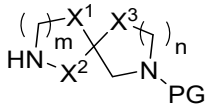
CLAIMS

1. A method of separating enantiomers of a compound of Formula I:



Formula I

the method comprising the steps of:

a) contacting the compound of Formula I with a chiral acid to form a diastereomeric salt of the compound of Formula I; and

b) separating each diastereomer of the diastereomeric salt, thereby separating enantiomers of a compound of Formula I;

wherein:

n and m are each, independently, 0, 1, 2, 3, 4, or 5;

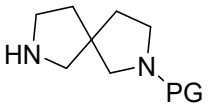
PG is a nitrogen protecting group; and

X^1, X^2, and X^3 are each, independently, $-CH_2-$, -CHF-, $-CF_2-$, -C(O)-, or -O-.

2. The method of claim 1, wherein the chiral acid comprises a chiral carboxylic acid.

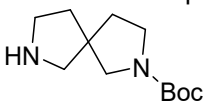
3. The method of claim 1 or 2, wherein the separating step (b) comprises recrystallization.

4. The method of any one of claims 1 to 3, wherein the compound of Formula I is further described by Formula Ia:



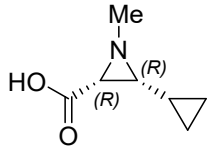
Formula Ia .

5. The method of any one of claims 1 to 4, wherein the compound of Formula I is Compound B:



Compound B .

6. A barium salt of a compound of Compound A:

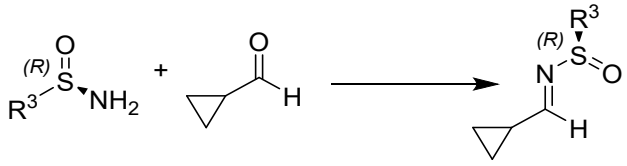


Compound A.

7. The barium salt of claim 6, wherein the barium salt is a 2:1 (compound A: barium) salt.

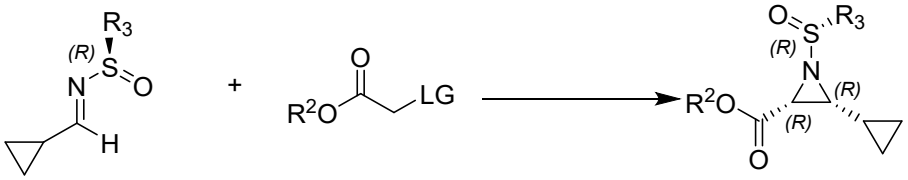
8. A method of preparing the barium salt of claim 6 or 7, the method comprising the steps of:

a) condensing a compound of Formula IIa and Compound C to form a compound of Formula IIb:



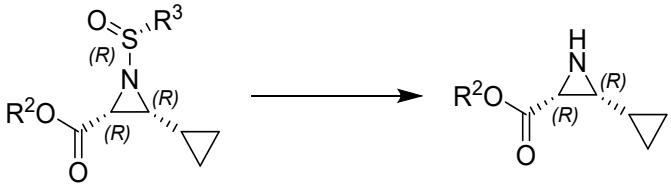
Formula IIa **Compound C** **Formula IIb**

b) cyclizing the compound of Formula IIb and a compound of Formula IIc to form a compound of Formula IId:



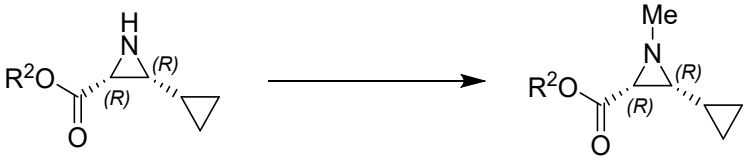
Formula IIb **Formula IIc** **Formula IId**

c) hydrolyzing the compound of Formula IId to form a compound of Formula IIe:



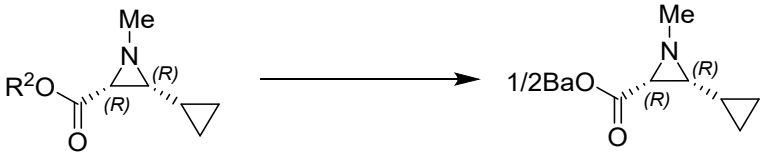
Formula IId **Formula IIe**

d) methylating the compound of Formula IIe to form a compound of Formula IIf:



Formula IIe **Formula IIf** ; and

e) hydrolyzing the compound of Formula IIf to form the barium salt of Compound A:



Formula IIf **Compound A Barium Salt**

wherein:

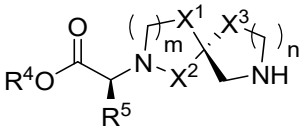
R^2 and R^3 are each, independently, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, or optionally substituted C_6-C_{10} aryl, and

LG is a leaving group selected from the group consisting of halogen, triflate, mesylate, and tosylate.

9. The method of claim 8, wherein the methylating step (d) comprises contacting the compound of Formula IIe with $MeB(OH)_2$.

10. The method of claim 8 or 9, wherein the hydrolyzing step (e) comprises contacting the compound of Formula IIf with barium hydroxide.

11. A method of preparing a compound, or a salt thereof, of Formula III:



Formula III

the method comprising the steps of:

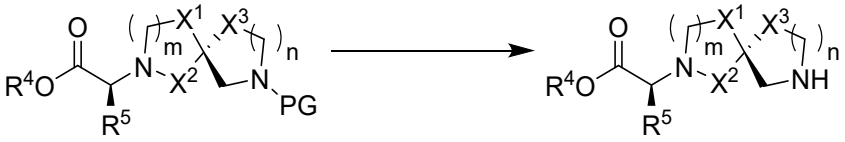
a) coupling a compound of Formula IIId with a compound of Formula I or salt thereof to form a compound of Formula IIIe:



Formula IIId **Formula I** **Formula IIIe** ;

and

b) deprotecting the compound of Formula IIIe to form the compound of Formula III or salt thereof:



Formula IIIe **Formula III**

wherein

n and m are each, independently, 0, 1, 2, 3, 4, or 5;

PG is a nitrogen protecting group;

R^4 is optionally substituted C_1-C_6 alkyl or optionally substituted C_6-C_{10} aryl;

R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3- to 6-membered cycloalkyl, or optionally substituted 3- to 6-membered heterocycloalkyl; and

X^1, X^2, and X^3 are each, independently, $-CH_2-$, -CHF-, $-CF_2-$, -C(O)-, or -O-.

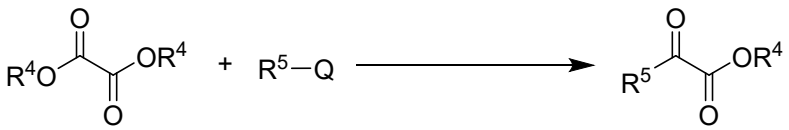
12. The method of claim 11, wherein m and n are each 1; R^4 is optionally substituted C_1-C_6 alkyl; R^5 is 3- to 6-membered cycloalkyl; and X^1, X^2, and X^3 are each $-CH_2-$.

13. The method of claim 11 or 12, wherein PG is Boc.

14. The method of any one of claims 11 to 13, wherein the combining step (a) includes contacting the compound of Formula IIId with triflic anhydride to form a triflate, followed by contacting the triflate with the compound of Formula I to form the compound of Formula IIIe.

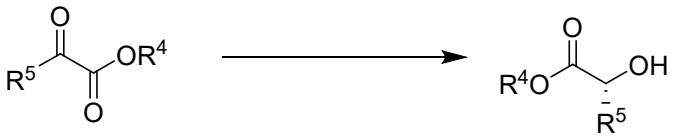
15. The method of any one of claims 11 to 14, wherein the compound of Formula IIId is prepared by a method comprising the steps of:

A1) combining a compound of Formula IIIa and a compound of Formula IIIb to form a compound of Formula IIIc:



Formula IIIa **Formula IIIb** **Formula IIIc**

B1) reducing the compound of Formula IIIc to form the compound of Formula IIId:



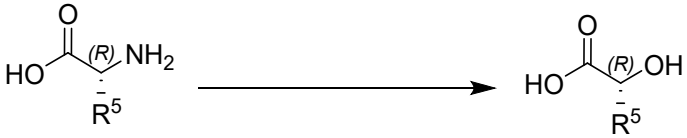
Formula IIIc **Formula IIId** .

wherein Q is MgBr, MgCl, MgI, or Li.

16. The method of claim 15, wherein the reducing step (B1) comprises contacting the compound of Formula IIIc with a ketoreductase enzyme.

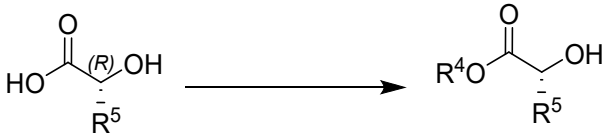
17. The method of any one of claims 11 to 14, wherein the compound of Formula IIId is prepared by the steps of:

A2) converting a compound of Formula IIIf to form a compound of Formula IIIg:



Formula IIIf **Formula IIIg** ; and

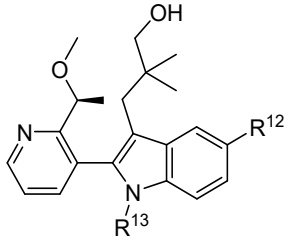
B2) reacting the compound of Formula IIIg to form the compound of Formula IIId:



Formula IIIg **Formula IIId** .

18. The method of claim 17, wherein the converting step (A2) comprises forming a diazonium salt of the compound of Formula IIIf.

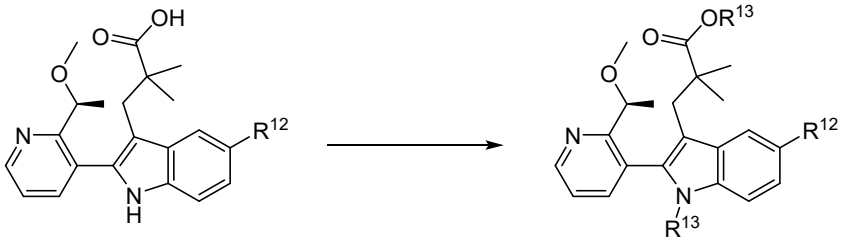
19. A method of preparing a compound, or a salt thereof, of Formula VIII:



Formula VIII

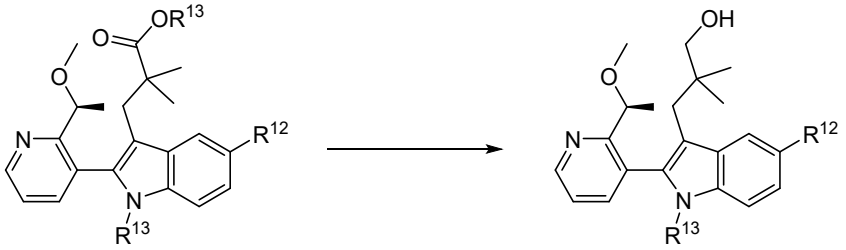
the method comprising the steps of:

a) esterifying and N-alkylating a compound of Formula VIIIa to form a compound of Formula VIIIb:



Formula VIIIa **Formula VIIIb** ;

b) reducing the compound of Formula VIIIb to form a compound of Formula VIIIc as a mixture of atropisomers:



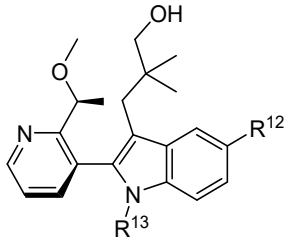
Formula VIIIb **Formula VIIIc** ; and

c) separating the mixture of atropisomers of Formula VIIIc to obtain an atropisomer of the compound of Formula VIII;

wherein R^{12} is halogen; and

each R^{13} is independently optionally substituted C_1-C_6 alkyl.

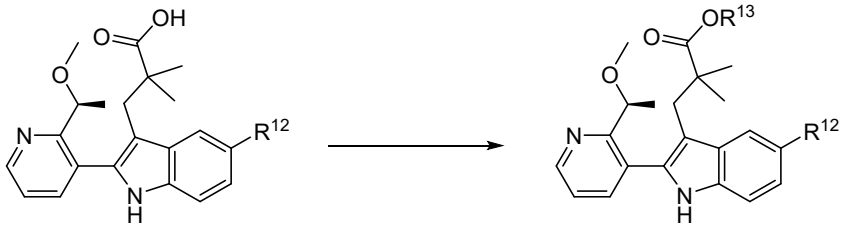
20. A method of preparing a compound, or a salt thereof, of Formula VIII:



Formula VIII

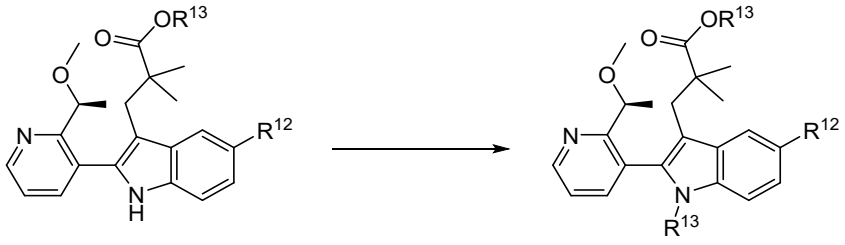
the method comprising the steps of:

a) esterifying a compound of Formula VIIIa to form a compound of Formula VIIId:



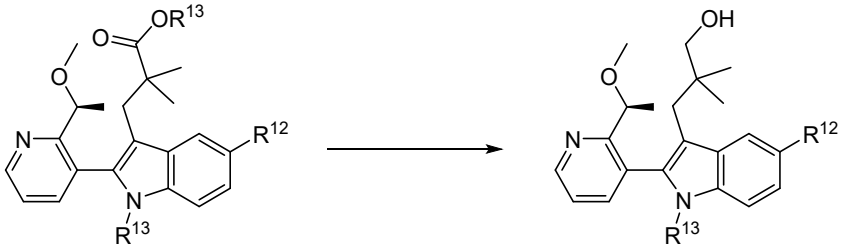
Formula VIIIa **Formula VIIId** ;

b) N-alkylating the compound of Formula VIIId to form the compound of Formula VIIIb:



Formula VIIId **Formula VIIIb** ;

c) reducing the compound of Formula VIIIb to form a compound of Formula VIIIc as a mixture of atropisomers:



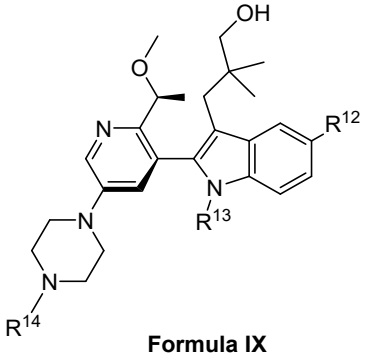
Formula VIIIb **Formula VIIIc** ; and

d) separating the mixture of atropisomers of Formula VIIIc to obtain the stereoisomer of the compound of Formula VIII;

wherein R^{12} is halogen; and

each R^{13} is independently optionally substituted C_1-C_6 alkyl.

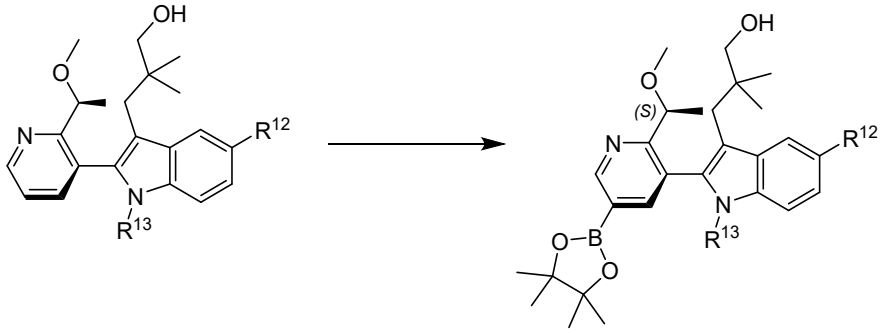
21. A method of preparing a compound, or a salt thereof, of Formula IX:



Formula IX

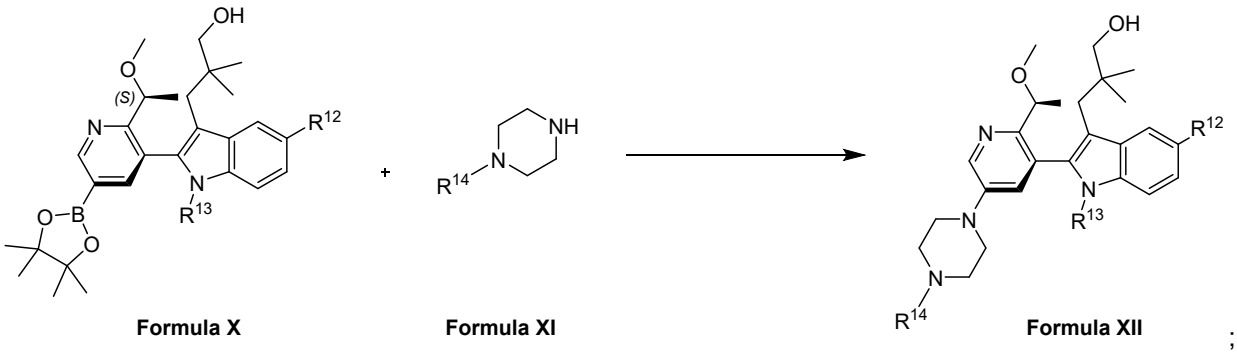
the method comprising the steps of:

a) borylating a compound of Formula VIII to form a compound Formula X:



Formula VIII **Formula X** ; and

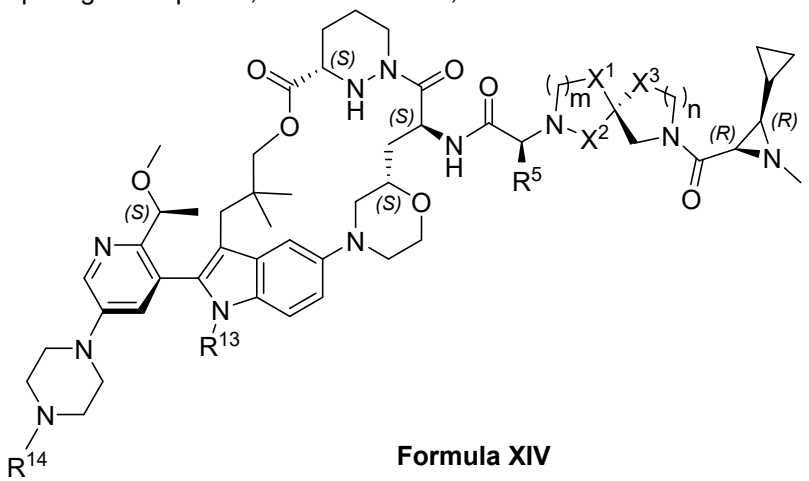
b) coupling the compound of Formula X with a compound of Formula XI to form the compound of Formula XII:



Formula X **Formula XI** **Formula XII** ;

wherein R^{12} is halogen;
R^{13} is optionally substituted C_1-C_6 alkyl; and
R^{14} is optionally substituted 3- to 6-membered cycloalkyl.

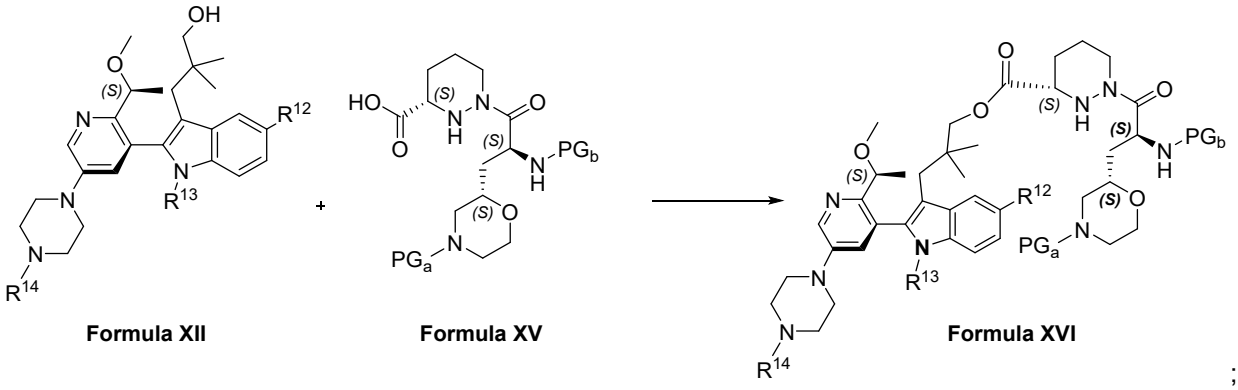
22. A method of preparing a compound, or a salt thereof, of Formula XIV:



Formula XIV

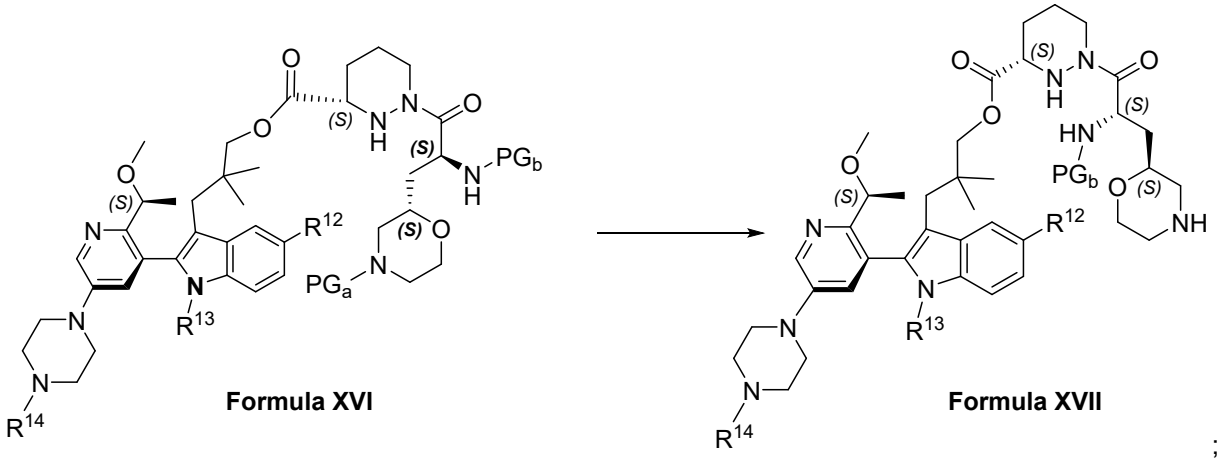
the method comprising the steps of:

a) reacting a compound of Formula XV with a compound of Formula XII to form a compound of Formula XVI:



Formula XII **Formula XV** **Formula XVI** ;

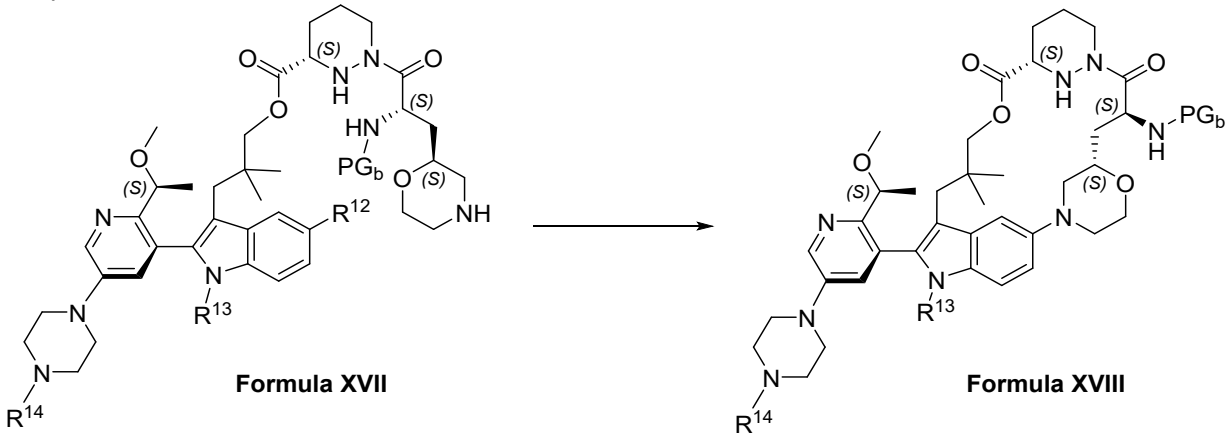
b) removing PG_a of the compound of Formula XVI to form a compound of Formula XVII:



Formula XVI **Formula XVII**

;

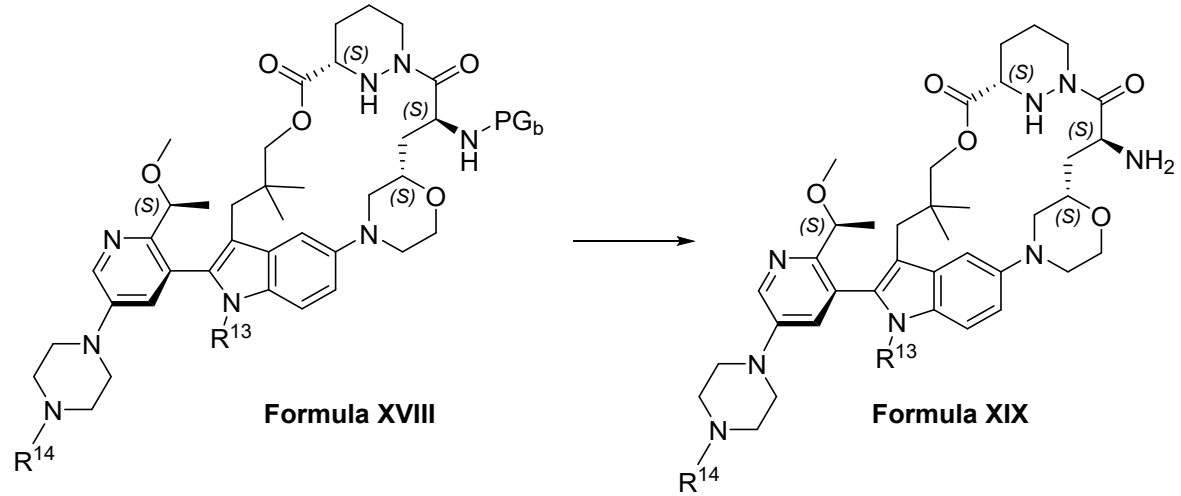
c) cyclizing the compound of Formula XVII in the presence of a transition metal catalyst to form a compound of Formula XVIII:



Formula XVII **Formula XVIII**

;

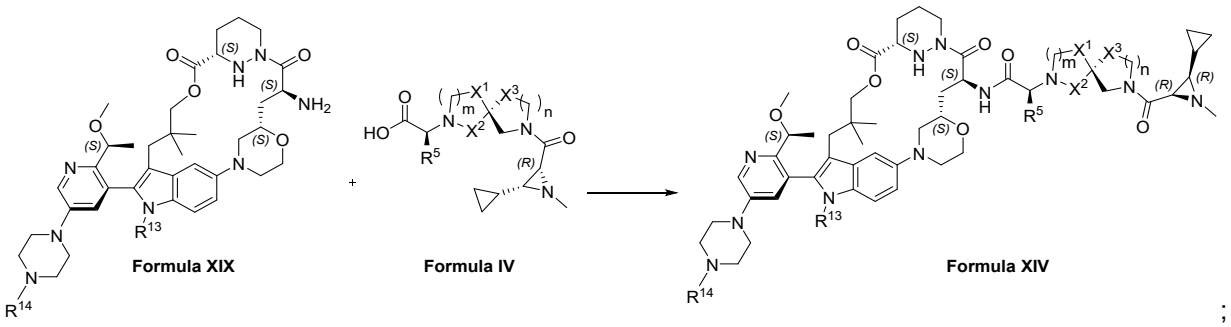
d) removing PG_b of the compound of Formula XVIII to form a compound of Formula XIX:



Formula XVIII **Formula XIX**

; and

e) coupling the compound of Formula XIX with a compound of Formula IV to form the compound of Formula XIV, or salt thereof:



Formula XIX **Formula IV** **Formula XIV**

;

wherein:

n and m are each, independently, 0, 1, 2, 3, 4, or 5;

X^1, X^2, and X^3 are each, independently, $-CH_2-$, -CHF-, $-CF_2-$, -C(O)-, or -O-;

R^{12} is halogen;

R^{13} is optionally substituted C_1-C_6 alkyl;

R^{14} is optionally substituted 3- to 6-membered cycloalkyl;

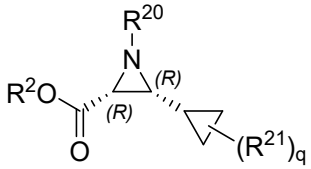
PG_a is an acid-labile protecting group; and

PG_b is an acid-stable protecting group.

23. The method of claim 22, wherein step (a) comprises reacting the compound of Formula XII and the compound of Formula XV in the presence of a carbodiimide coupling reagent, an anti-racemization agent, and a base.

24. The method of claim 22 or 23, wherein step (e) comprises coupling the compound of Formula XIX and the compound of Formula IV in the presence of a coupling reagent, an anti-racemization reagent, and a base.

25. A compound of Formula IIf-1:



Formula IIf-1

or a salt thereof, wherein

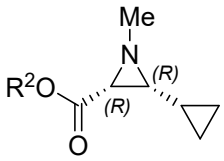
R^2 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, or optionally substituted C_6-C_{10} aryl;

R^{20} is hydrogen or C_1-C_6 alkyl optionally substituted with 1 or 2 substituents independently selected from CN, OH, C_1-C_6 alkoxy, and C_1-C_6 haloalkyl;

R^{21} is OH, halogen, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_1-C_6 haloalkyl; and

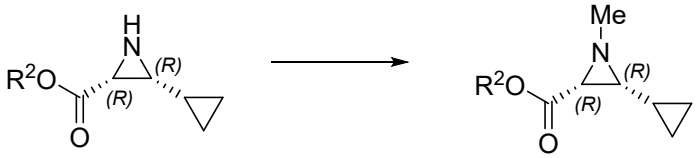
q is 0, 1, or 2.

26. A method of preparing a compound of Formula IIf:



Formula IIf

the method comprising methylating a compound of Formula IIe with a methylating agent:

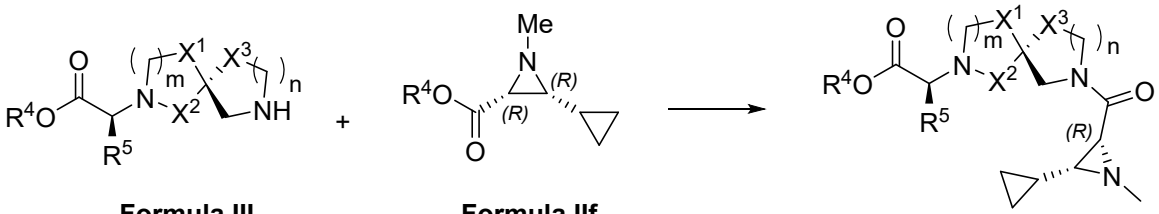


Formula IIe **Formula IIf**

wherein R^2 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, or optionally substituted C_6-C_{10} aryl.

27. The method of claim 26, wherein the methylating agent comprises trimethylboroxine.

28. A method of preparing a compound of Formula IVa the method comprising coupling a compound of Formula III with a compound of Formula IIf to form the compound of Formula IVa:



Formula III **Formula IIf** **Formula IVa**

wherein:

n and m are each, independently, 0, 1, 2, 3, 4, or 5;

R^4 is optionally substituted C_1-C_6 alkyl or optionally substituted C_6-C_{10} aryl;

R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3- to 6-membered cycloalkyl, or optionally substituted 3- to 6-membered heterocycloalkyl; and

X^1, X^2, and X^3 are each, independently, -CH_2-, -CHF-, -CF_2-, -C(O)-, or -O-.

29. The method of claim 28, wherein the coupling comprises contacting the compound of Formula III and the compound of Formula IIf in the presence of a base.

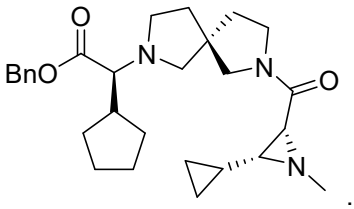
30. The method of claim 28 or 29, further comprising hydrolyzing the compound of Formula IVa to form the compound of Formula IV:



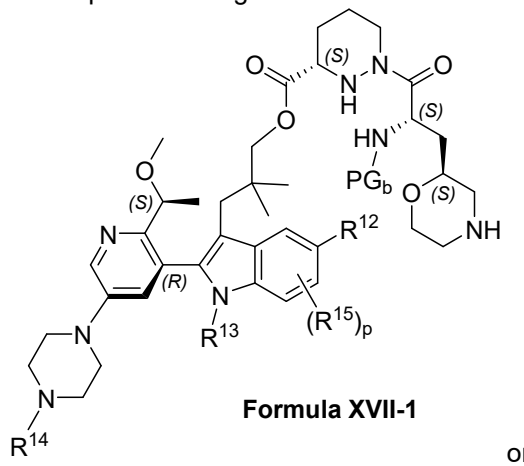
Formula IVa **Formula IV**

31. The method of any one of claims 28 to 30, wherein n and m are both 1; R^4 is benzyl; R^5 is isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; and X^1, X^2, and X^3 are each -CH_2-.

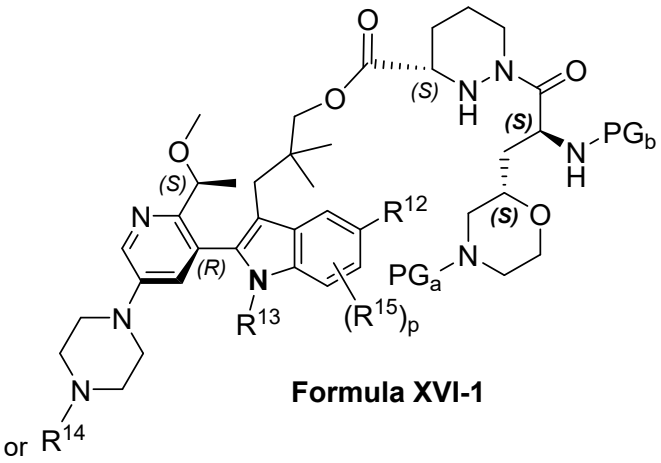
32. The method of any one of claims 28 to 31, wherein the compound of Formula IVa is:



33. A compound having the structure of Formula XVII-1 or XVI-1:



Formula XVII-1



Formula XVI-1

wherein

R^{12} is halogen;

R^{13} is optionally substituted C_1-C_6 alkyl;

R^{14} is optionally substituted 3- to 6-membered cycloalkyl;

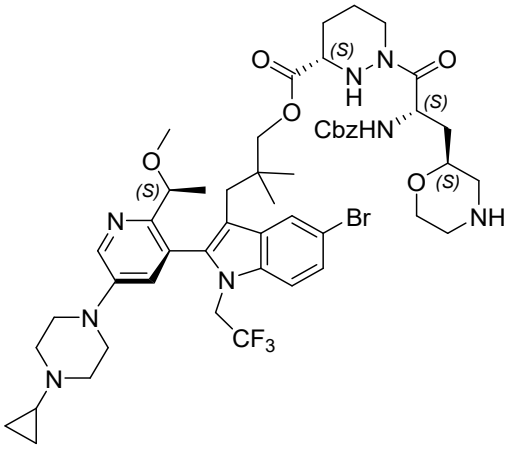
each R^{15} is, independently, hydrogen, halogen, optionally substituted C_1-C_3 alkyl, optionally substituted C_1-C_3 alkoxy, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl;

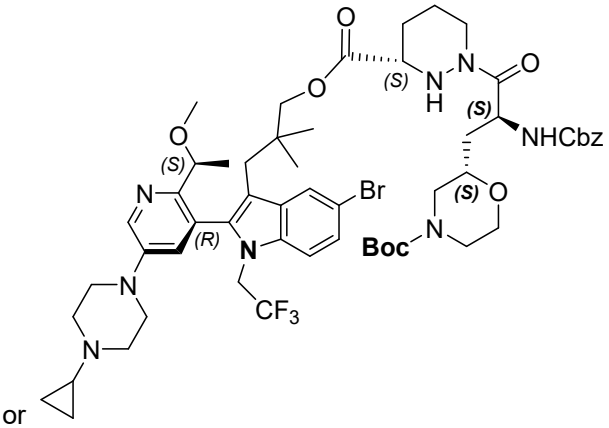
p is 0, 1, 2, or 3;

PG_a is an acid-labile protecting group; and

PG_b is an acid-stable protecting group.

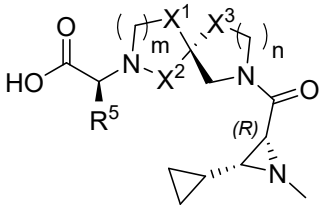
34. The compound of claim 33, wherein the compound is:





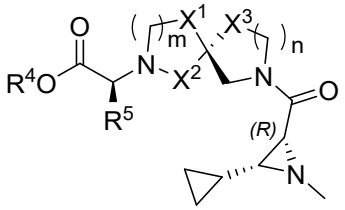
.

35. A compound having the structure of Formula IV or Formula IVa:



Formula IV

or



Formula IVa

wherein

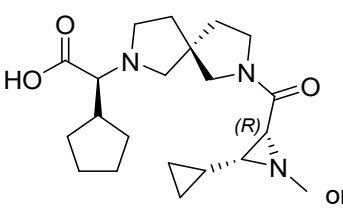
n and m are each, independently, 0, 1, 2, 3, 4, or 5;

R^4 is optionally substituted C_1-C_6 alkyl or optionally substituted C_6-C_{10} aryl;

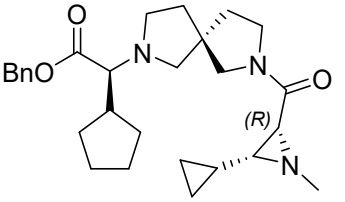
R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3- to 6-membered cycloalkyl, or optionally substituted 3- to 6-membered heterocycloalkyl; and

X^1, X^2, and X^3 are each, independently, -CH_2-, -CHF-, -CF_2-, -C(O)-, or -O-.

36. The compound of claim 35, wherein the compound is:



or



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