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# Synthesis of 5-Dialkylaminomethyl-3′-azido and 3′-Fluoro-2′,3′-dideoxyuridines for Evaluation as Anti-HIV Agents

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**Summary.** Uracil (**8**) was substituted in a Mannich reaction to give the 5-substituted dialkylaminomethyluracils **11a–f** in 65–85% yield. Compounds **11a–f** were silylated with hexamethyldisilazane and coupled with 2,3-dideoxy-3-fluoro-*D-erythro*-pentofuranoside **4** and 3-azido-2,3-dideoxy-*D-erythro*-pentofuranoside **7** to give the corresponding 3′-fluoro-2′,3′-dideoxynucleosides **13a–f** and 3′-azido-2′,3′-dideoxy nucleosides **16d, f**, respectively, by using trimethylsilyl trifluoromethanesulfonate as a catalyst. Deprotection of the 5-O-(4-phenylbenzoyl) protected nucleosides **13a–f** and **16d, f** with saturated methanolic ammonia and separation by chromatography yielded the new derivatives of 2′,3′-dideoxy-3′-fluorouridines **14a–f** and **15a–f** and 2′,3′-dideoxy-3′-azidouridines **17d, f** and **18d, f**.

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

**Synthese von 5-Dialkylaminomethyl-3′-azido- und 3′-Fluor-2′,3′-didesoxyuridinen zur Überprüfung ihrer Anti-HIV-Aktivität**

**Zusammenfassung.** Aus Uracil (**8**) wurden in einer Mannich-Reaktion in 65–85% Ausbeute die 5-substituierten Dialkylaminomethyluracile **11a–f** hergestellt. Verbindungen **11a–f** wurden mit Hexamethyldisilazan silyliert und mit 2,3-Didesoxy-3-fluor-*D-erythro*-pentofuranosid (**4**) und 3-Azido-2,3-didesoxy-*D-erythro*-pentofuranosid (**7**) unter Verwendung von Trimethylsilyl-trifluormethansulfonat als Katalysator zu den entsprechenden 3′-Fluor-2′,3′-didesoxynucleosiden **13a–f** und 3′-Azido-2′,3′-didesoxynucleosiden **16d, f** umgesetzt. Deprotektion der 5-O-(4-Phenylbenzoyl)- geschützten Nucleoside **13a–f** und **16d, f** mit gesättigtem methanolischem Ammoniak und Trennung mittels Chromatographie ergab die neuen 2′,3′-Didesoxy-3′-fluoruridine **14a–f** unf **15a–f**, sowie die 2′,3′-Didesoxy-3′-azidouridine **17d, f** und **18d, f**.

## Introduction

Reverse transcriptase inhibitors [1, 2] have thus far proven to be the most potent medications for containing the effects of the human immunodefieciency virus (HIV) in virulent stages of infections. The most promising agents of this class of drugs

are 3′-deoxy DNA nucleosides or analogues thereof, capable of undergoing 5-phosphorylation by host Kinase, but teleologically incapable of DNA chain continuation. 3′-Azido-3′-deoxythymidine (*AZT*), the prototype of the class, was the first drug receiving wide clinical usage. Despite its efficacy [3, 4] *AZT* suffers from serious disadvantages [4, 6]. Several other 2′,3′-dideoxy- and 2′,3′-unsaturated-2′,3′-dideoxynucleosides have shown promising in vitro activity [5, 7–12]. However, from the studies of Herdewijn et al. [8] it has become evident that not only a 3′-azido, but also a 3′-fluoro substituent is compatible with anti-HIV activity. In fact, 3′-deoxy-3′-fluorothymidine (*FT*) is more potent as inhibitor of HIV than *AZT* however, its toxicity deserves further investigation [13]. Moreover, other 3′-fluoro analogues demonstrate a selectivity against HIV that is quite comparable to that of their 3′-azido counterparts [14–16].

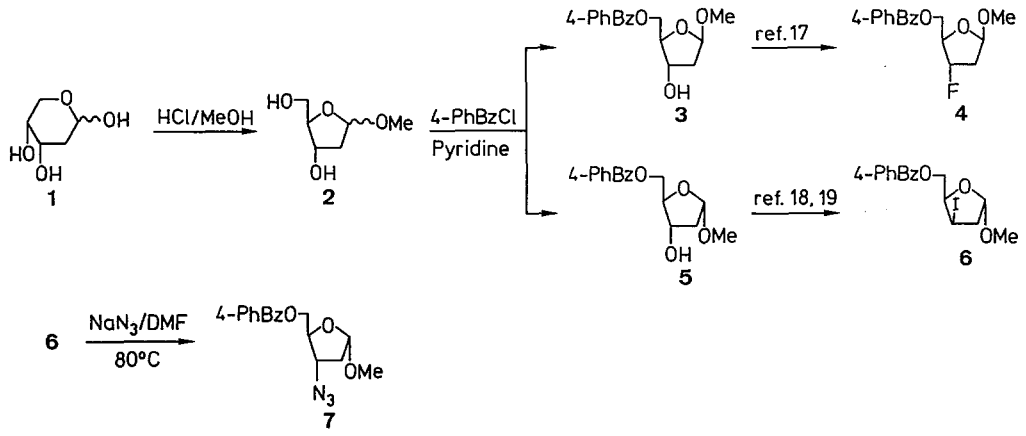
These clinical bindings and the urgent need for new selective antiretroviral drugs have prompted us to synthesize a series of 3′-azido and 3′-fluoro-2′,3′-dideoxy nucleoside analogues modified at the 5-position of the pyrimidine moiety which may produce a biologically active compound with an interesting activity against HIV. Therefore, it was of interest to prepare various Mannich bases of uracil and to synthesize their corresponding 3′-azido and 3′-fluoro-2′,3′-dideoxy nucleoside analogues to test them for their potential antiviral activity.

## Results and Discussion

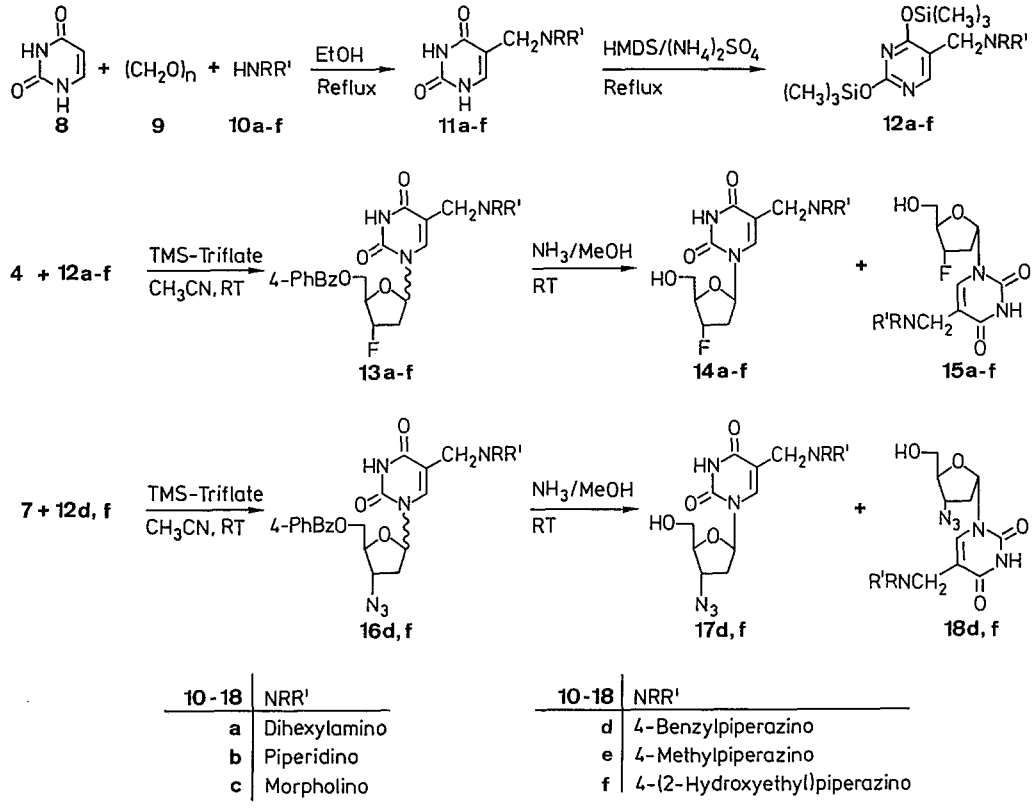
Recently, we have reported [17] the syntheses of methyl 2,3-dideoxy-3-fluoro-5-O-(phenylbenzoyl)-*β-D-erythro*-pentofuranside (**4**) as an intermediate suitable for elaboration to 3′-fluoro-2′,3′-dideoxy nucleosides. The fluoro derivative **4** was prepared from the *β*-anomer **3** by epimerisation of 3-OH, via oxidation and reduction, followed by reaction with diethylaminosulfur trifluoride (*DAST*). Thus, our approach was to use the fluoro sugar **4** as a key intermediate, which can then be condensed with these heterocyclic bases.

The methyl 3-azido-2,3-dideoxy-5-O-(phenylbenzoyl)-*α-D-erythro*-pentofuranoside (**7**) was prepared in 4-steps from 2-deoxy-*D*-ribose (**1**) in 31% overall yield according to a reported [18] procedure, but using the 4-phenylbenzoyl group as the protecting group at the 5-position of the sugar [19] (Scheme 1). For the latter preparations we used the *α*-anomer **5**, unsuitable for preparation of the fluoro derivative **4**, to prepare the iodo derivative **6** from which the azido sugar **7** was obtained by reaction with sodium azide in *N*,*N*-dimethylformamide.

The Mannich bases **11a–f** were prepared according to previously reported procedures [20]. Uracil (**8**) was reacted with paraformaldehyde (**9**) and various secondary amines **10a–f** to give the corresponding 5-substituted dialkyl aminomethyluracils **11a–f** in 65–85% yields [21]. Then, the Mannich bases **11a–f** were silylated using hexamethyldisilazane (*HMDS*) and ammonium sulfate as catalyst [22] to give the corresponding silylated compounds **12a–f** which were used without further purification. Coupling of **4** and **7** with **12a–f** and **12d, f** in dry acetonitrile in the presence of the Lewis acid trimethylsilyl trifluoromethanesulfonate (*TMS*-triflate) as catalyst [23] afforded an anomeric mixture of the corresponding 3′-fluoro-2′,3′-dideoxy nucleoside **13a–f** and 3′-azido-2′,3′-dideoxy nucleoside **16d, f** after purification by column chromatography on silica.




**Scheme 1**




| 10-18 | NRR' |
|---|---|
| a | Dihexylamino |
| b | Piperidino |
| c | Morpholino |

| 10-18 | NRR' |
|---|---|
| d | 4-Benzylpiperazino |
| e | 4-Methylpiperazino |
| f | 4-(2-Hydroxyethyl)piperazino |

**Scheme 2**

For the 3′-fluoro nucleosides series, the $\alpha$:$\beta$ ratio varied for the different bases from 1:2 to 1:6; **13a** 1:4; **13b** 1:3; **13c** 1:2; **13d** 1:2; **13e** 1:2 and **13f** 1:6 as estimated from the $^{13}C$ NMR spectra of the crude products **13a–f**. Treatment of **13a–f** with saturated ammonia in deprotection of the 5′-OH group gave compounds **14a–f** in 24–27% yield and the corresponding $\alpha$-anomers **15a–f** in 0–13% yield after

**Table 1.** $^{13}$C-NMR data ($\delta$ in $CDCl_3$/*TMS*) of compounds **14a–f** and **15a–e**[a]

| C | **14a** | **14b** | **14c** | **14d** | **14e** | **14f**[b] | **15a** | **15b** | **15c** | **15d** | **15e**[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1′ | 87.7 | 86.1 | 86.7 | 86.4 | 87.0 | 84.1 | 86.9 | 86.7 | 86.8 | 86.9 | 88.50 |
| 2′ | 38.1 | 38.9 | 38.2 | 38.3 | 38.3 | 37.1 | 39.6 | 39.6 | 39.6 | 39.7 | 40.5 |
| | (20.4) | (20.9) | (20.6) | (20.7) | (20.7) | (19.5) | (20.6) | (20.1) | (20.8) | (20.0) | (20.8) |
| 3′ | 94.4 | 94.5 | 94.4 | 94.4 | 94.7 | 94.8 | 94.2 | 94.3 | 94.4 | 94.5 | 95.8 |
| | (177.4) | (176.9) | (177.1) | (177.1) | (176.1) | (174.0) | (176.9) | (176.0) | (175.6) | (176.0) | (174.8) |
| 4′ | 85.7 | 86.0 | 85.5 | 85.5 | 85.7 | 85.9 | 87.8 | 87.9 | 87.9 | 87.9 | 89.5 |
| | (24.3) | (24.5) | (24.4) | (24.2) | (24.2) | (22.6) | (22.5) | (22.6) | (20.9) | (22.1) | (22.1) |
| 5′ | 62.0 | 61.5 | 61.9 | 61.8 | 62.1 | 60.8 | 62.3 | 62.1 | 62.2 | 62.3 | 62.8 |
| | (11.1) | (10.8) | (10.7) | (10.9) | (11.1) | (10.1) | (11.3) | (11.6) | (11.3) | (11.6) | (6.0) |
| 2 | 150.1 | 150.1 | 150.3 | 150.3 | 150.8 | 150.1 | 150.6 | 150.6 | 150.6 | 150.7 | 152.4 |
| 4 | 163.3 | 163.8 | 163.5 | 163.6 | 164.0 | 163.0 | 163.7 | 164.0 | 163.8 | 163.8 | 166.2 |
| 5 | 111.2 | 106.3 | 109.9 | 109.9 | 110.3 | 109.5 | 111.4 | 108.4 | 109.8 | 110.0 | 110.2 |
| 6 | 140.4 | 143.0 | 140.1 | 139.7 | 139.9 | | 138.4 | 139.9 | 138.4 | 138.6 | 140.4 |
| $CH_2N$ | 49.2 | 52.2 | 53.1 | 52.5 | 53.0 | 52.6 | 49.5 | 53.2 | 53.5 | 53.2 | 54.0 |

[a] Values in parentheses refer to C–F coupling constants in Hz

[b] In *DMSO-$d_6$*

[c] In $CD_3OD$

separation by using column chromatography on silica gel. In the case of **14e, f** and **15e, f** where chromatographic separation proved difficult, reversed phase HPLC was used instead. However, it was not possible to isolate the α-anomer **15f** due to the low yield of this anomer. For the 3′-azido-nucleoside series, the α:β ratio was 1:1, as estimated from the $^{13}C$ NMR spectra of the crude products **16d, f**. Treatment of **16d** with saturated ammonia gave compound **17d** in 22% and the corresponding α-anomer **18d** in 24% yield after separation by column chromatography on silica gel. In the case of **16f** it was not possible to separate the deprotected anomeric mixture **17f** + **18f**, which was obtained in 35% yield.

The assignment of the anomeric configuration was made by $^1H$ NMR spectra: the anomeric protons of the α-anomers were observed further downfield than those of the corresponding β-anomers. Furthermore, the H-4′ proton of the α-anomers appears downfield from that observed for the β-anomers, and the H-5′ protons of the α-anomers appear upfield from those observed for the β-anomers [24, 25] (see Exp.). The structures of the new products were confirmed by mass, $^1H$ NMR, $^{13}C$ NMR spectroscopy and elemental analysis (experimental and for $^{13}C$ NMR data, see Table 1).

The compounds **14b–e**, **15b–d** and the mixture of **17f** and **18f** did not show any significant activity at 100 $\mu M$ against Herps 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 any activity at 100 $\mu M$ against HIV-1 (strain HTLV-IIIB) in MT-4 cells. MT-4 cells were incubated with virus, washed and added in a proportion of 1:10 to uninfected MT-4 cells which had been preincubated in test compound containing culture medium (RPM 1640 containing 10% FCS) for 2 h. The MT-4 cells were maintained in culture medium likewise containing the test compound. Expression of HIV in culture medium was quantitated by HIV antigen detection ELISA [26]. Compound **14a** showed toxicity against SIRC at 100 $\mu M$ and MT-4 at 50 $\mu M$. At 10 $\mu M$ activity was neither observed against HIV-1 nor HSV-1.

## Experimental Part

The C,H,N-analyses of **11a, d, e, f** and **7**, and the high resolution mass spectral data ($M^+$) for **14e, f**, **17d**, **18d**, and **17f** + **18f** were in good agreement with the proposed molecular masses.

*5-(Dihexylaminomethyl)uracil* [**11a**; $C_{17}H_{31}N_3O_2$]

A mixture of uracil (**8**) (5.4 g, 48 mmol), paraformaldehyde (**9**) (2.4 g, 81 mmol) and *n*-dihexylamine (**10a**) (15.3 g, 83 mmol) in 1,2-dimethoxyethane (600 ml) was heated at 80 °C for 14 h. The reaction mixture was cooled and the insoluble material was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was chromatographed on silica gel (150 g, 0.040–0.063 mm) with $CH_2Cl_2$/*Me*OH (24:1 *v/v*) as eluent to give 9.8 g (66%) as needles from ethanol. M.p. 134–136 °C; $^1H$-NMR (*DMSO-d*$_6$) δ 0.85 (6H, t, $J$ = 6.4Hz, 2 × $CH_3$), 1.23 (16H, s, 2 × $(CH_2)_4$), 1.34 (4H, m, 2 × $CH_2$), 2.32 (4H, t, $J$ = 6.8Hz, $N(CH_2)_2$), 3.14 (2H, s, $CH_2N$), 7.20 (1H, s, H-6), 10.87 (1H, br s, NH). $^{13}C$-NMR (*DMSO-d*$_6$) δ 13.8 ($CH_3$), 22.0 ($CH_2$), 26.4 ($CH_2$), 26.7 ($CH_2$), 31.1 ($CH_2$), 48.9 ($CH_2N$), 53.2 (N–$CH_2$), 109.7 (C-5), 139.0 (C-6), 151.1 (C-2), 164.2 (C-4); MS, *m/z* 309 ($M^+$, 0.76).

*General Procedure for* **11b–f**

A mixture of uracil (**8**) (5.6 g, 50 mmol), paraformaldehyde (**9**) (1.7 g, 57 mmol) and the corresponding amine **10b–f** (50 mmol) in ethanol (500 ml) was refluxed for 24 h. The reaction mixture was filtered while it was hot to remove any insoluble material. The filtrate was concentrated under reduced pressure and the residue treated with hot acetone. The white solid obtained was filtered off and washed several times with hot acetone and dried. Recrystallization from ethanol gave pure products **11b–f** in 65–85% yield.

*5-(Piperidinomethyl)uracil* (**11b**)

Yield 7.8 g (75%); M.p. > 350 °C (Lit. [20] M.p. > 350 °C); $^1$H-NMR (*DMSO-d*$_6$) $\delta$ 1.40 (6H, m, 3 × $CH_2$), 2.30 (4H, t, $J$ = 5.1Hz, $N(CH_2)_2$), 3.05 (2H, s, $CH_2N$), 7.22 (1H, s, H-6), 10.87 (1H, s, NH); $^{13}$C-NMR (*DMSO-d*$_6$) $\delta$ 23.8 ($CH_2$), 25.5 ($CH_2$), 53.1 ($CH_2N$), 53.5 (N–$CH_2$), 108.2 (C-5), 139.7 (C-6), 151.2 (C-2), 164.2 (C-4).

*5-(Morpholinomethyl)uracil* (**11c**)

Yield 6.9 g (65%); M.p. 216–218 °C (Lit. [20] M.p. 217 °C); $^1$H-NMR (*DMSO-d*$_6$) $\delta$ 2.34 (4H, t, $J$ = 4.4 Hz; $N(CH_2)_2$), 3.10 (2H, s, $CH_2N$), 3.55 (4H, t, $J$ = 4.4Hz, $(CH_2)_2O$), 7.30 (1H, s, H-6), 10.83 (1H, br s, NH); $^{13}$C-NMR (*DMSO-d*$_6$) $\delta$ 52.7 (N–$CH_2$), 52.9 ($CH_2N$), 66.1 ($CH_2O$), 107.5 (C-5), 140.3 (C-6), 151.2 (C-2), 164.2 (C-4).

*5-(4-Benzylpiparazinomethyl)uracil* [**11d**; $C_{16}H_{20}N_4O_2$]

Yield 12.8 g (85%); M.p. 234 °C; $^1$H-NMR (*DMSO-d*$_6$) $\delta$ 2.36 (8H, m, $N(CH_2CH_2)_2$), 3.11 (2H, s, $CH_2N$), 3.44 (2H, s, N–$CH_2$*Ph*), 7.26 (1H, s, H-6), 7.28 (5H, m, phenyl), 10.93 (2H, br s, NH); $^{13}$C-NMR (*DMSO-d*$_6$) $\delta$ 52.1 ($CH_2$), 52.4 ($CH_2N$), 52.4 ($CH_2$), 61.9 ($CH_2$*Ph*), 107.8 (C-5), 126.6, 127.9, 128.5, 138.1 (phenyl), 139.9 (C-6), 151.1 (C-2), 164.1 (C-4); MS, *m/z* 300 ($M^+$, 2.1).

*5-(4-Methylpiperazinomethyl)uracil* [**11e**; $C_{10}H_{16}N_4O_2 \cdot H_2O$]

Yield 8.85 g (79%); M.p. 215–216 °C; $^1$H-NMR (*DMSO-d*$_6$) $\delta$ 2.23 (3H, s, $CH_3$), 2.43 (8H, s, 4 × $CH_2$), 3.17 (2H, s, $CH_2$), 7.38 (1H, s, H-6); $^{13}$C-NMR (*DMSO-d*$_6$) $\delta$ 45.5 ($CH_3$), 52.0 (2 × $CH_2$); 52.4 (2 × $CH_2$); 54.6 ($CH_2$), 107.9 (C-5), 139.7 (C-6), 150.9 (C-2), 163.9 (C-4); MS, *m/z* 224 ($M^+$, 10).

*5-[4-(2-Hydroxyethyl)piperazinomethyl]uracil* [**11f**; $C_{11}H_{18}N_4O_3 \cdot 0.5\ H_2O$]

Yield 9.93 g (78%); M.p. 194–196 °C; $^1$H-NMR (*DMSO-d*$_6$) $\delta$ 2.63 (10H, s, 5 × $CH_2$), 3.23 (2H, s, $CH_2$), 3.50 (3H, t, $J$ = 6.15Hz, $CH_2O$), 7.32 (1H, s, H-6); $^{13}$C-NMR (*DMSO-d*$_6$) $\delta$ 52.18 (2 × $CH_2$), 52.40 (2 × $CH_2$), 53.08 ($CH_2$), 58.34, 60.11 (–$CH_2$–$CH_2$), 107.75 (C-5), 139.83 (C-6), 150.95 (C-2), 163.97 (C-4); MS, *m/z* 254 ($M^+$, 1.7).

*Methyl 3-Azido-2,3-dideoxy-5-O-(4-phenylbenzoyl)-α-D-erythro-pentofuranoside* [**7**; $C_{19}H_{19}N_3O_4$]

A mixture of **6** [19] (3.75 g, 8.56 mmol) and $NaN_3$ (5.56 g, 85.6 mmol) in *DMF* (100 ml) was heated overnight at 75–80 °C. The reaction mixture was allowed to cool to room temperature and then added slowly to ice-water (200 ml) with vigorous stirring. The aqueous solution was extracted with $CHCl_3$ (2 × 100 ml) and the organic phases were evaporated to dryness in vacuo. Chromatographic purification on silica gel with $Et_2O$/petroleum ether b.p. 60–80 °C (1:4) gave **7** as a pale yellow oil. Yield 2.23 g (74%); $^1$H-NMR ($CDCl_3$) $\delta$ 2.2–2.4 (2H, m, H-2), 3.40 (3H, s, $OCH_3$), 4.22–4.29 (1H, m,

H-3), 4.37–4.44 (1H, m, H-4); 4.49–4.64 (2H, m, H-5), 5.18–5.21 (1H, dd, $J_{1-2a} = 1.8$ Hz, $J_{1-2b} = 5.0$ Hz, H-1), 7.36–8.14 (9H, m, *PhBz*); $^{13}$C-NMR ($CDCl_3$) $\delta$ 39.22 (C-2), 55.33 ($OCH_3$), 61.77 (C-3), 63.05 (C-5), 77.00 (C-4), 103.96 (C-1), 126.98, 127.16, 128.08, 128.47, 128.82, 130.13, 139.85, 145.79 (phenylbenzoyl), 165.97 (C=O); MS, *m/z* 353 ($M^+$, 2); IR (KBr): 2106 $cm^{-1}$ ($N_3$).

*2',3'-Dideoxy-3'-fluoro-uridines* **14a–f** *and Their α-Anomers* **15a–f**. *General Procedure*

A mixture of the 5-dialkylaminomethyl uracil **11a–f**. (4 mmol), $(NH_4)_2SO_4$ (30 mg) and hexamethyldisilazane (20 ml) was refluxed for 7 h. The solvent was removed under reduced pressure to dryness and the resulting oily residue of compounds **12a–f** was then dissolved in dry *Me*CN (50 ml), cooled to $-20$ °C and a solution of the fluoro sugar **4** (1 g, 3 mmol) in dry *Me*CN (30 ml) was added. A solution of trimethylsilyl trifluoromethanesulfonate (1.5 ml, 8 mmol) in dry *Me*CN (20 ml) was added dropwise to the mixture under a nitrogen atmosphere and the mixture was stirred at $-20$ °C for 30 min. Then the temperature was allowed to raise to room temperature and stirring was continued for 2.5 h. The mixture was diluted with methylene chloride (200 ml), washed with a cold saturated aqueous solution of $NaHCO_3$ (150 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 (50 g, 0.40–0.063 mm) with $CH_2Cl_2$/*Me*OH (95:5 *v/v*) to obtain the anomeric mixture of compounds **13a–f**. The compound **13a–f** was then dissolved in saturated solution of ammonia in methanol (100 ml) and stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel (30 g, 0.040–0.063 mm) with the eluent $CH_2Cl_2$/*Me*OH (95:5 *v/v*) to separate the β-anomers **14a–f** and the α-anomers **15a–e**. For separation of **14c** and **15c**, the eluent $CH_2Cl_2$/*Et*OH (95:5 *v/v*) was used.

*2',3'-Dideoxy-5-(dihexylaminomethyl)-3'-fluorouridine* (**14a**)

The less polar zone, reddish syrup: Yield 350 mg (27%); $^1$H-NMR ($CDCl_3$) $\delta$ 0.88 (6H, t, $J = 6.6$ Hz, 2 × $CH_3$), 1.24 (16H, s, 2 × $(CH_2)_4$),1.48 (4H, m, 2 × $CH_2$), 2.53 (6H, m, H-2'β, H-2'α and $N(CH_2)_2$), 3.80 (1H, dd, $J_{5',5'} = 12.3$, $J_{4',5'} = 2.2$Hz, H-5'), 3.93 (1H, dd, $J_{5',5'} = 12.3$, $J_{4',5'} = 1.0$Hz, H-5'), 4.32 (1H, m, $J_{F,H\text{-}4'} = 27.8$Hz, H-4'), 4.93 (br s, 5'-OH), 5.33 (1H, m, $J_{F,H\text{-}3'} = 54.2$Hz, H-3'), 6.20 (1H, dd, $J_{1',2'\alpha} = 8.9$, $J_{1',2'\beta} = 5.8$Hz, H-1'), 7.89 (1H, s, H-6); MS, *m/z* 427 ($M^+$, 2), 356 (14), 224 (13), 184 (21), 125 (11), 114 (100).

*1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuransoyl)-5-(dihexylaminomethyl)uracil* (**15a**)

Colorless syrup: Yield 80 mg (6%); $^1$H-NMR ($CDCl_3$) $\delta$ 0.87 (6H, t, $J = 6.5$Hz, 2 × $CH_3$), 1.26 (16H, s, 2 × $(CH_2)_4$), 1.46 (4H, m, 2 × $CH_2$), 2.49 (6H, m, H-2'β, H-2'α and $N(CH_2)_2$), 3.42 (2H, s, $CH_2N$), 3.73 (2H, m, H-5'), 4.67 (1H, m, $J_{F,H\text{-}4'} =$ 24.2Hz, H-4'), 5.29 (1H, m, $J_{F,H\text{-}3'} = 54.3$Hz, H-3'), 6.42 (1H, d, $J = 6.8$Hz, H-1'), 7.74 (1H, s, H-6); MS, *m/z* 427 ($M^+$, 5), 356 (76), 224 (55), 184 (100), 125 (64), 114 (32).

*2',3'-Dideoxy-3'-fluoro-5-(piperidinomethyl)uridine* (**14b**)

The less polar zone, orange gum: Yield 250 mg (25%); $^1$H-NMR ($CDCl_3$) $\delta$ 1.56 (2H, m, H-4'' of piperidine), 1.76 (4H, m, H-3'' of piperidine), 2.34 (1H, m, H-2'β), 2.62 (1H, m, H-2'α), 2.83 (4H, m, $N(CH_2)_2$), 3.64 (2H, s, $CH_2N$), 3.79 (1H, dd, $J_{5',5'} = 12.5$, $J_{4',5'} = 1.9$Hz, H-5'), 3.97 (1H, dd, $J_{5',5'} = 12.5$, $J_{4',5'} = 0.9$Hz, H-5'), 4.32 (1H, m, $J_{F,H\text{-}4'} = 27.9$Hz, H-4'), 5.30 (3H, m, $J_{F,H\text{-}3'} = 54.7$Hz, H-3' and 5'-OH), 6.32 (1H, dd, $J_{1',2'\alpha} = 9.1$, $J_{1',2'\beta} = 5.4$Hz, H-1') 8.28 (1H, s, H-6); MS, *m/z* 327 ($M^+$, 8); 209 (15); 84 (100).

*1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-5-(piperidinomethyl)uracil* (**15b**)

Orange gum: Yield 100 mg (10%); $^1$H-NMR ($CDCl_3$) $\delta$ 1.48 (2H, m, H-4″ of piperidine), 1.65 (4H, m, H-3″ of piperidine), 2.60 (6H, m, H-2′$\beta$, H-2′$\alpha$ and $N(CH_2)_2$), 3.41 (2H, s, $CH_2N$); 3.65 (2H, m, H-5′), 4.73 (1H, m, $J_{F,H\text{-}4'} = 24.1$Hz, H-4′), 5.28 (1H, m, $J_{F,H\text{-}3'} = 54.1$Hz, H-3′), 6.36 (1H, d, $J =$ 6.9Hz, H-1′), 7.73 (1H, s, H-6); MS, *m/z* 327 ($M^+$, 10), 209 (16), 84 (100).

*2′,3′-Dideoxy-3′-fluoro-5-(morpholinomethyl)uridine* (**14c**)

The less polar zone, orange gum: Yield 270 mg (27%); $^1$H-NMR ($CDCl_3$) $\delta$ 2.46 (6H, m, H-2′$\beta$, H-2′$\alpha$ and $N(CH_2)_2$), 3.30 (2H, s, $CH_2N$), 3.81 (6H, m, H-5′ and $O(CH_2)_2$), 4.32 (1H, m, $J_{F,H\text{-}4'} = 27.5$Hz, H-4′), 5.32 (1H, m, $J_{F,H\text{-}3'} = 54.0$Hz, H-3′), 6.27 (1H, dd, $J_{1',2'\alpha} = 8.9$, $J_{1',2'\beta} = 5.6$Hz, H-1′), 7.82 (1H, s, H-6); MS, *m/z* 329 ($M^+$, 22), 211 (22), 153 (43), 86 (100).

*1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-5-(morpholinomethyl)uracil* (**15c**)

Orange gum: Yield 130 mg (13%); $^1$H-NMR ($CDCl_3$) $\delta$ 2.67 (6H, m, H-2′$\beta$, H-2′$\alpha$ and $N(CH_2)_2$), 3.30 (2H, q, $J = 7.2$Hz, $CH_2N$), 3.58 (6H, m, H-5′ and $O(CH_2)_2$), 4.66 (1H, m, $J_{F,H\ 4'} = 24.4$Hz, H-4′), 5.29 (1H, m, $J_{F,H\text{-}3'} = 54.1$Hz, H-3′), 6.41 (1H, d, $J = 6.5$Hz, H-1′), 7.57 (1H, s, H-6); MS, *m/z* 329 ($M^+$, 14), 211 (8), 153 (20), 86 (100).

*5-(4-Benzylpiperazinomethyl)-2′,3′-dideoxy-3′-fluoro-uridine* (**14d**)

Yield 330 mg (26%); M.p. 104–106 °C; $^1$H-NMR ($CDCl_3$) $\delta$ 2.41 (10H, m, H-2′$\beta$, H-2′$\alpha$ and $N(CH_2CH_2)_2$), 3.37 (2H, s, $CH_2N$), 3.51 (2H, s, N–$CH_2$–*ph*), 3.78 (2H, m, H-5′), 4.30 (1H, m, $J_{F,H\text{-}4'} = 27.5$Hz, H-4′), 5.29 (1H, m, $J_{F,H\text{-}3'} = 54.0$Hz, H-3′), 6.27 (1H, dd, $J_{1',2'\alpha} = 8.9$, $J_{1',2'\beta} = 5.6$Hz, H-1′), 7.26 (5H, m, phenyl), 7.85 (1H, s, H-6), MS, *m/z* 418 ($M^+$, 2) 176 (34), 134 (100), 91 (54).

*5-(4-Benzylpiperazinomethyl)-1-(2,3-dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)uracil* (**15d**)

Yield 100 mg (8%); M.p. 84–86 °C; $^1$H-NMR ($CDCl_3$) $\delta$ 2.55 (10H, m, H-2′$\beta$, H-2′$\alpha$ and $N(CH_2CH_2)_2$), 3.26 (2H, m, H-5′), 3.51 (2H, s, $CH_2N$), 3.68 (2H, s, N–$CH_2$–*ph*), 4.63 (1H, m, $J_{F,H\text{-}4'} = 24.1$Hz, H-4′), 5.26 (1H, m, $J_{F,H\text{-}3'} = 56.2$Hz, H-3′), 6.38 (1H, d, $J = 6.8$Hz, H-1′), 7.28 (5H, m, phenyl), 7.53 (1H, s, H-6), MS, *m/z* 418 ($M^+$, 36), 175 (100), 134 (65), 91 (64).

*2′,3′-Dideoxy-3′-fluoro-5-(4-methylpiperazinomethyl)uridine* [**14e**; $C_{15}H_{23}FN_4O_4$ (MS)]

Yield 225 mg (27%); M.p. 110–113 °C, $^1$H-NMR ($CDCl_3$) $\delta$ 2.27 (3H, s, $CH_3$), 2.35 (2H, m, H-2′$\beta$ and H-2′$\alpha$), 2.54 (8H, m, $N(CH_2CH_2)_2$), 3.12 (2H, s, $CH_2N$), 3.85 (2H, m, H-5′), 4.32 (1H, m, $J_{F,H\text{-}4'} =$ 27.4 Hz H-4′), 5.31 (1H, m, $J_{F,H\text{-}3'} = 54.0$Hz, H-3′), 6.27 (1H, dd, $J_{1',2'\alpha} = 8.8$, $J_{1',2'\beta} = 5.8$Hz, H-1′), 7.80 (1H, s, H-6); MS, *m/z*: 342 ($M^+$, 20), 153 (47), 100 (37), 99 (100).

*1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-5-(4-methylpiperazinomethyl)uracil* (**15e**).

$^1$H-NMR ($CD_3OD$) $\delta$ 2.30 (3H, s, $CH_3$), 2.54 (8H, m, $N(CH_2CH_2)_2$), 2.67 (2H, m, H-2′$\beta$ and H-2′$\alpha$), 3.36 (2H, s, $CH_2N$), 3.68 (2H, m, H-5′), 4.72 (1H, m, $J_{F,H\text{-}4'} = 24.6$Hz, H-4′), 5.33 (1H, $J_{F,H\text{-}3'} =$ 54.1Hz, H-3′), 6.31 (1H, H-1′), 7.68 (1H, s, H-6).

*2′,3′-Dideoxy-3′-fluoro-5-[4-(2-hydroxyethyl)piperazinomethyl]uridine* [**14f**; $C_{16}H_{25}FN_4O_5$ (MS)]

Yield 270 mg (24%); M.p. 140–143 °C; $^1$H-NMR (*DMSO-$d_6$*) $\delta$ 1.80 (2H, s, $CH_2CH_2O$), 2.36 (8H, m,

$N(CH_2CH_2)_2$), 2.48 (2H, m, H-2′β and H-2′α), 3.13 (2H, s, $CH_2N$), 3.46 (2H, t, $J = 6.2$Hz, $CH_2OH$), 3.60 (2H, m, H-5′), 4.18 (1H, m, $J_{F,H\text{-}4'} = 27.3$ Hz, H-4′), 5.33 (1H, m, $J_{F,H\text{-}3'} = 53.8$Hz, H-3′), 6.23 (1H, dd, $J_{1',2'\alpha} = 8.2$, $J_{1',2'\beta} = 5.4$Hz, H-1′), 7.78 (1H, s, H-6); MS, *m/z* 372 ($M^+$, 2), 223 (12), 112 (14), 100 (18), 99 (100).

*5-Dialkylaminomethyl-3′-azido-2′,3′-dideoxyuridines* **17d, f** *and Their α-Anomers* **18d, f.**
*General Procedure*

The appropriate 5-dialkylaminomethyluracil **11d, f** (2.12 mmol) was silylated by heating with excess hexamethyldisilazane (*HMDS*) (15 ml) at 160 °C for 4 h in the presence of $(NH_4)_2SO_4$ (50 mg). The excess *HMDS* was removed by co-distillation with 2 × 50 ml portions of dry toluene leaving **12d, f** as an oily residue. To a solution of the silylated nucleobase **12d, f** and **7** (0.5 g, 1.4 mmol) in dry *Me*CN (50 ml) was added trimethylsilyl trifluoromethanesulfonate (0.4 ml, 2.1 mmol). The resulting solution was stirred at room temperature overnight, diluted with $CH_2Cl_2$ (125 ml). Washed with saturated $NaHCO_3$ (2 × 100 ml) and water (2 × 150 ml) and dried over $Na_2SO_4$. The solvent was evaporated in vacuo and the residual syrup purified by silica gel chromatography with $CHCl_3$/*Me*OH (95:5 *v/v*) to give an anomeric mixture of **16d, f**. **16d, f** was suspended in saturated ammonia in methanol (50 ml) and stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was chromatographed on silica (2 × 30 cm; 40 g) with $CHCl_3$/*Et*OH (90:10 *v/v*) to obtain the deprotected nucleosides **17d** and **18d**. It was not possible to separate the anomers **17f** and **18f**.

*3-Azido-5-(4-benzylpiperazinomethyl)-2′,3-dideoxy-uridine* [**17d**; $C_{21}H_{27}N_7O_4$ (MS)]

Yield 135 mg (22%); M.p. 152–154 °C; $^1$H-NMR ($CD_3OD$) δ 2.31 (1H, m, H-2′a), 2.63 (8H, br s, 4 × $CH_2$), 2.86 (1H, m, H-2′b), 3.40 (2H, s, $CH_2N$), 3.62 (2H, s, N–$CH_2$*Ph*), 3.98 (2H, d, $J = 5.9$Hz, H-5′), 4.24 (1H, m, H-4′), 4.49 (1H, m, H-3′), 4.91 (1H, br s, 5′-OH), 6.22 (1H, dd, $J_{1',2'} = 7.7$Hz, $J_{1',2'} = 2.6$Hz, H-1′), 7.38 (5H, m, phenyl), 7.94 (1H, s, H-6); $^{13}$C-NMR ($CD_3OD$) δ 39.50 (C-2′), 53.32 (N–$CH_2$, piperazine), 53.55 (N–$CH_2$, piperazine), 53.83 ($CH_2N$), 61.34 (C-3′), 62.43 (–N–$CH_2$), 63.88 (C-5′), 84.73 (C-4′), 86.26 (C-1′), 110.18 (C-5), 128.45, 129.31, 130.73, 138.16 (phenyl), 140.77 (C-6), 152.05 (C-2), 165.68 (C-4); MS, *m/z* 441 ($M^+$, 0.6); IR (KBr): 2113 $cm^{-1}$ ($N_3$).

*1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-(4-benzylpiperazinomethyl)uracil*
[**18d**, $C_{21}H_{27}N_7O_4$ (MS)]

Yield 147 mg (24%); M.p. 120–121 °C; $^1$H-NMR ($CD_3OD$) δ 2.65 (10H, br s, H-2a, H-2b, 4 × $CH_2$), 3.41 (2H, s, $CH_2N$), 3.64 (2H, s, N–$CH_2$–*Ph*), 3.84 (2H, d, $J = 5.2$Hz, H-5′), 4.56 (2H, m, H-3′ and H-4′), 5.01 (1H, br s, 5′-OH), 6.20 (1H, t, $J = 6.7$Hz, H-1′), 7.40 (5H, m, phenyl), 7.74 (1H, s, H-6); $^{13}$C-NMR ($CD_3OD$) δ 39.26 (C-2′), 53.05 (N–$CH_2$, piperazine), 53.42 (N-$CH_2$, piperazine), 53.65 ($CH_2N$), 61.80 (C-3′), 63.7 (C-5′ and N–$CH_2$*Ph*), 84.62 (C-4′), 88.14 (C-1′), 110.29 (C-5), 128.60, 129.39, 130.85, 137.75 (phenyl), 141.91 (C-6), 151.98 (C-2), 165.85 (C-4); MS, *m/z* 441 ($M^+$, 8); IR (KBr): 2108 $cm^{-1}$ ($N_3$).

*1-(3-Azido-2,3-dideoxy-α,β-D-erythro-pentofuranosyl)-5-(4-(2-hydroxethyl)piperazinomethyl)uracil*
[**17f** + **18f**; $C_{16}H_{27}N_7O_5$ (MS)]

Yield 193 mg (35%); $^1$H-NMR ($CD_3OD$) δ 2.47 (1H, m, H-2′a (β)), 2.6–2.85 (19H, m, 8 × $CH_2$, H-2′b (β), H-2′a (α), H-2′b (α)), 3.34 (4H, m, 2 × $CH_2N$), 3.63–4.45 (12H, m, H-3′ (α), H-3′ (β), H-4′ (α), H-4′ (β), H-5′ (α), H-5′ (β), $CH_2OH$ (α) and $CH_2OH$ (β)), 4.90 (2H, br s, 5′-OH (α) and 5′-OH (β)), 6.20 (2H, m, H-1′(α) and H-1′ (β)), 7.78 (1H, s, H-6 (α)), 8.03 (1H, s, H-6 (β)); $^{13}$C-NMR ($CD_3OD$) δ 38.5, 38.9 (C-2′), 52.9, 53.0, 54.1, 54.2 (N–$CH_2$, piperazine), 59.5, 61.0, 61.5, 62.3, 62.7, 63.4 (C-3′, C-5′,

N–$CH_2$–$CH_2$OH), 86.1, 86.3 (C-1′ ($\beta$), C-4′), 88.4 (C-1′ ($\alpha$)), 110.4, 110.1 (C-5), 141.0, 141.6 (C-6), 152.1 (C-2), 165.7, 165.8 (C-4); MS, *m/z* 395 ($M^+$, 2); IR (KBr): 2110 $cm^{-1}$ ($N_3$).

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