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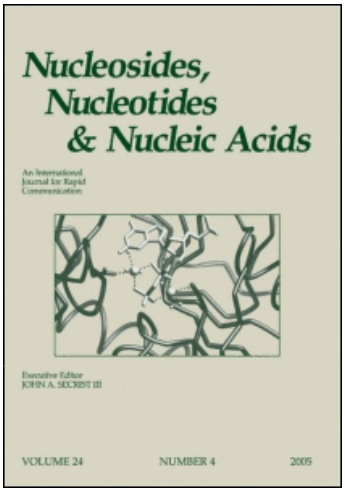

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Synthesis of 2',3'-Didehydro-2',3'-Dideoxy-3'-C-Methyl Substituted Nucleosides

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NUCLEOSIDES & NUCLEOTIDES, 12(8), 865-877 (1993)

SYNTHESIS OF 2′,3′-DIDEHYDRO-2′,3′-DIDEOXY-3′-*C*-METHYL SUBSTITUTED NUCLEOSIDES.

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Abstract. *1-(2,3-Dideoxy-3-C-hydroxymethyl-β-D-threo-pentofuranosyl)-, 1-(2,3-didehydro-2,3-dideoxy-3-C-hydroxymethyl-β-D-glycero-pentofuranosyl)- and 1-(3-C-azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-glycero-pentofuranosyl)uracil, thymine and cytosine were synthesized and evaluated for anti-HIV activity. The synthetic strategy was based on an allylic alcohol transposition of the corresponding 3′-C-methylene-nucleoside analogues.*

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INTRODUCTION

Three nucleoside analogues AZT, DDI and DDC have so far been approved for the treatment of HIV infection. These compounds are targeting the HIV-specific enzyme reversed transcriptase (RT), and exert their antiviral effects either as competitive inhibitors of RT, and/or as chain terminators of the growing viral DNA.

As part of an ungoing project, we are synthesizing 2′-*C*- and 3′-*C*-hydroxymethylsubstituted dideoxynucleoside analogues to evaluate their anti-HIV/antiviral activity.[1-3] We have previously synthesized 2′,3′-didehydro-2′,3′-dideoxy-2′-*C*-hydroxymethyl pyrimidine nucleosides,[2] which were inactive, 2′,3′-dideoxy-2′-*C*-hydroxymethylcytidine[1] which showed a moderate anti-HIV activity and 2′,3′-dideoxy-3′-*C*-hydroxymethylcytidine[3] which showed a potent anti-HIV activity *in vitro*.

We now report on the synthesis and anti-HIV activity of 3′-*C*-hydroxymethyl substituted pyrimidine nucleosides having the *threo* configuration **1-3**, 2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-hydroxymethyl pyrimidine nucleosides **4-6** and 3′-*C*-azidomethyl-2′,3′-didehydro-2′,3′-dideoxy pyrimidine nucleosides **7-9**.

The synthetic methodology used, an allylic alcohol transposition, was developed for the synthesis of the corresponding 2′-isomers.[2,4]

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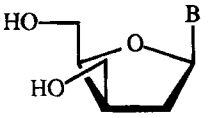
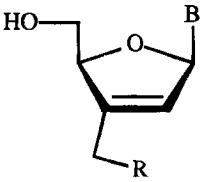
During the course of this work, Czernecki and Ezzitouni[5] have described a route to substances **7** and **8** via a S_N2' opening of 5′-*O*-triphenylmethyl 2,2′-anhydro-3′-*C*-methylene-nucleoside analogues with azide.





1. B= Thymin-1-yl
2. B= Uracil-1-yl
3. B= Cytosin-1-yl

4. R= OH, B= Thymin-1-yl
5. R= OH, B= Uracil-1-yl
6. R= OH, B= Cytosin-1-yl
7. R= N_3, B= Thymin-1-yl
8. R= N_3, B= Uracil-1-yl
9. R= N_3, B= Cytosin-1-yl

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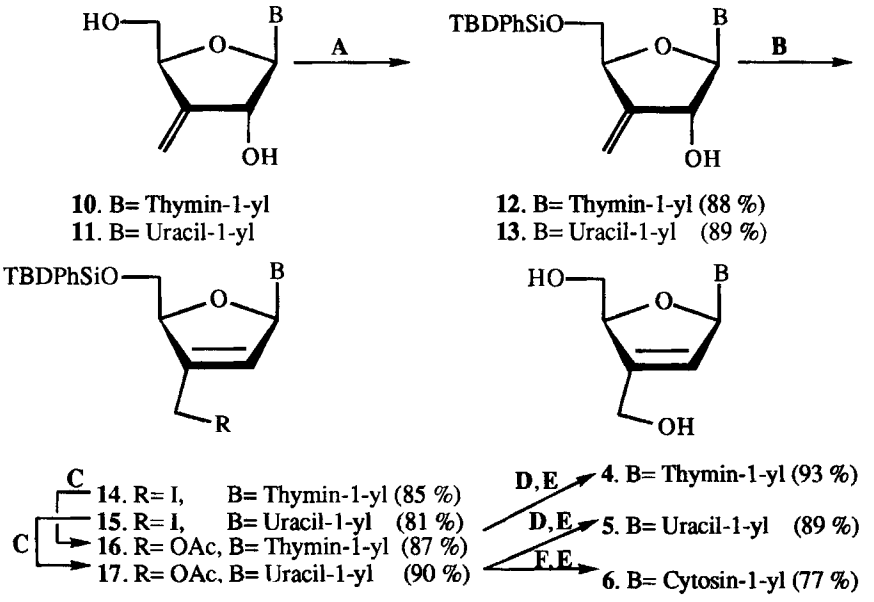
RESULTS AND DISCUSSION

Protection of the primary hydroxyl group of **10** and **11**[6] (*Scheme 1*) as *tert*-butyldiphenylsilyl ethers gave **12** and **13** in 88 % and 89 % yield respectively. Reacting **12** and **13** first with 1.2 equiv. of freshly distilled chlorodiphenylphosphine and 1.2 equiv. imidazole in methylene chloride at 0 °C followed by the addition of 1.2 equiv. iodine in methylene chloride, gave the primary allylic iodides **14** or **15** in 85 % and 81 % yield respectively. Substitution of the allylic iodide in **14** and **15** with tetrabutyl-ammonium acetate[2,7] gave **16** and **17** in 87 % and 90 % yield respectively.

De-*O*-acetylation followed de-*O*-silylation[8] of **16** and **17** gave **4** and **5** in 93 % and 89 % yield respectively. In **17** the uracil moiety was converted to cytosine,[6] and the protecting groups removed to give **6** in 77 % yield.

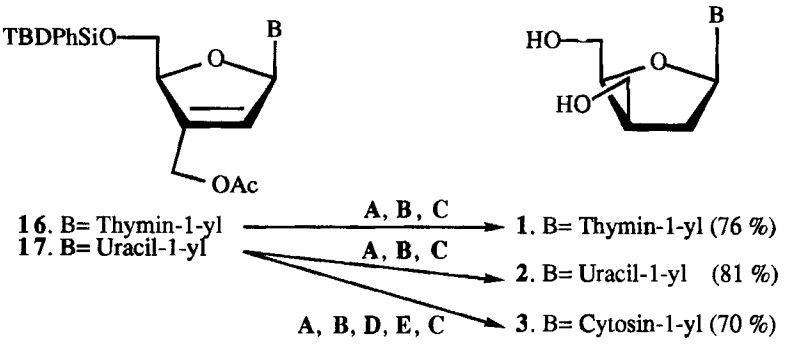
De-*O*-acetylation of **16** and **17** followed by catalytic hydrogenation[2,9,10] (*Scheme 2*) at ambient pressure over $Rh(PPh_3)_3Cl$ in ethanol gave, after de-*O*-silylation, the desired products **1** and **2** in 76 % and 81 % yield, respectively. To obtain the cytidine analogue **3**, compound **17** was de-*O*-acetylated, hydrogenated (*e.g. vide supra*), and re-*O*-acetylated before the uracil moiety was converted to cytosine and deprotected to give **3** in 70 % yield.

Reacting **14** and **15** with 3.5 equiv. sodium azide in DMF at 60 °C (*Scheme 3*) followed by de-*O*-silylation gave **7** and **8** in 95 % and 91 % yield respectively.[2] The cytidine analogue **9** was prepared in 72 % yield from **15** (*e.g vide supra*).



Scheme 1.

A. TBDPhSiCl, pyridine, r.t. **B.** Ph_2PCl, imidazole, CH_2Cl_2, 0 °C then I_2 in CH_2Cl_2. **C.** $N(Bu)_4OAc$, CH_2Cl_2. **D.** MeOH sat. with NH_3. **E.** $N(Bu)_4F$ in THF. **F.** 1,2,4-triazole, $POCl_3$, Et_3N, CH_3CN then MeOH sat. with NH_3, 45 °C.



Scheme 2.

A. MeOH sat with NH_3. **B.** H_2, $Rh(PPh_3)_3Cl$, EtOH. **C.** $N(Bu)_4F$ in THF. **D.** Pyridine-Ac_2O (2:1), **E.** 1,2,4-Triazole, $POCl_3$, Et_3N, CH_3CN then MeOH sat. with NH_3, 50 °C.

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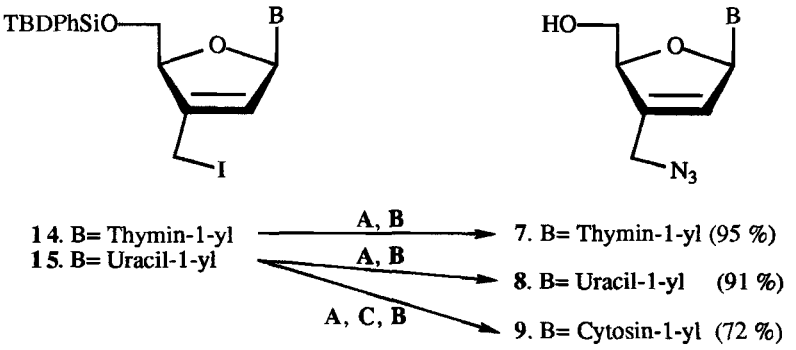

Scheme 3.

A. NaN_3, DMF, 60 °C. **B.** $N(Bu)_4F$ in THF. **C.** 1,2,4-Triazole, $POCl_3$, Et_3N, CH_3CN then MeOH sat. with NH_3, 40 °C.

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BIOLOGICAL RESULTS

Compounds **1-9** were tested for anti-HIV activity and cytopathic effect in a soluble formazan assay.[11] All compounds were found to be inactive.

EXPERIMENTAL

General methods: All solvents were distilled prior to use. Thin layer chromatography was performed using silica gel 60 F-254 (Merck) plates with detection by UV and/or by charring with 8% sulfuric acid. Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35-70 m, Amicon). Organic phases were dried over anhydrous magnesium sulfate or sodium sulfate. Concentrations were performed under reduced pressure. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter. NMR-spectra were recorded on a JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $CDCl_3$ and CD_3OD, and from acetone (^1H: δ 2.23, ^{13}C: δ 31.04) in D_2O. FAB-MS spectra were recorded on a JEOL SX-102 instrument. The pseudo molecular ions were identified via comparison of the experimental and the simulated ion cluster.

1-(5-*O*-*tert*-Butyldiphenylsilyl-3-deoxy-3-*C*-methylene-β-D-*erythro*-pentofuranosyl)thymine (12). *tert*-Butylchlorodiphenylsilane (0.803 ml, 3.09 mmol) was added to a stirred solution of 1-(3-deoxy-3-*C*-methylene-β-D-*erythro*-pentofuranosyl)thymine (**10**) (0.714 g, 2.81 mmol) in pyridine (10 ml). Stirring was continued for 28 h. The solution was concentrated, co-evaporated twice with added toluene and the residue purified by column chromatography (chloroform-methanol 25:1)

yielding **12** (1.22 g, 88 %): $[\alpha]_D$ +107.4° (*c* 0.81, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 12.0 (CH_3, thymine), 19.3 (C-tert), 26.9 (3 x CH_3), 66.3 (C-5′), 76.2 (C-2′), 81.3 (C-4′), 88.8 (C-1′), 109.2 (C-6′), 111.2 (C-5), 127.8-135.6 (8 x ArC, C-6), 146.3 (C-3′), 151.7 (C-4), 164.2 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.06 (s, 9 H, 3 x CH_3), 1.56 (s, 3H, CH_3, thymine), 3.88 (m, 2H, H-5′, H-5′′), 4.72 (m, 3H, H-2′, H-4′, OH), 5.14 (s, 1H, H-6′), 5.48 (s, 1H, H-6′′), 5.93 (d, $J_{1',2'}$= 6.23 Hz, 1H, H-1′), 7.34-7.67 (m, 11H, 10 ArH, H-6), 10.29, (s, 1H, H-3).

1-(5-*O*-*tert*-Butyldiphenylsilyl-3-deoxy-3-*C*-methylene-β-D-*erythro*-pentofuranosyl)uracil (13). *tert*-Butylchlorodiphenylsilane (1.25 ml, 4.81 mmol) was added to a stirred solution of 1-(3-deoxy-3-*C*-methylene-β-D-*erythro*-pentofuranosyl)uracil (**11**) (1.05 g, 4.37 mmol) in pyridine (20 ml). Stirring was continued for 25 h. The solution was concentrated, co-evaporated twice with added toluene and the residue purified by column chromatography (toluene-ethyl acetate 3:1) yielding **13** (1.86 g, 89 %): $[\alpha]_D$ +97.0° (*c* 1.02, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 19.3 (C-tert), 26.9 (3 x CH_3), 66.1 (C-5′), 76.6 (C-2′) 81.9 (C-4′), 89.9 (C-1′), 102.6 (C-5), 110.1 (C-6′), 127.9-135.7 (8 x ArC), 140.1 (C-6), 145.8 (C-3′), 151.6 (C-4), 163.5 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.05 (s, 9 H, 3 x CH_3), 3.76 (m, H-5′, H-5′′), 4.33 (s, 1H, OH), 4.68, 4.75 (m, 2H, H-2′, H-4′), 5.16 (s, 1H, H-6′), 5.47 (m, 2H, H-5, H-6′′), 5.89 (d, $J_{1',2'}$= 5.86 Hz, 1H, H-1′), 7.35-7.80 (m, 11H, 10 ArH, H-6), 9.95 (s, 1H, H-3).

1-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-3-*C*-iodomethyl-β-D-*glycero*-pentofuranosyl)thymine (14). Freshly distilled chlorodiphenylphosphine (0.284 ml, 1.58 mmol) was added, under a nitrogen atmosphere, to a stirred and cooled (ice-bath) solution of **12** (0.650 g, 1.32 mmol) and imidazole (0.108 g, 1.58 mmol) in methylene chloride (25 ml). After 5 min. iodine (0.402 g, 1.58 mmol) dissolved in methylene chloride was added. After stirring for 3 h., methylene chloride (75 ml) and aqueous $NaHCO_3$ (sat.) (50 ml) were added and the phases were separated. The organic phase was washed with water, dried and concentrated. The residue was purified by flash column chromatography (toluene-ethyl acetate 3:2) yielding **14** (0.673 g, 85 %): $[\alpha]_D$ +27.4° (*c* 0.91, $CHCl_3$): Positive FAB-MS (M+H), *m/z* 603; ^{13}C NMR ($CDCl_3$, 25 °C) δ -5.9 (C-6′), 11.6 (CH_3, thymine) 19.5 (C-tert), 27.1 (3 x CH_3), 64.0 (C-5′), 86.0 (C-4′), 88.4 (C-1′), 111.3 (C-5), 124.3-145.1 (8 x ArC, C-2′, C-3′, C-6), 150.8 (C-4), 163.8 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.09 (s, 9 H, 3 x CH_3), 1.32 (s, 3H, CH_3, thymine), 4.00 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 5.05 (m, 1H, H-4′), 5.93 (m, 1H, H-1′), 6.79 (m, 1H, H-2′) 7.07-7.68 (m, 11H, 10 ArH, H-6), 9.23 (s, 1H, H-3).

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1-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-3-*C*-iodomethyl-β-D-*glycero*-pentofuranosyl)uracil (15). Freshly distilled chlorodiphenylphosphine (0.450 ml, 2.51 mmol) was added, under a nitrogen atmosphere, to a stirred and cooled (ice-bath) solution of **13** (1.00 g, 2.09 mmol) and imidazole (0.171 g, 2.51 mmol) in methylene chloride (30 ml). After 5 min. iodine (0.636 g, 2.51 mmol) dissolved in methylene chloride was added. After stirring for 2.5 h., methylene chloride (100 ml) and aqueous $NaHCO_3$ (sat.) (50 ml) were added and the phases were separated. The organic phase was washed twice with water (50 ml), dried and concentrated. The residue was purified by flash column chromatography (toluene-ethyl acetate 3:1) yielding **15** (0.996 g, 81 %): $[\alpha]_D$ +28.6° (*c* 0.98, $CHCl_3$): Positive FAB-MS (M+H), *m/z* 589; ^{13}C NMR ($CDCl_3$, 25 °C) δ -6.4 (C-6′), 19.4 (C-tert), 27.1 (3 x CH_3), 63.3 (C-5′), 86.5 (C-4′), 88.4 (C-1′), 102.6 (C-5), 124.4-144.8 (8 x ArC, C-2′, C-3′, C-6), 150.5 (C-4), 163.1 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.11 (s, 9 H, 3 x CH_3), 3.97 (m, 4H, H-5′, H-5″, H-6′, H-6″), 5.07 (m, 2H, H-4′, H-5), 5.94 (m, 1H, H-1′), 6.88 (m, 1H, H-2′) 7.07-7.78 (m, 11H, 10 ArH, H-6,), 8.98 (s, 1H, H-3).

1-(3-*C*-Acetoxymethyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)thymine (16). Tetrabutylammonium acetate (0.460 g, 1.53 mmol) was added to a stirred solution of **14** (0.613 g, 1.02 mmol) in methylene chloride (40 ml). After 25 h. the mixture was concentrated and the residue purified by column chromatography (toluene-ethyl acetate 1:1) yielding **16** (0.473 g, 87 %): $[\alpha]_D$ +13.9° (*c* 0.92, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 11.7 (CH_3, thymine), 19.5 (C-tert), 20.7 (CH_3, acetate), 27.1 (3 x CH_3), 59.5 (C-6′), 64.5 (C-5′), 85.9 (C-4′), 88.7 (C-1′), 111.3 (C-5), 122.5-143.7 (8 x ArC, C-2′, C-3′, C-6), 150.9 (C-4), 163.8 (C-2), 170.2 (carbonyl, acetate); ^1H NMR ($CDCl_3$, 25 °C) δ 1.06 (s, 9 H, 3 x CH_3), 1.35 (CH_3, thymine), 2.09 (CH_3, acetate), 3.94 (m, 2H, H-5′, H-5″), 4.80 (m, 3H, H-6′, H-6″, H-4′), 5.78 (m, 1H, H-1′), 6.97 (s, 1H, H-2′) 7.16-7.64 (m, 11H, 10 ArH, H-6), 9.02 (H-3).

Anal.Calcd for $C_{29}H_{34}O_6N_2Si$: C, 65.14; H, 6.41; N, 5.24. Found: C, 65.07; H, 6.36; N, 5.11.

1-(3-*C*-Acetoxymethyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)uracil (17). Tetrabutylammonium acetate (0.515 g, 1.71 mmol) was added to a stirred solution of **15** (0.670 g, 1.14 mmol) in methylene chloride (25 ml). After 30 h. the mixture was concentrated and the residue purified by column chromatography (toluene-ethyl acetate 3:1) yielding **17** (0.533 g, 90 %): $[\alpha]_D$ +13.0° (*c* 0.94, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 19.4 (C-tert), 20.7

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(CH_3, acetate), 27.1 (3 x CH_3), 59.3 (C-6'), 63.9 (C-5'), 86.2 (C-4'), 88.6 (C-1'), 102.5 (C-5), 122.8-143.3 (8 x ArC, C-2', C-3', C-6), 150.6 (C-4), 163.2 (C-2), 170.2 (carbonyl, acetate); ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.09 (s, 9 H, 3 x CH_3), 2.10 (s, 3H, CH_3, acetate), 3.97 (m, 2H, H-5', H-5''), 5.01 (m, 4H, H-5, H-4', H-6', H-6''), 5.79 (m, 1H, H-1'), 7.01 (m, 1H, H-2'), 7.35-7.70 (m, 11H, 10 ArH, H-6), 8.82 (s, 1H, H-3).

Anal.Calcd for $C_{28}H_{32}O_6N_2Si$: C, 64.59; H, 6.19; N, 5.38. Found: C, 64.30; H, 6.08; N, 5.45.

1-(2,3-Didehydro-2,3-dideoxy-3-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)thymine (4). A solution of **16** (0.100 g, 0.187 mmol) in methanol saturated with ammonia (5 ml) was stirred at room temperature. After 15 h. the solution was concentrated and the residue dissolved in THF (3 ml). Tetrabutylammonium fluoride (1M in THF) (0.222 ml, 0.222 mmol) was added and after 20 min. the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 8:1) yielding **4** (0.044 g, 93 %): $[\alpha]_D$ +18.6° (*c* 0.86, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 12.3 (CH_3, thymine), 58.7 (C-6'), 62.9 (C-5'), 88.2 (C-4'), 90.2 (C-1'), 111.1 (C-5), 121.4 (C-2'), 139.2 (C-6), 150.3 (C-3'), 152.9 (C-4), 166.6 (C-2); ^{1}H NMR (D_2O, 40 °C) δ 1.83 (d, *J*= 1.1 Hz, 3H, CH_3, thymine), 3.79 (m, 2H, H-5', H-5''), 4.32 (s, 2H, H6', H-6''), 4.69 (m, 1H, H-4'), 5.75 (m, 1H, H-1'), 6.89 (m, 1H, H-2'), 7.81 (d, *J*= 1.1 Hz, 1H, H-6).

Anal.Calcd for $C_{11}H_{14}O_5N_2$: C, 51.97; H, 5.55; N, 11.02. Found: C, 52.05; H, 5.48; N, 10.90.

1-(2,3-Didehydro-2,3-dideoxy-3-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)uracil (5). A solution of **17** (0.100 g, 0.192 mmol) in methanol saturated with ammonia (10 ml) was stirred at room temperature. After 18 h. the solution was concentrated and the residue purified by column chromatography (toluene-ethyl acetate 1:1). The residue was dissolved in THF (3 ml). Tetrabutylammonium fluoride (1M in THF) (0.233 ml, 0.233 mmol) was added and after 20 min. the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 7:1) yielding **5** (0.041 g, 89 %): $[\alpha]_D$ -61.2° (*c* 0.84, water): ^{13}C NMR (D_2O, 40 °C) δ 57.9 (C-6'), 62.0 (C-5'), 87.5 (C-4'), 90.5 (C-1'), 102.4 (C-5), 120.2 (C-2'), 143.6 (C-6'), 149.1 (C-3'), 153.0 (C-4), 167.2 (C-2); ^{1}H NMR (D_2O, 40 °C) δ 3.78 (m, 2H, H-5', H-5''), 4.35 (m, 2H, H6', H-6''), 4.93 (m, 1H, H-4'), 5.84 (d, m, *J*= 8.1 Hz, 2H, H-5, H-1'), 6.89 (m, 1H, H-2'), 7.80 (d, *J*= 8.1 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{12}O_5N_2$: C, 50.00; H, 5.03; N, 11.66. Found: C, 49.85; H, 5.11; N, 11.57.

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1-(2,3-Didehydro-2,3-dideoxy-3-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)cytosine (6). 1,2,4-Triazole (0.279 g, 4.03 mmol) and phosphoryl chloride (0.077 ml, 0.845 mmol) were stirred in acetonitrile (3 ml) under a nitrogen atmosphere. The solution was cooled on an ice-bath and triethylamine (0.535 ml, 3.84 mmol) was added. To this mixture **17** (0.200 g, 0.384 mmol) in acetonitrile (2 ml) was added and the mixture was stirred for 2 h. at room temperature. Triethylamine (0.40 ml) and water (0.20 ml) were added and the resulting mixture was concentrated. The residue was dissolved in methylene chloride (50 ml) and the solution was extracted twice with water (20 ml). The organic phase was dried, concentrated, and the residue dissolved in methanol saturated with ammonia (15 ml). The resulting solution was heated to 45 °C for 50 h, cooled, concentrated and purified by column chromatography (chloroform-methanol 7:1). The residue was dissolved in THF (4 ml) and tetrabutylammonium fluoride (1M in THF) (0.345 ml, 0.345 mmol) was added. After 10 min. the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 2:1) yielding **6** (0.071 g, 77 %): $[\alpha]_D$ +27.4° (*c* 0.99, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 58.7 (C-6′), 63.1 (C-5′), 88.3 (C-4′), 91.4 (C-1′), 96.0 (C-5), 122.2 (C-2′), 143.8 (C-6), 149.6 (C-3′), 158.8 (C-4), 167.9 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 3.78 (m, 2H, H-5′, H-5′′), 4.30 (m, 2H, H6′, H-6′′), 4.82 (m, 1H, H-4′), 5.76 (m, 1H, H-1′), 5.84 (d, *J*= 7.3 Hz, 1H, H-5), 6.94 (m, 1H, H-3′), 7.96 (d, *J*= 7.3 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{13}O_4N_3$ x 0.55 H_2O: C, 48.21; H, 5.70; N, 16.87. Found: C, 48.48; H, 5.39; N, 16.40.

1-(2,3-Dideoxy-3-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)-thymine (1). A solution of **16** (0.100 g, 0.187 mmol) in methanol saturated with ammonia (5 ml) was stirred for 15 h. at room temperature. The solution was concentrated and the residue purified by flash column chromatography (chloroform-methanol 20:1). The residue was dissolved in ethanol (10 ml) and tris(triphenylphosphine)rhodium chloride (0.037 g, 0.040 mmol) was added. The resulting mixture was hydrogenated at atmospheric pressure for 28 h. The resulting dark solution was filtered through Celite and concentrated. The residue was purified by flash column chromatography (chloroform-methanol 15:1). The residue was dissolved in THF (3 ml) and tetrabutylammonium fluoride (1M in THF) (0.222 ml, 0.222 mmol) was added. After 10 min, the solution was concentrated and the residue was purified by column chromatography (chloroform-methanol 7:1) yielding **1** (0.036 g, 76 %): $[\alpha]_D$ +69.6° (*c* 0.48, water): ^{13}C NMR (CD_3OD, 40 °C) δ 12.4 (CH_3, thymine), 34.6 (C-2′), 42.8 (C-3′), 60.7 (C-6′), 62.3 (C-5′), 81.2 (C-4′), 85.3 (C-1′), 111.1 (C-5), 137.4 (C-6), 151.7 (C-4), 165.6 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 1.89, (d, m, *J*= 1.1 Hz, 4H, CH_3, thymine, H-2′), 2.33 (m, 1H, H-2′′), 2.71 (m, 1H, H-3′), 3.83 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.17 (m,

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1H, H-4'), 6.06 (dd, $J_{1,2'}$= 5.9 Hz, $J_{1,2''}$= 5.9 Hz, 1H, H-1'), 7.96 (d, J=1.1 Hz, 1H, H-6).

Anal.Calcd for $C_{11}H_{16}O_5N_2$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.51; H, 6.14; N, 10.78.

1-(2,3-Dideoxy-3-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)-uracil (2). A solution of **17** (0.100 g, 0.192 mmol) in methanol saturated with ammonia (5 ml) was stirred for 10 h. at room temperature. The solution was concentrated and the residue was purified by flash column chromatography (toluene-ethyl acetate 1:4). The residue was dissolved in ethanol (5 ml) and tris(triphenylphosphine)rhodium chloride (0.039 g, 0.42 mmol) was added. The resulting mixture was hydrogenated at atmospheric pressure for 27 h. The resulting dark solution was filtered through Celite and concentrated. The residue was purified by flash column chromatography (chloroform-methanol 20:1). The residue was dissolved in THF (7 ml) and tetrabutylammonium fluoride (1M in THF) (0.229 ml, 0.229 mmol) was added. After 10 min, the solution was concentrated and the residue purified by column chromatography (chloroform-methanol 7:1) yielding **2** (0.038 g, 81 %): $[\alpha]_D$ +66.4° (*c* 0.96, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 35.8 (C-2'), 43.8 (C-3'), 61.6 (C-6'), 62.8 (C-5'), 82.4 (C-4'), 86.70 (C-1'), 102.5 (C-5), 142.6 (C-6), 152.4 (C-4), 166.3 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 1.94, (m, 1H, H-2'), 2.45 (m, 1H, H-2''), 2.73 (m, 1H, H-3'), 3.78 (m, 4H, H-5', H-5'', H-6', H-6''), 4.19 (m, 1H, H-4'), 5.69 (d, J= 8.1 Hz, 1H, H-5), 6.04 (dd, $J_{1,2'}$= 6.2 Hz, $J_{1,2''}$= 5.9 Hz, 1H, H-1'), 8.10 (d, J= 8.1 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{14}O_5N_2$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.34; H, 5.68; N, 11.47.

1-(2,3-Dideoxy-3-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)-cytosine (3). A solution of **17** (0.160 g, 0.307 mmol) in methanol saturated with ammonia (10 ml) was stirred for 22 h. at room temperature. The solution was concentrated and the residue purified by flash column chromatography (chloroform-methanol 20:1). The residue was dissolved in ethanol (10 ml) and tris(triphenylphosphine)rhodium chloride (0.058 g, 0.063 mmol) was added. The resulting mixture was hydrogenated at atmospheric pressure for 25 h. The resulting dark solution was filtered through Celite and concentrated. The residue was purified by flash column chromatography (chloroform-methanol 30:1) yielding 1-(5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)uracil: ^1H NMR ($CDCl_3$, 25 °C) δ 1.09 (s, 9H, 3 x CH_3), 1.86, (m, 1H, H-2'), 2.51, (m, 1H, H-2''), 2.75 (m, 2H, H-3', OH), 3.87 (m, 4H, H-5', H-5'', H-6', H-6''), 4.19 (m, 1H,

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H-4′), 5.43 (d, J= 8.1 Hz, 1H, H-5), 6.07 (dd, $J_{1,2'}$= 6.2 Hz, $J_{1,2''}$= 7.5 Hz, 1H, H-1′), 7.38-7.72 (11H, 10 ArH, H-6)), 9.32 (s, 1H, H-3): ^{13}C NMR ($CDCl_3$, 25 °C) δ 19.2 (C-tert), 27.0 (3 x CH_3), 34.6 (C-2′), 42.4 (C-3′), 61.7 (C-6′), 63.4 (C-5′), 80.0 (C-4′), 84.6 (C-1′), 102.2 (C-5), 128.1-140.0 (8 ArC, C-6), 150.5 (C-4), 163.4 (C-2). The residue was dissolved in pyridine (4 ml) and acetic anhydride (2 ml). After 1 h. at 0 °C, the solution was co-evaporated twice with added toluene and the residue purified by flash column chromatography (toluene-ethyl acetate, 1:2). The residue was dissolved in acetonitrile (1 ml) under a nitrogen atmosphere and added to a mixture of 1,2,4-triazole (0.221 g 3.19 mmol), phosphoryl chloride (0.061 ml, 0.669 mmol) and triethylamine (0.424 ml, 3.04 mmol) in acetonitrile (2 ml). The stirring was continued for 4 h. where after triethylamine (0.30 ml) and water (0.15 ml) were added. The solution was concentrated and the residue dissolved in methylene chloride (10 ml) and washed twice with water (5 ml). The organic phase was dried and concentrated. The residue was dissolved in methanol saturated with ammonia (15 ml) and heated in a sealed vessel to 50 °C for 52 h. After cooling, the solution was concentrated and the residue was purified by column chromatography (chloroform-methanol 8:1). The residue was dissolved in THF (4 ml). Tetrabutylammonium fluoride (1M in THF) (0.307 ml, 0.307 mmol) was added and after 10 min, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 2:1) yielding **3** (0.052 g, 70 %): $[\alpha]_D$ +101.2° (*c* 0.32, water): ^{13}C NMR (CD_3OD, 40 °C) δ 36.6 (C-2′), 44.0 (C-3′), 61.7 (C-6′), 62.9 (C-5′), 82.7 (C-4′), 87.8 (C-1′), 95.9 (C-5), 142.8 (C-6), 158.5 (C-4), 167.8 (C-2); ^{1}H NMR (CD_3OD, 40 °C) δ 1.82, (m, 1H, H-2′), 2.49, (m, 1H, H-2′′), 2.67 (m, 1H, H-3′), 3.72 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.18 (m, 1H, H-4′), 5.87 (d, J= 7.3 Hz, 1H, H-5), 6.01 (dd, $J_{1,2''}$= 5.9 Hz, $J_{1,2''}$= 5.9 Hz, 1H, H-1′), 8.06 (d, J=7.6 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{15}O_4N_3$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.54; H, 6.17; N, 17.30.

1-(3-*C*-Azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)thymine (7). Sodium azide (0.031 g, 0.465 mmol) was added to a stirred solution of **14** (0.082 g, 0.136 mmol) in DMF (2 ml) and the mixture was heated to 60 °C for 40 min. The solution was allowed to cool to room temperature and toluene (20 ml) and water (10 ml) were added. The phases were separated, the organic phase washed with water (10 ml), dried and concentrated. The residue was dissolved in THF (2 ml) and tetrabutylammonium fluoride (1M in THF) (0.146 ml, 0.146 mmol) was added. After 30 min., the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 8:1) yielding **7** (0.036 g, 95 %): ^{1}H NMR was in accordance with

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that published:[5] ^{13}C NMR ($CDCl_3$, 25 °C) δ 12.2 (CH_3, thymine), 47.5 (C-6′), 61.8 (C-5′), 86.9 (C-4′), 88.8 (C-1′), 110.6 (C-5), 123.4 (C-2′), 137.3 (C-3′), 143.0 (C-6), 150.8 (C-4), 164.4 (C-2).

1-(3-*C*-Azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)uracil (8). Sodium azide (0.050 g, 0.774 mmol) was added to stirred solution of **15** (0.130 g, 0.221 mmol) in DMF (3 ml) and the mixture was heated at 60 °C for 30 min. After the solution was allowed to cool to room temperature, toluene (30 ml) and water (10 ml) were added. The phases were separated, the organic phase washed with water (10 ml), dried and concentrated. The residue was dissolved in THF (3 ml) and tetrabutylammonium fluoride (1M in THF) (0.265 ml, 0.265 mmol) was added. After 30 min, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 9:1) yielding **8** (0.053 g, 91 %): ^1H NMR was in accordance with that published:[5] ^{13}C NMR (CD_3OD, 40 °C) δ 48.4 (C-6′), 62.5 (C-5′), 88.4 (C-4′), 90.3 (C-1′), 102.5 (C-5), 124.0 (C-2′), 143.2 (C-6), 145.0 (C-3′), 152.7 (C-4), 166.3 (C-2).

1-(3-*C*-Azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)cytosine (9). Sodium azide (0.081 g, 1.25 mmol) was added to a stirred solution of **15** (0.210 g, 0.357 mmol) in DMF (5 ml) and the mixture was heated at 60 °C for 30 min. After the solution was allowed to cool to room temperature, toluene (40 ml) and water (20 ml) were added. The phases were separated and the organic phase washed with water (15 ml) dried and concentrated. The residue was dissolved in acetonitrile (2 ml) and added to a cooled (ice-bath) mixture of 1,2,4-triazole (0.274 g, 3.96 mmol), phosphoryl chloride (0.076 ml, 0.830 mmol) and triethylamine (0.526 ml, 3.77 mmol) in acetonitrile (3 ml) under a nitrogen atmosphere. The stirring was continued for 2 h. and triethylamine (0.40 ml) and water (0.20 ml) were added. The solution was concentrated and the residue was dissolved in methylene chloride (20 ml) and washed twice with water (10 ml). The organic phase was dried and concentrated. The residue was dissolved in methanol saturated with ammonia (15 ml) and heated in a sealed vessel to 45 °C for 60 h. The solution was concentrated and the residue was purified by column chromatography (chloroform-methanol 10:1). The residue was dissolved in THF (4 ml), and tetrabutylammonium fluoride (1M in THF) (0.373 ml, 373 mmol) was added. After 20 min. the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 3:1) yielding **9** (0.068 g, 72 %): $[\alpha]_D$ +4.1° (*c* 0.99, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 48.5 (C-6′), 62.7 (C-5′), 88.3 (C-4′), 91.3 (C-1′), 96.1 (C-5), 125.0 (C-2′), 143.7 (C-6), 144.1 (C-3′), 158.7 (C-4),

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167.9 (C-2); ^{1}H NMR (CD_3OD, 40 °C) δ 3.80 (m, 2H, H-5′, H-5′′), 4.13 (m, 2H, H-6′, H-6′′), 4.81 (m, 1H, H-4′), 5.87 (m, 2H, H-5, H-1′), 6.97 (m, 1H, H-3′), 7.98 (d, *J*= 7.3 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{12}O_3N_6$: C, 45.45; H, 4.48; N, 31.80. Found: C, 45.31; H, 4.51; N, 31.85.

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