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Synthesis of 3′-Deoxy-3′-fluoro and -3′-amino Nucleosides from 2-Methylthiopyrimidin-4(1*H*)-ones

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Summary. Methyl 2,3-dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-*β-D-erythro*-pentofuranoside (**3**) as well as 1,5-di-O-acetyl-2,3-dideoxy-3-phthalimodo-*β-D-erythro*-pentofuranose (**12**) were condensed with silylated 2-methylthiopyridin-4(1*H*)-ones **2a, b** in the presence of trimethylsilyl triflate as a catalyst to produce the corresponding nucleosides **5, 6, 13**. In these reactions, an endocyclic cleavage of C–O in **3** took place; therefore, acyclic nucleosides **4a, b** were also formed. All 3′-fluoro nucleosides were deprotected with NH_3/MeOH; the 3′-phthalimido nucleosides were deprotected with methylamine in ethanol. The latter method resulted in a concomitant substitution reaction in the pyrimidine moiety with replacement of the methylthio group. The 2-methylthio analogue of 3′-deoxy-3′-fluorothylmidine showed moderate activity against HIV-1.

Keywords. Nucleosides, convergent synthesis of; Nucleosides, 2′,3′-dideoxy-3′-fluoro; Nucleosides, 2′,3′-dideoxy-3′-amino; 2-Methylthiopyridin-4(1*H*)-one nucleosides; Human immunodeficiency virus; Herpes simplex virus.

Synthese von 3′-Deoxy-3′-fluoro- und -3′-amino-nucleosiden aus 2-Methylthiopyrimidin-4(1*H*)-onen

Zusammenfassung. Methyl-2,3-didesoxy-3-fluoro-5-O-(4-phenylbenzoyl)-*β-D-erythro*-pentofuranosid (**3**) und 1,5-di-O-Acetyl-2,3-didesoxy-3-phthalimido-*β-D-erythro*-pentofuranose (**12**) wurden in Gegenwart von Trimethylsilyltriflat als Katalysator mit den silylierten 2-Methylthiopyridin-4(1*H*)-onen **2a, b** zu den entsprechenden Nucleosiden **5–6** und **13** kondensiert. Bei diesen Reaktionen tritt als Nebenreaktion eine Öffnung der endocyclischen C–O – Bindung auf, sodaß auch die acyclischen Nucleoside **4a, b** gebildet werden. Die 3′-Fluoronucleoside wurden mit NH_3/MeOH entschützt, die 3′-Phthalimidonucleoside mit Methylamin in Ethanol. Letztere Reaktion resultierte in eine gleichzeitigen Substitution der Pyrimidineinheit unter Austausch der Methylthiogruppe. Das 2-Methylthioanalogon zu 3′-Desoxy-3′-fluorthymidin zeigt mäßige Aktivität gegen HIV-1.

Introduction

The onset of AIDS has presented many challenges to the medical and pharmaceutical professions. The most difficult one of these may prove to be the development of

drugs capable of preventing or reserving the neurological complications associated with AIDS [1,2]. There is evidence that the AIDS dementia complex is caused wholly or partially by direct HIV-1 infection of the brain; the virus frequently enters the central nervous system (CNS) early in the course of infection, even in asymphomatic victims [3]. To date it has become evident that not only 3′-azido-3′-deoxythymidine (*AZT*) but also 3′-deoxy-3′- fluorothymidine (*FLT*) are compatible with anti-HIV activity.

In fact, a 3′-fluoro substituent is a more potent inhibitor of HIV than *AZT*; however, its toxicity deserves further investigations [4]. Furthermore, other 3′-azido and 3′-fluoro analogues demonstrate a selectivity against HIV which is quite comparable to that of *AZT* [5–7]. Therefore, there is still a demand for compounds that are at least as active but less toxic than *AZT*. On the other hand, 3′-amino-3′-deoxythymidine has been reported as a potent tumor cell growth inhibitor [8–9].

We found it of great interest to synthesize a modification of different 3′-fluoro-as well as 3′-amino-3′-deoxynucleosides with a methylthio group in the 2-position of the pyrimidine moiety. Such compounds could be promising anti-HIV agents if they could be metabolized into the active compounds after cell uptake. Due to higher lipophilicity of the prodrug this could take place more easily, even into the central nervous system. For this purpose, we have investigated the possibility of condensing 2-methylthiopyrimidin-4(1*H*)-ones with an appropriate 3-fluoro [10] as well as a 3-phthalimido [11] sugar.

Results and Discussion

In this investigation we synthesized 2-methylthiopyrimidin-4(1*H*)-ones by the method of *Brown et al.* [12] and treated them according to Ref. [13] with 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) in the presence of a catalytic amount of ammonium sulfate at reflux temperature in order to obtain the silylated derivatives **2a, b**. These were condensed with methyl 2,3-dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-β-*D*-*erythro*-pentofuranoside (**3**) as well as with 1,5-di-O-acetyl-2,3-dideoxy-3-phthalimido-β-*D*-*erythro*-pentofuranose (**12**) in dry acetonitrile using trimethylsilyl trifluoromethanesulfonate (*TMS* triflate) as a catalyst according to the method given in Ref. [14]. After chromatographic work-up of the condensation products, the β anomers **5a, b** were obtained in 32–37% yield whereas the α anomer **6** was isolated in 18% yield. Acyclic nucleosides **4a, b** with the methoxy group intact were isolated in 33–37% yield from the same product mixture.

The formation of the acyclic nucleosides **4a, b** could be explained *via* an acyclic pentofuranosyl oxo-carbonium ion as reported previously [15]. It is assumed that an acyclic carbonium ion is easily formed at the anomeric carbon by an endocyclic cleavage of the C–O bond on treatment with *TMS* triflate. This carbonium ion reacts with the nucleobase under formation of an acyclic nucleoside of type **4** which can undergo ring closure with formation of the nucleosides **5** and **6** under the reaction conditions. The acyclic pathway in the case of 3-fluoro sugars is supported by the substantial amount of isolated aminal nucleoside **4**. In support of this mechanism, the ring closure of acyclic aminal nucleosides into normal nucleosides under acid conditions has been reported earlier [16].

During deprotection of the acyclic nucleoside **4a** at 5′-OH with ammonia in methanol, the methylthio group in the pyrimidine moiety is also susceptible to a nucleophilic substitution reaction and was replaced by a methoxy group. The ^{13}C NMR spectrum of the pyrimidine moiety of **7** resembled closely the one of the corresponding O^2-methyluridine [17]. This nucleophilic substitution reaction could also be the reason why upon deprotection of **5b** and **6** the methylthio derivatives **10** and **11** were obtained in low yields. When the uracil nucleoside **5a** was deprotected, it was not possible to detect the corresponding deprotected methylthio derivatives. The substituted reaction was followed by a demethylation reaction of the methoxy group affording 2′,3′-dideoxy-3′-fluorouridine (**9**) which has previously been synthesized *via* other routes [18, 19]. Another explanation for the formation of this compound could be hydrolysis by water in methanol.

The condensation of silylated 2-methylthiopyrimidin-4(1*H*)-ones **2a, b** with the phthalimido sugar [11, 22] **12** by the trimethylsilyl triflate method [14] in dry acetonitrile gave after chromatographic purification the anomeric mixture **13a, b** in 88% and 90% yield, respectively.

During the deprotection of the anomeric mixture **13a** at 3′-NH_2 and 5′-OH with a 33% solution of methylamine in absolute ethanol at reflux temperature for 2 hours, the products were observed as two spots on a TLC plate. After chromatographic separtion, the NMR spectra of the upper spot identified it as the β anomer **14** with the methylthio group intact, whereas the NMR spectra of the lower spot proved nucleophilic substitution of the methylthio group with methylamine to give the anomeric mixture of the N^2-methyl isocytidine derivatives **15** and **16** which was separated by HPLC (eluent: H_2O).

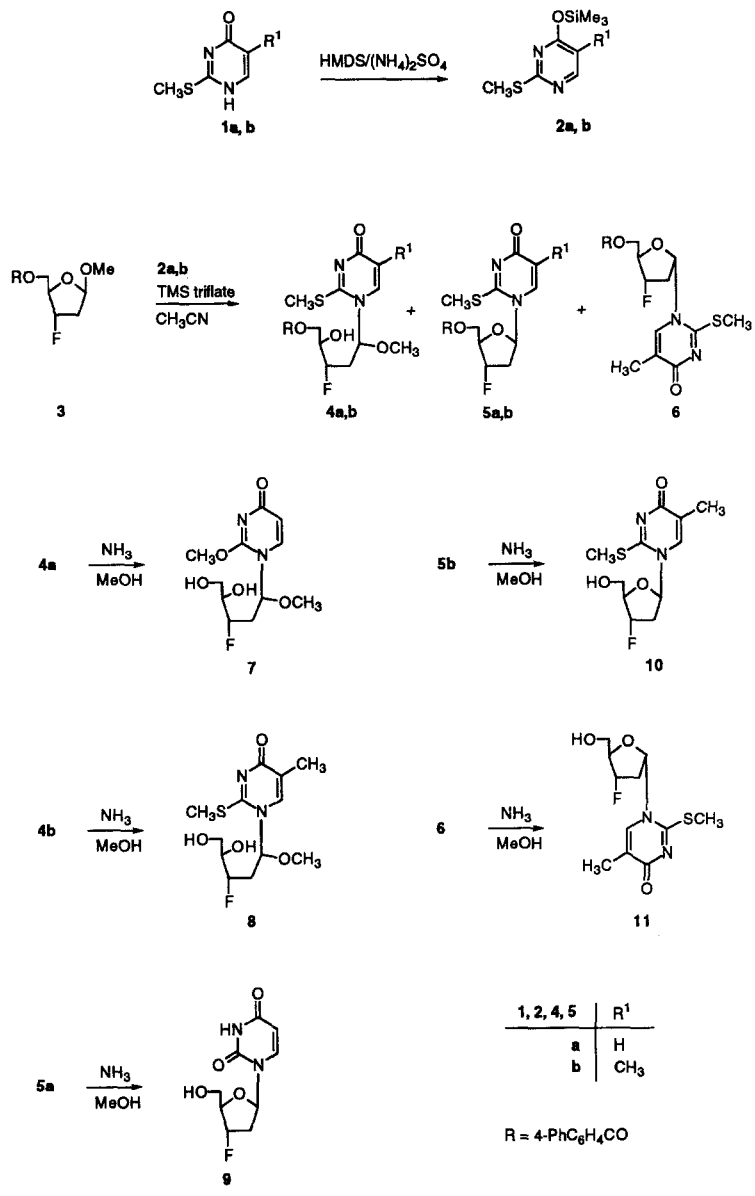
However, when deprotecting **13b**, the anomeric mixture **17**/**18** was obtained after 1 h still with the methylthio group intact without nucleophilic substitution. The anomeric mixture was separated by reversed phase HPLC using H_2O as eluent to give the nucleosides **17** and **18**.

The deprotection of **13b** using *n*-$BuNH_2$ at reflux temperature for 2 h affords **19** and **20** in good yields. However, if the time was extended to 8 h, the NMR spectra of the impure products indicated a complete deprotection (3′-NH_2, 3′-OH) and that a nucleophilic substitution reaction of the methylthio group had taken place. However, we were not successful in obtaining the pure products by reversed phase HPLC.

For both 3′-amino and 3′-fluoro nucleosides, it seems easier to obtain the nucleosides with an intact 2-methylthio group in the case of thymine, whereas for the uracil nucleosides the 2-methylthio group easily undergoes substitution with a nucleophile during the deprotection reaction. This difference is ascribed to the electron donating properties of the 5-methyl group in thymine retarding the nucleophilic substitution reacion on the pyrimidine ring.

The assignment of the anomeric configuration was achieved by ^1H NMR spectroscopy. The H-4′ proton of the α anomers appears downfield from that of the β anomers, and H-5′ of the α anomers appears upfield from H-5′ of the β anomers [10, 20, 21]. The ^{13}C NMR spectra of **4a,b**, **7**, and **8** showed the presence of a methoxy group at 56.6 ppm in accordance with the NMR data reported by *Jørgensen et al.* [15].

A moderate activity was found against HIV-1 for compound **10** which is the 2-methylthio analogue of *FLT*. The effective dose (ED_{50}) of achieving 50% reduction

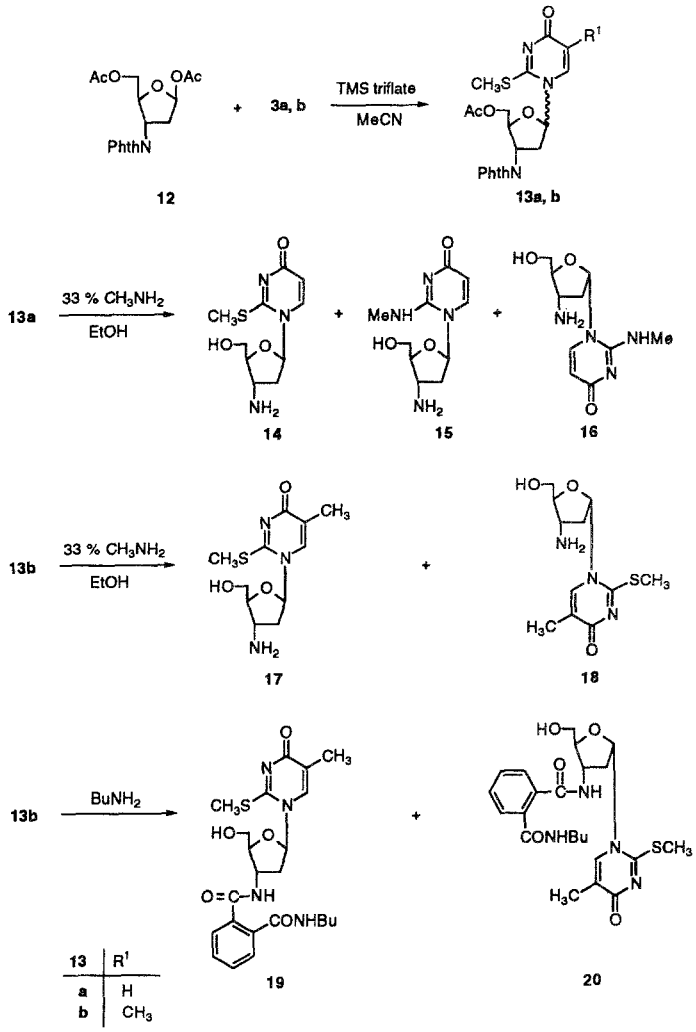


Scheme 1

of HIV anti-gene production in cultures of MT-4 cells was 19 μM which was considerably higher than the one found for *FLT* ($ED_{50} = 0.003\,\mu M$) in a control experiment. Compound **10** was found non toxic at 100 μM which was the highest concentration tested.

Experimental

Analytical silica gel TLC was performed on Merck precoated 60 F_{254} plates. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. NMR spectra were recorded on a Bruker AC-250 FT spectrometer at 250 MHz for ^1H NMR and 62.9 MHz for ^{13}C NMR; δ-values



Scheme 2

are in ppm relative to tetramethylsilane as internal standard. Mass spectra (MS) were recorded using electron ionization (EI) on a Varian Mat 311A spectrometer and fast atom bombardment spectra (FAB) on a Kratos MS 50 spectrometer.

General procedure for the preparation of **4a, b, 5a, b,** *and* **6**

2-Methylthiopyrimidin-4-(1*H*)-ones **1a, b** [12] (5 mmol) were treated with 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) (30 ml) and ammonium sulfate at reflux temperature for 1 h (clear solution after 0.5 h), and the solvent was removed *in vacuo*. The residue was dissolved in dry MeCN (20 ml), and the sugar **3** [10] (3 mmol) in dry MeCN (50 ml) was added. The mixtue was cooled to −30 °C under magnetic stirring. A solution of $CF_3SO_3SiMe_3$ (1.1 ml, 6 mmol) in dry MeCN (5 ml) was then added dropwise with stirring over a period of 10 min. The reaction mixture was stirred at −30 °C for 0.5 h and then at room temperature for 0.5 h. The reaction mixture was diluted with 200 ml of CH_2Cl_2 and washed with ice-cold sat. aq. $NaHCO_3$ (3 × 250 ml). The organic phase was separated, washed with cold H_2O (3 × 150 ml), dried over Na_2SO_4, and evaporated to obtain the crude products which were chromatog-

raphed on a silica gel column with ethylacetate/petroleum ether (65–70 °C) (1:4 v/v) to obtain the α anomer **6** in 18% yield, β anomers **5a**, **b** in 32–37% yield and acyclic nucleosides **4a**, **b** in 33–37% yield.

2,3-Dideoxy-3-fluoro-1-O-methyl-1-C-(2-methylthio-4-oxo-1(4H)-pyrimidinyl)-5-O-(4-phenylbenzoyl)-D-erythro-pentitol (**4a**)

Yield: 630 mg (33%); yellow gum; ^{1}H NMR ($CDCl_3$): $\delta = 2.15$ (m, 2H, H-2′), 2.58 (s, 3H, SCH_3), 3.31 (s, 3H, OCH_3), 4.19 (m, 1H, H-4′), 4.3–4.8 (m, 3H, H-3′, H-5′), 5.68 (dd, 1H, $J = 5.3$, 7.0 Hz, H-1′), 6.10 (d, 1H, $J = 7.6$ Hz, H-5), 7.45 (m, 3H, arom), 7.62 (m, 5H, H-6, arom), 8.10 (d, 2H, $J = 8.5$ Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.50$ (SCH_3), 37.42 (d, $J_{F,C\text{-}2'} = 20.3$ Hz, C-2′), 56.61 (OCH_3), 65.73 (C-5′), 70.68 (d, $J_{F,C\text{-}4'} = 24.0$ Hz, C-4′), 88.07 (C-1′), 88.47 (d, $J_{F,C\text{-}3'} = 173.9$ Hz, C-3′), 110.29 (C-5), 127.07, 127.21, 128.09, 128.15, 128.31, 129.97, 139.62, 145.81 (arom), 137.64 (C-6), 163.45 (C-2), 166.66 (CO), 168.31 (C-4) ppm.

2,3-Dideoxy-3-fluoro-1-O-methyl-1-C-(5-methyl-2-methylthio-4-oxo-1(4H)-pyrimidinyl)-5-O-(4-phenylbenzoyl)-D-erythro-pentitol (**4b**)

Yield: 660 mg (37%); foam; ^{1}H NMR ($CDCl_3$): $\delta = 1.79$ (s, 3H, CH_3), 1.90–2.30 (m, 2H, H-2′), 2.43 (s, 3H, SCH_3), 3.16 (s, 3H, OCH_3), 4.00–4.50 (m, 4H, H-3′, H-4′, H-5′), 5.43 (dd, 1H, $J = 5.0$, 7.4 Hz, H-1′), 7.09 (s, 1H, H-6), 7.45 (m, 3H, arom), 7.52 (m, 4H, arom), 7.84 (d, 2H, $J = 8.2$ Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.95$ (CH_3), 14.76 (SCH_3), 35.62 (d, $J_{F,C\text{-}2'} = 21.2$ Hz, C-2′), 56.58 (OCH_3), 64.66 (d, $J_{F,C\text{-}5'} = 7.4$ Hz, C-5′), 70.94 (d, $J_{F,C\text{-}4'} = 23.5$ Hz, C-4′), 87.89 (C-1′), 89.18 (d, $J_{F,C\text{-}3'} = 174.5$ Hz, C-3′), 119.95 (C-5′), 127.05, 127.13, 128.08, 128.36, 129.94, 130.65, 145.86, (arom), 132.89 (C-6), 161.84 (C-2), 165.86 (CO), 168.89 (C-4) ppm.

1-(2,3-Dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-β-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-one (**5a**)

Yield: 600 mg (37%); oil; ^{1}H NMR ($CDCl_3$): $\delta = 2.15$ (m, 1H, H-2′), 2.50 (s, 3H, SCH_3), 2.74 (m, 1H, H-2′), 4.50–4.80 (m, 3H, H-4′, H-5′), 5.31 (dd, 1H, $J = 4.9$, 53.4 Hz, H-3′), 5.92 (d, 1H, $J = 7.7$, H-5), 6.17 (dd, 1H, $J = 5.2$, 8.8 Hz, H-1′), 7.38 (m, 3H, arom), 7.51 (m, 5H, H-6, arom), 7.97 (d, 2H, $J = 8.5$ Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.27$ (SCH_3), 39.04 (d, $J_{F,C\text{-}2'} = 21.4$ Hz, C-2′), 63.17 (d, $J_{F,C\text{-}5'} = 10.6$ Hz, C-5′), 83.07 (d, $J_{F,C\text{-}4'} = 24.4$ Hz, C-4′), 87.66 (C-1′), 92.96 (d, $J_{F,C\text{-}3'} = 180.1$ Hz, C-3′), 109.74 (C-5), 126.96, 127.04, 127.87, 127.92, 129.66, 129.77, 139.02, 146.27 (arom), 136.66 (C-6), 161.70 (C-2), 165.38 (CO), 167.78 (C-4) ppm.

1-(2,3-Dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-β-D-erythro-pentofuranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**5b**)

Yield: 530 mg (32%); foam; ^{1}H NMR ($CDCl_3$): $\delta = 1.75$ (s, 3 H. CH_3), 2.00–2.25 (m, 1H, H-2′), 2.61 (s, 3H, SCH_3), 2.81 (ddd, 1H, $J = 5.2$, 14.6, 19.9 Hz, H-2′), 4.67 (m, 1H, H-4′), 4.68 (d, 2H, $J = 2.8$ Hz, H-5′), 5.40 (dd, 1H, $J = 4.8$, 53.0 Hz, H-3′), 6.27 (dd, 1H, $J = 5.1$, 8.9 Hz, H-1′), 7.40 (m, 4H, H-6, arom), 7.59 (d, 2H, $J = 6.8$ Hz, arom), 7.68 (d, 2H, $J = 8.1$ Hz, arom), 8.05 (d, 2H, $J = 8.2$ Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.65$ (CH_3), 14.58 (SCH_3), 39.34 (d, $J_{F,C\text{-}2'} = 21.3$ Hz, C-2′), 63.53 (d, $J_{F,C\text{-}5'} = 11$Hz, C-5′), 83.18 (d, $J_{F,C\text{-}4'} = 26$ Hz, C-4′), 87.74 (C-1′), 93.32 (d, $J_{F,C\text{-}3'} = 180.1$ Hz, C-3′), 119.39 (C-5), 127.14, 127.32, 127.38, 128.41, 128.92, 129.84, 139.30, 146.76 (arom), 132.63 (C-6), 160.60 (C-2), 165.59 (CO), 168.81 (C-4) ppm.

1-(2,3-Dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-α-D-erythro-pentofuranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**6**)

Yield: 300 mg (18%); foam; ^{1}H NMR ($CDCl_3$): $\delta = 2.01$ (s, 3H, CH_3), 2.25–3.10 (m, 5H, H-2′, SCH_3), 4.56 (m, 2H, H-5′), 5.02 (m, 1H, $J = 22.4$ Hz, H-4′), 5.37 (dd, 1H, $J = 5.1$, 53.1 Hz, H-3′), 6.30 (dd, 1H,

J = 1.6, 7.6 Hz, H-1′), 7.45 (m, 3H, arom), 7.48 (m, 5H, H-6, arom), 8.09 (d, 2H, J = 8.1 Hz, arom) ppm; ^{13}C NMR ($CDCl_3$): δ = 14.01 (CH_3), 14.45 (SCH_3), 39.83 (d, $J_{F,C\text{-}2'}$ = 21.1 Hz, C-2′), 63.29 (d, $J_{F,C\text{-}5'}$ = 11.3 Hz, C-5′), 85.06 (d, $J_{F,C\text{-}4'}$ = 24.4 Hz, C-4′), 88.84 (C-1′), 93.25 (d, $J_{F,C\text{-}3'}$ = 179.5 Hz, C-3′), 118.68 (C-5), 126.95, 127.11, 127.48, 128.32, 128.81, 129.99, 139.45, 146.465 (arom), 133.05 (C-6), 159.89 (C-2) ppm.

General Procedure for the preparation of **7–11**

Saturated ammonia in methanol (40 ml) was added dropwise with stirring to a solution of **4a**, **b**, **5a**, **b**, or **6** (2 mmol) in methanol (20 ml) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and the solvent was evaporated *in vacuo*. The resiude was chromatographed on a silica gel column with 0–3% MeOH in $CHCl_3$.

2,3-Dideoxy-3-fluoro-1-C-(2-methoxy-4-oxo-1(4H)-pyrimidinyl)-1-O-methyl-D-erythro-pentitol (**7**)

Yield: 100 mg (28%); foam; 1H NMR ($CDCl_3$): δ = 2.26–2.45 (m, 2H, H-2′), 3.31 (s, 3H, OCH_3), 3.68–3.77 (m, 3H, H-4′, H-5′), 4.01 (s, 3H, OCH_3), 4.33–4.59 (m, 1H, H-3′), 5.73 (dd, 1H, J = 5.2, 7.3 Hz, H-1′), 6.07 (d, 1H, J = 7.5 Hz, H-5) 7.46 (d, 1H, J = 7.7 Hz, H-6) ppm; ^{13}C NMR ($CDCl_3$): δ = 36.92 (d, $J_{F,C\text{-}2'}$ = 20.2 Hz, C-2′), 55.89 (OCH_3), 56.59 (OCH_3), 62.41 (d, $J_{F,C\text{-}5'}$ = 4.1 Hz, C-5′), 72.18 (d, $J_{F,C\text{-}4'}$ = 24.2 Hz, C-4′), 86.23 (C-1′), 88.02 (d, $J_{F,C\text{-}3'}$ = 172.3 Hz, C-3′), 109.21 (C-5), 137.13 (C-6), 156.68 (C-2′), 171.89 (C-4) ppm.

2,3-Dideoxy-3-fluoro-1-O-methyl-1-C-(5-methyl-2-methylthio-4-oxo-1(4H)-pyrimidinyl)-D-erythro-pentitol (**8**)

Yield: 250 mg (63%); foam; ^{1}H NMR ($CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.35–2.50 (m, 2H, H-2′), 2.57 (s, 3H, SCH_3), 3.31 (s, 3H, OCH_3), 3.69–3.95 (m, 3H, H-4′, H-5′), 4.40–4.70 (m, 2H, H-3′), 5.65 (dd, 1H, J = 5.5, 7.1 Hz, H-1′), 7.39 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): δ = 13.64 (CH_3), 14.52 (SCH_3), 37.40 (d, $J_{F,C\text{-}2'}$ = 22.4 Hz, C-2′), 56.53 (OCH_3), 62.52 (d, $J_{F,C\text{-}5'}$ = 3.6 Hz, C-5′), 72.33 (d, $J_{F,C\text{-}4'}$ = 24.2 Hz, C-4′), 88.19 (C-1′), 88.27 (d, $J_{F,C\text{-}3'}$ = 172.4 Hz, C-3′), 119.25 (C-5), 134.39 (C-6), 162.52 (C-2), 169.66 (C-4) ppm.

2′,3′-Dideoxy-3′-fluorouridine (**9**)

Yield: 70 mg (23%); ^{1}H NMR (CD_3OD): δ = 2.12 (m, 2H, H-2′), 3.54 (m, 2H, H-5′), 4.21 (m, 1H, H-4′), 5.16 (dd, 1H, J = 4.9, 53.9 Hz, H-3′), 5.61 (d, 1H, J = 8.1 Hz, H-5), 6.11 (dd, 1H, J = 5.5, 9.0 Hz, H-1′), 7.88 (d, 1H, J = 8.1 Hz, J-6) ppm; ^{13}C NMR (CD_3OD): δ = 39.32 (d, $J_{F,C\text{-}2'}$ = 20.9 Hz, C-2′), 62.65 (d, $J_{F,C\text{-}5'}$ = 11.0 Hz, C-5′), 88.78 (d, $J_{F,C\text{-}4'}$ = 11.5 Hz, C-4′), 87.25 (C-1′), 95.90 (d, $J_{F,C\text{-}3'}$ = 175.6 Hz, C-3′), 102.97 (C-5), 142.20 (C-6), 152.18 (C-2), 166.05 (C-4) ppm.

1-(2,3-Dideoxy-3-fluoro-β-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-one (**10**)

Yield: 100 mg (33%); colourless solid; m.p.: 153–154 °C; ^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 3 H, CH_3), 2.30–2.80 (m, 5H, H-2′, SCH_3), 3.99 (br s, 2H, H-5′), 4.41 (d, 1H, J = 27.5 Hz, H-4′), 5.20–5.60 (m, 1H, H-3′), 6.27 (m, 1H, H-1′), 8.24 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): δ = 13.22 (CH_3), 14.54 (SCH_3), 39.42 (d, $J_{F,C\text{-}2'}$ = 17.2 Hz, C-2′), 61.80 (d, $J_{F,C\text{-}5'}$ = 11.6 Hz, C-5′), 86.34 (d, $J_{F,C\text{-}4'}$ = 23.7 Hz, C-4′), 88.39 (C-1′), 94.73 (d, $J_{F,C\text{-}3'}$ = 176.9 Hz, C-3′), 118.57 (C-5), 135.54 (C-6), 161.12 (C-2), 170.08 (C-4) ppm; MS: m/z = 274 (M^+, 7%).

1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-one (**11**)

Yield: 40 mg (24%); ^{1}H NMR ($CDCl_3$): δ = 2.00 (s, 3H, CH_3), 2.33 (dd, 1H, J = 15.5, 24.0 Hz, H-2′), 2.60 (s, 3H, SCH_3), 2.95 (2 × m, 1H, J = 35.1 Hz, H-2′), 3.81 (m, 2H, H-5′), 4.75 (2 × m, 1H, J = 23.9 Hz, H-4′),

5.39 (dd, 1H, $J = 4.8$, 53.9 Hz, H-3′), 6.28 (d, 1H, $J = 7.0$ Hz, H-1′), 7.49 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.88$ (CH_3), 14.04 (SCH_3), 40.63 (d, $J_{F,C\text{-}2'} = 20.5$ Hz, C-2′), 62.26 (d, $J_{F,C\text{-}5'} = 11.5$ Hz, C-5′), 88.45 (d, $J_{F,C\text{-}4'} = 21.8$ Hz, C-4′), 89.59 (C-1′), 94.25 (d, $J_{F,C\text{-}3'} = 176.8$ Hz, C-3′), 118.23 (C-5), 134.67 (d, $J_{F,C\text{-}6'} = 6.1$ Hz, C-6), 160.16 (C-2), 169.96 (C-4) ppm.

General procedure for the preparation of **13a, b**

A mixture of 2-methyluracils **1a, b** (8 mmol), ammonium sulfate (40 mg), and 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) (40 ml) were refluxed for 1 h. The solvent was removed *in vacuo*. The residue was dissolved in dry MeCN (30 ml), and the phthalimido sugar **12** (1.73 g, 4 mmol) was added. The reaction mixture was stirred and cooled to −30 °C. A solution of *TMS* triflate (1.3 ml, 6.5 mmol) in dry MeCN (5 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred for 0.5 h at −25 °C. The temperature was raised to room temperature, and the mixture was stirred for 0 .5 h. The mixture was diluted with CH_2Cl_2 (200 ml), washed with a cold sat. aq. $NaHCO_3$ (350 ml), water (3 × 150 ml), and then dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column using 0–2% MeOH in CH_2Cl_2 to give the anomeric mixtures **13a, b** in 88% and 90% yield, respectively.

1-(5-O-Acetyl-2,3-dideoxy-3-phthalimido-α,β-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-one (**13a**)

Yield: 1.88 g (88%); foam; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.01$ (s, 3 H, $COCH_3$ α), 2.04 (s, 3 H, $COCH_3$ β), 2.52 (m, 7H, 2 × H-2′ β, SCH_3), 2.83 (m, 1H, H-2′, β), 2.83 (m, 2H, H-2′ α), 4.17 (m, 2H, H-5′ α), 4.26 (d, 2H, $J = 4$ Hz, H-5′ β), 4.49 (m, 1H, H-4′ β), 4.88 (m, 2H, H-3′, H-4′ α), 6.03 (d, 1H, $J = 7.7$ Hz, H-5 β), 6.12 (d, 1H, $J = 7.7$ Hz, H-5 α), 6.27 (t, 1H, $J = 6.7$ Hz, H-1′ α), 6.54 (t, 1H, $J = 6.6$ Hz, H-1′ β), 7.87 (m, 9H, H-6 β, arom), 8.03 (d, 1H, $J = 7.8$ Hz, H-6 α) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.97$ (SCH_3), 20.36 ($COCH_3$), 33.73 (C-2′ α), 34.73 (C-2′ β), 48.46 (C-3′ β), 49.27 (C-3′ α), 63.58 (C-5′ β), 63.83 (C-5′ α), 77.26 (C-4′ α), 78.97 (C-4′ β), 87.84 (C-1′ α), 87.96 (C-1′ β), 109.09 (C-5 β), 109.33 (C-5 α), 123.0, 131.45, 134.35 (Phth), 138.54 (C-6 α), 139.00 (C-6 β), 161.49 (C-2), 166.33 (C-4), 167.38 (CO), 169.95 (CH_3CO) ppm.

1-(5-O-Acetyl-2,3-dideoxy-3-phthalimido-α,β-D-erythro-pentofuranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**13b**)

Yield: 1.99 g (90%); foam; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.87$ (s, 3 H, CH_3 β), 1.93 (s, 3H, CH_3 α), 2.01 (s, 3H, $COCH_3$ α), 2.05 (s, 3H, $COCH_3$ β), 2.52 (m, 7H, H-2′ β, 2 × SCH_3), 2.81 (m, 1H, H-2′ β), 2.81 (m, 3H, H-2′ α, H-2′ β), 4.18 (m, 2H, H-5′ α), 4.28 (d, 2H, $J = 4.3$ Hz, H-5′ β), 4.48 (q, 1H, $J = 4.6$ Hz, H-4′ β), 4.89 (m, 2H, H-3′, H-4′), 6.26 (t, 1H, $J = 6.8$ Hz, H-1′ α), 6.52 (t, 1H, $J = 6.8$ Hz, H-1′ β), 7.89 (m, 9H, H-6, arom) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.31$ (CH_3), 14.01 (SCH_3), 20.36 ($COCH_3$), 33.49 (C-2′ α), 34.60 (C-2′ β), 48.45 (C-3′ β), 49.27 (C-3′ α), 63.62 (C-5′ β), 63.82 (C-5′ α), 77.02 (C-4′ α), 78.86 (C-4′ β), 87.69 (C-1′ α), 87.86 (C-1′ β), 117.59 (C-5 β), 117.82 (C-5 α), 112.98, 131.44, 134.34 (Phth), 135.68 (C-6), 160.29 (C-2), 167.37 (CO), 167.47 (C-4), 169.93 ($COCH_3$) ppm.

General procedure for the preparation of nucleosides **14–18**

To a stirred solution of **13a** or **13b** (4 mmol) in 99.9% ethanol, a 33% solution of $MeNH_2$ in absolute ethanol (60 ml) was added at room temperature. The mixture was refluxed (**13a**: 2 h, **13b**: 1 h) and then cooled to room temperature. The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column with 5–10% MeOH in CH_2Cl_2 to remove impurities and then with 10–15% MeOH in CH_2Cl_2 to give **14** as a pure compound and the anomeric mixture **15**/**16** which, after reversed phase column (RP-4, 15–20 μm, 300 A) HPLC separation using water and the buffer triethylamine/acetic acid (pH 7.0), afforded compounds **15** and **16**. Compounds **17** and **18** were

obtained by HPLC separation using 100% water and the same buffer as above after the deprotection of **13b**.

1-(3-Amino-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-one (**14**)

Yield: 255 mg (25%); yellow gum; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.16$ (t, 2H, $J = 6.4$ Hz, H-2′), 2.49 (s, 3H, SCH_3), 3.17–3.45 (m, 1 H, H-3′), 3.48–3.58 (m, 1H, H-4′), 3.62–3.70 (m, 2H, H-5′), 5.90 (d, 1H, $J = 7.6$ Hz, H-5), 6.04 (t, 1H, $J = 5.5$ Hz, H-1′), 8.10 (d, 1H, $J = 7.7$ Hz, H-6) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.83$ (SCH_3), 41.89 (C-2′), 50.35 (C-3′), 60.19 (C-5′), 87.33 (C-1′), 88.16 (C-4′), 108.46 (C-5), 139.08 (C-6), 160.86 (C-2), 166.68 (C-4) ppm; MS (FAB, *DMSO* + 3-nitrobenzylalcohol): $m/z = 258$ ($M + H^+$).

1-(3-Amino-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2-methylaminopyrimidin-4(1H)-one (**15**)

Yield: 190 mg (20%); yellow gum; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.06$–2.17 (m, 2H, H-2′), 2.72 (s, 3H, NCH_3), 3.38–3.68 (m, 4H, H-3′, H-4, H-5′), 5.50 (d, 1H, $J = 7.5$ Hz, H-5), 5.80 (t, 1H, $J = 5.3$ Hz, H-1′), 7.05 (br s, 1H, NH), 7.67 (d, 1H, $J = 7.7$ Hz, H-6) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 27.93$ (NCH_3), 40.10 (C-2′), 50.37 (C-3′), 60.04 (C-5′), 86.99 (C-1), 87.62 (C-4′), 105.25 (C-5), 138.38 (C-6), 152.80 (C-2), 169.32 (C-4) ppm; MS: $m/z = 240$ (M^+, 0.7%).

1-(Amino-2,3-dideoxy-α-D-erythro-pentofuranosyl)-2-methylaminopyrimidin-4(1H)-one (**16**)

Yield: 105 mg (11%); yellow gum; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.71$–1.83 (m, 1H, H-2′), 2.51–2.66 (m, 1H, H-2′), 2.73 (s, 3H, NCH_3), 3.36–3.55 (m, 3H, H-3′, H-5′), 3.84–3.87 (m, 1H, H-4′), 5.55 (d, 1H, $J = 7.7$ Hz, H-5), 5.79 (t, 1H, $J = 6.0$ Hz, H-1′), 7.39 (br s, 1H, NH), 7.69 (d, 1H, $J = 7.7$ Hz, H-6) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 27.92$ (NCH_3), 39.96 (C-2′), 51.83 (C-3′), 61.40 (C-5′), 87.39 (C-1′), 87.84 (C-4′), 105.22 (C-5), 138.75 (C-6), 152.67 (C-2), 169.56 (C-4) ppm; MS: $m/z = 240$ (M^+, 0.7%).

1-(3-Amino-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**17**)

Yield: 430 mg (40%); brown foam; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.88$ (s, 3 H, CH_3), 2.16 (t, 2H, $J = 6.2$ Hz, H-2′), 2.49 (s, 3H, SCH_3), 3.48–3.72 (m, 4H, H-3′, H-4′, H-5′), 5.27 (br s, 3H, NH_2, OH), 6.04 (t, 1H, $J = 5.5$ Hz, H-1′), 8.03 (s, 1H, H-6) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.43$ (CH_3), 13.90 (SCH_3), 41.20 (C-2′), 50.25 (C-3′), 60.22 (C-5′), 87.19 (C-1′), 87.92 (C-4′), 116.98 (C-5), 135.19 (C-6), 159.59 (C-2), 167.68 (C-4) ppm; MS (FAB, *DMSO* + 3-nitrobenzylalcohol): $m/z = 272$ ($M + H^+$).

1-(3-Amino-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**18**)

Yield: 170 mg (16%); brown gum; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.81$–1.88 (m, 4 H, H-2′, CH_3), 2.48–2.66 (m, 4H, H-2′, SCH_3), 3.41–3.67 (m, 3H, H-4′, H-5′), 3.99–4.18 (br s, 3H, NH_2, OH), 6.00 (m, 1H, H-1′), 8.05 (s, 1H, H-6) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.44$ (CH_3), 13.96 (SCH_3), 40.95 (C-2′), 51.91 (C-3′), 61.52 (C-5′), 87.21 (C-1′), 88.40 (C-4′), 116.93 (C-5), 135.99 (C-6), 159.69 (C-2), 167.78 (C-4) ppm; MS (FAB, *DMSO* + 3-nitrobenzylalcohol): $m/z = 272$ ($M + H^+$).

Deprotection of **13b** *with n-butylamine*

A solution of freshly distilled *n*-butylamine (60 ml) was added to **13b** (1.77 g, 4 mmol) at room temperature. The reaction mixture was refluxed for 2 h and then cooled to room temperature. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column with 3–5% MeOH in CH_2Cl_2 to give the pure β-anomer **19** and the anomeric mixture **19**/**20** in 40% and 36% yield, respectively.

1-[3-[2-(Butylaminocarbonyl)benzamido]-2,3-dideoxy-β-D-erythro-pentofuranosyl]-5-methyl-2-methylthiopyrimidin-4(1H)-one

Yield: 40% foam; ^{1}H NMR (*DMSO*-d_6): $\delta = 0.89$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.23–1.42 (m, 2H, CH_2), 1.45–1.50 (m, 2H, CH_2), 1.84 (s, 3H, CH_3), 2.32–2.46 (m, 2H, H-2′), 2.49 (s, 3H, SCH_3), 3.18 (q, 2H, $J = 6.0$ Hz, CH_2), 3.69–3.75 (m, 2H, H-5′), 4.01–4.04 (m, 1H, H-4′), 4.48–4.54 (m, 1H, H-3′), 5.18 (t, 1H, $J = 5.0$ Hz, OH), 6.18 (t, 1H, $J = 6.2$ Hz, H-1′), 7.48 (m, 4H, arom), 8.10 (s, 1H, H-6), 8.20 (t, 1H, $J = 5.5$ Hz, NH), 8.67 (d, 1H, $J = 7.4$ Hz, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.45$ (CH_3), 13.57 (CH_3), 13.92 (SCH_3), 19.47 (CH_2), 30.97 (CH_2), 37.62 (CH_2), 38.66 (C-2′), 49.22 (C-3′), 61.00 (C-5′), 85.61 (C-4′), 87.56 (C-1′), 117.19 (C-5), 127.38, 129.15, 135.14, 136.04 (Phth), 136.17 (C-6), 159.80 (C-2), 167.47 (CO), 168.79 (C-4) ppm; MS (FAB, *DMSO* + 3-nitrobenzylalcohol): $m/z = 475$ ($M + H^+$).

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