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A SIMPLE STEREOSPECIFIC ROUTE TO 5-C-ALKOXY-D-GALACTOPYRANOSIDES AND TO L-*arabino*-HEXOS-5-ULOSES

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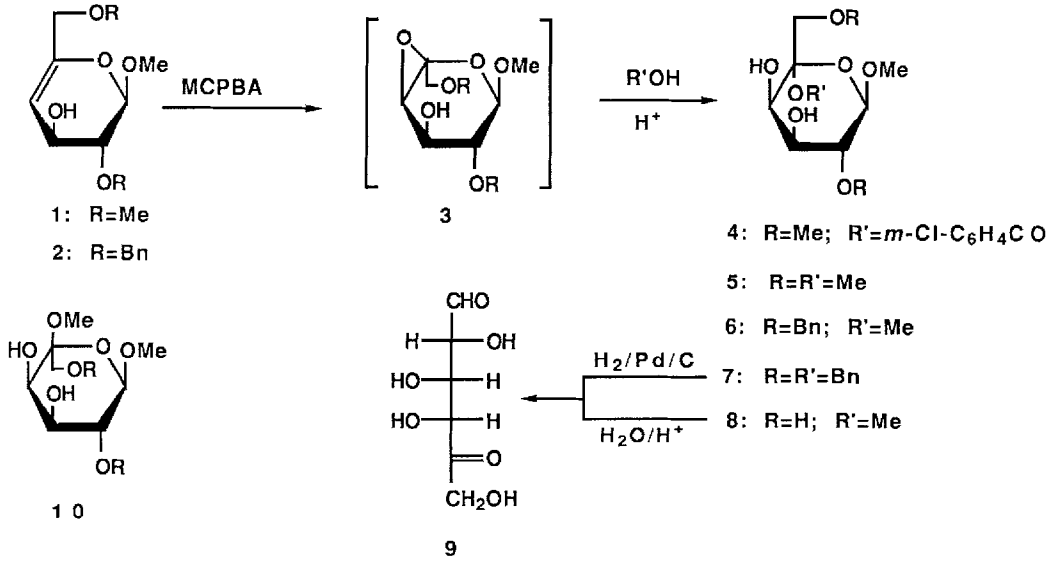
Summary 5-C-alkoxy-β-D-galactopyranosides, which are easily convertible into L-*arabino*-hexos-5-uloses, can be prepared from β-D-galactopyranosides *via* peroxyacid oxidation in an alcoholic solvent of intermediate 4-deoxy-α-L-*threo*-hex-4-enopyranosides

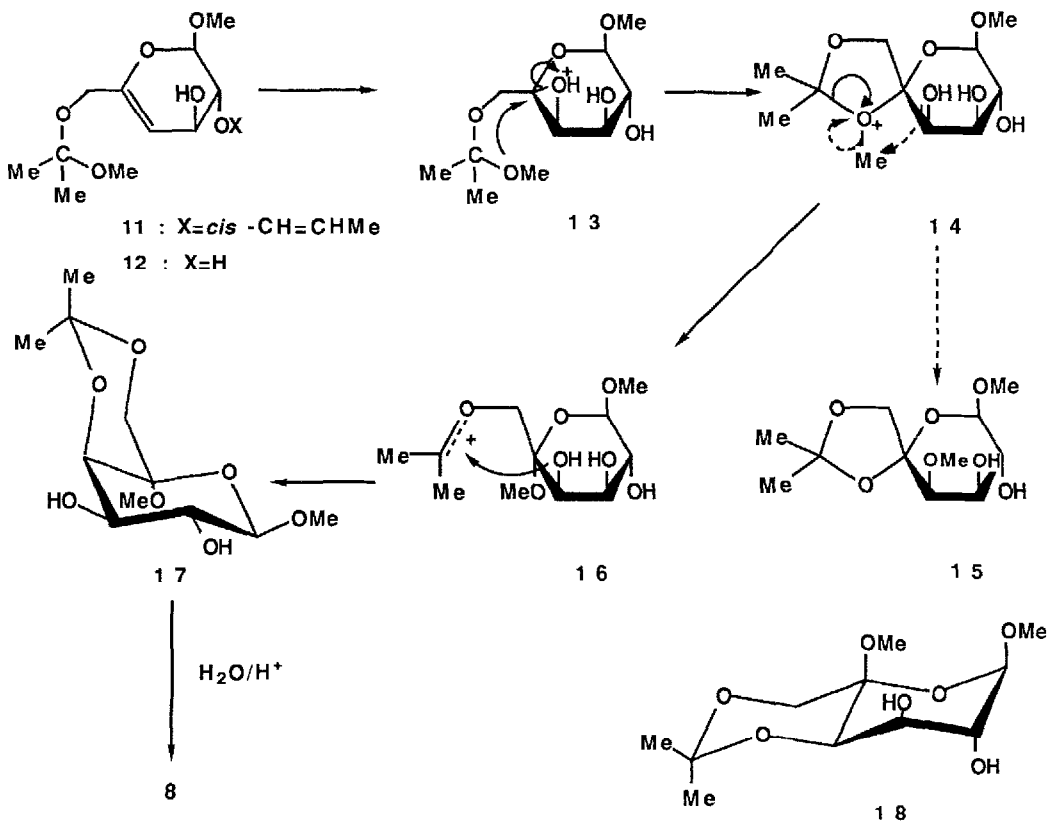
4-Deoxy-α-L-*threo*-hex-4-enopyranosides, which recently became easily available from 3,4-O-isopropylidene-β-D-galactopyranosides by treatment with *t*-BuOK in DMF or DMSO,[1] are interesting intermediates with a highly nucleophilic double bond. For istance, compound **1**, readily prepared from methyl β-D-galactopyranoside, is converted in moderate yield by *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 into the 5-C-(3-chlorobenzoyloxy) adduct **4** through the unstable primarily formed epoxide **3**.[1]

We have now found that, if the reaction of **1** or **2** with MCPBA is carried out in an alcoholic solvent, opening of the oxirane ring of **3** occurs exclusively by alcoholysis to give in a regio- and diastereospecific way 5-C-alkoxygalactopyranosides. Compounds such as **5**, **6**, and **7** were thus easily prepared in better than 80 % isolated yields.



Hydrogenolysis of **6** over Pd/C gave methyl 5-C-methoxy-β-D-galactopyranoside **8**, a bis-glycoside of the hydrated pyranosidic form of L-*arabino*-hexos-5-ulose **9**. The latter, so far unknown, keto aldose was obtained from **8** by acid catalyzed hydrolysis. It was also prepared directly by hydrogenolysis of **7**, but in lower yield, since it was difficult to avoid some overreduction that produced L-tagatose.

The high diastereoselectivity in the formation of compounds **5-7** is ensured by the well-known preference for epoxidation syn to an allylic OH in six-membered ring systems,[2] the regioselectivity of the epoxide ring opening by the stabilization of a positive charge on carbon 5 Structures and configurations of compounds **5-8** were easily deduced by their ^{1}H- and ^{13}C-NMR spectra,[3] and particularly by the high values of $J_{1,2}$ and $J_{2,3}$ and by the low one for $J_{3,4}$, proving an eq/eq/eq/ax sequence for the substituents on carbons 1 to 4. Only the configuration at C-5, carrying no protons, was not immediately deducible from the NMR spectra, even if the high preference for anti-opening of oxirane rings made the β-D-galacto configuration likely, but by no means sure: syn opening may occur under acidic conditions in epoxide rings carrying carbocation stabilizing substituents as in the case of **3**. This would produce the α-L-altro configuration **10**.



An unequivocal proof of the β-D-galacto structures came, however, from an unexpected course of the reaction with MCPBA in CH_2Cl_2 of compound **11**.[4] As previously reported the peroxyacid easily cleaves *cis*-propenyl groups as 2-(*m*-chlorobenzoyloxy)propanal to produce **12**.[4] Further action of MCPBA attacks the endocyclic double bond to produce a mixture, from which a pure compound was isolated in 35 % yield. It was not the expected analogue of ester **4**, since it did not incorporate *m*-chlorobenzoic acid, and analysed for $C_{11}H_{20}O_7$. The hypothesis that it was simply an epoxide of type **3** was immediately ruled out: in the ^{1}H-NMR spectrum in C_6D_6 the two C-Me singlets were separated by 0.2 p.p.m., whereas in 6-O-(1-methoxy-1-methylethyl) derivatives they are isochronous. This pointed to the formation of a rigid cyclic isopropylidene structure. Furthermore, the chemical shift of 4-H was not consistent with that of a proton on an oxirane ring. The two formulations **15** and **17** appeared possible for this compound, both originating from the protonated epoxide **13**, through the spirocyclic intermediate **14**. This could undergo either an intramolecular transfer of methyl from the oxonium center to the vicinal 4-OH, to give **15**, or an opening of the dioxolane ring to the stabilized cation **16**, followed by cyclization on the 4-OH to produce the 4,6-O-isopropylidene derivative **17**. ^{13}C-NMR spectra were definitely in favor of the latter structure, since the three signals for the Me_2C group were fully consistent with an 1,3-dioxane, but not with an 1,3-dioxolane structure, according to Buchanan's rules for cyclic isopropylidene acetals.[5,6]

Mild hydrolysis of **17** lead to the selective removal of the isopropylidene group and produced a compound found to be identical with **8**, thus allowing direct correlation between the two series of experiments, and providing the final proof for the D-galacto configuration at C-5 of **6**. An alternative L-altro configuration **18** could allow bridging between 4-OH and 6-OH only if the pyranose ring were in the $^1C_4$ conformation, which is ruled out by the coupling constants between the pyranose ring protons pointing clearly to a $^4C_1$ conformation. The 5-C-alkoxy derivatives described in this paper therefore all belong to the D-galacto series.

5-C-Alkoxyhexopyranosides have as yet received little attention. Ferrier[8] has described a different approach to some of these compounds of the D-gluco series, precursors of D-*xylo*-hexos-5-uloses. Our methods provide an easy access to the D-galacto series and to L-*arabino*-hexos-5-ulose and many of their selectively O-substituted derivatives. These ketoaldoses are useful intermediates, to be used, for instance, in the biomimetic synthesis of inososes and inositols.[9]

Acknowledgement We thank C.N.R. (Progetto Finalizzato Chimica Fine) for financial support.

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3) All new compounds gave correct elemental analyses. $[\alpha]_D$ (c ≈ 1.0) . **5** (m.p. 86-88°) -87.4° ($CHCl_3$); **6** (syrup) -19.1° ($CHCl_3$); **7** (m.p. 99-101°) -6.8° ($CHCl_3$); **8** (syrup) -66° (MeOH); **8** tetracetate

Complete ^{1}H- and ^{13}C-NMR data will be presented and discussed in the subsequent full paper. Some representative data are given below (Bruker AC 200 instrument): **5** diacetate: ^{1}H-NMR (CD_3CN) δ: 5.16 (d, 1 H, $J_{3,4}$ = 3.41 Hz, H-4); 5.03 (dd, 1 H, $J_{2,3}$ = 10 17 Hz, H-3); 4.49 (d, 1 H, $J_{1,2}$ = 7.84 Hz, H-1); 3.55 (d, 1 H, $J_{6,6'}$ = 10.91 Hz, H-6); 3.49 (s, 3 H, OMe-1); 3.44 and 3 25 (2s, 6 H, OMe-2 and 6), 3.31 (s, 3 H, OMe-5); 3.30 (dd, 1 H, H-2); 3 25 (d, 1 H, H-6); 2 09 and 1.94 (2s, 6 H, MeCO). ^{13}C-NMR (CD_3CN) δ: 169.98 and 169.48 (Me*C*O); 100.21 (C-1); 99.40 (C-5); 77.67 (C-2); 70 69 (C-3); 67.75 (C-4); 67.09 (C-6); 59.81 and 58.34 (OMe-2 and 6); 56.22 (OMe-1); 47.91 (OMe-5), 19.90 and 19.74 (*Me*CO). **8** tetracetate ^{1}H-NMR (CD_3CN) δ: from 5.25 to 5.08 [m, 3 H, parameters determined by computer simulation: 5.23 (H-4); 5.18 (H-3); 5 07 (H-2); $J_{2,3}$ = 10.45, $J_{3,4}$ = 2.92 Hz]; 4.66 (d, 1 H, $J_{1,2}$ = 8.16 Hz, H-1); 4.24 (d, 1 H, $J_{6,6'}$ = 12 43 Hz, H-6); 4.10 (d, 1 H, H-6'), 3.47 (s, 3 H, OMe-1); 3.36 (s, 3 H, OMe-5); 2.07, 2.01, 1.96 and 1.90 (4s, 12 H, MeCO) ^{13}C-NMR (CD_3CN) δ:169 83, 169.52, 169.37, and 169.37 (Me*C*O); 99.16 (C-5); 97.91 (C-1); 68 77 (C-3); 67.95 (C-2); 67.27 (C-4); 57.58 (C-6); 56.30 (OMe-1); 48.23 (OMe-5); 19.78 and 19.63 (*Me*CO). **17** diacetate ^{1}H-NMR (CD_3CN) δ: from 5.21 to 5.08, from 4.64 to 4.60, and from 4.15 to 4.13 [3 m, 4 H, parameters determined by computer simulation: 5 16 (H-3); 5.13 (H-2); 4.62 (H-1); 4.14 (H-4); $J_{1,2}$ = 7.99; $J_{2,3}$ = 10.58; $J_{3,4}$ = 3 04 Hz]; 3.90 (d, 1 H, $J_{6,6'}$ = 11.95 Hz, H-6); 3.81 (d, 1 H, H-6'); 3.48 (s, 3 H, OMe-1); 3.30 (s, 3 H, OMe-5); 2.00 and 1.99 (2s, 6 H, MeCO); 1.38 and 1.37 (2s, 6 H, Me_2C). ^{13}C-NMR (C_6D_6) δ: 169.94 and 168.93 (Me*C*O); 99.55 (Me_2C), 98.10 (C-1); 93.91 (C-5), 69.61 (C-3 and C-4); 68 55 (C-2); 64.28 (C-6); 55.15 (OMe-1); 47.66 (OMe-5); 27.95 and 19.16 (Me_2C); 20.48 and 20.42 (*Me*CO).

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6) A somewhat similar case of migration of a methoxy group from a mixed acetal function to a potentially cationic carbon was recently reported (ref. 7) in the treatment of a 2-O-(1-methoxytetrahydropyranyl) derivative of a xylofuranonucleoside with DAST a side-product was isolated in 4 % yield, deriving from a displacement of an -O-SF_2-NEt_2 group in position 3 by the acetal methoxyl group We thank Dr Daniel Anker (Université Claude Bernard, Villeurbanne, France) for drawing our attention to this reference.

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