organic layer was dried and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel (1:1 petroleum ether/EtOAc) to give 60 mg (75%) of pure hydroxy derivative 18: gum; IR ($CHCl_3$) 3450, 1740, 1670, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 4.93 (s br, 1 H, 14-H), 4.84 (s br, 1 H, 14'-H), 4.84 (d, 1 H, J = 11 Hz, 6-H), 4.3 (s, 2 H, 13-H, 13'-H), 2.80 (ddd, 1 H, J = 12, 5, 2 Hz, 8-H); 2.39 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 0.87 (s, 3 H, 15-H); MS m/e (relative intensity) 248 (M^+; 17), 230 (M^+ - 18; 87). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.5; H, 8.12. Found: C, 72.1; H, 8.17.

13-Acetoxy-7,11-ene-β-cyclocostunolide (19). A solution of 18 (50 mg) in pyridine (2 mL) was treated with acetic anhydride (5 mL) for 24 h. The usual workup and chromatography give 19 (45 mg): gum; IR (film) 1740, 1660, 880 cm^{-1}; ^1H NMR ($CDCl_3$) 4.93 (s br, 1 H, 14-H), 4.83 (s br, 1 H, 14'-H), 4.72 (s, 2 H, 13-H, 13'-H), 4.84 (d, 1 H, J = 11 Hz, 6-H), 2.90 (d br, 1 H, J = 12 Hz, 8-H), 2.40 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 0.87 (s, 3 H, 15-H), 1.99 (s, 3 H, CH_3COO); MS m/e (relative intensity) 291 (M^+ + 1; 8), 230 (M^+ - 60; 73).

Arbusculin A (20): mp 77-78 °C in agreement with these reported in the literature;[28] IR (KBr) 3480, 1770, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 6.02 (d, 1 H, J = 3.0 Hz, 13-H), 5.36 (d, 1 H, J = 3.0 Hz, 13'-H), 3.92 (t, 1 H, J = 11 Hz, 6-H), 2.97 (s br, 1 H, CHO*H*), 2.6 (t br, 1 H, J = 11 Hz, 7-H), 1.76 (d, 1 H, J = 11 Hz, 5-H), 1.27 (s, 3 H, 14-H), 0.90 (s, 3 H, 15-H); MS m/e (relative intensity) 251 (M^+ + 1; 4.0), 235 (M^+ - 15; 7.2). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.07; H, 8.90.

11β,13-Dibromoarbusculin A (21). Arbusculin A (20; 100 mg) was dissolved in dioxane, TMPAP (200 mg) was added, and the mixture was stirred overnight at room temperature. After workup described for 10, chromatography afforded 21 (85%): gum; IR (KBr) 3450, 2950, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) 4.41 (dd, 1 H, J = 11, 9.7 Hz, 6-H), 4.16 (d, 1 H, J = 11 Hz, 13-H), 3.84 (d, 1 H, J = 11 Hz, 13'-H), 2.41 (ddd, 1 H, J = 9.7, 4.5 Hz, 7-H), 1.87 (d, 1 H, J = 11 Hz, 5-H), 1.37 (s, 3 H, 14-H), 1.01 (s, 3 H, 15-H). Anal. Calcd for $C_{15}H_{22}O_3Br_2$: C, 43.90; H, 5.41. Found: C, 43.86; H, 5.28.

13-Bromo-7,11-enearbusculin A (22). Compound 21 (100 mg) was dissolved in DMF (10 mL) and treated with $LiBr/Li_2CO_3$ (175:150 mg) as described before for 14. Chromatography (ethyl acetate/light petroleum (3:7)) gave 22 (95%): yellow gum; IR (KBr) 3480, 2970, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) 4.85 (d, 1 H, J = 9.8, 6-H), 4.0 (s br, 2 H, 13-H, 13'-H), 2.82 (dd, 1 H, J = 12, 5 Hz, 8-H), 2.4 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 1.47 (d, 1 H, J = 9.8 Hz, 5-H), 1.32 (s, 3 H, 14-H), 0.99 (s, 3 H, 15-H).

Arbusculin D (23). Compound 22 (100 mg) dissolved in dioxane/H_2O ((1:0.5), 10 mL) was treated with Ag_2CO_3 as described for 18, obtaining after chromatography on silica gel (1:1 petroleum ether/EtOAc) 23 (70%): mp 171-172 °C in agreement with those reported in the literature;[21] ^1H NMR ($CDCl_3$) 4.88 (d, 1 H, J = 11 Hz, 6-H), 4.30 (s br, 2 H, 13-H, 13'-H), 2.86 (dd, 1 H, J = 12, 5 Hz, 8-H), 2.42 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 1.43 (d, 1 H, J = 11 Hz, 5-H) 1.33 (s, 3 H, 14-H), 0.99 (s, 3 H, 15-H) 3.20 (s br, 1 H, C-4-O*H*), 2.7 (m, 1 H, C-13-O*H*); MS m/e (relative intensity) 266 (M^+; 1.5), 251 (M^+ - 15; 12), 248 (M^+ - 18; 5), 230 (M^+ - 2×18; 9). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.78; H, 8.43.

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Synthesis of L-3'-Azido-3'-deoxythymidine and Its Stereoisomers

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We report the first synthesis of the L isomer of 3'-azido-3'-deoxythymidine (L-AZT). L-Arabinose was used as starting material for preparation of appropriately protected α,β-unsaturated aldehyde 5. Michael-type addition of azide to 5 gave 3-azido-2,3-dideoxypentofuranoses 7 and 8 suitable for nucleoside coupling with silylated thymine to afford after deprotection L-AZT (11), 1-(3-azido,-2,3-dideoxy-α-L-*erythro*-pentofuranosyl)thymine (12), 1-(3-azido-2,3-dideoxy-β-L-*threo*-pentofuranosyl)thymine (13) and 1-(3-azido-2,3-dideoxy-α-L-*threo*-pentofuranosyl)thymine (14). Anti-HIV activity of L-AZT is discussed.

Introduction

In the treatment of AIDS blocking, one or more steps of the replicative cycle of the human immunodeficiency virus (HIV) is a possible chemotherapeutic strategy.[1,2] Thus, different 2',3'-dideoxy nucleosides have turned out to be promising antiviral agents against AIDS, acting as inhibitors of the retrovirus reverse transcriptase.[1,3-5] Among the 2',3'-dideoxynucleosides, 3'-azido-3'-deoxythymidine (AZT) is very potent in its antiviral action, and at the present time it is the most successful agent used in the treatment of patients with AIDS.[1,5,6] But still there is an urgent need for new compounds with improved potency and selectivity in their antiviral action. Therefore, we decided to prepare the L isomer of 3'-azido-3'-deoxythymidine 11 (L-AZT) with special reference to testing this new mirror image of AZT against AIDS, having in mind that two enantiomeric forms of a biologically active compound often show differences in action and selectivity.

Results and Discussion

Originally, AZT was synthesized by Horwitz et al. from thymidine.[7] Recently, AZT has been prepared in multistep syntheses via 3-azido-2,3-dideoxypentoses from D-xylose[8] and D-mannitol.[9]

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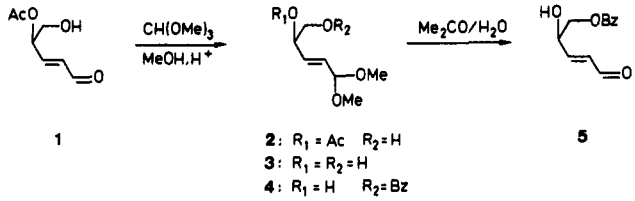
Scheme I



1 2: R_1 = Ac R_2 = H; 3: R_1 = R_2 = H; 4: R_1 = H R_2 = Bz; 5

For the synthesis of L-AZT, we used a method recently developed in our laboratories for the preparation of the L and D enantiomers of 3′-amino-2′,3′-dideoxynucleosides.[10,11] L-Arabinose was used as starting material for the synthesis of 3,4-di-*O*-acetyl-L-arabinal by a known procedure.[12] 3,4-Di-*O*-acetyl-L-arabinal was hydrolyzed to the α,β-unsaturated aldehyde (2*E*,4*R*)-4-acetoxy-5-hydroxy-2-pentenal **1**.[13] Contrary to similar 1,4-addition of phthalimide under alkaline conditions,[10,11] reaction of **1** with NaN_3 in 80% acetic acid gave exclusively undesired L-3-azido-2,3-dideoxypyranoses because of lack of acetyl shift from 4-O to 5-O under these acidic conditions. Therefore, we decided to protect the carbonyl group as the dimethyl acetal by reaction with absolute methanol, trimethyl orthoformate, and a catalytic amount of *p*-toluenesulfonic acid to give 4-*O*-acetyl dimethyl acetal **2**. Without any workup, **2** was directly deprotected with potassium carbonate to give unprotected dimethyl acetal **3** in quantitative yield from aldehyde **1**.

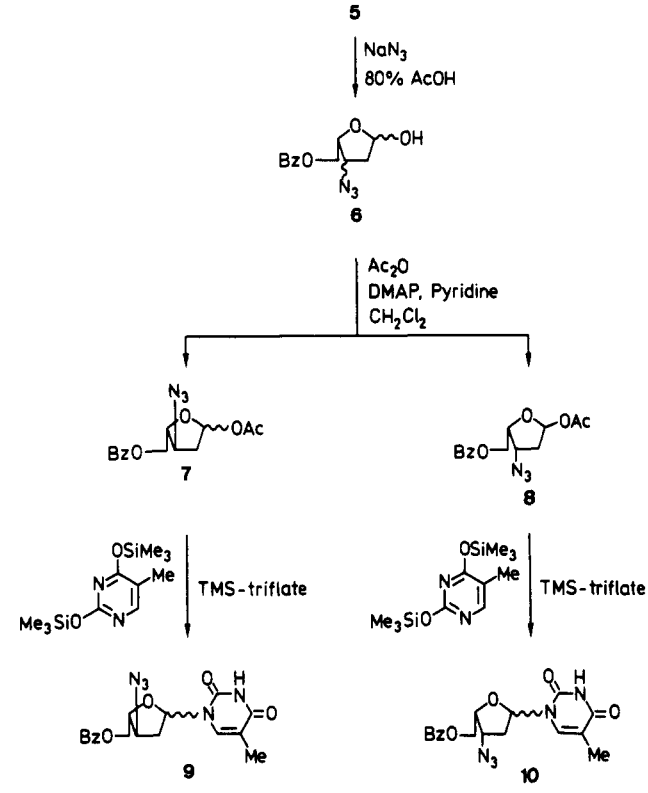
Selective benzoylation of the primary hydroxy group gave the 5-*O*-benzoyl dimethyl acetal **4** in 78% yield. Subsequent deacetalation afforded 5-*O*-benzoyl aldehyde **5** in quantitative yield (Scheme I).

With **5** as a convenient precursor, it was possible to achieve the desired 3-azido-2,3-dideoxy-L-pentose **6** in the furanose form by a Michael-type addition of azide with NaN_3 in 80% acetic acid. Direct acetylation of **6** gave after chromatographic purification 1-*O*-acetyl-3-azido-5-*O*-benzoyl-2,3-dideoxy-L-*erythro*-pentofuranose (**7**) in 22% yield from **5** as an anomeric mixture and 1-*O*-acetyl-3-azido-5-*O*-benzoyl-2,3-dideoxy-L-*threo*-pentofuranose (**8**) in 53% yield from **5**.

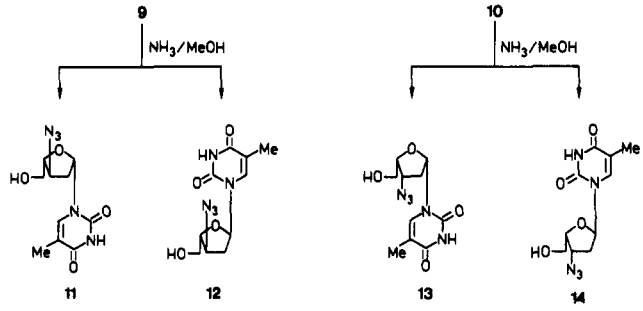
In the synthesis of thymine nucleosides **9** and **10**, we used the silyl-Hilbert-Johnson method as modified by Vorbrüggen et al.[14,15] using silylated thymine and trimethylsilyl trifluoromethanesulfonate (TMS-triflate) as reagent. By these reactions, we obtained 1-(3-azido-5-*O*-benzoyl-2,3-dideoxy-L-*erythro*-pentofuranosyl)thymine (**9**) and 1-(3-azido-5-*O*-benzoyl-2,3-dideoxy-L-*threo*-pentofuranosyl)thymine (**10**) as anomeric mixtures. Deprotection of **9** and **10** using saturated NH_3 in absolute methanol gave the final nucleosides **11**–**14**.

The nucleosides with erythro configuration **11** and **12** were separated by flash chromatography, affording the β-anomer **11** (L-AZT) in 64% yield and the α-anomer **12** in 35% yield. The anomeric mixture of the nucleosides with threo configuration was separated by fractional crystallization to give the β-anomer **13** in 49% yield and the α-anomer **14** in 40% yield (Scheme II).

Scheme II



Scheme III



The ^1H NMR, ^{13}C NMR, and IR data for compounds **11** and **12** are in close agreement with data reported[8] for the corresponding D forms except for interchanging the assignments 3′-H and 4′-H, which we have based on 2D-COSY ^1H NMR. This proves the configuration and stereochemistry of compounds **7**, **9**, **11**, and **12** (Scheme III).

The low melting point and the ^1H NMR data for compound **13** are in agreement with data reported[16] for the corresponding D form. Especially important is the fact that H′-1 of **13** is a double doublet with coupling constants equal to the β-D-*threo* isomer,[16] whereas compound **14** shows a triplet for H′-1. Furthermore, the 4′-H proton of the α-anomer appears downfield from that observed for the β-anomer and the 5′-H protons of the α-anomer appear upfield from those observed for the β-anomers.[17,18]

In anti-HIV studies, we used the HIV strain HTLV-IIIB and the MT-4 cell line. Compounds **9**, **12**, and **14** did not show anti-HIV activity at 100 μM. In toxicity studies on

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MT-4 cells, compound **10** caused a reduction of cell growth to 54% of control at 100 μM and **13** a reduction to 40% at 100 μM, but without showing significant anti-HIV activity at subtoxic levels. L-AZT (**11**) showed anti-HIV activity at 100 μM as virus activity was reduced to 30% of control according to HIV antigen by ELISA.[19]

The anti-HIV activity of L-AZT (**11**) is thus ~10 000 times lower than that reported for AZT.[20-22] One should notice that the anti-HIV activity of L-AZT (**11**) found in this investigation could come from a small amount of D sugar present in L-arabinose used as starting material or from racemerization during the synthesis of L-AZT due to enolization of the unsaturated sugar aldehydes **1** or **5**. Because of the low activity against HIV, we conclude that the present synthesis of L-AZT (**11**) is without any appreciable racemization and that the optical purity of this product is close to 99.99%.

Experimental Section

Merck silica gel 230–400 mesh was used for column chromatography.

(2*E*,4*R*)-1,1-Dimethoxy-4,5-dihydroxy-2-pentene (3). Aldehyde **1** (14.0 g, 89.1 mmol) was dissolved in absolute MeOH (60 mL) containing molecular sieves (3 Å, 5 g) and cooled to 0 °C. Trimethyl orthoformate (50 mL) was added together with a catalytic amount of *p*-toluenesulfonic acid (60 mg, 0.3 mmol). After 1 h at 0 °C, analytical TLC (ether/hexane v/v (80:20), 2× elution) showed disappearance of aldehyde and formation of **2**. K_2CO_3 (1.0 g, 7.3 mmol) was added, and after 45 min the solution was filtered and evaporated to an oil under reduced pressure. Flash chromatographic purification on a silica gel column (250 g) eluting with CH_2Cl_2/CH_3OH (9:1) gave 14.4 g (100%) of unprotected acetal **3**: ^1H NMR ($CDCl_3$) δ 3.32 (s, 6 H, OCH_3), 3.46 (dd, 1 H, J = 11.4 and 7.5 Hz, 5-Ha), 3.64 (dd, 1 H, J = 11.4 and 3.3 Hz, 5-Hb), 3.96 (br, 1 H, OH), 4.27 (ddd, 1 H, J = 7.5, 4.8, and 3.3 Hz, 4-H), 4.79 (d, 1 H, J = 4.3 Hz, 1-H), 5.75 (dd, 1 H, J = 15.9 and 4.3 Hz, 2-H), 5.86 (dd, 1 H, J = 15.9 and 4.8 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 52.68 (OCH_3), 65.94 (C-5), 71.86 (C-4), 102.38 (C-1), 127.83 (C-3), 133.40 (C-2). Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.44; H, 8.65.

(2*E*,4*R*)-5-(Benzoyloxy)-1,1-dimethoxy-4-hydroxy-2-pentene (4). A solution of benzoyl chloride (6.9 g, 0.049 mol) in CH_2Cl_2 (15 mL) was added dropwise during 30 min to a solution of the dimethyl acetal **3** (8.0 g, 0.049 mol) in CH_2Cl_2 (100 mL) and dry pyridine (50 mL) at 0 °C with stirring. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and poured into a mixture of 4 M HCl (100 mL) and ice (100 mL). The organic phase was washed with cold saturated aqueous $NaHCO_3$ (2 × 100 mL) and H_2O (100 mL). After drying (Na_2SO_4) and filtration, the solvents were evaporated under reduced pressure to give an oil. The oil was chromatographed on a silica gel column (100 g), eluting with CH_2Cl_2/CH_3OH (49:1). The solvents were evaporated under reduced pressure to give **4** in 75% yield (9.8 g, 0.037 mol) as a clear oil: ^1H NMR ($CDCl_3$) δ 3.31 (s, 6 H, OCH_3), 4.26–4.45 (m, 2 H, 5-Ha, 5-Hb), 4.56–4.59 (m, 1 H, 4-H), 4.83 (d, 1 H, J = 4.0 Hz, 1-H), 5.86 (dd, 1 H, J = 4.0 and 15.8 Hz, 2-H), 5.98 (dd, 1 H, J = 15.8 and 4.7 Hz, 3-H), 7.41–8.07 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$), δ 52.60 (OCH_3), 68.07 (C-4), 69.90 (C-5), 101.96 (C-1), 129.02 (C-3), 132.53 (C-2), 128.29, 129.57, 133.09 (aryl); EIMS m/z (relative intensity) 248 (2), 235 (2), 205 (5), 204 (7), 112 (16), 105 (100), 100 (19).

(2*E*,4*R*)-5-(Benzoyloxy)-4-hydroxy-2-pentenal (5). The dimethyl acetal **4** (8.6 g, 0.032 mol) was stirred in a mixture of acetone (200 mL) and 1.0 M HCl (40 mL) for 15 min at room temperature. After dilution with CH_2Cl_2 (200 mL) and subsequent extraction, the organic phase was washed with cold saturated aqueous $NaHCO_3$ (200 mL) and water (2 × 100 mL). After drying (Na_2SO_4), filtration, and evaporation under reduced pressure, **5** was obtained in 100% yield (7.1 g, 0.032 mol) as a white solid: mp 76–77 °C; ^1H NMR ($CDCl_3$) δ 4.36–4.55 (m, 2 H, 5-Ha, 5-Hb), 4.82–4.84 (m, 1 H, 4-H), 6.48 (dd, 1 H, J = 7.8 and 15.7 Hz, 2-H), 6.88 (dd, 1 H, J = 4.1 and 15.7 Hz, 3-H), 7.41–8.04 (m, 5 H, aryl), 9.59 (d, 1 H, J = 7.8 Hz, 1-H); ^{13}C NMR ($CDCl_3$) δ 67.06 (C-4), 69.41 (C-5), 132.64 (C-2), 128.38, 129.56, 133.70 (aryl), 153.72 (C-3), 193.11 (C-1); EIMS m/z (relative intensity) 220 (M^+, 1.3), 202 (14), 105 (100). Anal. Calcd $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.41; H, 5.53.

3-Azido-5-*O*-benzoyl-2,3-dideoxy-L-pentofuranose (6). **5** (5.1 g, 0.023 mol) was dissolved in 80% AcOH (40 mL) and added dropwise to a solution of NaN_3 (4.5 g, 0.069 mol) in 80% AcOH (170 mL). The mixture was stirred for 3 h at room temperature and then diluted with H_2O (150 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The organic phase was washed with cold saturated aqueous $NaHCO_3$ (3 × 150 mL) and H_2O (2 × 100 mL), dried (Na_2SO_4), and filtrated. Evaporation under reduced pressure to remove the solvents afforded **6** in 95% yield (5.8 g, 0.022 mol) as a clear oil. This oil was used without further purification for the preparation of **7** and **8**: IR (neat) 3440 (br m, OH), 2953 (m, CH), 2109 (s, N_3), 1719 (s, C=O), 1602 (m), 1452 (m), 1274 (s), 1071 (s), 1027 (s) cm^{-1}.

1-*O*-Acetyl-3-azido-5-*O*-benzoyl-2,3-dideoxy-L-*erythro*-pentofuranose (7) and 1-*O*-Acetyl-3-azido-5-*O*-benzoyl-2,3-dideoxy-L-*threo*-pentofuranose (8). To a solution of **6** (5.5 g, 0.021 mol) in CH_2Cl_2 (120 mL) was added dry pyridine (3.2 g, 0.041 mol), Ac_2O (6.1 g, 0.060 mol), and 4-(dimethylamino)pyridine (DMAP; 20 mg, 0.16 mmol). This mixture was stirred at room temperature for 90 min and then poured into a mixture of 4 M HCl (60 mL) and ice (60 mL). The organic phase was washed with cold saturated aqueous $NaHCO_3$ (2 × 200 mL) and H_2O (2 × 100 mL), dried (Na_2SO_4), and filtered. Evaporation under reduced pressure to remove the solvents afforded an oil (6.4 g). The crude product was chromatographed on a silica gel column (240 g), eluting with hexane/Et_2O (2:1). An anomeric mixture of **7** (ratio between the anomers ~1:5) was obtained (lower band) as a colorless oil in 22% yield (1.4 g, 0.046 mol). During the concentration of the fractions containing the higher band, **8** started to precipitate, and after this mixture was cooled in the refrigerator for 24 h, **8** was obtained as white crystals in 52% yield (3.3 g, 0.011 mol).

For **7**: ^1H NMR ($CDCl_3$ dominating anomer) δ 1.94 (s, 3 H, CH_3), 2.20–2.35 (m, 1 H, 2β-H), 2.44–2.52 (m, 1 H, 2α-H), 4.21–4.59 (m, 4 H, 3-H, 4-H, 5-Ha, 5-Hb), 6.36 (d, 1 H, J = 5.1 Hz, 1-H), 7.42–8.10 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 20.92 and 21.07 (CH_3), 37.86 and 38.19 (C-2), 60.25 and 60.37 (C-3), 63.81 and 63.89 (C-5), 82.31 and 82.47 (C-4), 97.39 and 97.61 (C-1), 128.32, 128.39, 129.45, 129.63 and 133.22 (aryl), 165.93 (C=O), 169.58 and 169.99 ($C-H_3C$=O); IR (neat) 2952 (m, CH), 2108 (s, N_3), 1752 (s, C=O), 1724 (s, C=O), 1602 (m), 1452 (m), 1377 (m), 1316 (m), 1274 (s), 1179 (m), 1099 (s), 1072 (s), 1045 (m), 1027 (m), 1011 (s) cm^{-1}; EIMS m/z (relative intensity) 246 (7), 207 (7), 165 (6), 105 (100). Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.82; H, 4.97; N, 13.97.

For **8**: mp 65–66 °C; ^1H NMR ($CDCl_3$) δ 2.06 (s, 3 H, CH_3), 2.37–2.56 (m, 2 H, 2α-H, 2β-H), 4.36–4.64 (m, 4 H, 3-H, 4-H, 5a-H, 5b-H), 6.44 (dd, 1 H, J = 3.0 and 5.4 Hz, 1-H), 7.41–8.07 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$), δ 21.01 (CH_3), 38.58 (C-2), 61.06 (C-3), 62.71 (C-5), 78.70 (C-4), 96.97 (C-1), 128.92, 129.59, 133.10 (aryl), 166.01 (C=O), 169.81 (CH_3C=O); IR (neat) 2949 (w, CH), 2113 (s, N_3), 1740 (s, C=O), 1714 (s, C=O), 1602 (m), 1452 (m), 1384 (m), 1317 (m), 1277 (s), 1243 (s), 1180 (m), 1110 (s), 1074 (m), 1051 (m), 1028 (m), 1015 (s) cm^{-1}; EIMS m/z (relative intensity) 246 (9), 207 (8), 165 (7), 105 (100). Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 55.35; H, 4.99; N, 13.73.

1-(3-Azido-5-*O*-benzoyl-2,3-dideoxy-L-*erythro*-pentofuranosyl)thymine (9). A mixture of 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine[23] (828 mg, 3.07 mmol) and the anomeric mixture of azide **7** (720 mg, 2.36 mmol) dissolved in dry CH_3CN was cooled to −30 °C. *tert*-Butyldimethylsilyl trifluoro-

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methanesulfonate (678 mg, 3.07 mmol) was added, and the reaction mixture was stirred 20 min at −30 °C and 30 min at room temperature. After this time, analytical silica TLC (CH_2Cl_2/CH_3OH (9:1)) showed disappearance of azide **7**. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and quenched with a saturated solution of $NaHCO_3$ (50 mL). After 10 min, the organic phase was successively washed with a saturated solution of $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 950 mg of crude product, which was purified by flash chromatography on a silica gel column (80 g), eluting with CH_2Cl_2/CH_3OH (19:1) to give 820 mg (72%) of an analytically pure anomeric mixture of **9** (α:β ratio ≈ 2:3): ^1H NMR ($CDCl_3$) δ 1.69 (d, J = 1.0 Hz, CH_3), 1.97 (s, CH_3), 2.27 (ddd, J = 14.6, 7.9, and 4.0 Hz, 2′α-H (α-anomer)), 2.39 (dd, J = 13.9 and 6.5 Hz, 2′β-H (β-anomer)), 2.54 (ddd, J = 13.9, 6.5, and 1.5 Hz, 2′α-H (β-anomer)), 2.88 (dt, J = 14.6 and 7.0 Hz, 2′β-H (α-anomer)), 4.19–4.72 (m, 3′-H, 4′-H, 5′-Ha, 5′-Hb), 6.19 (t, J = 6.5 Hz, 1′-H (β-anomer)), 6.27 (dd, J = 7.0 and 4.0 Hz, 1′-H (α-anomer)), 7.11–8.02 (m, arom), 9.60 (s, NH); ^{13}C NMR ($CDCl_3$, α-anomer) δ 12.53 (CH_3), 37.94 (C′-2), 61.29 (C′-3), 63.94 (C′-5), 83.32 (C′-1), 86.10 (C′-4), 110.88 (C-5), 128.50, 129.06, 129.54, 133.45 (arom), 134.81 (C-6), 150.35 (C-2), 163.81 (C-4), 165.88 (ester); (β-anomer) δ 12.11 (CH_3), 37.61 (C′-2), 60.50 (C′-3), 63.49 (C′-5), 81.84 (C′-1), 85.19 (C′-4), 111.30 (C-5), 128.58, 129.06, 129.06, 133.65 (arom), 133.56 (C-6), 150.09 (C-2), 163.61 (C-4), 165.88 (ester). Anal. Calcd for $C_{17}H_{17}N_5O_5$: C, 54.98; H, 4.61; N, 18.86. Found: C, 54.93; H, 4.65; N, 18.32.

1-(3-Azido-5-*O*-benzoyl-2,3-dideoxy-L-*threo*-pentofuranosyl)thymine (10). A mixture of 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine[23] (920 mg, 3.41 mmol) and azide **8** (800 mg, 2.62 mmol) in dry CH_3CN was cooled to −35 °C. *tert*-Butyldimethylsilyl triflate (757 mg, 3.41 mmol) was added, and the reaction mixture was stirred 45 min at −35 °C and 30 min at room temperature. After this time, analytical silica TLC (CH_2Cl_2/CH_3OH (9:1)) showed disappearance of azide **8**. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and quenched with a saturated solution of $NaHCO_3$ (50 mL). After 10 min, the organic phase was successively washed with a saturated solution of $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 780 mg of crude product, which was purified by flash chromatography on a silica gel column (80 g), eluting with CH_2Cl_2/CH_3OH (19:1) to give 560 mg (58%) of an analytically pure anomeric mixture of **10** (α:β ratio ≈ 5:3): ^1H NMR ($CDCl_3$) δ 1.92 (s, CH_3), 1.93 (s, CH_3), 2.22 (dd, J = 14.8 and 3.3 Hz, 2′β-H (β-anomer)), 2.60 (dt, J = 14.3 and 6.5 Hz, 2′α-H (α-anomer)), 2.71 (ddd, J = 14.3, 6.5, and 3.3 Hz, 2′β-H (α-anomer)), 2.82 (ddd, J = 14.8, 7.6, and 7.0 Hz, 2′α-H (β-anomer)), 4.33–4.78 (m, 3′-H, 4′-H, 5′-Ha, 5′-Hb), 6.07 (t, J = 6.5 Hz, 1′-H (α-anomer)), 6.23 (dd, J = 7.6 Hz and 3.3 Hz, 1′-H (β-anomer)), 7.09–8.07 (m, 5 H, arom), 9.42 (s, NH), 9.51 (s, NH); ^{13}C NMR ($CDCl_3$; α-anomer) δ 12.38 (CH_3), 38.09 (C′-2), 62.35 (C′-3), 63.01 (C′-5), 80.34 (C′-1), 87.88 (C′-4), 111.06 (C-5), 128.37, 129.60, 133.24 (arom), 136.05 (C-6), 150.12 (C-4), 163.79 (C-2), 166.05 (ester); (β-anomer) δ 12.52 (CH_3), 38.54 (C′-2), 61.07 (C′-3), 62.47 (C′-5), 79.82 (C′-1), 83.94 (C′-4), 111.16 (C-5), 128.37, 129.60, 133.34 (arom), 135.06 (C-6), 150.42 (C-4), 163.79 (C-2), 166.05 (ester). Anal. Calcd for $C_{17}H_{17}N_5O_5 \cdot {}^1/_4H_2O$: C, 54.33; H, 4.69; N, 18.63. Found: C, 54.73; H, 4.65; N, 18.63.

1-(3-Azido-2,3-dideoxy-β-L-*erythro*-pentofuranosyl)thymine (11) and 1-(3-Azido-2,3-dideoxy-α-L-*erythro*-pentofuranosyl)thymine (12). The anomeric mixture of **9** (700 mg, 1.89 mmol) was dissolved in a saturated solution of NH_3 in absolute CH_3OH (40 mL). The reaction mixture was stirred 20 h at room temperature and evaporated to dryness under reduced pressure. Flash chromatographic purification on a silica gel column (80 g) eluting with EtOAc gave the β-anomer **11** (L-AZT) as the less polar anomer (325 mg, 64%) and the α-anomer **12** as the most polar anomer (175 mg, 35%).

For **11**: mp 119–121 °C (hygroscopic); $[\alpha]^{20}_D$ −56° (c 1.0 in MeOH); ^1H NMR (CD_3OD) δ 1.92 (d, 3 H, J = 1.1 Hz, CH_3), 2.35–2.52 (m, 2 H, 2′α-H, 2′β-H), 3.78 (dd, 1 H, J = 12.1 and 3.4 Hz, 5′-Ha), 3.90 (dd, 1 H, J = 12.1 and 3.2 Hz, 5′-Hb), 3.92–3.97 (m, 1 H, 4′-H), 4.36–4.85 (m, 1 H, 3′-H), 6.20 (t, 1 H, J = 6.4 Hz, 1′-H), 7.83 (q, 1 H, J = 1.1 Hz, 6-H); ^{13}C NMR (CD_3OD) δ 12.42 (CH_3), 38.25 (C′-2), 61.67 (C′-3), 62.43 (C′-5), 86.07 (C′-1, C′-4), 111.61 (C-5), 138.05 (C-6), 152.29 (C-2), 166.35 (C-4). Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot {}^1/_4H_2O$: C, 44.20; H, 5.01; N, 25.77. Found: C, 44.55; H, 4.92; N, 25.67.

For **12**: mp 72–73 °C (hygroscopic); $[\alpha]^{20}_D$ −41° (c 0.8 in MeOH); ^1H NMR (CD_3OD) δ 1.95 (d, 3 H, J = 1.1 Hz, CH_3), 2.03–2.30 (m, 1 H, 2′α-H), 2.78–2.89 (m, 1 H, 2′β-H), 3.65 (dd, 1 H, J = 12.1 and 3.9 Hz, 5′-Ha), 3.72 (dd, 1 H, J = 12.1 and 3.9 Hz, 5′-Hb), 4.32–4.50 (m, 2 H, 3′-H, 4′-H), 6.17 (dd, 1 H, J = 6.8 and 3.8 Hz, 1′-H), 7.59 (q, 1 H, J = 1.1 Hz, 6-H); ^{13}C NMR (CD_3OD) δ 12.49 (CH_3), 38.74 (C′-2), 62.38 (C′-3), 63.20 (C′-5), 87.75 and 87.90 (C′-1, C′-4), 111.13 (C-5), 137.72 (C-6), 152.26 (C-2), 166.49 (C-4). Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 45.26; H, 5.13; N, 26.42.

1-(3-Azido-2,3-dideoxy-β-L-*threo*-pentofuranosyl)thymine (13) and 1-(3-Azido-2,3-dideoxy-α-L-*threo*-pentofuranosyl)thymine (14). The anomeric mixture of **10** (485 mg, 1.31 mmol) was dissolved in a saturated solution of NH_3 in absolute CH_3OH (30 mL). The reaction mixture was stirred 20 h at room temperature and evaporated to dryness under reduced pressure. Flash chromatographic purification on a silica gel column (80 g) eluting with EtOAc gave a pure anomeric mixture of **13** and **14** (310 mg, 89%). After being dried with an oil pump and addition of dry CH_2Cl_2, the α-anomer **14** was crystallized from the mixture (170 mg, 49%) and the β-anomer **13** was obtained by evaporation of the mother liquid (140 mg, 40%).

For **13**: mp 44–45 °C; ^1H NMR (CD_3OD) δ 1.94 (d, 3 H, J = 1.0 Hz, CH_3), 2.24 (ddd, 1 H, J = 14.9, 3.1, and 1.8 Hz, 2′β-H), 2.81 (ddd, 1 H, J = 14.9, 7.7, and 6.2 Hz, 2′α-H), 3.92 (d, 2 H, J = 5.8 Hz, 5′-Ha, 5′-Hb), 4.15 (td, 1 H, J = 5.8 and 4.1 Hz, 4′-H), 5.19 (ddd, 1 H, J = 6.2, 4.1, and 1.8 Hz, 3′-H), 6.15 (dd, 1 H, J = 7.7 and 3.1 Hz, 1′-H), 7.70 (q, 1 H, J = 1.0 Hz, 6-H); ^{13}C NMR (CD_3OD) δ 12.61 (CH_3), 39.17 (C′-2), 61.31 (C′-3), 62.44 (C′-5), 84.25 (C′-1), 85.66 (C′-4), 111.21 (C-5), 137.70 (C-6), 152.32 (C-4), 166.35 (C-2). Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot {}^1/_4H_2O$: C, 44.20; H, 5.01; N, 25.77. Found: C, 44.32; H, 4.85; N, 25.63.

For **14**: mp 164–165 °C; ^1H NMR (CD_3OD) δ 1.94 (d, 3 H, J = 1.1 Hz, CH_3), 2.49–2.60 (m, 1 H, 2′α-H), 2.66 (ddd, 1 H, J = 14.4, 6.7, and 1.9 Hz, 2′β-H), 3.79 (d, 2 H, J = 5.4 Hz, 5′-Ha, 5′-Hb), 4.48–4.55 (m, 2 H, 3′-H, 4′-H), 6.17 (t, 1 H, J = 6.7 Hz, 1′-H), 7.53 (q, 1 H, J = 1.1 Hz, 6-H); ^{13}C NMR (CD_3OD) δ 12.36 (CH_3), 38.97 (C′-2), 61.89 (C′-3), 63.88 (C′-5), 84.52 (C′-1), 87.85 (C′-4), 111.67 (C-5), 138.06 (C-6), 152.27 (C-4), 166.46 (C-2). Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot {}^1/_4H_2O$: C, 44.20; H, 5.01; N, 25.77. Found: C, 44.52; H, 4.86; N, 25.71.

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