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Synthesis of 3′-*O*-(2-Aminoethyl)-2′-deoxyuridines

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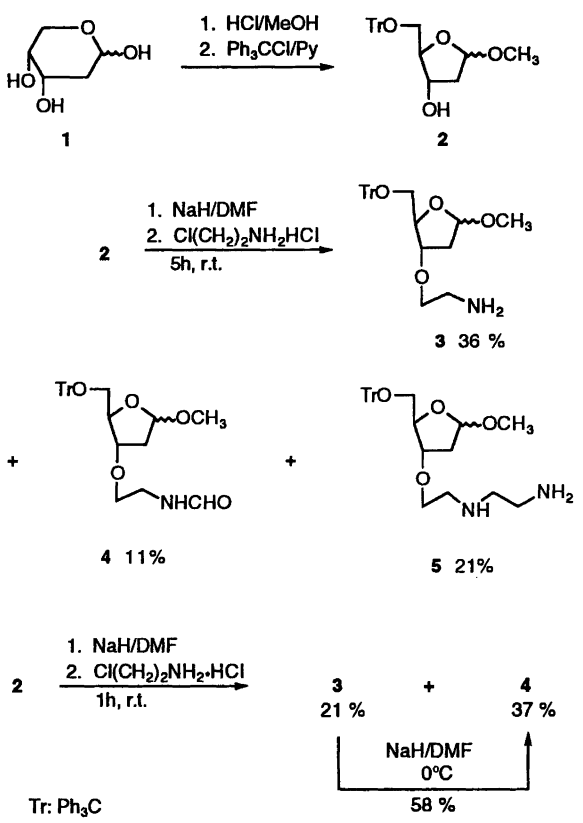
Methyl 2-deoxy-3-*O*-[2-(formylamino)ethyl]-5-*O*-trityl-D-*erythro*-pentofuranoside (**4**) was obtained in a 3-*O* alkylation reaction by treatment with 2-chloroethylamine in DMF. Compound **4** afforded α nucleosides as the main products when condensed with uracils under the Vorbrüggen conditions. The nucleosides were deblocked by treatment with 80% acetic acid and subsequently with sodium methoxide in methanol.

Recently, we reported a new carboxamide linkage able to replace the natural phosphate linkage in DNA.[1] This linkage was synthesized by alkylation of 5′-*O*-(4,4′-dimethoxytrityl)thymidine with 2-chloroethylamine and subsequent reaction with thymidine-5′-carboxylic acid. Good hybridization to natural DNA was observed when this dimeric DNA was incorporated into DNA and similar results have been observed recently with other carboxamide linkers.[2–6] In order to use nucleosides with unnatural nucleobases in our investigations on DNAs with carboxamide linkages we found it of interest to develop other routes of synthesizing monomeric 3′-*O*-(2-aminoalkyl) nucleosides. Also we considered such nucleosides as potential agents against human immunodeficiency virus (HIV). Many nucleosides with anti-HIV activity have been synthesized and their structure and antiviral activity relationship has been reviewed[7,8] but no hint was given as to whether 2-aminoethylation on 3′-*O* in 2′-deoxyuridines could result in antiviral compounds with activity against HIV.

Results and discussion

Methyl 2-deoxy-α,β-D-*erythro*-pentofuranoside[9] was synthesized from 2-deoxy-D-ribose (**1**) by treatment with methanolic hydrogen chloride and selective protection by tritylation[10] gave methyl 5-*O*-trityl-*erythro*-pentofuranoside (**2**). It was possible to obtain the pure α anomer **2α** by chromatography. The anomeric configuration was easily assigned since the 2α-H signal could be identified in the ^{1}H NMR spectrum as a doublet with a large geminal coupling constant 12.8 Hz. The absence of couplings to 1′-H or 3′-H proved the latter two protons to be *trans* to 2α-H.[11–13]



Scheme 1.

After trying the literature procedures,[14–18] we found that the 2-aminoethyl derivative **3** was best obtained when a large excess of sodium hydride was used in *N*,*N*-dimethylformamide for the alkylation reaction. In this way we obtained the alkylated product **3**, its *N*-formyl derivative **4** and the repeatedly alkylated product **5** in

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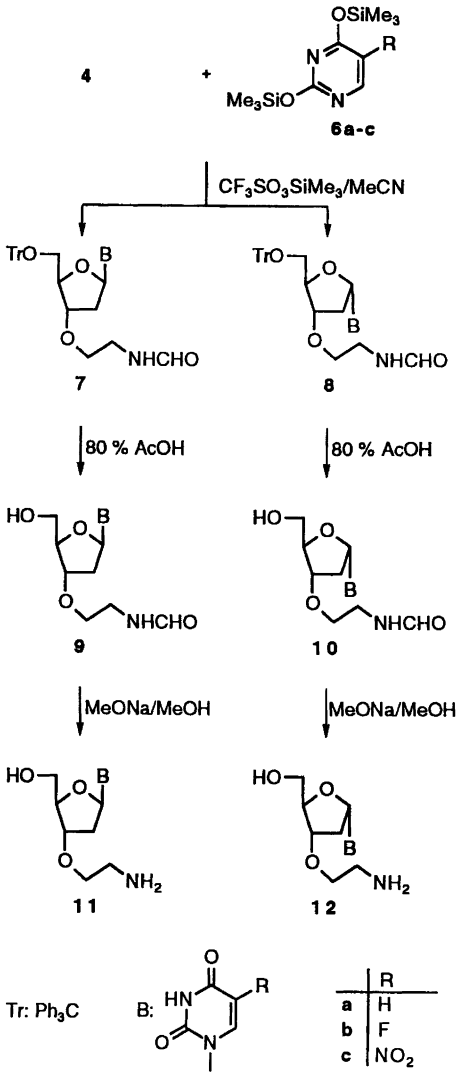
moderate yields (11–36%) after stirring the reaction mixture at room temperature for 5 h. Compound **5** was not observed when the reaction was stopped after 1 h. Instead the yield of the *N*-formyl alkylated product **4** was increased to 37% and **3** was formed in 27% yield. Formylation of **3** to give **4** easily took place under the above reaction conditions. Treatment of **3** with sodium hydride in dry DMF for 1 h at 0 °C resulted in formation of **4** in 58% yield. The assignment of ^{1}H NMR and ^{13}C NMR spectra of the compounds **3**, **4** and **5** were determined by 2D NMR. One of the anomers of **3** was easily assigned as the α anomer due to a characteristic doublet of 2α-H at 2.07 ppm. It was possible to separate **3** into its anomers by chromatography.

Since adequate *N* protection concurrently took place during the alkylation reaction of **2** to give **4**, or could easily be achieved by formylation of **3**, it was decided to use **4** in the nucleoside syntheses. Coupling of **4** with silylated uracil **6a–c** using the trimethylsilyl triflate method of Vorbrüggen[19] gave anomeric mixtures of protected nucleosides **7** and **8** in total yields of 20–57%. Relative intensities in the ^{13}C NMR spectrum of the anomeric mixture of **7b** and **8b** revealed a 1:2 mixture. By chromatographic separation of the anomeric mixtures, the nucleosides **7a** and **8a** were isolated in the ratio 1:2 and the nucleosides **7c** and **8c** in the ratio 1:3.

The fully deprotected nucleosides **11a** and **12a** were obtained in 59% and 50% overall yields from **7a** and **8a**, respectively, by treatment with refluxing 80% acetic acid for 10 min followed by refluxing the residue overnight with sodium methoxide in methanol. We first attempted to obtain the deprotected nucleosides **11** and **12** by treating the intermediately formed nucleosides **9** and **10** with methanolic ammonia overnight at room temperature, but no reaction was observed. Instead, a 33% solution of $MeNH_2$ in absolute ethanol afforded the deprotected nucleosides, but in very low yields (about 15 %). A more effective deprotection reagent was sodium methoxide in refluxing methanol. The detritylated nucleosides **9b** and **10b** were obtained in 24% and 40% yields, respectively, by reaction of the anomeric mixture **7b**/**8b** in 80% acetic acid. Compound **10c** was obtained in 46% yield by reaction of the pure anomer **8c**. The reactions were easily followed by TLC by observing the appearance of the detritylated product with a lower R_f than the starting material. When the β anomer **9b** and the α anomer **10b** were refluxed overnight with sodium methoxide in methanol, the fully deprotected nucleosides **11b** and **12b** were obtained in 64% and 73% yields, respectively, after chromatographic purification. Unfortunately, decomposition occurred on attempted deprotection of the 5-nitro nucleosides **10c**.

The assignments of proton chemical shifts in the ^{1}H NMR spectrum of **8a** was determined by ^{1}H–^{1}H 2D-NMR. ^{1}H nuclear Overhauser effects (NOE difference spectroscopy) was used for determination of its anomeric configuration. Irradition of 2′β-H generated large NOEs in 3′-H (6%) and 1′-H (8%), whereas insignificant



Scheme 2.

NOEs were observed for the same protons when 2′α-H was irradiated. The α configuration of **8a** was further confirmed by irradiation of 4′-H which generated a large NOE in 6-H (4%). In fact, observing 2′α-H as doublets in the ^{1}H-NMR spectra of **8a, b, 10b, c** and **12a, b** in all cases confirmed the α configuration.[11–13] We also found the 4′-H proton *syn* to the nucleobase in the α anomer to appear at lower field than the 4′-H proton *anti* to the nucleobase in the β anomer.[20,21]

Since the main products from the nucleoside coupling reactions are the α anomers, this opens up a route for the synthesis of α DNAs with an unnatural carboxamide linkage between the nucleosides. This work is in progress in our laboratory since the corresponding α DNAs with natural phosphate linkers according to the group of Imbach can be used as antisense oligonucleotides.[22]

The detritylated nucleosides **10c, 11a, b** and **12a, b** did not show any significant activity against HIV-1 in MT-4 cells or toxicity against MT-4 cells at 100 μM . Expres-

sion of HIV in culture medium was quantified by HIV antigen detection ELISA. The same compounds were also devoid of any activity at 100 μM against herpes simplex virus, type 1 (HSV-1), strain McIntyre when tested in African green monkey kidney cell line Vero. Only compound **11b** showed toxicity against Vero cells (ED_{50} = 100 μM). The tritylated nucleosides **7a** and **8a, c** were toxic against MT-4 and Vero cells at 100 μM, but no activity was observed against HIV-1 or HSV-1 at subtoxic concentrations.

Experimental

*Methyl 5-*O*-trityl-α,β-*D*-*erythro*-pentofuranoside* (**2**). To a suspension of methyl 2-deoxy-α,β-D-*erythro*-pentofuranoside[9] (1.48 g, 10 mmol) in dry pyridine (10 ml) was added trityl chloride (2.87 g, 10.35 mmol) and the mixture shaken. A clear solution was obtained within 5 min, and then crystals, presumably pyridine hydrochloride, separated out. The mixture was kept for 4 h at room temperture, and methyl alcohol (1 ml) was added. The solution was concentrated to a gum at room temperature. Chloroform (20 ml) was added, and the solution was washed with water (2 × 10 ml) and dried over sodium sulfate. Chromatography on silica gel (150 g, 0.040–0.063 mm) with CH_2Cl_2–methanol (98:2) afforded **2**, yield 2.8 g (72%). The first fractions from the chromatography contained pure α anomer.

*Methyl 2-deoxy-5-*O*-trityl-α-*D*-*erythro*-pentofuranoside* (**2α**). ^{1}H NMR ($CDCl_3$): δ 2.00 (d, *J* 13.7 Hz, 1 H, 2α-H), 2.16–2.22 (m, 1 H, 2β-H), 3.11–3.16 (m, 2 H, 5-H), 3.37 (s, 3 H, OCH_3), 4.19–4.22 (m, 2 H, 3-H, 4-H), 5.12 (d, *J* 2.2 Hz, 1 H, 1-H), 7.21–7.43 (m, 15 H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 40.88 (C-2), 54.69 (OCH_3), 64.14 (C-5), 73.32 (C-3), 86.57 (C-4), 105.43 (C-1), 126.93, 127.70, 128.57 (C_{arom}), 143.72 (*C*Ph_3)

*Methyl 2-deoxy-5-*O*-trityl-β-*D*-*erythro*-pentofuranoside* (**2β**). ^{1}H NMR ($CDCl_3$): δ 1.96–2.24 (m, 2 H, 2-H), 3.18–3.24 (m, 2 H, 5-H), 3.26 (s, 3 H, OCH_3), 3.99–4.03 (m, 1 H, 3-H), 4.35–4.38 (m, 1 H, 4-H), 5.10–5.12 (m, 1 H, 1-H), 7.40–7.62 (m, 15 H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 40.09 (C-2), 54.82 (OCH_3), 65.11 (C-5), 72.37 (C-3), 84.79 (C-4), 104.81 (C-1), 123.59, 126.81, 128.50 (C_{arom}), 143.81 (*C*Ph_3).

*Alkylation of methyl 2-deoxy-5-*O*-trityl-α,β-*D*-erythro-pentofuranoside* (**2**) *to give* **3**, **4** *and* **5**. To an ice-cold solution of methyl 5-*O*-trityl-α,β-*erythro*-pentofuranoside (**2**, 10 g, 0.026 mol) in dry DMF (150 ml) was added portionwise 55–60% oil-immersed sodium hydride (11.2 g, 0.26 mol) over 1 h. After complete addition, the reaction mixture was stirred at room temperature for 1 h. The chloroethylamine hydrochloride (17.8 g, 0.154 mmol) was added portionwise over 1 h at (0 °C to − 5 °C) and the reaction mixture was stirred at room temperature for 5 h. The excess of NaH was destroyed by addition of methanol at 0 °C to − 5 °C, and the solvent was evaporated off under reduced pressure. The residue was mixed with water (400 ml) and then extracted with CH_2Cl_2. The CH_2Cl_2 phase was dried over Na_2SO_4, evaporated and chromatographed on silica gel (400 g, 0.040–0.063 mm) with 2–15% MeOH in CH_2Cl_2 to give **3**: 4.0 g (36%), **4**: 1.2 g (11%) and **5**: 2.3 g (21%).

*Alkylation of methyl 2-deoxy-5-*O*-trityl-α,β-*erythro*-pentofuranoside* (**2**) *to give* **3** *and* **4**. The same procedure was used as above. After complete addition of chloroethylamine hydrochloride, over 1 h at 0 °C to − 5 °C, the mixture was stirred at room temperture for 1 h. Work-up and chromatography as above afforded **3**: 3.1 g (28%) and **4**: 4.15 g (37%). The α and β anomers could be separated by chromatography.

*Formylation of methyl 3-*O*-(2-aminoethyl)-2-deoxy-5-*O*-trityl-α,β-*D*-erythro-pentofuranoside* (**3**) *to give* **4**. To an ice cold solution of **3** (10 g, 0.023 mol) in dry DMF (150 ml) was added portionwise 55–60% oil-immersed sodium hydride (5.0 g, 0.115 mol), over 30 min. The mixture was stirred in an ice bath for 1 h. The excess of NaH was destroyed by addition of methanol at 0 °C. After evaporation of the solvent under reduced presure, the residue was mixed with water (300 ml), extracted with CH_2Cl_2, and dried over Na_2SO_4. Chromatography on silica gel (300 g, 0.040–0.063 mm) with CH_2Cl_2–MeOH (98:2) afforded **4**, 6.1 g (58%).

*Methyl 3-*O*-(2-aminoethyl)-2-deoxy-5-*O*-trityl-α-*D*-erythro-pentofuranoside* (**3α**). ^{1}H NMR ($CDCl_3$): δ 2.07 (d, *J* 14.0 Hz, 1 H, 2α-H), 2.18 (m, 1 H, 2β-H), 2.85 (m, 2 H, CH_2), 3.16–3.23 (m, 2 H, 5-H), 3.36 (s, 3 H, OCH_3), 3.61 (s, 2 H, CH_2), 3.93 (m, 1 H, 3-H), 4.20 (m, 1 H, 4-H), 5.09 (d, *J* 5.1 Hz, 1 H, 1-H), 7.16–7.48 (m, 15 H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 38.30 (CH_2NH_2), 40.49 (C-2), 54.68 (OCH_3), 63.93 (C-5), 69.62 (OCH_2), 80.05 (C-3), 82.63 (C-4), 86.34 (*C*Ph_3), 104.97 (C-1), 126.68, 127.45, 127.68, 143.51 (C_{arom}). FAB MS: *m/z* = 434 ($M + H^+$).

*Methyl 3-*O*-(2-aminoethyl)-2-deoxy-5-*O*-trityl-β-*D*-erythro-pentofuranoside* (**3β**). ^{1}H NMR ($CDCl_3$): δ 2.02–2.13 (m, 2 H, 2-H), 2.78 (m, 2 H, CH_2), 3.21 (m, 2 H, 5-H), 3.24 (s, 3 H, OCH_3), 3.38 (t, *J* 5.0 Hz, 2 H, CH_2), 4.06–4.10 (m, 2 H, 3-H, 4-H), 5.06 (t, *J* 2.0 Hz, 1-H), 7.16–7.49 (m, 15 H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 39.00 (CH_2NH_2), 41.72 (C-2), 54.80 (OCH_3), 64.85 (C-5), 71.61 (OCH_2), 80.12 (C-3), 82.91 (C-4), 86.47 (*C*Ph_3), 105.13 (C-1), 126.82, 127.60, 128.57, 143.86 (C_{arom}). FAB MS: *m/z* = 434 ($M + H^+$). Anal. $C_{27}H_{31}NO_4 \cdot H_2O$: C, H, N.

Methyl 2-deoxy-3-O-*[2-(formylamino)ethyl]-5-*O*-trityl-α,β-*D*-erythro-pentofuranoside* (**4**). ^{1}H NMR ($CDCl_3$): δ 2.01–2.24 (m, 2 H, 2-H), 3.17 (m, 2 H, 5-H), 3.24 (s, 3 H, OCH_3), 3.39 (m, 4 H, 2 × CH_3), 3.80–4.20 (m, 2 H, 3-H and 4-H), 5.03 (m, 1 H, 1-H), 7.10–7.50 (m, 15 H, H_{arom}), 7.99 (s, 1 H, CHO). ^{13}C NMR ($CDCl_3$): δ 36.18,

37.53 (OCH_3), 38.89, 38.98 (C-2 and CH_2NH), 54.78, 54.94 (OCH_3), 64.06, 64.76 (C-5), 67.08, 67.86 (OCH_2), 80.18, 86.56 (CPh_3), 105.24, 105.14 (C-1), 126.81, 126.88, 127.57, 127.63, 128.50, 128.76 (C_{arom}), 143.61, 143.72 (C_{arom}), 160.87 (CHO). FAB MS: $m/z = 484$ ($M + Na^+$). Anal. C_{28} $H_{31}NO_5 \cdot 1.5$ H_2O: C, H, N.

*Methyl 3-O-(5-amino-3-azapentyl)-2-deoxy-5-O-trityl-α,β-*D-erythro-*pentofuranoside* (**5**). ^1H NMR ($CDCl_3$): δ 1.85 (s, 2 H, NH_2), 2.00–2.07 (m, 2 H, 2-H), 2.64–2.75 (m, 6 H, 3 CH_2), 3.22–3.26 (m, 2 H, 5-H), 3.25, 3.39 (2 × s, 3 H, OCH_3), 3.50 (m, 2 H, CH_2), 4.08–4.22 (m, 2 H, 3-H and 4-H), 5.10 (m, 1 H, 1-H), 7.21–7.48 (m, 15 H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 38.57, 38.95 (CNH_2), 41.37, 41.44 (C-2), 48.84, 48.99 (CH_2NH), 51.85, 52.00 (CH_2NH), 54.78, 54.85, (OCH_3), 64.15, 64.88 (C-5), 68.66, 68.83 (OCH_2), 80.19 (C-3), 82.56, 82.87 (C-4), 86.46 (CPh_3), 105.11 (C-1), 126.80, 127.58, 128.52 (C_{arom}), 143.73, 143.81 (C_{arom}). FAB MS: $m/z = 477$ ($M + H^+$).

*1-{2-Deoxy-3-*O*-[2-(formylamino)ethyl]-5-*O*-trityl-α,β-*D-erythro-*pentofuranosyl}uracil derivatives* (**7/8**). To a stirred solution of compound **4** (2.0 g, 4.3 mmol) and *O,O'*-bis(trimethylsilyl)uracil derivatives **6a–c**[23] (6.07 mmol) in dry MeCN (50 ml) was added dropwise trimethylsilyl trifluoromethanesulfonate (0.84 ml, 4.3 mmol) in MeCN (10 ml) at −30 °C. After complete addition, the mixture was stirred for 12–36 h (**a**: 12 h, **b**: 12 h, **c**: 36 h) at room temperature. The mixture was diluted with CH_2Cl_2 (200 ml) and extracted with ice-cold sat. $NaHCO_3$ (150 ml). The aqueous solution was extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers were washed with cold H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to give the anomeric mixtures **7/8**. The anomeric mixtures **7a/8a** and **7c/8c** were chromatographed on silica gel (150 g, 0.040–0.063 mm) with CH_2Cl_2–MeOH (98:2) to afford **7a, 7c, 8a** and **8c** as gums, yield 5–20 %. It was not possible to separate the anomeric mixture **7b/8b** of which was obtained 1.26 g (57%).

*2'-Deoxy-3'-*O*-[2-(formamido)ethyl]-5'-*O*-trityluridine* (**7a**). Yield 227 mg (9%). ^1H NMR ($CDCl_3$): δ 2.09–2.17 (m, 1 H, 2'-H), 2.43–2.44 (m, 1 H, 2'-H), 3.33 (m, 2 H, 5'-H), 3.41 (m, 4 H, 2 × CH_2), 4.08–4.13 (m, 2 H, 3'-H, 4'-H), 5.45 (d, *J* 7.1 Hz, 1 H, 5-H), 6,10 (br s, 1 H, NH), 6.28 (t, *J* 6.1 Hz, 1 H, 1'-H), 7.00–7.39 (m, 15 H, H_{arom}), 7.70 (d, *J* 8.1 Hz, 1 H, 6-H), 8.12 (s, 1 H, CHO), 9.10 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 37.75, 38.09 (NCH_2 and C-2'), 63.50 (C-5'), 67.99 (OCH_2), 79.59 (C-3'), 83.78 (C-1'), 84.99 (C-4'), 87.55 (CPh_3), 102.43 (C-5), 127.41, 127.96, 128.52 (C_{arom}), 139.66 (C-6), 143.04 (C_{arom}), 150.25 (C-2), 161.16 (C-4), 162.91 (C = O). FAB MS: $m/z = 542$ ($M + H^+$).

*1-{2-Deoxy-3-*O*-[2-(formamido)ethyl]-5-*O*-trityl-α-*D-erythro-*pentofuranosyl}uracil* (**8a**). Yield 454 mg (20%). ^1H NMR ($CDCl_3$): δ 2.27 (d, *J* 15.0 Hz, 1 H, 2'α-H), 2.59–2.67 (m, 1 H, 2'β-H), 3.17–3.27 (m, 2 H, 5'-H), 3.37–3.47 (m, 4 H, 2 × CH_2), 3.98 (d, *J* 5.4 Hz, 1 H, 3'-H), 4.46 (t, *J* 4.2 Hz, 1 H, 4'-H), 5.70 (d, *J* 8.1 Hz, 1 H, 5-H), 6.04 (br s, 1 H, NH), 6.25 (d, *J* 5.9 Hz, 1 H, 1'-H), 7.19–7.39 (m, 15 H, H_{arom}), 7.58 (d, *J* 8.2 Hz, 1 H, 6-H), 8.10 (s, 1 H, CHO), 9.46 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 37.73, 38.15 (NCH_2 and C-2'), 64.00 (C-5'), 67.73 (OCH_2), 80.30 (C-3'), 86.02 (C-1'), 87.19 (CPh_3), 87.37 (C-4'), 100.93 (C-5), 127.83, 127.89, 128.44 (C_{arom}), 140.52 (C-6), 143.28 (C_{arom}), 150.29 (C-2), 161.20 (C-4), 163.55 (C = O). FAB MS: $m/z = 542$ ($M + H^+$).

*2'-Deoxy-3'-*O*-[2-(formamido)ethyl]-5-nitro-5'-*O*-trityluridine* (**7c**). Yield 120 mg (5%). ^1H NMR ($CDCl_3$): δ 2.14–2.19 (m, 1 H, 2'-H), 2.69 (m, 1 H, 2'-H), 3.21–3.32 (m, 2 H, 5'-H), 3.41 (m, 4 H, 2 × CH_2), 4.01 (s, 1 H, 3'-H), 4.19 (s, 1 H, 4'-H), 6.06 (m, 1 H, 1'-H), 6.38 (s, 1 H, NH), 7.22–7.39 (m, 16 H, H_{arom} and 6-H), 8.14 (s, 1 H, CHO), 9.01 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 37.74, 38.87 (NCH_2 and C-2'), 63.47 (C-5'), 67.86 (OCH_2), 79.73 (C-3'), 84.87 (C-1'), 87.48, 87.64 (CPh_3 and C-4'), 125.61 (C-5), 127.72, 127.93, 128.40 (C_{arom}), 143.05 (C_{arom}), 143.87 (C-6), 148.49 (C-2), 154.68 (C-4), 161.71 (C = O). FAB MS: $m/z = 587$ ($M + H^+$).

*1-{2-Deoxy-3-*O*-[2-(formamido)ethyl]-5-*O*-trityl-α-*D-erythro-*pentofuranosyl}-5-nitrouracil* (**8c**). Yield 337 mg (16 %). ^1H NMR ($CDCl_3$): δ 2.36 (d, *J* 15.2 Hz, 1 H, 2'α-H), 2.63–2.69 (m, 1 H, 2'β-H), 3.15–3.19 (m, 2 H, 5'-H), 3.31–3.51 (m, 4 H, 2 × CH_2), 3.98 (d, *J* 4.9 Hz, 1 H, 3'-H), 4.62 (m, 1 H, 4'-H), 6.29 (d, *J* 6.8 Hz, 1 H, 1'-H), 6.53 (s, 1 H, NH), 7.23–7.59 (m, 16 H, H_{arom} and 6-H), 8.08 (s, 1 H, CHO), 9.08 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 38.00, 38.48 (NCH_2 and C-2'), 63.94 (C-5'), 68.33 (OCH_3), 80.29 (C-3'), 87.00 (C-1'), 87.34 (C-4'), 88.78 (CPh_3), 113.41 (C-5), 127.77, 127.94, 128.43 (C_{arom}), 143.20 (C_{arom}), 145.87 (C-6), 148.40 (C-2), 154.89 (C-4), 162.05 (C = O). FAB MS: $m/z = 587$ ($M + H^+$).

Detritylation of the nucleoside **8c** *and the anomeric mixture* **7b/8b** *to give* **9b** *and* **10b, c**. *General procedure.* The anomeric mixture **7b/8b**, or compound **8c** (0.5 mmol) was refluxed for 10 min with aq. 80% acetic acid (3 ml). The reaction mixture was left at room temperture for 3 h. Precipitated triphenylmethanol was filtered off and washed with cold aq. 80% acetic acid (2 ml). The combined filtrates were poured into ice–water (20 ml). Water and acetic acid were evaporated off under reduced presure. The residue was chromatographed on silica gel (50 g, 0.040–0.063 mm) with CH_2Cl_2–MeOH (5–10%) to give **9b** and **10b, c** in 24–46% yield.

*2'-Deoxy-5-fluoro-3'-*O*-[2-(formamido)ethyl]uridine* (**9b**). Yield 129 mg (24%). ^1H NMR (CD_3OD): δ 2.16 (m, 1 H, 2'-H), 2.39 (m, 1 H, 2'-H), 3.31–3.57 (m, 6 H,

5′-H and 2 × CH_2), 3.77 (m, 1 H, 3′-H), 4.05, 4.18 (2 × m, 2 H, 3′-H and 4′-H), 6.18 (m, 1 H, 1′-H), 8.07 (s, 1 H, CHO), 8.20 (d, *J* 6.9 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 39.32, 40.47 (NCH_2 and C-2′), 63.35 (C-5′), 68.97 (OCH_2), 81.27 (C-3′), 87.15 (C-1′ and C-4′), 126.42 (d, *J* 35.0 Hz, C-6), 142.16 (d, *J* 232.8 Hz, C-5), 151.11 (C-2), 164.27 (C = O). FAB MS: *m/z* = 318 ($M + H^+$).

*1-{2-Deoxy-3-*O*-[2-(formamido)ethyl]-*α-erythro-*pentofuranosyl}-5-fluorouracil* (**10b**). Yield 217 mg (40%). ^{1}H NMR (CD_3OD): δ 2.17 (d, *J* 8.7 Hz, 1 H, 2′α-H), 2.59–2.70 (m, 1 H, 2′β-H), 3.30–3.32 (m, 2 H, 5′-H), 3.37–3.42 (m, 4 H, 2 × CH_2), 4.14 (d, *J* 5.8 Hz, 1 H, 3′-H), 4.50 (t, *J* 4.5 Hz, 1 H, 4′-H), 6.22 (d, *J* 7.3 Hz, 1 H, 1′-H), 7.94 (d, *J* 6.9 Hz, 1 H, 6-H), 8.05 (s, 1 H, CHO). ^{13}C NMR (CD_3OD): δ 39.36, 40.40 (NCH_2 and C-2′), 63.78 (C-5′), 68.90 (OCH_2), 81.52 (C-3′), 88.85, 89.04 (C-1′ and C-4′), 127.15 (d, *J* 34.90 Hz, C-6), 141.16 (d, *J* 231.33 Hz, C-5), 151.10 (C-2), 159.93 (d, *J* 26.4 Hz, C-4), 164.26 (C = O). FAB MS: *m/z* = 318 ($M + H^+$).

*1-{2-Deoxy-3-*O*-[2-(formamido)ethyl}-*α-D-erythro-*pentofuranosyl)-5-nitrouracil* (**10c**). Yield 90 mg (46%). ^{1}H NMR (CD_3OD): δ 2.39 (d, *J* 15.07 Hz, 1 H, 2′α-H), 2.67 (m, 1 H, 2′β-H), 3.49 (m, 2 H, 5′-H), 3.57 (m, 4 H, 2 × CH_2), 4.17 (m, 1 H, 3′-H), 4.62 (m, 1 H, 4′-H), 6.27 (d, *J* 6.4 Hz, 1 H, 1′-H), 8.01 (s, 1 H, 6-H), 9.12 (m, 1 H, CHO). ^{13}C NMR (CD_3OD): δ 39.21, 40.48 (NCH_2 and C-2′), 63.66 (C-5′), 68.94 (OCH_2), 81.57 (C-3′), 89.89, 90.24 (C-1′ and C-4′), 126.54 (C-5), 147.54 (C-6), 150.57 (C-2), 157.29 (C-4), 164.26 (CHO). FAB MS: *m/z* = 345 ($M + H^+$).

Deformylation of the nucleosides **9** *and* **10** *to give* **11** *and* **12**. General procedure. A stirred solution of the compounds **9** or **10** (0.4 mmol) in MeOH (10 ml) and NaOMe (1.2 mmol) in MeOH (5 ml) was refluxed overnight. The mixture was cooled and neutralized by addition of NH_4Cl, after which the solvent was evaporated off and the crude material purified by column chromatography on silica gel (50 g, 0.040–0.063 mm) with 5–15% MeOH in CH_2Cl_2 to give **11** and **12** in 64–72% yield.

*3′-*O*-(2-Aminoethyl)-2′-deoxyuridine* (**11a**). Detritylation and deformylation as described above, but without purification of the intermediate **9a**, afforded compound **11a**. Yield 65 mg (59% overall yield from **7a**). ^{1}H NMR (CD_3OD): δ 2.12–2.17 (m, 1 H, 2′-H), 2.39–2.46 (m, 1 H, 2′-H), 2.89 (m, 2 H, NCH_2), 3.58, 3.74 (2 × m, 2 H, 5′-H and OCH_2), 4.09, 4.17 (2 × m, 2 H, 3′-H and 4′-H), 5.71 (d, *J* 8.0 Hz, 1 H, 5-H), 6.23 (t, *J* 6.75 Hz, 1 H, 1′-H), 7.96 (d, *J* 8.0 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 38.74 (C-2′), 42.16 (CNH_2), 63.50 (C-5′), 70.73 (OCH_2), 81.55 (C-3′), 87.01 (C-1′), 87.04 (C-4′), 103.13 (C-5), 142.63 (C-6), 152.71 (C-2), 166.67 (C-4). EI MS: *m/z* = 271 (M^+, 1).

*1-[3-*O*-(2-Aminoethyl)-2-deoxy-*α-D-erythro-*pentofuranosyl]uracil* (**12a**). Detritylation and deformylation as described above, but without purification of the intermediate **10a**, afforded compound **12a**. Yield 113 mg (50% overall yield from **8a**). ^{1}H NMR (CD_3OD): δ 2.28 (d, *J* 14.7 Hz, 1 H, 2′α-H), 2.57–2.68 (m, 1 H, 2′-H), 2.83–2.88 (t, *J* 5.5 Hz, 2 H, NCH_2), 3.50–3.60 (m, 4 H, 5′-H and OCH_2), 4.14 (d, *J* 5.8 Hz, 1 H, 3′-H), 4.50 (t, *J* 4.3 Hz, 1 H, 4′-H), 5.68 (d, *J* 8.1 Hz, 1 H, 5-H), 6.17 (dd, *J* 1.2, 7.0 Hz, 1 H, 1′-H), 7.80 (d, *J* 8.1 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 39.35 (C-2′), 41.91 (CNH_2), 63.84 (C-5′), 70.06 (OCH_2), 81.75 (C-3′), 89.03, 89.06 (C-1′ and C-4′), 101.86 (C-5), 143.12 (C-6), 152.58 (C-2), 166.84 (C-4). FAB MS: *m/z* = 272 ($M + H^+$).

*3′-*O*-(2-Aminoethyl)-2′-deoxy-5-fluorouridine* (**11b**). Yield 75 mg (64%). ^{1}H NMR (CD_3OD): δ 2.16 (m, 1 H, 2′-H), 2.44 (m, 1 H, 2′-H), 3.15 (m, 2 H, CNH_2), 3.75 (m, 4 H, 5′-H and OCH_2), 4.11, 4.22 (2 × m, 2 H, 3′-H and 4′-H), 6.23 (m, 1 H, 1′-H), 8.18 (d, *J* 6.6 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 38.60 (C-2′), 40.94 (CNH_2), 63.35 (C-5′), 66.58 (OCH_2), 81.94 (C-3′), 86.89, 87.13 (C-1′ and C-4′), 126.35 (d, *J* 34.7 Hz, C-6), 142.23 (d, *J* 232.9 Hz, C-5), 151.26 (C-2), 159.98 (d, *J* 26.10 Hz, C-4). FAB MS: *m/z* = 290 ($M + H^+$).

*1-[3-*O*-(2-Aminoethyl)-2-deoxy-*α-D-erythro-*pentofuranosyl]-5-fluorouracil* (**12b**). Yield 143 mg (73%). ^{1}H NMR (CD_3OD): δ 2.29 (d, *J* 15.0 Hz, 1 H, 2′α-H), 2.66 (m, 1 H, 2′β-H), 3.03 (m, 2 H, CNH_2), 3.63 (m, 4 H, 5′-H and OCH_2), 4.18 (d, *J* 5.9 Hz, 1 H, 3′-H), 4.53 (t, *J* 4.4 Hz, 1 H, 4′-H), 6.21 (d, *J* 7.1 Hz, 1 H, 1′-H), 7.89 (d, *J* 6.8 Hz, 1 H, 6-H). ^{13}C NMR (CD_3OD): δ 39.17 (C-2′), 41.13 (CNH_2), 63.73 (C-5′), 67.81 (OCH_2), 81.80 (C-3′), 88.66, 88.92 (C-1′ and C-4′), 126.57 (d, *J* 37.0 Hz, C-6), 142.05 (d, *J* 233.3 Hz, C-5), 152.51 (C-2), 161.71 (d, *J* 24.46 Hz, C-4). FAB MS: *m/z* = 290 ($M + H^+$).

References

1. Chur, A., Holst, B., Dahl, O., Valentin-Hansen, P. and Pedersen, E. B. *Nucleic Acids Res. 21* (1993) 5179.
2. Idziak, I., Just, G., Damha, M. J. and Giannaris, P. A. *Tetrahedron Lett. 34* (1993) 5417.
3. Lebreton, J., Waldner, A., Fritsch, V., Wolf, R. M. and De Mesmaeker, A. *Tetrahedron Lett. 35* (1994) 5225.
4. Lebreton, J., De Mesmaeker, A., Waldner, A., Fritsch, V., Wolf, R. M. and Freier, S. M. *Tetrahedron Lett. 34* (1993) 6383.
5. De Mesmaeker, A., Waldner, A., Sanghvi, Y. S. and Lebreton, J. *Bioorg. Med. Chem. Lett. 4* (1994) 395.
6. De Mesmaeker, A., Lebreton, J., Waldner, A., Fritsch, V. and Wolf, R. M. *Bioorg. Med. Chem. Lett. 4* (1994) 873.
7. De Clercq, E. *AIDS Res. Human Retrovir. 8* (1992) 119.
8. Nasr, M., Cradock, J. and Johnson, M. I. *AIDS Res. Human Retrovir. 8* (1992) 135.
9. Motawia, M. S. and Pedersen, E. B. *Liebigs Ann. Chem.* (1990) 599.
10. Horwitz, J. P., Urbanski, J. A. and Chua, J. *J. Org. Chem. 27* (1962) 3300.

11. Fronza, G., Funganti, C. and Grasselli, P. *J. Chem. Soc., Perkin Trans 1* (1982) 885.
12. Karplus, M. *J. Chem. Phys. 30* (1959) 11.
13. Hall, L. D., Steiner, P. R. and Pedersen, C. *Can. J. Chem. 48* (1970) 1155.
14. Griffin, B. E. and Todd, A. *J. Chem. Soc.* (1958) 1389.
15. Nyilas, A., Glemarec, C. and Chattopadhyaya, J. *Tetrahedron 46* (1990) 2149.
16. Gait, M. J., Jones, A. S. and Walker, R. T. *J. Chem. Soc., Perkin Trans. 1* (1974) 1684.
17. Tate, M. E. and Bishop, C. T. *Can. J. Chem. 41* (1963) 1801.
18. El-Kousy, S., Pedersen, E. B. and Nielsen, C. *Monatsh. Chem. 125* (1994) 713.
19. Vorbrüggen, H., Krolikewicz, K. and Bennua, B. *Chem. Ber. 114* (1981) 1234.
20. Nuhn, P., Zschunke, A., Heller, D. and Wagner, G. *Tetrahedron 25* (1969) 2139.
21. Okabe, M., Sun, R.-C., Tam, S. Y.-K., Tadaro, L. J. and Coffen, D. L. *J. Org. Chem. 53* (1988) 4780.
22. Bloch, E., Lavignon, M., Bertrand, J.-R., Pognan, F., Morvan, F., Malvy, C., Rayner, B., Imbach, J.-L. and Paoletti, C. *Gene 72* (1988) 349.
23. Wittenburg, E. *Z. Chem. 4* (1964) 303.

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