A Convenient Synthesis of Pyranoid Ene Lactones from Phenyl Glycosyl Sulfones

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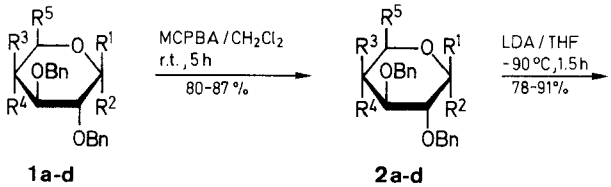
Dedicated to Prof. Bestmann on the occasion of his 65th birthday

O-Benzyl protected pyranoid ene lactones (5,6-dihydro-2*H*-pyran-2-ones) **4a–c, 8** were obtained in high yield in a two-step procedure. Treatment of the phenyl glycosyl sulfones **2a–d, 6**, which were readily prepared from their corresponding sulfides, with lithium diisopropylamide (LDA) at −90 °C afforded the elimination products **3a–c, 7**. These intermediates were then treated with sodium methoxide in the presence of dicyclohexano-18-crown-6 to give the compounds **4a–c, 8**.

Pyranoid ene lactones (2,3-dideoxyhex- and -pent-2-enono-1,5-lactones) represent a class of simple sugar compounds that are of considerable synthetic utility as many natural products possess α,β-unsaturated δ-lactone moieties.[1,2] There are various methods known for the preparation of this type of compound from monosaccharides; the majority resort to direct oxidation of glycals[3] or their allylic rearrangement and subsequent oxidation.[4–7] Recently Lichtenthaler and co-workers[8] reported a similar method, in which boron trifluoride-catalyzed peroxidation of glycals afforded such dihydropyran-2-ones in high yield. Herein we report a new and convenient method for the synthesis of pyranoid ene lactones from phenyl glycosyl sulfones.

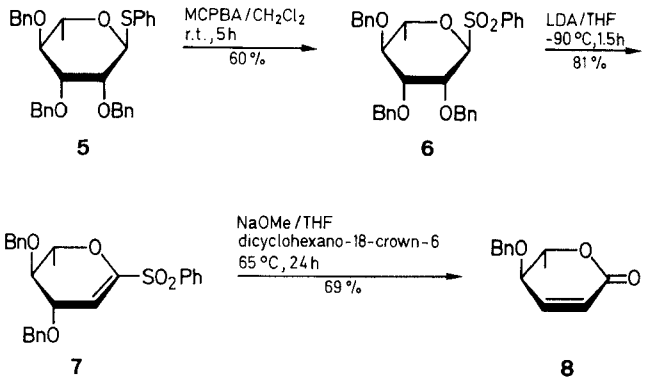
O-Benzyl protected phenyl glycosyl sulfones **2a–d, 6** (Schemes **A** and **B**) are readily obtained from the corresponding *S*-phenyl 1-thio-glycopyranosides **1a–d, 5**,[9,10] of D-glucose, D-galactose, D-xylose, and L-rhamnose, respectively, by oxidation with 3-chloroperoxybenzoic acid (MCPBA) at room temperature. Compounds **2a–d, 6** are treated with one equivalent of lithium diisopropylamide (LDA) at −90 °C to give the phenylsulfonyl glycals **3a–c** and **7** in 78–91% yields (**3c** was obtained from **2c** or **2d**). The intermediates **3a–c** and **7** are also of interest in direct 2-*C*-lithiation of glycals.[11] Treatment of these phenylsulfonyl glycals with sodium methoxide in presence of dicyclohexano-18-crown-6 in THF at reflux for 12–24 h afforded directly the required pyranoid ene lactones **4a–c, 8** in 63–93% yields (see Tables 1, 2, 3).



1	R^1	R^2	2	R^1	R^2
a	SPh	H	a	SO_2Ph	H
b	SPh	H	b	SO_2Ph	H
c	SPh	H	c	SO_2Ph	H
d	H	SPh	d	H	SO_2Ph

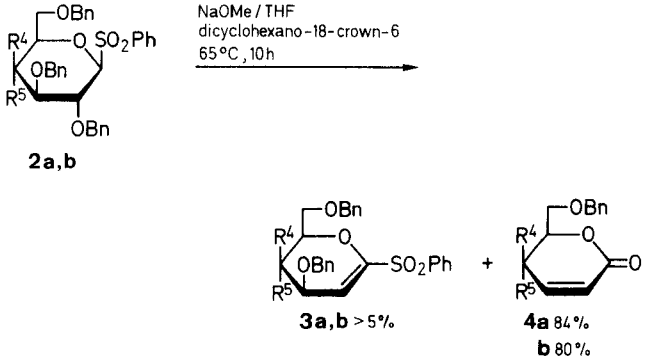
1–4	R^3	R^4	R^5
a	H	OBn	CH_2OBn
b	OBn	H	CH_2OBn
c	H	OBn	H
d	H	OBn	H

Scheme **A**



Scheme **B**

The two-step reaction from **2** (or **6**) to **4** (or **8**) mentioned above can also be completed in one-pot when the sulfones **2, 6** were reacted under the same conditions as described for the second step. This is demonstrated for the sulfones **2a** and **2b** (Scheme **C**). As a result, pyranoid ene lactones **4a** and **4b** were obtained in 84% and 80% yield, respectively; in addition, small amounts of phenylsulfonyl glycals **3a** and **3b** (< 5%) were isolated.



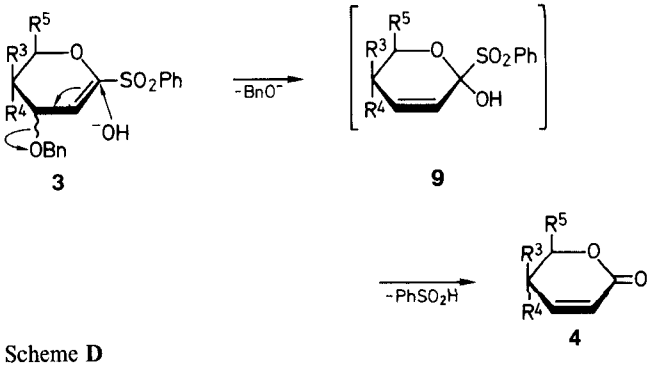
Scheme **C**

The reaction course for the second step (Scheme **D**) starts probably by addition of hydroxide which is present in trace amounts in the solution, to the phenylsulfonyl glycals **3** (or **7**) followed by a shift of the double

bond to generate intermediate **9**, which then eliminates phenylsulfinic acid providing the pyranoid ene lactones **4** (or **8**).

Phenyl 2,3,4,6-Tetra-*O*-benzyl-1-thio-β-D-glucopyranosyl Sulfone (2a); Typical Procedure:

To a solution of *S*-phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[9,10] (**1a**; 3.16 g, 5 mmol) in CH_2Cl_2 (50 mL) is added a dried (Na_2SO_4) solution of MCPBA (2.17 g, 12.6 mmol) in CH_2Cl_2 (50 mL). The mixture is stirred at r.t. for 5 h until **1a** has totally disappeared. The mixture is washed with sat. aq $NaHCO_3$ and then with H_2O and dried (Na_2SO_4). The solvent is removed *in vacuo* and the residue is purified by flash chromatography on silica gel using



Scheme **D**

Table 1. Phenyl Glycosyl Sulfones **2a–d**, **6** Prepared

Product	Yield[a] (%)	mp[b] (°C)	R_f[c] (PE/EA)	$[\alpha]_D^{25}$ ($c = 1$, $CHCl_3$)	Molecular Formula[d] or Lit. mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)[e]
2a[10]	80	135–136	–	–	$C_{40}H_{40}O_7S$ (664.8)	–
2b	83	93–94	0.59 (2:1)	+0.5	$C_{40}H_{40}O_7S$ (664.8)	3.64 (q, 1H, $J_{2,3}$ = 9.3, $J_{3,4}$ = 2.6, H-3), 3.84 (m, 3H, H-5, H-6), 4.32 (t, 1H, J = 9.3, H-2), 4.40 (d, 1H, J = 9.3, H-1), 4.25, 4.71 (2s, 4H, 2 × $ArCH_2$), 4.53, 5.02 (2d, 2H, J = 11.2), 4.86, 4.90 (2d, 2H, J = 9.2, 2 × $ArCH_2$), 7.13–7.95 (m, 25H_{arom})
2c	87	97–98	0.60 (2:1)	+14.2	$C_{32}H_{32}O_6S$ (544.6)	3.16 (q, 1H, $J_{2,3}$ = 9.0, $J_{3,4}$ = 6.9, H-3), 3.72 (t, 1H, J = 9.0, H-2), 3.92–4.02 (m, 2H, H-4, H-5), 4.39 (d, 1H, J = 9.0, H-1), 4.55, 4.65 (2d, 2H, J = 11.6, $ArCH_2$), 4.84, 5.03 (2d, 2H, $ArCH_2$), 4.87 (d, 2H, J = 3, $ArCH_2$), 7.15–7.92 (m, 20H_{arom})
2d	80	81–82	0.42 (2:1)	+70.5	$C_{32}H_{32}O_6S$ (544.6)	3.48 (m, 1H, H-4), 3.78 (q, 1H, $J_{2,3}$ = 7.3, $J_{1,2}$ = 4.9, H-2), 4.05 (m, 1H, H-5), 4.31 (t, 1H, J = 7.3, H-3), 4.78 (d, 1H, J = 5.0, H-1), 4.79 (2d, 4-H, J = 8.5, 2 × $ArCH_2$), 4.58 (2d, 2H, J = 8.5, $ArCH_2$), 7.13–7.90 (m, 20H, ArH)
6	60	oil	0.31 (2:1)	−42.5	$C_{33}H_{34}O_6S$ (558.6)	1.20 (d, 3H, J = 6.2, CH_3), 3.58 (t, 1H, J = 8.5, H-2), 4.20 (q, 1H, $J_{2,3}$ = 4.3, $J_{3,4}$ = 8.3, H-3), 4.35 (m, 1H, H-5), 4.73 (d, 1H, J = 2.3, H-1), 4.53–4.71 (m, 7H, H-2, 3 × $ArCH_2$), 7.25–7.87 (m, 20H_{arom})

[a] Yield of pure, isolated product.

[b] Melting points are taken from samples purified for elemental analysis, measured on a BÜCHI (Swizerland) melting point apparatus, uncorrected.

[c] The R_f values for all compounds are obtained on Merck Silica gel 60 F_{254}, 0.2 mm; petroleum ether (PE, bp 30–60 °C) and EtOAc (EA) are distilled.

[d] Satisfactory microanalyses obtained: C ±0.41, H ±0.40.

[e] Obtained on a Bruker WM 250 spectrometer at 250 MHz.

Table 2. Compounds **3a–c**, **7** Prepared

Product	Yield[a] (%)	mp[b] (°C)	R_f[c] (PE/EA)	$[\alpha]_D^{25}$ ($c = 1$, $CHCl_3$)	Molecular Formula[d]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)[e]
3a	89	83–84	0.6 (2:1)	−57.3	$C_{33}H_{32}O_6S$ (556.6)	3.64–3.67 (m, 2H, H-4, H-5), 3.83 (q, 1H, $J_{2,3}$ = 3.1, $J_{3,4}$ = 6.0, H-3), 4.11–4.22 (m, 2H, H-6), 4.30–4.72 (m, 6H, 3 × $ArCH_2$), 6.21 (d, 1H, J = 3.1, H-2), 7.13–7.95 (m, 20H_{arom})
3b	91	78–79	0.61 (2:1)	−112.1	$C_{33}H_{32}O_6S$ (556.6)	3.53–3.62 (m, 2H, H-6), 3.96 (m, 1H, H-5), 4.26–4.91 (m, 8H, H-3, H-4, 3 × $ArCH_2$–), 6.20 (q, 1H, $J_{2,3}$ = 1.5, $J_{2,4}$ = 1.0, H-2), 7.11–7.90 (m, 20H_{arom})
3c	91[f] 78[g]	102–103	0.44 (2:1)	−127.8	$C_{25}H_{24}O_5S$ (436.5)	3.65 (m, 1H, H-4), 4.01–4.25 (m, 3H, H-3, H-5), 4.45–4.65 (m, 4H, $ArCH_2$), 6.25 (q, 1H, J = 3.6, H-2), 7.10–7.95 (m, 15H_{arom})
7	81	oil	0.56 (2:1)	+156.7	$C_{26}H_{27}O_5S$ (451.5)	1.29 (d, 3H, J = 6.5, CH_3), 3.45 (q, 1H, $J_{3,4}$ = 6.1, $J_{4,5}$ = 8.4, H-4), 4.08 (m, 2H, H-5), 4.26 (q, 1H, $J_{2,3}$ = 2.9, $J_{3,4}$ = 6.1, H-3), 4.56–4.81 (m, 4H, 2 × $ArCH_2$), 6.22 (d, 1H, J = 2.9, H-2), 7.22–7.95 (m, 15H_{arom})

[a–e] See Table 1.

[f] Yield from compound **2c**.

[g] Yield from compound **2d**.

Table 3. Pyranoid Ene Lactones **4a–c**, **8** Prepared

Product	Yield[a] (%)	mp[b] (°C)	R_f[c] (PE/EA)	$[\alpha]_D^{25}$ ($c = 1$, $CHCl_3$)	Molecular Formula[d]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)[e]
4a	90	oil	0.75 (2:1)	+68.7	$C_{20}H_{20}O_4$ (324.4)	1690	3.73 (d, 2H, $J = 3.2$, H-6), 4.14–5.01 (m, 6H, H-4, H-5, 2 × $ArCH_2$–), 5.31 (d, 1H, $J = 4.8$, H-2), 7.14–7.31 (m, 11H, H-3, 2 × ArH)
4b	93	oil	0.73 (2:1)	−18.1	$C_{20}H_{20}O_4$ (324.4)	1674	3.62 (m, 1H, H-4), 3.64–3.70 (m, 2H, H-6), 4.37–4.61 (m, 5H, H-5, 2 × $ArCH_2$–), 5.37 (q, 1H, $J_{2,3} = 4.5$, $J_{2,4} = 1.5$, H-2), 7.18–7.23 (m, 11H, H-3, 2 × ArH)
4c	63	oil	0.38 (2:1)	+13.0	$C_{12}H_{12}O_3$ (204.2)	1682	3.83 (m, 1H, H-4), 4.43 (m, 1H, H-5), 4.85, 4.63 (2d, 2H, $J = 11.9$, $ArCH_2$–), 5.43 (q, 1H, $J_{2,3} = 6.0$, $J_{2,4} = 0.9$, H-2), 7.19–7.38 (m, 6H, H-3, ArH)
8	69	oil	0.60 (2:1)	−341.8	$C_{13}H_{14}O_3$ (218.3)	1682	1.43 (d, 3H, $J = 6.4$, CH_3), 3.72 (d, 1H, $J = 9.8$, H-4), 4.48 (m, 1H, H-5), 4.64, 5.04 (2d, $J = 11.6$, $ArCH_2$–), 5.37 (d, 1H, $J = 3.6$, H-2), 7.35 (m, 6H, H-3, ArH)

[a–e] See Table 1.

petroleum ether (bp 30–60 °C)/EtOAc (from 10:1 to 7:3) as eluents (Table 1). Compounds **2a–c** can be recrystallized from EtOH.

Phenyl 2,3,4-Tri-O-benzyl-6-deoxy-1-thio-β-D-glucopyranosyl Sulfone (**6**); this compound is prepared according to the typical procedure for **2a** (Table 1).

1,5-Anhydro-3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfonyl-D-*arabino*-hex-1-enitol (3a); Typical Procedure:

To a solution of **2a** (0.5 g, 0.76 mmol) in dry THF (50 mL) is added dropwise at −90 °C a solution of LDA (0.76 mmol) in dry THF (50 mL). The mixture is stirred at −90 °C for 1.5 h and then warmed slowly to r.t. The mixture is added to H_2O and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase is washed with dilute HCl and H_2O and dried (Na_2SO_4). The solvent is removed *in vacuo* and the residue is purified by flash chromatography on silica gel using petroleum ether (bp 30–60 °C)/EtOAc (from 10:1 to 7:3) as eluents (Table 2).

1,5-Anhydro-3,4-di-O-benzyl-1,2,6-trideoxy-1-phenylsulfonyl-D-arabino-hex-1-enitol (**7**); compound **7** is prepared according to the typical procedure for **3a** (Table 2).

(+)-(5*S*,6*R*)-5-Benzyloxy-6-benzyloxymethyl-5,6-dihydro-2*H*-pyran-2-one (4a); Typical Procedure:

A solution of **3a** (56 mg, 0.1 mmol), 0.5 N NaOMe (0.1 mol) and 7.4 mg of dicyclohexano-18-crown-6 (0.02 mmol) in THF (5 mL) is refluxed at + 65 °C for 10 h (for **4b**: 10 h, for **4c**, **8**: 24 h). Then the mixture is cooled to r.t., Et_2O (10 mL) is added, and the organic phase is washed with 10% HCl (2 mL), sat. $NaHCO_3$ and H_2O and dried (Na_2SO_4). The solvent is removed *in vacuo* and the residue is purified by flash chromatography on silica gel using petroleum ether (bp 30–60 °C)/EtOAc (from 10:1 to 7:3) (Table 3).

(−)-(5R,6S)-5-Benzyloxy-6-methyl-5,6-dihydro-2H-pyran-2-one (**8**); compound **8** is prepared according to the typical procedure for **4a** (Table 3).

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