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Stereoselective Synthesis of C-Glycosides with a Glycosyl Dianion**

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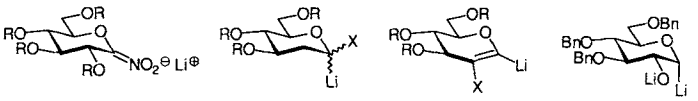
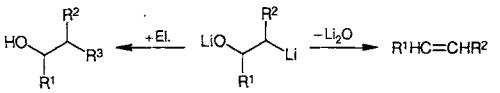
During the past few years the interest in the synthesis of C-glycosides[1] has greatly increased. This is chiefly due to the discovery of C-glycosidic or analogue structures in many natural products,[2] and their potential use as antimetabolites.[3] As with the synthesis of O-glycosides, the traditional approach to C-glycosides is based upon the addition of a suitable C-nucleophile to the electrophilic anomeric center of a 1-activated carbohydrate. The use of glycosyl radicals[1,4] and glycosylidene carbenes[5] has also been described. Direct 1-C-lithiation of sugars generally leads to the elimination of functional groups in the 2-position.[6] Paulsen et al. first reported the C-elongation of open-chain carbohydrates by polarity inversion (umpolung) at the anomeric center via dianions of hydroxy-1,3-dithianes.[7] However, in the case of pyranoses the concept of umpolung has been limited so far to 1-nitrosugars **1**,[8] 2-deoxysugars **2** (X = H,[6a,9] SO_2PH,[10] $^{\oplus}PPh_3$,[11] CO_2R[12]), and glycals **3** (X = H,[9d,13] SOPh,[14] SPh,[15] OBn[15]). Chain elongation of nitrosugars **1** followed by substitution of the nitro group by a hydroxy group leads to higher ketopyranoses with the added residue in the equatorial position. Glycals **3** offer the possibility of subsequent introduction of the missing hydroxy group and therefore access to β-C-glycosides.



1 **2** **3** **4**

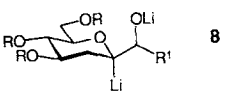
In this communication we present the application of the dilithio compound **4** in the synthesis of C-glucosides. Simple lithiation of the 2-hydroxy group functions both as a means of protection, and efficiently prevents β elimination. Subsequent reaction with electrophiles directly produces 2-hydroxy-substituted C-glucopyranosides, exclusively with α-configuration (see Scheme 1).

Dianions of the general type **5** may be obtained from β-hydroxy organomercury compounds,[16] chlorohydrins,[17] epoxides,[18] carbonyl compounds,[10a,19] or hydroxy-1,3-dithianes,[7] and were used either as carbanions for C–C-coupling reactions (**5** → **6**, El. = electrophile)[7,16–18,19a] or in the synthesis of olefins by Li_2O elimination (**5** → **7**).[19,20]



6 **5** **7**

The suitability of **4** for chain elongation reactions at the anomeric center or its tendency to eliminate to give the glucal were not readily predictable. It was reported,[17] for example, that compounds **5** in which lithium is located at a primary carbon (R^2 = H) are stable up to − 60 °C. On the other hand in the case of R^2 = alkyl, they decompose spontaneously even at − 100 °C to the olefin by β elimination. Only compounds **5** with stabilizing substituents like R^2 = Ph or CO_2Et, or cyclic β-lithiocyclohexanolate (R^1,[10] R^2 = $-(CH_2)_4-$) can be converted into the corresponding deuterated alcohols **6** (R^3 = D). Beau and Sinaÿ have postulated[10] the presence of the dilithio derivative **8** and demonstrated that protonation without β elimination is possible.



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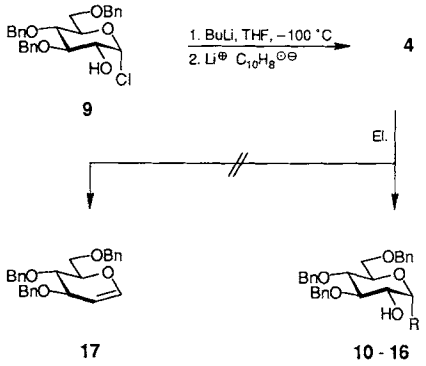
In a first experiment we treated 3,4,6-tri-O-benzyl-α-D-glucopyranosyl chloride **9**[21] in THF at − 78 °C dropwise with 1.1 equivalents of *n*-butyllithium (to generate the alcoholate), and after 15 minutes with 2.2 equivalents of lithium naphthalenide. After a further 15 minutes, quenching with MeOD, work up under acidic conditions, and chromatography on silica gel yielded a mixture of deuterated sugar **10** (66%), the corresponding β-configurated compound (3.1%), and the protonated compound **11** (17%) (Scheme 1). These products suggest that the dilithio compound **4** was formed intermediately during the reaction. The axial configuration of deuterium in **10** is based on the ^{1}H NMR spectrum (250 MHz, $CDCl_3$, $^3J_{H1,H2}$ = 5.3 Hz). The *a*/β ratio of 21 : 1 was determined by deuterium NMR spectroscopy. Obviously no Li_2O elimination leading to 3,4,6-tri-O-benzyl-D-glucal **17** takes place under these conditions.



Scheme 1. Synthesis of the α-C-glucosides **10**–**16** (cf. Table 1). Bn = CH_2Ph, El. = electrophile.

Table 1. Results of the C-glucoside synthesis according to Scheme 1.

Electrophile	Product [a]	R	Yield [%] [b]
MeOD	**10**	D	75
MeOH	**11**	H	82
MeCHO	**12a/b**	CH(OH)Me	62
PhCHO	**13a/b**	CH(OH)Ph	70
*i*PrCHO	**14a/b**	CH(OH)*i*Pr	59
HCHO	**15** [23]	CH_2OH	17
MeI [c]	**16**	Me	72

[a] Products were characterized by ^{1}H and ^{13}C NMR spectroscopy (see Table 2) and FAB-MS. [b] Yields of α-anomers after chromatography on silica gel. [c] Addition of 10% CuI.

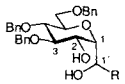
The best yields were obtained by *quick* addition of the lithium naphthalenide solution. To avoid undue increase of reaction temperature, a precooled lithium naphthalenide solution (−78 °C) is recommended. However, since the solubility of lithium naphthalenide in THF is greatly reduced at this temperature, it is better to work at − 100 °C and add the reagent uncooled. The results presented in Table 1 were obtained by using the latter method.

We next turned our attention to the possibility of using the lithiated sugar **4** in the synthesis of α-C-glucosides. The reaction of **4** with acetaldehyde affords a mixture of diastereomers **12a/b**[22] (ratio 1.4 : 1) in 62% yield. In the same manner benzaldehyde and isobutyraldehyde produced **13a/b** (1 : 1, 70%) and **14a/b** (1 : 1, 59%), respectively. In all cases axial configurated C-glucosides were produced with high stereoselectivity ($\alpha/\beta \geq 20:1$). The use of gaseous formaldehyde gave the desired hydroxymethyl C-glucoside **15** in an unsatisfactory 17% yield; in this case large quantities of polyoxymethylene were formed. However, alkylation of the dianion **4** with MeI proceeded without complications to give α-methyl-C-glucoside **16** in 58% yield. An improved yield of 72% could be obtained by addition of 10% of CuI before addition of the electrophile.

Table 2. Selected ^{1}H and ^{13}C NMR chemical shifts (δ values) and coupling constants *J* [Hz] of **10**–**16** [a,b]. ax = axial, eq = equatorial, n.d. = not determinable.

Compd.	H-1	H-2	H-1′	C-1	C-2	C-1′	$^3J_{H\ 1,H-2}$
10	3.95	3.69		69.1	70.0		5.3
11	3.97 (eq)	3.69		69.5	70.1		5.3 (eq-ax)
	3.18 (ax)						11.1 (ax-ax)
12a	3.50	3.69	4.04	73.6	67.6	67.7	1.6
12b	3.57	3.98	4.10	73.7	68.4	67.0	2.9
13a	3.75	3.34	4.97	73.8	66.1	73.9	1.0
13b	3.93	3.93	5.00	72.4	67.4	74.0	n.d. [c]
14a	3.78	3.75	3.60	69.2	68.9	76.8	<1.0
14b	3.77	3.97	3.77	69.8	68.1	74.3	2.0
15	3.97	3.76	3.76	71.1	68.7	62.2	2.7
			3.87				
16	4.09	3.61	1.23	68.1	70.4	14.2	3.8

[a] NMR spectra in $CDCl_3$ at 300 K, internal standard TMS. ^{1}H: 500 MHz, ^{13}C: 125 MHz. [b] To facilitate comparison, atoms are numbered following that used for the starting sugar **9**.



[c] Identical chemical shifts of H1 and H2.

It is remarkable that the formation of tribenzylglucal **17** was not observed under any circumstances. Thus, the dilithio compound **4** proves to be a species which is stable at − 78 °C and reacts with electrophiles with *retention* of configuration at the anomeric center to give a variety of 2-hydroxy-α-C-glucosides. The precursor **9** is crystalline and stable at − 20 °C,[21] and is easily obtained from acetobromoglucose in a four-step synthesis in an overall yield of approximately 55%.

Experimental Procedure

Under argon a 0.15 M solution of **9** in dry THF at − 100 °C was treated with 1.1 equivalents of *n*BuLi (1.6 M in THF), followed by quick addition of 2.2 equivalents of lithium naphthalenide (1 M in THF). After 15 minutes, 1.5 equivalents of aldehyde or MeI were added, and the mixture was stirred for 1 h at − 100 °C and then allowed to warm up to room temperature. A saturated aqueous solution of NH_4Cl was added and the mixture extracted with dichloromethane. After the organic layer had been dried over $MgSO_4$, the product was purified by chromatography on silica gel (eluent: toluene/ethyl acetate or hexane/ethyl acetate).

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