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Palladium-Mediated Cyclisation on Carbohydrate Templates A New Route to Bis-Annulated Pyranosides

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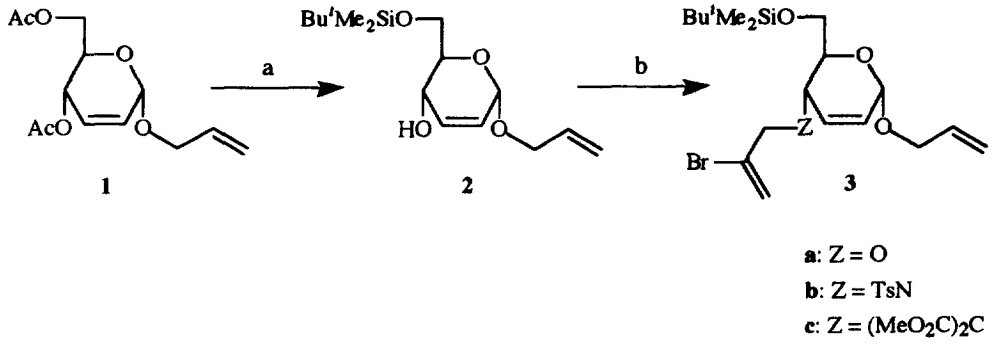
Key Words: Palladium-catalysed cyclisation, Heck reaction, carbohydrate templates, bis-annulated pyranosides

Abstract: A new and efficient route to bis-annulated pyranosides by palladium(0)-catalysed cascade cyclisation is described. The appropriate 2,3-unsaturated allylglycosides are subjected to Heck reaction under smooth Jeffery's conditions to produce the tricyclic derivatives in good yields.

Over the past few years, the use of transition metal complexes has provided important new methodologies for the stereospecific elaboration of a variety of carbo- and heterocycles, sometimes *via* cascade reactions.[1] Despite the precise stereochemistry and rich functionality of the carbohydrate core in the synthesis of polycyclic molecules, the use of sugar templates for such organometallic-catalysed stereoselective cyclisation remains still quite rare. Some examples of homochiral substituted cyclopentanes and their heterocyclic analogues were prepared *via* palladium-mediated cyclisation of the appropriate pseudoglycals.[2] Bis-annulated pyranosides were also obtained by the Pauson-Khand reaction.[3]

Recent work in our laboratory was interested about the development of new synthetic methodologies in carbohydrate chemistry involving organometallic catalysis.[4] Herein, we whish to report a novel cascade-cyclisation strategy for the construction of bis-annulated pyranosides.

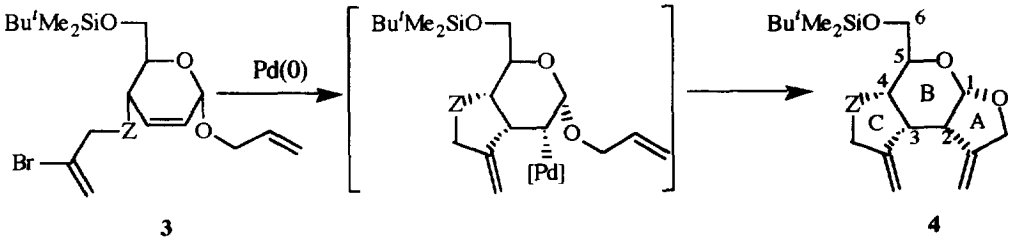
The appropriate carbohydrate precursors **3** for the present study were prepared from readily accessible allyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **1** by standard methods.[6] Deacetylation of compound **1** followed by reaction with 1.25 equivalents of Bu^tMe_2SiCl furnished the 2,3-dideoxyhexenopyranoside **2**. The intermediate **3a** was then obtained by etherification of **2** with 2,3-dibromopropene. The precursors **3b** and **3c** were synthesised by palladium-catalysed alkylation[7] of the carbonate derived from **2**, respectively with N-*p*-toluenesulfonyl(2-bromo-2-propenyl)amine and methyl (4-bromo-2-methoxycarbonyl)4-pentenoate (Scheme 1).



Reagents and conditions: a) CH_3ONa, CH_3OH, quant.; 1.25 eq. Bu^{t}Me$_2$SiCl, 1.3 eq. NEt_3, 0.05 eq. imidazole, CH_2Cl_2, r.t., 24 h, 80 %; b) for compound **3a**: 2 eq. $BrCH_2CBr{=}CH_2$, 2 eq. NaH, dry THF, 60 °C, 24 h, 70 %; for compound **3b**: 5 eq. $ClCOOCH_3$, 5 eq. NEt_3, CH_2Cl_2, r.t., 24 h, 75 %, then 2 eq. $TsNHCH_2CBr{=}CH_2$, 0.05 eq. $Pd_2(dba)_3$, 0.10 eq. dppb, dry THF, 60 °C, 24 h, 70 %; for compound **3c**: 5 eq. $ClCOOCH_3$, 5 eq. NEt_3, CH_2Cl_2, r.t., 24 h, 75 %, then 2 eq. $(MeO_2C)_2CHCH_2CBr{=}CH_2$, 0.05 eq. $Pd_2(dba)_3$, 0.10 eq. dppb, THF, 60 °C, 6 h, 80 %

Scheme 1

The carbohydrate derivatives **3** were converted into the corresponding bis-annulated pyranosides **4** *via* a 5-*exo trig* cascade cyclisation, in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3, under Jeffery's conditions, in quite good yields (Scheme 2).[8]



Reagents and conditions: 0.10 eq. $Pd(OAc)_2$, 0.20 eq. PPh_3, 2.5 eq. NEt_3, 1.0 eq. Bu_4NBr, CH_3CN / H_2O (5 / 1), 80 °C, 24 h (Z = O), 20 h (Z = NTs), 16 h [Z = $(MeO_2C)_2C$]

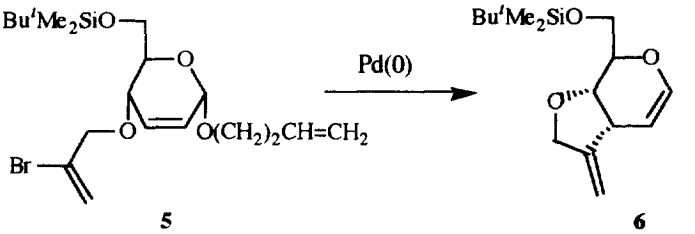
Scheme 2

The formation of the tricyclic structures **4** can easily be explained by an oxidative addition of compounds **3** to the palladium complex, followed by an insertion of the double bond into the carbon-

palladium linkage. Reaction of the σ-palladium intermediate with the unsaturated aglycone and β-elimination allows the formation of compounds **4**.

Detailed ^{1}H NMR examinations of structures **4** show that the central tetrahydrofurane ring (B) is *cis*-fused to both A and C rings, the angular hydrogen atoms H-2 and H-3 being *syn*. For **4a**, we measure following vicinal coupling constants: $J_{1,2}$ = 6.6 Hz, $J_{2,3}$ = 7.4 Hz and $J_{3,4}$ = 7.4 Hz, in accord with these particularities. Irradiation of the H-2 signal at 3.17-3.22 ppm shows an exaltation of 16 and 12% respectively for the H-1 and H-3 signals. An NOE enhancement of 11 and 3% is also observed respectively for H-4 and H-2 by irradiation of the H-3 signal at 2.93 ppm. This stereochemistry is in agreement with the above described mechanistic pathway.

It is noteworthy that treatment of the homoallylic compound **5**, prepared by the usual methodology, only affords the bicyclic compound **6** as previously obtained from the unsaturated ethyl glycoside in 78 % yield.[10] In this case, the β-alkoxy elimination pathway seems to be favored over the second insertion of the unsaturation into the carbon-palladium linkage which would lead here to a six-membered ring *via* a 6-*exo*-*trig* mechanism (Scheme 3). It should be nevertheless noticed that such a process has been observed and studied by Grigg *et al.*[11]



5 **6**

Reagents and conditions: 0.10 eq. $Pd(OAc)_2$, 0.20 eq. PPh_3, 2.5 eq. NEt_3, 1.0 eq. Bu_4NBr, CH_3CN / H_2O (5 / 1), 80 °C, 3 h, 78 %

Scheme 3

The scope and limitations of these transformations are currently under investigation in our laboratory.

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9. All new compounds show convenient spectroscopic and analytical data. Selected values for structure **4a** are as follow:
   oil; $[\alpha]_D^{25}$ +53 (c 1.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3 H, $SiMe_2$), 0.09 (s, 3 H, $SiMe_2$), 0.90 (s, 9 H, Me_3C), 3.00 (dddd, *J* = 7.4, 7.4, 3.0, 1.1 Hz, 1 H, H-3), 3.17-3.22 (m, 1 H, H-2), 3.63 (ddd, *J* = 7.8, 4.8, 2.8 Hz, 1 H, H-5), 3.75 (dd, *J* = 11.4, 4.8 Hz, 1 H, H-6), 3.86 (dd, *J* = 11.4, 2.8 Hz, 1 H, H-6'), 4.06 (dd, *J* = 7.4, 7.4, Hz, 1 H, H-4), 4.31 (dddd, *J* = 13.6, 3.5, 2.6, 1.1 Hz, 1 H, H-12), 4.43 (ddd, *J* = 13.0, 2.5, 2.2 Hz, 1 H, H-8), 4.45 (ddd, *J* = 13.5, 2.7, 1.9 Hz, 1 H, H-12'), 4.68 (dddd, *J* = 13.0, 2.5, 2.2, 2.3 Hz, 1 H, H-8'), 4.98 (ddd, *J* = 2.5, 2.2, 2.1 Hz, 1 H, H-10), 5.17 (ddd, *J* = 2.5, 2.1, 2.1 Hz, 1 H, H-14), 5.25 (ddd, *J* = 2.5, 2.5, 2.5 Hz, 1 H, H-14'), 5.29 (ddd, *J* = 2.5, 2.5, 2.5 Hz, 1 H, H-10'), 5.59 (d, *J* = 6.6 Hz, 1 H, H-1) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.27 (Me_2Si), 18.49 (CMe_3), 26.03 (CMe_3), 41.05 and 42.83 (C-2 and C-3), 64.68 (C-6), 72.75 and 73.47 (C-8 and C-12), 73.58 (C-5), 77.08 (C-4), 102.90 (C-1), 107.07 and 107.65 (C-10 and C-14), 147.11 and 149.11 (C-9 and C-13) ppm.
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