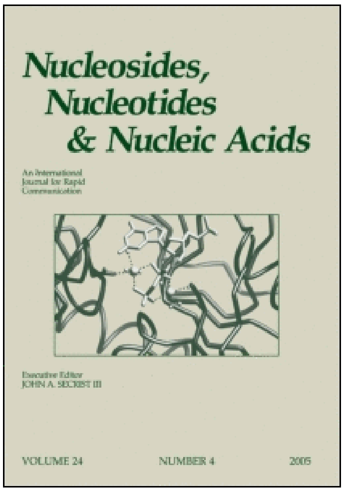

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Synthesis of Isonucleosides Related to AZT and AZU

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SYNTHESIS OF ISONUCLEOSIDES RELATED TO AZT AND AZU[§]

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Abstract- Approaches to 1,4-anhydro-3-azido-2,3-dideoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-arabinitol, and the related uracil derivative, have been developed. These conceptually new, optically active analogs of AZT, derived from 1,4-anhydro-D-ribitol, are among the first examples of regioisomeric analogs of AZT.

A number of nucleoside analogues have been found to possess antiviral activity against HIV-1.[1] AZT (3'-azido-3'-deoxythymidine) emerged as the first compound to be approved for clinical use in the United States for patients with AIDS and AIDS related complex (ARC).[2,3] However, the induction of bone marrow toxicity[4] and the observed emergence of viral resistant strains [5] pose some limitations on its clinical effectiveness. In the last few years, an extensive amount of research has been focused on the development of both purine and pyrimidine nucleosides related to AZT such as AZU,[6] AzddG,[7] AzddA,[8] and analogs thereof.[9] Recently, the synthesis of 2-azido-2,3-dideoxy-β-D-*threo*-[10] and 2-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosylthymine have been reported.[11,12] However, there are no examples in the literature of regioisomeric analogs of AZT involving the glycosidic bond. Interestingly, several isomeric nucleoside analogs which involve a similar transposition of the glycosidic bond from C-1' to C-2' have exhibited activity against both HIV-1[13,14] and HSV.[15,16] This paper reports on the

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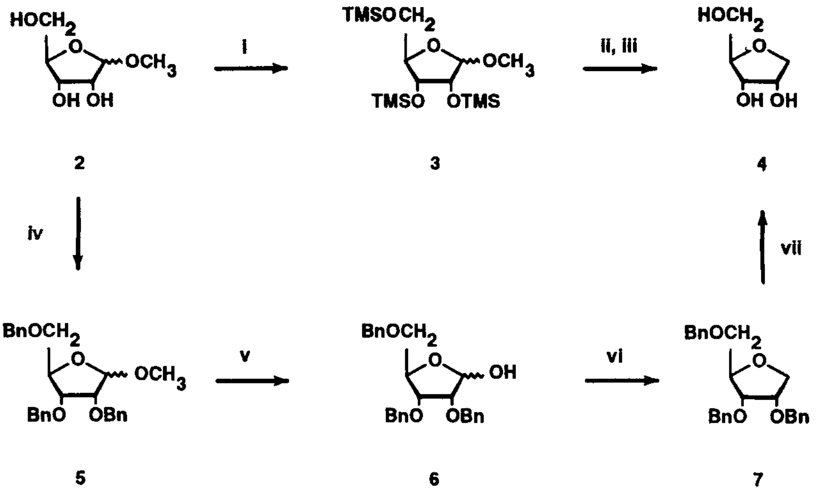
[§] This paper is dedicated to the memory of Roland K. Robins



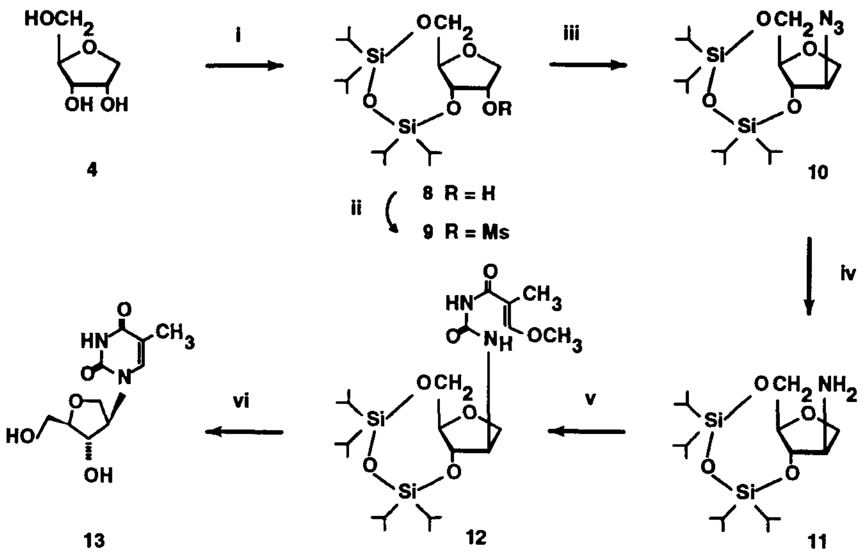
i. HMDS, TMSCl, CH_3CN, Δ; ii. TMSOTf, TES, CH_3CN; iii. H_2O, Dowex OH^-; iv. BnBr, NaH, DMF; v. H_2O, HCl, AcOH, Δ; vi. TES, $BF_3 \cdot OEt$, CH_3CN; vii. H_2, 10% Pd/C, EtOH.

Scheme 1

synthesis of conceptually new, optically active, isomeric analogs of AZT and AZU derived from 1,4-anhydro-D-ribitol.[17,18]

The starting compound for the synthesis of the AZT analog (**1**) was 1,4-anhydro-D-ribitol (**4**).[19] Bennek and Gray have reported the synthesis of **4** *via* silylation of the methyl glycoside **2** followed by reductive cleavage in the presence of triethylsilane (TES) and TMS triflate (TMSOTf).[20] However, in our hands, the reaction gave poor results on a multigram scale. Compound **7**, previously prepared from either the reduction of the 1-halogenated sugar[19] or deoxygenation of **6** in the presence of a pyridine-borane complex,[21] appeared to be an attractive alternative (Scheme 1). We have found that high yields of **7** could be obtained by treatment of **6** with TES and $BF_3 \cdot OEt$.[22] Deprotection of **7** by catalytic hydrogenation afforded crystalline **4** in nearly quantitative yield (Scheme 1).

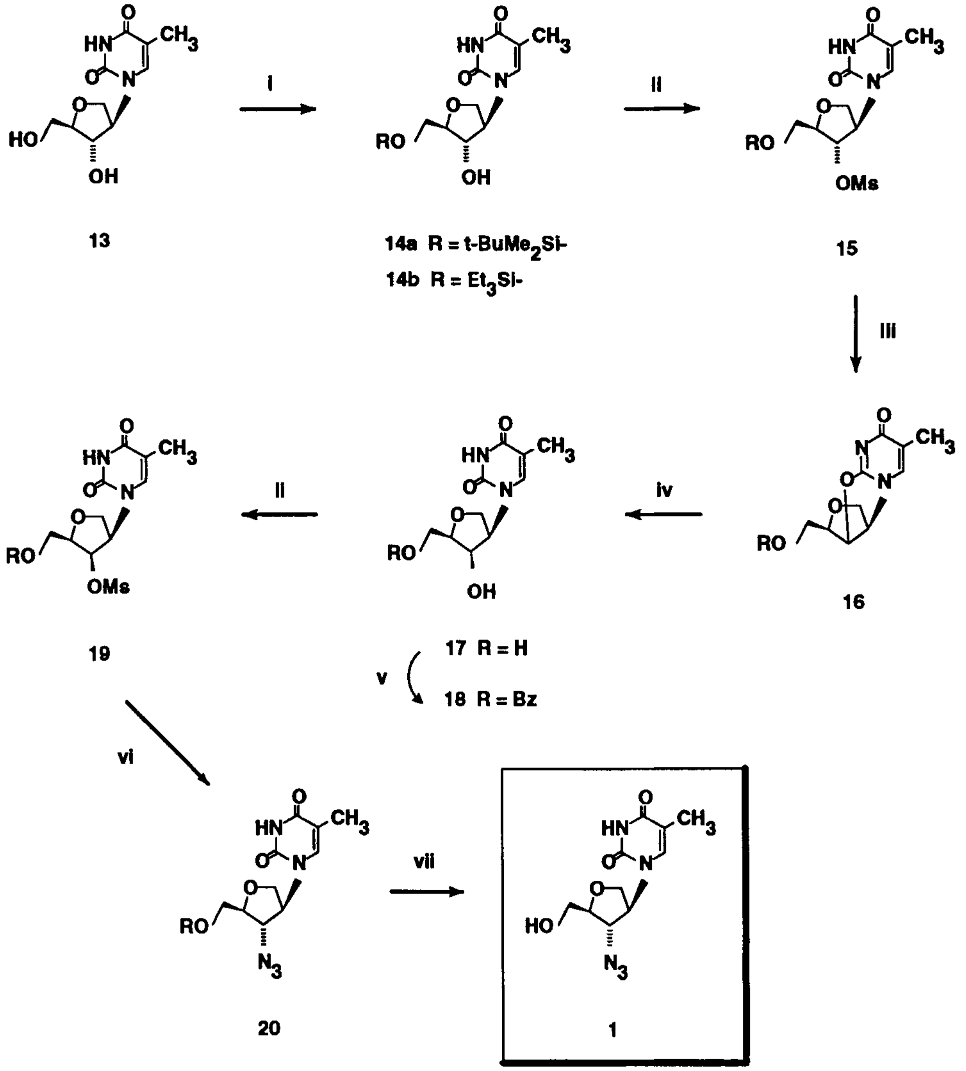
Selective protection of the hydroxyl functionalities at C-3 and C-5 was accomplished by treatment of **4** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDS-



i. TIPDS-Cl_2, pyridine, -15 °C to room temperature; ii. MsCl, Et_3N, CH_2Cl_2, 0 °C; iii. NaN_3, DMF, Δ; iv. 5% Pd/C, H_2, EtOH; v. 3-methoxy-2-methylacryloyl isocyanate, toluene, DMF, 0 °C to room temperature; vi. dioxane, 2N H_2SO_4, Δ.

Scheme 2

Cl_2) in pyridine to afford **8** in 70-75% yields (Scheme 2). Several attempts at the displacement of the mesylate of **8** (i.e. **9**) by the appropriate pyrimidine under a variety of conditions (i.e. thymine, K_2CO_3, 18-crown-6, DMF or NaH, DMSO) led to poor overall yields of the N-1 alkylated product, accompanied by decomposition and O-alkylated products. However, the displacement of the mesylate (or tosylate) **9** was readily accomplished with sodium azide in DMF to afford the protected 2-azido-2-deoxy-D-arabinitol **10** in 80-85% yields. Construction of the pyrimidine ring was readily accomplished from the protected 2-amino-2-deoxy-1,4-anhydro-D-arabinitol **11**, derived from **10** by catalytic hydrogenation.[23] Treatment of **11** with 3-methoxy- 2-methylacryloyl isocyanate, prepared *in situ* from 3-methoxy-2-methylacryoyl chloride and silver isocyanate,[24] afforded the intermediate acryloylurea **12** in approximately 85-90% yields for the two steps. Cyclization of **12** with concomitant deprotection was readily accomplished



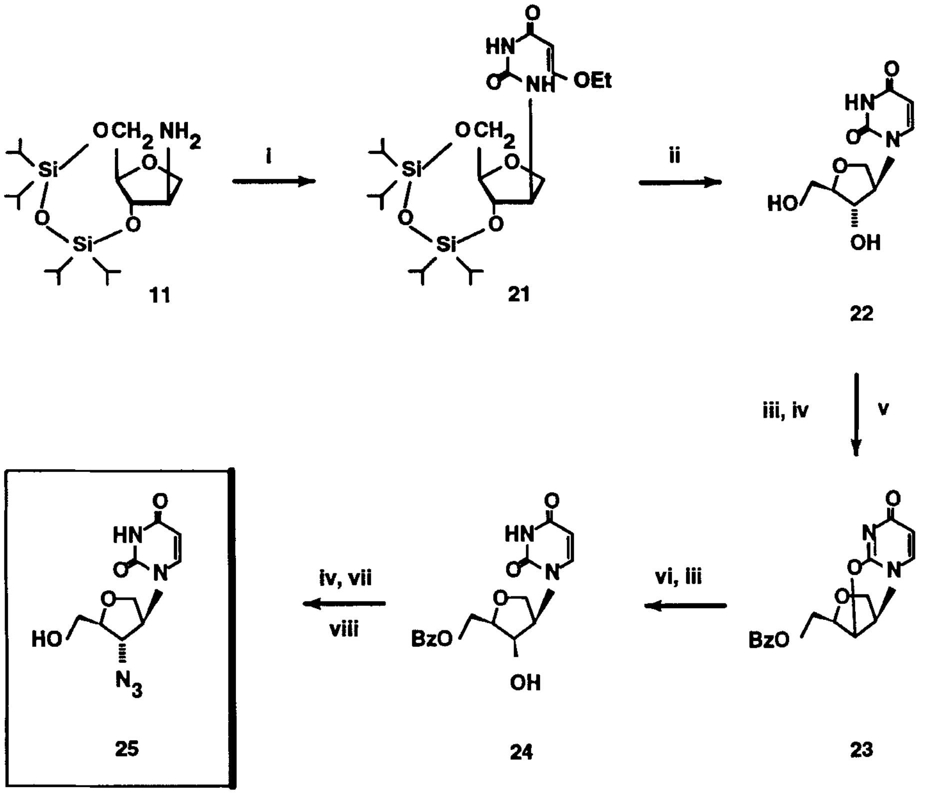
i. *t*-BuMe$_2$SiCl, DMAP, TEA, DMF; ii. MsCl, pyridine, 0 °C to room temperature; iii. DBU, THF, Δ; iv. 1N NaOH, EtOH; v. BzCl, pyridine, 0 °C to room temperature; vi. LiN$_3$, DMF, Δ; vii. NH$_3$, MeOH, 0 °C.

Scheme 3

under acid-catalyzed conditions[25] (dilute sulfuric acid in refluxing dioxane) to afford **13** in nearly quantitative yields.

Specific protection of the primary hydroxyl group of **13** proved difficult under a variety of conditions. We had reported previously[18] that reaction of **13** with a slight excess of *tert*-butyldimethylsilyl chloride, in the presence of triethylamine and DMAP in DMF,[26] was sluggish even at 55 °C, consistently giving yields of less than 50%. However, in the presence of 3 equivalents of the silylating agent and excess triethylamine, a 71% yield of **14a** was obtained (Scheme 3). Interestingly, only 11% of the *bis*-silylated derivative was isolated even after 30 hours at room temperature. A second protection strategy was tested with the more reactive chlorotriethylsilane under similar conditions. Although **14b** could be obtained in 50% yield, the lack of regioselectivity (even at ice-bath temperatures) and the inherent hydrolytic instability of this protecting group precluded further utilization. Transformation of the protected arabinitol (**14a**) into the new anhydro lyxitol analog **16** was readily accomplished by intramolecular cyclization of the mesylate **15** in the presence of DBU in refluxing THF (94% yield for 2 steps). The structure of the anhydro lyxitol isonucleoside (**16**) was confirmed by the dramatic shift in its UV spectrum (**13**, λ_{max} 270 nm; **16**, λ_{max} 256.5 nm) and the large downfield shift of the protons at C-2 and C-3 in **16** compared to **13** (see experimental).

Attempted ring opening of protected anhydro nucleoside (**16**) with azide ions under a variety of conditions (e.g. with HMPA or DMF in the presence of an acid catalyst[11,27]) was difficult (cf. references 28,29) and only low yields of the corresponding azido arabinitol (**1**), accompanied by significant decomposition products, were isolated after deprotection. Unlike the 6-membered ring anhydro nucleosides, the relatively strain free tricyclic nucleoside (**16**) containing a five-membered anhydro ring displays unexpectedly remarkable stability toward nucleophilic ring opening of this anhydro linkage. This stability exceeds that of "normal" five-membered ring anhydro nucleosides and is comparable to anhydro C-nucleosides which are also resistant to nucleophilic ring opening with azide ions.[30,31]



i. 3-ethoxyacryloyl isocyanate, toluene, DMF, 0 °C to room temperature; ii. dioxane, 2N H_2SO_4, Δ; iii. BzCl, pyridine, 0 °C to room temperature; iv. MsCl, pyridine, 0 °C to room temperature; v. DBU, THF, Δ; vi. 1N NaOH, EtOH; vii. LiN_3, DMF, Δ; viii. NH_3, MeOH, 0 °C.

Scheme 4

However, opening of the anhydro analog was possible by treatment of **16** with dilute sodium hydroxide in aqueous ethanol followed by neutralization to pH 7, which afforded the novel deprotected 1,4-anhydro-D-lyxitol derivative (**17**) in 95% yield. This conversion proceeded with retention of the stereochemistry at C-3 which was confirmed by high-field NMR data. Compound **17** was also partially formed (< 30%) during the attempted ring-opening of **16** with sodium azide in moist DMF in the presence of excess trifluoroacetic acid (reflux, 24 hours). Selective monobenzoylation of **17**, followed by mesylation gave the protected mesylate (**19**) which was smoothly converted to the protected azido derivative (**20**) upon treatment with lithium azide in anhydrous DMF (86%). Deprotection of **20** with methanolic ammonia followed by purification by reversed-phase HPLC (Waters Delta Pak C_{18}, 20% EtOH/ H_2O) afforded the novel AZT analog (**1**) (63%). The structure of **1** including its stereochemistry was established by IR, mass spectrometry, and high-field NMR data. The spectral data for **1** obtained in low yields by the nucleophilic ring opening of **16** with inversion (involving azide ions) was identical to the data obtained for compound **1** derived from the lyxo nucleoside (**17**).

These studies were extended to the synthesis of the novel AZU analog (**25**). The precursor, protected 2-amino-D-arabinitol (**11**) on treatment with 3-ethoxyacryloyl isocyanate[32] gave **21** in 92% yield (Scheme 4). The corresponding isouridine analog (**22**)[23] was obtained from acid-catalyzed ring-closure of the protected acryloylurea in 92% yield. Protection of the primary hydroxyl group as the mono-benzoate (71%), mesylation of the secondary hydroxyl group, followed by intramolecular cyclization of the intermediate mesylate in the presence of DBU afforded the lyxitol analog **23** (56%). Transformation of **23** to **25** was conducted as described for the conversion of **16** to **1** (25%, 5 steps). Further extension of these synthetic studies to other stereochemically defined regioisomeric analogs of AZT and AZU and evaluations of biological activities are still in progress.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover open stage melting point apparatus and are uncorrected. Mass spectra were obtained on a VG Trio 1 single quadrapole instrument at 70 eV. Infrared spectra were obtained using a Mattson Cygnus model 25 Fourier transform instrument. The ^1H and ^{13}C NMR were recorded on either a Bruker MSL 300, AC 300, or WM 360 in $CDCl_3$ or Me_2SO-d_6. Chemical shift values are reported in δ, parts per million, relative to the internal standard. Elemental analysis were carried out at the University of Iowa on a Perkin-Elmer 2400 Series II Elemental Analyzer.

UV spectra were recorded on a Varian Cary 3 or a Gilford Response spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Preparative layer chromatography plates were made from E. Merck PF_{254} silica gel. TLC plates were visualized by ultraviolet absorbance or charring for several minutes after exposure to either a 20% sulfuric acid / methanol solution or a 12% phosphomolybdic acid / ethanol solution.

1,4-Anhydro-D-ribitol (4). Method A. This compound was prepared from methyl ribofuranoside (**2**) by a modification of the procedure described by Bennek and Gray.[20] For the reductive cleavage, 4 equiv. of TMSOTf and triethylsilane (TES) were employed. The resulting oil, after hydrolysis and neutralization (Dowex OH^-), was purified by careful column chromatography (plug) with 10 - 15% MeOH / $CHCl_3$ as the eluent to obtain **4** (83%) as a white solid after pooling the appropriate fractions: mp 100-102 °C (isopropanol) [mp (lit.)[19] 101-102 °C (isopropanol)].

Method B. Hydrolysis of **5** (3.09 g, 7.12 mmol) was accomplished by refluxing in a mixture of H_2O, HCl, and acetic acid.[33] After workup, the crude oil (**6**, 3.13 g) was dissolved in dry acetonitrile (35 mL), under N_2, followed by the sequential addition of triethylsilane (3.34 g, 28.7 mmol) and $BF_3 \cdot OEt$ (2.12 g, 14.9 mmol). The reaction mixture was stirred for 2 h at room temperature then quenched with H_2O (35 mL) and diluted with CH_2Cl_2 (35 mL). After separation of the phases, the organic layer was successively washed with aq. satd. $NaHCO_3$ (35 mL) and H_2O (2 X 35 mL). The separated organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography with $CHCl_3$ followed by 1% MeOH / $CHCl_3$ to afford **7** (2.45 g, 6.06 mmol, 85%) as a light yellow oil. The spectral characteristics were in complete agreement with those reported previously.[21] Compound **7** was deprotected quantitatively by catalytic hydrogenation in ethanol to afford **4** as a clear oil which crystallized upon standing: mp 94-96 °C. Recrystallization from isopropanol gave mp 100.5-102 °C.

1,4-Anhydro-3,5-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-ribitol (8). A solution of **4** (1.08 g, 8.05 mmol) dissolved in dry pyridine (30 mL) was cooled to -15 °C. To this solution was slowly added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (3.04 g, 9.66 mmol) in pyridine (20 mL) over 5 h at that temperature. After being warmed to room temperature gradually, the mixture was stirred overnight. The reaction was quenched with isopropanol (3 mL), stirred 10 min, and concentrated to dryness. The residue was partitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). The aqueous layer was back-extracted with an additional 25 mL CH_2Cl_2. The combined organic layers were washed successively with aq. satd. $NaHCO_3$ (2 X 25 mL), water (2 X 25 mL), and brine (25 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography with 7:1 hexanes / EtOAc as the eluent to afford **8** (2.24g, 5.95 mmol, 74%) as a clear oil. An analytical sample was obtained from the intermediate fractions: $[\alpha]_D^{25}$ + 3.6° (*c* 0.91, MeOH); TLC R_f 0.45 (5:1 hexanes / EtOAc); ^{13}C NMR ($CDCl_3$, 75.48 MHz) δ 12.7 - 13.3 (*i*-Pr), 17.0-17.4 (*i*-Pr), 62.6, 70.9, 73.0, 73.6, 80.8; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (m, 28H), 2.86 (s, 1H), 3.77 (m, 2H), 3.88 (dd, 1H, *J* = 5.4, 12.1 Hz), 3.98 (dd, 1H, *J* = 3.4, 12.1 Hz), 4.06 (dd, 1H, *J* = 4.4, 10.0 Hz), 4.19 (m, 2H); MS (EI) *m/z* 333 (M^+ - *i*-Pr, 6.3), 235 (base). *Anal. Calcd* for $C_{17}H_{36}O_5Si_2$: C, 54.21; H, 9.65. Found: C, 54.06; H, 9.84.

1,4-Anhydro-2-O-methanesulfonyl-3,5-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-ribitol (9). Compound **8** (0.513 g, 1.36 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Triethylamine (0.75 mL, 5.36 mmol) and methanesulfonyl chloride (0.20 mL, 2.68 mmol) were added sequentially *via* syringe. Stirring was continued at this temperature for 3 h under N_2. After quenching with the addition of cold 5% aq. $NaHCO_3$ (10 mL), the mixture was extracted with CH_2Cl_2 (2 X 20 mL), dried (Na_2SO_4), filtered, and concentrated to dryness *in vacuo*. The resulting brown oil crystallized upon standing under vacuum to afford **9** (0.561 g, 1.29 mmol, 95%) which was used directly in the next reaction without purification: TLC R_f 0.28 (5:1 hexanes/ EtOAc); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ 12.7 - 13.4 (*i*-Pr), 16.8 - 17.5 (*i*-Pr), 39.0, 60.1, 70.9, 71.3, 79.6, 81.3; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.08 (m, 28H), 3.08 (s, 3H), 3.79 (dt, 1H, *J* = 2.4, 9.3 Hz), 3.92 (dd, 1H, *J* = 2.4, 12.0 Hz), 4.03 (d, 1H, *J* = 12.0 Hz), 4.24 (dd, 1H, *J* = 4.3, 11.0 Hz), 4.30 (dd, 1H, *J* = 4.5, 11.0 Hz), 5.19 (pseudo t, 1H, *J* = 4.3 Hz); MS (EI) *m/z* 316 (M^+ - *i*-Pr - OMs, base).

1,4-Anhydro-2-azido-2-deoxy-3,5-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-arabinitol (10). A mixture of the crude mesylate **9** from above (0.551 g, 1.27 mmol) and sodium azide (0.247 g, 3.80 mmol) in reagent grade DMF (10 mL) was heated to 100°C with stirring for 3.5 h. The reaction mixture was concentrated to dryness under reduced pressure and the semi-solid residue partitioned between EtOAc (10 mL) and 10% aq. $NaHCO_3$ (10 mL). The organic layer was washed with H_2O (2 X 10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography with 9:1 hexanes / EtOAc as the eluent. The appropriate fractions were pooled and concentrated *in vacuo* to afford **10** (0.429 g, 1.07 mmol, 84%) as a clear oil: $[\alpha]_D^{25}$ - 16.5° (*c* 1.30, MeOH); TLC R_f 0.66 ($CHCl_3$); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ 12.5 - 13.4 (*i*-Pr), 16.9 - 17.4 (*i*-Pr), 62.8, 67.6, 69.5, 78.4, 84.2; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.08 (m, 28H), 3.70 (m, 1H), 3.76 (dd, 1H, J = 4.4, 10.5 Hz), 3.82 (dd, 1H, J = 6.8, 10.5 Hz), 4.01 (m, 3H), 4.24 (m, 1H); FTIR (CCl_4) 2947, 2869, 2104 cm^{-1}; MS (EI) *m/z* 358 (M^+ - *i*-Pr, 9.9), 330 (M^+ - *i*-Pr - N_2, 2.6), 260 (base). *Anal. Calcd* for $C_{17}H_{35}N_3O_4Si_2$: C, 50.82; H, 8.80; N, 10.46. Found: C, 50.82; H, 8.91; N, 10.42.

1,4-Anhydro-2-amino-2-deoxy-3,5-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-arabinitol (11). A solution of **10** (0.372 g, 0.92 mmol) and 5% Pd/C (40 mg) in 95% ethanol was hydrogenated at 40 psi at room temperature for 3 h. The catalyst was filtered and the filtrate concentrated to dryness under reduced pressure to afford **11** (quantitative) as a clear oil which was used directly in the next reaction without purification: TLC R_f 0.33 ($CHCl_3$); MS (EI) *m/z* 332 (M^+ - *i*-Pr, 27.0).

3-Methoxy-2-methylacryloyl chloride. This compound was prepared by chlorination of sodium 3-methoxy-2-methylacrylate by the procedure of Shaw and Warrener[24] in a 74% yield: bp 65-68 °C (2.2 mm Hg) [lit.[24] 102 °C (35 mm Hg); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76 (s, 3H), 3.96 (s, 3H), 7.67 (s, 1H); FTIR (neat) 2947, 1780(s), 1733(s), 1635, 1251 cm^{-1}.

1,4-Anhydro-2-deoxy-2-[[[(3-methoxy-2-methyl-1-oxo-2-propenyl)amino]-carbonyl]amino]-3,5-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-arabinitol (12). To a solution of the acid chloride prepared above (0.370 g, 2.75 mmol) in anhydrous toluene (5 mL) was added silver cyanate (0.743 g, 4.96 mmol, dried *in vacuo* at 65 °C overnight with protection from light). The suspension was refluxed under a N_2 atmosphere with stirring for 30 min and cooled to room temperature. The isocyanate (FTIR: 2241, 1644 cm^{-1}) solution was added dropwise *via* cannula to a stirred solution of **11** (0.322 g, 0.85 mmol) in anhydrous DMF (5 mL) under a N_2 atmosphere at 0 ° C. The reaction mixture was then allowed to gradually warm to room temperature with stirring. After 16 h the volatiles were removed under reduced pressure, the residue evaporated with ethanol (3 mL), and concentrated to dryness. The filtrate was purified by preparative TLC with 4% MeOH / $CHCl_3$ as the developing solvent. The band at R_f 0.56 afforded **12** (0.380 g, 0.74 mmol, 86%) as a gum: ^{13}C NMR ($CDCl_3$, 75.48 MHz) δ 8.6, 12.3-17.4 (*i*-Pr), 57.4, 61.3, 63.3, 70.6, 78.4, 84.6, 107.7, 154.8, 158.2, 169.8; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (m, 28 H), 1.73 (s, 3H), 3.72 (m, 3H), 3.83 (s, 3H), 3.99 (m, 2H), 4.21 (pseudo t, 1H, *J* = 5.3 Hz), 4.40 (ddd, 1H, *J* = 5.2, 9.7, 10.0 Hz), 7.37 (s, 1H), 9.12 (d, 1H, *J* = 8.0 Hz), 9.26 (s, 1H); MS (EI) *m/z* 473 (M^+ - *i*-Pr, 23.6), 99 (base); UV (EtOH) λ_{max} 254 nm. *Anal. Calcd* for $C_{23}H_{44}N_2O_7Si_2$: C, 53.46; H, 8.58; N, 5.42. Found: C, 53.65; H, 8.53; N, 5.38.

1,4-Anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-arabinitol (13). A solution of **12** (0.340 g, 0.66 mmol), dioxane (5 mL), and sulfuric acid (2N, 10 mL) was refluxed with stirring for 3.5 h. After cooling to room temperature, the reaction mixture was neutralized with 2N NaOH to pH 7 and concentrated to dryness *in vacuo*. The white solid was extracted with boiling ethanol (3 X 30 mL), the extracts combined, concentrated, and purified by preparative TLC with 18% MeOH / $CHCl_3$ as the developing solvent. The band at R_f 0.52 afforded **13** (0.158 g, 0.65 mmol, 99%) as a hygroscopic, tacky glass: ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 1.76 (s, 3H), 3.52 (m, 2H), 3.65 (m, 1H), 3.82 (dd, 1H, *J* = 4.3, 9.9 Hz), 3.98 (dd, 1H, *J* = 7.4, 9.9 Hz), 4.11 (m, 1H), 4.80 (ddd, 1H), 4.91 (t, 1H, exchangeable), 5.60 (d, 1H, exchangeable), 7.54 (s, 1H), 11.22 (br s, 1H, exchangeable); UV (EtOH) λ_{max} 270 nm (ε 9400).[15]

1,4-Anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-5-O-(*tert*-butyldimethylsilyl)-D-arabinitol (14a). To a solution of **13** (0.117 g, 0.48 mmol), *tert*-butyldimethylsilyl chloride (0.080 g, 0.53 mmol) and DMAP (0.030 g, 0.24

mmol) in anhydrous DMF (3 mL) under a N_2 atmosphere was added triethylamine (0.22 mL, 1.58 mmol). The reaction became turbid within seconds and was stirred at room temperature under a N_2 atmosphere. Additional *tert*-butyldimethylsilyl chloride (0.080 g, 0.53 mmol) was added after 12 h and 24 h. After 30 h, the reaction was quenched by addition of Et_3N (0.33 mL, 2.40 mmol) and MeOH (1 mL) and stirred an additional 30 min. The reaction mixture was concentrated to dryness under reduced pressure and the residue partitioned between EtOAc (10 mL) and H_2O (5 mL). The organic layer was washed with H_2O (2 X 5 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by preparative TLC with 4:1 EtOAc / hexanes as the developing solvent. The band at R_f 0.63 afforded **14a** (0.126 g, 0.35 mmol, 71%) as a white solid: ^{13}C NMR ($CDCl_3$, 75.48 MHz) δ -5.4, 12.6, 18.5, 25.9, 62.1, 64.2, 69.7, 77.7, 86.4, 111.6, 137.1, 151.9, 164.2; ^1H NMR (Me_2SO-d_6, 300 MHz) δ 0.05 (m, 6H), 0.87 (m, 9H), 1.76 (s, 3H), 3.59 (m, 1H), 3.71 (dd, 1H, *J* = 4.8, 11.5 Hz), 3.83 (m, 2H), 4.00 (dd, 1H, *J* = 7.3, 10.0 Hz), 4.08 (m, 1H), 4.78 (dt, 1H, *J* = 4.8, 10.0 Hz), 5.62 (d, 1H, *J* = 4.0 Hz, exchangeable), 7.36 (s, 1H), 11.28 (br, s, 1H, exchangeable); UV (EtOH) λ_{max} 264.5 nm. *Anal. Calcd* for $C_{16}H_{28}N_2O_5Si$: C, 53.90; H, 7.92; N, 7.86. Found: C, 53.73; H, 7.93; N, 7.74.

1,4-Anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-5-O-(triethylsilyl)-D-arabinitol (14b). A mixture of **13** (0.162 g, 0.65 mmol), chlorotriethylsilane (0.11 mL, 0.66 mmol) and DMAP (0.012 g, 0.10 mmol) in anhydrous DMF (4 mL) was cooled to 0 °C under a N_2 atmosphere. The cooled solution was treated dropwise with triethylamine (0.10 mL, 0.72 mmol), and the reaction mixture gradually warmed to room temperature with stirring. After 10 h, the reaction was filtered, washed with DMF and the filtrate concentrated to dryness. The residue was purified by preparative TLC with 10% MeOH / $CHCl_3$ (2 immersions) as the developing solvent. The band at R_f 0.65 afforded **14b** (0.12 g, 0.33 mmol, 51%) as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.53 (m, 6H), 0.87 (m, 9H), 1.78 (s, 3H), 3.68 (m, 2H), 3.83 (dd, 1H, *J* = 3.7, 12.5 Hz), 3.93 (dd, 1H, *J* = 1.1, 11.0 Hz), 4.08 (dd, 1H, *J* = 6.1, 11.0 Hz), 4.19 (m, 1H), 4.86 (m, 1H), 5.06 (br s, 1H, exchangeable), 7.30 (s, 1H), 10.55 (br s, 1H, exchangeable).

2-Deoxy-1,4-O^2,3-dianhydro-2-[3,4-dihydro-4-oxo-5-methyl-1(2*H*)-pyrimidinyl]-5-O-(*tert*-butyldimethylsilyl)-D-lyxitol (16). A solution of **14a** (0.066 g, 0.18 mmol) in dry pyridine (2 mL) was stirred under a N_2 atmosphere and cooled to 0 °C. Methanesulfonyl chloride (0.05 mL, 0.56 mmol) was added dropwise and the mixture stirred for 3.5 h at 0 °C. The reaction was quenched by the addition of ice and partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **15** as a light yellow oil which was used directly in the next reaction after drying *in vacuo*. Data for **15**: ^{13}C NMR ($CDCl_3$, 75.48 MHz) δ -5.5, 12.8, 18.4, 25.8, 38.6, 60.7, 61.2, 70.0, 83.2, 85.0, 112.2, 136.4, 151.2, 163.5; ^1H NMR (Me_2SO-d_6, 300 MHz) δ 0.04 (m, 6H), 0.85 (m, 9H), 1.76 (s, 3H), 3.79 (dd, 1H, *J* = 4.3, 11.6 Hz), 3.87 (dd, 1H, *J* = 2.8, 11.6 Hz), 3.96 (m, 1H), 4.05 (dd, 1H, *J* = 6.8, 10.5 Hz), 4.18 (dd, 1H, *J* = 3.5, 10.5 Hz), 4.99 (m, 1H), 5.10 (dd, 1H, *J* = 3.1, 5.0 Hz), 7.36 (s, 1H), 11.42 (br s, 1H, exchangeable).

The crude mesylate **15** was taken up in dry THF and refluxed in the presence of DBU (0.03 mL, 0.22 mmol) under N_2 with stirring. After 3 h, the reaction mixture was concentrated to near dryness and purified by preparative TLC with CH_3CN as the developing solvent. The band at R_f 0.67 afforded **16** (0.059 g, 0.17 mmol, 94%) as a white amorphous solid: mp 223-226 °C; $[\alpha]_D^{25}$ - 143.5° (*c* 0.45, MeOH); ^{13}C NMR ($CDCl_3$, 75.48 MHz) δ -5.5, 13.9, 18.2, 25.7, 60.0, 63.4, 72.0, 82.7, 83.8, 118.7, 131.1, 160.3, 172.5; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.02 (m, 6H), 0.83 (m, 9H), 1.86 (d, 3H, *J* = 1.1 Hz), 3.73 (dd, 1H, *J* = 4.0, 11.2 Hz), 3.78 (m, 1.5H, part of dd), 3.84 (d, 0.5H, *J* = 5.8 Hz), 3.91 (dd, 1H, *J* = 5.8, 10.0 Hz), 4.14 (d, 1H, *J* = 11.2 Hz), 5.17 (dd, 1H, *J* = 4.0, 7.4 Hz), 5.38 (dd, 1H, *J* = 3.3, 7.4 Hz), 7.29 (d, 1H, *J* = 1.1 Hz); UV (EtOH) λ_{max} 265.5 nm. *Anal. Calcd* for $C_{16}H_{26}N_2O_4Si$: C, 56.77; H, 7.74; N, 8.28. Found: C, 56.66; H, 7.63; N, 8.16.

1,4-Anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-lyxitol (17). A mixture of **16** (0.06 g, 0.18 mmol), aq. NaOH (1N, 0.5 mL) and 50% aq. EtOH (5 mL) was stirred at room temperature overnight. The solution was neutralized with HOAc / EtOH (1:1, v/v) to pH 7 and concentrated *in vacuo*. The residue was purified by preparative TLC with 18% MeOH / $CHCl_3$ as the developing solvent to afford **17** (0.043 g, 0.18 mmol, 95%) as a white semi-crystalline solid: mp 218-219 °C; $[\alpha]_D^{25}$ + 97.8 (*c* 0.18, MeOH); ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 1.76 (s, 3H), 3.52 (m, 1H), 3.62 (m, 1H), 3.77 (m, 1H), 3.85 (dd, 1H, *J* = 1.0, 8.5 Hz), 3.96 (dd, 1H, *J* = 6.8, 9.0 Hz), 4.20 (m, 1H: sharpens to dd upon D_2O exchange, *J* = 4.0, 5.4 Hz), 4.59 (t, 1H, exchangeable), 5.03 (ddd, 1H), 5.27 (d, 1H, exchangeable), 7.37 (s, 1H), 11.22 (br s, 1H, exchangeable); UV (MeOH) λ_{max} 270 (ε 10 000), 208 nm (8680). *Anal. Calcd* for $C_{10}H_{14}N_2O_5 \cdot 1/2H_2O$: C, 47.80; H, 6.02; N, 11.15. Found: C, 48.09; H, 5.98; N, 11.19.

1,4-Anhydro-5-O-benzoyl-2-deoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-lyxitol (18). A mixture of **17** (0.063 g, 0.26 mmol) in dry pyridine (5 mL) at 0 °C was added benzoyl chloride (0.43 mL, 0.31 mmol) by dropwise addition. The reaction proceeded at 0 °C for 2 h then gradually warmed to room temperature. After 12 h, the reaction was quenched with MeOH (1 mL), stirred 10 min. and concentrated *in vacuo*. The residue was coevaporated with toluene and purified directly by preparative TLC with 5:1 EtOAc / hexanes as the developing solvent. The band at R_f 0.55 afforded **18** (0.072 g, 0.21 mmol, 80%) as a white foam under vacuum: ^{13}C NMR ($CDCl_3$, 75.48 MHz) δ 12.2, 57.4, 63.3, 68.9, 70.7, 80.7, 109.4, 128.3-133.3 (aromatics), 140.1, 152.,1, 164.9, 166.7; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.77 (s, 3H), 4.03 (m, 2H), 4.19 (m, 1H), 4.56 (dd, 1H, *J* = 7.6, 12.2 Hz), 4.78 (m, 2H), 5.36 (m, 1H), 5.45 (br s, 1H), 7.35 - 8.08 (m, 6H, aromatic and pyrimidine H-6), 10.81 (br s, 1H). *Anal. Calcd* for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.23; N, 8.09. Found: C, 58.76; H, 5.21; N, 7.73.

1,4-Anhydro-3-azido-2,3-dideoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-arabinitol (1). Compound **18** was mesylated under similar conditions to that described for the synthesis of **15**. Purification by preparative TLC with 9% MeOH / $CHCl_3$ as the developing solvent gave R_f 0.50 to afford **19** as an off-white solid (0.041 g, 0.10 mmol, 80%). The mesylate was dissolved in dry DMF (2 mL) and heated to 100 °C in the presence of LiN_3 (0.02 g, 0.5 mmol) for 8 h. Workup, similar to that described for **10**, afforded crude **20**. The protected azide analog was dissolved in MeOH (5 mL), chilled to 0°C, and saturated with gaseous NH_3. The reaction proceeded overnight at room temperature and was concentrated to dryness. The residue was purified by preparative TLC with 13:1 EtOAc / hexanes as the developing solvent to afford a clear glass. Purification by reversed phase HPLC (Waters C_{18} Delta Pak, 80:20 H_2O / EtOH) and lyophilization of the appropriate fractions afforded **1** as a white powder (12.3 mg, 0.046 mmol, 40% for three steps): mp 135-138 °C (lyophilized powder); $[\alpha]_D$ + 30 (*c* 0.28, MeOH); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 1.78 (s, 3H), 3.60 (m, 3H), 3.95 (dd, 1H, J = 7.0, 10.5 Hz), 4.05 (dd, 1H, J = 3.7, 10.5 Hz), 4.24 (dd, 1H, J = 4.2, 7.2 Hz), 4.92 (ddd, 1H), 5.15 (t, 1H, exchangeable), 7.47 (s, 1H), 11.36 (br s, 1H, exchangeable); UV (MeOH) λ 269 nm (ε 9400); FTIR (KBr) 2108 cm^{-1}; MS (EI) *m/z* 267 (M^+, 1.7), 126 (B^+ + H, 55.3), 66 (base). *Anal. Calcd* for $C_{10}H_{13}N_5O_4$: C, 44.93; H, 4.91; N, 26.21. Found: C, 44.90; H, 4.90; N, 26.10.

3-Ethoxyacryloyl chloride. This compound was prepared by chlorination of sodium 3-ethoxyacrylate by the procedure of Shaw and Warrener[32] in a 59% yield: bp 75°C (10.0 mm) [lit.[32] 104°C (35 mm); FTIR (neat) 1749, 1616 cm^{-1}.

1,4-Anhydro-2-deoxy-2-[[[(3-methoxy-1-oxo-2-propenyl)amino]carbonyl]-amino]-3,5-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-arabinitol (21) was prepared as described for **12** in a 92% yield to produce a clear viscous oil: ^1H NMR ($CDCl_3$) δ 1.0 (m, 28H), 1.34 (t, 3H, J = 7.1 Hz), 3.60-4.48 (m, 9H), 5.29 (d, 1H, J = 12.2 Hz), 7.61 (d, 1H, J = 12.2 Hz), 8.92 (d, 1H, J = 7.8 Hz), 9.23 (br, 1H); UV (EtOH) λ_{max} 246 nm. *Anal. Calcd* for $C_{23}H_{44}N_2O_7Si_2$: C, 53.46; H, 8.58; N, 5.42. Found: C, 53.31; H, 8.55; N, 5.42.

1,4-Anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-arabinitol (22) was prepared as described for **13** in a 91% yield: R_f 0.35 (20% MeOH / $CHCl_3$). The spectral characteristics are in complete agreement with those reported previously.[23] UV (EtOH) λ_{max} 266 nm.

5-O-Benzoyl-2-deoxy-1,4-O^2,3-dianhydro-2-[3,4-dihydro-4-oxo-1(2*H*)-pyrimidinyl]-D-lyxitol (23) was prepared in a 36% yield from **22** as described for the conversion of **13** to **16**: R_f 0.18 (10% MeOH / $CHCl_3$); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 3.78 (dd, 1H, *J* = 3.9, 7.3 Hz), 4.20 (m, 2H), 4.42 (dd, 1H, *J* = 4.2, 7.2 Hz), 4.68 (dd, 1H, *J* = 4.1, 7.7 Hz), 5.16 (dd, 1H, *J* = 3.4, 4.3 Hz), 5.62 (dd, 1H, *J* = 3.5, 3.8 Hz), 5.89 (d, 1H, *J* = 7.39 Hz), 7.54 (m, 2H), 7.68 (m, 1H), 7.86 (d, 1H, *J* = 7.44 Hz), 7.97 (m, 2H); UV (EtOH) λ_{max} 254, 224 nm. *Anal. Calcd* for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.13; H, 4.54; N, 8.86.

1,4-Anhydro-5-O-benzoyl-2-deoxy-2-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-lyxitol (24) was prepared as described for **18** in a 71% yield over the last 2 steps: R_f 0.57 (10% MeOH / $CHCl_3$); mp 223-225 °C ^1H NMR (Me_2SO-d_6, 300 MHz) δ 3.92 (t, 1H, *J* = 9.1 Hz), 4.02 (dd, 1H, *J* = 3.1, 6.4 Hz), 4.18 (m, 1H), 4.38 (m, 2H), 4.50 (dd, 1H, *J* = 3.9, 8.0 Hz), 5.11 (dd, 1H, *J* = 6.2, 7.7 Hz), 5.53 (d, 1H, *J* = 8.0 Hz), 5.64 (d, 1H, *J* = 5.4 Hz), 7.52 (d, 1H, *J* = 8.2 Hz), 7.54 (t, 2H, *J* = 7.7 Hz), 7.67 (t, 1H, *J* = 7.2 Hz), 7.98 (d, 2H, *J* = 7.5 Hz), 11.25 (s, 1H); UV (EtOH) λ_{max} 264 nm. *Anal. Calcd* for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.69; H, 4.76; N, 8.44.

1,4-Anhydro-3-azido-2,3-dideoxy-2-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-arabinitol (25) was prepared as described for **1** in a 33% yield from **24**: mp 94-96 °C (lyophilized powder); $[\alpha]_D^{25}$ + 65.3° (*c* 0.46, MeOH); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 3.58 (m, 3H), 3.95 (dd, 1H, *J* = 3.9, 6.8 Hz), 4.08 (dd, 1H, *J* = 3.3, 7.4 Hz), 4.24 (dd, 1H, *J* = 2.2, 3.7 Hz), 4.90 (m, 1H), 5.02 (t, 1H, *J* = 5.0 Hz), 5.62 (d, 1H, *J* = 8.0 Hz), 7.58 (d, 1H, *J* = 8.0 Hz), 11.37 (br s, 1H); UV (EtOH) λ_{max} 266 nm (ε 9900); FTIR (CCl_4) 2107 cm^{-1}. *Anal. Calcd* for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.66. Found: C, 42.66; H, 4.37; N, 27.53.

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