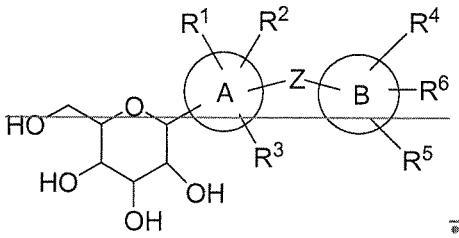
WHAT IS CLAIMED IS:

1. A method for the preparation of a complex of Formula I:



•(amino acid)$_n$ (I)

wherein the subscript n is 1 or 2;

the rings designated by A and B are each independently an aromatic or heteroaromatic ring or fused ring system, selected from the group consisting of benzene, naphthalene, pyrazole, oxazole, oxadiazole, imidazole, thiazole, thiadiazole, triazole, thiophene, furan, pyridine, pyridazine, pyrimidine, pyrazine, benzotriazole, benzimidazole, indole, indazole, triazolopyridine, triazolopyrimidine, purine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,5-naphthyridine, 1,6-naphthyridine, benzothiophene, benzofuran and benzothiazole;

R^1, R^2 and R^3 are each members independently selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_5-C_{10} cycloalkenyl, C_1-C_6 alkyloxy, C_3-C_{10} cycloalkyloxy, cyano and nitro, wherein alkyl and cycloalkyl groups or portions are optionally mono- or polysubstituted by fluorine, or optionally one or more of R^1, R^2 and R^3 are absent, and

when R^1 and R^2 are bound to two adjacent C atoms, R^1 and R^2 are optionally joined together to form a C_3-C_5 alkylene, C_3-C_5 alkenylene or butadienylene bridge, which is optionally partly or completely fluorinated and is optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3 alkoxy and C_1-C_3 alkyl, and wherein one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and wherein one or two methyne groups are optionally replaced by N;

R^4, R^5 and R^6 are each members independently selected from the group consisting of hydrogen, halo, cyano, nitro, hydroxy, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_3 alkyloxy and C_3-C_{10} cycloalkyloxy, wherein alkyl and cycloalkyl groups or portions are optionally mono- or polysubstituted by fluorine, or optionally one or more of R^4, R^5 and R^6 are absent, and

when R^4 and R^5 are bound to two adjacent C atoms, R^4 and R^5 are optionally joined together to form a C_3-C_5-alkylene, C_3-C_5-alkenylene or butadienylene bridge, which is optionally partly or completely fluorinated and is optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3-alkoxy and C_1-C_3-alkyl, and wherein one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and wherein one or two methyne groups are optionally replaced by N;

and optionally, one of R^3 and R^6 is -V-W-X-Y, wherein

V is a member selected from the group consisting of oxygen; sulfur; SO; SO_2; and a single bond;

W is a member selected from the group consisting of C_1-C_6-alkylene, C_2-C_6-alkenylene, C_2-C_6-alkynylene, C_3-C_{10}-cycloalkylene, C_5-C_{10}-cycloalkenylene and (C_3-C_{10}-cycloalkylene)(C_1-C_6-alkylene) wherein the C_3-C_{10}-cycloalkylene portion bonds to V and the C_1-C_6-alkylene portion bonds to X, and

wherein alkylene, alkenylene, alkynylene, cycloalkylene and cycloalkenylene groups or portions are optionally partly or completely fluorinated and are optionally mono- or disubstituted by substituents independently selected from the group consisting of chlorine, hydroxy, C_1-C_3-alkyl, C_1-C_3-alkoxy, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyloxy, C_5-C_{10}-cycloalkenyl and C_5-C_{10}-cycloalkenyloxy, and in cycloalkylene and cycloalkenylene groups or portions one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and one or two methyne groups are optionally replaced by N;

X is a member selected from the group consisting of a single bond; oxygen; sulfur; NR^a, SO; and SO_2;

Y is a member selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{10}-cycloalkyl, C_5-C_{10}-cycloalkenyl, (C_3-C_{10}-cycloalkyl)C_1-C_4-alkyl, (C_5-C_{10}-cycloalkenyl)C_1-C_3-alkyl, (C_3-C_{10}-cycloalkyl)C_2-C_4-alkenyl, C_3-C_6-cycloalkylidenmethyl, (C_5-C_{10}-cycloalkenyl)C_2-C_4-alkenyl, (C_1-C_4-alkyloxy)C_1-C_3-alkyl, (C_2-C_4-alkenyloxy)C_1-C_3-alkyl, (C_3-C_{10}-cycloalkyloxy)C_1-C_3-alkyl, (C_5-C_{10}-cycloalkenyloxy)C_1-C_3-alkyl, (amino)C_1-C_3-alkyl, (C_1-C_4-alkylamino)C_1-C_3-alkyl, di-(C_1-C_3-alkylamino)C_1-C_3-alkyl, (C_1-C_6-alkyl)carbonyl(C_1-C_3)alkyl, (C_2-C_6-alkenyl)carbonyl(C_1-C_3)alkyl, (C_2-C_6-alkynyl)carbonyl(C_1-C_3)alkyl, (arylcarbonyl)C_1-C_3-alkyl, (heteroarylcarbonyl)C_1-C_3-alkyl, (C_1-C_6-alkylsulfonyl)C_1-C_3-alkyl, (C_2-C_6-alkenylsulfonyl)C_1-C_3-alkyl, (C_2-C_6

alkynylsulfonyl)C_1-C_3-alkyl, (arylsulfonyl)C_1-C_3-alkyl, (heteroarylsulfonyl)C_1-C_3-alkyl, (C_1-C_6-alkyl)aminocarbonyl(C_1-C_3)alkyl, (C_2-C_6-alkenyl)aminocarbonyl(C_1-C_3)alkyl, (C_2-C_6-alkynyl)aminocarbonyl(C_1-C_3)alkyl, (arylaminocarbonyl)C_1-C_3-alkyl, (heteroarylaminocarbonyl)C_1-C_3-alkyl, (C_1-C_6-alkyl)carbonyl, (C_2-C_6-alkenyl)carbonyl, (C_2-C_6-alkynyl)carbonyl, arylcarbonyl, heteroarylcarbonyl, (C_1-C_6-alkyl)sulfonyl, (C_2-C_6 alkenyl)sulfonyl, (C_2-C_6-alkynyl)sulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_6 alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, (C_1-C_6-alkyl)aminocarbonyl, (C_2-C_6 alkenyl)aminocarbonyl, (C_2-C_6-alkynyl)aminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, (C_1-C_6-alkylsulfinyl)C_1-C_3-alkyl, (arylsulfinyl)C_1-C_3-alkyl, (heteroarylsulfinyl)C_1-C_3-alkyl,

wherein alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl groups or portions are optionally partly or completely fluorinated and are optionally mono- or disubstituted by substituents independently selected from the group consisting of chlorine, hydroxy, C_1-C_3-alkyl, C_1-C_3-alkoxy, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyloxy, C_5-C_{10}-cycloalkenyl, C_5-C_{10}-cycloalkenyloxy, and NR^bR^e, and in cycloalkyl and cycloalkenyl groups or portions one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and one or two methyne groups are optionally replaced by N, wherein the heterocycle formed by said optional replacement is other than heteroaryl; and

Z is a member selected from the group consisting of oxygen; sulfur; SO; SO_2; 1,1-cyclopropylene; carbonyl; and methylene optionally substituted with one to two substituents independently selected from halo, hydroxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_6 cycloalkyl and C_3-C_6-cycloalkyloxy;

R^a is a member independently selected from the group consisting of H, C_1-C_6-alkyl, C_3-C_6 cycloalkyl and (C_1-C_4-alkyl)carbonyl, wherein alkyl and cycloalkyl groups or portions are optionally partly or completely fluorinated;

each R^b is a member independently selected from the group consisting of H, C_1-C_4-alkyl and (C_1-C_4-alkyl)carbonyl, wherein alkyl groups or portions are optionally partly or completely fluorinated;

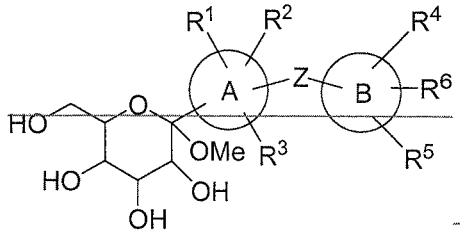
each R^e is a member independently selected from the group consisting of H, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, CHR^dR^e, SO_2R^d, $C(O)OR^d$ and $C(O)NR^dR^e$, wherein alkyl and cycloalkyl groups are optionally partly or completely fluorinated; and

R^d and R^e each independently represent H or C_1-C_6-alkyl, wherein alkyl groups are optionally partly or completely fluorinated;

and pharmaceutically acceptable salts thereof;

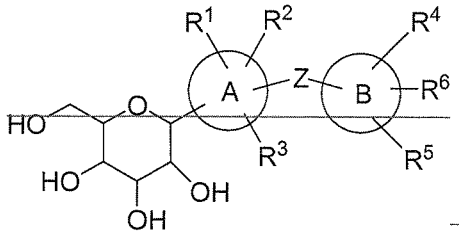
comprising:

(a) reacting a compound of Formula II



(II)

with a reducing agent in the presence of an activating group to form a compound of Formula III



(III); and

(b) contacting said compound of Formula III with an amino acid to form said complex of Formula I;

wherein steps (a) and (b) are performed without purification of said compound of Formula III and wherein steps (a) and (b) are performed sequentially without an intervening protection or deprotection step.

2. A method in accordance with claim 1, wherein said process is conducted in a single reaction vessel.

3. A method in accordance with claim 2, wherein said complex of Formula I is isolated as a crystalline solid.

4. A method in accordance with claim 1, wherein rings designated by A and B are each benzene rings.

5. A method in accordance with claim 1, wherein R^6 is -V-W-X-Y and W is selected from the group consisting of C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, C_3-C_{10} cycloalkylene and (C_3-C_{10} cycloalkylene)(C_1-C_6 alkylene), wherein alkylene, alkenylene, alkynylene, cycloalkylene and cycloalkenylene groups or portions are optionally partly or completely fluorinated and are optionally mono- or disubstituted by substituents independently selected from the group consisting of chlorine, hydroxy, C_1-C_3 alkyl, C_1-C_3

~~alkoxy, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyloxy, C_5-C_{10}-cycloalkenyl and C_5-C_{10} cycloalkenyloxy, and in cycloalkylene and cycloalkenylene groups or portions one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and one or two methyne groups are optionally replaced by N.~~

~~6. A method in accordance with claim 5, wherein W is selected from the group consisting of C_1-C_6-alkylene, C_2-C_6-alkenylene, C_2-C_6-alkynylene and C_3-C_{10} cycloalkylene, wherein alkylene, alkenylene, alkynylene, cycloalkylene and cycloalkenylene groups or portions are optionally partly or completely fluorinated and are optionally mono- or disubstituted by substituents independently selected from the group consisting of chlorine, hydroxy, C_1-C_3-alkyl, C_1-C_3-alkoxy, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyloxy, C_5-C_{10} cycloalkenyl and C_5-C_{10}-cycloalkenyloxy, and in cycloalkylene and cycloalkenylene groups or portions one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and one or two methyne groups are optionally replaced by N.~~

~~7. A method in accordance with claim 1, wherein R^6 is -V-W-X-Y and X is selected from the group consisting of oxygen, sulfur, a single bond and NR^a.~~

~~8. A method in accordance with claim 7, wherein X is selected from the group consisting of oxygen and a single bond.~~

~~9. A method in accordance with claim 1, wherein R^6 is -V-W-X-Y and Y is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{10}-cycloalkyl, (C_3-C_{10}-cycloalkyl)C_1-C_4 alkyl, (C_1-C_4-alkyloxy)C_1-C_3-alkyl, (C_3-C_{10}-cycloalkyloxy)C_1-C_3-alkyl, (amino)C_1-C_3-alkyl, (C_1-C_4-alkylamino)C_1-C_3-alkyl, (C_1-C_6-alkyl)carbonyl, (C_2-C_6-alkenyl)carbonyl, (C_2-C_6 alkynyl)carbonyl, (C_1-C_6-alkyl)sulfonyl, (C_2-C_6-alkenyl)sulfonyl, or (C_2-C_6-alkynyl)sulfonyl, wherein alkyl, alkenyl, alkynyl and cycloalkyl groups or portions are optionally partly or completely fluorinated and are optonally mono- or disubstituted by substituents independently selected from chlorine, hydroxy, C_1-C_3-alkyl, C_1-C_3-alkoxy and C_3-C_6 cycloalkyl, and in cycloalkyl groups or portions one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and one or two methyne groups are optionally replaced by N.~~

10. A method in accordance with claim 9, wherein Y is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl and (C_1-C_4 alkyloxy)C_1-C_3 alkyl.

11. A method in accordance with claim 1, wherein R^6 is -V-W-X-Y and Z is selected from the group consisting of oxygen, sulfur, or methylene optionally substituted with one to two substituents independently selected from halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl and C_3-C_6 cycloalkyloxy.

12. A method in accordance with claim 11, wherein Z is methylene.

13. A method in accordance with claim 1, wherein R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkyloxy and cyano.

14. A method in accordance with claim 13, wherein R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo and C_1-C_6 alkyl.

15. A method in accordance with claim 14, wherein R^1 is selected from the group consisting of hydrogen, halo and C_1-C_6 alkyl, and R^2 and R^3 are each hydrogen.

16. A method in accordance with claim 1, wherein R^6 is -V-W-X-Y and R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkyloxy and cyano.

17. A method in accordance with claim 16, wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo and C_1-C_6 alkyl.

18. A method in accordance with claim 17, wherein R^4 and R^5 are each hydrogen.

19. A method in accordance with claim 1, wherein said reducing agent is an alkylsilyl hydride and the activating agent is a Lewis acid.

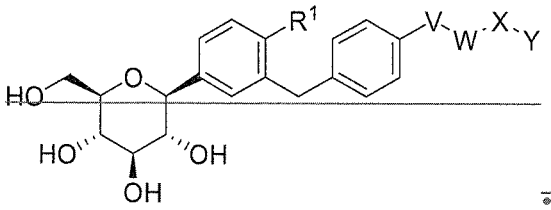
20. A method in accordance with claim 19, wherein said said reducing agent is triethylsilane and said Lewis acid is BF_3·Et_2O.

~~21. A method in accordance with claim 1, wherein step (a) is carried out in a solvent or solvent mixture comprising a member selected from the group consisting of acetonitrile and dichloromethane.~~

~~22. A method in accordance with claim 1, wherein step (b) is carried out in a solvent or solvent mixture comprising a member selected from the group consisting of ethanol, water and hexane.~~

~~23. A method in accordance with claim 1, wherein step (a) is carried out in a solvent or solvent mixture comprising a member selected from the group consisting of acetonitrile and dichloromethane, and step (b) is carried out in a solvent or solvent mixture comprising a member selected from the group consisting of ethanol, water and hexane.~~

~~24. A method in accordance with claim 1, wherein said complex of Formula I has Formula IA:~~



~~.(amino acid)$_n$ (IA)~~

~~wherein~~

~~R^1 is a member selected from the group consisting of hydrogen, halo and C_1-C_6 alkyl;~~

~~V is a member selected from the group consisting of oxygen and a single bond;~~

~~W is a member selected from the group consisting of C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, C_3-C_{10} cycloalkylene, and (C_3-C_{10} cycloalkylene)(C_1-C_6 alkylene);~~

~~X is a member selected from the group consisting of oxygen, a single bond, and NR^a; and~~

~~Y is a member selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl)C_1-C_4 alkyl, (C_1-C_4 alkyloxy)C_1-C_3 alkyl, (C_3-C_{10} cycloalkyloxy)C_1-C_3 alkyl, (amino)C_1-C_3 alkyl, (C_1-C_4 alkylamino)C_1-C_3 alkyl, (C_1-C_6 alkyl)carbonyl, (C_2-C_6 alkenyl)carbonyl, (C_2-C_6 alkynyl)carbonyl, (C_1-C_6 alkyl)sulfonyl, (C_2-C_6 alkenyl)sulfonyl, and (C_2-C_6 alkynyl)sulfonyl,~~

~~wherein alkyl, alkenyl, alkynyl and cycloalkyl groups or portions of W, X and Y are optionally partly or completely fluorinated and optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3 alkyl, C_1-C_3~~

alkoxy, and C_3-C_6-cycloalkyl, and in cycloalkyl groups or portions one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR^b, and one or two methyne groups are optionally replaced by N.

25. A method in accordance with claim 1, wherein said complex of Formula I is an amino acid complex of a compound selected from the group consisting of:
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-(2-methoxyethoxy)ethoxy)-benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(3-(4-(2-(allyloxy)ethoxy)benzyl)-4-chlorophenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-(prop-2-ynyloxy)ethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(1-(prop-2-ynyloxy)propan-2-yloxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(4-hydroxybut-2-ynyloxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(4-methoxybut-2-ynyloxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-(cyclopentyloxy)ethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(3-cyclopropylprop-2-ynyloxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-(difluoromethoxy)ethyl)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-(2,2,2-trifluoroethoxy)ethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-(cyclohex-2-enyloxy)ethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol; and
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-((E)-3-cyclopropylallyloxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

~~26. A method in accordance with any of claims 1 to 25 wherein said amino acid is selected from the group consisting of proline and phenylalanine.~~

~~27. A method in accordance with claim 26, wherein said amino acid is proline and the subscript n is 2.~~

~~28. A method in accordance with any of claims 1 to 25 wherein said complex of Formula I is isotopically labeled.~~

WHAT IS CLAIMED IS:

~~29~~1. A crystalline form of (*2S,3R,4R,5S,6R*)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy) benzyl)phenyl)-6- (hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, bis(*L*-proline) complex characterized by an X-ray powder diffraction pattern that comprises peaks at 4.08, 17.19 and 21.12 degrees 2θ (± 0.05 degrees 2θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation.

~~30~~2. A crystalline form in accordance with claim ~~29~~1, characterized by an X-ray powder diffraction pattern that comprises peaks at 4.08, 6.04, 17.19, 19.86 and 21.12 degrees 2θ (± 0.05 degrees 2θ).

~~31~~3. A crystalline form in accordance with claim ~~29~~1, characterized by an X-ray powder diffraction pattern that comprises peaks at 4.08, 6.04, 14.23, 16.45, 17.19, 17.89, 19.86, 20.61 and 21.12 degrees 2θ (± 0.05 degrees 2θ).

~~32~~4. A crystalline form in accordance with claim ~~29~~1, characterized by an X-ray powder diffraction pattern that comprises peaks at 4.08, 6.04, 7.50, 9.88, 12.31, 14.23, 16.45, 17.19, 17.89, 18.47, 18.97, 19.86, 20.61 and 21.12 degrees 2θ (± 0.05 degrees 2θ).

~~33~~5. A crystalline form of (*2S,3R,4R,5S,6R*)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy) benzyl)phenyl)-6- (hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, bis(*L*-proline) complex characterized by a melting point of about 151 °C ± 1°C, as determined by differential scanning calorimetry with heating from 50°C to 200°C at a rate of 10°C/min.