Intramolecular Heck Cyclisation-β-Alkoxy Elimination in Carbohydrate Chemistry. A Simple Route to to Enantiopure Annelated Dioxatricyclic Compounds

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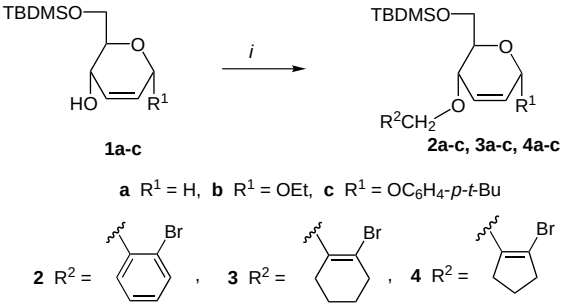
Abstract: Enantiopure *cis*-fused pyrano[2,3c]pyrans are obtained from glycals *via* an intramolecular Heck cyclization followed by a palladium-β-alkoxy elimination

Key words: palladium, cyclisation, carbohydrates, enantiopure heterocyles

Palladium-catalyzed cyclisation processes are now widely used for the stereospecific synthesis of carbon- and heterocyclic systems, sometimes via a cascade reaction.[1] We recently described the use of an intramolecular palladium-catalyzed Heck reaction in carbohydrate chemistry leading to unsaturated enantiopure bicyclo[4.3.0]nonane and tricyclo[7.3.0.$2^{2,6}$]dodecane systems exhibiting at least one *exo*-methylene bond,[2] the last step of the catalytic cycle being an unusual palladium-β-alkoxy elimination. The cyclization leading to 5-membered rings occurred mainly using a catalytic amount of $Pd(OAc)_2/PPh_3$ in CH_3CN/H_2O in the presence of Bu_4NHSO_4 and NEt_3. This letter reports the results concerning the access to unsaturated enantiopure *cis*-fused pyrano[2,3c]pyrans using this methodology.

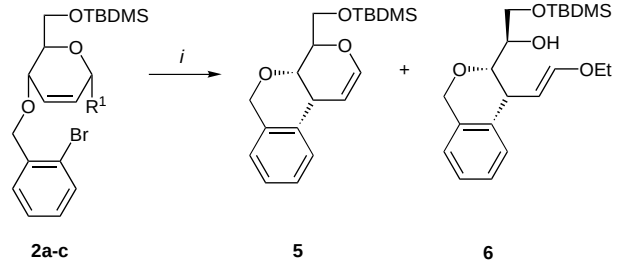
The requisite hex-2-enopyranosides **2**-**4** chosen for the cyclization reaction were easily prepared (Scheme 1). Thus, treatment of compound **1a**, obtained from tri-*O*-acetyl-D-glucal according to literature procedures,[2,3] with NaH and 2-bromobenzyl bromide, (2-bromocyclohex-1-enyl)methyl bromide, and (2-bromocyclopent-1-enyl) methyl bromide, in THF at 60 °C for 24 h, gave the corresponding bromo derivatives **2a**, **3a**, and **4a**, in 70, 68, and 74% yields, respectively. The same methodology was applied to ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1b**)[2] and *p*-*tert*-butylphenyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1c**)[2] to give bromo derivatives **2b**, **3b**, **4b**, **2c**, **3c**, and **4c**, in 86, 83, 61, 80, 53, and 63% yields, respectively.

As with our analogous work,[2] initial studies involved palladium-catalyzed cyclization starting from **2b** and used $Pd(OAc)_2/PPh_3$ in CH_3CN/H_2O in the presence of Bu_4NHSO_4 and NEt_3 (Table). However, under these conditions, compound **2b** failed to cyclize and only formation of ethyl 4-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro* -hex-2-enopyranoside in 50% yield



Scheme 1: *i* : NaH, THF, R^2CH_2Br, 60 °C, 24 h

and some byproducts were observed; formation of this compound by palladium-reduction of the starting material was probably due to the presence of water.[4] Fortunately, going from CH_3CN/H_2O to DMF as the solvent, at 80 °C (Scheme 2), we observed the formation of the expected bicyclic compound **5** in 15% yield together with the ring opened product **6** in 13% yield (Table, entry 2).



Scheme 2: *i* : $Pd(OAc)_2$, PPh_3, Bu_4NHSO_4, Et_3N, DMF, 80 °C, 48 h

It was anticipated that the presence of a better leaving group at the anomeric position would favor the formation of the bicyclic compound.[5] Indeed, unsaturated *p*-*tert*-butylphenyl hex-2-enopyranoside **2c** gave the expected unsaturated compound **5** as the sole product in 40% yield after purification by column chromatography (Table, entry 3). Compound **5** was also obtained in 70% yield start-

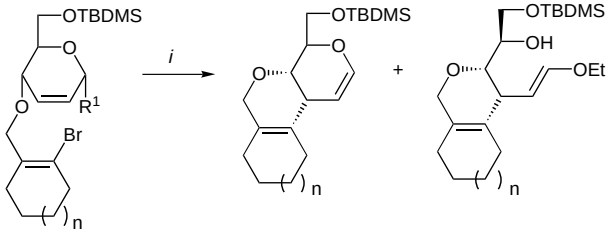
ing from unsaturated substrate **2a** *via* a usual intramolecular Heck reaction (Table, entry 1).

These new conditions were extended for the cyclization of other hex-2-enopyranosides (Scheme 3). Compounds **3a** and **4a**, having no aglycon moiety, gave the expected cyclized products **7** and **8** in 75 and 68% yields, respectively (Table, entries 4 and 7). The ethyl hex-2-enopyranosides **3b** and **4b** gave a mixture of cyclized compounds **7** and **9** and ring opened products **8** and **10** in low yields (Table, entries 5 and 8). However substituting the ethyl aglycon by a *p*-*tert*-butylphenyl group gave again the cyclized products **7** and **9** as the sole products in 44 and 47% yield, respectively (Table, entries 6 and 9).

Table Palladium(0) mediated cyclization of **2**-**4**[a]

Entry	Substrate	Products (yield %)[b]
1	**2a**	**5** (70)
2	**2b**	**5** (15) + **6** (13)
3	**2c**	**5** (40)
4	**3a**	**7** (75)
5	**3b**	**7** (10) + **8** (15)
6	**3c**	**7** (44)
7	**4a**	**9** (68)
8	**4b**	**9** (16) + **10** (12)
9	**4c**	**9** (47)

[a] All reactions were carried out in DMF at 80 °C for 48 h using the unsaturated substrate (10 equiv), $Pd(OAc)_2$ (1 equiv), PPh_3 (2 equiv), Bu_4NHSO_4 (1 equiv), Et_3N (25 equiv).
[b] Not optimized isolated yields.



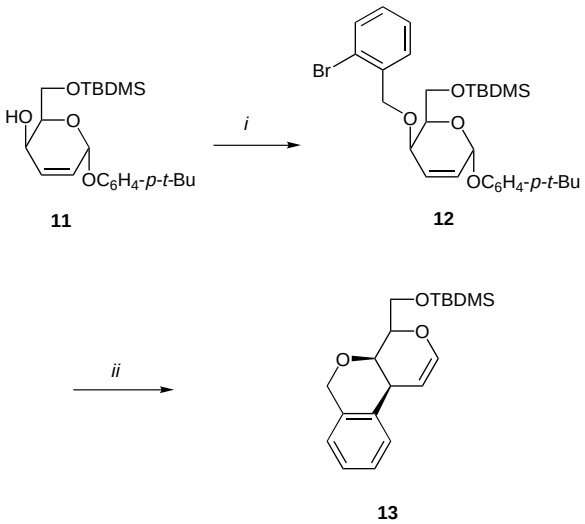
3a-c, 4a-c **7, 9** **8, 10**

a R^1 = H
b R^1 = OEt
c R^1 = OC_6H_4-*p*-*t*-Bu

3, **7**, **8** : n = 1; **4**, **9**, **10** : n = 0

Scheme 3: *i* : $Pd(OAc)_2$, PPh_3, Bu_4NHSO_4, Et_3N, DMF, 80 °C, 48 h

Finally *threo* hex-2-enopyranoside **12**, derived from *p*-*tert*-butylphenyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (**11**), was cyclized under the reported conditions to provide the *cis*-fused bicycle **13** in 55% yield (Scheme 4).



11 **12** **13**

Scheme 4: *i* : NaH, THF, $BrCH_2C_6H_4$-*o*-Br, 60 °C, 24 h, 84%; *ii* : $Pd(OAc)_2$, PPh_3, Bu_4NHSO_4, Et_3N, DMF, 80 °C, 48 h

The structures of compounds **5**, **7**, **9** and **13** were determined from ^1H and ^{13}C NMR and the *cis* stereochemistry was confirmed by NOE experiments. For example, irradiation of the H-3 signal of compound **7** at δ 2.41 ppm gave an enhancement of the signals corresponding to H-2 and H-4 of 7 and 10%, respectively, in agreement with the *cis* arrangement of these two hydrogens. In the case of compound **13**, irradiation of the H-3 signal at δ 3.48 ppm gave an enhancement of the signals of H-2, H-4 and H-5 of 7, 9 and 4%, respectively, showing that these three hydrogens are on the same side of the dihydropyran ring.

In summary, we have shown that suitably functionalized unsaturated pyranosides gave bi- and tricyclic enantiopure derivatives containing six-membered rings *via* an intramolecular Heck reaction followed by a β-palladium-alkoxy elimination. This methodology extended the field of this type of cyclization in carbohydrate chemistry.

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(6) All new compounds gave satisfactory analytical and spectroscopic data. Selected spectroscopic data:
5: $[\alpha]_D^{25}$ +128.6 (*c* 1, CH_2Cl_2), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H, SiMe), 0.91 (s, 9H, $SiCMe_3$), 3.37 (bs, 1H, H-3), 3.77 (dd, 1H, *J* = 10.6, 7.4 Hz, H-6), 3.85 (dd, 1H, *J* = 10.6, 5.7 Hz, H-6), 4.10 (m, 1H, H-4), 4.28 (ddd, 1H, *J* = 7.4, 5.7, 2.2 Hz, H-5), 4.65 (ddd, 1H, *J* = 6.3, 2.2, 1.8 Hz, H-2), 4.89 (d, 1H, *J* = 15.1 Hz, CH_2), 4.92 (d, 1H, *J* = 15.1 Hz, CH_2), 6.30 (dd, 1H, *J* = 6.3, 2.6 Hz, H-1), 7.02 (bd, 1H, *J* = 7.3 Hz, H_{arom}), 7.17-7.26 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ -5.4, -5.3, 18.3, 25.9, 30.6, 61.8, 68.0, 69.4, 76.6, 102.3, 124.3, 126.4, 127.2, 128.6, 134.2, 135.7, 140.6.
7: $[\alpha]_D^{25}$ +337.7 (*c* 2.6, CH_2Cl_2), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H, SiMe), 0.90 (s, 9H, $SiCMe_3$), 1.44-1.72 (m, 8H, CH_2), 2.41 (m, 1H, H-3), 3.70 (dd, 1H, *J* = 10.8, 7.0 Hz, H-6), 3.82 (dd, 1H, *J* = 10.8, 6.1 Hz, H-6), 3.93 (m, 1H, H-4), 4.01 (d, 1H, *J* = 16.2 Hz, CH_2), 4.07 (d, *J* = 16.2 Hz, 1H, CH_2), 4.21 (ddd, 1H, *J* = 9.7, 7.0, 6.1 Hz, H-5), 4.64 (ddd, 1H, *J* = 6.3, 2.1, 1.9 Hz, H-2), 6.29 (dd, 1H, *J* = 6.3, 2.5 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ -5.5, -5.3, 18.3, 22.3, 22.7, 25.0, 25.9, 26.9, 31.6, 61.9, 68.4, 69.1, 76.6, 99.4, 126.8, 127.5, 140.5.
9: $[\alpha]_D^{25}$ +233.6 (*c* 2.5, CH_2Cl_2), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H, SiMe), 0.90 (s, 9H, $SiCMe_3$), 1.86-1.98 (m, 2H, CH_2), 2.25-2.29 (m, 3H, CH_2), 2.50 (m, 1H, CH_2), 2.70 (m, 1H, H-3), 3.74 (dd, 1H, *J* = 10.7, 6.6 Hz, H-6), 3.80 (dd, 1H, *J* = 10.7, 6.3 Hz, H-6), 3.84 (ddd, 1H, *J* = 9.2, 4.4, 1.5 Hz, H-4), 4.17 (ddd, 1H, *J* = 9.2, 6.6, 6.3 Hz, H-5), 4.18 (d, 1H, *J* = 15.4 Hz, CH_2), 4.24 (d, 1H, *J* = 15.4 Hz, CH_2), 4.62 (ddd, 1H, *J* = 6.3, 2.6, 1.5 Hz, H-2), 6.28 (dd, 1H, *J* = 6.3, 2.6 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ -5.4, -5.3, 18.3, 21.93, 25.9, 29.8, 33.1, 33.3, 62.0, 65.9, 76.1, 77.4, 99.2, 132.9, 133.8, 140.8.
13: $[\alpha]_D^{25}$ -23.4 (*c* 0.6, CH_2Cl_2), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H, SiMe), 0.92 (s, 9H, $SiCMe_3$), 3.48 (m, 1H, H-3), 3.86 (dd, 1H, *J* = 13.2, 10.3 Hz, H-6), 4.00 (dd, 1H, *J* = 13.2, 8.8 Hz, H-6), 4.07 (m, 1H, H-5), 4.09 (m, 1H, H-4), 4.68 (d, 1H, *J* = 5.9 Hz, H-2), 4.81 (d, 1H, *J* = 15.4, CH_2), 4.92 (d, 1H, *J* = 15.4, CH_2), 6.37 (d, 1H, *J* = 5.9 Hz, H-1), 7.02 (d, 1H, *J* = 5.9, H_{arom}),), 7.16-7.26 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ -5.4, -5.3, 18.4, 26.0, 34.1, 61.3, 68.3, 68.4, 76.6, 104.1, 124.2, 126.4, 127.1, 128.8, 134.2, 135.9, 141.9.

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