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Stereoselective Palladium(0)-Mediated Synthesis of 1,4-Disaccharides

Denis Sinou, [a]* Isabelle Frappa,[a] Paul Lhoste, [a] Stanislaw Porwanski, [a,b] and Boguslaw Kryczka[b]

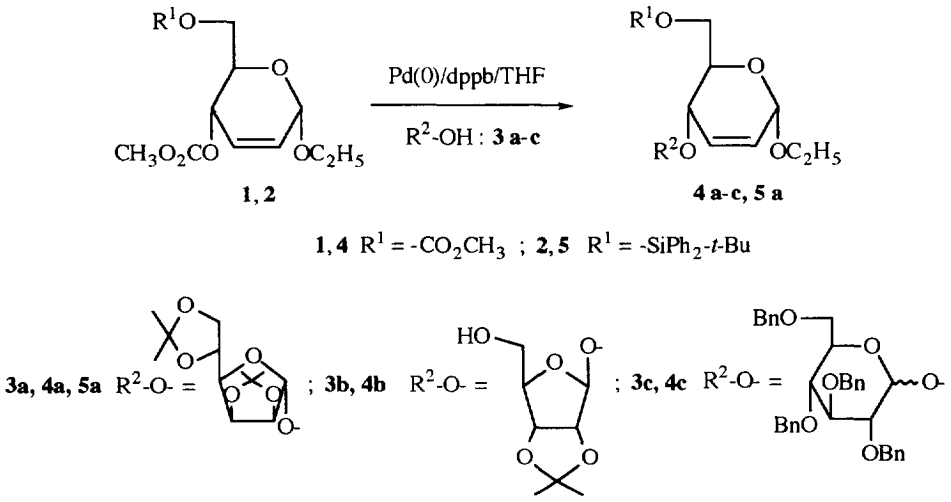
[a] Laboratoire de Synthèse Asymétrique, associé au CNRS, Université Lyon I, C.P.E. Lyon
43, boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

[b] Department of Organic and Applied Chemistry, University of Lodz, ul. Narutowicza 68, 90-136 Lodz, Poland

Abstract: Unsaturated 1,4-disaccharides are obtained in fairly good yields by alkylation of ethyl α-*O*-Δ^2-glycosides which have a leaving group at the position 4 with various carbohydrates having a free anomeric hydroxyl group in the presence of a catalytic amount of palladium(0).

Due to the important biological implications of glycoconjugates in molecular recognition, the *O*-glycosylation methodology and particularly the preparation of oligosaccharides is again becoming more and more important. Since the historical Kœnigs-Knorr synthesis the new methodologies, and particularly the Fischer-Helferich method, the variations of the Kœnigs-Knorr method, the trichloroacetamidate method and the anomeric *O*-alkylation method, have been directed towards the efficiency of this reaction (high chemical yield, regio- and stereoselectivity).[1] If the direct anomeric *O*-alkylation of pyranoses and furanoses with simple alkylating agents has been well established, there are surprisingly few examples of the use of this very simple methodology in complex saccharides synthesis.[2] A possible explanation was the ring-chain tautomerism between the two anomeric forms and the open-chain form leading to a non stereoselective reaction. However, this methodology was successfully used in the stereocontrolled glycoside and saccharide synthesis by direct anomeric *O*-alkylation of sugars by primary triflates. Following our interest in the formation of the carbon-oxygen bond catalyzed by palladium(0) complexes and particularly the use of this methodology in carbohydrate chemistry,[3] we expected the reaction of a sugar having a free anomeric hydroxyl group with an appropriate unsaturated carbohydrate to lead stereospecifically to the formation of an unsaturated disaccharide. By appropriate functionalization such unsaturated disaccharides would be valuable intermediates in the synthesis of complex natural or unnatural oligosaccharides.

The glycosylation reaction was conducted at room temperature under nitrogen in tetrahydrofuran in the presence of a catalyst prepared from $Pd_2(dba)_3$ and dppb [1,4-bis(diphenylphosphino)butane] using the unsaturated carbohydrate **1** or **2** as the π-allyl precursor and various carbohydrates **3** with a free anomeric hydroxyl group as the nucleophiles (Scheme 1). The results summarized in Table 1 showed that the unsaturated disaccharides were obtained with moderate to high chemical yields and that the reaction was regiospecific with *O*-alkylation occurring only at the C-4 position of the unsaturated carbohydrate; it was also



Scheme 1

Table 1. Preparation of 1,4-Disaccharides **4-5** [a]

Entry	Unsaturated carbohydrate	Unprotected carbohydrate	Product	α:β	Yield (%) [b]
1	**1**	**3a**	**4a**	100:0	43
2	**2**	**3a**	**5a**	100:0	85
3	**1**	**3b**	**4b**	0:100	54
4	**1**	**3b**	**4b**	0:100	70 [c]
5	**1**	**3c**	**4c**	59:41	37
6	**1**	**3c**	**4c**	44:56 [d]	23

[a] General procedure: a solution of substrates **1** or **2** (1 mmol) and **3** (2 mmol) in THF (3.5 mL) was added to a solution of $Pd_2(dba)_3$ (0.025 mmol) and 1,4-bis(diphenylphosphino)butane (0.1 mmol) in THF (3.5 mL) under argon. The mixture was stirred at room temperature for 24 h; after evaporation of the solvent, the product was purified by column chromatography. All new compounds show spectroscopic (^1H and ^{13}C NMR) and analytical data in accordance with their assigned structures. [b] Yield of purified product and not optimized. [c] **[3b]/[1]/[Pd]/[dppb]** = 10/20/1/2. [d] $P(C_6H_4\text{-}o\text{-}CH_3)_3$ was used as the ligand.

found that the reaction was stereoselective with complete retention of configuration at the unsaturated sugar, as expected with the *exo*-attack of the nucleophile on the π-allyl complex obtained by reaction of the palladium(0) complex on **1**. This stereochemistry was easily confirmed by ^1H NMR (Table 2)[4]; for example, a coupling constant of 9.5 Hz was observed for $J_{4,5}$ of the unsaturated moiety of the disaccharide **4a**, **4b**

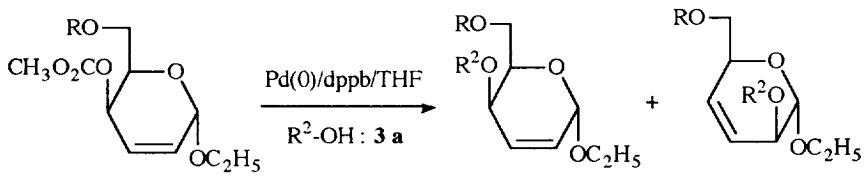
Table 2. Some Characteristic NMR Values of 1,4-Disaccharides **4-5**

Compound	δ H-4 ppm	$J_{4,5}$ Hz	δ H-1' ppm	$J_{1',2'}$ Hz
4a	4.22	9.5 (ddd)	5.12	(s)
5a	4.01	9.5 (ddd)	5.12	(s)
4b	4.25	9.5 (bd)	5.22	(s)
4c	α 4.24	9.8 (bd)	4.95	3.5 (d)
	β 4.28	9.5 (bd)	4.79	9.6 (d)

and **5a**, which is characteristic of an axial-axial position of two hydrogens. As expected, compounds **4a** and **5a** and compound **4b** had respectively the α and β configuration at the anomeric centre of the saturated carbohydrate moiety, the signal of H-1' being a singlet. The reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **3c** with the unsaturated carbohydrate **1** gave a mixture of α and β anomers in a ratio 59:41. This ratio could be changed to 44:56 using $P(C_6H_4\text{-}o\text{-}CH_3)_3$ as the palladium ligand. The α and β configurations of the glucopyranose moiety were easily assigned by comparing the coupling constant of H-1' at δ = 4.79 ppm for the β anomer ($J_{1',2'}$ = 9.6 Hz) and at δ = 4.95 ppm for the α anomer ($J_{1',2'}$ = 3.5 Hz). The reaction was again stereoselective at the unsaturated sugar ($J_{4,5}$ = 9.8 Hz and 9.5 Hz for respectively the α and β anomer).

It is to be noted that the reaction of compound **2**, where the carbonate at the 6-position was substituted by a diphenyl-*t*-butylsilyl protective group, with **3a** gave a 85 % chemical yield of the disaccharide **5a** (43 % using **1** as the starting material). In the case of the ribose derivative **3b**, which has two free hydroxyl groups, increasing the amount of this carbohydrate leads to the formation of the 1,4-disaccharide **4b** only, but now with 70 % chemical yield.

Under the usual conditions, the unsaturated carbohydrate **6** (R = Si-*t*-$BuPh_2$) reacted with the mannofuranose derivative **3a** to give a mixture of the two regioisomers **7** and **8** in respectively 21 and 61 % chemical yields (Scheme 2). The formation of these two regioisomers agrees with Baer's results [5] concerning the alkylation of unsaturated carbohydrates with malonate in the presence of palladium(0). The formation of compound **7** was again stereospecific with a coupling constant $J_{4,5}$ = 2.4 Hz characteristic of an equatorial-axial positioning of the two hydrogens.



6 **7** **8**

Scheme 2

Further applications of this mild methodology of glycosylation to the synthesis of other unsaturated di- and trisaccharides and their transformations into both common and less common carbohydrates is now under investigation.

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References and notes

1. a) Wulff, G.; Röhle, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 157-170.
   b) Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*; Pergamon Press: Oxford, 1979.
   c) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155-173.
   d) Paulsen, H. *Chem. Soc. Rev.* **1984**, *13*, 15-45.
   e) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212-235.
   f) Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 294-308.
   g) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257-1270.
   h) Schmidt, R. R. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 6, pp. 33-64.
   i) Sinay, P. *Pure Appl. Chem.* **1991**, *63*, 519-528.
   j) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167-1195.
   k) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503-1531.
2. a) Schmidt, R. R.; Reichrath, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 466-467.
   b) Schmidt, R. R.; Reichrath, M.; Moering, U.*Tetrahedron Lett.* **1980**, *21*, 3561-3564.
   c) Schmidt, R. R.; Moering, U.; Reichrath, M. *Chem. Ber.* **1982**, *115*, 39-49.
   c) Schmidt, R. R.; Moering, U.; Reichrath, M. *Tetrahedron Lett.* **1980**, *21*, 3565-3568.
   d) Schmidt, R. R.; Reichrath, M.; Moering, U. *J. Carbohydr. Chem.* **1984**, *3*, 67-84.
   e) Oltvoort, J. J.; Kloosterman, M.; Van Boeckel, C. A. A.; Van Boom, J. H. *Carbohydr. Res.* **1984**, *130*, 147-163.
3. a) Lakhmiri, R.; Lhoste, P.; Boullanger, P; Sinou, D. *J. Chem. Res (S)* **1990**, 342; *(M)* **1990**, 2301-2315.
   b) Goux, C.; Lhoste, P.; Sinou, D. *Synlett* **1992**, 725-727.
   c) Lakhmiri, R.; Lhoste, P.; Kryczka, B.; Sinou, D. *J. Carbohydr. Chem.* **1993**, *12*, 223-235.
4. H' refers to the glycosyl part of the disaccharides.
5. Baer, H. H.; Hanna, Z. S. *Can. J. Chem.* **1981**, *51*, 889-906.

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