Stereoselective Synthesis of 3-Azido-2,3-dideoxy-D-ribose Derivatives and its Utilization for the Synthesis of Anti-HIV Nucleosides [1]

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Dedicated to the memory of Dr. Roland K. Robins

Detail account of the synthesis of 3'-azido nucleosides utilizing 3-azido-2,3-dideoxy-D-ribose derivative **7** as the key intermediate was described. The key intermediate **7** was synthesized from D-mannitol in 8 steps in a preparative scale. The Michael reaction of the azide group with α,β-unsaturated-γ-butyrolactone **4** was affected by the steric bulkiness of the substituent at the 5-O position. A bulky *t*-butyldiphenylsilyl substitution at 5-O gave almost exclusively the α-azido adduct **5b**, while unsubstitution at 5-O produced 1:1 mixture of α-and β-adducts. The ratio of α to β anomers in the condensation between azido acetate **7a** and pyrimidine bases for the preparation of AZT and AZDU was greatly influenced by the solvent and the Lewis acid catalyst used. In the synthesis of **12** (AZDU, CS-87), the combination of dichloroethane and trimethylsilyl triflate gave an optimal result, while in the case of **14** (AZT), various conditions gave similar ratio of α,β anomers. The azido intermediate **7b** was also utilized for the synthesis of several 3'-azido purine-like nucleosides **16-27**. The glycosylation was also affected by the Lewis acid catalyst. Boron trifluoride etherate gave the desired N_1-glycosylated compounds in which the α-anomer was major, but other catalysts such as trimethylsilyl triflate or stannic chloride produced N_2-glycosylated compounds as the major products. The newly synthesized purine-like compounds have been tested against HIV, however, none of them showed any significant activity.

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The discovery of 3'-azido-3'-deoxythymidine (AZT) [2] (**1**) as a potent anti-HIV agent *in vitro* and subsequent development as a clinically useful antiviral agent for patients with AIDS and AIDS related complexes [3] led to the synthesis of a number of 3'-azido substituted nucleosides, including 3'-azido-2',3'-dideoxyuridine [4,5] (AZDU or CS-87) (**2**) (Figure 1).

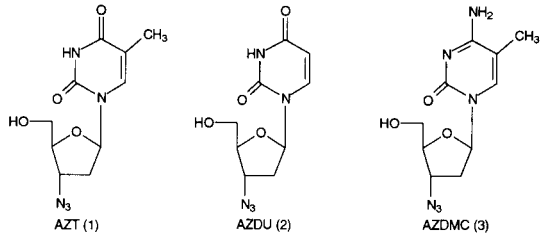


Figure 1. Structures of AZT, AZDU, and AZDMC

AZDU has been undergoing phase I clinical trials as an antiviral agent for patients with AIDS and AIDS related complexes [5]. Although its role as a clinically useful anti-HIV agent remains to be determined, the main advantage of AZDU seems to be its low bone marrow toxicity. It is phosphorylated to its triphosphate and inhibits HIV reverse transcriptase *in vitro* in a similar fashion as AZT-triphosphate [4]. Another interesting nucleoside with 3'-azido group is 3'-azido-2',3'-dideoxy-5-methylcytidine (AZDMC or CS-92) [6] (**3**). AZDMC exhibits a potent anti-HIV activity (EC_{50} = 0.09 μM) in peripheral blood mononuclear cells and it shows low bone marrow suppression. Its triphosphate also inhibits the HIV reverse transcriptase *in vitro* [6]. Interestingly, AZDMC does not seem to undergo deamination in mice [6]. However, a significant amount of AZDMC undergoes deamination to AZT in monkeys [6]. Thus, AZDMC may serve as a prodrug of AZT and potentially decrease the toxicity of AZT in humans. Ultimately clinical trials may prove or disprove this hypothesis.

In addition to the above mentioned nucleosides, a number of 3'-azido substituted pyrimidine and purine nucleosides have been synthesized as potential anti-HIV agents [7]. Two distinctive methods are available for the synthesis of 3'-azido nucleosides [8-13]. Although the methods utilizing a preformed nucleoside such as thymidine is useful and the starting materials are readily available in some cases [8-11], there is no flexibility to the synthesize various derivatives of a parent nucleoside for the study of structure-activity relationships. Thus, it was desirable to develop an intermediate which could be used for the preparation of a variety of pyrimidine and purine nucleosides. Herein we wish to report the detailed accounts of the synthesis of 3'-azido nucleosides utilizing 3-azido-2,3-dideoxy-D-ribose derivative **7** as the key intermediate, since a number of inquiries have been received for the experimental details for the preparation of **7** [1].

Although the preparation of the 3-azido-2,3-dideoxyribose derivatives has been previously reported by Fleet *et*

al [12] and Dyatkina and Azhayev [13] from D-xylose, it required lengthy steps to reach the intermediate **7**. Thus, we were interested in developing a more efficient and stereoselective method for the 3-azido intermediate **7**. For this purpose α,β-unsaturated γ-butyrolactone **4** seemed to be an ideal intermediate for the preparation of the azido intermediate **5**. The γ-butyrolactone **4** could be efficiently prepared from D-mannitol in 5 steps in a preparative scale [14]. Glyceraldehyde **1**, readily prepared by the oxidative cleavage of 1,2:5,6-*O*-di-isopropylidene-D-mannitol with lead tetraacetate in ethyl acetate, was treated with a stabilized Wittig reagent in methanol at 0° to obtain mainly the *Z*-isomer **2a** (Z/E = 9/1). Cyclization to γ-lactone **3** [14-16] followed by the protection of primary hydroxyl group with *t*-butyldiphenylsilyl or *t*-butyldimethylsilyl group gave **4** in good yield. The addition of the azide group to the α,β-unsaturated butyrolactones **4** was investigated to maximize the yield as well as the desired stereoselectivity to obtain the azidolactone **5**. From this study, it was found that a bulky group such as *t*-butyldiphenylsilyl at 5-O promoted the addition from the α-face, while unsubstituted compound at 5-O produced **5** as a 1:1 mixture of α- and β-azido compound, which was determined by ^{1}H nmr. *t*-Butyldimethylsilyl substituent gave an α,β-mixture in favor of the desired α-isomer **5a** (98:2 ratio determined by ^{1}H nmr). Thus, it was apparent that bulky substitution at 5-O influences the 1,4-addition of the azide group, to prevent the addition from the β-face. No β-azido addition was observed with *t*-butyldiphenylsilyl substitutent. The azidolactone **5** was reduced to lactol **6** with DIBAL in methylene chloride in 77% yield, which was acetylated to the desired intermediate **7** for condensation with heterocyclic bases.

In order to find the optimal conditions, various methods of glycosylation were tried for the preparation of AZT and AZDU (Table 1). Interestingly, in the synthesis of AZDU condensation of **7a** with silylated uracil in acetonitrile in the presence of stannic chloride gave a 7:3 α/β mixture, while reaction with trimethylsilyl triflate in acetonitrile produced a 1:1 mixture of α/β-isomers. Condensation in 1,2-dichloroethane with trimethylsilyl triflate gave a 1:2 mixture of α/β-isomers. However, the condensation of **7a** with silylated thymine only produced a 1:1 mixture of α/β-anomers under all of the above conditions. The free nucleoside, AZDU (**12**) was obtained from the desilylation of the α,β-mixture **8** and **9** obtained from the above glycosylation reaction, in which after silica gel column chromatographic separation, the β-isomer **12** was isolated by crystallization from isopropanol. The α-isomer **13** was obtained by desilylation of pure α-isomer **9** obtained by crystallization from ether (Method A). AZT **14** and its α-isomer **15** were obtained by desilylation of an α,β-mixture **10** and **11** followed by silica gel column chromatographic separation.

The azido intermediate **7b** was also utilized for the synthesis of several purine-like nucleosides with 3′-azido substituent as potential anti-HIV agents (Scheme 3). Condensation of the intermediate **7b** with silylated 4-aminopyrazolo[3,4-*d*]pyrimidine in the presence of borontrifluoride etherate in dry 1,4-dioxane gave four products as inseparable

Scheme 1

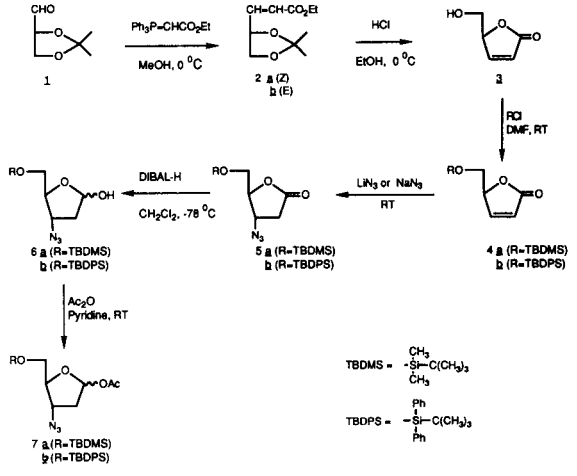
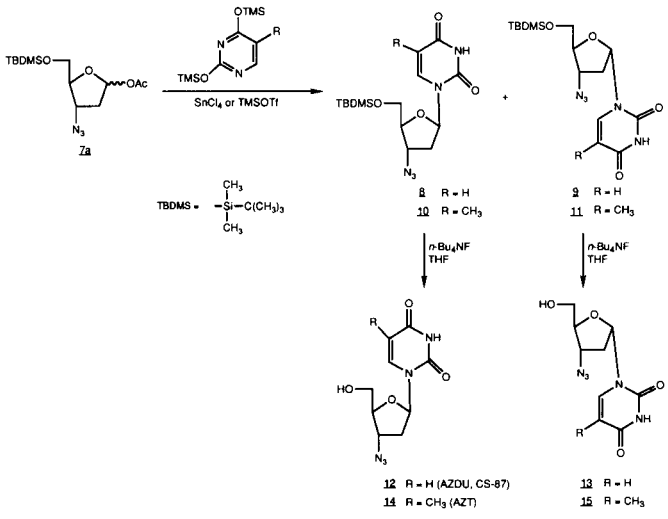


Table 1: Condensation reaction conditions of **7a** and pyrimidines

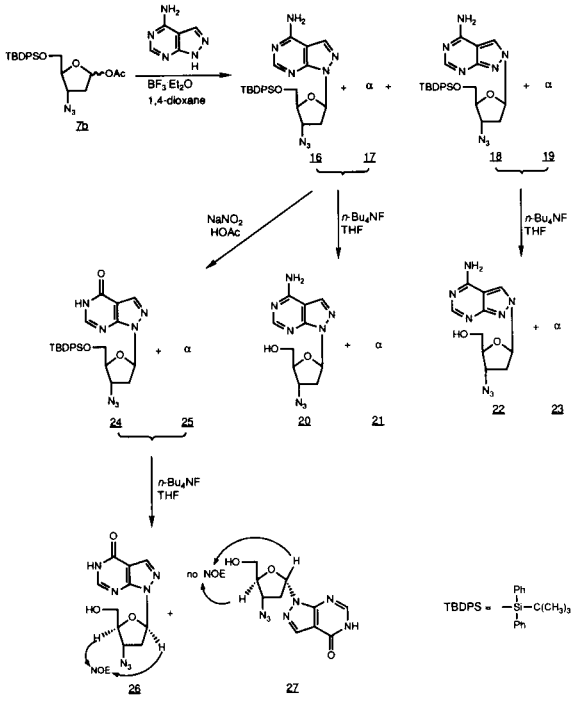
Solvent and Catalyst	R=H(AZDU) α/β ratio[a]	R=CH3(AZT) α/β ratio[a]
Stannic Chloride Acetonitrile	7:3	1:1
Trimethylsilyl Triflate Acetonitrile	1:1	1:1
Trimethylsilyl Triflate 1,2 Dichloroethane	1:2	1:1

[a] Determined by ^{1}H nmr

Scheme 2



Scheme 3



ble α,β-mixtures of N_1-glycosylated nucleosides **16** and **17** (65%) and N_2-substituted nucleosides **18** and **19** (13%). Condensation with other catalysts such as trimethylsilyl triflate or stannic chloride produced the N_2-substituted nucleosides as major products with only trace amounts of N_1-substituted nucleosides. However, in both cases, the α-anomer was produced as the major product during condensation. The corresponding free nucleosides **20** and **21** were obtained from the desilylation of **16** and **17** followed by silica gel column chromatographic separation. In the case of N_2-substituted nucleosides, **18** and **19** were separated by silica gel column chromatography in a small scale for analytical sample. However, it was more convenient to desilylate the mixture and then separate the individual isomers **22** and **23**. The inosine derivatives **26** and **27** were prepared from the deamination of the α,β-mixture **16** and **17** with sodium nitrite and acetic acid followed by desilylation and silica gel column separation. The structural assignments of regioisomers **20-27** were confirmed by their ultraviolet spectra, in which the absorption maxima of N_1- and N_2-regioisomers were 275 nm and 292 nm, respectively, which were identical with those of authentic N_1- and N_2-glycosides, respectively [17,18]. The anomeric configurations of **26** and **27** were confirmed by ^{1}H nmr (300 MHz) and NOE experiment. NOE experiments showed that upon irradition of 4′-H in **26** and **27**, enhancement of 1′-H peak in **26**, was observed, suggesting *cis* orientation, while no enhancement was observed in **27**, indicating the *trans* configuration.

The newly synthesized compounds **20-27** were tested against the human immunodeficiency virus (HIV). However, no significant anti-HIV activity was detected.

EXPERIMENTAL

Melting points were determined on a Mel-temp II, Laboratory device and are uncorrected. The ^{1}H and ^{13}C nmr spectra were recorded on a JEOL FX 90Q Fourier transform spectrometer or a Bruker AM 300 nmr spectrometer with tetramethylsilane as internal standard: chemical shifts (δ) are reported in parts per million and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). The uv spectra were obtained on a Beckman DU-7 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 Digital Polarimeter. Analyses (tlc) were performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

(*Z*)- and (*E*)- Ethyl (*S*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)acrylates **2a** and **2b**.

Method A.

(Carbethoxymethylene)triphenylphosphorane (885.64 g, 2.538 moles) was added to an ice-cold solution of 2,3-*O*-isopropylidene-D-glyceraldehyde [14] **1** (110.0 g, 0.846 mole) in anhydrous methanol (3500 ml) and the mixture was stirred for 1 hour. To the reaction mixture, ethyl ether (3000 ml) was added and cooled in an ice-water bath. The precipitate (triphenylphosphine oxide) was filtered off and the filtrate was concentrated *in vacuo* to a syrup. The residual triphenylphosphine oxide was separated by column using hexanes-ethyl acetate (4:1) as the eluent. The *Z*- and *E*-isomers (8:1) were separated by vacuum flash chromatography on a silica gel column (19 x 8.5 cm) using hexanes-ethyl acetate (8:1) as the eluent. The less polar *Z*-isomer **2a** was obtained as a colorless liquid (90.26 g, 53%), $[\alpha]_D^{25}$ = 117.48 (c 2.13, chloroform) [lit [14] 104.3 (c 18.9, chloroform, *Z*/*E* = 89:11)]; ir (neat): 1720 (ester); ^{1}H

nmr (deuteriochloroform): δ 1.29 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.61 (dd, 1H, J = 6.8, 8.1 Hz, H-5), 4.25 (m, 3H, CH_2CH_3 and H-5), 5.50 (dq, 1H, J = 1.5, 6.6 Hz, H-4), 5.83 (dd, 1H, J = 1.5, 11.4 Hz, H-2), 6.36 (dd, 1H, J = 6.9, 11.4 Hz, H-3).

The more polar *E*-isomer **2b** was obtained as a colorless liquid (12.97 g, 8%), ir (neat): 1720 (ester); ^{1}H nmr (deuteriochloroform): δ 1.29 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.41 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.67 (dd, 1H, J = 7.0, 8.1 Hz, H_a-5), 4.21 (m, 3H, CH_2CH_3 and H_b-5), 4.67 (m, 1H, H-4), 6.08 (dd, 1H, J = 1.3, 15.6 Hz, H-2), 6.89 (dd, 1H, J = 5.5, 15.6 Hz, H-3).

Method B.

A mixture of **1** (65.0 g, 0.5 mole) and (carbethoxymethylene)triphenylphosphorane (191.65 g, 0.55 mole) in dry acetonitrile (1000 ml) was refluxed for 2 hours. After removal of acetonitrile *in vacuo*, the residue was triturated with anhydrous ethyl ether (500 ml). The precipitated solid was filtered off and the filtrate was concentrated *in vacuo* and column chromatography on silica gel using hexanes-ethyl acetate (4:1) as the eluent yielded the (*E*/*Z*)-mixture (7:1) of **2**, as a colorless liquid (62.5 g, 63%). The isomeric mixture can be separated by vacuum flash chromatography on a silica gel column (12 x 7 cm) using hexanes-ethyl acetate (8:1) as the eluent. The *Z*-isomer (8.95 g, 9%) obtained was found to be identical in physical and spectral characteristics with the product **2a** from Method A.

The *E*-isomer **2b** was separated as a more polar fraction (53.55 g, 54%), which was identical in physical and spectral characteristics with the *E*-isomer **2b** obtained from Method A.

5(*S*)-Hydroxymethyl-5*H*-furan-2-one (**3**).

Concentrated hydrochloric acid (80 ml) was added to a solution of **2a** (60.0 g, 0.3 mole) in anhydrous ethanol (300 ml) and the reaction mixture was stirred at room temperature for 2 hours. Solvent was removed *in vacuo* and the residue was co-evaporated with benzene (100 ml) several times. The resulting pale yellow syrup was filtered through a silica gel column using methylene chloride-ethyl ether (4:1) as the eluent. Evaporation of the appropriate fractions yielded a colorless syrup which on trituration with hexanes gave a colorless solid. Recrystallization from ethyl ether yielded **3** (27.7 g, 81%), mp 38-39° [lit [14] 42°]; $[\alpha]_D^{25}$ = −145.3 (c 1, water) [lit [14] −143 (c 1.135, water)]; ir (potassium bromide): 3700-3150 (hydroxyl), 1750 (lactone) and 1600 cm^{-1} (C=C); ^{1}H nmr (deuteriochloroform): δ 3.51-4.10 (m, 3H, CH_2 and OH), 5.16 (m, 1H, H-5), 6.19 (dd, 1H, J = 2.0, 5.71 Hz, H-3), 7.53 (dd, 1H, J = 1.5, 5.7 Hz, H-4).

5(*S*)-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5*H*-furan-2-one (**4a**).

t-Butyldimethylsilyl chloride (29 g, 0.192 mole) was added to a solution of the lactone **3** (20 g, 0.175 mole) and imidazole (23.8 g, 0.345 mole) in DMF (200 ml) and the reaction mixture was stirred for 1 hour. The solvent was removed *in vacuo* and the residue was dissolved in chloroform, washed with water, dried (magnesium sulfate), filtered, and concentrated. The resulting syrup was purified by a silica gel vacuum flash column using 5% ethyl acetate-benzene as the eluent to give **4a** (38 g, 95%) as a syrup which was solidified on standing, mp 30-32° [lit [14] 31-32°]; $[\alpha]_D^{25}$ = −140.3 (c 1.20, chloroform) [lit [14] −136.2 (c 1.13, chloroform)]; ir (potassium bromide): 1770 cm^{-1} (lactone); ^{1}H nmr (deuteriochloroform): δ 0.063 (s, 6H, 2 x methyl), 0.875 (s, 9H, *t*-butyl), 3.87 (t, 2H, J = 5.0 Hz, CH_2), 4.90-5.15 (m, 1H, H-4); 6.15 (dd, 1H, J = 2.0, 6.0 Hz, H-2), 7.49 (dd, 1H, J = 2.0, 6.0 Hz, H-3).

5(*S*)-[(*tert*-Butyldiphenylsilyl)oxymethyl]-5*H*-furan-2-one (**4b**).

t-Butyldiphenylsilyl chloride (32.8 g, 0.119 mole) was added to an ice-cold solution of lactone **3** (11.4 g, 0.10 mole) and imidazole (13.3 g, 0.196 mole) in dry dimethylformamide (300 ml) and the mixture was stirred at room temperature for 1.5 hours. Solvents were removed *in vacuo* and residue was dissolved in chloroform (500 ml), washed with water (100 ml x 2), dried (magnesium sulfate), and evaporated to yield a yellowish syrup. The syrup was purified by vacuum flash chromatography on a silica gel column using hexanes-ethyl acetate (8:1) as the eluent. Compound **4b** was obtained as a crystalline solid (30.5 g, 87%), mp 86-88° [lit [19] 79-80°]; $[\alpha]_D^{25}$ = −73.12 (c 1.93, chloroform) [lit [19] −81.8 (c 10.5, chloroform)]; ir (potassium bromide): 1780 cm^{-1} (lactone); ^{1}H nmr (deuteriochloroform): δ 1.04 (s, 9H, *t*-butyl), 3.89 (d, 2H, J = 4.6 Hz, CH_2), 5.5 (m, 1H, H-4), 6.17 (dd, 1H, J = 1.8, 5.7 Hz, H-2), 7.31-7.70 (m, 11H, H-3 and phenyl protons).

4(*R*)-Azido-5(*S*)-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3,4-dihydro-5*H*-furan-2-one (**5a**).

A solution of lithium azide (1.23 g, 25 mmoles) in water (1 ml) was added to a solution of protected lactone **4a** (2.28 g, 10 mmoles) in a mixture of glacial acetic acid (10 ml) and tetrahydrofuran (2.5 ml) and the reaction mixture was stirred at room temperature for 72 hours and from time to time tlc (hexanes-ethyl acetate, 4:1) was performed to monitor the progress of the reaction. Additional quantities of lithium azide (3.69 g) in water were added in order to complete the reaction. Analysis (tlc) indicated the formation of azidolactone **5a** as the sole product of the reaction at the end of 36 hours along with the starting material **4a**. However, as the reaction time increased, the formation of a new product with low R_f was observed, probably desilylated product. After neutralization with sodium bicarbonate, the reaction mixture was extracted with ethyl ether (150 ml x 4). Ethereal extracts were combined, dried (magnesium sulfate) and evaporated to yield a pale yellow syrup which was purified by vacuum flash silica gel chromatography (ethyl acetate-hexanes, 1:8). Azido lactone **5a** (1.4 g, 52%) was obtained as a colorless crystalline compound, mp 35-36°; ir (neat): 2110 cm^{-1} (azide) and 1790 cm^{-1} (lactone); ^{1}H nmr (deuteriochloroform): δ 0.08 (s, 6H, methyl), 0.89 (s, 9H, *t*-butyl), 2.50 (dd, 1H, J = 18.0, 3.3 Hz, H-3), 2.97 (dd, 1H, J = 18.0, 7.3 Hz, H-3), 3.84 (m, 2H, CH_2), 4.40 (m, 2H, H-4 and H-5).

Anal. Calcd. for $C_{11}H_{21}N_3O_3Si$: C, 48.68; H, 7.80; N, 15.49. Found: C, 48.58; H, 7.82; N, 15.45.

4(*R*)-Azido-5(*S*)-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4-dihydro-5*H*-furan-2-one (**5b**).

Sodium azide (20.0 g, 0.31 mole) was added to a solution of lactone **4b** (10 g, 28.41 mmoles) in glacial acetic acid (50 ml), distilled water (10 ml), and tetrahydrofuran (15 ml) and the reaction mixture was stirred at room temperature for 80 hours. Analysis (tlc) (hexanes-ethyl acetate, 2:1) of the reaction mixture was performed at regular intervals (6 hours) and additional sodium azide was added twice (7.0 g each) after stirring for 24 hours and 48 hours, respectively. After removal of large part of solvents under vacuum, the residue was partitioned between methylene chloride (150 ml) and water (150 ml). The aqueous layer was extracted with methylene chloride (150 ml x 3). The combined organic layer was successively washed with water (100 ml), saturated sodium bicarbonate solution, water and dried (magnesium sulfate). The solvent was evaporated to yield colorless syrup, which was purified

by vacuum flash chromatography on a silica gel column using hexanes-ethyl acetate (8:1) as the eluent. The azidolactone **5b** was isolated as colorless crystals after the evaporation of appropriate fractions (8.0 g, 71%), mp 72-74°; $[\alpha]_D^{25}$ = 18.95 (c 1.53, chloroform); ir (potassium bromide): 2100 cm^{-1} (azide), 1780 cm^{-1} (lactone); ^1H nmr (deuteriochloroform): δ 1.06 (s, 9H, *t*-butyl), 2.54 (dd, 1H, J = 3.3, 18.0 Hz, H_a-3), 3.01 (dd, 1H, J = 7.3, 18.0 Hz, H_b-3), 3.83 (m, 2H, CH_2), 4.30-4.45 (m, 2H, H-4 and H-5), 7.30-7.71 (m, 10H, phenyl protons).

Anal. Calcd. for $C_{21}H_{25}O_3N_3Si$: C, 63.77; H, 6.37; N, 10.62. Found: C, 63.60; H, 6.38; N, 10.53.

Later fractions of the eluent yielded unreacted starting material **4b** (1.0 g).

3-Azido-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α,β-D-*erythro*-pentofuranose (**6a**).

DIBAL-H (diisobutylaluminum hydride) (1 *M* in hexanes, 22.0 ml, 22.0 mmoles) was added dropwise to a well stirred solution of silylated azidolactone **5a** (4.0 g, 14.74 mmoles) in methylene chloride (65 ml) under nitrogen at −78°. The colorless solution was stirred at −78° for 2 hours and then quenched with methanol (2.6 ml) in chloroform (130 ml). The reaction mixture was warmed to room temperature and washed with a solution of sodium tartrate (1 *M*, 130 ml). The organic layer was dried (magnesium sulfate) and concentrated *in vacuo* to yield a colorless oil (3.712 g), which was further purified by vacuum flash chromatography on a silica gel column using hexanes-ethyl acetate (16:1) as the eluent. Evaporation of the appropriate fractions yielded **6a** as a colorless oil (3.1 g, 77%); ir (neat): 3600-3100 (hydroxyl), and 2110 cm^{-1} (azide); ^1H nmr (deuteriochloroform): δ 0.07 and 0.13 (2 x s, 6H, methyl), 0.89 and 0.93 (2 x s, 9H, *t*-butyl), 2.00-2.51 (m, 2H, H-2), 2.99 (d, 1H, J = 6.4 Hz, OH, deuterium oxide exchangeable), 3.5-3.8 (m, 2H, H-5), 4.01-4.32 (m, 2H, H-3 and H-4), 5.42-5.61 (m, 1H, H-1).

Anal. Calcd. for $C_{11}H_{23}N_3O_3Si$: C, 48.32; H, 8.48; N, 15.37. Found: C, 48.39; H, 8.52; N, 15.28.

3-Azido-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α,β-D-*erythro*-pentofuranose (**6b**).

DIBAL-H (1 *M* in hexanes, 11.6 ml, 11.6 mmoles) was added dropwise to a well stirred solution of silylated azidolactone **5b** (3.03 g, 0.77 mmole) in methylene chloride (20 ml) under nitrogen at −78°. The colorless solution was stirred at −78° for 4 hours and then quenched with a solution of methanol (26 ml) in chloroform (130 ml). The reaction mixture was warmed to room temperature, and washed with a solution of sodium tartrate (1 *M*, 130 ml). The organic layer was dried (magnesium sulfate) and concentrated *in vacuo* to yield a colorless oil (3.01 g), which was further purified by vacuum flash chromatography on a silica gel column using hexanes-ethyl acetate (8:1) as the eluent. Evaporation of the appropriate fractions yielded **6b** as a colorless oil (2.44 g, 80%); $[\alpha]_D^{25}$ = 11.47 (c 1.41, chloroform); ir (neat): 2110 cm^{-1} (azide); ^1H nmr (deuteriochloroform): δ 0.99 and 1.06 (2 x s, 9H, *t*-butyl), 2.01-2.49 (m, 2H, H-2), 3.02 (d, 1H, J = 6.4 Hz, OH, deuterium oxide exchangeable), 3.6-3.8 (m, 2H, H-5), 3.91-4.30 (m, 2H, H-3 and H-4), 5.45-5.62 (m, 1H, H-1), 7.31-8.85 (m, 10H, phenyl protons).

Anal. Calcd. for $C_{21}H_{27}O_3N_3Si$: C, 63.44; H, 6.85; N, 10.57. Found: C, 63.40; H, 6.82; N, 10.27.

1-*O*-Acetyl-3-azido-2,3-dideoxy-5-*O*-(*tert*-butyldimethylsilyl)-α,β-D-*erythro*-pentofuranoside (**7a**).

Acetic anhydride (6.2 ml) and pyridine (5 drops) were added to the azidolactol **6a** (3.1 g, 11.34 mmoles) and the reaction mixture was stirred at room temperature for 15 hours. The mixture was evaporated under reduced pressure and the residue was purified by vacuum flash chromatography on a silica gel column using hexanes-ethyl acetate (10:1) as the eluent. Evaporation of the appropriate fractions yielded an anomeric mixture (ratio 2:1) of **7a** as a colorless oil (3.1 g, 87%), ir (neat): 2110 (azide) and 1755 cm^{-1} (ester); ^1H nmr (deuteriochloroform): δ 0.06 and 0.09 (2 x s, 6H, methyl), 0.89 and 0.92 (2 x s, 9H, *t*-butyl), 2.03 and 2.08 (2 x s, 3H, acetate), 2.15-2.51 (m, 2H, H-2), 3.51-4.01 (m, 2H, H-5), 4.00-4.35 (m, 2H, H-3 and H-4), 6.30 (m, 1H, H-1).

Anal. Calcd. for $C_{13}H_{25}N_3O_4Si$: C, 49.52; H, 7.93; N, 13.33. Found: C, 49.60; H, 8.03; N, 13.30.

1-*O*-Acetyl-3-azido-2,3-dideoxy-5-*O*-(*tert*-butyldiphenylsilyl)-α,β-D-*erythro*-pentofuranoside (**7b**).

Acetic anhydride (6.2 ml) and pyridine (1 ml) were added to the azidolactol **6b** (3.07 g, 7.72 mmoles) and the reaction mixture was stirred at room temperature for 2 hours. The mixture was evaporated under reduced pressure and the residue was purified by vacuum flash chromatography on a silica gel column using hexanes-ethyl acetate (10:1) as the eluent. Evaporation of the appropriate fractions yielded an anomeric mixture (ratio 2:1) of **7b** as a colorless oil (2.75 g, 81%); ir (neat): 2110 (azide) and 1755 cm^{-1} (ester); ^1H nmr (deuteriochloroform): δ 0.99 and 1.06 (2 x s, 9H, *t*-butyl), 1.85 and 2.05 (2 x s, 3H, acetate), 2.18-2.40 (m, 2H, H-2), 3.68-3.80 (m, 2H, H-5), 3.90-4.38 (m, 2H, H-3 and H-4), 6.25-6.38 (m, 1H, H-1), 7.30-7.79 (m, 10H, phenyl protons.

Anal. Calcd. for $C_{23}H_{29}O_4N_3Si$: C, 62.84; H, 6.65; N, 9.56. Found: C, 62.54; H, 6.60; N, 9.26.

1-[3-Azido-2,3-dideoxy-5-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]uracil (**8**) and 1-[3-Azido-2,3-dideoxy-5-*O*-(*tert*-butyldimethylsilyl)-α-D-*erythro*-pentofuranosyl]uracil (**9**).

Method A.

Anhydrous stannic chloride (1.65 g, 6.34 mmoles) was added to a stirred solution of the acetate **7a** (1 g, 3.17 mmoles) and 2,4-bistrimethylsilyloxypyrimidine (1.6 g, 6.25 mmoles) in acetonitrile (50 ml, dried over 4 Å molecular sieves) and the reaction mixture stirred at room temperature 18 hours under nitrogen. At the end of this time, the reaction mixture was diluted with saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), filtered and concentrated. The residue was chromatographed on a silica vacuum flash column using 30% ethyl acetate-benzene as the eluent to give a mixture of α and β isomers which were solidified after removal of solvents (0.95 g, 82%, ratio = 66:34 by nmr). Upon trituration of this solid with diethylether the pure α-isomer **9** (0.509 g) precipitated out, mp 133-134°; $[\alpha]_D^{25}$ = −8.3° (c 0.55, methanol); ir (potassium bromide): 2120 cm^{-1} (azide); uv (methanol): λ max 262 mm; ^1H nmr (deuteriochloroform): δ 0.09 (s, 6H, 2 x methyl), δ 0.91 (s, 9H, *t*-butyl), 2.15 (dt, 1H, J = 15.0, 2.0 Hz, H_a-2'), 2.82 (dt, 1H, J = 15.0, 7.0 Hz, 1.0H, H_b-2'), 3.7 (d, 2H, J = 4.0 Hz, H-5'), 4.2-4.4 (m, 2H, H-3' and H-4'), 5.70 (dd, 1H, J = 8.1, 2.3 Hz, H-5'), 6.18 (dd, 1H, J = 7.2, 2.1 Hz, H-1'), 7.52 (d, 1H, J = 8.4 Hz, H-6), 8.42 (br s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{15}H_{25}N_5O_4Si$: C, 49.04; H, 6.8; N, 19.07. Found: C, 49.10; H, 6.9; N, 19.06.

Addition of hexanes to the mother liquor gave a solid which was found by ^{1}H nmr to be an α:β mixture of **9** and **8** in a ratio of 3:7 (0.394 g).

Method B. Condensation using Trimethylsilyl Triflate in Acetonitrile.

A mixture of acetate **7a** (0.14 g, 0.44 mmole) and 2,4-bistrimethylsilyloxypyrimidine (0.35 g, 1.37 mmoles) in dry acetonitrile (15 ml) was treated with trimethylsilyl triflate (0.149 g, 0.67 mmole) at room temperature for 24 hours. Workup of the reaction mixture as described under method A, followed by chromatographic purification (silica gel, chloroform-methanol 19:1) yielded an α:β mixture (1:1) of **9** and **8** (0.125 g, 76%).

Method C. Condensation using Trimethylsilyl Triflate in Dichloroethane.

Reaction of **7a** (1.0 g, 3.17 mmoles) with 2,4-bistrimethylsilyloxypyrimidine (2.0 g, 7.8 mmoles) in the presence of trimethylsilyl triflate (1.15 g, 5.2 mmoles) in dry dichloroethane (20 ml), according to the procedure described under method A, yielded α:β mixture of **9** and **8** (0.65 g, 55%) in a ratio of 1:2 as indicated by ^{1}H nmr.

1-(3-Azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)uracil (AZDU, CS-87) (**12**).

A 1 *M* solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1 ml, 1.0 mmole) was added to a solution of the α,β-mixture (30:70) of 5-*t*-butyldimethylsilyl ethers **9** and **8** (0.26 g, 0.708 mmole) in tetrahydrofuran (10 ml) and the reaction mixture was stirred at room temperature. After 0.5 hour, the reaction mixture was concentrated and the residue was chromatographed on a silica vacuum flash column using 5% methanol-ethyl acetate as the eluent. The fractions containing the β-isomer with small amounts of α-isomer were combined and concentrated. The residue was crystallized from 2-propanol to yield pure **12** (0.066 g, 33%), mp 168-169° [lit [20] 161-163° (ethanol)]; $[\alpha]_D$ = +79.25° (c 0.54, methanol); ir (potassium bromide): 2120 cm^{-1} (azide); uv (methanol): λ max 261 nm; ^{1}H nmr (DMSO-d_6): δ 2.33 (t, 2H, J = 6.2 Hz, H-2'), 3.60 (m, 2H, H-5'), 3.85 (q, 1H, J = 6.1 Hz, H-3'), 4.41 (q, 1H, J = 4.2 Hz, H-4'), 5.18 (t, 1H, J = 5.3 Hz, OH-5', deuterium oxide exchangeable), 5.63 (d, 1H, J = 8.2 Hz, H-5), 6.07 (t, 1H, J = 6.1 Hz, H-1'), 7.83 (d, 1H, J = 8.2 Hz, H-6), 11.3 (br s, 1H, NH, exchangeable).

Anal. Calcd. for $C_9H_{11}N_5O_4$: C, 42.68; H, 4.35; N, 27.66. Found: C, 42.61; H, 4.41; N, 27.56.

The deprotection of a α,β-mixture (1:2) of **9** and **8** from Method C (0.65 g) according to the above procedure yielded 0.167 g of AZDU **12** (37%) (20% overall yield from **7a**).

1-(3-Azido-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)uracil (**13**).

A 1 *M* solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1 ml, 1 mmole) was added to a stirred solution of **9** (0.30 g, 0.817 mmole) in tetrahydrofuran (15 ml). After 0.5 hour, the reaction mixture was concentrated and the residue was chromatographed on a silica vacuum flash column using 5% methanol-chloroform as the eluent. The fractions were combined and concentrated to give the α-isomer **13** as a hygroscopic foam, (0.165 g, 80%), $[\alpha]_D^{25}$ = −4.6° (c 0.49, methanol); ir (potassium bromide): 2120 cm^{-1} (azide); uv (methanol): λ max 262 nm; ^{1}H nmr (DMSO-d_6): δ 2.10 (dt, 1H, J = 14, 4 Hz, H_a-2'), 2.73 (dt, 1H, J = 14, 7 Hz, H_b-2'), 3.47 (m, 2H, H-5'), 4.11-4.45 (m, 2H, H-3' and 4'), 5.02 (t, 1H, J = 5.2 Hz, OH-5', deuterium oxide exchangeable), 5.63 (d, 1H, J = 8.1 Hz, H-5), 6.07 (dd, 1H, J = 7.2, 4.3 Hz, H-1'), 7.67 (d, 1H, J = 8.2 Hz, H-6), 11.27 (br s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_9H_{11}N_5O_4$: C, 41.94; H, 4.46; N, 27.18. Found: C, 41.95; H, 4.55; N, 27.08.

1-(3-Azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine, AZT (**14**) and 1-(3-Azido-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)-thymine (**15**).

Method A.

Stannic chloride (0.55 ml, 4.7 mmoles) was added to a solution of the acetate **7a** (1.0 g, 3.17 mmoles) and 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine (4.2 g, 15.5 mmoles) in dry acetonitrile (125 ml) and the reaction mixture was stirred at room temperature for 18 hours and filtered. The filtrate was neutralized wirh a saturated sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (50 ml x 4). The organic layer was dried (magnesium sulfate) and concentrated to give an inseparable anomeric mixture of **10** and **11** as a syrup (0.825 g, 68%). The syrup was dissolved in dry tetrahydrofuran (20.9 ml) and a 1 *M* solution of tetra-*n*-butylammonium fluoride (2.3 ml) was added dropwise and stirred at room temperature for 0.5 hour. The solvent was removed *in vacuo* and the brownish syrupy residue was purified by column chromatography on silica gel (200-400 mesh, 45 x 3.2 cm) using ethyl acetate-hexanes (10:1) as the eluent to yield 3'-azido-3'-deoxythymidine **14** as a less polar fraction (0.19 g, 31%), mp 120-122° [lit [8] 119-121°]; $[\alpha]_D^{25}$ = +41.5 (c 1, water); ir (potassium bromide): 2100 (azide) cm^{-1}; uv (methanol): λ max 266 nm; ^{1}H nmr (DMSO-d_6): δ 1.78 (d, 3H, J = 0.88 Hz, methyl), 2.32 (m, 2H, H-2'), 3.61 (m, 2H, H-5'), 3.82 (m, 1H, H-3'), 4.39 (m, 1H, H-4'), 5.18 (t, 1H, J = 5.3 Hz, OH, deuterium oxide exchangeable), 6.09 (t, 1H, J = 6.4 Hz, H-1), 7.67 (d, 1H, J = 0.88 Hz, H-6), 11.3 (br s, 1H, NH, deuterium oxide exchangeable).

The more polar α-isomer **15** was obtained as colorless crystals (0.26 g, 45%) (hygroscopic); $[\alpha]_D$ = +42.6 (c 1, water); ir (potassium bromide); 2110 cm^{-1} (azide); uv (water): λ max 268 nm; ^{1}H nmr (DMSO-d_6): δ 1.8 (d, 3H, J = 1.2 Hz, methyl), 2.17 (m, 1H, H_a-2), 2.75 (m, 1H, H_b-2), 3.49 (m, 2H, H-5'), 4.28 (m, 2H, H-3' and H-4'), 5.01 (t, 1H, J = 5.6 Hz, OH, deuterium oxide exchangeable), 5.99 (dd, 1H, J = 4.4, 6.4 Hz, H-1), 7.54 (s, 1H, H-6), 11.27 (br s, 1H, NH, exchangeable).

Method B.

Condensation of **7a** (1.0 g, 3.17 mmoles) with 5-methyl-2,4-bis-(trimethylsiloxy)pyrimidine (2.1 g, 7.8 mmoles) in the presence of trimethylsilyl triflate (1.15 g, 5.2 mmoles) in anhydrous dichloroethane (20 ml) at room temperature for 24 hours and the usual workup followed by vacuum flash chromatography on silica gel using chloroform-methanol (19:1) as the eluent yielded a α,β-mixture of protected **10** and **11** (0.8 g, 66%) in 55:45 ratio as indicated by ^{1}H nmr spectrum.

Method C.

Condensation of **7a** (1.0 g, 3.17 mmoles) with 5-methyl-2,4-bis-(trimethylsiloxy)pyrimidine (2.1 g, 7.8 mmoles) in the presence of trimethylsilyl triflate (1.15 g, 5.2 mmoles) in anhydrous acetonitrile (20 ml) at room temperature for 24 hours and the usual workup followed by vacuum flash chromatography on silica gel using chloroform-methanol (19:1) as the eluent yielded a α,β-mixture of protected **10** and **11** (0.8 g, 66%) in 53:47 ratio as indicated by ^{1}H

nmr spectrum.

Condensation of Acetate **7b** with Silylated 4-Aminopyrazolo[3,4-*d*]pyrimidine.

A mixture of 4-aminopyrazolo[3,4-*d*]pyrimidine (0.923 g, 6.83 mmoles), hexamethyldisilazane (100 ml) and ammonium sulfate (0.09 g, 0.681 mmole) was refluxed for 3 hours. The resulting clear solution was concentrated *in vacuo* and the residue was dissolved in dry 1,4-dioxane (50 ml). A solution of acetate **7b** (1.50 g, 3.42 mmoles) in dry 1,4-dioxane (20 ml) and boron trifluoride etherate (0.93 ml) were added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into saturated sodium bicarbonate solution (40 ml), stirred for an additional 30 minutes, and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine (2 x 100 ml) and dried (magnesium sulfate). After removal of the solvent, the residue was purified by silica gel column chromatography (chloroform-methanol, 20:1) to give an inseparable anomeric mixture (1.15 g, 65%, β:α = 1:3 by ^{1}H nmr) of **16** and **17** of the *N*-1 isomer and β-anomer **18** (0.073 g, 4.1%) and α-anomer **19** (0.147 g, 8.4%) of the *N*-2 isomer.

4-Amino-1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-azido-2,3-dideoxy-β,α-D-*ribo*-furanosyl]pyrazolo[3,4-*d*]pyrimidine (**16**) and its α-Anomer **17**.

The inseparable α,β-anomeric mixture was obtained as a white foam; ir (potassium bromide): 2100 cm^{-1} (azide); uv (methanol): λ max 274 nm; ^{1}H nmr (deuteriochloroform): δ 1.03, 1.08 (s, 9H, *t*-butyl), 2.90-3.21 (m, 2H, H-2'), 3.81-4.00 (m, 3H, H-4' and H-5'), 4.31-4.60 (m, 1H, H-3'), 5.95 (br s, 2H, NH_2), 6.67-6.82 (m, 1H, H-1'), 7.26-7.77 (m, 10H, 2 x C_6H_5), 7.95 (s, 1H, H-6), 8.38, 8.36 (s, s, 1H, H-3).

Anal. Calcd. for $C_{26}H_{30}O_2N_8Si$: C, 60.68; H, 5.88; N, 21.77. Found: C, 60.58; H, 5.91; N, 21.66.

4-Amino-2-[5-*O*-(*tert*-butyldiphenylsilyl)-3-azido-2,3-dideoxy-β-D-*ribo*-furanosyl]pyrazolo[3,4-*d*]pyrimidine (**18**).

This compound was obtained as a white foam; uv (methanol): λ max 287 nm; ir (potassium bromide): 2090 cm^{-1} (azide); ^{1}H nmr (deuteriochloroform): δ 1.06 (s, 9H, *t*-butyl), 2.66-3.05 (m, 2H, H-2'), 3.90-4.13 (m, 3H, H-4' and H-5'), 4.43 (m, 1H, H-3'), 5.65 (br s, 2H, NH_2), 6.25 (dd, 1H, J = 3.0, 6.1 Hz, H-1'), 7.34-7.70 (m, 10H, pheneyl proton), 8.30 (s, 1H, H-6), 8.40 (s, 1H, H-3).

Anal. Calcd. for $C_{26}H_{30}O_2N_8Si$: C, 60.68; H, 5.88; N, 21.77. Found: C, 60.72; H, 5.91; N, 21.81.

4-Amino-2-[5-*O*-(*tert*-butyldiphenylsilyl)-3-azido-2,3-dideoxy-α-D-*ribo*-furanosyl]pyrazolo[3,4-*d*]pyrimidine (**19**).

This compound was obtain as a white foam; ir (potassium bromide): 2100 cm^{-1} (azide); uv (methanol): λ max 292 nm; ^{1}H nmr (deuteriochloroform): δ 1.09 (s, 9H, *t*-butyl), 2.91 (t, 2H, H-2'), 3.80 (d, 2H, H-5'), 4.03-4.39 (m, 2H, H-3' and H-4'), 5.85 (br s, 2H, NH_2), 6.31 (t, 1H, H-1'), 7.34-7.72 (m, 10H, phenyl protons), 8.21 (s, 1H, H-6), 8.45 (s, 1H, H-3).

Anal. Calcd. for $C_{26}H_{30}O_2N_8Si$: C, 60.68; H, 5.88; N, 21.77. Found: C, 60.57; H, 5.90. N, 21.67.

4-Amino-1-(3-azido-2,3-dideoxy-β-D-*ribo*-furanosyl)pyrazolo[3,4-*d*]pyrimidine (**20**) and 4-Amino-1-(3-azido-2,3-dideoxy-α-D-*ribo*-furanosyl)pyrazolo[3,4-*d*]pyrimidine (**21**).

A 1 *M* solution of tetra-*n*-butylammonium fluoride (1.28 ml, 1.28 mmoles) was added to a mixture of **16** and **17** (0.44 g, 0.856 mmole) in tetrahydrofuran (15 ml) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform-methanol, 10:1) to give **20** (0.060 g, 23%) and **21** (0.182 g, 70%) as a white foam, which was crystallized from ethyl ether and methanol.

Compound **20** had $[\alpha]_D^{25}$ = −65.52° (c 0.2, methanol); uv (methanol): λ max 275 nm (ϵ 10,990), (sh) 261 nm (9550); (*p*H 2): λ max 259 nm (ϵ 10,230); (*p*H 11): λ max 275 nm (ϵ 12,130); ir (potassium bromide): 2100 cm^{-1} (azide); ^{1}H nmr (DMSO-d_6): δ 2.47 (m, 1H, H_a-2'), 2.99 (m, 1H, H_b-2'), 3.49 (m, 2H, H-5'), 3.92 (q, 1H, J = 5.4, 10.8 Hz, H-4'), 4.61 (q, 1H, J = 5.7, 11.2 Hz, H-3'), 5.05 (t, 1H, J = 5.4 Hz, OH-5', deuterium oxide exchangeable), 6.55 (t, 1H, J = 5.4 Hz, H-1'), 7.35 (br d, 2H, NH_2, deuterium oxide exchangeable), 8.22 (s, 1H, H-6), 8.23 (s, 1H, H-3); ^{13}C nmr (DMSO-d_6): δ 36.8, 61.6, 62.7, 85.2, 85.3, 102.7, 134.9, 155.4, 157.4, 160.2.

Anal. Calcd. for $C_{10}H_{12}O_2N_8 \cdot 0.51\ C_4H_{10}O$: C, 46.04; H, 5.48; N, 35.68. Found: C, 45.64; H, 5.14; N, 35.95.

Compound **21** had $[\alpha]_D^{25}$ = 208.3° (c 1, methanol); uv (methanol): λ max 275 nm (ϵ 9,600); (*p*H 2): λ max 259 nm (ϵ 9,200); (*p*H 11): λ max 275 nm (ϵ 9,700); ir (potassium bromide): 2100 cm^{-1} (azide); ^{1}H nmr (DMSO-d_6): δ 2.78 (m, 1H, H_a-2'), 2.96 (m, 1H, H_b-2'), 3.53 (m, 2H, H-5'), 4.01 (m, 1H, H-4'), 4.21 (q, 1H, J = 5.8, 12.0 Hz, H-3'), 5.00 (t, 1H, J = 5.6 Hz, OH-5', deuterium oxide exchangeable), 6.54 (t, 1H, J = 6.8 Hz, H-1'), 7.75 (br d, 2H, NH_2, deuterium oxide exchangeable), 8.19 (s, 1H, H-6), 8.20 (s, 1H, H-3); ^{13}C nmr (DMSO-d_6): δ 35.3, 61.6, 61.9, 83.5, 84.5, 106.0, 133.4, 154.0, 156.2, 158.1.

Anal. Calcd. for $C_{10}H_{12}O_2N_8$: C, 43.48; H, 4.38; N, 40.56. Found: C, 43.51; H, 4.40; N, 40.47.

4-Amino-2-(3-azido-2,3-dideoxy-β-D-*ribo*-furanosyl)pyrazolo-[3,4-*d*]pyrimidine (**22**) and its α-Anomer (**23**).

A 1 *M* solution of tetra-*n*-butylammonium fluoride (0.5 ml, 0.5 mmole) was added to a mixture of **18** and **19** (0.22 g, 0.428 mmole) in tetrahydrofuran (4 ml) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform-methanol, 10:1) to give **22** (0.018 g, 15%) and **23** (0.083 g, 70%) as a white solids, which were recrystallized from ethanol.

Compound **22** had $[\alpha]_D^{25}$ = −53.0° (c 1, methanol); uv (methanol): λ max 292 nm (ϵ 8,980), (*p*H 2): λ max 271 nm (ϵ 8,170); (*p*H 11): λ max 292 nm (ϵ 9,170); ir (potassium bromide): 2090 cm^{-1} (azide); ^{1}H nmr (DMSO-d_6): δ 2.42-2.89 (m, 2H, H-2'), 3.56 (t, 2H, J = 5.1 Hz, H-5'), 4.05 (q, 1H, J = 5.1, 5.5 Hz, H-4'), 4.58 (q, 1H, J = 5.0, 5.5 Hz, H-3'), 5.07 (t, 1H, J = 5.5 Hz, OH-5', deuterium oxide exchangeable), 6.37 (dd, 1H, J = 4.2, 6.8 Hz, H-1'), 7.75 (br s, 2H, NH_2, deuterium oxide exchangeable), 8.15 (s, 1H, H-6), 8.51 (s, 1H, H-3); ^{13}C nmr (methanol-d_4): δ 39.1, 62.2, 62.9, 87.9, 92.9, 102.8, 124.8, 155.7, 160.8, 162.4.

Anal. Calcd. for $C_{10}H_{12}O_2N_8$: C, 43.48; H, 4.38; N, 40.56. Found: C, 43.55; H, 4.42; N, 40.46.

Compound **23** had $[\alpha]_D^{25}$ = 131.4° (c 0.5, methanol); uv (methanol): λ max 292 nm (ϵ 10,000); (*p*H 2): λ max 271 nm (ϵ 11,230); (*p*H 11): λ max 292 nm (ϵ 10,300), ir (potassium bromide): 2090 cm^{-1} (azide); ^{1}H nmr (DMSO-d_6): δ 2.50-3.15 (m, 2H, H-2'), 3.57 (m, 2H, H-5'), 4.14-4.41 (m, 2H, H-3' and H-4'), 5.08 (t, 1H, J = 5.5 Hz, OH-5', deuterium oxide exchangeable), 6.33 (dd, 1H, J = 3.3, 6.7 Hz, H-1'), 7.66 (br s, 2H, NH_2, deuterium oxide exchangeable), 8.15 (s, 1H, H-6), 8.54 (s, 1H, H-3).

Anal. Calcd. for $C_{10}H_{12}O_2N_8 \cdot 0.3\ C_2H_5OH$: C, 44.26; H, 4.95; N, 38.24. Found: C, 43.91; H, 4.88; N, 37.91.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-azido-2,3-dideoxy-α,β-D-*ribo*-furanosyl]pyrazolo[3,4-*d*]pyrimidin-4-one (**24**) and its α-Anomer (**25**).

Excess sodium nitrite (5 g) and glacial acetic acid (7 ml) were added to a mixture of **16** and **17** (1.15 g, 2.24 mmoles) in 1:1 mixture (60 ml) of 1,4-dioxane and water and the reaction mixture was stirred at room temperature. Additional sodium nitrite (15 g) and glacial acetic acid (20 ml) were added to reaction mixture until starting material disappeared (7 days for completion). The solvents were evaporated and the residue was dissolved in ethyl acetate (150 ml), washed with saturated sodium bicarbonate solution (50 ml), brine (50 ml x 2) and dried (magnesium sulfate). After the removal of solvent, the residue was purified by silica gel column chromatography to give an inseparable anomeric mixture of **24** and **25** (0.9 g, 78%) as a white foam; uv (methanol): λ max 252 nm; (*p*H 11): λ max 270 nm; (*p*H 2): λ max 252 nm; ir (potassium bromide): 2100 cm^{-1} (azide); ^1H nmr (DMSO-d_6): δ 0.98, 1.02 (s, s, 9H, *t*-butyl), 2.30-2.86 (m, 2H, H-2'), 3.71-3.96 (m, 2H, H-5'), 4.12-4.38 (m, 2H, H-3' and H-4'), 6.09-6.58 (m, 1H, H-1'), 7.34-7.69 (m, 10H, phenyl protons), 8.15, 8.13 (s, s, 1H, H-6), 8.31, 8.18 (s, s, 1H, H-3), 12.4 (br s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{26}H_{29}O_3N_7Si$: C, 60.56; H, 5.67; N, 19.02. Found: C, 60.32; H, 5.70; N, 18.89.

1-(3-Azido-2,3-dideoxy-β-D-*ribo*-furanosyl)pyrazolo[3,4-*d*]pyrimidin-4-one (**26**) and its α-Anomer (**27**).

A 1 *M* solution of tetra-*n*-butylammonium fluoride (1.6 ml, 1.6 mmoles) was added to a mixture of **24** and **25** (0.70 g, 1.36 mmoles) in tetrahydrofuran (10 ml) and the reaction mixture was stirred at room temperature for 1 hour. After the removal of solvent, the residue was purified by silica gel column chromatography (chloroform-methanol, 10:1) to give β-anomer **26** (0.265 g, 70%) as a white solid and α-anomer **27** (0.087 g, 23%) as a white solid.

Compound **26** had $[\alpha]_D^{25} = -45.59°$ (c 1, methanol); uv (methanol): λ max 251 nm (ε 124,900); (*p*H 11): λ max 269 nm; (*p*H 2): λ max 251 nm (123900); ir (potassium bromide): 2100 cm^{-1} (N_3); ^1H nmr (DMSO-d_6): δ 2.49 (m, 1H, H_a-2'), 2.93 (m, 1H, H_b-2'), 3.46 (d, 2H, J = 5.7 Hz, H-5'), 3.91 (q, 1H, J = 6.1, 11.3 Hz, H-4'), 4.58 (q, 1H, J = 6.3, 11.7 Hz, H-3'), 6.50 (dd, 1H, J = 4.2, 6.5 Hz, H-1'), 8.14 (s, 1H, H-6), 8.18 (s, 1H, H-3), 12.3 (br s, 1H, NH, exchangeable); ^{13}C nmr (DMSO-d_6): δ 35.5, 60.2, 61.0, 83.6, 83.7, 106.7, 135.8, 148.9, 152.9, 157.5.

Anal. Calcd. for $C_{10}H_{11}N_7O_3$: C, 43.32; H, 4.00; N, 35.37. Found: C, 43.25; H, 4.06; N, 35.29.

Compound **27** had $[\alpha]_D^{25} = 110.8°$ (c 1, methanol); uv (methanol): λ max 252 nm (ε 7,100); (*p*H 11): 272 nm; (*p*H 2): 252 nm (ε 7,030); ir (potassium bromide): 2090 cm^{-1} (azide); ^1H nmr (DMSO-d_6): δ 2.75 (m, 1H, H_a-2'), 2.95 (m, 1H, H_b-2'), 3.65 (dd, 1H, J = 4.4, 13.1 Hz, H_a-5'), 3.74 (dd, 1H, J = 3.3, 12.6 Hz, H_b-5'), 3.98 (q, 1H, J = 6.0, 12.0 Hz, H-4'), 4.28 (q, 1H, J = 6.9, 14.3 Hz, H-3'), 4.98 (t, 1H, J = 3.8 Hz, OH-5', exchangeable), 6.55 (dd, 1H, J = 5.5, 7.4 Hz, H-1'), 8.11 (s, 1H, H-6), 8.13 (s, 1H, H-3), 12.3 (br s, 1H, NH, exchangeable); ^{13}C nmr (DMSO-d_6): δ 35.5, 60.8, 61.8, 83.6, 84.8, 105.8, 135.5, 148.8, 153.1, 157.1.

Anal. Calcd. for $C_{10}H_{11}N_7O_3$: C, 43.32; H, 4.00; N, 35.37. Found: C, 43.44; H, 4.03; N, 35.44.

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