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Branched-chain Nucleosides : Synthesis of 3'-Deoxy-3'-C-Hydroxymethyl-α-L-Lyxopyranosyl Thymine and 3'-Deoxy-3'-C-Hydroxymethyl-α-L-Threofuranosyl Thymine.

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Abstract : The synthesis of 3'-deoxy-3'-C-hydroxymethyl branched nucleosides with α -L-lyxopyranosyl and α -L-threeofuranosyl sugar moieties is described. The synthetic scheme makes use of a furanose \rightarrow pyranose conversion and of the formation of both furanose and pyranose nucleosides during Vörbruggen sugar-base condensation reaction starting from tetra-O-acetyl-3-deoxy-3-C-hydroxymethyl-L-lyxo-(1,6)-furanose. The conformation of the target molecules is discussed.

INTRODUCTION

Non natural pyranose nucleosides have attracted considerable attention during last years. This is due to the finding that hexitol nucleosides exert antiviral activity¹ and that hexitol nucleic acids are promising antisense constructs². Previously, based on modeling experiments³, we synthesized and evaluated the properties of 3'-deoxy-3'-hydroxymethyl aldopentopyranosyl oligonucleotides^{4,5}. As a continuation of this work we here report on the synthesis and conformational behaviour of 3'-deoxy-3'-*C*-hydroxymethyl- α -L-lyxopyranosyl thymine 1 which may be considered as the "ribo" analogue of the aforementioned 3'-branched aldopentopyranosyl nucleosides. The same synthetic scheme also led to a procedure for the preparation of 3'-deoxy-*C*-hydroxymethyl- α -L-threofuranosyl thymine 2.



This efficient synthesis is based on two interesting rearrangements : the conversion of 1,2isopropylidene-3-deoxy-3-C-hydroxymethyl-L-lyxofuranose **3** into 2,4-di-O-acetyl-1,6-anhydro-3deoxy-3-C-hydroxymethyl-L-lyxopyranose **4** by two convergent pathways and the formation of 2',4',6'tri-O-acetyl-3'-deoxy-3'-C-hydroxymethyl- α -L-lyxopyranosyl thymine 7 and 2',4',5'-tri-O- acetyl-3-deoxy-3-C-hydroxymethyl- α -L-lyxo-(1,6)-furanosyl thymine 8 by treatment of tetra-()-acetyl-3-deoxy-3-C-hydroxymethyl-L-lyxo-(1,6)-furanose 5 with silylated thymine under Vörbruggen conditions (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

The starting compound for the synthesis of both 1 and 2 was the known⁶ ulose 10 prepared from 5-tbutyldiphenylsilyl-1,2-isopropylidene-L-arabinofuranose 9 by CrO_3 -Ac₂O-Py oxidation (Scheme 2).

Scheme 2



On treatment of 10 with μ -chloro- μ -methylene-[bis(cyclopentadienyl)titanium]dimethylaluminium or Tebbe reagent^{7,8}, olefin 12 was obtained in 60% yield. Due to a high price of the reagent we applied

Peterson olefination⁹ procedure as an alternative. Treatment of 10 with trimethylsilylmetyl lithium at -78° gave a tertiary alcohol 11 in 84% yield, which subjected to NaH induced fragmentation gave 12 (97%) in 82% for two steps. This sequence could be run on 34 mmol scale without any detectable epimerization at C4 during the first step. Moisture had to be rigorously excluded in the second step to avoid base-induced desilylation of 12 to give 13. Hydroboration of the olefin 12 furnished 14. Due to a spacial orientation of the functionalities at C1, C2 and C5 in 12, it could be anticipated that the addition of diborane would take place only anti to furnish 14 as the only product. Fluoride ion desilylation of 14 lead to 3. On treatment of 3 with 90% trifluoroacetic acid a process depicted in Scheme 3 took place.

Scheme 3



In this process, compound 3 is converted into 4 by CF₃COOH treatment followed by acetylation via two different pathways. The primary product of hydrolysis of the isopropylidene group 15 tended to minimize unfavourable steric interaction between two hydroxymethyl groups oriented syn by opening of the furanosyl ring. Rotation along the C3-C4 bond anticlockwise and subsequent ring closure through C5-OH lead to a pyranose 16. Alternatively, rotation along the C2-C3 bond also anticlockwise and ring closure through C6-OH lead to a furanose 17. At this point we expected to get a mixture of 16 and 17, which, after acetylation should furnish 6 and 5^* . However, suprisingly easy intramolecular glycosylation took place in a reaction medium which lead to a bicyclic product 18. It should be noticed that irrespectively if this process took place via a pyranose 16 or via a furanose 17, the same compound 18 resulted, isolated as diacetate 4. The structure of this product was confirmed by X-ray analysis¹⁰.

Formation of the anhydro compound 4 did not adversly effect our approach to a target 6 and further to 7, because acetolytic cleavage of the internal glycoside 4 was possible in Ac_2O -AcOH- H_2SO_4 mixture (Scheme 4).

Scheme 4



This reaction furnished a pyranose 6 as a single α anomer, a furanose 5 as a 1:1 α/β mixture and small amount of an open chain hexaacetate 19, in 48%, 23% and 10% yield, respectively. Preferential formation of 6 is a consequence of greater reactivity of a furanosyl ring in 4, when compared to reactivity of a pyranosyl ring scission of which lead to 5. Small amount of 19 was an inconvenience because it was difficult to separate it from slightly less polar 5.

However, we tried to circumvent formation of the internal glycoside 18 by protection of the hydroxyl group bound to the carbon atom C6 in compound 14 (Scheme 5).

^{*} An open chain Fisher projection of 15, 16, 17 is shown below. Systematic name of this compound is 3-deoxy-3-Chydroxymethyl-L-lyxose. This compound can form one pyranosyl form, 16, but two different furanosyl forms 15 and 17. Furanose 15 is referred to as an L-lyxo-(4,1)-furanose, whereas 17 as an L-lyxo-(6,1)-furanose.







Attempted benzylation of 14 performed in a phase-transfer catalysis mode furnished a dibenzyl ether 20 isolated in 48% yield as the main product. Formation of 20 must have been a consequence of hydrolysis of the t-butyldiphenylsilyl group under basic conditions and subsequent etherification. This was an unexpected finding since t-butyl-diphenylsilyl group is considered stable under basic conditions¹¹. It can be that a propensity of the silicon atom to form pentavalent species like 21 associated with the known migratory capacity of silyl ethers under basic conditions¹¹, can be linked with formation of 20. From this standpoint it was impossible to prove by the NMR data that a second product isolated was 22 or a product 23 with transposed functionalities at the primary carbon atoms C5,6. The product 23 would result from attack of benzyl bromide at C5 in 21. Since the atom C6 is sterically more crowded than C5, it would be difficult for a bulky t-butyldiphenylsilyl group to migrate onto it from a more comfortable atom C5. On this basis we believe that the isolated compound has a structure 22. Low yield of its formation prompted us to find an alternative approach. It turned out that a simple acetylation served the purpose very well. Thus, diol 3 was acetylated to furnish 24, which was de-acetalated with 90% trifluoroacetic acid (Scheme 6)

Scheme 6



i : Dependent on the reaction circumstances (see text) mixtures of 6:5:26 (6:4:1) or 6:5 (3:2 or 1:3.7) were obtained. Compound 24 gives a mixture of 19 and 26 upon treatment with Ac₂O, AcOH, H₂SO₄ (ii).

After evaporation of TFA, co-evaporation with ethyl acetate and xylene, ¹³C spectrum of the crude reaction mixture showed six signals at the anomeric region. This proves extensive migration of acetyl groups in a primary product 25 during a TFA treatment and/or during work-up. Acetylation of this mixture furnished a pyranose 6 and both furanoses 5 and 26, all three separable by gravitational column chromatography^{*}. However, when the crude reaction mixture was deacetylated and re-acetylated only 6 and 5 were isolated in ca 3:2 proportion. In a separate experiment this proportion was reverted and the furanosyl compound 5 was isolated as dominant one. Thus, after deacetalation with 90% TFA and evaporation of the acid, the residual TFA was co-evaporated with DMF. This took ca 30 min and permitted for longer exposure to low pH. After deacetylation and re-acetylation three fractions were obtained : anhydro compound 4 formed in 4% yield, a pyranose 6, 10%, and a furanose 5, 37%. It is not clear why 5 was a dominant product in this case because after TFA treatment, the mixture of products was deacetylated in both cases to give 16 and 17, which after acetylation should furnish 6 and 5 in roughly the same proportion, which is not a case. It can be that formation of a furanose 17 is promoted by acid, and once formed it doesn't revert to a pyranose 16 easily, because a hydroxymethyl group at C3 in 16 is flanked by two syn oriented OH groups which destabilize a pyranosyl form. When the open chain product 19 was deacetylated to allow for cyclization, and re-acetylated (Scheme 7), the pyranose 6α together with a product identified as its β anomer, were again principal components of the mixture, besides 5 as an α , β mixture, and surprisingly tetraacetate 26 as a single anomer α . formed in proportion 57:35:8 by integration of the anomeric region of the ¹H NMR spectrum of the crude reaction mixture.

Scheme 7



Ratio $6\alpha/6\beta$: 5:26 is 57:35:8 as integrated from ¹H NMR signals.

Anomeric configuration of 6α and 6β and their conformational characteristics could be inferred from the ¹H NMR spectra. Coupling constants of 6α listed in Figure 1 agree with the ¹C₄ conformation of the pyranosyl ring. Since this compound could be prepared during acetolytic cleavage of 4, i.e. under conditions of thermodynamic control, anomeric configuration was assumed to be α because axial C1 acetoxyl group gains the anomeric effect stabilization.

^{*} Identity of the furanose 26 was confirmed by its synthesis from acetonide 24 by acetolysis, which also furnished the hexaacetate 19 as byproduct.



Figure 1: Conformational properties of the pyranoses $6\alpha_{\beta}\beta$ (coupling constants in Hz, recorded in CDCl₃).

Also the coupling constant $J_{1,2} = 1.8$ Hz is smaller than a value $J_{1,2} = 2.4$ for 6β as expected for diequatorial orientation of the hydrogen atoms H-1 and H-2 in 6α , when compared with axial-equantorial counterparts in 6β . The β anomer in turn is evidently unstable conformationally as evidenced from the coupling constants $J_{3,4} = J_{4,5ax} = 7.0$. In a ${}^{4}C_{1}$ conformation the molecule is stabilized by the anomeric effect, but destabilized by two axially disposed functionalities at the carbon atoms C-3 and C-4. In a ${}^{1}C_{4}$ conformation, steric tension is minimized, but at the expence of a loss of the anomeric effect. Interplay of these effects results in an equilibrium with ${}^{1}C_{4}$ form predominating.

Anomeric configuration of the furanoses 5α and 5β was established by comparison of their coupling constants $J_{1,2}$ and $J_{2,3}$ with those of the nucleosides 8, 2 and 34 (Figure 2).

Configuration of 34 was established by a Nuclear Overhauser Effect measurement (see below)^{*}, so the coupling constants of this compound could be used as a reference. Configuration α was ascribed to a compound characterized by the couplings $J_{1,2} = 4.2$ Hz and $J_{2,3} = 9.8$ Hz, because these values are closer to those of 34 (and its predecessors 8 and 2) than the values of $J_{1,2} = 0$ Hz and $J_{2,3} = 3.6$ Hz belonging to 5 β .

Anomeric configuration of 26 was established by comparison of the ¹³C chemical shifts of the carbon atom C-1 with published shifts of both α and β tetra-*O*-acetyllyxofuranoses 27 and 28¹². A value of 98.52 ppm recorded for 26 coincides with a value for 27 (98.04 ppm) and is significantly different from a shift of C-1 in 28 (93.02 ppm). Also, a magnitude of the J_{1,2} and J_{2,3} ¹H-¹H coupling constants of 26 agree better with the corresponding values of the α anomer 27 (or a tetra-*O*-benzoyl- α -lyxofuranose¹³) rather than with the values of the β anomer 28 (or its benzoylated counterpart¹³).

Glycosylation of 6 using trimethylsilylated thymine under Vorbrüggen conditions furnished a pyranosyl nucleoside 7 in 62% yield (Scheme 8). This compound adopts exclusively ${}^{4}C_{1}$ formation in solution (as well as in crystalline state¹⁰). Value of the coupling constant $J_{1',2'} = 10.0$ Hz and a broadened singlet of the proton H-4' sustains this. A tendency of the pentopyranosyl nucleoside to localize a nucleobase an equatorial

^{*} During preparation of this manuscript, a synthesis of 2 was published¹⁴ based on D-apiose. The coupling constants presented here are the same as in reference 14.

position even at the expense of axial orientation of up to three other functionalities at the carbon atoms C-2', C-3' and C-4' has been observed before^{4,5,15}. Conventional deacetylation of 7 furnished a target compound 1, which also adopts a conformation ${}^{4}C_{1}$. The 2'-deoxygenated counterpart of this compound has already been synthesized for antiviral screening and for preparation of antisense constructs^{4,5}.

Unusual results were obtained during glycosylation of the furanose 5 with trimethylsilyl thymine under Vorbrüggen conditions (Scheme 8). Two compounds were isolated from this condensation reaction : the expected furanosyl nucleoside 8 unseparable from ~ 5% of the β anomer, and the pyranosyl nucleoside 7, the same as obtained from 6 as described above. Proportion of 8 to 7 was 2:1.

Scheme 8



Formation of either 8 or 7 in this reaction depends on a mode of anchimeric stabilization of the cation 29 formed by abstraction of the anomeric acetoxyl group from the substrate 5. If 2-OAc group stabilizes the cation 29 via 30, than a furanosyl nucleoside 8 is formed. Configuration α of 8 was proven on a later stage (see below). An alternative mode of stabilization of 29 is to form a six membered ring using the oxygen atom bound to C-5 which leads to a cation 31. This progeny cation can be transformed into 32 via migration of the acetylcarbocation from the "pyranosyl" oxygen atom joining carbon atoms C-5 and C-1 towards the "furanosyl" oxygen atom joining C-6 and C-1. Subsequent rupture of the bond between this oxygen atom and C-1 leads to 33 which is the same cation that the one formed by abstraction of the anomeric acetoxyl group from a pyranose 6. Cation 33 then forms a pyranosyl nucleoside 7 via participation of the 2-O-acetyl group.



Aco	প্ল	0.0b	5.1	8.7	98.52
Aco OAc	287	4.6 ^b	5.4	4.7	93.02
Aco OAc	<u>27</u> 7	2.1	5.1	5.4	98.04
NBZOONBZ		4,9d	7.3	ı	ł
et e	7	5.4c	7.1	ł	ı
ve log	901	4.7b	6.9	J	ſ
OAC OAC	58	0 ^{.0}	3,6	E	ſ
ove ove	50	4.2 ^b	9.8	ı	ſ
		J _{1,2}	J2,3	J _{3,4}	C-1

^a These compounds have been originally examined in ref. 12 as D isomers; ^b in CDCl₃; ^c in CD₃OD; ^d in DMSO- d_6

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Nucleoside 8 was converted into 2 by deacetylation, periodate cleavage of the resulting vicinal diol and reduction with NaBH₄. This compound was also noncrystalline, so it was converted into bis-(p-nitro)benzoate 34, which crystallized as a single α anomer. Configuration α was proved by a differential NOE measurement. Irradiation of the H-3' signal gave a positive signal of the proton H-1'. Irradiation of the H-6 signal gave positive signal of the P-1' and less intensive positive signal of H-2' (but the signals of both H-4' and H-5' were nulled). These results can be interpreted in terms of the anomeric configuration α , syn conformation of the thymine with χ angle close to 0° and preferential S puckering of the furanosyl ring. The hydroxymethyl group bound to the carbon atom C-3' evidently controls a magnitude of the angle χ by virtue of its steric bulk. Unfortunately the crystalls of the compound 34 were unsuitable for X-ray analysis to confirm conformational features of 34 deduced from NOE measurements.

In conclusion, we have devised a simple way of synthesis of a representative example 1 of a new class of pyranosyl nucleosides. This compound was obtained from a branched pyranose 6 which has a hydroxymethyl group attached to the atom C-3. Compound 5, one of a possible furanosyl form of 6 is also a precursor of 1, because of an unusual migration of the acetyl carbocation during a Vorbrüggen condensation. The possibility to use a furanose 5 as substrate for obtaining a pyranosyl product like 1, is a manifestation of the constitution of both 6 and 5, which already manifested itself at a stage of surprisingly easy formation of the internal glycoside 4.

EXPERIMENTAL SECTION

General conditions are the same as in ref. 4.

5-(t-Butyldiphenylsilyl)-3-deoxy-3-C-methylene-1,2-isopropylidene-L-threo-pentofuranose 12

A. Using Tebbe reagent

Ulose 10 (4.82 g, 11.3 mmol) [prepared from t-butyldiphenylsilyl-1,2-isopropylidene-L-arabinofuranose 9⁶ (5.24 g, 12.2 mmol) by CrO₃-Ac₂O-Py oxidation] in THF (70 ml) was treated with 0.5 M μ -chloro- μ -methylene[bis(cyclopentadienyl)titanium]-dimethylaluminium (Tebbe reagent) in toluene (23 ml) at room temperature. Slight heating took place during the addition. The homogenous mixture was left overnight. TLC showed a new intensively charing spot of the product 12, less polar than a spot of substrate 10. MeOH was added (with cooling in ice-bath) and the jelly residue was filtered through a bed of silica gel under vacuum. The silica gel was washed with CH₂Cl₂. Combined filtrates were evaporated to give reddish oil. Gravitational chromatography in hexane-EtOAc 20:1 furnished 2.90 g (60%) of 12 as oil.

B. Using Peterson olefination

Ulose 10 (12g, 28 mmol) in CH_2Cl_2 (170 ml) was cooled in EtOH-dry ice bath, and trimethylsilylmethylithium in pentane (1 M, 28 ml) was added from a siringe dropwise. 1 h later the cooling bath was removed. When the solution reached room temperature, it was poured into a aq.NH₄Cl. After extractive work-up and evaporation, the residual viscous brown liquid was chromatographed in hexane-EtOAc 15:1 to give 11 as oil (10.1 g or 84%). A solution of this material (17.5 g, 34 mmol) in THF (500 ml) was cooled in ice-water bath, and 3.0 g of NaH (60% suspension in mineral oil, pre-washed with

hexane, 75 mmol) was added. When evolution of hydrogen stopped, the flask was warmed up in an oil bath to maintain a gentle reflux during 3 h. TLC showed that the substrate was converted into slightly more polar compound 12. The flask was cooled in ice-water again, and aq.sat.NH₄Cl was added dropwise until evolution of hydrogen stopped. The precipitate was filtered out. The filtrate was evaporated to ca 1/3 of its original volume, and the remining solution was transfered to a separatory funnel filled with $CH_2Cl_2-H_2O$ to perform extraction. The colloidal solution was passed through a glass-wool. The two layers formed at this stage were separated. The water layer was back-extracted with CH_2Cl_2 . Combined extracts were washed with water, dried, filtered and evaporated to furnish 14 g, 97% of yellowish oil, which was directly used in the hydroboration step.

If anhydrous conditions were not maintained during NaH induced fragmentation, a desilylated product 13 was also formed in small quantity. Separation of 12 and 13 was possible by chromatography using a gradient elution with hexane-EtOAc 2:1 followed by hexane-EtOAc 2:1.

12 ¹H (CDCl₃) : 7.77-7.68 and 7.48-7.35, 10H, Ph; 5.85 (dd, 1H, $J_{1,2} = 3.9$ Hz, J = 1.1. Hz, H-1); 5.50 (bs, half-width 4.4 Hz, 1H, H-6'); 5.36 (q, 1H, J = 1.5 Hz, H-6"); 4.89 (apparent d, 1H, $J_{2,1} = 3.8$ Hz, H-2); 4.65 (tt, 1H, $J_{4,5'} = J_{4,5''} = 5.9$ Hz, $J_{4,6} = 1.6$ Hz, J = 1.6 Hz, H-4); 3.94 (ddd, $J_{5',1} = 1.5$ Hz, $H_{5',4} = 6.4$ Hz, $J_{5',5''} = -10.0$ Hz, H-5'); 3.80 (ddd, $J_{5'',1} = 1.3$ Hz, $J_{5'',4} = 7.0$ Hz, $J_{5'',5''} = -10.0$ Hz, H-5") [after irradiation of H-1, both H-5' and H-5" are dds]; 1.38, 1.35 CMe₂; 1.10 C(Me)₃. ¹³C (CDCl₃) : 145.60 C-3; 135.61, 133.34, 133.25, 129.57, 127.61 Ph; 113.92 C-6 [without decoupling of protons : t, J = 159.5 Hz]; 113.05 CMe₂; 105.36 C-1; 82.98, 81.35 C-2, C-4; 67.12 C-5; 27.27, 26.43 CMe₂; 26.77 CMe₃; 19.17 CMe₃. Exact mass (thioglycerol-NaOAc) : calc. for C₂₅H₃₂O₄Si+Na 447.1968; found 447.1985.

13 ¹H (CDCl₃): 5.85 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1); 5.50 (dd, 1H, J = 1.0 and 2.1 Hz, H-6') [after irradiation of H-2 : d, J = 2.0 Hz]; 5.28 (apparent t, 1H, J = 1.8 Hz, H-6"); [after irradiation of H-2 : d, J = 1.6 Hz]; 4.91 (apparent dd, $J_{2,1} = 3.8$ Hz, J = 1.8 Hz, H-2); 4.66 (ddd, 1H, $J_{4,6} = -1.9$ Hz, $J_{4,5"} = 4.0$ Hz, $J_{4,5'} = 8.9$ Hz, H-4); 3.83 (dd, $J_{5',4} = 7.0$ Hz, $J_{5',5"} = -11.7$ Hz, H-5'); 3.71 (dd, $J_{5",4} = 4.1$ Hz, $J_{5",5'} = -11.9$ Hz, H-5"); 2.56 (bs, OH); 1.57, 1.36 CMe₂. ¹³C (CDCl₃) : 144.87, C-3; 113.70 C-6 [without decoupling of protons : t, J = 160.2 Hz]; 113.31 CMe₂; 105.19 C-1; 83.59, 81.12 C-2, C-4; 65.77 C-5; 27.18, 26.40 CMe₂. MS : Molecular ion was not seen in LSIMS mode.

5-t-Butyldiphenylsilyl-3-deoxy-3-C-hydroxymethyl-1,2-isopropylidene-L-lyxo-(1,4)-furanose 14

Olefin 12(14 g) in 160 ml of THF was cooled down in ice-water, and treated with 70 ml of 1 M B_2H_6 in THF added via a canula. The mixture was left for 3 h at room temperature, and cooled in ice-water bath. A 1:1 mixture of THF-H₂O (40 ml) was added dropwise, followed by 2N NaOH (51 ml) and 33% H₂O₂ (41 ml). This heterogenous mixture was vigorously stirred during 2.5 h at room temperature, cooled down again and treated with 150 ml of aq. sat.Na₂S₂O₃. The layers were separated. The aqueous layer was extracted with CH₂Cl₂. Combined organic layer were washed with water, dried and evaporated. Graviational chromatography in hexane-EtOAc 4:1 \rightarrow 3:1 furnished 13.6 g, 93% of 14, mp. 97-98° (hexane-EtOAc).

14 ¹H (CDCl₃) : 7.74-7.66 and 7.48-7.39, 10H, Ph; 5.78 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1); 4.67 (dd, 1H, $J_{2,1} = 4.0$ Hz, $J_{2,3} = 5.3$ Hz, H-2); 4.48 (ddd, 1H, $J_{4,5''} = 3.7$ Hz, $J_{4,3} = 7.6$ Hz, $J_{4,5'} = 10.2$ Hz, H-4); 4.22 (dd, $\Sigma J = 22$

Hz, H-6'); 4.20 (t, $J_{5',4} = |J_{5',5''}| = 10.1$ Hz, H-5'); 4.07-3.94 (m, H6", OH) [after exhange with D₂O : 3.99, dd, $J_{6'',3} = 6.2$ Hz, $J_{6'',6'} = -12.0$ Hz]; 3.75 (dd, 1H, $J_{5'',4} = 3.8$ Hz, $J_{5'',5'} = -9.9$ Hz, H-5"); 2.99-2.93, OH; 2.77 (ddd, 1H, $J_{3,2} = 5.3$ Hz, $J_{3,6'} = J_{3,4} = 7.5$ Hz, $J_{3,6''} = 9.1$ Hz, H-3); 1.31, 1.26 CMe₂; 1.11 CMe₃. ¹³C (CDCl₃) 135.45, 132.48, 132.18, 129.92, 127.82 Ph; 112.14 CMe₂; 106.09 C-1; 82.06, 80.68 C-2, C-4; 64.51, 58.53 C-5, C-6; 47.56 C-3; 26.75 CMe₃; 26.43, 25.33 CMe₂; 18.98 CMe₃. Exact mass (thioglycerol-NaOAc) calc. for C₂₅H₃₄O₅Si+Na 465.2073; found 465.2050

1,2-Isopropylidene-3-deoxy-3-C-hydroxymethyl-L-lyxofuranose 3

Compound 14 (12.4 g, 28.1 mmol) was desilvated with 15 g of Bu₄NF-3H₂O in THF (150 ml) during 3 h. The solvent was evaporated to furnish brownish oil. Gravitational chromatography in hexane-EtOAc 1:3 \rightarrow neat EtOAc furnished 5.2 g (91%) of 3, mp. 66-67°, cryst. from hexane-EtOAc.

¹H (DMSO) : 5.71 (d, 1H, $J_{1,2} = 3.7$ Hz, H-1); 4.65-4.50 (unresolved, 4H, H-2, 2 x OH) [after exchange with D_2O : 4.61 (t, $J_{2,1} = 4.0$ Hz, $J_{2,3} = 4.8$ Hz, H-2)]; 4.05 (q, 1H, $J_{4,3} = J_{4,5'} = J_{4,5''} = 7.1$ Hz, H-4); 3.63-3.51 (m, 4H, 2 x H-5, 2 x H-6); 2.43 (ddd, $J_{3,2} = 5.0$, $J_{3,4}$, $J_{3,6''}$, $J_{3,6''} = 7.5$ Hz, 7.8 Hz and 8.8 Hz, these values are taken from a projection of this multiplet on a J axis in a 2DJ resolved spectrum, H-2); 1.43, 1.21, CMe₂. ¹³C (DMSO) : 111.25 CMe₂; 105.68 C-1; 83.08, 80.12 C-2, C-4; 61.77, 56.03 C-5, C-6; 47.31 C-3; 26.80, 25.67 CMe₂. Exact mass (thioglycerol) calc. for C9H₁₆O₅+H 205.1076; found 205.1074.

2,4-Di-O-acetyl-1,6-anhydro-3-deoxy-3-C-hydroxymethyl-L-lyxopyranose 4

Diol 3 (0.10 g) was treated with 20 ml of 90% trifluoroacetic acid during 10 min. The acid was evaporated, and co-evaporated with EtOAc. Water was added and the solution was neutralized with Dowex 1X8 OH⁻. After filtration of the resin and evaporation of water, 0.058 g of glassy solid was obtained. Conventional acetylation and chromatography in hexane-EtOAc 1:1 furnished 0.061 g (54%) of 4, mp. 105-106° (hexane-EtOAc). ¹H (CDCl₃) : 5.38 and 5.32, two s, H-1, H-2; 5.01 (dd, 1H, $J_{4,5} = 3.2$ Hz, $J_{4,3} = 4.7$ Hz, H-4); 4.15 (dd, $J_{6',3} = 4.3$ Hz, $J_{6',6''} = -9.0$ Hz, H-6'); 4.01 (d, $J_{6'',6''} = -8.9$ Hz, H-6''); 3.91 (dd, $J_{5ax,4} = 2.9$ Hz, $J_{5ax,5eq} = -13.5$ Hz, H-5ax); 3.69 (d, 1H, $J_{5eq,5ax} = -13.6$ Hz, H-5eq); 2.91 (t, 1H, $J_{3,4} = J_{3,6'} = 4.4$ Hz, H-3); 2.18, 2.11, OAc. ¹³C (CDCl₃) : 170.39, 169.95 COMe; 99.96 C-1; 73.98, 72.15 C-2, C-4; 69.16, 61.95 C-5, C-6; 41.53 C-3; 21.05, 20.83 COMe. Exact mass (thioglycerol) calc. for C₁₀H₁₄O₆+H 231.0869; found 231.0862.

Tetra-O-acetyl-3-deoxy-3-C-hydroxymethyl-α-L-lyxopyranose 6, tetra-O-acetyl-3-deoxy-3-C-hydroxymethyl-α,β-L-lyxo-(1,6)-furanose 5 and hexa-O-acetyl-3-deoxy-3-C-hydroxymetyl-aldehydo-L-lyxose 19.

A. From anhydro compound 4.

Diacetate 4 (0.15 g) was subjected to acetolytic cleavage with 8 ml of a mixture prepared from 4.6 ml of Ac₂O, 12 ml of glacial AcOH and 0.4 ml of conc. H_2SO_4 , during 16 h. TLC (hexane-EtOAc 7:3) showed three partially overlapping spots : $R_f 0.31$ of 6, $R_f 0.24$ of 5 and $R_f 0.18$ of 19. Extractive work-up and

gravitational column in hexane-EtOAc 7:3 furnished 0.105 g (48%) of 6, 0.050 g (23%) of 5 and 0.028 g (10%) of 19 eluted in this order.

- B. From diol 3 via diacetate 24.
 - I. To get a pyranose 6 as a predominant product.

Diol 3 (0.58 g) was acetylated in Ac₂O-Py mixture. Evaporation of volatiles followed by coevaporation with xylene furnished 24. This material was treated with 90% trifluoroacetic acid during 15 min. The acid was evaporated, and co-evaporated with a mixture of ethyl acetate and xylenes^{*}. After drying on an oil pump (15 min), the residue was dissolved in MeOH and small pieces of sodium were added (with external cooling of the flask) to neutralize traces of a residual TFA still present and to deacetylate the transient diacetate 25 and other products of acetyl group migration, and to allow for pyranose/furanose equilibration. A piece of dry ice was added and methanol was evaporated. The residue was dried using oil pump, and acetylated in pyridine-Ac₂O overnight. After evaporation, coevaporation with xylene and chromatography in hexane-EtOAc 7:3 0.23 g of 6 as a pure α anomer (24% for four steps) and 0.16 g of 5 as a $1:1 \alpha/\beta$ mixture (17% for four steps) was obtained.

II. To get a furanose 5 as a predominant product.

Diol 3 (3.04 g) was acetylated and worked up as above to furnish 4.30 g of 24, which was de-acetylated with 90 ml of 90% TFA during 10 min. The acid was evaporated and co-evaporated with DMF (~ 100 ml). This took ca. 30 minutes, and permitted longer contact with TFA to promote preferential formation of the furanose 17, but also for internal glycoslyation to 18 in limitted extend. After drying on an oil pump, deacetylation as above, acetylation and chromatography, three fractions were obtained : 4 (0.127 g, 4%), 6 as a pure α anomer (0.515 g, 10%) and 5 [1.810 g (as 1:1 anomeric mixture), 37%], eluted in this order. All percent yields are calculated for four consecutive reactions (acetylation, deacetylation, deacetylation.

6α ¹H (CDCl₃) : 5.96 (d, 1H, $J_{1,2} = 1.8$ Hz, H-1); 5.09 (dt, $J_{4,5eq} = 5.6$ Hz, $J_{4,5ax} = J_{4,3} = 10.7$ Hz, H-4); 5.06 (dd, $J_{2,3} = 2.9$ Hz, $J_{2,1} = 1.8$ Hz, H-2); 4.17 (dd, $J_{6',3} = 5.5$ Hz, $J_{6',6''} = -11.2$ Hz, H-6''); 3.91 (dd, 1H, $J_{5eq,4} = 5.4$ Hz, $J_{5eq,5ax} = -10.8$ Hz, H-5eq); 3.57 (t, 1H, $J_{5ax,4} = |J_{5ax,5eq}| = 10.6$ Hz, H-5ax); 2.59 (dddd, 1H, $J_{3,2} = 2.9$ Hz, $J_{3,6'} = 5.5$ Hz, $J_{3,6''} = 8.6$ Hz, $J_{3,4} = 11.3$ Hz, H-3), 2.16, 2.14, 2.08, 2.06, OAc. ¹³C (CDCl₃) : 170.58, 169.96, 169.78, 168.46 <u>COMe</u>; 88.95 C-1; 67.51, 65.07 C-2, C-4; 61.32, 60.26 C-5, C-6; 37.81 C-3; 20.69, CO<u>Me</u>. Exact mass (thioglycerol-NaOAc) calc. for C₁₄H₂₀O₉+Na 355.1005; found 355.0996.

6β ¹H (CDCl₃) : The only signals identifiable form a mixture obtained under BI, are those of H-1, H-3 and H-5eq. H-1 : δ 5.97, d, $J_{1,2} = 2.4$ Hz. H-5eq : δ 3.61, dd, $J_{5eq,4} = 5.2$ Hz, $J_{5eq,5ax} = -12.5$ Hz. H-3 : δ 2.49, dq, $J_{3,2} = 4.3$ Hz, $J_{3,4} = J_{3,6^{11}} = J_{3,6^{11}} = 7.0$ Hz.

^{* &}lt;sup>13</sup>C NMR of the reaction mixture at this stage showed the following signals of the anomeric region (in CDCl₃) : 102.19, 100.07, 94.80, 93.24 and 90.56, proving extensive migration of the acetyl groups in the primary product 25. Acetylation of this mixture of products furnished 6 as a pure α anomer, 5 as an α/β mixture contaminated with a compound which is probably β anomer of 6 (unseparable) and 26 as a pure α anomer, formed in proportion 6:4:1 and eluted in this order.

5α ¹H (CDCl₃): 6.33 (d, $J_{1,2} = 4.2$ Hz, H-1); 5.23 (ddd, J = 5.0 Hz, 5.0 Hz and 3.6 Hz, H-4); 4.95 (dd, $J_{2,1} = 4.1$ Hz, $J_{2,3} = 9.8$ Hz, H-2); 2.84 (dq, $J_{3,2} = 9.1$ Hz, J = 9.1 Hz, 9.1 Hz, 4.6 Hz, H-3); 4.45-3.90 (m, H5',5",6',6" of both anomers); 2.10, 2.08, 2.07, 2.03, OAc of both anomers. ¹³C (see β anomer)

5 β ¹H (CDCl₃) : 6.14 (s, H-1); 5.36 (ddd, J_{4,3} = 3.1 Hz, J = 5.4 Hz, 8.1 Hz, H-4); 5.09 (d, J_{2,3} = 3.6 Hz, H-2); 2.65 (dq, J_{3,2} = 3.5 Hz, J = 8.0 Hz, 8.0 Hz, 7.9 Hz, H-3); H5',5",6',6" and OAc : see α anomer. ¹³C (CDCl₃) (both anomers) : 170.44, 170.37, 169.97, 169.66, 169.43 <u>C</u>OMe; 100.32, 93.79 C-1; 79.40, 72.68, 70.17, 68.94 C-2, C-4; 69.51, 66.55, 64.00, 63.91 C-5, C-6; 45.82, 41.06 C-3; 21.06, 20.84, 20.73, 20.45 COMe. Exact mass (thioglycerol-NaOAc) calc. for C₁₄H₂₀O₉+Na 355.1005; found 355.0991.

19 ¹H (CDCl₃) : 7.00 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1); 5.47 (ddd, 1H; $J_{4,3} = 3.8$ Hz, $J_{4,5'} = 3.8$ Hz, $J_{4,5'} = 7.4$ Hz, H-4); 5.22 (d, 1H, $J_{2,1} = 3.4$ Hz, $J_{2,3} = 7.4$ Hz, H-2); 4.36 (dd, $J_{5',4} = 4.2$ Hz, $J_{5',5''} = -11.9$ Hz, H-5'); 4.31 (dd, $J_{6',3} = 5.0$ Hz, $J_{6',6''} = -12.1$ Hz, H-6'); 4.21 (dd, $J_{6'',3} = 7.3$ Hz, $J_{6'',6'} = -11.1$ Hz, H-6'); 4.16 (dd, $J_{5'',4} = 7.4$ Hz, $J_{5'',5''} = -11.9$ Hz, H-5'); 2.42 (dddd, 1H, $J_{3,2} = J_{3,6''} = 7.5$ Hz, $J_{3,4} = 3.9$ Hz, $J_{3,6'} = 5.0$ Hz, H_{-3}); 2.14, 2.09, 2.07, 2.06, 2.03, COMe. ¹³C (CDCl₃) : 170.47, 169.81, 168.42 COMe; 87.44 C-1; 69.07, 67.92 C-2, C-4; 63.90, 60.34 C-5, C-6; 39.01 C-3; 20.72, 20.56 COMe. Exact mass (thioglycerol-NaOAc) cald. for C₁₈H₂₆O₁₂+Na 457.1322; found 457.1260.

5-O-(t-Butyldiphenylsilyl)-3-deoxy-3-C-benzyloxymethyl-1,2-isopropylidene-L-lyxo-(1,4)-furanose 22 and 5-O-benzyl-3-deoxy-3-C-benzyloxymethyl-1,2-isopropylidene-L-lyxo-(1,4)-furanose 20.

Compound 14 (0.50 g, 1.13 mmol) in CH_2Cl_2 (20 mL), benzyl bromide (0.7 ml, 5.9 mmol) and 20% of aq.NaOH were vigorously stirred overnight. TLC (hexane-EtOAc 3:1) showed a spot of 22 R_f 0.77 and 20 R_f 0.57. Aqueous layer was separated and extracted with CH_2Cl_2 . Combined organic layers were evaporated. Chromatography of the residual oil furnished 0.113 g (19%) of 22 (eluted with hexane-EtOAx 6:1) and 0.209 g (48%) of 20 (eluted with hexane-EtOAc 45:10), both as oils.

22 ¹H (CDCl₃) : 7.65-7.60 and 7.40-7.31, 15H, Ph; 5.77 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1); 4.71 (dd, 1H, $J_{2,1} = 4.3$ Hz, $J_{2,3} = 4.7$ Hz, H-2); 4.52 (AB, J = 12.2 Hz and 15.4 Hz, OCH₂Ph); 4.33 (dt, $J_{4,3} = 5.7$ Hz, $J_{4,5'} = J_{4,5''} = 7.9$ Hz, H-4); 3.91 (dd, $J_{5',4} = 7.8$ Hz, $J_{5',5''} = 10.2$ Hz, H-5'); 3.81-3.69 (unresolved, H-5'', 2 x H-6); 2.67 (dddd, 1H, $J_{3,4} = J_{3,2} = 5.7$ Hz, $J_{3,6''} = J_{3,6''} = 8.1$ Hz, H-3); 1.27, 1.25, CMe₂; 1.01, CMe₃. ¹³C (CDCl₃) : 138.35, 135.61, 133.46, 133.22, 129.66, 128.38, 127.71 Ph; 111.96 CMe₂; 106.07 C-1; 82.23, 80.35 C-2, C-4; 73.27 CH₂Ph; 65.12, 64.32 C-5, C-6; 45.75 C-3; 26.84 CMe₃; 26.48, 25.57 CMe₂; 19.15 CMe₃ Exact mass (n-nitrobenzyl alcohol-NaOAc) calc. for C₃₂H₄₀O₅Si+Na 555.2543; found 555.2535.

20 ¹H (CDCl₃) : 7.31-7.24, 10H, Ph; 5.82 (d, 1H, $J_{1,2} = 3.9$ Hz, H-1); 4.68 (dd, 1H, $J_{2,1} = 3.9$ Hz, $J_{2,3} = 5.1$ Hz, H-2); 4.62-4.37 (m, 5H, 2 x OCH₂Ph, H-4); 3.76-3.56 (m, 4H, 2 x H-5, 2 x H-6); 2.68 (dddd, 1H, $J_{3,2} = 5.2$ Hz, J = 7.1 Hz, 8.1 Hz, 8.1 Hz, H-3); 1.41, 1.27 CMe₂. ¹³C (CDCl₃) : 138.16, 128.31, 127.74, 127.62, 127.51 Ph; 112.01 CMe₂; 106.06 C-1; 80.75, 80.31 C-2, C-4; 73.24, 73.17 CH₂Ph; 70.22, 64.98 C-5, C-6; 45.38 C-3; 26.48, 25.49 CMe₂. Exact mass (n-nitrobenzyl alcohol-NaOAc) calc. for C₂₃H₂₈O₅+Na 407.1835; found 407.1822.

3-Deoxy-3-C-hydroxymethyl-1,2-isopropylidene-L-lyxo-(1,4)-furanosyl diacetate 24

For analytical purpose diacetate 24 was prepared by conventional acetylation in $Py-Ac_2O$ mixture 1:2, evaporation of volatiles, co-evaporation with xylenes and chromatography in hexane-EtOAc 2:1.

¹H (CDCl₃) : 5.86 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1); 4.71 (dd, 1H, $J_{2,1} = 3.9$ Hz, $J_{2,3} = 5.1$ Hz, H-2); 4.44-4.19 (m, 4H, 2 x H-5, 2 x H-6); 2.74 (dq, $J_{3,2} = 4.6$ Hz, $J_{3,4} = J_{3,6'} = 7.9$ Hz, H-3); 2.09 (s, 6H, COMe); 1.58, 1.31 CMe₂. ¹³C (CDCl₃) : 170.64 COMe; 112.68 CMe₂; 106.15 C-1; 79.79, 79.01 C-2, C-4; 64.24, 59.13 C-5, C-6; 44.03 C-3; 26.45, 25.42 CMe₂; 20.82 COMe. Exact mass (thioglycerol-NaOAc) calc. for C₁₃H₂₀O₇+Na 311.1107; found 311.1113.

Tetraacetyl 3-deoxy-3-C-hydroxymethyl-α-L-lyxo-(1,4)-furanose 26

Acetonide 24 0.072 g was treated with 3 ml of an Ac₂O-AcOH-H₂SO₄ mixture prepared as described above for 6, 5 and 19, during 16 h. After extractive work-up and chromatography in hexane-EtOAc 2:1 0.043 g, (52%) of 26 (syrup) was obtained as a single anomer and 0.019 g (23%) of 19 eluted in this order.

¹H (CDCl₃): 6.19 (s, 1H, H-1); 5.27 (d, 1H, $J_{2,3} = 5.1$ Hz, H-2); 4.60 (ddd, 1H, $J_{4,5'} = 4.7$ Hz, $J_{4,5''} = 7.6$ Hz, $J_{4,3} = 8.7$ Hz, H-4); 4.34-4.08 (m, 4H, 2 x H-5, 2 x H-6); 3.12 (dddd, 1H, $J_{3,2} = 5.1$ Hz, $J_{3,6''} = 7.1$ Hz, $J_{3,4} = J_{3,6''} = 8.6$ Hz, H-3); 2.12, 2.10, 2.08, 2.07 COCH₃. ¹³C (CDCl₃): 170.57, 169.53, 169.16 COCH₃; 98.52 C-1; 78.04, 75.70 C-2, C-4; 64.15, 57.99 C-5, C-6; 40.61 C-3; 21.04, 20.75 COCH₃. Exact mass (thioglycerol-NaOAc) calc. for C₁₄H₂₀O₉+Na 355.1005; found 355.1005.

2',4,6'-Tri-O-acetyl-3'-deoxy-3'-C-hydroxymethyl-a-L-lyxopyranosyl thymine 7

Pyranose 6 (0.23 g, 0.69 mmol) in 15 ml of 1,2-dichloroethane was added to trimethylsilylated thymine (prepared from a free base, 0.13 g, 1.02 mmol, hexamethyldisilazane and cat. $(NH_4)_2SO_4$ at bp during 5 h, followed by evaporation of volatiles, co-evaporation with xylenes and final drying on oil pump), followed by TMSOTf (0.13 ml, 0.68 mmol). External temp. of 80° was maintained overnight. TLC showed a UV-absorbing spot R_f 0.41 (CH₂Cl₂-MeOH 20:0.7) of 7. Unreacted carbohydrate 6 was still present. After extractive workup and chromatography, 0.17 g (62%) of 7 was obtained as a glassy solid.

¹H (CDCl₃) : 9.30 H-3; 7.18 (d, 1H, J_{H,CH3} = -1.0 Hz, H-6); 5.97 (d, 1H, J_{1',2'} = 10.0 Hz, H-1'); 5.35 (dd, 1H, J_{2',1'} = 9.7 Hz, J_{2',3'} = 6.2 Hz, H-2'); 5.06 (bs, half width 6 Hz, H-4'); 4.44 (dd, J_{6',3'} = 7.0 Hz, J_{6',6''} = -12.0 Hz, H-6'); 4.37 (dd, J_{6'',3'} = 3.6 Hz, J_{6'',6''} = -12.0 Hz, H-6''); 4.14 (dd, J_{5',4'} = 1.5 Hz, J_{5',5''} = -13.6 Hz, H-5'); 4.04 (d, J_{5'',5'} = -13.6 Hz, H-5''); 2.87-2.72 (unresolved, H-3'); 2.20, 2.15, 2.05 COMe; 1.96 (d, J_{CH3,6''} = -1.0 Hz, CH₃). Exact mass (thioglycerol) calc. for C₁₇H₂₂N₂O₉+H 399.1403; found 399.1399.

3'-Deoxy-3'-C-hydroxymethyl-a-L-lyxopyranosyl thymine 1

Deacetylation of 7 (0.102 g) in MeOH and cat. NaOMe, followed by neutralization with a piece of dry ice, evaporation and chromatography through a short bed of silica gel (in CH_2Cl_2 -MeOH 5:1) furnished 0.051 g (73%) of 1, as a glassy solid.

¹H (CD₃OD) : 7.69 (d, 1H, $J_{6,CH_3} = -1.1$ Hz, H-6); 5.72 (d, 1H, $H_{1',2'} = 9.7$ Hz, H-1'); 4.23 (dd, $J_{2',3'} = 5.9$ Hz, $J_{2',1'} = 9.7$ Hz, H-2'); 4.12-4.02 and 3.92-3.78 (two groups of multiplets, H4', 2 x H-5', 2 x H-6'); 2.55-2.41 (unresolved, 1H, H-3'); 1.94 (d, 3H, $J_{CH_3,6} = -1.1$ Hz, CH₃). ¹³C (CD₃OD) : 166.27, 153.10 C-2, C-4; 137.98 C-6; 111.82 C-5; 82.59 C-1'; 69.82 C-6'; 68.56, 66.91 C-2', C-4'; 59.13 C-5'; 49.29 C-4'; 12.38 CH₃. Exact mass (thioglycerol) calc. for C₁₁H₁₆N₂O₆+H 273.1087; found 273.1093.

2',4',5'-Tri-O-acetyl-3-deoxy-3-C-hydroxymethyl- α -L-lyxo-(1,6)-furanosyl thymine 8 and 2',4',6'-tri-O-acetyl-3'-deoxy-3'-C-hydroxymethyl- α -L-lyxopyranosyl thymine 7

Furanose 5 (0.33 g, 1 mmol) in 30 ml of 1,2-dichloroethane was added to trimethylsilylated thymine prepared from 0.19 g (1.5 mmol) of thymine as described above, followed by 0.19 ml (1 mmol) of TMSOTf. External temp. 60° was maintained during 18 h. TLC showed two partially overlapping spots (R_f of a mid-point was 0.40 in CH₂Cl₂-MeOH 20:0.7). The upper spot belonged to a pyranosyl nucleoside 7, the lower one to a furanosyl nucleoside 8. Extractive work-up and chromatography in CH₂Cl₂-MeOH 20:0.4 furnished 0.096 g (24%) of 7 and 0.188 g (47%) of 8, which was contaminated with ca 5% of the β anomer most probably.

¹H (CDCl₃) : 9.19, H-3; 7.07 (q, 1H, $J_{6,CH_3} = -1.2$ Hz, H-6); 5.71 (d, 1H, $J_{1',2'} = 4.7$ Hz, H-1'); 5.35 (dd, $J_{2',1'} = 4.8$ Hz, $J_{2',3'} = 6.9$ Hz, H-2'); 5.29 (ddd, $J_{4',5'} = 3.3$ Hz, $J_{4',5''} = 5.2$ Hz, $J_{4',3'} = 7.2$ Hz, H-4'); 4.36 (dd, $J_{5',4'} = 3.6$ Hz, $J_{5',5''} = -12.4$ Hz, H-5'); 4.21 (apparent dd, J = 2.6 Hz and 8.3 Hz, 2 x H-6'); 4.07 (dd, $J_{5'',4'} = 5.2$ Hz, $J_{5'',5''} = -12.3$ Hz, H-5''); 2.85 (dddd, $J_{3',2'} = J_{3',4'} = J_{3',6''} = 7.7$ Hz, H-3'); 2.11, 2.10, 2.07 COCH₃; 1.95 (d, $J_{CH_{3,6}} = -1.1$ Hz, CH₃). ¹³C (CDCl₃) : 170.36, 170.00 <u>C</u>OCH₃; 163.70, 150.52 C-2, C-4; 136.01 C-6; 111.31 C-5; 91.41 C-1'; 76.89, 69.68 C-2', C-4'; 69.47, 63.69 C-5', C-6'; 45.22 C-3'; 20.77, 20.61 CO<u>C</u>H₃; 12.50 CH₃. Exact mass (thioglycerol) calc. for C₁₇H₂₂N₂O₉+H 399.1403; found 399.1409.

3'-Deoxy-3'-C-hydroxymethyl-a-L-threofuranosyl thymine 2

Compound 8 (0.134 g, 0.34 mmol) was deacetylated in 20 ml of MeOH and cat. NaOMe. After neutralization with a piece of dry ice, 1.4 mol eq of aq. NaIO₄ was added. The solution was filtered (30 min later) through fritted glass to remove precipitated sodium iodate, and 5.8 mol eq of aq. NaBH₄ solution (having pH = 8.0 adjusted with 0.1 N NaOH) was added. The solution was evaporated (30 min later) to near dryness. Chromatography of the residue (in CH₂Cl₂-MeOH 20:3) furnished 0.044 g of 2 (54% for three steps) as a glassy compound, which was contaminated with ca 5% of the β anomer most probably.

¹H (CD₃OD) : 7.50 (q, 1H, $J_{6,CH_3} = -1.2$ Hz, H-6); 5.76 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1'); 4.27 (dd, $J_{2',1'} = 5.3$ Hz, $J_{2',3'} = 7.1$ Hz, H-2'); 4.26 (t, $J_{5',3'} = 8.4$ Hz, $J_{5',5''} = -8.4$ Hz, H-5'); 4.10 (t, J = 8.1 Hz and 8.8 Hz, H-5''); 3.78 (dd, $J_{4',3'} = 5.1$ Hz, $J_{4',4''} = -11.1$ Hz, H-4'); 3.69 (dd, $J_{4'',3'} = 6.8$ Hz, $J_{4'',4'} = -11.2$ Hz, H-4''); 2.52 (ddddd, $J_{3',4'} = 5.0$ Hz, $J_{3',2'} = 7.2$ Hz, $J_{3',4''} = 7.7$ Hz, $J_{3',5'} = 3.4$ Hz, H-3'); 1.93 (d, 3H, $J_{CH_3,6} = -1.1$ Hz, CH₃). ¹³C (CD₃OD) : 166.43, 152.75 C-2, C-4; 138.33 C-6; 111.62 C-5; 93.52 C-1'; 76.94 C-2'; 71.45, 61.65 C-4', C-5'; 49.45 C-3'; 12.37 CH₃. Exact mass (thioglycerol) calc. for C₁₀H₁₄N₂O₅+H 243.0981; found 243.0980.

2',5'-Di-O-(p-nitro)benzoyl-3'-deoxy-3'-C-hydroxymethyl-a-L-threofuranosyl thymine 34

Diol 2 (0.033 g, 0.14 mmol) was conventionally converted into bis-(p-nitro)benzoate 34 using 0.055 g (0.3 mmol) of p-nitrobenzoyl chloride in pyridine (15 ml). After extractive work-up and chromatography in CH_2Cl_2 -MeOH 20:0.4, 0.069 g (94%) of 34 was obtained, mp. 198-201° (CH_2Cl_2 -iPrOH).

¹H (500 MHz, DMSO-*d*₆) : 11.384 H-3; 8.284-8.094 H aromatic; 7.632 (q, $J_{6,CH_3} = -0.92$ Hz, H-6); 5.958 (d, $J_{1',2'} = 4.88$ Hz, H-1'); 5.821 (dd, $J_{2,1'} = 5.18$ Hz, $J_{2',3'} = 7.32$ Hz, H-2'); 4.667 (dd, $J_{5',3'} = 7.33$ Hz, $J_{5',5''} = -11.30$ Hz, H-5'); 4.595 (dd, $J_{5'',3'} = 6.41$ Hz, $J_{5'',5'} = -10.98$ Hz, H-5''); 4.326 (t, $J_{4',3'} = 8.24$ Hz, $J_{4',4''} = -8.54$ Hz, H-4'); 4.212 (t, $J_{4'',4''} = -8.54$ Hz, $J_{4'',3'} = 8.85$ Hz, H-4''); 3.253 (sextet, J = 7.6 Hz, H-3'). ¹³C (50 MHz, DMSO-*d*₆) : 164.00, 163.77 <u>C</u>OPh; 150.54, 150.23, 150.07, 137.86, 134.62, 134.09, 130.77, 130.55, 123.58 C-2, C-4, C-6, Ph; 109.36 C-5; 90.71 C-1'; 78.56 C-2'; 69.59, 63.99 C-4', C-5'; 43.10 C-3'; 11.95 CH₃. Exact mass (m-nitrobenzyl alcohol, negative mode) calc. for C₂₄H₂₀N₄O₁₁ 540.1128; found 540.1131.

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