Synthesis of 1',2'-Seco Analogues of Dideoxy Didehydro Nucleosides as Potential Antiviral Agents

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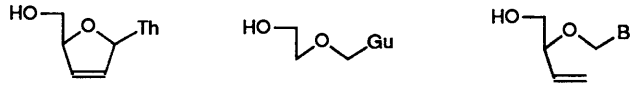
The racemic 1',2'-seco analogues of dideoxy didehydro nucleosides have been synthesized *via* a six-step chemical sequence. In this way (±)-1-[(1'-hydroxybut-3'-en-2'-yloxy)methyl]thymine **3d** or cytosine **3b** and (±)-9-[(1'-hydroxybut-3'-en-2'-yloxy)methyl] adenine **3a** or guanine **3c** have been obtained and their antiviral evaluation is reported.

The discovery of the human immunodeficiency virus (HIV) as the causative agent of AIDS and the identification of HIV as a retrovirus prompted the search for agents that would be able to block the HIV replication process.[1] In this respect, the inhibitory effect of the 2',3'-dideoxy series have been confirmed[2] and compounds such as AZT (azidothymidine), ddC (dideoxycytidine) and D4T **1** have been extensively studied;[3] however the search for new therapeutic compounds is still of current interest in order to reach anti-HIV derivatives with higher therapeutic indexes. Furthermore, it is well established that acyclic variation[4] in the sugar moiety of nucleosides produce important antiviral compounds such as acyclovir **2**.

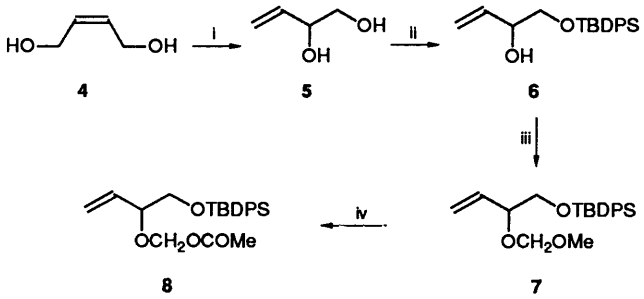


1 **2** **3**

These two essential structural nucleosidic features (*i.e.* a 2',3' double bond and an acyclic sugar moiety) prompted us to synthesize and evaluate a series of racemic 1',2'-seco analogues of D4 nucleosides **3**.

Results

For our purposes we used the efficient coupling procedure we described recently[5,6] between the easily accessible acyclic synthon **8** and the four nucleobases (Ad, Cy, Th, Gu). The synthesis (Scheme 1) started with (*Z*)-but-2-ene-1,4-diol **4**

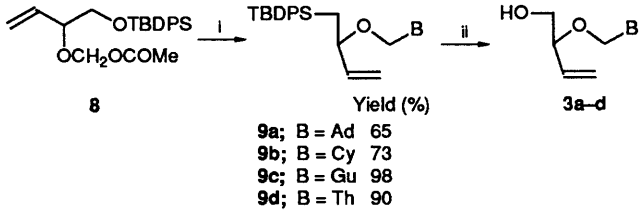


4 **5** **6** **8** **7**

Scheme 1 *Reagents and conditions:* i, ref. 7; ii, TBDPSCl, pyridine, room temp., 1 h; iii, $CH_2(OMe)_2$, $CHCl_3$, P_2O_5, 40 °C, 24 h; iv, $BF_3{\cdot}Et_2O$, Et_2O, 4 °C, 48 h

which was isomerized into but-3-ene-1,2-diol **5** by reaction with $HgSO_4$–H_2SO_4 in 70% yield according to the new procedure of Ramarao.[7] In order to protect the primary hydroxy function in a compatible way with the fourth step of the synthesis, the *tert*-butyldiphenylsilyl (TBDPS) group was selected and introduced specifically: thus, the diol **5** gave **6** quantitatively.

Subsequent treatment of **6** with dimethoxymethane and phosphorus pentaoxide[8] in chloroform afforded the methoxymethylene ether **7** (73%) the acetoxylation of which in acetic anhydride and boron trifluoride–diethyl ether at 4 °C gave **8** (95%). This was the required synthon for the coupling step with the four trimethylsilylated nucleobases (Scheme 2). This



8 Yield (%) **3a–d**

9a; B = Ad 65
9b; B = Cy 73
9c; B = Gu 98
9d; B = Th 90

Scheme 2 *Reagents and conditions:* i, $B(SiMe_3)_3$, KI, 18-crown-6, PhMe–MeCN, 80 °C; ii, TBAF/THF, room temp., 3 h

condensation was accomplished by a solid-liquid phase transfer catalysis method with KI-dibenzo-18-crown-6 in toluene–acetonitrile (1:1, v/v). As mentioned in our previous work,[5,6] this efficient procedure gave the expected regiospecific 1-*N* pyrimidyl or 9-*N* purinyl unsaturated acyclonucleosides **9a–d** in good yields (see Scheme 2). Further removal of the TBDPS group with tetrabutylammonium fluoride in THF (tetrahydrofuran) and recrystallization when possible of the crude products gave the fully deprotected nucleosidic analogues **3a–d** (95%). The regioisomerism of these four compounds is ascertained by means of their UV spectra[9] in two different media (see Experimental section).

Although biological evaluation showed a marginal anti-HIV activity for **3d**, the analogue of D4T, none of the four acyclic unsaturated nucleosides had any effect against various DNA or RNA viruses in cell cultures.

Experimental

M.p.s were obtained with a Büchi (capillary) apparatus and were uncorrected. UV spectra were determined on a Cary 1186 spectrophotometer. Elemental analyses were performed by the 'Service de Microanalyse du CNRS, Division de Vernaison'. ^1H NMR spectra were determined on a Brüker AC250, or a Varian EM390 spectrometer. *J* Values are given in Hz.

(±)-1-*tert*-*Butyldiphenylsilyloxybut*-3-*en*-2-*ol* **6**.—To a solution of (±)-but-3-ene-1,2-diol **5** (9 g, 0.102 mol) in anhydrous pyridine (80 cm^3) was added dropwise *tert*-butyldiphenylchlorosilane (31.4 cm^3, 0.122 mol). After being stirred for 1 h at room temp. the solvent was evaporated under reduced pres-

sure and the residue extracted into CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated to yield the *title compound*; R_f 0.76 (99:1; CH_2Cl_2–MeOH), δ_H(90 MHz; $CDCl_3$) 1.05 (9 H, s, 3 Me), 2.7 (1 H, s, OH), 3.7 (2 H, m, CH_2), 4.25 (1 H, m, CH), 5.1–6.15 (3 H, m, CH=CH_2) and 7.3–7.9 (10 H, m, aromatic) (Found: C, 73.45; H, 8.0. $C_{20}H_{26}O_2Si$ requires C, 73.56; H, 8.02%).

(±)-1-tert-*Butyldiphenylsilyloxy*-2-*methoxymethylenoxybut*-3-*ene* **7**.—To a solution of **6** (1 g, 3.06 mmol) in anhydrous chloroform (10 cm^3) and formaldehyde dimethyl acetal (0.411 cm^3, 4.65 mmol) was added phosphorus pentaoxide (0.4 g) portionwise with vigorous stirring, the temperature being maintained at 40–45 °C. The mixture was then stirred at room temp. for 24 h. The supernatant was diluted with dichloromethane (50 cm^3), decanted and washed with water, saturated aqueous $NaHCO_3$ and once with water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the product. Column chromatography of the latter on silica gel eluting with cyclohexane–diethyl ether (99:1) afforded pure *title compound* **7** (0.825 g, 73% yield) as an oil; R_f 0.59 (9:1 cyclohexane–diethyl ether); δ_H(90 MHz; $CDCl_3$) 1.0 (9 H, s, 3 Me), 3.36 (3 H, s, OMe), 3.7 (2 H, m, CH_2OSi), 4.2 (1 H, m, CH), 4.73 (2 H, s, OCH_2O), 5.05–6.1 (3 H, m, CH=CH_2) and 7.34–7.65 (10 H, m, aromatic) (Found: C, 71.6; H, 8.2. $C_{22}H_{30}O_3Si$ requires C, 71.30; H, 8.16%.

(±)-1-tert-*Butyldiphenylsilyloxy*-2-*acetoxymethylenoxybut*-3-*ene* **8**.—To a solution of **7** (3.6 g, 9.74 mmol) in anhydrous diethyl ether (40 cm^3) at −20 °C was added acetic anhydride (1.3 cm^3, 13.7 mmol) and boron trifluoride–diethyl ether (0.356 cm^3, 2.84 mmol). This mixture was stirred at 4 °C for 48 h after which it was poured in ice–water (25 cm^3), neutralized with saturated aqueous $NaHCO_3$ and extracted twice with diethyl ether (100 cm^3). The ethereal extracts were washed once with 10% aqueous $NaHCO_3$ and twice with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual yellow oil was flash chromatographed on a silica gel column with 98:2 cyclohexane–diethyl ether as the eluting system and afforded **8** (3.6 g, 95% yield); R_f 0.33 (9:1 cyclohexane–diethyl ether), δ_H(90 MHz; $CDCl_3$) 1.0 (9 H, s, 3 Me), 1.96 (3 H, s, MeCO), 3.63 (2 H, m, CH_2OSi), 4.2 (1 H, m, CH), 5.15–5.36 (4 H, m, CH_2=, OCH_2CO), 5.73 (1 H, m, CH=) and 7.34–7.65 (10 H, m, aromatic) (Found: C, 69.35; H, 7.6. $C_{23}H_{30}O_4Si$ requires C, 69.31; H, 7.58%).

Preparation of Seconucleosides **9a–d**: *General Procedure.*—*Silylation of nucleobases.* Unprotected nucleobase (Ad, Cy, Gu, Th) (6 mmol) in hexamethyldisilazane (25 cm^3) and a catalytic amount of ammonium sulphate were refluxed for 1 d in the case of pyrimidines and for 2 d in the case of purines. The reagent was cautiously removed under reduced pressure.

PTC glycosylation. A solution of **8** (1 mmol) and silylated nucleobase (1.2 mmol) in acetonitrile–toluene (1/1 v/v; 10 cm^3) containing dibenzo-18-crown-6 ether (0.2 mmol) and potassium iodide (0.8 mmol) was stirred for 2–8 h at 80 °C under an atmosphere of argon. The insoluble material was filtered off and the filtrate evaporated under reduced pressure to give an oil which was chromatographed on a silica gel column using methanol–dichloromethane as the eluting system.

(±)9-[(1′-tert-*Butyldiphenylsilyloxybut*-3′-*en*-2′-*yloxy*)-*methyl*]*adenine* **9a**.—The *title compound* was obtained as an oil following the aforementioned procedure (8 h). After chromatography with methanol–dichloromethane (1:99) as the eluent **9a** was recrystallized (65% yield) from chloroform–pentane; R_f 0.23 (methanol–dichloromethane 5:95), m.p. 145–146 °C, λ_{max}(EtOH, 95%)/nm 259, δ_H(90 MHz; $CDCl_3$) 0.98 (9 H, s, 3 Me), 3.61 (2 H, m, CH_2), 4.06 (1 H, m, CH), 5.23 (2 H, m, OCH_2N), 5.63 (3 H, m, CH=CH_2), 5.78 (2 H, s, NH_2), 7.29–7.63 (10 H, m, aromatic), 7.91 (1 H, s, 2-H) and 8.38 (1 H, s, 8-H) (Found: C, 65.9; H, 6.45; N, 14.8; Si, 5.85). $C_{26}H_{31}N_5O_2Si$ requires C, 65.93; H, 6.59; N, 14.78; Si, 5.92%).

(±)1-[(1′-tert-*Butyldiphenylsilyloxybut*-3′-*en*-2′-*yloxy*)-*methyl*]*cytosine* **9b**.—The *title compound* was obtained as an oil following the aforementioned procedure (6 h). After chromatography with methanol–dichloromethane (3:97) as the eluent **9b** was recrystallized (73% yield) from chloroform–pentane; R_f 0.28 (methanol–dichloromethane 5:95); m.p. 130–131 °C, λ_{max}(EtOH, 95%)/nm 269, δ_H(90 MHz; $CDCl_3$) 1.03 (9 H, s, 3 Me), 3.60 (2 H, m, CH_2), 4.11 (1 H, m, CH), 5.1–5.35 (4 H, m, CH_2=, OCH_2N), 5.63 (2 H, m, CH=, 5-H) and 7.33–7.65 (11 H, m, aromatic, 6-H) (Found: C, 66.85; H, 7.05; N, 9.4. $C_{25}H_{31}N_3O_3Si$ requires C, 66.78; H, 6.94; N, 9.34; Si, 6.24%).

(±)9-[(1′-tert-*Butyldiphenylsilyloxybut*-3′-*en*-2′-*yloxy*)-*methyl*]*guanine* **9c**.—The *title compound* was obtained as an oil following the aforementioned procedure (4 h). After chromatography with methanol–dichloromethane (4:96) as the eluent **9c** was recrystallized (98% yield) from chloroform–pentane. R_f 0.28 (10% methanol in dichloromethane), m.p. 232–234 °C; λ_{max}(EtOH, 95%)/nm 253; δ_H(90 MHz; $CDCl_3$) 0.90 (9 H, s, 3 Me), 3.53 (2 H, m, CH_2), 4.03 (1 H, m, CH), 5.13–5.37 (4 H, m, CH_2=, NCH_2O), 5.61 (1 H, m, CH=), 6.08 (2 H, s, NH_2), 7.26–7.53 (10 H, m, aromatic), 7.77 (1 H, s, 8-H) and 10.54 (1 H, s, NH) (Found: C, 63.85; H, 6.45; N, 14.25; Si, 5.4. $C_{26}H_{31}N_5O_3Si$ requires C, 63.77; H, 6.38; N, 14.30; Si, 5.73%).

(±)1-[(1′-tert-*Butyldiphenylsilyloxybut*-3′-*en*-2′-*yloxy*)-*methyl*]*thymine* **9d**.—The *title compound* was obtained as an oil following the aforementioned procedure (2 h). After chromatography with methanol–dichloromethane (4:96) as the eluent **9d** was recrystallized (90% yield) from chloroform, m.p. 105–106 °C, R_f 0.31 (methanol–dichloromethane 5:95), λ_{max}(EtOH, 95%)/nm 263, δ_H(90 MHz; $CDCl_3$) 1.03 (9 H, s, 3 Me), 1.87 (3 H, s, Me), 3.65 (2 H, m, CH_2), 4.05 (1 H, m, CH), 5.05–5.35 (2 H, m, CH_2=), 5.65 (1 H, m, CH=), 7.12 (1 H, s, 6-H), 7.34–7.68 (10 H, m, aromatic) and 8.77 (1 H, s, NH) (Found: C, 67.2; H, 6.9; N, 6.05; Si, 6.2. $C_{26}H_{32}N_2O_4Si$ requires C, 67.21; H, 6.94; N, 6.02; Si, 6.04%).

Desilylation of Seconucleosides: General Procedure.—To a stirred solution of silylated acyclonucleoside **9** (1 mmol) in THF (2.5 cm^3) was added a solution (3 mmol, 0.9 cm^3) of tetrabutylammonium fluoride (1.1 mol dm^{-3} in THF) at room temp. for 3 h. The solvent was evaporated under reduced pressure and the free seconucleoside **3** was obtained after recrystallization in 95% yield.

(±)9-[(1′-*Hydroxybut*-3′-*en*-2′-*yloxy*)*methyl*]*adenine* **3a**. R_f 0.27 (methanol–dichloromethane 1:9), m.p. 182–183 °C (from methanol–dichloromethane), λ_{max}(EtOH, 95%)/nm 258, λ_{max}(0.1 mol dm^{-3} KOH)/nm 259, δ_H(250 MHz; [$^2H_6$]DMSO) 3.33 (2 H, m, CH_2), 4.06 (1 H, q, *J* 5.96, CH), 4.81 (1 H, t, *J* 5.79, OH), 5.17 (2 H, m, NCH_2O), 5.52–5.75 (3 H, m, CH=CH_2), 7.30 (2 H, s, NH_2), 8.18 (1 H, s, 2-H) and 8.26 (1 H, s, 8-H) (Found: C, 50.65; H, 5.65; N, 29.25. $C_{10}H_{13}N_5O_2$ requires C, 51.05; H, 5.57; N, 29.77%).

(±)1-[(1′-*Hydroxybut*-3′-*en*-2′-*yloxy*)*methyl*]*cytosine* **3b**. M.p. 167–168 °C (from THF), R_f 0.17 (methanol–dichloromethane 1:9), λ_{max}(EtOH, 95%)/nm 268, λ_{max}(0.1 mol dm^{-3} HCl)/nm 276, δ_H(250 MHz; [$^2H_6$]DMSO) 3.32 (2 H, m, CH_2), 4.00 (1 H, q, CH), 4.79 (1 H, t, *J* 5.63, OH), 5.03–5.29 (4 H, m, CH_2=, NCH_2O), 5.75 (2 H, m, CH=, 5-H), 7.20 (2 H,

d, *J* 10.15, NH_2) and 7.60 (1 H, d, *J* 7.17, 6-H) (Found: C, 51.05; H, 6.1; N, 19.5. $C_9H_{13}N_3O_3$ requires C, 51.17; H, 6.20; N, 19.89%).

(±)9-[(1′-*Hydroxybut*-3′-*en*-2′-*yloxy*)*methyl*]*guanine* **3c**. M.p. 280 °C (decomp.) (from dichloromethane–acetonitrile), R_f 0.41 (propan-2-ol–ammonia–water 7:0.5:0.5): λ_{max}(EtOH, 95%)/nm 252; λ_{max}(0.1 mol dm^{-3} KOH)/nm 266 and 257sh; δ_H(250 MHz; [$^2H_6$]DMSO) 3.33 (2 H, m, CH_2), 4.01 (1 H, q, CH), 4.79 (1 H, t, *J* 5.7, OH), 5.07–5.42 (4 H, m, NCH_2O, CH_2=), 5.69 (1 H, m, CH=), 6.53 (2 H, s, NH_2), 7.80 (1 H, s, 8-H) and 10.68 (1 H, s, NH) (Found: C, 47.65; H, 5.2; N, 27.6. $C_{10}H_{13}N_5O_3$ requires C, 47.80; H, 5.21; N, 27.87%).

(±)1-[(1′-*Hydroxybut*-3′-*en*-2′-*yloxy*)*methyl*]*thymine* **3d**. M.p. 92–93 °C (from ethanol), R_f 0.35 (methanol–dichloromethane 1:9), λ_{max}(EtOH, 95%)/nm 262, λ_{max}(0.1 mol dm^{-3} HCl)/nm 263; δ_H(250 MHz; [$^2H_6$]DMSO) 1.75 (3 H, s, Me), 3.33 (2 H, m, CH_2), 3.96 (1 H, q, *J* 6.29, CH), 4.78 (1 H, t, *J* 5.8, OH), 5.02–5.28 (4 H, m, CH_2=, NCH_2O), 5.71 (1 H, m, CH=), 7.56 (1 H, s, 6-H) and 11.29 (1 H, s, NH) (Found: C, 53.5; H, 6.35; N, 12.1. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.23; N, 12.38%).

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