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Practical Synthesis of the anti-HIV Drug, PMPA

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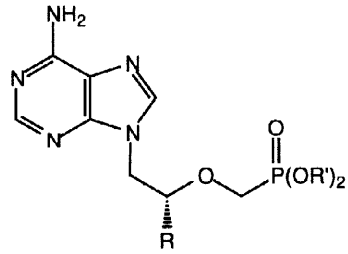
Abstract: The anti-HIV nucleotide analogue PMPA can be prepared on a kilogram-scale by a three step sequence: i) condensation of adenine with (*R*)-propylene carbonate, ii) alkylation of the resulting (*R*)-9-(2-hydroxypropyl)adenine with diethyl *p*-toluenesulfonyloxymethanephosphonate using lithium *tert*-butoxide and iii) cleavage of the phosphonate ester functionalities with bromotrimethylsilane.

The acyclic derivatives of adenosine monophosphate, 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA, **1**) and (*R*)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA, **2**) have shown potent and selective activity against human immunodeficiency virus (HIV) and other retroviruses.[1,2] The diester prodrugs, bis(POM)PMEA **3** and bis(POC)PMPA **4**, are currently being tested in clinical trials as oral therapies for AIDS and/or hepatitis B infection.[3,4] In order to supply the ongoing toxicological and clinical studies, a practical kilogram-scale preparation of **2** was needed.



1 R = H, R' = H
2 R = Me, R' = H
3 R = H, R' = $CH_2OC(O)t$-Bu
4 R = Me, R' = $CH_2OC(O)OCH(CH_3)_2$

Figure 1.

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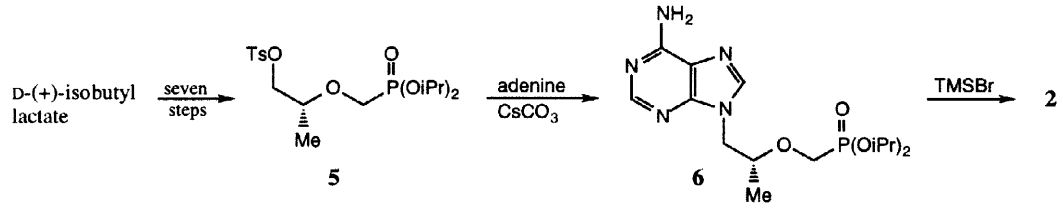
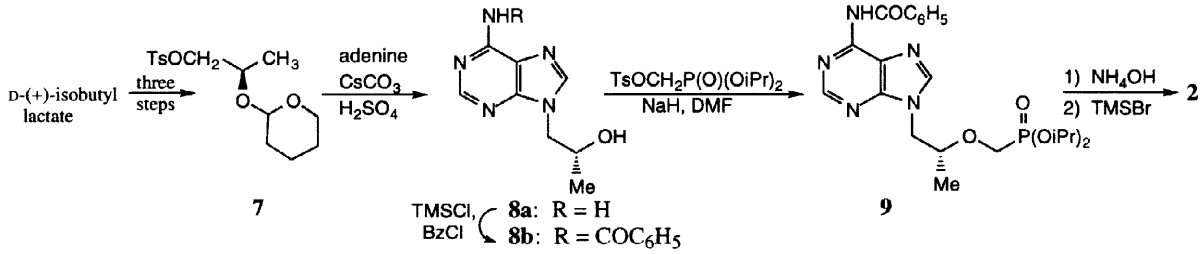
Two syntheses of **2** have been previously reported by Holy, both of which employed the readily available reagents, dialkyl *p*-toluenesulfonyloxymethanephosphonates.[5] The first approach (Scheme 1) was based on alkylation of adenine with the side-chain **5** already functionalized with the protected phosphonate.[6]



Scheme 1

The second approach (Scheme 2) built up the side chain stepwise by treatment of adenine with a protected tosyl alcohol **7** to afford, after deprotection, (*R*)-9-(2-hydroxypropyl)adenine (HPA, **8a**).[7] After protection of N6 as the benzoyl derivative **8b**, methylene phosphonate **9** was obtained by sodium hydride-mediated alkylation with diisopropyl *p*-toluenesulfonyloxymethanephosphonate.



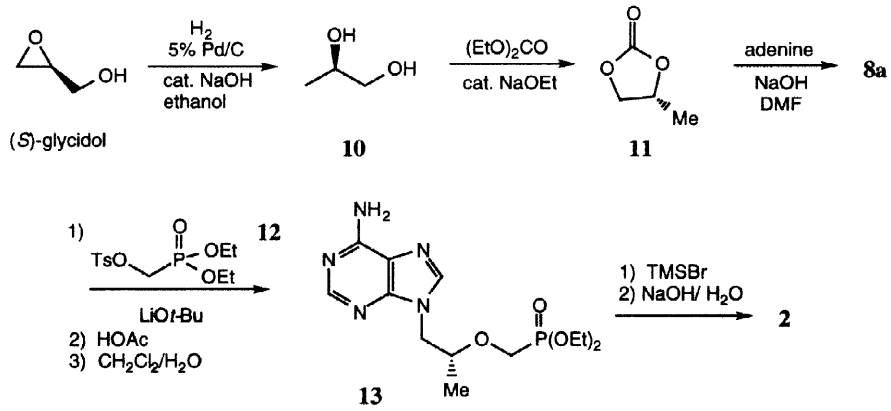
Scheme 2

The chiral synthon for both routes to **2** was derived from D-(+)-isobutyl lactate, which required aluminum hydride reagents for the ester reduction and transient protection of the lactate hydroxyl as a THP- or benzyl-ether. Both routes also required multiple chromatographic purifications. The alkylation of **8a,b** with sodium hydride (3 eq.) scaled-up poorly due to reaction heterogeneity, delayed-onset exotherms, and cross reactions between the tosylate reagent and sodium hydride. Careful quenching of excess sodium hydride was needed and the copious off-gassing of hydrogen necessitated nitrogen dilution. An alternative synthetic route was developed which was more amenable to scale-up while minimizing the use of protecting groups.

The related phosphonate **1** had been prepared via base catalyzed condensation of adenine with ethylene carbonate to generate 9-(2-hydroxyethyl)adenine (HEA).[8] Based on this precedent, it was proposed that **8a** could be prepared using (*R*)-propylene carbonate **11** (Scheme 3).

The preparation of (*R*)-propylene carbonate commenced with commercially available (*S*)-glycidol (86% ee) which was hydrogenated[9] to afford (*R*)-1,2-propanediol **10** using 5% palladium on carbon[10] (5% wt.) in ethanol (1 M) at ca. 25 psi hydrogen (6 h) with the addition of a catalytic amount of sodium hydroxide (0.05 eq.). Addition of the sodium hydroxide was found to be critical to avoid stalling on scale-up. After filtration and concentration, crude **10** was condensed with diethyl carbonate (1.2 eq.) in the presence of catalytic (0.04

eq.) sodium ethoxide.[11] The reaction was driven to completion by distillation of ethanol, followed by isolation of **11** by vacuum distillation (100 °C, 3 mm). The overall yield of **11** from (*S*)-glycidol was 75-80%. Chiral gas chromatographic analysis indicated no change in optical purity (86% ee) for the two-step sequence.[12]



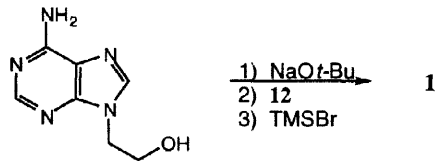
Scheme 3

Coupling of adenine with **11** (1.1 eq.) was accomplished in dimethylformamide (DMF) at 140 °C for 20 hours in the presence sodium hydroxide (0.02 eq.). Only two minor byproducts were formed at approximately 3% and 6% levels.[13] The pure alcohol **8a** could be isolated by crystallization directly from the reaction mixture by addition of toluene or, more conveniently, the crude **8a** DMF solution could be used directly in the next step.

Treatment of a 1 M DMF solution of **8a** with lithium *tert*-butoxide (1.1 eq., 2 M in THF) afforded a thick suspension of lithium salts. Addition of diethyl *p*-toluenesulfonyloxymethanephosphonate **12** (0.5 eq.) at 30-35 °C afforded a homogenous solution (ca. 1 h). This was followed by charging additional lithium *tert*-butoxide (0.4 eq) and **12** (1.0 eq.) to achieve complete reaction. The reaction was quenched with acetic acid and water, and the diethylphosphonate ester **13** was extracted into methylene chloride. Yields of crude **13** were typically 55-65% from adenine (by external standard HPLC).[13]

To complete the synthesis of **2**, the crude diethyl ester **13** was subjected to excess bromotrimethylsilane (3.5 eq.) in refluxing acetonitrile.[6,7] After disappearance of mono- and di-ethyl esters by HPLC, the reaction was concentrated, diluted with water and extracted with dichloromethane to remove silylated byproducts. The phosphonic acid product **2** was precipitated by addition of 50% NaOH bringing the aqueous solution to pH 3. The product precipitated slowly over several hours under these dilute conditions (ca. 0.57 M) and resulted in enrichment of the chiral purity of the product from 86% ee to > 98% ee.[14] A final recrystallization from boiling water (14 L/kg) afforded **2** as a stable monohydrate in 30-35% overall yield from adenine.

An alkoxide-alkylation process has also been used to prepare PMEA **1** from HEA **14** (Scheme 4). Optimal results in this case were obtained with sodium *tert*-butoxide (1.75 eq.) which afforded a *homogeneous* solution of sodium salts upon mixing with a suspension of **14** in DMF (5 L/kg). Alkylation with tosylate **12** and TMSBr cleavage afforded PMEA **1** in 35-45% overall yield from adenine.



14

Scheme 4

In summary, an efficient process has been developed to prepare the anti-HIV agent, PMPA. Notable features include a practical preparation of (*R*)-propylene carbonate, a novel key alkylation using lithium *tert*-butoxide, a simple crystallization process for chiral enrichment and no chromatography. Multi-kilogram batches of PMPA have been prepared by this process in standard pilot plant equipment.

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10. Best results were obtained with catalyst type E101 NO/W 5% (53.75% water) available from Degussa Corp., Chemical Catalyst Div., 5150 Gilbertsville Hwy., Calvert City, KY 42029.
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12. The chiral purity of 1,2-propylene carbonate **11** was determined using a proprietary gas chromatography method (Chiraldex G-PN) available from Advanced Separation Technologies, Inc., 37 Leslie Court, P.O. Box 297, Whippany, NJ, 07981.
13. HPLC method: Mobile Phase A = 10 mM NH_4OAc in 5% MeOH in water, Mobile Phase B = MeOH; linear ramp over 20 min. from 0% B to 60% B. Column conditions: Hypersil ODS (C18), 5 µm, 4.6 x 150 mm, (Alltech Assoc., 2051 Waukegan Road, Deerfield, IL, 60015); 10 µL injection; flow rate 1 mL/min.; detection @ 262 nm by absorbance; ambient temperature.
14. The chiral purity of PMPA **2** was determined by HPLC analysis of a ternary complex of **2** with Cu(II) and L-phenylalanine in the mobile phase (0.7 mg/mL **2**, 3.8 mM L-Phe; 1.9 mM $CuSO_4$; 19.2 mM $NH_4H_2PO_4$ in a 3.8% [v/v] solution of acetonitrile in water). Column conditions: Hypersil ODS (C18), 5 µm, 4.6 x 250 mm, (Alltech Assoc., 2051 Waukegan Road, Deerfield, IL, 60015); 10 µL injection; flow rate 0.6 mL/min. (isocratic); detection @ 274 nm by absorbance; ambient temperature; RT(*ent*-**2**) = 10.5 to 12.5 min; RT(*R*-**2**) = 12.5 to 14.5 min.