A Stereoselective and Preparative Entry to 1,2-Anhydrosugars through Oxidation of Glycals with Perfluoro-*cis*-2,3-dialkyloxaziridines

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Perfluoro-*cis*-2,3-dialkyloxaziridines **1** perform the direct epoxidation of glycals **2** to give cleanly corresponding 1,2-anhydrosugars **3** with medium to complete diastereoselection; elaboration of these glycals to glycosyl fluorides and lipid conjugates is also reported.

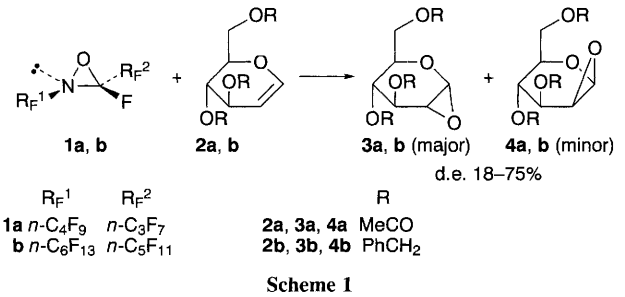
1,2-Anhydrosugars **3** have good glycosyl donor properties, probably due to the ring strain in the alkoxy-epoxide moiety. While they have been used for the synthesis of glycosyl fluorides and sulfides[1,2] and, more interestingly, in a reiterative strategy to α- or β-linked oligosaccharides and glyco conjugates,[3–5] the full synthetic potential of these compounds has not been exploited, probably owing to a lack of broad availability of such oxiranes. In fact, direct epoxidation of glycals **2** with peracids affords products deriving from the reaction of initially produced 1,2-anhydrosugars with either solvent or co-formed acids.[6]

Perfluoro-*cis*-2,3-dialkyloxaziridines **1** are powerful, yet selective oxidizing agents which can work in aprotic and non-nucleophilic solvents.[7–11] The co-product of the oxidation reaction are perfluoroazaalkenes which are inert and volatile materials.[12,13] For these reasons we thought that oxaziridines **1** could not only perform the epoxidation of glycals **2** to 1,2-anhydrosugars **3**, but also allow these latter products to be generated in a non-reactive medium. This is a prerequisite for the conjugation of the 1,2-anhydrosugar with a defined nucleophile. Here we report our preliminary results on this interesting epoxidation reaction.

When tri-*O*-acetyl-D-glucal **2a** was reacted with an equimolar amount of perfluoro-1-*n*-butyl-3-*n*-propyloxaziridine **1a** at room temperature and in trichlorofluoromethane solution a rapid reaction occurred to afford corresponding 1,2-anhydro derivatives **3a** and **4a** in nearly pure form and as a 1 : 1 mixture and in nearly quantitative yields (^{1}H NMR analyses of crude reaction mixture, Scheme 1). The stereoselectivity of the process and the chemical yields did not change substantially at lower (−78 °C) or higher temperatures (80 °C), but better results were obtained by using other solvents ($CHCl_3$, d.e. 18%; CCl_4, d.e. 30%; $CFCl_2CF_2Cl$, d.e. 42%). Perfluoro-1-*n*-pentyl-3-*n*-hexyloxaziridine **1b**, while showing a similar behaviour, allowed slightly higher diastereoselectivities to be obtained (*e.g.* $CFCl_2CF_2Cl$, d.e. 50%). In all cases chemical yields remained high and the prevailing diastereoisomer had the 1,2-anhydro-α-D-glucopyranose structure **3a**.†

Best results were obtained by changing the protective groups at the hydroxy residues in the starting glucal, *i.e.* by using the tri-*O*-benzyl-D-glucal **2b** (**1a**, $CHCl_3$, d.e. 68%; **1b**, $CHCl_3$, d.e. 75%).

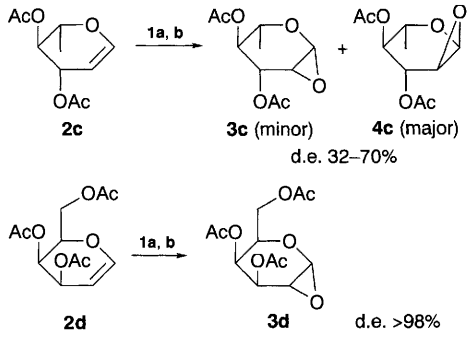
The epoxidation reaction had been performed successfully also on the di-*O*-acetyl-L-rhamnal **2c** (Scheme 2). The stereochemical preference paralleled strictly that observed on glucal **2a** as was expected given the fact that the two compounds have the same relative configurations. The epoxide **4c**, in which the oxirane ring is *trans* to the ring appendages at C-3 and C-5 of the sugar moiety, was in fact formed preferentially (d.e. 32–70%) and once again ^{1}H NMR of the crude reaction mixture showed that nearly quantitative yields were obtained. Finally, on epoxidation of tri-*O*-acetyl-D-galactal **2d**, the same diastereofacial preference was observed, but the process occurred with complete stereoselection using both **1a** and **1b** and the 1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-galactopyranose **3d** was obtained exclusively (yields >90%).



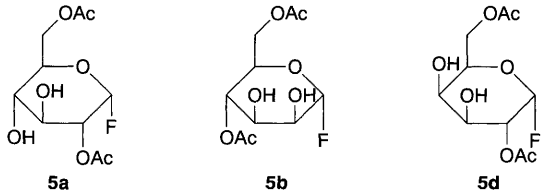
Scheme 1

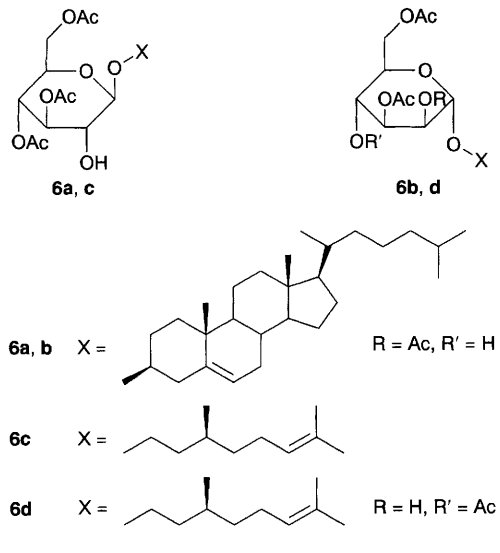
Spectroscopic properties of anhydrosugars **3a–d** and **4a–c** did not enable a direct assignment of their configuration to be established.[2] For this reason and as a first exploitation of their effectiveness as glycosyl donors, epoxides **3** were opened with fluorine and oxygen nucleophiles to give corresponding glycosyl fluorides[14,15] **5** and lipid conjugates **6**. For instance, when the crude anhydrosugar **3d** was reacted with NBu^n_4F[16] (TBAF, Aldrich, THF solution) a single fluoride **5d** was formed which possessed spectroscopic parameters diagnostic of the configuration shown at C-1 and C-2.[17] The α-D-*galacto*-pyranosyl configuration was assigned to this compound and consequently to the precursor anhydrosugar **3d**.‡ Similarly, the configuration of epoxides **3a** and **4a** was established from the fact that on treatment with TBAF they afforded two pyranosyl fluorides **5a** and **5b** having α-D-*gluco* and α-D-*manno* configurations, respectively.

Furthermore, reaction of crude epoxides obtained from glucal **2a** with cholesterol in the presence of zinc(II) chloride afforded cholesteryl β-D-gluco-pyranoside **6a** and α-D-*manno*-pyranoside **6b** in 62% isolated yield.§ Similarly, when (*S*)-citronellol was used, the corresponding glyco conjugates **6c** and **6d**, having the β-D-*gluco* and α-D-*manno* configurations, respectively, were formed.¶



Scheme 2





In conclusion, a new and preparative approach to 1,2-anhydrosugars is described. A stereospecific elaboration to give pyranosyl fluorides and glyco conjugates is also reported thus showing that the anhydrosugars produced through our methodology are pure enough to undergo subsequent conjugation with a defined nucleophile. Other reactions to afford interesting disaccharides are under study.

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Footnotes

† In a standard reaction, a solution of the oxaziridine **1** in the halogenated solvent was added dropwise to a solution of the glycal **2** in the same solvent at room temperature. After 5 min, the reaction mixture was washed with perfluorotri-*n*-butyl amine, the co-formed perfluoroazaalkene was removed and a solution of nearly pure anhydrosugar **3** was obtained. Diastereoisomer ratios were established through ^{1}H NMR of crude reaction mixtures. *Selected spectral properties*: 1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-*gluco*-pyranose **3a**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.23 (dd, 1H, *J* 1.2 and 8.2 Hz, H-3), 5.03 (dd, 1H, *J* 10.4 and 8.2 Hz, H-4), 5.02 (d, 1H, *J* 2.2 Hz, H-1), 4.32 (dd, 1H, ^3J 4.1 Hz, J_{gem} 12.5 Hz, H-6), 4.07 (dd, 1H, ^3J 2.4 Hz, J_{gem} 12.5 Hz, H-6′), 3.98 (ddd, 1H, *J* 4.1, 2.4 and 10.4 Hz, H-5), 3.01 (d, 1H, *J* 2.2 Hz, H-2), 2.086, 2.069 and 2.027 (s, 3H each, CH_3CO); 1,2-anhydro-3,4,6-tri-*O*-acetyl-β-D-*manno*-pyranose **4a**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.37–5.28 (m, 2H, H-3 and H-4), 5.00 (d, 1H, *J* 2.8 Hz, H-1), 4.19 (dd, 1H, ^3J 4.6 Hz, J_{gem} 12.5 Hz, H-6), 4.10 (dd, 1H, ^3J 2.4 Hz, J_{gem} 12.5 Hz, H-6′), 3.94 (ddd, 1H, *J* 4.6, 2.4 and 7.0 Hz, H-5), 3.44 (dd, 1H, *J* 2.8 and 2.1 Hz, H-2), 2.094, 2.075 and 2.022 (s, 3H each, CH_3CO); 1,2-anhydro-6-deoxy-3,4-di-*O*-acetyl-β-L-*manno*-pyranose **3c**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.15 (dd, 1H, *J* 1.2 and 8.3 Hz, H-3), 4.90 (br s, 1H, H-1), 4.75 (dd, 1H, *J* 10.2 and 8.3 Hz, H-4), 3.85 (dd, 1H, *J* 10.2 and 6.3 Hz, H-5), 2.97 (d, 1H, *J* 2.3 Hz, H-2), 2.044 and 1.982 (s, 3H each, CH_3CO), 1.14 (d, 3H, *J* 6.3 Hz, Me); the acetyl groups gave two singlets at δ 2.07 and 2.04 and were not assigned; 1,2-anhydro-6-deoxy-3,4-di-*O*-acetyl-α-L-*gluco*-pyranose **4c**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.24 (dd, 1H, *J* 2.3 and 8.6 Hz, H-3), 5.09 (dd, 1H, *J* 10.2 and 8.6 Hz, H-4), 4.91 (br s, 1H, H-1), 3.81 (dd, 1H, *J* 10.2 and 6.3 Hz, H-5), 3.41 (dd, 1H, *J* 2.4 and 2.4 Hz, H-2), 2.070 and 2.037 (s, 3H each, CH_3CO), 1.15 (d, 3H, *J* 6.3 Hz, Me); 1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-*galacto*-pyranose **3d**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.22 (dd, 1H, *J* 1.2 and 4.3 Hz, H-3), 5.17 (dd, 1H, *J* 1.0 and 4.3 Hz, H-4), 5.03 (d, 1H, *J* 2.4 Hz, H-1), 4.12–3.99 (m, 3H, AMX system, H-5, H-6 and H-6′ strongly coupled), 2.98 (dd, 1H, *J* 2.4 and 1.2 Hz, H-2), 2.197, 2.054 and 2.048 (s, 3H each, CH_3CO).

‡ Values of fluorine chemical shift (δ_F −150.8) and heteronuclear coupling constants ($^3J_{F-H-2}$ = 24.8 Hz) show that F and H-2 are in a *trans*-diaxial relationship; furthermore the homonuclear coupling constants $^3J_{H-1-H-2}$ = 2.7 Hz and $^3J_{H-2-H-3}$ = 9.5 Hz are consistent with H-1 equatorial and H-2 and H-3 axial in a six-membered $^4C_1$(D) conformation. These data are not consistent with the alternative structure of an α-*talo*-pyranosyl fluoride and consequently the β-*talo*-pyranose structure was ruled out for the precursor anhydrosugar. The stereochemistry of **3b,c** and **4b,c** was assigned through spectral correlation with **3a,d** and **4a**. The TBAF ring-opening of **3a**, **4a** and **3d** was accompanied by the release of one acetate group yielding the corresponding di-*O*-acetyl derivatives. Scrambling of acetyl groups was also observed.

§ Minor amounts (18% yield) of other cholesteryl pyranosides having the β-D-*gluco* and α-D-*manno* configuration and formed by scrambling of the acetyl residues were also obtained. *Selected spectral properties*: cholesteryl 3,4,6-tri-*O*-acetyl-β-D-*gluco*-pyranoside **6a**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.36 (ddd, 1H, *J* 1.7, 1.7 and 5.2 Hz, H-6), 5.11 (dd, 1H, *J* 9.3 and 9.3 Hz, H-3′), 5.00 (dd, 1H, *J* 9.3 and 9.9 Hz, H-4′), 4.45 (d, 1H, *J* 7.8 Hz, H-1′), 4.26 (dd, 1H, *J* 5.1 and 12.2 Hz, H-6′), 4.08 (dd, 1H, *J* 2.6 and 12.2 Hz, H-6″), 3.67 (ddd, 1H, *J* 2.6, 5.1 and 12.2 Hz, H-5′), 3.57 (m, 1H, H-3), 3.53, (dd, 1H, *J* 7.8 and 9.4 Hz, H-2′), 2.065, 2.058 and 2.014, (s, 3H each, CH_3CO). Cholesteryl 2,3,6-tri-*O*-acetyl-α-D-*manno*-pyranoside **6b**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.37–5.33 (m, 1H, H-6), 5.23 (dd, 1H, *J* 3.4 and 9.8 Hz, H-3′), 5.17 (dd, 1H, *J* 1.8 and 3.4 Hz, H-2′), 4.94 (d, 1H, *J* 1.8 Hz, H-1′), 4.50 (dd, 1H, *J* 5.0 and 12.2 Hz, H-6′), 4.33 (dd, 1H, *J* 2.2 and 12.2 Hz, H-6″) 3.96 (ddd, 1H, *J* 2.2, 5.0 and 9.9 Hz, H-5′), 3.81 (dd, 1H, *J* 9.9 and 9.9 Hz, H-4′), 3.53–3.43 (m, 1H, H-3), 2.124, 2.114 and 2.076, (s, 3H each, CH_3CO).

¶ *Selected spectral properties*: citronellyl 3,4,6-tri-*O*-acetyl-β-D-*gluco*-pyranoside **6c**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.10 (ddd, 1H, *J* 9.4 and 9.4 Hz, H-3′), 5.07 (m, 1H, H-6), 5.00 (dd, 1H, *J* 9.4 and 9.8 Hz, H-4′), 4.33 (d, 1H, *J* 7.8 Hz, H-1′), 4.26 (dd, 1H, *J* 4.9 and 12.2 Hz, H-6′), 4.10 (dd, 1H, *J* 2.5 and 12.2 Hz, H-6″), 3.94 (ddd, 1H, *J* 5.7, 7.8 and 9.6 Hz, H-1a), 3.67 (ddd, 1H, *J* 2.5, 4.9 and 9.9 Hz, H-5′), 3.57 (ddd, 1H, *J* 6.9, 7.5 and 9.6 Hz, H-1b) 3.54, (dd, 1H, *J* 7.8 and 9.4 Hz, H-2′), 2.057, 2.055 and 2.009, (s, 3H each, CH_3CO). Citronellyl 3,4,6-tri-*O*-acetyl-α-D-*manno*-pyranoside **6d**: ^{1}H NMR ($CDCl_3$, 400 MHz, 303 K) δ 5.32 (dd, 1H, *J* 9.8 and 9.8 Hz, H-4′), 5.26 (dd, 1H, *J* 9.8 and 2.9 Hz, H-3′), 5.10 (m, 1H, H-6), 4.86 (d, 1H, *J* 2.0 Hz, H-1′), 4.27 (dd, 1H, *J* 5.2 and 12.2 Hz, H-6′), 4.12 (dd, 1H, *J* 2.3 and 12.2 Hz, H-6″), 4.02 (m, 1H, H-2′), 3.97 (ddd, 1H, *J* 2.3, 5.2 and 9.8 Hz, H-5′), 3.73 (ddd, 1H, *J* 7.4, 7.4 and 9.7 Hz, H-1a), 3.51 (ddd, 1H, *J* 5.8, 7.4 and 9.7 Hz, H-1b), 2.087, 2.082 and 2.034, (s, 3H each, CH_3CO).

References

1 D. M. Gordon and S. J. Danishefsky, *Carbohydr. Res.*, 1990, **206**, 361.
2 D. B. Berkowitz, S. J. Danishefsky and G. K. Schulte, *J. Am. Chem. Soc.*, 1992, **114**, 4518.
3 K. K.-C. Liu and S. J. Danishefsky, *J. Org. Chem.*, 1994, **59**, 1892.
4 K. K.-C. Liu and S. J. Danishefsky, *J. Org. Chem.*, 1994, **59**, 1895.
5 R. L. Halcomb and S. J. Danishefsky, *J. Am. Chem. Soc.*,1989, **111**, 6661.
6 F. Sweet and R. B. Brown, *Can J. Chem.*, 1966, **44**, 1751.
7 A. Arnone, M. Cavicchioli, V. Montanari and G. Resnati, *J. Org. Chem.*, 1994, **59**, 5511.
8 D. D. DesMarteau, V. A. Petrov, V. Montanari, M. Pregnolato and G. Resnati, *J. Org. Chem.*, 1994, **59**, 2762.
9 M. Cavicchioli, V. Montanari and G. Resnati, *Tetrahedron Lett.*, 1994, **35**, 6329.
10 D. D. DesMarteau, A. Donadelli, V. Montanari, V. A. Petrov and G. Resnati, *J. Am Chem. Soc.*, 1993, **115**, 4897.
11 D. D. DesMarteau, V. A. Petrov, V. Montanari, M. Pregnolato and G. Resnati, *Tetrahedron Lett.*, 1992, **33**, 7245.
12 V. A. Petrov and D. D. DesMarteau, *Inorg. Chem.*, 1992, **31**, 3776.
13 V. A. Petrov and D. D. DesMarteau, *J. Org. Chem.*, 1993, **58**, 4754.
14 P. J. Card, *J. Carbohydr. Chem.*, 1985, **4**, 451.
15 J. L. Randall and K. C. Nicolau, in *Fluorinated Carbohydrates*, ed. N. F. Taylor, *ACS Symp. Ser.*, 1988, **374**, 13.
16 G. Resnati, *Tetrahedron*, 1993, **42**, 9385.
17 L. Cavalli, *Annu. Rep. NMR Spectrosc.*, 1976, **6B**, 43.