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Synthesis of 3′-Dialkylamino-2′,3′-dideoxynucleosides from a 2,3′-Anhydrothymidine or an α,β-Unsaturated Aldehyde

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Reaction of 2,3′-anhydro-5′-*O*-(4-methoxybenzoyl)thymidine (**2**) with morpholine, piperidine and piperazine gives the corresponding deprotected 3′-dialkylaminonucleosides **3a–c** in 7–47% yield and with 1,2,4-triazole the protected analog **4** in 8% yield. The reaction of **2** with triazole, in the presence of phosphoryl trichloride cleaved the glycosidic bond and triazole replaced the nucleobase to give the glycosylated α and β nucleosides **5** and **6** with the 2,3′-ether bond intact to the pyrimidine ring, but also with a triazole ring substituted into the 4-position of the pyrimidine ring. (2*E*,4*S*)-5-Acetoxy-4-hydroxy-2-pentenal (**10**), readily accessible from tri-*O*-acetyl-D-glucal (**9**), reacted with piperidine and morpholine to give anomeric mixtures of 2,3-dideoxy-3-piperidino and 2,3-dideoxy-3-morpholino-α,β-D-*erythro*-pentofuranoses which were acetylated to give **11**. Trimethylsilyl trifluoromethanesulfonate catalyzed reactions of **11** with silylated forms of thymine and N^4-isobutyrylcytosine gave, after chromatographic separation, the acetylated D-*erythro* nucleosides, which by treatment with methanolic ammonia were deprotected to the free nucleosides **3**, **12–14**.

Since the discovery of 3′-azido-2′,3′-dideoxythymidine (AZT) as a selective anti-HIV agent, further search for effective inhibitors of HIV replication has led to the discovery of a variety of 2′,3′-dideoxynucleosides. Unfortunately all 2′,3′-dideoxynucleosides with appreciable anti-HIV activity have considerable cytotoxic effects as well.[1–3] Therefore, the need for new compounds, with improved potency and selectivity in their antiviral action, is still urgent. A great deal of effort has been made for the development of specific chemical transformations suitable for introducing the desired modifications into the sugar moiety of nucleosides. In this respect the introduction of primary and secondary amino groups at C-3′, has proved to be a particularly difficult task. Simple 3′-aminonucleosides were earlier prepared from the corresponding natural 2′-deoxynucleosides via the introduction of an azide[4–6] or phthalimide[7] group using an S_N2 reaction, followed by reduction or deblocking to give the corresponding 3′-aminonucleoside. Vial *et al.* have recently tried to introduce different alkylamino groups at C-3′ by nucleophilic displacement of 3′-*O*-mesylnucleosides.[8] This gave mainly the elimination product, except in the reaction of 1-(5-*O*-trityl-2-deoxy-3-*O*-mesyl-β-D-*threo*-pentofuranosyl)thymine with morpholine, which afforded 2′,3′-dideoxy-3′-morpholinothymidine (**3b**) and was reported to show some selective inhibition of HIV replication. Anhydropyrimidine nucleosides have been used as intermediates in the synthesis of a variety of nucleosides. Cleavage of the O^2,2′-linkage of 2,2′-anhydrouridine with a variety of nucleophiles such as ammonia,[9] hydrogen sulfide,[10,11] fluorine, chlorine and bromine ion[12] and azide[13] have been reported. In a similar type of reaction treatment of 2,3′-anhydro-2′-deoxythymidine with phthalimide, thiobenzoic acid or sodium azide gave the corresponding 3′-amino, 3′-thio and 3′-azido compounds.[14,15] This type of reaction has also been achieved via *N*-3 alkylation of 2,3′-anhydrothymidine.[16]

In this paper we report the synthesis of 3′-alkylamino-2′,3′-dideoxynucleosides by two routes: one using an 2,3′-anhydrothymidine as the starting material (*nucleoside route*) and the other an α,β-unsaturated aldehyde (*sugar route*).

Results and discussion

Nucleoside route. 2,3′-Anhydro-5′-*O*-(4-methoxybenzoyl)-thymidine (**2**) was prepared in a 'one pot' transformation

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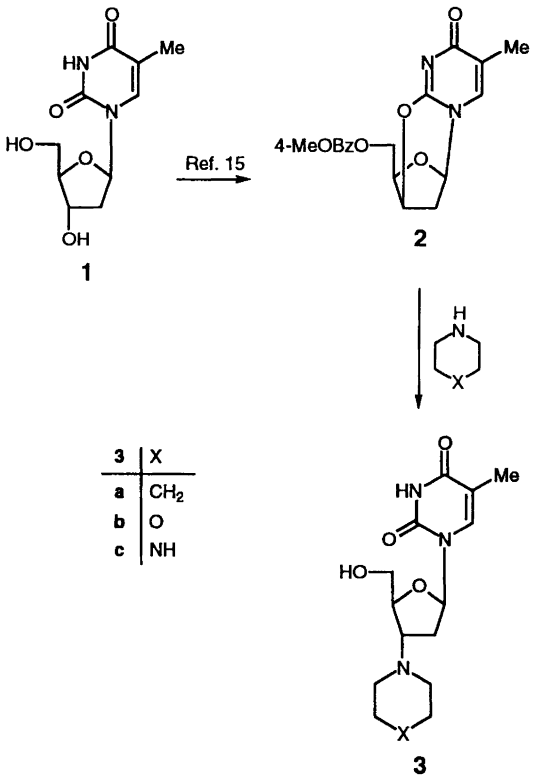
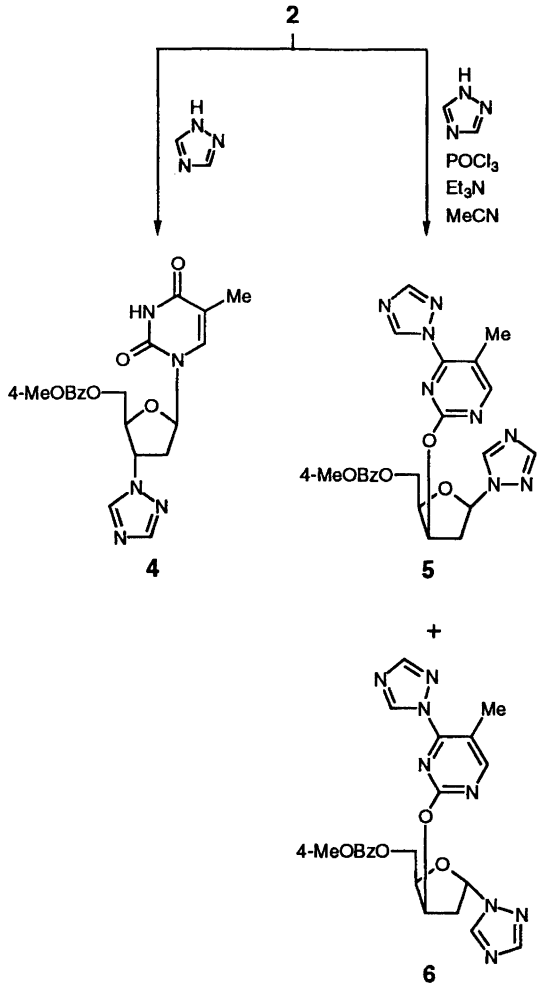
from thymidine (**1**) as previously reported.[15] Reaction of piperidine, morpholine and piperazine with **2** at 120–160 °C for 1–6 days gave, after purification by column chromatography on silica, the corresponding deprotected 2′,3′-dideoxy-3′-alkylaminonucleosides **3a–c** in 7–47% yield. No cleavage of the glycosidic bond or base-induced β-elimination was observed under these conditions, but other unidentified decomposition products were observed.



Scheme 1.

The reaction of **2** with 1,2,4-triazole at 160 °C for 4 h gave 2′,3′-dideoxy-5′-*O*-(4-methoxybenzoyl)-3′-(1,2,4-triazol-1-yl)thymidine (**4**) in 8% yield after separation by a column chromatography on silica gel.

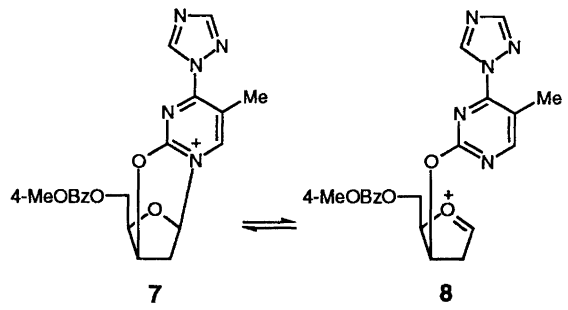
The same reaction was carried out in the presence of phosphoryl trichloride and triethylamine in anhydrous acetonitrile first at 0 °C, then 90 min at room temperature and finally 1 day at 50 °C. Purification by column chromatography on silica afforded 1-{2,3-dideoxy-5-*O*-(4-methoxybenzoyl)-3-*O*-[5-methyl-4-(1,2,4-triazol-1-yl)-2-pyrimidinyl]-β-D-*threo*-pentofuranosyl}-1,2,4-triazole (**5**) and the corresponding α anomer **6** in 7% yield. It was only possible to separate the isomers by the use of reversed-phase HPLC. It was not possible to deprotect **5** and **6** because of complex reaction mixtures. The NMR data of **5** and **6** showed the presence of two sets of triazole rings and only one set of sugar ring signals. If one of these triazole rings were attached to the 3′-position we would expect a signal in the ^{13}C NMR spectrum at around 58 ppm.[17] However, such a signal was not



Scheme 2.

present and instead we observed a downfield shift of the C-3′ signal (δ = 75). These results led us to consider a structure corresponding to the bistriazole nucleoside **5**, with an intact 2,3′-ether bond. The ^{13}C NMR value for C-3′ is consistent with those reported by Goulaouic *et al.*[18] for the 3-(2-pyrimidinyl)oxy-2,3-dideoxyxylofuranosyl azide. These compounds were obtained by reaction of 2,3′-anhydrothymidine with alkyl triflate followed by NaN_3 and the structures were confirmed by X-ray diffraction. According to ^1H–^1H and ^1H–^{13}C 2D NMR spectra the following order was established. The 3″-H and 5″-H of the triazole ring attached to C-1′ of **5** appears at higher field than the corresponding 3″-H and 5″-H of the triazole ring at C-4. Comparison of the ^1H NMR spectra of **5** and **2** showed that H-6 in **5** resonates at lower field than that in **2** (δ 8.41 versus δ 7.54) consistent with the reported observations.[18] The formation of an anomeric mixture of C-1′ triazole substituted compound **5** and **6** may be explained by the formation of the oxonium ion **8** via the pyrimidinium salt **7**.

Sugar route. Our research group has developed a method for the synthesis of anomalously coupled nucleosides by

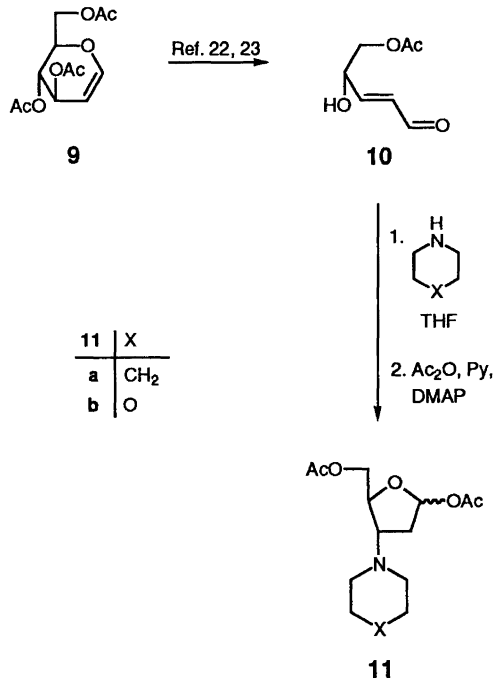


7 8

Scheme 3.

Michael-type addition reaction to α,β-unsaturated sugar aldehydes.[19–22] This method leads in few steps to 3′-substituted-2′,3′-dideoxynucleosides starting from commercially accessible sugars or glucals. Lichtenthaler *et al.* has used the commercially available tri-*O*-acetyl-D-glucal (**9**) for a one-step synthesis of (2*E*,4*S*)-5-acetoxy-4-formyloxy-2-pentenal,[23] a convenient intermediate which can be synthesized on a large scale. In a recent paper[24] we have shown this α,β-unsaturated aldehyde to be selectively deformylated with sodium bicarbonate in methanol, to give (2*E*,4*S*)-5-acetoxy-4-hydroxy-2-pentenal (**10**). By a Michael-type reaction of piperidine and morpholine with the α,β-unsaturated aldehyde **10** and subsequent acetylation with acetic anhydride in dry pyridine and 4-dimethylaminopyridine (DMAP), we obtained anomeric mixtures of 2,3-dideoxy-3-piperidino-D-*erythro*-pentofuranose **11a** in 29% yield and 2,3-dideoxy-3-morpholino-D-*erythro*-pentofuranose **11b** in 30% yield, respectively. Only the *erythro* isomer was isolated. This is in agreement with previously reported results, where formation of the *threo* isomer was not observed when piperidine was reacted in a Michael-type reaction with 4,6-di-*O*-acetyl-2,3-dideoxyhex-2-enose.[25]

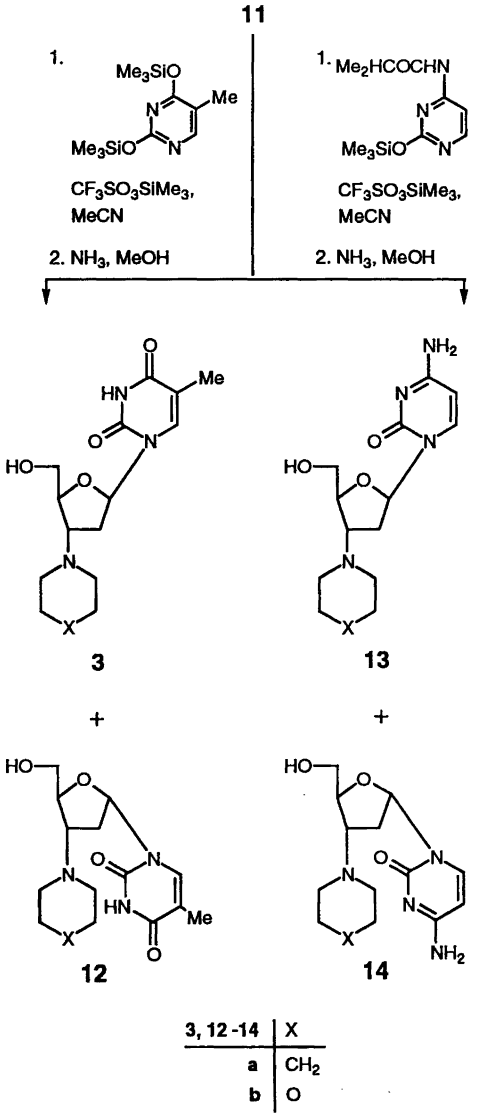
Using the silyl Hilbert–Johnson method as modified by Vorbrüggen *et al.*[26,27] with trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the Friedel–Crafts catalyst, coupling of the sugars **11** with silylated thymidine[28] or silylated N^4-isobutyrylcytosine[28] in acetonitrile gave 1:1 anomeric mixtures of the corresponding nucleosides. Column chromatography was used for separation of the anomers. Deprotection using ammonia in methanol gave the final nucleosides **3**, **12–14**.



9 10 11

11	X
a	CH_2
b	O

Scheme 4.



3, 12-14	X
a	CH_2
b	O

Scheme 5.

The assignment of the anomeric configuration of all new nucleosides was made by ^{1}H NMR analysis by comparing the chemical shifts for 1′-H, 4′-H and 5′-H. The anomeric protons of the α-anomers were observed further downfield than those of the corresponding β-anomers. The 4′-H shift from the α-anomers appears at lower field

than the 4′-H shift from the β-anomer, and the 5′-H shift from the α-anomer appears at higher field than the 5′-H shift from the β-anomer.[18,29]

In summary, two methods for the synthesis of 3′-dialkylamino nucleosides are presented. Although, the nucleoside route in general gives higher overall yields, the sugar route strategy has the advantage that it can be extended to the preparation of a variety of modified nucleosides from just one precursor **11**.

Experimental

NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C.

2′,3′-Dideoxy-3′-dialkylaminonucleosides **3a–c** *and triazole nucleoside* **4**. *General procedure.* A mixture of **2**[15] (0.5 g, 1.4 mmol) and the corresponding amine (14 mmol) was refluxed for 5 days (**3a**), 6 days (**3b**), 1 day (**3c**) and 4 h (**4**). The reaction mixture was cooled and evaporated *in vacuo*. Chromatographic purification on silica gel with $CHCl_3$–MeOH (99:1 v/v) for **4**, $CHCl_3$–MeOH (96:4 v/v) for **3b**, and $CHCl_3$–MeOH (95:5 v/v) for **3a,c** gave **3a–c** in 7–47% and **4** in 8% yield.

2′,3′-Dideoxy-3′-piperidinothymidine (**3a**). Yield: 28 mg (7%). This compound was also synthesized by the sugar route. See the general procedure for compounds **3** and **12**. ^{1}H NMR (CD_3OD): δ 1.59–1.76 (m, 6 H, 3 × CH_2), 1.97 (d, *J* 1.1 Hz, 3 H, 5-CH_3), 2.10–2.22 (m, 1 H, 2′β-H), 2.60–2.73 (m, 5 H, 2′α-H, 2 × CH_2), 3.40–3.48 (m, 1 H, 3′-H), 3.80 (dd, *J* 4.0 and 12.0 Hz, 1 H, 5′-H), 3.95 (dd, *J* 2.7 and 12.0 Hz, 1 H, 5′-H), 4.23 (dd, *J* 4.0 and 7.1 Hz, 1 H, 4′-H), 6.23 (t, *J* 6.9 Hz, 1 H, 1′-H), 7.95 (d, *J* 1.1 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 12.42 (5-CH_3), 25.09, 26.73, 52.13 (piperidino), 34.25 (C-2′), 64.23, 66.52 (C-3′, C-5′), 83.90, 87.10 (C-1′, C-4′), 111.39 (C-5), 138.18 (C-6), 152.41 (C-2), 166.43 (C-4). MS: *m/z* (%) 309 (11, M^+), 249 (3), 184 (5), 124 (100), 110 (16). Anal $C_{15}H_{23}N_3O_4 \cdot H_2O$: C, H, N.

2′,3′-Dideoxy-3′-morpholinothymidine (**3b**). Yield: 98 mg (23%) as a foam. NMR spectra were identical with those previously reported.[8] This compound was synthesized in the sugar route. See the general procedure for compounds **3** and **12**.

2′,3′-Dideoxy-3′-piperazin-1-ylthymidine (**3c**). Yield: 202 mg (47%). ^{1}H NMR (CD_3OD): δ 1.75 (s, 3 H, 5-CH_3), 1.91–1.99 (m, 1 H, 2′-H), 2.33–2.64 (m, 9 H, 2′-H, piperazinyl), 3.11–3.27 (m, 1 H, 3′-H), 3.58 (dd, *J* 3.6 and 11.7 Hz, 1 H, 5′-H), 3.68–3.76 (m, 1 H, 5′-H), 3.97 (m, 1 H, 4′-H), 6.01 (t, *J* 6.5 Hz, 1 H, 1′-H), 7.79 (s, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 12.96 (5-CH_3), 35.71 (C-2′), 48.10, 50.16 (piperazinyl), 64.20 (C-5′), 66.31 (C-3′), 83.99 (C-4′), 87.06 (C-1′), 111.59 (C-5), 138.41 (C-6), 152.82 (C-2), 166.88 (C-4). FAB MS (DMSO, glycerol): *m/z* (%) 311 (58, $M + H^+$).

2′,3′-Dideoxy-5′-O-(4-methoxybenzoyl)-3′-(1,2,4-triazol-1-yl)thymidine (**4**). Yield: 46 mg (8%), m.p. 83–85°C. ^{1}H NMR ($CDCl_3$): δ 1.77 (5-CH_3), 2.63–2.75 (m, 1 H, 2′-H), 2.98–3.09 (m, 1 H, 2′-H), 3.86 (s, 3 H, OCH_3), 4.55–4.67 (m, 3 H, 4′-H, 5′-H), 5.26–5.34 (m, 1 H, 3′-H), 6.29 (dd, *J* 5.5 and 7.1 Hz, 1 H, 1′-H), 6.93 (d, *J* 8.8 Hz, 2 H, ArH), 7.23 (d, *J* 0.9 Hz, 1 H, 6-H), 7.95 (d, *J* 8.9 Hz, 2 H, ArH), 8.03 (s, 1 H, 3″-H triazole), 8.30 (s, 1 H, 5″-H triazole), 9.73 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 12.16 (5-CH_3), 37.70 (C-2′), 55.38 (OCH_3), 58.94 (C-3′), 62.92 (C-5′), 81.67 (C-4′), 86.94 (C-1′), 111.25 (C-5), 113.83, 121.25, 131.57 (aryl), 136.00 (C-6), 143.40 (C-5″, triazole), 150.15 (C-2), 152.75 (C-3″, triazole), 163.71, 163.83, 165.70 (aryl, C-4, C=O). FAB MS ($CHCl_3$, NBA): *m/z* (%) 428 (61, $M + H^+$).

*1-{2,3-Dideoxy-5-O-(4-methoxybenzoyl)-3-O-[5-methyl-4-(1,2,4-triazol-1-yl)-2-pyrimidinyl]-β-D-*threo*-pentofuranosyl}-1,2,4-triazole* (**5**) *and* 1-{2,3-*dideoxy*-5-O-*(4-methoxybenzoyl)-3-O-[5-methyl-4-(1,2,4-triazol-1-yl)-2-pyrimidinyl]-α-D-*threo*-pentofuranosyl}-1,2,4-triazole* (**6**). A solution of 2,3′-anhydro-5′-*O*-(4-methoxybenzoyl)thymidine (**2**)[15] in dry MeCN (70 ml) was added dropwise to a suspension of 1,2,4-triazole (5.2 g, 75 mmol), $POCl_3$ (2.5 g, 16.1 mmol) and Et_3N (7.3 g, 72 mmol) in MeCN (100 ml) at 0°C. The temperature was allowed to rise and after being stirred at room temperature for 90 min the mixture was heated at 50°C for 1 day. During this time the mixture became yellow. After cooling, the reaction was quenched with Et_3N (6.9 ml, 44.6 mmol) in H_2O (2 ml). The solvents were evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (200 ml) and washed with sat. aq. $NaHCO_3$ (2 × 100 ml). The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel (50 g) with CH_2Cl_2–MeOH (95:5 v/v) to yield an anomeric mixture of **5** and **6** in 7% yield. The anomers were separated by reversed-phase HPLC (RP-18, 300 Å, 15 μ, H_2O–EtOH, 95:5 v/v) to give compounds **5** and **6** as white solids.

Compound **5**. 91 mg (2%), m.p. 82°C. ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3 H, 5-CH_3), 2.94–2.99 (m, 2 H, 2′-H), 3.83 (s, 3 H, OCH_3), 4.70–4.81 (m, 3 H, 4′-H, 5′-H), 5.87–5.88 (m, 1 H, 3′-H), 6.28 (dd, *J* 2.5 and 6.2 Hz, 1 H, 1′-H), 6.84 (d, *J* 9.0 Hz, 2 H, ArH), 7.88 (d, *J* 8.8 Hz, 2 H, ArH), 7.96 (s, 1 H, 5″-H, triazole at C-1′), 8.11 (s, 1 H, 5″-H, triazole at C-4), 8.41 (s, 1 H, 6-H), 8.72 (s, 1 H, 3″-H, triazole at C-1′), 9.12 (s, 1 H, 3″-H, triazole at C-4). ^{13}C NMR ($CDCl_3$): δ 16.12 (5-CH_3), 38.82 (C-2′), 55.28 (OCH_3), 62.28 (C-5′), 75.39 (C-3′), 81.12 (C-4′), 88.21 (C-1′), 113.48 (aryl), 115.10 (C-5), 121.66, 131.52 (aryl), 142.50, 144.07, 151.07, 153.03 (triazole), 154.45 (C-4), 161.75, 163.47, 165.45 (aryl, C-2, C=O), 164.15 (C-6). FAB MS ($CHCl_3$, 3-nitrobenzyl alcohol): *m/z* (%) 479 (49, $M + H^+$).

Compound **6**. 217 mg (5%), m.p. 83°C. ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3 H, 5-CH_3), 2.83 (ddd, *J* 3.6, 7.1 and 14.6 Hz, 1 H, 2′-H), 3.27 (ddd, *J* 4.1, 6.2 and 14.5 Hz,

1 H, 2′-H), 3.83 (s, 3 H, OCH_3), 4.54 (dd, *J* 6.5 and 12.0 Hz, 1 H, 5′-H), 4.69 (dd, *J* 4.9 and 12.0 Hz, 1 H, 5′-H), 4.90 (dt, *J* 4.8 and 9.8 Hz, 1 H, 4′-H), 6.13–6.19 (m, 1 H, 3′-H), 6.38 (dd, *J* 4.1 and 7.1 Hz, 1 H, 1′-H), 6.84 (d, *J* 9.0 Hz, 2 H, ArH), 7.88 (d, *J* 8.8 Hz, 2 H, ArH), 8.01 (s, 1 H, 5″-H, triazole at C-1′), 8.13 (s, 1 H, 5″-H, triazole at C-4), 8.31 (s, 1 H, 3″-H, triazole at C-1′), 8.46 (s, 1 H, 6-H), 9.16 (s, 1 H, 3″-H, triazole at C-4). ^{13}C NMR ($CDCl_3$): δ 16.12 (5-CH_3), 38.82 (C-2′), 55.28 (OCH_3), 62.28 (C-5′), 76.56 (C-3′), 79.61 (C-4′), 86.32 (C-1′), 113.48 (aryl), 115.10 (C-5), 126.66, 131.52 (aryl), 143.44, 144.07, 152.39, 153.03 (triazole), 154.45 (C-4), 162.20, 163.47, 165.45 (aryl, C-2, C = O), 164.34 (C-6). FAB MS ($CHCl_3$, 3-nitrobenzyl alcohol): *m/z* (%) 479 (19, $M + H^+$).

1,5-Di-O-*acetyl-2,3-dideoxy-3-piperidino-α,β-D*-erythro-*pentofuranose* (**11a**). The unsaturated aldehyde **10** (5.0 g, 31.6 mmol) in dry THF (200 ml) was added dropwise over 1 h to a solution of piperidine (3.2 g, 37.6 mmol) in dry THF (300 ml). The reaction mixture was stirred for 2 h at room temperature. After addition of dry pyridine (14 g, 0.177 mol), Ac_2O (24 g, 0.235 mol) and 4-dimethylaminopyridine (DMAP, 0.6 g, 4.9 mmol) stirring was continued for 2 h at room temperature. After evaporation of the solvent under reduced pressure a brown oil was obtained. For purification of this oil column chromatography on silica gel (200 g) with CH_2Cl_2–CH_3OH, 99:1 (v/v) was used and **11a** was obtained as a yellow oil; yield: 2.6 g (29%). ^1H NMR ($CDCl_3$) predominant anomer: δ 1.44–1.59 (m, 6 H, 3 × CH_2), 2.03 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.14–2.22 (m, 2 H, 2-H), 2.40–2.47 (m, 4 H, 2 × CH_2), 2.98–3.06 (m, 1 H, 3-H), 4.06–4.32 (m, 3 H, 4-H, 5-H), 6.31 (dd, *J* 1.7 and 4.4 Hz, 1 H, 1-H). ^{13}C NMR ($CDCl_3$) predominant anomer: δ 20.49, 20.97 (2 × OAc), 23.92, 25.66, 51.85 (piperidino), 35.04 (C-2), 65.40, 66.70 (C-3, C-5), 80.26 (C-4), 98.65 (C-1), 169.57, 170.38 (2 × OAc). MS: *m/z* (%) 287 (11, M^+), 226 (48), 166 (100), 140 (48), 124 (45), 43 (20).

1,5-Di-O-*acetyl-2,3-dideoxy-3-morpholino-α,β-D*-erythro-*pentofuranose* (**11b**). Same procedure as for **11a** except that morpholine (3.3 g, 37.9 mmol) was used instead of piperidine. For purification a silica gel column (200 g) with petroleum ether–diethyl ether, 1:1 (v/v) was used and **11b** was obtained as an oil; yield: 2.7 g (30%). ^1H NMR ($CDCl_3$) predominant anomer: δ 2.05 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.13–2.23 (m, 2 H, 2-H), 2.48–2.56 (m, 4 H, 2 × CH_2), 3.01–3.07 (m, 1 H, 3-H), 3.66–3.74 (m, 4 H, 2 × CH_2), 4.05–4.34 (m, 3 H, 4-H, 5-H), 6.32–6.35 (m, 1 H, 1-H). ^{13}C NMR ($CDCl_3$) predominant anomer: δ 20.82, 21.30 (2 × OAc), 35.24 (C-2), 51.52, 66.87 (morpholino), 65.77, 67.06 (C-3, C-5), 80.64 (C-4), 98.86 (C-1), 169.87, 170.74 (2 × OAc). MS: *m/z* (%) 287 (20, M^+), 228 (70), 168 (100), 142 (79), 126 (53), 43 (62).

Compounds **3** *and* **12**. *General procedure*. 2,4-*O*-Bis(trimethylsilyl)thymine (0.74 g, 28 mmol) was dissolved in dry MeCN (10 ml) and **11** (1.8 mmol) dissolved in dry MeCN (10 ml) was added. The mixture was cooled to −30°C and $CF_3SO_3SiMe_3$ (0.42 ml, 19 mmol) was added dropwise with stirring. After 2 h at −30°C and 18 h at room temperature, CH_2Cl_2 (100 ml) was added to the mixture. This solution was washed with cold sat. aq. $NaHCO_3$ (3 × 50 ml) and cold water (3 × 50 ml). The organic phase was dried over Na_2SO_4 and subsequently evaporated under reduced pressure. The residue was chromatographed on a silica column (70 g) with 1–3% MeOH in CH_2Cl_2 to give the protected β anomer as the more polar isomer and the α anomer as the less polar isomer. Each of the protected nucleosides were dissolved in sat. ammonia in methanol, and stirred at room temperature for 20 h. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (60 g) with 3–5% MeOH in CH_2Cl_2 to obtain the unprotected nucleosides **3** and **12**. Yield **3a** 115 mg (21%) as an oil and **3b** 100 mg (18%) as a foam.

1-(2,3-Dideoxy-3-piperidino-α-D-erythro-*pentofuranosyl)-thymine* (**12a**). Yield: 110 mg (20%) as an oil. ^1H NMR ($CDCl_3$): δ 1.58–1.72 (m, 6 H, 3 × CH_2), 2.00 (d, *J* 0.9 Hz, 3 H, 5-CH_3), 2.24 (dd, *J* 6.8 and 13.5 Hz, 1 H, 2′β-H), 2.56–2.67 (m, 5 H, 2 × CH_2, 2′α-H), 3.05–3.15 (m, 1 H, 3′-H), 3.67 (dd, *J* 5.0 and 12.1 Hz, 1 H, 5′-H), 3.81 (dd, *J* 3.3 and 12.1 Hz, 1 H, 5′-H), 4.46 (dd, *J* 4.9 and 8.3 Hz, 1 H, 4′-H), 6.26 (t, *J* 6.3 Hz, 1 H, 1′-H), 7.87 (d, *J* 1.0 Hz, 1 H, 6-H). ^{13}C NMR ($CDCl_3$): δ 12.77 (5-CH_3), 25.42, 27.14, 54.17 (piperidino), 36.17 (C-2′), 65.12, 67.11 (C-3′, C-5′), 84.63, 87.09 (C-1′, C-4′), 111.58 (C-5), 138.76 (C-6), 152.70 (C-2), 166.71 (C-4). MS: *m/z* (%) 309 (8, M^+), 249 (3), 184 (5), 124 (100), 110 (18). Anal $C_{15}H_{23}N_3O_4 \cdot 0.75H_2O$: C, H, N.

1-(2,3-Dideoxy-3-morpholino-α-D-erythro-*pentofuranosyl)-thymine* (**12b**). Yield: 90 mg (16%) as a foam. ^1H NMR (CD_3OD): δ 2.00 (d, *J* 1.0 Hz, 3 H, 5-CH_3), 2.28 (td, *J* 5.6 and 13.9 Hz, 1 H, 2′β-H), 2.54–2.64 (m, 5 H, 2 × CH_2, 2′α-H), 3.02–3.09 (m, 1 H, 3′-H), 3.62–3.82 (m, 6 H, 2 × CH_2, 5′-H), 4.50 (dd, *J* 4.6 and 8.4 Hz, 1 H, 4′-H), 6.27 (dd, *J* 5.4 and 6.4 Hz, 1 H, 1′-H), 7.90 (d, *J* 1.1 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 12.82 (5-CH_3), 35.48 (C-2′), 53.44, 68.21 (morpholino), 64.83, 66.99 (C-3′, C-5′), 84.86, 87.36 (C-1′, C-4′), 111.19 (C-5), 138.99 (C-6), 152.65 (C-2), 166.70 (C-4). MS: *m/z* (%) 311 (7, M^+), 185 (10), 142 (3), 126 (100), 112 (7), 86 (8). Anal $C_{14}H_{21}N_3O_5 \cdot H_2O$: C, H, N.

Compounds **13** *and* **14**. *General procedure*. 2-*O*-Trimethylsilyl-N^4-isobutyrylcytosine[28] (0.89 g, 3.5 mmol) was dissolved in dry MeCN (10 ml) and **11** (0.70 g, 2.5 mmol) dissolved in dry MeCN (10 ml) was added. The mixture was cooled to −30°C and $CF_3SO_3SiMe_3$ (0.60 ml, 2.6 mmol) was added dropwise. After 2–4 h at −30°C analytical TLC showed no more starting material **11**. The

mixture was diluted with CH_2Cl_2 (100 ml) and washed with cold sat. aq. $NaHCO_3$ (100 ml) and cold water (3 × 50 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (60–200 g) with 2–3% MeOH in CH_2Cl_2 to give the protected more polar β anomer and the less polar α anomer. The protected nucleosides were each dissolved in sat. ammonia in methanol, and stirred at room temperature for 20 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (60 g) with CH_2Cl_2–MeOH, 90:10 (v/v).

2′,3′-Dideoxy-3′-piperidinocytidine (**13a**). Yield: 150 mg (20%) as a foam. ^{1}H NMR (CD_3OD): δ 1.59–1.74 (m, 6 H, 3 × CH_2), 2.05–2.17 (m, 1 H, 2′β-H), 2.63–2.80 (m, 5 H, 2′α-H, 2 × CH_2), 3.43–3.53 (m, 1 H, 3′-H), 3.80 (dd, *J* 4.2 and 12.0 Hz, 1 H, 5′-H), 3.93 (dd, *J* 2.8 and 12.0 Hz, 1 H, 5′-H), 4.29 (dd, *J* 4.0 and 7.1 Hz, 1 H, 4′-H), 6.03 (d, *J* 7.5 Hz, 1 H, 5-H), 6.22 (t, *J* 6.6 Hz, 1 H, 1′-H), 8.14 (d, *J* 7.5 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 24.92, 26.55, 52.04 (piperidino), 35.08 (C-2′), 64.20, 66.63 (C-3′, C-5′), 83.99, 88.39 (C-1′, C-4′), 96.06 (C-5), 142.65 (C-6), 158.40 (C-2), 167.52 (C-4). MS: *m/z* (%) 294 (1, M^+), 183 (35), 152 (38), 140 (81), 124 (52), 111 (100), 84 (65). Anal $C_{14}H_{22}N_4O_3 \cdot 2H_2O$: C, H, N.

2′,3′-Dideoxy-3′-morpholinocytidine (**13b**). Yield: 76 mg (10%) as an oil. ^{1}H NMR (CD_3OD): δ 2.13 (m, 1 H, 2′-H), 2.65–2.75 (m, 5 H, 2′-H, 2 × CH_2), 3.32–3.41 (m, 1 H, 3′-H), 3.77–3.83 (m, 5 H, 2 × CH_2, 5′-H), 3.94 (dd, *J* 3.0 and 12.1 Hz, 1 H, 5′-H), 4.24 (dd, *J* 4.2 and 8.0 Hz, 1 H, 4′-H), 6.12 (d, *J* 7.4 Hz, 1 H, 5-H), 6.21 (t, *J* 6.4 Hz, 1 H, 1′-H), 8.15 (d, *J* 7.5 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 35.16 (C-2′), 52.02, 68.18 (morpholino), 64.19, 66.17 (C-3′, C-5′), 84.28, 88.32 (C-1′, C-4′), 96.30 (C-5), 143.02 (C-6), 158.60 (C-2), 167.73 (C-4). MS: *m/z* (%) 296 (1, M^+), 185 (22), 154 (19), 142 (85), 126 (32), 111 (100), 87 (51). Anal $C_{13}H_{20}N_4O_4 \cdot 0.75H_2O$: C, H, N.

*1-(2,3-Dideoxy-3-piperidino-α-D-*erythro*-pentofuranosyl) cytosine* (**14a**). Yield: 230 mg (31%) as a foam. ^{1}H NMR (CD_3OD): δ 1.59–1.72 (m, 6 H, 3 × CH_2), 2.17 (td, *J* 6.6 and 13.5 Hz, 1 H, 2′α-H), 2.54–2.72 (m, 5 H, 2′β-H, 2 × CH_2), 3.08–3.16 (m, 1 H, 3′-H), 3.68 (dd, *J* 5.1 and 12.1 Hz, 1 H, 5′-H), 3.82 (dd, *J* 3.3 and 12.0 Hz, 1 H, 5′-H), 4.45 (dd, *J* 5.1 and 8.4 Hz, 1 H, 4′-H), 6.03 (d, *J* 7.5 Hz, 1 H, 5-H), 6.19 (t, *J* 6.1 Hz, 1 H, 1′-H), 7.95 (d, *J* 7.5 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 25.47, 27.09, 53.83 (piperidino), 36.41 (C-2′), 65.06, 67.05 (C-3′, C-5′), 84.73, 88.28 (C-1′, C-4′), 96.10 (C-5), 142.92 (C-6), 158.64 (C-2), 167.95 (C-4). MS: *m/z* (%) 294 (3, M^+), 183 (46), 152 (51), 140 (40), 124 (69), 111 (100), 84 (63). Anal $C_{14}H_{22}N_4O_3 \cdot 1.5H_2O$: C, H, N.

*1-(2,3-Dideoxy-3-morpholino-α-D-*erythro*-pentofuranosyl)-cytosine* (**14b**). Yield: 91 mg (12%) as an oil. ^{1}H NMR (CD_3OD): δ 2.30 (td, *J* 5.0 and 13.9 Hz, 1 H, 2′-H), 2.48–2.66 (m, 5 H, 2 × CH_2, 2′-H), 3.02–3.09 (m, 1 H, 3′-H), 3.64–3.82 (m, 6 H, 2 × CH_2, 2 × 5′-H), 4.51 (dd, *J* 4.3 and 8.6 Hz, 1 H, 4′-H), 6.05 (d, *J* 7.4 Hz, 1 H, 5-H), 6.20 (t, *J* 5.0 Hz, 1 H, 1′-H), 7.98 (d, *J* 7.2 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 35.58 (C-2′), 53.22, 68.16 (morpholino), 64.75, 66.91 (C-3′, C-5′), 85.26, 88.73 (C-4′, C-1′), 95.83 (C-5), 143.38 (C-6), 158.74 (C-2), 167.84 (C-4). MS: *m/z* (%) 296 (1, M^+), 185 (22), 154 (19), 142 (85), 126 (32), 111 (100), 87 (51). Anal $C_{13}H_{20}N_4O_4 \cdot 1.5H_2O$: C, H, N.

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