Synthesis of the Phosphonate Isostere of Carbocyclic 5-Bromovinyldeoxyuridine Monophosphate

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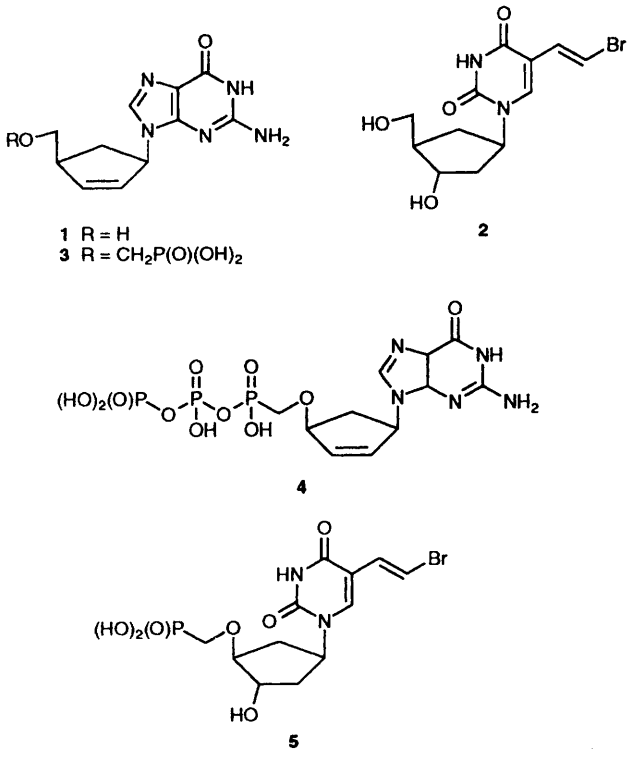
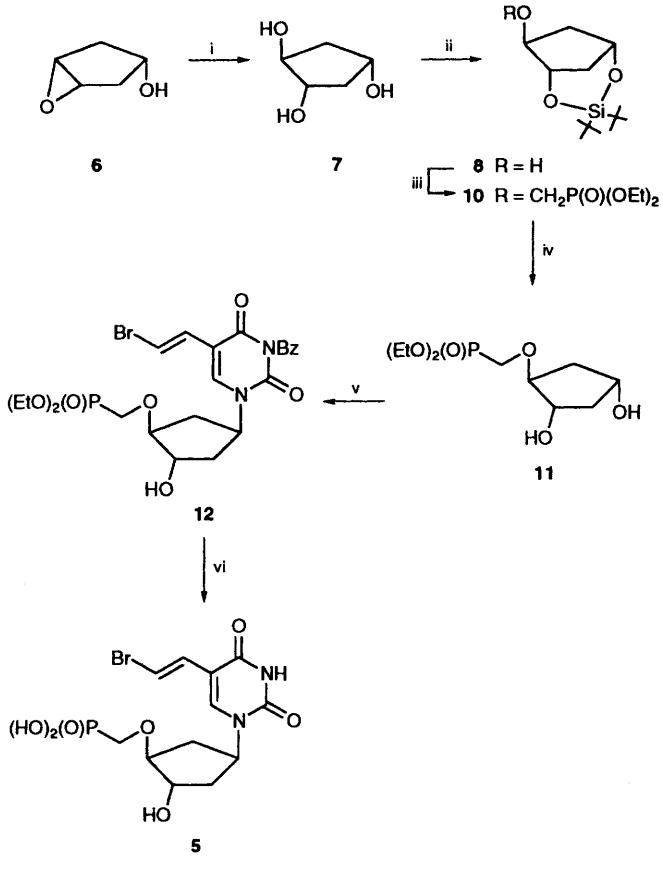
The nucleotide analogue **5** has been synthesized, *via* formation of the diol **11**, and has been shown to be inactive against HSV *in vitro*. Resolution of the intermediate diol **11** was effected using a highly stereoselective enzyme-catalysed acetylation.

There is considerable current interest in the chemistry and biological activity of carbocyclic nucleosides.[1] In particular, the anti-HIV activity of carbovir **1**[2] and the anti-herpes activity of carbocyclic 5-bromovinyldeoxyuridine (C-BVDU) **2**[3] have been featured in other papers. Previously we have prepared the phosphonate isostere of carbovir **3** and the corresponding diphosphorylphosphonate **4**; we have shown that the latter compound is a potent inhibitor of HIV-reverse transcriptase.[4] Consequently we were interested in synthesizing and testing compound **5** (an isostere of C-BVDU monophosphate) and we report here the results of our investigations.

6-Oxabicyclo[3.1.0]hexan-3-*endo*-ol **6** was hydrolysed to afford the triol **7** (Scheme 1) which, protected as the silyl derivative **8**, provided the opportunity of allowing the residual hydroxy group to react with triflate **9**[5] to afford the phosphonate **10**. The silyl group was removed and the resulting diol **11** was subjected to modified Mitsunobu reaction conditions[6] using 3-benzoyl-5-(2-bromovinyl)uracil[7] as the nucleophile. The required alcohol **12** was the only identifiable product isolated from this reaction (60% yield). Presumably S_N2 substitution of the (activated) hydroxyl group adjacent to the phosphonate moiety by the base unit is prohibited for steric reasons. Deprotection of the compound **12** in two steps (73% overall yield) furnished the target compound **5**.

A route to the nucleotide analogue **5** in optically active form could be envisaged using an enzyme-catalysed acylation process. The racemic diol **11** was esterified using Amano lipase PS in vinyl acetate to give two esters which were readily





Scheme 1 *Reagents and conditions:* i, KOH, 85% aq. DMSO, heat 3.5 h then Ac_2O, pyridine, DMAP, room temp., 24 h then 2% K_2CO_3 in MeOH, 2.5 h, 48%; ii, $Bu^t_2Si(OTf)_2$ 2,6-dimethylpyridine, DMF, 0 °C, 80 min. 90%; iii, BuLi, THF, $(EtO)_2P(O)CH_2OTf$, **9** THF, −25 °C, 30 min., 90%; iv, 40% aq. HF/MeCN, room temp. 8.5 h, 80%; v, Ph_3P, DMAD, 3-benzoyl-5-bromovinyluracil, THF, −78 °C ⟶ room temp. 60%; vi, conc. aq. NH_4OH, MeOH, 0 °C ⟶ room temp. 3 h then Me_3SiBr, DMF, 0 °C ⟶ room temp. 24 h, then MeOH, 0 °C, 73%

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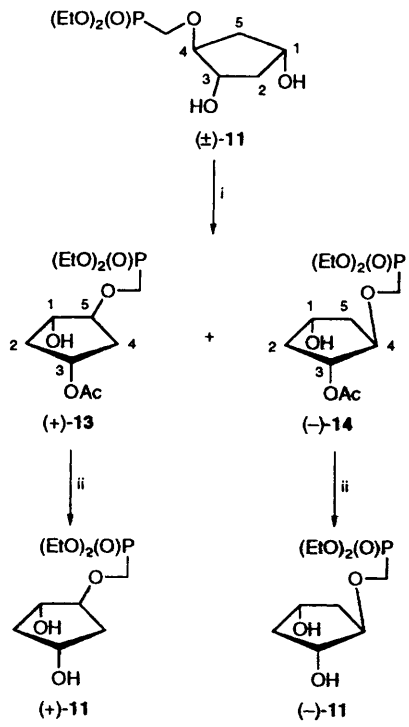
separated. Based on our previous experience,[8] we tentatively assign the absolute stereochemistry of the two acetates as shown in Scheme 2. Hydrolysis of the acetates (+)-**13** and (−)-**14** using KCN in methanol[9] gave the dextrorotatory diol (+)-**11** (72% e.e.) and laevorotatory diol (−)-**11** (95% e.e.). The optically active diols (+)- and (−)-**11** were not converted into optically active **5** since (±)-**5** was shown to be inactive against herpes simplex virus-1 *in vitro*. Presumably, unlike some acyclic phosphonates,[10] compound **5** does not gain access into virally infected cells and/or is not phosphorylated to the corresponding diphosphorylphosphonate by the available kinase enzymes. Chemical formation of this diphosphorylphosphonate and testing it against relevant HSV-polymerases should clarify the situation; this study is continuing and will be reported in due course.



Scheme 2 *Reagents and conditions:* i, Amano lipase PS, vinyl acetate, 26 h, 30 °C; ii, KCN, MeOH

Experimental

1-[(1′β,3′α,4′β)-4′-(*Diethylphosphonomethoxy*)-3′-*hydroxycyclopentyl*]-3-*benzoyl*-5-(2-*bromovinyl*)*uracil.* **12.**—To a stirred solution of Ph_3P (242.3 mg, 0.925 mmol) in anhydrous THF (4 cm^3) at −78 °C was added distilled DMAD (135 mg, 0.925 mmol) dropwise over 10 min under an argon atmosphere. After 30 min, a solution of (1α,3α,4β)-4-(diethylphosphonomethoxy)cyclopentane-1,3-diol (100 mg, 0.37 mmol) and 3-benzoyl-5-(2-bromovinyl)uracil (237.5 mg, 0.74 mmol) in THF (4 cm^3) was added dropwise over 15 min to the stirred white slurry at −78 °C. The mixture was stirred for 20 min at −78 °C and then allowed to warm to ambient temperature where it was kept for 3 h. Solvent was removed under reduced pressure at 30 °C, and the residue was chromatographed [methanol–ethyl acetate (5:95) as eluent] to afford the title compound **12** as a thick oil (129 mg, 60%) (Found: $[M + H]^+$ 571.0850. $C_{23}H_{29}BrN_2O_8P$ requires $[M + H]^+$ 571.0845); ν_{max}(neat)/cm^{-1} 3360, 2992, 1750, 1702, 1665, 1448, 1237 and 1026; δ_H(300 MHz, CD_3OD) 7.97 (m, 2 H, ArH), 7.95 (s, 1 H, 6-H), 7.71 (m, 1 H, ArH), 7.54 (m, 2 H, ArH), 7.34 (d, 1 H, *J* 13.5, HC=), 6.95 (d, 1 H, *J* 13.5, HC=), 5.30 (m, 1 H, 1′-H), 4.35 (m, 1 H, 3′-H), 4.23 (m, 4 H, 2 × CH_3CH_2), 3.99 (m, 2 H, PCH_2O), 3.90 (m, 1 H, 4′-H), 2.62 (m, 1 H, 5α′-H), 2.15 (m, 2 H, 2 × 2′-H), 1.90 (m, 1 H, 5β′-H) and 1.37 (m, 6 H, 2 × CH_3); δ_C(75.5 MHz, CD_3OD) 170.1 (COPh), 162.1 (CO, C-4), 150.4 (CO, C-2), 142.5 (C-6), 136.3 (*C*=CHBr), 132.8 (ArC), 131.5 (2 × ArC), 131.4 (ArC), 130.3 (2 × ArC), 112.5 (C-5), 109.5 (C=*C*HBr), 88.5 (C-4′), 75.0 (C-3′), 64.1 (CH_3CH_2), 64.0 (CH_3CH_2), 63.0 (d, *J* 168, CH_2P), 55.5 (C-1′), 39.4 (C-2′), 36.5 (C-5′), 16.9 (CH_3) and 16.8 (CH_3); δ_P(121.5 MHz, CD_3OD) 23.5.

Enzyme Resolution of (±)-(1α,3α,4β)-4-(*Diethylphosphonomethoxy*)*cyclopentane*-1,3-*diol* **11**.—Lipase PS Amano (90 mg) was added to a solution of (±)-(1α,3α,4β)-4-(diethylphosphonomethoxy)cyclopentane-1,3-diol (100 mg, 0.373 mmol) in vinyl acetate (8 cm^3) and the mixture was stirred in an orbital incubator (200 rev min^{-1}) at 30 °C for 26 h. The enzyme was then filtered off and the residue was washed with ethyl acetate. The combined filtrate and washings were concentrated under reduced pressure and the residue was chromatographed [methanol–dichloromethane (5:95) as eluent] to give (+)-(1α,3α,5β)-3-acetoxy-5-(diethylphosphonomethoxy)cyclopentanol (+)-**13** (48.5 mg, 42%) as an oil; $[\alpha]_D^{21}$ +19.8 (*c* 0.96, $CHCl_3$) (Found: M^+, 310.1190. $C_{12}H_{23}O_7P$ requires M^+ 310.1181); ν_{max}(neat)/cm^{-1} 3389, 2987, 1735, 1374, 1247 and 1028; δ_H(300 MHz, $CDCl_3$) 5.09 (m, 1 H, 3-H), 4.14 (m, 5 H, 2 × CH_3CH_2O + 1-H), 3.93 (m, 1 H, 5-H), 3.85 (ddd, 2 H, *J* 36.5, 14.2, 8.0, PCH_2O), 2.43 (m, 1 H, 2β-H), 2.05 (m, 2 H, 4α-H + 4β-H), 2.00 (s, 3 H, CH_3CO), 1.68 (m, 1 H, 2α-H) and 1.32 (m, 6 H, 2 × CH_3CH_2O); δ_C (75.5 MHz, $CDCl_3$) 170.6 (CO), 88.6 (d, *J* 9, C-5), 75.5 (C-1), 72.1 (C-3), 64.5 (d, *J* 167, CH_2P), 62.9 (d, *J* 6, CH_3CH_2O), 62.5 (d, *J* 6, CH_3CH_2O), 38.4 (C-2), 36.6 (C-4), 21.1 (CH_3CO), 16.4 (CH_3CH_2O) and 16.3 (CH_3CH_2O). Further elution gave (−)-(1α,3α,4β)-3-acetoxy-4-(diethylphosphonomethoxy)cyclopentanol (−)-**14** (46.5 mg, 40%); $[\alpha]_D^{21}$ −8.2 (*c* 0.94, $CHCl_3$) (Found: M^+, 310.1180. $C_{12}H_{23}O_7P$ requires M^+, 310.1181); ν_{max}(neat)/cm^{-1} 3409, 2986, 1735, 1244 and 1026; δ_H(300 MHz, $CDCl_3$) 5.05 (m, 1 H, 3-H), 4.42 (m, 1 H, 1-H), 4.15 (m, 5 H, 2 × CH_3CH_2O + 4-H), 3.85 (ddd, 2 H, *J* 31.0, 13.8, 9.2, PCH_2O), 2.45 (m, 1 H, 2-βH), 2.06 (s, 3 H, CH_3CO), 2.00 (m, 2 H, 5α-H + 5β-H), 1.70 (m, 1 H, 2α-H) and 1.33 (t, 6 H, *J* 7.0, 2 × CH_3CH_2O); δ_C (75.5 MHz, $CDCl_3$) 170.2 (CO), 85.8 (d, *J* 14, C-4), 78.0, 72.0 (C-3), 70.8 (C-1), 63.8 (d, *J* 188, CH_2P), 62.5 (CH_3CH_2O), 62.4 (CH_3CH_2O), 40.3 (C-2), 39.7 (C-5), 21.1 (CH_3CO), 16.4 (CH_3CH_2O) and 16.3 (CH_3CH_2O).

Treatment of (+)-**13** (42 mg, 0.135 mmol) with anhydrous potassium cyanide (4.4 mg, 0.068 mmol) in dry methanol (1.5 cm^3), with stirring of the mixture overnight under an argon atmosphere and subsequent evaporation, gave an oil which was purified by chromatography (methanol–ethyl acetate, 8:92 as eluent) to give (+)-**11** (34 mg, 94%); $[\alpha]_D^{21}$ +10.2 (*c* 1, $CHCl_3$) (72% e.e). Similar treatment of compound (−)-**14** (27.6 mg, 0.089 mmol) afforded (−)-**11** (23 mg, 96%); $[\alpha]_D^{21}$ −9.7 (*c* 0.9, $CHCl_3$) (95%e.e).

The IR and ^1H and ^{13}C NMR spectra of both enantiomers were identical with those of the racemic compound.

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