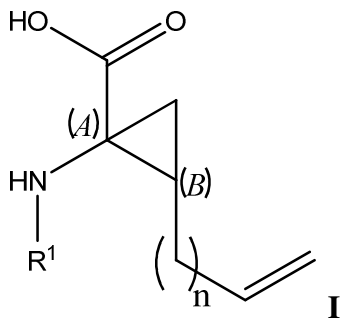
resulting in loss of about half of the product produced. Therefore, racemic approaches to these novel stapled peptide building blocks have limited appeal.

[0008] The class of alkenyl ACCs is novel and little structural information is available in the literature. Additionally, there is a lack of a stereoselective method for the production of ACCs whereby the requisite (1*R*,2S) or (1S,2*R*) stereocentres can be selected, as all current methods rely on the production of a racemic mixture which is then separated into the corresponding racemates. The asymmetric synthesis described herein allows the formation of either (1*R*,2*S*) or (1*S*,2*R*)-ACCs by simply changing the stereochemistry of the starting material.

[0009] The invention disclosed herein represents the first example of an asymmetric synthesis of long-chain alkenyl ACCs. Functionalisation of glycine templates with alkenyl aldehydes is also novel.

Summary

[00010] There is provided a method for producing a compound of Formula I



I

wherein:

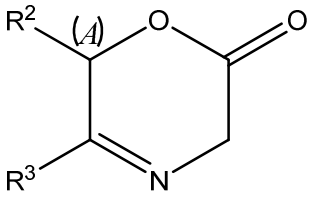
R^1 is a protecting group;

n is an integer between 1 and 10, and;

A and B are chiral centers such that when A is *S*, B is *R* and when A is *R*, B is *S*;

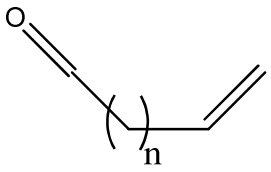
said method comprising the steps of :

a) condensing a chiral compound of Formula Ia



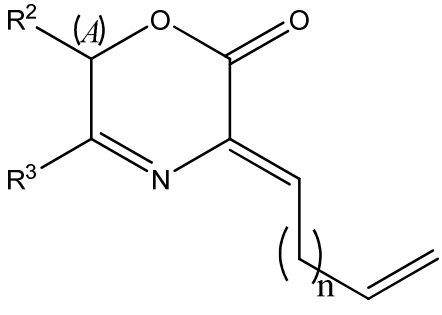
Ia

with a compound of Formula Ib



Ib

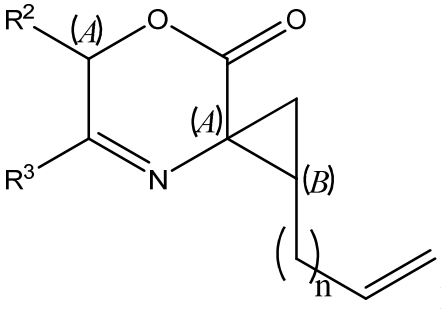
to produce a compound of Formula Ic



Ic

wherein A is a chiral center, R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A, and R^3 is aryl or heteroaryl;

b) reacting the non-terminal carbon-carbon double bond formed in step a) to produce a cyclopropyl group, so as to form a compound of Formula Id

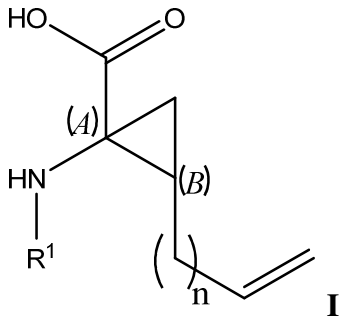


Id

and;

c) hydrolyzing the compound of Formula Id and protecting an ensuing amine (i.e., a free amine produced by the hydrolysis) with an R^1 protecting group to produce the compound of Formula I.

[00010a] In one aspect of the present disclosure, there is provided a method for producing a compound of Formula I



I

wherein:

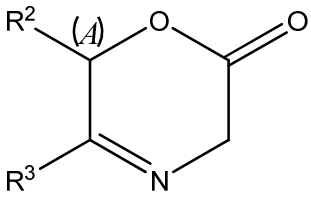
R^1 is a protecting group;

n is an integer between 1 and 10, and;

A and B are chiral centers such that when A is *S*, B is *R* and when A is *R*, B is *S*;

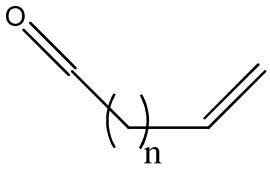
said method comprising the steps of:

a) condensing a chiral compound of Formula Ia



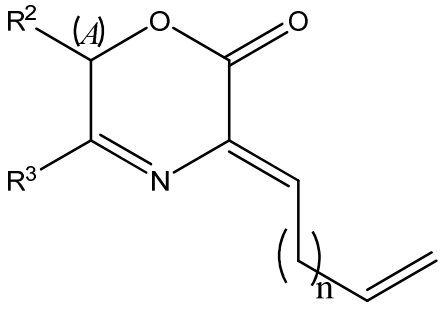
Ia

with a compound of Formula Ib



Ib

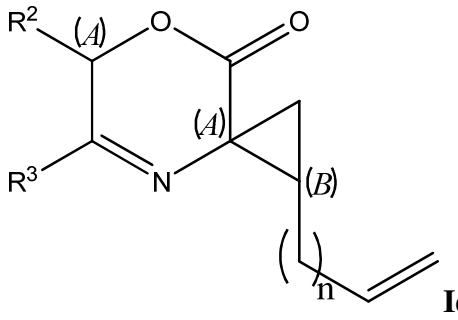
to produce a compound of Formula Ic



Ic

wherein A is a chiral center, R^2 is an aliphatic group with a tertiary or quaternary carbon atom covalently bonded to the chiral center A, and R^3 is aryl or heteroaryl;

b) reacting the non-terminal carbon-carbon double bond formed in step a) to produce a cyclopropyl group, so as to form a compound of Formula Id



Id

and;

c) hydrolyzing the compound of Formula Id and protecting a free amine produced by the hydrolysis with a reagent comprising R^1 to produce the compound of Formula I.

[00011] The following options may be used in conjunction with the above, either individually or in any suitable combination.

[00012] The R^1 group may be removable in basic solution. For example it may be Fmoc (fluorenylmethyloxycarbonyl), or it may be 9-(2-sulfo)fluorenylmethyl carbamate, or it may be Peoc (2-phosphonioethoxycarbonyl), or it may be Ppoc (l-Methyl-l-(triphenylphosphonio) ethyl). The R^2 group may be a branched hydrocarbyl group. It may be isopropyl, *sec*-butyl, *tert*-butyl or *sec*-pentyl. The R^3 group may be heteroaryl or it may be aryl. When R^3 is aryl, it may be phenyl. The variable n may be an integer between 1 and 10, or between 1 and 6, 1 and 4, 2 and 6, 2 and 4, 3 and 6 or 4 and 6. It may be any one of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

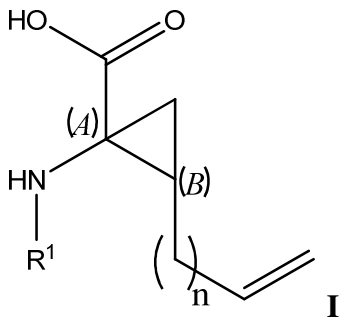
[00013] In the compound of Formula I, A may be *S* so that B is *R*, or A may be *R* so that B is *S*.

[00014] Step (a) may be conducted in the presence of a catalyst. It may be conducted in the presence of a base. It may be conducted in the presence of both a catalyst and a base. When a catalyst is used, the catalyst may be a tetraalkylammonium salt. The tetraalkylammonium salt may be tetra-n-butylammonium bromide or may be some other tetra-n-butylammonium halide. When a base is used, it may be a basic inorganic salt. It may be potassium carbonate. The condensation reaction of step (a) is conducted in a solvent. The solvent may be an aprotic solvent. It may be a polar solvent. It may be dichloromethane or it may be acetonitrile. The temperature at which step (a) is conducted may be between about 0 °C and about 25 °C, e.g., between about 10 °C and 25 °C, 15 °C and 25 °C or 20 °C and 25 °C. It may be about 5, 10, 15, 20, or 25 °C.

[00015] Step (b) may comprise the reaction of a compound of Formula Ic with a trialkyl sulfoxonium halide. The trialkyl sulfoxonium halide comprises three alkyl groups, each independently selected from methyl, ethyl, propyl, butyl and pentyl. At least one of the three alkyl groups should be methyl. The trialkyl sulfoxonium halide may comprise three methyl groups (i.e., it may be a trimethyl sulfoxonium halide). The halide of the trialkyl sulfoxonium halide may be fluoride, chloride, bromide, or iodide. The trialkyl sulfoxonium halide may be for example trimethyl sulfoxonium chloride. The reaction may be conducted in the presence of a group I hydride, e.g., it may be LiH, NaH, or KH. The reaction may be conducted in an organic solvent. The solvent may be a polar aprotic solvent. It may be tetrahydrofuran. The temperature at which step (b) is conducted may be between about 20 °C and 100 °C, e.g.,

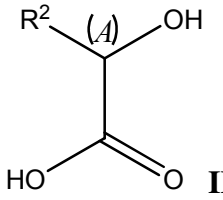
sterically-hindered base, such that it can only bind to protons. It may be N,N-diisopropylethylamine. The dipolar aprotic solvent may be THF. The temperature at which this reaction is conducted may be between about 15°C and about 30 °C, e.g., between about 15 °C and 25 °C or between 20 °C and 25 °C. It may be for example 15, 20, 25 or 30 °C. It may be conducted at a room temperature.

[00022] In one example, the process of the present disclosure involves producing a compound of Formula I



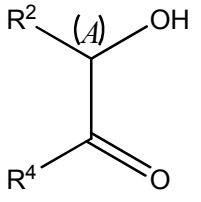
I

wherein R^1 is a protecting group; n is 2, A is either *S* or *R*, and B is *R* when A is *S* or B is *S* when A is *R*. The process involves exposing a compound of Formula IId,



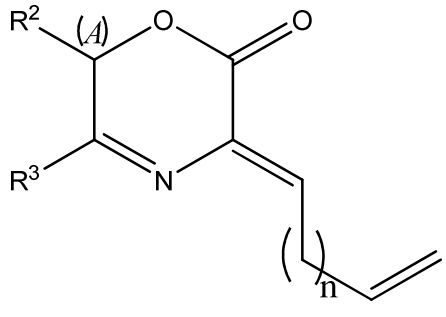
IId.

where R^2 is isopropyl, to N,N-diisopropylethylamine, hydroxybenzotriazole, N,N-dicyclohexylcarboiimide and dimethylamine hydrohalide in a dipolar aprotic solvent at a room temperature between about 15°C and about 30°C, to produce a compound of Formula IIc. The next step in this process involves exposing the compound of Formula IIc



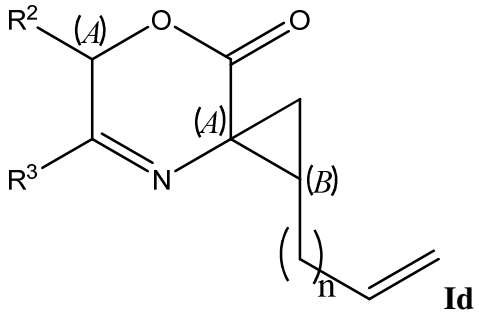
IIc

where R^2 is isopropyl and R^4 is $N(Me)_2$, to a Grignard reagent of formula R^3MgBr in a dipolar aprotic solvent to produce a compound of Formula IIb. This may be conducted at an initial



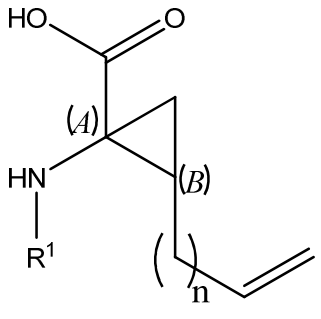
Ic

where R^2 is isopropyl, R^3 is aryl, A is either *S* or R, and n is 2, is then exposed to trimethyl sulfoxonium chloride and a group I hydride in a dipolar aprotic solvent at a temperature between about 20°C and about 100°C to produce a compound of Formula Id. The next step is to expose a compound of Formula Id



Id

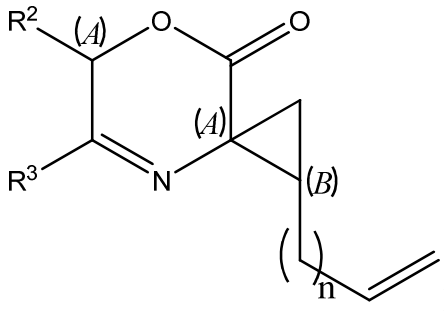
where R^2 is isopropyl, R^3 is aryl, A is either *S* or *R*, B is *R* when A is *S* or B is *S* when A is *R*, and n is 2, to aqueous NaOH in ethanol to hydrolyze the oxazine ring, and then expose this product to a halide salt of a protecting group in aqueous THF to protect the amine group, to produce a compound of Formula I



I

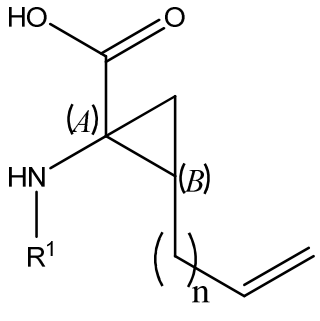
where R^1 is a protecting group, A is *S* and B is *R*, or A is *R* and B is *S*, and n is 2.

[00023] In another example, the process of the present disclosure involves producing a compound of Formula I



Id

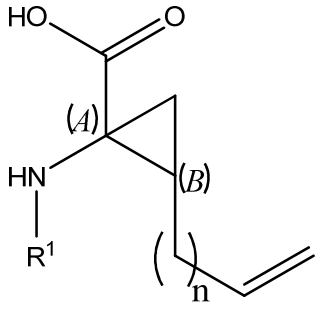
where R^2 is isopropyl, R^3 is phenyl, A is either *S* or *R*, B is *R* when A is *S* or B is *S* when A is *R* and n is 5, to aqueous NaOH in ethanol to hydrolyze the oxazine ring, and then expose this product to a halide salt of a protecting group in aqueous THF to protect the amine group, to produce a compound of Formula I



I

where R^1 is a protecting group, A is either *S* or *R*, B is *R* when A is *S* or B is *S* when A is *R* and n is 5.

[00024] In a second aspect of the present disclosure, there is provided a compound of Formula I



I

wherein:

R^1 is a protecting group;

n is an integer between 1 and 10, and;

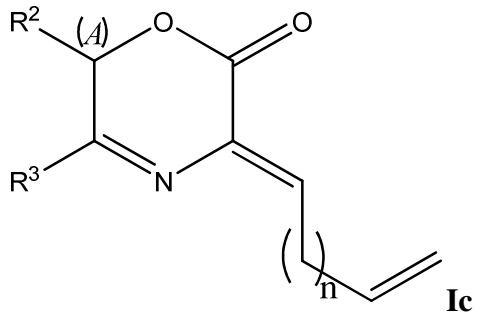
A and B are chiral centers such that when A is *S*, B is *R* and when A is *R*, B is *S*.

[00025] The following options may be used in conjunction with the second aspect, either individually or in any suitable combination.

[00026] The compound may have an R^1 group that is a protecting group removable in a basic solution. It may be Fmoc (fluorenylmethyloxycarbonyl), 9-(2-sulfo)fluorenylmethyl carbamate, Peoc (2-phosphonioethoxycarbonyl), or Ppoc (l-Methyl-l-(triphenylphosphonio) ethyl). The n may be an integer between 1 and 10, or between 1 and 6, 1 and 4, 2 and 6, 2 and 4, 3 and 6 or 4 and 6. It may be any one of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. A may be *S* and B may be *R* or A may be *R* and B may be *S*.

[00027] The compound of Formula I may be Fmoc-protected (1*S*,2*R*)-1-amino-2-(but-3-en-1-yl)cyclopropane-1-carboxylic acid. It may be Fmoc-protected (1*R*,2*S*)-1-amino-2-(hept-6-en-1-yl)cyclopropane-1-carboxylic acid. It may be Fmoc-protected (1*R*,2*S*)-1-amino-2-(but-3-en-1-yl)cyclopropane-1-carboxylic acid. It may be Fmoc-protected (1*S*,2*R*)-1-amino-2-(hept-6-en-1-yl)cyclopropane-1-carboxylic acid.

[00028] There is provided a compound of Formula Ic



Ic

wherein:

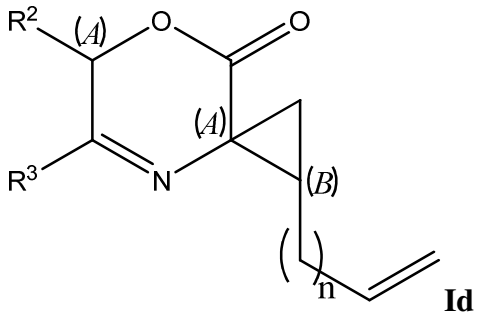
R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A;

R^3 is aryl or heteroaryl;

n is an integer between 1 and 10, and;

A is a chiral center.

[00029] There is provided a compound of Formula Id



Id

wherein:

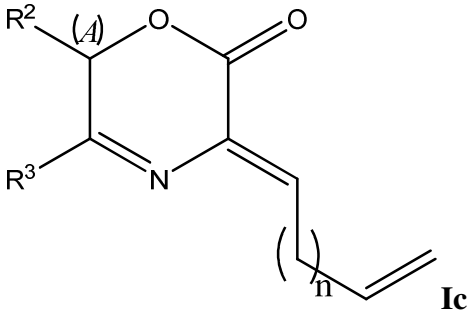
R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A;

R^3 is aryl or heteroaryl;

n is an integer between 1 and 10, and;

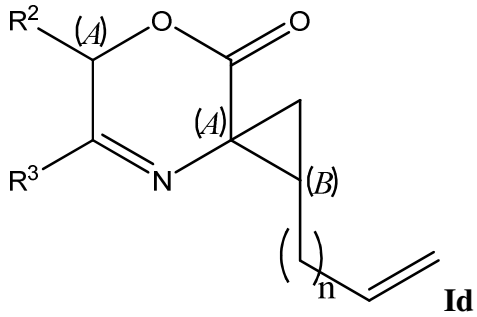
A is a chiral center.

[00029a] In a third aspect of the present disclosure, there is provided a compound of Formula Ic



Ic

or Formula Id



Id

wherein:

R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A, optionally a branched hydrocarbyl group;

R^3 is aryl or heteroaryl;

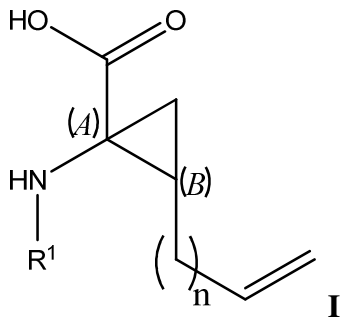
n is an integer between 1 and 10, and;

A is a chiral center and B is a chiral center such that when A is *S*, B is *R* and when A is *R*, B is *S*.

[00030] The following options may be used in conjunction with the third aspect, either individually or in any suitable combination.

[00031] The aliphatic R^2 group may be a branched hydrocarbyl group. It may be isopropyl, *sec*-butyl, *tert*-butyl or *sec*-pentyl. The R^3 group may be aryl. It may be phenyl.

[00032] There is provided a use of a compound according to Formula I



I

wherein:

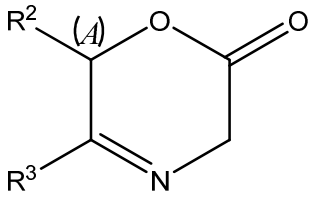
R^1 is a protecting group;

n is an integer between 1 and 10, and;

A and B are chiral centers such that when A is *S*, B is *R* and when A is *R*, B is *S*;

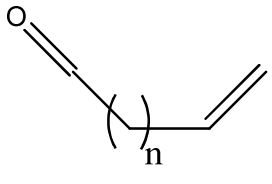
to synthesize a stapled peptide.

[00033] There is provided a use of a compound of Formula Ia



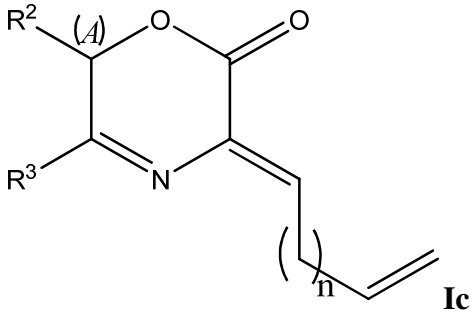
Ia

in a reaction with a compound of Formula Ib



Ib

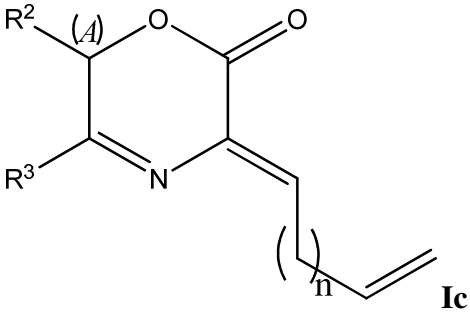
to produce a compound of Formula Ic



Ic

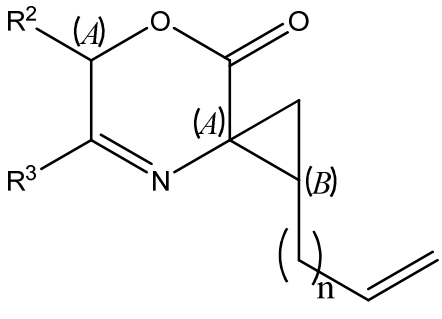
wherein A is a chiral center, R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A, R^3 is aryl or heteroaryl and n is an integer between 1 and 10.

[00034] There is provided a use of a compound of Formula Ic



Ic

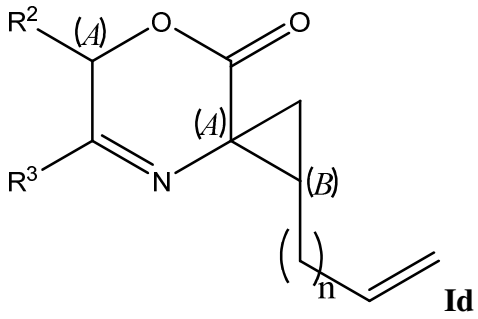
in a reaction with a trialkyl sulfoxonium halide to produce a compound of Formula Id



Id

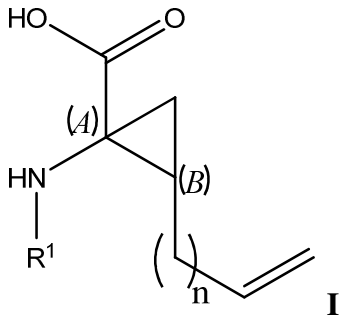
wherein A is a chiral center, R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A, R^3 is aryl or heteroaryl and n is an integer between 1 and 10.

[00035] There is provided a use of a compound of Formula Id



Id

to produce a compound of Formula I



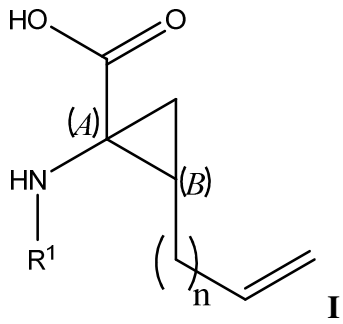
I

wherein R^1 is a protecting group, n is an integer between 1 and 10, A and B are chiral centers such that when A is *S*, B is *R* and when A is *R*, B is *S*, R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A, and R_3 is aryl or heteroaryl.

Brief Description of Drawings

CLAIMS

1. A method for producing a compound of Formula I



I

wherein:

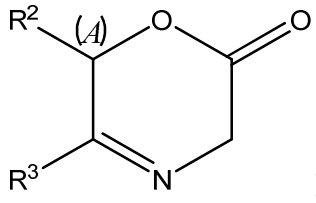
R^1 is a protecting group;

n is an integer between 1 and 10, and;

A and B are chiral centers such that when A is *S*, B is *R* and when A is *R*, B is *S*;

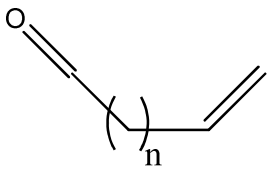
said method comprising the steps of:

a) condensing a chiral compound of Formula Ia



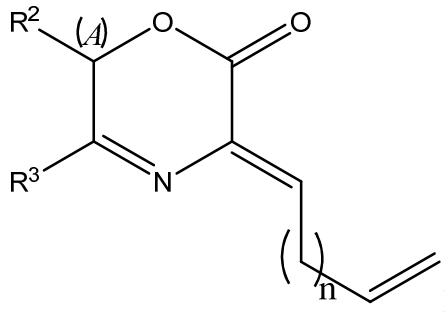
Ia

with a compound of Formula Ib



Ib

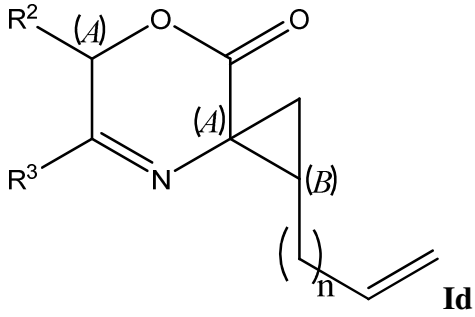
to produce a compound of Formula Ic



Ic

wherein A is a chiral center, R^2 is an aliphatic group with a tertiary or quaternary carbon atom covalently bonded to the chiral center A, and R^3 is aryl or heteroaryl;

b) reacting the non-terminal carbon-carbon double bond formed in step a) to produce a cyclopropyl group, so as to form a compound of Formula Id



Id

and;

c) hydrolyzing the compound of Formula Id and protecting a free amine produced by the hydrolysis with a reagent comprising R^1 to produce the compound of Formula I.

2. The method of claim 1 wherein:
   - R^1 is a protecting group which is removable in a basic solution; and/or
   - R^2 is a branched hydrocarbyl group; and/or
   - R^3 is aryl; and/or
   - n is an integer between 1 and 6; and/or
   - A is *S* and B is *R* or A is *R* and B is *S*.

3. The method of claim 1 or claim 2, wherein step a) is conducted in the presence of a catalyst and a base, wherein the catalyst is a quaternary ammonium salt and the base is a basic inorganic salt.

4. The method of claim 3 wherein the catalyst is a tetraalkylammonium salt.

5. The method of claim 4, wherein the catalyst is tetra-n-butylammonium bromide.

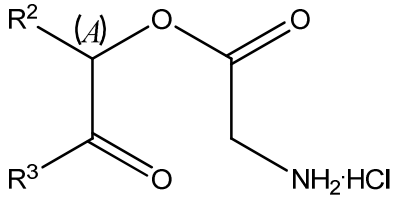
6. The method of any one of claims 1 to 5, wherein step a) is conducted in a dipolar aprotic solvent and at a temperature between 0°C and 25°C, and step b) is conducted at a temperature between 20°C and 100°C.

7. The method of any one of claims 1 to 6, wherein step b) comprises the reaction of compound Ic with a trialkyl sulfoxonium halide, in the presence of a group I hydride and an organic solvent, wherein:

- the trialkyl sulfoxonium halide species comprises three alkyl groups independently selected from methyl, ethyl, propyl, butyl and pentyl, wherein at least one alkyl group is methyl; and/or
- the halide group of the trialkyl sulfoxonium halide species is selected from the group comprising fluoride, chloride, bromide and iodide, optionally wherein the trialkyl sulfoxonium halide species is trimethyl sulfoxonium chloride; and/or
- wherein the group I hydride is LiH, NaH or KH; and/or
- wherein the organic solvent is a polar aprotic solvent, optionally wherein the organic solvent is tetrahydrofuran.

8. The method of any one of claims 1 to 7, wherein step c) comprises exposing the compound of Formula Id to an aqueous strong base and a compound of general formula R^1X, wherein R^1 is as defined in claim 1 or claim 2, X is a halogen selected from fluorine, chlorine, bromine and iodine, and the strong base is LiOH, NaOH, KOH or NH_4OH, and wherein step c) is conducted at room temperature.

9. The method of any one of claims 1 to 8, further comprising the step of preparing the compound of Formula Ia by carrying out a dehydration reaction of a compound of Formula IIa



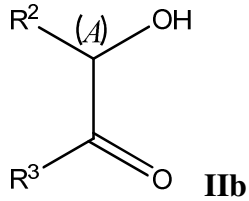
IIa.

to form an oxazine ring, wherein the dehydration reaction comprises exposing the compound of Formula Ia to a trialkylamine, wherein the trialkylamine comprises three alkyl groups, each independently selected from the group comprising methyl, ethyl, propyl and butyl, and

wherein the dehydration reaction is conducted at room temperature in an acidified organic solvent, wherein the acidified organic solvent is an acidified organic ester and comprises HF, HCl, HBr or HI.

10. The method of claim 9, wherein about one molar equivalent of the trialkylamine is used when compared to the amount of conjugate acid of Formula IIa that is present.

11. The method of claim 9 or 10, further comprising a step of preparing the compound of Formula IIa, said step comprising the addition of a protected glycine compound to a compound of Formula IIb



IIb

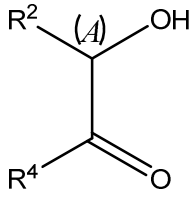
wherein the protected glycine compound comprises a covalently bound protecting group.

12. The method of claim 11, wherein the glycine is added by exposing a compound of Formula IIa to a nucleophilic catalyst, a coupling agent and the protected glycine compound, wherein:

- the nucleophilic catalyst is a basic nucleophilic catalyst; and/or
- the coupling agent is capable of converting carboxylic acids to activated esters; and/or
- the protecting group is an acid labile protecting group.

13. The method of claim 12, wherein the reaction is conducted at room temperature.

14. The method of claim 12 or 13, further comprising a step of preparing the compound of Formula IIb by conducting a reaction between a compound of Formula IIc



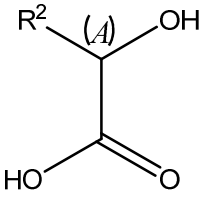
IIc

wherein R^4 is a dialkylamino group, and a Grignard reagent of general formula R^3MgBr in an organic ether solvent, optionally:

- wherein the dialkylamino group of R^4 comprises two alkyl groups, each independently selected from the group comprising methyl, ethyl, propyl and butyl; and/or
- the Grignard reagent is arylmagnesium bromide, optionally wherein the Grignard reagent is phenylmagnesium bromide.

15. The method of claim 14, wherein the reaction begins at a temperature of -78 °C and rises to room temperature during the reaction.

16. The method of claim 14 or 15, further comprising a step preparing the compound of Formula IIc by performing an amidation reaction on a compound of Formula IId



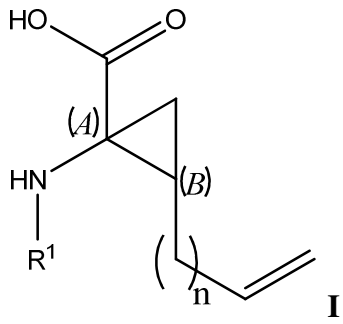
IId

wherein the amidation reaction is conducted by exposing a compound of Formula IId to a base, a catalyst, a coupling agent and a dialkyamine hydrohalide salt, wherein:

- the dialkyamine hydrohalide salt is of general formula $R^4H{\cdot}HX$, wherein R^4 is a dialkylamino group comprising two alkyl groups, and each alkyl group is independently selected from the group comprising methyl, ethyl, propyl and butyl, and X is a halogen; and/or

- the dehydrating agent is N,N'-dicyclohexylcarbodiimide or (2-(thiophen-2-yl)phenyl)boronic acid; and/or
- the catalyst is hydroxybenzotriazole; and/or
- the base is a sterically hindered base.

17. A compound of Formula I



I

wherein:

R^1 is a protecting group;

n is an integer between 1 and 10, and;

A and B are chiral centers such that when A is *S*, B is *R* and when A is *R*, B is *S*.

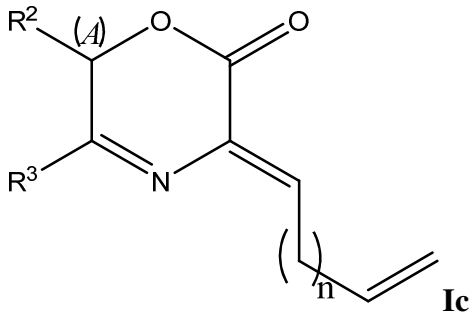
18. A compound according to claim 17, wherein R^1 is a protecting group removable in a basic solution.

19. A compound according to claim 17 or 18, wherein A is *S* and B is *R*.

20. A compound according to claim 17 or 18, wherein A is *R* and B is *S*.

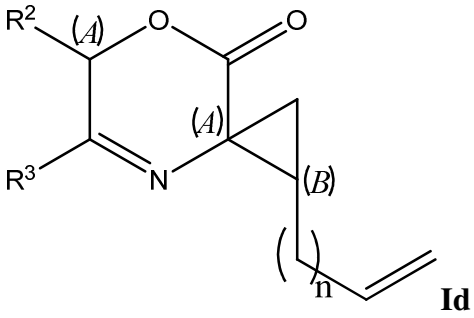
21. A compound of Formula I according to claim 17 or 18 being selected from the group consisting of: Fmoc-protected (1*S*,2*R*)-1-amino-2-(but-3-en-1-yl)cyclopropane-1-carboxylic acid; Fmoc-protected (1*R*,2*S*)-1-amino-2-(hept-6-en-1-yl)cyclopropane-1-carboxylic acid; Fmoc-protected (1*R*,2*S*)-1-amino-2-(but-3-en-1-yl)cyclopropane-1-carboxylic acid; and Fmoc-protected (1*S*,2*R*)-1-amino-2-(hept-6-en-1-yl)cyclopropane-1-carboxylic acid.

22. A compound of Formula Ic



Ic

or Formula Id



Id

wherein:

R^2 is an aliphatic group with a secondary or tertiary carbon atom covalently bonded to the chiral center A, optionally a branched hydrocarbyl group;

R^3 is aryl or heteroaryl;

n is an integer between 1 and 10, and;

A is a chiral center and B is a chiral center such that when A is *S*, B is *R* and when A is *R*, B is *S*.