SYNTHESIS OF 2-ALKYLTHIO ANALOGUES OF AZT AND THEIR ACTIVITY AGAINST HIV-1

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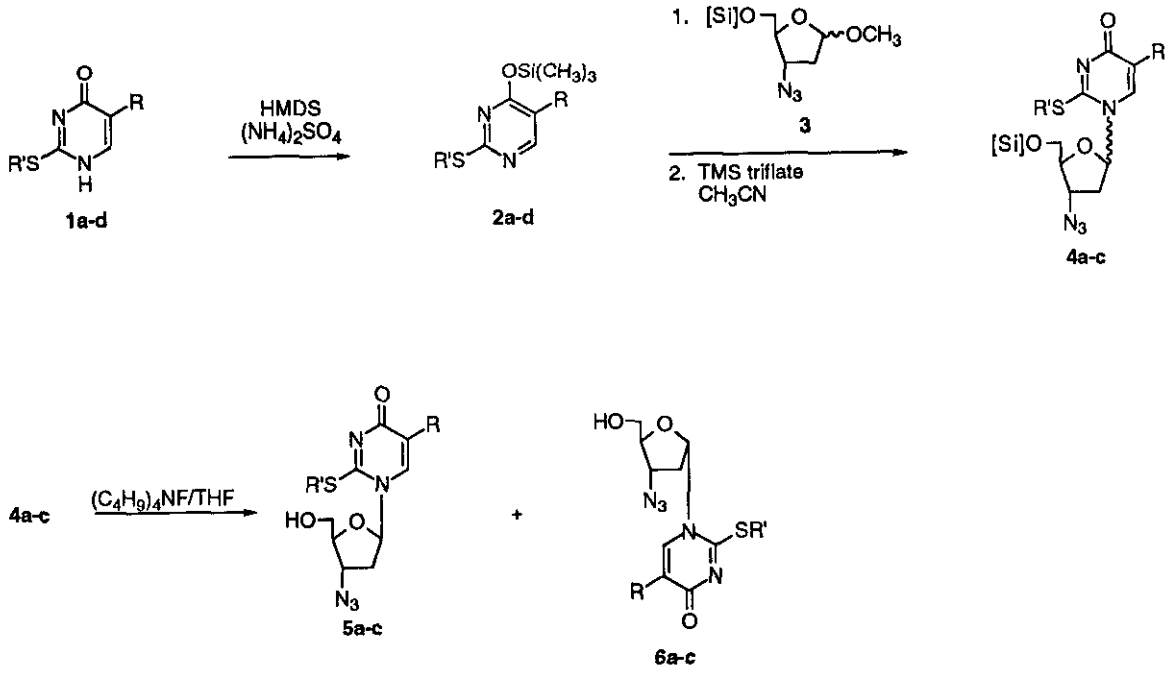
Abstract - S^2-Alkylated 3'-azido-2',3'-dideoxy-2-thiouridines **(5)** and their corresponding α anomers have been synthesized through two routes: 1) by condensation of silylated 2-alkylthiopyridin-4(1*H*)-ones **(2)** with methyl 3-azido-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α,β-D-*erythro*-pentofuranoside **(3)**; 2) by condensation with methyl 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-3-iodo-α,β-D-*threo*-pentofuranoside **(7)**, followed by reaction of the obtained iodonucleoside **(8)** with sodium azide to give the protected azidonucleoside **(10)** and the 3',4'-didehydro-2',3'-dideoxy nucleoside **(11)**.

3'-Azido-3'-deoxythymidine (AZT) was the first drug used against acquired immunodeficiency syndrome (AIDS).[1-4] It was demonstrated that dideoxynucleosides could suppress the replication of human immunodeficiency virus (HIV) in monocytes and macrophages *in vitro*.[5] During the last ten years a number of 2',3'-dideoxynucleosides derivatives have been identified as being active against HIV, at least *in vitro*, and a great deal of knowledge in terms of structure activity relations has emerged.[5-11] However, all of these drugs have serious dose-limiting toxicities.

In the present investigation we have synthesized new nucleoside analogues of AZT where the 2-oxo group has been replaced by alkylthio groups in the nucleobase moiety. Such compounds could be potential prodrugs of AZT if the alkylthio group could be metabolized into an oxo group under *in vivo* conditions. Such compounds could also have some resemblence to 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT)[12] and 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidine (DABO)[13] compounds which acts by binding to a non-substrate pocket of the reverse transcriptase enzyme.

RESULTS AND DISCUSSION



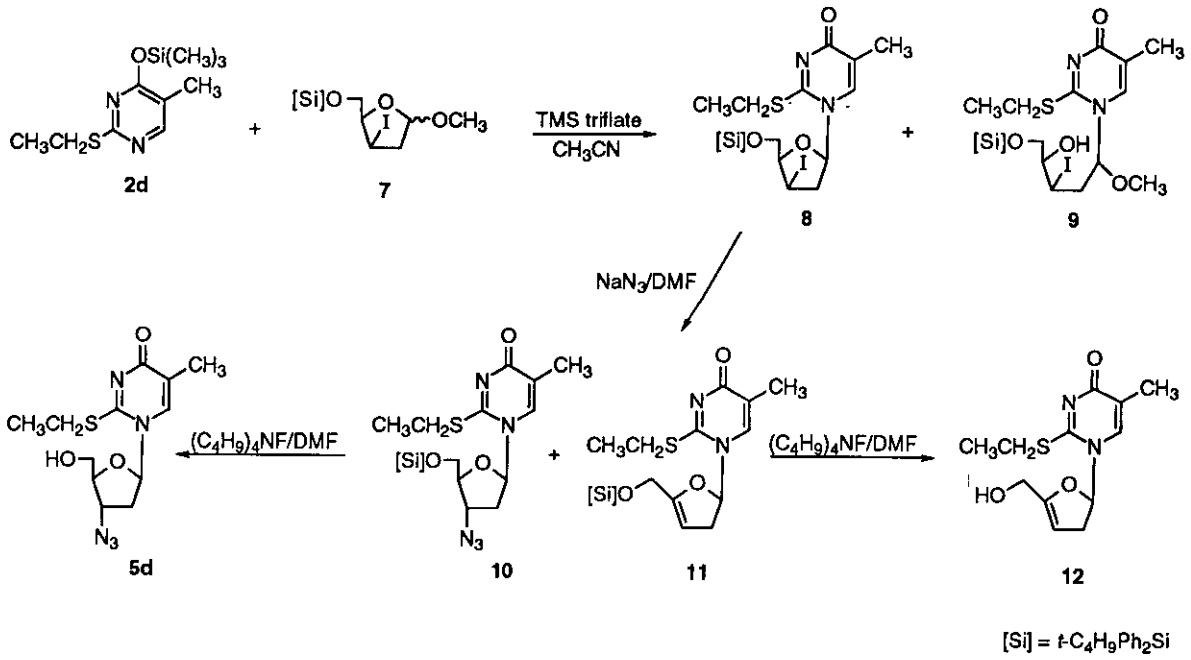
[Si] = *t*-$C_4H_9Ph_2Si$

1, 2, 4, 5, 6	R	R'
a	H	CH_3
b	CH_3	CH_3
c	CH_2Ph	CH_3
d	CH_3	CH_2CH_3

Scheme 1

2-Alkylthiopyrimidin-4(1*H*)-ones **(1a-d)** were synthesized according to Brown *et al.*[14] by heating 2-thiouracils with the appropriate alkyl halide in the presence of sodium hydroxide. Silylation of **1a-d** with

1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate was performed according to Wittenburg[15] to give the derivatives **(2a-d)**. The latter were condensed with methyl 3-azido-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α,β-D-*erythro*-pentofuranoside[16] **(3)** using the trimethylsilyl trifluoromethanesulfonate (TMS triflate) method of Vorbrüggen *et al.*[17,18] in anhydrous acetonitrile to give anomeric mixtures of the nucleosides **(4a-c)** in 72-78% yield with the α/β ratio 2:1. Treatment of these protected nucleosides, after their chromatographic purification, with tetrabutylammonium fluoride in tetrahydrofuran (THF) at 0 °C for 0.5-1 h resulted in complete deprotection of the 5'-hydroxy group. The anomeric mixture **(5c)** and **(6c)** was separated by silica gel column chromatography while **5a,b** and **6a,b** with preparative silica gel tlc. The α anomers **(6a-c)** were obtained in 18-44% yield and the β anomers **(5a-c)** in 17-34% yield.



Scheme 2

On the other hand ultilizing methyl 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-3-iodo-α,β-D-*threo*-pentofuranoside **(7)** for the nucleoside synthesis, more favorable β/α ratios have been reported.[16] Condensation with the silylated compound **(2d)** using TMS triflate as the Lewis acid catalyst according

to the method described by Vorbrüggen *et al.*[17,18] gives the β anomer **(8)** in 42% yield as the only anomer besides the acyclic nucleoside **(9)** in 13% yield as a pure anomer having the methoxy group intact. The nmr spectra showed only one set of signals. One could propose a charge-tranfer complex between the iodo substituent and the silylated 2-ethylthio-5-methylpyrimidin-4-one **(2d)** as the reason for the stereoselective formation of **8** with preferential attack on the β face of the sugar ring. Formation of the acyclic nucleoside **(9)** is easily explained by a mechanism in which the ring oxygen of the sugar is silylated making endocyclic cleavage of the carbon oxygene bond possible which results in ring opening with formation of an acyclic carbonium ion which, in turn, can condense with the silylated nucleobase **(2d)** to furnish the corresponding acyclic nucleoside **(9)**.[19,20] The β anomer **(8)** was reacted with sodium azide in dry *N,N*-dimethylformamide (DMF) (Scheme 2). Surprisingly, the tlc showed two spots close to each other and silica gel column chromatographic separation afforded the corresponding azido nucleoside **(10)** in 68% yield besides the unsaturated nucleoside **(11)** contaminated with the azido nucleoside **(10)**. Treatment of the protected nucleosides **(10)** and **(11)** with tetrabutylammonium fluoride followed by chromatographic purification afforded the unprotected 3'-azido nucleoside **(5d)** in 46% yield and the unsaturated nucleoside **(12)** in 23% yield after further reversed phase hplc purification.

The ^{1}H and ^{13}C nmr data for compounds **(4-6, 8, 10** and **12)** are in close agreement with data previously reported.[21-23] In agreement with the reported data,[24,25] the 4'-H protons of the α anomers **(6a-c)** appear downfield from those observed for the β anomers **(5a-c)**. The 2'α-H resonances of **6a-c** exhibited large geminal couplings and very small or vanishing coupling constants to 1'-H and 3'-H which proved the latter two protons to be located *trans* to 2'α-H in the sugar ring. This in turn proves the α configuration.

Compounds **(5a-d** and **6a-c)** were testest for their activity against HIV-1 in MT-4 cells. Only the β anomers **(5b)** and **(5d)** showed activity against HIV-1 with the effective does ED_{50} = 120 μM and 3 μM, respectively (AZT: ED_{50} = 0.05 μM) but this activity is most likely due to a small impurity of AZT according to hplc analysis. No toxicity was observed at 200 μM for compound **(5b)** whereas low toxicity

(CD_{50} = 52 μM) was observed for compound **(5d)**. The MT-4 cells were incubated with the virus, washed, and added in proportion of 1 : 10 to uninfected MT-4 cells which had been preincubated in test componds containing culture medium (RPM 1640 containing 10 % FCS) for 2 h. Cultures were maintained for 7 days, and the expression of HIV was quantified 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

^1H and ^{13}C nmr spectra were recorded on a Bruker AC 250 FT-nmr spectrometer at 250 MHz for ^1H nmr and at 62.9 MHz for ^{13}C nmr. EI mass spectra were obtained on a Varian MAT-311A spectrometer, and fast atom bombardment (FAB) on a Kratos MS 50-spectrometer. Ir spectra were recorded on a Perkin Elmer 1720 spectrophotometer. Analytical tlc plates 60 F_{254} and silica gel (0.040-0.063 mm) were purchased from Merck. Anhydrous CH_3CN was distilled from P_2O_5 followed by distillation from CaH_2. All other solvents were used after distillation and drying.

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-α,β-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-ones **(4a-c)**. *General procedure.*

2-Methylthiopyrimidin-4(1*H*)-ones **(1a-c)** (7 mmol) and $(NH_4)_2SO_4$ (50 mg, 0.37 mmol) were dissolved in HMDS (25 ml) and the solution was heated under reflux for 3 h. The solvent was evaporated *in vacuo* and the silylated 2-methylthiopyrimidin-4-ones **(2)** was used in the following reaction without further purification. To **2a-c** (7 mmol) dissolved in MeCN (40 ml) was added **3** (2.1 g, 5 mmol) dissolved in MeCN (10 ml). The solution was cooled to -30 °C and TMS triflate (1.2 ml, 6.5 mmol) in MeCN (5 ml) was added dropwise (20 min). The temperature was allowed to raise to the room temperature and the reaction mixture was stirred for 0.5-1 h. The mixture was then diluted with CH_2Cl_2 (150 ml) and neutralized with sat. cold aqueous $NaHCO_3$ (250 ml). The organic phase was separated, dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product which after silica gel column chromatography with

MeOH/$CHCl_3$ (3:97, v/v) (compound **(4c)** eluated with MeOH/CH_2Cl_2 (3:97, v/v)) afforded the anomeric mixture of the nucleosides **(4a-c)**; yield 72-78%.

1-(3-Azido-2,3-dideoxy-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-ones **(5a-c)** *and* **(6a-c)**. *General procedure.*

To a stirred solution of **4a-c** (5 mmol) in THF (50 ml) at 0 °C was slowly added (30 min) tetrabutylammonium fluoride (5 ml, 1M solution in THF). After stirring for 1 h at room temperature, the THF was evaporated *in vacuo*. The crude product obtained was separated by preparative silica gel tlc with MeOH/EtOAc 5-10% (compounds **(5c, 6c)** were chromatographed on a silica gel column with Et_2O/EtOAc (1:1, v/v) and then with pure EtOAc).

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-one (**5a**): Yield: 240 mg (17%) as a glass. Ms: *m/z* (%) = 283 (M^+, 1.5), 142 (100), 95 (22). ^{1}H-Nmr ($CDCl_3$): δ 2.47 (m, 2H, 2'-H), 2.60 (s, 3H, CH_3S), 3.88 (m, 1H, 5'-H), 4.03-4.07 (m, 2H, 4'-H, 5'-H), 4.47 (m, 1H, 3'-H), 5.24 (br s, 1H, OH), 5.27 (d, 1H, J = 7.8 Hz, 5-H), 6.12 (t, 1H, J = 6.1 Hz, 1'-H), 8.37 (d, 1H, J = 7.8 Hz, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 14.47 (CH_3S), 39.07 (C-2'), 60.05, 61.07 (C-3' and C-5'), 85.79 (C-4'), 87.91 (C-1'), 108.93 (C-5), 139.42 (C-6), 162.18 (C-2), 169.47 (C-4). Ir (Film): υ = 2104 cm^{-1} (N_3). Anal. Calcd for $C_{10}H_{13}N_5O_3S$ 0.33 H_2O: C, 41.52; H, 4.76; N, 24.21; S, 11.08. Found: C, 41.80; H, 4.78; N, 23.87; S, 10.70.

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-2-methylthiopyrimidin-4(1H)-one (**6a**): Yield: 260 mg (18%) as a glass. Ms: *m/z* (%) = 283 (M^+, 1), 142 (100), 96 (18). ^{1}H-Nmr ($CDCl_3$): δ 2.15 (d, 1H, J = 14.6 Hz, 2'α-H), 2.61 (s, 3H, CH_3S), 3.06 (m, 1H, 2'β-H), 3.77 (br s, 2H, 5'-H), 4.46 (m, 2H, 3'-H, 4'-H), 4.84 (br s, 1H, OH), 6.12 (d, 1H, J = 7.6 Hz, 5-H), 6.19 (dd, 1H, J = 7.0, 2.3 Hz, 1'-H), 7.71 (d, 1H, J = 7.8 Hz, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 14.14 (CH_3S), 39.43 (C-2'), 61.40, 62.47 (C-3' and C-5'), 87.89

(C-4'), 89.36 (C-1'), 108.67 (C-5), 139.51 (C-6), 161.64 (C-2), 169.26 (C-4). Ir (Film): υ = 2109 cm^{-1} (N_3). Peak matching for $C_{10}H_{13}N_5O_3S$: Calcd: 283.0719. Found: 283.0729.

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**5b**): Yield: 500 mg (34%); mp 92-93 °C (EtOAc). Ms: *m/z* (%) = 297 (M^+, 1), 156 (100), 110 (20). ^{1}H-Nmr ($CDCl_3$): δ 1.96 (s, 3H, 5-CH_3), 2.44 (m, 2H, 2'-H), 2.60 (s, 3H, CH_3S), 3.94 (m, 1H, 5'-H), 4.09 (m, 2H, 4'-H, 5'-H), 4.49 (m, 1H, 3'-H), 6.12 (t, 1H, *J* = 6.1 Hz, 1-H), 8.21 (s, 1H, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 13.84 (5-CH_3), 14.53 (CH_3S), 38.90 (C-2'), 60.11, 61.29 (C-3' and C-5'), 85.58 (C-4'), 87.64 (C-1'), 118.41 (C-5), 135.51 (C-6), 160.67 (C-2), 170.09 (C-4). Anal. Calcd for $C_{11}H_{15}N_5O_3S{\cdot}H_2O$: C, 41.91; H, 5.43; N, 22.21; S, 10.17. Found: C, 41.58; H, 5.09; N, 21.98; S, 9.97.

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**6b**): Yield: 650 mg (44%) as a glass. Ms: *m/z* (%) = 297 (M^+, 1), 156 (100), 110 (16). ^{1}H-Nmr ($CDCl_3$): δ 2.02 (s, 3H, 5-CH_3), 2.10 (dt, 1H, *J* = 14.5, 3.0 Hz, 2'α-H), 2.61 (s, 3H, CH_3S), 3.06 (m, 1H, 2'β-H), 3.76-3.83 (m, 2H, 5'-H), 4.41-4.49 (m, 2H, 3'-H, 4'-H), 5.31 (s, 1H, OH), 6.17 (dd, 1H, *J* = 7.0, 3.2 Hz, 1'-H), 7.54 (s, 1H, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 13.99 (5-CH_3), 14.53 (CH_3S), 39.38 (C-2'), 61.23, 62.52 (C-3' and C-5'), 87.36 (C-4'), 89.04 (C-1'), 118.24 (C-5), 134.53 (C-6), 160.22 (C-2), 169.87 (C-4). Ir (Film): υ = 2104 cm^{-1} (N_3). Peak matching for $C_{11}H_{15}N_5O_3S$: Calcd: 297.0895. Found: 297.0873.

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-benzyl-2-methylthiopyrimidin-4(1H)-one (**5c**): Yield: 407 mg (22%); mp 164-165 °C (EtOAc). Ms: *m/z* (%) = 373 (M^+, 1.5), 232 (100), 91 (15). ^{1}H-Nmr ($CDCl_3$): δ 2.13 (m, 1H, 2'-H), 2.37 (m, 1H, 2'-H), 2.59 (s, 3H, CH_3), 3.66 (br s, 2H, 5'-H), 3.71 (s, 2H, CH_2), 3.97 (m, 1H, 4'-H), 4.25 (m, 1H, 3'-H), 6.06 (t, 1H, *J* = 6.4 Hz, 1'-H), 7.20-7.34 (m, 5H, H_{arom}), 7.60 (s, 1H, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 14.48 (CH_3S), 33.66 (CH_2), 36.60 (C-2'), 60.67, 61.83 (C-3' and C-5'), 85.07 (C-4'), 87.86 (C-1'), 122.18 (C-5), 126.15, 128.38, 129.59, 138.59 (C_{arom}), 135.42 (C-6),

160.49 (C-2), 168.63 (C-4). Ir (Film): υ = 2105 cm^{-1} (N_3). Anal. Calcd for $C_{17}H_{19}N_5O_3S$: C, 54.68; H, 5.13; N, 18.75; S, 8.59. Found: C, 54.48; H, 5.14; N, 18.65; S, 8.48.

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-benzyl-2-methylthiopyrimidin-4(1H)-one (**6c**): Yield: 481 mg (26%); mp 144-145 °C (EtOAc). Ms *m/z* (%) = 373 (M^+, 1) 232 (100), 91 (15). ^{1}H-Nmr ($CDCl_3$): δ 1.96 (dt, 1H, *J* = 14.7, 1.9 Hz, 2'α-H), 2.57 (s, 3H, CH_3S), 2.83 (m, 1H, 2'β-H), 3.64-3.83 (m, 4H, CH_2, 5'-H), 4.12 (br s, 1H, 4'-H), 4.32 (m, 2H, OH, 3'-H), 6.12 (dd, 1H, *J* = 7.2, 2.2 Hz, 1'-H), 7.19-7.35 (m, 6H, H_{arom}, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 14.54 (CH_3S), 33.65 (CH_2), 39.26 (C-2'), 61.36, 62.63 (C-3' and C-5'), 87.74 (C-4'), 89.33 (C-1'), 122.10 (C-5), 126.46, 128.44, 129.16, 137.77 (C_{arom}), 135.76 (C-5), 160.15 (C-2), 168.98 (C-4). Ir (Film): υ = 2104 cm^{-1} (N_3). Anal. Calcd for $C_{17}H_{19}N_5O_3S{\cdot}0.25\ H_2O$: C, 54.03; H, 5.20; N, 18.53; S, 8.47. Found: C, 54.42; H, 5.15; N, 18.62; S, 7.95.

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-D-threo-pentofuranosyl)-2-ethylthio-5-methylpyrimidin-4(1H)-one (**8**) *and 5-O-tert-butyldiphenylsilyl-2,3-dideoxy-1-C-(2-ethylthio-5-methyl-4-oxo-1(4H)-pyrimidinyl)-3-iodo-1-O-methyl-D-threo-pentitol* (**9**)

2-Ethylthio-5-methylpyrimidin-4(1*H*)-one (**1d**) (2.0 g, 12 mmol) was dissolved in HMDS (40 ml). $(NH_4)_2SO_4$ (50 mg, 0.37 mmol) was added and the solution was heated under reflux overnight. The solvent was evaporated *in vacuo*. The silylated 2-ethylthio-5-methylpyrimidin-4(1*H*)-one **(2d)** dissolved in MeCN (60 ml) and methyl 3-iodofuranoside (**7**) (4.2 g, 8.5 mmol) dissolved in MeCN (10 ml) were mixed. The solution was cooled to -30 °C and TMS triflate (2.2 ml, 12 mmol) in MeCN (5 ml) was added dropwise (20 min). After 1 h the temperature was allowed to increase to -20 °C and the mixture was stirred at -20 °C for 3 h. The mixture was then diluted with CH_2Cl_2 (200 ml) and neutralized with cold sat. aqueous $NaHCO_3$ (500 ml). The organic phase was separated, dried over Na_2SO_4 and evaporated *in vacuo* to give a crude grey product which after silica gel column chromatography with petroleum ether (bp 60-70 °C)/Et_2O (9:1 - 0:1 v/v) afforded **8** in 42% yield and **9** in 13% yield.

Compound 8: Yield: 2.28 g (42%) as a glass. FAB Ms (3-nitrobenzyl alcohol): *m/z* (%) = 635 ($M + H^+$). ^{1}H-Nmr ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu), 1.35 (t, 3H, *J* = 7.3 Hz, CH_3CH_2S), 2.00 (s, 3H, CH_3), 2.66 (m, 1H, 2'-H), 3.27 (m, 3H, 2'-H, SCH_2), 3.87 (m, 1H, 3'-H), 4.04 (m, 2H, 5'-H), 4.47-4.53 (m, 1H, 4'-H), 6.25 (t, 1H, *J* = 5.8 Hz, 1'-H), 7.26-7.73 (m, 11H, H_{arom} and 6-H). ^{13}C-Nmr ($CDCl_3$): δ 13.92 (CH_3), 14.17 (CH_3), 19.01 (Me_3C), 20.32 (C-3'), 26.24 (SCH_2), 26.68 (Me_3C), 45.53 (C-2'), 68.27 (C-5'), 83.59 (C-4'), 88.72 (C-1'), 119.12 (C-5), 127.71, 127.74, 129.88, 132.49, 133.05, 135.45 (C_{arom}), 135.51 (C-6), 159.74 (C-2), 169.06 (C-4).

Compound 9: Yield: 700 mg (13%) as a glass. ^{1}H-Nmr ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu), 1.37 (t, 3H, *J* = 7.4 Hz, CH_3CH_2) 1.95 (s, 3H, CH_3), 2.05 (m, 1H, 2'-H), 2.43 (m, 1H, 2'-H), 3.14-3.36 (m, 3H, 4'-H, SCH_2), 3.38 (s, 3H, OCH_3), 3.71 (m, 2H, 5'-H), 3.88 (br s, 1H, OH), 4.63 (dd, 1H, *J* = 12.0, 7.8 Hz, 3'-H), 5.65 (dd, 1H, *J* = 10.0, 2.5 Hz, 1'-H), 7.25-7.70 (m, 11H, H_{arom} and 6-H). ^{13}C-Nmr ($CDCl_3$): δ 13.68 (CH_3), 13.86 (CH_3), 19.12 (Me_3C), 26.75 (SCH_2), 26.80 (Me_3C), 36.87 (C-2'), 42.53 (C-3'), 57.36 (OCH_3), 67.22 (C-5'). 73.43 (C-4'), 91.32 (C-1'), 119.15 (C-5), 127.67, 129.74, 132.88, 133.04, 133.56, 135.40 (C_{arom}), 135.54 (C-6), 161.09 (C-2), 169.25 (C-4).

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2-ethylthio-5-methylpyrimidin-4(1H)-one (**10**).

To a stirred solution of **8** (2.1 g, 3.31 mmol) dissolved in DMF (20 ml), was added NaN_3 (2.14 g, 33 mmol). After heating at 60 °C for 4 h and cooling to room temperature, the solvent was evaporated *in vacuo*. The mixture was diluted with H_2O (100 ml) and CH_2Cl_2 (150 ml). The organic phase was separated, dried over Na_2SO_4 and evaporated *in vacuo*. The products were separated on silica gel column with MeOH/$CHCl_3$ (0:100-1:200) to give **10**: 1.23 g (68%) as a glass and a mixture of **10** and **11** (0.43 g). The latter mixture was used for deprotection in order to isolate **12**.

Compound 10: FAB Ms (3-nitrobenzyl alcohol): *m/z* % = 550 (M + H^+). ^{1}H-Nmr ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu), 1.37 (t, 3H, *J* = 7.3 Hz, 3H, CH_3CH_2), 1.73 (s, 3H, CH_3), 2.31-2.47 (m, 2H, 2'-H), 3.28 (m, 2H, SCH_2), 3.81 (dd, 1H, *J* = 11.8, 2.3 Hz, 5'-H), 4.02 (m, 2H, 4'-H, 5'-H), 4.34 (m, 1H, 3'-H), 6.11 (t, 1H, *J* = 6.7 Hz, 1'-H), 7.27-7.70 (m, 11H, H_{arom} and H-6). ^{13}C-Nmr ($CDCl_3$): δ 13.53 (CH_3), 13.87 (CH_3), 19.19 (Me_3C), 26.31 (SCH_2), 26.86 (Me_3C), 38.33 (C-2'), 60.22 (C-3'), 63.22 (C-5'), 84.58 (C-4'), 86.89 (C-1'), 119.20 (C-5), 127.66, 129.82, 132.32, 133.20, 133.35, 135,13 (C_{Arom}), 135.35 (C-6), 159.98 (C-2), 168.93 (C-4).

Deprotection of the nucleosides **(10)** *and* **(11)**.

Compound **(10)** (1.20 g, 2.18 mmol) or **(11)** (430 mg, 0.85 mmol) were dissolved in distilled THF (40 ml) at 0 °C. 2.2 ml or 1.7 ml, respectively, of 1M Bu_4NF in THF were slowly added. The mixture was stirred for 2 h and the solvent evaporated *in vacuo*. Silica gel column chromatography with MeOH/$CHCl_3$ (1:99, v/v) afforded **5d** in 46 % yield. Reversed phase (C-18) hplc using H_2O as eluent afforded **12** in 23 % yield.

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2-ethylthio-5-methylpyrimidin-4(1H)-one **(5d)**. Yield: 311 mg (46%) as a glass. FAB Ms (3-nitrobenzyl alcohol): *m/z* % = 312 (M + H^+). ^{1}H-Nmr ($CDCl_3$): δ 1.36 (t, 3H, *J* = 7.3 Hz, CH_3CH_2), 1.93 (s, 3H, CH_3), 2.35-2.49 (m, 2H, 2'-H), 3.37 (m, 2H, SCH_2), 3.89-4.06 (m, 3H, 5'-H and 4'-H), 4.28-4.49 (m, 1H, 3'-H), 6.11 (t, 1H, *J* = 6.1 Hz, 1'-H), 7.30 (s, 1H, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 13.80 (CH_3), 26.18 (SCH_2), 38.71 (C-2'), 59.99 (C-3'), 61.22 (C-5'), 85.41 (C-4'), 87.36 (C-1'), 118.50 (C-5), 135.04 (C-6), 159.97 (C-2), 169.66 (C-4).

1-(2,3-Dihydro-5-hydroxymethylfuran-2-yl)-2-ethylthio-5-methylpyrimidin-4-(1H)-one **(12)**.

Yield: 105 mg (46%) as a glass. FAB Ms (3-nitrobenzyl alcohol) *m/z* % = 269 (M + H^+). ^{1}H-Nmr ($CDCl_3$): δ 1.37 (t, 3H, *J* = 7.5 Hz, CH_3CH_2), 1.96 (s, 3H, CH_3), 2.62-2.69 (m, 1H, 2'-H), 3.22-3.28 (m, 3H, 2'-H, SCH_2), 4.29 (br s, 2H, 5'-H), 5.11 (br s, 1H, 3'-H), 5.21 (br s, 1H, OH), 6.47 (dd, 1H, *J* = 9.3,

3.5 Hz, 1'-H), 7.45 (*s*, 1H, 6-H). ^{13}C-Nmr ($CDCl_3$): δ 13.46 (CH_3), 13.51 (CH_3), 25.89 (SCH_2), 37.11 (C-2'), 56.26 (C-5'), 87.76 (C-1'), 95.27 (C-3'), 118.57 (C-5), 134.16 (C-6), 157.01 (C-4'), 159.30 (C-2), 169.20 (C-4).

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