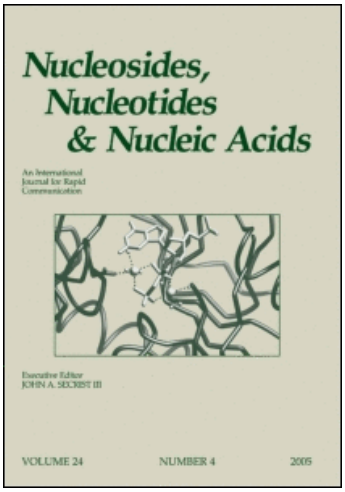

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SYNTHESIS OF 1',2'-*SECO*-NUCLEOSIDE ANALOGUES OF AZT§[1]

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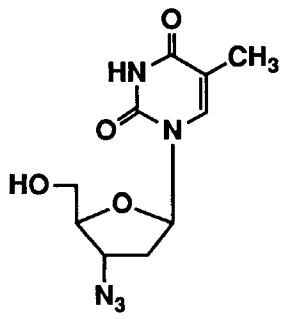
Abstract: 1',2'-*Seco*-AZT (**3**) and its 3'*R*,4'*S* diastereomer (**19**) were prepared and evaluated as antiviral agents. The chiral, acyclic side chains of these thymine acyclonucleosides were derived from *D*-isoascorbic acid. The two AZT analogues, **3** and **19**, were screened against HIV, other RNA viruses, and two DNA viruses and they were found to be inactive.

3'-Azido-3'-deoxythymidine (**1**, AZT) is a potent and selective inhibitor of HIV replication and, to date, it is one of two drugs approved for the treatment of AIDS or AIDS-related complex (ARC).[2] Even though AZT is efficacious in the treatment of AIDS, it does have some serious side effects. For example, long-term clinical use causes myelosuppression.[3] In an effort to circumvent this serious side effect, while maintaining the clinical effectiveness of this drug, several laboratories have explored various chemical modifications of this nucleoside. One area involves the synthesis of acyclonucleosides which resemble AZT[4-8], *e.g.*, **2**. With the exception of two



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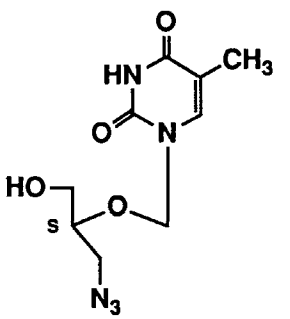

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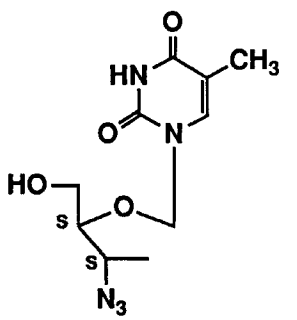

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§This manuscript is dedicated to the memory of Professor Tohru Ueda

recent reports,[7,8] which described the chiral synthesis of **2**, all of the other analogues prepared were racemic. We are actively engaged in the synthesis of 1',2'-*seco*-nucleosides/tides,[9] acyclonucleosides/tides whose acyclic side chains incorporate the same chiral, structural features of *D* (and *L*)-pentoses. Thus, as part of our antiviral program, we prepared 1',2'-*seco*-AZT (**3**) and its 3'*R*,4'*S* counterpart (**19**). We now describe the syntheses of these acyclonucleosides and report on their antiviral activity.

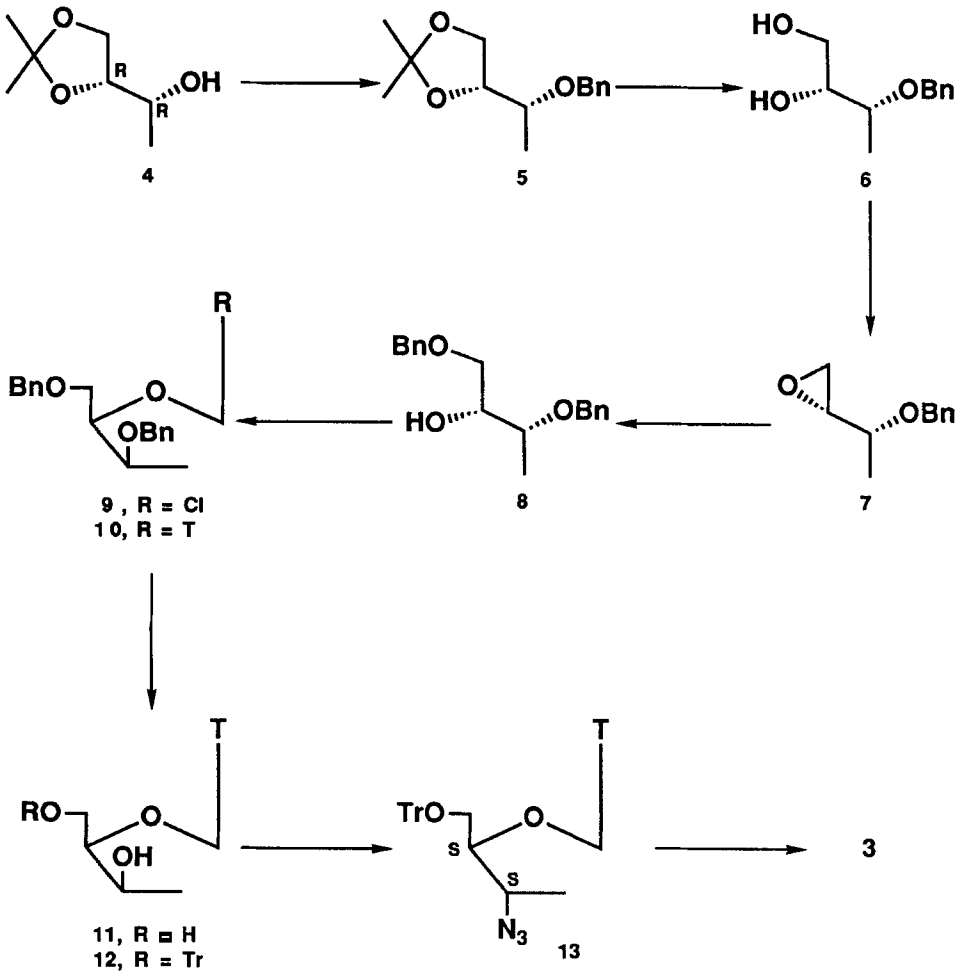
CHEMISTRY

Our synthetic approach to **3** and **19** centered on the preparation of the 1',2'-*seco*-nucleosides of thymine **11** (Scheme 1) and **16** (Scheme 2), respectively, followed by inversion of their 3'-hydroxy groups[10] with hydrazoic (HN_3) acid *via* the Mitsunobu reaction. The synthesis of **11** started with (2*R*,3*R*)-1,2-*O*-isopropylidenebutane-1,2,3-triol (**4**)[10], a chiron previously prepared in our laboratory.[11] Benzylation of **4** to give **5** was achieved with benzyl bromide in dry DMF in the presence of sodium hydride at room temperature. The isopropylidene moiety of **5** was cleaved using activated Amberlite IR-120 (H^+) in aqueous ethanol and the resulting diol **6** was converted to the epoxide **7** by the Mitsunobu reaction.[12] Regiospecific ring opening of **7** with sodium benzylate[11] afforded the alcohol **8** in a 38% overall yield from **4**. Compound **8** was then chloromethylated and coupled with persilylated thymine in the presence of a catalytic amount of tetraethylammonium iodide to furnish the protected acyclonucleoside.[10] Debenzylation of the acyclic side chain was accomplished by transfer hydrogenation over Pearlman's catalyst[12] to provide **11**. Compound **11**, the 3'*R*-diastereomer of 1',2'-*seco*-thymidine (**16**), was tritylated (53%) and then subjected to HN_3 under Mitsunobu conditions to give **13** (95%). Detritylation of **13** provided 1',2'-*seco*-AZT (**3**, 80%).

With the exception of the tritylation step (**16**→**17**), the synthesis of **19**, the 3'*R*,4'*S*-diastereomer of **3**, was carried out in the same manner (see Scheme 2). The tritylation step was modified to enhance the yield. 1',2'-*Seco*-thymidine[14] (**16**) was added to a mixture of trityl chloride and powdered, dry 4Å molecular sieves in pyridine/methylene chloride (1:3 V/V) and the suspension stirred for 40 h at room temperature under anhydrous conditions. This modification provided **17** in 80% yield. The 5'-*O*-trityl derivative **17** was then treated with HN_3 in the present of triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD) to give the 3'*R*-azide **18** which in turn was deprotected to furnish the target analogue **19** in 56% overall yield from **16**. The site of alkylation of **11** and **16**, and thus **3** and **19**, respectively, was determined by UV spectroscopy.

ANTIVIRAL TESTING

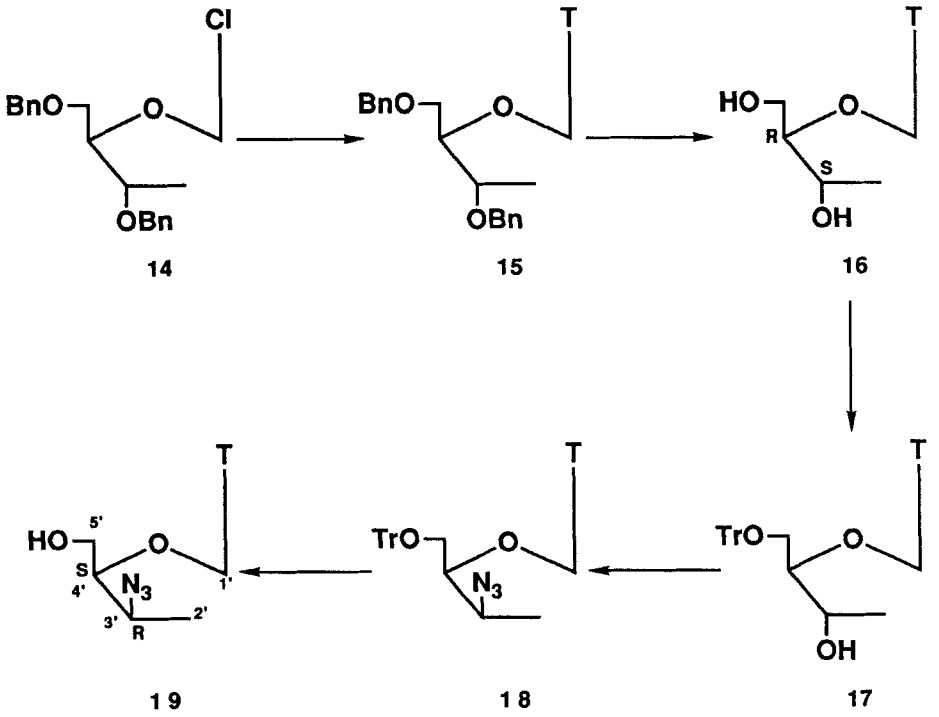
The 1',2'-*seco*-nucleosides **3** and **19** were screened for activity (*in vitro*) against Adenovirus type 2 (AD2) virus, Vaccinia (VV) virus, Human Immunodeficiency virus (HIV),



Bn = Benzyl, T = Thymine, Tr = Trityl

Scheme 1

Japanese Encephalitis (JE) virus, Pichinde (PIC) virus, Punta Toro (PT) virus, Rift Valley Fever (RVF) virus, Sandfly Fever (SF) virus, Venezuelan Equine Encephalomyelitis (VEE) virus, Vesicular Stomatitus (VSV) virus, and Yellow Fever (YF) virus. The two compounds were devoid of activity. The antiviral testing was conducted under the auspices of the USAMRIID antiviral drug screening program.



Scheme 2

EXPERIMENTAL SECTION

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on either a Varian EM-390 or Bruker 300 MHz spectrometer. Chemical shifts are in parts per million with respect to TMS. High resolution mass spectra (EI) were obtained on a MAT 731 instrument. Optical rotations were measured on a Perkin-Elmer Model-141 digital readout polarimeter. Silica gel (Merck grade 60, 230-400 mesh, 60Å) suitable for column chromatography was purchased from Aldrich. All solvent proportions are by volume unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

(2*R*,3*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidenebutane-1,2,3-triol (5). (2*R*,3*R*)-1,2-*O*-isopropylidenebutane-1,2,3-triol[11] (**4**; 11.8 g, 81 mmol) in 24 mL of dry DMF was added dropwise to a cold (10 °C), mechanically stirred suspension of NaH (5.0 g, 125 mmol, 60%; prewashed with hexane) in dry DMF (179 mL). After stirring at 10 °C for 2 h, a solution of benzyl

bromide (15.8 g, 11.0 mL, 92.5 mmol) in dry DMF (16 mL) was added over a 20 min period, and the resulting mixture stirred for 2 h. Next, water (6 mL) was carefully added to the reaction flask, the mixture was stirred, and then poured into water (1L). The product was extracted with ethyl ether (4 x 150 mL). The ether extracts were combined, washed with water (5 x 100 mL), and dried over anhydrous $MgSO_4$. The dried ether layer was concentrated under diminished pressure and the oily residue purified by silica gel column chromatography using hexanes-ethyl acetate (9:1) as eluent. Pure **5** (18.4 g) was obtained in 95.6% yield: $[\alpha]^{25}_D$ +7.91 (*c* 2.605 EtOH); ^{1}H NMR ($CDCl_3$), δ 1.1 (d, 3, J = 6 Hz, C*H*$_3$), 1.35 (s, 3, C*H*$_3$), 1.4 (s, 3, C*H*$_3$), 3.3-4.3 (m, 4), 4.6 (s, 2, C*H*$_2$C$_6$H$_5$), 7.28 (s, 5, C$_6$*H*$_5$).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.26; H, 8.33.

(2*R*,3*R*)-3-*O*-Benzylbutane-1,2,3-triol (6). Amberlite IR-120 resin (30.4 g), water (35 mL), and concentrated HCl (5 mL) were added to a solution of **5** (36.1 g, 0.153 mol) in 95% ethanol (360 mL). The mixture was stirred for 20 h at room temperature, filtered, and the filtrate was concentrated under diminished pressure to give an oil. This material was dissolved in Et_2O (100 mL) and dried over anhydrous $MgSO_4$. Filtration and removal of the excess solvent furnished pure **6** (28.9g, 96.4%): $[\alpha]^{25}_D$ -24.5 (*c* 2.46 EtOH);^{1}H NMR ($CDCl_3$), δ 1.1 (d, 3, J =6 Hz, C*H*$_3$), 2.83 (br s, 1, O*H*; D_2O exchangeable), 3.17 (br s, 1; D_2O exchangeable), 3.32-3.83 (m, 4), 4.5 (q_{AB}, 2, J =11.25 Hz, C*H*$_2$C$_6$H$_5$), 7.28 (s, 5, C$_6$*H*$_5$).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22. Found: C, 67.20; H, 8.07.

(2*R*,3*R*)-3-(Benzyloxy)-1,2-epoxybutane (7). To a stirred solution of **6** (28.3 g, 0.144 mol) and TPP (43.6 g, 0.166 mol) in dry benzene (425 mL), DIAD (33.6 g, 0.166 mol) was added dropwise. Removal of the benzene under diminished pressure, followed by distillation of this reaction mixture (90-96 °C @ 0.03 mmHg), gave 23.8 g of a mixture of **7** and H_2DIAD.[15] Silica gel column chromatography of this mixture using hexanes-ethyl acetate (95:5) as eluent provided pure **7** (20.83 g, 81%): $[\alpha]^{25}_D$ +12.7 (*c* 2.005 EtOH);^{1}H NMR ($CDCl_3$), δ 1.12 (d, 3, J = 6 Hz, C*H*$_3$), 2.35-2.48 (q, 1, J = 3 Hz, C(1)*H*), 2.67 (t, 1,J = 4.5 Hz, C(1)*H*), 2.83-302 (m, 1, C(2)*H*), 3.18 (q, 1, J = 4.5 Hz, C(3)*H*), 4.67 (q_{AB}, 2, J =12 Hz, C*H*$_2$C$_6$H$_5$), 7.0-7.43 (m, 5, C$_6$*H*$_5$).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.96; H, 8.12.

(2*R*,3*R*)-1,2-O-Dibenzylbutane-1,2,3-triol (8). Benzyl alcohol (26 mL, 0.25 mol), sodium hydroxide (3.5 g, 87.5 mmol) dissolved in water (3.5 mL), and *tert*-butyl alcohol (70 mL) were stirred at reflux for 30 min. The epoxide **7** (7.5 g, 42.1 mmol) was then added to this hot mixture and the reaction continued at reflux. The reaction was monitored by TLC (hexanes - ethyl acetate, 3:2) and when **7** was no longer detectable, the reaction was allowed to cool and stirred at room temperature for *ca.* 12 h. The solvents were removed under diminished pressure and the

aqueous residue was extracted with methylene chloride (CH_2Cl_2, 3 x 100 mL). The CH_2Cl_2 layer was dried (anhydrous Na_2SO_4), concentrated, the benzyl alcohol distilled off, and the remaining residue column chromatographed (silica gel) using hexanes-ethyl acetate (80:20) as eluent. The fractions containing the title compound were combined to furnish **8** (6.14 g, 50.9%): $[\alpha]^{25}_D$ -21.95 (***c*** 1.455, EtOH); ^{1}H NMR ($CDCl_3$), δ 1.18 (d, 3, J = 6 Hz, C*H*$_3$), 2.64 (br s, 1, O*H*, D_2O exchangeable), 3.44-3.86 (m, 4), 4.46 (s, 2, C*H*$_2$C$_6$H$_5$), 4.48 (q_{AB}, 2, J = 12 Hz, C*H*$_2$C$_6$H$_5$), 7.26 (s, 10, CH$_2$C$_6$*H*$_5$).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.33; H, 7.85.

(2*R*,3*R*)-1,2-bis(benzyloxy)-2-(chloromethoxy)butane (**9**). To a three-necked, flame-dried flask fitted with a gas-inlet and a drying tube were added, under N_2, paraformaldehyde (0.24 g, 8.0 mmol), **8** (2.2 g, 7.7 mmol), and dry CH_2Cl_2 (70 mL). The mixture was cooled to 0 °C in an ice bath, the N_2 flow discontinued, and dry HCl gas was bubbled into the solution for 5 h while the temperature was maintained at 0 °C. Calcium chloride (*ca.* 5 g) was added cautiously and the mixture stirred for 15 min. After filtration, the solution was concentrated under diminished pressure to give an oily material (2.45 g), which contains *ca.* 90% of the chloromethyl ether **9** as indicated by ^{1}H NMR analysis[16]: ($CDCl_3$), δ 1.15 (d, 3, J = 6 Hz, C*H*$_3$), 3.5-4.0 (m, 4), 4.25-4.7 (m, 4, C*H*$_2$C$_6$H$_5$), 5.6 (s, 2, OC*H*$_2$N), 7.22 (s, 10, CH$_2$C$_6$*H*$_5$).

1[[1,3(*R*)-bis(benzyloxy)-2(*R*)-butoxy]methyl]thymine (**10**). Thymine (1.4 g, 12 mmol) was heated with HMDS (50 mL) at reflux and a catalytic amount of ammonium sulfate (50 mg) for 2 h. Excess HMDS was removed under diminished pressure and the silylated heterocycle was coupled with **9** (2.45 g, 90% pure, 7 mmol) in the presence of tetraethylammonium iodide (50 mg) in dry CH_2Cl_2 (70 mL) at reflux for 12 h. The product (2.6 g) after chromatography (hexanes - ethyl acetate, 7:3), gave pure **10** (2.17 g, 67.5%), as a viscous material, and 0.13 g of the N-3 isomer. ^{1}H NMR ($CDCl_3$), δ 1.10 (d, 3, J = 6 Hz, C*H*$_3$), 1.7 (s, 3, C*H*$_3$), 3.4-3.9 (m, 4), 4.2-4.6 (m, 4, C*H*$_2$C$_6$H$_5$), 5.15 (S, 2, OC*H*$_2$N), 6.95-7.4 (m, 11, CH$_2$C$_6$*H*$_5$ and C(6)*H*), 9.47 (s, 1, NH, D_2O exchangeable).

Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.99; H, 6.70; N, 6.48.

1[[1,3(*R*)-bis(hydroxy)-2(*R*)-butoxy]methyl]thymine (**11**). Compound **10** (0.530 g, 1.25 mmol) was dissolved in absolute ethanol (8 mL) to which 20% Pd(OH)$_2$/C (0.2 g) and cyclohexene (4 mL) were added. The reaction mixture was then heated under reflux for 6 h, filtered through celite and solvents were removed under vacuum. The residue was then dissolved in water, extracted with CH_2Cl_2 (2x10 mL) and the aqueous layer was lyophilized to give **11** (250 mg, 82%). An analytical sample was prepared by crystallization from ethanol, to give an extremely

hygroscopic solid: $[\alpha]^{25}_D$ -10.2 (*c* 1.2, EtOH); ^{1}H NMR (D_2O), δ 1.15 (d, 3, J = 6 Hz, C*H*$_3$), 1.9 (s, 3, C*H*$_3$), 3.33-3.98 (m, 4), 5.3 (s, 2, OC*H*$_2$N), 7.49 (s, 1, C(6)*H*); UV λ_{max} (pH 1) 266 nm (ε 12 390), λ_{max} (water) 264 nm (ε 10 820), λ_{max} (pH 11) 267 nm (ε 12 210).

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.60; N, 11.47. Found: C, 49.08; H, 6.79; N, 11.45.

1-[[1-*O*-Trityl-3(*R*)-hydroxy-2(*R*)-butoxy]methyl]thymine (12). Trityl chloride (190 mg, 0.682 mmol) was added to a solution of **11** (160 mg, 0.676 mmol) in dry pyridine (4 mL). The mixture was stirred at room temperature for 12.5 h and then concentrated to a viscous residue. The residue was dissolved in chloroform (100 mL) and the solution was washed with water (3 x 50 mL). After drying over anhydrous Na_2SO_4, the organic layer was concentrated and the residue was chromatographed over basic alumina. The column was eluted with ethyl acetate-methanol (9:1) to afford crystalline **12** (173 mg, 53%): mp 94-96 °C; $[\alpha]^{25}_D$ -3.76 (*c* 1.09 $CHCl_3$);^{1}H NMR ($CDCl_3$), δ 1.02 (d,3, J = 6 Hz, C*H*$_3$), 2.45-4.1 (m, 5), 5.2 (q_{AB}, 2, J = 10.5 Hz, OC*H*$_2$N), 6.87-7.57 (m, 16, 3 x C_6H_5 and C(6)*H*), 8.97-9.53 (br s, 1, N*H*, D_2O exchangeable).

Anal. Calcd. for $C_{29}H_{30}N_2O_5 \cdot 0.5\ H_2O$: C, 70.29; H, 6.31; N, 5.65. Found: C, 70.61; H, 6.35; N, 5.45.

1-[[3(*S*)-Azido-1-*O*-trityl-2(*S*)-butoxy]methyl]thymine (13). Hydrazoic acid in benzene (1.3 mL, 1.56 N; **CAUTION: REACTION MUST BE RUN IN A WELL-VENTILATED FUME HOOD**) and DIAD (350 mg, 1.71 mmol) in dry THF (5 mL) were added, successively, to a stirred solution of **12** (680 mg, 1.41 mmol) and TPP (450 mg, 1.70 mmol) in dry THF (25 mL). After stirring for 1.5 h at room temperature, the reaction was vented and the solvent removed under diminished pressure to give a viscous liquid. This material was placed on a basic alumina column and the column was eluted with hexanes-ethyl acetate (4:1), ethyl acetate, and ethyl acetate-methanol (9:1). H_2DIAD was removed with the first two solvent systems followed by pure **13** (600 mg, 95.4%) with the third system: mp 66-68 °C; $[\alpha]^{25}_D$ -0.70 (*c* 1.145 $CHCl_3$);^{1}H NMR ($CDCl_3$), δ 1.08 (d, 3, J = 6 Hz, C*H*$_3$), 1.87 (s, 3, C*H*$_3$), 2.97-3.4 (m, 2), 3.43-3.97 (m, 2), 5.18 (q_{AB}, J =11.25 Hz, 2, OC*H*$_2$N), 7.05 (s, 1, C(6)*H*), 6.82-7.77 (m, 15, C_6H_5), 9.3-9.75 (br s, 1, N*H*, D_2O exchangeable).

Anal. Calcd. for $C_{29}H_{29}N_5O_4 \cdot 0.5\ H_2O$: C, 66.91; H, 581; N, 13.45. Found: C, 67.01; H, 5.62; N, 13.60.

1-[[3(*S*)-Azido-1-hydroxy-2(*S*)-butoxy]methyl]thymine (3). 80% Acetic acid (5 mL) was added to the 1',2'-*seco*-nucleoside **13** (690 mg, 1.344 mmol) and the solution stirred at reflux for 1 h. The excess acetic acid and water were removed *in vacuo* and the resulting

residue was dissolved in methanol (15 mL) and made alkaline with a saturated potassium carbonate solution. After 16 h of stirring at room temperature, the solvents were removed and the resulting solid was extracted with methanol. The product, obtained after evaporation of methanol, was absorbed on silica gel and placed on top of a silica gel column. Elution with hexanes-ethyl acetate (4:1) and hexanes-ethyl acetate (1:1) removed trityl alcohol and continued elution with ethyl acetate afforded pure **3** (300 mg, 84%), as a gum: $[\alpha]^{25}_D$ +35.5 (*c* 1.145 $CHCl_3$); ^1H NMR ($CDCl_3$), δ 1.23 (d, 3, J = 6 Hz, C*H*$_3$), 1.9 (s, 3, C*H*$_3$), 3.02-4.43 (m, 5; one hydrogen exchangeable), 5.27 (q_{AB}, 2, OC*H*$_2$N), 7.23 (s, 1, C(6)H), 9.93-10.67 (br s, 1, N*H*; exhangeable); HRMS (EI) for $C_{10}H_{15}N_5O_4$ *m/z*. Calcd. 269.1123, Found 269.1117.

1-[[1,3(*S*)-bis(benzyloxy)-2(*R*)-butoxy]methyl]thymine (**15**). Thymine (2.58 g, 19 mmol) was silylated with HMDS (70 mL) in the presence of ammonium sulfate (0.71 g), as described for **10**. This silylated heterocycle was coupled with **14**[16] (8.1 g, 70% pure, 19 mmol) with a catalytic amount of tetraethylammonium iodide (29 mg) in dry CH_2Cl_2 (70 mL) at reflux for 5 h. The product (10.52 g) after chromatography, gave pure **15** (4.75 g, 58.7%), as a viscous material, and 750 mg of the N3-isomer. Physical constants of **15**: $[\alpha]^{25}_D$ +4.17 (*c* 3.36, EtOH); ^1H NMR ($CDCl_3$), δ 1.15(d, 3, J = 6 Hz, C*H*$_3$), 1.77 (s, 3, C*H*$_3$), 3.28-4.12 (m, 4), 4.22-4.68 (m, 4, C*H*$_2$C$_6$H$_5$), 5.23 (s, 2, OC*H*$_2$N), 6.95-7.48 (m, 11, $CH_2C_6H_5$ and C(6)H), 9.57 (s, 1, NH, D_2O exchangeable).

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.75; H, 6.42; N, 6.88.

1-[[1,3(*S*)-bis(hydroxy)-2(*R*)-butoxy]methyl]thymine (**16**). Compound **15** (3.1 g, 7.31 mmol) was dissolved in absolute ethanol (40 mL) to which 20% $Pd(OH)_2$/C (0.95 g) and cyclohexene (16.5 mL) were added. The reaction was conducted as described for **11** and provided a quantitative yield of **16**. An analytical sample was prepared by crystallization from ethanol: mp 127-129 °C; $[\alpha]^{25}_D$ -2.65 (**c** 0.85, EtOH); ^1H NMR (DMSO-d_6), δ 0.98 (d, 3, J = 6 Hz, C*H*$_3$), 1.77 (s, 3, C*H*$_3$), 3.2-3.9 (m, 4) 4.32-4.8 (m, 2, O*H*, D_2O exchangeable), 5.1 (s, 2, OC*H*$_2$N), 7.53 (s, 1, C(6)*H*), 11.5 (s, 1, N*H*, D_2O exchangeable); UV λ_{max} (pH 1) 265 nm (ε 10 550), λ_{max} (water) 264 nm (ε 9 375), λ_{max} (pH 11) 263 nm (ε 9 048).

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.6; N, 11.47. Found: C, 49.16; H, 6.63; N, 11.31.

1-[[3(*S*)-Hydroxy-1-*O*-trityl-2(*R*)-butoxy]methyl]thymine (**17**). Trityl chloride (1.22 g, 4.30 mmol) was added to a mixture of **16** (1.0 g, 4.10 mmol), powdered 4Å molecular sieves (10 g, pre-dried at 200 °C for 3 h), and dry pyridine (20 mL) in dry CH_2Cl_2 (60 mL). After 16, and 20 h of reaction time, 0.1 mole % of trityl chloride was added. After stirring 24 h, the

reaction was filtered and the molecular sieves were washed with chloroform (50 mL). The combined filtrate was concentrated to a liquid residue, which was placed on a basic alumina column. The column was eluted with ethyl acetate-methanol (95:5) to furnish crystalline **17** (1.60 g, 80.5%): mp 79-81 °C; $[\alpha]^{25}_D$ -6.72 (*c* 1.235 $CHCl_3$);^{1}H NMR ($CDCl_3$), δ 1.0 (d, 3, J = 6 Hz, C*H*$_3$), 1.8 (s, 3, C*H*$_3$), 2.78 (br d, 1, O*H*, exchangeable with D_2O), 3.211 (d, 2, J = 4.5 Hz, C*H*$_2$OTr), 3.53-4.1(m, 2), 5.23 (q_{AB}, 2, OC*H*$_2$N), 6.77-7.78 (m, 16, C$_6$*H*$_5$ and C(6)*H*), 9.67 (s, 1, N*H*, exchangeable with D_2O).

Anal. Calcd. for $C_{29}H_{30}N_2O_5 \cdot 1.5\ H_2O$: C, 67.82; H, 6.48; N, 5.45. Found: C, 67.92; H, 6.30; N, 5.35.

1-[[3(*R*)-Azido-1-*O*-trityl-2(*S*)-butoxy]methyl]thymine (18). Treatment of **17** (1.28 g, 2.63 mmol) in dry THF (25 mL) was carried out, as described for **13**, with hydrazoic acid in benzene (1.56 N, 2.5 mL) in the presence of TPP (840 mg, 3.17 mmol) and DIAD (660 mg, 3.19 mmol). This reaction provided 0.93 g (69%) of crystalline **18**: mp 83-86 °C; $[\alpha]^{25}_D$ -2.92 (*c* 1.37 $CHCl_3$);^{1}H NMR ($CDCl_3$), δ 1.05 (d, 3, J = 6 Hz, C*H*$_3$), 1.87 (s, 3, C*H*$_3$), 2.92-3.45 (m, 2) 3.52-3.92 (m, 2), 5.2 (q_{AB}, 2, J = 11.25 Hz, OC*H*$_2$N), 7.0-7.62 (m, 16, C$_6$*H*$_5$ and C(6)*H*), 9.52 (br s, 1, N*H*, exchangeable with D_2O).

Anal. Calcd. for $C_{29}H_{29}N_5O_4 \cdot 1.5\ H_2O$: C, 66.91; H, 5.81; N, 13.45. Found: C, 66.46; H, 5.64; N, 13.03.

1-[[3(*R*)-Azido-1-*O*-trityl-2(*S*)-butoxy]methyl]thymine (19). Deprotection of **18** (1.08 g, 2.11 mmol) was carried-out as described for **3**. The title compound **19** was obtained in quantitative yield, as a gum: $[\alpha]^{25}_D$ +4.82 (c 0.85 $CHCl_3$);^{1}H NMR ($CDCl_3$), δ 1.23 (d, 3, J = 6 Hz, C*H*$_3$), 1.92 (s, 3, C*H*$_3$), 2.88-4.55 (m, 5); 5.28 (q_{AB}, 2, OC*H*$_2$N), 7.27 (s, 1, C(6)*H*), 10.73-10.93 (br s, 1, N*H*); HRMS (EI) for $C_{10}H_{15}N_5O_4$ *m/z* . Calcd. 269.1123. Found 269.1125.

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10. In the text and Experimental Section, the butanetriols (**4-8**) are named and numbered in accordance with butanetriol nomenclature. The naming and numbering of the 1',2'-*seco*-nucleosides follow nucleoside nomenclature in the text and schemes, however, in the Experimental Section butanetriol nomenclature is used.

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15. Dissolving this mixture in hexanes and allowing it to stand for 30 min at 4 °C precipitates most of the dihydro-DIAD (H_2DIAD). After filtration and removal of solvent, the epoxide **7** is sufficiently pure for further use.

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