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Toward the synthesis of fine chemicals from lactose: preparation of D-*xylo* and L-*lyxo*-aldohexos-5-ulose derivatives ☆

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ABSTRACT

The transformation of (5*R*)-2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-galactopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**8**) into partially protected derivatives of D-*xylo*- and L-*lyxo*-aldohexos-5-ulose has been reported, applying appropriate epimerisation methods to its 3′-*O*- and 4′-*O*-protected alcoholic derivatives.

1. Introduction

Lactose is the most abundant naturally occurring reducing disaccharide, which is obtained from whey as a by-product of the agro-industrial cheese production. Although it has a large worldwide availability, which is estimated at about 500,000 tons/year,[2a] only a low percentage of recovered lactose is utilised mainly in the food, feed and pharmaceutical fields. The chemical valorisation of lactose is achieved through simple transformations into commercially available products such as lactobionic acid,[2] a component of the preservative solution for transplanting organs, lactitol,[2] a suitable component of sugar-free, reduced caloric and low glycemic products and lactulose and galacto-oligosaccharides (GOS),[2] largely used in probiotic therapy.

Since lactose is inexpensive and there is a potential environmental risk connected with the uncontrolled dispersion of whey in freshwater, new synthetic channels need to be investigated in order to synthesise fine chemicals starting from this renewable raw material.

Recently, we planned a synthetic strategy to elaborate the non-reducing unit without modifying the reducing one, as is commonly done. This useful approach takes advantage of the large availability[3] of the two polyacetonides **1** and **2** (Fig. 1), which could be considered as simple β-D-galactopyranosides, due to the complete protection of the D-glucose unit. Aldohexos-5-uloses (**3**) represent an interesting, although yet poorly investigated class of dicarbonyl hexoses,[4] that are useful synthetic intermediates for the preparation of high value-added compounds such as iminosugars[5] and cyclitols, as inositols,[6] or polyhydroxycyclopentanes.[7]

A general approach (Chart 1) to aldohexos-5-uloses (**3**) was developed[8] using the key reaction, the epoxidation–methanolysis of hex-4-enopyranosides of type **5**, which are in turn obtained from 3,4-*O*-isopropylidene-β-D-galactopyranosides (**6**).

In this communication, we present the synthesis of partially protected derivatives of D-*xylo* and L-*lyxo*-aldohexos-5-uloses achieved here from the disaccharide 1′,5′-bis-glycoside **8**, analogous to **4**, which is in turn easily obtained from lactose,[9] following the same general approach outlined in Chart 1. The influence of the

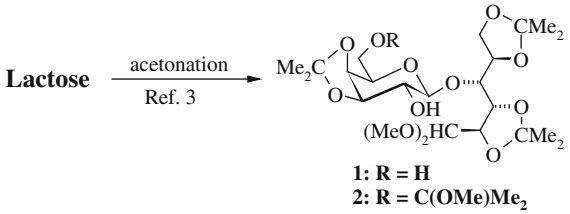

Figure 1. Polyacetonides directly obtained by acetonation of lactose.

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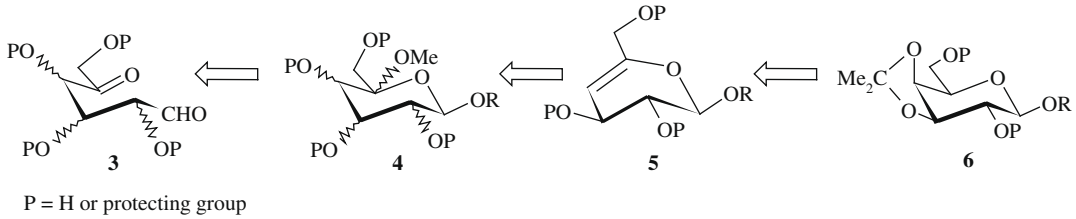


Chart 1. General approach to aldohexos-5-uloses from-D-galactopyranosides.

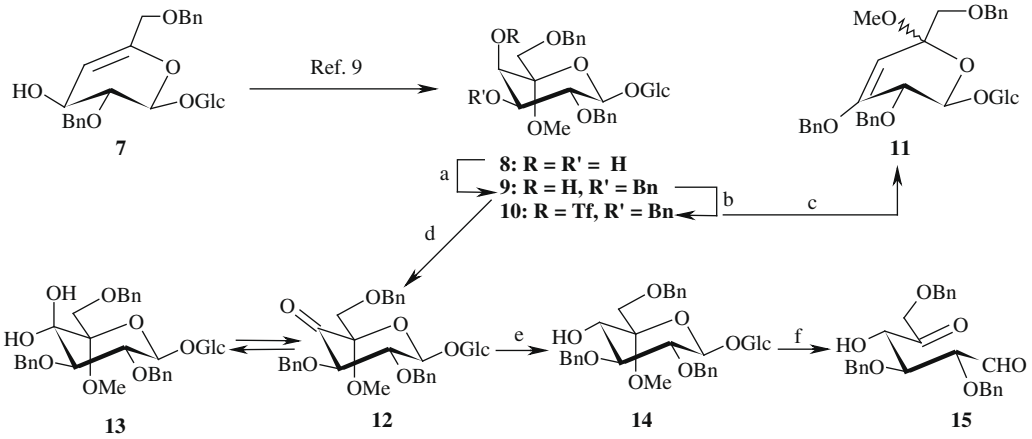
axial C-5′-OMe group on the chemo- and stereoselectivity of some reactions performed on the bis-glycoside unit is also observed and discussed.

2. Results and discussion

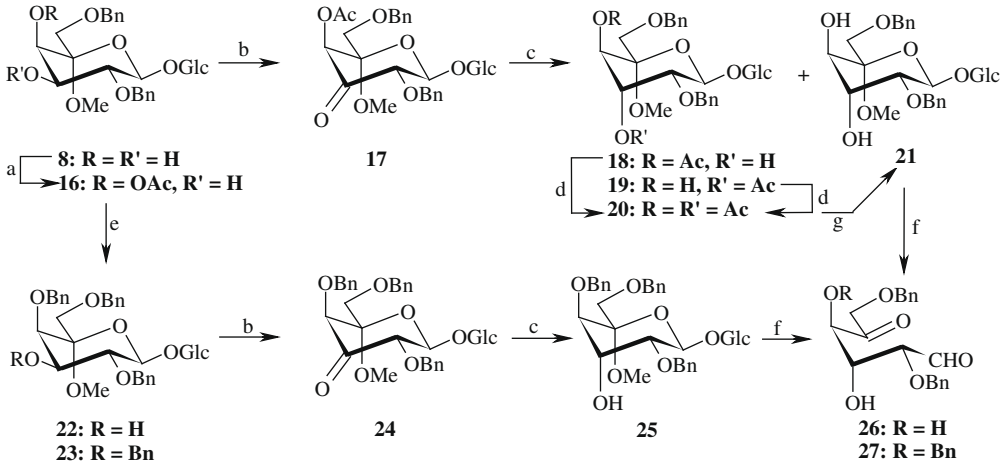
Preliminary attempts to obtain 1,5-bis-glycopyranosides of the D-*xylo* series through epoxidation–methanolysis of a 3′-*O*-protected derivative of the known disaccharide hex-4′-enopyranoside **7**,[9] following the method which was previously used in monosaccharide series,[8b] were abandoned due to the difficulties encountered in the separation of the complex crude diastereoisomeric mixture. An alternative way based on the regioselective protection of 3′-OH of the known diol **8**,[9] followed by stereoselective epimerisation at C-4′ (Scheme 1), was then considered. The first step was easily achieved through a stannylidene acetal-mediated alkylation. The method, which has largely been used to differentiate 1,2-*cis*-diols of a sugar,[10] has never been reported until now, on a 1,5-bis-glycopyranoside. As in the case of β-D-galactopyranosides,[10] the alkylation took place with complete regioselectivity on the 3′-OH group, leading in almost quantitative yield to the alcohol **9**.

The first C-4′ epimerisation strategy was attempted via an S_N2 displacement on the triflate **10**, which was obtained from **9** in high isolated yield (88%) by treatment with Tf_2O in pyridine. Surprisingly, the treatment of **10** with Bu_4NNO_2 in toluene led to the formation of enol ether **11**, isolated in 70% yield, instead of the desired inverted bis-glycoside **14**. This result is quite unexpected in light of the high yields reported for nucleophilic substitutions of structurally related 4-*O*-triflates of galactopyranosides[11] and is evidently due to some interference between the axial 5′-OMe group and the nucleophile approaching the vicinal reacting centre. The complementary strategy based on an oxidation–reduction sequence of **9** was thus explored. Also in the oxidation of **9**, the presence of the axial C-5′ methoxyl group sensibly influenced the reaction. Swern oxidation attempts failed completely, while treatment with PCC showed a low conversion even after long reaction times. Better results were obtained with the TPAP–NMO system, employing, however, an unexpectedly high catalyst molar ratio (40%) with respect to that usually needed (5%).[12] NMR analysis of the crude oxidation product showed a mixture of the 4′-ulosyl derivative **12** (C-4′ ^{13}C chemical shift: 198.3 ppm) and of its hydrate **13** (C-4′ ^{13}C chemical shift: 97.1 ppm). In the crude oxidation mixture, compounds **12** and **13**, which were isolated in about 89% yield, were present in about 4:1 ratio, as determined on the basis of the relative intensity of the ^{13}C 5′-OMe signals. Chromatographic purification led again to a mixture of **12** and **13** in the same 4:1 ratio, but with substantial loss of product, lowering the yield to a modest 56%. The reduction of the crude oxidation mixture with $NaBH_4$ in MeOH led to **14** and **9** in 64% and 20% isolated yields, respectively, indirectly confirming the structures of **12** and **13** and the extensive loss of the uloside during the chromatography on silica gel. In the case of the hydride reduction, the presence of the axial 5′-OMe group was beneficial for the stereoselectivity, determining the prevalence, although not complete, of attack on the β-face. This result is at variance with respect to the hydride reduction of analogous 4-keto-D-*arabino*-hexopyranosides, mainly leading to D-galactopyranosides.[13] Finally, the target 2,6-di-*O*-benzyl-D-*xylo*-aldohexos-5-ulose (**15**) was obtained from **14** (72% yield) by acid hydrolysis with CF_3COOH in CH_3CN–water (50 °C, 12 h) and by separation from D-glucose by extraction with EtOAc. As previously reported,[8b] **15** was present in CD_3CN as a 55:45 α,β-1,4-furanose mixture, as confirmed by NMR analysis.

The preparation of L-*lyxo* derivatives was based on the same approach used in the monosaccharide series,[8c] providing an oxidation–reduction sequence of a 3-OH free 1,5-bis-methyl L-*arabino*-hexopyranoside, obtained through the completely regioselective



Scheme 1. Stereoselective synthesis of 2,3,6-tri-*O*-benzyl-D-*xylo*-hexos-5-ulose. Reagents and conditions: (a) Bu_2SnO, $C_6H_5CH_3$, reflux, 12 h, then BnBr, Bu_4NBr, reflux, 1.5 h (94%); (b) Tf_2O, 1:1 CH_2Cl_2-Py, rt, 6 h (88%); (c) Bu_4NNO_2, $C_6H_5CH_3$, reflux, 8 h (70%); (d) TPAP, NMO, CH_2Cl_2, 4 Å, rt, 4 h; (e) $NaBH_4$, MeOH, rt, 1.5 h, (64% from **9**); (f) 90% aq CF_3COOH, 4:1 CH_3CN-H_2O, 50 °C, 12 h (72%).



Scheme 2. Synthesis of 2,6-di-*O*-benzyl- and 2,4,6-tri-*O*-benzyl-L-*lyxo*-aldohexos-5-ulose. Reagents and conditions: (a) $CH_3C(OEt)_3$, TsOH, $C_6H_5CH_3$, 45 °C, 25 min, then 80% aq AcOH, rt, 15 min (quantitative); (b) TPAP, NMO, CH_2Cl_2, 4 Å, rt, 45 min (**17**: 98%, **24**: 76%); (c) $NaBH_4$, MeOH, rt, 20 min (**25**: 88%); (d) 1:2 Ac_2O-Py, rt, 20 h; (e) NaH, BnBr (1 equiv), DMF, 0 °C, 25 min (**22**: 75% + **23**: 15%); (f) 90% aq CF_3COOH, 4:1 CH_3CN-H_2O, 50 °C, 4 h (**26**: 78%, **27**: 86%); (g) 0.1 M MeONa-MeOH, rt, 2 h (quantitative).

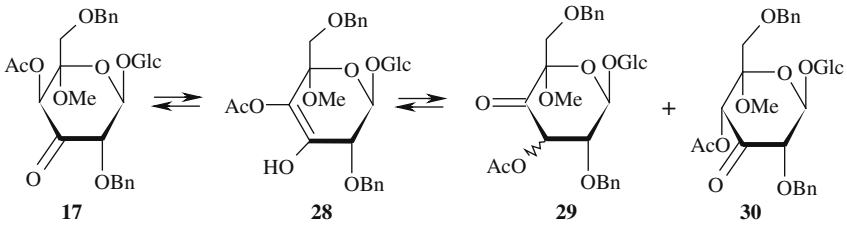
orthoester-mediated 4′-O-acetylation of the diol **8** (Scheme 2). As expected, the treatment of **8** with $CH_3C(OEt)_3$ and TsOH in toluene, followed by the opening of the *ortho*-acetate ring with AcOH, afforded the alcohol **16** in almost quantitative yield. The next oxidation step was achieved again by using the TPAP–NMO system under milder reaction conditions with respect to those used before (TPAP 5%, 2 h, 98% yield). The reduction of **17** ($NaBH_4$ in MeOH) appeared not as that simple as that for the analogous 1,5-bis-methyl-glycopyranoside, for which only the formation of the two 5′-OMe L-*lyxo* and L-*arabino* diastereoisomers in a 5:1 ratio was reported.[8c] In fact, the reduction of the uloside **17** led to a complex product mixture constituted (TLC, 1:1 EtOAc–hexane) of at least four components displaying two well-differentiated ranges of R_f values on silica gel. The flash chromatography permitted only a partial separation of the two faster moving components (R_f 0.39 and 0.34, respectively), surprisingly identified (NMR) as the two isomeric L-*lyxo* monoacetates **18** and **19**, accounting for a combined 52% yield. The structure of the above compounds was further confirmed through conventional acetylation leading, in both cases, to the same diacetate **20**. Two other fractions containing the lower moving components (R_f 0.23 and 0.20) were collected, one constituted by the pure L-*lyxo* diol **21** (13% yield) and the other by a mixture (about 1:1, combined yield 26%) of **18** and one other, yet unidentified,[†] diastereoisomeric diol. While the presence of the 4′-*O*-acetyl **18** could be simply explained by a lower base-promoted O-deacetylation rate with respect to the monosaccharide analogue,[8c] it is difficult to imagine the formation of the 3′-*O*-acetyl **19** directly from **18** through an acetyl shift taking place, after the reduction, from the axial 4′-OH group to the axial *anti* 3′-OH one. A better hypothesis as to why **19** is formed would be due to an acyl shift on an enolic intermediate such as **28**, where the 3′-OH group and the 4′-OAc one are co-planar (Scheme 3). The enolisation of **17** could explain both the migration of the acetyl group and the loss of stereochemical purity either at C-4′ and C-3′, which also gives rise to the isolation in low amount of an unidentified diastereoisomeric diol.

The O-deacetylation of **20** (MeONa–MeOH) afforded quantitatively **21**, raising its overall yield to an acceptable 65%. Diol **21** was finally subjected to acid hydrolysis (CF_3COOH–CH_3CN–water) to give the previously reported 2,6-di-*O*-benzyl-L-*lyxo*-aldohexos-5-ulose (**26**).[8c]

The problems encountered in the reduction of **17** could be avoided simplifying the chromatographic purifications, by changing the protection of the 4′-OH group from the acetate to a base-stable ethereal one. The direct monobenzylation of **8** was considered as the method of choice for the 4′-regioselective protection on the basis of the findings from Bernet and Vasella,[14] which underlined, in both sugars and inositols, an enhanced acidity for axial hydroxy groups having a vicinal *anti*-alkoxy group. The benzylation with BnBr (1 equiv) and NaH in DMF at 0 °C pleasantly led to the 4′-*O*-monobenzyl derivative **22**, isolated in a satisfactory 75% yield, after an easy chromatographic separation from the 3,4-di-*O*-benzyl derivative **23** (Scheme 2). No traces of the product of 3′-O-monobenzylation (**14**) were observed at any stage of the reaction. A specific role of the axial 5′-OMe in enhancing the acidity of 4′-OH is outlined by comparing the lower regioselectivity in the monobenzylation of methyl 2,6-di-*O*-benzyl-β-D-galactopyranoside, where 3-OH and 4-OH alkylation products were obtained in a 1:2 ratio.[15] The alcohol **22** was then submitted to an oxidation reaction with TPAP–NMO, and the desired 3′-ulosyl derivative **24** was obtained in 76% yield. The reduction of **24** with $NaBH_4$ in MeOH afforded **25** in a completely stereoselective way, owing to the negative 1,3-*syn* diaxial interaction between the 5′-OMe group and the hydride attacking from the α-face. 2,4,6-Tri-*O*-benzyl-L-*lyxo*-aldohexos-5-ulose (**27**) was obtained after removal of the acetal groups by acid hydrolysis (CF_3COOH and CH_3CN–water), and its NMR data were identical to those of the sample which was previously reported,[6b] pointing to a complex tautomeric mixture, whose structure was indirectly confirmed by its transformation into the expected inosose.[6b]

In conclusion, with this work an understanding of the potentiality of lactose as a renewable starting material for the synthesis of fine chemicals has been increased via the preparation of aldohexos-5-ulose derivatives in the D-*xylo* and L-*lyxo* series. The crucial role of the axial anomeric 5′-OMe group of the 1′,5′-bis-glycosides has also been pinpointed in both the synthetic routes. In the first one, which leads to the D-*xylo* derivative **15**, it decreases the reactivity in the C-4′ oxidation, and in addition, completely turns the reactivity of the axial 4′-*O*-trifluoromethansulfonate from substitution to elimination. Moreover, for steric reasons, the outcome of the 4′-uloside reduction diastereoselection is changed from a near-complete *galacto* to a predominant *gluco* configuration. In the second synthetic pathway, leading to the L-*lyxo*-hexos-5-ulose

[†] Unexpectedly, this second diastereoisomeric diol did not correspond to the L-*arabino* derivative **8**. Owing to the difficulties to obtain a pure sample of this compound, present in the crude reaction mixture in low yield (about 13%), we abandoned any effort to further elucidate its structure, a point that was outside the scope of the present work.



Scheme 3. Base-promoted isomerisation of the uloside **17**.

27, the presence of the axial C-5′ methoxyl group allows the regioselective alkylation of 4′-OH group and the completely stereoselective reduction of the intermediate 3′-uloside.

3. Experimental

3.1. General methods

General methods are those reported in Ref. 16. Compound **8** was prepared according to the described procedure.[9]

3.2. (5*R*)-2,3,6-Tri-*O*-benzyl-5-*C*-methoxy-α-L-*arabino*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (9)

A solution of **8**[9] (3.94 g, 5.80 mmol) in toluene (90 mL) was treated with Bu_2SnO (1.86 g, 7.44 mmol), heated to reflux and subjected to azeotropic removal of water with a Dean–Stark apparatus. The reaction mixture was stirred at reflux (12 h), and then treated with Bu_4NBr (944 mg, 2.90 mmol) and BnBr (0.94 mL, 7.88 mmol) and further stirred until the starting material disappeared (1.5 h, TLC, 7:3 hexane–EtOAc). The solvent was removed under diminished pressure, and the residue (9.02 g) was subjected to flash chromatography (first hexane 400 mL, then 7:3 hexane–EtOAc) to give **9** (4.20 g, 94% yield) as a colourless syrup; $[\alpha]_D$ +4.0 (*c* 1.2, $CHCl_3$); R_f 0.29 (7:3 hexane–EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): see Table 1 and δ 7.35–7.26 (m, 15H, Ar–H), 4.84, 4.68 (AB system, 2H, $J_{A,B}$ 11.1 Hz, CH_2Ph), 4.72, 4.47 (AB system, 2H, $J_{A,B}$ 12.3 Hz, CH_2Ph), 4.68 (s, 2H, CH_2Ph), 4.49 (dd, 1H, $J_{1,2}$ 6.5 Hz, $J_{2,3}$ 7.7 Hz, H-2), 4.31 (d, 1H, H-1), 4.26 (bq, 1H, H-5), 4.14 (dd, 1H, $J_{5,6b}$ 5.5 Hz, $J_{6a,6b}$ 8.9 Hz, H-6b), 4.02 (dd, 1H, $J_{3,4}$ 1.0 Hz, H-3), 3.88 (m, 1H, H-6a), 3.86 (dd, 1H, $J_{4,5}$ 5.8 Hz, H-4), 3.27, 3.26, 3.23 (3s, each 3H, 3 × OMe), 2.48 (d, 1H, $J_{4',OH}$ 1.9 Hz, OH-4′), 1.40, 1.38, 1.37, 1.36 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 138.6, 138.0, 137.7 (3 × Ar–C), 128.4–127.4 (Ar–CH), 109.9, 108.5 (2 × CMe_2), 75.2, 73.5, 72.5 (3 × CH_2Ph), 55.7, 52.5 (2 × OMe-1), 47.9 (OMe-5′), 27.3, 26.9, 26.5, 25.3 (2 × CMe_2). Anal. Calcd for $C_{42}H_{56}O_{13}$: C, 65.61; H, 7.34. Found: C, 65.70; H, 7.39.

3.3. (5*R*)-2,3,6-Tri-*O*-benzyl-4-*O*-trifluoromethansulfonyl-5-*C*-methoxy-α-L-*arabino*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (10)

To a solution of **9** (213 mg, 0.277 mmol) in dry 1:1 Py–CH_2Cl_2 (3 mL) cooled to −14 °C was added dropwise Tf_2O (55 μL, 0.333 mmol) dissolved in dry CH_2Cl_2 (10 mL). The mixture was warmed to room temperature and stirred until the starting material disappeared (6 h, TLC, 6:4 hexane–EtOAc). Satd aq $NaHCO_3$ (8 mL) was added, and the mixture was partitioned between water and CH_2Cl_2. The aq phase was extracted with CH_2Cl_2 (3 × 25 mL), the organic extracts were collected, dried ($MgSO_4$) and concentrated under diminished pressure. The residue (264 mg) was subjected to flash chromatography (3:1 hexane–EtOAc) to give **10** (0.221 g, 88% yield) as a colourless syrup; $[\alpha]_D$ +15.7 (*c* 1.2, $CHCl_3$); R_f 0.29 (7:3 hexane–EtOAc); ^{1}H NMR (250 MHz, CD_3CN): see Table 1 and δ 7.59–7.27 (m, 15H, Ar–H), 4.83, 4.59 (AB system, 2H, $J_{A,B}$ 11.3 Hz, CH_2Ph), 4.79, 4.67 (AB system, 2H, $J_{A,B}$ 11.4 Hz, CH_2Ph), 4.63, 4.49 (AB system, 2H, $J_{A,B}$ 11.5 Hz, CH_2Ph), 4.36 (m, 2H, H-1, H-2), 4.24 (bq, 1H, H-5), 4.08 (dd, 1H, $J_{5,6b}$ 5.7 Hz, $J_{6a,6b}$ 8.6 Hz, H-6b), 4.03 (m, 1H, $J_{3,4}$ 1.7 Hz, H-3), 3.88 (dd, 1H, $J_{4,5}$ 5.9 Hz, H-4), 3.87 (dd, 1H, $J_{5,6a}$ 5.4 Hz, H-6a), 3.32 (s, 6H, 2 × OMe-1), 3.22 (s, 3H, OMe-5′), 1.36, 1.35, 1.33, 1.26 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (62.9 MHz, CD_3CN): see Table 2 and δ 139.2, 138.6, 138.4 (3 × Ar–C), 129.3–128.5 (Ar–CH), 110.3, 109.2 (2 × CMe_2), 100.3 (C-1′), 75.9, 73.8, 73.7 (3 × CH_2Ph), 56.5, 53.6 (2 × OMe-1), 49.3 (OMe-5′), 27.4, 26.9, 26.7, 25.3 (2 × CMe_2). Anal. Calcd for $C_{42}H_{53}F_3O_{14}S$: C, 57.92; H, 6.13; F, 6.54; S, 3.68. Found: C, 57.94; H, 6.14; F, 6.56; S, 3.69.

3.4. (5*R*)-2,3,6-Tri-*O*-benzyl-4-deoxy-5-*C*-methoxy-β-D-*glycero*-hex-3-enopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (11)

A solution of **10** (102 mg, 0.113 mmol) in dry toluene (5 mL) was treated with Bu_4NNO_2 (147 mg, 0.51 mmol) at room temperature and warmed to reflux under stirring. After 8 h, when the starting material disappeared (TLC, 3:2 hexane–EtOAc), the mixture

Table 1
^{1}H NMR parameters (δ, ppm; *J*, Hz) of the nonreducing unit of **9–11**, **14**, **16–20** and **22–25**

Compound	Solvent	H-1′	H-2′	H-3′	H-4′	H-6′a	H-6′b	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{6'a,6'b}$
9	$CDCl_3$	4.86	3.61	3.89	4.11	3.59	3.50	7.9	9.4	3.7	10.4
10	CD_3CN	4.92	3.51	4.02	5.33	3.70	3.38	7.9	9.8	2.4	11.0
11	CD_3CN	5.15	3.91	—	5.06	3.65	3.31	6.2	—	—	10.2
14	CD_3CN	4.86	3.38	3.60	3.79	3.72	3.58	8.0	9.1	9.1	10.1
16	$CDCl_3$	4.93	3.42	3.97	5.41	3.42	3.25	7.9	10.0	3.4	10.8
17	$CDCl_3$	5.04	4.04	—	5.09	3.57	3.34	7.3	—	—	10.6
18	$CDCl_3$	5.24	3.45	3.45	5.10	3.33	3.27	8.2	3.3	n.d.	10.3
19	$CDCl_3$	5.31	3.63	5.24	3.42	3.52	3.46	8.2	3.6	3.3	10.6
20	$CDCl_3$	5.31	3.42	5.21	5.08	3.42	3.24	8.3	3.4	3.0	10.5
22	$CDCl_3$	4.86	3.52	4.00	3.87	3.53	3.45	7.9	9.9	3.4	10.3
23	$CDCl_3$	4.82	3.82	3.82	4.05	3.57	3.41	7.6	n.d.	n.d.	10.1
24	CD_3CN	4.91	4.31	—	3.74	3.61	3.55	7.5	—	—	10.6
25	$CDCl_3$	5.17	3.51	3.99	3.73	3.55	3.42	8.4	3.4	3.2	10.2

Table 2
Selected ^{13}C NMR signals (δ, ppm) of the disaccharide derivatives **9–11**, **14** and **16–25**[a]

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
9	$CDCl_3$	105.5	74.4	77.8	75.0	77.2	65.5	98.9	78.8	78.6	67.2	100.3	64.7
10	CD_3CN	106.4	75.7	76.6	76.5	77.7	66.1	100.3	79.2	78.3	82.7	99.8	65.3
11	CD_3CN	106.6	76.0	78.8	76.5	77.9	66.2	99.6	76.5	155.3	99.4	99.5	70.3
14	CD_3CN	106.9	76.2	78.4	76.9	77.8	66.2	99.7	82.8*	82.0*	74.1	99.9	74.4
16	$CDCl_3$	105.5	74.5*	77.8*	76.4	77.6*	64.8	98.4	74.3*	69.6*	68.8*	99.5	64.1
17	$CDCl_3$	106.1	75.0*	77.6	75.1*	76.9	65.3	100.0	80.2	197.2	74.9*	99.9	64.2
18	$CDCl_3$	106.2	75.5	77.7	75.2	77.3	65.4	96.4	74.3	69.3*	69.2*	101.6	64.9
19	$CDCl_3$	105.6	74.8*	78.0	74.7*	77.7	65.3	96.2	73.8*	71.6	68.4	101.4	66.2
20	$CDCl_3$	105.8	74.8	77.9*	75.1	77.8*	65.2	95.9	73.1	68.5*	68.4*	100.5	65.2
21	$CDCl_3$	105.9	74.7	77.8	75.4	77.5	65.4	96.1	74.7	71.6	69.6	102.3	65.9
22	$CDCl_3$	105.4	74.3	77.8	74.6	77.3	65.2	99.1	79.6	70.7	77.5	100.8	64.7
23	$CDCl_3$	105.2	74.0	77.6	74.8	76.9	65.4	99.1	79.4	79.2	75.1	100.6	64.5
24	CD_3CN	106.5	75.8	78.4	77.4	77.7	66.2	100.9	82.0	202.3	82.0	101.6	64.9
25	$CDCl_3$	106.4	74.9	77.9	75.2	76.3	65.7	97.3	78.5*	70.1	78.3*	103.5	66.2

[a] Assignments (*) may be interchanged.

was cooled to room temperature and concentrated under diminished pressure. The residue (160 mg) was subjected to flash chromatography (4:1 hexane–EtOAc) to give **11** (60 mg, 70% yield) as a colourless syrup; $[\alpha]_D$ −24.0 (*c* 1.36, $CHCl_3$); R_f 0.29 (7:3 hexane–EtOAc); ^1H NMR (250 MHz, CD_3CN): see Table 1 and δ 7.43–7.25 (m, 15H, Ar–H), 4.90, 4.84 (AB system, 2H, $J_{A,B}$ 11.9 Hz, CH_2Ph), 4.74 (s, 2H, CH_2Ph), 4.55, 4.49 (AB system, 2H, $J_{A,B}$ 12.0 Hz, CH_2Ph), 4.37 (d, 1H, $J_{1,2}$ 5.5 Hz, H-1), 4.34 (dd, 1H, $J_{2,3}$ 6.4 Hz, H-2), 4.23 (m, 1H, H-5), 4.12 (dd, 1H, $J_{5,6b}$ 1.3 Hz, $J_{6a,6b}$ 8.5 Hz, H-6b), 4.06 (dd,1H, $J_{3,4}$ 1.6 Hz, H-3), 4.03 (dd, 1H, $J_{5,6a}$ 6.1 Hz, H-6a), 3.88 (dd, 1H, $J_{4,5}$ 5.3 Hz, H-4), 3.34, 3.30, 3.25 (3s, each 3H, 2 × OMe-1, OMe-5′), 1.33, 1.32, 1.30, 1.26 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (62.9 MHz, CD_3CN): see Table 2 and δ 139.5, 139.4, 137.8 (3 × Ar–C), 129.4–128.6 (Ar–CH), 110.5, 109.1 (2 × CMe_2), 74.8, 74.1, 73.0 (3 × CH_2Ph), 56.6, 53.5 (2 × OMe-1), 50.0 (OMe-5′), 27.5, 27.1, 26.8, 25.4 (2 × CMe_2). Anal. Calcd for $C_{41}H_{52}O_{11}$: C, 68.31; H, 7.27. Found: C, 68.35; H, 7.29.

3.5. (5*R*)-2,3,6-Tri-*O*-benzyl-5-*C*-methoxy-α-L-*threo*-hex-4-ulopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (12)

A solution of **9** (493 mg, 0.641 mmol) in dry CH_2Cl_2 (12 mL) and pre-dried 4-methylmorpholine-*N*-oxide (NMO) (123 mg, 1.05 mmol) containing 4 Å powdered molecular sieves (120 mg) was stirred under an argon atmosphere for 30 min at room temperature. Tetrapropylammonium perruthenate (TPAP) (90 mg, 40%) was added, and the resulting green mixture was stirred for further 4 h at room temperature. The reaction mixture was filtered through alternate pads of Celite and silica gel and extensively washed with CH_2Cl_2 and then with EtOAc. The combined organic phases were concentrated under diminished pressure to give a syrup (439 mg) constituted (^{13}C NMR, $CDCl_3$) by a mixture of **12** and **13** in a ratio of about 4:1 as estimated on the basis of the relative 5′-OMe NMR signal intensities. Flash chromatographic purification of the crude residue, eluting with 6:4 hexane–EtOAc, gave a 4:1 mixture of **12** and **13** (276 mg combined yield about 56%) as a colourless syrup; $[\alpha]_D$ +9.3 (*c* 1.1, $CHCl_3$); R_f 0.92 (9:1 CH_2Cl_2–Me_2CO); selected ^{13}C NMR (50 MHz, CD_3CN) signals: *major component* **12**: δ 198.3 (C-4′), 139.7, 137.4, 137.3 (3 × Ar–C), 110.4, 109.2 (2 × CMe_2), 106.6 (C-1), 99.4 (C-5′), 99.1 (C-1′), 84.7, 82.3 (C-2′, C-3′), 78.4, 77.9 (C-3, C-5), 76.7, 75.9 (C-4, C-2), 75.7, 75.7, 74.1 (3 × CH_2Ph), 67.2, 66.0 (C-6, C-6′), 56.6, 53.9 (2 × OMe-1), 50.2 (OMe-5′); *minor component* **13**: δ 139.8, 138.9, 138.2 (3 × Ar–C), 110.3, 109.2 (2 × CMe_2), 106.4 (C-1), 99.4 (C-5′), 99.4 (C-1′), 97.1 (C-4′), 82.5, 81.5 (C-2′, C-3′), 81.4, 78.4 (C-3, C-5), 77.6, 77.5 (C-4, C-2), 76.4, 75.7, 74.1 (3 × CH_2Ph), 70.3, 66.0 (C-6, C-6′), 56.4, 53.6 (2 × OMe-1), 48.8 (OMe-5′). Cluster of signals for both components: δ 129.4–127.5 (Ar–CH), 27.8–25.4 (CMe_2).

3.6. (5*R*)-2,3,6-Tri-*O*-benzyl-5-*C*-methoxy-β-D-*xylo*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (14)

A solution of a mixture of crude **12** and **13** (912 mg) in dry MeOH (50 mL) was cooled at 0 °C and treated with $NaBH_4$ (180 mg, 4.77 mmol). The reaction mixture was gently warmed to room temperature and left stirring until the TLC analysis (7:3 hexane–EtOAc) showed the complete disappearance of the starting material (1.5 h). Water (15 mL) was added, the solution was stirred for 30 min, and then concentrated under diminished pressure. The residue was partitioned between water (40 mL) and CH_2Cl_2 (80 mL). The aq phase was extracted with CH_2Cl_2 (3 × 80 mL), and the organic extracts were collected, dried ($MgSO_4$) and concentrated under diminished pressure. The residue (869 mg) was subjected to flash chromatography over silica gel (7:3 hexane–EtOAc) to give **14** (583 mg, 64% yield) and **9** (187 mg, 20% yield).

Compound **14**: colourless syrup; $[\alpha]_D$ −15.9 (*c* 1.0, $CHCl_3$); R_f 0.12 (7:3 hexane–EtOAc); ^1H NMR (200 MHz, CD_3CN): see Table 1 and δ 7.39–7.26 (m, 15H, Ar–H), 4.84, 4.66 (AB system, 2H, $J_{A,B}$ 11.4 Hz, CH_2Ph), 4.81, 4.75 (AB system, 2H, $J_{A,B}$ 11.3 Hz, CH_2Ph), 4.62, 4.48 (AB system, 2H, $J_{A,B}$ 11.8 Hz, CH_2Ph), 4.48 (dd, 1H, $J_{1,2}$ 6.3 Hz, $J_{2,3}$ 7.4 Hz, H-2), 4.33 (d, 1H, H-1), 4.21 (m, 1H, H-5), 4.09 (dd, 1H, $J_{5,6b}$ 5.7 Hz, $J_{6a,6b}$ 8.5 Hz, H-6b), 4.08 (dd, 1H, $J_{3,4}$ 1.6 Hz, H-3), 3.87 (dd, 1H, $J_{5,6a}$ 6.2 Hz, H-6a), 3.85 (bd, 1H, H-4), 3.36, 3.32, 3.30 (3s, each 3H, 2 × OMe-1, OMe-5′), 1.36, 1.35, 1.34, 1.26 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (50 MHz, CD_3CN): see Table 2 and δ 140.2, 139.7, 139.2 (3 × Ar–C), 129.3–128.2 (Ar–CH), 110.4, 109.2 (2 × CMe_2), 75.7, 75.5, 74.3 (3 × CH_2Ph), 56.6, 54.3 (2 × OMe-1), 49.0 (OMe-5′), 27.5, 27.1, 27.0, 25.5 (2 × CMe_2). Anal. Calcd for $C_{42}H_{56}O_{13}$: C, 65.61; H, 7.34. Found: C, 65.73; H, 7.38.

Compound **9**: colourless syrup; NMR parameters were identical to those of the sample prepared above.

3.7. 2,3,6-Tri-*O*-benzyl-D-*xylo*-hexos-5-ulose (15)

A solution of **14** (276 mg, 0.359 mmol) in 4:1 (v/v) CH_3CN–water (7 mL) was treated with 90% aq CF_3COOH (1.4 mL) and warmed to 50 °C with stirring until TLC analysis (EtOAc) showed the complete disappearance of the starting material (12 h). The mixture was concentrated under diminished pressure and repeatedly co-evaporated with toluene (4 × 20 mL) under diminished pressure. The crude residue was partitioned between brine (20 mL) and EtOAc (30 mL), and the aq phase was extracted with

EtOAc (3 × 30 mL). The organic phases were collected, dried ($MgSO_4$) and concentrated under diminished pressure to give a residue (125 mg) that was directly filtered onto silica gel, eluting with 3:7 hexane–EtOAc, to give pure **15** (122 mg, 72% yield) as a colourless syrup. NMR data were in full agreement with those reported.[8b]

3.8. (5*R*)-4-*O*-Acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-α-L-*arabino*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (16)

To a solution of **8**[9] (341 mg, 0.502 mmol) in dry toluene (10 mL) warmed to 45 °C, $CH_3C(OEt)_3$ (1.1 mL, 6.02 mmol) and TsOH (9.5 mg, 0.05 mmol) were added. The solution was stirred for 2 h at 45 °C until TLC analysis (1:1 hexane–EtOAc) showed the complete disappearance of the starting material (R_f 0.38) with the formation a faster moving product (R_f 0.60). The mixture was allowed to attain room temperature, treated with Et_3N (0.1 mL) and further stirred for 10 min. The solution was concentrated under diminished pressure, and the residue (228 mg) was treated with 80% aq AcOH (3.0 mL) and stirred at room temperature until the product at R_f 0.60 was completely reacted (TLC, 1:1 hexane–EtOAc, 15 min). The mixture was diluted with CH_2Cl_2 (20 mL) and carefully neutralised with 40% aq NaOH (4 mL). The reaction mixture was diluted with water (7 mL), and the aq phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under diminished pressure. The residue (356 mg) was constituted exclusively (NMR) of **16** (quant yield). An analytical sample of **16** was obtained through flash chromatography eluting with 3:2 hexane–EtOAc. Pure **16** (308 mg, 85% yield) was a white foam; $[\alpha]_D$ −24.2 (*c* 0.95, $CHCl_3$); R_f 0.51 (1:1 hexane–EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 7.35–7.26 (m, 10H, Ar–H), 4.92, 4.59 (AB system, 2H, $J_{A,B}$ 11.3 Hz, CH_2Ph), 4.49 (dd, 1H, $J_{1,2}$ 6.7 Hz, $J_{2,3}$ 7.0 Hz, H-2), 4.46 (s, 2H, CH_2Ph), 4.32 (d, 1H, H-1), 4.30–3.95 (m, 5H, H-3, H-4, H-5, H-6a, H-6b), 3.34, 3.33 (2s, each 3H, 2 × OMe-1), 3.27 (s, 3H, OMe-5′), 2.22 (bs, 1H, OH-3′), 1.96 (s, 3H, *Me*CO), 1.45, 1.32 (2s, each 3H, C*Me*$_2$), 1.41 (s, 6H, C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ see Table 2 and 169.5 (Me*CO*), 137.8, 136.9 (2 × Ar–C), 129.4–127.4 (Ar–CH), 109.6, 108.1 (2 × CMe_2), 74.3, 73.1 (2 × CH_2Ph), 55.6, 52.9 (2 × OMe-1), 47.8 (OMe-5′), 26.8, 26.1, 26.0, 24.7 (2 × C*Me*$_2$), 20.4 (*Me*CO). Anal. Calcd for $C_{37}H_{52}O_{14}$: C, 61.65; H, 7.27. Found: C, 61.59; H, 7.23.

3.9. Oxidation–reduction of (5*R*)-4-*O*-Acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-α-L-*arabino*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (16)

3.9.1. Oxidation of 16

A suspension of **16** (356 mg, 0.494 mmol) in dry CH_2Cl_2 (6 mL) and pre-dried 4-methylmorpholine-*N*-oxide (NMO) (98 mg, 0.841 mmol) containing 4 Å powdered molecular sieves (250 mg) was stirred under an argon atmosphere for 30 min at room temperature. Tetrapropylammonium perruthenate (TPAP) (35 mg, 20%) was added, and the resulting green mixture was stirred until TLC analysis (13:7 hexane–EtOAc) revealed the disappearance of the starting material (45 min, R_f 0.25). The reaction mixture was filtered through alternate paths of Celite and silica gel and extensively washed first with CH_2Cl_2 and then with EtOAc. The combined organic phases were concentrated under diminished pressure to give a syrup (352 mg) constituted exclusively (NMR) by the uloside **17**; R_f 0.17 (13:7 hexane–EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 7.30–7.22 (m, 10H, Ar–H), 4.80, 4.65 (AB system, 2H, $J_{A,B}$ 11.9 Hz, CH_2Ph), 4.52, 4.43 (AB system, 2H, $J_{A,B}$ 12.4 Hz, CH_2Ph), 4.46 (dd, 1H, $J_{1,2}$ 6.6 Hz, $J_{2,3}$ 7.1 Hz, H-2), 4.32 (d, 1H, H-1), 4.25 (m, 1H, H-5), 4.17–3.85 (m, 4H, H-3, H-4, H-6a, H-6b), 3.36 (s, 6H, 2 × OMe-1), 3.29 (s, 3H, OMe-5′), 1.86 (s, 3H, *Me*CO), 1.41, 1.38, 1.35, 1.31 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 168.5 (Me*CO*), 137.1, 136.8 (2 × Ar–C), 129.7–127.8 (Ar–CH), 109.9, 108.6 (2 × CMe_2), 73.2, 72.9 (2 × CH_2Ph), 56.2, 53.6 (2 × OMe-1), 48.7 (OMe-5′),27.2, 26.5, 26.3, 25.3 (2 × C*Me*$_2$), 20.3 (*Me*CO).

3.9.2. Reduction of 17

A solution of crude **17** (352 mg, 0.489 mmol) in dry MeOH (10 mL) was cooled to 0 °C and treated, under an argon atmosphere, with $NaBH_4$ (138 mg, 3.65 mmol). The reaction mixture was gently warmed to room temperature and left under stirring until TLC analysis (1:1 hexane–EtOAc) showed the complete disappearance of the starting material (30 min). Water (15 mL) was added and the solution was stirred for 4 h, and then concentrated under diminished pressure. The residue was partitioned between water (20 mL) and CH_2Cl_2 (40 mL). The aq phase was extracted with CH_2Cl_2 (5 × 25 mL), and the organic extracts were collected, dried ($MgSO_4$) and concentrated under diminished pressure. The residue (307 mg) was subjected to flash chromatography (first 11:9 hexane–EtOAc, then 2:3 hexane–EtOAc), collecting four main fractions. The first two fractions were constituted by the monoacetates **18** (65 mg) and **19** (120 mg), each in mixture with about 10% of the other, accounting for an overall 52% yield. The third fraction contained pure diol **21** (43 mg, 13% yield), and the fourth one contained a 1:1 mixture of **21** and another yet unidentified diastereoisomeric diol (86 mg, each about 13% yield).

3.9.2.1. (5*R*)-4-*O*-Acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-α-L-*xylo*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (18).

R_f 0.39 (1:1 hexane–EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 7.34–7.18 (m, 10H, Ar–H), 4.71, 4.59 (AB system, 2H, $J_{A,B}$ 12.0 Hz, CH_2Ph), 4.56, 4.49 (AB system, 2H, $J_{A,B}$ 12.0 Hz, CH_2Ph), 4.42 (dd, 1H, $J_{1,2}$ 6.4 Hz, $J_{2,3}$ 7.0 Hz, H-2), 4.32 (d, 1H, H-1), 4.25 (m, 2H, H-5, H-6a), 4.05–3.90 (m, 3H, H-3, H-4, H-6b), 3.32, 3.30. 3.29 (3s, each 3H, 2 × OMe-1, OMe-5′), 2.69 (d, 1H, $J_{4',OH}$ 5.3 Hz, OH-4′), 2.02 (s, 3H, *Me*CO), 1.41, 1.32 (2s, each 3H, C*Me*$_2$); 1.40 (s, 6H, C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 170.5 (Me*CO*), 138.2, 137.4 (2 × Ar–C), 128.5–126.9 (Ar–CH), 110.0, 108.4 (2 × CMe_2), 73.4, 72.6 (2 × CH_2Ph), 55.8, 52.8 (2 × OMe-1), 48.1 (OMe-5′), 27.3, 26.6, 26.3, 25.4 (2 × C*Me*$_2$), 20.9 (*Me*CO). Anal. Calcd for $C_{37}H_{52}O_{14}$: C, 61.65; H, 7.27. Found: C, 61.58; H, 7.25.

3.9.2.2. (5*R*)-3-*O*-Acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-α-L-*xylo*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (19).

R_f 0.34 (1:1 hexane–EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 7.33–7.26 (m, 10H, Ar–H), 4.81, 4.63 (AB system, 2H, $J_{A,B}$ 12.1 Hz, CH_2Ph), 4.47, 4.40 (AB system, 2H, $J_{A,B}$ 11.7 Hz, CH_2Ph), 4.47 (dd, 1H, $J_{1,2}$ 6.4 Hz, $J_{2,3}$ 7.6 Hz, H-2), 4.28–3.94 (m, 3H, H-5, H-6a, H-6b), 4.32 (d, 1H, H-1), 4.06 (dd, 1H, $J_{3,4}$ 1.2 Hz, H-3), 3.92 (dd, 1H, $J_{4,5}$ 5.0 Hz, H-4), 3.37, 3.36, 3.35 (3s, each 3H, 2 × OMe-1, OMe-5′), 3.14 (d, 1H, $J_{3',OH}$ 8.0 Hz, OH-3′), 1.78 (s, 3H, *Me*CO), 1.43 (s, 6H, C*Me*$_2$); 1.42, 1.32 (2s, each 3H, C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 168.5 (Me*CO*), 137.9, 137.3 (2 × Ar–C), 128.3–127.6 (Ar–CH), 109.9, 108.5 (2 × CMe_2), 73.3, 72.5 (2 × CH_2Ph), 56.1, 53.7 (2 × OMe-1), 48.4 (OMe-5′), 27.2, 26.5, 26.4, 25.3 (2 × C*Me*$_2$), 20.5 (*Me*CO). Anal. Calcd for $C_{37}H_{52}O_{14}$: C, 61.65; H, 7.27. Found: C, 61.60; H, 7.22.

3.9.2.3. (5*R*)-2,6-Di-*O*-benzyl-5-*C*-methoxy-α-L-*xylo*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (21).

White foam; $[\alpha]_D$ −27.2 (*c* 0.99, $CHCl_3$); R_f 0.32 (2:3 hexane–EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31–7.22 (m, 10H, Ar–H), 5.18 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.81, 4.65 (AB system, 2H, $J_{A,B}$ 12.2 Hz, CH_2Ph), 4.57, 4.50 (AB system, 2H, $J_{A,B}$ 12.3 Hz, CH_2Ph), 4.47 (dd, 1H, $J_{1,2}$ 6.7 Hz, $J_{2,3}$ 7.1 Hz, H-2), 4.31 (d, 1H, H-1), 4.30–4.17 (m, 2H, H-5, H-6b), 4.05–3.98 (m, 5H, H-3′,

H-4′, H-3, H-4, H-6a), 3.60–3.50 (m, 3H, H-2′, H-6′a, H-6′b), 3.31 (s, 9H, 2 × OMe-1, OMe-5′), 3.13 (d, 1H, $J_{3',OH}$ 7.5 Hz, OH-3′), 2.60 (d, 1H, $J_{4',OH}$ 5.2 Hz, OH-4′), 1.41 (s, 9H, C*Me*$_2$); 1.32 (s, 3H, C*Me*$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): see Table 2 and δ 138.1, 137.2 (2 × Ar–C), 128.5–127.5 (Ar–CH), 109.9, 108.5 (2 × *C*Me$_2$), 73.3, 72.6 (2 × *CH*$_2$Ph), 56.0, 53.1 (2 × OMe-1), 48.4 (OMe-5′), 27.2, 26.6, 26.5, 25.3 (2 × C*Me*$_2$). Anal. Calcd for $C_{35}H_{50}O_{13}$: C, 61.93; H, 7.42. Found: C, 61.90; H, 7.39.

3.9.2.4. Unidentified diol. Selected ^{13}C NMR (50 MHz, $CDCl_3$) data for the unidentified diastereoisomeric diol isolated in mixture with **21**: δ 106.0 (C-1), 98.6 (C-5′), 98.2 (C-1′), 81.2 (C-2′), 77.8, 77.6, 77.3 (C-3, C-4, C-5), 75.5, 74.8, 71.6 (C-2, C-3′, C-4′), 73.7, 73.74 (2 × *CH*$_2$Ph), 69.9 (C-6′), 65.2 (C-6), 56.0, 53.6 (2 × OMe-1), 48.5 (OMe-5′).

3.10. (5*R*)-3,4-Di-*O*-acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-α-L-*lyxo*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (20)

Compound **21** (40 mg, 0.059 mmol) was acetylated with a 1:2 mixture of Ac_2O and pyridine (3 mL) and stirred at room temperature. After 20 h, the reaction mixture was repeatedly co-evaporated with toluene (4 × 10 mL) at diminished pressure. Flash chromatographic purification (13:7 hexane–EtOAc) of the residue (52 mg) gave **20** (44 mg, 97% yield) as a syrup; $[\alpha]_D$ −46.9 (*c* 0.9, $CHCl_3$); R_f 0.38 (3:2 hexane–EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 7.35–7.23 (m, 10H, Ar–H), 4.68, 4.58 (AB system, 2H, $J_{A,B}$ 11.9 Hz, *CH*$_2$Ph), 4.43, 4.40 (s, 2H, *CH*$_2$Ph), 4.46 (dd, 1H, $J_{1,2}$ 6.5 Hz, $J_{2,3}$ 7.3 Hz, H-2), 4.33 (d, 1H, H-1), 4.26 (m, 1H, H-5), 4.03 (dd, 1H, $J_{3,4}$ 1.3 Hz, H-3), 4.16 (dd, 1H, $J_{5,6b}$ 6.2 Hz, $J_{6a,6b}$ 8.5 Hz, H-6b), 3.98 (m, 2H, H-4, H-6a), 3.34, 3.33, 3.32 (3s, each 3H, 2 × OMe-1, OMe-5′), 2.00, 1.85 (2s, each 3H, 2 × *Me*CO), 1.41 (s, 6H, C*Me*$_2$); 1.40, 1.32 (2s, each 3H, C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 169.5, 168.1 (2 × Me*CO*), 137.8, 137.3 (2 × Ar–C), 128.4–127.5 (Ar–CH), 110.1, 108.4 (2 × *C*Me$_2$), 73.4, 72.6 (2 × *CH*$_2$Ph), 55.8, 53.4 (2 × OMe-1), 48.1 (OMe-5′), 27.2, 26.6, 26.2, 25.4 (2 × C*Me*$_2$), 20.8, 20.6 (2 × *Me*CO). Anal. Calcd for $C_{39}H_{54}O_{15}$: C, 61.41; H, 7.14. Found: C, 61.38; H, 7.12.

The acetylation of the fractions containing either **19** (115 mg, 0.160 mmol) or **18** (65 mg, 0.090 mmol) as reported above gave, after chromatographic purification (13:7 hexane–EtOAc), **21** (183 mg, 96% yield) having NMR parameters identical to those of the sample prepared above.

3.11. (5*R*)-2,6-Di-*O*-benzyl-5-*C*-methoxy-α-L-*lyxo*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (21)

To a solution of **20** (183 mg, 0.240 mmol) in dry MeOH (5 mL) was added 0.1 M methanolic solution of MeONa (0.2 mL) at room temperature. The reaction mixture was stirred until TLC analysis (3:2 hexane–EtOAc) showed the complete disappearance of the starting material (2 h) and the formation of a lower moving product. The solution was neutralised with resin acid (Amberlyst 15), and the suspension was filtered and concentrated to give a foam residue constituted by pure (NMR) **21** (162.5 mg, quantitative yield), identical to the sample obtained above. The combined overall yield of **21**, which was obtained by adding the sample that was directly isolated in the oxidation–reduction of **16**, was 65%.

3.12. 2,6-Di-*O*-benzyl-L-*lyxo*-hexos-5-ulose (26)

A solution of **21** (185 mg, 0.272 mmol) in 4:1 (v/v) CH_3CN–water (6 mL) was treated with 90% aq CF_3COOH (1.2 mL), warmed to 50 °C and stirred until 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 (5 × 20 mL). The residue was partitioned between brine (20 mL) and EtOAc (40 mL), and the aq phase was extracted with EtOAc (3 × 40 mL). The organic phases were collected, dried ($MgSO_4$) and concentrated under diminished pressure to give a residue (96 mg) that was directly subjected to a flash chromatographic purification, eluting with 1:3 hexane–EtOAc, to give pure **26** (75 mg, 78% yield) as colourless syrup. NMR data were in agreement with those reported.[8b]

3.13. (5*R*)-2,4,6-Tri-*O*-benzyl-5-*C*-methoxy-α-L-*arabino*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (22) and (5*R*)-2,3,4,6-tetra-*O*-benzyl-5-*C*-methoxy-α-L-*arabino*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (23)

A suspension of pre-washed (hexane) 60% NaH in mineral oil (1.29 g, 53.7 mmol) in dry DMF (25.0 mL) was cooled to 0 °C and treated, under an argon atmosphere, with a solution of **8** (3.62 g, 5.34 mmol) in dry DMF (100 mL). The mixture was warmed to room temperature and stirred for 30 min, cooled again to 0 °C and treated with BnBr (0.63 mL, 5.34 mmol) and further stirred until the starting material was consumed (25 min, TLC, 7:3 hexane–EtOAc). MeOH (12 mL) and water (100 mL) were slowly added, and the reaction mixture was extracted with Et_2O (4 × 50 mL). The combined extracts were collected, dried ($MgSO_4$) and concentrated under diminished pressure. The residue (4.68 g) was subjected to flash chromatography (first hexane 600 mL, then 4:1 hexane–EtOAc) to give **22** (3.09 g, 75% yield) and **23** (684 mg, 15% yield).

Compound **22**: colourless syrup; $[\alpha]_D$ +16.8 (*c* 1.07, $CHCl_3$); R_f 0.24 (7:3 hexane–EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): see Table 1 and δ 7.36–7.22 (m, 15H, Ar–H), 4.76, 4.60 (AB system, 2H, $J_{A,B}$ 11.6 Hz, *CH*$_2$Ph), 4.62, 4.58 (AB system, 2H, $J_{A,B}$ 11.3 Hz, *CH*$_2$Ph), 4.58, 4.34 (AB system, 2H, $J_{A,B}$ 12.1 Hz, *CH*$_2$Ph), 4.49 (dd, 1H, $J_{1,2}$ 6.5 Hz, $J_{2,3}$ 7.6 Hz, H-2), 4.31 (d, 1H, H-1), 4.27 (bq, 1H, H-5), 4.16 (dd, 1H, $J_{5,6b}$ 5.6 Hz, $J_{6a,6b}$ 8.7 Hz, H-6b), 4.00 (m, 1H, H-4), 3.95 (dd, 1H, $J_{5,6a}$ 6.2 Hz, H-6a), 3.92 (dd, 1H, $J_{3,4}$ 0.8 Hz, H-3), 3.27, 3.25, 3.22 (3s, each 3H, 2 × OMe-1, OMe-5′), 1.43, 1.41, 1.38, 1.31 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 138.6, 138.3, 137.2 (3 × Ar–C), 128.3–127.2 (Ar–CH), 109.8, 108.4 (2 × *C*Me$_2$), 74.9, 74.5, 73.2 (3 × *CH*$_2$Ph), 55.6, 52.3 (2 × OMe-1), 47.9 (OMe-5′), 27.2, 26.5, 26.4, 25.0 (2 × C*Me*$_2$). Anal. Calcd for $C_{42}H_{56}O_{13}$: C, 65.61; H, 7.34. Found: C, 65.73; H, 7.44.

Compound **23**: colourless syrup; $[\alpha]_D$ +17.6 (*c* 1.2, $CHCl_3$); R_f 0.38 (7:3 hexane–EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 7.33–7.23 (m, 20H, Ar–H), 4.95, 4.57 (AB system, 2H, $J_{A,B}$ 11.5 Hz, *CH*$_2$Ph), 4.83, 4.73 (AB system, 2H, $J_{A,B}$ 10.7 Hz, *CH*$_2$Ph), 4.70 (s, 2H,*CH*$_2$Ph), 4.56, 4.28 (AB system, 2H, $J_{A,B}$ 12.1 Hz, *CH*$_2$Ph), 4.54 (dd, 1H, $J_{1,2}$ 6.7 Hz, $J_{2,3}$ 9.7 Hz, H-2), 4.31 (d, 1H, H-1), 4.18 (m, 1H, H-5), 4.05 (m, 2H, H-4, H-6b), 3.98 (dd, 1H, $J_{3,4}$ 2.9 Hz, H-3), 3.87 (dd, 1H, $J_{5,6a}$ 5.8 Hz, $J_{6a,6b}$ 8.9 Hz, H-6a), 3.25, 3.22, 3.21 (3s, each 3H, 2 × OMe-1, OMe-5′), 1.42, 1.41, 1.37, 1.30 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 138.7, 138.5, 138.4, 137.2 (4 × Ar–C), 128.1–127.1 (Ar–CH), 109.6, 108.3 (2 × *C*Me$_2$), 74.8, 74.5, 73.1, 72.6 (4 × *CH*$_2$Ph), 55.4, 52.0 (2 × OMe-1), 47.8 (OMe-5′), 27.2, 26.6, 26.1, 25.1 (2 × C*Me*$_2$). Anal. Calcd for $C_{49}H_{62}O_{13}$: C, 68.51; H, 7.27. Found: C, 68.63; H, 7.34.

3.14. (5*R*)-2,4,6-Tri-*O*-benzyl-5-*C*-methoxy-α-L-*threo*-hex-3-ulopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (24)

A suspension of **22** (1.03 g, 1.34 mmol) in dry CH_2Cl_2 (27 mL), pre-dried 4-methylmorpholine-*N*-oxide (NMO) (275 mg, 2.34 mmol) and 4 Å powdered molecular sieves (400 mg) was stirred under an

argon atmosphere for 30 min at room temperature. Tetrapropylammonium perruthenate (TPAP) (47 mg, 10%) was added, and the resulting green mixture was stirred for 4 h at room temperature until the TLC (9:1 CH_2Cl_2–Me_2CO) showed the complete disappearance of the starting material. The reaction mixture was filtered through alternate paths of Celite and silica gel, and extensively washed with CH_2Cl_2 and EtOAc. The solution and washings were combined and concentrated under diminished pressure to give almost pure **24** (NMR). A sample of the residue was subjected to flash chromatography (7:3 hexane–EtOAc) to give **24** (76% yield) as a colourless syrup; $[\alpha]_D$ −37.4 (*c* 1.16, $CHCl_3$); R_f 0.73 (9:1 CH_2Cl_2–Me_2CO); ^{1}H NMR (200 MHz, CD_3CN): see Table 1 and δ 7.38–7.13 (m, 15H, Ar–H), 4.70, 4.64 (AB system, 2H, $J_{A,B}$ 12.5 Hz, CH_2Ph), 4.53, 4.47 (AB system, 2H, $J_{A,B}$ 12.4 Hz, CH_2Ph), 4.40–4.32 (m, 4H, H-1, H-2, CH_2Ph), 4.21 (m, 1H, H-5), 4.07 (dd, 1H, $J_{5,6b}$ 6.0 Hz, $J_{6a,6b}$ 8.5 Hz, H-6b), 4.03 (dd, 1H, $J_{2,3}$ 6.9 Hz, $J_{3,4}$ 1.1 Hz, H-3), 3.93 (dd, 1H, $J_{5,6a}$ 6.3 Hz, H-6a), 3.87 (dd, 1H, $J_{4,5}$ 5.5 Hz, H-4), 3.31, 3.25, 3.23 (3s, each 3H, 2 × OMe-1, OMe-5′), 1.34, 1.33, 1.32, 1.27 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (50 MHz, CD_3CN): see Table 2 and δ 138.8, 138.6, 137.8 (3 × Ar–C), 129.3–128.8 (Ar–CH), 110.4, 109.2 (2 × CMe_2), 74.0, 73.9, 73.0 (3 × CH_2Ph), 56.5, 53.8 (2 × OMe-1), 49.1 (OMe-5′), 27.4, 26.9, 26.8, 25.5 (2 × CMe_2). Anal. Calcd for $C_{42}H_{54}O_{13}$: C, 65.78; H, 7.10. Found: C, 65.88; H, 7.38.

3.15. (5*R*)-2,4,6-Tri-*O*-benzyl-5-*C*-methoxy-α-L-*lyxo*-hexopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (25)

A solution of **24** (760 mg, 0.99 mmol) in dry MeOH (22 mL) was cooled to 0 °C and treated, under an argon atmosphere, with $NaBH_4$ (113 mg, 2.98 mmol). After 5 min, the reaction mixture was gently warmed to room temperature and left stirring until **24** was consumed (1.5 h, TLC, 9:1 CH_2Cl_2–Me_2CO). Water (15 mL) was added, the solution stirred for 30 min and concentrated under diminished pressure. The residue was partitioned between water (60 mL) and CH_2Cl_2 (150 mL). The aq phase was extracted with CH_2Cl_2 (2 × 150 mL), and the organic extracts were collected, dried ($MgSO_4$) and concentrated under diminished pressure. The residue (784 mg) was subjected to flash chromatography (6:4 hexane–EtOAc) to give **25** as a colourless syrup (668 mg, 88% yield); $[\alpha]_D$ +2.20 (*c* 0.7, $CHCl_3$); R_f 0.38 (9:1 CH_2Cl_2–Me_2CO); ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 7.38–7.05 (m, 15H, Ar–H), 4.81, 4.63 (AB system, 2H, $J_{A,B}$ 12.2 Hz, CH_2Ph), 4.58, 4.36 (AB system, 2 H, $J_{A,B}$ 12.1 Hz, CH_2Ph), 4.48 (dd, 1 H, $J_{1,2}$ 6.7 Hz, $J_{2,3}$ 7.6 Hz, H-2), 4.47, 4.39 (AB system, 2H, $J_{A,B}$ 11.4 Hz, CH_2Ph), 4.31 (d, 1H, H-1), 4.24 (m, 1H, H-5), 4.03 (dd, 1H, $J_{3,4}$ 1.0 Hz, H-3), 4.00 (m, 2H, H-6a, H-6b), 3.88 (dd, 1H, $J_{4,5}$ 5.2 Hz, H-4), 3.28, 3.25, 3.15 (3s, each 3H, 2 × OMe-1, OMe-5′), 1.44, 1.43, 1.42, 1.33 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 138.9, 138.3, 138.1 (3 × Ar–C), 128.9–128.3 (Ar–CH), 110.5, 109.2 (2 × CMe_2), 73.9, 73.7, 73.2 (3 × CH_2Ph), 56.5, 53.4 (2 × OMe-1), 48.9 (OMe-5′), 27.9, 27.2, 27.1, 26.0 (2 × CMe_2). Anal. Calcd for $C_{42}H_{56}O_{13}$: C, 65.61; H, 7.34. Found: C, 65.68; H, 7.41.

3.16. 2,4,6-Tri-*O*-benzyl-L-*lyxo*-hexos-5-ulose (27)

A solution of **25** (456 mg, 0.594 mmol) in 4:1 (v/v) CH_3CN–water (11 mL) was treated with 90% aq CF_3COOH (2.3 mL) and warmed to 50 °C with stirring until TLC analysis (EtOAc) showed the complete disappearance of the starting material (4 h). The mixture was concentrated under diminished pressure and repeatedly co-evaporated with toluene (5 × 20 mL). The residue was partitioned between brine (20 mL) and EtOAc (40 mL), and the aq phase was extracted with EtOAc (3 × 40 mL). The organic phases were collected, dried ($MgSO_4$) and concentrated under diminished pressure to give a residue (285 mg) that was directly subjected to a flash chromatographic purification, eluting with 4:6 hexane–EtOAc, to give **27** (228 mg, 86% yield) as a colourless syrup. NMR data were in agreement with those of the sample previously prepared by us.[6b]

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