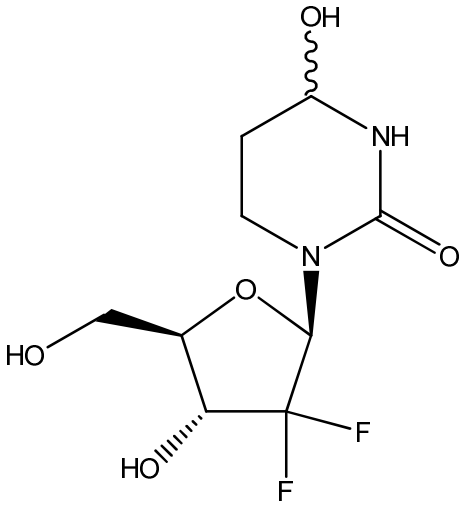
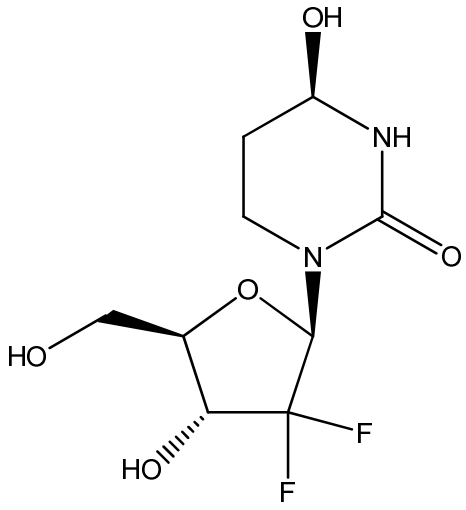


2; and

(d) precipitating or crystallizing compound 2 in the presence of a catalyst to produce compound 1:



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or a salt thereof;

wherein the method comprises the following steps:

(i) wherein the hydrogenating step (a) is performed under hydrogen atmosphere with a palladium catalyst in the presence of water;

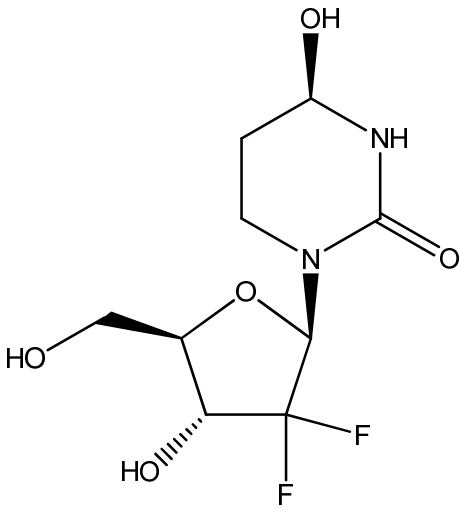
(ii) wherein the reducing step (b) is performed at a temperature of -12°C to -5°C;

(iii) wherein the deprotecting step (c) is performed in the presence of an organic base; and

(iv) wherein the work-up of the deprotected compound from deprotecting step (c) is performed under non-aqueous conditions.

[0006] Another example of the disclosure relates to a method of producing compound **1** (named (4R)-1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-4-hydroxytetrahydropyrimidin-2(1*H*)-one)):

(d) precipitating or crystallizing compound **2** in the presence of a catalyst to produce compound **1**:



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or a salt thereof;

wherein the method comprises one or more of the following in any combination:

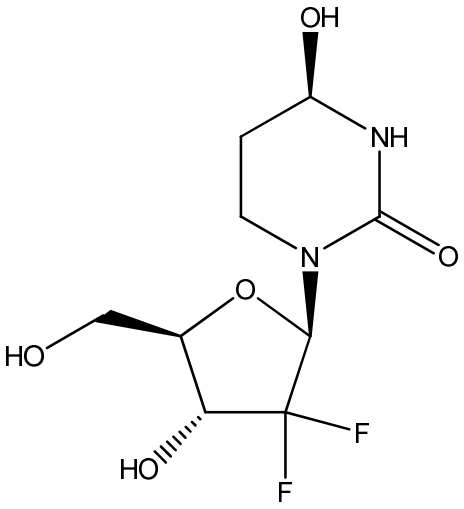
(i) wherein the hydrogenating step (a) is performed under hydrogen atmosphere with a palladium catalyst;

(ii) wherein the reducing step (b) is performed at a temperature of about -12°C to about -5°C;

(iii) wherein the deprotecting step (c) is performed in the presence of an organic base; and/or

(iv) wherein the work-up of the deprotected compound from deprotecting step (c) is performed under non-aqueous conditions. In some embodiments, the present disclosure further comprises a step wherein the final product is recrystallized and the recrystallizing is performed at a pH of about 6.0 to about 7.4 and carried out by dissolving the final product at a temperature of about 50°C to about 55°C to produce a solution and then cooling the solution to about 5°C.

[0006a] In another example, the present disclosure describes to a composition comprising compound 1:



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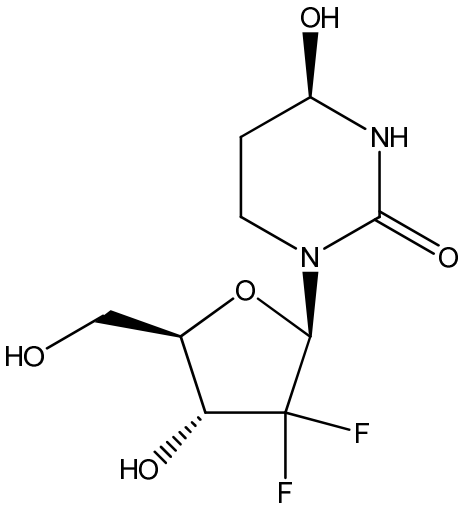
or a salt thereof;

wherein the composition comprises less than 10, 9, 8, 7, 6, or 5 measurable impurities.

[0006b] In yet another aspect, the present disclosure refers to a composition comprising compound 1:



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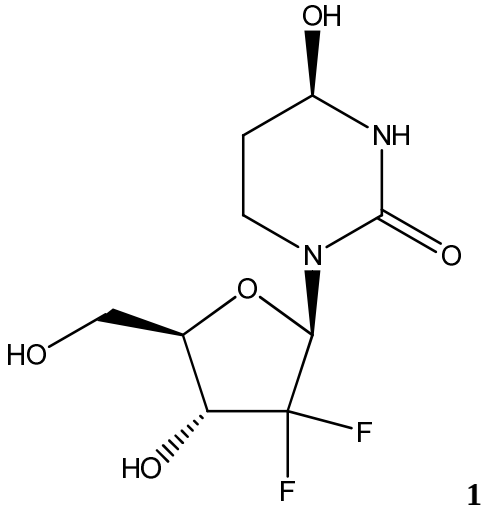
or a salt thereof; wherein the composition comprises less than 7 measurable impurities, wherein no impurity is present in the composition at a level greater than 1.0 wt% of the composition, and wherein compound 1 has a purity of at least 99% of the composition.

[0007] A further example of the disclosure relates to high purity compound **1** (for example compound **1** having a purity of at least about 80%, *e.g.*, at least about 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%):

What is claimed is

1. A method of producing compound 1:



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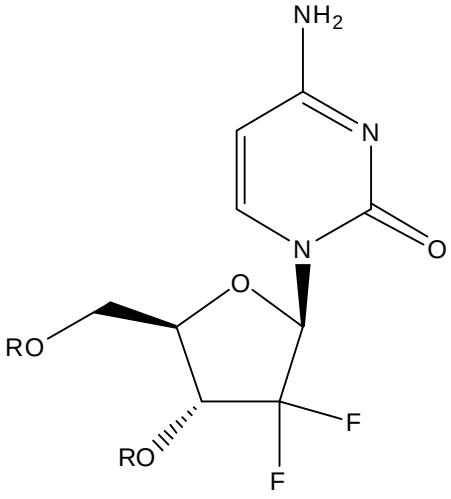
or a salt thereof;

comprising the steps of:

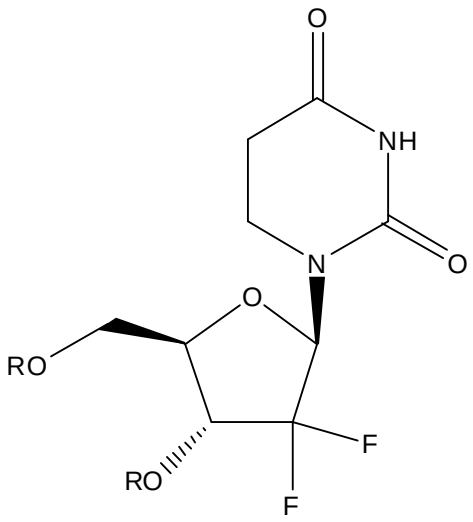
(a) hydrogenating a compound of Formula IV:



IV

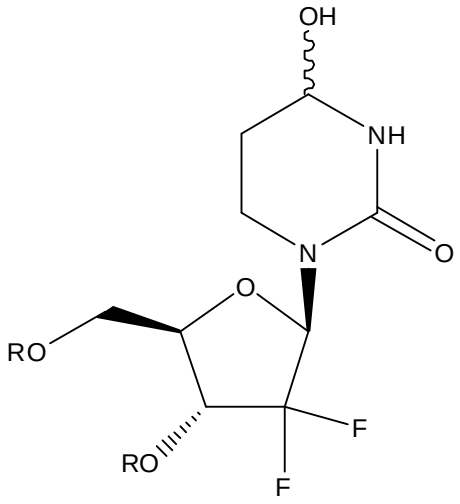
wherein R is a hydroxyl protecting group,

to produce a compound of Formula IIa:



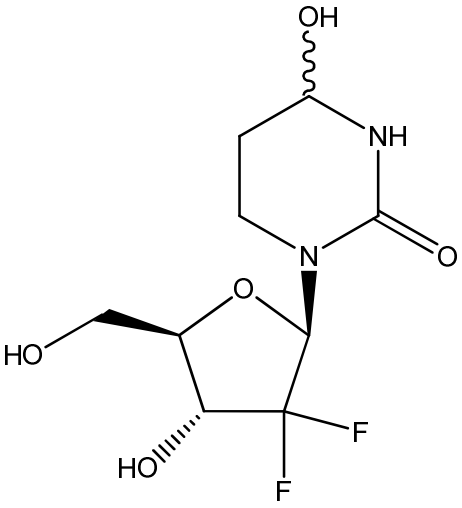
IIa;

(b) reducing the compound of Formula IIa to produce a compound of Formula IIIa:



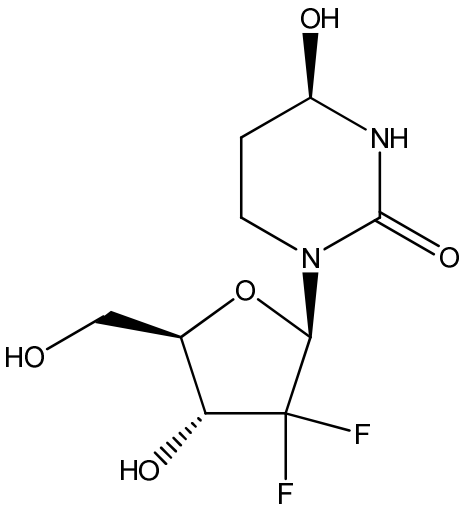
IIIa;

(c) deprotecting the compound of Formula IIIa to produce compound 2:



2; and

(d) precipitating or crystallizing compound 2 in the presence of a catalyst to produce compound 1:



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or a salt thereof;

wherein the method comprises the following steps:

(i) wherein the hydrogenating step (a) is performed under hydrogen atmosphere with a palladium catalyst in the presence of water;

(ii) wherein the reducing step (b) is performed at a temperature of -12°C to -5°C;

(iii) wherein the deprotecting step (c) is performed in the presence of an organic base; and

(iv) wherein the work-up of the deprotected compound from deprotecting step (c) is performed under non-aqueous conditions.

2. The method of claim 1, wherein the catalyst is 1 mol% to 20 mol% 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU).

3. The method of claim 2, wherein the catalyst is 5 mol% to 10 mol% DBU.

4. The method of claim 3, wherein the catalyst is about 5 mol% DBU.

5. The method of claim 1, wherein the catalyst is acetic acid, trifluoroacetic acid, diisopropylethylamine, or ammonium hydroxide.

6. The method of claim 1, wherein the deprotecting step (c) further comprises a step of trituration.

7. The method of claim 1, further comprising recrystallizing or slurrying compound 1.

8. The method of claim 7, wherein the recrystallizing is performed at a pH of 6.0 to 7.4 and carried out by dissolving compound 1 at a temperature of 50°C to 55°C to produce a solution and then cooling the solution to about 5°C.

9. The method of claim 1, wherein step (d) is carried out in the presence of a solution comprising acetonitrile.

10. The method of claim 1, wherein step (d) is carried out in the presence of a solution comprising acetone or tetrahydrofuran.

11. The method of claim 1, wherein step (b) is carried out in the presence of $CeCl_3$.

12. The method of claim 1, wherein the R is a benzoyl group.

13. The method of claim 1, wherein the palladium catalyst used in step (i) is palladium on charcoal (Pd/C).

14. The method of claim 13, wherein the amount of the Pd/C used in step (i) is a catalytic amount of not more than 0.1 part by weight per one part by weight of the compound of Formula IV.

15. The method of claim 13, wherein the amount of the Pd/C used in step (i) is 0.025 to 0.05 parts by weight per one part by weight of the compound of Formula IV.

16. The method of claim 1, wherein step (i) is performed in a mixed solvent comprising ethyl acetate, acetic acid, and water.

17. The method of claim 1, wherein step (i) is performed under ambient or increased pressure.

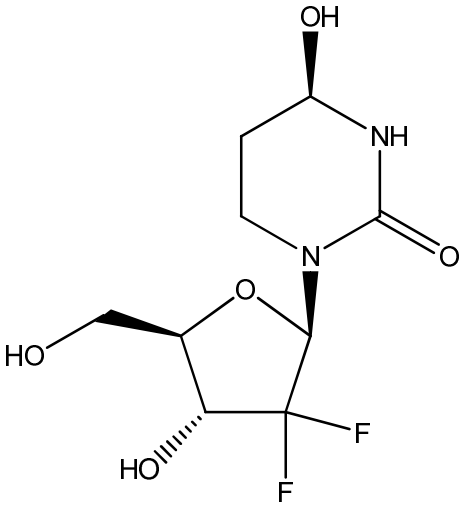
18. The method of claim 1, wherein step (i) is performed under increased pressure of 0.1 to 0.5 MPa.

19. The method of claim 1, wherein the organic base used in step (iii) is one or more bases selected from the group consisting of DBU, triethylamine, DMAP, and DABCO.

20. The method of claim 1, wherein the amount of the organic base used in step (iii) is 0.01 to 2.2 moles per mole of the compound of Formula IIIa.

21. The method of claim 1, wherein the organic base used in step (iii) is DBU.

22. A composition comprising compound 1:



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or a salt thereof;

wherein the composition comprises less than 7 measurable impurities, wherein no impurity is present in the composition at a level greater than 1.0 wt% of the composition, and wherein compound 1 has a purity of at least 99% of the composition.

23. The composition of claim 22, wherein the composition comprises less than 6 measurable impurities.

24. The composition of claim 22, wherein the composition comprises less than 5 measurable impurities.

25. The composition of claim 22, wherein no impurity is present in the composition at a level greater than 0.5wt% of the composition.

26. The composition of claim 22, wherein no impurity is present at a level greater than 0.25wt% of the composition.

27. The composition of claim 22, wherein compound 1 has a purity of at least about 99.5% by weight of the composition.