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Larger laboratory scale synthesis of 5-methyluridine and formal synthesis of its L-enantiomer

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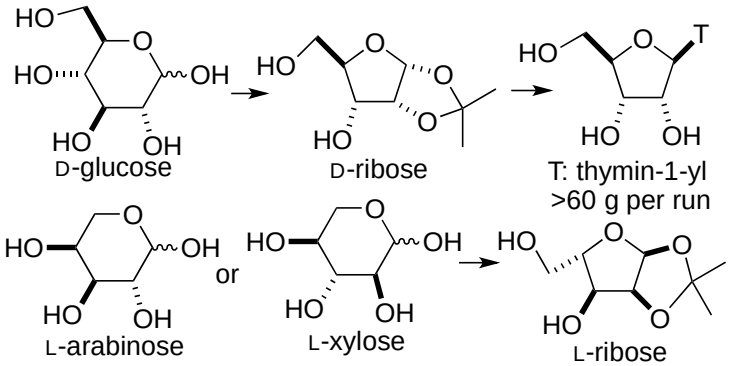
Abstract

A larger laboratory scale synthesis (>60 g per run) of 5-methyluridine is presented. The critical intermediate 1,2-*O*-isopropylidene-α-D-ribofuranose was prepared from very cheap D-glucose via D-allose. Its L-enantiomer was obtained from L-arabinose via L-glucose, and also from L-xylose.

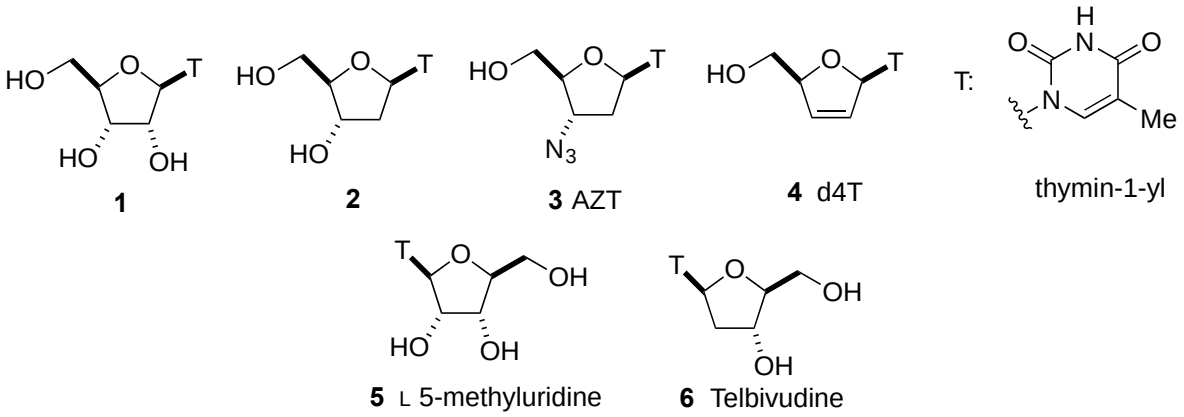


5-Methyluridine was prepared from D-glucose via 1,2-isopropylidene-a-D-ribofuranose as intermediate, the L-enantiomer of which was prepared from L-arabinose via L-glucose, and independently from L-xylose.

Keywords: 5-Methyluridine, chiral pool, stereoselective synthesis, D- and L-carbohydrates

Introduction

5-Methyluridine **1** is a component of the ribonucleic acids from which it can be isolated, however demand for it far exceeds a supply in this way. 5-Methyluridine is a starting compound for the synthesis of 3′-azido-2′,3′-dideoxythymidine or AZT (Zidovudine, Retrovir) **3** (via 2′-deoxy compound **2**) and also to obtain 2′,3′-dideoxy-2′,3′-didehydrothymidine or d4T (Zerit) **4**, both used as potent inhibitors of the reverse transcriptase, a critical enzyme necessary for multiplication of the HIV virus responsible for the AIDS epidemic.[1] The sugar moieties present in **1**-**4** belong to the D series. L-Thymidine **6** is very active inhibitor of the reverse transcriptase of the hepatitis B virus (HBV).[2] Compound **6** is marketed under the name Telbivudine (Sebvio, Tyzeka) and is the enantiomer of **2**. As such it can be prepared from the L 5-methyluridine **5** via deoxygenation at its 2′-position.[3] Considering the demand for both enantiomers **1** and **5**, uniform access to both of them is an attractive synthetic goal.

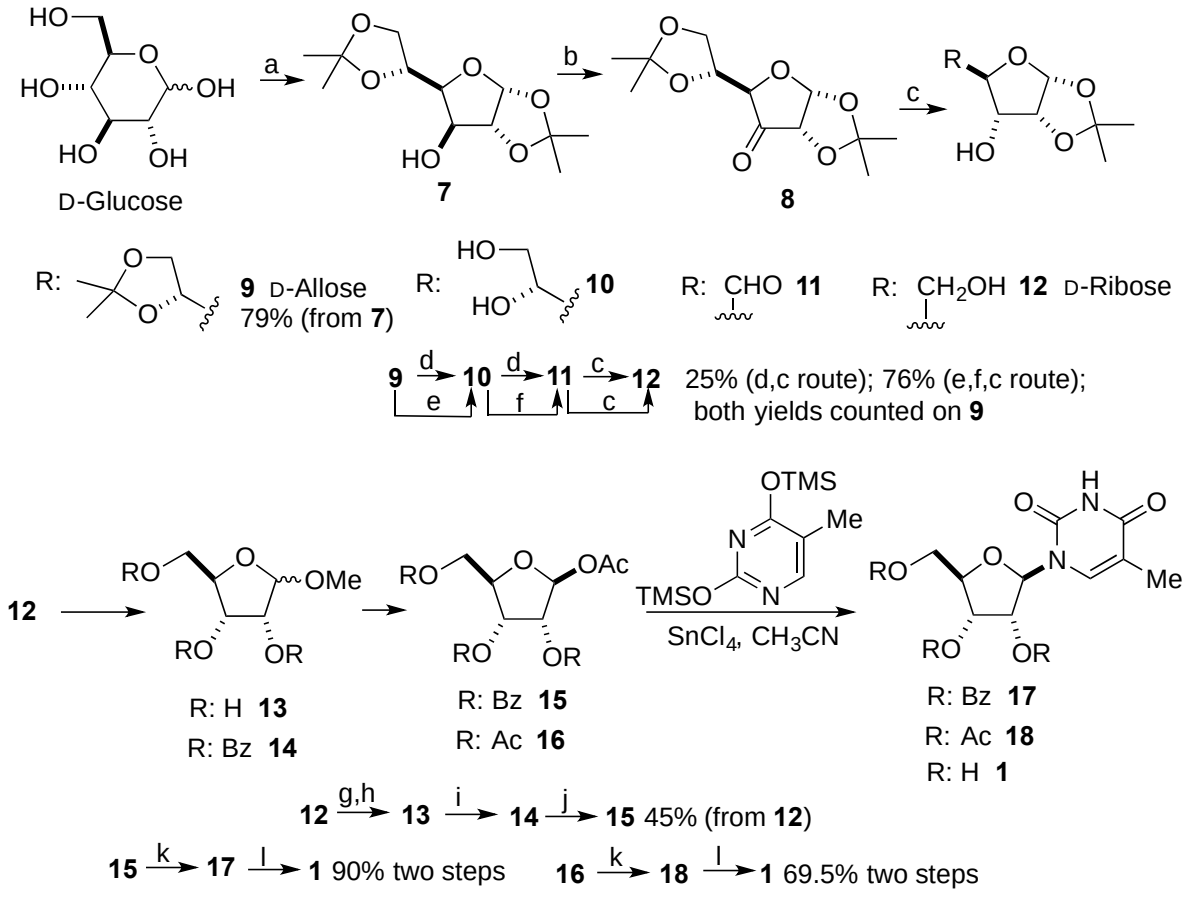


The stereochemical characteristics of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose **7** permit its transformation into 1,2-*O*-isopropylidene-α-D-ribofuranose **12**[4] and further to 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **15** and finally to 5-methyluridine **1**. It is obvious that the same sequence of reactions performed on L-glucose will furnish L 5-methyluridine **5**. Compound **15** can be directly prepared form D-ribose using HCl-MeOH (→ **13**),[5,6] H_2SO_4-MeOH[7] or AcCl-MeOH[8] followed by benzoylation (→ **14**) and acetolysis (→ **15**), but since D-glucose is abundant and is one of the cheapest chiral compounds available, we used it to obtain D-ribose and finally **1** at a larger laboratory scale (> 60 g per run) in excellent cumulative yields of ca. 90% for the sequence **15**→ **17**→ **1**. We also tried to obtain 1,2-*O*-isopropylidene-α-L-ribofuranose **32** using L-glucose which was obtained from L-arabinose via the nitromethane one-carbon extension (Fischer-Sowden reaction[9,10] which is a carbohydrate version of the Henry reaction,[11-15]) followed by a Nef reaction (sodium aci salt of nitroalditols, H_2SO_4).[10] The other versions of this process include ozonization,[16,17] and peroxomolybdate-H_2O_2;[17,18] non-carbohydrate examples include among others "basic silica gel",[19] $NaClO_2$[20] and H_2O_2-K_2CO_3;[21] the Nef reaction has been recently reviewed.[22,23] This met with a limited success due to difficulties in separation of the necessary L-glucose **27** from the L-mannose **28** by chromatography (see below). A much better result was obtained using reasonably priced L-xylose which was converted to the L-ribose **32** in batches of ca. 15 g per run. Since **32** can be elaborated to produce L 5-methyluridine **5** by the same set of conditions as those applied to reach 5-methyluridine **1** from the D-ribose **12**, we can claim that a formal synthesis of L **5** was also realized.

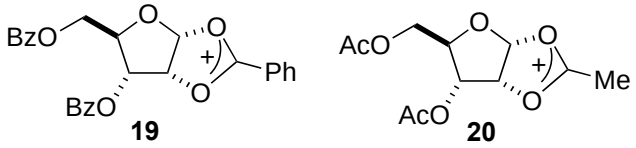
Results and Discussion

A transformation of D-glucose into D-ribose via inversion of the configuration at the C3 position followed by fission of the C5–C6 bond (dehomologation) is known, and we followed the published procedures with some additional modifications. Alternative methods to produce D-ribose have been reviewed.[24] The critical inversion of configuration at the C3 position of D-glucose to get D-allose **9** requires the transient ulose **8**. Reduction of **8** proceeds with practically complete stereoselectivity (→ **9**) using $NaBH_4$ but application of the $LiAlH_4$ gives mixtures of **7** and **9**.[25] Some care must be exercised during the oxidation step (**7**→ **8**). The cheapest and operationally easiest oxidant is DMSO-Ac_2O mixture,[26] even though foul smelling divalent sulfur compounds are formed. The other oxidants include DMSO-P_2O_5,[27] pyridinium dichromate-Ac_2O,[28] pyridinium chlorochromate,[29] and $RuCl_3$-$NaIO_4$,[30] (RuO_2-$NaIO_4$[31] was reported to also form Baeyer-Villiger overoxidation products) and finally Dess-Martin periodinane.[32] DMSO-Ac_2O is not a very active system and its application may result in incomplete conversion of **7** into **8**, and consequently, the next reduction step may furnish a mixture of the allose **9** and unreacted glucose **7**, which are difficult to separate. In fact, unreacted **7** was reported to be present even after 24 h of reaction time.[26] The same kind of problem has been observed before in different context.[33] The very active CrO_3-Py-Ac_2O mixture[34] provided complete oxidation in less than 1 hour at room temperature for 25-39 g batches of **7**. A weak point of this method is formation of insoluble tars composed of the reduced chromium compounds complexed with pyridine. A very interesting one-pot oxidation-reduction procedure was published which consists of the addition of the $NaBH_4$ directly to the DMSO-oxalyl chloride oxidation mixture,[35] although this was performed on small scale. The dehomologation step (**9**→ **10**→ **11**→ **12**), i.e. a transformation of the D-allose (a hexose) to D-ribose (a pentose) can be performed using orthoperiodic acid H_5IO_6 followed by $NaBH_4$ reduction.[36,37] The orthoperiodic acid is strong enough (pKa ca 3.3[38]) to promote a hydrolysis of the more reactive C5–C6 acetonide in **9** to liberate a diol **10** which was subsequently cleaved by the same reagent to furnish the aldehyde **11** which in turn was subjected to $NaBH_4$ reduction to yield the *ribo* compound **12**. This procedure is very attractive and in fact it was successfully used on a small scale (1 g) in good yields (e.g. **29**→ **32**, see below). When applied to **9** at a 27 g scale however, it furnished the 1,2-*O*-isopropylidene-α-D-ribofuranose **12** in yield as low as 25%. The reason for this is unclear, but probably can be traced to incomplete removal of the iodic acid HIO_3 formed during oxidation of the C5–C6 diol. HIO_3 crystallized in the reaction mixture and must have been filtered off. In the case of incomplete crystallization and removal, $NaBH_4$ reduced it to the transient hypoiodous acid[39] which presumably degraded the aldehyde **11** oxidatively. To avoid this it was much better to perform separately the hydrolysis (**9**→ **10**) using 0.8% H_2SO_4 in MeOH-H_2O mixture[40] followed by $NaIO_4$ oxidation (→ **11**) and final $NaBH_4$ reduction to get the 1,2-*O*-isopropylidene-α-D-ribofuranose **12** in much better yield (**9**→ **12**, 76%). Removal of the acetonide (70% aq. AcOH, 80 °C) followed by Fischer type glycosylation (MeOH, cat. H_2SO_4 or HCl) furnished kinetically controlled furanosides **13** which, upon conventional benzoylation (BzCl, Py) followed by acetolysis (Ac_2O, AcOH, cat. H_2SO_4), furnished the necessary 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **15**. The best cumulative yields for this sequence was 45% based on **12**. There are some variations in the published conditions and the yields of **15** obtained by acetolysis.[5,6,41] Cimpoia *et al*.[41] reported that the best procedure was with a decreased amount of H_2SO_4 in relation to AcOH and Ac_2O and low temperature to avoid formation of the open-chain acetal acetates. Transformations of **12** to **15** were performed without isolation of the intermediates. The compound **15** must be thoroughly dried since traces of *i*-PrOH used for its crystallization react with $SnCl_4$ during the next coupling step to liberate HCl which may compromise the yield of **17**. The compound **15** was finally coupled with the trimethysilylated thymine (thymine, HMDS, cat.$(NH_4)_2SO_4$, bp., 3-4 h) under the influence of $SnCl_4$ in CH_3CN[42] to get 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl

thymine **17** in nearly quantitative yield. Alternative versions of this coupling include different activating groups at the anomeric position, like chloride,[43] methylcarbonate,[44] 1,2-epoxide,[45] *N*-phenyl trifluoracetimidate,[46] or *S*-tolyl group,[47] different catalysts like TMSOTf,[48] $BiBr_3$,[49] or Ph_3PAu^+ $^-N(SO_2CF_3)_2$,[50] different pattern of protection of the ribofuranosyl moiety like 1,2,3,5-tetra-*O*-acetate[49] or 1,2-di-*O*-acetyl-3,5-di-*O*-benzoate,[51] different activation of the thymine moiety via bis(tributylstannylation)[52] rather than bis(trimethylsilylation), and finally a solvent-free ball milling procedure.[53] Compound **17** was finally deprotected using Zemplén conditions (MeOH, cat. NaOMe). Methyl benzoate (an oil) formed during this reaction interferes with the crystallization of **1** and for this reason was removed by partition between $CHCl_3$ and water (**1** remained in the water phase). The 5-methyluridine **1** formed in this way was isolated in ca 90% yield for two steps (coupling and deprotection). It is interesting to note that the commercial 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose **16** under the same coupling conditions furnished 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl thymine **18** in lower yield (69.5%) even though a clear spot-to-spot reaction also took place. This probably can be attributed to inferior stabilization of the reactive cation **20** in comparison to the benzylic cation **19**. Scheme 1 summarizes this part of the project.

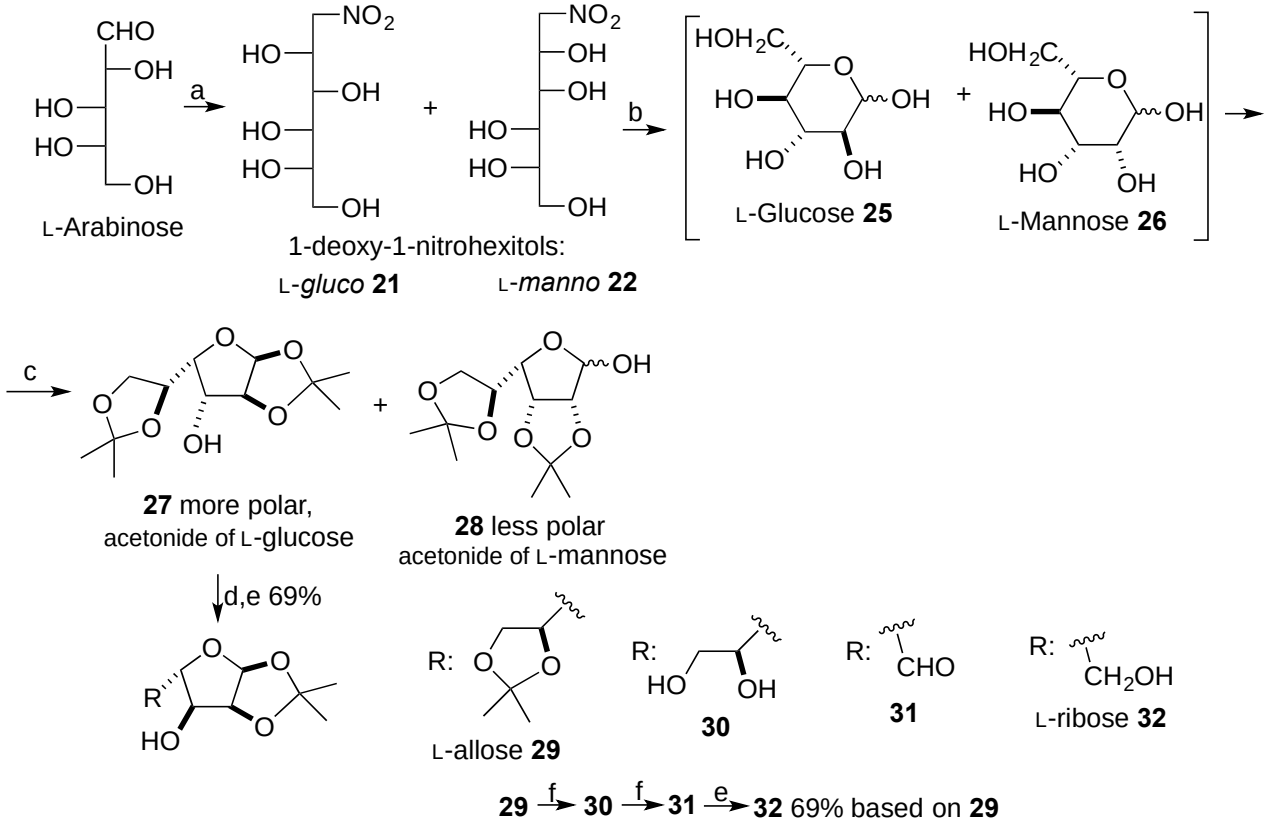


Conditions: a. acetone, H_2SO_4; b. DMSO, Ac_2O or CrO_3, Py, Ac_2O; c. $NaBH_4$; d. H_5IO_6, one pot; e. 0.8% H_2SO_4, MeOH; f. $NaIO_4$; g. AcOH, H_2O; h. MeOH, H_2SO_4; i. BzCl, Py; j. AcOH, Ac_2O, H_2SO_4; k. (TMS)T, $SnCl_4$; l. MeOH, MeONa



Scheme 1. Synthesis of 5-methyluridine **1** starting from D-glucose via D-allose.

L-Ribose,[54,55] a necessary substrate to obtain the L 5-methyluridine **5** is a known compound that can be obtained from L-arabinose via epimerization at the C2 position catalyzed by molybdic acid (Bílik reaction),[56,57] starting from D-fructose,[58] D-galactose,[59] D-lyxose,[60] or D-ribose via transposition of the C1–C5 position.[61,62] The latter transformation is possible due to the enantiotopic relationship between both $-CH_2OH$ groups in D-ribitol (and also in any alditol which has a plane of symmetry like galactitol or allitol. In fact D-galactose was transformed into L-galactose[63] by the same kind of transposition). However, having accomplished a synthesis of **1** using D-glucose, we wanted to apply L-glucose for the same purpose to obtain the L enantiomer **5**. L-Glucose can be prepared from D-glucose by the published procedure.[64] It is also commercially available but due to the prohibitively high price we tried to obtain it from reasonably priced L-arabinose via a one carbon atom extension. This approach is shown in the Scheme 2. The Henry reaction (aldehyde/ketone, nitroalkane, base)[9-15] performed on L-arabinose and CH_3NO_2 and NaOMe [9,10] furnished a mixture of crystalline 1-deoxy-1-nitro-L-glucitol **21** and 1-deoxy-1-nitro-L-mannitol **22** in approximately equal proportion. This addition to diastereotopic sides of the carbonyl group should follow the Felkin-Anh model[65] as shown in **23** and **24** (Figure 1) where the C3-C5 fragment is treated as a large group and the C2-OH as a medium one.



Conditions: a. CH_3NO_2, NaOMe; b. H_2SO_4, H_2O; c. acetone, H^+, ultrasound; d. CrO_3, Py, Ac_2O; e. $NaBH_4$; f. H_5IO_6 **29** via **30** to **31**, one pot.

Scheme 2. Synthesis of 1,2-*O*-isopropylidene-α-L-ribose **32** starting from L-arabinose.

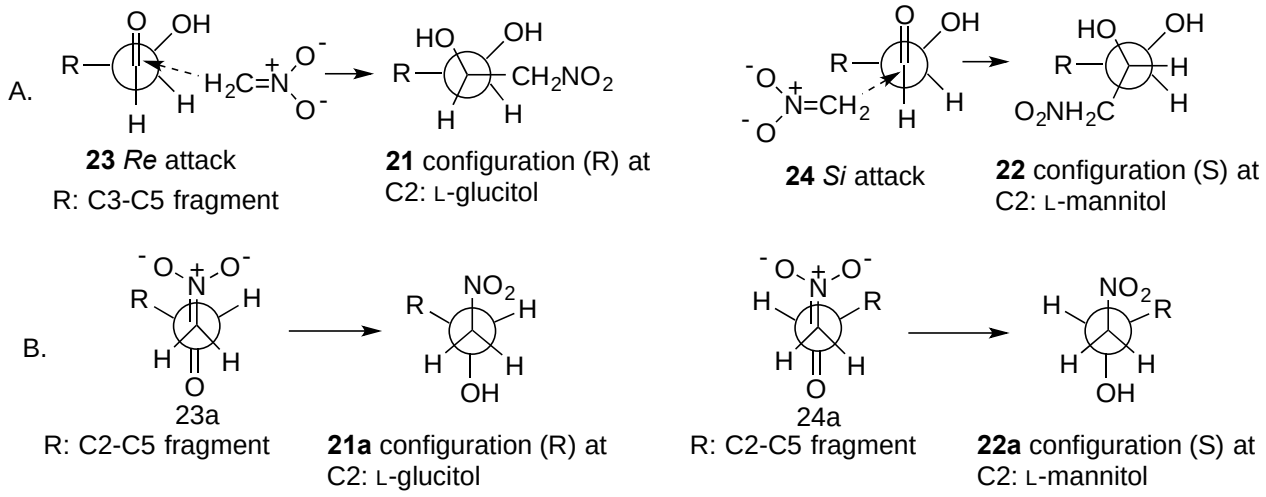
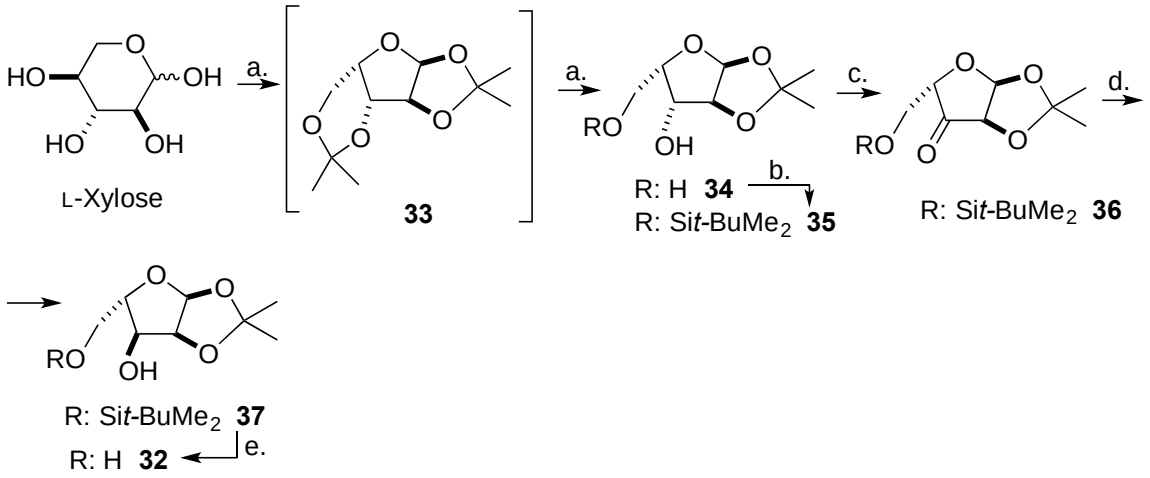


Figure 1. Stereochemistry of formation of nitroalcohols **21** and **22** according to the Felkin-Anh model (A) and according to the ref. 66 (B).

The privileged attack on the *Re* side should furnish the R configuration at the C2 atom, i.e. the L-*gluco* diastereoisomer **21** should predominate. It is not a case, though. A reason for this is unclear, but one can consider extensive hydrogen bonding between a solvent (MeOH) and the C=O group. This may override the steric and stereoelectronic factors which control the Felkin-Anh transition state. Also, a fully formed carbonyl group might not even have been present. Rather, reactive forms might have been the species with the hemiacetal rings being partially opened with retained α or β configuration. This may additionally influence the steric outcome. Theoretical calculations show that the transition states during the Henry reactions are such, that the negatively charged NO_2 moiety is far away from the carbonyl oxygen[66] atom as in **23a** and **24a** which apparently have the same energies. Consequently, both epimeric products **21** and **22** are formed without much stereoselection. This is additionally influenced by reversibility of the addition in basic medium. Irrespective of the mechanism, there is no preference for **21** over **22**. The **21**/**22** mixture was described as being separable by tedious fractional crystallization[9,10] and the resulting 1-nitro-L-glucitol and 1-nitro-L-mannitol were subjected separately to the Nef reaction to give L-glucose and L-mannose, respectively. However, since we needed the 2,3;5,6-di-*O*-isopropylidene-L-mannofuranose for another project we performed the Nef reaction (a. **21**/**22**, NaOH; b. H_2SO_4)[10] without fractional crystallization. A mixture of L-glucose **25** and L-mannose **26** thus obtained was subjected to isopropylidenation (acetone, H_2SO_2, ultrasound)[67] to yield a mixture of the di-*O*-isopropylidenated compounds **27** and **28** which were separated by vacuum-dry chromatography[68,69] at this stage. Eluted first was the L-mannose **28** followed by more polar L-glucose **27**. The NMR characteristics of both **27** and **28** are identical to those of their D-enantiomers. Due to small difference of the R_f values of **27** and **28**, their separation was successful at small scale only (ca 2 g of mixture per run). The 1,2;5,6-di-*O*-isopropylidene-α-L-glucofuranose **27** was then subjected to the oxidation/reduction (a. CrO_3-Py-Ac_2O;[34] b. $NaBH_4$) sequence to invert the configuration at the C3 position to produce the L-allose **29** which in turn was subjected to dehomologation (a. H_5IO_6, b. $NaBH_4$[36,37]) at a 1 g scale which furnished the 1,2-*O*-isopropylidene-α-L-ribofuranose **32** in a cumulative 69% yield (**29**→ **32**). As mentioned above for the D-enantiomer this process did not function well at elevated scale. Considering the overall length of this process, difficulties during the separation of **27** and **28**, and the low overall yield of the 1,2-*O*-isopropylidene-α-L-ribofuranose **32**, a more efficient route was devised using L-xylose.



Conditions: a. acetone, H_2SO_4 followed by Na_2CO_3, H_2O, one pot, 74%; b. *t*-$BuMe_2SiCl$, imidazole, 90%; c. CrO_3, Py, Ac_2O; d .$NaBH_4$, 75.6%, two steps; e. Bu_4NF 89%.

Scheme 3. Alternative access to L-ribose **32** via L-xylose.

This commercially available pentose was transformed in one pot[70] [a. acetone, H_2SO_4; b. partial neutralization with Na_2CO_3, H_2O] to the 1,2-*O*-isopropylidene-α-L-xylose. Selective protection of the primary OH group via silylation (*t*-$BuMe_2SiCl$, imidazole; *t*-$BuPh_2Si$-[71] and Tr-[72] were published for the same purpose) was nearly quantitative (**34**→ **35**). The compound **35** was subjected to inversion of configuration at the C3 position via oxidation-reduction (a. CrO_3-Py-Ac_2O;[34] b. $NaBH_4$) followed by desilylation to furnish the 1,2-*O*-isopropylidene-α-L-ribofuranose **32** with a total selectivity and good yield. Compound **32** is the L enantiomer of the intermediate D **12**, and can be further elaborated to obtain the L 5-methyluridine **5**.

Conclusions

In conclusion, a larger laboratory scale route to obtain 5-methyluridine **1** is described using D-glucose as a precursor of the pivotal 1,2-*O*-isopropylidene-α-D-ribofuranose **12**. Its enantiomer L **32** was obtained starting from either L-arabinose via L-glucose and L-allose, or (much better) from L-xylose.

Experimental Section

General. EtOAc was dried by azeotropic removal of water; ca. 20% of a forerun was rejected and the rest was distilled. Acetone and CH_2Cl_2 were dried by shaking with P_2O_5 during 20 min, rapid filtration and distillation. DMF was dried by azeotropic removal of water using benzene or toluene (ca. 20% of the volume of DMF). Pyridine was dried by storage over KOH. MeOH was dried by Mg/I_2 method. The ^1H and ^{13}C spectra were obtained on the Varian 300 MHz spectrometer unless otherwise stated. Exact mass measurements were obtained on the Waters Xevo G2-XS QTof spectrometer. Optical rotations were measured on the Jasco P-2000 241 automatic polarimeter at ca 26 °C. Moisture-sensitive reactions were performed using protecting atmosphere of argon dried by passage through "blue silica gel". Evaporations of the solvents were performed at ca 40 °C. $MgSO_4$ was used to dry the extracts. Column chromatography was performed using silica gel 70-

230 mesh from the Fluka. TLC chromatography was performed on the 0.2 mm silica gel aluminum plates (Fluka) and the spots were reveled using 10% H_2SO_4 in MeOH and heating at ca. 110 ° C.

1,2;5,6-Di-*O*-isopropylidene-α-D-allofuranose 9. A round-bottom flask equipped with a reflux condenser and magnetic stirring bar was charged with CH_2Cl_2 700 (mL) and CrO_3 (60 g, 600 mmol). The flask was immersed in ice-water, and pyridine (97 mL, 1200 mmol) was added portion wise during 10 min. The cooling bath was removed. After stirring for 1 h at rt, the dark brown mixture was cooled again with ice-water bath and **7** (39.3 g, 151 mmol) was added portionwise. After each addition of **7** a small volume of Ac_2O was added. The total volume of Ac_2O was 75 mL, 61.3 g, 600 mmol. After these intermittent additions which required 15 min the cooling bath was removed and oxidation continued for 25 min counting from the end of additions. TLC showed complete conversion of **7** R_f 0.49 into more polar ulose **8** R_f 0.33 (hexane - EtOAc 1:1). Most of CH_2Cl_2 was evaporated below 40 °C and 1:1 mixture of toluene - EtOAc, (500 mL) was added. This resulted in precipitation of insoluble black tar. The supernatant was decanted and the solid residue was washed twice with the same solvent. The combined solutions were passed through a short silica gel column prepared in toluene - EtOAc 1:2 using over pressure. The column was eluted with the same solvent system and product-containing fractions were evaporated. Xylenes (100 mL) were added and evaporation was continued to expel all residual pyridine. The oil obtained was dissolved in 96% EtOH (300 mL), cooled in ice-water bath and $NaBH_4$ (5 g, 132 mmol) was added portionwise while maintaining magnetic stirring. The cooling bath was removed and stirring was continued overnight. TLC showed allose **9** R_f 0.36 slightly less polar than the ulose **8** (hexane - EtOAc 1:1). Acetone (10 mL) was added to destroy the excess of $NaBH_4$ and most of the volatiles were evaporated. The residue was taken up in CH_2Cl_2 and washed with water. The organic phase was dried ($MgSO_4$) and evaporated to yield solid crude **9** (31.1 g, 79% for two steps). Mp 72-75 °C (hexane - EtOH), $[\alpha]_D^{26}$ +36.7 (*c* 2 $CHCl_3$); lit.[32] mp 74-75° C (toluene), $[\alpha]_D$ +38.8 (c 1.03 $CHCl_3$). NMR: see L-enantiomer **29**.

1,2-*O*-Isopropylidene-α-D-ribofuranose 12

A. Via H_5IO_6/$NaBH_4$. Compound **9** (27 g, 103.8 mmol) was dissolved in dry EtOAc (150 mL) and stirred with H_5IO_6 (99% pure, 28.7 g, 124.6 mmol) added in three portions. A white precipitate soon appeared. TLC showed the aldehyde **11** Rf 0.29 (hexane - EtOAc 1:2); the substrate **9** has R_f 0.36 (hexane - EtOAc 1:1). After 2 h filtration was performed using a sintered glass and the precipitate was washed with EtOAc. The volatiles were removed by evaporation. Some solid material appeared. EtOAc (50 mL) was added and filtration/evaporation was repeated. The residual oil was briefly dried on an oil pump, dissolved in 96% EtOH (100 mL), cooled in ice-water bath and treated with $NaBH_4$ (5 g, 132 mmol). The cooling bath was removed. R_f of the product **12** was 0.46 in CH_2Cl_2 - MeOH 20:1.5. After 3 h most of EtOH was evaporated and the residue was dissolved in CH_2Cl_2 and this solution was washed with water. The water phase was back extracted twice with CH_2Cl_2. The combined organic phases were dried, filtered and evaporated. Purification by chromatography CH_2Cl_2 - MeOH 20 :1.4 furnished **12** (4.9 g, 25%).

B. Via stepwise hydrolysis and $NaIO_4$/$NaBH_4$ treatment. To a cold (ice bath) solution of **9** (35 g, 134.6 mmol) in MeOH (300 mL) was added cold 0.8% H_2SO_4 (250 mL), and the mixture was left overnight at rt. TLC showed that **9** (R_f 0.36 in hexane - EtOAc 1:1) reacted to form **10** R_f ~0 in the same solvent system, or R_f 0.21 in CH_2Cl_2 - MeOH 9:1. Amberlite IRA 410 (OH^-) was added to neutralize the acid and was removed by filtration and washed with MeOH. The volatiles were removed by evaporation to yield crude **10** as a syrup. A small amount of this material was purified by chromatography using CH_2Cl_2 - MeOH 9:1 to get the crystalline material, mp 130-134 °C (EtOAc - EtOH); lit.[32] mp. 131-133 °C (Et_2O - MeOH) The bulk of the crude product was dissolved in 96% EtOH (250 mL) and treated with a suspension of $NaIO_4$ (30 g, 140 mmol), in H_2O (100 mL) with magnetic stirring. A white precipitate started to deposit immediately. After 4 h TLC showed a conversion of **10** into the

aldehyde **11** R_f 0.29 in hexane - EtOAc 1:2. The whole mixture was filtered on a sintered glass and the solid material was washed with EtOH. $NaBH_4$ (6 g, 158.7 mmol) was added to the cold (ice bath) filtrate and the mixture was stirred magnetically during 5 h at rt. The work-up and purification as described above furnished **12** (16.9 g, 76% for three steps). **12**: mp 85 °C (hexane - EtOAc), $[\alpha]_D^{26}$ + 69 (*c* 2.2, EtOH); lit.[73] 85.5-86 °C, $[\alpha]_D$ + 65 (c 1.0 EtOH). NMR: see L enantiomer **32**.

1-*O*-Acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose 15. The conversion of **12** into **15** was performed without isolation of the intermediates. The acetonide **12** (25 g, 132 mmol) in 70% AcOH (150 mL) was maintained at 80 °C during 3 h, whereupon the volatiles were removed by evaporation below 40 °C. Coevaporation with xylenes and drying on an oil pump furnished glassy material, which was dissolved in dry MeOH (400 mL) and the mixture was cooled down in ice bath and magnetically stirred. H_2SO_4 (97%, 2 mL) was added slowly and the mixture was left for 18 h in a refrigerator. Saturated aq $Ba(OH)_2$ was added to neutrality and precipitated $BaSO_4$ was removed by filtration through Celite. The volatiles were removed on an evaporator and on an oil pump. To the residue was added pyridine(300 mL), followed by BzCl (54 mL, 64.6 g, 460 mmol), added dropwise under magnetic stirring and with cooling in an ice bath and under a blanket of argon. After an overnight reaction, TLC ($CHCl_3$ - MeOH 9:1) showed two products having R_f 0.68 and 0.80, presumably both anomeric compounds **14**. Water (5 mL) was added to hydrolyze the excess of BzCl and 2 h later an extraction was performed (CH_2Cl_2 - ice - 5N HCl). The organic phase was washed with aq Na_2CO_3, water (2 x), dried and evaporated. To the residue (58 g) was added AcOH (40 mL) and Ac_2O (90 mL). The solution was chilled in an ice - salt bath and conc. H_2SO_4 (14 mL) was added dropwise under a blanket of argon and with manual swirling. The flask was closed with a rubber septum and left at ca. -5 °C for 10 h. TLC showed the compound **15** R_f 0.60 (hexane – EtOAc, 2:1) together with less and more polar byproducts. CH_2Cl_2 was added and the solution was transferred to a separatory funnel charged with ice and water and extraction was performed. The organic layer was washed with water (3 x), dried and evaporated. Addition of *i*-PrOH resulted in spontaneous crystallization. Filtration, washing with cold *i*-PrOH and prolonged drying on an oil pump furnished **15** (29.8 g, 45% cumulative yield), which was the best yield obtained.

mp 130-133 °C (*i*-PrOH), $[\alpha]_D^{26}$ +43.1 (*c* 2, $CHCl_3$); lit.[5] 131-132 °C, $[\alpha]_D$ +45.1 (*c* 1.32 $CHCl_3$). ^{1}H ($CDCl_3$): 8.01-7.32 (15H), 6.44 (1H, *s*), 5.91 (1H, dd, *J* 5.0 Hz and 6.4 Hz), 5.79 (1H, d, *J* 4.8 Hz), 4.82-4.75 (2H, unresolved), 4.52 (1H, dd, *J* 5.7 Hz and 13.9 Hz), 2.00 (3H, *s*). ^{13}C ($CDCl_3$): 169.2, 166.1, 165.5, 165.2, 133.8, 133.7, 133.4, 130.0, 129.9, 128.7, 128.6, 98.6, 80.2, 75.2, 71.6, 63.9, 21.0.

5-Methyluridine 1

A. via 2,3,5-tri-*O*-benzoyl-5-methyluridine 17. Thymine (35.9 g, 297 mmol), HMDS (400 mL) and $(NH_4)_2SO_4$ (0.5 g) were refluxed under argon until a clear solution was obtained (ca. 4 h). Excess of the reagent was evaporated. Co-evaporation with toluene was performed followed by drying on an oil pump. CH_3CN (700 mL) was added, followed by **15** (145 g, 288 mmol). The flask was immersed in ice-water bath and $SnCl_4$ (76 mL, 167 g, 649 mmol) was added using a syringe while maintaining magnetic stirring. After 1 h counting from the end of addition, the cooling bath was removed and the reaction proceeded at rt. After a total time of 6 h TLC showed that all **15** had reacted to form a more polar product **17** (R_f 0.85 and 0.31, respectively, in hexane-EtOAc, 2:1). The mixture was transferred to a separatory funnel charged with CH_2Cl_2 (700 mL) and ice-cold water (4 L), and extraction was performed. The organic layer was washed again with water, dried and the volatiles were evaporated. The hard crystalline mass thus obtained weighed 182 g. A small amount crude **17** was purified by chromatography in hexane-EtOAc, 2:1 to get an analytical sample. The abovementioned mass was dissolved in 1,4-dioxane (200 mL) with warming, and MeOH (600 mL) was added followed by few pieces of sodium and the mixture was left over the weekend. Amberlite IRA 120 H^+ was added to remove the Na cations, and was filtered off and washed with MeOH. Most of the volatiles were evaporated to a point that the

crystallization did not start. Water was added followed by $CHCl_3$ and extraction was performed three times to remove methyl benzoate. The water phase was evaporated until turbidity and was incubated in a refrigerator for 24 h. To the resulting semi-crystalline mass was added small volume of cold 96% EtOH. The crystals were removed by filtration, washed twice with cold 96% EtOH and with Et_2O. Final drying on oil pump gave **1** (67 g, ca. 90% for two steps). **17**: mp 161-164 °C (EtOH); lit.[48] mp 163-164 °C. Exact mass: calc. for $[C_{31}H_{11}N_2O_9$ + Na$]^+$= 593.1531, found: 593.1523. ^{1}H ($CDCl_3$): 9.59 (1H, exchangeable), 8.14-7.34 (15H, four groups of signals), 7.17 (1H, unresolved q, *J* 1Hz), 6.43 (1H, d, *J* 6 Hz), 5.92 (1H, dd, *J* 3 Hz and 6 Hz), 5.77 (1H, t, *J* 6 Hz), 4.87 (1H, dd, *J* 3 Hz and 12 Hz), 4.71-4.66 (1H, unresolved), 4.63 (1H, d, *J* 6 Hz), 1.58 (3H, unresolved d, *J* 1 Hz). ^{13}C ($CDCl_3$): 165.9, 165.3, 163.7, 150.4, 134.9, 133.7, 133.6, 133.5, 129.8, 129.7, 129.5, 129.1, 128.7, 128.5, 128.4, 112.1, 86.9, 80.4, 73.3, 71.3, 63.9, 12.0.

1: mp 180-182 °C (96% EtOH), $[\alpha]_D^{26}$ -8.9 (*c* 1.9, H_2O); lit.[48] 182-184 °C, lit.[74] $[\alpha]_D$ +4.5 (c 1 H_2O) for the L 5-methyluridine. ^{1}H (D_2O): 7.61 (1H, unresolved d, *J* 1 Hz), 5.81 (1H, d, *J* 4.5 Hz, 4.25 (1H, t, *J* 5.1 Hz), 4.15 (1H, t, *J* 5.2 Hz), 4.09-4.00 (1H, unresolved), 3.84 (1H, dd, *J* 3 Hz and *J* 12.5), 3.73 (1H, dd, *J* 4.2 and 12.9 Hz), 1.80 (3H, *s*). ^{1}H (DMSO-d_6): 11.30 (bs, exchangeable). ^{13}C (D_2O): 166.6, 151.9, 137.5, 111.6, 89.2, 84.3, 73.7, 69.5, 60.8, 11.7.

B. Via 2,3,5-tri-*O*-acetyl-5-methyluridine 18. Thymine (8.63 g, 77 mmol), hexamethyldisilazane (100 mL) and $(NH_4)_2SO_4$ (0.1 g) were refluxed under argon until the solution became clear (ca. 3 h). Excess of the HMDS was removed by evaporation and the oily residue was dried on an oil pump. Vacuums were broken using balloons with argon. To the residue was added CH_3CN (400 mL), followed by **16** (98% pure, 25 g, 77 mmol) and $SnCl_4$ (19.9 mL, 169 mmol) added via a syringe. The mixture was stirred magnetically during 11 h. TLC showed that **16** was consumed and more polar **18** was formed (R_f 0.65 and 0.18, respectively, in hexane-EtOAc, 1:1). Most of CH_3CN was evaporated below 30 °C and the residue was transferred to a separatory funnel charged with CH_2Cl_2 and ice cold water, and extraction was performed. The organic layer was washed with water, dried and the volatiles were evaporated to give a sticky oil. A small amount of this material was purified by chromatography in hexane-EtOAc, 1:1 to get a sample for analysis. The bulk of the crude extract was dissolved in 1,4-dioxane (50 mL) and MeOH (300 mL). A piece of Na was added and the mixture was left overnight. Amberlite IRA 120 H^+ was added and 15 min later was removed by filtration on sintered glass and washed with MeOH. Evaporation of the volatiles was conducted until spontaneous crystallization started. The flask was left in a refrigerator overnight. To a semi-solid mass was added cold 96% EtOH and the crystals were filtered off, washed with cold 96% EtOH and finally with Et_2O. Drying on oil pump furnished **1** (14.1 g, 69.5% for two steps). **18**: syrup; $[\alpha]_D^{26}$ -10.5 (*c* 1, CH_2Cl_2), lit.[75] $[\alpha]_D$ -14.6 (*c* 0.40 EtOH). ^{1}H (400 MHz, $CDCl_3$): 9.45 (1H, bs, exchangeable), 7.17 (1H, bs), 6.05 (1H, apparent d), 5.32 (2H, apparent d, *J* 4 Hz), 4.34-4.30 (3H, unresolved), 2.13, 2.10, 2.07 three s, 3H each, 1.91 (3H, unresolved d, *J* 1 Hz). ^{13}C (100 MHz, $CDCl_3$): 170.1, 169.7, 163.6, 150.5, 134.9, 111.9, 86.9, 79.8, 72.5, 70.3, 63.2, 20.7, 20.5, 20.4, 12.6.

1,2;5,6-Di-*O*-isopropylidene-α-L-glucofuranose 27 and 2,3;5,6-di-*O*-isopropylidene-L-mannofuranose 28 via 1-deoxy-1-nitro-L-glucitol 21 and 1-deoxy-1-nitro-L-mannitol 22. To a solution of NaOMe prepared from Na (3.7 g, 0.16 mol) and MeOH (200 mL) was added CH_3NO_2 (60 mL, 68.2 g, 1.1 mol) and L-arabinose (15 g, 0.1 mol). The whole was stirred magnetically under a protecting atmosphere of dry argon during 18 h. The precipitated sodium salts of the nitroglucitol and nitromannitol were filtered off, washed with cold MeOH, dissolved in cold (ca. 5°C) water 100 mL, and this solution was added dropwise during 10 min to a solution of conc. H_2SO_4 (20 mL) in water (25 mL) at rt. 5 min after the end of addition, neutralization was performed using a warm (ca. 45 °C) solution of $Ba(OH)_2$. Precipitated $BaSO_4$ was removed by filtration through a bed of Celite. The filtrate as demineralized through passage through a column of 200 mL of the Amberlite IRA 120 H^+ followed by the Amberlite IRA 410 OH^-. The resins were washed with water (2 x 100 mL). The combined

aqueous solutions were evaporated and the glassy residue obtained was dried on oil pump overnight. Acetone (250 mL) was added followed by conc. H_2SO_4 (7 mL) and the mixture was subjected to ultrasound[67] in a domdesstic cleansing bath for 50 min. This was performed in round-bottom flask even though it was recommended to use flat-bottom flasks due to smaller dispersion of the ultrasound. TLC showed the L-*manno* compound **28** R_f 0.46 and more polar L-*gluco* compound **27** R_f 0.40 (in hexane-EtOAc, 2:1). The reaction mixture was neutralized with cold conc. NH_4OH and precipitated $(NH_4)_2SO_4$ was removed by filtration through Celite. The solids were washed with acetone and the combined brownish solutions were evaporated to leave material (2 g) which was separated using vacuum-dry chromatography[68,69] (in hexane-EtOAc, 2:1) to yield less polar **28** (0.75 g) and more polar **27** (0.43 g). Due to the presence of impurities, no effort was made to isolate 1,2-*O*-isopropylidene-L-glucofuranose invariably present during acetonation of glucose.

27: mp 103-106 °C (hexane - EtOAc), $[\alpha]_D^{26}$ +17.5 (*c* 2, acetone); lit.[67] 105-106° C, $[\alpha]_D$ -18.7 (c not mentioned, acetone) for the D enantiomer. ^{1}H (400 MHz, $CDCl_3$): 5.94 (1H, d, *J* 4.0 Hz), 4.53 (1H, d, *J* 3.5 Hz), 4.37-4.31 (2H, unresolved), 4.16 (1H, dd, *J* 6.5 Hz and 8.8 Hz), 4.07 (1H, dd, *J* 2.8 Hz and 7.8 Hz), 4.00 (1H, dd, *J* 5.4 Hz and 8.8 Hz), 2.70 (1H, exchangeable, d, *J* 3.7 Hz), 1.68, 1.62, 1.53, 1.48 four s, 3H each. ^{13}C (100 MHz, $CDCl_3$): 111.6, 109.3, 105.0, 85.0, 81.1, 74.5, 72.8, 67.4, 26.6, 26.0, 25.0.

28: mp 120-124 °C (hexane - EtOAc), $[\alpha]_D^{26}$ -14.0 (*c 2*, EtOH); lit.[76] 121.5-122.5, $[\alpha]_D$ -15.7 (*c* 2.5 EtOH).

^{1}H ($CDCl_3$): 5.73 (s, residual water), 4.80 (1H, dd, *J* 3.7 Hz and 5.9 Hz), 4.61 (1H, d, *J* 5.9 Hz), 4.44-4.38 (2H, m), 4.18 (1H, dd, *J* 3.6 Hz and 7.1 Hz), 4.08 (1H, dd, *J* 5.9 Hz and 8.7 Hz), 4.05 (1H, dd, *J* 5.0 Hz and 8.7 Hz), 3.27 (1H, exchangeable, *J* 2.5 Hz), 1.47, 1.46, 1.36, 1.32 four s, 3H each. ^{13}C ($CDCl_3$) 112.6, 109.1, 101.2, 85.4, 80.1, 79.6, 73.2, 66.5, 26.8, 25.8, 25.1, 24.4.

1,2;5,6-Di-*O*-isopropylidene-α-L-allofuranose 29. Following the directions described for the D enantiomer, **7** and proportional quantities of the reagents, **27** (2.1 g) furnished **29** (1.45 g, 69%). Mp 74-77 °C (hexane - EtOAc), $[\alpha]_D^{26}$ -34.5 (*c* 2 $CHCl_3$), lit.[32] mp. 78-79° C, $[\alpha]_D$ -36.2 (*c* 0.5 $CHCl_3$). Exact mass: calc. for $[C_{12}H_{20}O_6]^+$= 260.1259, found: 260.1254; calc. for $[C_{12}H_{20}O_6 + Na]^+$ = 283.1152, found: 283.1149. ^{1}H (400 MHz, $CDCl_3$): 5.81 (1H, d, *J* 4.0 Hz), 4.62 (1H, dd, *J* 4.0 Hz and 5.0 Hz), 4.32 (1H, dt, *J* 5.0 Hz and 6.0 Hz and 6.0 Hz), 4.11-4.00 (3H, m), 3.83 (1H, dd *J* 5.0 Hz and 8.5 Hz), 2.63 (1H, exchangeable, *J* 9.0 Hz), 1.60, 1.48, 1.40, 1.38 four *s*, 3H each. ^{13}C (100 MHz, $CDCl_3$): 112.7, 109.7, 103.8, 79.6, 78.9, 75.5, 72.4, 65.7 26.5, 26.4, 26.2, 25.2.

1,2-*O*-Isopropylidene-α-L-ribofuranose 32

A. By degradation of 29. Following the directions described for the transformation of **9** into **12** using the Conditions B and proportional quantities of the reagents, L-allose **29** (1.1 g) was transformed into **32** (0.76 g, 69%) after chromatography in CH_2Cl_2 – MeOH, 20:1.

B. By desilylation of 37. To a solution of **37** (13.2 g, 38.8 mmol) in THF (50 mL) was added 1 M Bu_4NF in THF (41 mL). After 3 h, TLC showed that the substrate **37** (R_f 0.51, hexane-EtOAc 4:1) had been consumed to form a product **32** R_f 0.41 (CH_2Cl_2-MeOH 20:1). The solvent was evaporated and residual oil was purified by chromatography (CH_2Cl_2-MeOH 20:1) to give **32** (7.3 g, 89%). Mp 83-86 °C (hexane - EtOAc), $[\alpha]_D^{26}$ -42.0 (*c* 2.2, CH_2Cl_2); lit.[72] 84-86 ° C, $[\alpha]_D$ -45.3 (*c* 1.00 CH_2Cl_2). Exact mass: cal. for $[C_8H_{14}O_5 + Na]^+$= 213.0733, found: 213.0740. NMR^{1}H ($CDCl_3$): 5.81 (1H, d, *J* 3.7 Hz), 4.58 (1H, t, *J* 4.4 Hz), 4.02-3.96 (2H, *m*), 3.84 (1H, dt, *J* 3.1 Hz and 3.1 Hz and 4.4 Hz), 3.74 (1H, dd, *J* 3.6 Hz and 12.2 Hz), 2.47 (bs), 1.57, 1.37 3H each, two *s*. ^{13}C ($CDCl_3$): 112.7, 103.9, 80.6, 78.7, 70.8, 60.8, 26.5, 26.4.

1,2-*O*-isopropilidene-α-L-xylofuranose 34. To a magnetically stirred suspension of L-xylose (15 g, 100 mmol) in acetone (400 mL) was added dropwise conc. H_2SO_4 (15 mL, 27.6 g, 181 mmol) during 5 min. After 30 min counting from the end of addition, the mixture was cooled in ice-water bath and a solution of Na_2CO_3 (20 g, 189 mmol) in H_2O (190 mL) was slowly added while maintaining the internal temperature below 20 °C. After 2.5 h TLC showed nearly complete hydrolysis of the bis-acetonide **33** R_f ca 0.90 and formation of the diol **34** R_f

0.45 (CH_2Cl_2-MeOH 20:1). More Na_2CO_3 (10 g) was added to effect a complete neutralization. After stirring for 10 min the solid material was removed by filtration through sintered glass and was washed with acetone. Evaporation of acetone and chromatography in CH_2Cl_2-MeOH 20:1 furnished **34** (14 g, 74%); mp 37-38 °C; $[\alpha]_D^{26}$ +17 (*c* 3, $CHCl_3$); lit.[77] for the D enantiomer: oil, $[\alpha]_D$ -13.9 (*c* 0.34 $CHCl_3$). Alternative approach to get **34** was reported in the ref. 78. NMR ^{1}H (DMSO-d_6): 5.79 (1H, d, *J* 3.7 Hz), 5.13 (exchangeable, d, *J* 4.7 Hz), 4.61 (exchangeable, t, *J* 5.6 Hz), 4.36 (exchangeable, d, *J* 3.7 Hz), 4.00-3.92 (2H, unresolved), 3.64-3.57 (1H, m of five lines, *J* 5.6 Hz), 3.54-3.46 (1H, m of five lines, *J* 5.6 Hz), [after D_2O exchange: 3.62 (dd, *J* 5.0 Hz and 11.2 Hz; 3.50 (dd, *J* 6.1 Hz and 11.2 Hz)], 1.38 and 1.23 (two s, 3H each). ^{13}C (DMSO-d_6): 110.2, 104.2, 85.0, 81.3, 73.4, 58.8, 26.6, 26.1.

5-*O*-*t*Butyldimethylsilyl-1,2-*O*-isopropylidene-α-L-xylofuranose 35. The title compound was obtained as an oil following the published procedure[79] in higher yield, 90% vs. 75%. $[\alpha]_D^{26}$ +9.1 (*c* 4, $CHCl_3$); lit.[79] $[\alpha]_D$ +11 (*c* 5.4 $CHCl_3$)**.** ^{1}H (400 MHz, $CDCl_3$): 5.96 (1H, d, *J* ~ 0.8 Hz), 4.50 (1H, d, *J* 4.0 Hz), 4.37 and 4.33 (1H each, bs), 4.15-4.10 (3H, unresolved), 1.48 and 1.32 (3H each, two s), 0.90 (9H, s), 0.11 (6H, s). ^{13}C (100 MHz, $CDCl_3$): 111.5, 105.0, 85.6, 78.1, 77.1, 62.3, 26.8, 26.1, 25.7, 18.1, -5.5, -5.7.

5-*O*-*t*Butyldimethylsilyl-1,2-*O*-isopropylidene-α-L-ribofuranose 37. To a magnetically stirred suspension of CrO_3 (15.8 g, 158 mmol) in dry CH_2Cl_2 (250 mL) was added pyridine, (25.4 mL, 25 g, 316 mmol). The mixture warmed and 30 min later a solution of **35** (16 g, 52.6 mmol_ in CH_2Cl_2 (70 mL) was added followed by Ac_2O (14.9 mL, 16.1 g, 158 mmol). Slight warming took place again. 10 min later the reaction was quenched by addition of toluene – EtOAc mixture (1:1, 300 mL). The supernatant was drained and the black residue was washed with the same solvent mixture. The combined solutions were passed through a bed of silica gel prepared in toluene – EtOAc, 1:2. The fractions containing the ulose **36** R_f 0.44 (hexane – EtOAc 17:3) were pooled together and the volatiles were evaporated. Co-evaporation with toluene was performed to expel residual pyridine. After brief drying on an oil pump, 96% EtOH (150 mL) was added and the solution was cooled in an ice-bath. $NaBH_4$ (5.1 g , 135 mmol) was added in one portion while maintaining magnetic stirring. 2 h later TLC showed the product **37** R_f 0.51 (hexane – EtOAc 4:1). Acetone (10 mL) was added to destroy the excess of $NaBH_4$ and 30 min later most of the volatiles were removed by evaporation. The residue was taken up in CH_2Cl_2 and washed with water. After conventional work-up (drying, flirtation, evaporation) and chromatography in hexane – EtOAc, 5:1, **37** as an oil (12.1g, 75.6% for two steps) was obtained.

Exact mass: cal. for $[C_{14}H_{28}O_5Si + H]^+$= 305.1779, found: 305.1778.

$[\alpha]_D^{26}$ – 27.3 (*c* 2.1 $CHCl_3$); lit.[77] for the D enantiomer: $[\alpha]_D$ +30.7 (*c* 1.1 $CHCl_3$). NMR ^{1}H (400 MHz, $CDCl_3$): 5.79 (1H, d, *J* 3.8 Hz), 4.56 (1H, dd, *J* 4.1 Hz and 4.9 Hz), 3.99 (1H, ddd, *J* 5.2 Hz and 7.9 Hz and 9.5 Hz), 3.91 (1H, dd, *J* 4.1 Hz and 12.6 Hz), 3.84-3.78 (2H, unresolved), 2.41 (1H, exchangeable, *J* 9.6 Hz), 1.57, 1.37 two *s*, 3H each, 0.89 (9H, *s*), 0.08 and 0.07 (two *s*, 6H). ^{13}C (100 MHz, $CDCl_3$): 112.5, 104.2, 81.2, 78.8, 71.2, 61.8, 26.6, 25.9, 18.4, -5.3, -5.4.

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