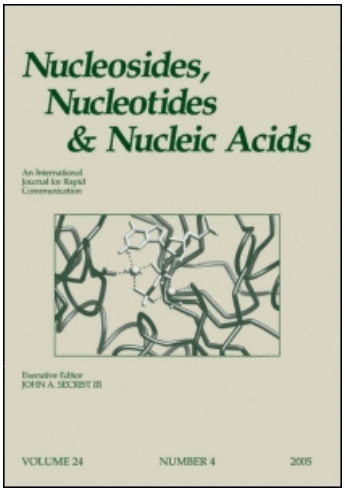

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POLYDEOXYAMINOHEXOPYRANOSYLNUCLEOSIDES. SYNTHESIS OF 1-(2,3,4-TRIDEOXY-3-NITRO-β-D-*erythro*- AND *threo*-HEXOPYRANOSYL)-URACILS FROM URIDINE[1]

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Abstract. The first synthesis of nitro-multideoxy-sugar containing nucleosides was achieved. 1-(4,6-*O*-Benzylidene-3-deoxy-3-nitro-β-D-glucopyranosyl)uracil (**3**) was converted in 75% yield into 1-(4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-*arabino*hexopyranosyl)uracil (**7**) by acetylation followed by $NaBH_4$ reduction in methanol. De-*O*-benzylidenation with CF_3CO_2H afforded crystalline 1-(2,3-dideoxy-3-nitro-β-D-*arabino*hexopyranosyl)uracil (**8**) was obtained in 87% yield. Raney Ni reduction of **8** afforded the corresponding 3'-amino-nucleoside **9**. Acetylation of **8** followed by $NaBH_4$ treatment afforded an 8:1 mixture from which 1-(2,3,4-trideoxy-3-nitro-β-D-*threo*hexopyranosyl)-uracil (**14**) was obtained in pure crystalline form. After Raney Ni reduction of the mixture, 1-(3-amino-2,3,4-trideoxy-β-D-*threo*-hexopyranosyl)uracil (**16**) and its *erythro* epimer **21** were isolated. 1-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*lyxo*hexopyranosyl)uracil (**24**) was prepared in 72% yield from 1-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-galactopyranosyl)uracil (**4**) by acetylation and subsequent reduction with $NaBH_4$. De-*O*-benzylid-enation of **23** afforded 1-(2,3,4-trideoxy-3-nitro-β-D-*lyxo*hexopyranosyl)uracil (**25**) in 83% yield. Schmidt-Rutz reaction of **25** followed by $NaBH_4$ reduction afforded a mixture of *threo* and *erythro* isomers of 2',3',4'-trideoxy-3'-nitro-hexopyranosyluracil, from which pure **16** and **21** were obtained.

INTRODUCTION

Nitro-sugar[2] containing nucleosides have been mainly synthesized from natural ribo-nucleosides by Baer-Fischer reaction:[3] *i.e.*, periodate oxidation to the corresponding 2',3'-dialdehyde, followed by base-catalyzed cyclization with nitromethane to give 3'-nitrohexopyranosyl nucleosides.[4-8] There are a few exceptions for the synthesis of nitro-sugar

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This paper is dedicated to the 75th birthday of Professor Yoshihisa Mizuno.

nucleosides, which include the use of nitroethane instead of nitromethane in the cyclization with a nucleoside dialdehyde,[9] condensation of a protected nitrosugar with purines,[10,11] and condensation of nitromethane with a 3',5'-bisprotected 2'-keto-uridine to form a branched sugar nucleosides.[12] These nitro-sugar nucleosides have, except in one occasion,[12] been used solely as intermediates for amino-sugar nucleosides. The chemistry of nitro-sugar nucleosides has little been developed. In this report, we describe the first synthesis of nucleoside containing a nitro-multi-deoxysugar by exploitation of Schmidt-Rutz reaction.

We have earlier demonstrated that cyclization of "uridine 2',3'-dialdehyde" (FIGURE 1) in the presence of nitromethane gave crystalline sodium *aci*-nitronate. Upon neutralization in non-aqueous conditions, 1-(3-deoxy-3-nitro-β-D-galactopyranosyl)uracil (**2**) was obtained together with the gluco isomer (**1**).[13] Under aqueous conditions, however, **1** was obtained almost exclusively.[4, 14] Later, it was found that the crystalline **1** origninally reported was contaminated with **2**.[15,16]

A crude mixture of **1** and **2**, prepared from uridine,[14] was treated with α,α-dimethoxytoluene (benzaldehyde dimethylacetal) in DMF in the presence of *p*-toluenesulfonic acid afforded a mixture, from which 1-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranosyl)uracil (**3**) and 1-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-galactopyranosyl)-uracil (**4**) were isolated in 68% and 11% yield, respectively. Dehydration of nitrohydrin *via* acetylation is known as Schmidt-Rutz reaction.[17] Compound **3** was acetylated with acetic anhydride in ethyl acetate in the presence of *p*-dimethylaminopyridine, and the unstable product **5** (SCHEME 1) which already was contaminated with **6**, was treated with $NaBH_4$ in MeOH to give crystalline 1-(4,6-*O*-benzylidene-2,3-dideoxy-β-D-*arabino*hexopyranosyl)-uracil (**7**) in 75% overall yield from **3**. De-*O*-benzylidenation of **7** with 90% aqueous trifluoroacetic acid afforded 1-(2,3-dideoxy-3-nitro-β-D-*arabino*hexopyranosyl)uracil (**8**) in crystalline form in 87% yield. The large $J_{3',4'}$ value of 9.5 Hz clearly established H3' and H4' to be in the di*axial* disposition, *i.e.*, the *arabino*hexopyranosyl configuration. No *ribo*hexosyl isomer was detected in the reaction mixture. Raney Ni reduction of **8** resulted in 1-(3-amino-2,3-dideoxy-β-D-*arabino*hexopyranosyl)uracil (**9**) which was further converted into the triacetate **10**.

Acetylation of the 3'-nitro nucleoside **8** gave diacetate **11** which, without purification, was treated with $NaBH_4$ in methanol (SCHEME 2). Under the basic conditions, Schmits-

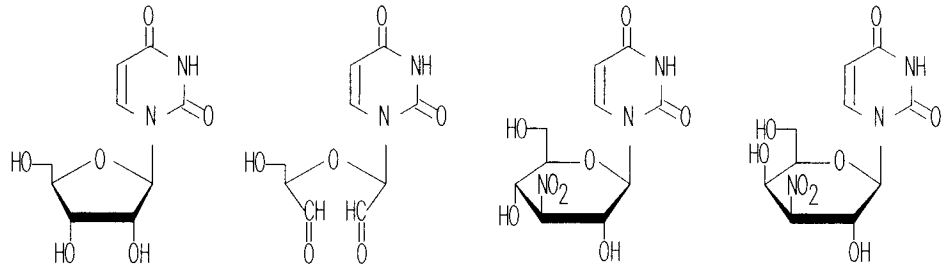
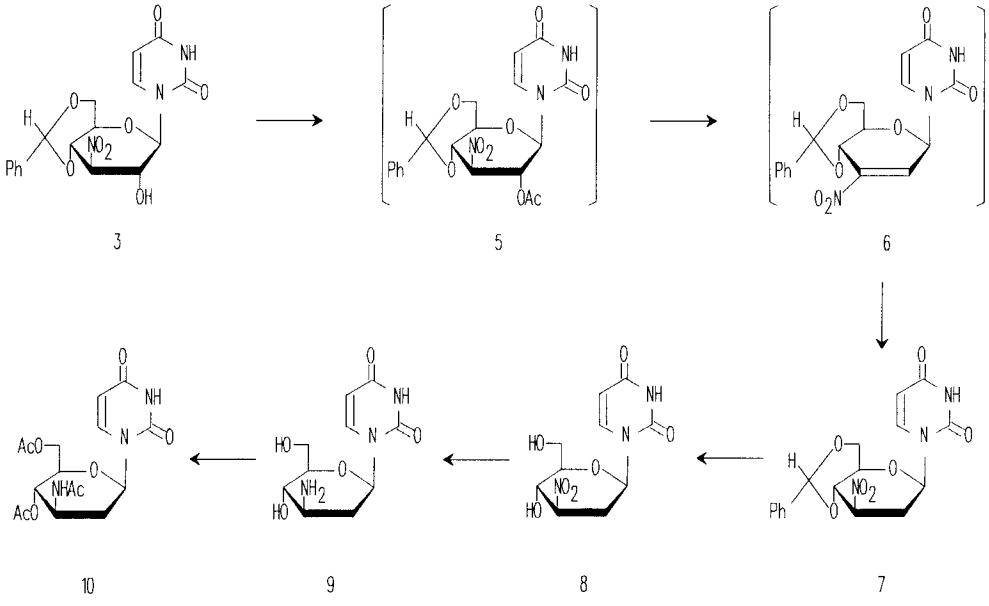
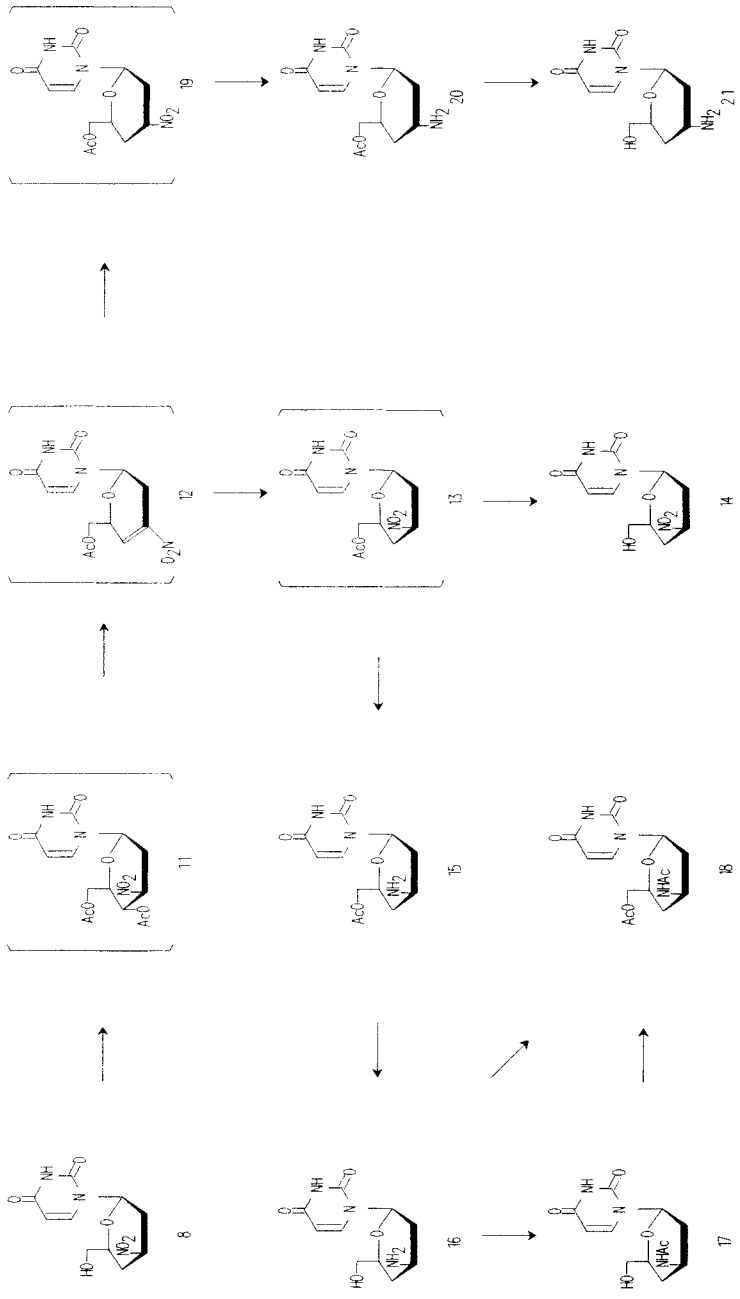


FIGURE 1



SCHEME 1



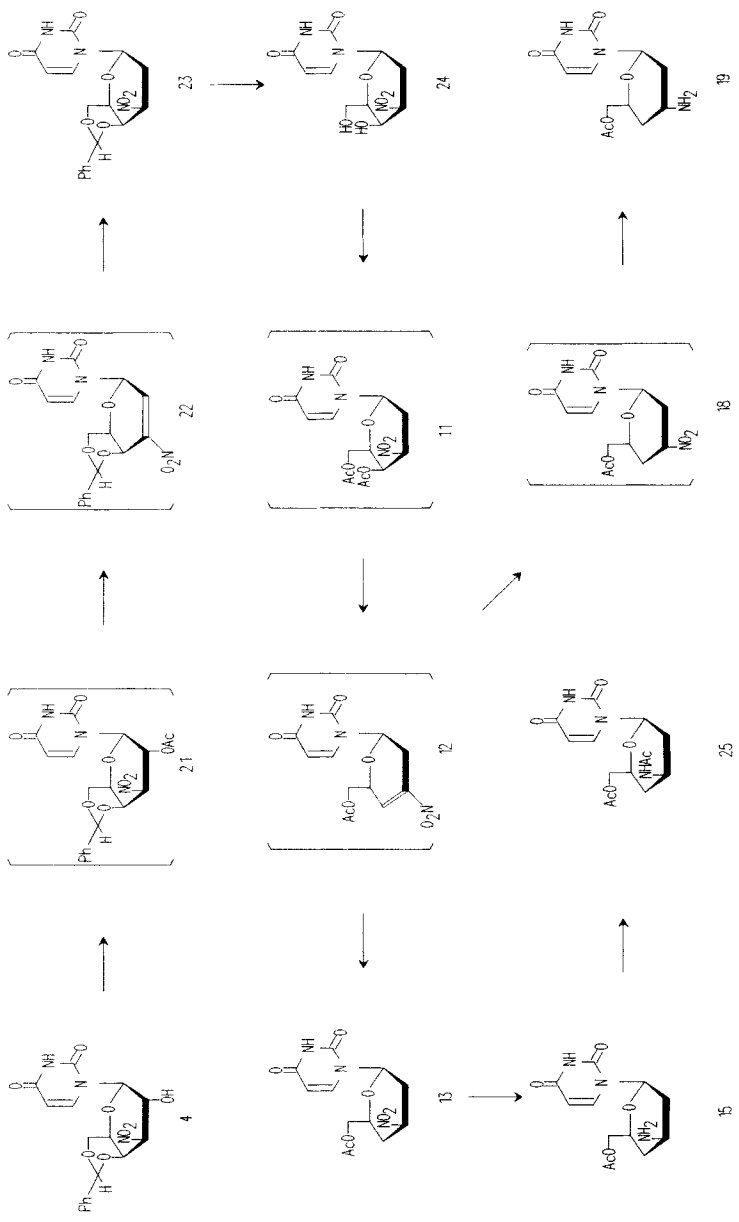
SCHEME 2

Rutz reaction occurred first, and the resulting olefin **12** was then reduced. In addition to 1-(6-*O*-acetyl-2,3,4-trideoxy-3-nitro-β-D-*threo*hexopyranosyl)uracil (**13**), a minor product was always formed. The broad multiplet of H3' of **13** was indicative of axial conformation for H3', but when **13** was converted in two steps into the 3'-amino nucleoside **16**, H3' in ^{1}H NMR appeared as first order triple triplets coupling strongly with two adjacent *axial* protons ($J_{2'a,3'} = J_{3',4'a} = 11.4$ Hz) weakly with equatorial protons ($J_{2'e,3'} = J_{3',4'e} = 4.3$ Hz) clearly establishing the 3'-amino-2',3',4'-trideoxy-β-D-*threo*hexopyranosyl structure for **16**, since no epimerization should have taken place at C1' or C5'. Treatment of **16** with acetic anhydride in methanol afforded 1-(3-acetamido-2,3,4-tri-deoxy-β-D-*threo*hexopyranosyl)uracil (**17**). Although the monoacetyl derivative **17** was obtained as colorless crystals, 1-(3-acetamido-6-*O*-acetyl-2,3,4-trideoxy-β-D-*threo*hexopyranosyl)uracil (**18**) did not crystallize even after chromatographic purification.

The minor product **20** was isolated in pure state in 10.5% yield after reduction followed by chromatographic separation from the major component **15**. De-*O*-acetylation of **20** gave crystalline 1-(3-amino-2,3,4-trideoxy-β-D-*erythro*hexopyranosyl)uracil (**21**). The *erythro* structure for **21** is obvious from the ^{1}H NMR analysis. The first order quintet for H3'($J_{2'a,3'} = J_{2'e,3'} = J_{3',4'a} = J_{3',4'e} = 3.1$ Hz) clearly shows that this proton is in the *equatorial* orientation. Thus, **21** is the C3' epimer of **16**. It should be interesting to note that a very similar mixture was obtained from 3'-nitro-galacto nucleoside **4** (*vide infra*).

Acetylation of **4**, followed by $NaBH_4$ treatment afforded crystalline 1-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-*lyxo*hexopyranosyl)uracil (**24**, SCHEME **3**) in 71% yield. No evidence was obtained for the formation of the *xylo* isomer. Acidic de-*O*-benzylidenation afforded 1-(3-deoxy-3-nitro-β-D-*lyxo*hexopyranosyl)uracil (**25**), which was subjected to Schmidt-Rutz reaction and $NaBH_4$ reduction to give a mixture, from which **13** was isolated in crystalline form in 58.5% yield. After Raney Ni reduction of the mixture from the mother liquor followed by silica gel column chromatography, nucleosides **15** and **20** were obtained. Saponification of these nucleosides afforded the crystalline 3'-amino nucleosides (**16** and **21**, respectively). These nucleosides were identical with the samples of **15, 16, 20** and **21** obtained from **3**.

In summary, we synthesized 3'-amino-2',3',4'-trideoxy-β-D-*erythro*- and *threo*-hexopyranosyl-uracils (**16** and **21**) from uridine. These compounds can be viewed as homologues of 3'-amino-2',3'-dideoxynucleosides.



SCHEME 3

EXPERIMENTAL

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX90Q spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (qualtet), m (multiplet), dd (double doublet), brs (broad singlet), brd (broad doublet). Exchangeable signals are reported as those, which disappear upon exchange with D_2O. Values given for coupling constants are first order. TLC was performed on Uniplates (Analtech Co., Newark, DE) and column chromatography on Woelm silica gel (70-230 mesh). Microanalyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN).

1-(4,6-*O*-Benzylidene-3-deoxy-3-nitro-β-D-glucopyranosyl)uracil (3). To a solution of crude **1** (70 g, 0.23 mol) in a mixture of dry DMF (100 mL) and benzaldehyde dimethylacetal (45 mL) was added TsOH·H_2O (3.0 g). The mixture was stirred at 50-55 °C under reduced pressure (ca. 20 mmHg). After 24 h, TsOH·H_2O (1 g) and benzaldehyde dimethylacetal (10 mL) were charged, the stirring continued for further 8 h, and then the reaction was quenched by addition of EtOAc (88 mL). The mixture was extracted with H_2O (100 mL x 5). The organic layer was dried (Na_2SO_4), condensed to dryness *in vacuo*, and the residue was tritulated with cyclohexane (150 mL x 2). Recrystallization of the residue from hot EtOH afforded pure **1-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranosyl)uracil (3)**, 61.3 g (68.1%), mp 258-9 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 3.84 (m, 2 H, H6',6"), 4.32 (m, 3 H, H2',4',5'), 5.26 (t, 1 H, H3', $J_{2',3'} = J_{3',4'} = 10.1$ Hz), 5.68 (s, 1 H, PhC*H*=), 5.74 (d, 1 H, H1', $J_{1',2'} = 7.9$ Hz), 5.82 (d, 1 H, H5, $J_{5,6} = 8.2$ Hz), 6.50 (d, 1 H, 2'-OH, exchangeable), 7.39 (s, 5 H, Ph), 7.87 (d, 1 H, H6, $J_{5,6} = 8.2$ Hz), 11.44 (brs, 1 H, NH, exchangeable). *Anal.* Calcd for $C_{17}H_{17}N_3O_8$: C, 52.18; H, 4.38; N, 10.74. Found: C, 52.30; H, 4.49; N, 10.71.

The mother liquer was chromatographed over a silica gel column (6.5 x 35 cm) using 8 % EtOH in $CHCl_3$. Compound **3** (4.3 g) was eluted first to give a total yield of 72.4% (65.6 g), followed by a mixture of **3** and **4** (5 g), and then **1-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-galactopyranosyl)uracil (4)** was obtained, 7.6 g (7.8 %) after recrystallization from EtOH, mp 243-4 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 4.02 (s, 1 H, H5'), 4.14 (s, 2 H, H6',6"), 4.46 (m, 1 H, H2'), 4.82 (brs, 1 H, H4'), 5.37 (dd, 1 H, H3', $J_{2',3'} = 9.8$, $J_{3',4'} = 3.7$

Hz), 5.68 (s, 1 H, PhC*H*=), 5.72 (d, 1 H, H1', $J_{1',2'}$ = 9.2 Hz), 5.76 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 6.22 (d, 1 H, 2'-OH, exchangeable), 7.39 (s, 5 H, Ph), 7.61 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz), 11.45 (brs, 1 H, NH, exchangeable). *Anal.* Calcd for $C_{17}H_{17}N_3O_8.H_2O$: C, 49.88; H, 4.68; N, 10.26. Found: C, 50.25; H, 4.50; N, 10.05.

1-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*arabino*hexopyranosyl)uracil (7). To a suspension of **3** (22.68 g, 60 mmol) and *p*-dimethylaminopyridine (2.0 g) in EtOAc (400 mL) was added Ac_2O (11.4 mL, 120 mmol), and the mixture was stirred at room temperature for 30 min. A clear solution resulted was extracted with H_2O (100 mL x 3), dried (Na_2SO_4), concentrated to dryness *in vacuo*, and then the residue was dissolved in MeOH (400 mL). To the solution was added $NaBH_4$ (10 g) portionwise within 15 min, and the mixture was stirred at room temperature until precipitation of colorless crystals occurred (ca. 30 min). The precipitates were collected by filtration, and washed well with EtOH and Et_2O to give 9.15 g (40.7%) of **7**. The filtrate was acidified with 80% aqueous AcOH (15 mL), and concentrated to dryness *in vacuo*. The residue was dissoved in EtOAc (250 mL), washed with H_2O (50 mL x 3), dried (Na_2SO_4), concentrated *in vacuo*, and crystallized from EtOH to give 7.26 g of **7**, a total yield of 16.42 g, 75.4%, mp 243-4 °C. ^{1}H NMR (DMSO-d_6) δ: 2.54 (m, 2 H, H2',2"), 3.83 (m, 2 H, H6',6"), 4.27 (m, 2 H, H4',5'), 5.46 (m, 1 H, H3'), 5.69 (d, 1 H, H5, $J_{5,6}$ = 8.0 Hz), 5.73 (s, 1 H, PhC*H*=), 6.07 (m, 1 H, H1'), 7.39 (s, 5 H, Ph), 7.90 (d, 1 H, H6, $J_{5,6}$ = 8.0 Hz), 11.48 (brs, 1 H, NH, exchangeable). *Anal.* Calcd for $C_{17}H_{17}N_3O_7$: C, 54.40; H, 4.57; N, 11.19. Found: C, 54.62; H, 4.73; N, 11.25.

1-(2,3-Dideoxy-3-nitro-β-D-*arabino*hexopyranosyl)uracil (8). Compound **7** (1.62 g, 4.3 mmol) was treated with 90% aqueous CF_3CO_2H (10 mL) for 3 h. After removal of solvent *in vacuo*, traces of CF_3CO_2H were removed by several co-evaporations with 50% aqueous EtOH, and the residue was crystallized from H_2O to give 1.08 g (87%) of **8**, mp 168-8 °C (dec).^{1}H NMR (DMSO-d_6) δ: 2.37 (m, 2 H, H2',2"), 3.47-3.99 (m, 4 H, H4',5',6',6"), 5.37 (m, 1 H, H3'), 5.64 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 5.87 (m, 1 H, H1'), 7.87 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz), 11.42 (brs, 1H, NH, exchangeable); (pyridine-d_5) δ: 2.21-2.40 (m, 2 H, H2'a,e), 3.78 (m, 2 H, H3',5'), 3.99 (d, 2 H, H6',6", spacing 2.8 Hz), 4.26 (t, 1 H, H4', $J_{3',4'}$ = $J_{4',5'}$ = 9.5 Hz), 5.55 (d, 1 H, H5, $J_{5,6}$ = 7.9), 6.04 (dd, 1 H, H1', $J_{1',2'e}$ = 4, $J_{1',2'a}$ = 9.2 Hz), 7.54 (d, 1 H, H6, $J_{5,6}$ = 7.9 Hz). *Anal.* Calcd for $C_{10}H_{13}N_3O_7$: C, 41.82; H, 4.56; N, 14.63. Found: C, 41.66; H, 4.68; N, 14.44.

1-(3-Amino-2,3-dideoxy-β-D-*arabino*hexopyranosyl)uracil (9). A mixture of **8** (2.87 g, 10 mmol) and activated Raney Ni (6 g, wet weight) in 40% aqueous EtOH (50 mL) was shaken for 1 h in a Parr apparatus in an H_2 atmosphere (40 psi at the initial pressure). The catalyst was filtered and washed well with aqueous EtOH. The combined filtrate and washings were evaporated to dryness *in vacuo*, and the residue was crystallized from EtOH to give 2.25 g of **8** (88%), mp 246-7 °C (dec). ^{1}H NMR (pyridine-d_5) δ: 1.83-2.18 (m, 1 H, H2'a), 2.31-2.42 (m, 1 H, H2'e), 3.31 (m, 1 H, H3'), 3.91 (m, 2 H, H4',5'), 4.30 (brs, 2 H, H6',6"), 5.94 (d, 1 H, H5, $J_{5,6}$ = 7.9 Hz), 6.04 (brs, 1 H, H1'), 7.90 (d, 1 H, H6, $J_{5,6}$ = 7.9 Hz). *Anal.* Calcd for $C_{10}H_{15}N_3O_5 \cdot 1/4H_2O$: C, 45.89; H, 5.97; N, 16.05. Found: C, 46.23; H, 6.31; N, 16.03.

1-(3-Acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*arabino*hexopyranosyl)uracil (10). To a solution of **9** (1.5 g, 5.8 mmol) in dry pyridine (100 mL) was added Ac_2O (3.3 mL). The mixture was stirred for 4.5 h, evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (3 x 10 cm) using 4% EtOH/$CHCl_3$ as the eluent. The UV absorbing fractions were collected, condensed to dryness in vacuo, and the residue was crystallized from benzene to give 2.2 g of **10** (98%), mp 104-5 °C. ^{1}H NMR (DMSO-d_6) δ: 1.77 (s, 3 H, NAc), 1.99 (m, 8 H, 2 OAc overlapped with H2'a,e), 4.06 (m, 4 H, H3',5',6',6"), 4.73 (m, 1 H, H4'), 5.69 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 5.86 (m, 1 H, H1'), 7.62 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz), 7.92 (brs, 1 H, N*H*Ac), 11.42 (brs, 1 H, 3N*H*). *Anal.* Calcd for $C_{16}H_{21}N_3O_8$: C, 50.13; H, 5.52; N, 10.96. Found: C, 50.24; H, 5.72; N, 10.71.

1-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*lyxo*hexopyranosyl)uracil (24). A mixture of **4** (4.5 g, 11.5 mmol), 4-dimethylaminopyridine (500 mg) and Ac_2O (2mL) in EtOAc (500 mL) was stirred at room temperature for 20 min, then extracted with H_2O (30 mL x 3), dried (Na_2SO_4), evaporated *in vacuo*, and the residue was dissolved in MeOH (200 mL). To the solution was added portionwise $NaBH_4$ (2 g, over 10 min period) with stirring. After 1 h, the mixture was acidified with AcOH (3 mL), and concentrated to a half volume *in vacuo*. Compound **24** precipitated as while crystals was filted and washed with MeOH and Et_2O, 3.1 g (72%). This compound did not have a clear melting point but slowly decomposed above 300 °C. ^{1}H NMR (DMSO-d_6) δ: 2.3-2.5 (m, 2 H, H2'a,e), 3.91 (s, 1H, H4'), 4.16 (brs, 2 H, H6',6"), 4.81 (brs, 1 H, H5'), 5.49 (m, 1 H, H3'), 5.72 (s, 1 H, PhC*H*=), 5.77 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 5.85 (m, 1 H, H1'), 7.40 (s, 5 H, Ph), 7.73 (d, 1 H, H6, $J_{5,6}$

= 8.2 Hz), 11.47 (brs, 1 H, NH). *Anal.* Calcd for $C_{17}H_{17}N_3O_7$: C, 54.40; H, 4.57; N, 11.19. Found: C, 54.41; H, 4.54; N, 11.11.

1-(2,3-Dideoxy-3-nitro-β-D-*lyxo*hexopyranosyl)uracil (25). Coumpound **24** (800 mg) was dissolved in 90% aqueous CF_3CO_2H (20 mL), and the solution was left standing at room temperature for 1 h. The solvent was removed *in vacuo*, and the residue was crystallized from EtOH to give **25** (511 mg, 83%), mp 167-9 °C. ^{1}H NMR (DMSO-d_6) δ: 2.28-2.52 (m, 2 H, H2'a,e), 3.50 (brs, 2 H, H6',6"), 3.71 (brd, 1 H, H4'), 4.27 (brs, 1 H, H5'), 5.20 (brm, 1 H, H3'), 5.73 (m, 2 H, H5,1'), 7.86 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz). *Anal.* Calcd for $C_{10}H_{13}N_3O_7$: C, 41.82; H, 4.56; N, 14.63. Found C, 41.79; H, 4.60; N, 14.60.

1-(2,3,4-Trideoxy-3-nitro-β-D-*threo*hexopyranosyl)uracil (14). A. From compound 8. To a suspension of **8** (5.74 g, 20 mmol) in EtOAc (350 mL) was added 4-dimethylaminopyridine (500 mg), and then Ac_2O (7.6 mL, 80 mmol). The mixture was stirred at room temperature for 40 min, and the resulting solution was was washed with H_2O (50 mL x 3), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in MeOH (250 mL). $NaBH_4$ (4 g) was added portionwise over 10 min to the solution while stirring. After 1 h, the mixture was acidified with 80% aq. AcOH (6 mL), concentrated to dryness *in vacuo*, and the resitue was partitioned between EtOAc (250 mL) and H_2O (50 mL). The organic phase was dried (Na_2SO_4), concentrated *in vacuo*, and the residue was crystallized from MeOH to give 3.14 g, mp 184-188 °C. A second crop 1.90 g (mp 184-188 °C) was obtained from the mother liquor (which was concentrated, and the residue was crystallized from benezene) to make a total yield of 5.04 g, 81% of **1-(6-*O*-acetyl-2,3,4-trideoxy-3-nitro-β-D-hexopyranosyl)uracil** as an approximately 8:1 mixture of the *threo* (**13**) and *erythro* (**19**) isomers. ^{1}H NMR ($CDCl_3$) δ: 1.72-2.18 (m, 2 H, H2'a,4'a), 2.12 (s, 3 H, NAc), 2.42-2.87 (m, 2 H, H2'e,4'e), 3.91-4.05 (m, 1 H, H5'), 4.17-4.25 (m, 2 H, H6',6"), 4.66-4.94 (m, 1 H, H3'), 5.73-5.86 (m, H1' of major product with H5), 6.05 (dd, H1' of minor product, $J_{1',2'e}$ = 2, $J_{1',2'a}$ = 11.0 Hz), 7.35-7.46 (m, 1 H, H6 major and minor), 9.12 (brs, NH of minor), 9.33 (brs, NH of major). *Anal.* Calcd for $C_{12}H_{15}N_3O_7$: C, 46.01; H, 4.83; N, 13.41. Found: C, 46.11; H, 4.95; N, 13.34.

The above mixture (500 mg, 1.6 mmol) was treated with 2% HCl/MeOH (100 mL) for 4 h at room temperature, and then concentrated in vacuo. The residue was co-evaporated several times with EtOH, and then tritulated with EtOH to give **14** (371 mg, 86%), mp 190-2

°C. ^{1}H NMR (DMSO-d_6) δ: 1.54-1.98 (5 lines, 2 H, H2'a,4'a), 2.09-2.38 (m, 2 H, H2'e,4'e), 3.46 (m, 2 H, H6',6"), 3.73 (m, 1 H, H5'), 5.19 (m, 1 H, H3'), 5.65 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 5.75 (dd, 1 H, H1', $J_{1',2'e}$ = 1.5, $J_{1',2'a}$ = 10.4 Hz), 7.79 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz). *Anal.* Calcd for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49. Found: C, 44.47; H, 4.93; N, 15.42.

B. From compound 25. A mixture of **25** (1 g, 3.5 mmol), 4-dimethylaminopyridine (200 mg) in EtOAc (150 mL) and Ac_2O (1 mL) was stirred for 20 min at room temperature, and then extracted with H_2O (20 mL x 3), dried (Na_2SO_4), evaporated *in vacuo*. The residue in MeOH (150 mL) was treated with $NaBH_4$ (800 mg) at room temperature. After 30 min, the mixture was acidified with 80% aqueous AcOH (1.2 mL), concentrated to dryness, and the residue was crystallized from MeOH to give 635 mg (58.5%) of product, mp 184-188 °C. The ^{1}H NMR spectrum of this product was identical with that of the product obtained from **8**, namely, about 8:1 mixture of **13** and **19**.

1-(6-*O*-Acetyl-2,3,4-trideoxy-3-amino-β-D-*threo*hexopyranosyl)uracil (15) and 1-(6-*O*-Acetyl-2,3,4-trideoxy-3-amino-β-D-*erythro*hexopyranosyl)uracil (20). An 8:1 mixture of **13** and **19** (2.0 g) was dissolved in 90% aqueous EtOH (100 mL). Activated Raney Ni (6 g, wet weight) was added to the solution, and the mixture was shaken in an H_2 atmosphere for 1 h. The mixture was concentrated to dryness *in vacuo*, the residue was dissolved in $CHCl_3$ (200 mL), and chromatographed on a silica gel column (3 x 45 cm), and eluted with 8% EtOH/$CHCl_3$ (500 mL) eluting 189 mg (10.5%) of **20** which was obtained as an oil. ^{1}H NMR (DMSO-d_6) δ: 2.03 (s, 3 H, OAc), 5.63 (d, 1 H, H5, $J_{5,6}$ = 8.1 Hz), 6.09 (brd, 1 H, H1', $J_{1',2'a}$ = 8.1 Hz), 7.68 (d, 1 H, H6, $J_{5,6}$ = 8.1 Hz). Further elution with the same solvent (500 mL) gave a mixture of **20** and **15** (82 mg). The column was then washed with 20% EtOH/$CHCl_3$ (2 L) to give **15** (1.34 g, 74%) as an oil. ^{1}H NMR (DMSO-d_6) δ: 2.03 (s, 3 H, OAc), 5.57 (brd, 1 H, H1', $J_{1',2'a}$ = 8.0 Hz), 5.65 (d, 1 H, H5, $J_{5,6}$ = 8.1 Hz), 7.63 (d, 1 H, H6, $J_{5,6}$ = 8.1 Hz).

1-(3-Amino-2,3,4-trideoxy-β-D-*threo*hexopyranosyl)uracil (16). Compound **15** (1.1 g) was treated with NH_3/MeOH (50 mL, saturated at 0 °C) for 24 h. The mixture was concentrated to dryness, and the residue was crystallized from EtOH to give **16** (871 mg, 93%), mp 216-8 °C. ^{1}H NMR (pyridine-d_5) δ: 1.32-1.78 (m, 2 H, H2'a,4'a), 1.93-2.27 (m, 2 H, H2'e,4'e), 3.11 (9 lines, 1 H, H3', $J_{2'e,3'} = J_{4'e,3'}$ = 4.3, $J_{2'a,3'} = J_{4'a,3'}$ = 11.4 Hz), 3.91 (brs, 3 H, H5',6',6"), 5.12 (brs, 3 H, NH_2,OH, exchangeable), 5.83 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 5.98

(dd, 1 H, H1', $J_{1',2'e}$ = 2.1, $J_{1',2'a}$ = 11.0), 7.66 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz). *Anal.* Calcd for $C_{10}H_{15}N_3O_4$: C, 49.78; H, 6.27; N, 17.42. Found: C, 49.70; H, 6.41; N, 17.29.

1-(3-Acetamido-2,3,4-trideoxy-β-D-*threo*hexopyranosyl)uracil (17). To a suspension of **16** (365 mg, 1.5 mmol) in MeOH (100 mL) was added Ac_2O (1 mL), and the mixture was stirred at room temperature for 2 h. After condensation of the mixture *in vacuo*, the residue was crystallized from EtOH to give **17** (409 mg, 95%), mp 231-3 °C. ^{1}H NMR (pyridine-d_5) δ: 1.43-1.86 (m, 2 H, H2'a,4'a), 2.00-2.33 (m, 2 H, H2'e,4'e), 2.04 (s, 3 H, NAc), 3.64-3.85 (m, 3 H, H5', 6',6"), 4.39 (m, 1 H, H3'), 5.67 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 5.98 (dd, 1 H, H1', $J_{1',2'e}$ = 2.1, $J_{1',2'a}$ = 8.9 Hz), 7.54 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz). *Anal.* Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.95; H, 6.14; N, 14.75.

1-(3-Acetamido-6-*O*-acetyl-2,3,4-trideoxy-β-D-*threo*hexopyranosyl)uracil (18). To a solution of **16** (670 mg, 2.8 mmol) in pyridine (10 mL) was added Ac_2O, and the mixture was stirred overnight at room temperature. The reaction was quenched by addition of EtOH (5 mL), and the mixture was concentrated *in vacuo*. The residue was chromatographed on a silica gel column using 8% EtOH/$CHCl_3$ as the eluent to give 900 mg (100%) of **18** as a foam. ^{1}H NMR (pyridine-d_5) δ: 1.15-1.67 (m, 2 H, H2'a,4'a), 1.78 (s, 3 H, NAc), 1.93 (s, 3 H, OAc), 2.00-2.35 (m, 2 H, H2'e,4'e), 3.85 (m, 1 H, H5'), 4.08 (m, 2 H, H6',6"), 4.13 (m, 1 H, H3'), 5.64 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 6.00 (dd, 1 H, H1', $J_{1',2'e}$ = 1.5, $J_{1',2'a}$ = 8.6 Hz), 7.49 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz). *Anal.* Calcd for $C_{14}H_{19}N_3O_6$: C, 51.69; H, 5.89; N, 12.92. Found: C, 51.47; H, 6.00; N, 12.73.

The same compound was obtained from **17** by acetylation.

1-(3-Amino-2,3,4-trideoxy-β-D-*erythro*hexopyranosyl)uracil (21). Compound **20** (150 mg) was dissolved in NH_3/MeOH (20 mL, saturated at 0 °C). After 20 h, the solvent was removed *in vacuo*, and the residue was crystallized from EtOH to give 87 mg (68%) of **21**, mp 209-210 °C (dec). ^{1}H NMR (pyridine-d_5) δ: 163-197 (m, 4 H, H2'a,2'e,4'a,4'e), 3.69 (quintet, 1 H, H3', $J_{2'a,3'} = J_{2'e,3'} = J_{3',4'a} = J_{3',4'e}$ = 3.1 Hz), 3.90 (d, 2 H, H6',6"), 4.70 (7 lines, 1 H, H5' = $J_{4'e,5'} = J_{5',6'} = J_{5',6"}$ = 4.6, $J_{4'a,5'}$ = 13.7 Hz), 4.92 (brs, 3 H, NH_2, OH, dissociable), 5.55 (d, 1 H, H5, $J_{5,6}$ = 8.2 Hz), 6.49 (m, 1 H, H1'), 7.41 (d, 1 H, H6, $J_{5,6}$ = 8.2 Hz). *Anal.* Calcd for $C_{10}H_{15}N_3O_4$: C, 49.78; H, 6.27; N, 17.42. Found: C, 49.61; H, 6.25; N, 17.27.

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