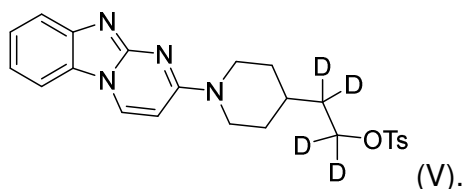


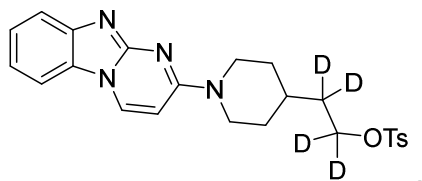
[0010] In particular, the disclosure comprises a coupling step that can make a substituted imidazo-pyrimidine in high yield.

[0011] Selective N-phosphorylation of aminoimidazoles results in a key steering element that controls isomeric selectivity in the condensation of β -ethoxy acrylamides and amino-imidazoles to furnish imidazo[1,2-a]pyrimidines. Conditions that provide highly selective (99:1) phosphorylation at the endo- or exocyclic nitrogen are disclosed. Either the 2-amino or 4-amino isomer of the (benzo)imidazo[1,2-a]pyrimidine products can be isolated in 64 – 95% yield.

[0012] The disclosure further includes a compound of formula (V):

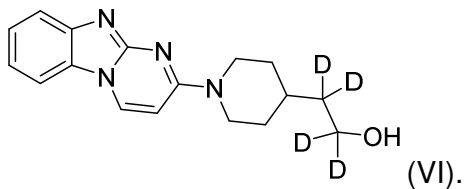


[0012a] In one aspect, the present disclosure refers to a compound of formula:

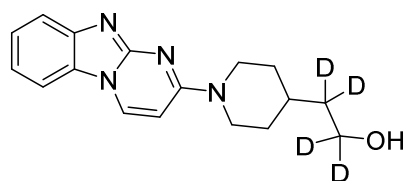


[0013] In particular, compound (V) may have a deuterium enrichment factor of 3,000 or greater at each of the positions shown as occupied by a deuterium atom.

[0014] The disclosure further includes a compound of formula (VI):

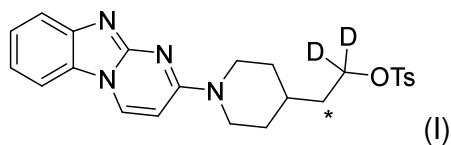


[0014a] In another aspect, the present disclosure refers to a compound of formula:



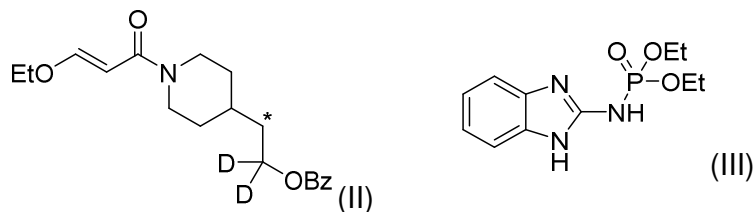
[0015] In particular, compound (VI) may have a deuterium enrichment factor of 3,000 or greater at each of the positions shown as occupied by a deuterium atom.

[0016] The disclosure further comprises a method of synthesizing the compound of formula (I),

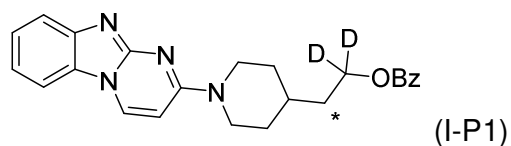


the method comprising:

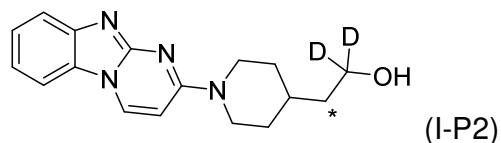
at least a step of coupling a compound of formula (II) with a compound of formula (III)



in the presence of POCl_3 and Et_3N in a non-aqueous solvent to give a first precursor (I-P1).

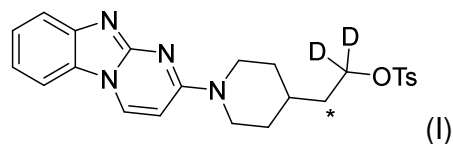


The synthesis further comprises removing the benzoate group in I-P1 to give a second precursor (I-P2); and

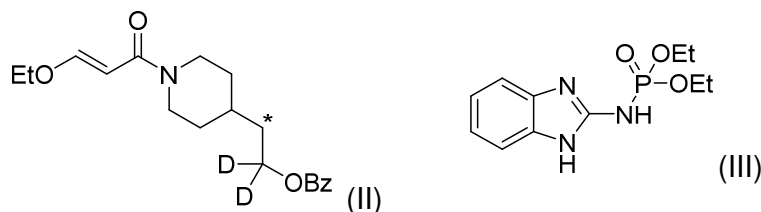


replacing the hydroxyl group in I-P2 by a tosyl group to give compound (I), wherein, in formulae (I), (II), (I-P1) and (I-P2), the carbon atom labeled (*) is optionally doubly-deuterated.

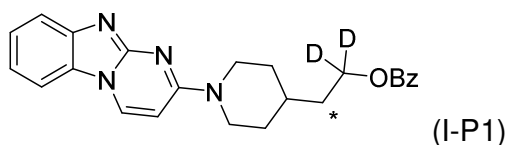
[0016a] In another aspect, the present disclosure refers to a method of synthesizing the compound of formula (I), the method comprising:



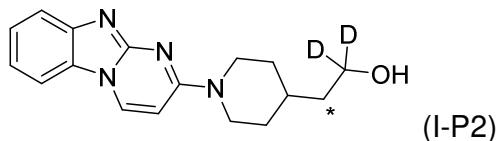
coupling a compound of formula (II) with a compound of formula (III)



in the presence of POCl₃ and Et₃N in a non-aqueous solvent to give a first precursor (I-P1);

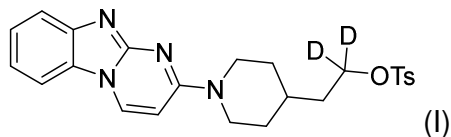


removing the benzoate group in I-P1 to give second precursor (I-P2); and



replacing the hydroxyl group in I-P2 by a tosyl group to give compound (I), wherein, in formulae (I), (II), (I-P1) and (I-P2), the carbon atom labeled (*) is optionally doubly-deuterated.

[0016b] In another aspect, the present disclosure refers to a composition comprising a compound of formula (I), wherein the di-deuterated compound is present at an isotopic purity of > 95% relative to non-deuterated and mono-deuterated forms.



BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 shows a first flow-chart of a process as described herein.

[0018] FIG. 2 shows a second flow-chart of a process as described herein.

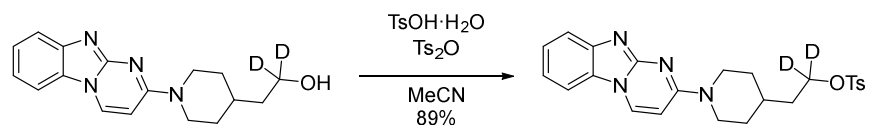
DETAILED DESCRIPTION

[0019] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will

was then heated to 60–80 °C and stirred for 30–90 min. After reaction completion was confirmed, the mixture was concentrated to 10 L via vacuum distillation. EtOH (10.0 L) was added and a constant-volume distillation was performed while maintaining the internal temperature below 55 °C. Water (7.5 L) was then added and the constant-volume distillation was maintained while maintaining the temperature below 60 °C. Vacuum was disabled and the solution was cooled to 5 °C over 7 h. An additional charge of a 21 w/w% solution of NaOEt in EtOH was added (300 g, 0.75 mol, 0.25 equiv) and the reaction was heated to 70–80 °C for 1.5 h. After which, the reactor was cooled to 5 °C over the course of 7 h then held at this temperature for a minimum of 2 h. The mixture was filtered and rinsed with a pre-cooled 3:1 water:EtOH solution (4.0 L) at 5–15 °C followed by a wash with water (4.0 L) at 15–25 °C. The solids were then dried under vacuum at 40 °C for a minimum of 12 h to afford **2-(1-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperidin-4-yl)ethan-1,1-d₂-1-ol** as a light-yellow solid (684.0 g, corrected yield: 71%, 97.9% HPLC purity): mp 186 °C.

[0067] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 4.55 (s, 2H), 4.36 (s, 1H), 2.99 (t, *J* = 12.7 Hz, 2H), 1.82 – 1.69 (m, 3H), 1.38 (d, *J* = 6.2 Hz, 2H), 1.12 (ddt, *J* = 15.6, 11.8, 6.0 Hz, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 157.8, 152.1, 144.1, 134.2, 127.7, 124.0, 118.9, 117.0, 110.1, 95.8, 44.6, 38.7, 32.1, 31.8.

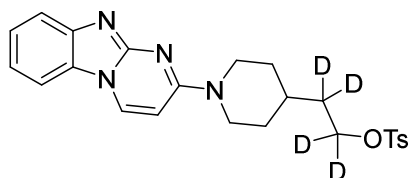
Step 9 – 2-(1-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperidin-4-yl)ethyl-1,1-d₂ 4-methylbenzenesulfonate



[0068] To a reactor under nitrogen was charged **2-(1-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperidin-4-yl)ethan-1,1-d₂-1-ol** (0.6874 kg, 2099 mol, 1.0 equiv) followed by TsOH·H₂O (0.531 kg, 2764 mmol, 1.2 equiv). MeCN (3.434 L) was then added and the reaction was stirred for a minimum of 15 min. Next, Ts₂O (1.504 kg, 4607 mmol, 2.0 equiv) was added followed by MeCN (0.628 L) to rinse the reaction vessel. This slurry was then stirred at 20 °C for 16 h. After reaction completion was confirmed,

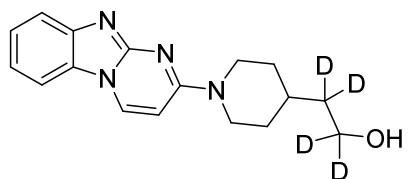
WHAT IS CLAIMED:

1. A compound of formula:



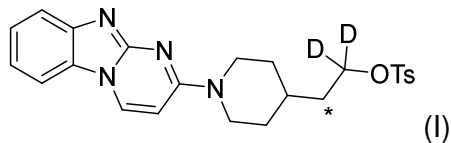
2. The compound of claim 1, having a deuterium enrichment factor of 3,000 or greater at each deuterium atom.

3. A compound of formula:

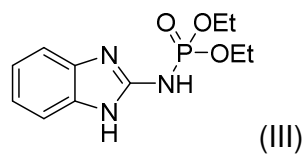
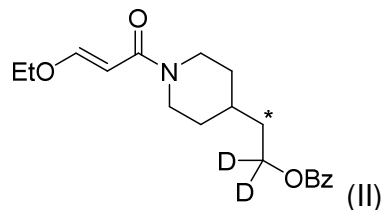


4. The compound of claim 3, having a deuterium enrichment factor of 3,000 or greater at each deuterium atom.

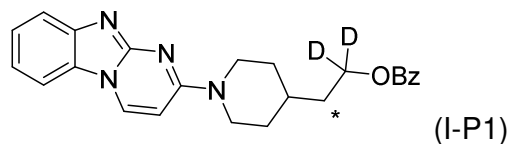
5. A method of synthesizing the compound of formula (I), the method comprising:



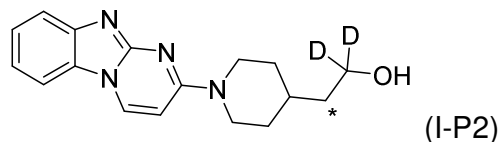
coupling a compound of formula (II) with a compound of formula (III)



in the presence of POCl₃ and Et₃N in a non-aqueous solvent to give a first precursor (I-P1);

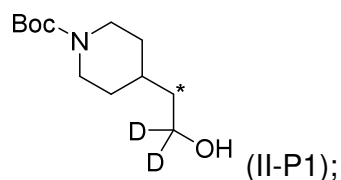
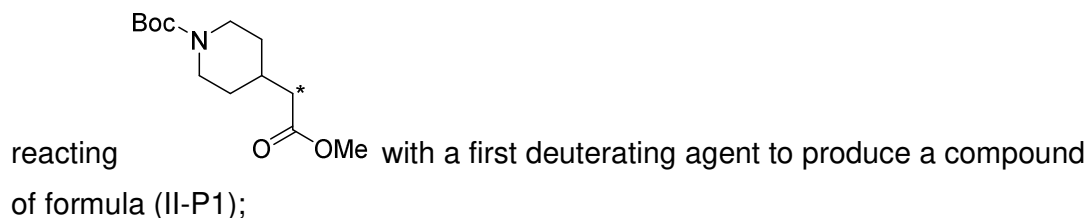


removing the benzoate group in I-P1 to give second precursor (I-P2); and

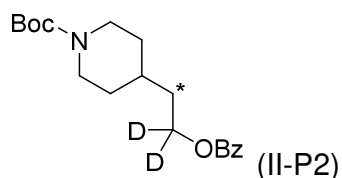


replacing the hydroxyl group in I-P2 by a tosyl group to give compound (I), wherein, in formulae (I), (II), (I-P1) and (I-P2), the carbon atom labeled (*) is optionally doubly-deuterated.

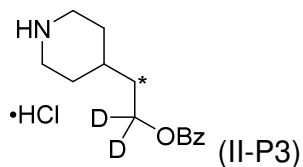
6. The method of claim 5, wherein the compound of formula (II) is synthesized by a method comprising:



introducing a benzoyl group to the hydroxyl group of (II-P1) to produce a compound of formula (II-P2);



removing the Boc protecting group from (II-P2) to produce a hydrochloride salt (II-P3); and

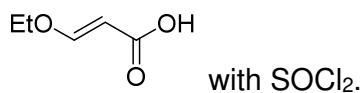


reacting (II-P3) with $\text{EtO}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{OH}$ (IV) or $\text{EtO}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{Cl}$ (IVa) to produce the compound of formula (II).

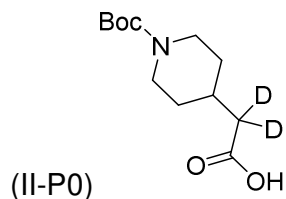
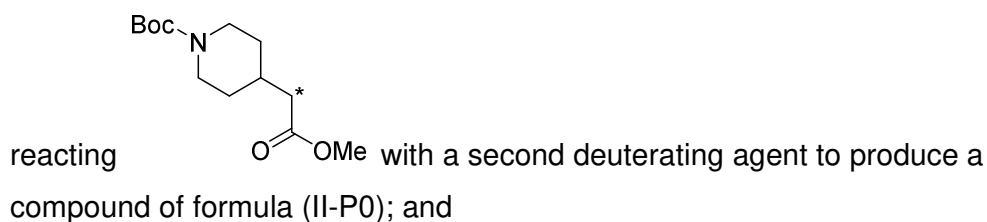
7. The method of claim 6, wherein the first deuterating agent comprises LiAlD_4 .

8. The method of claim 6, wherein the first deuterating agent comprises D_2 gas.

9. The method of claim 6, wherein compound (IVa) is formed by reacting

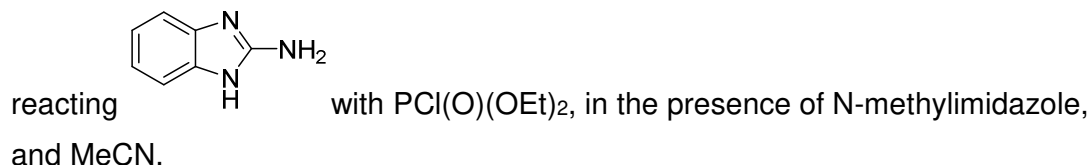


10. The method of claim 6, wherein the carbon atom labeled (*) is doubly deuterated, and wherein compound (II-P1) is created by:



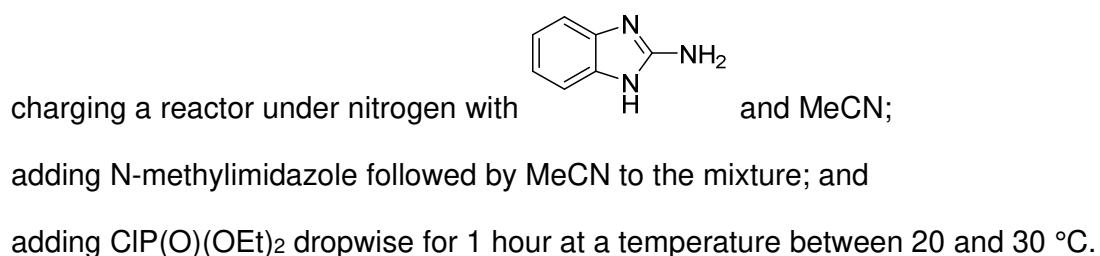
reacting the first deuterating agent with (II-P0) to form d_4 -(II-P1).

11. The method of claim 5 wherein the compound of formula (III) is synthesized by a method comprising:



12. The method of claim 11, wherein the PCl(O)(OEt)_2 is formed *in situ* by reacting diethyl hydrogen phosphate with 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione.

13. The method of claim 11, wherein the compound of formula (III) is formed by:



14. The method of claim 11, wherein the compound of formula (III) is formed by:
charging a flask under nitrogen with 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione and MeCN;

adding diethyl hydrogen phosphate and Et_3N to the flask;

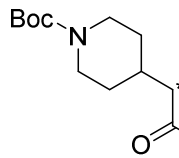
cooling the flask to 0 °C and adding 1H-benzo[d]imidazol-2-amine dissolved in THF; and

warming the reaction mixture to 15 – 25 °C for 1 hour.

15. The compound of claim 1, having a deuterium enrichment factor of 4,000 or greater at each deuterium atom.
16. The compound of claim 3, having a deuterium enrichment factor of 4,000 or greater at each deuterium atom.

17. The method of claim 5, further comprising radio-labeling the compound of formula (I) by replacing the tosylate group with an ^{18}F atom.
18. The method of claim 5, wherein the removing the benzoate group from compound (I-P1) occurs in the presence of NaOEt and EtOH.
19. The method of claim 18, wherein the removing takes place in a reactor under nitrogen.
20. The method of claim 5, wherein the replacing the hydroxyl group in compound (I-P2) with a tosyl group additionally includes basification after reacting (I-P2) with tosylate.
21. The method of claim 20, wherein:
the reacting with tosylate occurs in a reactor under nitrogen in a solvent mixture comprising MeCN and NMP; and
the basification is carried out with K_3PO_4 .
22. The method of claim 5, wherein the coupling of the compound of formula (II) with the compound of formula (III) comprises:
charging a reactor under nitrogen with MeCN followed by compound (II) and compound (III);
adding MeTHF and Et_3N to the reactor;
cooling the reactor to between -10 and $10\text{ }^\circ\text{C}$;
adding POCl_3 to the reactor;
heating the contents of the reactor to $65 - 95\text{ }^\circ\text{C}$ over a minimum of 2 hours;
maintaining the contents of the reactor at $80\text{ }^\circ\text{C}$ for at least 1.5 hours;
cooling the contents to $15 - 25\text{ }^\circ\text{C}$ and adding 25 w/w% solution of K_2CO_3 .
23. The method of claim 5, wherein the carbon atom labeled (*) is doubly deuterated, and wherein removing the benzoate group from d_4 -(I-P1) comprises:
adding NaOH to a solution of d_4 -(I-P1).

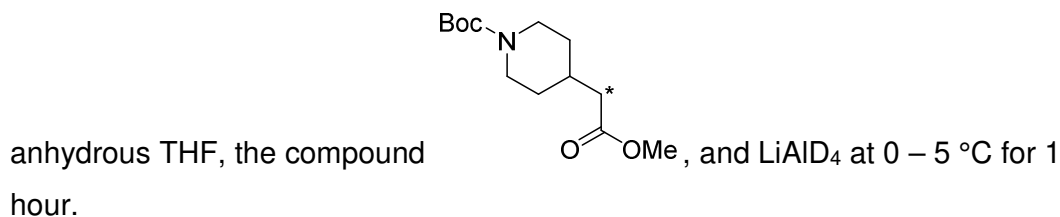
24. The method of claim 5, wherein the carbon atom labeled (*) is doubly deuterated, and wherein the replacing the hydroxyl group in d_4 -(I-P2) by a tosyl group to give compound d_4 -(I), comprises:
adding 4-methylbenzenesulfonic anhydride to a solution of d_4 -(I-P2) and TsOH·H₂O in MeCN; and
heating the mixture to 40 °C.



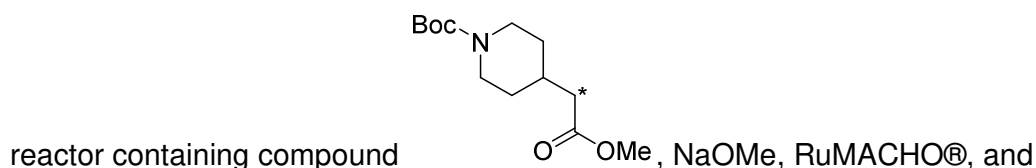
25. The method of claim 6, wherein the compound  is purified by a method comprising passing the compound over charcoal, filtering and drying the resulting oil.
26. The method of claim 6, wherein the introducing a benzoyl group to the hydroxyl group of (II-P1) comprises:
charging compound (II-P1) to a reactor under nitrogen, with toluene, Et₃N, DMAP, and benzoyl chloride at a temperature between -5 and 5 °C.
27. The method of claim 6, wherein the removing the Boc protecting group from (II-P2) comprises:
charging a reactor under nitrogen at 0 – 5 °C with AcCl and 1-PrOH, compound (II-P2) in toluene solution; and
heating the mixture to 50 °C for 1 hour.
28. The method of claim 6, wherein the reacting (II-P3) with (IV) comprises:
charging a reactor under nitrogen at 20 – 30 °C with compound (II-P3), (*E*)-3-ethoxyacrylic acid (IV), and Et₃N; and
heating the mixture to 40 °C for 1 hour.
29. The method of claim 6, wherein the compound of formula (II) is formed by reacting (II-P3) with (IVa), and (IVa) is formed by reacting (IV) with SOCl₂ in DCM.

30. The method of claim 6, wherein the carbon atom labeled (*) is doubly deuterated, and wherein compound (II-P2) is created by:
adding BzCl to a solution of II-P1 in Et₃N and THF at 0 – 10 °C for 1 hour.
31. The method of claim 6, wherein the carbon atom labeled (*) is doubly deuterated, and wherein the removing the Boc protecting group from compound (II-P2) comprises:
adding HCl in EtOAc to a solution of (II-P2) in EtOAc.
32. The method of claim 6, wherein the carbon atom labeled (*) is doubly deuterated and the reacting *d*₄-(II-P3) with (IVa) comprises:
adding (IVa) to *d*₄-(II-P3) in Et₃N and THF at 0 – 10 °C for 1 hour.
33. The method of claim 6, wherein the carbon atom labeled (*) is doubly deuterated and the coupling of the compound of formula (II) with the compound of formula (III) comprises:
forming a solution of compound (III) and *d*₄-(II) in 2-MeTHF and MeCN;
adding Et₃N followed by POCl₃ to the solution;
heating the solution to 80 °C for 4 hours; and
adding NaHCO₃ to the solution.

34. The method of claim 7, wherein a reactor under nitrogen was charged with



35. The method of claim 8, wherein the deuterium gas was applied to a pressure



PhMe, at a temperature of 100 °C, and a pressure of 20 atmospheres for 24 hours.

36. The method of claim 10, wherein the second deuterating agent is CD_3ONa in CD_3OD , and the reacting with the second deuterating agent takes place at 80 °C for 12 hours.
37. The method of claim 10, wherein the first deuterating agent is LiAlD_4 in THF, and the reacting takes place at $-10\text{ }^\circ\text{C}$.
38. A composition comprising a compound of formula (I), wherein the di-deuterated compound is present at an isotopic purity of $> 95\%$ relative to non-deuterated and mono-deuterated forms.

