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CONVENIENT SYNTHESES OF SUBSTITUTED PYRANOID GLYCALS FROM THIOPHENYL GLYCOSIDES AND GLYCOSYL PHENYLSULFONES[1]

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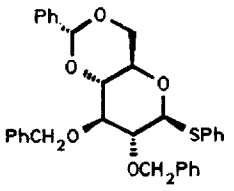
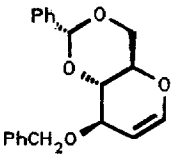
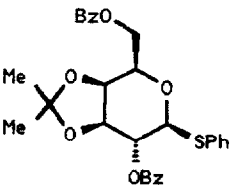
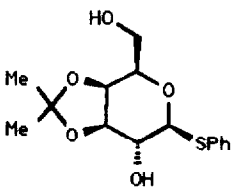
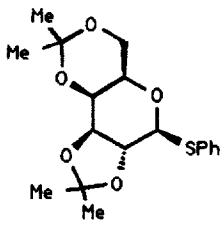
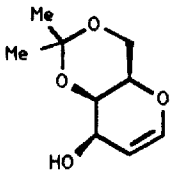
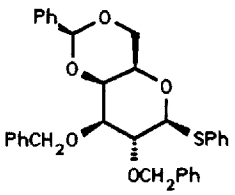
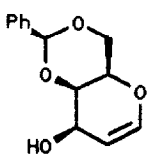
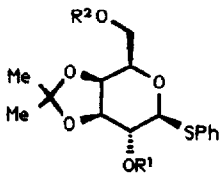
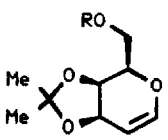
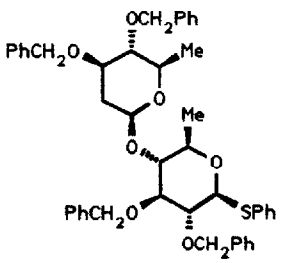
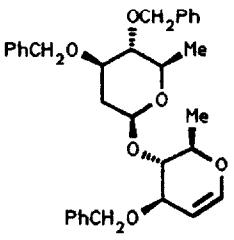
Abstract: A series of substituted thiophenyl glycosides and glycosyl phenylsulfones were converted in high yield into glycals after reductive lithiation with lithium naphthalenide, followed by elimination of the substituent at C-2.

Pyranoid glycals are useful intermediates in synthetic carbohydrate chemistry[2], especially as precursors of glycosyl donors[3]. An interesting method for their preparation involved the formation of an unstable C-1 anion from a *glycosyl halide*, either with lithium in liquid ammonia[4], or with sodium naphthalenide in tetrahydrofuran at room temperature[5], followed by a fast β-elimination of the C-2 leaving group.

Thiophenyl glycosides offer efficient temporary protection of the anomeric center and are *stable* under a variety of reaction conditions (acylation, alkylation, acetal formation). They have thus attracted considerable attention, especially as glycopyranosyl donors in oligosaccharide syntheses[6]. The already observed[7] reductive lithiation of a sulfide suggests an attractive possibility[8] of circumventing the preparation of a glycosyl halide as an intermediate to the synthesis of a glycal. We would like to report several new, direct and highly efficient conversions of various thiophenyl glycosides--or the corresponding glycosyl phenylsulfones--into glycals, which are compatible with *both* acid and base labile protecting groups.

When a thiophenyl glycoside was treated with lithium naphthalenide (LN) (2 equiv.) in THF at -78°C, the corresponding glycal was usually obtained in high yield (see Table I)[10]. The interest of this procedure is outlined by the smooth conversion of disaccharide **9** into the glycal **17**, an intermediate in the synthesis of orthosomycin fragments[18]. The sensitivity of the 2'-deoxy glycosidic linkage in **9** precludes the use of acidic conditions, and the presence of benzyl ethers calls for a selective reductive system. Diacetate **5** was also converted into glycal **14**, a result which enlarges the scope of the method. This is in sharp contrast with the behavior of the dibenzoate **7**, where no trace of galactal was isolated as a result of a selective electron transfer on the benzoyl group at C-2. In the case of **8**, concomitant *O*-debenzylation could not be avoided so that the allylic alcohol **16** was obtained.

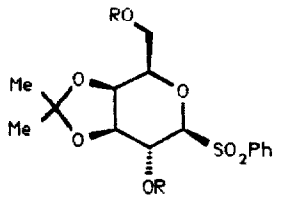
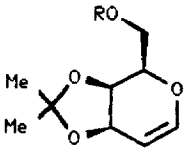
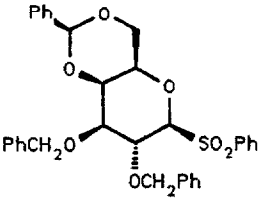
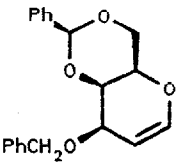
Table I. Conversion of thiophenyl glycosides into glycals[a].

Substrate	Product[17] (yield %)	Substrate	Product (yield %)
			
1[11]	10 (98)	7[13]	15[14] (58)
			
2[12]	11 (85)	8[11]	16 (75)
			
3[13] $R^1 = R^2 = CH_2Ph$ 4[13] $R^1 = R^2 = Me$ 5[13] $R^1 = R^2 = Ac$ 6[15] $R^1 = CH_2Ph, R^2 = H$	12 R = CH_2Ph (97) 13 R = Me (96) 14 R = H (68) 14 R = H (92)	9[16]	17 (92)

[a]Conditions: 2.0 equiv. of a 1*M* LN solution in THF, THF, - 78°C. In the case of substrate 1, 3 and 9, the reaction mixture was stirred for 30 min at -78°C after disappearance of the starting material (t.l.c.), then neutralized at -78°C (THF-acetic acid, 4:1), to avoid *O*-debenzylation. In other instances, the reaction mixture was neutralized at room temperature. In case of unavoidable concomitant cleavage of protecting groups (reductive lithiations of 5 and 8), the amount of LN to be used will be higher than 2 equiv. (control of the reaction by t.l.c.).

As anomeric phenylsulfones are known to undergo fast reductive lithiation[19], an extension of the reaction for the preparation of glycals has now been developed (see Table II).

Table II. Conversion of glycosyl phenylsulfones into glycals[a]

Substrate	Product (yield %)	Substrate	Product (yield %)
			
18[20] R = CH_2Ph **19**[20] R = Me **20**[20] R = Bz	**12** R = CH_2Ph (95) **13** R = Me (85) **14** R = H (82)	**21**[20]	**22** (30)[22]

[a] Conditions: see Table I (more than 2 equiv. of LN were used for the conversion of **20** into **14**).

References and notes

1 Part of this work was presented at the 14th International Carbohydrate Symposium, Stockholm (Sweden), (1988) B35, p. 189.

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6 For a review see: P. Fügedi, P.J. Garegg, H. Lönn and T. Norberg, Glycoconjugate J., 4, 97 (1987).

7 C.G. Screttas and M. Micha-Screttas, J. Org. Chem., 43, 1064 (1978).

8 Indeed, treatment of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside with LN (2 equiv., THF, -78°C, 15 min) resulted[9] in the *quantitative* formation of 3,4,6-tri-*O*-benzyl-D-glucal.

9 J.-M. Lancelin, L. Morin-Allory and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 355 (1984).

10 All new compounds gave satisfactory microanalytical and spectral data. Optical rotations were measured for solutions in $CHCl_3$ at 20°C.

11 A. Liptàk, I. Jodál, J. Harangi, and P. Nánási, Acta Chim. Hung., 113, 415 (1983).

12 **2** (m.p. 101-103°C (hexane), $[\alpha]_D$ -66°) was prepared (95%) from phenyl 1-thio-β-D-galactopyranoside (2-methoxypropene, DMF, CSA, 1 h, 20°C).

13 **3** (m.p. 61-62°C (hexane), $[\alpha]_D$ -22°); **4** ($[\alpha]_D$ -23°); **5** ($[\alpha]_D$ +32°) and **7** (m.p. 129-131°C (EtOH), $[\alpha]_D$ +29°) were routinely prepared (95%) from phenyl 3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside **15**[14].

14 G. Catelani, F. Colonna and A. Marra, Carbohydr. Res., **182**, 297 (1988).

15 **6** ($[\alpha]_D$ -1.5°) was prepared in 59% yield from phenyl 1-thio-β-D-galactopyranoside by *i*) dimethoxypropane, CSA, 48 h, 20°, *ii*) $PhCH_2Br$, NaH, THF, 2 h, 45°C, *iii*) MeOH, CSA, 10 min, 20°C.

16 M. Trumtel, A. Veyrières and P. Sinaÿ, Tetrahedron Lett., first paper in this issue.

17 Selected data:
10: m.p. 101-102°C (hexane), $[\alpha]_D$ -41°; ^{1}H-n.m.r. (C_6D_6): δ 6.12 (1 H, dd, $J_{1,2}$ 6.2, $J_{1,3}$ 1.6 Hz, H-1).
11: m.p. 48-50°C, $[\alpha]_D$ +18°; ^{1}H-n.m.r. (C_6D_6): δ 6.31 (1 H, dd, $J_{1,2}$ 6.2, $J_{1,3}$ 1.8 Hz, H-1).
12: $[\alpha]_D$ +18°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.45 (1 H, d, $J_{1,2}$ 6.4 Hz, H-1).
13: $[\alpha]_D$ +19°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.49 (1 H, d, $J_{1,2}$ 6.2 Hz, H-1).
14: $[\alpha]_D$ +28°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.49 (d, 1 H, $J_{1,2}$ 6.1 Hz, H-1).
16: m.p. 151-152°C (AcOEt-hexane) $[\alpha]_D$ +47°; ^{1}H-n.m.r.($CDCl_3$): δ 6.48 (1 H, dd, $J_{1,2}$ 6.8, $J_{1,3}$ 2.0 Hz, H-1).
17: m.p. 80-83°C (AcOEt-hexane), $[\alpha]_D$ -45°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.40 (1 H, dd, $J_{1,2}$ 6.0, $J_{1,3}$ 1.0 Hz, H-1).
22: $[\alpha]_D$ +122°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.55 (1 H, dd, $J_{1,2}$ 6.5, $J_{1,3}$ 2.0 Hz, H-1).

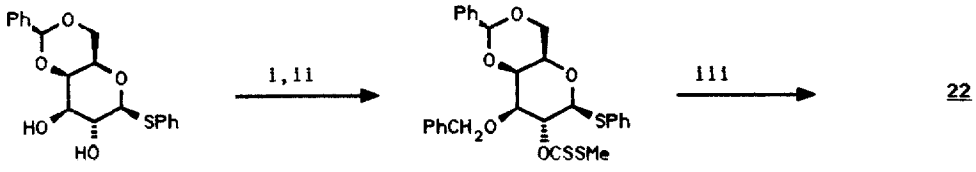
18 M. Trumtel, A. Veyrières and P. Sinaÿ, 14th International Carbohydrate Symposium, Stockholm (Sweden), (1988) B36, p. 190.

19 J.-M. Beau and P. Sinaÿ, Tetrahedron Lett., **26**, 6185 (1985).

20 We found that thiophenyl glycosides are quantitatively converted into sulfones in the presence of sodium periodate and a catalytic amount of ruthenium trichloride, in a biphasic system CCl_4-H_2O-CH_3CN[21].
18: $[\alpha]_D$ +5°; ^{1}H-n.m.r. ($CDCl_3$): δ 4.47 (1 H, d, $J_{1,2}$ 7.5 Hz, H-1).
19: m.p. 125-126°C (EtOH), $[\alpha]_D$ -3°; ^{1}H-n.m.r. ($CDCl_3$): δ 4.28 (1 H, d, $J_{1,2}$ 7.5 Hz, H-1).
20: m.p. 220-221°C (AcOEt-hexane), $[\alpha]_D$ +35°; ^{1}H-n.m.r. ($CDCl_3$): δ 4.66 (1 H, d, $J_{1,2}$ 9.0 Hz, H-1).
21: m.p. 164-166°C (EtOH), $[\alpha]_D$ -3°; ^{1}H-n.m.r. ($CDCl_3$): δ 4.55 (1 H, d, $J_{1,2}$ 9.5 Hz, H-1).

21 P.H.J. Carlsen, T. Katsuki, V.S. Martin and K.B. Sharpless, J. Org. Chem., **46**, 3936 (1981).

22 A severe side reaction was a fast deprotonation of the medium by the strongly basic C-1 anion leading to 1,5-anhydro-2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactitol (<46%, m.p. 95-97°C (AcOEt-hexane), $[\alpha]_D$ +76°>. This limited yield was increased by using the following radical reductive elimination:



i) Bu_2SnO, CH_3CN, 12 h, reflux, then, $Bu_4N^+Br^-$, $PhCH_2Br$, 1 h, reflux (70%); *ii*) CS_2, NaH, THF, ICH_3, 1 h, 25°C (79%); *iii*) Bu_3SnH, AIBN, $PhCH_3$, reflux, 10 min (90%).
To our knowledge, this represents the first example of the synthesis of a glycal[23] by a neutral radical process and is complementary to existing methods.

23 Radical reductive elimination has been applied to the synthesis of vinyl ethers, J.-M. Vatele, Tetrahedron Lett., **25**, 5997 (1984).

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