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Asymmetric synthesis of both enantiomers of two acyclic nucleoside analogues related to d4T and acyclovir

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Abstract—The enantiomers of 1-{[(2-hydroxy-1-phenyl)ethoxy]methyl}thymine and 9-{[(2-hydroxy-1-phenyl)ethoxy]methyl}-guanine have been obtained in high yield in five steps from (*R*)- and (*S*)-1-phenylethan-1,2-diol. These chiral compounds are acyclic nucleoside analogues of d4T and acyclovir, respectively.

In recent years there has been significant interest in nucleosides as potential antiviral agents against Human Immunodeficiency Virus (HIV) and Herpes Simplex Virus (HSV). Compounds approved by the US Food and Drug Administration for the treatment of AIDS include nucleoside analogues AZT,[1] ddC,[2] ddI,[3] 3TC,[4] d4T[5] and ABC.[6] Acyclovir[7] is an acyclic nucleoside which is effective in treatment of HSV infection.

In the search for new compounds with a higher therapeutic index attention has focused mainly upon the transformation of the sugar moiety of nucleosides. As part of our continuing efforts to study the structure–activity relationships of various nucleosides as antiviral agents convenient methods have been developed[8–11] in our laboratory for the synthesis of analogues of d4T based on a benzo[*c*]furan core, e.g. compounds such as the thymine derivative bfT (Fig. 1). We now report an efficient asymmetric synthesis of both enantiomers of nucleoside analogues based on the acyclic glycone [(2-hydroxy-1-phenyl)ethoxy]methanol. These compounds which can be viewed as *seco*-benzo[*c*]furan species but, more importantly, compounds 1-{[(2-hydroxy-1-phenyl)ethoxy]methyl}thymine (**1**) and 9-{[(2-hydroxy-1-phenyl)ethoxy]methyl}guanine (**2**) are analogues of d4T and acyclovir, respectively, and hence have interesting therapeutic potential. Furthermore, the presence of a phenyl group may increase the ease of phosphorylation as has been observed for some imidazole ribonucleosides[12] and will certainly enhance the lipophilicity relative to these established drugs.

Compound **1** and the analogous uracil derivative were obtained in racemic form by Chu and co-workers[13] as intermediates in a preparation of HEPT[14] and EBPU[15] analogues. A much more efficient route is shown in

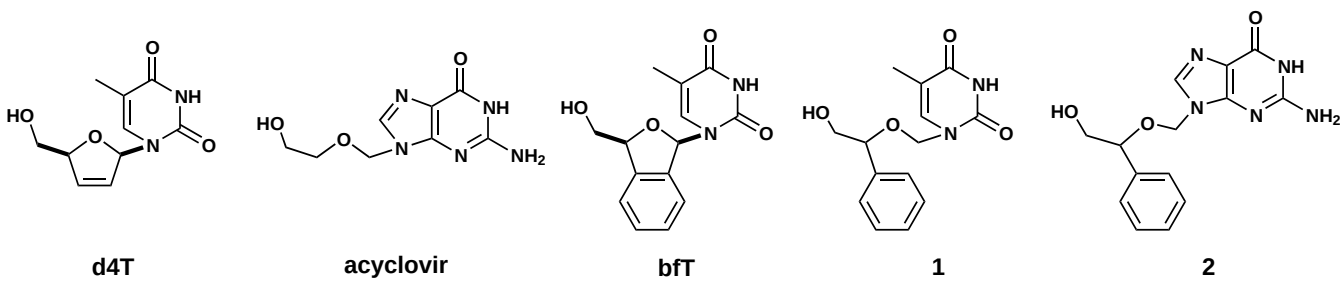

Figure 1.

Keywords: acyclic nucleosides; d4T; acyclovir; asymmetric dihydroxylation.
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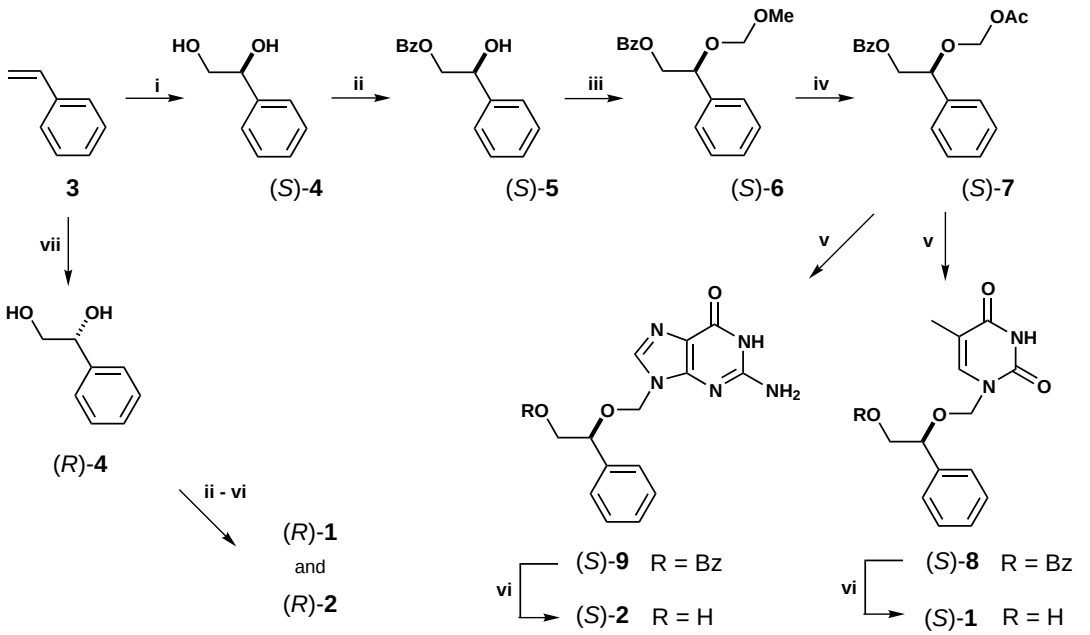

Scheme 1. (i) AD-mix α, *t*-BuOH, H_2O; (ii) BzCl, pyridine; (iii) dimethoxymethane, P_2O_5, chloroform; (iv) acetic anhydride, BF_3–Et_2O; (v) silylated base, dibenzo-18-crown-6-ether, KI, acetonitrile, toluene; (vi) K_2CO_3, MeOH; (vii) AD-mix β, *t*-BuOH, H_2O.

Scheme 1, which gives access to both enantiomers of **1** and **2**.

The diols (*S*)-**4** and (*R*)-**4** were obtained in 99% yield from styrene using the Sharpless Asymmetric Dihydroxylation reagents AD-mix α and AD-mix β, respectively. Both enantiomers of **4** were obtained in 97% ee similar to the value reported by Sharpless and coworkers.[16] After protection of the primary hydroxyl function of the diol (*S*)-**4** with a benzoyl group, the benzoate (*S*)-**5** was converted to the methoxymethylene ether (*S*)-**6** in 80% yield by treatment with dimethoxymethane and P_2O_5 in chloroform at 45°C. Acetoxylation of (*S*)-**6** was accomplished with boron trifluoride–diethyl ether in acetic anhydride at 4°C to give the corresponding acetate (*S*)-**7** in 89% yield. NMR studies with the europium chiral shift reagent Eu(D-3-trifluoroacetylcamphorate)$_3$ confirmed that chiral integrity was maintained through this sequence of steps. Condensation of acetate (*S*)-**7** with silylated thymine or silylated guanine was realised by solid–liquid phase transfer catalysis with KI–dibenzo-18-crown-6 in toluene–acetonitrile to afford the nucleoside analogues (*S*)-**8** and (*S*)-**9** in 98 and 70% yields, respectively. Removal of the benzoyl group with potassium carbonate in methanol gave the deprotected nucleoside analogues (*S*)-**1**[17] and (*S*)-**2**[18] in quantitative yield. The overall yield from the diol was 61% for (*S*)-**1** and 43% for (*S*)-**2**. An analogous sequence of steps starting from (*R*)-**4** gave the other enantiomeric species (*R*)-**1** and (*R*)-**2** in similar yields. These compounds had NMR spectra identical to those of the *S*-enantiomers.

It is notable that the convenient high yield synthesis of these novel acyclic nucleosides having one asymmetric carbon atom starts with the asymmetric dihydroxylation procedure. The biological evaluation of these acyclic nucleosides for anti-viral activity is underway.

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17. Selected data for compounds (*S*)-**1** and (*R*)-**1**; ^{1}H NMR (CD_3OD): δ 1.72 (3H, d, J 0.9, Me), 3.50 (1H, dd, $J_{1,2a}$ 2.7, $J_{2a,2b}$ 9.1, H-2a), 3.64 (1H, dd, $J_{1,2b}$ 6.3, $J_{2a,2b}$ 9.1, H-2b), 4.58 (1H, dd, $J_{1,2a}$ 2.7, $J_{1,2b}$ 6.3, H-1), 4.84 (1H, s, OH), 5.19 (2H, ABq, CH_2), 7.22–7.31 (6H, m, aromatic H, thymine H-6). For (*S*)-**1** $[\alpha]_D^{22}$ +79.0° (*c* 1.82 in MeOH). For (*R*)-**1** $[\alpha]_D^{22}$ −79.8° (*c* 1.76 in MeOH).
18. Selected data for compounds (*S*)-**2** and (*R*)-**2**; ^{1}H NMR ($(CD_3)_2SO$): δ 3.40 (1H, m, H-2a), 3.48 (1H, m, H-2b), 4.58 (1H, dd, $J_{1,2a}$ 3.2, $J_{1,2b}$ 5.5, H-1), 4.88 (1H, t, OH), 5.28 (1H, d, J 8.2, CH_2), 5.39 (1H, d, J 8.2, CH_2), 6.48 (2H, s, NH_2), 7.21–7.32 (5H, m, aromatic H), 7.69 (1H, s, guanine H-8), 10.60 (1H, s, guanine H-1). For (*S*)-**2** $[\alpha]_D^{22}$ +100.2° (*c* 0.61 in DMSO). For (*R*)-**2** $[\alpha]_D^{22}$ −100.3° (*c* 1.05 in DMSO).