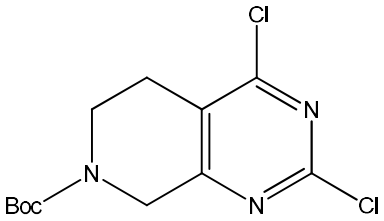
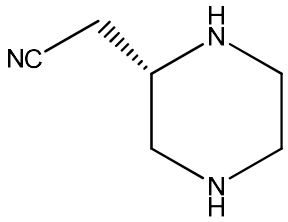
WHAT IS CLAIMED IS:

1. A method of synthesizing adagrasib, comprising step (a'), wherein the step (a') comprises:

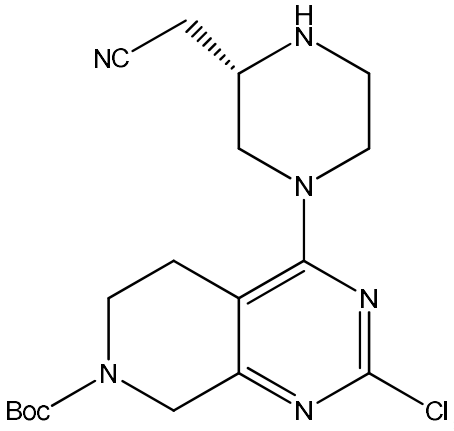
a') reacting a compound of the following structure:



with the compound of the following structure:

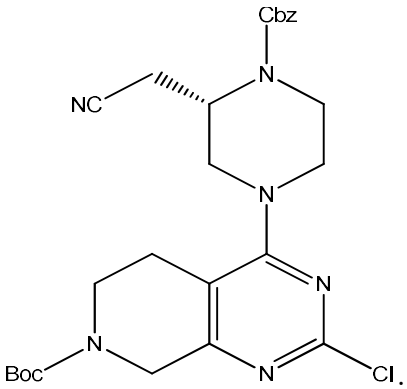


in the presence of a polar aprotic solvent and a base to produce the compound of the following structure:



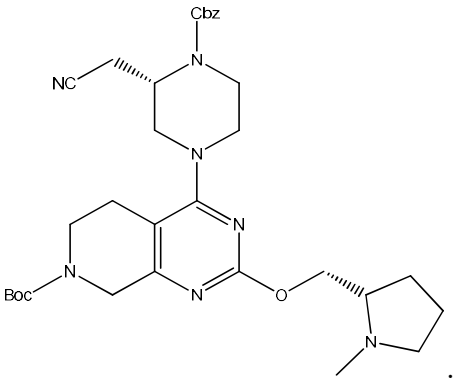
, and then

reacting this compound with benzyl chloroformate in the presence of sodium carbonate, methyl tert-butyl ether (MTBE) and water to produce a final compound of step (a') with the following structure:



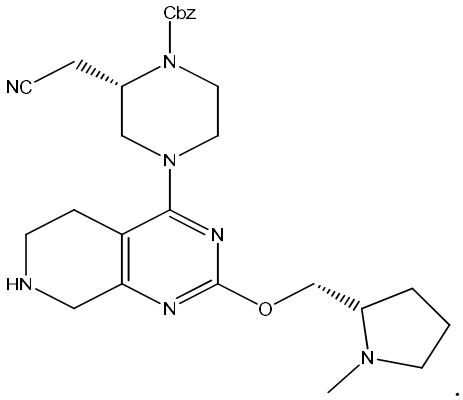
2. The method of claim 1, further comprising step (b):

b) reacting the final compound of step (a') with (*S*)-(1-methylpyrrolidin-2-yl)methanol in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce a final compound of step (b) with the following structure:

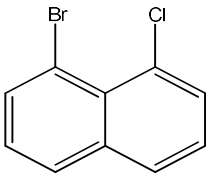


3. The method of claim 2, further comprising step (c):

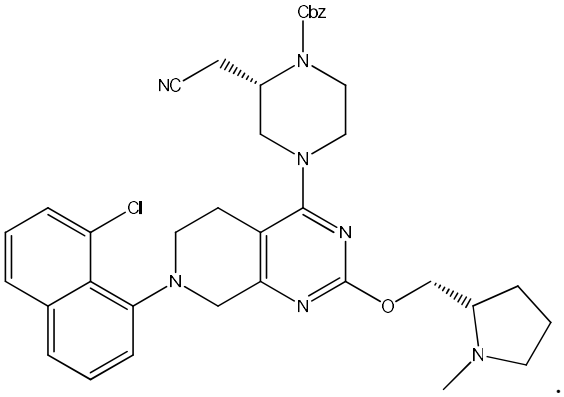
c) reacting the final compound of step (b) with an acid to remove a Boc protecting group from the final compound of step (b) to produce a salt or free base of a final compound of step (c) with the following structure:



4. The method of claim 3, further comprising step (d):

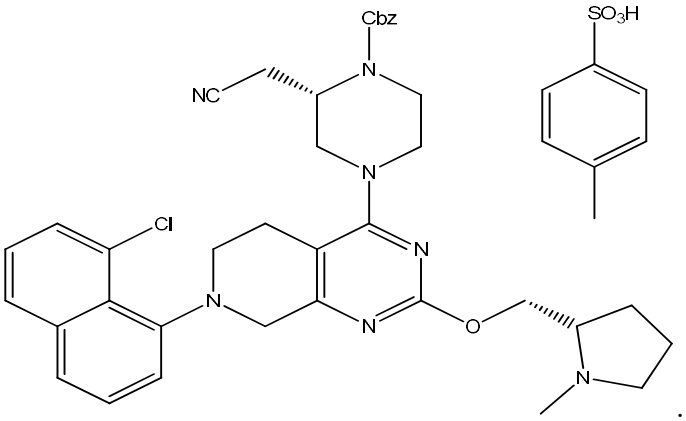
d) reacting the salt or free base of the final product of step (c) with 

in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce a final compound of step (d) with the following structure:



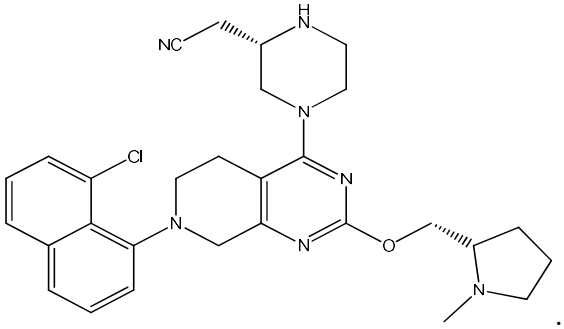
5. The method of claim 4, further comprising step (e):

e) reacting the final compound of step (d) with *p*-toluenesulfonic acid in the presence of a first solvent selected from acetone, methyl isobutyl ketone (MIBK), and methyl ethyl ketone (MEK), and an anti-solvent to produce a final compound of step (e) with the following structure:



6. The method of claim 5, further comprising step (f):

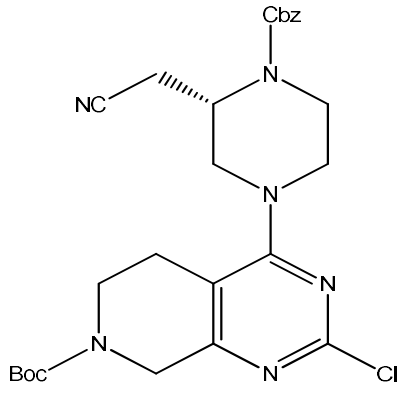
f) reacting the final compound of step (e) with a thiol or thiolate in the presence of a base and a polar aprotic solvent to produce a final compound of step (f) with the following structure:

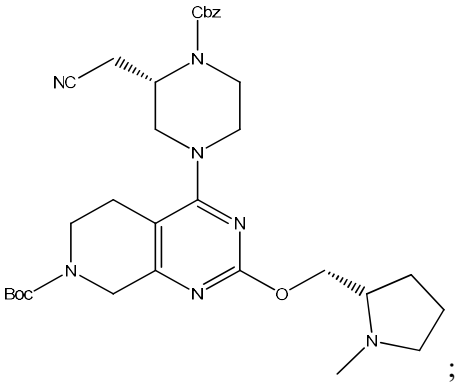


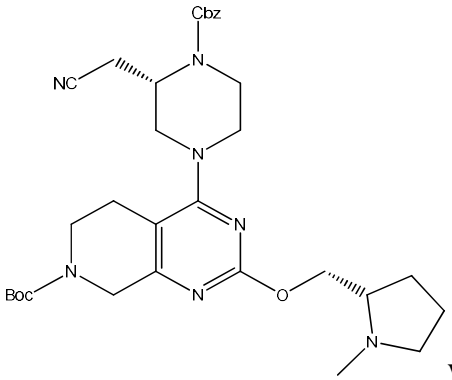
7. The method of claim 6, further comprising step (g):

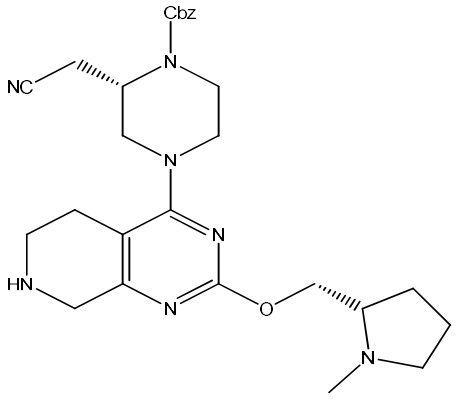
(g) reacting the final compound of step (f) with 2-fluoroacrylic acid with a coupling agent in the presence of a solvent and a base to produce adagrasib.

8. A method of synthesizing adagrasib, comprising the steps of:

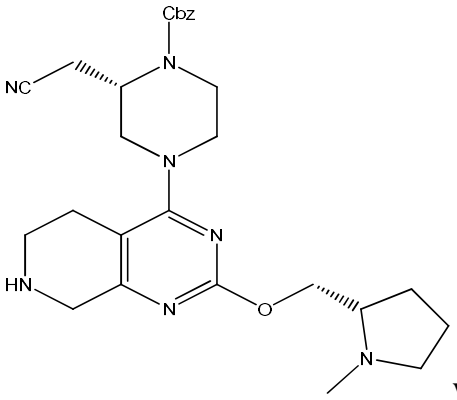
-reacting  with (*S*)-(1-methylpyrrolidin-2-yl)methanol in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce:

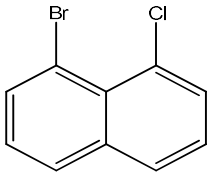
;

-reacting  with an acid to remove a Boc protecting group to produce a salt or free base of:



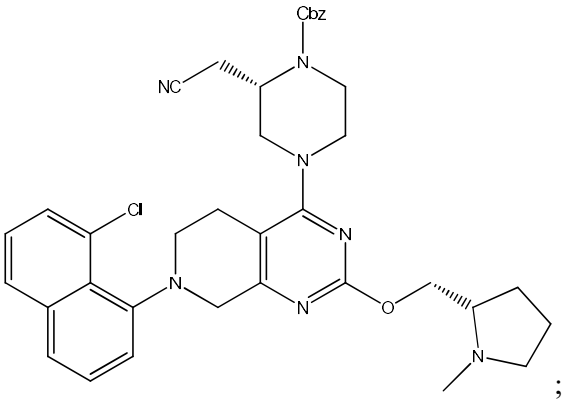
;



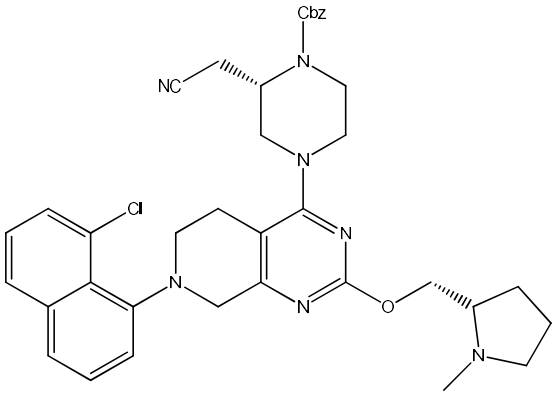


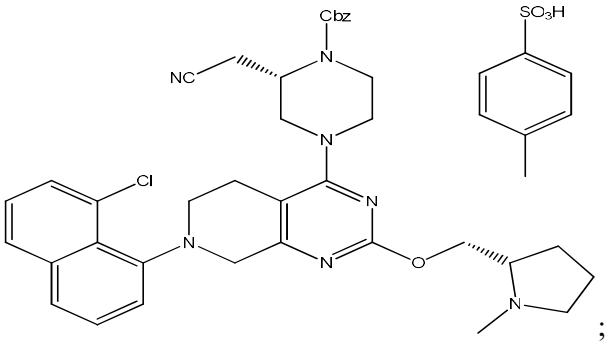
-reacting the salt or free base of with

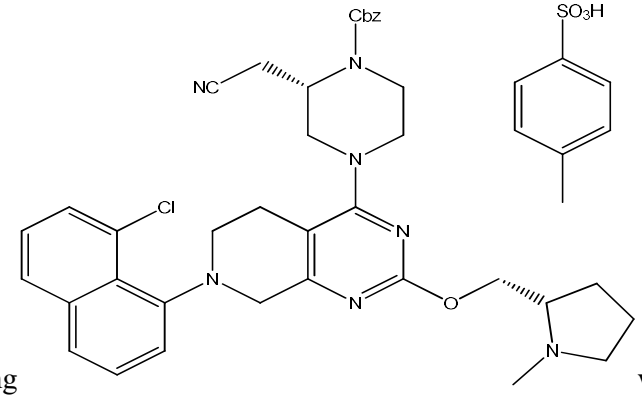
in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce



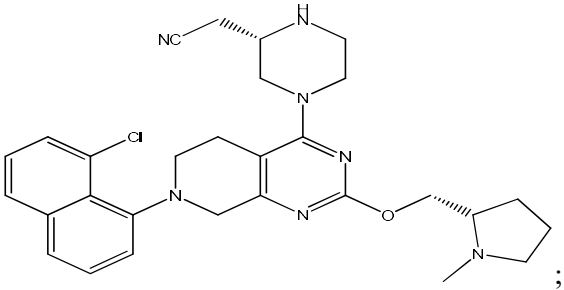
;

-reacting  with *p*-toluenesulfonic acid in the presence of a first solvent selected from acetone, methyl isobutyl ketone (MIBK), and methyl ethyl ketone (MEK), and an anti-solvent to produce

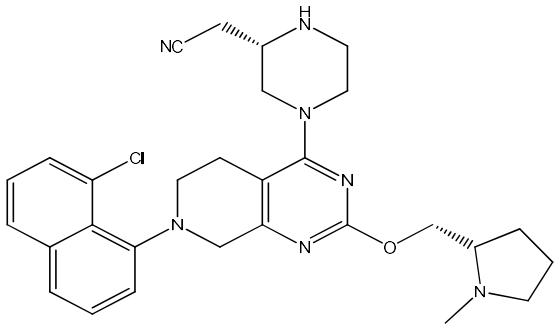
;



-reacting with a thiol or thiolate in the presence of a base and a polar aprotic solvent to produce

; and

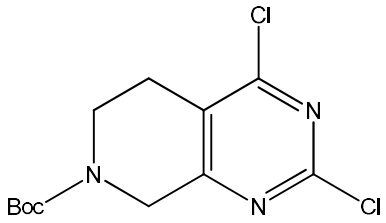
-reacting



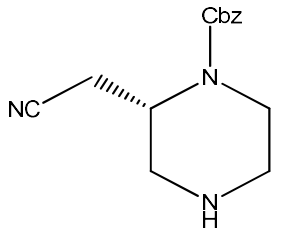
with 2-fluoroacrylic acid with a coupling agent in the presence of a solvent and a base to produce adagrasib.

9. A method of synthesizing adagrasib, comprising the steps of:

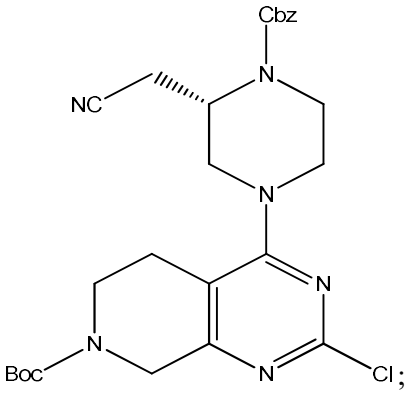
a) reacting a compound of the following structure:



with a salt of a compound of the following structure:

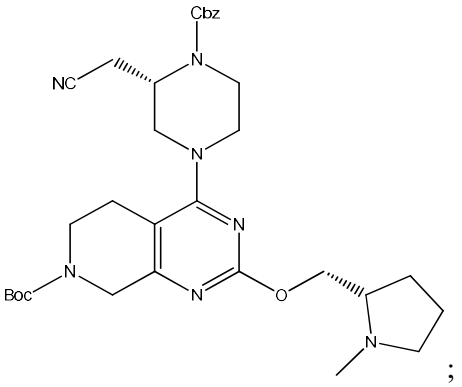


in the presence of a polar aprotic solvent and an organic or an inorganic base to produce a final compound of step (a) with the following structure:



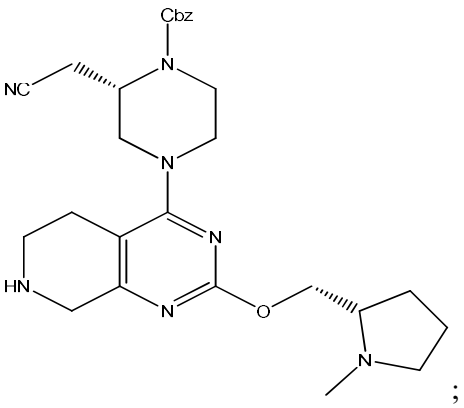
;

b) reacting the final compound of step (a) with (*S*)-(1-methylpyrrolidin-2-yl)methanol in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce a final compound of step (b) with the following structure:

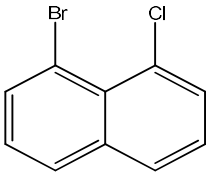


;

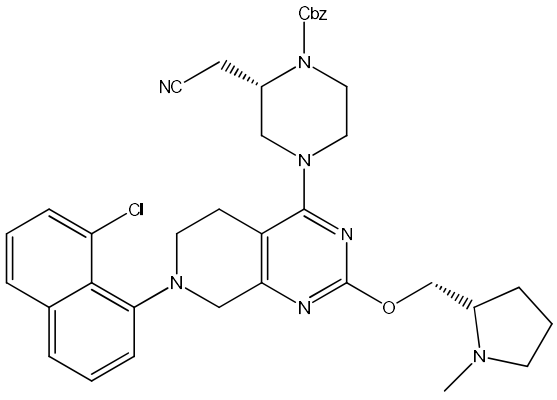
c) reacting the final compound of step (b) with an acid to remove a Boc protecting group from the final compound of step (b) to produce a salt or free base of a final compound of step (c) with the following structure:



;

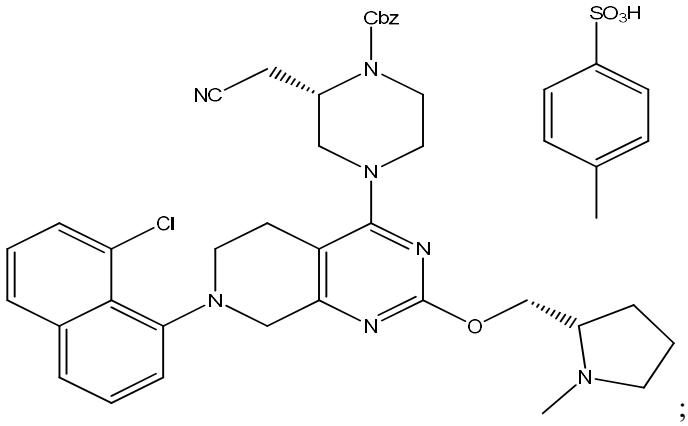
d) reacting the salt or free base of the final product of step (c) with 

in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce a final compound of step (d) with the following structure:



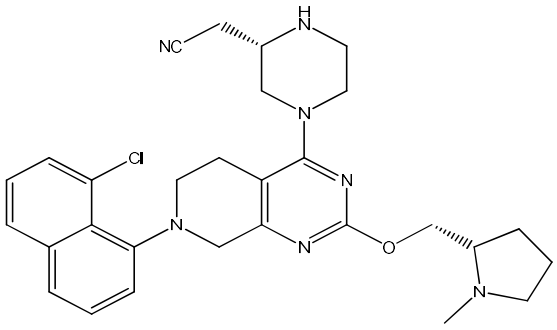
;

e) reacting the final compound of step (d) with *p*-toluenesulfonic acid in the presence of a first solvent and an anti-solvent to produce a final compound of step (e) with the following structure:



;

f) reacting the final compound of step (e) with a thiol or thiolate in the presence of a base and a polar aprotic solvent to produce a final compound of step (f) with the following structure:

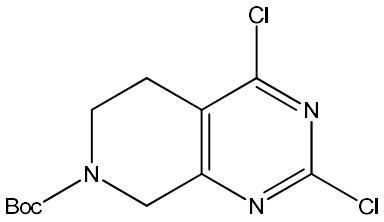


; and

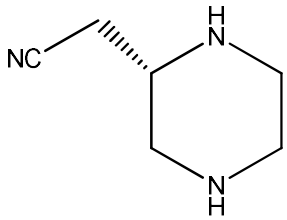
g) reacting the final compound of step (f) with 2-fluoroacrylic acid with a coupling agent in the presence of a solvent and a base to produce adagrasib.

10. A method of synthesizing adagrasib, comprising the steps of:

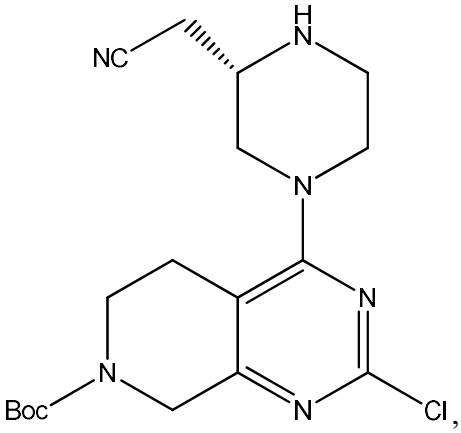
a') reacting a compound of the following structure:



with the compound of the following structure:

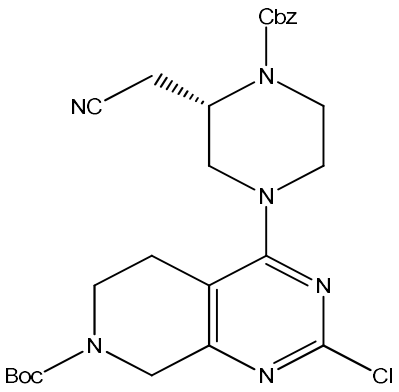


in the presence of a polar aprotic solvent and a base to produce the compound of the following structure:

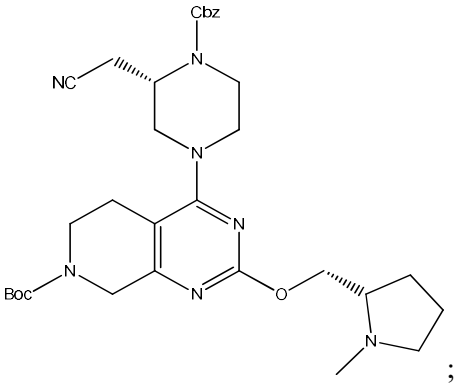


, and then

reacting this compound with benzyl chloroformate in the presence of sodium carbonate, methyl tert-butyl ether (MTBE) and water to produce a final compound of step (a') with the following structure:

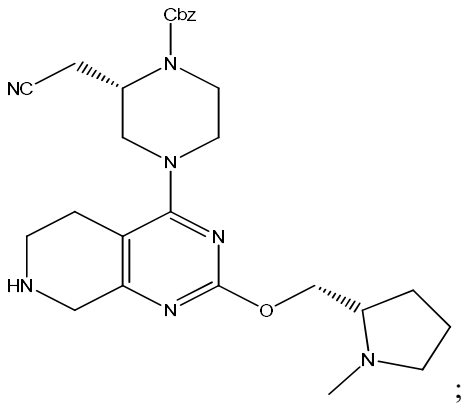


b) reacting the final compound of step (a') with (*S*)-(1-methylpyrrolidin-2-yl)methanol in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce a final compound of step (b) with the following structure:

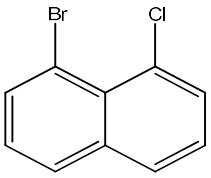


;

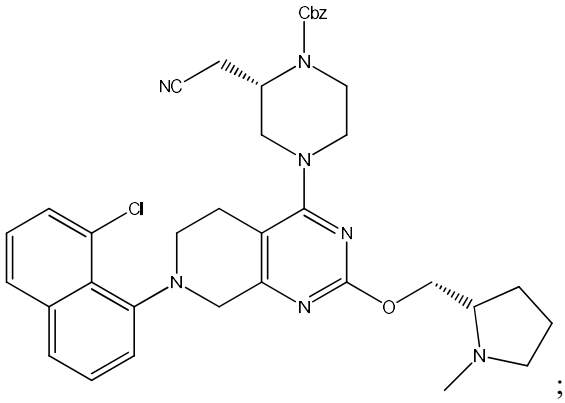
c) reacting the final compound of step (b) with an acid to remove a Boc protecting group from the final compound of step (b) to produce a salt or free base of a final compound of step (c) with the following structure:



;

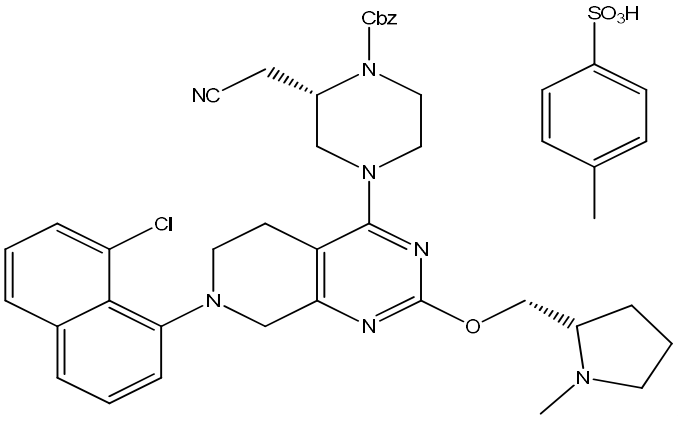
d) reacting the salt or free base of the final product of step (c) with 

in the presence of a palladium catalyst, a base, a phosphorous-based ligand, and an aprotic solvent to produce a final compound of step (d) with the following structure:



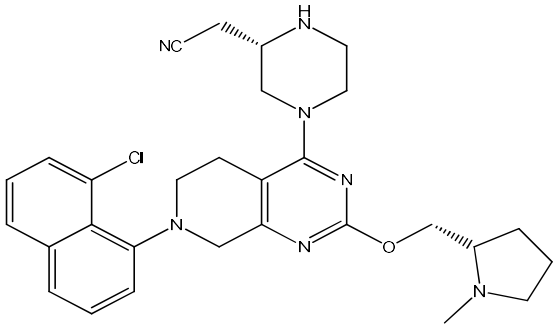
;

e) reacting the final compound of step (d) with *p*-toluenesulfonic acid in the presence of a first solvent selected from acetone, methyl isobutyl ketone (MIBK), and methyl ethyl ketone (MEK), and an anti-solvent to produce a final compound of step (e) with the following structure:



;

f) reacting the final compound of step (e) with a thiol or thiolate in the presence of a base and a polar aprotic solvent to produce a final compound of step (f) with the following structure:



; and

g) reacting the final compound of step (f) with with 2-fluoroacrylic acid with a coupling agent in the presence of a solvent and a base to produce adagrasib.

11. The method of claim 9 or claim 10, wherein in step (a) or step (a'), the polar aprotic solvent is selected from the group consisting of dimethylacetamide (DMAc), dimethylformamide (DMF), 1,4-dioxane, tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), and *N*-methylpyrrolidone (NMP).

12. The method of claim 9 or claim 10, wherein in step (a) or step (a'), the polar aprotic solvent is dimethylacetamide (DMAc).

13. The method of claim 9 or claim 10, wherein in step (a) or step (a'), the base is an organic base.

14. The method of claim 13, wherein the organic base is selected from the group consisting of *N,N*-diisopropylethylamine (DIPEA), triethylamine (Et_3N), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

15. The method of claim 13, wherein the organic base is *N,N*-diisopropylethylamine (DIPEA).

16. The method of claim 9 or claim 10, wherein in step (a) or step (a'), the base is an inorganic base.

17. The method of claim 16, wherein the inorganic base is selected from the group consisting of carbonate, bicarbonate, and phosphate.

18. The method of claim 9 or claim 10, wherein in step (a) or step (a'), the salt is an organic salt.

19. The method of claim 18, wherein the organic salt is selected from the group consisting of fumarate, tartrate, malate, and citrate.

20. The method of claim 18, wherein the organic salt is a fumarate salt.

21. The method of claim 9 or claim 10, wherein in step (a) or step (a'), the salt is a mineral salt.

22. The method of claim 21, wherein the mineral salt is selected from the group consisting of hydrochloride, hydrobromide, sulfate and phosphate.

23. The method of claim 9, wherein step (a) is carried out at a temperature from -10 °C to 80° C.

24. The method of claim 9, wherein in step (b), the palladium catalyst is in the oxidation state 0 or II.

25. The method of claim 9, wherein in step (b), the palladium catalyst is selected from the group consisting of $Pd_2(dba)_3$, $Pd(dba)_2$, and $Pd(OAc)_2$.

26. The method of claim 9, wherein in step (b), the palladium catalyst is pre-activated.

27. The method of claim 9, wherein in step (b), the base is an organic base.

28. The method of claim 27, wherein the organic base is selected from the group consisting of *N,N*-diisopropylethylamine (DIPEA), triethylamine (Et_3N), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

29. The method of claim 9, wherein in step (b), the base is an inorganic base.

30. The method of claim 29, wherein the inorganic base is selected from the group consisting of carbonate, bicarbonate, and phosphate.

31. The method of claim 9, wherein in step (b), the phosphorous-based ligand is selected from the group consisting of a monodentate phosphorous-based ligand and a bidentate phosphorous-based ligand.

32. The method of claim 31, wherein the phosphorous-based ligand is a monodentate phosphorous-based ligand.

33. The method of claim 31, wherein the phosphorous-based ligand is a bidentate phosphorous-based ligand.

34. The method of claim 31, wherein the phosphorous-based ligand is Xantphos.

35. The method of claim 9, wherein in step (b), the aprotic solvent is seleted from the group consisting of toluene, 1,4-dioxane, tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), and *N*-Methylpyrrolidone (NMP).

36. The method of claim 9, wherein step (b) is carried out at a temperature from 20 °C to 120° C.

37. The method of claim 9, wherein in step (c), the acid is a mineral acid.

38. The method of claim 37, wherein the mineral acid is selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid.

39. The method of claim 9, wherein step (c) is carried out at a temperature from 20 °C to 120° C.

40. The method of claim 9, wherein in step (d), the palladium catalyst is in the oxidation state 0 or II.

41. The method of claim 9, wherein in step (d), the palladium catalyst is selected from the group consisting of $Pd_2(dba)_3$, $Pd(dba)_2$, and $Pd(OAc)_2$.

40. The method of claim 9, wherein in step (d), the palladium catalyst is pre-activated.

41. The method of claim 9, wherein in step (d), the base is an organic base.

42. The method of claim 41, wherein the organic base is selected from the group consisting of DIPEA, Et_3N, DABCO, and DBU.

43. The method of claim 9, wherein in step (d), the base is an inorganic base.

44. The method of claim 43, wherein the inorganic base is selected from the group consisting of carbonate, bicarbonate, and phosphate.

45. The method of claim 9, wherein in step (d), the phosphorous-based ligand is selected from the group consisting of a monodentate phosphorous-based ligand and a bidentate phosphorous-based ligand.

46. The method of claim 45, wherein the phosphorous-based ligand is a monodentate phosphorous-based ligand.

47. The method of claim 45, wherein the phosphorous-based ligand is a bidentate phosphorous-based ligand.

48. The method of claim 9, wherein in step (d), the aprotic solvent is seleted from the group consisting of toluene, 1,4-dioxane, THF, 2-MeTHF, MeCN, DMSO, and NMP.

49. The method of claim 9, wherein the ketone is selected from the group consisting of acetone, methyl isobutyl ketone (MIBK), and methyl ethyl ketone (MEK).

50. The method of claim 9, wherein in step (e), the anti-solvent is selected from the group consisting of 2-MeTHF and or isopropyl acetate (IPAc).

51. The method of claim 9, wherein in step (f), the thiol or thiolate is selected from the group consisting of 2-mercaptoethanol, dithiothreitol (DTT) and 2-(dimethylamino)ethanethiol hydrochloride.

52. The method of claim 9, wherein in step (f), the base is an organic base.

53. The method of claim 52, wherein the organic base is selected from the group consisting of DIPEA, Et_3N, DABCO, and DBU.

54. The method of claim 9, wherein in step (f), the base is an inorganic base.

55. The method of claim 54, wherein the inorganic base is selected from the group consisting of carbonate, bicarbonate, and phosphate.

56. The method of claim 9, wherein in step (f), the polar aprotic solvent is selected from the group consisting of DMAc, DMF, 1,4-dioxane, THF, 2-MeTHF, MeCN, DMSO, and NMP.

57. The method of claim 9, wherein step (f) is carried out at a temperature from 20 °C to 120° C.

58. The method of claim 9, wherein in step (g) the solvent is selected from the group consisting of DMAc, DMF, 1,4-dioxane, THF, 2-MeTHF, MeCN, DMSO, dichloromethane (DCM), ethyl acetate (EtOAc), isopropyl acetate (IPAc), and NMP.

59. The method of claim 9, wherein in step (g), 2-fluoroacrylic acid is in the neutral form, free acid, or ionic form.

60. The method of claim 9, wherein in step (g), the coupling agent is selected from the group consisting of propylphosphonic anhydride (T3P®), carbonyldiimidazole (CDI), the carbodiimide, the phosphonium, and uronium.

61. The method of claim 60, wherein the carbodiimide is selected from the group consisting of dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), and ethyl-(*N',N'*-dimethylamino)propylcarbodiimide hydrochloride (EDC.HCl).

62. The method of claim 60, wherein the phosphonium is selected from the group consisting of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP).

63. The method of claim 60, wherein the uronium is selected from the group consisting of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU).

64. The method of claim 9, wherein in step (g), the base is an organic base.

65. The method of claim 64, wherein the organic base is selected from the group consisting of DIPEA, Et_3N, DABCO, and DBU.

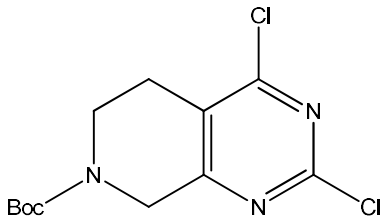
66. The method of claim 9, wherein in step (g), the base is an inorganic base.

67. The method of claim 66, wherein the inorganic base is selected from the group consisting of carbonate, bicarbonate, and phosphate.

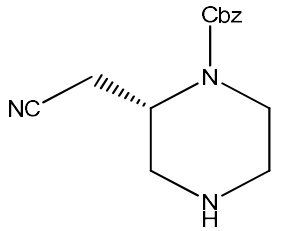
68. The method of claim 9, wherein step (g) is carried out at a temperature from -10 °C to 50° C.

69. A method of synthesizing adagrasib comprising the steps of:

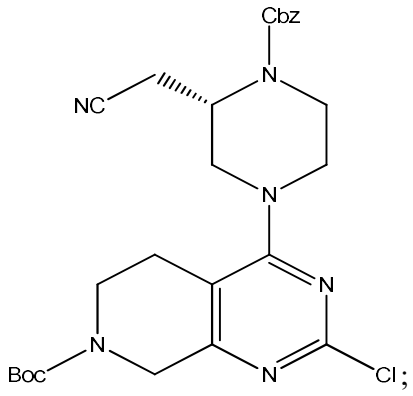
a) reacting a compound of the following structure:



with a fumarate salt of a compound of the following structure:

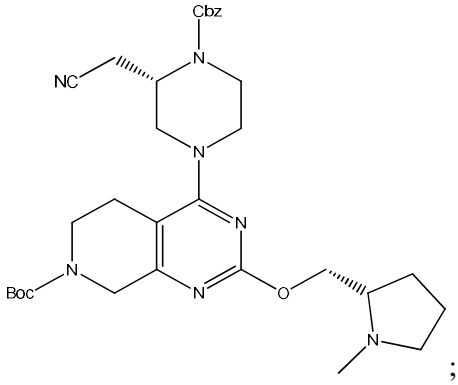


in the presence of DIPEA and DMAc to produce a final compound of step (a) with the following structure:



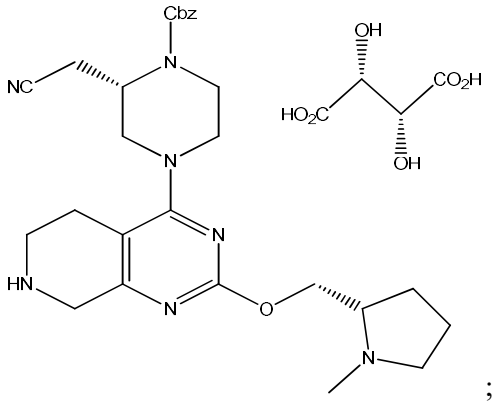
;

b) reacting the final compound of step (a) with (*S*)-(1-methylpyrrolidin-2-yl)methanol in the presence of $Pd_2(dba)_3$, (R)-BINAP, K_3PO_4, and 2-MeTHF to produce a final compound of step (b) with the following structure:

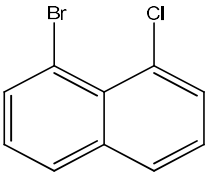


;

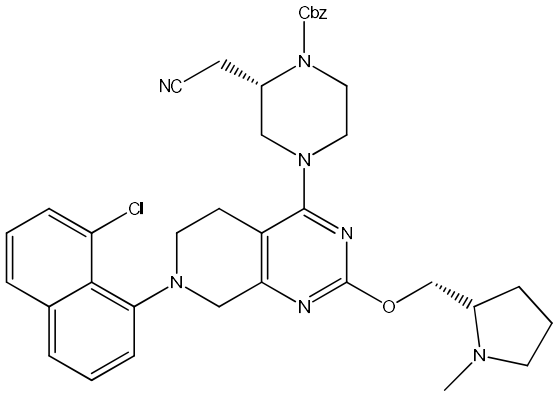
c) reacting the final compound of step (b) with a hydrochloric acid and L-tartaric acid to remove a Boc protecting group from the final compound of step (b) to produce a L-tartrate salt of a final compound of step (c) with the following structure:



;

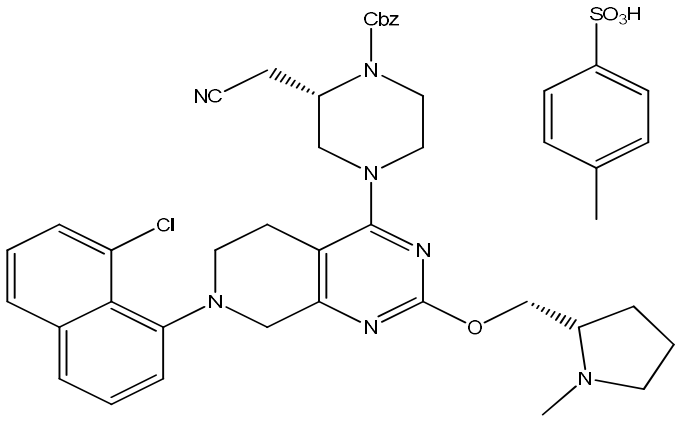
d) reacting the free base of the final product of step (c) with 

in the presence of $Pd_2(dba)_3$, (R)-BINAP, K_3PO_4, and 2-MeTHF to produce a final compound of step (d) with the following structure:

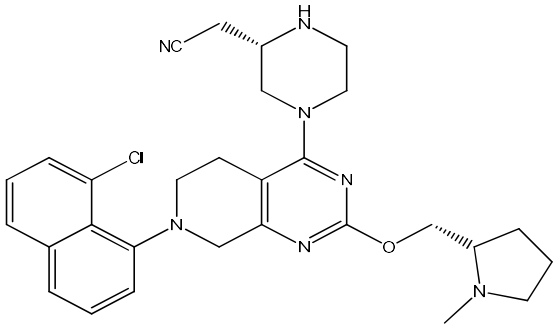


;

e) reacting the final compound of step (d) with *p*-toluenesulfonic acid in the presence of a acetone and 2-MeTHF to produce a final compound of step (e) with the following structure:



f) reacting the final compound of step (e) with 2-mercaptoethanol in the presence of K_3PO_4 and DMAc to produce a final compound of step (f) with the following structure:

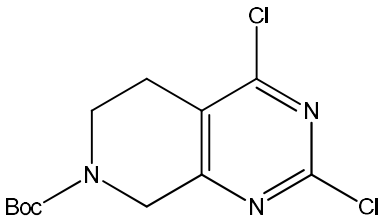


; and

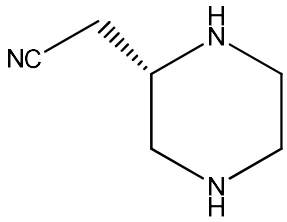
g) reacting the final compound of step (f) with the sodium salt of 2-fluoroacrylic acid in the presence of MeCN and propylphosphonic anhydride to produce adagrasib.

70. A method of synthesizing adagrasib comprising the steps of:

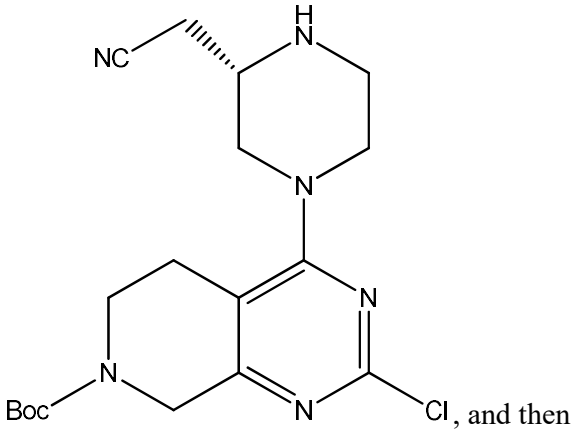
a') reacting a compound of the following structure:



with a compound of the following structure:

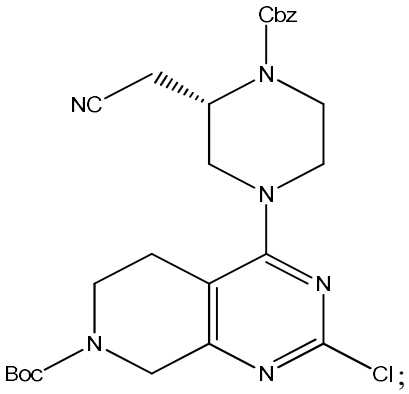


in the presence of DIPEA and DMAc to produce the compound of the following structure:



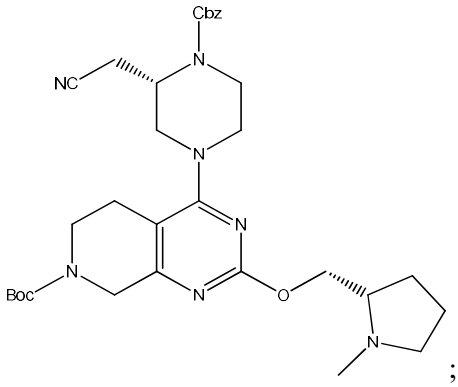
, and then

reacting this compound with benzyl chloroformate in the presence of sodium carbonate, methyl tert-butyl ether (MTBE) and water to produce a final compound of step (a') with the following structure:



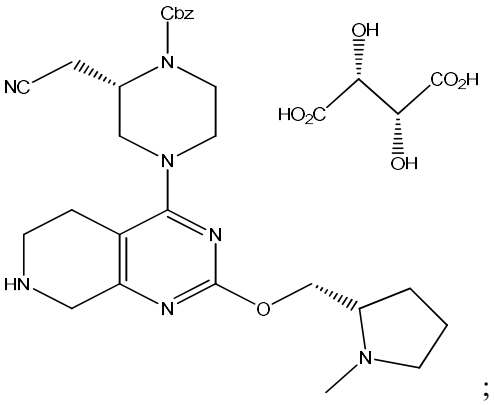
;

b) reacting the final compound of step (a') with (*S*)-(1-methylpyrrolidin-2-yl)methanol in the presence of $Pd_2(dba)_3$, Xantphos, K_3PO_4, and 2-MeTHF to produce a final compound of step (b) with the following structure:

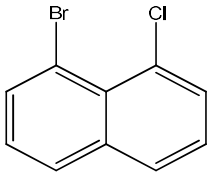


;

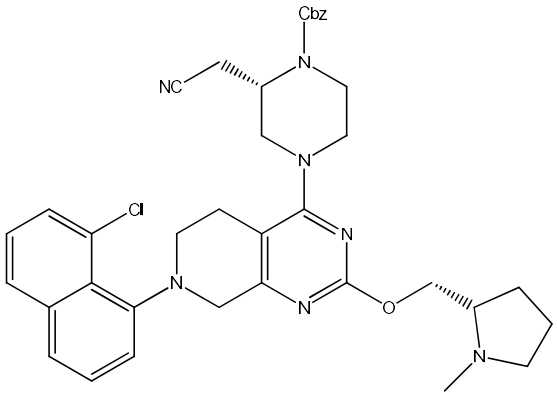
c) reacting the final compound of step (b) with a hydrochloric acid and L-tartaric acid to remove a Boc protecting group from the final compound of step (b) to produce a L-tartrate salt of a final compound of step (c) with the following structure:



;

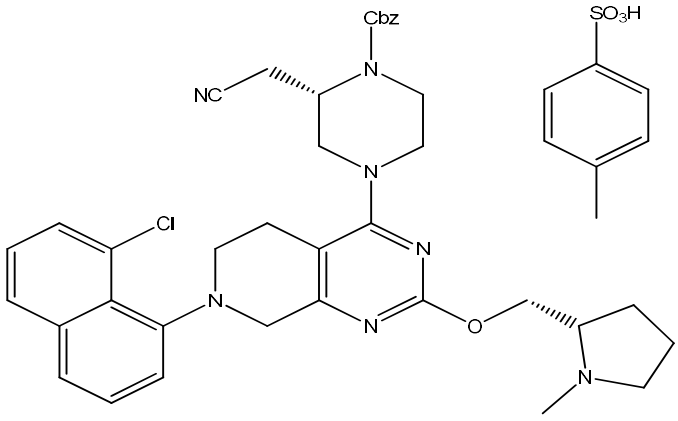
d) reacting the free base of the final product of step (c) with 

in the presence of $Pd_2(dba)_3$, (R)-BINAP, K_3PO_4, and 2-MeTHF to produce a final compound of step (d) with the following structure:

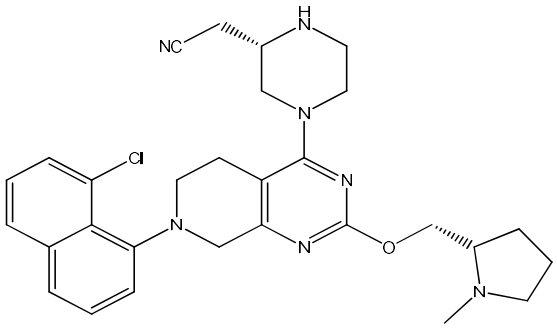


;

e) reacting the final compound of step (d) with *p*-toluenesulfonic acid in the presence of a acetone and 2-MeTHF to produce a final compound of step (e) with the following structure:



f) reacting the final compound of step (e) with 2-mercaptoethanol in the presence of K_3PO_4 and DMAc to produce a final compound of step (f) with the following structure:



; and

g) reacting the final compound of step (f) with the sodium salt of 2-fluoroacrylic acid in the presence of MeCN and propylphosphonic anhydride to produce adagrasib.