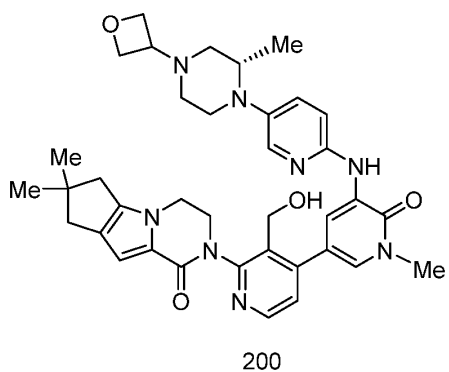


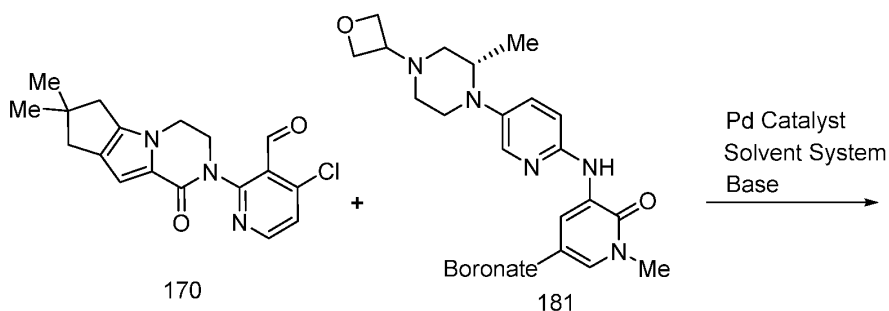
WHAT IS CLAIMED IS:

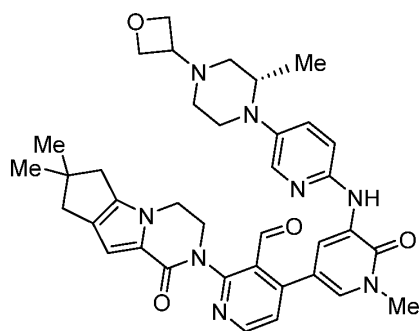
1. A method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



the method comprising:

- (i) (1) forming a first reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system comprising water, and 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 about 0.005:1 to about 0.05:1,
 - (2) reacting the first reaction mixture to form a first reaction product mixture comprising compound 190 according to the following scheme:





190

, and

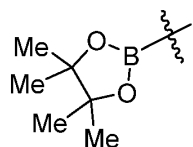
- (3) isolating compound 190 from the first reaction product mixture; and
- (ii) (1) forming a second reaction mixture comprising compound 190, a reducing agent, a base and a solvent, (2) reacting the second reaction mixture to reduce the aldehyde moiety of compound 190 and form a second reaction product 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 about 5:1 to about 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 about 0.005:1 to about 0.02:1, or about 0.01:1.

3. The method of claim 1 or claim 2 wherein:
- (i) the catalyst is $\text{Pd(dppf)Cl}_2 \cdot \text{DCM}$;
- (ii) (1) the base in the first reaction mixture is K_3PO_4 , and (2) the solvent system in the first reaction mixture comprises water and tetrahydrofuran, wherein the volume ratio of water to tetrahydrofuran is from about 0.1:1 to about 0.4:1; and
- (iii) (1) the base in the second reaction mixture is sodium hydroxide, and the equivalent ratio of sodium hydroxide to compound 190 is from about 0.3:1 to about 0.7:1, (2) the solvent in the second reaction mixture is selected from tetrahydrofuran, methyl tert-butyl ether, and 2-methyltetrahydrofuran, wherein the ratio of solvent volume to compound 190 weight is from about 4:1 to about

8:1 liters to kg, (3) the reducing agent is sodium borohydride, wherein the equivalent ratio of sodium borohydride to compound 190 is from about 0.2:1 to about 0.8:1, and (4) the boronate is 4,4,5,5-tetramethyl-1,3,2-dioxaborolane of the structure:



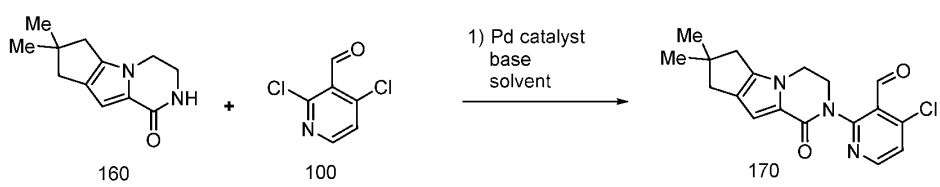
4. The method of any one of claims 1 to 3 wherein:

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,

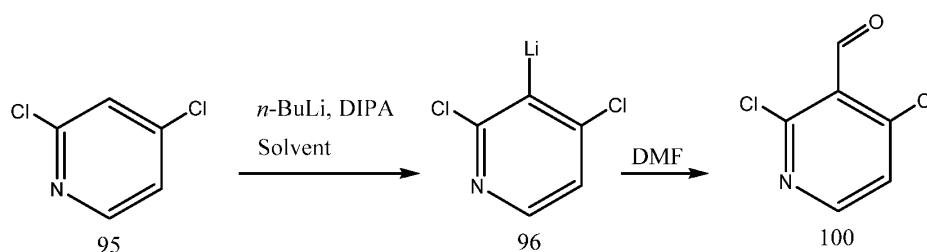
wherein the yield of compound 170 based on compound 160 is at least 80%, at least 85% or at least 90%, and wherein the purity of compound 170 is at least 95%, at least 98% or at least 99%.

6. The method of claim 5 wherein the ratio of the solvent volume to compound 160 weight in the reaction mixture is from about 5:1 to about 20:1 liters per kg, from about

5:1 to about 15:1 liters per kg, or about 10:1 liters per kg, and wherein the equivalent ratio of catalyst to compound 160 is from about 0.01:1 to about 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,



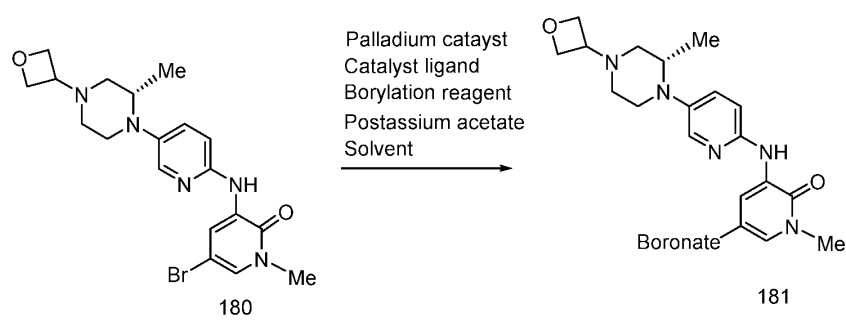
the method comprising:

- (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 about 1.2:1 to about 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 about 3:1 to about 10:1, from about 4:1 to about 6:1, or about 5:1; the mole ratio of DMF to compound 95 is from about 1.1:1 to about 2:1, or from about 1.3:1 to about 1.5:1; and the mole ratio of diisopropylamine to compound 95 is from about 1.2:1 to about 2:1, or from about 1.4:1 to about 1.8:1.

10. The method of any one of claims 1 to 9 wherein compound 181 is prepared by:
- forming a reaction mixture comprising compound 180, a palladium catalyst, a catalyst ligand, a borylation reagent, potassium acetate, and a polar aprotic solvent;
 - reacting the reaction mixture to form a reaction product mixture according to the following scheme:

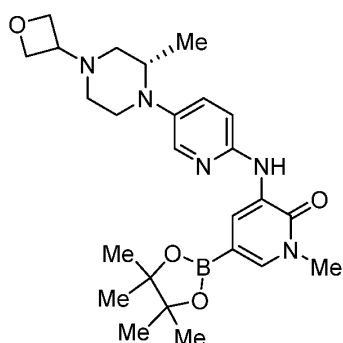


and

- 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 about 5:1 to about 20:1 liters to kg, from about 5:1 to about 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 about 0.005:1; an equivalent ratio of catalyst ligand to catalyst of from about 1.5:1 to about 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:

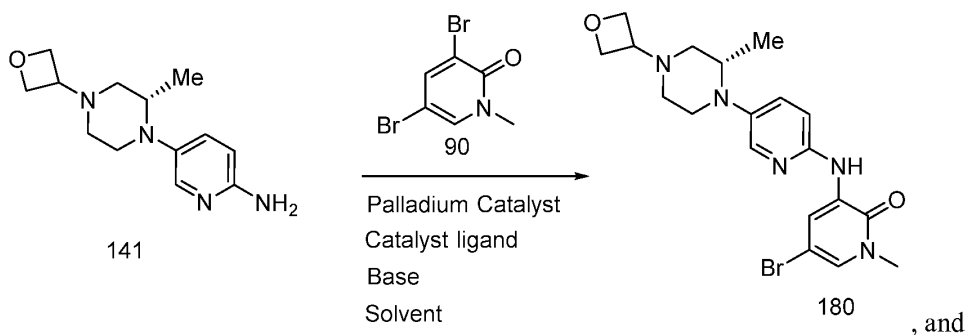


182

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:

- (i) forming a reaction mixture comprising compound 141, compound 90, a palladium catalyst and an aryl phosphate catalyst ligand, a base, and an aprotic solvent;
- (ii) reacting the reaction mixture to form a reaction product mixture according to the following scheme:



- (iii) 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%.

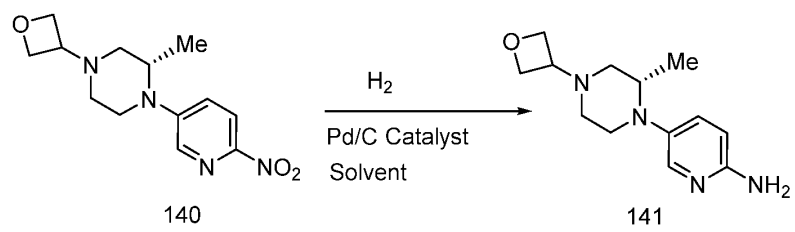
15. The method of claim 14 wherein: the palladium catalyst is $\text{Pd}_2(\text{dba})_3$; the catalyst ligand is Xantphos; the base is potassium carbonate or tripotassium phosphate wherein the equivalent ratio of the base to compound 141 is from about 1.5:1 to about 3:1; the reaction mixture comprises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

0.03:1; the equivalent ratio of the catalyst ligand to the catalyst is from about 1.5:1 to about 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 about 5 to about 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:

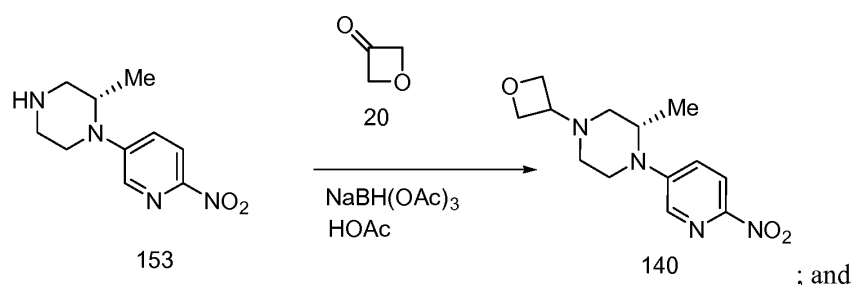
- (i) forming a reaction mixture comprising compound 140, a palladium on carbon catalyst, hydrogen, a solvent selected from methanol, ethanol, isopropanol, dioxane, toluene, and combinations thereof; and
- (ii) reacting the reaction mixture to form a reaction product mixture according to the following 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 about 3:1 to about 20:1 liters to kg, from about 3:1 to about 10:1 liters to kg, or from about 4:1 to about 6:1 liters to kg, and wherein the weight ratio of the catalyst to compound 140 is from about 10 w/w% to about 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, $\text{NaBH}(\text{OAc})_3$, 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%.

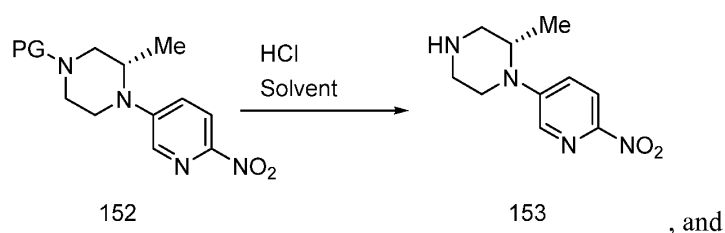
20. The method of claim 19 wherein: the equivalent ratio of compound 20 to compound 153 is from about 1.3:1 to about 1.9:1; the equivalent ratio of acetic acid to compound 153 is from about 1.1:1 to about 3:1; the equivalent ratio of $\text{NaBH}(\text{OAc})_3$ to compound 153 is greater than 1.5:1.

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 about 2 to about 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 about 0.3:1 to about 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:



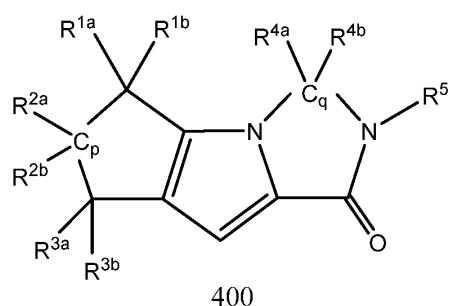
- (iii) isolating compound 153 from the reaction product mixture wherein the yield of compound 153 is at least 80% or at least 90%.

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

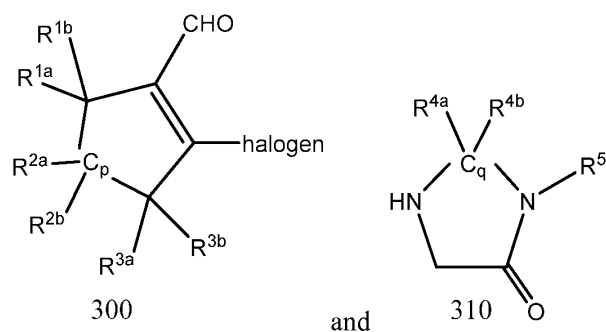
25. The method of any one of claims 5 to 23 wherein compound 160 is prepared by the method of claim 43.

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

27. A method for preparing a tricyclic lactam of formula 400, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



the method comprising forming a reaction mixture comprising an organic solvent, an organic base, and formulas 300 and 310



and reacting the reaction mixture to form a reaction product mixture comprising the tricyclic lactam of formula 400,

wherein:

R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{3a} , R^{3b} , R^{4a} and R^{4b} are independently selected from H, and C_{1-6} alkyl;

R^5 is selected from H, C_{1-6} alkyl, cycloalkyl, aryl, substituted aryl, benzyl, substituted benzyl, heteroaryl, substituted heteroaryl;

p is 1, 2, 3 or 4; and

q is 1, 2, 3 or 4.

28. The method of claim 27 wherein p is 1 or 2, and q is 1 or 2.

29. The method of claim 27 or claim 28 wherein the organic base is a tri- C_{1-6} alkyl amine.

30. The method of claim 29, wherein the organic base is selected from 4-methylmorpholine and N-ethyldiisopropylamine.

31. The method of any one of claims 27 to 30 wherein the solvent is a polar aprotic solvent.

32. The method of claim 31 wherein the solvent is selected from N-methylpyrrolidone and dimethylformamide.

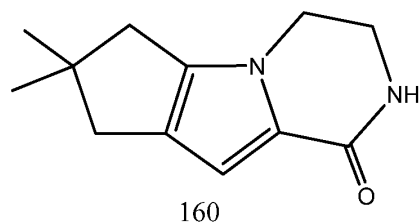
33. The method of any one of claims 27 to 32 wherein halogen is Cl.

34. The method of any one of claims 27 to 33 wherein p is 1 and q is 2.

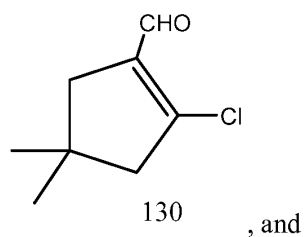
35. The method of any one of claims 27 to 34 wherein R^{1a} , R^{1b} , R^{3a} , R^{3b} , R^{4a} , R^{4b} and R^5 are H, and R^{2a} and R^{2b} are $-CH_3$.

36. The method of any one of claims 27 to 35 wherein the reaction mixture comprises from about 0.25 to about 2 moles per liter, from about 0.5 to about 1.5 moles per liter or from about 0.5 to about 1 moles per liter of formula 300; between 1 and 2 equivalents, or from about 1.1 to about 1.5 equivalents base; and between 0.7 and 1 equivalents, from about 0.75 to about 0.95 equivalents, or from about 0.8 to about 0.9 equivalents of formula 310.

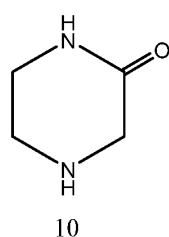
37. The method of any one of claims 27 to 36 wherein the tricyclic lactam of formula 400 is species formula 160 of the structure:



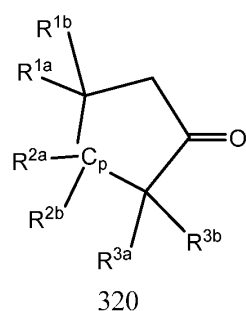
formula 300 is the species of formula 130 of the structure:



formula 310 is piperazine-2-one of formula 10:



38. The method of any one of claims 27 to 37 wherein formula 300 is prepared by forming a reaction mixture comprising a polar aprotic solvent, a non-polar solvent, phosphorous oxychloride and formula 320:



and reacting the reaction mixture to form a reaction product mixture comprising formula 300.

39. The method of claim 38 wherein the polar aprotic solvent is dimethylformamide, the non-polar solvent is dichloromethane, the mole ratio of phosphorous oxychloride to formula 320 is from about 1.5:1 to about 2.7:1 or from about 1.8:1 to about 2.4:1, and the mole ratio of the polar aprotic solvent to formula 320 is from about 1.5:1 to about 3.5:1 or from about 2:1 to about 3:1.

40. The method of claim 38 or claim 39 wherein compound 320 is the subgenus compound 321 wherein

R^{1a} and R^{1b} are each independently selected from the group consisting of H and C_{1-6} alkyl;

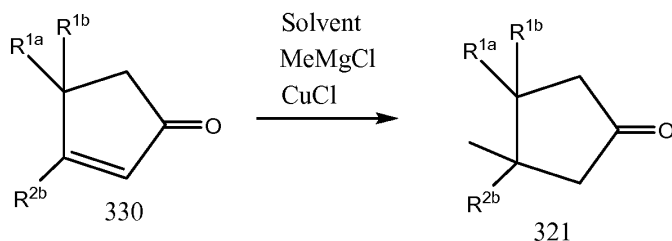
R^{2a} is $-CH_3$;

R^{2b} is selected from the group consisting of H and C_{1-6} alkyl;

R^{3a} and R^{3b} are each H;

p is 1; and

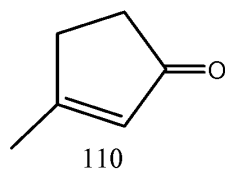
wherein compound 321 is prepared by forming a reaction mixture comprising a polar aprotic solvent, methyl magnesium chloride, copper (I) chloride and compound 330 and reacting the reaction mixture to form a reaction product mixture comprising compound 321 according to the following reaction scheme:



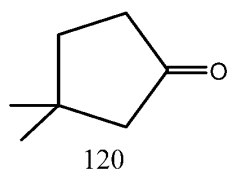
41. The method of any one of claims 38 to 40 wherein

R^{1a} , R^{1b} , R^{3a} and R^{3b} are H, p is 1, and R^{2a} and R^{2b} are $-CH_3$,

wherein compound 321 is the species of compound 120 prepared by forming a reaction mixture comprising a polar aprotic solvent, methyl magnesium chloride, copper (I) chloride and compound 110:



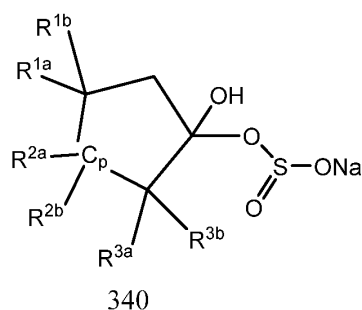
and reacting the reaction mixture to form a reaction product mixture comprising compound 120



42. The method of claim 41 wherein the solvent is tetrahydrofuran, the mole ratio of methyl magnesium chloride to compound 110 in the reaction mixture is between 1:1 and 2:1, or from about 1.1:1 to about 1.4:1, and the mole ratio of copper (I) chloride to compound 110 in the reaction mixture is from about 0.1:1 to about 0.5:1, or from about 0.15:1 to about 0.25:1.

43. The method of any one of claims 38 to 42 further comprising purifying compound 320, the purification comprising:

- (i) forming a first reaction mixture comprising crude compound 320, an organic solvent that is not miscible with water, and an aqueous solution of sodium bisulfite, and reacting the first reaction mixture to form a first reaction product mixture comprising the solid ketone bisulfite adduct of compound 340:



- (ii) isolating solid compound 340 from the first reaction product mixture,
- (iii) forming a second reaction mixture comprising isolated compound 340, water, a low boiling solvent that is not miscible with water, and sodium bicarbonate, and reacting the second reaction mixture to form a second reaction product mixture comprising a first phase comprising dichloromethane and the predominant amount of purified compound 320 is in solution in the first phase, and a second phase comprising water, and

- (iv) separating the first phase comprising the purified compound 320 from the aqueous phase.

44. The method of claim 43 wherein:

- (i) crude compound 320 is in solution in organic solvent that is not miscible with water, the ratio of water volume to the crude compound 320 weight in the first reaction mixture is from about 1:1 L/kg to about 10:1 L/kg, from about 1.5:1 L/kg to about 4:1 L/kg, or from about 2:1 L/kg to about 3:1 L/kg, and the equivalent ratio of sodium bisulfite to compound 320 in the first reaction mixture is from about 2:1 to about 5:1 or from 3:1 to about 5:1;
- (ii) the second reaction mixture comprises a ratio of water volume to isolated solid 340 weight of from about 5:1 L/kg to about 15:1 L/kg, or from about 7.5:1 L/kg to about 10.5:1 L/kg, the ratio of water volume to the low boiling solvent volume that is not miscible with water in the second reaction mixture is from about 1:1 to about 3:1 or from about 1.5:1 to about 2.5:1, and the equivalent ratio of sodium bicarbonate to compound 340 in the second reaction mixture is between 1:1 and 2:1, or from about 1.25:1 to about 1.75:1, and
- (iii) the yield of purified compound 320 is at least 60% based on compound 330 and the purity of purified compound 330 is at least 98% or at least 99%.

45. The method of claim 43 or claim 44 wherein the organic solvent that is not miscible with water in the first reaction mixture is a hexane, and wherein the low boiling solvent that is not miscible with water in the second reaction mixture is dichloromethane.

46. The method of any one of claims 27 to 37 wherein,

R^{1a} and R^{1b} are each independently selected from the group consisting of H and C_{1-6} alkyl;

R^{2a} is $-CH_3$;

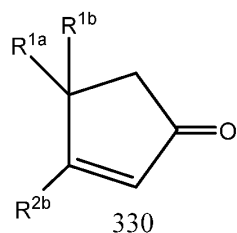
R^{2b} is selected from the group consisting of H and C_{1-6} alkyl;

R^{3a} and R^{3b} are each H;

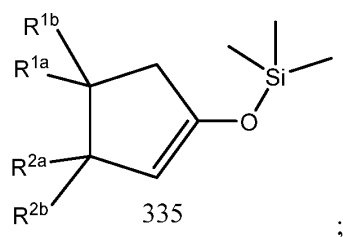
p is 1; and

wherein compound 300 is prepared by:

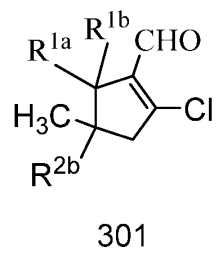
- (i) forming a first reaction mixture comprising a first polar aprotic solvent, methyl magnesium chloride, copper (I) chloride, lithium chloride, chlorotrimethylsilane, and compound 330:



and reacting compound 330 to form a first reaction product mixture comprising compound 335 where R^{2a} is -CH₃



- (ii) quenching the first reaction product mixture with methanol as a first quenching agent;
- (iii) further quenching with a second quenching agent in aqueous solution and adding a non-polar water-immiscible solvent to the quenched reaction product mixture;
- (iv) separating the phases and collecting the organic phase comprising the predominant amount of compound 335 and concentrating the organic phase to obtain compound 335 in solution;
- (v) forming a second reaction mixture comprising a second polar aprotic solvent, phosphorous oxychloride, and the solution of compound 335, and reacting the second reaction mixture to form a second reaction product mixture comprising compound 301 of the structure



- (vi) quenching the second reaction product mixture with a third quenching agent in aqueous solution; and

- (vii) separating the phases and collecting the organic phase comprising the predominant amount of compound 301 in solution.

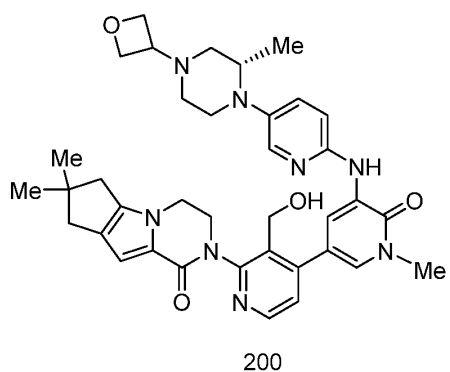
47. The method of claim 46 wherein the first polar aprotic solvent is tetrahydrofuran, the second quenching agent is ammonium chloride, the non-polar water-immiscible solvent is toluene, the second polar aprotic solvent is dimethylformamide, and the third quenching agent is potassium phosphate.

48. The method of claim 46 or claim 47 wherein:

- (i) the first reaction mixture comprises: from about 0.25 to about 2, or from about 0.5 to about 1.1 moles per liter of compound 330; a stoichiometric excess of methylmagnesium chloride as compared to compound 330, a mole ratio of methylmagnesium chloride to compound 330 of between 1:1 and 1.5:1, or from about 1.1:1 to about 1.3:1; a stoichiometric excess of chlorotrimethylsilane as compared to compound 330, a mole ratio of chlorotrimethylsilane to compound 330 of between 1:1 and 1.2:1, or from about 1.01:1 to about 1.1:1; a mole ratio of copper (I) chloride to compound 330 of from about 0.05:1 to about 0.2:1, or from about 0.05:1 to about 0.15:1; and a mole ratio of lithium chloride to compound 330 of from about 0.05:1 to about 0.2:1, or from about 0.07:1 to about 0.15:1,
- (ii) the second reaction mixture comprises: from about 0.5 to about 2 moles per liter or from about 0.7 to about 1.3 moles per liter compound 335; and a mole ratio of phosphorous oxychloride to compound 335 of from about 1.5:1 to about 3.1:1, or from about 2.1:1 to about 2.6:1, and
- (iii) the yield of compound 300 based on compound 330 is at least 70% or at least 75%, and the purity of compound 301 is at least 85% or at least 88%.

49. The method of any one of claims 46 to 48 wherein R^{1a} and R^{1b} are each H and R^{2b} is $-CH_3$.

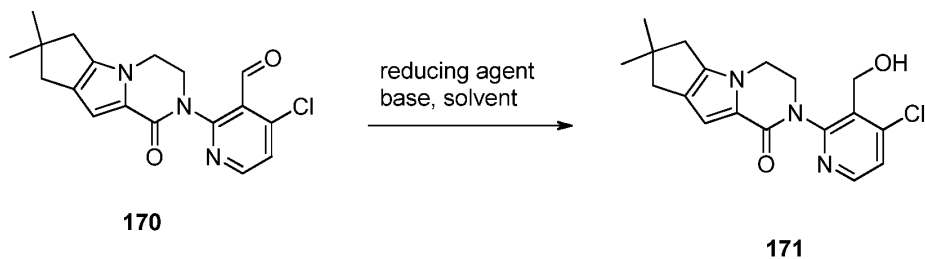
50. A method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,

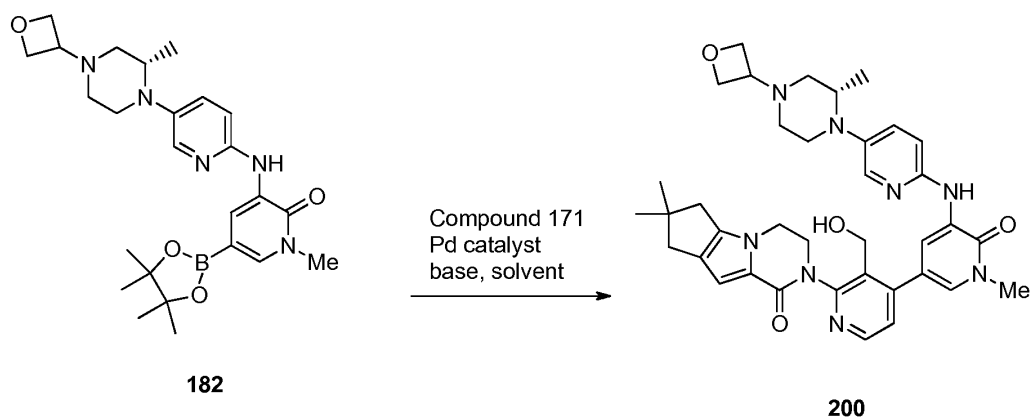


the method comprising:

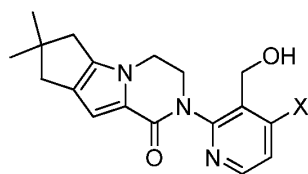
- (i) (1) forming a first reaction mixture comprising compound 170, a reducing agent, a base and a solvent, to reduce the aldehyde moiety of compound 170 to form compound 171, and
(2) isolating compound 171 from the first product mixture,
- (ii) (1) forming a second reaction mixture comprising compound 171, compound 182, a palladium catalyst, a solvent system comprising water, and a base, to form compound 200, and
(2) isolating compound 200 from the second product mixture,

according to the following scheme:





51. The method of claim 50, wherein the reducing agent in step (i) is NaBH_4 .
52. The method of claim 50 or 51, wherein the base in step (i) is K_2HPO_4 .
53. The method of any of claims 50 to 52, wherein the solvent in step (i) is THF.
54. The method of any of claims 50 to 53, wherein the Pd catalyst in step (ii) is $\text{Pd}(\text{PCy}_3)_2$.
55. The method of any of claims 50 to 54, wherein the base in step (ii) is K_3PO_4 , Et_3N or Di-isopropylethylamine.
56. The method of any of claims 50 to 55, wherein the equivalent ratio of the Pd catalyst to compound 171 is less than 0.05:1.
57. The method of any of claims 50 to 56, wherein the ratio of compound 182 to compound 171 is greater than 1:1.
58. A compound having the structure:



wherein X is selected from the group consisting of Cl, Br, and I.

59. A compound of claim 58, wherein X is Cl.