

Lactose as cheap starting material for aldohexos-5-uloses preparation: synthesis of *L-ribo* and *D-lyxo* derivatives[‡]

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Abstract – Partially protected derivatives of *L-ribo*- and *D-lyxo*-aldohexos-5-ulose have been prepared starting from triacetone lactose dimethyl acetal derivatives. Key steps of the synthetic sequences are a) the synthesis of 4'-deoxy-4'-eno- and 6'-deoxy-5'-eno lactose derivatives, and b) the epoxidation-methanolysis of the above enol ethers to give 1,5-bis-glycopyranosides, masked form of the target 1,5-dicarbonyl hexoses.

Keywords: Lactose, L-ribo-Aldohexos-5-ulose, D-lyxo-Aldohexos-5-ulose, 1,5-Bis-glycopyranosides, Epimerization

1. Introduction

Aldohexos-5-uloses (**3**) represent an interesting, although yet poorly investigated class of dicarbonyl hexoses,² which are useful synthetic intermediates for the preparation of high added value compounds such as azasugars³ and cyclitols, as inositols⁴ and polyhydroxycyclopentanes.⁵

A useful approach (Chart 1) to aldohexos-5-uloses (**3**) is based on a selective C-5 oxidation by epoxidation of 4-deoxy-hex-4-eno⁶ (**1**) or 6-deoxy-hex-5-enopyranosides⁷ (**2**). In the frame of a general research aimed at the chemical valorisation of lactose as cheap and renewable starting material, we planned the preparation of a representative of each diastereoisomeric series of

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aldohexos-5-uloses and gained this goal preparing the *L-arabino*,^{7c,d} the *D-xylo*^{7e} and the *L-lyxo*^{7e} ones.

In this communication we present the preparation of partially protected *L-ribo* and *D-lyxo* derivatives following either the hex-4- and hex-5-enopyranoside approach. Some unexpected results observed during the planned synthetic routes are also described and discussed.

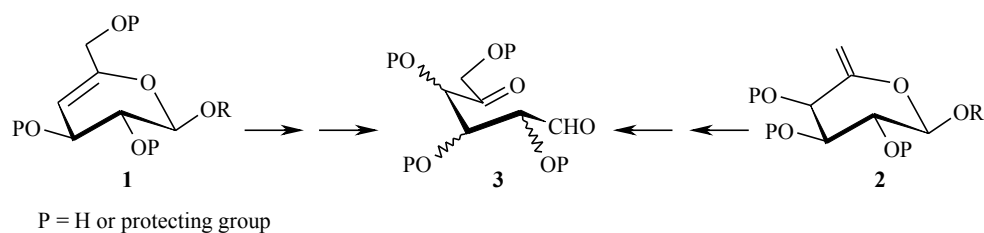


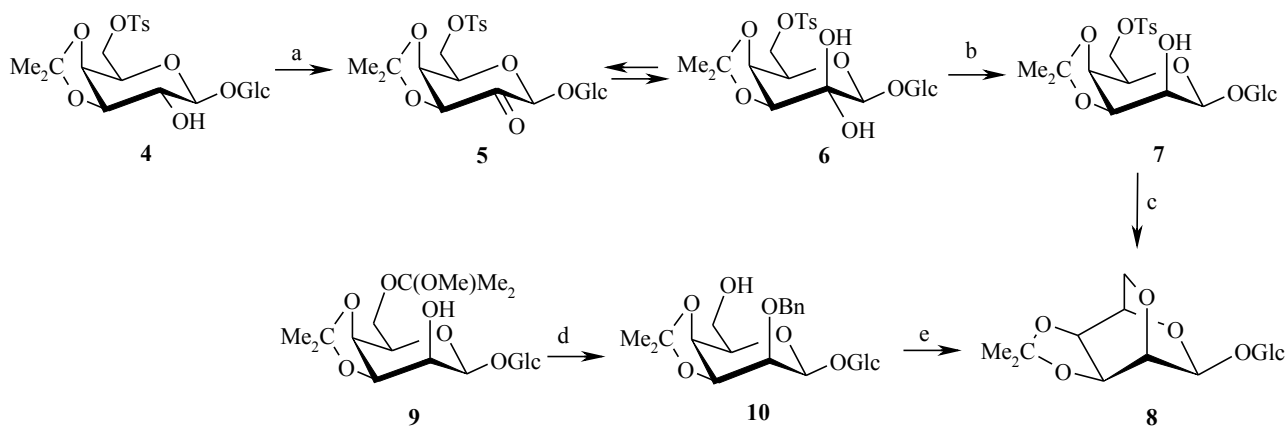
Chart 1. General approach to aldohexos-5-uloses from hex-4- and hex-5-enopyranosides

2. Results and Discussion

To prepare a representative of the remaining aldohexos-5-ulose stereoserries, the *ribo* one, from lactose, we decided to investigate a different strategy with respect to that reported starting from monosaccharide precursors⁸ and thus to epimerize the C-2' position on the *D*-galactopyranoside moiety in the earlier stage of the synthetic sequence (Scheme 1). Compound **4**^{7c,d} was subjected to an oxidation with the system TPAP and NMO in CH₂Cl₂ obtaining a crude mixture of the uloside **5** and its hydrate **6** (about 3:1). The reduction (NaBH₄/MeOH) of the crude mixture gave in an overall 90% yield the corresponding *D-talo*-derivative **7** as the sole isolated diastereoisomer. The C-2' epimerization was firmly confirmed by the changes in the $J_{1,2'}$ and $J_{2,3'}$ coupling constant values from 8.1 and 6.9 Hz in compound **4**^{7c,d} to 2.5 and 4.1 Hz.

The tosylate **7** was then transformed into 6-deoxy-hex-5-enol ether by treatment with NaH in DMF under the conditions reported^{7c,d} for the transformation of the *galacto* epimer **4**, but only the 2,5-anhydro derivative **8** was obtained in almost quantitative yield (96%) as a result of an intramolecular S_N2 displacement. The presence of this concurrent pathway was not unexpected in view of the favourable axial orientation of the C-2' alkoxide. Furthermore, the conformational

flattening caused by the 3',4'-cis-dioxolane ring, and the high stability of the 2,5-dioxabicyclo[2,2,2]octane system³ could explain the exclusive formation of **8**.

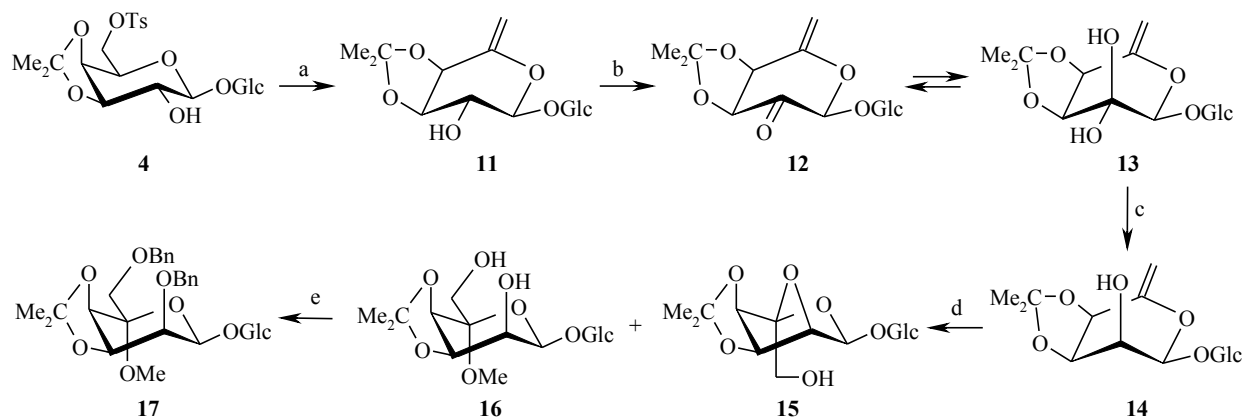


Scheme 1. Attempts to prepare a β -D-*talo*-6-deoxy-hex-5-enopyranoside. Reagent and conditions: (a) TPAP, NMO, CH₂Cl₂, 4Å, rt, 1 h (91%); (b) NaBH₄, MeOH, rt, 1 h, (90% from **4**); (c) NaH, DMF, rt, 1.5 h (96%); (d) BnBr, NaH, DMF, rt, 40 min, then 5% aq HCl, CH₂Cl₂ (90%); (e) NaH, DMF, Im₂SO₂, -30 °C, 3 h (96%).

In order to suppress this unwanted reaction, we considered the preparation of a 6'-*O*-sulfonate analogous of **4**, protected as benzyl ether to HO-2'. First was prepared the alcohol **10**, which was easily obtained in 90% yield by treatment (Scheme 1) of the known alcohol **9**¹⁰ with NaH and BnBr in dry DMF, followed by selective removal of the mixed acetal 6'-*O* protecting group by mild acid treatment of the crude benzylation product in a biphasic system (CH₂Cl₂-5% aqueous HCl). However, the subsequent introduction of a leaving group in the primary position failed using Ts₂O in pyridine leaving alcohol **10** completely unchanged, probably because of the steric hindrance of either the 3',4'-*O*-isopropylidene and the 2'-*O*-benzyl ether protecting group. An effective activation of the alcohol **10** was obtained using the conditions (NaH-DMF followed by Im₂SO₂) usually employed for the preparation of imidazylates,¹¹ but, surprisingly, derivative **8** was again obtained in excellent yield (96%) as the sole reaction product. Although intramolecular substitution involving a benzyl ether group as nucleophile are known,¹² the observed behaviour corroborates the above hypothesis of a high conformational strain due to the *talo*-configuration and the 3',4'-*O*-isopropylidene fusion which implies this reaction.

³ The high stability of this kind of bicyclooctane system originates the unexpected high preference for the ring-closed hemiacetal form of 6-OH-3,4-O-isopropylidene- β -D-*lyxo*-2-ulopyranosides (Ref. 9).

This problem was overtaken following a different strategy, which involved first the elimination reaction and then the C-2' inversion (Scheme 2). Compound **4** was treated with NaH in DMF and the hex-5-enopyranoside **11** was obtained in 85% yield. However, the oxidation of **11** with the TPAP-NMO system was much less evident than expected.

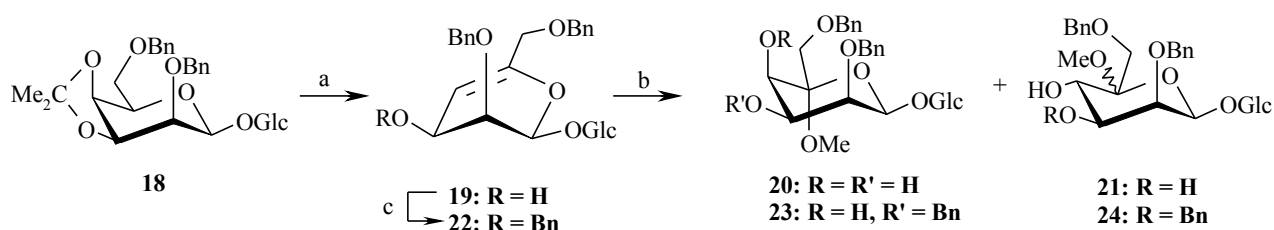


Scheme 2. Synthesis of *L-ribo*-hexos-5-ulose-1,5-bis-glycopyranosides through the hex-5-enopyranosides approach. Reagent and conditions: (a) NaH, DMF, rt, 3.2 h (85%); (b) TPAP, NMO, 9:1 CH₂Cl₂-CH₃CN, 4Å, rt, 2.5 h; (c) NaBH₄, MeOH, -40 °C, 2.5 h, (50% from **11**); (d) MCPBA, MeOH, rt, 4.5 h (**15**: 13% + **16**: 47%); (e) KOH, BnBr, 18-crown-6, rt, 4.5 h (94%).

A complete conversion of the alcohol **4** into a 1:4 mixture of the uloside **12** and its hydrate **13** was obtained operating at low temperature (0 °C) and employing 9:1 CH₂Cl₂-CH₃CN as the solvent, which is reported in some cases to enhance the catalytic turnover.¹³ A reduced stability of the hex-5-eno-2-ulopyranoside **12-13** was evidenced by the loss of material observed during the silica gel chromatographic purification, lowering the yield to a rather modest 55%. The following reduction step was accomplished with high stereoselectivity but in a rather modest overall yield (50%) treating a crude sample of **12-13** with NaBH₄ in MeOH at -40 °C. When the reduction was run at higher temperatures, a substantial drop of the yield was observed, pointing out again the low stability of **12-13**. Furthermore, the presence of some fragmentation pathways was evidenced by the formation of appreciable amounts of the known¹⁴ 2,3:5,6-di-*O*-isopropylidene-*aldehydo* dimethyl acetal (not shown). The *L-ribo* configuration of the 6'-deoxy-hex-5'-enopyranoside **14** was well confirmed by the *J*_{1,2'} coupling constant value (3.3 Hz), which highlighted the new H-1', H-2' axial-equatorial disposal.

Compound **14** was then subjected to the epoxidation-methanolysis reaction (MCPBA-MeOH) in order to oxidise the C-5' enol ether group. This reaction gave some unexpected results, showing the formation of **15** (13%) and of only one of the two possible C-5' anomers (**16**, 47%). The C-5' configuration of **15** and **16** was assigned on the basis of 1D-NOE experiments. Thus, the irradiation of the H-1' resonance gave enhancements of the H-3' and 5'-OMe resonances for **16**, whereas for **15** was clear the enhancement of the H-3', H-6'a and H-6'b resonances. On the basis of the epoxidation-methanolysis results of analogous *exo*-glycals,⁷ one could suppose the formation of two non isolable epoxide intermediates which were opened in an *anti* fashion, in the case of the β -epoxide by an intermolecular methanol α -attack and in the case of the α one by an intramolecular 2'-OH β -attack. Derivative **16** was then benzylated by treatment with powder KOH, BnBr in wet THF and led to **17** in excellent yield (94%).

Although with this sequence the targeted 1,5-bis-*L*-ribo-hexopyranosides were obtained, the rather modest yields of the overall process (about 20% from the tosylate **4**) and the chemical fragility of some intermediates pushed us to explore the complementary hex-4-enopyranoside approach illustrated in the Scheme 3. The known compound **18**¹⁰ was subjected to an acetone elimination employing *t*-BuOK in THF (reflux, 15 min) and **19** was obtained in good yield (81%).



Scheme 3. Synthesis of *L*-ribo-hexos-5-ulose 1,5-bis-glycopyranosides and *D*-lyxo-hexos-5-ulose 1,5-bis-glycopyranosides through the hex-4-enopyranoside approach. Reagents and conditions: (a) *t*-BuOK, THF, reflux, 15 min, (81%); (b) MCPBA, MeOH, rt, 24 h (**20**: 58%, **21**: 15%, **23**: 17%, **24**: 48%); (c) BnBr, NaH, DMF, rt, 30 min, (88%).

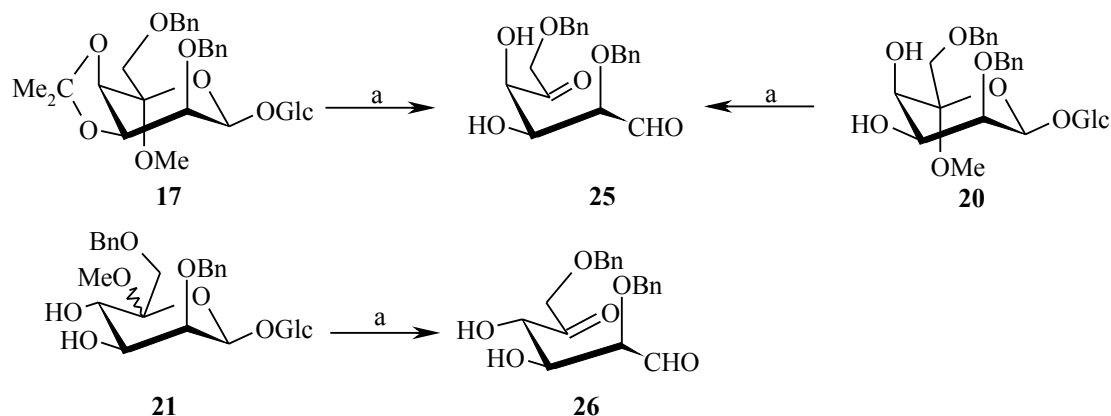
It is noteworthy to underline that the acetone elimination on **18** required milder conditions, with respect to those used for 3,4-*O*-isopropylidene-*D*-galactopyranosides^{7c,d} analogues, giving rise to complex mixtures of inseparable products using *t*-BuOK in DMF at 80 °C or lower temperatures.

Probably the enhanced reactivity of the *talo* series is due to the unfavourable *syn* interaction between the axial 2'-OR group and the 3',4'-*O*-isopropylidene one, determining a higher strain release in the acetone elimination. Derivative **19** was subjected to the epoxidation-methanolysis reaction (MCPBA-MeOH) and gave the two 1,5-bis-glycosides **20** and **21**, easily isolated in 58% and 15% yield, respectively, through chromatography. The structure of **20** was confirmed by NMR spectra ($J_{3',4'}$ 3.0 Hz) and its C-5' configuration by its transformation into **17** through an acid promoted transacetalation reaction with TsOH in DMP (93% yield). In the case of **21** the *D*-*lyxo* configuration was easily assigned by NMR spectra ($J_{3',4'}$ 10.0 Hz), but the anomeric C-5' configuration could not be inferred by routine NMR analysis.

The rather low diastereoselection (*L*-*ribo*/*D*-*lyxo* ratio of about 4:1) observed in the epoxidation-methanolysis is somewhat unexpected owing to the general operativity of a complete *syn* directing effect of a free allylic hydroxyl group in the epoxidation reaction.¹⁵ The presence of an appreciable amount of the bis-glycoside **21** arising from a peroxide attack *anti* to the allylic 3'-OH group followed by epoxide opening by MeOH, could reasonably be attributed to the steric hindrance of the axial 2'-OBn, which shields the β face of **19**. Reasoning on this point, we tried to reverse the stereoselectivity of the 1,5-bis-glycosides formation performing the epoxidation-methanolysis on the 3'-*O*-benzyl derivative **22**, easily obtained in good yield by routine benzylation of **19**. This objective was achieved, although in a not complete manner, obtaining a mixture of the *D*-*lyxo*- and *L*-*ribo*-1,5-bis-pyranosides **24** and **23** in an about 3:1 ratio and in an overall 65% yield. The C-5' configuration of **23** is suggested considering the close analogy between its NMR data with those of **20**.

The final transformation of 1,5-bis-glycopyranosides into hexos-5-uloses exposing both the two dicarbonyl groups was performed by acid hydrolysis (90% aq CF₃COOH in 4:1 CH₃CN-water at 50 °C) of the two *L*-*ribo* derivatives **17** and **20** (Scheme 4), obtaining, after separation from *D*-glucose, the known dicarbonyl hexose **25**⁸ in satisfactory isolated yield (66-73%). In an identical way bis-glycoside **21** gave **26**, that is the enantioform of the previously reported 2,6-*O*-dibenzyl-*L*-*lyxo*-

aldohexos-5-ulose, in 72% yield as an anomeric mixture of 1,4-furanose tautomers (**26 α** :**26 β** 66:34).¹⁶



Scheme 4. Synthesis of 2,6-di-*O*-benzyl-*L*-ribo- and 2,6-di-*O*-benzyl-*D*-lyxo-hexos-5-uloses. Reagent and conditions: (a) 90% aq CF₃COOH, 4:1 CH₃CN-H₂O, 50 °C, 4-5 h (**25**: 66% from **17** and 73% from **20**, **26**: 72%).

In conclusion, with this work the usefulness of lactose as starting material for accessing all the diastereoisomeric series of aldohexos-5-uloses has been demonstrated, opening the way to a new synthetic channel for the valorisation of whey, a waste product of the cheese industry, into sophisticated chemical synthons for the preparation of biologically active compounds. Some examples of synthetic use of hexos-5-uloses belonging to the *lyxo*-series are reported,^{4b,17} while synthetic elaboration of *L*-ribo-hexos-5-ulose derivatives are currently under investigation in our group and will be reported in a forthcoming paper.⁴

3. Experimental

3.1. General methods

General methods are those reported in Ref. 19. Compound **4**,^{7c} **9**,¹⁰ and **18**¹⁰ were prepared according to the described procedures.

⁴The stereoselective synthesis of *cis*- and *epi*-inositol derivatives have been recently synthesised starting from *L*-ribo-hexos-5-ulose precursors (Ref. 18).

3.2. 3,4-*O*-Isopropylidene-6-*O*-*p*-toluenesulfonyl- α -*D*-lyxo-hex-2-ulopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-*D*-glucose dimethyl acetal (**5**) and its hydrate (**6**)

A suspension of **4**^{7c} (2.02 g, 3.00 mmol) in dry CH₂Cl₂ (20 mL) and pre-dried 4-methylmorpholine-*N*-oxide (NMO) (618 mg, 5.30 mmol) containing 4Å powdered molecular sieves (240 mg) was stirred under argon atmosphere for 30 min at room temperature. Tetrapropylammonium perruthenate (TPAP) (106 mg, 10%) was added and the resulting green mixture was stirred at room temperature (1 h). The reaction mixture was filtered through alternate paths of Celite and silica gel and extensively washed with CH₂Cl₂ and then EtOAc. The combined organic phases were concentrated under diminished pressure to give a syrup (2.00 g) constituted (¹³C NMR, CDCl₃) by a mixture of **5** and **6** in a ratio of about 3:2 estimated on the basis of the relative C-1' NMR signal intensities (δ 99.5 and 103.7 respectively). Flash chromatographic purification of a crude sample, eluting with 9:1 CH₂Cl₂-Me₂CO, afforded a 3:1 mixture of **5** and **6** (1.81 g, combined yield about 91%) as a colourless syrup; $[\alpha]_D$ -9.9 (*c* 1.17, CHCl₃); *R*_f 0.45 (9:1 CH₂Cl₂-Me₂CO); selected ¹³C NMR (50 MHz, CDCl₃) signals: *major component 5*: δ 196.4 (C-2'), 144.9, 132.0 (2 \times Ar-C), 111.1, 110.2, 107.7 (3 \times Me₂C), 104.7 (C-1), 99.5 (C-1'), 77.4, 77.3, 77.0, 76.9 (C-4, C-2, C-3, C-5), 75.7, 74.7 (C-3', C-4'), 70.2 (C-5'), 67.5 (C-6'), 64.8 (C-6), 55.4, 53.1 (2 \times OMe-1), 27.0, 26.6, 25.9, 25.8, 25.7, 25.3 (3 \times CMe₂), *minor component 6*: δ 144.6, 132.1 (2 \times Ar-C), 110.1, 109.7, 107.9 (3 \times Me₂C), 104.3 (C-1), 103.7 (C-1'), 90.0 (C-2'), 77.6, 77.5, 77.2, 76.3 (C-4, C-2, C-3, C-5), 74.4, 72.2 (C-3', C-4'), 70.0 (C-5'), 68.1 (C-6'), 64.2 (C-6), 55.8, 52.6 (2 \times OMe-1), 26.8, 26.1, 25.6, 25.5, 24.4, 24.0 (3 \times CMe₂). Cluster of signals for both components: δ 129.7, 127.6 (Ar-CH), 21.2 (MePh).

3.3. 3,4-*O*-Isopropylidene-6-*O*-*p*-toluenesulfonyl- β -*D*-talopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-*D*-glucose dimethyl acetal (**7**)

A crude mixture of **5** and **6** (800 mg) was dissolved in dry MeOH (14 mL), the solution was cooled to 0 °C, treated with NaBH₄ (228 mg, 6.03 mmol) and gently warmed to room temperature. The reaction mixture was stirred until the TLC analysis (9:1 CH₂Cl₂-Me₂CO) showed the complete disappearance of the starting material (1 h), treated with satd aq NH₄Cl (10.0 mL), stirred for 15 min and extracted with CH₂Cl₂ (4 \times 30 mL). The collected organic extracts were dried, filtered and concentrated under diminished pressure to give a residue (740 mg), which was directly subjected to flash chromatographic purification (3:2 hexane-EtOAc) affording **7** (728 mg, 90% yield calculated from **4**) as a colourless syrup; $[\alpha]_D$ -2.2 (*c* 1.16, CHCl₃); *R*_f 0.40 (9:1 CH₂Cl₂-Me₂CO); ¹H NMR

(200 MHz, CDCl₃): δ 7.80, 7.36 (AA'XX' system, 4H, Ar-H), 4.93 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1'), 4.47 (dd, 1H, $J_{2,3}$ 7.1 Hz, H-2), 4.38 (d, 1H, $J_{1,2}$ 6.2 Hz, H-1), 4.32 (dd, 1H, $J_{3,4}$ 6.7 Hz, H-3'), 4.28-4.00 (m, 7H, H-4', H-6'a, H-6'b, H-4, H-5, H-6a, H-6b), 3.93 (m, 1H, H-5'), 3.92 (dd, 1H, $J_{3,4}$ 1.4 Hz, H-3), 3.79 (dd, 1H, $J_{2,3}$ 4.1 Hz, H-2'), 3.42, 3.41 (2s, each 3H, 2 \times OMe), 2.46 (s, 3H, MePh), 2.45 (bs, 1H, OH), 1.49, 1.42, 1.37, 1.36, 1.35, 1.28 (6s, each 3H, 3 \times CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 144.8, 132.4 (2 \times Ar-C), 129.8, 127.8 (Ar-CH), 110.1, 110.1, 107.8 (3 \times CMe₂), 104.7 (C-1), 100.5 (C-1'), 77.9, 77.7, 76.0, 74.7 (C-2, C-4, C-3, C-5), 73.7, 71.0, 70.0 (C-3', C-4', C-5'), 68.3 (C-6'), 66.5 (C-2'), 64.8 (C-6), 55.6, 53.0 (2 \times OMe), 27.1, 26.2, 26.1, 25.4, 25.1, 24.8 (3 \times CMe₂), 21.5 (MePh). Anal. Calcd for C₃₀H₄₆O₁₄S: C, 54.37; H, 7.00. Found: C, 54.41; H, 7.08.

3.4. 2-O-Benzyl-3,4-O-isopropylidene- β -D-talopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (**10**)

A suspension of pre-washed (hexane) 60% NaH in mineral oil (417 mg, 10.4 mmol) in dry DMF (20 mL) was cooled to 0 °C under and treated, under argon atmosphere with a solution of **9**¹⁰ (2.02 g, 3.48 mmol) in dry DMF (30 mL). The mixture was warmed to room temperature and stirred for 10 min, cooled again to 0 °C and treated with BnBr (0.66 mL, 5.57 mmol), warmed to room temperature and further stirred until the starting material was consumed (40 min, TLC, 3:7 hexane-EtOAc). MeOH (5 mL) and water (20 mL) were slowly added and the mixture was extracted with CH₂Cl₂ (4 \times 20 mL). The collected organic layers were treated with 5% aq HCl until TLC analysis (3:7 hexane-EtOAc) revealed the complete disappearance of the product with R_f 0.58 and the formation of a slower-moving product (R_f 0.39). The aqueous phase was further extracted with CH₂Cl₂ (20 mL) and the organic extracts were dried, filtered and concentrated under diminished pressure. The residue was subjected to flash chromatography, eluting with 1:1 hexane-EtOAc, to give **10** (1.87 g, 90% yield), as a colourless syrup; $[\alpha]_D^{25} +19.3$ (c 1.23, CHCl₃); R_f 0.17 (4:6 hexane-EtOAc); ¹H NMR (200 MHz, CDCl₃): δ 7.45-7.22 (m, 5H, Ar-H), 4.89, 4.83 (AB system, 2H, $J_{A,B}$ 12.8 Hz, CH₂Ph), 4.71 (dd, 1H, $J_{2,3}$ 7.9 Hz, H-2), 4.57 (s, 1H, H-1'), 4.38 (d, 1H, $J_{1,2}$ 6.7 Hz, H-1), 4.30-4.15 (m, 2H, H-3', H-4'), 4.15-4.05 (m, 3H, H-5, H-6a, H-6b), 3.95 (m, 2H, H-6a', H-6b'), 3.90 (dd, 1H, $J_{3,4}$ 1.4 Hz, H-3), 3.81 (m, 1H, H-5'), 3.71 (d, 1H, $J_{2,3}$ 5.5 Hz, H-2'), 3.69 (m, 1H, H-4), 3.48 (s, 6H, 2 \times OMe), 1.50, 1.35, 1.34, 1.31, 1.26, 1.25 (6s, each 3H, 3 \times CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 138.1 (Ar-C), 127.7-126.9 (Ar-CH), 110.2, 109.5, 107.4 (3 \times CMe₂), 106.4 (C-1), 102.1 (C-1'), 78.2, 77.5, 74.9, 74.8, 74.7, 74.6 (C-2, C-3, C-4, C-5, C-3', C-4'), 74.0 (CH₂Ph), 72.0 (C-2'), 70.8 (C-5'), 64.6 (C-6), 62.0 (C-6'), 57.0, 53.1 (2 \times OMe-1), 26.5, 26.3,

26.1, 25.5, 25.4, 25.2 ($3 \times CMe_2$). Anal. Calcd for $C_{30}H_{46}O_{12}$: C, 60.19; H, 7.74. Found: C, 60.25; H, 7.81.

3.5. 2,6-Anhydro-3,4-*O*-isopropylidene- β -D-talopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**8**)

3.5.1. From **7** with NaH in DMF.

To a suspension of pre-washed (hexane) 60% NaH in mineral oil (90 mg, 1.51 mmol) in dry DMF (2.0 mL) was added, under argon atmosphere at 0 °C, a solution of **7** (200 mg, 0.30 mmol) in dry DMF (5 mL). After warming to room temperature and 1.5 h stirring, TLC analysis (3:7 hexane-EtOAc) showed the disappearance of the starting material. MeOH (5 mL) and water (13 mL) were slowly added and the mixture was extracted with Et₂O (2 \times 30 mL). The collected organic layers were dried, filtered and concentrated under diminished pressure. The residue (150 mg) was purified by flash chromatography (3:7 hexane-EtOAc) to give **8** (142 mg, 96% yield) as a colourless syrup; $[\alpha]_D -19.6$ (c 1.2, CHCl₃); R_f 0.55 (3:7 hexane-EtOAc); ¹H NMR (200 MHz, CD₃CN): δ 5.04 (d, 1H, $J_{1,2}$ 1.7 Hz, H-1'), 4.47 (t, 1H, $J_{2,3}$ 6.6 Hz, H-2), 4.36 (d, 1H, $J_{1,2}$ 6.6 Hz, H-1), 4.34 (m, 1H, H-5), 4.22 (dd, 1H, $J_{3,4}$ 6.1 Hz, H-3'), 4.18 (dd, 1H, $J_{4,5}$ 4.6 Hz, H-4'), 4.08 (dd, 1H, $J_{3,4}$ 1.5 Hz, H-3), 4.05-3.90 (m, 5H, H-5', H-6'a, H-6'b, H-6a, H-6b), 3.89 (dd, 1H, $J_{4,5}$ 4.5 Hz, H-4), 3.79 (t, 1H, $J_{2,3}$ 1.7 Hz, H-2'), 3.38, 3.36 (2s, each 3H, 2 \times OMe), 1.48, 1.39, 1.34, 1.33, 1.32, 1.28 (6s, each 3H, 3 \times CMe_2); ¹³C NMR (200 MHz, CD₃CN): δ 112.5, 111.3, 109.0 (3 \times CMe_2), 106.4 (C-1), 99.8 (C-1'), 78.6, 78.0, 76.8, 76.6 (C-2, C-4, C-3, C-5), 74.7, 71.3, (C-2', C-3'), 69.8, 68.0 (C-4', C-5'), 65.8 (C-6), 63.3 (C-6'), 56.5, 54.0 (2 \times OMe), 27.7, 26.9, 26.7, 26.1, 25.3, 24.9 (3 \times CMe_2). Anal. Calcd for $C_{23}H_{38}O_{11}$: C, 56.32; H, 7.81. Found: C, 56.41; H, 7.90.

3.5.2. From **10** with NaH, Im₂SO₂ in DMF

To a suspension of pre-washed (hexane) 60% NaH in mineral oil (95 mg, 2.37 mmol) in dry DMF (2.4 mL) was added, under argon atmosphere at 0 °C, a solution of **10** (284 mg, 0.47 mmol) in dry DMF (9.5 mL). The mixture was warmed to room temperature and stirred for 30 min, then cooled to -30 °C and treated with *N,N*-sulfonyl-diimidazole (Im₂SO₂) (142 mg, 0.71 mmol, 1.5 equiv). After 3 h at -30 °C, TLC analysis (EtOAc) showed the disappearance of the starting material, and the mixture was cooled to -40 °C, treated with MeOH and water (5 mL) and extracted with Et₂O (2 \times 20 mL). The organic extracts collected, dried, filtered and concentrated under diminished pressure afforded a residue (240 mg) which was subjected to a filtration over silica gel (3:7 hexane-EtOAc) to give pure **8** (221 mg, 96% yield) as a colourless syrup, identical to the above described sample.

3.6. 6-Deoxy-3,4-*O*-isopropylidene- α -L-arabino-hex-5-enopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**11**)

A suspension of pre-washed (hexane) 60% NaH in mineral oil (1.91 g, 47.4 mmol) in dry DMF (60 mL) was cooled to 0 °C and treated under argon atmosphere with a solution of **4**^c (6.30 g, 9.51 mmol) in dry DMF (45 mL). The mixture was gently warmed to room temperature, left under stirring until **4** was consumed (TLC: 3:7 hexane-EtOAc). After 3.2 h the reaction mixture was cooled to 0 °C, treated with crushed ice (50 mL) and extracted with Et₂O (5 \times 40 ml). The collected organic extracts were dried, filtered and concentrated under diminished pressure to give a residue (4.83 g), which was directly subjected to flash chromatographic purification (7:3 hexane-EtOAc + 0.1 % Et₃N) to give **11** (3.96 g, 85% yield); as a clear syrup; $[\alpha]_D$ -22.8 (*c* 1.3, CHCl₃); *R*_f 0.22 (7:3 hexane-EtOAc); ¹H NMR (200 MHz, CDCl₃): δ 4.85 (d, 1H, *J*_{1',2'} 8.0 Hz, H-1'), 4.82 (bt, 1H, *J*_{6'a,6'b} = *J*_{4',6'a} 1.0 Hz, H-6'a), 4.73 (bt, 1H, *J*_{6'a,6'b} = *J*_{4',6'b} 1.1 Hz, H-6'b), 4.67 (dd, 1H, *J*_{1,2} 6.2 Hz, *J*_{2,3} 7.7 Hz, H-2), 4.65 (m, 1H, H-4'), 4.48 (d, 1H, H-1), 4.29 (ddd, 1H, *J*_{5,6a} 6.0 Hz, *J*_{4,5} 2.0 Hz, H-5), 4.17 (m, 1H, H-4), 4.28-4.13 (m, 2H, H-3', H-6a), 4.07 (dd, 1H, *J*_{6a,6b} 8.7 Hz, *J*_{5,6b} 6.9 Hz, H-6b), 3.99 (dd, 1H, *J*_{3,4} 1.5 Hz, H-3), 3.76 (t, 1H, *J*_{2,3'} 8.0 Hz, H-2'), 3.50, 3.51 (2s, each 3H, 2 \times OMe), 1.60, 1.57, 1.48, 1.47, 1.46, 1.39 (6s, each 3H, 3 \times CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 153.1 (C-5'), 110.9, 110.1, 108.1 (3 \times CMe₂), 105.0 (C-1), 103.1 (C-1'), 96.8 (C-6'), 78.9, 77.8, 77.2 76.9, (C-2, C-3, C-4, C-5), 74.8, 73.8, 72.8 (C-2', C-3', C-4'); 64.4 (C-6), 55.9, 52.9 (2 \times OMe), 27.3, 27.7, 26.3, 25.5, 25.4, 23.9 (3 \times CMe₂). Anal. Calcd for C₂₃H₃₈O₁₁: C, 56.32; H, 7.81. Found: C, 56.13; H, 7.77.

3.7. Oxidation-reduction of 6-deoxy-3,4-*O*-isopropylidene- α -L-arabino-hex-5-enopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**11**)

3.7.1 Oxidation of **11**

A suspension of **11** (1.02 g, 2.08 mmol) in dry 9:1 CH₂Cl₂-CH₃CN mixture (14 mL) and pre-dried 4-methylmorpholine-*N*-oxide (NMO) (410 mg, 3.5 mmol) containing 4Å powdered molecular sieves (380 mg) was stirred under argon for 30 min at room temperature. Tetrapropylammonium perruthenate (TPAP) (73 mg, 2.08 mmol, 10%) was added and the resulting green mixture was stirred at room temperature. After 2.5 h, TLC analysis (9:1 CH₂Cl₂-acetone) showed the complete disappearance of **11**, and the reaction mixture was filtered through alternate paths of Celite and silica gel and extensively washed first with CH₂Cl₂ and then with EtOAc. The combined organic phases were concentrated under diminished pressure to give a syrup (882 mg, combined yield about

84%) constituted (^{13}C NMR, C_6D_6) by a mixture of **12** and its hydrate **13** in a ratio of 1:4 established on the basis of the integration of the H-1' signals (δ 5.15 and 5.64 respectively). The flash chromatographic purification (7:3 hexane-EtOAc) of a sample (210 mg), gave a 1:1 mixture of **12** and **13** (135 mg, combined yield about 55%); as a clear syrup; $[\alpha]_{\text{D}} -19.4$ (c 1.18, CHCl_3); R_f 0.09 (7:3 hexane-EtOAc); Selected ^1H NMR (200 MHz, C_6D_6) signals *component 12*: δ 5.17, 4.85 (2 bs, each 1H, H-6'a, H-6'b), 5.15 (s, 1H, H-1'), 4.76 (dd, 1H, $J_{2,3}$ 7.5 Hz, H-2), 4.28 (d, 1H, $J_{1,2}$ 5.7 Hz, H-1), 4.15 (dd, 1H, $J_{3,4}$ 1.5 Hz, H-3), 3.30, 3.19 (2s, each 3H, 2 x OMe-1); *component 13*: δ 5.64 (s, 1H, H-1'), 4.96 (dd, 1H, $J_{2,3}$ 7.9 Hz, H-2), 4.37 (d, 1H, $J_{1,2}$ 5.7 Hz, H-1), 4.08 (dd, 1 H, $J_{3,4}$ 1.7 Hz, H-3), 4.85, 4.69 (2 bs, each 1H, H-6'a, H-6'b), 3.25, 3.17 (2s, each 3H, 2 x OMe-1); selected ^{13}C NMR (50 MHz, C_6D_6) signals: *component 12*: δ 197.8 (C-2'), 152.6 (C-5'), 111.6, 110.3, 108.3 ($3 \times \text{CMe}_2$), 105.7 (C-1), 102.4 (C-6'), 100.4 (C-1'), 78.3, 78.1, 77.0, 76.4, 76.3, 75.3 (C-3, C-2, C-4, C-5, C-3', C-4'), 65.3 (C-6), 56.6, 53.7 ($2 \times \text{OMe-1}$); *component 13*: δ 154.7 (C-5'), 112.2, 110.6, 108.5 ($3 \times \text{CMe}_2$), 106.1 (C-1), 103.0 (C-1'), 94.2 (C-6'), 91.4 (C-2'), 78.6, 78.4, 78.2, 77.6 (C-2, C-4, C-5, C-3'), 75.6, 73.1 (C-3, C-4'), 65.3 (C-6), 56.7, 53.3 ($2 \times \text{OMe-1}$); Cluster of signals for both components: δ 27.5-24.9 ($3 \times \text{CMe}_2$).

3.7.2 Reduction of the 12-13 mixture

A solution of crude **12-13** mixture in dry MeOH (15 mL) was treated, under argon atmosphere, at -40 °C with NaBH_4 (132 mg, 3.5 mmol) and then stirred at the same temperature until TLC analysis (9:1 CH_2Cl_2 - Me_2CO) revealed the complete disappearance of the starting material (2.5 h). The mixture was diluted with CH_2Cl_2 (20 mL) and treated with water (20 mL), warmed to room temperature and extracted with CH_2Cl_2 (4×30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under diminished pressure. The residue (642 mg) was subjected to flash chromatography (3:1 hexane-EtOAc) to give **14** (390 mg) in 50% yield calculated from **11**.

3.7.2.1 6-Deoxy-3,4-O-isopropylidene- α -L-ribo-hex-5-enopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (14). Colourless syrup; $[\alpha]_{\text{D}} 18.6$ (c 0.97, CHCl_3); R_f 0.56 (3:7 hexane-EtOAc); ^1H NMR (200 MHz, C_6D_6): δ 5.39 (d, 1H, $J_{1,2'}$ 3.3 Hz, H-1'), 4.85 (bs, 1H, H-6'b), 4.83 (d, 1H, $J_{2',\text{OH}}$ 10.5 Hz, OH), 4.78 (dd, 1H, $J_{2,3}$ 8.0 Hz, H-2), 4.70 (bs, 1H, H-6'a), 4.35 (m, 1H, H-4), 4.32 (d, 1H, $J_{1,2}$ 5.6 Hz, H-1), 4.26 (m, 1H, H-5), 4.23-4.03 (m, 2H, H-6a, H-6b), 4.15 (d, 1H, $J_{3,4'}$ 6.7 Hz, H-4'), 4.05 (dd, 1H, $J_{2,3'}$ 4.2 Hz, H-3'), 4.00 (dd, 1H, $J_{3,4}$ 1.6 Hz, H-3), 3.67 (bdt, 1H, H-2'), 3.26, 3.15 (2s, each 3H, 2 x OMe), 1.58, 1.57, 1.44, 1.33, 1.26, 1.20 (6s, each 3H, $3 \times \text{CMe}_2$); ^{13}C NMR (50 MHz, C_6D_6): δ 154.2 (C-5'), 110.9, 109.8, 108.3 ($3 \times \text{CMe}_2$),

105.7 (C-1), 101.4 (C-1'), 97.5 (C-6'), 78.5, 78.4, 77.9, 75.5 (C-2, C-3, C-4, C-5), 74.1, 72.6 (C-3', C-4'), 67.3 (C-2'), 65.7 (C-6); 56.2, 53.3 (2 × OMe), 27.3, 27.2, 27.0, 26.4, 25.6, 25.5 (3 × CMe₂). Anal. Calcd for C₂₃H₃₈O₁₁: C, 56.32; H, 7.81. Found: C, 56.41; H, 7.92.

3.8. Epoxidation of 6-deoxy-3,4-*O*-isopropylidene- α -L-ribo-hex-5-enopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**14**)

A solution of **14** (655 mg, 1.32 mmol) in MeOH (12 mL) was cooled at 0 °C, treated with 70% commercial MCPBA (Fluka, 407 mg, 1.98 mmol), warmed to room temperature and left to stirring. After 4.5 h TLC analysis (3:7 hexane-EtOAc) showed the complete disappearance of the starting material and the formation of three spots at *R_f* 0.56, 0.40 and 0.29. Satd aq NaHCO₃ (40 mL) was added, the solution was further stirred for 15 min and concentrated under diminished pressure. The residue was partitioned between water (30 mL) and CH₂Cl₂ (75 mL), the aq phase was extracted with CH₂Cl₂ (2 × 50 mL) and the combined organic extracts were dried, filtered and concentrated under diminished pressure. The residue (623 mg) was subjected to flash chromatography (7:3 hexane-EtOAc) to give **15** (87 mg, 13% yield) and **16** (337 mg, 47% yield).

3.8.1. (5S)-2,5-Anhydro-3,4-*O*-isopropylidene- α -L-ribo-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (15**).** Colourless syrup; [α]_D -48.3 (*c* 1.0, CHCl₃); *R_f* 0.40 (3:7 hexane-EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 5.09 (s, 1H, H-1'), 4.60 (s, 1H, H-2'), 4.40 (dd, 1H, *J*_{2,3} 7.2 Hz, H-2), 4.35 (d, 1H, *J*_{1,2} 6.0 Hz, H-1), 4.34 (d, 1H, *J*_{3',4'} 5.5 Hz, H-3'), 4.26 (d, 1H, H-4'), 4.25 (m, 1H, H-5), 4.09, 4.08 (AB system, 2H, *J*_{A,B} 13.0 Hz, H-6'a, H-6'b), 4.00 (m, 3H, H-4, H-6a, H-6b), 3.91 (dd, 1H, *J*_{3,4} 2.1 Hz, H-3), 3.46, 3.45 (2s, each 3H, 2 × OMe), 1.44, 1.40, 1.37, 1.36, 1.34, 1.28 (6s, each 3H, 3 × CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 113.9 (C-5'), 110.3, 108.3, 107.8 (3 × CMe₂), 105.6 (C-1), 98.3 (C-1'), 82.7 (C-2'), 80.8 (C-4'), 80.1 (C-3'), 80.0, 77.9 (C-3, C-5), 75.9 (C-2), 73.5 (C-4), 64.7 (C-6); 58.4 (C-6'), 56.6, 54.2 (2 × OMe), 27.7, 26.3, 26.1, 25.9, 25.4, 24.9 (3 × CMe₂). Anal. Calcd for C₂₃H₃₈O₁₂: C, 54.54; H, 7.56. Found: C, 54.48; H, 7.52.

3.8.2. (5R)-3,4-*O*-Isopropylidene-5-*C*-methoxy- α -L-ribo-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (16**).** Colourless syrup; [α]_D -15.8 (*c* 1.25, CHCl₃); *R_f* 0.29 (3:7 hexane-EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 5.10 (d, 1H, *J*_{1',2'} 3.1 Hz, H-1'), 4.53 (dd, 1H, *J*_{2,3} 7.8 Hz, H-2), 4.40 (dd, 1H, *J*_{2,3'} 4.5 Hz, *J*_{3',4'} 7.2 Hz, H-3'), 4.38 (d, 1H, *J*_{1,2} 6.4 Hz, H-1), 4.25 (dt, 1H, *J* 6.8 Hz, *J* 2.4 Hz, H-5), 4.16 (d, 1H, H-4'), 4.08 (m, 3H, H-4, H-6a, H-6b), 4.00

(m, 1H, H-2'), 3.91 (dd, 1 H, $J_{3,4}$ 1.6 Hz, H-3), 3.80, 3.72 (AB system, 2H, $J_{A,B}$ 12.0 Hz, H-6'a, H-6'b), 3.44, 3.43 (2s, each 3H, $2 \times$ OMe-1), 3.37 (s, 3H, OMe-5'), 2.99 (bd, 1H, OH), 2.21 (bs, 1H, OH), 1.56, 1.44, 1.40, 1.37, 1.35, 1.34 (6s, each 3H, $3 \times$ CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 109.9, 109.8, 107.9 ($3 \times$ CMe₂), 105.4 (C-1), 98.4 (C-5'), 98.2 (C-1'), 77.9 (C-3), 77.8 (C-5), 76.8 (C-4), 74.5 (C-2), 73.2 (C-4'), 72.5 (C-3'), 65.5 (C-2'), 64.9 (C-6); 60.7 (C-6'), 56.2, 52.8 ($2 \times$ OMe-1), 48.7 (OMe-5'), 26.9, 26.2, 26.0, 25.7, 25.0, 24.5 ($3 \times$ CMe₂). Anal. Calcd for C₂₄H₄₂O₁₃: C, 53.52; H, 7.86. Found: C, 53.61; H, 7.90.

3.9. (5*R*)-2,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-5-*C*-methoxy- α -*L*-ribo-hexopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-*D*-glucose dimethyl acetal (**17**)

To a solution of **16** (276 mg, 0.51 mmol) in THF containing 0.5% of water (4.1 mL) was added 18-crown-6 (14 mg), powdered KOH (230 mg, 4.09 mmol) and the mixture was stirred at room temperature for 30 min. BnBr (0.24 mL, 2.05 mmol) was added and the suspension was stirred at room temperature until TLC analysis (3:7 hexane-EtOAc) revealed the complete disappearance of starting material (4.5 h, R_f 0.20) and the formation of a major faster-moving product (R_f 0.64). MeOH (10 mL) was added and the reaction mixture was further stirred at room temperature for 30 min. Solvents were removed under diminished pressure and the residue was partitioned between CH₂Cl₂ (50 mL) and water (15 mL). The aq phase was extracted with CH₂Cl₂ ($3 \times$ 50 mL) and the combined organic extracts were dried, filtered and concentrated under diminished pressure. The residue (630 mg) was subjected to flash chromatography (first hexane and then 3:1 hexane-EtOAc) to give **17** (345 mg, 94% yield) as a colourless syrup; $[\alpha]_D +0.9$ (c 1.12, CHCl₃); R_f 0.64 (3:7 hexane-EtOAc); ¹H NMR (200 MHz, CDCl₃): δ 7.43-7.23 (m, 10H, Ar-H), 4.91 (d, 1H, $J_{1,2}$ 1.4 Hz, H-1'), 4.82 (s, 2H, CH₂Ph), 4.68, 4.50 (AB system, 2H, $J_{A,B}$ 12.3 Hz, CH₂Ph), 4.54 (dd, 1H, $J_{1,2}$ 6.5 Hz, $J_{2,3}$ 7.6 Hz, H-2), 4.33 (d, 1H, H-1), 4.31 (dd, 1H, $J_{2,3}$ 5.0 Hz, $J_{3,4}$ 6.1 Hz H-3'), 4.15 (d, 1H, H-4'), 4.20 (dt, 1H, J 3.3 Hz, J 6.6 Hz, H-5), 4.02 (dd, 1H, $J_{6a,6b}$ 8.9 Hz, $J_{5,6a}$ 6.7 Hz, H-6b), 3.96-3.88 (m, 3H, H-3, H-4, H-6a), 3.75 (d, 1H, H-2'), 3.67, 3.57 (AB system, 2H, $J_{A,B}$ 10.3 Hz, H-6'a, H-6'b), 3.30, 3.29, 3.23 (3s, each 3H, $2 \times$ OMe-1, OMe-5'), 1.50, 1.36, 1.33, 1.30, 1.28, 1.25 (6s, each 3H, $3 \times$ CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 138.2, 137.9 ($2 \times$ Ar-C), 128.2-127.2 (Ar-CH), 109.9, 109.7, 107.8 ($3 \times$ CMe₂), 105.1 (C-1), 99.0 (C-5'), 96.9 (C-1'), 77.9, 77.7, 76.6 (C-3, C-4, C-5), 73.9, 73.3 ($2 \times$ CH₂Ph), 73.3, 73.0 (C-2, C-4'), 72.5, 72.0 (C-2', C-3'), 66.2 (C-6'), 64.9 (C-6), 55.9, 51.6 ($2 \times$ OMe-1), 47.8 (OMe-5'), 26.8, 26.7, 26.4, 25.7, 25.5, 25.0 ($3 \times$ CMe₂). Anal. Calcd for C₃₈H₅₄O₁₃: C, 63.49; H, 7.57. Found: C, 63.51; H, 7.58.

3.10. 2,6-Di-*O*-benzyl-4-deoxy- α -L-erythro-hex-4-enopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**19**).

A solution of **18**¹⁰ (5.45 g, 7.90 mmol) in dry THF (100 mL) was warmed to reflux and treated with solid *t*-BuOK (9.70 g, 79.2 mmol). After 15 min, TLC analysis (1:1 hexane-EtOAc) showed the complete disappearance of starting material and satd aq NaHCO₃ (100 mL) was added. The aq phase was extracted with CH₂Cl₂ (3 \times 200 mL), the collected organic extracts were dried, filtered and concentrated under diminished pressure. The residue (5.35 g) was subjected to flash chromatography (3:2 hexane-EtOAc, 0.1% Et₃N) to give **19** (4.04 g, 81% yield) as a colourless syrup; [α]_D -25.1 (*c* 1.0, CHCl₃); *R*_f 0.4 (3:2 hexane-EtOAc); ¹H NMR (250 MHz, CD₃CN): δ 7.43-7.27 (m, 10H, Ar-H), 5.62 (dd, 1H, *J*_{1',2'} 2.3 Hz *J*_{1',3'} 1.1 Hz, H-1'), 5.17 (dt, 1H, *J*_{3',4'} 5.3 Hz, *J*_{4',6a} = *J*_{4',6b} 0.8 Hz, H-4'), 4.77, 4.64 (AB system, 2H, *J*_{A,B} 11.6 Hz, CH₂Ph), 4.52 (s, 2H, CH₂Ph), 4.32 (d, 1H, *J*_{1,2} 6.6 Hz, H-1), 4.23 (ddd, 1H, *J*_{4,5} 3.8 Hz, *J*_{5,6a} 6.3 Hz, *J*_{5,6b} 7.0 Hz, H-5), 4.18 (m, 1H, *J*_{2',3'} 4.0 Hz, H-3'), 4.12 (dd, 1H, *J*_{2,3} 7.1 Hz, *J*_{3,4} 1.4 Hz, H-3), 4.07 (dd, 1H, H-4), 4.05- 3.88 (m, 4H, H-6a, H-6b, H-6'a, H-6'b), 4.02 (dd, 1 H, H-2), 3.73 (dd, 1H, H-2'), 3.38, 3.34 (2s, each 3H, 2 \times OMe), 3.12 (d, 1H, *J*_{3',OH} 10.1 Hz, OH), 1.37, 1.31, 1.30, 1.28 (4s, each 3H, 2 \times CMe₂); ¹³C NMR (62.9 MHz, CD₃CN): δ 149.0 (C-5'), 139.7, 139.6 (2 \times Ar-C), 129.3-128.5 (Ar-CH), 110.7, 108.9 (2 \times CMe₂), 106.6 (C-1), 102.9 (C-4'), 98.8 (C-1'), 78.5, 78.5 (C-4, C-5), 77.3 (C-2), 75.3 (C-2'), 75.0 (C-3), 73.1, 71.7 (2 \times CH₂Ph), 69.6 (C-6'), 65.8 (C-6), 61.3 (C-3'), 56.8, 54.7 (2 \times OMe-1), 27.3, 27.2, 26.8, 25.4 (2 \times CMe₂). Anal. Calcd for C₃₄H₄₆O₁₁: C, 64.75; H, 7.35. Found: C, 64.77; H, 7.38.

3.11. Epoxidation-methanolysis of 2,6-di-*O*-benzyl-deoxy- α -L-erythro-hex-4-enopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**19**).

A solution of **19** (5.81 g, 9.21 mmol) in MeOH (180 mL) was cooled to 0 °C and treated with 70% commercial MCPBA (2.95 g, 11.9 mmol). After 5 min the reaction mixture was gently warmed to room temperature and left under stirring until **19** was consumed (TLC, 1:1 hexane-EtOAc, 24 h). Satd aq NaHCO₃ (50 mL) was added, the solution was further stirred for 30 min and the solvent was removed under diminished pressure. The residue was partitioned between water (60 mL) and CH₂Cl₂ (150 mL), the aq phase was extracted with CH₂Cl₂ (2 \times 150 mL) and the collected organic extracts were dried, filtered and concentrated under diminished pressure. The residue (5.4 g) was subjected to flash chromatography (3:2 hexane-EtOAc) to give **20** (3.63 g, 58% yield) and the 4'-epimer **21** (920 mg, 15% yield).

3.11.1. (5R)-2,6-Di-O-benzyl-5-C-methoxy- α -L-ribo-hexopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (20). Colourless syrup, $[\alpha]_D -22.8$ (c 1.3, CHCl_3); R_f 0.33 (1:1 hexane-EtOAc); $^1\text{H NMR}$ (200 MHz, CD_3CN): δ 7.39-7.31 (m, 10H, Ar H), 4.97, 4.69 (AB system, 2H, $J_{A,B}$ 11.4 Hz, CH_2Ph), 4.60, 4.45 (AB system, 2H, $J_{A,B}$ 11.9 Hz, CH_2Ph), 4.88 (d, 1H, $J_{1',2'}$ 0.9 Hz, H-1'), 4.44 (dd, 1H, $J_{1,2}$ 6.5 Hz, $J_{2,3}$ 7.0 Hz, H-2), 4.34 (d, 1H, H-1), 4.25 (m, 1H, H-5), 4.10-3.90 (m, 5H, H-3, H-4, H-6a, H-6b, H-4'), 3.99 (dd, 1H, $J_{2',3'}$ 1.5 Hz, H-2'), 3.85 (dt, 1H, $J_{3',4'}$ 3.0 Hz, $J_{3',\text{OH}}$ 2.3 Hz, H-3'), 3.67, 3.53 (AB system, 2H, $J_{A,B}$ 10.2, H-6'a, H-6'b), 3.30, 3.26, 3.24 (3s, each 3H, $2 \times \text{OMe-1}$, OMe-5'), 1.36, 1.31, 1.30, 1.26 (4s, each 3H, $2 \times \text{CMe}_2$); $^{13}\text{C NMR}$ (50 MHz, CD_3CN): δ 139.2, 139.1 ($2 \times \text{Ar-C}$), 128.8-128.6 (Ar-CH), 110.3, 108.7 ($2 \times \text{CMe}_2$), 106.3 (C-1), 102.6 (C-5'), 99.1 (C-1'), 80.3 (C-2'), 78.6, 78.5, 77.7, 75.6 (C-2, C-3, C-4, C-5), 76.0, 73.8 ($2 \times \text{CH}_2\text{Ph}$), 71.1 (C-3'), 66.8 (C-4'), 65.9, 65.5 (C-6, C-6'), 56.4, 53.1 ($2 \times \text{OMe-1}$), 48.8 (OMe-5'), 27.1, 27.0, 26.9, 25.2 ($2 \times \text{CMe}_2$). Anal. Calcd for $\text{C}_{35}\text{H}_{50}\text{O}_{13}$: C, 61.93; H, 7.42. Found: C, 61.96; H, 7.45.

The structure of **20** was confirmed by transformation into **17** by treatment of **20** (0.112 g, 0.165 mmol) with TsOH (3 mg, 0.0167 mmol) in DMP (3 mL) at room temperature. After 4 h the TLC (1:1 hexane-EtOAc) revealed the complete disappearance of starting material, Et_3N (0.4 mL) was added and the solution was stirred at room temperature. After 15 min the solution was concentrated under diminished pressure and the residue (125 mg) subjected to flash chromatography (7:3 hexane-EtOAc) to give **17** (0.110 g, 93% yield) as a colourless syrup, identical to the sample described above.

3.11.2. (5S or 5R)-2,6-Di-O-benzyl-5-C-methoxy- β -D-lyxo-hexopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (21). Colourless syrup; $[\alpha]_D -42.0$ (c 1.07, CHCl_3); R_f 0.13 (1:1 hexane-EtOAc); $^1\text{H NMR}$ (200 MHz, CD_3CN): δ 7.39-7.25 (m, 10H, Ar-H), 4.95, 4.69 (AB system, 2H, $J_{A,B}$ 11.8 Hz, CH_2Ph), 4.72, 4.45 (AB system, 2H, $J_{A,B}$ 11.7 Hz, CH_2Ph), 4.53 (dd, 1H, $J_{1,2}$ 6.3 Hz, $J_{2,3}$ 7.6 Hz, H-2), 4.39 (d, 1H, $J_{1',2'}$ 1.0 Hz, H-1'), 4.35 (d, 1H, H-1), 4.25 (dt, 1H, J 3.4 Hz, J 6.6 Hz, H-5), 4.05-3.94 (m, 4H, H-3, H-4, H-6a, H-6b), 3.95 (d, 1H, 1H, $J_{3',4'}$ 10.0 Hz, H-4'), 3.89 (dd, 1H, $J_{2',3'}$ 3.2 Hz, H-2'), 3.75, 3.58 (AB system, 2H, $J_{A,B}$ 10.5, H-6'a, H-6'b), 3.67 (dd, 1H, H-3'), 3.36, 3.31 (2s, each 3H, $2 \times \text{OMe-1}$), 3.29 (s, 3H, OMe-5'), 1.36, 1.30, 1.28, 1.23 (4s, each 3H, $2 \times \text{CMe}_2$); $^{13}\text{C NMR}$ (50 MHz, CD_3CN): δ 140.1, 139.4 ($2 \times \text{Ar-C}$), 129.2-128.2 (Ar-CH), 110.3, 108.2 ($2 \times \text{CMe}_2$), 106.7 (C-1), 100.3 (C-5'), 99.4 (C-1'), 79.4 (C-2'), 78.7, 78.5, 78.1, 76.3 (C-2, C-3, C-4, C-5), 75.2, 74.3 ($2 \times \text{CH}_2\text{Ph}$), 70.8, 71.8 (C-3', C-4'), 70.7 (C-6'), 65.6 (C-6), 56.7, 54.0 ($2 \times \text{OMe-1}$), 49.0 (OMe-5'), 27.1, 27.0, 26.9, 25.1 ($2 \times \text{CMe}_2$). Anal. Calcd for $\text{C}_{35}\text{H}_{50}\text{O}_{13}$: C, 61.93; H, 7.42. Found: C, 61.97; H, 7.44.

3.12. 2,3,6-Tri-*O*-benzyl-deoxy- α -L-erythro-hex-4-enopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**22**).

A solution of **19** (317 mg, 0.50 mmol) in dry DMF (8 mL) was treated at 0 °C with a 60% NaH in mineral oil (60 mg, 2.50 mmol) and the mixture was stirred for 15 min at 0 °C. Benzyl bromide (160 μ L, 0.65 mmol) was added and the reaction mixture warmed to room temperature and further stirred. After 30 min TLC analysis (3:2 hexane-EtOAc) showed the disappearance of starting material (R_f 0.31) and the formation of a major faster-moving product (R_f 0.51). Excess of NaH was destroyed with MeOH (0.5 mL) under stirring for 10 min at 0 °C, CH₂Cl₂ (15 mL) and H₂O (8 mL) was added, and the aq phase was further extracted with CH₂Cl₂ (2 x 15 mL). The combined organic extracts were dried, filtered and concentrated under diminished pressure and the crude product (350 mg) was subjected to flash chromatography (7:3 hexane-EtOAc) to give pure **22** (318 mg, 88% yield) as a colourless syrup, R_f 0.31 (3:2 hexane-EtOAc); $[\alpha]_D$ -25.0 (c 1.04, CHCl₃); ¹H NMR (250 MHz, CD₃CN): δ 7.41-7.24 (m, 15H, Ar-H), 5.32 (t, 1H, $J_{1,2'} = J_{1,3'}$ 1.0 Hz, H-1'), 4.94 (dt, 1H, $J_{3',4'}$ 2.8 Hz, $J_{4',6'a} = J_{4',6'b}$ 0.8 Hz, H-4'), 4.86, 4.73 (AB system, 2H, $J_{A,B}$ 11.6 Hz, CH₂Ph), 4.56, 4.52 (AB system, 2H, $J_{A,B}$ 12.0 Hz, CH₂Ph), 4.53, 4.47 (AB system, 2H, $J_{A,B}$ 11.8 Hz, CH₂Ph), 4.43 (dd, 1H, $J_{1,2}$ 6.3 Hz, $J_{2,3}$ 7.2 Hz, H-2), 4.35 (d, 1H, H-1), 4.26 (dt, 1H, $J_{4,5}$ 3.8 Hz, $J_{5,6a} = J_{5,6b}$ 6.3 Hz, H-5), 4.24 (m, 1H, $J_{2,3'}$ 5.4 Hz, H-3'), 4.08 (dd, 1H, $J_{6a,6b}$ 10.5 Hz, H-6b), 4.07 (dd, 1H, $J_{3,4}$ 2.0 Hz, H-3), 4.04 (dd, 1H, H-4), 3.97 (m, 2H, H-6a, H-2'), 3.90 (m, 2H, H-6'a, H-6'b), 3.35, 3.33 (2s, each 3H, 2 x OMe), 1.34, 1.31, 1.30, 1.29 (4s, each 3H, 2 x CMe₂); ¹³C NMR (62.9 MHz, CD₃CN): δ 150.4 (C-5'), 139.8, 139.7, 139.5 (3 x Ar-C), 129.2-128.4 (Ar-CH), 110.6, 108.7 (2 x CMe₂), 106.3 (C-1), 101.0 (C-1'), 100.4 (C-4'), 78.7 (C-3), 78.5 (C-5), 76.9 (C-4), 76.0 (C-2), 73.9, 72.8, 71.4 (3 x CH₂Ph), 73.6 (C-2'), 71.8 (C-3'), 69.9 (C-6'), 65.9 (C-6), 56.2, 53.8 (2 x OMe-1), 27.3, 27.2, 26.9, 25.1 (2 x CMe₂). Anal. Calcd for C₄₁H₅₂O₁₁: C, 68.31; H, 7.27. Found: C, 68.28; H, 7.29.

3.13. Epoxidation-methanolysis of 2,3,6-tri-*O*-benzyl-deoxy- α -L-erythro-hex-4-enopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal (**22**).

A solution of **22** (233 mg, 0.323 mmol) in MeOH (12 mL) was cooled to 0 °C and treated with 70% commercial MCPBA (111.4 mg, 0.388 mmol). After 5 min the reaction mixture was gently warmed to room temperature and left under stirring until **22** was consumed (TLC, 1:1 hexane-EtOAc, 14 h). Satd aq NaHCO₃ (10 mL) was added, the solution was further stirred for 10 min and the solvent was removed under diminished pressure. CH₂Cl₂ (20 mL) was added, the aq phase was

extracted with CH₂Cl₂ (2 × 20 mL) and the collected organic extracts were dried, filtered and concentrated under diminished pressure. The residue was subjected to flash chromatography (3:2 hexane-EtOAc) to give **23** (42.8 mg, 17% yield) and the 4'-epimer **24** (120 mg, 48% yield).

3.13.1. (5R)-2,3,6-Tri-O-benzyl-5-C-methoxy- α -L-ribo-hexopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (23**).** Colourless syrup, $[\alpha]_D -14.6$ (*c* 0.96, CHCl₃); *R_f* 0.33 (3:2 hexane-EtOAc); ¹H NMR (250 MHz, CD₃CN): δ 7.43-7.26 (m, 15H, Ar H), 4.88, 4.74 (AB system, 2H, *J_{A,B}* 11.4 Hz, CH₂Ph), 4.63, 4.50 (AB system, 2H, *J_{A,B}* 11.9 Hz, CH₂Ph), 4.60, 4.44 (AB system, 2H, *J_{A,B}* 11.8 Hz, CH₂Ph), 4.81 (d, 1H, *J_{1',2'}* 1.1 Hz, H-1'), 4.42 (dd, 1H, *J_{1,2}* 6.5 Hz, *J_{2,3}* 7.5 Hz, H-2), 4.33 (d, 1H, H-1), 4.24 (dt, 1H, *J_{4,5}* 3.4 Hz, *J_{5,6a}* = *J_{5,6b}* 6.6 Hz, H-5), 4.09 (m, 1H, H-2'), 4.01 (dd, 1H, *J_{6a,6b}* 8.5 Hz, H-6b), 3.96 (m, 3H, H-3, H-4, H-6a), 3.82 (ddd, 1H, *J_{3',4'}* 3.1 Hz, *J_{4',OH}* 9.9 Hz, *J_{2',4'}* 1.2 Hz, H-3'), 3.81 (d, 1H, OH-4'), 3.74 (dd, 1H, *J_{2',3'}* 2.9 Hz, H-3'), 3.70, 3.50 (AB system, 2H, *J_{A,B}* 10.2, H-6'a, H-6'b), 3.28, 3.25, (2s, each 3H, 2 × OMe-1), 3.19 (s, 3H, OMe-5'), 1.30 (s, 12H, 2 × CMe₂); ¹³C NMR (62.9 MHz, CD₃CN): δ 139.5, 139.3, 139.2 (3 × Ar-C), 129.3-128.6 (Ar-CH), 110.4, 108.7 (2 × CMe₂), 106.3 (C-1), 102.9 (C-5'), 98.8 (C-1'), 78.6 (C-3), 78.5 (C-5), 78.2 (C-2'), 77.7 (C-4), 75.9, 73.9, 70.5 (3 × CH₂Ph), 75.6 (C-2), 74.0 (C-3'), 68.5 (C-4'), 65.9 (C-6'), 65.5 (C-6), 56.4, 53.1 (2 × OMe-1), 48.9 (OMe-5'), 27.1, 27.0, 26.9, 25.1 (2 × CMe₂). Anal. Calcd for C₄₂H₅₆O₁₃: C, 65.61; H, 7.34. Found: C, 65.58; H, 7.28.

3.13.2. (5S or 5R)-2,3,6-Tri-O-benzyl-5-C-methoxy- β -D-lyxo-hexopyranosyl-(1 \rightarrow 4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (24**).** Colourless syrup; $[\alpha]_D -54.6$ (*c* 0.99, CHCl₃); *R_f* 0.44 (3:2 hexane-EtOAc); ¹H NMR (250 MHz, CD₃CN): δ 7.39-7.236 (m, 15H, Ar-H), 4.93, 4.70 (AB system, 2H, *J_{A,B}* 11.8 Hz, CH₂Ph), 4.73, 4.47 (AB system, 2H, *J_{A,B}* 11.7 Hz, CH₂Ph), 4.59 (s, 2H, CH₂Ph), 4.90 (d, 1H, *J_{1',2'}* 0.7 Hz, H-1'), 4.53 (dd, 1H, *J_{1,2}* 6.2 Hz, *J_{2,3}* 7.5 Hz, H-2), 4.35 (d, 1H, H-1), 4.26 (dt, 1H, *J* 3.2 Hz, *J* 6.7 Hz, H-5), 4.18 (d, 1H, 1H, *J_{3',4'}* 10.1 Hz, H-4'), 4.05 (m, 1H, H-6b), 4.04 (dd, 1H, *J_{2',3'}* 3.0 Hz, H-2'), 3.98 (dd, 1H, *J_{3,4}* 1.3 Hz, H-3), 3.96 (m, 2H, H-4, H-6a), 3.59 (dd, 1H, H-3'), 3.78, 3.61 (AB system, 2H, *J_{A,B}* 10.5, H-6'a, H-6'b), 3.37, 3.32 (2s, each 3H, 2 × OMe-1), 3.30 (s, 3H, OMe-5'), 1.31, 1.30, 1.29, 1.27 (4s, each 3H, 2 × CMe₂); ¹³C NMR (62.9 MHz, CD₃CN): δ 140.2, 139.9, 139.5 (3 × Ar-C), 129.2-128.1 (Ar-CH), 110.4, 108.7 (2 × CMe₂), 106.7 (C-1), 100.3 (C-5'), 99.3 (C-1'), 78.8 (C-5), 78.6 (C-3), 78.5 (C-3'), 77.9 (C-4), 76.9 (C-2'), 76.3 (C-2), 75.0, 74.3, 72.4 (3 × CH₂Ph), 68.8 (C-4'), 70.7 (C-6'), 65.5 (C-6), 56.7, 54.0 (2 × OMe-1), 49.0 (OMe-5'), 27.2, 27.1, 26.9, 25.2 (2 × CMe₂). Anal. Calcd for C₄₂H₅₆O₁₃: C, 65.61; H, 7.34. Found: C, 65.58; H, 7.31.

3.14. 2,6-Di-*O*-benzyl-L-ribo-hexos-5-ulose (**25**)

A solution of **17** (344 mg, 0.479 mmol) in a 4:1 CH₃CN-H₂O (8.5 mL) solution was treated with 90% aq CF₃COOH (24.2 mL) and stirred at 50 °C until the TLC analysis (EtOAc) showed the complete disappearance of the starting material (5 h). The mixture was concentrated under diminished pressure and repeatedly co-evaporated with toluene (4 × 30 mL). The crude residue was partitioned between brine (20 mL) and EtOAc (40 mL) and the aq phase extracted with EtOAc (3 × 40 mL). The organic phases were collected, dried, concentrated under diminished pressure to give a residue, that was directly subjected to a flash chromatographic purification, eluting with 3:7 hexane-EtOAc, to give **25** (113 mg, 66% yield) as an amorphous solid constituted (NMR) by a mixture of α- and β-1,4-furanose anomers in a ratio of about 7:3 estimated on the basis of the relative C-1' NMR signal intensities (δ 100.9 and 97.4 respectively); *R*_f 0.31 (1:1 hexane-EtOAc); mp 121-125 °C; Lit.⁸ mp 120-124 °C; [α]_{D²⁰} -20.5 (*c* 0.7; CHCl₃).

Hydrolysis of **20** (456 mg, 0.67 mmol) was performed in 4:1 (v/v) CH₃CN-H₂O (11 mL) with 90% aq CF₃COOH (2.3 mL) according to the procedure described above. After 4 h the reaction mixture was subjected to the work-up described above and the crude reaction product was flash chromatographed (2:3 hexane-EtOAc), to give **25** (175 mg, 73% yield) as an amorphous solid, identical to the above sample.

3.15. 2,6-Di-*O*-benzyl-D-lyxo-hexos-5-ulose (**26**)

Compound **26** was obtained by the method described above for **25**, with the following reagents: 331 mg of **21** (0.49 mmol) in 2:1 (v/v) CH₃CN-H₂O (18 mL) and 90% aq CF₃COOH (1.4 mL). After 1.5 h at 60 °C TLC analysis showed the complete disappearance of the starting material and the reaction mixture was subjected to the work-up described above for **25**. The residue (135 mg) was subjected to a flash chromatographic purification, eluting with 3:7 hexane-EtOAc, to give **26** (126 mg, 72% yield) as a white solid; constituted (¹³C NMR, CD₃CN) by a mixture of α- and β-1,4-furanose anomers in a ratio of about 65:35 estimated on the basis of the relative C-1 signal intensities (δ 101.6 and 97.4 respectively); [α]_{D²⁰} -15.5 (*c* 1.0, CHCl₃); *R*_f 0.29 (4:1 CH₂Cl₂-Et₂O); Lit.¹⁶ for the L-enantiomer [α]_{D²⁰} +15.1 (*c* 0.96, CHCl₃).

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