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A Pd(0)-catalyzed route to functionalized β-C-Glycosides from β-C-Glycosylaldehydes

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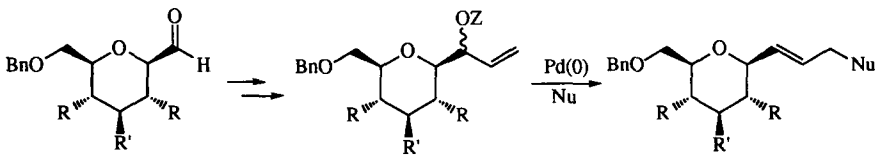
Abstract : *C-glycosides are synthesized in five steps starting from β-C-glycosylaldehydes 1 and 2. The key step is a Pd(0)-catalyzed alkylation that leads regio and stereoselectively to exotic compounds by formation of C-C and C-N bonds.* © 1997 Published by Elsevier Science Ltd.

C-glycosides are an important class of compounds which have raised frantic efforts by chemists and biochemists[1]. They are important building blocks in the synthesis of natural products[2] and carbohydrate biological probes which are inert to O-glycosidic bond cleavage by glycosidases.[1] Several methods for their preparation have been developed[1] but few of them use the potential of a transition metal.[1, 3] As part of an ongoing program in palladium catalyzed alkylations,[4] we wish to report a general synthesis of functionalized C-glycosides. In connection with our studies towards the synthesis of ambruticin,[5] we recently developed a methodology to afford β-C-glycosylaldehydes,[6] which are potential precursors of C-glycosides. Our strategy, described in Scheme 1 starts from β-C-glycosylaldehydes **1** or **2**. The allylic compounds **3** reacted with several nucleophiles to give the C-glycosides **4**.



1 R = R' = OBn
2 R = H, R' = OtBu

3

4

Scheme 1

The allylic compounds were synthesized in five steps as illustrated in Scheme 2. The aldehydes[7] were treated with an excess of the Grignard reagent of trimethylsilylacetylene in diethyl ether in the presence of anhydrous magnesium bromide[8] at low temperature to give two diastereomers[9].

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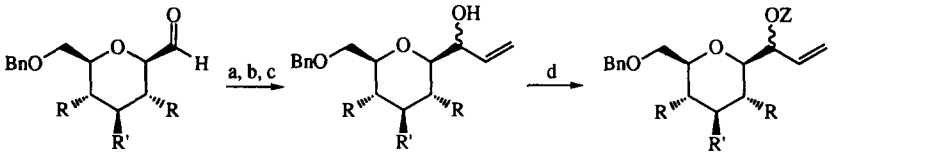
Desilylation followed by partial hydrogenation gave the allylic alcohols in high yields. The Pd(0) leaving group has been introduced either by treatment with 2,4-dichlorobenzoyl chloride to give **7** and **9** or ethylchloroformate to give **8**.



1 R = R' = OBn
2 R = H, R' = OtBu

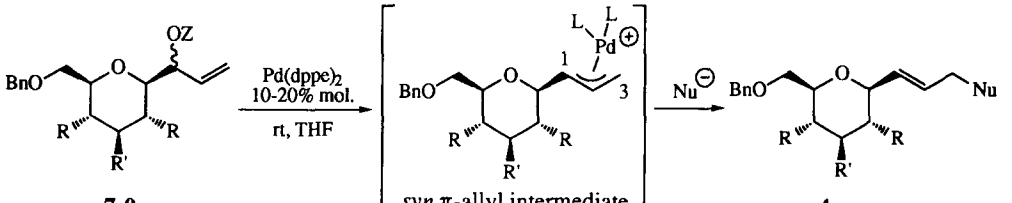
5 R = R' = OBn
6 R = H, R' = OtBu

7 R = R' = OBn Z = CO-2,4-$Cl_2C_6H_3$
8 R = R' = OBn Z = CO_2Et
9 R = H, R' = OtBu Z = CO-2,4-$Cl_2C_6H_3$

(a) $MgBr_2$ 8eq, Et_2O, then $Me_3SiCCMgBr$ 4eq, -30°C, 41-73%. (b) K_2CO_3, MeOH, rt, 99%. (c) Pd Lindlar, quinoline, AcOEt, H_2, rt, 97%. (d) ClCO-2,4-$Cl_2C_6H_3$ or $ClCO_2Et$, pyridine, CH_2Cl_2, 0°C-rt, 80-99%.

Scheme 2

The alkylation reactions were easily carried out in tetrahydrofuran at room temperature. The $Pd(dppe)_2$ catalyst (10-20% mol.) was first generated by the addition of the diphosphine ligand to $Pd(OAc)_2$. To a solution of this catalyst and the allylic substrate in tetrahydrofuran at room temperature was added the desired nucleophile as its sodium salt anion. The palladium-catalyzed reaction was first examined for the anions derived from dimethyl malonate (Table 1, entries 1,2) and ethyl nitroacetate (Table 1, entries 3,4). In both cases, for the tetra-O-benzyl **7** and the dideoxy **9**, the corresponding C-glycosides **4a-4d** were obtained in good yield. This S_N2' reaction was cleanly regio- and stereoselective. The structure of the C-glycosidic products and especially the *E*-stereochemistry of the double bond were confirmed by proton and carbon NMR. These results suggest that the reaction proceeds through a common transient intermediate, a palladium π-allyl complex (Scheme 3)[10]. The total regioselectivity is in favor of addition of the nucleophile on the terminal carbon atom, C_3. The *E*-stereoselectivity observed in those reactions arises from the *syn* π-allylic intermediate which is more stable.



7-9

syn π-allyl intermediate

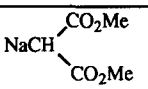
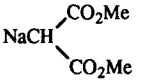
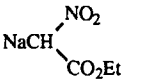
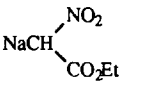
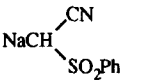
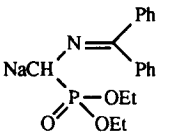
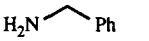
4a-g

Scheme 3

This reaction was further exploited in the case of the tetra-O-benzyl compound **7** with the use of (phenylsulfonyle)acetonitrile (entry 5) and a Schiff phosphonic base[11] (entry 6). The resulting C-glycosides **4e**

and **4f** were isolated after chromatography in 44 to 58 % yield (Table 1). The formation of a C-N bond was also realized by the addition of benzylamine (entry 7) to tetra-O-benzyl **8**.

Table 1. Palladium catalyzed reaction of allylic C-glycosides **3**

Entry	Substrate	Nucleophile	Product	Yield (%)
1[a]	**7**		**4a**	71[12]
2[a]	**9**		**4b**	55[c]
3[b]	**7**		**4c**	48
4[a]	**9**		**4d**	65[12]
5[b]	**7**		**4e**	58
6[a]	**7**		**4f**	44[d]
7[a]	**8**		**4g**	44[12]

(a) 10% $Pd(dppe)_2$ (b) 20% $Pd(dppe)_2$ (c) and 21% of recovery starting material
(d) and 39% of recovery starting material

In summary, a new and simple method for the synthesis of functionalized β-C-glycosides has been developed from β-C-glycosylaldehydes using π-allyl palladium chemistry.

Acknowledgement

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(7) In the case of the aldehyde **2**, the methodology described in ref. 6 was applied starting from the corresponding lactone synthesized by Dujardin, G..

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(9) The separation of these diastereomers has been realized but is not required for the next step.

(10) The intramolecular alkylation of π-allyl palladium complexes bearing an oxygen at the C_4-position shows high regioselectivity, namely 1,4-addition took place rather than 1,2-addition, for seminal examples of this useful synthetic method see : (a) Genêt, J.P.; Piau, F.; Ficini, J. *Tetrahedron Lett.* **1980**, *21*, 3183-3186. (b) Genêt, J.P.; Piau, F. *J. Org. Chem.* **1981**, *46*, 2414-2417. (c) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575-2578. (d) Trost, B.M.; Molander, G.A. *J. Am. Chem. Soc.* **1981**, *103*, 5969-5972.

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(12) **4a** $[\alpha]_D^{20}$ = +10 (c = 1, $CHCl_3$). IR (neat): 1680, 1740. ^1H NMR (200 MHz, $CDCl_3$): 7.37-7.13 (m, 20H), 5.83 (dt, 1H, J = 15.5, 6.5 Hz), 5.66 (dd, 1H, J = 15.5, 6.3 Hz), 4.96-4.51 (m, 8H), 3.71 ; 3.70 (2s, 6H), 3.77-3.43 (m, 6H), 3.46 (t, 1H, J = 7Hz), 3.31 (app. t, 1H, J = 9Hz), 2.69 (app. t, 2H, J = 7, 6.5Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 169.1, 169.0, 138.5, 138.0, 137.9, 130.3, 129.7, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 86.6, 82.3, 79.5, 78.6, 78.1, 52.5, 75.5, 74.9, 73.4, 68.8, 51.1, 31.6. MS (C.I.): m/z = 712 ($M+NH_4^+$). **4d** ^1H NMR (250 MHz, $CDCl_3$): 7.34-7.26 (m, 5H), 5.71 (dt, 1H, J = 4.6, 15.6Hz), 5.58 (dd, 1H, J = 6.3, 15.6Hz), 5.12 (m, 1H), 4.59; 4.52 (ABsyst, 2H, J = 12.2Hz), 4.27 (q, 2H, J = 7.2Hz), 3.86-3.38 (m, 5H), 2.88 (m, 2H), 1.76 (m, 2H), 1.32 (t, 3H, J = 7.2Hz), 1.24 (m, 2H), 1.19 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$): 164.1, 138.3, 136.3, 136.2, 128.4, 127.8, 127.7, 122.9, 122.7, 87.6, 87.5, 75.7, 75.5, 75.4, 73.9, 73.5, 73.3, 67.3, 63.2, 40.8, 40.7, 37.5, 33.1, 28.6, 14.0. MS (C.I.): m/z = 467 ($M+NH_4^+$). **4g** IR (neat): 3255, 1685. ^1H NMR (250 MHz, $CDCl_3$): 7.32-7.01 (m, 25H), 5.98 (dt, 1H, J = 15.5, 5.9 Hz), 5.71 (dd, 1H, J = 15.5, 6.5 Hz), 4.94-4.38 (m, 8H), 3.81-3.27 (m, 9H), 2.2 (bs , 1H). ^{13}C NMR (63 MHz, $CDCl_3$): 139.8, 138.7, 138.6, 138.2, 138.1, 132.4, 129.1, 129.0, 128.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.4, 127.1, 86.9, 82.5, 79.8, 78.8, 78.3, 75.8, 75.1, 73.6, 69.1, 53.2, 50.5. MS (C.I.): m/z = 670 ($M+NH_4^+$).

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