Synthesis of 3'-Alkylthio-2',3'-dideoxy Nucleosides with Potential Anti-HIV Activity from 2-Deoxy-D-ribose, Using a Phosphorus Pentoxide Reagent

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Direct condensation of 2-deoxy-D-ribose (**1**) with mercaptans using the $P_4O_{10}/H_2O/Bu_3N$ reagent in chloroform resulted in coupling at C-3 to give the anomeric mixtures of the corresponding pentopyranoses **2** and pentofuranoses **3**. After acetylation with acetic anhydride in dry pyridine of these 3-alkylthio pentofufanoses, coupling with the nucleobases uracil, thymine, and cytosine in accordance with the *Friedel-Crafts* catalyzed silyl *Hilbert-Johnson* method yielded the acetylated D-*erythro* nucleosides **7** as anomeric mixtures, separable only by means of chromatography either before or after deprotection with ammonia. The nucleosides **8a-e** were devoid of any activity against HSV-1 and HIV-1.

Synthese von 3'-Alkylthio-2',3'-didesoxy Nukleosiden mit potentieller Wirksamkeit gegen HIV aus 2-Desoxy-D-ribose

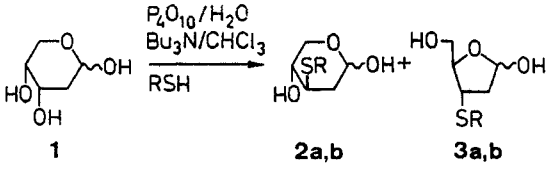
Kondensation von 2-Desoxy-D-ribose (**1**) mit Mercaptanen unter Einsatz von $P_4O_{10}/H_2O/Bu_3N$-Reagens in $CHCl_3$ führte durch Kupplung an C-3 zu einem Anomerengemisch der entspr. Pentopyranosen **2** und Pentofuranosen **3**. Die 3-Alkylthiopentofuranosen wurden mit Acetanhydrid/Pyridin acetyliert und nach der Methode von *Hilbert-Johnson* mit Uracil, Thymin oder Cytosin kondensiert. Die Nukleoside **7** entstanden als Anomerengemische, die nur chromatographisch – vor oder nach Entacetylierung mit NH_3 – getrennt werden konnten. Die Nukleoside **8a-e** zeigen keine Wirksamkeit gegen HSV-1 and HIV-1.

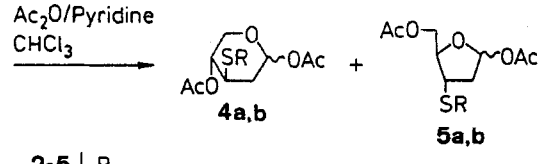
During the last few years, interesting biological activities of several 2',3'-dideoxy-3'-substituted nucleosides have been reported. Some compounds have inhibitory effects on retrovirus, particularly the human immunodeficiency virus (HIV) and hence are of potential use in the therapy of AIDS. Among the most potent antiretroviral agents *in vitro* are 3'-azido-3'-deoxythymidine (AZT) and several other 2',3'-dideoxy nucleosides[1,2].

Still a real need for compounds that may be effective in the therapy of AIDS exists, and this need together with challenging synthetic problems prompted us to investigate a direct and convenient route to the synthesis of 3'-alkylthio-2',3'-dideoxy nucleosides, as remarkably little research has been directed towards these compounds. Actually, one of the only compounds in this class that has been tested for anti-viral effect on HIV is 1-(2,3-dideoxy-3-ethylthio-β-D-*erythro*-pentofuranosyl)thymine which proved capable of protecting ATH8 cells against HIV infection at concentrations above 100 μM[2]. This investigation describes the coupling of 1,5-di-*O*-acetyl-2,3-dideoxy-3-ethylthio-D-*erythro*-pentofuranose (**5a**) and 1,5-di-*O*-acetyl-3-benzylthio-2,3-dideoxy-D-*erythro*-pentofuranose (**5b**) with the suitably silylated nucleobases of uracil, thymine, and cytosine.

Results

As described by *Andersen* and *Pedersen*[3] P_4O_{10} reacts with water and tributylamine in chloroform to give a homogeneous solution of tributylammonium phophate, pyrophosphate, and trimetaphosphate (P_4O_{10}-reagent). In this reagent 2-deoxy-D-ribose (**1**) produces 3-alkylthio-2,3-dideoxy-D-*threo*-pentopyranose **2** and 3-alkylthio-2,3-dideoxy-D-*erythro*-pentofuranose **3** in the presence of alkylmercaptan during 7-9 days at 40°C.





2-5	R
a	Et
b	Bzl

Scheme 1

Without any workup the products were acetylated according to the standard procedure[4] with acetic anhydride in dry pyridine at room temp. for 24 h to give the anomeric mixture of 1,4-di-*O*-acetyl-3-alkylthio-2,3-dideoxy-D-*threo*-pentopyranose **4** and the anomeric mixture of 1,5-di-*O*-acetyl-3-alkylthio-2,3-dideoxy-D-*erythro*-pentofuranose **5** in a combined yield of 80%. After silica column chromatography **4a** and **4b** could be isolated as oils in 56% and 43% yield, respectively, and **5a** and **5b** as oils in 21% and 36% yield, respectively. Coupling with the nucleobase was carried out according to the *Friedel-Crafts* catalyzed silyl *Hilbert-Johnson* reaction[5] which requires a silylated nucleobase **6**. Silylation with hexamethyldisilazane (HMDS) was carried out according to *Vorbrüggen* et al.[6] by refluxing the

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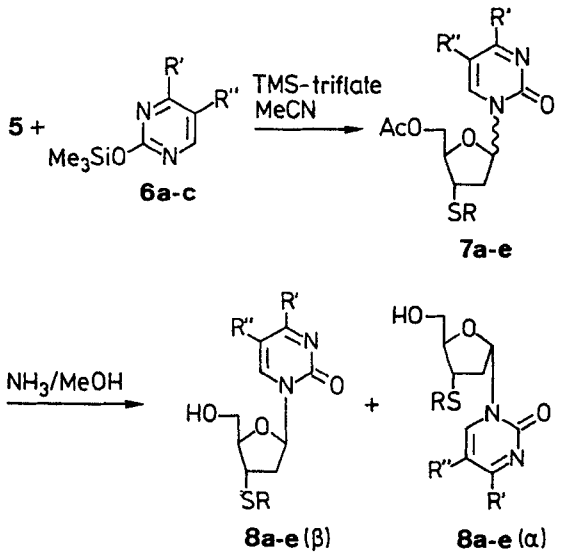


6	R'	R''
a	Me_3SiO	H
b	Me_3SiO	Me
c	$NHCOCHMe_2$	H

7, 8	R	R' (7)	R' (8)	R''
a	Bzl	OH	OH	H
b	Bzl	OH	OH	Me
c	Bzl	$NHCOCHMe_2$	NH_2	H
d	Et	OH	OH	H
e	Et	$NHCOCHMe_2$	NH_2	H

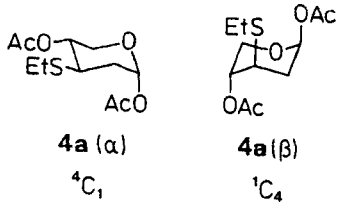
Scheme 2

nucleobase in HMDS in the presence of catalytic amounts of ammonium sulfate. Instead of cytosine itself, N^4-isobutyrylcytosine was used (as its silylated nucleobase), due to its greater solubility in organic solvents[7].

The coupling of the pentofuranose **5** and the silylated pyrimidine base **6** was performed in dry acetonitrile using trimethylsilyl trifluoromethanesulfonate (TMS-triflate) as the catalyst, producing **7** in 30-69% yield with an α/β ratio close to 2. Separation of the anomeric mixture **7** into α- and β-anomers was only possible for 1-(1-*O*-acetyl-2,3-dideoxy-3-ethylthio-D-*erythro*-pentofuranosyl)-N^4-isobutyrylcytosine (**7e**) using ether as the eluent on a silica column. The remaining anomeric mixtures **7a-d** were deprotected as such with a saturated solution of ammonia in methanol[8] giving **8a-d** as the anomeric mixtures. 1-(2,3-Dideoxy-3-ethylthio-D-*erythro*-pentofuranosyl)cytosine (**8e**) was obtained by deprotection of the pure anomers **7e**. Separation and purification of the mixtures **8a-d** was performed by silica chromatography, reverse phase HPLC, or both. Some of the compounds (**8a** (α), **8b** (and β) and **8d** (α)) suffered even after chromatography from contamination with acetamide which is a by-product in the deprotection reaction. In order to devise a method to remove this impurity, coevaporation of **8d** (α) *in vacuo* with both *m*-xylene and *p*-xylene was attempted to azeotropically remove the acetamide. Since this treatment had no effect, **8d** (α) was subjected to reverse phase HPLC ($EtOH/H_2O$, 20/80, v/v which proved effective as a means of purification.

Discussion

As indicated in Scheme 1 the mercaptan acts as a nucleophile towards the carbohydrate. *Motawia* et al. have proposed a mechanism for this reaction with a purine base acting as the nucleophile[8]. This mechanism involves a ring opening of 2-deoxy-D-ribose (**1**) followed by dehydration to give the corresponding α,β-unsaturated aldehyde which subsequently undergoes a *Michael*-type addition to yield the 3-substituted product, present as the pyranose **2** and the furanose **3**.



Scheme 3

Elucidation of the absolute configuration of the pyranose **4a** was accomplished by the joint consideration of the ^1H-^1H homonuclear-shift-correlation 2D-NMR spectrum and the coupling constants. Theoretically, **4** can exist in four possible configurations (α or β and *erythro* or *threo*), of which evidently only two are present in the spectrum. One of these isomers gives no axial-axial couplings to H-1, but two axial-axial couplings to H-3. Consequently only one possibility exists for this isomer: 1,4-di-*O*-acetyl-2,3-dideoxy-3-ethylthio-α-D-*threo*-pentopyranose. Confirmation of this configuration is provided by the fact that two axial-axial couplings are observed for H-4. The other isomer is the corresponding β-anomer, since no axial-axial couplings are observed for neither H-1, H-3 nor H-4. The α- and β-anomers each exist in a chair conformation, $^4C_1$ and $^1C_4$, respectively, both of them having the acetyl group at C-1 axial, as is to be expected on the basis of the anomeric effect.

Hence both the thio group at C-3 and the acetoxy group at C-4 are in axial positions in the β-anomer. Other examples are known[9], where the anomeric effect plays an overriding role in determining the conformation favored. Besides, the *anti*-effect may also contribute to the stability of the $^1C_4$ conformation. Due to the *anti*-effect, the axial-axial conformation is also the predominant one for *trans*-1,2-dihalocyclohexanes[10,11]. Hence it might be concluded that the unfavorable 1,3-diaxial steric interaction between the acetyl group at C-1 and the thio group at C-3 is outweighed by the combination of the anomeric effect and the *anti*-effect. Retrieving the characteristic features of the spectra of **4a** in the spectra of **4b** allowed the assignment of the *threo* configuration for this anomeric mixture also.

Table 1: ^{1}H-NMR data $\delta^{a,b}$.

	8a		8b		8c		8d		8e	
	α	β	α	β	α	β	α	β	α	β
H-1'	6.10 (t)	6.05 (t)	6.13 (t)	6.08 (t)	5.96 (t)	6.04 (t)	6.18 (t)	6.04 (dd)	5.99 (t)	6.07 (t)
H-2'α	1.94	2.28	1.92	2.32	1.84 (ddd)	2.21	2.01	2.27	1.87 (ddd)	2.30
H-2'β	2.77 (ddd)	2.28	2.72 (ddd)	2.32	2.68 (ddd)	2.21	2.97 (ddd)	2.27	2.80 (ddd)	2.30
H-3'	3.28 (q)	3.36 (q)	3.28 (q)	3.48 (q)	3.26 (q)	3.30 (q)	3.44 (q)	3.40 (q)	3.40	3.39 (q)
H-4'	4.15	3.84[c]	4.14 (ddd)	3.84	4.16	3.82[c]	4.17	3.75	4.12	3.78
H-5'	3.76	3.68	3.77[c]	3.84	3.52	3.67	3.87 (dd)	3.75	3.55	3.78
H-5'	3.54 (dd)	3.56	3.56 (dd)	3.84	3.39	3.55	3.67 (dd)	3.59 (dd)	3.40	3.62 (dd)
H-5	5.75 (d)	5.62 (d)			5.73 (d)	5.70 (d)	5.78 (d)	5.51 (d)	5.76 (d)	5.75 (d)
H-6	7.50 (d)	7.92 (d)	7.27 (s)	7.32 (s)	7.66 (d)	7.87 (d)	7.55 (d)	7.95 (d)	7.67 (d)	7.96 (d)
Ph	7.30 (s)	7.34 (s)	7.32 (s)	7.31 (s)	7.32 (s)	7.32 (s)				
CH_3							1.27 (t)	1.20 (t)	1.18 (t)	1.22 (t)
CH_2	3.78 (s)	3.87 (s)	3.80 (s)	3.80 (s)	3.82 (s)	3.86 (s)	2.62 (q)	2.61 (q)	2.58 (q)	2.63 (q)

[a] $CDCl_3$/TMS: **8a**(α), **8b**, **8d**(α). [D_6]DMSO/TMS: **8a**(β), **8c**, **8d**(β), **8e**.
[b] Multiplets when no hyperfine splitting is given.
[c] Signal obscured by SCH_2.

Table 2: ^{1}H-^{1}H coupling constants (Hz).

	8a		8b		8c		8d		8e	
	α	β	α	β	α	β	α	β	α	β
1'-2'	6	6	6	6	6	6	6	7 4	6	6
2'-2'	14		14		14		14		14	
2'-3'	7	7	7	7	7	7	7	8	7	8
3'-4'	7	7	7	7	7	7	7	8		8
4'-5'[a]			2				3			
4'-5'[b]	4		4				4	2		3
5'-5'	12		12				12	12		12
5-6	8	8			7	7	8	8	7	7
EtS							7	7	7	7

[a] Downfield H-5'. [b] Upfield H-5'.

Formation of both α- and β-anomers of the protected nucleoside **7** is observed in the coupling of the 2-deoxy-furanose **5** and the silylated nucleobase **6**. The lack of a stabilizing and bulky functionality in the 2-position renders the carbocation, resulting from *Lewis* acid attack on and subsequent removal of the 1-acetyl group[12], susceptible to base attack at both the α- and the β-face of the ring.

In order to determine the absolute configuration of C-3' and C-1' of the nucleosides **8**, the ^{1}H-NMR spectrum was completely assigned by considering the ^{1}H-^{1}H homonu-

Table 3: ^{13}C-NMR data δ[a].

	8a		8b		8c		8d		8e	
	α	β	α	β	α	β	α	β	α	β
C-1'[b]	86.48	85.50	85.91	85.79	85.96	85.34	86.64	85.88	86.29	85.79
C-2'[c]	40.23		40.17	40.24			40.66			
C-3'[c]	41.42	40.74	41.39	41.61	41.58	40.74	41.37		41.23	
C-4'[b]	86.04	83.92	85.41	85.44	85.83	85.53	86.03	83.89	85.87	84.53
C-5'	62.36	60.45	62.31	61.16	61.58	60.58	62.33	60.22	61.52	60.32
C-2	150.54	150.27	150.42	150.72	154.91	154.88	150.53	150.30	155.09	155.00
C-4	163.74	163.05		164.19	165.56	165.48	163.61	163.09	165.66	165.48
C-5	102.28	101.34	111.08	111.13	93.56	93.52	102.33	101.26	93.74	93.52
C-6	139.70	140.38	135.17	136.53	140.81	140.80	139.58	140.49	140.87	140.89

[a] $CDCl_3$/TMS: **8a**(α), **8b**, **8d**(α). [D_6]DMSO/TMS: **8a**(β), **8c**, **8d**(β), **8e**.
Where no values for C-2' and C-3' are given, these were obscured by the DMSO signal.
[b] May be interchanged.
[c] May be interchanged.

clear-shift-correlated 2D-NMR spectra of **8d**(α). Subjecting **8d**(α) to NOE experiments provided the basis for assigning the absolute configuration. Irradiation of H-6 causes an NOE in H-4' (4%) thus indicating α-form. This is supported by irradiation of H-4' which gives NOE at H-6 (4%). The two H-2' protons have different chemical shifts and β configuration was assigned to the one appearing further downfield on basis of the NOE observed at this proton (6%) when irradiating H-1' and the very large NOE observed at H-6 (21%) when irradiating the upfield proton (*i.e.* H-2'α). Irradiation of the H-2'β proton itself not only confirms this assignment with a large NOE at H-1' (9%), but also results in a large NOE at H-3' (8%) evidential of *erythro* configuration. The NOE's at SCH_2 (2% and 4% when irradiating H-2'β and H-2'α, respectively) support the assignment of *erythro* configuration. Assignment of configuration for the remaining nucleosides was accomplished by retrieving the characteristic features of the spectra of **8d**(α) of **8d**(β) in the spectra of the compound in question. If the H-4' proton is *syn* to the nucleobase, it will appear at a lower field than if it is *anti* to the nucleobase due to a larger deshielding. The same relationship is true for the H-5' protons[13]. These considerations add up to the α configuration having the H-4' proton at a lower field and the H-5' protons at a higher field, than is the case for the β configuration.

Considering the ^{1}H-NMR data of Table 1 these trends are clearly evident for H-4', but less clear cut for H-5'. For H-4' there is typically a significant difference of 0.3-0.4 ppm between the α and β form, allowing the assignment to be made without ambiguity.

Anti-Viral Evaluation

The α- and β-anomers of the nucleosides **8a-e** did not show any significant activity at 100 μM against Herpes 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. Both α- and β-anomers of the nucleoside **8b** showed some cytotoxicity at 100 μM. The compounds **8a-e** were also devoid of any activity 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[14]. Only the β-anomer of the nucleoside **8b** showed cytotoxicity against MT-4 cells with TD_{50} = 100 μM. At sub-toxic concentrations this compound did not show any significant activity against HIV-1.

Experimental Part

^{13}C- and ^{1}H-NMR spectra: Bruker 250 FT NMR.- NOE experiments: Bruker AM 500 spectrometer, difference method, subsequently decoupling the characteristic lines in the spectrum of **8d**(α).- Peakmatchings: Varian MAT 311A spectrometer.- Microanalyses: Novo Nordisk Microanalytical Laboratory A/S, Novo Allé, DK-2880 Bagsvaerd.- Silica used in all column chromatographic separations: Merck 9385, 230-400 mesh (0.040-0.063 mm).

P_4O_{10}-reagent

Water (42.3 g, 2.35 mol) was added dropwise to a stirred solution of P_4O_{10} (200 g, 0.704 mol) in chloroform (800 ml). After addition of water, chloroform (400 ml) was added and the reaction mixture refluxed for 1/2 h at 80°C. To the cold solution was gradually added tributylamine (272 g, 1.47 mol) and a clear solution was obtained. Subsequent to cooling chloroform was added to a total volume of 2 l.

1,4-Di-O-acetyl-3-alkylthio-2,3-dideoxy-D-threo-pentopyranose (**4**) *and 1,5-di-O-acetyl-3-alkylthio-2,3-dideoxy-D-erythro-pentofuranose* (**5**)

The appropriate mercaptan (57 mmol) was added to the P_4O_{10}-reagent (250 ml). Tributylamine (30 g, 162 mmol) was added and the stirred mixture was refluxed for 1/2 h at 80°C. Subsequent to cooling 2-deoxy-D-ribose (**1**) (15.2 g, 114 mmol) was added. The reaction mixture was kept for 7-9 days at 40°C. Without workup of **2** + **3**, the mixture was added dropwise to a stirred mixture of acetic anhydride (91.3 g, 894 mmol), dry pyridine (50 ml), and chloroform (75 ml) cooled to -20°C. The reaction mixture was left cold for 1/2 h after the addition and then left at room temp. for 24 h. Evaporation *in vacuo* yielded a dark brown, highly viscous residue which was extracted with 1.5 l of ether. The combined ether extracts were washed with cold water, ice-cold saturated aqueous $NaHCO_3$ and with cold water again, and then dried (Na_2SO_4). The residue resulting from evaporation of the ether *in vacuo* was chromatographed on a silica column using ether/cyclohexane (1/9, v/v) affording **4a** (7.34 g, 56%) and *1,5-di-O-acetyl-2,3-dideoxy-3-ethylthio-D-erythro-pentofuranose* (**5a**) (2.84 g, 21%) or using ether/petroleum ether (3/7, v/v) yielding **4b** (7.95 g, 43%) and *1,5-di-O-acetyl-3-benzylthio-2,3-dideoxy-D-erythro-pentofuranose* (**5b**) (6.53 g, 36%) as oils.

4a α-anomer: ^{1}H-NMR ($CDCl_3$/TMS): δ = 1.26 (t, 3H, Me), 1.85-1.99 (m, 1H, H-2β), 2.12 (s, 6H, Ac), 2.23 (dt, 1H, H-2α), 2.64 (q, 2H, SCH_2), 3.12 (ddd, 1H, H-3), 3.65 (dd, 1H, H-5α), 3.94 (dd, 1H, H-5β), 4.79-4.88 (m, 1H, H-4), 6.05 (t, 1H, H-1). J (1, 2α) = J (1, 2β) = 3 Hz, J (2α, 2β) = 14 Hz, J (2α, 3) = 4 Hz, J (2β, 3) = 11 Hz, J (3, 4) = 9 Hz, J (4, 5α) = 9 Hz, J (4, 5β) = 5 Hz, J (5α, 5β) = 11 Hz, J (SEt) = 7 Hz.

4a β-anomer: ^{1}H-NMR ($CDCl_3$/TMS): δ = 1.28 (t, 3H, Me), 1.85-1.99 (m, 1H, H-2), 2.11 (s, 6H, Ac), 2.45 (ddd, 1H, H-2), 2.64 (q, 2H, SCH_2), 2.98 (q, 1H, H-3), 3.63 (dd, 1H, H-5), 4.37 (dd, 1H, H-5), 4.79-4.88 (m, 1H, H-4), 5.96 (t, 1H, H-1). J (1, 2α) = J (1, 2β) = 4 Hz, J (2α, 2β), = 14 Hz, J (2α, 3) = J (2β, 3) = 5 Hz, J (3, 4) = 5 Hz, J (4, 5 (at 3.63 ppm)) = 4 Hz, J (4, 5 (at 4.37 ppm)) = 3 Hz, J (5α, 5β) = 13 Hz, J (SEt) = 7 Hz.

4a: $C_{11}H_{18}O_5S$ Calcd. C 50.37 H 6.92 Found C 50.66 H 6.97.

4b α-anomer: ^{1}H-NMR ($CDCl_3$/TMS): δ = 1.90-1.97 (m, 1H, H-2), 2.09 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.12-2.20 (m, 1H, H-2), 3.08 (ddd, 1H, H-3), 3.66 (dd, 1H, H-5α), 3.84 (m, 2H, SCH_2), 3.98 (dd, 1H, H-5β), 4.85-4.96 (m, 1H, H-4), 6.03 (t, 1H, H-1), 7.25-7.36 (m, 5H, Ph). J (1, 2α) = J (1, 2β) = 3 Hz, J (2α, 3) = 5 Hz, J (2β, 3) = 11 Hz, J (3, 4) = 9 Hz, J (4, 5α) = 9 Hz, J (4, 5β) = 5 Hz, J (5α, 5β) = 11 Hz.

4b β-anomer: ^{1}H-NMR ($CDCl_3$/TMS): δ = 1.78-1.89 (m, 1H, H-2), 2.13 (s, 6H, Ac), 2.41 (ddd, 1H, H-2), 2.93 (q, 1H, H-3), 3.65 (dd, 1H, H-5), 3.84 (m, 2H, SCH_2), 4.42 (dd, 1H, H-5), 4.85-4.96 (m, 1H, H-4), 5.97 (t, 1H, H-1), 7.25-7.36 (m, 5H, Ph). J (1, 2α) = J (1, 2β) = 3 Hz, J (2α, 2β) = 15 Hz, J (2α, 3) = J (2β, 3) = 5 Hz, J (3, 4) = 5 Hz, J (4, 5 (at 3.65 ppm)) = J (4, 5 (at 4.42 ppm)) = 2 Hz, J (5α, 5β) = 13 Hz.

4b: $C_{16}H_{20}O_5S$ Calcd. C 59.24 H 6.21 Found C 59.21 H 6.25.

5a (one anomer): ^{13}C-NMR ($CDCl_3$/TMS): δ = 14.73 (Me), 20.61, 21.11 (Ac), 25.63 (SCH_2), 40.76, 41.26 (C-2, C-3), 65.05 (C-5), 83.88 (C-4), 97.90 (C-1), 169.67, 170.44 (C=O).

5b (anomeric mixture): ^{13}C-NMR ($CDCl_3$/TMS): δ = 20.60, 20.80, 21.08 (Ac), 36.24, 36.43 (SCH_2), 40.33, 40.55, 41.15, 41.41 (C-2, C-3), 63.55, 64.84 (C-5), 82.71, 83.57 (C-4), 97.82, 97.91 (C-1), 127.26, 128.53, 128.60, 137.43 (Ph), 169.65, 170.34 (C=O).

5-O-Acetyl-3-alkylthio-2,3-dideoxy-D-erythro-pentofuranosyl nucleosides (**7**)

Under N_2 the appropriate silylated pyrimidine (5.5 mmol, 1.1 equiv.) in dry acetonitrile (20-30 ml) was added dropwise to a solution of the appropriate **5** (5.0 mmol, 1 equiv.) in dry acetonitrile (30 ml) at -30°C. A solution of TMS-triflate (6.0 mmol, 1.2 equiv.) in dry acetonitrile (10-20 ml) was added dropwise to the reaction mixture at -30°C. When the reaction was complete after 2 h, as witnessed by TLC (MeOH/$CHCl_3$, 1/9, v/v), the mixture was dissolved in CH_2Cl_2 and extracted with ice-cold saturated aqueous $NaHCO_3$ (500 ml) which was extracted several times with additional CH_2Cl_2. The combined CH_2Cl_2 phases were neutralized by washing with cold water and then dried (Na_2SO_4). Evaporation of the solvent afforded an oily residue which was chromatographed on a silica column (MeOH/CH_2Cl_2, 2/98 or 1/99, v/v) to give the anomeric mixtures **7** in the following yields: **7a**, 57%, **7b**, 33%, **7c**, 30%, **7d**, 69%. In one instance (**7e**) using ether as the eluent, separation into α and β was accomplished, affording *1-(5-O-acetyl-2,3-dideoxy-3-ethylthio-α-D-erythro-pentofuranosyl)-N^4-isobutyrylcytosine* (**7e**(α)) in 21% yield and the corresponding anomer **7e**(β) in 13% yield. All compounds were obtained as syrups.

3-Alkylthio-2,3-dideoxy-D-erythro-pentofuranosyl nucleosides **8**

The residue **7** was dissolved in ammonia saturated MeOH (100 ml) and stirred at room temp. for at least 5 h. Evaporation *in vacuo* followed by silica chromatography (MeOH) and evaporation again afforded an oily residue in yields of 41%, 33%, 22%, and 39% (based on **5**) for the anomeric mixtures **8a-d**, respectively (α/β: **8a**, 2.7; **8b**, 2.1; **8c**, 2.5; **8d**, 2.4), which were either chromatographed (ether or ether/$CHCl_3$, 1/1, v/v), subjected to prep. TLC (MeOH/$CHCl_3$, 1/9 or 5/95, v/v) or both to give the pure α-anomers of **8a**, **b**, **d**, and **e** in overall (based on **5**) yields of 14%, 9%, 16%, and 21%, respectively, and the corresponding β-anomers in yields of 13%, 6%, 8%, and 12 %, respectively. **8c** could only be separated by reverse phase HPLC (EtOH/H_2O, 26/74, v/v) giving the α-anomer in 5% overall yield and the β-anomer in 4% overall yield from **5**.

8a(α): $C_{16}H_{18}N_2O_4S$ Calcd. 334.0987 Found 334.1016 (MS)
8a(β): $C_{16}H_{18}N_2O_4S$ Calcd. 334.0987 Found 334.1012 (MS)
8b(α): $C_{17}H_{20}N_2O_4S$ Calcd. 348.1144 Found 348.1167 (MS)
8b(β): $C_{17}H_{20}N_2O_4S$ Calcd. 348.1144 Found 348.1125 (MS)
8c(α): $C_{16}H_{19}N_3O_3S$ Calcd. 333.1147 Found 333.1161 (MS)
8c(β): $C_{16}H_{19}N_3O_3S$ Calcd. 333.1147 Found 333.1148 (MS)
8d(α): $C_{11}H_{16}N_2O_4S$ Calcd. 272.0831 Found 272.0831 (MS)
8d(β): $C_{11}H_{16}N_2O_4S$ Calcd. 272.0831 Found 272.0862 (MS)
8e(α): $C_{11}H_{17}N_3O_3S$ Calcd. 271.0991 Found 271.1008 (MS)
8e(β): $C_{11}H_{17}N_3O_3S$ Calcd. 271.0991 Found 271.1005 (MS).

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