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Glycosyl Phenyl Sulfoxides as a Source of Glycosyl Carbanions: Stereoselective Synthesis of C-Fucosides[¶]

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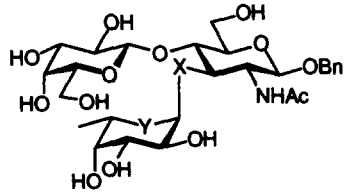
Abstract

Phenylsulfinyl-lithium exchange on glycosyl phenyl sulfoxides leads to configurationally stable anomeric carbanions which can react stereoselectively with electrophiles. Thus, the reaction of 3,4-*O*-isopropylidene-α-L-fucopyranosyl phenyl sulfoxide with *t*BuLi followed by treatment with isobutyraldehyde led to the α-configured C-glycoside; the β-anomer furnished the corresponding β-C-glycoside.

Keywords: Carbanions; Carbohydrates; C-Glycosides; Addition reactions.

C-Glycosides are regarded as non-hydrolyzable analogues of O-glycosides, and the study of their synthesis [1] and structural properties [2,3] is subject of current interest. Among this group of substances, C-disaccharides have emerged as mimics [4] of oligosaccharide fragments. Within this context, we were interested in the preparation of analogues of the biologically important [5] Lewis X trisaccharide (**1**) in which one of the anomeric oxygens of the fucosyl moiety has been replaced by a sulfur atom (**2**) [6,7] or a methylene group (compounds **3** and **4** [8]). The preparation of the C-disaccharide fragment of **3** was envisaged by using a fucosyl anomeric carbanion and a 3-C-branched glucosamine electrophile.



1 X = Y = O
2 X = S, Y=O
3 X = CH_2, Y = O
4 X = O, Y = CH_2

Non-stabilized, anomeric carbanions bearing oxygenated substituents at position 2 have been previously generated by sequential two electron transfer with either lithium naphthalenide [9] (from glycosyl chlorides) or samarium diiodide (from glycosyl sulfones [10,11], phosphates [12] or chlorides [13]), or by tin-lithium exchange with *n*-butyl lithium [14,15] (from glycosyl stannanes). In this communication we describe a new method to

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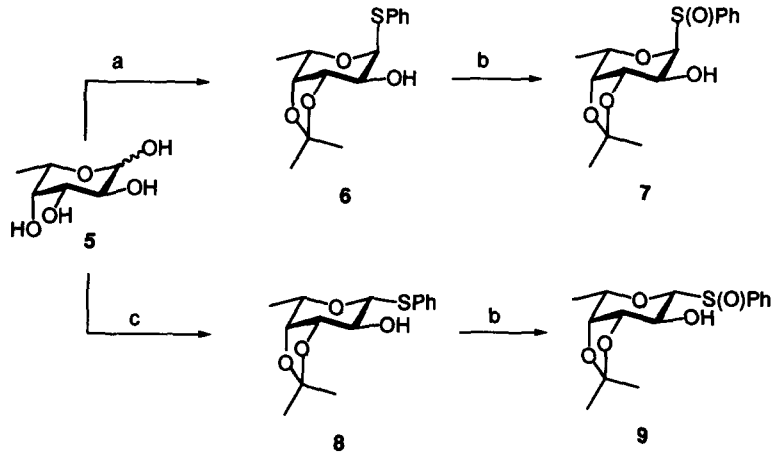
generate anomeric carbanions from easily accessible glycosyl sulfoxides, and their stereoselective reaction with electrophiles with retention of the configuration at the anomeric centre.

Fucopyranosyl phenyl sulfoxides **7** and **9** were stereoselectively prepared from L-fucose **5** as outlined in Scheme 1. The α-anomeric sulfoxide **7** was obtained through an original route whose key step, the formation of phenyl α-thioglycoside **6**, was performed by a modified procedure for the synthesis of α-fucopyranosides [16].

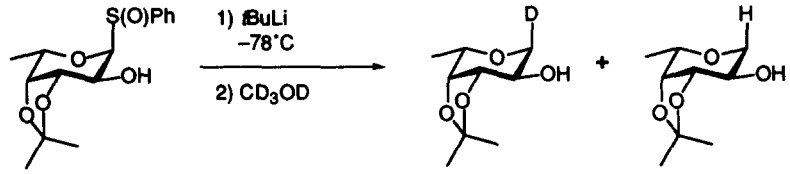


Scheme 1. *Reagents and conditions.* (a) 1. Et_3N, TMSCl, DMF, 25°C; 2. TMSI, CH_2Cl_2, 25°C; 3. 2,6-di-*tert*-butyl-4-methylpyridine, PhSH, CH_2Cl_2, 5°C; 4. MeOH, CH_2Cl_2, 25°C; 5. 2,2-dimethoxypropane, *p*-TsOH, Me_2CO, 25°C, 79% (5 steps); (b) $NaHCO_3$, *m*-CPBA, CH_2Cl_2, -78°C, 86% for **7** and 92% for **9**. (c) 1. Ac_2O, Py, 25°C; 2. PhSH, $SnCl_4$, CH_2Cl_2, -20 to 0°C; 3. NaOMe, MeOH, 25°C; 4. 2,2-dimethoxypropane, *p*-TsOH, Me_2CO, 25°C, 69% (4 steps)

Phenylsulfinyl-lithium exchange [17,18] was tried on **7**, quenching the anomeric carbanion with deuterated methanol, which led to a mixture of the corresponding deuterated and protonated 1,5-anhydrofucitols **10** and **11**, respectively, plus recovered starting material (Table 1). Among the solvents tested (C_6H_6, toluene, DME, THF, and Et_2O) the best yields of metallation were obtained in THF and Et_2O. The reaction was tried varying the number of equivalents of *t*BuLi and CD_3OD, the time of metallation and deuteration steps, and in the presence of MeLi·LiBr prior to *t*BuLi treatment [19] (Table 1). The best results in terms of yield and ratio of **10**:**11**, were obtained in Et_2O and adding one equivalent of MeLi·LiBr (Exp. 5 in Table 1). ^{1}H-N.m.r. experiments of the crude mixtures showed, in all experiments, the only presence of the above-mentioned products. Hence, the anomeric carbanion seems to be configurationally stable, leading to a stereospecific reaction, since no β-deuterated 1,5-anhydrofucitol could be detected. This was further supported by the results obtained from reaction of the fucosyl lithium so generated with isobutyraldehyde, which led (Scheme 2) to a diastereomeric mixture of the α-configured C-glycosides **12**.[1] Again, no β-C-glycosides

[1] Experimental Procedure: Under argon a 0.033 M solution of **7** in dry Et_2O at -78°C was treated with 1.1 equivalents of MeLi.LiBr (1.5 M in Et_2O) followed by slow addition of 5 equivalents of *t*-BuLi (1.64 M in hexanes). After 25 min, 3 equivalents of *i*-PrCHO were added, and the mixture was stirred for 90 min at -78°C and then quenched with saturated aqueous solution of NH_4Cl. After partitioning between water and dichloromethane, the organic layer was dried over Na_2SO_4 and concentrated to give a residue containing a diastereomeric mixture of **12**, which were separated by flash chromatography (eluent: hexane/ethyl acetate 6:1) and characterized as their diisopropylidene derivatives.

could be detected by ^{1}H-n.m.r. The structures of diastereoisomers **12** were confirmed by their transformation into the diacetals **13** and **14**, which gave also further information about the new chiral center created in the C-glycosylation.[2]



7 **10** **11**

Table 1.

Phenylsulfinyl-lithium exchange of **7**[a]

Exp.	Solvent	eq/t [min][b]	eq/t [min][c]	Yield[%]	**10:11**
1	THF	5/0.5	3/0.5	61	67:33
2	THF	5/5	6/5	80	65:35
3	Et_2O	5/5	6/5	63	77:23
4[d]	Et_2O	5/5	6/5	54	89:11
5[d]	Et_2O	5/20	6/5	77	87:13

[a] Yields and ratio of **10:11** were determined by ^{1}H N.m.r. spectroscopy.
[b] Eq: Equivalents of *t*BuLi; t: time of metallation step.
[c] Eq: Equivalents of CD_3OD; t: time of deuteration step.
[d] 1 eq of MeLi·LiBr was added prior to *t*BuLi treatment [19].

Additional evidence for the stereospecificity of the process was obtained from the reaction of fucosyl phenyl sulfoxide **9**, prepared (Scheme 1) analogously to **7** from phenyl thioglycoside **8** [20]. In this case, phenylsulfinyl-lithium exchange was slower, and the corresponding β-configured fucosyl lithium species proved to be less efficient in the C-glycosylation, although it afforded only the corresponding β-C-glycosides **15** (Scheme 2), whose structure was again secured after acetalation.

In summary, a new method for the preparation of C-glycosides has been described, which makes use of a stereospecific phenylsulfinyl-lithium exchange. The required fucosyl phenyl sulfoxides have been efficiently prepared in a highly stereoselective manner. The identification of other and more complex electrophiles, as well as its use for the preparation of Lewis X analogues, is currently underway.

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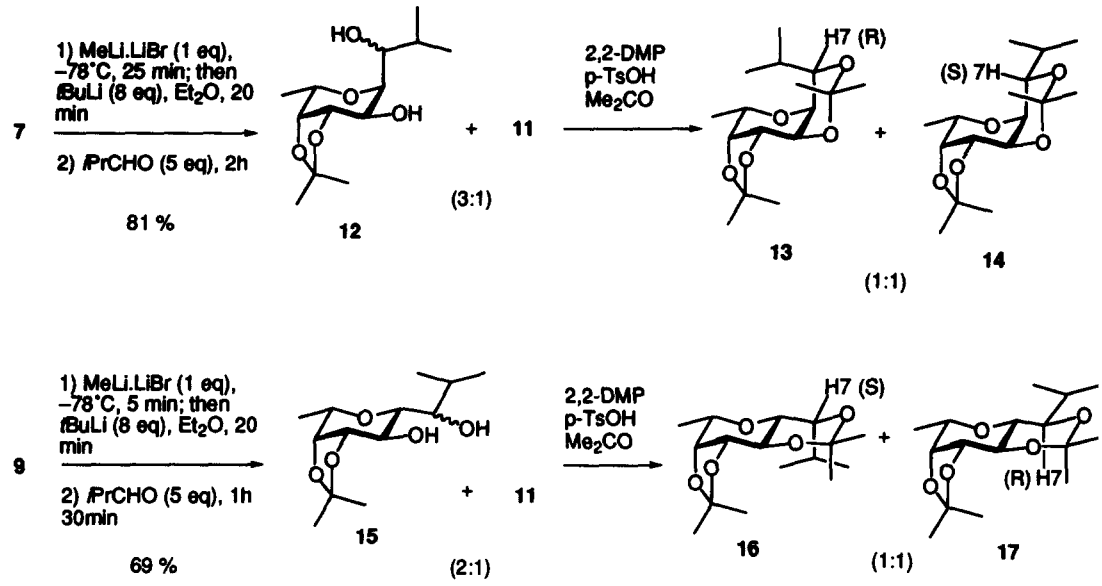
[2] All new compounds gave satisfactory elemental analyses and their expected ^{1}H-NMR spectra. Selected ^{1}H-NMR data (200 MHz, $CDCl_3$) for **13**: δ 3.98 (t, 1H, *J* = 2.7 Hz, H-2), 3.73 (dd, 1H, *J* = 2.5 and 1.4 Hz, H-1), 3.16 (dd, 1H, *J* = 1.4 and 9.4 Hz, H-7). For **14**: δ 4.13 (dd, 1H, *J* = 5.3 and 2.7 Hz, H-2), 4.08 (dd, 1H, *J* = 5.3 and 8.4 Hz, H-1), 3.34 (dd, 1H, *J* = 8.4 and 5.4 Hz, H-7). For **16**: δ 3.66 (dd, 1H, *J* = 8.6 and 9.6 Hz, H-2), 3.46 (dd, 1H, *J* = 6.3 and 9.5 Hz, H-7), 3.19 (dd, 1H, *J* = 6.3 and 9.6 Hz, H-1). For **17**: δ 3.71 (dd, 1H, *J* = 7.0 and 9.7 Hz, H-2), 3.60 (dd, 1H, *J* = 3.4 and 9.4 Hz, H-7), 2.89 (t, 1H, *J* = 9.6 Hz, H-1).



Scheme 2

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