Synthesis of 5-Benzyl and 5-Benzyloxybenzyl-3'-azido-2',3'-dideoxyuridine and their Analogues as Potential Anti-AIDS Agents

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5-Benzyl and 5-benzyloxybenzyl-substituted 3'-azido-2',3'-dideoxyuridine, (**8a** and **8b**), 3'-halogeno-2',3'-dideoxyuridine, **9a**, **9b**, **10a**, **10b**, **11a** and **11b**, and 2',3'-dideoxyuridine, **12a** and **12b**, of Scheme I were synthesized as potential anti AIDS agents. Synthesis of epimers of **8a** and **8b**, 5-benzyl- and 5-benzyloxy-benzyl-1-(3'-azido-2',3'-dideoxy-β-D-threo-pentafuranosyl)uracil, **15a** and **15b**, and 5-benzyl- and 5-benzyloxy-5'-azido-2',5'-dideoxyuridine, **16a** and **16b**, shown in Scheme II, were also reported.

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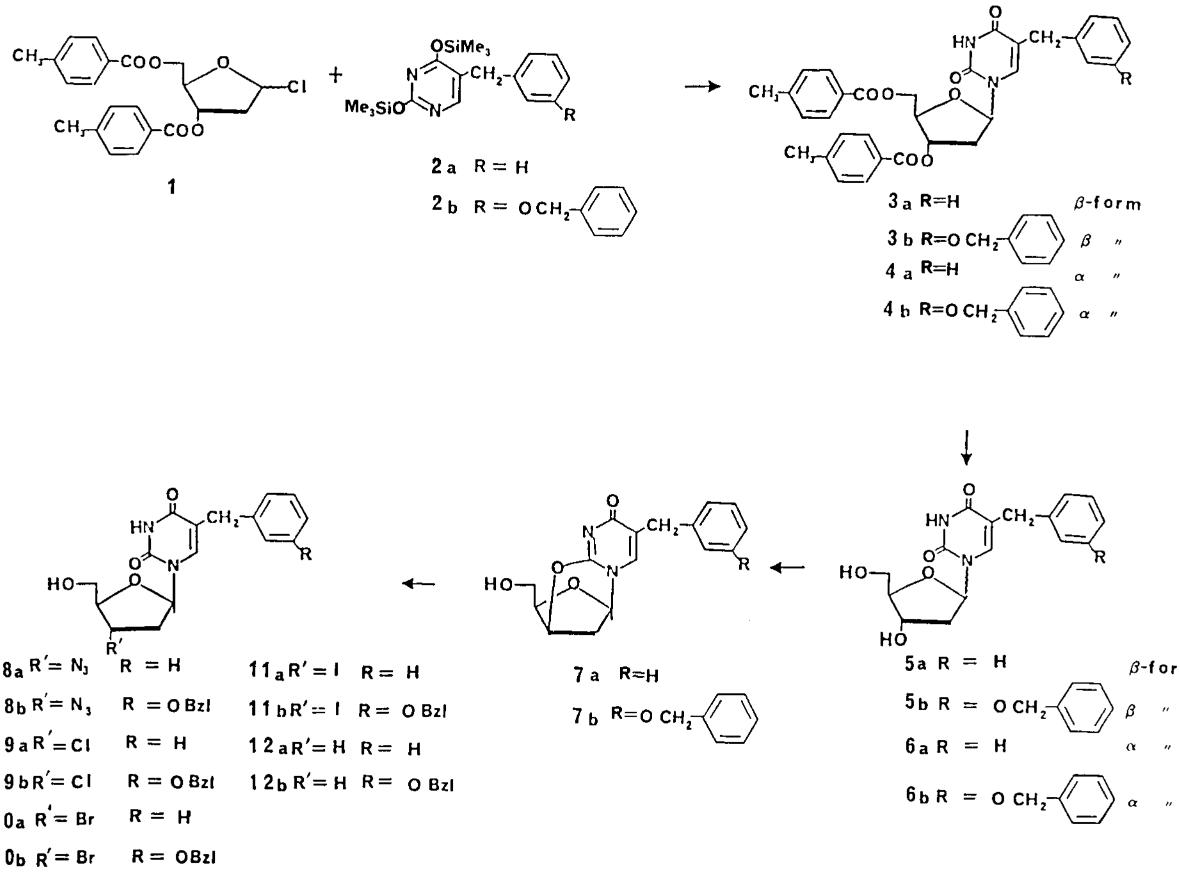
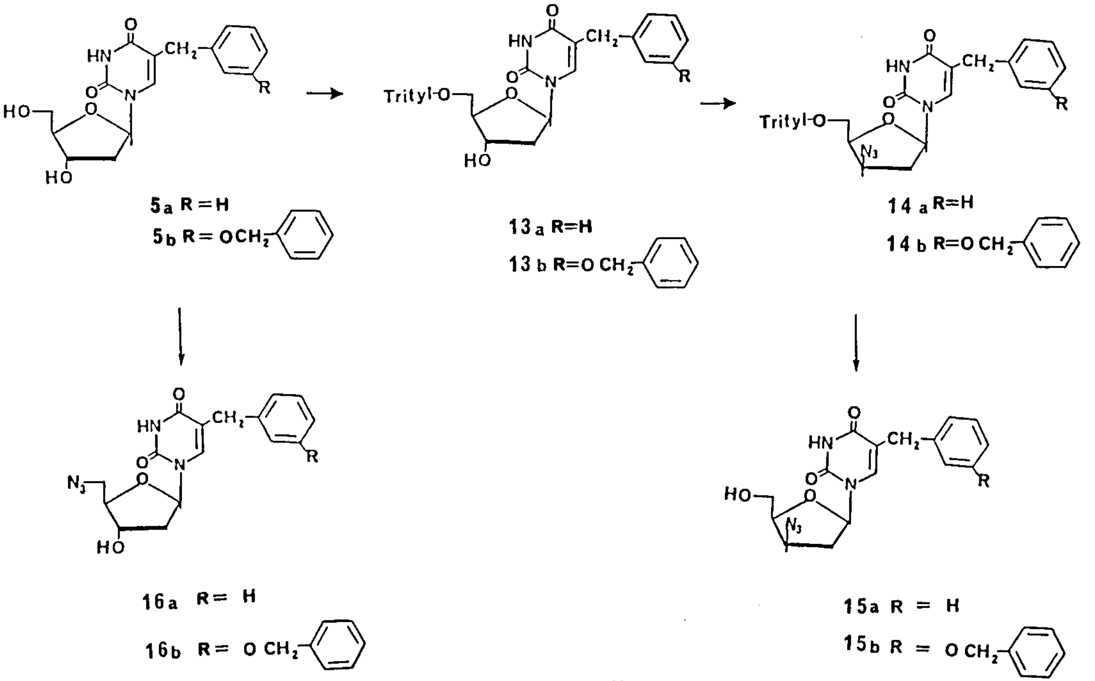
Among compounds currently being studied as inhibitors of acquired immunodeficiency syndrome (AIDS), the best appear to be the nucleoside analogues 3'-azido-3'-deoxythymidine (AZT) [1] and certain 2',3'-dideoxy nucleosides (DDN) [2] [3]. Since they lack the 3'-hydroxyl group required for further polymerization, AZT, DDN and their 5'-triphosphates function as inhibitors of the enzyme reverse transcriptase as well as of DNA polymerase [3] [4]. However these drugs are not entirely satisfactory as chemotherapeutic agents, due to high levels of toxicity and low therapeutic index.

The considerable bone marrow toxicity of these drugs can be to some extent reversed by injecting high doses of exogenous uridine, according to Sommadossi [5]. Another method of raising both plasma and tissue uridine levels recently reported by Darnowski and Handschumacher [6], by the administration of non-toxic 5-benzylacyclouridine (BAU) was reported to reverse AZT bone marrow toxicity



Scheme I



Scheme II

of AZT [7]. Benzylacycloudines, originally developed as pyrimidine phosphorylase inhibitors, therefore may contain useful modifications to known anti-AIDS analogues that will lower toxicity and improve therapeutic effectiveness.

In this paper we wish to report the synthesis of 5-benzyl- and 5-benzyloxybenzyl-3′-azido-2′,3′-dideoxyuridines, **8a** and **8b**, 5-benzyl- and 5-benzyloxybenzyl-2′,3′-dideoxyuridines, **12a** and **12b** and their 3′-halogeno-2′,3′-dideoxyuridine analogues **9a**, **9b**, **10a**, **10b**, **11a** and **11b**. Epimers of **8a** and **8b**, **15a** and **15b** and 5′-azido-2′,5′-dideoxyuridine, **16a** and **16b**, were also synthesized.

2-Deoxy-3,5-ditoluoyl-D-erythro-pentosyl chloride [8] was reacted with the bis-silylated derivative of 5-benzyluracil (**2a**) or 5-benzyloxybenzyluracil (**2b**) to give a mixture of 5-benzyl-2′-deoxyuridine (**3a**) and its α-isomer **4a** or 5-benzyloxybenzyl-2′-deoxyuridine (**3b**) and its α-isomer **4b**. The isomers could be separated by chromatography on silica gel and then hydrolyzed with potassium hydroxide in methanol to give pure 5-benzyl-2′-deoxyuridine (**5a**), 5-benzyloxybenzyl-2′-deoxyuridine (**5b**) and their α-isomers **6a** and **6b**. Compounds **5a** and **5b** have been previously synthesized from 5-benzyluridine and 5-benzyloxybenzyluridine in this laboratory [9].

5-Benzyl- and 5-benzyloxybenzyl-2′-deoxyuridines **5a** and **5b** were converted into the corresponding 2,3′-anhydro-2′-deoxyuridines **7a** and **7b** by treatment with 2-chloro-1,1,2-trifluorotriethylamine at room temperature in methylene chloride. Ring opening of the anhydronucleosides **7a** and **7b** was accomplished by reacting it with lithium azide in dry DMF in the presence of ammonium chloride, to give 5-benzyl-3′-azido-2′,3′-dideoxyuridine (**8a**) and 5-benzyloxybenzyl-3′-azido-2′,3′-dideoxyuridine (**8b**). Reactions of anhydronucleosides **7a** and **7b** with hydrogen halides in DMF gave 5-benzyl-3′- halogeno-2′,3′-dideoxyuridines **9a**, **10a** and **11a** and 5-benzyloxybenzyl-3′-halogeno-2′,3′-dideoxyuridines **9b**, **10b** and **11b**. 5-Benzyl-3′-bromo-2′,3′-dideoxyuridine (**10a**) was subjected to catalytic hydrogenation in the presence of 5% Pd-C and potassium carbonate to give 5-benzyl-2′,3′-dideoxyuridine (**12a**). 5-Benzyloxybenzyl-2′,3′-dideoxyuridine (**12b**) could be prepared by the reduction of 5-benzyloxybenzyl-3′-bromo-2′,3′-dideoxyuridine (**10a**) with tributyltin hydride in toluene in the presence of 2,2′-azo-bis-2-methylpropionitrile (AIBN). These reactions are shown in Scheme I.

Scheme II shows the conversion of 5-benzyl-2′-deoxyuridine (**5a**) and 5-benzyloxybenzyl-2′-deoxyuridine (**5b**) into 5′-*O*-trityl derivatives **13a** and **13b** and then, following treatment with triphenylphosphine, lithum azide and carbon tetrabromide in dry DMF, to 5-benzyl- and 5-benzyloxybenzyl-1-(5′-*O*-trityl-3′-azido-2′,3′-dideoxy-β-D-threo-pentafuranosyl)uracils **14a** and **14b**. The latter compounds were hydrolyzed with 75% acetic acid to yield the 5-benzyl and 5-benzyloxybenzyl-1-(3′-azido-2′,3′-dideoxy-β-D-threo-pentafuranosyl)uracils **15a** and **15b**. Reactions of **5a** and **5b** with triphenylphosphine, carbon tetrabromide and lithium azide gave 5-benzyl-5′-azido-2′,5′-dideoxyuridine (**16a**) and 5-benzyloxybenzyl-5′-azido-2′,5′-dideoxyuridine (**16b**).

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The uv absorption maxima and extinction coefficients were obtained using a Perkin-Elmer Model 402 recording spectrophotometer, and optical rotation on a Perkin-Elmer Model #241 automated polarimeter. The ^{1}H nmr spectra were run on a Bruker WM-250 instrument in DMSO-d$_6$ or deuteriochloroform using trimethylsilane as an internal standard. Analyses were performed by the Baron Consulting Co., of Orange, CT and the Galbraith Laboratories, of Knoxville, TN.

3',5'-Ditoluoyl-5-benzyldeoxyuridine (**3a**) and its α-Anomer **4a**.

A suspension of dry powdered 5-benzyluracil (20.2 g, 0.1 mole) and ammonium sulfate (0.5 g) in 80 ml of hexamethyldisilazane was heated under reflux for three hours with the exclusion of moisture, and cooled to room temperature. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml of xylene and evaporated again to remove any remaining hexamethyldisilazane. The residue was then redissolved in 150 ml of acetonitrile and 39 g (0.1 mole) of 2-deoxy-3,5-ditoluoyl-D-erythro-pentosyl chloride (**1**) was added. The reaction mixture was refluxed for 4 hours under anhydrous conditions, and stirred at room temperature overnight. The mixture was then treated with 20 ml of water and evaporated at room temperature under reduced pressure to remove acetonitrile. The residue was redissolved in methylene chloride and washed with water. After removal of solvent the residue was chromatographed on a silica gel column and eluted with methyl chloride:methanol (30:1) to give 21.5 g of less polar compound **3a** (39%) and 16.5 g of **4a** (30%).

Compound **3a** had mp 176-178°; $[\alpha]_D^{16}$ = -29.8° (ethanol, 0.2); uv (ethanol): λ max 266 nm (12,374); ^{1}H nmr (DMSO-d$_6$): δ 2.33 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$), 2.55 (m, 2H, 2'-H), 3.30 (d, 1H, 5-CH$_2$, J = 1.5 Hz) 3.37 (d, 1H, 5-CH$_2$, J = 1.5 Hz), 4.47-4.61 (m, 3H, 5'-H, 4'-H), 5.61 (m, 1H, 3'-H'), 6.31 (t, 1H, 1'-H, J = 7 Hz) 7.09-7.22 (m, 6H, ArH, 6-H), 7.28 (d, 1H, *m*-H of toluoyl group, J = 8.2 Hz), 7.37 (d, 1H, *m*-H of toluoyl group), 7.92 (d, 1H, *o*-H of toluoyl group), 11.4 (br s, 1H, NH).

Anal. Calcd. for $C_{32}H_{30}N_2O_7$: C, 69.30; H, 5.45; N, 5.05. Found: C, 69.57; H, 5.53; N, 4.99.

Compound **4a** had mp 168-170°; $[\alpha]_D^{16}$ = +26.1° (ethanol, 0.2); uv (ethanol): λ max 266 nm (10,786); ^{1}H nmr (DMSO-d$_6$): δ 2.35 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$), 2.91 (m, 2H, 2'-H), 3.50 (dd, 2H, 5-H, J = 33.1, 14.9 Hz), 4.46 (d, 2H, 5'-H, J = 4.8 Hz), 4.96 (t, 1H, 4'-H, J = 4.6 Hz), 5.53 (d, 1H, 3'-H, J = 6.0 Hz), 6.20 (dd, 1H, 1'-H, J = 7.0, 2.0 Hz), 7.08-7.24 (m, 6H, ArH, 6-H), 7.22 (d, 1H, *m*-H of toluoyl group, J = 8.2 Hz), 7.27 (d, 1H, *m*-H of toluoyl group, J = 8.2 Hz), 7.78 (d, 1H, *o*-H of toluoyl group, J = 8.2 Hz), 7.91 (d, 1H, *o*-H of toluoyl group, J = 8.2 Hz), 11.4 (br s, 1H, NH).

Anal. Calcd. for $C_{32}H_{30}N_2O_7$: C, 69.30; H, 5.45; N, 5.05. Found: C, 69.25; H, 5.53; N, 5.03.

3',5'-Ditoluoyl-5-benzyloxybenzyldeoxyuridine (**3b**) and its α-Anomer **4b**.

These compounds were prepared from 5-benzyloxybenzyluracil by the method indicated above.

Compound **3b** had mp 111-113°; $[\alpha]_D^{25}$ = +27.4° (ethanol, 0.2); uv (ethanol): λ max 266 nm (12,700); ^{1}H nmr (deuteriochloroform): δ 2.34 (s, 3H, CH$_3$), 2.42 (s, 3H, CH$_3$), 2.26 (m, 1H, 2'-H), 2.70 (m, 1H, 2'-H), 3.36 (dd, 2H, 3'-H), 4.50 (m, 1H, 4'-H), 4.57 (m, 2H, 5'-H), 5.01 (s, 2H, CH$_2$ of term Bzl), 5.55 (m, 1H, 3'-H), 6.40 (t, 1H, 1'-H, J = 7.7 Hz), 6.50-6.80 (m, 3H, *o*- and *p*-H of inner Bzl), 7.08-7.43 (m, 11H, ArH, 6-H), 7.86 (d, 2H, *o*-H of toluoyl, J = 8.3 Hz), 7.91 (d, 2H, *o*-H of toluoyl, J = 8.3 Hz).

Anal. Calcd. for $C_{39}H_{36}N_2O_8$: C, 70.89; H, 5.49; N, 4.24. Found: C, 71.09; H, 5.70; N, 4.69.

Compound **4b** was obtained as an amorphous solid; $[\alpha]_D^{25}$ = +27.62° (ethanol, 0.5); uv (ethanol): λ max 266 nm (12,571); ^{1}H nmr (deuteriochloroform): δ 2.27 (m, H, 2'-H), 2.33 (s, 3H, CH$_3$), 2.44 (s, 3H, CH$_3$), 2.70 (m, 1H, 2'-H), 3.31 (d, 1H, 5-CH$_2$, J = 15.4 Hz), 3.41 (d, 1H, 5-CH$_2$, J = 15.5 Hz), 4.49 (m, 1H, 4'-H), 4.57 (m, 2H, 5'-H), 5.00 (s, 2H, CH$_2$ of term Bzl), 5.56 (m, 1H, 3'-H), 6.39 (dd, 1H, 1'-H, J = 5.4, 8.7 Hz), 6.61-6.81 (m, 3H, *o*- and *p*-H of inner Bzl), 7.08-7.44 (m, 11H, Ar-H, 6-H) 7.86 (d, 2H, *o*-H of toluoyl, J = 8.34 Hz), 7.91 (d, 2H, *o*-H of toluoyl, J = 8.3 Hz).

Anal. Calcd. for $C_{39}H_{36}N_2O_8 \cdot ½\ H_2O$: C, 69.88; H, 5.38; N, 4.18. Found: C, 69.71; H, 5.52; N, 3.80.

5-Benzyl-2'-deoxyuridine (**5a**) and its α-Anomer **6a**.

3',5'-Ditoluoyl-5-benzyluridine (**3a**, 1.0 g) was suspended in a solution of 0.3 g of potassium hydroxide in 20 ml of methanol, and stirred at room temperature for 3 hours. After neutralization with 6*N* hydrochloric acid the solution was evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride and washed with water. After evaporation of methylene chloride the residue was chromatographed on silica gel and eluted with 3% methanol in methylene chloride, to give 493 mg (86%) of **5a**, mp 122-123°; uv (*p*H 1): λ max 270 nm (8729); (*p*H 11): λ max 268 nm (6972); $[\alpha]_D^{16}$ = +26.0° (ethanol); ^{1}H nmr (DMSO-d$_6$): 2.09 (m, 2H, 2'-H), 3.51 (s, 2H, 5-CH$_2$), 3.49 (m, 2H, 5'-H), 3.76 (m, 1H, 4'-H), 4.22 (m, 1H, 3'-H), 6.16 (t, 1H, 1'-H, J = 7 Hz), 7.15-7.30 (m, 6H, Ar-H, 6-H).

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.26; H, 5.68; N, 8.86.

Compound **6a** was prepared from **4a** by the same method in 85% yield, mp 168-170°; uv (ethanol) (*p*H 1): λ max 268 nm (8096); uv (ethanol) (*p*H 11): λ max 266 (6646); $[\alpha]_D^{18}$ = -7.78° (ethanol); ^{1}H nmr (DMSO-d$_6$): δ 1.93 (m, 1H, 2'-H), 2.54 (m, 1H, 2'-H), 3.39 (s, 2H, 5-CH$_2$), 3.54 (dd, 2H, 5'-H, J = 18.4, 3.3 Hz), 4.12 (m, 1H, 4'-H), 4.22 (d, 1H, 3'-H, J = 5.7 Hz), 6.09 (dd, 1H, 1'-H, J = 7.5, 2.7 Hz), 7.15-7.29 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; H, 8.80. Found: C, 60.02; H, 5.92; N, 8.59.

5-Benzyloxybenzyl-2'-deoxyuridine (**5b**) and its α-Anomer **6b**.

These two compounds were prepared from **3b** and **4b** by the method indicated above.

Compound **5b** had mp 157-161°; $[\alpha]_D^{25}$ = +19.11° (ethanol, 0.3); uv (ethanol): λ max 268 nm (10027); ^{1}H nmr (deuteriochloroform): δ 2.09 (m, 2H, 2'-H), 3.51 (s, 2H, 5-CH$_2$), 3.54 (m, 2H, 5'-H), 3.77 (dd, 1H, 4'-H, J = 6, 4 Hz), 4.23 (m, 1H, 3'-H), 5.05 (s, 2H, CH$_2$ of term Bzl), 6.16 (t, 1H, 1'-H, J = 7 Hz), 6.81 (m, 2H, *o*-H of inner Bzl), 6.87 (d, 1H, *p*-H of inner Bzl), 7.18 (t, 1H, *m*-H of inner Bzl), 7.30-7.46 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.14; H, 5.74; N, 6.40.

Compound **6b** was obtained as an amorphous solid; $[\alpha]_D^{25}$ = -3.29° (ethanol, 0.3); uv (ethanol): λ max 268 (10744); ^{1}H nmr (deuteriochloroform): δ 2.10 (m, 1H, 2'-H), 2.55 (m, 1H, 2'-H), 3.55 (m, 4H, 5-CH$_2$, 5'-H), 4.18 (m, 1H, 4'-H), 4.30 (m, 1H, 3'-H), 4.98 (s, 2H, CH$_2$ of term Bzl), 6.04 (dd, 1H, 1'-H), 6.76-6.83 (m, 3H, *o*-,*p*-H of inner Bzl), 7.15 (t, 1H, *m*-H of inner Bzl), 7.30-7.38 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{23}H_{24}N_2O_8$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.89; H, 5.86; H, 6.31.

Benzyl-2,3'-anhydrodeoxyuridine (**7a**).

To a suspension of 1 g (3.14 mmoles) of 5-benzyldeoxyuridine (**5a**) in 5 ml of methylene chloride was added 1 g, (5.7 mmoles) of 2-chloro-1,1,2-trifluorotriethylamine at 10°. The whole was stirred at room temperature for 3 hours. After evaporation of solvent, the residue was chromatographed on silica gel. Elution with methylene chloride:methanol (10:1) gave 630 mg (67%) of **7a**, mp 196-198°; uv (ethanol): λ max 252 nm (8607); ^{1}H nmr (DMSO-d_6): δ 2.43 (m, 1H, 2'-H), 2.58 (d, 1H, 2'-H, J = 12 Hz), 3.49 (m, 2H, 5'-H), 3.52 (s, 2H, 5-CH_2), 4.19 (m, 1H, 4'-H), 5.06 (t, 1H, 3'-H, J = 5.4 Hz), 5.86 (d, 1H, 1'-H, J = 3.8 Hz), 7.10-7.35 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.93; H, 5.60; N, 9.12.

5-Benzyloxybenzyl-2,3'-anhydrodeoxyuridine (**7b**).

This compound was prepared from 5-benzyloxybenzyldeoxyuridine (**5b**) in 80% yield by the method indicated above; uv (ethanol): λ max 252 nm (9351); ^{1}H nmr (deuteriochloroform): δ 2.40 (m, 1H, 2'-H), 2.54 (d, 1H, 2'-H, J = 12.3 Hz), 3.60 (d, 1H, 5-$CH_{2'}$ J = 15.9 Hz), 3.71 (d, 1H, 5-$CH_{2'}$ J = 15.9 Hz), 3.81 (m, 2H, 5'-H), 4.32 (m, 1H, 4'-H), 5.05 (s, 2H, CH_2 of term Bzl), 5.35 (d, 1H, 3'-H), 6.56 (t, 1H, 1'-H, J = 1.1 Hz), 6.80-6.89 (m, 3H, *o*-and *p*-H of inner Bzl), 7.20-7.45 (m, 7H, *m*-H of inner Bzl, Ar-H, 6-H).

Anal. Calcd. for $C_{23}H_{22}N_4O_5$: C, 67.80; H, 5.46; N, 6.89. Found: C, 67.39; H, 5.64; N, 6.65.

5-Benzyl-3'-azido-2',3'-dideoxyuridine (**8a**).

A mixture of 1.5 g (3.33 mmoles) of 5-benzyl-2,3'-anhydrodeoxyuridine (**7a**), dry lithium azide (1.5 g, 30.6 mmoles), ammonium chloride (150 mg) and 30 ml of dry DMF was stirred at 90° for 2 days under nitrogen. The solvent was then evaporated under reduced pressure. To the residue 15 ml of water was added and the mixture was extracted with ether. The ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. After evaporation of solvent, the residue was subjected to chromatography on silica gel and eluted with methylene chloride:ether (10:1), to give 1.18 g (69%) of **8a**; uv (ethanol) (*p*H 1): λ max 266 nm (9886); (*p*H 11): λ max 266 nm (11,043); ^{1}H nmr (DMSO-d_6): δ 2.35 (m, 2H, 2'-H), 3.54 (s, 2H, 5-CH_2), 3.58 (m, 2H, 5'-H), 3.83 (dd, 1H, 4'-H, J = 8.7, 4.2 Hz), 3.39 (m, 1H, 3'-H), 6.09 (t, 1H, 1'-H J = 6.4 Hz), 7.12-7.30 (m, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40. Found: C, 55.68; H, 5.03; N, 20.68.

5-Benzyloxybenzyl-3'-azido-2',3'-dideoxyuridine (**8b**).

This compound was prepared from 5-benzyloxybenzyl-2,3'-anhydrodeoxyuridine (**7b**) in 71% yield by the method indicated above; uv (ethanol) (*p*H 1): λ max 266 nm (9878); (*p*H 11): λ max 266 nm (8301); ^{1}H nmr (deuteriochloroform): δ 2.32 (m, 2H, 2'-H), 3.62 (s, 2H, 5-CH_2), 3.60 (dd, 1H, 5'-H, J = 11.8, 2.4 Hz), 3.70 (dd, 1H, 5'-H, J = 11.8, 2.4 Hz), 3.89 (m, 1H, 4'-H), 4.23 (m, 1H, 3'-H), 5.05 (s, 2H, CH_2 of term Bzl), 6.04 (t, 1H, 1'-H, J = 6.6 Hz), 6.87 (m, 3H, *o*- and *p*-H of inner Bzl), 7.14 (t, 1H, 6-H, J = 1.3 Hz), 7.28 (t, 1H, *m*-H of inner Bzl, J = 7.5 Hz), 7.32-7.48 (m, 10H, ArH).

Anal. Calcd. for $C_{23}H_{23}N_5O_5$: C, 61.47; H, 5.12; N, 15.19. Found: C, 61.46; H, 5.01; N, 15.37.

5-Benzyl-3'-chloro-2',3'-dideoxyuridine (**9a**).

5-Benzyl-2,3'-anhydrodeoxyuridine (**7a**, 200 mg, 0.66 mmole) was dissolved in a solution of 2 ml of 15% hydrogen chloride in DMF. It was stirred at room temperature for 18 hours. The DMF was evaporated under reduced pressure at room temperature. The residue was subjected to chromatography on silica gel and eluted with methylene chloride:ether (10:1) to give 178 mg (79%) of **9a**; uv (ethanol): λ max 266 nm (9360); ^{1}H nmr (DMSO-d_6): δ 2.50 (m, 2H, 2'-H), 3.66 (m, 4H, 5-$CH_{2'}$ 5'-H), 4.15 (m, 1H, 4'-H), 4.42 (m, 1H, 3'-H), 6.21 (t, 1H, 1'-H, J = 6.5 Hz), 7.15-7.39 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{17}N_2O_4Cl$: C, 57.06; H, 5.09; N, 8.32. Found: C, 57.29; H, 5.31; N, 8.29.

5-Benzyloxybenzyl-3'-chloro-2',3'-dideoxyuridine (**9b**).

This compound was prepared in 70% yield from 5-benzyloxybenzyl-2,3'-anhydrodeoxyuridine by the method indicated above; uv (ethanol): λ max 266 nm (9626); ^{1}H nmr (deuteriochloroform): δ 2.42 (m, 2H, 2'-H), 3.61 (m, 4H, 5-$CH_{2'}$ 5'-H), 4.07 (m, 1H, 4'-H), 4.34 (m, 1H, 3'-H), 5.08 (s, 2H, CH_2 of term Bzl), 6.11 (t, 1H, 1'-H, J = 6.4 Hz), 6.80 (m, 3H, *o*- and *p*-H of inner Bzl), 7.10-7.29 (m, 7H, *m*-H of inner Bzl, ArH, 6-H).

Anal. Calcd. for $C_{23}H_{23}N_2O_5Cl$: C, 62.37; H, 5.19; N, 6.37. Found: C, 62.09; H, 5.45; N, 6.17.

5-Benzyl-3'-bromo-2',3'-dideoxyuridine (**10a**).

A solution of 200 mg (0.66 mmole) of 5-benzyl-2,3'-anhydrodeoxyuridine (**7a**), and 2 ml of 10% hydrogen bromide in dry DMF was heated at 85° for 15 minutes. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel and eluted with methylene chloride:ether (10:1) to give 172 mg (68%) of **10a**; uv (ethanol): λ max 266 nm (9333); ^{1}H nmr (DMSO-d_6): δ 2.56 (m, 2H, 2'-H), 3.70 (m, 4H, 5-CH_2, 5'-H), 4.25 (m, 1H, 4'-H), 4.41 (m, 1H, 3'-H), 6.19 (t, 1H, 1'-H, J = 6.1 Hz), 7.18-7.36 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{17}N_2O_4Br$: C, 50.40; H, 4.50; N, 7.35. Found: C, 50.21; H, 4.46; N, 7.32.

5-Benzyloxybenzyl-3'-bromo-2',3'-dideoxyuridine (**10b**).

5-Benzyloxybenzyl-2,3'-anhydrodeoxyuridine (**7b**, 203.2 mg, 0.5 mmole) was dissolved in a solution of 8% hydrogen bromide in dry DMF at 0° and allowed to stand in the refrigerator for 15 hours. The solvent was evaporated under reduced pressure. The residue was subjected to chromatography on silica gel and eluted with methylene chloride:ether 10:1 to yield 177 mg (73%) of **10b**; uv (ethanol): λ max 266 nm (9575); ^{1}H nmr (deuteriochloroform): δ 2.63 (m, 2H, 2'-H), 3.61 (s, 2H, 5-CH_2), 3.69 (m, 2H, 5'-H), 4.24 (m, 1H, 4'-H), 4.36 (m, 1H, 3'-H), 5.06 (s, 2H, CH_2 of term Bzl), 6.85 (m, 3H, *o*- and *p*-H of inner Bzl), 7.21-7.45 (m, 7H, ArH, 6-H).

Anal. Calcd. for $C_{23}H_{23}N_2O_5Br$: C, 56.68; H, 4.76; N, 5.75. Found: C, 56.39; H, 4.46; N, 5.55.

5-Benzyl-3'-iodo-2',3'-dideoxyuridine (**11a**).

5-Benzyl-2,3'-anhydrodeoxyuridine (**7a**, 100 mg, 0.33 mmole) was added to a mixture of hydriodic acid (57%, 0.1 ml) and 1 ml of DMF, and stirred at room temperature for 15 hours. The reaction mixture was evaporated to dryness under reduced pressure at 30°. The residue was extracted with ether, washed with water and then chromatographed on silica gel. Elution with methylene chloride:ether (10:1) yielded 92 mg (65%) of **11a**; uv (ethanol): λ max 266 nm (9295); ^{1}H nmr (deuteriochloroform): δ 2.64 (m, 2H, 2'-H), 3.64 (s, 2H, 5-CH$_2$), 3.71 (m, 2H, 5'-H), 4.25 (m, 2H, 4'-H, 3'-H), 6.07 (t, 1H, 1'-H, J = 5.5 Hz), 7.18-7.38 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{17}N_2O_4I$: C, 44.87; H, 4.00; N, 6.54. Found: C, 45.26; H, 4.17; N, 6.75.

5-Benzyloxybenzyl-3'-iodo-2',3'-dideoxyuridine (**11b**).

5-Benzyloxybenzyl-2,3'-anhydrodeoxyuridine (**7b**, 101 mg, 0.25 mmole) was dissolved in 1 ml of DMF and cooled to -10°, and 0.1 ml of 57% of hydriodic acid was added to it. The reaction mixture was stirred at -10° for 5 hours. After neutralization with sodium bicarbonate solution, the solvent was removed under reduced pressure and the residue was directly applied to a silica gel column. Some impurities were removed by washing with methylene chloride and subsequent elution with methylene chloride:ether (10:1) gave 77 mg (57.6%) of **11b**; uv (ethanol): λ max 266 nm (9433); ^{1}H nmr (deuteriochloroform): δ 2.63 (m, 2H, 2'-H), 3.64 (s, 2H, 5-CH$_2$), 3.20 (m, 2H, 5'-H), 4.26 (m, 1H, 4'-H), 4.38 (m, 1H, 3'-H), 5.06 (s, 2H, CH$_2$ of term Bzl), 6.16 (t, 1H, 1'-H, J = 6.1 Hz), 6.82-6.89 (m, 3H, *o*- and *p*-H of inner Bzl), 7.22-7.44 (m, 7H, ArH, 6-H), 8.53 (br s, 1H, NH).

Anal. Calcd. for $C_{23}H_{23}N_2O_5I$: C, 51.70; H, 4.34; N, 5.24. Found: C, 51.48; H, 4.65; N, 5.05.

5-Benzyl-2',3'-dideoxyuridine (**12a**).

5-Benzyl-3'-bromo-2',3'-dideoxyuridine (**10a**, 500 mg, 1.31 mmoles) was dissolved in 5 ml of ethanol. The solution was subjected to catalytic hydrogenation at atmospheric pressure in the presence of 5% palladium on carbon (0.5 g) and potassium carbonate (0.3 g). It was filtered and evaporated to dryness. The residue was chromatographed on silica gel and eluted with methylene chloride:ether (1:1) to give 314 mg (79%) of **12a**; uv (ethanol) (*p*H 1): λ max 266 nm (10,934); (*p*H 11): λ max 266 nm (8808); ^{1}H nmr (deuteriochloroform): δ 1.77 (m, 1H, 3'-H), 1.97 (m, 2H, 2'-H, 3'-H), 2.32 (m, 1H, 2'-H), 3.66 (s, 2H, 5-CH$_2$), 3.68 (m, 2H, 5'-H), 4.09 (m, 1H, 4'-H), 6.03 (dd, 1H, 1'-H, J = 6.3, 4.1 Hz), 7.20-7.39 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.81; H, 6.15; N, 9.40.

5-Benzyloxybenzyl-2',3'-dideoxyuridine (**12b**).

5-Benzyloxybenzyl-3'-bromo-2',3'-dideoxyuridine (**10b**, 100 mg, 0.205 mmole) was dissolved in 2 ml of toluene containing tributyltin hydride (200 mg, 0.69 mmole) and AIBN (20 mg). The reaction mixture was heated at 85° for 2 hours and the solvent evaporated under reduced pressure. The residue was then chromatographed on silica gel and eluted with 5% methanol in methylene chloride, to give 61 mg (73%) of **12b**; uv (ethanol (*p*H 1): λ max 266 nm (9860); (*p*H 11); (*p*H 11): λ max 266 nm (8506); ^{1}H nmr (deuteriochloroform): δ 1.85 (m, 3H, 3'-H, 2'-H), 2.31 (m, 1H, 2'-H), 3.63 (s, 2H, 5-CH$_2$), 3.66 (m, 2H, 5'-H), 4.12 (m, 1H, 4'-H), 5.07 (s, 2H, CH$_2$ of inner Bzl), 6.02 (dd, 1H, 1'-H, J = 2.5, 6.8 Hz), 6.80-6.90 (m, 3H, *o*- and *p*-H of inner Bzl), 7.20-7.50 (m, 7H, ArH, 6-H), 8.22 (br s, 1H, NH).

Anal. Calcd. for $C_{23}H_{23}N_2O_5I$: C, 51.70; H, 4.34; N, 5.24. Found: C, 51.48; H, 4.65; N, 5.05.

5'-*O*-Trityl-5-benzyldeoxyuridine (**13a**).

A solution of 5-benzyluridine (**5a**, 3.08 g, 10 mmoles) and triphenylmethyl chloride (3.34 g, 10 mmoles) in 30 ml of dry pyridine was heated at 100° for 45 minutes. The reaction mixture was cooled to room temperature and slowly poured into 200 ml of vigorously stirred ice water. The precipitate was filtered, washed with water and dried overnight in a vacuum desiccator over phosphorous pentoxide. Recrystallization from ethanol gave 4.8 g (41%) of **13a**; mp 215-216°; uv (ethanol): λ max 266 nm (10,805): ^{1}H nmr (deuteriochloroform): δ 2.20 (m, 2H, 2'-H), 3.14 (m, 4H, 5'-H, 5-CH$_2$), 3.86 (dd, 1H, 4'-H, J = 8.1, 3.6 Hz), 5.35 (d, 1H, 3'-H, J = 3.6 Hz), 6.20 (t, 1H, 1'-H, J = 6.8 Hz), 6.98-7.50 (m, 21 H, ArH, 6-H).

Anal. Calcd. for $C_{35}H_{32}N_2O_5$: C, 74.98; H, 5.76; N, 4.99. Found: C, 74.74; H, 6.12; N, 4.86.

5'-*O*-Trityl-5-benzyloxybenzyldeoxyuridine (**13b**).

This compound was prepared from **5b** by the same method as above, mp 133-135°; uv (ethanol): λ max 266 nm (8611); ^{1}H nmr (deuteriochloroform): δ 2.28 (m, 1H, 2'-H), 2.36 (m, 1H, 2'-H), 3.09 (d, 1H, 5-CH$_2$, J = 15.2 Hz), 3.35 (d, 1H, 5-CH$_2$, J = 15.2 Hz), 3.72 (d, 2H, 5'-H, J = 3.5 Hz), 3.98 (d, 1H, 4'-H, J = 3.5 Hz), 4.51 (m, 1H, 3'-H), 4.94 (s, 2H, CH$_2$ of term Bzl), 6.35 (t, 1H, 1'-H J = 6.3 Hz), 6.70 (m, 3H, *o*- and *p*-H of inner Bzl), 7.05 (t, 1H, *m*-H of inner Bzl), 7.20-7.64 (m, 21H, ArH, 6-H).

Anal. Calcd. for $C_{42}H_{38}N_2O_6$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.60; H, 5.77; N, 3.94.

5-Benzyl-1-(5'-*O*-trityl-3'-azido-2',3'-dideoxy-β-D-threo-pentafuranosyl)uracil (**14a**).

To a mixture of 5'-*O*-trityl-5-benzyldeoxyuridine (**13a**, 1.12 g, 2 mmoles), triphenylphosphine (783 mg, 3 mmoles) and lithium azide (490 mg, 10 mmoles) in 5 ml of dry DMF was added carbon tetrabromide (1.47 g, 3 mmoles). The mixture was stirred at 35° for 24 hours and then 2 ml of methanol was added. The mixture was allowed to stand at room temperature for 30 minutes. The solvent was removed in vacuum and the residue was washed several times with water and then dissolved in methylene chloride. After drying over magnesium sulfate, the solvent was evaporated and the residue chromatographed on a column of silica gel and eluted with methylene chloride:methanol (30:1) to yield 0.62 g (53%) of **14a**, mp 172-173°; uv (ethanol): λ max 266 nm (9878); ir: 2100 cm^{-1} (C-N$_3$); ^{1}H nmr (deuteriochloroform): δ 1.99 (dd, 1H, 2'-H, J = 2.1, 15.2 Hz), 2.60 (ddd, 1H, 2'-H, J = 6.1, 12.1, 15.2 Hz), 3.16 (dd, 1H, 5'-H, J = 6.1, 10 Hz), 3.44 (dd, 1H, 5'-H, J = 6.1, 10 Hz), 3.48 (dd, 1H, 5-CH$_2$, J = 1.2, 16.1 Hz), 3.64 (dd, 1H, 5-CH$_2$, J = 1.2, 16.1 Hz), 3.98 (m, 1H, 4'-H), 4.13 (dd, 1H, 3'-H, J = 3.6, 5.7 Hz), 6.14 (dd, 1H, 1'-H, J = 2.2, 9.0 Hz), 7.05-7.50 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{35}H_{31}N_5O_4$: C, 71.78; H, 5.34; N, 11.96. Found: C, 71.81; H, 5.34; N, 12.00.

5-Benzyloxybenzyl-1-(5'-*O*-trityl-3'-azido-2',3'-dideoxy-β-D-threo-pentafuranosyl)uracil (**14b**).

This compound was prepared from **13b** by the method indicated above in 71% yield, mp 177-178°; uv (ethanol): λ max 266 nm (8412); ir: 2100 cm^{-1}, (C-N$_3$); ^{1}H nmr (deuteriochloroform): δ 2.01 (dd, 1H, 2'-H, J = 2.0, 15.1 Hz), 2.62 (ddd, 1H, 2'-H, J = 6.2, 8.3, 15.1 Hz), 3.23 (dd, 1H, 5'-H, J = 6.2, 10 Hz), 3.50 (dd, 1H, 5'-H, J = 6.2, 10 Hz), 3.46 (d, 1H, 5-CH$_2$, J = 15.8 Hz), 3.60 (d, 1H, 5-CH$_2$, J = 15.8 Hz), 3.98 (m, 1H, 4'-H), 4.16 (dd, 1H, 3'-H, J = 3.5, 5.5 Hz), 4.98 (s, 2H, CH$_2$ of term Bzl), 6.14 (dd, 1H, 1'-H, J = 2.2, 9.0 Hz), 6.72 (m, 3H, *o*- and *p*-H of inner Bzl), 7.04 (m, 1H, *m*-H of Bzl), 7.16 (s, 1H, 6-H), 7.24-7.46 (m, 5H, ArH).

Anal. Calcd. for $C_{42}H_{37}N_5O_5{\cdot}H_2O$: C, 71.08; H, 5.56; N, 7.83.

Found: C, 71.18; H, 5.49; N, 7.50.

5-Benzyl-1-(3'-azido-2',3'-dideoxy-β-D-threo-pentafuranosyl)uracil (**15a**).

A solution of 5-benzyl-1-(5'-*O*-trityl-3'-azido-2',3'-dideoxy-β-D-threo-pentafuranosyl)uracil (**14a**, 700 mg, 1.12 mmoles) in 20 ml of 75% acetic acid was stirred at 80° for 2 hours. After evaporation of the solvent under reduced pressure, the residue was dissolved in methylene chloride, washed with water and concentrated to a small volume. It was chromatographed on silica gel and eluted with methylene chloride:methanol (20:1) to yield 310 mg (80%) of **15a**; uv (ethanol) (*p*H 1): λ max 267 nm (8971); (*p*H 11): λ max 267 nm (7340); ir: 2100 cm^{-1}, (C-N$_3$); ^{1}H nmr (deuteriochloroform): δ 1.95 (dd, 1H, 2'-H, J = 2.1, 14.9 Hz), 2.67 (m, 1H, 2'-H), 3.55 (m, 4H, 5-CH$_2$, 5'-H), 3.96 (m, 1H, 4'-H), 4.38 (m, 1H, 3'-H), 6.01 (dd, 1H, 1'-H, J = 8.0, 2.5 Hz), 7.19-7.33 (m, 6-H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.39. Found: C, 55.82; H, 5.15; N, 19.98.

5-Benzyloxybenzyl-1-(3'-azido-2',3'-dideoxy-β-D-threo-pentafuranosyl)uracil (**15b**).

This compound was prepared from **14b** by the method indicated above in 87% yield, mp 141-142°; uv (ethanol (*p*H 1): λ max 266 nm (8594); (*p*H 11): λ max 266 nm (8256); ^{1}H nmr (deuteriochloroform): δ 2.10 (ddd, 1H, 2'-H, J = 2.2, 3.1, 14.9 Hz), 2.65 (ddd, 1H, 2'-H, J = 1.2, 7.7, 14.9 Hz), 3.67 (m, 4H, 5-CH$_2$, 5'-H), 4.04 (m, 1H, 4'-H), 4.21 (m, 1H, 3'-H), 5.04 (s, 2H, CH$_2$ of term Bzl), 6.16 (dd, 1H, 1'-H, J = 3.1, 7.7 Hz), 6.85 (m, 3H, *o*- and *p*-H inner Bzl), 7.21-7.45 (m, 7H, ArH, 6-H).

Anal. Calcd. for $C_{23}H_{23}N_5O_5$: C, 61.47; H, 5.12; N, 15.07. Found: C, 61.06; H, 5.20; N, 15.07.

5-Benzyl-5'-azido-2',5'-dideoxyuridine (**16a**).

To a mixture of 5-benzyl-2'-deoxyuridine (**5a**, 954 mg, 3 mmoles), triphenylphosphine (787 mg, 3 mmoles) and dry lithium azide (730 mg, 15 mmoles) in 10 ml of dry DMF there was added 1.01 g of carbon tetrabromide (3 mmoles) and the mixture stirred at room temperature for 24 hours. Two ml of methanol was added and the mixture stirred for 30 minutes. After evaporation of solvent under reduced pressure, the product was extracted with methylene chloride and then washed with water. Methylene chloride was removed under reduced pressure and the residue was subjected to chromatography on silica gel. Elution using methylene chloride:methanol (20:1) yielded a solid. Recrystallization from methanol gave 420 mg (41%) of pure **16a**, mp 167-168°; uv (ethanol) (*p*H 1): λ max 266 nm (9070); (*p*H 11): λ max 266 nm (7218); ir: 2100 cm^{-1}, (C-N$_3$); ^{1}H nmr (deuteriochloroform): δ 2.12 (m, 1H, 2'-H), 2.21 (m, 1H, 2'-H), 3.49 (m, 2H, 5'-H), 3.56 (s, 2H, 5-CH$_2$), 3.83 (m, 1H, 4'-H), 4.16 (m, 1H, 3'-H), 6.19 (t, 1H, 1'-H, J = 6.8 Hz), 7.18-7.50 (m, 6H, ArH, 6-H).

Anal. Calcd. for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.39. Found: C, 56.08; H, 5.22; N, 20.43.

5-Benzyloxybenzyl-5'-azido-2,3-dideoxyuridine (**16b**).

This compound was prepared from **5b** by the method indicated above, in 79% yield, mp 141-142°; uv (ethanol) (*p*H 1): λ max 266 m, (11,177); (*p*H 11): λ max 266 nm (9588); ^{1}H nmr (deuteriochloroform): δ 2.12 (m, 1H, 2'-H), 2.35 (m, 1H, 2'-H), 3.39 (dd, 1H, 5'-H, J = 4.1, 13.0 Hz), 3.47 (dd, 1H, 5'-H, J = 4.1, 13.0 Hz), 3.63 (dd, 2H, 5-CH$_{2'}$ J = 16.1, 19.9 Hz), 3.96 (dd, 1H, 4'-H, J = 4.1, 6.0 Hz), 4.30 (m, 1H, 3'-H), 5.05 (s, 2H, CH$_2$ of term Bzl), 6.22 (t, 1H, 1'-H, J = 6.7 Hz), 6.85 (m, 3H, *o*- and *p*-H of inner Bzl), 7.06 (t, 1H, 6-H, J = 1.0 Hz), 7.22-7.45 (m, 6H, ArH).

Anal. Calcd. for $C_{23}H_{23}N_5O_5$: C, 61.46; H, 5.16; N, 15.58. Found: C, 61.19; H, 4.91; N, 15.29.

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