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Synthesis of 1-(3-azido-2,3-dideoxy-β-D-allofuranosyl)thymine, 1-(2,3-dideoxy-β-D-allofuranosyl)thymine, and 1-(2,3-dideoxy-β-D-*erythro*-hex-2-enofuranosyl)thymine*

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ABSTRACT

1-(2-*O*-Acetyl-3,5,6-tri-*O*-benzoyl-β-D-glucofuranosyl)thymine (**1**) was converted into the 2,2′-anhydro derivative **4** by selective deacetylation, mesylation, and treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene. Cleavage of the 2,2′-anhydro ring in **4** with hydrogen bromide or hydrogen chloride led to the 2′-bromo (**5**) or 2′-chloro (**6**) derivative, respectively. Dehalogenation of **6** with tributylstannane and then debenzoylation gave 1-(2-deoxy-β-D-*arabino*-hexofuranosyl)thymine (**8**). Isopropylidenation of **8** followed by mesylation, azide displacement, and deprotection gave 1-(3-azido-2,3-dideoxy-β-D-*ribo*-hexofuranosyl)-thymine (**12**). Oxidation of **12** with Dowex 1 (IO_4^-) resin followed by reduction with Dowex 1 (BH_4^-) resin gave 1-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine (AZT). Catalytic hydrogenation of **5** afforded a mixture of 1-(5,6-di-*O*-benzoyl-2,3-dideoxy-β-D-*erythro*-hexofuranosyl)thymine (**13**) and 1-(3,5,6-tri-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexofuranosyl)thymine (**7**). Reaction of **5** with a Cu/Zn couple gave 1-(5,6-di-*O*-benzoyl-2,3-dideoxy-β-D-*erythro*-hex-2-enofuranosyl)thymine (**15**). 1-(2,3-Dideoxy-β-D-*erythro*-hexofuranosyl)thymine (**14**) and 1-(2,3-dideoxy-β-D-*erythro*-hex-2-enofuranosyl)thymine (**16**) were obtained by debenzoylation.

INTRODUCTION

3′-Azido-2′,3′-dideoxythymidine (AZT) significantly inhibits[1] the replication of HIV and is in clinical use for the treatment of AIDS patients. Since AZT can cause severe side effects and adversely affects bone marrow[2], many other nucleoside analogues have been synthesised and their structure–antiviral activity relationships investigated[3].

In the allofuranosyl series, Hiebl and Zbiral[4] synthesised 1-(3-azido-2,3,5-trideoxy-β-D-allofuranosyl)thymine and we now report the synthesis of the title analogues.

RESULTS AND DISCUSSION

The title compounds were synthesised from 1,2-di-*O*-acetyl-3,5,6-tri-*O*-benzoyl-D-glucofuranose[5] which was condensed with silylated thymine under catalysis of tin(IV) chloride[6] to give **1**. Selective deacetylation of **1** with conc. hydrochloric acid–1,4-

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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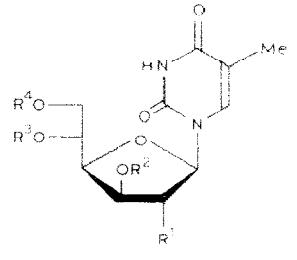
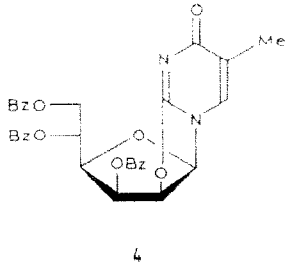
dioxane at room temperature for 3 days gave **2**, HO-2′ of which was mesylated to give **3**. Treatment of **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at room temperature gave the 2,2′-anhydro derivative **4**. Cleavage of the 2,2′-anhydro bond in **4** with hydrogen chloride in *N*,*N*-dimethylformamide at 100° led to the chloro derivative **6**, which was reduced with tributylstannane in boiling toluene, with catalysis by 2,2′-azobis(2-propiononitrile) to give **7**. *O*-debenzoylation of which gave 1-(2-deoxy-β-D-*arabino*-hexofuranosyl)thymine (**8**). Treatment of **8** with 2,2-dimethoxypropane–acetone–*N*,*N*-dimethylformamide gave the 5′,6′-*O*-isopropylidene derivative **9**, mesylation of which gave **10**. Displacement of the mesyl group in **10** with lithium azide in *N*,*N*-dimethylformamide at 100° afforded the azido derivative **11**, which was deprotected by the action of Dowex 50 (H^+) resin in boiling aqueous 80% methanol to give 1-(3-azido-2,3-dideoxy-β-D-*ribo*-hexofuranosyl)thymine (**12**).

Oxidation of **12** with Dowex 1 (IO_4^-) resin followed by reduction with Dowex 1 (BH_4^-) resin in aqueous methanol gave AZT. This sequence constitutes an alternative synthesis of AZT from easily available starting materials[7].

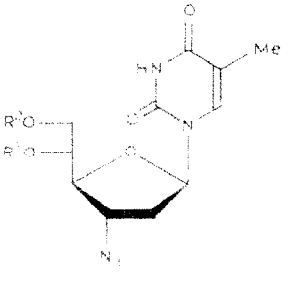
Hydrogenation (Pd/C) of the bromo derivative **5** in *N*,*N*-dimethylformamide afforded a mixture of the dideoxy (**13**, 61%) and deoxy (**7**, 24%) derivatives. Similar reactions were observed in syntheses of 2′,3′-dideoxytubercidin and 2′,3′-dideoxyformycin[8]. Treatment of **5** with a Cu/Zn couple in *N*,*N*-dimethylformamide gave the dideoxydidehydro derivative **15**. *O*-Debenzoylation of **13** and **15** with methanolic sodium methoxide gave 1-(2,3-dideoxy-β-D-*erythro*-hexofuranosyl)thymine (**14**) and 1-(2,3-dideoxy-β-D-*erythro*-hex-2-enofuranosyl)thymine (**16**), respectively.



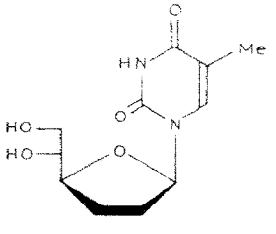
1 R^1 = OAc, R^2 = R^3 = R^4 = Bz
2 R^1 = OH, R^2 = R^3 = R^4 = Bz
3 R^1 = OMs, R^2 = R^3 = R^4 = Bz
5 R^1 = Br, R^2 = R^3 = R^4 = Bz
6 R^1 = Cl, R^2 = R^3 = R^4 = Bz
7 R^1 = H, R^2 = R^3 = R^4 = Bz
8 R^1 = R^2 = R^3 = R^4 = H
9 R^1 = R^2 = H, R^3, R^4 = CMe_2
10 R^1 = H, R^2 = Ms, R^3, R^4 = CMe_2



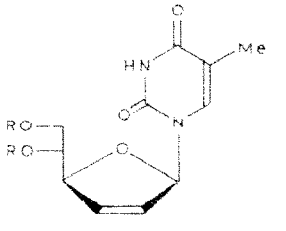
4



11 R^1 = R^2 = CMe_2
12 R^1 = R^2 = H



13 R = Bz
14 R = H



15 R = Bz
16 R = H

None of the above allofuranosyl nucleosides exhibited activity against HIV. The azido derivative **12** was significantly active against HSV-1 (IC_{50} 2 μg/mL) with low cytotoxicity.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler block and are uncorrected. Optical rotations were obtained at 20° with a Perkin–Elmer 241 polarimeter. ^{1}H-N.m.r. spectra were measured in solutions in $(CD_3)_2SO$ (internal Me_4Si). Column chromatography was performed on silica gel (30–60 μm, Service Laboratories of this Institute). T.l.c. was carried out on Silufol UV 254 (Kavalier, Votice), using *A*, ethyl acetate; *B*, ethyl acetate–toluene (1:1); and *C*, ethyl acetate–acetone–ethanol–water (36:6:5:3). Unless stated otherwise, solvents were evaporated at 40°/2 kPa and compounds were dried over phosporus pentaoxide at 13 Pa.

1-(2-O-Acetyl-3,5,6-tri-O-benzoyl-β-D-glucofuranosyl)thymine (**1**). — Tin(IV) chloride (5 mL) was added to a solution of 1,2-di-*O*-acetyl-3,5,6-tri-*O*-benzoyl-D-glucofuranose[5] (28.82 g, 50 mmol) and 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine (13.46 g, 52.5 mmol) in 1,2-dichloroethane (100 mL). The mixture was stored overnight at room temperature, then poured dropwise into stirred aq. 10% sodium hydrogencarbonate (1.5 L). After 5 h, the clear aqueous layer was removed and the organic layer was concentrated. The residue was extracted with ethyl acetate (3 × 250 mL), the combined extracts were washed with aq. 10% sodium hydrogencarbonate (200 mL) and dried ($MgSO_4$), and the solvent was evaporated. Column chromatography (2.5 kg of silica gel, solvent *B*) of the residue gave amorphous **1** (21.27 g, 66%), $[\alpha]_D$ −38° (*c* 0.2, ethyl acetate), R_F 0.35 (solvent *B*). ^{1}H-N.m.r. data: δ 1.76 (s, 3 H, Me-5), 2.13 (s, 3 H, Ac), 4.56 (dd, 1 H, $J_{6'a,5'}$ 6.0, $J_{6'a,6'b}$ 12.5 Hz, H-6'a), 4.81 (m, 2 H, H-4',6'b), 5.46 (t, 1 H, $J_{2',1'}$ 1.5, $J_{2',3'}$ 1.5 Hz, H-2'), 5.81 (dd, 1 H, $J_{3',4'}$ 4.5 Hz, H-3'), 5.92 (m, 1 H, H-5'), 6.09 (dd, 1 H, H-1'), 6.80–7.94 (m, 16 H, H-6 and 3 Ph), 11.40 (s, 1 H, H-3).

Anal. Calc. for $C_{34}H_{30}N_2O_{11}$: C, 63.55; H, 4.71; N, 4.36. Found: C, 63.26; H, 4.70; N, 4.15.

1-(3,5,6-Tri-O-benzoyl-β-D-glucofuranosyl)thymine (**2**). — A mixture of **1** (2.57 g, 4 mmol), 1,4-dioxane (24 mL), and conc. hydrochloric acid (1.6 mL) was stirred at room temperature for 2 days, then diluted with ethyl acetate (100 mL), washed with water (30 mL), and aq. 10% sodium hydrogencarbonate (30 mL), dried ($MgSO_4$), and concentrated. The residue was crystallised from toluene to give **2** (2.07 g, 86%), m.p. 116–119°, $[\alpha]_D$ −57° (*c* 0.4, ethyl acetate), R_F 0.24 (solvent *B*). ^{1}H-N.m.r. data: δ 1.75 (s, 3 H, Me-5), 4.40 (dd, 1 H, $J_{2',OH}$ 4.0, $J_{2',1'}$ 1.5 Hz, H-2'), 4.59 (dd, 1 H, $J_{6'a,5'}$ 6.0, $J_{6'a,6'b}$ 13.0 Hz, H-6'a), 4.88 (m, 2 H, H-4',6'b), 5.49 (d, 1 H, $J_{3',4'}$ 3.2 Hz, H-3'), 5.88 (d, 1 H, H-1'), 5.93 (m, 1 H, H-5'), 6.40 (d, 1 H, HO-2'), 7.35–7.92 (m, 16 H, H-6 and 3 Ph), 11.38 (s, 1 H, H-3).

Anal. Calc. for $C_{32}H_{28}N_2O_{10}$: C, 63.99; H, 4.70; N, 4.66. Found: C, 63.92; H, 4.85; N, 4.55.

The reaction of crude **1**, performed as described above, gave 67% of **2**.

1-(3,5,6-Tri-O-benzoyl-2-O-methanesulfonyl-β-D-glucofuranosyl)thymine (**3**). —

Methanesulfonyl chloride (5 mL) was added dropwise to a stirred, cooled (ice-bath) solution of **2** (9 g, 15 mmol) in pyridine (50 mL). After storage at room temperature for 4 h, water (2 mL) was added and the mixture was concentrated. A solution of the residue in ethyl acetate (300 mL) was washed with water (2 × 100 mL), aq. 5% hydrochloric acid until the washings were acidic, water (100 mL), and aq. 10% sodium hydrogencarbonate (50 mL), dried ($MgSO_4$), and concentrated. Light petroleum was added dropwise to a solution of the residue in the minimum volume of toluene, to give amorphous **3** (9.8 g, 96%), $[\alpha]_D$ −37° (*c* 0.4, ethyl acetate), R_F 0.36 (solvent *B*). ^{1}H-N.m.r. data: δ 1.80 (s, 3 H, Me-5), 3.38 (s, 3 H, Ms), 4.60 (dd, 1 H, $J_{6'a,5'}$ 5.5, $J_{6'a,6'b}$ 12.5 Hz, H-6'a), 4.93 (m, 2 H, H-4',6'b), 5.62 (dd, 1 H, $J_{2',1'}$ 2.5, $J_{2',3'}$ 2.0 Hz, H-2'), 5.87 (dd, 1 H, $J_{3',4'}$ 4.0 Hz, H-3'), 5.96 (m, 1 H, H-5'), 6.20 (d, 1 H, H-1'), 7.30–7.96 (m, 16 H, H-6 and 3 Ph), 11.49 (s, 1 H, H-3).

Anal. Calc. for $C_{33}H_{30}N_2O_{12}S$: C, 58.40; H, 4.46; N, 4.13; S, 4.72. Found: C, 58.21; H, 4.40; N, 4.06; S, 4.57.

*2,2'-Anhydro-1-(3,5,6-tri-*O*-benzoyl-β-*D*-mannofuranosyl)thymine* (**4**). — A solution of **3** (9.5 g, 14 mmol) and DBU (3 mL, 20 mmol) in acetonitrile (100 mL) was set aside at room temperature overnight, then concentrated to 30 mL, and diluted with ethyl acetate (300 mL). The solution was washed with water (100 mL), aq. 1% hydrochloric acid (100 mL), water (50 mL), and aq. 5% sodium hydrogencarbonate (50 mL), dried ($MgSO_4$), and concentrated. The residue was crystallised from methanol to give **4** (7.73 g, 95%), m.p. 174–176°, $[\alpha]_D$ −148 (*c* 0.5, ethyl acetate), R_F 0.51 (solvent *C*). ^{1}H-N.m.r. data: δ 1.82 (s, 3 H, Me-5), 4.45 (dd, 1 H, $J_{6'a,5'}$ 5.5, $J_{6'a,6'b}$ 12.5 Hz, H-6'a), 4.83 (dd, 1 H, $J_{6'b,5'}$ 2.2 Hz, H-6'b), 4.97 (dd, 1 H, $J_{4',5'}$ 9.2, $J_{4',3'}$ 4.5 Hz, H-4'), 5.57 (m, 1 H, H-5'), 5.75–6.01 (m, 2 H, H-2',3'), 6.36 (d, 1 H, $J_{1',2'}$ 6.0 Hz, H-1'), 7.28–7.94 (m, 16 H, H-6 and 3 Ph).

Anal. Calc. for $C_{32}H_{26}N_2O_9$: C, 65.97; H, 4.50; N, 4.81. Found: C, 65.68; H, 4.51; N, 4.87.

*1-(3,5,6-Tri-*O*-benzoyl-2-bromo-2-deoxy-β-*D*-glucofuranosyl)thymine* (**5**). — A solution of **4** (2.91 g, 5 mmol) in M hydrogen bromide in *N,N*-dimethylformamide (10 mL) was heated to 100° for 20 min, then concentrated. Added xylene (20 mL) was evaporated from the residue, a solution of which in ethyl acetate (70 mL) was washed with water (20 mL) and aq. 5% sodium hydrogencarbonate (20 mL), dried ($MgSO_4$), and concentrated. Column chromatography [200 g of silica gel, ethyl acetate–toluene (1:2)] of the residue gave amorphous **5** (3.02 g, 91%), $[\alpha]_D$ −14 (*c* 0.4, ethyl acetate), R_F 0.56 (solvent *B*). ^{1}H-N.m.r. data: δ 1.78 (s, 3 H, Me-5), 4.61 (dd, 1 H, $J_{6'a,6'b}$ 12.7, $J_{6'a,5'}$ 5.5 Hz, H-6'a), 4.88–5.16 (m, 3 H, H-2',4',6'b), 5.78 (dd, 1 H, $J_{3',4'}$ 4.0, $J_{3',2'}$ 2.0 Hz, H-3'), 6.04 (m, 1 H, H-5'), 6.36 (d, 1 H, $J_{1',2'}$ 3.0 Hz, H-1'), 7.36–7.95 (m, 16 H, H-6 and 3 Ph), 11.44 (s, 1 H, H-3).

Anal. Calc. for $C_{32}H_{27}BrN_2O_9$: C, 57.93; H, 4.10; N, 4.22; Br, 12.04. Found: C, 58.00; H, 4.27; N, 4.06; Br, 11.95.

*1-(3,5,6-Tri-*O*-benzoyl-2-chloro-2-deoxy-β-*D*-glucofuranosyl)thymine* (**6**). — A solution of **4** (5.83 g, 10 mmol) in M hydrogen chloride in *N,N*-dimethylformamide (20 mL) was heated to 100° for 45 min, then worked-up, as described for **5**, to give

amorphous **6** (5.61 g, 91%), $[\alpha]_D$ −28° (*c* 0.5, ethyl acetate), R_F 0.56 (solvent *B*). ^{1}H-N.m.r. data δ 1.79 (s, 3 H, Me-5), 4.62 (dd, 1 H, $J_{6'a,6'b}$ 12.7, $J_{6'a,5'}$ 5.5 Hz, H-6'a), 4.88–5.13 (m, 3 H, H-2',4',6'b), 5.75 (dd, 1 H, $J_{3',4'}$ 4.0, $J_{3',2'}$ 2.0 Hz, H-3'), 6.06 (d, 1 H, $J_{1',2'}$ 3.0 Hz, H-1'), 7.37–7.94 (m, 16 H, H-6 and 3 Ph), 11.47 (s, 1 H, H-3).

Anal. Calc. for $C_{32}H_{27}ClN_2O_9$: C, 62.09; H, 4.40; N, 4.53; Cl, 5.73. Found: C, 62.02; H, 4.56; N, 4.41; Cl, 5.49.

*1-(3,5,6-Tri-*O*-benzoyl-2-deoxy-β-*D*-*arabino*-hexofuranosyl)thymine* (**7**). — M Tributylstannane in toluene (20 mL) and 2,2'-azobis(2-methylpropiononitrile) (200 mg) were added to a stirred solution of **6** (6.19 g, 10 mmol) in toluene (30 mL) at 100°. After 45 min heating, the mixture was concentrated and the residue was triturated with light petroleum (100 mL). The precipitate was collected and washed with light petroleum, and to a stirred solution in toluene (15 mL), light petroleum was added dropwise. The precipitate was collected, washed with light petroleum, and dried in air to give **7** (5.55 g, 95%), m.p. 94–96°, $[\alpha]_D$ −61° (*c* 0.5, ethyl acetate), R_F 0.32 (solvent *B*). ^{1}H-N.m.r. data: δ 1.72 (s, 3 H, Me-5), 2.31 (dd, 1 H, $J_{2'a,1'}$ 2.2, $J_{2'a,2'b}$ 15.5 Hz, H-2'a), 3.00 (m, 1 H, H-2'b), 4.63 (m, 2 H, H-4',6'a), 4.94 (dd, 1 H, $J_{6'b,3'}$ 2.1, $J_{6'b,6'a}$ 12.0 Hz, H-6'b), 5.78 (t, 1 H, $J_{3',2'b}$ 4.0, $J_{3',4'}$ 4.0 Hz, H-3'), 5.95 (m, 1 H, H-5'), 6.31 (dd, 1 H, $J_{1',2'b}$ 8.0 Hz, H-1'), 7.38–7.98 (m, 16 H, H-6 and 3 Ph), 11.39 (s, 1 H, H-3).

Anal. Calc. for $C_{32}H_{28}N_2O_9$: C, 65.75; H, 4.83; N, 4.79. Found: C, 65.99; H, 4.91; N, 4.61.

*1-(2-Deoxy-β-*D*-arabino-hexofuranosyl)thymine* (**8**). — A solution of **7** (4.98 g, 8.5 mmol) in methanolic 0.1M sodium methoxide (50 mL) was set aside at room temperature overnight, then neutralised with Dowex 50 (H^+) resin, filtered, and concentrated. The residue was triturated with ether to afford **8** (1.93 g, 83%), m.p. 168–169°, $[\alpha]_D$ −6° (*c* 0.6, water); lit.[9] m.p. 166–168°, $[\alpha]_D$ −10.5°.

*1-(2-Deoxy-5,6-*O*-isopropylidene-β-*D*-arabino-hexofuranosyl)thymine* (**9**). — Conc. sulfuric acid (0.1 mL) was added to a solution of **8** (5.44 g, 20 mmol) in acetone (100 mL), 2,2-dimethoxypropane (30 mL), and *N,N*-dimethylformamide (50 mL). After 30 min, powdered sodium hydrogencarbonate (2 g) was added, and the mixture was stirred for 15 min, filtered, and concentrated. Xylene (50 mL) was evaporated from the residue which was crystallised from 2-propanol–ether to give **9** (4.01 g, 64%). Column chromatography (80 g of silica gel, ethyl acetate) of the material in the mother liquors and crystallisation gave more **9** (1.03 g, 16%), m.p. 176–177°, $[\alpha]_D$ −21° (*c* 0.5, methanol), R_F 0.69 (solvent *A*). ^{1}H-N.m.r. data: δ 1.29, 1.32 (2 s, each 3 H, Me_2C), 1.66–1.96 (m, 1 H, H-2'a), 1.76 (s, 3 H, Me-5), 2.59 (m, 1 H, H-2'b), 3.65–4.45 (m, 5 H, H-3',4',5',6'a,6'b), 5.51 (d, 1 H, $J_{OH,3'}$ 3.4 Hz, HO-3'), 6.12 (dd, 1 H, $J_{1',2'a}$ 2.0, $J_{1',2'b}$ 9.0 Hz, H-1'), 7.80 (d, 1 H, *J* 1.0 Hz, H-6), 11.22 (s, 1 H, H-3).

Anal. Calc. for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.46; N, 8.97. Found: C, 53.93; H, 6.40; N, 8.98.

*1-(2-Deoxy-5,6-*O*-isopropylidene-3-*O*-methanesulfonyl-β-*D*-arabino-hexofuranosyl)thymine* (**10**). — Methanesulfonyl chloride (2 mL) was added to a stirred, cooled (ice-bath) solution of **9** (1.87 g, 6 mmol) in pyridine (20 mL). After storage of the mixture at room temperature for 4 h, water (2 mL) was added to the cooled mixture and, after 10

min, the solvent was evaporated. The residue was diluted with ethyl acetate (70 mL), washed with water (2 × 20 mL), aq. 2% hydrochloric acid (10 mL), water (10 mL), and aq. 10% sodium hydrogencarbonate (10 mL), and dried ($MgSO_4$), and the solvent was evaporated to give amorphous **10** (2.14 g, 91%), $[\alpha]_D$ −48° (*c* 0.6, ethyl acetate), R_F 0.54 (solvent *A*). ^{1}H-N.m.r. data: δ 1.29, 1.35 (2 s, each 3 H, Me_2C), 1.77 (s, 3 H, Me-5), 2.25 (dd, 1 H, $J_{2'a,1'}$ 3.0, $J_{2'a,2'b}$ 16.2 Hz, H-2'a), 2.90 (m, 1 H, $J_{2'b,1'}$ 8.5, $J_{2'b,3'}$ 5.3 Hz, H-2'b), 3.26 (s, 3 H, Ms), 3.77–4.45 (m, 4 H, H-4',5',6'a,6'b), 5.25 (dd, 1 H, $J_{3',2'b}$ 5.3, $J_{3',4'}$ 3.0 Hz, H-3'), 6.21 (dd, 1 H, H-1'), 7.38 (d, 1 H, *J* 1.0 Hz, H-6), 11.35 (s, 1 H, H-3).

Anal. Calc. for $C_{15}H_{22}N_2O_8S$: C, 46.14; H, 5.68; N, 7.18; S, 8.21. Found: C, 46.40; H, 5.91; N, 6.92; S, 7.97.

*1-(3-Azido-2,3-dideoxy-5,6-O-isopropylidene-β-*D*-ribo-hexofuranosyl)thymine* (**11**). — A solution of **10** (1.95 g, 5 mmol) and lithium azide (1.1 g) in *N*,*N*-dimethylformamide (20 mL) was concentrated to 10 mL and then heated to 100° for 5 h under argon. After cooling, the solvent was evaporated. A solution of the residue in ethyl acetate (70 mL) was washed with water (3 × 10 mL) and dried ($MgSO_4$), and the solvent was evaporated. Column chromatography [150 g of silica gel, ethyl acetate–toluene (4:1)] afforded amorphous **11** (1.39 g, 82%), $[\alpha]_D$ −7° (*c* 0.6, methanol). R_F 0.72 (solvent *A*). ^{1}H-N.m.r. data: δ 1.31, 1.40 (2 s, each 3 H, Me_2C), 1.80 (s, 3 H, Me-5), 2.17–2.69 (m, 2 H, H-2'a,2'b), 3.69–4.61 (m, 5 H, H-3',4',5',6'a,6'b), 6.11 (t, 1 H, $J_{1',2'a}$ 6.5, $J_{1',2'b}$ 6.5 Hz, H-1'), 7.25 (d, 1 H, *J* 1.0 Hz, H-6), 11.32 (s, 1 H, H-3).

Anal. Calc. for $C_{14}H_{19}N_5O_5$: C, 49.84; H, 5.68; N, 20.76. Found: C, 50.01; H, 5.57; N, 20.92.

*1-(3-Azido-2,3-dideoxy-β-*D*-ribo-hexofuranosyl)thymine* (**12**). — Dowex 50 (H^+) resin (1.6 mL) was added to a solution of **11** (1.01 g, 3 mmol) in aq. 80% methanol (16 mL). The mixture was stirred under reflux for 40 min, then filtered, and concentrated. The residue was crystallised from water to give **12** (842 mg, 94%), m.p. 164–165°, $[\alpha]_D$ +21° (*c* 0.5, methanol), R_F 0.66 (solvent *C*). ^{1}H-N.m.r. data: δ 1.79 (s, 3 H, Me-5), 2.13–2.43 (m, 2 H, H-2'a,2'b), 3.44 (t, 2 H, $J_{6',OH}$ 4.5, $J_{6',5'}$ 4.5 Hz, H-6',6'), 3.67 (m, 1 H, $J_{5',OH}$ 4.5, $J_{5',4'}$ 4.1 Hz, H-5'), 3.86 (t, 1 H, $J_{4',3'}$ 3.9 Hz, H-4'), 4.50 (m, 1 H, $J_{3',2'a}$ 3.9, $J_{3',2'b}$ 7.3 Hz, H-3'), 4.71 (t, 1 H, HO-6'), 5.33 (d, 1 H, HO-5'), 6.09 (t, 1 H, $J_{1',2'a}$ 6.7, $J_{1',2'b}$ 6.7 Hz, H-1'), 7.65 (d, 1 H, *J* 1.0 Hz, H-6), 11.30 (s, 1 H, H-3).

Anal. Calc. for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.26; H, 4.98; N, 23.65.

*1-(3-Azido-2,3-dideoxy-β-*D*-erythro-pentofuranosyl)thymine (AZT).* — Dry Dowex 1 (IO_4^-) resin (1.5 g) was added to a solution of **12** (297 mg, 1 mmol) in aq. 80% methanol (7 mL). The mixture was stirred at room temperature for 1.5 h, the resin was collected and washed with methanol until the u.v. absorption of the filtrate disappeared, and the combined filtrate and washings were concentrated to 7 mL. Dry Dowex 1 (BH_4^-) resin (1.5 g) was added, and the mixture was stirred at room temperature for 1.5 h. The resin was collected, and washed with methanol until the u.v. absorption of the filtrate disappeared, and the combined filtrate and washings were concentrated. The residue was crystallised from water, to give AZT (217 mg, 82%), m.p. 119–122°; lit.[10] m.p. 119–121°.

*1-(5,6-Di-O-benzoyl-2,3-dideoxy-β-D-*erythro*-hexofuranosyl)thymine* (**13**). — Magnesium oxide (2 g) and 10% Pd/C were added to a solution of **5** (3.32 g, 5 mmol) in *N,N*-dimethylformamide (10 mL). The mixture was stirred under hydrogen at room temperature for 20 h, then filtered, and concentrated. Column chromatography [250 g of silica gel, ethyl acetate–toluene (2:1)], followed by precipitation of the material in the first fraction from a solution in the minimum amount of toluene with light petroleum, afforded **7** (690 mg, 24%). Crystallisation of the second fraction from toluene afforded **13** (1.41 g, 61%), m.p. 171–172°, $[\alpha]_D$ −49° (*c* 0.4, ethyl acetate), R_F 0.15 (solvent *B*). ^{1}H-N.m.r. data: δ 1.37 (s, 3 H, Me-5), 2.16 (m, 4 H, H-2′,2′,3′,3′), 4.30–4.58 (m, 2 H, H-4′,6′a), 4.77 (dd, 1 H, $J_{6'b,6'a}$ 12.0, $J_{6'b,5'}$ 3.0 Hz, H-6′b), 5.73 (m, 1 H, H-5′), 6.07 (m, 1 H, H-1′), 7.22 (d, 1 H, *J* 1.0 Hz, H-6), 7.40–8.06 (m, 10 H, 2 Ph), 11.27 (s, 1 H, H-3).

Anal. Calc. for $C_{25}H_{24}N_2O_7$: C, 64.65; H, 5.21; N, 6.03. Found: C, 64.51; H, 5.19; N, 5.90.

*1-(2,3-Dideoxy-β-D-*erythro*-hexofuranosyl)thymine* (**14**). — Compound **13** (929 mg, 2 mmol) was stirred with methanolic 0.1M sodium methoxide (15 mL) until dissolution. After storage at room temperature overnight, the solution was neutralised with Dowex 50 (H^+) resin, filtered, and concentrated. The residue was triturated with ether and crystallised from 2-propanol to afford **14** (419 mg, 82%), m.p. 145–146°, $[\alpha]_D$ +21° (*c* 0.4, methanol), R_F 0.40 (solvent *C*). ^{1}H-N.m.r. data: δ 1.77 (s, 3 H, Me-5), 1.61–2.45 (m, 4 H, H-2′,2′,3′,3′), 3.38 (t, 2 H, $J_{6',OH}$ 5.1, $J_{6',5'}$ 5.1 Hz, H-6′,6′), 3.78 (m, 1 H, H-5′), 3.99 (m, 1 H, H-4′), 4.63 (t, 1 H, HO-6′), 5.13 (d, 1 H, $J_{OH,5'}$ 5.3 Hz, HO-5′), 5.96 (dd, 1 H, $J_{1',2'a}$ 3.2, $J_{1',2'b}$ 6.4 Hz, H-1′), 7.90 (d, 1 H, *J* 1.0 Hz, H-6), 11.19 (s, 1 H, H-3).

Anal. Calc. for $C_{11}H_{16}N_2O_5$: C, 51.55; H, 6.29; N, 10.93. Found: C, 51.80; H, 6.18; N, 11.06.

*1-(5,6-Di-O-benzoyl-2,3-dideoxy-β-D-*erythro*-hex-2-enofuranosyl)thymine* (**15**). — A solution of **5** (2.65 g, 4 mmol) in *N,N*-dimethylformamide (3 mL) was added to a suspension of Cu/Zn couple[11] (0.67 g) in *N,N*-dimethylformamide (20 mL). The mixture was stirred at room temperature for 1 h, then filtered through Celite, and concentrated. A solution of the residue in ethyl acetate (50 mL) was washed with aq. 2% hydrochloric acid (20 mL), water (20 mL), and aq. 5% sodium hydrogencarbonate (10 mL), and dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallised from ethanol, to give **15** (1.50 g, 81%), m.p. 194–195°, $[\alpha]_D$ −153° (*c* 0.4, chloroform), R_F 0.22 (solvent *B*). ^{1}H-N.m.r. data: δ 1.08 (d, 3 H, *J* 0.9 Hz, Me-5), 4.66 (m, 2 H, H-6′a,6′b), 5.22 (m, 1 H, H-4′), 5.62 (m, 1 H, $J_{5',4'}$ 3.4, $J_{5',6'a}$ 3.3, $J_{5',6'b}$ 7.5 Hz, H-5′), 6.12 (dt, 1 H, $J_{3',1'}$ 1.7, $J_{3',2'}$ 6.0, $J_{3',4'}$ 2.3 Hz, H-3′), 6.50–6.68 (m, 2 H, H-1′,2′), 6.94 (d, 1 H, *J* 1.0 Hz, H-6), 7.61–7.93 (m, 10 H, 2 Ph), 11.36 (s, 1 H, H-3).

Anal. Calc. for $C_{25}H_{22}N_2O_7$: C, 64.93; H, 4.80; N, 6.06. Found: C, 64.68; H, 4.70; N, 6.05.

*1-(2,3-Dideoxy-β-D-*erythro*-hex-2-enofuranosyl)thymine* (**16**). — Methanolysis of **15** (926 mg, 2 mmol), as described for **13**, gave **16** (417 mg, 82%), m.p. 178–179°, $[\alpha]_D$ −17° (*c* 0.6, methanol), R_F 0.42 (solvent *C*). ^{1}H-N.m.r. data: δ 1.72 (s, 3 H, Me-5), 3.48 (m, 3 H, H-6′,6′), 4.78 (m, 2 H, H-4′ and HO-6′), 5.12 (d, 1 H, $J_{OH,5'}$ 4.3 Hz, HO-5′), 5.86 (dt, 1 H, $J_{3',1'}$ 1.5, $J_{3',2'}$ 6.0, $J_{3',4'}$ 2.3 Hz, H-3′), 6.44 (dt, 1 H, $J_{2',1'}$ 1.6, $J_{2',4'}$ 1.5 Hz, H-2′), 6.81 (m, 1 H, $J_{1',4'}$ 3.3 Hz, H-1′), 7.70 (d, 1 H, *J* 1.0 Hz, H-6), 11.26 (s, 1 H, H-3).

Anal. Calc. for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.22; H, 5.40; N, 11.22.

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