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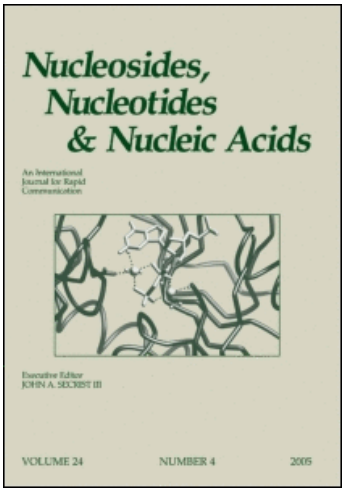

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Synthesis of 4-Deoxy-4-C-hydroxymethyl-α-L-Lyxo-Pyranosyl Thymine

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NUCLEOSIDES & NUCLEOTIDES, 15(9), 1495-1518 (1996)

SYNTHESIS OF 4-DEOXY-4-C-HYDROXYMETHYL-α-L-LYXO-PYRANOSYL THYMINE

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Abstract

The synthesis of 1-[4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine has been accomplished by two synthetic routes both starting from methyl 2,3-O-isopropylidene-β-D-ribopyranoside. The first route makes use of a ring opening, ring closure reaction sequence to increase the proportion of the desired L-isomers. The second route utilizes the soft nucleophilic character of malonyl anions and ozonolytic cleavage of enol ether to introduce the branched chain. The newly obtained pyranosyl nucleoside obtains a $^4C_1$ conformation with an equatorially oriented thymine moiety.

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INTRODUCTION

Because of the broad substrate specificity of herpes virus enzymes involved in nucleoside metabolism, many nucleoside analogues are phosphorylated selectively in viral infected cells and, hence, demonstrate selective antiviral activity[1,2]. In search for new and more potent antiherpes agents, nucleosides were synthesized in which the naturally occuring furanosyl carbohydrate moiety was replaced by a six membered ring. This research has resulted in the discovery of 1,5-anhydrohexitol nucleosides (**1a**) (Figure 1) as promising antiherpes agents[3,4]. These nucleoside analogues (**1a**) were also used as building blocks for oligonucleotide synthesis. This research led to the discovery of the strong hybridizing properties of 1,5-anhydrohexitol nucleic acids[5,6,7]. An interesting structure feature of compound **1a** is that the base moiety occupies an axial position[3,4] while heterocyclic bases are oriented equatorially in most pyranosyl nucleosides[8]. In order to be able to further study this structure-activity relationship, we became interested in the synthesis of the analogues of **1a** that are depicted in Figure 1 (**1b-d**).

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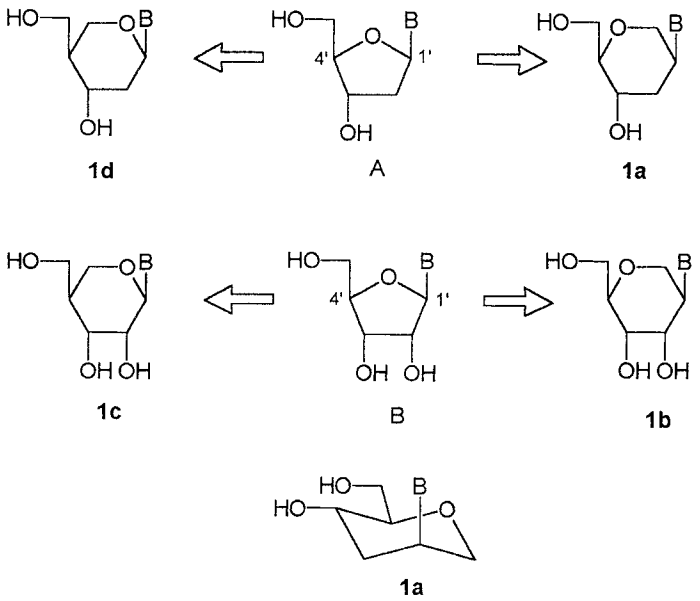

Fig. 1. Structure of analogues of 2'-deoxynucleosides (A) and ribonucleosides (B) with a methylene group inserted between C1' and O4' (**1a** and **1b**) and between C4' and O4' (**1c** and **1d**). In contrast with compounds **1a** and **1b**, compounds **1c** and **1d** possess an anomeric centre. The conformation of **1a** as derived from X-ray and NMR analysis[3,4] is given.

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Compound **1a** (Figure 1) was initially synthesized as an analogue of 2'-deoxythymidine with a methylene group inserted between C1' and the endocyclic oxygen atom[3]. The 2-deoxy-D-*altro*-hexitol analogue **1b** (Figure 1) can be considered as the "*ribo*" analogue of **1a**[9].

Compound **1b** (base : uracil) also has an axial oriented base moiety (unpublished results) and the study of its antiviral activity is in progress. The influence of the position of the endocyclic oxygen atom on the conformational preference can be studied by synthesizing **1c** and **1d** (Figure 1). Here a methylene group is inserted between the carbon C4' and the endocyclic oxygen atom of a *ribo*-nucleoside and deoxyribonucleoside, respectively. This means that the base moiety occupies an anomeric position in **1d** and **1c**. No anomeric centre is present in compounds **1a** and **1b**. The synthesis of 1-[4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine (**1c**, B : thymin-1-yl), starting from methyl 2,3-O-isopropylidene-β-D-ribopyranoside is described and its conformation is deduced from ^{1}H NMR data.

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RESULTS AND DISCUSSION

Synthesis of 1c from methyl 4-*C*-methylidene-2,3-O-isopropylidene-β-D-*erythro*-pentopyranoside (4).

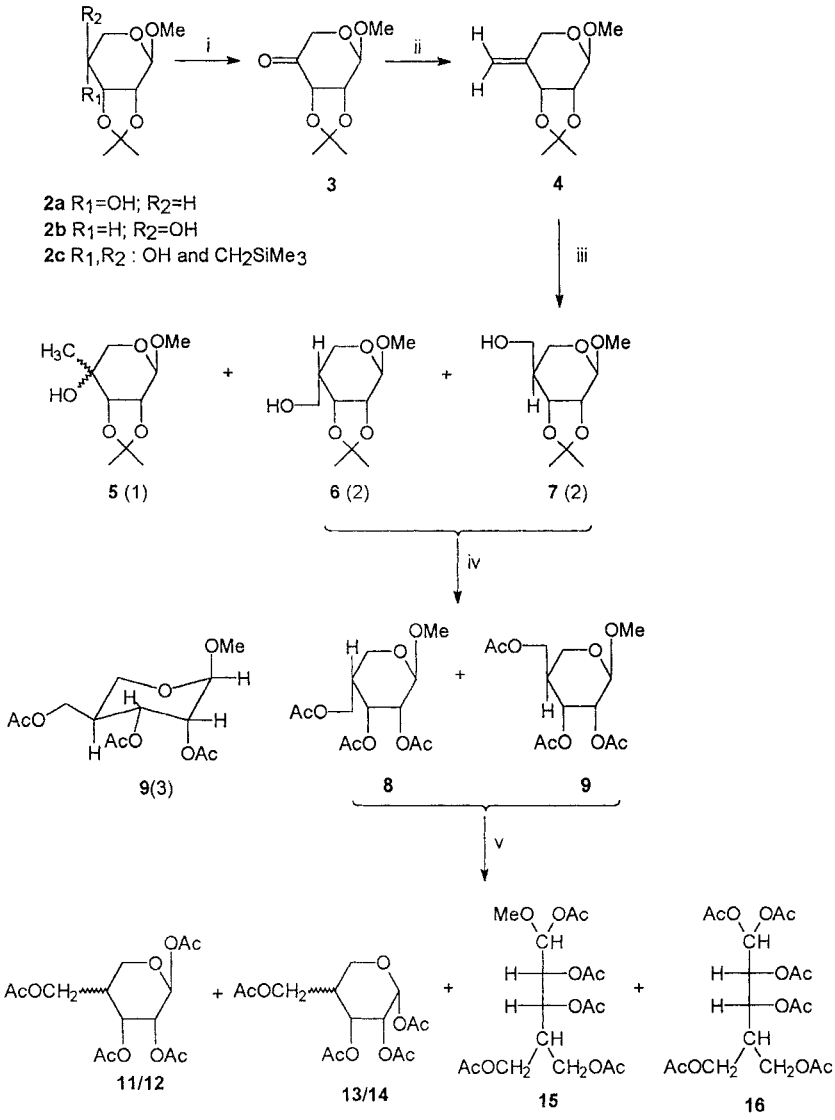
Our first approach to compounds of type **1c** started from methyl 2,3-O-isopropylidene-β-D-ribopyranoside **2a**[10] or methyl 2,3-O-isopropylidene-α-L-lyxo-pyranoside **2b**[11]. Oxidation of either **2a** or **2b** using CrO_3-pyridine-Ac_2O[12] yielded *ulose* **3**. Without characterization **3** was subjected to either a Peterson olefination[13] or a Wittig reaction to furnish **4**. The intermediary tertiary alcohol of the Peterson olefination **2c** of undefined configuration was isolated as a single stereoisomer. Hydroboration of **4** using diborane proceeded with surprisingly poor regiochemical outcome and furnished a product **5** as a 95:5 unseparable mixture of both epimeric alcohols, together with an unseparable mixture of oily **6/7** formed as 9:1 mixture. The ratio of **6/7** to **5** changed from ca 4:3 in a small scale preparation to ca 2:1 on a larger scale.

In an effort to try to find analogues of **6** and **7** which can be separated more easily, acetonides **6/7** were converted into noncrystalline triacetates **8/9** using 90% trifluoroacetic acid and Ac_2O in pyridine.

These compounds could not be separated, likewise. However, when **8/9** were converted to tri-(p-nitro)benzoates (a. NaOMe/MeOH; b. pNBzCl, Py), a single crystalline C4 epimer **10** (Figure 2) was obtained after three crystallizations, and shown to be a *ribo* isomer by analysis of the coupling constants in its ^1H NMR spectrum. The compound is conformationally unstable and exists as a mixture of the $^4C_1$ and $^1C_4$ conformers as shown in Fig. 2.

In the $^4C_1$ conformation, **10** minimizes steric repulsions, but no anomeric effect is present. In the $^1C_4$ conformation the anomeric effect operates, however this gain is offset by a 1,3-diaxial interaction of the functionalities at C2 and C4. These opposing factors result in a conformational equilibrium as evidenced by the averaged values of the ^1H-^1H coupling constants. The same is true for triacetate **8** although the proportion of the $^4C_1$ conformer is higher. This conclusion is clear from increasing values of $J_{1,2}$ and $J_{4,5''}$. Even though the anomeric effect of the acetoxy group is greater than that of the methoxy group[14,15], the tetraacetate **11** (see below), having the same configuration as both **8** and **10**, resides predominantly if not exclusively in the $^4C_1$ form (Fig. 2 and Fig. 3).

In conclusion, hydroboration of the olefin **4** furnished predominantly the undesired *ribo* stereoisomer **6.** However, because the centre of chirality of the carbon atom C4 is lost if any of the compounds **6-14** is written in an open chain Fischer projection (Fig. 4), compound **6** can still be used as intermediate for the synthesis of nucleosides of type **1c**. This projection displays two pro-



Scheme 1 : i : Ac_2O-Pyr-CrO_3, CH_2Cl_2; ii : $LiCH_2SiMe_3$, CH_2Cl_2; NaH, THF or $CH_2{=}PPh_3$, THF; iii : diborane, THF; iv : CF_3COOH, Ac_2O-pyr; v : Ac_2O, AcOH, H_2SO_4.
(1) **5** as 95:5 unseparable mixture of stereoisomers; (2) **6** and **7** are formed as 9:1 unseparable mixture; (3) conformation of compound **9**.

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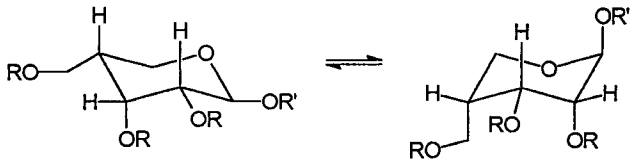

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5'}$	$J_{4,5''}$
8[a]	4.9	3.7	3.9	3.7	6.2
10[b]	3.4	3.4	4.8	3.3	4.2
11[a]	6.2	3.3	3.3	ND	ND

Fig. 2. Conformers of **8** (R=Ac, R'=Me), **10** (R=$COC_6H_4pNO_2$, R'=Me) and **11** (R=R'=Ac) as observed by ^1H NMR measurements. Coupling constants given in Hz; solvents a : $CDCl_3$; b : C_6D_6; ND : not determined.

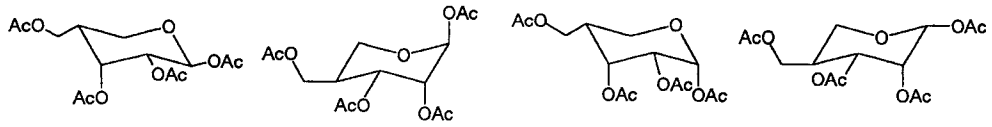

Fig. 3. Preferred conformers and abundancies of **11, 12, 13, 14** formed after acetolytic cleavage of **8/9**, deacetylation and re-acetylation (ratio **12+14/11+13**=3/2)

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chiral hydroxymethyl groups. If pro-S group forms a hemiacetal bond, then the preferred l-*lyxo* compound is formed. This epimer seems to be the preferred one, because it is free from steric congestion resulting from *syn* oriented functionalities in the alternative D-*ribo* epimer. Since the anomeric position is unprotected, there is a possiblility of equilibration, and this equilibrium opens a way to increase the proportion of the desired 4-"up" stereoisomer.

When the inseparable mixture of **8/9** (ratio 9:1) was subjected to acetolysis, followed by deacetylation to allow for equilibration at C4, and a final acetylation, a mixture of four compounds **11-14** was formed. Careful integration of the anomeric region revealed their abundances to be as shown in Fig. 3. TLC of the reaction mixture showed two spots only, the upper one corresponding to **11/12**, and the lower one to **13/14**. For analytical purpose a chromatographic separation was carried out to furnish an inseparable mixture of **11/12** and **13/14**. Since the signals of the protons H1,2,3,4 were separated in the NMR spectra of both mixtures, it was possible to establish a

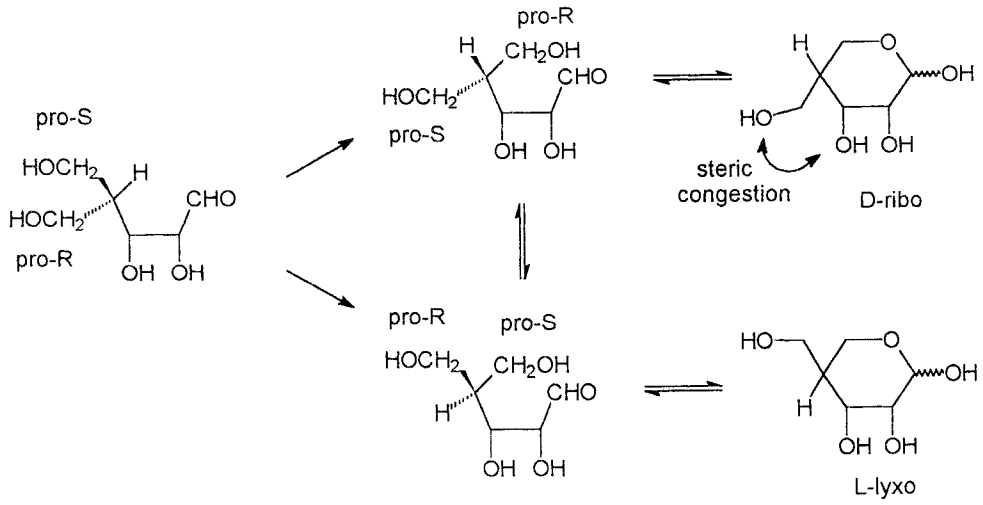

Fig. 4. Compounds expected after opening and reclosure of **6/7** mixture.

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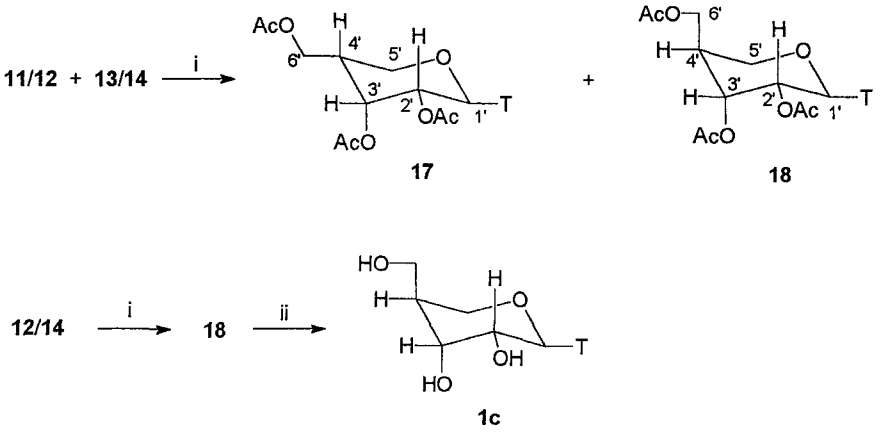
connectivity pattern using a proton-proton correlation spectroscopy, and hence to identify the values of the coupling constants $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ necessary to establish the configurations and conformations at the compounds (Fig. 3). These assignments were confirmed by comparison with the NMR spectra of **12** and **14** prepared by an independent synthesis from a configurationally defined malonate **22** (see below). The proportion of **12** and **14** to **11** and **13** was 3:2 (i.e. the 4"up" stereoisomers are now in excess). A significant increase of the percentage content of the desired stereoisomers **12** and **14** was obtained (ratio **6/7** was 9:1).

Unfortunately, we were unable to obtain pure **11** or **13**, so their spectroscopic data were obtained from a comparison of the NMR spectra of mixtures **11/12** and **13/14** with those of pure **12** and **14**, respectively. During acetolysis of **8/9** we observed the formation of two additional products **15** and **16** (scheme 1), which resulted from opening of a pyranosyl ring. Separation of both of them was quite difficult, however, prolonged acetolysis converted **15** into **16**. Eventually, a very small amount of **15** was also obtained during chromatography using large excess of silica gel. It should be noted that the hexaacetate **16** could be also used as a source of **11/12** and **13/14**. If this compound is deacetylated and re-acetylated, a process depicted in Fig. 4 takes place. Both ^{1}H and ^{13}C spectra of **11-14** formed in this way were indistinguishable from those discussed above.

Since it was impossible to obtain pure **12** nor **14** at this stage, we used a mixture of **11, 12, 13, 14** (enriched in **12** and **14** as discussed above) in a glycosylation by trimethylsylilated thymine



Scheme 2. T : thymin-1-yl; i : TMS(T), TMS OTfl, $C_2H_4Cl_2$; ii : NaOMe, MeOH.

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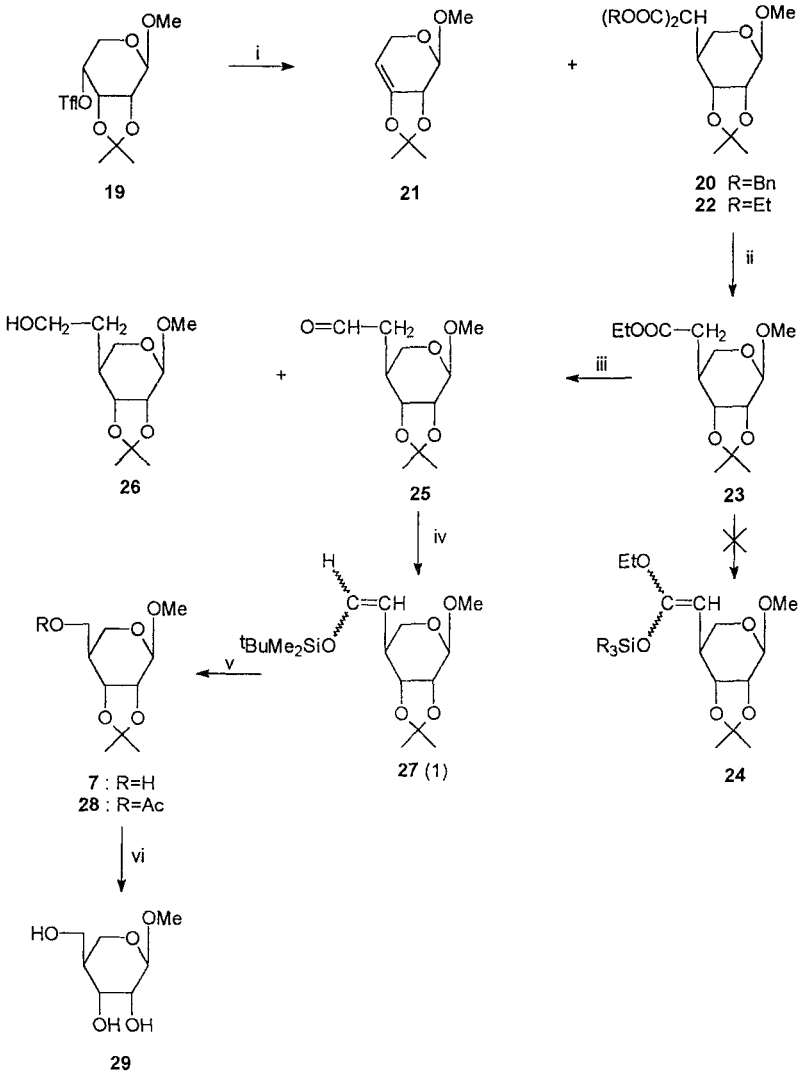
under Vorbrüggen conditions. This procedure yielded 53% of **17/18** inseparable by column chromatography. The magnitude of the coupling constants recorded (**17**: $J_{1',2'}$=9.9Hz, $J_{2',3'}=J_{3',4'}$=2.3Hz; **18**: $J_{1',2'}$=9.9Hz, $J_{2',3'}=J_{3',4'}$=2.9Hz) indicate a $^4C_1$ conformation of both nucleosides. Compound **18** therefore must have both functionalities of C3',4' oriented diaxially. Strong tendancy of the purines and pyrimidines to adopt equatorial orientation on anomeric position in hexopyranosyl nucleosides even at the expense of axial disposition of up to three other substituents at C2',3',4' has already been observed[16-18].

Synthesis of 1c from methyl 4-deoxy-4-*C*-diethylmalonyl-2,3-O-isopropylidene-α-L-lyxopyranoside (22).

As we were not able to separate **18** from **17**, we modified the original approach to **18** using the same starting material (**2a**). The alternative scheme to **12** and **14** makes use of an S_N2 substitution at position C4 of D-ribopyranose **2a** and a malonyl moiety as a synthon for a hydroxymethyl group (Scheme 3). Reaction of the triflate **19**, obtained from **2a**, with the sodium salt of dibenzyl malonate furnished **20** in low yields (24 % from **2a**) together with the elimination product **21**. The position of the double bond in **21** was deduced from the ^{13}C spectrum of **21** run in an Attached Proton Teste mode. This spectrum showed a quaternary atom signal at 146.8 ppm ascribed to C3, and a signal at 63.7 ppm, ascribed to C5. If a carbon-carbon double bond was formed between C4-C5, the methylene group would not be present.



Scheme 3. i: $NaCH(COOBn)_2$ or $NaCH(COOEt)_2$, DMF; ii : DMSO, H_2O, LiCl, bp, 4h; iii : DIBAL, CH_2Cl_2; iv : $tBuMe_2Si$-OTfl, ET_3N, CH_2Cl_2; v : O_3, MeOH; $NaBH_4$; vi : CF_3COOH 90% RT.
(1) **27** as a E/Z mixture of 1:1.

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The sodium salt of diethyl malonate, however, reacted with **19** in higher yield (53 % from **2a**) giving compound **22**. Mono-de-alkoxycarbonylation[19,20] of **22** furnished **23** in quantitive yield. Attempts to generate a ketene acetal **24** using either LDA-trimethylsilyl chloride[21] or t-butyldimethylsilyl trifluoromethanesulfonate-Et_3N[22], uniformely failed. However, reduction of the ester **23** with DIBAL furnished the aldehyde **25** together with marginal quantity of the overreduced product **26**.

Compound **25** could be converted into the enol ether **27** with $tBuMe_2Si$-OTf/Et_3N[22] (formed as a 1:1 mixture of E,Z-isomers as evidenced by its ^{13}C NMR). This product was subsequently subjected to ozonolytic cleavage in methanol followed by in situ reduction with $NaBH_4$[23] to give **7** in 65% yield. About 7% of the less polar acetate **28** was isolated from the ozonolytic mixture, probably due to transesterification during chromatography using EtOAc as solvent. Since **28** could be converted quantitatively to **7**, final yield of **7** was 72%. The compound **7** formed in this way was configurationally pure. The utilization of the soft nucleophilic character of malonyl anions to introduce a hydroxymethyl group with inversion of configuration, finds its precedent in the field of inositol chemistry[24], which started from Meldrum's acid and utilized organoantimony compound in a critical oxidative decarboxylation step. It should be noted that attempts to substitute the triflate of **19** with other carbon nucleophiles like cyanide ion, Me_3SiCH_2Li/Cu_2LiCL_4 or H_2C=CHMgBr/CuI failed. Also, attempted free-radical incorporation of a styryl moiety into **2a** (i. ClCS(OPh), Py ii. PhCH=CHSnBn_3, AIBN[25]) as a synthon of a CH_2OH group[26,27], failed.

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The isopropylidene group in **7** was hydrolyzed with 90% trifluoroacetic acid to give **29**, which was acetylated to form **9**. The NMR data of **9** were used as an independent proof of configuration at C4 of both epimeric products **8** and **10**. Compound **9** adopts exclusively a $^1C_4$ conformation (Scheme 1) with an axially oriented anomeric substituent. This is clear from coupling constants $J_{3,4}$=10.9Hz and $J_{4,5ax}$=11.0Hz, indicative of diaxial position of the H3,4,5_{ax} protons. The coupling $J_{1,2}$=2.0Hz is small as expected for diequatorially oriented protons H1,2. These values differ considerably from the averaged values of coupling constants obtained for both **8** and **10**.

Acetolytic cleavage of **28** preceeded in surprisingly low yield. Both anomeric tetraacetates **12** and **14** were isolated in 16% yield only, together with 8% of **16**. When **9** was used instead, 64% of **12/14** mixture and 26% of **16** was obtained. The α-anomer **12** strongly predominates since conditions of acetolytic cleavage favour the thermodynamically most stable compound. Compounds **12** and **14** display conformational characteristics as shown in Fig. 3. Both **12** and **14** reside in a $^1C_4$ conformation. This is clear from the large diaxial coupling for H3,4,5_{ax} for both compounds together with small values of $J_{1,2}$. The equatorial anomeric proton in **12** resonates at

lower field than the axial counterpart in **14**, as expected for anomeric configurations shown. Carbon atoms C6 in **12** and **14** are in a similar chemical environment, so their chemical shifts shouldn't differ much. On this basis one can tentatively ascribe a signal δ=61.0 to C6 in **12** and a signal δ=60.5 to C6 in **14**. A signal δ=62.8 in **12** therefore belongs to C5, and a signal δ=64.9 in **14** to C5. Due to the steric congestion resulting from syndiaxially disposed proton $H5_{ax}$ and the anomeric acetoxy group, the C5 signal in **12** is shifted upfield when compared to its counterpart in **14**. Anomeric carbon atoms, however, are less sensitive to changes in environment in vicinity of the carbon nuclei[28,29] (α anomer **12**: δC1=91.4; β anomer **14**: δC1=90.9). Using the same reasoning it was possible to identify tentatively the signals of the carbon atoms C5,6 in **11** and **13**.

Glycosylation of **12:14** (Scheme 2) using trimethylsilylated thymine under Vorbrüggen conditions furnished 78% of **18**, which was deacetylated to give a target compound **1b** (B:thymin-1-yl). Due to superposition of the signals of the protons H5',5",6',6" in the 200 MHz ^{1}H NMR spectrum, full interpretation of the data can not be given. However, important coupling constants between protons H1',2',3' and 4' were obtained: $J_{1',2'}$=9.5Hz, $J_{2',3'}=J_{3',4'}$=2.5Hz (recorded in CD_3OD). These values indicate a preferential $^4C_1$ conformation of **1b**, similar to its acetylated predecessor.

Compound **1c** is a representative example of a new series of pyranosyl nucleosides. Further work in terms of additional functionalization of **1c** e.g. 2'-deoxygenation and formation of 2',3' carbon-carbon double bond, and synthesis of analogues with other nucleobasis is in progress. In conclusion, a method is developed to substitute a hydroxyl group in methyl 2,3-O-isopropylidene-β-D-ribopyranose by a hydroxymethyl group with full stereospecificity. This method utilizes the good leaving properties of a trifluoromethanesulfonyloxy group and the soft nucleophilic character of malonyl anions, and adds to an arsenal of methods and synthesis of branched-chain carbohydrates[30,31,32]. Compound **29** formed in this way was further transformed into **1b**, a member of the hitherto unknown analogues of nucleosides. This compound (B:thymin-1-yl) adopts a $^4C_1$ conformation which places the base moiety in an equatorially position, as often observed with pyranosyl nucleosides[8]. Unfortunately, **1c** does not show antiviral activity when tested against HSV-1 and HSV-2.

EXPERIMENTAL

General

NMR spectra have been recorded with a Varian 200 or 500 spectrometer in solvents as indicated. Exact mass measurements have been performed on a Kratos Concept 1H mass

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spectrometer (Kratos, Manchester, UK). Anhydrous solvents were obtained as follows: pyridine was refluxed overnight in the presence of KOH and distilled; CH_2Cl_2 was obtained by distillation after reflux overnight with CaH_2; THF was first refluxed with $LiAlH_4$ before distillation; H_2O was removed from N,N-dimethylformamide (DMF) by storing on Linde type-4-Å molecular sieves, followed by distillation under reduced pressure. TLC: precoated Merck silica gel F254 plates; detection with UV light at 254 nm and sulfuric acid, anisaldehyde spray. Column chromatography: SÜD-chemie silica gel (0.2-0.05 mm). Melting points were taken with a Bucchi-Totoli apparatus and are uncorrected. Elemental analyses were performed at the University of Konstanz, Germany.

Methyl 4-*C*-methylidene-2,3-O-isopropylidene-β-D-*erythro*-pentopyranoside (4).

A. via Peterson fragmentations. Ulose (**3**) was prepared from either methyl 2,3-O-isopropylidene-β-D-ribopyranoside (**2a**) or methyl-2,3-O-isopropylidene-α-L-lyxopyranoside (**2b**) using a CrO_3-Py-Ac_2O procedure: CrO_3 (1.2 g) was added to CH_2Cl_2 (24 ml), followed by pyridine (2 cm^3). After 20 min of stirring, a solution of either **2a** or **2b** in CH_2Cl_2 (5-8 cm^3) was added following acetic anhydride (1.2 cm^3). After 10 min, ethyl acetate (12 cm^3) and toluene (12 cm^3) were added to precipitate chromium salts. Decanted solution was passed through a silica gel column (prepared in toluene-ethyl acetate 1:2) and eluted with the same solvent mixture using slight overpressure of nitrogen. Fractions containing a product **3** were pooled, evaporated, co-evaporated with toluene, and dried on an oil pump (0.47 g, 76%). The compound **3** forms a faint spot on TLC, which is less polar than either **2a** or **2b**. This material in THF (20 cm^3) was treated with 1M solution of trimethylsilyl methyl lithium in pentane (3 cm^3), at -78°. After 1 h, more reagent (1.5 cm^3) was added and the cooling bath was removed. After stirring overnight, MeOH (1 cm^3) was added to destroy excess of the reagent. Celite was added and the mixture was evaporated. Celite was applied on a top of a silica gel column prepared in hexane-EtOAc (12:1). Flash chromatography yielded tertiary alcohol **2c** (0.40 g, 59%) as oil, which is less polar than **3**. **2c**: ^1H ($CDCl_3$): 4.63 (d, 1 H, J_{12} 3.6 Hz, H-1); 4.02 (d, J_{32} 5.8 Hz, H-3); 3.96 (dd, J_{21} 3.6 Hz, J_{23} 5.8 Hz, H-2); 3.50 (AB, 2 H, J 11.6 and 19.3 Hz, 2xH-5); 3.46 (s, OMe); 2.37 (s, OH); 1.56, 1.37 CMe_2; 0.94 (s, 2 H, CH_2Si); 0.09 (s, 9 H, $SiMe_3$). ^{13}C ($CDCl_3$): 109.52 $\underline{C}Me_2$; 100.95 C-1; 78.71, 75.08 C-2,3; 69.84 C-4; 67.41 C-5; 26.88, 25.70 CMe_2; 26.35 CH_2SiMe_3; 0.28 CH_2SiMe_3. Exact mass: molecular was not seen in LSIMS in 20 ml mode. An amount of **2c** (0.4 g) in THF (20 cm^3) and 60% NaH (0.28 g) was refluxed during 7 h. TLC showed a conversion of **2c** into a slightly less polar product **4**. The reaction flask was cooled in ice. Methanol (3 cm^3) was added to destroy excess of sodium hydride. After evaporation and gravitational chromatography in hexane-EtOAc (20:1), **4** was obtained as oil (0.242 g, 88%).

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4: (Found : C, 59.28; H, 7.94. $C_{10}H_{16}O_4$ requires C, 59.48; H, 8.05%). ^1H ($CDCl_3$): 5.32 (q, 1 H, J 0.9 Hz) and 5.19 (bs, 1 H, 2xH-6); 4.71 (d, 1 H, J_{32} 6.2 Hz, H-3); 4.63 (d, 1 H, J_{12} 3.2 Hz, H-1); 4.25 (bs, 2 H, 2xH-5); 4.05 (dd, 1 H, J_{21} 3.0 Hz, J_{23} 6.1 Hz, H-2); 1.54, 1.40 CMe_2. ^{13}C ($CDCl_3$): 139.48 C-4; 114.96 C-6; 109.98 CMe_2; 100.62 C-1; 76.14, 74.57 C-2,3; 63.26 C-5; 58.88 OMe; 27.44, 25.86 CMe_2. Exact mass: molecular ion was not seen using LSIMS mode.

B. via Wittig reaction. Methyl triphenylphosphonium bromide (2.50 g, 7 mmol) in THF (25 cm^3) was cooled in ethanol-dry ice bath, and 1.6M BuLi in hexane (4 cm^3) was added. The cooling bath was removed to allow the reaction mixture to reach ambient temperature. Fourty minutes later cooling was reapplied and a solution of **3** (0.47 g) in THF (11 cm^3) was added. Cooling was removed and after 1.5 h, aqueous-saturated NH_4Cl was added at 0° and two layers were separated. Aqueous layer was extracted with EtOAc. Combined organic phases were dried and evaporated. Addition of EtOAc-hexane 1:1 gave a precipitate which was filtered out. The filtrate was evaporated and the residual material subjected to chromatographic purification in hexane-EtOAc (2:1) to furnish **4** as an oil (0.39 g, 84% from **3**). This process was later scaled up. From **2a** (6.2 g), **4** (3.88 g) was obtained using CrO_3 (12 g), pyridine (20 cm^3) and Ac_2O (12 cm^3) for the oxidation step, and methyl triphenylphosphonium bromide (16 g) and 1.6M BuLi (25 cm^3) for the olefination step.

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Methyl 4-deoxy-4-*C*-hydroxymethyl-2,3-O-isopropylidene-β-D-ribopyranoside (6), methyl 4-deoxy-4-*C*-hydroxymethyl-2,3-O-isopropylidene-α-L-lyxopyranoside 7 and tertiary alcohols 5. An amount of **4** (0.242 g, 1.21 mmol) in THF (20 cm^3) was treated with 1M diborane (2 cm^3) in THF at 0°C. After 2 h at rt, more diborane (1 cm^3) was added, and 30 min later, 2M NaOH (8 cm^3) was added followed by 35% H_2O (8 cm^3) and stirring was continued overnight. Diethyl ether (20 cm^3) was added and layers were separated. The aqueous layer was extracted with CH_2Cl_2. Combined organic layers were dried and evaporated. Chromatography furnished **5** (0.083 g, 31%) as an unseparable mixture (95:5) of both epimers (eluent hexane - EtOAc 3:1) and unseparable mixture of **6** (major) and **7** (eluent hexane-EtOAc 1:1) as oily compounds (0.144 g, 43%) (9:1 ratio). Repetition of this procedure using **4** (3.7 g), 1M B_2H_6 (45 cm^3), 2M NaOH (40 cm^3) and 35% H_2O_2 (25 cm^3), furnished **5** (1.1 g, 27%) and **6** and **7** (2.7 g, 67%). **5** : The product is ca 95:5 mixture of both epimeric products. Data of the main isomer are listed.

^1H ($CDCl_3$): 4.39 (dd, 1 H, J_{12} 3.8 Hz, $J_{15"}$ 1.0 Hz, H-1); 4.10 (s, H-3); 4.09 (d, J_{21} 4.0 Hz, H-2); 3.72 (d, 1 H, $J_{5'5"}$ -11.8 Hz, H-5'); 3.60 (dd, $J_{5"5'}$ -11.9 Hz, $J_{5"1}$ 1.0 Hz, H-5"); 3.54 (s, OMe); 3.48 (s, OH); 1.51, 1.37 CMe_2, 1.23Me. ^{13}C ($CDCl_3$): 109.80 CMe_2; 102.32 C-1; 78.61, 74.65 C-2,3;

69.46 C-4; 56.62 OMe; 27.52, 25.48 C<u>M</u>e$_2$; 20.87 Me. Exact mass: m-nitrobenzyl alcohol-NaOAc: calc. for $C_{10}H_{18}O_5$+Na:241.1052. Found: 241.1055. Only the data of the predominant **6** is listed. **6**: ^{1}H ($CDCl_3$): 4.49 (dd, J_{34} 3.7 Hz, J_{32} 5.9 Hz, H-3); 4.36 (d, 1 H, J_{12} 5.2 Hz, H-1); 3.93 (t, J_{23} 5.7 Hz, J_{21} 5.5 Hz, H-2); 3.86 (dd, $J_{5'4}$ 5.1 Hz, $J_{5'5"}$ -10.3 Hz, H-5'); 3.82-3.62 (m, H-5", 2xH-6); 3.50 (s, OMe, major isomer); 3.47 (s, OMe, minor isomer, ca 10%); 2.41-2.25 (m, 2 H, H-4, OH); [after exchange with D_2O: ddddd, J_{43} 3.5 Hz, $J_{45'}$ 5.6 Hz, $J_{45"}$, $J_{46'}$, $J_{46"}$ 5.6 Hz, 5.6 Hz, 11.2 Hz] 1.53, 1.38 C<u>M</u>e$_2$. ^{13}C ($CDCl_3$): 109.77 <u>C</u>Me$_2$; 102.24 C-1; 75.45, 74.01 C-2,3; 61.72, 61.55 C-5,6; 56.44 OMe; 37.82 C-4; 27.48, 25.61 C<u>M</u>e)$_2$. Exact mass: m-nitrobenzyl alcohol - NaOAc: calc. for $C_{10}H_{18}O_5$ + Na: 241.1052. Found: 241.1050. **Comments** : If a bulkier 9-borabicyclononane (9-BBN) was used, hydroboration was unsuccessful even though a considerable excess of 9-BBN in boiling THF was used. Cathecholborane (used in combination with $LiBH_4$ to speed up the addition step[13]) did not improve the regioselectivity of the reaction.

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Methyl 4-deoxy-4-*C*-hydroxymethyl-2,3,6-tri-O-acetyl-β-D-ribopyranoside 8 (major) and methyl 4-deoxy-4-*C*-hydroxymethyl-2,3,6-tri-O-acetyl-α-L-lyxopyranoside (9) (minor).

Acetonides **6, 7**, (0.114 g) were treated with 90% trifluoroacetic acid (10 cm^3) during 10 min. After evaporation, water was added followed by Dowex 1x8 (OH^-) to neutralize residual acid. The resin was removed by filtration and washed with water. Combined water filtrates were evaporated and the residue was thoroughly dried under high vacuum. The resulting glassy material was acetylated overnight using pyridine (10 cm^3), acetic anhydride (5 cm^3) and cat. quantity of 4-dimethyl aminopyridine. The volatiles were co-evaporated with xylenes. The residue was purified by gravitational chromatography in hexane-EtOAc (7:3) to furnish **8** (major) and **9** (0.126 g, 79% for two reactions), which failed to crystalize. Ring signals of the predominant isomer are listed. **8**: ^{1}H ($CDCl_3$): 5.46 (t, 1 H, J_{32} 3.7 Hz, J_{34} 3.9 Hz, H-3); 4.88 (ddd, 1 H, J_{23} 3.1 Hz, J_{21} 4.9 Hz, J_{24} -0.8 Hz, H-2); 4.63 (d, 1 H, J_{12} 4.8 Hz, H-1); 4.18 (d, 2 H, J_{64} 7.0 Hz, 2xH-6); 3.89 (dd, 1 H, $J_{5'4}$ 3.7 Hz, $J_{5'5"}$ -11.7 Hz, H-5'); 3.70 (dd, 1 H, $J_{5"4}$ 6.2 Hz, $J_{5"5'}$ -12.0 Hz, H-5"); 3.45 (s, OMe, major isomer); 3.40 (s, OMe, minor isomer); 2.39-2.25 (m, 1 H, H-4); 2.09, 2.08, 2.06 Oac. ^{13}C ($CDCl_3$): 170.78, 169.72 <u>C</u>OMe; 99.36 C-1; 69.63, 67.02 C-2,3; 60.57, 60.42 C-5,6; 55.74 OMe; 38.03 C-4; 20.80 CO<u>M</u>e. Exact mass (thioglycerol-NaOAc): calc. for $C_{13}H_{20}O_8$ + Na: 327.1056. Found: 327.1055.

Methyl 4-deoxy-4-*C*-hydroxymethyl-2,3,6-tri-O-(p-nitro)benzoyl-β-D-ribopyranoside 10.

Compound **8/9** (0.126 g, 0.41 mmol) was deacetylated using cat. NaOMe/HOMe system. After

neutralization with dry ice and removal of methanol, the residue was taken-up in pyridine (20 cm^3) and treated with p-nitrobenozyl chloride (0.31 g, 1.66 mmol) overnight. Pyridine was co-evaporated with xylene. The residue was passed through a silica gel column using hexane-EtOAc (3:1) as eluent to furnish 0.19 g (73%) of an oil which spontaneously crystalized. After three recrystallizations from ethanol-ethyl acetate a pure 4-"down" isomer was obtained, m.p. : 84° softening, melting 132-136°. **10**: (Found : C, 54.07; H, 3.70; N, 6.56. $C_{28}H_{23}N_3O_{14}$ requires C, 53.77; H, 3.71; N, 6.72%). ^1H (C_6D_6, 500MHz): 7.945-7.913 and 7.788-7.632 H aromatic; 5.898 (dd, 1 H, J_{32} 3.4 Hz, J_{34} 4.8 Hz, H-3); 5.613 (dt, 1 H, J_{21} J_{23} 3.4 Hz, J_{24} 0.6 Hz, H-2); 4.773 (t, 1 H, $J_{6'4}$ $J_{6'6"}$ 10.1 Hz, H-6'); 4.726 (d, 1 H, J_{12} 3.4 Hz, H-1); 4.600 (dd, 1-H, $J_{6"4}$ 4.1 Hz, $J_{6"6'}$ -10.8 Hz, H-6"); 3.755 (dd, 1 H, $J_{5'4}$ 3.3 Hz, $J_{5'6"}$ -12.0 Hz, H-5'); 3.694 (dd, 1 H, $J_{5"4}$ 4.2 Hz, $J_{5"5'}$ -12.O Hz, H-5"); 3.264 (s, 3 H, OMe) 2.324 (septette, 1 H, J_{43} $J_{45'}$ $J_{45"}$ $J_{46"}$ 4.3 Hz, $J_{46'}$ 8.7 Hz, H-4). ^{13}C (C_6D_6, 50Mhz): 163.53, 162.85, 162.62 carbonyl C; 150.04, 149.90; 149.77 C-NO_2; 133.54, 133.30, 133.16 C-C=O; 129.69, 129,52, 129.42, 127.41, 127,00, 126.53, 122.84, 122.66, 122.56 Nbz; 98.61 C-1; 69.84, 67.97, 61.32, 58.67. C-2,3,5,6; 54.28 OMe; 37.28 C-4. Exact mass (thioglycerol-NaOAc): calc. for $C_{28}H_{23}N_3O_{14}$ + Na: 648.1078. Found 648.1055.

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Tetra-O-acetyl-4-deoxy-4-*C*-hydroxymethyl-β-D-ribopyranose 11 and α anomer 13, tetra-O-acetyl-4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranose 12 and β anomer 14, hexa-O-acetyl-4-deoxy-4-*C*-hydroxymethyl-D-*erythro*-aldehydopentose 16 and mixed acetal 15.

A. By acetolysis of 6 and 7. A mixture of epimeric products **6** and **7** (resulting from hydroboration of **4**) (2.7 g) was kept in a mixture of Ac_2O (10 cm^3), AcOH (24 cm^3), and conc. H_2SO_4 (0.9 cm^3) for 16 h at ambient temp. TLC (hexane-EtOAc 2:1) showed the fastest moving spot corresponding to a mixture of **11** and **12**, a slightly more polar spot corresponding to a mixture of **13** and **14**, and a marginally more polar mixture of **15** and **16**. After extractive work-up and gravitational chromatography in hexane-EtOAc (2:1), an unseparable mixture of **11** and **12** (1.13 g) was obtained. Proportion of **11** and **12** does not differ from this of **6** and **7**, i.e. **11** is the predominant product (ca. 90%). No pure fraction containing **13/14, 15** and **16** was obtained at this stage. However, after re-submission of this combined material (1.01 g) to acetolysis as above and chromatography, a mixture of **13/14** (0.94 g) was obtained. Small amount of pure **16** was also obtained (0.022 g). Compound **15** was completely transformed into **16** during a second acetolysis. Total yield of **11/12** and **13/14** was 2.07 g (50%). Mixed fractions containing **13/14** and **16** were not isolated. **11**: ^1H ($CDCl_3$): 5.93 (d, 1 H, J_{12} 6.2 Hz, H-1); 5.54 (t, 1 H, J_{32} J_{34} 3.5 Hz); 4.92 (dd, 1 H, J_{23} 3.3 Hz, J_{21} 6.2 Hz, H-2); 4.15 (dd, J 6.6 Hz and 11.2 Hz); 4.06 (dd, J 8.0 Hz and 11.3

Hz); 3.93 (dd, J 4.4 Hz and 11.8 Hz); 3.81 (dd, J 7.7 Hz and 11.9 Hz); 2.48-2.33 (m, H-4); 2.13, 2.12, 2.06, 2.05 OAc. ^{13}C ($CDCl_3$): 170.58, 169.73, 169.41, 168.99 $\underline{C}OCH_3$; 90.75 C-1; 68.75, 66.64 C-2,3; 62.37 C-5; 60.09 C-6; 37.84 C-4; 20.58 $CO\underline{C}H_3$. Exact mass (thioglycerol-NaOAc): calc. for $C_{14}H_{20}O_9$ + Na: 355.1005; found: 355.0991. This measurement was performed on a mixture of **11** and **12**. **16**: (Found : C, 49.87; H, 5.83. $C_{18}H_{26}O_{12}$ requires C, 49.77; H, 6.03%). ^1H ($CDCl_3$): 6.94 (d, 1 H, J_{12} 3.0 Hz, H-1); 5.46 (dd, J_{21} 3.0 Hz, J_{23} 8.0 Hz, H-2); 5.36 (dd, J_{32} 3.3 Hz, J_{34} 8.0 Hz, H-3); 4.24 (dd, J 6.0 Hz and -11.5 Hz, H-5'(6'); 4.14-4.03 (m, H-6'(5'), 5",6"); 2.45 (dq, 1 H, J 6.1 Hz, 6.1 Hz, 6.1 Hz, 6.2 Hz, 4.0 Hz, H-4); 2.16, 2.12, 2.08, 2.07, 2.06 OAc. ^{13}C ($CDCl_3$): 170.68, 170.54, 169.50, 169.40, 168.36, 168.18 $\underline{C}OMe$; 86.11 C-1; 69.70, 68.09 C-2,3; 62.18, 60.51 C-5,6; 37.88 C4; 20.58 $CO\underline{M}e$. Exact mass (thioglycerol-NaOAc): calc. for $C_{18}H_{26}O_{12}$ + Na : 457.1322. Found: 457.1330.

B. By equilibration at C4. A mixture of **11, 12, 13** and **14** (2.079 g) was deacetylated with cat. NaOMe in HOMe. After neutralization with a piece of dry ice, evaporation and drying on an oil pump, 80% aqueous acetic acid (80 cm^3) was added, and the solution was kept at 70° for 1 h. Volatiles were evaporated and co-evaporated with DMF. After final drying using an oil pump, acetylation was performed overnight (Py-Ac_2O 2:1). Volatiles were evaporated and the residue was partitioned between CH_2Cl_2-dil.-HCl. Organic layer was washed with water, dried and evaporated. After final drying on an oil pump a thick oil (1.89 g) was obtained. TLC showed two spots: the upper one corresponding to **11** and **12**, the lower one corresponding to **13** and **14**. Integration of expanded anomeric region showed the following ratio of compounds. **13** 12%, **12** 34%, **11** 29%, **14** 25%, or L-*lyxo* anomers: 59%, D-*ribo* anomers: 41%. Chromatography furnished small amount of the more polar mixture **13/14**. The NMR parameters of **13** listed below were obtained from comparison of a spectrum of pure **14** prepared independently and a spectrum of a mixture of **13** and **14**. Only ring signals are listed. **13**:^1H ($CDCl_3$): 6.09 (d, 1 H, J_{12} 3.7 Hz, H-1); 5.47 (t, 1 H, J_{32} J_{34} 3.0 Hz, H-3); 5.08 (t, J_{21} J_{23} 3.5 Hz, H-2); 4.19-3.90 (m, 3 H), 3.66 (dd, 1 H, J 5.5 Hz and 11.7 Hz, H-5(6)); 2.56-2.41 (m, H-4, superimposed on a H-4 signal of the C-4 epimer). ^{13}C ($CDCl_3$): 89.08 C-1; 67.35, 65.72, C-2,3; 60.37 C-6; 59.02 C-5; 37.04 C-4. Exact mass (thioglycerol-NaOAc): calc. for $C_{14}H_{20}O_9$-AcOH: 272.0895. Found: 273.0965. This measurement was performed for a mixture of both C4 epimers.

C. From the open chain product **16** by ring closure and acetylation. Deacetylation of **16** using cat. NaOMe in HOMe, followed by neutralization with CO_2, evaporation, drying and acetylation furnished a mixture which was undistinghuishable in terms of ^1H and ^{13}C NMR from this obtained under B. Intermediary acid treatment in B is therefore not necessary to establish a predominant proportion of L-*lyxo* over D-*ribo* isomers.

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Tri-O-acetyl-4-deoxy-4-*C*-hydroxymethyl-β-D-ribopyranosyl thymine 17 and tri-O-acetyl-4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl thymine (18). Thymine (97% pure, 0.26 g, 2 mmol) was trimethylsilylated in boiling HMDS and cat. $(NH_4)_2SO_4$ during 6 h. Volatiles were evaporated and co-evaporated with xylenes. The residue was finally dried on an oil pump. To the residual opaque oil was added a solution of both C-4 epimeric tetraacetates **11/12** and **13/14** (*Lyxo:ribo*≈3:2, 0.33 g) in 1,2-dichloroethane (40 cm³), followed by trimethylsilyl trifluoromethanesulfonate (0.23 ml, 1.2 mmol). The flask was immersed in an oil bath (~70°). After 16 h, extractive work-up and chromatography in toluene-EtOAc (2:3) gave unseparable 1:1 mixture of both **17** and **18** (0.211 g, 53%). Comparison of ^1H and ^{13}C spectra of this mixture with those of **18** prepared independently, allowed identification of the following signals of **17**. **17**: ^1H ($CDCl_3$): 9.62 (bs, NH); 7.15 (apperent d, $J_{6\text{-}CH3}$ 1.2 Hz, H-6); 6.04 (d, $J_{1',2'}$ 9.9 Hz, H-1'); 5.67 (t, $J_{3'4'}$ $J_{3'2'}$ 2.3 Hz, H-3'); 4.99 (dd, $J_{2'1'}$ 9.9 Hz, $J_{2'3'}$ 3.1 Hz, H-2'); 4.04 (dd, $J_{5'eq4'}$ 7.9 Hz, $J_{5'eq5'ax}$ -11.4 Hz, H-5'$_{eq}$); 3.99 (d, $J_{6',6''}$ -11.2 Hz, H-6'); 3.91 (d, $J_{6''6'}$ -11.2 Hz, H-6"); 3.84 (dd, $J_{5'ax4'}$ 11.7 Hz, $J_{5'ax5'eq}$ -12.0 Hz, H-5'$_{ax}$); 2.57 (ddd, 1 H, $J_{4'3'}$ 2.4 Hz, $J_{4'5'eq}$ 7.0 Hz, $J_{4'5'ax}$ 11.5 Hz, H-4'); 1.92 (d, $J_{CH3\text{-}6}$ 1.1 Hz, CH_3). ^{13}C ($CDCl_3$): Signal possible to identify were those of C-1',2',3',4',5',6' and C-5-CH_3: 78.16 C-1'; 68.65, 67.06, C-2',3', 64.82, 59.87 C-5',6'; 38.55 C-4'; 15.12 CH_3. Exact mass (thioglycerol): calc. for $C_{17}H_{22}N_2O_9$ + H: 399.1403. Found: 399.1426.

Methyl 4-deoxy-4-*C*-(dibenzylmalonyl)-2,3-O-isopropylidene-α-L-lyxopyranoside 20 and elimination product 21. Compound **2a** (0.77 g, 3.8 mmol) in CH_2Cl_2 (20 cm³) and pyridine (2 cm³) was treated with Tfl_2O (1.3 cm³, 7.6 mmol). After 5 h, extractive work-up furnished triflate **19** as yellowish oil. A solution of sodium benzylmalonate was prepared from dibenzylmalonate (1.9 cm³, 7.5 mmol) and 60% NaH (0.3 g, 7.5 mmol) in DMF (10 cm³) with stirring during 30 min. This solution was transferred via a canula to a flask containg **19**, using overpressure of nitrogen. The reaction flask was immersed in an oil bath (65-70°), 3 h later the triflate **19** was completely reacted. TLC (hexane-EtOAc 8:1) showed the following compound **21** R_f 0.43, dibenzyl malonate R_f 0.31, and the product **20** R_f 0.20. The reaction mixture was divided between CH_2Cl_2 and water. The organic layer was dried and evaporated. The residual oil was subjected to gravitational chromatography in hexane-EtOAc (8:1) to furnish a small amount of **21** (unstable oil) and **20** (0.42 g) as oil (24% for two steps). **20**: (Found: C, 66.54; H, 6.57. $C_{26}H_{30}O_8$ requires C, 66.37; H, 6.43%).^1H ($CDCl_3$): 7.33-7.25 (10 H, 2xPh); 5.22-5.06 (m, 4 H, O$\underline{C}H_2$Ph); 4.76 (d, 1 H, J_{12} 1.9 Hz, H-1); 4.20 (dd, 1 H, J_{32} 5.2 Hz, J_{34} 8.1 Hz, H-3); 3.95 (dd, 1 H, J_{21} 2.0 Hz, J_{23} 5.2 Hz, H-2); 3.68 (dd, $J_{5'4}$ 4.6 Hz, $J_{5'5''}$ -11.5 Hz, H-5'); 3.63 (d, J_{64} 6.8 Hz, H-6); 3.59 (dd, $J_{5''4}$ 8.5

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Hz, $J_{5''-5'}$ -11.5 Hz, H-5"); 3.36 (s, OMe); 2.62 (dddd, 1 H, $J_{45'}$ 5.2 Hz, J_{46} 6.9 Hz, $J_{45''}$ J_{43} 8.4 Hz, H-4); 1.45, 1.28 CMe_2. ^{13}C ($CDCl_3$): 167.99, 167.53 $\underline{C}O(OBn)$; 135.13, 128. 56, 128.27 Ph; 109.14 $\underline{C}Me_2$; 99.58 C-1; 73.84, 73.24 C-2,3; 67.40, 67.31 $O\underline{C}H_2Ph$; 58.76 C-5; 55.34 OMe; 51.07 C-6; 39.11 C-4; 28.07, 26.37 $C\underline{M}e_2$. Exact mass (thioglycerol-NaOAc): calc. for $C_{26}H_{30}O_8$ + Na: 493.1839. Found: 493.1845.

21: ^1H ($CDCl_3$): 4.74 (q, 1 H, $J_{45'}$ $J_{45''}$ J_{42} 2.3 Hz, H-4); 4.45-4.20 (unresolved, 4 H, H-1,2,5',5"); 1.51, 1.48 $C\underline{M}e_2$. ^{13}C ($CDCl_3$): 146.78 C-3; 111.91 $\underline{C}Me_2$; 102.03 C-4; 89.92 C-1; 73.45 C-2; 63.64 C-5; 56.04 OMe; 26.43, 24.60 $C\underline{M}e_2$. Exact mass (thioglycerol-2,3,5,6-tetrachlorobenzoquinone): calcl. for $C_9H_{14}O_4$-H: 185.0814. Found 185.0585.

Methyl 4-deoxy-4-*C*-(diethylmalonyl)-2,3-O-isopropylidene-α-L-lyxopyranoside 22. Triflate **19** was prepared from **2a** (12 g, 58.8 mmol) and of Tfl_2O (20 cm³, 119 mmol) in CH_2Cl_2 (150 cm³) and pyridine (40 cm³) as described above. Sodium salt of diethylmalonate was prepared from diethyl malonate (22 cm³, 145 mmol) in DMF (30 cm³) by addition of 60% NaH (5.2 g, 130 mmol) in three portions with external cooling in ice-water, and intensive stirring. When evolution of hydrogen ceased (ca. 30 min) this solution was transferred via a canula to a solution of **19** in DMF (100 cm³). The reaction flask was immersed in an oil bath at 58°, and left overnight. After extractive work-up and chromatography (hexane-EtOAc 8:1) **22** as oil was isolated (10.79 g, 53%). **22**: (Found : C, 55.21; H, 7.29. $C_{16}H_{26}O_8$ requires C, 55.48; H, 7.57%). ^1H ($CDCl_3$): 4.80 (d, 1 H, J_{12} 1.9 Hz, H-1); 4.29-4.13 (m, 5 H, H-3, 2x$O\underline{C}H_2CH_3$); 3.98 (dd, 1 H, J_{21} 1.9 Hz, J_{23} 5.3 Hz, H-2); 3.78 (d, J 5.4 Hz, H-5'(6)); 3.67 (d, J 8.5 Hz, H-6(5')); 3.53 (d, 1 H, $J_{5''4}$ 6.7 Hz, H-5"); 3.40 (s, OMe); 2.57 (dddd, 1 H, J 6.4 Hz, 6.4 Hz, 6.5 Hz, 8.3 Hz, H-4); 1.51, 1.33 $C\underline{M}e_2$; 1.28 (t, J 7.1 Hz, $OCH_2\underline{C}H_3$). ^{13}C ($CDCl_3$): 168.23, 167.77 $\underline{C}OMe$; 109.03 $\underline{C}Me_2$; 99.46 C-1; 73.82, 73.25 C-2,3; 61.67, 61.46, 58.67 C-5, $O\underline{C}H_2CH_3$; 55.23 OMe; 50.96 C-6; 28.03, 26.33 $C\underline{M}e_2$; 13.93 $OCH_2\underline{C}H_3$. Exact mass (thioglycerol-NaOAc): calc. for $C_{16}H_{26}O_8$ + Na: 369.1526. Found: 369.1538.

Methyl 4-deoxy-4-*C*-(ethoxycarbonylmethyl)-2,3-O-isopropylidene-α-L-lyxopyranoside 23. A mixture of compound **22** (9.79 g, 28.3 mmol) in DMSO (70 cm³), H_2O (8 cm³) and LiCl (6.1 g, 141 mmol) was immersed in an oil bath (ca. 220°) to allow for a gentle reflux during 4 h. TLC (hexane-EtOAc 6:1) showed that **23** had the same Rf value than **22**, but both spots differ in colour. The mixture was transferred to a separatory funnel charged with CH_2Cl_2 and water. The organic layer was washed two more times with water, dried and evaporated. After final dyring on an oil

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pump 7.74 g (quantitative yield) of crude product was obtained. **23**: ^{1}H ($CDCl_3$): 4.73 (d, 1 H, J_{12} 2.3 Hz, H-1); 4.14 (q, 2 H, J 7.2 Hz, $OC\underline{H}_2CH_3$); 3.98 (dd, J_{32} 5.3 Hz, J_{34} 6.6 Hz, H-3); 3.92 (dd, J_{21} 2.4 Hz, J_{23} 5.2 Hz, H-2); 3.65 (dd, 1 H, $J_{5'4}$ 4.1 Hz, $J_{5'5''}$ -11.8 Hz, H-5'); 3.49 (dd, $J_{5''4'}$ 8.2 Hz, $J_{5''5'}$ -11.7 Hz, $J_{6'6''}$ -13.8 Hz, H-6'); 2.42-2.28 (m, H-4); 2.24 (dd, $J_{6''4}$ 8.3 Hz, $J_{6''6'}$ -13.9 Hz, H-6''); 1.52, 1.35 $C\underline{M}e_2$; 1.26 (t, 3 H, J 7.1 Hz, $OCH_2C\underline{H}_3$). ^{13}C ($CDCl_3$): 171.84 $\underline{C}O(OEt)$; 109.14 $\underline{C}Me_2$; 100.16 C-1; 75.55, 73.88 C-2,3; 61.00, 60.52 C-5, $O\underline{C}H_2CH_3$; 55.55 OMe; 35.59 C-3; 34.49 C-6; 28.17, 26.37 $C\underline{M}e_2$; 14.19 $CH_2\underline{C}H_3$. Exact mass (thioglycerol-NaOAc): calc. for $C_{15}H_{22}O_6$ +Na: 297.1314. Found: 297.1317.

Aldehyde 25 and the alcohol 26. Crude product **23**, (3.15 g, 11.5 mmol) in CH_2Cl_2 (100 cm^3) was cooled in dry ice-ethanol bath, whereupon 1M DIBAL (14 cm^3) in hexane was added dropwise from a syringe. Intensive stirring was maintained during the addition which took ca. 20 min, 30 min later (counting from the end of addition) TLC (hexane-EtOAc 1:1) showed that **23** (R_f 0.74) disappeared with formation of **25** R_f 0.61 and traces of **26** R_f 0.25 (Identity of **26** was independently confirmed by a reduction of **23** with $LiALH_4$). Water (10 cm^3) was added dropwise and cooling bath was removed. The mixture was passed through a pad of celite. The absorbers were washed with CH_2Cl_2. Combined CH_2Cl_2 washings were evaporated. Flash chromatography (hexane-EtOAc 3:1) gave **25** (2.47 g, 93%). Elution with hexane-EtOAc 1:1 furnished few mg of **26**. **25** ^{1}H ($CDCl_3$): 9.79 (t, 1 H, J 1.6 Hz, $CO\underline{H}$); 4.76 (d, 1 H, J_{12} 2.0 Hz, H-1); 3.97 (t, J_{34} J_{32} 5.4 Hz, H-3); 3.93 (dd, J_{21} 2.1 Hz, J_{23} 5.1 Hz, H-2); 3.61 (dd, $J_{5'4}$ 4.0 Hz, $J_{5'5''}$ -11.6 Hz, H-5') 3.46 (dd, $J_{5''4}$ 8.1 Hz, $J_{5''5'}$ -11.7 Hz, H-5''); 3.42 (s, OMe); 2.66-2.34 (m, 3 H, H-4, 2xH-6); 1.52, 1.34 $C\underline{M}e_2$. ^{13}C ($CDCl_3$): 200.34 C-7; 109.17 $\underline{C}Me_2$; 99.91 C-1; 75.60, 73.79 C-2,3; 60.77 C-5; 55.46 OMe; 43.67 C-6; 33.69 C-4; 28.09, 26.26 $C(O\underline{M}e)_2$. Exact mass (m-nitrobenzyl alcohol): calc. for $C_{11}H_{18}O_5$+H : 231.1332. Found: 231.1235. **26**: ^{1}H ($CDCl_3$): 4.84 (d, 1 H, J_{12} 1.2 Hz, H-1); 4.02 (dd, J_{32} 5.2 Hz, J_{34} 8.0 Hz, H-3); 3.97 (dd, J_{21} 1.6 Hz, J_{23} 5.3 Hz, H-2); 3.83-3.65 (unresolved, 2 H, 2xH-7); 3.50 (dd, $J_{5'4}$ 4.6 Hz, $J_{5'5''}$ -10.8 Hz, H-5'); 3.42 (dd, $J_{5''4}$ 9.6 Hz, $J_{5''5'}$ -11.5 Hz, H-5''); 3.40 (s, 3 H, OMe); 2.81 (t, 1 H, J 5.2 Hz, OH); 2.03-1.88 (m, 1 H, H-4) [after irradiation of H-3: dddd, $J_{45'}$ 5.0 Hz, $J_{45''}$ 9.8 Hz, $J_{46'}$ and $J_{46''}$ 5.0 Hz and 9.8 Hz]; 1.63-1.44 (m, 2 H, 2xH-6); 1.55; 1.36 $C\underline{M}e)_2$. ^{13}C ($CDCl_3$): 108.93 $\underline{C}Me_2$; 99.15 C-1; 76.57, 73.62 C-2,3; 61.15, 60.96 C-5,7; 55.18 OMe; 37.00 C-4; 33.67 C-6; 28.09, 26.25 $C\underline{M}e_2$. Exact mass (thioglycerol-NaOAc): calc. for $C_{11}H_{20}O_5$ + H: 233.1389. Found: 233.1384.

Methyl 4-deoxy-4-*C*-(E/Z-t-butyldimethylsilyloxyethenyl)-2,3-O-isopropylidene-α-L-lyxo-pyranoside 27. Aldehyde **25** (2.47g, 10.7 mmol) in CH_2Cl_2 (50 cm^3) and Et_3N (4.2 cm^3) was

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cooled in ice-salt bath. t-Butyldimethylsilyl trifluoromethanesulfonate (3.45 cm^3, 15 mmol) was added dropwise from a syringe. Intensive stirring was maintained during this operation. When addition was finished, the ice-salt bath was replaced with an ice-bath. After 4 h TLC (hexane-EtOAc 5:1) showed that **25** reacted completely forming two less polar overlaping spots of E/Z isomers **27**: R_f 0.61 and 0.57. Partition between CH_2Cl_2-ice water, followed by washing of organic phase with ice-water, drying and evaporation furnished an oil. Flash chromatography (hexane-EtOAc 20:1) yielded **27** (2.62 g, 71%). All these operations should be performed in one day. If a crude **27** was stored in a dry-ice dewar for two days without chromatographic purification. The yield of **27** was 62%. **27**: ^{13}C ($CDCl_3$): 142.84, 141.42 C-7; 108.82 $\underline{C}Me_2$; 108.28, 106.91 C-6; 100.29, 99.78 C-1; 76.45, 73.92, 73.80 C-2,3; 62.06, 61.43 C-5; 55.51, 55.38 OMe; 38.21, 34.71 C-4; 28.24, 26.39 $C\underline{M}e_2$; 25.62 SiC $(\underline{M}e)_3$; 18.26 $\underline{C}Me_3$; -5.26, -5.46 $Si\underline{M}e_2$. Exact mass (m-nitrobenzyl alcohol): calc. for $C_{17}H_{32}O_5Si$+H: 345.2097. Found: 345.2100.

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Methyl 4-deoxy-4-*C*-hydroxymethyl-2,3-O-isopropylidene-α-L-lyxopyranoside 7 and methyl 4-deoxy-4-*C*-acetoxymethyl-2,3-O-isopropylidene-α-L-lyxopyranoside 28. Silyl enol ether **27** (2.62 g) in methanol (40 cm^3) was cooled in dry ice-ethanol bath, and a stream of O_3/O_2 was passed through until the solution became bluish (~15 min). Two hours later $NaBH_4$ was added (~0.1 g), and cooling bath was removed. When a solution was reaching ambient temperature, more $NaBH_4$ was added in (~0.05 g) portions (total $NaBH_4$ added was 0.5 g). Methanol was evaporated and the residue was taken up in CH_2Cl_2 and washed with water. Organic phase was dried and evaporated. Gravitational chromatography of the residue performed in hexane-EtOAc 3:2 furnished **28** (0.135 g, 7%) and **7** (1.08 g, 65%). Since the acetate **28** could be transformed into **7** quantatively (cat. NaOMe in HOMe), a yield of **7** increased to 72%. **28**: ^1H ($CDCl_3$): 4.76 (d, 1 H, J_{12} 2.2 Hz, H-1); 4.22 (dd, 1 H, $J_{6'4}$ 4.6 Hz, $J_{6'6''}$ -11.4 Hz, H-6'); 4.09 (dd, J_{32} 5.3 Hz, J_{34} 7.5 Hz, H-3); 4.05 (dd, $J_{6''4}$ 7.3 Hz, $J_{6''6'}$ -11.4 Hz, H-6"); 3.96 (dd, J_{21} 2.3 Hz, J_{23} 5.3 Hz, H-2); 3.63 (dd, $J_{5'4}$ 5.1 Hz, $J_{5'5''}$ -11.7 Hz, H-5); 3.55 (dd, $J_{5''4}$ 8.3 Hz, $J_{5''5'}$ -11.8 Hz, H-5"); 2.16 (qt, 1 H, J 4.8 Hz, 4.8 Hz, 7.7 Hz, 7.7 Hz, 7.7 Hz, H-4); 2.06 (H, OAc); 1.51 and 1.35 $C\underline{M}e_2$. ^{13}C ($CDCl_3$): 170.75 $\underline{C}OCH_3$; 109.00 $\underline{C}Me_2$; 99.82 C-1; 73.63, 72.20 C-2,3; 62.66, 59.23 C-5,6; 55.38 OMe; 38.37 C-4; 28.12, 26.21 $\underline{C}Me_2$; 20.71 $CO\underline{C}H_3$. Exact mass (thioglycerol-NaOAc): calc. for $C_{12}H_{20}O_6$ +Na: 283.1158. Found: 283.1188. **7**: (Found : C, 54.97; H, 8.32. $C_{10}H_{18}O_5$ requires C, 55.03; H, 8.3%).^1H ($CDCl_3$): 4.69 (d, 1 H, J_{12} 3.0 Hz, H-1); 4.19 (dd, 1 H, J_{32} 5.5 Hz, J_{34} 6.6 Hz, H-3); 3.96 (dd, 1 H, J_{21} 3.0 Hz, J_{23} 5.4 Hz, H-2); 3.84-3.59 (m, 4 H, 2xH-5,6) [after irradiation of the H-4 signal: 3.73 (AB, J 10.4 Hz and 26.0 Hz); 3.68 (AB, J 9.0 Hz and 16.0 Hz)]; 3.44 (s,

OMe); 2.15-2.03 (m, 1 H, H-4); 1.53 and 1.36 C<u>Me</u>$_2$. ^{13}C ($CDCl_3$): 108.99 <u>C</u>Me$_2$, 100.63 C-1; 73.98, 73.63 C-2,3; 62.69, 60.14 C-5,6; 55.69 OMe; 40.54 C-4; 28.15, 26.23 C<u>Me</u>$_2$. Exact mass (thioglycerol): calc. for $C_{10}H_{18}O_5$+H: 219.1232. Found: 219.1207.

Methyl 4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranoside (29). Acetonide **7** (1.7 g) was treated with 90% trifluoroacetic acid (70 cm^3) at room temperature during 10 min. After evaporation and co-evaporation with EtOAc (twice), the residue was passed through a silica gel column (in CH_2Cl_2-MeOH 10:1; R_f of **29** is 0.32) to furnish **29** (1.32 g, 95%) as glassy material. **29**: (Found: C, 47.25; H, 7.88. $C_7H_4O_5$ requires C, 47.19; H, 7.92%). ^{1}H (CD_3OD, reference line δ 3.35 ppm): 4.64 (d, 1 H, J_{12} 2.3 Hz, H-1); 3.83-3.72 and 3.63-3.52 (two groups of multiplets, 5 H, H-3, 2xH-5, 6); 3.67 (dd; J_{21} 2.3 Hz, J_{23} 3.0 Hz, H-2); 3.39 (s, OMe); 2.16 (dddd, 1 H, J 10.8 Hz, 10.8 Hz, 6.9 Hz, 4.3 Hz, 4.3 Hz, H-4). ^{13}C (CD_3OD, reference line δ 49.00 ppm): 103.41 C-1; 70.59, 68.10 C-2,3; 62.15, 61.62 C-5,6; 55.25 OMe; 41.36 C-4. Exact mass (thioglycerol-NaOAc): calc. for $C_7H_{14}O_5$+Na: 201.0739. Found: 201.0746.

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Methyl tri-O-acetyl-4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranoside (9). Conventional acetylation of **29** (1.32 g) and chromatography in hexane-EtOAc (2:1) furnished **9** (2.01 g, 89%). **9**: (Found : C, 51.15; H, 6.43. $C_{13}H_{20}O_8$ requires C, 51.31; H, 6.62%).^{1}H (CD_3OD): 5.18 (dd, J_{32} 3.2 Hz J_{34} 10.9 Hz, H-3); 5.16 (dd, J_{21} 2.0 Hz, J_{23} 3.3 Hz, H-2); 4.70 (d, 1 H, J_{12} 1.9 Hz, H-1); 4.15 (dd, $J_{6'4}$ 5.8 Hz, $J_{6'6''}$ -11.6 Hz, H-6'); 4.06 (dd, $J_{6''4}$ 3.5 Hz, $J_{6''6'}$ -11.5 Hz, H-6''); 3.83 (dd, J_{5eq4} 5.7 Hz, J_{5eq5ax} -11.4 Hz, H-5_{eq}); 3.75 (t, J_{5ax4} J_{5ax5eq} 11.0 Hz, H-5_{ax}); 3.44 (s, OMe); 2.51 (ddddd, 1 H, $J_{46''}$ 3.5 Hz, $J_{46'}$ and J_{45eq} 5.3 Hz and 5.6 Hz, J_{43} J_{45ax} 10.8 Hz, H-4); 2.15, 2.07, 2.03 OAc. ^{13}C (CD_3OD): 172.45, 171.76 <u>C</u>OMe; 100.54 C-1; 69.34, 68.56 C-2,3; 62.31, 61.58, 61.58 C-5,6; 55.54 OMe; 36.94 C-4; 20.76 CO<u>C</u>H$_3$. Exact mass (thioglycerol-NaOAc): calc. for $C_{13}H_{20}O_8$ + Na: 327.1056. Found: 327.1059.

4-Deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl tetraacetate 12, β anomer 14 and the open chain compounds 15 and 16. Glycoside **9** (0.21 g) was subjected to acetolytic cleavage in a mixture (15 cm^3) prepared from AcOH (24 cm^3), Ac_2O (10 cm^3) and conc. H_2SO_4 (1 cm^3), during 12 h. After extractive work-up and chromatography a mixture of **12** and **14** (0.148 g, 64%) was obtained (>90% of **12**). Pure β anomer **14,** slightly more polar than **12** was obtained in 0,02 yield. The most polar product was **(16)** was obtained in 26% yield (0.078 g). In a separate experiment **9** (2.01 g) was treated with a mixture of AcOH (48 cm^3), Ac_2O (20 cm^3) and conc. H_2SO_4 (2 cm^3)

during 2 h. After extractive work-up and chromatography **12** (1.19 g) contaminated with ca. 10% of a mixture of **14** and **15**, and ca. 1:1 mixture of **15** and **16** (1.04 g) was obtained. Pure **15** was isolated in 0.025 g quantity for analytical purpose. R_f values of **14** and **15** are practically the same. Acetolysis of acetate **28** during 48 h furnished much smaller yield of **12/14**, (16%) and **16**, (8%). **12**: ^{1}H ($CDCl_3$): 6.03 (d, 1 H, J_{12} 2.2 Hz, H-1); 5.22 (dd, J_{34} 11.0 Hz, J_{32} 3.3 Hz, H-3); 5.16 (dd, J_{23} 3.4 Hz, J_{21} 2.1 Hz, H-2); 4.11 (dd, $J_{6'6"}$ -11.6 Hz, $J_{6'4}$ 4.2 Hz, H-6'); 4.03 (dd, $J_{6"6'}$ -11.6 Hz, $J_{6"4}$ 6.2 Hz, H-6"); 3.93 (dd, J_{5eq5ax} -11.8 Hz, J_{5eq4} 5.0 Hz, H-5_{eq}); 3.76 (t, J_{5ax5eq} -11.5 Hz, J_{5ax4} 11.3 Hz, H-5_{ax}); 2.59 (ddddd, 1 H, $J_{46'}$ 4.3 Hz, J_{45eq} 5.0 Hz, $J_{46"}$ 6.3 Hz, J_{43} J_{45ax} 11.3 Hz, H-4); 2.16, 2.15, 2.07, 2.04 Oac. ^{13}C ($CDCl_3$): 170.60, 169.94, 169.69, 168.60 COMe; 91.41 C-1; 66.88, 66.72 C-2,3; 62.78 C-5; 61.03 C-6; 35.24 C-4; 20.85, 20.65 COMe. Exact mass (thioglycerol-NaOAc): calc. for $C_{14}H_{20}O_9$+Na: 355.1005. Found: 355.0994. **14**: ^{1}H ($CDCl_3$): 5.79 (d, 1 H, J_{12} 1.5 Hz, H-1); 5.42 (dd, 1 H, J_{21} 1.6 Hz, J_{23} 3.1 Hz, H-2); 5.07 (dd, 1 H, J_{32} 3.0 Hz, J_{34} 10.6 Hz, H-3); 4.22-4.01 (m, 3 H, H-5_{eq}, 2xH-6); 3.59 (dd, 1 H, J_{5ax4} 10.4 Hz, J_{5ax5eq} -12.1 Hz, H-5_{ax}); 2.49 (ddddd, 1 H, J_{45ax} J_{43} $J_{46'}$ 9.6 Hz, J_{45eq} and $J_{46'}$ 1.8 Hz and 5.2 Hz, H-4); 2.20, 2.13 2.09, 2.07 COMe. ^{13}C ($CDCl_3$): 170.73, 170.16, 169.82, 168.64 COMe; 90.85 C-1; 68.28, 66.99 C-2,3; 64.48 C-5; 60.54 C-6; 35.25 C-4; 20.73 COMe. Exact mass (thioglycerol-NaOAc): calc. for $C_{14}H_{20}O_9$+Na: 355.1005. Found: 355.1009. **15**: ^{1}H ($CDCl_3$): 5.90 (d, 1 H, J_{12} 5.5 Hz, H-1); 5.32 (t, J_{32} J_{34} 5.2 Hz, H-3); 5.24 (t, J_{21} J_{23} 5.3 Hz, H-2); 4.27-4.01 (m, 4 H, CH_2OAc); 3.43 (s, 3 H, OMe); 2.54-2.41 (m, 1 H, H-4); 2.09, 2.06, 2.05, 2.04 OAc. ^{13}C ($CDCl_3$): 170.66, 170.52, 169.61, 169.33 COCH3; 95.05 C-1; 71.00, 69.06 C-2,3; 62.07, 60.83 2xCH_2; 57.20 OMe; 37.95 C-4; 20.68, 20.58 COCH_3. Exact mass (thioglycerol-NaOAc) calc. for $C_{17}H_{26}O_{11}$ + Na 429.1373. Found: 429.1369

1-[Tri-O-acetyl-4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine (18). An amount of **12** (1.19 g, contaminated with ca 10% of **14** and **15**) in 1,2-dichloroethane (75 cm^3) was added to a trimethylsilylated thymine, followed by TMSOTf (0.77 cm^3). External temperature of 70° was maintained during 18 h. The solution was transferred to a separatory funnel, CH_2Cl_2 and water were added and extraction was performed. Organic layer was washed one more time with water, dried and evaporated. Gravitational chromatography of a residue (in CH_2Cl_2-MeOH 20:0.7) furnished **18** (0.995 g, 78%). **19** m.p. 130-132° (cryst. EtOH); (Found : C, 51.02; H, 5.58; N, 6.93. $C_{17}H_{22}N_2O_9$ requires C, 51.26; H, 5.57; N, 7.03%). ^{1}H ($CDCl_3$): 9.39 (s, 1 H, NH); 7.14 (d, 1 H, $J_{6\text{-}CH3}$ -1.2 Hz, H-6); 6.04 (d, 1 H, $J_{1',2'}$ 9.9 Hz, H-1'); 5.56 (t, 1 H, $J_{3'2'}$ $J_{3'4'}$ 2.8 Hz, H-3'), 5.10 (dd, 1 H, $J_{2'1'}$ 9.9 Hz, $J_{2'3'}$ 3.3 Hz, H-2'); 4.34 (apparent dd, $J_{6'4'}$ 1.8 Hz, $J_{6"4'}$ 8 0 Hz, 2xH-6'); 4.16

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(dd, $J_{5'4'}$ 2.9 Hz, $J_{5'5''}$ -12.4 Hz, H-5'); 3.93 (d, 1H, $J_{5''5'}$ -12.4 Hz, H-5"); 2.34-2.22 (m, partialy superimposed on OAc signals, H-4'); 2.19, 2.14, 1.98 OAc; 1.94 (d, 3 H, J_{CH3-6} -1.1 Hz, CH_3). ^{13}C ($CDCl_3$): 170.73, 169.68, 169.54 $\underline{C}OCH_3$; 163.45, 150.68 C-2,4; 134.57 C-6; 111.95 C-5; 78.79 C-1'; 68.01, 66.08 C-2'3'; 64.70, 61.84 C-5'6'; 39.60 C-4'; 20.86, 20.69, 20.43 $CO\underline{C}H_3$; 12.40 CH_3. Exact mass: calc. for $C_{17}H_{22}N_2O_9$+H: 399.1403. Found: 399.1401.

1-[4-Deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine (1c). Deacetylation of **18** was performed with cat. NaOMe in methanol. After neutralization with dry ice and evaporation, the residue was passed through a short bed of silica gel (in $CHCl_3$-MeOH 3:1) to furnish **1c** (0.080 g, 89%). **1c:** (Found : C, 48.52; H, 5.73; N, 10.12. $C_{11}H_{16}N_2O_6$ requires C, 48.53; H, 5.92; N, 10.29%).^1H (CD_3OD, reference time δ=3.35 ppm): 7.26 (d, 1 H, J_{6-CH3} -1.6 Hz, H-6); 5.96 (d, 1 H, $J_{1'2'}$ 9.5 Hz, H-1'); 4.26 (t, $J_{3'2'}$ $J_{3'4'}$ 2.5 Hz, H-3'); 4.14 (dd, J 2.5 and -11.7 Hz, H-5'(6')); 3.91-3.71 (m, 3 H, H-6'(5'),5",6"); 2.07-1.98 (unresolved, H-4'); 1.86 (d, J_{CH3-6} -0.8 Hz, CH_3). ^{13}C (CD_3OD, reference time δ=49.00 ppm): 174.84, 160.12 C-2,4; 137.27 C-6; 111.94 C-5; 83.01 C-1'; 70.81, 68.72 C-2'3'; 64.77, 61.61 C-5',6'; 46.78 C-4'; 13.63 Me. Exact mass (thioglycerol): calc. for $C_{11}H_{16}N_2O_6$ + Na: 295.0906. Found: 295.0899.

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