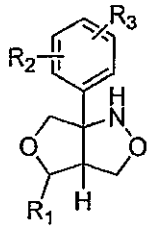
We claim:

1. A method of making a compound of **Formula I**,



I

wherein:

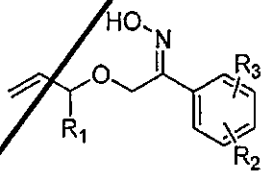
R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo,

or a salt thereof,

said method comprising heating a mixture comprising:

(i) an oxime of **Formula A**:



A ,

wherein R_1, R_2 and R_3 are as given above;

(ii) hydroquinone; and

(iii) a hydrocarbon solvent,

to a temperature of from 90°C to 160°C,

to make said compound of **Formula I**, or a salt thereof.

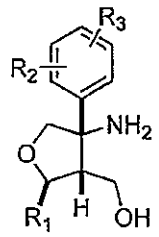
2. The method of claim 1, wherein the hydrocarbon solvent is selected from the group consisting of: benzene, toluene, and xylenes.

3. The method of claim 1, wherein the hydrocarbon solvent is xylenes.

4. The method of any one of claims 1-3, wherein said heating is to a temperature of from 110°C to 140°C.

5. The method of any one of claims 1-3, wherein said heating is to a temperature of from 120°C to 140°C.

6. A method of making a stereochemically pure compound of **Formula IIa**:



IIa

wherein:

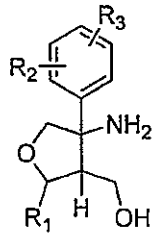
R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo,

or a salt thereof,

said method comprising the steps of :

(a) adding a mixture of stereoisomers of the compound of **Formula II**:



II

wherein R_1, R_2 and R_3 are as given above,

to a solvent comprising a chiral carboxylic acid compound, to form a mixture of diastereomeric salts of the compound of **Formula II**; and then

(b) crystallizing a single diastereomeric salt formed of the compound of **Formula II**,

to make said stereochemically pure compound of **Formula IIa**, or a salt thereof.

7. The method of claim 6, wherein said stereochemically pure compound has greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound.

8. The method of claim 6, wherein said stereochemically pure compound has greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound.

9. The method of any one of claims 6-8, wherein said crystallizing step is performed by cooling the mixture of diastereomeric salts of the compound of **Formula II**.

10. The method of claim 9, wherein said cooling is from a temperature of from 40°C to 80°C, to a temperature of from -10°C to 29°C.

11. The method of any one of claims 6-10, wherein the solvent is an alcohol.

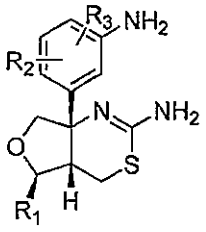
12. The method of any one of claims 6-10, wherein the solvent is ethanol.

13. The method of any one of claims 6-10, wherein the solvent is a mixture of two or more solvents.

14. The method of claim 13, wherein the mixture is a toluene – acetonitrile mixture, a toluene – acetone mixture, a toluene – tetrahydrofuran mixture, or an alcohol – water mixture.

15. The method of any of claims 6-14, wherein the chiral carboxylic acid compound is selected from the group consisting of: D-dibenzoyl tartaric acid, L-dibenzoyl tartaric acid, D-ditoluyl tartaric acid, and L-ditoluyl tartaric acid.

16. A compound of **Formula VII**:



VII

wherein:

R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo,

or a salt thereof.

17. The compound of claim 16, wherein:

R_1 is methyl or a salt thereof.

18. The compound of claim 16, wherein:

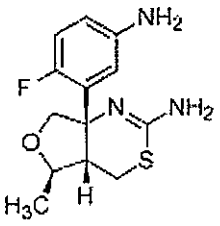
R_1 is methyl;

R_2 is fluoro; and

R_3 is hydrogen,

or a salt thereof.

19. The compound of claim 16, wherein said compound is:



or a salt thereof.

20. A method of making a compound of **Formula VII**, or a salt thereof, comprising:

reducing a compound of **Formula VI** to form a compound of **Formula VII**, as shown below



VI **VII** ;

wherein:

R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo,

to make said compound of **Formula VII**, or a salt thereof.

21. The method of claim 20, wherein R_1 is methyl.

22. The method of claim 20, wherein:

R_1 is methyl;

R_2 is fluoro; and

R_3 is hydrogen.

23. The method of any one of claims 20-22, wherein said reducing of the compound of **Formula VI** to form the compound of **Formula VII** comprises the steps of:

(a) adding powdered iron to a carbinol solvent to form a mixture thereof;

(b) adding hydrochloric acid (HCl) to the mixture of step *(a)*;

(c) heating the mixture of step *(b)* to a temperature of from 31°C to the boiling point of the mixture of step *(b)* to form a heated mixture; and

(d) adding the compound of **Formula VI**, or a salt thereof, to the heated mixture of step *(c)*,

to thereby reduce said compound of **Formula VI** to form said compound of **Formula VII**, or a salt thereof.

24. The method of claim 23, wherein said heating of step *(c)* is to a temperature of from 31°C to 80°C.

25. The method of claim 23, wherein said heating of step *(c)* is to a temperature of from 31°C to 80°C for from 0 to 4 hours.

26. The method of claim 24 or claim 25, wherein said heating of step *(c)* is to a temperature of from 40°C to 75°C.

27. The method of claim 24 or claim 25, wherein said heating of step *(c)* is at a temperature of from 50°C to 65°C.

28. The method of any one of claims 23-27, wherein said method further comprises the step of:

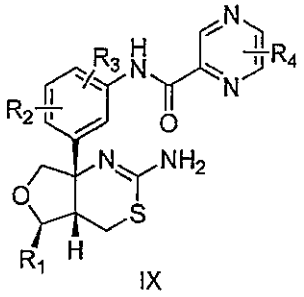
(e) cooling the mixture of step *(d)* to a temperature of from 0°C to 30°C to form a cooled mixture.

29. The method of claim 28, wherein said cooling is from 0 to 4 hours.

30. The method of any of claims 23-29, wherein the HCl is concentrated hydrochloric acid.

31. The method of any of claims 23-30, wherein the HCl is provided in an amount selected from the group consisting of: an amount of HCl stoichiometric with respect to the amount of the compound of **Formula VI**; and an amount of HCl in molar excess with respect to the amount of the compound of **Formula VI**.

32. A method of making a compound of **Formula IX**



IX

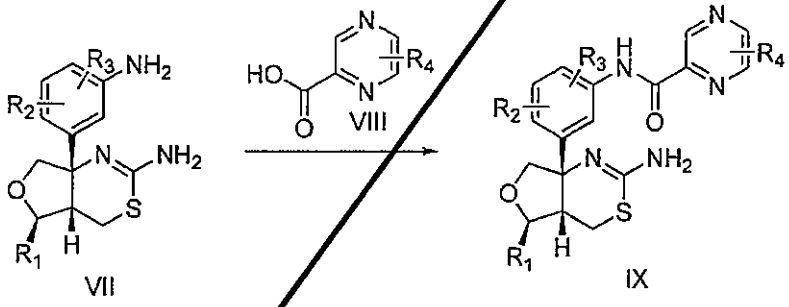
wherein:

R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo; and

R_4 is halo-C_{1-6}alkyl or a salt thereof,

comprising reacting a compound **Formula VII** with a pyrazine carboxylic acid of Formula VIII:



VII VIII IX

wherein R_1, R_2, R_3 and R_4 are as given above,

to form said compound of **Formula IX**, or a salt thereof.

33. The method of claim 32, wherein said reacting comprises the steps of:

(a) adding thionyl chloride to a solution comprising a compound of **Formula VIII** in a solvent to make a formed mixture; and

(b) adding a compound of **Formula VII** to the formed mixture of step *(a)*,

to form said compound of **Formula IX**, or a salt thereof.

34. The method of claim 33, wherein said solution comprising a compound of **Formula VIII** in a solvent is cooled prior to or during said adding step *(a)*.

35. The method of claim 33, wherein said solution comprising a compound of **Formula VIII** in a solvent is cooled to a temperature of from 0°C to 25°C prior to said adding step *(a)*.

36. The method of any of claims 33-35, wherein the solvent is selected from the group consisting of: N,N'-dimethylimidazoline-2-one, toluene, methylene chloride, dimethylformamide, N-methylpyrrolidine, and dimethylacetamide.

37. The method of any of claims 33-35, wherein the solvent is N,N'-dimethylimidazoline-2-one.

38. The method of claim 32, wherein said reacting comprises the steps of:

(a) adding ethyl acetate (EtOAc) to a compound of **Formula VIII** and a compound of Formula VII to make a formed mixture; and

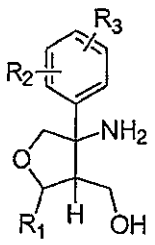
(b) adding an alkyl phosphonic acid anhydride to the formed mixture of step *(a)*, to form said compound of **Formula IX**, or a salt thereof.

39. The method of claim 38, wherein said alkyl phosphonic acid anhydride is propane phosphonic acid anhydride.

40. The method of claim 38, wherein said alkyl phosphonic acid anhydride is n-propyl phosphonic acid anhydride.

41. The method of any of claims 38-40, wherein said formed mixture is maintained at a temperature of from 0°C to 35°C during said adding step *(a)*.

42. A method of making a compound of **Formula II**



II

wherein:

R_1 is C_{1-4}alkyl; and

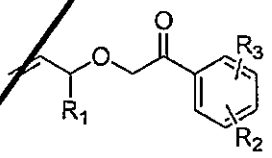
R_2 and R_3 are each independently hydrogen or halo;

or a salt thereof,

comprising the steps of:

(a) heating a mixture comprising:

(i) a ketone of **Formula B**:



B

wherein R_1, R_2 and R_3 are as given above for **Formula II**;

(ii) hydroxylamine or a salt thereof;

(iii) a base; and

(iv) a solvent selected from: water and an alcohol,

to at least 90° Celsius produce a heated mixture,

(b) cooling the heated mixture to a temperature of at or below 60° Celsius, and then,

(c) adding an organic solvent, an acid, and zinc to the mixture, wherein said mixture is maintained at or below 60° Celsius during said adding,

to make said compound of **Formula II**.

43. The method of claim 42, wherein said heating is to a temperature of at least 100° Celsius.

44. The method of claim 42, wherein said heating comprises boiling.

45. The method of claim 42, wherein said heating comprises refluxing.

46. The method of claim 42, wherein said heating to at least 90° Celsius is carried out for at least 30 hours.

47. The method of any of claims 42-46, wherein said solvent is a C_{3-8} alcohol.

48. The method of any of claims 42-46, wherein said solvent is water.

49. The method of any of claims 42-48, wherein said cooling is to a temperature of at or below 50° Celsius.

50. The method of any of claims 42-48, wherein said cooling is to a temperature of at or below 45° Celsius.

51. The method of any of claims 42-50, wherein said mixture is maintained at or below 50° Celsius during said adding.

52. The method of any of claims 42-50, wherein said mixture is maintained at or below 45° Celsius during said adding.

53. The method of any of claims 42-50, wherein said mixture is maintained between 25 and 50° Celsius during said adding.

54. The method of any of claims 42-50, wherein said mixture is maintained between 30 and 45° Celsius during said adding.

55. The method of any of claims 42-50, wherein said mixture is maintained between 35 and 45° Celsius during said adding.

56. The method of any of claims 42-55, wherein the base is selected from the group consisting of: acetate, propionate, a tertiary amine base, pyridine, or a salt thereof.

57. The method of claim 56, wherein the tertiary amine base is triethylamine or diethylisopropylamine.

58. The method of any of claims 42-55, wherein the base is acetate.

59. The method of any of claims 42-58, wherein the organic solvent is tetrahydrofuran or an ether solvent.

60. The method of claim 59, wherein the ether solvent is diethyl ether or methyl *tert*-butyl ether.

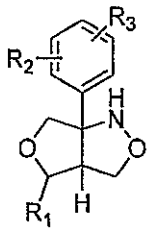
61. The method of any of claims 42-60, wherein the acid is a carboxylic acid or a mineral acid.

62. The method of claim 61, wherein the mineral acid is hydrochloric acid or sulfuric acid.

63. The method of any of claims 42-60, wherein the acid is acetic acid.

64. The method of any of claims 42-63, wherein the zinc comprises zinc powder or zinc dust.

65. A method of making a compound of **Formula I**,



I

wherein:

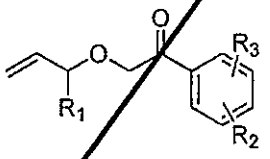
R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo,

or a salt thereof,

said method comprising heating a mixture comprising:

(i) a compound of **Formula B**:



B

wherein R_1, R_2 and R_3 are as given above;

(ii) acetate;

(iii) hydroxylamine or a salt thereof; and

(iv) a hydrocarbon solvent,

to a temperature of from 90°C to 160°C,

to make said compound of **Formula I**, or a salt thereof.

66. The method of claim 65, wherein the hydrocarbon solvent is selected from the group consisting of: benzene, toluene, and xylenes.

67. The method of claim 65, wherein the hydrocarbon solvent is toluene.

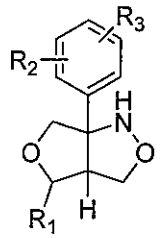
68. The method of any of claims 65-67, wherein said heating is to a temperature of from 110°C to 140°C.

69. The method of any of claims 65-67, wherein said heating is to a temperature of from 100°C to 120°C.

70. The method of any of claims 65-67, wherein said heating is to a temperature of from 120°C to 140°C.

We claim:

1. A method of making a compound of **Formula I**,



I

wherein:

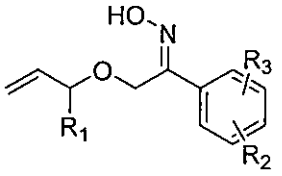
R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo,

or a salt thereof,

said method comprising heating a mixture comprising:

(i) an oxime of **Formula A**:



A ,

wherein R_1, R_2 and R_3 are as given above;

(ii) hydroquinone; and

(iii) a hydrocarbon solvent,

to a temperature of from 90°C to 160°C,

to make said compound of **Formula I**, or a salt thereof.

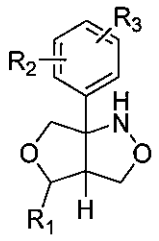
2. The method of claim 1, wherein the hydrocarbon solvent is selected from the group consisting of: benzene, toluene, and xylenes.

3. The method of claim 1, wherein the hydrocarbon solvent is xylenes.

4. The method of any one of claims 1-3, wherein said heating is to a temperature of from 110°C to 140°C.

5. The method of any one of claims 1-3, wherein said heating is to a temperature of from 120°C to 140°C.

6. A method of making a compound of **Formula I**,



I

wherein:

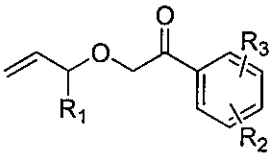
R_1 is C_{1-4}alkyl; and

R_2 and R_3 are each independently hydrogen or halo,

or a salt thereof,

said method comprising heating a mixture comprising:

(i) a compound of **Formula B**:



B ,

wherein R_1, R_2 and R_3 are as given above;

(ii) acetate;

(iii) hydroxylamine or a salt thereof; and

(iv) a hydrocarbon solvent,

to a temperature of from 90°C to 160°C,

to make said compound of **Formula I**, or a salt thereof.

7. The method of claim 6, wherein the hydrocarbon solvent is selected from the group consisting of: benzene, toluene, and xylenes.

8. The method of claim 6, wherein the hydrocarbon solvent is toluene.

9. The method of any of claims 6-8, wherein said heating is to a temperature of from 110°C to 140°C.

10. The method of any of claims 6-8, wherein said heating is to a temperature of from 100°C to 120°C.

11. The method of any of claims 6-8, wherein said heating is to a temperature of from 120°C to 140°C.