Synthesis of 2′,3′-Dideoxy-D-*erythro*-hexofuranosyl Nucleosides and 3′-Azido-2′,3′-dideoxy-D-*arabino*-hexofuranosyl Nucleosides From Tri-*O*-acetyl-D-glucal via an α,β-Unsaturated Hexose Aldehyde

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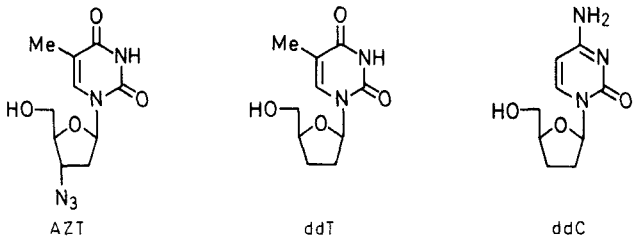
Dedicated to Prof. H.J. Bestmann

α,β-Unsaturated aldehyde **2** prepared from tri-*O*-acetyl-D-glucal was acetalated and benzoylated to give α,β-unsaturated acetal **6**. Hydrogenation of the double bond followed by methanolysis resulted in methyl 2,3-dideoxyfuranosyl glycoside **8** which was used for nucleoside coupling with silylated N^6-isobutyrylcytosine and silylated thymine. Protected 3-azido-2,3-dideoxy-*arabino*-furanose **26** was prepared by 1,4-addition of hydrazoic acid to disilylated α,β-unsaturated aldehyde **24** followed by acetylation. Compound **26** was used for the preparation of 3′-azido-2′,3′-dideoxy-D-*arabino*-hexofuranosyl nucleosides **28** and **29**.

Since 3′-azido-2′,3′-dideoxythymine (AZT), first prepared by Horwitz et al.,[1] was reported as a potent antiviral agent against human immunodeficiency virus HIV,[2] a great numer of synthetic nucleosides has been tested against this retrovirus.[3,4] From the reported data,[3,4] the best suggestion has been to modify the structure at carbon C-2′ and C-3′ by substitution of the natural hydroxy groups with an azido group, a fluorine atom or simply by a proton, but many other modifications have been tried as well.

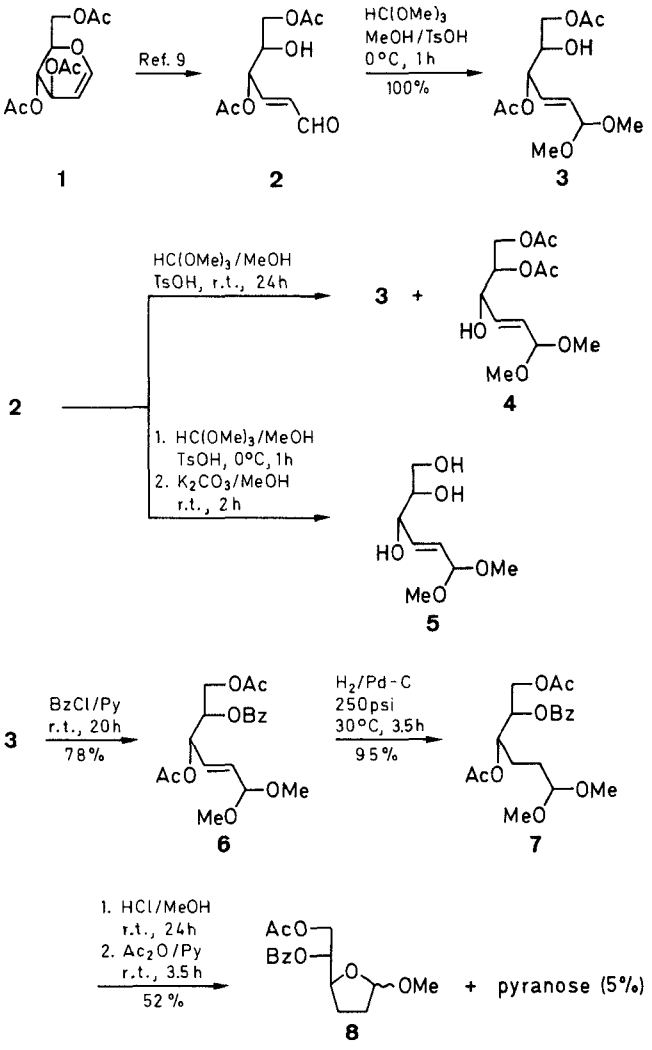
Among the tremendous number of tested compounds 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxycytidine (ddC) and 3′-deoxythymidine (ddT) belong to the very few active candidates which show a reasonably high chemotherapeutic index. Unfortunately, the side effects in their clinical use are very serious and there is still an urgent need for new compounds with improved potency and selectivity in their antiviral actions.



2′,3′-Dideoxynucleosides are generally synthesized by a linear route from 2′-deoxynucleosides via Barton-type deoxygenation reactions[5] or from intact nucleosides through 2′,3′-unsaturated dideoxynucleosides.[6] Another approach has been to synthesize an appropriate carbohydrate precursor which was then coupled with different nucleobases.[7] AZT was originally synthesized directly from thymidine,[1] but non-linear synthesis by coupling of 3-azido-2,3-dideoxyfuranose derivatives with thymine has also been reported.[8]

The non-linear strategy involving the synthesis of an appropriate carbohydrate precursor gives the possibility of introducing different nucleobases producing a number of nucleosides for biological tests. In this paper we want to extend this area by reporting the synthesis of hexofuranose analogues of AZT, ddC and ddT via α,β-unsaturated acetals.

α,β-Unsaturated aldehyde **2** prepared by Perlin transformation[9] of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) was treated with trimethyl orthoformate in methanol together with a catalytic amount of *p*-toluenesulfonic acid. α,β-Unsaturated acetal **3** was isolated in quantitative yield when the reaction was run for only 1 hour at 0 °C whereas longer reaction time at room temperature promoted an acetyl shift from 4-O to 5-O and a 1:1 mixture of **3** and **4** was obtained. It was not possible to induce a complete acetyl migration, and the two isomers **3** and **4** were difficult to separate. Deacetylated acetal **5** was obtained after 2 hours in 85% yield by addition of potassium carbonate to the reaction mixture of **3**. (Scheme 1). The



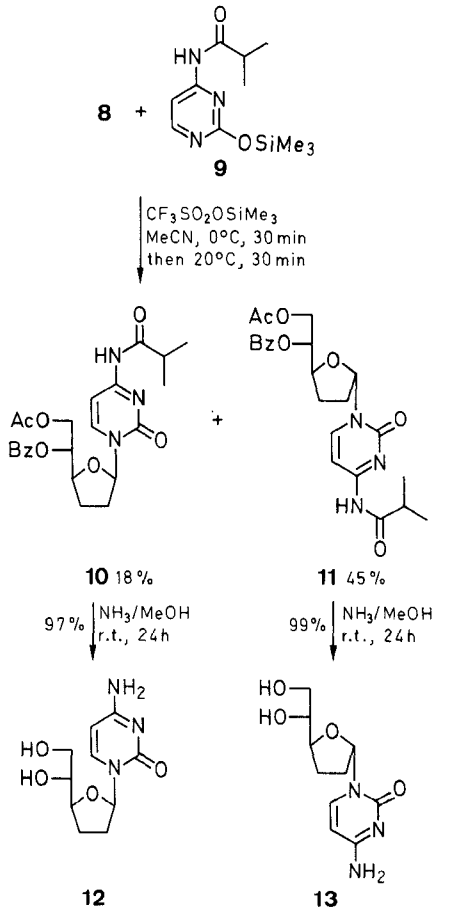
Scheme 1

acetal **5** was not used in the synthesis sequence but was important as a reference compound for the structural assignment of the different protected acetals produced later.

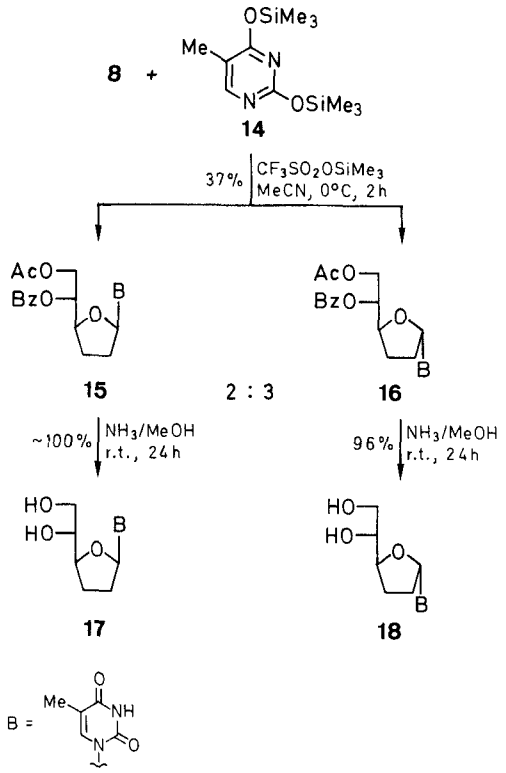
As the critical problem in the synthesis of furanose carbohydrates is to get an unprotected C-4 hydroxy group which can react selectively with the aldehyde functionality, compound **3** was benzoylated at 5-O to give compound **6** in 78% yield.

Catalytic hydrogenation of the double bond with 5% palladium on charcoal at 250 psi gave acetal **7** in 95% yield. In the next step methanolysis of **7** resulted in deacetylation at 6-O and 4-O followed by ring closure to the desired furanose form. After acetylation of the crude product, silica chromatographic purification gave **8** in 52% yield together with a minor fraction containing a pyranose form (Scheme **1**).

Methyl glycoside **8** was coupled with silylated N^6-isobutyrylcytosine[10] **9** with trimethylsilyl trifluoromethanesulfonate (Me_3Si-triflate) as Lewis acid according to the method of Vorbrüggen et al.[11] Flash chromatographic separation gave β-nucleoside **10** in 18% yield and α-nucleoside **11** in 45% yield. After deprotection with a saturated solution of ammonia in methanol the final nucleosides **12** and **13** were obtained in almost quantitative yields (Scheme **2**). Thus, the two nucleosides were prepared in only 8 steps from commercially available tri-*O*-acetyl-D-glucal **1**. When silylated thymine **14** was used as nucleobase, it was necessary to use reverse phase HPLC in order to separate the two anomers **15** and **16**. Deprotection of the separated anomers gave the final thymine derivatives **17** and **18** (Scheme **3**). In both coupling reactions we thus obtained predominantly α-nucleosides. In the D-pentose series, the α,β-ratio of 2',3'-dideoxycytidine anomers was also unfavorable[12] in similar couplings.



Scheme **2**

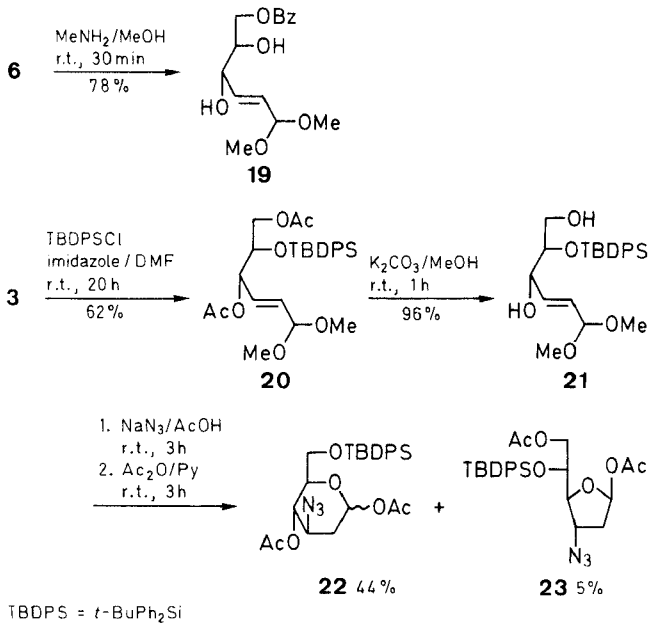


Scheme **3**

The structural assignment of the α- and β-nucleosides was done by comparison with the NMR data of the corresponding pentose derivatives. Especially, the deshielding effect of the nucleobase generates a considerable down field shift of proton 5'-H when the nucleobase is changed from the α- to the β-face of the furanose ring. On the contrary, proton 4'-H is changed upfield when the nucleobase is changed from the α- to the β-face of the furanose ring.[7]

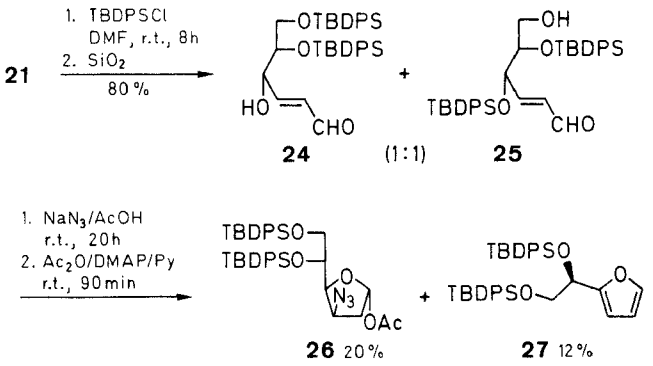
Next, we focused on the synthesis of a 3-azido-2,3-dideoxyhexofuranose which could be used for the preparation of a new AZT analogue. The strategy was to perform a 1,4-addition of hydrazoic acid to an α,β-unstaurated aldehyde with an unprotected 4-hydroxy group, which afterwards could ring close to give the desired furanose ring. The main problem in this synthesis was to obtain the furanose configuration instead of the more stable pyranose configuration. Initial experiments with different protected α,β-unsaturated carbohydrate aldehydes were very disappointing due to elimination of hydrazoic acid from the 1,4-adduct and migration of the 5-*O*-protecting group.[13,14] In order to prevent these side effects it was necessary to use a substrate which could make ring closure immediately after 1,4-addition of

hydrazoic acid. 5-*O*-Benzoylated α,β-unsaturated acetal **6** was therefore used as a candidate for preparation of the needed substrate. Unfortunately, the benzoyl group migrated to the terminal hydroxy group when **6** was deacetylated with methylamine in methanol to give compound **19** (Scheme **4**). As it was not possible to deacetylate **6** under acidic conditions, we decided to change the protecting group at 5-O. Compound **3** was silylated with *tert*-butylchlorodiphenylsilane in dimethylformamide to give compound **20** in 62% yield. Deacetylation with potassium carbonate in methanol gave acetal **21** which was subjected to 1,4-addition of hydrazoic acid in acetic acid followed by acetylation of the anomeric oxygen. A migration of the silyl protecting group to the terminal hydroxy group during the 1,4-addition resulted in pyranose compound **22** as the major component while the furanose compound **23** was isolated in 5% yield only (Scheme **4**).

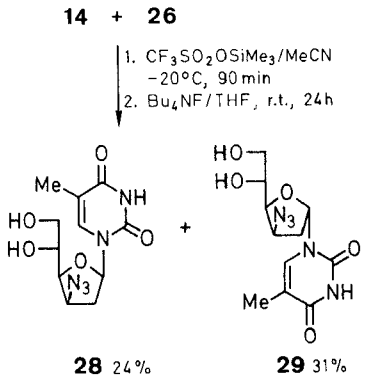


Scheme **4**

In order to prevent this migration we decided to protect the terminal hydroxy group of compound **21**, Silylation of **21** with *tert*-butylchlorodiphenylsilane in dimethylformamide gave a 1:1 mixture of disilylated α,β-unsaturated aldehydes **24** and **25** in 80% yield after silica chromatographic purification which resulted in deprotection of the aldehyde. As it was not possible to separate **24** and **25**, 1,4-addition of hydrazoic acid was done on the mixture of both aldehydes. After acetylation of the anomeric oxygen β-D-*arabino* furanose **26** was isolated in 41% yield calculated from **24**. Besides, the furan derivative **27** was obtained as a byproduct (Scheme **5**). Nucleoside coupling with **26** and silylated thymine gave a 1:1 mixture of β- and α-nucleosides. After deprotection with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran, the anomers were separated on reverse phase HPLC to give the β-anomer **28** in 24% yield and the α-anomer **29** in 31% yield (Scheme **6**).



Scheme **5**



Scheme **6**

In continuation of this work we tried to prepare 5-deoxy analogues of the 2,3-dideoxyfuranose **8** and the 3-azido-2,3-dideoxyfuranose **26** starting from the unsaturated acetal **3**. Thus, **3** was reacted with phenyl thioformate together with 4-dimethylaminopyridine (DMAP) in dichloromethane to give a phenoxythiocarbonyl compound in 64% after chromatographic purification. Attempted Barton type deoxygenation of this derivative with tributyltin hydride and the radical initiator α,α'-azoisobutyronitrile (AIBN) in toluene at 80°C failed. Deoxygenation of the C-5 hydroxy group of compound **3** via the tosylate, mesylate and iodo derivatives was also tried, but without success.

The structural assignment of β-D-*ribo* hexofuranose **23**, α-D-*arabino* hexofuranose **26**, β-thymine derivative **28** and α-thymine derivative **29** was done by comparison of NMR data with those from similar pentose compounds and 1-(3-azido-2,3-dideoxypentofuranosyl)thymines[8,15,16] and by 2D ^{1}H-NMR and NOE ^{1}H-NMR experiments. The magnitude of NOEs diminishes rapidly as the interproton distance is increased and is thus suitable for determination of stereochemical configuration. Results from NOE experiments are summarized in the Table. The configurations of compounds **23, 26, 28** and **29** were unambiguously assigned on the basis of the NOEs calculated.

The nucleosides **10–13, 16–18, 28** and **29** did not show activity against human immunodeficiency virus (HIV) strain HTLV-IIIB or cytotoxicity in MT-4 cells at 100 μM.

Table. NOE (%) of Compounds **23**, **26**, **28** and **29**

NOE	Irradiated Proton	Compound			
		23	**26**	**28**	**29**
1'-H	2'α-H	18	11	9	
1'-H	2'β-H	7	24		10
2'α-H	3'-H		7		5
2'β-H	1'-H		5		
2'β-H	3'-H	5			
3'-H	2'α-H		17	10	14
3'-H	2'β-H	8	4		
3'-H	4'-H			8	4
3'-H	5'-H	7			
4'-H	2'α-H		3		
4'-H	3'-H		8	5	
5'-H	3'-H	8			
6-H	2'α-H				5
6-H	2'β-H			3	
6-H	4'-H				5

NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for ^{1}H-NMR and 62.5 MHz for ^{13}C-NMR. Microanalyses were carried out at NOVO-NORDISK Microanalytical Laboratory A/S, Novo Allé, DK-2880 Bagsvaerd. EI mass spectra were recorded on a Varian MAT 311A spectrometer and FAB mass spectra on a Kratos MS-50 spectrometer. IR data were recored on a Perkin Elmer 1720 FTIR spectrophotometer. HPLC was done on Waters Delta Prep 3000 HPLC system. Silica gel (230–400 mesh) was purchased from Merck.

(2*E*,4*S*,5*R*)-4,6-Diacetoxy-5-hydroxy-2-hexenal Dimethyl Acetal (3):

α,β-Unsaturated aldehyde **2**[9] (56.0 g, 0.24 mol) and trimethyl orthoformate (200 mL) are dissolved in absolute MeOH (400 mL) over molecular sieves (3 Å, 10 g). After cooling to 0 °C in an ice/salt bath catalytic amount of TsOH (800 mg, 4.6 mmol) is added. Analytical silica TLC (Et_2O/hexane, 4:1, two times elution) shows the acetal **3** as the only product after 1 h. The mixture is filtered and diluted with CH_2Cl_2 (400 mL). After washing with sat. aq $NaHCO_3$ (2 × 100 mL) and aq NaCl (100 mL), the organic phase is dried ($MgSO_4$) and evaporated to give analytically pure acetal **3** as an oil; yield: 66.0 g (~ 100%).

$C_{12}H_{20}O_7 \cdot 0.25 H_2O$ (280.8) calc. C 51.33 H 7.36 found 51.58 7.26

^{1}H-NMR ($CDCl_3$): δ = 2.09 (s, 3H, $OCOCH_3$), 2.10 (s, 3H, $OCOCH_3$), 3.31 (s, 6H, OCH_3), 3.99 (dt, 1H, *J* = 6.0, 5.2 Hz, 5-H), 4.15 (d, 2H, *J* = 5.2 Hz, 6-Ha, 6-Hb), 4.83 (d, 1H, *J* = 3.8 Hz, 1-H), 5.37 (t, 1H, *J* = 6.0 Hz, 4-H), 5.73 (dd, 1H, *J* = 15.8, 3.8 Hz, 2-H), 5.93 (dd, 1H, *J* = 15.8, 6.0 Hz, 3-H).

^{13}C-NMR ($CDCl_3$): δ = 20.53 ($OCOCH_3$), 20.75 ($OCOCH_3$), 52.37 (OCH_3), 52.43 (OCH_3), 64.53 (C-6), 70.76 (C-5), 73.66 (C-4), 101.32 (C-1), 128.30 (C-3), 131.16 (C-2), 169.69 ($OCOCH_3$), 170.93 ($OCOCH_3$).

MS (FAB, glycerol, NaI): *m/z* = 299 ($M + Na^+$, 8%)

MS: *m/z* (%) = 213 ($M^+ - 63$, 19), 153 (14), 142 (37), 125 (11), 111 (25), 103 (18), 100 (100), 99 (28).

(2*E*,4*S*,5*R*)-5,6-Diacetoxy-4-hydroxy-2-hexenal Dimethyl Acetal (4):

Same procedure as for **3** with the following changes: The reaction is run at r.t. for 24 h to give a 1:1 ratio of acetal **3** and **4**. Longer reaction times does not give higher **3**:**4** ratio. Flash chromatographic purification (silica gel CH_2Cl_2/MeOH, gradient 97:3 → 90:10) gives acetal **4**.

^{1}H-NMR ($CDCl_3$): δ = 2.07 (s, 3H, $OCOCH_3$), 2.10 (s, 3H, $OCOCH_3$), 3.31 (s, 6H, OCH_3), 4.25–4.38 (m, 3H, 4-H, 6-Ha, 6-Hb), 4.80 (d, 1H, *J* = 4.0, 1-H), 5.06 (td, 1H, *J* = 5.6, 3.5 Hz, 5-H), 5.78 (dd, 1H, *J* = 15.9, 4.0 Hz, 2-H), 5.89 (dd, 1H, *J* = 15.9, 5.4 Hz, 3-H).

^{13}C-NMR ($CDCl_3$): δ = 20.63 ($OCOCH_3$), 20.82 ($OCOCH_3$), 52.55 (OCH_3), 52.64 (OCH_3), 62.41 (C-6), 70.74 (C-4), 73.74 (C-5), 101.90 (C-1), 129.83 (C-3), 129.79 (C-2), 170.30 ($OCOCH_3$), 170.82 ($OCOCH_3$).

MS: *m/z* (%) = 244 ($M^+ - 32$, 0.3), 213 ($M^+ - 63$, 6), 201 (10), 173 (26), 153 (42), 111 (42), 100 (100), 99 (81).

(2*E*,4*S*,5*R*)-4,5,6-Trihydroxy-2-hexenal Dimethyl Acetal (5):

Same procedure as for **3** with the following changes: Before filtration, K_2CO_3 is added until the mixture becomes alkaline. The reaction mixture is stirred for 2 h at r.t. and then filtered. The solvent is removed under reduced pressure and the crude product purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 4:1) to give the unprotected acetal **5**; yield: 85%.

^{1}H-NMR (DMSO-d_6): δ = 3.21 (s, 6H, OCH_3), 3.44–3.59 (m, 3H, 5-H, 6-Ha, 6-Hb), 3.84–4.00 (m, 1H, 4-H), 4.40 (broad, 1H, OH), 4.56 (d, 1H, *J* = 4.3 Hz, OH), 4.74 (d, 1H, *J* = 5.2 Hz, 1-H), 4.82 (d, 1H, *J* = 5.5 Hz, OH), 5.53 (ddd, 1H, *J* = 15.8, 5.2, 1.2 Hz, 2-H), 5.91 (dd, 1H, *J* = 15.8, 5.5 Hz, 3-H).

^{13}C-NMR (DMSO-d_6): δ = 52.12 (OCH_3), 63.05 (C-6), 71.41 (C-4), 74.72 (C-5), 102.57 (C-1), 126.29 (C-3), 135.48 (C-2).

MS (FAB, glycerol, NaI): *m/z* = 215 ($M + Na^+$, 28%).

(2*E*,4*S*,5*R*)-5-Benzoyloxy-4,6-diacetoxy-2-hexenal Dimethyl Acetal (6):

Acetal **3** (20.0 g, 72.4 mmol) is dissolved in dry pyridine (100 mL) and benzoyl chloride (15.0 g, 106.3 mol) is added. After 20 h at r.t. the mixture is diluted with CH_2Cl_2 (300 mL) and washed with ice cold aq HCl (2M, 3 × 50 mL) and H_2O (50 mL). After drying ($MgSO_4$) the organic phase is concentrated under reduced pressure. The crude product is purified by flash chromatography (silica gel, 3 × 60 cm, Et_2O/hexane, 1:1) to give analytically pure **6** as an oil; yield: 21.5 g (78%).

$C_{19}H_{24}O_8 \cdot 0.25 H_2O$ (384.9) calc. C 59.29 H 6.42 found 59.44 6.37

^{1}H-NMR ($CDCl_3$): δ = 2.04 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 3.27 (s, 6H, OCH_3), 4.36 (d, 2H, *J* = 5.3 Hz, 6-Ha, 6-Hb), 4.83 (d, 1H, *J* = 3.8 Hz, 1-H), 5.51 (q, 1H, *J* = 5.3 Hz, 5-H), 5.67 (dd, 1H, *J* = 6.4, 5.3 Hz, 4-H), 5.79 (dd, 1H, *J* = 15.8, 3.8 Hz, 2-H), 5.95 (dd, 1H, *J* = 15.8, 6.4 Hz, 3-H).

^{13}C-NMR ($CDCl_3$): δ = 20.39 ($OCOCH_3$), 20.60 ($OCOCH_3$), 52.20 (OCH_3), 52.27 (OCH_3), 61.58 (C-6), 71.50 (C-5), 71.72 (C-4), 101.01 (C-1), 127.50 (C-3), 128.22, 129.33, 129.50 (C_{arom}), 131.82 (C-2), 133.10, (C_{arom}), 165.28 ($OCOC_6H_5$), 169.22 ($OCOCH_3$), 170.26 ($OCOCH_3$).

(4*S*,5*R*)-5-Benzoyloxy-4,6-diacetoxyhexanal Dimethyl Acetal (7):

Unsaturated acetal **6** (10.0 g, 26.3 mmol) is dissolved in MeOH (300 mL) and 5% Pd-C (1.0 g) is added. The solution of **6** is hydrogenated 3.5 h at 250 psi of H_2 at 30 °C. The mixture is filtered through Celite and concentrated under reduced pressure to give analytically pure saturated acetal **7** as an oil; yield: 9.6 g (95%).

$C_{19}H_{26}O_8$ (296.3) calc. C 59.68 H 6.85 found 59.34 6.87

^{1}H-NMR ($CDCl_3$): δ = 1.61–1.82 (m, 4H, 2-Ha, 2-Hb, 3-Ha, 3-Hb), 2.04 (s, 3H, $OCOCH_3$), 2.08 (s, 3H, $OCOCH_3$), 3.30 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 4.34–4.38 (m, 3H, 1-H, 6-Ha, 6-Hb), 5.25 (td, *J* = 6.9, 4.6 Hz, 4-H), 5.45 (td, *J* = 6.2, 4.6 Hz, 5-H), 7.43–8.04 (m, 5H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 20.56 ($OCOCH_3$), 20.74 ($OCOCH_3$), 25.01 (C-3), 25.36 (C-2), 52.63 (OCH_3), 53.03 (OCH_3), 61.97 (C-6), 71.57 (C-5), 71.85 (C-4), 103.80 (C-1), 128.34, 129.63, 133.17 (C_{arom}), 165.51 ($OCOC_6H_5$), 170.12 ($OCOCH_3$), 170.57 ($OCOCH_3$).

MS: *m/z* (%) = 382 (M^+, 1), 277 (10), 115 (37), 105 (100).

Methyl 6-*O*-Acetyl-5-*O*-benzoyl-2,3-dideoxy-D-*erythro*-hexofuranoside (8):

Saturated acetal **7** (5.0 g, 13.1 mmol) is dissolved in a solution of HCl in absolute MeOH (1.0 M, 30 mL). After 24 h at r.t. the reaction is neutralized by addition of Ag_2CO_3 (6.0 g). After 10 min

the mixture is filtered and concentrated under reduced pressure. The crude product is dissolved in dry CH_2Cl_2 (100 mL) and Ac_2O (2.7 g, 26.5 mmol) and pyridine (2.1 g, 26.5 mmol) are added. After 3.5 h at r.t. the mixture is diluted with CH_2Cl_2 (100 mL) and washed with an ice cold solution of aq HCl (1 M, 3 × 40 mL) and H_2O (40 mL). The organic phase is dried ($MgSO_4$) and concentrated to an oil under reduced pressure. Flash chromatographic purification (silica gel, 3 × 40 cm, Et_2O/hexane, 1:1) gives 1.0 g (25%) of the most polar anomer of **8** and 1.1 g (27%) of the less polar anomer of **8**. Besides, a small fraction 0.2 g (5%) of a pyranose isomer is obtained. All isolated isomers are oils.

Most polar anomer of **8**:

$C_{16}H_{20}O_6$ (308.3) calc. C 62.33 H 6.54 found 62.12 6.59

^{1}H-NMR ($CDCl_3$): δ = 1.85–2.10 (m, 7H, 2-Ha, 2-Hb, 3-Ha, 3-Hb, $OCOCH_3$), 3.24 (s, 3H, OCH_3), 4.26–4.37 (m, 2H, 6-Ha, 4-H), 4.54 (dd, 1H, J = 12.1, 2.9 Hz, 6-Hb), 4.97 (d, 1H, J = 4.4 Hz, 1-H), 5.36 (td, 1H, J = 6.4, 2.9 Hz, 5-H), 7.40–8.05 (m, 5 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 20.67 ($OCOCH_3$), 25.88 (C-3), 32.61 (C-2), 54.69 (OCH_3), 63.25 (C-6), 73.72 (C-5), 78.29 (C-4), 105.31 (C-1), 128.26, 129.65, 133.00 (C_{arom}), 166.28 ($OCOC_6H_5$), 169.88 ($OCOCH_3$).

Less polar anomer of **8**:

$C_{16}H_{20}O_6 \cdot 0.25H_2O$ (317.3) calc. C 61.43 H 6.61 found 61.54 6.50

^{1}H-NMR ($CDCl_3$): δ = 1.85–2.22 (m, 7H, 2-Ha, 2-Hb, 3-Ha, 3-Hb, $OCOCH_3$), 3.33 (s, 3H, OCH_3), 4.23–4.41 (m, 2H, 4-H, 6-Ha), 4.47 (dd, 1H, J = 12.1, 3.2 Hz, 6-Hb), 5.03 (dd, 1H, J = 5.0, 1.1 Hz, 1-H), 5.37 (td, 1H, J = 6.4, 3.2 Hz, 5-H), 7.41–8.06 (m, 5 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 20.64 ($OCOCH_3$), 25.31 (C-3), 31.53 (C-2), 54.61 (OCH_3), 63.12 (C-6), 72.85 (C-5), 76.21 (C-4), 105.20 (C-1), 128.31, 129.53, 133.08 (C_{arom}), 165.66 ($OCOC_6H_5$), 170.63 ($OCOCH_3$).

1-(6-*O*-Acetyl-5-*O*-benzoyl-2,3-dideoxy-β-D-*erythro*-hexofuranosyl)-N^4-isobutyrylcytosine (10) and 1-(6-*O*-acetyl-5-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hexofuranosyl)-N^4-isobutyrylcytosine (11):

To a solution of methyl glycoside **8** (2.30 g, 6.92 mmol) and silylated N^4-isobutyrylcytosine[10] (2.24 g, 8.84 mmol) in dry MeCN (40 mL) cooled to 0°C on an ice bath is dropwise added Me_3Si-triflate (1.80 mL, 9.92 mmol). After 30 min at 0°C and 30 min at 20°C TLC (silica gel CH_2Cl_2/MeOH, 95:5) shows no more starting glycoside **8**. The mixture is diluted with CH_2Cl_2 (100 mL) and quenched with sat. aq $NaHCO_3$ (2 × 25 mL). After washing with H_2O (25 mL) the organic phase is dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatographic purification (silica gel, 3 × 40 cm, EtOAc/MeOH, 97:3) gives the β-anomer **10** (0.58 g, 18%) as the most polar isomer, and the α-anomer **11** (1.42 g, 45%) as the less polar isomer.

10:

$C_{23}H_{27}N_3O_7 \cdot 0.5H_2O$ (466.5) calc. C 59.22 H 6.05 N 9.01 found 59.29 6.03 8.76

^{1}H-NMR ($CDCl_3$): δ = 1.20 (d, 3H, J = 6.8 Hz, CH_3), 1.23 (d, 3H, J = 6.8 Hz, CH_3), 2.01–2.20 (m, 6H, 2'-Hb, 3'-Ha, 3'-Hb, $OCOCH_3$), 2.54–2.65 [m, 2H, 2'-Ha, $CH(CH_3)_2$], 4.28 (dd, 1H, J = 12.1, 6.4 Hz, 6'-Ha), 4.36 (q, 1H, J = 6.1 Hz, 4'-H), 4.59 (dd, 1H, J = 12.1, 3.6 Hz, 6'-Hb), 5.66 (td, 1H, J = 6.1, 3.7 Hz, 5'-H), 6.08 (dd, 1H, J = 6.5, 3.2 Hz, 1'-H), 7.14 (d, 1H, J = 7.45 Hz, 5-H), 7.27–8.04 (m, 6H, 5 H_{arom}, 6-H), 8.42 (br, 1H, NH).

^{13}C-NMR ($CDCl_3$): δ = 18.93 (CH_3), 20.60 ($OCOCH_3$), 25.26 (C'-3), 32.70 [$CH(CH_3)_2$], 36.64 (C'-2), 62.94 (C'-6), 71.78 (C'-5), 79.75 (C'-4), 87.55 (C'-1), 95.91 (C-5), 128.61, 129.08, 129.59, 133.59 (C_{arom}), 143.48 (C-6), 154.90 (C-2), 162.12 (C-4), 165.45 ($OCOC_6H_5$), 170.46 ($OCOCH_3$), 176.46 ($CONH_2$).

MS: m/z (%) = 457 (M^+, 1), 277 (32), 182 (33), 138 (42), 112 (15), 105 (100).

11:

$C_{23}H_{27}N_3O_7 \cdot 0.25H_2O$ (462.0) calc. C 59.80 H 6.00 N 9.10 found 59.61 6.02 8.75

^{1}H-NMR ($CDCl_3$): δ = 1.20 [d, 6H, J = 6.9 Hz, $CH(CH_3)_2$], 2.05–2.16 (m, 6H, 2'-Ha, 3'-Ha, 3'-Hb, $OCOCH_3$), 2.62–2.77 [m, 2H, 2'-Hb, $CH(CH_3)_2$] 4.36 (dd, 1H, J = 12.1, 6.1 Hz, 6'-Ha), 4.53 (dd, 1H, J = 12.1, 3.4 Hz, 6'-Hb), 4.69 (q, 1H, J = 6.1 Hz, 4'-H), 5.45 (td, 1H, J = 6.1, 3.4 Hz, 5'-H), 6.08 (dd, 1H, J = 5.8, 2.5 Hz, 1'-H), 7.44–8.02 (m, 5 H_{arom}, 5-H, 6-H), 9.99 (br, 1H, NH).

^{13}C-NMR ($CDCl_3$): δ = 18.83 (CH_3), 18.94 (CH_3), 20.55 ($OCOCH_3$), 25.38 (C'-3), 32.44 [$CH(CH_3)_2$], 36.30 (C'-2), 62.91 (C'-6), 71.93 (C'-5), 79.72 (C'-4), 89.21 (C'-1), 95.97 (C-5), 128.39, 129.23, 129.56, 133.33 (C_{arom}), 143.12 (C-6), 154.12 (C-2), 162.54 (C-4), 165.42 ($OCOC_6H_5$), 170.40 ($OCOCH_3$), 177.23 ($CONH_2$).

MS: m/z (%) = 457 (M^+, 2), 277 (26), 182 (29), 138 (39), 112 (14), 105 (100).

1-(2,3-Dideoxy-β-D-*erythro*-hexofuranosyl)cytosine (12):

Nucleoside **10** (0.45 g, 0.98 mmol) is dissolved in sat. methanolic (absolute) NH_3 (20 mL). After 24 h at r.t., the solvent is removed and the crude product purified by flash chromatography (silica gel, 1 × 30 cm, EtOH) to give the unprotected nucleoside **12** as an oil; yield: 0.23 g (97%).

$C_{10}H_{15}N_3O_4 \cdot 0.5H_2O$ (250.3) calc. C 48.00 H 6.44 N 16.79 found 48.26 6.48 16.38

^{1}H-NMR (CD_3OD): δ = 1.91–2.10 (m, 3H, 2'-Hb, 3'-Ha, 3'-Hb), 2.38–2.48 (m, 1H, 2'-Ha), 3.58 (dd, 1H, J = 11.4, 6.4 Hz, 6'-Ha), 3.66 (dd, 1H, J = 11.1, 4.8 Hz, 6'-Hb), 3.99 (q, 1H, J = 6.4 Hz, 4'-H), 4.14 (td, 1H, J = 6.4, 4.8 Hz, 5'-H), 5.91 (d, 1H, J = 7.5 Hz, 5-H), 6.06 (dd, 1H, J = 6.4, 2.2 Hz, 1'-H), 7.68 (d, 1H, J = 7.5 Hz, 6-H).

^{13}C-NMR (CD_3OD): δ = 22.09 (C'-3), 33.91 (C'-2), 64.93 (C'-6), 74.64 (C'-5), 83.31 (C'-4), 87.93 (C'-1), 95.34 (C-5), 142.88 (C-6), 158.29 (C-2), 167.63 (C-4).

MS: m/z (%) = 241 (M^+, 2), 131 (14), 112 (100), 111 (69).

1-(2,3-Dideoxy-α-D-*erythro*-hexofuranosyl)cytosine (13):

Nucleoside **11** (1.15 g, 2.51 mmol) is dissolved in sat methanolic (absolute) NH_3 (50 mL). After 24 h at r.t. the solvent is removed under reduced pressure and the crude product purified by chromatography (silica gel, 3 × 40 cm, EtOH) to give the unprotected nucleoside **13** as a white hygroscopic foam; yield: 0.60 g (99%).

$C_{10}H_{15}N_3O_4 \cdot 0.5H_2O$ (250.3) calc. C 48.00 H 6.44 N 16.79 found 48.18 6.99 16.31

^{1}H-NMR (CD_3OD): δ = 2.00–2.15 (m, 3H, 2'-Ha, 3'-Ha, 3'-Hb), 2.42–2.59 (m, 1H, 2'-Hb), 3.57–3.80 (m, 3H, 5'-H, 6'-Ha, 6'-Hb), 4.42 (q, 1H, J = 6.0 Hz, 4'-H), 5.95 (d, 1H, J = 7.4 Hz, 5-H), 6.08 (dd, 1H, J = 6.3, 3.8 Hz, 1'-H), 7.69 (d, 1H, J = 7.4 Hz, 6-H).

^{13}C-NMR (CD_3OD): δ = 25.60 (C'-3), 32.66 (C'-2), 64.42 (C'-6), 74.38 (C'-5), 82.80 (C'-4), 89.52 (C'-1), 95.67 (C-5), 141.96 (C-6), 158.29 (C-2), 167.70 (C-4).

MS: m/z (%) = 241 (M^+, 1), 131 (12), 112 (44), 111 (100).

1-(6-*O*-Acetyl-5-*O*-benzoyl-2,3-dideoxy-β-D-*erythro*-hexofuranosyl)-thymine (15) and 1-(6-*O*-Acetyl-5-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hexofuranosyl)thymine (16):

A solution of methylglycoside **8** (0.90 g, 2.71 mmol) and silylated thymine (0.40 g, 3.17 mmol) in dry MeCN (25 mL) is cooled to 0°C in an ice bath. Me_3Si-triflate (0.6 mL, 3.31 mmol) is added dropwise. After 2 h at 0°C TLC (silica gel CH_2Cl_2/and MeOH, 95:5) shows no more starting glycoside **8**. The mixture is diluted with CH_2Cl_2 (50 mL) and quenched with sat. aq $NaHCO_3$ (2 × 15 mL). After washing with H_2O (15 mL) the organic phase is dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatographic purification (silica gel, 2 × 35 cm, EtOAc) gives analytically pure nucleosides **15** and **16** as an anomeric mixture (α:β ~ 3:2); yield: 0.41 g (37%).

$C_{20}H_{22}N_2O_7 \cdot 0.25H_2O$ (402.4) calc. C 59.04 H 5.57 N 6.88 found 59.21 5.62 6.73

The anomeric mixture of **15** and **16** is separated by reverse phase HPLC (Waters Delta Pak 300 Å, 15 μ, 57 × 300 mm, EtOH and H_2O 30:70):

15: HPLC retention time = 40 min.

^{1}H-NMR ($CDCl_3$): δ = 1.94 (s, 3 H, CH_3), 2.00–2.30 (m, 6 H, 2'-Hb, 3'-Ha, 3'-Hb, $OCOCH_3$), 2.35–2.50 (m, 1 H, 2'-Ha), 4.24 (dd, 1 H, J = 12.2, 6.6 Hz, 6-Ha), 4.26 (q, 1 H, J = 6.6 Hz, 4'-H), 4.52 (dd, 1 H, J = 12.2, 2.8 Hz, 6-Hb), 5.66 (td, 1 H, J = 6.6, 2.8 Hz, 5'-H), 6.08 (dd, J = 6.5, 5.3 Hz, 1'-H), 7.41 (s, 1 H, 5-H), 7.44–8.06 (m, 5 H_{arom}), 9.09 (br, 1 H, NH).

^{13}C-NMR ($CDCl_3$): δ = 11.86 (CH_3), 20.61 ($OCOCH_3$), 25.50 (C'-3), 31.29 (C'-2), 62.90 (C'-6), 71.76 (C'-5), 78.37 (C'-4), 85.28 (C'-1), 110.62 (C-5), 128.44, 129.45, 129.63, 133.60 (C_{arom}), 135.05 (C-6), 150.06 (C-2), 163.70 (C-4), 165.51 ($OCOC_6H_5$), 170.60 ($OCOCH_3$).

MS: m/z (%) = 402 (M^+, 2), 278 (11), 277 (68), 105 (100).

16: HPLC retention time = 70 min.

^{1}H-NMR ($CDCl_3$): δ = 1.94 (s, 3 H, CH_3), 2.04–2.29 (m, 6 H, 2'-Ha, 3'-Ha, 3'-Hb, $OCOCH_3$), 2.51–2.63 (m, 1 H, 2'-Hb), 4.33 (dd, 1 H, J = 12.1, 6.3 Hz, 6'-Ha), 4.51 (dd, 1 H, J = 12.1, 3.3 Hz, 6'-Hb), 4.62 (q, 1 H, J = 6.3 Hz, 4'-H), 5.40 (td, 1 H, J = 6.3, 3.3 Hz, 5'-H), 6.06 (dd, 1 H, J = 6.3, 4.6 Hz, 1-H), 7.12 (s, 1 H, 5-H), 7.45–8.06 (m, 5 H_{arom}), 9.25 (br, 1 H, NH).

^{13}C-NMR ($CDCl_3$): δ = 12.66 (CH_3), 20.77 ($OCOCH_3$), 26.58 (C'-3), 32.05 (C'-2), 62.74 (C'-6), 72.33 (C'-5), 79.44 (C'-4), 87.68 (C'-1), 110.77 (C-5), 128.58, 129.44, 129.77, 133.52 (C_{arom}), 135.19 (C-6), 150.23 (C-2), 163.92 (C-4), 165.65 ($OCOC_6H_5$), 170.64 ($OCOCH_3$).

MS: m/z (%) = 402 (M^+, 2), 278 (10), 277 (59), 105 (100).

1-(2,3-Dideoxy-β-D-*erythro*-hexofuranosyl)thymine (17):

Nucleoside **15** (80 mg, 0.20 mmol) is dissolved in sat. methanolic (absolute) NH_3 (10 mL). After 24 h at r.t. the solvent is removed under reduced pressure and the crude product purified by flash chromatography (silica gel, 1 × 20 cm, CH_2Cl_2/MeOH, 9:1) to give the unprotected nucleoside **17** as a foam; yield: 50 mg (100%).

^{1}H-NMR (CD_3OD): δ = 1.87 (d, 3 H, J = 0.9 Hz, CH_3), 1.99–2.11 (m, 3 H, 2'-Hb, 3'-Ha, 3'-Hb), 2.32–2.41 (m, 1 H, 2'-Ha), 3.53–3.62 (m, 2 H,6'-Ha, 6'-Hb), 3.96 (q, 1 H, J = 6.0 Hz, 4'-H), 4.06–4.13 (m, 1 H, 5'-H), 6.04 (dd, 1 H, J = 6.6, 1.6 Hz, 1'-H), 7.97 (q, 1 H, J = 0.9 Hz, 5-H).

^{13}C-NMR (CD_3OD): δ = 12.51 (CH_3), 22.12 (C'-3), 33.21 (C'-2), 64.90 (C'-6), 73.54 (C'-5), 83.07 (C'-4), 88.50 (C'-1), 111.30 (C-5), 138.58 (C-6), 152.41 (C-2), 166.55 (C-4).

1-(2,3-Dideoxy-α-D-*erythro*-hexofuranosyl)thymine (18):

Nucleoside **16** (120 mg, 0.30 mmol) is dissolved in sat. methanolic (absolute) NH_3 (20 mL). After 24 h at r.t. the solvent is removed under reduced pressure and the crude product purified by flash chromatography (silica gel, 1 × 20 cm, CH_2Cl_2/MeOH, 9:1) to give the unprotected nucleoside **18** as a foam; yield: 70 mg (96%).

^{1}H-NMR (CD_3OD): δ = 1.89 (s, 3 H, CH_3), 2.05–2.10 (m, 3 H, 2'-Ha, 3'-Ha, 3'-Hb), 2.40–2.48 (m, 1 H, 2'-Hb), 3.40–3.70 (m, 3 H, 5'-H, 6'-Ha, 6'-Hb), 4.36–4.41 (m, 1 H, 4'-H), 6.08 (dd, 1 H, J = 6.4, 4.6 Hz, 1'H), 7.45 (1 H, 5-H).

^{13}C-NMR (CD_3OD): δ = 12.48 (CH_3), 26.37 (C'-3), 33.01 (C'-2), 64.43 (C'-6), 74.48 (C'-5), 82.71 (C'-4), 88.51 (C'-1), 111.30 (C-5), 137.76 (C-6), 152.32 (C-2), 166.55 (C-4).

(2*E*,4*S*,5*R*)-6-Benzoyloxy-4,5-dihydroxy-2-hexenal Dimethyl Acetal (19):

Acetal **6** (1.50 g, 3.9 mmol) is dissolved in 33% $MeNH_2$ in absolute EtOH at r.t.. After 30 min the solvent is removed under reduced pressure. The crude product is purified by flash chromatography (silica gel, 2.5 × 30 cm, Et_2O) to give analytically pure **19** as an oil; yield 0.90 g (78%).

$C_{15}H_{20}O_6 \cdot 0.25H_2O$	calc.	C 59.89	H 6.87
(300.8)	found	60.09	6.83

^{1}H-NMR ($CDCl_3$): δ = 2.96 (br, 1 H, OH), 3.14 (br, 1 H, OH), 3.31 (s, 6 H, OCH_3), 4.02 (q, 1 H, J = 5.8 Hz, 5-H), 4.35 (t, 1 H, J = 5.8 Hz, 4-H), 4.45 (d, 2 H, J = 5.8 Hz, 6-Ha, 6-Hb), 4.81 (d, 1 H, J = 4.4 Hz, 1-H), 5.82 (dd, 1 H, J = 15.8, 4.4 Hz, 2-H), 6.02 (dd, 1 H, J = 15.8, 5.8 Hz, 3-H), 7.41–8.06 (m, 5 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 52.67 (OCH_3), 65.55 (C-6), 72.36 (C-5), 72.53 (C-4), 101.99 (C-1), 128.32 (C_{arom}), 129.38 (C-3), 129.62 (C_{arom}), 132.24 (C-2), 133.16 (C_{arom}), 166.93 ($OCOC_6H_5$).

MS: m/z (%) = 233 (M^+ − 63, 4), 165 (8), 105 (100), 100 (100), 99 (40).

(2*E*,4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxy-4,6-diacetoxy-2-hexenal Dimethyl Acetal (20):

Acetal **3** (10.0 g, 36.1 mmol) is dissolved in dry DMF (100 mL). Imidazole (10.0 g, 0.15 mol) and *tert*-butylchlorodiphenylsilane chloride (13.0 g, 47.3 mmol) is added. After 20 h at r.t. the mixture is diluted with CH_2Cl_2 (200 mL) and washed with ice cold aq HCl (1 M, 3 × 50 mL) and H_2O (50 mL). After drying ($MgSO_4$), the organic phase is concentrated to an oil under reduced pressure. Flash chromatographic purification (silica gel 3 × 50 cm, Et_2O/hexane, 1:1) gives **20** as an oil which crystallizes on standing in the refrigerator at −18 °C; Yield: 11.5 g (62%); mp 61–62 °C.

^{1}H-NMR ($CDCl_3$): δ = 1.07 (s, 9 H, t-C_4H_9), 1.73 (s, 3 H, $OCOCH_3$, 1.98 (s, 3 H, $OCOCH_3$, 3.28 (s, 6 H, OCH_3), 3.92 (dd, 1 H, J = 10.0, 3.0 Hz, 6-Ha), 4.02 (dt, 1 H, J = 6.7, 3.0 Hz, 5-H), 4.09 (dd, 1 H, J = 10.0, 6.7 Hz, 6-Hb), 4.80 (d, 1 H, J = 4.2 Hz, 1-H), 5.32 (dd, 1 H, J = 6.5, 3.0 Hz, 4-H), 5.61 (dd, 1 H, J = 15.9, 4.2 Hz, 2-H), 5.92 (dd, 1 H, J = 15.9, 6.5 Hz, 3-H), 7.33–7.73 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 19.26 [$C(CH_3)_3$], 20.30 ($OCOCH_3$), 20.76 ($OCOCH_3$), 26.66 [$C(CH_3)_3$] 52.28 (OCH_3), 52.33 (OCH_3), 64.67 (C-6), 72.31 (C-5), 74.30 (C-4), 101.32 (C-1), 127.36, 127.49 (C_{arom}), 128.34 (C-3), 129.39, 129.57 (C_{arom}), 130.99 (C-2), 132.55, 133.57, 135.60, 135.94 (C_{arom}), 169.46 ($OCOCH_3$), 170.49 ($OCOCH_3$).

MS: m/z (%) 483 (M^+ − 32, 0.5%), 341 (11), 242 (20), 241 (100), 213 (10), 199 (37), 185 (11), 163 (10), 153 (11), 135 (22), 125 (12).

(2*E*,4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxy-4,6-dihydroxy-2-hexenal Dimethyl Acetal (21):

Acetal **20** (10.0 g, 19.4 mmol) is dissolved in anhydr. MeOH (200 mL) and K_2CO_3 (2.0 g) added. After 1 h at r.t. the mixture is filtered and diluted with CH_2Cl_2 (300 mL). After washing with ice cold aq HCl (2 M, 3 × 50 mL) and H_2O (50 mL), the organic phase is dried ($MgSO_4$) and concentrated to an oil under reduced pressure. Flash chromatographic purification (silica gel, 3 × 40 cm, Et_2O/hexane, gradient elution, 1:1 → 3:2) gives analytically pure **21** as an oil; yield: 8.0 g (96%).

$C_{24}H_{34}O_5Si$	calc.	C 66.94	H 7.96
(430.6)	found	66.73	8.04

^{1}H-NMR ($CDCl_3$): δ = 1:06 (s, 9 H, t-C_4H_9), 2.84–2.90 (m, 2 H, 4-OH, 6-OH), 3.24 (s, 3 H, OCH_3), 3.25 (s, 3 H, OCH_3), 3.52–3.83 (m, 3 H, 5-H, 6-Ha, 6-Hb), 4.29–4.39 (m, 1 H, 4-H), 4.77 (d, 1 H, J = 4.4 Hz, 1-H), 5.75 (dd, 1 H, J = 15.9, 4.4 Hz, 2-H), 5.92 (dd, 1 H, J = 15.9, 5.2 Hz, 3-H), 7.35–7.67 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 19.00 [$C(CH_3)_3$], 26.68 [$C(CH_3)_3$], 52.40 (OCH_3), 64.64 (C-6), 72.75 (C-4), 73.32 (C-5), 102.01 (C-1), 127.69 (C_{arom}), 128.36 (C-3), 129.78 (C_{arom}), 132.96 (C-2), 135.38 (C_{arom}).

MS: m/z (%) = 367 (M^+ − 63, 0.3), 309 (10), 242 (21), 241 (100), 221 (16), 213 (21), 199 (39), 163 (24), 135 (20), 113 (17), 101 (10), 100 (47).

1,4-Di-*O*-acetyl-3-azido-6-*O*-*tert*-butyldiphenylsilyl-D-*arabino*-hexopyranoside (22) and 1,6-Di-*O*-acetyl-3-azido-5-*O*-*tert*-butyldiphenylsilyl-β-D-*ribo*-hexafuranoside (23):

Unsaturated acetal **21** (4.0 g, 9.3 mmol) is dissolved in 80% AcOH (50 mL) and NaN_3 (2.4 g, 36.9 mmol) is added. After 3 h at r.t. TLC (Et_2O/hexane, 4:1) shows no more starting acetal **21**. The mixture is diluted with CH_2Cl_2 (150 mL) and poured onto ice. The organic phase is washed with sat. aq $NaHCO_3$ (5 × 50 mL) and H_2O (50 mL). After drying ($MgSO_4$) the solvent is removed under reduced pressure. The crude product is acetylated in CH_2Cl_2 (50 mL) with Ac_2O (20 mL) in the presence of pyridine (10 mL).

After 3 h at r.t. the mixture is diluted with CH_2Cl_2 (100 mL) and washed with ice cold aq HCl (2 M, 3 × 30 mL) and H_2O (30 mL). After drying ($MgSO_4$) the organic layer phase is concentrated to an oil under reduced pressure. The crude product is purified by flash chromatography (silica gel Et_2O/hexane, 3:7) to give the α-anomer of **22** as the less polar isomer, the β-anomer of **22** as the middle fraction, and the furanose isomer **23** as the most polar product.

22 (α-anomer); yield: 1.60 g (34%).

$C_{26}H_{33}N_3O_6Si$	calc.	C 61.04	H 6.50	N 8.21
(511.7)	found	61.36	6.93	8.50

^{1}H-NMR ($CDCl_3$): 1.04 (s, 9 H, *t*-C_4H_9), 1.87 (ddd, 1 H, J = 13.7, 10.9, 3.0 Hz, 2-H*a*), 1.99 (s, 3 H, $OCOCH_3$), 2.09 (s, 3 H, $OCOCH_3$), 2.18 (dd, 1 H, J = 13.7, 4.9 Hz, 2-H*e*), 3.69 (d, 2 H, J = 3.4 Hz, 6-Ha, 6-Hb), 3.73–3.92 (m, 2 H, 3-H, 5-H), 5.08 (t, 1 H, J = 9.9 Hz, 4-H), 6.27 (d, 1 H, J = 3.0 Hz, 1-H), 7.34–7.67 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 19.07 [$\underline{C}(CH_3)_3$], 19.11 ($OCO\underline{C}H_3$), 20.47 ($OCO\underline{C}H_3$), 26.59 [$\underline{C}(CH_3)_3$], 33.77 (C-2), 57.53 (C-3), 62.46 (C-6), 69.73 (C-5), 73.73 (C-4), 90.43 (C-1), 127.50, 129.56, 133.05, 133.12, 135.55 (C_{arom}), 168.61 ($O\underline{C}OCH_3$), 169.19 ($O\underline{C}OCH_3$)

IR (film): ν = 2109 cm^{-1} (azide).

22 (β-anomer); yield: 0.48 g (10%).

$C_{26}H_{33}N_3O_6Si \cdot 0.75H_2O$	calc.	C 59.49	H 6.62	N 8.00
(525.2)	found	59.42	6.47	8.06

IR (film): ν = 2104 cm^{-1} (azide).

^{1}H-NMR ($CDCl_3$): ν = 1.05 (s, 9 H, t-C_4H_9), 1.78 (dt, 1 H, J = 12.6, 9.9 Hz, 2-H*a*), 1.97 (s, 3 H, $OCOCH_3$), 2.13 (s, 3 H, $OCOCH_3$), 2.24 (ddd, 1 H, J = 12.6, 4.8, 2.2 Hz, 2-H*e*), 3.50–3.69 (m, 2 H, 3-H, 5-H), 3.72 (d, 2 H, J = 3.8 Hz, 6-Ha, 6-Hb), 4.98 (t, 1 H, J = 9.6 Hz, 4-H), 5.76 (dd, 1 H, J = 9.8, 2.2 Hz, 1-H), 7.34–7.69 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 19.14 [$\underline{C}(CH_3)_3$], 20.46 ($OCOCH_3$), 20.84 ($OCOCH_3$), 26.61 [$C(\underline{C}H_3)_3$], 34.51 (C-2), 59.63 (C-3), 62.77 (C-6), 69.49 (C-5), 76.15 (C-4), 91.17 (C-1), 127.48, 127.54, 129.58, 133.12, 133.28, 135.63 (C_{arom}), 168.77 ($O\underline{C}OCH_3$), 169.34 ($O\underline{C}OCH_3$).

23; yield: 0.25 g (5%).

$C_{26}H_{33}N_3O_6Si$	calc.	C 61.04	H 6.50	N 8.21
(511.7)	found	61.16	6.69	8.07

IR (film): ν = 2110 cm^{-1} (azide).

^{1}H-NMR ($CDCl_3$): δ = 1.05 (s, 9 H, *t*-C_4H_9), 1.97 (s, 3 H, $OCOCH_3$), 2.09 (s, 3 H, $OCOCH_3$), 2.24 (ddd, 1 H, J = 13.0, 7.6, 5.3 Hz, 2α-H), 2.40 (ddd, 1 H, J = 13.0, 7.6, 1.4 Hz, 2β-H), 3.84 (d, 2 H, J = 4.1 Hz, 6-Ha, 6-Hb), 4.21 (td, 1 H, J = 7.6, 5.0 Hz, 3-H), 4.30 (dd, 1 H, J = 7.6, 5.0 Hz, 4-H), 5.01 (dt, J = 7.6, 4.1 Hz, 5-H), 6.33 (dd, 1 H, J = 5.3, 1.4 Hz, 1-H), 7.25–7.68 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 19.16 [$\underline{C}(CH_3)_3$], 20.93 ($OCO\underline{C}H_3$), 26.62 [$C(\underline{C}H_3)_3$], 38.45 (C-2), 61.39 (C-3), 62.46 (C-6), 74.44 (C-5), 82.39 (C-4), 97.67 (C-1), 127.54, 127.65, 129.72, 133.04, 135.46 (C_{arom}), 169.50 ($O\underline{C}OCH_3$), 170.10 ($O\underline{C}OCH_3$).

(2*E*,4*S*,5*R*)-5,6-Bis(*tert*-butyldiphenylsiloxy)-4-hydroxy-2-hexenal (24) and (2*E*,4*S*,5*R*)-4,5-Bis(*tert*-butyldiphenylsiloxy)-6-hydroxy-2-hexenal (25):

Acetal **21** (8.0 g, 18.6 mmol) is dissolved in dry DMF (100 mL). Imidazole (10.0 g, 0.15 mol) and *tert*-butylchlorodiphenylsilane chloride (5.6 g, 20.4 mmol) is added. After 8 h at r.t. the mixture is diluted with CH_2Cl_2 (200 mL) and washed with ice cold aqueous HCl (3 M, 3 × 50 mL) and H_2O (50 mL). After drying ($MgSO_4$) the organic phase is concentrated to an oil under reduced pressure. Flash chromatographic purification (silica gel, 3 × 60 cm, Et_2O/hexane, 2:3) gives a 1:1 mixture of unsaturated aldehydes **24** and **25**, which cannot be separated; yield: 9.9 g (80%). This mixture is used directly for the next step.

24 and **25**:

$C_{38}H_{46}O_4Si_2 \cdot H_2O$	calc.	C 71.21	H 7.55	
(641.0)	found	71.48	7.47	

^{1}H-NMR ($CDCl_3$): δ = 1.05 (s, *t*-C_4H_9), 1.07 (s, *t*-C_4H_9), 3.57 (dd, J = 5.9, 2.0 Hz, 6-Ha, 6-Hb), 3.68 (d, J = 5.3 Hz, 6-Ha, 6-Hb), 3.79–3.87 (m, 5-H), 4.50 (td, J = 5.7, 1.7 Hz, 4-H), 4.57 (td, J = 5.2, 1.0 Hz, 4-H), 6.01 (ddd, J = 15.8, 7.9, 1.0 Hz, 2-H), 6.27 (*ddd*, J = 15.7, 8.0, 1.7 Hz, 2-H), 6.60 (dd, J = 15.8, 6.1 Hz, 3-H), 6.72 (dd, J = 15.7, 4.3 Hz, 3-H), 7.25–7.73 (m, H_{arom}), 9.29 (d, J = 7.9 Hz, 1-H), 9.39 (d, J = 8.0 Hz, 1-H).

^{13}C-NMR ($CDCl_3$): δ = 18.96, 19.03, 19.21, 19.25 [$\underline{C}(CH_3)_3$], 26.47, 26.71, 26.85, 26.90 [$C(\underline{C}H_3)_3$], 64.03, 65.44 (C-6), 73.86 (C-5), 74.56, 74.93 (C-4), 127.62, 127.72, 127.81, 129.54, 130.03 (C_{arom}), 131.72, 133.07 (C-2), 134.70, 135.38, 135.47, 135.63, 135.68 (C_{arom}), 154.21, 155, 37 (C-3), 193.05, 193.22 (C-1).

1-*O*-Acetyl-3-azido-5,6-di-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-α-D-*arabino*-hexofuranose (26) and 2-[1,2-Bis(*tert*-butyldiphenyl siloxy)ethyl]furan (27):

The 1:1 mixture of unsaturated aldehydes **24** and **25** (9.0 ~ 14.5 mmol) is dissolved in 80% AcOH (100 mL) and added dropwise to a solution of NaN_3 (5.0 g ~ 76.9 mmol) in 80% AcOH (300 mL). This mixture is stirred for 20 h at r.t., then diluted with H_2O (400 mL) and extracted with CH_2Cl_2 (2 × 400 mL). The organic phase is washed with cold sat. aq $NaHCO_3$ (3 × 200 mL) and H_2O (2 × 150 mL), dried (Na_2SO_4) and filtered. Evaporation under reduced pressure is continued until the volume of the organic phase is ~ 150 mL). To this mixture is added dry pyridine (5.0 g, 63.2 mmol), 4-dimethylaminopyridine (40 mg, 0.33 mmol) and Ac_2O (10.0 g, 98.0 mmol). Stirring is continued for 90 min at r.t., then the mixture is poured into 4 M HCl (60 mL) and ice (60 mL). The organic phase is washed with cold sat. $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 100 mL), dried (Na_2SO_4) and filtered. Evaporation under reduced pressure affords an oil which is chromatographed on a silica gel column (4 × 50 cm, Et_2O/hexane, 1:10) to give **26** as a clear oil; yield: 2.1 g (20%). The furan derivative **27** is isolated as a byproduct; yield: 0.9 g (12%).

26:

$C_{40}H_{49}N_3Si_2O_5$	calc.	C 67.86	H 6.98	N 5.93
(708.0)	found	68.24	7.24	5.86

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.02–1.07 (m, 18 H, *t*-C_4H_9), 1.95 (s, 3 H, $OCOCH_3$), 2.37 (ddd, 1 H, J = 15.1, 5.9, 4.1 Hz, 2α-H), 2.57 (ddd, 1 H, J = 15.0, 6.1, 1.1 Hz, 2β-H), 3.56 (dd, 1 H, J = 11.1, 2.4 Hz, 6a-H), 3.69 (dd, 1 H, J = 11.1, 2.4 Hz, 6b-H), 3.88 (dt, 1 H, J = 8.2, 2.4 Hz, 5-H), 4.31 (m, 1 H, 3-H), 4.56 (dd, 1 H, J = 8.2, 3.5 Hz, 4-H), 6.37 (dd, 1 H, J = 6.0, 4.2 Hz, 1-H), 7.28–7.66 (m, 20 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 19.03, 19.26 [$\underline{C}(CH_3)_3$], 21.03 ($OCO\underline{C}H_3$), 26.75, 26.82 [$C(\underline{C}H_3)_3$], 38.75 (C-2), 61.50 (C-3), 64.92 (C-6), 71.82 (C-5), 80.42 (C-4), 96.74 (C-1), 127.3–135.9 (C_{arom}), 169.92 ($O\underline{C}OCH_3$).

IR (film): ν = 3072 (m), 3050 (m), 2932 (s, C-H), 2858 (s), 2104 (s, N_3), 1752 (s, C=O), 1473 (s), 1463 (m), 1428 (s), 1363 (s), 1235 (s), 1109 cm^{-1} (s).

27:

$C_{32}H_{39}Si_2O_3 \cdot 0.5H_2O$	calc.	C 71.60	H 7.51	
(536.7)	found	71.48	7.47	

^{1}H-NMR ($CDCl_3$): δ = 0.94 (s, 9 H, *t*-C_4H_9), 1.02 (s, 9 H, *t*-C_4H_9), 3.81 (dd, 1 H, J = 10.0, 6.2 Hz, 2'a-H), 3.94 (dd, 1 H, J = 10.0, 6.2 Hz, 2'b-H), 4.81 (t, 1 H, 1'-H, J = 6.2 Hz), 5.95 (d, 1 H, J = 3.1 Hz, 3-H), 6.16 (dd, 1 H, J = 3.1, 1.8 Hz, 4-H), 7.22–7.71 (m, 21 H_{arom} + 5-H).

^{13}C-NMR ($CDCl_3$): δ = 19.04 and 19.24 [$\underline{C}(CH_3)_3$], 26.69 and 26.77 [$C(\underline{C}H_3)_3$], 66.80 (C-2'), 69.93 (C-1'), 107.60 (C-4), 109.82 (C-3), 127.2–135.8 (C_{arom}), 141.16 (C-5), 154.41 (C-2).

1-(3-Azido-2,3-dideoxy-β-D-*arabino*-hexofuranosyl)thymine (28) and 1-(3-Azido-2,3-dideoxy-α-D-*arabino*-hexofuranosyl)thymine (29):

A mixture of 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine **14** (760 mg, 2.8 mmol) and azide **26** (1.2 g, 1.7 mmol) dissolved in dry MeCN (40 mL) is cooled to −20 °C. Me_3Si-triflate (450 mg, 2.0 mmol) is added and the mixture is stirred 90 min at −20 °C. After this time analytical silica TLC (CH_2Cl_2/MeOH, 3:97) shows no more azide **26**. The mixture is diluted with CH_2Cl_2 (60 mL) and quenched with sat. aq $NaHCO_3$. The organic phase is successively washed with sat. aq $NaHCO_3$ (2 × 40 mL) H_2O (50 mL) and dried

($MgSO_4$). Evaporation of the solvent gives the protected nucleosides as an oil. This oil is purified by column chromatography on silica gel (6 × 8 cm, CH_2Cl_2/MeOH, 1:49) to give a glassy product. This is dissolved in dry THF (18 mL) followed by addition of TBAF (3.4 mL of a 1.0 M solution of TBAF in THF, 3.4 mmol). After stirring at r.t. for 24 h the mixture is concentrated to an oil by evaporation of the solvent. Examination of this oil by NMR reveals it to be an anomeric mixture of **28** and **29** ($\alpha:\beta$ ratio ~ 1:1). Attempt to separate the anomers by flash chromatography on silica gel (3 × 40 cm, EtOAc) is unsuccessful. However, the mixture of **28** and **29** is separated by reverse phase HPLC Waters Delta Pak 300 Å, 15 μ, 57 × 300 mm, H_2O/EtOH, 97:3). In this way **28** is obtained as a glass; yield: 120 mg (24%). Compound **29** is also obtained as a glass; yield: 155 mg (31%).

28: HRMS: *m/z*, $C_{11}H_{15}N_5O_5$ calc. 297.1073 (M^+); found 297.1053 (± 6.7 ppm).

HPLC retention time = 50 min.

^{1}H-NMR (CD_3OD): δ = 1.94 (d, 3H, J = 0.9 Hz, CH_3), 2.20 (dd, 1H, J = 15.3, 2.5 Hz, 2′β-H), 2.82 (ddd, 1H, J = 15.3, 8.4, 6.5 Hz, 2′α-H), 3.64–3.86 (m, 3H, 5′H, 6′a-H, 6′b-H), 4.00 (d, 1H, J = 1.4 Hz, 4′-H), 4.44 (dd, 1H, J = 5.9, 1.4 Hz, 3′-H), 6.17 (dd, 1H, J = 8.2, 2.5 Hz, 1′-H), 7.63 (d, 1H, 6-H, J = 0.9 Hz).

^{13}C-NMR (CD_3OD): δ = 12.64 (CH_3), 39.37 (C-2′), 63.18 (C-3′), 65.28 (C-6′), 71.50 (C-5′), 83.32 (C-1′), 85.79 (C-4′), 111.31 (C-5), 137.71 (C-6), 152.49 (C-2), 166.54 (C-4).

29: HRMS: *m/z*, $C_{11}H_{15}N_5O_5$ calc. 297.1073 (M^+); found 297.1048 (± 8.4 ppm).

HPLC retention time = 75 min.

^{1}H-NMR (CD_3OD): δ = 1.93 (s, 3H, CH_3), 2.44–255 (ddd, 1H, J = 14.1, 8.1, 5.1 Hz, 2′α-H), 2.60–2.68 (dd, 1H, J = 14.1, 6.2 Hz, 2′β-H), 3.65–3.87 (m, 3H, 5′-H, 6′a-H, 6′b-H), 4.37 (dd, 1H, J = 9.0, 3.3 Hz, 4′-H), 4.53 (t, 1H, J = 4.0 Hz, 3′-H), 6.16 (dd, 1H, J = 7.9, 6.3 Hz, 1′-H), 7.53 (d, 1H, J = 0.9 Hz, 6-H).

^{13}C-NMR (CD_3OD): δ = 12.41 (CH_3), 39.16 (C-2′), 64.92, 65.04 (C-3′, C-6′), 71.51 (C-5′), 83.16 (C-1′), 87.82 (C-4′), 111.80 (C-5), 137.83 (C-6), 152.41 (C-2), 166.59 (C-4).

Danisk Technical Research Council and Danish Natural Science Research Council are gratefully acknowledged for their support.

Received: 3 April 1991; revised 29 July 1991

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