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SYNTHESIS OF CARBON BRIDGED C-DISACCHARIDES[1]

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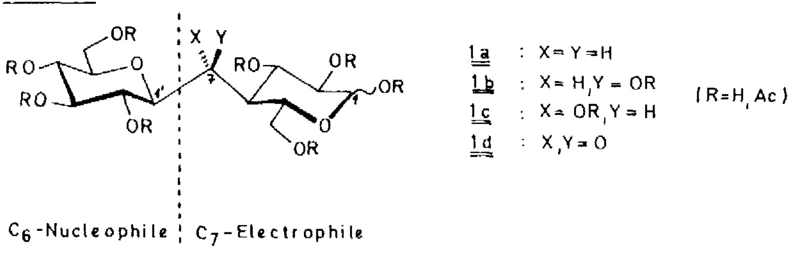
Abstract: Direct lithiation of the readily available 2-phenylsulfinyl-D-glucal **2** provides the 1-C-lithiated species **2A** furnishing with 4-deoxy-4-formyl-D-glucose derivative **7** in a diastereocontrolled reaction the C-disaccharide intermediate **8**. This compound is transformed into the carbon bridged cellobiose derivative **1b** [Glc-β(1→4C)Glc derivative]. Analogously, the corresponding Glc-β(1→4C)Gal derivative was obtained.

The great importance of natural and unnatural glycosidase inhibitors [2,3] created interest in the synthesis of hexopyranose derived carbon bridged C-disaccharides.[4-7] The first synthesis reported for a β(1-6)-methylene bridged gentiobiose derivative follows a C_6-electrophile + C_7-nucleophile course; it requires diastereocontrol only at the C_6-species.[4] The addition of glycosyl radicals to sugar 2-methylene lactones leads preferentially to α(1-2)-connection with 2,3-*trans* stereochemistry in the former lactone species.[5] The synthesis of **1a** type compounds (Scheme 1) by Kishi and coworkers[6] uses a combination of C_5-electrophile + C_8-nucleophile species; commonly, it leads to all four possible diastereomers at position 1' and 2'.

Based on the ready access to heteroatom-stabilized 1-C-lithiated glycals[8,9] as C_6-nucleophiles, a diastereocontrolled synthesis of carbon bridged C-disaccharides of **1b** type and related compounds was developed necessitating additionally a C_7-electrophilic species (Scheme 1).

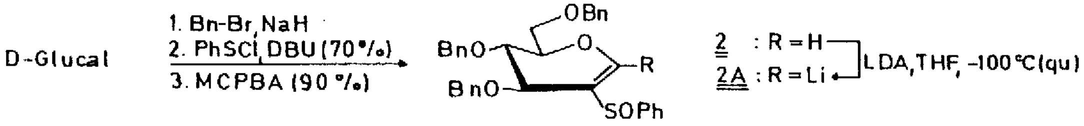
Scheme 1



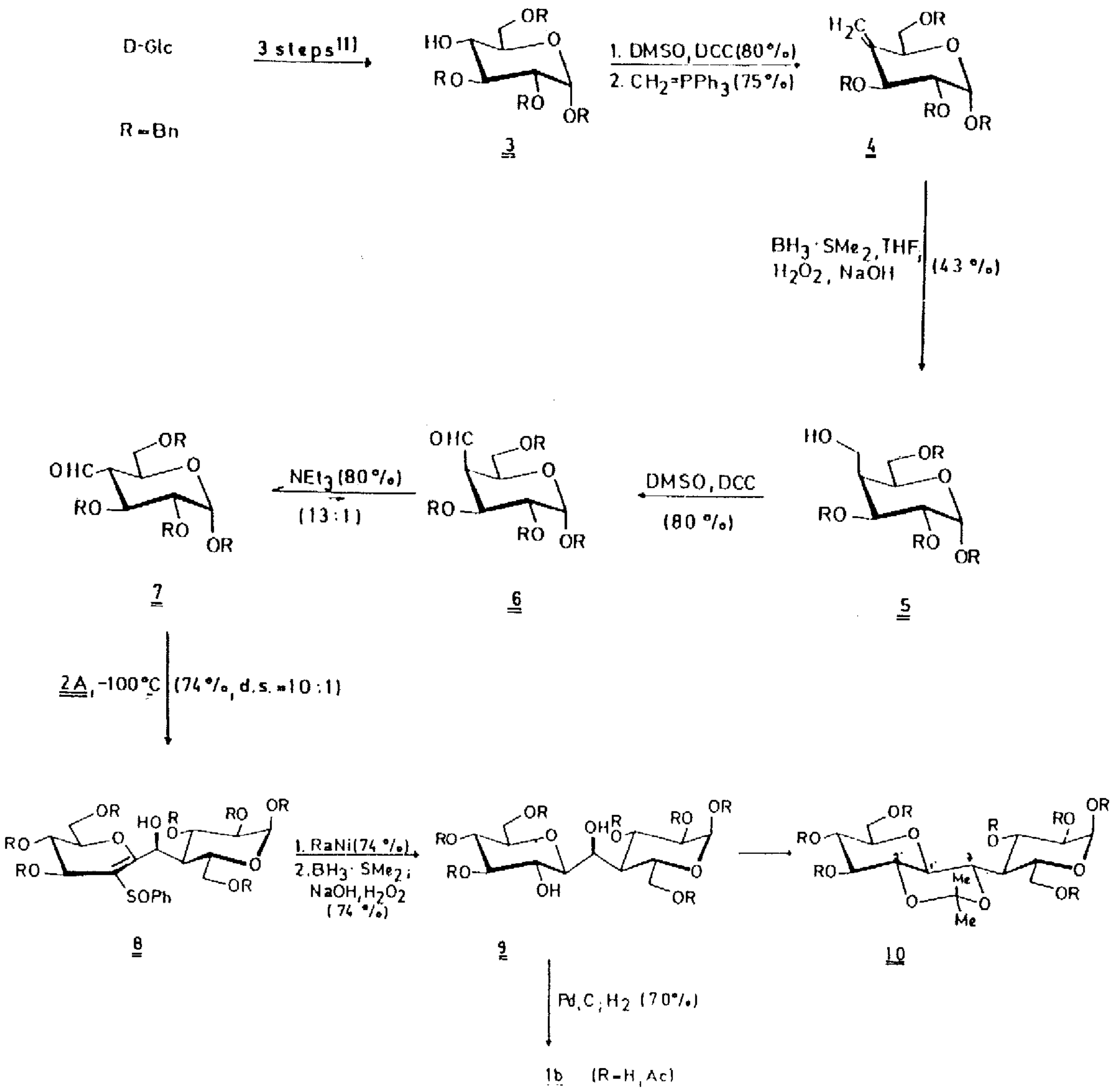
This method should be applicable to a great variety of different C-disaccharides also with modifications at the bridging position (for instance, transformations into compounds **1a**, **1c**, and **1d**, respectively) of possible value for glycosidase inhibiting character.

The required C_6-nucleophile **2A** (Scheme 2) was readily obtained from D-glucal.[9] Phenylsulfenyl chloride addition to 3,4,6-tri-O-benzyl glucal and subsequent DBU treatment afforded the corresponding 2-phenylthio glu-

Scheme 2



Scheme 3



cal which upon oxidation with m-chloro-perbenzoic acid (MCPBA) gave the sulfoxide **2**.[10] Treatment with LDA in THF at -100°C resulted in quantitative generation of the 1-C-lithiated species **2A**.

The required C_7-electrophiles **6** and **7**, respectively, were obtained from D-glucose via the 4-O-unprotected derivative **3**[11] (Scheme 3). DMSO/DCC-oxidation and subsequent Wittig methylenation gave the 4-methylene compound **4** in high overall yield. Borane addition and then treatment with H_2O_2/NaOH afforded compound **5** with "*galacto*"-configuration and in addition a minor byproduct from reverse borane addition, which was separated. Compound **5** was readily transformed into the desired *galacto*-aldehyde **6**[12]; triethylamine treatment led to isomerisation to the thermodynamically more stable *gluco*-aldehyde **7**[12] in high yield (**6**:**7** equilibrium ratio ≈ 1:13). Thus, both diastereomers were readily accessible.

Reaction of vinyllithium species **2A**, for instance, with *gluco*-aldehyde **7** resulted in high diastereocontrol providing compound **8** with S-configuration at 7-C as the main product (diastereomer ratio ≈ 10:1). Removal of the phenylsulfinyl group with Raney-nickel and *gluco*-specific hydrogen and hydroxy group addition to the enol ether moiety with borane dimethylsulfide and then H_2O_2/NaOH provided the carbon bridged cellobiose derivative **9** which gave after hydrogenolytic debenzylation the desired compound **1b** (R = H). This compound was characterized as the fully O-acetylated compound **1b** (R = Ac).[10] The ^{1}H-NMR data support the configurational assignments. Proof for the assigned 4-C-, 7-C-, 1'-C-, and 2'-C-chirality came from O-isopropylidenation of compound **9** providing the 7,2'-O-isopropylidene derivative **10**. The $J_{3,4} = J_{4,5} = 10.0$ Hz and the $J_{1',7} = J_{1',2'} = 8.0$ Hz coupling constants display the required antiperiplanar hydrogen atom allocation of 3-H/4-H/5-H and 7-H/1'-H/2'-H, respectively.

Similarly, from vinyllithium species **2A** and *galacto*-aldehyde **6** the corresponding Glc-β(1→4C)Gal C-disaccharide was obtained in practically identical yields and diastereoselectivities.[12]

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10. Compound **2** is a 1:1-diastereomer mixture with R_f 0.37 and 0.26, respectively, on TLC (silica gel; eluent: petroleum ether/ ethyl acetate, 3:2). For the reactions here the isomer with R_f 0.26 was used.

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12. ^{1}H-NMR data (250 MHz) of the synthesized compounds: **1b** (R = Ac, 1:1-anomeric mixture) in $CDCl_3$: δ = 6.31 (d, $J_{1,2}$ = 3.6 Hz, 0.5 H, 1-H_α), 5.62 (d, J = 8.1 Hz, 0.5 H, 1-H_β), 5.33-4.91 (m, 6 H), 4.42-3.76 (m, 7 H), 2.57 (ddd, $J_{3,4} = J_{4,5}$ = 11.3 Hz, $J_{4,7}$ = 3.4 Hz, 0.5 H, 4-H), 2.52 (ddd, $J_{3,4} = J_{4,5}$ = 11.3, $J_{4,7}$ = 3.5 Hz, 0.5 H, 4-H), 2.21-1.97 (m, 27 H).- **6** ($CDCl_3$): δ = 9.90 (d, $J_{4,7}$ = 5.2 Hz, 1 H, 7-H), 3.00 (ddd, J = 2.4, 5.2, 5.5 Hz, 1 H, 4-H). - **7** ($CDCl_3$): δ = 9.65 (d, $J_{4,7}$ = 2.7 Hz, 1 H, 7-H), 2.99 (ddd, $J_{3,4} = J_{4,5}$ = 10.7, $J_{4,7}$ = 2.7 Hz, 1 H, 4-H). - **10** ($CDCl_3$): δ = 7.40-7.16 (m, 35 H, 7 Ph), 5.02-4.21 (m, 18 H), 4.15 (dd, J = 8.9, J = 10.8 Hz, 1 H), 3.91 (br.d, J = 9.8 Hz, 1 H), 3.67-3.38 (m, 8 H), 3.19 (br.d, J = 9.8 Hz, 1 H), 2.79 (dd, $J_{1',2'} = J_{1',7}$ = 8.0 Hz, 1 H, 1'-H), 2.21 (ddd, $J_{3,4} = J_{4,5}$ = 10.0, $J_{4,7}$ = 3.2 Hz, 1 H, 4-H), 1.24, 1.20 (2 s, 6 H, 2 Me).- Glc-β(1-4C)Gal derivative corresponding to **10** in C_6D_6: δ = 7.48-7.04 (m, 35 H, 7 Ph), 5.26 (d, $J_{1,2}$ = 2.4 Hz, 1 H, 1-H), 5.06-4.28 (m, 18 H), 3.92-3.61 (m, 7 H), 3.27-3.23 (m, 2 H), 3.09 (dd, $J_{1',2'} = J_{1',7}$ = 8.0 Hz, 1 H, 1'-H), 1.30, 1.18 (2 s, 6 H, 2 Me).

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