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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN COMPANY LLC** [US/US]; 7000 Portage Road, Kalamazoo, Michigan 49001-0199 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BETCHE, Hans-Juergen** [DE/DE]; Im Gottesacker 8, 79279 Vorstetten (DE). **IRDAM, Erwin, Ayandra** [US/US]; 6296 Village Green Circle, Portage, MI 49024 (US). **PADILLA, Amphlett, Greg** [US/US]; 10137 South Westnedge, Portage, MI 49002 (US). **PEARLMAN, Bruce** [US/US]; 3411 Willow Lake Drive, Kalamazoo, MI 49008 (US). **PERRAULT, William, Roland** [US/US]; Pfizer Global Research and Development, 7000 Portage Road, Kalamazoo, MI 49001 (US). **VANALSTEN, John** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). **FRANCZYK, Thaddeus, S.** [US/US]; Pfizer Global Research and Development, 7000 Portage Road, Kalamazoo, MI 49001 (US).

(74) Agent: **FULLER, Grover, F., Jr.**; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

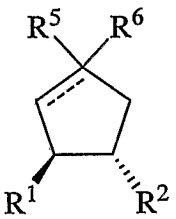
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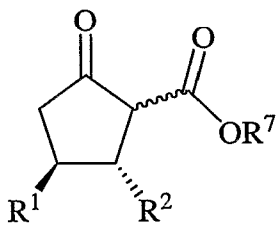
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(54) Title: STEREOSELECTIVE SYNTHESIS OF 3,4-DISUBSTITUTED CYCLOPENTANONES AND RELATED COMPOUNDS



(13)



(18)

(57) Abstract: Methods and materials for preparing optically active 3,4-disubstituted cyclopentanones are disclosed. The method includes hydrolyzing one or more compounds represented by Formula (13), or removing an ester moiety from a compound represented by Formula (18).

WO 2007/010387 A2

STEREOSELECTIVE SYNTHESIS OF 3,4-DISUBSTITUTED CYCLOPENTANONES AND RELATED COMPOUNDS

BACKGROUND OF THE INVENTION

FIELD OF INVENTION

[0001] This invention relates to materials and methods for preparing chiral ketones, and more particularly, to the stereoselective synthesis of optically active 3,4-disubstituted cyclopentanones. The substituted cyclopentanones can be used to make various optically-active cyclic amino acids, which are useful for treating pain and a variety of psychiatric and sleep disorders.

DISCUSSION

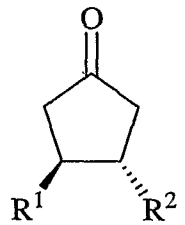
[0002] United States Patent No. US 6,635,673 B1 to Bryans et al. (the '673 patent) describes a number of optically-active cyclic amino acids and their pharmaceutically acceptable salts, including (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid. These compounds bind to the alpha-2-delta ($\alpha 2\delta$) subunit of a calcium channel. They are useful for treating a number of diseases including insomnia, epilepsy, faintness attacks, hypokinesia, depression, anxiety, panic, pain, irritable bowel syndrome, and arthritis, among others.

[0003] The '673 patent describes a number of methods for preparing the optically-active cyclic amino acids. Many of these methods employ, as chemical intermediates, optically active 3,4-disubstituted cyclopentanones, including (*S*,*S*)-3,4-dimethyl-cyclopentanone. Although methods exist for preparing cyclopentanones, many of the processes may be problematic for pilot- or full-scale production because of efficiency and cost concerns or because the processes use non-commercial starting materials. See, e.g., U.S. Patent No. 6,872,856 to Blakemore et al. Thus, improved methods for preparing 3,4-disubstituted cyclopentanones would be desirable.

SUMMARY OF THE INVENTION

[0004] This invention provides a comparatively efficient and cost-effective method for preparing optically active 3,4-disubstituted cyclopentanones (Formula 1, below) from commercially available starting materials. For example, (*S*,*S*)-3,4-dimethyl-cyclopentanone may be prepared from (*R*)-2-methyl-succinic acid 4-methyl ester in five steps. The 3,4-disubstituted cyclopentanones can be used to prepare optically-active cyclic amino acids (Formula 14, below), such as (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, which are thought to be useful for treating pain, as well as various psychiatric and sleep disorders.

[0005] One aspect of the present invention provides a method of making a compound of Formula 1,



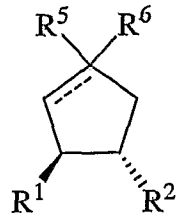
1 ,

or an opposite enantiomer thereof, wherein

R^1 and R^2 are each independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl, wherein aryl may be optionally substituted with from one to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, hydroxy, halogeno, fluoro-C_{1-6} alkyl, and nitro,

the method comprising:

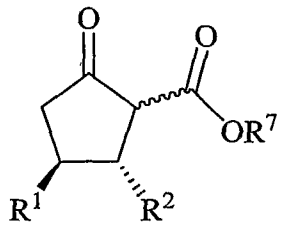
hydrolyzing one or more compounds of Formula 13,



13 ,

or opposite enantiomers thereof or salts thereof, wherein R^1 and R^2 in Formula 13 are as defined above for Formula 1, and R^5 and R^6 are each independently hydrogen, methylsulfanyl, methylsulfinyl, oxysulfonyl anion, hydroxy, or absent, provided that R^5 and R^6 are different.

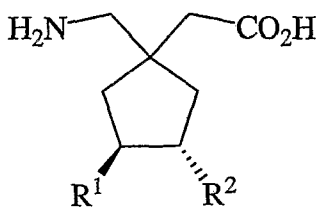
[0006] Another aspect of the present invention provides a method of making the compound of Formula 1, above, or an opposite enantiomer thereof, and includes the step of removing an ester moiety from a compound of Formula 18,



18 ,

or an opposite enantiomer thereof, wherein R^1 and R^2 in Formula 18 are as defined above for Formula 1, and R^7 is independently selected from the substituents that define R^1 and R^2 in Formula 1.

[0007] Another aspect of the present invention provides a method of making a compound of Formula 14,



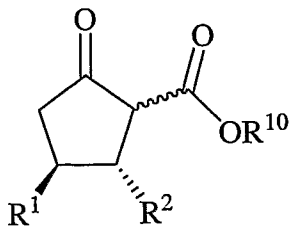
14 ,

or an opposite enantiomer thereof, or a pharmaceutically acceptable salt of the compound of Formula 14 or opposite enantiomer thereof, wherein R^1 and R^2 in Formula 14 are as defined above for Formula 1. The method comprises the steps of (a) hydrolyzing one or more compounds of Formula 13, above, their opposite enantiomers, or their salts, to give the compound of Formula 1 or its opposite enantiomer; and (b) converting the compound of Formula 1 or its opposite enantiomer to the compound of Formula 14 or its opposite enantiomer, or to a pharmaceutically acceptable salt of the compound of Formula 14 or its opposite enantiomer.

[0008] Another aspect of the present invention provides a method of making the compound of Formula 14, above, or its opposite enantiomer, or a pharmaceutically acceptable salt of the compound of Formula 14 or its opposite enantiomer. The method includes the steps of (a) removing an ester moiety from a compound of Formula 18, above, or its opposite enantiomer, to give a compound of Formula 1, above, or its opposite enantiomer; and (b) converting the compound of Formula 1 or its opposite enantiomer, to the compound of Formula 14 or its opposite enantiomer, or to a pharmaceutically acceptable salt of the compound of Formula 14 or its opposite enantiomer.

[0009] Another aspect of the present invention provides compounds of Formula 13, above, such as (3*S*,4*S*)-1-methanesulfinyl-3,4-dimethyl-1-methylsulfanyl-cyclopentane, (3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene, and (3*S*,4*S*)-1-hydroxy-3,4-dimethyl-cyclopentanesulfonate sodium salt, including opposite enantiomers of the foregoing compounds.

[0010] Another aspect of the present invention provides compounds of Formula 19,



19

including opposite enantiomers and salts thereof, wherein R^1 and R^2 are as defined above for Formula 1 and R^{10} is independently selected from hydrogen atom and the groups that define R^1 and R^2.

[0011] Compounds of Formula 19 include (2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester, (1*S*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester, and (1*R*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester, including opposite enantiomers of the foregoing compounds. Other compounds of Formula 19 include (2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid, (1*S*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid, (1*R*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid, opposite enantiomers of the foregoing compounds, and salts of the foregoing compounds.

[0012] Another aspect of the present invention provides compounds selected from (*S*,*S*)-3,4-dimethyl-hexanedioic acid, (*S*,*S*)-3,4-diethyl-hexanedioic acid, (*S*,*S*)-3,4-dipropyl-hexanedioic acid, (*R*,*R*)-3,4-diisopropyl-hexanedioic acid, (*S*,*S*)-3,4-dibenzyl-hexanedioic acid, opposite enantiomers of the foregoing compounds, and salts of the foregoing compounds.

[0013] The present invention includes all salts, whether pharmaceutically acceptable or not, complexes, solvates, hydrates, and polymorphic forms of the above compounds, where possible.

DETAILED DESCRIPTION

DEFINITIONS AND ABBREVIATIONS

[0014] Unless otherwise indicated, this disclosure uses definitions provided below. Some of the definitions and formulae may include a dash ("-") to indicate a bond between atoms or a point of attachment to a named or unnamed atom or group of atoms. Other definitions and formulae may include an equal sign ("=") or an identity symbol ("≡") to indicate a double bond or a triple bond, respectively. Other formulae may include one or more wavy bonds ("∿∿∿"). When attached to a

stereogenic center, the wavy bonds refer to both stereoisomers, either individually or as mixtures. Likewise, when attached to a double bond, the wavy bonds indicate a *Z*-isomer, an *E*-isomer, or a mixture of *Z* and *E* isomers. Some formulae may include a dashed bond "=====" to indicate a single or a double bond.

[0015] "Substituted" groups are those in which one or more hydrogen atoms have been replaced with one or more non-hydrogen atoms or groups, provided that valence requirements are met and that a chemically stable compound results from the substitution.

[0016] "About" or "approximately," when used in connection with a measurable numerical variable, refers to the indicated value of the variable and to all values of the variable that are within the experimental error of the indicated value (e.g., within the 95% confidence interval for the mean) or within ±10 percent of the indicated value, whichever is greater.

[0017] "Alkyl" refers to straight chain and branched saturated hydrocarbon groups, generally having a specified number of carbon atoms (i.e., C_{1-6} alkyl refers to an alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms). Examples of alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2,2-trimethyleth-1-yl, and *n*-hexyl.

[0018] "Alkenyl" refers to straight chain and branched hydrocarbon groups having one or more unsaturated carbon-carbon bonds, and generally having a specified number of carbon atoms. Examples of alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-1-yl, 1-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methyl-1-propen-1-yl, 2-methyl-2-propen-1-yl, 1,3-butadien-1-yl, and 1,3-butadien-2-yl.

[0019] "Alkynyl" refers to straight chain or branched hydrocarbon groups having one or more triple carbon-carbon bonds, and generally having a specified number of carbon atoms. Examples of alkynyl groups include ethynyl, 1-propyn-1-yl, 2-propyn-1-yl, 1-butyn-1-yl, 3-butyn-1-yl, 3-butyn-2-yl, and 2-butyn-1-yl.

[0020] "Alkanoyl" refers to alkyl-C(O)-, where alkyl is defined above, and generally includes a specified number of carbon atoms, including the carbonyl carbon. Examples of alkanoyl groups include formyl, acetyl, propionyl, butyryl, pentanoyl, and hexanoyl.

[0021] "Alkoxy" and "alkoxycarbonyl" refer, respectively, to alkyl-O- and alkyl-O-C(O)-, where alkyl is defined above. Examples of alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *s*-butoxy, *t*-butoxy, *n*-pentoxy, and *s*-pentoxy. Examples of alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, *i*-propoxycarbonyl, *n*-butoxycarbonyl, *s*-butoxycarbonyl, *t*-butoxycarbonyl, *n*-pentoxycarbonyl, and *s*-pentoxycarbonyl.

[0022] "Halo," "halogen" and "halogeno" may be used interchangeably, and refer to fluoro, chloro, bromo, and iodo.

[0023] "Haloalkyl" refers to an alkyl group substituted with one or more halogen atoms, where alkyl is defined above. Examples of haloalkyl groups include trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

[0024] "Cycloalkyl" refers to saturated monocyclic and bicyclic hydrocarbon rings, generally having a specified number of carbon atoms that comprise the ring (i.e., C_{3-7} cycloalkyl refers to a cycloalkyl group having 3, 4, 5, 6 or 7 carbon atoms as ring members). The cycloalkyl may be attached to a parent group or to a substrate at any ring atom, unless such attachment would violate valence requirements. Likewise, the cycloalkyl groups may include one or more non-hydrogen substituents unless such substitution would violate valence requirements. Useful substituents include alkyl, alkoxy, alkoxycarbonyl, alkanoyl, and halo, as defined above, and hydroxy, mercapto, nitro, and amino.

[0025] Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of bicyclic cycloalkyl groups include bicyclo[1.1.0]butyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.0]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.0]heptyl, bicyclo[3.1.1]heptyl, bicyclo[4.1.0]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl,

bicyclo[4.1.1]octyl, bicyclo[3.3.0]octyl, bicyclo[4.2.0]octyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.0]nonyl, bicyclo[3.3.2]decyl, bicyclo[4.2.2]decyl, bicyclo[4.3.1]decyl, bicyclo[4.4.0]decyl, bicyclo[3.3.3]undecyl, bicyclo[4.3.2]undecyl, and bicyclo[4.3.3]dodecyl.

[0026] "Cycloalkenyl" refers monocyclic and bicyclic hydrocarbon rings having one or more unsaturated carbon-carbon bonds and generally having a specified number of carbon atoms that comprise the ring (i.e., C_{3-7} cycloalkenyl refers to a cycloalkenyl group having 3, 4, 5, 6 or 7 carbon atoms as ring members). The cycloalkenyl may be attached to a parent group or to a substrate at any ring atom, unless such attachment would violate valence requirements. Likewise, the cycloalkenyl groups may include one or more non-hydrogen substituents unless such substitution would violate valence requirements. Useful substituents include alkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, alkanoyl, and halo, as defined above, and hydroxy, mercapto, nitro, and amino.

[0027] "Cycloalkanoyl" and "cycloalkenoyl" refer to cycloalkyl-C(O)- and cycloalkenyl-C(O)-, respectively, where cycloalkyl and cycloalkenyl are defined above. References to cycloalkanoyl and cycloalkenoyl generally include a specified number of carbon atoms, excluding the carbonyl carbon. Examples of cycloalkanoyl groups include cyclopropanoyl, cyclobutanoyl, cyclopentanoyl, cyclohexanoyl, cycloheptanoyl, 1-cyclobutenoyl, 2-cyclobutenoyl, 1-cyclopentenoyl, 2-cyclopentenoyl, 3-cyclopentenoyl, 1-cyclohexenoyl, 2-cyclohexenoyl, and 3-cyclohexenoyl.

[0028] "Cycloalkoxy" and "cycloalkoxycarbonyl" refer, respectively, to cycloalkyl-O- and cycloalkenyl-O and to cycloalkyl-O-C(O)- and cycloalkenyl-O-C(O)-, where cycloalkyl and cycloalkenyl are defined above. References to cycloalkoxy and cycloalkoxycarbonyl generally include a specified number of carbon atoms, excluding the carbonyl carbon. Examples of cycloalkoxy groups include cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, 1-cyclobutenoxy, 2-cyclobutenoxy, 1-cyclopentenoxy, 2-cyclopentenoxy, 3-cyclopentenoxy, 1-cyclohexenoxy, 2-cyclohexenoxy, and 3-cyclohexenoxy. Examples of

cycloalkoxycarbonyl groups include cyclopropoxycarbonyl, cyclobutoxycarbonyl, cyclopentoxycarbonyl, cyclohexoxycarbonyl, 1-cyclobutenoxycarbonyl, 2-cyclobutenoxycarbonyl, 1-cyclopentenoxycarbonyl, 2-cyclopentenoxycarbonyl, 3-cyclopentenoxycarbonyl, 1-cyclohexenoxycarbonyl, 2-cyclohexenoxycarbonyl, and 3-cyclohexenoxycarbonyl.

[0029] "Aryl" and "arylene" refer to monovalent and divalent aromatic groups, respectively, including 5- and 6-membered monocyclic aromatic groups that contain 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Examples of monocyclic aryl groups include phenyl, pyrrolyl, furanyl, thiopheneyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isooxazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl. Aryl and arylene groups also include bicyclic groups and tricyclic groups, including fused 5- and 6-membered rings described above. Examples of multicyclic aryl groups include naphthyl, biphenyl, anthracenyl, pyrenyl, carbazolyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiopheneyl, quinolinyl, isoquinolinyl, indolyl, benzofuranyl, purinyl, and indolizinyl. They aryl and arylene groups may be attached to another group at any ring atom, unless such attachment would violate valence requirements. The aryl and arylene groups may include one or more non-hydrogen substituents unless such substitution would violate valence requirements. Useful substituents include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, alkanoyl, cycloalkanoyl, cycloalkenoyl, alkoxycarbonyl, cycloalkoxycarbonyl, and halo, as defined above, and hydroxy, mercapto, nitro, amino, and alkylamino.

[0030] "Heteroaryl" and "heteroarylene" refer, respectively, to monovalent and divalent aryl and arylene groups, as defined above, which contain at least one heteroatom.

[0031] "Heterocycle" and "heterocyclyl" refer to saturated, partially unsaturated, or unsaturated monocyclic or bicyclic rings having from 5 to 7 or from 7 to 11 ring members, respectively. The monocyclic and bicyclic groups have ring members made up of carbon atoms and from 1 to 4 or from 1 to 6 heteroatoms, respectively, that are independently nitrogen, oxygen or sulfur, and may include any bicyclic group

in which any of the above-defined monocyclic heterocycles are fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to another group at any heteroatom or carbon atom unless such attachment would violate valence requirements. Any of the carbon or nitrogen ring members may include a non-hydrogen substituent unless such substitution would violate valence requirements. Useful substituents include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, alkanoyl, cycloalkanoyl, cycloalkenoyl, alkoxycarbonyl, cycloalkoxycarbonyl, and halo, as defined above, and hydroxy, mercapto, nitro, amino, and alkylamino.

[0032] Examples of heterocycles include acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*, 6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0033] "Arylalkyl" and "heteroarylalkyl" refer, respectively, to aryl-alkyl and heteroaryl-alkyl, where aryl, heteroaryl, and alkyl are defined above. Examples include benzyl, fluorenylmethyl, and imidazol-2-yl-methyl.

[0034] "Leaving group" refers to any group that leaves a molecule during a fragmentation process, including substitution reactions, elimination reactions, and addition-elimination reactions. Leaving groups may be nucleofugal, in which the group leaves with a pair of electrons that formerly served as the bond between the leaving group and the molecule, or may be electrofugal, in which the group leaves without the pair of electrons. The ability of a nucleofugal leaving group to leave depends on its base strength, with the strongest bases being the poorest leaving groups. Common nucleofugal leaving groups include nitrogen (e.g., from diazonium salts); sulfonates, including alkylsulfonates (e.g., mesylate), fluoroalkylsulfonates (e.g., triflate, hexaflate, nonaflate, and tresylate), and arylsulfonates (e.g., tosylate, brosylate, closylate, and nosylate). Others include carbonates, halide ions, carboxylate anions, phenolate ions, and alkoxides. Some stronger bases, such as NH_2^- and OH^- can be made better leaving groups by treatment with an acid. Common electrofugal leaving groups include the proton, CO_2, and metals.

[0035] "Enantiomeric excess" or "ee" is a measure, for a given sample, of the excess of one enantiomer over a racemic sample of a chiral compound and is expressed as a percentage. Enantiomeric excess is defined as 100 x (er - 1) / (er + 1), where "er" is the ratio of the more abundant enantiomer to the less abundant enantiomer.

[0036] "Diastereomeric excess" or "de" is a measure, for a given sample, of the excess of one diastereomer over a sample having equal amounts of diastereomers and is expressed as a percentage. Diastereomeric excess is defined as 100 x (dr - 1) / (dr + 1), where "dr" is the ratio of a more abundant diastereomer to a less abundant diastereomer.

[0037] "Stereoselective," "enantioselective," "diastereoselective," and variants thereof, refer to a given process (e.g., hydrogenation) that yields more of one stereoisomer, enantiomer, or diastereoisomer than of another, respectively.

[0038] "High level of stereoselectivity," "high level of enantioselectivity," "high level of diastereoselectivity," and variants thereof, refer to a given process that yields a product having an excess of one stereoisomer, enantiomer, or diastereoisomer, which comprises at least about 90% of the product. For a pair of enantiomers or diastereomers, a high level of enantioselectivity or diastereoselectivity would correspond to an ee or de of at least about 80%.

[0039] "Stereoisomerically enriched," "enantiomerically enriched," "diastereomerically enriched," and variants thereof, refer, respectively, to a sample of a compound that has more of one stereoisomer, enantiomer or diastereomer than another. The degree of enrichment may be measured by % of total product, or for a pair of enantiomers or diastereomers, by ee or de.

[0040] "Substantially pure stereoisomer," "substantially pure enantiomer," "substantially pure diastereomer," and variants thereof, refer, respectively, to a sample containing a stereoisomer, enantiomer, or diastereomer, which comprises at least about 95% of the sample. For pairs of enantiomers and diastereomers, a substantially pure enantiomer or diastereomer would correspond to samples having an ee or de of about 90% or greater.

[0041] A "pure stereoisomer," "pure enantiomer," "pure diastereomer," and variants thereof, refer, respectively, to a sample containing a stereoisomer, enantiomer, or diastereomer, which comprises at least about 99.5% of the sample. For pairs of enantiomers and diastereomers, a pure enantiomer or pure diastereomer" would correspond to samples having an ee or de of about 99% or greater.

[0042] "Opposite enantiomer" refers to a molecule that is a non-superimposable mirror image of a reference molecule, which may be obtained by inverting all of the stereogenic centers of the reference molecule. For example, if the reference molecule has *S* absolute stereochemical configuration, then the opposite enantiomer has *R*

absolute stereochemical configuration. Likewise, if the reference molecule has *S,S* absolute stereochemical configuration, then the opposite enantiomer has *R,R* stereochemical configuration, and so on.

[0043] "Stereoisomers" of a specified compound refer to the opposite enantiomer of the compound and to any diastereoisomers or geometric isomers (*Z*/*E*) of the compound. For example, if the specified compound has *S,R,Z* stereochemical configuration, its stereoisomers would include its opposite enantiomer having *R,S,Z* configuration, its diastereomers having *S,S,Z* configuration and *R,R,Z* configuration, and its geometric isomers having *S,R,E* configuration, *R,S,E* configuration, *S,S,E* configuration, and *R,R,E* configuration.

[0044] "Solvate" refers to a molecular complex comprising a disclosed or claimed compound and a stoichiometric or non-stoichiometric amount of one or more solvent molecules (e.g., EtOH, acetone, water).

[0045] "Hydrate" refers to a solvate comprising a disclosed or claimed compound and a stoichiometric or non-stoichiometric amount of water.

[0046] "Pharmaceutically acceptable complexes, salts, solvates, or hydrates" refers to complexes, acid or base addition salts, solvates or hydrates of claimed and disclosed compounds, which are within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

[0047] "Treating" refers to reversing, alleviating, inhibiting the progress of, or preventing a disorder or condition to which such term applies, or to preventing one or more symptoms of such disorder or condition.

[0048] "Treatment" refers to the act of "treating," as defined immediately above.

[0049] Table 1 lists abbreviations used throughout the specification.

TABLE 1. List of abbreviations

Abbreviation	Description
Ac	acetyl
ACN	acetonitrile
Ac_2O	acetic anhydride
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
BnOH	benzyl alcohol
Boc	*tert*-butoxycarbonyl
Bs	brosyl or *p*-bromo-benzenesulfonyl
Bn	benzyl
BnBr, BnCl	benzylbromide, benzylchloride
Bu	butyl
t-Bu	tertiary butyl
t-BuOK	potassium tertiary-butoxide
t-BuOLi	lithium tertiary-butoxide
t-BuONa	sodium tertiary-butoxide
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
Diglyme	diethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
eq	equivalents (molar)
Et	ethyl
Et_3N	triethyl-amine
EtOH	ethyl alcohol
Et_2O	diethyl ether

Abbreviation	Description
EtOAc	ethyl acetate
FAMSO	formaldehyde dimethylmercaptal S-oxide
Fmoc	9-fluoroenylmethoxycarbonyl
h, min, s	hour(s), minute(s), second(s)
HOAc	acetic acid
KF	Karl Fischer
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride ($LiAlH_4$)
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LICA	lithium *N*-isopropyl-*N*-cyclohexyl amide
LTMP	2,2,6,6-tetramethylpiperidine
Me	methyl
$MeCl_2$	methylene chloride
MEK	methylethylketone or butan-2-one
MeOH	methyl alcohol
mp	melting point
Ms	mesyl or methanesulfonyl
MTBE	methyl *tert*-butyl ether
Ph	phenyl
Pr	propyl
n-PrOH	*n*-propanol
i-Pr	isopropyl
i-PrOH	isopropanol
PTFE	polytetrafluoroethylene
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
RT	room temperature (approximately 20°C to 25°C)
TAPO-5	titanium framework-substituted aluminophosphate number 5 in the Int'l Zeolite Association classification system
TCA	trichloroacetic acid

Abbreviation	Description
TEA	triethanolamine
Tf	triflyl or trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tr	trityl or triphenylmethyl
Ts	tosyl or *p*-toluenesulfonyl

[0050] Some of the schemes and examples below may omit details of common reactions, including oxidations and reductions, which are known to persons of ordinary skill in the art of organic chemistry. The details of such reactions can be found in a number of treatises, including Richard Larock, *Comprehensive Organic Transformations* (1999), and the multi-volume series edited by Michael B. Smith and others, *Compendium of Organic Synthetic Methods* (1974 et seq.). Starting materials and reagents may be obtained from commercial sources or may be prepared using literature methods. For example, one of the starting materials described below, (*R*)-2-methyl-succinic acid 4-methyl ester, may be obtained via esterase-mediated hydrolysis of a corresponding diester or through asymmetric hydrogenation of an appropriate unsaturated monoester. *See* S. G. Cohen & A. J. Milovanovic, *J. Am. Chem. Soc.* 90:3495 (1968); and M. Ostermeier et al., *Eur. J. Org. Chem.* 17:3453 (2003).

[0051] In some of the reaction schemes and examples below, certain compounds can be prepared using protecting groups, which prevent undesirable chemical reaction at otherwise reactive sites. Protecting groups may also be used to enhance solubility or otherwise modify physical properties of a compound. For a discussion of protecting group strategies, a description of materials and methods for installing and removing protecting groups, and a compilation of useful protecting groups for common functional groups, including amines, carboxylic acids, alcohols, ketones, and

aldehydes, see T. W. Greene and P. G. Wuts, *Protecting Groups in Organic Chemistry* (1999) and P. Kocienski, *Protective Groups* (2000).

[0052] Generally, the chemical transformations described throughout the specification may be carried out using substantially stoichiometric amounts of reactants, though certain reactions may benefit from using an excess of one or more of the reactants. Additionally, many of the reactions may be carried out at about RT, but particular reactions may require the use of higher (e.g., up to reflux) or lower temperatures (e.g., 0°C or less), depending on reaction kinetics, yields, and other considerations. Many of the chemical transformations may also employ one or more compatible solvents, which may influence the reaction rate and yield, and depending on the nature of the reactants, may be polar protic solvents (e.g., water, MeOH, EtOH, PrOH, *i*-PrOH, formic acid, HOAc, formamide); polar aprotic solvents (e.g., acetone, THF, MEK, EtOAc, ACN, DMF, DMSO); non-polar solvents (e.g., hexane, benzene, toluene, diethyl ether, $MeCl_2$, $MeCl_3$, CCl_4); or some combination of these. Any reference in the disclosure to a range, including a concentration range, a temperature range, and a pH range, includes the indicated endpoints.

[0053] This disclosure concerns materials and methods for preparing optically active 3,4-disubstituted cyclopentanones (Formula 1) and opposite enantiomers thereof. As noted above, R^1 and R^2 in Formula 1 may include C_{1-6} alkyl, such as Me, Et, Pr, *i*-Pr, *n*-Bu, *s*-Bu, *t*-Bu, as well as aryl-C_{1-3} alkyl, such as Bn. Representative 3,4-disubstituted cyclopentanones thus include (*S*,*S*)-3,4-dimethyl-cyclopentanone, (*S*,*S*)-3,4-diethyl-cyclopentanone, (*S*,*S*)-3,4-dipropyl-cyclopentanone, (*R*,*R*)-3,4-diisopropyl-cyclopentanone, and (*S*,*S*)-3,4-dibenzyl-cyclopentanone, including their opposite enantiomers, (*R*,*R*)-3,4-dimethyl-cyclopentanone, (*R*,*R*)-3,4-diethyl-cyclopentanone, (*R*,*R*)-3,4-dipropyl-cyclopentanone, (*S*,*S*)-3,4-diisopropyl-cyclopentanone, and (*R*,*R*)-3,4-dibenzyl-cyclopentanone.

[0054] Scheme I shows a method for preparing the chiral cyclopentanones (Formula 1) and their opposite enantiomers. The method includes reacting an optically active, 2-substituted succinic acid monoester or succinamic acid (Formula 2) with an alkylating agent (Formula 3) to give a 2,3-disubstituted succinic acid

monoester or succinamic acid (Formula 4). Reduction of the disubstituted monoester gives a diol (Formula 5), which is subsequently activated via reaction with, e.g., a sulfonylating agent (Formula 8). The resulting activated diol (Formula 9) is cyclized via bisalkylation with FAMSO. Hydrolysis of the resulting thioketal S-oxide (Formula 10) yields the desired cyclopentanone (Formula 1). Substituents R^1 and R^2 in Formula 2-5, 9, and 10 are as defined above for Formula 1; R^3 in Formula 2 and 4 is R^1O- or amino; R^4 in Formula 8 and 9 is a C_{1-6} alkylsulfonyl (e.g., mesyl), a fluoro-C_{1-6} alkylsulfonyl (e.g., triflyl), or an arylsulfonyl (e.g., tosyl, brosyl, closyl, and nosyl); X^1 in Formula 3 and X^2 in Formula 8 are leaving groups (e.g., halogeno, R^4O-).

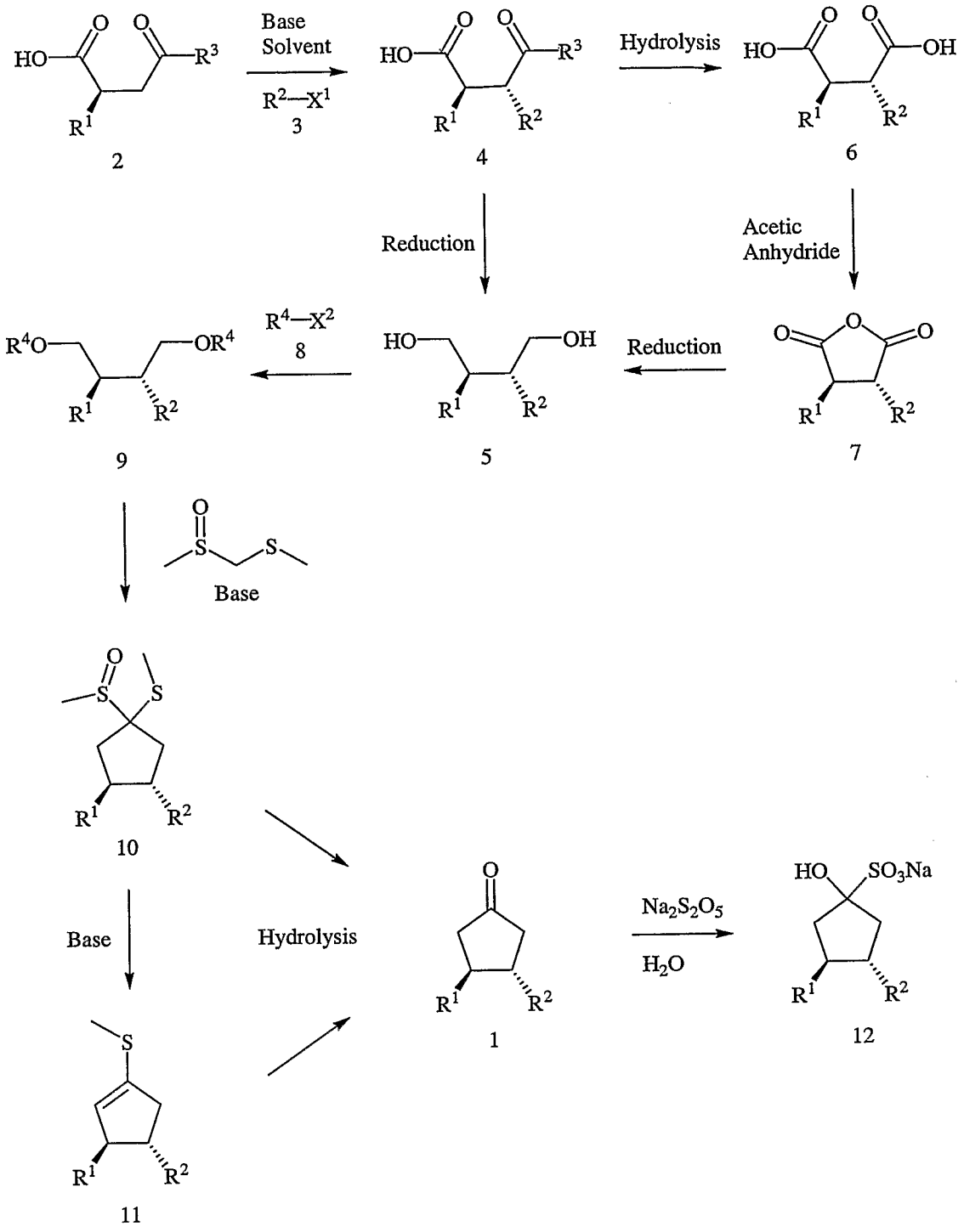
[0055] Representative R^1 and R^2 in Formula 2-5, 9, and 10 include C_{1-6} alkyl and aryl-C_{1-3} alkyl, and representative R^3 in Formula 2 include amino, C_{1-6} alkoxy, such as methoxy, ethoxy, *n*-propoxy, *i*-propoxy, and *t*-butoxy, and aryl-C_{1-3} alkoxy, such as benzoxy. Useful starting materials (Formula 2) thus include (*R*)-2-methyl-succinic acid 4-methyl ester, (*R*)-2-methyl-succinic acid 4-ethyl ester, (*R*)-2-methyl-succinic acid 4-propyl ester, (*R*)-2-methyl-succinic acid 4-isopropyl ester, (*R*)-2-methyl-succinic acid 4-*tert*-butyl ester, (*R*)-2-methyl-succinamic acid, (*R*)-2-ethyl-succinic acid 4-methyl ester, (*R*)-2-ethyl-succinic acid 4-ethyl ester, (*R*)-2-ethyl-succinic acid 4-propyl ester, (*R*)-2-ethyl-succinic acid 4-isopropyl ester, (*R*)-2-ethyl-succinic acid 4-*tert*-butyl ester, and (*R*)-2-ethyl-succinamic acid, including opposite enantiomers thereof.

[0056] Similarly, representative 2,3-disubstituted succinic acid monoesters or succinamic acids (Formula 4) thus include (*R*,*R*)-2,3-dimethyl-succinic acid 4-methyl ester, (*R*,*R*)-2,3-diethyl-succinic acid 4-methyl ester, (*R*,*R*)-2,3-dipropyl-succinic acid 4-methyl ester, (*R*,*R*)-2,3-diisopropyl-succinic acid 4-methyl ester, (*R*,*R*)-2,3-dibenzyl-succinic acid 4-methyl ester, (*R*,*R*)-2,3-dimethyl-succinic acid 4-ethyl ester, (*R*,*R*)-2,3-diethyl-succinic acid 4-ethyl ester, (*R*,*R*)-2,3-dipropyl-succinic acid 4-ethyl ester, (*R*,*R*)-2,3-diisopropyl-succinic acid 4-ethyl ester, (*R*,*R*)-2,3-dibenzyl-succinic acid 4-ethyl ester, (*R*,*R*)-2,3-dimethyl-succinamic acid, (*R*,*R*)-2,3-diethyl-succinamic

acid, (*R*,*R*)-2,3-dipropyl-succinamic acid, (*R*,*R*)-2,3-diisopropyl-succinamic acid, and (*R*,*R*)-2,3-dibenzyl-succinamic acid, including opposite enantiomers thereof.

[0057] Alkylation of the mono-substituted succinic acid monoester or succinamic acid (Formula 2) is carried out using a suitable base in a compatible solvent. Suitable bases include those that are capable of deprotonating the methylene group that is adjacent (α) to the ester or amide moiety (Formula 2). These include non-nucleophilic or hindered bases, including lithium amide bases, such as LDA, LHMDS, KHMDS, LICA, LTMP, $LiNEt_2$, lithium dicyclohexylamide, and corresponding magnesium amide bases, such as $(i\text{-Pr})_2NMgCl$ and Et_2NMgCl. The lithium and magnesium amide bases may be represented by $LiNR^1R^2$ and $R^1R^2NMgX^3$, respectively, where R^1 and R^2 are as defined above for Formula 1 and X^3 is halogeno. Compatible solvents include those whose conjugate acids have pKa's less than or equal to 9, typically less than or equal to 4, and often less than or equal to 1. Such solvents include, e.g., THF, Et_2O, DMSO, ACN, DMF, and acetone, but do not include ammonia.

[0058] The use of these classes of bases and solvents yields an excess of the desired *anti*-diastereomer (as depicted in Formula 4). Typically, the ratio of the *anti*-diastereomer to the *syn*-diastereomer is equal to or greater than about 85/15, 90/10, or 92/8. Thus, as shown in the Examples below, alkylation of (*R*)-2-methyl-succinic acid 4-methyl ester using LHMDS in THF gives the *anti*-diastereomer, (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester with a de of about 80% or greater. In contrast, the alkylation of (*R*)-2-methyl-succinic acid 4-methyl ester using $LiNH_2$ in NH_3 and Et_2O yields an excess of the undesired *syn*-diastereomer. See W. G. Kofron & L. G. Wideman, *J. Org. Chem.* 37:555 (1972).



Scheme I

[0059] As noted above, the alkylating agent (Formula 3) includes a leaving group (X^1), which may include halo substituents, Cl, Br, and I, and sulfonate substituents, such as toluene-*p*-sulfonate, methylsulfonate, *p*-bromo-benzene-sulfonate, and triflate.

Representative alkylating agents (Formula 3) thus include C_{1-6} alkyl halides, such as MeCl, MeBr, MeI, EtCl, EtBr, EtI, *n*-PrCl, *n*-PrBr, *n*-PrI, *i*-PrCl, *i*-PrBr, and *i*-PrI, and C_{1-6} alkylsulfonate esters, such as, MeOTs, MeOMs, MeOBs, MeOTf, EtOTs, EtOMs, EtOBs, EtOTf, *n*-PrOTs, *n*-PrOMs, *n*-PrOBs, *n*-PrOTf, *i*-PrTs, *i*-PrMs, *i*-PrBs, and *i*-PrTf. The alkylating agents may be obtained from commercial sources or may be prepared using known methods.

[0060] The alkylation reaction may employ stoichiometric amounts of the reactants (i.e., molar ratio of the 2-substituted succinic acid monoester or succinamic acid to the alkylating agent of 1:1), but to improve conversion, minimize side-products, and so on, the alkylation step may employ an excess of one of the reactants (e.g., molar ratio of 1:1.1 to 1.1:1, 1:1.5 to 1.5:1, 2:1 to 1:2, 3:1 to 1:3). Similarly, the alkylation reaction may employ stoichiometric amounts of base (i.e., base to substrate molar ratio of 2:1), but may also employ an excess of base (e.g., molar ratio of 2.1:1, 2.5:1, 3:1).

[0061] The alkylation may be run at temperatures of about -30°C to reflux. The reaction is typically carried out at RT, but may benefit from higher or lower temperatures. For example, and as described in the Examples, the reaction mixture may be cooled to a temperature of about -30°C to about -25°C during addition of the starting material (Formula 2) to the base and subsequent addition of the alkylating agent (Formula 3). The resulting mixture may then be allowed to react at RT until complete.

[0062] The contacting scheme may influence the yield. As described in the Examples, subsurface addition of the starting material (Formula 2) and the alkylating agent (Formula 3) may increase the de of the *anti*-diastereomer (Formula 3) when compared to above-surface reactant addition.

[0063] As shown in Scheme I, the disubstituted succinic acid monoester (Formula 4) is reduced to a diol (Formula 5) via reaction with LAH in one or more ethereal (absolute) solvents, such as THF, MTBE, and Et_2O. Other useful reducing agents and solvents include $NaBH_4$ and $AlCl_3$ in diglyme; B_2H_6 in THF; 9-BBN in

THF; $LiAlH(OMe)_3$ in THF; AlH_3 in THF; DIBAL-H in THF; and Red-Al in toluene or THF. The reaction normally employs a molar excess of the reducing agent (e.g., greater than 4 eq of LAH) and is run at a temperature ranging from about RT to reflux.

[0064] As in the alkylation, the contacting scheme of the reduction workup may influence yield. A conventional (Fieser) workup following reduction using LAH—sequential addition of H_2O, 15% NaOH aq, and H_2O to the reaction mixture—may lead to processing difficulties when run at large (kg) scale. For example, the initial water quench results in a rapid release of a large quantity of hydrogen gas and also traps a significant fraction of the product (Formula 5) in a solid byproduct. Some of the trapped product may be recovered by washing and filtering the solids, but the process is inefficient and time-consuming because much of the wash liquid flows around the filter cake rather than through it. Furthermore, once it is depleted of liquid, the filter cake often cracks irreversibly. These cracks channel wash liquid away from the interior of the filter cake, which further reduces the effectiveness of the recovery process.

[0065] As shown in the Examples, modifying the conventional contacting scheme so that the reaction mixture is fed to a large excess of aqueous base, decreases the rate of hydrogen evolution and appears to increase the yield and recovery of the diol (Formula 5). As the reaction mixture is added to the aqueous base, an aluminum alkoxide intermediate undergoes base-catalyzed hydrolysis to give the desired diol (Formula 5) as well as aluminum hydroxide, which precipitates from solution. Because the diol remains in solution, it can be separated from the precipitate by decanting the liquid phase. Furthermore, carefully controlling the rate of addition of the reaction mixture to the aqueous base, permits tight regulation of the rate of hydrogen gas production.

[0066] As shown in Scheme I, the method optionally provides for conversion of the disubstituted succinic acid monoester or succinamic acid (Formula 4) into a diacid (Formula 6) or salt thereof, via acid or base hydrolysis of the ester or amide moieties. For example, treating the ester or amide with HCl or H_2SO_4 and with excess H_2O,

generates the diacid. Similarly, treating the succinic acid monoester or succinamic acid with an aqueous inorganic base, such as LiOH, KOH, NaOH, CsOH, Na_2CO_3, K_2CO_3 or Cs_2CO_3, in an optional polar solvent (e.g., THF, MeOH, EtOH, acetone, or ACN) gives a base addition salt of the diacid, which may be treated with an acid to generate the free diacid. Generally excess acid or base is used and the ester and amide hydrolysis is carried out at RT or at temperatures up to reflux.

[0067] Following hydrolysis of the disubstituted succinic acid monoester or succinamic acid (Formula 4), the resulting diacid (Formula 6) or a salt thereof, is treated with acetic anhydride to give a cyclic anhydride (Formula 7). The reaction is ordinarily run in an aprotic polar solvent, such as THF, at a temperature ranging from about RT to reflux, though reaction temperatures ranging from about 50°C to about 75°C may be used. Excess acetic anhydride (e.g., 1.5 eq or greater) may be used to ensure complete conversion of the diester.

[0068] Representative reaction substrates (Formula 6) include(*R*,*R*)-2,3-dimethyl-succinic acid, (*R*,*R*)-2,3-diethyl-succinic acid, (*R*,*R*)-2,3-dipropyl-succinic acid, (*R*,*R*)-2,3-diisopropyl-succinic acid, and (*R*,*R*)-2,3-dibenzyl-succinic acid, including salts thereof. Representative cyclic anhydrides (Formula 7) include (*R*,*R*)-3,4-dimethyl-dihydro-furan-2,5-dione, (*R*,*R*)-3,4-diethyl-dihydro-furan-2,5-dione, (*R*,*R*)-3,4-dipropyl-dihydro-furan-2,5-dione, (*R*,*R*)-3,4-diisopropyl-dihydro-furan-2,5-dione, and (*R*,*R*)-3,4-dibenzyl-dihydro-furan-2,5-dione, including opposite enantiomers thereof.

[0069] Preparation of the cyclic anhydride (Formula 7) may provide advantages over direct reduction of the monoester or amide (Formula 4). For example, in contrast to the monoester, the cyclic anhydride is easily recrystallized and therefore can be isolated prior to reduction. Recrystallization of the cyclic anhydride appears to improve the efficiency of downstream isolation of the activated diol (Formula 9) by suppressing formation of mono-alkylated side-products and undesired diastereomers. Additionally, the higher purity of crystalline cyclic anhydride should lead to improved throughput of the reduction step since the reducing agent (e.g., LAH) is not consumed by impurities or by the carboxylic acid moiety. The comparatively high purity of the diol (Formula 5) also permits isolation via recrystallization.

[0070] As shown in Scheme I, the diol (Formula 5) is activated via reaction with the compound of Formula 8. Useful diols include (*R*,*R*)-2,3-dimethyl-butan-1,4-diol, (*R*,*R*)-2,3-diethyl-butan-1,4-diol, (*R*,*R*)-2,3-dipropyl-butan-1,4-diol, (*R*,*R*)-2,3-diisopropyl-butan-1,4-diol, and (*R*,*R*)-2,3-dibenzyl-butan-1,4-diol, including opposite enantiomers thereof. Useful compounds of Formula 8 include sulfonylating agents, such as TsCl, MsCl, BsCl, NsCl, and TfCl, and their corresponding anhydrides (e.g., *p*-toluenesulfonic acid anhydride).

[0071] Compounds of Formula 5 may be reacted with TsCl or MsCl in the presence of pyridine or Et_3N and an aprotic solvent, such as ethyl acetate, $MeCl_2$, ACN, or THF, to give, e.g., (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, (*R*,*R*)-2,3-diethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, (*R*,*R*)-2,3-dipropyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, (*R*,*R*)-2,3-diisopropyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, (*R*,*R*)-2,3-dibenzyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, (*R*,*R*)-1,4-bis-(methanesulfonyloxy)-2,3-dimethyl-butane, (*R*,*R*)-2,3-diethyl-1,4-bis-(methanesulfonyloxy)-butane, (*R*,*R*)-1,4-bis-(methanesulfonyloxy)-2,3-dimpropyl-butane, (*R*,*R*)-2,3-diisopropyl-1,4-bis-(methanesulfonyloxy)-butane, or (*R*,*R*)-2,3-dibenzyl-1,4-bis-(methanesulfonyloxy)-butane, including opposite enantiomers thereof. Typically, the reaction is carried out with an excess (e.g., 2.5 eq or more) of the sulfonylating agent (Formula 8) and with an excess of the base (e.g., 3 eq or more) and at a temperature of about RT or less (e.g., about 0°C).

[0072] As shown in Scheme I, the resulting activated intermediate (Formula 9) is cyclized via bisalkylation with FAMSO and a base that is strong enough to deprotonate the methylene moiety (pKa of FAMSO is 29 in DMSO); hydrolysis of the resulting thioketal S-oxide (Formula 10) with aqueous acid yields the desired cyclopentanone (Formula 1). The reaction is typically carried out in excess base (i.e., more than two molar equivalents of base). It is often desirable to minimize contact with the base because the activated intermediate (Formula 9) and thioketal S-oxide (Formula 10) are susceptible to base-induced degradation, which may reduce the yield of the desired cyclopentanone. For example, the thioketal S-oxide may undergo base-induced degradation to a vinyl sulfide (Formula 11) shown in Scheme I. Such contact may be minimized by pre-mixing the base (e.g., 2.0 eq to 2.5 eq) with a substantially

equimolar amount of FAMSO, so that the base is consumed before addition of the substrate (Formula 9). However, this wastes one molar equivalent of FAMSO.

[0073] One way to address this difficulty is to add the base (e.g., 2.0 eq to 2.5 eq) to a mixture of the substrate (Formula 9) and a slight excess of FAMSO (e.g., 1.1 eq to 1.4 eq) over an extended period of time and at a temperature high enough so that the base is substantially consumed as it is being added. Useful bases include lithium amides, such as LHMDS (in THF), which are added over, e.g., 1 h, 2 h, 3 h, 4 h, 5 h, or more and are reacted at temperatures of about 10°C, 15°C, 20°C, 25°C, 30°C, 35°C, 40°C or higher. As described in the Examples, reacting (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane with FAMSO using an extended addition of LHMDS (over 3 or more hours) at temperatures of about 12°C to RT, results in yields of (*S*,*S*)-3,4-dimethyl-cyclopentanone ranging from 94% to 96%. In comparison, carrying out the same reaction via batch-wise addition of the base at temperatures of -3°C to -1°C resulted in yields ranging from 47% to 74%.

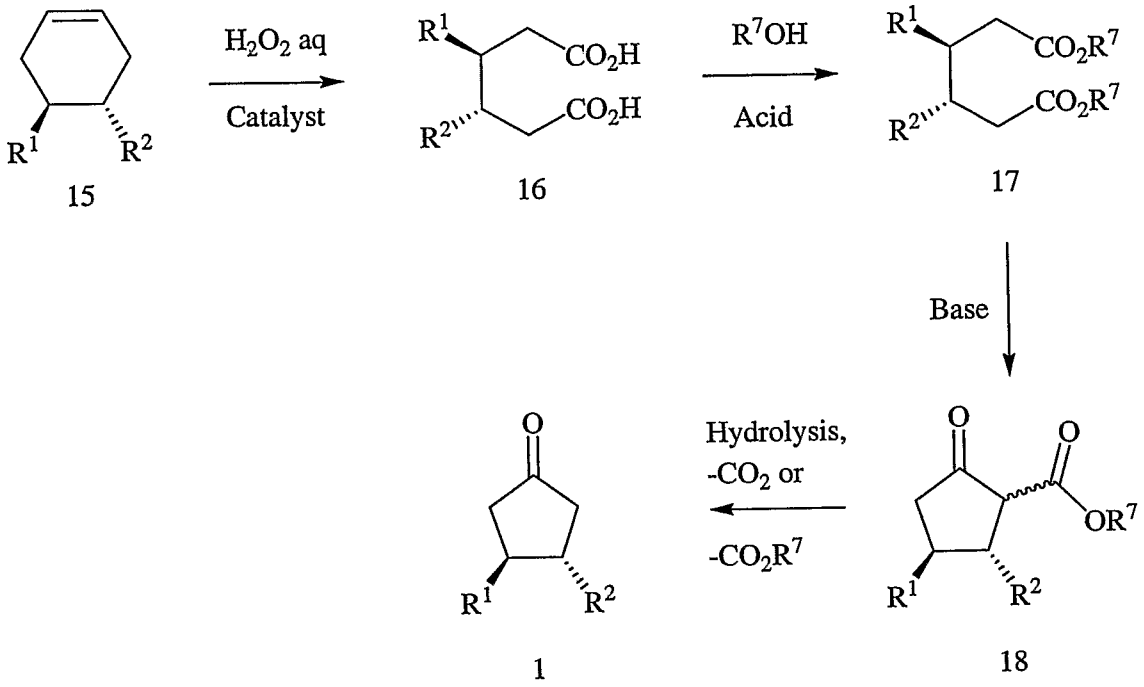
[0074] Another way to address the yield loss associated with the vinyl sulfide (Formula 11) is to convert the thioketal S-oxide (Formula 10) to the cyclopentanone (Formula 1) without first isolating it. Since the vinyl sulfide is volatile, it is apparently lost during workup and isolation of the thioketal S-oxide, thereby lowering the yield of the cyclopentanone. By using the crude product of the FAMSO bisalkylation, any vinyl sulfide formed during cyclization is converted to the cyclopentanone during subsequent acid hydrolysis of the thioketal S-oxide.

[0075] Hydrolysis of the thioketal S-oxide (Formula 10) and the vinyl sulfide (Formula 11) is carried out in the presence of an aqueous acid at about RT or above. The reaction may utilize a water-soluble solvent, such as THF, which appears to minimize formation of a 1,1-bis-methylsufanyl-3,4-substituted cyclopentane impurity. Representative thioketal S-oxides include (3*S*,4*S*)-1-methanesulfinyl-3,4-dimethyl-1-methylsulfanyl-cyclopentane, (3*S*,4*S*)-1-methanesulfinyl-3,4-diethyl-1-methylsulfanyl-cyclopentane, (3*S*,4*S*)-1-methanesulfinyl-3,4-dipropyl-1-methylsulfanyl-cyclopentane, (3*S*,4*S*)-1-methanesulfinyl-3,4-diisopropyl-1-methylsulfanyl-cyclopentane, and (3*S*,4*S*)-1-methanesulfinyl-3,4-dibenzyl-1-

methylsulfanyl-cyclopentane, including opposite enantiomers thereof. Representative vinyl sulfides include (3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene, (3*R*,4*S*)-3,4-diethyl-1-methylsulfanyl-cyclopentene, (3*R*,4*S*)-3,4-dipropyl-1-methylsulfanyl-cyclopentene, (3*R*,4*R*)-3,4-diisopropyl-1-methylsulfanyl-cyclopentene, and (3*R*,4*S*)-3,4-dibenzyl-1-methylsulfanyl-cyclopentene, including opposite enantiomers thereof.

[0076] As shown in Scheme I, the method optionally includes conversion of the cyclopentanone (Formula 1) to a bisulfite adduct (Formula 12). In many cases, the desired cyclopentanone (Formula 1) is a liquid, which is difficult to purify by distillation because of the presence of impurities having comparable boiling points. Reaction of the cyclopentanone (Formula 1) with a source of $NaHSO_3$ at a temperature of about 0°C to about RT, gives the bisulfite addition compound (Formula 12) as a crystalline solid. Hydrolyzing the bisulfite adduct with aqueous acid or base regenerates the cyclopentanone in high purity (e.g., (*S*,*S*)-3,4-dimethyl-cyclopentanone having less than about 0.1% impurities based on HPLC area). Representative bisulfite adducts include sodium salts of (*S*,*S*)-1-hydroxy-3,4-dimethyl-cyclopentanesulfonate, (*S*,*S*)-1-hydroxy-3,4-diethyl-cyclopentanesulfonate, (*S*,*S*)-1-hydroxy-3,4-dipropyl-cyclopentanesulfonate, (*S*,*S*)-1-hydroxy-3,4-diisopropyl-cyclopentanesulfonate, and (*S*,*S*)-1-hydroxy-3,4-dibenzyl-cyclopentanesulfonate, including opposite enantiomers thereof.

[0077] Scheme II shows an additional method for preparing the chiral cyclopentanones (Formula 1) and their opposite enantiomers. The method includes oxidizing a chiral 4,5-disubstituted cyclohexene (Formula 15) to give an optically active adipic acid derivative (Formula 16). The diacid (Formula 16) or its salt is reacted with an alcohol (R^7OH) in the presence of an acid to give an optically active diester (Formula 17), which is subsequently treated with a base to provide a cyclopentanone carboxylic acid ester (Formula 18). Removal of the ester moiety provides the desired chiral cyclopentanone (Formula 1), which as shown in Scheme I, may be optionally converted to a bisulfite adduct (Formula 12) that is subsequently hydrolyzed to give the desired cyclopentanone in high purity.



Scheme II

[0078] As shown in Scheme II, the chiral cyclohexene (Formula 15) may be oxidized via treatment with aq H_2O_2 in the presence of a catalyst at temperatures ranging from about 50°C to about 95°C or from about 75°C to about 90°C. The hydrogen peroxide concentration of the aq H_2O_2 solution may vary from about 30% to about 60%, based on weight, and the molar ratio of hydrogen peroxide to chiral cyclohexene may be about 4:1 or greater. Useful catalysts include sodium tungstate (Na_2WO_4) together with a phase transfer catalyst, such as Me(*n*-octyl)$_3N^+HSO_3^-$, which may be present in molar ratios of about 1:1. Other useful catalysts include molecular sieves, such as those based on TAPO-5. The molar ratio of the chiral cyclohexene to each catalyst generally ranges from about 10:1 to about 1000:1 (e.g., about 100:1). For a discussion of oxidation catalysts, see K. Sato et al., *Science* 281: 1646 (1998) and references cited therein; see also, S. Lee, *Angew. Chem. Int. Ed.* 42:1520 (2003) and references cited therein.

[0079] Representative compounds of Formula 15 include (*S*,*S*)-4,5-dimethyl-cyclohexene, (*S*,*S*)-4,5-diethyl-cyclohexene, (*S*,*S*)-4,5-dipropyl-cyclohexene, (*R*,*R*)-4,5-diisopropyl-cyclohexene, (*R*,*R*)-4,5-dibenzyl-cyclohexene, and opposite

enantiomers thereof. Representative compounds of Formula 16 thus include (*S*,*S*)-3,4-dimethyl-hexanedioic acid, (*S*,*S*)-3,4-diethyl-hexanedioic acid, (*S*,*S*)-3,4-dipropyl-hexanedioic acid, (*R*,*R*)-3,4-diisopropyl-hexanedioic acid, (*S*,*S*)-3,4-dibenzyl-hexanedioic acid, and opposite enantiomers thereof.

[0080] Following oxidation of the chiral cyclohexene (Formula 15), the resulting diacid (Formula 16) undergoes acid catalyzed esterification at temperatures ranging from about RT to reflux. The reaction generally employs excess alcohol (R^7OH) since it may also serve as the solvent. The reaction also utilizes catalytic amounts (e.g., about 0.05 eq to about 0.5 eq) of the acid, based on the amount of the substrate (Formula 16). Useful acid catalysts include strong acids having a pKa of about 1 or less, including inorganic acids, such as H_2SO_4, HCl, HBr, HI, HNO_3, and organic acids, such as TFA and TCA.

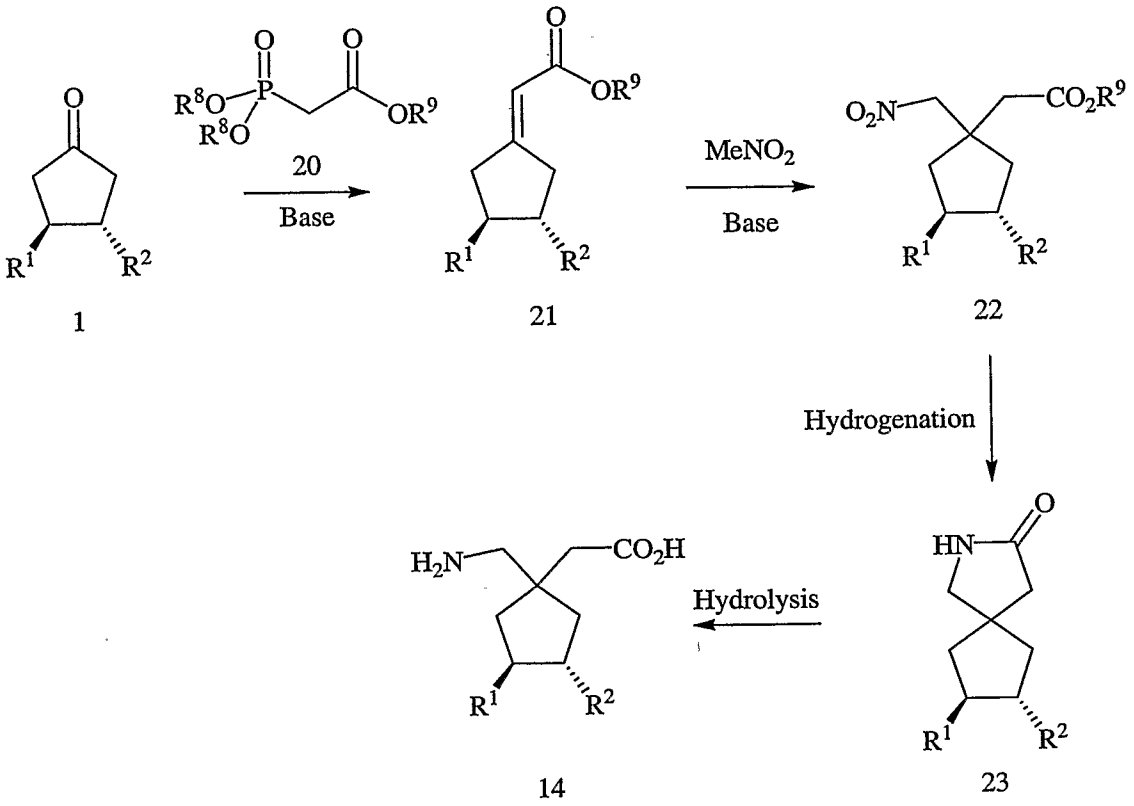
[0081] Substituent R^7 of the alcohol, the diester (Formula 17), and the cyclopentanone carboxylic acid ester (Formula 18) is independently selected from the substituents that define R^1 and R^2 in Formula 1. Representative alcohols include MeOH, EtOH, PrOH, and BnOH. Representative compounds of Formula 17 thus include C_{1-6} alkyl or aryl-C_{1-3} alkyl diesters (e.g., dimethyl, diethyl, dipropyl, and dibenzyl esters) of (*S*,*S*)-3,4-dimethyl-hexanedioic acid dimethyl ester, (*S*,*S*)-3,4-diethyl-hexanedioic acid, (*S*,*S*)-3,4-dipropyl-hexanedioic acid, (*R*,*R*)-3,4-diisopropyl-hexanedioic acid, (*S*,*S*)-3,4-dibenzyl-hexanedioic acid, and opposite enantiomers thereof.

[0082] As noted above, the diester (Formula 17) is cyclized via treatment with a strong base to give a cyclopentanone carboxylic acid ester (Formula 18). The reaction is typically carried out in a polar aprotic solvent, such as THF, with a molar excess of base (e.g., about 1.1 to about 1.5 eq), and at a temperature which may range from about RT to reflux. Suitable bases include those which are strong enough to deprotonate a methylene group which is located adjacent (α) to one of the ester moieties (Formula 17), and include *t*-BuOK and *t*-BuONa. Representative compounds of Formula 18 include C_{1-6} alkyl or aryl-C_{1-3} alkyl esters (e.g., methyl, ethyl, propyl, and benzyl esters) of (1*S*/*R*,2*R*,3*S*)-2,3-dimethyl-5-oxo-

cyclopentanecarboxylic acid, (1*S*/*R*,2*R*,3*S*)-2,3-diethyl-5-oxo-cyclopentanecarboxylic acid, (1*S*/*R*,2*R*,3*S*)-2,3-dipropyl-5-oxo-cyclopentanecarboxylic acid, (1*S*/*R*,2*R*,3*R*)-2,3-diisopropyl-5-oxo-cyclopentanecarboxylic acid, (1*R*/*S*,2*R*,3*S*)-2,3-dibenzyl-5-oxo-cyclopentanecarboxylic acid, and opposite enantiomers thereof, where *R*/*S* means that the named compound is a mixture of epimers, each of the epimers having opposite stereoconfiguration about the indicated carbon.

[0083] As noted above, the ester moiety of the cyclopentanone carboxylic acid ester (Formula 18) is removed to give the desired chiral cyclopentanone (Formula 1). As noted in Scheme II, the ester moiety may first be hydrolyzed via treatment with an aqueous base or acid to give a corresponding acid (Formula 19, above), which is subsequently decarboxylated under acidic conditions by heating (e.g., 45°C to reflux) to give the compound of Formula 1. Hydrolysis may be carried out using conditions described above in connection with the conversion of the succinic acid monoester (Formula 4) to the diacid (Formula 6). Alternatively, the ester moiety may be removed via Krapcho dealkoxycarbonylation, which involves heating the cyclopentanone carboxylic acid ester (Formula 18) in a dipolar aprotic solvent at a temperature of about 90°C to about 200°C or from about 120°C to about 160°C, in the presence of water or a salt or both. Useful dipolar aprotic solvents include DMSO and DMF; useful salts include LiCl, NaCl, LiI, NaCN, and KCN. For a review of Krapcho dealkoxycarbonylation, see A. P. Krapcho, *Synthesis* 805-822, 893-914 (1982).

[0084] Scheme III shows a method for converting the chiral cyclopentanone (Formula 1) to a compound of Formula 14. The method includes reacting the cyclopentanone (Formula 1) with a phosphono-acetic acid ester (Formula 20) to give an enoate ester (Formula 21). Addition of nitromethane yields a nitro ester (Formula 22), which upon reduction, cyclizes to furnish a lactam (Formula 23). Hydrolysis of the lactam gives the desired cyclic amino acid (Formula 14). Substituents R^1 and R^2 in Formula 14 and 21-23 are as defined above for Formula 1; substituent R^8 in Formula 20 and substituent R^9 in Formula 20-22 are each independently selected from the same groups as substituent R^1 and R^2 in Formula 1 and from C_{1-6} haloalkyl.



Scheme III

[0085] The Horner-Emmons reaction shown in Scheme III may be carried out by reacting the phosphono-acetic acid ester (Formula 20) with a base at a temperature of about -10°C to about 25°C or about 10°C to about 22°C. The resulting enolate anion is subsequently contacted with the chiral cyclohexanone (Formula 14) at a temperature of about -20°C to about 20°C or about 0°C to about 15°C, and the reaction mixture is stirred at a temperature of about 10°C to about 30°C or about 10°C to about 20°C. Useful bases include alkoxides (e.g., *t*-BuOK, *t*-BuOLi, *t*-BuONa), NaH, and LDA.

[0086] Representative R^8 and R^9 in Formula 20-22 include C_{1-6} alkyl and C_{1-6} haloalkyl. Useful phosphono-acetic acid esters (Formula 20) thus include di-C_{1-6} alkylphosphono-acetic acid C_{1-6} alkyl esters, such as trimethyl phosphonoacetate and triethyl phosphonoacetate, and di-C_{1-6} haloalkylphosphono-acetic acid C_{1-6} alkyl esters, such as bis(2,2,2-trifluoroethyl)phosphono-acetic acid methyl ester. Similarly, representative enoate esters (Formula 21) include (*S*,*S*)-(3,4-dimethyl-

cyclopentylidene)-acetic acid methyl ester, (*S*,*S*)-(3,4-dimethyl-cyclopentylidene)-acetic acid ethyl ester, (*S*,*S*)-(3,4-diethyl-cyclopentylidene)-acetic acid methyl ester, (*S*,*S*)-(3,4-diethyl-cyclopentylidene)-acetic acid ethyl ester, (*S*,*S*)-(3,4-dipropyl-cyclopentylidene)-acetic acid methyl ester, and (*S*,*S*)-(3,4-dibenzyl-cyclopentylidene)-acetic acid ethyl ester, including opposite enantiomers thereof.

[0087] As shown in Scheme III, the enoate ester (Formula 21) is converted to the nitroester (Formula 22) via conjugate addition. The Michael addition is typically carried out at a temperature which may range from about RT to reflux. The reaction generally employs excess nitromethane and catalytic amounts of base (e.g., about 0.05 eq to about 0.5 eq) based on the amount of substrate (Formula 21). Useful catalysts include bases that are strong enough to deprotonate the methyl group of nitromethane, which may include inorganic bases, such as Cs_2CO_3, K_2CO_3, and Na_2CO_3, and organic bases, such as DBU and tetramethyl guanidine.

[0088] Representative nitroesters (Formula 22) include (3*S*,4*S*)-(3,4-dimethyl-1-nitromethyl-cyclopentyl)-acetic acid methyl ester, (3*S*,4*S*)-(3,4-dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester, (3*S*,4*S*)-(3,4-diethyl-1-nitromethyl-cyclopentyl)-acetic acid methyl ester, (3*S*,4*S*)-(3,4-diethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester, (3*S*,4*S*)-(3,4-dipropyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester, and (3*S*,4*S*)-(3,4-dibenzyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester, including opposite enantiomers thereof.

[0089] According to Scheme III, the nitroester (Formula 22) is reduced and cyclized in situ by treatment with a reducing agent to furnish the lactam (Formula 23). The reaction is typically performed in an alcoholic solvent, such as MeOH or *i*-PrOH, with a metal catalyst in the presence of hydrogen gas at pressures ranging from atmospheric to 250 psig, and at a temperature ranging from about RT to reflux. Useful metal catalysts include sponge nickel. The reaction can be run in a conventional "batch mode" in which the catalyst and substantially all of the substrate (Formula 22) are first charged to a reaction vessel and hydrogen gas is subsequently added to effect conversion. Alternatively, the reaction may be carried out in a "semi-batch" mode to reduce side products and to increase yield. In the semi-batch mode,

catalyst and hydrogen are present in the vessel at the beginning of the reaction, and the nitroester (Formula 22) is subsequently fed to the reactor at a rate comparable to the rate of reduction. As in the batch mode, hydrogen gas is also added to the reaction vessel during reduction of the nitro group. See Examples 53 and 54, below.

[0090] The lactam (Formula 23) shown in Scheme III may be hydrolyzed via treatment with acid at temperatures ranging from about RT to about reflux or from about 80°C to about 95°C to furnish the desired amino acid (Formula 14) or its salt. The acid concentration may vary from about 1% to about 50%, and the molar ratio may vary from about 1:1 to about 10:1. Useful acids include inorganic acids, such as HCl, H_2SO_4, HBr, HI, and HNO_3, and organic acids, such as TFA and TCA.

[0091] Representative lactams (Formula 23) include (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one, (7*S*,8*S*)-7,8-diethyl-2-aza-spiro[4.4]nonan-3-one, (7*S*,8*S*)-7,8-dipropyl-2-aza-spiro[4.4]nonan-3-one, and (7*S*,8*S*)-7,8-dibenzyl-2-aza-spiro[4.4]nonan-3-one, including opposite enantiomers thereof. Likewise, representative amino acids (Formula 14) include (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3*S*,4*S*)-(1-aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid, (3*S*,4*S*)-(1-aminomethyl-3,4-dipropyl-cyclopentyl)-acetic acid, and (3*S*,4*S*)-(1-aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid, including opposite enantiomers thereof.

[0092] Some of the compounds described in this disclosure, including those represented by Formula 2, 4-6, 13, 14, 16, and 19 are capable of forming pharmaceutically acceptable salts. These salts include acid addition salts (including di-acids) and base salts. Pharmaceutically acceptable acid addition salts include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, and phosphorous, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide,

acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, malate, tartrate, and methanesulfonate.

[0093] Pharmaceutically acceptable base salts include nontoxic salts derived from bases, including metal cations, such as an alkali or alkaline earth metal cation, as well as amines. Examples of suitable metal cations include sodium cations (Na^+), potassium cations (K^+), magnesium cations (Mg^{2+}), and calcium cations (Ca^{2+}). Examples of suitable amines include *N*,*N*'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, *N*-methylglucamine, and procaine. For a discussion of useful acid addition and base salts, see S. M. Berge et al., "Pharmaceutical Salts," 66 *J. of Pharm. Sci.*, 1-19 (1977); see also Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* (2002).

[0094] One may prepare an acid addition salt (or base salt) by contacting a compound's free base (or free acid) with a sufficient amount of a desired acid (or base) to produce a nontoxic salt. One may then isolate the salt by filtration if it precipitates from solution, or by evaporation to recover the salt. One may also regenerate the free base (or free acid) by contacting the acid addition salt with a base (or the base salt with an acid). Some physical properties (e.g., solubility, crystal structure, hygroscopicity) of a compound's free base, free acid, or zwitterion may differ from its acid or base addition salt. Generally, however, references to the free acid, free base or zwitterion of a compound would include its acid and base addition salts.

[0095] Disclosed and claimed compounds may exist in both unsolvated and solvated forms and as other types of complexes besides salts. Useful complexes include clathrates or compound-host inclusion complexes where the compound and host are present in stoichiometric or non-stoichiometric amounts. Useful complexes may also contain two or more organic, inorganic, or organic and inorganic components in stoichiometric or non-stoichiometric amounts. The resulting

complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J. K. Haleblian, *J. Pharm. Sci.* 64(8):1269-88 (1975). Pharmaceutically acceptable solvates also include hydrates and solvates in which the crystallization solvent may be isotopically substituted, e.g., D_2O, d_6-acetone, d_6-DMSO. Generally, for the purposes of this disclosure, references to an unsolvated form of a compound also include the corresponding solvated or hydrated form of the compound.

[0096] Some of the compounds disclosed in this specification may contain an asymmetric carbon, sulfur or phosphorus atom (a stereogenic center) and therefore may exist as an optically active stereoisomer (i.e., one enantiomer of a pair of enantiomers). Some of the compounds may also contain an alkenyl or cyclic group, so that *cis/trans* (or *Z/E*) stereoisomers (diastereoisomers) are possible. Still other compounds may contain two or more stereogenic centers so that diastereoisomers are possible, each of which may be optically active (i.e., comprise one enantiomer of a pair of enantiomers). Finally, some of the compounds may contain a keto or oxime group, so that tautomerism may occur. In such cases, the scope of the present disclosure includes all tautomers and all stereoisomers, including enantiomers, diastereoisomers, and *Z/E* isomers, whether they are pure, substantially pure, or mixtures.

[0097] Desired enantiomers of any of the compounds disclosed herein may be further enriched through classical resolution, chiral chromatography, or recrystallization. For example, a mixture of enantiomers may be reacted with an enantiomerically-pure compound (e.g., acid or base) to yield a pair of diastereoisomers, each composed of a single enantiomer, which are separated via, say, fractional recrystallization or chromatography. The desired enantiomer is subsequently regenerated from the appropriate diastereoisomer. Additionally, the desired enantiomer may be further enriched by recrystallization in a suitable solvent when the enantiomer is available in sufficient quantity (e.g., typically not much less than about 85 % ee, and in some cases, not much less than about 90 % ee).

[0098] The disclosed compounds also include all pharmaceutically acceptable isotopic variations, in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes suitable for inclusion in the disclosed compounds include isotopes of hydrogen, such as ^{2}H and ^{3}H; isotopes of carbon, such as ^{13}C and ^{14}C; isotopes of nitrogen, such as ^{15}N; isotopes of oxygen, such as ^{17}O and ^{18}O; isotopes of phosphorus, such as ^{31}P and ^{32}P; isotopes of sulfur, such as ^{35}S; isotopes of fluorine, such as ^{18}F; and isotopes of chlorine, such as ^{36}Cl. Use of isotopic variations (e.g., deuterium, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements. Additionally, certain isotopic variations of the disclosed compounds may incorporate a radioactive isotope (e.g., tritium, ^{3}H, or ^{14}C), which may be useful in drug and/or substrate tissue distribution studies.

EXAMPLES

[0099] The following examples are intended as illustrative and non-limiting, and represent specific embodiments of the present invention.

EXAMPLE 1. Preparation of (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester

[0100] A solution of (*R*)-2-methyl-succinic acid 4-methyl ester (24.5105 g, 0.1677 mol) in THF (25 mL) was filtered to remove a white solid (26.3 mg; soluble in water, insoluble in CH_2Cl_2) and was added to a –30°C solution of LHMDS/THF (1.0 M; 360 mL, 0.360 mol, 2.15 eq) at a rate such that the temperature remained below –25°C (1.5 h). The mixture was warmed to –10°C, stirred for 1 h, cooled back to –30°C, and treated with a solution of methyl iodide (25.12 g, 0.1770 mol, 1.06 eq) in THF (25 mL) at a rate such that the temperature did not exceed –25°C (1.5 h). The mixture was stirred at –25°C for 2 h, then allowed to warm to RT, stirred for 15.5 h, cooled to 0°C, and cautiously quenched with a solution of NH_4Cl (25 g, 0.467 mol, 2.79 eq) in H_2O (75 mL) at a rate such that the temperature did not exceed about 0°C (except for a brief excursion to 14°C; the first 2 mL was added over 30 min, the rest over 1 h). The mixture was diluted with H_2O (100 mL) to dissolve solids and the

layers were separated. The organic layer was treated with Et_3N (2.4 mL) to quench residual methyl iodide and discarded. The aqueous layer was acidified with 6N HCl to pH 1.92 and extracted with MTBE (4 x 150 mL). The aqueous layer (about pH 3) was discarded. The organic extracts were combined and vacuum concentrated to a dark amber oil identified as the above-titled compound by ^{13}C-NMR and ^{1}H-NMR. The ratio of *anti/syn/monomethyl* was determined to be 88.5:7.8:3.7 by GC. Weight: 28.01 g; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 180.97 (s); 175.67 (s); 51.80 (q); 41.36 (d); 41.23 (d); 13.50 (q); 13.40 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.53 (1H, br s); 3.69 (3H, s); 2.84 (2H, overlapping mults); 1.20 (3H, d, J = 4.3 Hz); 1.18 (3H, d, J = 4.4 Hz).

EXAMPLE 2. Preparation of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol

[0101] The dark amber oil from Example 1 (27.82 g) was diluted with THF (137 mL, filtered to remove insolubles, 57.1 mg) and was added to a 0°C suspension of LAH (16.48 g, 0.4343 mol, 2.61 eq) in THF (434 mL) over 40 min. The mixture was stirred at 5°C for 1 h then at 30°C for 17.5 h and then cooled to 0°C. The mixture was carefully quenched by addition of H_2O (16.5 g, 0.916 mol, 5.50 eq) over 70 min, followed by 15% NaOH aq solution (16.5 mL) over 10 min, and followed by H_2O (50 mL) over 10 min. All three solutions were added at a rate such that the internal temperature remained in the range of 5°C to 15°C. The off-white slurry was filtered (coarse frit, slow filtration), rinsing with THF (165 mL). The filtrate was concentrated to an oil. To azeotropically remove water, the oil was diluted with toluene (135 mL) and distilled to a pale tan oil identified as the above-titled compound by ^{13}C-NMR and ^{1}H-NMR. The ratio of dl:meso:monomethyl was determined to be 92.65:5.91:1.43 by GC. Weight: 17.16 g (0.1452 mol, 87.2% overall from (*R*)-2-methyl-succinic acid 4-methyl ester; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 65.56 (t); 37.18 (d); 13.13 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.85 (6H, d, J = 6.6 Hz); 1.72 (2H, mult); 3.45 (2H, dd, J = 10.9, 6.5 Hz); 3.55 (2H, dd, J = 10.9, 4.4 Hz); 4.10 (2H, d, J = 7.4 Hz).

EXAMPLE 3. Preparation of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane

[0102] A solution of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol (15.75 g, 0.1333 mol) and *p*-toluenesulfonyl chloride (63.53 g, 0.3332 mol, 2.50 eq) in ACN (169 mL) was cooled to 0°C and treated with neat Et_3N (56 mL, 40.66 g, 0.4018 mol, 3.01 eq) at a rate such that the temperature did not exceed 5°C (35 min). The mixture was stirred at 0°C for 2 h then at RT for 19 h. The mixture was diluted with EtOAc (107 mL) and H_2O (103 mL). The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 92 mL). The organic layers were combined, washed with H_2O (115 mL) followed by 10% $NaHCO_3$ aq solution (103 mL) and by 80 mL 25% NaCl aq, and concentrated to an off-white/yellow solid. The solid was dissolved in MTBE (345 mL) and EtOH (27 g) at 60°C, cooled to 0°C over 7 h, stirred at 0°C for 16 h, and filtered. The cake was washed with 0°C MTBE (2 x 25 mL) and dried by N_2 stream to afford a white solid identified as the above-titled compound by ^{13}C-NMR and ^{1}H-NMR. The ratio of dl:meso:monomethyl was determined to be 96.72:1.79:1.49 by HPLC. Weight: 38.20 g (0.8956 mol, 67.2%); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.91 (s); 132.71 (s); 129.90 (d); 127.82 (d); 72.59 (t); 32.97 (d); 21.62 (q); 11.20 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.75 (6H, d, J = 6.7 Hz); 1.97 (2H, mult); 2.47 (6H, s); 3.84 (4H, d, J = 5.5 Hz); 7.36 (4H, d, J = 8.1 Hz); 7.77 (4H, d, J = 8.2 Hz).

EXAMPLE 4. Preparation of (*S*,*S*)-3,4-dimethyl-cyclopentanone

[0103] A 1 L 3-neck flask was charged with (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (50.0 g of 98.6 wt% pure material, 49.3 g, 0.1156 mol), THF (90 mL, stabilized with BHT), and FAMSO (14.0 mL, 17.1 g, 0.1375 mol, 1.19 eq), rinsing with THF (12 mL). The mixture was cooled to 18°C. The resulting thin slurry was treated drop wise with a solution of LHMDS in THF (Chemetall Foote Corp.; 205 mL of 1.28 M solution, 0.2624 mol, 2.27 eq) over 3.5 hours. HPLC analysis revealed that the ratio of thioketal monoxide to ditosylate was 69.2:30.8 (normalized wt%). Stirring was continued for another 18 h, at which time the ratio was 97.7:2.3. The reaction mixture was quenched with water (10 mL). The resulting

greenish solution was transferred to a graduated cylinder. The volume was 358 mL. The yield of thioketal monoxide was determined to be 79.1 chem% by HPLC. The greenish solution was diluted with saturated brine (110 mL) and water (56 mL). The lower aqueous was separated. The upper organic layer was shaken with saturated brine (50 mL) and water (10 mL). The lower aqueous layer was separated. The two aqueous layers were combined, diluted with water (100 mL) and extracted with $MeCl_2$ (125 mL). The volume of the aqueous was 368 mL. The organic phases were combined and concentrated (200 Torr; final pot temp 50°C) to a final volume of about 100 mL then diluted with water (25 mL). The reaction mixture (40°C) was treated over about 15 min with 37% HCl (35 mL, 42 g, containing 15.54 g or 3.69 eq HCl). Over the course of the addition, the temperature increased to 56°C. The reaction mixture was diluted with water (100 mL) and vacuum steam distilled (pot temp 74°Ct o 104°C/200 Torr) to give a two-phase distillate. To insure that the azeotrope is completely condensed, –10°C EtOH was put on the condenser. The lower aqueous phase (85 mL) was extracted with MTBE (20 mL), which was combined with the upper organic phrase (95 mL). The combined organic layers (111 mL) were analyzed by GC and found to contain the above-titled ketone (0.876 M, 0.09724 mol, 84.1 chem%), $MeCl_2$ (1.44 area%), Me_3SiOH (12.70 area%), THF (28.96 area%), $(Me_3Si)_2O$ (34.23 area%), MeSSMe (4.58 area%), thioketal (0.12 area% or less), and water (1.185 wt% KF).

EXAMPLE 5. Purification of (*S*,*S*)-3,4-dimethyl-cyclopentanone via bisulfite adduct

[0104] Crude (*S*,*S*)-3,4-dimethyl-cyclopentanone (24.0 g of 90.20 wt% pure material, 21.65 g, 0.1930 mol; impurities include 0.46 area% des-methyl and unidentified later-eluting impurities, 0.15, 0.31, 1.56, 0.36, 0.30, and 0.71 area%) was added to a solution of sodium metabisulfite $Na_2S_2O_5$ (29.45 g, 0.3098 mol as bisulfite, 1.61 eq) in H_2O (50 mL). The two-phase mixture was stirred at RT. After 5 min, solids began to precipitate. After 30 min, the slurry became unstirrable, so more H_2O (35 mL) was added. After stirring for 2 h, the slurry was filtered to afford a white solid identified as the ketone bisulfite adduct, (*S*,*S*)-1-hydroxy-3,4-dimethyl-cyclopentanesulfonate, by ^{1}H-NMR and ^{13}C-NMR. Weight: 21.95 g (0.1015 mol,

52.6 chem% yield); ^{13}C-NMR (100 MHz, 1:1 CD_3OD:D_2O): δ 93.71 (s); 45.53 (t); 40.77 (d); 17.39 (q) (signals for ketone also present at about 25% of height of signals for bisulfite, attributed to dissociation on dissolution); ^{1}H-NMR (400 MHz, 1:1 CD_3OD:D_2O): δ 0.98 (3H, br s); 1.09 (3H, d, J = 5.6 Hz); 1.39 (1H, dd, J = 14.4, 10.0 Hz); 1.4-1.9 (3H, mults); 2.44 (1H, dd, J = ~18, 4.8 Hz); 2.62 (1H, dd, J = 14.4, 8.4 Hz); 4.74 (1H, br s).

[0105] The bisulfite adduct (21.95 g, 0.1015 mol) was dissolved in H_2O (90 mL), covered with pentane (100 mL), and treated with 6N HCl (70 mL, 0.42 mol, 4.14 eq). The two-phase mixture was stirred at RT for 2 h. The organic phase was separated, washed with water, dried with $MgSO_4$, and concentrated on a Rotovap to an oil, which was distilled (bp 116°C/500 Torr) to afford a colorless oil identified as the above-titled compound in pure form by ^{13}C-NMR, ^{1}H-NMR, MS, and GC (contains less than 0.1 area% des-methyl or any other impurity). Weight: 11.61 g (0.1035 mol, 102.0 chem% yield); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.10 (2C, s); 39.16 (2C, d); 47.48 (2C, t); 218.70 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.09 (6H, br d); 1.73-1.84 (4H, mults); 2.40 (2H, d, 12.4 Hz); MS (CI, NH_3): m/e 141 (100%, P +HCO_2H – OH).

EXAMPLE 6. Preparation of (*R*,*R*)-3,4-dimethyl-dihydro-furan-2,5-dione

[0106] A solution of (*R*)-2-methyl-succinic acid 4-methyl ester (133.5 kg, 912 mol) in THF (125 kg) at –22°C was added to LHMDS (322.6 kg, 1928 mol, 2.11 eq) in THF (1190 L) at –34°C over 1.5 h while maintaining the reaction mixture at –34°C to –26°C. The substrate was rinsed in with THF (10 kg). The solution was stirred at –26°C to -30°C for 1 h, then warmed to –12°C over 1.5 h. The mixture was stirred at –12°C to –10°C for 5 min, and then cooled to –34°C over 7.8 h. A solution of MeI (140 kg, 986 mol, 1.08 eq) in THF (153 L) at –21°C was added to the dianion solution over 5 h while maintaining -34°C to –27°C and rinsed in with THF (45 L). The mixture was stirred at –27°C to –29°C for 4 h, warmed to 20°C over 1.5 h, stirred at 20°C to 21°C for 12 h, and cooled to 5°C. A solution of NH_4Cl (136 kg, 2543 mol, 2.79 eq) in water (400 L) was added over 7.3 h while maintaining the temperature of the mixture at 5°C to 25°C. Water (540 L) was added and the upper

phase discarded. To the lower aqueous phase was added water (240 L), followed by pH adjustment to 1 with HCl (300 kg, 35 wt%, 2880 mol, 3.16 eq) while maintaining the temperature of the reaction mixture at 4°C to 11°C. Following a water rinse (10 L), the product was extracted with MTBE (4 x 304 kg) and concentrated to give (*R,R*)-2,3-dimethyl-succinic acid monomethyl ester as an oil (167 kg, 78.6 wt% by internal standard GC, 89.7% yield, 6.4 area% cis, 0.4% des-methyl, 3.3% trimethyl).

[0107] A sample of crude (*R,R*)-2,3-dimethyl-succinic acid monomethyl ester (350.81 g, 78.6 wt%, 1.72 mol) was mixed with water (500 mL) to give a biphasic mixture. To this mixture was added NaOH (50 wt%, 351.45 g, 4.39 mol, 2.55 eq) while maintaining the temperature of the mixture at 45°C or less. The mixture was stirred for 10 min at 45°C, then the pH was adjusted from 10.4 to 0.5 with HCl (438 g, 37.5 wt%, 4.50 mol, 2.62 eq) while maintaining the temperature of the mixture at 30°C or less. The solution was extracted with EtOAc (3 x 1 L), dried on $MgSO_4$, and concentrated to a thick slurry (412 g net weight). Acetic anhydride (250 mL, 2.645 mol, 1.54 eq) was added and the mixture warmed to 109°C. NMR showed complete conversion to the cyclic anhydride; a subsequent experiment showed the cyclization reaction was rapid at 75°C. The solution was cooled to 50°C and seeded to give a slurry. Tert-Amyl alcohol (1 L) was added and the slurry cooled to –8°C. The precipitate was collected by vacuum filtration, washed with branched octanes, and dried in a nitrogen stream to afford (*R,R*)-3,4-dimethyl-dihydro-furan-2,5-dione as a white solid (196.91 g, 89.4%, 80.2% from (*R*)-2-methyl-succinic acid 4-methyl ester) mp 103.5-105.4°C; $[\alpha]^{25}_D = 103.07°$ (dioxane, c = 1.00); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (d, J = 7 Hz, 6 H), 2.98 (octet, J = 4 Hz, 2 H);^{13}C NMR (100 MHz, DMSO-d_6) δ 12.73, 42.12, 174.57; MS (EICI) m/z (rel intensity) 127 [(M-H)$^-$,100]; Anal. Calc'd for $C_6H_8O_3$: C, 56.25; H, 6.29; N, 0.00; Found: C, 56.24; H, 6.25; N, <0.05; methanolysis to (*R,R*)-2,3-dimethyl-succinic acid monomethyl ester showed 1.3% cis isomer and <0.1% of any other related impurity by GC.

EXAMPLE 7. Preparation of (*R,R*)-2,3-dimethyl-butane-1,4-diol

[0108] To a solution of (*R,R*)-3,4-dimethyl-dihydro-furan-2,5-dione (40.04 g, 312.52 mmol) in MTBE (440 mL) and THF (58 mL) at 45°C was added a solution of

LAH in THF (175 mL, 2.4 M, 420 mmol) drop wise via addition funnel over 0.5 h while maintaining the reaction mixture at a temperature of 45°C to 54°C (reflux) followed by a THF rinse (10 mL). For the first 150 mL of the LAH addition, the mixture was a stirrable slurry which turned to a solution at the end of the addition. A strong, slightly delayed exotherm was present for the first 150 mL of the addition, followed by a very mild endotherm for the final 25 mL. The resulting solution was cannulated into a –7°C biphasic mixture of NaOH (50%, 1.38 g, 17.25 mmol, 0.055 eq), water (55 mL) and THF (275 mL) over 40 min while maintaining the reaction mixture at a temperature of 13°C or less. Residual solution was rinsed in with THF (40 mL) and the resulting slurry was warmed to 55°C over 1 h and stirred for 2 h at 55°C. The precipitate was removed by vacuum filtration at 55°C (4 min filtration time) and washed twice with a 55°C mixture of MTBE (330 mL) and MeOH (28 mL) (15 min filtration for each wash). The combined filtrates were dried on $MgSO_4$, clarified and concentrated in vacuo to a light oil (47.43 g). Branched octanes (100 g) were added and the biphasic mixture seeded at 20°C to afford a slurry after stirring for 5 min. Branched octanes (200 g) were added and the mixture was cooled to 3°C. The precipitate was collected by vacuum filtration, washed with branched octanes and dried in a nitrogen stream to give the above-titled compound as a white solid (34.24 g, 92.7%), mp 42.5–44.5°C; $[\alpha]^{25}_D = 103.07°$ (diethyl ether, c = 1.00); ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 7 Hz, 6 H), 1.71 (m, 2 H), 3.44 (dd, J = 6.5 Hz, J = 11 Hz, 2 H), 3.54 (dd, J = 6.5 Hz, J = 11 Hz, 2 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 13.21, 37.25, 65.53; MS (EICI) m/z (rel intensity) 117 [$(M-H)^-$, 100]; Anal. Calc'd for $C_6H_{14}O_2$: C, 60.98; H, 11.94; N, 0.00; Found: C, 60.91; H, 12.27; N, <0.05.

EXAMPLE 8. Preparation of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane

[0109] To a slurry of *p*-toluenesulfonyl chloride (20.255 g, 106.24 mmol, 2.52 eq) in ACN (75 mL) at –10°C was added (*R*,*R*)-2,3-dimethyl-butane-1,4-diol (4.982 g, 42.16 mmol). Et_3N (17.7 mL, 127.0 mmol, 3.01 eq) was added over 1 min while maintaining the reaction mixture at a temperature of 0°C or less. The slurry was stirred at 0°C to 5°C for 3.5 h and warmed to 20°C. Water (40 mL) and EtOAc (60

mL) were sequentially added and the phases were separated at 29°C. The aqueous layer was washed with EtOAc (2 x 50 mL) and the combined organic layers were washed with water (40 mL), 10% $NaHCO_3$ aq solution (40 mL) and saturated NaCl aq solution (40 mL). The organic fraction was dried on $MgSO_4$ and concentrated in vacuo to 22.56 g of an oil. Toluene (100 mL) was added to give a solution. Following addition of branched octanes (50 mL), the product was allowed to crystallize over 10 min. Branched octanes (150 mL) were added and the precipitate was collected by vacuum filtration. The solids were washed with branched octanes and dried in a nitrogen stream to give the above-titled compound as a white solid (15.563 g, 86.5%); mp 83.1-83.6°C; $[\alpha]^{25}_D$ = -5.55 (ethyl acetate, c = 1.00); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6 Hz, 6 H), 1.97 (m, 2 H), 2.47 (s, 6 H), 3.85 (d, *J* = 6 Hz, 4 H), 7.37 (d, *J* = 8 Hz, 4 H), 7.78 (d, *J* = 8 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.20, 21.64, 32.96, 72.51, 127.84, 129.90, 132.70, 144.90; MS (TSP) m/z (rel intensity) 427 [$(M+H)^+$, 20], 444 [$(M+H_2O)^+$, 100]; Anal. Calc'd for $C_{20}H_{26}O_6S_2$: C, 56.32; H, 6.14; N, 0.00; Found: C, 56.25; H, 6.00; N, 0.05; HPLC: (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, 99.6 area%; (*R*,*S*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, 0.08 area%; (*R*)-2-methyl-1,4-bis-(toluene-4-sulfonyloxy)-butane, 0.08 area%.

EXAMPLE 9. Preparation of (*R*,*R*)-3,4-dimethyl-dihydro-furan-2,5-dione

[0110] To a solution of LHMDS in THF (24.4 wt%, 518.5 g, 756.1 mmol, 2.12 eq) at –30°C was added (*R*)-2-methyl-succinic acid 4-methyl ester (52.127 g, 356.69 mmol) in THF (52 mL) over 0.5 h while maintaining the reaction mixture temperature at –29°C. The substrate was rinsed in with THF (6 mL). The mixture was stirred for 25 min at -29°C, then a solution of MeI (53.32 g, 375.65 mmol, 1.05 eq) in THF (105 mL) was added over 0.5 h while maintaining the reaction mixture at –30°C. MeI was rinsed in with THF (15 mL). The mixture was stirred at –30°C for 2 h, warmed to 0°C, and stirred for 1 h. GC showed a mixture of (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester, 78.8 area%, (*R*)-2-methyl-succinic acid 4-methyl ester, 15.0 area%, and meso isomer, (*R*,*S*)-2,3-dimethyl-succinic acid, 6.2 area%.

[0111] A mixture of NaOH (50.0 %, 57.0 g, 713 mmol, 2.00 eq) and water (200 mL) was added over 10 min while maintaining the temperature of the reaction mixture at 0°C. The mixture was stirred at 20°C for 16 h and sodium bisulfite (66.6% SO_2, 1.68 g, 17.5 mmol, 0.049 eq) was added. The pH was adjusted from 10.67 to 0.11 with HCl (37.5 wt%, 208.6 g, 2.145 mol, 3.01 eq) while maintaining the temperature of the reaction mixture at 25°C or less. The phases were separated and toluene (200 mL) was added to the organic layer followed by saturated NaCl aq solution (50 mL). The phases were separated and the aqueous layer was extracted with EtOAc (750 mL). The combined organic fractions were dried on $MgSO_4$ and concentrated in vacuo to 90.91 g of material. Toluene (150 mL) was added and the slurry was warmed to 75°C to give a solution. Acetic anhydride (44.67 g, 437.6 mmol, 1.23 eq) was added over 5 min and the mixture stirred at 75°C for 0.5 h at which point NMR showed complete conversion. The solution was cooled to 30°C and branched octanes (200 mL) and t-amyl alcohol (200 mL) were added. The product was allowed to crystallize after seeding, and branched octanes (200 mL) were added. The slurry was cooled to –8°C and the precipitate collected by vacuum filtration, washed with branched octanes and dried in a nitrogen stream to give (*R*,*R*)-2,3-dimethyl-succinic acid as a beige solid (29.38 g, 64.3%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (d, J = 7 Hz, 6 H), 2.98 (octet, J = 4 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.73, 42.12, 174.58; ^{13}C NMR indicated 93.7% (*R*,*R*)-2,3-dimethyl-succinic acid, 2.9% meso-isomer (10.75, 38.14 ppm) and 3.5% des-methyl (14.74, 35.33, 35.74 ppm).

EXAMPLE 10. Preparation of (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester

[0112] A solution of (*R*,*R*)-3,4-dimethyl-dihydro-furan-2,5-dione (40.06 g, 312.6 mmol) in MeOH (400 mL) was refluxed at 65°C for 6 h. The resultant solution was concentrated in vacuo to give the above-titled compound as a light beige oil (49.80 g, 99.4%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7 Hz, 6 H), 2.82 (q, J = 7 Hz, 1 H), 2.88 (q, J = 7 Hz, 1 H), 3.70 (s, 3 H), 10.61 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.41, 13.52, 41.20, 41.38, 51.92, 175.59, 181.43; MS (EICI) m/z (rel intensity) 159

[(M-H)$^-$, 100]; Anal. Calc'd for $C_7H_{12}O_4$: C, 52.49; H, 7.55; N, 0.00; Found: C, 52.20; H, 7.76; N, <0.05.

EXAMPLE 11. Preparation of (*R*,*R*)-2,3-dimethyl-succinic acid

[0113] To a biphasic mixture of crude (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester (3.2177 g, 20.09 mmol GC: 85.9 area%, 6.1 % cis isomer, 1.8% des methyl impurity, 3.3 % trimethyl impurity) and water (11 mL) was added 50 wt% NaOH aq solution (4.08 g, 50.94 mmol, 2.54 eq) while maintaining the temperature of the reaction mixture at 25°C or less. The resulting solution was stirred at 20°C for 39 min and then HCl (37.5 wt% 5.36 g, 55.1 mmol) was added. The resulting solution was extracted with $MeCl_2$ (5 mL then 2 x 10 mL) and EtOAc (3 x 35 mL). The organic layers were dried on $MgSO_4$ and concentrated to dryness. The crude solids were dissolved in *i*-PrOH (10 mL) and branched octanes (30 mL) were added. The solution was concentrated in vacuo to 20 mL total volume and cooled to give a slurry. Branched octanes (10 mL) were added and the mixture was cooled to 0°C. The precipitate was collected by vacuum filtration, washed with branched octanes and dried in a nitrogen stream to give the above-titled compound as a white solid (1.4592 g, 49.7 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (d, J = 7 Hz, 6 H), 2.58 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.40, 40.96, 176.38; ^{13}C-NMR shows 1.6% meso isomer (14.77 ppm, 41.87 ppm).

EXAMPLES 12-23. Preparation of (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester via subsurface addition

[0114] A solution of LHMDS (1300 kg, 24.9% by weight. 1.93 kg-mol, 2.1 eq) in THF is charged to a tank and cooled to –30°C. (*R*)-2-Methyl-succinic acid 4-methyl ester (133 kg, 0.91 kg-mol, 1 eq) is mixed with an equal volume of THF and fed sub-surface to the lithium reagent, using a dip tube mounted in the reactor such that its outlet is about 0.3 m from the tip of the vessel agitator. During the addition of the substrate, the temperature of the reaction mixture is maintained at –25°C or less. The resulting mixture is stirred and warmed to –10°C, then cooled to –30°C. MeI (136 kg, 0.96 kg-mol, 1.05 eq) is mixed with a 2 volumes of THF and fed subsurface to the

reaction mixture, while maintaining the temperature of the reaction mixture at –25°C or less. The temperature is adjusted over 8 h to RT. NH_4Cl (136 kg) is dissolved in water (400 L) and is fed slowly to the reactor vessel to quench the reaction. More water (550 L) is added with stirring and then the agitator is stopped to allow the phases to separate. The organic phase is discarded. The aqueous phase is acidified with a mixture of 37% HCl (300 kg) and water (250 L), and is extracted with MTBE (4 x 400 L). The MTBE phases are combined and distilled to yield the above-titled compound as an oil.

[0115] Table 2 shows the yields of the desired anti-diastereomer, (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester, and the undesired syn-diastereomer, (*R*,*S*)-2,3-dimethyl-succinic acid monomethyl ester, using subsurface reactant addition. For comparison purposes, Table 2 also shows the yields of the two diastereomers using a process similar to that described in the preceding paragraph except that the reactants are added via above-surface addition.

TABLE 2. Yield of anti- and syn-diastereomers using subsurface (Examples 12-20) and above-surface (Examples 21-23) addition of reactants

Example	Anti-diastereomerr[1]	Syn-diastereomer[2]
Subsurface Addition		
12	87.1	6.8
13	86.6	6.9
14	87.0	6.5
15	85.5	6.1
16	87.2	6.5
17	82.5	6.1
18	86.9	6.2
19	86.4	6.0
20	85.4	5.7
Average	86.1	6.3
Above-surface Addition		
21	80.1	8.4

Example	Anti-diastereomer[1]	Syn-diastereomer[2]
22	82.3	8.5
23	78.8	7.7
Average	80.4	8.2

[1](*R*,*R*)-2,3-Dimethyl-succinic acid monomethyl ester

[2](*R*,*S*)-2,3-Dimethyl-succinic acid monomethyl ester

EXAMPLES 24-30. Preparation of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol

[0116] (*R*,*R*)-2,3-Dimethyl-succinic acid monomethyl ester (150 kg, 0.91 kg-mol) is diluted with THF (260 L) and MTBE (1500 L) and is heated to 60°C. A 10% LAH solution (530 kg in THF, 1.33 kg-mol) is fed to this solution resulting in slurry containing a light aluminum alkoxide intermediate. Heat generated by the reaction is removed by solvent boil up and condensation. A second tank is charged with THF (about 970 L), water (220 L), and 50% NaOH aq solution (5 kg) and is heated to approximately 50°C. The aluminum alkoxide slurry is fed in a controlled fashion to the tank containing THF, water, and NaOH. The agitator is then shut off, the aluminum hydroxide is allowed to settle for 10 min to 15 min, and the product is removed by decanting. The solids are washed with MTBE (3 x 600 L) to extract additional product. The organic liquids are collected and distilled to yield the above-titled compound.

[0117] Table 3 shows yields of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol via LAH reduction of (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester using the workup described in the preceding paragraph (i.e., addition to excess base, Examples 24-28). For comparison purposes, Table 3 also shows yields of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol using a Fieser workup—sequential addition of H_2O, 15% NaOH aq, and H_2O following LAH reduction.

TABLE 3. Yield of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol via LAH reduction and addition to excess base (Examples 24-28) or Fieser workup (Examples 29 and 30)

Example	24	25	26	27	28	29	30
Yield, wt%	78	73	77	80	92	66	56
Cycle time, days	3	3	3	3	3	6	6
Batch size, kg	150	150	150	150	150	75	75

EXAMPLE 31. Preparation of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane

[0118] A reactor vessel is dry-charged with *p*-toluenesulfonyl chloride (400 kg, 2.14 kg-mol, 2.5 eq). Acetonitrile (1000 L) is subsequently added and the resulting slurry is cooled to 0°C. (*R*,*R*)-2,3-Dimethyl-butan-1,4-diol (100 kg, 0.85 kg-mol, 1 eq) is added to the reactor. Et_3N (260 kg, 2.5 kg-mol, 3 eq) is subsequently fed to the reactor at a rate to maintain the reactor temperature at not more than 5°C. EtOAc (660 L) and water (640 L) are added with stirring to quench the reaction. Stirring is stopped to allow the organic and aqueous phases to separate. The aqueous phase is washed with EtOAc (560 L) and the resulting organic phase is combined with the organic phase from the reaction quench. The combined organic phases are washed successively with a 10% $NaHCO_3$ aq solution (720 kg) and a 25% NaCl aq solution (670 kg). EtOAc is distilled-off at atmospheric pressure to give a liquid volume of about 400 L, to which is added MTBE (1100 L) and EtOH (170 kg). The mixture is heated to reflux and subsequently cooled to about 20°C to crystallize the crude product, which is collected by filtration. The crude product is dispersed in MTBE (2200 L) and the mixture is heated to reflux to dissolve the solids. Following dissolution, water (200 L) is added with stirring and the phases are allowed to separate. The aqueous phase is discarded. EtOH (150 kg) is added to the organic phase and the mixture is cooled to 20 C to crystallize the above-titled compound, which is collected by filtration.

EXAMPLE 32. Degradation of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane by LHMDS

[0119] A solution of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (269 mg, 0.631 mmol) in THF (1.5 mL) was treated with a solution of LHMDS in THF (1.0 mL of 1.35 M solution, 1.35 mmol, 2.14 eq) and stirred at 17°C for 6.5 h, at which time 55.5% of the original ditosylate remained by quantitative HPLC analysis.

EXAMPLE 33. Degradation of thioketal S-oxide, (3*S*,4*S*)-1-methanesulfinyl-3,4-dimethyl-1-methylsulfanyl-cyclopentane, to vinyl sulfide, (3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene, by LHMDS

[0120] A solution of (3*S*,4*S*)-1-methanesulfinyl-3,4-dimethyl-1-methylsulfanyl-cyclopentane (318 mg, 1.541 mmol) in THF (1.5 mL) was treated with a solution of LHMDS in THF (2.0 mL of 1.35 M solution, 2.70 mmol, 1.75 eq) and was stirred at 17°C for 6.5 h, at which time HPLC analysis indicated that 32.3% of the original thioketal S-oxide had been converted to (3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene. Another experiment carried out by a similar procedure afforded the vinyl sulfide in pure form after standard workup and flash chromatography on silica gel (eluant: straight pentane). Spectra for (3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene: ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.75 (s); 125.90 (s); 47.92 (d); 43.92 (t); 42.16 (d); 19.76 (q); 19.29 (q); 14.89 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.03 (3H, s); 1.08 (3H, s); 1.87 (1H, heptet, J = 7.2 Hz); 2.06 (1H, mult); 2.27 (3H, s); 2.3 (1H, partially obscured mult); 2.57 (1H, dd, J = 15.3,dd 8.2 Hz); 5.13 (1H, s); UV: λ_{max} = 226 nm.

EXAMPLE 34. Hydrolysis of vinyl sulfide, (3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene, to (*S*,*S*)-3,4-dimethyl-cyclopentanone

[0121] A solution containing (3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene (3.985 mmol) in THF (19 mL) was acidified with aq HCl. After stirring for 2.5 h at RT, quantitative HPLC analysis indicated that hydrolysis to (*S*,*S*)-3,4-dimethyl-cyclopentanone was complete. Quantitative GC analysis indicated that the yield of (*S*,*S*)-3,4-dimethyl-cyclopentanone was 73.2%.

EXAMPLE 35. Preparation of (*S*,*S*)-3,4-dimethyl-cyclopentanone; base addition at 15-17°C

[0122] To a solution of ditosylate, (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (5.02 g of 91.6 wt% pure material, 4.598 g, 10.780 mmol) and FAMSO (1.4 mL, 1.708 g, 13.750 mmol, 1.28 eq) in THF (9 mL) at 15-17°C was added a solution of LHMDS in THF (Chemetall Foote Corp.; 21.5 mL of 1.35 M solution, 29.02 mol, 2.69 eq) over a 5 h period. The mixture was warmed to 20°C and stirred for 16 h at which time HPLC analysis revealed that conversion of the ditosylate to the thioketal S-oxide, (3*S*,4*S*)-1-methanesulfinyl-3,4-dimethyl-1-methylsulfanyl-cyclopentane, was complete. The reaction mixture was quenched with water (7.2 mL) and the lower aqueous phase was separated and extracted with $MeCl_2$ (5 mL, then 10 mL). The organic layers were combined and concentrated to a two-phase mixture, which was diluted with THF (3 mL), treated with 6 N HCl (6 mL, 36 mmol, 3.34 eq), and stirred at RT for 23 h. The yield of the above-titled compound was 86.3% by quantitative GC analysis.

EXAMPLE 36. Preparation of (*S*,*S*)-3,4-dimethyl-cyclopentanone; base addition at -2°C

[0123] To a solution of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (5.05 g of 91.6 wt% pure material, 4.626 g, 10.845 mmol) and FAMSO (1.4 mL, 1.708 g, 13.750 mmol, 1.27 eq) in THF (9 mL) at –2°C was added a solution of LHMDS in THF (Chemetall Foote Corp.; 21.5 mL of 1.35 M solution, 29.02 mmol, 2.68 eq) over a 3.5 h period. The mixture was warmed to 20°C. After 1 h, HPLC analysis revealed that the ratio of (3*S*,4*S*)-1-methanesulfinyl-3,4-dimethyl-1-methylsulfanyl-cyclopentane to the ditosylate was 52.4:47.6 (normalized wt%). Stirring was continued for another 17 hr at which time the ratio was 98.2:1.8. The reaction mixture was quenched with water (11 mL). The lower aqueous layer was separated and the upper organic layer was shaken with saturated brine (10 mL). The lower aqueous layer was separated. The two aqueous layers were combined, diluted with water (10 mL), and extracted with $MeCl_2$ (10 mL). The organic phases were combined, concentrated to a low volume, treated with 6N HCl (6 mL, 36 mmol, 3.32

eq), and stirred at RT for 66 h. The yield of the above-titled compound was 71.3% by quantitative GC analysis.

EXAMPLE 37. Preparation of (*S*,*S*)-3,4-dimethyl-cyclopentanone

[0124] A reactor was charged with (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (368.8 kg, 0.8646 kg-mol), THF (600 L), and FAMSO (127.8 kg, 1.0288 kg-mol, 1.19 eq). The mixture was cooled to –3°C and treated with a solution of LHMDS in THF (Chemetall Foote Corp.; 1432 kg of 20 wt% solution, 286.4 kg, 1.712 kg-mol, 1.98 eq). The mixture was stirred at 0°C for 1 h, then at 20°C for 10 h. The mixture was quenched with water (480 L), extracted with EtOAc (3 x 370 kg), and washed with water (340 L). The organic phases were distilled under vacuum to a volume of 200 L, diluted with THF (100 L) and MTBE (150 L), treated with 6N HCl (160 L, 0.960 kg-mol, 1.11 eq), stirred at 10°C for 19 h, and diluted with water (100 L). The lower aqueous layer was separated and extracted with MTBE (160 L). The organic phase was vacuum concentrated to a volume of 150 L, treated with water (240 L), and steam distilled to a final volume of 150 L. The lower aqueous layer in the receiver was separated. The upper phase was identified as the above-titled compound (52.3 wt% pure) by GC. Weight: 109.2 kg (57.11 kg, 0.5092 kg-mol, 58.9%).

EXAMPLE 38-45. Preparation of (*S*,*S*)-3,4-dimethyl-cyclopentanone

[0125] Table 4 lists yields (mol%) of (*S*,*S*)-3,4-dimethyl-cyclopentanone as a function of the temperature at which LHMDS is added to a mixture of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane and FAMSO. Examples 38-40 were carried out using the general procedure of Example 37; Examples 41-45 were carried out using the general procedure of Example 4.

TABLE 4. Yield of (*S*,*S*)-3,4-dimethyl-cyclopentanone as a function of LHMDS addition temperature

Example	Ditosylate, kg	Temperature of LHMDS addition, °C	Yield, mole%
37	369	-3	58.9
38	46.5	-1	46.7

Example	Ditosylate, kg	Temperature of LHMDS addition, °C	Yield, mole%
39	103	-3	71.3
40	100	-3	74.3
41	300	12 to 25	94
42	230	12 to 25	95
43	300	12 to 25	94.8
44	300	12 to 25	94.7
45	300	12 to 25	95.6

EXAMPLE 46. Preparation of (*S*,*S*)-3,4-dimethyl-hexanedioic acid

[0126] To a reactor was charged (*S*,*S*)-4,5-dimethylcyclohexene (52.204 kg, 473.7 mol), (*n*-octyl)$_3$MeNH$_4^+$·HSO4$^-$ (2.231 kg, 4.790 mol, 0.0101 eq), $Na_2WO_4 \cdot 2H_2O$ (1.586 kg, 4.808 mol, 0.0102 eq), and H_2O (21.5 L). The mixture was degassed with nitrogen, heated to 88.5°C, and treated with 30% aqueous H_2O_2 (240.35 kg, containing 72.105 kg or 2.120 kmol H_2O_2, 4.48 eq) over about 16 h. The mixture was then stirred at 99°C for 1 h and then cooled to RT. The mixture was extracted with EtOAc (206 L, then 2 x 33 L). A solution of ferrous sulfate heptahydrate (23.6 kg), NaCl (15.5 kg), and 37% HCl (5.97 kg) in H_2O (262 L) was prepared. The combined organic extracts were washed with the ferrous sulfate solution (3 x 100 L), followed by aq NaCl (2 x 80 L). The organic extracts were dried over anhydrous Na_2SO_4 (33.5 kg) and concentrated to give the titled compound as an oil, which was dissolved in MeOH (139 L) to form a red solution. Weight: 69.757 kg (400.4 mol, 84.5%).

EXAMPLE 47. Preparation of (*S*,*S*)-3,4-dimethyl-hexanedioic acid dimethyl ester

[0127] A solution of (*S*,*S*)-3,4-dimethyl-hexanedioic acid (24.18 kg, 138.8 mol) in MeOH (43 L) was diluted with MeOH (111 L), treated with H_2SO_4 (2.22 kg, 22.63 mol, 0.16 eq), and heated at 41°C for 5 h. The mixture was concentrated, diluted with water (156 L), extracted with toluene (3 x 87 L), and concentrated to give the titled compound, which was dissolved in THF (20 L). Weight: 26.11 kg (129.1 mol, 93.0%).

EXAMPLE 48. Preparation of (1*S*/*R*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester

[0128] A solution of (*S*,*S*)-3,4-dimethyl-hexanedioic acid dimethyl ester in THF (48.5 kg, containing 38.5 kg or 190.4 mol. of the ester) was diluted with THF (344 L) and added over 3.5 h to a refluxing (67°C) mixture of *t*-BuOK (28.58 kg, 254.7 mol, 1.34 eq) and THF (762 L). During the addition, some of the THF (198 L) of was distilled off. The mixture was refluxed for 2 h, then cooled to 10-15°C. The pH was adjusted from 12.5 to 2 by addition of 1N HCl (280 L, 280 mol, 1.47 eq). The mixture was extracted with EtOAc (250 L, then 170 L). The combined organic extracts were washed with saturated brine (220 L) and concentrated to give the titled compound as an oily residue. Weight: 33.24 kg (195.3 mol, 102.6% calc'd yield).

EXAMPLE 49. Preparation of (*S*,*S*)-3,4-dimethyl-cyclopentanone

[0129] A solution of (1*S*/*R*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester (63.84 kg, 375.1 mol) and H_2O (11.5 L) in DMSO (175 L) was heated to 120-140°C and kept at that temperature for 5 h. The mixture was cooled to 5-15°C and added to a solution of NaCl (55.87 kg) in H_2O (800 L). The mixture was extracted with MTBE (4 x 196 L). The extracts were concentrated and distilled under vacuum (bp 43-57°C/5-12 mm Hg) to give the titled compound as a clear, colorless liquid which was identified by NMR and GC retention time comparison with an authentic sample. Weight: 27.41 kg (244.4 mol, 65.1%).

EXAMPLE 50. Preparation of (*S*,*S*)-(3,4-dimethyl-cyclopentylidene)-acetic acid ethyl ester

[0130] A solution of lithium *t*-butoxide (9.02 g, 0.1127 mol, 1.61 eq) in THF (15 mL) was cooled to 10°C and treated with neat triethyl phosphonoacetate (26.84 g, 0.1197 mol, 1.71 eq) at a rate such that the temperature did not exceed 22°C (20 min). (*S*,*S*)-3,4-Dimethyl-cyclopentanone (68.8 g, 0.0701 mol, 1.00 eq) in THF (86 mL) was added by syringe to the phosphonate solution at a rate such that the temperature remained less than 15°C (20 min). The reaction mixture was stirred at 21°C for 16 h.

The reaction mixture was cooled to 5°C and quenched with water (200 mL). The aqueous layer was extracted with heptane (3 x 50 mL). The organic extracts were combined, concentrated to approximately 50 mL, diluted with heptane (120 mL), washed with water (3 x 50 mL), and concentrated to an oil. Because the oil contained water, the mixture was diluted with heptane (100 mL) and distilled to give (*S*,*S*)-(3,4-dimethyl-cyclopentylidene)-acetic acid ethyl ester as a clear, pale yellow oil, which was identified by GC (12.88 g, 0.0668 mol, 95.4%).

EXAMPLE 51. Preparation of (*S*,*S*)-(3,4-dimethyl-cyclopentylidene)-acetic acid ethyl ester directly from (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane

[0131] A 1L 3-neck flask was charged with ditosylate (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (49.3 g, 0.1156 mol), THF (90 mL), and formaldehyde dimethylmercaptal S-oxide (14.0 mL, 17.1 g, 0.1375 mol, 1.19 eq), with a THF (12 mL) rinse. The mixture was cooled to 18°C. The resulting thin slurry was treated dropwise with a solution of lithium bis(trimethylsilyl)amide in THF (205 mL of 1.28 M solution, 0.2624 mol, 2.27 eq) over 3.5 hours. Stirring was continued for another 18 h. The reaction mixture was quenched with water (10 mL). The greenish solution was diluted with brine (110 mL) and water (56 mL). The lower aqueous layer was separated. The upper organic layer was shaken with brine (50 mL) and water (10 mL). The two aqueous layers were combined, diluted with water (100 mL), and extracted with methylene chloride (125 mL). The organic phases were combined and concentrated to a final volume of about 100 mL, then diluted with water (25 mL). The reaction mixture (40°C) was treated over about a 15 min period with 37% hydrochloric acid (35 mL, 42 g, 0.426 mol HCl). The reaction mixture was diluted with water (100 mL) and vacuum distilled to give a two-phase distillate. The lower aqueous layer (85 mL) was extracted with MTBE (20 mL), and the resulting aqueous phase was combined with the upper organic layer (95 mL). The combined organic layers were analyzed by ESTD GC and were found to contain (*S*,*S*)-3,4-dimethyl-cyclopentanone (0.876 M, 0.09724 mol, 84.1 chem%), CH_2Cl_2 (1.44 area%), Me_3SiOH (12.70 area%), THF (28.96 area%), $(Me_3Si)_2O$ (34.23 area%), MeSSMe (4.58 area%), and water (1.185 wt% by KF).

[0132] The cyclopentanone solution was stirred over anhydrous potassium carbonate (calcined fine powder, 4 g) for 2 h, at which time the mixture was determined to be dry by KF assay (0.14 eq water). The supernatant was decanted (68 mL) and the potassium carbonate filtered. The cake was washed with THF (2 x 3 mL) and the washings combined with the supernatant. A solution of solid lithium *t*-butoxide (9.0243 g, 0.1127 mol, 1.61 eq) in THF (15 mL) was cooled to 10°C and treated with neat triethyl phosphonoacetate (26.8431 g, 0.1197 mol, 1.71 eq) at a rate such that the temperature did not exceed 22°C (20 min). The ketone solution was added by syringe to the phosphonate solution at a rate such that the temperature remained less than 15°C (20 min). The reaction mixture was stirred at 21°C for 16 h. The reaction mixture was cooled to 5°C and quenched with water (200 mL). The aqueous layer was extracted with heptane (3 x 50 mL). The organic extracts were combined, concentrated to a volume of about 50 mL, diluted with heptane (120 mL), washed with water (3 x 50 mL), and concentrated under vacuum to an oil containing a drop of water. The mixture was diluted with heptane (100 mL) and distilled atmospherically. The initial fraction of distillate (about 15 mL) contained the drop of water. The solution was concentrated under vacuum to give a clear, pale yellow oil, identified as (*S*,*S*)-(3,4-dimethyl-cyclopentylidene)-acetic acid ethyl ester by GC (12.1802 g, 0.066829 mol, 95.4 chem%).

EXAMPLE 52. Preparation of (3*S*,4*S*)-(3,4-dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester

[0133] A 250 mL round bottom flask was evacuated with nitrogen and charged with cesium carbonate (6.3 g, 0.019 mol, 0.2 eq), dimethyl sulfoxide (87 mL), nitromethane (7.4 mL, 8.4 g, 0.137 mol, 1.4 eq) and (*S*,*S*)-(3,4-dimethyl-cyclopentylidene)-acetic acid ethyl ester (17.6 g, 0.097 mmol, 1.0 eq). The mixture was evacuated with nitrogen and the slurry stirred at 80°C for 10 h under nitrogen. The contents of the reaction vessel were cooled to less than 10°C and the vessel was charged slowly with acetic acid (2.43 g, 0.041, 0.4 eq) in water (183 mL), while maintaining the temperature less than 25°C. MTBE (88 mL) was added and the resulting aqueous and organic layers were separated. The aqueous layer was

extracted with MTBE (1 x 175 mL). The organic layers were combined, washed with water (2 x 260 mL), and concentrated in vacuo to give (3*S*,4*S*)-(3,4-dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester as a light brown oil (24.1g, 94% corrected for GC purity).

EXAMPLE 53. Preparation of (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one via batch hydrogenation

[0134] An aqueous slurry of molybdenum promoted sponge nickel (Johnson Matthey, Type A-7000, 19.53 g slurry, 8.79 g calc'd dry catalyst mass), (3*S*,4*S*)-(3,4-dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester (42.58 g, 41 mL, about 175.0 mmol), and MeOH (261 mL) was charged to a 450-mL glass Parr stirred vessel equipped with a four-bladed self-aspirating gas-dispersing radial impeller. The vessel was sealed, carefully purged with hydrogen and pressurized to about 50 psig with hydrogen. The mixture was stirred at 1150 rpm and heated to about 80°C while maintaining a pressure of about 50 psig in the vessel with hydrogen. After hydrogen uptake had essentially ceased, the reactor temperature was increased to 90°C and its contents stirred for an additional 5 h. After cooling and holding overnight, the product mixture was carefully vacuum filtered and washed with MeOH (65% average yield upon isolation).

EXAMPLE 54. Preparation of (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one via semi-batch hydrogenation

[0135] An aqueous slurry of molybdenum promoted sponge nickel (Johnson Matthey, Type A-7000, 9.82 g slurry occupying 6.0 mL, 4.47 g calc'd dry catalyst mass) and MeOH (100 mL) was charged to a 450-mL glass Parr stirred vessel equipped with a four-bladed self-aspirating gas-dispersing radial impeller. The vessel was sealed, carefully purged with hydrogen and pressurized to about 50 psig with hydrogen. The mixture was heated to a temperature of about 50°C with the agitator stirring at about 1100 rpm. A solution of (3*S*,4*S*)-(3,4-dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester (21.74 g, 21 mL, about 89.35 mmol) in MeOH (21 mL) was then metered into the vessel containing the catalyst suspension using a

Milton Roy piston pump over a 1.8 h period while hydrogen was supplied on demand to maintain a total system pressure of 50 psig. The pumping system was subsequently rinsed with MeOH (2 x 10 mL) into the reactor and the reactor temperature was raised to 90°C and held for 5 h. After cooling and holding overnight, the product mixture was carefully vacuum filtered, washed with MeOH, and the combined filtrate and wash liquids were carried forward for isolation (85% average yield upon isolation).

EXAMPLE 55. Isolation of (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one

[0136] A 1-L four-necked round bottom flask equipped with a mechanical stirrer and marked at the 87 mL level was charged with a methanolic solution of (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one (theory = 17.2 g, 103 mmol). The mixture was concentrated to 87 mL by vacuum distillation. The residue was twice diluted with ethyl acetate (170 mL) and redistilled to 87 mL. The resulting organic solution was extracted first with 1 N HCl (87 mL) and then with 1 N NaOH (87 mL). The aqueous phases were washed in series with ethyl acetate (45 mL). The combined organic phases were charged to a 1-L four necked round bottom flask along with branched octanes (170 mL). The mixture was concentrated to 87 mL by vacuum distillation. The distillate was diluted with branched octanes (170 mL) and again concentrated to 87 mL by vacuum distillation. This dilution/distillation procedure was repeated two more times. The resulting 87 mL solution was cooled to ambient temperature over 1 h during which time crystals formed. The resulting slurry was cooled to about 0°C and stirred for 30 min before vacuum filtration. The recovered crystals were washed with cold branched octanes (3 x 25 mL) and dried under vacuum at 65°C for 1 h to afford (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one (11.6 g, 67%).

EXAMPLE 56. Preparation of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid

[0137] To a 500 mL 4 neck round bottom flask (RBF) equipped with overhead agitation, reflux condenser, and PTFE coated thermocouple, was charged (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one (20.0 g, 0.12 mol, 1.0 eq), HCl (37% w/w, 35.0 g, 0.35 mol, 3.0 eq), and water (20.0 g) under a nitrogen blanket. The mixture was

heated to 90°C and stirred until the reaction was complete (greater than 97% conversion by HPLC, typically within 24 hours). The resulting solution was cooled to a temperature of 50 to 60°C and was extracted with toluene (2 x 30 mL). The toluene washes were discarded. The aqueous phase was adjusted to pH 2.0 with 50% NaOH (approximately 19g, 0.23 mol, 2.0 eq). Activated carbon (4.0g), a filtering agent (4.0g), and water (10g) were added to the flask and the contents stirred for 30 min at 50°C. The slurry was heated to 60°C and was filtered through a course frit and a 0.5 μm PTFE membrane, while maintaining the slurry at a temperature greater than 55°C. The filter cake was rinsed with water (25 mL) that had been heated to a temperature greater than 50°C. The combined aqueous layers were cooled to a temperature less than 40°C and vacuum distilled to a final volume of about 70 mL. The concentrated solution, which contained the product, was adjusted to a pH of 6.5 to 7.5 with 50% NaOH (approximately 8.2g, 0.1 mol, 0.9 eq) to form a precipitate. The mixture was cooled with an ice bath to a temperature less than 5°C. The resulting slurry was stirred at a temperature less than 5°C for 60 min and then filtered to isolate the crude (solid) product. The cake was rinsed while still wet with water (20 g) and then allowed to dry on the filter for 24 to 48 h.

[0138] The crude (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (20 g), and isopropanol/water (125 mL of a 40 wt% *i*-PrOH aq solution) were charged to a 500 mL 4 neck RBF equipped with overhead agitation, reflux condenser, and thermocouple, under a nitrogen blanket. The slurry was heated to reflux (approximately 85°C). The solution was stirred for 15 min and clarified by filtering it through a 0.5 μm PTFE membrane and sintered glass frit (which was heated to 60°C) using nitrogen pressure. An isopropanol/water (20 mL of a 40 wt% *i*-PrOH aq solution) was charged to the flask and heated to reflux. The rinse was transferred through the membrane and frit with nitrogen pressure and combined with the product solution filtrate. The combined filtrates were transferred to a pre-marked (at 102 mL) 500 mL 4 neck RBF equipped with overhead agitation, distillation condenser, and thermocouple, under a nitrogen blanket. The solution was cooled to less than 40°C. The slurry was vacuum distilled at 40 to 50°C to a total volume of 102 mL. The

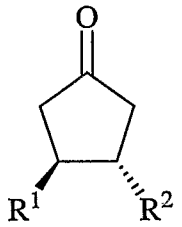
isopropanol content was adjusted to 24 to 27 wt% *i*-PrOH. The slurry was re-heated to reflux (about 87°C) and held until all solids were in solution. The solution was slowly cooled at a rate of 20°C/h to 5°C and was held for 60 min to precipitate the product. The final (solid) product was isolated by vacuum filtration and washed with isopropanol (30 mL, cooled to less than 5°C). The filter cake was dried at 40°C under vacuum for 24 hours to provide (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (21.0 g, 95%).

[0139] It should be noted that, as used in this specification and the appended claims, singular articles such as "a," "an," and "the," may refer to one object or to a plurality of objects unless the context clearly indicates otherwise. Thus, for example, reference to a composition containing "a compound" may include a single compound or two or more compounds.

[0140] It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. The scope of the invention should, therefore, be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.

WHAT IS CLAIMED IS:

1. A method of making a compound of Formula 1,

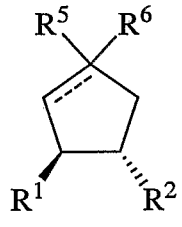


1 ,

or an opposite enantiomer thereof, wherein

R^1 and R^2 are each independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl, wherein aryl may be optionally substituted with from one to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, hydroxy, halogeno, fluoro-C_{1-6} alkyl, and nitro,

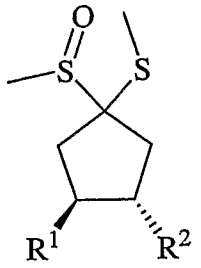
the method comprising hydrolyzing one or more compounds of Formula 13,



13 ,

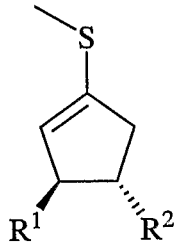
or opposite enantiomers thereof, or salts of the one or more compounds of Formula 13 or opposite enantiomers thereof, wherein R^1 and R^2 in Formula 13 are as defined above for Formula 1, and R^5 and R^6 are independently hydrogen, methylsulfanyl, methylsulfinyl, oxysulfonyl anion, hydroxy or absent, provided that R^5 and R^6 are different.

2. The method of claim 1, wherein the one or more compounds of Formula 13 are selected from a compound of Formula 10,



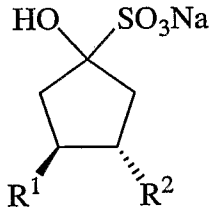
10 ,

or an opposite enantiomer thereof, or from a compound of Formula 11,



11 ,

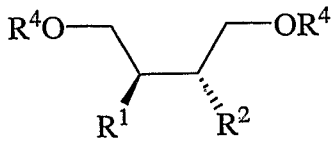
or an opposite enantiomer thereof, or from a compound of Formula 12,



12 ,

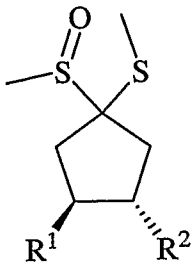
or an opposite enantiomer thereof, or from a mixture of the compound of Formula 10 or the opposite enantiomer thereof and the compound of Formula 11 or the opposite enantiomer thereof, wherein R^1 and R^2 in Formula 10, 11, and 12 are as defined above for Formula 1.

3. The method of claim 1, further comprising reacting a compound of Formula 9,



9 ,

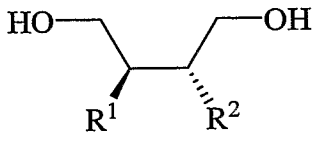
or an opposite enantiomer thereof, with formaldehyde dimethylmercaptal S-oxide (FAMSO) in the presence of a base to give a compound of Formula 10,



10 ,

or an opposite enantiomer thereof, wherein R^1 and R^2 in Formula 9 and Formula 10 are as defined above for Formula 1 and R^4 is C_{1-6} alkylsulfonyl, fluoro-C_{1-6} alkylsulfonyl, or arylsulfonyl.

4. The method of claim 3, further comprising reacting a compound of Formula 5,



5 ,

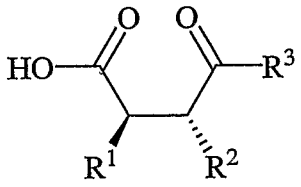
or an opposite enantiomer thereof, with a compound of Formula 8,



8 ,

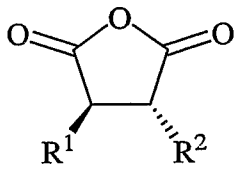
to give the compound of Formula 9 or the opposite enantiomer thereof, wherein R^1 and R^2 in Formula 5 are as defined above for Formula 1, R^4 in Formula 8 is as defined above for Formula 9, and X^2 is a leaving group.

5. The method of claim 4, further comprising reducing a compound of Formula 4,



4 ,

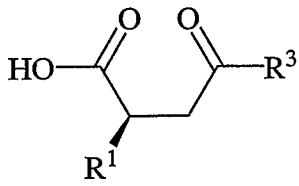
or an opposite enantiomer thereof, or a compound of Formula 7,



7 ,

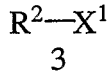
or an opposite enantiomer thereof, to give the compound of Formula 5 or the opposite enantiomer thereof, wherein R^1 and R^2 in Formula 4 and Formula 7 are as defined above for Formula 1, and R^3 in Formula 4 is R^1O- or amino.

6. The method of claim 5, further comprising reacting a compound of Formula 2,



2 ,

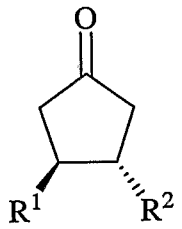
or an opposite enantiomer thereof, with a compound of Formula 3,



3 ,

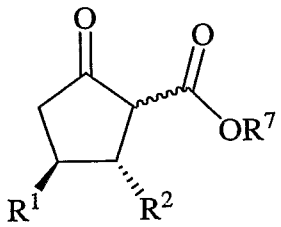
to give the compound of Formula 4 or the opposite enantiomer thereof, wherein R^1 in Formula 2 and R^2 in Formula 3 are as defined above for Formula 1, and R^3 in Formula 2 is as defined above for Formula 4.

7. A method of making a compound of Formula 1,



1 ,

or an opposite enantiomer thereof, the method comprising removing an ester moiety from a compound of Formula 18,

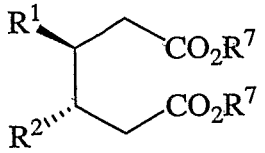


18 ,

or an opposite enantiomer thereof, wherein

R^1, R^2 and R^7 are each independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl, wherein may be optionally substituted with from one to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, hydroxy, halogeno, fluoro-C_{1-6} alkyl, and nitro.

8. The method of claim 7, further comprising treating a compound of Formula 17,

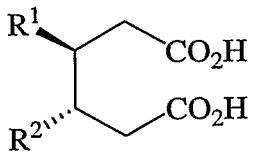


17 ,

or an opposite enantiomer thereof, with a base to give the compound of Formula 18 or the opposite enantiomer thereof, wherein the base is capable of deprotonating a methylene group that is located adjacent to one of the ester moieties of the compound of Formula 17, and R^1, R^2, and R^7 in Formula 17 are as defined for Formula 1 and Formula 18.

9. The method of claim 8, further comprising:

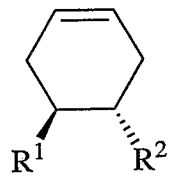
(a) reacting a compound of Formula 16,



16 ,

or an opposite enantiomer thereof, with an alcohol, R^7OH, in the presence of an acid catalyst to give the compound of Formula 17 or the opposite enantiomer thereof; and

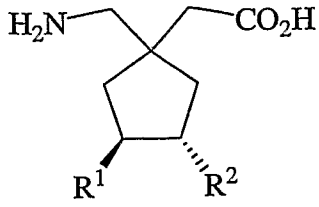
(b) optionally oxidizing a compound of Formula 15,



15 ,

or an opposite enantiomer thereof, to give the compound of Formula 16 or the opposite enantiomer thereof, wherein R^1 and R^2 in Formula 15 and 16 are as defined for Formula 1, and R^7 in the alcohol is as defined for Formula 18.

10. A method of making a compound of Formula 14,



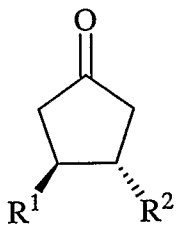
14 ,

or an opposite enantiomer thereof, or a pharmaceutically acceptable salt of the compound of Formula 14 or the opposite enantiomer thereof, wherein

R^1 and R^2 are each independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl, wherein aryl may be optionally substituted with from one to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, hydroxy, halogeno, fluoro-C_{1-6} alkyl, and nitro,

the method comprising:

(a) making a compound of Formula 1,



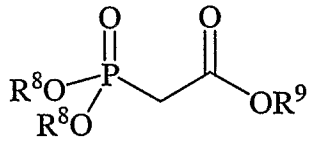
1 ,

or an opposite enantiomer thereof, in accordance with in any of the preceding claims; and

(b) converting the compound of Formula 1 or the opposite enantiomer thereof, to the compound of Formula 14 or the opposite enantiomer thereof, or to the pharmaceutically acceptable salt of the compound of Formula 14 or the opposite enantiomer thereof, wherein R^1 and R^2 in Formula 1 are as defined above for Formula 14.

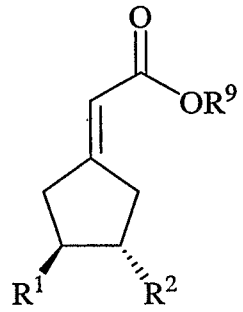
11. The method of claim 10, wherein converting the compound of Formula 1 to the compound of Formula 14 comprises:

(a) reacting the compound of Formula 1 or the opposite enantiomer thereof with a compound of Formula 20,



20 ,

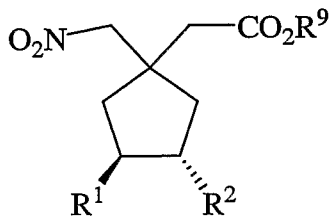
to give a compound of Formula 21,



21 ,

or an opposite enantiomer thereof;

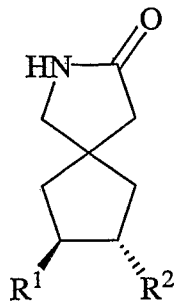
(b) reacting the compound of Formula 21 or the opposite enantiomer thereof with nitromethane to give a compound of Formula 22,



22 ,

or an opposite enantiomer thereof;

(c) reducing a nitro moiety of the compound of Formula 22 or the opposite enantiomer thereof to give a compound of Formula 23,



23 ,

or an opposite enantiomer thereof, wherein the nitro moiety is optionally reduced by semi-batch hydrogenation;

(d) hydrolyzing the compound of Formula 23 or the opposite enantiomer thereof to give the compound of Formula 14 or the opposite enantiomer thereof, or a salt of the compound of Formula 14 or the opposite enantiomer thereof; and

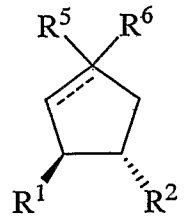
(e) optionally converting the compound of Formula 14 or the opposite enantiomer thereof, or the salt of the compound of Formula 14 or the opposite enantiomer thereof, to a pharmaceutically acceptable salt of the compound of Formula 14 or the opposite enantiomer thereof; wherein

R^1 and R^2 in Formula 21 to 23 are as defined for Formula 14;

R^8 in Formula 20 and R^9 in Formula 20 to 22 are each independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl, wherein aryl may be optionally substituted with from one to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, hydroxy, halogeno, fluoro-C_{1-6} alkyl, and nitro.

12. A method in accordance with any of the preceding claims in which R^1, R^2, and R^7 are each independently selected from C_{1-6} alkyl or from C_{1-3} alkyl or from methyl.

13. A compound of Formula 13,



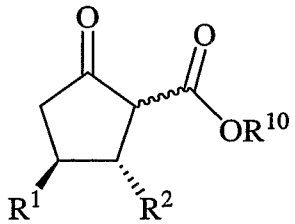
13 ,

or an opposite enantiomer thereof, or a salt of the compound of Formula 13 or the opposite enantiomer thereof, wherein

R^1 and R^2 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl, wherein aryl may be optionally substituted with from one to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, hydroxy, halogeno, fluoro-C_{1-6} alkyl, and nitro; and

R^5 and R^6 are independently hydrogen, methylsulfanyl, methylsulfinyl, oxysulfonyl anion, hydroxy, or absent, provided that R^5 and R^6 are different.

14. A compound of Formula 19,



19 ,

or an opposite enantiomer thereof, or a salt of the compound of Formula 19 or the opposite enantiomer thereof, wherein

R^1 and R^2 and are each independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl; and

R^{10} is selected from hydrogen atom, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, C_{3-6} cycloalkenyl-C_{1-3} alkyl, or aryl-C_{1-3} alkyl;

wherein aryl in each of the foregoing aryl-C_{1-3} alkyl groups may be optionally substituted with from one to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, hydroxy, halogeno, fluoro-C_{1-6} alkyl, and nitro.

15. A compound selected from:

(3*S*,4*S*)-1-methanesulfinyl-3,4-dimethyl-1-methylsulfanyl-cyclopentane;

(3*R*,4*S*)-3,4-dimethyl-1-methylsulfanyl-cyclopentene;

(3*S*,4*S*)-1-hydroxy-3,4-dimethyl-cyclopentanesulfonate sodium salt;

(2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester;

(1*S*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester;

(1*R*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester;

(2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid;

(1*S*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid;

(1*R*,2*R*,3*S*)-2,3-dimethyl-5-oxo-cyclopentanecarboxylic acid;

(*S*,*S*)-3,4-dimethyl-hexanedioic acid;

(*S*,*S*)-3,4-diethyl-hexanedioic acid;

(*S*,*S*)-3,4-dipropyl-hexanedioic acid;

(*R*,*R*)-3,4-diisopropyl-hexanedioic acid; and

(*S*,*S*)-3,4-dibenzyl-hexanedioic acid; and

opposite enantiomers of the foregoing compounds; and

salts of the foregoing compounds and opposite enantiomers thereof.