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C-1 LITHIATION OF C-2 ACTIVATED GLUCALS [1)]

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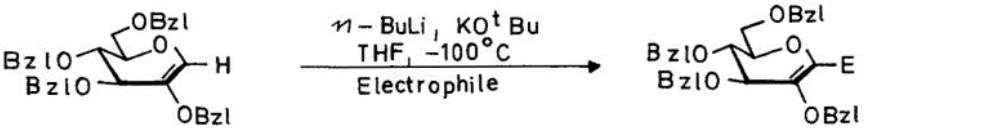
Abstract: Direct lithiation of the readily available 2-benzyloxy and the 2-phenylthio glucals 1 and 7 at the anomeric carbon atom leads to intermediates reacting with different electrophiles. Subsequent removal of the phenylthio group in compounds 9a,b with Raney-nickel and diastereospecific 1-hydrogen- and 2-hydroxy-transfer with the $BH_3 \cdot SMe_2/H_2O_2$, NaOH system provides a convenient entry into functionalized C-glucopyranosides.

C-Glycosides have gained special interest because they are found as such in nature with interesting biological properties and because many natural products contain structural moieties related to these compounds, for instance, the polyether antibiotics [2-4)]. Therefore several strategies have been developed recently for their synthesis where the anomeric carbon atom of the glycosyl group participates either as an electrophile or as a radical in the CC-bond formation step [2,5,6)]. Intermediate generation of a nucleophilic anomeric carbon atom was possible with the help of a nitro group at the anomeric position [7)]; mainly elimination of the functional group in 2-position is observed when direct lithiation at the anomeric carbon atom is investigated [8)]. However, 2-deoxy sugars could be lithiated at the anomeric position [9)].

Direct lithiation of glycals at the anomeric position, relating to C-1 enol ether lithiation [10)], would provide a convenient access to glycal C-glycosides, which could be transformed into C-2-functionalized and 2-deoxy sugars. However, with the readily available 3,4,6-tri-O-benzyl-D-glucal (Scheme 2, compound 6) nonsatisfactory results were obtained thus far [11)]. Therefore a sulfone/tributyltin/lithium exchange procedure of O-silyl protected glucal derivatives has been introduced recently [12-14)]. From our experience in direct lithiation at vinylic positions it is quite obvious that functional groups in the 2-position of this enolether moiety will activate direct C-1 lithiation of glycals through inductive effects and/or intramolecular complexation in the lithiated species [1,8,15)]. However, previous investigations with 2-benzyloxy-3,4,6-tri-O-benzyl-D-

Scheme 1

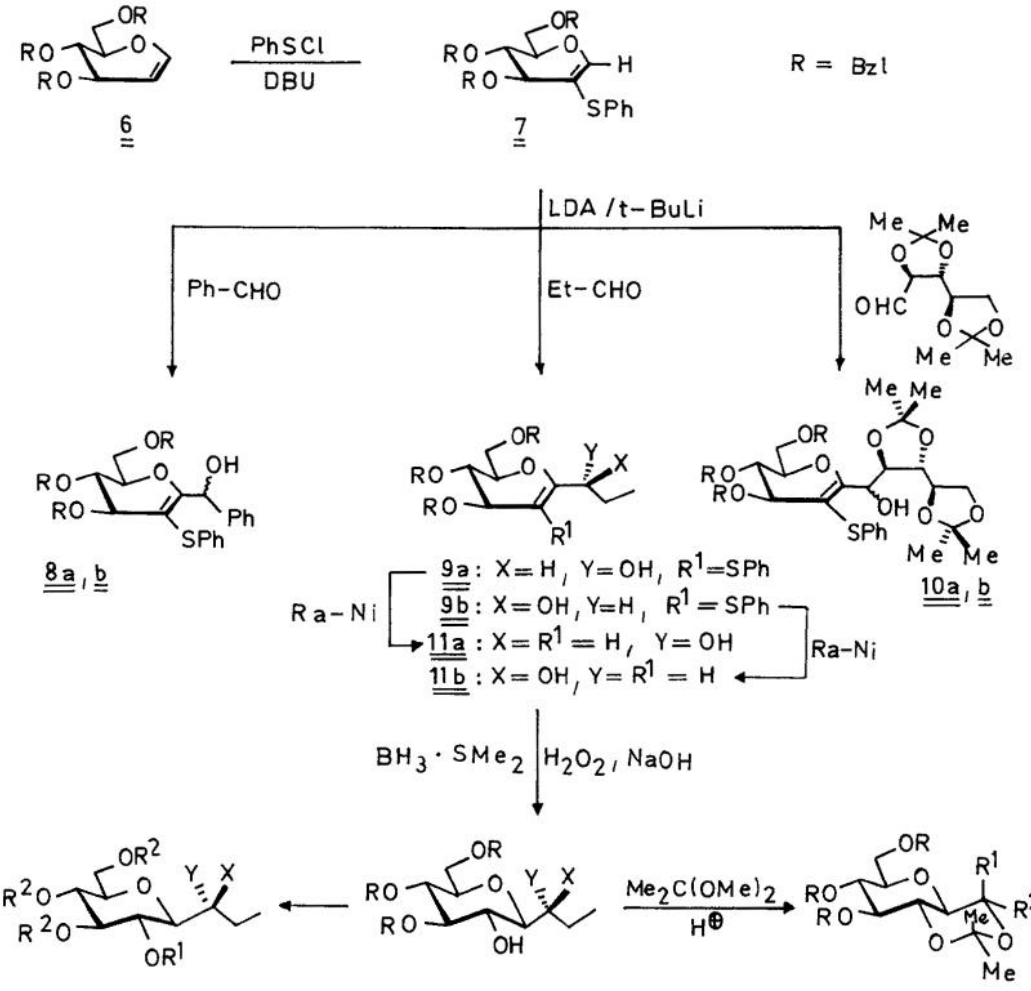


1

2 : E = D ; 4 : E = SMe

3 : E = Me ; 5 : E = COOMe

Scheme 2



6

7

8a, b

9a : X = H, Y = OH, R^1 = SPh

9b : X = OH, Y = H, R^1 = SPh

11a : X = R^1 = H, Y = OH

11b : X = OH, Y = R^1 = H

10a, b

13a : X = H, Y = OAc, R^1 = Ac, R^2 = Bzl

13b : X = OAc, Y = H, R^1 = R^2 = Ac

12a : X = H, Y = OH

12b : X = OH, Y = H

14a : R^1 = Et, R^2 = H

14b : R^1 = H, R^2 = Et

glucal (Scheme 1, compound 1) were not as promising as expected [16]. A strong base system was required for lithiation which provided the deuterated compound 2 only in 63 % yield (isolated yield 70 %, deuteration 90 %). With the electrophiles methyl iodide, dimethyl disulfide, and ClCOOMe the products 3-5 [17] were obtained in 47 %, 49 %, and 35 % isolated yields, respectively. Side reactions were competing lithiations at the benzyl methylene groups, mainly at C-2.

Next we turned our attention to phenylthio group activation because this group should be easily removable after C-1 hydrogen substitution [3]. The required starting material 7 [17] could be readily obtained from O-benzyl protected D-glucal 6 in a one pot procedure by phenylsulfenyl chloride addition and subsequent hydrogen chloride elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Compound 7 was cleanly lithiated with lithium diisopropylamide (LDA) as indicated by deuteration with MeOD (recovery of starting material: quantitative; deuteration: 75 %). Stronger lithiating agents, for instance, tert.-butyllithium increased the percentage of lithiation; however, due to side reactions the overall yield of C-1 deuterated material was not increased.

Reaction of the lithiated species (from LDA treatment of 7) with three different types of aldehydes (benzaldehyde, propionaldehyde, and 2,3:4,5-di-O-isopropylidene-D-arabinose) afforded without side product formation the desired α-hydroxy alkyl derivatives 8-10 [17] as diastereomeric mixtures (8a:8b = 1:1, 9a:9b = 2:1, 10a:b = 1:3; yields 90 % based on 50 % recovery of 7). The diastereoisomers could be readily separated by chromatography.

An important aspect in this procedure is the convenient phenylthio group removal with Raney-nickel yielding for instance from 9a,b compounds 11a,b in quantitative yields. Subsequent treatment with the borane dimethylsulfide/basic hydrogen peroxide system provided, as found already previously [3], in a diastereospecific 1-hydrogen- and 2-hydroxy transfer the ß-D-glucopyranosyl compounds 12a [17] and 12b [17], respectively.

Proof for the ß-glucopyranosyl structure of compounds 12a,b came from O-acetylation (- 13a) and debenzylation and O-acetylation (- 13b), respectively. Both compounds showed the required $J_{1,2}$, $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ coupling constants of 9-10 Hz. The configuration at the α-hydroxy carbon atom was obtained via O-isopropylidenation of compounds 12a,b with 2,2-dimethoxypropane providing compounds 14a,b; with a $J_{1,C\alpha}$ coupling constant of 10 Hz for compound 14b the S-configuration for the minor isomer is assigned.

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17) Physical data of the synthesized compounds (PE = Petroleum ether (b.p.35-70°C); EA = ethyl acetate): 3: Tlc (PE/EA, 9:1) R_F 0.32; $[\alpha]_{578}^{25}$ +12.2 (c=1, $CHCl_3$); 4: tlc (PE/EA, 9:1) R_F 0.39; mp. 60-61°C; $[\alpha]_{578}^{25}$ -15.7 (c=1, $CHCl_3$; 5: tlc (PE/EA, 4:1) R_F 0.32; mp. 67-68°C; $[\alpha]_{578}^{25}$ -19.1 (c=1, $CHCl_3$); 8a: tlc (PE/EA, 7:3) R_F 0.55; $[\alpha]_{589}^{22}$ -117.3 (c=1, $CHCl_3$); 8b: tlc (PE/EA, 7:3) R_F 0.51; 9a: tlc (PE/EA, 7:3) R_F 0.45; $[\alpha]_{589}^{22}$ -40.3 (c=1, CH_2Cl_2); 9b: tlc (PE/EA, 7:3) R_F 0.36; $[\alpha]_{589}^{22}$ -6.4 (c=1, $CHCl_3$); 10a: tlc (PE/EA, 7:3) R_F 0.51; $[\alpha]_{589}^{22}$ -12.4 (c=1, CH_2Cl_2); 10b: tlc (PE/EA, 7:3) R_F 0.49; $[\alpha]_{589}^{22}$ -17.8 (c=1, CH_2Cl_2); 12a tlc (PE/EA, 3:2) R_F 0.39; $[\alpha]_{589}^{22}$ +12.7) c=0.5, $CHCl_3$); 12b: tlc (PE/EA, 3:2) R_F 0.46; $[\alpha]_{589}^{22}$ +23.6 (c=1, $CHCl_3$).

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