Synthesis of Unsaturated 4′-Azido Pyranosyl Thymines as Potential Antiviral and anti-HIV Agents

Michel Bessodes, Marie-José Egron, Jean Filippi and Kostas Antonakis
Institut de Recherches Scientifiques sur le Cancer, CNRS, 94801 Villejuif Cedex, France

Condensation of thymine with diacetyl-D-xylal and triacetyl-D-glucal afforded the unsaturated nucleosides **1**, **6** and **7**. After deacetylation and selective protection of the primary hydroxy groups in the case of the glucose derivatives, these compounds were either submitted to Mitsunobu reaction with hydrazoic acid to give the azides **4**, **14** and **15**, or oxidised with PDC–molecular sieves to give the unsaturated keto nucleosides **3**, **12** and **13**. Reduction of the azides **4**, **14** and **15** afforded the amino derivatives **5**, **18** and **19**. Oxidation of the latter two compounds gave the aminouronate nucleosides **20** and **21**. Preliminary testing on various virus models, including HIV, showed the ketones **3**, **12** and **13** to be the most active compounds of this series.

The increasing discovery of new viral diseases has prompted a growing interest in antiviral drugs. In particular, the most threatening problem of AIDS deserved particular attention, especially after it was shown that the retroviral agent Human Immunodeficiency Virus (HIV) was responsible for that disease.[1,2] Although there is to date no cure for AIDS, the best therapeutic agents evaluated so far are 3′-deoxy-3′-azidothymidine (AZT)[3–6] and various 2′,3′-dideoxy nucleosides.[7–9]

Although AZT is currently the only anti-AIDS drug approved for clinical use, it induces bone marrow toxicity leading to severe anaemia and neutropaenia.[10,11] For this reason, there is urgent need for the design of analogues with greater specificity.

Conformational properties of AZT have been studied by means of the molecular mechanics force field approach. It was concluded that the azido group did not significantly change the drug's conformational properties as compared with other deoxynucleosides.[12] Thus the intrinsic properties of the azide group should be considered of prime importance in terms of antiviral activity.

Many pentofurano analogues have been synthesised since AZT, bearing different functions at the 3′-position, such as H,[7] F,[8] CN,[13] and 2′,3′-olefinic derivatives,[14,15] however, little effort has been directed towards conformational modifications. To implement this gap we have studied the synthesis of pyranose analogues of AZT, as it is well established that pyranose nucleosides are found among important antibiotic and antitumour compounds having a wide spectrum of biological activities.[16–22] In addition the versatility of ketohexose and aminohexose nucleosides has been demonstrated both from the chemical and the biological viewpoint,[23,24] thus we also describe the synthesis and properties of two related unsaturated keto nucleosides and amino nucleosides with which the azides were compared.

Results and Discussion

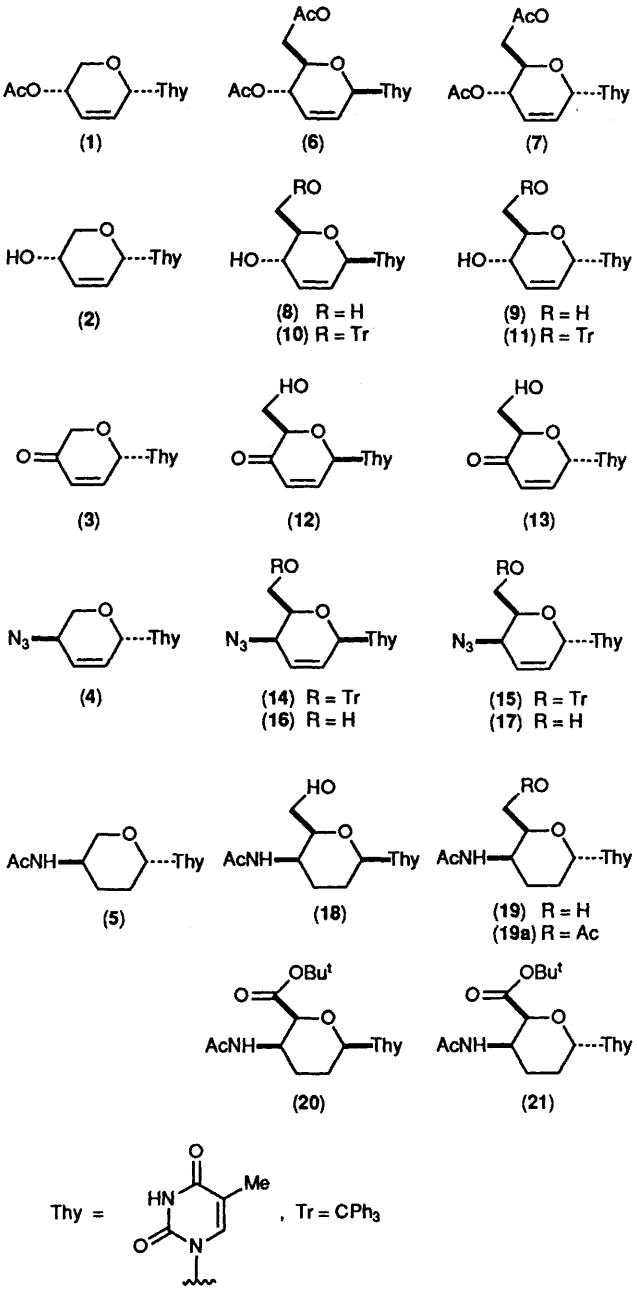
Reaction of diacetyl-D-xylal[25] with persilylated thymine in the presence of perchlorate catalyst led to the unsaturated nucleoside **1**. It is interesting to note that, in the case of xylal, only one anomer could be detected at the end of the reaction. This difference with what was observed in the case of hexopyranoses[26] can be attributed to the fact that in this case no steric hindrance could impair the S_N2' mechanism to the benefit of oxonium formation. The kinetic product was therefore obtained. This was confirmed by examination of the NMR spectrum: the coupling constants observed for $J_{3',4'}$ (2.7 Hz) and $J_{1',2'}$ (1.8 Hz) are consistent with the α-configuration,[27] along with the positive optical rotation.

Deacetylation of compound **1** with sodium methoxide led to the nucleoside **2** which was subjected to Mitsunobu reaction in the presence of hydrazoic acid,[28] to give the desired azide **4**. It should be noted that the experimental conditions for this reaction were very critical and that only the described procedure gave satisfactory results. The azide group was identified by its IR vibration at 2100 cm^{-1} and by the shielding effect observed on proton 4′-H (δ 3.89 compared with δ 4.27 in **2**). Catalytic hydrogenation of azide **4** in the presence of acetic anhydride gave the corresponding saturated amide **5**. On the other hand, pyridinium dichromate (PDC)–molecular sieve[29] oxidation of compound **2** gave the corresponding unsaturated keto nucleoside **3**. The presence of the carbonyl group at C-4′ was ascertained by the disappearance of proton 4′-H and the general deshielding effect on the other protons, especially on 5′-H (δ 4.39 compared with δ 3.57 in **2**).

In order to investigate the effect of a hydroxymethyl group at position 5′, the same set of reactions was performed on the glucose derivative. Condensation of thymine with diacetyl-D-glucal gave[25] a mixture of the anomers **6** and **7**. Deacetylation with sodium methoxide led to compounds **8** and **9**, which were selectively protected at the 6′-position by tritylation, to give ethers **10** and **11**. PDC–molecular sieve oxidation followed by immediate detritylation with aq. acetic acid gave the unsaturated keto nucleosides **12** and **13**. Mitsunobu reaction on ethers **10** and **11** gave the corresponding azides **14** and **15**, which were subsequently deprotected in acetic acid to afford compounds **16** and **17**. The inversion of configuration at carbon C-4′ was evidenced by the change in the coupling constant of the NMR signal attributed to 3′-H. As shown in Fig. 1, as an example in the case of the α-azido-nucleoside **17**, a larger $J_{3',4'}$ coupling constant was obtained [spectrum (*b*)].

Azides **14** and **15** were hydrogenated over palladium in the presence of acetic anhydride to give directly the unprotected acetamides **18** and **19**. The unstable compound **19** was acetylated to give compound **19a** for analytical purposes. In addition the esters **20** and **21**, which are analogues of natural antibiotics such as gougerotine,[30] were synthesised *via* chromium(VI) oxidation of compounds **18** and **19** in the presence of t-butyl alcohol.

The antiviral activity of these compounds against some viral strains, including HIV and herpes simplex has been



investigated. Preliminary tests showed some interesting activity for the unsaturated keto nucleosides **3**, (ED_{50} 2 μg ml^{-1}; HIV-MT4),* **12** and **13** (ED_{50} 10 and 15 μg ml^{-1}; herpes simplex). The other compounds tested presented weak or no activity (ED_{50} > 250 μg ml^{-1}) against all the studied viruses. An extensive evaluation is in progress and complete results will be published in due course.

Experimental

General Methods.—TLC was carried out on silica gel 60 F_{254} (Merck); flash chromatography was performed on column filled with silica gel 60 (230–400 mesh, SDS). UV spectra were recorded with a Varian UV–VIS M635 spectrophotometer. ^1H NMR spectra were taken on a Bruker MSL 300 spectrometer for solutions in deuteriated chloroform with Me_4Si as an internal standard coupling constants are given Hz. Optical rotations were meaasured with a Roussel-Jouan Quick polarimeter.

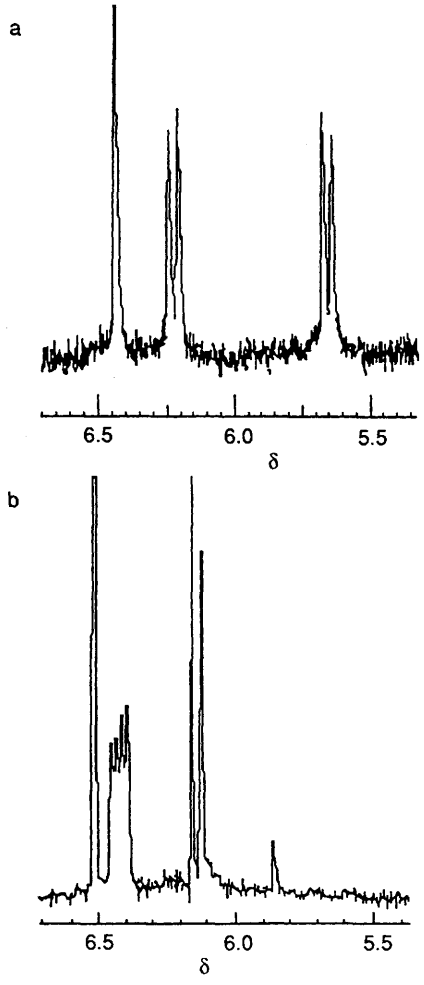


Fig. 1. ^1H NMR spectra (*a*) compound **9** and (*b*) compound **17**, showing the inversion of configuration at C-4′.

1-(4′-O-*Acetyl*-2′,3′-*dideoxy*-α-D-glycero-*pent*-2′-*enopyranosyl*)*thymine* **1**.—To a 1,2-dichloroethane solution of bis-(trimethylsilyloxy)thymine (175 mg, 1.4 mmol), were added successively di-*O*-acetyl-D-xylal (200 mg, 1 mmol), lithium perchlorate (106 mg, 0.5 mmol) and trityl perchlorate (342 mg, 1 mmol). The mixture was stirred for 10 min at room temperature, then neutralised with aqueous sodium hydrogen carbonate, washed with water, dried and concentrated. Flash chromatography (ethyl ether) gave *compound* **1** which crystallised in diethyl ether–ethyl acetate (200 mg, 75% yield); m.p. 175 °C, $[\alpha]_D^{20}$ +175° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 13 300); δ_H 8.35 (1 H, br s, NH), 7.04 (1 H, s, 6-H), 6.41 (1 H, d, $J_{1',2'}$ 2, 1′-H), 6.34 (1 H, dd, $J_{2',3'}$ 10, $J_{3',4'}$ 2.7, 3′-H), 5.88 (1 H, dd, $J_{1',2'}$ 1.8, $J_{2',3'}$ 10.3, 2′-H), 5.36 (1 H, m, 4′-H), 4.15 (1 H, dd, $J_{4',5'}$ 4.8, J_{gem} 11.8, 5′-H), 3.81 (1 H, dd, $J_{4',5'}$ 6.4, J_{gem} 11.9, 5′-H), 2.1 (3 H, s, Ac) and 1.92 (3 H, s, Me) (Found: C, 53.8; H, 5.2; N, 10.4. $C_{12}H_{14}N_2O_5$ requires C, 54.1; H, 5.3; N, 10.5%).

1-(2′,3′-*Dideoxy*-α-D-glycero-*pent*-2′-*enopyranosyl*)*thymine* **2**.—Compound **1**, (266 mg, 1 mmol) dissolved in methanol (10 ml) was treated with sodium methoxide (2 mol l^{-1}; 1 ml) for 15 min, neutralised with IR 120 Amberlite, filtered and concentrated. The residue was crystallised in methanol to give *compound* **2**, (213 mg, 95%); m.p. 171 °C; $[\alpha]_D^{20}$ +80° (*c* 0.1,

* ED_{50} = effective dose (concentration) required to reduce test organism to 50% of its initial population (after 4 days).

methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 10 012); δ_H 10.1 (1 H, br s, NH), 7.46 (1 H, s, 6-H), 6.23 (1 H, d, $J_{1',2'}$ 1.9, 1'-H), 5.83 (1 H, d, $J_{2',3'}$ 10.1, 3'-H), 5.76 (1 H, dd, $J_{1',2'}$ 1.9 $J_{2',3'}$ 10.2, 2'-H), 4.27 (1 H, m, 4'-H), 3.91 (1 H, dd, $J_{4',5'}$ 3.4 J_{gem} 12, 5'-H), 3.57 (1 H, dd, $J_{4',5'}$ 7.1, J_{gem} 11.4, 5'-H) and 1.80 (3 H, s, Me) (Found: C, 53.4; H, 5.4; N, 12.9. $C_{10}H_{12}N_2O_4$ requires C, 53.6; H, 5.35; N, 12.5%).

(6'-R)-2',6'-*Dihydrothymidin*-1-*yl*)-3'-*pyrone* **3**.—To a solution of compound **2** (224 mg, 1 mmol) in dichloromethane (5 ml), were added successively PDC, (550 mg, 1.5 mmol) and molecular sieves (3 Å; 800 mg). After stirring for 3 h, the mixture was diluted with ethyl acetate (20 ml), filtered and concentrated. Column purification (hexane–ethyl acetate, 50:50) gave *compound* **3**, which crystallised from ethyl acetate (178 mg, 80%); m.p. 178°; $[\alpha]_D^{20}$ +25 (*c* 0.1 methanol); λ_{max}/nm: 261 (ε/l mol^{-1} cm^{-1}: 10 456); δ_H 8.6 (1 H, s, NH), 7.09 (1 H, s, 6-H), 6.91 (1 H, d, $J_{2',3'}$ 10.4, 2'-H), 6.69 (1 H, s, 1'-H), 6.47 (1 H, dd, $J_{2',3'}$ 10.4, 3'-H), 4.39 (2 H, s, 5'-H) and 1.95 (3 H, s, CH_3) (Found: C, 53.6; H, 4.55; N, 12.6. $C_{10}H_{10}N_2O_4$, 0.1 H_2O requires C, 53.6; H, 4.5; N, 12.5%).

1-(4'-*Azido*-2',3',4'-*trideoxy*-α-L-glycero-*pent*-2'-*enopyranosyl*)*thymine* **4**.—Compound **2** (224 mg, 1 mmol) was dissolved in tetrahydrofuran (5 ml), triphenyl phosphine (525 mg, 2 mmol) was added and the mixture was cooled to 0 °C under nitrogen. A mixture of diethyl azodicarboxylate (0.3 ml, 2 mmol) and hydrazoic acid (0.53 ml, 1.9 mol l^{-1} in benzene) was then added. After a few minutes it was concentrated and chromatographed on silica gel (diethyl ether) to give *compound* **4** which crystallised in diisopropyl oxide–ethyl acetate (124 mg, 50%); m.p. 110 °C, $[\alpha]_D^{20}$ −215° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 9810); δ_H 8.8 (1 H, s, NH), 7.23 (1 H, s, 6-H), 6.41 (2 H, m, 1'-H, 3'-H), 6.02 (1 H, d, $J_{2',3'}$ 10, 2'-H), 4.18 (1 H, d_{AB}, *J* 13, 5'-H), 4.08 (1 H, d_{AB}, *J* 13, 5'-H), 3.89 (1 H, m, 4'-H) and 1.91 (3 H, s, Me) (Found: C, 48.1; H, 4.5; N, 27.6. $C_{10}H_{11}N_5O_3$ requires C, 48.2; H, 4.4; N, 28.1%).

1-(4'-*Acetamido*-2',3',4'-*trideoxy*-α-L-glycero-*pentopyranosyl*)*thymine* (**5**).—A methanolic solution (10 ml) of compound **4** (100 mg, 0.4 mmol) was hydrogenated in the presence of palladium-on-carbon (100 mg) and acetic anhydride (1 ml), over 6 h at ambient temperature and pressure. After filtration and concentration, the residue was chromatographed on silica gel (ethyl acetate, then ethyl acetate–methanol 8:2). Compound **5** was obtained as a semicrystalline powder from ether (87 mg, 90%); $[\alpha]_D^{20}$ −15° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1} 9718); δ_H 8.6 (1 H, s, NH), 7.4 (1 H, s, 6-H), 5.9 (1 H, m, $J_{1',2'}$ 10.2, 1'-H), 5.7 (1 H, d, *J* 9.4, NH), 4.22 (1 H, m, 5'-H), 4.02 (1 H, m, 4'-H), 3.75 (1 H, dd, J_{gem} 12, $J_{4',5'}$ 4.5, 5'-H), 2.25–1.7 (4 H, m, 2 × 2'-H, 2 × 3'-H), 2.05 (3 H, s, Ac) and 1.95 (3 H, s, Me) (Found: C, 53.6; H, 6.1; N, 15.4. $C_{12}H_{17}N_3O_4$ requires C, 53.9; H, 6.4; N, 15.7%).

1-(2',3'-*Dideoxy*-β-D-erythro-*hex*-2'-*enopyranosyl*)*thymine* **8**.—Compound **6**[25] (1 g, 3 mmol) was dissolved in methanol (10 ml), sodium methoxide (2 mol l^{-1}; 2 ml) was added and the mixture was stirred 15 min, neutralised with Amberlite resin (IR 120, H^+), filtered and concentrated. The residue gave compound **8** as a semicrystalline solid in ether (700 mg, 95%); m.p. 80°, $[\alpha]_D^{20}$ −25° (*c* 0.1, methanol); λ_{max}/nm: 265 (ε/l mol^{-1} cm^{-1}: 9753); δ_H 8.6 (1 H, s, NH), 7.57 (1 H, s, 6-H), 6.34 (1 H, d, $J_{2',3'}$ 10.3, 3'-H), 6.29 (1 H, s, 1'-H), 5.84 (1 H, d, $J_{2',3'}$ 10.3 2'-H), 4.14 (1 H, m, 4'-H), 3.75 (1 H, m, 5'-H), 3.68 (1 H, m, J_{gem} 11.6, 6'-H), 3.55 (1 H, m, 6'-H), 2.06 (2 H, m, 2 × OH) and 1.83 (3 H, s, Me) (Found: C, 48.8; H, 5.7; N, 10.1. $C_{11}H_{14}N_2O_5 \cdot H_2O$ requires C, 48.5; H, 5.9; N, 10.3%).

1-(2',3'-*Dideoxy*-6'-O-*trityl*-β-D-erythro-*hex*-2'-*enopyranosyl*)*thymine* **10**.—To a solution of **8** (508 mg, 2 mmol) in dichloromethane (5 ml), were added trityl chloride (669 mg, 2.4 mmol) and 4-(dimethylamino)pyridine (12 mg, 0.1 mmol). After 12 h the mixture was diluted with dichloromethane (10 ml) and washed twice with water, decanted, dried ($MgSO_4$) and concentrated. Purification on column (ethyl acetate–hexane 50:50) gave *compound* **10** which crystallised from ethyl acetate (694 mg, 70%); m.p. 224 °C, $[\alpha]_D^{20}$ −25° (*c* 0.1, methanol); λ_{max}/nm: 265 (ε/l mol^{-1} cm^{-1}: 13 739); δ_H 8.5 (1 H, s, NH), 7.41–7.25 (15 H, m, 3 × Ph), 6.32 (1 H, d, $J_{2',3'}$ 10.1, 3'-H), 6.25 (1 H, s, 1'-H), 5.68 (1 H, d, $J_{2',3'}$ 10.2, 2'-H), 4.21 (1 H, m, 4'-H), 3.59 (1 H, m, 5'-H), 3.48 (1 H, m, 6'-H), 3.37 (1 H, m, 6'-H), 3.15 (1 H, s, OH) and 1.95 (3 H, s, Me) (Found: C, 72.6; H, 5.8; N, 5.3. $C_{30}H_{28}N_2O_5$ requires C, 72.6; H, 5.6; N, 5.6%).

1-(2',3'-*Dideoxy*-β-D-glycero-*hex*-2'-*enopyranos*-4-*ulosyl*)*thymine* **12**.—Compound **10** (496 mg, 1 mmol) was dissolved in dichloromethane (10 ml) and pyridinium dichromate (550 mg, 1.6 mmol) and 3 Å molecular sieves (800 mg) were added. After 1 h the mixture was diluted with ethyl acetate and filtered over Celite, then concentrated. The residue was dissolved in aqueous acetic acid (60%; 25 ml) and heated at 60 °C for 40 min. Trityl alcohol was removed by filtration when the mixture had cooled and the filtrate was concentrated and chromatographed on a column (ethyl acetate). *Compound* **12** crystallised from ether (100 mg, 40%); m.p. 90 °C, $[\alpha]_D^{20}$ +75° (*c* 0.1, methanol); λ_{max}/nm: 261 (ε/l mol^{-1} cm^{-1}: 11 642); δ_H 8.5 (1 H, s, NH), 7.10 (1 H, s, 6-H), 6.95–6.91 (2 H, m, 1'-H, 2'-H), 6.51 (1 H, d, $J_{2',3'}$ 11.1, 3'-H), 4.40 (1 H, dd, $J_{5',6'}$ 4.5, 5'-H), 4.10 (1 H, dd, $J_{5',6'}$ 14.4, J_{gem} 11.8, 6'-H), 4.01 (1 H, dd, $J_{5',6'}$ 3.6, J_{gem} 1.8, 6'-H) and 1.95 (3 H, s, Me) (Found: C, 53.9; H, 5.4; N, 10.3. $C_{11}H_{12}N_2O_5 \cdot 0.5Et_2O$ requires C, 54.0; H, 5.9; N, 9.7%).

1-(4'-*Azido*-2',3',4'-*trideoxy*-6'-O-*trityl*-β-D-threo-*hex*-2'-*enopyranosyl*)*thymine* **14**.—To a solution of compound **10** (496 mg, 1 mmol) in benzene (5 ml) was added triphenyl phosphine (525 mg, 2 mmol) and the mixture was cooled to 0 °C. A mixture of diethyl azodicarboxylate (0.3 ml, 2 mmol) and hydrazoic acid (0.53 ml; 1.9 mol l^{-1} in benzene) was then added under nitrogen. The reaction mixture was concentrated and the residue was chromatographed on a column (ether). *Compound* **14** was crystallised from methanol (208 mg, 40%); m.p. 154 °C, $[\alpha]_D^{20}$ −225° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 10 159); δ_H 8.2 (1 H, s, NH), 7.4–7.2 (15 H, m, 3 × Ph), 7.06 (1 H, s, 6-H), 6.5 (1 H, m, 3'-H), 6.3 (1 H, s, 1'-H), 6.15 (1 H, d, $J_{2',3'}$ 10.3, 2'-H), 3.67 (2 H, m, 4'-H, 5'-H), 3.5–3.4 (2 H, m, 2 × 6'-H) and 1.94 (3 H, s, Me) (Found: C, 66.3; H, 5.3; N, 13.2. $C_{30}H_{27}N_5O_4 \cdot 1.5H_2O$ requires C, 65.9; H, 5.1; N, 12.8%).

1-(4'-*Azido*-2',3',4'-*trideoxy*-β-D-threo-*hex*-2'-*enopyranosyl*)-*thymine* **16**.—Compound **14** (200 mg, 0.38 mmol) was dissolved in aqueous acetic acid (60%; 10 ml) and stirred at 60 °C for 45 min. The mixture was filtered and concentrated to give *compound* **16** (75 mg, 70%); $[\alpha]_D^{20}$ −405° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 10 434); δ_H 8.4 (1 H, s, NH), 7.60 (1 H, s, 6-H), 6.61 (1 H, dd, $J_{3',4'}$ 5.8, $J_{2',3'}$ 9.3, 3'-H), 6.4 (1 H, s, 1'-H), 6.35 (1 H, d, $J_{2',3'}$ 9, 2'-H), 4.14 (1 H, ddd, *J* 6.3, *J* 2.2, 5'-H), 3.78–3.71 (3 H, m, 2 × 6'-H. 4'-H) and 1.91 (3 H, s, Me) (Found: C, 45.5; H, 4.9; N, 23.8. $C_{11}H_{13}N_5O_4$; 0.5 H_2O requires C, 45.8; H, 4.9; N, 24.3%).

1-(4'-*Acetamido*-2',3',4'-*trideoxy*-β-D-threo-*hexapyranosyl*)-*thymine* **18**.—To a solution of compound **14** (100 mg, 0.19 mmol) in methanol (10 ml), acetic anhydride (1 ml) and Pd/C (10%; 100 mg) were added. The mixture was hydrogenated overnight at ambient pressure and temperature, whereupon it was filtered, concentrated and purified on column (ethyl acetate, then ethyl acetate–methanol 8:2) to give *compound* **18**

which crystallised from methanol (28 mg, 50%), m.p. 216 °C, $[\alpha]_D^{20}$ −25° (*c* 0.1, methanol); λ_{max}/nm: 265 (ε/l mol^{-1} cm^{-1}: 9860); δ_H 7.21 (1 H, s, 6-H), 6.05 (1 H, d, *J* 7.6, NH), 5.99 (1 H, dd, $J_{1',2'}$ 6, $J_{1',2'}$ 2.5, 1'-H), 4.38–4.32 (1 H, m, 4'-H), 4.21 (1 H, dd, $J_{5',6'}$ 5 J_{gem} 11, 6'-H), 4.01 (1 H, m, 5'-H), 3.85 (1 H, dd, $J_{5',6'}$ 5.5, J_{gem} 11.8, 6'-H), 2.13–1.89 (4 H, m, 2'-H, 3'-H), 2.02 (3 H, s, COMe), 1.96 (3 H, s, Me) (Found: C, 50.9; H, 6.35; N, 13.4. $C_{13}H_{19}N_3O_5$·0.5H_2O requires C, 51.0; H, 6.5; N, 13.7%).

t-Butyl 4'-*Acetamido*-1',2',3',4'-*tetradeoxy*-β-1'-(*thymidin*-1-*yl*)-D-threo-*hexopyranuronate* **20**.—Chromium(VI) oxide (400 mg, 4 mmol) and pyridine (0.65 ml, 8 mmol) were dissolved in a 4:1 mixture of dichloromethane and DMF (6 ml), the mixture was stirred 15 min at room temperature. A solution of compound **18** (297 mg, 1 mmol) in the same mixture (4 ml) was added, followed by acetic anhydride (0.75 ml, 8 mmol) and t-butyl alcohol (1.88 ml, 20 mmol) and the mixture was stirred for 16 h at ambient temperature, diluted with ethyl acetate (50 ml), filtered on Celite and concentrated. The residue was chromatographed by reversed-phase preparative TLC (RP18, acetonitrile 50%). *Compound* **20** was obtained as a white powder in ether (37 mg, 10%); $[\alpha]_D^{20}$ +30 ° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 9468); δ_H 8.4 (1 H, s, NH), 7.22 (1 H, s, 6-H), 6.66 (1 H, d, *J* 8.8, NH), 6.0 (1 H, dd, $J_{1',2'}$ 2.9, $J_{1',2'}$ 10.4, 1'-H), 4.46–4.38 (2 H, m, 4'-H, 5'-H), 2.01 (3 H, s, Ac), 2.06–1.47 (4 H, m, 2 × 2'-H, 2 × 3'-H), 1.94 (3 H, s, Me) and 1.56 (9 H, s, 3 × Me) (Found: C, 54.2; H, 7.4; N, 10.5. $C_{17}H_{25}N_3O_6$·0.5H_2O requires C, 54.3; H, 6.9; N, 11.2%).

1-(2',3'-*Dideoxy*-α-D-erythro-*hex*-2'-*enopyranosyl*)*thymine* **9**.—Compound **7**[25] (1 g, 3 mmol) was treated in the same way as in the preparation of compound **8** to give compound **9** which crystallised from ethanol (690 mg, 90%), m.p. 203 °C, $[\alpha]_D^{20}$ +150 °C (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 9779); δ_H(AcOD) 7.27 (1 H, s, 6-H), 6.5 (1 H, d, $J_{1',2'}$ 1.5, 1'-H), 6.28 (1 H, dd, $J_{2',3'}$ 10.2, 3'-H), 5.75 (1 H, dd, $J_{2',3'}$ 10, $J_{1',2'}$ 1.8 2'-H), 4.42 (1 H, dd, $J_{3',4'}$ 2.1, $J_{4',5'}$ 8.8, 4'-H), 4.0–3.76 (3 H, m, 2 × 6'-H, 5'-H) and 1.89 (3 H, s, Me) (Found: C, 52.1; H, 5.6; N, 10.9. $C_{11}H_{14}N_2O_5$ requires C, 52.0; H, 5.5; N, 11%).

1-(2',3'-*Dideoxy*-6'-O-*trityl*-α-D-erythro-*hex*-2'-*enopyranosyl*)*thymine* **11**.—Tritylation of compound **9** (497 mg, 1.96 mmol) under the same conditions as in the preparation of compound **10** gave *compound* **11** which crystallised from ethanol (730 mg, 75%); m.p. 217 °C, $[\alpha]_D^{20}$ +62.5° (*c* 0.1, methanol); λ_{max}/nm: 265 (ε/l mol^{-1} cm^{-1}: 8580); δ_H 8.4 (1 H, s, NH), 7.43–7.27 (15 H, m, 3 × Ph), 6.95 (1 H, s, 6-H), 6.43 (1 H, s, 1'-H), 6.22 (1 H, d, $J_{2',3'}$ 10.3, 3'-H), 5.65 (1 H, d, $J_{2',3'}$ 10.3, 2'-H), 4.34–4.28 (1 H, m, 4'-H), 3.81 (1 H, m, 5'-H), 3.6 (1 H, dd, $J_{5',6'}$ 4.6, J_{gem} 9.8, 6'-H), 3.32 (1 H, dd, $J_{5',6'}$ 6.9, J_{gem} 9.9, 6'-H), 2.95 (1 H, d, *J* 4, OH) and 1.80 (3 H, s, Me) (Found: C, 72.9; H, 5.5; N, 5.35. $C_{30}H_{28}N_2O_5$ requires C, 72.6; H, 5.6; N, 5.6%).

1-(2',3'-*Dideoxy*-α-D-glycero-*hex*-2'-*enopyranos*-4-*ulosyl*)-*thymine* **13**.—Oxidation of compound **11** (496 mg, 1 mmol) as described in the preparation of compound **12**, followed by detritylation, gave *compound* **13** (163 mg, 65%); $[\alpha]_D^{20}$ −20° (*c* 0.1, methanol); λ_{max}/nm: 261 (ε/l mol^{-1} cm^{-1}: 13 633); δ_H 8.2 (1 H, s, NH), 7.06 (1 H, s, 6-H), 6.9 (1 H, d, $J_{2',3'}$ 10.4, 3'-H), 6.79 (1 H, d, $J_{1',2'}$ 1.9, 1'-H), 6.46 (1 H, dd, $J_{1',2'}$ 2.2, $J_{2',3'}$ 10.2, 2'-H), 4.39 (1 H, m, 5'-H), 4.03 (2 H, m, 2 × 6'-H), 2.2 (1 H, m, OH) and 1.95 (3 H, s, Me) (Found: C, 52.8; H, 5.1; N, 10.7. $C_{11}H_{12}N_2O_5$ requires C, 52.4; H, 4.8; N, 11.1%).

1-(4'-*Azido*-2',3',4'-*trideoxy*-6'-O-*trityl*-α-D-threo-*hex*-2'-*enopyranosyl*)*thymine* **15**.—Compound **11** (496 mg, 1 mmol) was treated as in the preparation of compound **14** to give compound **15** which crystallised from ethanol (440 mg, 85%); m.p. 174 °C, $[\alpha]_D^{20}$ −185° (*c* 0.1, methanol); λ_{max}/nm: 263 (ε/l mol^{-1} cm^{-1}: 12 347); δ_H 8.5 (1 H, s, NH), 7.42–7.24 (15 H, m, 3 × Ph), 6.48 (1 H, s, 1'-H), 6.34 (1 H, dd, $J_{3',4'}$ 7.1, $J_{2',3'}$ 10.5, 3'-H), 5.96 (1 H, d, $J_{2',3'}$ 10.4, 2'-H), 4.31 (1 H, m, 5'-H), 3.94 (1 H, m, 4'-H), 3.35 (1 H, dd, $J_{5',6'}$ 6.4, J_{gem} 9.6, 6'-H), 3.11 (1 H, dd, $J_{5',6'}$ 5.9, J_{gem} 9.6, 6'-H) and 1.97 (3 H, s, Me) (Found: C, 67.8; H, 5.25; N, 13.4. $C_{30}H_{27}N_5O_4$·0.5H_2O requires C, 67.9; H, 5.2; N, 13.2%).

1-(4'-*Azido*-2',3',4'-*trideoxy*-α-D-threo-*hex*-2'-*enopyranosyl*)-*thymine* **17**.—Detritylation of compound **15** (526 mg, 1 mmol) under the conditions described for compound **16** gave *compound* **17** (195 mg, 70%); $[\alpha]_D^{20}$ −165° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 12 200); δ_H 7.48 (1 H, s, 6-H), 6.5 (1 H, s, 1'-H), 6.4 (1 H, dd, $J_{2',3'}$ 10, $J_{3',4'}$ 5.8, 3'-H), 6.26 (1 H, d, $J_{2',3'}$ 9.9, 2'-H), 4.1 (1 H, m, 5'-H), 3.84–3.82 (2 H, m, 2 × 6'-H), 3.67 (1 H, d, $J_{3',4'}$ 5.89, 4'-H) and 1.87 (3 H, s, Me) (Found: C, 46.75; H, 4.8; N, 24.0. $C_{11}H_{13}N_5O_4$·0.3H_2O requires C, 46.4; H, 4.8; N, 24.6).

1-(4'-*Acetamido*-2',3'-,4'-*trideoxy*-α-D-threo-*hexopyranosyl*)-*thymine* **19**.—Hydrogenation of compound **15** (100 mg, 0.19 mmol) as described for compound **18** gave compound **19**. However characterisation of this compound was not possible due to its instability. It was therefore acetylated under standard conditions (acetic anhydride–pyridine) to give compound **19a** (45 mg, 70%); m.p. 171 °C, $[\alpha]_D^{20}$ −5° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 9051); δ_H 8.3 (1 H, s, NH), 7.16 (1 H, s, 6-H), 5.97 (1 H, d, *J* 2, NH), 5.63 (1 H, dd, $J_{1',2'}$ 3.2, $J_{1',2'}$ 9.9, 1'-H), 4.24 (1 H, m, 4'-H), 4.24–4.11 (2 H, m, 5'-H, 6'-H), 4.05 (1 H, m, 6'-H), 2.13–1.76 (4 H, m, 2'-H, 3'-H), 2.07–2.05 (6 H, 2 × s, 2 × Me), 1.96 (3 H, s, Me) (Found: C, 50.3; H, 6.4; N, 11.2. $C_{15}H_{21}N_3O_6$·H_2O requires C, 50.4; H, 6.4; N, 11.8%).

t-Butyl 4'-*Acetamido*-1',2',3',4'-*tetradeoxy*-α-1'-(*thymin*-1-*yl*)-D-threo-*hexopyranosuronate* **21**.—Oxidation of compound **19** (297 mg, 1 mmol) was performed according to the procedure described for compound **20**. *Compound* **21** was isolated as a white powder (148 mg, 40%); $[\alpha]_D^{20}$ −5° (*c* 0.1, methanol); λ_{max}/nm: 264 (ε/l mol^{-1} cm^{-1}: 7700); δ_H 8.4 (1 H, s, NH), 7.29 (1 H, s, 6-H), 6.58 (1 H, d, *J* 8.7, NH), 5.71 (1 H, dd, $J_{1',2'}$ 2.6, $J_{1',2'}$ 7.6, 1'-H), 4.49 (1 H, m, 4'-H), 4.37 (1 H, d, $J_{4',5'}$ 2.2, 5'-H), 2.2–1.6 (4 H, m, 2'-H, 3'-H), 2.02 (3 H, s, Ac), 1.92 (3 H, s, Me) and 1.45 (9 H, s, 3 × Me) (Found: C, 54.0; H, 6.55; N, 10.8. $C_{17}H_{25}N_3O_6$·0.5H_2O requires C, 54.25; H, 6.9; N, 11.2%).

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