Synthesis of 2′-Azido, 2,2′-Anhydro and 2′,5′-Anhydro Nucleosides with Potential Anti-HIV Activity

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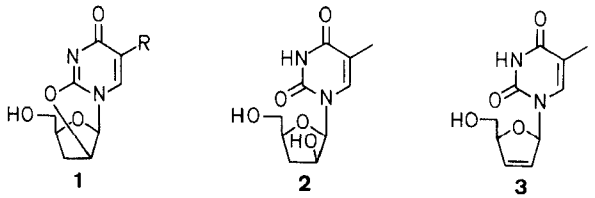
Reaction of methyl 2-bromo-2,3-dideoxy-5-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranoside (**7**) with silylated uracils **9** using trimethylsilyl triflate as catalyst afforded the corresponding 2′-bromonucleosides **10**. 2,3-Didehydro sugar **8** was prepared by heating **7** with sodium azide in dimethylformamide. 2,2′-Anhydro nucleosides **1** were prepared by treating the nucleosides **10** with sodium methoxide at room temperature. 1-(2-Azido-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (**15**) and its α-anomer (**16**) were prepared by treating **10c** with sodium azide and subsequently methanolic ammonia. Treatment of 1-(2-bromo-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)thymine (**11c**) with excess of sodium methoxide under reflux gave the corresponding 2′,5′-anhydro nucleoside **17**.

In an attempt to increase the antiviral activity against human immunodeficiency virus (HIV-1) and to decrease cytotoxicity of 3′-azido-2′,3′-dideoxythymidine (AZT), Lin et al.[1] synthesized the corresponding 2,5′-anhydro derivative of AZT. It showed significant antiviral activity but with less activity than AZT. Herdewijn et al.[2] investigated 1-(3′,5′-anhydro-2′-deoxy-β-D-*threo*-pentofuranosyl) cytosine for its activity against HIV, but found only little activity.

We found it of interest to synthesize a series of 2,2′-anhydro nucleosides **1** which can be considered as prodrugs of either 3′-deoxy-β-D-*threo*-pentofuranosylthymine (**2**) or 3′-deoxy-2′,3′-didehydrothymidine (d4T) (**3**).

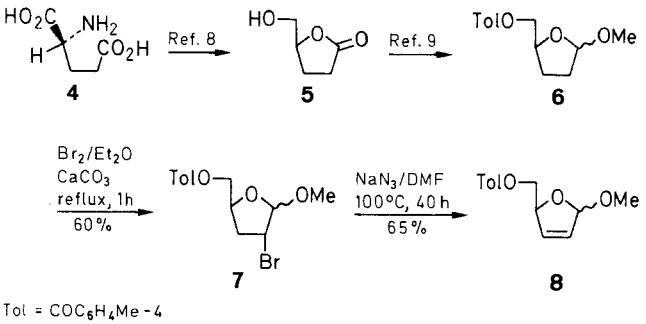


1 **2** **3**

The latter compound shows potent anti-HIV activity in peripheral blood mononuclear cells (PBM)[3] and in the human T4-lymphocyte cell line MT-4[4] whereas **2** had no significant protective effects on a human CD4$^+$ T-cell clone, ATH8, exposed to HIV.[5]

Most compounds inhibiting the reverse transcriptase of human immunodeficiency virus (HIV) are 2′,3′-dideoxynucleosides.[6] Synthesis of new nucleoside analogues offers a chance to find compounds with less prominent side effects than those observed for AZT and 2′,3′-dideoxycytidine (ddC). In the case of AZT, the key toxicity that should be obviated is the suppression of bone marrow; in the case of ddC, the key toxicity is peripheral neurophathy.[7]

The starting materials **5**[8] and **6**[9] have already been described. The reaction of **6** with bromine in diethyl ether in the presence of calcium carbonate afforded a bromo derivative **7** (60 %). From NMR we observed two isomers in the ratio 1:8 which may be two anomers of **7** or possibly two stereoisomers. Because of difficulties in separating such isomers, the mixture was used as such in the following nucleoside coupling reactions and the pro-

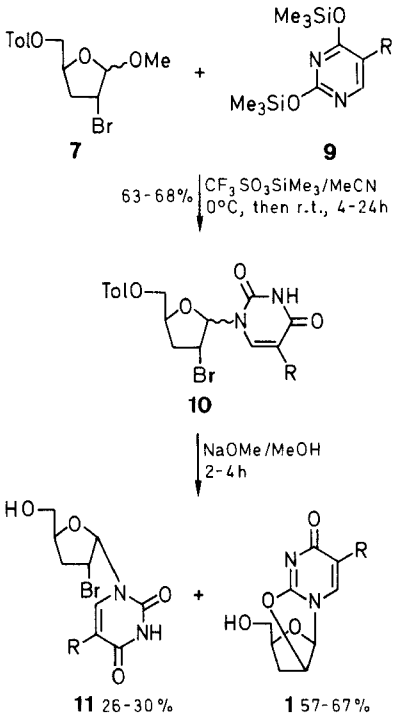


4 **5** **6** **7** **8**

ducts isolated proves the major isomer to be the *erythro* isomer **7**. Treatment of **7** with excess of sodium azide in dry dimethylformamide under reflux gave an anomeric mixture of the unsaturated compound **8** (65%) with an IR absorption at 1613 cm^{-1} indicating a double bond. By applying the reported[10] procedure for synthesis of nucleosides using trimethylsilyl triflate, the reaction of **8** with silylated thymine[11] **9c** in dry acetonitrile (−35°C) or in dry dichloromethane (−60°C) did not result in formation of nucleosides, since **8** easily decomposes under acidic conditions or on extended heating which has previously been described for methyl 5-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranoside.[12]

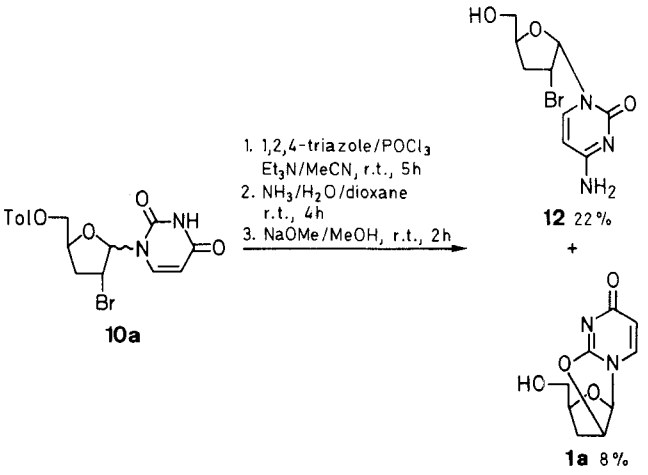
Coupling of **7** with silylated uracil **9a–c** using the trimethylsilyl triflate method of Vorbrüggen[10] gave a 3:5 (α/β) anomeric mixture of protected nucleosides **10a–c** (63–68%). Treatment of this anomeric mixture with sodium methoxide in methanol followed by chromatographic purification gave the deprotected 2′-bromo-α-nucleosides **11a–c** (26–30%) and 2,2′-anhydro nucleosides **1a–c** (57–67%).

Deprotection of the β-anomer of **10** to give the corresponding β-anomer of **11** is observed in TLC as a spot close to the one of the α-anomer of **11**. However, deprotonation of the uracil followed by an intramolecular S_N2 reaction rapidly results in formation of the 2,2′-anhydro nucleoside **1**.

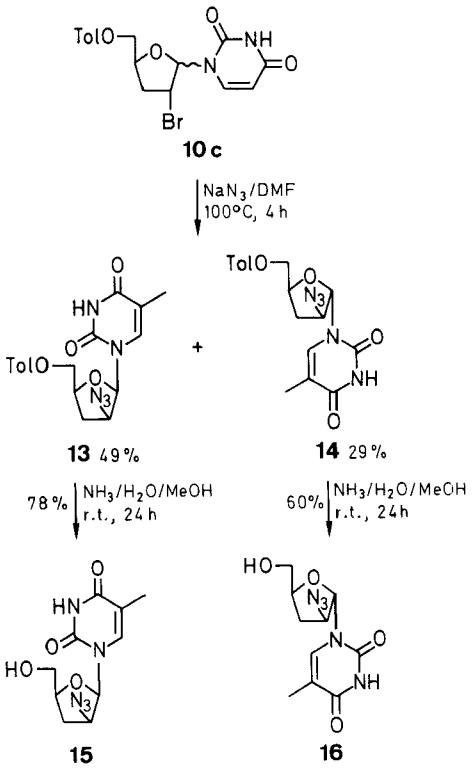


1, 9, 11	a	b	c
R	H	F	Me

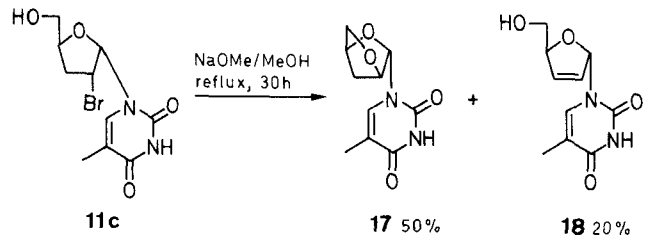
The 4-(1*H*-1,2,4-triazol-1-yl)pyrimidin-2-one derivative was prepared by treating **10a** with putative tris(1*H*-1,2,4-triazol-1-yl)phosphine oxide[13] in the presence of 1*H*-1,2,4-triazole and triethylamine in acetonitrile at room temperature. Reaction of the 4-triazole derivative with aqueous ammonia in dioxane solution at room temperature yielded the cytosine derivative. Subsequent removal of the toluoyl group by treatment with sodium methoxide in methanol at room temperature and followed by chromatographic purification afforded the unprotected cytosine derivative **12** (22% from **10a**) and the 2,2′-anhydro compound **1a** (8% from **10a**).



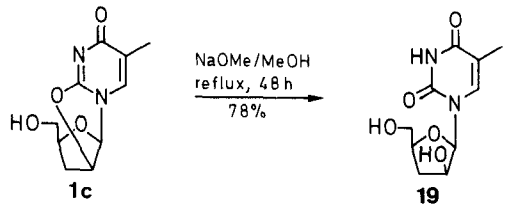
The reaction of **10c** with 10 equivalents of sodium azide in dry dimethylformamide (4 h at 100°C) afforded an anomeric mixture of protected 2′-azido nucleosides which were separated. Deprotection with methanolic ammonia followed by chromatographic purification gave **15** (78%) and **16** (60%).



On treatment of **11c** with excess of sodium methoxide in methanol under reflux gave a separable mixture of the 2′,5′-anhydro nucleoside **17** (50%) and the 2′,3′-didehydro nucleoside **18** (20%).



Treatment of the 2,2'-anhydro nucleoside **1c** under the same conditions as for **11c** resulted in cleavage of the anhydro linkage with formation of **19** (78%) of which the structure was assigned by literature precedent.[5] Since anhydrous methanol was used, the latter reaction seems not to be a simple hydrolysis. Instead one can assume an initial attack by methoxide on the pyrimidine ring followed by a demethylation reaction.



^{1}H-NMR, ^{13}C-NMR and MS spectra confirmed the structures of all new compounds. ^{1}H-NMR spectra were recorded at 250 MHz and ^{13}C-NMR spectra at 62.5 MHz. The assignments of proton chemical shifts in the ^{1}H-NMR spectra were determined by using ^{1}H-^{1}H homonuclear shift-correlated (COSY) 2D-NMR, and the ^{1}H nuclear Overhauser effects (NOE difference spectroscopy). The protons of the carbohydrate moiety were irradiated in **1a** and irradiation of 2'α-H generated large NOE's in 1'α-H (8%) and 3'α-H (6%); irradiation of 4'-H also generated large NOE's in 3'α-H (5%) but smaller in 5'-H (2%). In compound **12** irradiation of 3'α-H generated large NOE's in 4'-H (7%) but smaller in 2'β-H (3%), irradiation of 3'β-H generated large NOE's in 2'β-H (9%) but smaller in 4'-H (6%). Irradiation of 4'-H generated large NOE's in 3'α-H (7%). Irradiation of 2'β-H generated large NOE's in 1'α-H (11%). The α- and β-isomer assignments of **15** and **16** were made by preparing the 2'-azido nucleoside **16** from deprotected 2-bromo derivative **11c** by reaction with sodium azide.

Compounds **1a–c, 10a–c, 11a–c, 12–17** and **19** did not show activity against human immunodeficiency virus (HIV) strain HTLV-IIIB in MT-4 cells. Washaw and Watanabe[14] similarly reported no significant anti-HIV activity for 2'-azido-2'3,'-dideoxythymidine.

Methyl 2-Bromo-2,3-dideoxy-5-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranoside (7):
To a vigorously stirred solution of methyl 2,3-dideoxy-5-*O*-(4-methylbenzoyl)-D-*glycero*-pentofuranoside (**6**, 8.3 g, 0.033 mol) in anhydr. Et_2O (100 mL) in the presence of $CaCO_3$ (4.1 g, 0.041 mol) at r.t. (Br_2 (5.53 g, 0.035 mol) is added. Stirring is continued for 1 h under reflux. After cooling the insoluble materials are filtered off and washed with Et_2O. The combined Et_2O phases are then neutralized with 5% KOH in MeOH. The solvent is evaporated under reduced pressure. Benzene (150 mL) is added and the insoluble materials are filtered off. Evaporation of the filtrate left an orange coloured oil which is chromatographed on silica gel (130 g, 0.04–0.063 mm) with petroleum ether (bp 60–80°C)/Et_2O (98:2) to afford **7**; yield: 6.52 g (60%) of colourless oil.

Methyl 2,3-Dideoxy-5-*O*-(4-methylbenzoyl)-D-*glycero*-pent-2-enofuranoside (8):
2-Bromo derivative **7** (3.3 g, 0.01 mol) and NaN_3 (6.5 g, 0.1 mol) in dry DMF (100 mL) is stirred at 100°C for 40 h. After cooling the mixture is filtered and the filtrate is evaporated under reduced pressure. The residue is chromatographed on silica gel (40 g, 0.04–0.063 mm) with petroleum ether (bp 60–80°C)/Et_2O, (95:5) to obtain **8**; yield: 1.61 g (65%) as colourless oil.
IR (KBr): $\nu = 1613\ cm^{-1}$ (C=C).

1-(2-Bromo-2,3-dideoxy-5-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl)uracil Derivatives 10a–c; General Procedure:
To a stirred solution of compound **7** (4.9 g, 0.015 mol) and *O,O'*-bis(trimethylsilyl)uracil derivatives[11] **9a–c** (0.017 mol) in dry MeCN (70 mL) is added dropwise trimethylsilyl triflate (5.4 mL, 0.03 mol) in MeCN (10 mL) at 0°C. After addition, the mixture is stirred for 4–24 h (**a**: 12 h; **b**: 4 h; **c**: 24 h) at r.t. The mixture is then diluted with CH_2Cl_2 (300 mL) and extracted with ice cold sat. $NaHCO_3$ (300 mL). The aqueous solution is extracted with

Table 1. Yields and Physical Data of the New Compounds Prepared

Compound	Yield[a] (%)	mp (°C)	Molecular Formula[b]	MS *m/z* (%)
1a	66	hydroscopic (solid)	$C_9H_{10}N_2O_4 \cdot 2{,}5H_2O$ (255.2)	210 (M^+, 30), 112 (100), 69 (81)
1b	57	207–209	$C_9H_9FN_2O_4$ (228.2)	228 (M^+, 100), 197 (71), 155 (65)
1c	67	187–188	$C_{10}H_{12}N_2O_4 \cdot H_2O$ (242.2)	224 (M^+, 100), 126 (38), 82 (73), 69 (94)
7	60	oil	$C_{14}H_{17}BrO_4$ (329.2)	328, 330 (M^+, 0.3), 192, 194 (32), 119 (100)
8	65	oil	$C_{14}H_{16}O_4$ (248.3)	248 (M^+, 1.1), 119 (100), 91 (24)
11a	27	114–117	$C_9H_{11}BrN_2O_4$ (291.1)	290, 292 (M^+, 8), 179, 181 (100), 57 (74)
11b	26	57–61	$C_9H_{10}BrFN_2O_4$ (309.1)	308, 310 (M^+, 11), 179, 181 (100), 57 (90)
11c	30	159–160	$C_{10}H_{13}BrN_2O_4 \cdot 0.25H_2O$ (309.6)	304, 306 (M^+, 7), 179, 181 (40), 126 (100), 57 (81)
12[c]	22	184–187	$C_9H_{12}BrN_3O_3$ (290.1)	
15	78	165–166	$C_{10}H_{13}N_5O_4$ (267.25)	267 (M^+, 0.7), 224 (M^+-HN_3, 0.7), 126 (60), 114 (100)
16	60	105–107	$C_{10}H_{13}N_5O_4$ (267.25)	224 (M^+-HN_3, 0.6), 126 (62), 114 (100)
17	50	217–218	$C_{10}H_{12}N_2O_4$ (224.2)	224 (M^+, 90), 99 (70), 69 (100), 43 (94)
18	20	130–132	$C_{10}H_{12}N_2O_4$ (224.2)	224 (M^+, 0.3), 69 (98), 55 (100), 40 (89)

[a] Yield of pure product. [b] Satisfactory microanalysis obtained: C ±0.5, H ±0.5, N ±0.5. [c] Decomposed in the mass spectrometer.

Table 2. NMR Data of the New Compounds Prepared

Compound	^{1}H-NMR (solvent/TMS) δ, J (Hz)	^{13}C-NMR (solvent/TMS) δ, J (Hz)
1a	(DMSO-d_6): 2.25 (dd, 1H, J = 14.8, 1.8, 3′α-H), 2.47 (m, 1H, 3′β-H), 3.20 (t, 2H, J = 5.2, 5′-H), 4.35 (m, 1H, 4′-H), 4.93 (t, 1H, J = 5.2, OH), 5.56 (t, 1H, J = 6.1, 2′-H), 5.84 (d, 1H, J = 7.4, 5-H), 6.23 (d, 1H, J = 5.6, 1′-H), 7.85 (d, 1H, J = 7.4, 6-H)	(DMSO-d_6): 32.84 (C-3′), 63.86 (C-5′), 82.04 (C-2′), 84.03 (C-4′), 90.64 (C-1′), 108.35 (C-5), 136.90 (C-6), 159.97 (C-2), 171.36 (C-4)
1b	(DMSO-d_6): 2.26 (m, 1H, 3′α-H), 2.49 (m, 1H, 3′β-H), 3.24 (m, 2H, 5′-H), 4.39 (m, 1H, 4′-H), 4.92 (t, 1H, J = 5.1, OH), 5.59 (t, 1H, J = 6.5, 2′-H), 6.19 (d, 1H, J = 5.7, 1′-H), 8.24 (d, 1H, J = 4.7, 6-H)	(DMSO-d_6): 32.77 (C-3′), 62.73 (C-5′), 82.38 (C-2′), 84.97 (C-4′), 91.36 (C-1′), 121.29 (C-6, J = 37.1), 145.15 (C-5, J = 248.1), 157.61 (C-2), 163.63 (C-4, J = 16.9)
1c	(DMSO-d_6): 1.79 (s, 3H, CH_3), 2.21 (m, 1H, 3′α-H), 2.45 (m, 1H, 3′β-H), 3.18 (t, 2H, J = 5.1, 5′-H), 4.33 (m, 1H, 4′-H), 4.90 (t, 1H, J = 5.1, OH), 5.52 (t, 1H, J = 5.9, 2′-H), 6.20 (d, 1H, J = 5.6, 1′-H), 7.74 (s, 1H, 6-H)	(DMSO-d_6): 13.44 (CH_3), 32.87 (C-3′), 62.90 (C-5′), 82.97 (C-2′), 83.71 (C-4′), 90.82 (C-1′), 116.38 (C-5), 132.28 (C-6), 159.54 (C-2), 171.76 (C-4)
7[a]	Predominant anomer ($CDCl_3$): 2.38 (m, 1H, 3α-H), 2.40 (s, 3H, p-CH_3), 2.56 (m, 1H, 3β-H), 3.33 (s, 3H, OCH_3), 4.27–4.35 (m, 2H, 2-H, 5-H), 4.48 (dd, 1H, J = 11.7, 3.5, 5-H), 4.78 (m, 1H, 4-H), 5.13 (s, 1H, 1-H), 7.23 (d, 2H_{arom}, J = 8.1), 7.97 (d, 2H_{arom}, J = 8.1)	($CDCl_3$): 21.49 (p-CH_3), 35.79, 36.71 (C-3), 47.92, 50.03 (C-2), 54.49, 54.74 (OCH_3), 65.85, 66.06 (C-5), 76.17, 77.21 (C-4), 109.69, 110.38 (C-1), 127.07 (C-1 phenyl), 128.94, 129.61, 129.69 (CH phenyl), 143.63 (C-4 phenyl), 166.22 (C=O)
8	Predominant anomer ($CDCl_3$): 2.39 (s, 3H, p-CH_3), 3.40 (s, 3H, OCH_3), 4.39 (m, 2H, 5-H), 5.01 (br s, 1H, 4-H), 5.73–5.92 (m, 2H), 1-H, 2-H), 6.20 (m, 1H, 3-H), 7.22 (d, 2H_{arom}, J = 8.0), 7.97 (d, 2H_{arom}, J = 8.0 Hz)	($CDCl_3$): 21.63 (p-CH_3), 54.12, 54.61 (OCH_3), 65.69, 66.46 (C-5), 83.41, 83.67 (C-4), 109.49 (C-1), 127.40 (phenyl), 128.32, 128.51 (C-2), 129.05, 129.11, 129.74, 129.82 (phenyl). 131.80, 132.27 (C-3), 143.65, 143.78 (phenyl)
11a	(DMSO-d_6): 2.38 (m, 1H, 3′α-H), 2.64 (m, 1H, 3′β-H), 3.46 (d, 1H, J = 11.8, 5′-H), 3.60 (d, 1H, J = 11.8, 5′-H), 4.55 (m, 1H, 4′-H), 4.97 (br s, 1H, OH)(, 5.04 (m, 1H, 2′-H), 5.64 (d, 1H, J = 8.1, 5′-H), 5.97 (d, 1H, J = 4.2, 1′-H), 7.65 (d, 1H, J = 8.1, 6-H), 11.41 (s, 1H, N3-H)	(DMSO-d_6): 36.62 (C-3′), 52.87 (C-2′), 62.43 (C-5′), 79.84 (C-4′), 86.42 (C-1′), 100.35 (C-5), 140.25 (C-6), 150.00 (C-2), 163.01 (C-4)
11b	(DMSO-d_6): 2.39 (m, 1H, 3′α-H), 2.64 (m, 1H, 3′β-H), 3.45 (br s, 1H, 5′-H), 3.61 (dd, 1H, J = 11.8, 3.2, 5′-H), 4.61 (m, 1H, 4′-H), 5.05 (m, 1H, 2′-H), 5.98 (d, 1H, J = 3.3, 1′-H), 7.96 (d, 1H, J = 7.0, 6-H), 11.99 (br s, 1H, N3-H)	(DMSO-d_6): 36.62 (C-3′), 52.60 (C-2′), 62.42 (C-5′), 80.08 (C-4′), 87.57 (C-1′), 124.8 (C-6, J = 34.9), 139.27 (C-5, J = 230.4), 148.53 (C-2), 156.96 (C-4, J = 26.0)
11c	(DMSO-d_6): 1.82 (s, 3H, CH_3), 2.39 (m, 1H, 3′α-H), 2.64 (m, 1H, 3′β-H), 3.46 (dd, 1H, J = 11.3, 3.6, 5′-H), 3.60 (dd, 1H, J = 11.3, 3.0, 5′-H), 4.57 (br s, 1H, 4′-H), 4.99–5.03 (m, 2H, OH, 2′-H), 5.98 (d, 1H, J = 5.2, 1′-H), 7.48 (s, 1H, 6-H), 11.35 (br s, 1H, N3-H)	(DMSO-d_6): 12.14 (CH_3), 36.63 (C-3′), 52.63 (C-2′), 62.54 (C-5′), 79.78 (C-4′), 86.25 (C-1′), 108.02 (C-5), 135.72 (C-6), 150.02 (C-2), 163.75 (C-4)
12	(DMSO-d_6): 2.36 (dd, 1H, J = 13.1, 5.9, 3′α-H), 2.65 (m, 1H, 3′β-H), 3.51 (m, 1H, 5′-H), 3.61 (m, 1H, 5′-H), 4.50 (m, 1H, 4′-H), 4.95 (t, 1H, J = 5.6, OH), 5.05 (br s, 1H, 2′-H), 5.75 (d, 1H, J = 7.5, 5-H), 5.88 (d, 1H, J = 3.6, 1′-H), 7.17 (s, 1H, NH_2), 7.24 (s, 1H, NH_2), 7.61 (d, 1H, J = 7.5, 6-H)	(DMSO-d_6): 36.83 (C-3′), 54.28 (C-2′), 62.45 (C-5′), 79.10 (C-4′), 86.92 (C-1′), 92.68 (C-5), 140.65 (C-6), 154.66 (C-2), 165.74 (C-4)
15	(DMSO-d_6): 1.76 (s, 3H, CH_3), 1.91 (m, 1H, 3′α-H), 2.16 (m, 1H, 3′β-H), 3.56 (d, 1H, J = 11.7, 5′-H), 3.78 (d, 1H, J = 11.7, 5′-H), 4.21 (br s, 1H, 4′-H), 4.46 (br s, 1H, 2′-H), 5.20 (br s, 1H, OH), 5.75 (s, 1H, 1′-H), 7.87 (s, 1H, 6-H), 11.34 (br s, 1H, N3-H)	(DMSO-d_6): 12.01 (CH_3), 30.14 (C-3′), 60.96 (C-5′), 65.22 (C-2′), 80.74 (C-4′), 88.78 (C-1′), 108.60 (C-5), 135.40 (C-6), 150.13 (C-2), 163.61 (C-4)
16	(DMSO-d_6): 1.80–1.93 (m, 4H, CH_3, 3′α-H), 2.42 (m, 1H, 3′β-H), 3.46 (br s, 2H, 5′-H), 4.50 (m, 2H, 2′-H, 4′-H), 4.91 (br s, 1H, OH), 5.77 (d, 1H, J = 4.3, 1′-H), 7.48 (s, 1H, 6-H), 11.36 (s, 1H, N3-H)	(DMSO-d_6): 11.87 (CH_3), 31.37 (C-3′), 62.92 (C-5′), 63.98 (C-2′), 80.60 (C-4′), 89.21 (C-1′), 109.47 (C-5), 135.80 (C-6), 150.28 (C-2), 163.60 (C-4)
17	(DMSO-d_6): 1.72 (s, 2H, 3′α-H, 3′β-H), 1.78 (s, 1H, CH_3), 3.34 (s, 2H, 5′-H), 4.54 (s, 1H, 4′-H), 4.96 (s, 1H, 2′-H), 5.41 (s, 1H, 1′-H), 7.43 (s, 1H, 6-H), 11.33 (s, 1H, N3-H)	(DMSO-d_6): 11.98 (CH_3), 31.20 (C-3′), 72.17, 76.61, 77.24 (C-2′, C-4′ and C-5′), 86.93 (C-1′), 108.27 (C-5), 134.70 (C-6), 149.84 (C-2), 163.67 (C-4)
18	(DMSO-d_6): 1.77 (s, 1H, CH_3), 3.48 (br s, 2H, 5′-H), 4.80 (br s, 1H, 4′-H), 5.07 (br s, 1H, OH), 5.93 (br s, 1H, 2′-H), 6.42 (br s, 1H, 3′-H), 6.87 (br s, 1H, 1′-H), 7.12 (s, 1H, 6-H), 11.25 (br, 1H, N3-H)	(DMSO-d_6): 11.84 (CH_3), 63.10 (C-5′), 87.58 (C-4′), 89.41 (C-1′), 109.69 (C-5), 125.49 (C-2′), 134.97 (C-3′), 135.60 (C-6), 150.46 (C-2), 163.66 (C-4)
19[a]	(D_2O): 1.89 (m, 4H, CH_3, 3′-H), 2.46 (m, 1H, 3′-H), 3.77 (m, 1H, 5′-H), 3.88 (m, 1H, 5′-H), 4.24 (br s, 1H, 4′-H), 4.62 (br s, 1H, 2′-H), 6.00 (br s, 1H, 1′-H), 7.77 (s, 1H, 6-H)	(D_2O): 14.23 (CH_3), 35.82 (C-3′), 65.31 (C-5′), 72.76 (C-2′), 80.73 (C-4′), 88.91 (C-1′), 112.52 (C-5), 141.38 (C-6), 154.21 (C-2), 169.11 (C-4)

[a] ^{1}H-NMR data correspond well with the corresponding data reported on an 80 MHz IBM NR/80 spectrometer.[5]

CH_2Cl_2 (2 × 150 mL). The organic layers are washed with cold H_2O, dried (Na_2SO_4), and evaporated under reduced pressure to give **10a–c** as crude product which is chromatographed on silica gel (100 g, 0.04–0.063 mm) using Et_2O/petroleum ether (bp 60–80°C), (2:1) to afford **10a–c** as a solid; yield: 63–68%.

1-(2-Bromo-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)uracil Derivatives 11a–c and 2,2′-Anhydro-3′-deoxyuridine Derivatives 1a–c; General Procedure:

To a stirred solution of **10a–c** (0.006 mol) in MeOH (40 mL), NaOMe [prepared from Na (0.138 g, 0.006 mol)] in MeOH (10 mL) is added dropwise at r.t. and stirring is continued for 2–4 h (**a**: 4 h; **b**: 2 h; **c**: 3 h). The stirred solution is neutralized by addition of NH_4Cl (0.32 g, 0.006 mol). The solvent is evaporated and the crude material is purified by column chromatography on silica gel (45 g, 0.04–0.063 mm) with 5–10% MeOH in CH_2Cl_2 to give **11a–c**; yield: 26–30%. The second fraction affords **1a–c**; yield: 57–67%.

1-(2-Bromo-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)cytosine (12) and 2,2′-Anhydro-3′-deoxyuridine (1a):

Et_3N (8.4 mL, 0.06 mol) is added dropwise to a stirred, cooled (ice-water bath) mixture of 1*H*-1,2,4-triazole (4.35 g, 0.063 mol), $POCl_3$ (1.26 mL, 0.0135 mol) and MeCN (50 mL). Compound **10a** (2.86 g, 0.007 mol) in MeCN (20 mL) is added and the mixture is stirred at r.t. for 5 h. Et_3N (5.84 ml, 0.042 mol) and H_2O (1.5 mL) are then added. After 10 min the solvent is evaporated under reduced pressure. The residue is partitioned between $CHCl_3$ (150 mL) and sat. aq $NaHCO_3$ (150 mL) and the phases are separated. The aqueous phase is extracted with $CHCl_3$ (200 mL). The combined organic layers are dried ($MgSO_4$) and evaporated. The residue is then dissolved in solution of 20% aq NH_3 (16.6 mL) and dioxane[15] (50 mL). The solution is stirred at r.t. After 4 h the mixture is evaporated under reduced pressure. The residue is then dissolved in solution of NaOMe [prepared from Na (69 mg, 0.003 mol] in MeOH (30 mL) and the solution is stirred for 2 h. The stirred solution is neutralized by addition of NH_4Cl (160 mg, 0.003 mol). The solvent is evaporated and the crude material is purified by column chromatography on silica gel (45 g, 0.04–0.063 mm) with Et_2O/MeOH (9:1) to give **12**; yield: 0.63 g (22%); the second fraction affords **1a**: 0.23 g (8%).

1-(2-Azido-2,3-dideoxy-5-*O*-(4-methylbenzoyl)-β-D-*threo*-pentofuranosyl)thymine (13) and its α-Anomer (14):

Compound **10c** (1.21 g, 0.00286 mol) is dissolved in dry DMF (30 mL) and NaN_3 (1.86 g, 0.0286 mol) is added. The solution is stirred for 4 h at 100°C. Working up in the same way as reported for **5**[8] followed by chromatography on silica gel (40 g, 0.04–0.063 mm) with Et_2O/petroleum ether (bp 60–80°C), (95:5) to give **13**; yield: 0.54 g (49%); the second fraction affords **14**; yield: 0.32 g (29%).

1-(2-Azido-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (15) and Its α-Anomer (16):

Compound **13** or **14** (0.46 g, 0.0012 mol) in a 1:1 mixture (34 mL) of MeOH and conc. NH_3 is stirred at r.t. for 24 h. The solvent is evaporated under reduced pressure. The residue is chromatographed on silica gel (35 g, 0.04–0.063 mm) with Et_2O to give **15**; yield: 0.25 g (78%).

IR (KBr): $\nu = 2133\ cm^{-1}$ (azido).

16; yield: 0.192 g (60%).

IR (KBr): $\nu = 2112\ cm^{-1}$ (azido).

1-(2,5-Anhydro-3-deoxy-α-D-*threo*-pentofuranosyl)thymine (17) and 1-(2,3-dideoxy-α-D-*glycero*-pent-2-enofuranosyl)thymine (18):

To a stirred solution of **11c** (0.397 g, 0.0013 mol) in MeOH (30 mL) is added a solution of NaOMe [prepared from Na (0.239 g, 0.0104 mol)] in MeOH (20 mL). The stirred solution is then refluxed for 30 h. After cooling to r.t., the mixture is neutralized with NH_4Cl (0.556 g, 0.0104 mol). The solvent is evaporated and the crude material is purified by column chromatography on silica gel (40 g, 0.04–0.063 mm) with 2% of MeOH in CH_2Cl_2 to give **17**; yield: 146 mg (50%). The second fraction affords **18**; yield: 58 mg (20%).

IR (KBr): $\nu = 1690\ cm^{-1}$ (C=O).

1-(3-Deoxy-β-D-*threo*-pentofuranosyl)thymine (19):

Compound **1** (0.291 g, 0.0013 mol) is treated with NaOMe for 48 h under reflux in the same way as described for **17** and **18**. Silica gel chromatography with 5% of MeOH in CH_2Cl_2 affords **19**; yield: 0.246 g (78%);

UV (EtOH): $\lambda_{max} = 268$ nm ($\varepsilon = 7100$), Lit.[5] UV: (EtOH): $\lambda_{max} = 268$ nm ($\varepsilon = 9500$).

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