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Aglycon Directed Palladium β-Alcoxyelimination on Carbohydrate Templates

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Abstract:

The palladium(0)-catalyzed Heck-type cyclisation reaction of *erythro* or *threo* aryl 2,3-unsaturated glycosides gave the enantiopure bicyclic compounds in quite good yields *via* a palladium β-alcoxyelimination.

Key words: carbohydrates; palladium(0); bicyclic compounds; β-alcoxyelimination.

Carbohydrates are cheap raw materials available for the preparation of enantiomerically pure molecules.Their transformation into densely functionalized and enantiomerically pure carbocycles, particularly *via* radical cyclisation, is now a well established methodology [1-3]. Organometallic-catalyzed access to such structures is less common. The palladium-mediated cyclisation of the appropriate glycals or pseudoglycals gave enantiopure functionalized cyclopentanes and their heterocyclic analogues [4,5]. The key step in the synthesis of enantiopure cyclopentenones and cyclopentadienes was a palladium-mediated [3 + 2] cycloaddition [6]. The Pauson-Khand reaction was also applied to the synthesis of bis-annulated pyranosides [7].

We recently described the use of an intramolecular palladium-catalyzed Heck reaction in carbohydrate chemistry. The *erythro* pseudo-glucal **1**α or β led to the formation of the bicyclic glucal **2**, whereas the *threo* derivative **3**α or β gave the functionalized tetrahydrofuran **4**, *via* an unusual dealkoxypalladation pathway [8]. We postulated for this reaction a non-concerted mechanism. We present in this paper conditions leading to the formation of the bicyclic glucal in the *erythro* and the *threo* series.

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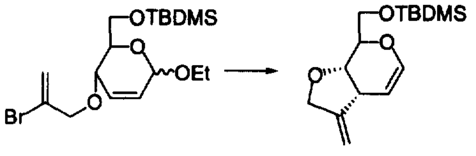
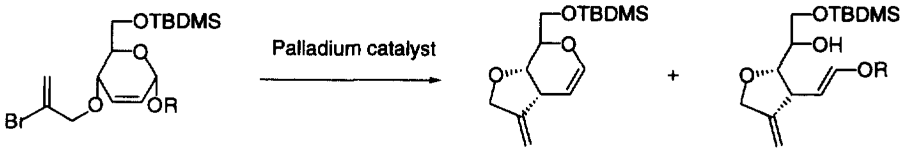


1 *α/β erythro* **2**

3 *α/β threo* **4**

The 2,3-unsaturated glycosides **5 a-c** having the *erythro* configuration were prepared from ethyl, *p-tert*-butylphenyl, and *p*-nitrophenyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-**D**-*erythro*-hex-2-enopyranosides [9, 10], respectively, according to the procedure previously described [8]. The same methodology was used for the preparation of 2,3-unsaturated carbohydrates **8 a-d** having the *threo* configuration, after inversion of configuration at C-4 *via* a Mitsunobu reaction.

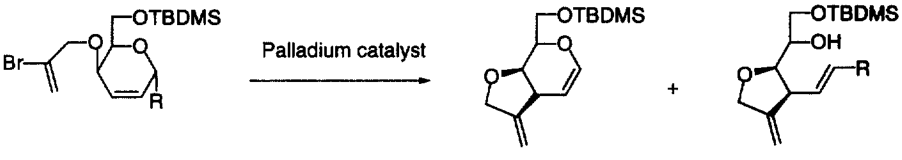
Treatment of 2,3-unsaturated carbohydrates **5a-c** in a CH_3CN-H_2O (5-1) mixture in the presence of Bu_4NHSO_4 (1 equiv), Et_3N (2.5 equiv), $Pd(OAc)_2$ (0.1 equiv), and PPh_3 (0.2 equiv), gave the bicyclic derivative **6** in 72, 32, and 23 % yield, respectively (entries 1, 3 and 5) (Table). However, for compounds **5b** and **5c**, the reaction has to be conducted at lower temperature due to the degradation of the starting material at 80 °C. When the reaction was performed in DMF instead of CH_3CN-H_2O, compound **5a** lead to the formation of the bicyclic derivative **6** and the tetrahydrofuran derivative **7a** in 50 % and 20 % yield, respectively (entry 2). In this case we observed the cleavage of the carbon-oxygen bond of the ring and also of the aglycon moiety. However, under the same conditions, compound **5b** gave only the bicyclic structure **6** in quite good yield (70 %) (entry 4); this quite different behaviour is probably due to the replacement of the -OEt group by a O-C_6H_4-*p*-Bu^t which is a better leaving group and so could be cleaved more easily.



5 a-c **6** **7 a**

a: R = C_2H_5; **b**: R = C_6H_4-*p*-Bu^t; **c**: R = C_6H_4-*p*-NO_2

Using CH_3CN-H_2O as the solvent, the unsaturated *threo* derivative **8b** gave the tetrahydrofuran structure **10b** resulting from the cleavage of the cyclic carbon-oxygen bond in 57 % yield (entry 7) [8]. Conversely the aryl 2,3-unsaturated glycosides **8c** and **8d** led to the bicyclic product **9** resulting from the fragmentation of the aglycon moiety in 32 and 30 % yield, respectively (entries 8 and 9). The reaction has also to be performed at lower temperature, due to the formation of large amounts of by-products at 80 °C. The structure of the bicyclic compound **9** was confirmed by NMR [11], and also by synthesis; treatment of dihydropyran **8a** by a catalytic amount of palladium-catalyst in CH_3CN-H_2O in the presence of NEt_3 and Bu_4NHSO_4 at 50 °C gave compound **9** in 51 % yield *via* a classical Heck-type cyclisation reaction. This quite different behaviour between **8b** and **8c-d** could be attributed to the presence of a better leaving group at the anomeric center. These results are also in good agreement with the before proposed ionic mechanism [8].



8 a-d **9** **10 b**

a: R = H; **b**: R = OC_2H_5; **c**: R = OC_6H_4-*p*-Bu^t; **d**: R = OC_6H_4-*p*-NO_2

Table : Palladium(0)-mediated Cyclisation of Unsaturated Carbohydrates **5** and **8**.[a]

Entry	Starting material	T °C/time (h)	Solvant	Compounds (Yield)[b]
1	**5a**	80/10	CH_3CN-H_2O (5-1)	**6** (72 %)
2	**5a**	80/24	DMF	**6** (50 %) + **7a** (20 %)
3	**5b**	50/30	CH_3CN-H_2O (5-1)	**6** (32 %)
4	**5b**	80/24	DMF	**6** (70 %)
5	**5c**	40/27	CH_3CN-H_2O (5-1)	**6** (23 %)
6	**8a**	50/17	"	**9** (51 %)
7	**8b**	80/10	"	**10b** (57 %)
8	**8c**	50/53	"	**9** (32 %)
9	**8d**	40/29	"	**9** (30 %)

[a] [**5**] or [**8**]:[NEt_3];[Bu_4NHSO_4]:[$Pd(OAc)_2$]:[PPh_3] = 10:25:10:1:2

[b] Isolated yields after column chromatography on silica gel. Analytical data for **7a** and **9** are given in ref. [11].

In conclusion we have shown that bicyclic carbohydrate-derivatized compounds could be obtained from 2,3-unsaturated glycosides having the *erythro* or the *threo* configuration using a Heck-type cyclisation reaction by a judicious choice of the aglycon moiety, expanding the scope of this unusual cyclisation reaction.

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[11] Selected spectroscopic data. Compound **7a**: oil; R_f 0.35 (petroleum ether:ethyl acetate 10:1); $[\alpha]_D^{20}$ -20 (c 0.7, CH_2Cl_2); ^{1}H (200 MHz, $CDCl_3$) δ 0.07 (s, 6H, SiMe), 0.09 (s, 9H, $SiCMe_3$), 1.29 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.40 (s, 1H, OH), 3.32 (bdd, 1H, J = 7.2 and 7.2 Hz, >CH-CH=), 3.63-3.92 (m, 5H, CH_2OSi, >CHO-, $CH_3C\mathit{H}_2O$), 4.27 (bd, 1H, J = 13.2 Hz, OCH_2), 4.42 (ddd, 1H, J = 13.2, 1.9 and 1.9 Hz, OCH_2), 4.82 (dd, 1H, J = 12.8 and 9.2 Hz, =CH-C), 4.98 (dd, 1H, J = 4.0 and 1.8 Hz, $=CH_2$), 5.01 (dd, 1H, J = 4.0 and 2.2 Hz, $=CH_2$), 6.35 (d, 1H, J = 12.5 Hz, $=C\mathit{H}\text{-}OC_2H_5$); ^{13}C (50 MHz, $CDCl_3$) δ -5.4 (SiMe), -5.3 (SiMe), 14.8 (CH_3), 18.4 ($Si\mathit{C}Me_3$), 26.0 ($SiC\mathit{Me}_3$), 46.1 (CH-CH=), 64.7 and 64.8 (CH_2OSi and $CH_3\mathit{C}H_2O$), 70.5 (OCH_2), 70.7 (CHOH), 82.1 (CHO), 101.1 (-CH=), 105.8 ($=CH_2$), 148.0 (=CH-O), 151.4 ($\text{-}\mathit{C}{=}CH_2$). Calcd for $C_{17}H_{32}O_4Si$: C, 62.16; H, 9.83. Found: C, 61.85; H, 9.66. Compound **9**: oil; R_f 0.14 (petroleum ether:ethyl acetate 30:1); $[\alpha]_D^{20}$ -138 (c 1, CH_2Cl_2); ^{1}H (200 MHz, $CDCl_3$) δ 0.09 (s, 6H, SiMe), 0.91 (s, 9H, $SiCMe_3$), 3.23 (m, 1H, >CH-CH=), 3.80-3.91 (m, 3H, CH_2OSi, CHO), 4.26 (dd, 1H, J = 7.1 and 1.5 Hz, CHO), 4.26 (ddd, 1H, J = 13.0, 2.4 and 2.0 Hz, CH_2O), 4.56 (ddd, 1H, J = 13.0, 2.4 and 2.0 Hz, CH_2O), 4.51-4.59 (m, 1H, -CH=), 4.92 (ddd, 1H, J = 5.7, 2.0 and 2.0 Hz, $=CH_2$), 5.05 (ddd, 1H, J = 5.7, 2.4 and 2.4 Hz, $=CH_2$), 6.39 (dd, 1H, J = 5.9 and 1.6 Hz, O-CH=); ^{13}C (50 MHz, $CDCl_3$) δ -6.0 (SiMe), -5.7 (SiMe), 18.5 ($Si\mathit{C}Me_3$), 26.0 ($SiC\mathit{Me}_3$), 40.6 (CH-CH=), 62.8 (CH_2OSi), 70.7 (OCH_2), 74.0 and 76.2 (CHO), 102.5 (-CH=), 105.0 ($=CH_2$), 143.2 (OCH=), 150.9 ($\mathit{C}{=}CH_2$). Calcd for $C_{15}H_{26}O_3Si$: C, 63.46; H, 9.39. Found: C, 63.79; H, 9.28.