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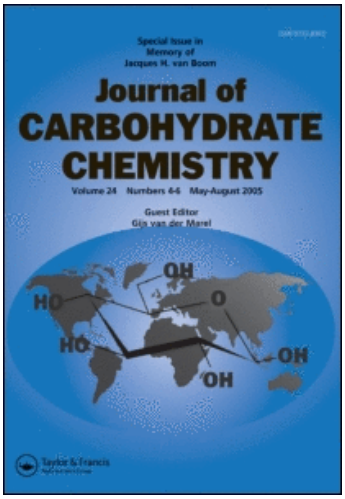

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SYNTHETIC APPROACH TO KDO GLYCOSIDES VIA EXO-GLYCAL EPOXIDES AND RATIONALIZATION OF THE STEREOCHEMICAL OUTCOME

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ABSTRACT

The use of epoxides obtained by dimethyldioxirane epoxidation of 2,3-anhydro-1,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*manno*-oct-1-enitol as glycosyl donors is described. This method offers a simple and stereoselective access to precursors of Kdo glycosides. The stereochemical outcome of the reaction is rationalized by means of semiempirical calculations of the transition states leading to glycosides formation.

INTRODUCTION

The occurrence and the biological role of 3-deoxy-D-*manno*-2-octulosonic acid (Kdo) is well documented.[1] Kdo is a ketosidic component in all lipopolysaccharides (LPS) of gram-negative bacteria where its incorporation appears to be an essential step in the growth of the bacteria, as well as in many acidic exopolysaccharides (K antigens) located at the cell surface of the bacteria.

This fact stimulated much synthetic effort towards the preparation of Kdo and its glycosides and analogues.[2] Recently Sinaÿ described[3] an interesting approach to their

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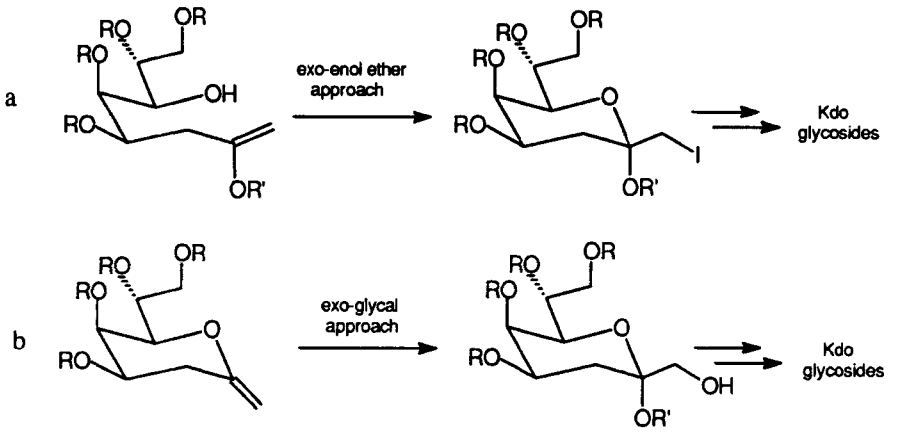

Scheme 1

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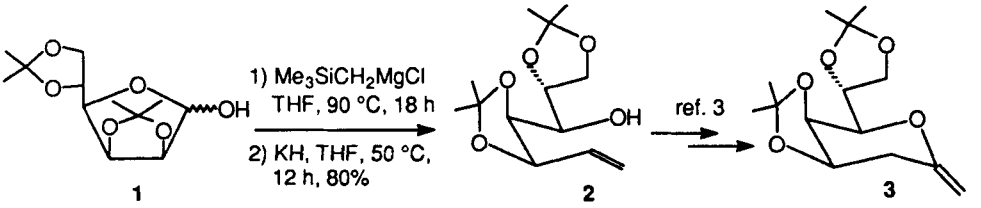
synthesis by iodocyclization of hydroxy enol ethers (Scheme 1-a). However, some attempts to apply the same reaction in the intermolecular version starting from exo-glycals indicate that the reaction is not of general use.

Continuing our work on epoxidation of sugar enol ethers, we pursued[4] an approach to the synthesis of glycosides of ketosugars starting from exo-glycals through their conversion into the corresponding epoxides followed by a glycosylation reaction (Scheme 1-b). Encouraged by these results we planned to exploit this approach for the synthesis of glycosides and oligosaccharides of Kdo starting from the already known[3] exo-glycal **3**.

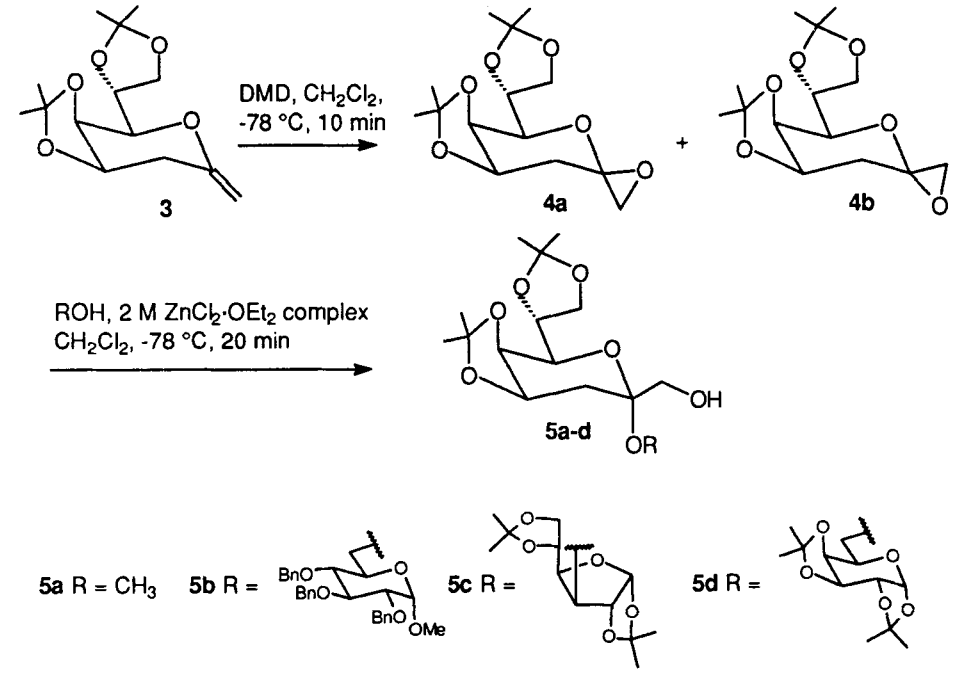
RESULTS AND DISCUSSION

The synthesis of **3** from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[5] (**1**) was performed essentially as described[3] apart from the first step. In fact, compound **1** was converted into the heptenitol **2** through Peterson olefination[6] which gave a better and especially more reproducible yield (80%) with respect to the previously described[3] Wittig reaction. Compound **2** was then transformed into the exo-glycal **3**[7] according to ref. 3.

Compound **3** was also obtained from the corresponding lactone using dicyclopentadienyl dimethyltitanium[8] in dry toluene at 50 °C for 2 days in 82% yield. Having in hand the desired exo-glycal we started with our synthetic procedure.



Scheme 2



Scheme 3

Compound **3** was converted into a mixture of the epoxides **4a,b** using 3,3-dimethyl dioxirane (DMD)[9] (Scheme 3). Due to their instability it was not possible to determine the epoxides ratio but the ^1H NMR of the crude epoxidation mixture clearly showed the presence of two diastereomers in a comparable amount, together with some decomposition products.

Although compounds **4a,b** are quite unstable compared to epoxides of exo-glycals with an allylic oxygen such as **7a,b**, they can be smoothly obtained as DMD is a very

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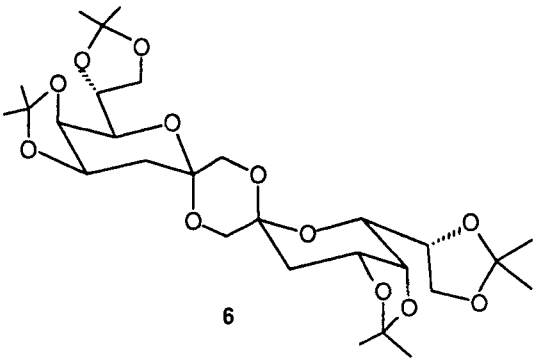

6

Figure 1

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efficient epoxidizing agent acting under mild conditions. Glycosylation with the epoxides **4** was performed at -78 °C in dichloromethane in the presence of various acceptors and promoted by $ZnCl_2$.[4] Methanol, and three sugars, two with a primary hydroxy group and a third one with a secondary hydroxy group, were used as glycosyl acceptors. The donor-acceptor ratio was varied in the preparation of **5b-d** and the better yields (based on the limiting reagent) were obtained with the ratios described in the experimental part.

The reaction occurred smoothly to give the hydroxymethyl ketopyranosides **5a-d** in moderate to good yields (37-80%, see experimental). Performing the reaction on 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, even with an excess of the acceptor, part of the donor reacted intramolecularly to give the dianhydride **6**[10] shown in Figure 1.

It is worthy of note that, different from our previous results on model compounds,[4] although **4** is a diastereomeric mixture, the glycosylation reaction is highly stereoselective giving only the α-glycoside, even if a large excess of a very reactive alcohol such as methanol is used.

Compound **5a-d** can then be easily oxidized, as already demonstrated by Sinaÿ,[3] to give Kdo glycosides. Therefore the above scheme constitutes a formal synthesis of Kdo glycosides.

Rationalization of the Stereochemical Outcome

To better understand the origin of the observed stereoselectivity we performed some calculations using a semiempirical quantum mechanics program (AM1)[11] which is

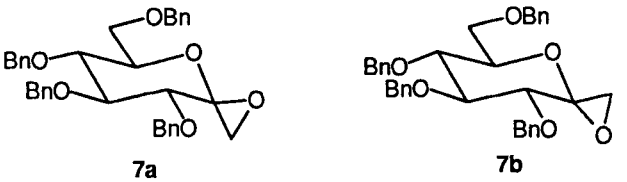

Figure 2

known to behave well both for neutral and positively charged molecules.

The glycosylation reaction of the epoxides can reasonably proceed either by a classical S_N2 reaction, or through the intermediacy of a carbocation which is stabilized by the oxonium form, and the stereochemical outcome of the reaction is a consequence of the mechanism. We can also be confident of the kinetic control of the reaction that is performed at a low temperature in a very short time. We decided to model the reaction using the protonated epoxides as intermediates.[12] We also verified the whole procedure in a case where the experimental data give a product ratio different from 100:0. Therefore, we considered two cases in comparison: the one described in the present paper and another chosen from a previous work.[4] In the former, only one isomer is obtained, probably through a carbocation intermediate. In the second, the glycosylation of compounds **7a,b** (Figure 2) with MeOH gave an anomeric ratio of the products (α/β 6:4), reflecting that of the epoxides (α/β 4:6), which suggests an S_N2 pathway, as the presence of an oxygen atom at C-3 will disfavour the formation of a carbocation.

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Conformational Analysis of the Diverse Structures

Compounds **4** can exist in different ring conformations.[13] A search through the conformers allowed the selection of three stable conformers with similar energy for each diastereoisomer: **4a-1** ($^{3,6}B$), **4a-2** ($B_{3,6}$), **4a-3** ($^5C_2$), **4b-1** ($^{3,6}B$), **4b-2** ($B_{3,6}$), **4b-3** ($^5C_2$) (see Figure 3).

For compounds **7a,b** the boat conformation ($^{3,6}B$) can be reliably assigned to the ring and a search of the rotational space permitted the selection of the conformation for each compound (Table 1). The eight structures selected so far have been then considered as potential starting products.

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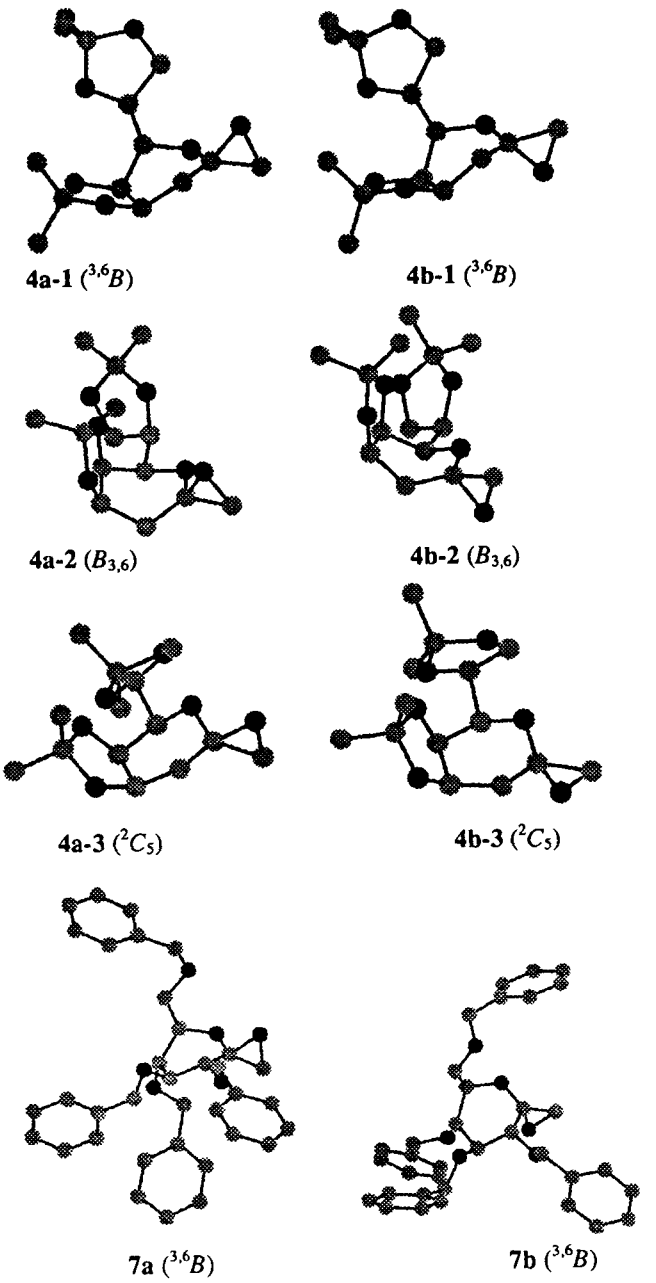

Figure 3. Low energy conformers of compounds **4a,b** and **7a,b**

Table 1. Energies of ground state structures[a]

Structure	Epoxide	Protonated epoxide	Carbocation
4a-1	-4017.133	-4024.861	-4025.165
4a-2	-4017.317	-4024.751	
4a-3	-4017.308	-4025.094	
4b-1	-4017.192	-4024.972	
4b-2	-4017.294	-4024.725	
4b-3	-4017.401	-4025.041	
7a	-6895.938	-6903.868	-6903.947
7b	-6895.844	-6903.989	

a. Energies in eV.

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All the 8 conformers (**4a1-3, 4b1-3, 7a, 7b**) were thus protonated and optimized. Looking at the obtained structures it is worth noting that one of the epoxide bonds has elongated to 2.3-2.4 Å in agreement with their tendency to transform into carbocations. To confirm this behaviour we optimized the corresponding carbocations, i.e., starting the calculation from the already formed cation, and the results show that their energy is very similar to those obtained from protonated epoxides. We have used both the protonated epoxides and the carbocations in the reaction analysis.

Reaction Coordinates and Transition States

The reaction partner chosen to carry the reaction coordinate analyses was MeOH. The search was carried out positioning the MeOH molecule at a distance of 3.5 Å from the sugar epoxide where the interactions with the sugar derivatives are absent or minimal. In all cases the MeOH molecule was positioned orienting the oxygen atom towards the anomeric sugar carbon atom, with the methyl group positioned in the least crowded area. The reaction step was 0.2 Å between 3.5 and 2.5 Å and 0.1 between 2.5 and 1.6 Å. All the points along the coordinate were fully optimized.

The analysis of the reaction coordinate concerning the protonated epoxides **4** showed their complete transformation into the corresponding carbocations at great distances (3.2 - 3.0 Å). Therefore we abandoned the protonated epoxides **4** and continued our analysis considering six intermediates only: the two approaches of MeOH

Table 2. Energies of transition states[a]

	epoxide[b]			carbocation[c]		
	cdR[d]	TS[e]	TS force[f]	cdR[d]	TS[e]	TS force[f]
4α[g]				-4529.379	-4529.466	-4529.597
4β[g]				-4529.446	-4529.286	-4529.144
7α[g]	-7408.384	-7408.403	-7408.864	-7408.087	-7408.146	-7408.581
7β[g]	-7408.252	-7408.262	-7408.267	-7408.256	-7408.364	-7408.638

a. Energies in eV. b. Energies of epoxide reaction. c. Energies of carbocation reaction. d. Highest energy of reaction coordinate. e. Transition state energy by SADDLE option. f. Refined transition state energy. g. α and β respectively correspond to addition from the α and β side of the carbocation or of the epoxide having the required stereochemistry.

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to the carbocations derived from **4** and **7**, and the approach of MeOH to the two protonated epoxides **7a** and **7b**.

All the calculated reaction coordinates show a point of gradient inversion (approximately around 2.0 Å); the structures of the points near the inversion derived from the protonated epoxides **7** are different from those of the corresponding carbocations.

The search for the transition states (TS) has been initially performed using the SADDLE option of the AM1 program. For each compound of the preceeding analysis two intermediates have been chosen and used to perform the calculations. The results show a clear preference for one of the two possible isomers in all cases (Table 2).

This fact is in agreement with the experimental data in the case of compounds **4**, but not in the case of compounds **7**, where the formation of a nearly equimolar mixture is observed. Consequently a refinement of the found TSs has been performed using the FORCE option of the AM1 program; at the same time those calculations would have permitted control of the second order derivatives assuring the location of true TSs.

The final results (see Table 1 and 2) can now be discussed.

1. Regarding compounds **4** the energy difference of the refined TSs is equal to 0.453 eV (10.54 kcal) in full agreement with the experimental selectivity and with the predicted one through carbocation mechanism.
2. The situation is more complex for compounds **7**. In fact, considering the TSs obtained from the carbocation intermediates, their energy difference is equal to

0.057 eV (1.31 kcal) which corresponds to a ratio of approximately 95:5. On the contrary, considering the TSs coming from the epoxide intermediates their energy difference is equal to 0.597 eV (13.77 kcal) that suggests a higher reaction rate for the epoxide **7a**. However, both results can be considered in agreement with the experimental results. In fact, if the mechanism passes through a carbocation intermediate the calculated energy difference, considered the methodological approximation, does not select one of the two products; if the mechanism is S_N2, one of the epoxides will react much faster than the other but the product ratio would be dictated by the epoxide ratio, excluding any chance of reequilibration.[14]

In conclusion, this approach allows a direct access to Kdo glycosides from exo-glycal epoxides in an intermolecular glycosylation reaction, thus avoiding the cumbersome conversion of the CH_2I group, obtained by iodocyclization in the exo-enol ether approach, to CH_2OH. Moreover the stereochemical course of the reaction is rationalized.

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EXPERIMENTAL

General methods. All reactions were performed under a nitrogen atmosphere. Reagents and dry solvents were added *via* oven-dried syringes through septa. Dichloromethane and pyridine were distilled from calcium hydride. Oxolane was distilled from sodium/benzophenone ketyl. Flash chromatography was performed as described on *J. Org. Chem.*, **43**, 2923 (1978). Thin-layer chromatography was performed on Merck silica gel F_{254} glass plates, and visualized by charring with a 1:1 mixture of a 20% sulphuric acid and 10 g I_2 - 100 g KI in 500 mL of H_2O followed by heating. ^1H NMR spectra: chemical shifts are reported in parts per million downfield from TMS. Mass spectra: recorded on a VG 70-70 EQ spectrometer.

1,2-Dideoxy-3,4:6,7-di-*O*-isopropylidene-D-*manno*-hept-1-enitol (2). To a stirred suspension of magnesium (3 g, 123 mmol) with a small crystal of iodine in dry oxolane (100 mL), was dropwise added chloromethyltrimethylsilane (15 mL, d = 0.883 g/mL, 108 mmol). After the Grignard reagent formation was complete, a solution of **1**[5] (10 g, 39 mmol) dissolved in dry oxolane (20 mL) was added and the mixture was refluxed for 18 h. The reaction was quenched with a saturated solution of NH_4Cl and the

mixture was extracted with dichloromethane. After drying (Na_2SO_4) and evaporation of the solvent, column chromatography (hexane/ethyl acetate 2:1 v/v) gave the intermediate silyl derivative: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.35 (dd, 1H), 4.2-3.8 (m, 5H), 3.58 (m, 1H), 3.3-2.5 (3d, 2H exch. with D_2O), 1.6-1.3 (cluster of singlets, 12H), 1.1-0.7 (m, 2H), 0.05 (s, 9H). The crude addition mixture was dissolved in dry oxolane (80 mL) and treated with an excess of potassium hydride. Stirring was continued for 12 h at 50 °C. The reaction mixture was quenched with methanol at 0 °C, washed with saturated aqueous NH_4Cl and then extracted with dichloromethane. After drying (Na_2SO_4) and evaporation of the solvent, column chromatography (hexane/ethyl acetate 4:1 v/v) afforded **2** (7.95 g, 80%) as colourless syrup: $[\alpha]_D$ -31° (*c* 1.0, chloroform) [lit.[3] -33° (*c* 0.7, chloroform)].

Anal. Calcd for $C_{13}H_{22}O_5$ (258.31): C, 60.45; H, 8.58. Found: C, 60.24; H, 8.77.

2,6-Anhydro-1,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*manno*-oct-1-enitol (3). To a solution of 2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-*manno*-heptonic acid 1,5-lactone (50 mg, 0.18 mmol) in dry toluene (2 mL) Cp_2TiMe_2[8] (100 mg, 0.48 mmol) was added. The mixture was stirred for 2 days in the dark at 50 °C. The solution was concentrated in vacuo and the residue was dissolved in the minimum amount of toluene. Chromatography (hexane/ethyl acetate 4:1 v/v + 0.5% Et_3N) afforded **3** (40 mg, 82%): ^1H NMR ($CDCl_3$, 300 MHz, COSY) δ 4.55 (dt, 1H, $J_{4,3a} = J_{4,3b}$ =2.7 Hz, $J_{4,5}$ = 8.0 Hz, H-4), 4.46 (dd, 1H, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 1.5 Hz, H-5), 4.28 (m, 1H, H-7), 4.24 (br s, 1H, H-1a), 4.11 (dd, 1H, $J_{8a,8b}$ = 8.8 Hz, $J_{8a,7}$ = 5.9 Hz, H-8a), 4.05 (dd, 1H, $J_{8a,8b}$ = 8.8 Hz, $J_{8b,7}$ = 3.9 Hz, H-8b), 3.92 (br s, 1H, H-1b), 3.65 (dd, 1H, $J_{6,7}$ = 7.7 Hz, $J_{6,5}$ = 1.5 Hz, H-6), 2.54 (dd, 1H, $J_{3a,3b}$ = 15.7 Hz, $J_{3a,4}$ = 2.7 Hz, H-3a), 2.46 (dq, 1H, $J_{3a,3b}$ = 15.7 Hz, $J_{3b,4}$ = $J_{3b,1a}$ = $J_{3b,1b}$ = 2.7 Hz, H-3b), 1.45, 1.40, 1.38, 1.36 (4s, 12H, CH_3); ^1H NMR (C_6D_6, 300 MH) δ 4.49 (br s, 1H, H-1a), 4.44 (m, 1H, H-7), 4.22 (br d, 1H, $J_{5,4}$ = 7.4 Hz, H-5), 4.10 (dd, 1H, $J_{8a,8b}$ = 8.8 Hz, $J_{8a,7}$ = 5.2 Hz, H-8a), 4.04 (dd, 1H, $J_{8a,8b}$ = 8.8 Hz, $J_{8b,7}$ = 4.9 Hz, H-8b), 3.95-3.90 (m, 2H, H-1b, H-4), 3.49 (br d, 1H, $J_{6,7}$ = 7.7 Hz, H-6), 2.25 (dd, 1H, $J_{3a,3b}$ = 15.6 Hz, $J_{3a,4}$ = 1.9 Hz, H-3a), 1.88 (dq, 1H, $J_{3a,3b}$ = 15.6 Hz, $J_{3b,4}$ = $J_{3b,1a}$ = $J_{3b,1b}$ = 1.9 Hz, H-3b), 1.49, 1.41, 1.26, 1.15 (4s, 12H, CH_3).

Anal. Calcd for $C_{14}H_{22}O_5$ (270.33): C, 62.20; H, 8.20. Found: C, 61.96; H, 8.51.

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Methyl 3-Deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*manno*-octulopyranoside (5a). Compound **3** (120 mg, 0.444 mmol) was dissolved in dry dichloromethane. The solution was cooled at -78 °C and treated with 1.5 eq of a 0.07 M solution of DMD in acetone.[9] The reaction mixture was stirred for 10 min then concentrated at 0 °C with a stream of nitrogen to give a mixture of the epoxides **4a,b** [^{1}H NMR ($CDCl_3$, 300 MHz): 2.87 and 2.59 (AB system, J = 3.6 Hz, 0.9H, H-1a and H-1b of the minor isomer), 2.67 and 2.63 (AB system, J = 3.5 Hz, 1.1H, H-1a and H-1b of the major isomer)]. The residue was dissolved in dry dichloromethane (5 mL) in the presence of 4 Å molecular sieves. Excess of dry MeOH (2 mL) and 300 μL of $ZnCl_2$-diethyl ether complex (2.2 M in dichloromethane) were added at -78 °C. After being stirred for 20 min at -78 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with dichloromethane and filtered through a celite pad. It was then extracted with dichloromethane, dried (Na_2SO_4) and concentrated and the residue was purified by chromatography (hexane/ethyl acetate 1:1 v/v) to afford crystalline **5a** (100 mg, 70% from **3**): mp 68-69 °C (from hexane) (lit.[3] 70-71°C from hexane); $[\alpha]_D$ +26° (*c* 1.0, chloroform) [lit.[3] +27° (*c* 1.0, chloroform)].

Anal. Calcd for $C_{15}H_{26}O_7$ (318.37): C, 56.59; H, 8.23. Found: C, 56.44; H, 8.09.

Methyl 6-*O*-(3-Deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*manno*-octulopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5b). Compound **5b** was prepared from **3** (100 mg, 0.370 mmol) as previously described for the synthesis of **5a** using methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (86 mg, 0.5 molar eq) as acceptor. Chromatography (hexane/ethyl acetate 7:3 v/v) afforded **5b** (109 mg, 80% based on the acceptor) as a colourless syrup: $[\alpha]_D$ +8° (*c* 1.0, chloroform) [lit.[3] +7° (*c* 0.15, chloroform)].

Anal. Calcd for $C_{42}H_{54}O_{12}$ (750.88): C, 67.18; H, 7.25. Found: C, 66.96; H, 7.44.

3-*O*-(3-Deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*manno*-octulopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5c). Compound **5c** was prepared from **3** (100 mg, 0.370 mmol) as previously described for the synthesis of **5a** using 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (190 mg, 2 molar eq) as acceptor. Chromatography (hexane/ethyl acetate 7:3 v/v) afforded bis(3-deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*manno*-octulopyranose)-1,2':2,1'-dianhydride **6** (26 mg, 26%) and **5c** as a colourless syrup (74 mg, 37% from **3**): $[\alpha]_D$ -18° (*c* 1.0, chloroform) [lit.[3] -19° (*c* 1.7 chloroform)].

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Anal. Calcd for $C_{26}H_{42}O_{12}$ (546.61): C, 57.13; H, 7.74. Found: C, 56.92; H, 7.96.

Compound **6**: mp 217-219 °C (lit.[10] 220-222 °C); $[\alpha]_D$ +113° (*c* 1.0, chloroform) [lit.[10] +122° (*c* 0.98, ethyl acetate)]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.51 (dt, 1H, $J_{4,3a}$ = $J_{4,3b}$ = 3.1 Hz, $J_{4,5}$ = 7.8 Hz, H-4), 4.28 (dd, 1H, $J_{5,4}$ = 7.8 Hz, $J_{5,6}$ = 1.6 Hz, H-5), 4.22 (ddd, 1H, $J_{7,8a}$ = 6.5 Hz, $J_{7,8b}$ = 4.1 Hz, $J_{7,6}$ = 8.7 Hz, H-7), 4.08 (dd, 1H, $J_{8a,8b}$ = 8.4 Hz, $J_{8a,7}$ = 6.5 Hz, H-8a), 3.98 (dd, 1H, $J_{8a,8b}$ = 8.4 Hz, $J_{8b,7}$ = 4.1 Hz, H-8b), 3.71 (d, 1H, $J_{1a,1b}$ = 12.3 Hz, H1a), 3.58 (d, 1H, $J_{1b,1a}$ = 12.3 Hz, H1b), 3.50 (dd, 1H, $J_{6,7}$ = 8.7 Hz, $J_{6,5}$ = 1.6 Hz, H-6), 2.38 (dd, 1H, $J_{3a,3b}$ = 15.5 Hz, $J_{3a,4}$ = 3.1 Hz, H-3a), 1.64 (dd, 1H, $J_{3b,3a}$ = 15.5 Hz, $J_{3b,4}$ = 3.1 Hz, H-3b), 1.40, 1.38, 1.30, 1.25 (4s, 12H, CH_3); MS (CI) *m/z* 573 (MH^+).

Anal. Calcd for $C_{28}H_{44}O_{12}$ (572.65): C, 58.73; H, 7.74. Found: C, 58.61; H, 7.91.

6-*O*-(3-Deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*manno*-octulopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (5d). Compound **5d** was prepared from **3** (100 mg, 0.370 mmol) as previously described for the synthesis of **5a** using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (48 mg, 0.5 molar eq) as acceptor. Chromatography (hexane/ethyl acetate 7:3 v/v) afforded **5d** as a colourless syrup (85 mg, 82% based on the acceptor): $[\alpha]_D$ -1.6° (*c* 1.0, chloroform) [lit.[3] -19° (*c* 1.7 chloroform)]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.50 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 4.62 (dd, 1H, $J_{2,3}$ = 7.8 Hz, $J_{3,4}$ = 2.1 Hz, H-3), 4.50 (dt, 1H, $J_{4',3'a}$ = $J_{4',3'b}$ = 3.5 Hz, $J_{4',5'}$ = 7.7 Hz, H-4'), 4.35-4.20 (m, 4H, H-2, H-4, H-5', H-7'), 4.09-3.92 (m, 3H, H-5, H-8a', H-8b'), 3.76 (br d, 1H, $J_{1'a,1'b}$ = 11.7 Hz, H-1'a), 3.68 (dd, 1H, $J_{6',5'}$ = 1.8 Hz, $J_{6',7'}$ = 7.6 Hz, H-6'), 3.62-3.51 (m, 3H, H-1'b, H-6a, H6b), 3.42 (br d, 1H, $J_{OH,1'b}$ = 9.5 Hz, OH), 2.56 (dd, 1H, $J_{3'a,3'b}$ = 15.5 Hz, $J_{3'a,4'}$ = 3.5 Hz, H-3'a), 1.60-1.25 (m, 25H, H-3'b, CH_3).

Anal. Calcd for $C_{26}H_{42}O_{12}$ (546.61): C, 57.13; H, 7.74. Found: C, 56.84; H, 7.91.

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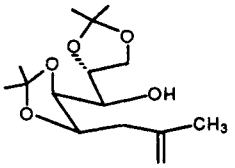
7. The ^{1}NMR spectrum of compound **3** was different from that reported in the literature even at different temperatures and concentrations. Careful examination of the reaction mixture showed the presence of a more polar byproduct which was isolated in 3-4% yield. Its spectrum matched exactly that reported for **3** in ref. 3 except for the signals at δ 2.2 (s, 3H) and 2.1 (d, 1H, J = 7.4 Hz, exch.with D_2O). The ^{1}H NMR spectrum of this byproduct is consistent with the structure reported in the following figure and could originate from a nucleophilic attack of a methyl group on the C-1 of the lactone followed by Tebbe olefination of the resulting hemiketal.



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12. Although the use of protonated epoxides does not exactly reproduce the experimental conditions that use $ZnCl_2$ as Lewis acid, it was considered a sufficient approximation.
13. Studies carried out on conformational aspects of compounds related to Kdo derivatives proposed as main conformations the $B_{3,6}$ and the $^5C_2$ (see M. Orbe, C. Luthman and T. Wåglund, *Carbohydr. Res.*, **211**, 1 (1991)). However, none of the studied compounds shows the presence of a spiro cyclopropyl ring on the anomeric carbon and they are consequently not directly comparable to compounds **4a,b**. In addition, our study considered the three more stable conformations (the $B_{3,6}$ and the $^5C_2$ included), showing their conversion to a common carbocationic intermediate.
14. It is obvious that, when using less reactive alcohols, the epoxide ratio will not completely control the products ratio and the mechanism is expected to pass in part through the carbocation intermediate.

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