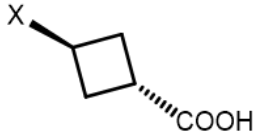
fully stereospecific Deoxybromination process eliminates chromatography which results in higher yields and greater faster throughput to prepare compound (1), specifically compound (1a).

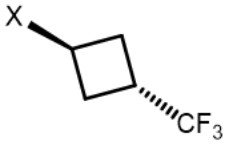
[0011] Overall, the present inventors have invented a new process for the manufacture of compounds of formula (1) and (2) which offer a number of relevant benefits as compared to processes known in the art in the following ways: (a) A highly stereoselective reaction; (b) Subsequent purification using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

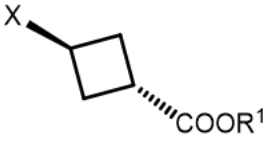
SUMMARY

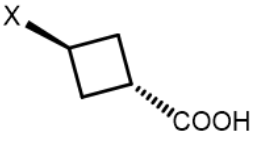
[0012] A first example of the present disclosure provides a stereoselective, improved, safer, cost effective and scalable process for the preparation of a compound having formula (2):



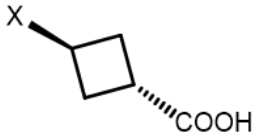
(2); wherein X is halo; or a pharmaceutically acceptable salt thereof.

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

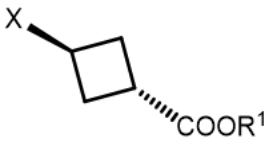
(1); comprising: (a) contacting a compound of formula (3): 

(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); 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.

[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

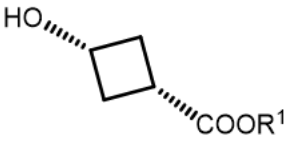
[0014] (a) contacting a compound of formula (3): 

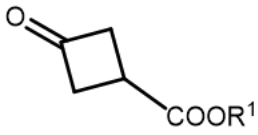
(3); wherein X is as defined above in compound (2); and $COOR^1$ is an ester group; with an ester hydrolyzing agent in a solvent; to form said compound (2); and optionally followed by a process of purifying said compound (2) by

[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:

[0018] (b) contacting a compound of formula (4):  (4); wherein said R^1 is as defined above in compound (3); with a deoxyhalogenating agent in an organic solvent, optionally at a low temperature, to form said compound (3).

[0019] In example 1b, the present disclosure provides the process according to examples 1 and 1a, further comprising preparing said compound (4) comprising: contacting a compound of formula (5):  (5); wherein said R^1 is as defined above in compound (4) with;

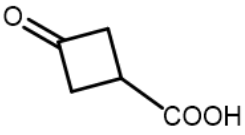
[0020] (c1) a metal catalyst in an organic solvent at a low temperature; or

[0021] (c2) a biocatalytic agent in an organic solvent and in the presence of a buffer solution; to form said compound (4).

[0022] Preferably, the process (c1) provides a higher than 90% stereomeric selectivity; more preferably higher than 95% stereomeric selectivity; for the *cis* configuration of the compound (4) product.

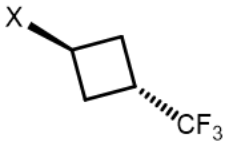
[0023] Preferably, the process (c2) provides a higher than 95% stereomeric selectivity; more preferably higher than 99% stereomeric selectivity; for the *cis* configuration of the compound (4) product.

[0024] In example 1c, the present disclosure provides the process according to examples 1, 1a, and 1b, further comprising preparing compound (5) comprising:

[0025] (d) contacting a compound of formula (6):  (6); with an R^1 agent, in the presence of a base; wherein R^1 is as defined above in compound (5); in an organic solvent to form said compound (5).

[0026] Another example of the present disclosure provides a stereoselective, improved, safer, cost effective and scalable process for the preparation of a compound having of formula (1) from said compound of formula (2).

[0027] In this example of the disclosure, in example 2, the present disclosure provides the process according to example 1, including any of sub-examples 1a-1c, further

comprising preparing a compound of formula (1):  (1); wherein said X is as defined above in compound (2); comprising: contacting said compound (2) with a trifluoromethylating agent in an organic solvent to form said compound of formula (1).

[0028] In example 3, the present disclosure provides the process according to examples 1, 1a-1c, or 2, wherein X is bromo or iodo. Preferably, X is bromo.

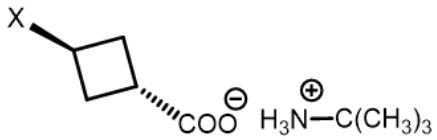
[0029] In example 4, the present disclosure provides the process according to examples 1, 1a-1c, 2, or 3, wherein R^1 is (C_1-C_6)alkyl, phenyl, or benzyl. Preferably, R^1 is benzyl.

[0030] In example 5, the present disclosure provides the process according to examples 1, 1a-1c, 2, 3, or 4, wherein in (a), said solvent is a mixture of methyl-THF and water.

[0031] In example 5a, in (a), said ester hydrolyzing agent is an alkali metal hydroxide or a lipase enzyme.

[0032] In example 5b, in (a), said ester hydrolyzing agent is alkali metal hydroxide and said solvent is a mixture of methyl-THF and water. In this example, preferably, the ester hydrolyzing agent is sodium hydroxide, potassium hydroxide, or lithium hydroxide. In this example, more preferably, said ester hydrolyzing agent is lithium hydroxide or sodium hydroxide.

[0033] In example 5c, in (a), said ester hydrolyzing agent is a lipase enzyme and said solvent is acetone or isopropyl alcohol. In this example, preferably, said ester hydrolyzing agent is amano lipase enzyme.

[0034] In example 6, the present disclosure provides the process according to examples 1, 1a-1c, 2, 3, 4, or 5, wherein in (a1), said base is a primary, secondary, or tertiary amine base. Preferably, said base is *tert*-butyl amine and said salt of compound (2) has a formula:  (2-*tert*-butyl amine salt). In this example, said salt of compound (2) is a non-hygroscopic salt.

[0035] In example 6a, in (a1), said solvent is a mixture of n-heptane and MTBE.

[0036] In example 7, the present disclosure provides the process according to examples 1, 1a-1c, 2, 3, 4, 5, 5a, 5b, 5c, 6, or 6a, wherein in (a2), said acid is sulphuric acid,

phosphoric acid, or acid halide selected from HCl or HBr. In this example, preferably said acid is halide acid selected from HCl, or HBr.

[0037] In example 7a, in (a2), said solvent is water.

[0038] In example 7b, in (a2), said at a low temperature is between 0°C to -5°C; or 0°C.

[0039] In example 8, the present disclosure provides the process according to examples 1, 1a-1c, 2, 3, 4, 5, 5a, 5b, 5c, 6, 6a, 7, 7a, or 7b, wherein in (b), said deoxyhalogenating agent is triphenyl phosphite in the presence of NBS; or triphenyl phosphine in the presence of NBS. Preferably, the deoxyhalogenating agent is triphenyl phosphite in the presence of NBS.

[0040] In example 8a, in (b), said organic solvent is DMF, acetonitrile, toluene, or dichloromethane.

[0041] In example 8b, in (b), said low temperature is below 0°C; or between -10°C to -5°C.

[0042] In example 9, the present disclosure provides the process according to examples 1, 1a-1c, 2, 3, 4, 5, 5a, 5b, 5c, 6, 6a, 7, 7a, 8, 8a, or 8b, wherein in (c1), said metal catalyst is a metal hydride.

[0043] In example 9a, in (c1), said metal hydride is sodium borohydride, lithium aluminum hydride, $LiAl(OtBu)_3$ or diisobutylaluminium hydride (DIBAL-H). Preferably, said metal hydride is $LiAl(OtBu)_3$.

[0044] In example 9b, in (c1), said solvent is THF, acetonitrile, toluene, dichloromethane, or (C_1-C_8)alcohol selected from methanol, ethanol, or isopropyl alcohol, or any mixtures thereof.

[0045] In example 9c, in (c1), said low temperature is between -78°C to -5°C; or between -10°C to -5°C; or 0°C. Preferably, said low temperature is 0°C.

[0046] In example 9d, in (c1), the metal hydride is DIBAL-H and said low temperature is -78°C.

[0047] In example 9e, in (c1), the metal hydride is $LiAl(OtBu)_3$ and said low temperature is between -10°C to -5°C; or 0°C.

[0048] In example 10, the present disclosure provides the process according to examples 1, 1a-1c, 2, 3, 4, 5, 5a, 5b, 5c, 6, 6a, 7, 7a, 8, 8a, 8b, 9, 9a, 9b, 9c, 9d, or 9e wherein in (c2), said biocatalytic agent is a ketoreductase enzyme.

[0049] In example 10a, in (c2), said ketoreductase enzyme is KRED, such as KRED-P3-G09, in the presence of a co-factor, including $NADP^+$.

[0050] In example 10b, in (c2), said solvent is (C_1-C_8)alcohol, or a mixture of water and (C_1-C_8)alcohol. Preferably, said solvent is methanol, ethanol, isopropanol, or any mixtures thereof.

[0051] In example 10c, in (c2), said buffer is triethanol amine buffer, potassium phosphate buffer, sodium phosphate buffer, potassium dihydrogen sulphate buffer, potassium sulphate buffer, sodium tetraethylborate buffer, or sodium tetraborate buffer. Preferably, said buffer is said buffer is triethanol amine buffer.

[0052] In example 11, the present disclosure provides the process according to examples 1, 1a-1c, 2, 3, 4, 5, 5a, 5b, 5c, 6, 6a, 7, 7a, 8, 8a, 8b, 9, 9a, 9b, 9c, 9d, 9e, 10, 10a, 10b, and 10c, wherein in (d), said R^1 agent is (C_1-C_6)alkyl halide, phenyl halide, or benzyl halide.

[0053] In example 11a, in (d), said R^1 agent is benzyl bromide.

[0054] In example 11b, (d) is performed in the presence of a base, wherein said base is a bicarbonate, carbonate, or tri(C_1-C_6)alkylamine base. Preferably, the base is bicarbonate or carbonate base.

[0055] In example 11c, in (d), said solvent is dichloromethane, DMF, THF, or acetonitrile. Preferably, said solvent is DMF.

[0056] In example 11d, (d) is performed at room temperature.

[0057] In example 12, the present disclosure provides the process according to example 2, wherein said trifluoromethylating agent is sulfur tetrafluoride (SF_4), in the presence of hydrogen fluoride (HF), and optionally in the presence of a solvent.

[0058] In example 12a, the present disclosure provides the process according to example 2, wherein said trifluoromethylating agent is sulfur tetrafluoride (SF_4), in the presence of hydrogen fluoride (HF), and said process is performed in the presence of dichloromethane.

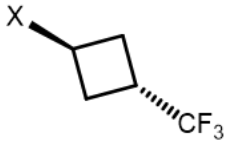
[0059] In example 12b, the present disclosure provides the process according to example 2, wherein said process is performed at a temperature between -78^{o}C to 30^{o}C. Preferably, the temperature is maintained under 30^{o}C.

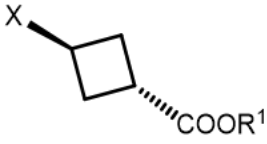
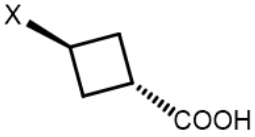
DETAILED DESCRIPTION

[0001] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

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:

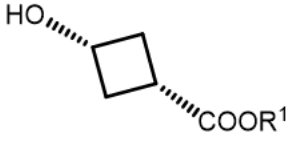
(a1) contacting said compound (2) with a base in a second solvent to form a salt of compound (2); and

(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

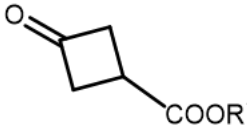
contacting said purified form of compound (2) with a trifluoromethylating agent in an organic fourth solvent to form said compound of formula (1),

wherein X is halo and $COOR^1$ is an ester group.

2. The process according to claim 1, further comprising preparing, prior to step (a), said compound (3) by a method 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).

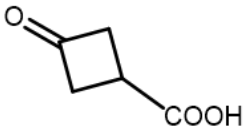
3. The process according to claim 2, further comprising, prior to step (b), preparing said compound (4) by a method comprising:

(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, further comprising, prior to step (c), preparing compound (5) by a method 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 (C_1-C_6)alkyl, phenyl, or benzyl; or 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;

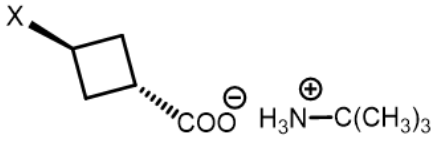
(iv) said ester hydrolyzing agent is lithium hydroxide or sodium hydroxide; or

(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, triethanol amine, PIPES, BICINE, TES, TRIS, HEPES, TRICINE, CHES, or CAPS; or

(iv) said buffer is triethanol amine.

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 claim 1, wherein said trifluoromethylating agent is sulfur tetrafluoride (SF_4) and hydrogen fluoride (HF), and wherein said organic fourth solvent is dichloromethane.