Displacement Reactions on 2,3,4,6-Tetra-*O*-benzyl-1,5-di-*O*-sulfonyl-D-glucitols. Synthesis of (3*R*,4*S*)-3,4-Dibenzyloxy-2-(2-benzyloxyethylidene)tetrahydrofuran

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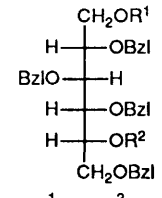
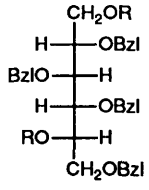
Treatment of the 1,5-dimesylate and 1,5-ditosylate of 2,3,4,6-tetra-*O*-benzyl-D-glucitol **1** with tetrabutylammonium acetate in acetonitrile leads, through nucleophilic attack by O-2 at C-5 and normal displacement at C-1, to 1-*O*-acetyl-2,5-anhydro-3,4,6-tri-*O*-benzyl-L-iditol. In contrast, the corresponding 1,5-ditriflate on similar treatment undergoes displacement at C-1 by attack of O-4 and elimination of triflic acid between C-4 and C-5 to afford (3*R*,4*S*)-3,4-dibenzyloxy-2-(2-benzyloxyethylidene)tetrahydrofuran.

In order to prepare 2,3,4,6-tetra-substituted-L-iditol derivatives required for another project, we recently reinvestigated a possible route involving inversion of configuration at C-5 in suitably substituted D-glucitol derivatives. We envisaged that 1,5-disulfonates of the readily available 2,3,4,6-tetra-*O*-benzyl-D-glucitol[1] **1** might, under suitable conditions, afford 1,5-di-*O*-substituted 2,3,4,6-tetra-*O*-benzyl-L-iditol **5**, although we were aware that Perlin and co-workers[1,2] had not been successful in a similar endeavour. Thus, these workers reported that 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-glucitol **2** on treatment with potassium superoxide[1] and caesium propionate[2] gave alkene **6** and 1-*O*-propionyl-2,5-anhydro-3,4,6-tri-*O*-benzyl-L-iditol **7**, respectively. They also noted[3] that reactions in which sodium or potassium acetate, or sodium benzoate was used in place of caesium propionate did not lead to 2,5-anhydro compounds. We have investigated, therefore, nucleophilic displacements on a series of 1,5-disulfonates of 2,3,4,6-tetra-*O*-benzyl-D-glucitol with tetrabutylammonium acetate in acetonitrile.

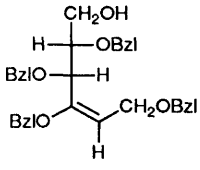


1 R^1 = H, R^2 = H
2 R^1 = R^2 = Ms
3 R^1 = R^2 = Ts
4 R^1 = R^2 = Tf

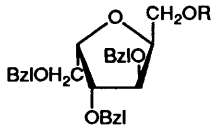


5

Bzl = $PhCH_2$—
Ms = $MeSO_2$—
Ts = 4-$MeC_6H_4SO_2$—
Tf = CF_3SO_2—



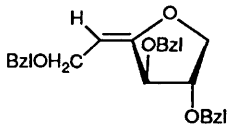
6



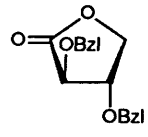
7 R = COEt
8 R = COMe
9 R = H

Treatment of 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-tosyl-D-glucitol **3**, prepared by tosylation of **1**, with tetrabutylammonium acetate in acetonitrile at 55 °C over several days led to formation of benzyl acetate and a compound containing, from its ^{1}H NMR spectrum, three benzyl groups and one acetyl group. A consideration of elemental analysis, the likelihood that displacement of the primary tosylate was favoured over the secondary one, and the expected preference for five-membered ring formation, led to the conclusion that the product was 1-*O*-acetyl-2,5-anhydro-3,4,6-tri-*O*-benzyl-L-iditol **8**. The structure was confirmed by the fact that its ^{1}H NMR spectrum was in excellent agreement with that reported[2] for the same compound and that its ^{13}C NMR spectrum was in good agreement with the corresponding 1-*O*-propionyl compound, except for the obvious differences because of the differing 1-*O*-acyl groups. Further, deacetylation of **8** afforded the known[2] 2,5-anhydro-3,4,6-tri-*O*-benzyl-L-iditol **9**. Similar treatment of 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-glucitol **2** with tetrabutylammonium acetate in acetonitrile again gave compound **8**.

In view of the superiority of trifluoromethanesulfonates (triflates) over other sulfonates in nucleophilic displacement reactions,[4] the 1,5-di-*O*-triflyl derivative **4** was subjected to treatment with tetrabutylammonium acetate in acetonitrile. Complete disappearance of **4** occurred in 15 min at room temperature with formation of a major product which showed in its ^{1}H NMR spectrum resonances for three benzyl groups but no acetyl groups. This spectrum contained a characteristic ^{1}H triplet at δ 5.371 for an alkenic hydrogen and the ^{13}C spectrum contained resonances for alkenic carbons at δ 99.2 and 158.0. These observations, together with an elemental analysis are consistent with the product being (*E*)-(3*R*,4*S*)-3,4-dibenzyloxy-2-(2-benzyloxyethylidene)tetrahydrofran **10**, the *E*-configuration being based on a consideration of the likely stereochemistry of elimination.

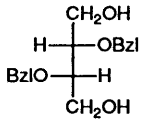


10

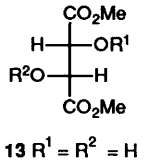


11

Bzl = $PhCH_2$—
Ms = $MeSO_2$—
Ts = 4-$MeC_6H_4SO_2$—
Tf = CF_3SO_2—



12



13 R^1 = R^2 = H
14 R^1 = R^2 = Bzl
15 R^1 = Bzl, R^2 = H

Proof of the skeletal structure was obtained by degradation through ozonolysis which afforded a compound identified as

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2,3-di-*O*-benzyl-L-threonolactone **11** from its ^{1}H NMR spectrum, from its IR spectrum (ν_{max} 1790 cm^{-1}) and from its conversion by reduction with lithium aluminium hydride into 2,3-di-*O*-benzyl-L-threitol **12**. The structure of the latter compound was confirmed unequivocally by synthesis from dimethyl L-tartrate **13** through benzylation with silver oxide/benzyl bromide followed by reduction with lithium aluminium hydride of the so-formed dimethyl 2,3-di-*O*-benzyl-L-tartrate **14**. From the benzylation of **13**, we also isolated the product of monoalkylation, dimethyl 2-*O*-benzyl-L-tartrate **15**.

An attempt to investigate the structure of **10** by acidic hydrolysis of the enol ether was unsuccessful. Treatment of **10** with trifluoroacetic acid (catalytic) in water-saturated ether and chromatographic separation of the product mixture afforded a compound which decomposed almost immediately to give a complex mixture.

The present example of yet another mode of action of an oxygen nucleophile on a disulfonate of **1** raises interesting questions regarding the mechanism of such displacement reactions and the reasons for the variations in products. Rao and Perlin suggest[2] that formation of the 2,5-anhydro-L-iditol derivative **7** in reactions of **2** with caesium propionate may depend on the highly polarisable caesium ion rather than the propionate moiety. The fact that we have obtained the equivalent 1-*O*-acetyl product, compound **8**, from **2** on reaction with an acetate in which the cation is tetrabutylammonium rather might throw doubt on the importance of cation polarisability in determining the course of reaction. Particularly surprising is the difference we have observed in the reaction products obtained on replacing the dimesylate **2** or the ditosylate **3** with the ditriflate **4** in reactions involving tetrabutylammonium acetate as the source of acetate nucleophile. Clearly, nucleofugality* plays a role in influencing the course of such reactions.

Experimental

^{1}H NMR spectra were recorded in [^{2}H]chloroform (internal Me_4Si) at 60 or (if stated) 400 MHz with a JEOL PMX60si or GX-400 spectrometer, respectively, and ^{13}C NMR spectra were recorded at 22.4 MHz using a JEOL EX-90 spectrometer in [^{2}H]chloroform (internal Me_4Si), unless stated otherwise. *J* Values are given in Hz. Rotations were measured with a Perkin-Elmer 141 polarimeter for chloroform solutions. $[\alpha]_D$ units are recorded in 10^{-1} deg cm^2 g^{-1}. TLC and column chromatography were performed on silica gel (Machery-Nagel, SIL G-25UV$_{254}$ and Silica Gel 60 (Merck, 70–230 mesh), respectively.

2,3,4,6-*Tetra*-O-*benzyl*-1,5-*di*-O-*tosyl*-D-*glucitol* **3**.—A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucitol[1] **1** (3 g, 5.53 mmol) and tosyl chloride (2.32 g, 12.16 mmol) in pyridine (5 cm^3) was stored at 4 °C for 48 h. Solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (100 cm^3). The solution was washed successively with 2.5 mol dm^{-3} hydrochloric acid (40 cm^3), water (50 cm^3), and saturated aqueous sodium hydrogen carbonate (40 cm^3) and then dried and concentrated to afford an oil which crystallised on trituration with hexane to give the disulfonate **3** (3.43 g, 73%), m.p. 99–101 °C (Found: C, 68.0; H, 6.0; S, 7.4. $C_{48}H_{50}O_{10}S_2$ requires C, 67.7; H, 5.9; S, 7.5%); $[\alpha]_D$ +9.1 (*c* 1.0); ν_{max}(Nujol)/cm^{-1} 1360 and 1175 (SO_2-O); δ_H 2.34 (3 H, s, *Me*Ar), 2.38 (3 H, s, *Me*Ar), 3.52–5.08 (16 H, complex) and 6.92–7.88 (28 H, complex, 4 × C_6H_5 and 2 × AA′BB′ systems of MeC_6H_4-SO_2^-).

* The term nucleofugality is used to describe the ability of a molecular fragment to act as a leaving group which carries away an electron pair (a nucleofuge).[5]

1-O-*Acetyl*-2,5-*anhydro*-3,4,6-*tri*-O-*benzyl*-L-*iditol* **8**.—(*a*) *From* **3**. A solution of **3** (1 g, 1.18 mmol) and tetrabutylammonium acetate (0.86 g, 2.83 mmol) in acetonitrile (20 cm^3) was stored at 55 °C for 10 days. TLC [ethyl acetate–hexane (3:7 v/v)] indicated loss of starting material (R_F 0.38) and formation of two components with R_F 0.76 (benzyl acetate) and 0.46. Isolation of the less mobile component by column chromatography with the same solvent system gave, as a colourless oil, compound **8** (0.45 g, 79%) (Found: C, 73.0; H, 6.8. $C_{29}H_{32}O_6$ requires C, 73.1; H, 6.8%); $[\alpha]_D$ +26.3 (*c* 1.0); ν_{max}(film)/cm^{-1} 1735 (CO); δ_H(400 MHz) 2.036 (3 H, s, Me), 3.698 (1 H, dd, $J_{6,6'}$ 9.7 and $J_{5,6}$ 6.1, 6-H), 3.727 (1 H, dd, $J_{5,6'}$ 6.7, 6′-H), 3.995 (1 H, dd, $J_{3,4}$ 1.2 and $J_{2,3}$ 4.0, 3-H), 4.029 (1 H, dd, $J_{4,5}$ 3.9, 4-H), 4.202 (1 H, dd, $J_{1,1'}$ 12.5 and $J_{1,2}$ 8.6, 1-H), 4.300–4.410 (3 H, complex, 1′-H, 2-H, 5-H), 4.381, 4.486, 4.514, 4.518, 4.522, 4.593 [each 1 H, 6 × d (3 × AB systems), J_{AB} 12.05, 12.05, 12.50, 3 × CH_2Ph] and 7.220–7.370 (15 H, br s, 3 × C_6H_5); δ_C 20.7 (Me), 63.3 (C-1), 68.0 (C-6), 72.2, 72.5, 73.3, 77.8, 79.0 (C-3, C-4, 3 × CH_2Ph), 80.9, 81.4 (C-2 and C-5), 127.3–128.6 and 137.4, 137.7, 138.1 (Ar-C) and 170.7 (CO).

(*b*) *From* **2**. A solution of the 1,5-dimesylate[2] **2** (0.5 g, 0.72 mmol) and tetrabutylammonium acetate (0.65 g, 2.15 mmol) in acetonitrile (20 cm^3) were heated under reflux for 2 days. Similar isolation of the product by column chromatography, as described in the preceding section (a), afforded **8** (0.2 g, 59%) with identical properties with the sample obtained from **3**.

2,5-*Anhydro*-3,4,6-*tri*-O-*benzyl*-L-*iditol* **9**.—Deesterification of **8** (0.2 g, 0.42 mmol) by treatment with a catalytic amount of sodium methoxide in methanol (10 cm^3) gave after column chromatography [ethyl acetate–hexane (9:11 v/v)], as an oil, the anhydro compound **9** (0.047 g, 26%); ν_{max}(film)/cm^{-1} 3440 (OH); δ_H 2.271 (1 H, br s, OH), 3.767 (1 H, dd, $J_{5,6}$ 6.4 and $J_{6,6'}$ 9.8, 6-H), 3.795 (1 H, dd, $J_{5,6'}$ 5.8, 6′-H), 3.842 (1 H, dd, $J_{1,1'}$ 11.9 and $J_{1,2}$ 4.9, 1-H), 3.915 (1 H, dd, $J_{1,2}$ 5.5, 1′-H), 4.142 (1 H, dd, $J_{3,4}$ 1.8 and $J_{4,5}$ 4.0, 4-H), 4.160 (1 H, dd, $J_{2,3}$ 4.8, 3-H), 4.316 (1 H, m, 2-H), 4.443 (1 H, m, 5-H), 4.443, 4.578, 4.595, 4.613, 4.621, 4.674 (each 1 H, 6 × d, [3 × AB systems], J_{AB} 12.1, 12.2, 9.9, 3 × CH_2Ph) and 7.305–7.434 (15 H, br s, 3 × C_6H_5). The ^{1}H NMR spectrum was in agreement with that reported for **9** prepared[2] by deesterification of the product of reaction of **2** with caesium propionate.

(E)-(3R,4S)-3,4-*Dibenzyloxy*-2-(*benzyloxyethylidene*)*tetrahydrofuran* **10**.—A solution of triflic anhydride (2.3 cm^3, 13.7 mmol) in dichloromethane (6 cm^3) was added dropwise over 15 min to a cooled (0 °C), stirred mixture of pyridine (1.84 cm^3, 22.8 mmol) and 2,3,4,6-tetra-*O*-benzyl-D-glucitol[1] (3.09 g, 5.7 mmol) in dichloromethane (50 cm^3). The reaction mixture was stirred for a further 15 min at 0 °C and then poured onto a mixture of ice and saturated aqueous sodium hydrogen carbonate (50 cm^3). The phases were separated and the aqueous phase was extracted with dichloromethane (50 cm^3). The combined organic phases were washed, in rapid succession, with 0.5 mol dm^{-3} hydrochloric acid (50 cm^3), water (50 cm^3), saturated aqueous sodium hydrogen carbonate (50 cm^3) and water (50 cm^3). On concentration the dried solution afforded, as an oil, the crude triflate **4** (3.02 g, 66%), ν_{max}(film)/cm^{-1} 1400 and 1200 (SO_2-O), which was used without further purification.

The crude triflate **4** was added directly to a stirred solution of tetrabutylammonium acetate (2.79 g, 8.97 mmol) in acetonitrile (50 cm^3). TLC [ethyl acetate–hexane (1:9 v/v)] after 15 min indicated complete disappearance of starting material (R_F 0.45) with formation of a new component having R_F 0.38. The solution was concentrated and the residue was partitioned between dichloromethane (60 cm^3) and water (60 cm^3). Concentration of the dried organic layer gave an oily residue

which was subjected to column chromatography [ethyl acetate–hexane (1:9 v/v)] to give, as an oil, the tetrahydrofuran **10** (0.87 g, 56%) (Found: C, 77.9; H, 6.7. $C_{27}H_{28}O_4$ requires C, 77.9; H, 6.8%); $[\alpha]_D$ −12.4 (*c* 0.3); ν_{max}(film)/cm^{-1} 1690 and 1050 (C=C–O); δ_H(400 MHz)* 4.040 (1 H, dd, $J_{7,7'}$ 11.7 and $J_{6,7}$ 8.0, 7-H), 4.105 (1 H, dd, $J_{6,7'}$ 8.0, 7'-H), 4.155 (1 H, d, $J_{4,5'}$ 3.3, 4-H), 4.250 (1 H, d, $J_{5,5'}$ 9.9, 5-H), 4.304 (1 H, dd, 5'-H), 4.474–4.637 (7 H, complex, 3-H and 3 × CH_2Ph), 5.371 (1 H, t, 6-H) and 7.301–7.428 (15 H, m, ArH); δ_C 66.2, 70.8, 71.2 (×2), 72.6, 77.5, 80.2, 99.2 (C-6) and 158.0 (C-2).

2,3-*Di*-O-*benzyl*-L-*threonolactone* **11**.—A solution of **10** (0.1 g, 0.24 mmol) in ethyl acetate (cm^3) was added to a saturated solution of ozone in ethyl acetate (40 cm^3) at −78 °C, causing most of the initial blue colour of the latter solution to be discharged. TLC [ethyl acetate–hexane 1:4 v/v)] indicated disappearance of starting material (R_F 0.36) and formation of a new component (R_F 0.32), as well as some base-line material. Nitrogen was passed through the solution which was then allowed to warm to room temperature. Solvent was evaporated and the residue was subjected to column chromatography with ethyl acetate–hexane (1:4 v/v) to afford, as an oil, the lactone **11** (0.046 g, 64%) (Found: C, 72.4; H, 6.1. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.1%); $[\alpha]_D$ +58 (*c* 0.3); ν_{max}(film)/cm^{-1} 1790 (γ-lactone); δ_H(400 MHz) 3.975 (1 H, dd, $J_{3,4}$ 6.1 and $J_{4,4'}$ 9.2, 4-H), 4.145 (1 H, d, $J_{2,3}$ 6.1, 2-H), 4.239 (1 H, ddd, $J_{3,4'}$ 6.7, 3-H), 4.317 (1 H, dd, 4'-H), 4.442 (1 H, d, $J_{a,b}$ 11.7, CH_aH$_b$Ph), 4.543 (1 H, d, $J_{a,b}$ 11.7, CH$_a$H$_b$Ph), 4.688 (1 H, d, $J_{a,b}$ 11.6, CH_aH$_b$Ph), 4.946 (1 H, d, $J_{a,b}$ 11.6, CH$_a$H$_b$Ph) and 7.171–7.321 (10 H, m, ArH).

Dimethyl 2,3-*Di*-O-*benzyl*-L-*tartrate* **14** *and Dimethyl* 2-O-*Benzyl*-L-*tartrate* **15**.—To a vigorously stirred solution of dimethyl L-tartrate **13** (2 g, 0.01 mol) in a mixture of 1,2-dimethoxyethane (8 cm^3) and benzyl bromide (4 cm^3) was added, in portions, silver oxide (7.81 g, 0.03 mol) at room temperature. After 30 min, the mixture was then stirred at 55 °C for a further 2 h. TLC [ethyl acetate–hexane (9:11 v/v)] revealed disappearance of **13** (R_F 0.17) and formation of two products with R_F values of 0.28 and 0.64. Filtration of the mixture through Kieselguhr and concentration of the filtrate gave an oil which was subjected to column chromatography with ethyl acetate–hexane (3:7 v/v) as eluent to give, firstly, the di-ether **14** (1.12 g, 31%) (Found: C, 67.3; H, 6.2. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%); $[\alpha]_D$ +121 (*c* 3.5); ν_{max}(film)/cm^{-1} 1760 (CO) and 1100 (COC); δ_H 3.68 (6 H, s, 2 × Me), 4.40 (2 H, s, 2 × CH), 4.48 (2 H, d, $J_{a,b}$ 11, 2 × CH_aH$_b$Ph), 4.88 (2 H, d, $J_{a,b}$ 11, 2 × CH$_a$H$_b$Ph) and 7.28–7.36 (10 H, m, ArH); δ_C 51.9 (Me), 73.0 (CH), 78.0 (CH$_2$), 127.8, 127.9, 128.1, 136.6 (4 × Ar-C) and 169.3 (CO).

Further elution gave, on crystallisation from ethyl acetate–hexane, the mono-ether **15** (0.94 g, 35%), m.p. 65–66 °C (Found: C, 58.6; H, 5.9. $C_{13}H_{16}O_6$ requires C, 58.2; H, 6.0%); $[\alpha]_D$ +84.3 (*c* 3.2); ν_{max}(film)/cm^{-1} 3490 (OH) and 1755 (CO); δ_H 3.10 (1 H, br s, OH), 3.64 (3 H, s, Me), 3.80 (3 H, s, Me), 4.24 (1 H, d, *J* 12, CH_aH$_b$Ph), 4.30–4.36 (1 H, m, CH), 4.56–4.60 (1 H, m, CH), 4.84 (1 H, d, *J* 12, CH$_a$H$_b$Ph) and 7.28 (5 H, m, ArH).

2,3-*Di*-O-*benzyl*-L-*threitol* **12**.—(*a*) *From* **11**. A solution of **11** (0.11 g, 0.37 mmol) in tetrahydrofuran (THF) (2 cm^3) was added at room temperature over 5 min to a stirred mixture of lithium aluminium hydride (0.19 g, 0.51 mmol) in dry THF (1 cm^3). After 5 min, ethyl acetate (0.03 cm^3), water (0.03 cm^3), 15% aqueous sodium hydroxide (0.03 cm^3), and water (0.09 cm^3) were added sequentially to the vigorously stirred mixture. The resulting granular precipitate was removed by filtration through Kieselguhr and the filtrate was dried and concentrated to leave a chromatographically homogeneous viscous oil (0.091 g, 81%) which, with time, solidified. The analytical sample was recrystallised from ethyl acetate–hexane to yield the diether **12**, m.p. 50–52 °C (Found: C, 71.4; H, 7.0. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%); $[\alpha]_D$ +17.3 (*c* 0.1); ν_{max}(film)/cm^{-1} 3400 (OH); δ_H(400 MHz) 2.269 (2 H, br s, 2 × OH), 3.586–3.763 (6 H, m, 2 × CH$_2$ and 2 × CH), 4.572 (4 H, s, 2 × CH_2Ph) and 7.214–7.297 (10 H, m, ArH).

(*b*) *From* **14**. A solution of **14** (0.18 g, 0.49 mmol) in THF was reduced with lithium aluminium hydride (0.047 g, 1.24 mmol) in THF (1.5 cm^3) and the crude product was isolated in a similar manner to that described in the preceding section (a). Column chromatography with ethyl acetate–hexane (9:11 v/v) as the eluent yielded **12** as a homogeneous oil (0.068 g, 46%) which crystallised with time. Recrystallisation (ethyl acetate–hexane) gave material m.p. 48–49 °C, mixed m.p. 49–51 °C with material prepared from **11**. The NMR and IR spectra of the samples of **12** prepared from **11** and **14** were identical.

Acknowledgements

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* For the purpose of describing the ^{1}H and ^{13}C NMR spectra of **10**, the vinylic and methylene carbons of the ethylidene moiety are numbered 6 and 7, respectively.