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D-GLYCOPYRANOSYL PHENYLSULFONES: THEIR USE IN A STEREOCONTROLLED SYNTHESIS OF CIS-2,6-DISUBSTITUTED TETRAHYDROPYRANS (β-D-C-GLYCOSIDES)[1]

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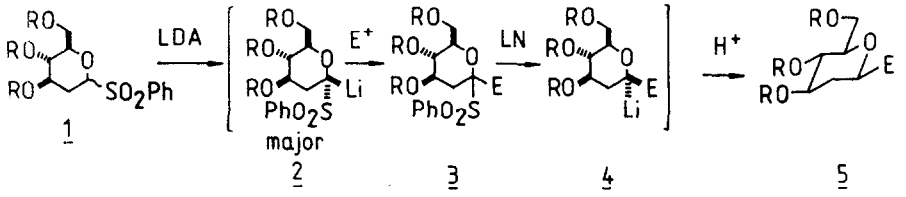
Summary: The lithiated anion derived from 3,4,6-tri-O-t-butyldimethylsilyl-2-deoxy-α, β-D-glucopyranosyl phenylsulfones **1** *reacts with various electrophiles leading to alkylated products, precursors of β-D-C-glycosides* **5a-g** *after stereocontrolled desulfonylation and hydrolysis.*

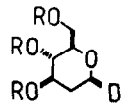
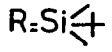
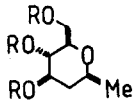
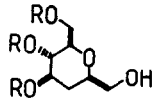
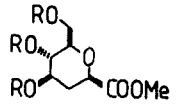
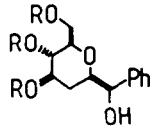
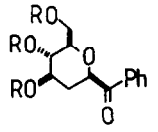
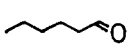
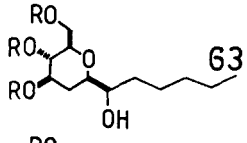
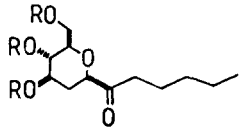
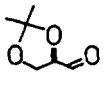
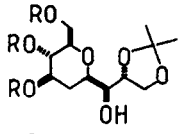
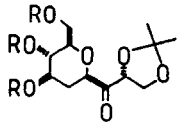
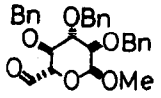
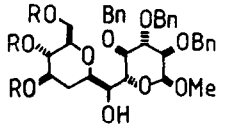
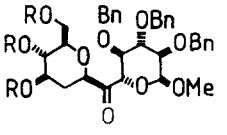
In the preceding communication we demonstrated that i) crystalline 2-deoxy-D-glucopyranosyl phenylsulfones are easily prepared from corresponding glucals, ii) their α-phenylsulfonyl lithiated anions are readily obtained, iii) phenylsulfones undergo a stereoselective reductive desulfonylation by treatment with lithium naphthalenide leading to configurationally stable glycosyl anions[2]. As a consequence of these findings, a combination of anomeric sulfones deprotonation-electrophilic trapping-reductive desulfonylation and proton quenching should provide a novel stereoselective preparation of *cis-2,6-disubstituted tetrahydropyrans (β-D-C-hexopyranosides)* as depicted in the following scheme (scheme 1).



Scheme 1

The lithiated anion of 3,4,6-tri-O-t-butyldimethylsilyl-2-deoxy-α, β-D-glucopyranosyl phenylsulfones[3] (LDA, 1.2 equiv., THF, hexanes, -78 °C, 5 min) reacted with benzaldehyde (1 equiv., 10 min)[4]. *In situ* reductive desulfonylation, (lithium naphthalenide, 2.5 equiv., 10 min) of the alkylated sulfones and hydrolysis of the anomeric anionic species thus produced gave the equatorial D-C-glycosides **5d**[5,6,7] (Table, entry d, 74% overall yield). As indicated in the Table, this one-pot sequence of transformations with other representative aldehydes (entries c-g) and methyl iodide (entry b) gave similar results. When secondary alcohols were produced (**5d-g**), the isomeric mixtures were oxidized (PCC, AcONa, molecular sieve 4Å, CH_2Cl_2, room temperature, 0.5 to 1 h) to single ketones: **6d**[6] (92%), $[\alpha]_D$ -5°; **6e**[6] (91%), $[\alpha]_D$ +22°; **6f**[6] (93%), $[\alpha]_D$ +18°; **6g**[6] (87%), $[\alpha]_D$ +6°. Primary alcohol **5c**[6] was further transformed [i) PCC, DMF, room temperature, 20 h; ii) CH_2N_2, MeOH-ethyl ether; iii) TBDMSCl, imidazole, DMF, room temperature, 8h] to methyl

ester **6c**[6]. As was the case with anomeric sulfones[2], reductive desulfonylation of these tertiary α-phenyl sulfonyl cyclic ethers occurs with a high degree of stereoselectivity although some stereoleakage (β:α ratio, 40) is observed in the case of **5c**.

Entry	Electrophile	5	Yield (%)[a]	6
a	D_2O		80	
b	MeI		43[b]	
c	HCHO		57	
d	PhCHO		74	
e			63	
f			62[c]	
g			51[d]	

a) Not optimized yields obtained after purification of the products;
b) HMPA was added to the alkylation mixture; c) See note 8;
d) The major isomer was further characterized by its hepta-O-acetate derivative.

Table

Diastereofacial selectivity in the addition of α-sulfonyl anion to n-hexanal (1:1), benzaldehyde (3:1) and methyl 6-aldehydo-2,3,4-tri-O-benzyl-α-D-glucopyranoside (entry g, 3:1) was low. Interestingly, the newly-formed exocyclic asymmetric centre in reaction with 1,2-O-isopropylidene-D-glyceraldehyde (entry f) was mostly S[8] (isomer ratio 9:1). The addition of lithium reagents to this aldehyde is well documented[9] and occurs generally with low selectivity. Facial discrimination in this instance most likely results from the asymmetric nature of the lithiated sulfone[10].

In conclusion, kinetic anomeric anions 4 where E=H,D[2], alkyl or CH(OLi)R are configurationally stable at -78 °C (THF, hexanes) thus leading selectively to equatorial D-C-glycosides after hydrolysis. A simple protonation ends the synthetic combination described here. Use of a second alkylation step is feasible and would constitute a stereoselective bis-alkylation of anomeric centres of monosaccharides; a study of this possibility is now in progress[11].

Typical procedure: To a stirred solution of phenylsulfones 1 (0.52 mmol) in anhydrous THF (5ml) under argon at -78 °C was added LDA (0.5M in hexanes, 1.1 ml, 1.05 equiv.) and 1,2-O-isopropylidene-D-glyceraldehyde (0.52 mmol) after 5 min. After an additional 10 min the reaction mixture was then successively treated with freshly prepared lithium naphthalenide (1M in THF, 1.3 mmol; 2.5 equiv., 15 min) and MeOH (2.6 mmol; 5 equiv., 15 min). The crude residue obtained after the usual workup was purified by column chromatography on silica gel (hexanes: diethyl ether, 30:1 then 10:1, 0.1% Et_3N) to provide alcohol **5f** (0.32 mmol, 62%, $[\alpha]_D$ -1°) and its diastereoisomer (0.035 mmol, 6.7%, $[\alpha]_D$ +4°).

References and Notes

1. Part of this work was presented at the 5th International Conference on Organic Synthesis (ICOS 5), Freiburg, August 1984.
2. J.-M. Beau and P. Sinaÿ, Tetrahedron Lett., preceding paper in this issue.
3. For their preparation, see Reference 2; an anomeric mixture (β:α ratio, 6) of starting sulfones was used routinely.
4. It would have been interesting to study the stereochemistry of the alkylation reaction; unfortunately isolation at this stage turned out to be troublesome. See also Note 7.
5. 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 in $CDCl_3$ solutions at 300 MHz with a Brucker AM-300WR spectrometer.
6. Selected ^{1}H-n.m.r. data:

5b: δ 1.31 (1H, m, $J_{2ax,3}$ 11.2, $J_{1,2ax}$ 11.5, $J_{2ax,2eq}$ 12.9 Hz, H-2ax); 1.88 (1H, ddd, $J_{1,2eq}$ 2.0, $J_{2eq,3}$ 4.9, $J_{2ax,2eq}$ 12.9 Hz, H-2eq); 3.49 (1H, m, $J_{1,2eq}$ 2.0, J_{1,CH_3} 6.0, $J_{1,2ax}$ 11.5 Hz, H-1).

5c: δ 1.39 (1H, dt, $J_{2ax,3}$ = $J_{1,2ax}$ 11.2, $J_{2ax,2eq}$ 13.1 Hz, H-2ax); 1.81 (1H, ddd, $J_{1,2eq}$ 1.5, $J_{2eq,3}$ 4.9, $J_{2ax,2eq}$ 13.1 Hz, H-2eq); 3.54 (1H, m, $J_{1,2eq}$ 1.5, $J_{1,CH}$ 7.8, $J_{1,CH}$ 9.8, $J_{1,2ax}$ 11.2 Hz, H-1).

6c: δ 1.61 (1H, m, $J_{2ax,3}$ 9.9, $J_{1,2ax}$ 12.1, $J_{2ax,2eq}$ 12.9 Hz, H-2ax); 2.21 (1H, ddd, $J_{1,2eq}$ 2.4, $J_{2eq,3}$ 4.9, $J_{2ax,2eq}$ 12.9 Hz, H-2eq); 4.02 (1H, dd, $J_{1,2eq}$ 2.4, $J_{1,2ax}$ 12.1 Hz, H-1).

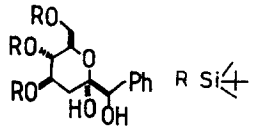
6d: δ 1.81 (1H, m, $J_{2ax,3}$ 11.2, $J_{1,2ax}$ 11.5, $J_{2ax,2eq}$ 13.4 Hz, H-2ax); 2.27 (1H, ddd, $J_{1,2eq}$ 2.5, $J_{2eq,3}$ 4.8, $J_{2ax,2eq}$ 13.4 Hz, H-2eq); 4.58 (1H, dd, $J_{1,2eq}$ 2.5, $J_{1,2ax}$ 11.5 Hz; H-1).

6e: δ 1.39 (1H, m, $J_{2ax,3}$ 11.0, $J_{1,2ax}$ 12.1, $J_{2ax,2eq}$ 13.1 Hz, H-2ax); 2.18 (1H, ddd, $J_{1,2eq}$ 2.4, $J_{2eq,3}$ 4.8, $J_{2ax,2eq}$ 13.1 Hz, H-2eq); 3.79 (1H, dd, $J_{1,2eq}$ 2.4, $J_{1,2ax}$ 12.1 Hz, H-1).

6f: δ 1.41 (1H, m, $J_{2ax,3}$ ~11.5, $J_{1,2ax}$ 12.1, $J_{2ax,2eq}$ 13.5 Hz, H-2ax); 2.30 (1H, ddd, $J_{1,2eq}$ 2.4, $J_{2eq,3}$ 4.9, $J_{2ax,2eq}$ 13.5 Hz, H-2eq); 4.03 (1H, dd, $J_{1,2eq}$ 2.4, $J_{1,2ax}$ 12.1 Hz, H-1).

6g: δ 1.50 (1H, m, $J_{2'ax,3'}$ 11.0, $J_{1',2'ax}$ 11.9, $J_{2'ax,2'eq}$ 13.1 Hz, H-2'ax); 2.14 (1H, ddd, $J_{1',2'eq}$ 2.2, $J_{2'eq,3}$ 4.9, $J_{2'ax,2'eq}$ 13.1 Hz, H-2'eq); 3.91 (1H, dd, $J_{1',2'eq}$ 2.2, $J_{1',2'ax}$ 11.9 Hz, H-1').

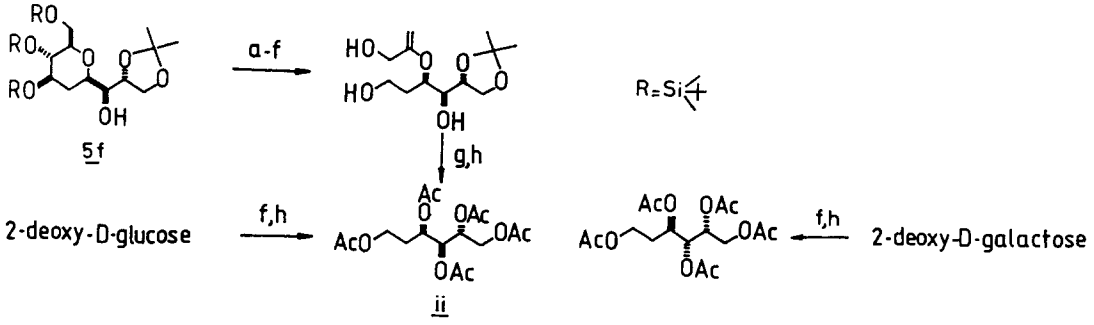
7. In this case, the hemiketal i (12%) was also isolated. Compound i was the major structure



i

identified among other degradation products when isolation of intermediate alkylated sulfones was attempted. A base-induced elimination of phenylsulfinic acid is assumed followed by hydration of intermediate enol. See also Reference 11. A similar solvolytic replacement of a nitro group by a hydroxy group in tertiary carbohydrate nitro ethers was observed. See B. Aebischer, J. H. Bieri, R. Prewo and A. Vasella, Helv. Chim. Acta, 65, 2251 (1982).

8. The absolute configuration at the exocyclic asymmetric centre (and, if necessary, the one at the anomeric carbon) was firmly established by degradation of compound **5f** to 2-deoxy-hexitol acetate **ii** and by comparison (300 MHz ^{1}H-n.m.r., optical rotation) with authentic samples derived from 2-deoxy-D-glucose and 2-deoxy-D-galactose as shown on the following scheme.



ii

a) Bu_4NF, THF; b) TsCl, pyridine, 1 equiv., CH_2Cl_2, 0 °C; c) NaI, DMF, 70 °C; d) DBU, THF, 70 °C; e) $NaIO_4$, MeOH; f) $NaBH_4$, MeOH; g) HCl, MeOH, H_2O; h) Ac_2O, pyridine.

9. See for example G. J. McGarvey, M. Kimura, T. Oh, and J. M. Williams, J. Carbohydr. Chem., 3, 125 (1984) and references cited.
10. We are currently evaluating the degree of diastereoselectivity obtained by reaction of the lithiated sulfone with 1,2-O-isopropylidene-L-glyceraldehyde and other enantiomeric pairs.
11. Synthetic transformations using the lithiated anion of 2-benzenesulfonyl tetrahydropyran appeared in print during the preparation of this manuscript. See S. V. Ley, B. Lygo and A. Wonnacott, Tetrahedron Lett., 26, 535 (1985).

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