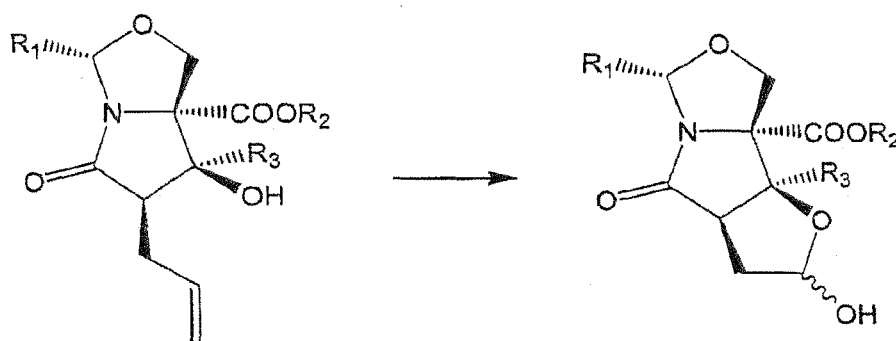
Scheme 6



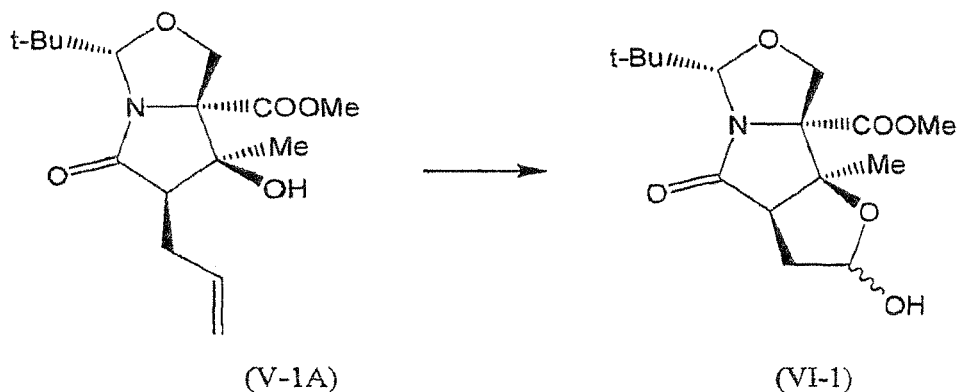
In step (d) of Scheme 6, the carbon-carbon double bond of the compound of formula (V) can be oxidatively cleaved and then cyclized to form a hemiacetal with the tertiary hydroxy group to form a compound of formula (VI), wherein R_1 can be hydrogen or unsubstituted or substituted C_{1-6} alkyl; R_2 can be hydrogen, or

substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl or arylalkyl; and R₃ can be substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, or arylalkyl. An exemplary method for preparing a compound of formula (VI) includes reacting a compound of formula (V) with a suitable oxidant or oxidant combination, such as OsO₄ and NMO for several hours and then adding an additional oxidant (e.g., NaIO₄ or Pb(OAc)₄) to the reaction mixture. The reaction can be quenched using suitable salt solutions.

Exemplary structures and stereochemistry of compounds of formulae (V) and (VI) are shown below:

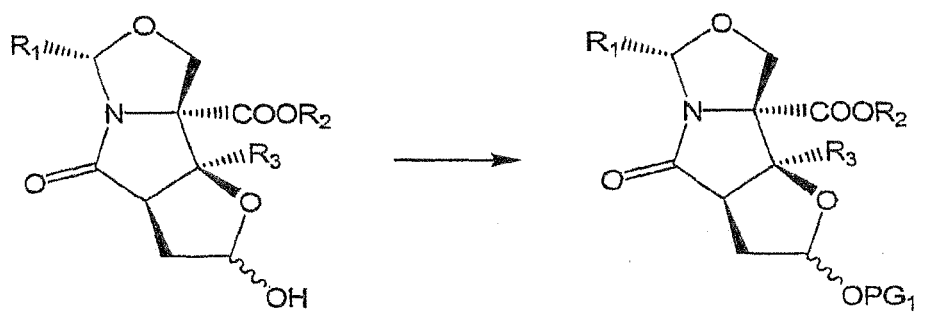


Examples of compounds of formulae (V) and (VI) are as follows:

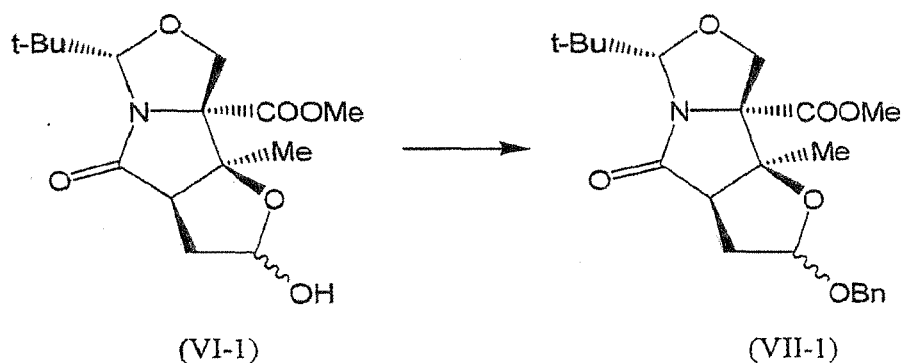


If desired, the hemiacetal of a compound of formula (VI) can be protected by forming an acetal using a protecting group moiety (e.g. benzyl, substituted benzyl, silyl, or methoxymethyl) to form a compound of formula (VII), as shown in step (e) of Scheme 6. In some embodiments, R₁, R₂, and R₃ can be the same as described with respect to the compound of formula (VI); and PG₁ can be a protecting group moiety. Examples of suitable protecting group moieties are described herein.

As an example, the compounds of formulae (VI) and (VII) may have the following structures and stereochemistry:

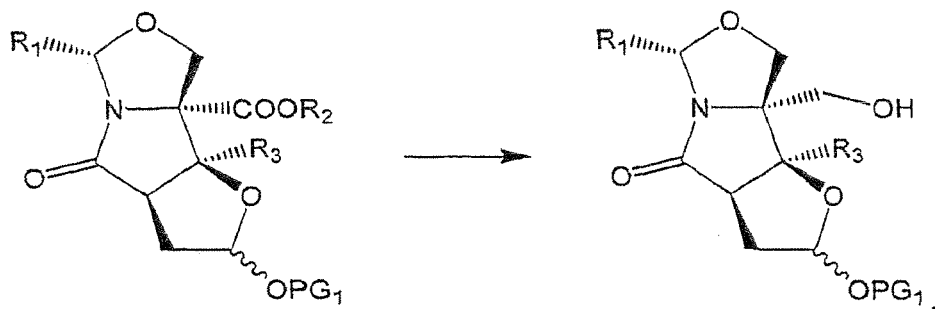


Exemplary structures of compounds of formulae (VI) and (VII) are shown below:

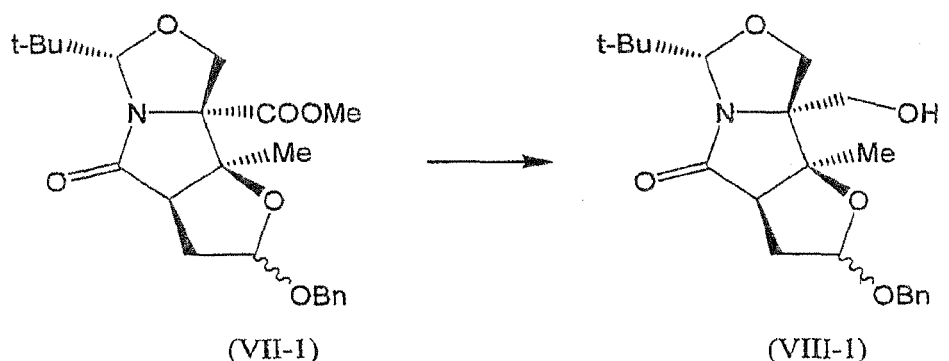


As shown in step (f) of Scheme 6, the COOR_2 group of a compound of formula (VII) can be reduced to an alcohol to form a compound of formula (VIII), wherein R_1 , R_3 , and PG_1 can be the same as described with respect to the compound of formula (VII). For example, the COOR_2 group can be reduced to an alcohol using a suitable reducing reagent (e.g., diisobutylaluminum hydride, lithium borohydride, lithium aluminum hydride, superhydride) and known techniques.

Exemplary structures and stereochemistry of compounds of formulae (VII) and (VIII) are shown below:

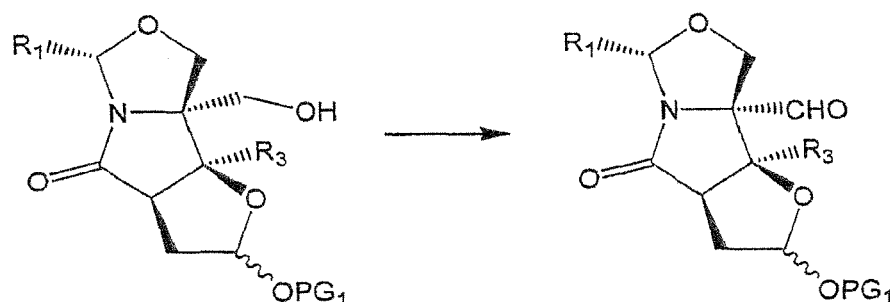


For example, compounds of formulae (VII) and (VIII) can have the following structures:

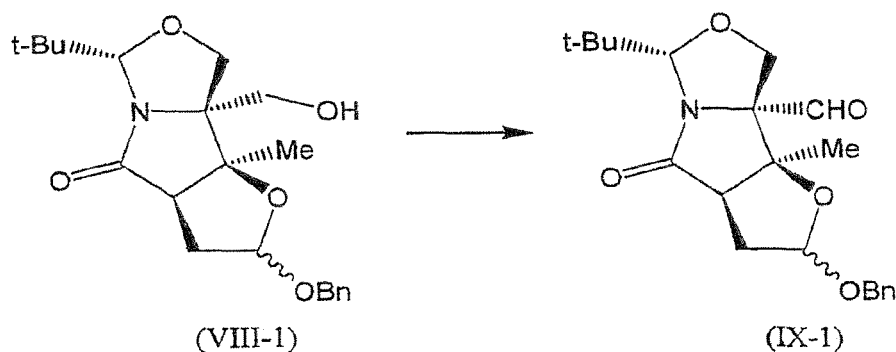


In step (g) of Scheme 6, the C-5 alcohol of the compound of formula (VIII) can be oxidized using an appropriate oxidizing agent to form the compound of formula (IX), wherein R_1 , R_3 , and PG_1 can be the same as described with respect to the compound of formula (VII). For example, an alcohol can be oxidized to an aldehyde using an oxidant such as Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, or PDC.

Compounds of formulae (VIII) and (IX) may have the following structures and stereochemistry:



Examples of compounds of formulae (VIII) and (IX) are as follows:



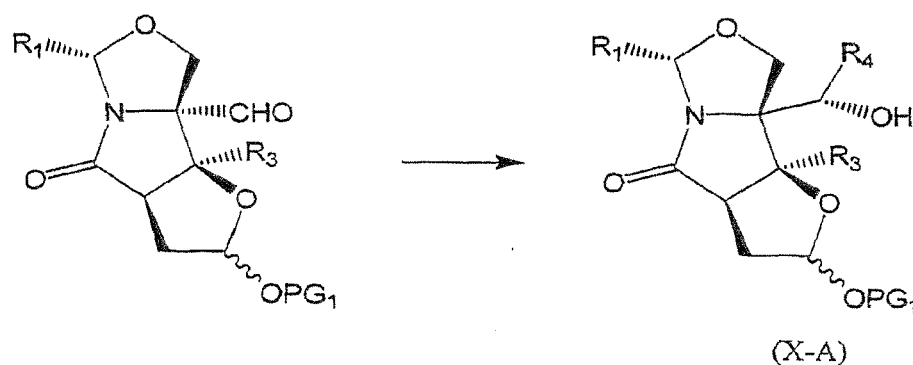
In another embodiment, the $COOR_2$ group of a compound of formula (VII) can be reduced directly to an aldehyde to give a compound of formula (IX) in a single step.

As shown in step (h) of Scheme 6, a compound of formula (X) can be synthesized by reacting an organometallic moiety containing at least one R_4 with a compound of formula (IX), wherein R_1 , R_3 , and PG_1 can be the same as described with respect to the compound of formula (VII); and R_4 can be selected from the group consisting of substituted or unsubstituted variants of the following: C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkenyl, C_3 - C_{12} cycloalkynyl, C_3 - C_{12} heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of a carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocynoalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl. In some embodiments, R_4 can be selected from the group consisting of: substituted or unsubstituted variants of the following: C_3 - C_{12} heterocyclyl, aryl, heteroaryl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of a carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocynoalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl.

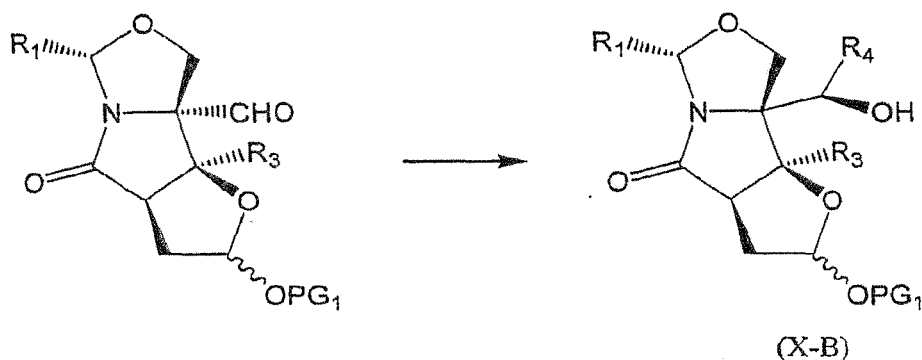
A non-limiting list of suitable organometallic moieties include organomagnesium compounds, organolithium compounds, organotin compounds, organocuprates compounds, organozinc, and organopalladium compounds, metal

carbonyls, metallocenes, carbene complexes, and organometalloids (e.g., organoboranes and organosilanes). In some embodiments, the organometallic moiety can be selected from the group consisting of $R_4\text{-MgR}_7$, $R_4\text{-ZnR}_7$, $R_4\text{-Li}$, $(R_4)_p\text{-B(R}_7\text{)}_{3-p}$, and $(R_4)_q\text{-Sn(R}_7\text{)}_{4-q}$; wherein R_7 can be selected from the group consisting of halogen, or substituted or unsubstituted variants of the following: alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, isopinocampheyl, hydroxy, alkoxy, and carbonylalkoxy, wherein if more than one R_7 is present, the R_7 groups can optionally be bonded together to form an optionally substituted cycloalkyl (e.g., 9-BBN), optionally substituted cycloalkenyl, optionally substituted heteroalkyl or optionally substituted heteroalkenyl ring; p can be an integer from 1 to 3; and q can be an integer from 1 to 4. In an embodiment, the organometallic moiety is $(R_4)_p\text{-B(R}_7\text{)}_{3-p}$. In certain embodiments, the organometallic moiety is $(R_4)_p\text{-B(R}_7\text{)}_{3-p}$, wherein R_4 is 2-cyclohexenyl. In some embodiments, the organometallic moiety is $(R_4)_p\text{-B(R}_7\text{)}_{3-p}$, wherein R_4 is 2-cyclohexenyl, p is 1, and the two R_7 groups are taken together to form an optionally substituted cycloalkyl. In another embodiment, the organometallic moiety is $R_4\text{-MgR}_7$. In certain embodiments, the organometallic moiety is $R_4\text{-MgR}_7$, wherein R_4 is 2-cyclohexenyl. In some embodiments, the organometallic moiety is $R_4\text{-MgR}_7$, wherein R_4 is 2-cyclohexenyl and R_7 is a halogen (e.g., chlorine).

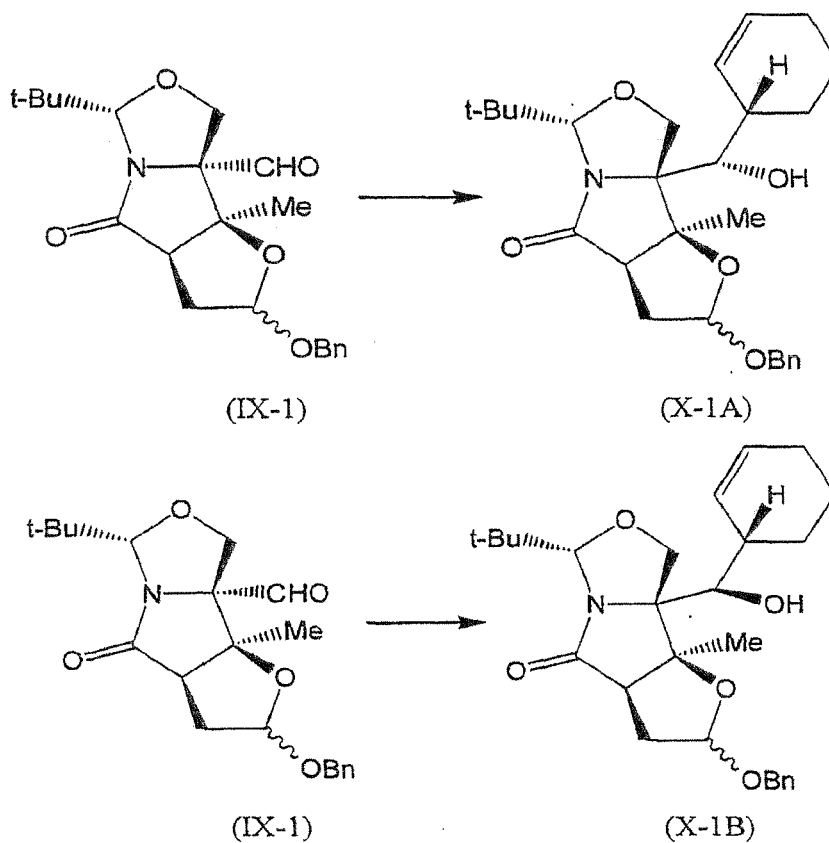
As an example, the compounds of formulae (IX) and (X) may have the following structures and stereochemistry:



As another example, the compounds of formulae (IX) and (X) may have the following structures and stereochemistry.

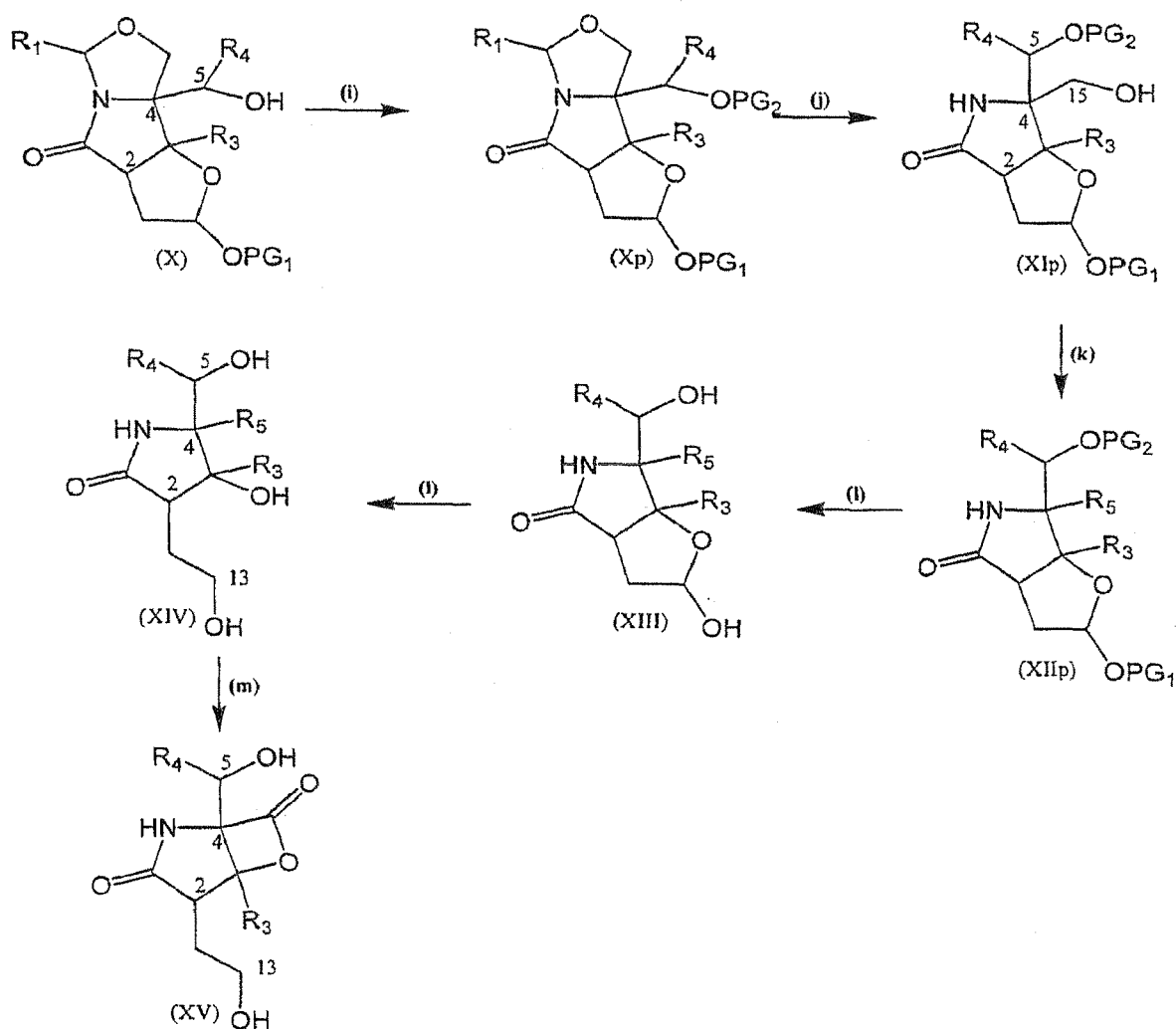


Exemplary structures of compounds of formulae (IX) and (X) are shown below:

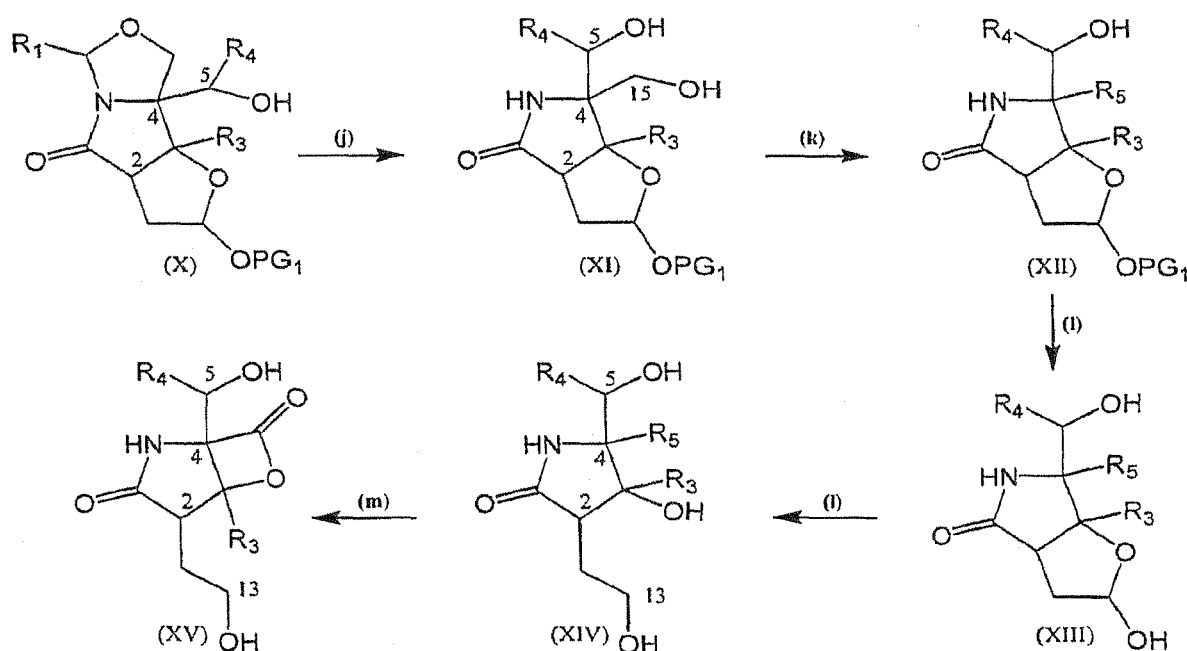


Various synthetic routes can be used to transform a compound of formula (X) to Salinosporamide A and analogs thereof. In an embodiment, the synthesis can proceed through the intermediate compound of formula (XV). Exemplary synthetic routes are shown Schemes 7-1 to 7-5.

Scheme 7-1

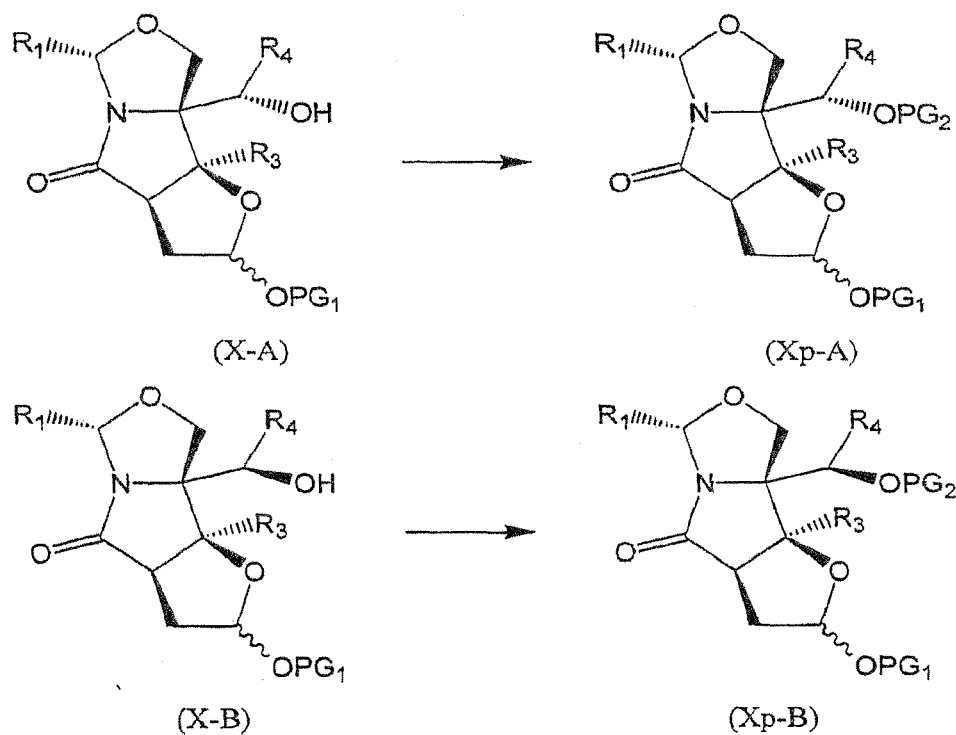


Scheme 7-2

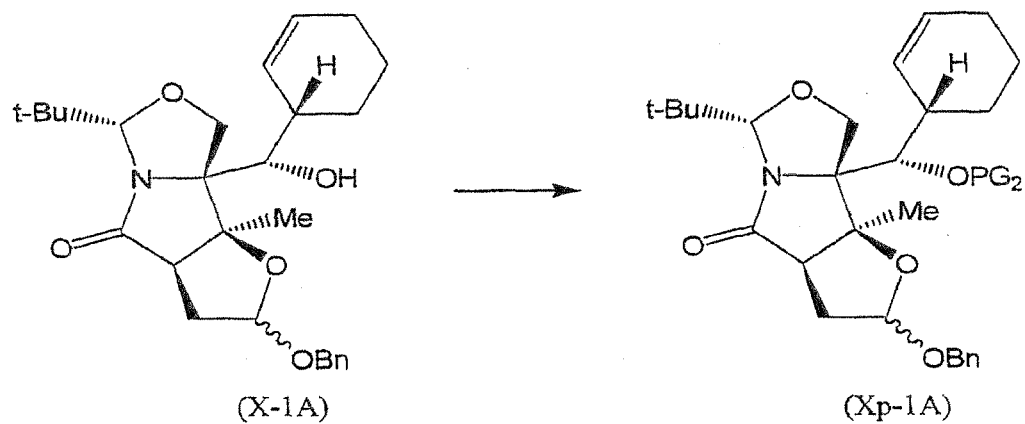


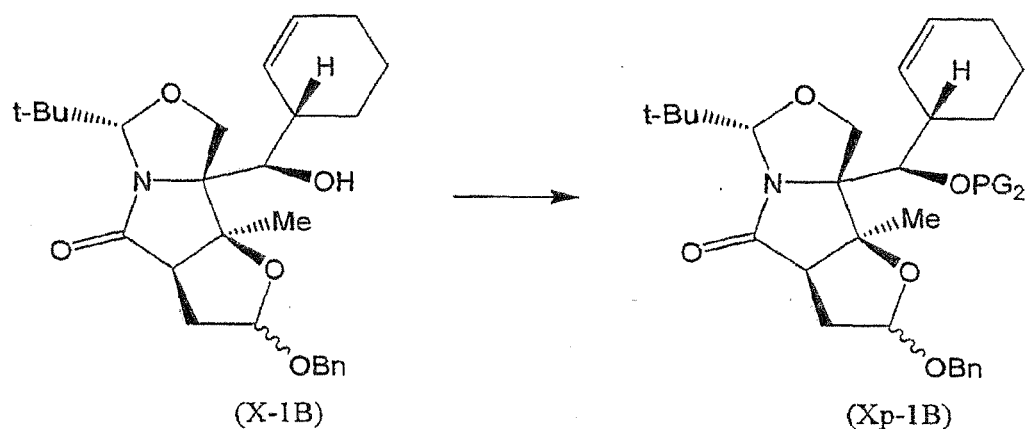
As shown in step (i) of Scheme 7-1, the C-5 secondary hydroxy group of a compound of formula (X) can be protected with a suitable protecting group moiety to form a compound of formula (Xp), wherein R₁, R₃, R₄ and PG₁ can be the same as described with respect to the compound of formula (X); and PG₂ can be a protecting group moiety. A non-limiting list of suitable protecting group moieties that can be used to protect the C-5 secondary hydroxy group of a compound of formula (X) include a substituted methyl ether (e.g. methoxymethyl), a substituted ethyl, a substituted benzylethyl, tetrahydropyranyl, a silyl ether (e.g. trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, or t-butyldiphenylsilyl), an ester (e.g. benzoate ester), or a carbonate (e.g. methoxymethylcarbonate). Alternatively, in some embodiments, the C-5 secondary hydroxy group of a compound of formula (X) can remain unprotected, as shown in Scheme 7-2.

Compounds of formulae (X) and (Xp) may have the following structures and stereochemistry:



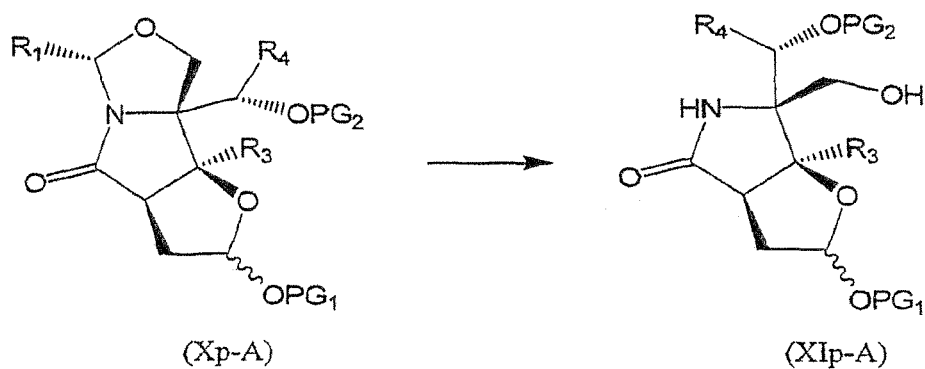
As examples, compounds of formulae (X) and (Xp) can have the following structures:

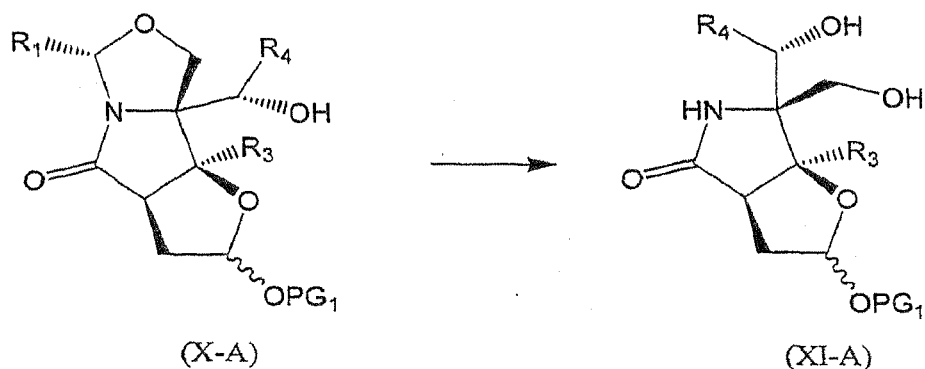




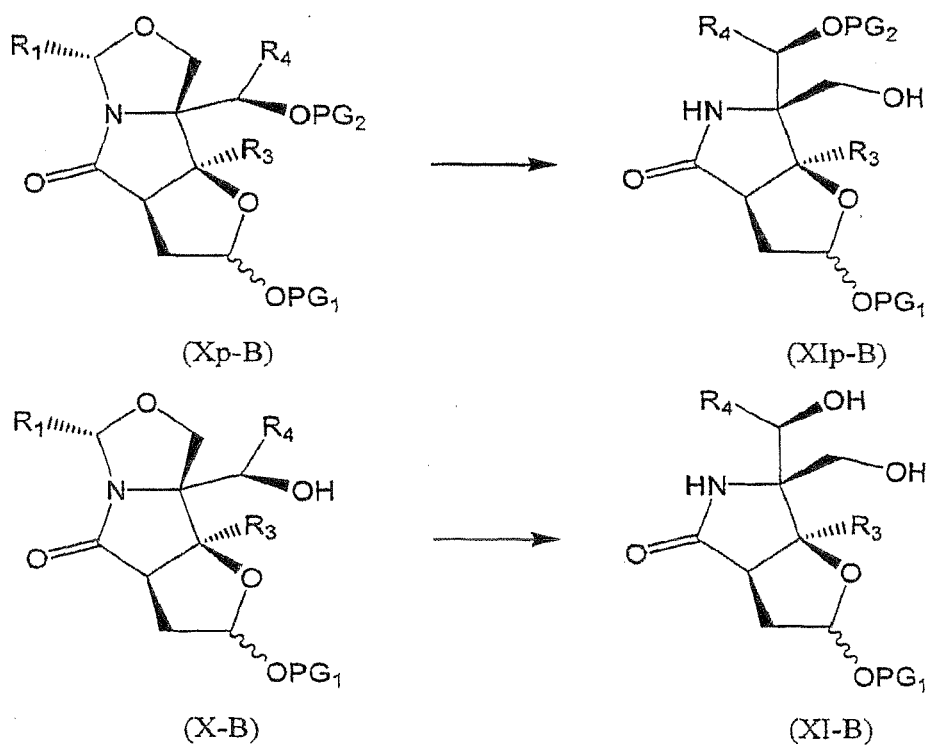
The amination of a compound of formula (Xp) can be cleaved using a suitable acid (e.g. triflic acid, HCl, PTSA, PPTS, TFA, camphor sulfonic acid) to form a compound of formula (XIp), as shown in Scheme 7-1. In instances in which the C-5 secondary hydroxy is unprotected, the same or another acid can be used to form a compound of formula (XI) from a compound of formula (X). See Scheme 7-2. The substituents and protecting group moieties (R_1 , R_3 , R_4 , PG_1 , and PG_2 where applicable) for compounds of formula (XI) and (XIp) can be the same as described with respect to the compound of formula (Xp).

Exemplary structures and stereochemistry of compounds of formulae (X), (Xp), (XI), and (XIp) are shown below:

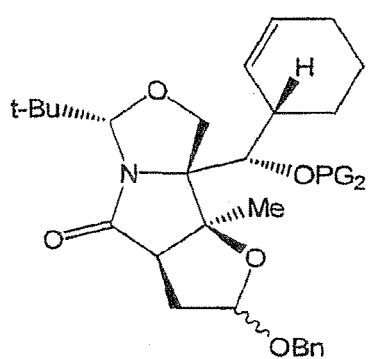




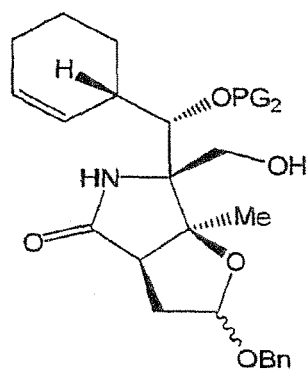
As another example, the compounds of formulae (X), (Xp), (XI), and (XIp) can have the following structures and stereochemistry:



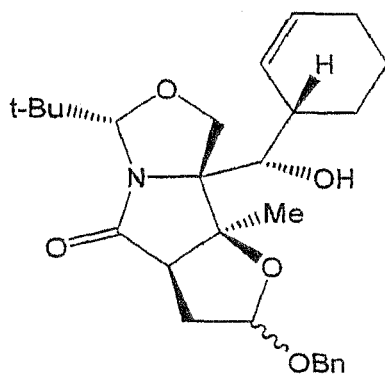
For example, compounds of formulae (X), (Xp), (XI) and (XIp) can have the following structures:



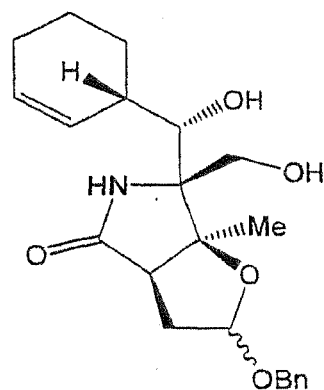
(Xp-1A)



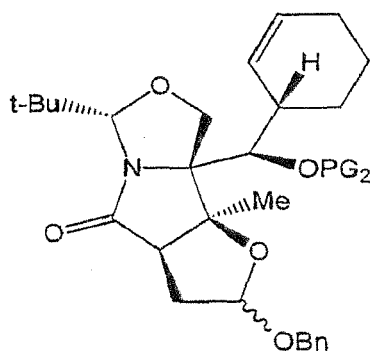
(XIp-1A)



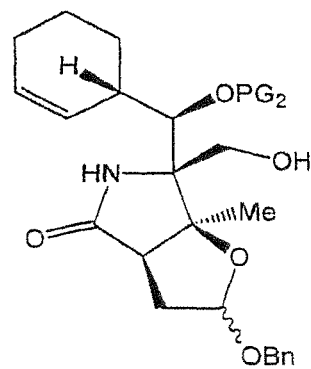
(X-1A)



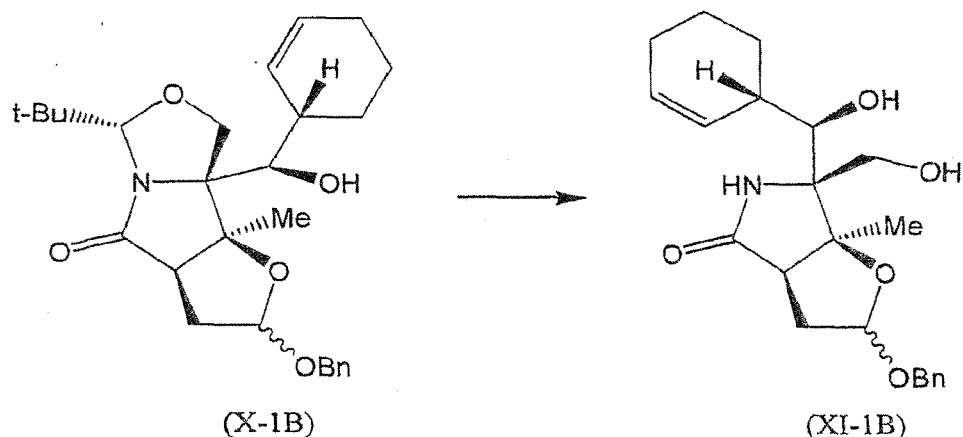
(XI-1A)



(Xp-1B)

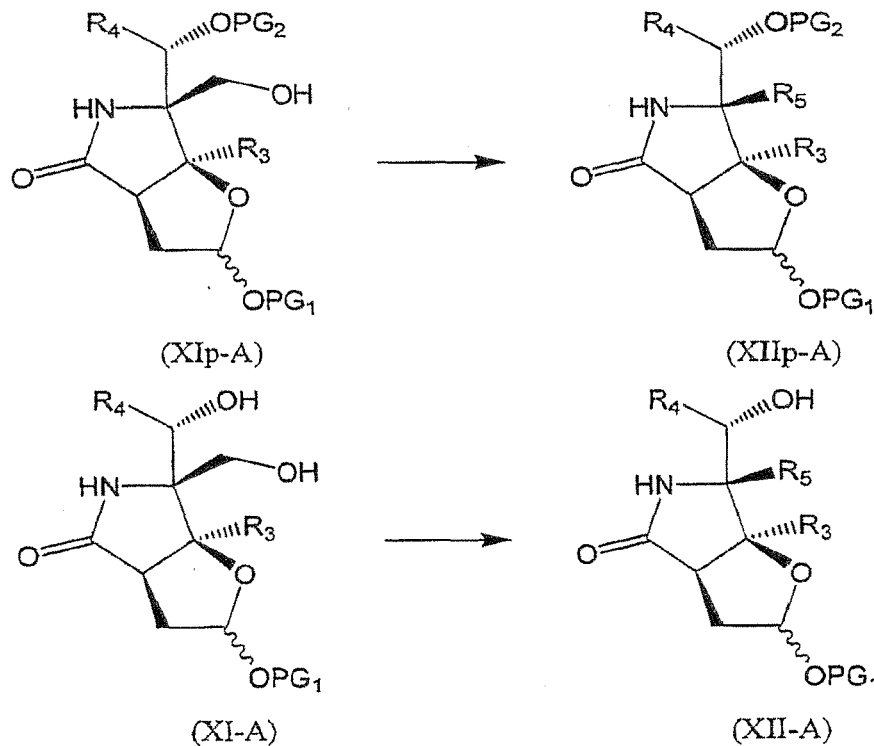


(XIp-1B)

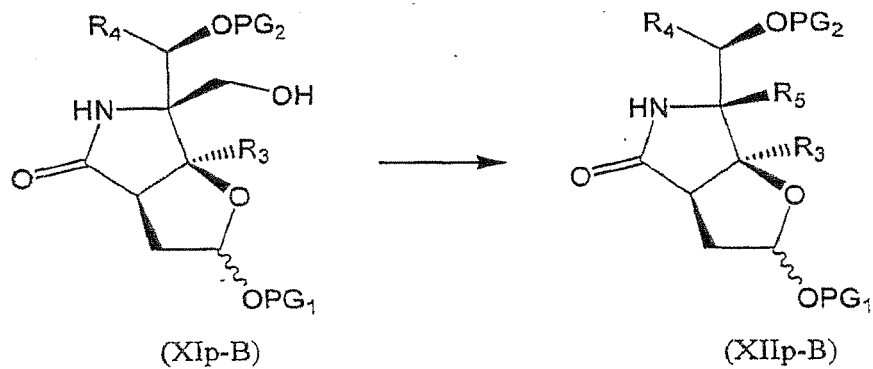


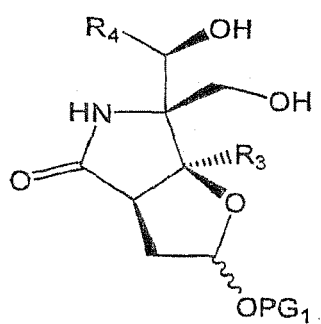
As shown in Scheme 7-1, step (k), the C-15 primary alcohol group of a compound of formula (XI_p) can be transformed to R₅ to form a compound of formula (XI_{lp}). Similarly when the C-5 secondary hydroxy group is unprotected, the C-15 primary alcohol group of a compound of formula (XI) can be transformed to R₅ to form a compound of formula (XII). See Scheme 7-2. R₃, R₄, PG₁, (and PG₂, where applicable) of the compounds of formulae (XII) and (XI_{lp}) can be the same as described with respect to the compound of formula (X_p); and R₅ can be selected from the group consisting of –C(=O)OR₆, –C(=O)SR₆, –C(=O)NR₆R₆, –C(=O)Z wherein each R₆ can be independently selected from the group consisting of hydrogen, halogen, or substituted or unsubstituted variants of the following: C₁–C₂₄ alkyl, acyl, alkylacyl, arylacyl, aryl, arylalkyl, p-nitrophenyl, pentafluorophenyl, pentafluoroethyl, trifluoroethyl, trichloroethyl, and heteroaryl; and Z can be a halogen. For example, the primary alcohol group can be converted to a carboxylic acid using appropriate oxidation conditions such as Jones oxidation. Alternatively, the carboxylic acid group can be prepared from the primary alcohol group of the compound of formula (XI) or (XI_p) through an aldehyde. The primary alcohol group of the compound of formula (XI) or (XI_p) can first be converted to aldehyde using appropriate oxidant such as Dess-Martin periodinane, TPAP, Swern oxidation reagent, PCC, or PDC and then the resulting aldehyde can be oxidized further to carboxylic acid using appropriate oxidants such as a combination of sodium chlorite/sodium phosphate dibasic/2-methyl-2-butene. If desired, the carboxylic acid can then be further converted to an ester, a thioester, acid halides (e.g., acid chloride) or an anhydride using an appropriate alcohol, thiol (e.g., thiophenol, cystine), thionyl or oxalyl chlorides, carboxylic acid (e.g., acetic acid, benzoic acid), and/or anhydride (e.g., acetic anhydride).

As an example, the compounds of formulae (XI), (XIp), (XII) and (XIIp) may have the following structures and stereochemistry:

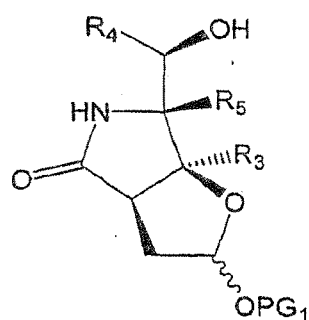


Other exemplary structures and stereochemistry of the compounds of formulae (XI), (XIp), (XII) and (XIIp) include following structures and stereochemistry:



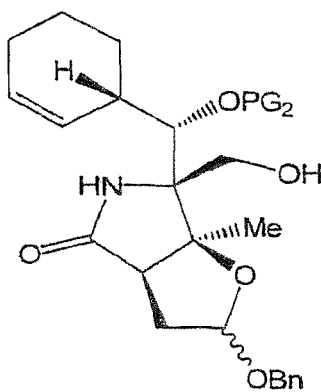
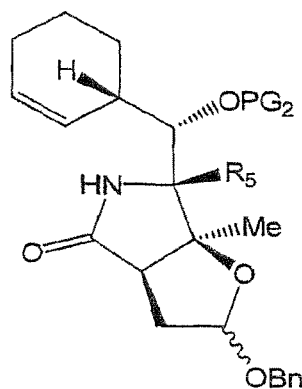
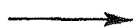
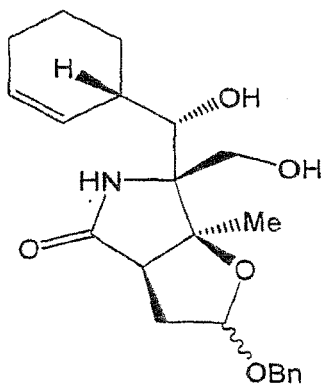


(XI-B)

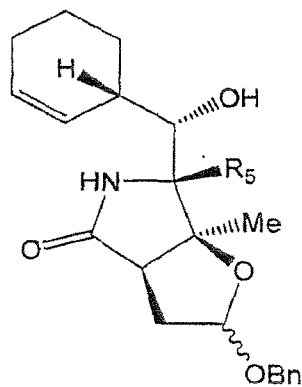


(XII-B)

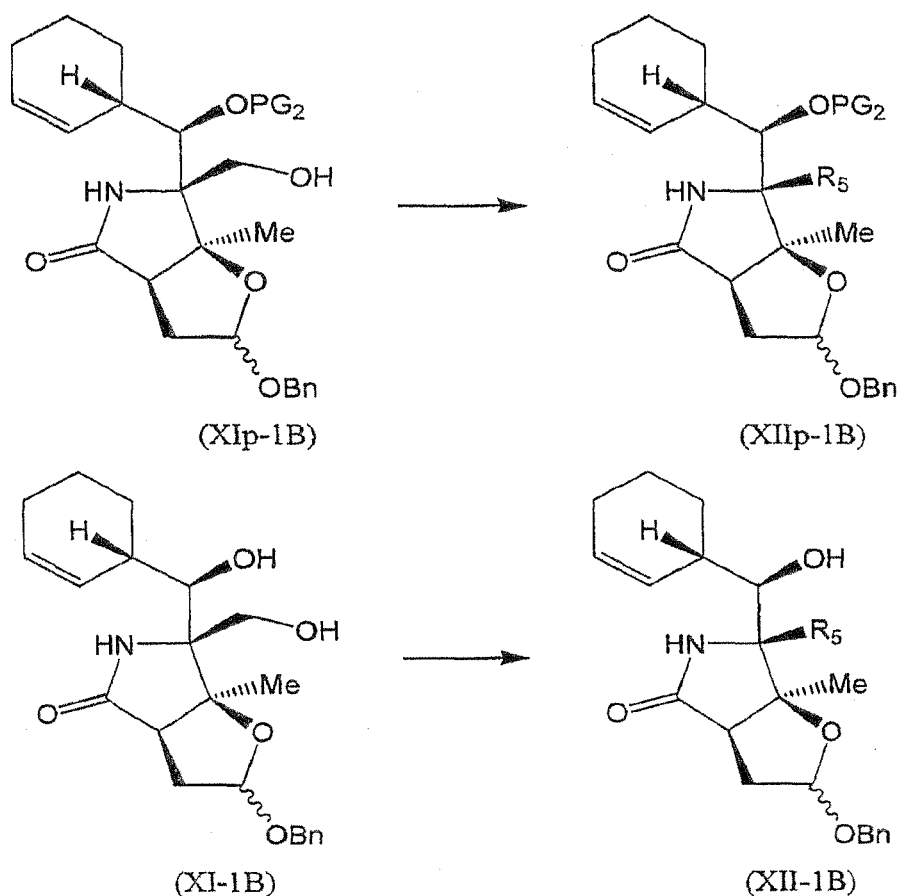
Exemplary structures of compounds of formulae (XI), (XI_p), (XII), and (XII_p) are as follows:

(XI_p-1A)(XII_p-1A)

(XI-1A)



(XII-1A)

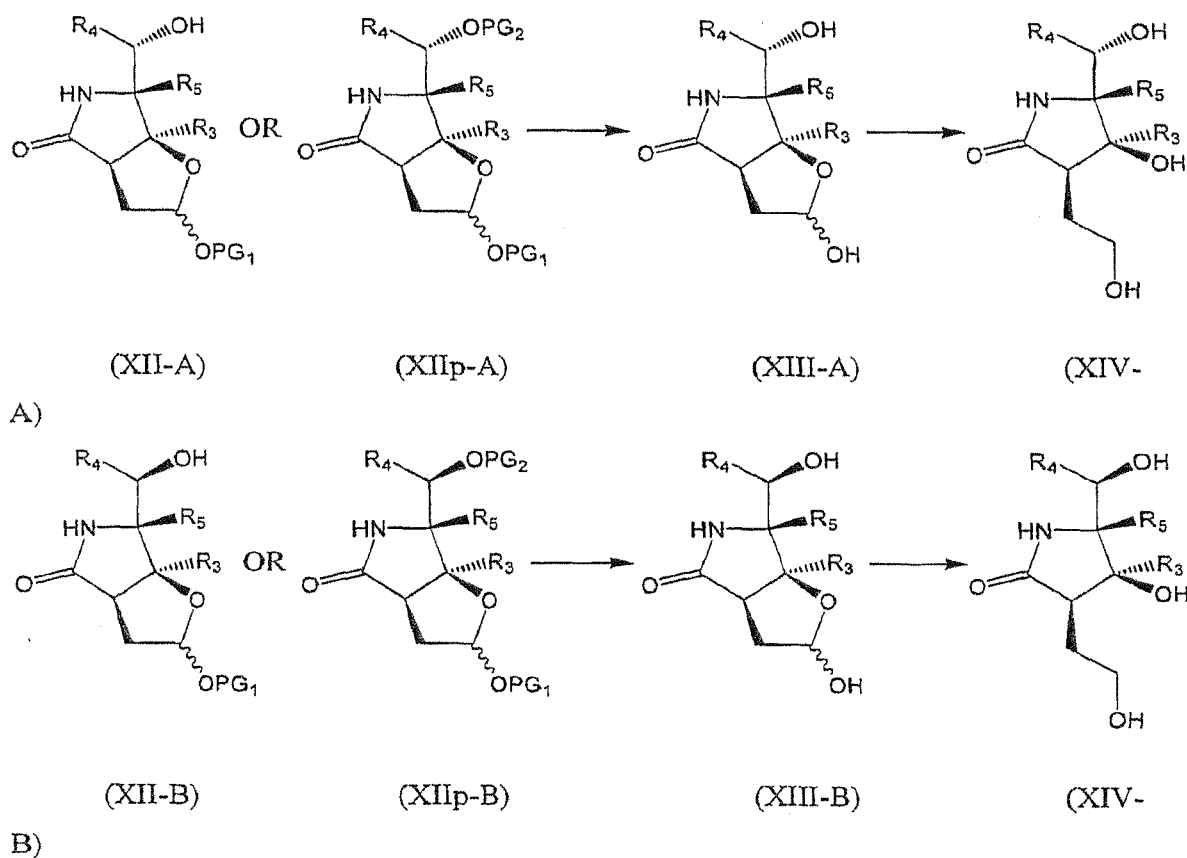


In some embodiments, a compound of formula (XII) can have the structure shown in Scheme 7-2, with the proviso that if a compound of formula (XII) has the structure and stereochemistry of the compound of formula (XII-1A), then R₅ cannot be -C(=O)OR₆, wherein R₆ is t-butyl.

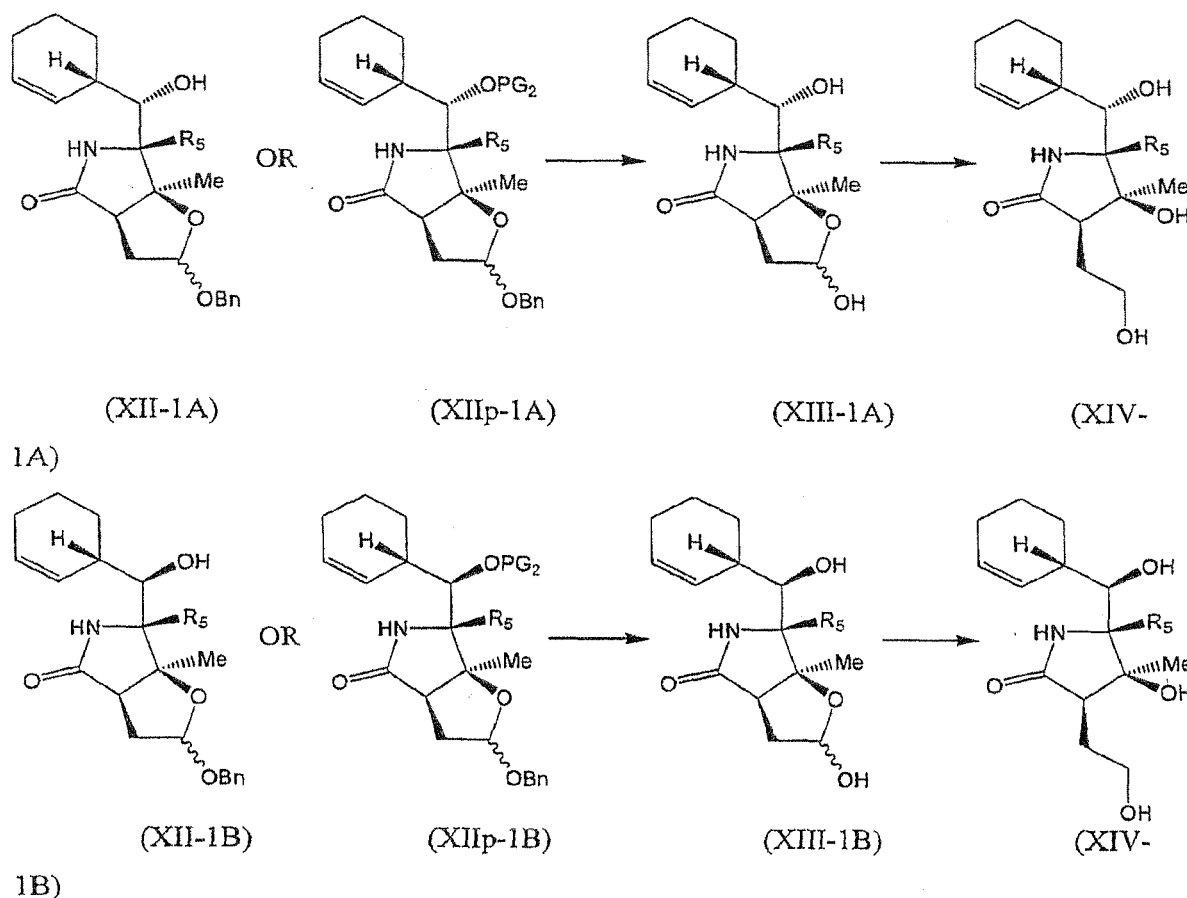
A compound of formula (XIV) can be synthesized by removing any protecting group moieties on the compound of formula (XII) and/or (XIIp) to form a compound of formula (XIII) and then cleaving the hemiacetal of the compound of formula (XIII). In some embodiments, R₃, R₄, and R₅ of the compounds of formulae (XIII) and (XIV) can be the same as described with respect to the compound of formula (XIIp). One method for reductively cleaving the hemiacetal can be using a suitable reducing reagent such as sodium borohydride. In one embodiment, the formation of a compound of formula (XIV) from a compound of formula (XII) or (XIIp) can be accomplished in a single step. In another embodiment, the protecting group moiety PG₁ on the compound of formula (XII) can be initially removed to form a compound of formula (XIII) and then the resulting hemiacetal can be reductively cleaved to form a

compound of formula (XIV). In another embodiment, the protecting group moieties PG₁ and PG₂ on the compound of formula (XIIp) can be removed simultaneously or sequentially to form a compound of formula (XIII) and then the resulting hemiacetal can be reductively cleaved to form a compound of formula (XIV). If the protecting group moieties on the compound of formula (XIIp) are removed sequentially, they can be removed in any order to form a compound of formula (XIII).

Compounds of formulae (XII), (XIIp), (XIII), and (XIV) may have the following structures and stereochemistry:



Exemplary structures of compounds of formulae (XII), (XIIp), (XIII), and (XIV) are shown below:



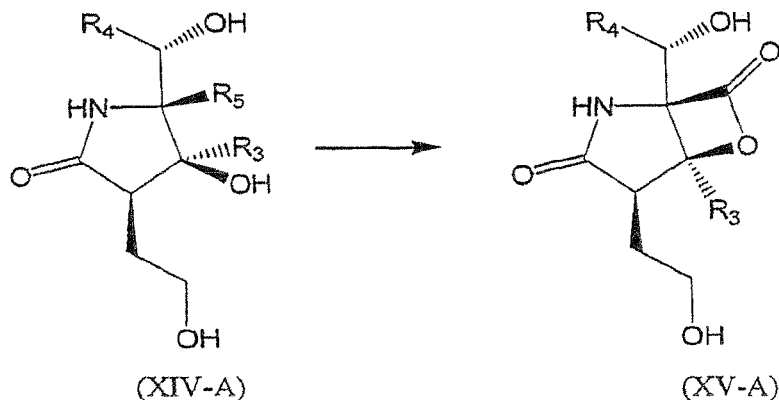
In some embodiments, a compound of formula (XIV) can be synthesized by removing any protecting group moieties on the compound of formula (XII) and/or (XIIp) and reductively cleaving the resulting hemiacetal of the compound of formula (XIII) with the proviso that if the compound of formula (XII) has the structure and stereochemistry of the compounds of formula (XII-1A), then R₅ cannot be $-\text{C}(=\text{O})\text{OR}_6$, wherein R₆ is t-butyl. In other embodiments, a compound of formula (XIV) can be synthesized by removing any protecting group moieties on the compound of formula (XII) and/or (XIIp) and reductively cleaving the resulting hemiacetal of the compound of formula (XIII) with the proviso that if the compound of formula (XIII) has the structure and stereochemistry of the compounds of formula (XIII-1A), then R₅ cannot be $-\text{C}(=\text{O})\text{OR}_6$, wherein R₆ is t-butyl.

In one embodiment, a compound of formula (XIII) can have the structure and stereochemistry of a compound of formula (XIII-1A), with the proviso that R₅ cannot be $-\text{C}(=\text{O})\text{OR}_6$, wherein R₆ is t-butyl. In an embodiment, a compound of formula (XIV) can have structure shown herein, with the proviso that if the compound of

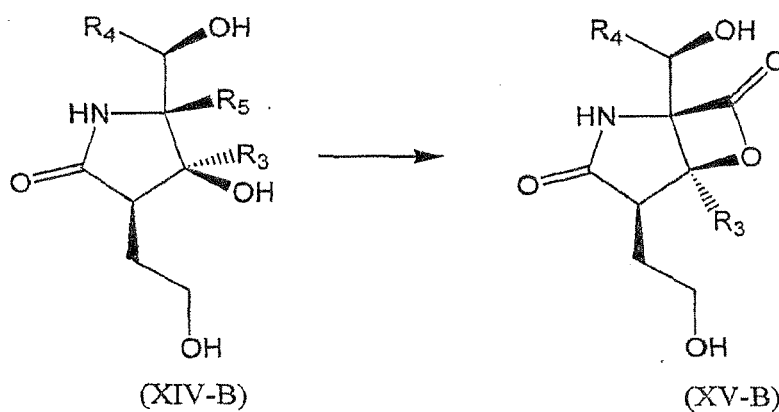
formula (XIV) has the structure and stereochemistry of the compound of formula (XIV-1A), then R_5 cannot be $-C(=O)OR_6$, wherein R_6 is hydrogen, methyl, or t-butyl.

Finally, in step (m) of Schemes 7-1 and 7-2, a compound of formula (XV) can be formed by treating a compound of formula (XIV) with an appropriate base (e.g., BOPCl/pyridine, triethylamine) to induce a lactonization reaction and form the 4-membered heterocyclic ring, wherein R_3 , R_4 , and R_5 can be same as described with respect to the compound of formula (XII) or (XIIp). In an embodiment, if R_5 is an ester, it can first be transformed to a carboxylic acid, an activated acid (e.g., acid halide), or an activated ester (e.g., p-nitrophenyl ester, pentafluorophenyl ester, pentafluoroethyl ester, trifluoroethyl ester, trichloroethyl ester, a thioester, etc.) before being treated with an appropriate reagent to induce the lactonization reaction. For example, when R_5 is carboxylic acid, it can be treated with an appropriate base to affect the lactonization reaction. In some embodiments, if R_5 is an amide, it can first be transformed to a carboxylic acid, an activated acid, or an activated ester such as those described herein before being treated with an appropriate base to induce the lactonization reaction.

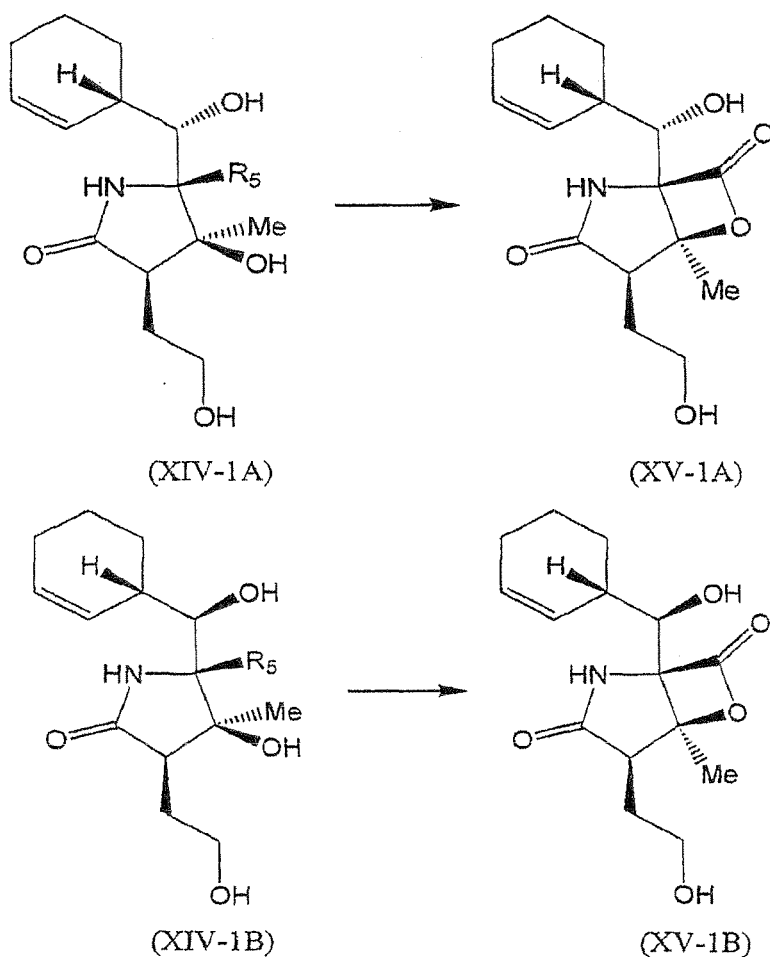
As an example, the compounds of formulae (XIV) and (XV) may have the following structures and stereochemistry:



In another example, the compounds of formulae (XIV) and (XV) may have the following structures and stereochemistry:



Exemplary structures of compounds of formulae (XIV) and (XV) are as follows:

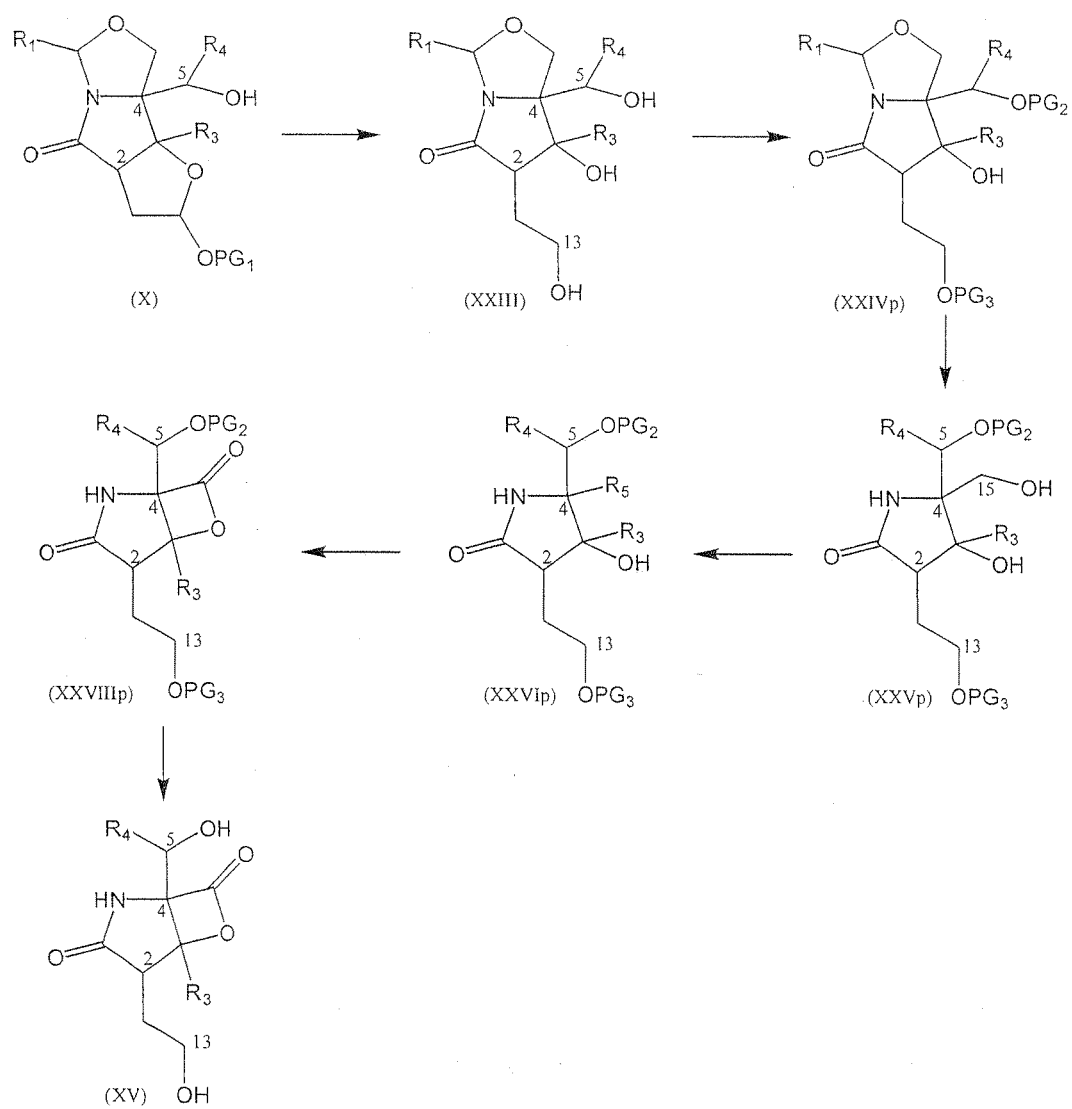


In an embodiment, R_5 of the compound of formula (XIV-1A) can be a carboxylic acid. In some embodiments, R_5 of the compound of formula (XIV-1A) can be an activated acid (e.g., acid chloride). In certain embodiments, R_5 of the compound of formula (XIV-1A) can be an activated ester such as p-nitrophenyl ester, pentafluorophenyl ester, pentafluoroethyl ester, trifluoroethyl ester, trichloroethyl ester, thioester, etc. In an embodiment, R_5 of the compound of formula (XIV-1B) can be a carboxylic acid. In some embodiments, R_5 of the compound of formula (XIV-1B) can be an activated acid (e.g., acid chloride). In certain embodiments, R_5 of the compound of formula (XIV-1B) can be an activated ester such as p-nitrophenyl ester, pentafluorophenyl ester, pentafluoroethyl ester, trifluoroethyl ester, trichloroethyl ester, thioester, etc.

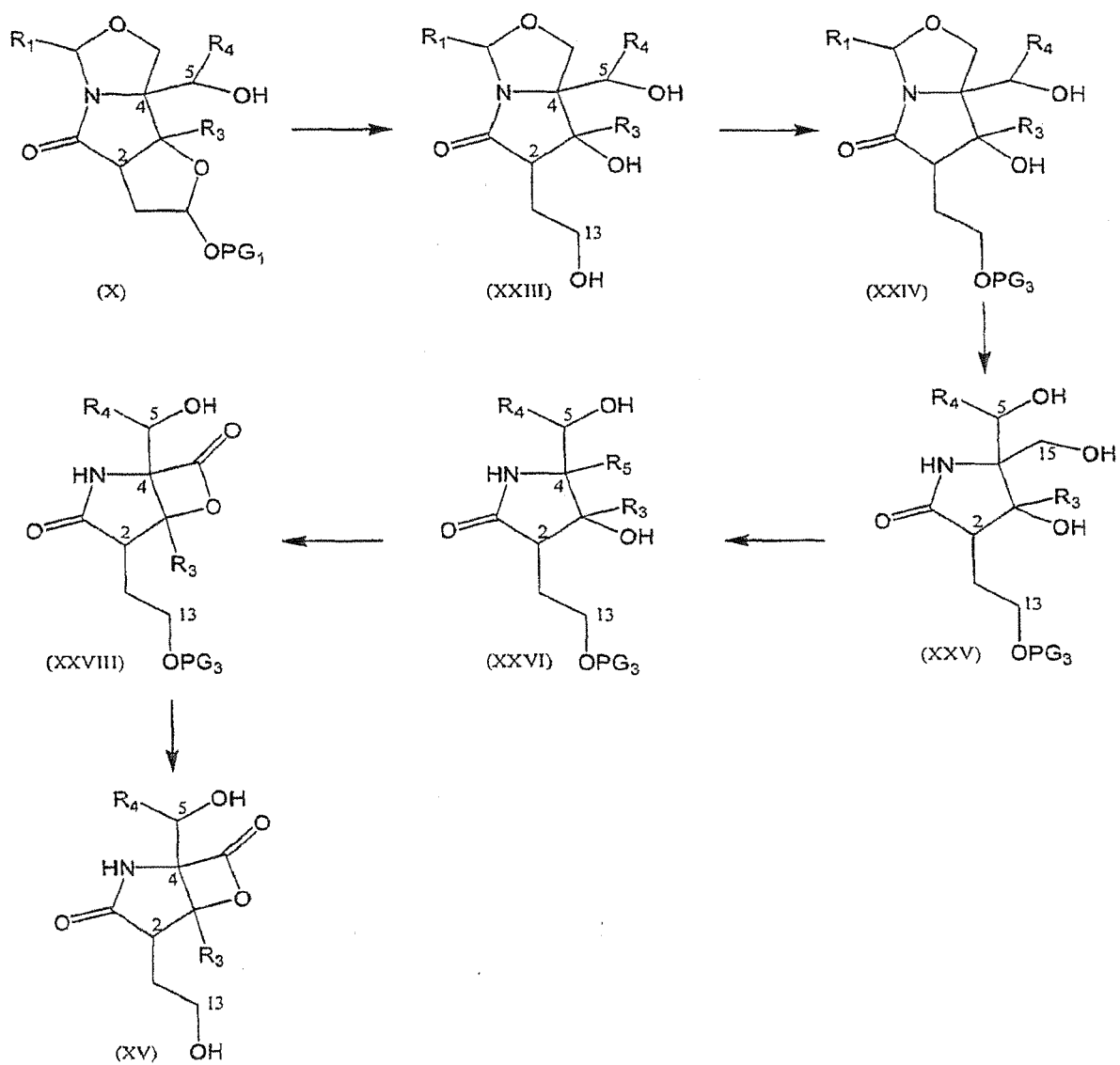
In some embodiments, a compound of formula (XV) can be synthesized by performing a lactonization reaction on a compound of formula (XIV) with the proviso that if the compounds of formulae (XIV) and (XV) have the same structures and stereochemistry as the compounds of formulae (XIV-1A) and (XV-1A), then R_5 cannot be $-C(=O)OR_6$, wherein R_6 is hydrogen. In other embodiments, the lactonization reaction includes the further proviso that R_6 cannot be methyl or t-butyl when the compounds of formulae (XIV) and (XV) have the structures and stereochemistry of the compounds of formulae (XIV-1A) and (XV-1A). In some embodiments, a compound of formula (XV) can be synthesized by performing a lactonization reaction on a compound of formula (XIV) and/or (XIV-A) with the proviso that if R_5 is $-C(=O)OR_6$, wherein R_6 is hydrogen, methyl or t-butyl then R_4 cannot be isopropyl. In an embodiment, a compound of formula (XV) can have the structure shown herein with the proviso that if the compound of formula (XV) has the structure and stereochemistry of the compound of formula (XV-A) and R_3 is methyl then R_4 cannot be 2-cyclohexenyl. In some embodiments, a compound of formula (XV) can have the structure shown herein with the proviso that if R_3 is methyl then R_4 cannot be isopropyl, cyclohexyl, or phenyl. In one embodiment, a compound of formula (XV) can have the structure shown herein with the proviso that if the compound of formula (XV) has the structure and stereochemistry of the compound of formula (XV-A) and R_3 is methyl then R_4 cannot be isopropyl.

[0191] A compound of formula (XV) can also be synthesized from a compound of formula (X) as shown in Scheme 7-3. By modifying the protection/deprotection sequence, a compound of formula (XV) can also be obtained from a compound of formula (X) as shown in Schemes 7-4 and 7-5.

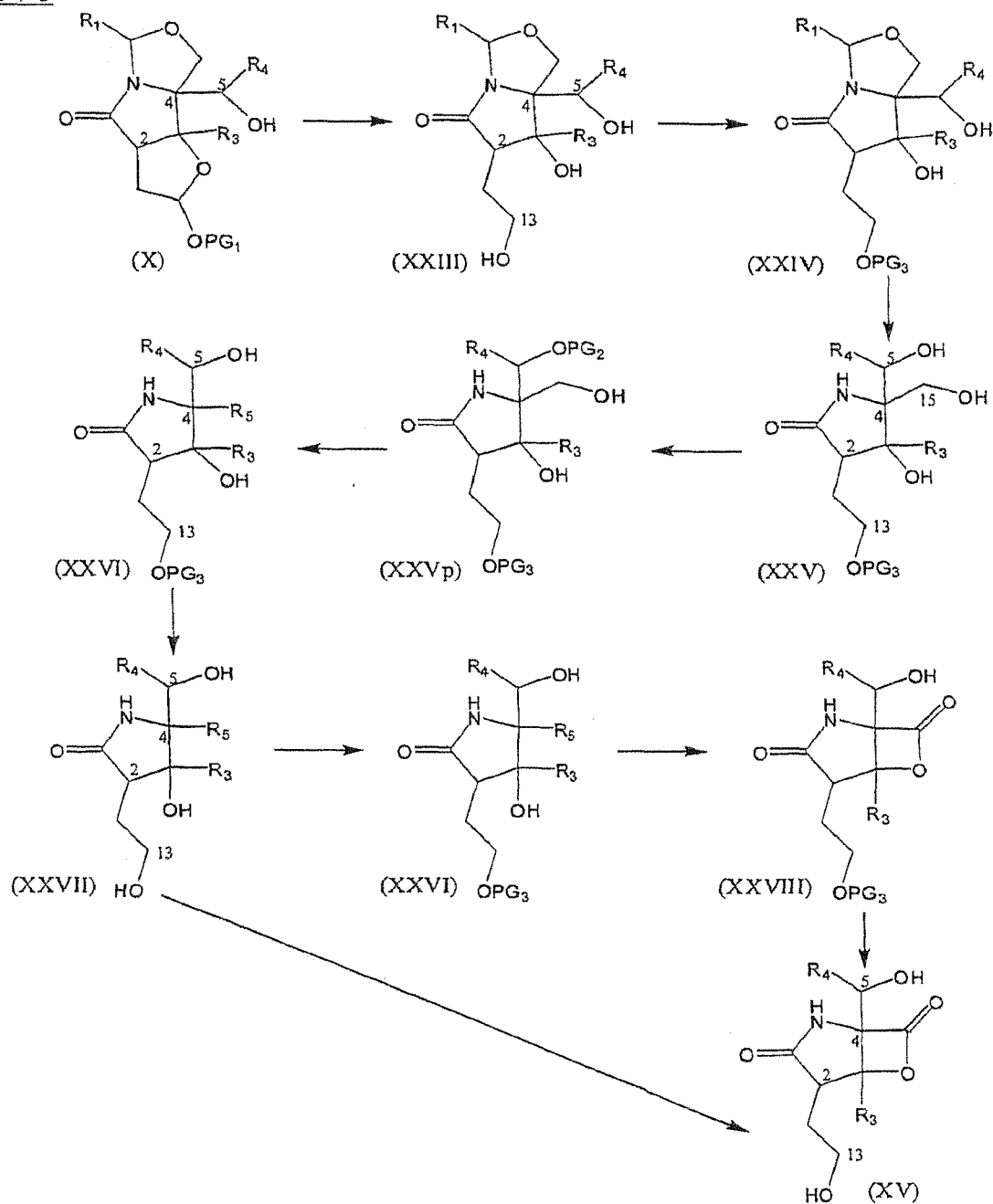
Scheme 7-3



Scheme 7-4



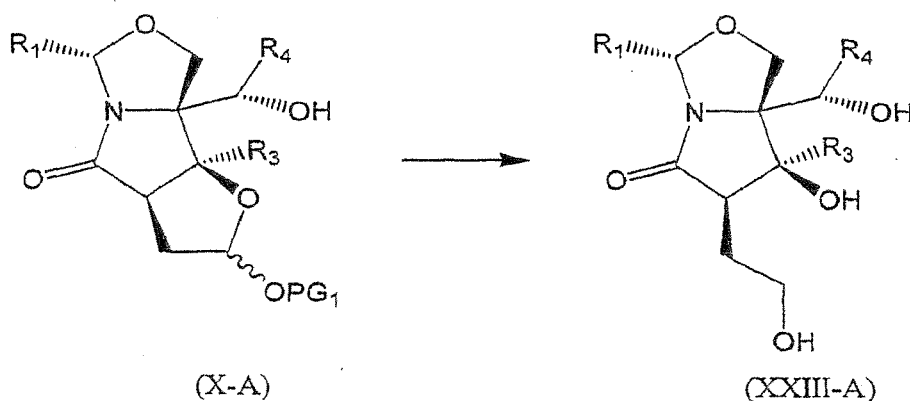
Scheme 7-5

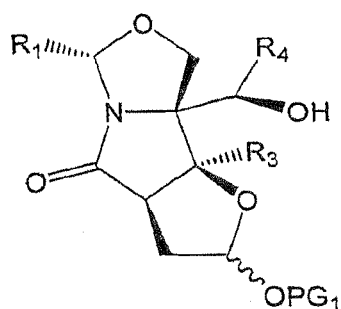


A compound of formula (XXIII) can be synthesized by removing the protecting group moiety on the compound of formula (X) and reductively opening the hemiacetal. The protecting group moiety can be removed using known methods and the hemiacetal can be reductively opened using a reducing agent (e.g., sodium borohydride). In some embodiments, the substituents (and protecting group moiety where applicable)

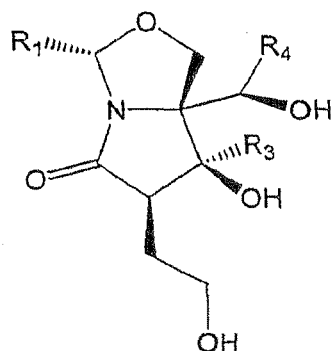
(R₁, R₃, R₄, and PG₁) for compound of formulae (X) and (XXIII) can be selected from the following: R₁ can be hydrogen or an unsubstituted or substituted C₁₋₆ alkyl; R₃ can be substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, or arylalkyl; R₄ can be selected from the group consisting of substituted or unsubstituted variants of the following: C_{1-C12} alkyl, C_{2-C12} alkenyl, C_{2-C12} alkynyl, C_{3-C12} cycloalkyl, C_{3-C12} cycloalkenyl, C_{3-C12} cycloalkynyl, C_{3-C12} heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylalkyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of a carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocyanalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonoxyalkyl, salt of a phosphonoxyalkyl, (alkylphosphoxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl..

Compounds of formulae (X) and (XXIII) may have the following structures and stereochemistry:



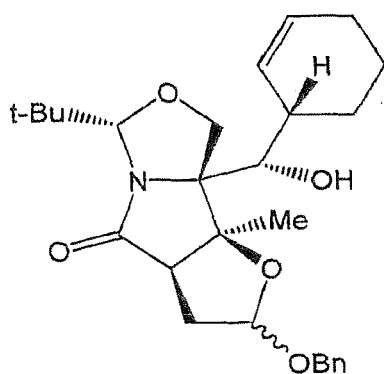


(X-B)

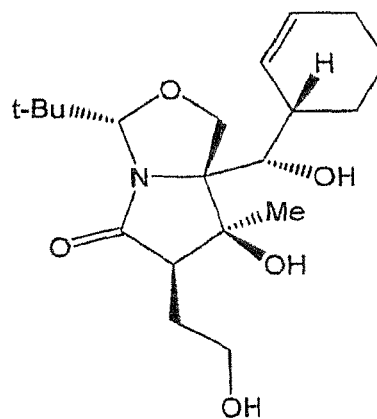


(XXIII-B)

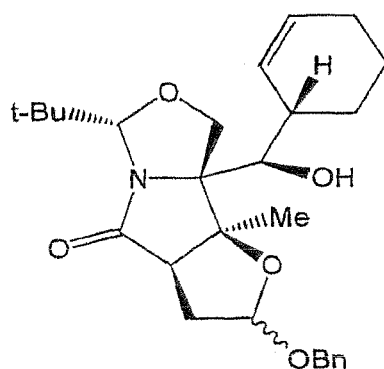
As examples, compounds of formulae (X) and (XXIII) can have the following structures:



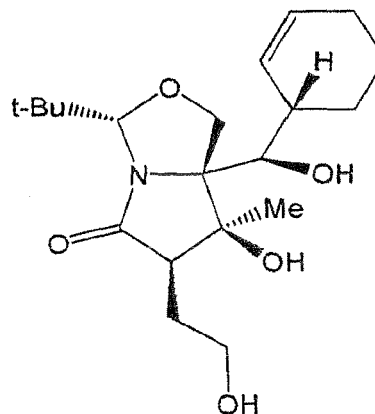
(X-1A)



(XXIII-1A)



(X-1B)

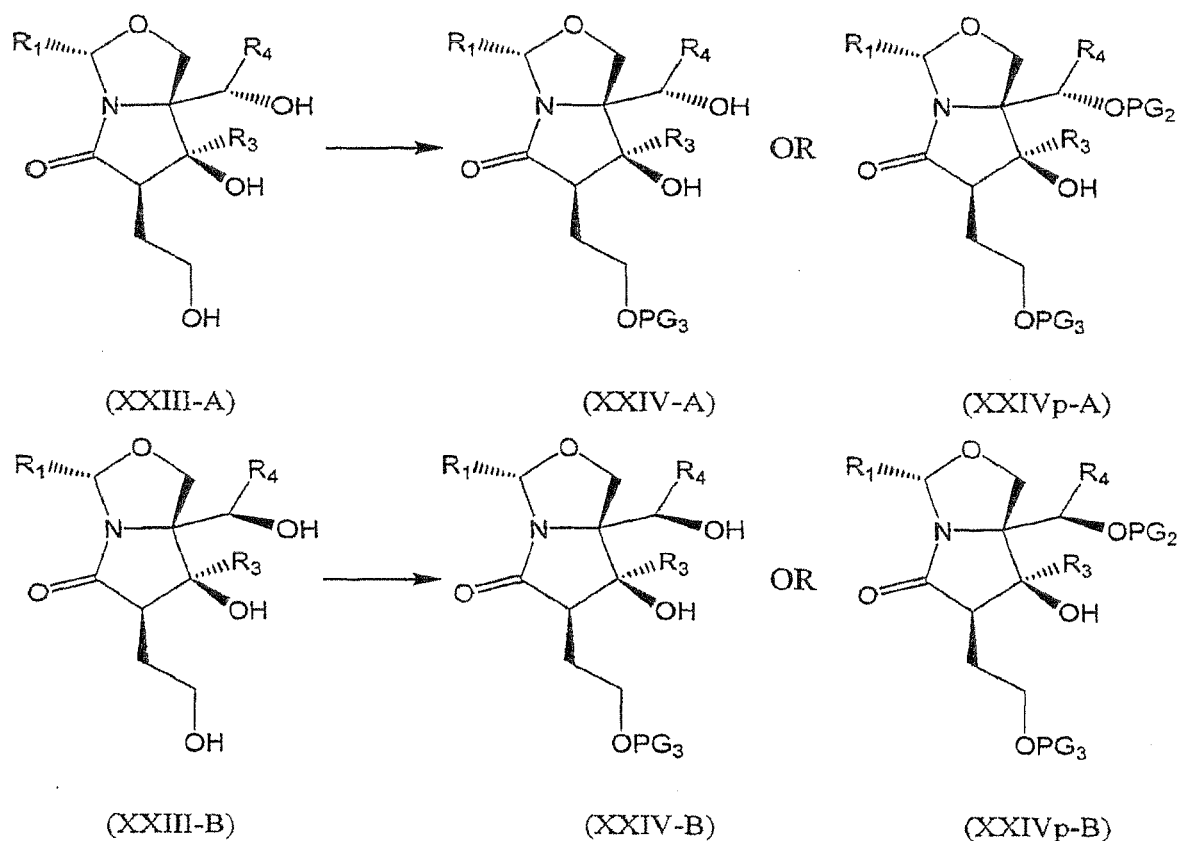


(XXIII-1B)

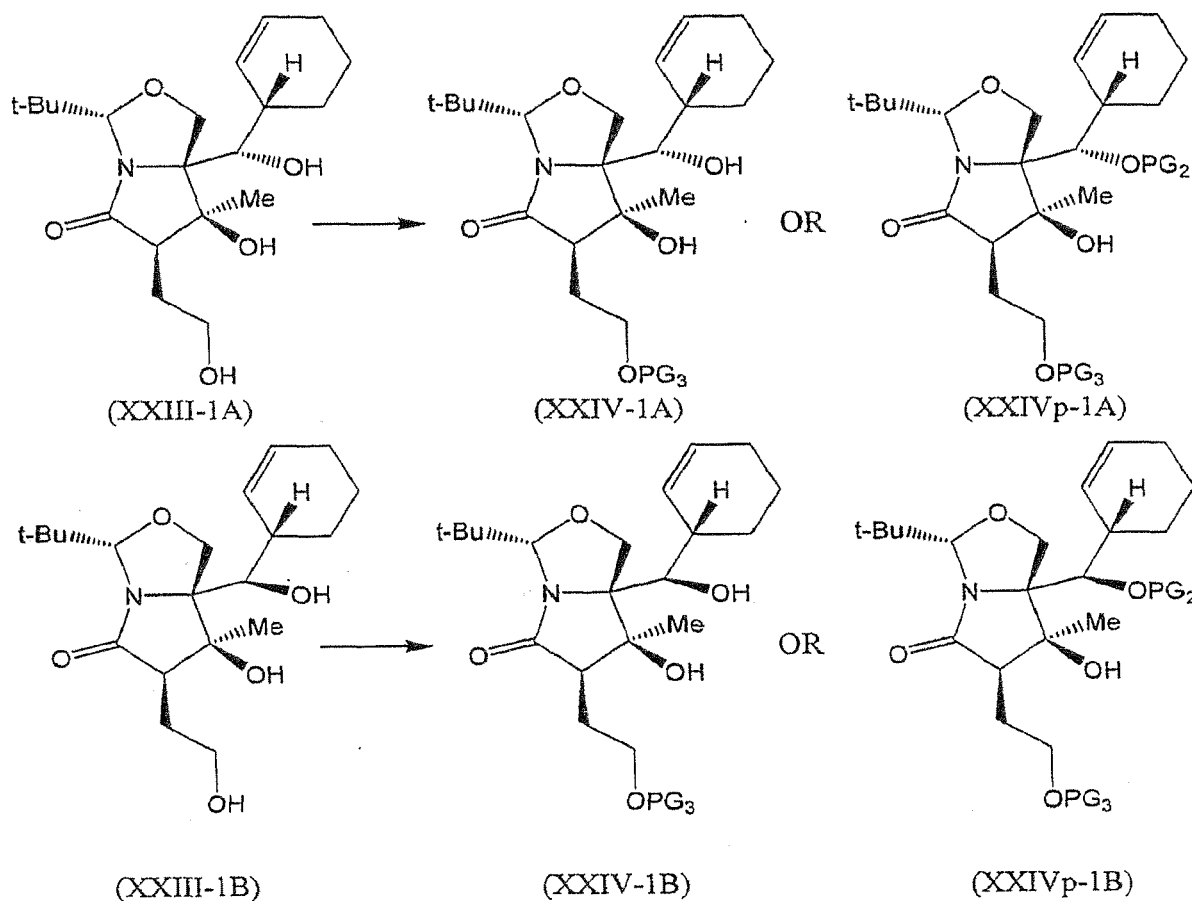
If desired, the C-13 primary and C-5 secondary hydroxy groups of a compound of formula (XXIII) can be protected using suitable protecting group moieties as described herein to form a compound of formula (XXIVp), as shown in Scheme 7-3. Alternatively, only the C-13 primary hydroxy group of a compound of formula (XXIII)

can be protected to form a compound of formula (XXIV), as shown in Scheme 7-4 and 7-5. In some embodiments, R_1 , R_3 , and R_4 of the compound of formula (XXIV) can be the same as described with respect to the compound of formula (X) and PG_3 can be a protecting group moiety. In certain embodiments, PG_3 can be selected from the group consisting of substituted or unsubstituted arylcarbonyls (e.g., benzoyl); substituted or unsubstituted alkyl carbonyl (e.g. acetyl); substituted methyl ether (e.g. methoxymethyl); substituted ethyl ether; substituted or substituted benzyl ether (e.g. benzyl, 4-methoxybenzyl); tetrahydropyranyl ether; silyl ethers (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, or t-butyldiphenylsilyl); carbonates (e.g. methoxymethylcarbonate); and sulfonates (e.g. mesylate, tosylate. In an embodiment, R_1 , R_3 and R_4 of the compound of formula (XXIVp) can be the same as described with respect to the compound of formula (X), and PG_2 and PG_3 can be protecting group moieties. In some embodiments, PG_3 cannot be an alkyl carbonyl (e.g., $-C(=O)CH_2CH_3$). In other embodiments, PG_3 cannot be a sulfonate (e.g., methylate).

As an example, the compounds of formulae (XXIII), (XXIV), and (XXIVp) may have the following structures and stereochemistry:

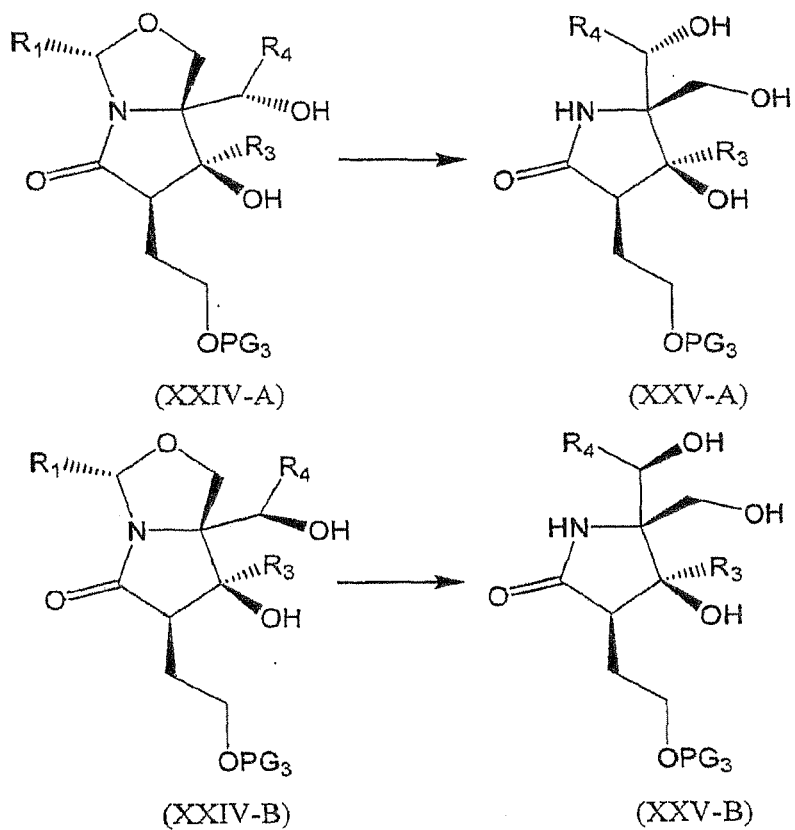


Other examples of the structures and stereochemistry of the compounds of formulae (XXIII), (XXIV), and (XXIVp) include the following:

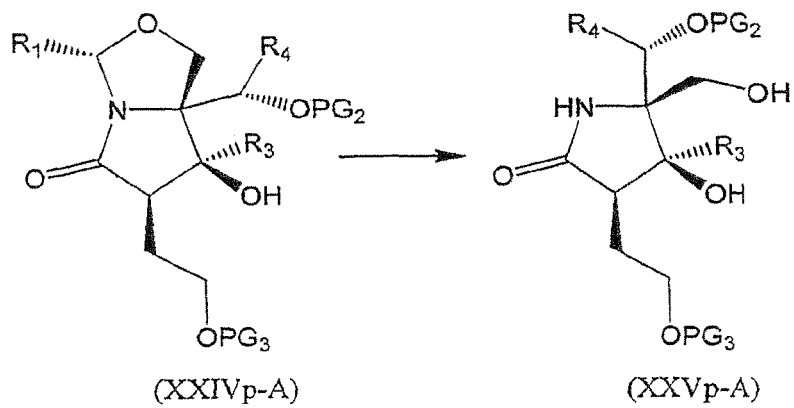


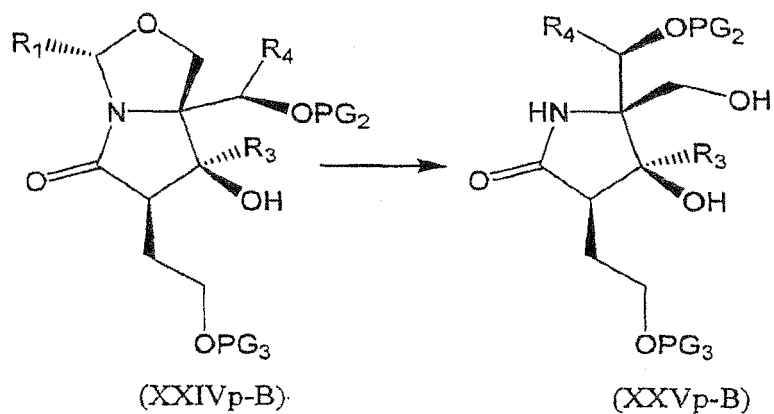
Similar to step (j) of Schemes 7-1 and 7-2, the amination of a compound of formula (XXIV) can be cleaved using a suitable acid as described herein to form a compound of formula (XXV). In the case where the C-5 secondary hydroxy has been protected, the amination of a compound of formula (XXIVp) can also be cleaved using a suitable acid to form a compound of formula (XXVp). In some embodiments, R₃ and R₄ of the compound of formula (XXV) can be the same as described with respect to the compound of formula (X), and PG₃ can be a protecting group moiety. In some embodiments, R₃ and R₄, and PG₂ for compound of formula (XXVp) can be the same as described with respect to the compound of formula (X), and PG₂ and PG₃ can be protecting group moieties.

Exemplary structures and stereochemistry of compounds of formulae (XXIV) and (XXV) are shown below:

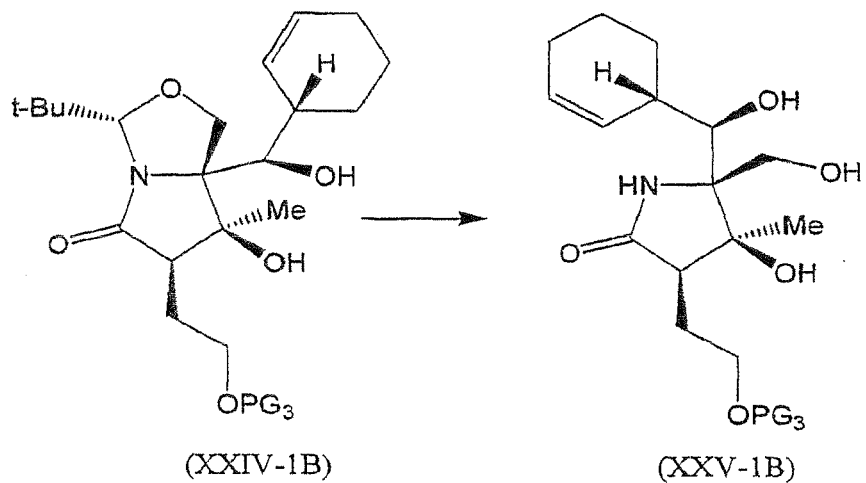
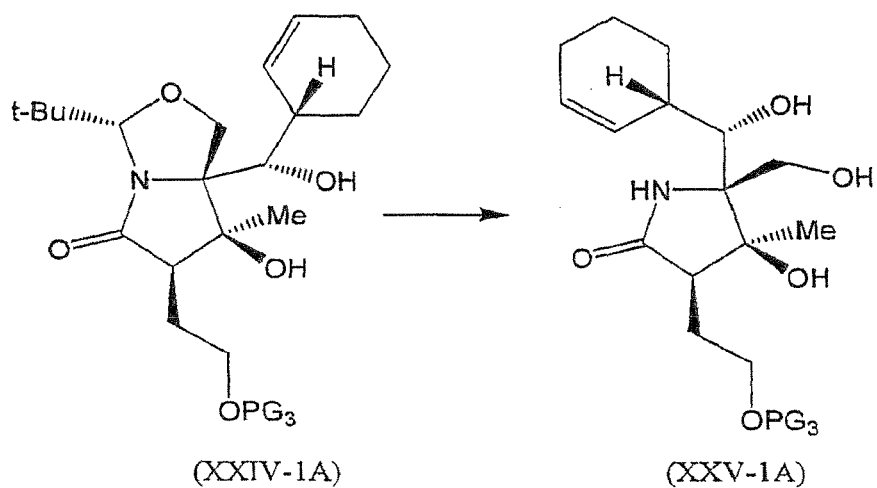


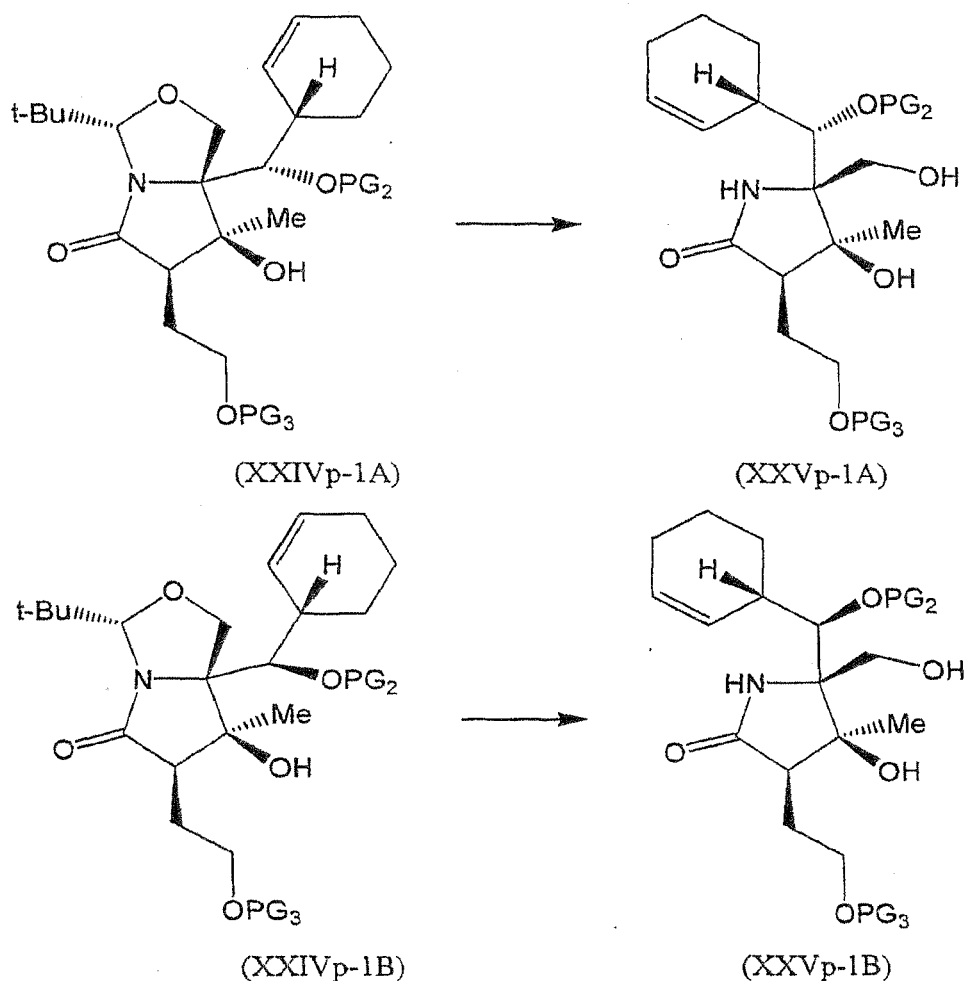
Additional examples of the structures and stereochemistry of compounds of formulae (XXIVp), and (XXVp) can be as follows:





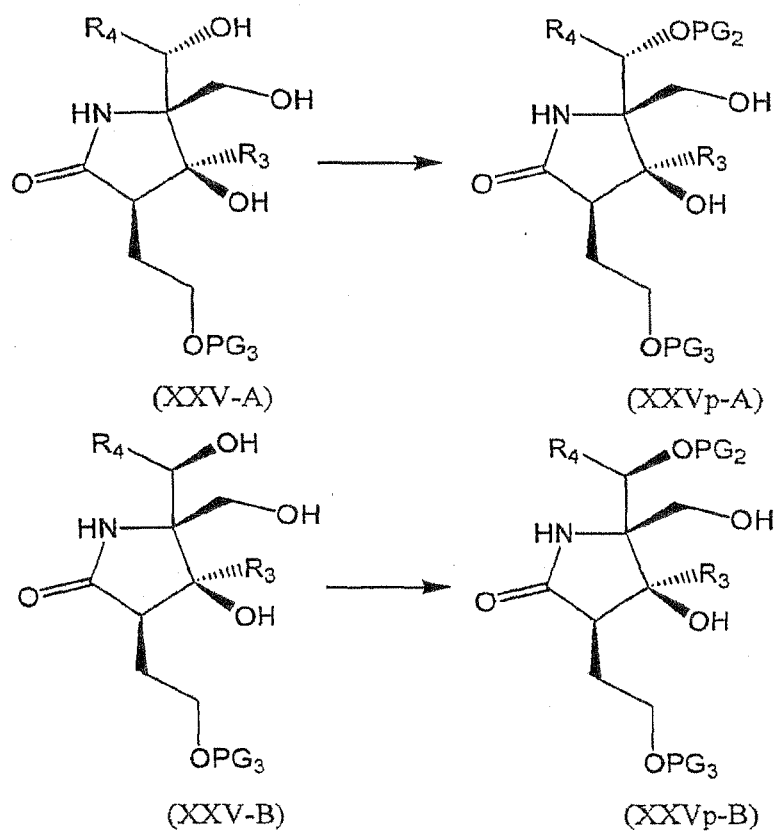
Compounds of formulae (XXIV), (XXIVp), (XXV), and (XXVp) may also have the following structures and stereochemistry:



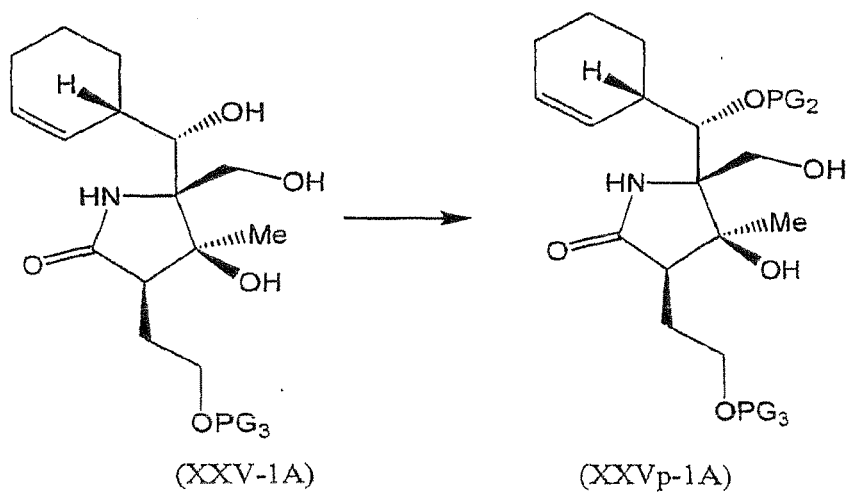


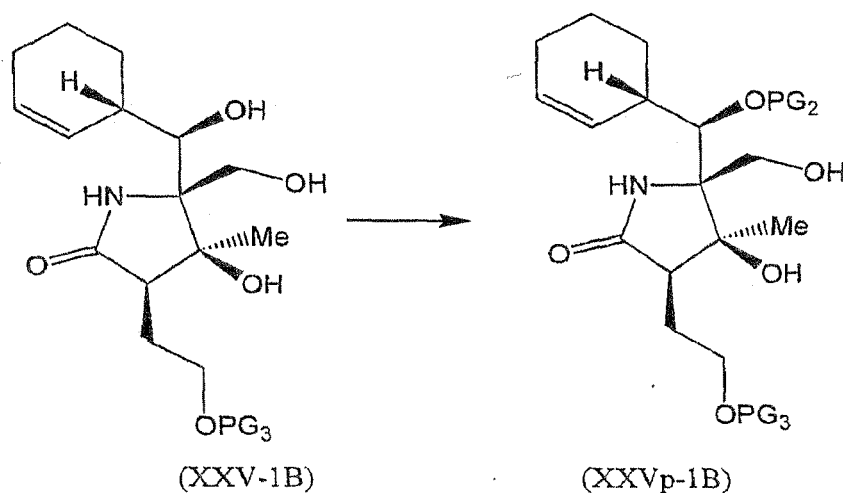
As shown in Scheme 7-5, the acetal of the compound of formula (XXIV) can first be cleaved using one of methods described herein to form a compound of formula (XXV). The C-5 secondary hydroxy group of the compound of formula (XXV) can then be protected with an appropriate protecting group moiety to form a compound of formula (XXVp). In some embodiments, R₃, R₄, PG₂, and PG₃ of the compounds of formulae (XXV) and (XXVp) can be the same as described in the preceding paragraphs.

Exemplary structures of compounds of formulae (XXV) and (XXVp) are as follows:



As an example, the compounds of formulae (XXV) and (XXVp) may have the following structures and stereochemistry:



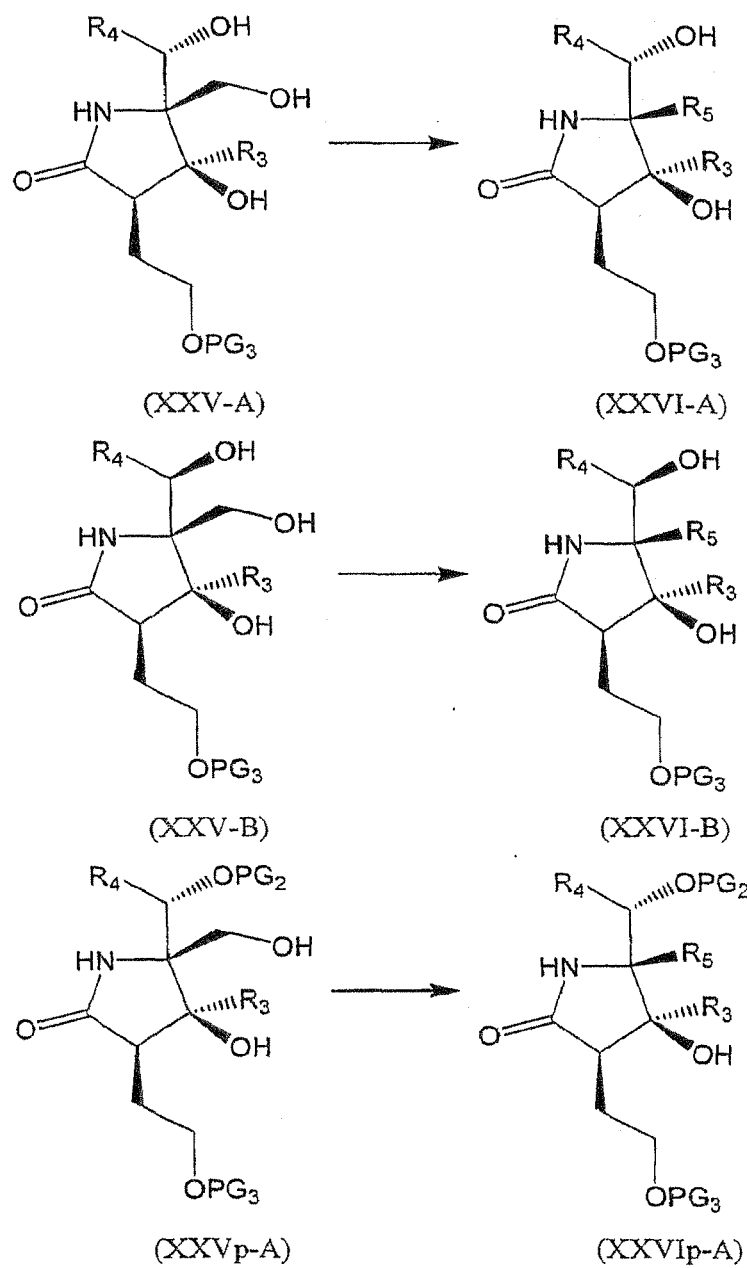


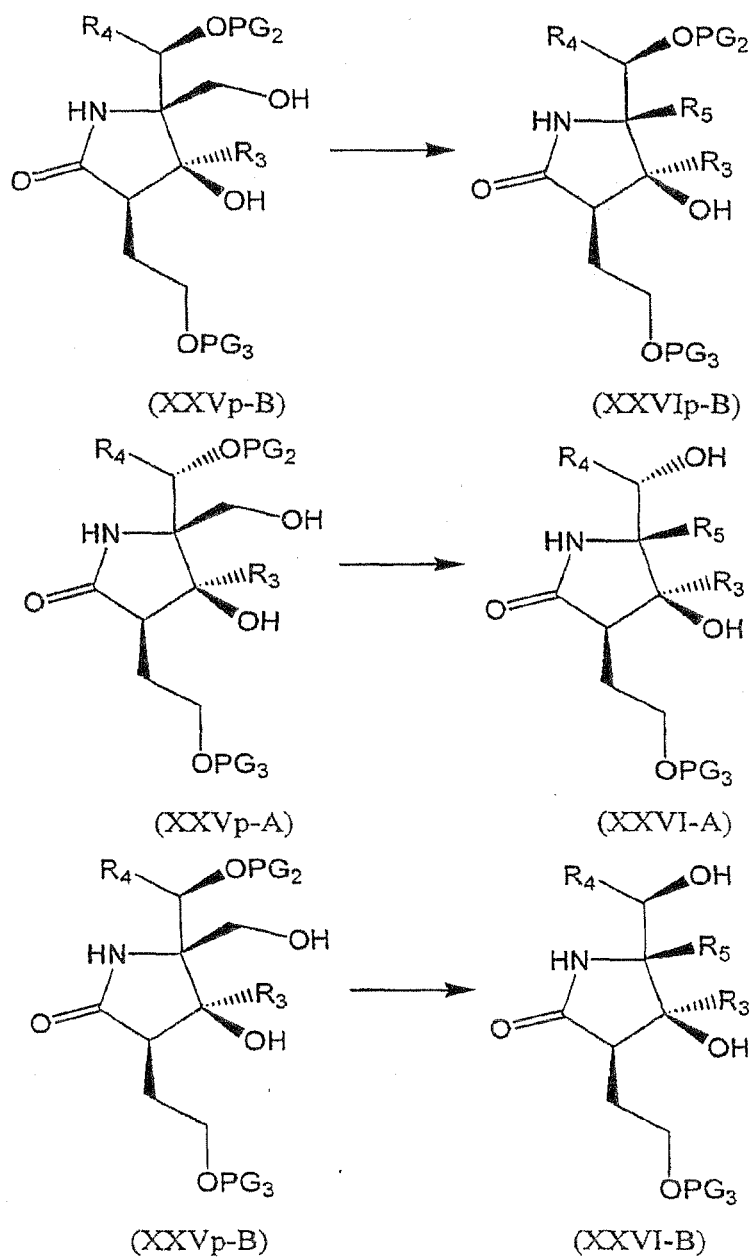
In an embodiment, the primary alcohol group of the compound of formula (XXV) and/or (XXVp) can be transformed to R_5 to form a compound of formula (XXVI) and/or (XXVIp), respectively (see Schemes 7-3 and 7-4, respectively).

In some embodiments, the compound of formula (XXVp) can be transformed directly to a compound of formula (XXVI) as shown in Scheme 7-5. In an embodiment, the protecting group moiety, PG_2 , on the compound of formula (XXVp) can be removed simultaneously with the transformation of the C-15 primary alcohol to R_5 group to form a compound of formula (XXVI). Alternatively, in an embodiment, PG_2 can be removed before or after the transformation of the primary alcohol.

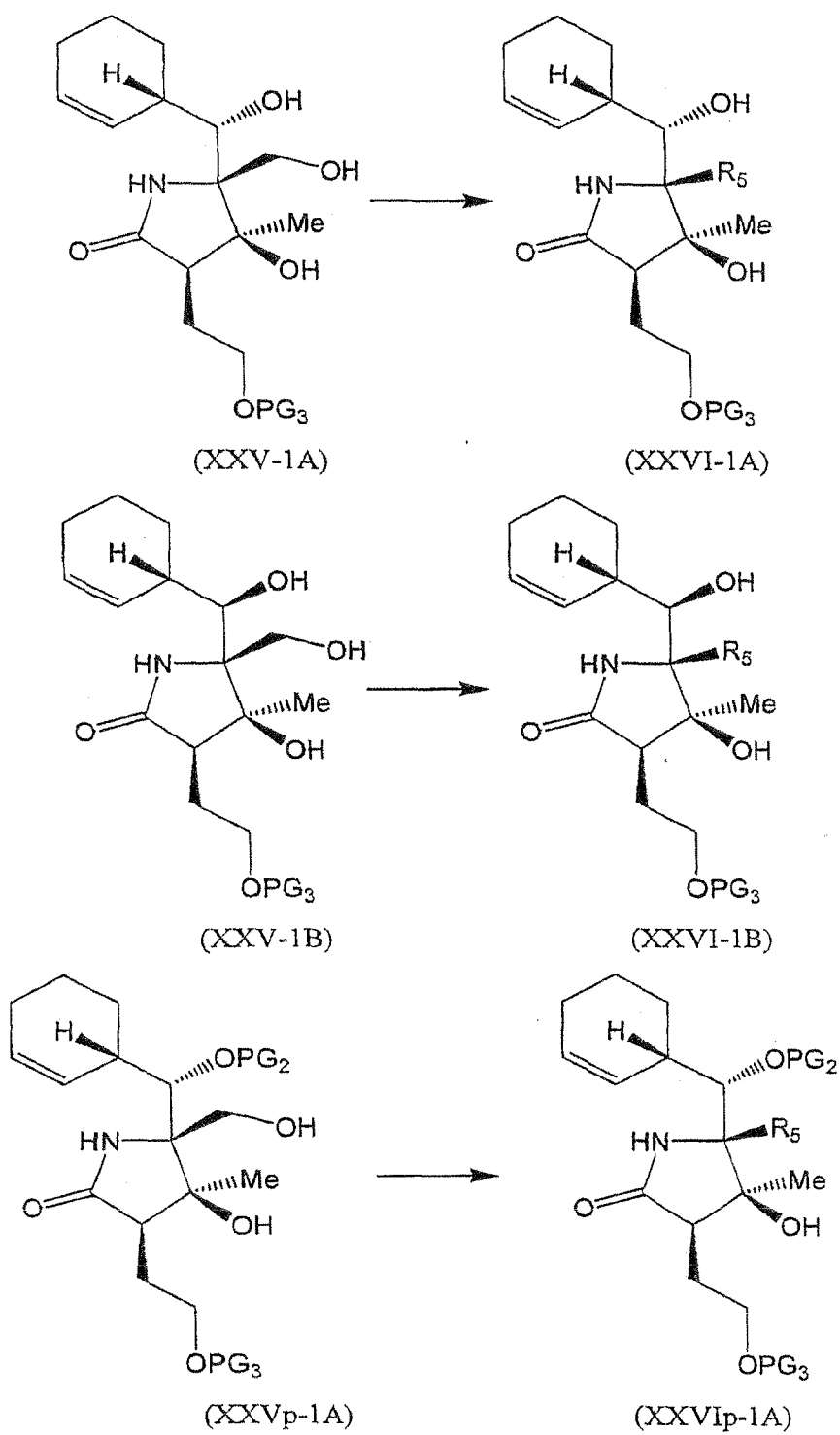
The transformation of the C-15 primary alcohol group to an R_5 group can be achieved using the same or a similar method to the one described in step (k) of Schemes 7-1 and/or 7-2. In some embodiments, R_3 , R_4 , and R_5 of the compounds of formulae (XXVI) and (XXVIp) can be the same as described with respect to the compound of formulae (XII) or (XIIp) of Schemes 7-1 and/or 7-2, and PG_2 and PG_3 can be a protecting group moieties.

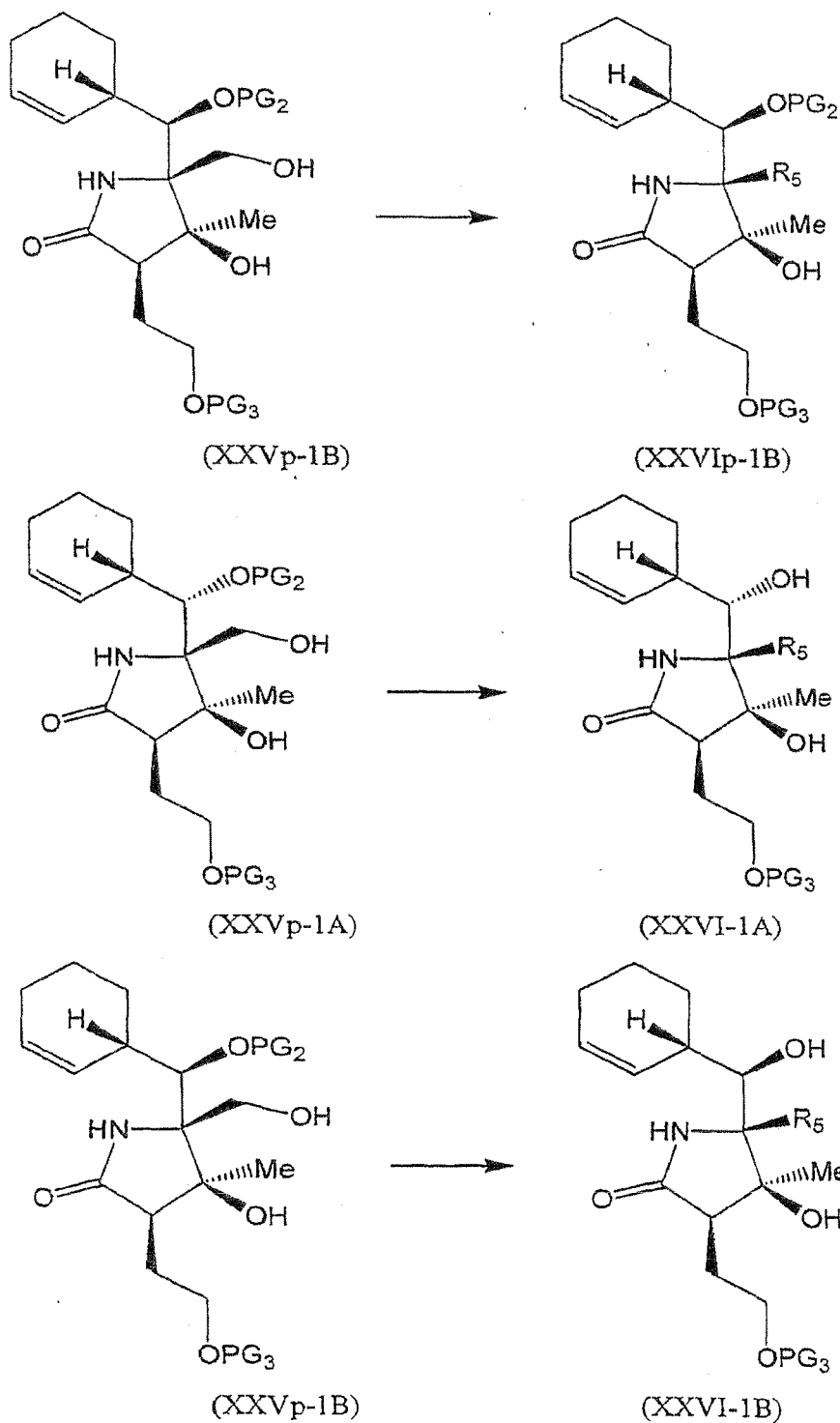
Exemplary structures and stereochemistry of the compounds of formulae (XXV), (XXVp), (XXVI), and (XXVIp) can have the following structures and stereochemistry:





Other examples of the structures and stereochemistry of the compounds of formulae (XXV), (XXVp), (XXVI), and (XXVIp) are shown below:

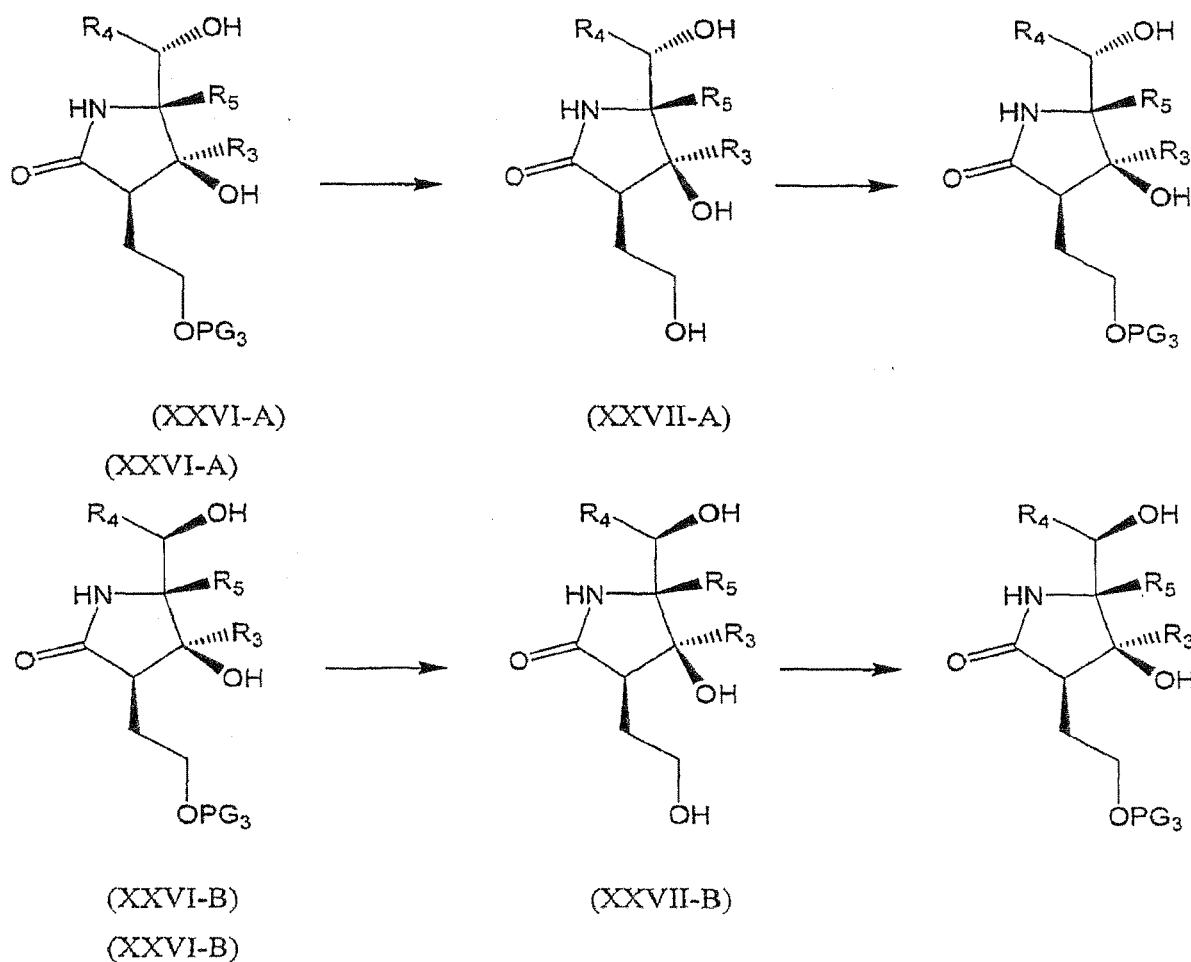


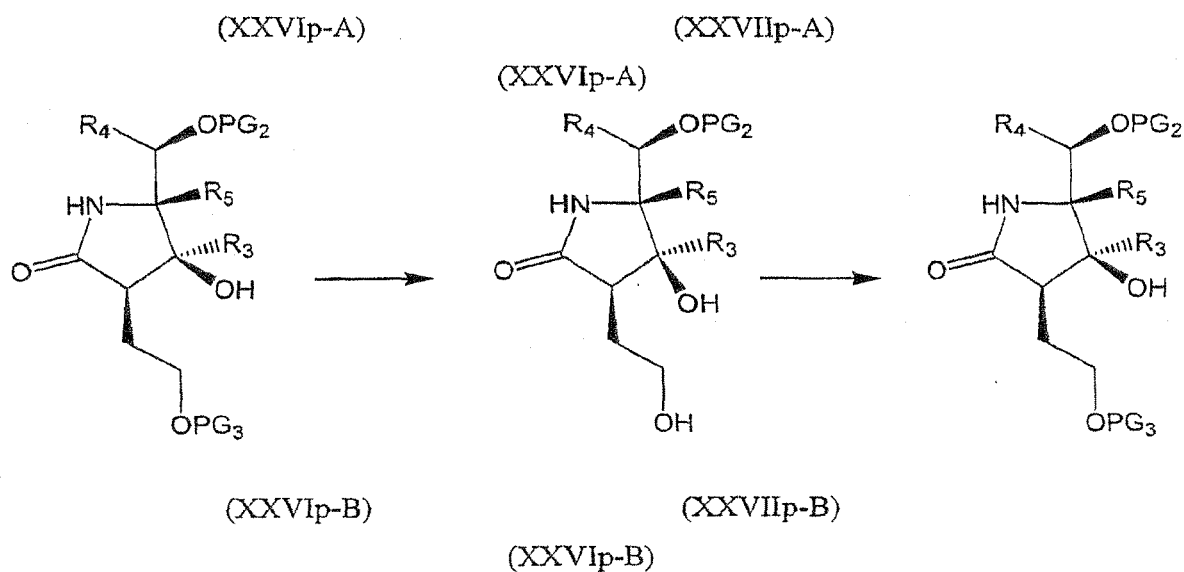
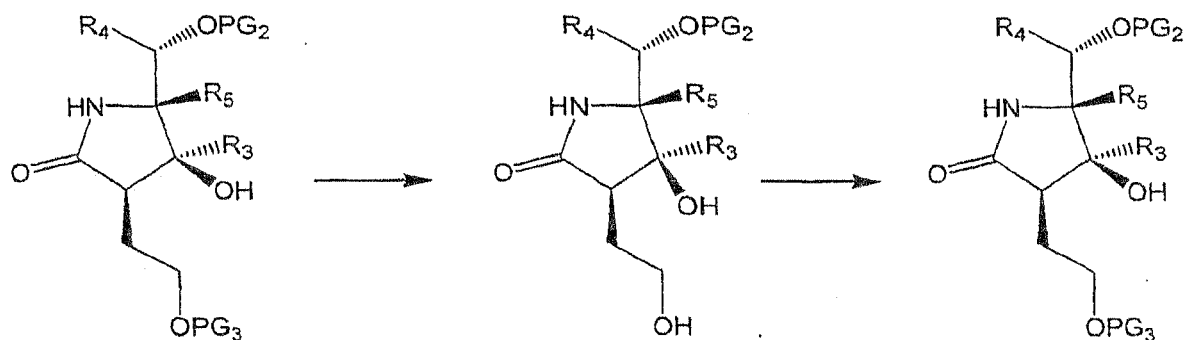


In some embodiments, the protecting group PG₃ on compounds of formulae (XXVI) and (XXVIp) can be removed to form a compound of formulae (XXVII) and (XXVIIp), respectively. See Scheme 7-5. The C-13 primary hydroxy of the

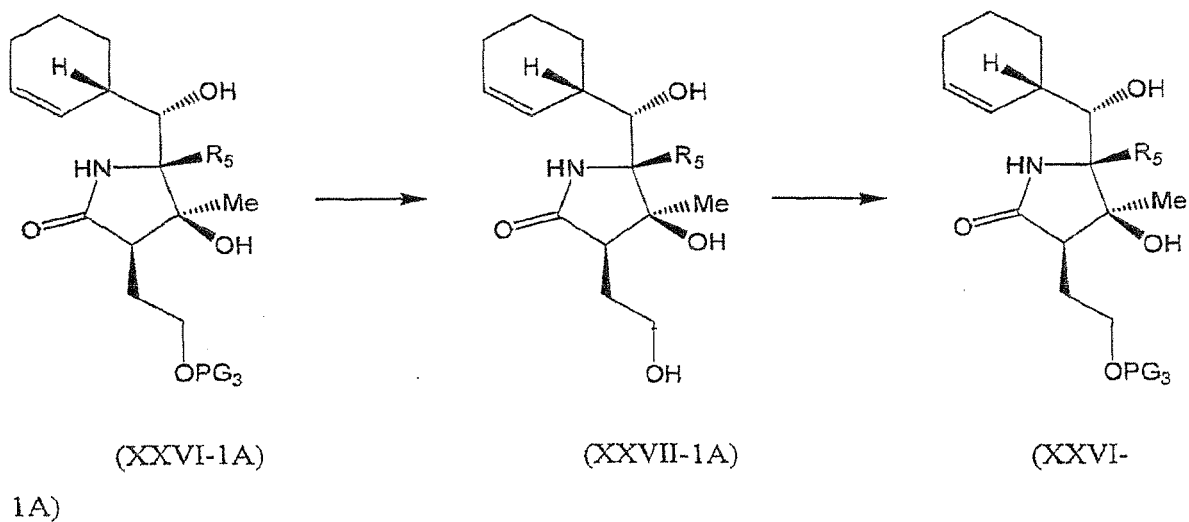
compounds of formulae (XXVII) and (XXVIIp) can then be reprotected with the same or different protecting group. For example, in one embodiment, a benzoyl group protecting the C-13 hydroxy on a compound of formula (XXVI) or (XXVIp) can be removed and replaced with a TBS or TES protecting group. Suitable methods for removing protecting groups are known to those skilled in the art. For example, a benzoyl protecting group ($PG_3 = Bz$) can be removed using a suitable base such as K_2CO_3 to form a compound of formula (XXVII) or (XXVIIp).

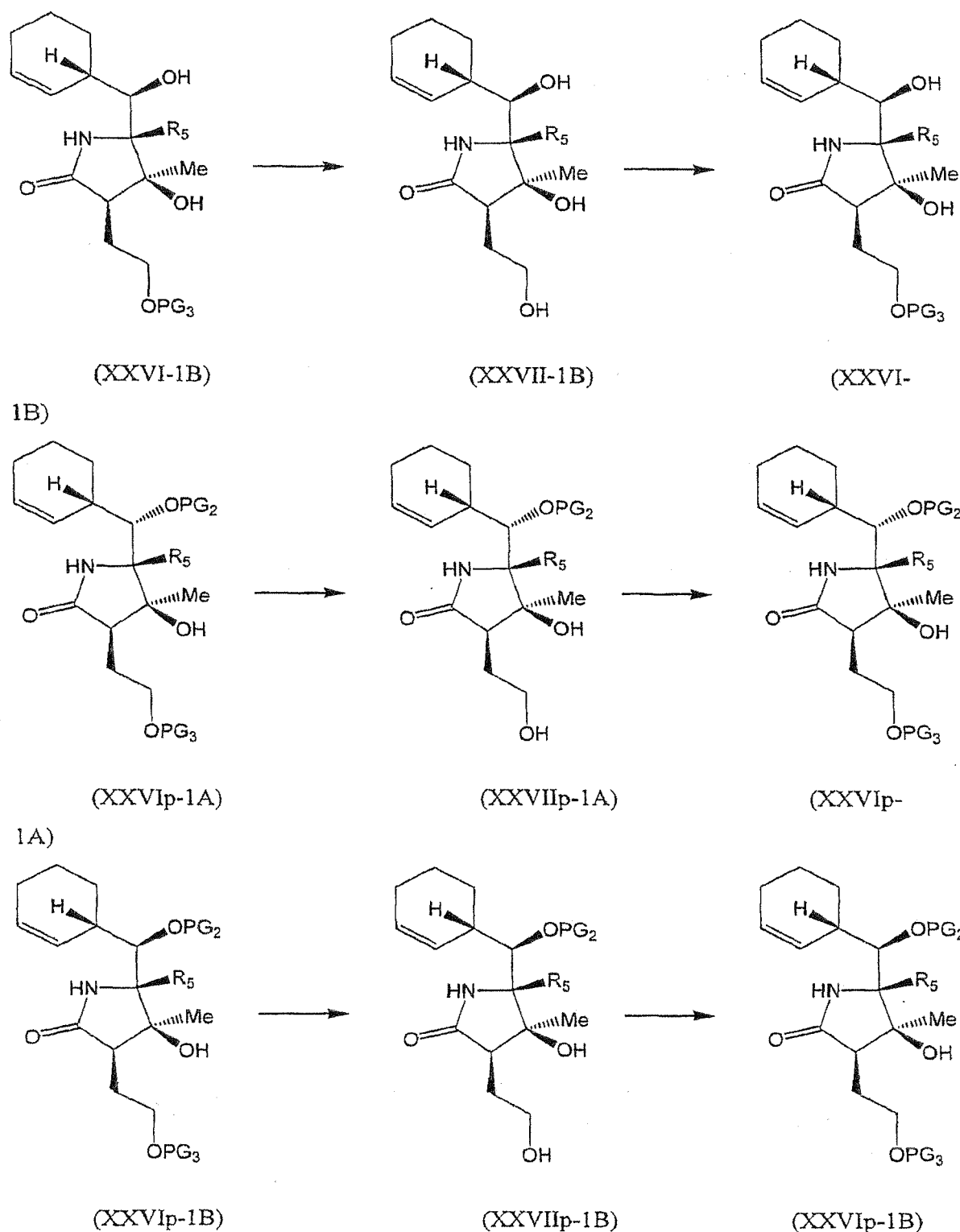
Exemplary structures and stereochemistry of compounds of formulae (XXVI), (XXVIp), (XXVII) and (XXVIIp) are shown below:



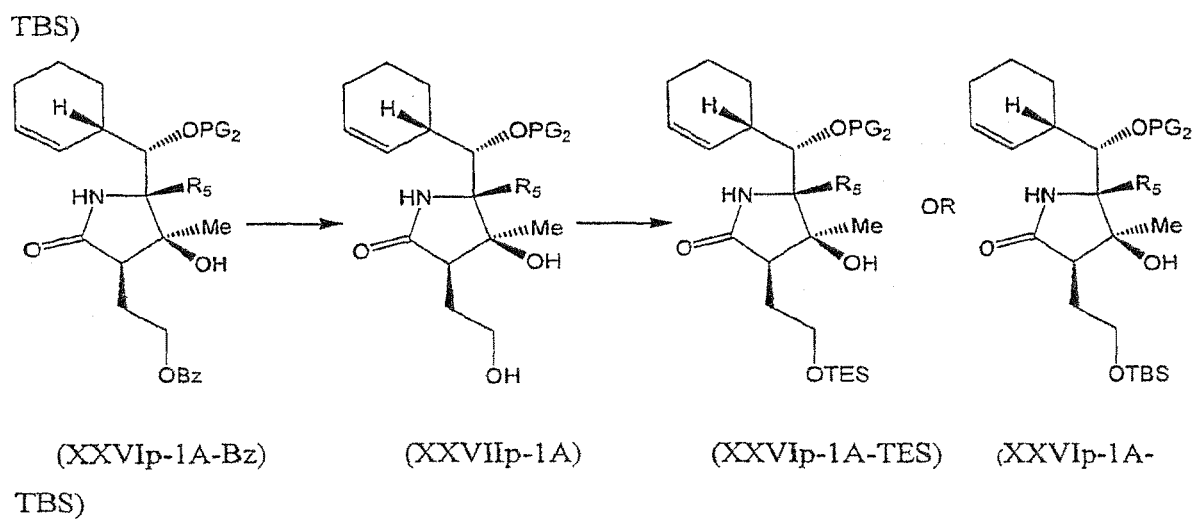
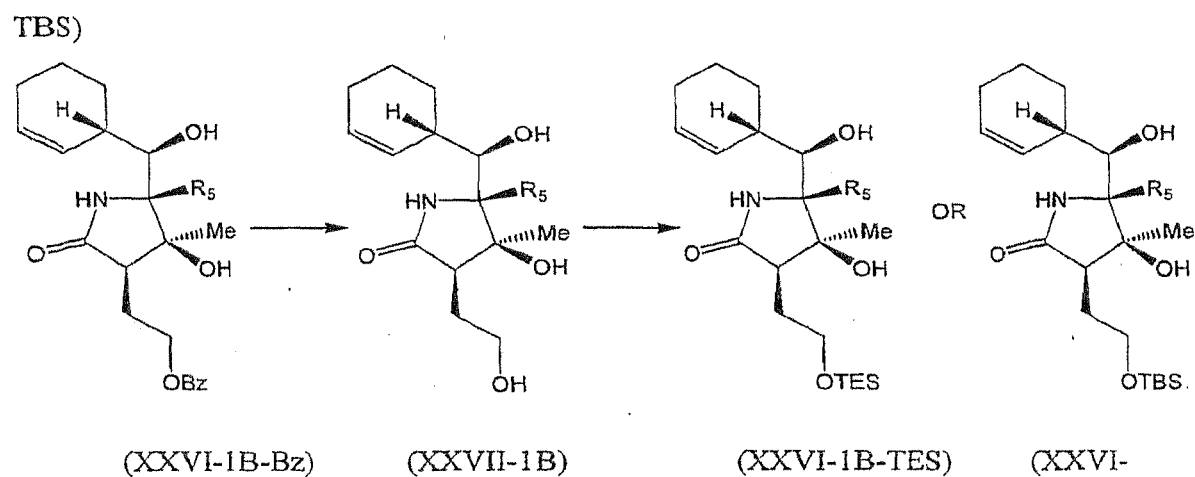
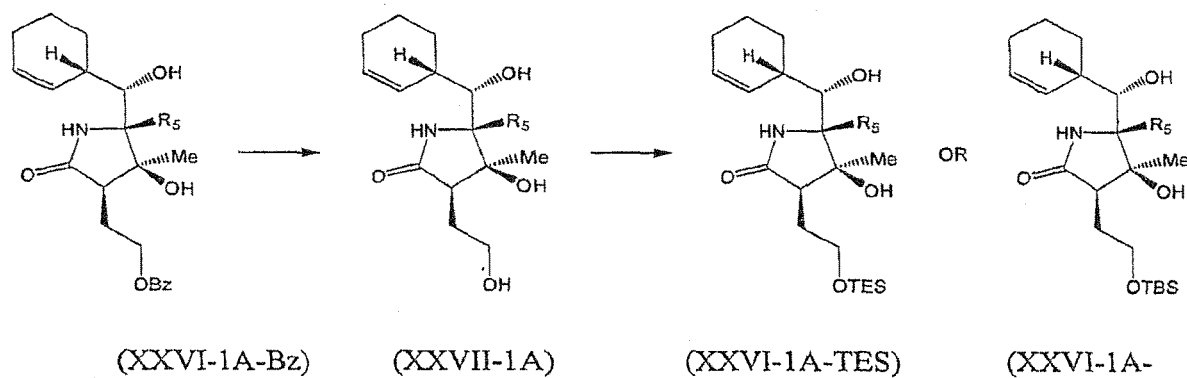


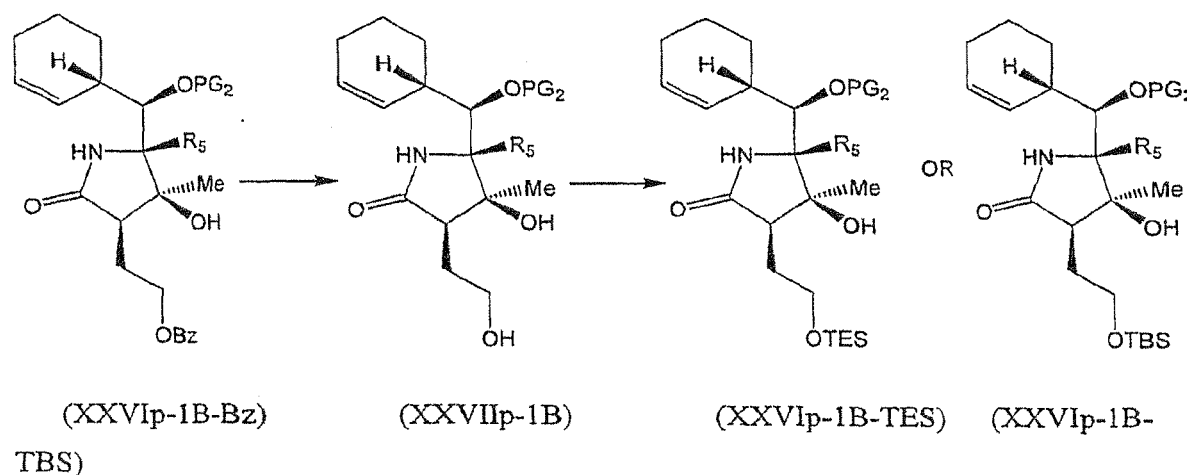
Additional examples of the structures and stereochemistry of compounds of formulae (XXVI), (XXVIp), (XXVII) and (XXVIIp) can be as follows:





Further examples of the structures and stereochemistry of compounds of formulae (XXVI), (XXVIp), (XXVII) and (XXVIIp) can be as follows:

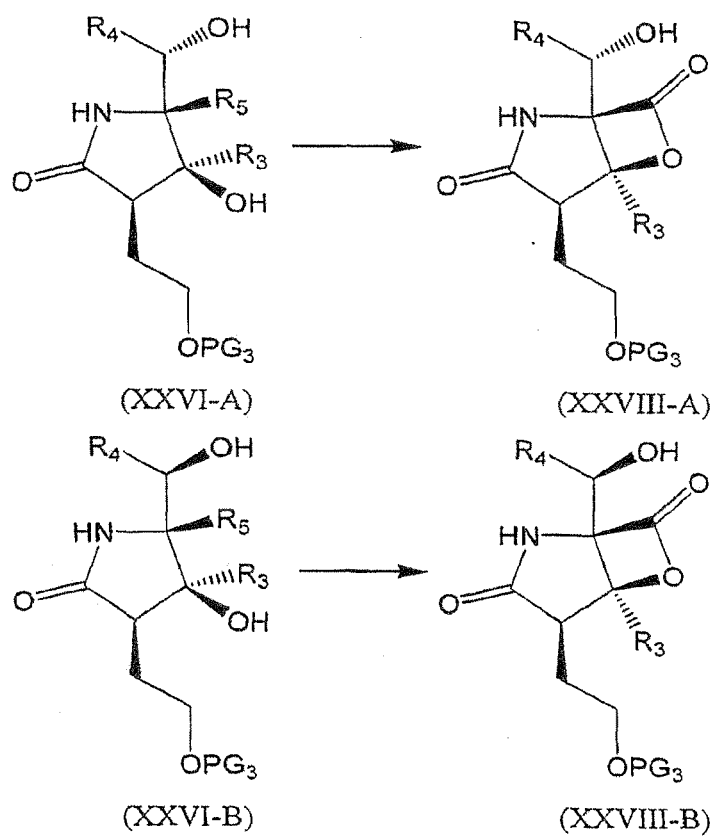




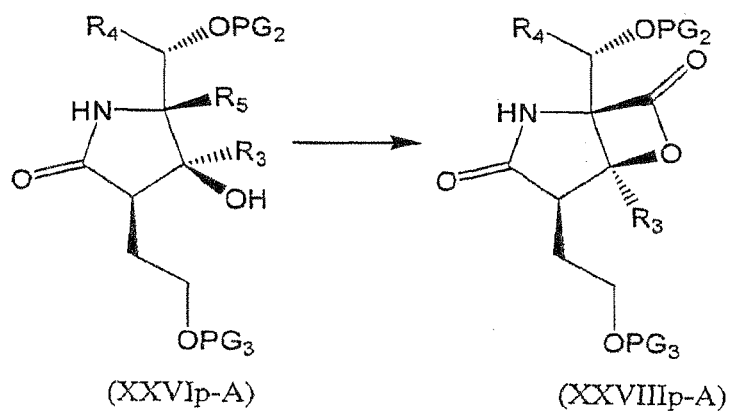
Using an appropriate base, a compound of formula (XXVIII) and/or (XXVIIIp) can be synthesized via a lactonization reaction from a compound of formula (XXVI) and (XXVIp), respectively. See Schemes 7-3, 7-4 and 7-5. In some embodiments, R₃, R₄, R₅ (and PG₂, where relevant) for compounds of formulae (XXVIII) and (XXVIIIp) can be the same as described with respect to the compound of formulae (XXVI) and (XXVIp), and PG₃ can be a protecting group moiety. In some embodiment, R₅ of the compound of formula (XXVI) or (XXVIp) can be a carboxylic acid. In an embodiment, R₅ of the compound of formula (XXVI) or (XXVIp) can be an activated acid (e.g., acid chloride). In certain embodiments, R₅ of the compound of formula (XXVI) or (XXVIp) can be an activated ester such as p-nitrophenyl ester, pentafluorophenyl ester, pentafluoroethyl ester, trifluoroethyl ester, trichloroethyl ester, thioester, etc.

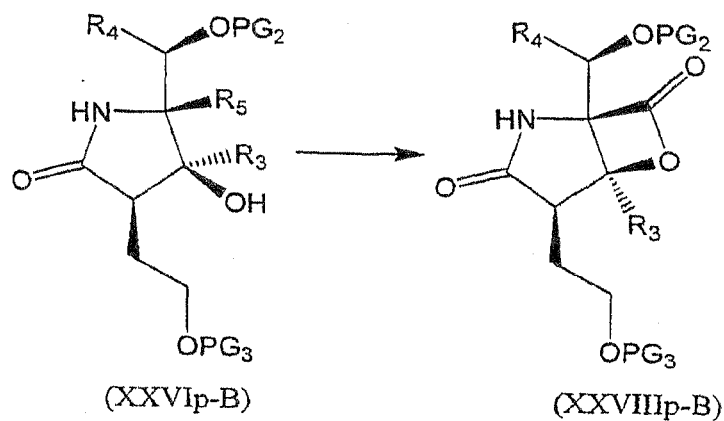
In some embodiments, a compound of formula (XXVIII) can be synthesized by performing a lactonization reaction on a compound of formula (XXVI) with the proviso that if the compounds of formulae (XXVIII) and (XXVI) have the same structures and stereochemistry of the compounds of formulae (XXVIII-1A) and (XXVI-1A), then R₅ cannot be -C(=O)OR₆, wherein R₆ is hydrogen. In other embodiments, the lactonization reaction includes the further the proviso that R₆ cannot be methyl or t-butyl when the compounds of formulae (XXVIII) and (XXVI) have the structures and stereochemistry of the compounds of formulae (XXVIII-1A) and (XXVI-1A). In an embodiment, the compound of formula (XXVIII) can have the structure shown herein with the proviso that if R₄ is 2-cyclohexenyl and R₃ is methyl, then PG₃ cannot be -C(=O)CH₂CH₃ and/or mesylate. In an embodiment, if the compound of formula (XXVIII) has the structure and stereochemistry of the compound of formula (XXVIII-A) and if R₄ is 2-cyclohexenyl and R₃ is methyl, then PG₃ cannot be -C(=O)CH₂CH₃ and/or mesylate.

As an example, compounds of formulae (XXVI) and (XXVIII) can have the structures and stereochemistry shown below:

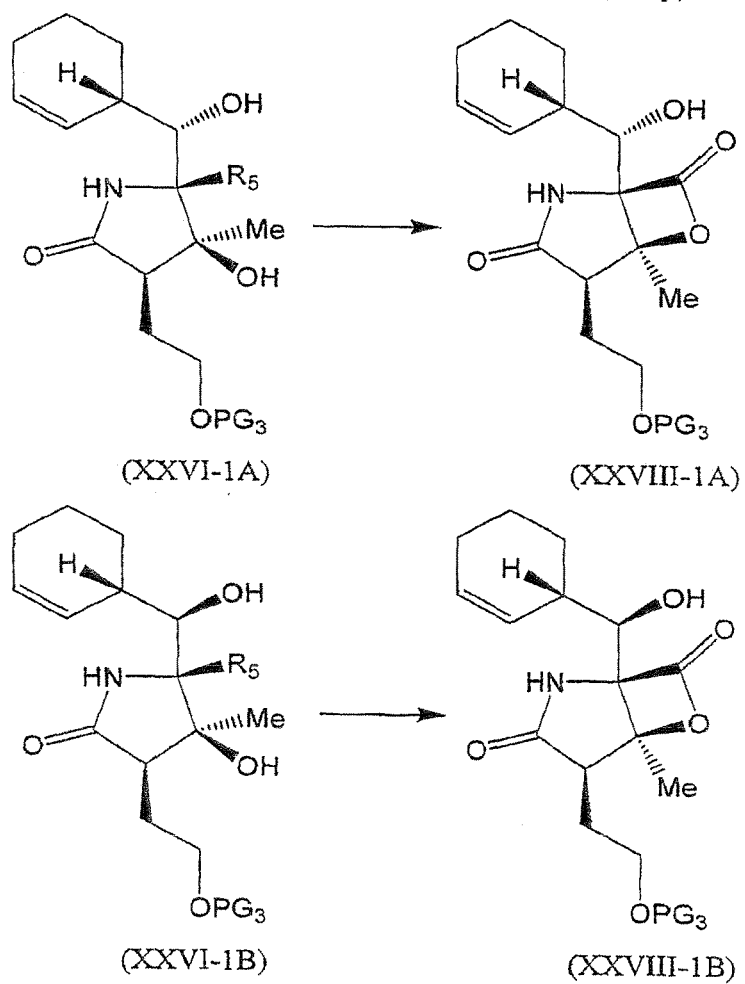


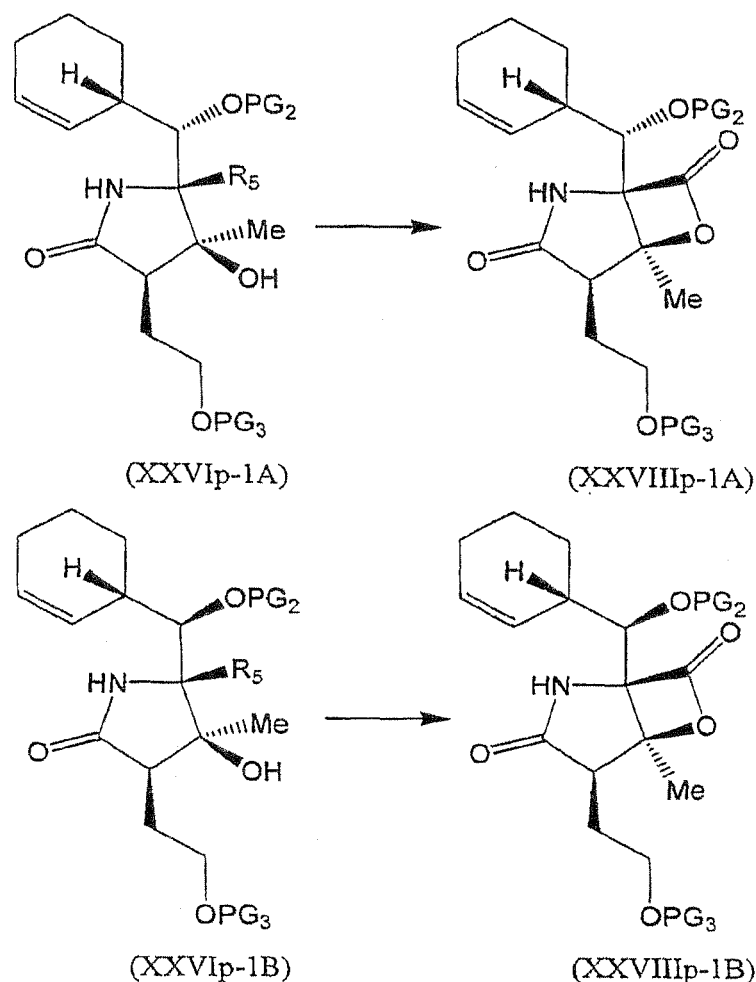
Other exemplary structures and stereochemistry of compounds of formulae (XXVIp) and (XXVIIIp) are as follows:





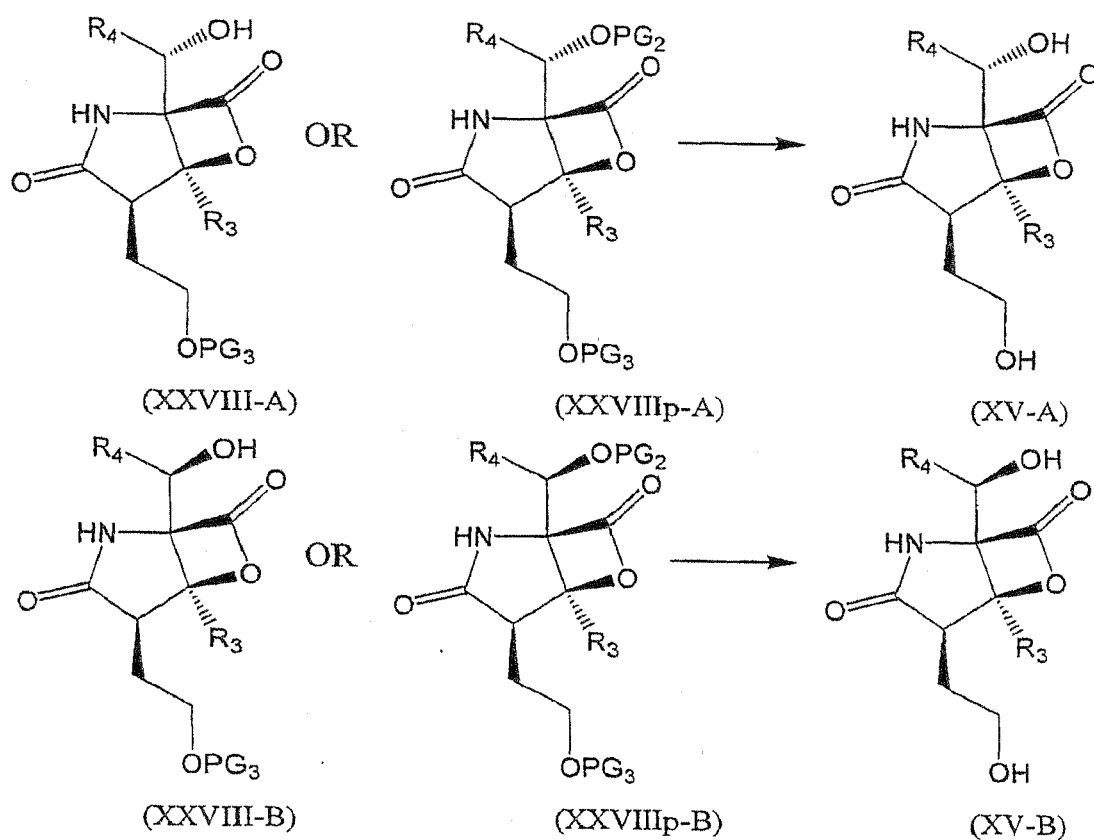
Additional examples of the structures and stereochemistry of compounds of formulae (XXVI), (XXVIp), (XXVIII), and (XXVIIIp) are shown below:



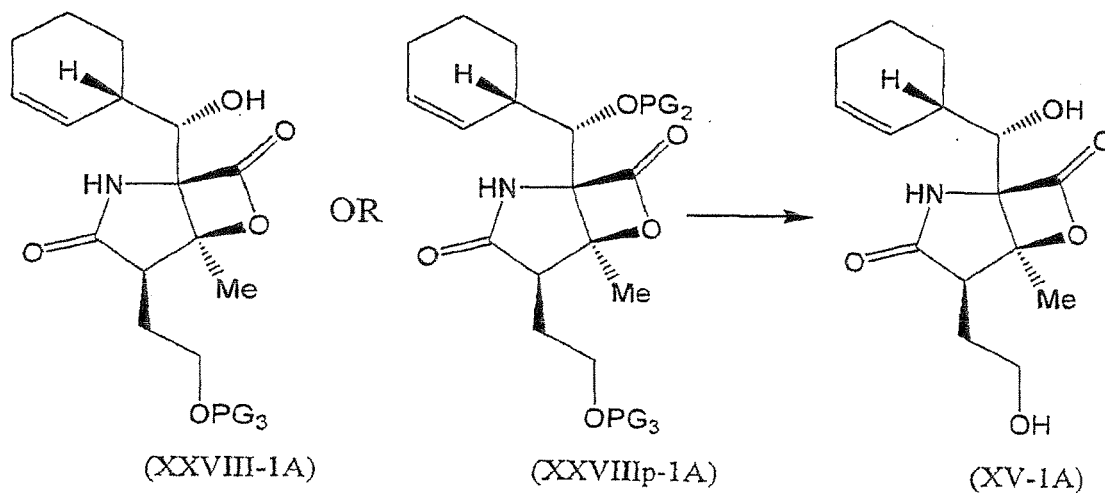


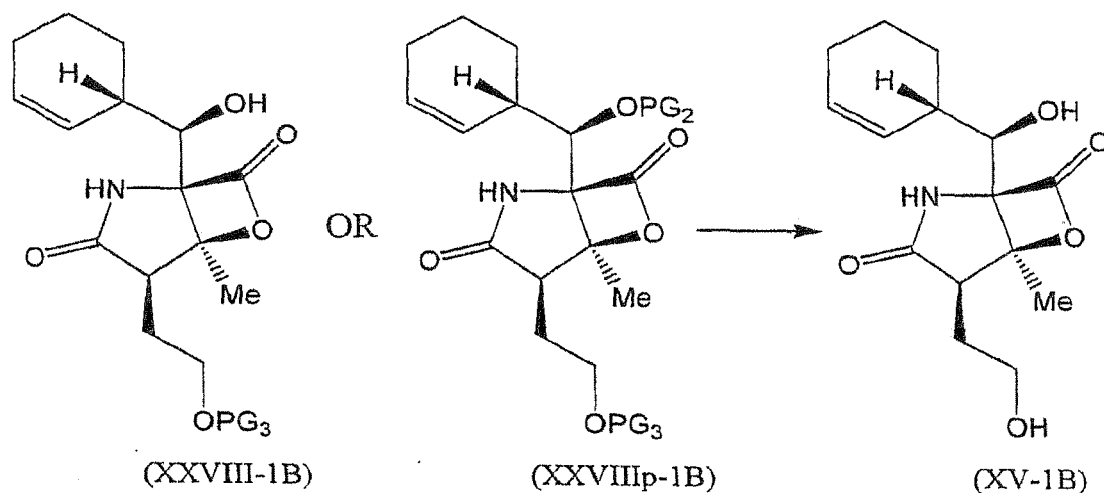
In the final step shown in Scheme 7-3, 7-4 and 7-5, any protecting group moieties can be removed from a compound of formula (XXVIII) and/or (XXVIIIp) to form a compound of formula (XV), respectively. In some embodiments, R_3 and R_4 (and PG_2 , where relevant) of the compounds (XXVIII), (XXVIIIp) and (XV) can be the same as described with respect to the compound of formulae (XXVI) or (XXVIp), and PG_3 can be a protecting group moiety. In another embodiment, the protecting groups PG_2 and PG_3 can be removed from a compound of formula (XXVIIIp) in a stepwise fashion to form a compound of formula (XV); the protecting groups can be removed in any order. In yet another embodiment, the protecting groups PG_2 and PG_3 are simultaneously removed from a compound of formula (XXVIIIp) to form a compound of formula (XV). In an embodiment, a compound of formula (XV) can have the structure shown herein with the proviso that if the compound of formula (XV) has the structure and stereochemistry of the compound of formula (XV-A) and R_3 is methyl then R_4 cannot be 2-cyclohexenyl.

Compounds of formulae (XXVIII), (XXVIIIp) and (XV) can have the following structures and stereochemistry:



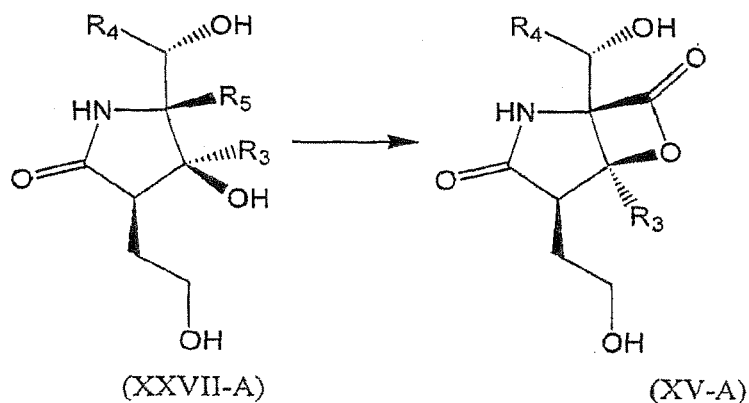
In addition, compounds of formula (XXVIII), (XXVIIIp) and (XV) can have the structures and stereochemistry shown below:

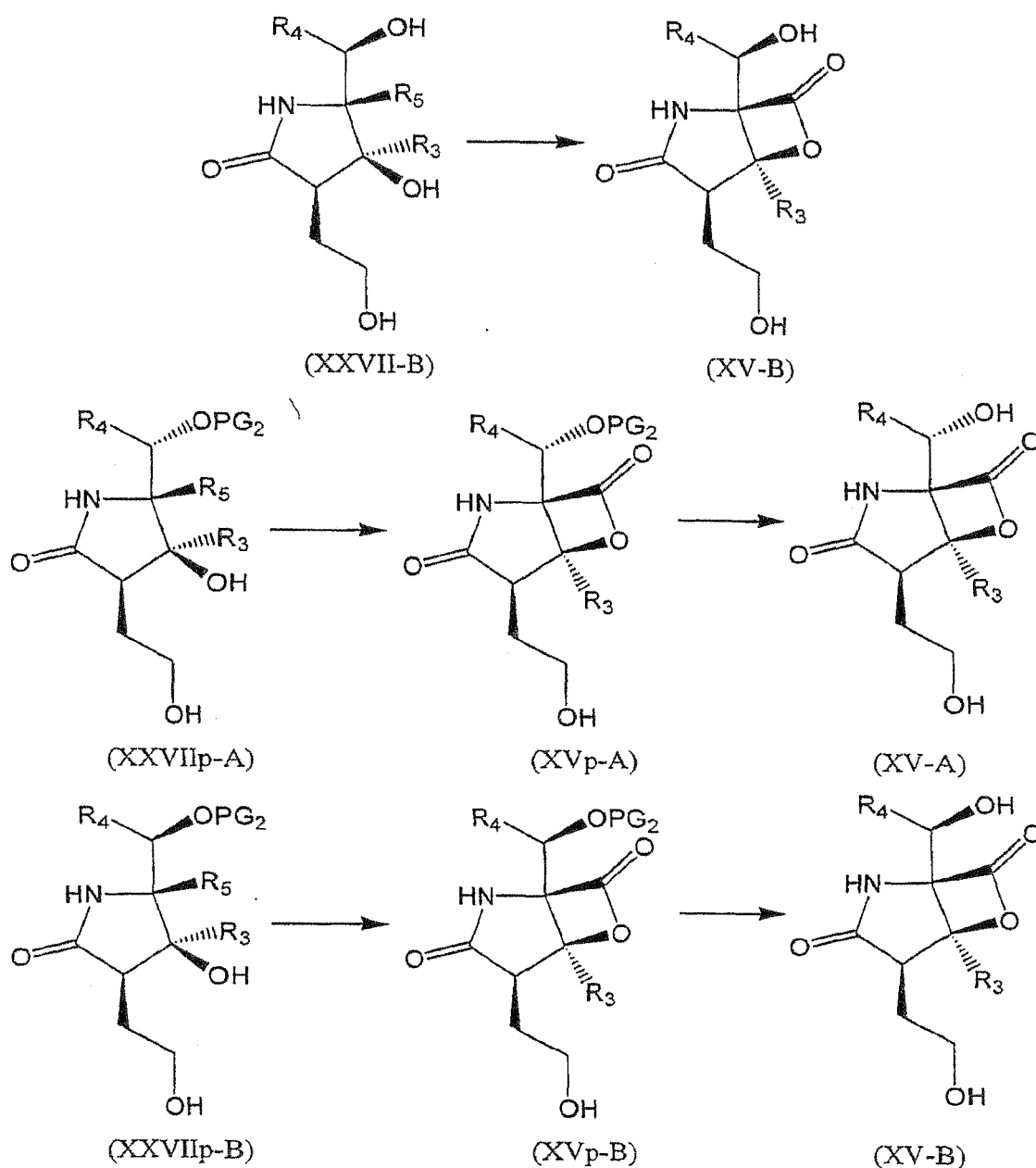




Using an appropriate base, a compound of formula (XV) can also be synthesized via a lactonization reaction from a compound of formula (XXVII), as shown in Scheme 7-5, or lactonization reaction from a compound of formula (XXVIIp) followed by deprotection. In some embodiments, R_3 , R_4 , R_5 , (and PG_2 , where relevant) for the compounds of formulae (XXVII), (XXVIIp), and (XV) can be the same as described with respect to the compound of formulae XVII or (XVIIp).

As an example, compounds of formulae (XXVII), (XXVIIp), (XVp) and (XV) can have the structures and stereochemistry shown below:



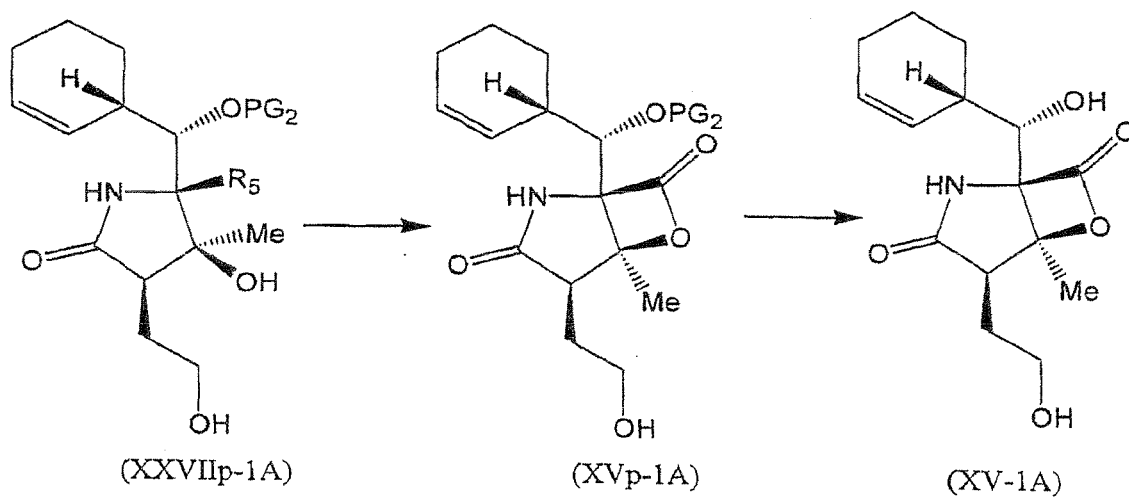
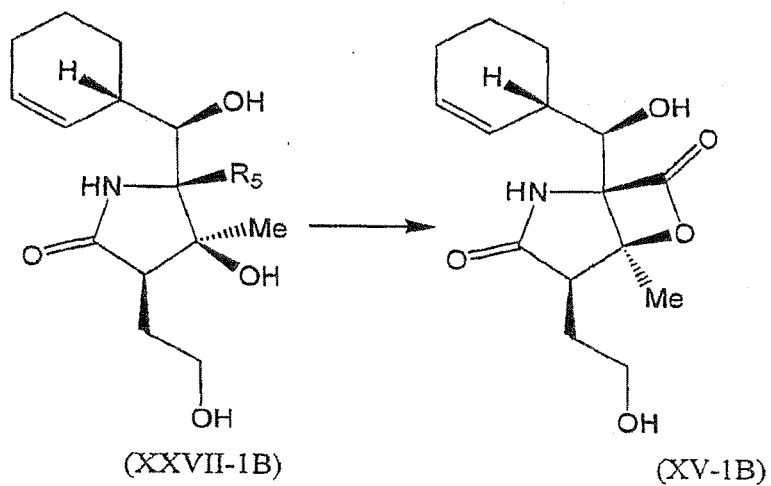
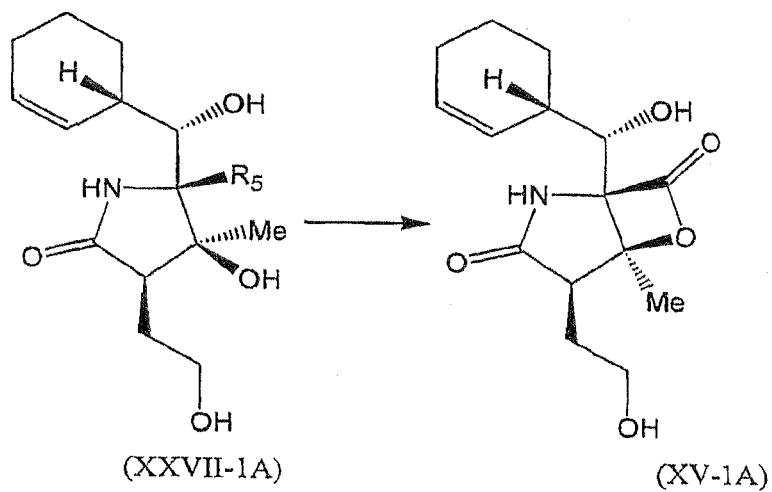


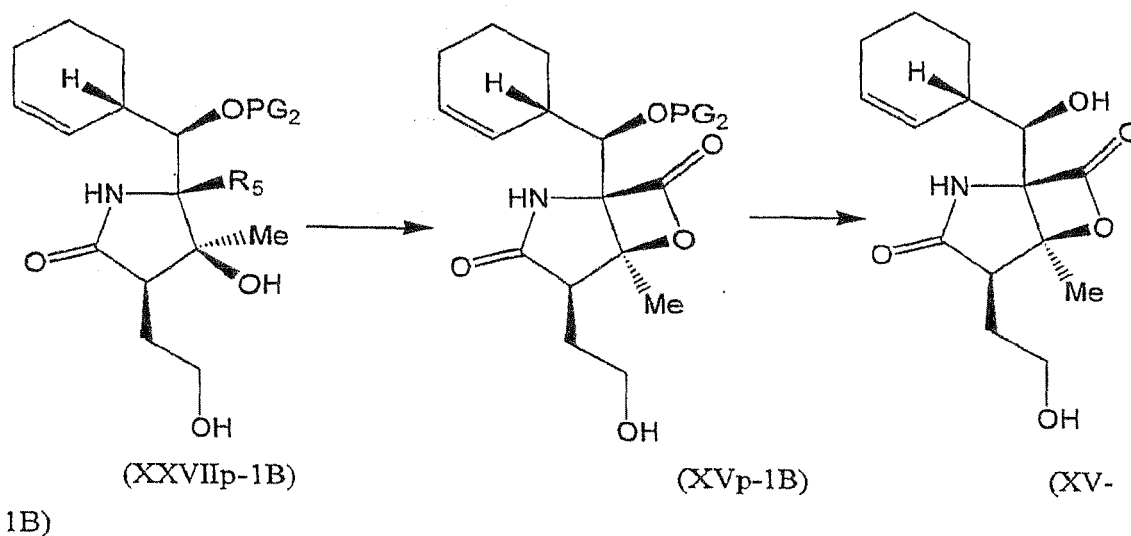
In some embodiments, a compound of formula (XV) can be synthesized by performing a lactonization reaction on a compound of formula (XXVII) with the proviso that if the compounds of formulae (XXVII) and (XV) have the same structures and stereochemistry as the compounds of formulae (XXVII-1A) and (XV-1A), then R_5 cannot be $-C(=O)OR_6$, wherein R_6 is hydrogen. In other embodiments, the lactonization reaction includes the further proviso that R_6 cannot be methyl or *t*-butyl when the compounds of formulae (XXVII) and (XV) have the structures and stereochemistry of the compounds of formulae (XXVII-1A) and (XV-1A). In some

embodiments, a compound of formula (XV) can be synthesized by performing a lactonization reaction on a compound of formula (XXVII) and/or (XXVII-A) with the proviso that if R_5 is $-C(=O)OR_6$, wherein R_6 is hydrogen, methyl or t-butyl then R_4 cannot be isopropyl. In an embodiment, a compound of formula (XV) can have the structure shown herein with the proviso that if the compound of formula (XV) has the structure and stereochemistry of the compound of formula (XV-A) and R_3 is methyl then R_4 cannot be 2-cyclohexenyl. In an embodiment, a compound of formula (XV) can have the structure shown herein with the proviso that if the compound of formula (XV) has the structure and stereochemistry of the compound of formula (XV-A) and R_3 is methyl then R_4 cannot be isopropyl. In an embodiment, a compound of formula (XVp) can have the structure shown herein with the proviso that if R_3 is methyl and R_4 is isopropyl then PG_2 cannot be DMIPS or TBS. In some embodiments, a compound of formula (XVp) can have the structure shown herein with the proviso that if the compound of formula (XVp) has the structure and stereochemistry of the compound of formula (XVp-A) and R_3 is methyl and R_4 is isopropyl then PG_2 cannot be DMIPS or TBS.

In an embodiment, a compound of formula (XXVII) can have the structure shown herein with the proviso that if the compound of formula (XXVII) has the structure and stereochemistry of the compound of formula (XXVII-A), R_3 is methyl, and R_5 is $-C(=O)OR_6$, wherein R_6 is methyl, H or t-butyl, then R_4 cannot be 2-cyclohexenyl. In one embodiment, a compound of formula (XXVIIp) can have the structure shown herein with the proviso that if the compound of formula (XXVIIp) has the structure and stereochemistry of the compound of formula (XXVIIp-A); R_3 is methyl; R_5 is $-C(=O)OR_6$, wherein R_6 is hydrogen or methyl; and PG_2 is TBS or DMIPS then R_4 cannot be isopropyl.

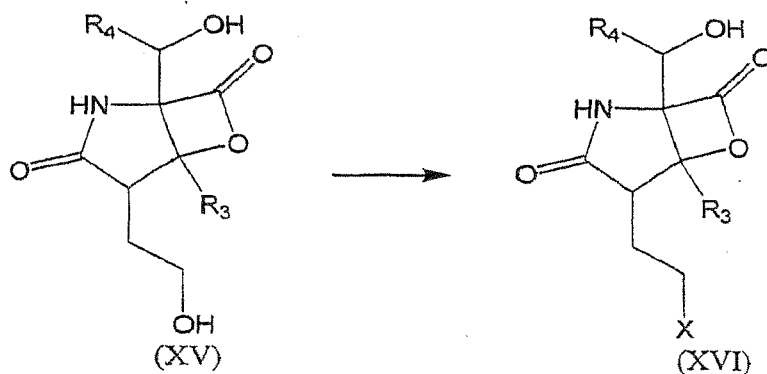
Other exemplary structures and stereochemistry of compounds of formulae (XXVII), (XXVIIp), (XVp) and (XV) are as follows:



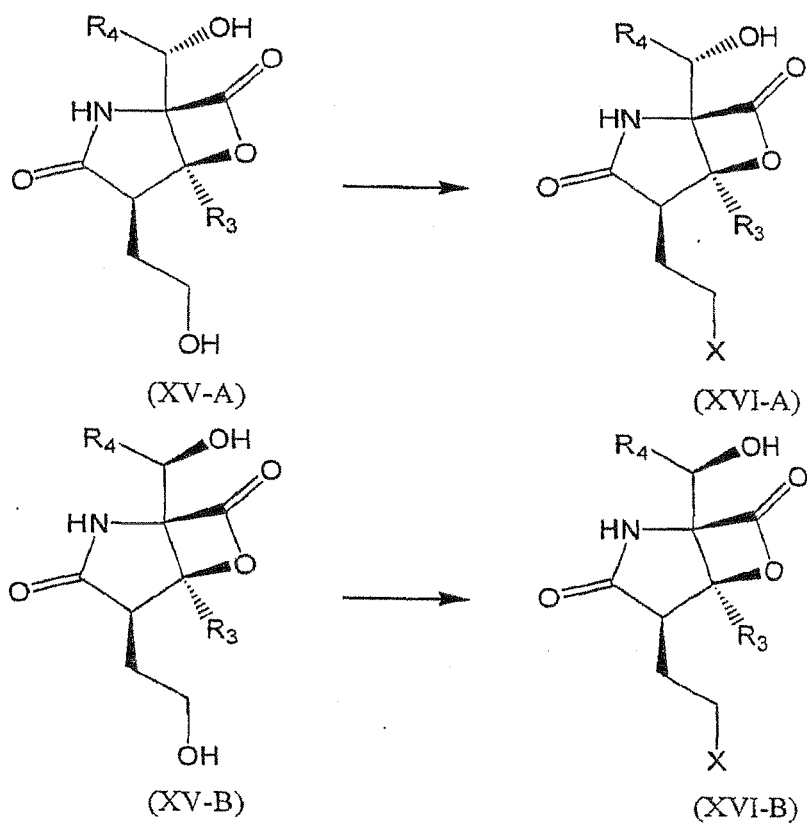


As shown in Scheme 7-6, a compound of formula (XV) can further be transformed by replacing the C-13 primary hydroxy group of the compound of formula (XV) to form a compound of formula (XVI), wherein R₃ and R₄ can be the same as described with respect to the compound of formula (X) and X can be a halogen (e.g., F, Cl, Br, and I). If desired or necessary, R₄, in some embodiments, can be protected and/or deprotected one or several times in any of the synthetic steps described herein.

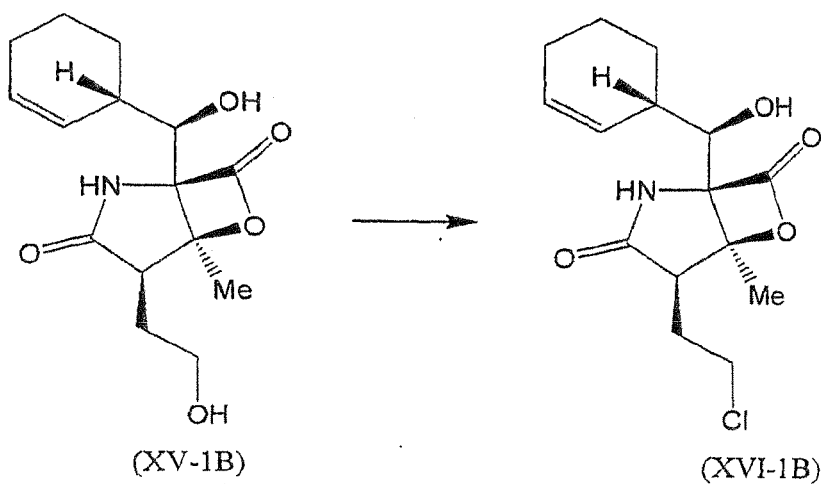
Scheme 7-6



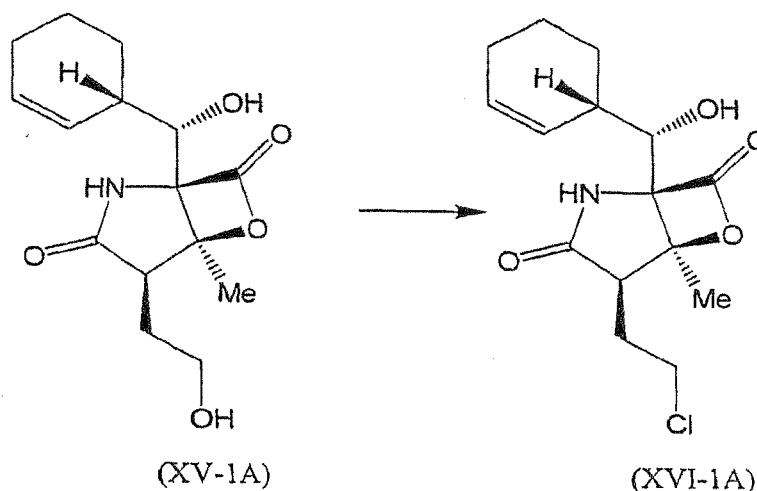
Examples of the structures and stereochemistry of compounds of formulae (XV) and (XVI) are shown below:



Further examples of the structures and stereochemistry of the compounds of formula (XV) and (XVI) are shown below:

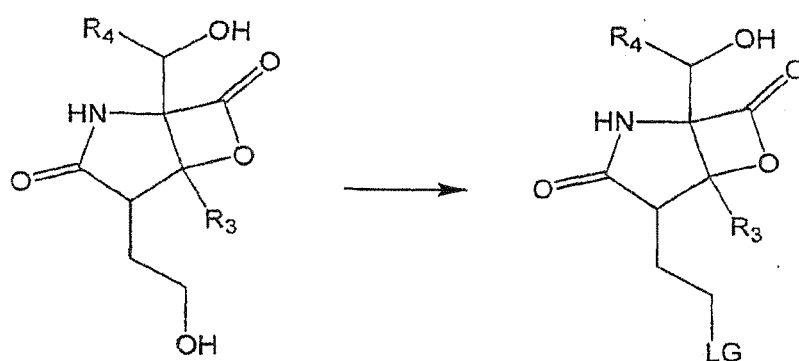


In one embodiment, Salinosporamide A can be synthesized by chlorinating a compound of formula (XV), wherein R₄ is 2-cyclohexenyl and R₃ is methyl.

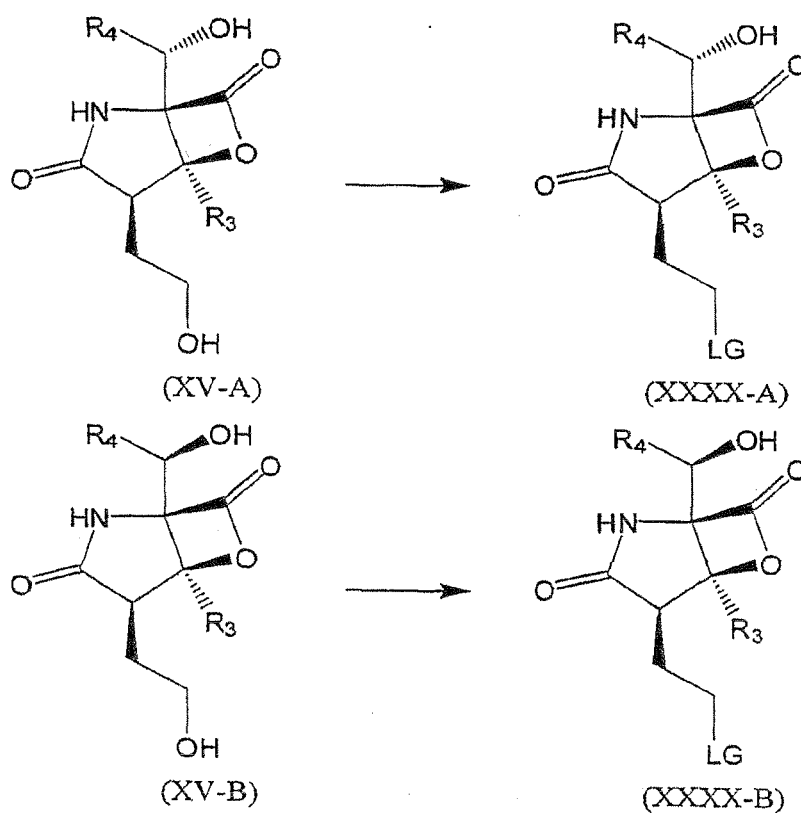


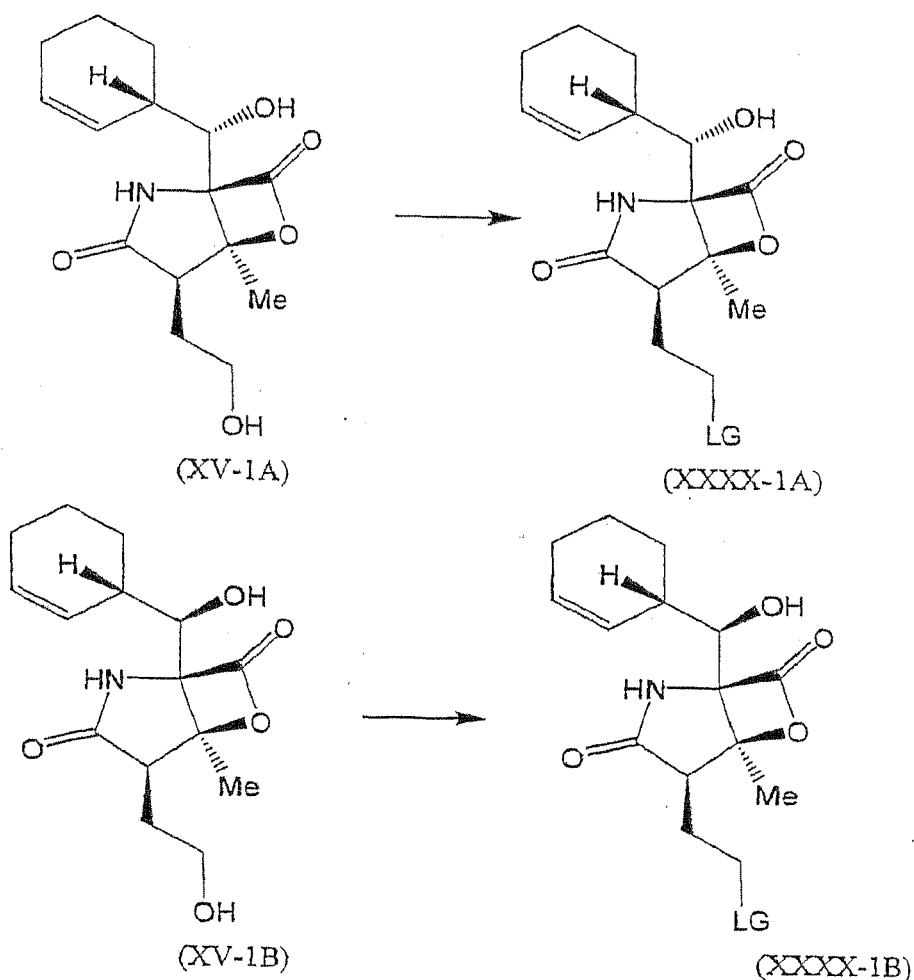
In some embodiments, a compound of formula (XVI) can be prepared by substituting the C-13 primary hydroxy group of the compound of formula (XV), with the proviso that the compounds of formula (XV) and (XVI) cannot be the compounds of formula (XV-1A) and (XVI-1A). In certain embodiments, if the compound of formula (XVI) has the structure and stereochemistry of the compound of formula (XVI-A), then R_4 cannot be isopropyl or 2-cyclohexenyl when R_3 is methyl and X is chlorine.

In an embodiment, the C-13 primary hydroxy group of the compound of formula (XV) can be converted to a leaving group, as shown in Scheme 7-7. A non-limiting list of suitable leaving groups (LG) includes sulfonate leaving groups (e.g. tosylate, (OTs), mesylate (OMs), triflate (OTf), tripsylate (OTps), and mesitylate (OMst)). In an embodiment, R_3 and R_4 can be the same as described with respect to the compound of formula (X). If desired, the C-5 secondary hydroxy can be protected or oxidized before converting the C-13 secondary hydroxy group of the compound of formula (XV). After the leaving group has been added, the C-5 center can be deprotected and/or reduced to a hydroxy group.

Scheme 7-7

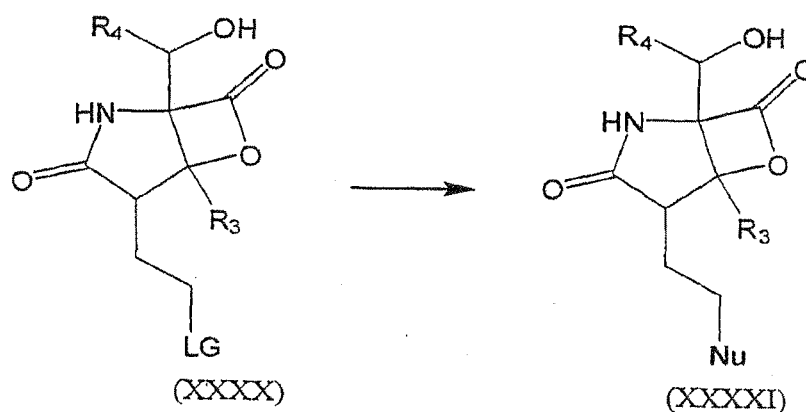
Examples of the structures and stereochemistry of compounds of formulae (XV) and (XXXX) with a leaving group attached to the C-13 oxygen are shown below:



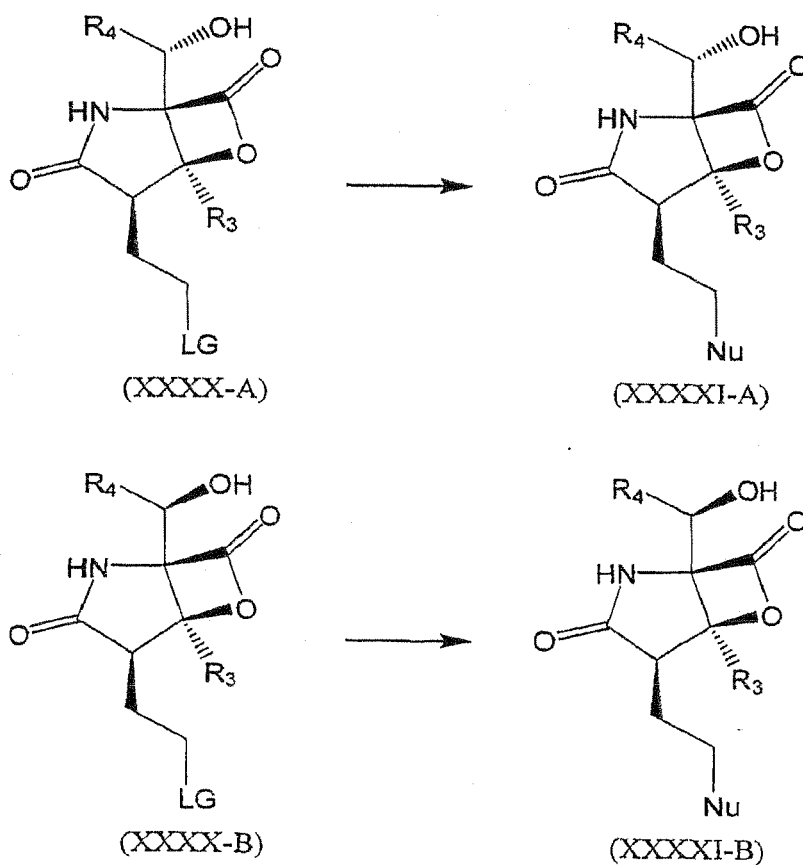


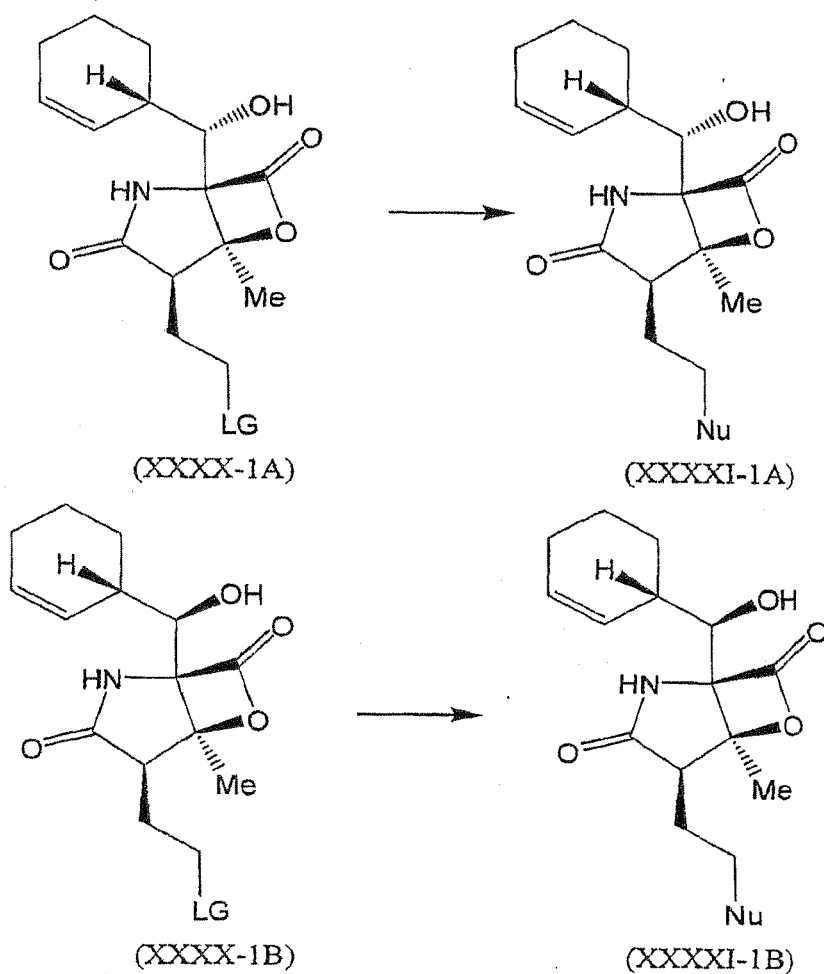
The leaving group of compounds of formula (XXXX) can be displaced with a nucleophile (Nu) using methods known to those skilled in the art to form a compound of formula (XXXXI). See Scheme 7-8. In an embodiment, R_3 and R_4 can be the same as described with respect to the compound of formula (XXXX). Suitable nucleophiles include R_9S^- , CN^- , R_9O^- , halide anion, $NR_{9a}R_{9b}^-$, N_3^- , $-CO_2R_9$, R_9OH , and R_9SH wherein R_9 , R_{9a} and R_{9b} can each be independently selected from the group consisting of hydrogen, or substituted or unsubstituted variants of the following: C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkenyl, C_3 - C_{12} cycloalkynyl, C_3 - C_{12} heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, and alkyl acyl, wherein R_{9a} and R_{9b} can be taken together to form an optionally substituted cycloalkyl.

Scheme 7-8



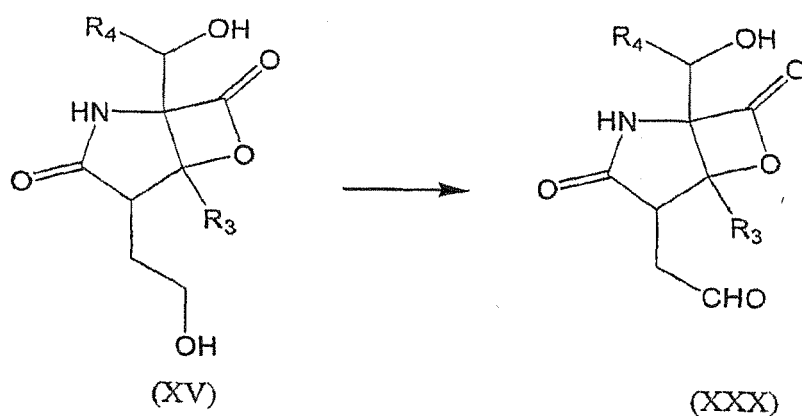
Exemplary structures and stereochemistry of compounds of formulae (XXXXX) and (XXXXXI) include:



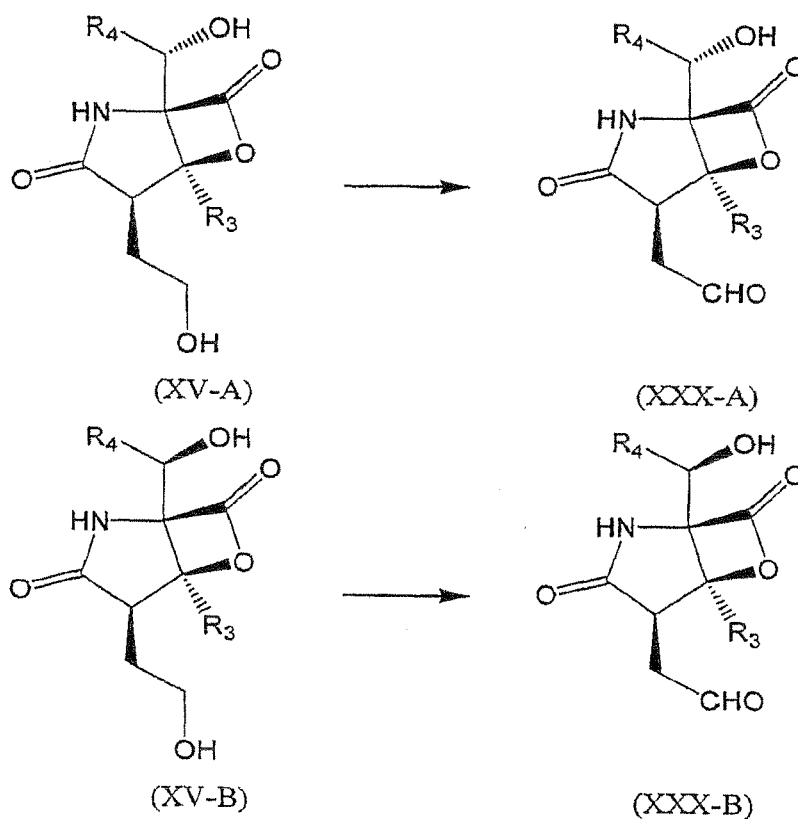


In some embodiments, the C-13 primary hydroxy group of the compound of formula (XV) can be oxidized. For example, in one embodiment, the C-13 primary hydroxy group can be oxidized to an aldehyde to form a compound of formula (XXX). See Scheme 7-9. In an embodiment, R_3 and R_4 of a compound of formula (XXX) can be the same as described with respect to the compound of formula (XVII). If desired, the C-5 secondary hydroxy can be protected or remained unprotected during the oxidation.

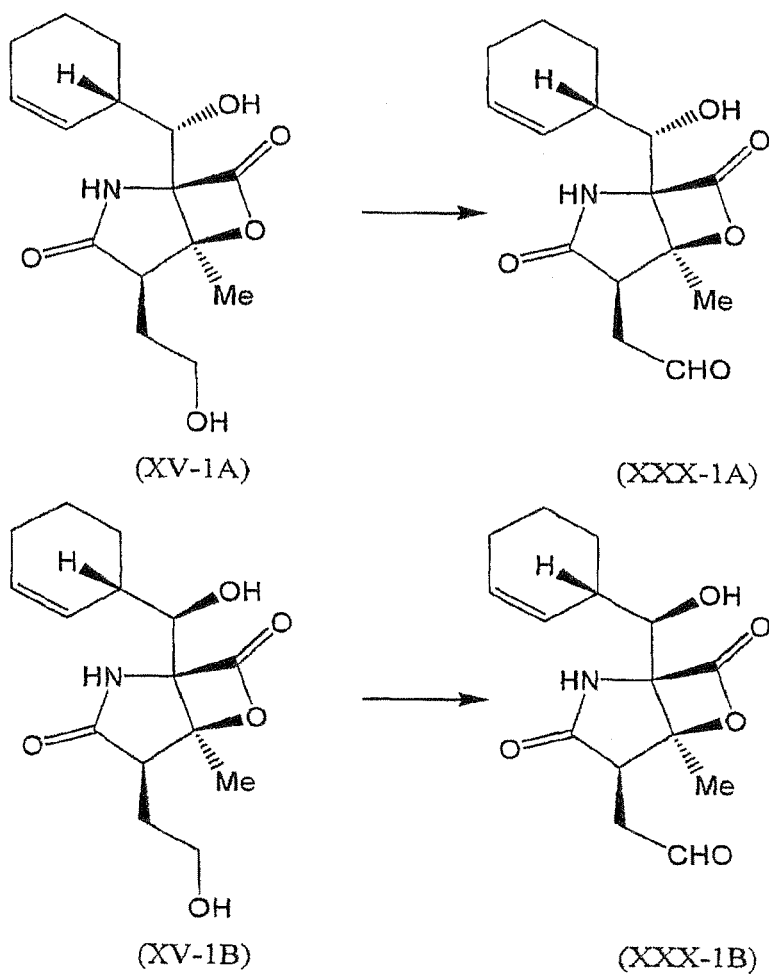
Scheme 7-9



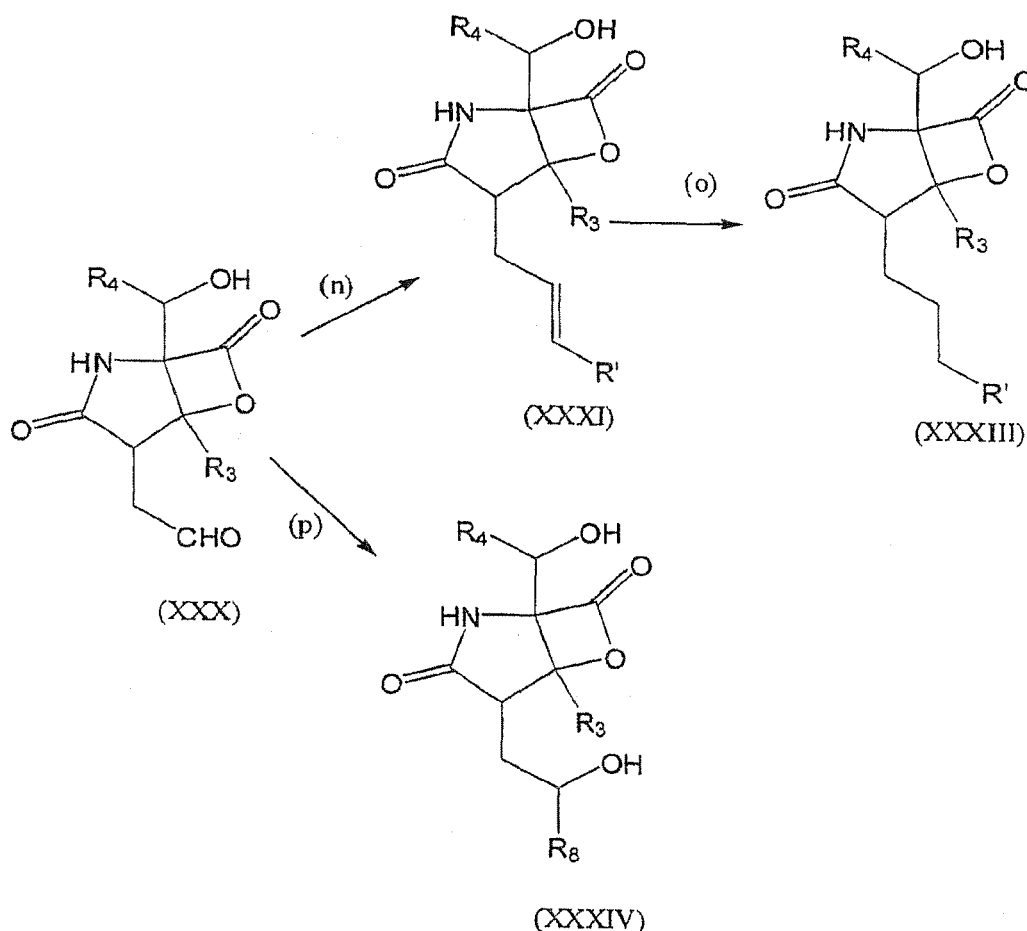
Exemplary structures and stereochemistry of compounds of formulae (XV) and (XXX) are shown below:



Additional examples of the structures and stereochemistry of compounds of formulae (XV) and (XXX) include the following:

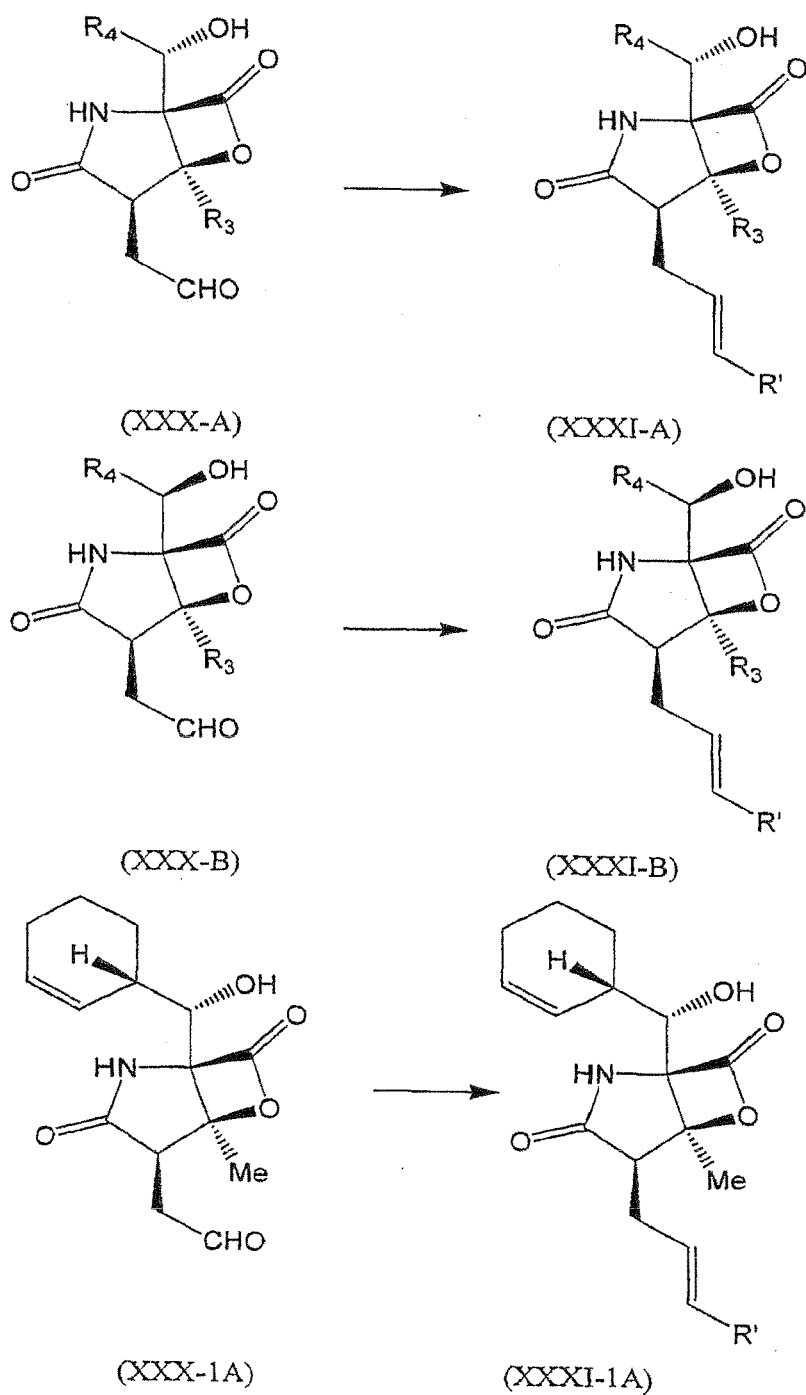


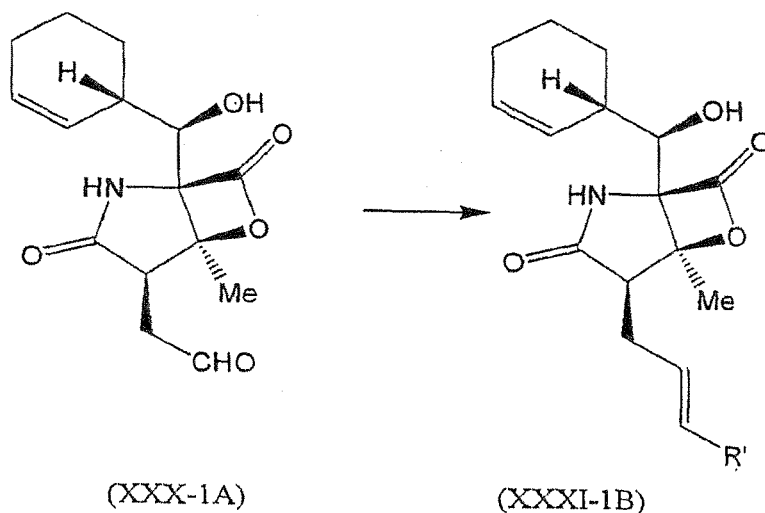
Scheme 7-10



A compound of formula (XXX) can further be transformed as shown in step (n) of Scheme 7-10. In one embodiment, a Wittig reaction can be used to convert a compound of formula (XXX) to compounds of formulae (XXXI), wherein R₃ and R₄ can be the same as described with respect to the compound of formula (XXX), R' can be hydrogen, halogen, -C(=O)R'', -C(=O)OR'', -C(=O)N(R'')₂, -C(=O)SR'', -CN, -(CH₂)_nOH, and -(CH₂)_nX; R'' can be a hydrogen or a substituted or unsubstituted variant of the following: alkyl, alkenyl, alkoxy, aryloxy, and arylalkoxy, and when more than one R'' is present, they may be the same or different; X can be a halogen; and n can be 0, 1, 2, 3, or 4. Appropriate conditions and reagents are known to those skilled in the art and include Wittig reagents such as triphenyl phosphonium ylides). In an embodiment, n can be 0. In another embodiment, n can be 1. In still another embodiment, n can be 2. In yet still another embodiment, n can be 3. In an embodiment, n can be 4.

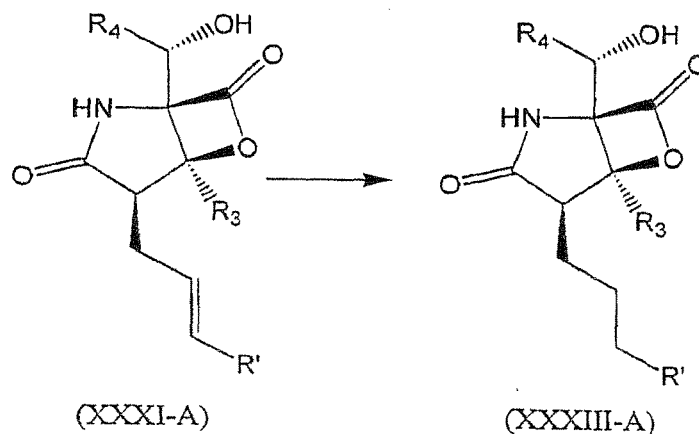
Examples of the structures and stereochemistry of compounds of formulae (XXX), and (XXXI) are shown below:

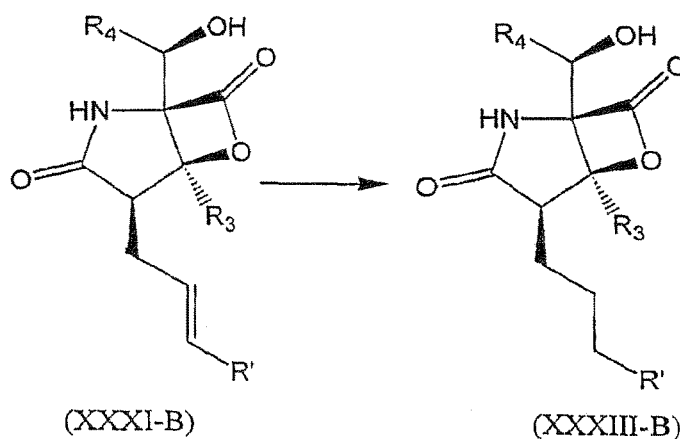




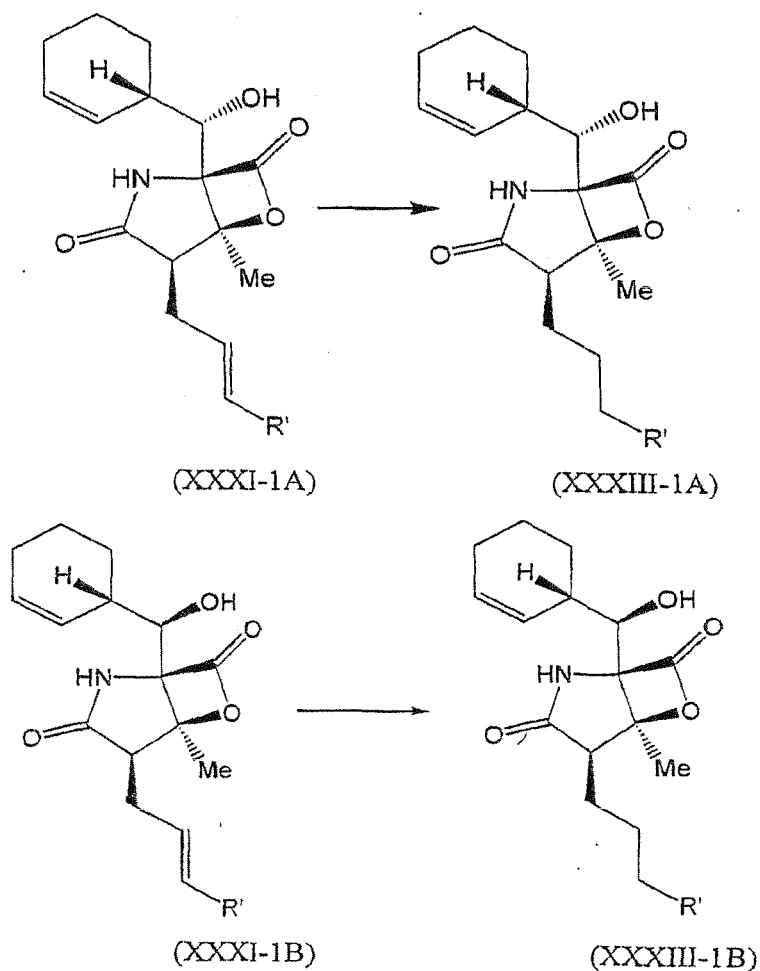
Selective hydrogenation of the side chain double bond of compound of formula (XXXI) can form a compound of formula (XXXIII), as shown in step (o) of Scheme 7-10. In an embodiment, R_3 , R_4 and R' of a compound of formula (XXXIII) can be the same as described with respect to the compound of formula (XXXI). In some embodiments, a compound of formula (XXXIII) can have the structure shown herein with the proviso that if R_3 is methyl and R' is hydrogen or chlorine then R_4 cannot be isopropyl, cyclohexyl, or phenyl.

Exemplary structures and stereochemistry of compounds of formulae (XXXI), and (XXXIII) are shown below:



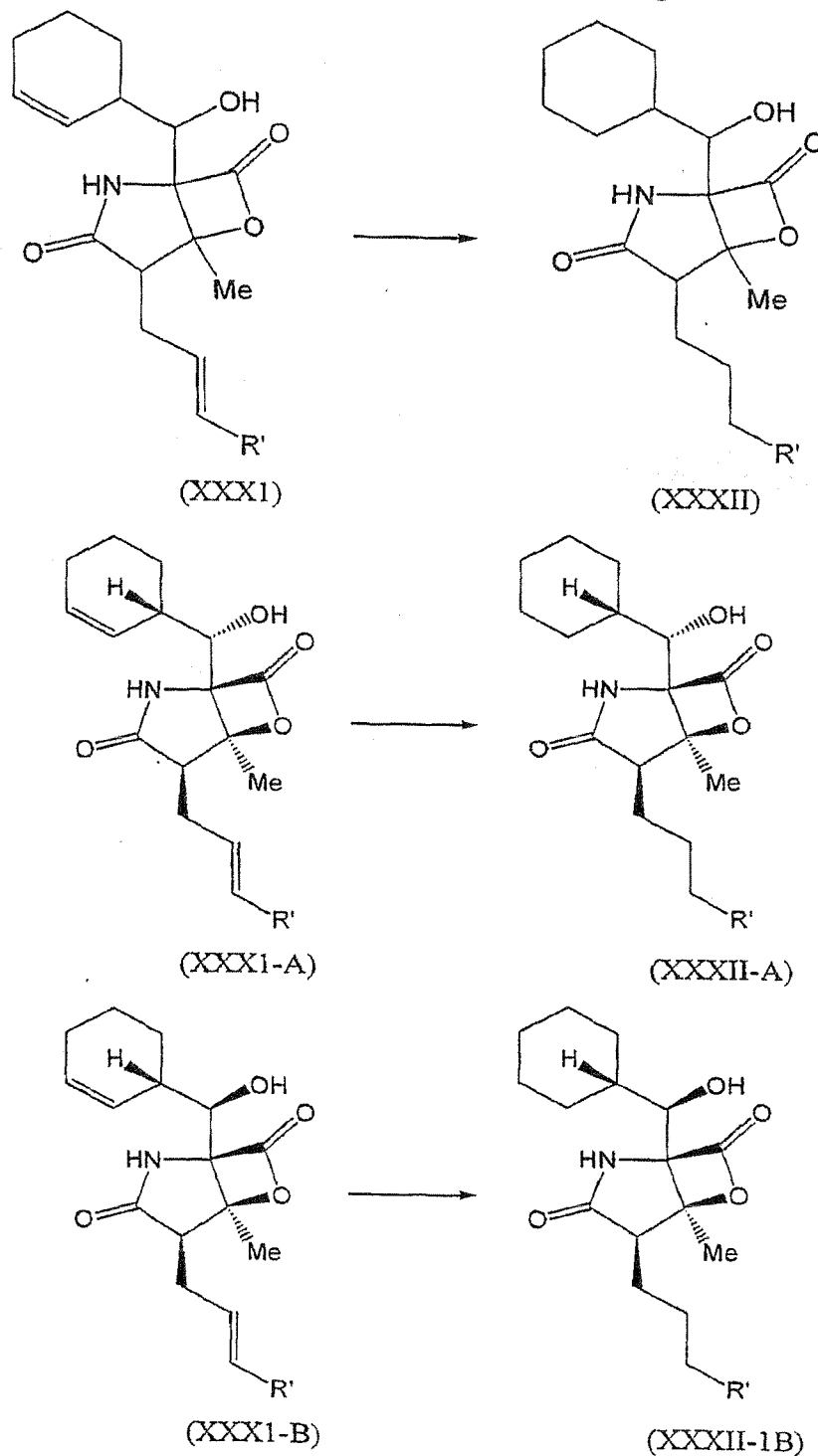


In certain embodiments, compounds of formulae (XXXI) and (XXXIII) can have the following structures and stereochemistry:



In another embodiment, nonselective reduction of the compound of formula (XXXI-1A) or (XXXI-1B) can be used to obtain the compounds of formulae

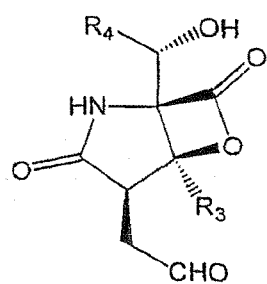
(XXXII), respectively. In some embodiments, a compound of formula (XXXII) can have the structure shown herein with the proviso that R' cannot be hydrogen or chlorine.



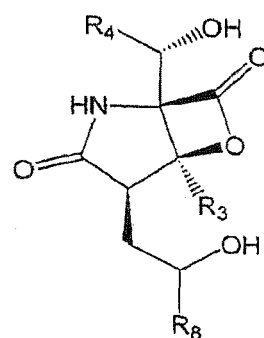
A compound of formula (XXX) can also be used to form a compound of formula (XXXIV) using an organometallic reagent as shown in step (p) of Scheme 7-

10. Suitable organometallic reagents include organolithium compounds, organotin compounds, organocuprates compounds, organozinc, and organopalladium compounds, metal carbonyls, metallocenes, carbene complexes, and organometalloids (e.g., organoboranes and organosilanes). In some embodiments, the organometallic moiety can be selected from the group consisting of R_8-MgR_7 , R_8-ZnR_7 , R_8-Li , $(R_8)_p-B(R_7)_{3-p}$, and $(R_8)_q-Sn(R_7)_{4-q}$; wherein R_7 can be selected from the group consisting of halogen, or substituted or unsubstituted variants of the following: alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, isopinocampheyl, hydroxy, alkoxy, and carbonylalkoxy, wherein if more than one R_7 is present, the R_7 groups can optionally be bonded together to form an optionally substituted cycloalkyl (e.g., 9-BBN), optionally substituted cycloalkenyl, optionally substituted heteroalkyl or optionally substituted heteroalkenyl ring; p can be an integer from 1 to 3; and q can be an integer from 1 to 4 and R_8 can be selected from the group consisting of substituted or unsubstituted variants of the following: alkyl, alkenyl, cycloalkyl, aryl, arylalkyl. In an embodiment, the organometallic moiety is $(R_8)_p-B(R_7)_{3-p}$. In certain embodiments, the organometallic moiety is $(R_8)_p-B(R_7)_{3-p}$, wherein R_8 is $-(CH_2)_aOH$. In some embodiments, the organometallic moiety is $(R_8)_p-B(R_7)_{3-p}$, wherein R_8 is $-(CH_2)_aOH$, p is 1, and the two R_7 groups are taken together to form an optionally substituted cycloalkyl. In another embodiment, the organometallic moiety is R_8-MgR_7 . In certain embodiments, the organometallic moiety is R_8-MgR_7 , wherein R_8 is $-(CH_2)_aOH$. In some embodiments, the organometallic moiety is R_8-MgR_7 , wherein R_8 is $-(CH_2)_aOH$ and R_7 is a halogen (e.g., chlorine). In some embodiments, R_3 and R_4 of a compound of formula (XXXIV) can be the same as described with respect to the compound of formula (XXVI). In an embodiment, a can be 1. In another embodiment, a can be 2. In still another embodiment, a can be 3. In yet still another embodiment, a can be 4. In an embodiment, a can be 5. In an embodiment, a can be 6. In still another embodiment, In an embodiment, a can be ≥ 7 .

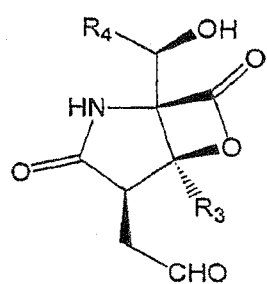
Examples of the structures and stereochemistry of compounds of formulae (XXX) and (XXXIV) are shown below:



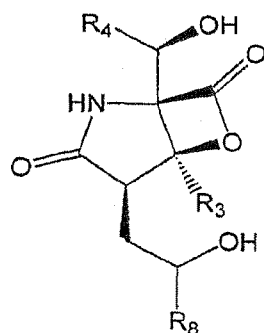
(XXX-A)



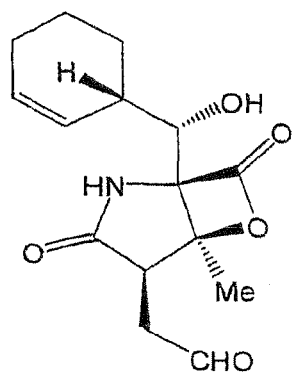
(XXXIV-A)



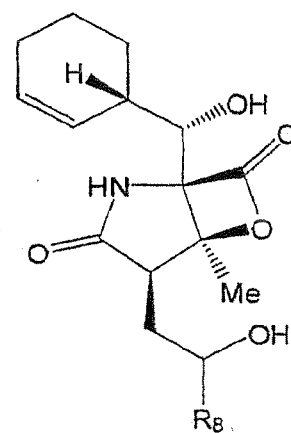
(XXX-B)



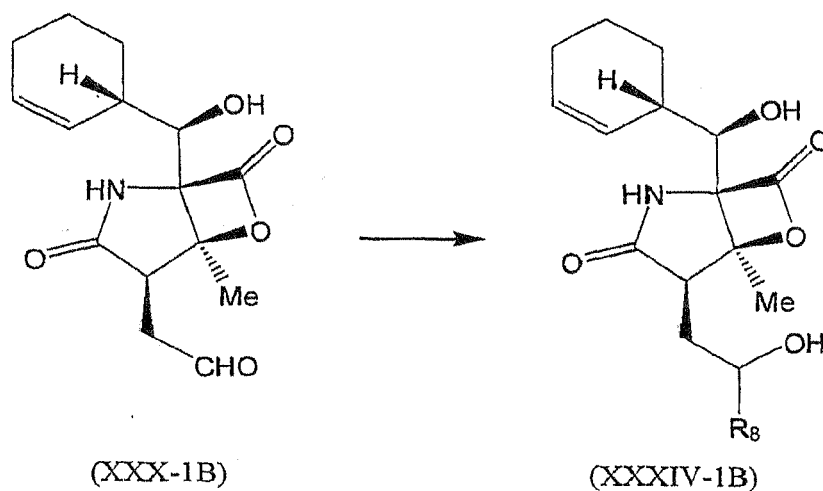
(XXXIV-B)



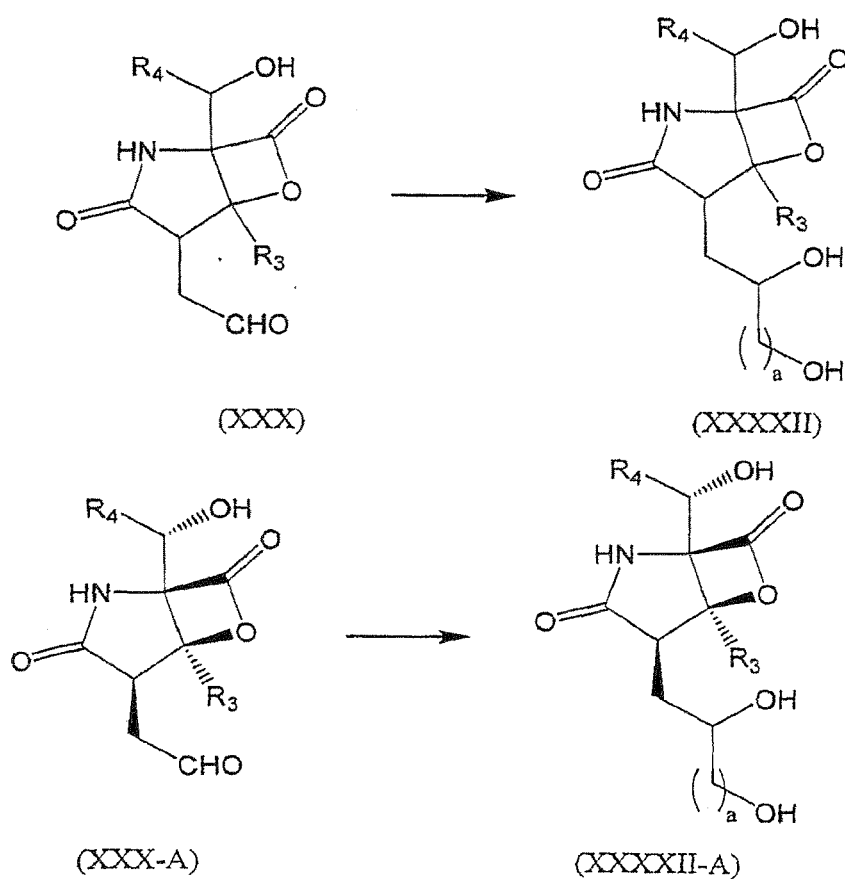
(XXX-1A)

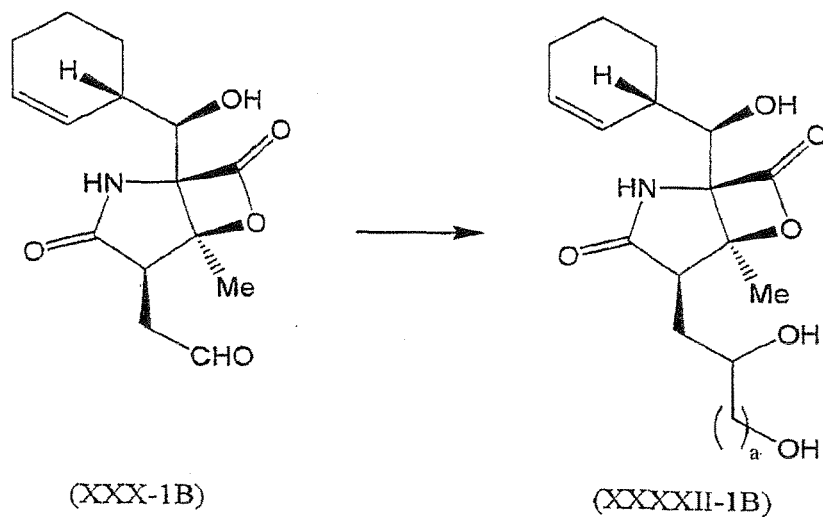
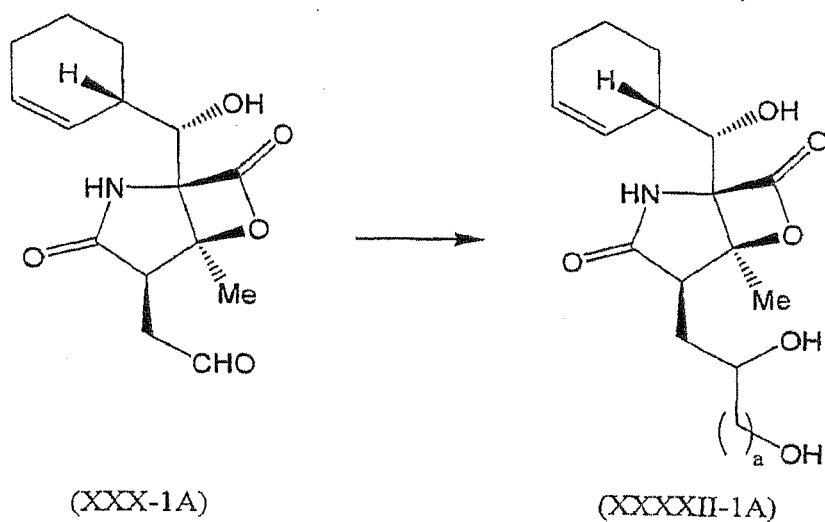
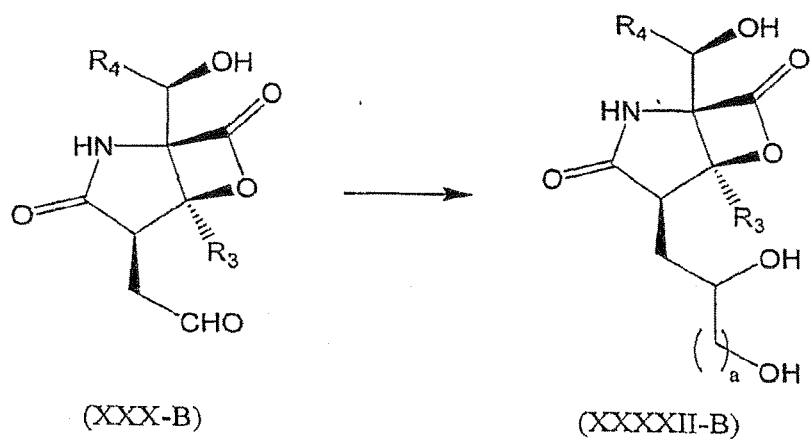


(XXXIV-1A)



In certain embodiments, R_8 can be $-(CH_2)_aOH$, wherein a can be selected from the group consisting of 1, 2, 3, 4, 6, or 7. Examples of the structures and stereochemistry of compounds of formulae (XXXIV-1B) when R_8 is $-(CH_2)_aOH$ is shown below:

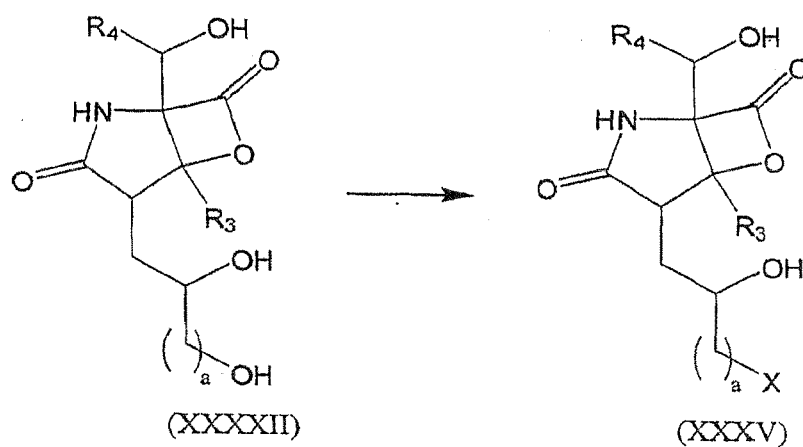




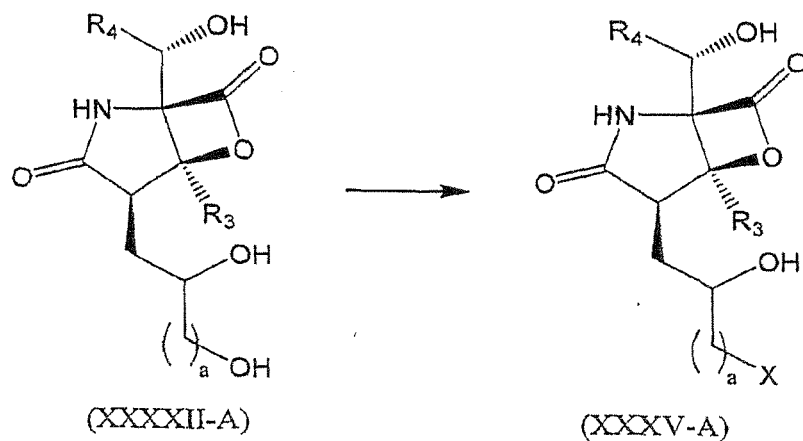
When R_8 is $-(CH_2)_aOH$, a compound of formula (XXXIV) can be halogenated to form a compound of formula (XXXV), wherein X is a halogen (e.g., F, Cl, Br, and I), as shown in Scheme 7-11. In some embodiments, R_3 and R_4 of a compound of

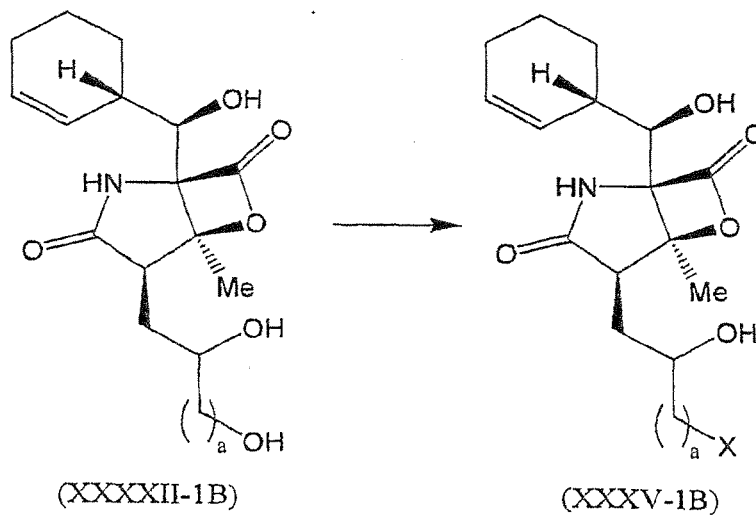
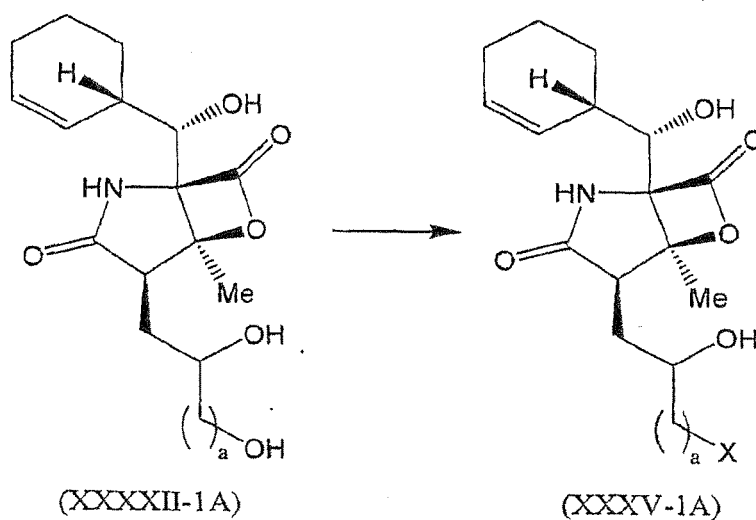
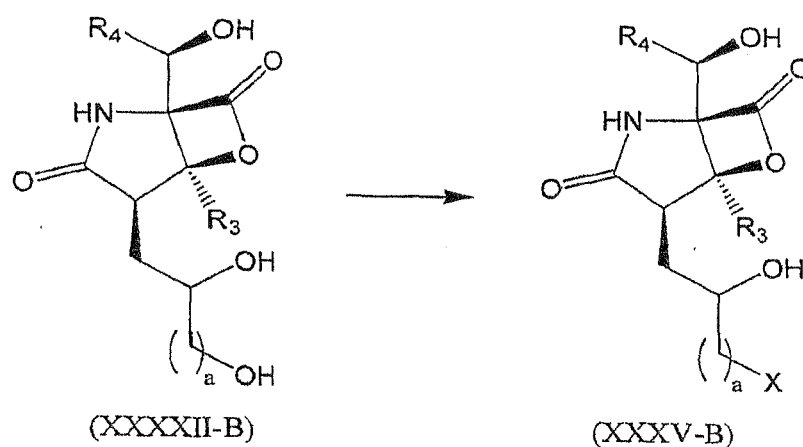
formula (XXXV) can be the same as described with respect to the compound of formula (XXVI). In an embodiment, a can be 1. In another embodiment, a can be 2. In still another embodiment, a can be 3. In yet still another embodiment, a can be 4. In an embodiment, a can be 5. In another embodiment, a can be 6. In still another embodiment, a can be 6. In yet still another embodiment, a can be ≥ 7 .

Scheme 7-11

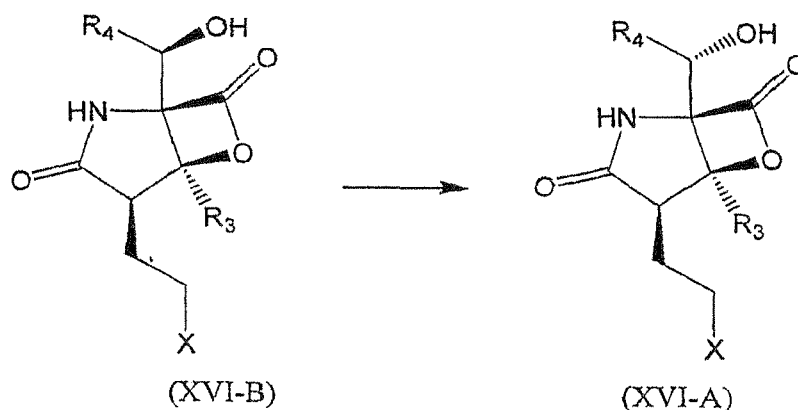


Examples of the structures and stereochemistry of compounds of formulae (XXXXXII) and (XXXV) are shown below:

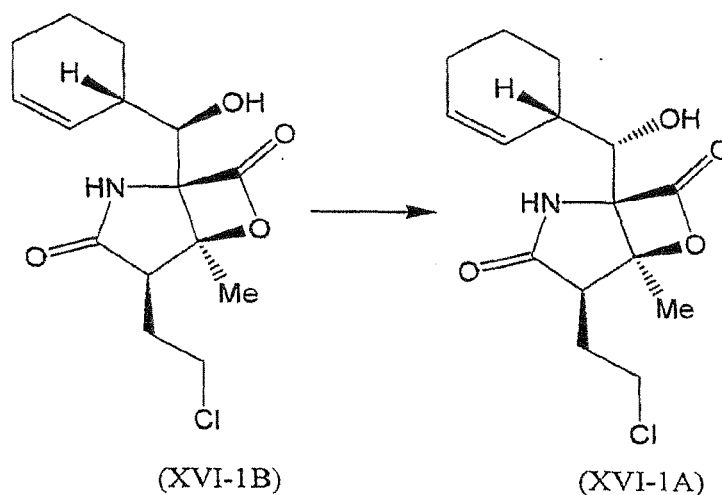




The stereochemistry of the secondary hydroxy group of the compound of formula (XVI-B) can be inverted (e.g., by a Mitsunobu transformation) to form a compound of formula (XVI-A).

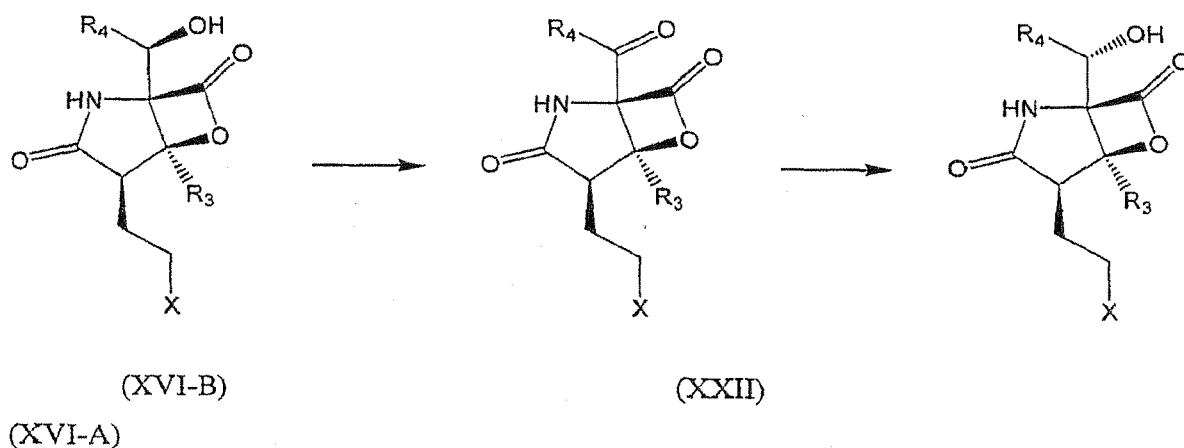


In one embodiment, Salinosporamide A can be synthesized from a compound with the structure and stereochemistry of formula (XVI-1B) as shown below:

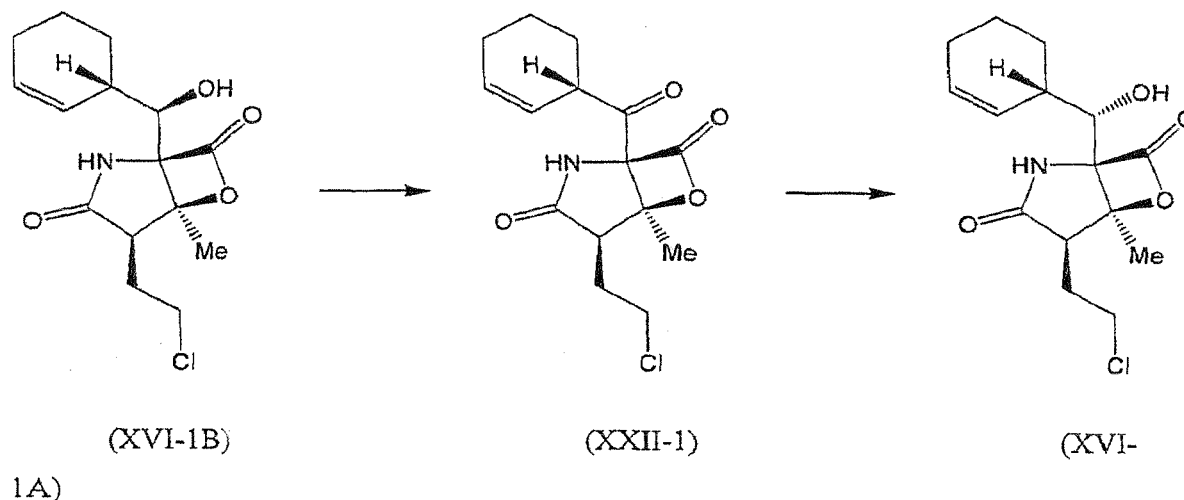


Alternatively, the stereochemistry of the C-5 secondary hydroxy can be inverted via a multistep process, for example, by oxidizing the secondary hydroxy to a ketone and then reducing the ketone to a secondary hydroxy of opposite stereochemistry. In one method, the compound of formula (XVI-B) can be oxidized with a suitable oxidizing agent (e.g., Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, or PDC) to form the compound of formula (XXII). In some embodiments of the compound of formula (XXII), R_4 cannot be substituted or unsubstituted cyclohexenyl, unsubstituted cyclohexa-1,3-dienyl, TMSO substituted cyclohexa-1,3-dienyl, unsubstituted phenyl, TMSO substituted phenyl, when R_3 is methyl and X is halogen. In an embodiment, if the compound of formula (XXII) has the structure and stereochemistry of the compound of formula (XXII-A), then R_4 cannot be substituted or unsubstituted cyclohexenyl, unsubstituted cyclohexa-1,3-dienyl, TMSO substituted cyclohexa-1,3-dienyl, unsubstituted phenyl, TMSO substituted phenyl, when R_3 is methyl and X is

halogen. The compound of formula (XXII) can then be reduced to a compound of formula (XVI-A) using a suitable chemical reagent such as sodium borohydride. In some embodiments, the reduction can be accomplished via selective enzymatic transformation. In certain embodiments, the reducing enzyme is a ketoreductase such as KRED-EXP-C1A and/or KRED-EXP-B1Y.



In another embodiment, Salinosporamide A can be synthesized from a compound with the structure and stereochemistry of formula (XVI-1B) as follows:

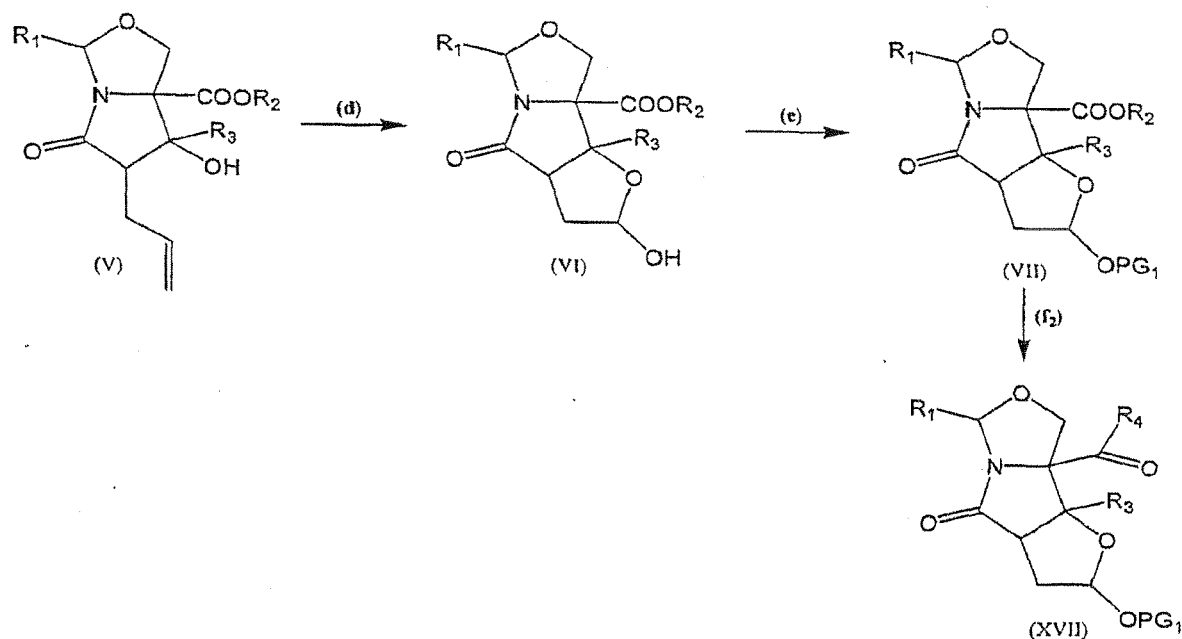


Moreover, the stereochemistry of the C-5 secondary hydroxy can be inverted at any time after the addition of the R₄ group to the compound of formula (X). For example, the stereochemistry of the C-5 secondary hydroxy can be inverted in the compounds of formulae (X), (Xp), (XI), (XI_p), (XII), (XII_p), (XIII), (XIV), (XV), (XXIII), (XXIV), (XXIV_p), (XXV), (XXV_p), (XXVI), (XXVI_p), (XXII), (XXVIII), and (XXVIII_p). In an embodiment, the stereochemistry of the C-5 secondary hydroxy can be inverted in a one step process as described herein (e.g., by a Mitsunobu transformation).

The inversion can also take place in multistep process. In an embodiment, the C-5 secondary hydroxy group can be oxidized using an appropriate oxidizing agent (e.g., Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, or PDC) to a keto group and then reduced to a hydroxy group using a suitable reducing agent such as sodium borohydride. In another embodiment, the keto group can be reduced via selective enzymatic transformation. In certain embodiments, the reducing enzyme is a ketoreductase such as KRED-EXP-C1A and/or KRED-EXP-B1Y.

An alternative method for synthesizing Salinosporamide A and its analogs from the compound of formula (V) can proceed through a compound of formula (XVII). Scheme 8-1 shows a method of synthesizing a compound of formula (XVII) from a compound of formula (V). Scheme 8-2 shows a method of synthesizing a compound of formula (XVII) from a compound of formula (X). Schemes 9-1 and 9-2 show methods of synthesizing Salinosporamide A and its analogs from a compound of formula (XVII).

Scheme 8-1

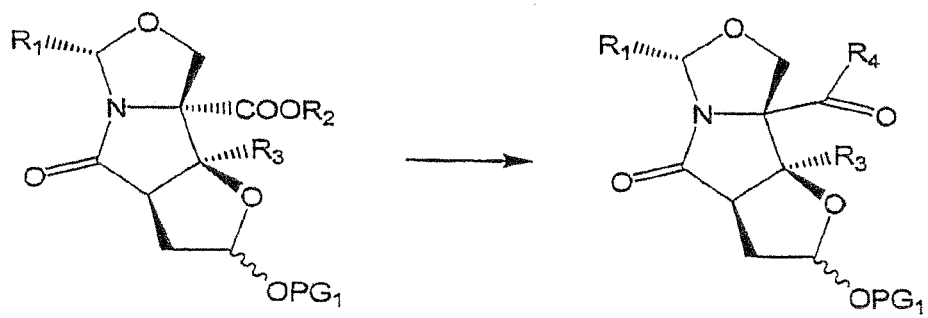


For some of the embodiments described herein, steps (d) and (e) of Scheme 8-1 can be the same as described above with respect to Scheme 6.

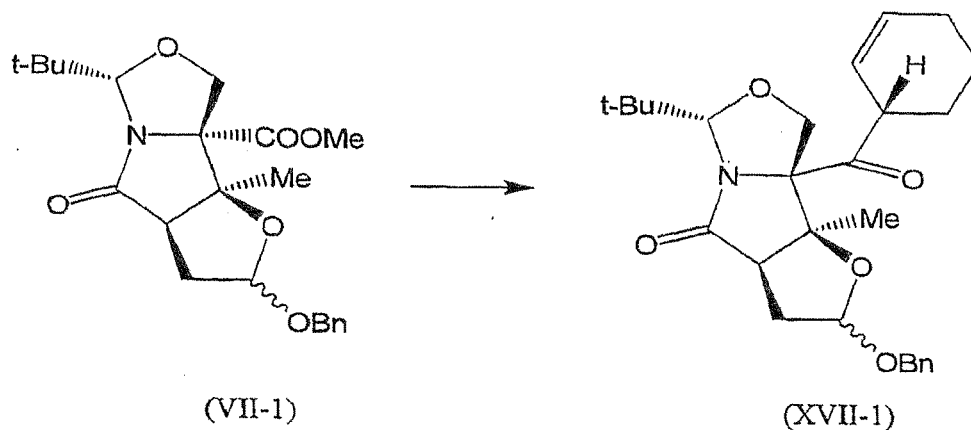
In step (f₂) of Scheme 8-1, R_4 can be added to a compound of formula (VII) using an organometallic moiety containing at least one R_4 to form a compound of formula (XVII), wherein R_1 can be hydrogen or unsubstituted or substituted C_{1-6} alkyl; R_2 can be a hydrogen substituted or unsubstituted variants of the following: C_{1-6} alkyl, aryl or arylalkyl; R_3 can be a substituted or unsubstituted variants of the following: C_{1-6} alkyl, a C_{3-6} cycloalkyl, a C_{2-6} alkenyl, C_{3-6} cycloalkenyl, aryl, or arylalkyl; PG_1 can be a protecting group moiety; and R_4 can be selected from the group consisting of substituted or unsubstituted variants of the following: $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_2\text{-C}_{12}$ alkenyl, $\text{C}_2\text{-C}_{12}$ alkynyl, $\text{C}_3\text{-C}_{12}$ cycloalkyl, $\text{C}_3\text{-C}_{12}$ cycloalkenyl, $\text{C}_3\text{-C}_{12}$ cycloalkynyl, $\text{C}_3\text{-C}_{12}$ heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylalkyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocyanalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of a guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl,

phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl. In some embodiments, R_4 can be selected from the group consisting of: substituted or unsubstituted variants of the following: C_3 - C_{12} heterocyclyl, aryl, heteroaryl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of a carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocyanalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl. Suitable organometallic moieties are described herein.

Exemplary structures and stereochemistry of compounds of formulae (VII) and (XVII) are shown below:

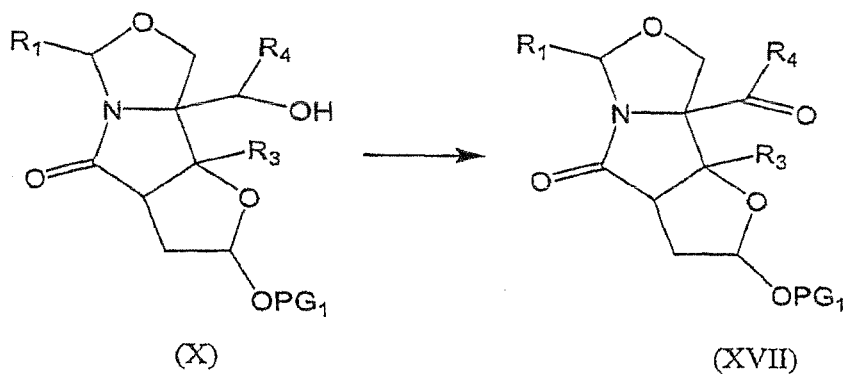


Examples of the structures of compounds of formulae (VII) and (XVII) are shown below:

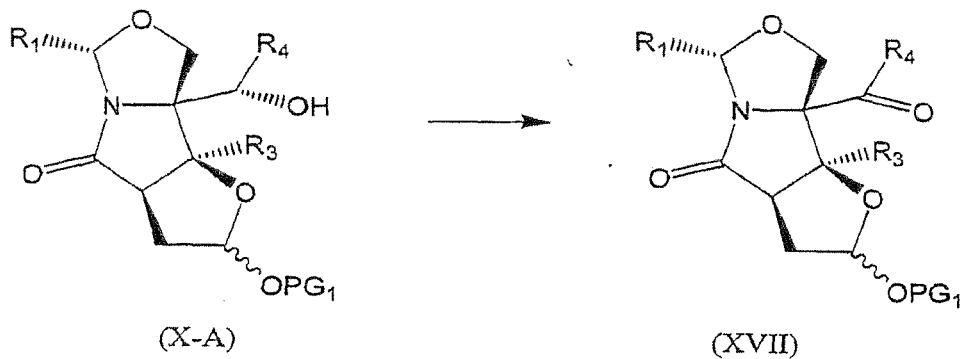


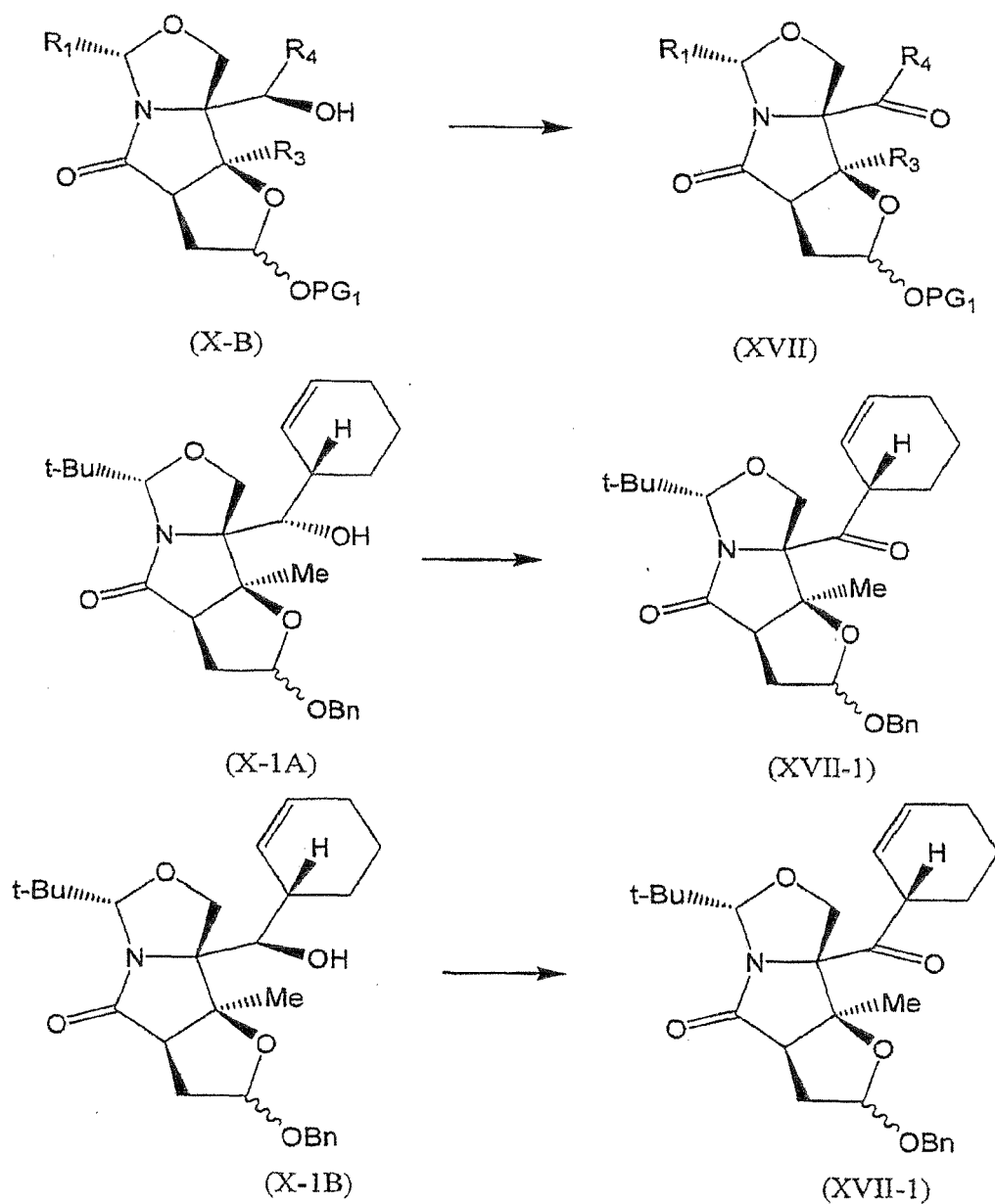
A compound of formula (XVII) can also be synthesized from a compound of formula (X) by oxidizing the secondary alcohol group of the compound of formula (X), according to Scheme 8-2. The compound of formula (X) can be synthesized as described in Scheme 6.

Scheme 8-2:



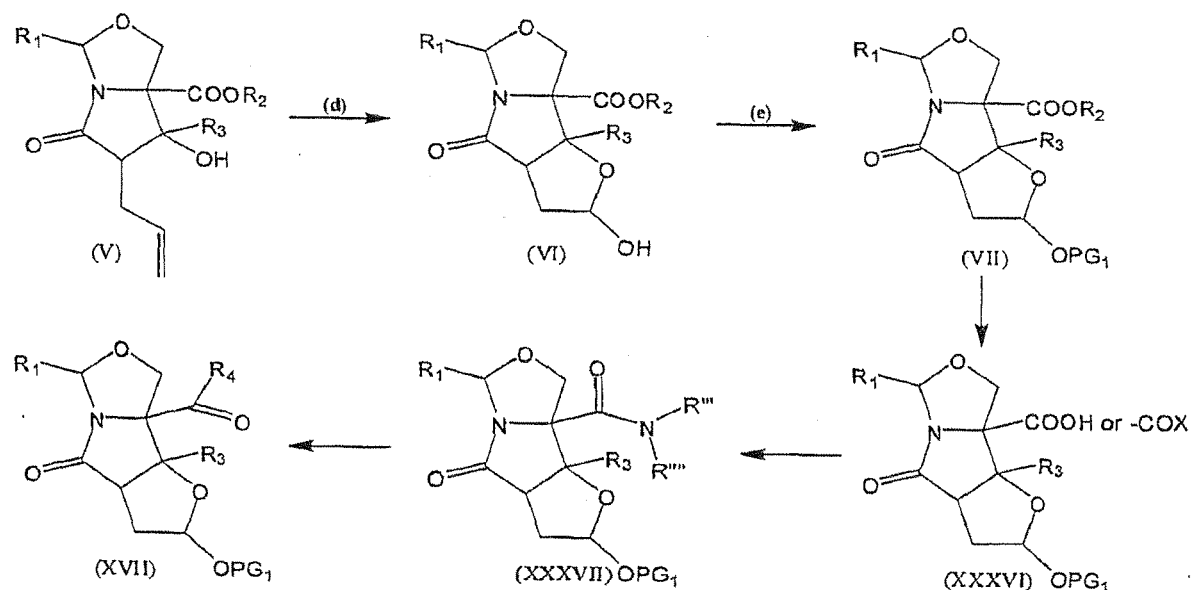
Exemplary structures of compounds of formula (X) and (XVII) are as follows:





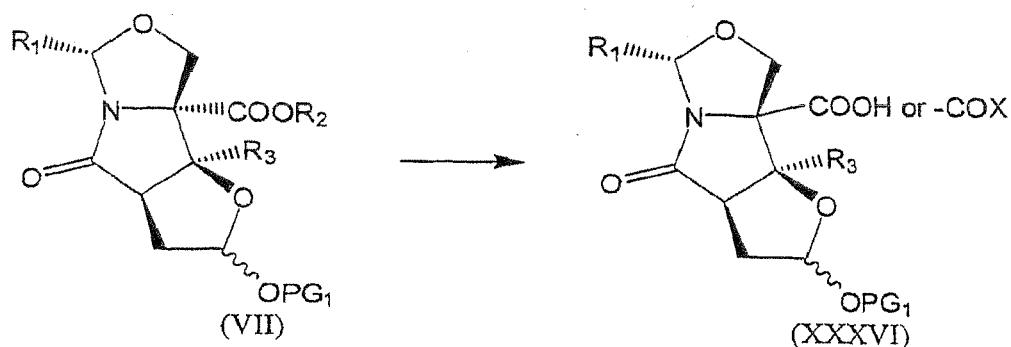
Additionally, a compound of formula (XVII) can be obtained via the synthetic Scheme 8-3.

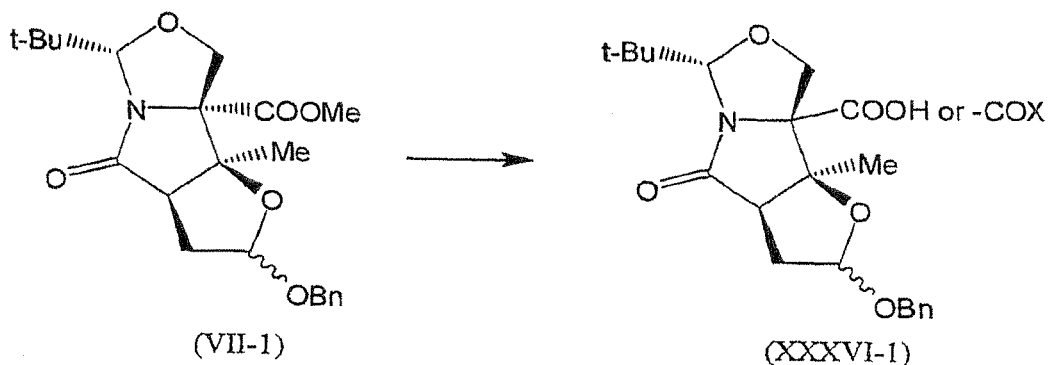
Scheme 8-3



A compound of formula (VII) can be synthesized from a compound of formula (V) via steps (d) and (e) of Scheme 8-3 that are described above with respect to Scheme 6. The ester of the compound of formula (VII) can be transformed to a carboxylic acid using methods known to those skilled in the art (e.g., hydrolysis by LiOH , alkaline thioates such as LiSMe , NaSMe , LiSC_2H_5 , etc.) which can be further transformed to acid halide using a suitable reagent (e.g. Oxalyl chloride, SOCl_2 etc.) to form a compound of formula (XXXVI). In an embodiment, R_1 , R_3 and PG_1 of the compound of formula (XXXVI) can be the same as described with respect to the compound of formula (VII) and X is a halogen.

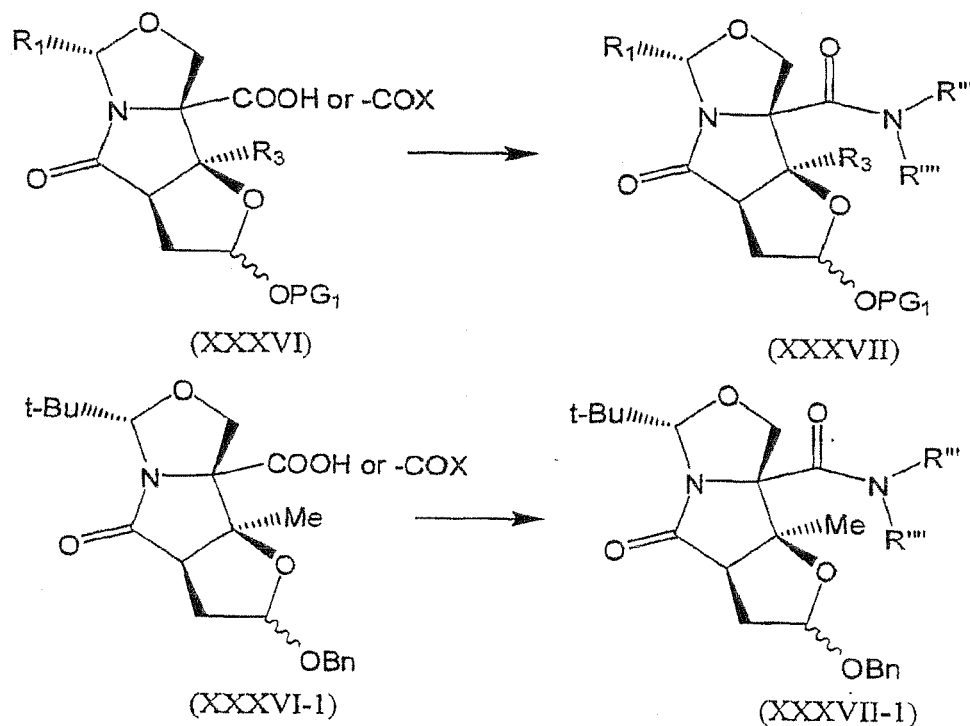
Examples of the structures of compounds of formula (VII) and (XXXVI) are shown below:





The carboxylic acid/acid halide of the compound of formula (XXXVI) can be reacted with an appropriate N,O-dimethylhydroxylamine hydrochloride [HCl.HNMe(OMe)] to form the corresponding Weinreb amide, wherein R_1 , R_3 and PG_1 can be the same as described with respect to the compound of formula (VII) and R''' and R'''' can each independently be selected from the group consisting of alkyl (e.g. methyl), alkoxy (e.g. methoxy).

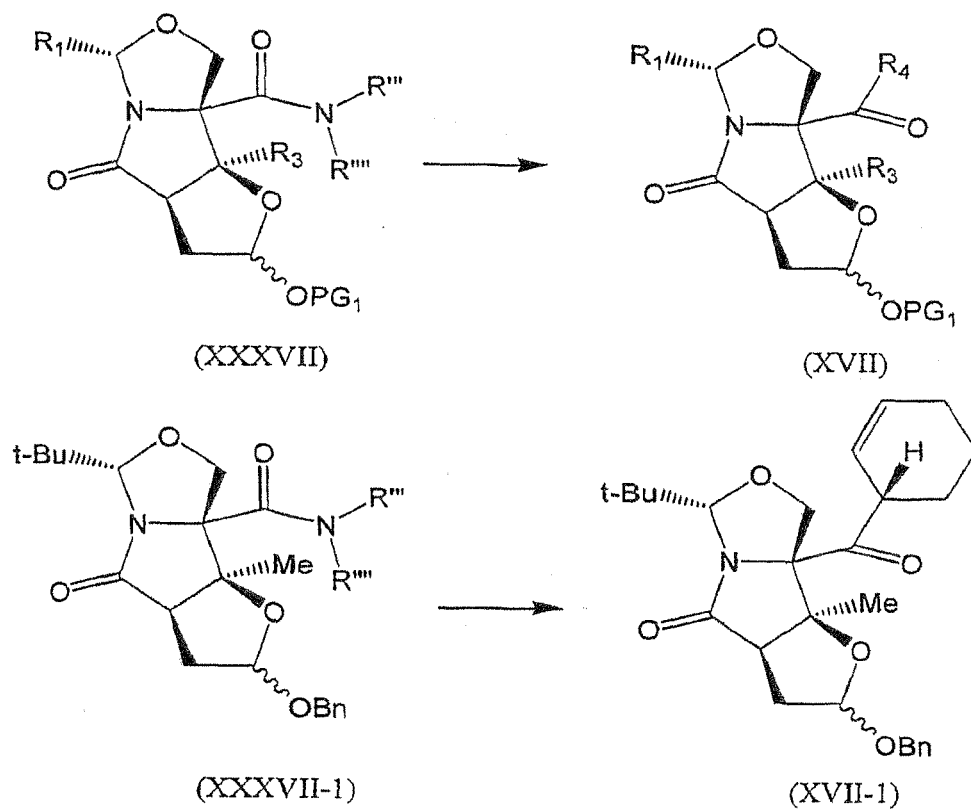
Exemplary structures of compounds of formula (XXXVI) and (XXXVII) are as follows:



The Weinreb amide of the compound of formula (XXXVII) can be reacted with an appropriate organometallic moiety containing at least one R_4 to form a compound of formula (XVII). In an embodiment, R_1 , R_3 and PG_1 can be the same as

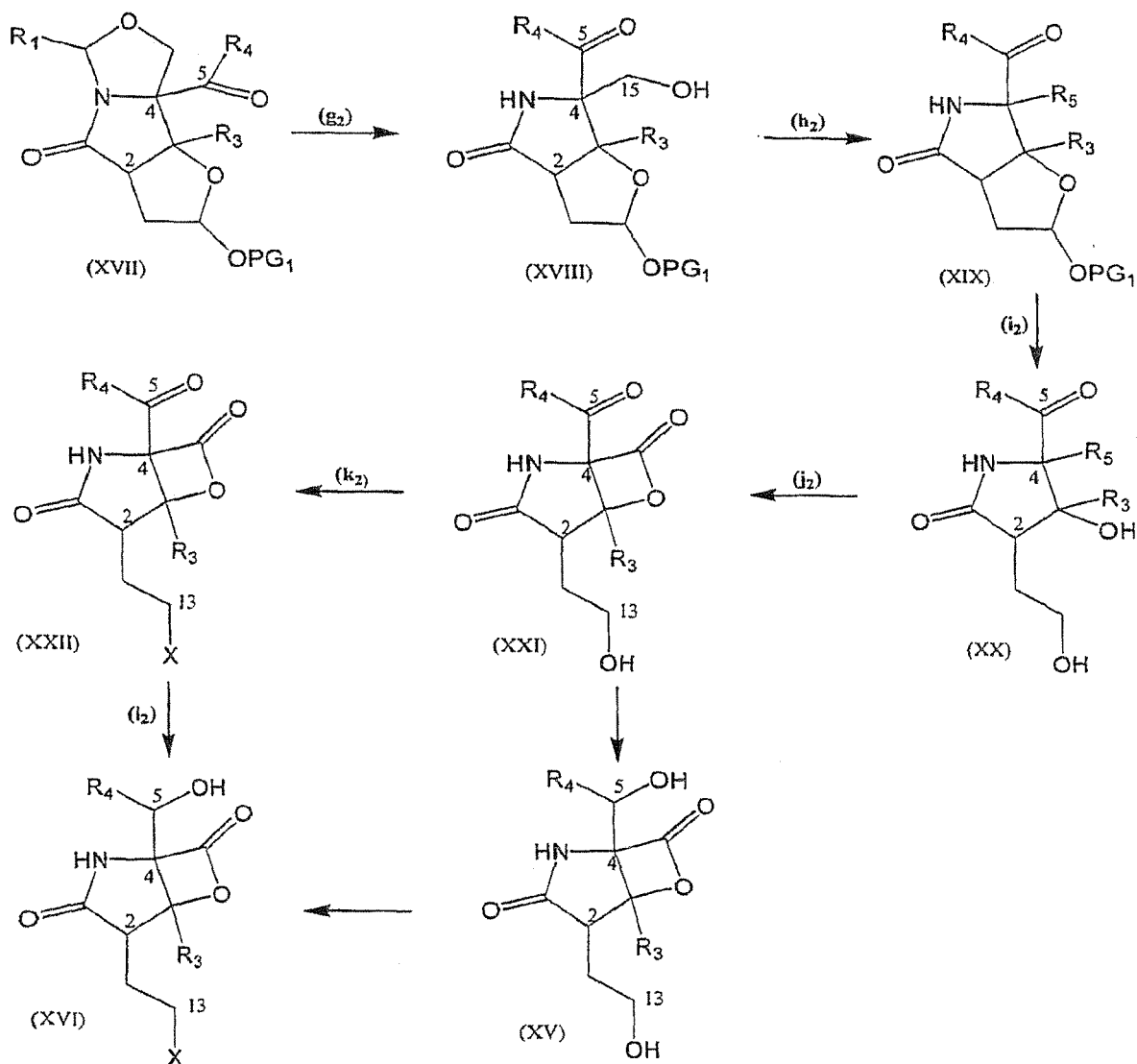
described with respect to the compound of formula (VII) and R_4 can be selected from the group consisting of substituted or unsubstituted variants of the following: C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkenyl, C_3 - C_{12} cycloalkynyl, C_3 - C_{12} heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocynoalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of a guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl. In some embodiments, R_4 can be selected from the group consisting of: substituted or unsubstituted variants of the following: C_3 - C_{12} heterocyclyl, aryl, heteroaryl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of a carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocynoalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl. Suitable organometallic moieties are described herein.

In certain embodiments, compounds of formulae (XXXVII) and (XVII) can have the following structures and stereochemistry:



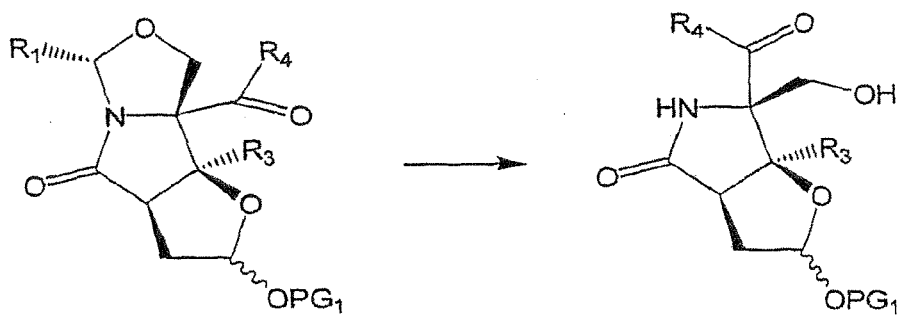
One method for obtaining Salinosporamide A and analogs thereof from a compound of formula (XVII) is shown in Scheme 9-1:

Scheme 9-1

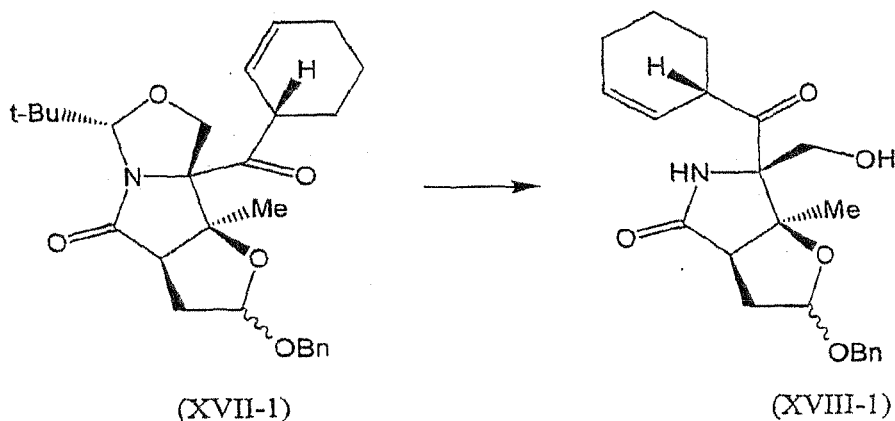


As shown in step (g₂) of Scheme 9-1, the amination of a compound of formula (XVII) can be cleaved to form a compound of formula (XVIII) using an acid reagent (e.g., triflic acid or HCl). In some embodiments, R₁, R₃, R₄ and PG₁ of a compound of formula (XVIII) can be the same as described with respect to the compound of formula (XVII).

As an example, the compounds of formula (XVII) and (XVIII) may have the following structures and stereochemistry:



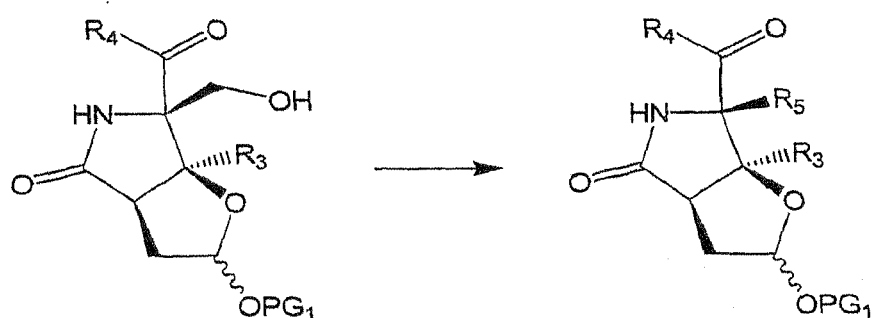
Exemplary structures of compounds of formula (XVII) and (XVIII) are shown below:



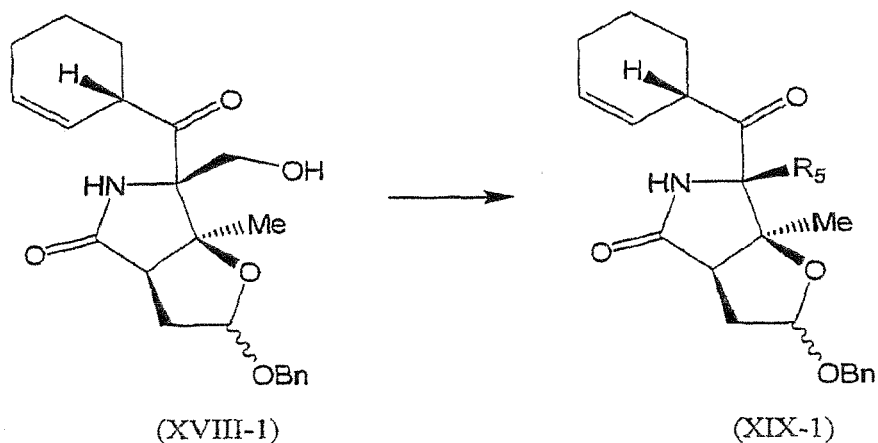
In step (h₂), the C-15 primary alcohol group of a compound of formula (XVIII) can be converted to R₅, which can be selected from the group consisting of $-C(=O)OR_6$, $-C(=O)SR_6$, $-C(=O)NR_6R_6$ and $-C(=O)Z$, wherein each R₆ can be independently selected from the group consisting of hydrogen, halogen, or substituted or unsubstituted variants of the following: C₁-C₂₄ alkyl, acyl, alkylacyl, arylacyl, aryl, arylalkyl, p-nitrophenyl, pentafluorophenyl, pentafluoroethyl, trifluoroethyl, trichloroethyl, and heteroaryl; and Z can be a halogen. The conversion of the primary alcohol group to R₅ may be achieved by converting the alcohol group to a carboxylic acid (R₆=H) using an appropriate oxidation conditions such as Jones oxidation. Alternatively the carboxylic acid group can be prepared from the primary alcohol group of the compound of formula (XVIII) through an aldehyde. The primary alcohol group of the compound of formula (XVIII) can first be converted to aldehyde using appropriate oxidant such as Dess-Martin periodinane, TPAP, Swern oxidation reagent, PCC, or PDC and then the resulting aldehyde can be oxidized further to carboxylic acid using

appropriate oxidants such as a combination of sodium chlorite/sodium phosphate dibasic/2-methyl-2-butene. If desired the carboxylic acid can then be converted to an ester, a thioester, or an anhydride to form a compound of formula (XIX) using an appropriate alcohol, thiol (e.g. thiophenol, cystine), carboxylic acid (e.g. acetic acid, benzoic acid), or anhydride (e.g. acetic anhydride). In some embodiments, R_3 and R_4 of a compound of formula (XIX) can be the same as described with respect to the compound of formula (XVIII).

Compounds of formula (XVIII) and (XIX) may have the following structures and stereochemistry:

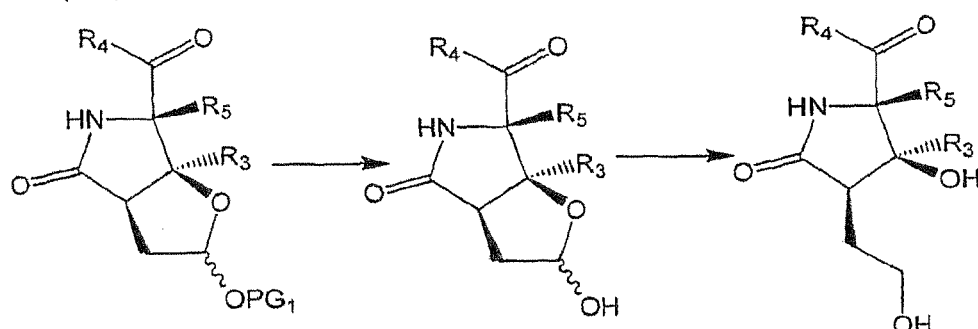


For example the compounds of formula (XVIII) and (XIX) may have the following structures:

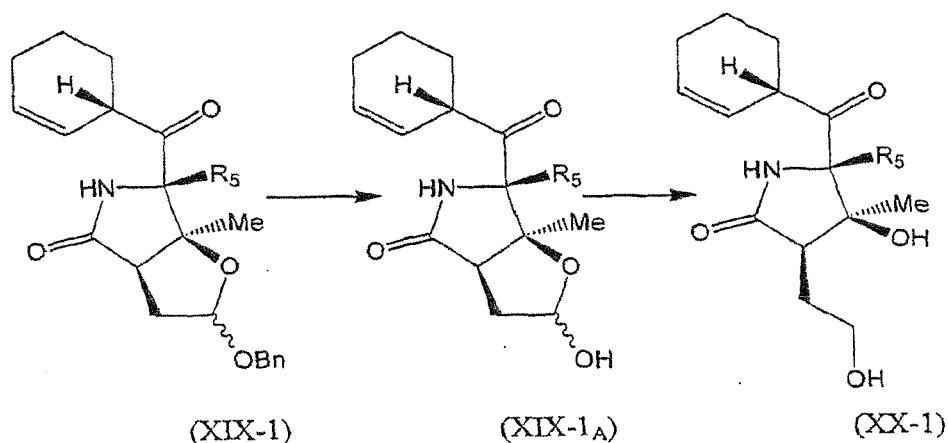


In step (i₂) of Scheme 9-1, a compound of formula (XX) can be synthesized by removing the protecting group moiety on the compound of formula (XIX) and reductively opening the resulting hemiacetal. As an example, the hemiacetal can be reductively opened using a reducing agent (e.g., sodium borohydride). In some embodiments, R_3 , R_4 , and R_5 of a compound of formula (XX) can be the same as described with respect to the compound of formula (XIX).

Exemplary structures and stereochemistry of compounds of formula (XIX) and (XX) can be as follows:

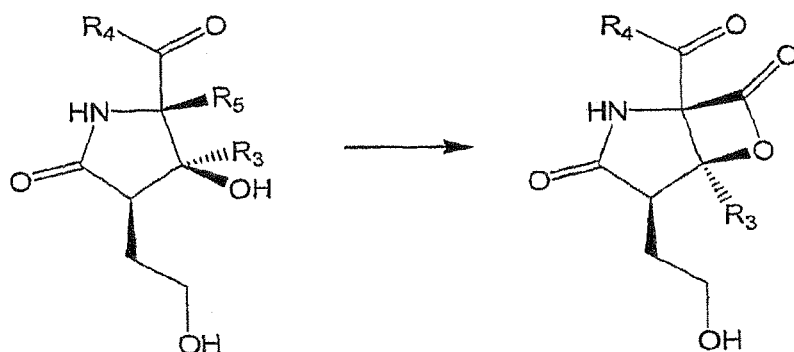


For example, compounds of formula (XIX) and (XX) can have the following structures:

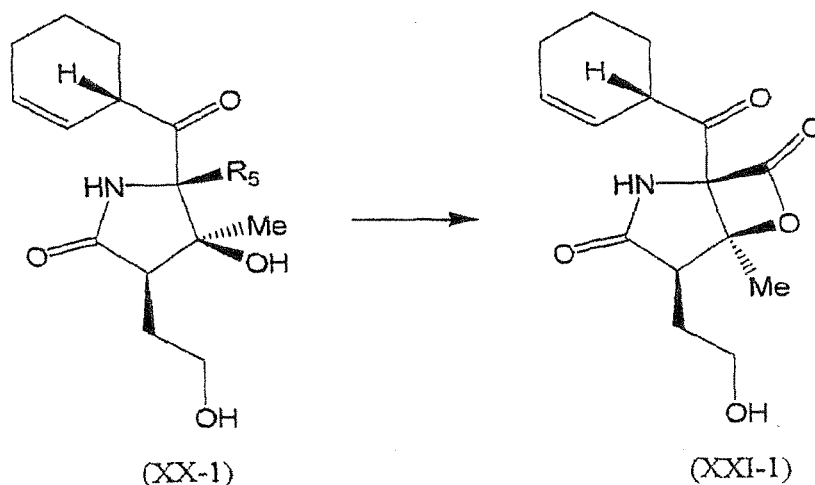


Using an appropriate base (e.g. BOPCl/pyridine), a compound of formula (XXI) can be synthesized from a compound of formula (XX) via a lactonization reaction, as shown in step (j₂) of Scheme 9-1. In an embodiment, R₃, R₄, and R₅ of a compound of formula (XXI) can be the same as described with respect to the compound of formula (XX).

Examples of the structures and stereochemistry of compounds of formula (XX) and (XXI) are shown below:

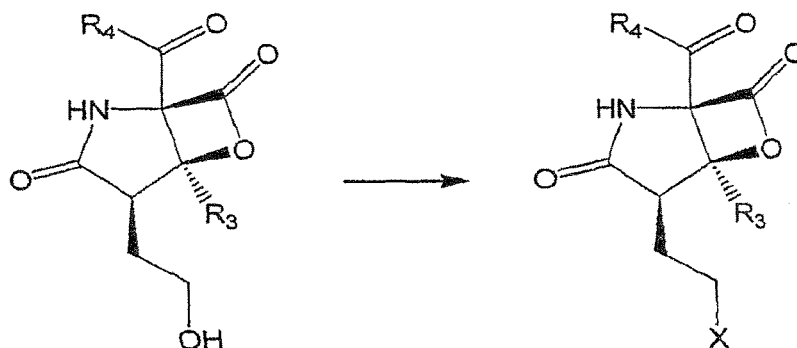


For example, compounds of formula (XX) and (XXI) can have the following structures:

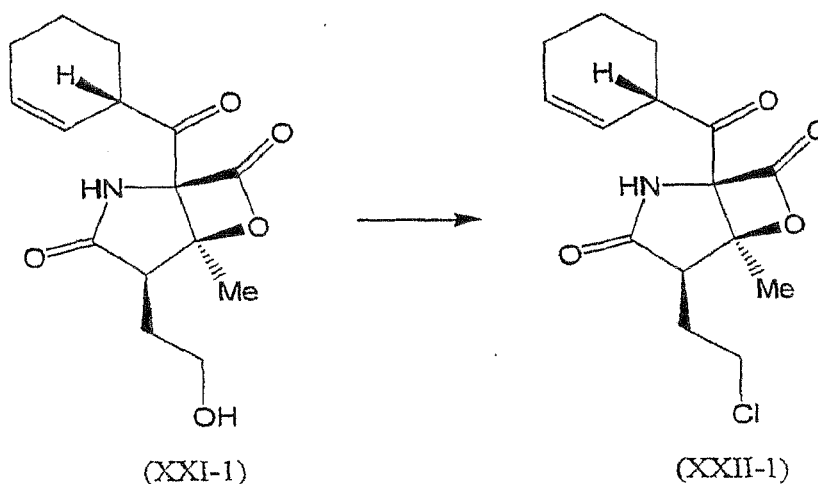


As shown in step (k₂) of Scheme 9-1, a compound of formula (XXI) can further be transformed by substituting the primary hydroxy of the compound of formula (XXI) to form a compound of formula (XXII). In some embodiments, R₃ and R₄ of a compound of formula (XXII) can be the same as described with respect to the compound of formula (XXI), and X can be a halogen.

Exemplary structures and stereochemistry of compounds of formula (XXI) and (XXII) are shown below:

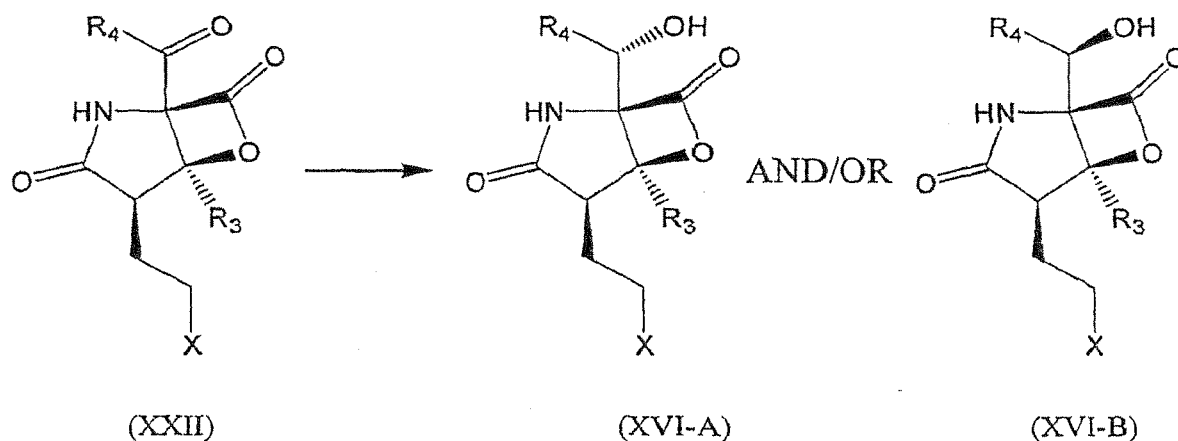


For example, compounds of formula (XXI) and (XXII) can have the following structures:

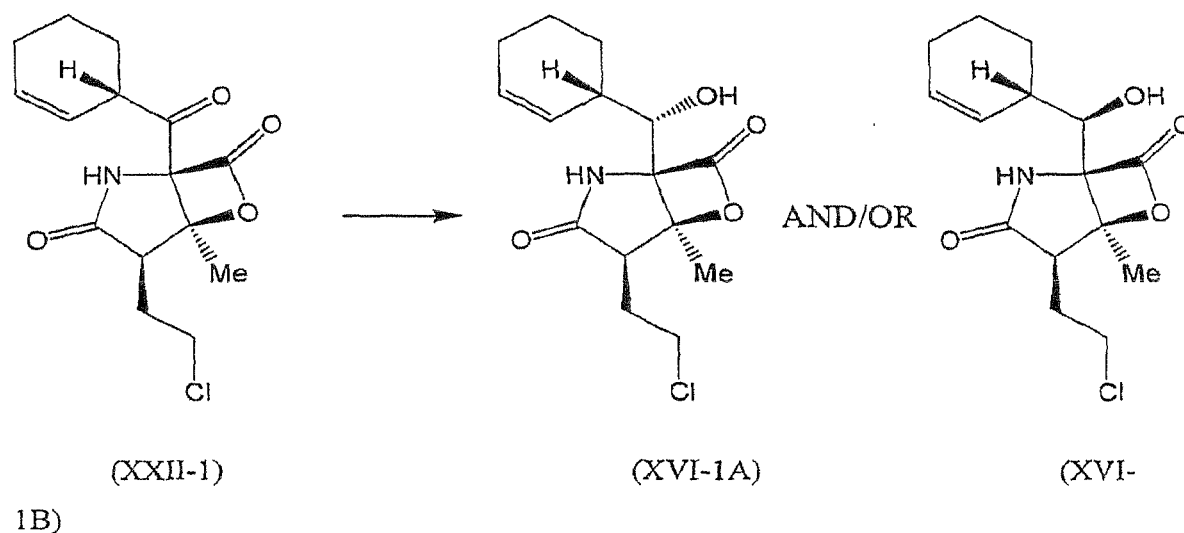


As shown step (I₂) of Scheme 9-1, the C-5 ketone group attached to the carbon adjacent to R₄ of a compound of formula (XXII) can be reduced to a secondary hydroxy group using a suitable reducing agent (e.g., sodium borohydride) or an enzyme to form a compound of formula (XVI). In one embodiment, the compound of formula (XXII) can be reduced to the compound of formula (XVI-A) and/or (XVI-B).

Examples of the structures and stereochemistry of compounds of formula (XXII) and (XVI) are shown below:



As another example, the compounds of formula (XXII) and (XVI) may have the following structures and stereochemistry:

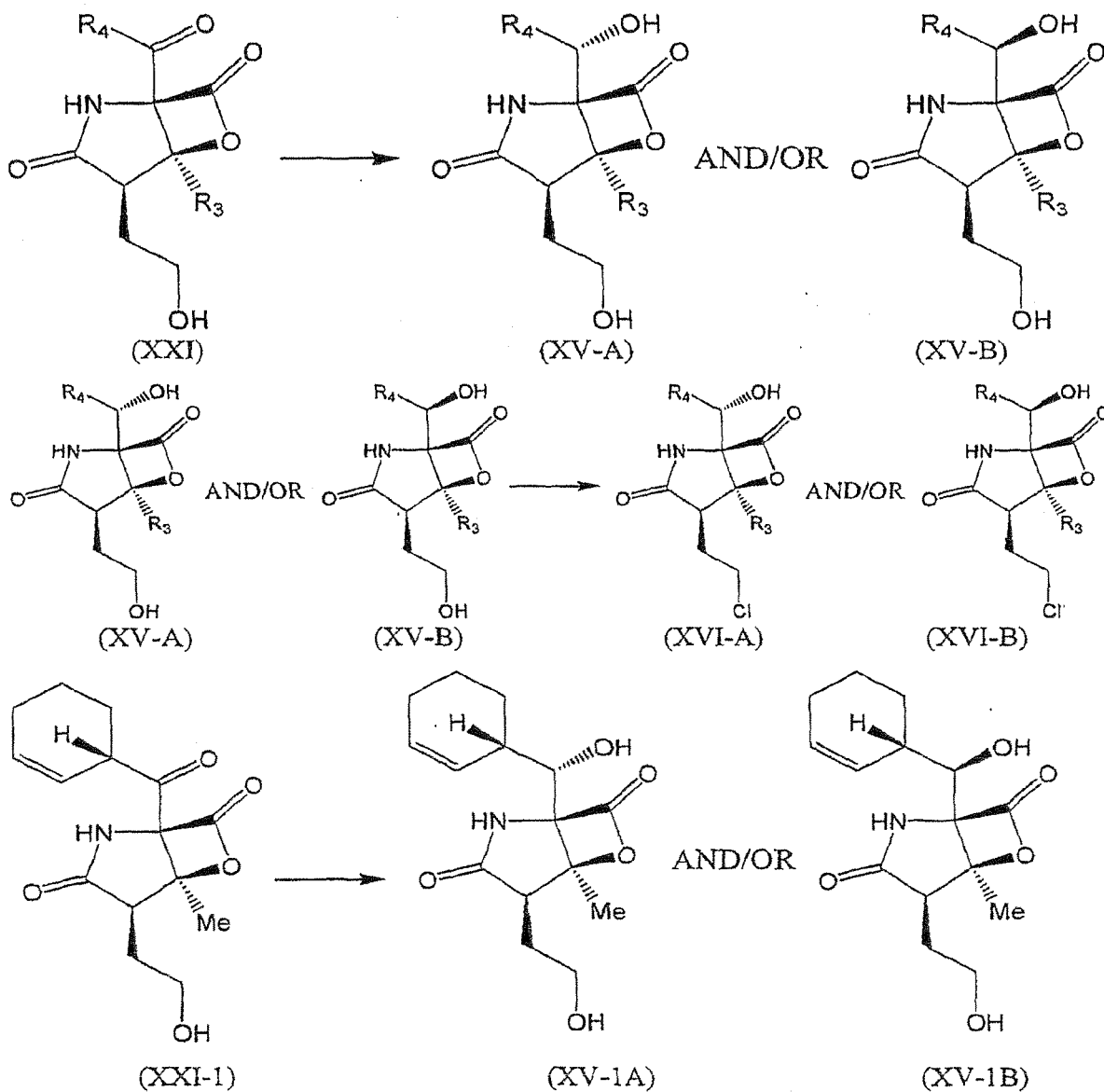


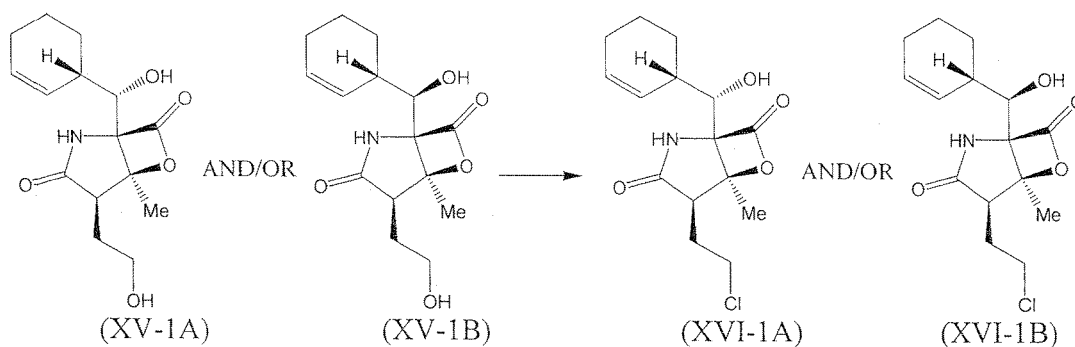
If desired, the stereochemistry of the secondary hydroxy of the compound of formula (XVI-B) can be inverted in a single step or a multistep process, as described herein.

A compound of formula (XXI) can also be used to synthesize a compound of formula (XV), as shown in Scheme 9-1. The C-5 keto group of the compound of formula (XXI) can be reduced using an appropriate reducing agent such as those described herein to form a compound of formula (XV). The C-13 primary hydroxy of the compound of formula (XV) can be used to obtain Salinosporamide A or analogs thereof following Schemes 7-6, 7-7, 7-8, 7-9, 7-10 and 7-11 described herein. The

stereochemistry of the secondary hydroxy of the compound of formula (XVI-B) can be inverted in a single step or a multistep process, such as those described.

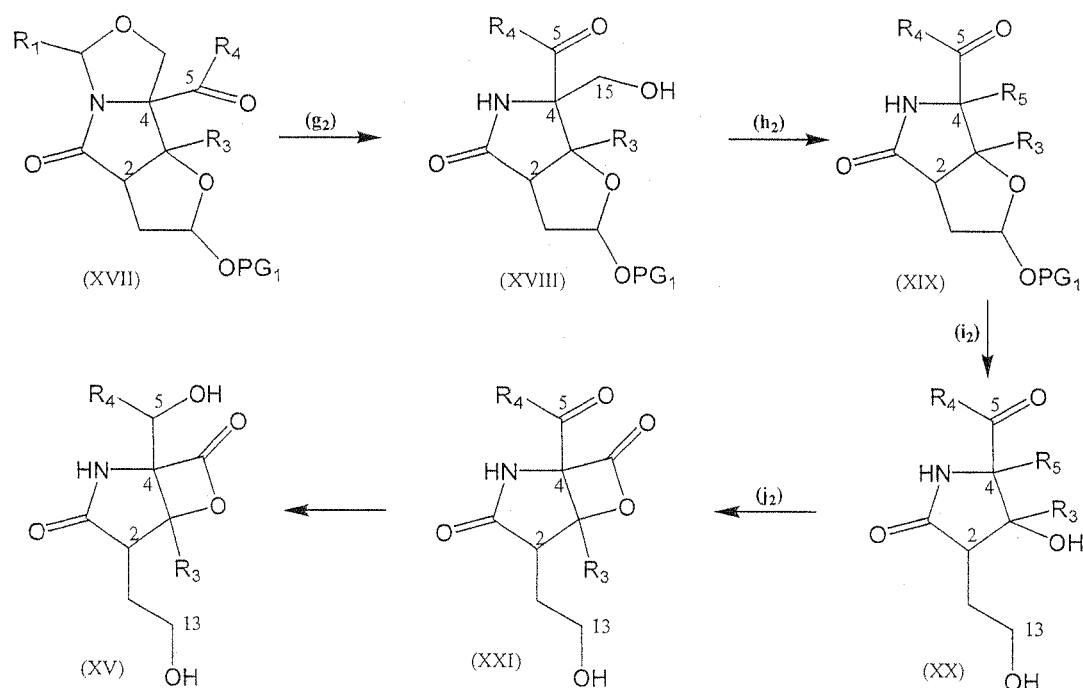
In certain embodiments, the compounds of formulae (XXI), (XV), and (XVI) can have the following structures and stereochemistry:





In some embodiments, compounds of formula (XV) can be synthesized via Scheme 9-2.

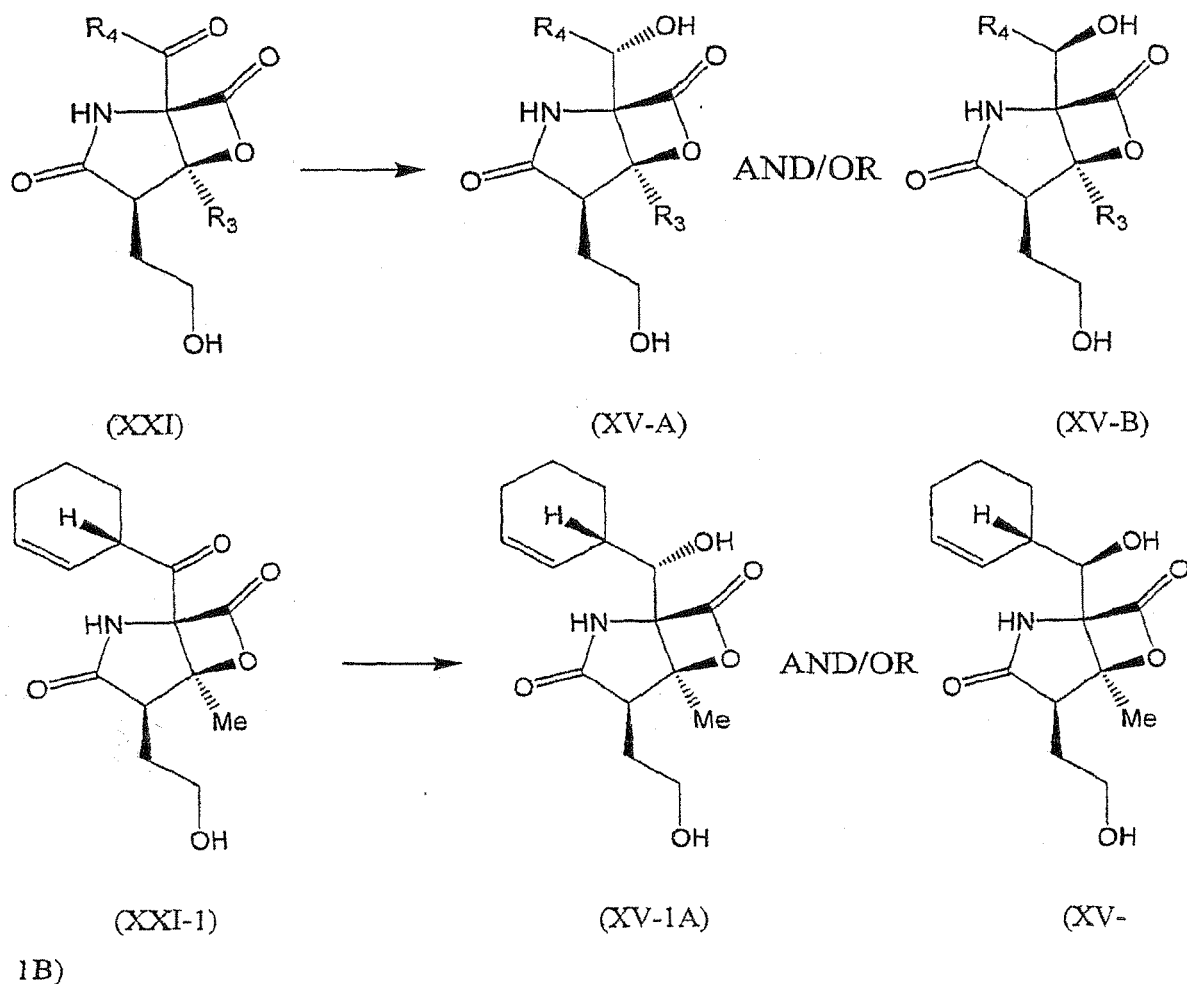
Scheme 9-2



A compound of formula (XXI) can be synthesized from a compound of formula (XVII) via steps (g₂), (h₂), (i₂) and (j₂) of Scheme 9-2 that are described above with respect to Scheme 9-1. The C-5 keto group of the compound of formula (XXI) can be reduced to a secondary hydroxy group using a suitable reducing agent (e.g., sodium borohydride) or an enzyme to form a heterocyclic compound of formula (XV), for example, compounds (XV-A) and/or (XV-B), wherein R₃, R₄, and X can be the same as described with respect to the compound of formula (XXII).

Exemplary structures and stereochemistry of the compounds (XXI) and (XV) are shown below:

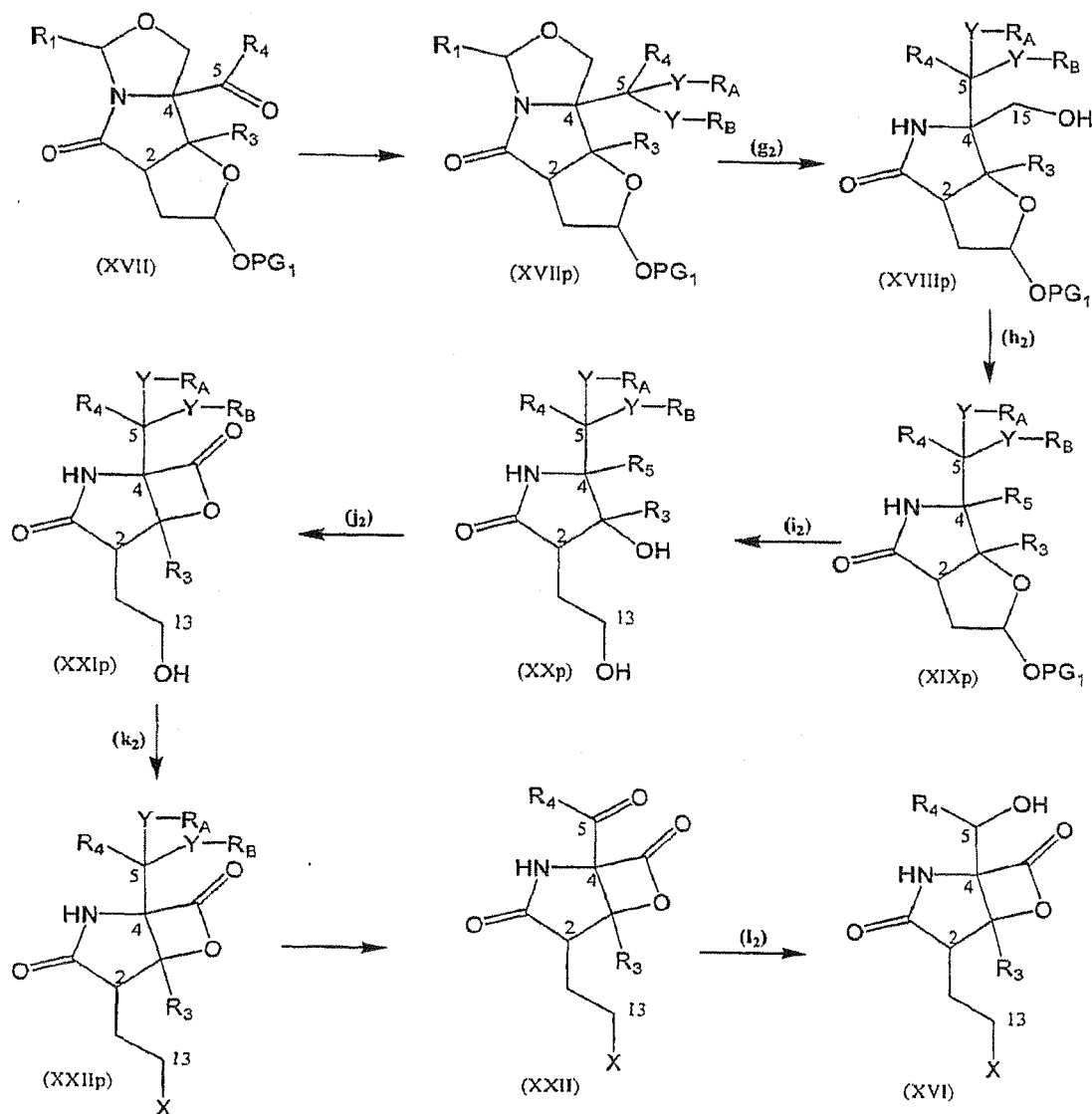
Exemplary structures and stereochemistry of the compounds (XXI) and (XV) are shown below:



The compound of formula (XV) can then be used to obtain Salinosporamide A or analogs thereof following Schemes 7-6, 7-7, 7-8, 7-9, 7-10 and 7-11 described herein.

Another method for obtaining Salinosporamide A and analogs thereof from a compound of formula (XVII) is shown in Scheme 9-3.

Scheme 9-3



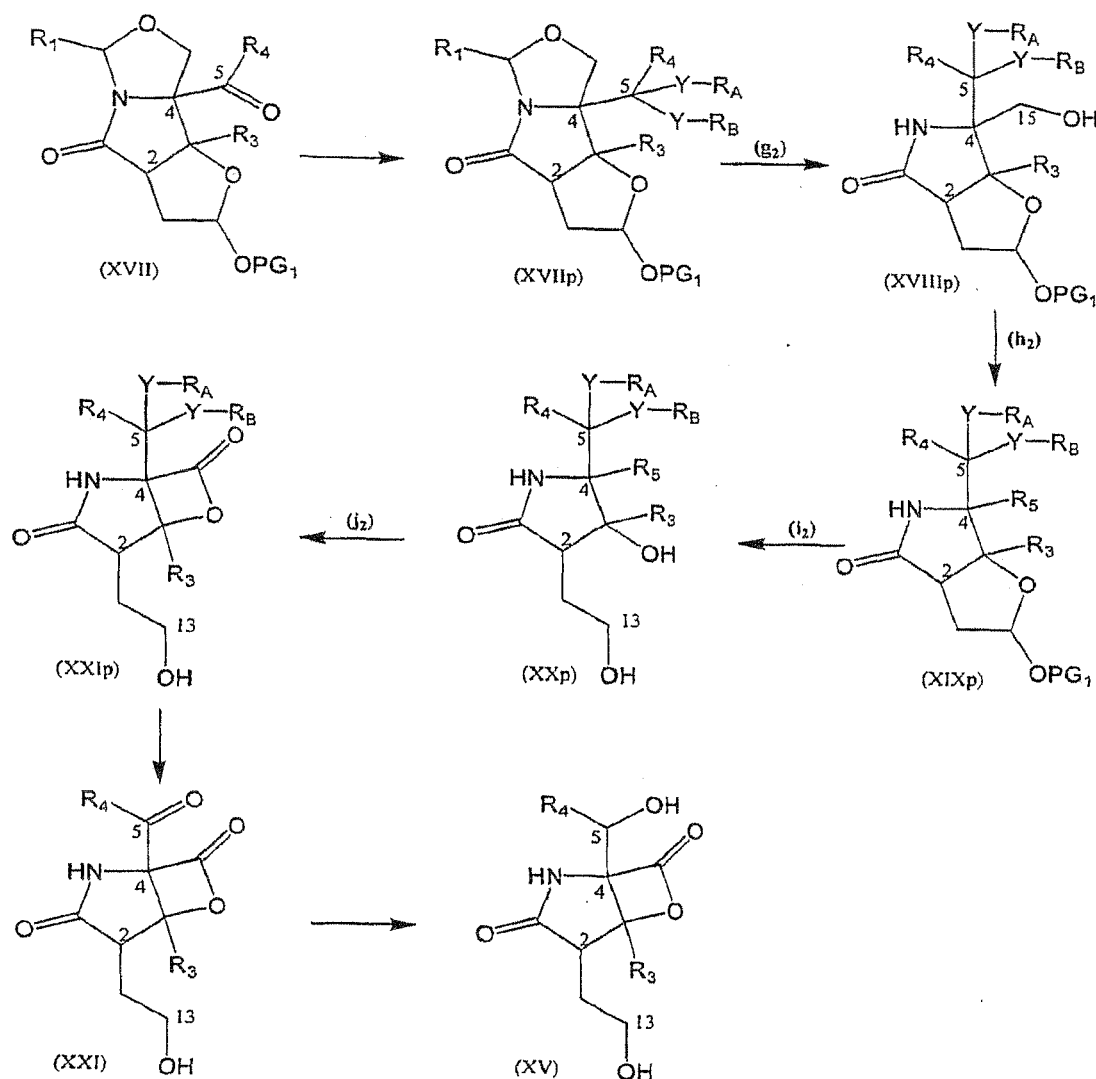
Preceding the cleavage of the aminal, the ketone group of a compound of formula (XVII) can be protected using a suitable protecting group moiety/moieties to form a compound of formula (XVIIp). In some embodiments, R₁, R₃, R₄, and PG₁ can be the same as described with respect to the compound of formula (XVII), each Y can be an oxygen or sulfur, and R_A and R_B can be each independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl, wherein R_A and R_B can be optionally bound together to form an optionally substituted 5, 6, 7, or 8 membered heterocyclyl.

As shown in Scheme 9-3, a compound of formula (XVIIp) can be transformed to a compound of formula (XXIIp) following the methods as described with respect to steps (g₂), (h₂), (i₂), (j₂), and (k₂) of Scheme 9-1. As shown in Scheme 9-3, the protecting group moiety/moieties, Y-R_A and Y-R_B, can be removed from a compound of formula (XXIIp) using a suitable method to obtain a compound of formula (XXII). For each step, the substituents of the ketone protected compounds can be selected from the same groups as those described with respect to the corresponding unprotected compounds. For example, R₃, R₄, PG₁ and R₅ of a compound of formula (XIXp) can be selected from the same groups as a compound of formula (XIX). In some embodiments, the compounds of formula (XVIIp), (XVIIIp), (XIXp), (XXp), (XXIp) and (XXIIp), can have the same structures and/or stereochemistry as the corresponding non-protected compounds of Scheme 9-1 except that the keto carbonyl group is protected with a suitable protecting group(s).

Finally, the ketone group attached to the carbon adjacent to R₄ of a compound of formula (XXII) can be reduced to a hydroxy group using a suitable reducing agent (e.g., sodium borohydride) or an enzyme to form a compound of formula (XVI), including (XVI-A) and/or (XVI-B), wherein R₃, R₄, and X can be the same as described with respect to the compound of formula (XXII).

In an embodiment, compounds of formula (XV) can be synthesized from a compound of formula (XVII) is shown in Scheme 9-4.

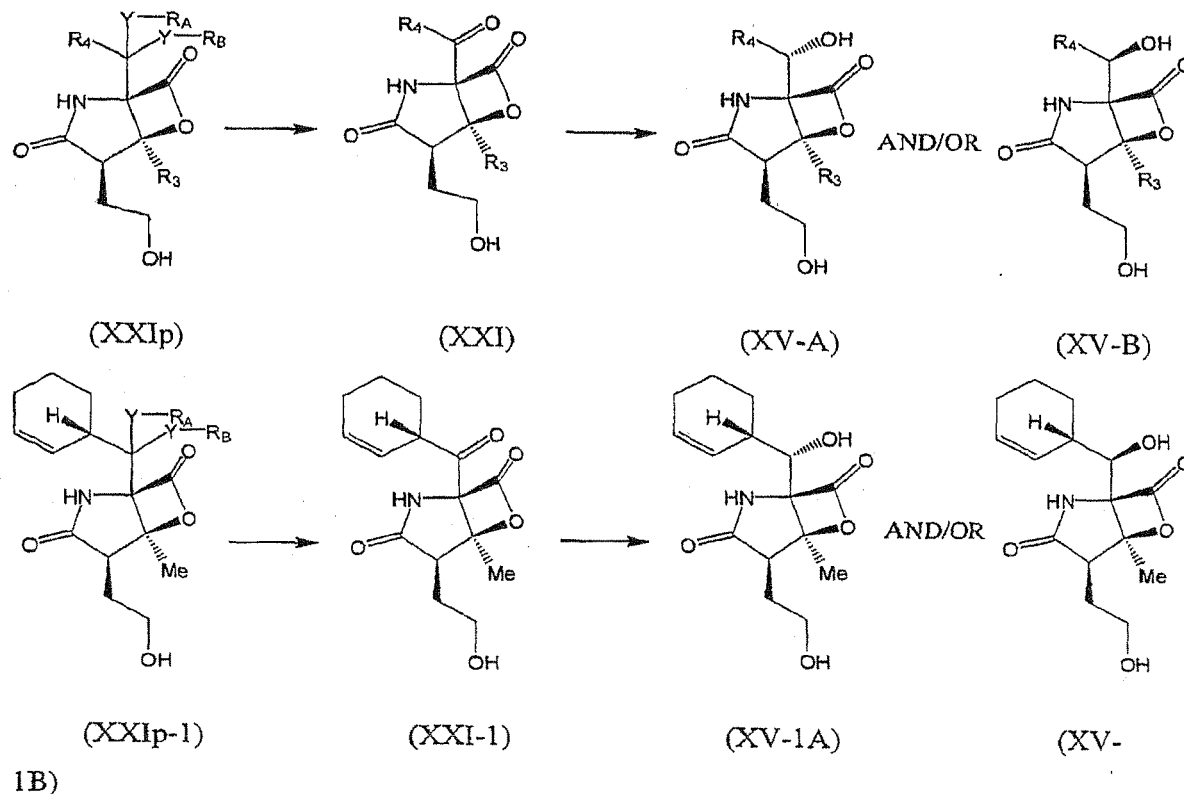
Scheme 9-4



A compound of formula (XXIp) can be synthesized from a compound of formula (XVII) via steps (g₂), (h₂), (i₂) and (j₂) of Scheme 9-4 that are described above with respect to Scheme 9-1. The protecting group moiety/moieties, Y-R_A and Y-R_B, can be removed from a compound of formula (XXIp) using a suitable method to obtain a compound of formula (XXI). In an embodiment, R₃ and R₄ can be the same as described with respect to the compound of formula (XVII). The C-5 keto group of the compound of formula (XXI) can be reduced to a secondary hydroxy group using a suitable reducing agent (e.g., sodium borohydride) or an enzyme to form a compound of formula (XV), including (XV-A) and/or (XV-B), wherein R₃ and R₄ can be the same as described with respect to the compound of formula (XXII). The compound of formula (XV) can then be

used to obtain Salinosporamide A or analogs thereof following Schemes 7-6, 7-7, 7-8, 7-9, 7-10, and 7-11 described herein.

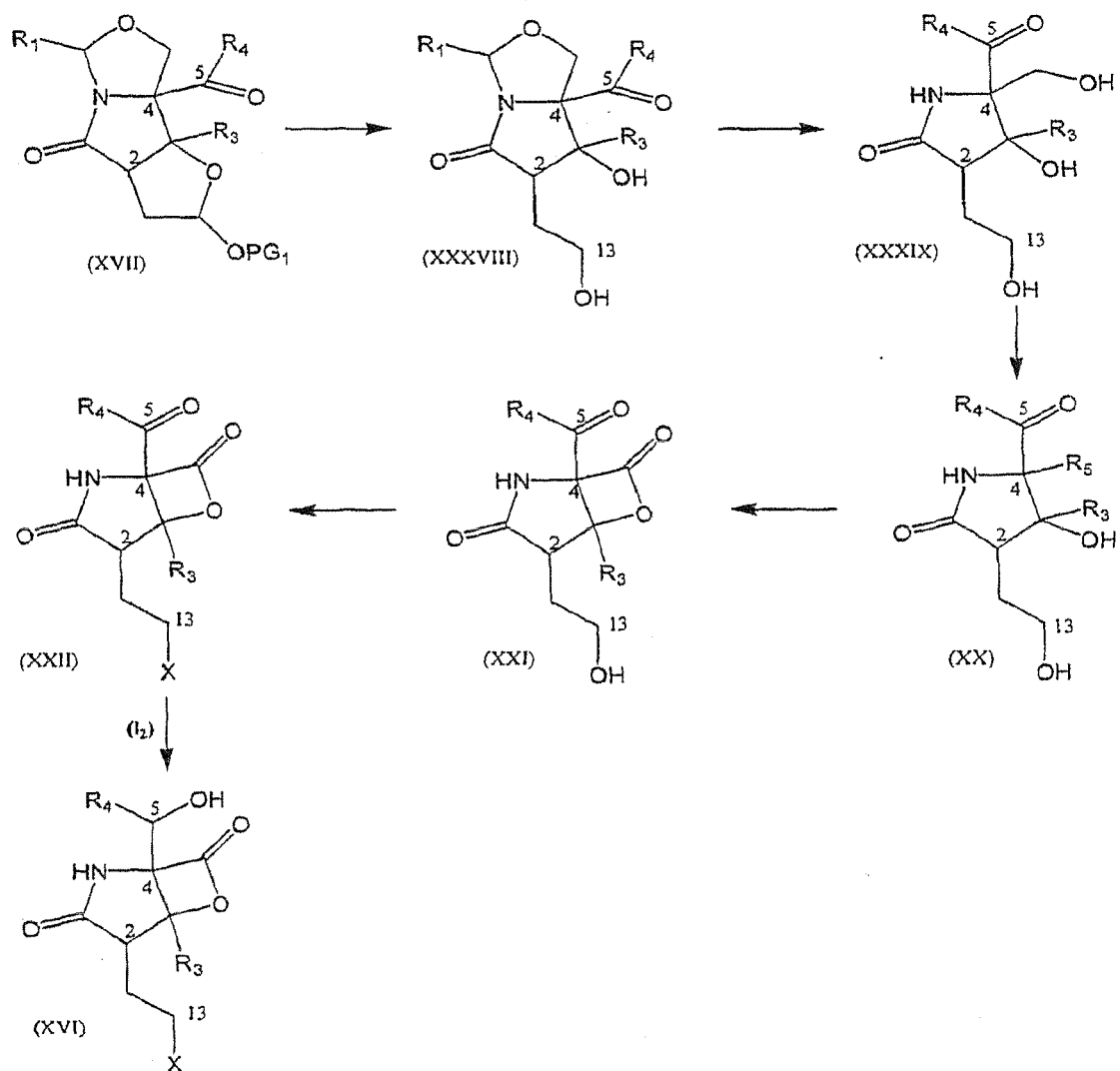
In certain embodiments, the compounds of formulae (XXIp), (XXI), and (XV) can have the following structures and stereochemistry:



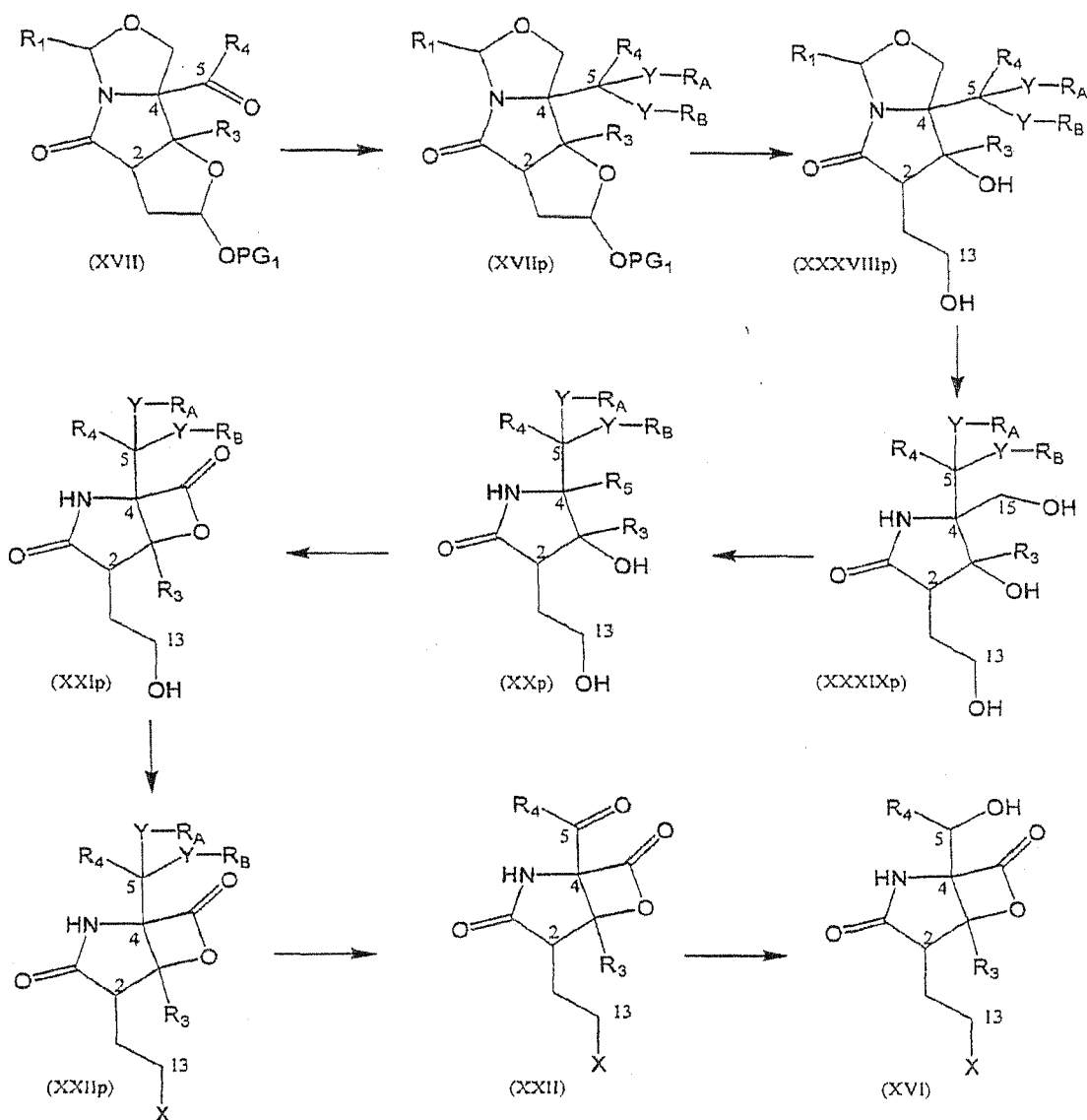
Additional methods for synthesizing Salinosporamide A and analogs thereof are shown below in Schemes 9-5 and 9-6. The PG₁ of the compound of formula (XVII) or (XVIIp) can be removed and the resulting hemiacetal can be reductively opened as described above to form compounds of formulae (XXXVIII) and (XXXVIIIp), respectively. The amination of the compounds of formulae (XXXVIII) and (XXXVIIIp) can be cleaved as described herein to form compounds of formula (XXXIX) and (XXXIXp), respectively. The C-15 primary alcohol group of the compounds of formula (XXXIX) and (XXXIXp) can be converted to R₅ using the methods described herein, wherein R₅ which can be selected from the group consisting of -C(=O)OR₆, -C(=O)SR₆, -C(=O)NR₆R₆ and -C(=O)Z, each R₆ can be independently selected from the group consisting of hydrogen, halogen, or substituted or unsubstituted variants of the following: each R₆ can be independently selected from the group consisting of hydrogen, halogen, or substituted or unsubstituted variants of the following: C₁-C₂₄ alkyl, acyl, alkylacyl, arylacyl, aryl,

arylalkyl, p-nitrophenyl, pentafluorophenyl, pentafluoroethyl, trifluoroethyl, trichloroethyl, and heteroaryl; and Z can be a halogen. After the transformation of R₅, a compound of formula (XVI) can be formed as described above with respect to Schemes 9-1 and 9-3. If desired, the C-13 primary hydroxy group can be protected during the oxidation of C-15 hydroxy group of compounds of formulae (XXXIX) and (XXXIXp) and then removed if desired.

Scheme 9-5



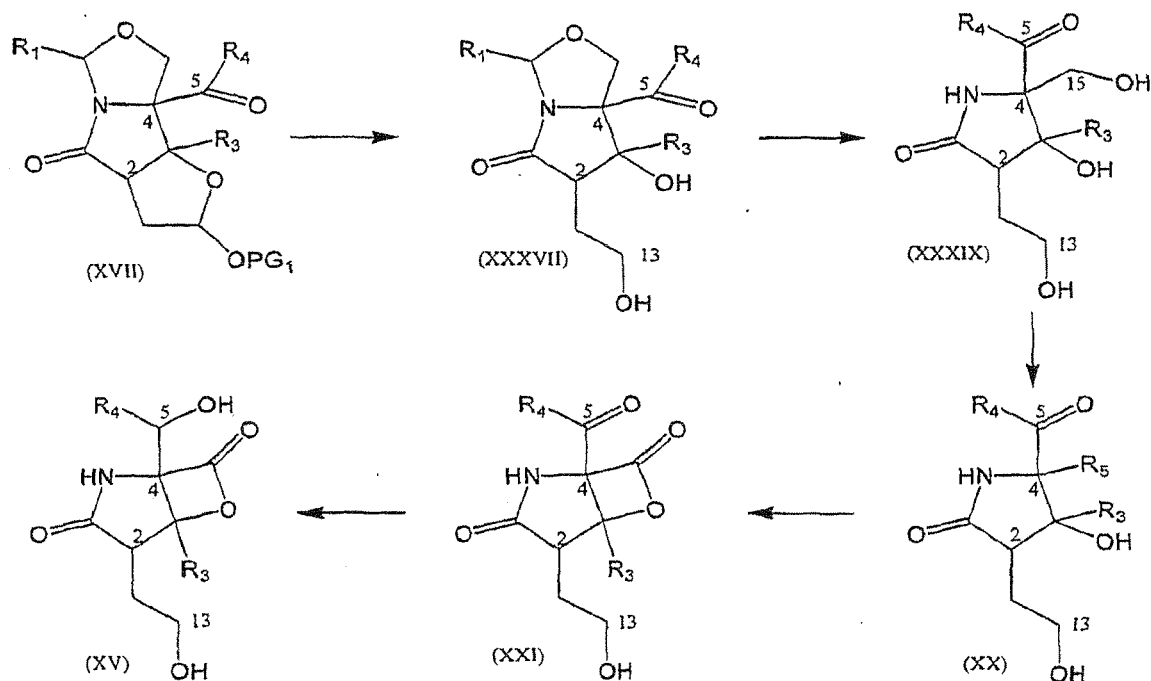
Scheme 9-6



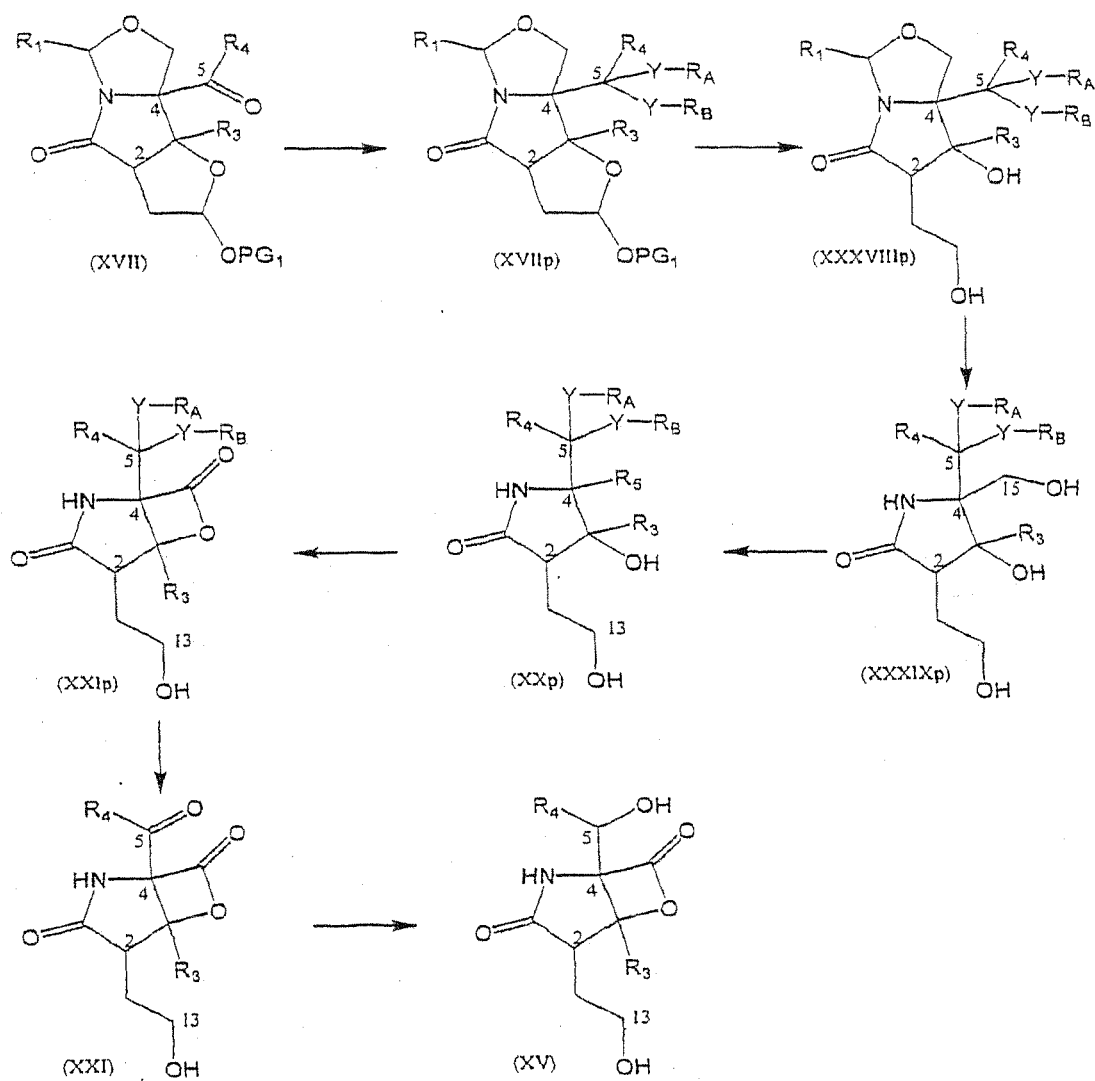
Additional methods of synthesizing compounds of formula (XV) are shown in Schemes 9-7 and 9-8. The PG₁ of the compound of formula (XVII) or (XVIIp) can be removed and the resulting hemiacetal can be reductively opened as described above to form compounds of formulae (XXXVIII) and (XXXVIIIp), respectively. The aminal of the compounds of formulae (XXXVIII) and (XXXVIIIp) can be cleaved as described herein to form compounds of formula (XXXIX) and (XXXIXp), respectively. The C-15 primary alcohol group of the compounds of formula (XXXIX) and (XXXIXp) can be converted to R₅ using the methods described herein, wherein R₅ which can be

selected from the group consisting of $-\text{C}(=\text{O})\text{OR}_6$, $-\text{C}(=\text{O})\text{SR}_6$, $-\text{C}(=\text{O})\text{NR}_6\text{R}_6$, $-\text{C}(=\text{O})\text{Z}$; each R_6 can be independently selected from the group consisting of hydrogen, halogen, or substituted or unsubstituted variants of the following: $\text{C}_1\text{-C}_{24}$ alkyl, acyl, alkylacyl, arylacyl, aryl, arylalkyl, p-nitrophenyl, pentafluorophenyl, pentafluoroethyl, trifluoroethyl, trichloroethyl, and heteroaryl, and Z can be a halogen. After the transformation of R_5 , a compound of formula (XVI) can be formed as described above with respect to Schemes 9-1, 9-2, 9-3, and 9-4. A compound of formula (XV) obtained via the methods of Schemes 9-7 and/or 9-8 can then be used to synthesize Salinosporamide A or analogs thereof following Schemes 7-6, 7-7, 7-8, 7-9, 7-10, and 7-11 as described herein.

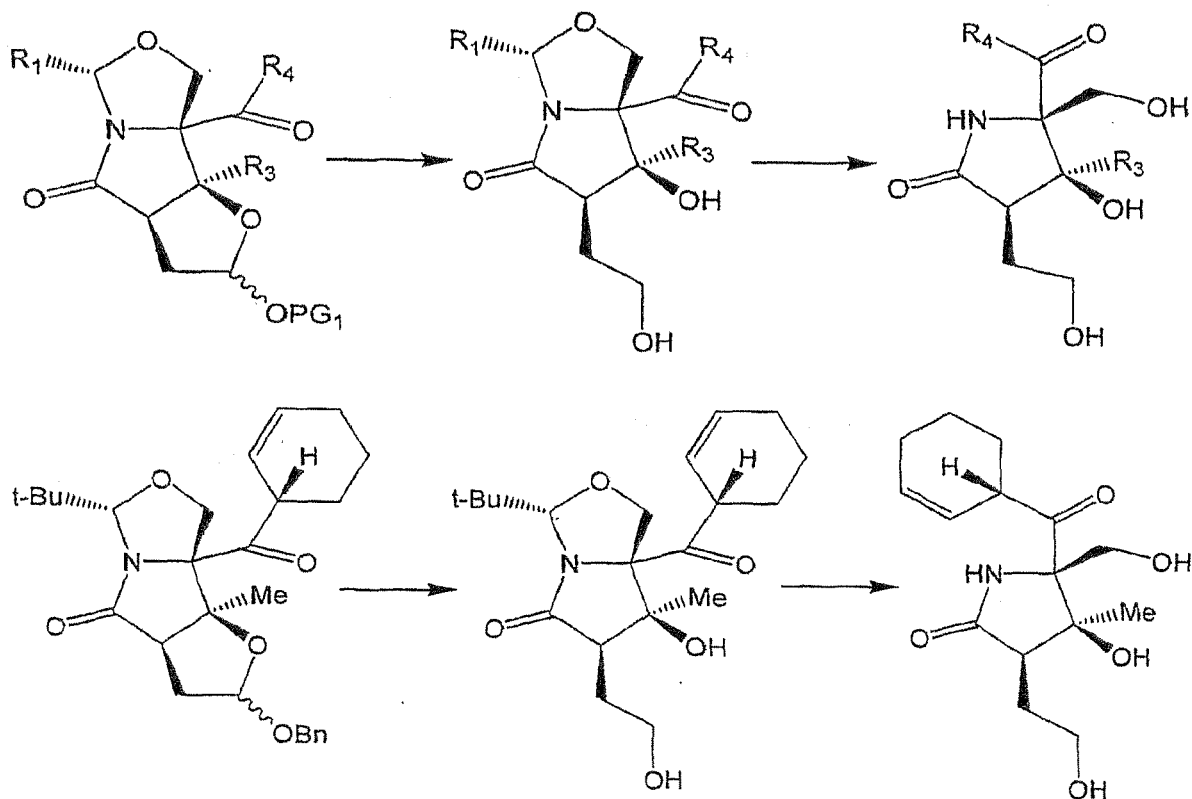
Scheme 9-7



Scheme 9-8

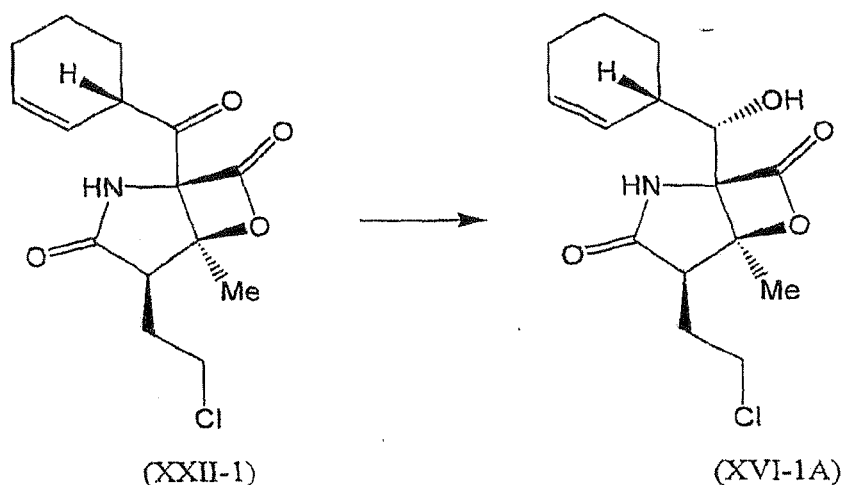


Examples of the structures and stereochemistry of the compounds of formulae (XXXVIII) and (XXXIX) (XXXIXp) are shown below:



In some embodiments, the compounds of formula (XXXVIIIp) and (XXXIXp) can have the same structures and/or stereochemistry as the corresponding non-protected compounds of formulae (XXXVIII) and (XXXIX) except that the keto carbonyl group is protected with a suitable protecting group(s).

In one embodiment, Salinosporamide A (compound XVI-1A) can be obtained from a compound of formula (XXII), wherein R₄ is 2-cyclohexenyl, R₃ is methyl and X is chlorine.



In another embodiment, the compound of formula (XXII-1) can be converted to a compound of formula (XVI-B). If desired, the stereochemistry of the C-5 secondary hydroxy of the compound of formula (XVI-B) can be inverted in a single step or a multistep process to give a compound of formula (XVI-A), as previously described herein.

Salinosporamide A or analogs thereof can also be obtained from the compound of formula (XXI) and/or (XXIp). In an embodiment, the C-13 primary hydroxy of the compounds of formulae (XXI) and (XXIp) can be modified following the procedures shown in Schemes 7-6, 7-7, 7-8, 7-9, 7-10, and 7-11 described herein. Reduction of the C-5 keto group to a hydroxy group using an appropriate reducing agent (e.g., sodium borohydride) to produce Salinosporamide A or analogs thereof can take place at any step shown in Schemes 7-6, 7-7, 7-8, 7-9, 7-10, and 7-11.

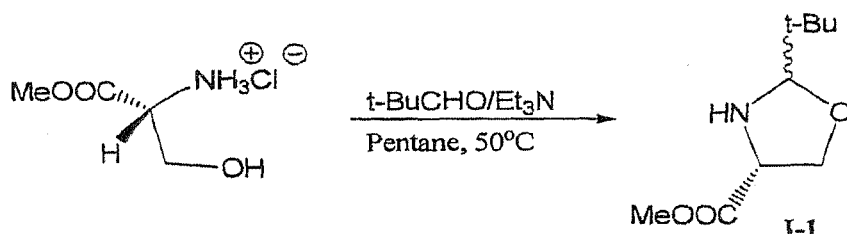
The stereochemistry of the C-5 secondary hydroxy can be inverted at any time using one of the methods described herein or one known to those skilled in the art. For example, the stereochemistry of the C-5 secondary hydroxy can be inverted in the compound of formula (XV). In an embodiment, the stereochemistry of the C-5 secondary hydroxy can be inverted in a one step process as described herein (e.g., by a Mitsunobu transformation). The inversion can also take place in multistep process. In an embodiment, the C-5 secondary hydroxy group can be oxidized using an appropriate oxidizing agent (e.g., Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, or PDC) to a keto group and then reduced to a hydroxy group using a suitable reducing agent such as sodium borohydride. In another embodiment, the keto group can be reduced via selective enzymatic transformation. In certain embodiments, the reducing enzyme is a ketoreductase such as KRED-EXP-C1A and/or KRED-EXP-B1Y.

In some embodiments, R_4 cannot be 2-cyclohexenyl in any of the compounds and methods described herein. In other embodiments, R_4 is 2-cyclohexenyl in any of the compounds and methods described herein. In some embodiments, R_4 cannot be isopropyl in any of the compounds and methods described herein. In other embodiments, R_4 is isopropyl in any of the compounds and methods described herein.

EXAMPLES

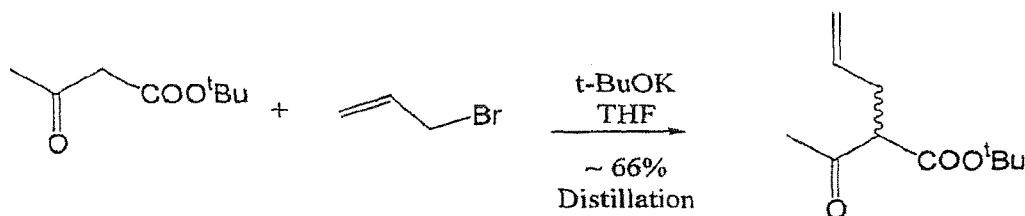
Commercially available compounds were obtained from Sigma-Aldrich and were used without purification unless stated. ^1H NMR, ^{13}C NMR, and ^1H - ^1H COSY spectra were recorded at 500 MHz on a Bruker spectrometer and chemical shifts are given in δ -values [ppm] referenced to the residual solvent peak chloroform (CDCl_3) at 7.24 and 77.00, respectively. The LC-MS data were obtained from an Agilent HP1100 HPLC equipped with an Agilent PDA detector (the mobile phase was a mixture of CH_3CN and H_2O) and MSD system. The optical rotations were obtained from Autopol-III automatic polarimeter and the melting point was from Mel-Temp apparatus.

EXAMPLE 1 SYNTHESIS OF (I-1)



To a suspension of D-serine methylester hydrochloride (25 g, 160.67 mmol) in pentane (800 mL) at room temperature were added t-butyl aldehyde (20.73 g, 241 mmol) and Et_3N (17.85 g, 176.74 mmol). The reaction mixture was refluxed for 15 hrs at 50°C using Dean-Stark apparatus. The resulting reaction mixture was cooled to room temperature, filtered through celite, and the celite cake was washed with pentane (2 x 40 mL). The combined filtrate was concentrated under reduced pressure and dried under high vacuum to afford product, I-1 (24.5 g, 131 mmol, 81.5% yield) as clear oil, which can be used without further purification. The compound I-1 was characterized by ^1H -NMR (CDCl_3 , 500 MHz). See Figure 2.

EXAMPLE 2
SYNTHESIS OF THE ESTER PRECURSOR OF COMPOUND (II-1)



Method A

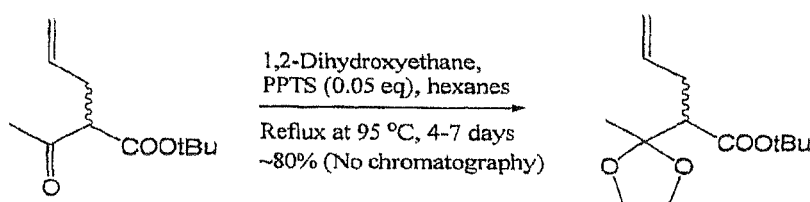
To a solution of t-butylacetoacetate (30 g, 0.19 mol) in dry THF (800 mL) at 0 °C was added t-BuOK (23.41 g, 95% w/w, 0.21 mol) and the solution was stirred for about 15 minutes. Allylbromide (18.39 g, 0.152 mol) was added and the solution was stirred at 0 °C for additional 15 min. The reaction mixture was then allowed to warm to room temperature and stirred for about 5 hours under an atmosphere of N₂. The above reaction mixture was then cooled to 0 °C, quenched with H₂O (300 mL), and extracted with EtOAc (3 x 200 mL). The combined organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (5 cm ID x 45 cm) using a solvent gradient of 100% hexanes (1.5 L) to 1.5% EtOAc/hexanes (3 L) to 2.5% EtOAc/hexanes (1 L) to 4% EtOAc/hexanes (700 mL) to afford pure product (14.5g, 0.073 mol, 38.5% yield). Alternatively, The crude product was purified by fractional distillation (130 °C oil bath, 90-95 °C bp) under high vacuum (12 mm Hg) to afford product, the ester precursor of the compound (II-1) (66% yield).

Method B

To a solution of t-BuOK (50g, 95% w/w, 0.42 mol) in dry THF (1.5 L) at 0 °C was added t-butylacetoacetate (65 g, 0.41 mol) and the solution was stirred for about 15 minutes under an atmosphere of N₂. Allylbromide (47g, 0.39mol) was added slowly and the solution was stirred at 0 °C for about 20 hours. The reaction mixture was allowed to warm to room temperature and stirred for additional 15 hours. The reaction mixture was then quenched with H₂O (1L) at 0 °C and extracted with EtOAc (3 x 0.5 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by fractional distillation (130 °C oil bath, 90-95 °C bp)

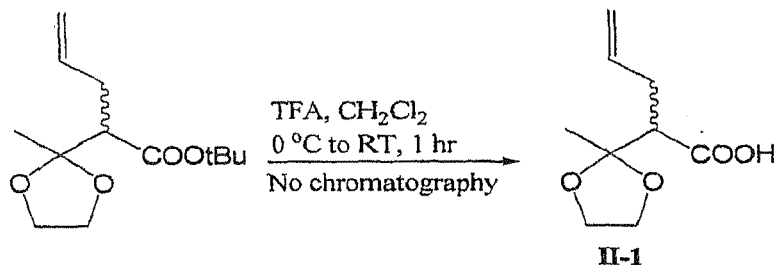
under high vacuum (12 mm Hg) to afford the product, the ester precursor of the compound (II-1) (54 g, 0.27mol, 66% yield). $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) (δ): 5.68 (m, 1H), 5.03 (br dd, $J=1$, 17 Hz, 1H), 4.97 (br dd, $J=1$, 10 Hz, 1H), 3.35 (t, $J=7.5$ 1H), 2.48 (br t, $J=7.0$, 2H), 2.16 (s, 3H), 1.39 (s, 9H). See Figure 3.

EXAMPLE 3
SYNTHESIS OF THE PROTECTED ESTER PRECURSOR OF COMPOUND (II-1)



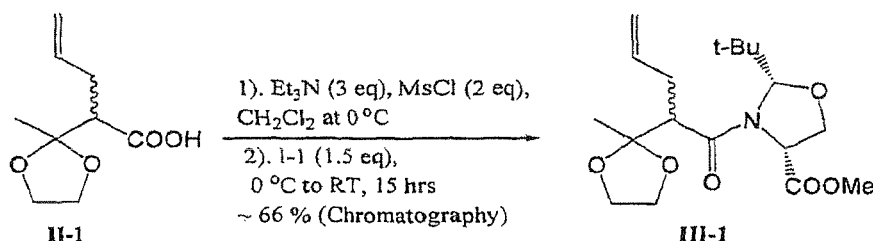
To a solution of the ester precursor (45 g, 0.23 mol) in hexanes (1.6 L) were added ethylene glycol (70.5 g, 1.15 mol) and PPTS (2.85 g, 0.011 mol). The reaction mixture was refluxed at 95 °C using Dean-Stark apparatus for 6 days (Note: 28.5 g, 0.46 mol of ethylene glycol was added to the reaction mixture every two days to maintain its concentration), then cooled to room temperature. The reaction mixture was then neutralized with 800 μL of Et_3N and diluted with H_2O (500 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford product, the protected ester precursor of the compound (II-1) (44 g, 0.18 mmol, 80% yield), which can be used for the next step without purification. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) (δ): 5.72 (m, 1H), 5.06 (dd, $J=1$, 17 Hz, 1H), 4.97 (d, $J=10$ Hz, 1H), 3.94 (m, 4H), 2.60 (dd, $J=3.6$, 11.5 Hz, 1H), 2.43 (m, 1H), 2.29 (m, 1H), 1.42 (s, 9H), 1.38 (s, 3H). See Figure 4.

EXAMPLE 4
SYNTHESIS OF COMPOUND (II-1)



To a solution of the ester with protecting group moieties precursor (28g, 0.115 mol) in CH_2Cl_2 (28 mL) at 0 °C was added trifluoroacetic acid (TFA neat, 56 mL, 0.727 mol) and the solution was stirred for about 5 min. The reaction mixture was then allowed to warm to room temperature and stirred for one hour. The reaction mixture was diluted with CH_2Cl_2 (400 mL) and extracted with ice cold water (3 x 300 mL). The organic layer was dried over Na_2SO_4 , concentrated under reduced pressure and dried under high-vacuum for about one hour (to remove the residual TFA) to afford the product, compound **II-1** (15.5g, 0.083 mol, 72% yield) as light yellow oil, which can be used for the next step without purification. The compound **II-1** was characterized by ^1H -NMR (CDCl_3 , 500 MHz): ^1H -NMR (CDCl_3 , 500 MHz) (δ): 5.77 (m, 1H), 5.10 (br dd, $J=1, 17$ Hz, 1H), 5.02 (br d, $J=10$ Hz, 1H), 4.00 (m, 4H), 2.76 (dd, $J=3.8, 11.0$ Hz, 1H), 2.43 (m, 2H), 1.41 (s, 3H). See Figure 5.

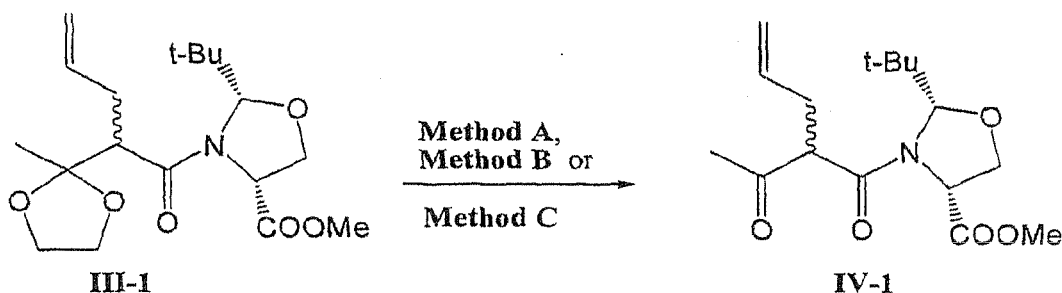
EXAMPLE 5
SYNTHESIS OF COMPOUND (III-1)



To a solution of compound **II-1** (4.8g, 25.81 mmol) in dry CH_2Cl_2 (200 mL) at 0 °C were added Et_3N (7.82g, 77.42 mmol) and methanesulfonyl chloride (5.89g, 51.62 mmol) and the solution was stirred for about 10 min. Then compound **I-1**

(5.31g, 28.4 mmol) was added, the reaction mixture was allowed to warm to room temperature slowly and stirred for about 15 hrs. Then the reaction mixture was quenched with H₂O (200 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to yield a mixture of two diastereomers (3:2). See Figure 6b. The crude product was purified by silica flash chromatography (3 cm ID x 30 cm) using a solvent gradient of 19:1 (500 mL) to 9:1 (500 mL) to 17:3 (500 mL) to 4:1 (1.5 L) to 3:1 (1 L) hexane/EtOAc to afford the product, compound **III-1** (6g, 16.9 mmol, 65.5% yield). The compound **III-1** was characterized by ¹H-NMR (CDCl₃, 500 MHz). See Figure 6. MS (ESI) m/z 356 [M+H].

EXAMPLE 6
SYNTHESIS OF COMPOUND (IV-1)



Method A: To a solution of compound **III-1** (6 g, 16.9 mmol) in CH₃CN (350 mL) were added sodium iodide (3.3 g, 21.97 mmol) and cerium (III) chloride heptahydrate (9.45 g, 25.35 mmol) and the reaction mixture was stirred at 60-65°C for 4 hours (the reaction progress can be monitored by LC-MS). The above reaction mixture was then quenched with water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layer (cloudy) was concentrated under reduced pressure to remove all of the CH₃CN/EtOAc, leaving about 20 mL of H₂O (CH₃CN soluble part), which was further extracted with EtOAc (100 mL). The organic layer was dried over Na₂SO₄, and concentrated under reduced pressure to afford the product, **IV-1** (4.4 g, 14.2 mmol, 83.5% yield) as a mixture of two diastereomers (3:2). See Figure 7e. If desired, the product can be used for the next step without purification. The compound **IV-1** was characterized by ¹H-NMR (CDCl₃, 500 MHz) and NOESY (CDCl₃, 500 MHz). See Figures 7a and 7b. MS (ESI) m/z 312 [M+H]. A portion of the product was further purified by reverse phase HPLC using C-18 column (150 mm x 21 mm), and an isocratic solvent system of 40% acetonitrile in H₂O at a flowrate of 14.5 mL/min to afford individual diastereomers **IV-1A**

and IV-1B as pure samples. The diastereomers IV-1A and IV-1B were characterized by ¹H-NMR (CDCl₃, 500 MHz). See Figures 7c and 7d.

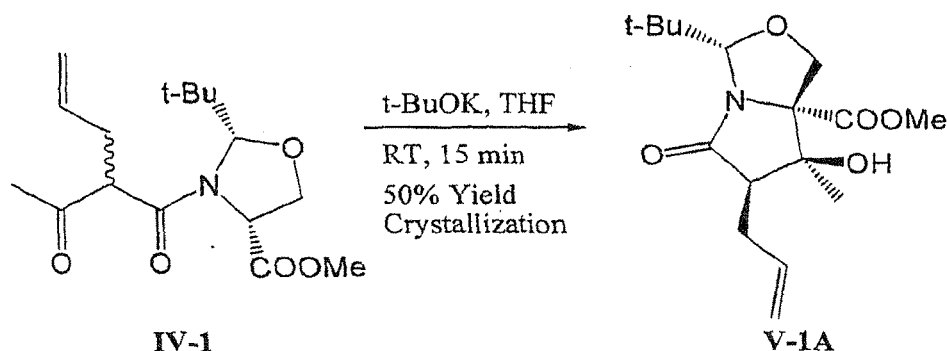
Compound IV-1A: ¹H-NMR (CDCl₃, 500 MHz) (δ): 5.73 (m, 1H), 5.34 (s, 1H), 5.12 (m, 1H), 5.05 (d, *J* = 10.1 Hz, 1H), 4.64 (d, *J* = 6.3 Hz, 1H), 4.53 (d, *J* = 8.2 Hz, 1H), 3.90 (t, *J* = 7.6 Hz, 1H), 3.80, (s, 3H), 3.67 (t, *J* = 7.6 Hz, 1H), 2.60 (m, 2H), 2.27 (s, 3H), 0.91 (s, 9H); MS (ESI) *m/z* 312 [M+H]⁺.

Compound IV-1B: ¹H-NMR (CDCl₃, 500 MHz) (δ): 5.76 (m, 1H), 5.28 (s, 1H), 5.18 (br d, *J* = 17.3 Hz 1H), 5.08 (d, *J* = 10.1 Hz, 1H), 4.88 (m, 1H), 4.52 (d, *J* = 8.2 Hz, 1H), 3.88 (m, 1H), 3.81, (m, 1H), 3.76 (s, 3H), 2.88 (m, 1H), 2.63 (m, 1H), 2.21 (s, 3H), 0.86 (s, 9H); MS (ESI) *m/z* 312 [M+H]⁺.

Method B: A mixture of compound III-1 (175 mg, 0.493 mmol) and iodine (12.52 mg, 0.0493 mmol) in acetone (20 mL) was refluxed at 56 °C for one hour. The reaction mixture was then cooled to RT, the acetone was removed under reduced pressure, and the crude reaction product was dissolved in CH₂Cl₂ (20 mL). The CH₂Cl₂ solution was washed successively with 5% aqueous sodium thiosulfate (10 mL), H₂O (10 mL) and brine (10 mL). The resulting organic phase was dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel plug column (2.5 cm ID x 6 cm) using a solvent gradient of 19:1(50 mL) to 9:1 (100 mL) to 4:1 (100 mL) to 3:1 (100 mL) to 7:3 (100 mL) hexanes/EtOAc to afford the product, compound IV-1 (97 mg, 0.312 mmol, 63.3% yield).

Method C: A mixture of compound III-1 (500 mg, 1.40 mmol) and LiBF₄ (200 mg, 2.1 mmol) in CH₃CN (6 mL, wet with 2% H₂O) was stirred at 70 °C for 1.5 to 2 hrs (the reaction progress can be monitored by LC-MS). The above reaction mixture was then quickly cooled to 0 °C, filtered through a short silica plug and concentrated under reduced pressure. The product was purified by silica gel column chromatography (1.25 cm ID x 5 cm) using a solvent gradient of 19:1 (50 mL) to 9:1 (50 mL) to 4:1 (50 mL) hexanes/EtOAc to afford the purified product, compound IV-1 (260 mg, 0.84 mmol, 60% yield).

EXAMPLE 7
SYNTHESIS OF COMPOUND (V-1A)

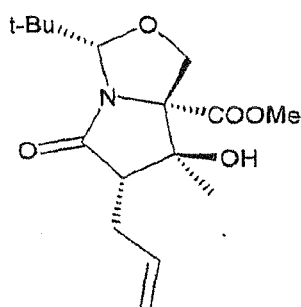
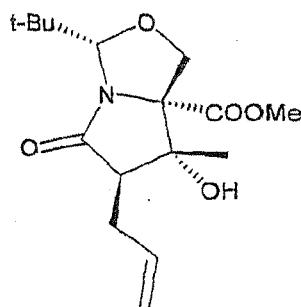
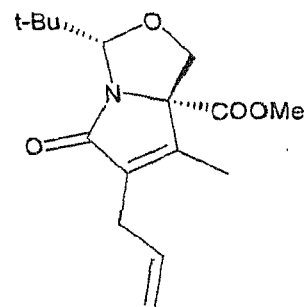


To a solution of compound IV-1 (26 g, 83.6 mmol) in dry THF (2.7 L) at RT was added t-BuOK (4.68 g, 41.8 mmol). The reaction mixture was stirred at RT for 15 min under an atmosphere of N₂ and then quenched with H₂O (900 mL) and extracted with EtOAc (3 x 400 mL). The combined organic phase was washed with saturated brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The reaction mixture was dissolved in 1:1 ether : hexanes (75 mL each) and transferred to a crystallization dish, where it was allowed to stand and crystallize. After an hour, the crystals (1st crop) were separated by decanting the mother liquor. The crystals were washed with ether (2 x 10 mL) and hexanes (2 x 10 mL). The combined mother liquor and washes was concentrated under reduced pressure and redissolved in 1:1 ether:hexanes (50 mL each) and the crystallization process was repeated the crystallization process as described above. The crystals (2nd crop) were separated by decanting the mother liquor. The crystals were washed with ether (2 x 10 mL) and hexanes (2 x 10 mL). The two crops of crystals were combined to obtain compound V-1A (13.5 g, 43.4 mmol, 51.9% yield by crystallization). The mother liquor was chromatographed on a silica gel flash column (30 x 4 cm) using solvent gradient of 19:1 (500 mL) to 9:1 (1 L) to 17:3 (500 mL) EtOAc/hexanes to yield the compound XXIX-1 (2.47 g), compound V-1A (3.05 g), compound V-1B (250 mg as a mixture) and compound V-1C (1.81 g). The two crops of crystals were combined to obtain a total yield of 63.6% of the compound V-1A. Compound V-1A was obtained as a colorless crystalline material. The structures of compounds V-1B, V-1C, and XXIX-1 are shown below.

Compound V-1A: ¹H-NMR (CDCl₃, 500 MHz) (δ): 5.96 (m, 1H), 5.15 (br dd, *J* = 1.5, 17.2 Hz, 1H), 5.05 (d, *J* = 10.1 Hz, 1H), 4.93 (s, 1H), 4.50 (d, *J* = 8.9 Hz, 1H), 4.26 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 3H), 3.10 (t, *J* = 6.7 Hz, 1H), 2.56 (m, 1H),

2.31 (m, 1H), 1.96 (s, 1H), 1.30 (s, 3H), 0.87 (s, 9H). ^{13}C -NMR (CDCl_3 , 125 MHz) (δ): 177.9, 171.8, 136.7, 116.6, 96.7, 80.4, 79.2, 68.0, 53.3, 52.6, 36.5, 27.9, 25.0 ($3\times\text{CH}_3$), 23.0. M.P. 113-114 °C (crystals obtained from 1:1; diethyl ether:hexanes). $[\alpha]_D^{22}$ 8.4 (c 0.96, CH_3CN). MS (ESI) m/z 312 ($\text{M}+\text{H}$). See Figure 8.

The compound **V-1A** was also characterized by ^{13}C -NMR (CDCl_3 , 125 MHz) and $^1\text{H} - ^1\text{H}$ COSY NMR (CDCl_3 , 500 MHz). See Figures 9 and 10. The structure of compound **V-1A** was confirmed by x-ray crystallography, as shown in Figure 11.

**V-1B****V-1C****XXIX-1**

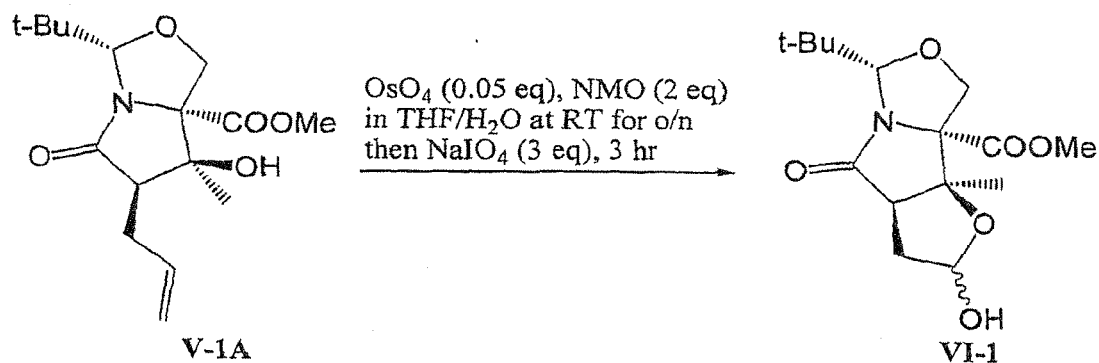
Compound V-1B: Compound **V-1B** was purified by reversed phase HPLC using the solvent gradient of 30% to 70% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ over 30 min, at a flow rate of 14.5 mL/min to yield pure compound. ^1H -NMR (CDCl_3 , 500 MHz) (δ): 5.88 (m, 1H), 5.09 (br dd, $J = 1.5, 17$ Hz, 2H), 4.9 (s, 1H), 4.52 (d, $J = 9$ Hz, 1H), 4.2 (d, $J = 9$ Hz, 1H), 3.77 (s, 3H), 2.68 (m, 1H), 2.51 (t, $J = 7$ Hz, 1H), 2.45 (m, 1H), 1.29 (s, 3H), 0.89 (s, 9H). See Figure 25. MS (ESI) m/z 312 [$\text{M}+\text{H}$] $^+$. The structure was confirmed by x-ray crystallography, Figure 26.

Compound V-1C: ^1H -NMR (CDCl_3 , 500 MHz) (δ): 5.93 (m, 1H), 5.16 (br dd, $J = 1, 17$ Hz, 1H), 5.06 (br d, $J = 10$ Hz, 1H), 4.88 (s, 1H), 4.58 (d, $J = 9.5$ Hz, 1H), 3.96 (d, $J = 9.5$ Hz, 1H), 3.79 (s, 3H), 3.43 (dd, $J = 6.3, 8.5$ Hz, 1H), 2.53 (m, 1H), 2.17 (m, 1H), 1.27 (s, 3H), 0.86 (s, 9H). See Figure 27. ^{13}C -NMR (CDCl_3 , 125 MHz) (δ): 175.8, 171.5, 135.8, 116.9, 96.2, 80.9, 78.3, 68.8, 53.3, 52.6, 36.5, 28.8, 25.0, 20.2. See Figure 28. MS (ESI) m/z 312 [$\text{M}+\text{H}$] $^+$. The relative stereochemistry was determined by NOESY, Figure 29.

Compound of XXIX-1: ^1H -NMR (CDCl_3 , 500 MHz) (δ): 5.81 (m, 1H), 5.04 (br dd, $J = 1.5, 7.5$ Hz, 1H), 5.02 (s, 1H), 4.78 (d, $J = 8.5$ Hz, 1H), 4.66 (s, 1H), 3.74 (s, 3H), 3.18 (d, $J = 8.5$ Hz, 1H), 2.97 (t, $J = 6.5$ Hz, 1H), 1.83 (s, 3H), 0.91 (s, 9H). See Figure 30. ^{13}C -NMR (CDCl_3 , 125 MHz) (δ): 178.4, 170.0, 151.9, 133.4, 132.8,

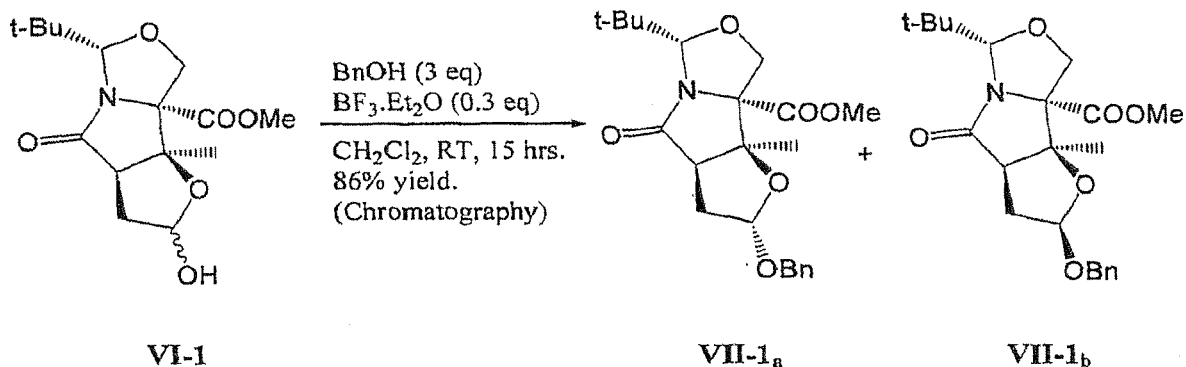
116.1, 96.9, 78.0, 70.5, 52.9, 35.2, 27.6, 24.7, 12.1. See Figure 31. MS (ESI) m/z 294 $[M+H]^+$.

EXAMPLE 8
SYNTHESIS OF COMPOUND (VI-1)



To a solution of compound V-1A (530 mg, 1.7 mmol) in THF/H₂O (1:1, 12 mL) were added NMO (50% w/w aqueous solution, 750 μ L, 3.4 mmol) and OsO₄ (2.5% wt.% in 2-methyl-2-propanol, 1.1 mL, 0.085 mmol). The resulting mixture was stirred at RT for 17 hours. Then, NaIO₄ (250 mg, 1.16 mmol) was added to the above reaction mixture and stirred for additional 3 hrs at 25 °C. The reaction mixture was quenched with saturated Na₂S₂O₃ (10 mL) and saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (1.25 cm ID x 5 cm) using a solvent gradient of 19:1(50 mL) to 9:1 (50 mL) to 4:1 (50 mL) hexanes/EtOAc to afford compound VI-1 (170 mg, 0.54 mmol, 94%) as a mixture of diastereomers. The compound VI-1 was characterized by ¹H-NMR (CDCl₃, 500 MHz). See Figure 12. MS (ESI) m/z 314 $[M+H]^+$.

EXAMPLE 9
SYNTHESIS OF COMPOUND (VII-1)



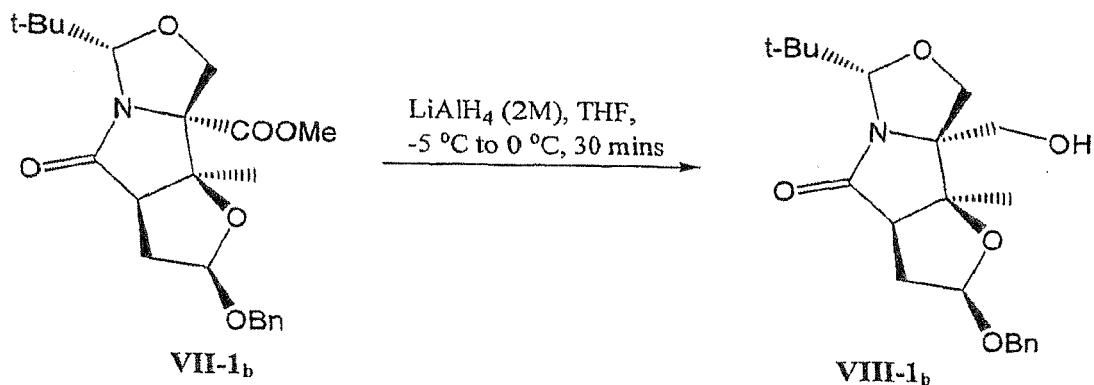
To a solution of compound **VI-1** (170 mg, 0.54 mmol) in dry CH_2Cl_2 (3 mL) was added BnOH (170 μL , 1.64 mmol) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (20 μL , 0.16 mmol). The reaction mixture was stirred at 25 °C for 15 hours. Then Et_3N (100 μL , 0.7 mmol) was added to the above reaction mixture which was directly concentrated, followed by silica flash column (1.25 cm ID x 5 cm) chromatography using a solvent gradient of 19:1 (50 mL) to 9:1 (50 mL) to 4:1 (50 mL) hexanes/ EtOAc to afford compound **VII-1_a** (83 mg, 0.21 mmol) and compound **VII-1_b** (104 mg, 0.26 mmol). 86% total yield of compound **VII-1_a** and compound **VII-1_b**.

Compound **VII-1_a**: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) (δ): 7.30 (m, 5H), 5.24 (dd, $J = 4.4, 6.3$ Hz, 1H), 4.77 (s, 1H), 4.72 (d, $J = 12.0$ Hz, 1H), 4.64 (d, $J = 8.5$ Hz, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.17 (d, $J = 8.5$ Hz, 1H), 3.78 (s, 3H), 3.36 (d, $J = 8.5$ Hz, 1H), 2.81 (ddd, $J = 1.0, 6.3, 14.2$ Hz, 1H), 2.13 (m, 1H), 1.37 (s, 3H), 0.86 (s, 9H). See Figure 13.

Compound **VII-1_b**: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) (δ): 7.27 (m, 5H), 5.19 (d, $J = 5.0$ Hz, 1H), 4.65 (d, $J = 11.4$ Hz, 1H), 4.65 (d, $J = 8.5$ Hz, 1H), 4.60 (s, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.21 (d, $J = 8.5$ Hz, 1H), 3.76 (s, 3H), 3.17 (d, $J = 8.5$ Hz, 1H), 2.60 (d, $J = 13.2$ Hz, 1H), 2.13 (m, 1H), 1.23 (s, 3H), 0.82 (s, 9H). MS (ESI) m/z 404 $[\text{M}+\text{H}]$. See Figure 14.

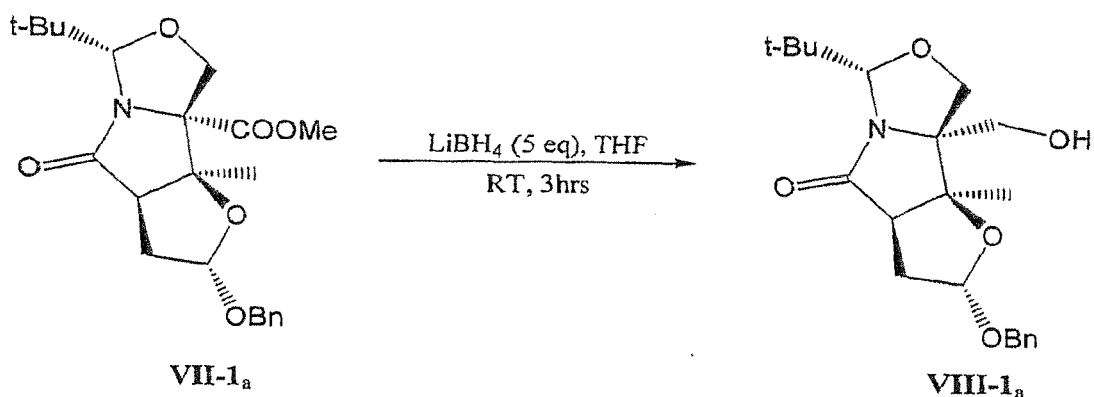
The structure of compound **VII-1_b** was confirmed by crystal structure, as shown in Figure 15.

EXAMPLE 10
SYNTHESIS OF COMPOUND (VIII-1_b)



To a solution of compound VII-1_b (40 mg, 0.1 mmol) in dry THF (2 mL) at -20 °C was added LiAlH₄ (2.0 M, 75 μ L, 0.15 mmol). The reaction mixture was allowed to warm up to -5 °C in 10 min and stirred for an additional 20 min. The reaction mixture was then quenched with saturated aqueous potassium sodium tartrate (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried with MgSO₄ and concentrated under reduced pressure to yield a crude product which was purified by silica flash chromatography (column 1.25 cm ID x 10 cm) using a solvent gradient of 19:1 (50 mL) to 9:1 (100 mL) to 4:1 (200 mL) hexanes/EtOAc to afford the product, compound VIII-1_b (19 mg, 0.051 mmol, 50% yield). The compound VIII-1_b was characterized by ¹H-NMR (CDCl₃, 500 MHz). See Figure 16. MS (ESI) *m/z* 376 [M+H].

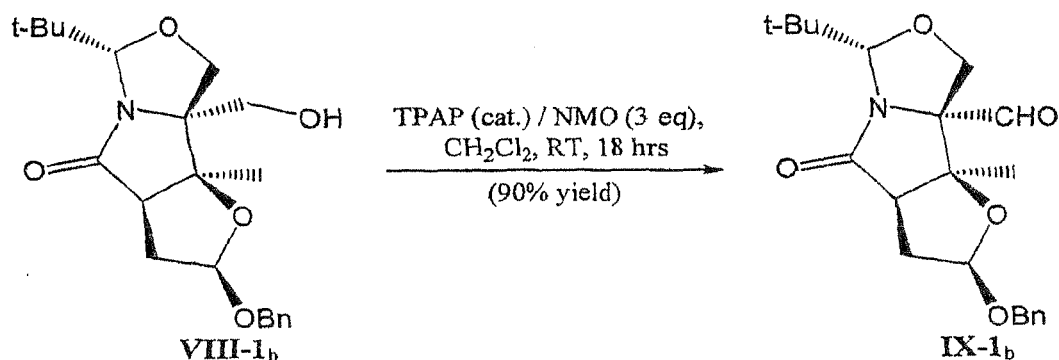
EXAMPLE 11
SYNTHESIS OF COMPOUND (VIII-1_a)



To a solution of compound VII-1_a (90 mg, 0.22 mmol) in dry THF (5 mL) was added lithium borohydride (2M solution in THF, 558 μ L, 1.1 mmol,) and stirred

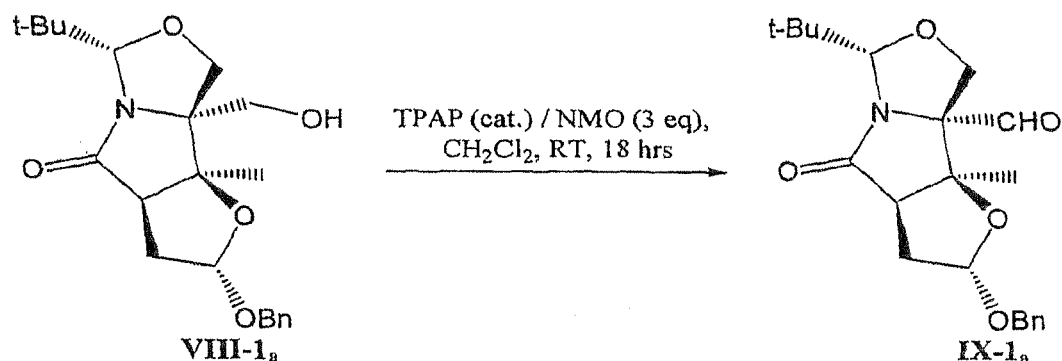
at RT. After 15 minutes of stirring, methanol (100 μ L) was added to the reaction mixture at RT (room temperature was maintained by cooling the reaction mixture with water bath). After 3 hours of additional stirring, the reaction mixture was quenched with H_2O (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the product, compound **VIII-1_a** as clear oil (75 mg, 0.2 mmol, 90.9% yield), which can be used in the next step without any column chromatography. The compound **VIII-1_a** was characterized by ^1H -NMR (CDCl_3 , 500 MHz). See Figure 17. MS (ESI) m/z 376 $[\text{M}+\text{H}]$ and 398 $[\text{M}+\text{Na}]$.

EXAMPLE 12
SYNTHESIS OF COMPOUND (IX-1_b)



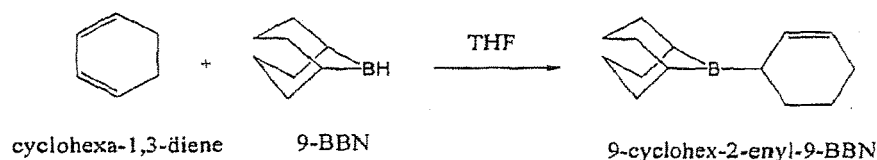
To a solution of **VIII-1_b** (30 mg, 0.08 mmol) in dry CH₂Cl₂ (1 ml) were added NMO (28 mg, 0.24 mmol) and TPAP (3.0 mg, 0.008 mmol). The resulting mixture was stirred at RT for 18 hours. The reaction mixture was then concentrated and purified by silica flash chromatography (column 1.25 cm ID x 10 cm) using a solvent gradient of 19:1 (50 mL) to 9:1 (100 mL) to 17:3 (200 mL) hexanes/EtOAc to afford the product, compound **IX-1_b**, as clear oil (27 mg, 0.072 mmol, 90% yield). The compound **IX-1_b** was characterized by ¹H-NMR (CDCl₃, 500 MHz). See Figure 18. MS (ESI) *m/z* 374 [M+H].

EXAMPLE 13
SYNTHESIS OF COMPOUND (IX-1_a)



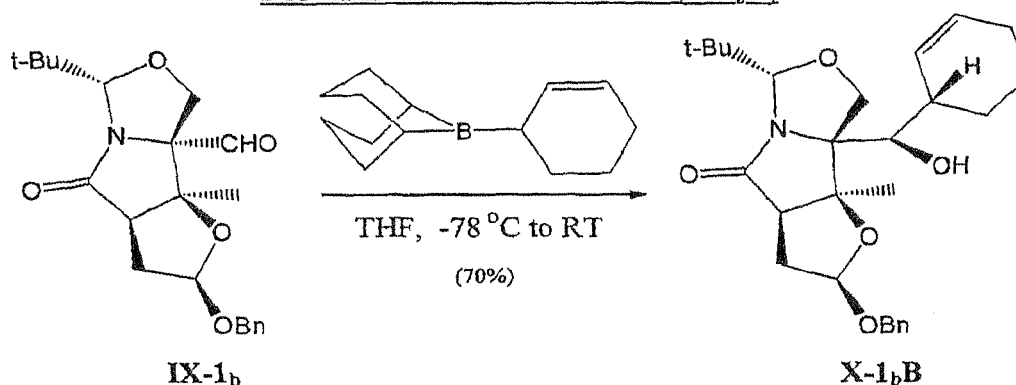
To a solution of alcohol, compound **VIII-1_a** (40 mg, 0.107 mmol) in dry CH_2Cl_2 (3 ml) were added NMO (37.5 mg, 0.32 mmol) and TPAP (3.78 mg, 0.01 mmol). The reaction mixture was stirred at RT for 18 hours. The above reaction mixture was then concentrated and purified by silica flash chromatography (column 2.5 cm ID x 6 cm) using a solvent gradient of 19:1(50 mL) to 9:1 (100 mL) to 17:3 (200 mL) hexanes/EtOAc to afford the product, compound **IX-1_a**, as a white solid (34 mg, 0.091 mmol, 85.5% yield). The compound **IX-1_a** was characterized by $^1\text{H-NMR}$ (CDCl_3 , 500 MHz). See Figure 19. MS (ESI) m/z 374 $[\text{M}+\text{H}]$ and 396 $[\text{M}+\text{Na}]$.

EXAMPLE 14
SYNTHESIS OF 9-CYCLOHEX-2-ENYL-9-BORABICYCLO[3.3.1]NONANE



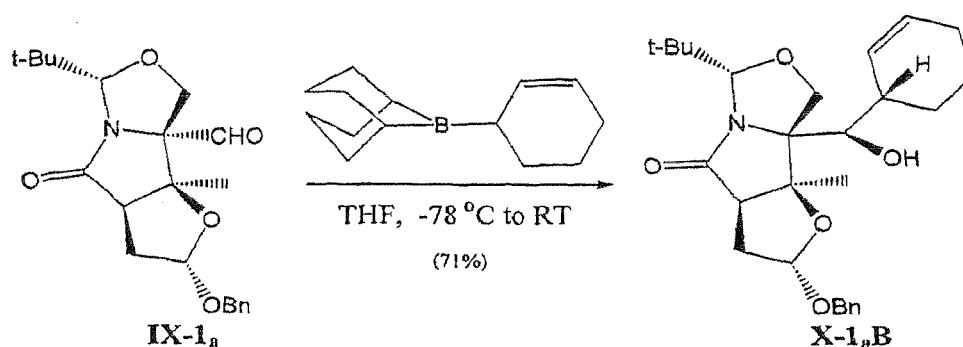
To a solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (0.5 M, 10.0 ml, 5.0 mmol) was added 1,3-cyclohexadiene (97%) (490 μl , 5.0 mmol) and stirred for 24 hrs at RT to afford a solution of 9-cyclohex-2-enyl-9-BBN in THF (0.5 M) which was directly used to couple with compound of formula **IX-1**.

EXAMPLE 15
SYNTHESIS OF COMPOUND (X-1_bB)



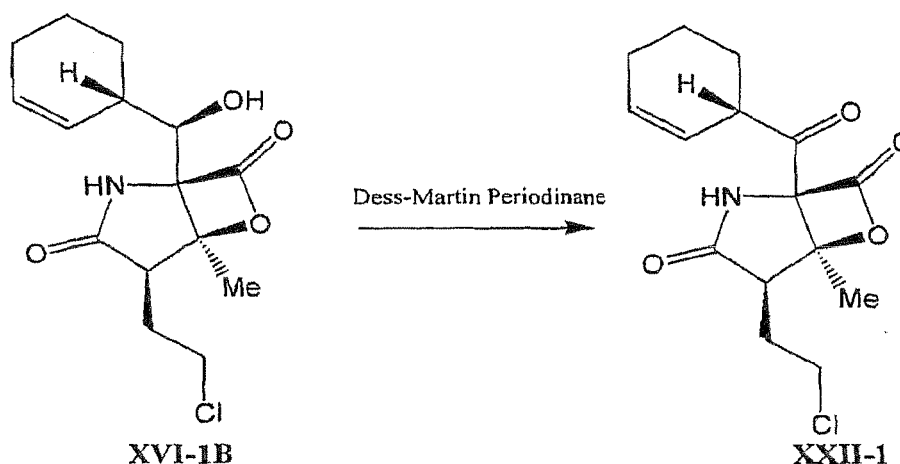
To a solution of compound **IX-1_b** (20 mg, 0.053 mmol) in THF (0.5 ml) at -78 °C was added the 9-cyclohex-2-enyl-9-BBN solution (see Example 12) in THF (0.5 M, 320 μ l, 0.16 mmol). The reaction mixture was allowed to warm to RT over 1.5 hr and stirred for additional 10 hrs at RT. Ethylamine (16 μ l, 0.265 mmol) was then added to the above reaction mixture, and stirring continued for an additional 16 hrs at RT. The reaction mixture was then concentrated under reduced pressure and the resulting residue was purified by silica flash chromatography (column 1.25 cm ID x 10 cm) using a solvent gradient of 19:1 (50 mL) to 9:1 (100 mL) to 17:3 (200 mL) hexanes/EtOAc to afford the product, compound **X-1_bB**, as a white solid (17.0 mg, 0.037 mmol, 70.4%) which was crystallized from hexanes/ethylether (1:1). The compound **X-1_bB** was characterized by ¹H-NMR (CDCl₃, 500 MHz), and ¹³C-NMR (CDCl₃, 125 MHz). See Figures 20 and 21. The structure of compound **X-1_bB** was confirmed by X-ray crystal structure. See Figure 22. MS (ESI) m/z 456 [M+H] and 478 [M+Na].

EXAMPLE 16
SYNTHESIS OF COMPOUND (X-1_aB)



To a solution of aldehyde, compound **IX-1_a**, (60 mg, 0.161 mmol) in THF (2.0 mL) at -78 °C was added the 9-cyclohex-2-enyl-9-BBN solution in THF (0.5 M, 0.96 mL, 0.48 mmol) and the reaction mixture was allowed to warm to RT over 1.5 hr and stirred for additional 10 hrs at RT. Ethylamine (50 μ l, 0.81 mmol) was then added to the above reaction mixture, and stirring continued for an additional 16 hrs at RT. The reaction mixture was then concentrated under reduced pressure and the resulting residue was purified by silica flash chromatography (column 1.25 cm ID x 10 cm) using a solvent gradient of 19:1(50 mL) to 9:1 (200 mL) of hexanes/EtOAc to afford a pure product, a compound **X-1_aB** (52.0 mg, 0.114 mmol, 70.9%). The compound **X-1_aB** was characterized by ¹H-NMR (CDCl₃, 500 MHz), and ¹³C-NMR (CDCl₃, 125 MHz). See Figures 23 and 24. MS (ESI) m/z 456 [M+H] and 478 [M+Na].

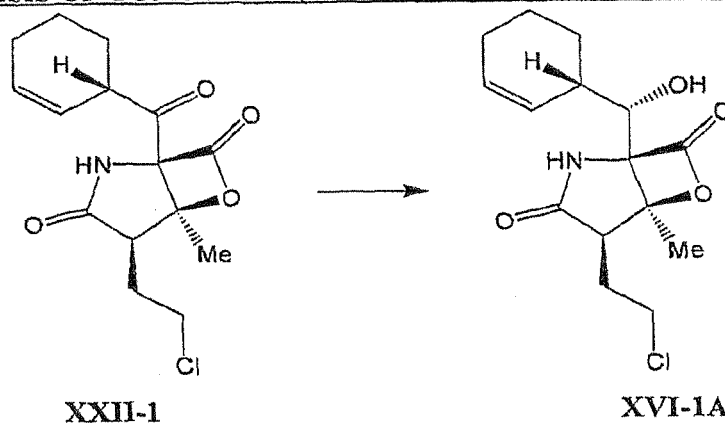
EXAMPLE 17
SYNTHESIS OF COMPOUND (XXII-1)



To a solution of compound **XVI-1B** (3.5 mg, 11.2 μ mol) in CH₂Cl₂ (1 ml) in a scintillation vial (20 ml) were added Dess-Martin periodinane (23.7 mg; 56 μ mol) and a magnetic stir bar. The reaction mixture was stirred at RT for about 16 hours. The progress of the reaction was monitored by analytical HPLC. The reaction mixture was then filtered through a membrane filter (0.2 μ m) and purified by normal phase HPLC using a Phenomenex Luna 10u Silica column (25 cm x 21.2 mm ID), ELSD detector, a solvent gradient of 25% to 80% EtOAc/hexanes over 19 min, 80 to 100% EtOAc/hexanes over 1 min, holding at 100% EtOAc for 5 min, at a flow rate of 14.5 ml/min to afford a pure compound of formula **XXII-1**. ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.54 (s, 3H), 1.59 (m, 2H), 1.66-1.70 (m, 1H), 1.73-1.80 (m, 1H), 1.96 (m, 2H), 2.0-2.11 (m, 2H), 3.09 (t,

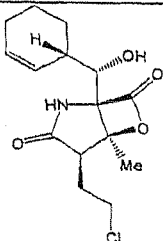
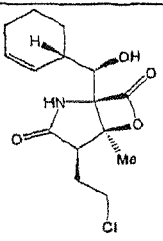
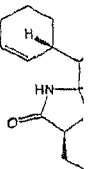
1H, $J = 7.0$ Hz), 3.63 (brs, 1H), 3.83-3.88 (m, 1H), 3.89-3.93 (m, 1H), 5.50 (dd, 1H, $J = 2, 10$ Hz), 5.92 (dd, 1H, $J = 2.5, 10$ Hz), 9.70 (s, 1H, NH); MS (ESI), m/z 312 ($M+H$)⁺ and 334 ($M+Na$)⁺.

EXAMPLE 18
SYNTHESIS OF COMPOUND (XVI-1A) VIA CHEMICAL REDUCTION



The compound of formula **XVI-1A** was synthesized by reducing the keto group of the compound of formula **XXII-1** with a common reducing agent(s) under various reaction conditions as shown in the Table 1.

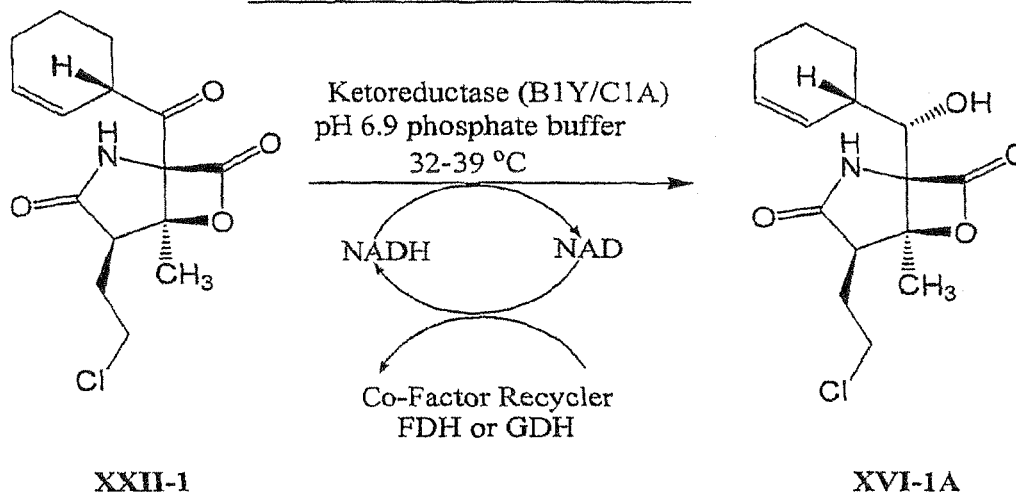
TABLE 1^a

Reaction Conditions				Product Ratio		
NaBH ₄ # eq	Solvent ^b	Temp in °C	Time in min	 (XVI-1A)	 (XVI-1B)	
1	Monoglyme + 1% water	- 78	14	5	95	0
1	Monoglyme + 1% water	- 10	14	30	50	20
1	Monoglyme + 1% water	0	14	33.3	33.3	33.3
2	Monoglyme + 1% water	RT	8	50	0	50
1	Monoglyme + 1% water	RT	8	45	10	45
0.5	Monoglyme + 1% water	RT	8	50	50	0
0.25	Monoglyme + 1% water	RT	8	50	50	0
1	IPA + 1% water	RT	10	50	0	50
0.5	IPA + 1% water	RT	12	60	10	30
0.25	IPA + 1% water	RT	8	50	40	10
0.25	IPA + 5% water	RT	8	10	0	10
0.5	IPA	RT	8	40	50	10
0.5	IPA	0	8	30	70	0
0.25	IPA	RT	8	No reaction		
1	THF + 1% water	RT	10	50	0	50
0.5	THF + 1% water	RT	12	50	50	0
0.25	THF + 1% water	RT	8	30	70	0
1 + LiCl	Monoglyme + 1% water	- 78	10	5	95	0
1 + LiCl	Monoglyme + 1% water	0	10	27.2	36.4	36.4
1 + LiCl	Monoglyme + 1% water	10	10	10	30	60
1 + CeCl ₃	Monoglyme + 1% water	- 78	10	5	95	0
1 + CeCl ₃	Monoglyme + 1% water	0	10	25	50	25
1 + CeCl ₃	Monoglyme + 1% water	10	10	20	60	20

^a Degradation or little to no product was observed using the following reagents, 1. NaBH₄ on 10% Basic Al₂O₃, 2. K-Selectride, 3. KS-Selectride, 4. BTHF-(R)-CBS, 5. BTHF-(S)-CBS, 6. NaBH(OAc)₃, 7. (CH₃)₄NBH(OAc)₃, and 8. iPrMgCl;

^b Methyl and ethyl ester derivatives were formed when MeOH and EtOH was used, respectively.

EXAMPLE 19
SYNTHESIS OF COMPOUND (XVI-1A) FROM COMPOUND (XXII-1)
VIA ENZYMATIC REDUCTION



Method A: Compound **XXII-1** was subjected to enzymatic reduction using ketoreductases KRED-EXP-C1A and KRED-EXP-B1Y (BioCatalytics, Pasadena CA). 20 mM of compound **XXII-1** (62 mg, added as a DMSO solution, 0.4 mL), 60 mg of KRED-EXP-C1A or KRED-EXP-B1Y, 50 mM sodium formate 1 mM NAD⁺ and 30 mg of FDH-101 were dissolved in 10mL of phosphate buffer (150 mM, pH 6.9). The reaction was stirred at 30 °C for 1 hour before it was extracted with EtOAc. The combined organic layers were evaporated to dryness using a speed-vacuum giving the product, compound **XVI-1A**, as a solid white powder. HPLC analysis (C18 reverse phase column (ACE C18, 5 m 150 X 4/6 nm)) and NMR showed only the formation of **XVI-1A**, as shown in Table 2. Both KRED-EXP-C1A and KRED-EXP-B1Y showed product formation. No detectable formation of the other diastereomeric alcohol, compound of formula **XVI-1B** was observed.

TABLE 2

Ketoreductase	XXII-1	XVI-1A	XVI-1B
KRED-EXP-C1A	18% ¹	82%	Not detected
KRED-EXP-B1Y	21% ¹	79%	Not detected

¹Includes a minor impurity similar to compound (**XXII-1**) in the calculated yield

Reactions (10-100 mg scale) were performed on KRED-EXP-C1A and KRED-EXP-B1Y using glucose and glucose dehydrogenase (GDH) as a cofactor recycler

at pH 6.9 (Method B is the optimized procedure). The products were extracted with EtOAc and analyzed by HPLC. The results are shown in Table 3.

TABLE 3

XXII-1 (mg)	Ketoreductase # eq (w/w)		GDH #eq (w/w)	% Solvent in water	Time (h)	% Conversion ^{a,b} from XXII-1 to XVI-1A
10	C1A	1	0.5	~20% DMSO	1	70
10	C1A	1	0.1	~20% DMSO	1	70
10	C1A	1	0.1	~20% DMSO	2	85
10	C1A	1	0.1	~20% DMSO	3	90
100	C1A	1	0.1	~20% DMSO	1	70
100	C1A	1	0.1	~20% DMSO	3	80 ^c
50	C1A	1	0.1	~20% DMSO	4	90 ^c
10	BIY	1	0.1	~20% DMSO	1	90
10	BIY	1	0.1	50% t-BuOAc	1	40
					20	50
10	BIY	1	0.1	50% n-BuOAc	1	0
					24	20
10	BIY	1	0.1	50% TBME	1	5
					24	80
10	BIY	2	0.2	~20% DMSO	0.67	95
10	C1A	2	0.2	~20% DMSO	0.67	70
20	BIY	2	0.2	~20% DMSO	0.67	95 ^d
50	BIY	2	0.2	~20% DMSO	0.67	90 ^e

^aAt pH 6.9 using GDH, NAD, glucose

^bBased on HPLC analysis of organic extract

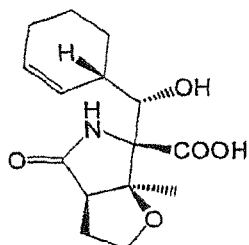
^cRecovered yield 40% after purification by flash column chromatography. Some decomposition product was detected in aqueous layer

^dRecovered yield 90% after purification by flash column chromatography

^eRecovered yield 85% after purification by crystallization

As shown in Table 3, when KRED-EXP-C1A ketoreductase was used, the conversion from XXII-1 to XVI-1A was 70% complete after 1 h on 10 mg scale. Based on HPLC analysis of the organic extract, the conversion was 90% complete when the reaction time was increased to 3 h, but subsequent evaluation of the aqueous extract revealed that a portion of the product had decomposed, which is an expected hydrolysis product that forms in aqueous solution. The decomposition product has the structure shown below. Decomposition was minimized when biphasic solutions (50% aqueous t-BuOAc, n-BuOAc, TBME) were used, but the percent conversion was generally very low even with longer reaction times (20-24 h), except in 50% aqueous TBME. Of the two

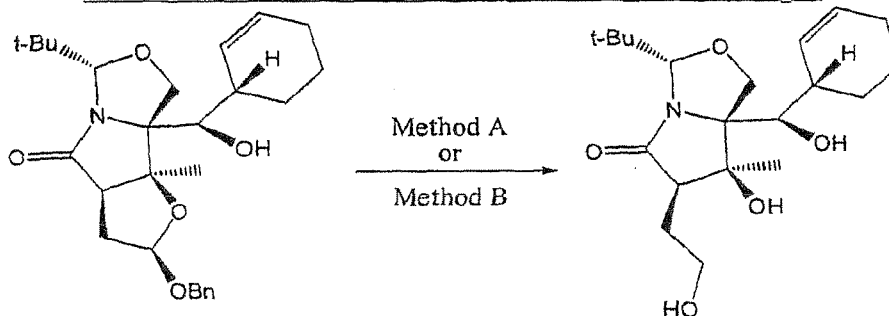
ketoreductase, KRED-EXP-B1Y ketoreductase was superior to KRED-EXP-C1A in the conversion of **XXII-1** to **XVI-1A**. Doubling the concentrations of KRED-EXP-B1Y and GDH and decreasing the reaction time resulted in better yields and minimal decomposition of product (2-5%).



Decomposition product:

Method B: see Example 31.

EXAMPLE 20
SYNTHESIS OF COMPOUND (XXIII-1B) VIA (X-1_bB)



Method A: 1) HCl (0.5 M); 2) NaBH₄

Method B: 1) Na/NH₃ (liq.); 2) NaBH₄

X-1_bB

XXIII-1B

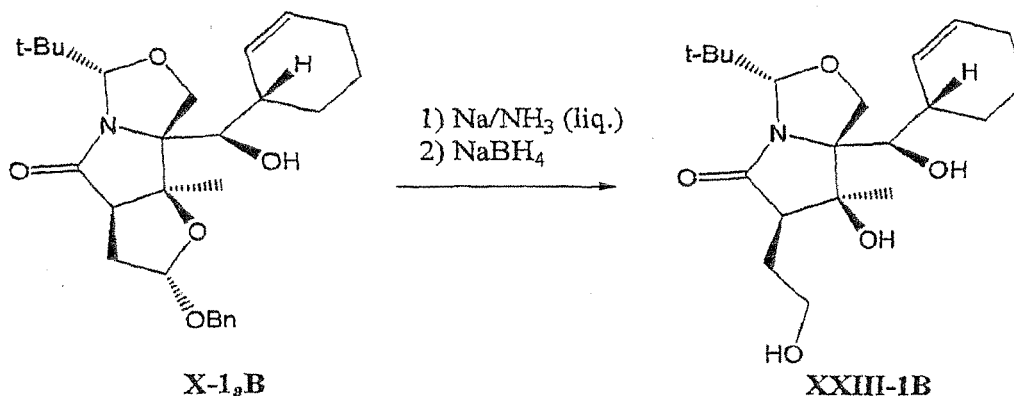
Method A: To a solution of **X-1_bB** (400 mg, 0.88 mmol) in THF (20 mL) was added aqueous HCl (0.5 M, 2 mL). The reaction mixture was warmed to 60 °C and stirred for 10 hrs at this temperature. The above reaction mixture was diluted with H₂O (20 mL), then extracted with EtOAc (2 X 20 mL) and CH₂Cl₂ (3 X 20 mL). The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude residue was re-dissolved in THF /H₂O ((2:1; 22.5 mL), then NaBH₄ (100 mg, 2.63 mmol) was added and stirred at 25 °C for 30 min. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (2 X 20 mL) and CH₂Cl₂ (3 X 20 mL), and the organic phase was dried over MgSO₄ and concentrated under reduced pressure to afford **XXIII-1B** as crude white solid (260 mg, 81%) which can be used in the next step without purification. The compound **XXIII-1B** was characterized by ¹H-NMR (CDCl₃,

500 MHz), and ^{13}C -NMR (CDCl_3 , 125 MHz). See Figures 32 and 33. MS (ESI) m/z 368.3 $[\text{M}+\text{H}]^+$.

Method B: Sodium metal (Na, 30mg, 1.30 mmol) was dissolved in liquid ammonia (3 mL) at -78°C and the resultant dark blue mixture was stirred for 5 min. A solution of **X-1_bB** (30mg, 0.066 mmol) in dry THF (0.5 mL) was slowly added to the above reaction mixture and stirred at -78°C for an additional 2 hrs. Solid ammonium chloride (NH_4Cl , 40mg) was added slowly to the reaction mixture, which was then allowed to warm to RT (by removing the dry ice-acetone cold bath). Ammonia was evaporated during warm up. The white residue was washed with brine and extracted with EtOAc. The organic phase was concentrated to afford crude hemiacetal, which was directly used in the next reaction without purification.

To a solution of the above hemiacetal in THF: H_2O (2:1; 1.5 mL) was added NaBH_4 (8 mg, 0.20 mmol). The reaction mixture was stirred for 1 hr at RT and then diluted with brine and extracted with EtOAc. The organic phase was dried with MgSO_4 , concentrated under reduced pressure and purified by silica flash chromatography (EtOAc in hexanes, 10% to 30%) to afford triol **XXIII-1B** as clear oil (18 mg, 0.049 mmol, 74.2% yield over two steps). The compound **XXIII-1B** was characterized by ^1H -NMR (CDCl_3 , 500 MHz), and ^{13}C -NMR (CDCl_3 , 125 MHz). See Figures 32 and 33. MS (ESI) m/z 368.3 $[\text{M}+\text{H}]^+$.

EXAMPLE 21
SYNTHESIS OF COMPOUND (XXIII-1B) VIA (X-1_bB)

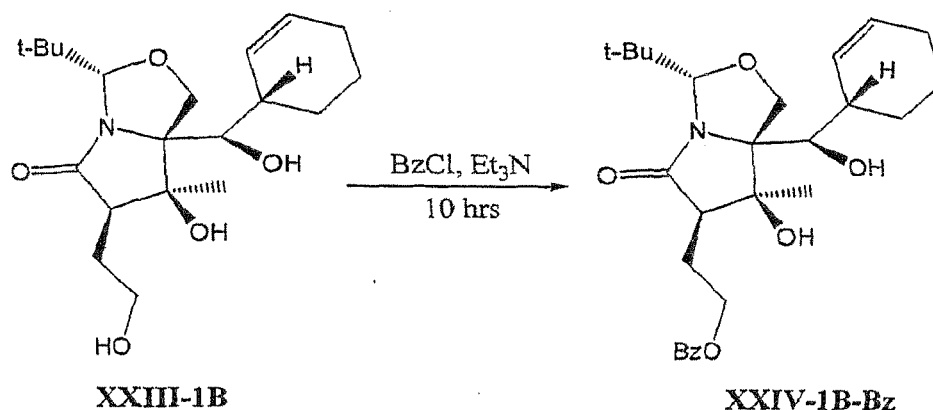


Sodium metal (Na, 20mg, 0.88 mmol) was dissolved in liquid ammonia (3ml) at -78°C and the resultant dark blue mixture was stirred for 5 min. A solution of compound **X-1_bB** (20mg, 0.044 mmol) in dry THF (0.5 mL) was slowly added to the above reaction mixture and stirred at -78°C for additional 2 hrs. Solid ammonium

chloride (NH_4Cl , 30mg) was added slowly to the reaction mixture, which was then allowed to warm to RT (by removing the dry ice-acetone cold bath). Ammonia was evaporated during warm up. The white residue was washed with brine and extracted with EtOAc. The organic phase was concentrated under reduced pressure to afford crude hemiacetal which was directly used in the next reaction without purification.

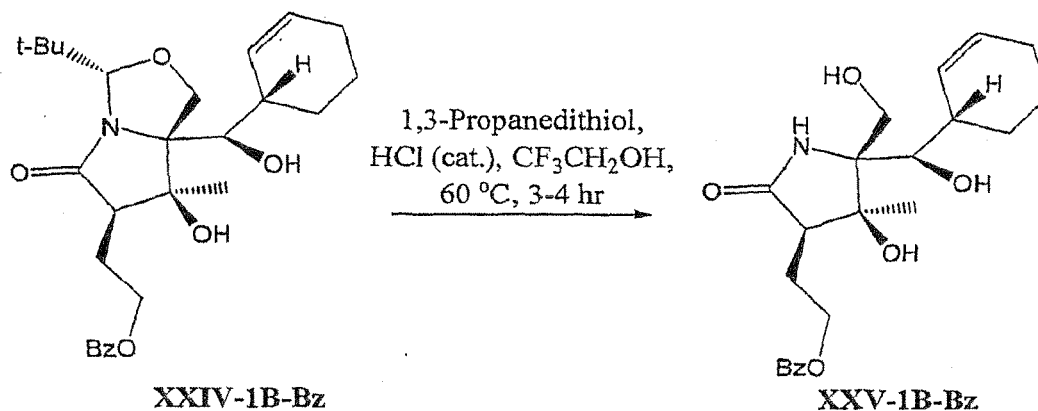
To a solution of the above hemiacetal in THF:H₂O (2:1; 1.5 ml) was added NaBH_4 (5 mg, 0.13 mmol). The reaction mixture was stirred for 1 hr at RT and then diluted with brine and extracted with EtOAc. The organic phase was dried with MgSO_4 , concentrated under reduced pressure and purified by silica flash chromatography (EtOAc in hexanes, 10% to 30%) to afford triol **XXIII-1B** as clear oil (11.3 mg, 0.031 mmol, 70% yield over two steps). The ^1H -NMR (CDCl_3 , 500 MHz) and ^{13}C -NMR (CDCl_3 , 125 MHz) spectra were the same as shown Figures 32 and 33, respectively. MS (ESI) m/z 368.3 $[\text{M}+\text{H}]$.

EXAMPLE 22
SYNTHESIS OF COMPOUND (XXIV-1B) VIA (XXIII-1B-Bz)



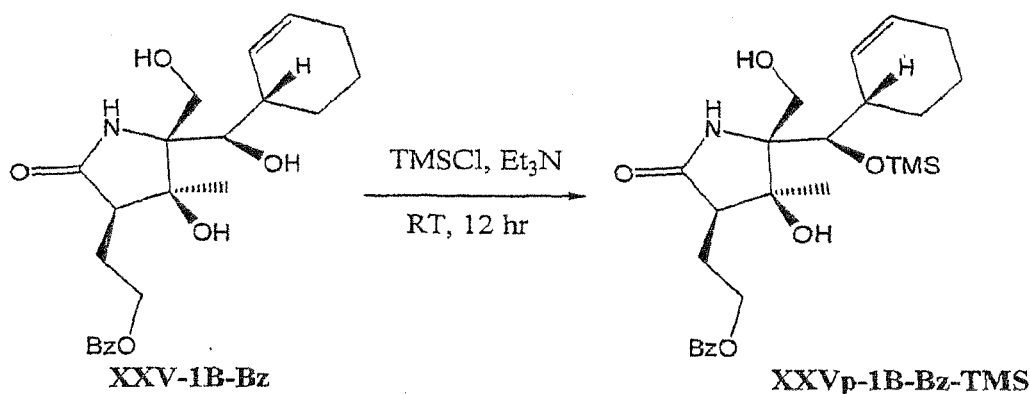
To a solution of **XXIII-1B** (120 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (120 μl , 0.86 mmol) and benzoyl chloride (BzCl , 60 μl , 0.52 mmol). The reaction mixture was stirred at 25 °C for 10 hrs. Then the reaction mixture was directly concentrated under reduced pressure and the resulting product was purified by silica flash chromatography (EtOAc in hexanes, 10% to 30%) to afford **XXIV-1B-Bz** (136 mg, 0.29 mmol, 87%). The compound **XXIV-1B-Bz** was characterized by ^1H -NMR (CDCl_3 , 500 MHz). See Figure 34. MS (ESI) m/z 472.3 $[\text{M}+\text{H}]^+$.

EXAMPLE 23
SYNTHESIS OF COMPOUND (XXV-1B-Bz) VIA (XXIV-1B-Bz)



To a solution of **XXIV-1B-Bz** (136 mg, 0.29 mmol) in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) were added 1,3-propanedithiol (200 μL , 2 mmol) and a catalytic amount of aqueous HCl (12N, 10 μL). The reaction mixture was stirred at 60 $^{\circ}\text{C}$ for 3-4 hr, concentrated under reduced pressure and the resulting crude product was then purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford **XXV-1B-Bz** (110 mg, 0.27 mmol, 94%). The compound **XXV-1B-Bz** was characterized by $^1\text{H-NMR}$ (CDCl_3 , 500 MHz), and $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz). See Figures 35 and 36. MS (ESI) m/z 404.3 $[\text{M}+\text{H}]^+$.

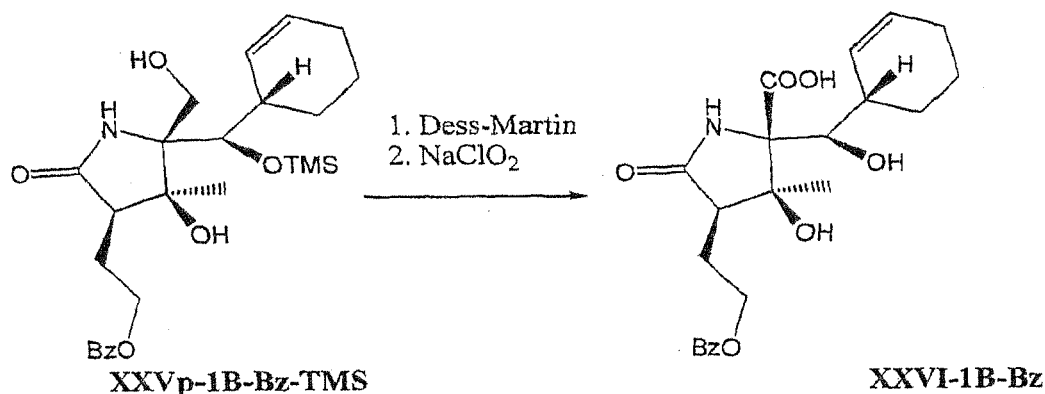
EXAMPLE 24
SYNTHESIS OF COMPOUND (XXVp-1B-Bz-TMS) VIA (XXV-1B-Bz)



To a solution of **XXV-1B-Bz** (70 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (480 μL , 3.47 mmol) and TMSCl (220 μL , 1.74 mmol) and the solution was stirred at 25 $^{\circ}\text{C}$ for 12 hrs. The reaction was quenched with saturated aqueous NaHCO_3 (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phase was

dried over MgSO_4 , concentrated under reduced pressure and then purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford **XXVp-1B-Bz-TMS** (44 mg, 0.093 mmol, 53% yield). The compound **XXVp-1B-Bz-TMS** was characterized by ^1H -NMR (CDCl_3 , 500 MHz), and ^{13}C -NMR (CDCl_3 , 125 MHz). See Figures 37 and 38. MS (ESI) m/z 476.3 $[\text{M}+\text{H}]^+$.

EXAMPLE 25
SYNTHESIS OF COMPOUND (XXVI-1B-Bz) VIA (XXVp-1B-Bz-TMS)

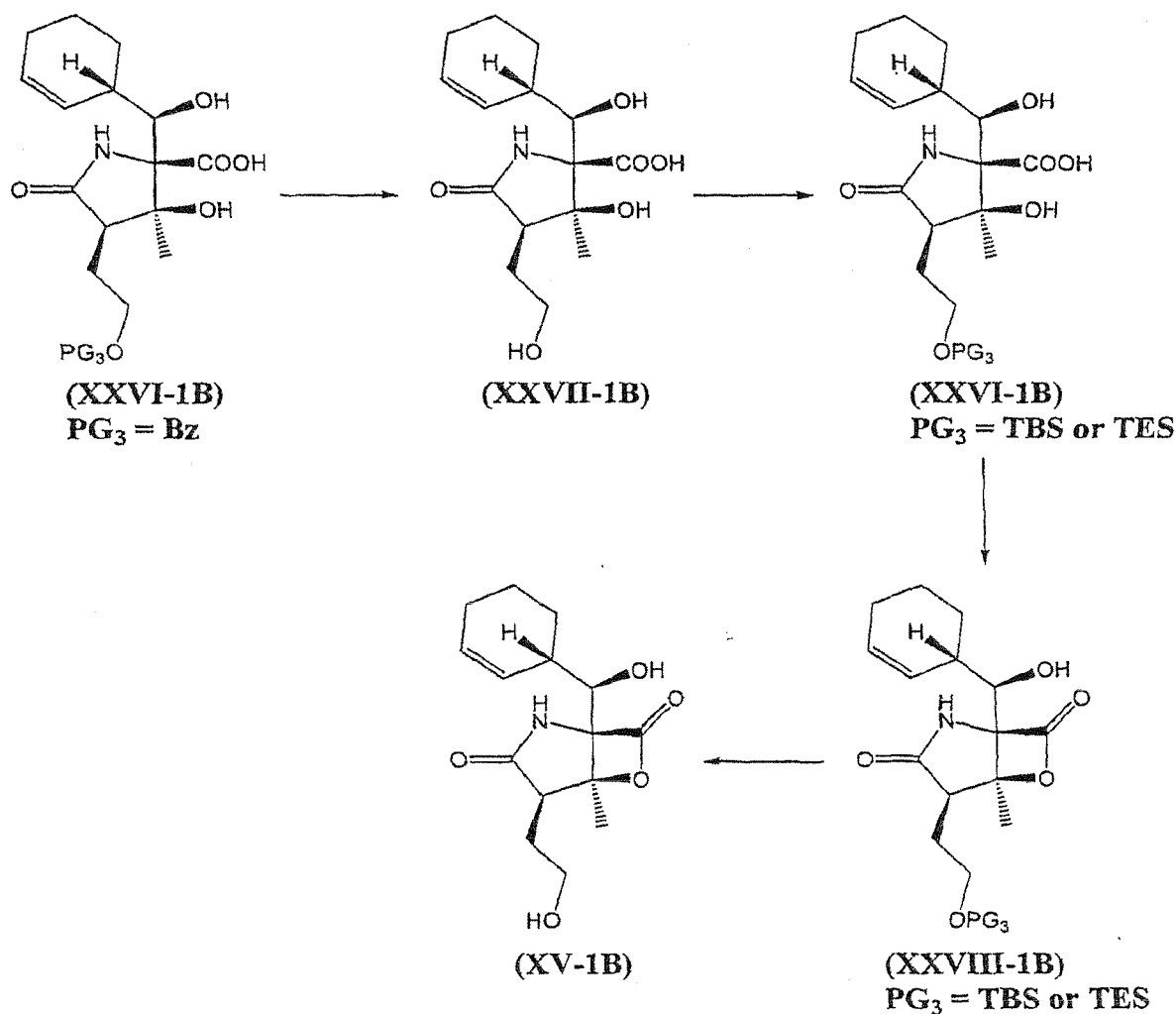


To a solution of **XXVp-1B-Bz-TMS** (120 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (118 mg, 0.278 mmol) and the reaction mixture was stirred at 25 °C for 2 hrs. The reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (3 mL) and saturated aqueous NaHCO_3 (2 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure to afford the crude aldehyde as a white powder which was used for the next step without purification.

To a solution of the above freshly prepared aldehyde in $t\text{-BuOH}/\text{H}_2\text{O}$ (2:1; 4.5 mL) was added NaH_2PO_4 (400 mg, 3.33 mmol) and the reaction mixture was cooled to 0 °C. Then 2-methyl-2-butene (2M in THF, 3.70 mL, 7.57 mmol) and NaClO_2 (175 mg, 1.93 mmol) were added sequentially and stirred at 0 °C for 1.5 hrs. The reaction mixture was then diluted with brine (5 mL) and extracted with EtOAc (2 x 5 mL). The aqueous phase was acidified with HCl (0.5 M) to pH 3.0 and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure to yield a white solid residue which was purified by reversed phase HPLC using an ACE 5 μ C18 column (150 x 21 mm ID) and a solvent gradient of 10% to 100% $\text{CH}_3\text{CN}/\text{H}_2\text{O}/0.05\%\text{TFA}$ over 22 min, holding at 100% $\text{CH}_3\text{CN}/0.05\%\text{TFA}$ for 3 min at a flow rate of 14.5 mL/min to afford the carboxylic acid **XXVI-1B-Bz** (66 mg,

0.16 mmol, 62.6% yield over two steps). The carboxylic acid **XXVI-1B-Bz** was characterized by ^1H -NMR (CD_3OD , 500 MHz), and ^{13}C -NMR (CD_3OD , 125 MHz). See Figures 39 and 40. MS (ESI) m/z 418.2 $[\text{M}+\text{H}]^+$.

EXAMPLE 26
SYNTHESIS OF COMPOUND (XV-1B) VIA (XXVI-1B-Bz)



Method A: 1) K_2CO_3 , MeOH; H^+ ; 2) TBSCl, imid.; 3) BOPCl; 4) HF.Pyr

To a solution of **XXVI-1B-Bz** (14 mg, 0.033 mmol) in MeOH (0.5 ml) was added K_2CO_3 (14 mg, 0.10 mmol) and the reaction mixture was stirred at 25 °C for 15 hrs. Then aqueous HCl (200 μl , 1.0 M) was added to this reaction mixture which was directly concentrated and dried under high vacuum to afford **XXVII-1B** in which the

benzoyl group has been replaced by hydrogen as a white residue, which was directly used in the next step without further purification.

To a solution of the product obtained from the previous step in CH_2Cl_2 (0.50 ml) were added imidazole (7.0 mg, 0.10 mmol) and TBSCl (10 mg, 0.066 mmol) and the mixture was stirred at 25 °C for 10 hrs. Then the reaction mixture was directly concentrated under reduced pressure and dried well by high vacuum to afford **XXVI-1B-TBS** a white residue, which was directly used in the next step without further purification.

To a solution of **XXVI-1B-TBS** in CH_3CN (0.40 ml) were added pyridine (0.40 ml) and BOPCl (17 mg, 0.066 mmol) and the reaction mixture was stirred at 25 °C for 16 hrs. Then the reaction mixture was concentrated under reduced pressure and the products purified by silica gel chromatography using EtOAc/hexanes gradients (20% to 80%) to afford the **XXVIII-1B-TBS** (5.0 mg; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) See Figure 41) and **XV-1B** (3.0 mg) as white solid.

To a solution of the above **XXVIII-1B-TBS** (5.0 mg) in THF (0.5 ml) were added pyridine (30 μl) and HF/pyridine (30 μl) and the reaction mixture was stirred at 25 °C for 2 hrs in a plastic tube. Then the reaction mixture was quenched with saturated aqueous NaHCO_3 (1 ml) and extracted with CH_2Cl_2 (3 x 1.0 ml). The organic phase was dried over MgSO_4 , concentrated under reduced pressure and purified by silica gel flash chromatography using a EtOAc/hexanes gradient (20% to 80%) to afford **XV-1B** (4.0 mg, 0.013 mmol). Overall Yield = 73%. The compound **XV-1B** was characterized by $^1\text{H-NMR}$ (acetone- d_6 , 500 MHz), and $^{13}\text{C-NMR}$ (acetone- d_6 , 125 MHz). See Figures 42 and 43. MS (ESI) m/z 296 $[\text{M}+\text{H}]^+$.

Method B: 1) K_2CO_3 , MeOH; H^+ ; 2) TESCl, imid.; 3) BOPCl; 4) HF.Pyr 28%

To a solution of **XXVI-1B-Bz** (240 mg, 0.575 mmol) in MeOH (3.0 ml) was added K_2CO_3 (240 mg, 1.74 mmol) and the reaction mixture was stirred at 25 °C for 15 hrs. Then aqueous HCl (600 μl , 1.0 M) was added to this reaction mixture which was directly concentrated and dried under high vacuum to afford **XXVII-1B** as a white residue, which was directly used for the next step without further purification.

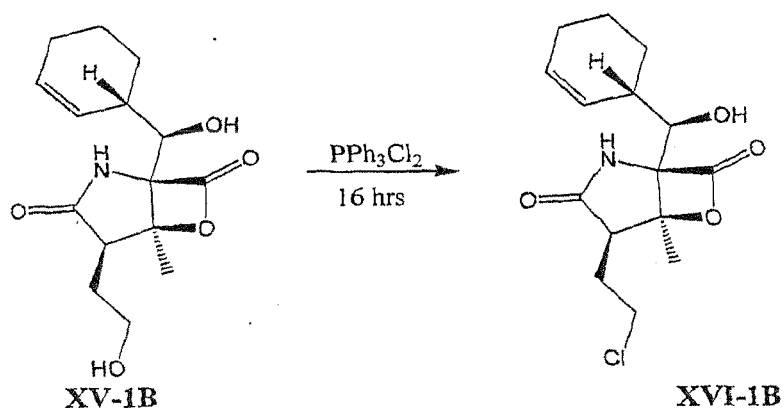
To a solution of the product obtained from the previous step in CH_2Cl_2 (5.0 ml) was added imidazole (195 mg, 2.87 mmol) and TESCl (0.39 ml, 2.30 mmol) and the reaction mixture was stirred at 25 °C for 18 hrs. Then the reaction mixture was directly concentrated under reduced pressure and dried well by high vacuum to afford

XXVI-1B-TES as a white residue, which was directly used in the next step without further purification.

To a solution of **XXVI-1B-TES** in CH_3CN (3.0 ml) were added pyridine (3.0 ml) and BOPCl (290 mg, 1.15 mmol) and the reaction mixture was stirred at 25 °C for 18 hrs. Then the reaction mixture was filtered through a short silica-plug; the filtrate was concentrated under reduced pressure and dried by high vacuum to afford TES- β -lactone **XXVIII-1B-TES** as a white residue, which was directly used in the next step without further purification.

To a solution of the above TES- β -lactone residue (**XXVIII-1B-TES**) in THF (5.0 ml) were added pyridine (150 μl) and HF.pyridine (150 μl) and the reaction mixture was stirred at 25 °C for 5-6 hrs in a plastic tube. Then the reaction mixture was quenched with saturated aqueous NaHCO_3 (10 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The organic phase was dried over MgSO_4 , concentrated under reduced pressure and purified by silica flash chromatography (EtOAc in hexanes, 10% to 80%) to afford β -lactone **XV-1B** (47.0 mg, 0.16 mmol). Overall Yield = 28%.

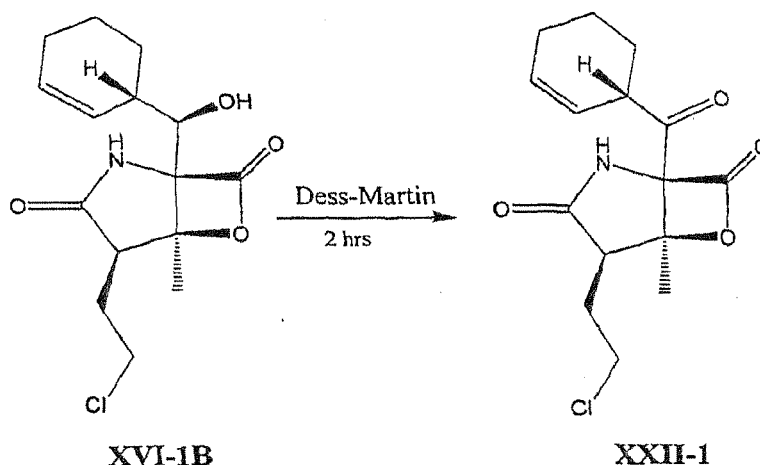
EXAMPLE 27
SYNTHESIS OF COMPOUND (XVI-1B) VIA (XV-1B)



To a solution of **XV-1B** (35 mg, 0.118 mmol) obtained from Example 26 in CH_3CN (250 μl) were added pyridine (250 μl) and Ph_3PCl_2 (80 mg, 0.24 mmol) and the reaction mixture was stirred at RT for 18 hrs. Then the reaction mixture was concentrated under reduced pressure and purified by silica gel flash chromatography using a EtOAc/hexanes gradient (5% to 20%) to afford **XVI-1B** (21 mg, 57% yield). The compound **XVI-1B** was characterized by ^1H -NMR (CDCl_3 , 500 MHz) and ^{13}C -NMR (CDCl_3 , 125 MHz). See Figures 44 and 45. MS (ESI) m/z 314 $[\text{M}+\text{H}]^+$. MS (ESI) m/z 314

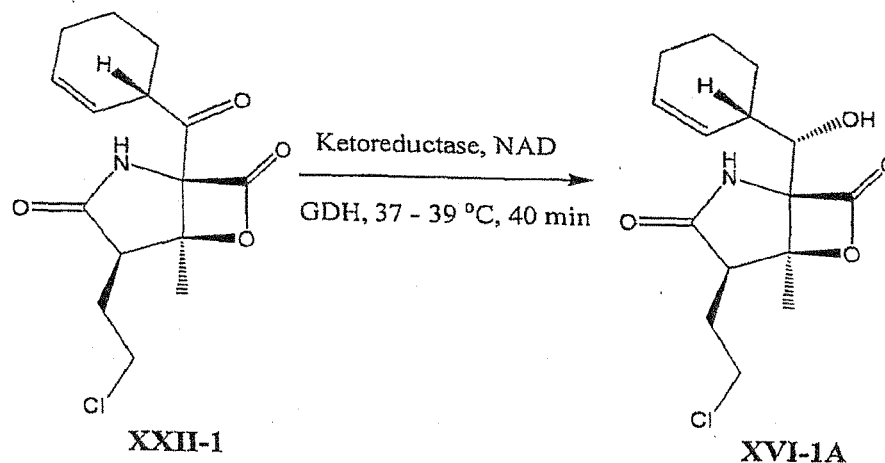
$[M+H]^+$. HRMS (ESI) m/z 314.1151 $[M+H]^+$ (calcd for $C_{15}H_{21}ClNO_4$, 314.1159, $\Delta = -2.4$ ppm).

EXAMPLE 28
SYNTHESIS OF COMPOUND (XXII-1) VIA (XVI-1B)



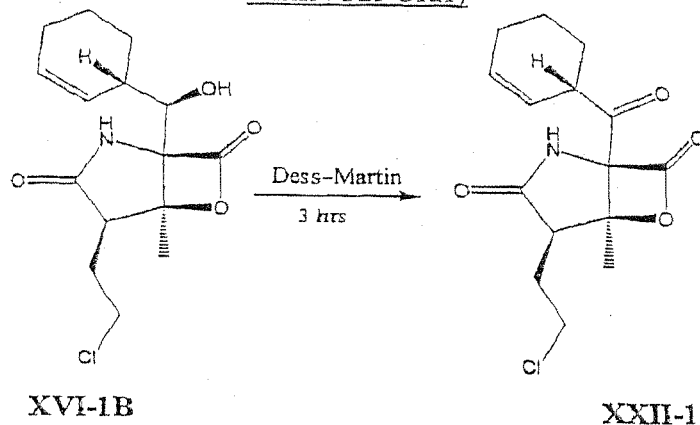
To a solution of compound **XVI-1B** (10 mg, 32 μ mol) obtained from Example 27 in CH_2Cl_2 (4 mL) in a round bottom flask (25 mL) were added Dess-Martin periodinane (20.35 mg, 48 μ mol) and a magnetic stir bar. The reaction mixture was stirred at RT for about 2 hours then quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and then extracted with CH_2Cl_2 (2 x 5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was then purified by silica flash column (0.4 cm ID x 3 cm) chromatography using a solvent gradient of 19:1 (5 mL) to 9:1 (5 mL) to 17:3 (5 mL) to 4:1 (10 mL) hexanes/EtOAc to afford **XXII-1** (6 mg, 19.3 μ mol, 60.3% yield). The compound **XXII-1** was characterized by 1H NMR ($CDCl_3$, 500 MHz). See Figure 46. MS (ESI), m/z 312 $[M+H]^+$ and 334 $[M+Na]^+$.

EXAMPLE 29
SYNTHESIS OF COMPOUND (XVI-1A) VIA (XXII-1) BY ENZYMATIC
REDUCTION



To a solution of **XXII-1** (6 mg, 19.3 μmol) in DMSO (0.4 mL) obtained from Example 28 in a round bottom flask (25 mL), 600 μL of potassium phosphate buffer (150 mM, pH 6.9), 12 mg of ketoreductase KRED-EXP-B1Y, 1.2 mg of glucose dehydrogenase (GDH), 300 μL of glucose (50 mM) and 300 μL of NAD (1 mM) were added. The above reaction mixture was stirred at 37-39 $^\circ\text{C}$ for about 40 min and then extracted with EtOAc (2 x 10 mL); the combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. This afforded about 5 mg of **XVI-1A**. (82.7% yield) as a crude product which was further purified by normal phase HPLC using a Phenomenex Luna 10 μ Silica column (25 cm x 21.2 mm ID) using a solvent gradient of 25% to 80% EtOAc/hexanes over 19 min, 80 to 100% EtOAc/hexanes over 1 min, holding at 100% EtOAc for 5 min, at a flow rate of 14.5 mL/min and monitoring the purification by evaporative light scattering detection (ELSD) to afford 2 mg of pure **XVI-1A**. $[\alpha]_{\text{D}} -70^\circ$ (c 0.05, CH_3CN). The compound **XVI-1A** was characterized by ^1H -NMR ($\text{DMSO}-d_6$, 500 MHz) and ^{13}C -NMR ($\text{DMSO}-d_6$, 125 MHz). See Figures 47 and 49. The ^1H NMR spectra were in complete agreement with those of an authentic sample of **XVI-1A** (Figures 48 and 50 respectively). MS (ESI) m/z 314 $[\text{M}+\text{H}]^+$. HRESIMS m/z 314.1173 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{15}\text{H}_{21}\text{ClNO}_4$, 314.1159, $\Delta = 4.5$ ppm).

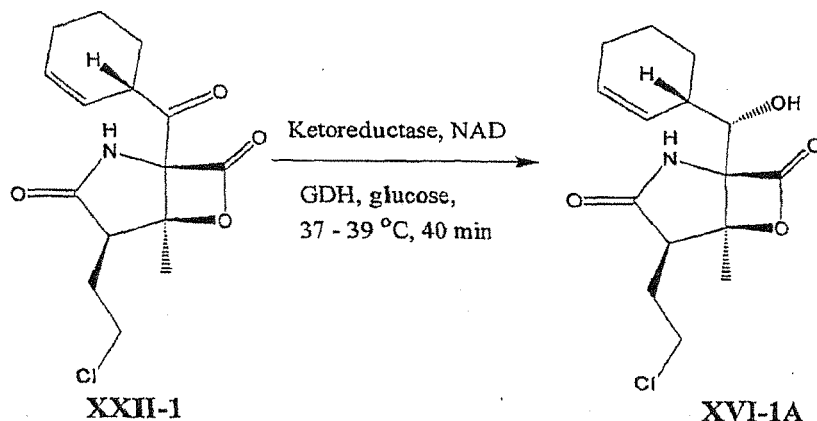
EXAMPLE 30
SYNTHESIS OF COMPOUND (XXII-1) VIA (XVI-1B) (OBTAINED AS A
SEMISYNTHETIC DERIVATIVE OF A FERMENTATION PRODUCT OF
SALINOSPORA)



To a solution of **XVI-1B** (75 mg, 0.24 mmol) (obtained as a semi-synthetic derivative of XVI-1A, which was obtained by fermentation of *Salinospora tropica* as disclosed in U.S. Patent No. 7,176,232, issued February 13, 2007)

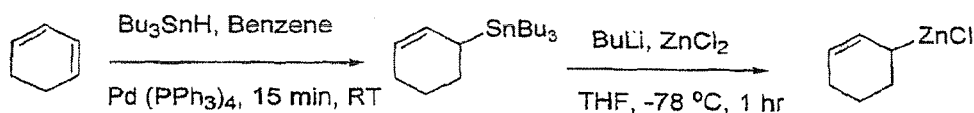
in CH₂Cl₂ (35 mL) in a round bottom flask (150 mL) were added Dess-Martin periodinane (202.5 mg; 0.48 mmol) and a magnetic stir bar. The reaction mixture was stirred at RT for about 3 hours, over which the progress of the reaction was monitored by analytical HPLC. The reaction mixture was then quenched with saturated aqueous Na₂S₂O₃ (40 ml) and saturated aqueous NaHCO₃ (40 ml), and extracted with CH₂Cl₂ (2 x 40 ml). The organic phase was dried over Na₂SO₄ and concentrated by reduced pressure to afford **XXII-1** (70 mg, 0.22 mmol, 94% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.54 (s, 3H), 1.59 (m, 2H), 1.66-1.70 (m, 1H), 1.73-1.80 (m, 1H), 1.96 (m, 2H), 2.0-2.11 (m, 2H), 3.09 (t, 1H, *J* = 7.0 Hz), 3.63 (brs, 1H), 3.83-3.88 (m, 1H), 3.89-3.93 (m, 1H), 5.50 (dd, 1H, *J* = 2, 10 Hz), 5.92 (dd, 1H, *J* = 2.5, 10 Hz), 9.70 (s, 1H, NH); MS (ESI), *m/z* 312 [M+H]⁺ and 334 [M+Na]⁺.

EXAMPLE 31
SYNTHESIS OF COMPOUND (XVI-1A) VIA (XXII-1) BY ENZYMATIC
REDUCTION



To a solution of **XXII-1** (50 mg, 0.16 mmol) obtained from Example 30 in DMSO (1 mL) in a round bottom flask (25 mL), 5 mL of potassium phosphate buffer (150 mM, pH 6.9), 100 mg of ketoreductase KRED-EXP-B1Y, 10 mg of glucose dehydrogenase (GDH), 2.5 mL of glucose (50 mM) and 2.5 mL of NAD (1 mM) were added. The above reaction mixture was stirred at 37-39 °C for 40 min and then extracted with EtOAc (2 x 25 mL); the combined organic phase was dried over Na₂SO₄ and concentrated under reduced pressure to yield a crude product which was crystallized in 1:1 acetone: heptane (6 mL) in a 20 mL scintillation vial (by slow evaporation under nitrogen gas) to afford **XVI-1A** as white crystalline solid (42 mg, 0.13 mmol, 85% yield). The structure of **XVI-1A** was confirmed by comparison of its mp, specific rotation and ¹H- and ¹³C-NMR spectra with those of an authentic sample.

EXAMPLE 32
SYNTHESIS OF 2-CYCLOHEXENYL ZINC CHLORIDE

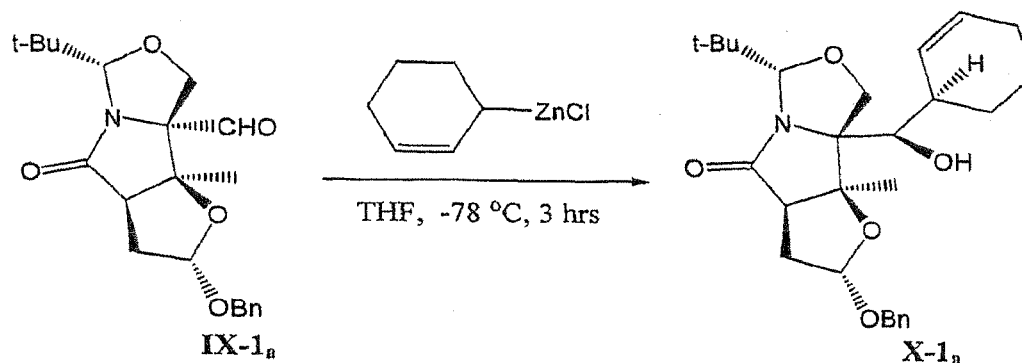


To a solution of 1, 3-cyclohexadiene (0.96 g, 12 mmol, d = 0.84, 1143 uL) and Pd(PPh₃)₄ (462.2 mg, 0.4 mmol) in benzene (10 mL) under nitrogen atmosphere, was added Bu₃SnH (1.16g, 4 mmol, d = 1.098, 1.06 mL) dropwise at room temperature and stirred for 15 minutes. After the solvent was removed on rotavap, the product was purified on silica flash chromatography (column 1.5 cm ID x 20 cm) using a solvent

gradient of 10:0 (100 mL) to 19:1(100 mL) to 9:1 (100 mL) of hexanes/EtOAc to afford cyclohexenyltributyltin (3.5 g, 9.4 mmol, 78.6% yield) as a clear liquid. Cyclohexenyltributyltin was characterized by $^1\text{H-NMR}$ (CDCl_3 , 500 MHz). See Figure 51.

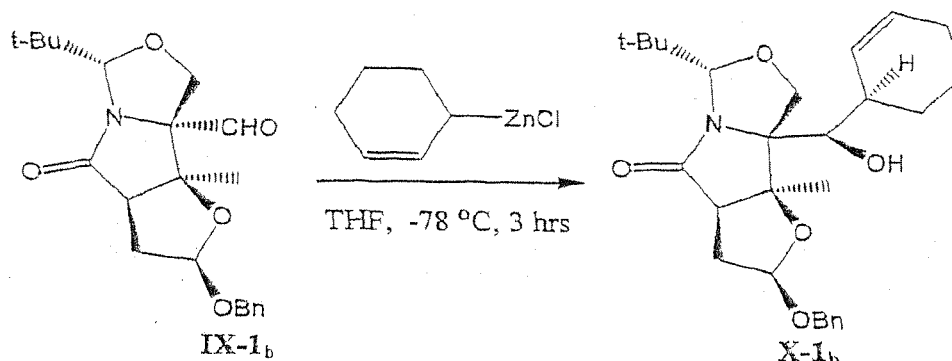
To a solution of cyclohexenyltributyltin (0.92 g, 2.5 mmol) in THF (5 mL) at $-78\text{ }^\circ\text{C}$ under nitrogen was added $n\text{BuLi}$ (1 mL, 2.5 M solution in hexane, 2.5 mmol). After an additional 30 min stirring, ZnCl_2 (340 mg, 2.5 mmol, dissolved in 2 mL of THF) was added and stirring was continued for 30 min at $-78\text{ }^\circ\text{C}$ to afford 2-cyclohexenyl zinc chloride.

EXAMPLE 33
SYNTHESIS OF COMPOUND X-1_a



To a solution of IX-1_a (30 mg, 0.08 mmol) in 5 mL of THF at $-78\text{ }^\circ\text{C}$, 1 mL of cyclohexenyl zinc chloride (freshly prepared; Example 32) was added and stirred at $-78\text{ }^\circ\text{C}$ for about 3 hrs. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude product which was purified by silica flash chromatography (column 2.5 cm ID x 6 cm) using a solvent gradient of 19:1 (50 mL) to 9:1 (50 mL) to 17:3 (50 mL) to 8:2 (50 mL) to 7:3 (50 mL) of hexanes/EtOAc to afford pure cyclohexene derivative X-1_a (26 mg, 0.057 mmol, 71.4% yield). The compound X-1_a was characterized by $^1\text{H-NMR}$ (CDCl_3 , 500 MHz), and $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz). See Figures 52 and 53. MS (ESI) m/z 456.3 $[\text{MH}]^+$ and 478.3 $[\text{M}+\text{Na}]^+$.

EXAMPLE 34
SYNTHESIS OF COMPOUND X-1_b



To a solution of IX-1_b (35 mg, 0.094 mmol) in 5 mL of THF at -78 °C, 1.2 mL of cyclohexenyl zinc chloride (freshly prepared; Example 32) was added and stirred at -78 °C for about 3 hrs. The reaction was quenched with H₂O (15 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to yield a liquid residue. This residue was dissolved in 5 mL of hexanes and allowed to stand for an hour. A white solid was precipitated from the residue, which was separated by decanting the solvent. The solid material was further washed with hexanes (2 x 2 mL) and dried on high-vacuum to afford pure X-1_b (32 mg, 0.066 mmol, 75% yield). The compound X-1_b was characterized by ¹H-NMR (CDCl₃, 500 MHz), and ¹³C-NMR (CDCl₃, 125 MHz). See Figures 54 and 55. MS (ESI) m/z 456.3 [M+H]⁺ and 478.3 [M+Na]⁺. The stereochemistry was determined by X-ray crystallography (See Figure 56).

EXAMPLE 35
IN VITRO INHIBITION OF 20S PROTEASOME ACTIVITY BY COMPOUND XVI-1A OBTAINED FROM SYNTHETIC AND FERMENTATION SOURCES

The compound XVI-1A as obtained synthetically using a method described herein and by fermentation as described in U.S. Patent No. 7,144,723.

Both the synthetic and fermentation compounds XVI-1A were prepared as 20 mM stock solution in DMSO and stored in small aliquots at -80°C. Purified rabbit muscle 20S proteasome was obtained from Boston Biochem (Cambridge, MA). To enhance the chymotrypsin-like activity of the proteasome, the assay buffer (20 mM HEPES, pH7.3, 0.5 mM EDTA, and 0.05% Triton X100) was supplemented with SDS resulting in a final SDS concentration of 0.035%.

The substrate used was suc-LLVY-AMC, a fluorogenic peptide substrate specifically cleaved by the chymotrypsin-like activity of the proteasome. Assays were performed at a proteasome concentration of 1 $\mu\text{g/ml}$ in a final volume of 200 μl in 96-well Costar microtiter plates. Both the synthetic and fermentation compounds XVI-1A were tested as eight-point dose response curves with final concentrations ranging from 500 nM to 158 pM. After addition of test compounds to the rabbit 20S proteasomes, the samples were preincubated at 37°C for five minutes in a temperature controlled Fluoroskan Ascent 96-well microplate reader (Thermo Electron, Waltham, MA). During this preincubation step, the substrate was diluted 25-fold in SDS-containing assay buffer. After the preincubation period, the reactions were initiated by the addition of 10 μl of the diluted substrate and the plates were returned to the plate reader. The final concentration of substrate in the reactions was 20 μM . Fluorescence of the cleaved peptide substrate was measured at λ_{ex} =390 nm and λ_{em} =460 nm. All data were collected every five minutes for 2 hour and plotted as the mean of duplicate data points. The IC_{50} values (the drug concentration at which 50% of the maximal relative fluorescence is inhibited) were calculated by Prism (GraphPad Software) using a sigmoidal dose-response, variable slope model. To evaluate the activity of the compounds against the caspase-like activity of the 20S proteasome, reactions were performed as described above except that Z-LLE-AMC was used as the peptide substrate. Both the synthetic and fermentation compounds XVI-1A were tested at concentrations ranging from 5 μM to 1.6 nM. For the evaluation of these compounds against the trypsin-like activity of the 20S proteasome, the SDS was omitted from the assay buffer and Boc-LRR-AMC was used as the peptide substrate. The concentration of the test compounds used in these assays ranged from 500 nM to 158 pM.

Results (IC_{50} values) shown in Table 4 and in Figures 57-59 illustrate that both synthetic and fermentation compounds XVI-1A have similar inhibitory activity against the chymotrypsin-like, trypsin-like and caspase-like activities of the 20S proteasome *in vitro*.

TABLE 4: *IN VITRO* INHIBITION OF PURIFIED RABBIT 20S PROTEASOMES BY THE SYNTHETIC AND FERMENTATION COMPOUNDS OF FORMULA XVI-1A

<u>Compound XVI-1A</u>	IC ₅₀ Values (nM)		
	Chymotrypsin-like	Trypsin-like	Caspase-like
Fermentation	2.6	35	387
Synthetic	3.2	37	467

EXAMPLE 36EFFECTS ON THE CHYMOTRYPSIN-LIKE ACTIVITY OF PROTEASOMES IN RPMI 8226 CELLS BY COMPOUNDS XVI-1A OBTAINED FROM SYNTHETICALLY AND FROM FERMENTATION

RPMI 8226 (ATCC, CCL-155), the human multiple myeloma cell line, was cultured in RPMI 1640 medium supplemented with 2 mM L-Glutamine, 1% Penicillin/Streptomycin, 10 mM HEPES and 10% Fetal Bovine Serum at 37°C, 5% CO₂ and 95% humidified air. To evaluate the inhibitory effects on the chymotrypsin-like activity of the 20S proteasome, test compounds prepared in DMSO were appropriately diluted in culture medium and added to 1x10⁶/ml RPMI 8226 cells at final concentration of 1, 5 or 10 nM. DMSO was used as the vehicle control at a final concentration of 0.1%. Following 1 hr incubation of RPMI 8226 cells with the compounds, the cells were pelleted by centrifugation at 2,000 rpm for 10 sec at room temperature and washed 3X with ice-cold 1X Dubach's Phosphate-Buffered Saline (DPBS, Mediatech, Herndon, VA). DPBS washed cells were lysed on ice for 15 min in lysis buffer (20 mM HEPES, 0.5 mM EDTA, 0.05% Triton X-100, pH 7.3) supplemented with protease inhibitor cocktail (Roche Diagnostics, Indianapolis, IN). Cell debris was pelleted by centrifugation at 14,000 rpm for 10 min, 4°C and supernatants (=cell lysates) were transferred to a new tube. Protein concentration was determined by the BCA protein assay kit (Pierce Biotechnology, Rockford, IL). The chymotrypsin-like activity of the 20S proteasome in the RPMI 8226 cell lysates was measured by using the Suc-LLVY-AMC fluorogenic peptide substrate in the proteasome assay buffer (20 mM HEPES, 0.5 mM EDTA, pH 8.0) containing a final concentration of 0.035% SDS. The reactions were initiated by the addition of 10 µL of 0.4 mM Suc-LLVY-AMC (prepared by diluting a 10 mM solution of the peptide in DMSO 1:25 with assay buffer) to 190 µL of the cell lysates in 96-well

Costar microtiter plate and incubated in the Thermo Lab Systems Fluoroskan plate reader at 37°C. Fluorescence of the cleaved peptide substrate was measured at λ_{ex} =390 nm and λ_{em} =460 nm. All data were collected every five minutes for 2 hour. The total protein used for each assay was 20 μg . The final concentration of Suc-LLVY-AMC and DMSO was 20 μM and 0.2%, respectively. After subtraction of the background (the values from wells containing buffer and substrate in the absence of cell lysate), the activity of test compound was expressed as % inhibition as normalized to the proteasome activity observed in the DMSO treated control cells.

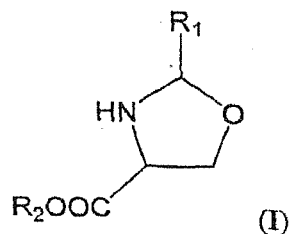
Results in Table 5 show that exposure of RPMI 8226 cells to the fermentation or synthetic compounds XVI-1A resulted in a dose-dependent inhibition of the 20S proteasome chymotrypsin-like activity. In addition, a similar inhibition profile was observed when cells were exposed to compound XVI-1A obtained via fermentation or to compound XVI-1A obtained synthetically.

TABLE 5: INHIBITION OF THE CHYMOTRYPSIN-LIKE ACTIVITY OF PROTEASOME IN RPMI 8826 CELLS BY SYNTHETIC AND FERMENTATION COMPOUNDS XVI-1A

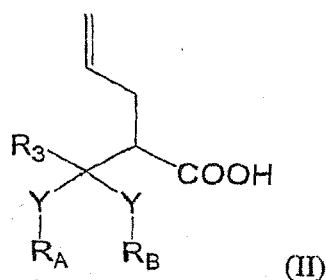
Concentration (nM)	% inhibition of the 20S proteasome chymotrypsin-like activity in RPMI 8826 cells	
	Fermentation	Synthetic
1	38	32
5	86	79
10	97	96

WHAT IS CLAIMED IS:

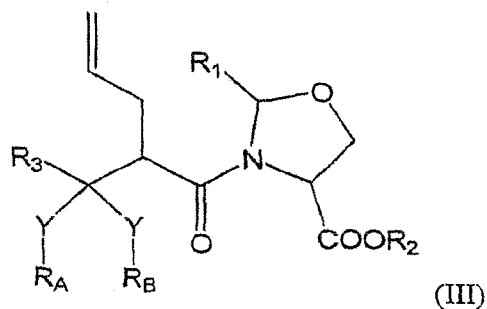
1. A method of chemical synthesis comprising the steps of:
 (a) reacting a compound of formula (I):



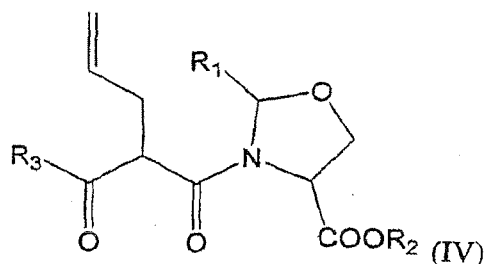
with a compound of formula (II):



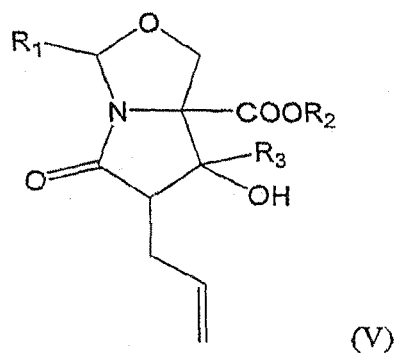
to form a compound of formula (III):



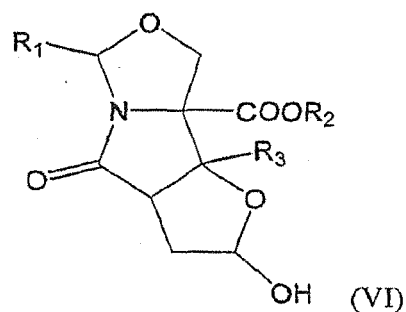
(b) deprotecting the compound of formula (III) to form a compound of formula (IV):



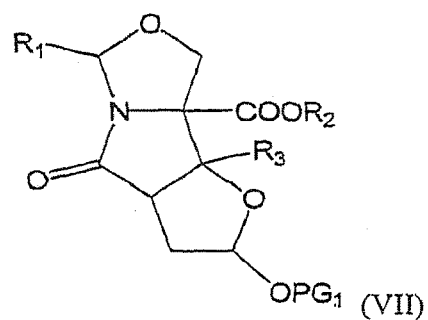
(c) performing an intramolecular aldol reaction on the compound of formula (IV) to form a compound of formula (V):



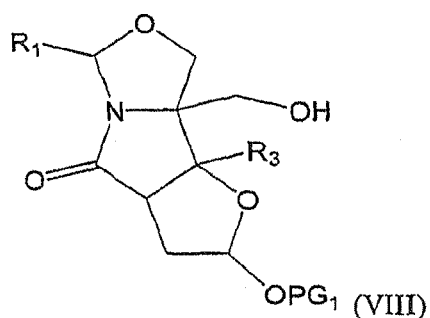
(d) cleaving the carbon-carbon double bond of the compound of formula (V) and cyclizing the cleaved double bond with the tertiary hydroxy group to form a compound of formula (VI):



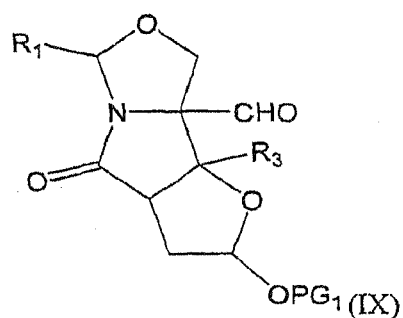
(e) protecting the hemiacetal of the compound of formula (VI) to form a compound of formula (VII):



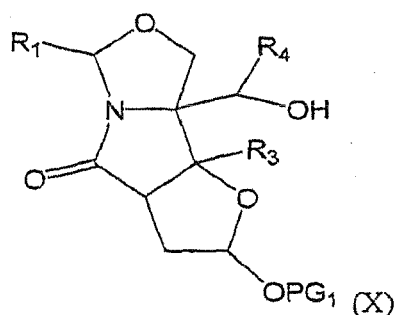
(f) reducing the $COOR_2$ group of the compound of formula (VII) to an alcohol to form a compound of formula (VIII):



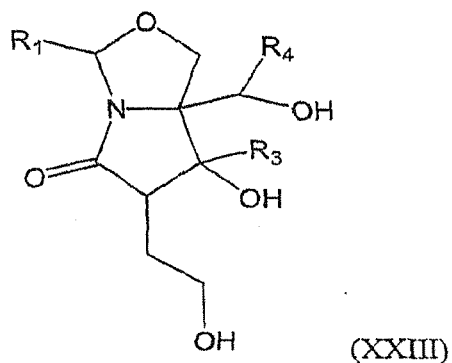
(g) oxidizing the alcohol of the compound of formula (VIII) to form a compound of formula (IX):



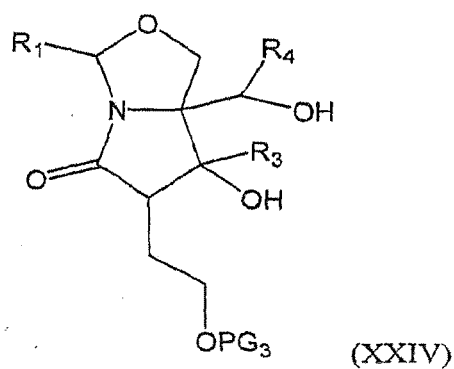
(h) adding R₄ to the compound of formula (IX) by reacting the compound of formula (IX) with an organometallic moiety containing at least one R₄ to form a compound of formula (X):



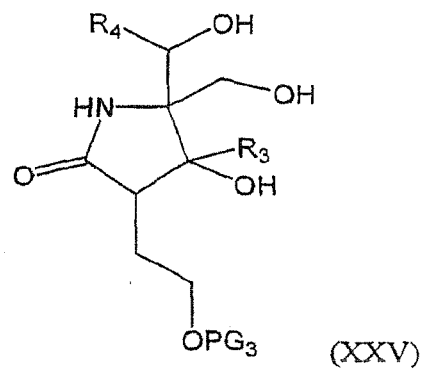
(i) removing PG₁ on the compound of formula (X) and reductively opening the hemiacetal of the compound of formula (X) to form a compound of formula (XXIII):



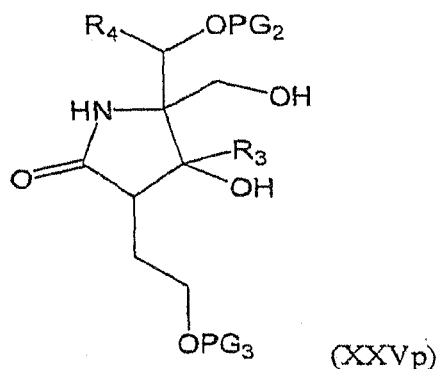
(j) protecting the primary hydroxy group of the compound of formula (XXIII) to form a compound of formula (XXIV):



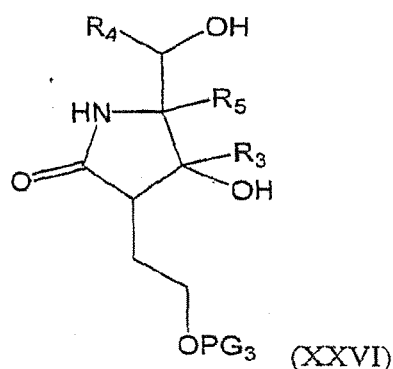
(k) cleaving the aминаl group of the compound of formula (XXIV) to form a compound of formula (XXV):



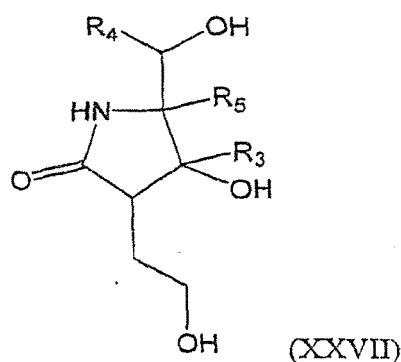
(l) protecting the secondary alcohol of the compound of formula (XXV) to form a compound of formula (XXVp):



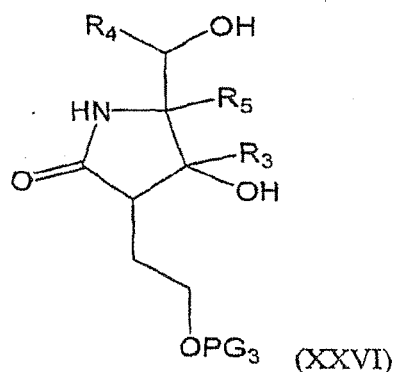
(m) converting the primary alcohol group and removing the PG₂ protecting group moiety on the secondary alcohol of the compound of formula (XXVp) to form a compound of formula (XXVI):



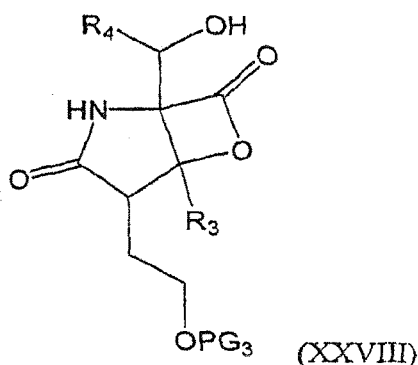
(n) removing the PG₃ protecting group moiety on the primary alcohol of the compound of formula (XXVI) to form a compound of formula (XXVII):



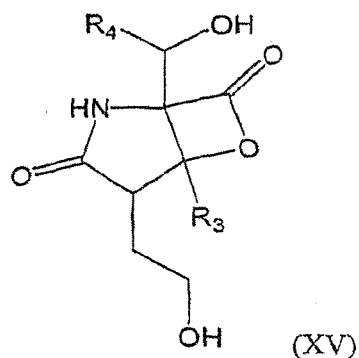
(o) protecting the primary alcohol of the compound of formula (XXVII) with the PG₃ protecting group moiety to form a compound of formula (XXVI), wherein the PG₃ can be same or different from the PG₃ in step (m):



(p) performing a lactonization reaction on the compound of formula (XXVI) to form a compound of formula (XXVIII):



(q) removing the PG₃ protecting group moiety on the compound of formula (XXVIII) to form a compound of formula (XV):



wherein:

R₁ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl;

R₂ is selected from the group consisting of hydrogen, or substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl, and arylalkyl;

R₃ is selected from the group consisting of substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, and arylalkyl;

R_4 can be selected from the group consisting of substituted or unsubstituted variants of the following: C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkenyl, C_3 - C_{12} cycloalkynyl, C_3 - C_{12} heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocynoalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of a guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl;

R_5 is selected from the group consisting of $-C(=O)OR_6$, $-C(=O)SR_6$, $-C(=O)NR_6R_6$ and $-C(=O)Z$;

each R_6 can be independently selected from the group consisting of hydrogen, halogen, or substituted or unsubstituted variants of the following: C_1 - C_{24} alkyl, acyl, alkylacyl, arylacyl, aryl, arylalkyl, p-nitrophenyl, pentafluorophenyl, pentafluoroethyl, trifluoroethyl, trichloroethyl, and heteroaryl;

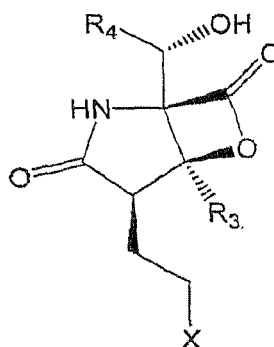
R_A and R_B are each independently selected from the group consisting of substituted or unsubstituted variants of the following: C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, wherein R_A and R_B can be optionally bound together to form an optionally substituted 5, 6, 7, or 8 membered heterocyclyl;

Y is oxygen or sulfur;

Z is a halogen; and

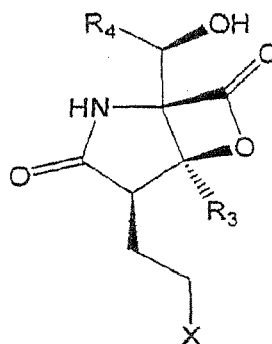
PG_1 and PG_3 are each a protecting group moiety.

2. The method of Claim 1, further comprising substituting the primary hydroxy group of the compound of formula (XV) to form a compound of formula (XVI), wherein the compound of formula (XVI) has the following structure:



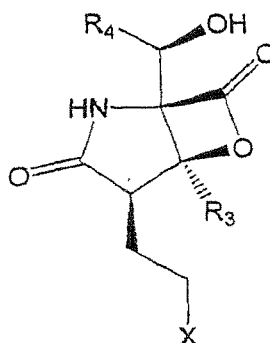
wherein X is a halogen.

3. The method of Claim 1, further comprising substituting the primary hydroxy group of the compound of formula (XV) to form a compound of formula (XVI-B), wherein the compound of formula (XVI-B) has the following structure:

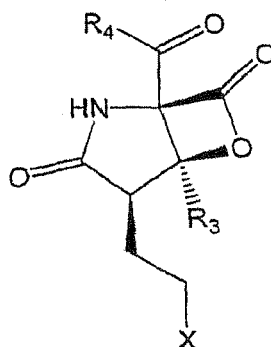


wherein X is a halogen.

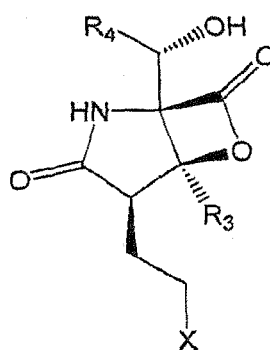
4. The method of Claim 3, further comprising the steps of:
 (1) oxidizing the secondary hydroxy group of the compound of formula (XVI-B) wherein the compound of formula (XVI-B) has the following structure:



to form a compound of formula (XXII):

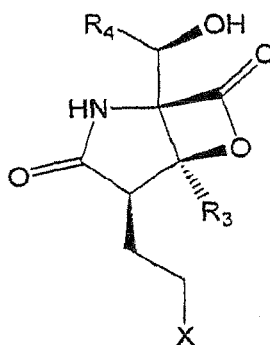


(2) reducing the keto group of the compound of formula (XXII) to form a compound of formula (XVI-A), wherein the compound of formula (XVI-A) has the following structure::

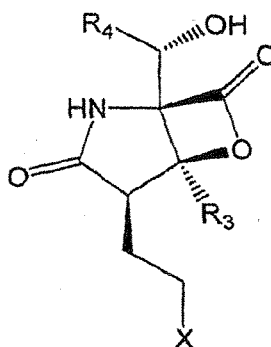


5. The method of Claim 3, further comprising the step of:

(1) inverting the stereochemistry of the secondary hydroxy carbon center of the compound of formula (XVI-B), wherein the compound of formula (XVI-B) has the following structure:



to form a compound of formula (XVI-A), wherein the compound of formula (XVI-A) has the following structure:



6. The method Claim 1, wherein PG₁ and PG₂ are each independently selected from the group consisting of benzyl, a substituted benzyl, an alkylcarbonyl, an arylalkylcarbonyl, a substituted methyl ether, a substituted ethyl ether, a substituted benzyl ether, a tetrahydropyranyl ether, a silyl ether, an ester, and a carbonate.

7. The method Claim 1, wherein the organometallic moiety is selected from the group consisting of an organomagnesium compound, an organolithium compound, an organotin compound, an organocuprates compound, organozinc compound, organoboron compound, and an organopalladium compound, a metal carbonyl, a metallocene, a carbene complex, and an organometalloid.

8. The of method Claim 1, wherein:

the organometallic moiety is selected from the group consisting of R₄-MgR₇, R₄-ZnR₇, -Li, (R₄)_p-B(R₇)_{3-p}, and (R₄)_q-Sn(R₇)_{4-q};

R₇ is selected from the group consisting of halogen, or substituted or unsubstituted variants of the following: alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, isopinocampheyl, hydroxy, alkoxy, and carbonylalkoxy, wherein if more than one R₇ is present, the R₇ groups can optionally be bond together to form an optionally substituted cycloalkyl, cycloalkenyl, heteroalkyl or heteroalkenyl ring;

p is an integer from 1 to 3; and

q is an integer from 1 to 4.

9. The method of Claim 1 wherein R₄ is 2-cyclohexenyl.

10. The method of Claim 1 wherein R₃ is methyl.

11. The method of Claim 1 wherein R₅ is -C(=O)OR₆; and R₆ is hydrogen or substituted or unsubstituted C₁-C₂₄ alkyl.

12. The method of Claim 1 wherein R₅ is -C(=O)Z; and Z is a halogen.

13. A method of forming a compound of formula (X) from a compound of formula (V) comprising the steps of:

cleaving the carbon-carbon double bond of the compound of formula (V) and cyclizing the cleaved double bond with the tertiary hydroxy group;

transforming $-\text{COOR}_2$ to an aldehyde, wherein R_2 is selected from the group consisting of hydrogen, or substituted or unsubstituted variants of the following: C_{1-6} alkyl, aryl, and arylalkyl; and

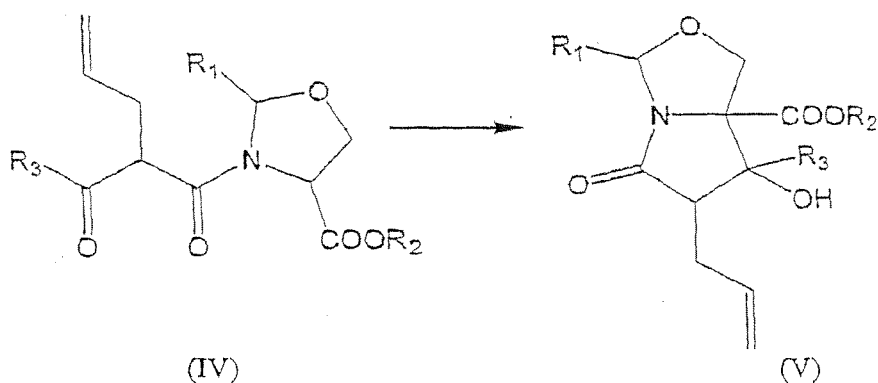
adding R_4 to the aldehyde using an organometallic moiety containing at least one R_4 , wherein R_4 is selected from the group consisting of substituted or unsubstituted variants of the following: $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_2\text{-C}_{12}$ alkenyl, $\text{C}_2\text{-C}_{12}$ alkynyl, $\text{C}_3\text{-C}_{12}$ cycloalkyl, $\text{C}_3\text{-C}_{12}$ cycloalkenyl, $\text{C}_3\text{-C}_{12}$ cycloalkynyl, $\text{C}_3\text{-C}_{12}$ heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl, (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocynoalkyl, boronic acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of a guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonoxyalkyl, salt of a phosphonoxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl and halogenated alkyl including polyhalogenated alkyl.

14. A method of forming a compound of formula (XVII) from a compound of formula (V) comprising the steps of:

cleaving the carbon-carbon double bond of the compound of formula (V) and cyclizing the cleaved double bond with the tertiary hydroxy group; and

- 5 adding R₄ after cyclization with the tertiary hydroxy group using an organometallic moiety containing at least one R₄, wherein R₄ is selected from the group consisting of substituted or unsubstituted variants of the following: C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, C₃-C₁₂ cycloalkynyl, C₃-C₁₂ heterocyclyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (cycloalkyl)alkyl,
- 10 (heterocyclyl)alkyl, acyl, acylalkyl, alkyloxycarbonyloxy, carbonylacyl, aminocarbonyl, azido, azidoalkyl, aminoalkyl, salt of an aminoalkyl, carboxyalkyl, salt of carboxyalkyl, alkylaminoalkyl, salt of an alkylaminoalkyl, dialkylaminoalkyl, salt of a dialkylaminoalkyl, phenyl, alkylthioalkyl, arylthioalkyl, carboxy, cyano, alkanesulfonylalkyl, alkanesulfinylalkyl, alkoxysulfinylalkyl, thiocynoalkyl, boronic
- 15 acidalkyl, boronic esteralkyl, guanidinoalkyl, salt of a guanidinoalkyl, sulfoalkyl, salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, salt of a phosphorylalkyl, (alkylphosphory)alkyl, pyridinylalkyl, salt of a pyridinylalkyl, salt of a heteroarylalkyl
- 20 and halogenated alkyl including polyhalogenated alkyl.

15. A method for preparing a compound of formula (V) comprising performing an intramolecular aldol reaction on the compound of formula (IV) to form a compound of formula (V):



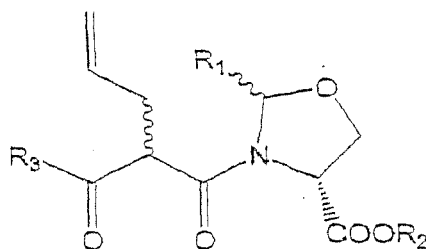
wherein:

R_1 is hydrogen or substituted or unsubstituted C_{1-6} alkyl;

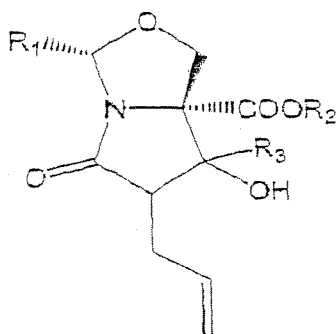
R_2 is selected from the group consisting of hydrogen, or substituted or unsubstituted variants of the following: C_{1-6} alkyl, aryl, and arylalkyl; and

R_3 is selected from the group consisting of substituted or unsubstituted variants of the following: C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{3-6} cycloalkenyl, aryl, and arylalkyl.

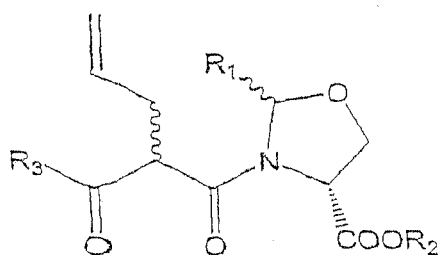
16. The method of Claim 15, wherein:
the compound of formula (IV) has the structure:



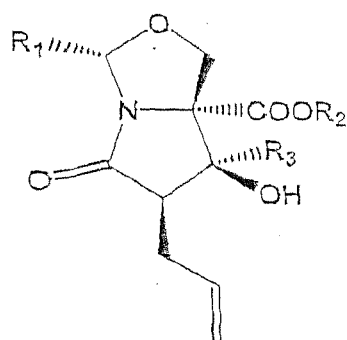
the compound of formula (V) has the structure:



17. The method of Claim 15, wherein:
the compound of formula (IV) has the structure:

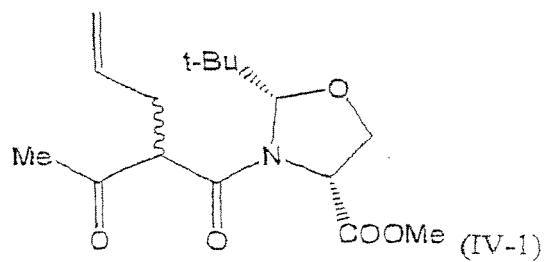


the compound of formula (V) has the structure:

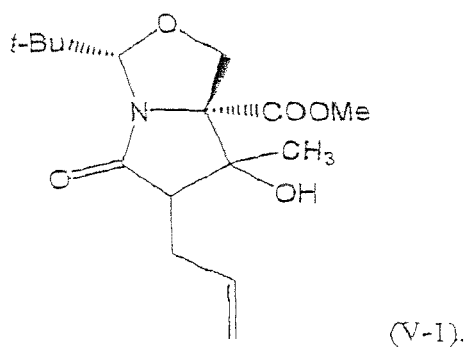


18. The method of Claim 15, wherein:

the compound of formula (IV) has the structure:



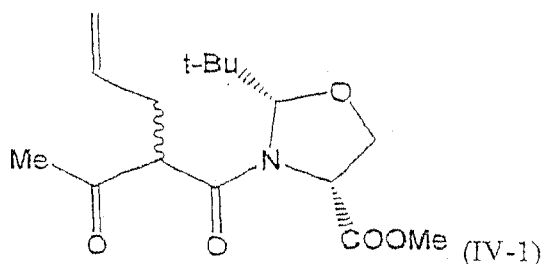
the compound of formula (V) has the structure:



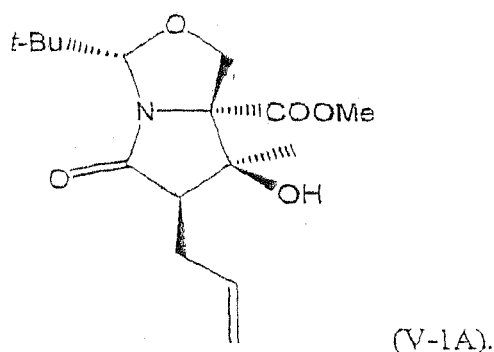
(V-1).

19. The method of Claim 15, wherein:

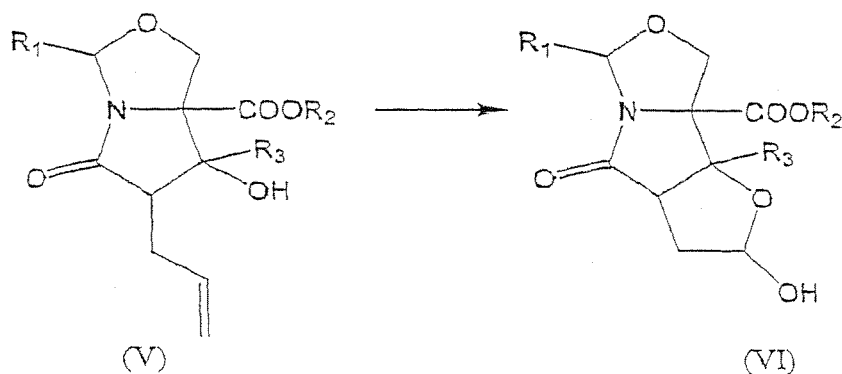
the compound of formula (IV) has the structure:



the compound of formula (V) has the structure:



20. A method of preparing a compound of formula (VI) comprising cleaving the double bond of the compound of formula (V) and cyclizing the cleaved double bond with the tertiary hydroxy group to form a compound of formula (VI):



wherein:

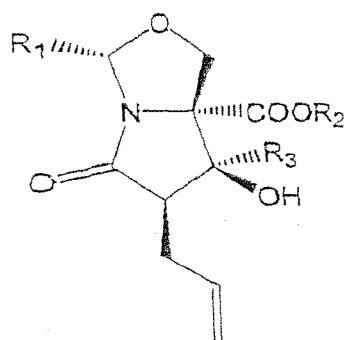
R₁ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl;

R₂ is selected from the group consisting of hydrogen, or substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl, and arylalkyl; and

R₃ is selected from the group consisting of substituted or unsubstituted variants of the following: C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, and arylalkyl.

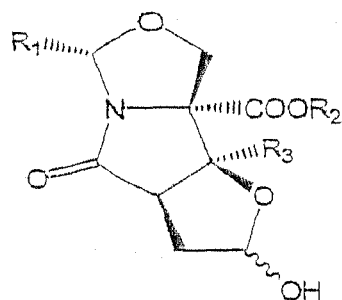
21. The method of Claim 20, wherein:

the compound of formula (V) has the structure:



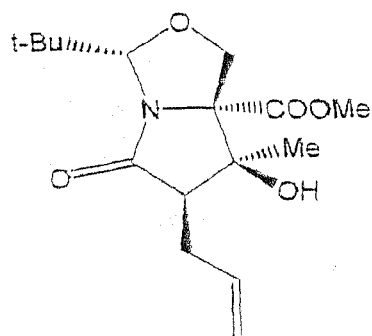
; and

the compound of formula (VI) has the structure:



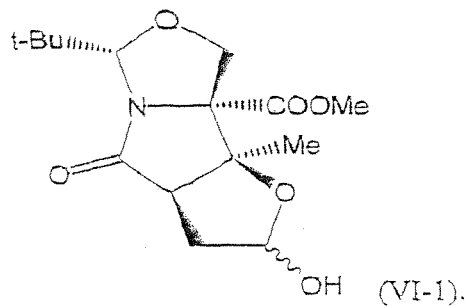
22. The method of Claim 20, wherein:

the compound of formula (V) has the structure:



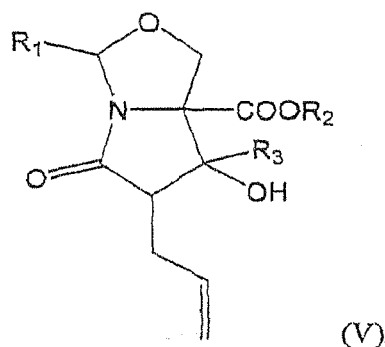
(V-1A) ; and

the compound of formula (VI) has the structure:



(VI-1).

23. A compound of formula (V):



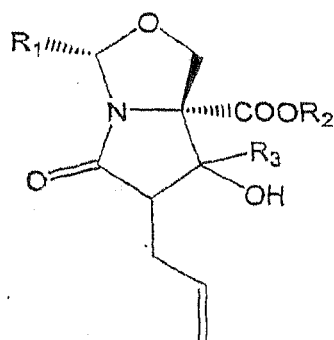
wherein:

R₁ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl;

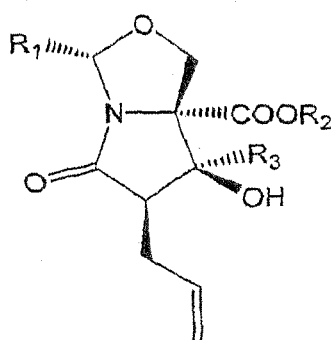
R₂ is selected from the group consisting of hydrogen, or substituted or unsubstituted variants of the following: C₁₋₆ alkyl, aryl, and arylalkyl; and

R₃ is selected from the group consisting of substituted or unsubstituted variants of the following: C₁₋₆ alkyl, a C₃₋₆ cycloalkyl, a C₂₋₆ alkenyl, C₃₋₆ cycloalkenyl, aryl, and arylalkyl.

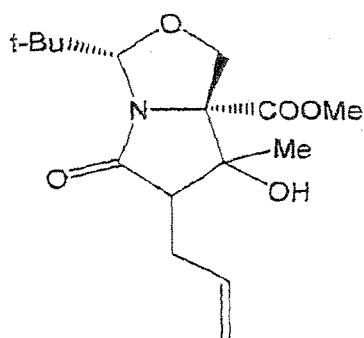
24. The compound of Claim 23, wherein the compound of formula (V) has the structure:



25. The compound of Claim 23, wherein the compound of formula (V) has the structure:

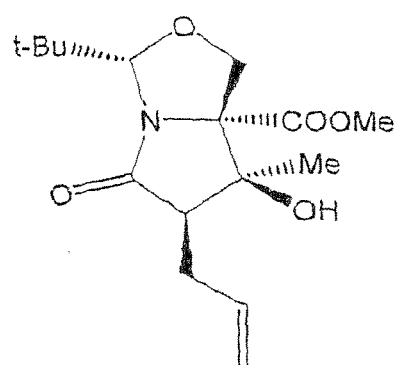


26. The compound of Claim 23, wherein the compound of formula (V) has the structure:



(V-1).

27. The compound of Claim 23, wherein the compound of formula (V) has the structure:



(V-1A).