Monatshefte für Chemie 129, 99–109 (1998)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Synthesis of 3′-Azido, 2′,3′-Didehydro, and 3′,4′-Didehydro Nucleosides from 5-Alkoxymethyluracils

Ahmed E.-S. Abdel-Megied[1], **Erik B. Pedersen**[1,*], and **Claus Nielsen**[2]

[1] Department of Chemistry, Odense University, DK-5230 Odense M, Denmark
[2] Retrovirus Laboratory, Department of Virology, Statens Seruminstitut, DK-2300 Copenhagen, Denmark

Summary. Reaction of methyl 5-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-*D-threo*-pentofuranoside (**3**) with silylated 5-alkoxymethyluracils **2a–c** using trimethylsilyl trifluoromethanesulfonate as a catalyst afforded the α nucleosides **4a–c** and the β nucleosides **5a–c**. The corresponding 3′,4′- and 4′,5′-didehydro nucleosides **6–9** were prepared in an elimination reaction by treating the iodo nucleosides **4a–c** or **5a–c** with 10 equivalents of sodium methoxide in methanol under reflux. The deprotected 3′-azido nucleosides **10a–c** and **11a–c** of the *AZT* type as well as the 4′,5′-didehydro nucleosides **7a–c** and **9a–c** were prepared by treating **4a–c** and **5a–c**, respectively, with sodium azide and subsequently with tetrabutylammonium fluoride.

Keywords. Nucleosides, convergent synthesis of; Nucleosides, 3′-azido-2′-deoxy; Nucleosides, 2′,3′-didehydro; Nucleosides, 3′,4′-didehydro; 5-Alkoxymethyluracil nucleosides; Human immunodeficiency virus; Herpes simplex virus.

Synthese von 3′-Azido-, 2′,3′-Didehydro- und 3′,4′-Didehydronucleosiden aus 5-Alkoxymethyluracilen

Zusammenfassung. Reaktion von Methyl-5-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-*D-threo*-pentofuranosid (**3**) mit den silylierten 5-Alkoxymethyluracilen **2a–c** unter Verwendung von Trimethylsilyltrifluormethansulfonat als Katalysator ergab die α-Nucleoside **4a–c** und die β-Nucleoside **5a–c**. Die entsprechenden 3′,4′- und 4′,5′-Didehydronucleoside **6–9** wurden durch Behandeln der Jodnucleoside **4a–c** oder **5a–c** mit 10 Äquivalenten Natriummethoxid in siedendem Methanol über eine Eliminierungsreaktion hergestell. Die entschützten 3′-Azidonucleoside **10a–c** und **11a–c** vom *AZT*-Typ wurden ebenso wie die 4′,5′-Didehydronucleoside **7a–c** und **9a–c** durch Umsetzung von **4a–c** und **5a–c** mit Natriumazid und nachfolgender Behandlung mit Tetrabutylammoniumfluorid erhalten.

Introduction

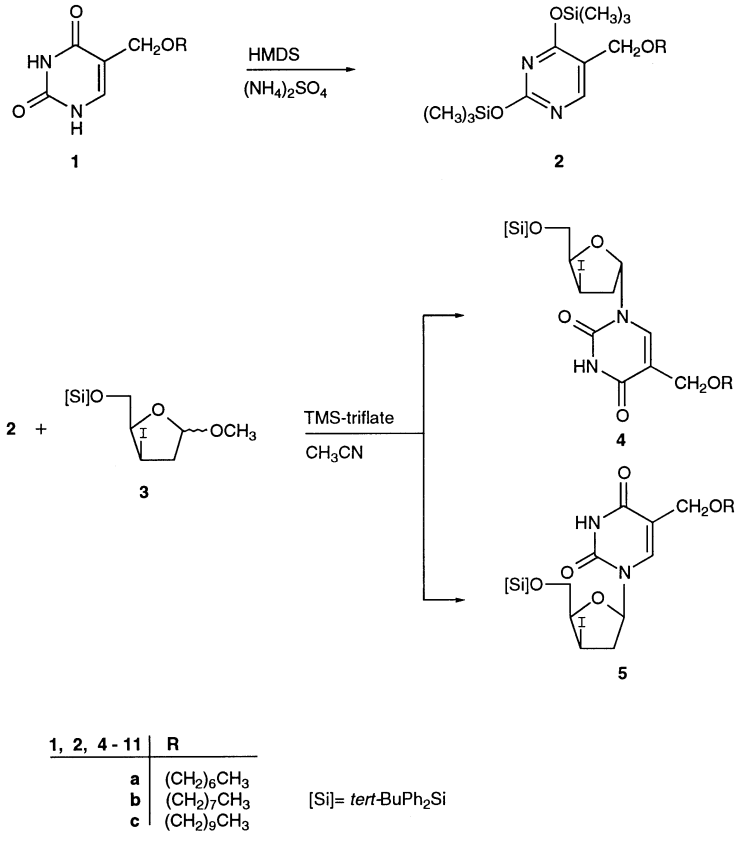
Among the 2′,3′-dideoxynucleosides [1], 3′-azido-3′-deoxythymidine (*AZT*) is very potent in its antiviral action against human immunodeficiency virus (HIV), and it was the first successful drug used in the treatment of patients with acquired

immunodeficiency syndrome (AIDS) [2–4]. The application of this compound has been met with some difficulties due to its side effects, the key toxicity being the suppression of bone marrow [5]. During recent years we have synthesized a large number of 3′-deoxythymidine derivatives in order to find new and less toxic agents against AIDS [6–8]. In this context we found it insufficient to adjust the electronic and lipophilic parameters of the 3′-substituent with those of the azido group in *AZT* in order to achieve activity against HIV in MT-4 cells [9]. We have also varied the properties of the 5-substituent in *AZT* by replacing methyl by C_1-C_6 alkoxymethyl groups [10] to correlate a large range of lipophilicities with the activity against HIV independently of the electron donating properties which for this series of substituents were assumed to show very little variation. Unfortunately, the 5-alkoxymethyl *AZT* analogues did not show any activity against HIV which was ascribed to the bulkiness of the 5-substituent. Instead, a surprising but moderate activity against HIV was found for the corresponding α anomers of the long chain 5-alkoxymethyl *AZT* analogues. Therefore, it was of interest to synthesize long chain alkoxymethyl *AZT* analogues and their corresponding α anomers in order to investigate their biological activity against HIV. In this work we have chosen a strategy different from that in the previous work for the synthesis of the desired compounds. Instead of preparing the nucleosides by coupling of the nucleobase with an appropriately substituted 3′-azidopentofuranoside, we decided to use a suitable 3′-iodopentofuranoside. In this way, after synthesizing the 3′-iodo nucleoside, it should not only be possible to obtain the *AZT* analogues in a substitution reaction, but also in an elimination reaction the corresponding 2′,3′-didehydro nucleosides which are the corresponding alkoxymethyl analogues of D4T (3′-deoxy-2′,3′-didehydrothymidine) which is also a potent drug against HIV.

Results and Discussion

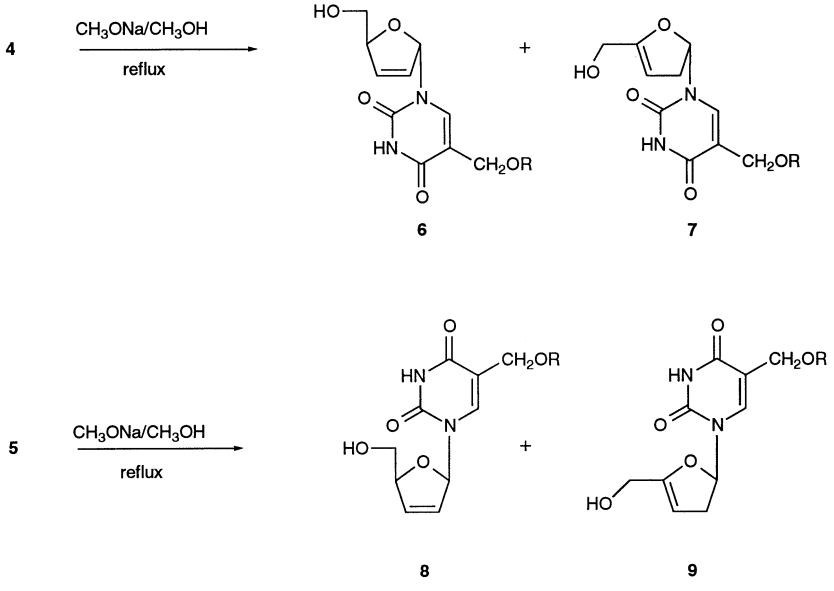
5-Alkoxymethyluracils **1a–c** were prepared by reaction of 5-hydroxymethyluracil [11] with 1-heptanol, 1-octanol, and 1-decanol, respectively, using conc. HCl as a catalyst as previously described for **1c** [12]. Silylation of **1a–c** with 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) was performed according to *Wittenburg* [13] prior to their coupling as silylated derivatives **2** with methyl 5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-3-iodo-α,β-*D-threo*-pentofuranoside (**3**) [14] which was accomplished using trimethylsilyl trifluoromethanesulfonate (*TMS* triflate) as *Lewis* acid catalyst according to the method of *Vorbrüggen et al.* [15]. Flash chromatographic separation gave the α nucleosides **4a–c** in 24–26% and the β nucleosides **5a–c** in 30–39% yield. In spite of expected sterical hindrance due to the iodine at the β site of the furanose ring, the α/β ratio was typically 2:3. One can speculate whether the iodo substituent can form a charge-transfer complex with the silylated uracil **2** due to its polarizability and in this way direct the attack of the nucleobase to the β site of the furanose ring.

Treatment of **4a–c** or **5a–c** with an excess of NaOMe/MeOH under reflux gave a separable mixture of the α-2′,3′-didehydro nucleosides **6a–c** (32–54%) and the 3′,4′-didehydro nucleosides **7a–c** (20–54%) or the β-2′,3′-didehydro nucleosides **8a–c** (37–59%) and the 3′,4′-didehydro nucleosides **9a–c** (14–22%). We failed to separate **6a** and **7a** by silica gel or reversed phase chromatography.



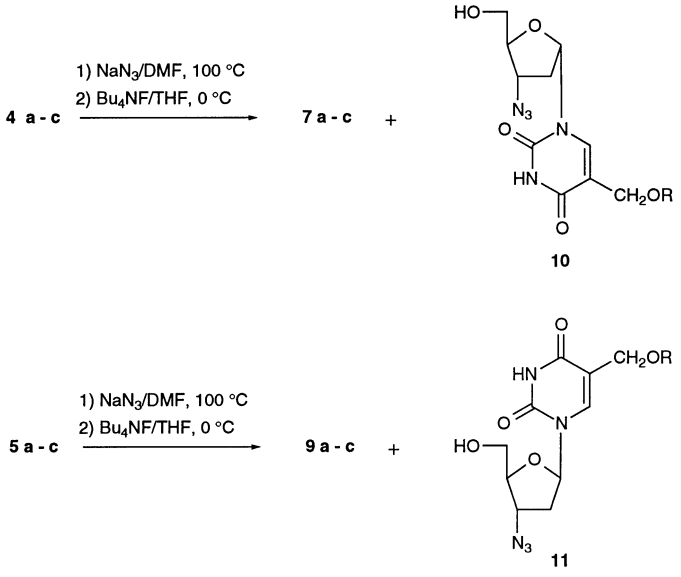
1, 2, 4 - 11	R
a	$(CH_2)_6CH_3$
b	$(CH_2)_7CH_3$
c	$(CH_2)_9CH_3$

Scheme 1



Scheme 2

The substitution reaction **4a–c** was performed with 10 equivalents of sodium azide in dry *N*,*N*-dimethylformamide (*DMF*) 4 h at 100°C). Subsequent removal of the silyl protecting group with tetrabutylammonium fluoride followed by chromatographic purification afforded the unprotected 3′-azido α nucleosides **10a–c** in 15–26% and the 3′,4′-didehydro nucleosides **7a–c** in 5–9% overall yield from **4a–c**. Treatment of **5a–c** under the same conditions gave the unprotected 3′-azido β nucleosides **11a–c** in 17–27% and the 3′,4′-didehydro nucleosides **9a–c** in 5–11% yield.



Scheme 3

The NMR data for compounds **6a–c** and **8a–c** are in close agreement with those reported [10, 16] for the corresponding anomers of D4T. This also proves the configuration of compounds **4a–c** and **5a–c**. The configurations of the azido nucleosides **10a–c** and **11a–c** were similarly assigned by comparison with the NMR data of *Fleet et al.* [17] for α and β anomers of *AZT*.

Compounds **4–11** did not show any significant activity at non-toxic concentrations against HIV-1 in MT-4 cells. Expression of HIV in culture medium was quantified by HIV antigen detection assay ELISA. The same compounds were also devoid of any activity against herpes simplex virus, type 1 (HSV-1), strain *McIntyre* when tested in African green monkey kidney cell line *Vero*.

Experimental

Anhydrous MeCN was distilled from P_2O_5 followed by distillation from CaH_2. All other solvents were used after distillation. Analytical TLC plates (60 F_{254}) and silica gel (230–400 mesh) were purchased from Merck. ^1H and ^{13}C NMR spectra: Bruker AC 250 FT NMR Spectrometer at 250 MHz for ^1H and 62.9 MHz for ^{13}C. EI mass spectra: Varian MAT 311 A Spectrometer.

5-Alkoxymethyluracils (**1a–b**) *General procedure*

Conc. HCl (4.5 ml) and 5-hydroxymethyluracil (9 g, 63 mmol) were added to 1-heptanol (450 ml), 1-octanol (450 ml), or 1-decanol (450 ml), respectively. The suspension was stirred at room temperature for 15 min and then kept on an oil bath for 4 h at 100°C; the mixture becoming homogenous after 20 min. After cooling the crystals were collected by filtration and recrystallized from ethanol-water to give **1a–b** in 64–71% yield.

5-Heptyloxymethyluracil (**1a**)

Yield: 10.9 g (71%); m.p.: 211–212°C; ^{1}H NMR (*DMSO*-d_6): $\delta = 0.86$ (t, 3H, $J = 6.6$ Hz, CH_3), 1.25 (br s, 8H, CH_2), 1.37 (m, 2H, CH_2), 3.37 (t, 2H, $J = 6.5$ Hz, OCH_2), 4.05 (s, 2H, CH_2O), 7, 36 (s, 1H, 6-H), 10.96 (br s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.7$ (CH_3), 21.9, 25.5, 28.4, 29.1, 31.1 (CH_2), 64.1 (CH_2O), 69.4 (OCH_2), 109.2 (C-5), 140.1 (C-6), 151.1 (C-2), 163.6 (C-4) ppm; MS: *m/z*: = 240 (M^+); $C_{12}H_{20}N_2O_3$; calcd.: C 59.98, H 8.39, N 11.66; found: C 60.59, H 8.59, N 11.86.

5-Octyloxymethyluracil (**1b**)

Yield: 10.3 g (64%); m.p.: 208–209°C; ^{1}H NMR (*DMSO*-d_6): $\delta = 0.86$ (t, 3H, $J = 6.5$ Hz, CH_3), 1.24 (br s, 10H, CH_2), 1.48 (m, 2H, CH_2), 3.36 (t, 2H, $J = 6.5$ Hz, OCH_2), 4.05 (s, 2H, CH_2O), 7.36 (s, 1H, 6-H), 10.94 (br s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.7$ (CH_3), 21.9, 25.5, 28.7, 29.0, 31.1 (CH_2), 64.1 (CH_2O), 69.4 (OCH_2), 109.2 (C-5), 140.0 (C-6), 151.11 (C-2), 163.6 (C-4) ppm; MS: $m/z = 254$ (M^+); $C_{13}H_{22}N_2O_3$; calcd.: C 61.39, H 8.72, N 11.01; found: C 61.89, H 8.84, N 11.21.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α,β-D-threo-pentofuranosyl)-5-alkyloxy-methyluracils (**4a–c** and **5a–c**); *General procedure*

O,O′-*Bis*(trimethylsilyl)uracil derivatives **2a–c** (12 mmol) were prepared according to the standard procedure [13] and mixed with compound **3** (4.2 g, 8.5 mmol) in dry MeCN (60 ml). *TMS* triflate (2.2 ml, 12 mmol) in MeCN was slowly added dropwise at −10°C. The mixture was then stirred for 1.5–4 h at 10°C, diluted with CH_2Cl_2 (100 ml), and washed with ice-cold saturated aqueous $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2 (2×200 ml). The combined organic layers were washed with cold water, dried with Na_2SO_4, and evaporated *in vacuo* to give a crude yellow product which was chromatographed on silica gel (100 g) with petroleum ether (65–70°C)/Et_2O (3:2, v/v) to give the α anomers **4a–c** in 24–36% and the β anomers **5a–c** in 30–39% yield.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-D-threo-pentofuranosyl)-5-heptyloxymethyluracil (**4a**)

Yield: 1.4 g (24%); ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (t, 3H, $J = 6.3$ Hz, CH_3), 1.03 (s, 9H, *tert*-butyl), 1.28 (m, 8H, CH_2), 1.60 (m, 2H, CH_2), 2.83 (m, 1H, 2′-H), 3.14 (m, 1H, 2′-H), 3.52 (t, 2H, $J = 6.7$ Hz, OCH_2), 3.79 (dd, 1H, $J = 4.7$ and 10.1 Hz, 5′-H) 3.93 (m, 1H, 4′-H), 4.03 (dd, 1H, $J = 4.4$ and 10.3 Hz, 5′-H), 4.22 (d, 1H, $J = 12.8$ Hz, CH_2O), 4.27 (d, 1H, $J = 12.9$ Hz, CH_2O), 4.56 (m, 1H, 3′-H), 6.16 (t, 1H, $J = 6.0$ Hz, 1′-H), 7.37–7.73 (m, 11H, aryl and 6-H), 9.39 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (CH_3), 19.0 ((CH_3)$_3C$), 22.4 (CH_2), 22.7 (C-3′), 25.9 (CH_2), 26.7 ((CH_3)$_3$C), 29.0, 29.5, 31.6 (CH_2), 44.7 (C-2′), 64.6 (CH_2O), 68.6 (C-5′), 71.3 (OCH_2), 83.2 (C-4′), 88.2 (C-1′), 112.0 (C-5), 127.7, 129.7, 132.8, 135.5 (aryl), 137.4 (C-6), 149.8 (C-2), 162.5 (C-4) ppm.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-D-threo-pentofuranosyl)-5-heptyloxymethyluracil (**5a**)

Yield: 1.8 g (30%); ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (t, 3H, $J = 6.5$ Hz, CH_3), 1.08 (s, 9H, *tert*-butyl), 1.25 (br s, 8H, CH_2), 1.54 (m, 2H, CH_2), 2.69 (m, 1H, 2′-H), 3.28 (m, 1H, 2′-H), 3.35–3.47 (m, 3H, 4′-H and OCH_2), 3.83 (dd, 1H, $J = 6.0$ and 10.6 Hz, 5′-H), 4.03 (dd, 1H, $J = 5.6$ and 10.6 Hz, 5′-H), 4.17 (d, 1H, $J = 12.6$ Hz, CH_2O), 4.22 (d, 1H, $J = 12.9$ Hz, CH_2O), 4.50 (m, 1H, 3′-H), 6.12 (dd, 1H, $J = 3.4$ and 7.6 Hz, 1′-H), 7.36–7.72 (m, 10H, aryl), 7.86 (s, 1H, 6-H), 8.91 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (CH_3), 19.1 (($CH_3)_3C$), 22.5 (C-3′), 23.0 (CH_2), 26.0 (CH_2), 26.8 (($CH_3)_3$C), 29.0 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 44.3 (C-2′), 64.8 (CH_2O), 68.5 (C-5′), 71.0 (OCH_2), 82.2 (C-4′), 85.1 (C-1′), 111.5 (C-5), 127.7, 129.8, 132.9, 135.4, 135.5 (aryl), 138.3 (C-6), 150.0 (C-2), 162.9 (C-4) ppm.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-D-threo-pentofuranosyl)-5-octyloxymethyluracil (**4b**)

Yield: 2.2 g (36%); ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 6.5$ Hz, CH_3), 1.08 (s, 9H, *tert*-butyl), 1.26 (br s, 10H, CH_2), 1.60 (m, 2H, CH_2), 2.84 (m, 1H, 2′-H), 3.04 (m, 1H, 2′-H), 3.51 (t, 2H, $J = 6.7$ Hz, OCH_2), 3.79 (dd, 1H, $J = 4.8$ and 10.3 Hz, 5′-H), 3.92 (m, 1H, 4′-H), 4.01 (dd, 1H, $J = 4.4$ and 10.3 Hz, 5′-H), 4.24 (d, 1H, $J = 12.6$ Hz, CH_2O), 4.25 (d, 1H, $J = 12.9$ Hz, CH_2O), 4.56 (m, 1H, 3′-H), 6.15 (t, 1H, $J = 6.1$ Hz, 1′-H), 7.36–7.72 (m, 11H, aryl and 6-H), 8.94 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (CH_3), 19.1 (Me_3C), 22.5 (CH_2), 22.7 (C-3′), 26.0 (CH_2), 26.7 (($CH_3)_3$C), 29.1, 29.3, 29.5, 31.7 (CH_2), 44.7 (C-2′), 64.6 (CH_2O), 68.6 (C-5′), 71.4 (OCH_2), 83.3 (C-4′), 88.3 (C-1′), 112.1 (C-5), 127.7, 129.8, 132.8, 135.5 (aryl), 137.4 (C-6), 149.7 (C-2), 162.3 (C-4) ppm.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-D-threo-pentofuranosyl)-5-octyloxymethyluracil (**5b**)

Yield: 2.3 g (38%); ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 6.5$ Hz, CH_3), 1.08 (s, 9H, *tert*-butyl), 1.24 (s, 10H, CH_2), 1.54 (m, 2H, CH_2), 2.69 (m, 1H, 2′-H), 3.27 (m, 1H, 2′-H), 3.35–3.47 (m, 3H, 4′-H and OCH_2), 3.83 (dd, 1H, $J = 5.9$ and 10.7 Hz, 5′-H), 4.03 (dd, 1H, $J = 5{,}5$ and 10.7 Hz, 5′-H), 4.16 (d, 1H, $J = 12.7$ Hz, CH_2O), 4.23 (d, 1H, $J = 13.0$ Hz, CH_2O), 4.50 (m, 1H, 3′-H), 6.11 (d, 1H, $J = 3.6$ and 7.6 Hz, 1′-H), 7.37–7.72 (m, 10H, aryl), 7.86 (s, 1H, 6-H), 8.81 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (CH_3), 19.1 (($CH_3)_3C$), 22.5 (CH_2), 23.0 (C-3′), 26.1 (CH_2), 26.8 (($CH_3)_3$C), 29.2, 29.3, 29.6, 31.7 (CH_2), 44.3 (C-2′), 64.8 (CH_2O), 68.5 (C-5′), 71.1 (OCH_2), 82.2 (C-4′), 85.1 (C-1′), 111.5 (C-5), 127.7, 129.8, 132.9, 135.5 (aryl), 138.3 (C-6), 150.0 (C-2), 162.3 (C-4) ppm.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-D-threo-pentofuranosyl)-5-decyloxymethyluracil (**4c**)

Yield: 2.2 g (34%); ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 6.6$ Hz, CH_3), 1.08 (s, 9H, *tert*-butyl), 1.26 (br s, 14H, CH_2), 1.59 (m, 2H, CH_2), 2.84 (m, 1H, 2′-H), 3.04 (m, 1H, 2′-H), 3.51 (t, 2H, $J = 6.7$ Hz, OCH_2), 3.79 (dd, 1H, $J = 5.9$ and 10.6 Hz, 5′-H), 3.93 (m, 1H, 4′-H), 4.00 (dd, 1H, $J = 5.5$ and 10.7 Hz, 5′-H), 4.20 (d, 1H, $J = 12.6$ Hz, CH_2O), 4.23 (d, 1H, $J = 12.6$ Hz, CH_2O), 4.53 (m, 1H, 3′-H), 6.15 (t, 1H, $J = 6.1$ Hz, 1′-H), 7.37–7.73 (m, 11H, aryl and 6-H), 9.39 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (CH_3), 19.0 (($CH_3)_3C$), 22.5 (CH_2), 22.7 (C-3′), 26.0 (CH_2), 26.7 (($CH_3)_3$C), 29.2, 29.3, 29.4, 29.5, 31.8, 33.3 (CH_2), 44.7 (C-2′), 64.6 (CH_2O), 68.6 (C-5′), 71.3 (OCH_2), 83.3 (C-4′), 88.3 (C-1′), 112.1 (C-5), 127.7, 129.8, 132.8, 135.5 (aryl), 137.4 (C-6), 149.8 (C-2), 162.5 (C-4) ppm.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-D-threo-pentofuranosyl)-5-decyloxymethyluracil (**5c**)

Yield: 2.2 g (35%); ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 6.1$ Hz, CH_3), 1.08 (s, 9H, *tert*-butyl), 1.24 (s, 14H, CH_2), 1.53 (m, 2H, CH_2), 2.68 (m, 1H, 2′-H), 3.28 (m, 1H, 2′-H), 3.35–3.51 (m, 3H, 4′-H and OCH_2), 3.83 (dd, 1H, $J = 5.9$ and 10.7 Hz, 5′-H), 4.03 (dd, 1H, $J = 5$, 5 and 10.6 Hz, 5′-H), 4.20 (d, 1H, $J = 12.7$ Hz, CH_2O), 4.23 (d, 1H, $J = 12.9$ Hz, CH_2O), 4.50 (m, 1H, 3′-H), 6.16 (dd, 1H, $J = 3.5$ and 7.6 Hz, 1′-H), 7.35–7.73 (m, 10H, aryl), 7.86 (s, 1H. 6-H), 9.46 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (CH_3), 19.1 (($CH_3)_3C$), 22.5 (CH_2), 23.0 (C-3′), 26.1 (CH_2), 26.8 (($CH_3)_3$C), 29.2, 29.4, 29.5, 29.6, 31.8, 33.3 (CH_2), 44.3 (C-2′), 64.0 (CH_2O), 68.5 (C-5′), 71.0 (OCH_2), 82.2 (C-4′), 85.1 (C-1′), 111.5 (C-5), 127.7, 129.8, 132.9, 135.4, 135.5 (aryl), 138.2 (C-6), 150.2 (C-2), 162.6 (C-4) ppm.

5-Alkoxymethyl-1-(2,3-dideoxy-D-glycero-pent-2-enofuranosyl)uracils (**6a–c** and **8a–c**); 5-Alkoxymethyl-1-(2,3-dihydro-5-hydroxymethylfuran-2-yl)uracils (**7a–c** and **9a–c**); *General procedure*

To a stirred solution of **4a–c** or **5a–c** (1.1 mmol) in methanol (30 ml), a solution of sodium methoxide prepared from sodium (0.25 g, 11 mmol) and methanol (20 ml) was added. The stirred solution was heated at reflux for 7–10 h. After cooling to room temperature the mixture was neutralized with NH_4Cl (0.6 g, 11 mmol). The solvent was evaporated and the crude material purified by column chromatography on silica gel (30 g) with 10% petroleum ether (60–80°C)/ether.

1-(2,3-Dideoxy-α-D-glycero-pent-2-enofuranosyl)-5-(octyloxymethyl)uracil (**6b**)

Yield: 123 mg (32%) as white crystals; m.p.: 105–106°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.3$ Hz, CH_3), 1.28 (s, 10H, CH_2), 1.58 (m, 2H, CH_2), 3.10, (br s, 1H, OH), 3.49 (t, 2H, J = 6.6 Hz, OCH_2), 3.65 (dd, 1H, $J = 4.5$ and 12.0 Hz, 5′-H), 3.83 (dd, 1H, $J = 3.1$ and 12.0 Hz, 5′-H), 4.20 (d, 1 H, $J = 13.0$ Hz, CH_2O), 4.26 (d, 1H, $J = 12.8$ Hz, CH_2O), 5.14 (br s, 1H, 4′-H), 5.92 (m, 1H, 2′-H), 6.34 (m, 1H, 3′-H), 7.11 (m, 1H, 1′-H), 7.18 (s, 1H, 6-H), 9.70 (br, 1H, NH) ppm; MS: $m/z = 352$ (M^+); peak matching: calc. 352.199, found 352.200.

1-(2,3-Dideoxy-α-D-glycero-pent-2-enofuranosyl)-5-(decyloxymethyl)uracil (**6c**)

Yield: 200 mg (48%); m.p.: 97–98°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.2$ Hz, CH_3), 1.27 (s, 14H, CH_2), 1.56 (m, 2H, CH_2), 3.49 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.65 (dd, 1H, $J = 4.7$ and 12.0 Hz, 5′-H), 3.83 (dd, 1H, $J = 3.2$ and 11.9 and Hz, 5′-H), 4.20 (d, 1H, $J = 13.3$ Hz, CH_2), 4.26 (d, 1H, $J = 12.9$ Hz, CH_2O), 5.15 (br s, 1H, 4′-H), 5.93 (m, 1H, 2′-H), 6.34 (m, 1H, 3′-H), 7.11 (m, 1H, 1′-H), 7.17 (s, 1H, 6′-H) ppm; MS: $m/z = 362$ (M^+-H_2O); peak matching: calc. 380.2311, found 380.231.

(S)-1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-(octyloxymethyl)uracil (**7b**)

Yield: 90 mg (23%) as an oil; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.4$ Hz, CH_3) 1.27 (s, 10H, CH_2), 1.58 (m, 2H, CH_2), 2.65 (m, 1H, 2′-H), 3.25 (m, 1H, 2′-H), 3.50 (t, 2H, $J = 6.7$ Hz, OCH_2), 4.23 (m, 4H, 5′-H and CH_2O), 5.05 (s, 1H, 3′-H), 6.70 (dd, 1H, $J = 3.9$ and 9.6 Hz, 1′-H), 7.38 (s, 1H, 6′-H) ppm; MS: $m/z = 334$ (M^+-H_2O).

(S)-1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-(decyloxymethyl)uracil (**7c**)

Yield: 85 mg (20%) as an oil; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.4$ Hz, CH_3), 1.26 (s, 14H, CH_2), 1.58 (m, 2H, CH_2), 2.65 (m, 1H, 2′-H), 3.25 (m, 1H, 2′-H), 3.50 (t, 2H, $J = 6.7$, OCH_2), 4.23

(m, 4H, 5′-H and CH_2O), 5.05 (s, 1H, 3′-H), 6.71 (dd, 1H, $J = 3.9$ and 9.6 Hz, 1′-H), 7.37 (s, 1H, 6′-H) ppm; MS: $m/z = 362$ (M^+-H_2O).

1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)-5-(heptyloxymethyl)uracil (**8a**)

Yield: 205 mg (55%); m.p.: 114–115°C; ^{1}H NMR (*DMSO*-d_6): $\delta = 0.86$ (t, 3H, $J = 6.3$ Hz, CH_3), 1.25 (s, 8H, CH_2), 1.47 (m, 2H, CH_2), 3.35 (br s, 2H, OCH_2), 3.58 (br s, 2H, 5′-H), 4.01 (d, 2H, $J = 12.1$ Hz, CH_2O), 4.07 (d, 1H, $J = 12.1$ Hz, CH_2O), 4.78 (br s, 1H, 4′-H), 4.97 (br s, 1H, OH), 5.94 (m, 1H, 2′-H), 6.43 (m, 1H, 3′-H), 6.89 (br s, 1H, 1′-H), 7.74 (s, 1H, 6′-H), 11.38 (br s, 1H, NH) ppm; MS: $m/z = 338$ (M^+): $C_{18}H_{28}N_2O_5$; calcd.: C 61.24, H 7.95, N 7.95; found: C 61.07, H 8.08, N 7.98.

1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)-5-(octyloxymethyl)uracil (**8b**)

Yield: 230 mg (59%); m.p.: 120–121°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 5.9$ Hz, CH_3), 1.27 (s, 10H, CH_2), 1.56 (m, 2H, CH_2), 3.47 (t, 2H, $J = 6{,}6$ Hz, OCH_2), 3.75 (dd, 1H, $J = 3.3$ and 12.3 Hz, 5′-H), 3.91 (m, 1H, 5′-H), 4.15 (d, 1H, $J = 13.0$ Hz, OCH_2), 4.21 (d, 1H, $J = 12.9$ Hz, CH_2O), 4.92 (br s, 1H, 4′-H), 5.84 (m, 1H, 2′-H), 6.34 (m, 1H, 3′-H), 7.04 (br s, 1H, 1′-H), 7.71 (s, 1H, 6-H) ppm; MS: $m/z = 334$ (M^+-H_2O).

1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)-5-(decyloxymethyl)uracil (**8c**)

Yield: 154 mg (37%); m.p.: 120–122°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.4$ Hz, CH_3), 1.26 (br s, 14H, CH_2), 1.57 (m, 2H, CH_2), 2.65 (br s, 1H, OH), 3.48 (t, 2H, $J = 6.7$ Hz, OCH_2), 3.77 (dd, 1H, $J = 3.5$ and 12.4 Hz, 5′-H), 3.94 (m, 1H, 5′-H), 4.19 (s, 2H, CH_2O), 4.93 (br s, 1H, 4′-H), 5.85 (m, 1H, 2′-H), 6.33 (m, 1H, 3′-H), 7.04 (m, 1H, 1′-H), 7.71 (s, 1H, 6-H), 8.81 (s, 1H, NH) ppm; MS: $m/z = 362$ (M^+-H_2O); peak matching: calc. 380.234, found 380.231.

(R)-1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-(heptyloxymethyl)uracil (**9a**)

Yield: 80 mg (22%); ^{1}H NMR (*DMSO*-d_6): $\delta = 0.86$ (br s, 3H, CH_3), 1.25 (br s, 8H, CH_2), 1.46 (m, 2H, CH_2), 2.60 (m, 1H, 2′-H), 3.77 (m, 1H, 2′-H), 3.38 (br s, 2H, OCH_2), 4.07 (m, 4H, 5′-H and CH_2O), 5.01 (br s, 1H, 3′-H), 6.59 (dd, 1H, $J = 2.8$ and 9.9 Hz, 1′-H), 7.38, (s, 1H, 6H) ppm.

(R)-1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-(octyloxymethyl)uracil (**9b**)

Yield: 55 mg (14%); ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.4$ Hz, CH_3), 1.28 (br s, 10H, CH_2), 1.57 (m, 2H, CH_2), 2.68 (m, 1H, 2′-H), 3.25 (m, 1H, 2′-H), 3.50 (t, 2H, $J = 6.5$ Hz, OCH_2), 4.23 (m, 4H, 5′-H and CH_2O), 5.05 (br s, 1H, 3′-H), 6.71 (dd, 1H, $J = 3.8$ and 9.4 Hz, 1′-H), 7.37 (s, 1H, 6-H) ppm; MS: $m/z = 352$ (M^+).

(R)-1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-5-(decyloxymethyl)uracil (**9c**)

Yield: 60 mg (14%); ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.4$ Hz, CH_3), 1.26 (br s, 14H, CH_2), 1.57 (br s, 2H, CH_2), 2.65 (m, 1H, 2′-H), 3.32 (m, 1H, 2′-H), 3.49 (t, 2H, $J = 6.5$ Hz, OCH_2), 4.22 (m, 4H, 5′-H and CH_2O), 5.04 (br s, 1H, 3′-H), 6.71 (dd, 1H, $J = 3.9$ and 9.5 Hz, 1′-H), 7.37 (s, 1H, 6-H), 9.58 (s, 1H, NH) ppm; MS: $m/z = 362$ (M^+-H_2O).

5-Alkoxymethyl-1-(3-azido-2,3-dideoxy-D-erythro-pentofuranosyl)uracils (**10a–c** and **11a–c**); *General procedure*

Compounds **4a–c** or **5a–c** (1.5 mmol) were dissolved in dry N,N-dimethylformamide (20 ml). Sodium azide (0.99 g, 15 mmol) was added, and the mixture was stirred for 4 h at 100°C. After cooling the mixture was concentrated *in vacuo* and the residue partitioned between water (100 ml) and CH_2Cl_2 (150 ml). The aqueous solution was extracted with CH_2Cl_2 (150 ml). The combined organic phases were dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was dissolved in tetrahydrofuran (30 ml) at 0°C and 1.5 ml of 1 *M* Bu_4NF in *THF* was added slowly with stirring. After 30 min at 0°C the solvent was evaporated *in vacuo* and the crude product was chromatographed on silica gel (40 g) with ether/petroleum ether (65–70°C) (9:1) (compound **11a** with petroleum ether (65–70°C)/ethyl acetate (3:2) and **11c** with petroleum ether (65–70°C)/ether (3:2)) to give **10a–c** (15–26%) and **7a–c** (5–9%) or **11a–c** (17–27%) and **9a–c** (5–11%).

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-(heptyloxymethyl)uracil (**10a**)

Yield: 157 mg (15%); m.p.: 90–91°C; IR (KBr): 2108 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.5$ Hz, CH_3), 1.29 (br s, 8H, CH_2), 1.61 (m, 2H, CH_2), 2.17 (m, 1H, 2′-H), 2.87 (m, 1H, 2′-H), 3.51 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.68 (m, 1H, 5′-H), 3.82 (m, 1H, 5′-H), 4.28 (m, 4H, 3′-H, 4′-H and CH_2O), 6.31 (m, 1H. 1′-H), 7.60 (s, 1H, 6-H) ppm; MS: $m/z = 381$ (M^+); peak matching: calc. 381.201, found 381.201.

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-(octyloxymethyl)uracil (**10b**)

Yield: 280 mg (26%); m.p.: 76–79°C; IR (KBr): 2108 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.4$ Hz, CH_3), 1.27 (br s, 10H, CH_2), 1.58 (m, 2H, CH_2), 2.18 (m, 1H, 2′-H), 2.56 (br s, 1H, OH), 2.80 (m, 1H, 2′-H), 3.51 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.69 (m, 1H, 5′-H), 3.82 (m, 1H, 5′-H), 4.27 (m, 4H, 3′-H, 4′-H and CH_2O), 6.28 (dd, 1H, $J = 4.2$ and 6.7 Hz, 1′-H), 7.29 (s, 1H, 6-H), 9.15 (br s, 1H, NH) ppm; MS: $m/z = 395$ (M^+); peak matching: calc. 395.219, found 395.217.

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-(decyloxymethyl)uracil (**10c**)

Yield: 180 mg (16%); IR (KBr): 2108 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.6$ Hz, CH_3), 1.27 (br s, 14H, CH_2), 1.59 (m, 2H, CH_2), 2.16 (m, 1H, 2′-H), 2.87 (m, 1H, 2′-H), 3.51 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.68 (m, 1H, 5′-H), 3.83 (m, 1H, 5′-H), 4.27 (m, 4H, 3′-H, 4′-H, CH_2O), 6.30 (dd, 1H, $J = 4.2$ and 6.7 Hz, 1′-H), 7.60 (s, 1H, 6-H) ppm; MS: $m/z = 423$ (M^+); peak matching: calc. 423.249, found 423.248.

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-(heptyloxymethyl)uracil (**11a**)

Yield: 210 mg (20%) as an oil; IR (KBr): 2104 cm^{-1} (N_3); ^1H NMR (CD_3OD): $\delta = 0.89$ (t, 3H, $J = 5.5$ Hz, CH_3), 1.30 (br s, 8H, CH_2), 1.57 (m, 2H, CH_2), 2.42 (m, 2H, 2′-H), 3.48 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.74 (dd, 1H, $J = 4.3$ and 12.1 Hz, 5′-H), 3.84 (dd, 1H, $J = 3.3$ and 12.1 Hz, 5′-H), 4.20 (s, 2H, CH_2O), 4.36 (m, 1H, 4′-H), 4.81 (br s, 1H, OH), 6.17 (t, 1H, $J = 6.2$ Hz, 1′-H), 8.01 (s, 1H, 6-H) ppm; MS: $m/z = 381$ (M^+); peak matching: calc. 381.202, found 381.201.

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-(octyloxymethyl)uracil (**11b**)

Yield: 185 mg (17%) as an oil; IR (KBr): 2105 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 5.9$ Hz, CH_3), 1.27 (br s, 10H, CH_2), 1.59 (m, 2H, CH_2), 2.46 (m, 2H, 2′-H), 3.51 (t, 2H, $J = 6.7$ Hz,

Table 1. ^{13}C NMR data (δ, $CDCl_3$/*TMS*) of compounds **6a–c – 11a–c**

	Anomer	C-1′	C-2′	C-3′	C-4′	C-5′	C-2	C-4	C-5	C-6	CH_2OR
6a[a]	α	89.8	125.8	135.2	87.9	63.2	151.3	163.8	109.3	140.3	13.9, 22.1, 25.7, 28.5, 29.2, 31.3, 64.3, 69.5
6b	α	90.4	126.4	134.0	87.8	63.9	150.7	162.6	112.6	136.6	13.9, 22.5, 26.0, 29.1, 29.3, 29.5, 31.6, 64.6, 71.2
6c	α	90.5	126.5	134.0	87.8	64.0	150.6	162.4	112.7	136.6	13.9, 22.5, 26.0, 29.2, 29.3, 29.4, 29.5, 31.8, 64.6, 71.2
7a[a]	*S*	84.5	35.2	95.6	157.2	55.7	149.7	162.3	111.5	136.9	13.7, 21.8, 25.4, 28.3, 29.1, 31.0, 64.1, 69.6
7b	*S*	85.4	36.6	96.2	156.8	57.3	150.2	162.8	113.2	136.9	14.1, 22.7, 26.1, 29.3, 29.4, 29.5, 31.8, 64.8, 71.4
7c	*S*	85.2	36.5	96.1	156.5	57.3	149.9	162.3	113.1	136.5	13.9, 22.5, 26.0, 29.2, 29.3, 29.4, 29.5, 31.8, 64.6, 71.3
8a[a]	β	89.0	125.5	134.9	87.2	62.3	150.4	162.4	110.4	138.7	13.7, 21.8, 25.4, 28.3, 28.9, 31.0, 62.3, 69.4
8b	β	90.0	126.0	134.5	87.4	63.3	150.6	162.7	111.9	138.5	13.9, 22.5, 25.9, 29.1, 29.2, 29.4, 31.6, 64.6, 71.2
8c	β	90.1	126.2	134.4	87.3	63.4	150.5	162.4	112.1	138.4	14.0, 22.5, 26.0, 29.2, 29.4, 29.5, 29.6, 31.8, 64.7, 71.3
9a[a]	*R*	84.5	35.2	95.0	157.1	55.7	149.6	162.3	111.5	136.9	13.6, 21.6, 25.4, 28.3, 29.0, 31.0, 64.1, 69.6
9b	*R*	85.2	36.4	96.1	156.6	57.2	150.0	162.4	113.1	136.5	13.9, 22.5, 26.0, 29.1, 29.3, 29.5, 31.7, 64.6, 71.3
9c	*R*	85.2	36.4	96.0	156.6	57.2	149.9	162.4	113.0	136.6	13.9, 22.5, 26.0, 29.2, 29.3, 29.4, 29.5, 29.6, 31.7, 64.6, 71.2
10a	α	86.2	38.1	60.8	86.0	62.5	150.5	162.6	112.3	137.0	13.9, 22.5, 26.0,29.0, 29.5, 31.7, 64.7, 71.2
10b	α	86.3	38.1	60.7	85.9	62.5	150.3	162.3	112.3	136.9	14.0, 22.5, 26.1, 29.2, 29.4, 29.6, 31.7, 64.7, 71.2
10c	α	86.2	38.1	60.7	86.0	62.5	150.4	162.5	112.3	136.9	13.9, 22.5, 26.0, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 64.7, 71.2
11a[b]	β	86.4	38.5	61.6	86.2	62.3	152.0	165.0	112.5	140.6	14.4, 23.6, 27.1, 30.2, 30.4, 32.9, 66.0, 71.8
11b	β	86.3	37.2	59.8	84.6	61.5	150.2	162.8	112.0	134.6	13.8, 22.4, 25.8, 29.2, 29.3, 29.4, 31.5, 64.4, 71.1
11c	β	86.5	38.5	61.6	86.2	62.4	152.0	165.0	112.5	140.7	14.4, 23.7, 27.2, 30.1, 30.4, 30.5, 30.6, 33.0, 66.0, 71.8

[a] ^{13}C NMR in *DMSO*-d_6; [b] ^{13}C NMR in CD_3OD

OCH_2), 3.78 (m, 1H, 5′-H), 3.93 (m, 2H, 3′-H, 5′-H), 4.24 (s, 2H, CH_2O), 4.38 (m, 1H, 4′-H), 6.10 (t, 1H, $J = 6.3$ Hz, 1′-H), 7.72 (s, 1H, 6-H), 10.09 (br s, 1H, NH) ppm; MS: $m/z = 395$ (M^+); peak matching: calc. 395.217, found 395.217.

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-(decyloxymethyl)uracil (**11c**)

Yield: 300 mg (27%) as an oil; IR (KBr): 2104 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): $\delta = 0.91$ (t, 3H, $J = 5.6$ Hz, CH_3), 1.30 (br s, 14H, CH_2), 1.59 (m, 2H, CH_2), 2.43 (m, 2H, 2′-H), 3.49 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.78 (m, 1H, 5′-H), 3.84 (m, 1H, 5′-H), 3.94 (m, 1H, 3′-H), 4.20 (s, 2H, CH_2O), 4.32 (m, 1H, 4′-H), 4.84 (br s, 1H, OH) 6,17 (m, 1H, 1′-H), 8.03 (s, 1H, 6-H) ppm; MS: $m/z = 423$ (M^+); peak matching: calc. 423.249, found 423.248.

References

[1] De Clercq E (1987) Anticancer Res **7**: 1023
[2] Mitsuya H, Broder S (1987) Nature **325**: 773
[3] Ono K, Ogasawara M, Iwata Y, Nakane H, Fuji T, Sawai K, Saneyoshi M (1986) Biochem Biophys Res Common **140**: 498
[4] Mitsuya H, Weinhold KJ, Furman PA, St. Clair MH, Lehrman SN, Gallo RC, Bolognesi D, Barry DW, Broder S (1985) Proc Natl Acad Sci USA **82**: 7096
[5] Broder S (1988) Pharm Technology **12**: 24
[6] Larsen E, Danel K, Vaaben GB, El-Emam AA, Pedersen EB, Nielsen C (1996) Acta Chem Scand **50**: 417
[7] Dueholm KL, Aly YL, Jørgensen PT, El-Barbary AA, Pedersen EB, Nielsen C (1993) Monatsh Chem **124**: 37
[8] Wengel J, Lau J, Pedersen EB, Nielsen CM (1991) J Org Chem **56**: 56
[9] Motawia MS, Pedersen EB, Nielsen CM (1990) Arch Pharm (Weinheim) **323**: 971
[10] Abdel-Megied AE-S, Hansen P, Pedersen EB, Nielsen C, Nielsen CM (1993) Arch Pharm (Weinheim) **326**: 377
[11] Cline RE, Fink RM, Fink K (1959) J Am Chem Soc **81**: 2521
[12] Motawia MS, Abdel-Megied AE-S, Pedersen EB, Nielsen CM, Ebbesen P (1992) Acta Chem Scand **46**: 77
[13] Wittenburg E (1964) Z Chem **4**: 303
[14] Hansen P, Pedersen EB (1990) Acta Chem Scand **44**: 522
[15] Vorbrüggen H, Krolikiewicz K, Bennua B (1981) Chem Ber **114**: 1234
[16] Mansuri MM, Starrett JE, Gazzouli I, Hitchcack MJM, Sterzycki RZ, Brankovan V, Lin T-S, August ME, Prusoff WH, Sommadossi J-P, Martin JC (1989) J Med Chem **32**: 461
[17] Fleet GWJ, Son JC, Derome AE (1988) Tetrahedron **44**: 625

Received June 20, 1997. Accepted September 12, 1997