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A SIMPLE AND HIGHLY DIASTEREOSELECTIVE PREPARATION OF GLYCAL EPOXIDES USING THE MCPBA-KF COMPLEX#

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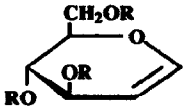
Abstract: *Glycals are converted to the corresponding epoxides in high yields by a diastereoselective one-step epoxidation using the* m*-chloroperoxybenzoic acid-KF complex in anhydrous dichloromethane.*

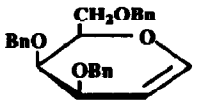
Epoxides of glycals are important intermediates in the synthesis of anomerically substituted carbohydrate derivatives.[1] Although "Brigl's anhydride"[2] has been known for a long time, generally the obtainment of such compounds presents several difficulties. Peroxyacids cannot be used for the epoxidation of glycals, because of the high reactivity of these oxiranes, which are rapidly opened by the acid formed during the course of the epoxidation. Direct epoxidation has recently become accessible through the use of dimethyldioxirane (DMD),[3] with which no acidic or nucleophilic species able to open the epoxide ring are formed. However, the low concentration of the DMD solutions makes scaling up difficult. Therefore, indirect methods involving the cyclization of halohydrins or of 2-tosyl derivatives are still being proposed[4] for the obtainment of anomeric epoxides.

In this communication we are reporting a diastereoselective one-step epoxidation of glycals of type **1-3** using the Camps reagent, *m*-chloroperoxybenzoic acid (MCPBA) and KF,[5] in dichloromethane (DCM) under anhydrous conditions. Whereas epoxides of aldopyranose glycals of type **4-7** had been obtained using the DMD or other methods[3,4] the analogous compounds **8** and **9**, derived from what can be considered as ketopyranose endo-glycals, namely **3a**, **3b** (derivatives of L-*arabino*-hexos-5-ulose) and **3c** (a derivative of L-*lyxo*-hex-2-ulosonic acid), have now been isolated for the first time, their intermediate formation in the epoxidation of **3** with peroxyacids having only been previously proven by their trapping by nucleophilic solvents or other nucleophilic species present in the reaction media.[6]



1

a: R = Bn
b: R = Ac



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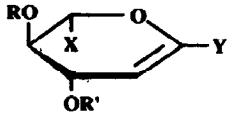
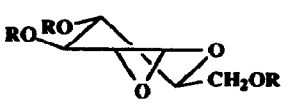


3

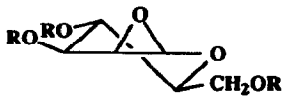
a: X = OMe; R = Bn; R' = H; Y = CH_2OBn
b: X = OMe; R = R'= Bn; Y = CH_2OBn
c: X = R'= H; R = Ac; Y=COOMe

#Dedicated to Professor Giancarlo Berti on occasion of his 70th birthday.

The addition of KF in the reaction medium sufficiently reduces the solubility of MCPBA and MCBA to prevent the formation of products arising from oxirane ring opening. However, anhydrous conditions are necessary to avoid the formation of the corresponding diols, so that the DCM solution of commercial MCPBA must be dried before the formation of the complex with KF.[7]

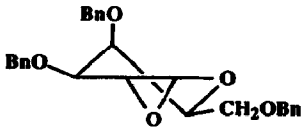


4



5

a: R = Bn
b: R = Ac



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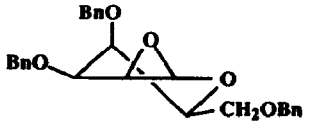

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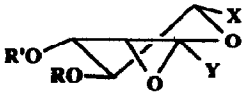

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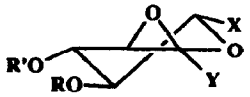

9

a: X = OMe; R = Bn; R' = H; Y = CH_2OBn
b: X = OMe; R = R' = Bn; Y = CH_2OBn
c: X = R' = H; R = Ac; Y = COOMe

As shown in Table 1, the products are generally formed in high yields. The epoxidation rate was increased by an increasing substitution on the double bond (compare **3a** and **3b** with **1a** and **2**), but the conjugation of the double bond with an electron-withdrawing carbomethoxy group in **3c** reduced its reactivity below that of **1a** and **2**. Similarly, the presence of acetoxy in place of benzyloxy substituents dramatically decreased the epoxidation rate of **1b** with respect to **1a**.

Table 1. Yields and diastereoisomeric ratios of glycal epoxides.

Glycals	Solvent	Time	Epoxides	
		h	yield	trans : cis[a]
1a	DCM	24	> 95[b]	9 : 1
1b	DCM	24	25[c]	8 : 2
2	DCM	24	> 95[b]	> 9.5 : <0.5
3a	DCM	3	> 95	<0.5 : >9.5
3b	$CDCl_3$	3	> 95	8 : 2
3c	DCM	24	80[c]	<0.5 : >9.5

[a] Cis and trans refer to the orientation of the epoxide ring with respect to the substituent at the adjacent carbon.

[b] After shorter reaction times considerable amounts of unreacted glycal was found.

[c] The remaining material was the unreacted glycal.

The yields reported in Table 1 are referred to the crude products, which were directly analysed by NMR. The ^{1}H and ^{13}C spectra of the epoxidation products of **1** and **2** were identical with those of the previously described compounds **4**-**7**.[4,8] The anti configurations of **4** and **6** were also proven by the obtainment of the corresponding β-glycopyranosides in their reactions with alcohols.[9]

Compounds **8** and **9** underwent decomposition on column chromatography, but could be stored as crude products. The configuration of **8a** was inferred from its NMR spectrum,[10] and was confirmed by the opening of the oxirane ring by methanol, which occurred stereospecifically with inversion at the more electrophilic C-5 to give the known methyl 2,6-di-*O*-benzyl-5-C-methoxy-β-D-galactopyranoside.[6a] This showed that MCPBA-KF reacts with **3a** to give with high preference epoxide **8a** arising by an attack syn to the 3-OH group. The cis configuration of epoxide **8c**, formed in a highly stereoselective way from **3c**, was established by the similar chemical shifts of the ^{13}C NMR spectra of **8a** and **8c**,[11] and by its transformation into the known methyl 5-*O*-acetyl-α-L-*lyxo*-hex-2-ulopyronosidic acid methyl ester[6b] by reaction with methanol.

The epoxides **8b** and **9b** could not be isolated because of a partial ring opening during work-up, which reduced the yields and complicated the spectral analysis. Their ratio has been determined by ^{1}H and ^{13}C NMR spectra of the solutions in $CDCl_3$,[12] in which the reaction had been carried out, after removal of the insoluble complexes by filtration. The two epoxides were present in a 8:2 ratio on the basis of the signals relative to the protons at C-6. The trans configuration of the excess diastereoisomer (**9b**) was deduced from the lower coupling constant between the protons at C-4 and C-3 with respect to the cis isomer, and by comparison with the NMR spectra of **8a**.[10] These configurations have been further confirmed by the stereochemistry of the bis-methyl glycopyranosides formed by methanolysis of **8b** and **9b**.[6c]

It is noteworthy that the benzylation of the allylic OH, although not affecting the reactivity of the double bond (compare **3a** and **3b** in Table 1), produced an inversion in the stereochemistry of the reaction. This result seems to indicate that, in analogy with the uncomplexed peracid reaction, the free hydroxyl group has a syn orienting effect, in the absence of which the stereochemistry is determined by the steric effect of substituents at C(3).

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7. Typical Procedure: KF (5 mmol) was added to a solution of *m*-chloroperoxybenzoic acid (2.5 mmol) in DCM (25 ml) previously dried with $MgSO_4$ and the suspension was maintained at room temperature with stirring. After 30 min the glycal was added (1 mmol) and the mixture was stirred for the time reported in Table 1. The insoluble complexes were then filtered off, and the solvent was removed under reduced pressure.

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10. Compound (**8a**) ^{1}H-NMR (CD_3CN) δ: 3.39 (d, 1H, $J_{3,4}$=2.52 Hz, H-4); 3.42 (dd, 1H, $J_{2,3}$=7.65 Hz, H-2); 3.47 (s, 3H, OMe); 3.60 and 3.83 (AB system, 2H, $J_{A,B}$=11.81 Hz, H-6 and H-6'); 4.00 (dd, 1H, H-3); 4.56 (dd, 1H, $J_{1,2}$=7.73 Hz, H-1); 4.593 (s, 2H, benzylic CH_2); 4.64 and 4.79 (AB system, 2H, $J_{A,B}$=11.53 Hz, benzylic CH_2); from 7.36 to 7.89 (m, 10H, aromatic H). ^{13}C-NMR (CD_3CN) δ: 57.13 (OMe); 60.35 (C-4); 69.95 (C-3); 70.16 (C-6); 73.94 and 74.71 (2 benzylic CH_2); 80.63 (C-2); 83.70 (C-5); 103.95 (C-1); from 128.43 to 129.31 (aromatic CH); 139.35 and 139.76 (2 aromatic C).

11. Compound (**8c**) ^{13}C-NMR (C_6D_6) δ: 20.46 (*Me*CO); 52.68 (OMe); 57.73 (C-3); 62.87 (C-6); 68.95 and 71.76 (C-4 and C-5); 81.59 (C-2); 165.9 (C-1); 170.18 (*CO*Me).

12. Selected NMR data ($CDCl_3$). Compound (**8b**) ^{1}H-NMR δ: (4.14 and 4.32 $J_{A,B}$=10.40 Hz, H-6 and H-6'); ^{13}C-NMR δ: 57.41 (OMe); 57.65 (C-4); 68.83 (C-6); 74.81, 74.94 and 75.42 (3 benzylic CH_2); 74.29 and 79.69 (C-3 and C-2); 83.02 (C-5); 103.6 (C-1). Compound (**9b**) ^{1}H-NMR δ: 3.32 (d, 1H, $J_{3,4}$~ 0.2 Hz, H-4); 3.42 (dd, 1H, $J_{1,2}$=6.79 Hz, H-2); 3.51 (s, 3H, OMe); 3.73 and 3.85 (AB system, 2H, $J_{A,B}$=11.75 Hz, H-6 and H-6'); 3.95 (dd, 1H, $J_{2,3}$=6.68 Hz, H-3); from 4.51 to 4.92 (m, 7H, H-1 and 3 benzylic CH_2); from 7.27 to 7.33 (m, 15H, aromatic H); ^{13}C-NMR δ: 55.82 (OMe); 56.99 (C-4); 68.23 (C-6); 72.73, 73.50 and 74.09 (3 benzylic CH_2); 76.33 and 77.89 (C-3 and C-2); 83.55 (C-5); 99.86 (C-1).

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