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PREPARATION AND REDUCTIVE LITHIATION OF 2-DEOXY-D-GLUCOPYRANOSYL PHENYLSULFONES: A HIGHLY STEREOSELECTIVE ROUTE TO C-GLYCOSIDES[1]

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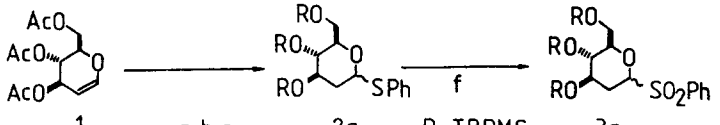
Summary: 2-Deoxy-D-glucopyranosyl phenylsulfones **3a-c** *have been synthesized in 75-83% yield from commercial tri-O-acetyl-D-glucal* **1**. *Their reductive desulfonylation by lithium naphthalenide and reaction of the intermediate glycosyl-lithium* **5** *with aldehydes leads to α-D-C-glucopyranosides with high stereoselectivity.*

Sulfones are now popular intermediates in organic synthesis[2], however α-alkoxysulfones have been rarely used[3]. Their phenylsulfonyl glycosides analogues have already been prepared in a few cases[4] although their chemistry has remained largely unexplored. Recently, considerable attention has been directed to the stereocontrolled preparation of 2,6-disubstituted tetrahydropyrans (C-glycopyranosides) from carbohydrate precursors[5-7] due to the potential usefulness of these structural units in the total synthesis of natural products. In this letter and in the following two[8], we report results that indicate the versatility of 2-deoxy-D-glucopyranosyl sulfones in organic synthesis and more particularly, in the construction of C-glycosides.

Conversion of commercially available 3,4,6-tri-O-acetyl-D-glucal **1** to the thiophenyl glycosides **2a**[9,10] (ratio β:α, 6) was accomplished in 83% yield by hydrochlorination (HCl, toluene, 0 °C, 1 h), treatment of the α chloride with thiophenol (1.5 equiv., $(iPr)_2NEt$, 1.5 equiv., room temperature, 2 h) (Scheme 1), and exchange of protecting groups (MeONa, MeOH, room temperature, 1 h then



1 a,b,c **2a** R=TBDMS **3a**
b,d,a **2b** R=Bn **3b**
b,e,a **2c** R=Me **3c**

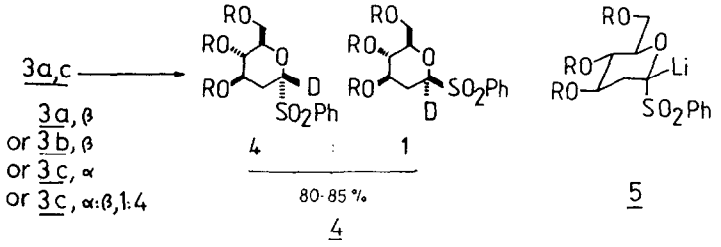
Scheme 1

a) HCl,$PhCH_3$; PhSH, $(iPro)_2NEt$; b) MeONa, MeOH; c) TBDMSCl, Im., DMF; d) BnBr, NaH, DMF; e) MeI, NaH,DMF; f) MCPBA, $NaHCO_3$,CH_2Cl_2.

TBDMSCl, imidazole, DMF, 60 °C, 2 days; 93%). Subsequent oxidation (MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h; quant.) easily afforded the phenylsulfonyl glycosides **3a**[11]. Separation of anomers **3a** (β:α ratio, 6) by crystallization or chromatography is possible[12] but offers no advantage as use of crystalline anomeric mixture is perfectly suitable for developing the chemistry we are interested in. In a similar fashion, phenylsulfonyl 3,4,6-tri-O-benzyl (or 3,4,6-tri-O-methyl)-2-deoxy-α,β-D-

arabino-hexopyranosides **3b** or **3c**[10] (β:α ratio, 10) were prepared from corresponding glycals (see Scheme 1) in overall yields of 77 and 75% respectively.

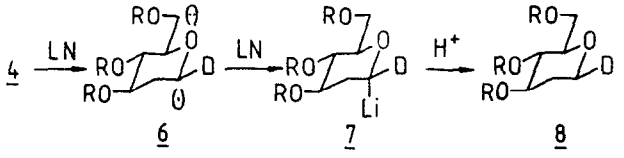
Clean deprotonation of the anomeric phenylsulfones **3a,c** by treatment with n-BuLi or LDA (THF, hexanes, -78 °C, 5 min) was demonstrated by quenching with D_2O (Scheme 2). Regardless



Scheme 2

of the starting mixture, the same anomeric composition of α-deuteriated sulfones **4** was obtained (α:β ratio, 4). Kinetic anions formed by equatorial and (or) axial deprotonation of the corresponding sulfones equilibrate to the more stable species **5** (Scheme 2) in which the lithium anomeric substituent, or the corresponding C^- lone pair, takes an equatorial orientation (anti-anomeric effect).

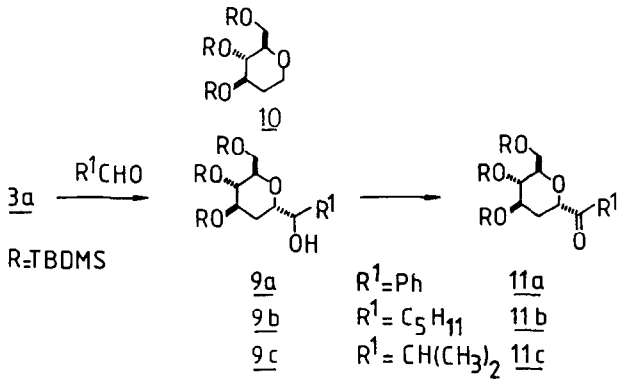
We found that reductive lithiation of the anomeric sulfones **4** *with lithium naphthalenide (LN, 2 equiv., THF, -78 °C, 5 min) was possible leading to a single β-D-(equatorial) deuteriated product* **8**[10] *after hydrolysis* (Scheme 3). The initial homolytic cleavage of the C-S bond in **4** gives σ-radical



Scheme 3

6 in which the half-occupied orbital adopts the configuration shown because of the stabilizing interactions with the axial non-bonding electron pair of the ring oxygen[6b,c,13]. The kinetic glycosyl-lithium **7** obtained by a second electron transfer do not isomerise in the conditions used (THF, -78 °C) and undergo an axial stereoselective introduction of a proton.

A straightforward consequence of this observation is that anomeric sulfones can be used in a stereoselective synthesis of α-D-(axial)C-glycosides using a reductive lithiation-alkylation sequence similar to the one recently reported by this laboratory from α-chloro or α, β-thiophenyl-2-deoxy-D-glucopyranosides[7b]. Thus, treatment of phenylsulfones **3a** with lithium naphthalenide (2 equiv., -78 °C, 3 min) and addition to the transient glycosyl-lithium reagent of benzaldehyde (1.2 equiv., -78 °C) gave the alcohols **9a** (ratio 1:1) in 66% yield and the reduction product **10** (26% yield)[14] (Scheme 4). Similarly, reaction of the lithiated reagent **7** with n-hexanal and iso-butyraldehyde afforded alcohols **9b** (ratio 3:1) and **9c** (ratio 2:1) in 45% and 59% yields respectively. Oxidation (PCC, AcONa, 4 Å molecular sieve, CH_2Cl_2, room temperature, 1 h) of alcohols **9a-c** gave single ketones: **11a**[10] (90%), $[\alpha]_D$ +15°; **11b**[10] (84%), $[\alpha]_D$ -9.5°, **11c**[10] (83%), $[\alpha]_D$ -12°. No equatorial



Scheme 4

isomers were detected by either high resolution ^{1}H-n.m.r. or chromatographic means.

This property of sulfones may prove to be generally useful in a variety of synthetic transformations. We are presently investigating additional applications.

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References and Notes

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9. All new compounds gave satisfactory microanalytical and spectral data. Optical rotations were measured for solutions in $CHCl_3$ at 20 °C. ^{1}H-N.m.r. spectroscopy was performed for $CDCl_3$ solutions at 300 MHz with a Brucker AM-300 WB spectrometer.
10. Selected ^{1}H-n.m.r. data:
2a: β isomer, δ 4.82 (1H, dd, $J_{1,2eq}$ 2.1, $J_{1,2ax}$ 11.5 Hz, H-1); α isomer, δ 5.51 (1H, dd, $J_{1,2eq}$ 3.8, $J_{1,2ax}$ 5.0 Hz, H-1).
2b: β isomer, δ 4.70 (1H, dd, $J_{1,2eq}$ 2.0, $J_{1,2ax}$ 11.3 Hz, H-1); α isomer, δ 5.65 (1H, dd, $J_{1,2eq}$ 1.3, $J_{1,2ax}$ 5.6 Hz, H-1).
2c: β isomer, δ 4.66 (1H, dd, $J_{1,2eq}$ 2.0, $J_{1,2ax}$ 11.5 Hz, H-1); α isomer, δ 5.62 (1H, dd, $J_{1,2eq}$ 1.3, $J_{1,2ax}$ 5.8 Hz, H-1).
3b: β isomer, δ 4.39 (1H, dd, $J_{1,2eq}$ 2.1, $J_{1,2ax}$ 12.0 Hz, H-1); α isomer, δ 4.82 (1H, dd, $J_{1,2'}$ 3.2, $J_{1,2}$ 6.9 Hz, H-1).
3c: β isomer, δ 4.36 (1H, dd, $J_{1,2eq}$ 2.1, $J_{1,2ax}$ 11.5 Hz, H-1); α isomer, δ 4.74 (1H, dd, $J_{1,2'}$ 3.4, $J_{1,2}$ 6.9 Hz, H-1).
8: δ 3.37 (1H, dd, $J_{1,2eq}$ 2.8, $J_{1,2ax}$ 10.2 Hz, H-1ax).
9a: one isomer, δ 4.05 (1H, m, $J_{1,2'}$~$J_{1,CH}$~1, $J_{1,2}$ 11.9 Hz, H-1); other isomer, δ 3.84 (1H, ddd, $J_{1,2'}$ 1, $J_{1,CH}$ 8.1, $J_{1,2}$ 11.3 Hz, H-1).
11a: δ 1.70 (1H, ddd, $J_{1,2'}$ 3.2, $J_{2',3}$ 4.7, $J_{2,2'}$ 13.5 Hz, H-2'); 2.39 (1H, ddd, $J_{2,3}$ 2.9, $J_{1,2}$ 9.5, $J_{2,2'}$ 13.5 Hz, H-2); 5.07 (1H, dd, $J_{1,2'}$ 3.2, $J_{1,2}$ 9.5 Hz, H-1); conformational change in C_6D_6: 4.84 (1H, dd, $J_{1,2'}$ 4.1, $J_{1,2}$ 6.3 Hz, H-1).
11b: δ 1.61 (1H, ddd, $J_{1,2'}$ 3.2, $J_{2',3}$ 5.0, $J_{2,2'}$ 13.2 Hz, H-2'); 2.07 (1H, ddd, $J_{2,3}$ 2.9, $J_{1,2}$ 9.8, $J_{2,2'}$ 13.2 Hz, H-2); 4.20 (1H, dd, $J_{1,2'}$ 3.2, $J_{1,2}$ 9.8 Hz, H-1).
11c: δ 1.64 (1H, ddd; $J_{1,2'}$ 3.4, $J_{2',3}$ 5.1, $J_{2,2'}$ 13.4 Hz, H-2'); 2.10 (1H, ddd, $J_{2,3}$ 3.0, $J_{1,2}$ 9.6 , $J_{2,2'}$ 13.4 Hz, H-2); 4.33 (1H, dd, $J_{1,2'}$ 3.4, $J_{1,2}$ 9.6 Hz, H-1).
11. Direct treatment of the α chloride with tetra-n-butylammoniumsulfinate afforded exclusively the corresponding α-sulfinates (isomeric ratio at sulfur, 1:1).
12. **3a, β isomer**: m.p. 84 °C (from MeOH-H_2O); $[\alpha]_D$ -15°; ^{1}H-n.m.r. data: δ 1.78 (1H, ddd, $J_{2ax,3}$ 10.8, $J_{1,2ax}$ 12.0, $J_{2ax,2eq}$ 12.8 Hz, H-2ax); 2.48 (1H, ddd, $J_{1,2eq}$ 2.0, $J_{2eq,3}$ 5.0, $J_{2ax,2eq}$ 12.8 Hz, H-2eq); 4.40 (1H, dd, $J_{1,2eq}$ 2.0, $J_{1,2ax}$ 12.0 Hz, H-1).
α isomer: m.p. 90 °C (from MeOH), $[\alpha]_D$ +26°, ^{1}H-n.m.r. data: δ 2.00 (1H, dt, $J_{1,2'}$ 4.7, $J_{2',3}$ 4.7, $J_{2,2'}$ 13.5 Hz, H-2'); 2.35 (1H, ddd, $J_{2,3}$ 2.9, $J_{1,2}$ 9.2, $J_{2,2'}$ 13.5 Hz, H-2); 4.77 (1H, dd, $J_{1,2'}$ 4.7, $J_{1,2}$ 9.2 Hz, H-1).
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14. We are currently investigating the precise origin of this side product.

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