

## Application of an Intramolecular Heck Reaction for the Construction of the Balanol Aryl Core Structure

Marie-Pierre Denieul and Troels Skrydstrup\*

Department of Chemistry, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

Received 31 March 1999; accepted 6 May 1999

**Abstract:** The highly functionalized aryl core structure of balanol has been synthesized employing a regioselective intramolecular Heck reaction as the key step. This approach can potentially lead to new types of analogues of the potent PKC inhibitor. © 1999 Elsevier Science Ltd. All rights reserved.

The recently isolated fungal metabolite, balanol (Figure 1), is a potent inhibitor of human PKC isozymes with inhibition constants in the nanomolar range.<sup>1</sup> Unfortunately, this inhibitor is not selective enough with respect to other kinases (such as PKA), and therefore much effort has been launched, in particular by Sphinx Pharmaceuticals, to identify a more selective inhibitor towards PKC based on the balanol structure.<sup>2</sup> Whereas a significant amount of work has been reported on the modification of the azepine ring, little has been published concerning variations of the benzophenone fragment, which is thought to mimic an ATP unit.<sup>3,4</sup>

With our interest in synthesizing balanol and analogues thereof, we show in this communication our approach for the construction of the important aryl core structure of this natural product employing a regioselective intramolecular Heck reaction.<sup>5</sup> We envisioned that this route should not only lead to the benzophenone fragment of balanol, but also to a variety of new analogues possessing modifications around the C=O bond.

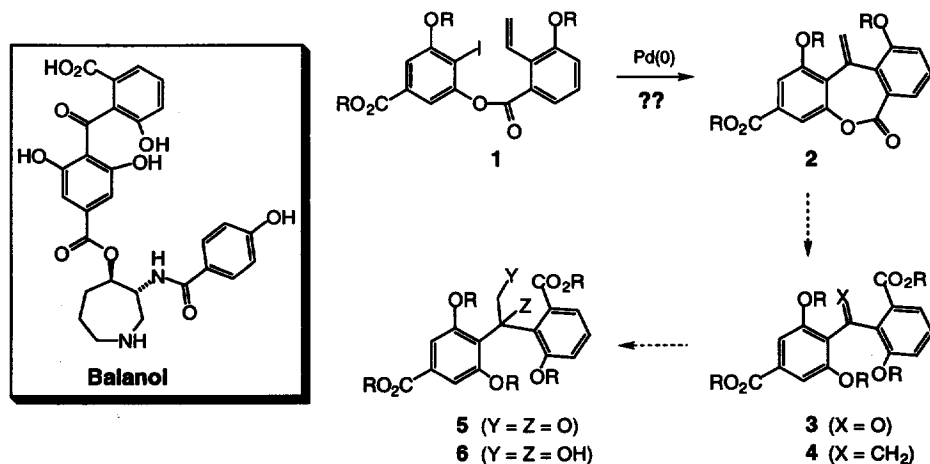
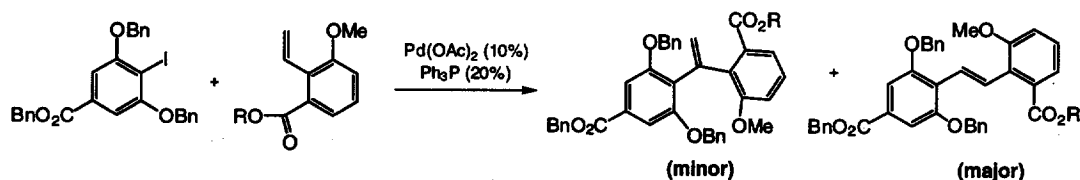


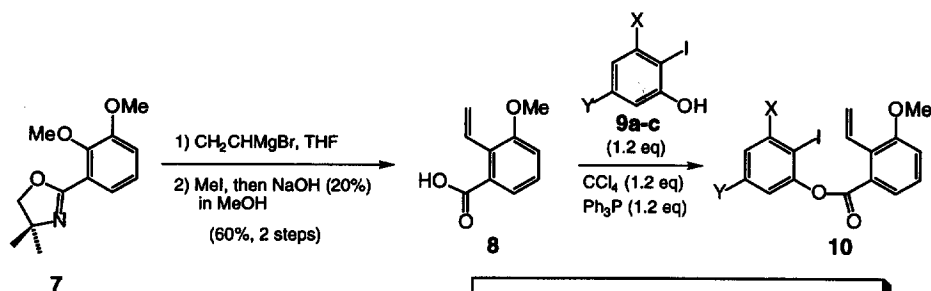
Figure 1



Scheme 1

In our initial effort to prepare the aryl core structure via an intermolecular Heck reaction, as depicted in Scheme 1, the desired coupled product was, not unexpectedly, obtained in low yields where instead C-C bond formation at the terminal carbon of the vinyl group was the major pathway. In an attempt to reverse the regioselectivity of this reaction, we decided to investigate an intramolecular version of the Pd-catalyzed reaction, such as with the phenyl benzoate **1** (figure 1), which if successful would lead to the 7-membered lactone **2**. The formation of two other isomeric lactones could also be anticipated from either 8-*endo* cyclization onto the vinyl group, or from a 6-membered ring closure via carbon substitution at the aryl C-H bond.<sup>6</sup> The latter was nevertheless expected to be a slower event compared to the larger ring formation owing to the disruption of aromaticity in the cyclization mechanism. With **2** in hand, lactone hydrolysis and oxidative cleavage would then be expected to lead to the benzophenone fragment **3** of balanol. On the other hand, **4** represents a C=C analogue of this moiety which itself could potentially be transformed to the other analogues, such as epoxide **5** or diol **6**.

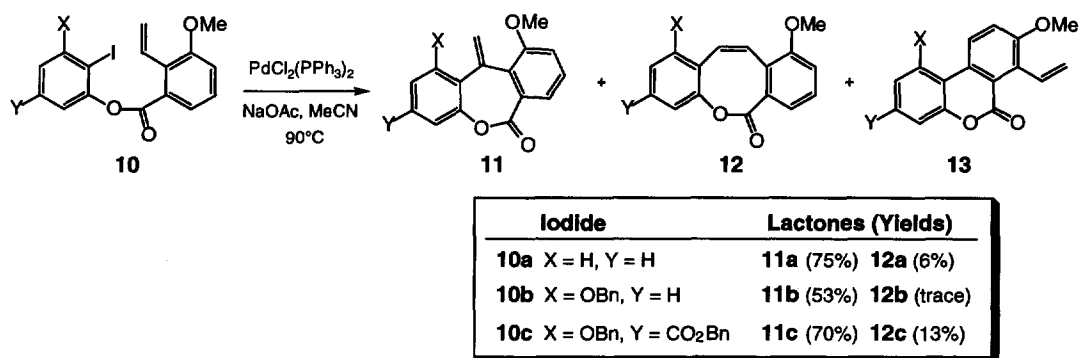
The synthesis of the aryl fragment began with the preparation of the benzoic acid **8**, as shown in scheme 2. Starting from the readily available oxazoline **7**,<sup>7</sup> nucleophilic aromatic substitution with vinyl magnesium bromide, followed by a 2-step hydrolysis procedure afforded **8** in 60% yield as a colorless solid.<sup>8</sup> In order to investigate the feasibility of the intramolecular Heck reaction in this approach, two model compounds **10a** and **10b** were prepared, including the correctly functionalized substrate **10c**.<sup>9</sup> The esterification step could be accomplished in good yields employing the mild conditions developed by Furukawa for the preparation of phenyl carboxylates.<sup>11</sup>



Phenol	Ester (Yield)
<b>9a</b> X = H, Y = H	<b>10a</b> (95%)
<b>9b</b> X = OBn, Y = H	<b>10b</b> (47%)
<b>9c</b> X = OBn, Y = CO <sub>2</sub> Bn	<b>10c</b> (72%)

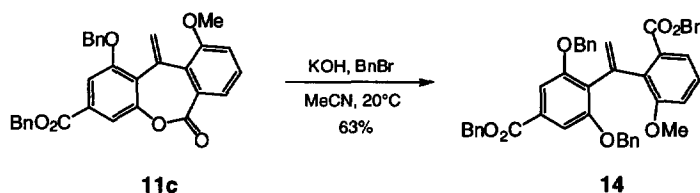
Scheme 2

The cyclization studies began with the simple model **10a**, the results of which are depicted in Scheme 3. With  $\text{PdCl}_2(\text{PPh}_3)_2$  as the catalyst, the use of solvents such as DMA and DMF led to quick reactions and indeed the formation of lactone **11a** as the major product (50%). However, **12a** was also formed along with traces of the 6-membered lactone **13a**, and regioselectivities were not satisfactory (**11a**:**12a**, approx. 4:1). Switching to acetonitrile as the solvent, greatly improved the yield (75%) and the regioselectivity (13:1) in favor of **11a**, with no formation of **13a**. Nevertheless, longer reaction times (approx. 48 h) were required and catalyst decomposition necessitated further addition during the reaction period, such that a total of approx. 0.5 equivalents of catalyst was added for the reaction to be completed. Whereas, the use of other catalysts or reaction conditions (for ex. Jeffrey's conditions<sup>12</sup>) greatly improved the reactions times, these were less selective for the 7-membered ring formation.



Scheme 3

Increasing the steric bulkiness of the iodide with **10b** also led to good selectivities with only traces of the 8-membered ring lactone being formed, implying that the *o*-BnO-substituent in the aryl ring does not impart significant steric hindrance in the coupling step to invert the regioselectivity of the Heck reaction. Finally, cyclization of the correctly substituted substrate **10c** afforded the product of 7-ring closure **11c** in a satisfactory yield of 70% yield along with **12c** (13%). The lactone ring in **11c** could then be opened (KOH, BnBr) to afford **14** in 63% yield, representing the methylene analogue of balanol's benzophenone fragment (Scheme 4).<sup>13</sup>



Scheme 4

In summary, a rapid synthesis of balanol's aryl core structure was achieved employing an intramolecular Heck reaction as the key step. Significant amounts of the palladium complex are still required for the reaction to be completed, and further work is underway to identify a more suitable catalyst. This synthetic approach should allow access to numerous analogues of balanol in order to study their binding to PKC. We are currently

investigating the feasibility of a Heck reaction with the corresponding aldehyde derivative of **10c**, which should lead directly to the benzophenone moiety. This study will be reported in due course.

We thank the Danish National Science Foundation and Aarhus University for generous financial support. A grant from La Ligue Nationale Contre Le Cancer (M.-P.D) is gratefully acknowledged.

## References and Notes

1. P. Kulanthaivel, Y.F. Hallock, C. Boros, S.M. Hamilton, W.P. Janzen, L.M. Ballas, C.R. Loomis, J.B. Jiang, *J. Am. Chem. Soc.*, 1993, **115**, 6452.
2. See, (a) J.M. Defauw, M.M. Murphy, G.E. Jagdmann, Jr., H. Hu, J.W. Lampe, S.P. Hollinshead, T.J. Mitchell, H.M. Crane, J.M. Heerding, J.S. Mendoza, J.E. Davis, J.W. Darges, F.R. Hubbard, S.E. Hall, *J. Med. Chem.*, 1996, **39**, 5215; (b) Y.-S. Lai, J.S. Mendoza, G.E. Jagdmann, Jr., D.S. Menaldino, C.K. Biggers, J.M. Heerding, J.W. Wilson, S.E. Hall, J.B. Jiang, W.P. Janzen, L.M. Ballas, *J. Med. Chem.*, 1997, **40**, 226, and references cited therein.
3. (a) K.C. Nicolaou, K. Koide, M.E. Bunnage, *Chem. Eur. J.*, 1995, **1**, 454; (b) K. Koide, M.E. Bunnage, L.G. Paloma, J. Kanter, S.S. Taylor, L.L. Brunton, K.C. Nicolaou, *Chem. Biol.*, 1995, **2**, 601.
4. J. Nielsen, L. Lyngsø, *Tetrahedron Lett.* 1996, **37**, 8439.
5. For the total synthesis of balanol and other approaches to the benzophenone fragment, see, (a) J.W. Lampe, P.F. Huges, C.K. Biggers, S.H. Smith, H. Hu, *J. Org. Chem.*, 1994, **59**, 5147; (b) S.P. Hollinshead, J.B. Nichols, J.W. Wilson, *J. Org. Chem.*, 1994, **59**, 6703; (c) J.W. Lampe, P.F. Huges, C.K. Biggers, S.H. Smith, H. Hu, *J. Org. Chem.*, 1996, **61**, 4572; (d) K.C. Nicolaou, K. Koide, M.E. Bunnage, *J. Am. Chem. Soc.*, 1994, **116**, 8402; (e) C.P. Adams, S.M. Fairway, C.J. Hardy, D.E. Hibbs, M.B. Hursthouse, A.D. Morley, B.W. Sharp, N. Vicker, I. Warner, *J. Chem. Soc. Perkin Trans. 1*, 1995, 2355; (f) D. Tanner, L. Tadenborg, A. Almario, I. Pettersson, I. Csoeregh, N.M. Kelly, P.G. Andersson, *Tetrahedron*, 1997, **53**, 4857; (g) H. Miyabe, M. Torieda, K. Inoue, K. Tajiri, T. Kiguchi, T. Naito, *J. Org. Chem.*, 1998, **63**, 4397; (h) J.P. Nilsson, C.-M. Andersson, *Tetrahedron Lett.*, 1997, **38**, 4635.
6. For recent reviews on the Heck reaction, see, (a) S. Bräse, A. de Meijere, In *Metal-catalyzed Cross-coupling Reactions*; F. Diederick, P.J. Stang, Eds.; Wiley-VCH: Weinheim, 1998; chapter 3; (b) J.T. Link, L.E. Overman, *ibid.*, chapter 6; (c) S.E. Gibson, R.J. Middleton, *Contemp. Org. Synth.*, 1996, **3**, 447.
7. Oxazoline **7** was easily prepared from 2,3-dimethoxybenzoic acid via its sequential treatment with thionyl chloride, 2-amino-2-methyl-1-propanol and then with additional thionyl chloride (ref. 8).
8. A.I. Meyers, R. Gabel, E.D. Mihelich, *J. Org. Chem.*, 1978, **43**, 1372.
9. The corresponding phenol was prepared by the selective iodination of 3,5-dihydroxybenzoic acid ( $I_2$ ,  $NaHCO_3$ , ref. 10) followed by a benzylation step.
10. I. Thomsen, K.B.G. Torssel, *Acta Chem. Scand.*, 1991, **45**, 539.
11. S. Hashimoto, I. Furukawa, *Bull. J. Chem. Soc.*, 1981, **54**, 2227.
12. T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1984, 1287.
13. Attempts to oxidize the ring opened product of **11a** with ozone or  $OsO_4$  led to decomposition or no reactivity, resp. On the other hand, a three step procedure involving epoxidation, hydrolysis and periodate oxidation did lead to the desired benzophenone. The application of this procedure to **11c** will be reported elsewhere.