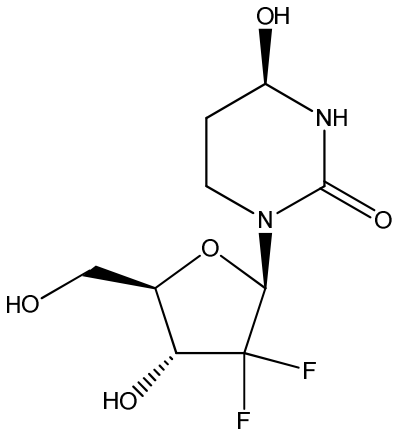


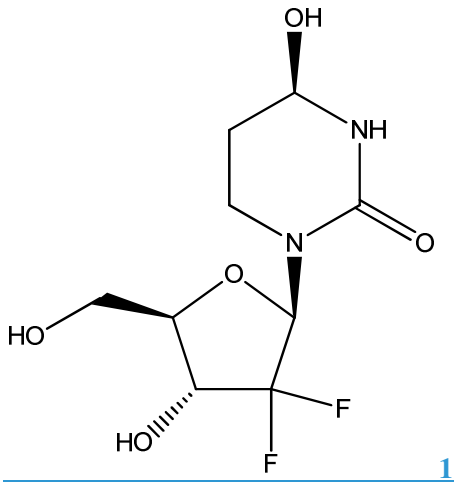
1.

[0004] A need exists for more efficient processes for producing CDA inhibitors such as 2'-deoxy-2',2'-difluorotetrahydrouridine for use in methods of treating cancer and other disorders.

SUMMARY ~~OF EMBODIMENTS OF THE INVENTION~~

[0005] The present ~~invention~~disclosure relates to the development of a more efficient method for synthesizing 2'-deoxy-2',2'-difluorotetrahydrouridine compounds and intermediates involved in the synthesis. Previous synthetic methods in the art were inconvenient due to the use of an inefficient transfer hydrogenation process and the use of preparative HPLC to isolate the final compound. The inventors of the present ~~invention~~disclosure developed a synthetic method with improved efficiency which achieved the ability of the final compound to be purified by precipitation or crystallization, *e.g.*, crystallization-induced diastereoselective transformation (CIDT) which converts the mixture of epimers to the desired compound and hence results in enhanced yield of the desired epimer (see WO 2015/066162). The present ~~invention~~disclosure improves on this method by reducing impurities, improving yield, shortening reaction time, and/or otherwise improving conditions for production at industrial scale.

[0005a] In one aspect, the present disclosure refers to a method of producing compound 1:



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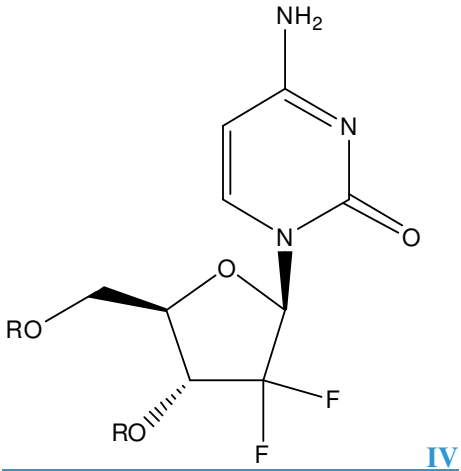
or a salt thereof;

comprising the steps of:

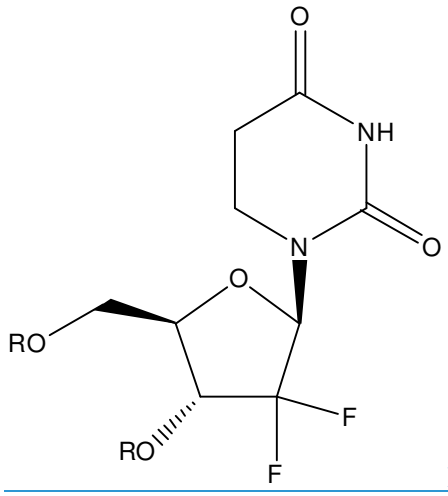
(a) hydrogenating a compound of Formula IV:



IV

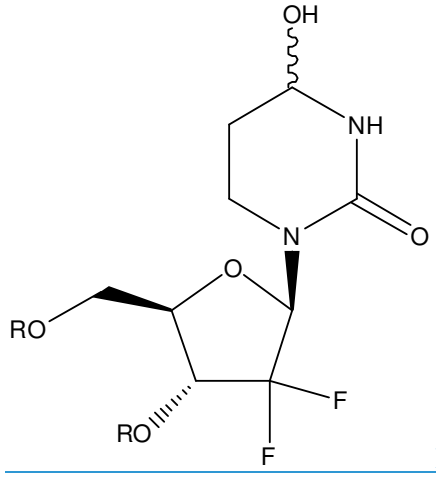
wherein R is a hydroxyl protecting group,

to produce a compound of Formula IIa:



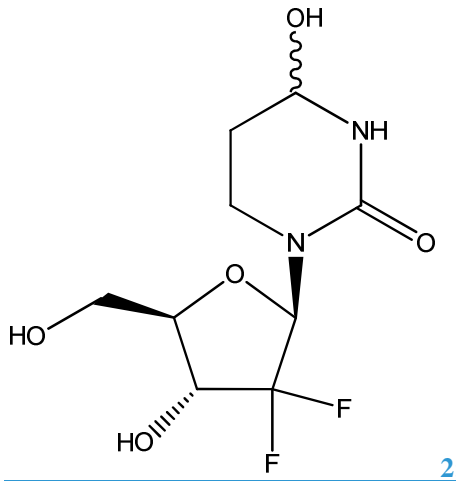
IIa;

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



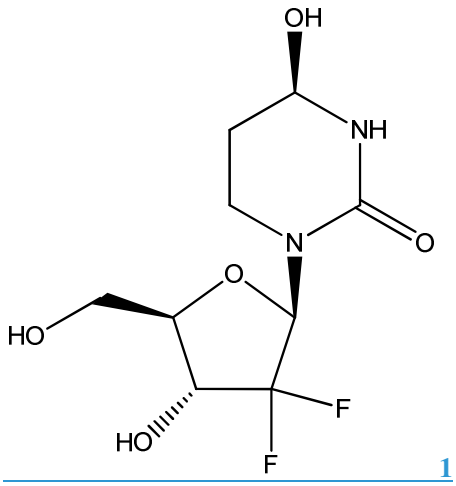
IIIa;

(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 one or more of the following in any combination:

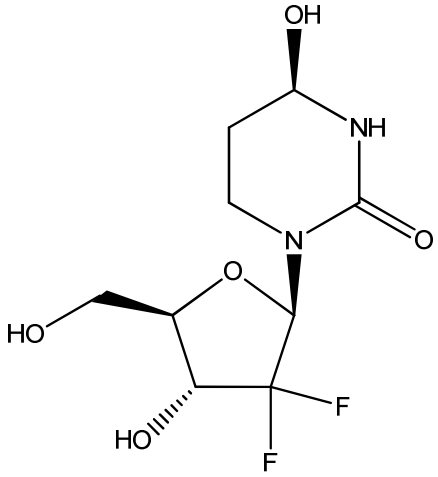
(i) wherein the hydrogenating step (a) is performed under hydrogen atmosphere with a palladium catalyst;

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

[0006] Another ~~aspect~~ example of the ~~invention~~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)):



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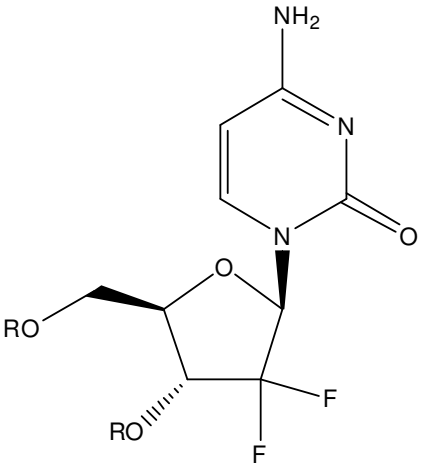
or a salt thereof;

comprising the steps of:

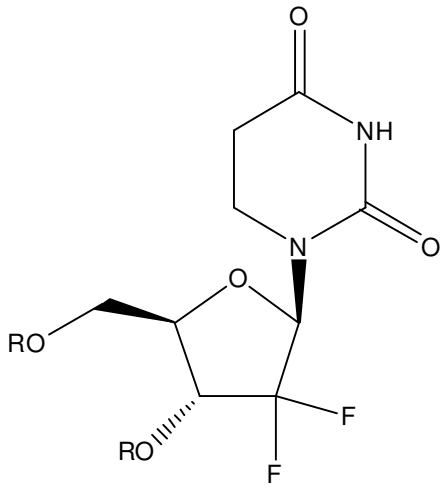
(a) hydrogenating the starting compound of Formula IV:



IV

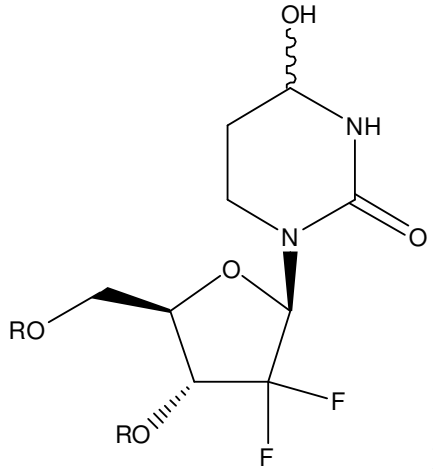
wherein R is a hydroxyl protecting group,

to produce the compound of Formula IIa:



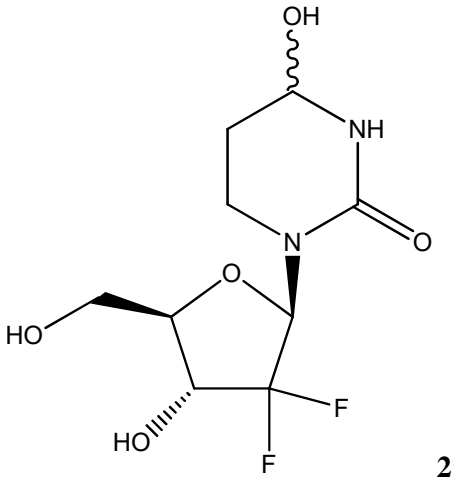
IIa;

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



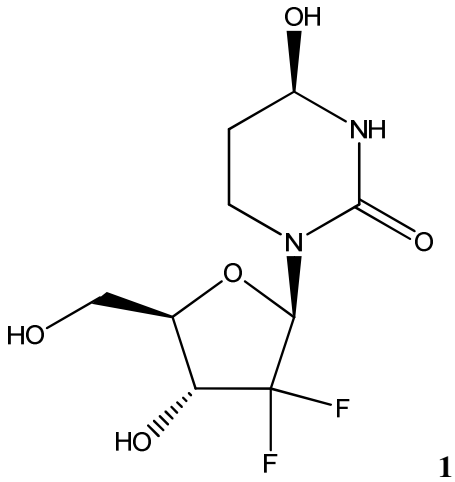
IIIa;

(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 one or more of the following in any combination:

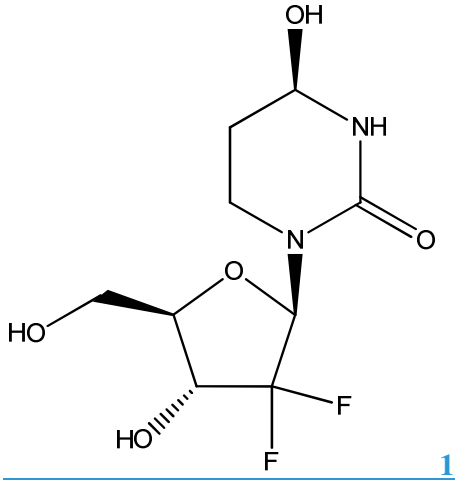
(i) wherein the hydrogenating step (a) is performed under hydrogen atmosphere with a palladium catalyst;

(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 ~~invention~~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 aspect, the present disclosure refers to a composition comprising compound 1:



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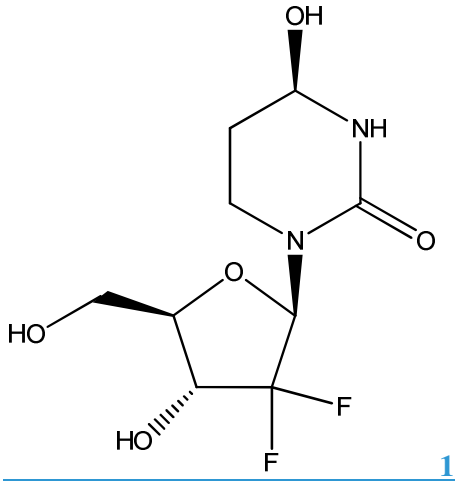
or a salt thereof;

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

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

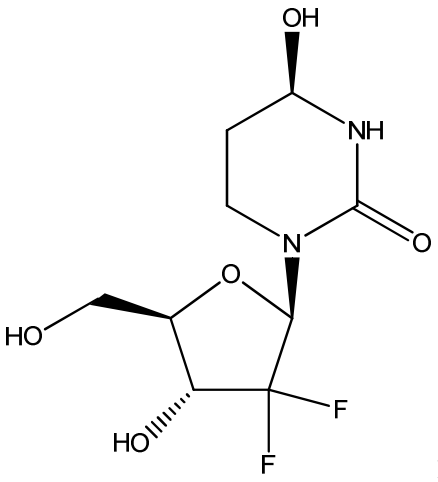


1

or a salt thereof;

wherein no impurity is present in the composition at a level greater than 1.0 wt%, 0.5 wt%, 0.25 wt%, 0.2 wt%, 0.15 wt%, or 0.1 wt% of the composition.

[0007] A further ~~aspect~~ example of the ~~invention~~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%):



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or a salt thereof. The high purity compound **1** may be produced by the methods of the ~~invention~~disclosure. Other aspects of the ~~invention~~disclosure relate to compound **1** comprising a lower number of impurities and/or lower levels of individual impurities and total impurities compared to compound **1** produced by prior methods.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0008] The present invention now will be described hereinafter with reference to the accompanying examples, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein.

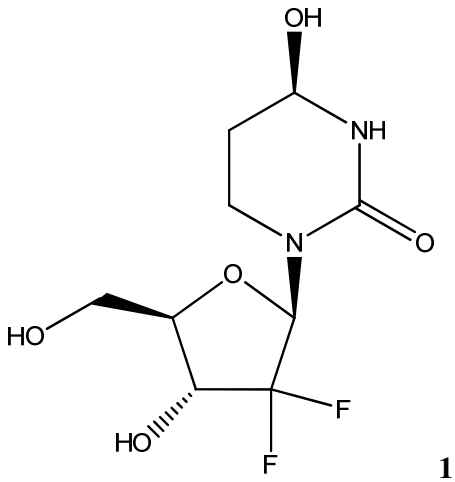
[0009] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention.

[0010] Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination. Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted. To illustrate, if the specification states that a composition comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

[0011] For purposes herein, if there is any ambiguity as between a written chemical name and a drawn chemical structure, the drawn chemical structure will control.

What is claimed is:

1. A method of producing compound 1:



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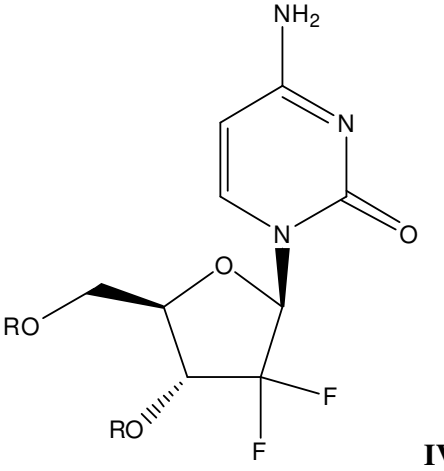
or a salt thereof;

comprising the steps of:

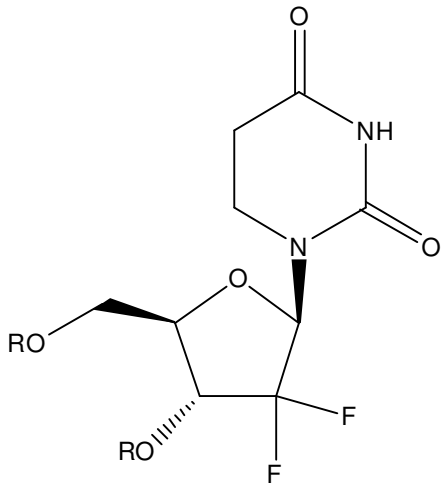
(a) hydrogenating a compound of Formula IV:



IV

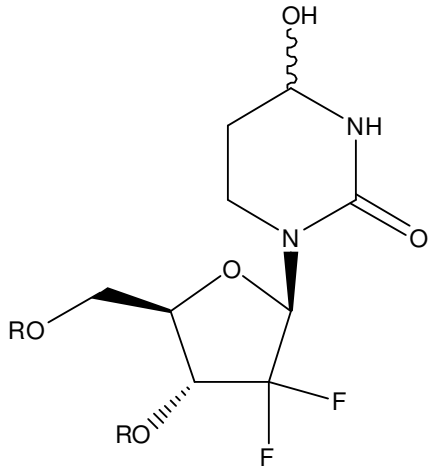
wherein R is a hydroxyl protecting group,

to produce a compound of Formula IIa:



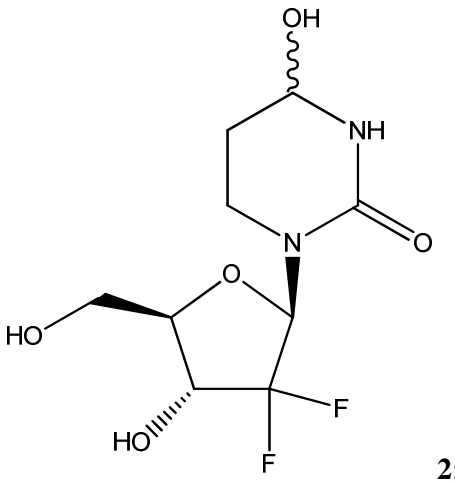
IIa;

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



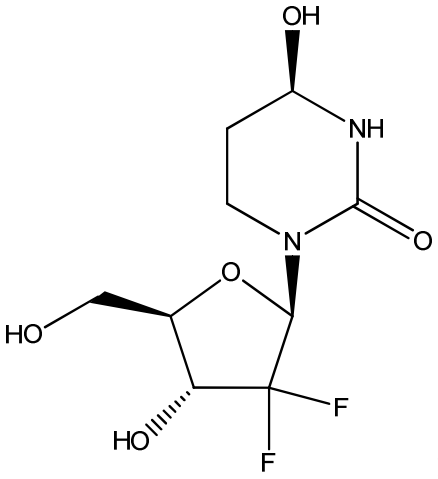
IIIa;

(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 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.

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

3. The method of claim 2, wherein the catalyst is ~~about~~ 5 mol% to ~~about~~ 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 ~~about~~ 6.0 to ~~about~~ 7.4 and carried out by dissolving compound 1 at a temperature of ~~about~~ 50°C to ~~about~~ 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 the method comprises step (i) and step (i) is performed in a mixed solvent comprising ethyl acetate, acetic acid, and water.

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

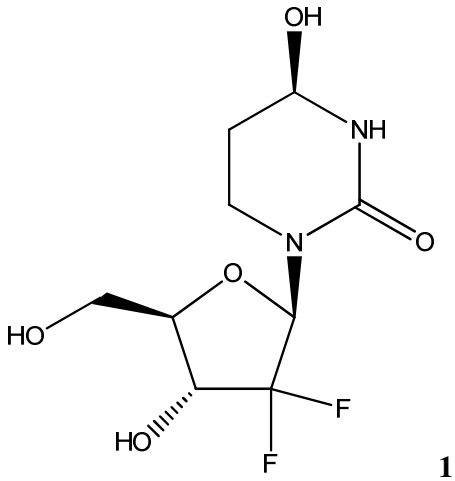
18. The method of claim 1, wherein the method comprises step (i) and step (i) is performed under increased pressure of 0.1 to 0.5 MPa.

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

22. A composition comprising compound 1:



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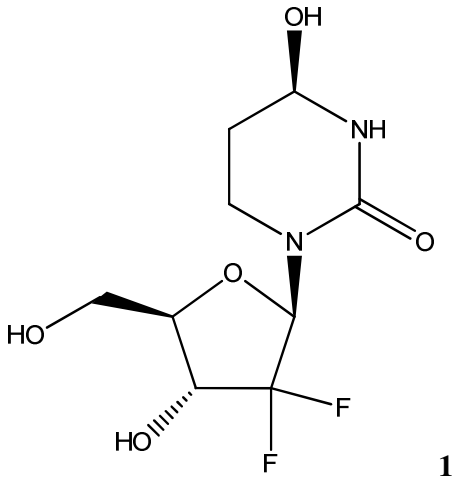
or a salt thereof;

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

23. The composition of claim 22, wherein no impurity is present at a level greater than 1.0 wt%, 0.5 wt%, 0.25 wt%, 0.2 wt%, 0.15 wt%, or 0.1 wt% of the composition.

24. The composition of claim 22 or 23, wherein compound 1 has a purity of at least about 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% by weight of the composition.

25. A composition comprising compound 1:



1

or a salt thereof;

wherein no impurity is present in the composition at a level greater than 1.0 wt%, 0.5 wt%, 0.25 wt%, 0.2 wt%, 0.15 wt%, or 0.1 wt% of the composition.

26. The composition of claim 25, wherein the composition comprises less than 10, 9, 8, 7, 6, or 5 measurable impurities.

27. The composition of claim 25 or 26, wherein compound 1 has a purity of at least about 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% by weight of the composition.