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A Concise Synthesis of the Pentacyclic Framework of Cortistatins

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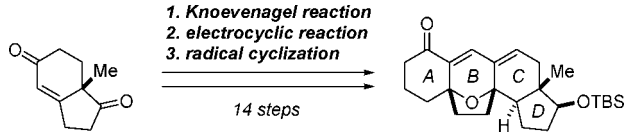
ABSTRACT

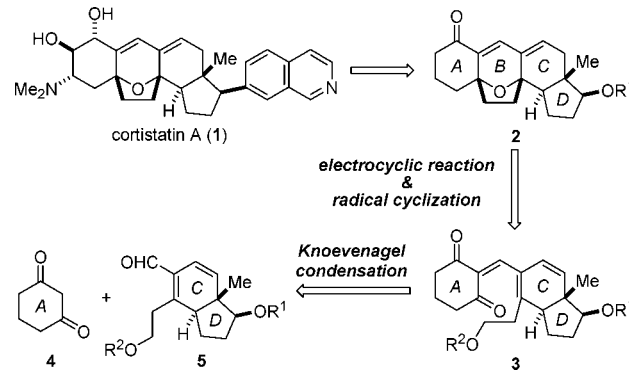


An efficient synthesis of the pentacyclic framework of cortistatins has been developed. The key strategy comprises assembly of the A- and the CD-ring fragments by Knoevenagel reaction, facile formation of the pyran ring via electrocyclization, and construction of the seven-membered B-ring by radical addition to an α,β-unsaturated ketone.

Cortistatins, which are unique *abeo*-9(10,19)-androstane-type steroidal alkaloids, were first isolated from the marine sponge *Corticium simplex* by Kobayashi et al.[1] Cortistatin A (**1**), the most potent congener, was found to inhibit the proliferation of human umbilical vein endothelial cells with extreme selectivity among cell lines.[1a,2] Because angiogenesis in solid tumors involves proliferation of endothelial cells, **1** has high potential as a selective antitumor agent. As represented by Baran's excellent synthesis from prednisone,[3] the biological activity and unique structure-including an oxabicyclo[3.2.1]octene moiety as well as an isoquinoline substituent-of **1** attracts synthetic chemists. Herein, we report a stereoselective synthesis of the ABCD-ring framework of cortistatins.

As illustrated in Scheme 1, we envisioned the construction of **1** via the key intermediate **2** after functionalization of the A-ring and introduction of the isoquinoline unit to the D-ring.

Scheme 1. Structure and Synthetic Plan of Cortistatin A (**1**)



The pentacyclic **2** would be formed through an electrocyclic reaction of dienone **3** followed by radical cyclization. Knoevenagel reaction between diketone **4** and α,β-unsaturated aldehyde **5** was expected to produce the conjugated dienone **3**.

First, the requisite CD-ring moiety was prepared from commercially available (+)-Hajos-Parrish ketone **6** (Scheme 2).[4] Chemo- and stereoselective reduction of **6** with $NaBH_4$ in MeOH at low temperature and subsequent TBS protection of the resulting secondary alcohol produced silyl ether **7** in

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(1) (a) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148. (b) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074. (c) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485.

(2) SAR studies of cortistatins: Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsujikawa, K.; Yamamoto, H.; Kobayashi, M *Bioorg. Med. Chem.* **2007**, *15*, 6758.

(3) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241.

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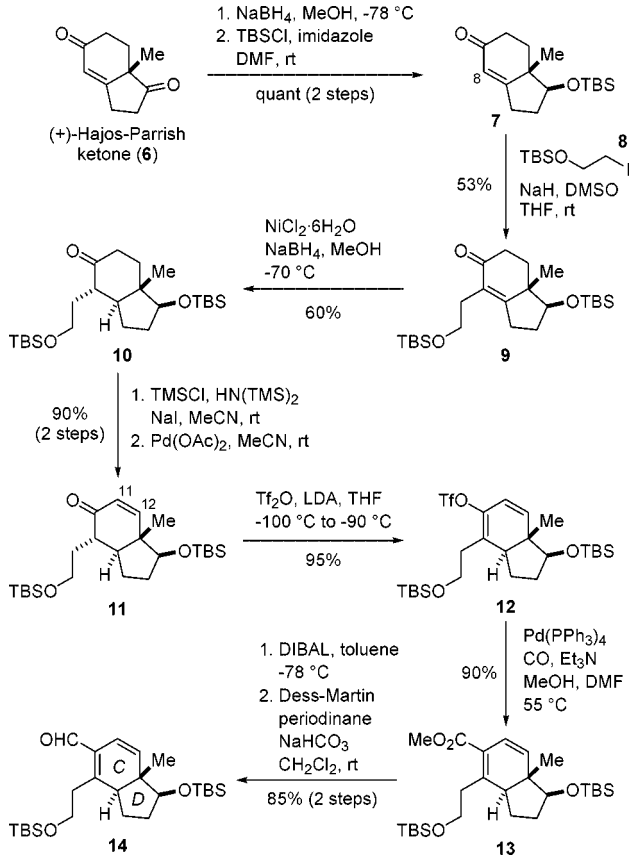
Scheme 2. Synthesis of the α,β-Unsaturated Aldehyde **14**

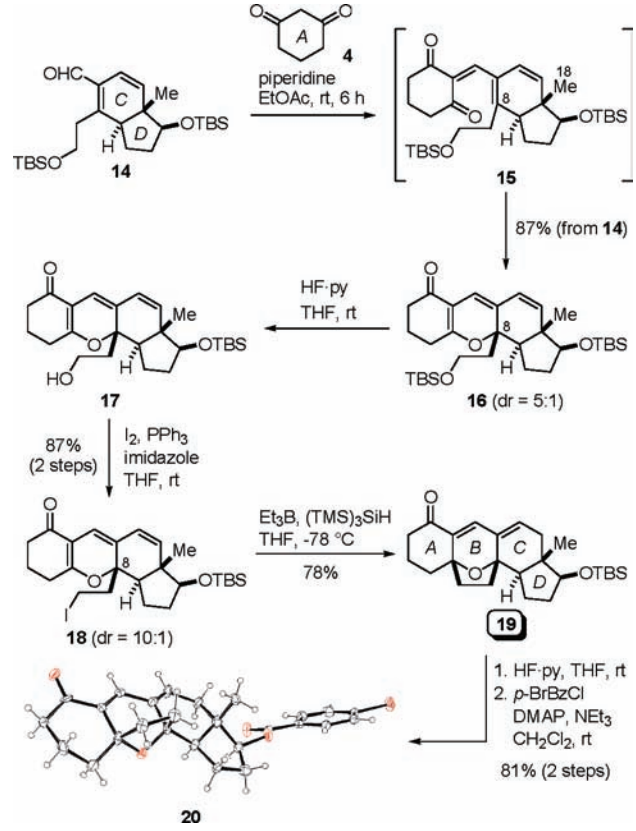


quantitative yield.[5] *C*-alkylation of **7** at the C8-position with iodide **8** was accomplished under Molander's conditions (NaH, DMSO in THF)[6] to give indanone **9** in 53% yield; this was stereoselectively reduced by $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ to give the desired *trans*-fused ketone **10**.[6a,7] The stereochemistry of **10** was verified by NOESY experiments (see Supporting Information). Other reductive conditions (H_2, Pd/C; *t*-BuCuH; or Birch reduction)[8] did not give **10** as a major product.

Regioselective TMS-enol ether formation from **10** followed by oxidation under Saegusa conditions[9] furnished the C11,12 double bond. Treatment of enone **11** with lithium diisopropylamide and triflic anhydride resulted in the formation of dienyl triflate **12**, which underwent Pd-catalyzed methoxycarbonylation to give methyl ester **13**.[10] Finally, DIBAL reduction and subsequent Dess-Martin oxidation[11] provided the α,β-unsaturated aldehyde **14** in 73% overall yield from **11**.

With the requisite aldehyde **14** in hand, construction of the oxabicyclo[3.2.1]octene B-ring was pursued (Scheme 3).

Scheme 3. Synthesis of the Framework of Cortistatins



Treatment of **14** with cyclohexane-1,3-dione (**4**) (1.5 equiv) in the presence of piperidine (1.1 equiv) in EtOAc (15 mM) for 6 h produced the desired pyran **16** along with its C8-epimer as a 5:1 mixture in one pot (87% combined yield). Knoevenagel reaction between **14** and **4** gave the condensed product **15**, which underwent spontaneous electrocyclization to give **16** as a major product.[12] Selective TBS removal of the primary alcohol, without affecting the secondary one, using HF·pyridine gave **17**, which was treated with I_2, Ph_3P, and imidazole[13] to afford iodide **18** in 87% overall yield (10:1 diastereomeric mixture). Interestingly, when **18** was kept at −30 °C for 12 h, it crystallized, and the **18**/C8-epimer ratio increased to 20:1, as confirmed by NMR in $CDCl_3$. However, the ratio changed to 7:1 when the mixture was kept for 1 h in $CDCl_3$, and then became 5:1 after 7 h at room temperature.

(4) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(5) (a) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675. (b) Gardner, J. N.; Anderson, B. A.; Oliveto, E. P. *J. Org. Chem.* **1969**, *34*, 107.
(6) (a) Molander, G. A.; Quirmbach, M. S.; Silva, L. F.; Spenver, K. C., Jr.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257. (b) Hajos, Z. G.; Parrish, D. R.; Oliveto, E. P. *Tetrahedron* **1968**, *24*, 2039.
(7) For a general review, see: (a) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763. (b) Shigehisa, H.; Mizutani, T.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2005**, *61*, 5057.
(8) For a review, see: (a) Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071.
(9) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(10) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(12) For a recent review for constructing 1-oxadecalin, see: Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785.
(13) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.

These results clearly indicate that **18** equilibrates with the C8-epimer via retrocyclization to the corresponding dienone in solution.

Finally, formation of the seven-membered B-ring was achieved by radical cyclization. After a considerable number of experiments, it was found that treatment of **18** with Et_3B and $(TMS)_3SiH$ furnished the most stable conjugated dienone (**19**) in 78% yield as the sole product.[14] The structure of **19**, the key intermediate in the total synthesis of cortistatins, was unambiguously confirmed by X-ray crystallographic analysis of the corresponding *p*-bromobenzoate **20**.

In conclusion, we have developed a concise and stereocontrolled synthetic route to the pentacyclic framework of cortistatins. The key intermediate **19** was prepared in only 14 steps from the commercially available **6**, including (1) Knoevenagel condensation, (2) spontaneous electrocyclization (**14**→**16**), and (3) highly chemoselective internal radical addition (**18**→**19**). The strategy developed here will contribute toward the total synthesis of cortistatins, which is being actively investigated in our laboratory.

(14) For selected examples of radical addition to α,*β*-unsaturated carbonyl compounds, see: (a) Middleton, D. S.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 545. (b) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831.

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Supporting Information Available: Experimental procedures and spectroscopic data for synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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