An Unexpected Palladium-catalysed Cyclisation on Carbohydrate Templates

Jean-Flaubert Nguefack, Véronique Bolitt and Denis Sinou*

Laboratoire de Synthèse Asymétrique, URA 463, Université Claude Bernard Lyon I, CPE Lyon, 43 boulevard du 11 Novembre 1918, 69622 Villeurbanne Cédex, France

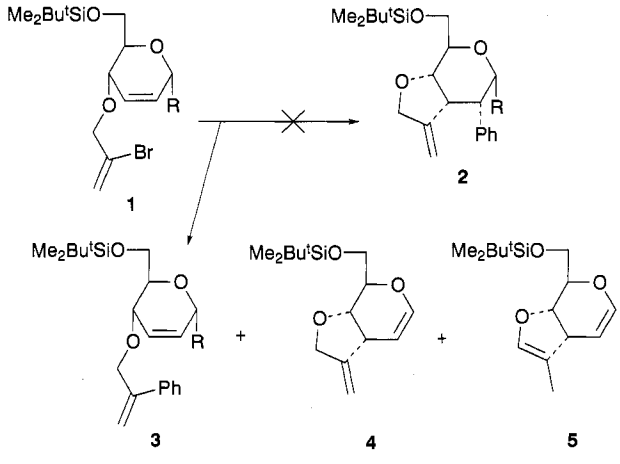
Alkyl 4-*O*-bromoalkenyl α-Δ^2-glycopyranosides **1** undergo a palladium-mediated Heck-type cyclisation providing bicyclic glycals **4** in good yields *via* a *syn*-dealkoxypalladation pathway.

Palladium-catalysed cyclisation processes provide a powerful methodology for the elaboration of carbocyclic as well as heterocyclic derivatives, allowing for example the stereoselective formation of bridged rings or spirocycles.[1] The use of sugar templates in cyclisation reactions *via* free-radical processes leading to chiral cyclopentanes and their heterocyclic analogues has been extensively studied.[2] Examples of such organometallic-induced transformations in carbohydrate chemistry are less common; reports concerning the application of the Pauson–Khand reaction,[3] the cyclisation of enynes[4] or [3 + 2] cycloaddition[5] have recently appeared. Recent studies in our laboratory were concerned with the use of palladium as a tool for the stereoselective transformation of carbohydrates.[6] We now report our first results in the synthesis of furanoid backbones *via* an unexpected intramolecular Heck-type reaction.

Although the intramolecular Heck reaction is now widely used in organic synthesis, and particularly in cascade cyclisation,[1e,f] the lack of success of this methodology in carbohydrate chemistry is probably due to the stability of the σ-palladium complex intermediate which, in most cases, contains no *syn*-hydrogen atom in a suitable β-position for the release of palladium(0) into the catalytic cycle.

Our expectation was that the σ-palladium intermediate formed from carbohydrate **1a** in the presence of a catalytic amount of palladium(0) could be trapped *in situ* by $NaBPh_4$ or Bu_3SnPh, as recently shown by Grigg *et al.*,[1e] leading to the chiral bicyclic furanoid **2** (Scheme 1). We were surprised to observe either no reaction or only formation of compound **3**,† arising from the coupling of the first σ-palladium complex with $NaBPh_4$ or Bu_3SnPh (Table 1, entries 1 and 2). However, performing the reaction in the presence of a base such as Na_2CO_3 allowed the formation of another product, namely the bicyclic compound **4**‡ (Table 1, entries 3 and 4). So, we thought that omitting $NaBPh_4$ or Bu_3SnPh and working under Jeffery's conditions[7] would increase the yield of the bicyclic product **4**.

In our further experiments, we always used acetonitrile–water mixture (5 : 1) as the solvent. Investigaton of this reaction in the presence of a combination of tetra-*n*-butylammonium bromide or hydrogenosulfate, triethylamine or sodium carbonate, and a catalytic amount of palladium(II) acetate or bis(acetylacetonato)palladium and triphenylphosphine showed that the best results were obtained using Bu_4NHSO_4 and NEt_3 (Table 1, entries 6–8). When the reaction was performed in the presence of Na_2CO_3 as the base, the formation of another bicyclic product **5**§ arising from the isomerisation of the double bond from the *exo* to the *endo* position was observed. Excess of Br^-, added as LiBr (Table 1, entry 11), gave rise to the



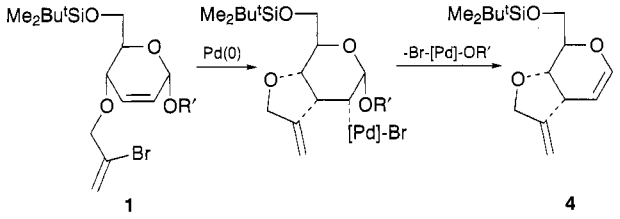
Scheme 1

a; R = OEt, **b**; R = OBu^t, **c**; R = $OC_6H_4Bu^t$-*p*, **d**; R = H

Table 1 Palladium(0)-catalysed cyclisation of compound **1**[a]

Entry	Compound **1**	Added salt	Base	*T*/°C	*t*/h	Conversion (%)	Product[b] (% isolated yield)
1	**a**[c]	Bu_4NBr	None	80	48	traces	—
2	**a**[d]	Bu_4NBr	None	80	24	100	**3** (40)
3	**a**[c]	Bu_4NBr	Na_2CO_3	80	20	100	**3** (33) + **4** (27)
4	**a**[c]	Bu_4NBr	Na_2CO_3	50	24	100	**4** (43)
5	**a**	Bu_4NBr	Na_2CO_3	50	24	25	By-products[e]
6	**a**	Bu_4NBr	NEt_3	80	24	100	**4** (61)
7	**a**	Bu_4NHSO_4	NEt_3	80	24	100	**4** (65)
8	**a**[f]	Bu_4NHSO_4	NEt_3	80	15	100	**4** (72)
9	**a**	Bu_4NHSO_4	NEt_3	50	24	90	**4** (55)
10	**a**	Bu_4NHSO_4	Na_2CO_3	80	24	100	**4** (39) + **5** (13)
11	**a**	Bu_4NHSO_4[g]	NEt_3	80	24	100	By-products[e]
12	**b**	Bu_4NHSO_4	NEt_3	80	24	30	**4** (20)
13	**c**	Bu_4NHSO_4	NEt_3	80	24	70	**4** (35)
14	**d**	Bu_4NBr	Na_2CO_3	80	10	100	**4** (49) + **5** (16)
15	**d**	Bu_4NHSO_4	NEt_3	80	10	100	**4** (65) + **5** (7)
16	**d**	Bu_4NHSO_4	NEt_3	80	20	100	**4** (42) + **5** (28)

[a] Usual conditions: **1** (0.50 mmol) in acetonitrile (15 ml) and water (3 ml) in the presence of $Pd(OAc)_2$ (0.05 mmol), triphenylphosphine (0.10 mmol), the added salt (0.50 mmol) and eventually the base (1.22 mmol) were heated at the indicated temperature. [b] Isolated yields for the spectroscopically homogeneous products. [c] 1.2 mmol of $NaBPh_4$ were added. [d] 2 mmol of Bu_3SnPh were added; acetonitrile alone was used as the solvent. [e] The by-products were not characterised. [f] $Pd(acac)_2$ was used instead of $Pd(OAc)_2$. [g] 3 mmol of LiBr were added.



Scheme 2

formation of a complex mixture, although the conversion of the starting material **1a** was complete.

When the reaction was performed under our standard conditions ($MeCN–H_2O$, Bu_4NHSO_4, NEt_3, 80 °C), using *tert*-butylglycoside **1b** or phenylglycoside **1c** as the starting material, the bicyclic product **4** was also formed although in lower yields (Table 1, entries 12 and 13).

The same bicyclic compound **4** was obtained starting from dihydropyran **1d**; however with Na_2CO_3 as the base or prolonged heating led to the formation of the rearranged product **5** in larger amounts (Table 1, entries 14 and 16).

From a mechanistic point of view, this cyclisation process starts with the formation of a σ-palladium intermediate (Scheme 2) by oxidative addition of compound **1** to the palladium(0) complex followed by an insertion reaction leading to a new σ-palladium species. The unsaturated compound **5** is obtained *via* a *syn*-dealkoxypalladation. There are few examples of *syn*-dehydroxypalladation in the literature, including σ-bonded palladium(II) intermediates of tetrahydrofurans,[8] and features of the present *syn*-dealkoxypalladation seem to be unique. Entries 7, 12 and 13 of the Table 1 could suggest a coordination of the acetal oxygen to the palladium resulting in an easier β-Pd-OR elimination. However, the use of the β-anomer of compound **1a** as starting material instead of the α-anomer led to the formation of the same product **4** in 50% chemical yield; so, in spite of the presence of a *syn*-hydrogen at the β-position in this case, we observed an *anti*-dealkoxypalladation. More work is needed to have a deeper insight into the reaction mechanism.

This new cyclisation procedure should provide a broad strategy for the synthesis of homochiral functionalised bicyclic compounds starting from carbohydrates. The extension of this transformation to the synthesis of chiral five membered carbocyclic and azacyclic derivatives is currently under investigation.

Support by the CNRS, the French MRES and MESRES for a fellowship (J. F. N.) are gratefully acknowledged.

Received, 25th May 1995; Com. 5/03370E

Footnotes

† ^{1}H NMR data for **3**: δ (200 MHz, $CDCl_3$) 0.09 (6 H, s, MeSi), 0.90 (9 H, s, But Si), 1.23 (3 H, t, CH_2CH_3), 3.45–4.01 (6 H, m, H-4, H-5, H-6, CH_2CH_3), 4.35 (1 H, d, *J* 12.6 Hz, OCH_2C=), 4.55 (1 H, d, *J* 12.6 Hz, OCH_2C=), 4.99 (1 H, s, H-1), 5.34 (1 H, d, *J* 1.1 Hz, CH_2=), 5.52 (1 H, d, *J* 1.1 Hz, CH_2=), 5.76 (1 H, brd, *J* 10.2, H-3), 6.04 (1 H, brd, *J* 10.2 Hz, H-2), 7.30–7.60 (5 H, m, C_6H_5).

‡ ^{1}H NMR data for **4**: δ (200 MHz, $CDCl_3$) 0.09 (6 H, s, MeSi), 0.90 (9 H, s, But Si), 3.00–3.10 (1 H, m, H-3), 3.50 (1 H, ddd, *J* 7.4, 5.1, 3.5 Hz, H-5), 3.75 (1 H, dd, *J* 11.4, 5.1 Hz, H-6), 3.85 (1 H, dd, *J* 11.4, 3.5 Hz, H-6′), 4.10 (1 H, dd, *J* 7.4, 7.4 Hz, H-4), 4.30 (2 H, br. s, OCH_2C=), 4.80 (1 H, dd, *J* 6.0, 4.3 Hz, H-2), 4.91–4.94 (2 H, m, $=CH_2$), 6.30 (1 H, dd, *J* 6.0, 1.7 Hz, H-1). ^{13}C NMR data for **4**: (50 MHz, $CDCl_3$) δ −5.3 (MeSi), 18.5 (Me_3CSi), 26.0 (Me_3C), 38.4 (C-3), 62.5 (C-6), 70.0 (OCH_2C=), 73.7 and 74.9 (C-4 and C-5), 99.7 (C-2), 105.6 ($=CH_2$), 143.2 (C-1), 150.7 ($>C=CH_2$).

§ ^{1}H NMR data for **5**: δ (200 MHz, $CDCl_3$) 0.09 (6 H, s, MeSi), 0.90 (9 H, s, But Si), 1.50 (3 H, d, *J* 1.4 Hz, CH_3), 3.35 (1 H, m, H-3), 3.50 (1 H, ddd, *J* 9.1, 4.7, 2.6 Hz, H-5), 3.85 (1 H, dd, *J* 11.4, 4.7 Hz, H-6), 3.95 (1 H, dd, *J* 11.4, 2.6 Hz, H-6′), 4.60 (1 H, dd, *J* 9.1, 9.1 Hz, H-4), 4.92 (1 H, dd, *J* 6.0, 4.1 Hz, H-2), 5.95 (1 H, brs, OCH=), 6.45 (1 H, dd, *J* 6.0, 2.0 Hz, H-1). ^{13}C NMR data for **5**: δ (50 MHz, $CDCl_3$) −5.3 (MeSi), 9.2 (CH_3), 18.5 (Me_3CSi), 26.0 (Me_3C), 41.1 (C-3), 63.0 (C-6), 74.2 and 74.8 (C-4, C-5), 100.4 (C-2), 115.2 (CH_3C=), 138.4 (OCH=), 144.7 (C-1).

References

1 (*a*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1173; (*b*) B. M. Trost, *Acc. Chem. Res.*, 1990, **23**, 34; (*c*) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 38; (*d*) W. Oppolzer, *Pure Appl. Chem.*, 1988, **60**, 39; (*e*) R. Grigg, *Heterocycles*, 1994, **31**, 631; (*f*) A. de Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379; (*g*) A. Heumann and M. Regnier, *Tetrahedron*, 1995, **51**, 975.

2 R. J. Ferrier and S. Middleton, *Chem. Rev.*, 1993, **93**, 2779; D. P. Curran, *Synthesis*, 1988, 417, 489; M. Ramaiah, *Tetrahedron*, 1987, **43**, 3541; C. Lesueur, R. Nouguier, M. P. Bertrand, P. Hoffmann and A. De Mesmaeker, *Tetrahedron*, 1994, **50**, 5369 and references cited therein.

3 N. Naz, T. M. Al-Tel, Y. Al-Abed and W. Voelter, *Tetrahedron Lett.*, 1994, **35**, 858; W. E. Lindsell, P. N. Preston and A. B. Rettie, *Carbohydr. Res.*, 1994, **254**, 311; J. Marco-Contelles, *Tetrahedron Lett.*, 1994, **35**, 5059.

4 G. J. Engelbrecht and C. W. Holzapfel, *Tetrahedron Lett.*, 1991, **32**, 216.

5 B. M. Trost, P. Sevanne, S. Mignani and M. Acemogen, *J. Am. Chem. Soc.*, 1989, **111**, 7487.

6 M. Brakta, P. Lhoste and D. Sinou, *J. Org. Chem.*, 1989, **54**, 1890; V. Bolitt, B. Chaguir and D. Sinou, *Tetrahedron Lett.*, 1992, **33**, 2481; B. Chaguir, M. Brakta, V. Bolitt, P. Lhoste and D. Sinou, *J. Carbohydr. Chem.*, 1992, **11**, 609; R. Lakhmiri, P. Lhoste, B. Kryczka and D. Sinou, *J. Carbohydr. Chem.*, 1993, **12**, 223; M. Brakta, R. N. Farr, B. Chaguir, G. Massiot, C. Lavaud, W. R. Anderson, D. Sinou and G. D. Daves, Jr., *J. Org. Chem.*, 1993, **58**, 2992.

7 T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1984, 1287; T. Jeffery, *Tetrahedron Lett.*, 1994, **35**, 3051.

8 U. Hacksell and G. D. Daves, Jr., *Organometallics*, 1983, **2** 772; J. W. Francis and P. M. Henry, *Organometallics*, 1992, **11**, 2832; S. Saito, T. Hara, N. Takahashi, M. Hirai and T. Moriwake, *Synlett*, 1992, 237; T. Hosokawa, T. Sagafuji, T. Yamanaka and S. I. Murahashi, *J. Organomet. Chem.*, 1994, **470**, 253; S. Ma and X. Lu, *J. Organomet. Chem.*, 1993, **447**, 305; M. Kimura, H. Harayama, S. Tanaka and Y. Tamaru, *J. Chem. Soc., Chem. Commun.*, 1994, 2531.