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5′-Azido and 5′-Fluoro α-Nucleosides as Analogues of AZT and FLT

Lone Schmidt,[a] Erik B. Pedersen[a] and Claus Nielsen[b]

[a]Department of Chemistry, Odense University, DK-5230 Odense M, Denmark and [b]Retrovirus Laboratory, Department of Virology, Statens Seruminstitut, Artillerivej 5, DK-2300 Copenhagen, Denmark

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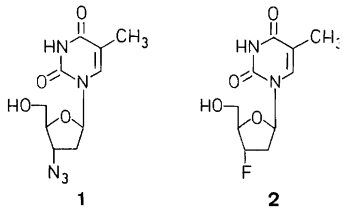
5-Azido-2,5-dideoxy-β-D-*erythro*-pentofuranosyl nucleosides **10** and their corresponding α-anomers **11** have been synthesized by condensation of methyl 3-*O*-acetyl-5-azido-2,5-dideoxy-β-D-*erythro*-pentofuranoside (**7**) with silylated nucleobases followed by deprotection with methanolic ammonia. Reaction of silylated thymine (**19**) with methyl 2,3-di-*O*-benzoyl-5-deoxy-5-fluoro-D-*arabino*-pentofuranoside (**15**) and methyl 5-azido-2,3-di-*O*-benzoyl-5-deoxy-α-D-*arabino*-pentofuranoside (**17α**) afforded a mixture of the α-nucleosides **20** and the acyclo nucleosides 5-fluoro- and 5-azido-2,3-*O*-dibenzoyl-5-deoxy-1-*O*-methyl-1-(thymin-1-yl)-D-arabinitol (**22**). Compounds **20** and **22** were deprotected with methanolic ammonia to give the acyclic nucleosides **21** and **23**, respectively. The new nucleosides were inactive against HSV-1 and HIV-1.

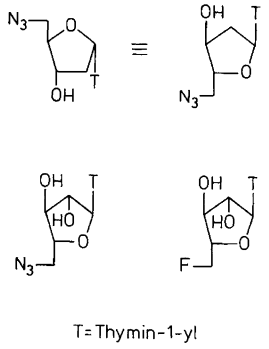
Since the discovery of human immunodeficiency virus (HIV) as the etiological agent of acquired immunodeficiency syndrome (AIDS)[1,2] many nucleoside derivatives have been reported to inhibit replication of this virus, particularly 2′,3′-dideoxy nucleosides such as AZT[3] (3′-azido-3′-deoxythymidine) (**1**) and FLT[4,5] (3′-deoxy-3′-fluorothymidine) (**2**).



1 **2**

A common feature of these compounds is the absence of the 3′-hydroxy group in the carbohydrate moiety. Their mode of action[5] requires metabolism to the corresponding 5′-triphosphate derivatives which act as inhibitors of reverse transcriptase and/or as chain terminators by incorporation in the growing strand of viral DNA.

Although α anomers have been assumed by most investigators to be biologically inactive Acton *et al.*[6] have reported activity of α anomers. They postulated phosphorylation of the α anomer to take place on the 3′-hydroxy group which replaced the 4′-hydroxymethyl group of the β anomer. Likewise they assumed the furanose oxygen to be replaced by C-2′ and *vice versa*. In analogy, the rotated structure of 5′-azido α nucleosides may be compared to that of AZT. Also 5′-azido- and 5′-fluoro-α-arabinose nucleosides will be of interest as deduced from their rotated structures in Scheme 1.



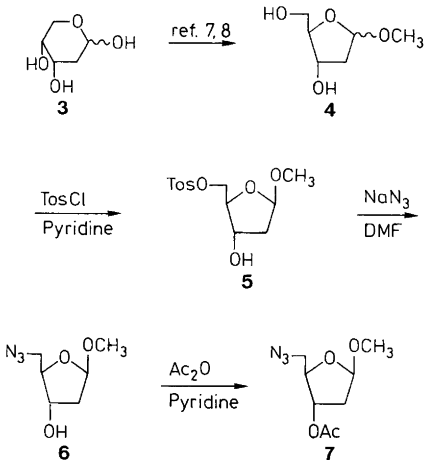
T= Thymin-1-yl

Scheme 1.

Results and discussion

The methyl furanoside **4** was prepared from 2-deoxy-D-ribose (**3**) using the modified Fischer method[7,8] of glycosidation. Subsequent treatment with *p*-toluenesulfonyl chloride in dry pyridine afforded the β anomer **5** as a white solid in 13% yield after chromatographic purification. In 1971 David and Fischer[9] also synthesized **5** which had the same melting point as our compound but they did not assign the anomeric configuration which is now established in this paper as β. Compound **5** was treated with sodium azide in dry *N*,*N*-dimethylformamide (DMF) to give the 5-azido derivative **6** in 94% yield

which upon treatment with acetic anhydride in dry pyridine afforded the 3-*O*-acetylated sugar **7** in 84% yield.

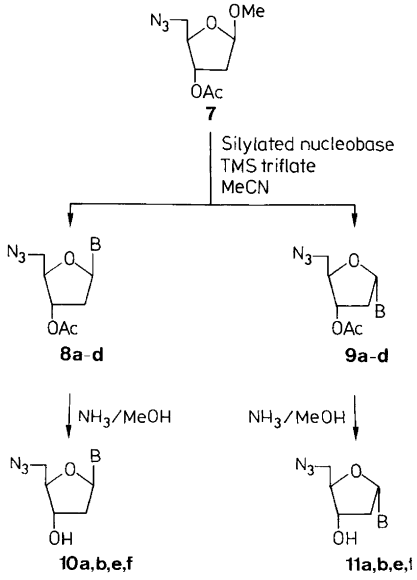


Scheme 2.

The anomeric configuration of **5**, **6** and **7** as β was deduced from an NOE spectrum of **6**. On irradiation of 3-H an NOE of 3.2% is observed for the 2β-H at 2.46 ppm and 1.4% for 2α-H at 2.09 ppm while the observed NOE in 3-H on irradiation of the 2-H protons is 8.6% for 2β-H and 5.6% for 2α-H. On irradiation of the 1-H proton an NOE of 4% is observed for 2α-H and 1.2% for 2β-H. The β anomeric configuration of **6** is further confirmed by an NOE of 5.2% and 2.4% in 1-H on irradiating of 2α-H and 2β-H, respectively. The small coupling constant of 1.9 Hz between 2β-H and 1-H further confirms the β-configuration, because a small value is typical for vicinal hydrogens in a *trans*-relationship.[10–12]

The nucleobases thymine, uracil, N^4-isobutyrylcytosine and N^6-isobutyryladenine were silylated according to standard procedures by being refluxed in hexamethyldisilazane (HMDS) in the presence of catalytic amounts of ammonium sulfate[13,14] before condensation with methyl 3-*O*-acetyl-5-azido-2,5-dideoxy-β-D-*erythro*-pentofuranoside (**7**). The condensation was carried out according to the Friedel–Crafts catalysed[15] silyl Hilbert Johnson reaction modified by Vorbrüggen *et al.*[14] by performing the reaction in dry acetonitrile in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate). This produced **8** in 5–35% and **9** in 2–13% yield. The α:β ratios of the products were as follows: **9a**:**8a** 3:7; **9b**:**8b** 3:7; **9c**:**8c** 3:7 and **9d**:**8d** 2:3. Owing to the complexity of the reaction mixture from condensation with the silylated adenine derivative, compounds **8d** and **9d** were isolated in only 5% and 2% yield, respectively. The protected nucleosides were deblocked with methanolic ammonia to give **10** and **11**.

The assignment of the ^{1}H and ^{13}C NMR spectra was made by comparison with analogous compounds[16–18] and by 2D ^{1}H NMR spectra. It was possible to assign the anomeric configuration from the ^{1}H NMR spectra:



8-11	B
a	thymin-1-yl
b	uracil-1-yl
c	N^4-isobuturylcytosin-1-yl
d	N^6-isobuturyladenin-1-yl
e	cytosin-1-yl
f	adenin-9-yl

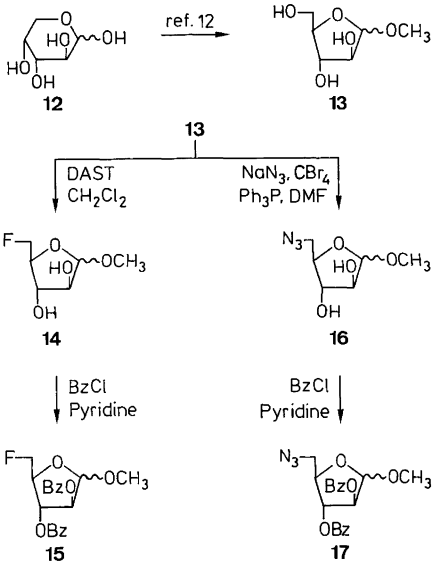
Scheme 3.

the 4′-H of the α anomers appear at lower field than those of the β anomers and the 5′-H protons of the α anomers appear at a higher field than those of the β anomers.[19,20] The products **10a,b,f** have previously been synthesized and their ^{1}H NMR spectra were exactly as reported by Hiebl *et al.*[16] and Herdewijn *et al.*[17]

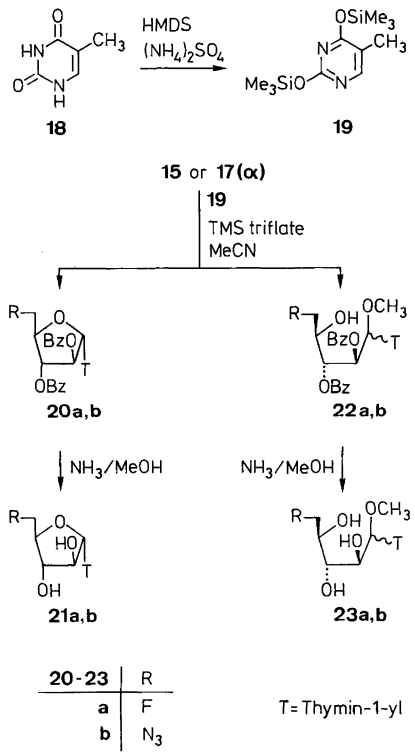
The conversion of D-(−)-arabinose (**12**) into its methyl glycoside **13** has already been described[21] and its ^{13}C NMR spectrum was reported by Beier.[22] Treatment of **13** with diethylaminosulfur trifluoride (DAST) in dry dichloromethane[23] resulted in replacement of the 5-hydroxy group to give the 5-fluoro derivative **14** which was treated with benzoyl chloride in dry pyridine to give **15** in 18% yield based on **13**.

Compound **15** was obtained as an anomeric mixture and the presence of fluorine in the 5-position was confirmed by ^{19}F NMR spectroscopy which revealed a triplet of doublets for each anomer with coupling constants of 47.1 Hz and 25.2 Hz for the predominant anomer in agreement with those measured in the ^{1}H NMR spectrum.

Compound **13** was also reacted with sodium azide in a mixture of tetrabromomethane and triphenylphosphine in dry DMF[24,25] to give **16** in 75% yield which was protected by reaction with benzoyl chloride to give **17** in 74% yield. From the anomeric mixture of **17** the major anomer could be isolated as white crystals by addition of petroleum ether. From the ^{1}H NMR spectrum the



Scheme 4.



Scheme 5.

anomeric configuration of this anomer was deduced to be α because no coupling was observed between the 1-H and the 2-H.[10–12]

Thymine **18** was silylated in order to obtain **19** by the procedure described previously.[13,14] Condensation of methyl 2,3-di-*O*-benzoyl-5-deoxy-5-fluoro-D-*arabino*-pentofuranoside (**15**) and methyl 5-azido-2,3-di-*O*-benzoyl-5-deoxy-α-D-*arabino*-pentofuranoside (**17α**) with the silylated thymine **19** was carried out as before[14,15] to give **20** exclusively as α nucleosides in accordance with the *trans* rule of Baker[26] [yields: **20a** (2.5%) and **20b** (2.8%)]. The protected nucleosides **20** were deblocked by treatment with methanolic ammonia and separated by silica-gel column chromatography to give **21a** in 43% yield and **21b** in 75% yield. The expected nucleoside **20** was isolated only as the minor product in the coupling reaction. Instead, two acyclic nucleosides **22a** and **22b** with the methoxy group intact were obtained as the major products. Each of them were isolated as a C-1′ epimeric mixture with nearly uniform ^{13}C NMR spectra of the two epimers.[27] The total yield of **22a** was 44% and by silica gel column chromatography it was possible to separate a small amount of both epimers as pure compounds. The ^{13}C NMR spectra of the more polar epimer of **22a** revealed variable degrees of benzoylation due to migration of the benzoyl groups, but on deprotection only one epimer of **23a** was isolated. Compound **22b** was obtained in a total yield of 5.9% and it was also possible in this case to separate the mixture into the two C-1′ epimers. Compounds **22** were deprotected with ammonia in methanol to give the corresponding debenzoylated compounds **23** as their corresponding pure epimers.

The identities of the products **20–23** were ascertained by comparison of their NMR spectra with those of analogous compounds.[27–29] A comparison of the ^{13}C NMR spectra of **20** and **22** showed that C-1′ resonates for the former at lower field than for **22** (90 ppm versus 83–85 ppm). The ^{13}C NMR spectra of **22** and **23** showed the presence of a methoxy group at 57 ppm in accordance with the NMR data reported by Jørgensen *et al.*,[27] who have prepared analogous compounds from methyl 2,3,5-tri-*O*-benzoyl-D-arabinoside.

Compounds **10e**, **11a,b,e,f**, **21a,b** and **23a,b** did not show any significant activity at 100 μM against herpes simplex virus, type 1 (HSV-1), strain McIntyre, when tested in a continuous cell line from rabbit cornea (SIRC) which was maintained in Eagle's MEM containing 1% fetal calf serum (FCS) and the test compound. The same compounds were also devoid of any activity against HIV-1 (strain HTLV-IIIB) in MT-4 cells. MT-4 cells were incubated with virus, washed and added in a proportion of 1:10 to uninfected MT-4 cells which had been preincubated in test compound containing culture medium (RPM 1640 containing 10% FCS) for 2 h. The MT-4 cells were maintained in culture medium likewise containing the test compound. Expression of HIV in the culture medium was quantitated by HIV antigen detection ELISA.[30] Cytotoxicity was observed against neither SIRC nor MT-4 cells at 100 μM.

Experimental

*Methyl 2-deoxy-5-*O*-(*p*-toluenesulfonyl)-β-*D*-*erythro*-pentofuranoside (**5**).* Compound **4** (51.9 g, 0.35 mol) was dissolved in dry pyridine (300 ml). *p*-Toluenesulfonyl chloride (66.7 g, 0.35 mol) was added slowly at 0°C and

stirred for 24 h at room temperature. Water (200 ml) was added and the mixture stirred for 2 h before the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (1200 ml), washed with a saturated solution of $NaHCO_3$ (5 × 300 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and traces of pyridine were removed by coevaporation with toluene (2 × 40 ml). The residue was chromatographed on silica gel with a gradient from 0–2% MeOH in CH_2Cl_2 to give compound **5** as white crystals which were recrystallised from a mixture of Et_2O and petroleum ether (4:1). Yield 13.06 g (13%). M.p. 81°C; Lit.[9] 81°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.04 (ddd, *J* 5.2, 6.2 and 13.3 Hz, 1 H, 2-H), 2.19 (ddd, *J* 1.9, 6.8 and 13.3 Hz, 1 H, 2-H), 2.45 (s, 3 H, CH_3), 2.61 (s, 1 H, OH), 4.05 (m, 3 H, 3-H and 5-H), 4.40 (dt, *J* 3.4 and 6.6 Hz, 1 H, 4-H), 5.03 (dd, *J* 1.9 and 5.2 Hz, 1 H, 1-H), 7.35 (d, *J* 8 Hz, 2 H, H_{arom}), 7.80 (d, *J* 8 Hz, 2 H, H_{arom}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.63 (CH_3), 41.24 (C-2), 54.98 (OCH_3), 70.04 (C-5), 72.24 (C-3), 82.97 (C-4), 105.41 (C-1), 127.96, 129.98, 132.56, 145.15 (C_{arom}).

*Methyl 5-azido-2,5-dideoxy-β-*D*-*erythro*-pentofuranoside* (**6**). A mixture of **5** (5.47 g, 18.1 mmol) and NaN_3 (6.49 g, 99.8 mmol) in dry DMF (150 ml) was stirred for 4 h at 85°C. After removal of the solvent under reduced pressure, the residue was dissolved in dry Et_2O (200 ml) and the insoluble salts were filtered off. After evaporation of the solvent *in vacuo* **6** was obtained as a yellow oil. Yield 2.94 g (94%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.09 (ddd, *J* 5.4, 6.5 and 13.4 Hz, 1 H, 2α-H), 2.46 (ddd, *J* 1.9, 6.8 and 13.4 Hz, 1 H, 2β-H), 2.53 (s, 1 H, OH), 3.37–3.40 (m, 5 H, 5-H and OCH_3), 3.99 (m, 1 H, 4-H), 4.37 (m, 1 H, 3-H), 5.09 (dd, *J* 1.9 and 5.4 Hz, 1 H, 1-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 41.45 (C-2), 53.77 (C-5), 55.42 (OCH_3), 72.86 (C-3), 84.61 (C-4), 105.46 (C-1).

*Methyl 3-*O*-acetyl-5-azido-2,5-dideoxy-β-*D*-*erythro*-pentofuranoside* (**7**). To a stirred solution of **6** (2.85 g, 16.5 mmol) in dry pyridine (50 ml) was slowly added acetic anhydride (3.37 g, 33.0 mmol) at 0°C. The reaction mixture was stirred 4 h at 0°C and 22 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with a gradient of Et_2O in petroleum ether (0–11%) to give **7** as a yellow oil. Yield 2.99 g (84%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.05 (s, 3 H, Ac), 2.18 (dt, *J* 14.1 and 5.3 Hz, 1 H, 2-H), 2.37 (ddd, *J* 2.4, 7.3 and 14.1 Hz, 1 H, 2-H), 3.36–3.46 (m, 5 H, 5-H and OCH_3), 4.14 (dt, *J* 3.3 and 6.1 Hz, 1 H, 4-H), 5.10–5.16 (m, 2 H, 1-H and 3-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 20.86 (Ac), 38.39 (C-2), 54.13 (C-5), 55.50 (OCH_3), 75.48 (C-3), 83.28 (C-4), 105.91 (C-1), 170.57 (C=O). Anal. $C_8H_{13}N_3O_4$ calc.: C 44.65, H 6.09, N 19.53. Found C 45.08, H 6.27, N 19.36%.

Preparation of **8** *and* **9**. *General procedure*. A mixture of the nucleobase (3.5 mmol), $(NH_4)_2SO_4$ (50 mg) and hexamethyldisilazane (20 ml) was refluxed overnight. The solvent was removed under reduced pressure and the resulting oily residue was dissolved in dry MeCN (10 ml), cooled to −40°C and a solution of methyl 3-*O*-acetyl-5-azido-2,5-dideoxy-β-D-*erythro*-pentofuranoside (**7**) (0.5 g, 2.3 mmol) in dry MeCN (20 ml) was added at −40°C. A solution of TMS triflate (0.6 ml, 3.5 mmol) in dry MeCN (20 ml) was added dropwise at −40°C and the mixture was stirred as follows depending on the nucleobase: thymine, 2 h at −40°C, 1 h at −30°C, 1.5 h at −20°C, 1 h at −10°C, 3 h at 0°C and 16 h at room temperature; uracil, 1 h at −40°C, 1 h at −30°C, 0.5 h at −20°C, 0.5 h at −10°C, 3 h at 0°C and 16 h at room temperature; N^4-isobutyrylcytosine, 1 h at −40°C, 1 h at −30°C, 1 h at −20°C, 1 h at 0°C and 24 h at room temperature; N^6-isobutyryladenine, 1 h at −40°C, 1 h at −30°C, 1 h at −20°C, 0.5 h at −10°C and 0.5 h at 0°C. The mixture was diluted with CH_2Cl_2 (200 ml), washed with saturated aqueous $NaHCO_3$ (3 × 100 ml) and dried over Na_2SO_4 before the solvent was removed *in vacuo*. The products **8a,b** and **9a,b** were separated by silica gel column chromatography with $CHCl_3$, while **8c,d** and **9c,d** were separated by reversed-phase HPLC (RP-18, 300 Å, 15 μ), (**8c**/**9c**: H_2O/EtOH, 68/32, v/v and **8d**/**9d**: H_2O/EtOH 80/20, v/v). The yields of the products **8** and **9** were as follows: **8a**,**9a**: 127 mg (18%), 50 mg (7%); **8b**,**9b**: 240 mg (35%), 90 mg (13%); **8c**,**9c**: 200 mg (24%), 85 mg (10%); **8d**,**9d**: 43 mg (5%), 20 mg (2%).

Preparation of **10** *and* **11**. *General procedure*. The products **8** and **9** were dissolved in a saturated solution of ammonia in MeOH (30 ml) and stirred at room temperature for 16 h. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with a gradient from 0–10% MeOH in CH_2Cl_2.

*1-(5-Azido-2,5-dideoxy-α-*D*-*erythro*-pentofuranosyl)thymine* (**11a**). Yellow oil. Yield 17 mg (76%). ^{1}H NMR (250 MHz, CD_3OD): δ 1.98 (d, *J* 1.1 Hz, 3 H, 5-CH_3), 2.19 (dt, *J* 14.5 and 3.0 Hz, 1 H, 2′-H), 2.80 (ddd, *J* 6.4, 7.4 and 14.5 Hz, 1 H, 2′-H), 3.47 (dd, *J* 4.4 and 13.0 Hz, 1 H, 5′-H), 3.55 (dd, *J* 5.4 and 13.0 Hz, 1 H, 5′-H), 4.39 (dt, *J* 6.4 and 3.0 Hz, 1 H, 3′-H), 4.47 (m, 1 H, 4′-H), 6.31 (dd, *J* 3.0 and 7.4 Hz, 1 H, 1′-H), 7.84 (q, *J* 1.1 Hz, 1 H, 6-H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 12.53 (5-CH_3), 41.16 (C-2′), 53.56 (C-5′), 72.90 (C-3′), 87.90, 88.58 (C-1′ and C-4′), 111.03 (C-5), 138.64 (C-6), 152.41 (C-2), 166.60 (C-4). Calc. for $C_{10}H_{13}N_5O_4$ 267.097. Found 267.099 (MS).

*1-(5-Azido-2,5-dideoxy-α-*D*-*erythro*-pentofuranosyl)uracil* (**11b**). Yellow oil. Yield 63 mg (81%). ^{1}H NMR (250 MHz, CD_3OD): δ 2.03 (dt, *J* 14.6 and 2.5 Hz, 1 H, 2′-H), 2.61 (ddd, *J* 6.3, 7.3 and 14.6 Hz, 1 H, 2′-H), 3.32 (dd, *J* 4.8 ad 13.2 Hz, 1 H, 5′-H), 3.36 (dd, *J* 4.8 and 13.2 Hz, 1 H, 5′-H), 4.21 (dt, 6.3 and 2.5 Hz, 1 H, 3′-H), 4.30 (dt, *J* 2.5 and 4.6 Hz, 1 H, 4′-H), 5.61 (d, *J* 8.1 Hz, 1 H, 5-H), 6.11 (dd, *J* 2.5 and 7.3 Hz, 1 H, 1′-H), 7.82

(d, *J* 8.1 Hz, 1 H, 6-H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 41.58 (C-2′), 53.91 (C-5′), 73.18 (C-3′), 88.72, 89.26 (C-1′ and C-4′), 102.33 (C-5), 143.29 (C-6), 152.80 (C-2), 167.08 (C-4). Calc. for $C_9H_{11}N_5O_4$ 253.081. Found 253.081 (MS).

5′-Azido-2′,5′-dideoxycytidine (**10e**). Yellow oil. Yield 29 mg (85%). ^{1}H NMR (250 MHz, CD_3OD): δ 2.27 (m, 1 H, 2′-H), 2.45 (ddd, *J* 4.3, 6.5 and 13.7 Hz, 1 H, 2′-H), 3.71 (m, 2 H, 5′-H), 4.07 (m, 1 H, 4′-H), 4.39 (m, 1 H, 3′-H), 6.03 (d, *J* 7.5 Hz, 1 H, 5-H), 6.34 (t, *J* 6.5 Hz, 1 H, 1′-H), 7.85 (d, *J* 7.5 Hz,1 H, 6-H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 41.54 (C-2′), 53.70 (C-5′), 72.73 (C-3′), 86.62, 87.65 (C-1′ and C-4′), 96.61 (C-5), 142.59 (C-6), 158.25 (C-2), 167.75 (C-4).

*1-(5-Azido-2,5-dideoxy-α-D-*erythro*-pentofuranosyl)cytosine* (**11e**). White foam. Yield 42 mg (72%). ^{1}H NMR (250 MHz, CD_3OD): δ 2.23 (dt, *J* 14.6 and 2.5 Hz, 1 H, 2′-H), 2.81 (dt, *J* 14.6 and 7.1 Hz, 1 H, 2′-H), 3.48 (dd, *J* 5.5 and 13.2 Hz, 1 H, 5′-H), 3.56 (dd, *J* 4.3 and 13.2 Hz, 1 H, 5′-H), 4.40 (m, 1 H, 3′-H), 4.54 (m, 1 H, 4′-H), 6.14 (d, *J* 7.6 Hz, 1 H, 5-H), 6.32 (dd, *J* 2.5 and 7.1 Hz, 1 H, 1′-H), 8.03 (d, *J* 7.6 Hz, 1 H, 6-H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 41.88 (C-2′), 53.97 (C-5′), 73.24 (C-3′), 89.42, 89.67 (C-1′ and C-4′), 96.70 (C-5), 143.54 (C-6), 159.27 (C-2), 167.40 (C-4).

*9-(5-Azido-2,5-dideoxy-α-D-*erythro*-pentofuranosyl)adenine* (**11f**). White foam. Yield 11 mg (75%). ^{1}H NMR (250 MHz, CD_3OD): δ 2.54 (m, 1 H, 2′-H), 2.91 (m, 1 H, 2′-H), 3.49 (m, 2 H, 5′-H), 4.40 (m, 2 H, 3′-H and 4′-H), 6.45 (dd, *J* 2.7 and 7.9 Hz, 1 H, 1′-H), 8.22, 8.41 (2 × s, 1 H, 2-H and 8-H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 41.54 (C-2′), 53.96 (C-5′), 73.74 (C-3′), 86.78, 88.85 (C-1′ and C-4′), 142.13 (C-8), 150.36 (C-4), 153.91 (C-2), 157.72 (C-6).

*Methyl 2,3-di-*O*-benzoyl-5-deoxy-5-fluoro-D-*arabino*-pentofuranoside* (**15**). Compound **13** (10.75 g, 65.5 mmol) was dissolved in dry CH_2Cl_2 and diethylaminosulfur trifluoride (DAST) (49.10 ml, 392.8 mmol) was added dropwise at −40 °C under a nitrogen atmosphere. The mixture was stirred for 1 h while the temperature was allowed to increase to 10 °C before it was cooled to −10 °C and 10 ml of MeOH was added. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with a gradient of MeOH in CH_2Cl_2 (0–8%) and **14** was obtained as an impure fraction which was dissolved in dry pyridine (50 ml). Benzoyl chloride (8.40 ml, 72.2 mmol) was slowly added at 0 °C and the temperature was allowed to increase to room temperature. Stirring was continued for 16 h and water (5 ml) was added. CH_2Cl_2 (50 ml) was added and the mixture was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 50 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue chromatographed on silica gel with petroleum ether and Et_2O (9:1, v/v) to obtain compound **15** as a colourless oil. Yield: 4.41 g (18%) from **13**. ^{1}H NMR of the predominant anomer (250 MHz, $CDCl_3$): δ 3.48 (s, 3 H, OCH_3), 4.41 (ddd, $J_{F,4\text{-}H}$ = 25.2 Hz, *J* 3.4 and 8.2 Hz, 1 H, 4-H), 4.82 (2 × m, $J_{F,5\text{-}H}$ = 47.1 Hz, 2 H, 5-H), 5.18 (s, 1 H, 1-H), 5.44 (m, 1 H, 3-H), 5.53 (s, 1 H, 2-H), 7.40–8.08 (m, 10 H, H_{arom}). ^{13}C NMR of the predominant anomer (62.9 MHz, $CDCl_3$): δ 55.04 (OCH_3), 77.04 (d, $J_{F,C\text{-}3}$ = 7.9 Hz, C-3), 81.58 (C-2), 81.72 (d, $J_{F,C\text{-}5}$ = 173.8 Hz, C-5), 82.14 (d, $J_{F,C\text{-}4}$ = 18.6 Hz, C-4), 107.08 (C-1), 128.48, 128.53, 129.92, 129.96, 133.58, 133.64 (C_{arom}), 165.40, 165.92 (C = O). Anal. $C_{20}H_{19}FO_6$ calc. C 64.14, H 5.12. Found: C 64.38, H 5.12%.

*Methyl 5-azido-5-deoxy-D-*arabino*-pentofuranoside* (**16**). CBr_4 (30.29 g, 91.4 mmol) was added to a mixture of **13** (10.00 g, 60.9 mmol), Ph_3P (20.76 g, 179.2 mmol) and NaN_3 (11.87 g, 182.7 mmol) in dry DMF (500 ml). The mixture was stirred for 7 days at room temperature. The solvent was removed *in vacuo* and dry Et_2O (200 ml) was added to remove the insoluble salts by filtration. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column with CH_2Cl_2 and MeOH (95:5, v/v) to obtain **16** as a yellow oil. Yield 8.8 g (75%). ^{1}H NMR of the predominant anomer (250 MHz, DMSO-d_6): δ 3.26–3.39 (m, 5 H, 5-H, OCH_3), 3.51 (m, 1 H, 3-H), 3.65 (m, 1 H, 2-H), 3.79 (m, 1 H, 4-H), 4.66 (s, 1 H, 1-H), 5.34 (d, *J* 5.4 Hz, 1 H, 2-OH), 5.46 (d, *J* 5.0 Hz, 1 H, 3-OH). ^{13}C NMR of the predominant anomer (62.9 MHz, DMSO-d_6): δ 51.41 (C-5), 54.68 (OCH_3), 72.84, 81.35, 81.75 (C-2, C-3, C-4), 108.99 (C-1).

*Methyl 5-azido-2,3-di-*O*-benzoyl-5-deoxy-D-*arabino*-pentofuranoside* (**17**). To a mixture of **16** (4.00 g, 2.7 mmol) in dry pyridine (50 ml) was slowly added benzoyl chloride (7.21 ml, 62.1 mmol) at 0 °C. The same procedure as used to prepare the benzoylated sugar **15** was followed to give **17** as an anomeric mixture. Yield 6.05 g (74%). From this anomeric mixture 2.66 g (32%) of the α anomer could be isolated as white crystals by addition of 50 ml of petroleum ether. M.p. 66.5–66.9 °C. ^{1}H NMR of the α anomer (250 MHz, $CDCl_3$): δ 3.48 (s, 3 H, OCH_3), 3.64 (dd, *J* 5.0 and 13.3 Hz, 1 H, 5-H), 3.82 (m, 1 H, 5-H), 4.39 (m, 1 H, 4-H), 5.18 (s, 1 H, 1-H), 5.38 (d, *J* 4.8 Hz, 1 H, 3-H), 5.52 (d, *J* 1.2 Hz, 1 H, 2-H), 7.42–8.10 (m, 10 H, H_{arom}). ^{13}C NMR of the α anomer (62.9 MHz, $CDCl_3$): δ 51.91 (C-5), 55.03 (OCH_3), 78.51, 81.94, 82.58 (C-2, C-3, C-4), 106.92 (C-1), 128.56, 129.87, 129.96, 133.59 (C_{arom}), 165.42, 165.96 (C = O).

Preparation of **20** *and* **22**. *General procedure.* A mixture of thymine (**18**) (10 mmol), $(NH_4)_2SO_4$ (50 mg) and hexamethyldisilazane (50 ml) was refluxed overnight and the solvent was removed under reduced pressure. The resulting oily residue **19** was dissolved in dry MeCN, cooled to 0 °C and a solution of the sugar **15** (2 g, 5.3 mmol) or **17**(α) (2 g, 5.0 mmol) in dry MeCN (20 ml) was added

dropwise. The reaction mixture was stirred at room temperature for 5 days. The mixture was diluted with CH_2Cl_2 (150 ml) and washed with saturated aqueous $NaHCO_3$ (3 × 150 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column with $CHCl_3$ to obtain the compounds **20** and **22**.

*1-(5-Azido-2,3-di-*O*-benzoyl-5-deoxy-α-D-*arabino*-pentofuranosyl)thymine (***20b***).* Yield: 69 mg (2.8%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.90 (s, 3 H, 5-CH_3), 3.69 (m, 2 H, 5′-H), 4.78 (m, 1 H, 4′-H), 5.66 (t, *J* 3.3 Hz, 1 H, 3′-H),6.00 (t, *J* 3.3 Hz, 1 H, 2′-H), 6.13 (d, *J* 3.3 Hz, 1 H, 1′-H), 7.22 (s, 1 H, 6-H), 7.26–8.07 (m, 10 H, H_{arom}), 9.32 (s, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.34 (5-CH_3), 59.3 (C-5′), 77.10, 88.02; 84.24 (C-2′, C-3′, C-4′), 91.38 (C-1′), 111.15 (C-5), 128.51, 128.53, 129.68, 129.84, 133.78, 133.82 (C_{arom}), 136.14 (C-6), 150.13 (C-2), 163.63 (C-4), 165.13, 165.29 (C = O).

*2,3-Di-*O*-benzoyl-5-deoxy-5-fluoro-1-*O*-methyl-1-(thymin-1-yl)-D-arabinitol (***22a***).* Yield of all fractions of **22a**: 1.168 g (44%). *The less polar compound*: 0.067 g (2.5%) as a white foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.85 (s, 3 H, 5-CH_3), 3.31 (s, 3 H, OCH_3), 3.60 (s, 1 H, OH), 3.99 (2 × m, $J_{F,4'-H}$ = 20.9 Hz, 1 H, 4′-H), 4.47 (2 × m, $J_{F,5'-H}$ = 48.0 Hz, 2 H, 5′-H), 5.69 (dd, *J* 1.8 and 9.3 Hz, 1 H, 3′-H), 5.79 (dd, *J* 1.8 and 8.4 Hz, 1 H, 2′-H), 5.91 (d, *J* 8.4 Hz, 1 H, 1′-H), 7.25 (s, 1 H, 6-H), 7.37–8.11 (m, 10 H, H_{arom}), 9.07 (s, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.23 (5-CH_3), 57.02 (OCH_3), 68.31 (d, $J_{F,C-4'}$ = 19.5 Hz, C-4′), 70.03 (d, $J_{F,C-3'}$ = 6.6 Hz, C-3′), 70.92 (C-2′), 83.42 (C-1′), 83.60 (d, $J_{F,C-5'}$ = 171.0 Hz, C-5′), 111.77 (C-5), 127.96, 128.58, 129.77, 129.86, 133.66, 133.88, 134.38 (C_{arom}, C-6), 151.18 (C-2), 163.44 (C-4), 165.27, 165.83 (C = O). *The more polar compound*: 0.344 g (13%) as a white foam.

*5-Azido-2,3-di-*O*-benzoyl-5-deoxy-1-*O*-methyl-1-(thymin-1-yl)-D-arabinitol (***22b***).* Yield of all fractions of **22b**: 156 mg (5.9%). *The less polar compound*: 44 mg (1.7%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.87 (s, 3 H, 5-CH_3), 3.32–3.88 (m, 6 H, 4′-H, 5′-H, OCH_3), 5.63–5.72 (m, 2 H, 2′-H, 3′-H), 5.88 (d, *J* 8.4 Hz, 1 H, 1′-H), 7.21 (s, 1 H, 6-H), 7.31–8.11 (m, 10 H, H_{arom}), 8.60 (s, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.31 (5-CH_3), 53.17 (C-5′), 57.12 (OCH_3), 68.82, 71.16, 71.29 (C-2′, C-3′, C-4′), 83.44 (C-1′), 111.96 (C-5), 127.81, 128.68, 129.84, 129.91, 129.97, 133.80, 134.00, 134.13, 134.30 (C_{arom}, C-6), 151.01 (C-2), 163.10 (C-4), 165.35 (C = O). *The more polar compound*: 0.112 g (4.2%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.60 (s, 3 H, 5-CH_3), 3.29–3.91 (m, 6 H, 4′-H, 5′-H, OCH_3), 5.59 (dd, *J* 3.8 and 8.7 Hz, 1 H, 3′-H), 5.87 (t, *J* 3.8 Hz, 1 H, 2′-H), 6.03 (d, *J* 3.8 Hz, 1 H, 1′-H), 7.14 (s, 1 H, 6-H), 7.38–8.03 (m, 10 H, H_{arom}), 9.54 (s, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 11.90 (5-CH_3), 53.38 (C-5′), 57.26 (OCH_3), 69.38, 70.86, 71.67 (C-2′, C-3′, C-4′), 85.37 (C-1′), 111.41 (C-5), 127.30, 128.36, 128.49, 129.10, 129.63, 129.72, 133.33, 133.68, 134.35 (C_{arom}, C-6), 150.86 (C-2), 163.54 (C-4), 165.43, 165.90 (C = O).

*1-(5-Deoxy-5-fluoro-α-D-*arabino*-pentofuranosyl)thymine (***21a***). Typical procedure for deprotection of* **20a,b** *and* **22a,b**. Compound **20a** (50 mg, 0.11 mmol) was dissolved in a saturated solution of ammonia in MeOH (25 ml) and stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with a gradient of MeOH in $CHCl_3$ (0–8%) to obtain **21a** as a yellow oil. Yield: 12 mg (43%). ^{1}H NMR (500 MHz, CD_3OD): δ 1.98 (d, *J* 1.2 Hz, 1 H, 5-CH_3), 4.18 (t, *J* 4.6 Hz, 1 H, 3′-H), 4.39 (t, *J* 4.6 Hz, 1 H, 2′-H), 4.52 (2 × m, $J_{F,4'-H}$ = 21.4 Hz, 1 H, 4′-H), 4.63 (2 × m, $J_{F,5'-H}$ = 48.2 Hz, 2 H, 5′-H), 5.89 (d, *J* 4.6 Hz, 1 H, 1′-H), 7.66 (q, *J* 1.2 Hz, 1 H, 6-H). ^{13}C NMR (125.7 MHz, CD_3OD): δ 12.35 (5-CH_3), 76.02 (d, $J_{F,C-3'}$ = 6.4 Hz, C-3′), 80.96 (C-2′), 83.32 (d, $J_{F,C-5'}$ = 170.3 Hz, C-5′), 85.82 (d, $J_{F,C-4'}$ = 19.24 Hz, C-4′), 92.79 (C-1′), 111.26 (C-5), 138.85 (C-6), 152.55 (C-2), 166.50 (C-4). Calc. for $C_{10}H_{13}FN_2O_5$ 260.078. Found 260.080 (MS).

*1-(5-Azido-5-deoxy-α-D-*arabino*-pentofuranosyl)thymine (***21b***).* Yield 25 mg (75%) as a yellow oil. ^{1}H NMR (500 MHz, CD_3OD): δ 1.98 (s, 3 H, 5-CH_3), 3.60 (m, 2 H, 5′-H), 4.14 (t, *J* 4.8 Hz, 1 H, 3′-H), 4.37 (t, *J* 4.8 Hz, 1 H, 2′-H), 4.45 (dd, *J* 4.8 Hz and 9.9 Hz, 1 H, 4′-H), 5.93 (d, 4.8 Hz, 1 H, 1′-H), 7.65 (s, 1 H, 6-H). ^{13}C NMR (125.7 MHz, CD_3OD): δ 12.38 (5-CH_3), 53.28 (C-5′), 77.61, 81.20, 86.47 (C-2′, C-3′, C-4′), 92.96 (C-1′), 111.25 (C-5), 138.86 (C-6), 152.58 (C-2), 166.57 (C-4). Calc. for $C_{10}H_{13}N_5O_5$ 283.092. Found 283.092 (MS).

*5-Deoxy-5-fluoro-1-*O*-methyl-1-(thymin-1-yl)-D-arabinitol (***23a***).* **22a** (*the less polar compound*) (60 mg, 0.12 mmol) afforded **23a** as a white solid. Yield 23 mg (66%); m.p. 118–120 °C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.00 (s, 3 H, 5-CH_3), 3.44 (s, 3 H, OCH_3), 3.91 (m, 2 H, 3′-H, 4′-H), 4.07 (d, *J* 8.5 Hz, 1 H, 2′-H), 4.69 (2 × m, $J_{F,5'-H}$ = 51.2 Hz, 2 H, 5′-H), 5.80 (d, *J* 8.5 Hz, 1 H, 1′-H), 7.52 (s, 1 H, 6-H). ^{13}C NMR (125.7 MHz, CD_3OD): δ 12.41 (5-CH_3), 56.91 (OCH_3), 70.08 (d, $J_{F,C-3'}$ = 6.4 Hz, C-3′), 70.89 (C-2′), 71.14 (d, $J_{F,C-4'}$ = 18.4 Hz, C-4′), 86.28 (d, $J_{F,C-5'}$ = 167.7 Hz, C-5′), 87.37 (C-1′), 112.22 (C-5), 137.75 (C-6), 154.12 (C-2), 166.48 (C-4). **2a** (*the more polar compound*) (274 mg, 0.55 mmol) afforded **23a** as a colourless oil. Yield 114 mg (71%). ^{1}H NMR (250 MHz, CD_3OD): δ 1.95 (d, *J* 1.0 Hz, 3 H, 5-CH_3), 3.38–3.60 (m, 4 H, 3′-H, OCH_3), 3.89 (2 × m, $J_{F,4'-H}$ = 25.0 Hz, 1 H, 4′-H), 4.06 (dd, *J* 1.6 Hz and 6.4 Hz, 1 H, 2′-H), 4.61 (2 × m, $J_{F,5'-H}$ = 47.8 Hz, 2 H, 5′-H), 5.70 (d, *J* 6.4 Hz, 1 H, 1′-H), 7.50 (q, *J* 1.0 Hz, 1 H, 6-H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 12.75 (5-CH_3), 57.69 (OCH_3), 70.42 (d, $J_{F,C-3'}$ = 6.7 Hz, C-3′), 71.28 (d, $J_{F,C-4'}$ = 18.0 Hz, C-4′), 72.28 (C-2′), 86.29 (d, $J_{F,C-5'}$

= 167.6 Hz, C-5′), 89.38 (C-1′), 112.28 (C-5), 138.18 (C-6), 153.51 (C-2), 16.49 (C-4).

5-Azido-5-deoxy-1-O-methyl-1-(thymin-1-yl)-D-arabinitol (**23b**). **22b** (*the less polar compound*) (40 mg, 0.076 mmol) afforded **23b** as a yellow oil. Yield 18 mg (75%). ^{1}H NMR (250 MHz, CD_3OD): δ 2.00 (d, *J* 1.1 Hz, 3 H, 5-CH_3), 3.08–3.87 (m, 6 H, 3′-H, 4′-H, 5′-H, OCH_3), 4.06 (d, *J* 8.6 Hz, 1 H, 2′-H), 5.79 (d, *J* 8.6 Hz, 1 H, 1′-H), 7.52 (q, *J* 1.1 Hz, 1 H, 6-H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 12.44 (5-CH_3), 55.70 (C-5′), 56.86 (OCH_3), 70.82, 71.45, 71.55 (C-2′, C-3′, C-4′), 87.35 (C-1′), 112.18 (C-5), 137.70 (C-6), 154.06 (C-2), 166.45 (C-4). **22b** (*the more polar compound*) (85 mg, 0.16 mmol) afforded **23b** as a yellow oil. Yield 18 mg (45%). ^{1}H NMR (500 MHz, CD_3OD): δ 1.99 (d, *J* 1.2 Hz,3 H, 5-CH_3), 3.41–3.48 (m, 5 H, 4′-H, 5′-H, OCH_3), 3.59 (dd, *J* 2.4 Hz and 12.8 Hz, 1 H, 5′-H), 3.90 (m, 1 H, 3′-H), 4.04 (dd, *J* 1.8 and 6.6 Hz, 1 H, 2′-H), 5.71 (d, *J* 6.6 Hz, 1′-H), 7.50 (q, *J* 1.2 Hz, 1 H, 6-H). ^{13}C NMR (125.7 MHz, CD_3OD): δ 12.45 (5-CH_3), 55.33 (C-5′), 57.42 (OCH_3), 71.51, 71.70, 72.15 (C-2′, C-3′, C-4′), 88.49 (C-1′), 112.05 (C-5), 137.92 (C-6), 153.38 (C-2), 166.32 (C-4).

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