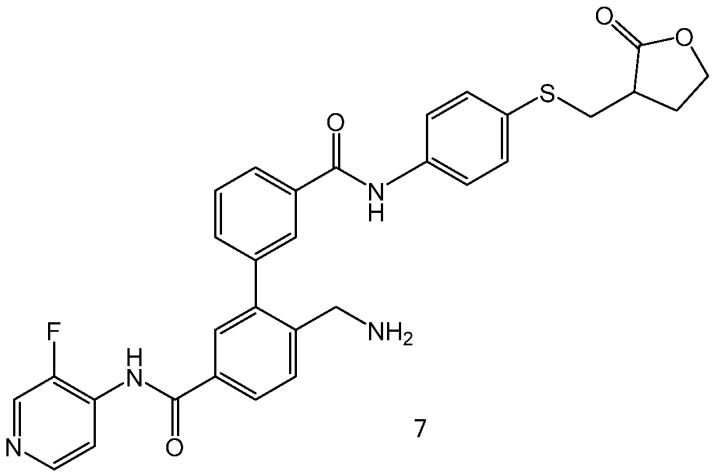
Method of making kinase inhibitors

[0001] This invention relates to methods for producing single enantiomer and crystalline forms of 4-(aminomethyl)-N-(3-fluoropyridin-4-yl)-3-{3-[(4-{[(2-oxooxolan-3-yl)methyl]sulfanyl}phenyl)carbamoyl]phenyl}benzamide (Compound 7). Compound 7 is a Rho-associated protein kinase (ROCK) inhibitor, useful in the treatment of fibrotic diseases, e.g. fibrostenotic Crohn's disease.

BACKGROUND

[0002] 4-(aminomethyl)-N-(3-fluoropyridin-4-yl)-3-{3-[(4-{[(2-oxooxolan-3-yl)methyl]sulfanyl}phenyl)carbamoyl]phenyl}benzamide (Compound 7) is an effective Rho-associated protein kinase (ROCK) inhibitor useful in the treatment of fibrotic diseases (see WO2014/118133). In particular Compound 7 has been designed to work specifically at the site of fibrosis in the gastrointestinal (GI) tract and to degrade quickly, if absorbed into the bloodstream, through enzyme-mediated metabolism.



7

[0003] Crohn's disease is a chronic inflammatory bowel disease that affects 1.5m people globally and >70,000 new cases are diagnosed each year. Up to 50% of patients with Crohn's disease can develop significant fibrosis and stricture formation within ten years after diagnosis; this fibrosis associated with Crohn's disease is known as fibrostenotic Crohn's disease.

[0004] The current management of fibrotic strictures of the GI tract is primarily surgical as no drugs are specifically approved for fibrosis, which can progress despite intervention with anti-inflammatory therapies.

[0005] Relapse rate post surgical intervention is high with >50% patients requiring further surgery within 10 years, many within 12 months. Consequently, patients suffer progressive

loss of GI function and repeated resections can lead to major health complications such as short bowel syndrome.

[0006] Preclinical data has shown that Compound 7 exhibits strong anti-fibrotic therapeutic effects in multiple animal models of inflammatory bowel disease.

[0007] The freebase of Compound 7 has low stability.

[0008] WO2024052704 discloses the *S*-enantiomer of compound 7. The S-enantiomer has been found to have a potentially better safety profile than the *R*-enantiomer. WO2024052704 also discloses a series of stable crystalline salt forms of compound 7. In particular, crystalline form II of the HCl salt of compound 7 was found to have good stability and solubility properties.

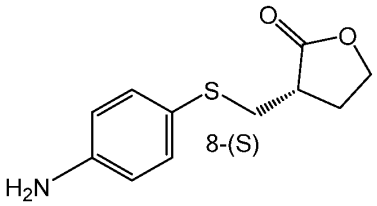
[0009] It is an aim of certain embodiments of this invention to provide a process of producing the S-enantiomer of compound 7. It is an aim of certain embodiments of this invention to provide a process of producing crystalline form II of the HCl salt of compound 7. It is an aim of certain embodiments to provide processes that may be more efficient, more selective or otherwise preferable to the processes for making these products described in the prior art.

[0010] Certain embodiments of this invention satisfy some or all of the above aims.

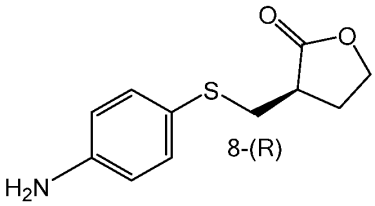
BRIEF SUMMARY OF THE DISCLOSURE

[0011] In accordance with a first aspect of the present invention, there is provided a process for the preparation of substantially enantiopure S-enantiomer of compound 8 (8-(S)) in, the process comprising steps a) and b):

a) reacting a mixture of 8-(S) and the R-enantiomer of compound 8 (8-(R)) with a substantially enantiopure chiral carboxylic acid to form a mixture of the carboxylic acid salt of the S-enantiomer of compound 8 and the carboxylic acid salt of the R-enantiomer of compound 8;



and



b) allowing the carboxylic acid salt of the S-enantiomer of compound 8 to crystallise from a solvent S1 and collecting the carboxylic acid salt of the S-enantiomer of compound 8 as a solid and the carboxylic acid salt of the R-enantiomer of compound 8 as a solution in solvent S1.

[0012] The inventors have found that the two enantiomers of compound 8 can be separated via a resolution with a chiral acid. This provides access to a substantially enantiopure intermediate for the production of the S-enantiomer of compound 7.

[0013] It may be that step a) is carried out in solvent S1 and in step b) the carboxylic acid salt of the S-enantiomer of compound 8 is allowed to crystallise out of the reaction mixture of step a).

[0014] The carboxylic acid may be selected from: (+)-Di-p-toluoyl-D-tartaric acid and (R)-mandelic acid. These acids have been shown to provide particularly effective resolution of the compound 8 enantiomers. The carboxylic acid may be (+)-Di-p-toluoyl-D-tartaric acid. The carboxylic acid may be mandelic acid.

[0015] The solvent S1 may comprise a solvent selected from ethanol, acetonitrile, ethyl acetate, methanol, isopropyl alcohol and mixtures thereof. These solvents have been shown to provide particularly effective resolution of the compound 8 enantiomers. The solvent S1 may comprise a solvent selected from ethanol, acetonitrile, ethyl acetate and mixtures thereof. The solvent S1 may comprise acetonitrile. The solvent S1 may comprise ethyl acetate. The solvent S1 may comprise ethanol. The solvent S1 may comprise methanol. The solvent S1 may comprise water. The solvent S1 may be a mixture of water and a solvent selected from ethanol, acetonitrile, ethyl acetate, methanol and isopropyl alcohol. The solvent S1 may be a mixture of water and a solvent selected from ethanol, acetonitrile, ethyl acetate. The solvent S1 may be a mixture of acetonitrile and water.

[0016] It may be that the solvent S1 comprises ethanol and the carboxylic acid is (+)-Di-p-toluoyl-D-tartaric acid. It may be that the solvent S1 comprises methanol and the carboxylic acid is (+)-Di-p-toluoyl-D-tartaric acid.

[0017] It may be that the solvent S1 comprises acetonitrile and the carboxylic acid is (+)-Di-p-toluoyl-D-tartaric acid. It may be that the solvent S1 is a mixture of acetonitrile and water and the carboxylic acid is (+)-Di-p-toluoyl-D-tartaric acid.

[0018] It may be that the solvent S1 comprises ethyl acetate and the carboxylic acid is mandelic acid.

[0019] It may be that the solid obtained after step b) is subjected to one or more further crystallisation processes from the solvent S1. It may be that the solid obtained after step b) is subjected to two or more further crystallisation processes from the solvent S1. It may be that the solid obtained after step b) is subjected to from one to four further crystallisation processes from the solvent S1. It may be that the solid obtained after step b) is subjected to from two to three further crystallisation processes from the solvent S1. It may be that the solid obtained after step b) is subjected to one further crystallisation

process from the solvent S1. It may be that the solid obtained after step b) is subjected to two further crystallisation processes from the solvent S1. It may be that the solid obtained after step b) is subjected to three further crystallisation processes from the solvent S1.

[0020] It may be that the carboxylic acid salt of the R-enantiomer of compound 8 obtained in step b) is racemised to provide a mixture of the S-enantiomer of compound 8 (8-(S)) and the R-enantiomer of compound 8 (8-(R)). This mixture can be recycled into the process again by using it as the starting material for step a). This increases the overall efficiency of the process. Typically, this racemisation process will be carried out by:

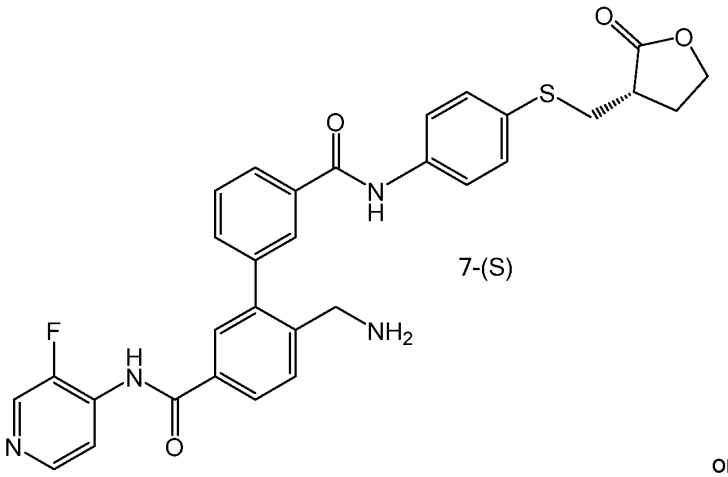
x) converting the carboxylic acid salt of the *R*-enantiomer to the free base of the *R*-enantiomer of compound 8;

y) reacting the *R*-enantiomer to provide a mixture of the S-enantiomer of compound 8 (8-(S)) and the R-enantiomer of compound 8 (8-(R)).

[0021] Step x) will typically be performed be contacting a solution of the R-enantiomer of compound 8 (e.g. the solution of the R-enantiomer of compound 8 in solvent S1 obtained at the end of step b)) with an inorganic base B1 to provide the free base of the *R*-enantiomer of compound 8. B1 may be a carbonate or bicarbonate salt, e.g. sodium carbonate. Said salt will typically be in the form of an aqueous solution. The amount of the inorganic salt used may be enough to achieve a pH of between 8 and 9.

[0022] Step y) may comprise contacting the free base of the *R*-enantiomer of compound 8 with an organic base to provide a mixture of the S-enantiomer of compound 8 (8-(S)) and the R-enantiomer of compound 8 (8-(R)). The organic base may be DBU. Step y may be conducted in a solvent S4. S4 may comprise an organic solvent, e.g. a polar aprotic organic solvent. S4 may be an organic solvent, e.g. a polar aprotic organic solvent. S4 may comprise acetonitrile. S4 may be acetonitrile.

[0023] It may be the carboxylic acid salt of the S-enantiomer of compound 8 is converted to S-enantiomer of compound 7 (7-(S)):

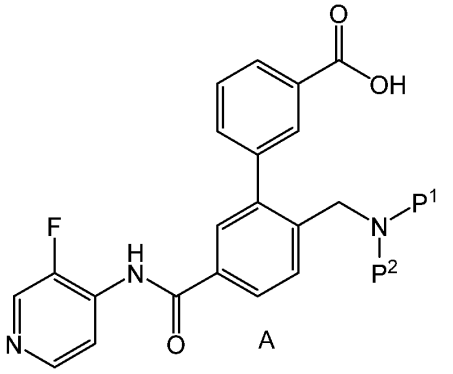


7-(S)

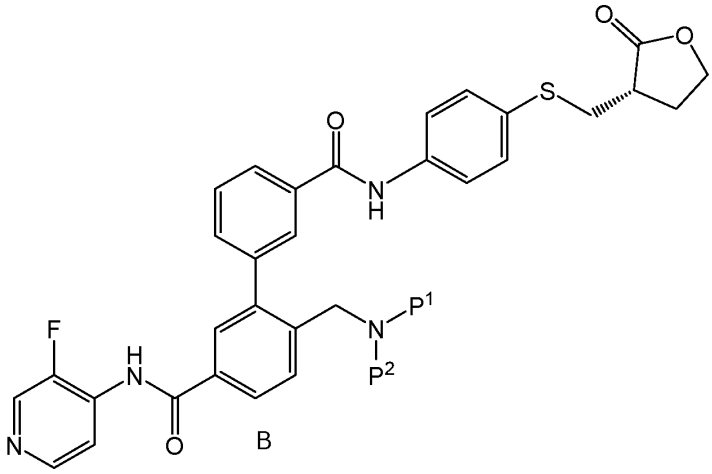
or a pharmaceutically acceptable salt thereof, in substantially enantiopure form. The carboxylic acid salt of the S-enantiomer of compound 8 is converted to 7-(S), or a pharmaceutically acceptable salt thereof, according to steps c), d) and e):

c) converting the carboxylic acid salt of the S-enantiomer of compound 8 to the freebase of the S-enantiomer of compound 8;

d) reacting the freebase of the S-enantiomer of compound 8 with a compound of formula A to obtain a compound of formula B;



A



B

wherein P^1 and P^2 are each selected from H and a protecting group; wherein at least one of P^1 and P^2 is a protecting group;

e) deprotecting the protecting group P^1 and/or P^2 to provide 7-(S), or a pharmaceutically acceptable salt thereof, in substantially enantiopure form.

[0024] It may be that P^1 is a carbonate protecting group, e.g. Boc. It may be that P^2 is H. It may be that P^1 is Boc and P^2 is H.

[0025] Step c) will typically be performed be contacting a solution of the S-enantiomer of compound 8 with an inorganic base B1 to provide the free base of the *S*-enantiomer of compound 8. B1 may be a carbonate or bicarbonate salt, e.g. sodium carbonate. Said salt will typically be in the form of an aqueous solution. The amount of the inorganic salt used may be enough to achieve a pH of between 8 and 9.

[0026] Step d) may be performed using one of the range of amide coupling conditions known to the skilled person. An illustrative example would be: T3P, NMI and DMAP, e.g. using DCM as a solvent.

[0027] The deprotection conditions of step e) will be selected dependent on the identity of P^1 and/or P^2. The skilled person would know how to select deprotection conditions for

any given protecting group that would not be expected to have any negative effect on other functional groups present in the molecule. Where P1 is a Boc group, it may be removed using an acid. For example, it may be that the deprotection of step e) is performed using HCl and 7-(S) is formed as the HCl salt.

[0028] It may be that 7-(S) is formed as crystalline form I of the HCl salt in step e) and the process comprises step f):

f) converting crystalline form I of the HCl salt of 7-(S) to crystalline form II of the HCl salt of 7-(S).

[0029] Step f) may be performed by dissolving form I in a solvent S2 and allowing crystalline form II to crystallise out of the solvent S2 to form crystalline form II of the HCl salt of 7-(S).

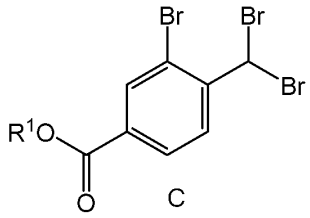
[0030] Solvent S2 may comprise acetone. Solvent S2 may be a mixture of acetone and water. Details of how to carry out step f) under these conditions can be found in WO2024052704.

[0031] Solvent S2 may comprise ethanol. Solvent S2 may be ethanol. The inventors have found that ethanol is an effective solvent for conversion of crystalline form I of the HCl salt of 7-(S) to crystalline form II of the HCl salt of 7-(S). The ethanol may have a water content below 15% by volume. The ethanol may have a water content below 5%. The ethanol may have a water content below 1%. Solvent S2 may comprise anhydrous ethanol. The inventors have found that when S2 comprises ethanol, crystal form II is formed more effectively in ethanol that has a low water content.

[0032] Step f) may be carried out by heating a suspension of crystalline form I of the HCl salt of 7-(S) to a temperature T1 in a solvent S2 until a solution is formed and allowing the solution to cool to a temperature T2 to provide crystalline form II of the HCl salt of 7-(S). The hot solution can be filtered to remove any undissolved solids but this is preferably avoided. T1 may be a temperature in the range from 30 °C to 60 °C. T1 may be a temperature in the range from 45 °C to 55 °C. The suspension may be heated up to T2 gradually, e.g. over a time period in the range from 30 mins to 3 hours. The suspension may be held at T2 for a period of time in the range from 2 to 6 hours. T2 may be a temperature in the range from 0 °C to 30 °C. T2 may be a temperature in the range from 20 °C to 30 °C.

[0033] The crystalline form II of the HCl salt of 7-(S) formed in step f) is typically collected by filtration. The crystals are typically washed and/or dried.

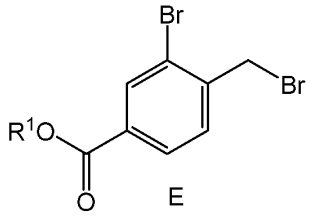
[0034] The process may comprise converting a compound of formula C to the compound of formula A:



wherein R^1 is selected from H and C_1-C_4-alkyl.

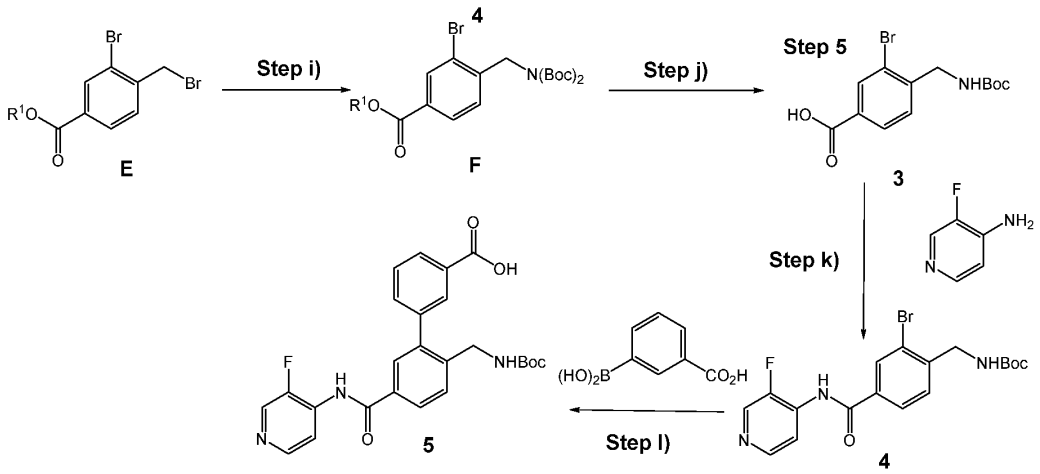
[0035] The conversion of a compound of formula C to a compound of formula A may comprise step h):

h) reacting the compound of formula C with diethyl phosphite to form a compound of formula E:



. Step h) may be conducted in the presence of DIPEA using toluene as a solvent.

[0036] The process may comprise converting a compound of formula E to the compound of formula A. Where P^1 is Boc and P^2 is H, the conversion of a compound of formula E to a compound 5 (compound A where P^1 is Boc and P^2 is H) may comprise steps i), j), k) and l):



[0037] Step i) may be achieved through reaction of the compound of formula E with $NH(Boc)_2$, e.g. in the presence of K_3PO_4 using NMP and toluene as the solvent.

[0038] Where R^1 is H, step j is not needed. Where R^1 is C_1-C_4-alkyl, the conditions of step j) will depend on the identity of R^1. Where R^1 is methyl step j) may be achieved through reaction of the compound of formula F with NaOH, e.g. using water and methanol as the solvent.

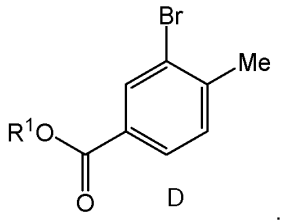
[0039] Step k) may be performed using one of the range of amide coupling conditions known to the skilled person. An illustrative example would be: TCFH and NMI, e.g. using acetonitrile as the solvent.

[0040] Step l) may be performed using one of the range of Suzuki coupling conditions known to the skilled person. An illustrative example would be: $Pd(OAc)_2$, PPh_3, K_3PO_4, water and 1,4-dioxane.

[0041] Other suitable conditions for the production of compounds of formulae E and for steps i) to l) can be found in S. Boland et al.; *Bioorg. Med. Chem. Lett.*; 23 (2013); 6442–6446 and S. Boland et al.; *J. Med. Chem.*; 2015; 58; 4309−4324.

[0042] The process may comprise step g):

g) reacting a compound of formula D with NBS and a radical initiator in a solvent S3 at reflux to form the compound of formula C:



D

[0043] The inventors have found that it is cleaner and more efficient, relative to prior art methods, to produce bromides of formula E from compounds of formula D by dibrominating to form compounds of formula C and then removing one of the bromines using diethyl phosphite

[0044] It may be that during step g), a portion of the compound of formula D is converted to a compound of formula E. Where this occurs it may be that the compounds of formula C and E do not need to be separated. The mixture of compounds of formula C and E may be subjected, without separation, to step h).

[0045] S3 may be acetic acid.

[0046] R^1 may be C_1-C_4-alkyl. R^1 may be methyl.

[0047] In a second aspect of the invention is provided a process for the preparation of crystalline form II of the HCl salt of enantiomer of compound 7 (7-(S)), the process comprising step f):

f) dissolving crystalline form I of the HCl salt of 7-(S) in a solvent S2 and allowing crystalline form II to crystallise out of the solvent S2 to form crystalline form II of the HCl salt of 7-(S).

[0048] Step f) may be performed by dissolving form I in a solvent S2 and allowing crystalline form II to crystallise out of the solvent S2 to form crystalline form II of the HCl salt of 7-(S).

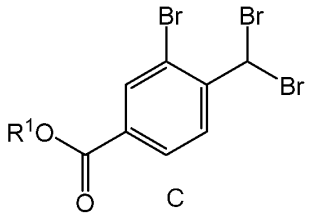
[0049] Solvent S2 may comprise ethanol. Solvent S2 may be ethanol. The inventors have found that ethanol is more easily removed from crystalline form II of the HCl salt of 7-(S) than other solvents. The ethanol may have a water content below 15% by volume. The ethanol may have a water content below 5%. The ethanol may have a water content below 1%. Solvent S2 may comprise anhydrous ethanol. The inventors have found that when S2 comprises ethanol, crystal form II is formed more effectively in ethanol that has a low water content.

[0050] Step f) may be carried out by heating a suspension of crystalline form I of the HCl salt of 7-(S) to a temperature T1 in a solvent S2 until a solution is formed and allowing the solution to cool to a temperature T2 to provide crystalline form II of the HCl salt of 7-(S). The hot solution can be filtered to remove any undissolved solids but this is preferably avoided. T1 may be a temperature in the range from 30 °C to 60 °C. T1 may be a temperature in the range from 45 °C to 55 °C. The suspension may be heated up to T2 gradually, e.g. over a time period in the range from 30 mins to 3 hours. The suspension may be held at T2 for a period of time in the range from 2 to 6 hours. T2 may be a temperature in the range from 0 °C to 30 °C. T2 may be a temperature in the range from 20 °C to 30 °C.

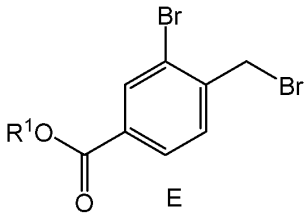
[0051] The crystalline form II of the HCl salt of 7-(S) formed in step f) is typically collected by filtration. The crystals are typically washed and/or dried.

[0052] In a third aspect of the invention is provided a process of making a compound of formula E, the process comprising step h):

h) reacting a compound of formula C with diethyl phosphite to form a compound of formula E:



C



E

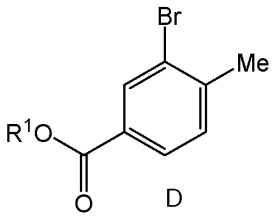
wherein R^1 is selected from H and C_1-C_4-alkyl.

[0053] The inventors have found that it is cleaner and more efficient, relative to prior art methods, to produce bromides of formula E from compounds of formula D by dibrominating to form compounds of formula C and then removing one of the bromines using diethyl phosphite

[0054] Step h) may be conducted in the presence of DIPEA using toluene as a solvent.

[0055] The process may comprise step g):

g) reacting a compound of formula D with NBS and a radical initiator in a solvent S3 at reflux to form the compound of formula C:



D

[0056] S3 may be acetic acid.

[0057] R^1 may be C_1-C_4-alkyl. R^1 may be methyl.

[0058] It may be that during step g), a portion of the compound of formula D is converted to a compound of formula E. Where this occurs it may be that the compounds of formula C and E do not need to be separated. The mixture of compounds of formula C and E may be subjected, without separation, to step h).

[0059] The process may comprise converting the compound of formula E to S-enantiomer of compound 7 (7-(S)), or a pharmaceutically acceptable salt thereof, in substantially enantiopure form. This conversion of the formula E to the S-enantiomer of compound 7 (7-(S)) can be performed using any of the methods described above in relation to the first aspect of the invention.

DETAILED DESCRIPTION

[0060] The chemical terms used in the specification have their generally accepted meanings in the art.

[0061] The term "alkyl" as used herein refers to a linear or branched saturated monovalent hydrocarbon chain. For example, C_1-C_4-alkyl may refer to methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *sec*-butyl or *tert*-butyl. The alkyl groups may be unsubstituted or substituted by one or more substituents. The alkyl groups are typically unsubstituted

[0062] The term "aryl" refers to an aromatic hydrocarbon ring system. The ring system has 4n +2 electrons in a conjugated π system within a ring where all atoms contributing to the conjugated π system are in the same plane. For example, the "aryl" may be phenyl and naphthyl. The aryl system itself may be substituted with other groups.

[0063] The term "heteroaryl" refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S. The ring or ring system has 4n +2 electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. For example, the "heteroaryl" may be imidazole, thiene, furane, thianthrene, pyrrole, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine and indole.

[0064] The term "protecting group" as used herein is given its ordinary meaning which is readily understandable to those of skill in the art. It is a group that can prevent a reactive group from reacting at an unintended point in a synthetic route. Methods of protecting and deprotecting reactive groups are well known to those of skilled in the art. In particular, methods of protection and deprotection such as those described by T.W. GREENE (Protective Groups in Organic Synthesis, A. Wiley- Interscience Publication, 1981) or by P. J. Kocienski (Protecting groups, Georg Thieme Verlag, 1994), can be used. It the present specification, the term "protecting group" refers to a group suitable for protecting a primary amine. Exemplary protecting groups suitable for protecting a primary amine include tert-butyloxycarbonyl group (Boc group), benzyloxycarbonyl group (Cbz), *tert*-butyl group (^{t}Bu), *para*-methoxybenzyl (PMB) and phthalimide.

[0065] The term "carbonate protecting group" as used herein refers to a group having a general formula C(O)Rx, wherein Rx is an alkyl, CH_2-aryl or CH_2-heteroaryl group, e.g. a C_1-C_4-alkyl or benzyl group. The alkyl, CH_2-aryl or CH_2-heteroaryl group may be substituted or unsubstituted. Typically, the alkyl, CH_2-aryl or CH_2-heteroaryl group is unsubstituted. Exemplary carbonate protecting groups suitable for protecting a primary amine include tert-butyloxycarbonyl group (Boc group), benzyloxycarbonyl group (Cbz) and fluorenylmethoxycarbonyl (Fmoc).

[0066] Where multiple protecting groups are present on the same compound, the protecting groups may or may not be orthogonal to one another (i.e. if a first protecting group can be removed without also removing a second protecting group, the two groups are said to be orthogonal). In the methods of the present invention, where there are

multiple protecting groups, the protecting groups are typically not orthogonal to one another.

[0067] The compounds produced in methods of the invention may be obtained, stored and/or used in the form of a pharmaceutically acceptable salt. Suitable salts include, but are not limited to, salts of acceptable inorganic acids such as hydrochloric, sulfuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, malic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulfonic, toluenesulfonic, benzenesulfonic, salicylic, sulfanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids. Suitable salts also include salts of inorganic and organic bases, e.g. counterions such as Na, Ca, K, Li, Mg, ammonium, trimethylsulfonium. The compounds may also be obtained, stored and/or used in the form of an N-oxide. Also included are acid addition salts or base salts wherein the counter ion is optically active; for example, d-lactate or l-lysine, or racemic; for example, dl-tartrate or dl-arginine.

[0068] The compounds produced in methods of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[0069] The present disclosure also encompasses compounds produced in methods of the invention as defined herein which comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, $^{2}H(D)$, and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; and O may be in any isotopic form, including ^{16}O and ^{18}O; and the like. Similarly, isotopic variants of N, S and P may be utilised.

[0070] It may be that the steps described in this specification as individual steps are performed in tandem. In other words, it may be that a reaction product from one step is not fully isolated and purified before the next step. It may be that the reagents for one step are added into the reaction mixture obtained in the immediately preceding step once the reaction of the first step is complete. Similarly, it may be that simple extraction work-up techniques (e.g. extraction into an organic solvent and/or acid, base, saline washes) or filtration techniques (e.g. through a sintered funnel or a plug of celite or silica) are performed on the reaction mixture of one step but the product mixture is not separated into its component parts before the next step.

[0071] Throughout the description and claims of this specification, the words “comprise” and “contain” and variations of them mean “including but not limited to”, and they are not

intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[0072] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[0073] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

EXAMPLES

[0074] List of abbreviations: DIPEA: N, N-Diisopropylethylamine; MeCN: Acetonitrile; AIBN: Azobisisobutyronitrile; NBS: N-Bromosuccinimide; NMP: N-Methyl-2-pyrrolidone; NMI: 1-Methylimidazole; NAC: N-acetyl cysteine; DCM: Dichloromethane; DMAP: 4-Dimethylaminopyridine; T3P: Propylphosphonic anhydride; v and vol: volumes; MTBE: Methyl tert-butyl ether; TCFH: N,N,N′,N′-Tetramethylchloroformamidinium hexafluorophosphate; DMSO: Dimethylsulfoxide; EA: Ethyl acetate; THF: Tetrahydrofuran; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; aq.: Aqueous; eq.: Equivalents.

[0075] The HRMS spectrum was measured using the Waters Acquity Xevo G2-XS Q-Tof UPLC/MS system

[0076] Compound identity and purity confirmations were performed by LCMS UV using an Agilent 1260 LC system with G6125B MSD.

Method 1:

[0077] The diode array detector wavelength was 210nM/220nM/254nM and the MS was in positive and negative electrospray mode (m/z: 70-1000). The column used was Agilent SB-C18, 4.6 x 50 mm, 1.8µm maintained at 40°C. The samples were eluted at a flow rate of 1.0mL/min with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in MeCN) according to the gradients outlined in Table 1 below. Retention times RT are reported in minutes.

Table 1

Method 1		
Time (min)	%A	%B
0	90.0	10.0
6.0	5.0	95.0
8.0	5.0	95.0
8.1	90.0	10.0

Method 2:

[0078] The diode array detector wavelength was 210nM/220nM/230nM/254nM and the MS was in positive and negative electrospray mode (m/z: 70-1200). The column used was Agilent SB-C18, 4.6 x 50 mm, 1.8µm maintained at 40°C. The samples were eluted at a flow rate of 1.0mL/min with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in MeCN) according to the gradients outlined in Table 2 below. Retention times RT are reported in minutes.

Table 2

Method 2		
Time (min)	%A	%B
0	90.0	10.0
4.0	5.0	95.0
6.0	5.0	95.0
6.1	90.0	10.0

Method 3:

[0079] The diode array detector wavelength was 210nM and the MS was in positive and negative electrospray mode (m/z: 70-1200). The column used was Waters XBridge C18 4.6×150mm,3.5µm maintained at 30°C. The samples were eluted at a flow rate of 1.0mL/min with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water)

and B (0.1% (v/v) Formic Acid in MeCN) according to the gradients outlined in Table 3 below. Retention times RT are reported in minutes.

Table 3

Method 3		
Time (min)	%A	%B
0	95.0	5.0
10.0	5.0	95.0
15.0	5.0	95.0
15.1	95.0	5.0
20.0	95.0	5.0

[0080] Compound identity and purity confirmations were also performed by LCMS UV using an Agilent 1260 LC system with G6135B MSD.

Method 4:

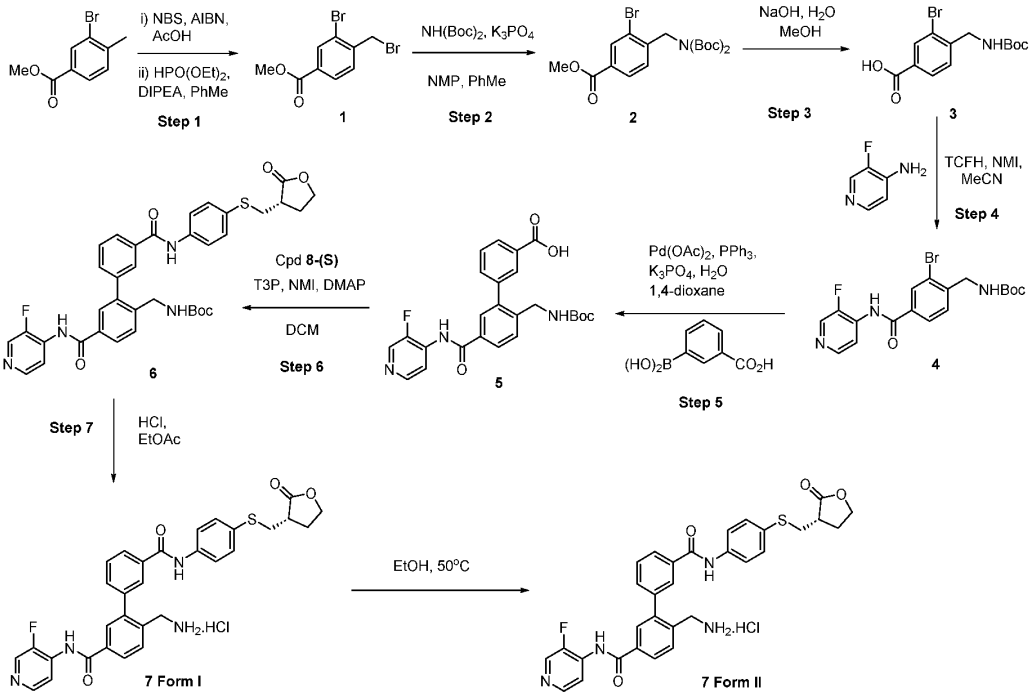
[0081] The diode array detector wavelength was 210nM/220nM/254nM and the MS was in positive and negative electrospray mode (m/z: 70-1200). The column used was Agilent SB-C18, 4.6 x 50 mm, 1.8µm maintained at 40°C. The samples were eluted at a flow rate of 1.0mL/min with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in MeCN) according to the gradients outlined in Table 4 below. Retention times RT are reported in minutes.

Table 4

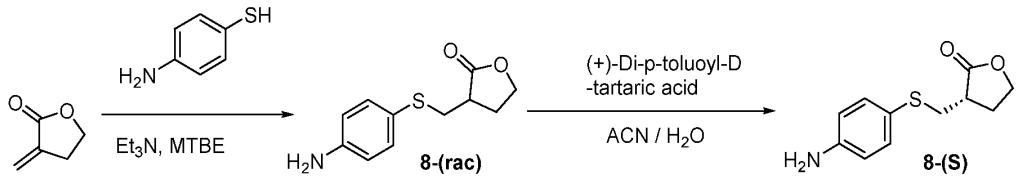
Method 4		
Time (min)	%A	%B
0	90.0	10.0
6.0	5.0	95.0
8.0	5.0	95.0
8.1	90.0	10.0

NMR was also used to characterise final compounds. NMR spectra were obtained on a Bruker AVANCE III HD 400 MHz NMR.

[0082] In a specific implementation of the presently described process, crystalline form II of the HCl salt of the S-enantiomer of compound 7 can be made according to **Schemes 1 and 2**:



Scheme 1

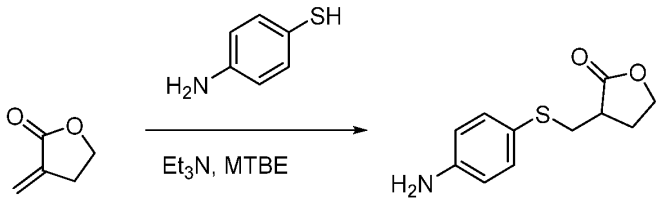


Step 9 **Step 10**

Scheme 2

Example 1: Synthesis of Intermediate 8-(S)

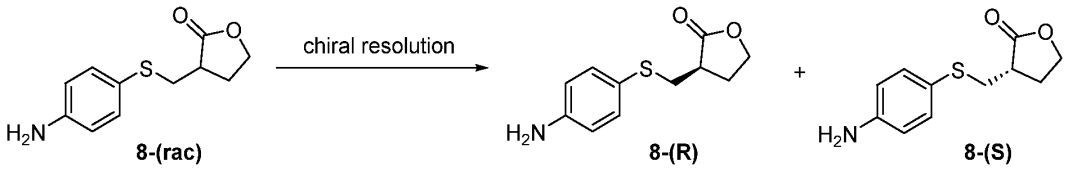
Step 9 – Synthesis of rac-3-(((4-aminophenyl)thio)methyl)dihydrofuran-2(3H)-one, 8-(rac).



Step 9 **8-(rac)**

[0083] 4-aminobenzenethiol (1.05 eq.) and MTBE (5.0 vol.) were charged to the reaction vessel at 20°C and stirred. Et_3N (0.25 eq.) was then added to the reaction mixture slowly, maintaining the temperature at 20°C. A solution of 3-methylenedihydrofuran-2(3H)-one (4.5Kg, 1.0 eq.) in MTBE (2.0 vol.) was then added to the mixture. Further MTBE (1.0 vol.) was added to the reaction mixture to aid stirring and the mixture stirred for 1 hour at 20°C and then heated to 30°C for 2 hours. The reaction was then cooled to 20°C and heptane (3.0 vol.) added dropwise. The mixture was then cooled to 0°C, filtered and the filter cake washed with heptane (2 x 1.0 vol.) and dried at 40°C to give rac-3-(((4-aminophenyl)thio)methyl)dihydrofuran-2(3H)-one (**8-(rac)**) (7.7Kg, 82% yield).

Step 10 – Chiral acid selection



[0084] A number of enantiomerically pure chiral acid derivatives in combination with five different solvents were screened in order to assess if any were suitable for the chiral resolution of **8-(rac)** into **8-(S)**, as shown in **Tables 5 and 6** below.

Table 5

Solvent / Acid	EtOH ee %	THF ee %	Acetone ee %	MeCN ee %	EA ee %
(+)-Di-p-toluoyl-D-tartaric acid	74.0	No solid	No solid	62.9	41.7
D-tartaric acid	3.7	2.7	3.4	1.5	0.9
(R)-mandelic acid	0.3	No solid	No solid	No solid	69.4
L-Aspartic acid	0.2	0.5	0.1	0.7	17.1
N-carbobenzyloxy-L-valine	0.1	No solid	No solid	No solid	No solid

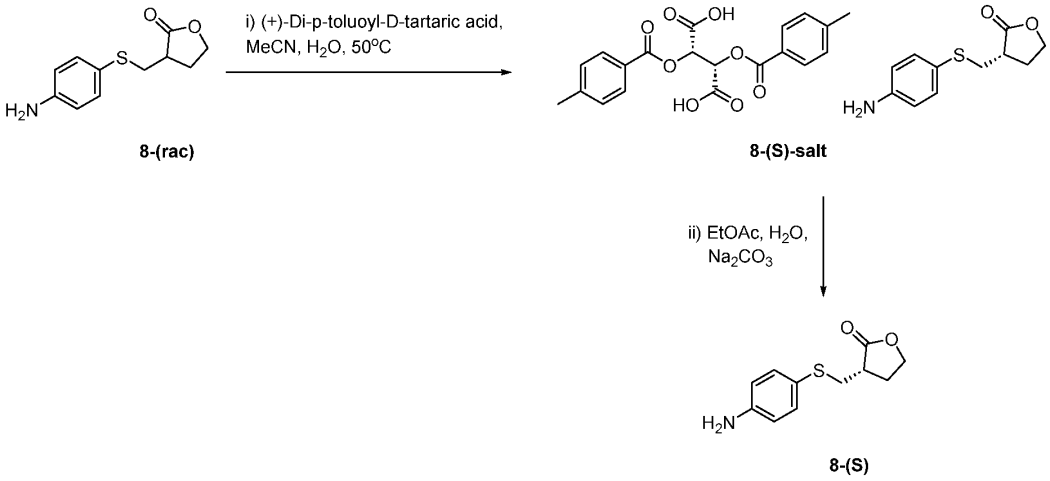
N-Acetyl-trans-4-hydroxy-L-proline	0.1	3.4	1.3	0.2	4.8
D-proline	13.6	0	0.3	2.1	0.6
L-Phenylalanine	0.4	1.3	0.6	4.2	0.1
D(+)-10-Camphorsulfonic acid	No solid	No solid	No solid	0.8	0.2
L-Pyroglutamic acid	0.2	0.4	0.2	1.1	1.5
L-Glutamic acid	0.3	0.6	0.1	3.3	3.0
Dibenzoyl-L-tartaric acid	No solid	No solid	No solid	30.1	7.0
L-Lysine	0.2	0	0	0.9	0.5
D-(-)-Lactic acid	0.2	No solid	No solid	No solid	No solid
R-chloropropionic acid	No solid	No solid	No solid	No solid	No solid
Boc-Aib-OH	0.4	No solid	No solid	No solid	No solid
D-(+)-Camphoric acid	0.3	No solid	No solid	13.5	No solid
N-Cbz-L-Proline	No solid	No solid	No solid	No solid	No solid
Ascorbic acid	0.2	1.5	2.1	0.8	5.2
L-(-)-Malic acid	0.2	No solid	No solid	No solid	5.7

Table 6

Acid	Solvent system	ee
((S)-α-methoxy-α-(trifluoromethyl)phenylacetic acid)	10V EtOAc / 10V Heptane	38.7%

[0085] Conclusion: Whilst many acids provided at least some chiral resolution the most effective carboxylic acids were (+)-Di-p-toluoyl-D-tartaric acid and (R)-mandelic acid. Whilst many solvents provided at least some chiral resolution, the most effective solvents were ethanol, acetonitrile and ethyl acetate. The most effective combinations were: a) ethanol and (+)-Di-p-toluoyl-D-tartaric acid; b) acetonitrile and (+)-Di-p-toluoyl-D-tartaric acid; and c) ethyl acetate and mandelic acid.

Step 10 – Synthesis of (S)-3-(((4-aminophenyl)thio)methyl)dihydrofuran-2(3H)-one, 8.



8-(rac) **8-(S)-salt** **8-(S)**

Step 10

Chiral resolution procedure:

[0086] Intermediate **8-(rac)** (5.1Kg), (+)-Di-p-toluoyl-D-tartaric acid (1.0 eq.), MeCN (12.0 v) and H_2O (0.6 v) were charged into the reactor at 20°C. The mixture was stirred and heated to 50°C for 2 hours before being cooled back to 20°C and stirred for an additional 16 hours. The mixture was then centrifuged and the wet cake washed with MeCN/H_2O (20/1) (2 x 1.0 v). Three separate batches of 5.1 Kg were combined to give a total of 18.5Kg of wet cake **8-(S)-salt** at 73.5% ee.

[0087] **8-(S)-salt** at 73.5% ee, MeCN/H_2O (4.5 v, 20/1) were charged into the reactor at 20°C. The mixture was stirred and heated to 50°C for 2 hours before being cooled back to 20°C and stirred for an additional 16 hours. The mixture was then centrifuged and the wet cake washed with MeCN/H_2O (20/1) (2 x 1.0 v). Two separate batches of 9.2Kg and 9.3Kg were combined to give a total of 11.9Kg of wet cake **8-(S)-salt** at 94.3% ee.

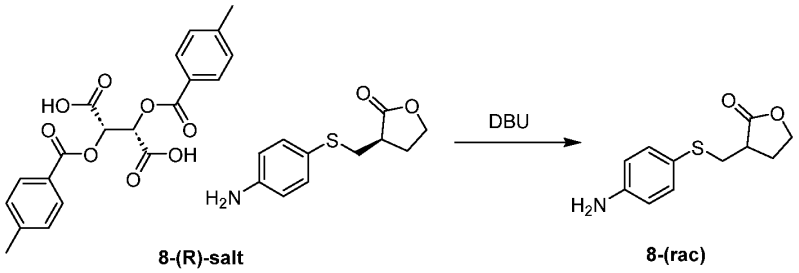
[0088] **8-(S)-salt** at 94.3% ee, MeCN/H_2O (4.5v, 20/1) were charged into the reactor at 20°C. The mixture was stirred and heated to 50°C for 2 hours before being cooled back to 20°C. Additional MeCN/H_2O (1.0v, 20/1) were charged into the reactor at 20°C. The mixture was stirred and heated to 50°C for 2 hours before being cooled back to 20°C and stirred for an additional 16 hours. The mixture was then centrifuged and the wet cake washed with MeCN/H2O (20/1) (2 x 1.0 v). Two separate batches of 9.2Kg and 9.3Kg were combined to give a total of 8.4Kg of wet cake **8-(S)-salt**. at 98.3% ee.

Salt break procedure:

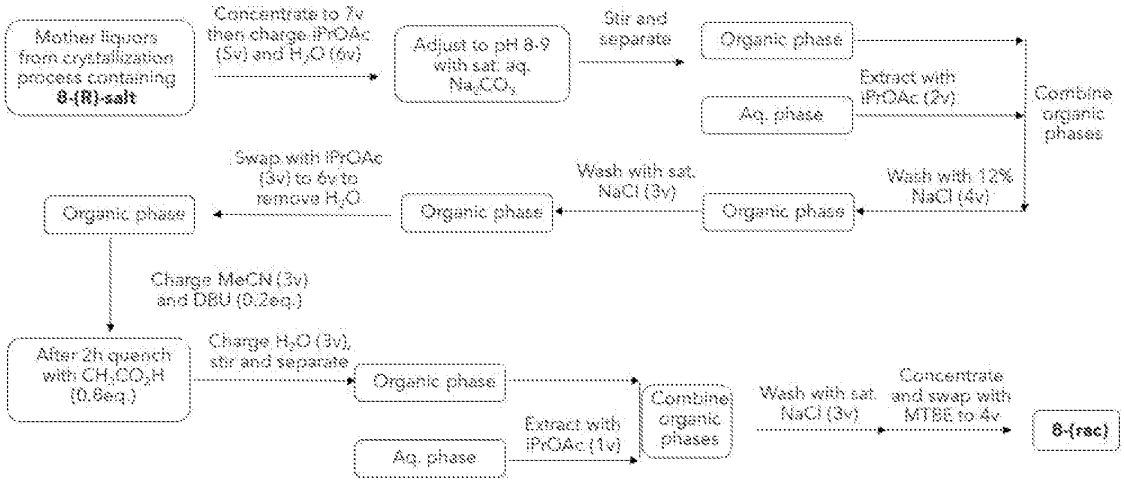
[0089] **8-(S)-salt** (9.1Kg, 1.0 eq.), EtOAc (4.0 v) and H_2O (4.0 v) were added to the reactor at 20°C and stirred. The pH was adjusted to 8.5 using sat. aq. Na_2CO_3 and the resulting solution stirred for 30 minutes. The aqueous phase was then separated and extracted with EtOAc (2.0 v). the combined organic phases were washed with sat. aq. NaCl (4.0 v) and concentrated to 1-2 v. MTBE (4.0 v) was added and the mixture concentrated to 1-2 v. This process was repeated a further two times. N-Heptane (2.5 v) was then charged and the resulting mixture stirred for 16 hours at 20°C. The mixture was then combined with an identical reaction which used 7.2Kg of **8-(S)-salt** and the combined mixture filtered and the wet cake washed with MTBE/n-heptane (2 x 1 v; 1/1). The wet cake was then dried at 40°C to give **8-(S)** (5.8Kg, 98.3% ee) as a solid.

[0090] UPLC-MS (ES+, Method 1): 2.41 min; m/z = 224.00 $[M+H]^+$

[0091] Optionally, the mother liquors obtained during the process which contain mainly the unwanted **8-(R)-salt** may be racemised to give back **8-(rac)** which can be recycled and fed back into the start of the process. This is shown in the schematic below.

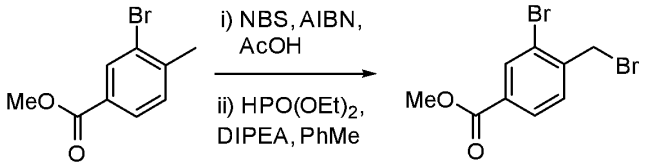


8-(R)-salt **8-(rac)**



Example 2: Synthesis of S-7

Step 1 – Synthesis of methyl 3-bromo-4-(bromomethyl)benzoate, 1.

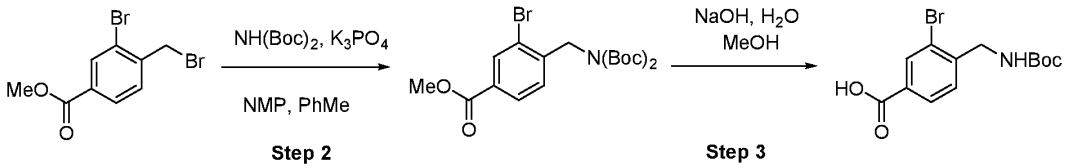


Step 1 **1**

[0092] Methyl 3-bromo-4-methylbenzoate (5.2Kg) was stirred with AcOH (3.0 vol.) and AIBN (0.1eq) under a nitrogen atmosphere at room temperature. The reaction was heated to 80°C and then a solution of NBS (1.4eq.) in MeCN (7.0 vol.) was added dropwise and stirring continued for 1 hour. The reaction mixture was then cooled to 20°C and concentrated to approximately 4 volumes. Water (5.0 vol.) and toluene (5.0 vol.) were then added and the resulting mixture stirred and then the organic layer separated. The organic layer was washed with sat. aq. 8% $NaHCO_3$ (5.0 vol.). The organic layer was separated, charged into the reaction vessel and stirred at 20°C. DIPEA (0.5 eq.) and diethyl phosphite (0.5 eq.) were each added dropwise to the reaction and the reaction then stirred for 2 hours at 20°C upon completion of addition. Water (5 vol.) was then added at 20°C and the organic later separated. The organic layer was then washed with sat. aq. $NaHCO_3$ (5.0 vol.), sat. aq. NaCl (3.0 vol.) and the resulting organic phase solution of methyl 3-bromo-4-(bromomethyl)benzoate (**1**) was then used directly in the next step. Three identical reactions on the same scale were performed for this step.

[0093] UPLC-MS (ES+, Method 1): 5.77 min; m/z = 308.80 $[M+H]^+$

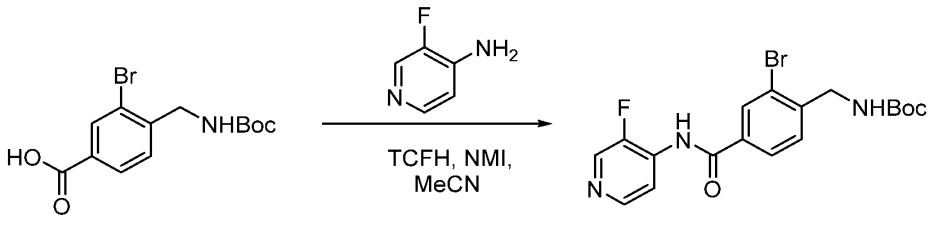
Steps 2 and 3 – Synthesis of 3-bromo-4-(((tert-butoxycarbonyl)amino)methyl)benzoic acid, 3.



NMP (1.5 vol.), $NHBoc_2$ (1.2 eq.) and K_3PO_4 (1.2 eq.) were charged to the reaction vessel under a nitrogen atmosphere at 25°C and stirred. The toluene solution obtained from Step 1 was then charged to the reaction mixture and stirring continued for 2 hours. The reaction was then heated to 35°C and stirred for a further 2 hours before being cooled back down to 25°C. MeOH (2.0 vol.) and a NaOH solution (3.0M, 5.0 eq.) were added and the reaction heated to 70°C for 6 hours. The reaction was then cooled to 60°C and water (7.0 vol.) added. The reaction was then cooled to 25°C and the phases separated. The aqueous layer was adjusted to pH 3-4 using 8M HCl and then the mixture cooled to 0°C and stirred for 1 hour. This step was again performed as three separate reactions on the same scale. At this point the three mixtures were then filtered together, and the filter cake washed with water (2.0 vol.). The mixture was then slurried with water (5.0 vol.), filtered and dried for 16 hours at 50°C to give 3-bromo-4-(((tert-butoxycarbonyl)amino)methyl)benzoic acid (17.9Kg, 78% yield over 3 steps) as a solid.

[0094] UPLC-MS (ES+, Method 2): 3.89 min; m/z = 352.00, 354.00 $[M+Na]^+$

Step 4 – Synthesis of tert-butyl (2-bromo-4-((3-fluoropyridin-4-yl)carbamoyl)benzyl)carbamate - 4.

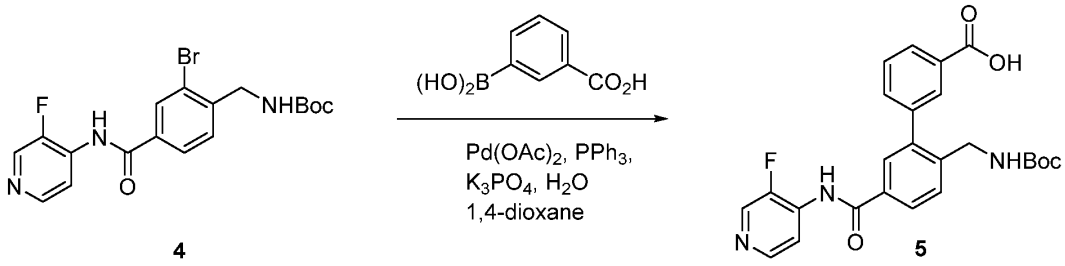


[0095] MeCN (3.0 vol.) and 3-bromo-4-(((tert-butoxycarbonyl)amino)methyl)benzoic acid (**3**) (6.5Kg, 1 eq.) were combined and stirred in a reaction vessel under a nitrogen atmosphere at 20°C. NMI (3.0 eq.) was then added dropwise. Upon completion of addition TCFH (1.2 eq.) was added in batches, maintaining the temperature below 24°C. The resulting mixture was stirred for 2 hours. 3-Fluoropyridin-4-amine (1.2 eq.) was then added to the reaction, maintaining the temperature below 22°C and the resulting reaction mixture

stirred for 2 hours. Water (6.0 vol.) was then added to the reaction mixture at 25°C and the resulting mixture stirred for 2 hours. At this point it was combined with an identical reaction performed on 6.1Kg of **3** and the mixture was then filtered and the filter cake washed with water (2 x 2 vol.) and the filter cake dried at 50°C to give tert-butyl (2-bromo-4-((3-fluoropyridin-4-yl)carbamoyl)benzyl)carbamate (14.1Kg, 87% yield) (**4**) as a solid.

[0096] UPLC-MS (ES+, Method 1): 4.87 min; m/z = 424.00 $[M+H]^+$

Step 5 – Synthesis of 2'-(((tert-butoxycarbonyl)amino)methyl)-5'-((3-fluoropyridin-4-yl)carbamoyl)-[1,1'-biphenyl]-3-carboxylic acid – 5.

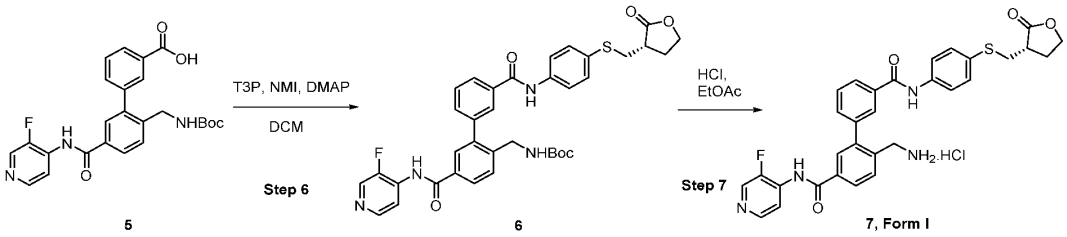


[0097] 1,4-Dioxane (3.0 vol.), K_3PO_4 and water (3.0 vol.) were charged into the reaction vessel at 20°C and the mixture stirred. The vessel was evacuated and flushed with N_2 3 times and then 3-boronobenzoic acid (1.2 eq.) and tert-butyl (2-bromo-4-((3-fluoropyridin-4-yl)carbamoyl)benzyl)carbamate (**4**) (5.4Kg, 1.0 eq.) were added to the mixture. The vessel was then evacuated and flushed with N_2 3 times and then $Pd(OAc)_2$ (0.01 eq.) and PPh_3 (0.02 eq.) were added. The vessel was then again evacuated and flushed with N_2 3 times and heated to 62°C for 12 hours. A solution of NAC (5% w/w) in water (2.0 vol.) was then added to the reaction mixture dropwise at 60°C and the reaction mixture then stirred at this temperature for 5 hours. The reaction mixture was then cooled to 20°C, filtered and the filter cake washed with water (2 x 2.0 vol.). The filtrate was then extracted with toluene (5.0 vol.). The aqueous phase was collected and the pH adjusted to 5-6 using 2N HCl (~5 vol.). The resulting solid was filtered and the filter cake washed with water (2 x 1.0 vol.). The wet filter cake was dissolved in THF (10.0 vol.) and sat aq. NaCl (10 vol.) was added. The mixture was stirred and then separated. The organic phase was collected and charcoal (15 w/w%) was added and the resulting mixture stirred for 12 hours and then filtered. Silicagel thiol (10 w/w%) was then added to the filtrate and the resulting mixture stirred at 60°C for 4 hours before being cooled down to 20°C. the mixture was filtered and the filtrate concentrated to ~3.5 volumes. Heptane (4.0 vol.) was added dropwise and the resulting mixture stirred at 20°C for 2 hours. At this point the reaction was combined with

an identical reaction on the same scale and the mixture was then filtered and the wet cake washed with THF/heptane (1/1; 2 x 1.0 vol.) and the solid dried for 12 hours at 50°C to give 2'-(((tert-butoxycarbonyl)amino)methyl)-5'-((3-fluoropyridin-4-yl)carbamoyl)-[1,1'-biphenyl]-3-carboxylic acid (11.0Kg, 89% yield) (**5**) as a solid.

[0098] UPLC-MS (ES+, Method 3): 8.07 min; m/z = 466.10 $[M+H]^+$

Step 6 & 7 - (S)-4-(aminomethyl)-N-(3-fluoropyridin-4-yl)-3-{3-[(4-{[(2-oxooxolan-3-yl)methyl]sulfanyl}phenyl)carbamoyl]phenyl}benzamide hydrochloride, Form I, - 7.



[0099] DCM (5.0 vol.), 2'-(((tert-butoxycarbonyl)amino)methyl)-5'-((3-fluoropyridin-4-yl)carbamoyl)-[1,1'-biphenyl]-3-carboxylic acid (2.1Kg, 1.0 eq.) (**5**), (S)-3-(((4-aminophenyl)thio)methyl)dihydrofuran-2(3H)-one (1.02 eq.) and DMAP (0.1 eq.) were charged to the reaction vessel at 20°C. NMI (3.0 eq.) was then added dropwise followed by dropwise addition of T3P (1.3 eq.) and the resulting mixture stirred for 3 hours. Water (5.0 vol.) was then added dropwise and the resulting reaction mixture stirred for 4 hours. The reaction mixture was then filtered through celite and the filter cake washed with DCM (2.0 vol.). The phases were then separated, and the organic phase washed with citric acid (5.0 vol. of a 2.0 w/w% solution) and water (5.0 vol.). The organic phase was then concentrated to ~2.5 vol. and swapped with EtOAc (3 x 5.0 vol. resulting in a ~7.5 vol. EtOAc solution) and the resulting EtOAc solution used directly in the next step.

[00100] UPLC-MS (ES+, Method 4): 4.26 min; m/z = 671.30 $[M+H]^+$

[00101] The obtained EtOAc solution was charged to the reaction vessel and water (1.0 vol.) added at 25°C. To this stirred mixture was added HCl (4M solution in EtOAc, 10.0 eq.) dropwise. The resulting reaction mixture was stirred for 3 hours, cooled to 20°C and then water (1.0 eq.) added dropwise. The pH was adjusted to between 5.0 and 5.2 using sat. aq. Na_2CO_3 solution and the resulting mixture stirred for 1 hour. The mixture was then centrifuged and the wet cake centrifuged with water (2 x 2.0 vol.). The wet cake was then added to water (5.0 vol.) at 20°C and the resulting mixture stirred for 1 hour. The mixture was then centrifuged and the wet cake centrifuged with water (2 x 2.0 vol.) and the wet cake dried at 50°C to give (S)- 4-(aminomethyl)-N-(3-fluoropyridin-4-yl)-3-{3-[(4-{[(2-

oxooxolan-3-yl)methyl]sulfanyl}phenyl)carbamoyl]phenyl}benzamide hydrochloride (2.27Kg, 82% yield) (**7, Form I**).

[00102] UPLC-MS (ES+, Method 1): 3.53 min; m/z = 571.10 $[M+H]^+$

[00103] XRPD diffractogram was collected with an X-ray diffractometer. The sample was prepared on a zero-background silicon wafer by gently pressing onto the flat surface. The parameters of XRPD diffraction are given below.

[00104] Parameters of XRPD Testing

Instrument	PANalytical, Empyrean
Radiation	Cu Kα (λ = 1.5418 Å)
Detector	PIXcel^{1D}
Scan angle	3-40° (2θ)
Scan step	0.013° (2θ)
Scan speed	20.4 s/step
Tube voltage/current	45 kV/40 mA
Divergence slit	1/8°
Rotation	On
Sample holder	Zero-background sample pan

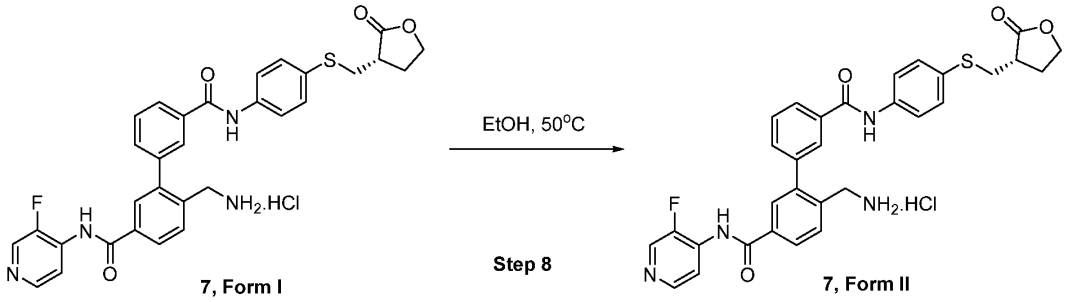
[00105] XRPD of 7-(S) HCl Salt form I (see also Figure 1)

Pos. [°2θ]	Rel. Int. [%]
24.0066	100
16.2248	96
25.3699	53.78
24.9127	45.63
23.2962	32.79
22.7155	26.92
22.5886	23.04
20.2571	20.05
24.6041	19.95
20.5891	19.33

[00106]

Example 3 – Conversion of 7-(S), HCl salt form I to 7-(S), HCl salt form II

[00107] Step 8 – Synthesis of give (S)-4-(aminomethyl)-N-(3-fluoropyridin-4-yl)-3-{3-[(4-{[(2-oxooxolan-3-yl)methyl]sulfanyl}phenyl)carbamoyl]phenyl}benzamide hydrochloride Form II (**7, Form II**).



7, Form I 7, Form II

[00108] (S)- 4-(aminomethyl)-N-(3-fluoropyridin-4-yl)-3-{3-[(4-{[(2-oxooxolan-3-yl)methyl]sulfanyl}phenyl)carbamoyl]phenyl}benzamide hydrochloride (2.2Kg, 1.0 eq.) and EtOH (5.0 vol.) were added to the reaction vessel and stirred at 25°C. The mixture was heated to 30°C and stirred for 1 hour. The mixture was then heated to 40°C and stirred for a further 1 hour before being heated to 50°C and stirred for 4 hours. The mixture was then cooled to 25°C and stirred for 2 hours before being filtered and the wet cake washed with EtOH (2 x 1.0 vol.). The wet cake was then dried at 55°C at <0.1Mpa for 24 hours to give (S)-4-(aminomethyl)-N-(3-fluoropyridin-4-yl)-3-{3-[(4-{[(2-oxooxolan-3-yl)methyl]sulfanyl}phenyl)carbamoyl]phenyl}benzamide hydrochloride (2.1Kg, 99.6% ee, 95% yield, Form II).

[00109] HRMS spectrum showed the ion peak of [M+H]+ at m/z 571.1813, with a deviation of less than 5 ppm, (Observed neutral mass: 570.1741, Neutral mass: 570.1737), indicated a base of molecular formula of C31H27FN4O4S, which was consistent with the structure of **7**.

[00110] ^{1}H-NMR (400MHz, DMSO-d6) δ/ppm: 10.82 (br s, 1H), 10.64 (s, 1H), 8.71 (br s, 2H), 8.61 (d, J = 2.8Hz, 1H), 8.42 (d, J = 5.2Hz, 1H), 8.26 (t, J = 2.0Hz, 1H), 8.14 – 8.12 (m, 2H), 8.10 (dt, J = 7.6Hz, 1.6Hz, 1H), 7.96 (d, J = 8.4Hz, 1H), 7.92 – 7.91 (3H, m), 7.74 (dt, J = 7.6Hz, 1.6Hz, 1H), 7.71 (t, J = 7.6Hz, 1H), 7.43 (d, J = 8.8Hz, 2H), 4.32 (td, J = 8.4Hz, 2.4Hz, 1H), 4.20 – 4.14 (m, 1H), 4.09 (s, 2H), 3.36 (dd, J = 13.2Hz, 4.0Hz, 1H), 3.07 (dd, J = 13.6Hz, 8.2Hz, 1H), 2.97 – 2.85 (m, 1H), 2.40-2.32 (m, 1H), 2.11-2.06 (m, 1H).

[00111] XRPD conditions were the same as those described in Example 2 for the XRPD analysis of HCl Salt form I.

[00112] XRPD peaks of 7-(S) HCl Salt form II (see also Figure 2)

Pos. [°2θ]	Rel. Int. [%]
16.1933	100
13.6249	55.56
14.4085	39.56
14.48	37.81

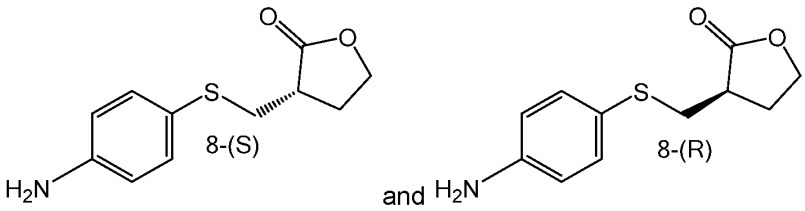
16.5458	32.86
23.55	22.48
17.3667	22.34
25.053	21.46
9.5696	19.76
20.3741	16.16

[00113] The inventors have found that ethanol is a very effective solvent for the conversion of Form I to Form II giving excellent purity and yield. Not all solvents are effective at this (examples of poor solvents for this purpose include MTBE, toluene, heptane, water, IPA). The inventors have also found that it is challenging to remove residual solvents from Form II. Ethanol has a more favourable safety tolerance relative to other solvents that are similarly effective so the difficulty removing residual solvent is not expected to be an impediment to the use of crystalline form II.

CLAIMS

1. A process for the preparation of substantially enantiopure S-enantiomer of compound 8 (8-(S)) in, the process comprising steps a) and b):

   a) reacting a mixture of 8-(S) and the R-enantiomer of compound 8 (8-(R)) with a substantially enantiopure chiral carboxylic acid to form a mixture of the carboxylic acid salt of the S-enantiomer of compound 8 and the carboxylic acid salt of the R-enantiomer of compound 8;



   b) allowing the carboxylic acid salt of the S-enantiomer of compound 8 to crystallise from a solvent S1 and collecting the carboxylic acid salt of the S-enantiomer of compound 8 as a solid and the carboxylic acid salt of the R-enantiomer of compound 8 as a solution in solvent S1.

2. The process of claim 1, wherein step a) is carried out in solvent S1 and in step b) the carboxylic acid salt of the S-enantiomer of compound 8 is allowed to crystallise out of the reaction mixture of step a).

3. The process of claim 1 or claim 2, wherein the carboxylic acid is selected from: (+)-Di-p-toluoyl-D-tartaric acid and (R)-mandelic acid.

4. The process of claim 1 or claim 2, wherein the carboxylic acid is (+)-Di-p-toluoyl-D-tartaric acid.

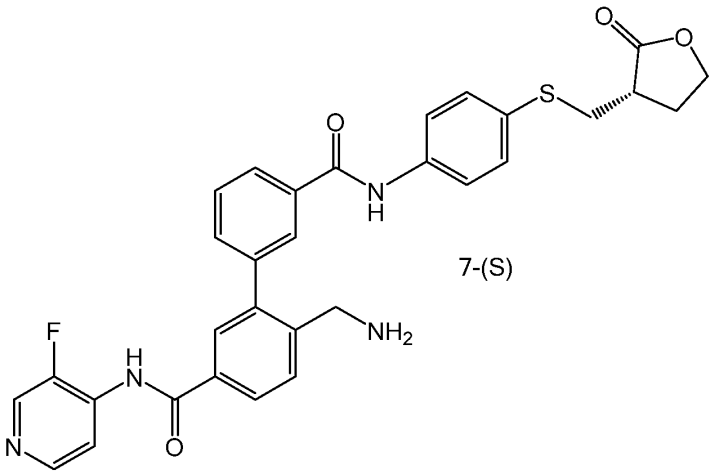
5. The process of any one of claims 1 to 4, wherein the solvent S1 comprises a solvent selected from ethanol, acetonitrile, ethyl acetate and mixtures thereof.

6. The process of claim 5, wherein the solvent S1 is a mixture of acetonitrile and water.

7. The process of any one of claims 1 to 6, wherein the solid obtained after step b) is subjected to one or more further crystallisation processes from the solvent S1.

8. The process of any one of claims 1 to 7, wherein the carboxylic acid salt of the R-enantiomer of compound 8 obtained in step b) is racemised to provide a mixture of the S-enantiomer of compound 8 (8-(S)) and the R-enantiomer of compound 8 (8-(R)).

9. The process of any one of claims 1 to 8, wherein the carboxylic acid salt of the S-enantiomer of compound 8 is converted to S-enantiomer of compound 7 (7-(S)):



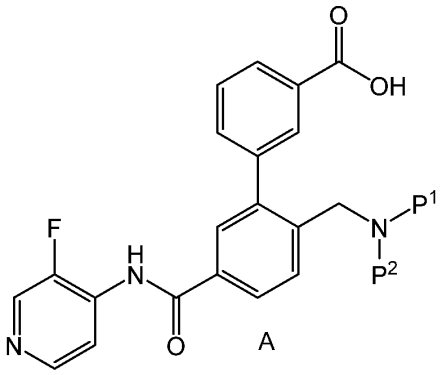
7-(S)

or a pharmaceutically acceptable salt thereof, in substantially enantiopure form.

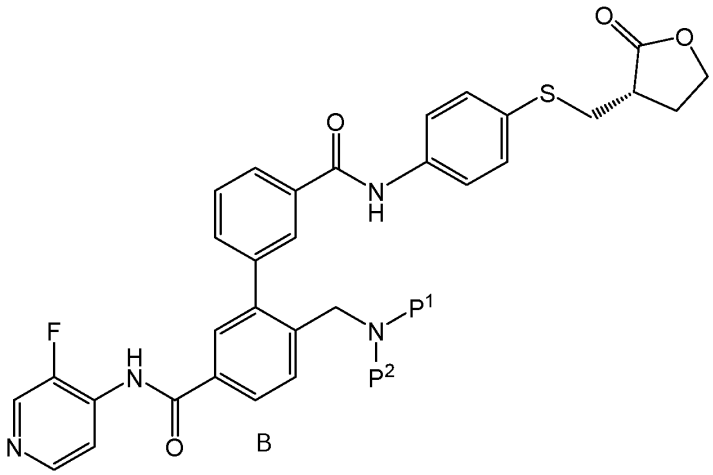
10. The process of claim 9, wherein the carboxylic acid salt of the S-enantiomer of compound 8 is converted to 7-(S), or a pharmaceutically acceptable salt thereof, according to steps c), d) and e):

c) converting the carboxylic acid salt of the S-enantiomer of compound 8 to the freebase of the S-enantiomer of compound 8;

d) reacting the freebase of the S-enantiomer of compound 8 with a compound of formula A to obtain a compound of formula B;



A



wherein P^1 and P^2 are each selected from H and a protecting group; wherein at least one of P^1 and P^2 is a protecting group;

e) deprotecting the protecting group P^1 and/or P^2 to provide 7-(S), or a pharmaceutically acceptable salt thereof, in substantially enantiopure form.

11. The process of claim 10, wherein P^1 is Boc and P^2 is H.

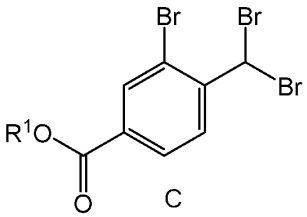
12. The process of claim 11, wherein the deprotection of step e) is performed using HCl and 7-(S) is formed as the HCl salt.

13. The process of claim 12, wherein 7-(S) is formed as crystalline form I of the HCl salt and the process comprises step f):
f) converting crystalline form I of the HCl salt of 7-(S) to crystalline form II of the HCl salt of 7-(S).

14. The process of claim 13, wherein step f) is performed by dissolving form I in a solvent S2 and allowing crystalline form II to crystallise out of the solvent S2 to form crystalline form II of the HCl salt of 7-(S).

15. The process of claim 14, wherein the solvent S2 is ethanol.

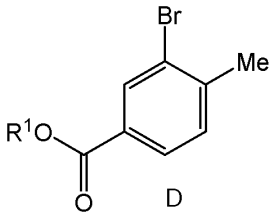
16. The process of any one of claims 10 to 15, wherein the process comprises converting a compound of formula C to the compound of formula A:



wherein R^1 is selected from H and C_1-C_4-alkyl.

17. The process of claim 16, wherein process comprises step g):

g) reacting a compound of formula D with NBS and a radical initiator in a solvent S3 at reflux to form the compound of formula C:

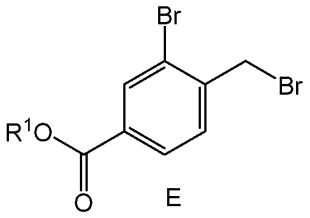


D

18. The process of claim 17, wherein the solvent S3 is acetic acid.

19. The process of any one of claims 16 to 18, wherein the process comprises step h):

h) reacting the compound of formula C with diethyl phosphite to form a compound of formula E:



E

20. The process of any one of claims 16 to 19, wherein R^1 is methyl.

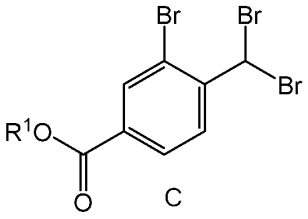
21. A process for the preparation of crystalline form II of the HCl salt of enantiomer of compound 7 (7-(S)), the process comprising step f):

f) dissolving crystalline form I of the HCl salt of 7-(S) in a solvent S2 and allowing crystalline form II to crystallise out of the solvent S2 to form crystalline form II of the HCl salt of 7-(S).

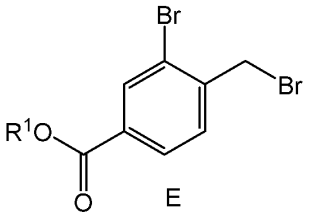
22. The process of claim 21, wherein the solvent S2 is ethanol.

23. A process of making a compound of formula E, the process comprising step h):

h) reacting a compound of formula C with diethyl phosphite to form a compound of formula E:



C

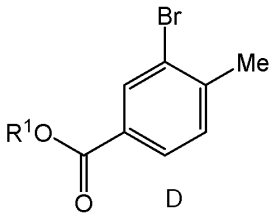


E

wherein R^1 is selected from H and C_1-C_4-alkyl.

24. A process of claim 23, the process comprising step g):

g) reacting a compound of formula D with NBS and a radical initiator in a solvent S3 at reflux to form the compound of formula C:

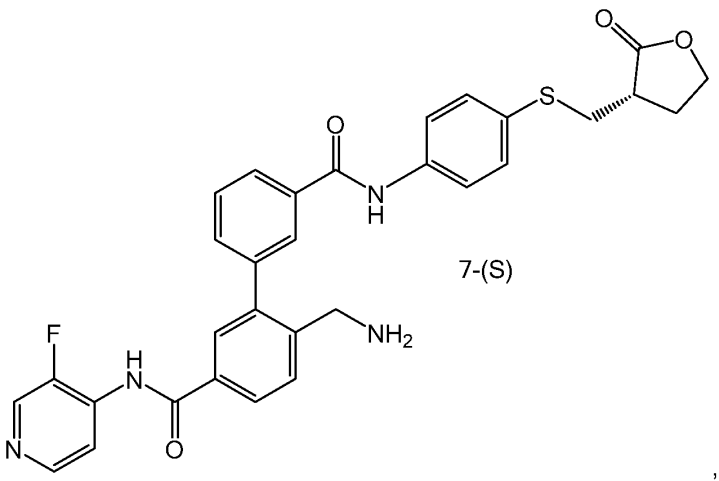


D

.

25. The process of claim 24, wherein the solvent S3 is acetic acid.

26. The process of any one of claims 23 to 25, wherein the process comprises converting the compound of formula E to S-enantiomer of compound 7 (7-(S)):



7-(S)

, or a pharmaceutically acceptable salt thereof, in substantially enantiopure form.