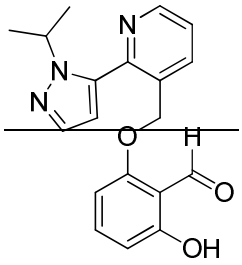
What is claimed is:

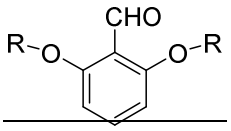
~~1. A process of synthesizing Compound (I):~~



~~(I)~~

~~the process comprising:~~

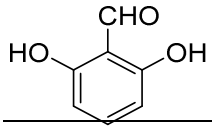
~~Step (i): treating a compound of formula (2):~~



~~(2)~~

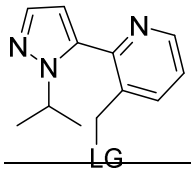
~~wherein each R is $-CH(CH_2R^1)-OR^2$ or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl; and wherein R^1 is hydrogen or alkyl, and R^2 is alkyl;~~

~~with an acid to provide compound (1):~~



~~(1)~~

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

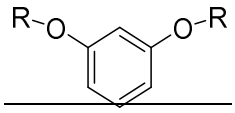


~~(3)~~

~~wherein LG is a leaving group under alkylation reacting conditions to provide Compound (I); and~~

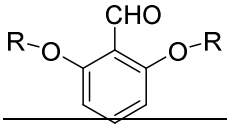
~~Step (iii): optionally crystallizing Compound (I) from Step (ii) from heptane and methyl *tert* butyl ether at 45º +/- 5 ºC to 55º +/- 5 ºC.~~

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



~~(4)~~

~~to provide the compound of formula (2):~~

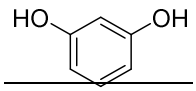


~~(2)~~

~~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~~

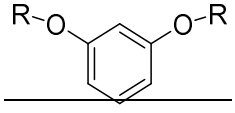
~~R^1 is hydrogen or alkyl, and R^2 is alkyl.~~

~~3. The process of claim 2 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 R^1 is hydrogen or alkyl and R^2 is alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl.~~

4. The process of claim 3 wherein compound (4) is treated *in situ* with a formylating agent to provide compound (2).

5. The process of claim 1 or 2 wherein compound (2) is treated *in situ* with an acid to provide compound (1).

6. The process of any one of claim 1 to 5 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 a XRPD pattern comprising a X-ray powder diffraction peak (Cu Kα radiation) at one or more of 13.37°, 14.37°, 19.95° or 23.92 ±0.2 °2θ.

7. The process of claim 6 wherein Compound (I) is crystallized at 45 ºC to 55 ºC to give Compound (I) wherein at least 95% by wt of Compound (I) is Form II.

8. The process of any one of claims 1 to 7 wherein LG is chloro.

9. The process of any one of claims 1-8 wherein R is $-CH(CH_3)-O-CH_2CH_3$.

10. The process of any one of claims 1-9 wherein the acid for removal of the R groups is an inorganic acid.

11. The process of claim 10 wherein the acid is hydrochloric acid.

12. The process of any one of claims 1-11 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.

13. The process of any one of claims 1-11 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 a XRPD pattern comprising a X-ray powder diffraction peak (Cu Kα radiation) at one or more of 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44° ±0.2 °2θ.

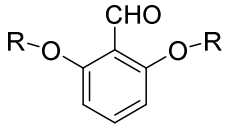
14. The process of any one of claims 1-11 wherein LG is chloro and the alkylation reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and a catalytic amount of NaI and Compound (I) is crystallized from the reaction mixture by addition of water at 40 ºC to 46º C to give Compound (I) that at least 95% by weight Form I characterized

~~by a XRPD pattern comprising a X-ray powder diffraction peak (Cu Kα radiation) at one or more of 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44° ±0.2 °2θ.~~

~~15. The process of any one of claims 3-14 wherein the weak acid is pyridinium tosylate.~~

~~16. The process of any one of claims 2-15 wherein the formylating agent is n-BuLi and DMF.~~

~~17~~1. A compound~~An intermediate~~ of formula (2):



(2)

wherein each R is $–CH(CH_2R^1)OR^2$; and

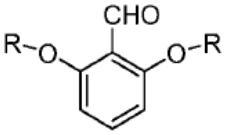
wherein each R^1 is independently hydrogen or alkyl, and each R^2 is independently alkyl.

2. The compound of claim 1, wherein each R is independently $-CH(CH_3)-O-CH_2CH_3$ or $-CH(CH_2CH_3)-O-CH_2CH_3$.

3. The compound of claim 1 or 2, wherein each R is $-CH(CH_3)-O-CH_2CH_3$.

4. The compound of claim 1 or 2, wherein each R is $-CH(CH_2CH_3)-O-CH_2CH_3$.

5. A method of preparing the compound of formula (2):

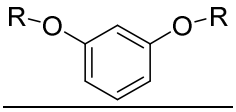


(2)

wherein each R is $-CH(CH_2R^1)OR^2$, and

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

comprising treating a compound of formula (4)



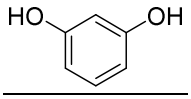
(4)

with a formylating agent to provide the compound of formula (2).

6. The method of claim 5, wherein the formylating agent is n-butyllithium (n-BuLi) and dimethylformamide (DMF).

7. The method of claim 5, wherein the formylating agent is N-formylmorpholine.

8. The method of claim 5, further comprising reacting compound (5):



(5)

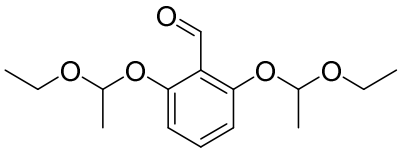
with a vinyl ether of formula $CHR^1=CHOR^2$ in the presence of a weak acid to provide a compound of formula (4);

wherein the compound of formula (4) is treated *in situ* with the formylating agent to provide the compound of formula (2).

9. The method of claim 8, wherein the formylating agent is n-butyllithium and dimethylformamide.

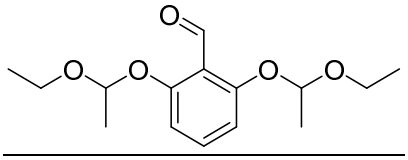
10. The method of claim 8, wherein the formylating agent is N-formylmorpholine.

11. A compound of formula (2a):



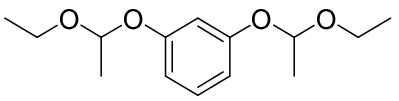
(2a).

12. A method of preparing a compound of formula (2a)



(2a),

comprising treating a compound of formula (4a)



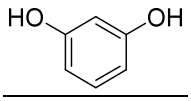
(4a)

with a formylating agent to provide the compound of formula (2a).

13. The method of claim 12, wherein the formylating agent is n-butyllithium and dimethylformamide.

14. The method of claim 12, wherein the formylating agent is N-formylmorpholine.

15. The method of claim 12, further comprising reacting compound (5):



(5)

with ethyl vinyl ether in the presence of a weak acid to provide a compound of formula (4a);

wherein the compound of formula (4a) is treated *in situ* with the formylating agent to provide the compound of formula (2a).

16. The method of claim 15, wherein the formylating agent is n-butyllithium and dimethylformamide.

17. The method of claim 15, wherein the formylating agent is N-formylmorpholine.