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Synthesis of 2-*O*-Ethyl Analogues of 3′-Azido- and 3′-Fluoro-2′,3′-dideoxyuridines and Evaluation of their Biological Activity against HIV

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Summary. 2-*O*-Ethyluracil and 2-*O*-ethylthymine were silylated with 1,1,1,3,3,3-hexamethyldisilazane and condensed in the presence of *TMS* triflate with 2,3-dideoxy-3-fluoro-*D-erythro*-pentofuranoside, 3-azido-2,3-dideoxy-*D-erythro*-pentofuranoside, and 2,3-dideoxy-3-phthalimido-*β-D-erythro*-pentofuranose derivatives to give the corresponding 2-*O*-ethyl nucleosides. Deprotection with saturated methanolic ammonia afforded the 2′,3′-dideoxy-3′-fluoro-2-*O*-ethyluridines, whereas 3′-azido-2′,3′-dideoxy-3-*O*-ethyluridine was obtained by deprotection with tetrabutylammonium fluoride in tetrahydrofuran. 3′-Amino-2′,3′-dideoxy-3-*O*-ethyluridine could be obtained only by treatment of the corresponding 3′-azido nucleoside with triphenylphosphine in pyridine. 3′-Deoxy-2-*O*-ethyl-3′-fluorothymidine (**6b**) showed moderate activity against HIV-1.

Keywords. Nucleosides, convergent synthesis of; Uridines, 2-*O*-ethyl; Uridines, 2′,3′-dideoxy-3′-fluoro; *AZT* analogues; Human immunodeficiency virus; Herpes simplex virus.

Synthese von 2-O-Ethyl-Analogen von 3′-Azido- und 3′-Fluor-2′3′-dideoxyuridinen und Bestimmung ihrer biologischen Aktivität gegenüber HIV

Zusammenfassung. 2-O-Ethyluracil und 2-O-Ethylthymin wurden mit 1,1,1,3,3,3-Hexamethyldisilazan silyliert und in Gegenwart von *TMS*-triflat mit 2,3-Dideoxy-3-fluoro-*D-erythro*-pentofuranosid, 3-Azido-2,3-dideoxy-*D-erythro*-pentofuranosid und 2,3-Dideoxy-3-phthalimido-*β-D-erythro*-pentofuranosederivaten zu den entsprechenden 2-O-Ethyl-Nucleosiden umgesetzt. Entfernung der Schutzgruppe mit gesättigter methanolischer Ammoniaklösung lieferte 2′,3′-Dideoxy-3′-fluor-2-O-ethyluridin; 3′-Azido-2′,3′-dideoxy-3-O-ethyl-uridin wurde durch Entschützung mit Tetrabutylammoniumfluorid in Tetrahydrofuran erhalten. 3′-Amino-2′,3′-dideoxy-3-O-ethyl-uridin konnte nur durch Behandeln des entsprechenden 3′-Azido-Nucleosids mit Triphenylphosphin in Pyridin hergestellt werden. 3′-Deoxy-2-O-ethyl-3′-fluor-thymidin (**6b**) zeigt geringe Aktivität gegenüber HIV-1.

Introduction

Since the discovery of 3′-azido-3′-deoxythymidine (*AZT*) as a potent drug against human immunodeficiency virus (HIV) [1], many nucleoside analogues have been designed and synthesized, including modifications of the carbohydrate moiety [2]

as well as of the base [3], in order to obtain an improved selectivity. *AZT* analogues with a 2-*O*-alkyl group have also been considered to be of interest [4]. Such analogues were synthesized in a linear route from thymidine *via* 3′-azido-3′-deoxy-5′-mesylthymidine which was refluxed in an appropriate alcohol. For the purpose of biological testing we thought it more easy to synthesize small quantities of 2-*O*-alkyl-3′-azido-2′,3′-dideoxyuridines simply by condensing the appropriate sugar with a silylated 2-*O*-alkyluracil derivative. In this context we also found it interesting to synthesize 2-*O*-ethyl analogues of 3′-deoxy-3′-fluorothymidine (*FLT*). The latter compound is even more potent against HIV than *AZT*, but also more toxic against the host cells [5–8]. We were unable to find any reports of 2-*O*-alkyl analogues of *FLT* in the literature.

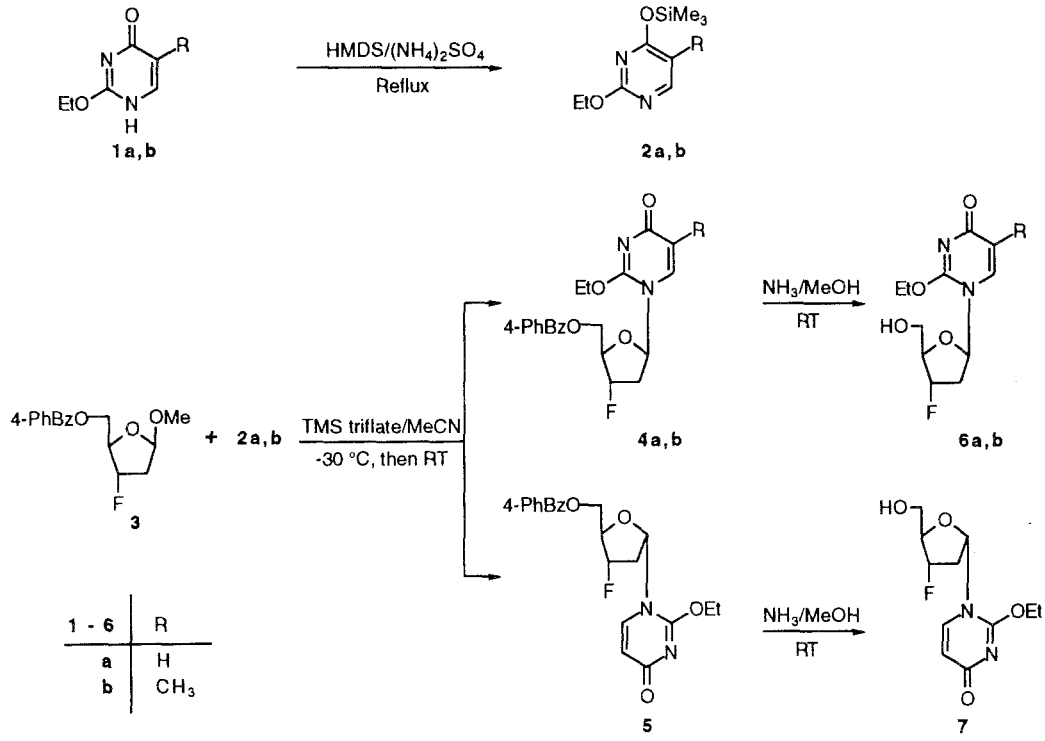
Results and Discussion

The 3-fluoro sugar **3** was first prepared by the method of *Motawia* and *Pedersen* [9]; however, we used the modified method of *Abdel-Bary et al.* who treated methyl 2,3-dideoxy-5-*O*-(4-phenylbenzoyl)-*β*-*D*-*erythro*-pentofuranoside with diethylamino-sulfur trifluoride (*DAST*) in a 1:10 molar ratio in dry CH_2Cl_2 [10]. The 2-*O*-ethyluracils **1a,b** obtained as described by *Hilbert* and *Jansen* [11] were silylated using 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) and ammonium sulfate as a catalyst [12] to give the corresponding silylated compounds **2a,b** which were used without further purification. Coupling of the 3-fluoro sugar **3** with **2a,b** in dry acetonitrile in the presence of the *Lewis* acid trimethylsilyl trifluoromethanesulfonate (*TMS* triflate) as the catalyst [13] afforded the *β* anomers **4a,b** in 55–71% yields and the *α* anomer **5** in 15% yield. Treatment of **4a,b** and **5** with saturated ammonia for deprotection of the 5′-OH group gave compounds **6a,b** in 75–82% yield and the corresponding *α* anomer **7** in 42% yield after purification by column chromatography on silica gel.

Condensation of the azido sugar **8** [14] with the silylated base **2a**, using the method mentioned above for 3-fluoro sugar **3**, gave **9** (75%) as an anomeric mixture for which the *α*/*β* ratio was 2:1. Treatment of the anomeric mixture **9**, after chromatographic purification, with tetrabutylammonium fluoride in tetrahydrofuran resulted in complete deprotection of the 5′-OH group. Subsequent silica gel column separation afforded the *β* anomer **11** in 25% yield and the *α* anomer **10** in 49% yield. Following the procedures reported in Refs. [15] and [16] on the utility of the azido group as a synthon for a terminal amino group in an oligonucleotide, we reduced the azido group of compound **11** using triphenylphosphine in pyridine and obtained the 3′-amino analogue **12** in 50% yield. Moreover, it has been reported [17] that masked amino nucleosides can be obtained by condensation of silylated bases with the easily available phthalimido sugar **13**. Indeed it was possible to condense the silylated base **2a** with the phthalimido sugar **13** in dry acetonitrile using *TMS* triflate as a catalyst [13]; the anomeric mixture of nucleoside **14** was obtained.

The standard procedure of deblocking the 3′-NH_2 and 5′-OH groups with 33% methylamine solution in absolute ethanol at reflux temperature failed; unknown products were formed.

The assignment of the anomeric configuration was performed by means of ^1H NMR spectroscopy.



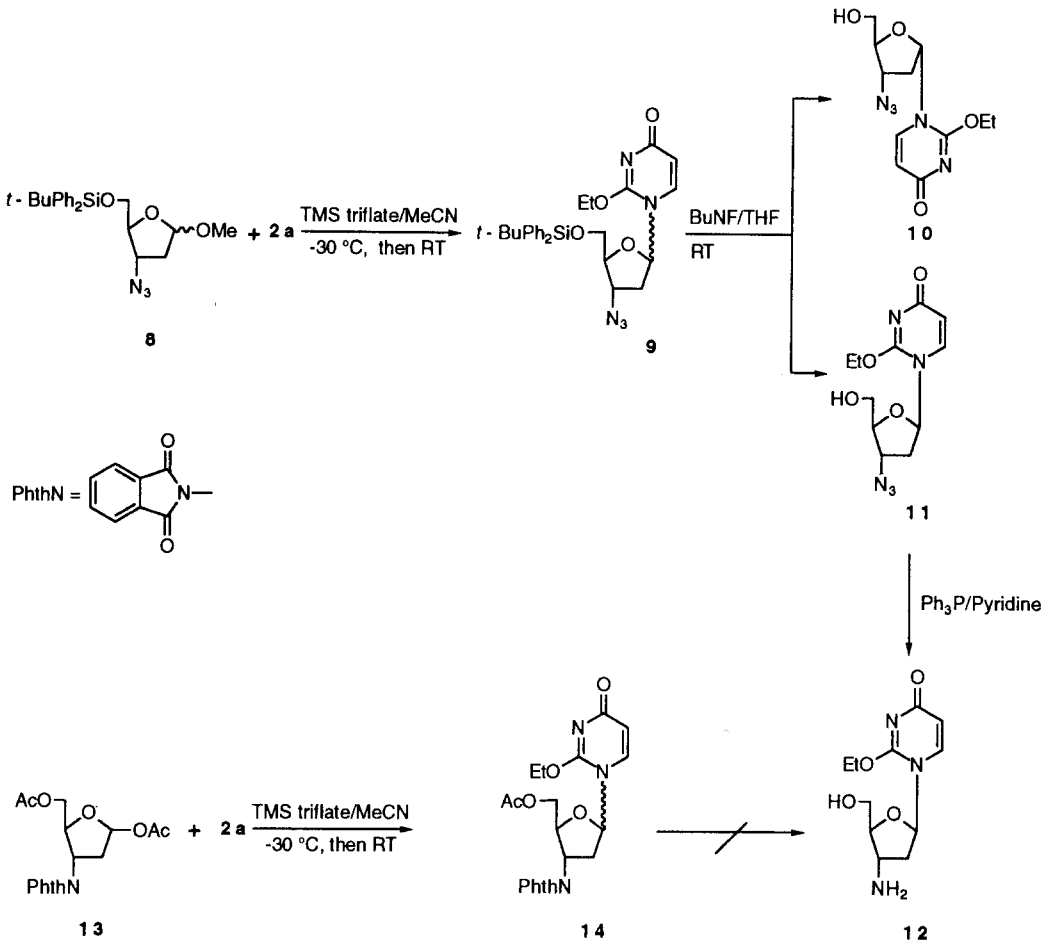
Scheme 1

The H-4′ protons of the α anomers appear downfield from those observed for the β anomers. The H-5′ protons of the α anomers appear upfield from those observed for the β anomers [18, 19].The H-2′α resonances of **5** and **7** exhibited only a doublet of a doublet due to a large geminal coupling and a coupling to fluorine. A coupling close to zero for H-1′ and H-3′ proved the latter two protons to be located *trans* to H-2′α in the sugar ring. This in turn proves the α configuration. Consequently, we observed small coupling constants (5.2 and 5.5 Hz, respectively) of C-6 in **5** and **7** which were ascribed to a through-space coupling to fluorine. This also proved anti configuration with respect to the glycosidic bond to the nucleobase. Through-space $^{13}C-^{19}F$ couplings are already known for adenine derivatives [20].

Compounds **6a, b**, **7**, **11** and **12** were testest for their activity against HIV-1 in MT-4 cells. Only the β anomer **6b** showed activity against HIV-1 with an effective dose $ED_{50} = 10\,\mu M$ (*AZT*: $ED_{50} = 0.05\,\mu M$), and no toxicity was observed at $800\,\mu M$ which was the highest concentration tested. The MT-4 cells were incubated with virus, washed, and added in proportion of 1:10 to uninfected MT-4 cells which had been preincubated in test compounds containing culture medium (RPM 1640 containing 10% FCS) for 2 h. Cultures were maintained for 7 days, and the expression of HIV was quantized by the ELISA method. The same compounds did not show any significant activity when tested against Herpes simplex virus, type 1, strain *McIntyre* in African green monkey kidney cells, *Vero* cell line.

Experimental

Column chromatography was performed on Merck silica gel (0.040–0.063 mm). Mass spectra were recorded on a Varian MAT 311A mass spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 250 FT-NMR spectrometer using tetramethylsilane as internal standard.



Scheme 2

Preparation of **4a,b** *and* **5**; *general procedure*

A mixture of the 2-*O*-ethyluracils **1a,b** (6 mmol), $(NH_4)_2SO_4$ (30 mg), and 1,1,1,3,3,3-hexamethyldisilazane (30 ml) was refluxed for 3 h. The solvent was removed under reduced pressure and the resulting oily residue of compounds **2a,b** was then dissolved in dry MeCN (30 ml), cooled to −30 °C, and a solution of the fluoro sugar **3** (1 g, 3 mmol) in dry MeCN (20 ml) was added. A solution of trimethylsilyl trifluoromethanesulfonate (1.3 ml, 6.5 mmol) in dry MeCN (5 ml) was added dropwise to the reaction mixture and the mixture was stirred at −25 °C for 30 min. Then the temperature was allowed to raise to room temperature and stirring was continued for 30 min. The mixture was diluted with methylene chloride (200 ml), washed with cold saturated aqueous $NaHCO_3$ solution (250 ml), cold water (3 × 150 ml), and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (40 g) with $CHCl_3$/MeOH (98:2 v/v) to obtain the β anomers **4a,b** in 55–71% yield and the α anomer **5** in 15% yield.

2′,3′-Dideoxy-2-O-ethyl-3′-fluoro-5′-O-(4-phenylbenzoyl)uridine (**4a**)

Yellow gum. Yield 720 mg (55%); ^{1}H NMR ($CDCl_3$): $\delta = 1.39$ (3H, t, $J = 7.2$ Hz, CH_3), 2.13 (1H, 2 × m, $J = 37.6$ Hz, 2′-H), 2.77 (1H, ddd, $J = 5.3$, 14.7, 20.7 Hz, 2′-H), 4.53 (2H, q, $J = 7.2$, 14.1 Hz, OCH_2), 4.59 (2H, m, 5′-H), 4.69 (1H, d, $J = 9.4$ Hz, 4′-H), 5.34 (1H, dd, $J = 4.9$, 53.0 Hz, 3′-H), 5.97 (1H, d, $J = 7.7$ Hz, 5-H), 6.25 (1H, dd, $J = 5.3$, 8.6 Hz, 1′-H), 7.47 (3H, m, arom), 7.59 (3H, m, arom and 6-H), 7.68 (2H, d,

$J = 8.3$ Hz arom), 8.02 (2H, d, $J = 8.3$ Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.07$ (CH_3), 39.59 (d, $J_{F,C-2'} = 21.1$ Hz, C-2'), 63.41 (d, $J_{F,C-5'} = 10.6$ Hz, C-5'), 65.24 (OCH_2), 83.20 (d, $J_{F,C-4'} = 26.4$ Hz, C-4'), 86.34 (C-1'), 93.32 (d, $J_{F,C-3'} = 180.1$ Hz, C-3'), 109.18 (C-5), 127.17, 127.31, 127.53, 128.53, 128.89, 129.88, 146.64 (biphenyl), 135.42 (C-6), 154.81 (C-2), 165.66 (CO), 170.86 (C-4) ppm; FAB MS ($CHCl_3$ + 1% CF_3COOH + glycerol): $m/z = 439$ ($M + H^+$).

3'-Deoxy-2-O-ethyl-3'-fluoro-5'-O-(4-phenylbenzoyl)thymidine (**4b**)

White foam. Yield 960 mg (71%); ^1H NMR ($CDCl_3$): $\delta = 1.35$ (3H, t, $J = 7.1$ Hz, CH_3), 1.76 (3H, s, CH_3), 2.15 (1H, 2 × m, $J = 38.0$ Hz, 2'-H), 2.73 (1H, ddd, $J = 5.2$, 14.6, 20.7 Hz, 2'-H), 4.52 (2H, q, $J = 7.0$, 14.1 Hz, OCH_2), 4.64 (1H, dd, $J = 3.0$, 24.0 Hz, 4'-H), 4.65 (2H, d, $J = 3.2$ Hz, 5'-H), 5.37 (1H, dd, $J = 4.9$, 53.1 Hz, 3'-H), 6.29 (1H, dd, $J = 5.2$, 8.9 Hz, 1'-H), 7.35–7.69 (8H, m, arom and 6-H), 8.04 (2H, d, $J = 8.3$ Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.48$ (CH_3), 14.13 (CH_3), 39.39 (d, $J_{F,C-2'} = 21.1$ Hz, C-2'), 63.55 (d, $J_{F,C-5'} = 10.5$ Hz, C-5'), 65.11 (OCH_2), 82.98 (d, $J_{F,C-4'} = 26.2$ Hz, C-4'), 85.89 (C-1'), 93.47 (d, $J_{F,C-3'} = 179.7$ Hz, C-3'), 118.04 (C-5), 126.99, 127.16, 127.36, 128.38, 128.81, 129.85, 131.28, 146.70 (biphenyl), 139.36 (C-6), 154.59 (C-2), 165.65 (CO), 171.43 (C-4) ppm; FAB MS ($CHCl_3$ + 1% AcOH + 3-nitrobenzylalcohol): $m/z = 453$ ($M + H^+$).

1-[2,3-Dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-α-D-erythro-pentofuranosyl]-2-ethoxypyrimidin-4(1H)-one (**5**)

Yellow gum. Yield 196 mg (15%); ^1H NMR ($CDCl_3$): $\delta = 1.37$ (3H, t, $J = 7.1$ Hz, CH_3), 2.47 (1H, dd, $J = 13.8$, 20.8 Hz, 2'-H(α)), 2.85 (1H, 2 × m, $J = 27.7$ Hz, 2'-H(β)), 4.47 (4H, m, OCH_2 and 5'-H), 4.95 (1H, td, $J = 3.4$, 22.9 Hz, 4'-H), 5.35 (1H, dd, $J = 1.1$, 7.2 Hz, 1'-H), 7.40–7.64 (6H, m, aromat and 6-H), 7.70 (2H, d, $J = 8.3$ Hz, arom), 8.08 (2H, d, $J = 8.3$ Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.99$ (CH_3), 39.57 (d, $J_{F,C-2'} = 21.0$ Hz, C-2'), 63.08 (d, $J_{F,C-5'} = 11.1$ Hz, C-5'), 64.86 (OCH_2), 84.94 (d, $J_{F,C-4'} = 24.6$ Hz, C-4'), 87.43 (C-1'), 93.05 (d, $J_{F,C-3'} = 179.3$ Hz, C-3'), 108.40 (C-5), 127.00, 127.07, 127.43, 128.22, 128.79, 129.78, 139.36, 146.26 (biphenyl), 136.20 (d, $J_{F,C-6} = 5.2$ Hz, C-6), 154.61 (C-2), 165.52 (CO), 171.19 (C-4) ppm; FAB MS ($CHCl_3$ + 1% AcOH + 3-nitrobenzylalcohol): $m/z = 439$ ($M + H^+$).

Formation of **6a,b** *or* **7** *by deprotection*

Saturated ammonia in methanol (30 ml) was added dropwise with stirring to a solution of **4a,b** or **5** (2 mmol) in methanol (20 ml) at 0 °C. The mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was chromatographed on a silica column with $CHCl_3$/MeOH (97:3 v/v) to give **6a,b** or **7**.

2',3'-Dideoxy-2-O-ethyl-3'-fluorouridine (**6a**)

Yield 285 mg (75%); m.p. 155–156 °C; ^1H NMR (CD_3OD): $\delta = 1.41$ (3H, t, $J = 7.2$ Hz, CH_3), 2.31 (1H, 2 × m, $J = 38.6$ Hz, 2'-H), 2.68 (1H, ddd, $J = 5.5$, 14.6, 21.4 Hz, 2'-H), 3.77 (2H, d, $J = 3.1$ Hz, 5'-H), 4.33 (1H, td, $J = 2.9$, 26.3 Hz, 4'-H), 4.51 (2H, q, $J = 7.1$ Hz, OCH_2), 5.28 (1H, dd, $J = 4.7$, 53.6 Hz, 3'-H), 6.02 (1H, d, $J = 7.7$ Hz, 5-H), 6.27 (1H, dd, $J = 5.7$, 8.3 Hz, 1'-H), 8.16 (1H, d, $J = 7.8$ Hz, 6-H) ppm; ^{13}C NMR (CD_3OD): $\delta = 14.62$ (CH_3), 40.80 (d, $J_{F,C-2'} = 20.9$ Hz, C-2'), 62.73 (d, $J_{F,C-5'} = 11.1$ Hz, C-5'), 67.05 (OCH_2), 88.14 (d, $J_{F,C-4'} = 23.5$ Hz, C-4'), 88.78 (C-1'), 96.04 (d, $J_{F,C-3'} = 176.3$ Hz, C-3'), 108.56 (C-5), 140.80 (C-6), 157.51 (C-2), 175.25 (C-4)ppm; MS; $m/z = 258$ (M^+, 6).

3'-Deoxy-2-O-ethyl-3'-fluorothymidine (**6b**)

White foam. Yield 440 mg (82%); ^1H NMR ($CDCl_3$): $\delta = 1.38$ (3H, t, $J = 7.1$ Hz, CH_3), 1.90 (3H, s, CH_3), 2.30 (1H, 2 × m, $J = 40.2$ Hz, 2'-H), 2.59 (1H, ddd, $J = 5.3$, 14.2, 20.9 Hz, 2'-H), 3.97 (2H, s, 5'-H), 4.49 (3H, m, OCH_2 and 4'-H), 5.38 (1H, dd, $J = 4.4$, 53.7 Hz, 3'-H), 6.30 (1H, dd, $J = 5.5$, 8.9 Hz, 1'-H), 7.95

(1H, s, 6-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.56$ (CH_3), 14.07 (CH_3), 39.59 (d, $J_{F,C-2'} = 15.0$ Hz, C-2'), 61.82 (d, $J_{F,C-5'} = 11.5$ Hz, C-5'), 64.99 (OCH_2), 86.05 (C-1'), 86.08 (d, $J_{F,C-4'} = 23.6$ Hz, C-4'), 94.82 (d, $J_{F,C-3'} = 176.4$ Hz, C-3'), 117.15 (C-5), 133.95 (C-6), 154.91 (C-2), 172.60 (C-4) ppm; MS: $m/z = 272$ (M^+, 12).

1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-2-ethtoxypyrimidin-4(1H)-one (**7**)

Yellow gum, Yield 160 mg (42%); ^{1}H NMR ($CDCl_3$): $\delta = 1.38$ (3H, t, $J = 6.9$ Hz, CH_3), 2.37 (1H, dd, $J = 15.6, 23.2$ Hz, 2'-H(α)), 2.84 (1H, 2 × m, $J = 33.9$ Hz, 2'-H(β)), 3.78 (2H, d, $J = 3.4$ Hz, 5'-H), 4.49 (2H, m, OCH_2), 4.69 (1H, td, $J = 3.3, 24.3$ Hz, 4'-H), 5.34 (1H, dd, $J = 4.9, 53.8$ Hz, 3'-H), 6.02 (1H, d, $J = 7.7$ Hz, 5-H), 6.25 (1H, d, $J = 6.7$ Hz, 1'-H), 7.53 (1H, d, $J = 7.6$ Hz, 6-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.10$ (CH_3), 40.45 (d, $J_{F,C-2'} = 20.6$ Hz, C-2'), 62.14 (d, $J_{F,C-6'} = 11.3$ Hz, C-5'), 65.00 (OCH_2), 88.27 (C-1'), 88.40 (d, $J_{F,C-4'} = 22.2$ Hz, C-4'), 94.02 (d, $J_{F,C-3'} = 176.3$ Hz, C-3'), 108.00 (C-5), 137.07 (d, $J_{F,C-6'} = 5.5$ Hz, C-6), 155.00 (C-2), 172.20 (C-4).

3'-Azido-2',3'-dideoxy-2-O-ethyluridine (**11**) *and its α anomer* **10**

The silylated base **2a** (1.12 g, 8 mmol) was dissolved in dry MeCN (40 ml), cooled to −30 °C, and a solution of the azido sugar **8** (2.05 g, 5 mmol) in dry MeCN (20 ml) was added. A solution of *TMS* triflate (1.3 ml, 6.5 mmol) in dry MeCN (5 ml) was added to the reaction mixture under stirring. The mixture was stirred at −25 °C for 30 min, then at room temperature for 30 min. The mixture was diluted with CH_2Cl_2 (250 ml), washed with cold saturated aqueous $NaHCO_3$ solution (300 ml), cold water (3 × 150 ml), and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by silica gel chromatography with $CHCl_3$/MeOH (98:2 v/v) to give the anomeric mixture **9**. Yield 1.9 g (75%). Treatment of the anomeric mixture **9** in *THF* (50 ml) with tetrabutylammonium fluoride (5 ml, 1*M* solution in *THF*) at 0 °C for 30 min and at room temperature for further 30 min resulted in complete deprotection of 5-OH. The mixture was separated into the anomeric compounds **10** and **11** by silica gel column chromatography with $CHCl_3$/MeOH (96:4 v/v).

10: Yellow gum. Yield 470 mg (33%); ^{1}H NMR ($CDCl_3$): $\delta = 1.38$ (3H, t, $J = 7.0$ Hz, CH_3), 2.13 (1H, d, $J = 14.6$ Hz, 2'-H(α)), 3.89 (1H, td, $J = 6.9, 14.3$ Hz, 2'-H(β)), 3.77 (2H, d, $J = 3.5$ Hz, 5'-H), 4.04–4.55 (4H, m, 3'-H, 4'-H and OCH_2), 4.56 (1H, broad s, OH), 6.03 (1H, d, $J = 7.6$ Hz, 5-H), 6.13 (1H, m, 1'-H), 7.59 (1H, d, $J = 7.6$ Hz, 6-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.93$ (CH_3), 39.02 (C-2'), 61.00 (C-3'), 62.23 (C-5'), 65.06 (OCH_2), 87.46 (C-4'), 88.00 (C-1'), 107.58 (C-5), 137.34 (C-6), 154.96 (C-2), 172.28 (C-4) ppm; MS: $m/z = 281$ (M^+, 2).

11: Yellow gum. Yield 240 mg (17%); ^{1}H NMR ($CDCl_3$): $\delta = 1.39$ (3H, t, $J = 7.2$ Hz, CH_3), 2.43 (2H, m, 2'-H), 3.86 (1H, d, $J = 10.6$ Hz, 5'-H), 4.03 (2H, m, 3'-H and 5'-H), 4.41 (1H, m, 4'-H), 4.49 (2H, q, $J = 7.2$ Hz, OCH_2), 5.10 (1H, broad s, OH), 5.96 (1H, d, $J = 7.6$ Hz, 5-H), 6.13 (1H, t, $J = 6.0$ Hz, 1'-H), 8.16 (1H, d, $J = 7.6$ Hz, 6-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.02$ (CH_3), 39.01 (C-2'), 60.03 (C-3'), 61.19 (C-5'), 65.22 (OCH_2), 85.61 (C-4'), 86.19 (C-1'), 107.94 (C-5), 138.21 (C-6), 155.09 (C-2), 172.44 (C-4) ppm; MS: $m/z = 281$ (M^+, 5).

3'-Amino-2',3'-dideoxy-2-O-ethyluridine (**12**)

Triphenylphosphine (40 mg, 0.152 mmol) and **11** (26 mg, 0.092 mmol) were dissolved in 2 ml of pyridine and kept at room temperature for 1 h. Concentrated ammonium hydroxide was added and the solution was allowed to stand for 3 h. Pyridine was removed *in vacuo* and the residue was chromatographed on a silica gel column by using 10% MeOH in $CHCl_3$ to give **12** as a yellow gum. Yield 12 mg (50%); ^{1}H NMR (CD_3OD): $\delta = 1.41$ (3H, t, $J = 7.2$ Hz, CH_3), 2.42 (2H, t, $J = 6.5$ Hz, 2'-H), 3.60–4.00 (3H, m, 4'-H, 5'-H), 4.28 (1H, m, 3'-H), 4.50 (2H, q, $J = 7.0$ Hz, OCH_2), 4.77 (2H, s, NH), 6.02 (1H, d, $J = 7.7$ Hz, 5-H), 6.21 (1H, t, $J = 6.9$ Hz, 1'-H), 8.21 (1H, d, $J = 7.7$ Hz, 6-H) ppm; MS: $m/z = 255$ (M^+, 3).

1-(5′-O-Acetyl-3′-phthalimido-2′,3′-dideoxy-α,β-D-erythro-pentofuranosyl)-2-ethoxy pyrimidin-4(1H)-one (**14**)

The silylated base **2a** (1.12 g, 8 mmol) was dissolved in dry MeCN (30 ml) and cooled to −30 °C. The solution of the phthalimido sugar **13** (1.73 g, 5 mmol) in dry MeCN (10 ml) was added to the reaction mixture with stirring. A solution of *TMS* triflate (1.3 ml, 6.5 mmol) in dry MeCN (5 ml) was added. The mixture was stirred at −25 °C for 30 min, then at room temperature for 1 h. The mixture was diluted with CH_2Cl_2 (200 ml), washed with cold saturated aqueous $NaHCO_3$ solution (200 ml), cold water (3 × 100 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by a silica gel column using CH_2Cl_2/MeOH (96:4 v/v) to give **14** as a foam. Yield 1.5 g (72%); ^{1}H NMR ($CDCl_3$): $\delta = 1.42$ (3H, m, CH_3), 2.06 (4H, m, $COCH_3$ and 2′-H(α)), 2.35 (1H, m, 2′-H(β)), 2.85 (1H, m, 2′-H(β)), 3.07 (1H, m, 2′-H(α)), 4.0–5.0 (4H, m, 3′-H, 4′-H and 5′-H), 6.05 (1H, d, $J = 7.6$ Hz, 5-H(β)), 6.15 (1H, d, $J = 7.6$ Hz, 5-H(α)), 6.29 (1H, t, $J = 5.6$ Hz, 1′-H(α)), 6.44 (1H, t, $J = 5.6$ Hz, 1′-H(β)), 7.61 (1H, d, $J = 7.6$ Hz, 6-H), 7.80 (4H, m, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.97$ (CH_3), 20.42 ($COCH_3$), 34.25 (C-2′(α)), 35.54 (C-2′(β)), 48.29 (C-3′(β)), 48.59 (C-3′(α)), 62.76 (C-5′(β)), 63.27 (C-5′(α)), 65.04 (OCH_2), 76.95 (C-4′(α)), 78.56 (C-4′(β)), 85.63 (C-1′(α)), 86.29 (C-1′(β)), 108.76 (C-5(β)), 109.30 (C-5(α)), 123.48 (C-4″, phth), 131.19 (C-3″, phth), 134.45 (C-5″, phth), 136.37 (C-6(β)), 136.43 (C-6(α)), 154.81 (C-2), 167.31 (C=O), 169.98 (CH_3CO), 170.90 (C-4) ppm.

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