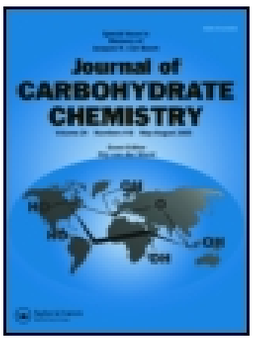

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PREPARATION OF L-*LYXO*-HEXOS-5-ULOSE THROUGH C-3 EPIMERIZATION OF BIS-GLYCOPYRANOSIDES OF L-*ARABINO*-HEXOS-5-ULOSE[1]

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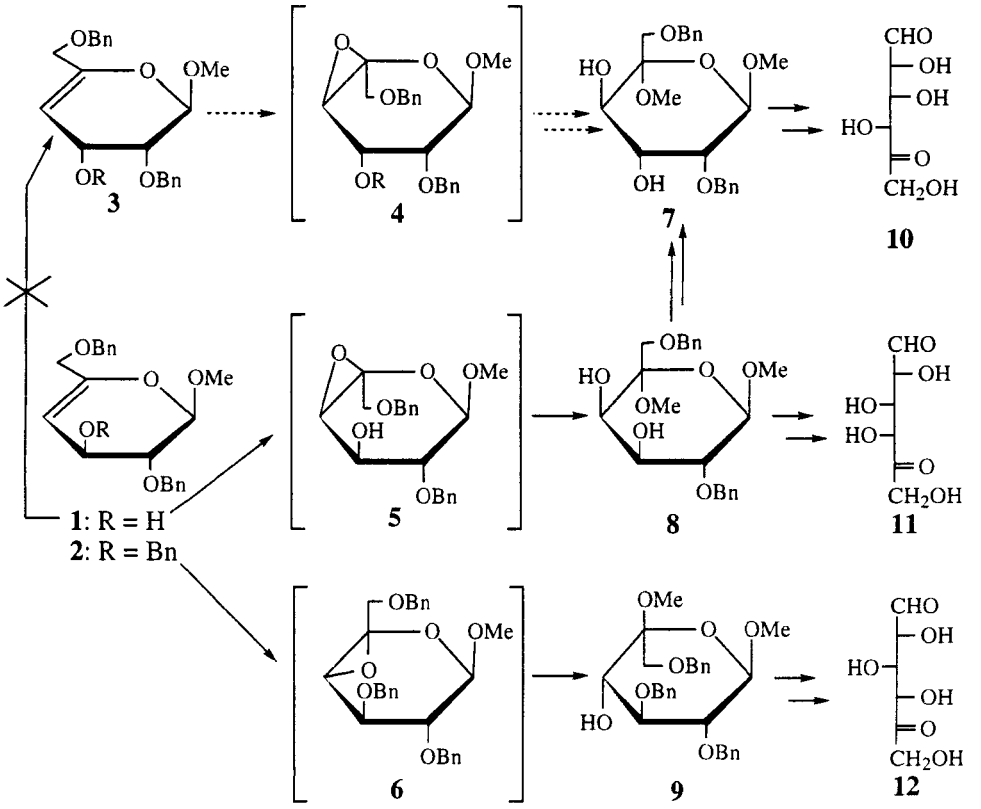
ABSTRACT

The unreported title compound and its 2,6-di-*O*-benzyl derivative have been prepared from methyl β-D-galactopyranoside through a sequence involving the bis-glycoside methyl 2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-galactopyranoside **8**, the precursor of L-*arabino*-hexos-5-ulose, that was converted to the L-*lyxo* series by inversion at C-3. The inversion was achieved in acceptable yields by selective triflation, followed by displacement with benzoate, and by an oxidation/reduction sequence. Whereas 2,5-di-*O*-benzyl-L-*lyxo*-hexos-5-ulose exists entirely as a mixture of the two anomeric 1,4-furanosic forms, the unprotected hexos-5-ulose involves at equilibrium in CD_3CN/D_2O at least eight tautomers, one of which is predominant.

INTRODUCTION

Aldohexos-5-uloses are an interesting class of dicarbonyl monosaccharides which has been investigated to a rather limited extent, in spite of the fact that they can be useful intermediates in syntheses of biologically relevant products, such as 1-deoxy-azapyranoses[2,3] and inositols,[4] of which they have also been assumed to be biosynthetic intermediates.[5,6] Only three of the eight possible stereoisomers of this series have been described in their free forms, the D-*xylo*,[4,7] the L-*arabino*[8] and the D-*lyxo*[2,21] ones. For



Scheme 1

some time, in the context of a project aimed at extending the use of milk-derived sugars as raw materials, we have been working on a new approach to aldohexos-5-uloses, starting from D-galactose derivatives, one of the final goals being the synthesis of all the unreported stereoisomers.[1]

The key intermediates of our method are 4-deoxy-4-hexeno-α-L-*threo*-pyranosides (Scheme 1), such as **1** and **2**, which are easily and efficiently obtained from methyl β-D-galactopyranoside.[9] They are 1-glycosido-5-endocyclic glycals of aldohexos-5-uloses, and can be converted into the parent dicarbonyl sugars by appropriate stereospecific oxidative and hydrolytic manipulations on the double bond. Compound **1** had thus been transformed into L-*arabino*-hexos-5-ulose (**11**) through deprotection of the bis-glycoside **8**, obtained with *m*-chloroperoxybenzoic acid in methanol in a one-pot reaction involving a stereospecific conversion to the epoxide **5**, immediately followed by a regio-and stereospecific methanolysis of the oxirane ring.[8]

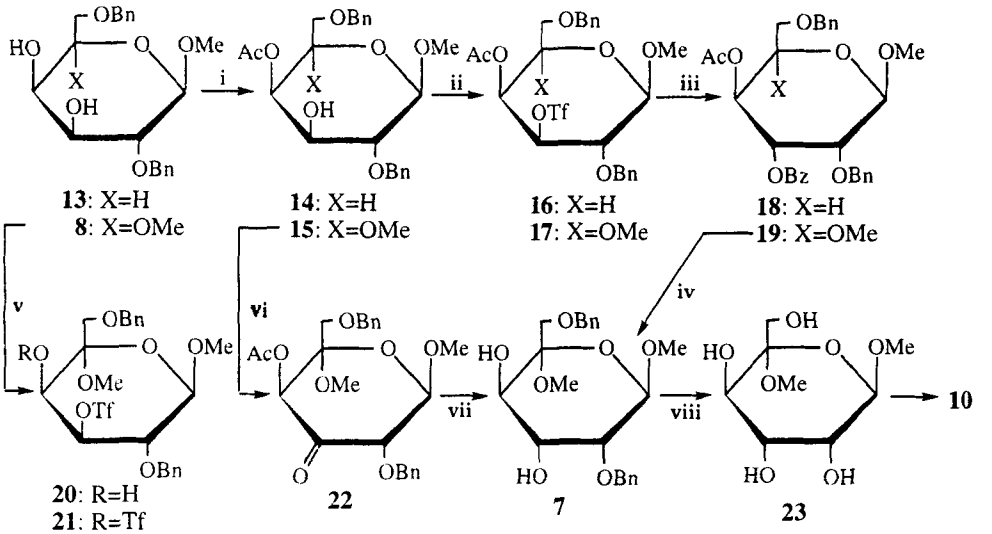
When the same sequence was applied to the 3-*O*-benzyl derivative **2**, in which the *syn*-directing effect of 3-OH was absent, the alternative *anti*-epoxide **6** became largely predominant, and gave **9**, which was converted to D-*xylo*-hexos-5-ulose (**12**).[7b]

In order to extend the use of this approach to other diastereomers of hexos-5-ulose, we investigated the possibility of inverting the configuration at one of the oxygenated positions during one of the intermediate stages of the reaction sequence. Preliminary attempts to epimerize the glycal **1** at C-3, in order to gain access to the unreported L-*lyxo* stereoisomer (**10**, *via* **3**, **4** and **7**), and to the D-*ribo* one (of which both enantiomers are unknown) gave disappointing results: the use of the Mitsunobu reaction, under the conditions used by Fraiser-Reid[10] for the epimerization of an allylic OH of a glycal, gave only a 15% yield of the desired product, and an unexplained resistance to the sulfonylation of the allylic OH prevented the use of the classical[11,12] S_N2 displacement reaction. A better result was achieved when C-3 epimerization was applied to intermediate **8**, which was thus converted into **7** that was further transformed into L-*lyxo*-hexos-5-ulose (**10**). This synthesis is the subject of the present paper.

RESULTS AND DISCUSSION

Although epimerization at specific ring positions is an extensively used procedure for the interconversion of glycopyranosides,[13] it does not always lead to the expected results.[14] No data were available on such inversions in 5-*C*-substituted compounds, such as **8**, where the presence of the axial 5-substituent could hinder axial approach of the nucleophile to the C-3 position.

Furthermore we found no reports on the C-3 epimerization of any alkyl β-D-galactopyranoside, apart from a recent interesting method involving the use of a chloral acetal,[15] which led to D-gulopyranoside in mixture with its 6-*O*-formyl derivative. We therefore decided to conduct parallel experiments on **8** and its 5-demethoxy analogue **13**, starting from the corresponding 3-*O*-triflates **17** and **16** (Scheme 2). A preliminary regiospecific 4-*O*-acetylation was performed, as previously described for other cases in the D-galactopyranoside series,[16] by mild acid cleavage (60% aq. AcOH) of an unpurified diastereomeric mixture of orthoacetates, obtained through triethyl orthoformate treatment of the 3,4-diol. Both the 4-*O*-acetates **14** and **15** were thus obtained in practically quantitative yields from the respective diols and the subsequent 3-*O*-triflation (Tf_2O in pyridine) occurred for both compounds in isolated yields of about 80%. The nucleophilic displacement on **16** and **17** was performed by treatment with tetrabutylammonium benzoate in toluene. Not unexpectedly, the reactivity of the two



Reagents: i) a. $CH_3C(OEt)_3$, TsOH, b. 60 % aq. AcOH; ii) Tf_2O, Py; iii) $Bu_4N^+BzO^-$, $C_6H_5CH_3$; iv) MeONa, MeOH; v) a. Bu_2SnO, $C_6H_5CH_3$, b. Tf_2O; vi) TPAP-NMO, 4Å, CH_2Cl_2; vii) $NaBH_4$, MeOH; viii) H_2, Pd/C, MeOH.

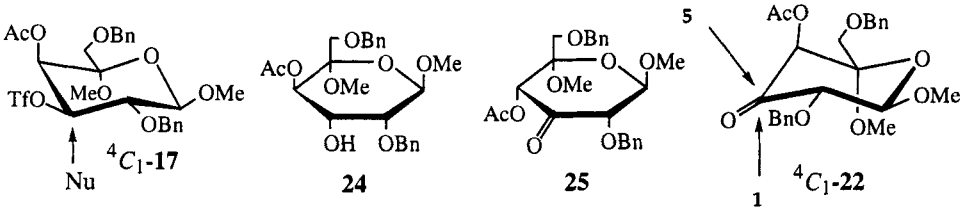
Scheme 2

derivatives was greatly different. The D-galactopyranoside triflate **16** reacted smoothly at room temperature in toluene giving, after 70 h, a crude product containing (TLC, NMR) **18** as the single component. Conversely, the triflate **17** proved to be completely unreactive under the above conditions and only when the reaction was conducted in refluxing toluene (110 °C), was it complete after 3 h, with **19** being obtained as the main product after chromatographic purification (67% yield). The highly different reactivities of **16** and **17** can be explained, as hypothesized above, by an unfavourable steric effect on the nucleophilic displacement on the latter in its more stable $^4C_1$ conformation, which occurs *syn*-diaxially to the 5-methoxy group. Very similar results were obtained when the reaction with tetrabutylammonium benzoate was conducted in DMF, whereas the use of the corresponding nitrite, in toluene, as the nucleophile[17] required temperatures as high as 110 °C and was much less satisfactory, giving directly the free alcohol **24**, but in only 44% isolated yield.

The structure of **18** was firmly established through ^1H NMR analysis on the basis of the vicinal coupling constants of H-2 and H-3 ($J_{1,2}$, $J_{2,3}$ and $J_{3,4}$, respectively, of 8.06, 3.42 and 3.87 Hz), pointing to an axial-axial-equatorial disposition of H-1, H-2 and H-3. A similar series of coupling constants was found for **19** ($J_{1,2}$, $J_{2,3}$ and $J_{3,4}$, respectively,

7.61, 3.66 and 3.80 Hz) confirming the equatorial orientation of H-3 and thus the 5-*C*-methoxy-D-*gulo* configuration of **19**.

In order to shorten the above epimerization sequence, the 3-*O*-triflate **20** was prepared directly from **8** through a stannylidene acetal intermediate, which was opened in a highly regioselective manner (82% isolated yield) by treatment with trifluoromethanesulphonic anhydride under the conditions recently proposed by Ley,[18] the sole isolated by-product being the 3,4-di-*O*-triflate **21** (10% isolated yield). Several reports[19] on the cleavage of stannylidene acetals of D-galactopyranoside 3,4-diols with other types of electrophiles are known to give 3-*O*-substitution in a regiospecific manner, indicating a closely similar behaviour between the D-*galacto* and the 5-*C*–methoxy-D-*galacto* series for these reactions. Unfortunately, the treatment of **20** with various combinations of carboxylates, solvents and reaction conditions led only to very complex mixtures of products, and this approach was abandoned.



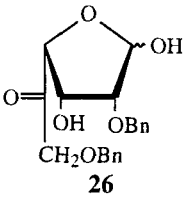
The alternative approach to epimerization, oxidation followed by reduction, was investigated on the 4-*O*-acetate **15**. Its oxidation was easily achieved with the tetrapropylammonium perruthenate (TPAP)/4-methylmorpholine-*N*-oxide (NMO) system, but complete conversion to the 3-ulopyranoside **22** required doubling the usual amount of catalyst.[20] In spite of the very high degree of conversion of **15** to **22**, isolation and purification of the latter involved significant losses, such that it was isolated in only 62% yield; losses during chromatography on silica were particularly high. One of the side-products generated during work-up was identified as the C-4 epimerization product **25**, obviously formed through an enolic form, in a conversion favoured by the passage from an axial to an equatorial substituent.

With the goal of obtaining the L-*lyxo* stereoisomer **23**, it was therefore more convenient to carry out the reduction step on the crude oxidation product, which was filtered on Celite and subjected to reaction with $NaBH_4$ in methanol. Reduction was complete in 10 minutes, and accompanied by deacetylation to give a 5:1 mixture of the diols **7** and **8** in a total yield of 90%; **7** and **8** were easily separated by flash chromatography. The satisfactory diastereomeric ratio in favour of **7** is probably the result of an unfavourable axial/axial interaction between the 5-OMe group of **22**, in the

presumably favoured $^4C_1$ conformation, and the incoming hydride ion, hindering attack more from the α than from the β side. A $J_{1,2}$ of 7.52 Hz in the ^1H NMR spectrum of **22** supports this assumed conformation.

Compound **7** was hydrolyzed with CF_3COOH in CH_3CN/H_2O to give 2,6-di-*O*-benzyl-L-*lyxo*-hexos-5-ulose, the NMR spectra of which revealed that it exists in CD_3CN/D_2O exclusively as a mixture of the α and β anomers of the furanose forms **26** (α/β ratio ≈ 65:35) as previously found[7b,8] for the corresponding 2,6-diprotected hexos-5-uloses of the L-*arabino* and D-*xylo* series.

Alternatively **7** was quantitatively hydrogenolyzed on palladiated carbon to the bis-glycoside **23**, from which the free hexosulose **10** was obtained, by CF_3COOH catalyzed hydrolysis in practically quantitative yield, as a complicated mixture of tautomers, at least eight on the basis of the anomeric proton doublets and correlated ^{13}C signals (NMR spectra in D_2O/CD_3CN).



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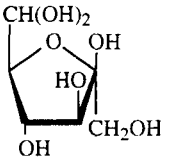

27

A recent paper by Kiely and co-workers[21] has analyzed the tautomeric equilibrium of the D-*lyxo* enantiomer of **10** in D_2O and identified seven different species. The close similarity between their ^1H and ^{13}C NMR parameters and ours confirm the identity of our product.

EXPERIMENTAL

General methods. 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}. ^1H NMR spectra (internal TMS) were recorded with a Bruker AC 200 spectrometer at 200 MHz. First-order spectral analysis was performed whenever possible, otherwise spectra were simulated with the PANIC (Bruker) or LAOCN-5 (QCPE QCMP 049) computer programs. Chemical shifts and coupling constants values were confirmed, when necessary, with COSY or homonuclear J resolved 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% phosphomolybdic or sulphuric acid, and heating. Kieselgel 60 (Merck, 70-230 and 230-400 mesh, respectively) was used for column and flash chromatography. Solvents were distilled and stored over 4Å molecular sieves activated at least 24 h at 400 °C. $MgSO_4$ was used as the drying agent for solutions.

Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-β-D-galactopyranoside (14). To a solution of **13**[8b] (1.04 g, 2.78 mmol) in anhydrous toluene (20 mL) were added triethyl orthoacetate (6.0 mL) and *p*-toluenesulfonic acid (35 mg). The reaction mixture was warmed for 30 min at 45 °C and, after cooling, treated with excess Et_3N and stirred for 10 min at room temperature. The solvent was evaporated under reduced pressure and the crude residue immediately treated with 60% aqueous AcOH (100 mL). The solution was warmed for 20 min at 45 °C, until TLC analysis showed a complete disappearance of the starting material. The reaction mixture, evaporated *in vacuo* and coevaporated repeatedly with toluene (3 x 30 mL), gave 1.28 g of crude product. A flash chromatography on silica gel (7:3 hexane/EtOAc) gave pure **14** (1.09 g, 94% yield) as a syrup, R_f 0.40 (1:1 hexane/EtOAc); $[\alpha]_D$ -7.2 (*c* 2.1, $CHCl_3$); ^1H NMR (CD_3CN) δ 2.03 (s, 3 H, CH_3CO), 3.32 (dd, 1 H, $J_{1,2}$ = 7.69 Hz, $J_{2,3}$ = 9.72 Hz, H-2), 3.49 (s, 3 H, OCH_3), 3.47 (dd, 1 H, $J_{5,6a}$ = 6.18 Hz, $J_{6a,6b}$ = 10.02 Hz, H-6a), 3.52 (dd, 1 H, $J_{5,6b}$ = 6.08 Hz, H-6b), 3.71 (dd, 1 H, $J_{3,4}$ = 3.58 Hz, H-3), 3.79 (ddd, 1 H, $J_{4,5}$ = 1.00 Hz, H-5), 4.30 (d, 1 H, H-1), 4.46 and 4.52 (2 d, 2 H, AB, J_{AB} = 11.85 Hz, PhCH_2), 4.67 and 4.84 (2 d, 2 H, AB, J_{AB} = 11.51 Hz, PhCH_2), 5.24 (dd, 1 H, H-4), 7.31-7.39 (m, 10 H, 2 Ph); ^{13}C NMR (CD_3CN) δ 21.15 (CH_3CO), 57.22 (OCH_3), 69.46 (C-6), 71.42 (C-4), 72.27 (C-5), 72.84 (C-3), 73.49 and 75.11 (2 PhCH_2), 80.74 (C-2), 105.35 (C-1), 128.30-140.10 (2 Ph), 171.23 (CH_3CO).

Anal. Calcd for $C_{23}H_{28}O_7$ (416.47): C, 66.33; H, 6.78. Found: C, 66.50; H, 6.95.

Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-3-*O*-trifluoromethanesulfonyl-β-D-galactopyranoside (16). A solution of **14** (1.00 g, 2.40 mmol) in dry pyridine (10 mL) cooled to -10 °C was treated with Tf_2O (0.89 mL, 5.27 mmol) and stirred 15 min at -10 °C and then 4 h at 0 °C, until TLC analysis showed complete disappearance of the starting material. The solution was treated with ice and repeatedly extracted with CH_2Cl_2 (3 x 30 mL); the solvent was evaporated from the combined organic extracts, and the crude residue was purified by flash chromatography on silica gel (8.5:2.5 hexane/EtOAc) to give pure **16** (1.04 g, 79% yield) as a syrup, R_f 0.60 (1:1 hexane/EtOAc); $[\alpha]_D$ -2.8 (*c* 2.0, $CHCl_3$); ^1H NMR (CD_3CN) δ 2.08 (s, 3 H, CH_3CO), 3.51 (dd, 1 H, $J_{5,6a}$ = 6.92 Hz,

$J_{6a,6b}$ = 9.86 Hz, H-6a), 3.55 (s, 3 H, OCH_3), 3.59 (dd, 1 H, $J_{5,6b}$ = 6.00 Hz, H-6b), 3.74 (dd, 1 H, $J_{1,2}$ = 7.66 Hz, $J_{2,3}$ = 9.99 Hz, H-2), 3.93 (ddd, 1 H, $J_{4,5}$ = 1.02 Hz, H-5), 4.47 (d, 1 H, H-1), 4.54 and 4.66 (2 d, 2 H, AB, J_{AB} = 11.72 Hz, PhCH_2), 4.66 and 4.89 (2 d, 2 H, AB, J_{AB} = 10.77 Hz, PhCH_2), 5.12 (dd, 1 H, $J_{3,4}$ = 3.55 Hz, H-3), 5.58 (dd, 1 H, H-4), 7.31-7.40 (m, 10 H, 2 Ph); ^{13}C NMR (CD_3CN) δ 20.63 (*C*H_3CO), 57.63 (OCH_3), 68.40 (C-6), 68.94 (C-4), 71.69 (C-5), 73.87 and 75.40 (2 Ph*C*H_2), 77.31 (C-2), 86.97 (C-3), 104.95 (C-1), 119.80 (CF_3), 129.22-139.08 (2 Ph), 170.54 (CH_3*C*O).

Anal. Calcd for $C_{24}H_{27}F_3O_9S$ (548.53): C, 52.55; H, 4.96. Found: C, 52.70; H, 5.10.

Methyl 4-*O*-Acetyl-3-*O*-benzoyl-2,6-di-*O*-benzyl-β-D-gulopyranoside (18). A solution of **16** (150 mg, 0.27 mmol) and $Bu_4N^+BzO^-$ (245 mg, 0.67 mmol) in toluene (9 mL) was stirred 68 h at room temperature. The solution was concentrated *in vacuo*, and the residue was taken up in CH_2Cl_2 (60 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 100 mL). The combined extracts, dried and concentrated under reduced pressure, left a crude product (76 mg) which, after flash chromatography on silica gel (8:2 hexane/EtOAc), gave pure **18** (111 mg, 81% yield) as a syrup, Rf 0.36 (7:3 hexane/EtOAc); $[\alpha]_D$ -53.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 2.03 (s, 3 H, C*H*$_3$CO), 3.53 (s, 3 H, OCH_3), 3.55 (dd, 1 H, $J_{5,6a}$ = 6.08 Hz, $J_{6a,6b}$ = 10.08 Hz, H-6a), 3.61 (dd, 1 H, $J_{5,6b}$ = 6.39 Hz, H-6b), 3.61 (dd, 1 H, $J_{1,2}$ = 8.06 Hz, $J_{2,3}$ = 3.42 Hz, H-2), 4.28 (ddd, 1 H, $J_{4,5}$ = 1.51 Hz, H-5), 4.48 and 4.55 (2 d, 2 H, AB, J_{AB} = 11.96 Hz, PhCH_2), 4.64 (s, 2 H, PhCH_2), 4.82 (d, 1 H, H-1), 5.04 (dd, 1 H, $J_{3,4}$ = 3.87 Hz, H-4), 5.66 (dd, 1 H, H-3); ^{13}C NMR (CD_3CN) δ 20.96 (*C*H_3CO), 56.90 (OCH_3), 69.13 (C-6), 69.13 (C-3), 69.36 (C-4), 72.19 (C-5), 73.17 and 73.85 (*C*H_2Ph), 75.60 (C-2), 102.38 (C-1), 128.48-139.42 (3 Ph), 165.76 (Ph*C*O), 170.62 (CH_3*C*O).

Anal. Calcd for $C_{30}H_{32}O_8$ (520.58): C, 69.22; H, 6.20. Found: C, 68.90; H, 6.43.

Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-galactopyranoside (15). A sample of methyl 2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-galactopyranoside (**8**)[7b] (1.00 g, 2.47 mmol) was submitted to selective acetylation by the method described above for **13**, giving 1.07 g of crude product which, after flash chromatography on silica gel (7.5:2.5 hexane/EtOAc), gave pure **15** (930 g, 92% yield), as a white solid, mp 103-106 °C, Rf 0.57 (1:1 hexane/EtOAc); $[\alpha]_D$ -74.8 (*c* 1.33, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.98 (s, 3 H, C*H*$_3$CO), 3.25 (s, 3 H, OCH_3-5), 3.28 and 3.56 (2 d, 2 H, AB, J_{AB} = 10.66 Hz, H-6a and H-6b), 3.36 (ddd, 1 H, $J_{1,2}$ = 7.90 Hz, $J_{2,3}$ = 9.79 Hz, $J_{2,4}$ = 0.38 Hz, H-2), 3.46 (s, 3 H, OCH_3-1), 3.97 (dd, 1 H, $J_{3,4}$ = 3.53 Hz, H-3), 4.38 and 4.46 (2 d, 2 H, AB, J_{AB} = 11.66 Hz, PhCH_2), 4.47 (d, 1 H, H-1), 4.65-4.70 (2 d, 2 H, AB, J_{AB} = 11.42 Hz, PhCH_2), 5.20 (dd, 1 H, H-4), 7.28-7.36 (m, 10 H, 2 Ph); ^{13}C NMR (CD_3CN) δ 21.16 (*C*H_3CO),

48.89 (OCH_3-5), 57.38 (OCH_3-1), 65.97 (C-6), 69.55 (C-3), 71.48 (C-4), 73.90 and 75.19 (2 Ph*C*H_2), 80.15 (C-2), 100.49 (C-5), 101.53 (C-1), 128.43-139.93 (2 Ph), 170.96 (CH_3*C*O).

Anal. Calcd for $C_{24}H_{30}O_8$ (446.50): C, 64.56; H, 6.77. Found: C, 64.84; H, 6.82.

Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-3-*O*-trifluoromethanesulfonyl-β-D-galactopyranoside (17). A sample of **15** (1.67 g, 3.74 mmol) was transformed into the corresponding triflate **17** by the method described above for **14**, to give 2.01 g of crude product. Flash chromatography on silica gel (8:2 hexane/EtOAc) gave pure **17** (1.72 g, 80% yield) as a solid, mp 65-67 °C, R_f 0.70 (1:1 hexane/EtOAc); $[\alpha]_D$ -56.5 (*c* 1.54, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 2.04 (s, 3 H, C*H*$_3$CO), 3.31 (s, 3 H, OCH_3-5), 3.36 and 3.65 (2 d, 2 H, AB, J_{AB}= 10.82 Hz, H-6a and H-6b), 3.54 (s, 3 H, OCH_3-1), 3.79 (ddd, 1 H, $J_{1,2}$ = 7.68 Hz, $J_{2,3}$ = 10.55 Hz, $J_{2,4}$ = 0.28 Hz, H-2), 4.42 and 4.51 (2 d, 2 H, AB, J_{AB} = 11.68 Hz, PhC*H*$_2$), 4.65 and 4.85 (2 d, 2H, AB, J_{AB} = 10.82 Hz, PhC*H*$_2$), 4.65 (dd, 1 H, $J_{1,3}$ = 0.46, Hz, H-1), 5.16 (ddd, 1 H, $J_{3,4}$ = 3.32 Hz, H-3), 5.52 (ddd, 1 H, H-4), 7.30-7.39 (m, 10 H, 2 Ph); ^{13}C NMR (CD_3CN) δ 20.69 (*C*H$_3$CO), 49.30 (OCH_3-5), 57.75 (OCH_3-1), 65.30 (C-6), 69.25 (C-4), 73.91 and 75.43 (2 Ph*C*H_2), 76.67 (C-2), 86.23 (C-3), 100.69 (C-5), 101.57 (C-1), 128.72-138.78 (2 Ph), 169.87 (CH_3*C*O).

Anal. Calcd for $C_{25}H_{29}F_3O_{10}S$ (578.56): C, 51.90; H, 5.05. Found: C, 52.20; H, 5.05.

Methyl 4-*O*-Acetyl-3-*O*-benzoyl-2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-gulopyranoside (19). A solution of **17** (1.50 g, 2.61 mmol) and $Bu_4N^+BzO^-$ (2.37 g, 6.52 mmol) in 10 mL of toluene was refluxed for 3 h and submitted to the same work-up as for compound **18**. The residue (3.50 g) purified by flash chromatography on silica gel (8:2 hexane/EtOAc) gave pure **19** (941 mg, 67% yield) as a syrup, R_f 0.45 (7:3 hexane/EtOAc); $[\alpha]_D$ -68.4 (*c* 1.02, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.99 (s, 3 H, C*H*$_3$CO), 3.41 (s, 3 H, OCH_3-5), 3.48 and 3.70 (2 d, 2 H, AB, J_{AB} = 10.31 Hz, H-6a and H-6b), 3.55 (s, 3 H, OCH_3-1), 3.71 (ddd, 1 H, $J_{1,2}$ = 7.61 Hz, $J_{2,3}$ = 3.66 Hz, $J_{2,4}$ = 0.41 Hz, H-2), 4.43 and 4.51 (2 d, 2 H, AB, J_{AB} = 11.70 Hz, PhC*H*$_2$), 4.67 (s, 2 H, PhC*H*$_2$), 5.04 (dd, 1 H, $J_{1,3}$ = 0.28 Hz, H-1), 5.20 (dd, 1 H, $J_{3,4}$ = 3.80 Hz, H-4), 5.56 (ddd, 1 H, H-3), 7.26-7.37 (m, 15 H, 3 Ph); ^{13}C NMR (CD_3CN) δ 21.02 (*C*H$_3$CO), 49.02 (OCH_3-5), 57.05 (OCH_3-1), 67.26 (C-6), 68.87 (C-4), 69.40 (C-3), 73.26 and 73.94 (2 Ph*C*H_2), 74.78 (C-2), 98.24 (C-1), 101.48 (C-5), 128.53-139.21 (3 Ph), 166.09 (Ph*C*O), 169.75 (CH_3*C*O).

Methyl 2,6-Di-*O*-benzyl-5-*C*-methoxy-β-D-gulopyranoside (7). To a solution of **19** (717 mg, 1.37 mmol) in MeOH (10 mL) was added methanolic 1 N MeONa (0.4 mL)

and the reaction mixture was stirred at room temperature until TLC analysis showed a complete disappearance of the starting material. After 15 h, saturated aqueous $NaHCO_3$ (2 mL) was added, the solvent was evaporated *in vacuo* and the residue partitioned between CH_2Cl_2 and H_2O. The organic phase, dried and concentrated under reduced pressure, gave a crude product (553 mg) which was purified by flash chromatography on silica gel (5.5:4.5 hexane/EtOAc) to give pure **7** (421 mg, 76% yield) as a yellow syrup, R_f 0.17 (7:3 hexane/EtOAc); $[\alpha]_D$ -59.9 (*c* 1.51, $CHCl_3$); ^1H NMR (CD_3CN) δ 3.28 (s, 3 H, OCH_3-5), 3.46 (s, 3 H, OCH_3-1), 3.51 (ddd, 1 H, $J_{1,2}$ = 7.87 Hz, $J_{2,3}$ = 3.51 Hz, $J_{2,4}$ = 0.44 Hz, H-2), 3.53 and 3.59 (2 d, 2 H, AB, J_{AB} = 10.50 Hz, H-6a and H-6b), 3.85 (dd, 1 H, $J_{3,4}$ = 3.40 Hz, H-4), 4.01 (ddd, 1 H, $J_{1,3}$ = 0.32 Hz, H-3), 4.48 and 4.62 (2 d, AB, 2 H, J_{AB} = 11.79 Hz, PhCH_2), 4.65 (s, 2 H, PhCH_2), 4.75 (dd, 1 H, H-1), 7.30-7.40 (m, 10 H, 2 Ph); ^{13}C NMR (CD_3CN) δ 48.92 (OCH_3-5), 57.02 (OCH_3-1), 67.09 (C-6), 69.17 (C-4), 71.59 (C-3), 72.60 and 73.93 (2 PhCH_2), 75.84 (C-2), 98.26 (C-1), 103.38 (C-5), 128.53-139.56 (2 Ph).

Anal. Calcd for $C_{22}H_{28}O_7$ (404.46): C, 65.33; H, 6.98. Found: C, 64.90; H, 7.40.

Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-*xylo*-hexopyranosyl-3-ulose (22). A solution of **15** (208 mg, 0.466 mmol) in anhydrous CH_2Cl_2 (6 mL) containing activated powdered 4Å molecular sieves (400 mg) and pre-dried ($MgSO_4$ in CH_2Cl_2) 4-methylmorpholine-*N*-oxide (NMO) (96.2 mg, 0.41 mmol) was stirred for 30 min, then tetrapropylammonium perruthenate (TPAP) (48 mg, 0.14 mmol) was added and the reaction was followed by TLC analysis until complete. After 30 min the suspension was filtered through Celite and the solvent was evaporated under reduced pressure to give a crude residue (215 mg), constituted (^1H and ^{13}C NMR) exclusively by **22**. Analytically pure **22** was obtained by flash chromatography on silica gel (7:3 hexane/EtOAc) (125 mg, 60% yield) as a white solid, mp 66-68 °C, R_f 0.30 (7:3 hexane/EtOAc); $[\alpha]_D$ -153.4 (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3CN) δ 1.98 (s, 3H, CH_3CO), 3.32 (s, 3 H, OCH_3-5), 3.52 (s, 3 H, OCH_3-1), 3.53 and 3.74 (2 d, 2 H, AB, J_{AB} = 10.81 Hz, H-6a and H-6b), 4.27 (d, 1 H, $J_{1,2}$ = 7.30 Hz, H-2), 4.45 and 4.56 (2 d, AB, 2 H, J_{AB} = 11.85 Hz, PhCH_2), 4.62 and 4.72 (2 d, AB, 2 H, J_{AB} = 11.50 Hz, PhCH_2), 4.67 (d, 1 H, H-1), 4.96 (s, 1 H, H-4), 7.30-7.39 (m, 10 H, 2 Ph); ^{13}C NMR (CD_3CN) δ 20.80 (CH_3CO), 49.47 (OCH_3-5), 57.49 (OCH_3-1), 65.31 (C-6), 73.82 (2 PhCH_2), 75.78 (C-4), 82.14 (C-2), 101.09 (C-5), 101.94 (C-1), 128.74-138.80 (2 Ph), 169.97 (CH_3CO), 198.63 (C-3).

Anal. Calcd for $C_{24}H_{28}O_8$ (444.48): C, 64.85; H, 6.35. Found: C, 64.75; H, 6.57.

Methyl 2,6-Di-*O*-benzyl-5-*C*-methoxy-β-D-gulopyranoside (7). To a solution of crude **22** (151 mg, 0.34 mmol) in MeOH (7 mL), cooled to 0 °C, was added $NaBH_4$ (94.3

mg, 2.49 mmol), and the reaction mixture was stirred at room temperature for 10 min until TLC analysis showed a complete disappearance of the starting material. The solution was treated with H_2O (10 mL), stirred for 5 h, and extracted with CH_2Cl_2 (5 x 15 mL). The combined dried organic extracts were concentrated *in vacuo* to leave a crude residue (137 mg) constituted (^{13}C NMR) exclusively by a mixture of compounds **7** and **8** in the ratio 5:1. Flash chromatography on silica gel (6:4 hexane/EtOAc) allowed a complete separation of the two components, **7** [R_f 0.26 (6:4 hexane/EtOAc), 104 mg, 76% yield] and **8** [R_f 0.16 (6:4 hexane/EtOAc), 22 mg, 16% yield]. When the same reaction was conducted on an analytically pure sample of **22**, an identical result was obtained.

Methyl 5-*C*-Methoxy-β-D-gulopyranoside (23). A solution of **7** (531 mg, 1.30 mmol) in dry MeOH (10 mL) containing 10% Pd on charcoal (120 mg) was stirred at room temperature under H_2 for 3 h until the starting material had disappeared (TLC analysis 9:1 EtOAc/MeOH). The suspension was filtered through a small layer of Celite and concentrated under reduced pressure to give a white amorphous solid residue (293 mg, quantitative yield) of pure **23** (^1H and ^{13}C NMR); mp 90-94 °C, R_f 0.16 (9:1 EtOAc/MeOH).^1H NMR (CD_3CN) δ 3.28 (s, 3 H, OCH_3-5), 3.45 (s, 3 H, OCH_3-1), 3.56 (ddd, 1 H, $J_{1,2}$ = 8.00 Hz, $J_{2,3}$ = 3.64 Hz, $J_{2,4}$ = 0.33 Hz, H-2), 3.58 (s, 2 H, H-6a and H-6b), 3.80 (dd, 1 H, $J_{3,4}$ = 3.90 Hz, H-4), 3.87 (ddd, 1 H, $J_{1,3}$ = 0.29 Hz, H-3), 4.59 (dd, 1 H, H-1); ^{13}C NMR (CD_3CN) δ 48.81 (OCH_3-5), 57.43 (OCH_3-1), 58.84 (C-6), 68.32 (C-2), 68.69 (C-4), 72.84 (C-3), 98.67 (C-1), 103.72 (C-5).

Compound **23** was characterized as its tetraacetate. A solution of **23** (97 mg, 0.31 mmol) in pyridine (4 mL) and Ac_2O (2 mL), was left at room temperature for 24 h. The reaction mixture was repeatedly co-evaporated *in vacuo* with toluene (3 x 20 mL) to give a residue (174.3 mg) which, after flash chromatography on silica gel (5.5:4.5, hexane/EtOAc), gave pure acetylated **23** (125 mg, 74% yield) as a white solid, mp 98-101 °C, R_f 0.41 (1:1 hexane/EtOAc); $[\alpha]_D$ -70.9 (*c* 1.02, $CHCl_3$); ^1H NMR (CD_3CN) δ 1.98, 2.01, 2.03, 2.05 (4s, 12 H, C*H*$_3$CO), 3.36 (s, 3 H, OCH_3-5), 3.48 (s, 3 H, OCH_3-1), 4.16 and 4.22 (2d, 2 H, AB, $J_{6a,6b}$ = 12.16 Hz, H-6a and H-6b), 4.91 (d, 1 H, $J_{1,2}$ = 6.57 Hz, H-1), 4.98 (m, 1 H, $J_{2,3}$ = 3.10, H-2), 5.17 (m, 2 H, $J_{3,4}$ = 5.61 Hz, H-3 and H-4); ^{13}C NMR (CD_3CN) δ 20.87 (4 *C*H_3CO), 49.25 (OCH_3-5), 57.17 (OCH_3-1), 61.49 (C-6), 67.82 and 68.56 (C-3 and C-4), 68.73 , (C-2), 97.18 (C-1), 101.09 (C-5), 170.89, 170.89, 170.49, 169.90 (4 CH_3*C*O).

Anal. Calcd for $C_{16}H_{24}O_{11}$ (392.36): C, 48.98; H, 6.17. Found: C, 48.86; H, 5.99.

2,6-Di-*O*-benzyl-α,β-L-*lyxo*-hexos-5-ulose (26). A solution of **7** (380 mg, 0.94 mmol) in 2:1 (*v/v*) CH_3CN/H_2O (20 mL) and CF_3COOH (1.6 mL) was stirred at 60 °C

Table: ^{1}H and ^{13}C NMR data of **27** compared with those by Kiely[21] (given in parentheses).

	H-1	H-2	H-3	H-4	H-6a	H-6b
δ (ppm)	4.88	3.54	4.08	3.95	3.44	3.44
	(5.00)	(3.63)	(4.19)	(4.08)	(3.58)	(3.53)
J (Hz)	5.58	6.54	7.75		n.d.	
	(6.10)	(6.30)	(8.04)		(12.20)	
δ (ppm)	C-1	C-2	C-3	C-4	C-5	C-6
	91.47	83.38	76.48	76.48	102.84	63.31
	(92.16)	(83.54)	(76.90)	(76.80)	(103.07)	(63.62)

for 1.5 h; the solvent was evaporated under reduced pressure and repeated coevaporation with toluene (3 x 20 mL) gave a residue (332 mg) which was purified by flash-chromatography on silica gel (1:1 hexane/EtOAc) to give pure **26** (298 mg, 93% yield) as a white solid, mp 85-90 °C, R_f 0.29 (8:2 CH_2Cl_2/Et_2O), $[\alpha]_{D\infty}$ +15.1 (*c* 0.96, $CHCl_3$); ^{1}H NMR (CD_3CN) δ α-anomer 3.23 (dd, 1 H, $J_{1,2}$ = 4.60 Hz, $J_{2,3}$ = 4.38 Hz, H-2), 4.35 (dd, 1 H, $J_{3,4}$ = 4.17 Hz, H-3), 4.40 (d, 2 H, H-6), 4.73 (dd, 1 H, H-4), 5.40 (d, 1 H, H-1); β-anomer 3.25 (dd, 1 H, $J_{1,2}$ = 4.54 Hz, $J_{2,3}$ = 4.06 Hz, H-2), 4.45 (d, 2 H, H-6), 4.52 (dd, 1 H, $J_{3,4}$ = n.d. Hz, H-4), 4.54 (dd, 1 H, H-3), 5.29 (dd, 1 H, H-1); ^{13}C NMR (CD_3CN) δ α-anomer 72.59 (C-3), 72.96 and 73.59 (2 PhCH_2), 74.91(C-6), 84.88 (C-4), 85.15 (C-2), 101.61 (C-1), 206.29 (C-5); β-anomer 71.70 (C-3), 72.45 and 73.59 (2 PhCH_2), 75.37 (C-6), 79.07 (C-2), 85.24 (C-4), 97.37 (C-1), 206.77 (C-5). The ratio between **α-26** and **β-26**, determined by the areas of the respective proton resonances, was 66:34.

Anal. Calcd. for $C_{20}H_{22}O_6$ (358.39): C, 67.03; H, 6.19. Found: C, 67.29; H, 6.21.

L-*lyxo*-Hexos-5-ulose (10). A solution of **23** (492 mg, 2.16 mmol) in 1:1 (*v/v*) CH_3CN/H_2O (25 mL) was treated with CF_3COOH (3.0 mL), stirred at 50 °C for 40 min, and then submitted to the same work-up as for **26**, giving **10** as an amorphous solid (380 mg, quantit. yield); $[\alpha]_{D\infty}$ +18.8 (*c* 1.3, H_2O); lit[21] for the D enantiomer -19.34 (*c* 0.93, H_2O). NMR spectra (3:1 D_2O/CD_3CN) of **10** showed the presence of at least 8 tautomers as evidenced by the doublets in the anomeric region of its proton spectrum and by their correlated carbons. One of these was predominant (38% of the total), the remaining ones being all below 15%.

During the course of our work, a paper by Kiely[21] on the D enantiomer of **10** was published in which the main tautomer (constituting 52% of the equilibrium mixture in

D_2O) was identified as the hydrated form **27**. Since the reported NMR parameters are very close to those we found for our main tautomer, the latter evidently is the enantiomer of **27** (Table). Small differences in chemical shifts and coupling constants and in the percentages with respect to the total tautomers may be due to the different solvents used to obtain the NMR spectra (pure D_2O vs. 1:1 D_2O/CD_3CN). Kiely also identified six of the minor tautomers, for which our partial NMR data are in satisfactory agreement.

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