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(54) **PREPARATION OF METHIONINE OR
SELENOMETHIONINE FROM HOMOSERINE
VIA A LACTONE INTERMEDIATE**

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(57) **ABSTRACT**

Provided herein are processes for the production of methion-
ine or selenomethionine from homoserine. In particular, the
processes proceed via the production of lactone intermedi-
ates.

PREPARATION OF METHIONINE OR SELENOMETHIONINE FROM HOMOSERINE VIA A LACTONE INTERMEDIATE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of PCT International Application No. PCT/US2011/027642, filed Mar. 9, 2011, which claims benefit of U.S. Provisional Application No. 61/312,012, filed Mar. 9, 2010, U.S. Provisional Application No. 61/312,020, filed Mar. 9, 2010, U.S. Provisional Application No. 61/312,024, filed Mar. 9, 2010, and U.S. Provisional Application No. 61/333,915, filed May 12, 2010, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

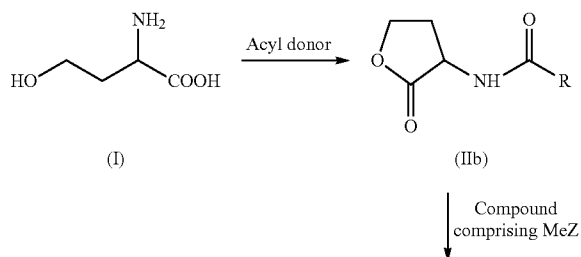
[0002] The present invention relates to the synthesis of methionine or selenomethionine from homoserine, wherein the synthesis pathway proceeds via the production of a lactone intermediate or derivatives thereof.

BACKGROUND OF THE INVENTION

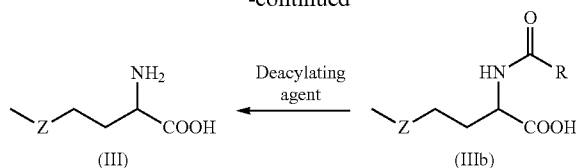
[0003] Methionine is utilized in a variety of fields, from pharmaceuticals to health and fitness products to feed supplements. Selenomethionine is also commercially important because it is a natural source of selenium. Methionine is produced industrially in large amounts; it is currently produced by a completely synthetic pathway that utilizes petroleum-based chemicals and hazardous chemicals. Because of price increases in petroleum, the high costs associated with hazardous waste management, as well as for safety and environmental reasons, there exists a need for alternate methionine or selenomethionine synthesis pathways.

SUMMARY OF THE INVENTION

[0004] Among the various aspects of the disclosure is the provision of a process for the production of a compound comprising Formula (III) or a pharmaceutically acceptable salt thereof from a compound comprising Formula (I). The process comprises contacting a compound comprising Formula (I) with an acyl donor to form a compound comprising Formula (IIb). The process further comprises contacting the compound comprising Formula (IIb) with a compound comprising MeZ to form a compound comprising Formula (IIIb). The final step of the process comprises contacting the compound comprising Formula (IIIb) with a deacylating agent to form the compound comprising Formula (III) or a pharmaceutically acceptable salt thereof:



-continued



[0005] wherein:

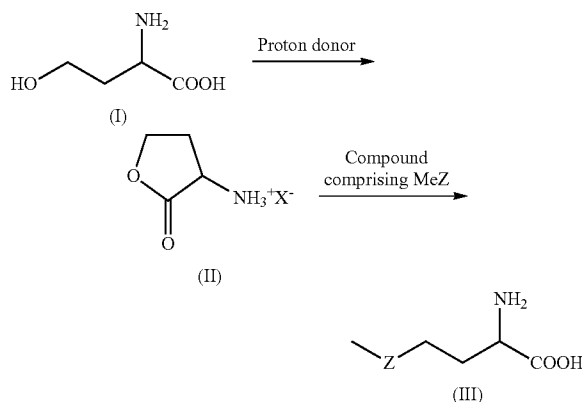
[0006] the compound comprising MeZ is an alkali metal methaneselenoate or methyl selenol;

[0007] Me is methyl;

[0008] R is chosen from hydrogen, hydrocarbyl, and substituted hydrocarbyl; and

[0009] Z is selenium.

[0010] A further aspect provides a process for preparing a compound comprising Formula (III) or a pharmaceutically acceptable salt thereof. The process comprises contacting a compound comprising Formula (I) with a proton donor (HX) to form a compound comprising Formula (II). The process further comprises contacting the compound comprising Formula (II) with a compound comprising MeZ to form the compound comprising Formula (III) or a pharmaceutically acceptable salt thereof:



[0011] wherein:

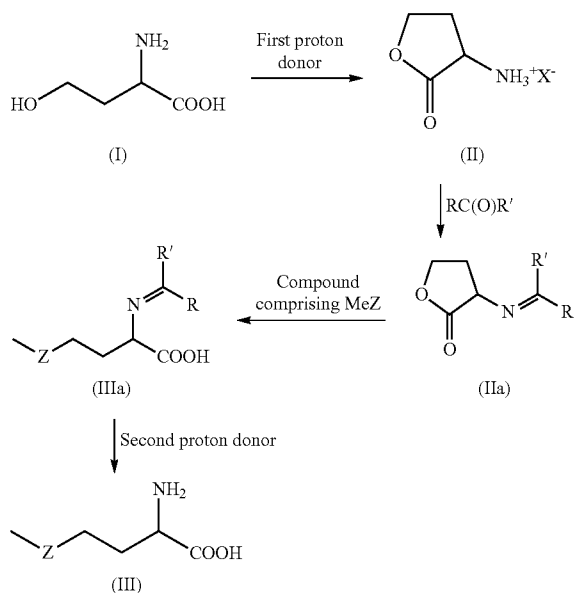
[0012] the compound comprising MeZ is chosen from an alkali metal methaneselenoate and methyl selenol;

[0013] Me is methyl;

[0014] X is an anion; and

[0015] Z is selenium.

[0016] In another aspect, a process for preparing a compound comprising Formula (III) or a pharmaceutically acceptable salt thereof is provided. The process comprises contacting the compound comprising Formula (I) with a first proton donor (HX) to form the compound comprising Formula (II). The compound comprising Formula (II) is then contacted with RC(O)R' to form a compound comprising Formula (IIa). The process further comprises contacting the compound comprising Formula (IIa) with a compound comprising MeZ to form a compound comprising Formula (IIIa). The process further comprises contacting the compound comprising Formula (IIIa) with a second proton donor to form the compound comprising Formula (III) or a pharmaceutically acceptable salt thereof:



[0017] wherein:

[0018] Me is methyl;

[0019] R is hydrocarbyl or substituted hydrocarbyl;

[0020] R' is hydrogen, hydrocarbyl, or substituted hydrocarbyl;

[0021] X is an anion; and

[0022] Z is sulfur or selenium.

[0023] Other aspects and features of the invention are described in more detail below.

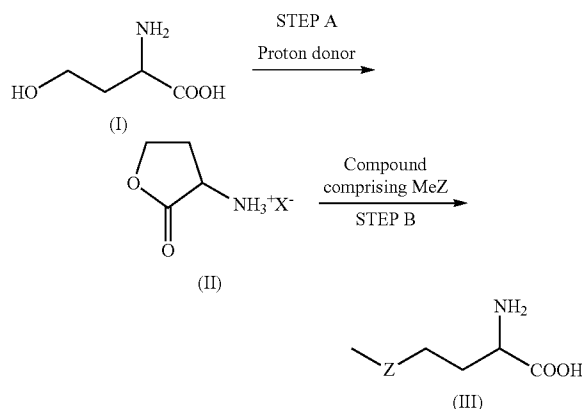
DETAILED DESCRIPTION

[0024] Provided herein are processes for the preparation of methionine or selenomethionine from homoserine, wherein the processes proceed via lactone intermediates. The lactone intermediate may comprise an unsubstituted homoserine lactone, a homoserine lactone Schiff base/imine complex, or an N-acylated homoserine lactone. These synthetic processes not only avoid the use of hazardous chemicals, but also utilize homoserine, which can be prepared using fermentation processes.

(I) Preparation of a Compound Comprising Formula (III) Via a Lactone Intermediate

[0025] One aspect of the present invention provides a process for preparing methionine or selenomethionine, i.e., a compound comprising Formula (III), from homoserine, wherein the process proceeds via a lactone intermediate. The process comprises Step A in which a compound comprising Formula (I) is contacted with a proton donor (HX) to form a compound comprising Formula (II). The process further comprises Step B in which the compound comprising Formula (II) is contacted with a compound comprising MeZ to form the compound comprising Formula (III) or a pharmaceutically acceptable salt thereof. For the purposes of illustration, Reaction Scheme 1 depicts this aspect of the invention:

Reaction Scheme 1:



wherein: Me is methyl;
X is an anion; and
Z is a sulfur or selenium.

(a) Step A—Reaction Mix

[0026] Step A of the process comprises contacting the compound comprising Formula (I) with a proton donor (HX) to form the compound comprising Formula (II). The process commences with the formation of a reaction mixture comprising the compound comprising Formula (I) and the proton donor.

[0027] (i) Proton Donor

[0028] A variety of proton donors may be used in Step A of the process. In general, the proton donor, HX, has a pKa less than about 0. Suitable proton donors include, without limit, HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₂SO₄, MeSO₃H, CF₃SO₃H, and p-toluene sulfonic acid. In one embodiment, the proton donor may be HCl.

[0029] The amount of proton donor that is contacted with the compound comprising Formula (I) can and will vary. In general, the molar ratio of the compound comprising Formula (I) to the proton donor may range from about 1:0.1 to about 1:10. In some embodiments, the molar ratio of the compound comprising Formula (I) to the proton donor may range from about 1:0.5 to about 1:5. In certain embodiments, the molar ratio of the compound comprising Formula (I) to the proton donor may be about 1:0.8, 1:0.9, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, or 1:2.0. In one embodiment, the molar ratio of the compound comprising Formula (I) to the proton donor may be about 1:1.2.

[0030] (ii) Solvent

[0031] Typically, the reaction mixture also comprises a solvent. In general, the solvent may be a protic solvent or an aprotic solvent. Suitable protic solvents include water, a C1-C4 alcohol, and mixtures thereof. Examples of C1-C4 alcohols include methanol, ethanol, isopropanol, n-propanol, isobutanol, n-butanol, s-butanol, t-butanol, and combinations thereof. In exemplary embodiments, the protic solvent may be water or isopropanol. Suitable aprotic solvents include, but are not limited to acetone, acetonitrile, dimethylsulfoxide, dioxane, pyrazine, tetrahydrofuran, toluene, diethoxymethane, and combinations thereof. In an exemplary embodiment, the aprotic solvent is toluene.

[0032] The amount of solvent included in the reaction mixture may vary. Typically, the molar ratio of the solvent to the

compound comprising Formula (I) may range from about 1:1 to about 50:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (I) may range from about 5:1 to about 25:1. In certain embodiments, the molar ratio of the solvent to the compound comprising Formula (I) may be about 6:1, 8:1, 10:1, 12:1, 14:1, 16:1, 18:1, or 20:1. In one embodiment, the molar ratio of the solvent to the compound comprising Formula (I) may be about 16:1.

(b) Step A—Reaction Conditions

[0033] The reaction of Step A is allowed to proceed at a temperature that may range from about 50° C. to about 150° C. In certain embodiments, the temperature of the reaction may be about 60° C., 65° C., 70° C., 75° C., 80° C., 85° C., 90° C., 95° C., 100° C., 105° C., 110° C., 115° C., or 120° C. In one embodiment, Step A is conducted at a temperature of about 100° C.

[0034] The pressure of the reaction can and will vary. The reaction may be conducted at a pressure ranging from about 0 psig to about 50 psig. In some embodiments, the pressure of the reaction may be autogenous. For example, in one embodiment, the solvent may be an alcohol, the temperature of the reaction may be about 100° C., and the pressure of the reaction may be autogenous.

[0035] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. For example, the duration of the reaction may range from about 0.1 minute to about 10 hours. The completeness of the reaction may be determined by any method known to one skilled in the art, such as IR, HPLC, or LC-MS. In this context, a “completed reaction” generally means that the reaction mixture contains a significantly diminished amount of the compound comprising Formula (I) and a significantly increased amount of the compound comprising Formula (II) compared to the amounts of each present at the beginning of the reaction. Typically, the amount of the compound comprising Formula (I) remaining in the reaction mixture may be less than about 3%, less than about 1%, or preferably less than about 0.5%. In some embodiments, water may be removed as the reaction proceeds. Water may be removed by any suitable means familiar to those skilled in the art including, but not limited to, azeotropic distillation and addition of water scavengers.

[0036] Upon completion of the reaction, the reaction mixture may be cooled and the compound comprising Formula (II) may be isolated by any means familiar to those of skill in the art. Suitable means include concentration, precipitation, filtration, distillation, phase extraction, crystallization, vacuum drying and the like. For example, the compound comprising Formula (II) may be concentrated and treated with an alcohol such as methanol to cause precipitation of the compound comprising Formula (II). The isolated product may be washed and dried, and analyzed by means familiar to those skilled in the art.

[0037] The yield of the compound comprising Formula (II) can and will vary. Typically, the yield of the compound comprising Formula (II) may be at least about 60% w/w. In some embodiments of the invention, the yield of the compound comprising Formula (II) may be at least about 65%, 70%, 75%, 80%, or 85% w/w. In further embodiments, the yield of the compound comprising Formula (II) may be at least about 90%, 95%, 97%, or 99% w/w.

(c) Step B—Reaction Mix

[0038] The process further comprises Step B in which the compound comprising Formula (II) is contacted with a compound comprising MeZ to form the compound comprising Formula (III) or salt thereof. As used herein, the “compound comprising MeZ” refers to a compound capable of donating a methyl sulfur moiety or a methyl selenium moiety to another compound. Non-limiting examples of suitable compounds comprising MeZ include alkali metal methanethiolates, methyl mercaptan, alkali metal methaneselenoates, and methyl selenol. Typically, the alkali metal will be sodium, potassium, or lithium.

[0039] (i) Alkali Metal Methanethiolates

[0040] In some embodiments, a salt of the compound comprising Formula (III) in which Z is sulfur may be prepared by contacting the compound comprising Formula (II) with an alkali metal methanethiolate (i.e., alkali metal MeS). Suitable alkali metal methanethiolates include sodium methanethiolate, potassium methanethiolate, or lithium methanethiolate. The alkali metal methanethiolate may be purchased from a commercial chemical supply company. Alternatively, the alkali metal methanethiolate may be synthesized prior to use.

[0041] Synthesis of Alkali Metal Methanethiolate.

[0042] The alkali metal methanethiolate may be synthesized by contacting methyl mercaptan (also called methanethiol) with an alkali metal hydroxide. Suitable alkali metal hydroxides include, but are not limited to, sodium hydroxide, potassium hydroxide, and lithium hydroxide.

[0043] The amount of alkali metal hydroxide contacted with methyl mercaptan can and will vary. In general, the molar ratio of methyl mercaptan to alkali metal hydroxide may range from about 1:0.1 to about 1:10. In one embodiment, the molar ratio of methyl mercaptan to alkali metal hydroxide may be about 1:1

[0044] Typically, contact with the alkali metal hydroxide is conducted in the presence of a solvent. The solvent may be a protic solvent, an aprotic solvent, an organic solvent, or combinations thereof. Non-limiting examples of suitable protic solvents include water; an alcohol such as methanol, ethanol, isopropanol, n-propanol, isobutanol, n-butanol, s-butanol, t-butanol; a diol such as propylene glycol, water, and combinations thereof. Examples of suitable aprotic solvent include without limit acetone, acetonitrile, cumene, diethoxymethane, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), N,N-dimethylpropionamide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), 1,2-dimethoxyethane (DME), dimethoxymethane, diethoxymethane (DEM), bis(2-methoxyethyl)ether, N,N-dimethylacetamide (DMAC), N-methyl-2-pyrrolidinone (NMP), ethyl formate, ethyl methyl ketone, formamide, hexachloroacetone, hexamethylphosphoramide, ionic liquids, N-methylacetamide, N-methylformamide, methylene chloride, nitrobenzene, nitromethane, propionitrile, sulfolane, tetramethylurea, tetrahydrofuran (THF), 2-methyl tetrahydrofuran, trichloromethane, and combinations thereof. Examples of suitable organic solvents include, but are not limited to, alkane and substituted alkane solvents (including cycloalkanes), aromatic hydrocarbons, esters, ethers, ketones, and combinations thereof. Specific organic solvents that may be used include, for example, benzene, chlorobenzene, ethyl acetate, heptane, hexane, isobutylmethylketone, isopropyl acetate, toluene, and combinations thereof.

[0045] In one embodiment, the alkali metal methanethiolate may be synthesized by contacting methyl mercaptan with a solution of alkali metal hydroxide comprising DMSO. In another embodiment, methyl mercaptan may be contacted with a solution of alkali metal hydroxide comprising DMSO and toluene. In yet another embodiment, methyl mercaptan may be contacted with a solution of alkali metal hydroxide comprising an alcohol such as n-butanol.

[0046] The amount of solvent included in the reaction mix can and will vary. In general, the molar ratio of the solvent to methyl mercaptan may range from about 0.5:1 to about 10:1. In various embodiments, the molar ratio of the solvent to methyl mercaptan may be about 1:1, 2:1, 3:1, 4:1, or 5:1.

[0047] The temperature of the reaction may also vary. Typically, the temperature of the reaction will range from about 0° C. to about 40° C. In some embodiments, the temperature of the reaction may be room temperature (i.e., about 22-25° C.). Typically, the reaction will be conducted under nitrogen or argon. Upon completion of the reaction, the resultant water and/or solvent may be removed by azeotropic distillation.

[0048] Reaction with Methanethiolate.

[0049] Contact between the compound comprising Formula (II) and the alkali metal methanethiolate produces a salt of the compound comprising Formula (III) in which Z is sulfur. The alkali metal may be any alkali metal may be sodium, lithium, or potassium. Typically, the molar ratio of the compound comprising Formula (II) to the alkali metal methanethiolate may range from about 1:0.5 to about 1:10. In some embodiments, the molar ratio of the compound comprising Formula (II) to the alkali metal methanethiolate may range from about 1:1 to about 1:4. In further embodiments, the molar ratio of the compound comprising Formula (II) to the alkali metal methanethiolate may be about 1:1.0, 1:1.2, 1:1.4, 1:1.6, 1:1.8, 1:2.0, 1:2.2, 1:2.4, 1:2.6, 1:2.8, 1:3.0, 1:3.2, 1:3.4, 1:3.6, 1:3.8, or 1:4.0. In one embodiment, the molar ratio of the compound comprising Formula (II) to the alkali metal methanethiolate may be about 1:2.2.

[0050] Reaction of the compound comprising Formula (II) with the alkali metal methanethiolate is generally conducted in the presence of a solvent. The solvent may be an aprotic solvent, a protic solvent, or combinations thereof. Examples of suitable aprotic and protic solvents are listed above. In particular, the aprotic solvent may be acetonitrile, 1,3-dimethyl-2-imidazolidinone, dimethyl sulfoxide, dimethyl sulfone, N,N-dimethylformamide, N,N-dimethylacetamide, diethoxymethane, N-methyl-2-pyrrolidinone, methyl t-butyl ether, formamide, ionic liquids, sulfalone, tetrahydrofuran, 2-methyl tetrahydrofuran, tetramethyl urea, or combinations thereof. Specific protic solvents that may be used include water, a C1-C4 alcohol, a diol such as propylene glycol, and combinations thereof. In one embodiment, the solvent may be dimethyl sulfoxide. In another embodiment, the solvent may be N,N-dimethylformamide.

[0051] The molar ratio of the solvent to the compound comprising Formula (II) can and will vary. In general, the molar ratio of the solvent to the compound comprising Formula (II) may range from about 1:1 to about 200:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (II) may be about 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, or 40:1, or 50:1, or 60:1, or 70:1, or 80:1, or 90:1, or 100:1, or 110:1, or 120:1, or 130:1, or 140:1, or 150:1, or 160:1, or 170:1, or 180:1, or 190:1, or 200:1. In one embodiment, the molar ratio of the solvent to the compound comprising Formula (II) may be about 25:1. In another

embodiment, the molar ratio of the solvent to the compound comprising Formula (II) may be about 100:1. In a further embodiment, the molar ratio of the solvent to the compound comprising Formula (II) may be about 150:1.

[0052] (ii) Methyl Mercaptan

[0053] In other embodiments, the compound comprising Formula (II) may be contacted with methyl mercaptan (MeSH) to form the compound comprising Formula (III) in which Z is sulfur. The molar ratio of the compound comprising Formula (II) to methyl mercaptan may range from about 1:10 to about 1:150. In various embodiments, the molar ratio of the compound comprising Formula (II) to methyl mercaptan may be about 1:20, 1:40, 1:60, 1:80, 1:100, 1:120, or 1:140. Reaction between the compound comprising Formula (II) and methyl mercaptan may be conducted in the presence of a catalyst. In some embodiments, the catalyst may be a proton donor having a pKa of less than 0. Non-limiting examples of proton donors having this characteristic include HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₂SO₄, MeSO₃H, CF₃SO₃H, alkyl sulfonic acids, aryl sulfonic acids, and the like. In general, the molar ratio acid of the compound comprising Formula (II) to the catalyst may range from about 1:1 to about 1:20. In some embodiments, molar ratio acid of the compound comprising Formula (II) to the catalyst may be about 1:3, 1:6, or 1:9.

[0054] Contact between the compound comprising Formula (II) and methyl mercaptan may be performed in the presence of a solvent. The solvent may be a protic solvent, an aprotic solvent, an organic solvent, or mixtures thereof. Examples of suitable solvents are listed above in section (I)(c)(i). The molar ratio of the solvent to the compound comprising Formula (II) may range from about 1:1 to about 50:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (II) may range from about 5:1 to about 25:1.

[0055] (iii) Alkali Metal Methaneselenoate

[0056] In still other embodiments, a salt of the compound comprising Formula (III) in which Z is selenium may be prepared by contacting the compound comprising Formula (II) with an alkali metal methaneselenoate (i.e., alkali metal MeSe). Suitable alkali metal methaneselenoates include sodium methaneselenoate, potassium methaneselenoate, or lithium methaneselenoate. As known to those of skill in the art, the alkali metal methaneselenoate may be prepared by a variety of methods. In one embodiment, for example, the alkali metal methaneselenoate may be prepared by contacting selenium metal with methyl lithium, methyl sodium, or a similar compound. In another embodiment, sodium methaneselenoate may be prepared by contacting sodium metal, sodium hydride, or sodium borohydride with dimethyldiselenide. In a further embodiment, the methaneselenoate may be prepared by contacting selenium metal with a Grignard reagent (i.e., an alkyl- or aryl magnesium halides such as methyl magnesium bromide or methyl magnesium iodide). In an alternate embodiment, the methaneselenoate may be prepared by contacting methyl selenol with a suitable base. In a further alternate embodiment, the methaneselenoate may be produced by reacting selenium metal with an alkali metal hydride, followed by an alkylating agent such as dimethylcarbonate or dimethylsulfate. Conditions for each of the above listed reactions are well known to those of skill in the art.

[0057] In general, the molar ratio of the compound comprising Formula (II) to the alkali metal methaneselenoate may range from about 1:0.5 to about 1:10. In some embodiments,

the molar ratio of the compound comprising Formula (II) to the alkali metal methaneselenoate may range from about 1:1 to about 1:4. In further embodiments, the molar ratio of the compound comprising Formula (II) to the alkali metal methaneselenoate may be about 1:1.0, 1:1.2, 1:1.4, 1:1.6, 1:1.8, 1:2.0, 1:2.2, 1:2.4, 1:2.6, 1:2.8, 1:3.0, 1:3.2, 1:3.4, 1:3.6, 1:3.8, or 1:4.0. In one embodiment, the molar ratio of the compound comprising Formula (II) to the alkali metal methaneselenoate may be about 1:2.2.

[0058] Contact between the compound comprising Formula (II) and the alkali metal methaneselenoate is generally conducted in the presence of a solvent. The solvent may be an aprotic solvent, a protic solvent, or combinations thereof. Examples of suitable aprotic and protic solvents are listed above in section (I)(c)(i). In particular, the aprotic solvent may be acetonitrile, cumene, dimethyl sulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone, formamide, ionic liquids, tetrahydrofuran, 2-methyl tetrahydrofuran, or combinations thereof. Specific protic solvents that may be used include water, a C1-C4 alcohol, a diol such as propylene glycol, and combinations thereof. In one embodiment, the solvent may be dimethyl sulfoxide. In another embodiment, the solvent may be N,N-dimethylformamide.

[0059] The molar ratio of the solvent to the compound comprising Formula (II) can and will vary. In general, the molar ratio of the solvent to the compound comprising Formula (II) may range from about 1:1 to about 50:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (II) may be about 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, or 40:1. In one embodiment, the molar ratio of the solvent to the compound comprising Formula (II) may be about 15:1. In another embodiment, the molar ratio of the solvent to the compound comprising Formula (II) may be about 20:1. In a further embodiment, the molar ratio of the solvent to the compound comprising Formula (II) may be about 25:1.

[0060] (iv) Methyl Selenol

[0061] In alternate embodiments, the compound comprising Formula (III) in which Z is selenium may be prepared by contacting the compound comprising Formula (II) with methyl selenol (MeSeH). The molar ratio of the compound comprising Formula (II) to methyl selenol may range from about 1:10 to about 1:150. In various embodiments, the molar ratio of the compound comprising Formula (II) to methyl selenol may be about 1:20, 1:40, 1:60, 1:80, 1:100, 1:120, or 1:140.

[0062] Reaction between the compound comprising Formula (II) and methyl selenol may be conducted in the presence of a catalyst. In some embodiments, the catalyst may be a proton donor having a pKa of less than 0. Non-limiting examples of proton donors having this characteristic include HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₂SO₄, MeSO₃H, CF₃SO₃H, alkyl sulfonic acids, aryl sulfonic acids, and the like. In general, the molar ratio acid of the compound comprising Formula (II) to the catalyst may range from about 1:1 to about 1:20. In some embodiments, molar ratio of the compound comprising Formula (II) to the catalyst may be about 1:3, 1:6, or 1:9.

[0063] Contact between the compound comprising Formula (II) and methyl selenol may be performed in the presence of a solvent. The solvent may be a protic solvent, an aprotic solvent, an organic solvent, or mixtures thereof. Examples of suitable solvents are listed above in section

(I)(c)(i). The molar ratio of the solvent to the compound comprising Formula (II) may range from about 1:1 to about 50:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (II) may range from about 5:1 to about 25:1.

(d) Step B—Reaction Conditions

[0064] The reaction of Step B is allowed to proceed at a temperature that may range from about 0° C. to about 200° C. In certain embodiments, the temperature of the reaction may be about 0° C., 10° C., 20° C., 30° C., 40° C., 50° C., 60° C., 70° C., 80° C., 90° C., 100° C., 110° C., or 120° C. In one embodiment, the reaction of Step B is conducted at a temperature of 50° C. In another embodiment, the reaction of Step B is conducted at a temperature of 80° C. The reaction may be conducted under ambient pressure, and under an inert atmosphere (e.g., nitrogen or argon).

[0065] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. Typically, the reaction may be allowed to proceed from about 5 minutes to about 10 hours. The reaction may be performed as a continuous process or a non-continuous process. The duration of the reaction may vary as a function of the temperature. For example, a reaction conducted at 50° C. may be allowed to proceed for about 5 hr; whereas a reaction conducted at 80° C. may be allowed to proceed for about 2 hr. The completeness of the reaction may be determined by any method known to one skilled in the art, such as IR, HPLC, or LC-MS. Typically, the amount of the compound comprising Formula (II) remaining in the reaction mixture may be less than about 3%, less than about 1%, or preferably less than about 0.5%. The reaction may proceed in a batch reaction or in a continuous flow process.

[0066] Upon completion of Step B of the process, the reaction mixture may be cooled and the compound comprising Formula (III) or salt thereof may be isolated by any means familiar to those of skill in the art. Suitable means include distillation, concentration, precipitation, filtration, phase extraction, crystallization, and the like. For example, the reaction mixture may be distilled to yield a distillate comprising the compound comprising Formula (III) or salt thereof. The distillate may be treated such that the compound comprising Formula (III) or its salt precipitates. The precipitated product may be isolated, washed, dried, and/or analyzed by means familiar to those skilled in the art.

[0067] The process disclosed herein may produce the compound comprising Formula (III) (i.e., a free acid) or a salt of the compound comprising Formula (III). In some embodiments in which the compound comprising MeZ is an alkali metal methanethiolate or an alkali metal methaneselenoate, the compound comprising Formula (III) prepared by the process will be a salt. The salt of the compound comprising Formula (III) may be neutralized with a proton donor (e.g., HCl) to form the compound comprising Formula (III). In embodiments in which the compound comprising MeZ is methyl mercaptan or methyl selenol, the compound produced by the process will be a free acid. In such embodiments, the free acid may be converted into a salt of the compound comprising Formula (III) using means well known to those of skill in the art. The compound comprising Formula (III) may have an L configuration, a D configuration, or mixture thereof.

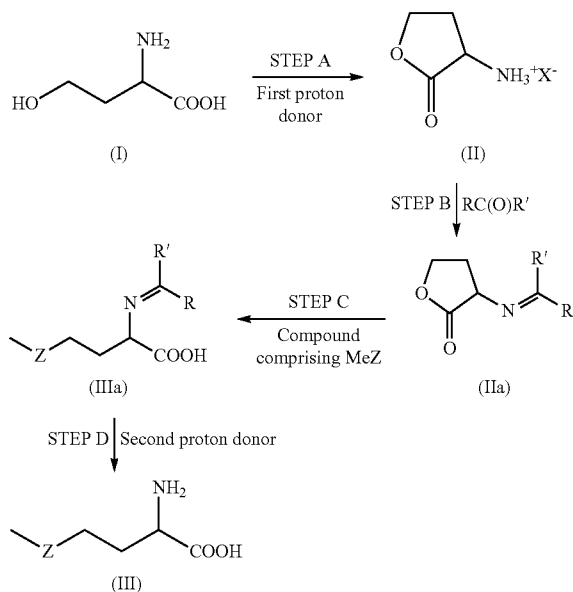
[0068] The yield of the compound comprising Formula (III) or salt thereof can and will vary. Typically, the yield of the compound comprising Formula (III) or its salt may be at

least about 60% w/w. In some embodiments, the yield of the compound comprising Formula (III) or its salt may be at least about 65%, 70%, 75%, 80%, or 85% w/w. In further embodiments, the yield of the compound comprising Formula (III) or salt thereof may be at least about 90%, 95%, 97%, or 99% w/w.

(II) Preparation of a Compound Comprising Formula (III) Via a Lactone Imine Intermediate

[0069] A further aspect of the invention encompasses a process for the preparation of the compound comprising Formula (III) from the compound comprising Formula (I), wherein the process proceeds via a lactone imine complex intermediate. The process comprises Step A in which the compound comprising Formula (I) is contacted with a first proton donor (HX) to form the lactone intermediate, i.e., a compound comprising Formula (II). The compound comprising Formula (II) is then contacted with $RC(O)R'$ in Step B of the process to form the lactone imine intermediate, i.e., a compound comprising Formula (IIa). The process further comprises Step C in which the compound comprising Formula (IIa) is contacted with a compound comprising MeZ to form the compound comprising Formula (IIIa) or a salt thereof. The final step of the process, Step D, comprises contacting the compound comprising Formula (IIIa) or salt thereof with a second proton donor to form the compound comprising Formula (III) or salt thereof. For illustrative purposes, Reaction Scheme 2 depicts the preparation of the compound comprising Formula (III) according to this aspect of the invention:

Reaction Scheme 2:



wherein: Me is methyl;
 R is hydrocarbyl or substituted hydrocarbyl;
 R' is hydrogen, hydrocarbyl, or substituted hydrocarbyl;
 X is an anion; and
 Z is sulfur or selenium.

(a) Step A—Reaction Mixture and Reaction Conditions

[0070] Step A of the process comprises contacting the compound comprising Formula (I) with a first proton donor to

form the compound comprising Formula (II). Sections (I)(a) and (I)(b) above detail suitable proton donors, solvents, and reaction conditions for this step of the process.

(b) Step B—Reaction Mixture

[0071] Step B of the process comprises contacting the compound comprising Formula (II) with $RC(O)R'$ to form the compound comprising Formula (IIa).

(i) $RC(O)R'$

[0073] A variety of compounds having formula $RC(O)R'$ may be used in Step B of the process. In some embodiments, R is chosen from alkyl, alkene, aryl, substituted alkyl, substituted alkene, and substituted aryl, and R' is chosen from hydrogen, alkyl, alkene, aryl, substituted alkyl, substituted alkene, and substituted aryl. In situations in which R' is hydrogen, suitable aldehyde compounds include, without limit, acetaldehyde, propionaldehyde, benzaldehyde, and so forth. When R' is not hydrogen, non-limiting examples of suitable ketone compounds include propionaldehyde, acetophenone, benzophenone, and the like.

[0074] The amount of $RC(O)R'$ that is contacted with the compound comprising Formula (II) can and will vary. In general, the molar ratio of the compound comprising Formula (II) to $RC(O)R'$ may range from about 1:0.1 to about 1:10. In some embodiments, the molar ratio of the compound comprising Formula (II) to $RC(O)R'$ donor may range from about 1:0.25 to about 1:5. In certain embodiments, the molar ratio of the compound comprising Formula (II) to $RC(O)R'$ may be about 1:0.5, 1:0.75, 1:1, 1:1.25, 1:1.5, 1:1.75, 1:2.0, 1:2.25, or 1:2.5. In one embodiment, the molar ratio of the compound comprising Formula (II) to $RC(O)R'$ may be about 1:1.

(ii) Solvent

[0076] Step B is typically conducted in the presence of solvent. The type of solvent used will vary depending upon the nature of $RC(O)R'$. The solvent may be a protic solvent, an aprotic solvent, an organic solvent, or combinations thereof. Examples of suitable solvents are listed above in section (I)(c). In one embodiment, the solvent may be dichloromethane.

[0077] The amount of solvent included in the reaction mixture can and will vary. Typically, the molar ratio of the solvent to the compound comprising Formula (II) may range from about 1:1 to about 50:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (II) may range from about 5:1 to about 25:1. In certain embodiments, the molar ratio of the solvent to the compound comprising Formula (II) may be about 6:1, 8:1, 10:1, 12:1, 14:1, 16:1, 18:1, or 20:1. In one embodiment, the molar ratio of the solvent to the compound comprising Formula (II) may be about 16:1.

(c) Step B—Reaction Conditions

[0078] The process of Step B is allowed to proceed at a temperature that may range from about 20° C. to about 170° C. In certain embodiments, the temperature of the reaction may be about 20° C., 25° C., 30° C., 35° C., 40° C., 45° C., 50° C., 55° C., 60° C., 65° C., 70° C., 75° C., 80° C., 85° C., 90° C., 95° C., 100° C., 105° C., 110° C., 115° C., 120° C., 125° C., 130° C., 135° C., 140° C., 145° C., 150° C., 155° C., or 160° C. In one embodiment, the process of step B may be conducted at a temperature of 100° C. In another embodi-

ment, the process may be conducted at a temperature of 115° C. In yet another embodiment, the process may be conducted at a temperature of 25° C.

[0079] The pressure of the reaction can and will vary. The reaction may be conducted at a pressure ranging from about 0 psig to about 50 psig. In some embodiments, the pressure of the reaction may be autogenous. For example, in one embodiment, the solvent may be an alcohol, the temperature of the reaction may be about 100° C., and the pressure of the reaction may be autogenous.

[0080] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. For example, the duration of the reaction may range from about 5 minutes to about 36 hours. The completeness of the reaction may be determined by any method known to one skilled in the art, such as IR, HPLC, or LC-MS. Typically, the amount of the compound comprising Formula (II) remaining in the reaction mixture may be less than about 3%, less than about 1%, or preferably less than about 0.5%.

[0081] Upon completion of the reaction, the reaction mixture may be cooled and the compound comprising Formula (IIa) may be isolated by any means familiar to those of skill in the art. Suitable means include chromatography, concentration, precipitation, filtration, distillation, phase extraction, crystallization, and the like. The isolated product may be washed and dried, and analyzed by means familiar to those skilled in the art.

[0082] The yield of the compound comprising Formula (IIa) can and will vary. Typically, the yield of the compound comprising Formula (IIa) may be at least about 60% w/w. In some embodiments, the yield of the compound comprising Formula (IIa) may be at least about 65%, 70%, 75%, 80%, or 85% w/w. In further embodiments, the yield of the compound comprising Formula (IIa) may be at least about 90%, 95%, 97%, or 99% w/w.

(d) Step C—Reaction Mixture

[0083] The process further comprises Step C in which the compound comprising Formula (IIa) is contacted with a compound comprising MeZ to form the compound comprising Formula (IIIa) or salt thereof. Non-limiting examples of suitable sources of MeZ include alkali metal methanethiolates, methyl mercaptan, alkali metal methaneselenoates, and methyl selenol.

[0084] In some embodiments, a salt of the compound comprising Formula (IIIa) in which Z is sulfur may be prepared by contacting the compound comprising Formula (IIa) with an alkali metal methanethiolate. The alkali metal methanethiolate may be purchased commercially or prepared as detailed above in section (I)(c)(i). In other embodiments, a salt of the compound comprising Formula (IIIa) in which Z is selenium may be prepared by contacting the compound comprising Formula (IIa) with an alkali metal methaneselenoate. The alkali metal methaneselenoate may be prepared by any of the methods detailed above in section (I)(c)(iii).

[0085] Typically, the molar ratio of the compound comprising Formula (IIa) to the alkali metal methanethiolate or the alkali metal methaneselenoate may range from about 1:0.25 to about 1:5. In some embodiments, the molar ratio of the compound comprising Formula (IIa) to the alkali metal methanethiolate or methaneselenoate may range from about 1:0.5 to about 1:2.5. In further embodiments, the molar ratio of the compound comprising Formula (IIa) to the alkali metal methanethiolate or methaneselenoate may be about 1:0.5, 1:0.6,

1:0.7, 1:0.8, 1:0.9, 1:1.0, or 1:1.1. 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, or 1:2.0. In one embodiment, the molar ratio of the compound comprising Formula (IIa) to the alkali metal methanethiolate or methaneselenoate may be about 1:1.1. In another embodiment, the molar ratio of the compound comprising Formula (IIa) to the alkali methanethiolate or methaneselenoate may be about 1:1.2.

[0086] In additional embodiments, the compound comprising Formula (IIIa) in which Z is sulfur may be prepared by contacting the compound comprising Formula (IIa) with methyl mercaptan. Suitable reaction mixtures and conditions are detailed above in section (I)(c)(ii). In other embodiments, the compound comprising Formula (IIIa) in which Z is selenium may be prepared by contacting the compound comprising Formula (IIa) with methyl selenol. Suitable reaction mixtures and conditions are detailed above in section (I)(c)(iv).

[0087] Contact between the compound comprising Formula (IIa) and the compound comprising MeZ is generally conducted in the presence of a solvent. In embodiments in which the compound comprising MeZ is an alkali metal methanethiolate or an alkali metal methaneselenoate, the solvent typically is an aprotic solvent, a protic solvent, or combinations thereof. In embodiments in which the compound comprising MeZ is methyl mercaptan or methyl selenol, the solvent may be an aprotic solvent, a protic solvent, an organic solvent, or combinations thereof. Examples of suitable solvents are detailed above in section (I)(c). In general, the molar ratio of the solvent to the compound comprising Formula (IIa) may range from about 1:1 to about 50:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (IIa) may be about 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, or 40:1. In one embodiment, the molar ratio of the solvent to the compound comprising Formula (IIa) may be about 15:1. In another embodiment, the molar ratio of the solvent to the compound comprising Formula (IIa) may be about 20:1. In a further embodiment, the molar ratio of the solvent to the compound comprising Formula (IIa) may be about 25:1.

(e) Step C—Reaction Conditions

[0088] The process of Step C is allowed to proceed at a temperature that may range from about 20° C. to about 200° C. In certain embodiments, the temperature of the reaction may be about 30° C., 40° C., 50° C., 60° C., 70° C., 80° C., 90° C., 100° C., 110° C., or 120° C. In one embodiment, the process of Step C is conducted at a temperature of 50° C. In another embodiment, the process of Step C is conducted at a temperature of 80° C. The reaction may be conducted under ambient pressure, and under an inert atmosphere (e.g., nitrogen or argon).

[0089] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. Typically, the reaction may be allowed to proceed from about 5 minutes to about 10 hours. The duration of the reaction may vary as a function of temperature. For example, a reaction conducted at 50° C. may be allowed to proceed for about 5 hr; whereas a reaction conducted at 80° C. may be allowed to proceed for about 2 hr. The completeness of the reaction may be determined by any method known to one skilled in the art, such as IR, HPLC, or LC-MS. Typically, the amount of the compound comprising Formula (IIa) remaining in the reaction mixture may be less than about 3%, less than about 1%, or preferably less than about 0.5%.

[0090] Upon completion of Step C of the reaction, the reaction mixture may be cooled and the compound comprising Formula (IIIa) or its salt may be isolated or concentrated by any means familiar to those of skill in the art. Suitable means include distillation, concentration, precipitation, filtration, phase extraction, crystallization, and the like.

[0091] The yield of the compound comprising Formula (IIIa) or salt thereof can and will vary. Typically, the yield of the compound comprising Formula (IIIa) or salt thereof may be at least about 60% w/w. In some embodiments of the invention, the yield of the compound comprising Formula (IIIa) or salt thereof may be at least about 65%, 70%, 75%, 80%, or 85% w/w. In further embodiments, the yield of the compound comprising Formula (IIIa) or salt thereof may be at least about 90%, 95%, 97%, or 99% w/w.

(f) Step D—Reaction Mixture

[0092] The process further comprises Step D in which the compound comprising Formula (IIIa) or salt thereof is contacted with a second proton donor to form the compound comprising (III). Suitable proton donors include, without limit, HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₂SO₄, MeSO₃H, CF₃SO₃H, and p-toluene sulfonic acid. In one embodiment, the proton donor may be HCl. The molar ratio of the compound comprising Formula (IIIa) or salt thereof to the proton donor may range from about 1:0.1 to about 1:10. In some embodiments, the molar ratio of the compound comprising Formula (IIIa) or salt thereof to the proton donor may range from about 1:0.5 to about 1:5. In certain embodiments, the molar ratio of the compound comprising Formula (IIIa) or salt thereof to the proton donor may be about 1:0.8, 1:0.9, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, or 1:2.0. In one embodiment, the molar ratio of the compound comprising Formula (IIIa) or salt thereof to the proton donor may be about 1:1.2.

[0093] Contact between the compound comprising Formula (IIIa) or salt thereof and the proton donor is typically conducted in the presence of a protic solvent. Examples of suitable protic solvents and amounts thereof are detailed above in section (I)(a)(ii).

(g) Step D—Reaction Conditions

[0094] The reaction of Step D is allowed to proceed at a temperature that may range from about 20° C. to about 100° C. In certain embodiments, the temperature of the reaction may be about 30° C., 35° C., 40° C., 45° C., 50° C., 55° C., 60° C., or 65° C. In one embodiment, the process of Step D is conducted at a temperature of about 40° C. In another embodiment, the process of Step D is conducted at a temperature of about 90° C. Typically, the reaction is performed at ambient pressure and atmosphere.

[0095] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. For example, the duration of the reaction may range from about 1 hr to about 10 hr. The completeness of the reaction may be determined by any method known to one skilled in the art, such as HPLC or LC-MS. Typically, the amount of the compound comprising Formula (IIIa) or salt thereof remaining in the reaction mixture may be less than about 3%, less than about 1%, or preferably less than about 0.5%.

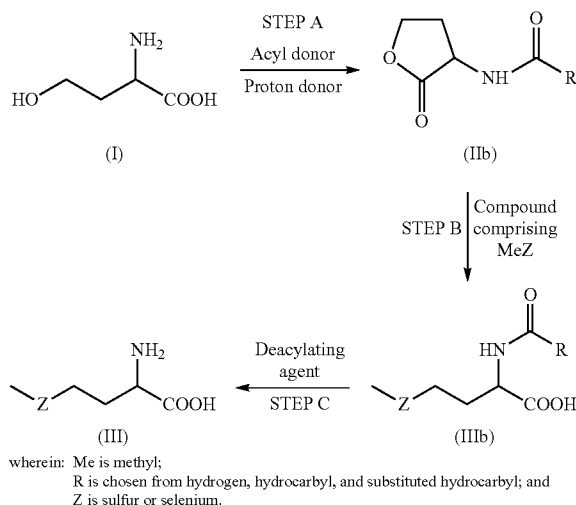
[0096] Upon completion of the reaction, the compound comprising Formula (III) may be isolated, and/or converted

into a salt, as detailed above in section (I)(d). The spatial configuration and yield of the compound comprising Formula (III) are also presented above in section (I)(d).

(III) Preparation of a Compound Comprising Formula (III) Via an N-Acyl Lactone Intermediate

[0097] Yet another aspect of the invention encompasses a process for the preparation of the compound comprising Formula (III) or a pharmaceutically acceptable salt thereof from the compound comprising Formula (I), wherein the process proceeds via an N-acyl lactone intermediate. The process comprises Step A in which the compound comprising Formula (I) is contacted with a proton donor and an acyl donor comprising R to form a compound comprising Formula (IIb). The process further comprises Step B in which the compound comprising Formula (IIb) is contacted with a compound comprising MeZ to form the compound comprising Formula (IIIb) or a pharmaceutically acceptable salt thereof. The final step of the process, Step C, comprises contacting the compound comprising Formula (IIIb) of the pharmaceutically acceptable salt thereof with a deacylating agent to form the compound comprising Formula (III) or the pharmaceutically acceptable salt thereof. For the purposes of illustration, Reaction Scheme 3 depicts the preparation of the compound comprising Formula (III) or the pharmaceutically acceptable salt thereof according to this aspect of the invention:

Reaction Scheme 3:



(a) Step A

[0098] Step A of the process comprises contacting the compound comprising Formula (I) with an acyl donor comprising R and a proton donor to form the compound comprising Formula (IIb). Proton donors that are suitable for use in Step A of this process, as well as suitable amounts of the proton donor, are presented above in section (I)(a)(i).

[0099] (i) Acyl Donor

[0100] A variety of acyl donors comprising R may be used in Step A of the process. As used herein, an “acyl donor” refers to a compound capable of donating an acyl group to another compound. In general, R of the acyl donor may be

hydrogen, alkyl, alkene, alkoxy, aryl, substituted alkyl, substituted alkene, substituted alkoxy, or substituted aryl. In some embodiments, R may be methyl, ethyl, propyl, butyl, or phenyl. In other embodiments, R may be methoxy or ethoxy.

[0101] In some embodiments, the acyl donor may be an acyl halide. Non-limiting examples of suitable acyl halides include acetyl chloride, acetyl bromide, propionyl chloride, propionyl bromide, butyryl chloride, butyryl bromide, formyl chloride, formyl fluoride, and so forth. In other embodiments, the acyl donor may be an acid anhydride. Suitable acid anhydrides include, without limit, acetic anhydride, propionic anhydride, and the like. In further embodiments, the acyl donor may be a carbamate. Non-limiting examples of suitable carbamates include methyl carbamate, ethyl carbamate, and thiocarbamate.

[0102] The amount of acyl donor that is contacted with the compound comprising Formula (I) can and will vary. In general, the molar ratio of the compound comprising Formula (I) to the acyl donor may range from about 1:0.1 to about 1:20. In some embodiments, the molar ratio of the compound comprising Formula (I) to the acyl donor may range from about 1:0.5 to about 1:10. In certain embodiments, the molar ratio of the compound comprising Formula (I) to the acyl donor may be about 1:0.8, 1:0.9, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.8, 1:2, 1:3, 1:5, 1:5, 1:6, or 1:7. In one embodiment, the molar ratio of the compound comprising Formula (I) to the acyl donor may be about 1:1.2. In another embodiment, the molar ratio of the compound comprising Formula (I) to the acyl donor may be about 1:1.5.

[0103] (ii) Optional Catalyst

[0104] Contact between the compound comprising Formula (I) and the acyl donor may be conducted in the presence of a catalyst. The catalyst can and will vary depending upon the reactants.

[0105] In embodiments in which the acyl donor is an alkyl halide or an acid anhydride, suitable catalysts include, but are not limited to, alkali or earth metal hydroxides, alkali metal alkoxides or aryloxides, alkali or alkaline earth metal amides, secondary amines, tertiary amines, and hindered amines. Non-limiting examples of suitable alkali or alkaline earth metal hydroxides include sodium hydroxide, potassium hydroxide, calcium hydroxide, and the like. Examples of suitable alkali metal alkoxides or aryloxides include, without limit, sodium ethoxide; potassium ethoxide, lithium ethoxide, sodium t-butoxide, potassium t-butoxide, and so forth. Non-limiting examples of suitable alkali or alkaline earth metal amides include sodium amide, potassium amide, calcium amide, and the like. Suitable secondary amines include, but are not limited to, dimethylamine, diethylamine, diisopropylamine, and so forth. Non-limiting examples of suitable tertiary amines such as e.g., trimethylamine, triethylamine, and so forth. Suitable hindered amines include, without limit, piperidine, pyrrolidine, and the like. In one embodiment, the catalyst may be a hindered amine such as dimethylaminopyridine.

[0106] The amount of optional catalyst included in the reaction mixture can and will vary. In general, the molar ratio of the compound comprising Formula (I) to the catalyst may range from about 1:0.001 to about 1:1. In some embodiments, the molar ratio of the compound comprising Formula (I) to the catalyst may range from about 1:0.005 to about 1:0.5.

[0107] (iii) Solvent and Reaction Conditions

[0108] The reaction mixture may also include a solvent. Section (I)(c) details solvents suitable for use in this reaction,

as well as appropriate amounts. Suitable reaction conditions are detailed above in section (II)(b). Similar to Step A of Reaction Scheme 2, the compound comprising Formula (I) may be contacted with the proton donor prior to contact with the acyl donor, contacted with the acyl donor prior to contact with the proton donor, or contacted with both simultaneously.

[0109] (b) Step B

[0110] In Step B of the process, the compound comprising Formula (IIb) is contacted with a compound comprising MeZ to form the compound comprising Formula (IIIb) or salt thereof. Suitable compounds comprising MeZ, solvents, ratios of reactants, and reaction conditions are presented above in sections (II)(d) and (II)(e).

[0111] (c) Step C

[0112] The process further comprises Step C in which the compound comprising Formula (IIIb) or salt thereof is contacted with a deacylating agent to form the compound comprising Formula (III) or salt thereof. In some embodiments, the deacylating agent may be a proton acceptor. Non-limiting examples of suitable proton acceptors include hydroxides of alkali metals and alkaline earth metals (such as, for example, NaOH and Ca(OH)₂ and the like), carbonate salts (such as, for example, Na₂CO₃, K₂CO₃, mixtures thereof, and the like), and group 1 salts of carbanions, amides, and hydrides (such as, for example, butyl lithium, sodium amide (NaNH₂), sodium hydride (NaH), and the like). In other embodiments, the deacylating agent may be a proton donor. Suitable proton donors are presented above in section (I)(a)(i). In other embodiments, the deacylating agent may be an acylase. Treatment of the compound comprising Formula (IIIb) or its salt with an acylase may be performed using methods well known to those of skill in the art.

[0113] The molar ratio of the compound comprising Formula (IIIb) or salt thereof to the deacylating agent may range from about 1:0.01 to about 1:20. In some embodiments, the molar ratio of the compound comprising Formula (IIIb) or salt thereof to the deacylating agent may range from about 1:0.5 to about 1:10. In certain embodiments, the molar ratio of the compound comprising Formula (IIIb) or salt thereof to the deacylating agent may range from about 1:1 to about 1:2, from about 1:2 to about 1:4, or from about 1:4 to about 1:8.

[0114] The reaction of Step C generally is conducted in the presence of a solvent. The solvent may be a protic solvent, an aprotic solvent, or combinations thereof, which are described above. The molar ratio of the solvent to the compound comprising Formula (IIIb) or salt thereof may range from about 1:1 to about 50:1. The reaction of Step C may be conducted at a temperature ranging from about 20° C. to about 100° C. The reaction is typically conducted at ambient pressure. The reaction generally is allowed to proceed for a sufficient period of time until the reaction is substantially complete.

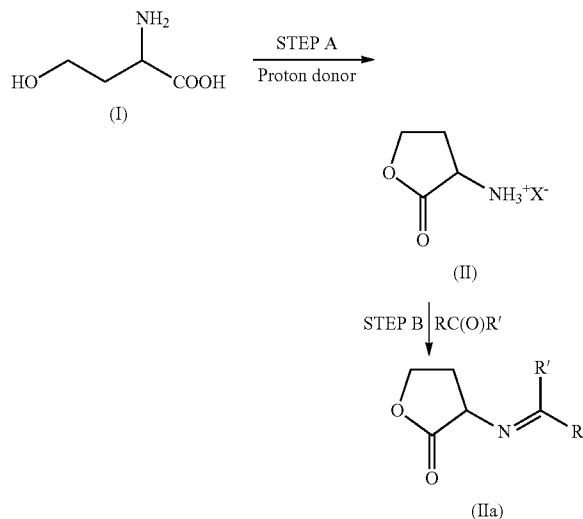
[0115] Upon completion of the reaction, the compound comprising Formula (III) may be isolated, and/or converted into a salt, as detailed above in section (I)(d). The spatial configuration and yield of the compound comprising Formula (III) are also presented above in section (I)(d).

(IV) Preparation of a Compound Comprising Formula (IIa) from a Compound Comprising Formula (I)

[0116] A further aspect of the disclosure encompasses a process for preparing a compound comprising Formula (IIa). The process comprises contacting a compound comprising Formula (I) with a proton donor to form a compound comprising Formula (II). The second step of the process com-

prises contacting the compound comprising Formula (II) with $RC(O)R'$ to form the compound comprising Formula (IIa). Reaction Scheme 4 illustrates this aspect of the disclosure:

Reaction Scheme 4:



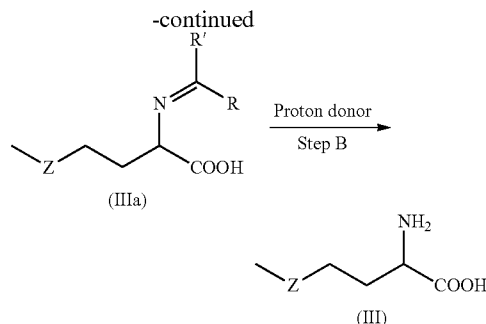
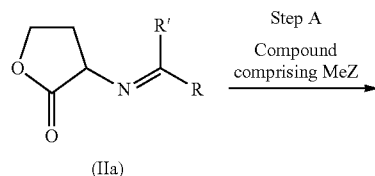
wherein: R is hydrocarbyl or substituted hydrocarbyl;
R' is hydrogen, hydrocarbyl, or substituted hydrocarbyl; and
X is an anion.

[0117] Step A of the process comprises contacting the compound comprising Formula (II) with a proton donor to form a lactone, i.e., a compound comprising Formula (II). Step A commences with formation of a reaction mixture as detailed above in section (I)(a). The reaction is conducted under conditions described above in section (I)(b). Step B of the process comprises contacting the lactone compound with $RC(O)R'$ to form a lactone imine compound; i.e., the compound comprising Formula (IIa). Details of the reaction mixture and reaction conditions are presented above in sections (II)(b) and (II)(c), respectively.

(V) Preparation of a Compound Comprising Formula (III) from a Compound Comprising Formula (IIa)

[0118] Yet another aspect provides a process in which a compound comprising Formula (IIa) is contacted with a compound comprising MeZ to form a compound comprising Formula (IIIa) or a pharmaceutically acceptable salt thereof. The process further comprises contacting the compound comprising Formula (IIIa) or the pharmaceutically acceptable salt thereof with a proton donor to form the compound comprising Formula (III) or salt thereof. This aspect of the invention is depicted in Reaction Scheme 5:

Reaction Scheme 5:

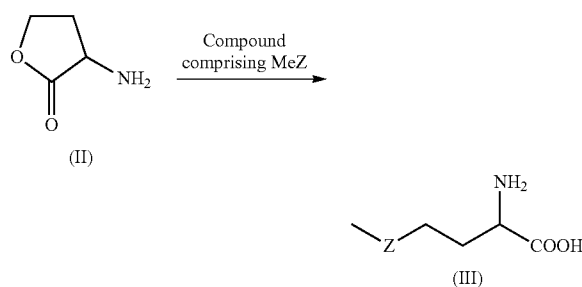


wherein: Me is methyl;
R is hydrocarbyl or substituted hydrocarbyl;
R' is hydrogen, hydrocarbyl, or substituted hydrocarbyl; and
Z is sulfur or selenium.

[0119] Step A of the process commences with formation of a reaction mixture as described above in section (II)(d). In some embodiments, R may be alkyl, alkene, aryl, substituted alkyl, substituted alkene, or substituted aryl, and R' may be hydrogen, alkyl, alkene, aryl, substituted alkyl, substituted alkene, or substituted aryl. Reaction between the compound comprising Formula (IIa) and the compound comprising MeZ is conducted under conditions detailed above in section (II)(e). Step B of the process comprises contact with a proton donor as detailed above in sections (II)(f) and (II)(g). (VI) Preparation of a Compound Comprising Formula (III) from a Compound Comprising Formula (II)

[0120] A further aspect provides a process in which a compound comprising Formula (II) or a pharmaceutically acceptable salt thereof is contacted with a compound comprising MeZ to form the compound comprising Formula (III) or the pharmaceutically acceptable salt thereof, as depicted in Reaction Scheme 7:

Reaction Scheme 7:



wherein: Me is methyl; and
Z is sulfur or selenium.

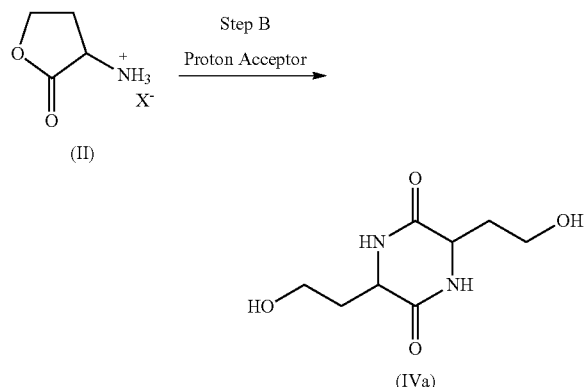
[0121] The process comprises contact with a compound comprising MeZ as detailed above in sections (I)(c) and (I)(d).

(VII) Preparation of a Compound Comprising Formula (III) from a Lactam Intermediate

[0122] In another embodiment, the process for preparing a compound comprising Formula (III) may proceed through both a lactone and a lactam intermediate as illustrated in Reaction Scheme 8. The process comprises Step A in which a compound comprising Formula (I) is converted to a compound comprising Formula (II) as described above (e.g., see sections (I)(a) and (I)(b)). The process further comprises Step

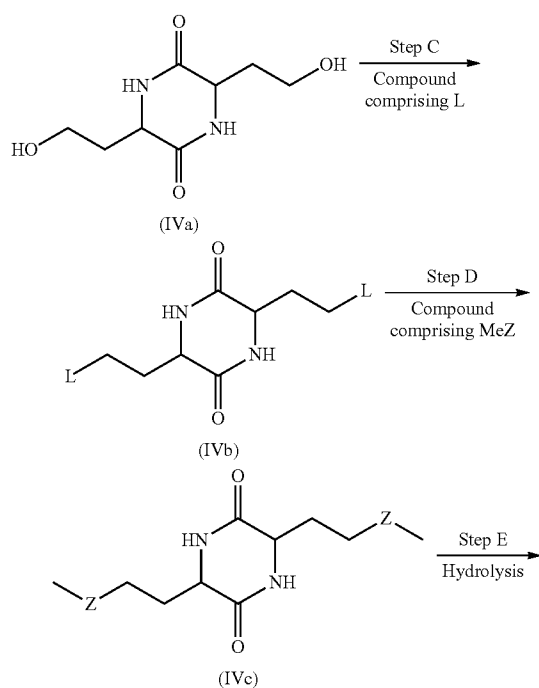
B in which the compound comprising Formula (II) is contacted with a proton acceptor to form the compound of Formula (IVa), a lactam.

Reaction Scheme 8:

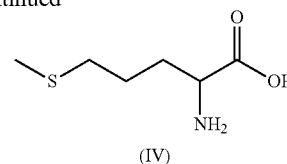


[0123] The compound comprising Formula (IVa) is then contacted with a compound comprising L to give the compound comprising Formula (IVb). Then the compound comprising Formula (IVb) may be contacted with a compound comprising MeZ to form the compound comprising Formula (IVc). Lastly, the compound comprising Formula (IVc) may be subjected to hydrolysis conditions to give the compound comprising Formula (III) or an acceptable salt thereof. The overall reaction from the compound comprising Formula (IVa) to the compound comprising Formula (IV) is shown in Reaction Scheme 9.

Reaction Scheme 9:



-continued



wherein:

L is a leaving group; and
 Z is sulfur or selenium.

(a) Step A—Homoserine to Homoserine Lactone

[0124] The conversion of the compound comprising Formula (I) to the compound comprising Formula (II) is described in sections (I)(a) and (I)(b).

(b) Step B—Reaction Mixture

[0125] Step B of the process comprises contacting the compound comprising Formula (II) with a proton acceptor to form the compound comprising formula (IVa). Suitable proton acceptors for the reaction include, but are not limited to, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium acetate, potassium acetate, triethylamine acetate, diisopropylethylamine acetate, dimethylaminopyridine, and combinations thereof. In a preferred embodiment the proton acceptor is sodium acetate.

[0126] The amount of proton acceptor that may be contacted with the compound comprising Formula (IVa) can and will vary. In general, the molar ratio of the compound comprising Formula (IVa) to the proton acceptor may range from about 1:0.1 to about 1:10. In some embodiments, the molar ratio of the compound comprising Formula (IVa) to the proton acceptor may range from about 1:0.5 to about 1:5. In certain embodiments, the molar ratio of the compound comprising Formula (IVa) to the proton acceptor may be about 1:0.8, 1:0.9, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.8, 1:2, 1:3, 1:5, 1:6, or 1:7. In one embodiment, the molar ratio of the compound comprising Formula (IVa) to the proton acceptor may be about 1:1.1.

[0127] The reaction of Step B may further comprise a leaving group to facilitate the reaction. Leaving groups may react with the alcohol groups on the compound comprising Formula (II) to facilitate the formation of the lactam. By way of non-limiting example, leaving groups may be selected from acetyl, sulfate, bromo, chloro, or iodo groups. In an exemplary embodiment, the leaving group may be acetate.

[0128] The reaction of Step B generally occurs in a solvent. Non-limiting examples of acceptable solvents for the reaction of Step B are methanol, ethanol, isopropanol, n-propanol, isobutanol, n-butanol, s-butanol, t-butanol, water, dimethyl sulfoxide, dimethylformamide, and combinations thereof. In an exemplary embodiment the solvent is isopropanol.

[0129] The amount of solvent included in the reaction mixture also may vary. Typically, the molar ratio of the solvent to the compound comprising Formula (IVa) may range from about 1:1 to about 50:1. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (IVa) may range from about 5:1 to about 25:1. In certain embodiments, the molar ratio of the solvent to the compound comprising Formula (IVa) may be about 6:1, 8:1, 10:1, 12:1, 14:1, 16:1, 18:1, 20:1, or 25:1. In an exemplary embodiment, the

molar ratio of the solvent to the compound comprising Formula (IVa) may be about 23:1.

(c) Step B—Reaction Conditions

[0130] The reaction of Step B is allowed to proceed at a temperature that may range from about 20° C. to about 80° C. In certain embodiments, the temperature of the reaction may be about 20° C., 30° C., 35° C., 40° C., 45° C., 50° C., 55° C., 60° C., or 65° C. In one embodiment, the process of Step B is conducted at a temperature of about 50° C. In another embodiment, the process of Step B is conducted at a temperature of about 20° C. Typically, the reaction is performed at ambient pressure and atmosphere.

[0131] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. For example, the duration of the reaction may range from about 10 min to about 3 hours. The completeness of the reaction may be determined by any method known to one skilled in the art, such as HPLC or LC-MS. In an exemplary embodiment the reaction may be conducted for about 1 hour.

[0132] Upon completion of the reaction, the compound comprising Formula (IVa) may be isolated by any means known in the art. In another embodiment, upon completion of the reaction, the compound comprising Formula (IVa) may be further reacted without isolation.

(d) Step C—Reaction Mixture

[0133] Step C of the reaction involves contacting the compound comprising Formula (IVa) with a compound comprising L to form the compound comprising Formula (IVb).

[0134] The compound comprising L may be any compound comprising L. The group comprising L generally serves as a leaving group in a later reaction where L may be displaced by a nucleophile such as a sulfur or selenium containing group. Thus, the group comprising L may be any group suitable for acting as a leaving group in the reaction with S or Se. By way of non-limiting example, L may be selected from compounds comprising acetate, sulfate esters, bromo, chloro, or iodo. In one embodiment L is sulfate or a sulfate ester. In another embodiment, L is acetate. In preferred embodiments, L may be O-acetate, O-tosylate, O-mesylate, or halo.

[0135] Step C may further comprise the addition of a proton acceptor. Suitable proton acceptors for the reaction include, but are not limited, to sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium acetate, potassium acetate, triethylamine acetate, diisopropylethylamine acetate, acetate, dimethylaminopyridine and combinations thereof. In a preferred embodiment the proton acceptor is sodium acetate.

[0136] The amount of the proton acceptor contacted with the compound comprising Formula (IVb) can and will vary. In general, the molar ratio of the compound comprising Formula (IVb) to the proton acceptor may range from about 1:0.1 to about 1:10. In some embodiments, the molar ratio of the compound comprising Formula (IVb) to the proton acceptor may range from about 1:0.5 to about 1:5. In certain embodiments, the molar ratio of the compound comprising Formula (IVb) to the proton acceptor may be about 1:0.8, 1:0.9, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.8, 1:2, 1:2.2, 1:2.4, 1:2.6, 1:2.8, 1:3, 1:5, 1:5, 1:6, or 1:7. In one embodiment, the molar ratio of the compound comprising Formula (IVb) to the proton acceptor may be about 1:2.

(e) Step C—Reaction Conditions

[0137] The reaction of Step C may be allowed to proceed at a temperature that may range from about 20° C. to about 80° C. In certain embodiments, the temperature of the reaction may be about 30° C., 35° C., 40° C., 45° C., 50° C., 55° C., 60° C., 65° C., 70° C., 75° C. or 80° C. In one embodiment, the process of Step C is conducted at a temperature of about 60° C. Typically, the reaction is performed at ambient pressure and atmosphere.

[0138] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. For example, the duration of the reaction may range from about 10 min to about 3 hours. The completeness of the reaction may be determined by any method known to one skilled in the art, such as HPLC or LC-MS. In an exemplary embodiment the reaction may be conducted for about 1 hour.

(f) Step D—Reaction Mixture

[0139] The process further comprises Step D in which the compound comprising Formula (IVb) is contacted with a compound comprising MeZ to form the compound comprising Formula (IVc) or salt thereof. Non-limiting examples of suitable sources of MeZ include alkali metal methanethiolates, methyl mercaptan, alkali metal methaneselenoates, and methyl selenol.

[0140] In some embodiments, a salt of the compound comprising Formula (IVc) in which Z is sulfur may be prepared by contacting the compound comprising Formula (IVb) with an alkali metal methanethiolate. The alkali metal methanethiolate may be purchased commercially or prepared as detailed above in section (I)(c)(i). In other embodiments, a salt of the compound comprising Formula (IVc) in which Z is selenium may be prepared by contacting the compound comprising Formula (IVb) with an alkali metal methaneselenoate. The alkali metal methaneselenoate may be prepared by any of the methods detailed above in section (I)(c)(iii).

[0141] Typically, the molar ratio of the compound comprising Formula (IVb) to the alkali metal methanethiolate or the alkali metal methaneselenoate may range from about 1:1 to about 1:3. In some embodiments, the molar ratio of the compound comprising Formula (IVb) to the alkali metal methanethiolate or methaneselenoate may range from about 1:1.9 to about 1:2.2. In further embodiments, the molar ratio of the compound comprising Formula (IVb) to the alkali metal methanethiolate or methaneselenoate may be about 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, 1:2.0, 1:2.1, 1:2.2, 1:2.3, 1:2.4, 1:2.5, 1:2.6, 1:2.7, 1:2.8, 1:2.9, or 1:3.0. In one embodiment, the molar ratio of the compound comprising Formula (IVb) to the alkali metal methanethiolate or methaneselenoate may be about 1:2.

[0142] In additional embodiments, the compound comprising Formula (IVc) in which Z is sulfur may be prepared by contacting the compound comprising Formula (IVb) with methyl mercaptan. Suitable reaction mixtures and conditions are detailed above in section (I)(c)(ii). In other embodiments, the compound comprising Formula (IIIa) in which Z is selenium may be prepared by contacting the compound comprising Formula (IVb) with methyl selenol. Suitable reaction mixtures and conditions are detailed above in section (I)(c)(iv).

[0143] Contact between the compound comprising Formula (IVb) and the compound comprising MeZ is generally

conducted in the presence of a solvent. In embodiments in which the compound comprising MeZ is an alkali metal methanethiolate or an alkali metal methaneselenoate, the solvent typically is an aprotic solvent, a protic solvent, or combinations thereof. In embodiments in which the compound comprising MeZ is methyl mercaptan or methyl selenol, the solvent may be an aprotic solvent, a protic solvent, an organic solvent, or combinations thereof. Examples of suitable solvents are detailed above in section (I)(c)(i). In general, the molar ratio of the solvent to the compound comprising Formula (IVb) may range from about 1:1 to about 1:75. In some embodiments, the molar ratio of the solvent to the compound comprising Formula (IVb) may be about 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 50:1, or 60:1. In one embodiment, the molar ratio of the solvent to the compound comprising Formula (IVb) may be about 10:1. In another embodiment, the molar ratio of the solvent to the compound comprising Formula (IVb) may be about 25:1. In a further embodiment, the molar ratio of the solvent to the compound comprising Formula (IVb) may be about 50:1.

(g) Step D—Reaction Conditions

[0144] The process of Step D is allowed to proceed at a temperature that may range from about 20° C. to about 150° C. In certain embodiments, the temperature of the reaction may be about 30° C., 40° C., 50° C., 60° C., 70° C., 80° C., 90° C., 100° C., 110° C., or 120° C. In one embodiment, the process of Step D is conducted at a temperature of 80° C. In another embodiment, the process of Step D is conducted at a temperature of 120° C. The reaction may be conducted under ambient pressure, and under an inert atmosphere (e.g., nitrogen or argon).

[0145] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. Typically, the reaction may be allowed to proceed from about 5 minutes to about 4 hours. The duration of the reaction may vary as a function of temperature. For example, a reaction conducted at 50° C. may be allowed to proceed for about 5 hr; whereas a reaction conducted at 80° C. may be allowed to proceed for about 2 hr. The completeness of the reaction may be determined by any method known to one skilled in the art, such as IR, HPLC, or LC-MS.

[0146] Upon completion of Step D of the reaction, the reaction mixture may be cooled and the compound comprising Formula (IVc) or its salt may be isolated or concentrated by any means familiar to those of skill in the art. Suitable means include distillation, concentration, precipitation, filtration, phase extraction, crystallization, and the like. In another embodiment, the compound comprising Formula (IVc) may be reacted further without isolation.

(h) Step E—Reaction Mixture

[0147] Step E of the process involves subjecting the compound comprising Formula (IVc) to hydrolysis conditions to release the compound of Formula (IV).

[0148] Step E may comprise hydrolysis with either an acid or a base. Non-limiting examples of suitable acids include hydrochloric, hydroiodic, sulfuric, phosphoric, and the like. Non-limiting examples of suitable bases include sodium hydroxide, potassium hydroxide, cesium hydroxide, water and combinations thereof.

[0149] The amount of acid or base that is contacted with the compound comprising Formula (IVc) can and will vary. In

general, the molar ratio of the compound comprising Formula (IVc) to the acid or base may range from about 1:0.1 to about 1:10. In some embodiments, the molar ratio of the compound comprising Formula (IVc) to the acid or base may range from about 1:0.5 to about 1:5. In certain embodiments, the molar ratio of the compound comprising Formula (IVc) to the acid or base may be about 1:0.8, 1:0.9, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.8, 1:2, 1:3, 1:5, 1:5, 1:6, or 1:7. In one embodiment, the molar ratio of the compound comprising Formula (IVc) to the acid or base may be about 1:1.1.

(i) Step E—Reaction Conditions

[0150] The process of Step E is allowed to proceed at a temperature that may range from about 35° C. to about 100° C. In certain embodiments, the temperature of the reaction may be about 40° C., 50° C., 60° C., 70° C., 80° C., 90° C., or 100° C. In one embodiment, the process of Step E is conducted at a temperature of 40° C. In another embodiment, the process of Step E is conducted at a temperature of 70° C. The reaction may be conducted under ambient pressure.

[0151] In general, the reaction is allowed to proceed for a sufficient period of time until the reaction is substantially complete. Typically, the reaction may be allowed to proceed from about 1 hour to about 36 hours. The duration of the reaction may vary as a function of temperature.

[0152] Upon completion of Step E of the reaction, the reaction mixture may be cooled and the compound comprising Formula (IV) or its salt may be isolated or concentrated by any means familiar to those of skill in the art. Suitable means include distillation, concentration, precipitation, filtration, phase extraction, crystallization, and the like.

[0153] The yield of the compound comprising Formula (IV) or salt thereof can and will vary. Typically, the yield of the compound comprising Formula (IV) or salt thereof may be at least about 60% w/w. In some embodiments of the invention, the yield of the compound comprising Formula (IV) or salt thereof may be at least about 65%, 70%, 75%, 80%, or 85% w/w. In further embodiments, the yield of the compound comprising Formula (IV) or salt thereof may be at least about 90%, 95%, 97%, or 99% w/w.

DEFINITIONS

[0154] To facilitate understanding of the invention, several terms are defined below.

[0155] The term “acyl,” as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxy group from the group COOH of an organic carboxylic acid, e.g., RC(O), wherein R is R¹, R¹O—, R¹R²N—, or R¹S—, R¹ is hydrocarbyl, heterosubstituted hydrocarbyl, or heterocyclo, and R² is hydrogen, hydrocarbyl or substituted hydrocarbyl.

[0156] The term “alkyl” as used herein describes groups which are preferably lower alkyl containing from one to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like.

[0157] The term “alkenyl” as used herein describes groups having at least one carbon-carbon double bond that preferably contain from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

[0158] The term “aryl” as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl.

[0159] The terms “halogen” or “halo” as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

[0160] The terms “hydrocarbon” and “hydrocarbyl” as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

[0161] The “substituted hydrocarbyl,” “substituted alkyl,” “substituted alkenyl,” “substituted aryl,” and “substituted heteroaryl” moieties described herein are hydrocarbyl, alkyl, alkenyl, aryl, and heteroaryl moieties, respectively, that are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, aryloxy, hydroxy, protected hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters, and ethers.

[0162] When introducing elements of the present invention or the preferred embodiments(s) thereof, the articles “a,” “an,” “the” and “said” are intended to mean that there are one or more of the elements. The terms “comprising,” “including” and “having” are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[0163] As various changes could be made in the above compounds and processes without departing from the scope of the invention, it is intended that all matter contained in the above description and in the examples given below, shall be interpreted as illustrative and not in a limiting sense.

EXAMPLES

[0164] The following examples detail various embodiments of the invention.

Example 1

Synthesis of Homoserine Lactone Hydrochloride in Water

[0165] L-Homoserine (250.1 g, 2.099 mol) was added to a 1000 mL, jacketed reactor equipped with an overhead stirrer, condenser, and a thermocouple. Hydrochloric acid (738.2 mL, 6M) was added to the dry homoserine. The solution was heated to reflux by setting the external heating oil in the jacketed reactor to 115° C. The solution mixed at reflux for 4 hours. The mixture was then cooled to 50° C. The majority of the acidic water was removed by distillation, to afford a white/yellow solid. This solid was dried overnight by high vacuum. Ethanol (90%, 400 mL) was added to the solid and mixed well. The solution was filtered and a white solid was isolated and dried under vacuum (280.89 g, 93.5% yield).

Homoserine lactone hydrochloride was verified by ¹H NMR and Elemental Analysis. Anal. Calcd for C₄H₈ClNO₂: C, 34.92; H, 5.86; N, 10.18; Cl, 25.77. Found: C, 33.4; H, 5.9; N, 9.82; Cl, 24.72; 96.2% Pure.

Example 2

Synthesis of Homoserine Lactone Hydrochloride in Isopropanol

[0166] Isopropanol (50 mL) was put into a reactor. Acetyl chloride (6 mL; 84 mmol) was added to the isopropanol over three minutes. The temperature of the solution increased from 22° C. to 56° C. The mixture was stirred for 30 minutes. Homoserine (5 g, 42 mmol) was added to the solution. The temperature increased from 26° C. to 28° C. The reaction was heated to 50° C. and was stirred for 1 h. The mixture was cooled to 0° C. and held for an hour. The mixture was filtered and the solid was washed with cold isopropanol. A white solid (5.51 g, 95% yield) was obtained and the structure was confirmed by NMR.

Example 3

Synthesis of Homoserine Lactone Hydrochloride in Ethanol

[0167] Ethanol (Denatured with 5% IPA, 1200 mL) was added to a 2 L jacketed reactor. The jacket temperature was then set to -5° C. Hydrogen chloride (anhydrous, 60 g, 1.64 mol, 1.3 molar equivalents) was added from a tared lecture tank equipped with a gas regulator at 10 psi. The temperature of the solution increased to 12.6° C. The solution was cooled to -2° C. L-Homoserine (150 g, 1.259 mol) was added to solution as a solid. The temperature of the acidic solution rose to 5° C. after the addition of the homoserine. After 1 hour at 5° C., the solution was homogeneous. The temperature of the solution was then heated to 50° C. After 45 minutes at 50° C., a white solid began precipitating out. The solution was stirred at 50° C. for 1 hour. The heterogeneous solution was transferred into two 1-L beakers and each was cooled in an ice bath. The solution was filtered and washed with cold denatured ethanol. The solid isolated was dried in a vacuum oven for 2 days at 50° C. to give 71.23 g (100% assay) of homoserine lactone hydrochloride. Anal. Calcd for C₄H₈NO₂Cl: C, 34.92; H, 5.9; N, 10.18; Cl, 25.7. Found: C, 34.91; H, 6.12; N, 9.98; Cl, 25.61; KF, <0.10%. The filtrate was stored at room temperature. After 2 days, the filtrate contained white, needle-like crystals. The solid was isolated by vacuum filtration to give an additional 31.29 g (99% assay). Anal. Calcd for C₄H₈NO₂Cl: C, 34.92; H, 5.9; N, 10.18; Cl, 25.7. Found: C, 34.85; H, 6.00; N, 9.94; Cl, 25.32; KF, <0.10%. The filtrate was evaporated to dryness. The residue remaining was a yellow paste. The residue was added to absolute ethanol (800 mL). The heterogeneous solution was heated to reflux for 30 minutes. The heterogeneous solution was cooled to 4° C. The solid was isolated using vacuum filtration: to give an additional 50.30 g (>98% assay). Anal. Calcd for C₄H₈NO₂Cl: C, 34.92; H, 5.9; N, 10.18; Cl, 25.7. Found: C, 34.78; H, 5.75; N, 9.83; Cl, 25.84; KF, 0.17%. Total isolated yield: 88.2%.

Example 4

Synthesis of Homoserine Lactone Bisulfate

[0168] An azeotropic distillation apparatus was assembled including a 100 mL round bottom flask, Dean-Stark trap and

reflux condenser. The reaction flask was charged with homoserine (6.62 g, 55.59 mmol). Toluene (37 mL) was added to the pot and to the Dean-Stark trap. The reaction mixture was heated to 85° C. at which point concentrated sulfuric acid (18M, 3.1 mL, 1.0 eq) was added. The temperature was increased until steady reflux was achieved (–105° C.). After the reaction completed (4 h), as indicated by the generation of an equivalent of water in the Dean-Stark trap, the reaction mixture was allowed to cool resulting in solidification of the oil into a solid. The reaction mixture was reheated to 105° C. and the material was dispersed with a spatula followed by slow cooling to 40° C. in 60 minutes. The material continued to be free-flowing. The solid was vacuum filtered and placed under high vacuum overnight. A light brown solid was isolated (10.11 g, 91.4% yield). Anal. Calcd for C₄H₉NO₆S: C, 24.12; H, 4.55; N, 7.03; S, 16.10; SO₄, 48.00. Found: C, 23.45; H, 4.22; N, 6.72; S, 15.99; SO₄, 46.77. KF (% H₂O) 1.27%. Purity: 96.4%.

Example 5

Conversion of Homoserine Lactone to Methionine

[0169] A one liter jacketed reactor system equipped with an overhead stirrer, IR probe, temperature probe, nitrogen inlet, and 500 mL pressure addition funnel was charged with DMSO (200 mL, anhydrous over sieves) and homoserine lactone hydrochloride (22.0 g, 97.4% pure, 15.6 mmol). Separately, sodium methane thiolate (24.019 g, 34.3 mmol) was weighed into a 250 mL volumetric flask and diluted to the line with DMSO, giving a 1.37 M solution. The thiolate solution was added to the lactone solution in the reactor at 22° C. over 2-3 minutes. The addition funnel was washed with another 150 mL of DMSO to rinse the remaining thiolate into the reactor. The reaction mixture was then heated to 100° C. over thirty minutes. The reactor was then cooled to 45° C. over 1 h. Concentrated HCl (12 M, 16 mL) was added to the reaction mixture, resulting in white precipitate. After stirring at 20° C. overnight, the precipitate was isolated by filtration and washed with 50 mL of acetone. The isolated solid was dried overnight in a vacuum oven at 50° C. A white powder was isolated (30.47 g, 57% assay, 75% yield). The filtrate contained 4.05 g of methionine (additional 17.5% yield).

Example 6

Conversion of Homoserine Lactone to Methionine

[0170] The reactions were performed in a glass reactor equipped with an overhead stirrer, reflux condenser, IR probe, N₂ inlet, temperature probe, and dosing inlet. Dimethylsulfoxide (25 mL) was added to the reactor under a positive flow of nitrogen and then heated to 80, 100, or 120° C. An IR spectrum was obtained, set as a reference, and subtracted from subsequent spectra. Homoserine lactone hydrochloride (2.03 g, 98.5% pure, 14.5 mmol) was added as a solid to the hot DMSO, and quickly dissolved. Next, one equivalent of sodium methane thiolate (11.5 mL, 1.26 M solution in DMSO, 14.5 mmol) was dosed into the reaction mixture over five minutes, resulting in the formation of a white precipitate. After approximately ten minutes, an additional 1.2 equivalents of sodium methane thiolate (13.9 mL, 1.26 M solution in DMSO, 17.5 mmol) was dosed into the reactor over 15, 30, or 60 minutes. The reaction was monitored by IR. Approximately 20 minutes after the dosing was complete, the reaction

mixture was cooled to room temperature and diluted to 100 mL with water. Results are shown in Table 1 below.

TABLE 1

Analytical results from experiments where temperature and time of thiolate addition were varied.			
Temp (° C.)	Time ^a (min)	Methionine (% Yield)	Homoserine (% Yield)
80	15	94.56	1.34
	30	92.29	1.41
	60	94.16	1.15
100	15	90.34	1.32
	30	90.19	1.54
	60	89.22	2.44
120	15	65.48	4.74
	30	82.10	2.82
	60	80.28	3.11

^aTime in which the second equivalent of sodium methane thiolate was dosed into the reactor.

Example 7

Conversion of Homoserine Lactone to Selenomethionine

[0171] Elemental selenium (1.263 g, 16.0 mmol) was suspended in anhydrous tetrahydrofuran (THF, 20 mL) in a dry 3-necked, 100 mL round bottom flask under a blanket of argon. After the solution was cooled in an ice bath, methyl lithium (10 mL, 1.6 M solution in ether, 16.0 mmol) was added via syringe over approximately 2-3 minutes. The ice bath was removed and the solution was allowed to warm to room temperature over 40 minutes. The solvent was then removed under reduced pressure, leaving a pale yellow residue. Homoserine lactone hydrochloride (1.016 g, 7.27 mmol, 98.5% pure) was dissolved in DMSO (15 mL) in an addition funnel attached to one of the side necks of the reaction flask. The flask was placed in an ice bath and DMSO (5 mL) was added to the selenolate residue. Over 1-2 minutes, the lactone solution was added to the selenolate solution. The addition funnel was then rinsed with DMSO (5 mL) and this was added to the reaction mixture. After the ice bath was removed, the solution was allowed to warm to room temperature and was then heated to 80° C. After heating for one hour, the solution was cooled to room temperature and diluted to 100 mL with water. The solution was analyzed by HPLC and shown to contain 1.07 g of selenomethionine (76% yield) and 0.067 g of homoserine (7.75% yield).

Example 8

Formation of Imine Protected Lactone

[0172] To a reactor tube equipped with stir bar and nitrogen blanket was charged 0.5 g (3.4 mmol, 1 eq) lactone HCl, 1.5 g (12.5 mmol, 3.7 eq) MgSO₄, and 5 mL dichloromethane. The tube was placed in the reactor under nitrogen blanket and 1.0 mL (6.8 mmol, 2 eq) triethylamine was added via syringe. Solids got even thicker. The slurry was stirred 5 minutes at room temperature then 0.5 mL (6.8 mmol, 2 eq) acetone was added via syringe. The slurry was stirred overnight at 20-23° C. with reflux cooling on. Next day, TLC (10% water/ACN) indicated that the starting lactone was depleted. The slurry was filtered to remove MgSO₄, stripped to a wet grainy solid, and extracted into MTBE to eliminate TEA.HCl. The MTBE

filtrate was stripped to a colorless mobile liquid (120 mg; 25% yield). Direct infusion MS and FTIR spectra were consistent with the desired imine.

Example 9

Formation of Imine Protected Lactone

[0173] Benzaldehyde (15.2433 g, 0.144 mmol) was added to a suspension of homoserine lactone hydrochloride (19.72 g, 0.143 mmol) in dichloromethane (CH_2Cl_2) (100 mL) at room temperature. Triethylamine (20.070 g, 0.287 mmol) was then added to the suspension. The reaction mixture became very thick, but thinned out slightly after several minutes. Finally magnesium sulfate was added to the flask, and the solution was allowed to stir at room temperature overnight. After 20 hours, the solution was placed on the rotary evaporator and concentrated to give a sticky white solid (115.3 g). The solid was re-suspended in ether (250 mL) and filtered. The white filter cake was further washed with 100 mL of ether. The filtrate was washed with 75 mL of saturated sodium chloride solution, and then the aqueous layer was extracted with ether (2×50 mL). The combined organic extracts were concentrated on the rotary evaporator, leaving a yellow oil (27.8 g). After sitting overnight under argon, needle-like crystals formed in the oil. The oil was decanted off of the crystals and stored in a separate flask. Ether (10 mL) was added to the crystals, and the solution was heated to reflux until the crystals dissolved. After cooling to room temperature and sitting undisturbed overnight, no precipitate had formed. The ether was removed on the rotary evaporator and then hexane (50 mL) was added to the resulting oil. Titration with hexane was attempted, but no precipitate formed. The solution was heated to reflux and ether was added slowly to dissolve the oil. After the addition of 150 mL of ether, the oil still had not dissolved. The solution was cooled to room temperature and the solvent was removed. The oil was then dissolved in ether and hexane was added to precipitate out the product, but an oil was formed. The solvent was stripped off. The oil was then dissolved in dichloromethane and hexane was added, but again, only an oil had formed. The solvent was stripped off, leaving a yellow oil. This product along with the oil that was decanted off of the original crystals contained the desired imine as shown by NMR analysis.

Example 10

Conversion of Imine-Protected Lactone to Methionine

[0174] NaSMe (2.2 equiv) was weighed into a reaction tube fitted with a stir bar and nitrogen blanket, and placed under nitrogen purge for 1 hour to remove oxygen. In a separate vial was weighed 1.0 equiv. of benzyl lactone imine, and DMSO (stored over molecular sieves) was added. After complete dissolution of the imine, the DMSO solution was added all at once via syringe to the reactor tube containing NaSMe at 25° C. All solids dissolved, and the reaction mixture turned bright orange in color. The mixture was heated to 80° C. for 1 hour, at which time the reaction mixture was dark red in color. The reaction mixture was cooled to <20° C. and a small amount water was added. The filtrate was diluted to 50.0 mL and was submitted for methionine assay by derivatization analysis. Results indicated a 59.4% yield by analysis.

[0175] Benzylimine lactone (0.877 g, 4.64 mmol) and sodium methane thiolate (0.390 g, 5.56 mmol) were com-

bined in DMSO (22 mL). An aliquot of the sample was removed for LCMS. The results from LCMS indicate a 32% chemical yield of methionine, and several unidentified peaks were seen in the chromatogram. The DMSO was then removed from the bulk reaction mixture by distillation, leaving a dark red residue (1.777 g). This material was redissolved in water (50 mL), and the pH was adjusted to approximately 4 with 3 M HCl. During this process, an orange gummy material precipitated out of solution and did not re-dissolve, even with gentle heating. The aqueous layer was decanted and concentrated to give a pale yellow residue (1.066 g). After placing under high vacuum, 0.377 g of product was collected. NMR data indicated that the residue is mostly methionine.

Example 11

Formation of N-Acyl Homoserine Lactone

[0176] To 1 equiv. of homoserine, may be added 2 equiv. of acetic anhydride and 0.05 equiv. of N,N-dimethylaminopyridine (DMAP) in 3 equiv. of solvent (acetic anhydride). The mixture may be heated to 60° C. for about 2 hr. The excess acetic anhydride may be removed by distillation. MIBK may be added to the mixture, which may be cooled such that N-acetyl homoserine lactone precipitates. The solid may be isolated by filtration and washed with cold MIBK.

[0177] The reactions were performed in a 100 mL glass reactor equipped with an overhead stirrer, reflux condenser, IR probe, N_2 inlet, temperature probe, and dosing inlet. Dimethylsulfoxide (DMSO) (25 mL) was added to the reactor under a positive flow of nitrogen and then heated to 80, 100, or 120° C. An IR spectrum was obtained, set as a reference, and subtracted from subsequent spectra. Homoserine lactone hydrochloride (2.03 g, 98.5% pure, 14.5 mmol) was added as a solid to the hot DMSO, and quickly dissolved. Next, one equivalent of sodium methane thiolate (11.5 mL, 1.26 M solution in DMSO, 14.5 mmol) was dosed into the reaction mixture over five minutes, resulting in the formation of a white precipitate. After approximately ten minutes, an additional 1.2 equivalents of sodium methane thiolate (13.9 mL, 1.26 M solution in DMSO, 17.5 mmol) was dosed into the reactor over 15, 30, or 60 minutes. The reaction was monitored by IR, and during the addition of the second equivalent of thiolate, free base lactone (1776 cm^{-1}) decreased while sodium methionine (1592 cm^{-1}) increased and eventually leveled off. Approximately 20 minutes after the dosing was complete, the reaction mixture was cooled to room temperature and diluted to 100 mL with water. An aliquot of this mixture (1.8 mL) was then diluted to 10 mL with water, and submitted for analysis by LC/MS.

Example 12

Formation of N-Acyl Homoserine Lactone

[0178] Homoserine (1 g, 8.39 mmol), acetic acid (20 mL), and water (0.5 mL) were mixed together and heated at 150° C. in a microwave for one hour. The solvent was removed using a rotary evaporator. The oily, orange residue was stirred in methyl t-butyl ether (MTBE) until the oil solidified. The mixture was filtered and the solid was washed with cold MTBE. The solid was dried in a vacuum oven at 60° C. The product was obtained as a white solid (1.03 g, 86.1%).

Example 13

Conversion of N-Acetyl Homoserine Lactone to N-Acetyl Methionine

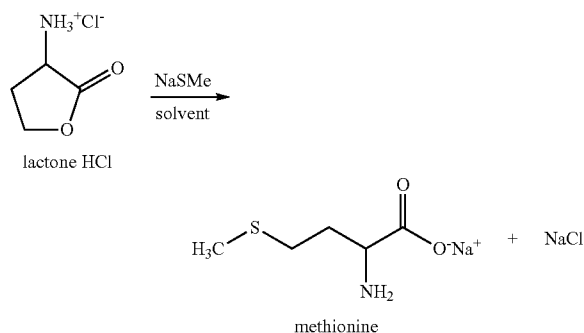
[0179] N-acetyl homoserine lactone may be combined with 10 equiv of DMF and 1.2 equiv. of NaSMe-DMF solution. The reaction mixture may be heated to about 50° C. for about 5 hr. The DMF may be removed by distillation, water may be added, and the resulting aqueous solution may be washed with methyl isobutyl ketone (MIBK) to remove impurities.

[0180] The solution of the sodium salt of N-acetyl methionine may be treated with water and 1.2 equiv. of 37% HCl. The solution may be heated to reflux for about 3 hr. The solution may be cooled, washed with MIBK, and then the pH of the washed solution may be adjusted to about 5.7 with NaOH. The precipitated methionine may be isolated by filtration. The mother liquid may be concentrated such that NaCl precipitates, which may be filtered at 95° C. Upon cooling of the mother liquor, the precipitated methionine may be isolated.

Example 14

Conversion of Homoserine Lactone to Methionine

[0181] Methionine sodium salt was prepared as depicted in the reaction scheme below:



[0182] To a 3-neck 500 mL flask fitted with magnetic stir bar, thermocouple, nitrogen purge/blanket, and 250 mL pressure-equalizing addition funnel fitted with septum was charged 5.0 g (93.4% assay, 0.034 moles, and 1 equiv.) of homoserine lactone hydrochloride. To this was added 5.6 g (0.080 mol, 2.2 equiv.) of NaSMe. The reactor was purged with nitrogen for 10 minutes then switched to a nitrogen blanket, and 135.0 g (125 mL, 25 mL/g substrate) of DMSO was charged to the addition funnel via cannula using nitrogen pressure. The DMSO was charged all at once to the solids, giving a slight exotherm (about 1.5° C.). The slurry was heated to 80° C. After 2 hours at 80° C. the reactor was cooled to room temperature (final net wt 145.4 g), and sampled for LCMS which indicated 80-94 ppm methionine in the diluted sample (theory=74 ppm) with 1 ppm homoserine.

[0183] A straight takeover distillation head with condenser, thermometer, vacuum connection, and receiver was fitted to the reactor and the pressure was reduced (initially, significant degassing was seen) to distill DMSO at 40-60 mTorr, vapor temperature 20-26° C., and mantle temperature up to 117° C. The residue (11.1 g) was a gooey, yellowish oil with solids. Distillate weight 128.8 g; trap and condenser contents 3.6 g.

Net difference from start: 1.9 g (some of which may have been the 1.6 g of MeSH potentially produced in the reaction).

[0184] The distillation pot residue was dissolved in 36.8 g water to give a ~1 M solution of Na-methionine as a blue-green solution. The solution was neutralized to the isoelectric point of methionine (initial pH 12.6, final pH 5.85), using 5.9 mL (0.035 mole, 1.03 equiv.) 6M HCl. The resulting solids were filtered and washed on the filter with water. The dried filter cake (sample #1) was 2.7 g of shiny off-white solid, presumed to be mostly methionine. The filtrate (70.4 g) was heated to boiling (100-107° C.) to remove excess water (43.6 g) and concentrate the filtrate. The resulting slurry was hot-filtered and washed on the filter with 100° C. saturated NaCl solution. The dried filter cake (sample #2), presumed to be mostly NaCl, and was 1.39 g. Upon filtration, additional solids precipitated out in the cooled solution. These were filtered and dried, yielding 0.72 g additional solids (sample #3). The filtrate from this material was cooled overnight at 0° C. to yield an additional 0.18 g of needles (sample #4). The aqueous solution was decanted off. Finally, the decantate was stripped at high vacuum (20 mTorr) to yield 9.07 g (sample #5) as an off-white solid, presumed mostly NaCl. Elemental analyses and ¹H and ¹³C NMR were obtained on all solid samples. The wt % methionine was determined by pre-column derivatization followed by HPLC-UV analysis. Table 2 presents the results.

TABLE 2

Sample Analysis and Material Balance.				
Sample #	¹ H, ¹³ C summary	Sample weight, grams	Wt % methionine by HPLC	Actual wt methionine, grams
1	Only methionine seen in both ¹ H and ¹³ C	2.7	100	2.7
3	Only methionine seen in both ¹ H and ¹³ C	0.72	98.6	0.71
4	Only methionine seen in both ¹ H and ¹³ C	0.18	80.1	0.14
5	Methionine, DMSO, and 2 unknown singlets	9.07	9.4	0.85
			Total =	4.40
			Theory =	5.08
			Methionine	86.6%
			Yield:	

Example 15

Conversion of Homoserine to Methionine without Isolation of the Lactone

[0185] DMSO (21 mL) was added to a 100 mL 3-necked round bottom flask equipped with a Teflon stir bar, an IR probe, condenser, a thermocouple and a N₂ purge. Homoserine (3.010 g, 25.26 mmol) was charged to the flask. The solution was heterogeneous, H₂SO₄ (1.54 mL, 18 M, 1.1 molar equivalent) was added to the solution. The temperature of the solution increased to 40° C., and then to 100° C. Additional DMSO (62 mL) was added to the reaction flask. NaSMe (3.88 g, 55.36 mmol, 2.2 molar equivalents) was charged to the flask. The solution boiled vigorously for about

30 seconds as 2 molar equivalents of methyl mercaptan were released. The solution was stirred for about 13 minutes. NaSMe (1.94 g, 28.11 mmol, 1.1 molar equivalents) was charged to the flask. The reaction was stirred for 8 min at 100° C. and then cooled to room temperature (30 minutes) The solution was analyzed by HPLC and afforded methionine: 53% overall yield and unreacted, homoserine: 22% yield.

Example 16

Conversion of Homoserine to Methionine Using Thioliates with Different Cations

[0186] Homoserine lactone hydrochloride (200 mg, 1.45 mmol) and the appropriate methanethiolate salt (3.20 mmol) were mixed together in DMSO (5 mL) and stirred at 80° C. or 120° C. for one hour. Each reaction mixture was analyzed using a quantitative HPLC method. Table 3 presents the results.

TABLE 3

Temp (° C.)	Time (hr)	Thiolate	Met (%)	Hser (%)
80	1	LiSCH ₃	22.66	62.36
80	1	LiSCH ₃	27.31	58.61
120	1	LiSCH ₃	12.58	27.25
120	1	LiSCH ₃	10.42	32.22
80	1	KSCH ₃	37.78	45.12
80	1	KSCH ₃	47.04	36.81
120	1	KSCH ₃	90.19	2.34
120	1	KSCH ₃	87.33	1.99
120	1	NaSCH ₃	82.84	3.09
120	1	NaSCH ₃	90.07	3.09

Example 17

Conversion of Homoserine Lactone to Selenomethionine

[0187] Methyl lithium was added via syringe to a suspension of elemental selenium (0.650 g, 8.23 mmol) in tetrahydrofuran (20 mL) at 0° C. The color of the solution changed from yellow to orange to red to nearly colorless as the selenium was consumed, after which the solution was allowed to warm to room temperature. The solvent was removed under vacuum leaving a yellow residue, which was then dissolved in DMF (10 mL) at room temperature. To this solution, N-acetylhomoserine lactone (0.980 g, 6.85 mmol) was added as a solution in DMF through an addition funnel. The reaction mixture was dark orange and slightly cloudy. After three hours at room temperature, TLC indicated that there was no starting material left in the solution. The DMF was distilled off, leaving a dark orange oil, which was then stirred in ether. After removal of the ether under vacuum, the residue was dissolved in 30 mL of 3 M HCl, and heated to reflux for three hours. There was a small amount of dark red insoluble material that was filtered off from the reaction mixture. The acid was then removed on a rotary evaporator. The orange oil was re-dissolved in a minimal amount of water (2 mL) and neutralized with 2 M NaOH, resulting in a yellow precipitate. This precipitate was then washed with cold water and dried under high vacuum. The solvent was evaporated from the filtrate, leaving an orange residue. Anal. Calcd for C₅H₁₁NO₂Se: C, 30.62; H, 5.65; N, 7.14. Found: C, 30.36; H,

5.55; N, 6.98. ¹H NMR (500 MHz) (D₂O): 3.87 (t, 1H); 2.66 (t, 2H); 2.32-2.18 (m, 2H); 2.06 (s, 3H).

Example 18

Conversion of Homoserine to Methionine Diketopiperazine

[0188] Homoserine diketopiperazine.

[0189] Acetyl chloride (113 mL, 1586 mmol) was added to isopropanol (1800 mL) over 10 minutes. The temperature increased from 27° C. to 50° C. The mixture was stirred for 30 minutes. Homoserine (180 g, 1511 mmol) was added and the mixture was heated to 80° C. The mixture was stirred for 90 minutes. Acetic acid (99 mL, 1737 mmol) was added followed by diisopropylethylamine (290 mL, 1662 mmol). The mixture was homogeneous after the diisopropylethylamine was added. The mixture was stirred for four hours at 80° C. A solid began to precipitate after about two hours. The mixture was cooled to 25° C. The mixture was filtered and the solid was washed with isopropanol. The solid was dried in a vacuum oven at 60° C. A white solid (104 g, 68% yield) was obtained.

[0190] Dichlorodiketopiperazine.

[0191] Homoserine diketopiperazine (120 g, 593 mmol) was suspended in acetonitrile (1800 mL). Thionyl chloride (88 mL, 1216 mmol) was slowly added while maintaining the temperature between 24° C. and 26° C. The addition was completed in 10 minutes, but the exotherm subsided about 30 minutes after the addition was completed. The substrate began to slowly dissolve and the product began to precipitate about 15 minutes after the addition was completed. The mixture was stirred for 5 hours. The mixture was filtered and the solid was washed with acetonitrile. The solid was dried in a vacuum oven at 60° C. A white solid (114 g, 80% yield) was obtained.

[0192] Methionine Diketopiperazine.

[0193] Tetramethylguanidine (214 mL, 1706 mmol) was dissolved in methanol (3200 mL). Methane thiol (80 g, 1673 mmol) was bubbled into the solution. Dichlorodiketopiperazine (160 g, 669 mmol) was added and the mixture was heated to 60° C. and held for 4 hours. The substrate slowly dissolved over 30 minutes. A solid began to precipitate after an hour. The mixture was cooled to 25° C. The mixture was filtered and the solid was washed with methanol. A white solid (111 g, 63%) was obtained.

Example 19

Conversion of Methionine Diketopiperazine to Methionine

[0194] Methionine diketopiperazine and 6M Hydrochloric acid were refluxed were refluxed for 20 hours in DMSO. The solvent was stripped using rotary evaporation to provide methionine in high yield.

Example 20

Preparation of N-Butyrylselenomethionine from N-Butyrylhomoserine Lactone

[0195] A three necked, 25 mL round bottom flask was equipped with a stir bar, addition funnel, reflux condenser, and a septum and the system was placed under argon. The glassware was dried with heat under vacuum. Elemental sele-

nium (0.117 g, 1.48 mmol) was weighed into the flask and suspended in THF or Me-THF (5 mL, anhydrous). After the solution was cooled in an ice bath, MeLi (1.6 M solution in ether, 1 mL, 1.60 mmol) was added to the suspension over several minutes via syringe. The ice bath was removed and the solution was allowed to warm to room temperature. After an additional ten minutes, the solvent was removed under reduced pressure, leaving an off-white residue, which was then dissolved in 6 mL of the desired solvent. N-isobutyryl-homoserine lactone (0.211 g, 1.23 mmol) was added as a solid through one of the side necks of the flask into the selenolate solution. The resulting solution was heated (see Table 4 for temperature and time) and then cooled to room temperature. The reaction mixture was quenched with 3 M formic acid (0.5 mL, 1.2 equiv.) and then diluted with water to a concentration less than 4000 ppm. Aliquots were submitted for analysis by LC/MS.

TABLE 4

Analytical results from screening experiments where N-acetylhomoserine lactone was treated with lithium methyl selenide in a variety of solvents.			
Solvent (addition of selenolate to N-acetyl lactone)	Temp (° C.)	Time (h)	Yield (%)
DMF	80	1	74
DMSO	80	2	83
THF	50	1	76
THF	65	1	82
Me-THF	80	1	86
CH ₃ CN	80	1	87
EtOH	80	1	16

Example 21

Preparation of Homoserine Lactone Ethyl Carbamate from Homoserine Lactone

[0196] Homoserine lactone HCl (1 mole), sodium bicarbonate (2 moles) and acetonitrile were mixed together in a reactor. Ethyl chloroformate (1 mole) was added over a period of 30 minutes. After the addition was completed, the mixture was heated to 40° C. The reaction was monitored for completeness once the evolution of carbon dioxide had ceased. The reaction mixture was cooled to room temperature and filtered through a coarse filter to remove the sodium chloride and excess sodium bicarbonate. The solid homoserine lactone ethyl carbamate was washed with acetonitrile. The filtrate was filtered again through a 5 µm filter to remove the fine, solid impurities.

[0197] The filtrate was then transferred into a reactor and the acetonitrile was exchanged for toluene via distillation. Once a final concentration of 20 mL of toluene/g of substrate was attained, the reaction mixture was cooled to 60° C. and was seeded using a slurry of homoserine lactone ethyl carbamate in toluene. The mixture was cooled to 45° C. to initiate product crystallization. The mixture was cooled to 0° C. and this temperature was held for an additional 2 hours. The mixture was filtered and the solid washed with toluene. The product was dried in a vacuum oven at 50° C.

Example 22

Preparation of Selenomethionine Ethyl Carbamate Lithium Salt

[0198] Homoserine lactone ethyl carbamate (1 mole) from Example 21 was mixed into a solvent media of tetrahydrofu-

ran contained in a reactor under a nitrogen blanket. The reaction mixture was heated to a temperature of 65° C. and the solution was allowed to reach reflux. At the point of reflux, lithium methyl selenide (prepared by reacting elemental selenium (~1 mole) with methyl lithium (1 mole) in a mixture of tetrahydrofuran and diethoxymethane at 0° C.-25° C.), was added by fast addition. The addition of the selenolate changed the color of the reaction mixture, from a clear liquid to a golden yellow color.

[0199] The reaction temperature of 65° was maintained for 1 hour and a sample was taken after every half-hour to test for the presence of both the starting material and the final product using HPLC and TLC. When the HPLC and TLC results showed a complete conversion of product, filtered water was added to the reaction mixture to quench any un-reacted methyl lithium or lithium methyl selenide. The THF was then removed from the reaction mixture via distillation under atmospheric pressure. The temperature was then increased to 87° C. to distill off any diethoxymethane present. The resultant mixture contained selenomethionine ethyl carbamate lithium salt.

Example 23

Preparation of Selenomethionine from Selenomethionine Ethyl Carbamate Lithium Salt

[0200] The selenomethionine ethyl carbamate lithium salt was hydrolyzed to form selenomethionine. For this, 50 wt % NaOH (5 moles) was added to the n-ethyl carbamate of selenomethionine (1 mole) mixture contained in a reactor. The two liquids were mixed together and heated to a temperature of 65° C. The reaction mixture was heated in 5° C. increments until the temperature reached 90° C. After all traces of solvents were removed, the reaction mixture was heated to 100° C. over a period of 30 minutes. The reaction mixture was maintained a temperature of 100° C. for 2 hours and samples were taken after every hour and tested to determine completion of the de-protection reaction. Once the product conversion was complete, the reaction mixture was cooled to a temperature of 40° C.

[0201] The pH of the solution of de-protected lithium salt of selenomethionine was measured (the pH was ~14). Concentrated aqueous HCl solution was added by drop-wise addition to the mixture until the pH was within a range of pH=9.2-9.5. The temperature was maintained within a range of 30-60° C. During this process, traces of elemental selenium appeared and were identified by their red or grey color. At a pH=9.2, the reaction mixture was stirred for 3 hours at room temperature. The traces of elemental selenium were filtered through a nylon membrane filter. The pH of the reaction mixture was then adjusted to the iso-electric point of selenomethionine, which is 5.7, using concentrated aqueous HCl solution while maintaining a temperature range of 30° C.-60° C.

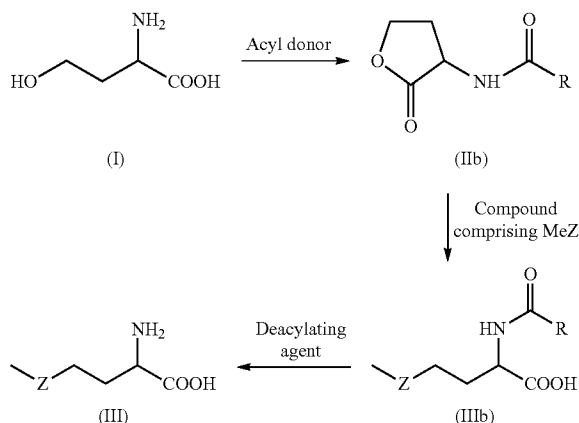
[0202] Isopropanol or methanol was then added to the reaction mixture and the mixture 3 was heated to a temperature at which the reaction mixture was homogeneous. The mixture was then gradually cooled until precipitation occurred and the mixture was held at that precipitation temperature for 1 hour. The mixture was then gradually cooled to 0° C. over a period of 2 hours and stirred to increase the recovery of the selenomethionine solid product. The product was then filtered and

further washed with cold isopropanol or methanol. The final product was dried in a vacuum oven at a temperature of 50° C. to a constant weight.

What is claimed is:

1. A process for preparing a compound comprising Formula (III) or a pharmaceutically acceptable salt thereof, the process comprising:

- contacting a compound comprising Formula (I) with an acyl donor comprising R to form a compound comprising Formula (IIb);
- contacting the compound comprising Formula (IIb) with a compound comprising MeZ to form a compound comprising Formula (IIIb); and
- contacting the compound comprising Formula (IIIb) with a deacylating agent to form the compound comprising Formula (III) or pharmaceutically acceptable salt thereof:



wherein:

the compound comprising MeZ is an alkali metal methaneselenoate or methyl selenol;

Me is methyl;

R is chosen hydrogen, hydrocarbyl, and substituted hydrocarbyl; and

Z is selenium.

2. The process of claim 1, wherein R is chosen from hydrogen, alkyl, alkene, alkoxy, aryl, substituted alkyl, substituted alkene, substituted alkoxy, and substituted aryl.

3. The process of claim 1, wherein the acyl donor is chosen from an acyl halide, an acid anhydride, and a carbamate; and the molar ratio of the compound comprising Formula (I) to the acyl donor is from about 1:0.5 to about 1:10.

4. The process of claim 1, wherein the reaction of step (a) further comprises a proton donor chosen from HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₃PO₄, poly H₃PO₄, H₂SO₄, MeSO₃H, CF₃SO₃H, and p-toluene sulfonic acid; and, optionally, further comprises a catalyst

5. The process of claim 1, wherein the molar ratio of the compound comprising Formula (IIb) to the alkali metal methaneselenoate or methyl selenol is from about 1:0.5 to about 1:5.

6. The process of claim 1, wherein the deacylating agent is a proton acceptor chosen from an alkali metal hydroxide, an alkaline earth metal hydroxide, a alkali metal carbonate, an amide, and a hydride; or the deacylating agent is a proton

donor chosen from HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₂SO₄, MeSO₃H, CF₃SO₃H, and p-toluene sulfonic acid.

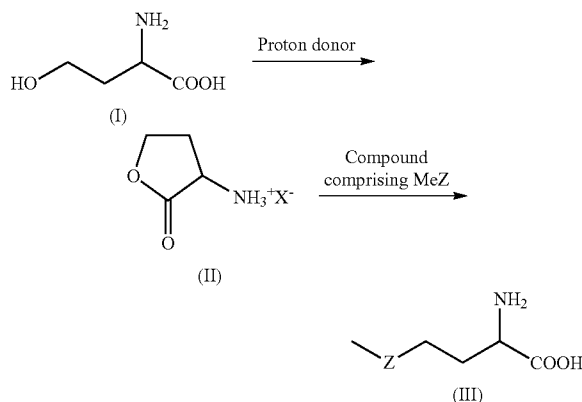
7. The process of claim 1, wherein steps (a)-(c) are conducted in the presence of a solvent at a temperature of about 20° C. to about 100° C. and at ambient pressure; the solvent being chosen from an aprotic solvent, a protic solvent, and combinations thereof; and the molar ratio of the solvent to the compound comprising Formula (I) is from about 1:1 to about 50:1.

8. The process of claim 1, wherein the compound comprising Formula (III) has an L configuration, a D configuration, or mixture thereof.

9. The process of claim 1, wherein R is ethoxy; the acyl donor is chloroformate; the proton donor is hydrochloric acid; the compound comprising MeZ is lithium methyl selenide, and the deacylating agent is sodium hydroxide.

10. A process for preparing a compound comprising Formula (III) or a pharmaceutically acceptable salt thereof, the process comprising:

- contacting a compound comprising Formula (I) with a proton donor (HX) to form a compound comprising Formula (II); and
- contacting the compound comprising Formula (II) with a compound comprising MeZ to form the compound comprising Formula (III) or pharmaceutically acceptable salt thereof:



wherein:

the compound comprising MeZ is chosen from an alkali metal methaneselenoate and methyl selenol;

Me is methyl;

X is an anion; and

Z is selenium.

11. The process of claim 10, wherein the proton donor is chosen from HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₂SO₄, MeSO₃H, CF₃SO₃H, and p-toluene sulfonic acid; and the molar ratio of the compound comprising Formula (I) to the proton donor is from about 1:0.1 to about 1:10.

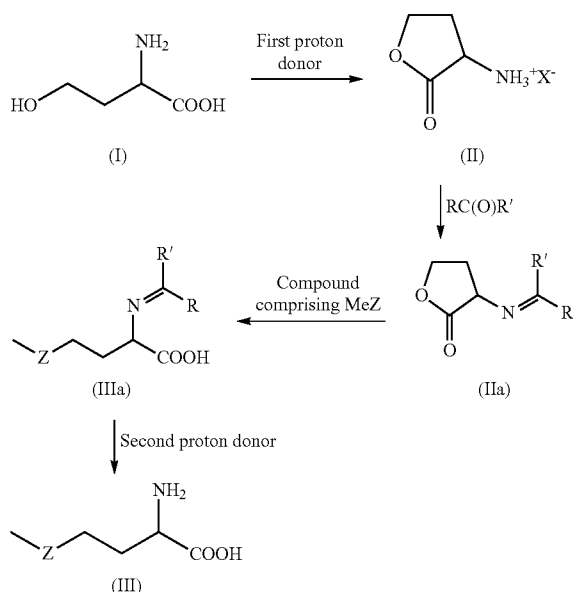
12. The process of claim 10, wherein the step (a) is conducted in the presence of a protic solvent chosen from water, a C₁₋₄ alcohol, and combinations thereof; the molar ratio of the solvent to the compound comprising Formula (I) is from about 1:1 to about 50:1; and the reaction is conducted at a temperature from about 50° C. to about 150° C.

13. The process of claim 10, wherein the molar ratio the compound comprising Formula (II) to the alkali metal methaneselenoate is from about 1:0.5 to about 1:10; the reaction is conducted in the presence a solvent chosen from an aprotic solvent, a protic solvent, and combinations thereof; the molar ratio of the solvent to the compound comprising Formula (II) is from about 1:1 to about 50:1; and the reaction is conducted at a temperature from about 20° C. to about 200° C., at ambient pressure, and under an inert gas chosen from nitrogen and argon.

14. The process of claim 10, wherein the molar ratio the compound comprising Formula (II) to methyl selenol is from about 1:10 to about 1:150; the reaction is conducted in the presence of a solvent chosen from a protic solvent, an aprotic solvent, an organic solvent, and combinations thereof; the molar ratio of the solvent to the compound comprising Formula (IIa) is from about 1:1 to about 50:1; and the reaction is conducted at a temperature from about 20° C. to about 200° C., at ambient pressure, and under an inert gas chosen from nitrogen and argon.

15. A process for preparing a compound comprising Formula (III) or a pharmaceutically acceptable salt thereof, the process comprising:

- contacting a compound comprising Formula (I) with a first proton donor (HX) to form a compound comprising Formula (II);
- contacting the compound comprising Formula (II) with $RC(O)R'$ to form a compound comprising Formula (IIa);
- contacting the compound comprising Formula (IIa) with a compound comprising MeZ to form a compound comprising Formula (IIIa) or a pharmaceutically acceptable salt thereof; and
- contacting the compound comprising Formula (IIIa) or pharmaceutically acceptable salt thereof with a second proton donor to form the compound comprising Formula (III) or a pharmaceutically acceptable salt thereof:



wherein:

Me is methyl;

R is hydrocarbyl or substituted hydrocarbyl;

R' is hydrogen, hydrocarbyl, or substituted hydrocarbyl;

X is an anion; and

Z is sulfur or selenium.

16. The process of claim 15, wherein R is chosen from alkyl, alkene, aryl, substituted alkyl, substituted alkene, and substituted aryl; and R' is chosen from hydrogen, alkyl, alkene, aryl, substituted alkyl, substituted alkene, and substituted aryl.

17. The process of claim 15, wherein the first proton donor is chosen from HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₂SO₄, MeSO₃H, CF₃SO₃H, and p-toluene sulfonic acid; and the molar ratio of the compound comprising Formula (I) to the first proton donor is from about 1:0.5 to about 1:5.

18. The process of claim 15, wherein $RC(O)R'$ is chosen from acetaldehyde, propionaldehyde, benzaldehyde, propionaldehyde, acetophenone, and benzophenone; and the molar ratio of the compound comprising Formula (I) to $RC(O)R'$ is from about 1:0.1 to about 1:10.

19. The process of claim 15, wherein steps (a) and (b) are conducted in the presence a solvent chosen from an aprotic solvent, a protic solvent, an organic solvent, and combinations thereof; the molar ratio of the solvent to the compound comprising Formula (I) is from about 1:1 to about 50:1; and steps (a) and (b) are conducted at a temperature from about 50° C. to about 150° C.

20. The process of claim 15, wherein the compound comprising MeZ is chosen from an alkali metal methanethiolate, an alkali metal methaneselenoate, methyl mercaptan, and methyl selenol.

21. The process of claim 20, wherein the molar ratio of the compound comprising Formula (IIa) to the alkali metal methanethiolate or the alkali metal methaneselenoate is from about 1:0.25 to about 1:5; the reaction is performed in the presence of a solvent chosen from an aprotic solvent, a protic solvent, and combinations thereof; the molar ratio of the solvent to the compound comprising Formula (IIa) is from about 1:1 to about 50:1; and the reaction is conducted at a temperature of about 20° C. to about 200° C., at ambient pressure, and under an inert gas chosen from nitrogen and argon.

22. The process of claim 20, wherein the molar ratio the compound comprising Formula (IIa) to methyl mercaptan or methyl selenol is from about 1:10 to about 1:150; the reaction is performed in the presence of a solvent chosen from an aprotic solvent, a protic solvent, an organic solvent, and combinations thereof; the molar ratio of the solvent to the compound comprising Formula (IIa) is from about 1:1 to about 50:1; and the reaction is conducted at a temperature of about 20° C. to about 200° C., at ambient pressure, and under an inert gas chosen from nitrogen and argon.

23. The process of claim 15, wherein the second proton donor is chosen from HCl, HBr, HI, HClO₃, HClO₄, HBrO₄, HIO₃, HIO₄, HNO₃, H₃PO₄, poly H₃PO₄, H₂SO₄, MeSO₃H, CF₃SO₃H, and p-toluene sulfonic acid; and the molar ratio of the compound comprising Formula (IIIa) to the second proton donor is from about 1:0.5 to about 1:10.

24. The process of claim 15, wherein step (d) is conducted in the presence of a protic solvent; the molar ratio of the solvent to the compound comprising Formula (IIIa) is from about 1:1 to about 50:1; and the reaction is conducted at a temperature of about 20° C. to about 100° C.

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