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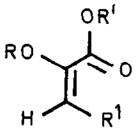
DIRECT LITHIATION OF GLYCALS.
SYNTHESIS OF C-2 BRANCHED SUGARS (1)

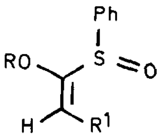
Richard R. Schmidt* and Jürgen Kast
Fakultät Chemie, Universität Konstanz
D-7750 Konstanz, Germany

Abstract: *Direct lithiation at the C-2 atom of 1-phenylsulfinyl substituted glucals 4a,b can be readily performed with LDA as indicated by reactions with different C-electrophiles. Phenylsulfinyl group removal takes place in the aldehyde reaction products by simple thermal treatment affording directly 2-alkylidene substituted gluconolactones.*

Direct lithiation at vinylic positions of functionally substituted acrylates has become a versatile tool in organic synthesis because it is compatible with a variety of other substituents (2). This approach to the generation of highly reactive intermediates bearing various functional groups was recently also extended to direct ß-lithiation of α-alkoxy acrylates 1 (3). Replacement of the carboxylate group by a phenylsulfinyl group as the promoting moiety for ß-lithiation (see compound 2) should greatly extend the versatility of this methodology because substitution of this group is easily achieved. This is exhibited in the synthesis of C-2 branched sugars derived from glucose (Schemes 1 and 2) (4).



1 : R^1 = H, Li



2 : R^1 = H, Li

The required glucal derivatives were obtained from phenyl tetra-O-benzyl-1-thio-ß-D-glucopyranoside (5). Oxidation with m-chloroperbenzoic acid (MCPBA) afforded sulfoxides 3a,b, which differ in chirality at the sulfur atom. These compounds are also of interest for C-1 lithiation of carbohydrates (6). Treatment of compounds 3a and 3b with lithium diisopropylamide (LDA) as a base provided the 1-phenylsulfinyl glucals 4a and 4b, respectively, in high yields. ^{1}H-NMR data favor the half chair conformation with the hydrogen atom at C-3 in an ideal position for proton removal. However, addition of LDA as a base led cleanly to vinylic lithiation at C-2 [generating intermediates 4a-(A) and 4b-(A)] as shown by addition of various electrophiles. Reaction with methyl chloroformate furnished compounds 5a and 5b with a methoxycarbonyl substituent at carbon atom C-2. Removal of the phenylsulfinyl group was accomplished in high yield by treatment with Raney-Nickel (Ra-Ni) affording from both precursors compound 10. For structural assignment compound 10 was debenzylated and fully acetylated to give compound 11 [7,8]. Reaction of the intermediates 4a,b-(A) with various aldehydes gave mainly mixtures of diastereoisomers; in some examples high diastereoselectivities were obtained (see Table 1). A structural assignment and a rationalisation of the results has not yet been possible. Reductive phenylsulfinyl group removal with Ra-Ni in THF afforded C-2 α-hydroxyalkyl substituted glucals 6A,B and 8A,B (for details, see Table 2).

Convenient 2-alkylidene lactone formation was achieved by formal thermal hydroxy group migration to C-1 and subsequent phenylsulfenic acid elimination

Scheme 1

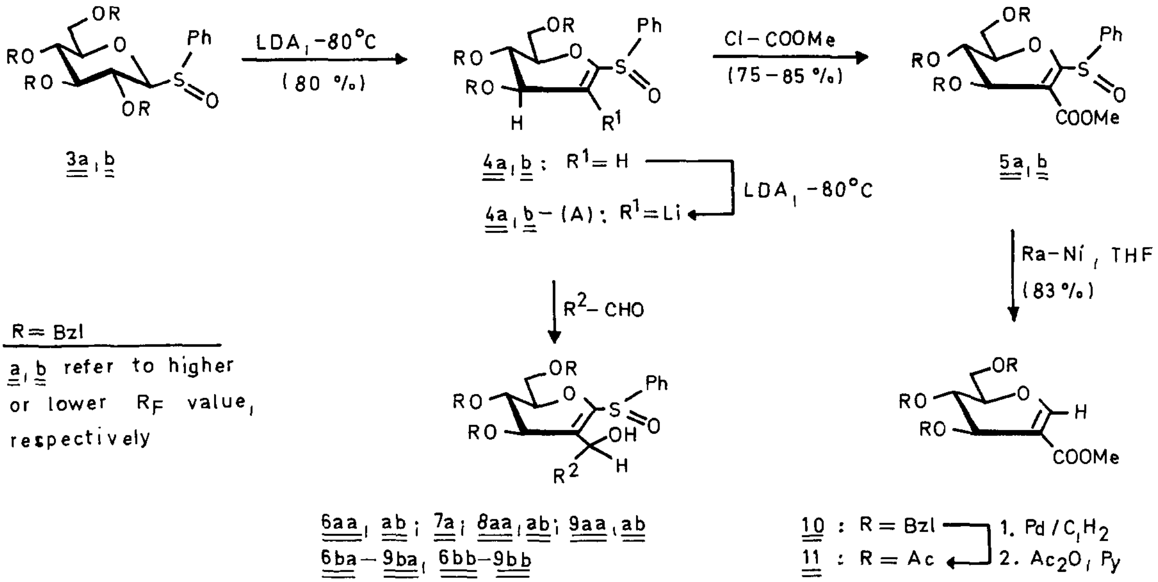
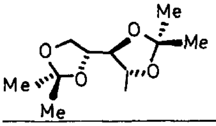


Table 1. Reaction of Compounds 4a,b with LDA and Aldehydes R^2-CHO.

R^2	Comp. from 4a	TLC PE/EA[a], R_F	Yield [%]	Ratio aa:ab	Comp. from 4b	TLC PE/EA[a], R_F	Yield [%]	Ratio ba:bb
Me	6aa 6ab	1:1, 0.41 1:1, 0.37	48	1:1	6ba 6bb	1:1, 0.30 1:1, 0.23	89	4:3
Et	7a[b]	2:1, 0.26	52	[b]	7ba 7bb	1:1, 0.50 1:1, 0.39	44	7:2
Ph	8aa 8ab	3:1, 0.30 3:1, 0.28	68	1:22	8ba 8bb	2:1, 0.30 2:1, 0.28	74	1:1
	9aa 9ab	1:1[c], 0.26 1:1[c], 0.21	43	1:1	9ba 9bb	1:1, 0.69 1:1, 0.65	49	9:1

[a] Petroleum ether (40-70°C)/ethyl acetate; [b] only one isomer obtained; [c] petroleum ether (40-70°C)/ether.

(Scheme 2). For instance, irrespective of the diastereoisomer 6aa, 6ab, 6ba or 6bb used, heating in DMSO at 160°C afforded the 2-ethylidene substituted gluconolactone 6-(E) with E-configuration (> 90 %). Similarly from compounds 8aa, 8ab, 8ba, and 8bb the 2-benzylidene gluconolactone 8-(E) was formed (> 90 %). This reaction could also be catalyzed by p-toluenesulfonic acid treatment. For instance, from compounds 6aa and 6ab a 7:1-mixture of the E- and Z-isomers 6-(E) and 6-(Z) was then obtained (81 %). The structural assignment of these compounds was based on the correlation of the shift of the vinylic protons with known values [8,9].

Hydrogenation of the ethylidene lactone 6-(E) with palladium on carbon as a catalyst occurred exclusively from the less hindered side. Concomitant debenzyl-

Scheme 2

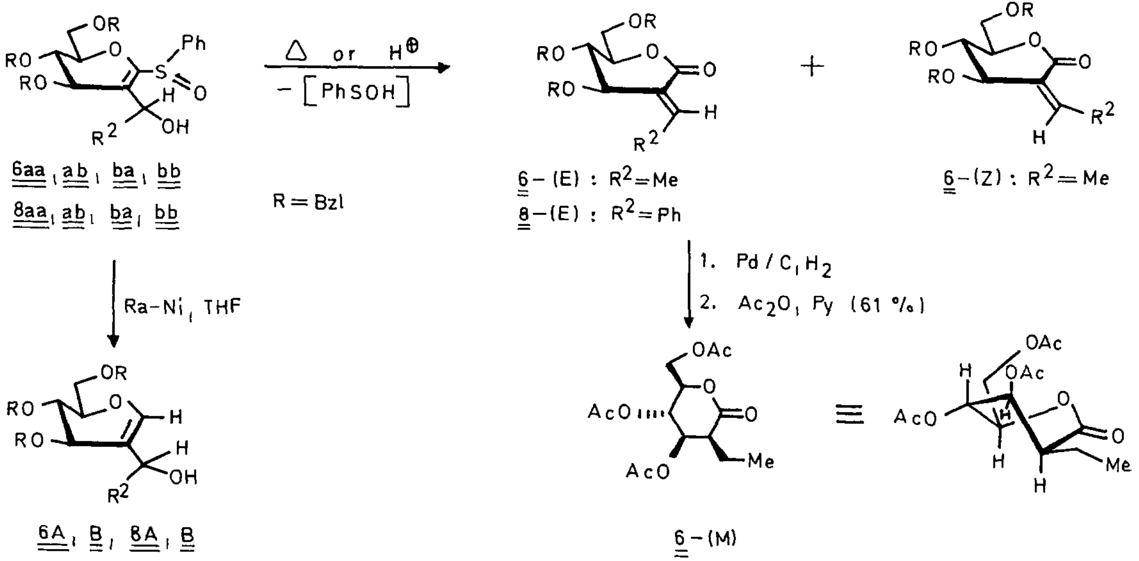


Table 2. Reaction of Compounds 6aa, ab, ba, bb and 8aa, ab, ba, bb, with Raney-Nickel

Starting Material	Yield [%]	Product	TLC PE/EA[a], R_F	$[\alpha]^{20}_{578}$ (c=1, $CHCl_3$)	^1H-NMR ($CDCl_3$) δ -CH=	CHOH
6aa	83	6A	2:1, 0.62	+ 4.9	6.53(s)	4.30-4.37(m)
6bb	85					
6ab	79	6B	2:1, 0.51	- 4.3	6.49(s)	4.20-4.28(m)
6bb	77					
8aa	73	8A	3:1, 0.57	+40.0	6.61(s)	5.20 (d)
8ba	77					
8ab	65	8B	3:1, 0.42	+19.8	6.29(s)	5.31 (d)
8bb	65					

[a] Petroleum ether (40-70°C)/ethylacetate

ation and subsequent acetylation afforded the 2-ethyl-branched lactone 6-(M) with "manno"-configuration. The ^{1}H-NMR data [8] support a twist-boat conformation with the carbon substituents in an equatorial position. This was also found for the structurally related rhamnonolactones [10].

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1) Vinyl carbanions, Part 31. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. - Part 30, see D. Lafont, M. Hoch, and R.R. Schmidt, J.Carbohydr.Chem., submitted.

2) R.R. Schmidt, Bull.Soc.Chim.Belg. 92, 825 (1983), R.R. Schmidt in Organic Synthesis an Interdisciplinary Challenge, V th IUPAC SYMPOSIUM, J. Streith, H. Prinzbach, and G. Schill editors, Backwell Scientific Publications, Oxford 1985, p. 281.

3) R.R. Schmidt, A. Enhsen, and R. Betz, Synthesis 1985, 160; and references.

4) J. Kast, Dissertation Universität Konstanz, 1986.

5) C.B. Purves, J.Am.Chem.Soc. 51, 3619 (1929); J.W. van Cleve, Carbohydr.Res. 70, 161 (1979).

6) R.R. Schmidt, Euchem Conference on Synthesis of Low-Molecular Weight Carbohydrates of Biological significance, Stockholm, June 1982; for this aim see also B. Aebischer, J.H. Bieri, R. Prewo, and A. Vasella, Helv.Chim.Acta 65, 2251 (1982).

7) This procedure afforded in addition 11 % of the 3-deoxy compound.

8) ^{1}H-NMR (250 MHz, $CDCl_3$, TMS): 6-(E): δ = 7.37-7.18 (m, 16H, $3C_6H_5$, CH=C), 4.63-4.34 (m, 8H, 3 CH_2Ph, 3-H, 5-H), 4.11-4.08 (m, 1H, 4-H), 3.81-3.79 (m, 2H, 6-H, 6'-H), 1.84 (d, 3H, CH_3, J = 7.3 Hz); 6-(Z): δ = 7.33-7.17 (m, 15H, $3C_6H_5$), 6.27 (q, 1H, CH = C, J = 7 Hz), 4.60-4.30 (m, 6H, 3 CH_2Ph), 4.2-4.1 (m, 2H, 3-H, 5-H), 3.94 (dd, 1H, 4-H, $J_{3,4}$ = 3 Hz, $J_{4,5}$ = 8.2 Hz), 3.73 (m, 2H, 6-H, 6'-H), 2.11 (d, 3H, CH_3, J = 7 Hz); 8-(E): δ = 7.99 (s, 1H, CH=C), 7.42-6.97 (m, 20H, $4C_6H_5$), 4.79 (d, 1H, 3-H, $J_{3,4}$ = 2.4 Hz), 4.57, 4.52 (2s, 4H, 2 CH_2Ph), 4.43-4.39 (m, 2H, 5-H, CH-Ph), 4.14-4.10 (m, 2H, 4-H, CH-Ph), 3.83 (d, 2H, 6-H, 6'-H, $J_{5,6} = J_{5,6'}$ = 4.5 Hz); 6-(M): δ = 5.33 (dd, 1H, 3-H), 4.97 (dd, 1H, 4-H), 4.45 (m, 1H, 5-H), 4.34 (dd, 1H, 6-H), 4.23 (dd, 1H, 6'-H), 2.72 (m, 1H, 2-H), 2.14, 2.10 (2s, 9H, 3 CH_3CO), 1.94 (m, 1H, CH_3-C$\underline{H}$), 1.47 (m, 1H, CH_3-C$\underline{H}$), 1.02 (t, 3H, CH_3), $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 1.9 Hz, $J_{4,5}$ = 8.9 Hz, $J_{5,6}$ = 3.1 Hz, $J_{5,6'}$ = 5.8 Hz, $J_{6,6'}$ = 11.5 Hz; 11: δ = 7.71 (s, 1H, 1-H), 5.66 (dd, 1H, 3-H, $J_{3,4}$ = 3 Hz, $J_{3,5}$ = 1.5 Hz), 5.16 (dd, 1H, 4-H, $J_{3,4} = J_{4,5}$ = 3 Hz), 4.58-4.54 (m, 1H, 5-H), 4.45 (dd, 1H, 6-H, $J_{5,6}$ = 7.6 Hz, $J_{6,6'}$ = 11.9 Hz), 4.16 (dd, 1H, 6'-H, $J_{5,6'}$ = 4.2 Hz, $J_{6,6'}$ = 11.9 Hz), 2.10, 2.08, 2.06 (3s, 9H, 3 CH_3CO).

9) M. Hesse, H. Meier, and B. Zeeh, Spektroskopische Methoden in der organischen Chemie, Thieme Verlag, Stuttgart 1979, p. 185.

10) O.J. Varela, A.F. Cirelli, and R.M. de Lederkremer, Carbohydr.Res. 79, 219 (1980).

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