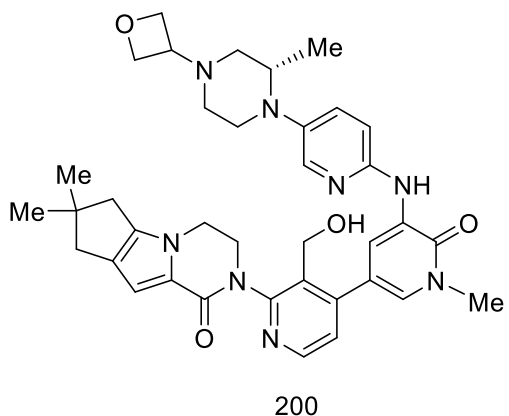
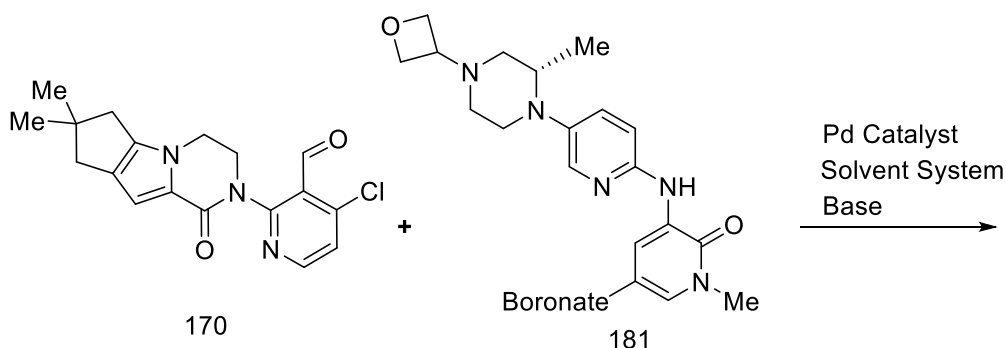


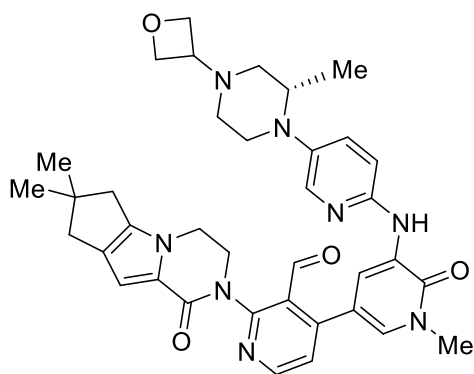
[0010a] One aspect of the disclosure is directed to a method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



the method comprising:

- (i) (1) forming a first reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system comprising water and tetrahydrofuran, and a base, wherein the ratio of solvent volume to compound 170 weight in the reaction mixture is less than 20:1 liters per kg, the equivalent ratio of compound 181 to compound 170 is greater than 1:1, and the equivalent ratio of the palladium catalyst to compound 170 is from 0.005:1 to 0.05:1, and wherein the palladium catalyst is $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$ and the base is K_3PO_4 ,
 (2) reacting the first reaction mixture to form a first reaction product mixture comprising compound 190 according to the following scheme:





190

, and

- (3) isolating compound 190 from the first reaction product mixture; and
- (ii) (1) forming a second reaction mixture comprising compound 190, a reducing agent, a base and a solvent, wherein the base is sodium hydroxide and the solvent is selected from tetrahydrofuran, methyl tert-butyl ether, and 2-methyltetrahydrofuran, (2) reacting the second reaction mixture to reduce the aldehyde moiety of compound 190 and form a second reaction product mixture comprising compound 200, and (3) isolating compound 200 from the second reaction product mixture,

wherein the yield of compound 190 is at least 50% based on compound 170, and the yield of compound 200 is at least 50% based on compound 190.

BRIEF DESCRIPTION OF THE DRAWINGS

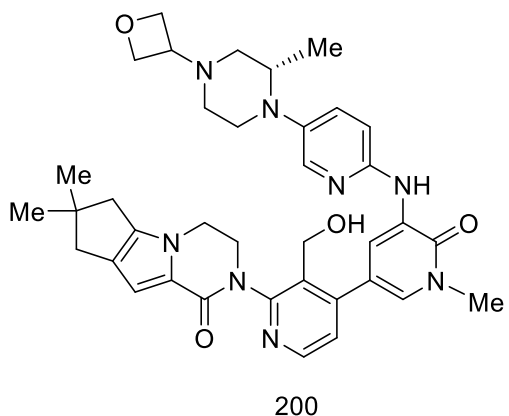
[0014] Figure 1 shows a method for the preparation of compounds 170, 182, 190 and 200.

[0015] Figure 2 shows a method for the preparation of compounds 170 and 182, and another method for the preparation of compounds 190 and 200.

[0016] Figure 3 shows a method for the preparation of compounds 70, 90, 40, 154, 153, 140, 141 and 180.

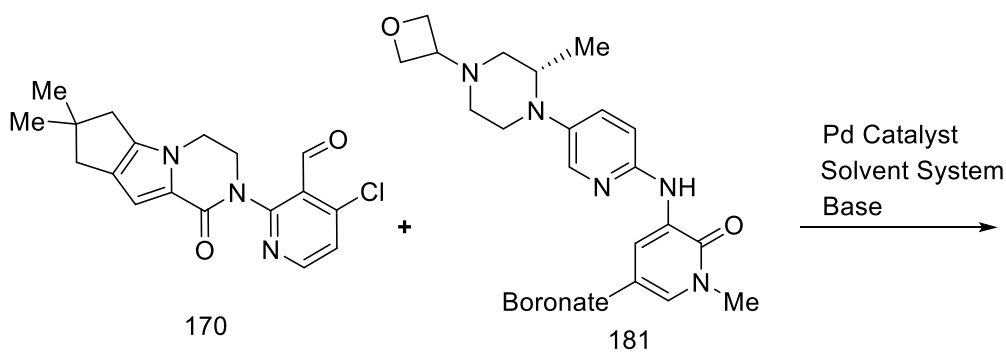
WHAT IS CLAIMED IS:

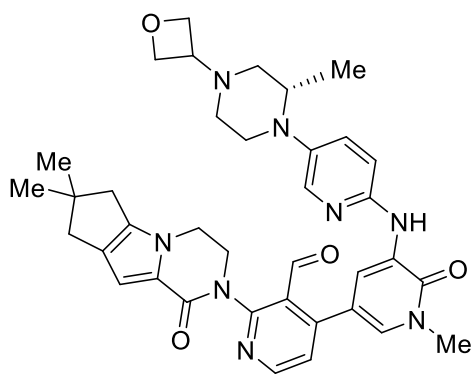
1. A method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



the method comprising:

- (i) (1) forming a first reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system comprising water and tetrahydrofuran, and a base, wherein the ratio of solvent volume to compound 170 weight in the reaction mixture is less than 20:1 liters per kg, the equivalent ratio of compound 181 to compound 170 is greater than 1:1, and the equivalent ratio of the palladium catalyst to compound 170 is from 0.005:1 to 0.05:1, and wherein the palladium catalyst is Pd(dppf)Cl₂•DCM and the base is K₃PO₄,
- (2) reacting the first reaction mixture to form a first reaction product mixture comprising compound 190 according to the following scheme:





190

, and

- (3) isolating compound 190 from the first reaction product mixture; and
- (ii) (1) forming a second reaction mixture comprising compound 190, a reducing agent, a base and a solvent, wherein the base is sodium hydroxide and the solvent is selected from tetrahydrofuran, methyl tert-butyl ether, and 2-methyltetrahydrofuran, (2) reacting the second reaction mixture to reduce the aldehyde moiety of compound 190 and form a second reaction product mixture comprising compound 200, and (3) isolating compound 200 from the second reaction product mixture,

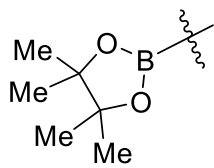
wherein the yield of compound 190 is at least 50% based on compound 170, and the yield of compound 200 is at least 50% based on compound 190.

2. The method of claim 1 wherein the volume to weight ratio of the solvent system to compound 170 in the reaction mixture is from 5:1 to 20:1 liters per kg, or about 10:1 liters per kg, and the equivalent ratio of compound 181 to compound 170 is greater than 1:1, and the equivalent ratio of the palladium catalyst to compound 170 is from 0.005:1 to 0.02:1, or about 0.01:1.

3. The method of claim 1 or claim 2 wherein:

- (i) the volume ratio of water to tetrahydrofuran in the solvent system of the first reaction mixture is from 0.1:1 to 0.4:1; and
- (ii) (1) the equivalent ratio of sodium hydroxide to compound 190 in the second reaction mixture is from 0.3:1 to 0.7:1, (2) the ratio of solvent volume to compound 190 weight in the second reaction mixture is from 4:1 to 8:1 liters to kg, (3) the reducing agent is sodium borohydride, wherein the equivalent

ratio of sodium borohydride to compound 190 is from 0.2:1 to 0.8:1, and (4) the boronate is 4,4,5,5-tetramethyl-1,3,2-dioxaborolane of the structure:



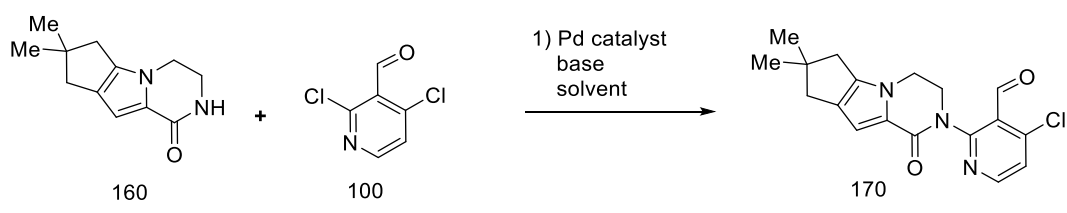
4. The method of any one of claims 1 to 3 wherein:

the yield of compound 190 is at least 60%, at least 70%, at least 80% or at least 90%, and the purity of compound 190 is at least 99 area% or at least 99.5 area%; and

the yield of compound 200 is at least 60%, at least 70%, at least 80%, or at least 85%, and the purity of compound 200 is at least 99 area% or at least 99.5 area%.

5. The method of any one of claims 1 to 4 wherein compound 170 is prepared by:

- (i) forming a reaction mixture comprising compound 160, a stoichiometric excess of compound 100, a palladium catalyst and a catalyst ligand, a base and a polar aprotic solvent, and
- (ii) reacting the reaction mixture to form a reaction product mixture comprising compound 170 according to the following scheme:



and

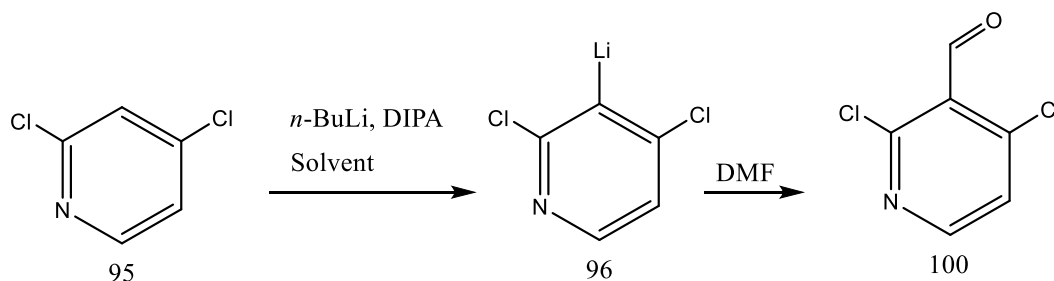
- (iii) isolating compound 170 from the reaction product mixture,

wherein the yield of compound 170 based on compound 160 is at least 80%, at least 85% or at least 90%, and wherein the purity of compound 170 is at least 95%, at least 98% or at least 99%.

6. The method of claim 5 wherein the ratio of the solvent volume to compound 160 weight in the reaction mixture is from 5:1 to 20:1 liters per kg, from 5:1 to 15:1 liters per kg, or about 10:1 liters per kg, and wherein the equivalent ratio of catalyst to compound 160 is from 0.01:1 to 0.03:1.

7. The method of claim 6 wherein the catalyst is $\text{Pd}(\text{OAc})_2$, the ligand is DPPF, the base is potassium carbonate, and the solvent is tetrahydrofuran.

8. The method of any one of claims 5 to 7 wherein compound 100 is prepared according to the following reaction scheme,



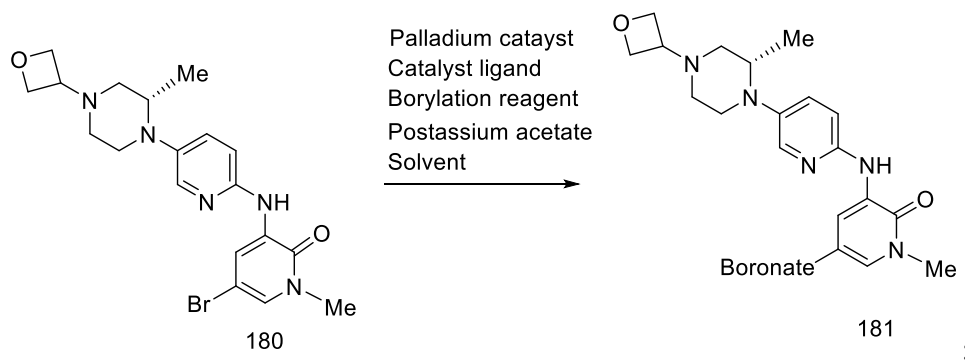
the method comprising:

- (i) forming a first reaction mixture comprising compound 95, n -butyl lithium, diisopropylamine, and a polar aprotic solvent, and reacting the first reaction mixture to form a first reaction product mixture comprising compound 96;
 - (ii) admixing the first reaction product mixture with dimethylformamide to form a second reaction mixture, and reacting the second reaction mixture to form a second reaction product mixture comprising compound 100; and
 - (iii) isolating compound 100 from the second reaction product mixture,
- wherein the yield of compound 100 is at least 70%, at least 80% or at least 85%, and wherein the purity of compound 100 is at least 90 area%, at least 95 area%, or at least 99.5 area%.

9. The method of claim 8 wherein the polar aprotic solvent is THF; the mole ratio of n -butyl lithium to compound 95 is between 1:1 and 2:1, or from 1.2:1 to 1.6:1; the first reaction mixture and the second reaction mixture are formed at a temperature of greater than -35°C ; of the solvent volume to compound 95 weight in the first reaction mixture is from 3:1 to 10:1, from 4:1 to 6:1, or about 5:1; the mole ratio of DMF to compound 95 is from 1.1:1 to 2:1, or from 1.3:1 to 1.5:1; and the mole ratio of diisopropylamine to compound 95 is from 1.2:1 to 2:1, or from 1.4:1 to 1.8:1.

10. The method of any one of claims 1 to 9 wherein compound 181 is prepared by:

- (i) forming a reaction mixture comprising compound 180, a palladium catalyst, a catalyst ligand, a borylation reagent, potassium acetate, and a polar aprotic solvent;
- (ii) reacting the reaction mixture to form a reaction product mixture according to the following scheme:

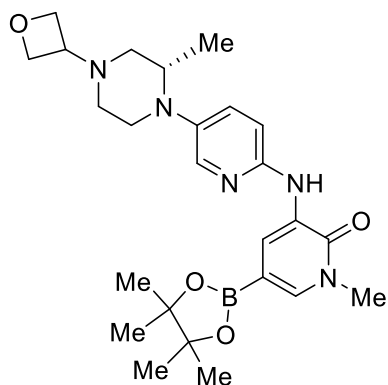


and

- (iii) isolating compound 181 from the reaction product mixture,
 wherein the yield of compound 181 is at least 85% or at least 90%, and the purity of compound 181 is at least 95%, at least 98%, or at least 99%.

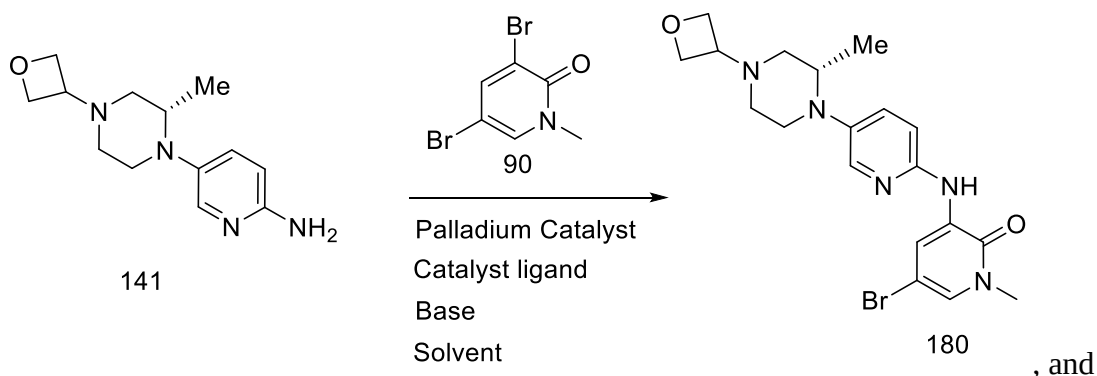
11. The method of claim 10 wherein the reaction mixture comprises: a ratio of solvent volume to compound 180 weight of from 5:1 to 20:1 liters to kg, from 5:1 to 15:1 liters to kg, or about 10:1 liters to kg; an equivalent ratio of borylation reagent to compound 180 of between 1 and 2; an equivalent ratio of palladium catalyst to compound 180 of from 0.001:1 to 0.005:1; an equivalent ratio of catalyst ligand to catalyst of from 1.5:1 to 3; and an equivalent ratio of potassium acetate to compound 180 of greater than 1:1.

12. The method of claim 10 or claim 11 wherein the palladium catalyst is $\text{Pd}_2(\text{dba})_3$, the catalyst ligand is an aryl phosphate ligand, the borylation reagent is bis(pinacolato)diboron, the solvent is tetrahydrofuran, the boronate is 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and boronate compound 181 is the species of compound 182:



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13. The method of claim 12 wherein the catalyst ligand is XPhos.
14. The method of any one of claims 10 to 13 wherein compound 180 is prepared by:
- forming a reaction mixture comprising compound 141, compound 90, a palladium catalyst and an aryl phosphate catalyst ligand, a base, and an aprotic solvent;
 - reacting the reaction mixture to form a reaction product mixture according to the following scheme:



- isolating compound 180 from the reaction product mixture wherein the yield of compound 180 is at least 60%, at least 70%, at least 80%, and the purity of compound 180 is at least 95%, at least 98%, or at least 99%.

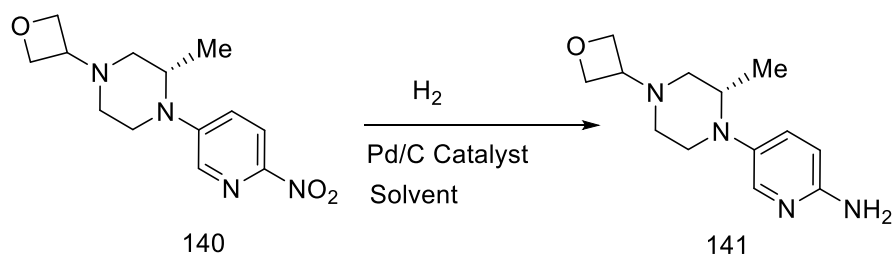
15. The method of claim 14 wherein: the palladium catalyst is $\text{Pd}_2(\text{dba})_3$; the catalyst ligand is Xantphos; the base is potassium carbonate or tripotassium phosphate wherein the equivalent ratio of the base to compound 141 is from 1.5:1 to 3:1; the reaction mixture comprises approximately equimolar amounts of compounds 141 and 90; the equivalent ratio of the palladium catalyst to compound 141 is from 0.01:1 to 0.03:1; the

equivalent ratio of the catalyst ligand to the catalyst is from 1.5:1 to 3:1; and the solvent is selected from methyl tetrahydrofuran, tetrahydrofuran, dioxane, toluene, and combinations thereof.

16. The method of claim 14 or claim 15 wherein compound 141 is a solution of compound 141 in the solvent, wherein the solution comprises from 5 to 15 percent by weight compound 141 and less than 0.15 percent by weight methanol.

17. The method of any one of claims 14 to 16 wherein compound 141 is prepared by:

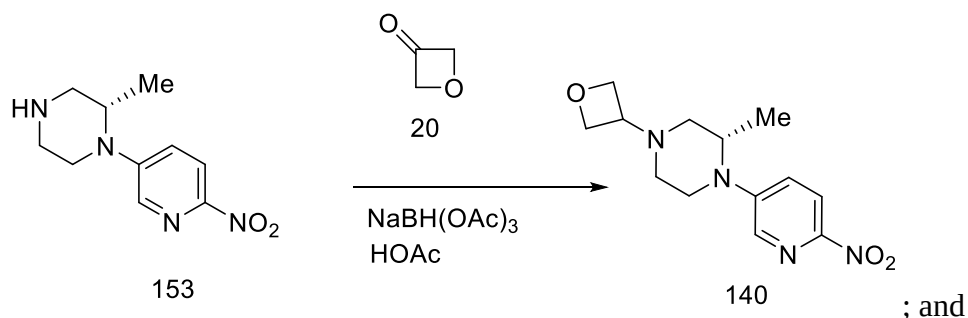
- (i) forming a reaction mixture comprising compound 140, a palladium on carbon catalyst, hydrogen, a solvent selected from methanol, ethanol, isopropanol, dioxane, toluene, and combinations thereof; and
- (ii) reacting the reaction mixture to form a reaction product mixture according to the following scheme:



wherein the yield of compound 141 is at least 90% or at least 95%.

18. The method of claim 17 wherein the ratio of the solvent volume to compound 140 weight in the reaction mixture is from 3:1 to 20:1 liters to kg, from 3:1 to 10:1 liters to kg, or from 4:1 to 6:1 liters to kg, and wherein the weight ratio of the catalyst to compound 140 is from 10 w/w% to 25 w/w%.

19. The method of claim 17 or claim 18 wherein compound 140 is prepared by:
 - (i) forming a reaction mixture comprising compound 153, compound 20, a solvent, NaBH(OAc)₃, acetic acid, and a drying agent;
 - (ii) reacting the reaction mixture to form a reaction product mixture according to the following scheme:



- (iii) isolating compound 140 as a solid wherein the yield of compound 140 is at least 85% or at least 90%, and wherein the purity of compound 140 is at least 95%, at least 98% or at least 98.5%.

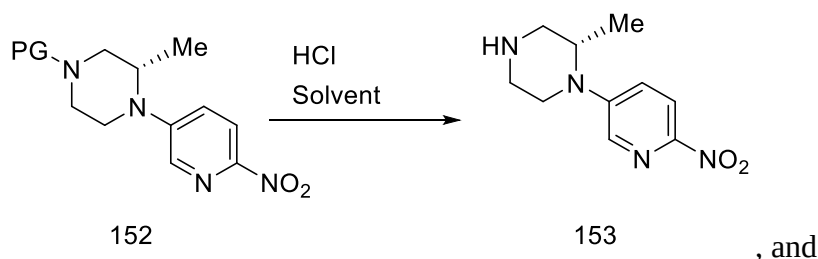
20. The method of claim 19 wherein: the equivalent ratio of compound 20 to compound 153 is from 1.3:1 to 1.9:1; the equivalent ratio of acetic acid to compound 153 is from 1.1:1 to 3:1; the equivalent ratio of NaBH(OAc)_3 to compound 153 is greater than 1.5:1.

21. The method of claim 19 or 20 wherein the solvent is selected from tetrahydrofuran, methyl tetrahydrofuran, dichloromethane, and combinations thereof, and compound 153 in solution in tetrahydrofuran, methyl tetrahydrofuran, dichloromethane, or a combination thereof, wherein the solution comprises from 2 to 10 percent by weight compound 153.

22. The method of any one of claims 19 to 21 wherein the drying agent is magnesium sulfate and the equivalent ratio of magnesium sulfate to compound 153 is from 0.3:1 to 0.6:1.

23. The method of any one of claims 19 to 22 wherein compound 153 is prepared by:

- (i) forming a reaction mixture comprising compound 152 comprising protecting group PG, hydrochloric acid, and a solvent comprising water,
- (ii) reacting the reaction mixture to form a reaction product mixture comprising deprotected compound 152 according to the following scheme:



- (iii) isolating compound 153 from the reaction product mixture wherein the yield of compound 153 is at least 80% or at least 90%.

24. The method of any one of claims 5 to 23 wherein compound 160 is prepared by the method of claim 37.

25. The method of any one of claims 5 to 23 wherein compound 160 is prepared by the method of claim 43.

26. The method of any one of claims 5 to 23 wherein compound 160 is prepared by the method of claim 46.