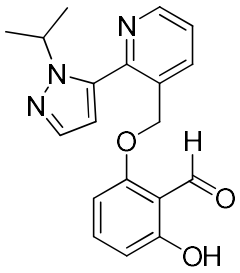
What is claimed is:

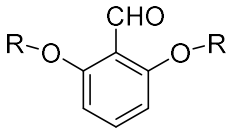
1. A process of synthesizing Compound (I):



(I)

the process comprising:

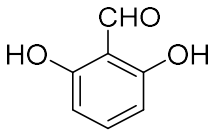
Step (i): treating a compound of formula (2):



(2)

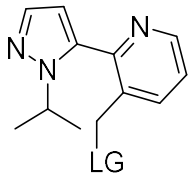
wherein each R is $–CH(CH_2R^1)-OR^2$ or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl; and wherein each R^1 is independently hydrogen or alkyl, and each R^2 is independently alkyl;

with an acid to provide compound (1):



(1)

Step (ii): reacting compound (1) with a compound of formula (3)



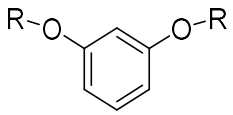
(3)

wherein LG is a leaving group under alkylation reaction conditions to provide Compound (I).

2. The process of claim 1 further comprising:

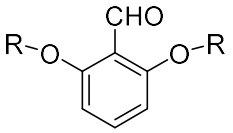
Step (iii): crystallizing Compound (I) from Step (ii) from heptane and methyl *tert*-butyl ether at 45° +/- 5 °C to 55° +/- 5 °C.

3. The process of claim 1 or 2 further comprising formylating a compound of formula (4):



(4)

to provide the compound of formula (2):

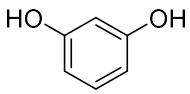


(2)

wherein each R in compound of formulae (2) and (4) is $–CH(CH_2R^1)-OR^2$ or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl; and

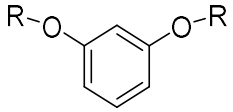
each R^1 is independently hydrogen or alkyl, and each R^2 is independently alkyl.

4. The process of claim 3 further comprising reacting compound (5):



(5)

with a vinyl ether of formula $CHR^1=CHOR^2$ (wherein R^1 is hydrogen or alkyl and R^2 is alkyl), or 3,4-dihydro-2H-pyran optionally substituted with one, two or three alkyl, in the presence of a weak acid to provide the compound of formula (4):



(4)

wherein each R is $–CH(CH_2R^1)-OR^2$ (where each R^1 is independently hydrogen or alkyl and each R^2 is independently alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl.

5. The process of claim 4 wherein compound (4) is treated *in situ* with a formylating agent to provide compound (2).

6. The process of any one of claims 1 to 3 wherein compound (2) is treated *in situ* with an acid to provide compound (1).

7. The process of any one of claims 1 to 6 wherein Compound (I) is crystallized from heptane and methyl *tert*-butyl ether at 45º +/- 5 ºC to 55 +/- 5 ºC to give Compound (I) in substantially pure Form II characterized by an XRPD pattern comprising X-ray powder diffraction peaks (Cu Kα radiation) at 13.37°, 14.37°, 19.95° and 23.92°, °2θ (each ± 0.2 °2θ).

8. The process of claim 7 wherein Compound (I) is crystallized at 45 ºC to 55 ºC to give Compound (I) wherein at least 95% by weight of Compound (I) is Form II.

9. The process of any one of claims 1 to 8 wherein LG is chloro.

10. The process of any one of claims 1 to 9 wherein R is $–CH(CH_3)-O-CH_2CH_3$.

11. The process of any one of claims 1 to 10 wherein the acid for removal of the R groups is an inorganic acid.

12. The process of claim 11 wherein the acid is hydrochloric acid.

13. The process of any one of claims 1 to 12 wherein LG is chloro and the alkylation reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and a catalytic amount of NaI.

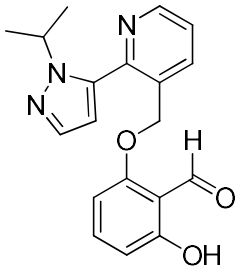
14. The process of any one of claims 1 to 12 wherein LG is chloro and the alkylation reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and a catalytic amount of NaI and Compound (I) is crystallized from the reaction mixture by addition of water at 40 ºC to 50º C to give substantially pure Form I characterized by an XRPD pattern comprising at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44°, °2θ (each ± 0.2 °2θ).

15. The process of any one of claims 1 to 12 wherein LG is chloro and the alkylation reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and a catalytic amount of NaI and Compound (I) is crystallized from the reaction mixture by addition of water at 40 °C to 46° C to give Compound (I) that is at least 95% by weight Form I characterized by an XRPD pattern comprising at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44°, °2θ (each ± 0.2 °2θ).

16. The process of any one of claims 4 to 15 wherein the weak acid is pyridinium tosylate.

17. The process of any one of claims 3 to 16 wherein the formylating agent is n-BuLi and DMF.

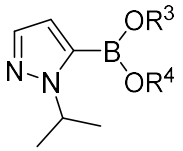
18. A process of synthesizing Compound (I):



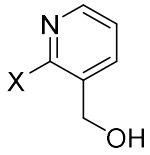
(I)

comprising:

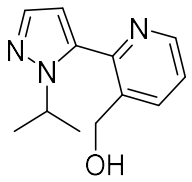
(i) reacting a boronic acid compound of formula:



wherein R^3 and R^4 are each independently alkyl or together form $–(CR'R")_2$ where R' and R" are each independently alkyl; with a compound of formula:

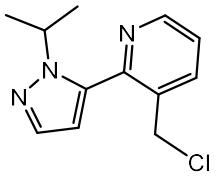


wherein X is halo or triflate, in the presence of a palladium catalyst and a base in an organic/aqueous reaction mixture to form compound (6):



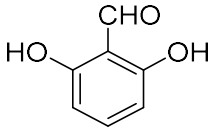
(6);

(ii) contacting compound (6) with sodium bicarbonate and a chlorinating agent to provide compound (3a):



(3a)

(iii) reacting compound (3a) with compound (1):



(1)

under alkylation reaction conditions to provide Compound (I).

19. The process of claim 18, further comprising crystallizing Compound (I) from heptane and methyl *tert*-butyl ether at 45º +/- 5 ºC to 55º +/- 5 ºC.