ORGANIC LETTERS

2003
Vol. 5, No. 22
4053−4055

# Concise Synthesis of the Chemopreventitive Agent (±)-Deguelin via a Key 6-Endo Hydroarylation

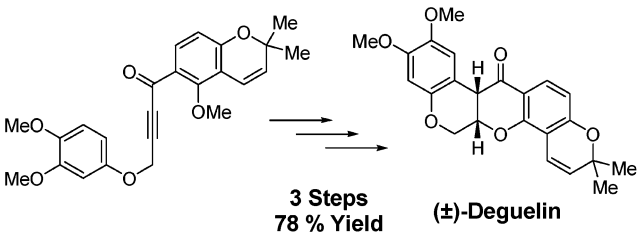
**Stefan J. Pastine and Dalibor Sames***

*Department of Chemistry, Columbia University, New York, New York 10027*

*sames@chem.columbia.edu*

**Received July 28, 2003**

## ABSTRACT




**A concise total synthesis of (±)-deguelin was achieved with a longest linear sequence of six steps in 68% yield. A key step was the platinum-catalyzed 6-endo hydroarylation of an alkynone intermediate.**

In part of a broad program focused on C−H bond functionalization, we became interested in C−H to C−C bond transformations at the arene nucleus.[1] In this context, we have centered our attention on intramolecular hydroarylation methodology, which would provide a direct route to various carbocyclic and heterocyclic compounds. Specifically, a structural search identified chromenes and coumarins as particularly attractive targets due to their frequent occurrence in biologically relevant natural products. Consequently, we have developed a new platinum-catalyzed hydroarylation method that provides direct access to chromene and coumarin scaffolds from arene-yne substrates.[2]

We set out to address the question of whether our hydroarylation method would be applicable to substrates of high complexity such as those leading to the rotenoid class of natural products. Specifically, we were interested in synthesizing deguelin **1**, which has recently received considerable attention for its promising pharmacological properties. Deguelin has been shown to be an efficacious chemopreventitive agent for both in vitro and in vivo models. For example, it has exhibited chemopreventitive effects in both skin and mammary tumerogenesis,[3] inhibited the growth of and induced apoptosis in premalignant and malignant human bronchial epithelial (HBE) cells with minimal effects on normal HBE cells,[4] and suppressed colonic preneoplastic lesions in Cf-1 mice.[5] Its activity has been linked to its potent inhibition of ornithine decarboxylase activity; in contrast to other members of the rotenoid family, deguelin does not inhibit microtubular assembly or tubulin polymerization.[6]

Previous synthetic efforts toward the rotenoid class, including two total syntheses of **1**,[7] have been lengthy and inefficient,[8] and thus a general solution for the synthesis of this class of compounds has not yet been realized. To obtain

(1) Sezen, B.; Sames. D. *J. Am. Chem. Soc.* **2003**, *125*, 5274−5275.

(2) (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055−1058. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, ASAP.

(3) Undeani, G. O.; Gerhauser, C. Thomas, C. F.; Moon, R. C.; Kosmeder, J. W.; Kinghorn, A. D.; Moriarty, R. M.; Pezzuto, J. M. *Cancer Res.* **1997**, *57*, 3424−3428.

(4) Chun, K. H.; Kosmeder, J. W, Sun, S.; Pezzuto, J. M.; Lotan, R.; Hong, W. K.; Lee, Y. H. *J. Natl. Cancer Inst.* **2003**, *95*, 291−302.

(5) (a) Murillo, G.; Salti, G. I.; Kosmeder, J. W.; Pezzuto, J. M.; Mehta, R. G. *Eur. J. Cancer* **2002**, *38*, 2446−2454. (b) Murillo, G.; Kosmeder, J. W.; Pezzuto, J. M.; Mehta, R. G. *Int. J. Cancer* **2003**, *104*, 7−11.

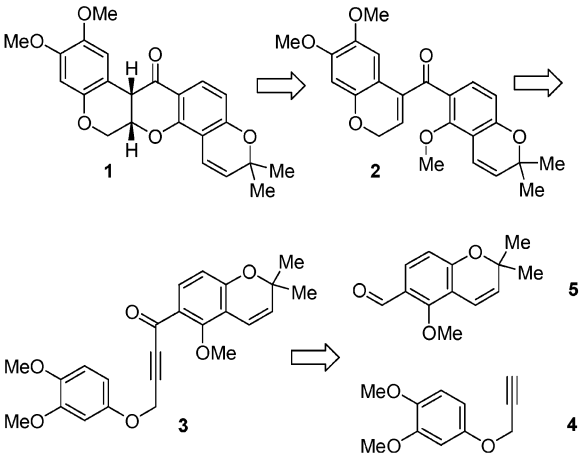
(6) (a) Gerhauser, C.; Lee, S. K.; Kosmeder, J. W.; Moriarty, R. M.; Hamal, E.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Cancer Res.* **1997**, *57*, 3429−3435. (b) Casida, J. E.; Fang, N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3380−3384.

(7) (a) Omokawa, H.; Yamashita, K. *Agr. Biol. Chem.* **1974**, *38*, *1731−1734*. (b) Fukami, H.; Oda, J.; Sakata, G.; Nakajima, M. *Agr. Biol. Chem.* **1961**, *25*, 252−256.

10.1021/ol035419j CCC: $25.00 
**Published on Web 09/26/2003**

appreciable quantities for pharmacological studies, deguelin was prepared in four steps from the related natural product, rotenone, in a modest overall yield (22%).[9] In light of the preceding points, we felt that developing an efficient total synthesis of deguelin was of interest.

**Scheme 1**




Our approach to **1** was based on two key cyclization steps, including the conversion bis-chromene **2** to **1** and the platinum-catalyzed 6-endo hydroarylation of alkynone **3** (Scheme 1).[10] Precursor **3** could then be assembled by the convergence of intermediates **4** and **5**. Although our hydroarylation protocol worked well with alkynoate esters, we were uncertain as to whether alkynones were viable substrates. Since the inherent electron-withdrawing ability of the ketone is greater than that of the ester moiety, we were uncertain about the regiochemical outcome of the hydroarylation step with respect to the 6-endo versus the 5-exo cyclization mode. To test this regiochemical issue, substrate **6** was prepared and subjected to our Pt(IV) protocol. Much to our delight, ketone **6** afforded the 6-endo cyclization product **7** exclusively in an encouraging 50% yield (Scheme 2). Noteworthy is the fact that 6-endo cyclization requires the *umpolung* of the alkynone group, effected in situ by the platinum catalyst. Treatment of **6** with $PtCl_2$ in toluene[11] also provided product **7**, however, in significantly lower yield (32%), and recovered starting material **6** (30%). Similar results were obtained with methyl ester **8**; the Pt(II) conditions gave lower yield (26%), while the Pt(IV) method afforded 51% yield of product **9**. These results were consistent with our previous studies, which had demonstrated that $PtCl_4$ was superior to $PtCl_2$ in the cyclization of electron-deficient alkynes.[2]

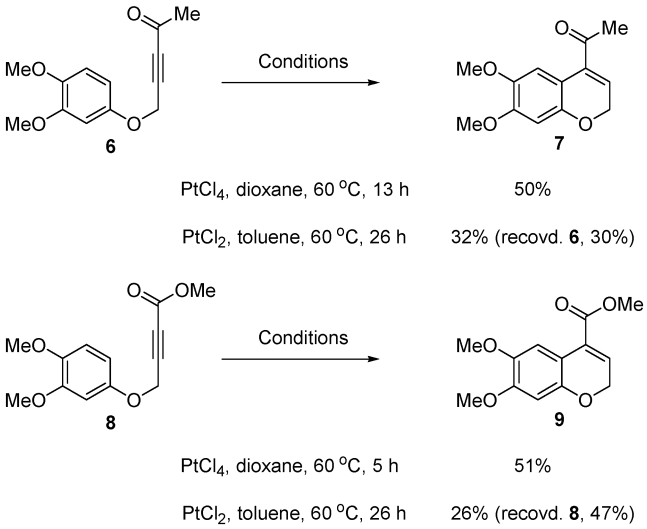
(8) For some representative examples, see: (a) Gabbutt, C. D.; Hepworth, J. D.; Heron, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 653−657. (b) Crombie, L.; Josephs, J. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2591−2597. (c) Ahmad-Junan, S. A.; Amos, P. C.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 539−545. (d) Lai, S. M. F.; Orchison, J. J. A.; Whiting, D. A. *Tetrahedron* **1989**, *45*, 5895−5906.

(9) Anzenveno, P. B. *J. Org. Chem.* **1979**, *44*, 2578−2580.

(10) Thermal Claisen rearrangements of acetylenic intermediates similar to **3** have resulted in poor yields; see refs 7a and 8b.

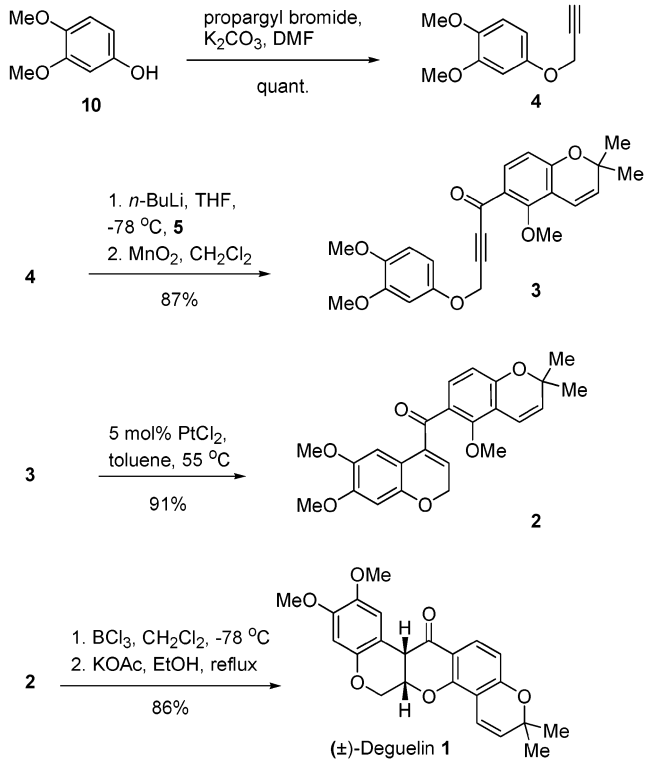
(11) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913−4918.

**Scheme 2**




Encouraged by these results, the synthesis commenced with conversion of phenol **10** to the propargyl ether **4** in quantitative yield (Scheme 3). Treatment of **4** with *n*-BuLi

**Scheme 3**




in THF, followed by reaction with aldehyde **5**,[12] produced the crude alcohol, which was oxidized without purification

(12) Aldehyde **5** was prepared in two steps according to a literature procedure: Geneive, H. E.; Jacobs, H. *Tetrahedron* **2001**, *57*, 5235−5338.

with manganese dioxide to yield the alkynone **3** in 87% yield for two steps. With this key intermediate in hand, we set out to apply the Pt(IV) hydroarylation protocol, mindful of the increased complexity of **3** relative to the substrates previously studied in our laboratory. Unfortunately, even after extensive optimization, we were only able to obtain the desired product **2** in a modest isolated yield (40%; 5 mol % $PtCl_4$, 0.1 M dioxane, 65 °C). Displeased with this result, we subsequently focused our attention on the use of $PtCl_2$ as a catalyst, although with some trepidation as the previous studies demonstrated that $PtCl_2$ was inefficient in converting alkynoate esters and alkynones to the chromene products. However, we were delighted to find that under the action of 5 mol % $PtCl_2$ (0.1 M toluene, 55 °C), alkyne **3** was converted to the desired cyclization product **2** in an excellent 91% yield. Remarkably, none of the undesired ortho cyclization product was detected in the crude reaction mixture.

The advanced intermediate **2** was finally converted to the target molecule in 86% yield by selective demethylation with boron trichloride, followed by base-catalyzed intramolecular oxo-Michael addition (Scheme 3). Thus, (±)-deguelin **1** was synthesized in six linear steps in 68% yield.

The key step of this sequence, namely, the 6-endo hydroarylation of alkynone intermediate **3**, was achieved in excellent yield and regioselectivity (91% isolated yield) in the presence of $PtCl_2$ as the catalyst. This was a surprising finding, since model studies (Scheme 2) and previous investigations in our laboratories[2] indicated that Pt(II) was poorly suited for hydroarylation of electron-deficient alkynes. At the same time, the higher reactivity of Pt(IV) in comparison to Pt(II) salts does not always translate into better yields, particularly in the context of electron-rich arene substrates. This may be due to the greater degree of decomposition of both the product and the starting material in the presence of a "hot" catalyst (see Scheme 2, no starting material was recovered in the experiments with $PtCl_4$). Thus, in the case of a complex substrate such as **3**, milder and more selective $PtCl_2$ proved to be far superior to $PtCl_4$, affording the desired product in excellent yield. This study further demonstrated the complementarity of Pt(II) and Pt(IV) catalysts for alkyne hydroarylation reactions and the applicability of this method to the synthesis of complex natural products.

In summary, (±)-deguelin has been prepared in 68% yield in six steps from known compounds. The crucial step in this synthesis involved the platinum-catalyzed 6-endo hydroarylation of a complex alkynone intermediate. This method should be applicable to the synthesis of other rotenoids.

**Acknowledgment.** Generous support for this work was provided by GlaxoSmithKline, Johnson & Johnson Pharmaceutical R&D, and Merck. D.S. is a recipient of the Alfred P. Sloan Fellowship and the Camille Dreyfus Teacher−Scholar Award. We thank Dr. J. B. Schwarz for editorial assistance.

**Supporting Information Available:** Experimental details and compound spectral characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035419J