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SYNTHESIS OF METHYLENE BRIDGED C-DISACCHARIDES[1)]

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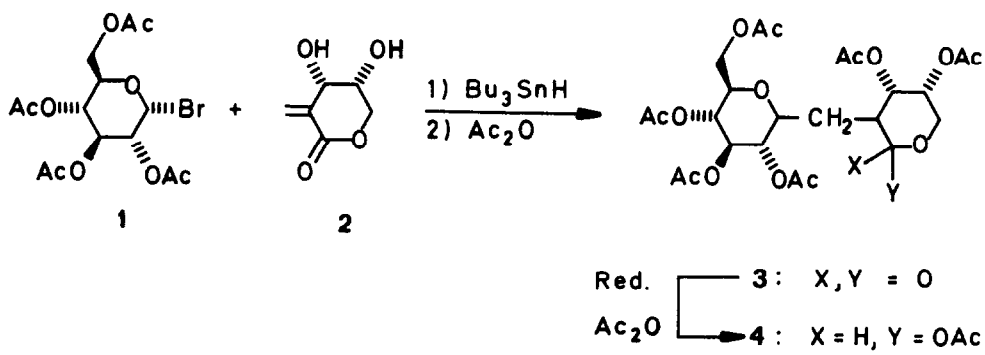
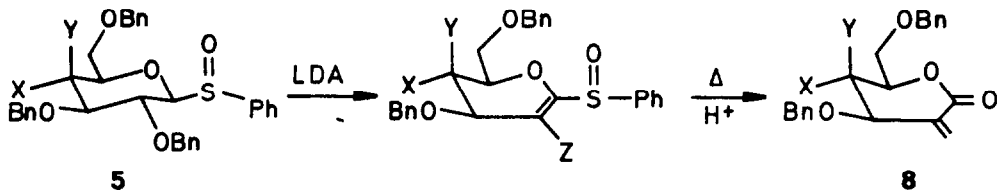
Abstract: Addition of glycosyl radicals to the α-methylene lactones **8** obtained from the corresponding glycopyranosyl phenylsulfoxides **5a,b** in convenient two step procedures provides methylene bridged C-disaccharides in high diastereoselectivities. Thus, after reduction of the lactone moiety the methylene bridged analogs **9-11** of kojibiose, ristobiose, and α-L-fucopyranosyl(1→2)-D-galactose, respectively, were obtained.

The C-disaccharide synthesis developed by Giese and Witzel permits the connection of two tetrahydropyran rings by a methylene group.[2)] This method is based on the addition of a glycosyl radical to an exo-methylene γ-lactone followed by hydrogen atom abstraction.[3)] Thus, from D-glucopyranosyl bromide **1**, α-methylene lactone **2**, and tributyltin hydride the C-disaccharide lactone **3** was obtained, which after reduction and O-acetylation provided the desired C-disaccharide **4**.[2)] Compounds of this type are above all of interest as potential enzyme inhibitors.[4)]



The formation of various glycosyl radical intermediates was possible without difficulties[5], however, the access to the required α-methylene γ-lactones of carbohydrates was very limited. This problem could now be solved by applying the α-alkylidene glycono-γ-lactone synthesis of Schmidt and Kast.[6]

The direct generation of C-2-lithiated glycals **6** from the readily available glycopyranosyl-phenylsulfoxides **5** (via the corresponding glycals) provides a simple route for reactions with electrophiles at C-2 of carbohydrates.[6] Reaction of formaldehyde with the species **6a** and **6b** generated from 2,3,4,6-tetra-O-benzyl-D-glucopyranosyl- and D-galactopyranosyl-phenylsulfoxides **5a,b**,[7] respectively, with two equivalents of lithium diisopropylamide (LDA) afforded the 2-hydroxymethyl substituted glycals **7a** and **7b** in excellent yields (**7a**: 77%; **7b**: 84%). Simple heating in toluene in presence of traces of acid led directly to the desired α-methylene γ-lactones **8a,b** of D-glucose and D-galactose (**8a**: 64% **8b**: 65%), which could be readily isolated and characterized. Thus, interesting starting materials are available for the synthesis of methylene group (1→2)-bridged C-disaccharides.



5 **8**

a : X = OBn, Y = H

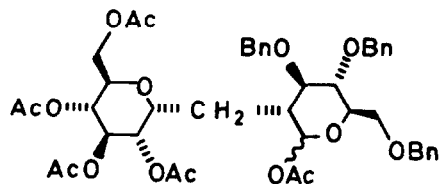
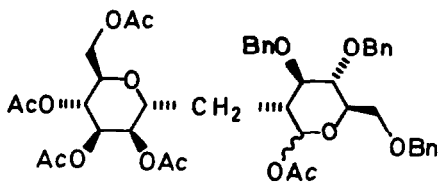
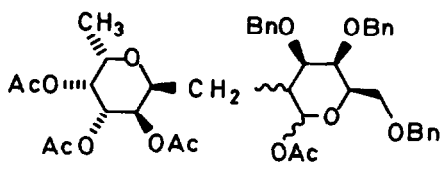
b : X = H, Y = OBn

CH_2O → **6** : Z = Li; **7** : Z = CH_2OH

Applying the radical CC-bond forming reaction to acetobromo-D-glucose (**1**) and α-methylene lactone **8a** provided after reduction and acetylation the methylene bridged analogue **9** of kojibiose in 45 % overall yield (Table).[8] The intermediate lactone was formed in 70 % yield. The high diastereoselectivity in the radical CC-bond formation between C-1 of compound **1** and the ß-methylene carbon of compound **8a**, and in the subsequent hydrogen donation of tributyltin hydride to the α-carbon of the lactone radical is noteworthy. Thus the methylene bridged disaccharide lactone with α-D-glucopyranosyl(1→2)-D-glucose structure was obtained which afforded after reduction with $Na[Al(OC_2H_4OMe)_2(OEt)H]$ and O-acetylation with acetic anhydride/pyridine the C-disaccharide **9** as a 2:1-mixture of the α/ß-anomers.[8] Similarly, from acetobromo-D-mannose and compound **8a** the methylene analogue **10** of ristobiose with α-D-mannopyranosyl(1→2)-D-glucose structure was obtained (1:1 α,ß-anomer mixture). The frequent occurence

of the α-L-fucopyranosyl-(1→2)-D-galactose moiety in glycoconjugates[9] was the reason to apply this methodology to acetobromo-L-fucose and the α-methylene lactone of D-galactose **8b**. Again the methylene bridged C-disaccharides **11** were obtained in good yield. However, only the CC-bond formation occured with high α-selectivity. The radical hydrogen abstraction gave the diastereoisomers in a 3:2-ratio.

Table: Synthesis of Methylene Bridged C-Disaccharides

Glycosyl Halide	Methylene Lactone	C-Disaccharide	Yield (%) Radical Addition (overall)
1	**8a**	 **9**	70 (45)
Tetraacetyl Mannosyl Bromide	**8a**	 **10**	57 (40)
Triacetal Fucosyl Bromide	**8b**	 **11**	62 (41)

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1) This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. - Vinyl carbanions, Part. 34. For Part 33, see: R.R. Schmidt, R. Preuss, Tetrahedron Lett., in print.

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6) R.R. Schmidt and J. Kast, Tetrahedron Lett. **27** (1986) 4007; J. Kast, Dissertation, Univ. Konstanz 1986.

7) Compounds **5a** and **5b** due to the sulfoxide chirality are used as 1:1 diastereomer mixtures.

8) All new compounds have elemental analysis and spectra that are consistent with the assigned structures. As a typical example, the ^{1}H-NMR data (300 MHz, $CDCl_3$) of **9** are given. The tetrahydropyran carbon atoms are numbered from 1 to 6 and 1' to 6', respectively; the bridging methylenegroup is 7.

9, α-Isomer: δ = 1,72 (m, 1H, H-2'), 1.96-2.25 (m, 17H, H-7, OAc), 3.62 (t, 1H, H-6b'), 3.67 (dd, 1H, H-6a'), 3.71-3.86 (m, 2H, H-6b, H-5'), 4.00 (dd, 1H, H-6a), 5.05-4.17 (m, 3H, H-1, H-5, H-4'), 4.51-5.03 (m, 9H, H-2, H-4, H-3', Bn), 5.19 (t, 1H, H-3), 6.21 (d, 1H, H-1'), 7.20-7.45 (m, 15H, Ph), $J_{2,3} = J_{3,4} = 9.0$, $J_{4,5} = 5.5$, $J_{5,6a} = 2.5$, $J_{5,6b} = J_{6a,6b} = 12.5$, $J_{1',2'} = 3.0$, $J_{5',6a'} = 1.5$, $J_{5',6b'} = 9.0$, $J_{6a',6b'} = 9.3$ Hz.

9: ß-Isomer: δ = 1.82 (m, 1H, H-2'), 1.95-2.20 (m, 17H, OAc), 3.34 (dd, 1H, H-6b'), 3.54 (ddd, 1H, H-5'), 3.68-3.79 (m, 3H, H-1, H-6b, H-6a'), 3.90 (dd, 1H, H-4'), 4.33 (ddd, 1H, H-5), 4.55-5.15 (m, 11H, H-2, H-3, H-4, H-6a, H-3', Bn), 5.46 (d, 1H, H-1'), 7.25-7.45 (m, 15H, Ph), $J_{2,3} = J_{3,4} = 9.5$, $J_{4,5} = 5.5$, $J_{5,6a} = 2.5$, $J_{5,6b} = 12.5$, $J_{1',2'} = 9.5$, $J_{5',6a'} = 2.0$, $J_{5',6b'} = 9.0$, $J_{6a',6b'} = 11.0$ Hz.

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