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Stereoselective glycosidations of olefinated sugars†

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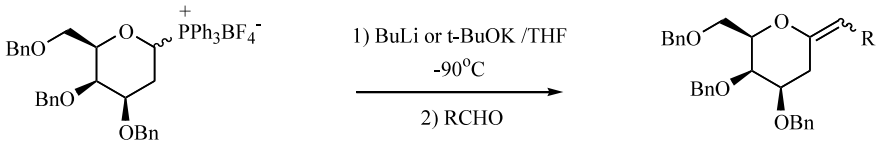
Abstract—The glycosidation of olefinated sugars using a catalytic amount of boron trichloride or triphenylphosphine hydrobromide proceeded in a highly stereoselective fashion to give the α anomers with good to high yields. The use of camphorsulphonic acid also afforded high stereoselectivity but lower yields were obtained.

During the last years the chemistry of *C*-glycosides has attracted much attention and the synthesis of *C*-glycosides analogues of biologically active molecules became of interest.[1] Particular useful are *exo*-glycals which are valuable in biological investigations: such compounds could be used as substrates for glycosidases to elucidate the enzymatic mechanism.[2] Also they are interesting intermediates in the synthesis of more complex *C*-glycosidic structures due to the highly reactive enol ether function.[3]

Various methods for glycosidations of *endo*-glycals have been reported. Mioskowski and Falck described the preparation of 2-deoxy-glucosides from glucals using triphenylphosphine hydrobromide.[4] The glucosides were obtained with good stereoselectivity (predominance of the α-anomer in all the cases). Later on Toshima et al. reported the glycosidation of glycals and different alcohols catalyzed by boron trichloride or tribromide.[5] The method afforded the glycosides with excellent stereoselectivity in high yields.

The glycosidation of *exo*-glycals is less addressed in the literature. Only recently Ikegami et al. have studied the syntheses of 1′-*C*-methyl-α-disaccharides by *O*-glycosidation of 1-methylene sugars catalyzed by trifluoromethansulfonic acid at −78°C.[6] During the writing of this work, Lin et al. reported the addition of alcohols to *exo*-glycals, synthesized by a nucleophilic addition of sugar lactones and subsequent dehydration.[7] In that method no preparation of disaccharides was reported.

For several years we have been interested in the syntheses of olefinated sugars at the anomeric center via



1

2a-b

a R= p-Clorophenyl
b R= Methyl

Scheme 1. Wittig reactions of phosphonium salt **1**.

Keywords: Wittig reaction; *exo*-glycals; *O*-glycosidation; disaccharides.

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Table 1. Wittig reaction of the phosphonium salt **1**[a]

exo-Glycal	R	Base	Yield (%)	Ratio (*E*/*Z*)
2a	*p*-Chlorophenyl-	BuLi	62	39/61
		t-BuOK	70	52/48
2b	Methyl	BuLi	65	18/82

[a] The reactions were carried out in THF at –90°C (2 h) and then 12 h at room temperature.

Wittig reaction of glycosyl phosphonium tetrafluorborates.[8] This methodology was also applied as a key step in the preparation of a galactopyranosyl alanine.[9] Here we describe the stereoselective glycosidation of tri-substituted exocyclic enol-ethers using boron trichloride, triphenylphosphine hydrogenbromide or camphorsulphonic acid as catalyst.

The *exo*-glycals were prepared by the Wittig reaction of the α,β-mixture of the 2-deoxigalactosyl phophonium salt[9] **1** with *p*-chlorobenzaldehyde or acetaldehyde to give the olefinated sugars **2a** and **2b** (Scheme 1).

After filtration on silica gel the exocyclic enol ethers were obtained spectroscopically pure in the yields and *E*/*Z* ratios shown in Table 1. The *E* and *Z* configurations could be assigned by the chemical shift of the vinyl protons according to increment calculations done for olefinic compounds[10a] and related enol ethers.[10b] The vinylic protons of the *E* isomers are shifted 0.3–0.7 ppm to a lower field than in the case of the *Z* isomers. This general trend was found previously by us in the synthesis of ribofuranosyl *exo*-glycals[8,9] and was confirmed by X-ray analysis of one *E*-isomer.[8] This trend was applied later by Taylor et al. to assign the configuration of *exo*-glycals prepared using the Bamberg–Bäcklund rearrangement.[8d]

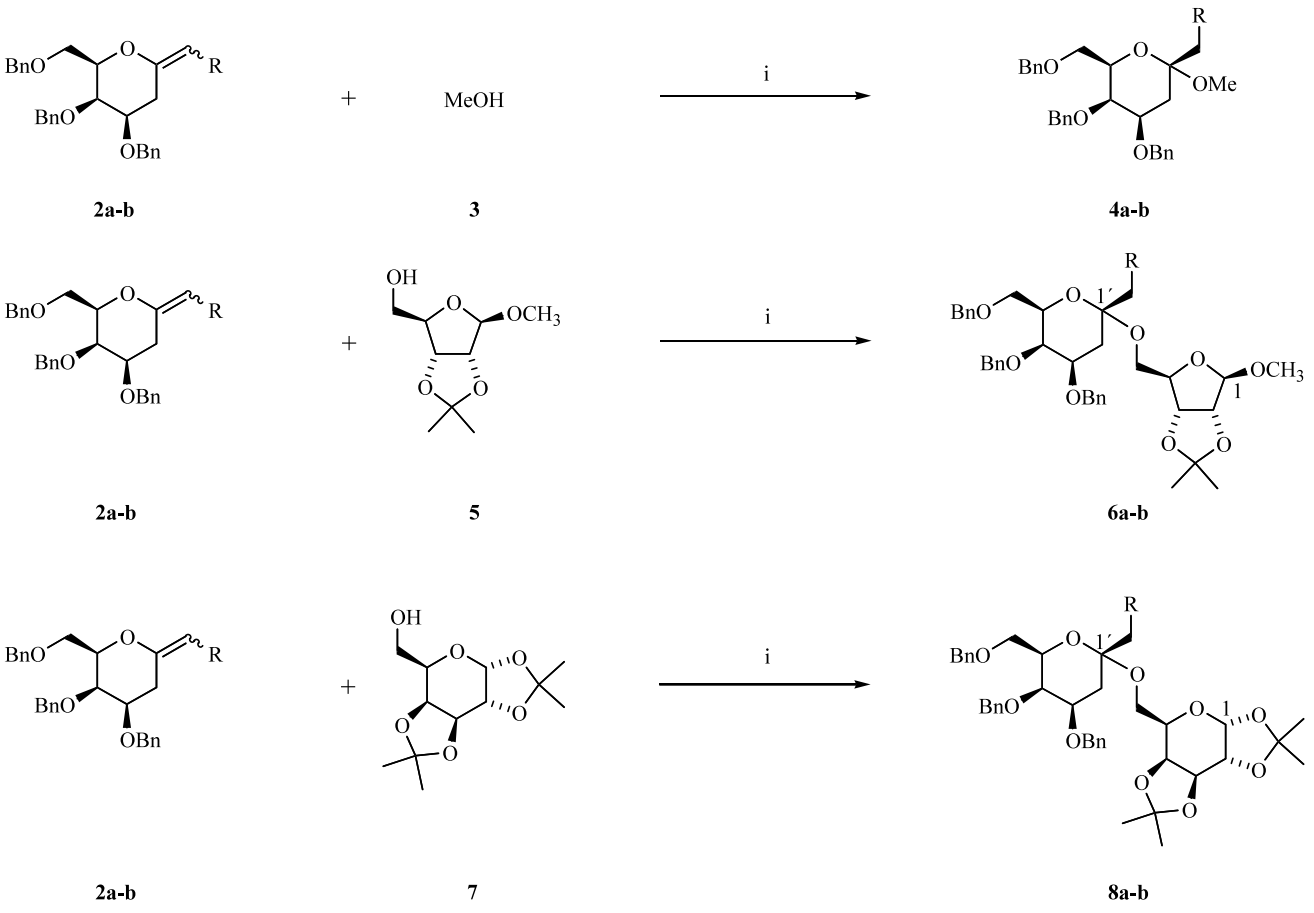
The mixture of the *E* and *Z* isomers was not separated and used directly in the next step. To a mixture of the enol ether (0.1 mmol) and the glycosyl acceptors (0.15 mmol) in dry methylenchloride, was added, under nitrogen, 0.05 equiv. of the catalyst in methylenchloride at the temperature indicated in Table 2.

Purification as usual afforded the glycosides **4a–b** and disaccharides **6a–b** and **8a–b** (Scheme 2).[11] In all the cases only the α anomeric isomer was found (in the reaction mixture and purified compound). The ^{1}H, ^{13}C NMR, 2D COSY (H–H, H–C) and NOESY experiments supported the proposed structures. The presence of NOE effect between the hydrogen of the methyl group and the H-5′ in compounds **4a–b**, the H-5 and H-5′ in compound **6a–b**, and H-6 and H-5′in compounds **8a–b** confirms the configuration of the glycosides. The high selectivity of the reaction and the stereochemical outcome is in accord with previous results found by us and other research groups in the additions to *exo*-glycals,[3b,6,7,9] and can be explained in terms of the approach of the nucleophile to the less hindered face of the enol ether, and also in the formation of the most thermodynamic stable α-isomer. The use of 0.10 equiv. of the catalyst only led to lower yields and they were not improved by using higher quantities of the glycosyl acceptor. The use of the different catalysts showed no effects on the stereoselectivity of the reaction but on the yields. Lower quantities of triphenylphosphine hydrobromide or camphorsulphonic acid showed no effect on the yields but longer reaction times were necessary.

In our method very low temperatures are not needed as in a previous reported synthesis[6] and it is possible to obtain a very valuable class of compounds, which could be used as marker in biological studies due to the presence of an aromatic substituent at the anomeric tetrasubstitued carbon. Also, our methodology used lower quantities of the nucleophiles as in other recently reported method.[7]

Table 2. Glycosidations of enol ethers **2a–b**

Enol ether	ROH	Catalyst	Time (min)	Temperature (°C)	Yield (%)
2a	**3**	BCl_3	30	0	84
		$HBr{\cdot}PPh_3$	60	Rt	73
		CSA	60	Rt	56
2b	**3**	BCl_3	10	0	80
		$HBr{\cdot}PPh_3$	15	Rt	61
		CSA	15	Rt	48
2a	**5**	BCl_3	30	0	89
		$HBr{\cdot}PPh_3$	60	Rt	72
		CSA	60	Rt	60
2b	**5**	BCl_3	10	0	78
		$HBr{\cdot}PPh_3$	15	Rt	70
		CSA	15	Rt	50
2a	**7**	BCl_3	30	0	77
		$HBr{\cdot}PPh_3$	60	Rt	57
		CSA	60	Rt	30
2b	**7**	BCl_3	10	0	78
		$HBr{\cdot}PPh_3$	15	Rt	53
		CSA	15	Rt	40



Scheme 2. *Reagents and conditions*: (i) Catalyst (0.05 equiv.), CH_2Cl_2, temperature and time as indicated in Table 2.

Further applications of the above method for the synthesis of various disaccharides will be presented in due course. Also, the deprotection of the disaccharides and enzymatic studies are currently in progress.

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11. Preparation of glycoside **6a**: To a mixture of 55 mg (0.1 mmol) of the enol ether **2a** (aprox E/Z 52:48) and 31 mg (0.15 mmol) of the methyl-2,3-di-*O*-isopropilidenribofuranoside **5** in 1 ml of dry methylenchloride was added, under nitrogen, 0.05 equiv. of the catalyst in methylenchloride. After stirring for the time indicated, the mixture was quenched with saturated $NaHCO_3$. The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a yellow oil. The residue was purified by chromatography on silica gel (eluent: hexane/ethyl acetate, 8:2) to give the product **6a** as a colorless syrup. IR (neat): 2936.3, 1492.6, 1453.6, 1369.8, 1208.3, 1093.8, 961.4, 869.4, 735, 697. ^{1}H NMR $\delta = 1.32$ (s, 3H, CH_3-C-O), 1.49 (s, 3H, CH_3-C-O), 1.83 (dd, 1H, $J = 4.4$, $J = 12.0$, 2′-Ha), 1.95 (t, 1H, $J = 12.0$, 2′-Hb), 2.84 (AB, 1H, $J = 14.1$, CH_2-Ph-Cl), 2.93 (AB, 1H, $J = 14.1$, CH_2-Ph-Cl), 3.28 (s, 3H, CH_3-O), 3.53 (m, 2H, 5-H), 3.63 (m, 2H, 6′-H), 3.8 (t, 1H, $J = 6.4$, 4′-H), 3.87 (bs, 1H, 3′-H), 3.9 (m, 1H, 5′-H), 4.5 (t, 1H, $J = 2.3$, 4-H), 4.26–2.6 (m, 7H, 2-H, 3-H, 2×CH_2-Ph, 1H, CH_2-Ph), 4.87 (AB, 1H, $J = 11.7$, CH_2Ph), 4.96 (bs, 1H, 1-H), 7.14–7.34 (m, 19H, Ph). ^{13}C NMR $\delta = 25.0$ ($\underline{C}H_3$-C-O), 26.5 ($\underline{C}H_3$-C-O), 33.4 (C-2′), 42.2 (CH_2-Ph-Cl), 54.9 ($\underline{C}H_3$-O), 61.0 (C-5), 69.3 (C-6′), 70.5 ($\underline{C}H_2$Ph), 71.6 (C-4′), 72.0 (C-5′), 73.4 ($\underline{C}H_2$Ph), 73.7 ($\underline{C}H_2$Ph), 75.7 (C-3′), 82.3 (C-4), 85.2 (C-2), 85.5 (C-3), 101.3 (C-1′), 109.4 (C-1), 112.3 ($(CH_3)_2\underline{C}$), 127.2–128.4, 131.6, 134.8, 138.1, 138.4, 139.1. HRMS (FAB): calcd for $C_{43}H_{49}O_9ClNa$: 767.2963, found: 767.2954.