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Wittig reaction of glycosyl phosphonium salts: a stereoselective route to *C*-disaccharides and *C,O*-trisaccharides☆

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Abstract—*C*-Disaccharides and *C,O*-trisaccharides, with a quaternary anomeric center, were prepared in good yields and excellent stereoselectivity by a route involving the Wittig reaction of glycosyl phosphonium salts and hydrogenation or glycosidation of *exo*-glycals as key steps.

C-Disaccharides, i.e. analogs of disaccharides in which the interglycosidic oxygen atom is replaced by a methylene group, form a class of carbohydrates mimics of increasing importance. Such compounds constitute useful glycosidase-resistant probes for the study, at the molecular level, of carbohydrate–protein interactions in lectins, antibodies and possible enzymes.

Of particular significance are the recent findings that methylene bridged analogs retain the same affinity as the substrate for their macromolecular receptors in a number of cases.[1,2] These results suggested that the interglycosidic oxygen atom of natural substrate is not involved in an essential interaction with the receptor. *C*-Disaccharides have been shown to have conformational properties close to those of the corresponding parent *O*-glycosides.[3] It is essential that the conformational behavior of the *C*-glycosides should be analogous to that of natural compound to minimize the entropic costs of the recognition process with receptor.[4]

C-Disaccharides have been the continuous pursuit of synthetic chemists and several methods have been developed. Sinaÿ and Rouzud reported the first example of a *C*-disaccharide, which was prepared by lactone and acetylide coupling.[5] Later on Schmidt and co-workers described the synthesis of *C*-disaccharides by condensation of nucleophilic 1-*C*-lithiated 2-(phenylsulphinyl)glycals with carbohydrate aldehydes.[6] Condensations of this class of aldehydes with enolates or furyllithium have been used for the preparation of *C*-disaccharides.[7,8] Other synthetic approach involves the coupling of carbohydrate derived aldehydes with glycosylnitromethane using Martin's procedure to afford 1-6 and 1-1 linked *C*-disaccharides.[9] Dondoni and co-workers reported that Wittig olefination of carbohydrate C-1 aldehydes with C-6 phosphoranes provided 1-6 linked *C*-disaccharides with very good yield.[10] Recently Taylor et al. have converted *S*-glycosides to *exo*-glycals via Ramberg–Bäcklund rearrangement. The synthetic sequence involved several steps with moderate yields. Subsequent hydrogenation afforded *C*-disaccharides.[11]

For several years we have been interested in the synthesis of olefinated sugars at the anomeric center via Wittig reaction of glycosyl phosphonium tetrafluoroborates.[12] Further interest is in the reaction of the enol ether function which affords numerous possibilities for transformations. This methodology was applied as a key step in the preparation of a galactopyranosyl alanine.[13] Recently we have reported the stereoselective glycosidations and the nitrile oxide additions to *exo*-glycals.[14,15] This synthetic approach allowed us to prepare carbohydrates with a quaternary anomeric carbon, with excellent stereoselectivity and very good yields. To build up this chemistry is indeed a synthetic challenge as can be seen, for example, in the recent synthesis of a novel galactosyltransferase inhibition. The preparation

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took more than six reaction steps from fully protected galactonolactone to construct two tethers extending from the anomeric center.[16]

We wish to report a method for the synthesis of *C*-disaccharides by a sequence involving the Wittig reaction as key step. Also we describe the glycosidation of these compounds to afford new *C*,*O*-trisaccharides.

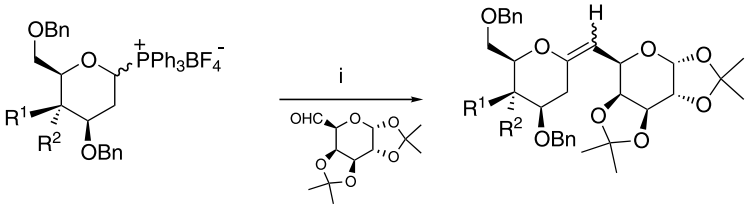
The enol ethers **3** were prepared by the Wittig reaction of the α,β mixture of 2-deoxiglycosyl phosphonium salts **1a**–**b** with the aldehyde **2** (Scheme 1). After filtration on silica gel the exocyclic enol ethers were obtained spectroscopically pure in the yields shown in Table 1, predominantly as the *Z* isomer.[17] The *E* and *Z* configurations were assigned on the basis of the chemical shifts of vinyl protons.[18]

The same reaction performed with the 2-deoxiribofuranosyl phosphonium salt only gave traces of the *exo*-glycals. Similar results were described by us in the reaction of this phosphonium salt with aliphatic aldehydes.[12]

The mixture of *E* and *Z* isomers was not separated and used directly in the next steps. Hydrogenation of the *exo*-glycals afforded the β *C*-disaccharides with good yields (Scheme 2). The presence of NOE effect between the H-7 and the H-11 in compounds **4** confirms the configuration of the disaccharides.[19]

The *O*-glycosidation employing the *exo*-glycals and the glycosyl acceptors **5** and **6** was illustrated in Scheme 3. To the best of our knowledge, no example of synthesis of this class of trisaccharides is known.

To a mixture of *E* and *Z* isomers and the glycosyl acceptors in dry methylenchloride, was added, under argon, 0.05 equiv. of BCl_3 at 0°C.[20] The results are shown in Table 2. Purification as usual afforded the trisaccharides **7** and **8** in good yields. In all cases ^1H NMR indicated the formation of one anomeric isomer (in the reaction mixtures and purified products). The ^1H, ^{13}C NMR, 2D COSY experiments and mass spectral data of the trisaccharides were in full accordance with their structure. The presence of NOE effect



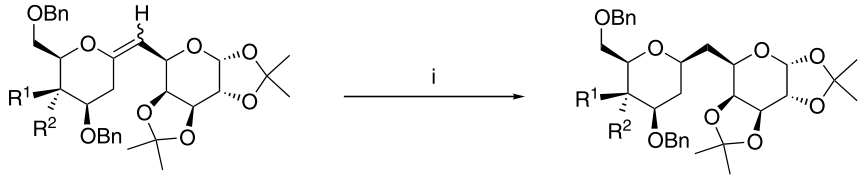
1a - b **2** **3a - b**

Scheme 1. *Reagents and conditions*: (i) BuLi, THF, –90°C, –90°C to rt.

Table 1. Wittig reaction of phosphonium salts **1a**–**b** with aldehyde **2**[a]

exo-Glycal		Yield (%)	Ratio (*E*/*Z*)[b]	NMR data of H-6	
				E	*Z*
3a	(Gal)	68	15:85	5.48	5.37
3b	(Glc)	63	10:90	5.60	5.32

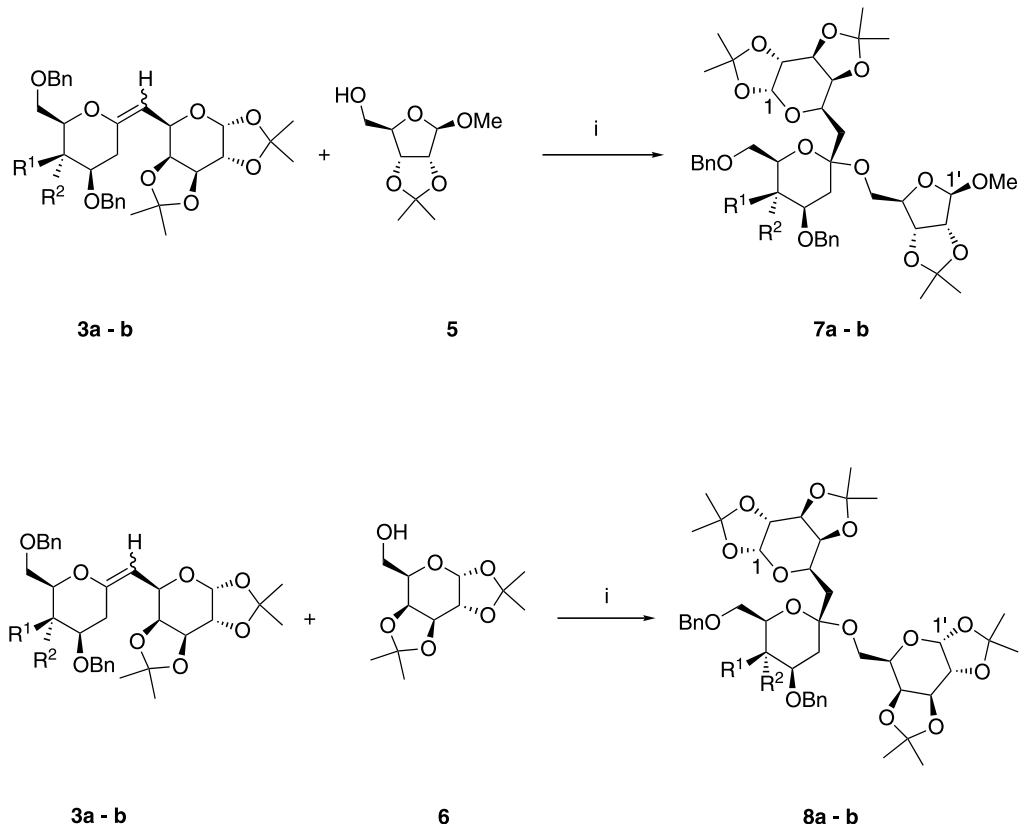
[a] The reactions were carried out in THF at –90°C (1 h) and then 12 h at room temperature.
[b] *E*/*Z* ratios determined by ^1H NMR of the reaction mixture.



3a - b **4a - b**

	R^1	R^2	Yield (%)
a	OBn	H	83
b	H	OBn	78

Scheme 2. *Reagents and conditions*: (i) H_2 (1 atm). Pd/C, Et_3N, MeOH.



Scheme 3. *Reagents and conditions*: (i) BCl_3 (0.05 equiv.), MS 4 Å, CH_2Cl_2, Ar, 0°C, 0.5 h.

Table 2. Glycosidations of *exo*-glycals **3a–b** with 0.05 equiv. of BCl_3[a]

exo-Glycal		R^1	R^2	ROH	Equiv.	Yield (%)
3a	(Gal)	OBn	H	**5**	1.5	45
					2	56
					3	63
					4	62
				6	1.5	38
					2	45
					3	60
					4	57
3b	(Glc)	H	OBn	**5**	3	60
				6	3	65

[a] The reactions were carried out at 0°C.

between the H-11 and H-5′ in compounds **7** and H-11 and H-6′ in compounds **8** confirms the configuration of the quaternary anomeric center. The high selectivity of the reaction and the stereochemical outcome can be explained in terms of the approach of the nucleophile to the less hindered face of the enol ether.[21] Higher quantities of the catalyst showed no effect on the reaction times or yields.[22]

Our methodology allowed us to prepare *C*-disaccharides in good yields and excellent stereoselectivity. Also the *O*-glycosidation of the intermediate *exo*-glycals proceeded in a highly stereoselective fashion to afford a new class of trisaccharides, which contained a quaternary anomeric center.

Further applications of the above method for the synthesis of various di- and trisaccharides will be presented in due course. Also the deprotection of the compounds described and enzymatic studies are currently in progress.

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17. The chemical shift of the vinyl protons could be assigned according to increment calculations carried out for olefinic compounds. See: (a) Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1969**, *49*, 164–168; (b) Pretsch, E.; Buhlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*; Springer Verlag: Berlin, 2000; 3rd English ed. Also the assignment was confirmed by comparison with earlier *exo*-glycals prepared by us. See: Refs. 12 and 13.
18. To a suspension of **1a** (770 mg, 1 mmol) in abs. THF (5 ml) at −90°C, *n*-BuLi (625 μL, 1.6 M in hexane, 1 mmol) was added over a period of 5 min. A solution of **2** (258 mg, 1 mmol) in abs. THF (2 mL) was added over a period of 10 min and the reaction was kept for 1 h at −90°C and then allowed to come to room temperature overnight. After evaporation in vacuo the solution of the residue in ethyl acetate was washed twice with $NaHCO_3$ (5%), twice with water, dried over $MgSO_4$ and concentrated in vacuo. The oily residue was treated with ethyl acetate/diethyl ether and then filtrated to separate off the triphenylphosphine oxide. After evaporation of the solvent in vacuo the residue was chromatographed on silica gel (eluent: hexane/ethyl acetate 8:2, containing 0.1% triethylamine) to afford compound **3a** as spectroscopically pure oil (458 mg, 68%, mixture $E/Z=$ 15:85).
    ^{1}H NMR (500 MHz, $CDCl_3$) Isomer *Z*: δ 1.30 (s, 3H, CH_3-C-O), 1.34 (s, 3H, CH_3-C-O), 1.44 (s, 3H, CH_3-C-O), 1.57 (s, 3H, CH_3-C-O), 2.62 (t, 1H, $J=13.4$, 8-Ha), 2.96 (dd, 1H, $J=4.7$, $J=13.4$, 8-Hb), 3.45 (m, 1H, 12-Ha), 3.58 (m, 1H, 12-Hb), 3.64 (m, 1H, 11-H), 3.76 (t, 1H, $J=6.3$, 9-H), 3.95 (s, 1H, 10-H), 4.08 (dd, 1H, $J=1.6$, $J=7.9$, 3-H), 4.29 (dd, 1H, $J=2.2$, $J=5.15$, 2-H), 4.39 (AB, 1H, $J=11.6$, CH_2Ph), 4.41 (m, 1H, 5-H), 4.47 (AB, 1H, $J=11.6$, CH_2Ph), 4.56–4.67 (m, 4H, 2′-H, CH_2Ph), 4.94 (AB, 1H, $J=11.5$, CH_2Ph), 5.37 (dd, 1H, $J=2.1$, $J=8.5$, 6-H), 5.56 (d, 1H, $J=5.15$, 1-H), 7.21–7.34 (m, 15H, Ph). Isomer *E*: 5.48 (d, 1H, $J=5$, 1-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2 ($\underline{C}H_3$-C-O), 24.8 ($\underline{C}H_3$-C-O), 26.0 ($\underline{C}H_3$-C-O), 26.4 ($\underline{C}H_3$-C-O), 27.2 (C-8), 63.5 (C-5), 68.9 (C-11), 69.8 (C-12), 70.0 ($\underline{C}H_2Ph$), 70.3 (C-2), 70.9 (C-4), 72.8 (C-10), 73.0 (C-3), 73.4 ($\underline{C}H_2Ph$), 74.2 ($\underline{C}H_2Ph$), 77.9 (C-9), 96.7 (C-1), 104.6 (C-6), 108.2 (O-$\underline{C}(CH_3)_2$), 108.9 (O-$\underline{C}(CH_3)_2$), 127.2–128.4, 137.9–138.7 (Ph), 155.4 (C-7). HRMS (FAB) calcd for $C_{39}H_{46}O_9Na$: 681.3039; found: 681.3039.
19. This high stereoselectivity was previously described by us and others in the hydrogenation of *exo*-glycals. See Refs. 11 and 13.
20. To a mixture of **3a** (338 mg, 0.5 mmol) and **5** (390 mg, 1.5 mmol) in dry CH_2Cl_2 (5 mL) was added, under argon, 5 μL of BCl_3 (1 M in CH_2Cl_2) at 0°C. The reaction was kept for 30 min at 0°C and then quenched with a satd solution of $NaHCO_3$ (10 mL). The organic layer was separated and washed with brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo to afford an oil. The residue was chromatographed on silica gel (eluent: hexane: ethyl acetate 8:2 containing 0.1% triethylamine) to afford **7a** as colorless syrup (298 mg, 63%).
    ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 3H, CH_3-C-O), 1.29 (s, 3H, CH_3-C-O), 1.33 (s, 3H, CH_3-C-O), 1.40 (s, 3H, CH_3-C-O), 1.43 (s, 3H, CH_3-C-O), 1.48 (s, 3H, CH_3-C-O), 2.00 (dd, 2H, $J=3.7$, $J=15.3$, 6-H), 2.04 (m, 1H, 8-Hb), 2.15 (t, 1H, $J=12$, 8-Ha), 3.23 (s, 3H, O-CH_3), 3.35 (m, 1H, 5′-Ha), 3.49 (t, 1H, 5′-Hb), 3.56 (m, 1H, 12-Ha), 3.61 (m, 1H, 12-Hb), 3.79 (t, 1H, $J=6.5$, 11-H), 3.87 (bs, 1H, 10-H), 3.94–3.99 (m, 2H, 5-H, 9-H), 4.09 (dd, 1H, $J=1.7$, $J=7.8$, 3-H), 4.20–4.25 (m, 2H, 2-H, 4′-H), 4.41–4.54 (m, 4H, CH_2Ph), 4.59 (m, 3H, CH_2Ph), 4.83 (d, 1H, $J=5.9$, 3′-H), 4.88 (AB, 1H, $J=11.7$, CH_2Ph), 4.92 (bs, 1H, 1′-H), 5.47 (d, 1H, $J=5.1$, 1-H), 7.14–7.35 (m, 15H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.5 ($\underline{C}H_3$-C-O), 24.9 ($\underline{C}H_3$-C-O), 25.0 ($\underline{C}H_3$-C-O), 25.9 ($\underline{C}H_3$-C-O), 26.0 ($\underline{C}H_3$-C-O), 26.5 ($\underline{C}H_3$-C-O), 33.8 (C-8), 37.1 (C-6), 54.8 (O-CH_3), 60.8 (C-5′), 63.9 (C-5), 69.4 (C-12), 70.2 (C-2), 70.4 ($\underline{C}H_2Ph$), 70.8 (C-4), 71.1 (C-11), 72.6 (C-10), 73.4 ($\underline{C}H_2Ph$), 73.9 (C-3), 74.2 ($\underline{C}H_2Ph$), 75.5 (C-9), 82.4 (C-3′), 85.2 (C-2′), 85.4 (C-4′), 96.5 (C-1), 100.8 (C-7), 108.5 (O-$\underline{C}(CH_3)_2$), 108.9 (O-$\underline{C}(CH_3)_2$), 109.5 (C-1′), 111.9 (O-$\underline{C}(CH_3)_2$), 127.3–128.8, 130.8, 132.4, 138.2, 138.7, 139.3 (Ph). HRMS (FAB) calcd for $C_{48}H_{62}O_{14}Na$: 885.4037; found: 885.4036.
21. Due to the fact that β isomer was not found in the reactions, the isomerization of the anomeric center under the reaction conditions could not be analyzed. Without these experiments, it is difficult to decide if kinetic or thermodynamic factors are responsible for the observed selectivity. Although, in related glycosidations using BCl_3 the predominance of the α isomer was shown to arise from the thermodynamic anomeric effect, see: Toshima, K.; Nagai, H.; Ushiki, Y.; Matsumura, S. *Synlett* **1998**, 1007–1009.
22. The use of other catalysts ($HBr{\cdot}PPh_3$, CSA) showed no effects on the stereoselectivity but lower yields were found. See Ref. 14.