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(54) **Title:** PREPARATION OF OPTICALLY-ACTIVE CYCLIC AMINO ACIDS

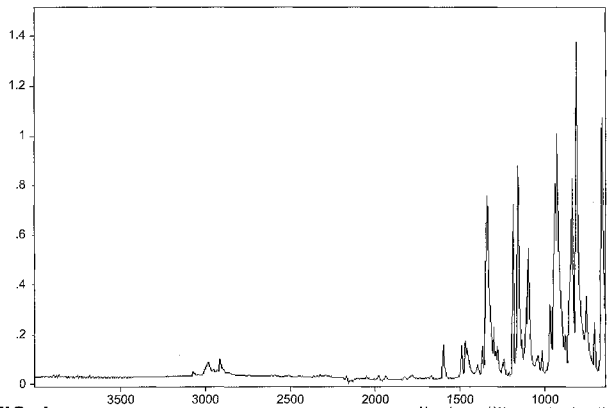
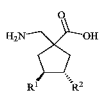


FIG. 1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(57) **Abstract:** Methods and materials for preparing an optically active compound of Formula (1), or a pharmaceutically acceptable salt thereof, or an opposite enantiomer of the compound of Formula (1) or pharmaceutically acceptable salt thereof, are disclosed. The method includes reducing a cyano moiety of a compound of Formula (5), or an opposite enantiomer thereof, or a salt of the compound of Formula (5) or opposite enantiomer thereof, to an amino moiety, wherein R^1, R^2, and R^5 are defined in the specification.

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PREPARATION OF OPTICALLY-ACTIVE CYCLIC AMINO ACIDS

FIELD OF INVENTION

This invention relates to materials and methods for preparing chiral cyclic amino acids which are useful for treating pain and a variety of psychiatric and sleep disorders.

BACKGROUND OF THE INVENTION

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.

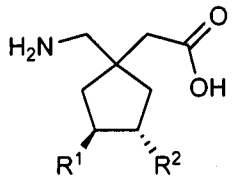
The '673 patent describes a number of methods for preparing the optically-active cyclic amino acids. Many of these methods employ, as intermediates or starting materials, chiral 3,4-disubstituted cyclopentanones, including (*S*,*S*)-3,4-dimethyl-cyclopentanone. Although methods for preparing cyclopentanones are known, many of these processes may be problematic for commercial-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. Furthermore, numerous steps may be needed to convert the chiral cyclopentanones into the desired optically-active cyclic amino acids. Thus, improved methods for preparing chiral cyclic amino acids would be desirable.

SUMMARY OF THE INVENTION

This invention provides a comparatively efficient and cost-effective method for preparing optically active cyclic amino acids (Formula 1, below)

from commercially available starting materials. For example, (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid may be prepared from (2*R*,3*R*)-1,4-dibromo-2,3-dimethyl-butane or (2*R*,3*R*)-2,3-dimethyl-butan-1,4-diyl-ditosylate in three or four steps.

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



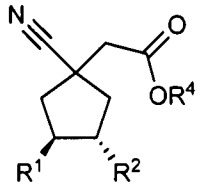
1

or a pharmaceutically acceptable salt thereof, or an opposite enantiomer of the compound of Formula 1 or pharmaceutically acceptable salt 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) reducing a cyano moiety of a compound of Formula 5,

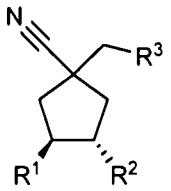


5

or an opposite enantiomer thereof, or a salt of the compound of Formula 5 or opposite enantiomer thereof, to an amino moiety, wherein R^1 and R^2 in Formula 5 are as defined above for Formula 1, and R^4 is selected from hydrogen atom and C_{1-6} alkyl; and

(b) optionally converting the compound of Formula 1 or the opposite enantiomer thereof to a pharmaceutically acceptable salt of the compound of Formula 1 or the opposite enantiomer thereof.

Another aspect of the present invention provides a compound of Formula 4,



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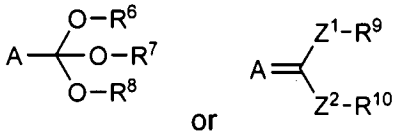
or an opposite enantiomer thereof, wherein and are defined above for Formula 1, and

R^3 is a carboxylic acid or ester protective group having a structure represented by



7 or 8

in which "A" in Formula 7 and Formula 8 represents a point of attachment to the remainder of the compound of Formula 4;

R^6, R^7, and R^8 are each independently a C_{1-6} alkyl, or together with the atoms to which they are attached, form a bicyclic heterocycle having only oxygen and carbon ring members;

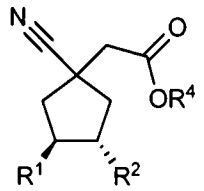
Z^1 and Z^2 are each independently selected from O and S;

R^9 is C_{1-6} alkyl;

R^{10} is selected from C_{1-6} alkyl, silyl, and C_{1-6} alkylsilyl;

or R^9 and R^{10}, together with the atoms to which they are attached, form a monocyclic heterocycle having only carbon and oxygen ring members, only carbon and sulfur ring members, or only carbon, oxygen, and sulfur ring members.

Another aspect of the present invention provides a compound of Formula 5,



5

or an opposite enantiomer thereof, or a salt of the compound of Formula 5 or an opposite enantiomer thereof, wherein R^1 and R^2 are as defined above for Formula 1; and

R^4 is selected from H, C_{1-6} alkyl, aryl-C_{1-3} alkyl, a Group 1 metal ion, a Group 2 metal ion, a primary ammonium ion, or a secondary ammonium ion;

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.

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

DESCRIPTION OF DRAWINGS

The FT-IR spectrum of Form A (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 1 (full spectrum) and FIG. 2 (fingerprint region).

The FT-Raman spectrum of Form A (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 3 (full spectrum) and FIG. 4 (fingerprint region).

The FT-IR spectrum of Form B (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 5 (full spectrum) and FIG. 6 (fingerprint region).

The FT-Raman spectrum of Form B (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 7 (full spectrum) and FIG. 8 (fingerprint region).

The Powder X-ray Diffraction (PXRD) pattern (full scale) of Form A (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 9.

The PXRD pattern (to 30,000 cps) of Form A (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 10.

The PXRD pattern (full scale) of Form B (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 11.

The PXRD pattern (to 30,000 cps) of Form B (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 12.

The Differential Scanning Calorimetry (DSC) thermogram of Form A (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 13.

The DSC thermogram of Form B (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane is shown in FIG. 14.

DETAILED DESCRIPTION

Definitions and Abbreviations

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.

"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.

"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.

"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.

"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.

"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.

"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.

"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.

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

"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.

"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.

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.

"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.

"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.

"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.

"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.

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

"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.

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.

"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.

"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.

"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.

"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.

"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.

"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%.

"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.

"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.

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.

"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.

"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.

"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).

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

"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.

"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.

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

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

Abbreviation	Description
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
EtOAc	ethyl acetate
FAMSO	formaldehyde dimethylmercaptal S-oxide
Fmoc	9-fluoroenylmethoxycarbonyl
h, min, s	hour(s), minute(s), second(s)

Abbreviation	Description
HOAc	acetic acid
KF	Karl Fischer
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride (LiAlH4)
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LICA	lithium *N*-isopropyl-*N*-cyclohexyl amide
LTMP	2,2,6,6-tetramethylpiperidine
Me	methyl
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
TEA	triethanolamine
Tf	triflyl or trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Abbreviation	Description
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tr	trityl or triphenylmethyl
Ts	tosyl or *p*-toluenesulfonyl

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).

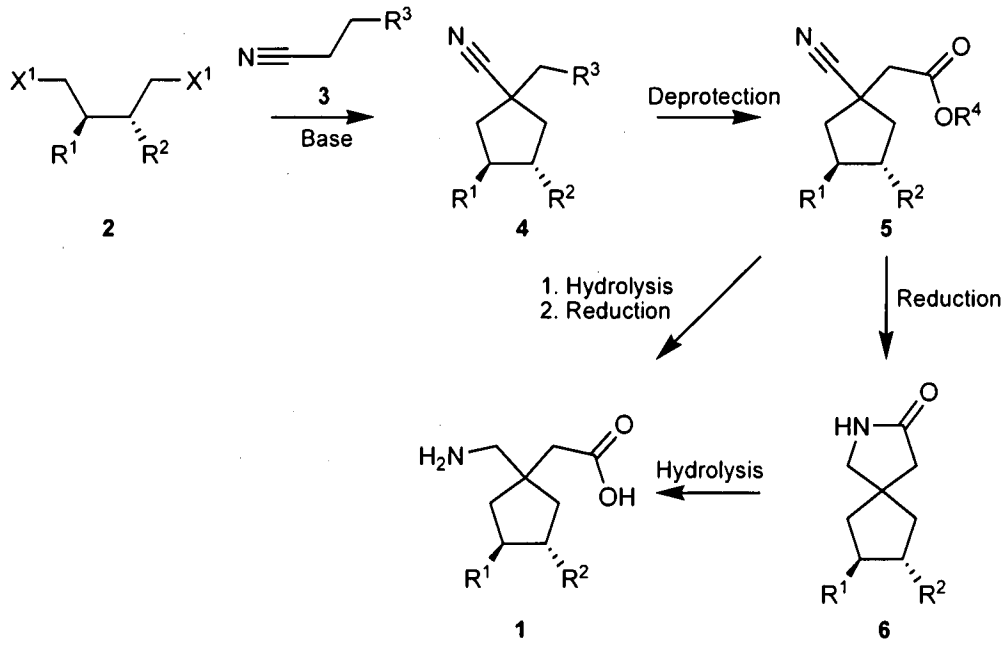
In some of the reaction schemes and examples below, certain compounds can be prepared using protective groups, which prevent undesirable chemical reaction at otherwise reactive sites. Protective groups may also be used to enhance solubility or otherwise modify physical properties of a compound. For a discussion of protective group strategies, a description of materials and methods for installing and removing protective groups, and a compilation of useful protective groups for common functional groups, including amines, carboxylic acids, alcohols, ketones, and aldehydes, see T. W. Greene and P. G. Wuts, *Protective Groups in Organic Chemistry* (1999) and P. Kocienski, *Protective Groups* (2000).

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 temperatures (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, CH_2Cl_2, $CHCl_3$, CCl_4); or some combination of these. Any reference in the disclosure to a range, including a concentration range, a temperature range, or a pH range, includes the indicated endpoints.

This disclosure concerns materials and methods for preparing optically active cyclic amino acids of Formula 1, their opposite enantiomers, and pharmaceutically acceptable complexes, salts, solvates, and hydrates of the compounds of Formula 1 and their opposite enantiomers. 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, phenyl-ethyl, and phenyl-propyl. Representative compounds of Formula 1 thus 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, their opposite enantiomers, and pharmaceutically acceptable complexes, salts, solvates, and hydrates of the foregoing compounds.

GENERAL REACTION SCHEMES

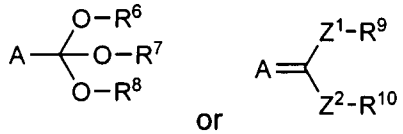
Scheme I



Scheme I shows a method for preparing compounds of Formula 1 and their opposite enantiomers. The method includes reacting a chiral 1,4-bis-electrophile (Formula 2) with a protected (masked) carboxylic acid (Formula 3) to give an optically active cyclopentanecarbonitrile (Formula 4). Deprotection (unmasking) of the carboxy moiety yields a 1-carboxyl-cyclopentanecarbonitrile or a salt or ester (Formula 5) thereof. Reduction of the nitrile ester (Formula 5, $R^4 \neq H$ or $R^4 \neq$ a cation, M^1) gives an amine that cyclizes to furnish a lactam (Formula 6), which upon hydrolysis, yields the desired cyclic amino acid (Formula 1). Alternatively, hydrolysis of the nitrile ester (if necessary), followed by reduction of the acid or its salt (Formula 5, $R^4 = H$ or M^1), gives the cyclic amino acid (Formula 1).

Substituents R^1 and R^2 in Formula 2 and Formula 4-6 are as defined above for Formula 1; R^4 in Formula 5 is H, C_{1-6} alkyl, aryl-C_{1-3} alkyl, or cation, M^1 (e.g., a Group 1 metal ion, a Group 2 metal ion, a primary ammonium ion,

or a secondary ammonium ion); and X^1 in Formula 2 is a leaving group, such as halogeno (e.g., Cl, Br, I) or R^5O-, where R^5 is C_{1-6} alkylsulfonyl (e.g., mesyl), a fluoro-C_{1-6} alkylsulfonyl (e.g., triflyl), or an arylsulfonyl (e.g., tosyl, brosyl, closyl, or nosyl). Substituent R^3 in Formula 2 and Formula 3 is a protective group for a carboxylic acid or ester. Useful R^3 include carboxylic acid or ester protective groups having a structure represented by



7 or 8 ,

in which "A" represents a point of attachment to the remainder of the compound of Formula 3 or 4. In Formula 7, R^6, R^7, and R^8 are each independently a C_{1-6} alkyl, or together with the atoms to which they are attached, form a bicyclic heterocycle having only oxygen and carbon ring members. In Formula 8, Z^1 and Z^2 are each independently selected from O and S; R^9 is C_{1-6} alkyl; R^{10} is selected from C_{1-6} alkyl, silyl, and C_{1-6} alkylsilyl; or R^9 and R^{10}, together with the atoms to which they are attached, form a monocyclic heterocycle having only carbon and oxygen ring members, only carbon and sulfur ring members, or only carbon, oxygen, and sulfur ring members. Useful R^3 include C_{1-3} alkyl orthoesters, orthobicyclooctyl esters, and 1,1-bis-C_{1-3} alkylsulfanyl-methan-1-ylidenes.

Representative R^1 and R^2 in Formula 2 and Formula 4-6 include C_{1-3} alkyl and aryl-C_{1-3} alkyl; representative X^1 in Formula 2 include Br and tosylate; representative R^3 in Formula 3 and Formula 4 include orthoesters, such as 4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl, and tri-C_{1-3} alkoxy esters, such as trimethoxy-methan-1-yl, triethoxy-methan-1-yl, and the like; and representative R^4 in Formula 5 include H, Me, Et, Pr, *i*-Pr, Bn, Li^+, Na^+, and K^+. Useful chiral 1,4-bis-electrophiles (Formula 2) thus include (*R*,*R*)-1,4-dibromo-2,3-dimethyl-butane, (*R*,*R*)-3,4-bis-bromomethyl-hexane, (*R*,*R*)-4,5-bis-bromomethyl-octane, (*R*,*R*)-1,4-dibromo-2,3-dibenzyl-butane, (*R*,*R*)-1,4-di-

p-toluenesulfonyloxy-2,3-dimethyl-butane, (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-diethyl-butane, (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dipropyl-butane, (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dibenzyl-butane, and opposite enantiomers thereof.

Representative masked carboxylic acids (Formula 3) include 3-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-propionitrile, 4,4,4-trimethoxy-butyronitrile, and 4,4,4-triethoxy-butyronitrile. Representative optically active cyclopentanecarbonitriles (Formula 4) include (*S*,*S*)-3,4-dimethyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dimethyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dimethyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-diethyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-diethyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-diethyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dipropyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dipropyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dipropyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dibenzyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dibenzyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile, (*S*,*S*)-3,4-dibenzyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile, and opposite enantiomers thereof.

Representative compounds of Formula 5 include (3*S*,4*S*)-(3,4-dimethyl-1-cyano-cyclopentyl)-acetic acid, (3*S*,4*S*)-(3,4-diethyl-1-cyano-cyclopentyl)-acetic acid, (3*S*,4*S*)-(3,4-dipropyl-1-cyano-cyclopentyl)-acetic acid, and (3*S*,4*S*)-(3,4-dibenzyl-1-cyano-cyclopentyl)-acetic acid; lithium, sodium, and potassium salts of the foregoing acids; methyl, ethyl, propyl, isopropyl, and benzyl esters of the foregoing acids; and opposite enantiomers of the aforementioned acids, salts, and esters.

Representative lactams (Formula 6) 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.

As noted above, the method described in Scheme I includes reacting a chiral 1,4-bis-electrophile (Formula 2) with a protected (masked) carboxylic acid (Formula 3) to give an optically active cyclopentanecarbonitrile (Formula 4); deprotection (unmasking) of the carboxy moiety yields a 1-carboxymethyl-cyclopentanecarbonitrile or a salt or ester (Formula 5) thereof. The cyclopentanecarbonitrile (Formula 4) is typically prepared in a polar aprotic solvent (e.g., THF) under basic conditions, and at a temperature in the range of from about -30°C to about RT or from about -20°C to about 5°C. Useful bases include hindered, non-nucleophilic bases such as LiHMDS, LDA, and lithium diethylamide.

The masked carboxylic acid (Formula 3) may be prepared using processes adapted from the literature. For example, 3-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-propionitrile may be prepared by reacting succinonitrile with MeOH and HCl in CH_2CH_2/MTBE at about 7-18°C for about 1.5 h and then at about 9°C for about 20 h to give methyl 3-cyanopropanimidate chloride. The imidate is reacted with 2-(hydroxymethyl)-2-methylpropane-1,3-diol in THF at about 40°C for about 15 h to give the orthobicyclooctyl ester. See E.J. Corey & K. Shimoji, *J. Am. Chem. Soc.* 105:1662 (1983). Similarly, 4,4,4-trimethoxy-butyronitrile may be prepared by methanolysis of methyl 3-cyanopropanimidate chloride using conditions described in the literature. See S.M. McElvain & J.P. Schroeder, *J. Am. Chem. Soc.* 71:40 (1949).

As shown in Scheme I, deprotection (unmasking) of the carboxy moiety in the compound of Formula 4 yields a 1-carboxymethyl-cyclopentanecarbonitrile or a salt or ester (Formula 5) thereof. Although reaction conditions will depend on the choice of protective group (R^3), deprotection is generally carried out via acid hydrolysis. For example, moderately acidic conditions (e.g., pH of about 3 or less) via contact with an aqueous acid (e.g., 6N HCl, 5% citric acid, 42% H_3PO_4, or 50% HOAc) at RT for about 5 h are sufficient to deprotect orthoesters (e.g., 4-methyl-2,6,7-

trioxa-bicyclo[2.2.2]octan-1-yl, trimethoxy-methan-1-yl, triethoxy-methan-1-yl) and 1,1-bis-C_{1-3} alkylsulfanyl-methan-1-ylidenes (e.g., 1,3-dithiolan-2-ylidene).

According to Scheme I, the cyanoester (Formula 5, R4 ≠ H or ≠ M) is reduced and cyclized *in situ* by treatment with a reducing agent to furnish the lactam (Formula 6). The reaction is typically performed in an alcoholic solvent, such as MeOH, EtOH, 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 nickel catalysts. The reaction can be run in a conventional "batch mode" in which the catalyst and substantially all of the substrate (Formula 5) 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 cyanoester (Formula 5) 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 nitrile group.

The lactam (Formula 6) shown in Scheme I 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 1) 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.

As noted above, the cyanoester (Formula 5) may be hydrolyzed and the resulting acid or acid salt may be reduced to give the compound of Formula 1. The cyanoester (Formula 5) may be hydrolyzed by treatment with an acid or a base or by treatment with a base (or acid) followed by treatment with an acid (or base). For example, treating the cyanoester (Formula 5) with HCl, H_2SO_4, and the like with excess H_2O generates the acid, which may be treated with a base (e.g., KOH) to give a base addition salt. Treating the

cyanoester (Formula 5) with an aqueous inorganic base, such as LiOH, KOH, NaOH, CsOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, and the like, in an optional polar solvent (e.g., THF, MeOH, EtOH, acetone, ACN, etc.) gives a base addition salt, which may be treated with an acid to generate the free acid. The ester hydrolysis may be carried out at RT or at temperatures up to reflux temperature. The resulting free acid or base addition salt is subsequently reduced via treatment with a reducing agent, e.g., contact with H_2 under conditions described above for preparation of the lactam (Formula 6) from the cyanoester (Formula 6).

As noted above, one of the useful chiral 1,4-bis-electrophiles of Formula 2 is (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane. Two crystalline forms (Form A and Form B) of this compound have been isolated and characterized by FT-IR, FT-Raman, PXRD and DSC.

FT-IR spectra of Form A and Form B were acquired using a ThermoNicolet Avatar 360 FT-IR spectrometer equipped with a Smart Golden Gate™ single reflection ATR accessory (diamond ATR crystal with zinc selenide optics) and d-TGS KBr detector. The spectrum was collected at $2cm^{-1}$ resolution and a co-addition of 128 scans. Happ-Genzel apodization was used. Because the FT-IR spectrum was recorded using single reflection ATR, no sample preparation was required. Using ATR FT-IR will cause the relative intensities of infrared bands to differ from those seen in an absorbance FT-IR spectrum using KBr disc or nujol mull sample preparations. Due to the nature of ATR FT-IR, the bands at lower wavenumber are more intense than those at higher wavenumber. Experimental error, unless otherwise noted, was ± 2 cm^{-1}. Peaks were picked using ThermoNicolet Omnic 6.1a software. Intensity assignments are relative to the major band in the spectrum (i.e., they are not based on absolute values measured from the baseline). When assessing split peaks, the intensity value was taken from the baseline but again the intensity was assigned relative to the strongest band in the spectrum.

The FT-Raman spectra of Form A and Form B were collected using a Bruker Vertex70 FT-IR spectrometer with a RamII FT-Raman module equipped with a 1064 nm NdYAG laser and LN-Germanium detector. All spectra were recorded using 2 cm^{-1} resolution and Blackman-Harris 4-term apodization, 350 mW laser power and 2048 scans. Each sample was measured directly from its glass vial and exposed to the laser radiation. The data are presented as intensity and as a function of Raman shift. Experimental error, unless otherwise noted, was ± 2 cm^{-1}. Peaks were picked using ThermoNicolet Omnic 6.1a software. Intensity assignments are relative to the major band in the spectrum (i.e., they are not based on absolute values measured from the baseline). When assessing split peaks, the intensity value was taken from the baseline but again the intensity was assigned relative to the strongest band in the spectrum.

The powder X-ray diffraction pattern was determined using a Bruker-AXS Ltd. D4 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slit, and a PSD Vantec-1 detector. The sample was prepared for analysis by mounting on a low background silicon wafer (with cavity) specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha1 X-rays (wavelength = 1.5406 Å) with the X-ray tube operated at 40kV/35mA. The analyses were performed with the goniometer running in continuous mode set for a 0.2 second count per 0.018° step over a two theta range of 2° to 50°. The peaks obtained were aligned against a silicon reference standard. The peaks were selected using Bruker-AXS Ltd. Evaluation software with a threshold of 1 and a peak width of 0.3° two theta. The data were collected at 21°C. Experimental error, unless otherwise noted, was ± 0.1 degrees 2Θ.

As will be appreciated by the skilled person, the relative intensities of the various peaks within Table 2 and 3 given below may vary due to a number of factors such as for example orientation effects of crystals in the X-ray beam or the purity of the material being analyzed or the degree of crystallinity of the

sample. The peak positions may also shift for variations in sample height but the peak positions will remain substantially as defined in the given table.

The skilled person will also appreciate that measurements using a different wavelength will result in different shifts according to the Bragg equation - $n\lambda = 2d \sin\theta$.

Such further PXRD patterns generated by use of alternative wavelengths are considered to be alternative representations of the PXRD patterns of the crystalline materials of the present invention and as such are within the scope of the present invention.

To obtain DSC thermograms, a sample of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane was heated from 20 to 150°C at 10°C per minute using a TA Instruments Q1000 DSC in aluminum pans with lids, with a nitrogen purge gas.

Form A of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane has an FT-IR spectrum with absorption band frequencies at 932, 844, 756, and 1160 cm^{-1}.

Form B of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane has an FT-IR spectrum with absorption band frequencies at 956, 1170, 832, and 1256 cm^{-1}.

Form A of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane has an FT-Raman spectrum with Raman band frequencies at 1163, 233, 800, and 165 cm^{-1}.

Form B of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane has an FT-Raman spectrum with Raman band frequencies at 1174, 1007, 740, 108, and 794 cm^{-1}.

Form A of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane has powder x-ray diffraction peaks at 6.5, 13.1, and 21.9 degrees 2Θ.

Form B of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane has powder x-ray diffraction peaks at 14.5, 25.1, and 26.0 degrees 2Θ.

The FT-IR spectrum of Form A, shown in FIG. 1 and FIG. 2, has absorption bands at the following wavenumbers (in cm^{-1}; w: weak, m:

medium, s: strong): 3070 w, 2979 w, 2911 w, 1597 w, 1492 w, 1468 w, 1394 w, 1374 w, 1369 w, 1345 s, 1303 w, 1293 w, 1282 w, 1242 w, 1212 w, 1188 s, 1160 s, 1135 w, 1111 w, 1097 m, 1040 w, 1018 w, 971 w, 945 s, 932 s, 881 w, 857 m, 852 m, 844 s, 817 s, 756 m, 710 w, and 669 s.

The FT-Raman spectrum of Form A, shown in FIG. 3 and FIG. 4, has Raman bands at the following Raman shift (in cm-1; w: weak, m: medium, s: strong, vs: very strong): 3191 w, 3145 w, 3070 vs, 3061 s, 3041 w, 3011 w, 2996 m, 2982 m, 2948 m, 2926 s, 2909 s, 2886 vs, 2849 w, 2789 w, 2762 w, 2746 w, 2731 w, 2585 w, 1598 s, 1575 w, 1499 w, 1473 m, 1417 w, 1384 w, 1371 w, 1352 m, 1341 w, 1304 w, 1293 w, 1284 w, 1250 w, 1212 w, 1190 s, 1163 vs, 1137 w, 1117 w, 1101 m, 1042 w, 1019 w, 965 w, 950 w, 942 w, 934 w, 882 w, 859 w, 848 w, 822 w, 800 s, 757 m, 712 w, 672 w, 638 s, 621 w, 610 w, 556 w, 504 w, 495 w, 471 w, 418 w, 396 m, 372 w, 351 w, 334 w, 292 s, 233 m, 221 m, 191 w, 165 s, 123 vs, 91 vs, 80 s, 72 vs, and 54 s.

The FT-IR spectrum of Form B, shown in FIG. 5 and FIG. 6, has absorption bands at the following wavenumbers (in cm^{-1}; w: weak, m: medium, s: strong): 3055 w, 2976 w, 2961 w, 2919 w, 2888 w, 1598 w, 1495 w, 1473 w, 1449w, 1404 w, 1388 w, 1355 s, 1344 s, 1309 m, 1294 m, 1256 w, 1244 w, 1212 w, 1189 m, 1170 s, 1123 w, 1096 m, 1042 w, 1018 m, 1007 m, 965 s, 956 s, 922 s, 857 w, 832 s, 812 s, 791 s, 705 m, 668 s, and 663 s.

The FT-Raman spectrum of Form B, shown in FIG. 7 and FIG. 8, has Raman bands at the following Raman shift (in cm-1; w: weak, m: medium, s: strong, vs: very strong): 3191 w, 3148 w, 3073 vs, 3056 m, 3040 m, 3033 m, 2996 s, 2986 s, 2967 s, 2958 s, 2929 s, 2918 s, 2887 m, 2848 w, 2760 w, 2718 w, 2591 w, 1598 s, 1577 w,1496 w, 1473 m, 1468 m, 1456 w, 1407 w, 1381 w, 1356 w, 1310 w, 1295 w, 1263 w, 1255 w,1212 w, 1190 m, 1174 vs, 1149 w, 1098 s, 1007 m, 976 w, 948 w, 924 w, 899 w, 856 w, 846 w, 832 w, 816 m, 794 vs, 740 m, 707 w, 670 w, 665 m, 635 s, 585 m, 574 m, 562 w, 556 m, 530 w, 509 m, 480 m, 420 m, 407 m, 375 m, 365 m, 342 m, 317 s, 293 vs, 266 m, 244 m, 213 m, 176 m, 108 vs, 89 vs, and 77 vs.

As a result of preferred orientation effects most PXRD peaks are below 10% in intensity. The twenty most intense PXRD peaks of Form A, from the pattern shown in FIG. 9 (full scale) and FIG. 10 (to 30,000 cps), are listed below in Table 2.

Table 2: PXRD peaks for Form A of (*R,R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane

Angle 2Θ (degrees)	Relative Intensity (%)	Angle 2Θ (degrees)	Relative Intensity (%)
6.5	10.6	23.5	1.4
13.1	100.0	24.5	1.3
14.8	2.3	26.3	1.7
15.2	0.8	27.4	1.4
16.6	0.9	28.5	1.1
19.7	2.1	28.6	1.0
20.5	1.4	33.1	1.6
20.7	1.4	39.2	1.0
21.9	12.6	42.2	1.0
23.1	5.3	43.5	1.0

The twenty most intense PXRD peaks of Form B, from the pattern shown in FIG. 11 (full scale) and FIG. 12 (to 30,000 cps), are listed below in Table 3.

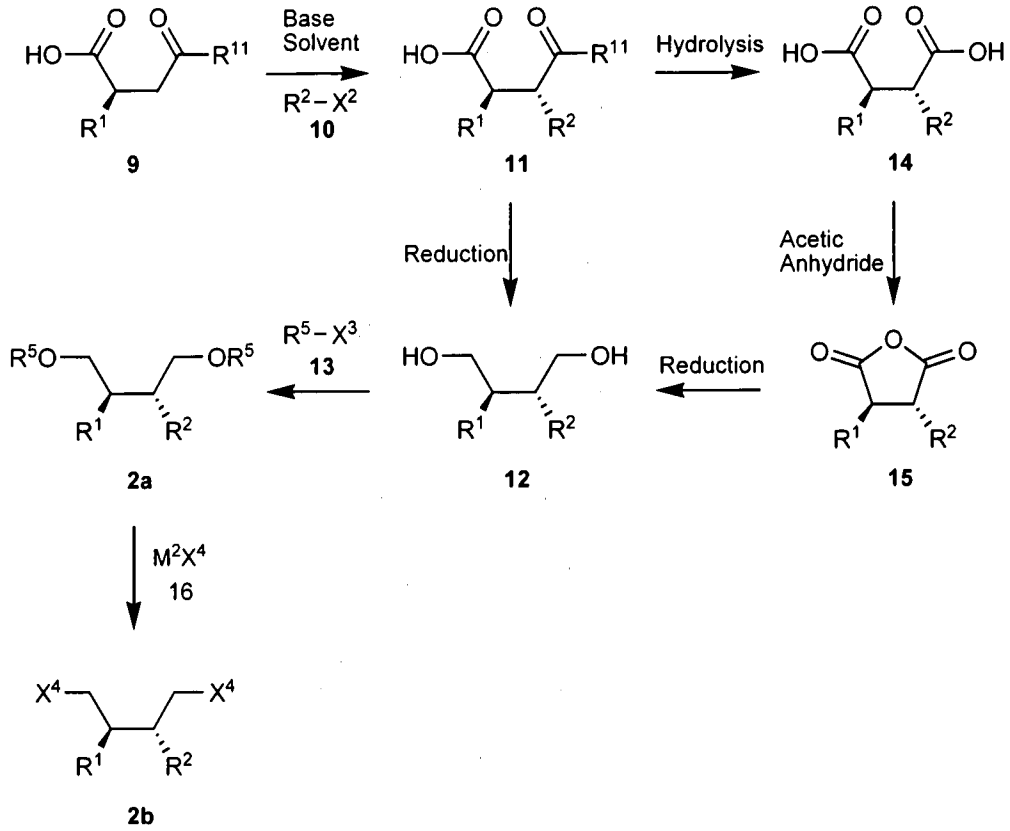
Table 3: PXRD peaks for Form B of (*R,R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane

Angle 2Θ (degrees)	Relative Intensity (%)	Angle 2Θ (degrees)	Relative Intensity (%)
13.3	34.3	25.1	13.6
14.1	5.5	26.0	13.1
14.2	5.7	27.1	8.3
14.5	32.8	28.2	5.0

Angle 2Θ (degrees)	Relative Intensity (%)	Angle 2Θ (degrees)	Relative Intensity (%)
15.3	6.4	28.5	5.9
16.4	3.7	29.2	17.4
20.4	4.0	30.2	7.2
21.6	5.8	37.8	7.7
22.9	100.0	42.7	6.0
24.0	3.5	49.7	3.3

The DSC thermograms of Form A and Form B are shown in FIG. 13 and FIG. 14, respectively. Form A of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane shows a sharp endothermic peak at 89°C ± 2°C with an onset of 87°C ± 2°C. Form B of (*R*,*R*)-1,4-di-*p*-toluenesulfonyloxy-2,3-dimethyl-butane shows a sharp endothermic peak at 92°C ± 2°C with an onset of 90°C ± 2°C.

Scheme II



Scheme II shows a method for preparing the chiral 1,4-bis-electrophiles (Formula 2), including activated chiral diols (Formula 2a), chiral dihalides (Formula 2b), and opposite enantiomers thereof. The method includes reacting an optically active, 2-substituted succinic acid monoester or succinamic acid (Formula 9) with an alkylating agent (Formula 10) to give a 2,3-disubstituted succinic acid monoester or succinamic acid (Formula 11). Reduction of the disubstituted monoester or succinamic acid gives a diol (Formula 12), which is subsequently activated via reaction with, e.g., a sulfonylating agent (Formula 13). The resulting activated chiral diol (Formula 2a) may be optionally reacted with a halide source (e.g., Formula 16) to give the chiral dihalide (Formula 2b). Substituents R^1 and R^2 in Formula 9-12 are as defined above for Formula 1; R^{11} in Formula 9 and 11 is R^1O- or amino; R^5 in Formula 2a and 13 is as defined above in connection with X^1 in Formula 2; X^2 in Formula 10 and X^3 in Formula 13 are leaving

groups (e.g., halogeno, R^5O-); X^4 is halogeno; and M^2 is a cation (e.g., Group 1 metal ion such as Li^+, Na^+, K^+ or an ammonium salt).

Representative R^1 and R^2 in Formulae 9-12 include C_{1-6} alkyl and aryl-C_{1-3} alkyl, and representative R^{11} in Formula 9 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 9) 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.

Similarly, representative 2,3-disubstituted succinic acid monoesters or succinamic acids (Formula 11) 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.

Alkylation of the mono-substituted succinic acid monoester or succinamic acid (Formula 9) 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 9). 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 $R^1R^2NMgX^4$, respectively, where R^1 and R^2 are as defined above for Formula 1 and X^4 is halogeno. Compatible solvents include those whose conjugate acids have pKa's ≤ 9, typically ≤ 4, and often ≤ 1. Such solvents include, e.g., THF, Et_2O, DMSO, ACN, DMF, and acetone, but do not include ammonia.

The use of these classes of bases and solvents yields an excess of the desired *anti*-diastereomer (as depicted in Formula 11). 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).

As noted above, the alkylating agent (Formula 10) includes a leaving group (X^2), which may include halo substituents, such as Cl, Br, and I, and sulfonate substituents, such as toluene-*p*-sulfonate, methylsulfonate, *p*-bromo-benzene-sulfonate, and triflate. Representative alkylating agents (Formula 10) thus include $C_{1\text{-}6}$ alkyl halides, such as MeCl, MeBr, MeI, EtCl, EtBr, EtI, *n*-PrCl, *n*-PrBr, *n*-PrI, *i*-PrCl, *i*-PrBr, and *i*-PrI, and $C_{1\text{-}6}$ 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.

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).

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 9) to the base and subsequent addition of the alkylating agent (Formula 10). The resulting mixture may then be allowed to react at RT until complete.

The contacting scheme may influence the yield. As described in the Examples, subsurface addition of the starting material (Formula 9) and the alkylating agent (Formula 10) may increase the de of the *anti*-diastereomer (Formula 10) when compared to above-surface reactant addition.

As shown in Scheme II, the disubstituted succinic acid monoester (Formula 11) is reduced to a diol (Formula 12) 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., > 4 eq of LAH) and is run at a temperature ranging from about RT to reflux.

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 12) 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.

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 12). As the reaction mixture is added to the aqueous base, an aluminum alkoxide intermediate undergoes base-catalyzed hydrolysis to give the desired diol (Formula 12) 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.

As shown in Scheme II, the method optionally provides for conversion of the disubstituted succinic acid monoester or succinamic acid (Formula 11) into a diacid (Formula 14) 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.

Following hydrolysis of the disubstituted succinic acid monoester or succinamic acid (Formula 11), the resulting diacid (Formula 14) or a salt thereof, is treated with acetic anhydride to give a cyclic anhydride (Formula 15). 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. The diol may be prepared by reduction of the cyclic anhydride (Formula 15), or by reduction of succinic acid monoester, succinamic acid (Formula 11) or the diacid (Formula 14). The reaction is typically performed with an excess of reducing agent (e.g., LAH) in polar aprotic solvents (e.g., THF) at temperatures ranging from about 40°C to reflux.

Representative reaction substrates (Formula 14) 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 15) 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.

Preparation of the diol (Formula 12) via the cyclic anhydride (Formula 15) may provide advantages over direct reduction of the monoester or amide (Formula 11) to the diol (Formula 12). 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 9a) 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 12) also permits isolation via recrystallization.

As shown in Scheme II, the diol (Formula 12) is activated via reaction with the compound of Formula 13. 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 13 include sulfonylating agents, such as TsCl, MsCl, BsCl, NsCl, and TfCl, and their corresponding anhydrides (e.g., *p*-toluenesulfonic acid anhydride).

Compounds of Formula 12 may be reacted with TsCl or MsCl in the presence of pyridine or Et_3N and an aprotic solvent, such as ethyl acetate, CH_2Cl_2, ACN, or THF, to give a ditosylate, as described above, or a dimesylate, e.g., (*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 13) 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).

As described above, the activated diol (Formula 2a) may be reacted with a halide source (Formula 16) to give a chiral dihalide (Formula 2b). The reaction may be carried out using a halide salt (e.g., LiBr, NaBr, KBr, LiCl, NaCl, KCl, LiI, NaI, KI, etc.) in a polar aprotic solvent (e.g., acetone) or in a non-polar solvent (e.g., toluene) with a small amount of water and phase transfer catalyst (e.g., nBu_4NBr, nBu_4NCl, nBu_4NI, etc.). The reaction is typically carried out with a stoichiometric excess of the halide salt (e.g., 3 eq or more) and at temperatures up to reflux.

Many of the compounds described in this disclosure 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.

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," *J. Pharm. Sci.*, 66:1-19 (1977); see also Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* (2002).

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.

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.

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.

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).

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

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

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

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

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 (*R*,*R*)-3,4-dimethyl-dihydro-furan-2,5-dione

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).

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 5: Preparation of (*R*,*R*)-2,3-dimethyl-butane-1,4-diol

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); ^{1}H 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 6: Preparation of (*R,R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane

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 7: Preparation of (*R*,*R*)-3,4-dimethyl-dihydro-furan-2,5-dione

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%.

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 8: Preparation of (*R,R*)-2,3-dimethyl-succinic acid monomethyl ester

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 9: Preparation of (*R,R*)-2,3-dimethyl-succinic acid

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% desmethyl 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 CH_2Cl_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 10-21: Preparation of (*R*,*R*)-2,3-dimethyl-succinic acid monomethyl ester via subsurface addition

A solution of LHMDS (1300 kg, 24.9% by weight. 1.93 kg-mol, 2.1 eq) in THF was 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) was 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 was about 0.3 m from the tip of the vessel agitator. During the addition of the substrate, the temperature of the reaction mixture was maintained at -25°C or less. The resulting mixture was stirred and warmed to -10°C, then cooled to -30°C. MeI (136 kg, 0.96 kg-mol, 1.05 eq) was 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 was adjusted over 8 h to RT. NH_4Cl (136 kg) was dissolved in water (400 L) and fed slowly to the reactor vessel to quench the reaction. More water (550 L) was added with stirring and then the agitator was stopped to allow the phases to separate. The organic phase was discarded. The aqueous phase was acidified with a mixture of 37% HCl (300 kg) and

water (250 L), and was extracted with MTBE (4 x 400 L). The MTBE phases were combined and distilled to yield the above-titled compound as an oil.

Table 4 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 4 also shows the yields of the two diastereomers using a process similar to that described in the preceding paragraph except that the reactants were added via above-surface addition.

Table 4: Yield of anti- and syn-diastereomers using subsurface (Examples 10-18) and above-surface (Examples 19-21) addition of reactants

Example No.	**Anti-diastereomer** ((R,R)-2,3-Dimethyl-succinic acid monomethyl ester)	**Syn-diastereomer** ((R,S)-2,3-Dimethyl-succinic acid monomethyl ester)
Subsurface Addition		
10	87.1	6.8
11	86.6	6.9
12	87.0	6.5
13	85.5	6.1
14	87.2	6.5
15	82.5	6.1
16	86.9	6.2
17	86.4	6.0
18	85.4	5.7
Average	86.1	6.3
Above-surface Addition		
19	80.1	8.4
20	82.3	8.5
21	78.8	7.7
Average	80.4	8.2

Examples 22-28: Preparation of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol

(*R*,*R*)-2,3-Dimethyl-succinic acid monomethyl ester (150 kg, 936 mol) was diluted with THF (260 L) and MTBE (1500 L) and was heated to 60°C. A 10% LAH solution (530 kg in THF, 1.33 kg-mol) was fed to this solution resulting in a slurry containing a light aluminum alkoxide intermediate. Heat generated by the reaction was removed by solvent boil-up and condensation. A second tank was charged with THF (about 970 L), water (220 L), and 50% NaOH aq solution (5 kg) and was heated to approximately 50°C. The aluminum alkoxide slurry was fed in a controlled fashion to the tank containing THF, water, and NaOH. The agitator was then shut off, the aluminum hydroxide was allowed to settle for 10 min to 15 min, and the product was removed by decanting. The solids were washed with MTBE (3 x 600 L) to extract additional product. The organic liquids was collected and distilled to yield the above-titled compound.

Table 5 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 22-26). For comparison purposes, Table 5 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 5: Yield of (*R*,*R*)-2,3-dimethyl-butan-1,4-diol via LAH reduction and addition to excess base (Examples 22-26) or Fieser workup (Examples 27 and 28)

Example No.	22	23	24	25	26	27	28
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 29: Preparation of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane

A reactor vessel was dry-charged with *p*-toluenesulfonyl chloride (400 kg, 2.14 kg-mol, 2.5 eq). Acetonitrile (1000 L) was subsequently added and the resulting slurry was cooled to 0°C. (*R*,*R*)-2,3-Dimethyl-butan-1,4-diol (100 kg, 0.85 kg-mol, 1 eq) was added to the reactor. Et_3N (260 kg, 2.5 kg-mol, 3 eq) was 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) were added with stirring to quench the reaction. Stirring was stopped to allow the organic and aqueous phases to separate. The aqueous phase was washed with EtOAc (560 L) and the resulting organic phase was combined with the organic phase from the reaction quench. The combined organic phases were washed successively with a 10% $NaHCO_3$ aq solution (720 kg) and a 25% NaCl aq solution (670 kg). EtOAc was distilled-off at atmospheric pressure to give a liquid volume of about 400 L, to which was added MTBE (1100 L) and EtOH (170 kg). The mixture was heated to reflux and subsequently cooled to about 20°C to crystallize the crude product, which was collected by filtration. The crude product was dispersed in MTBE (2200 L) and the mixture was heated to reflux to dissolve the solids. Following dissolution, water (200 L) was added with stirring and the phases were allowed to separate. The aqueous phase was discarded. EtOH (150 kg) was added to the organic phase and the mixture was cooled to 20°C to crystallize the above-titled compound, which was collected by filtration.

Example 30: Degradation of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane by LHMDS

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 31: Preparation of methyl 3-cyanopropanimidate chloride

Succinonitrile (12.124 g, 0.1514 mol) was dissolved in a minimum volume of warm dioxane (10 mL). Meanwhile, MeOH (6.2 mL, 4.90 g, 0.153 mol, 1.01 eq) was added to a solution of HCl in Et_2O (76 mL of 2M solution, 0.152 mol, 1.00 eq) at 10°C. The succinonitrile solution was added to the HCl/MeOH solution over 3 minutes. More HCl solution was then added (15 mL, 0.030 mol, 0.20 eq). After about 10 minutes, solids began to precipitate. After another 15 minutes, the slurry became thick. The mixture was stirred at 10°C for 26 h, then diluted with Et_2O (30 mL to compensate for evaporation) and filtered. The cake was washed with Et_2O (3 x 20 mL) and dried by N_2 stream to the above-titled compound as a white crystalline solid (17.196 g, 76.4 chem%). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 171.28 (s); 120.47 (s); 51.83 (q); 29.05 (t); 12.46 (t); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.86 (2H, t, J = 7.4 Hz); 2.46 (2H, t, J = 7.4 Hz); 3.35 (3H, s).

Example 32: Preparation of 3-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)propanenitrile

A suspension of methyl 3-cyanopropanimidate chloride (15.29 g, 0.1029 mol) and 2-(hydroxymethyl)-2-methylpropane-1,3-diol (12.363 g, 0.1029 mol, 1.00 eq) in dry THF (300 mL) was stirred at 40°C for 13.5 h, then insolubles were filtered off. The filtrate was combined with the filtrate from a smaller scale experiment (from 0.0035 mol imidate). The combined filtrates were concentrated to a white semi-solid residue, which was dissolved in CH_2Cl_2/EtOAc (~15 mL), applied to a pad of silica gel (40 g), and eluted with EtOAc/cyclohexane (500 mL of 10% followed by 500 mL of 20%). The filtrate was concentrated to a thick slurry, diluted with heptane (100 mL) and reconcentrated (twice), then filtered. The cake was washed with heptane (3 x 8 mL) and dried by N_2 stream to give the above-titled compound as a white crystalline solid (9.417 g, 48.3 chem%). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 119.62 (s); 107.32 (s); 72.74 (t); 32.35 (t); 30.32 (s); 14.31 (q); 11.78 (t); ^{1}H-NMR

(400 MHz, $CDCl_3$): δ 0.81 (3H, s); 2.01 (2H, t, J = 7.8 Hz); 2.48 (2H, t, J = 7.8 Hz); 3.89 (6H, s).

Example 33: Preparation of 3-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)propanenitrile

A published procedure was followed, see S.M McElvain & J.P. Schroeder, *J. Am. Chem. Soc.* 71:40 (1949). A solution of succinonitrile (107.53 g, 1.3426 mol) in dioxane (120 mL) was treated with Et_2O (930 mL). The two-phase mixture was treated with MeOH (43.4 g, 1.3546 mol, 1.01 eq) and cooled to 8°C. The resulting one-phase solution was cooled to 7°C and anhydrous HCl (58 g, 1.59 mol, 1.18 eq) was sparged into the solution through a gas dispersion tube at a rate such that the temperature was kept below 8°C (the add is exothermic). The mixture was stirred at 8°C overnight, then filtered. The cake was washed with Et_2O (500 mL) and dried by a stream of nitrogen. The cake was identified as methyl 3-cyanopropanimidate chloride (103.3 g, 0.6952 mol, 51.8 M%, >95% pure) by ^{13}C-NMR (CD_3CO_2D). A suspension of the imidate (1.0 g, 6.73 mmol), 2-(hydroxymethyl)-2-methylpropane-1,3-diol (2.4 g, 19.98 mmol, 2.97 eq), and BHT (24 mg, 0.109 mmol, 0.016 eq) in dry THF (10.5 mL) was stirred at 40°C for 17 h, then insolubles filtered off. The yield of above-titled compound was determined to be 80.5 M% by quantitative analysis of the filtrate by GC.

Example 34: Preparation of (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane

A mixture of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (5.375 g, 0.01260 mol) and LiBr (3.2839 g, 0.03782 mol, 3.00 eq) in toluene (50 mL) was heated to reflux. After 18 h, conversion to the above-titled compound was complete by TLC (eluant: 20% EtOAc/cyclohexane; char: PMA; R_f [ditosylate] = 0.31; R_f [dibromide] = 0.76). Insoluble solids (lithium tosylate) were filtered off through a small pad of celite and rinsed with toluene (4 x 5 mL). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 39.19 (t); 37.02 (d); 14.41 (q); ^{1}H-

NMR (400 MHz, $CDCl_3$): δ 0.99 (6H, d, J = 6.4 Hz); 2.05 (2H, mult.); 3.38 (2H, dd, J = 10.2, 5.0 Hz); 3.46 (2H, dd, J = 10.4, 5.2 Hz).

Example 35: Preparation of (3*S*,4*S*)-3,4-dimethyl-1-((4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)methyl)cyclopentanecarbonitrile

To the filtrate containing (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane was added 3-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)propanenitrile (3.0017 g, 0.01638 mol, 1.30 eq). The mixture was then treated dropwise at RT over 2 h with a solution of $LiN(SiMe_3)_2$ in THF (34 mL of 1.28 M solution, 0.0435 mol, 3.45 eq). After 30 minutes, GC and LC analysis revealed unreacted dibromide (25.4 chem% by GC, 32.9 chem% by LC) and unreacted cyanoorthoester (0.090 eq) along with product (46.5 chem%). More cyanoorthoester (1.151 g, 0.00628 mol, 0.50 eq) was added and the mixture stirred for another 16 h, at which time reaction was complete by GC (3.4 chem% dibromide and 10.2 chem% cyanoorthoester), so the reaction was quenched with water (50 mL). The upper organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The organic phases were combined and concentrated to give the above-titled compound as an orange-brown crystalline solid (5.7532 g, 94.7 chem% yield, ESTD GC; overall from ditosylate). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 126.24 (s); 107.68 (s); 72.60 (t); 48.46 (t); 47.25 (t); 45.30 (t); 41.52 (d); 40.55 (d); 36.72 (s); 30.40 (s); 18.49 (q); 17.42 (q); 14.50 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.70 (3H, s); 0.87 (3H, d, J = 6.4 Hz); 0.92 (3H, d, J = 6.8 Hz); 1.2-2.3 (8H, mults); 3.80 (6H, s).

Example 36: Preparation of (3*S*,4*S*)-3,4-dimethyl-1-((4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)methyl)cyclopentanecarbonitrile

A solution of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (214.4 mg, 0.5026 mmole) and 3-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)propanenitrile (239.9 mg, 1.3094 mmol, 2.61 eq) in THF (4.0 mL) at 21°C was treated dropwise over 2 h with a solution of $LiN(SiMe_3)_2$ in THF (2.50 mL of 1.28 M solution, 3.20 mmol, 6.37 eq) and stirred at RT for 62 h. The mixture

was quenched with H_2O (1 mL), stirred at RT for 30 minutes, then poured into H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The extracts were QS'd to 100.0 mL in a volumetric flask with acetonitrile. Quantitative analysis by GC and LC indicated the absence of the above-titled compound.

Example 37: Preparation of 2,2-dimethoxypropyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate

Crude (3*S*,4*S*)-3,4-dimethyl-1-((4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)methyl)cyclopentanecarbonitrile (2.5131 g, derived from 5.5044 mmol ditosylate) was dissolved in CH_2Cl_2 (25 mL) and treated with 6N aq HCl (25 mL). The two-phase mixture was stirred at RT for 30 minutes at which time hydrolysis of the reactant (R_f = 88) to the above-titled compound (R_f = 0.72) was complete by TLC. The mixture was transferred to a separatory funnel. To another separatory funnel was added water (25 mL). The organic phase in the first separatory funnel was transferred to the second separatory funnel, the mixture shaken, and the CH_2Cl_2 phase removed. The aqueous phases in the two separatory funnels were then extracted with CH_2Cl_2 in succession (4 x 25 mL). The extracts were combined and concentrated to a light tan oil that crystallized on standing to give the above-titled compound as an off-white solid in pure form (1.4177 g, 5.003 mmol, 90.9 chem% overall from ditosylate). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.02 (s); 125.35 (s); 67.28 (t); 66.97 (t); 47.47 (t); 46.23 (t); 43.91 (t); 41.83 (d); 40.68 (d); 40.39 (s); 36.96 (s); 17.89 (q); 17.19 (q); 16.80 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, s); 1.02 (3H, d, J = 6.4 Hz); 1.06 (3H, d, J = 6.5 Hz); 1.3-2.7 (8H, mults); 3.61 (4H, s); 3.91 (2H, t, J = 7.1 Hz); 4.24 (2H, s).

Example 38: Preparation of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid potassium salt

2,2-Dimethoxypropyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate (1.0034 g, 3.541 mmol) was added to a solution of KOH (247.7 mg of appx. 87.3% pure material, 216 mg, 3.85 mmol, 1.09 eq)

in water (1.5 mL). The suspension was stirred at 21°C for 1 h, at which time all solids had dissolved and TLC analysis revealed that hydrolysis of the reactant (R_f = 0.75) to the above-titled compound (R_f = 0.36) and to 1,1,1-tris(hydroxymethyl)ethane (R_f = 0.56) was complete. The solution was washed with MTBE (3 x 0.5 mL) to remove non-polar impurities. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.41 (s); 125.00 (s); 47.44 (t); 46.16 (t); 43.35 (t); 41.79 (d); 40.75 (d); 36.80 (s); 17.96 (q); 17.55 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, d, J = 6.4 Hz); 1.05 (3H, d, J = 6.4 Hz); 1.3-2.7 (8H, mults); 9.9 (1H, br s).

Example 39: Preparation of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid potassium salt

A solution of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid potassium salt in water (derived from 201.4 mg [0.7107 mmol] cyanoester and potassium hydroxide [49.6 mg of appx. 87.3% pure material, 43.3 mg, 0.772 mmol, 1.09 eq] in 0.3 mL water) was diluted with MeOH (3 mL), treated with sponge nickel A-7000 (128 mg), and stirred under H_2 (100 psig) at 35°C. After 14 h, reduction of cyanoacid (R_f = 0.41) to the above-titled compound (R_f = 0.29) was about 75% complete by TLC. The slurry was filtered and washed with water (0.3 mL). The filtrate was concentrated to a yellowish oil, which was dissolved in water (0.5 mL) and treated with glacial acetic acid (3 drops), producing a thick slurry, which was thinned with water (0.5 mL). The slurry was heated to 70°C, diluted with sufficient isopropanol to dissolve all solids (0.25 mL), then gradually cooled over 1.5 h to 0°C. The resulting slurry was filtered to give the above-titled compound as a solid contaminated with the reactant and 1,1,1-tris(hydroxymethyl)ethane by TLC comparison with authentic standards.

Example 40: Preparation of ((3*S*,4*S*)-3,4-dimethyl-1-((4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)methyl)cyclopentyl)methanamine

A solution of (3*S*,4*S*)-3,4-dimethyl-1-((4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)methyl)cyclopentanecarbonitrile (302.8 mg, 1.1411

mmol) in abs EtOH (4 mL) was treated with aq NaOH (135 mg of 50% solution, 67.5 mg, 1.687 mmol, 1.48 eq) followed by sponge nickel A-7000 (183 mg). The mixture was stirred under H_2 (50 psig) at RT for 21 h, then filtered, rinsing with water (3 x 1.5 mL). The filtrate was diluted with water (5 mL), extracted with MTBE (5 mL), dried over anhydrous K_2CO_3, and concentrated to give the above-titled compound as a pale yellow solid residue (333.9 mg, 1.2395 mmol, 108.6 chem% yield). TLC eluant: 70:20:5:5 EtOAc:MeOH:conc NH_4OH:H_2O; char: 50% aq H_2SO_4; R_f [amine] = 0.66, R_f [nitrile] = 0.79); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 107.46 (s); 70.37 (t); 49.29 (t); 45.23 (t); 45.01 (t); 42.59 (t); 42.28 (s); 39.81 (d); 39.49 (d); 28.23 (s); 16.34 (q); 15.98 (q); 12.10 (q).

Example 41: Preparation of (7S,8S)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one

A solution of ((3*S*,4*S*)-3,4-dimethyl-1-((4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)methyl)cyclopentyl)methanamine (200.5 mg, 0.7443 mmol) in aq HCl (2.3 mL of 1.0 M solution, 2.3 mmol, 3.1 eq) was stirred at RT for 75 minutes at which time hydrolysis to the aminoester, 3-hydroxy-2-(hydroxymethyl)-2-methylpropyl 2-((3*S*,4*S*)-1-(aminomethyl)-3,4-dimethylcyclopentyl)acetate, was complete by TLC (R_f [aminoorthoester] = 0.74, R_f [aminoester] = 0.64). The reaction was quenched with solid sodium bicarbonate (315.4 mg, 3.754 mmol, 5.0 eq), treated with sodium sulfate (103 mg), and extracted with THF (3 x 2 mL). The extracts were combined and heated at 50°C for 4.5 h at which time conversion of the aminoester (R_f = 0.66) to the above-titled lactam (R_f = 0.80) and 1,1,1-tris(hydroxymethyl)ethane (R_f = 0.56) was complete by TLC. The mixture also traces of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (R_f = 0.21) and BHT (R_f = 0.91). The mixture was concentrated to a yellow oil, which was dissolved in methylene chloride (3 mL), washed with water (3 x 3 mL) to remove the triol, then concentrated to an oily residue which was dissolved in heptane (0.5 mL) at 70°C and cooled to -20°C, whereupon

crystals separated. The mother liquor was decanted off, which, upon vacuum drying, gave the above-titled compound as a crystalline solid (78.9 mg, 0.472 mmol, 63.4 chem% from aminoorthoester, 68.9 chem% overall from cyanoorthoester). LC purity: 97.5 area% by comparison with an authentic sample; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 178.14 (s); 56.13 (t); 48.35 (t); 47.91 (t); 45.74 (t); 45.04 (s); 41.63 (d); 41.57 (d); 18.60 (q); 18.49 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.977 (3H, d, J = 6.0 Hz); 0.983 (3H, d, J = 6.0 Hz); 1.3-2.3 (8H, mults); 3.21 (1H, d, J = 9.6 Hz); 3.24 (1H, d, J = 10.4 Hz); 6.02 (1H, br s).

Example 42: Preparation of methyl 3-cyanopropanimidate chloride

To a 1L jacketed 3 neck flask with one neck vented to a scrubber (water) was charged succinonitrile (Aldrich; mw 80.09; 103.06 g, 1.2868 mol), 200 mL methylene chloride (E&M), 200 mL methyl-t-butylether (E&M), and MeOH (E&M; mw 32.04; 41.5 g, 1.2953 mol, 1.01 eq). The solution was cooled to 6.5°C and anhydrous hydrogen chloride (mw 36.46; 55.5 g, 1.5222 mol, 1.18 eq) was sparged into the solution through a gas dispersion tube at a rate such that the temperature was kept below 12°C (the add is exothermic). The weight of hydrogen chloride was measured by weighing the lecture bottle. The lecture bottle was held in a stand on a balance. It was connected to the gas dispersion tube through PVC tubing, which was clamped in such a way as to minimize tension in the tubing segment leading to the lecture bottle. The flow was regulated through an AGA Model LB 165-40-2F-BV corrosive gas regulator. The flow could not be well controlled using a simple valve because the pressure of the lecture bottle was too high. The add took 4 hours. About halfway through the add, the product imidate began to crystallize. When the add was complete, the jacket temp was adjusted to 12°C. After stirring for 25 h, the slurry had become very thick due to solvent evaporation, so 175 mL methylene chloride was added. The slurry, although thick, was easily stirrable and filterable. The mixture was filtered. The cake was washed with 325 mL methylene chloride and dried by RT nitrogen. The material was identified as the above-titled compound by a GC assay (column: 60 meter DB-1, 0.25 mm

ID w 1 micron film; temp gradient: 150°C for 3 min. then ramped 10°C/min to 225°C then held for 10 min.; sample prep: to ~100 mg [accurately weighed] imidate add 0.5 mL 1N HCl, solution allowed to stand for 5 min., solution transferred to 10 mL volumetric flask with 2 mL water, QS to 10 mL with MeOH; retention times: succinonitrile, 9.29 min.; methyl-3-cyanopropionate, 9.78 min.; dimethylsuccinate, 10.68 min.). Storage in the refrigerator is recommended. Some lots of imidate that were stored in amber bottles at room temperature decomposed to brown solids with significant gas evolution after 1-7 days. Weight: 178.97 g (mw 148.59; 1.2045 mol, 93.6 chem% yield [uncorr]).

Example 43: Preparation of 4,4,4-trimethoxybutanenitrile

To a 3L 3-neck flask was charged methyl 3-cyanopropanimidate chloride (mw 148.59; 176.77 g, 1.1896 mol) and 1.7L MeOH (E&M). On stirring, the imidate dissolved to produce a homogeneous solution. The solution was stirred at RT. After about 2 h, ammonium chloride began to precipitate. The next morning (after 13 h), the mixture had become a white slurry of granular solids. This reaction can be monitored by NMR (pull aliquot, dilute with ~20% CD_3OD). (Heating the slurry must be avoided as the ammonium chloride will react slowly with the orthoester to form methyl 3-cyanopropionate. For example, in a different experiment in which the reaction mixture was vacuum concentrated (pot temp 33°C) in an attempt to drive the reaction to completion by precipitation of ammonium chloride, 4% methyl 3-cyanopropionate was formed.) The slurry was filtered into a receiver containing triethylamine (mw 101.19; d 0.726; 180 mL, 130.68 g, 1.2914 mol, 1.09 eq), rinsing with a small amount of MeOH. The cake (ammonium chloride) weighed 19.76 g (mw 53.49; 0.3694 mol, 31.1% of theory). The filtrate is checked by NMR (run on neat aliquot diluted with ~20 vol% CD_3OD). If methyl ester is present, the filtrate is stirred overnight to allow the liberated ammonia to ammonolyze the methyl ester. The filtrate was treated with a solution of potassium hydroxide pellets (mw 56.11; 55.2 g, 87.3 wt%, 48.19 g,

0.8588 mol, 0.72 eq) in 160 mL water, which caused a solid to precipitate (presumably KCl). The slurry was filtered. The weight of the cake was 50.32 g (mw 74.56 if KCl; 0.6749 mol, 0.57 eq). To the filtrate was added a solution of sodium carbonate (mw 105.99; 32 g, 0.3019 mol, 0.25 eq) in 200 mL water. The mixture was Rotovaped (bath temp 47°C) to remove MeOH, leaving a homogeneous solution (vol.: ~575 mL). The solution was diluted with 95 mL H_2O and extracted with MTBE (700 mL, then 360 mL). Phase breaks were excellent. The MTBE extracts were combined, treated with anhydrous potassium carbonate (2.7 g), concentrated to a two-phase mixture, and treated with more potassium carbonate (53 g) to give a two-phase mixture with some solids. The MTBE phase was separated and the aqueous phase extracted with MTBE (50 mL). The MTBE extracts were combined, dried over anhydrous milled potassium carbonate (14 g), and distilled from anhydrous potassium carbonate (5 g). The heart cut (116.52 g; bp 92°C/26 mm) was a colorless liquid (KF 0.025) identified as the titled compound by NMR and GC. Weight: 116.52 g (mw 159.19; 94.60 wt%, 110.23 g, 0.6924 mol). The forecut (weight: 41.46 g; bp 92°C/27 mm) contained droplets of water (KF 0.479) and was reworked by redistillation from 25 mL toluene and 0.3 g calcined anhydrous potassium carbonate to give another colorless liquid (bp 82-83.6°C/25 mm). The KF taken after the toluene azeotropic distillation and prior to the product distillation was 0.011%. Weight: 37.2 g (mw 159.19; 95.93 wt%, 35.69 g, 0.2242 mol). (The problem of water carry-over in the extractions can be avoided by using toluene instead of MTBE as the extraction solvent.) By GC assay (column: 30 meter DB-5, 0.25 mm ID w 1 micron film; temp gradient: 70°C for 5 min., then ramped at 10°C /min to 320°C, then held for 2 min.; retention time: 15.88 min.), neither cut contained more than 1.7 area% of any impurity. The level of methyl 3-cyanopropionate was 0.05 area% in the heart cut, ND in the redistilled forecut. Yield (combined): 0.9166 mol, 77.1 chem% (purity corr). ^{13}C-NMR (100 MHz, CD_3OD): δ 121.49 (s); 115.98 (s); 50.64 (q); 28.00 (t); 12.59 (t); ^{1}H-NMR (400 MHz, CD_3OD): δ 2.11 (2H, t, J=7.4 Hz); 2.42 (2H, t, J=7.4 Hz); 3.25 (9H, s).

Example 44: Preparation of (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane

A mixture of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (mw 426.55; 200.0 g, 0.4689 mol) and sodium bromide (mw 102.89; 145.0 g, 1.4093 mol, 3.01 eq) in 1 L toluene was heated to 70°C to give a uniform slurry. A solution of tetrabutylammonium bromide (mw 322.38; 15.0 g, 0.0465 mol, 0.099 eq) in 15.0 mL H_2O was added. After 8 min., solids began to precipitate (sodium tosylate). The slurry was stirred at 70°C for 3 h then at 80°C for 17 h. The mixture was cooled to 50°C, washed with H_2O (350 mL, then 2 x 150 mL), and concentrated by Rotovap to an oil weighing 199.1 g.

Example 45: Preparation of (3*S*,4*S*)-3,4-dimethyl-1-(2,2,2-trimethoxyethyl)cyclopentanecarbonitrile

A solution of lithium hexamethyldisilazide in THF (Chemetall; mw 167.33; 0.226 g/mL; 1058.4 mL, 239.2 g, 1.4295 mol, 3.07 eq) was vacuum distilled (25°C jacket temp) to a very thick slurry (volume: 400 mL), which was diluted with 150 mL THF. This slurry was cooled to 0°C and treated over 20 min. with a portion of (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane from the previous Example (197.4 g, from 0.4649 mol ditosylate), rinsing with 50 mL THF. The add was slightly exothermic (brief excursion to +15°C before falling back to 0°C). At the end of the add, the mixture became a clear solution. To this solution was added neat 4,4,4-trimethoxybutyronitrile (mw 159.19; 105.84 g, 0.6649 mol, 1.43 eq) gradually over 6 h. During the add, the pot temperature was 0°C. At the end of the add, the temperature was reduced to -5°C. The mixture was stirred for 14 h then quenched with H_2O (252 mL). The first 13 mL were added over 50 min. (exotherm to +4°C), then the rest was added over 5 minutes. The mixture was warmed to 23°C to give a two phase mixture with a dark oil at the interface (identified as mineral oil, an impurity in the lithium hexamethyldisilazide/THF reagent). The aqueous layer was separated. The organic layer was concentrated to a volume of 350-400 mL, treated with 350 mL heptane, concentrated to a volume of 500-550 mL,

treated with 400 mL heptane, then concentrated to a volume of 450 mL. The heptane solution was washed with 0.05 N NaOH (325 mL, then 175 mL). A portion of a solution from another experiment was concentrated to an oil identified as the above-titled compound by ^{13}C-NMR and ^{1}H-NMR. ^{13}C-NMR (100 MHz, CD_3CD_2OD): δ 125.44 (s); 113.16 (s); 48.66 (3C, q); 47.50 (t); 46.44 (t); 41.12 (d); 39.76 (d); 38.76 (t); 37.06 (s); 18.08 (q); 16.82 (q); ^{1}H-NMR (400 MHz, CD_3CD_2OD): δ 1.05 (3H, d, J = 6.4 Hz); 1.09 (3H, d, J = 6.7 Hz); 1.46 (1H, t, J = 12.6 Hz); 1.5-2.3 (7H, mults); 3.29 (9H, s).

Example 46: Preparation of methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate

The entire heptane solution from the previous example containing (3*S*,4*S*)-3,4-dimethyl-1-(2,2,2-trimethoxyethyl)cyclopentanecarbonitrile was treated with sufficient 3N HCl to adjust the pH to <3 (d 1.0495; 207 g, 197.2 mL, 0.592 mol, 1.27 eq). The mixture was stirred at RT for 40 min., then the aqueous layer was separated and extracted with 100 mL heptane. The combined organic layers were washed with H_2O (50 mL). Weight: 425.19 g. A solution from a similar experiment was concentrated and distilled (bp 145-147°C/35.1 mm) to afford a liquid identified as the above-titled compound in essentially pure form by ^{13}C-NMR and ^{1}H-NMR and GC (99.0 A%). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.63 (s); 124.91 (s); 51.62 (q); 47.15 (t); 45.92 (t); 43.07 (t); 41.56 (d); 40.39 (d); 36.77 (s); 17.77 (q); 16.97 (q); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, d, J = 6.4 Hz); 0.97 (3H, d, J = 6.6 Hz); 1.29 (1H, t, J = 12.4 Hz); 1.46 (1H, mult); 1.67 (1H, mult); 1.84 (1H, dd, J = 13.8, 9.4 Hz); 2.05 (1H, dd, J = 13.8, 8.5 Hz); 2.38 (1H, dd, J = 13.2, 6.5 Hz); 2.58 (2H, s); 3.65 (3H, s).

Example 47: Preparation of (7*S*,8*S*)-7,8-dimethyl-2-aza-spiro[4.4]nonan-3-one

An aqueous slurry of molybdenum-promoted sponge nickel (Johnson Matthey A-7000; 33.33 g occupying 20.0 mL; calc'd dry wt: 15.55 g [0.35 g/g])

was treated with 13 mL MeOH, agitated, allowed to settle, and 13 mL of the supernatant decanted. The catalyst washing procedure was repeated two times. The methanolic catalyst slurry was placed in a 450 mL glass stirred reactor along with 60 mL MeOH. The vessel was sealed, purged with H_2, pressurized to 60 psig, and heated to 85°C while stirring. When the reactor temperature reached 85°C, the pressure was adjusted to and maintained at 60 psig. A portion of the heptane solution from the previous Example (208.60 g, from 0.2281 mol ditosylate; mw 195.26; theoretically containing 44.535 g of methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate) was concentrated to an oil (weight: 62.43 g) which was diluted with 119 mL MeOH to give a yellow-white emulsion, which was metered into the hydrogenation reactor over a 4.9 h period. The feed metering system was then rinsed with MeOH (3 x 5 mL) into the reactor and the completed mixture was held at 85°C /60 psig for an additional 5 h. After cooling to RT, the reaction mixture was vacuum filtered. The reactor and catalyst cake were rinsed with MeOH. The weight of the combined filtrate and washes was 399.11 g. A portion of this nearly colorless solution (396.29 g, from 0.2265 mol ditosylate) was vacuum distilled (pot temp 37°C) to a volume of 150 mL. The solution was then distilled at atmospheric pressure while portions of heptane were added (3 x 100 mL) until the bp of the distillate leveled off at 101°C. The resulting turbid solution was cooled to -5°C (crystallization occurred at 42°C). The slurry was filtered on a frit pre-cooled to -5°C. The cake was washed with 80 mL RT heptane and dried by N_2 pressure. The product was identified as the above-titled compound by ESTD LC comparison with an authentic sample (potency: 96.49 W%). Yield: 33.80 g (mw 167.25; 32.61 g [potency corr], 0.1950 mole, 86.1 M% overall from ditosylate). ESTD LC analysis of the filtrate found lactam (3.2 M% yield overall from ditosylate).

Example 48: Preparation of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid

(7*S*,8*S*)-7,8-Dimethyl-2-aza-spiro[4.4]nonan-3-one from the previous Example (mw 167.25; 32.80 g of 96.49 W% pure material, 31.65 g, 0.1892 mole) was treated with 37% HCl (mw 36.46; 57.4 g of 37 W% solution, 21.24 g, 0.5825 mole, 3.08 eq) and 32.8 mL RO water. The mixture was stirred at >88°C for 24 h. Analysis by LC found 2.06 M% residual lactam. The mixture was cooled to 60°C and the pH adjusted to ~2 (paper) by addition of 50% sodium hydroxide (30.85 g, containing 15.425 g [mw 40.00; 0.3856 mole, 2.04 eq] sodium hydroxide). The mixture was diluted with 43 mL H_2O and vacuum distilled (pot temp 48°C) until the solution became cloudy (final volume ~115 mL). The pH was adjusted to 6.5 (paper) by addition of 50% sodium hydroxide (14.81 g, containing 7.405 g [mw 40.00; 0.1851 mole, 0.98 eq] sodium hydroxide). The mixture was cooled to <5°C, stirred for 30 min., and filtered. The flask was rinsed twice with the filtrates. The cake was washed with 33 mL <10°C RO water and dried by N_2 stream. The product was identified as the above-titled compound by ESTD LC comparison with an authentic sample (potency: 88.6 W%). A screen for metals detected Mo (0.1 ppm) and Al (1 ppm). Weight: 35.43 g (mw 185.27; 31.39 g [potency corr], 0.1694 mole, 89.6 M%). The filtrate was concentrated to a residue (weight: 32.94 g). LC analysis for the title compound found 2.1 W% potency (0.692 g, 0.00373 mole, 2.0 M% from lactam).

A portion of the crude product (mw 185.27; 34.0 g of 88.6 W% pure material, 30.124 g, 0.1626 mole) was suspended in 120 mL RO water and 40 g isopropanol. The mixture was heated to reflux (85°C) at which point a solution formed. The solution was cooled to <5°C over 4 h, stirred for 1 h, and filtered. The cake was washed with 70 mL <5°C isopropanol and dried by N_2 stream for 17 h. The product was identified as the above-titled compound by ESTD LC comparison with an authentic sample (potency 99.6 W%). Weight: 29.15 g (mw 185.27; 29.03 g [potency corr], 0.1567 mole, 96.4 M% from crude product). The filtrate was concentrated to a residue (weight: 5.19 g). LC

analysis for the title compound found 51.6 W% potency (2.678 g, 0.01445 mole, 8.9 M% from crude product). ^{13}C-NMR (100 MHz, 4/1 CD_3OD/D_2O): δ 182.49 (s); 53.04 (t); 52.33 (t); 48.80 (t); 48.33 (t); 44.13 (d); 43.81 (d); 43.74 (s); 19.99 (q); 19.86 (q); ^{1}H-NMR (400 MHz, 4/1 CD_3OD/D_2O): δ 0.98 (3H, d, J = 6.3 Hz); 0.99 (3H, d, J = 6.2 Hz); 1.14 (1H, dd, J = 12.6, 10.2 Hz); 1.19 (1H, dd, J = 12.9, 10.2 Hz); 1.52 (2H, overlapping mults); 1.88 (1H, t, J = 13.6 Hz); 1.90 (1H, t, J = 13.9 Hz); 2.47 (1H, d, J = 15.2 Hz); 2.52 (1H, d, J = 15.2 Hz); 2.92 (1H, d, J = 12.9 Hz); 2.99 (1H, d, J = 12.9 Hz).

Example 49: Preparation of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid

A portion of the heptane solution from a previous example (208.53 g, from 0.2280 mol ditosylate; mw 195.26; theoretically containing 44.520 g of methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate) was treated with a solution of potassium hydroxide (mw 56.11; 29.46 g of 88 W% pure material, 25.925 g, 0.4620 mole, 2.03 eq) in 125 mL H_2O. The two phase mixture was stirred vigorously for 2 h, at which time hydrolysis was complete by TLC. The aqueous phase containing the potassium salt of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid was separated. Weight: 189.02 g.

A 450 mL glass stirred reactor was charged with an aqueous slurry of molybdenum promoted sponge nickel (Johnson Matthey A-7000; 20.0 mL, weighing 33.03 g; dry weight: 15.20 g [0.31 g/g]) and 60 mL MeOH. The vessel was sealed, purged with H_2, and pressurized to 25 psig with H_2. The reactor was stirred and warmed to about 50°C at which point the pressure was adjusted to and maintained at 50 psig by feeding from a high pressure reservoir of known volume. A portion of the above prepared aqueous phase (185.72 g, from 0.2240 mole ditosylate; containing 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid [mw 219.33; 49.130 g]) was metered into the hydrogenation vessel over 2.7 h. The feed system was rinsed with MeOH (3 x 5 mL) into the reactor. Hydrogen uptake appeared to be complete about 15 min. after completion of the final rinse. The reactor was maintained at 50°C for

an additional 5 h before being allowed to cool to RT. The reaction mixture was filtered and the catalyst cake rinsed with MeOH and water. The weight of the filtrate containing the potassium salt of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid was 610.92 g.

A portion of the above filtrate containing the potassium salt of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (608.55 g, from 0.2231 mole ditosylate) was concentrated by Rotovap to 188.04 g and transferred to a 3 neck jacketed flask, rinsing with H_2O (2 x 10 mL). Glacial acetic acid (mw 60.05; 27.14 g, 0.4520 mole, 2.03 eq) was added to adjust the pH from >14 to 6.72. The slurry was cooled to 0°C, stirred at 0°C for 3 h, filtered, and the cake dried by N_2 stream. The crystals were identified as the above-titled compound by TLC and LC. Weight: 40.51 g.

A portion of the crude (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (38.86 g, from 0.2140 mole ditosylate) was mixed with 307 mL isopropanol. The slurry was heated to 80°C for 2 h, then cooled to 0°C over 1.5 h and filtered. The filtrate was used to rinse the solids from the flask onto the filter. The cake was dried by N_2 stream. The crystals were off-white in color. Weight: 33.05 g.

The above (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid crystals were mixed with 165 mL 25 W% *i*-PrOH/H_2O. The slurry was heated to 80°C to produce a clear solution with only very minor cloudiness if any at all. The solution was cooled to 0°C over 4 h, stirred at 0°C for 1 h, then filtered. The cake was washed with the filtrate and dried by N_2 stream. The crystals contained no impurity above 0.1 A% by LC (potency: 99.6 W%). Weight: 30.55 g (mw 185.27; 30.43 g, 0.1642 mole, 76.7 M% overall from ditosylate).

Example 50: Preparation of (3*S*,4*S*)-3,4-dimethyl-1-(2,2,2-trimethoxyethyl)cyclopentanecarbonitrile

A mixture of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (mw 426.55; 200.0 g, 0.4689 mol) and potassium bromide (mw 119.01; 169.0

g, 1.4200 mole, 3.03 eq) in 400 mL toluene was degassed with N_2 for 45 min., then heated to 50°C, treated with a solution of tetrabutylammonium bromide (mw 322.38; 30.0 g, 0.09306 mole, 0.198 eq) in 30 mL H_2O was added. The mixture was refluxed for 21 h, then cooled to 50°C and washed with H_2O (400 mL, then 2 x 100 mL). The organic layer was diluted with 250 mL toluene and concentrated by Rotovap (bath temp 51°C) to give (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane as an oil weighing 208.7 g.

A solution of lithium hexamethyldisilazide in THF (Chemetall; mw 167.33; 0.226 g/mL; 1082.4 mL, 244.6 g, 1.4619 mol, 3.17 eq) was vacuum distilled to a volume of 500 mL, cooled to -2°C, and treated over 1 h with a portion of (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane (205 g, from 0.4606 mol ditosylate). The mixture was stirred at -2°C for 10 min., then treated with neat 4,4,4-trimethoxybutyronitrile (mw 159.19; 105.84 g, 0.6649 mol, 1.44 eq) gradually over 6 h. During the add, the pot temperature was kept at 0°C. The mixture was stirred for 14 h then quenched with H_2O (250 mL). The first 20 mL were added over 1 h (exotherm to +5°C), then the rest was added over 5 minutes. The mixture was warmed to 18°C and the layers separated. The aqueous layer was back-extracted with 50 mL THF and the extract combined with the first organic layer. The weight of the combined organic layers containing the above-titled compound was 786.7 g.

Example 51: Preparation of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid

A portion of the solution of crude (3*S*,4*S*)-3,4-dimethyl-1-(2,2,2-trimethoxyethyl)cyclopentanecarbonitrile in THF from the previous example (188.18 g, from 0.1102 mole ditosylate) was treated with 37% aq. HCl (mw 36.46; d 1.2 g/mL; 29 mL, 34.8 g, containing 12.88 g [0.3532 mole, 3.20 eq] hydrogen chloride) to adjust the pH to -1. During the add, the temperature rose to 52°C and solids precipitated. Water (65 mL) was added to dissolve the solids and the mixture was allowed to decrease to RT. The mixture was held (without agitation) at RT for 20 h, then the aqueous phase (pH 0.55)

separated. To the organic phase containing methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate was added a solution of potassium hydroxide (mw 56.11; 14.0 g of 87.3 W% material, 12.22 g, 0.2178 mole, 1.98 eq) in 50 mL H_2O. During the add the temperature rose to 36°C. The mixture was stirred at RT for 2 h, at which time TLC analysis indicated that the saponification was complete. The phases were separated and the aqueous phase containing the potassium salt of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid was concentrated to a volume of 60 mL (to remove MeOH and residual THF).

Aqueous HCl (37%, mw 36.46; d 1.2 g/mL; 19 mL, 22.8 g, containing 8.436 g [0.2314 mole, 2.10 eq] hydrogen chloride) was diluted with 57 mL H_2O, cooled to 0.3°C, and seeded with crystals of the potassium salt of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid. To this mixture was added dropwise over 75 min. the concentrated aqueous solution of cyanoacid potassium salt, keeping the pot temperature at -3 to -1°C. Throughout the add, crystals (non-sticky) separated. The slurry was stirred at -1°C for 1 h, then filtered. The cake was washed with 35 mL 0°C H_2O and dried by N_2 stream to KF 0.135%. The crystals were identified as the above-titled compound by ^{13}C-NMR and ^{1}H-NMR. Weight: 18.78 g (mw 181.24; 0.1036 mole, 94.0 M% yield overall from ditosylate).

Example 52: Preparation of (3*S*,4*S*)-3,4-dimethyl-1-(2,2,2-trimethoxyethyl)cyclopentanecarbonitrile

A mixture of (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sulfonyloxy)-butane (mw 426.55; 200.76 g, 0.4707 mol), sodium bromide (mw 102.89; 145.3 g, 1.4122 mol, 3.00 eq), and tetrabutylammonium bromide (mw 322.38; 15.0 g, 0.0465 mol, 0.099 eq) in 1.5 L toluene and 84 mL H_2O was heated to 93°C. The headspace of the flask nearly filled with foam. The temperature was reduced to 92°C, which reduced the amount of foam. The mixture was stirred at 89°C. The progress of the reaction was monitored by TLC (eluant: 30% EtOAc/cyclohexane; R_f [ditosylate] = 0.38, R_f [monotosylate-monobromide] =

0.54). At t = 2 h, much monotosylate-monobromide and a trace of ditosylate was detectable. At t = 6.5 h, a trace of monotosylate-monobromide was detectable. At t = 24 h, no ditosylate or monotosylate-monobromide were detectable, so the mixture was cooled to RT, filtered, and the cake (sodium tosylate) washed with 250 mL toluene. The toluene extracts were combined, washed with H_2O (2 x 250 mL), and vacuum concentrated (53°C /150 mm) to a volume of ~200 mL. The product was identified as (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane by ISTD GC (potency: 55.9 W%). Weight: 204.8 g (mw 243.97; containing 114.48 g [0.4693 mole, 99.7 M% yield] dibromide).

Neat hexamethyldisilazane (mw 161.40; 79.2 g, 0.4907 mole, 3.32 eq) was cooled to -11°C and treated with a solution of n-butyllithium in hexanes (177 mL of 2.5 M solution, 0.4425 mole, 3.00 eq) at a rate such that the temperature was kept below 4°C (35 min.). The resulting slurry was warmed to 25°C to give a clear solution, which was vacuum distilled to a thick slurry (volume ~100 mL), cooled to -3°C, and treated with 130 mL THF, resulting in an exotherm to 44°C. The mixture was cooled to -2°C and treated with a portion of the above prepared solution of (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane in toluene (mw 243.97; 64.4 g of 55.9 W% pure material, 36.00 g, 0.1476 mole) all at once. The mixture was stirred at -2°C for 10 min., then treated with neat 4,4,4-trimethoxybutyronitrile (mw 159.19; 37.4 g, 0.2349 mole, 1.59 eq) over 18 min. (brief excursion to 12°C). The mixture was stirred at -2°C. At t = 1.5 h, ISTD GC analysis indicated the presence of 2,3-dimethylbutadiene (0.62 W%), methyl 3-cyanopropionate (18.8 normM%), dibromide (10.0 normM%), methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate (69.7 normM%), and a 2:1 adduct (0.85 W%). At t = 18 h, ISTD GC analysis indicated the presence of dimethylbutadiene (1.8 W%), methyl 3-cyanopropionate (1.4 normM%), dibromide (2.3 normM%), methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate (93.5 normM%), 2:1 adduct (1.0 W%), and $MeO_2CCH_2CH_2COCH(CN)CH_2CO_2Me$ (0.57 A%). The mixture was quenched with 100 mL H_2O and warmed to 25°C to give a two-phase mixture. The aqueous phase was separated, extracted with 50 mL

heptane. The two organic phases were combined to give a solution containing the above-titled compound (weight: 328.12 g.).

Example 53: Preparation of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid

A portion of the solution of (3*S*,4*S*)-3,4-dimethyl-1-(2,2,2-trimethoxyethyl)cyclopentanecarbonitrile from the previous example (183.84 g, from 0.08270 mole dibromide) was treated with 1N HCl (41.4 mL, 0.0414 mole, 0.50 eq) followed by 6N HCl (37.7 mL, 0.2262 mole, 2.74 eq) to adjust the pH from ~11 to ~2 (paper). The two phase mixture was stirred at RT for 1 h, at which time hydrolysis of orthoester (ret time 22.0 min.) to methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate (ret time 19.7 min.) was complete by GC. The aqueous phase was separated and discarded. The organic phase was treated with 50% aq. sodium hydroxide (mw 40.00; 14.0 g, containing 7.0 g [0.175 mole, 2.12 eq] sodium hydroxide) and 40 mL H_2O. On contact with the base, the organic phase turned from orange to dark brown. The mixture was stirred at RT for 3 h, at which time hydrolysis to the sodium salt of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid was complete by TLC. The organic phase was separated, extracted with 20 mL H_2O. The aqueous phases were combined, the pH adjusted from 13.2 to 2.1 by addition of 6N HCl (28.25 mL, 0.1695 mole, 2.05 eq), and extracted with toluene (3 x 40 mL). The toluene extracts were combined, washed with 40 mL H_2O to remove polar unknowns (R_f = 0.02 and 0.06), and concentrated by Rotovap to a thick red-amber oil which rapidly and exothermically crystallized. The crystals were identified as the above-titled compound in essentially homogeneous form by TLC (R_f = 0.44; eluant: 70/20/5/5 EtOAc/MeOH/conc NH_4OH/H_2O). Weight: 14.8317 g (mw 181.24; 0.08183 mole, 99.0 M% yield from dibromide).

Example 54: Preparation of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid

Crystalline 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid from the previous example (mw 181.24; 14.8317 g, 0.08183 mole), after storage in the refrigerator for 45 days, was stirred with 60 mL 0°C MeOH to form a solution. To this solution was added a solution of potassium hydroxide (mw 56.11; 11.0873 g of 87.3 W% pure material, 9.6792 g, 0.1725 mole, 2.11 eq) in 40 mL MeOH. An aqueous slurry of molybdenum promoted sponge nickel (Johnson Matthey A-7000; 5.73 g dry weight [0.32 g/g cyanoacid potassium salt]) was placed in a 300 mL stainless steel autoclave along with 60 mL MeOH. The vessel was sealed, purged with H_2, pressurized to 50 psig with H_2, and warmed to 30°C. The above solution of cyanoacid potassium salt in MeOH (mw 219.33; 0.08183 mole, 17.9478 g) was metered into the hydrogenation vessel over 2.7 h. The mixture was held at 30°C /50 psig H_2. After 20 h, uptake essentially ceased.

After a total of 44 h, the mixture was vacuum filtered and the catalyst rinsed with MeOH. The combined filtrate and washes (weight: 249.10 g) were treated with 33 mL H_2O, concentrated by Rotovap, treated with 28 mL H_2O, and further concentrated to a weight of 51 g. This solution (pH 14.0) was treated with glacial acetic acid (mw 60.05; 10.88 g, 0.1812 mole, 2.21 eq) to give a slurry which was cooled to 0-5°C, stirred for 1 h, filtered, and dried by N_2 stream. The crystals were identified as the above-titled compound in essentially pure form by TLC (eluant: 70/20/5/5 EtOAc/MeOH/conc NH_4OH/H_2O; R_f [hydroxyacid] = 0.34; R_f [title compound] = 0.20). Weight: 15.601 g.

A portion of the crude above-titled compound (15.48 g, from 0.08120 mole cyanoacid) was suspended in 155 mL isopropanol, stirred at 80°C (bath temp) for 30 min., then cooled to 0-5°C, stirred for 1 h, then filtered. The filtrate was used to wash the solids out of the flask. The cake was dried by N_2 stream. Weight: 10.791 g. The filtrate was concentrated by Rotovap to solids (weight: 4.299 g).

A portion of the triturated above-titled compound (10.67 g, from 0.08029 mole cyanoacid) was suspended in 53 mL 25% (v/v) iPrOH/H_2O and heated to 80°C. The solids did not completely dissolve, so 3.6 mL isopropanol was added and the temperature increased to 87°C. The solids completely dissolved to form a golden amber solution. The solution was cooled to 0-5°C (solids crystallized out when the temperature was 78°C), stirred for 2 h, and filtered. The cake was washed with the filtrate and dried by N_2 stream. The product was identified as the above-titled compound by LC (99.8 W% potency). The crystals contained no impurity above 0.1 W% except for 0.18 A% of a later eluting peak (RRT 1.84) and 0.12 W% of an earlier eluting peak (RRT 0.48). A metals screen detected Ni (4.2 ppm) and Mo (0.6 ppm). Weight: 9.634 g (mw 185.27; 9.615 g, 0.05190 mole, 64.6 M% yield from cyanoacid).

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

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

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 (> 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 > 55°C. The filter cake was rinsed with water (25 mL) that had been heated to a temperature > 50°C. The combined aqueous layers were cooled to a temperature < 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 < 5°C. The resulting slurry was stirred at a temperature < 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.

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 < 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 < 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%).

Example 57: Preparation of (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane

To a dry, inert vessel was charged (*R*,*R*)-2,3-dimethyl-1,4-bis-(toluene-4-sufonyloxy)-butane (mw 426.56, 100 Kg, 234 mol, 1.00 eq), potassium bromide (mw 119.00, 60 Kg, 504 mol, 2.15 eq.), and 180 L toluene. The slurry was agitated and tetrabutylammonium bromide (mw 322.37, 6 Kg 18.60 mol, 0.08 eq.) in 6 L water was added. The slurry was heated to 89-93°C for at least 8 hours and then cooled to 60-65°C and 50 L toluene and 130 L water were added. The aqueous phase was removed and the organic phase washed at 50°C with two 50 L portions of water. The resulting product containing organic phase was cooled to less than 25°C. Vacuum was applied and the organic solution distilled to about a 50 wt% solution containing (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane (57.1 Kg, 234 mol).

Example 58: Preparation of methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate

To a dry, inert vessel was charged a solution of lithium hexamethyldisilazide in THF (mw 167.33; 24 wt%; 500 Kg, 3.3 eq.). The solution was vacuum distilled to about 50% of its initial volume. The toluene solution of (2*R*,3*R*)-1,4-dibromo-2,3-dimethylbutane (mw 243.97; 57.1 Kg, 234 mol, 1 eq) from the previous example was added maintaining the temperature below 5°C. 4,4,4-trimethoxybutyronitrile (mw 159.19; 51.0 Kg, 320 mol, 1.4 eq.) was added over 6 h maintaining the temperature between 0 and 5°C. When the reaction was deemed complete by GC the reaction was quenched by the controlled addition of 15 L water and then 135 L water was added and the mixture allowed to warm to 20°C. The two-phase mixture was separated and the lower aqueous phase discarded. The THF solvent was replaced by three vacuum ditillation chases of a total of 300 L n-heptane. The organic mixture containing (3*S*,4*S*)-3,4-dimethyl-1-(2,2,2-trimethoxyethyl)cyclopentanecarbonitrile was then washed with two 100 L portions of water. 60 L water and 5 L toluene were added and the mixture stirred vigorously. A controlled addition of concentrated hydrochloric acid (mw 36.46; 35 Kg of 37% solution, 355 mol) was performed to adjust the pH to less than pH 3 and the mixture stirred for 30 min. The lower aqueous phase was removed, a water wash was performed and the organic solution containing methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate was taken into the next step.

Example 59: Preparation of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid potassium salt

The solution of methyl 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetate from the previous example was treated with 45 wt% aq. potassium hydroxide (mw 56.11; 29 Kg solution, 233 mol) over about 1 h and then stirred for an additional 1 h until the saponification was complete.

The lower aqueous phase was removed and the organic phase washed with water and the aqueous phases combined. The weight of the aqueous solution containing the above-titled compound was approximately 100 Kg.

Example 60: Preparation of (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid

A hydrogenation autoclave was charged with molybdenum promoted sponge nickel (Johnson Matthey A-7000; 4 Kg), 45 wt% aq. potassium hydroxide (mw 56.11; 11 Kg, 88.21 mol), and 20 L of water. To this was added approximately 50 Kg of the solution of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid potassium salt from the previous example. The solution was treated with hydrogen at 50 psig while holding the temperature at 30°C. The reaction was complete after 12 h and the catalyst removed by filtration. The remaining 50 Kg of solution of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid potassium salt from the previous example was hydrogenated in the same manner. The two hydrogenation solutions were combined and charged to a tank containing L-tartaric acid (mw 150.09; 2.5 Kg, 16.66 mol) and agitated until the acid had dissolved. The pH of the solution was adjusted to about pH 11.0 with concentrated hydrochloric acid (mw 36.46; 35 Kg of 37% solution, 355 mol) maintaining the temperature between 20-25°C. At this point the crude product started to precipitate. The mixture was then adjusted to pH 6-8 with glacial acetic acid (mw 60.05; 2.5 Kg, 41.67 mol). The crude product was isolated by filtration, washed with 92 Kg propan-2-ol and dried with 40°C nitrogen to give crude (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (mw 185.27; 37 Kg, 199 mol).

The crude (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (mw 185.27; 37 Kg, 199 mol) was dissolved at about 80°C in a mixture of 130 L 2-propanol and 130 L water and solution filtered through a polishing filter. The solution was cooled to 50-55°C where the product began to crystallize. After further cooling to 20°C the slurry was vacuum distilled while

adding two 35 Kg portions of 2-propanol to displace the water. When a final distillation volume of about 4 L/Kg was reached the slurry was cooled to between 0-5°C and filtered. The filter cake was washed with 40 Kg 2-propanol and dried with 40°C nitrogen to give (3*S*,4*S*)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (mw 185.27; 30 Kg, 161.91 mol).

Example 61: Preparation of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid

To a clean inert vessel was charged a solution of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid potassium salt (mw 219.3; 106 Kg of 48% solution, 232 mol) and 35 L water. The solution was stirred and vacuum distilled to reduce the volume by 35 L and then, while maintaining the temperature at 0-5°C, slowly transferred to a vessel containing 92.8 Kg of 5.7M aqueous hydrochloric acid and seed crystals of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid. An additional 10 L water was added and once the transfer was complete the resulting slurry was stirred at 0°C for 1 h, filtered and washed with 75 L cold water. The cake was partially dried with a nitrogen sweep for about 1 h to give 86.82 Kg of a water wet cake of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid.

Example 62: Preparation of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid potassium salt

86 Kg of water wet 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid from the previous example was treated with 45 wt% aq. potassium hydroxide (mw 56.11; 63.2 Kg solution, 506 mol) over about 1 h to give a homogeneous solution containing 2 ((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid potassium salt.

Example 63: Preparation of 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid tert-butylamine salt

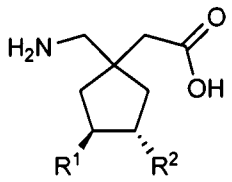
To a 250 mL 3-neck round bottom flask (RBF), equipped with nitrogen inlet and mechanical overhead stirrer was charged a 25 g aqueous solution containing 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid potassium salt (mw 219.3; 13.2 g, 0.06 mol) and potassium hydroxide (mw 56.11; 0.68 g, 0.012 mol), 25 mL water, and 55 mL toluene. Aq. hydrochloric acid (mw 36.43; 7.3 g of 37% solution, 0.075 mol) was added over about 3 minutes to adjust the pH to below pH 2. After stirring for 5 minutes the phases were allowed to separate and the lower aqueous phase removed. A 20 mL water wash of the product containing organic layer was performed and to the resulting toluene solution was added 10 mL 2-propanol. Maintaining the solution at 20-25°C tert-butyl amine (mw 73.14, 5.2 g, 0.07 mol, 1.2 eq) was added over about 5 minutes. The resulting slurry was warmed to 75°C providing a cloudy mixture. On cooling at a rate of about 20°C/hr to 5°C the salt precipitated. After stirring for an hour at 0-5°C the solids were filtered, washed with 50 mL toluene and dried in a vauum oven at 40°C to provide solid 2-((3*S*,4*S*)-1-cyano-3,4-dimethylcyclopentyl)acetic acid tert-butylamine salt (mw 254.1; 12.8 g 0.05 moles, 83%).

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.

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,



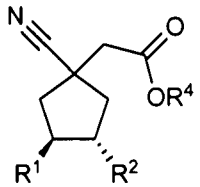
1

or a pharmaceutically acceptable salt thereof, or an opposite enantiomer of the compound of Formula 1 or pharmaceutically acceptable salt 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) reducing a cyano moiety of a compound of Formula 5,

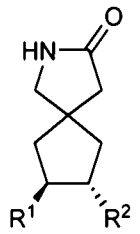


5

or an opposite enantiomer thereof, or a salt of the compound of Formula 5 or opposite enantiomer thereof, to an amino moiety, wherein R^1 and R^2 in Formula 5 are as defined above for Formula 1, and R^4 is selected from hydrogen atom and C_{1-6} alkyl; and

(b) optionally converting the compound of Formula 1 or the opposite enantiomer thereof to a pharmaceutically acceptable salt of the compound of Formula 1 or the opposite enantiomer thereof.

2. The method according to claim 1, further comprising hydrolyzing a compound of Formula 6,

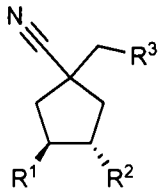


6

or an opposite enantiomer thereof, wherein R^1 and R^2 in Formula 6 are as defined above for Formula 1.

3. The method according to claim 1, further comprising hydrolyzing the compound of Formula 5.

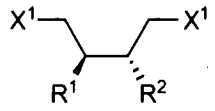
4. The method according to any one of claims 1-3, further comprising deprotecting a compound of Formula 4,



4

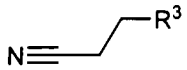
or an opposite enantiomer thereof, to give a compound of Formula 5 or an opposite enantiomer thereofwherein R^1 and R^2 in Formula 4 are as defined above for Formula 1, and R^3 in Formula 4 is a protective group for a carboxylic acid or ester.

5. The method according to claim 4, further comprising reacting a compound of Formula 2,



2 ,

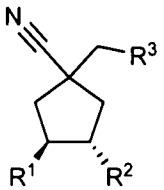
or an opposite enantiomer thereof, with a compound of Formula 3,



3 ,

in the presence of a base, to give the compound of Formula 5 or an opposite enantiomer thereof, or a salt of the compound of Formula 5 or opposite enantiomer thereof, wherein R^1 and R^2 in Formula 2 are as defined above for Formula 1, X^1 in Formula 2 is a leaving group, and R^3 in Formula 3 is as defined above for Formula 4.

6. A compound of Formula 4,

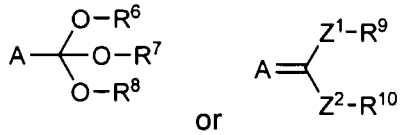


4 ,

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; and

R^3 is a carboxylic acid or ester protective group having a structure represented by



7 or 8

in which "A" in Formula 7 and Formula 8 represents a point of attachment to the remainder of the compound of Formula 4;

R^6, R^7, and R^8 are each independently a C_{1-6} alkyl, or together with the atoms to which they are attached, form a bicyclic heterocycle having only oxygen and carbon ring members;

Z^1 and Z^2 are each independently selected from O and S;

R^9 is C_{1-6} alkyl;

R^{10} is selected from C_{1-6} alkyl, silyl, and C_{1-6} alkylsilyl;

or R^9 and R^{10}, together with the atoms to which they are attached, form a monocyclic heterocycle having only carbon and oxygen ring members, only carbon and sulfur ring members, or only carbon, oxygen, and sulfur ring members.

7. A compound according to claim 6 selected from:

(*S*,*S*)-3,4-dimethyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-dimethyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-dimethyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-diethyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-diethyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-diethyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-dipropyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-dipropyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-dipropyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-dibenzyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-cyclopentanecarbonitrile;

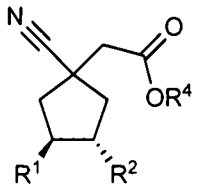
(*S*,*S*)-3,4-dibenzyl-1-(2,2,2-trimethoxy-ethyl)-cyclopentanecarbonitrile;

(*S*,*S*)-3,4-dibenzyl-1-(2,2,2-triethoxy-ethyl)-cyclopentanecarbonitrile;

opposite enantiomers of the foregoing compounds; and

salts of the foregoing compounds and opposite enantiomers thereof.

8. A compound of Formula 5,



5

or an opposite enantiomer thereof, or a salt of the compound of Formula 5 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; and

R^4 is selected from H, C_{1-6} alkyl, aryl-C_{1-3} alkyl, a Group 1 metal ion, a Group 2 metal ion, a primary ammonium ion, or a secondary ammonium ion;

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.

9. A compound according to claim 8 selected from:

(3*S*,4*S*)-(3,4-dimethyl-1-cyano-cyclopentyl)-acetic acid;

(3*S*,4*S*)-(3,4-diethyl-1-cyano-cyclopentyl)-acetic acid;

(3*S*,4*S*)-(3,4-dipropyl-1-cyano-cyclopentyl)-acetic acid;

(3*S*,4*S*)-(3,4-dibenzyl-1-cyano-cyclopentyl)-acetic acid;

methyl, ethyl, propyl, isopropyl, and benzyl esters of the foregoing acids;

salts of the aforementioned acids; and

opposite enantiomers of the aforementioned acids, salts, and esters.

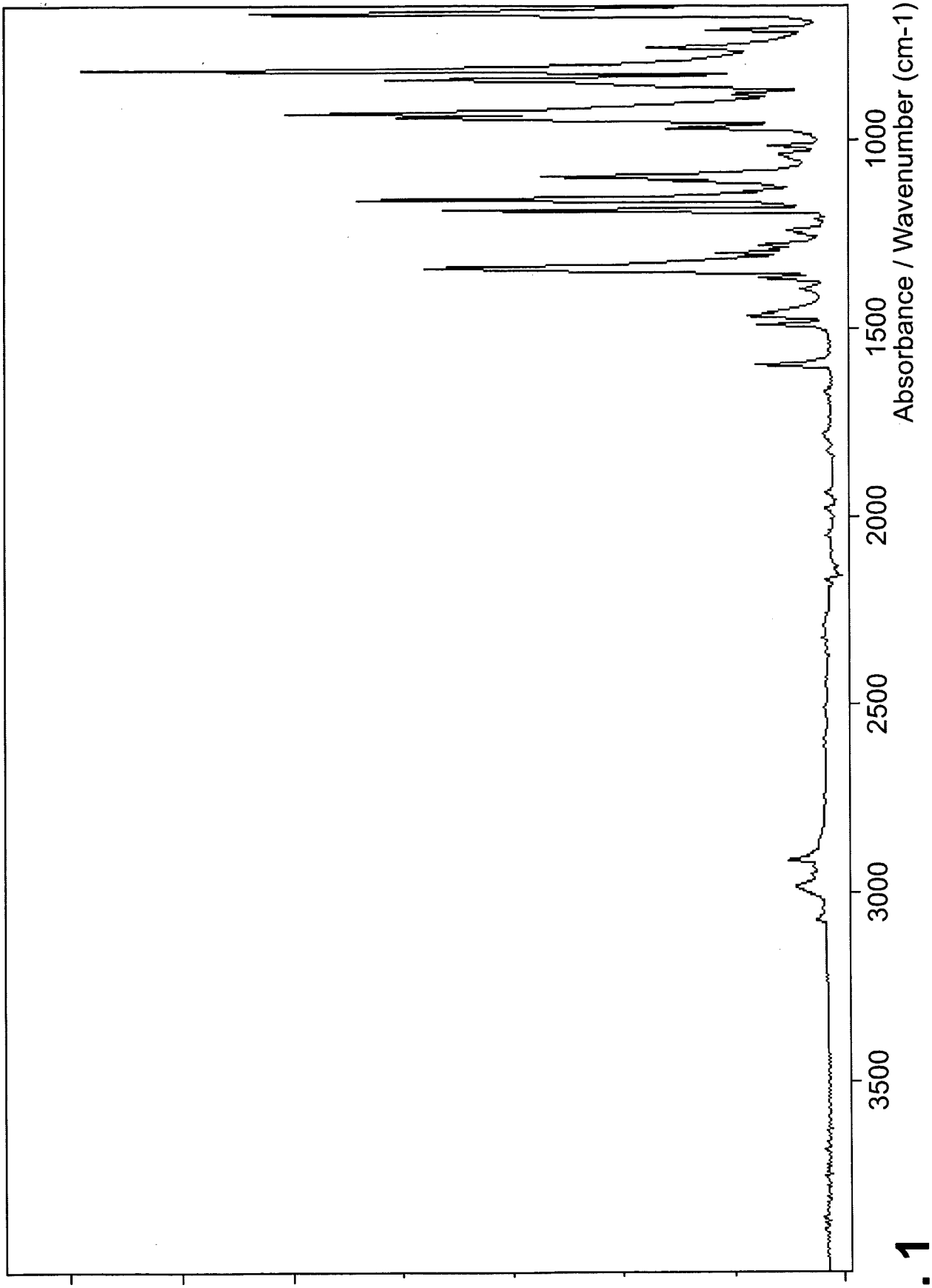

1.4
1.2
1
.8
.6
.4
.2
0
3500
3000
2500
2000
1500
1000
Absorbance / Wavenumber (cm-1)

FIG. 1

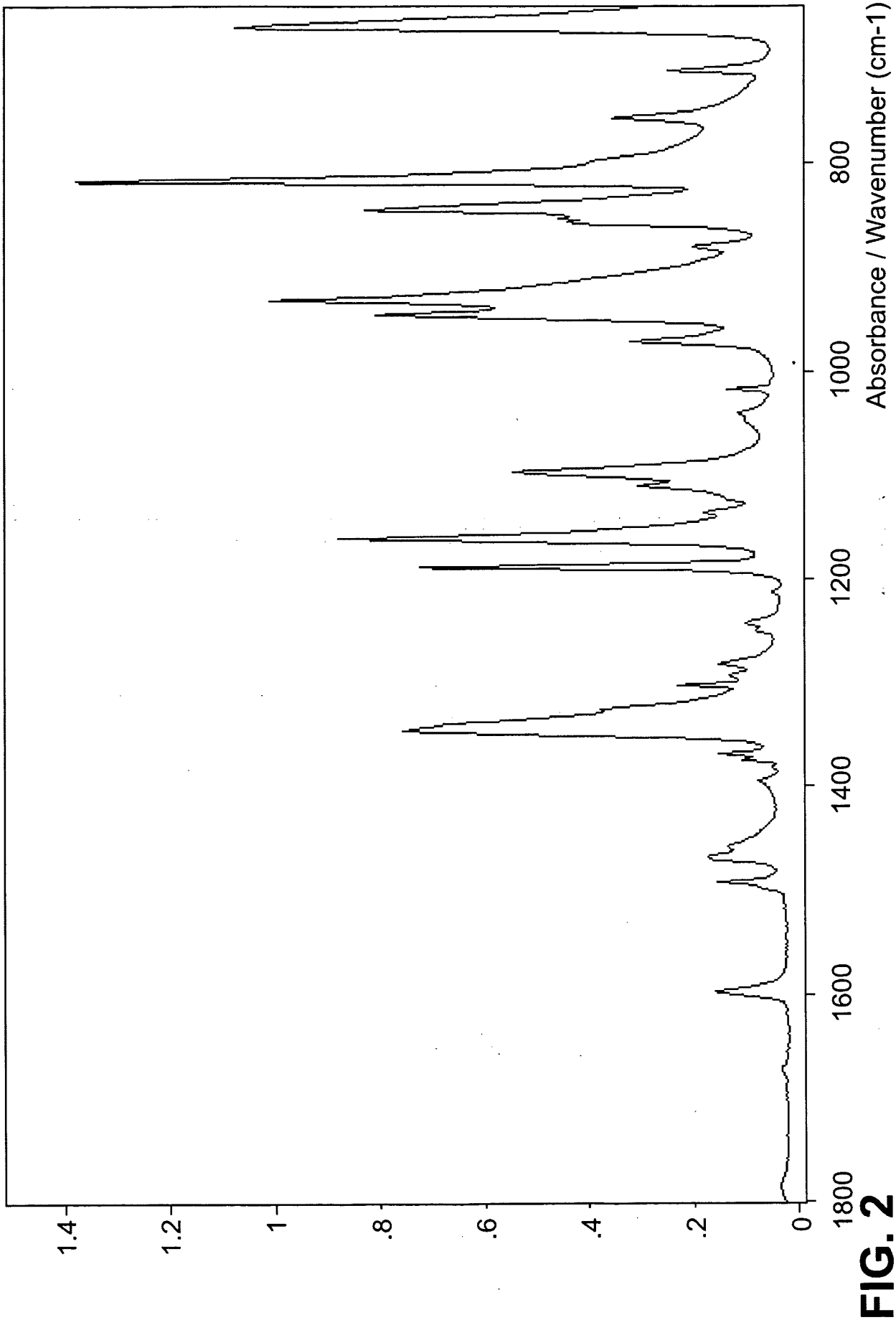

1.4
1.2
1
.8
.6
.4
.2
0
1800
1600
1400
1200
1000
800
Absorbance / Wavenumber (cm-1)

FIG. 2

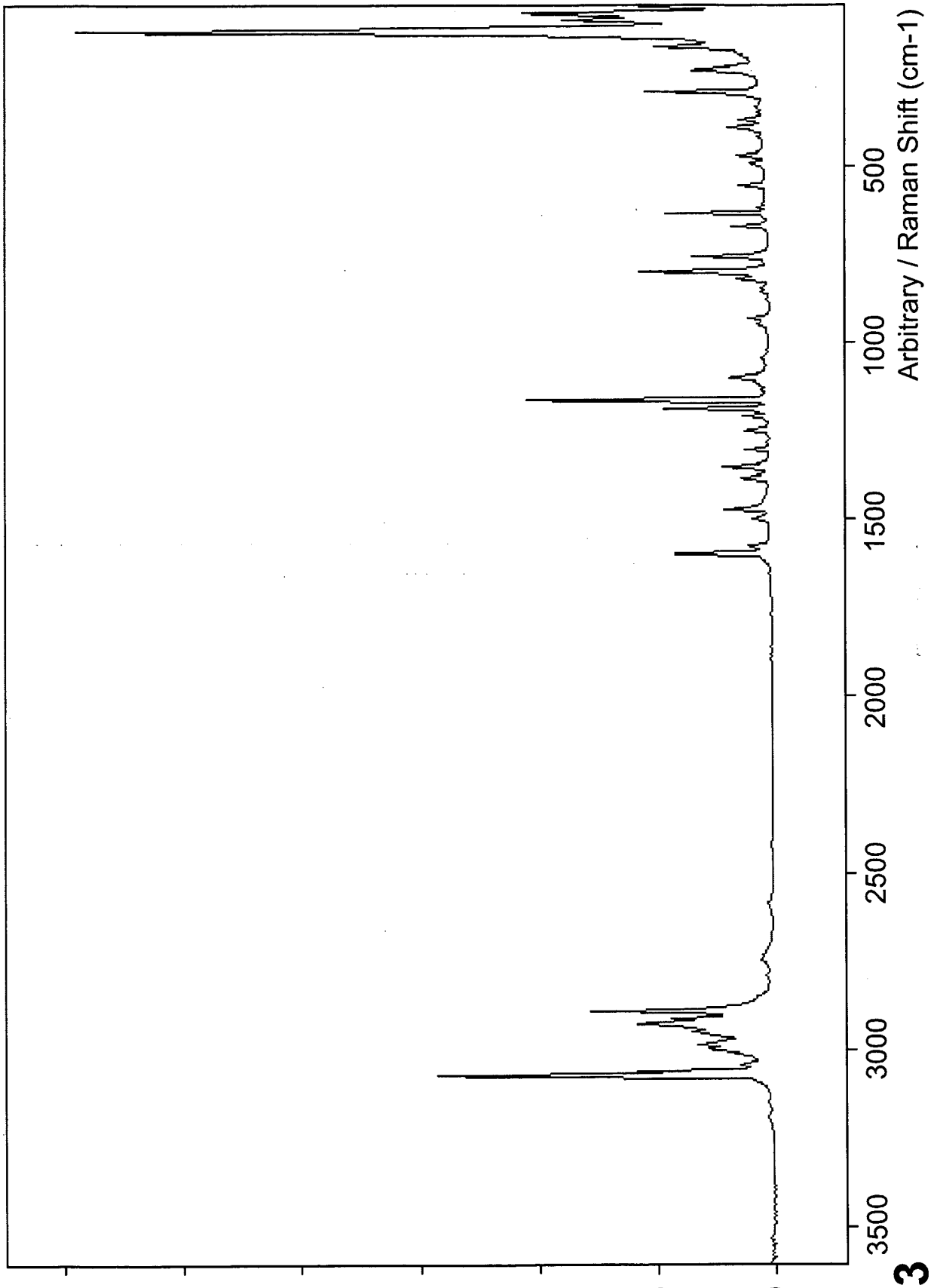

30
25
20
15
10
5
0
3500
3000
2500
2000
1500
1000
500
Arbitrary / Raman Shift (cm-1)

FIG. 3

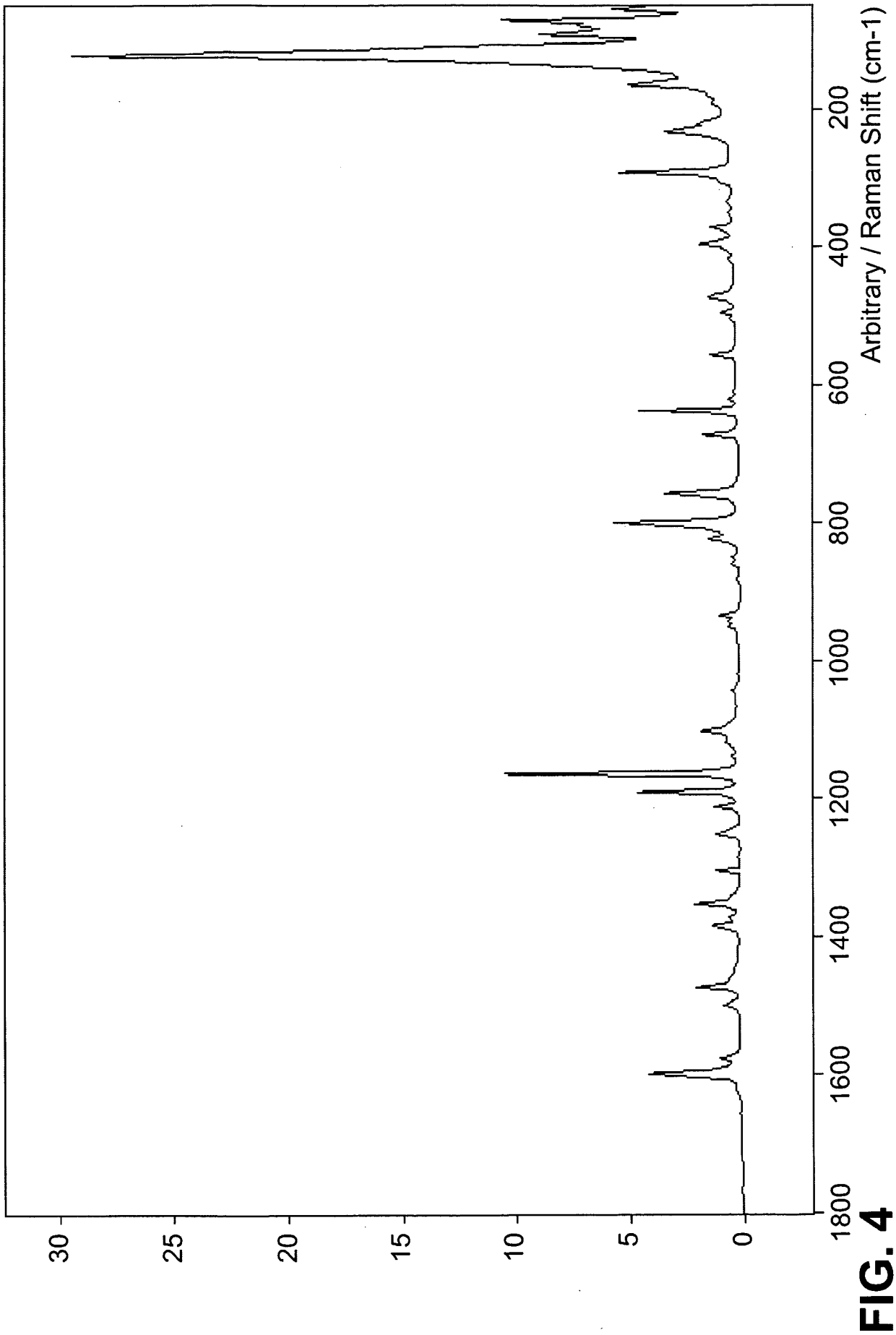

30
25
20
15
10
5
0
200
400
600
800
1000
1200
1400
1600
1800
Arbitrary / Raman Shift (cm-1)

FIG. 4

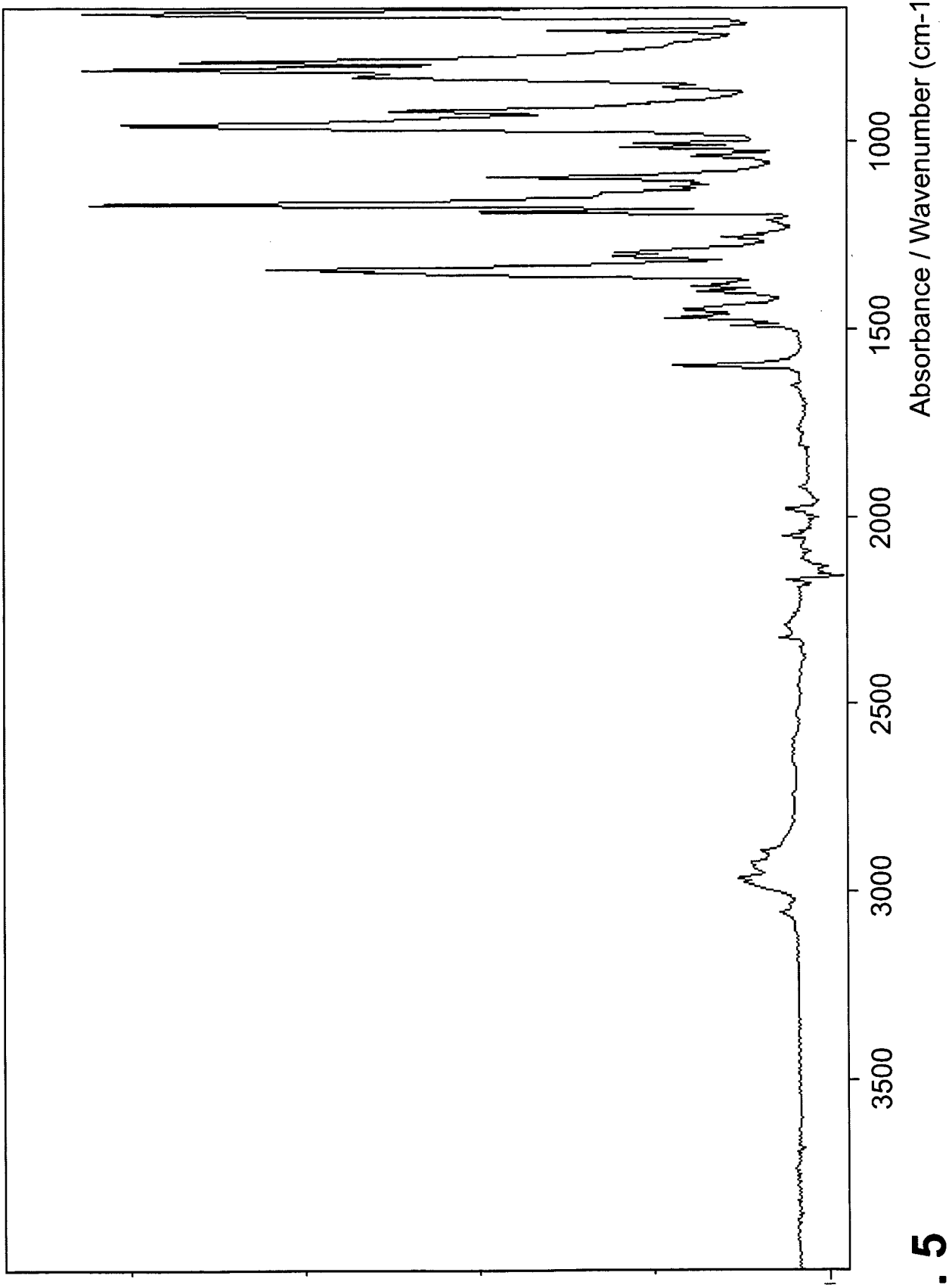

.4
.3
.2
.1
0
3500
3000
2500
2000
1500
1000
Absorbance / Wavenumber (cm-1)

FIG. 5

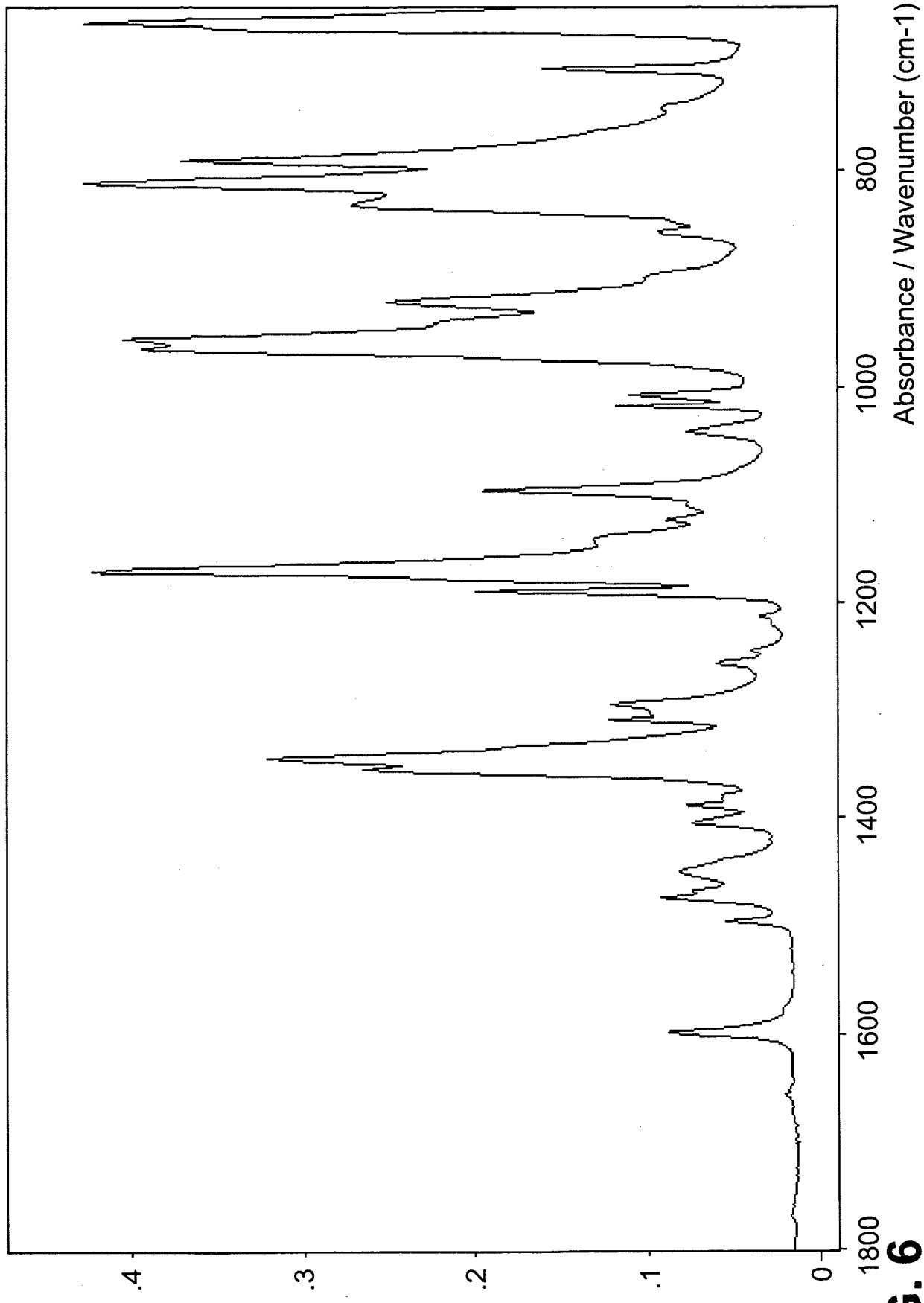

Absorbance / Wavenumber (cm-1)
1800
1600
1400
1200
1000
800
0
.1
.2
.3
.4

FIG. 6

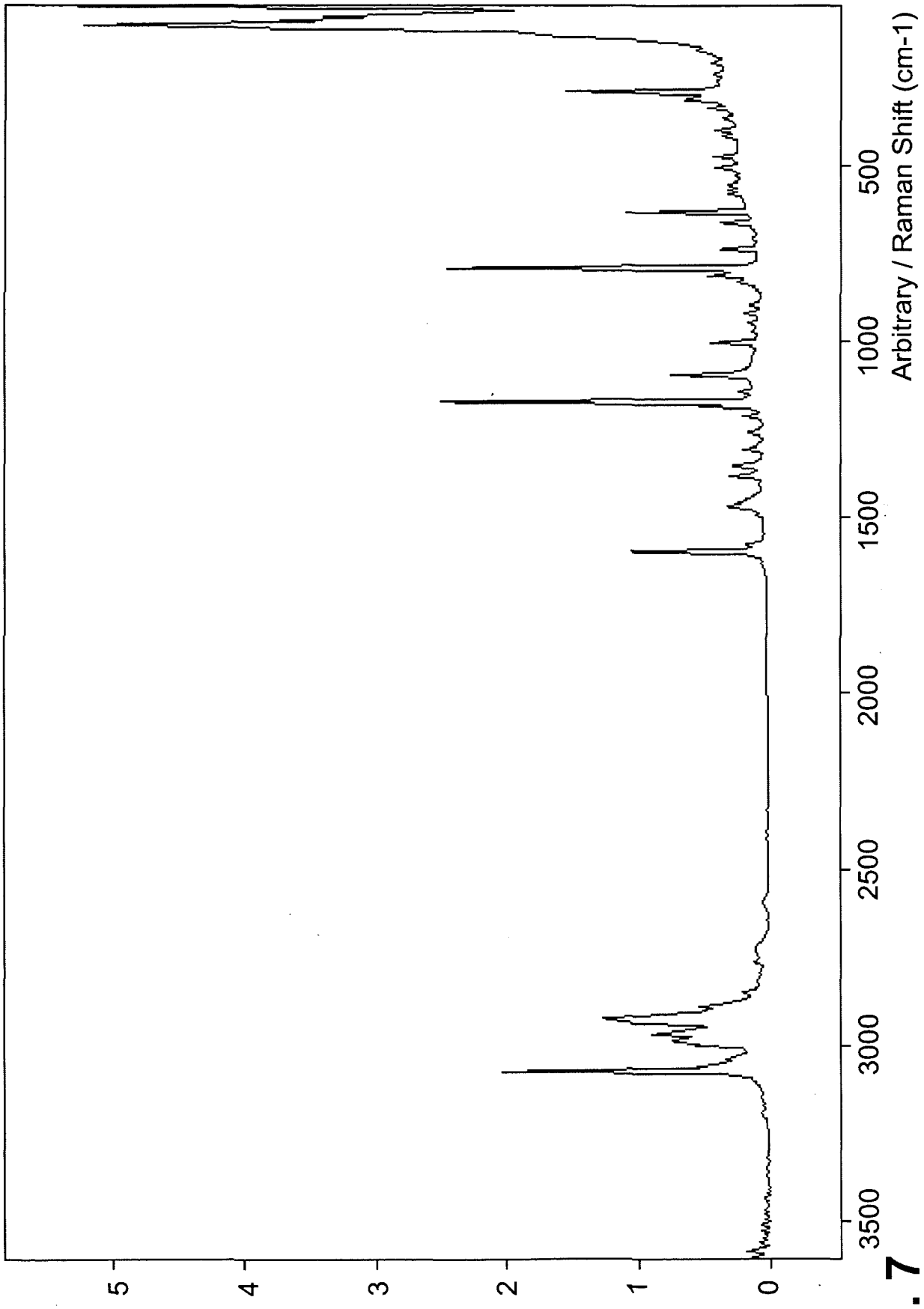

Arbitrary / Raman Shift (cm-1)
3500
3000
2500
2000
1500
1000
500
0
1
2
3
4
5

FIG. 7

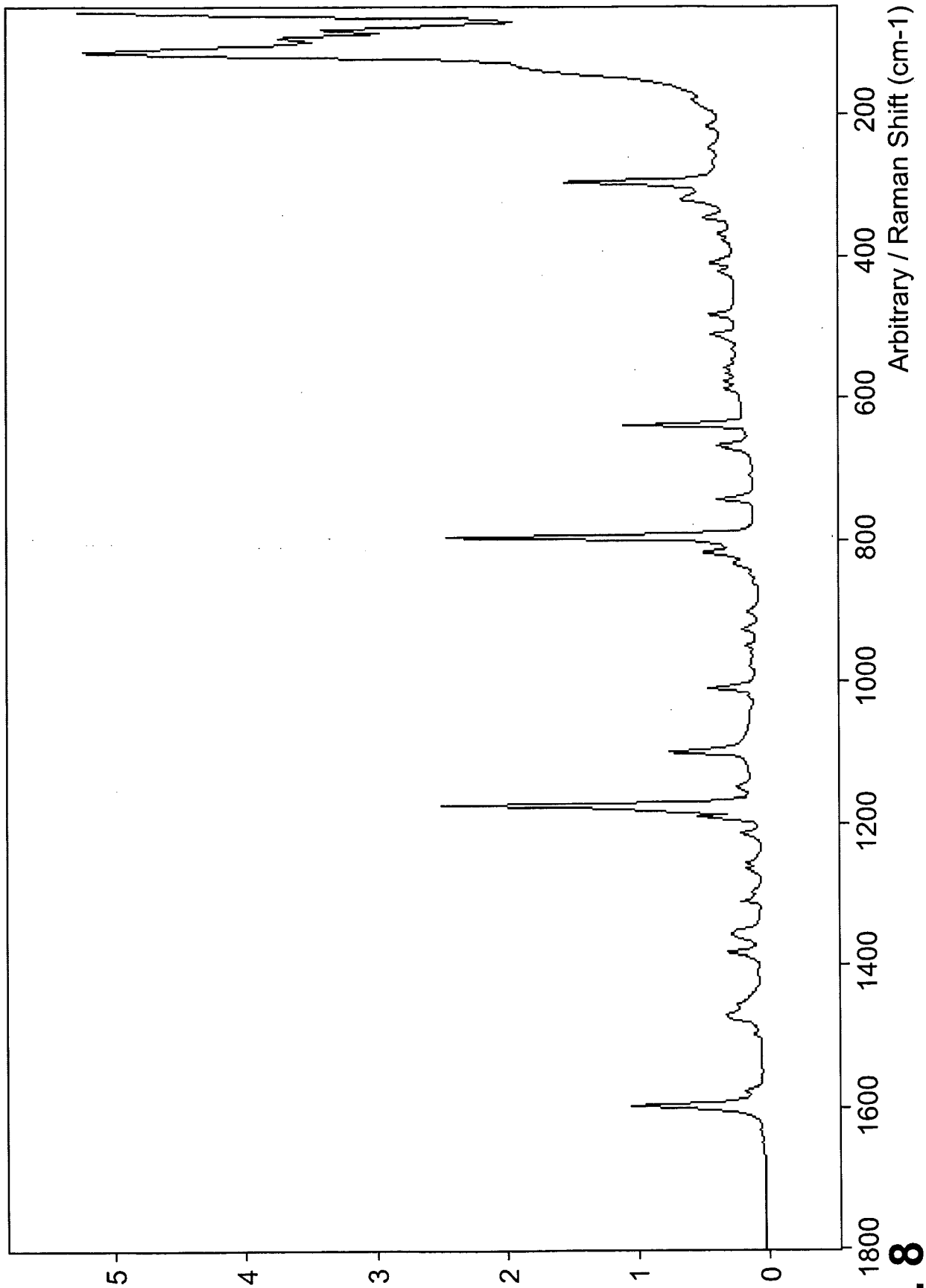

Arbitrary / Raman Shift (cm-1)
200
400
600
800
1000
1200
1400
1600
1800
0
1
2
3
4
5

FIG. 8

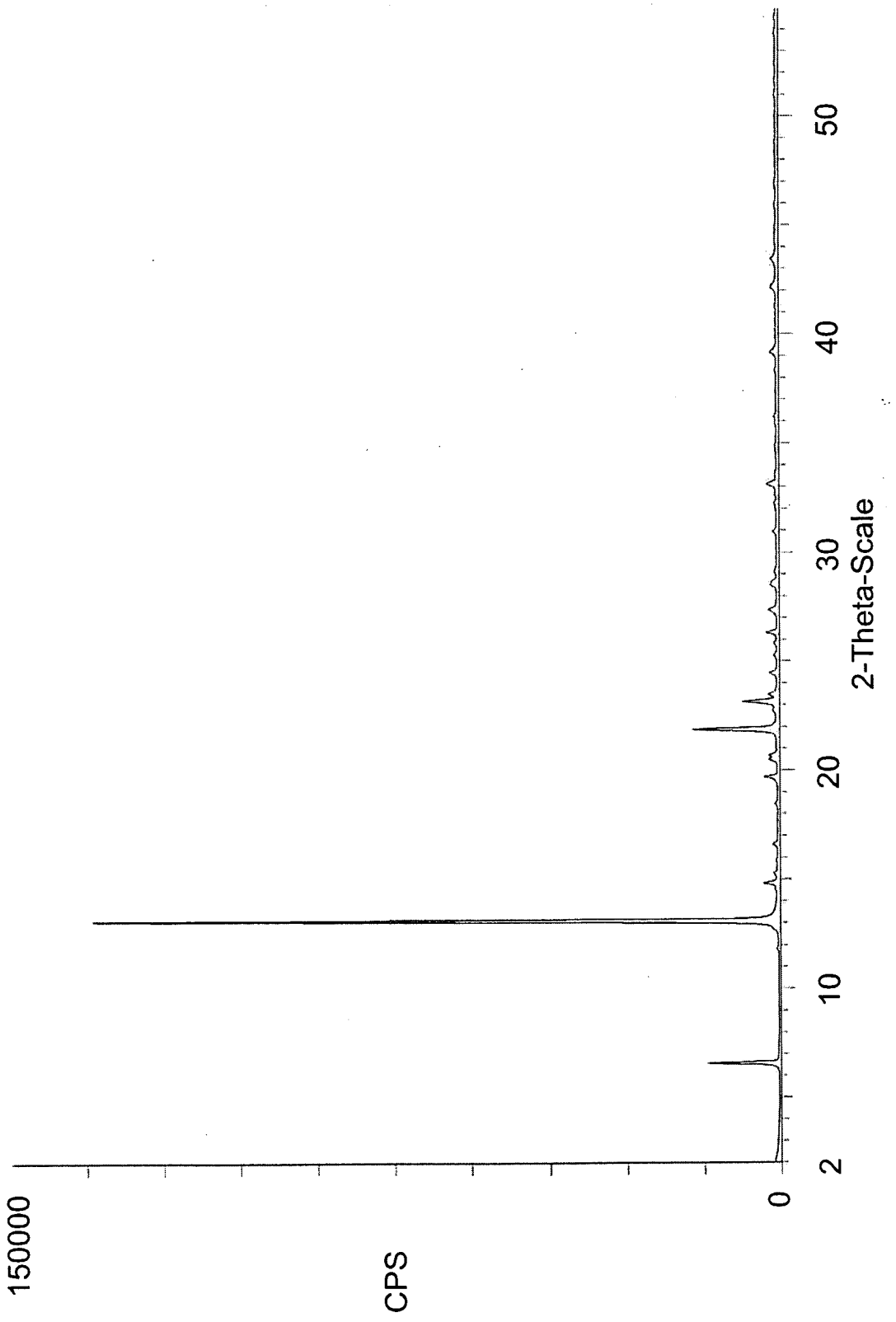


FIG. 9

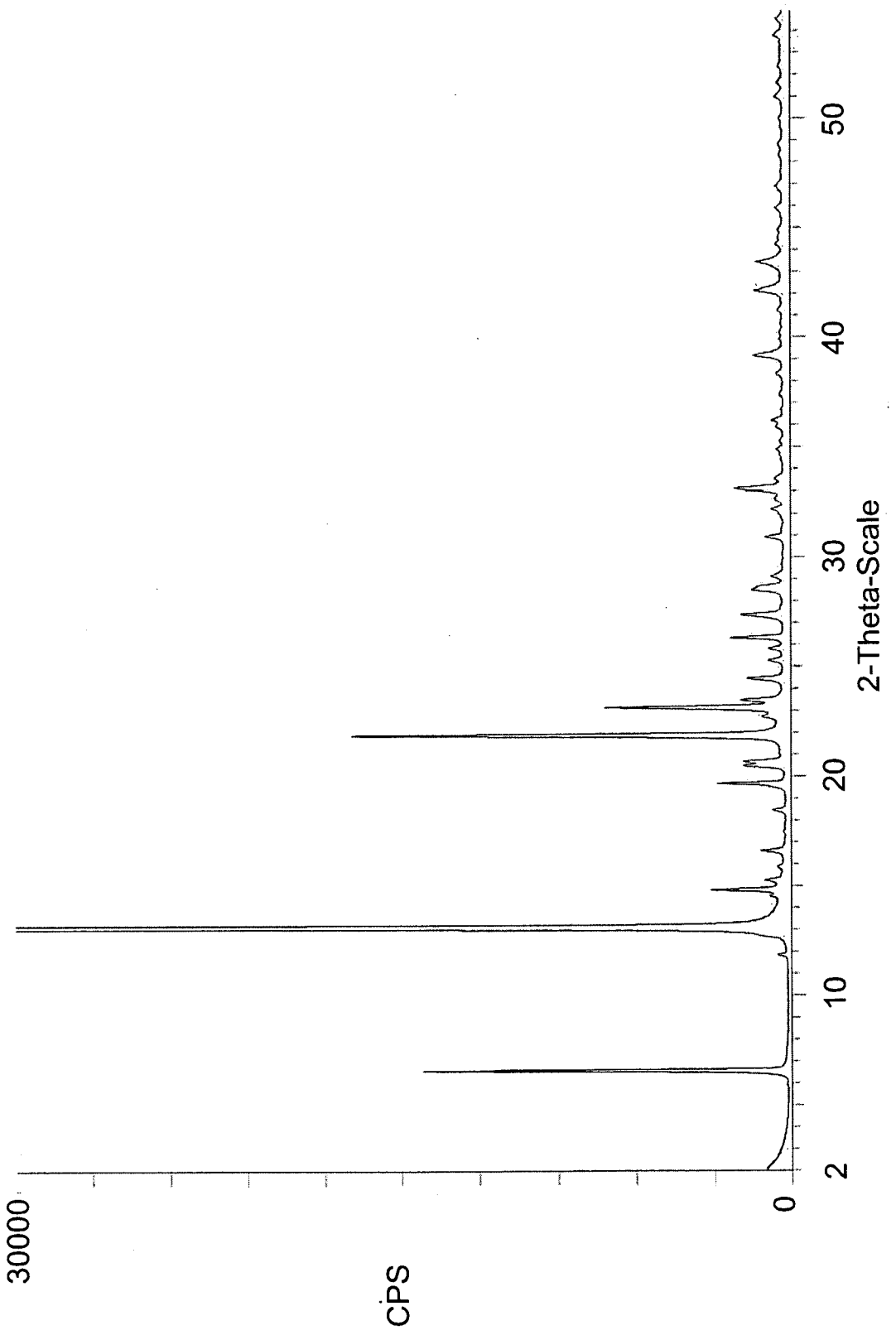


FIG. 10

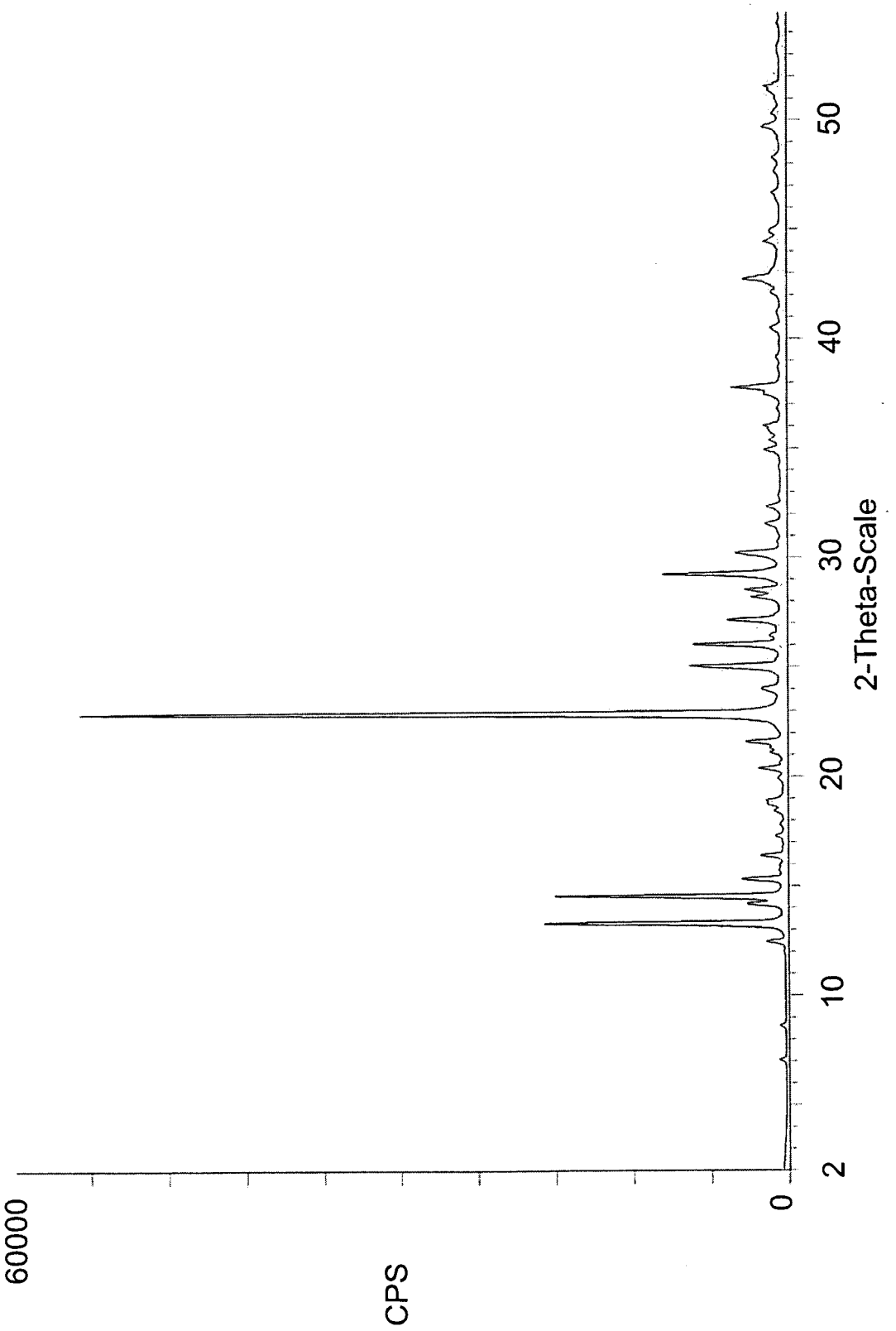


FIG. 11

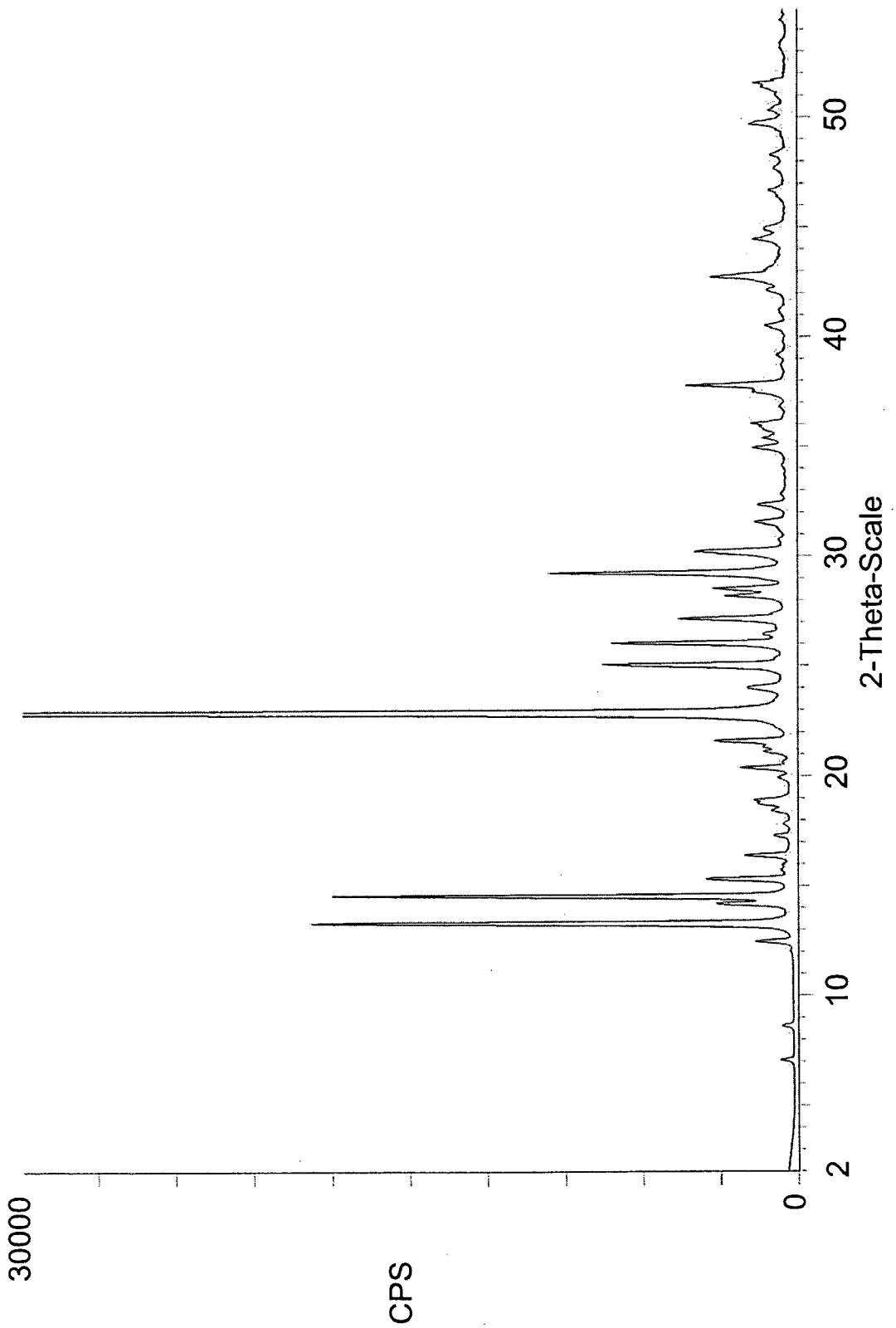


FIG. 12

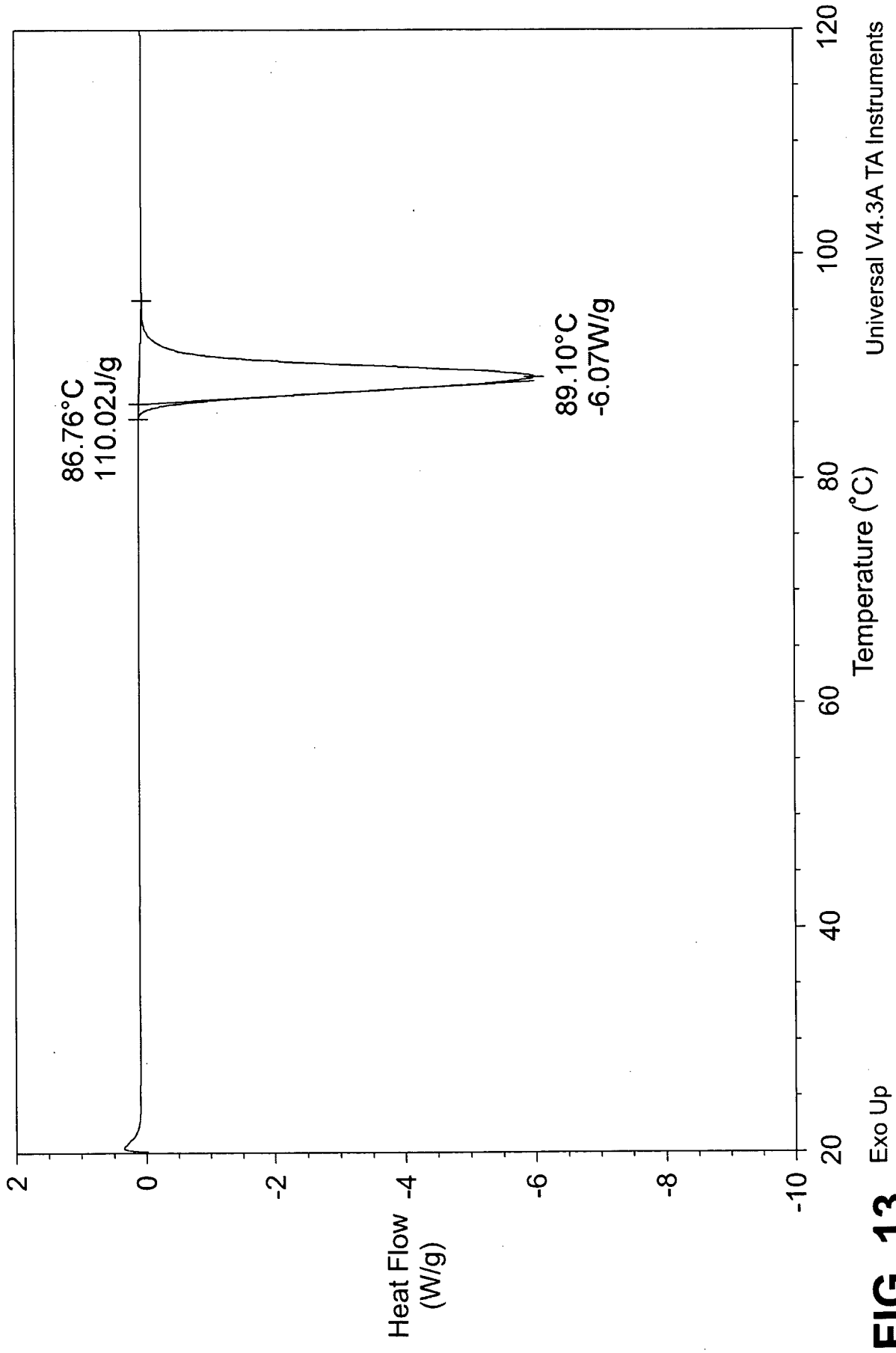

86.76°C
110.02J/g
89.10°C
-6.07W/g
Universal V4.3A TA Instruments
Temperature (°C)
Heat Flow (W/g)
Exo Up
2
0
-2
-4
-6
-8
-10
20
40
60
80
100
120

FIG. 13

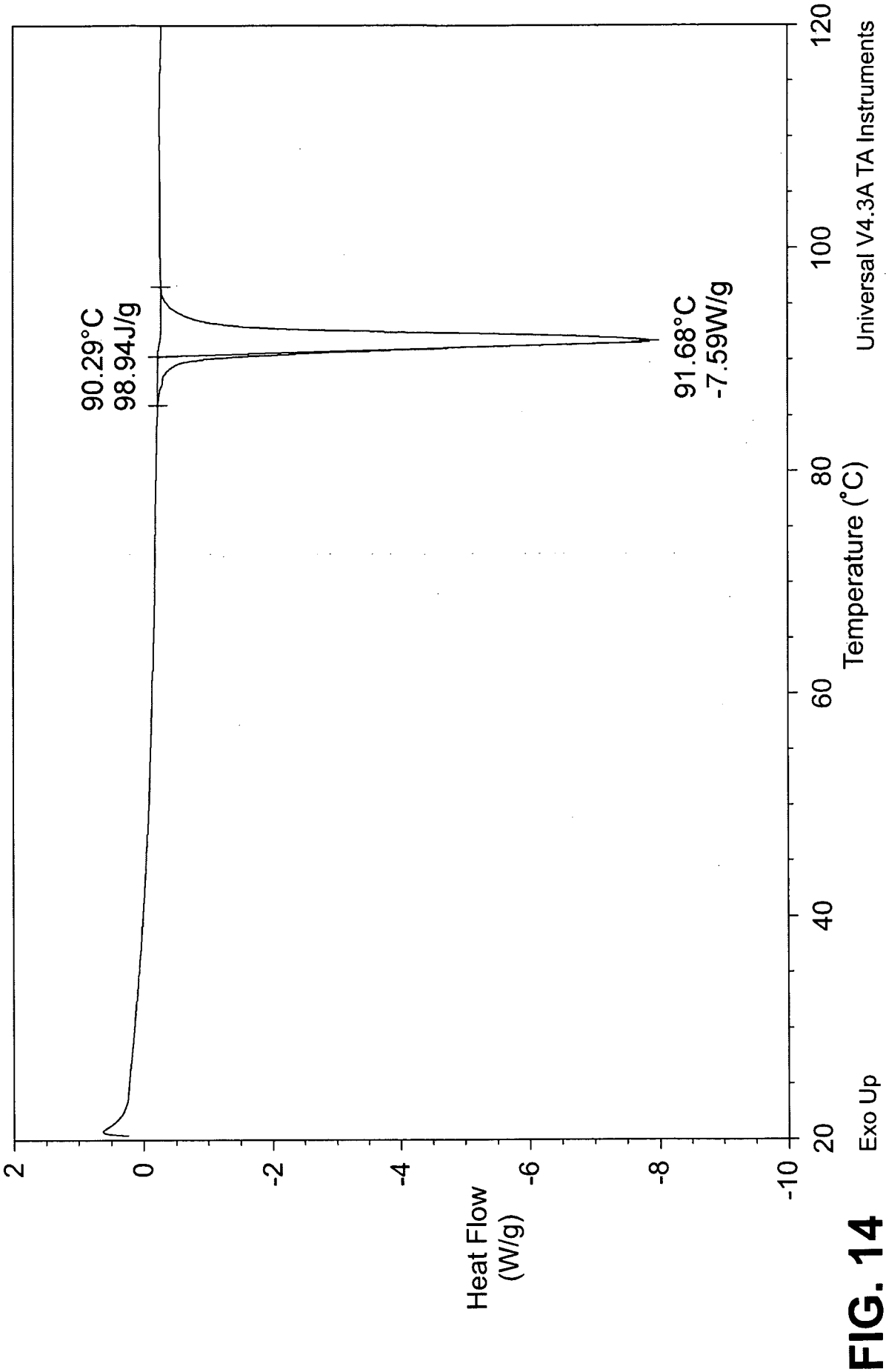

90.29°C
98.94J/g
91.68°C
-7.59W/g
Universal V4.3A TA Instruments
Temperature (°C)
Heat Flow (W/g)
Exo Up
2
0
-2
-4
-6
-8
-10
20
40
60
80
100
120

FIG. 14