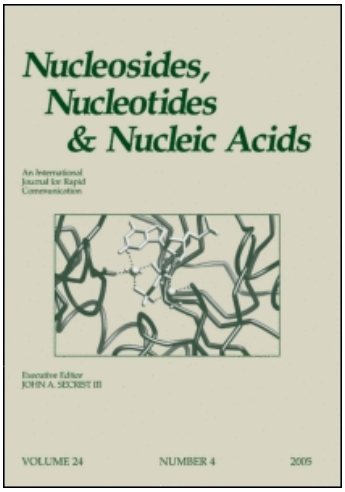

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Synthesis of 2',3'-Didehydro-2',3'-dideoxy-2'-*C*-methylsubstituted Nucleosides Using a Novel S_N2' Type Reaction

Panagiotis Ioannidis[a]; Björn Classon[a]; Bertil Samuelsson[a]; Ingemar Kvarnström[b]
[a] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden
[b] Department of Chemistry, University of Linköping, Linköping, Sweden

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SYNTHESIS OF 2′,3′-DIDEHYDRO-2′,3′-DIDEOXY-2′-*C*-METHYLSUBSTITUTED NUCLEOSIDES USING A NOVEL S_N2' TYPE REACTION.

Panagiotis Ioannidis, Björn Classon, Bertil Samuelsson,* Ingemar Kvarnström#

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

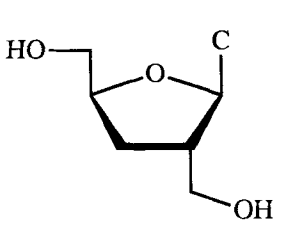
#Department of Chemistry, University of Linköping, S-581 83 Linköping, Sweden.

Abstract. *1-(2,3-Dideoxy-2-C-hydroxymethyl-β-D-threo-pentofuranosyl)-, 1-(2,3-didehydro-2,3-dideoxy-2-C-hydroxymethyl-β-D-glycero-pentofuranosyl)- and 1-(2-C-azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-glycero-pentofuranosyl)uracil, thymine and cytosine were synthesized and evaluated for their anti-HIV activities. A key step of the synthesis involves a novel alcohol transposition of 2-methylene-nucleoside analogues.*

INTRODUCTION

The nucleoside analogues 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxyinosine (DDI) and 2′,3′-dideoxycytidine (DDC) are so far the only drugs approved, in single or combination therapy for the treatment of HIV infection. Other nucleoside analogues are being evaluated in clinical or pre clinical programs.[1-6]

As part of a general program to evaluate the structure-activity relationship between anti-HIV effects and structures obtained by extending a one carbon branch to the sugar residue of nucleoside derivatives, we have recently synthesized 2′,3′-dideoxy-2′-*C*-methyl substituted nucleoside analogues with *erythro* configuration.[7] Among these, 2′,3′-dideoxy-2′-*C*-hydroxymethylcytidine (**1**) showed a moderate *in vitro* anti-HIV activity. In view of this result, we decided to synthesize and evaluate the biological activity of the corresponding 2′-epimers, having the *threo* configuration **2-4**; the 2′,3′-didehydro-2′,3′-dideoxy-2′-*C*-hydroxymethyl nucleosides **5-7**; and the 2′-*C*-azidomethyl-2′,3′-didehydro-2′,3′-dideoxy nucleosides **8-10**. After the completion of this work, Hassan and Matsuda published the synthesis of **9** via a S_N2' reaction between



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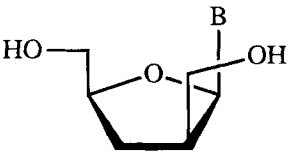
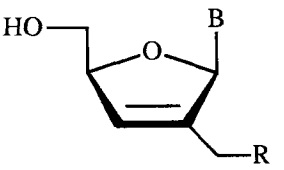


2. B= Thymin-1-yl
3. B= Uracil-1-yl
4. B= Cytosin-1-yl



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

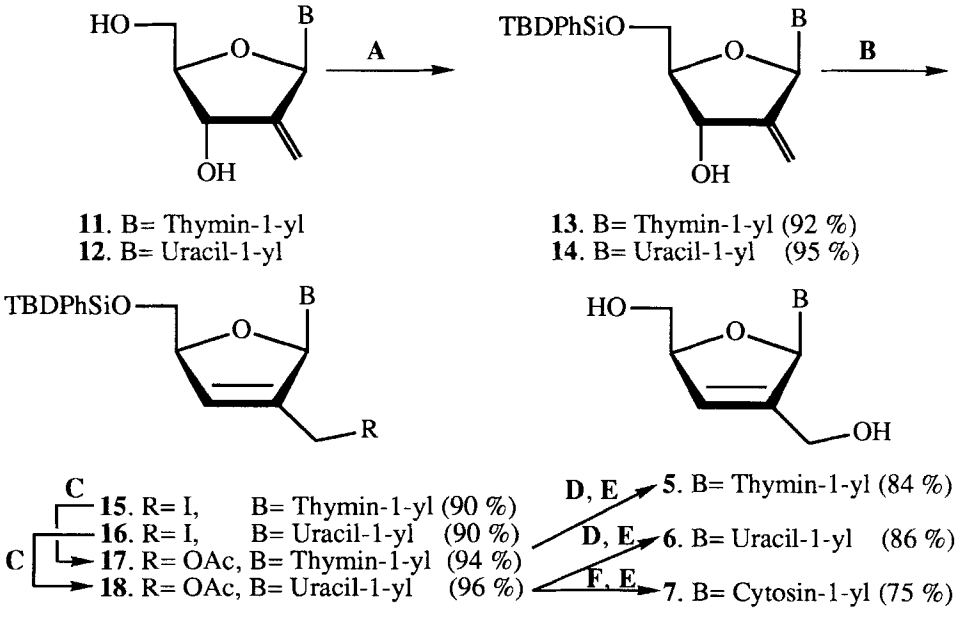
the 1-(5-*O*-trityl-2-deoxy-3-*O*-methanesulfonyl-2-*C*-methylene-β-D-*threo*-pentofuranosyl)uracil and an azide anion.[8]

RESULTS AND DISCUSSION

Protection of the primary hydroxyl group of **11** and **12** (*Scheme 1*)[9] using *tert*-butylchlorodiphenylsilane in pyridine for 26 h and 36 h respectively, gave **13** and **14** in 92 % and 95 % yield. Reacting **13** and **14** with 1.2 equiv. freshly distilled chlorodiphenylphosphine and 2.1 equiv. imidazole in a mixture of toluene-acetonitrile (2:1) at 0 °C for 10 min followed by the addition of 1.2 equiv. iodine in toluene-acetonitrile (2:1), gave the primary allylic iodides **15** and **16** in 90 % isolated yield after 5 min reaction time. This reagent system (chlorodiphenylphosphine-iodine-imidazole) has previously been described by Samuelsson *et al.* for the conversion of hydroxyls into iodides and for the reductive elimination of vicinal diols.[10,11] A plausible mechanism for this transposition is outlined in Figure 1.

Substitution of iodide **15** and **16** with tetrabutylammonium acetate[12] in methylene chloride for 20 h, gave **17** and **18** in 94 % and 96 % yield respectively. Standard deprotection of **17** and **18**, de-*O*-acetylation and de-*O*-silylation,[13] gave **5** and **6** in 84 % and 86 % yield respectively. In **18**, the uracil moiety was converted to cytosine,[9] and deprotected to give **7** in 75 % yield.

De-*O*-acetylation followed by catalytic hydrogenation[14,15] (*Scheme 2*) of **17** and **18** at ambient pressure over $Rh(PPh_3)_3Cl$ in ethanol gave, after de-*O*-silylation, the desired products **2** and **3** in 77 % and 63 % yield, respectively. To obtain the cytidine analogue **4**, **18** was subsequently de-*O*-acetylated, hydrogenated (*e.g.* vide supra), and re-*O*-acetylated. The uracil moiety was converted to cytosine and deprotected to give **4** in 68 % total yield.



Scheme 1.

A. TBDPhSiCl, pyridine, r.t. **B**. Ph_2PCl, imidazole, toluene-acetonitrile (2:1), 0 °C then I_2 in toluene-acetonitrile (2:1). **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, 40 °C.

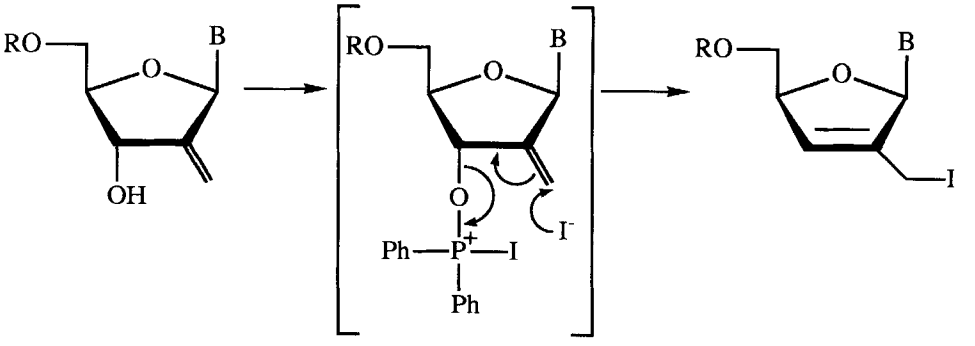
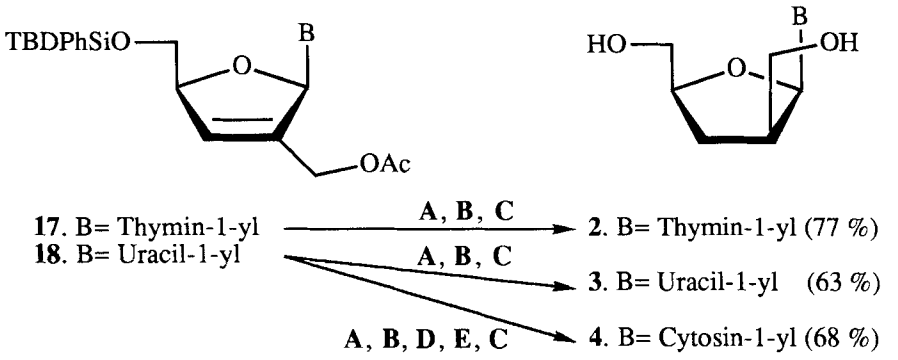
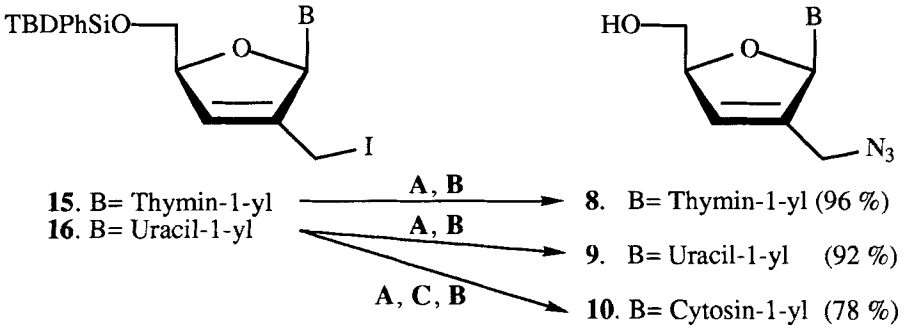


FIG. 1.



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, 40 °C.



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.

The configuration at C-2′of **2** and **4** was determined by comparing the ^{1}H-NMR coupling constants ($^3J_{H\text{-}1',H\text{-}2'}$) and the specific rotation of **2** and **4** with those of the 2′,3′-dideoxy-2′-*C*-hydroxymethyl-*erythro*-nucleosides previously synthesized.[7] The $^3J_{H\text{-}1',H\text{-}2'}$ (CD_3OD, 40 °C) of **2** and **4** are 7.0 Hz for both, compared with their 2′-epimers having (D_2O, 40 °C) 4.8 and 5.1 Hz respectively. The $[\alpha]_D$ of **2** and **4** were +69.7° (CH_3OH) and +90.2° (H_2O) respectively, compared with their 2′-epimers having +9.1° (H_2O) and +31.2° (H_2O) respectively.

Reacting **15** and **16** with 3.5 equiv. sodium azide in DMF at 60 °C for 30 min (*Scheme 3*) followed by de-*O*-silylation gave **8** and **9** in 96% and 92 % yield respectively. The cytidine analogue **10** was prepared from the uridine derivative **16** (78 % from **16**) in analogy with the method previously described.

BIOLOGICAL RESULTS

Compounds **2-10** were tested for anti-HIV activity in a H-9 cell system.[16] All compounds were found to be inactive in the assay.

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 pseudomolecular ions were identified via comparison of the experimental and the simulated ion cluster.

1-(5-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-*C*-methylene-β-D-*erythro*-pentofuranosyl)thymine (13). *tert*-Butylchlorodiphenylsilane (2.41 ml, 9.26 mmol) was added to a stirred solution of 1-(2,3-dideoxy-2-*C*-methylene-β-D-*erythro*-pentofuranosyl)thymine (**11**) (2.14 g, 8.42 mmol) in pyridine (40 ml). Stirring was continued at room temperature for 26 h. The solution was concentrated, co-evaporated twice with added toluene and the residue purified by column chromatography (chloroform-methanol 20:1) yielding **13** (3.88 g, 92 %): $[\alpha]_D$ -27.4° (*c* 1.10, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 12.1 (CH_3, thymine), 19.3 (C-tert), 26.9 (3 x CH_3), 62.3 (C-5′), 70.9 (C-3′) 83.6, 83.8 (C-1′, C-4′), 111.6 (C-5), 113.6 (C-6′), 127.8-135.4 (8 *x* ArC), 136.1 (C-6), 148.5 (C-2′), 150.8 (C-4), 163.6 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.08 (s, 9 H, 3 x CH_3), 1.67 (d, *J*= 1.1 Hz, 3H, CH_3, thymine) 3.79 (m, 1H, H-3′), 3.99 (m, 2H, H-5′, H-5′′), 4.85 (m, 1H, H-4′), 5.37 (m, 1H, H-6′), 5.59 (m, 1H, H-6′′), 6.70 (s, 1H, H-1′), 7.05 (m, 1H, H-6), 7.36-7.69 (m, 10H, 10 ArH), 9.10, (s, 1H, H-3).

1-(5-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-2-*C*-methylene-β-D-*erythro*-pentofuranosyl)uracil (14). *tert*-Butylchlorodiphenylsilane (2.70 ml, 10.40 mmol)

was added to a stirred solution of 1-(2,3-dideoxy-2-*C*-methylene-β-D-*erythro*-pentofuranosyl)uracil (**12**) (2.27 g, 9.45 mmol) in pyridine (60 ml). Stirring was continued at room temperature for 36 h. The solution was concentrated, co-evaporated twice with added toluene and the residue purified by column chromatography (chloroform-methanol 20:1) yielding **14** (4.30 g, 95 %): $[\alpha]_D$ -10.6° (*c* 1.01, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 19.3 (C-tert), 26.9 (3 x CH_3), 62.3 (C-5′), 70.2 (C-3′) 84.0, 84.5 (C-1′, C-4′), 102.3 (C-5), 113.8 (C-6′), 127.9-135.5 (8 x ArC), 140.7 (C-6), 148.5 (C-2′), 150.9 (C-4), 163.4 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.08 (s, 9 H, 3 x CH_3), 3.98 (m, 3H, H-3′, H-5′, H-5′′), 4.88 (m, 1H, H-4′), 5.50 (m, 3H, H-5, H-6′, H-6′′), 6.70 (s, 1H, H-1′), 7.35-7.68 (m, 11H, 10 ArH, H-6), 9.68 (s, 1H, H-3).

1-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-2-*C*-iodomethyl-β-D-*glycero*-pentofuranosyl)thymine (15). Freshly distilled chlorodiphenylphosphine (0.656 ml, 3.65 mmol) was added to a stirred solution of **13** (1.50 g, 3.04 mmol) and imidazole (0.435 g, 6.39 mmol) in toluene-acetonitrile (2:1, 75 ml) cooled in an ice-bath under a nitrogen atmosphere. After 10 min iodine (0.927 g, 3.65 mmol) dissolved in toluene-acetonitrile (2:1, 25 ml) was added. After 5 min. toluene (150 ml) and aqueous $NaHCO_3$ (sat.) (70 ml) was 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 5:2) yielding **15** (1.64 g, 90 %): $[\alpha]_D$ -18.7° (*c* 1.17, $CHCl_3$): Positive FAB-MS (M+H), *m/z* 603; ^{13}C NMR ($CDCl_3$, 25 °C) δ -7.8 (C-6′), 11.8 (CH_3, thymine) 19.5 (C-tert), 27.1 (3 x CH_3), 65.0 (C-5′), 86.0 (C-4), 89.5 (C-1′), 111.7 (C-5), 127.9-136.9 (8 x ArC, C-2′, C-3′, C-6), 150.9 (C-4), 163.8 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.19 (s, 9 H, 3 x CH_3), 1.45 (s, 3H, CH_3, thymine), 3.94 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.81 (m, 1H, H-4′), 6.29 (m, 1H, H-1′), 7.07-7.68 (m, 12H, 10 ArH, H-3′, H-6), 8.98 (s, 1H, H-3).

1-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-2-*C*-iodomethyl-β-D-*glycero*-pentofuranosyl)uracil (16). Freshly distilled chlorodiphenylphosphine (0.900 ml, 5.01 mmol) was added to a stirred solution of **14** (2.00 g, 4.18 mmol) and imidazole (0.600 g, 8.78 mmol) in toluene-acetonitrile (2:1, 105 ml) cooled on an ice-bath and under a nitrogen atmosphere. After 10 min iodine (1.27 g, 5.01 mmol) dissolved in toluene-acetonitrile (2:1, 20 ml) was added. After 5 min toluene (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 **16** (2.46 g, 90 %): $[\alpha]_D$ -15.2° (*c* 0.99, $CHCl_3$): Positive FAB-MS (M+H), *m/z* 589; ^{13}C

NMR ($CDCl_3$, 25 °C) δ -8.2 (C-6′), 19.4 (C-tert), 27.0 (3 x CH_3), 64.6 (C-5′), 86.2 (C-4′), 89.5 (C-1′), 103.0 (C-5), 127.9-140.5 (8 x ArC, C-2′, C-3′, C-6), 150.8 (C-4), 163.2 (C-2); ^1H NMR ($CDCl_3$, 25 °C) δ 1.09 (s, 9 H, 3 x CH_3), 3.95 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.80 (m, 1H, H-4′), 5.28 (d, *J*= 8.1 Hz, 1H, H-5), 6.22 (m, 1H, H-1′), 7.07-7.66 (m, 11H, 10 ArH, H-3′), 7.76 (d, *J*= 8.1 Hz, 1H, H-6), 9.08 (s, 1H, H-3).

1-(2-*C*-Acetoxymethyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)thymine (17). Tetrabutylammonium acetate (0.751 g, 2.49 mmol) was added to a stirred solution of **15** (1.00 g, 1.66 mmol) in methylene chloride (40 ml). After 28 h the mixture was concentrated and the residue purified by column chromatography (toluene-ethyl acetate 3:2) yielding **17** (0.832 g, 94 %): $[\alpha]_D$ +10.3° (*c* 0.99, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 11.8 (CH_3, thymine), 19.3 (C-tert), 20.6 (CH_3, acetate), 27.0 (3 x CH_3), 58.3 (C-6′), 65.5 (C-5′), 86.0 (C-4′), 89.2 (C-1′), 111.5 (C-5), 127.9-135.4 (8 x ArC, C-2′, C-3′, C-5), 150.9 8 (C-4), 163.7 (C-2), 170.2 (carbonyl, acetate); ^1H NMR ($CDCl_3$, 25 °C) δ 1.08 (s, 9 H, 3 x CH_3), 1.45 (CH_3, thymine), 2.02 (CH_3, acetate), 3.92 (m, 2H, H-5′, H-5′′), 4.63 (m, 2H, H-6′, H-6′′), 4.92 (m, 1H, H-4′), 6.25 (m, 1H, H-1′), 7.01-7.66 (m, 12H, 10 ArH, H-3′, H-6), 8.92 (H-3).

Anal.Calcd for $C_{29}H_{34}O_6N_2Si$: C, 65.14; H, 6.41; N, 5.24. Found: C, 64.97; H, 6.31; N, 5.09.

1-(2-*C*-Acetoxymethyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)uracil (18). Tetrabutylammonium acetate (0.845 g, 2.80 mmol) was added to a stirred solution of **16** (1.10 g, 1.87 mmol) in methylene chloride (50 ml). After 22 h the mixture was concentrated and the residue purified by column chromatography (toluene-ethyl acetate 3:2) yielding **18** (0.937 g, 96 %): $[\alpha]_D$ +12.2° (*c* 1.32, $CHCl_3$): ^{13}C NMR ($CDCl_3$, 25 °C) δ 19.4 (C-tert), 20.6 (CH_3, acetate), 27.0 (3 x CH_3), 58.1 (C-6′), 64.9 (C-5′), 86.2 (C-4′), 89.2 (C-1′), 102.8 (C-5), 127.9-135.6 (8 x ArC, C-2′, C-3′), 140.7 (C-6), 150.8 (C-4), 163.1 (C-2), 170.2 (carbonyl); ^1H NMR ($CDCl_3$, 25 °C) δ 1.08 (s, 9 H, 3 x CH_3), 2.02 (s, 3H, CH_3, acetate), 3.94 (ddd, $J_{4,5}$= 2.9 Hz, J_{gem}= 11.7 Hz, 2H, H-5′, H-5′′), 4.65 (dd, J_{gem}= 13.9 Hz, 2H, H-6′, H-6′′), 4.89 (m, 1H, H-4′), 5.22 (d, *J*= 8.1 Hz, 1H, H-5), 6.19 (m, 1H, H-1′), 7.03 (m, 1H, H-3′), 7.36-7.66 (m, 10H, ArH), 7.73 (d, *J*= 8.1 Hz, 1H, H-6), 9.09 (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, 64.86; H, 5.98; N, 5.50.

1-(2,3-Dideoxy-2-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)-thymine (2). A solution of **17** (0.110 g, 0.206 mmol) in methanol saturated with ammonia (5 ml) was stirred for 8 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 rhodium tris-(triphenylphosphine)chloride (0.032 g, 0.035 mmol) was added. The resulting mixture was hydrogenated at atmospheric pressure for 20 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 (10 ml) and tetrabutylammonium fluoride (1M in THF) (0.325 ml, 0.325 mmol) was added. After 30 min, the solution was concentrated and the residue was purified by column chromatography (chloroform-methanol 9:1) yielding **2** (0.041 g, 77 %): $[\alpha]_D$ +69.7° (*c* 0.87, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 12.5 (CH_3, thymine), 29.5 (C-3′), 47.8 (C-2′), 61.4 (C-6′), 62.8 (C-5′), 82.6 (C-4′), 87.3 (C-1′), 110.5 (C-5), 139.6 (C-6), 152.8 (C-4), 166.5 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 1.86, (d, m, *J*= 1.1 Hz, 4H, CH_3, thymine, H-3′), 2.02 (m, 1H, H-3′′), 2.84 (m, 1H, H-2′), 3.42-3.99 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.13 (m, 1H, H-4′), 6.19 (d, *J*= 7.0 Hz, 1H, H-1′), 8.03 (d, *J*=1.1 Hz, 1H, H-6).

Anal.Calcd for $C_{11}H_{16}O_5N_2$ x 0.3 H_2O: C, 50.69; H, 6.03; N, 10.75. Found: C, 50.80; H, 5.99; N, 10.86.

1-(2,3-Dideoxy-2-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)-uracil (3). A solution of **18** (0.087 mg, 0.167 mmol) in methanol saturated with ammonia (5 ml) was stirred for 20 h at room temperature. The solution was concentrated and the residue was purified by flash column chromatography (chloroform-methanol 20:1). The residue was dissolved in ethanol (5 ml) and rhodium tris(triphenylphosphine)chloride (0.027 g, 0.029 mmol) was added. The resulting mixture was hydrogenated at atmospheric pressure for 14 h. The resulting dark solution was filtered through Celite and concentrated. The residue was purified by flash column chromatography (chloroform-methanol 30:1). The residue was dissolved in THF (7 ml) and tetrabutylammonium fluoride (1M in THF) (0.300 ml, 0.300 mmol) was added. After 30 min, the solution was concentrated and the residue purified by column chromatography (chloroform-methanol 9:1) yielding **3** (0.035 g, 63 %): $[\alpha]_D$ +113.5° (*c* 0.89, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 30.0 (C-3′), 48.1 (C-2′), 61.7 (C-6′), 63.4 (C-5′), 83.2 (C-4′), 88.0 (C-1′), 102.2 (C-5), 144.4 (C-6), 153.2 (C-4), 166.9 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 1.84, (m, 1H, H-3′), 2.01 (m, 1H, H-3′′), 2.86 (m,

1H, H-2′), 3.42-3.95 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.12 (m, 1H, H-4′), 5.64 (d, *J*= 8.1 Hz, 1H, H-5), 6.20 (d, *J*= 7.3 Hz, 1H, H-1′), 8.12 (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, 49.36; H, 5.79; N, 11.32.

1-(2,3-Dideoxy-2-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)-cytosine (4). A solution of **18** (0.163 g, 0.313 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 rhodium tris(triphenylphosphine)chloride (0.049 g, 0.053 mmol) was added. The resulting mixture was hydrogenated at atmospheric pressure for 16 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-2-*C*-hydroxymethyl-β-D-*threo*-pentofuranosyl)uracil: ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.10 (s, 9H, 3 x CH_3), 1.92, (m, 2H, H-3′, H-3′′), 2.94 (m, 1H, H-2′), 3.51 (m, 1H, H-4′), 3.67-4.20 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 5.35 (d, *J*= 8.1 Hz, 1H, H-5), 6.27 (d, *J*= 6.6 Hz, 1H, H-1′), 7.37-7.68 (10H, ArH), 8.18 (d, *J*=8.1 Hz, 1H, H-6), 9.78 (s, 1H, H-3). The residue was dissolved in pyridine (4 ml) and acetic anhydride (2 ml). After 5 h, the solution was co-evaporated twice with added toluene and the residue purified by flash column chromatography (toluene-ethyl acetate, 1:1). The residue was dissolved in acetonitrile (1 ml) and added to a mixture of 1,2,4-triazole (0.180 g 2.61 mmol), phosphoryl chloride (0.050 ml, 0.547 mmol) and triethylamine (0.347 ml, 2.49 mmol) in acetonitrile (2 ml), cooled in an ice-bath under a nitrogen atmosphere. The stirring was continued for 2 h whereafter triethylamine (0.3 ml) and water (0.1 ml) were added. The solution was concentrated and the residue was 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 (20 ml) and heated in a sealed vessel to 40 °C for 40 h. After cooling, the solution was concentrated and the residue dissolved in THF (10 ml). Tetrabutylammonium fluoride (1M in THF) (0.627 ml, 0.627 mmol) was added and after 40 min, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 2:1) yielding **4** (0.052 g, 68 %) and **3** as a byproduct from the hydrolysis (11 mg, 14 %): $[\alpha]_D$ +90.2° (*c* 0.87, water): ^{13}C NMR (CD_3OD, 40 °C) δ 28.9 (C-3′), 47.7 (C-2′), 61.0 (C-6′), 62.8 (C-5′), 82.8 (C-4′), 88.4 (C-1′), 95.2 (C-5), 145.9 (C-6), 154.6 (C-4), 164.5 (C-2); ^{1}H NMR (CD_3OD, 40 °C) δ 1.97, (m, 2H, H-3′, H-3′′), 2.90 (m, 1H, H-2′), 3.50-

3.98 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.17 (m, 1H, H-4′), 6.07 (d, *J*= 7.7 Hz, 1H, H-5), 6.25 (d, *J*= 7.0 Hz, 1H, H-1′), 8.38 (d, *J*=7.7 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{15}O_4N_3$ x 2 H_2O: C, 43.32; H, 6.91; N, 15.15. Found: C, 43.02; H, 6.58; N, 15.36.

1-(2,3-Didehydro-2,3-dideoxy-2-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)thymine (5). A solution of **17** (0.105 g, 0.196 mmol) in methanol saturated with ammonia (5 ml) was stirred at room temperature. After 8 h, the solution was concentrated and the residue dissolved in THF (10 ml). Tetrabutylammonium fluoride (1M in THF) (0.295 ml, 0.295 mmol) was added and after 1 h, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 7:1) yielding **5** (0.042 g, 84 %): $[\alpha]_D$ -8.4° (*c* 0.98, water): ^{13}C NMR (CD_3OD, 40 °C) δ 12.2 (CH_3, thymine), 57.5 (C-6′), 63.6 (C-5′), 87.6 (C-4′), 90.1 (C-1′), 111.4 (C-5), 129.4 (C-3′), 138.4 (C-6), 140.6 (C-2′), 152.5 (C-4), 165.9 (C-2); ^1H NMR (D_2O, 40 °C) δ 2.09 (d, *J*= 1.1 Hz, 3H, CH_3, thymine), 4.03 (m, 2H, H-5′, H-5′′), 4.38 (s, 2H, H6′, H-6′′), 5.21 (m, 1H, H-4′), 6.56 (m, 1H, H-1′), 7.18 (m, 1H, H-3′), 7.84 (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, 51.72; H, 5.69; N, 10.83.

1-(2,3-Didehydro-2,3-dideoxy-2-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)uracil (6). Tetrabutylammonium fluoride (1M in THF) (0.277 ml, 0.277 mmol) was added to stirred solution of **18** (0.116 g, 0.223 mmol) in THF (5 ml). After 20 min, the mixture was concentrated and the residue purified by flash column chromatography (chloroform-methanol 10:1). The residue was dissolved in methanol saturated with ammonia (10 ml). After 13 h the solution was concentrated and the residue was purified by column chromatography (chloroform-methanol 5:1) yielding **6** (0.042 g, 86 %): $[\alpha]_D$ +4.6° (*c* 0.93, water): ^{13}C NMR (D_2O, 40 °C) δ 53.4 (C-6′), 59.4 (C-5′), 84.2 (C-4′), 86.6 (C-1′), 99.6 (C-5), 127.0 (C-3′), 134.7 (C-2′), 139.4 (C-6), 149.2 (C-4), 163.2 (C-2); ^1H NMR (D_2O, 40 °C) δ 4.01 (m, 2H, H-5′, H-5′′), 4.40 (s, 2H, H6′, H-6′′), 5.22 (m, 1H, H-4′), 6.10 (d, *J*= 8.1 Hz, 1H, H-5), 6.56 (m, 1H, H-1′), 7.18 (m, 1H, H-3′), 8.01 (d, *J*= 8.1 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{12}O_5N_2$ x 0.3 H_2O: C, 48.90; H, 5.17; N, 11.41. Found: C, 48.67; H, 4.79; N, 11.27.

1-(2,3-Didehydro-2,3-dideoxy-2-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)cytosine (7). 1,2,4-Triazole (0.083 g, 1.21 mmol) and phosphoryl

chloride (0.023 ml, 0.253 mmol) were stirred in acetonitrile (1 ml). The solution was cooled on an ice-bath and triethylamine (0.160 ml, 1.15 mmol) was added. To this mixture, **18** (0.060 g, 0.115 mmol) in acetonitrile (1 ml) was added and the mixture was stirred for 2 h at room temperature. Triethylamine (0.100 ml) and water (0.050 ml) were added to this mixture and the solution was concentrated. The residue was dissolved in methylene chloride (10 ml) and the solution was extracted twice with water (5 ml). The organic phase was dried, concentrated, and the residue was dissolved in methanol saturated with ammonia (6 ml). The resulting solution was heated to 45 °C for 48 h, cooled and concentrated. The residue was dissolved in THF (4 ml) and tetrabutylammonium fluoride (1M in THF) (0.300 ml, 0.300 mmol) was added. After 15 min, the mixture was concentrated and the residue was purified by column chromatography (chloroform-methanol 2:1) yielding **7** (0.021 g, 75 %): $[\alpha]_D$ +42.3° (*c* 0.90, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 58.0 (C-6'), 64.4 (C-5'), 88.3 (C-4'), 91.7 (C-1'), 96.6 (C-5), 129.5 (C-3'), 141.9 (C-2'), 143.7 (C-6), 158.7 (C-4), 167.6 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 3.75 (m, 2H, H-5', H-5''), 4.05 (m, 2H, H6', H-6''), 4.87 (m, 1H, H-4'), 5.91 (d, *J*= 7.7 Hz, 1H, H-5), 6.19 (m, 1H, H-1'), 7.00 (m, 1H, H-3'), 7.92 (d, *J*= 7.7 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{13}O_4N_3$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.05; H, 5.41; N, 17.12.

1-(2-*C*-Azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-glycero-pentofuranosyl)thymine (8). Sodium azide (0.076 g, 1.16 mmol) was added to stirred solution of **15** (0.200 g, 0.332 mmol) in DMF (3 ml) and the mixture was heated at 60 °C for 30 min. After the solution was allowed to come to room tempearture, toluene (40 ml) and water (10 ml) were added. The phases were separated and the organic phase washed with water (10 ml), dried and concentrated. The residue was dissolved in THF (5 ml) and tetrabutylammonium fluoride (1M in THF) (0.450 ml, 0.450 mmol) was added to the resulting solution. After 45 min, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 8:1) yielding **8** (0.089 g, 96 %): $[\alpha]_D$ +60.9° (*c* 1.23, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 12.4 (CH_3, thymine), 47.8 (C-6'), 63.7 (C-5'), 88.3 (C-4'), 90.7 (C-1'), 112.0 (C-5), 133.4 (C-3'), 135.8 (C-2'), 138.4 (C-6), 153.0 (C-4), 166.4 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 1.85 (d, *J*= 1.1 Hz, 3H, CH_3, thymine), 3.78 (m, 2H, H-5', H-5''), 3.94 (m, 2H, H-6', H-6''), 4.88 (m, 1H, H-4'), 6.34 (m, 1H, H-1'), 6.93 (m, 1H, H-3'), 7.83 (d, *J*= 1.1 Hz, 1H, H-6).

Anal.Calcd for $C_{11}H_{13}O_4N_5$: C, 47.31; H, 4.69; N, 25.08. Found: C, 47.17; H, 4.67; N, 24.94.

1-(2-*C*-Azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-glycero-pentofuranosyl)uracil (9). Sodium azide (0.058 mg, 0.892 mmol) was added to stirred solution of **16** (0.150 g, 0.255 mmol) in DMF (3 ml) and the mixture was heated at 60 °C for 30 min. After the solution was allowed to come to room tempearture, 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 (5 ml) and tetrabutylammonium fluoride (1M in THF) (0.400 ml, 0.400 mmol) was added. After 30 min, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 8:1) yielding **9** (0.062 g, 92 %): $[\alpha]_D$ +52.5° (*c* 1.00, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 46.3 (C-6′), 62.2 (C-5′), 86.9 (C-4′), 89.4 (C-1′), 101.8 (C-5), 132.0 (C-3′), 134.1 (C-2′), 141.3 (C-6), 151.3 (C-4), 164.7 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 3.79 (m, 2H, H-5′, H-5′′), 3.98 (m, 2H, H6′, H-6′′), 4.91 (m, 1H, H-4′), 5.72 (d, *J*= 8.1 Hz, 1H, H-5), 6.36 (m, 1H, H-1′), 6.94 (m, 1H, H-3′), 7.98 (d, *J*= 8.1 Hz, 1H, H-6).

Anal.Calcd for $C_{10}H_{11}O_4N_5$: C, 45.29; H, 4.18; N, 26.40. Found: C, 45.47; H, 4.07; N, 26.24.

1-(2-*C*-Azidomethyl-2,3-didehydro-2,3-dideoxy-β-D-glycero-pentofuranosyl)cytosine (10). Sodium azide (0.116 g, 1.784 mmol) was added to stirred solution of **16** (0.300 g, 0.510 mmol) in DMF (5 ml) and the mixture was heated at 60 °C for 30 min. After the solution was allowed to come to room temperature and toluene (60 ml) and water (20 ml) were added. The phases were separated and the organic phase washed with water (20 ml) dried and concentrated. The residue was dissolved in acetonitrile (2 ml) and added to a mixture of 1,2,4-triazole (0.350 g, 5.066 mmol), phosphoryl chloride (0.097 ml, 1.061 mmol) and triethylamine (0.672 ml, 4.825 mmol) in acetonitrile (4 ml) cooled on an ice-bath. The stirring was continued for 2 h and triethylamine (0.50 ml) and water (0.25 ml) were added. The solution was concentrated, and the residue was dissolved in methylene chloride (30 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 40 °C. The solution was concentrated and the residue was dissolved in THF (5 ml), and tetrabutylammonium fluoride (1M in THF) (0.500 ml, 0.500 mmol) was added. After 15 min, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 5:1) yielding **10** (0.106 g, 78 %): $[\alpha]_D$ +91.2° (*c* 1.02, methanol): ^{13}C NMR (CD_3OD, 40 °C) δ 47.9 (C-6′), 63.9 (C-5′), 88.2 (C-4′), 91.8 (C-1′), 96.7 (C-5), 132.7 (C-3′), 136.6 (C-2′), 143.4 (C-6), 158.7 (C-4), 167.7 (C-2); ^1H NMR (CD_3OD, 40 °C) δ 3.77 (m, 2H, H-5′, H-5′′), 3.91 (m, 2H, H-6′, H-6′′), 4.90 (m,

1H, H-4´), 5.90 (d, *J*= 7.3 Hz, 1H, H-5), 6.30 (m, 1H, H-1´), 7.01 (m, 1H, H-3´), 7.96 (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, 45.05; H, 4.35; N, 31.17.

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