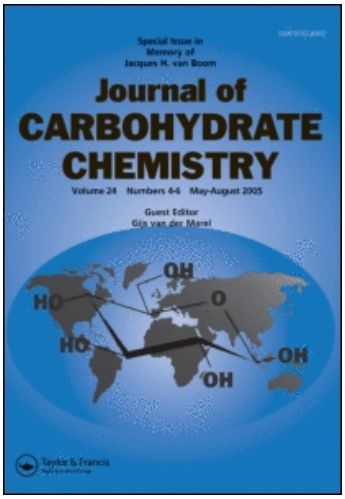

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A SINGLE-PROCESS DESULFONYLATION OF PERBENZYLATED-α- AND -β-D-GLYCOPYRANOSYL PHENYL (*TERT*-BUTYL)SULFONES

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ABSTRACT

Phenyl and/or *tert*-butyl α or β-D-glucopyranosyl sulfones were treated with lithium aluminum hydride and potassium hydroxide respectively to afford conveniently desulfonylated products (**4** and **5**). From the former reductive process was isolated the 2-deoxy-1,5-anhydro-D-glucitol derivative (**4**) as a major product and from the latter alkaline treatment was obtained the pyranoid-2-enono-δ-lactone derivative (**6**) in fairly good yields, effectively in a single process reaction.

INTRODUCTION

The growing significance of the sulfonyl group in synthetic methodologies has been widely recognized over the past two decades.[1] In particular, in the field of preparative carbohydrate chemistry, a number of papers[2] directed toward desulfonylation of glycosyl aryl or alkyl sulfones have appeared.

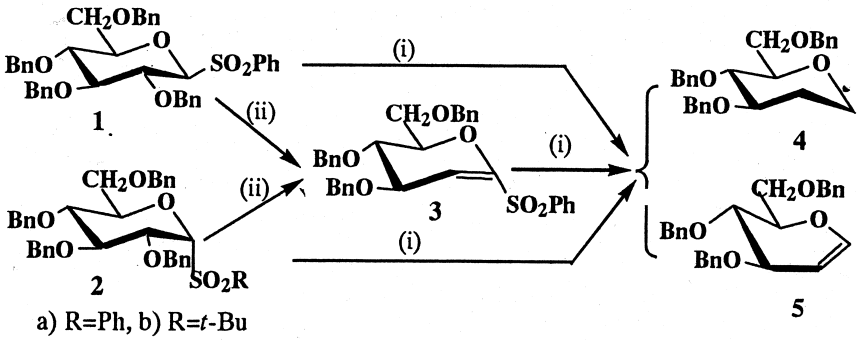
As part of our studies in the utilization of aryl glycopyranosyl sulfones, we previously reported[3] a direct preparation of 1,6-anhydro-D-glycitols of common disaccharides from the corresponding various peracetylated glycosyl aryl sulfones. We wish herein to describe two different modes of simple and convenient desulfonylation reactions toward perbenzylated α- and β-D-glucopyranosyl phenyl (**1**, **2a**) and/or *tert*-butyl sulfone **2b**, involving a new preparation of 2-deoxy-1,5-anhydro-D-glucitol derivative **4** via a direct hydride reduction of **1** and **2**, as well as a

single process formation of α,β-unsaturated-δ-lactone (**6**: 2-enono-1,5-lactone derivative) by direct alkaline treatment of **1**.

RESULTS AND DISCUSSION

The first trial of desulfonylation was easily achieved by reducing 2,3,4,6-tetra-*O* benzyl-β-D-glucopyranosyl phenyl sulfone **1**[4] directly with lithium aluminum hydride in dry THF under reflux for more than 3.5 h to yield 3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-D-glucitol **4** in 63% yield as a major product, and 3,4,6-tri-*O*-benzyl-D-glucal **5**[5] as a minor product (>5%). However, 2,3,4,6-tetra-*O*-benzyl-1,5-anhydro-D-glucitol (perbenzylated polygalitol),[6] which we had initially presumed would be formed from compound **1** by a direct S_N2 type reaction via displacement of phenylsufonyl group with the hydride, was not isolated at all. The corresponding α-anomer **2a** and 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl *tert*-butyl sulfone **2b** also gave the same results as in the case of β-anomer **1** under the same reaction conditions (Scheme 1). The intermediate of the above reaction, 1-phenylsulfonyl 3,4,6-tri-*O*-benzyl-D-glucal **3**[4] prepared from **1** by facile β-elimination of 2-*O*-benzyl group with *tert*-butoxide in *tert*-butyl alcohol, was isolated and subjected to the same reaction conditions. A rather smooth reduction of **3** took place within 2 h to yield the major compound **4** and the minor one **5** in 72 % and 13 % yields, respectively. Interestingly, when the reduction of **3** was conducted under the same reaction conditions as above with lithium aluminum deuteride (LAD), we observed that about 50 % hydrogen of the total C-1 proton of **4** was effectively transformed into deuterium [ca. 34 % at H-1e (δ 4.09) and 64 % at H-1a (δ 3.38) as well as 43 % at H-2e (δ 2.08) and 57 % at H-2a (δ 1.71) were estimated to be exchanged by deuterium, based on ^{1}H NMR proton integration. At the same time, it was also observed that the H-1 proton (δ 6.40) of the minor compound **5** completely disappeared after LAD reduction.

Almost the same results were obtained in the case of direct reduction of **1** with LAD and it was also confirmed that Michael addition of deuteride to phenylsulfonyl glucal **3** took place in a random fashion. Though the reaction mechanism



Scheme 1. (i)$LiAlH_4$/THF, reflux, 2-3.5 h (ii) t-BuOK/*t*-BuOH.

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of the final stage before the displacement of phenylsulfonyl group by deuterium cannot be clearly proposed at present, it is probable that a proton abstraction from the reaction media[7] effectively occurred at C-1 after the process of β-addition of deuteride, and the successive nucleophilic exchange of phenylsulfonyl group of **3** with deuterium took place to afford the major product **4**. It is also reasonable to speculate that the minor glucal **5** was formed via the direct hydride reduction[8] of vinylsulfone **3**, judging both from the complete disappearance of the H-1 proton of **5** by LDA reduction and from the increased yield of **5** in the case of hydride reduction of **3**.

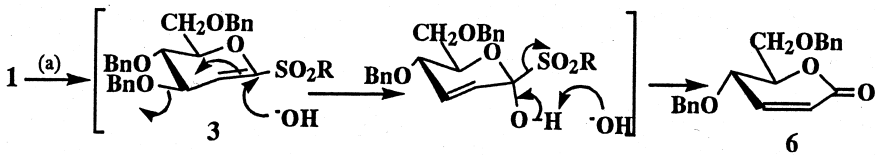
The above result was quite different from that of the Sinaÿ group[9] which employed single-electron reduction of **1** with SmI_2 in THF to yield **5** in a yield of 56 %.

The next trial of direct desulfonylation of **1** was also effectively achieved to give pyranoid-2-enono-lactone derivative **6** in 76 % yield, by a simple heating of **1** at 80°C for 3 h in a solvent system such as DMSO/CH_3OH (1 : 1) in the presence of 2.5 equiv of potassium hydroxide. Probably, the following successive reactions such as β-elimination, double-bond migration after hydroxide addition at C-1, and final desulfonylation took place in a stepwise manner (Scheme 2) as was reasonably proposed by Schmidt and Qiu,[2b] who prepared **6** under rather time-consuming conditions (sodium methoxide/crown-ether in THF, 65°C, 10–24 h). Phenylsulfonyl glucal **3** clearly played an important role as a key intermediate also in this reaction. Both α-anomers (**2a** and **2b**) newly prepared for comparison gave almost same results.

Pyranoid-2-enonolactone derivatives which can be thus prepared conveniently are potentially useful synthetic intermediates for various natural products[10] having an α,β-unsaturated δ-lactone skeleton, and the application toward synthesis of (+)-altholactone[11] is now in progress in our laboratory.

EXPERIMENTAL

General Methods. ^1H NMR spectra were recorded with JEOL spectrometers (JNM-GSX 400 MHz) for solutions in $CDCl_3$ containing tetramethylsilane as the internal reference. Melting points were determined on a Yazawa micro melting-point apparatus BY-2 and are uncorrected. Optical rotations were determined at 18°C, with a JASCO DIP-140 digital polarimeter. TLC was performed on precoated plates of silica gel 60 (Merck) with the solvent systems toluene-ethyl ac-



Scheme 2. (a) DMSO/MeOH/KOH.

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etate (10:1) or (5:1). Compounds were detected with iodine vapor or 5 % methanolic sulfuric acid spray followed by heating on a hot plate. Column chromatography was performed by the flash technique on silica gel (Wako-gel C-300).

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl phenyl sulfone (2a). To a solution of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside[4] (500 mg, 0.79 mmol) in dry toluene (15 mL) was added, at room temperature, 70 % 3-chloroperoxy benzoic acid (0.59 g, ca. 3.0 equiv). The reaction mixture was kept for 2 h with stirring, then diluted with ethyl acetate (50 mL), washed with saturated aq $NaHSO_3$, 0.2 mol NaOH , water, and dried over $MgSO_4$. After the solvent was removed, the residue was recrystallized from ethanol to give **2a** (480 mg, 92 %), mp 111–112°C, $[\alpha]_D$ +105°(*c* 0.13, acetone). ^{1}H NMR δ 3.44 (dd, 1H, $J_{6a,6b}$=11 Hz, $J_{5,6a}$=1.9 Hz, H-6a), 3.60–3.65 (m, 2H, H-4 and H-6b), 4.07 (dd, 1H, $J_{1,2}$=6.0 Hz, $J_{2,3}$=8.5 Hz, H-2), 4.32 (m, 1H, H_5), 4.53 (t, 1H, $J_{3,4}$=8.5 Hz, H-3), 4.30–4.96 (m, 8H, Ph$\underline{CH_2}$×4), 4.94 (d, 1H, H-1), 7.2–7.9 (m, 20H, Ph).

Anal. Calcd for $C_{40}H_{40}O_7S$: C, 72.27 ; H,6.06. Found: C, 72.15 ; H, 6.23.

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl *tert*-butyl sulfone (2b). To a solution of *tert*-butyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside[12] (250 mg, 0.41 mmol) in a mixture of acetic acid (5 mL) and ethyl acetate (5 mL) was added 30 % hydrogen peroxide (1 mL), and the reaction solution was kept at room temperature overnight. After TLC monitoring, the solution was poured into ice-water, extracted with ethyl acetate (10 mL × 3). The organic layer was washed with saturated aq $NaHCO_3$, water, and dried over $MgSO_4$, and concentrated *in vacuo* to a crystalline residue (0.252 g), which was recrystallized from ethanol to give white needles **2b** (195 mg, 74 %), mp 122–123°C, $[\alpha]_D$ + 87°(*c* 0.74, acetone). ^{1}H NMR δ 1.47 (s,9H, CH_3×3), 3.62–3.72 (m, 3H, H-4, H-6a, H-6b), 4.15 (dd, 1H, $J_{1,2}$=5.3 Hz, $J_{2,3}$=7.5 Hz, H-2), 424 (t, 1H, $J_{3,4}$=7.5 Hz, $J_{2,3}$=10.2 Hz, H-3), 4.36, 4.39, 4.42, 4.45, 4.55, 4.58, 4.61, 4.62, 4.64, 4.66, 4.67, 4.76, 4.78, 4.89, 4.92 (m, 8H, Ph $\underline{CH_2}$ × 4), 4.50 (m, 1H, H-5), 7.2–7.40 (m, 20H, Ph).

Anal. Calcd for $C_{38}H_{44}O_7S$: C, 70.78 ; H, 6.88 . Found: C, 70.69 ; H, 6.98.

1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1-phenylsulfonyl-D-*arabino*-hex-1-enitol (3). A mixture of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl phenyl sulfone **1**[4] (0.25 g, 0.38 mmol) and potassium *tert*-butoxide (45 mg, 1 equiv) in *tert*-butyl alcohol (15 mL) was heated to reflux for 15 min. The reaction mixture was then deionised with Dowex HCR-W2 (H^+), concentrated *in vacuo* to a residue, which was subjected to flash column chromatography to give a crystalline product **3** (160 mg, 75 %), mp 83–84°C (lit.,[4] mp 84–85°C).

Hydride reduction (A) of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl phenyl sulfones (1): preparation of 3,4,6-tri-*O*-benzyl-1,2-dideoxy-1,5-anhydro-D-*arabino*-hexitol (4) and 3,4,6-tri-*O*-benzyl-D-glucal (5). A mixture of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl phenylsulfone **1** (430 mg, 0.38 mmol) and lithium aluminum hydride (106 mg, 2.8 mmol) in dry tetrahydrofuran (20 mL)

was heated to reflux for 3 h. Ethyl acetate and water was then successively added to the reaction mixture, and the precipitates were filtered off. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* (< 1 mmHg) to a crude syrup, which was finally subjected to flash column chromatography to give 3,4,6-tri-*O*-benzyl-D-glucal **5** (14 mg, 5.2 %) from toluene fractions, mp 56–57°C (lit.,[5] mp 57–57.5°C). From toluene/ethyl acetate (10:1) fractions, 3,4,6-tri-*O*-benzyl-1,2-dideoxy-1,5-anhydro-D-glucitol **4** (172 mg, 63%) was obtained as a syrup: $[\alpha]_d$ + 85°(*c* 0.26, acetone). ^{1}H NMR δ 1.71 (m, 1H, $J_{2a,2e}$=12.7, $J_{1a,2a}$=12.5, $J_{2a,3}$=4.9Hz, H-2_a), 2.08 (m, 1H, $J_{1e,2e}$= 1.5 Hz, $J_{2e,3}$=2.4 Hz, H-2e), 3.34 (m, 1H, $J_{5,6a}$=4.9 Hz, $J_{5,6b}$=2.1 Hz, $J_{4,5}$= 9.4 Hz, H-5), 3.38 (td, $J_{1a,1e}$=12.5 Hz, H-1a), 3.49 (t, 1H, $J_{3,4}$= 9.0 Hz, $J_{4,5}$= 9.4, H-4), 3.66 (dd, 1H, $J_{6a,6b}$= 10 Hz, H-6a), 3.70 (dd, 1H, H_{6b}), 4.00 (qd, 1H, H-1e), 4.50–4.81 (m, 6H, Ph-$\underline{CH_2}$ ×3), 7.16–7.36 (m, 6H, Ph).

Anal. Calcd for $C_{27}H_{30}O_4$ (**4**): C, 77.48; H. 7.22. Found: C, 77.29 ; H,7.30.

Hydride reduction (B) of 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1-phenylsulfonyl-D-*arabino*-hex-1-enitol (3). A mixture of 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1-phenylsulfonyl-D-*arabino*-hex-1-enitol **3** (100mg, 0.17 mmol) and lithium aluminum hydride (30 mg, 0.72 mmol) in dry tetrahydrofuran (10 ml) was heated to reflux for 2 hr. The work-up was done as above and the compounds **4** (54 mg, 72 %) and **5** (10 mg, 13 %) were isolated, respectively, after flash column chromatography.

Alkali treatment of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopranosyl phenyl sulfone(1a): preparation of 4,6-di-*O*-benzyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (6). A solution of **1** (200 mg, 0.030 mmol) and potassium hydoxide (44 mg, 2.6 equiv) in a mixture of anhydrous DMSO (4 mL) and methanol (5 mL) was kept at 80°C for 2 h. After monitoring with TLC, the reaction solution was deionized with Dowex HCR-W2 (H^+) and concentrated *in vacuo* (< 1 mm Hg) to a syrup, which was purified with flash column chromatography to give an oily compound **6** (74 mg, 76%) in addition to a less polar component **3** (~10 mg, >5 %). Compound **6**: $[\alpha]_d$ +67° (*c* 0.5, acetone), (lit.,[2b] $[\alpha]_d$ +68.5° (*c* 1.0, $CHCl_3$). ^{1}H NMR (**6**) δ 3.80 (d, 2H, H-6), 4.23 (d, 1H, $J_{4,5}$=11.6 Hz, H-4), 4.43 (td, 1H, $J_{5.6}$ =3.1 Hz, H-5), 4.55 (dd, 2H, $\underline{CH_2}$Ph), 4.60–5.08 (d, 2H, $\underline{CH_2}$Ph), 5.38 (d, 1H, $J_{2,3}$=6.0 Hz, H-2), 7.26–7.38 (m, 11H, H-3 and Ph×2).

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