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 triacetonlactose 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 azasugars\(^3\) and cyclitols, as inositols\(^4\) 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-eno\(^6\) (1) or 6-deoxy-hex-5-enopyranosides\(^7\) (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
aldohexos-5-uloses and gained this goal preparing the \(\text{l-arabino}\)\(^{7c,d}\) the \(\text{d-xylo}\)\(^7c\) and the \(\text{l-lyxo}\)\(^7c\) ones.

In this communication we present the preparation of partially protected \(\text{l-ribo}\) and \(\text{d-lyxo}\) 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](https://example.com/chart1.png)

**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-uloose stereoseries, the \(\text{ribo}\) one, from lactose, we decided to investigate a different strategy with respect to that reported starting from monosaccharide precursors\(^8\) and thus to epimerize the C-2' position on the \(\text{d-galactopyranoside}\) 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 CH\(_2\)Cl\(_2\) obtaining a crude mixture of the uloside \(5\) and its hydrate \(6\) (about 3:1). The reduction (NaBH\(_4\)/MeOH) of the crude mixture gave in an overall 90% yield the corresponding \(\text{d-talo-derivative}\) \(7\) 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 \textit{galacto} epimer \(4\), but only the 2,5-anhydro derivative \(8\) was obtained in almost quantitative yield (96%) as a result of an intramolecular \(\text{S\_2}\) 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 system\(^3\) could explain the exclusive formation of 8.

![Scheme 1](image)

Scheme 1. Attempts to prepare a \(\beta\) -D-talo-6-deoxy-hex-5-enopyranoside. Reagent and conditions: (a) TPAP, NMO, CH\(_2\)Cl\(_2\), 4Å, rt, 1 h (91%); (b) NaBH\(_4\), 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, CH\(_2\)Cl\(_2\) (90%); (e) NaH. DMF, Im\(_2\)SO\(_2\), -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 (CH\(_2\)Cl\(_2\)-5% aqueous HCl). However, the subsequent introduction of a leaving group in the primary position failed using Ts\(_2\)O 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 Im\(_2\)SO\(_2\)) 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-\(\beta\)-\(\alpha\)-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.

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 1810 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-α-galactopyranosides7c,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 *ta*lo 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. 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 CF$_3$COOH in 4:1 CH$_3$CN-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 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 ($26\alpha:26\beta$ 66:34).\textsuperscript{16}

\[ \text{Scheme 4. Synthesis of 2,6-di-O-benzyl-L-ribo- and 2,6-di-O-benzyl-D-lyxo-hexos-5-ulates. Reagent and conditions: (a) 90% aq CF}_3\text{COOH, 4:1 CH}_3\text{CN-H}_2\text{O, 50 °C, 4-5 h (25: 66% from 17 and 73% from 20, 26: 72%).} \]

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,\textsuperscript{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.\textsuperscript{4}

3. Experimental

3.1. General methods

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

\textsuperscript{4}The 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-L-lyxo-hex-2-ulopyranosyl-(1→4)-2,3:5,6-di-O-isopropylidene-aldehydo-β-D-glucose dimethyl acetal (5) and its hydrate (6)

A suspension of 4\textsuperscript{c} (2.02 g, 3.00 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (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 CH\textsubscript{2}Cl\textsubscript{2} and then EtOAc. The combined organic phases were concentrated under diminished pressure to give a syrup (2.00 g) constituted (\textsuperscript{13}C NMR, CDCl\textsubscript{3}) 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 CH\textsubscript{2}Cl\textsubscript{2}-Me\textsubscript{2}CO, afforded a 3:1 mixture of 5 and 6 (1.81 g, combined yield about 91%) as a colourless syrup; [α]_D\textsubscript{20} -9.9 (c 1.17, CHCl\textsubscript{3}); R\textsubscript{f} 0.45 (9:1 CH\textsubscript{2}Cl\textsubscript{2}-Me\textsubscript{2}CO); selected \textsuperscript{13}C NMR (50 MHz, CDCl\textsubscript{3}) signals: \textit{major component} 5: δ 196.4 (C-2'), 144.9, 132.0 (2 × Ar-C), 111.1, 110.2, 107.7 (3 × Me\textsubscript{2}C), 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 × OMe-1), 27.0, 26.6, 25.9, 25.8, 25.7, 25.3 (3 × CMe\textsubscript{2}), \textit{minor component} 6: δ 144.6, 132.1 (2 × Ar-C), 110.1, 109.7, 107.9 (3 × Me\textsubscript{2}C), 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 × OMe-1), 26.8, 26.1, 25.6, 25.5, 24.4, 24.0 (3 × CMe\textsubscript{2}). 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-toluenesulfonfonyl-β-D-talopyranosyl-(1→4)-2,3:5,6-di-O-isopropylidene-aldehydo-β-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 NaBH\textsubscript{4} (228 mg, 6.03 mmol) and gently warmed to room temperature. The reaction mixture was stirred until the TLC analysis (9:1 CH\textsubscript{2}Cl\textsubscript{2}-Me\textsubscript{2}CO) showed the complete disappearance of the starting material (1 h), treated with satd aq NH\textsubscript{4}Cl (10.0 mL), stirred for 15 min and extracted with CH\textsubscript{2}Cl\textsubscript{2} (4 × 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; [α]_D\textsubscript{20} -2.2 (c 1.16, CHCl\textsubscript{3}); R\textsubscript{f} 0.40 (9:1 CH\textsubscript{2}Cl\textsubscript{2}-Me\textsubscript{2}CO); \textsuperscript{1}H NMR
(200 MHz, CDCl₃): δ 7.80, 7.36 (AA’XX’ system, 4H, Ar-H), 4.93 (d, 1H, J₁,₂ 2.5 Hz, H-1’), 4.47 (dd, 1H, J₂,₃ 7.1 Hz, H-2), 4.38 (d, 1H, J₁,₂ 6.2 Hz, H-1), 4.32 (dd, 1H, J₃,₄ 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, J₂,₃ 4.1 Hz, H-2'), 3.79 (dd, 1H, J₁,₂ 6.2 Hz, H-1), 3.79 (dd, 1H, J₃,₄ 4.1 Hz, H-2'), 3.42, 3.41 (2s, each 3H, 2 × 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 × CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 144.8, 132.4 (2 × Ar-C), 129.8, 127.8 (Ar-CH), 110.1, 110.1, 107.8 (3 × 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 × OMe), 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→4)-2,3:5,6-di-O-isopropylidene-aldehyde-α-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 (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 × 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 Rf 0.58 and the formation of a slower-moving product (Rf 0.39). The aqueous phase was further extracted with CH₂Cl₂ (4 × 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 Rf 0.58 and the formation of a slower-moving product (Rf 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; [α]D +19.3 (c 1.23, CHCl₃); Rf 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, J₆,₇ 12.8 Hz, CH₂Ph), 4.71 (dd, 1H, J₂,₃ 7.9 Hz, H-2), 4.57 (s, 1H, H-1’), 4.38 (d, 1H, J₁,₂ 6.7 Hz, H-1), 4.30-4.15 (m, 2H, H-4', H-3'), 4.15-4.05 (m, 3H, H-5, H-6a, H-6b), 3.95 (m, 1H, H-5'), 3.90 (dd, 1H, J₁,₂ 1.4 Hz, H-3), 3.81 (m, 1H, H-5'), 3.71 (d, 1H, J₂,₃ 5.5 Hz, H-2'), 3.69 (m, 1H, H-4), 3.48 (s, 6H, 2 × OMe), 1.50, 1.35, 1.34, 1.31, 1.26, 1.25 (6s, each 3H, 3 × CMe₂); ¹³C NMR (50 MHz, CDCl₃): δ 138.1 (Ar-C), 127.7-126.9 (Ar-CH), 110.2, 109.5, 107.4 (3 × 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 × OMe-1), 26.5, 26.3,

3.5. 2,6-Anhydro-3,4-O-isopropylidene-β-D-talopyranosyl-(1→4)-2,3:5,6-di-O-isopropylidene-aldehydo-β-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 × 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; [α]D -19.6 (c 1.2, CHCl₃); Rf 0.55 (3:7 hexane-EtOAc); ¹H NMR (200 MHz, CD₃CN): δ 5.04 (d, 1H, J₁',2' 1.7 Hz, H-1'), 4.47 (t, 1H, J₂,3 6.6 Hz, H-2), 4.36 (d, 1H, J₁,2 6.6 Hz, H-1), 4.34 (m, 1H, H-5), 4.22 (dd, 1H, J₃',₄ 6.1 Hz, H-3'), 4.18 (dd, 1H, J₄',₅ 4.6 Hz, H-4'), 4.08 (dd, 1H, J₅,₆ 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, J₄,₅ 4.5 Hz, H-4), 3.79 (t, 1H, J₂,₃ 1.7 Hz, H-2), 3.38, 3.36 (2s, each 3H, 2 × OMe), 1.48, 1.39, 1.34, 1.33, 1.32, 1.28 (6s, each 3H, 3 × CMe₂); ¹³C NMR (200 MHz, CD₃CN): δ 112.5, 111.3, 109.0 (3 × CMe₂), 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 × OMe), 27.7, 26.9, 26.7, 26.1, 25.3, 24.9 (3 × CMe₂). Anal. Calcd for C₂₃H₃₈O₁₂: 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 × 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-\(\alpha\)-l-arabino-hex-5-enopyranosyl-(1→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 Et\(_2\)O (5 × 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 % Et,N) to give 11 (3.96 g, 85% yield); as a clear syrup; \([\alpha]_D\) -22.8 (c 1.3, CHCl\(_3\)); \(R_f\) 0.22 (7:3 hexane-EtOAc); \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 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, \(J_{5a,6a} = J_{4a,6a}\) 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-4'), 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 × OMe), 1.60, 1.57, 1.48, 1.47, 1.46, 1.39 (6s, each 3H, 3 × CMe\(_2\)); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 153.1 (C-5'), 110.9, 110.1, 108.1 (3 × CMe\(_2\)), 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 × OMe), 27.3, 27.7, 26.3, 25.5, 25.4, 23.9 (3 × CMe\(_2\)). Anal. Calcd for C\(_{23}\)H\(_{38}\)O\(_{11}\): C, 56.32; H, 7.81. Found: C, 56.13; H, 7.77.

3.7. Oxidation-reduction of 6-deoxy-3,4-O-isopropylidene-\(\alpha\)-l-arabino-hex-5-enopyranosyl-(1→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 CH\(_2\)Cl\(_2\)-CH\(_3\)CN 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, a.208 mmol, 10%) was added and the resulting green mixture was stirred at room temperature. After 2.5 h, TLC analysis (9:1 CH\(_2\)Cl\(_2\)-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 CH\(_2\)Cl\(_2\) 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, \(\text{C}_6\text{D}_6\)) 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; [\(\alpha\)]\(_D\) -19.4 (c 1.18, CHCl\(_3\)); \(R_t\) 0.09 (7:3 hexane-EtOAc); Selected \(^1\)H NMR (200 MHz, \(\text{C}_6\text{D}_6\)) 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, \(\text{C}_6\text{D}_6\)) signals: component 12: δ 197.8 (C-2'), 152.6 (C-5'), 111.6, 110.3, 108.3 (3 x \(\text{C}Me_2\)), 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 x OMe-1); component 13: δ 154.7 (C-5'), 112.2, 110.6, 108.5 (3 x \(\text{C}Me_2\)), 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 x OMe-1); Cluster of signals for both components: δ 27.5-24.9 (3 x \(\text{C}Me_2\)).

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\(_2\)Cl\(_2\)-Me\(_2\)CO) revealed the complete disappearance of the starting material (2.5 h). The mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL) and treated with water (20 mL), warmed to room temperature and extracted with CH\(_2\)Cl\(_2\) (4 x 30 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)), 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-\(\alpha\)-ribo-hex-5-enopyranosyl-(1→4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (14). Colourless syrup; [\(\alpha\)]\(_D\) 18.6 (c 0.97, CHCl\(_3\)); \(R_t\) 0.56 (3:7 hexane-EtOAc); \(^1\)H NMR (200 MHz, \(\text{C}_6\text{D}_6\)) 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, \(J_{5,4'}\) 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 x \(\text{C}Me_2\)); \(^13\)C NMR (50 MHz, \(\text{C}_6\text{D}_6\)) δ 154.2 (C-5'), 110.9, 109.8, 108.3 (3 x \(\text{C}Me_2\)).
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 NaHCO\(_3\) (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 CH\(_2\)Cl\(_2\) (75 mL), the aq phase was extracted with CH\(_2\)Cl\(_2\) (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. \((5S)-2,5\text{-Anhydro}-3,4\text{-O-isopropylidene-α-L-ribo-hexopyranosyl-(1→4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (15)}\)

Colourless syrup; \([\alpha]_D^{\text{20}} \, -48.3 \, (c \, 1.0, \text{CHCl}_3); \, R_f \, 0.40 \, (3:7 \text{ hexane-EtOAc}); \, ^1H \text{ NMR} \ (600 MHz, \text{CDCl}_3): \ \delta \, 5.09 \, (s, \, 1H, \, H-1'), \, 4.60 \, (s, \, 1H, \, H-2'), \, 4.35 \, (d, \, 1H, \, J_{1',2'} \, 7.2 \, Hz, \, H-2), \, 4.34 \, (d, \, 1H, \, J_{1,2} \, 6.0 \, Hz, \, H-1), \, 4.09 \, (d, \, 1H, \, J_{3',4'} \, 5.5 \, Hz, \, H-3'), \, 4.09 \, (m, \, 1H, \, H-5), \, 4.00 \, (m, \, 3H, \, H-4, \, H-6a, \, H-6b), \, 3.91 \, (dd, \, 1H, \, J_{3,4} \, 2.1 \, Hz, \, H-3), \, 3.46 \, (2s, \, each \, 3H, \, 3 \times \text{CMe}_2), \, 3.38 \, (6s, \, each \, 3H, \, 3 \times \text{CMe}_2); \, ^{13}C \text{ NMR} \ (50 MHz, \text{CDCl}_3): \ \delta \, 113.9 \, (C-5'), \, 110.3, \, 108.3, \, 107.8 \, (3 \times \text{CMe}_2), \, 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 \times \text{OMe}), \, 27.7, \, 26.3, \, 26.1, \, 25.9, \, 25.4, \, 24.9 \, (3 \times \text{CMe}_2). \, \text{Anal. Calcd for C}_{23}\text{H}_{38}\text{O}_{12}: \, C, \, 54.54; \, H, \, 7.56. \, \text{Found: C, 54.48; H, 7.52.}

### 3.8.2. \((5R)-3,4\text{-O-Isopropylidene-5-C-methoxy-α-L-ribo-hexopyranosyl-(1→4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (16)}\)

Colourless syrup; \([\alpha]_D^{\text{20}} \, -15.8 \, (c \, 1.25, \text{CHCl}_3); \, R_f \, 0.29 \, (3:7 \text{ hexane-EtOAc}); \, ^1H \text{ NMR} \ (600 MHz, \text{CDCl}_3): \ \delta \, 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_{3',4'} \, 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, J3,4 1.6 Hz, H-3), 3.80, 3.72 (AB system, 2H, JAB 12.0 Hz, H-6'a, H-6'b), 3.44, 3.43 (2s, each 3H, 2 × 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 × CMe2); 13C NMR (50 MHz, CDCl3): δ 109.9, 109.8, 107.9 (3 × 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 × OMe-1), 48.7 (OMe-5'), 26.9, 26.2, 26.0, 25.7, 25.0, 24.5 (3 × CMe2). Anal. Calcd for C24H42O13: C, 53.52; H, 7.86. Found: C, 53.61; H, 7.90.

3.9. (5R)-2,6-Di-O-benzyl-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 (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, Rf 0.20) and the formation of a major faster-moving product (Rf 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 × 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; [α]D +0.9 (c 1.12, CHCl3); Rf 0.64 (3:7 hexane-EtOAc); 1H NMR (200 MHz, CDCl3): δ 7.43-7.23 (m, 10H, Ar-H), 4.91 (d, 1H, J1,2 1.4 Hz, H-1'), 4.82 (s, 2H, CH2Ph), 4.68, 4.50 (AB system, 2H, JAB 12.3 Hz, CH2Ph), 4.54 (dd, 1H, J1,2 6.5 Hz, J2,3 7.6 Hz, H-2), 4.33 (d, 1H, H-1), 4.31 (dd, 1H, J2,3 5.0 Hz, J3,4 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, J6a,6b 8.9 Hz, J5,6a 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, JAB 10.3 Hz, H-6'a, H-6b), 3.30, 3.29, 3.23 (3s, each 3H, 2 × OMe-1, OMe-5'), 1.50, 1.36, 1.33, 1.30, 1.28, 1.25 (6s, each 3H, 3 × CMe2); 13C NMR (50 MHz, CDCl3): δ 138.2, 137.9 (2 × Ar-C), 128.2-127.2 (Ar-CH), 109.9, 109.7, 107.8 (3 × 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 × 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 × OMe-1), 47.8 (OMe-5'), 26.8, 26.7, 26.4, 25.7, 25.0 (3 × CMe2). Anal. Calcd for C38H54O15: 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→4)-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (19).

A solution of 18\textsuperscript{19} (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 NaHCO\textsubscript{3} (100 mL) was added. The aq phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 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% Et\textsubscript{3}N) to give 19 (4.04 g, 81% yield) as a colourless syrup; [α]\textsubscript{D} –25.1 (c 1.0, CHCl\textsubscript{3}); R\textsubscript{f} 0.4 (3:2 hexane-EtOAc); \textsuperscript{1}H NMR (250 MHz, CD\textsubscript{3}CN): δ 7.43-7.27 (m, 10H, Ar-H), 5.62 (dd, 1H, J\textsubscript{1',2'} 2.3 Hz, J\textsubscript{1',3'} 1.1 Hz, H-1'), 5.17 (dt, 1H, J\textsubscript{3',4'} 5.3 Hz, J\textsubscript{4',6'a} = J\textsubscript{4',6'b} 0.8 Hz, H-4'), 4.77, 4.64 (AB system, 2H, J\textsubscript{A,B} 11.6 Hz, CH\textsubscript{2}Ph), 4.32 (d, 1H, J\textsubscript{1,2} 6.6 Hz, H-1), 4.23 (ddd, 1H, J\textsubscript{4,5} 3.8 Hz, J\textsubscript{5,6a} 6.3 Hz, J\textsubscript{5,6b} 7.0 Hz, H-5), 4.18 (m, 1H, J\textsubscript{2',3'} 4.0 Hz, H-3'), 4.12 (dd, 1H, J\textsubscript{2,3} 7.1 Hz, J\textsubscript{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 × OMe), 3.12 (d, 1H, J\textsubscript{3,OH} 10.1 Hz, OH), 1.37, 1.31, 1.30, 1.28 (4s, each 3H, 2 × CMe\textsubscript{2}); \textsuperscript{13}C NMR (62.9 MHz, CD\textsubscript{3}CN): δ 149.0 (C-5'), 139.7, 139.6 (2 × Ar-C), 129.3-128.5 (Ar-CH), 110.7, 108.9 (2 × CMe\textsubscript{2}), 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 × CH\textsubscript{2}Ph), 69.6 (C-6'), 65.8 (C-6), 61.3 (C-3'), 56.8, 54.7 (2 × OMe-1), 27.3, 27.2, 26.8, 25.4 (2 × CMe\textsubscript{2}). Anal. Calcd for C\textsubscript{34}H\textsubscript{46}O\textsubscript{11}: 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→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 NaHCO\textsubscript{3} (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 CH\textsubscript{2}Cl\textsubscript{2} (150 mL), the aq phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 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→4)-2,3:5,6-di-O-isopropylidene-aldehydo-α-glucose dimethyl acetal (20). Colourless syrup, [α]D -22.8 (c 1.3, CHCl3); Rf 0.33 (1:1 hexane-EtOAc); 1H NMR (200 MHz, CD3CN): δ 7.39-7.31 (m, 10H, Ar H), 4.97, 4.69 (AB system, 2H, Jαβ 11.4 Hz, CHPh), 4.60, 4.45 (AB system, 2H, Jαβ 11.9 Hz, CHPh), 4.88 (d, 1H, J1,2 0.9 Hz, H-1'), 4.44 (dd, 1H, J1,2 6.5 Hz, J2,3 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, J2,3 1.5 Hz, H-2'), 3.85 (dt, 1H, J3,OH 2.3 Hz, H-3'), 3.67, 3.53 (AB system, 2H, Jαβ 10.2, H-6'a, H-6'b), 3.30, 3.26, 3.24 (3s, each 3H, 2×OMe-1), 3.29 (s, 3H, OMe-5'), 1.36, 1.31, 1.29, 1.26 (4s, each 3H, 2×CMe2); 13C NMR (50 MHz, CD3CN): δ 139.2, 139.1 (2×Ar-C), 128.8-128.6 (Ar-CH), 110.3, 108.7 (2×CMe2), 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×CH2Ph), 71.1 (C-3'), 66.8 (C-4'), 65.9, 65.5 (C-6, C-6'), 56.4, 53.1 (2×Oe-1), 48.8 (Oe-5'), 27.1, 27.0, 26.9, 25.2 (2×CMe2). Anal. Calcd for C35H50O13: 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, Et3N (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→4)-2,3:5,6-di-O-isopropylidene-aldehydo-α-glucose dimethyl acetal (21). Colourless syrup; [α]D -42.0 (c 1.07, CHCl3); Rf 0.13 (1:1 hexane-EtOAc); 1H NMR (200 MHz, CD3CN): δ 7.39-7.25 (m, 10H, Ar-H), 4.95, 4.69 (AB system, 2H, Jαβ 11.8 Hz, CHPh), 4.72, 4.45 (AB system, 2H, Jαβ 11.7 Hz, CHPh), 4.53 (dd, 1H, J1,2 6.3 Hz, J2,3 7.6 Hz, H-2), 4.39 (d, 1H, J1,2 1.0 Hz, H-1'), 4.35 (d, 1H, H-1), 4.25 (dt, 1H, J1,2 3.4 Hz, J10,6 6.6 Hz, H-5), 4.05-3.94 (m, 4H, H-3, H-4, H-6a, H-6b), 3.95 (d, 1H, J1,2 1.0 Hz, H-1'), 4.35 (d, 1H, H-1), 4.25 (dt, 1H, J1,2 3.4 Hz, H-5), 3.89 (dd, 1H, J2,3 3.2 Hz, H-2'), 3.75, 3.58 (AB system, 2H, Jαβ 10.5, H-6'a, H-6'b), 3.67 (dd, 1H, H-3'), 3.36, 3.31 (2s, each 3H, 2×Oe-1), 3.29 (s, 3H, OMe-5'), 1.36, 1.30, 1.28, 1.23 (4s, each 3H, 2×CMe2); 13C NMR (50 MHz, CD3CN): δ 140.1, 139.4 (2×Ar-C), 129.2-128.2 (Ar-CH), 110.3, 108.2 (2×CMe2), 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×CH2Ph), 70.8, 71.8 (C-3', C-4'), 70.7 (C-6'), 65.6 (C-6), 56.7, 54.0 (2×Oe-1), 49.0 (OMe-5'), 27.1, 27.0, 26.9, 25.1 (2×CMe2). Anal. Calcd for C35H50O13: C, 61.93; H, 7.42. Found: C, 61.97; H, 7.44.
3.12. 2,3,6-Tri-O-benzyl-deoxy-\(\alpha\)-\(\epsilon\)-erythro-hex-4-enopyranosyl-(1→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 µL, 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 (Rf 0.31) and the formation of a major faster-moving product (Rf 0.51). Excess of NaH was destroyed with MeOH (0.5 mL) under stirring for 10 min at 0 °C, CH\(_2\)Cl\(_2\) (15 mL) and H\(_2\)O (8 mL) was added, and the aq phase was further extracted with CH\(_2\)Cl\(_2\) (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, Rf 0.31 (3:2 hexane-EtOAc); [\(\alpha\)]\(_D\) -25.0 (c 1.04, CHCl\(_3\)); \(^1\)H NMR (250 MHz, CD\(_3\)CN): \(\delta\) 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, \(J_{3',6'a} = J_{3',6'b} = 0.8\) Hz, H-4'), 4.86, 4.73 (AB system, 2H, \(J_{A,B} = 11.6\) Hz, CH\(_2\)Ph), 4.56, 4.52 (AB system, 2H, \(J_{A,B} = 11.8\) Hz, CH\(_2\)Ph), 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, \(J_{3,4} = 3.8\) Hz, \(J_{5,5'a} = J_{5,5'b} = 6.3\) Hz, H-5), 4.24 (m, 1H, \(J_{6',6'b} = 5.4\) Hz, H-3'), 4.08 (dd, 1H, \(J_{6,6'b} = 10.5\) 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-6'b), 3.90 (m, 2H, H-6'a, H-6'b), 3.35, 3.33 (2s, each 3H, 2 \(\times\) OMe), 1.34, 1.31, 1.30, 1.29 (4s, each 3H, 2 \(\times\) CMe\(_2\)); \(^{13}\)C NMR (62.9 MHz, CD\(_3\)CN): \(\delta\) 150.4 (C-5'), 139.8, 139.7, 139.5 (3 \(\times\) Ar-C), 129.2-128.4 (Ar-CH), 110.6, 108.7 (2 \(\times\) CMe\(_2\)), 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 \(\times\) CH\(_2\)Ph), 73.6 (C-2'), 71.8 (C-3'), 69.9 (C-6'), 65.9 (C-6), 56.2, 53.8 (2 \(\times\) OMe-1), 27.3, 27.2, 26.9, 25.1 (2 \(\times\) CMe\(_2\)). Anal. Calcd for C\(_{41}\)H\(_{52}\)O\(_{11}\): C, 68.3; H, 7.27. Found: C, 68.28; H, 7.29.

3.13. Epoxidation-methanolysis of 2,3,6-tri-O-benzyl-deoxy-\(\alpha\)-\(\epsilon\)-erythro-hex-4-enopyranosyl-(1→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 NaHCO\(_3\) (10 mL) was added, the solution was further stirred for 10 min and the solvent was removed under diminished pressure. CH\(_2\)Cl\(_2\) (20 mL) was added, the aq phase was
extracted with CH$_2$Cl$_2$ (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→4)-2,3:5,6-di-O-isopropylidene-aldehydo-α-glucose dimethyl acetal (23). Colourless syrup, [α]$_D$ -14.6 (c 0.96, CHCl$_3$); $R_f$ 0.33 (3:2 hexane- EtOAc); $^1$H NMR (250 MHz, CD$_3$CN): δ 7.43-7.26 (m, 15H, Ar H), 4.88, 4.74 (AB system, 2H, $J_{A,B}$ 11.4 Hz, CH$_2$Ph), 4.63, 4.50 (AB system, 2H, $J_{A,B}$ 11.9 Hz, CH$_2$Ph), 4.60, 4.44 (AB system, 2H, $J_{A,B}$ 11.8 Hz, CH$_2$Ph), 4.81 (d, 1H, $J_{1',2'}$ 1.1 Hz, H-1'), 4.42 (dd, 1H, $J_{A,B}$ 3.1 Hz, H$_{4(OH)}$), 3.81 (dd, 1H, $J_{2',3'}$ 1.2 Hz, H-3'), 3.81 (d, 1H, OH-4'),3.70, 3.50 (AB system, $J_{A,B}$ 10.2 Hz, H-6'a, H-6'b), 3.28, 3.25, (2s, each 3H, 2 x OMe-1), 3.19 (s, 12H, 2 x CMe$_2$); $^{13}$C NMR (62.9 MHz, CD$_3$CN): δ 139.5, 139.3, 139.2 (3 x Ar-C), 129.3-128.6 (Ar-CH), 110.4, 108.7 (2 x CMe$_2$), 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 x CH$_2$Ph), 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 x OMe-1), 48.9 (OMe-5'), 27.1, 27.0, 26.9, 25.1 (2 x CMe$_2$). Anal. Calcd for C$_{42}$H$_{56}$O$_{13}$: C, 65.61; H, 7.34. Found: C, 65.58; H, 7.31.

3.13.2. (5S or 5R)-2,3,6-Tri-O-benzyl-5-C-methoxy-β-D-lyxo-hexopyranosyl-(1→4)-2,3:5,6-di-O-isopropylidene-aldehydo-α-glucose dimethyl acetal (24). Colourless syrup; [α]$_D$ -54.6 (c 0.99, CHCl$_3$); $R_f$ 0.44 (3:2 hexane- EtOAc); $^1$H NMR (250 MHz, CD$_3$CN): δ 7.39-7.23 (m, 15H, Ar H), 4.93, 4.70 (AB system, 2H, $J_{A,B}$ 11.8 Hz, CH$_2$Ph), 4.73, 4.47 (AB system, 2H, $J_{A,B}$ 11.7 Hz, CH$_2$Ph), 4.59 (s, 2H, CH$_2$Ph), 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 Hz, J 6.7 Hz, H-5), 4.18 (d, 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 Hz, H-6'a, H-6'b), 3.37, 3.32 (2s, each 3H, 2 x OMe-1), 3.30 (s, 3H, OMe-5'), 1.31, 1.30, 1.29, 1.27 (4s, each 3H, 2 x CMe$_2$); $^{13}$C NMR (62.9 MHz, CD$_3$CN): δ 140.2, 139.9, 139.5 (3 x Ar-C), 129.2-128.1 (Ar-CH), 110.4, 108.7 (2 x CMe$_2$), 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 x CH$_2$Ph), 68.8 C-4), 70.7 (C-6'), 65.5 (C-6), 56.7, 54.0 (2 x OMe-1), 49.0 (OMe-5'), 27.2, 27.1, 26.9, 25.2 (2 x CMe$_2$). Anal. Calcd for C$_{42}$H$_{56}$O$_{13}$: C, 65.61; H, 7.34. Found: C, 65.58; H, 7.31.

A solution of 17 (344 mg, 0.479 mmol) in a 4:1 CH\(_3\)CN-H\(_2\)O (8.5 mL) solution was treated with 90% aq CF\(_3\)COOH (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 \(\times\) 30 mL). The crude residue was partitioned between brine (20 mL) and EtOAc (40 mL) and the aq phase extracted with EtOAc (3 \(\times\) 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 \(\alpha\)- and \(\beta\)-1,4-furanose anomers in a ratio of about 7:3 estimated on the basis of the relative C-1' NMR signal intensities (\(\delta\) 100.9 and 97.4 respectively); \(R_f\) 0.31 (1:1 hexane-EtOAc); mp 121-125 °C; Lit.\(^8\) mp 120-124 °C; \([\alpha]_D^{\infty}\) -20.5 (c 0.7; CHCl\(_3\)).

Hydrolysis of 20 (456 mg, 0.67 mmol) was performed in 4:1 (v/v) CH\(_3\)CN-H\(_2\)O (11 mL) with 90% aq CF\(_3\)COOH (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 chromatographated (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-\(\beta\)-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) CH\(_3\)CN-H\(_2\)O (18 mL) and 90% aq CF\(_3\)COOH (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 \(^{\text{13}}\text{C NMR, CD}_2\text{CN}\) by a mixture of \(\alpha\)- and \(\beta\)-1,4-furanose anomers in a ratio of about 65:35 estimated on the basis of the relative C-1 signal intensities (\(\delta\) 101.6 and 97.4 respectively); \([\alpha]_D^{\infty}\) -15.5 (c 1.0, CHCl\(_3\)); \(R_t\) 0.29 (4:1 CH\(_2\)Cl\(_2\)-Et\(_2\)O); Lit.\(^{16}\) for the \(\text{L}\)-enantiomer \([\alpha]_D^{\infty}\) +15.1 (c 0.96, CHCl\(_3\)).

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References


