# Synthesis of 5-Homologous AZT and D4T Derivatives

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The 3′-iodonucleosides **4** have been synthesized by condensation of silylated 5-alkyluracils **2** with methyl 5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-D-*threo*-pentofuranoside (**3**). **4** was treated with sodium azide and the deprotected nucleoside **5** was subsequently obtained by treatment with tetrabutylammonium fluoride. The nucleoside **4** produced the corrresonding 2′,3′-didehydro-2′,3′-dideoxy nucleoside **6** and 3′,4′-didehydro-2′,3′-dideoxy nucleoside **7** in elimination reactions on treatment with sodium methoxide.

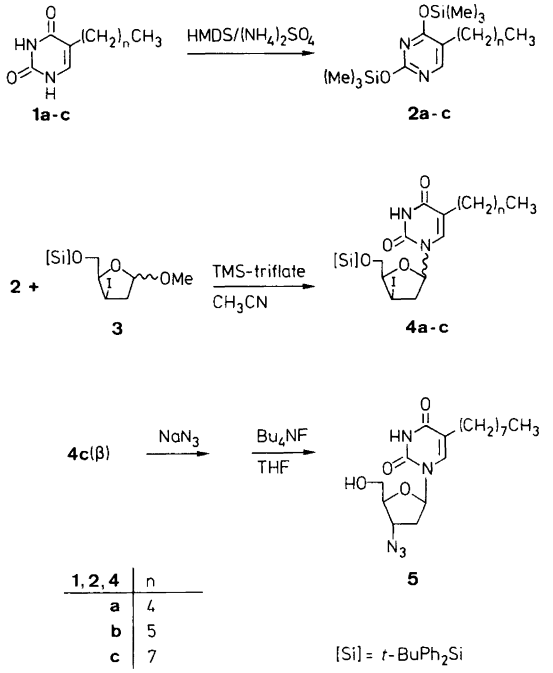
In the search for therapeutic compounds with activity against human immunodeficiency virus (HIV)[1–4] 3′-azido-2′,3′-dideoxyuridines and 2′,3′-didehydro-2′,3′-dideoxyuridines have been synthesized and investigated. From these investigations 3′-azido-3′-deoxythymidine (AZT)[5] and 2′,3′-didehydro-3′-deoxythymidine (D4T) were developed as potent drugs. In the present investigation it is demonstrated that appropriately substituted 2,3-dideoxypentofuranoses are useful substrates for a convergent synthesis of 5-homologous AZT and D4T derivatives.

## Results and discussion

The starting materials for 5-alkyluracils **1a–c**[6–9] were prepared by reaction of ethyl heptanoate, ethyl octanoate and ethyl decanoate, respectively, with ethyl formate and sodium. The intermediate products – the sodium salts of 2-formylalkanoates – were finally refluxed with urea for 5 h. The uracils **1a–c** so formed were silylated[10] with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) prior to coupling with methyl 5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-D-*threo*-pentofuranoside, prepared from 2-deoxy-D-ribose by successive glycosidation with methanolic HCl, selective 5-*O*-silylation with *tert*-butyldiphenylchlorosilane and introduction of 3-iodo substituent in a Mitsunobu reaction.[11–14]

The nucleoside coupling reaction was accomplished by using trimethylsilyl trifluoromethanesulfonate (TMS-triflate) as a Lewis acid catalyst according to the method described by Vorbrüggen *et al.*[15,16] to give 1:2 (α/β) anomeric mixtures of protected nucleosides **4a–c** in 21–53 % yields. Considering the steric hindrance caused by iodine at the β site of the sugar **3**, it is surprising to find the β-anomer of **4** to be formed in the higher yield. As an explanation one could propose a charge-transfer complex between the iodo substituent and the silylated uracil by which a preferential attack from the β site could be directed. The α- and β-anomers of **4a–c** were separated by chromatography on silica gel. The β anomer of compound **4c** was reacted with sodium azide in dry *N*,*N*-dimethylformamide (Scheme 1). Subsequent removal of the silyl protecting group with tetrabutylammonium fluoride followed by chromatographic purification afforded the unprotected 3′-azido derivative **5** in 46 % yield.

The iodo nucleosides **4** were also reacted with an excess of sodium methoxide[17] in methanol to give anomers of D4T homologues as separable mixtures from which **6a–c** were




*Scheme 1.*

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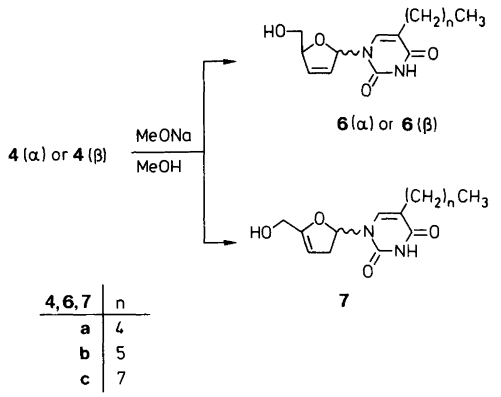
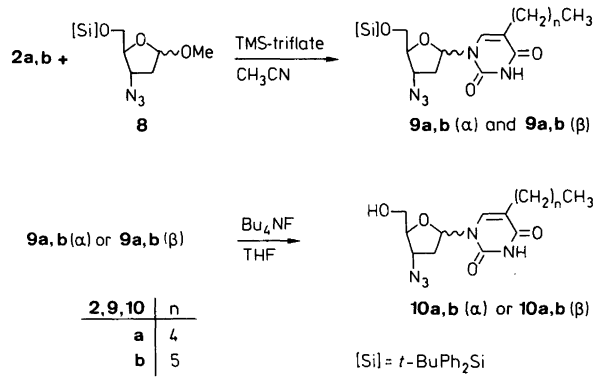



*Scheme 2.*

isolated in 6–68 % yields and **7a–c** in 4–29 % yields (Scheme 2).

In an attempt to obtain a better yield the 3'-azido nucleosides **9a,b** were synthesized by condensation of the silylated uracils **2a,b** with methyl 3-azido-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-*erythro*-pentofuranoside (**8**). The deprotected nucleosides **10a,b** were obtained by treatment with tetrabutylammonium fluoride and separated into α anomers in 26–35 % yields and into β anomers in 18–37 % yields, respectively (Scheme 3).




*Scheme 3.*

NMR data for compound **4a–c**, **6a–c** and **7** are in close agreement with data reported by Abdel-Megied *et al.*[17] and by Chu *et al.*[18] The identity of the azido derivatives **5** and **10a,b** were confirmed by comparison of the NMR data with those reported by Herdewijn *et al.*,[19] Abdel-Megied *et al.*[17] and Fleet *et al.*[20]

The azido derivatives **5**, **10a**(β), **10b**(β), **10a**(α), **10b**(α) and the 2',3'-didehydro derivative **6b**(β) were selected for *in vitro* studies of biological effects. The compounds did not show any significant activity at non-cytotoxic concentrations agains 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 compounds were also devoid of activity at non-cytotoxic concentrations 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 with the culture medium likewise containing the test compound. Expression of HIV in culture medium was quantitated by HIV antigene detection ELISA. For both HSV-1 and HIV-1 the concentration of the test compound was 100 μM, except for the compounds **5** and **6b**(β) which were toxic against SIRC and MT-4 cells at 100 μM. However at 10 μM neither **5** nor **6b**(β) showed activity against HSV-1 or HIV-1.

## Experimental

*1-(5-*O*-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-*D*-threo-pentofuranosyl)-5-alkyluracil derivatives* (**4a–c**). 5-Alkyluracil (12 mmol) was dissolved in HMDS (40 ml). $(NH_4)_2SO_4$ (50 mg, 0.37 mmol) was added and the solution was refluxed for 4 h. The solvent was evaporated *in vacuo* and the silylated 5-alkyluracil was ready for the coupling reaction. The silylated uracil **2a–c** (12 mmol) was dissolved in MeCN (60 ml) and 3-iodofuranoside **3** (4.2 g, 8.5 mmol) dissolved in 10 ml of MeCN was added. The solution was cooled to −25 °C and TMS-triflate (2.2 ml, 12 mmol) in 5 ml MeCN was added dropwise (20 min). After 0.5 h the temperature was allowed to increase to −17 °C and the reaction mixture was stirred at −17 °C for 10–12 h. The mixture was then diluted with $CH_2Cl_2$ (200 ml) and neutralized with cold aqueous $NaHCO_3$ (500 ml). The organic phase was separated, dried over $Na_2SO_4$ and evaporated *in vacuo* to give a crude yellow product which after silica gel column chromatography with petroleum ether (b.p. 60–70 °C)–$Et_2O$ (9:1) gave **4a–c** (α) (5–21 %) and **4a–c** (β) (13–32 %).

*1-(5-*O*-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-*D*-threo-pentofuranosyl)-5-pentyluracil* [**4a**(α)]. Yield 0.298 g, 5 %. $^1$H NMR ($CDCl_3$): δ 0.89 (t, *J* 6.7 Hz, 3 H, $CH_3$), 1.08 (s, 9 H, *t*-Bu), 1.26–1.42 (m, 6 H, $CH_2$), 2.31 (t, *J* 7.6 Hz, 2 H, $CH_2$), 2.79–2.87 (m, 1 H, 2'-H), 3.03–3.11 (m, 1 H, 2'-H), 3.75–3.88 (m, 2 H, 5'-H, 4'-H), 4.01 (dd, *J* 4.3 and 10.2 Hz, 1 H, 5'-H), 4.56 (dd, *J* 3.9 and 6.2 Hz, 1 H, 3'-H), 6.15 (t, *J* 6.2 Hz, 1 H, 1'-H), 7.08–7.73 (m, 11 H, ArH and 6-H), 9.30 (s, 1 H, NH). $^{13}$C NMR ($CDCl_3$): δ 14.04 ($CH_3$), 19.16 ($Me_3C$), 22.41 ($CH_2$), 26.80 ($Me_3C$), 26.99, 28.23, 31.44 ($CH_2$), 44.91 (C-2'), 68.74 (C-5'), 83.34 (C-4'), 88.08 (C-1'), 115.36 (C-5), 127.79, 127.80, 129.90, 135.27, 135.46 (aryl), 135.62 (C-6), 150.03 (C-2), 163.63 (C-4). Anal. $C_{30}H_{39}IN_2O_4Si$: C, H, N.

*1-(5-*O*-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-*D*-threo-pentofuranosyl)-5-pentyluracil* [**4a**(β)]. Yield 0.875 g (16 %). $^1$H NMR ($CDCl_3$): δ 0.83–0.89 (m, 3 H, $CH_3$), 1.08 (s, 9 H, *t*-Bu), 1.27–1.43 (m, 6 H, $CH_2$), 2.19–2.29 (m, 2 H, $CH_2$), 2.66 (ddd, *J* 2.6, 3.7 and 15.7 Hz, 1 H, 2'-H), 3.26

(td, *J* 7.3 and 14.7 Hz, 1 H, 2'-H), 3.40–3.49 (m, 1 H, 4'-H), 3.85 (dd, *J* 5.6 and 10.8 Hz, 1 H, 5'-H), 4.03 (dd, *J* 5.5 and 10.8 Hz, 1 H, 5'-H), 4.47–4.53 (m, 1 H, 3'-H), 6.12 (dd, *J* 3.9 and 7.6 Hz, 1 H, 1'-H), 7.25–7.73 (m, 11 H, ArH and 6-H), 8.44 (s, 1 H, NH). $^{13}$C NMR ($CDCl_3$): δ 14.10 ($CH_3$), 19.29 ($Me_3C$), 22.76 ($CH_2$), 26.94 ($Me_3C$), 26.99, 27.73, 31.64 ($CH_2$), 44.45 (C-2'), 68.79 (C-5'), 82.21 (C-4'), 85.05 (C-1'), 114.84 (C-5), 127.88, 130.02, 133.05, 135.66 (aryl), 136.10 (C-6), 150.13 (C-2), 163.23 (C-4). Anal. $C_{30}H_{39}IN_2O_4Si$: C, H, N.

*1-(5-*O-tert-*Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-*D-threo-*pentofuranosyl)-5-hexyluracil* [**4b**(α)]. Yield 0.500 g (9 %). $^1$H NMR ($CDCl_3$): δ 0.88 (m, 3 H, $CH_3$), 1.09 (s, 9 H, *t*-Bu), 1.26–1.52 (m, 6 H, $CH_2$), 2.31 (t, *J* 7.6 Hz, 2 H, $CH_2$), 2.79–2.87 (m, 1 H, 2'-H), 3.02–3.06 (m, 1 H, 2'-H), 3.76–3.88 (m, 2 H, 5'-H and 4'-H), 4.01 (dd, *J* 3.9 and 9.8 Hz, 1 H, 5'-H), 4.55 (dd, *J* 3.9 and 6.3 Hz, 1 H, 3'-H), 6.14 (t, *J* 6.2 Hz, 1 H, 1'-H), 7.07–7.73 (m, 11 H, ArH and 6-H), 9.30 (s, 1 H, NH). $^{13}$C NMR ($CDCl_3$): δ 14.06 ($CH_3$), 19.19 ($Me_3C$), 22.60 ($CH_2$), 26.86 ($Me_3C$), 27.04, 28.56, 28.96, 31.57 ($CH_2$), 44.99 (C-2'), 68.85 (C-5'), 83.39 (C-4'), 88.12 (C-1'), 115.42 (C-5), 127.81, 129.91, 132.98, 135.47 (aryl), 135.65 (C-6), 150.08 (C-2), 163.60 (C-4).

*1-(5-*O-tert-*Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-*D-threo-*pentofuranosyl)-5-hexyluracil* [**4b**(β)]. Yield 0.710 g (13 %). $^1$H NMR ($CDCl_3$): δ 0.86 (t, *J* 6.6 Hz, 3 H, $CH_3$), 1.09 (s, 9 H, *t*-Bu), 1.20–1.48 (m, 8 H, $CH_2$), 2.17–2.31 (m, 2 H, $CH_2$), 2.66 (ddd, *J* 2.8, 3.6 and 15.8 Hz, 1 H, 2'-H), 3.26 (td, *J* 7.3 and 14.7 Hz, 1 H, 2'-H), 3.37–3.49 (m, 1 H, 4'-H), 3.85 (dd, *J* 5.6 and 10.8 Hz, 1 H, 5'-H), 4.03 (dd, *J* 5.4 and 10.7 Hz, 1 H, 5'-H), 4.47–4.53 (m, 1 H, 3'-H), 6.14 (dd, *J* 3.9 and 7.5 Hz, 1 H, 1'-H), 7.25–7.74 (m, 11 H, ArH and 6-H), 9.39 (s, 1 H, NH). $^{13}$C NMR ($CDCl_3$): δ 14.08 ($CH_3$), 19.23 ($Me_3C$), 22.62, 22.94 ($CH_2$). 26.90 ($Me_3C$), 28.34, 28.93, 31.59 ($CH_2$), 44.35 (C-2'), 68.74 (C-5'), 82.11 (C-4'), 84.98 (C-1'), 114.85 (C-5), 127.83, 129.95, 132.97, 135.59 (aryl), 136.01 (C-6), 150.42 (C-2), 163.63 (C-4).

*1-(5-*O-tert-*Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-*D-threo-*pentofuranosyl)-5-octyluracil* [**4c**(α)]. Yield 1.22 g (21 %). $^1$H NMR ($CDCl_3$): δ 0.87 (m, 3 H, $CH_3$), 1.04–1.52 (m, 21 H, *t*-Bu and $CH_2$), 2.31 (t, *J* 7.6 Hz, 2 H, $CH_2$), 2.75–2.87 (m, 1 H, 2'-H), 3.02–3.11 (m, 1 H, 2'-H), 3.78–3.86 (m, 2 H, 5'-H and 4'-H), 4.01 (dd, *J* 5.9 and 9.7 Hz, 1 H, 5'-H), 4.54 (dd, *J* 3.5 and 6.1 Hz, 1 H, 3'-H), 6.14 (t, *J* 6.2 Hz, 1 H, 1'-H), 7.05–7.73 (m, 11 H, ArH and 6-H), 9.11 (s, 1 H, NH), $^{13}$C NMR ($CDCl_3$): δ 14.08 ($CH_3$), 19.19 ($Me_3C$), 22.64, 23.28 ($CH_2$), 26.94 ($Me_3C$), 27.06, 28.62, 29.26, 29.34, 31.86 ($CH_2$), 44.98 (C-2'), 68.84 (C-5'), 83.39 (C-4'), 88.12 (C-1'), 115.42 (C-5), 127.80, 129.91, 132.97, 135.52 (aryl), 135.65 (C-6), 150.01 (C-2), 163.50 (C-4).

*1-(5-*O-tert-*Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-*D-threo-*pentofuranosyl)-5-octyluracil* [**4c**(β)]. Yield 1.87 g (32 %). $^1$H NMR ($CDCl_3$): δ 0.84–0.89 (m, 3 H, $CH_3$), 1.09 (s, 9 H, *t*-Bu), 1.20–1.45 (m, 12 H, $CH_2$), 2.17–2.32 (m, 2 H, $CH_2$), 2.60 (ddd, *J* 2.8, 3.6 and 15.8 Hz, 1 H, 2'-H), 3.26 (td, *J* 7.3 and 14.7 Hz, 1 H, 2'-H), 3.37–3.49 (m, 1 H, 4'-H), 3.85 (dd, *J* 5.6 and 10.8 Hz, 1 H, 5'-H), 4.03 (dd, *J* 5.5 and 10.8 Hz, 1 H, 5'-H), 4.47–4.53 (m, 1 H, 3'-H), 6.12 (dd, *J* 3.9 and 7.6 Hz, 1 H, 1'-H), 7.25–7.74 (m, 11 H, ArH and 6-H), 9.25 (s, 1 H, NH). $^{13}$C NMR ($CDCl_3$): δ 14.10 ($CH_3$), 19.25 ($Me_3C$), 22.66 ($CH_2$), 22.94 ($CH_2$), 26.90 ($Me_3C$), 28.42, 29.29, 29.37, 29.70, 31.87 ($CH_2$), 44.36 (C-2'), 68.74 (C-5'), 82.13 (C-4'), 84.98 (C-1'), 114.87 (C-5), 127.84, 129.97, 132.98, 135.71 (aryl), 136.02 (C-6), 150.38 (C-2), 163.58 (C-4).

*1-(3-Azido-2,3-dideoxy-β-*D-erythro-*pentofuranosyl)-5-octyluracil* (**5**). To a stirred solution of **4c**(β) (1.00 g, 1.5 mmol) dissolved in DMF, (20 ml) was added $NaN_3$ (0.99 g, 15 mmol). After 4 h of reflux and cooling to room temperature the solvent was evaporated off. The reaction mixture was diluted with $H_2O$ (100 ml) and $CH_2Cl_2$ (150 ml). The organic phase was dried over $Na_2SO_4$ and evaporated *in vacuo*. The product was dissolved in THF (30 ml) and 1.5 ml of 1 M $Bu_4NF$ diluted with THF (5 ml) was added slowly at 0 °C. After 0.5 h the solvent was evaporated *in vacuo*. The product was purified on a silica gel column with petroleum ether (b.p. 60–80 °C)–$Et_2O$ (9:1). Yield 0.250 g (46 %). $^1$H NMR ($CDCl_3$): δ 0.89–1.09 (m, 3 H, $CH_3$), 1.23–1.63 (m, 12 H, $CH_2$), 2.38 (t, *J* 7.5 Hz, 2 H, $CH_2$), 2.44–2.52 (m, 2 H, 2'-H), 3.80–4.04 (m, 3 H, 3'-H and 5'-H), 4.41–4.47 (m, 1 H, 4'-H), 6.27 (t, *J* 6.4 Hz, 1 H, 1'-H), 7.88 (s, 1 H, 6-H). $^{13}$C NMR ($CDCl_3$): δ 14.41 ($CH_3$), 23.67, 27.77, 29.59, 30.31, 30.37, 30.42, 32.99 ($CH_2$), 38.39 (C-2'), 61.71 (C-3'), 62.42 (C-5'), 86.16 (C-4'), 86.24 (C-1'), 116.06 (C-5), 137.99 (C-6), 152.15 (C-2), 165.90 (C-4). Anal. $C_{17}H_{27}N_5O_4$: C, H, N.

*1-(2,3-Dideoxy-α,β-*D-glycero-*pent-2-enofuranosyl)-5-alkyluracil* (**6a–c**) *and* (R/S)-*1-(2,3-dihydro-5-hydroxymethylfuran-2-yl)-5-alkyluracil* (**7a–c**). To a stirred solution of **4a–c** (α or β) (1.00 g, 1.55 mmol) dissolved in 30 ml MeOH was added NaOMe prepared from Na (0.355 g, 15.4 mmol) in MeOH (20 ml). After reflux for 8 h and subsequent cooling to room temperature, the reaction mixture was neutralized with $NH_4Cl$ (0.82 g, 15.5 mmol) and the solvent evaporated off *in vacuo*. The products were separated on a silica gel column with MeOH–$CHCl_3$ (1:200) to give **6a–c**(α) in 15–25 % yield or **6a–c**(β) in 6–68 % yield and **7a–c** in 4–29 % yield.

*1-(2,3-Dideoxy-α-*D-glycero-*pent-2-enofuranosyl)-5-pentyluracil* [**6a**(α)]. Yield 0.110 g (25 %). $^1$H NMR ($CDCl_3$): δ 0.88 (t, *J* 6.6 Hz, 3 H, $CH_3$), 1.29–1.50 (m, 6 H, $CH_2$), 2.28 (t, *J* 7.5 Hz, 2 H, $CH_2$), 3.66 (dd, *J* 4.8 and 12.0 Hz, 1 H, 5'-H), 3.84 (dd, *J* 3.2 and 12.0 Hz, 1 H, 5'-H), 5.15 (br s, 1 H, 4'-H), 5.93 (m, 1 H, 2'-H), 6.35 (m, 1 H, 3'-H), 6.86 (s, 1 H, 1'-H), 7.10 (s, 1 H, 6-H). $^{13}$C NMR ($CDCl_3$): δ 14.01 ($CH_3$), 22.39, 26.91, 28.07, 31.38 ($CH_2$), 64.22 (C-5'), 87.89 (C-4'), 90.37 (C-1'), 116.03 (C-5), 126.77

(C-2'), 134.04 (C-3'), 134.83 (C-6), 150.89 (C-2), 163.54 (C-4).

*1-(2,3-Dideoxy-β-*D*-glycero-pent-2-enofuranosyl)-5-pentyluracil* [**6a**(β)]. Yield 0.295 g (68%). $^1$H NMR ($CDCl_3$): δ 0.85–0.90 (m, 3 H, $CH_3$), 1.21–1.50 (m, 6 H, $CH_2$), 2.18–2.31 (m, 2 H, $CH_2$), 3.70–3.82 (m, 1 H, 5'-H), 3.92–3.97 (m, 1 H, 5'-H), 4.93 (br s, 1 H, 4'-H), 5.86 (td, *J* 1.8 and 6.0 Hz, 1 H, 2'-H), 6.35 (td, *J* 1.7 and 6.0 Hz, 1 H, 3'-H), 7.05 (s, 1 H, 1'-H), 7.41 (6-H). $^{13}$C NMR ($CDCl_3$): δ 14.00 ($CH_3$), 22.37, 26.52, 27.91, 31.40 ($CH_2$), 63.35 (C-5'), 87.32 (C-4'), 89.98 (C-1'), 115.27 (C-5), 126.25 (C-2'), 134.75 (C-3'), 136.50 (C-6), 150.70 (C-2), 163.79 (C-4). Anal. $C_{14}H_{20}N_2O_4$: C, H, N.

*1-(2,3-Dideoxy-α-*D*-glycero-pent-2-enofuranosyl)-5-hexyluracil* [**6b**(α)]. Yield 0.067 g (15%). $^1$H NMR ($CDCl_3$): δ 0.87 (t, 3 H, $CH_3$), 1.05–1.46 (m, 8 H, $CH_2$), 2.20–2.37 (m, 2 H, $CH_2$), 3.68–3.98 (m, 2 H, 5'-H), 4.93 (br s, 1 H, 4'-H), 5.84 (m, 1 H, 2'-H), 6.35 (m, 1 H, 3'-H), 7.07 (s, 1 H, 1'-H), 7.27 (s, 1 H, 6-H). $^{13}$C NMR ($CDCl_3$): δ 14.07 ($CH_3$), 22.61, 26.73, 28.21, 28.93, 31.55 ($CH_2$), 63.38 (C-5'), 87.24 (C-4'), 89.99 (C-1'), 115.32 (C-5), 126.28 (C-2'), 134.68 (C-3'), 135.53 (C-6), 150.75 (C-2), 163.69 (C-4).

*1-(2,3-Dideoxy-β-*D*-glycero-pent-2-enofuranosyl)-5-hexyluracil* [**6b**(β)]. Yield 0.214 g (49%). $^1$H NMR ($CDCl_3$): δ 0.87 (t, 3 H, $CH_3$), 1.21–1.44 (m, 8 H, $CH_2$), 2.14–2.28 (m, 2 H, $CH_2$), 3.76–3.81 (m, 1 H, 5'-H), 3.93–3.98 (m, 1 H, 5'-H), 4.92 (br s, 1 H, 4'-H), 5.85 (m, 1 H, 2'-H), 6.36 (td, *J* 1.7 and 6.0 Hz, 1 H, 3'-H), 7.06 (s, 1 H, 1'-H), 7.40 (s, 1 H, 6-H), $^{13}$C NMR ($CDCl_3$): δ 14.05 ($CH_3$), 22.61, 26.70, 28.21, 28.94, 31.55 ($CH_2$), 63.32 (C-5'), 87.43 (C-4'), 90.02 (C-1'), 115.28 (C-5), 126.14 (C-2'), 134.81 (C-3'), 136.60 (C-6), 151.03 (C-2), 164.08 (C-4). Anal. $C_{15}H_{22}N_2O_4 \cdot 0.25\ H_2O$: C, H, N.

*1-(2,3-Dideoxy-β-*D*-glycero-pent-2-enofuranosyl)-5-octyluracil* [**6c**(β)]. Yield 0.030 g (6%). $^1$H NMR ($CD_3OD$): δ 0.98 (t, 3 H, $CH_3$), 1.10–1.50 (m, 12 H, $CH_2$), 2.31–2.37 (t, 2 H, $CH_2$), 3.74–3.91 (m, 2 H, 5'-H), 4.95 (br s, 1 H, 4'-H), 5.99 (m, 1 H, 2'-H), 6.49 (td, *J* 1.7 and 6.1 Hz, 1 H, 3'-H), 7.02–7.05 (m, 1 H, 1'-H), 7.78 (s, 1 H, 6-H). $^{13}$C NMR ($CD_3OD$): 14.40 ($CH_3$), 23.65, 27.14, 27.67, 29.51, 30.31, 30.40, 32.97 ($CH_2$), 63.84 (C-5'), 88.97 (C-4'), 91.13 (C-1'), 115.77 (C-5), 127.24 (C-2'), 135.95 (C-3'), 138.72 (C-6), 152.76 (C-2), 166.13 (C-4). Calc. for $C_{17}H_{26}N_2O_4$: 322.189. Found 322.185 (MS).

(R)-*1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-pentyluracil* [**7a** (*R*)]. Yield 0.058 g (13%) $^1$H NMR ($CDCl_3$): δ 0.88 (t, *J* 6.8 Hz, 3 H, $CH_3$), 1.08–1.54 (m, 6 H, $CH_2$), 2.30 (t, *J* 7.5 Hz, 2 H, $CH_2$), 2.59–2.66 (m, 1 H, 2'-H), 3.19–3.32 (m, 1 H, 2'-H), 4.25 (br s, 2 H, 5'-H), 5.07 (br s, 1 H, 3'-H), 6.74 (dd, *J* 4.1 and 9.7 Hz, 1 H, 1'-H), 7.07 (s, 1 H, H-6). $^{13}$C NMR ($CDCl_3$): δ 14.01 ($CH_3$), 22.39, 26.89, 27.99, 31.32 ($CH_3$), 36.48 (C-2'), 57.49 (C-5'), 85.04 (C-1'), 96.18 (C-3'), 116.58 (C-5), 134.68 (C-6), 150.06 (C-2), 156.68 (C-4'), 163.30 (C-4). Anal. $C_{14}H_{20}N_2O_4 \cdot H_2O$: C, H, N.

(S)-*1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-pentyluracil* [**7a** (*S*)]. Yield 0.093 g (22%) which has the same $^1$H and $^{13}$C NMR data as **7a** (*R*).

(R)-*1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-hexyluracil* [**7b** (*R*)]. Yield 0.130 g (29%). $^1$H NMR ($CDCl_3$): δ 0.87 (t, *J* 6.3 Hz, 3 H, $CH_3$), 1.07–1.46 (m, 8 H, $CH_2$), 2.29 (t, *J* 7.4, 2 H, $CH_2$), 2.59–2.65 (m, 1 H, 2'-H), 3.20–3.24 (m, 1 H, 2'-H), 4.24 (br s, 2 H, 5'-H), 5.07 (br s, 1 H, 3'-H), 6.74 (dd, *J* 4.0 and 9.7 Hz, 1 H, 1'-H), 7.07 (s, 1 H, H-6). $^{13}$C NMR ($CDCl_3$): δ 14.08 ($CH_3$), 22.61, 26.91, 28.27, 28.86, 31.56 ($CH_2$), 36.45 (C-2'), 57.37 (C-5'), 84.99 (C-1'), 95.13 (C-3'), 116.60 (C-5), 134.75 (C-6), 150.24 (C-2), 156.74 (C-4'), 163.58 (C-4).

(S)-*1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-hexyluracil* [**7b** (*S*)]. Yield 0.110 g (25%) which has the same $^1$H and $^{13}$C NMR data as **7b** (*R*).

(R)-*1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-octyluracil* [**7c** (*R*)]. Yield 0.020 g (4%). $^1$H NMR ($CD_3OD$): δ 0.95–1.57 (m, 15 H, $CH_2$ and $CH_3$), 2.38 (t, *J* 7.4 Hz, 2 H, $CH_2$), 2.69–2.72 (m, 1 H, 2'-H), 2.76–2.78 (m, 1 H, 2'-H), 3.23–3.59 (m, 1 H, 2'-H), 4.22 (br s, 2 H, 5'-H), 5.16 (br s, 1 H, 3'-H), 6.73 (dd, *J* 4.0 and 9.6 Hz, 1 H, 1'-H), 7.38 (s, 1 H, 6-H). $^{13}$C NMR ($CD_3OD$): δ 14.37 ($CH_3$), 23.64, 27.76, 29.58, 30.22, 30.31, 30.93, 32.96 ($CH_2$), 37.13 (C-2'), 57.57 (C-5'), 86.57 (C-1'), 97.05 (C-3'), 116.89 (C-5), 136.88 (C-6), 151.88 (C-2), 158.50 (C-4'), 165.76 (C-4). Calc. for $C_{17}H_{26}N_2O_4$: 322.189. Found 322.188 (MS).

*1-(3-Azido-2,3-dideoxy-α,β-*D*-erythro-pentofuranosyl)-5-alkyluracils* (**10**). The silylated uracils **2a** (9.3 mmol) or **2b** (5.38 mmol) were dissolved in MeCN (50 ml). The 3-azidofuranoside **8** (2.7 g, 6.6 mmol in case of **2a** or 1.7 g, 4.1 mmol in case of **2b**) dissolved in 10 ml MeCN was added. The solution was cooled to −25 °C and TMS-triflate (2.06 ml, 9.3 mmol for **2a** or 1.2 ml, 5.38 mmol for **2b**) was added dropwise over 20 min. The temperature was increased to room temperature and the mixture was stirred overnight (32 h). The mixture was then diluted with $CH_2Cl_2$ (150 ml) and neutralized with cooled aqueous $NaHCO_3$. The organic phase was separated, dried over $Na_2SO_4$ and evaporated *in vacuo* to give a crude yellow product which, after silica gel column chromatography with petroleum ether (b.p. 60–80 °C)–$Et_2O$ (9:1), afforded a 1:1 (α/β) anomeric mixture of protected nucleosides (**9a**,**b**) in 82–85% yield. **9a** (4.4 g, 7.8 mmol) or **9b** (2.00 g, 3.4 mmol) were dissolved in distilled THF (60 ml) at 0 °C. 7.8 ml or 3.4 ml, respectively, of 1 M $Bu_4NF$ in THF were slowly added. The mixture was stirred for 0.5 h and the solvent evaporated off *in vacuo*. Silica gel column

chromatography with MeOH–$CHCl_3$ (1:99) afforded the products **10a**,**b**(α) in 26–35 % yield and **10a**,**b**(β) in 18–37 %.

*1-(3-Azido-2,3-dideoxy-α-*D*-erythro-pentofuranosyl)-5-pentyluracil* [**10a**(α)]. Yield 0.870 g (35 %). $^1$H NMR ($CDCl_3$): δ 0.87–0.97 (m, 3 H, $CH_3$), 1.31–1.61 (m, 8 H, $CH_2$), 2.10–2.37 (m, 1 H, 2′-H), 2.68–2.92 (m, 1 H, 2′-H), 3.69 (dd, *J* 3.5 and 12.1 Hz, 1 H, 5′-H), 3.81 (dd, *J* 3.5 and 12.2 Hz, 1 H, 5′-H), 4.29–4.36 (m, 2 H, 4′-H and 3′-H), 6.31 (dd, *J* 3.9 and 7.1 Hz, 1 H, 1′-H), 7.30 (s, 1 H, 6-H). $^{13}$C NMR ($CDCl_3$): δ 13.99 ($CH_3$), 22.45, 26.88, 27.98, 31.33 ($CH_2$), 38.26 (C-2′), 61.10 (C-3′), 62.76 (C-5′), 86.20 (C-4′), 86.31 (C-1′), 115.54 (C-5), 135.22 (C-6), 150.63 (C-2), 163.62 (C-4). Anal. $C_{14}H_{21}N_5O_4 \cdot 0.25\ H_2O$: C, H, N.

*1-(3-Azido-2,3-dideoxy-β-*D*-erythro-pentofuranosyl)-5-pentyluracil* [**10a**(β)]. Yield 0.940 g (37 %). $^1$H NMR ($CDCl_3$): δ 0.89 (t, *J* 6.8 Hz, 3 H, $CH_3$), 1.24–1.54 (m, 6 H, $CH_2$), 2.28 (t, *J* 7.6 Hz, 2 H, $CH_2$), 2.35–2.58 (m, 2 H, 2′-H), 3.78–3.99 (m, 3 H, 5′-H and 4′-H), 4.37–4.44 (m, 1 H, 3′-H), 6.10 (t, *J* 6.4 Hz, 1 H, 1′-H), 7.43 (s, 1 H, 6-H), 9.83 (s, 1 H, NH). $^{13}$C NMR ($CDCl_3$): δ 13.75 ($CH_3$), 22.14, 26.47, 27.67, 31.13 ($CH_2$), 37.11 (C-2′), 59.90 (C-3′), 61.62 (C-5′), 84.48 (C-4′), 86.31 (C-1′), 115.43 (C-5), 136.43 (C-6), 150.34 (C-2), 163.68 (C-4). Anal. $C_{14}H_{21}N_5O_4 \cdot 0.25\ H_2O$: C, H, N.

*1-(3-Azido-2,3-dideoxy-α-*D*-erythro-pentofuranosyl)-5-hexyluracil* [**10b**(α)]. Yield 0.300 g (26 %). $^1$H NMR ($CDCl_3$): δ 0.86–0.99 (m, 3 H, $CH_3$), 1.30–1.53 (m, 10 H, $CH_2$), 2.09–2.37 (m, 1 H, 2′-H), 2.82–2.93 (m, 1 H, 2′-H), 3.69 (dd, *J* 3.2 and 12.1 Hz, 1 H, 5′-H), 3.82 (dd, *J* 3.0 and 12.2 Hz, 1 H, 5′-H), 4.31–4.37 (m, 2 H, 4′-H and 3′-H), 6.33 (dd, *J* 3.8 and 6.9 Hz, 1 H, 1′-H), 7.31 (s, 1 H, H-6). $^{13}$C NMR ($CDCl_3$): δ 13.99 ($CH_3$), 22.61, 26.96, 28.40, 28.88, 31.66 ($CH_2$), 38.31 (C-2′), 61.22 (C-3′), 62.89 (C-5′), 86.28 (C-4′), 86.35 (C-1′), 115.71 (C-5), 135.17 (C-6), 150.65 (C-2), 163.51 (C-4). Anal. $C_{15}H_{23}N_5O_4$: C, H, N.

*1-(3-Azido-2,3-dideoxy-β-*D*-erythro-pentofuranosyl)-5-hexyluracil* [**10b**(β)]. Yield 0.210 g (18 %). $^1$H NMR ($CDCl_3$): δ 0.86 (t, *J* 6.8 Hz, 3 H, $CH_3$), 1.19–2.48 (m, 8 H, $CH_2$), 2.29 (t, *J* 7.6 Hz, 2 H, $CH_2$), 2.34–2.53 (m, 2 H, 2′-H), 3.70–3.99 (m, 3 H, 5′-H, 4′-H and 5′-H), 4.37–4.40 (m, 1 H, 3′-H), 6.08 (t, *J* 6.5 Hz, 1 H, 1′-H), 7.38 (s, 1 H, 6-H), 9.44 (s, 1 H, NH). $^{13}$C NMR ($CDCl_3$): δ 13.84 ($CH_3$), 22.41, 26.62, 28.07, 28.72, 31.38 ($CH_2$), 37.18 (C-2′), 59.94 (C-3′), 61.73 (C-5′), 84.82 (C-4′), 86.51 (C-1′), 115.56 (C-5), 136.36 (C-6), 150.27 (C-2), 163.47 (C-4). Calc. for $C_{15}H_{23}N_5O_4$: 337.1750. Found 337.1749 (MS).

## References


1. Gallo, R. C., Salahuddin, S. Z., Popovic, M., Shearer, G. M., Kaplan, M., Haynes, B. F., Palker, T. J., Redfield, R., Oleske, J., Safai, B., White, G., Foster, P. and Markham, P. D. *Science 224* (1984) 500.
2. De Clerq, E. *J. Med. Chem. 29* (1986) 1561.
3. Mitsuya, H. and Broder, S. *Proc. Natl. Acad. Sci. USA 83* (1986) 1911.
4. Mitsuya, H. and Broder, S. *Nature (London) 325* (1987) 773.
5. Broder, S. *Pharm. Technol. 12* (1988) 24.
6. Fissekis, J. D. and Sweet, F. *Biochemistry 9* (1970) 3136.
7. Chesterfield, J. H., McOmie, J. F. W. and Tute, M. S. *J. Chem. Soc.* (1960) 4590.
8. Burckhalter, J. H. and Scarborough, H. C. *J. Am. Pharm. Assoc. 44* (1955) 545.
9. Anderson, G. W., Halverstadt, I. F., Miller, W. H. and Roblin, Jr., R. O. *J. Am. Chem. Soc. 67* (1945) 2197.
10. Wittenburg, E. *Z. Chem. 4* (1964) 303.
11. Hansen, P. and Pedersen, E. B. *Acta Chem. Scand. 44* (1990) 522.
12. Fischer, E. *Ber. Dtsch. Chem. Ges. 28* (1895) 1145.
13. Motawia, M. S. and Pedersen, E. B. *Liebigs Ann. Chem.* (1990) 599.
14. Mitsunobu, O. *Synthesis* (1981) 1.
15. Vorbrüggen, H., Krolikiewicz, K. and Bennua, B. *Chem. Ber. 114* (1981) 1234.
16. Vorbrüggen, H. and Höfle, G. *Chem. Ber. 114* (1981) 1256.
17. Abdel-Megied, A. E.-S., Hansen, P., Pedersen, E. B. and Nielsen, C. M. *Acta Chem. Scand. 45* (1991) 1060.
18. Chu, C. K., Bhadti, V. S., Doboszewski, B., Gu, Z. P., Kosugi, Y., Pullaiah, K. C. and Van Roey, P. *J. Org. Chem. 54* (1989) 2217.
19. Herdewijn, P., Balzarini, J., De Clercq, E., Pauwels, R., Baba, M., Broder, S. and Vanderhaeghe, H. *J. Med. Chem. 30* (1987) 1270.
20. Fleet, G. W. J., Son, J. C. and Derome, A. E. *Tetrahedron 44* (1988) 625.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