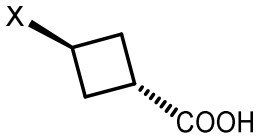
fully stereospecific Deoxybromination process eliminates chromatography which results in higher yields and greater faster throughput to prepare compound (1), specifically compound (1a).

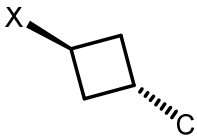
[0011] Overall, the present inventors have invented a new process for the manufacture of compounds of formula (1) and (2) which offer a number of relevant benefits as compared to processes known in the art in the following ways: (a) A highly stereoselective reaction; (b) Subsequent purification using chiral chromatography is eliminated; (c) Improved overall yield; (d) More efficient, greener and less costly overall reaction; and (e) Scalable reactions.

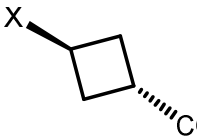
SUMMARY

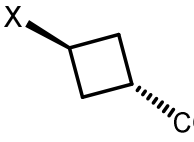
[0012] A first example of the present disclosure provides a stereoselective, improved, safer, cost effective and scalable process for the preparation of a compound having formula (2):



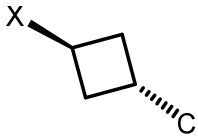
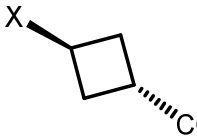
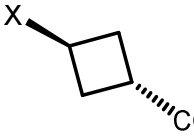
(2); wherein X is halo; or a pharmaceutically acceptable salt thereof.

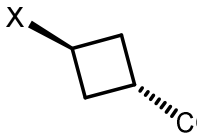
[0012a] In one example, the present disclosure provides a stereoselective process for the preparation of a compound of formula (1): 

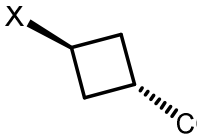
(1); comprising: (a) contacting a compound of formula (3): 

(3) with an ester hydrolyzing agent in a first solvent; to form a compound of formula (2): 

(2); followed by a process of purifying said compound (2) by: (a1) contacting said compound (2) with a base in a second solvent to form a salt of compound (2); and (a2) contacting said salt of compound (2) with an acid in a third solvent at a low temperature to form a purified form of compound (2); and contacting said purified form of compound (2) with a trifluoromethylating agent in an organic fourth solvent to form said compound of formula (1), wherein X is halo and $COOR^1$ is an ester group.

In one aspect, the present disclosure provides a stereoselective process for the preparation of a compound of formula (1):  (1); comprising: (a) contacting a compound of formula (3):  (3) with an ester hydrolyzing agent in a first solvent; to form a compound of formula (2):  (2); followed by a process of purifying said compound (2) by: (a1) contacting said compound (2) with a base in a second solvent to form a salt of compound (2) as a solid; and (a2) contacting said salt of compound (2) with an acid in a third solvent at a low temperature to form a purified form of compound (2); and contacting said purified form of compound (2) with a trifluoromethylating agent in an organic fourth solvent to form said compound of formula (1), wherein X is halo and R^1 is (C_1-C_6)alkyl, phenyl, or benzyl.

[0013] In example 1, the present disclosure provides a stereoselective process for the preparation of a compound having formula (2):  (2); wherein X is halo; comprising

[0014] (a) contacting a compound of formula (3):  (3); wherein X is as defined above in compound (2); and $COOR^1$ is an ester group; with an ester hydrolyzing agent in a solvent; to form said compound (2); and optionally followed by a process of purifying said compound (2) by

[0015] (a1) contacting said compound (2) with a base in a solvent to form a salt of compound (2); and

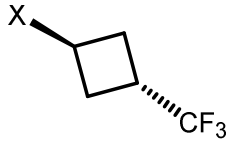
[0016] (a2) contacting said salt of compound (2) with an acid in a solvent at a low temperature to form a purified form of compound (2). Preferably, the process of purifying said compound (2) is performed.

[0017] In example 1a, the present disclosure provides the process according to example 1, further comprising preparing said compound (3) comprising:

CLAIM:

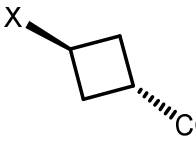
What is claimed is:

1. A stereoselective process for the preparation of a compound of formula (1):

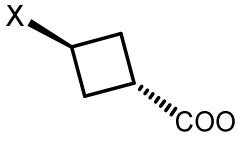


(1); comprising:

(a) contacting a compound of formula (3):



(3) with an ester hydrolyzing agent in a first solvent; to form a compound of formula (2):



(2); followed by a process of purifying said compound (2) by:

(a1) contacting said compound (2) with a base in a second solvent to form a salt of compound (2) as a solid; and

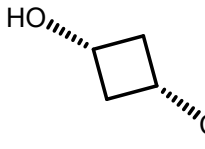
(a2) contacting said salt of compound (2) with an acid in a third solvent at a low temperature to form a purified form of compound (2); and

contacting said purified form of compound (2) with a trifluoromethylating agent in an organic fourth solvent to form said compound of formula (1),

wherein X is halo and R^1 is (C_1-C_6)alkyl, phenyl, or benzyl.

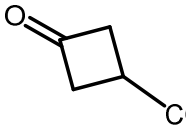
2. The process according to claim 1, wherein compound (3) is prepared by a process comprising:

(b) contacting a compound of formula (4):



(4) with a deoxyhalogenating agent in an organic fifth solvent, optionally at a low temperature, to form said compound (3).

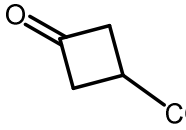
3. The process according to claim 2, wherein said compound (4) is prepared by a process comprising:

(c) contacting a compound of formula (5):  (5) with:

(c1) a metal catalyst in an organic sixth solvent at a low temperature; or

(c2) a biocatalytic agent in an organic seventh solvent and in the presence of a buffer solution; to form said compound (4).

4. The process according to claim 3, wherein compound (5) is prepared by a process comprising:

(d) contacting a compound of formula (6):  (6) with an R^1 agent, in the presence of a base and an organic eighth solvent, to form said compound (5).

5. The process according to any one of claims 1 to 4, wherein X is bromo or iodo; or wherein X is bromo.

6. The process according to any one of claims 1 to 5, wherein R^1 is benzyl.

7. The process according to any one of claims 1 to 4, wherein X is bromo and R^1 is benzyl.

8. The process according to any one of claims 1 to 7, wherein in (a):

(i) said ester hydrolyzing agent is an alkali metal hydroxide or a lipase enzyme;

(ii) said ester hydrolyzing agent is an alkali metal hydroxide and said first solvent is a mixture of methyl-THF and water;

(iii) said ester hydrolyzing agent is sodium hydroxide, potassium hydroxide, or lithium hydroxide;

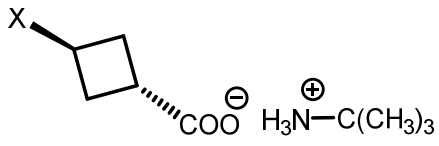
(iv) said ester hydrolyzing agent is lithium hydroxide or sodium hydroxide; or

(v) said ester hydrolyzing agent is a lipase enzyme and said first solvent is acetone or (C_1-C_6)alcohol.

9. The process according to any one of claims 1 to 8, wherein in (a1):

(i) said base is a primary, secondary, or tertiary amine base;

(ii) said base is *tert*-butyl amine and said salt of compound (2) has a formula:



(2-*tert*-butyl amine salt); or

(iii) said second solvent is a mixture of n-heptane and MTBE.

10. The process according to any one of claims 1 to 9, wherein in (a2):

(i) said acid is sulphuric acid, phosphoric acid, or acid halide selected from HCl or HBr; or

(ii) said third solvent is water.

11. The process according to any one of claims 2 to 10, wherein in (b):

(i) said deoxyhalogenating agent is triphenyl phosphite in the presence of NBS; or triphenyl phosphine in the presence of NBS; or

(ii) said organic fifth solvent is DMF, acetonitrile, toluene, or dichloromethane.

12. The process according to any one of claims 3 to 11, wherein in (c1):

(i) said metal catalyst is a metal hydride; or

(ii) said sixth solvent is THF, acetonitrile, toluene, dichloromethane, (C_1-C_8)alcohol, or any mixtures thereof.

13. The process according to any one of claims 3 to 12, wherein in (c2):

(i) said biocatalytic agent is a ketoreductase enzyme;

(ii) said seventh solvent is (C_1-C_8)alcohol, or a mixture of water and (C_1-C_8)alcohol;

(iii) said buffer is selected from phosphate, triethanolamine, PIPES, BICINE, TES, TRIS, HEPES, TRICINE, CHES, or CAPS; or

(iv) said buffer is triethanolamine.

14. The process according to any one of claims 4 to 13, wherein in (d):

(i) said R^1 agent is (C_1-C_6)alkyl halide, phenyl halide, or benzyl halide;

(ii) said base is a bicarbonate, carbonate, or tri(C_1-C_6)alkylamine base; or

(iii) the eighth solvent is dichloromethane, DMF, THF, or acetonitrile.

15. The process according to any one of claims 1 to 14, wherein said trifluoromethylating agent is sulfur tetrafluoride (SF_4) and hydrogen fluoride (HF), and wherein said organic fourth solvent is dichloromethane.