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D-GLYCOPYRANOSYL PHENYLSULFONES: ACYLATION OF THEIR LITHIATED ANIONS AND REDUCTIVE DESULFONYLATION OF THE RESULTING ACYLATED SULFONES. A SYNTHESIS OF α-D-C-GLYCOSIDES

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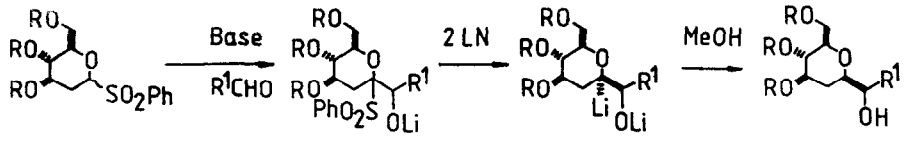
Summary: The lithiated anion of 3,4,6-tri-O-t-butyldimethylsilyl-2-deoxy-α,β-D-glucopyranosyl phenylsulfone reacts with dimethylcarbonate and various phenyl esters to give stable acylated products. Subsequent reductive lithiation leads to enolates which undergo kinetic protonation to afford selectively α-D-C-glucosides.

In the preceding paper[1], we established that coupling reaction between lithiated anions derived from 2-deoxy-D-glucopyranosyl sulfones and aldehydes (or primary iodides) leads to unstable tertiary sulfones **2** which are stereoselectively desulfonylated *in situ* to produce, after protonation, various simple or complex β-D-C-glucosides **4** (Scheme 1). The selectivity observed lies on the configurational

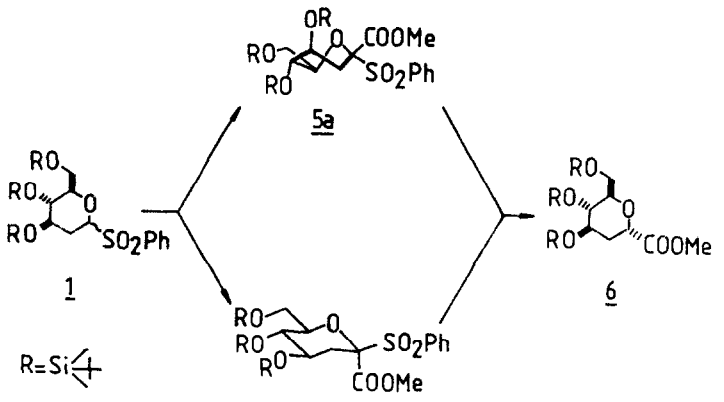


Scheme 1

stability[2] of the kinetic anion **3** formed during the course of the desulfonylation by lithium naphthalenide (LN). This transient dianionic species **3** is then hydrolyzed with axial introduction of a proton. We now describe the same sequence of reactions from anomeric sulfones **1** (sulfone deprotonation, electrophilic trapping, desulfonylation and protonation) using carboxylic acid derivatives as electrophiles with the anticipation that the overall stereochemical outcome could possibly be different.

Treatment of 3,4,6-tri-O-t-butyldimethylsilyl-2-deoxy-α,β-D-glucopyranosyl phenylsulfone **1** with LDA (1.2 equiv., THF-hexanes, -78 °C, 5 min) followed by dimethylcarbonate (1.3 equiv., - 78 to 0 °C, 1 h) and hydrolysis (NH_4Cl, 0 °C) provided the stable tertiary carboxymethylated sulfones **5a,b**[5,6] (93% yield, isomeric ratio **5a:5b**, 20:1) (Scheme 2). Configurational assignment at the tertiary carbon atom was based on the observed preference of α-D-phenylsulfonyl group to adopt an equatorial orientation[7]. Thus, from ^{1}H-n.m.r. spectroscopy, $J_{3,4}$ and $J_{4,5}$ of 8.2 and 8.8 Hz, respectively, for the minor isomer **5b** indicates that H-4 is mainly axial as would be expected in a $^4C_1$ (D) conformation[6]. The major isomer **5a** shows $J_{3,4}$ and $J_{4,5}$ of 2.0 and 7.6 Hz, respectively (H-4 mainly equatorial). Furthermore a $J_{2,4}$ value of 1.2 Hz is observed which points to a preferred $^OS_2$ (D) conformer in **5a**[6]. These results are consistent with the steric demand of the bulky phenylsulfonyl group[8] which tends to be equatorial in **5b** [$^4C_1$ (D) conformation] and **5a** [$^OS_2$ (D) conformation] and dominates the steric effect of the carboxymethyl group[9]. Desulfonylation of **5a,b** by LN (THF, -100 °C, 10 min) and proton quenching (MeOH, 5 equiv., -78 °C) gave selectively the α-D-C-glycoside **6**[10] (78%,

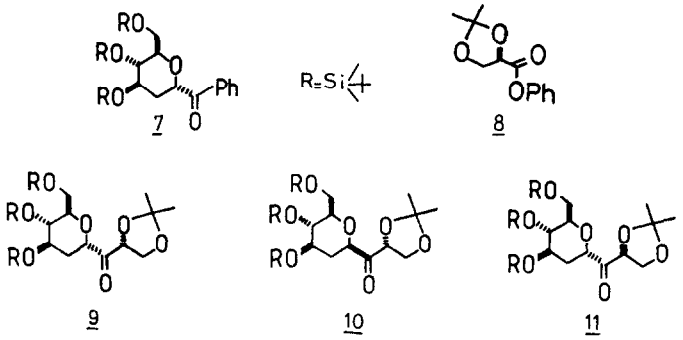
Scheme 2



5b

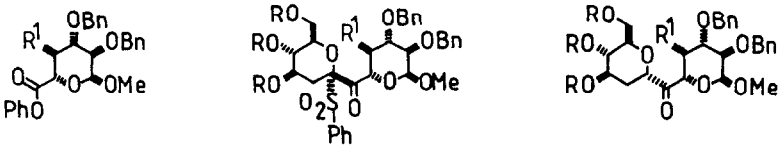
α:β ratio, 20:1). This sequence performed in a one-pot procedure from starting phenylsulfones **1** gave identical stereochemical results (72% overall yield).

The use of phenyl esters as acylating agents proved to be particularly convenient. Thus, ketone **7**[11] (72% yield, α:β ratio, 10:1) was obtained by the same one-pot sequence of reactions using phenyl benzoate (1 equiv.) as electrophile. Similarly, coupling reaction between lithiated sulfone[12] and phenyl



1,2-O-isopropylidene-D-glycerate **8**[13] gave the expected ketone **9**[10] (65.5%, $[\alpha]_D$ +1°), the previously described[1] β-D-C-glycoside **10** (3.1%) and the isomerised ketone **11** (2.4%)[10] (**9**:**10**:**11** ratio, 27:1.3:1).

Acylation of lithiated sulfone by phenyl (methyl 2,3-di-O-benzyl-4-deoxy-α-D-xylo-hexopyranosid)uronate **12** (1 equiv.) and phenyl (methyl 2,3,4-tri-O-benzyl-α-D-glucopyranosid)uronate **13**[15] (1 equiv.) proceeds well to give acylated sulfones **14**[10] (65% yield) and **15**[10] (70% yield)[16]. However,



12 R^1=H
13 R^1=OBn

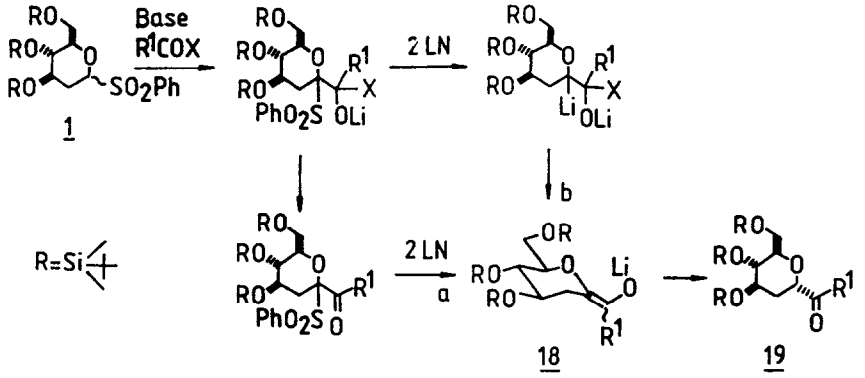
14 R^1=H
15 R^1=OBn

16 R^1=H
17 R^1=OBn

reductive desulfonylation by LN (same conditions) or by other reductive methods (Na(Hg), MeOH-AcOEt, Na_2HPO_4[17]) of **14** or **15** gave poor results, only limited amounts (10-30%) of the expected C-glycosides **16** and **17** being isolated[18].

The stereochemical outcome in the alkylation of metalated sulfones is ignored in most synthetic

applications as the sulfone group is readily removed. The acylation step described here shows good selectivity (from 20:1 to over) not relevant in this work but of interest for other transformations. The results are in agreement with the supposed structure of the lithiated sulfone[7,19]. The selective formation of α-D-C-glycosides following sulfone removal can probably be explained by the formation of the enolate **18** after reductive lithiation by LN either by enolization (desulfonylation on isolated



β-keto sulfone, path **a**) or by phenoxide (or methoxide) expulsion (one-pot procedure, path **b**). Ketonization by the subsequent approach of the proton donor from the exo side of the enol leads to the kinetically preferred α-product **19**[21].

References and Notes

1. J.-M. Beau and P. Sinaÿ, Tetrahedron Lett., preceding paper in this issue.
2. Configurational stability of **3** refers to precise experimental conditions (THF, -78 °C). Due to the high chemical unstability of anomeric anions[3,4], no attempts have been made to isomerize anionic species **3** to a more stable isomer.
3. J.-M. Lancelin, L. Morin-Allory and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 355 (1984).
4. P. Lesimple, J.-M. Beau and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 894 (1985).
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. **5a**: m.p. 107 - 112 °C (from MeOH); $[\alpha]_D$ +42°; selected ^{1}H-n.m.r. data: δ 2.72 (1H, ddd, $J_{2,4}$ 1.2, $J_{2,3}$ 4.4, $J_{2,2'}$ 14.4 Hz, H-2); 2.78 (1H, dd, $J_{2',3}$ 2.8 $J_{2,2'}$ 14.4 Hz, H-2'); 3.78 (1H, ddd, $J_{2,4}$ 1.2, $J_{3,4}$ 2.0, $J_{4,5}$ 7.6 Hz, H-4).
   5b: m.p. 135 °C (from MeOH); $[\alpha]_D$ +12°; selected ^{1}H-n.m.r. data: δ 2.14 (1H, dd, $J_{2ax,3}$ 10.8, $J_{2ax,2eq}$ 12.9 Hz, H-2ax); 2.90 (1H, dd, $J_{2eq,3}$ 4.3, $J_{2ax,2eq}$ 12.9 Hz, H-2eq); 3.50 (1H, dd, $J_{3,4}$ 8.2, $J_{4,5}$ 8.8 Hz, H-4).
7. Reference 9 in J.-M. Beau and P. Sinaÿ, Tetrahedron Lett., first paper in this issue.
8. E.L. Eliel and D. Kandasamy, J. Org. Chem., 41, 3899 (1976). The value given for the conformational free energy of a phenylsulfonyl group in a cyclohexane ring (-ΔG° of 2.5 kcal/mol) should be higher for the same substituent at position 2 in a tetrahydropyran ring[9].
9. E.L. Eliel, K.D. Hargrave, K.M. Pietrusiewicz and M. Manoharan, J. Am. Chem. Soc., 104, 3635 (1982).
10. Selected ^{1}H-n.m.r. data: (All following compounds have the numbering system for a 2-deoxy-D-gluco unit)
    6: δ 1.72 (1H, ddd, $J_{1,2}$ 3.2, $J_{2,3}$ 5.3, $J_{2,2'}$ 13.1 Hz, H-2); 2.23 (1H, dd, $J_{2',3}$ 2.8, $J_{1,2'}$ 9.4, $J_{2,2'}$ 13.1 Hz, H-2'); 4.45 (1H, dd, $J_{1,2}$ 3.2, $J_{1,2'}$ 9.4Hz, H-1).

9: δ 1.72 (1H, ddd, $J_{1,2}$ 3.0, $J_{2,3}$ 4.2, $J_{2,2'}$ 13.2 Hz, H-2); 2.06 (1H, ddd, $J_{2',3}$ 2.6, $J_{1,2'}$ 10.8, $J_{2,2'}$ 13.2 Hz, H-2'); 4.47 (1H, dd, $J_{1,2}$ 3.0, $J_{1,2'}$ 10.8 Hz, H-1).

11: δ 1.75 (1H, ddd, $J_{1,2}$ 3.0, $J_{2,3}$ 4.2, $J_{2,2'}$ 13.6 Hz, H-2); 1.99 (1H, ddd, $J_{2',3}$ 2.7, $J_{1,2'}$ 10.9, $J_{2,2'}$ 13.6 Hz, H-2'); 4.43 (1H, dd, $J_{1,2}$ 3.0, $J_{1,2'}$ 10.9 Hz, H-1).

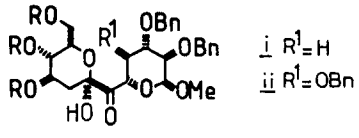
14: δ 2.15 (1H, dd, $J_{2,3}$ 6.4, $J_{2,2'}$ 14.6 Hz, H-2); 2.82 (1H, dd, $J_{2',3}$ 3.2, $J_{2,2'}$ 14.6 Hz, H-2'); 3.59 (1H, dd, $J_{3,4}$ 3.9, $J_{4,5}$ 8.5 Hz, H-4).

15: δ 2.47 (1H, dd, $J_{2,3}$ 9.0, $J_{2,2'}$ 14.5 Hz, H-2); 2.96 (1H, dd, $J_{2',3}$ 4.5, $J_{2,2'}$ 14.5 Hz, H-2'); 3.13 (1H, dd, $J_{3,4}$ 6.6, $J_{4,5}$ 9.0 Hz, H-4).

16: δ 1.74 (1H, ddd, $J_{1,2}$ 2.6, $J_{2,3}$ 3.7, $J_{2,2'}$ 13.1 Hz, H-2); 1.99 (1H, ddd, $J_{2',3}$ 2.6, $J_{1,2'}$ 11.2, $J_{2,2'}$ 13.1 Hz, H-2'); 4.57 (1H, dd, $J_{1,2}$ 2.6, $J_{1,2'}$ 11.2 Hz, H-1).

17: δ 1.53 (1H, ddd, $J_{1,2}$ 2.9, $J_{2,3}$ 4.9, $J_{2,2'}$ 13.2 Hz, H-2); 2.10 (1H, ddd, $J_{2',3}$ 2.9, $J_{1,2'}$ 9.9, $J_{2,2'}$ 13.2 Hz, H-2'); 4.51 (1H, dd, $J_{1,2}$ 2.9, $J_{1,2'}$ 9.9 Hz, H-1).

11. **7** was identical to ketone **11a** described in reference 7.
12. In this reaction, n-BuLi was used for sulfone deprotonation.
13. Phenyl 1, 2-O-isopropylidene-D-glycerate **8** ($[\alpha]_D$ +7.4°) was prepared in a 71% overall yield from 1,2-O-isopropylidene-D-glyceraldehyde by i) $KMnO_4$, KOH, water, room temperature[14], ii) $(COCl)_2$, THF, room temperature, 2h and iii) PhOH, pyridine, THF, room temperature, 1 h.
14. A. Tanaka and K. Yamashita, Agric. Biol. Chem., 44, 199 (1980).
15. Phenyl esters **12** ($[\alpha]_D$ +45°) and **13** ($[\alpha]_D$ +12°) were prepared from the corresponding alcohols in 59 and 55% overall yield, respectively by i) Jones oxidation, room temperature, ii) $(COCl)_2$, THF, pyridine, 0°, 30 min and iii) PhOH, pyridine, THF, room temperature, 30 min.
16. Only one isomer could be detected in both cases. The configurations at the quaternary carbon atom shown in **14** and **15** were proposed by comparing their ^{1}H-n.m.r. spectra with that of methyl ester **5a**.
17. M. Julia and J.-M. Paris, Tetrahedron Lett., 4833 (1973); B.M. Trost, H.C. Arndt, P.E. Strege and T.R. Verhoeven, Tetrahedron Lett., 3477 (1976).
18. Among other degradation products, hemi-ketals i and ii were isolated.



We have some indications, although not yet proven, that the usual homolytic cleavage of the C-1'-S bond leading to the expected products compete with the S-Ph cleavage. Further hydrolysis of the sensitive sulfonate thus produced would then give compounds i and ii. More experimentation is necessary to clarify this point.

19. The planar or tetrahydral nature of a carbanion stabilized by a sulfone group is still an unsettled problem. Important synthetic studies involving alkylation of lithiated allyl sulfones[20] strongly suggest these organometallic species to be pyramidal rather than planar. In our studies, lithiated anomeric sulfones are considered pyramidal.
20. B.M. Trost and N.R. Schmuff, J. Am. Chem. Soc., 107, 396 (1985).
21. Kinetic protonation or electrophilic attack of the exo-enolic moiety of conformationally biased six-membered ring compounds is under the control of steric factors which favors an exo (equatorial) approach[22]. Additional influence of electronic factors is not completely ruled out in our case.
22. H.E. Zimmerman and L.W. Linder, J. Org. Chem., 50, 1637 (1985) and references cited; H.O. House, B.A. Tefertiller and H.D. Olmstead, J. Org. Chem., 33, 935 (1968); H.O. House and B.M. Trost, J. Org. Chem., 30, 2502 (1965).

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