inflammation, have been shown to be mediated by receptor tyrosine kinases, such as ALK, ROS1, TRK, JAK2, SRC and FAK. For example, genetic and epigenetic alterations can accumulate in cancer cells leading to abnormal activation of signal transduction pathways which drive malignant processes. Manning, G. *et al., Science* 2002, *298*, 1912-1934. Pharmacological inhibition of these signaling pathways presents promising intervention opportunities for targeted cancer therapies. Sawyers, C., *Nature* 2004, *432*, 294-297.

[006] While Compound I has found application in treating disease associated with receptor tyrosine kinases, such as ALK, ROS1, TRK, JAK2, SRC and FAK, it is advantageous to have polymorphic forms having improved properties, such as improved crystallinity, dissolution properties, and/or decreased hygroscopicity, while maintaining chemical and enantiomeric stability properties.

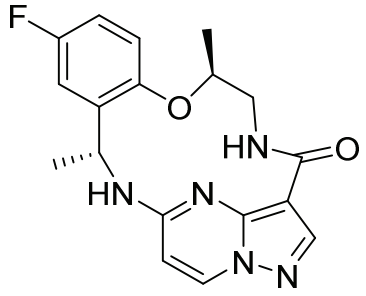
SUMMARY

[007] The present disclosure provides a crystalline form of (7S,13R)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxa-triazacyclotridecin-4(5H)-one.

[007a] In one aspect, there is provided a crystalline polymorph form of (7S,13R)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 9.4±0.1 and 27.4±0.1.

[008] In another embodiment, the crystalline polymorph form of (7S,13R)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxa-triazacyclotridecin-4(5H)-one is anhydrous.

[009] In another embodiment, the crystalline polymorph form 1 of compound I can be represented by the formula



I.

[010] In a further embodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 27.4±0.1. In a further embodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1 and 27.4±0.1. In a further embodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1, 18.8±0.1, and 27.4±0.1. In a further embodiment, the crystalline polymorph

What is Claimed is:

1. A crystalline polymorph form of (7S,13R)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1 and 27.4±0.1.

2. The crystalline polymorph form of claim 1, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1, 18.8±0.1, and 27.4±0.1.

3. The crystalline polymorph form of any one of claim 1 or 2, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1, 16.5±0.1, 18.8±0.1, and 27.4±0.1.

4. The crystalline polymorph form of any one of claims 1 to 3, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1, 16.5±0.1, 18.8±0.1, 22.8±0.1, and 27.4±0.1.

5. The crystalline polymorph form of any one of claims 1 to 4, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1, 16.1±0.1, 16.5±0.1, 18.8±0.1, 22.8±0.1, and 27.4±0.1.

6. The crystalline polymorph form of any one of claims 1 to 5, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4±0.1, 16.1±0.1, 16.5±0.1, 18.8±0.1, 21.2±0.1, 22.8±0.1, and 27.4±0.1.

7. A crystalline polymorph form of (7S,13R)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 1.

8. A pharmaceutical composition comprising the crystalline polymorph form of any one of the preceding claims.

9. Use of the crystalline polymorph form of any one of claims 1 to 7 in the manufacture of a medicament for treating a disease in a mammal, wherein the disease is selected from the group consisting of cancer, pain, neurological diseases, autoimmune diseases, and inflammation.

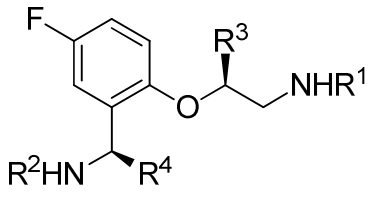
10. The use of claim 9, wherein the mammal is a human.

11. The use of claim 9 or 10, wherein the disease is cancer.

12. The use of claim 11, wherein the cancer is selected from the groups consisting of lung cancer, non-small cell lung cancer, small cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, hepatocellular carcinoma, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, gastric and esophago-gastric cancers, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, such as anaplastic large cell lymphoma, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), glioblastoma, primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, inflammatory myofibroblastic tumors, and combinations thereof.

13. The use of claim 12, wherein the cancer is non-small cell lung cancer.

14. A compound of the formula II



II

wherein R^1 and R^2 are each independently H or PG, wherein PG is a protecting group, and R^3 and R^4 are each independently C_1-C_4 alkyl.

15. The compound of claim 14, wherein R^1 and R^2 are PG.

16. The compound of claim 14, wherein R^2 is H.

17. The compound of claim 14, wherein R^1 is H.

18. The compound of claim 14 or 16, wherein R^1 is PG, and wherein PG is a protecting group.

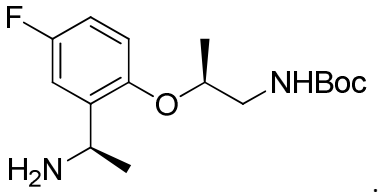
19. The compound of claim 14 or 17, wherein R^2 is PG, and wherein PG is a protecting group.

20. The compound of any one of claims 14 to 19, wherein R^3 and R^4 are methyl.

21. The compound of any one of claims 14 to 20, wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts.

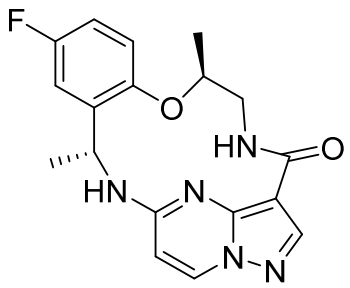
22. The compound of any one of claims 14 to 21, wherein PG is Boc.

23. A compound of the formula



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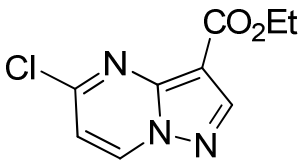
24. A process for preparing a compound of the formula I



I

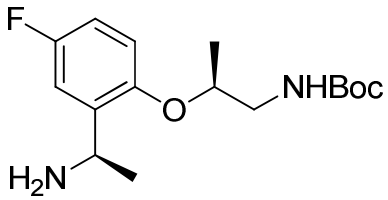
comprising

(a) contacting a compound of the formula A



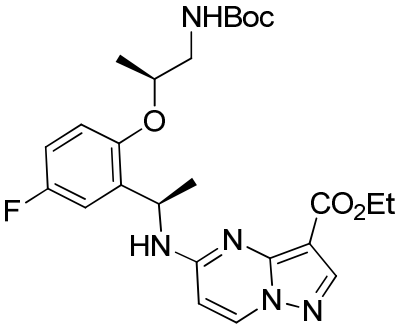
A

with a compound of the formula B-14



B-14

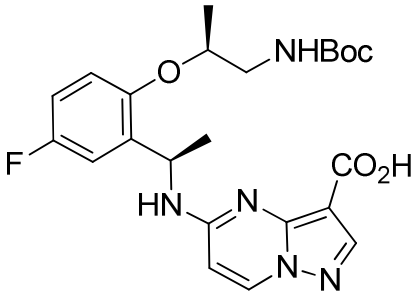
in the presence of a base to provide a compound of the formula C



; and

C

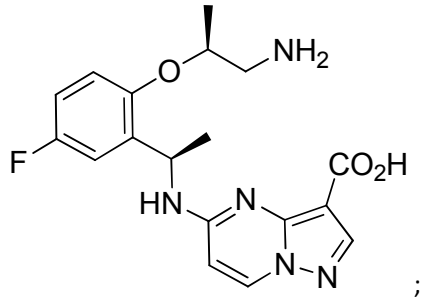
(b) contacting a compound of the formula C with an inorganic base to provide a compound of the formula D



; and/ or

D

(c) contacting a compound of the formula D with an acid to provide a compound of the formula E

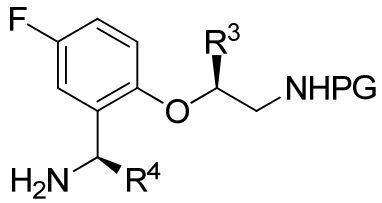


; and/ or

E

(d) contacting a compound of the formula E with a base in the presence of a phosphinate reagent to provide the compound of the formula I.

25. A process for preparing a compound of the formula B



B

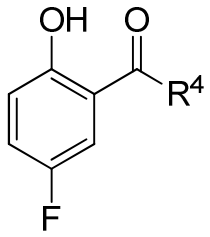
wherein

PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and

R^3 and R^4 are each independently C_1-C_4 alkyl;

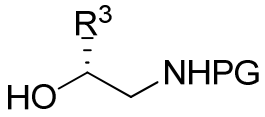
comprising

(a) contacting a compound of the formula B-1



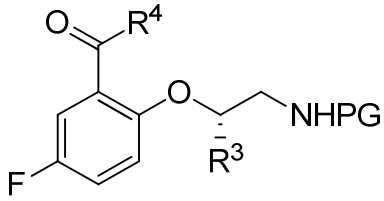
B-1

wherein R^4 is C_1-C_4 alkyl; with a compound of the formula B-2R



B-2R

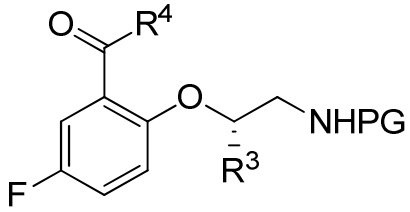
wherein R^3 is C_1-C_4 alkyl, and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; in the presence of an azodicarboxylate reagent and a phosphine reagent to provide a compound of the formula B-3



B-3

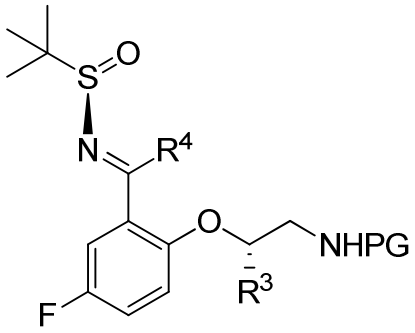
wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and R^3 and R^4 are each independently C_1-C_4 alkyl; and/ or

(b) contacting a compound of the formula B-3



B-3

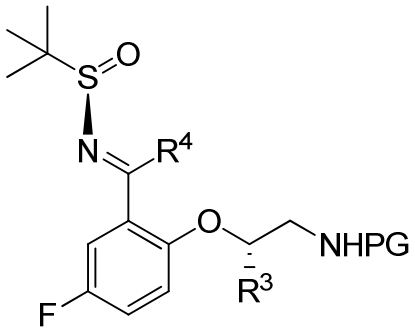
wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and R^3 and R^4 are each independently C_1-C_4 alkyl; with (R)-2-methyl-2-propanesulfinamide to provide a compound of the formula B-5



B-5

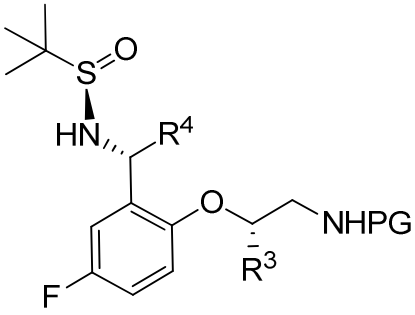
wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and R^3 and R^4 are each independently C_1-C_4 alkyl; and/ or

(c) contacting a compound of the formula B-5



B-5

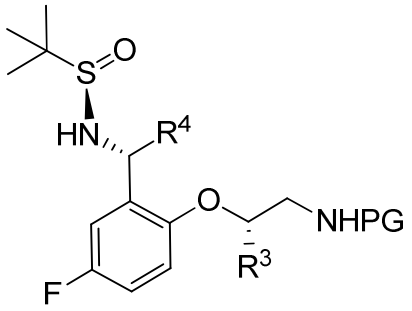
wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and R^3 and R^4 are each independently C_1-C_4 alkyl; with a reducing agent to provide a compound of the formula B-6



B-6

wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and R^3 and R^4 are each independently C_1-C_4 alkyl; and/ or

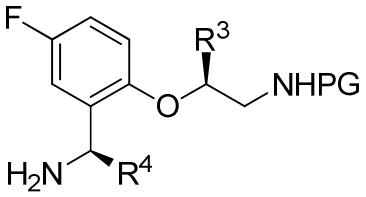
(d) contacting a compound of the formula B-6



B-6

wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and R^3 and R^4 are each independently C_1-C_4 alkyl; with an iodine reagent to provide a compound of the formula B.

26. A process for preparing a compound of the formula B



B

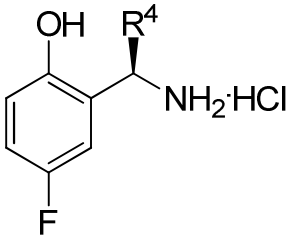
wherein

PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and

R^3 and R^4 are each independently C_1-C_4 alkyl;

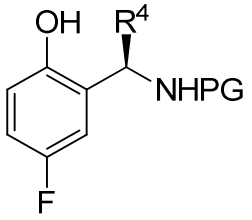
comprising

(a) reacting a compound of the formula B-7



B-7

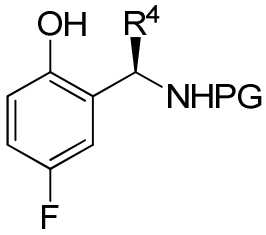
wherein R^4 is C_1-C_4 alkyl; under conditions suitable for preparing a compound of the formula B-8



B-8

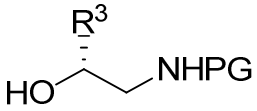
wherein R^4 is C_1-C_4 alkyl; and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and/ or

(b) contacting a compound of the formula B-8



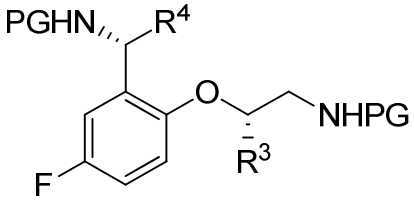
B-8

wherein R^4 is C_1-C_4 alkyl; and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; with a compound of the formula B-2R



B-2R

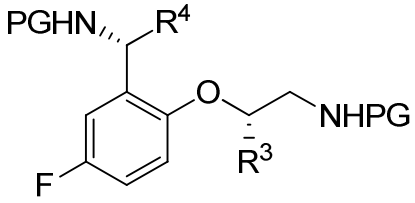
wherein R^3 is C_1-C_4 alkyl, and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; in the presence of an azodicarboxylate reagent and a phosphine reagent to provide a compound of the formula B-9



B-9

wherein each PG is independently selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts, provided that each PG is different; and R^3 and R^4 are each independently C_1-C_4 alkyl; and/ or

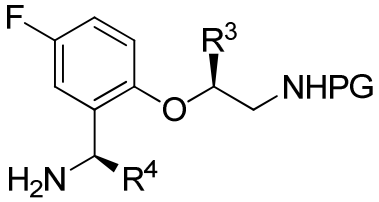
(c) contacting a compound of the formula B-9



B-9

wherein each PG is independently selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts, provided that each PG is different; and R^3 and R^4 are each independently C_1-C_4 alkyl; with an inorganic base to provide a compound of the formula B.

27. A process for preparing a compound of the formula B



B

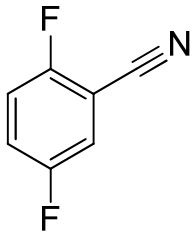
wherein

PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and

R^3 and R^4 are each independently C_1-C_4 alkyl;

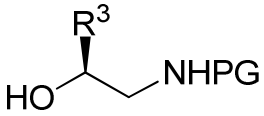
comprising

(a) reacting a compound of the formula B-10



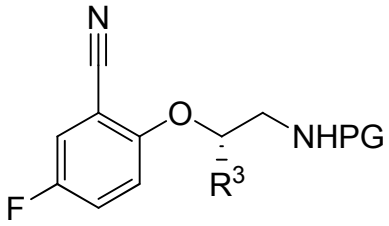
B-10

with a compound of the formula B-2S



B-2S

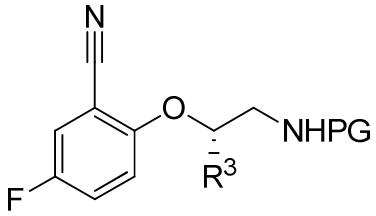
wherein R^3 is C_1-C_4 alkyl, and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; in the presence of a base to provide a compound of the formula B-11



B-11

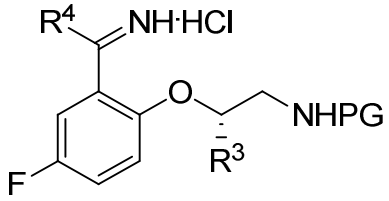
wherein R^3 is C_1-C_4 alkyl, and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and/ or

(b) contacting a compound of the formula B-11



B-11

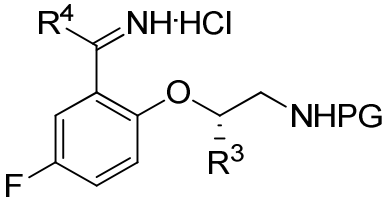
wherein R^3 is C_1-C_4 alkyl, and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; with a nucleophile to provide a compound of the formula B-12



B-12

wherein R^3 and R^4 are each independently C_1-C_4 alkyl, and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and/ or

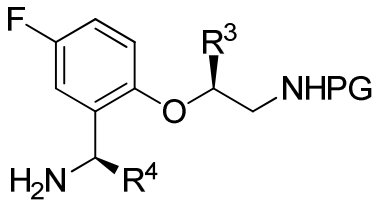
(c) contacting a compound of the formula B-12



B-12

wherein R^3 and R^4 are each independently C_1-C_4 alkyl, and PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; with a reducing agent to provide a compound of the formula B.

28. A process for preparing a compound of the formula B



B

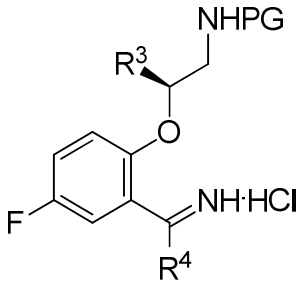
wherein

PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; and

R^3 and R^4 are each independently C_1-C_4 alkyl;

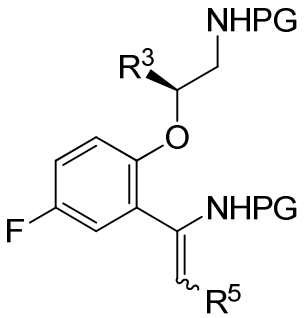
comprising

(a) reacting a compound of the formula B-12



B-12

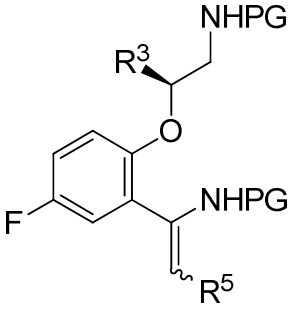
wherein PG is selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; R^3 and R^4 are each independently C_1-C_4 alkyl; under conditions suitable for preparing a compound of the formula B-13



B-13

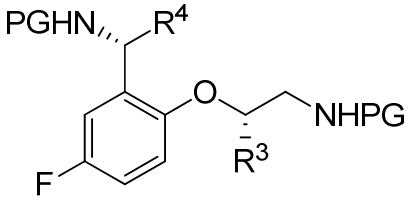
wherein each PG is independently selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts, provided that each PG is different; R^3 is C_1-C_4 alkyl; and R^5 is C_1-C_3 alkyl; and/ or

(b) contacting a compound of the formula B-13



B-13

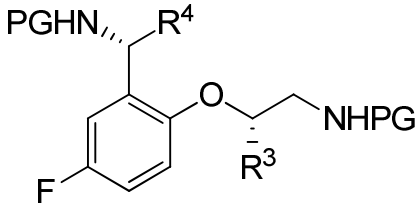
wherein each PG is independently selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts, provided that each PG is different; R^3 is C_1-C_4 alkyl; and R^5 is C_1-C_3 alkyl; with a reducing agent to provide a compound of the formula B-9



B-9

wherein each PG is independently selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts, provided that each PG is different; and R^3 and R^4 are each independently C_1-C_4 alkyl; and/ or

(c) contacting a compound of the formula B-9



B-9

wherein each PG is independently selected from the group consisting of FMOC, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts, provided that each PG is different; and R^3 and R^4 are each independently C_1-C_4 alkyl; with an inorganic base to provide a compound of the formula B.