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A Short, Scalable Synthesis of the Carbocyclic Core of the Anti-Angiogenic Cortistatins from (+)-Estrone by B-Ring Expansion

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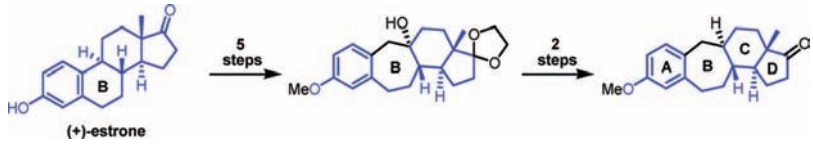
ABSTRACT



A rapid and scalable synthesis of the carbocyclic core of the potent antiangiogenic natural products, the cortistatins, is presented starting from readily available (+)-estrone. Key steps include a regio- and stereoselective benzylic cyanation and a Demjanov rearrangement.

In early 2006, the research group led by Kobayashi disclosed the structures of a series of novel steroidal alkaloids that showed potent antiangiogenic and antiproliferative activity against human umbilical vein endothelial cells (HUVECs).[1] To date, a total of 11 of these compounds, named cortistatins A−L, have been isolated from the marine sponge *Corticulum simplex*.[2] All cortistatins share a common carbocyclic core, featuring an unusual 9-(10,19)-*abeo*-androstane skeleton. Cortistatins A and J (Figure 1), the two most potent members of the family, inhibit the proliferation of human umbilical vein endothelial cells (HUVECs) at low nanomolar (nM) concentrations.

The present paper describes the initial results of our studies on the development of a methodology for the expansion of the estrone B ring.

Thus, cortistatins are of interest as potential anticancer agents since angiogenesis plays a key role in the delivery of blood and oxygen to solid tumors.[3] For this reason, it is not surprising that numerous research groups have embarked on the synthesis of cortistatins.[4]

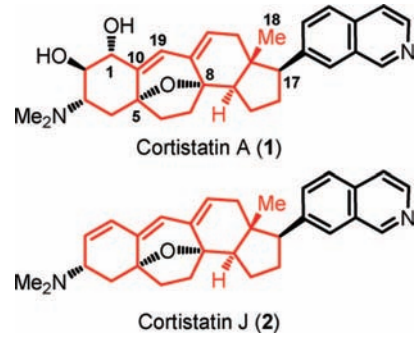


Figure 1. Cortistatins A and J, the two most biologically active members of this family of steroidal marine alkaloids.

We adopted a 2-fold approach to the exploitation of the discovery of the antiangiogenic activity of cortistatins. On the one hand, we have used the cortistatin structures as lead compounds to discover new and more readily accessible synthetic molecules of similar or superior biological activity.

(1) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149.

(2) (a) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485–4488. (b) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074–4079.

(3) Folkman, J. *N. Engl. J. Med.* **1971**, *285*, 1182–1186.

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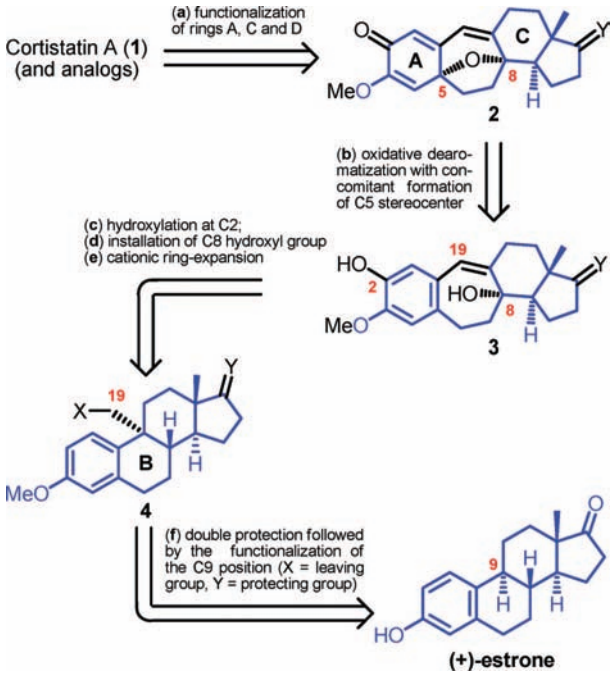
Additionally, we have studied the synthesis of the cortistatin skeleton by B-ring homologation of readily accessible estrone derivatives. Our group has in the past few years developed three efficient and simple enantioselective routes to estrone (and analogues).[5] This chemistry is potentially useful for the total synthesis of the cortistatins, as well as for simple analogues. A retrosynthetic sequence for such a synthesis is outlined in Scheme 1.

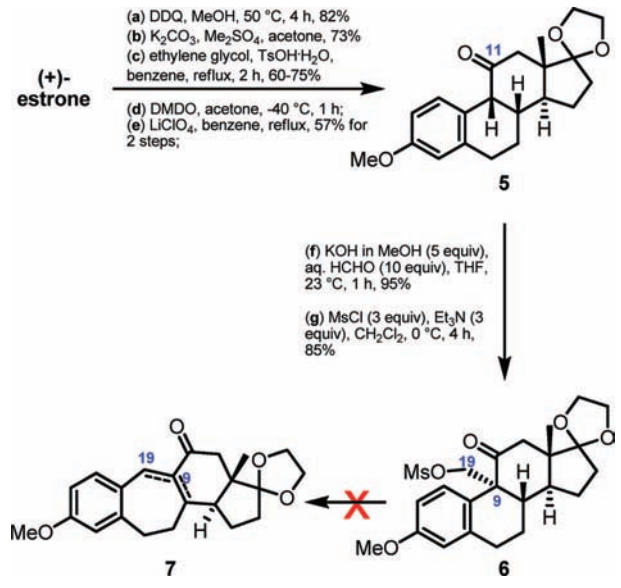
Scheme 1. Retrosynthetic Analysis of Cortistatin A and Structural Analogues



The two key steps in our retrosynthetic analysis (Scheme 1) are as follows: (1) cationic ring-expansion of intermediate **4** to expand ring B and (2) oxidative dearomatization of intermediate **3** to install the required [3.2.1]oxabicyclic ring system.

According to this plan, (+)-estrone was converted to the C11 ketone **5** in five steps: dehydrogenation,[6] methylation and ketalization, epoxidation with dioxirane, and $LiClO_4$-catalyzed epoxide−ketone rearrangement[7] (Scheme 2). α-Hydroxymethylation of **5** and mesylation gave **6**.

Scheme 2. First-Generation Functionalization of (+)-Estrone and Ring-Expansion Studies



Exposure of mesylate **6** (or the corresponding C19 chloride) to a variety of ionizing conditions (e.g., NaOAc, AcOH, reflux; $AgNO_3$, MeCN, reflux) did not yield any of the required B-ring homologated compound **7**. Analysis of the products isolated from these reactions indicated that substitution occurred at C19 rather than B-ring expansion of the intermediate phenonium ion (Figure 2).

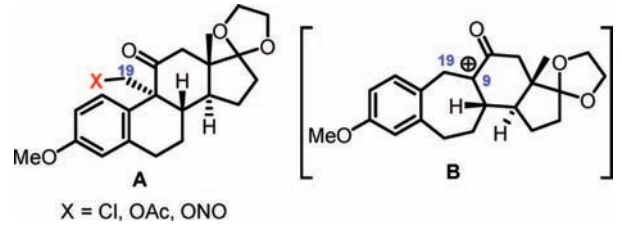


Figure 2. (A) Compounds that were prepared/isolated during the ring-expansion studies of **6**. (B) Hypothetical α-acyl cation intermediate.

We turned our attention to an alternative strategy which would allow the direct functionalization of the C9 benzylic position of estrone without requiring the presence of a carbonyl group at C11. We were guided by literature examples for the simultaneous oxidation/benzylic cyanation of various simple aromatic hydrocarbons using DDQ/TMSCN in CH_2Cl_2 or MeCN.[8]

After extensive experimentation, conditions were found in which compound **8** could be converted to the corresponding C9 benzylic cyanide derivative **9** in nearly quantitative yield (Scheme 3 and 4). During the optimization studies, we

(4) For recent total syntheses of (+)-cortistatin A, see: (a) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243. (b) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen David, Y. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310–7313. For other studies toward the synthesis of cortistatins, see: (c) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650–6653. (d) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415.

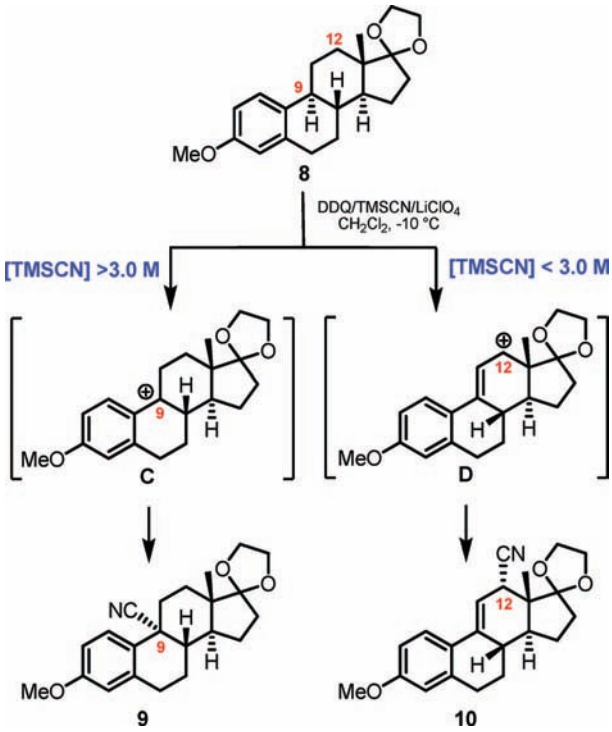
(5) (a) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347. (b) Canales, E.; Corey, E. J. *Org. Lett.* **2008**, *10*, 3271–3273. (c) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984–5986.

(6) Brown, W.; Findlay, J. W. A.; Turner, A. B. *Chem. Commun.* **1968**, *10*, 11.

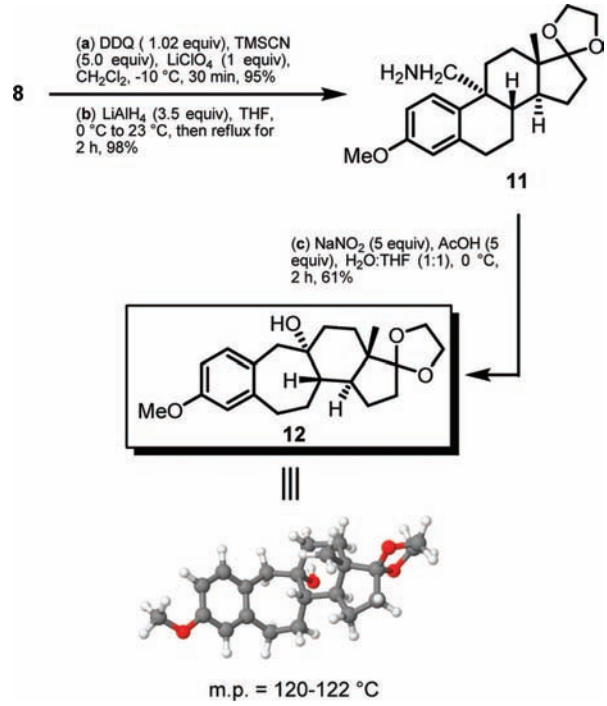
(7) (a) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1968**, *90*, 4193–4194. (b) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693–1700.

(8) Lemaire, M.; Doussot, J.; Guy, A. *Chem. Lett.* **1988**, 1581–1584.

Scheme 3. Benzylic Cyanation Studies on Doubly Protected Estrone **8**



Scheme 4. Three-Step Highly Scalable Preparation of the Carbocyclic Core of Cortistatins (**12**) from Doubly Protected Estrone **8**



discovered that the concentration of cyanide reagent (TMSCN) is critical. It was shown experimentally that when the overall cyanide reagent concentration is at least 3 M, only the desired C9 benzylic cyanide **9** is formed. However, when the overall cyanide reagent concentration is less than 3 M, the corresponding C12 allylic cyanide product **10** predominates (Scheme 3). These results clearly indicated that the intially formed C9 benzylic cation **C** could undergo rapid proton loss and then further oxidation by DDQ (to give cation **D**) at relatively low cyanide reagent concentrations. The optimum benzylic cyanation conditions entailed premixing $LiClO_4$ (1 equiv), TMSCN (5 equiv), and the substrate at room temperature in dichloromethane, cooling the reaction mixture to −10 °C, and adding DDQ (1.02 equiv) in five portions over 30 min (Scheme 4). The formation of a DDQ−substrate charge-transfer complex is clearly indicated by the appearance of a strong bluish-green color after each portion of DDQ is added; this color fades to yellow when the reaction is complete. Using this procedure, batches of up to 5 g of **8** were reproducibly converted to **9** in excellent yield and without the use of flash chromatography.

Benzylic cyanide **9** was efficiently reduced with $LiAlH_4$ to the corresponding primary amine **11** (Scheme 4). After some experimentation, conditions were found that facilitated the cationic ring-expansion of **11** to **12** without the loss of the ketal functionality. The deamination of **11** leads to aryl participation with rearrangement and results in clean and efficient formation of **12**.[9] The structure and stereochemistry of ring-expanded product **12** were confirmed by single-crystal X-ray crystallography (Scheme 4). Compound **12** embodies the carbocyclic core of the potent antiangiogenic cortistatins.

The five-step transformation of (+)-estrone to the ring-expanded product **12** is highly efficient (>50%) and requires only a single chromatographic purification at the end of the sequence. Over 10 g of **12** has been prepared to date as a result of the robustness of the *benzylic cyanation/aromatic Demjanov rearrangement* sequence.

B-ring homologated estrone and estradiol derivatives based on the *abeo*-6(5,19)-androstane skeleton **14** (Figure 3) are of considerable interest because of their ability to modulate tubulin polymerization and stabilization of microtubules, resembling paclitaxel (Taxol) and colchicine in their effects.[10]

Importantly, the major estrogen metabolite 2-methoxyestradiol (2ME) **15** (Figure 3) has been identified as an inhibitor of tumor growth by targeting both tumor cells and their blood supply.[11] In addition, 2ME was shown to target tumor cells without severe side effects, and it is currently being evaluated in clinical trials for several types of cancer.

(9) For a review on the Demjanov and Tiffeneau−Demjanov rearrangements, see: Smith, P. A. S.; Baer, D. R. *Org. React.* **1960**, *11*, 157–188.

(10) Wang, Z.; Yang, D.; Mohanakrishnan, A. K.; Fanwick, P. E.; Nampoothiri, P.; Hamel, E.; Cushman, M. *J. Med. Chem.* **2000**, *43*, 2419–2429.

(11) (a) Pribluda, V. S.; Green, S. J. *Science (Washington, D.C.)* **1998**, *280*, 987–988. (b) Edsall, A. B.; Mohanakrishnan, A. K.; Yang, D.; Fanwick, P. E.; Hamel, E.; Hanson, A. D.; Agoston, G. E.; Cushman, M. *J. Med. Chem.* **2004**, *47*, 5126–5139.

(12) (a) Galantay, E.; Weber, H. P. *Experientia* **1969**, *25*, 571–572. (b) Groen, M. B.; Zeelen, F. J. *Recl.: J. R. Neth. Chem. Soc.* **1984**, *103*, 169–173.

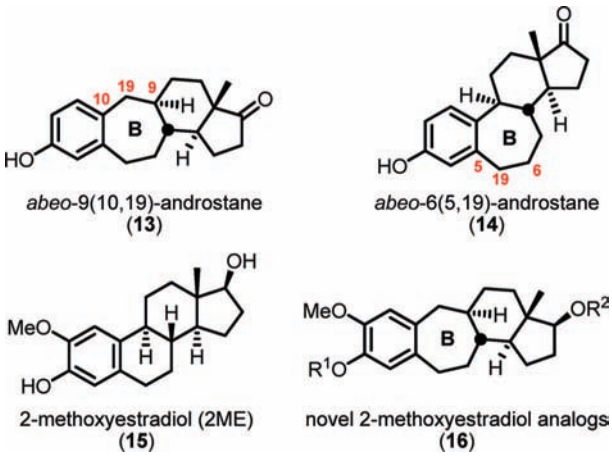


Figure 3. Two possible homo-B-estrones based on *abeo*-9(10,19)-androstane (**13**) and *abeo*-6(5,19) androstane (**14**) cores. Structures of 2-methoxyestradiol (**15**) and novel B-ring homologated novel 2-methoxyestradiol analogues (**16**).

While several methods are available for the preparation of B-ring homologated estrones based on the *abeo*-6(5,19)-androstane skeleton **14** (Figure 3),[12] access to the *abeo*-9(10,19)-androstane skeleton **13** is very limited.

Given the remarkable biological activities exhibited by compounds based on the skeleton of **14**, we recognized that compound **12** can be readily transformed to compounds like **13**, which might have similar or better activities.

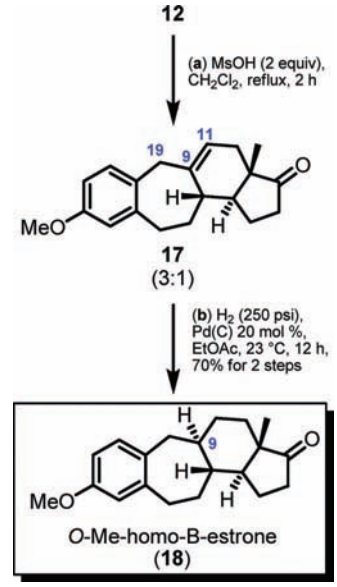
With large quantities of compound **12** secured, a rare B-ring homologated estrone **18** was prepared[13] by a two-step dehydration/hydrogenation sequence (Scheme 5): (1) dehydration under strongly acidic conditions to afford a 3:1 mixture of alkenes and (2) catalytic hydrogenation to give **18** in good yield.[14]

In summary, we have developed a short, scalable, and practical synthesis of **12** from (+)-estrone using a highly efficient benzylic cyanation and aromatic Demjanov rearrangement sequence. Compound **12** contains the carbocyclic core of cortistatins. We have been able to prepare in quantity the rare homo-B-estrone **18** from **12** that can provide ready access to novel 2-methoxyestradiol (2ME) analogues such as **16** (Figure 3). Further functionalization of **12** is currently underway. The preparation and biological evaluation of simple and extremely potent cortistatin structural analogues will be reported in due course.

(13) For the preparation of compound **18** in small quantities, see: Abushanab, E.; Lee, D.-Y.; Meresak, W. A.; Duax, W. L. *J. Org. Chem.* **1976**, *41*, 1601–1603. For the strucutural elucidation of compound **18**, see: Weeks, C. M.; Rohrer, D. C.; Duax, W. L.; Abushanab, E. *Steroids* **1976**, *27*, 261–268.

(14) Compound **18** was obtained as a >7:1 mixture of diastereomers at C9. Distereomerically pure **18** is obtained after crystallization from pentane/ether.

Scheme 5. Preparation of the *O*-Me-homo-B-estrone **18**



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Supporting Information Available: Detailed experimental procedures and characterization for all new compounds and X-ray crystallographic data for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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