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A New Route to D-*xylo*-Hexos-5-ulose and Some of Its Selectively Protected Derivatives from D-Galactose(#)(°)

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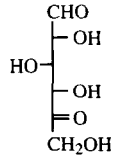
Abstract: A new approach to D-*xylo*-hexos-5-ulose, a useful synthetic intermediate, is described, starting from methyl β-D-galactopyranoside and involving as the key step an epoxidation/methanolysis of 3-*O*-protected methyl 2,6-di-*O*-benzyl-4-deoxy-α-L-*threo*-hex-4-enopyranosides, to produce bis-glycosides of the parent dicarbonylic sugar, which can be obtained free or selectively protected through hydrogenolytic and/or hydrolytic procedures. The diastereo- and regioselectivity of the epoxidation and solvolysis steps are investigated and tentatively interpreted, and new products characterized by NMR techniques.

Aldohexos-5-uloses are an interesting class of monosaccharides having recently gathered attention as synthetic intermediates for biologically relevant glycosidase inhibitors of the 1-deoxynojirimycin type, directly obtained by double reductive amination of these dicarbonylic precursors[1].

The most investigated member of this class of monoses is D-*xylo*-hexos-5-ulose (**1**), first synthesised in 1931 by Helferich and Bigelow[2]. Further studies on **1** were performed by Kiely, who described[3a] a more efficient preparation based on the C-5 oxidation of 3,6-di-*O*-protected 1,2-*O*-isopropylidene-D-glucofuranose derivatives followed by complete deprotection. He also described its transformation into inosones by intramolecular aldol condensation[3a], thus opening an interesting new approach to inositols, and, later, published a detailed NMR analysis of its complicated tautomeric equilibrium[3b].



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(#) Part 8 of the series, "Rare and Complex saccharides from D-Galactose and other Milk-derived Carbohydrates". For part 7, see Ref. 1d.

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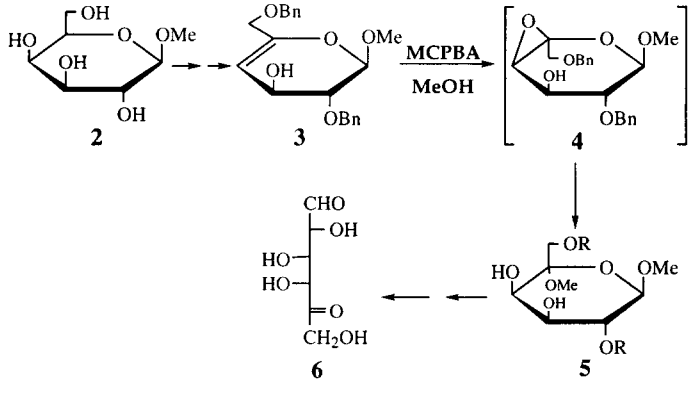
A shorter and more efficient preparation of **1**, using a tin-mediated regioselective C-5 oxidation of unprotected 1,2-*O*-isopropylidene-D-glucofuranose, was reported more recently by Baxter and Reitz[1c], in the frame of their work on the synthesis of 1-deoxynojirimycin.

We have recently reported[4] a new approach to the L-*arabino* diastereomer (**6**) of **1** (Scheme 1), starting from methyl β-D-galactopyranoside **2**, which is easily converted into the methyl 4-deoxy-α-L-*threo*-hex-4-enopyranoside (**3**), or other 2,6-di-*O*-protected analogues[5], the epoxidation-methanolysis (MCPBA in MeOH) of which produces the bis-glycoside **5** in a completely diastereo- and regiospecific way, owing to the well known *syn*-directing effect[6] of the free allylic hydroxyl group in the epoxidation step, giving exclusively the intermediate epoxide **4**, and to the high preference for nucleophilic attack of methanol at the highly electrophilic C-5. Subsequent deprotection and hydrolysis produces the free hexosulose **6** in high yield.

A synthesis of the D-*xylo* isomer **1** by the same method required formation of the alternative 4,5-epoxide with the oxirane ring on the α-side of the pyranose ring, and protection of the 3-OH group appeared as a viable route to achieve this goal.

Scheme 1



Protection of the allylic 3-OH group of methyl 4-deoxy-2,6-di-*O*-benzyl-α-L-*threo*-hex-4-enopyranoside (**3**) was efficiently achieved by its transformation through standard methods into the benzoate **7** (BzCl/Py, 83% yield) and the benzyl ether **8** (BnBr/NaH-DMF, 80% yield).

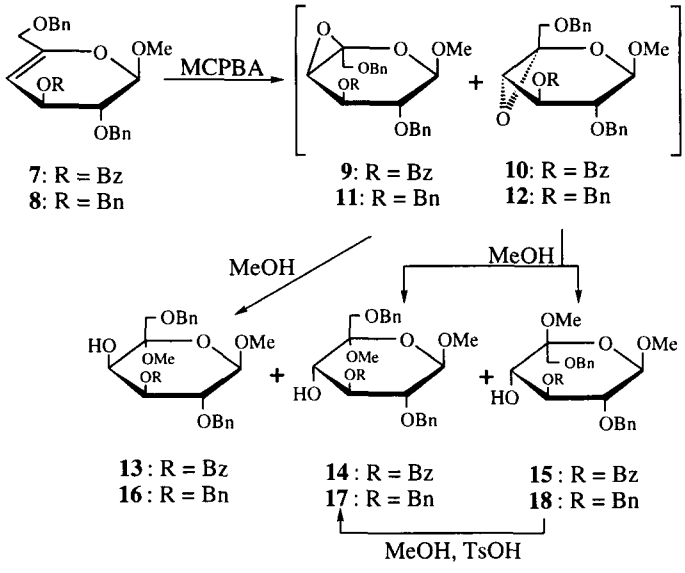
The epoxidation of **7** and **8** in methanol was not as diastereospecific as that of **3**, but produced both epoxides (**9/10** from **7** and **11/12** from **8**), which in the subsequent *in situ* solvolysis were opened to mixtures of three of the eight possible bis-glycosides, which were separated by chromatographic procedures and identified through complete resolution of their ^{1}H- and ^{13}C-NMR spectra (Tables 1 and 2) as the 5-*C*-methoxy-D-galacto (**13** and **16**), D-gluco (**14** and **17**) and L-ido (**15** and **18**) forms. None of the four possible products of epoxide opening at C-4 was present, thus confirming the high preference for nucleophilic attack at C-5 of these epoxides.

An approximate estimation of the compositions of the crude products was possible on the basis of chromatographic yields and of the relative intensities of the ^{13}C methoxyl signals, which in both series were well separated, between 48 and 50 (OMe-5) and 56 and 58 ppm (OMe-1). However, diastereoselection was much better in the case of the 3-*O*-benzyl ether **8** (**16**:**17**:**18** ratio *ca.* 15:20:65) than in that of the benzoate **7** (*ca.* 40:20:40), corresponding to an excess of *anti* epoxidation of *ca.* 85% for **8** and of *ca.* 60% for **7**.

These results confirmed the expectation that protection of the *syn*-directing 3-OH group would make the epoxidation more subject to steric effects such as those of the 3-*O*-benzyl or benzoyloxy groups and showed that the former is more efficient than the latter in orienting oxidation *anti* to itself, and therefore to be preferred for the use on the route to D-*xylo*-hexos-5-ulose.

Similar results had been previously obtained in the reactions of **3** and **8** with the MCPBA·KF complex in CH_2Cl_2[7], a reagent allowing isolation of highly sensitive epoxides, such as those derived from glycals, in which the non-protic nature of the solvent and complexation by KF of the *m*-chlorobenzoic acid formed from the peroxyacid prevent opening of the oxirane ring in the reaction medium.

Scheme 2



7: R = Bz
8: R = Bn

9: R = Bz
11: R = Bn

10: R = Bz
12: R = Bn

13: R = Bz
16: R = Bn

14: R = Bz
17: R = Bn

15: R = Bz
18: R = Bn

The possibility that the formation of the more stable *syn*-opening products **14/17** was due to isomerization of the *anti* ones **15/18** in the reaction medium, catalyzed by the *m*-chlorobenzoic acid deriving from the peroxyacid, owing to the known fact that anomerization of ketopyranoside glycosides is much easier than that of aldopyranosides, was ruled out when we found that product composition remained unchanged even when much longer reaction times were used, whereas stronger acids (such TsOH) converted completely L-ido into the more stable D-gluco anomers, as discussed below. A better explanation (Scheme 3) can be based on the particular nature of the oxirane ring of glycal epoxides.

It is well known[8] that the mechanism of oxirane ring opening reactions can range all the way from pure S_N2, involving stereospecific *anti* opening (diaxial in epoxycyclohexanes and analogues), to nearly pure S_N1, when substituents capable of stabilizing a positive charge are present, and both *syn* and *anti* opening products are obtained through an intermediate more or less developed carbocation. This is the case of epoxides **9-12**, in which the pyranose ring oxygen can provide mesomeric assistance to the stabilization of positive charge on C-5. The total absence of solvolytic attack at C-4 in all cases confirms the importance of this factor.

The case of **9** and **11**, and, as previously found, **4**, should be more favorable for a mechanism closer to S_N2, since a diaxial opening of the oxirane ring at C-5 requires it to be in its all-equatorial half-chair $^2H_1$ conformation, which should be definititely more stable than the alternative all-axial one $^1H_2$. This could

explain the exclusive formation of the 5-*C*-methoxy-D-galacto isomers **13** and **16**. On the other hand epoxides **10** and **12** would have to assume the less stable conformation $^{1}H_{2}$ to open diaxially at C-5, which would also involve approach by the nucleophile parallel to the two axial substituents on C-1 and C-3 (Scheme 3, path II). The alternative of a diequatorial opening on the $^{2}H_{1}$ conformer (path III) appears very unlikely, and that of its diaxial one is excluded, since it would give a structurally different product **19**. These difficulties could well explain a course closer to S_N1 and a consequent loss in diastereoselectivity, with formation of some of the *syn*-opening products **14** and **17**.

Table 1. Selected ^{1}H NMR parameters (δ, ppm, *J*, Hz, CD_3CN) of bis-glycopyranosides.

	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4	H-6 ($J_{6,6'}$)	H-6'
13	4.62 (7.70)	3.81 (10.15)	5.35 (3.12)	4.08	3.66 (10.41)	3.62
14	4.70 (7.95)	3.52 (9.65)	5.47 (9.94)	4.01	3.77 (10.19)	3.73
15	4.87 (6.99)	3.72 (9.35)	5.47 (7.86)	3.91	3.82 (10.41)	3.66
16	4.46 (7.77)	3.55 (9.57)	3.77 (3.16)	4.03	3.67 (10.40)	3.59
17	4.53 (8.03)	3.31 (8.85)	3.66 (9.47)	3.80	3.72 (10.20)	3.66
18[a]	4.83 (6.21)	3.95 (9.28)	4.02 (6.93)	4.24	3.69 (10.54)	3.66
21	4.47 (7.99)	3.16 (9.24)	3.66 (9.61)	3.62	3.67 (10.26)	3.63
22	4.63 (6.65)	3,36 (7.90)	3.67 (7.78)	3.60	3.69 (10.66)	3.57
24[b]	4.36 (8.09)	3.17 (9.32)	3.55 (8.93)	3.55	3.68 (10.21)	3.63

[a]In C_6D_6. [b]In CD_3CN/D_2O.

Other bis-glycosides of the above three stereochemical series were further obtained through standard deprotection methods. Thus, debenzoylation of **13-15** was carried out by transesterification with sodium methoxide to give **20-22**, and catalytic hydrogenolysis of **16** and **17** produced in high yields the deprotected bis-glycosides **23** and **24**. During the catalytic debenzylation of **18**, it was observed that when a sample of methanol, fortuitously containing an acid impurity was used as the solvent, anomerization at C-5 occurred, to give mixtures of L-ido and D-gluco isomers **25** and **24**. The addition of catalytic amount of a strong acid (TsOH) caused a fast and complete transformation of **25** into **24** .

As an extension of this practically useful observation, the three-product mixtures obtained from the epoxidation/methanolysis of **8** were easily converted into two-product ones (**17/16** in *ca.* 85:15 ratio) by

standing 36 hr in methanol containing TsOH, the anomerization of the L-ido compound **18** into the more stable D-gluco one **17** being again complete.

Scheme 3

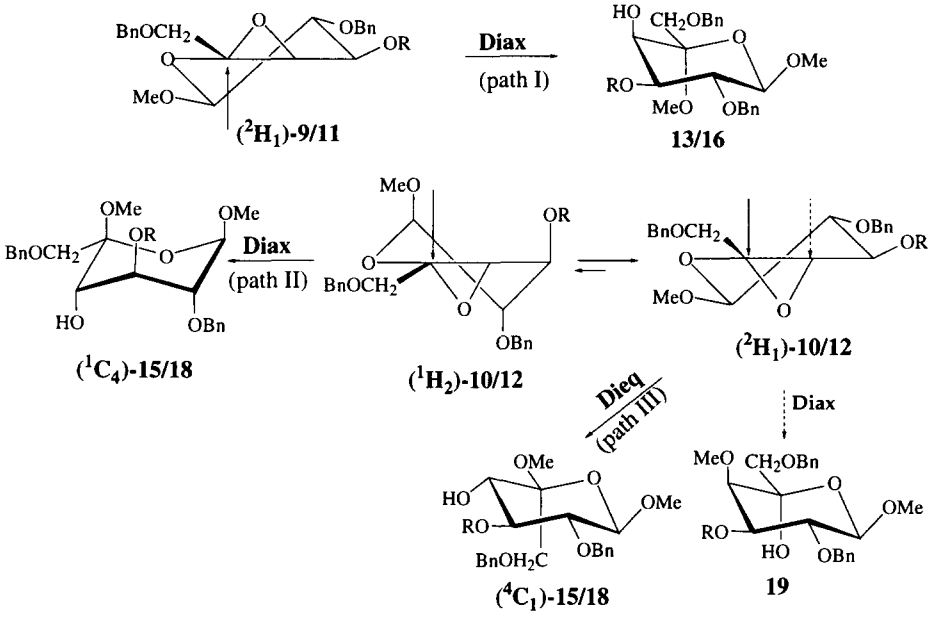


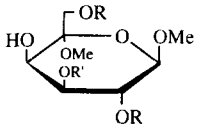
Table 2. Selected ^{13}C NMR parameters (δ, ppm, CD_3CN) of bis-glycopyranosides.

	C-1	C-2	C-3	C-4	C-5	C-6	OMe-1	OMe-5
13	101.80	77.14	74.27	68.33	101.80	66.08	57.29	48.86
14	101.23	80.32	75.01	71.73	100.18	70.15	57.63	49.45
15	102.50	80.32	76.47	73.01	101.70	70.18	56.83	49.66
16	101.54	79.32	79.01	67.43	101.20	66.89	57.15	48.60
17	101.17	82.56	81.78	73.85	99.81	70.31	57.37	49.15
18[a]	103.01	82.59	81.44	73.53	101.96	69.08	56.78	49.43
21	100.95	82.51	73.30	73.53	99.81	70.30	57.27	49.12
22	102.52	82.12	73.95	74.85	101.71	69.60	57.77	49.55
24[b]	100.80	74.35	73.56[c]	73.28[c]	100.09	62.40	57.61	49.24

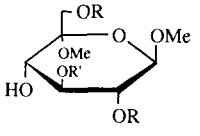
[a]In C_6D_6. [b]In CD_3CN/D_2O. [c]Assignments may have to be interchanged.

Hydrolysis of **18**, as well as that of **17**, was easily achieved with aqueous trifluoroacetic acid to give the 2,3,6-tri-*O*-benzyl derivative of D-*xylo*-hexos-5-ulose **26** which existed in CD_3CN/D_2O solution entirely as a

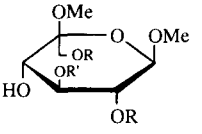
55:45 mixture of its α- and β-furanose anomers **27**. For the purpose of preparing non-protected D-*xylo*-hexos-5-ulose, the crude product of the epoxidation/methanolysis of **8**, after anomerization to a mixture of **16** and **17**, was catalytically debenzylated, giving, after chromatographic separation, **24** which was finally subjected to acid catalyzed hydrolysis. The free D-*xylo*-hexos-5-ulose, **1**, was thus obtained from **8** in 60% overall yield through a simple three-step sequence involving only one chromatographic separation. The D-*xylo*-hexos-5-ulose (**1**) was identified by its ^{13}C-NMR spectrum, as a mixture of furanosic and mono- and bicyclic pyranosic tautomers which corresponded well, in its signals, with those reported by Kiely in his very accurate study[3b].



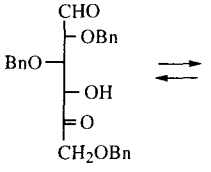
20 : R' = H, R = Bn
23 : R = R' = H



21 : R' = H, R = Bn
24 : R = R' = H



22 : R' = H, R = Bn
25 : R = R' = H



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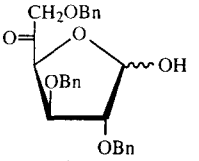

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The results of this work confirm that the 4-hexenopyranoside route to hexos-5-uloses can be competitive with other known methods, with the advantage of providing a range of selectively protected intermediates that could be useful for further interesting synthetic elaborations.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20±2°C; specific rotations are expressed in deg·cm^2·dag^{-1}. ^{1}H-NMR spectra (internal TMS) were recorded with a Bruker AC 200 instrument at 200 MHz. First-order spectral analysis was performed whenever possible, otherwise spectra were simulated with PANIC (Bruker) or LAOCN-5 (QCPE QCMP 049) computer programs. Chemical shifts and coupling constants values were confirmed, when necessary, with COSY or J-RES experiments. ^{13}C-NMR spectra were recorded with the same spectrometer at 50 MHz. Assignments were made with the aid of DEPT and HETCOR experiments. All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV light or with ethanolic 10% phosphomolibdic or sulphuric acid, and heating. Kieselgel 60 (Merck, 70-230 and 230-400 mesh, respectively) was used for column and flash cromatography. Solvents were distilled and stored over 4 Å molecular sieves activated at least 24 h at 400°C. $MgSO_4$ was used as the drying agent for solutions.

Methyl 2,6-di-*O*-benzyl-3-*O*-benzoyl-4-deoxy-α-L-*threo*-hex-4-enopyranoside (7).

A solution of **3**[4b] (1.15 g, 3.23 mmol) in dry pyridine (15 ml) was treated at room temperature with benzoyl chloride (0.60 ml, 5.20 mmol) and stirred for 5 h. The reaction mixture was poured onto cooled 10% acqueous NaOH (40 ml) and extracted with CH_2Cl_2 (4 x 25 ml). The combined extracts were washed with brine (20 ml), dried evaporated *in vacuo* and coevaporated repeteadly with toluene (3 x 25 ml). The crude residue (1.46 g) was constituted (NMR) mainly by **7**, obtained pure in 83% yield by flash-chromatography on

silica gel (toluene/AcOEt 19:1). **7** was a syrup, R_f 0.33 (toluene/ AcOEt 19:1); $[\alpha]_D$ +34.9 (*c* 1.0, $CHCl_3$); ^1H NMR (CD_3CN), δ : 3.49 (s, 3 H, OMe), 3.84 (ddd, 1 H, $J_{1,2}$ = 4.02 Hz, $J_{2,3}$ = 3.40 Hz, $J_{2,4}$ = 0.97 Hz, H-2), 3.97 (ddd, 2 H, $J_{3,6}$ and $J_{3,6'}$ = 1.05 Hz, $J_{4,6}$ and $J_{4,6'}$ = 0.75 Hz, H -6 and H-6'), 4.53 and 4.76 (2 s, 2 H each, 2 x C*H*$_2$Ph), 5.06 (dd, 1 H, $J_{1,3}$ = 0.86 Hz, H-1), 5.13 (dddd, 1 H, H-4), 5.45 (ddddd, 1 H, $J_{3,4}$ = 4.18 Hz, H-3), 7.27-7.98 (m, 15 H, aromatic H); ^{13}C NMR (CD_3CN) δ: 56.32 (OMe), 69.26 (C-6), 67.88 (C-3), 72.39 and 72.68 (2 x *C*H$_2$Ph), 75.44 (C-2), 97.38 (C-4), 100.93 (C-1), 127.53-132.91 (15 C, aromatic CH), 131.02, 138.52 and 138.69 (3 x quatern. aromatics), 151.37 (C-5), 166.25 (*C*OPh). Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 72.83; H, 6.23.

Methyl 2,3,6-tri-*O*-benzyl-4-deoxy-α-L-*threo*-hex-4-enopyranoside (8).

A suspension of NaH (20 mmol, obtained from 0.60 g of an 80% dispersion in mineral oil after washing three times with 20 ml of hexane) in dry DMF (25 ml) was cooled at 0°C and treated, under Ar, with a solution of **3**^{4b} (1.80 g, 5.05 mmol) in dry DMF (90 ml). The mixture was stirred 15 min at 0°C and 1 h at room temp., cooled again at 0°C and treated with benzyl bromide (2.54 ml, 21.34 mmol), stirred 15 min at 0°C and 4 h at room temp.. Excess NaH was destroyed by addition of methanol and stirring first at 0°C (15 min) then at room temp. (30 min). The solvents were evaporated *in vacuo*, the residue taken up in 40 ml of ice and water and extracted with CH_2Cl_2 (3 x 50 ml). The combined extracts were washed with brine (20 ml), dried and evaporated under reduced pressure. The crude residue (3.78 g) was submitted to flash-chromatography on silica gel (hexane/AcOEt 9:1) to give pure **8** (1.81 g, 80% yield) as a waxy solid, m.p. 27-29°C, R_f 0.45 (hexane/AcOEt 4:1); $[\alpha]_D$ +2.7 (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3CN), δ: 3.48 (s, 3 H, OMe), 3.68 (ddd, 1 H, $J_{1,2}$ = 5.37 Hz, $J_{2,3}$ = 4.39 Hz, $J_{2,4}$ = 0.55 Hz, H-2), 3.94 (m, 2 H, $J_{3,6}$ and $J_{3,6'}$ = 1.1 Hz, $J_{4,6}$ and $J_{4,6'}$ = 0.6 Hz, H-6 and H-6'), 4.03 (ddddd, 1 H, $J_{1,3}$ = 0.62 Hz, $J_{3,4}$ = 3.46 Hz, H-3), 4.52 and 4.57 (2 s, 2 H each, 2 x C*H*$_2$Ph), 4.67-4.75 (AB system, 2 H, J_{AB} = 11.62, C*H*$_2$Ph) 4.90 (dd, 1 H, H-1), 5.11 (dddd, 1 H, H-4), 7.30-7.38 (m, 15 H, aromatic H); ^{13}C NMR (CD_3CN), δ: 56.91 (OMe), 69.97 (C-6), 71.22, 72.71 and 73.54 (3 x *C*H$_2$Ph), 74.21 (C-3), 77.84 (C-2), 100.49 (C-4), 102.00 (C-1), 128.39-129.24 (15 C, aromatic CH), 139.41, 139.47 and 139.83 (3 x quatern. aromatics), 150.11 (C-5). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.13; H, 6.88.

Epoxidation-methanolysis of methyl 2,6-di-*O*-benzyl-3-*O*-benzoyl-4-deoxy-α-L-*threo*-hex-4-enopyranoside (7).

A solution of **7** (1.20 g, 2.61 mmol) in MeOH (10 ml) was treated at room temperature with a solution of commercial (Janssen) 70% *m*-chloroperoxybenzoic acid (0.764 g, 3.10 mmol) in MeOH (7 ml). The solution was stirred until TLC analysis showed the complete disappearance of the starting material (24 h). The solution was made slightly basic by addition of a saturated aqueous solution of $NaHCO_3$, the solvent was evaporated *in vacuo*, the residue further diluted with water (30 ml) and extracted with CH_2Cl_2 (5 x 30 ml). The combined extracts were dried and evaporated, to give a residue (1.30 g) constituted [TLC (toluene/AcOEt 4:1) and ^{13}C NMR] by an about 40:20:40 mixture of the bis-glycosides **13**, **14**, and **15**. Flash-chromatography on silica gel (toluene/AcOEt 9:1) gave in the order the following products.

*Methyl 2,6-di-*O*-benzyl-3-*O*-benzoyl-5-C-methoxy-β-D-glucopyranoside,* (**14**, 268 mg, 17% yield) as a syrup, R_f 0.25 (toluene/AcOEt 4:1); $[\alpha]_D$ -8.1 (*c* 1.2, $CHCl_3$); NMR data (CD_3CN) see Tables 1 and 2 and ^1H, δ : 3.37 (s, 3 H, OMe-5), 3.58 (s, 3 H, OMe-1), 4.55-4.78 (AB system, 2 H, J_{AB} = 11.67 Hz, C*H*$_2$Ph); 4.56-4.62 (AB system, 2 H, J_{AB} = 11.86 Hz, C*H*$_2$Ph), 7.12-8.09 (m, 15 H, aromatic); ^{13}C, δ: 74.09 and 74.20 (2 x

*C*H$_2$Ph), 128.43-134.18 (15 C, aromatic CH), 137.44-139.22 (3 x quatern. aromatics), 166.92 (CO). Anal. Calcd. for C$_{29}$H$_{32}$O$_8$: C, 68.49; H, 6.50. Found: C, 68.61; H, 6.34.

An about 1:1 mixture of **13** and **15** (1.150 g, 73% yield); R*f* 0.49 and 0.43 (toluene/AcOEt 4:1). A second flash-cromatography (CH$_2$Cl$_2$/Et$_2$O 98:2) of the **13** and **15** mixture gave in order:

Methyl 2,6-di-O-benzyl-3-O-benzoyl-5-C-methoxy-β-D-galactopyranoside, (**13**, 536 mg, 34% yield) as a syrup, R*f* 0.37 (CH$_2$Cl$_2$/Et$_2$O 98:2); [α]$_D$ +9.3 (*c* 1.0, CHCl$_3$); NMR data (CD$_3$CN) see Tables 1 and 2 and ^{1}H, δ: 3.32 (s, 3 H, OMe-5); 3.53 (s, 3 H, OMe-1), 4.08 (dd, 1 H, $J_{4,OH}$ = 5.42 Hz, H-4), 4.53 (s, 2H, C*H*$_2$Ph), 4.63-4.78 (AB system, 2 H J_{AB} = 11.66 Hz, C*H*$_2$Ph), 7.18-8.05 (m, 15 H, aromatic); ^{13}C, δ: 73.83 and 74.94 (2 x *C*H$_2$Ph), 128.38-134.15 (15 C, aromatic CH), 139.32-139.63 (3 x quatern. aromatics), 166.60 (CO).

Methyl 2,6-di-O-benzyl-3-O-benzoyl-5-C-methoxy-α-L-idopyranoside, (**15**, 583 mg, 37% yield) as a syrup, R*f* 0.29 (CH$_2$Cl$_2$/Et$_2$O 98:2); [α]$_D$ +15.7 (*c* 0.9, CHCl$_3$); NMR data (CD$_3$CN) see Tables 1 and 2 and ^{1}H, δ: 3.32 (s, 3 H, OMe-5), 3.49 (s, 3 H. OMe-1), 3.91 (dd, 1 H, $J_{4,OH}$ = 5.39 Hz, H-4), 4.53-4.71 (AB system, 2 H, J_{AB} = 11.67 Hz, C*H*$_2$Ph), 4.57 (s, 2 H, C*H*$_2$Ph), 7.12-8.04 (m, 15 H, aromatic); ^{13}C, δ: 74.09 and 74.20 (2 x *C*H$_2$Ph), 128.36-134.31 (15 C, aromatic CH), 139.13 (3 x quatern. aromatics), 166.79 (CO).

Epoxidation-methanolysis of methyl 2,3,6-tri-*O*-benzyl-4-deoxy-α-L-*threo*-hex-4-enopyranoside (8).

The same procedure was used for the epoxidation-methanolysis of **8** (883 mg, 1.98 mmol) to give a residue (1.02 g) constituted [TLC (CH$_2$Cl$_2$/Et$_2$O 98:2) and ^{13}C NMR] by an about 15:20:65 mixture of the bis-glycosides **16**, **17**, and **18**. Flash-chromatography on silica gel (CH$_2$Cl$_2$/Et$_2$O 98:2) gave in the order the following products.

Methyl 2,3,6-tri-O-benzyl-5-C-methoxy-β-D-glucopyranoside, (**17**, 186 mg, 19% yield) as a syrup, R*f* 0.47 (CH$_2$Cl$_2$/ Et$_2$O 98:2); [α]$_D$ -36.4 (*c* 1.0, CHCl$_3$); NMR data (CD$_3$CN) see Table 1 and 2 and ^{1}H, δ: 3.30 (s, 3 H, OMe-5), 3.51 (s, 3 H, OMe-1), 4.46-4.81 (AB system, 2 H, J_{AB} = 11.46 Hz, C*H*$_2$Ph), 4.54-4.59 (AB system, 2 H, J_{AB} = 12.10 Hz, C*H*$_2$Ph), 4.73-4.82 (AB system, 2 H, J_{AB} = 11.48 Hz, C*H*$_2$Ph), 7.25-7.38 (m, 15 H, aromatic H); ^{13}C, δ: 74.12, 75.02 and 75.65 (3 x *C*H$_2$Ph), 128.23-129.29 (15 C, aromatic CH), 139.19, 139.93 and 140.12 (3 x quatern. aromatics). Anal. Calcd. for C$_{29}$H$_{34}$O$_7$: C, 70.43; H, 6.93. Found: C, 70.29 70.43; H, 6.80 6.93

Methyl 2,3,6-tri-O-benzyl-5-C-methoxy-β-D-galactopyranoside, (**16**, 160 mg, 16% yield) as a syrup, R*f* 0.40 (CH$_2$Cl$_2$/Et$_2$O 98:2); [α]$_D$ -8.7 (*c* 2.1, CHCl$_3$); NMR data (CD$_3$CN) see Tables 1 and 2 and ^{1}H, δ: 3.24 (s, 3 H, OMe-5), 3.48 (s, 3 H, OMe-1), 4.52-4.58 (AB system, 2 H, J_{AB} = 11.87 Hz, C*H*$_2$Ph); 4.60-4.72 (AB system, 2 H, J_{AB} = 11.80 Hz, C*H*$_2$Ph), 4.71-4.79 (AB system, 2 H, J_{AB} = 11.80 Hz, C*H*$_2$Ph), 7.29-7.40 (m, 15 H, aromatic H); ^{13}C, δ: 72.36, 73.90 and 75.22 (3 x *C*H$_2$Ph), 128.27-129.26 (15 C, aromatic CH), 139.19, 139.93 and 140.19 (3 x quatern. aromatics). Anal. Calcd. for C$_{29}$H$_{34}$O$_7$: C, 70.43; H, 6.93. Found: C, 69.99 H, 6.91.

Methyl 2,3,6-tri-O-benzyl-5-C-methoxy-α-L-idopyranoside, (**18**, 570 mg, 58% yield) as a syrup, R*f* 0.20 (CH$_2$Cl$_2$/ Et$_2$O 98:2); [α]$_D$ -7.3 (*c* 1.0, CHCl$_3$); NMR (C$_6$D$_6$) data see Tables 1 and 2 and ^{1}H, δ: 3.20 (s, 3 H, OMe-5), 3.24 (s, 3 H, OMe-1), 4.20-4.22 (AB system, 2 H, J_{AB} = 12.24 Hz, C*H*$_2$Ph), 4.75-4.83 (AB system, 2 H, J_{AB} = 11.63 Hz, C*H*$_2$Ph), 4.83-4.90 (AB system, 2 H, J_{AB} = 11.85 Hz, C*H*$_2$Ph), 7.00-7.37 (m, 15 H, aromatic H); ^{13}C, δ: 74.15, 74.41 and 75.94 (3 x *C*H$_2$Ph), 127.52-138.12 (15 C, aromatic CH), 139.55 (3 x quatern. aromatics). Anal. Calcd. for C$_{29}$H$_{34}$O$_7$: C, 70.43; H, 6.93. Found: C, 70.52 ; H, 6.87.

In another run the reaction time was prolonged to 3 days, without any apparent change in product distribution and final isolated yields.

A solution of the crude **16**, **17** and **18** reaction mixture (246 mg, 0.50 mmol) and TsOH (42 mg) in MeOH (12 ml) was stirred at room temperature until TLC analysis (CH_2Cl_2/Et_2O 97:3) showed the complete disappearance of **18** (30 h). The solution was neutralized with excess Et_3N (0.1 ml), stirred for 15 min and then evaporated to give quantitatively a residue constituted (^{13}C NMR) by an about 85:15 mixture of the bis-glycosides **17** and **16**.

Methyl 2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-galactopyranoside (20).

A solution of **13** (250 mg, 0.49 mmol) in MeOH (10 ml) was treated at room temperature with 1.1 *N* methanolic MeONa (1 ml) and stirred until the starting materials had completely disappeared (TLC). The solution was neutralized by bubbling a stream of CO_2, evaporated and the crude residue directly submitted to flash-chromatography on silica (CH_2Cl_2/Me_2CO 9:1) to give the pure title compound **20** (171 mg, 86% yield).

Methyl 2,6-di-O-benzyl-5-C-methoxy-β-D-galactopyranoside (**20**) was a syrup, R*f* 0.59 (CH_2Cl_2/Me_2CO 9:1), identical with a previously prepared pure sample[4b].

Methyl 2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-glucopyranoside (21).

A solution of **14** (308 mg, 0.61 mmol) in MeOH (15 ml) was debenzoylated as described above for **13**. The crude reaction product was directly submitted to flash-chromatography on silica (CH_2Cl_2/Me_2CO 9:1) to give the pure title compound **21** (208 mg, 85% yield).

Methyl 2,6-di-O-benzyl-5-C-methoxy-β-D-glucopyranoside (**21**) was a syrup, R*f* 0.53 (CH_2Cl_2/Me_2CO 9:1); $[\alpha]_D$ -56.6 (*c* 1.0, $CHCl_3$); NMR data (CD_3CN) see Tables 1 and 2 and ^1H, δ: 3.27 (s, 3 H, OMe-5), 3.49 (s, 3 H, OMe-1), 4.53-4.57 (AB system, 2 H, J_{AB} = 11.90 Hz, C*H*$_2$Ph), 4.70-4.78 (AB system, 2 H, J_{AB} = 11.46 Hz, C*H*$_2$Ph), 7.31-7.39 (m, 10 H, aromatic); ^{13}C, δ: 74.08, and 74.71 (2 x *C*H_2Ph), 128.28-129.29 (10 C, aromatic CH), 139.23 and 140.12 (2 x quatern. aromatics). Anal. Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.55, H, 7.04.

Methyl 2,6-di-*O*-benzyl-5-*C*-methoxy-α-L-idopyranoside (22).

A solution of **15** (200 mg, 0.39 mmol) in MeOH (15 ml) was debenzoylated as described above for **13**. The crude reaction product was directly submitted to flash-chromatography on silica (CH_2Cl_2/Me_2CO 9:1) to give the pure title compound **22** (138 mg, 87% yield).

Methyl 2,6-di-O-benzyl-5-C-methoxy-α-L-idopyranoside (**22**) was a syrup, R*f* 0.48 (CH_2Cl_2/Me_2CO 9:1); $[\alpha]_D$ -13.1 (*c* 0.6, $CHCl_3$); NMR data (CD_3CN) see Tables 1 and 2 and ^1H, δ: 3.29 (s, 3 H, OMe-5), 3.40 (s, 3 H, OMe-1), 4.49-4.52 (AB system, 2 H, J_{AB} = 11.78 Hz, C*H*$_2$Ph), 4.66-4.71 (AB system, 2 H, J_{AB} = 11.43 Hz, C*H*$_2$Ph), 7.31-7.39 (m, 10 H, aromatic); ^{13}C, δ: 74.30 (2 x *C*H_2Ph), 128.40-129.29 (10 C, aromatic CH), 139.23 and 139.86 (2 x quatern. aromatics). Anal. Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 64.98 ; H, 6.82 .

Methyl 5-*C*-methoxy-β-D-glucopyranoside (24).

A solution of **17** (334 mg, 0.68 mmol) in MeOH (30 ml) was treated with 10% Pd on charcoal (100 mg) and stirred under a hydrogen atmosphere until TLC analysis shown the complete disappearance of the starting material. The suspension was filtered through Celite, washed with MeOH, the combined methanolic solutions were evaparated to give a residue constituted by pure **24** (150 mg, quantitative).

Methyl 5-C-methoxy-β-D-glucopyranoside (**24**) was a white solid, m.p. 56-61°C, R*f* 0.21 (AcOEt/MeOH 10:1); $[\alpha]_D$ -119.8 (*c* 1.6, CH_3OH); NMR data (CD_3CN/D_2O) see Tables 1 and 2 and ^1H, δ : 3.28 (s, 3 H, OMe-5), 3.46 (s, 3 H, OMe-1). Anal. Calcd. for $C_8H_{16}O_7$: C, 42.86; H, 7.19. Found: C, 42.80 ; H, 7.26 .

The same reaction applied to compound **18** (210 mg, 0.424 mmol) gave a crude (106 mg) constituted by

a mixture of **24** and *methyl 5-C-methoxy-α-L-idopyranoside*, **25** (ratio 80:20 by NMR analysis). NMR signals (CD_3CN/D_2O) of **25**, ^1H δ : 3.25 (s, 3 H, OMe-5), 3.42 (s, 3 H, OMe-1), 4.46 (d, 1 H, $J_{1,2}$=8.07 Hz, H-1); ^{13}C δ: 49.52 (OMe-5), 57.38 (OMe-1), 6.59 (C-6), 101.70 (C-5), 101.86 (C-1).

An about 85:15 mixture of **17** and **16** obtained through anomerization of the crude epoxidation/methanolysis of product **8** (1.04 g, 2.30 mmol) as previously described, was hydrogenolyzed under the above standard conditions. The crude reaction product was subjected to flash-chromatography (9:1 AcOEt/MeOH) giving *methyl 5-C-methoxy-β-D-galactopyranoside*, **23** (43 mg, 8% yield), R_f 0.25 (9:1 AcOEt/MeOH), identical to previously described sample[4b] followed by **24** (324 mg, 63 % yield), R_f 0.17 (9:1 AcOEt/MeOH).

2,3,6-Tri-*O*-benzyl-(α,β)-D-*xylo*-hexofuranos-5-ulose (27).

A solution of **17** (199 mg, 0.40 mmol) in a 2.5:1 mixture of CH_3CN and H_2O (14 ml) was treated with CF_3COOH (1.4 ml) and stirred at 65°C (bath temp.) until TLC analysis showed the complete disappearance of the starting material (5 h). After removal of solvents and reagents under reduced pressure, the crude residue was flash-chromatographed on silica (CH_2Cl_2/Et_2O 95:5) to give pure **27** (161.5 mg, 90% yield) as a 55:45 mixture of the α- and β-furanose forms.

2,6-Di-O-benzyl-(α,β)-D-xylo-hexofuranos-5-ulose (**27**) was a syrup, R_f 0.30 (CH_2Cl_2/Et_2O 95:5), $[\alpha]_D$ -9.4 (*c* 0.5, $CHCl_3$); ^{13}C NMR (CD_3CN) δ: 72.45, 72.89, 73.05, 73.37, 73.60 and 73.60 (3 x *C*H2Ph α + β), 75.29 and 75.08 (C-6 α + β), 81.35, 83.10, 83.28, 83.70, 85.48 and 86.42 (C-2, C-3 and C-4 α + β), 98.63 (C-1 β), 103.48 (C-1 α), 205.98 and 206.61 (C-5 α + β). Anal. Calcd. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 75.52 ; H, 6.39.

The same compound was also obtained from **18**; in this case the hydrolysis was complete in 1 h at 65°C (bath temp.) and the final yield of pure **27** was 92 %.

D-*xylo*-Hexos-5-ulose (1).

A solution of **24** (130 mg, 0.58 mmol) in a 2.5:1 mixture of CH_3CN and H_2O (7 ml) was treated with CF_3COOH (0.8 ml) and stirred at room temperature for 48 h. After removing of solvents and reagents under reduced pressure, the crude residue was stored 1 day at 0.01 mmHg in the presence of solid KOH, giving **1** as an amorphous solid (98 mg, 95% yield), $[\alpha]_D$ -12.2 (*c* 1.0, H_2O); lit.[3] $[\alpha]_D$ -14.6 (*c* 3.1, H_2O). The ^{13}C NMR spectrum (D_2O) corresponded well with that of the mixture of tautomers reported by Kiely[3b].

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