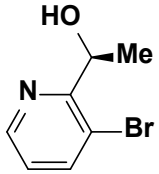
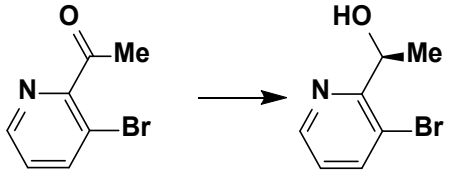
CLAIMS

1. A method of preparing Compound 4a:



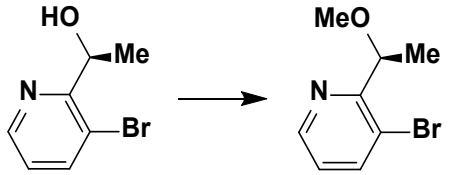
Compound 4a

the method comprising contacting Compound 4 with one or more ketoreductase enzymes to produce Compound 4a:



Compound 4 **Compound 4a**

2. The method of claim 1, further comprising combining Compound 4a with a methyl source to produce Compound 4b:



Compound 4a **Compound 4b**

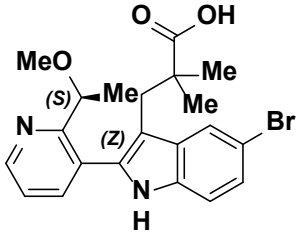
3. The method of claim 2, wherein Compound 4a is combined with a methyl source and a base to produce Compound 4b.

4. The method of claim 3, wherein the base is tert-butoxide.

5. The method of any one of claims 1 to 4, wherein Compound 4 is contacted with NADP and one or more ketoreductase enzymes in the presence of a buffer to produce Compound 4a, and the yield of Compound 4a is formed in at least 85% yield.

6. The method of any one of claims 2 to 4, wherein the methyl source is MeI.

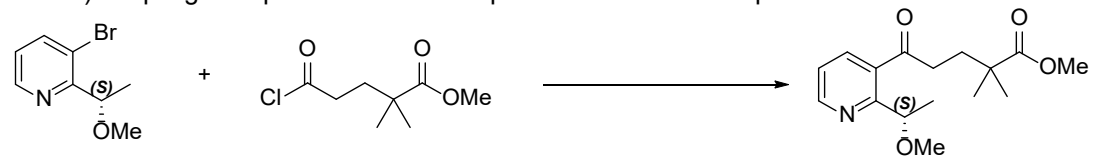
7. A method of preparing Compound 8:



Compound 8

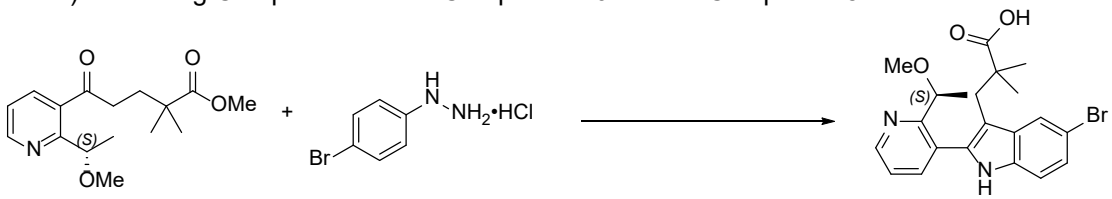
or a salt thereof, the method comprising:

a) coupling Compound 4b and Compound 20 to form Compound 21:



Compound 4b **Compound 20** **Compound 21** ; and

b) contacting Compound 21 and Compound 10 to form Compound 8:



Compound 21 **Compound 10** **Compound 8** .

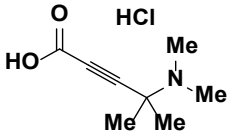
8. The method of claim 7, wherein the coupling in step (a) occurs in the presence of a zinc source and a copper source.

9. The method of claim 7, wherein the contacting in step (b) occurs in the presence of sulfuric acid.

10. The method of claim 7, wherein the coupling in step (a) occurs in the presence of PrMgCl•LiCl, $ZnCl_2$, and CuCl•2LiCl; and the contacting in step (b) occurs in the presence of sulfuric acid.

11. The method of any one of claims 7 to 10, wherein the method prepares a hemisulfate salt of Compound 8.

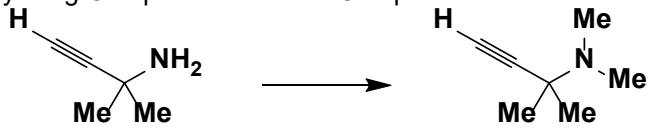
12. A method of preparing Compound 6:



Compound 6

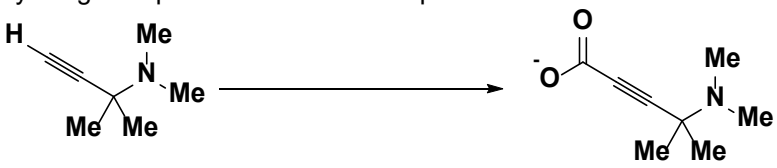
the method comprising:

a) bis-*N*-methylating Compound 7 to form Compound 7c:



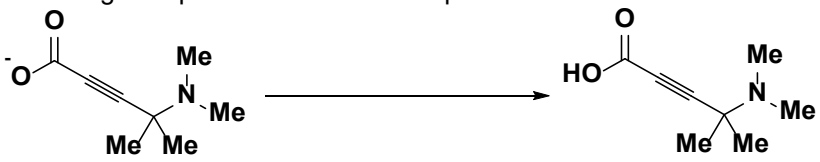
Compound 7 **Compound 7c** ;

b) carboxylating Compound 7c to form Compound 7a:



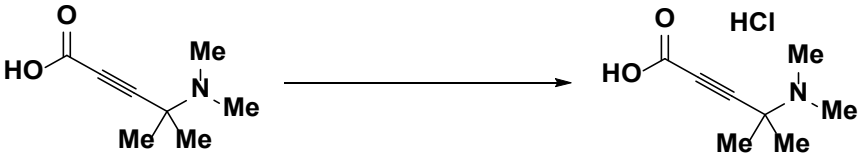
Compound 7c **Compound 7a** ;

c) protonating Compound 7a to form Compound 7b:



Compound 7a **Compound 7b** ; and

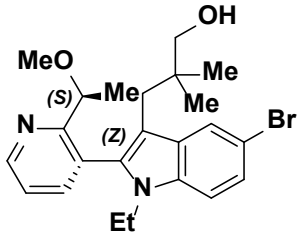
d) protonating compound 7b to form Compound 6:

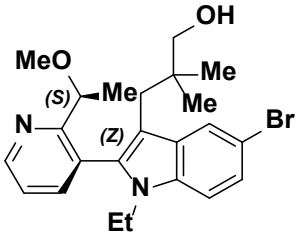


Compound 7b **Compound 6** .

13. The method of claim 12, wherein the bis-*N*-methylating in step (a) comprises contacting Compound 7 with an alkylating agent and a reducing agent; and the carboxylating in step (b) comprises contacting Compound 7c with a base.

14. A method of separating Compound 11a and Compound 11b:





Compound 11a **Compound 11b** .

the method comprising:

a) heating a mixture of Compound 11a and Compound 11b in a solvent or mixture of solvents for a period of time;

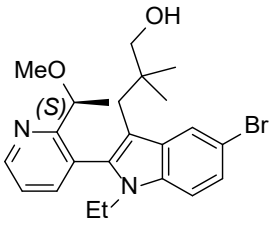
b) forming a mixture of a salt of Compound 11a and a salt of Compound 11b; and

c) separating the mixture of the salt of Compound 11a and Compound 11b.

15. The method of claim 14, wherein the salts are hydrochloride salts.

16. The method of claims 14 or 15, wherein the salts are formed in an alcoholic solvent.

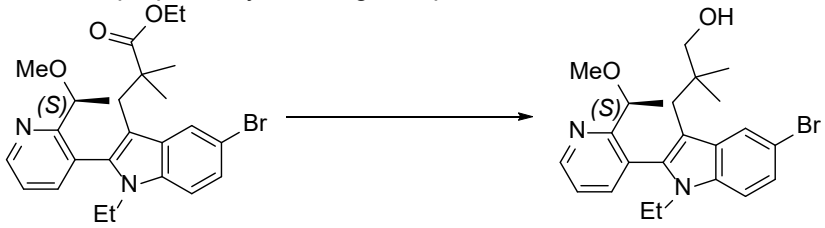
17. The method of claims 14 to 16, wherein the mixture of Compound 11a and Compound 11b is formed as Compound 11,



Compound 11

,

wherein Compound 11 is prepared by reducing Compound 24:

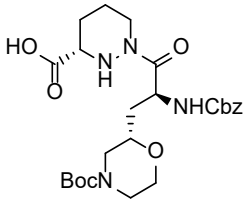


Compound 24 **Compound 11**

.

18. The method of claim 17, wherein the reducing comprises contacting Compound 24 with sodium borohydride in the presence of calcium chloride.

19. A method of preparing Compound 3a:

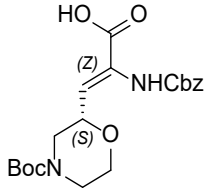


,

Compound 3a

the method comprising:

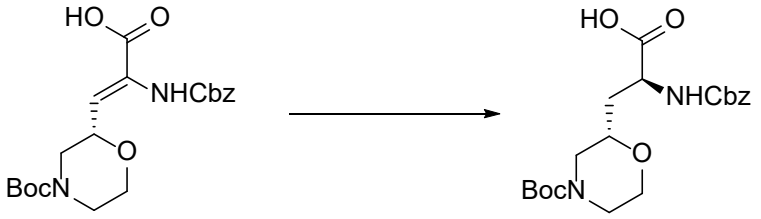
a) deprotonating compound 3b with a chiral base, thereby forming a diastereomeric salt of compound 3b:



;

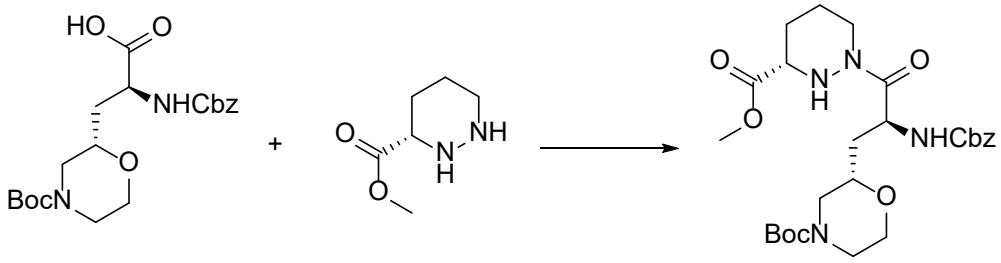
Compound 3b

b) reducing the diastereomeric salt of Compound 3b to form Compound 3c:



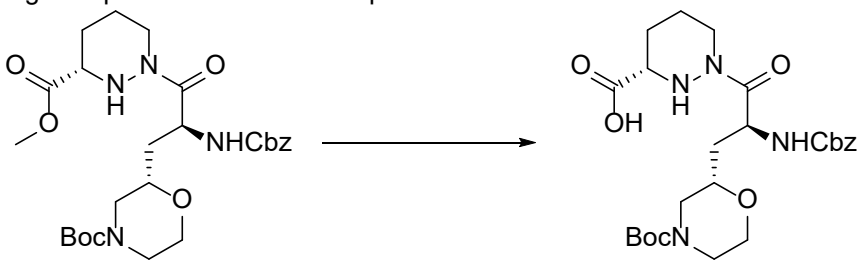
Compound 3b **Compound 3c** ;

c) coupling Compound 3c with Compound 3d, or a salt thereof, to form Compound 3e;



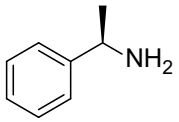
Compound 3c **Compound 3d** **Compound 3e** ; and

d) hydrolyzing Compound 3e to form Compound 3a:



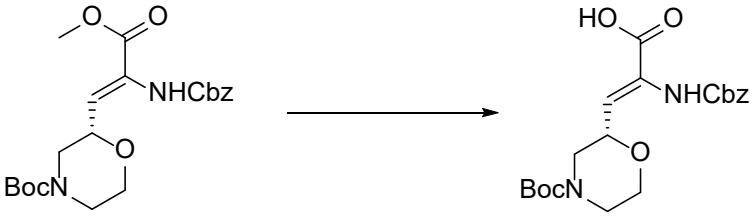
Compound 3e **Compound 3a** .

20. The method of claim 19, wherein the chiral base in step (a) is Compound 3f:



.

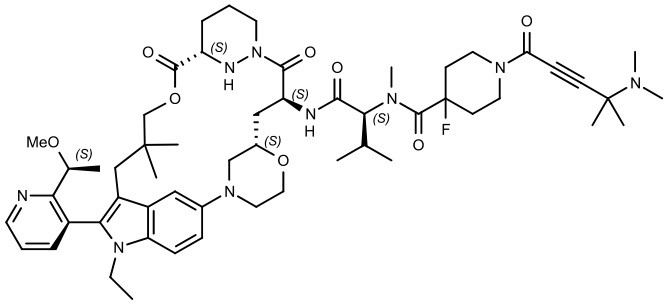
21. The method of claim 19, wherein Compound 3b is prepared by hydrolyzing Compound 3g to produce Compound 3b:



Compound 3g **Compound 3b** .

22. The method of any one of claims 19 to 21, wherein:
the reducing in step (b) comprises contacting Compound 3b with hydrogen gas in the presence of a rhodium catalyst and chiral ligand;
the coupling in step (c) is in the presence of a coupling reagent; and
the hydrolyzing in step (d) is in the presence of a hydroxide salt.

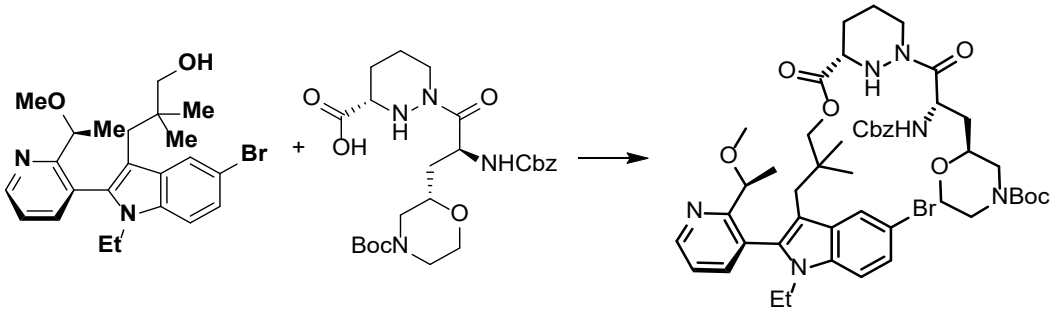
23. A method of preparing Compound A:



Compound A

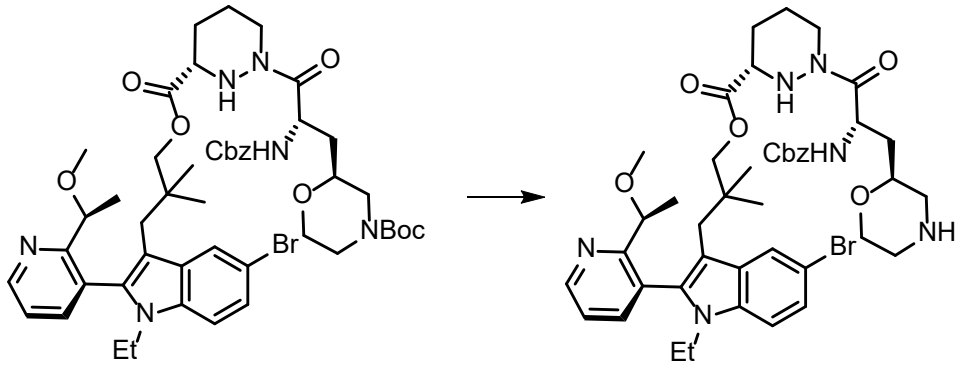
the method comprising:

a) coupling Compound 11a and Compound 3a to form Compound 12:



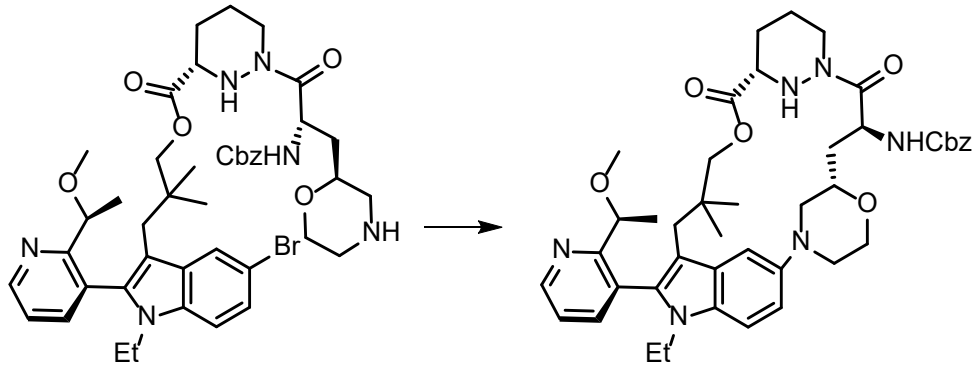
Compound 11a **Compound 3a** **Compound 12** ;

b) deprotecting Compound 12 to form Compound 13:



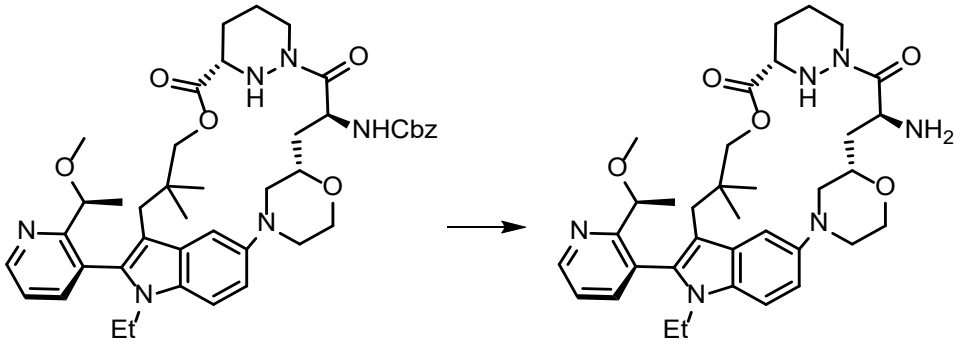
Compound 12 **Compound 13** ;

c) coupling Compound 13 to form Compound 14:



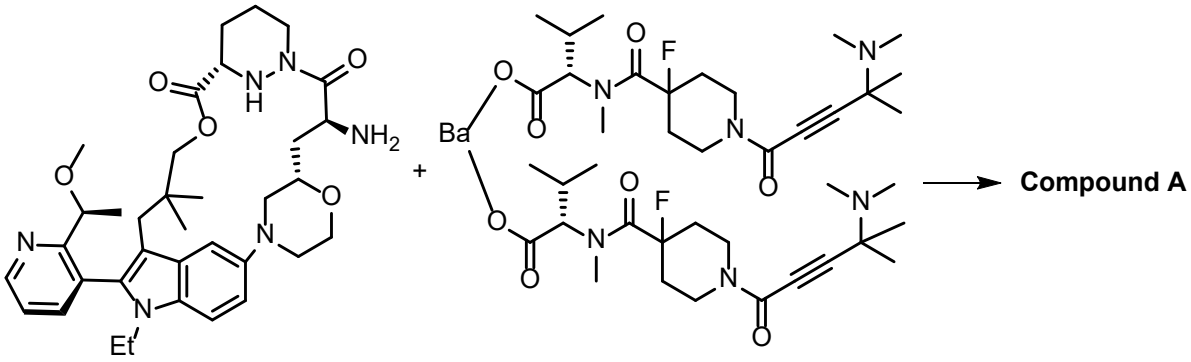
Compound 13 **Compound 14** ;

d) deprotecting Compound 14 to form Compound 15:



Compound 14 **Compound 15** ; and

e) coupling Compound 15 and Compound 2 to form Compound A:



Compound 15 **Compound 2** **Compound A**

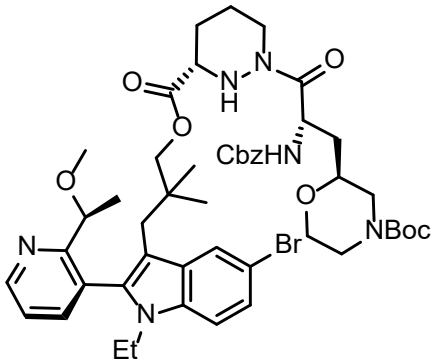
.

24. The method of claim 23, wherein the coupling in step (a) comprises contacting Compound 11a and Compound 3a with HObt, EDCI, and a base.

25. The method of claim 23, wherein the deprotecting in step (b) is in the presence of an acid; and the deprotecting in step (d) is in the presence of hydrogen gas and a palladium catalyst.

26. The method of any one of claims 23 to 25, wherein the coupling in step (c) is in the presence of a carbonate base and palladium catalyst; and the coupling in step (e) is in the presence of a coupling agent and a base.

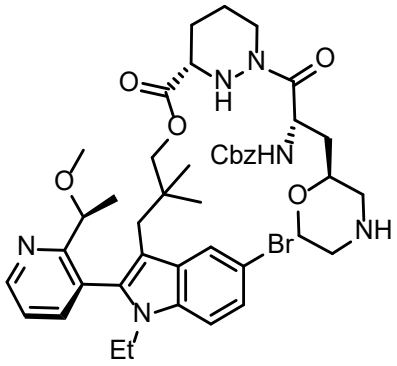
27. A compound having the structure of Compound 12:



Compound 12

or a salt thereof.

28. A compound having the structure of Compound 13:



Compound 13

or a salt thereof.