ORGANIC LETTERS

2011
Vol. 13, No. 13
3514–3517

Stereoselective Synthesis of Core Structure of Cortistatin A

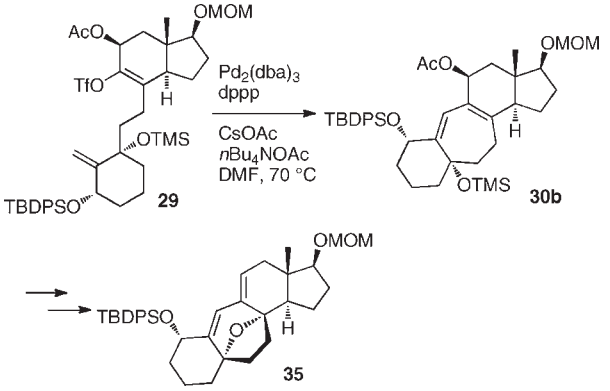
Naoyuki Kotoku,* Yuji Sumii, and Motomasa Kobayashi*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

kotoku@phs.osaka-u.ac.jp; kobayasi@phs.osaka-u.ac.jp

Received May 17, 2011

ABSTRACT



A stereoselective synthesis of the core structure of cortistatin A (1), a novel antiangiogenic steroidal alkaloid from Indonesian marine sponge, is described. An 8-oxabicyclo[3.2.1]octene system, a characteristic B-ring structure of 1, was elaborated by a 7-*endo* selective intramolecular Heck cyclization and a subsequent acid-mediated oxy-Michael reaction.

Angiogenesis, a formation of new blood capillaries from preexisting blood vessels, is critical for tumor growth and metastasis. A growing tumor needs an extensive network of capillaries to provide nutrients and oxygen, etc. In addition, the new blood vessels provide a way for tumor cells to enter into the circulation and to metastasize to another organ. Therefore, substances that inhibit angiogenesis have considerable potential to be novel therapeutic agents for the treatment of cancer.[1]

In the course of our study on the bioactive substances from marine organisms, we focused on a search for selective inhibitors of proliferation of human umbilical vein endothelial cells (HUVECs) as antiangiogenic substances and found cortistatins,[2] a family of novel *abeo*-9(10→19)-androstane-type steroidal alkaloids, from the Indonesian marine sponge of *Corticium simplex* (**1**–**11**, Figure 1). Cortistatin A (**1**), a major constituent, showed remarkably selective antiproliferative activity against HUVECs and also inhibited migration and tubular formation of HUVECs induced by VEGF or bFGF.[2a] A structure–activity relationship study among cortistatins revealed that the isoquinoline unit is crucial and the 9(11),10(19)-diene unit in the core structure (such as cortistatins A (**1**) and J (**9**)) might be important for selective antiproliferative activity against HUVECs.[2d]

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10.1021/ol201327u
Published on Web 06/09/2011

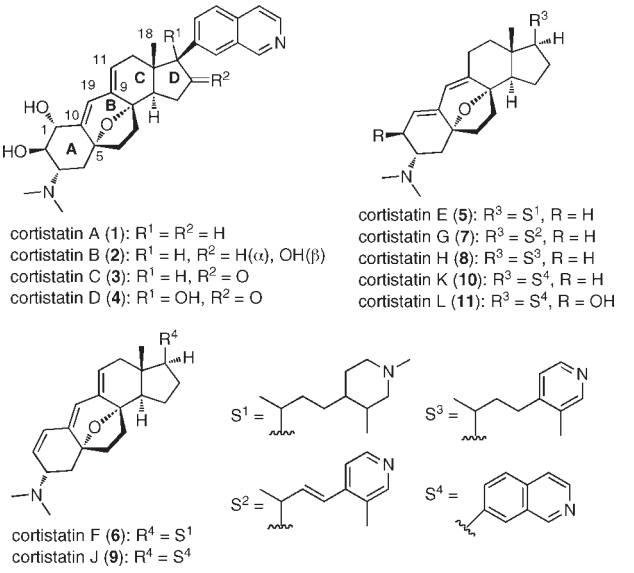

Figure 1. Structures of cortistatins A−L (**1**−**11**).

The unique structure and characteristic biological property of cortistatin A (**1**) attracted many synthetic chemists, and five total syntheses,[3] two formal syntheses,[4] and many synthetic studies[5] have been reported so far. We also engaged in the synthetic study of cortistatin A (**1**) and accomplished a stereoselective synthesis of the core structure of **1** through a 7-*endo*-selective intramolecular Heck reaction,[6] which will be described in this paper.

Cortistatin A (**1**) has a characteristic rearranged steroid skeleton, particularly with an 8-oxabicyclo[3.2.1]octene system in the B-ring. Our plan toward the synthesis of its complex ring system is a direct ring closure giving a seven-membered carbocycle through an intramolecular Heck-type reaction (**C** to **B**) and subsequent oxa-bridge formation (**B** to **A**) (Figure 2). In the cyclization intermediate for the Heck reaction, a 7-*endo* pathway was expected to be sterically more accessible than a 6-*exo* pathway, since steric hindrance of the *tert*-alcohol moiety (OR^2) placed at the C5 position would make the 6-*exo*-cyclizing intermediate much more disfavored. A cyclization precursor was divided into two fragments of A-ring fragment **E** and CD-ring fragment **F**.

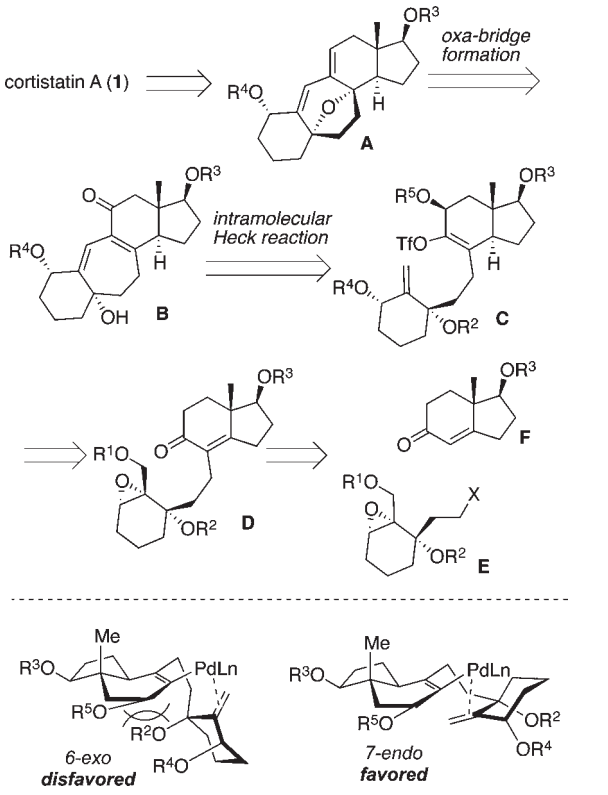

Figure 2. Retrosynthetic analysis of core structure **A** and plausible intermediate for intramolecular Heck reaction.

Preparation of the chiral A-ring fragment is summarized in Scheme 1. CBS reduction toward the known ketone **12**,[7] prepared from 2-cyclohexenone, gave an allylic alcohol **13** in 95% yield. The absolute stereochemistry and enantiomeric excess (82−90% ee) of **13** was determined by preparing its (+)- and (−)-MTPA esters. Subsequent vanadium-mediated diastereoselective epoxidation and Swern oxidation provided a chiral epoxy ketone **14** in good yield. Nucleophilic addition of the lithium enolate of *tert*-butyl acetate toward the ketone **14** proceeded only in the presence of CeF_3[8] to give compound **15** as a single diastereomer. An NOE experiment revealed that nucleophilic attack occurred from the opposite side of the epoxide, which provided a *tert*-alcohol moiety with the desired stereochemistry. MOM protection of the *tert*-alcohol moiety gave compound **16** in quantitative yield,

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(5) (a) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931. (b) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610. (c) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613. (d) Kotoku, N.; Sumii, Y.; Hayashi, T.; Kobayashi, M. *Tetrahedron Lett.* **2008**, *49*, 7078. (e) Kürti, L.; Czakó, B.; Corey, E. J. *Org. Lett.* **2008**, *10*, 5247. (f) Dai, M.; Danishefsky, S. J. *Heterocycles* **2009**, *77*, 157. (g) Magnus, P.; Littich, R. *Org. Lett.* **2009**, *11*, 3938. (h) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394. (i) Baumgartner, C.; Ma, S.; Liu, Q.; Stoltz, B. M. *Org. Biomol. Chem.* **2010**, *8*, 2915. (j) Yu, F.; Li, G.; Gao, P.; Gong, H.; Liu, Y.; Wu, Y.; Cheng, B.; Zhai, H. *Org. Lett.* **2010**, *12*, 5135. (k) Liu, L. L.; Chiu, P. *Chem. Commun.* **2011**, *47*, 3416. For reviews, see:(l) Nising, C. F.; Bräse, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9389. (m) Chen, D. Y.-K.; Tseng, C.-C. *Org. Biomol. Chem.* **2010**, *8*, 2900. (n) Hardin-Narayan, A. R.; Simmons, E. M.; Sarpong, R. *Eur. J. Org. Chem.* **2010**, *19*, 3553.

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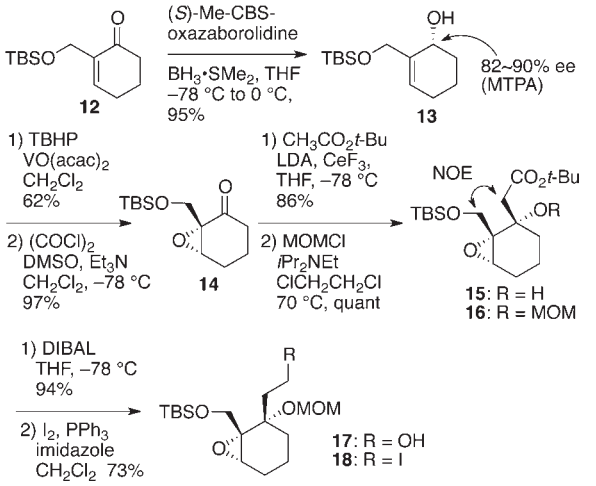
(8) Kabat, M. M.; Garofalo, L. M.; Daniewski, A. R.; Hutchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. *J. Org. Chem.* **2001**, *66*, 6141.

and the following DIBAL reduction and subsequent iodination afforded a requisite A-ring fragment, **18**.

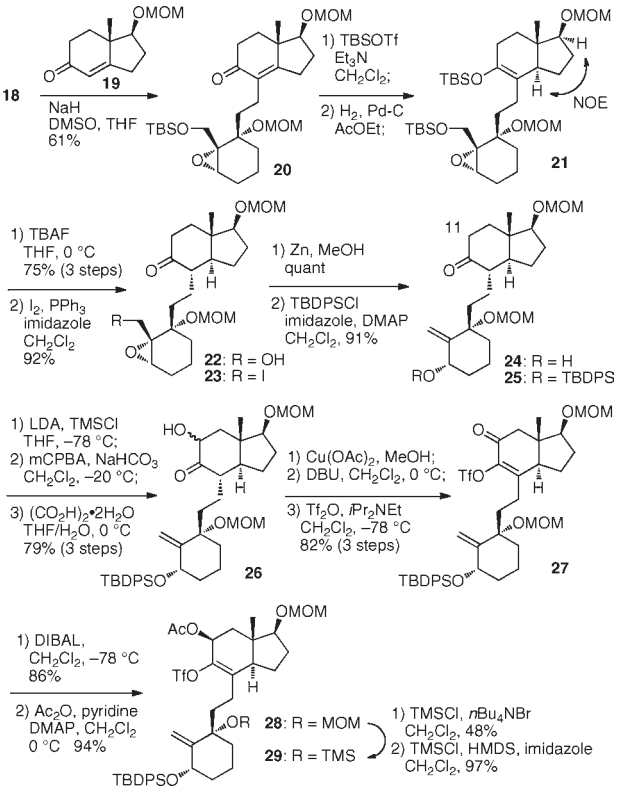
Scheme 1. Synthesis of A-Ring Fragment **18**



Coupling of A-ring fragment **18** and CD-ring fragment **19**[9] using Molander's method[10] gave compound **20** in moderate yield (Scheme 2). The following hydrogenation toward the dienol silyl ether generated from **20** proceeded diastereoselectively[3e,6a] to provide compound **21** having a *trans*-hydrindane skeleton. After removal of the two TBS groups by TBAF treatment, an *exo*-methylene moiety at the A-ring was constructed through iodination of the primary alcohol of **22** and subsequent reductive opening of the α-iodo epoxide with zinc dust in methanol. The resulting secondary alcohol moiety of **24** was protected as a TBDPS ether. Then, the following several conversions were executed to provide two desired cyclization precursors for Heck reaction. Thus, Rubottom oxidation at C11 position, α-diketone formation using $Cu(OAc)_2$, tautomerization by DBU treatment, and triflation[11] provided compound **27**. The C11 ketone of **27** was further converted to an acetoxy group (in the cyclization precursor **28**) by DIBAL reduction and Ac_2O treatment. To investigate the steric effect of the *tert*-alcohol moiety, a TMS-protected precursor **29** was also prepared by further two-step manipulations.

With two cyclization precursors **28** and **29** in hand, intramolecular Heck reaction was investigated (Table 1).[12] In the case of **28**, no cyclization product was obtained by using the conditions in our previous study[6a] (entry 1), while the addition of tetra-*n*-butylammonium bromide (TBAB) provided two cyclization products **30a** and **31a** with 69% recovery of the starting material (entry 2). Compound **30a**

Scheme 2. Synthesis of Cyclization Precursors **28** and **29**



might be formed through the desired 7-*endo* cyclization, and compound **31a**, having a different conjugated diene system, might be formed through the undesired 6-*exo* cyclization and ring expansion.[13] We examined various conditions (ligand, base, and additive). However, low yield and low selectivity (**30a**: 32%; **31a**: 25%) were obtained even in optimized conditions (entry 3). On the other hand, *endo*-cyclization product **30b** was obtained selectively in the case of **29** as a substrate, albeit in low yield (entry 4). After extensive study, the use of nBu_4NOAc as an additive was found to furnish the desired cyclization product **30b** in 56% yield (entry 5).

The final oxa-bridge formation was accomplished as follows (Scheme 3). Selective desilylation at the *tert*-alcohol moiety gave compound **32**, and subsequent DIBAL-mediated deacetylation and Dess–Martin oxidation provided enone **33** in good yield. The following oxy-Michael reaction proceeded only by acid treatment of **33**, using 10-camphorsulfonic acid (CSA) in THF, to give compound **34**

(9) Lepage, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091.

(10) (a) Molander, G. A.; Quirmbach, M. S.; Silva, L. F., Jr.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257. (b) Hajos, Z. G.; Parrish, D. R.; Oliveto, E. P. *Tetrahedron* **1968**, *24*, 2039.

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(12) For a review of the Heck reaction, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(13) Plausible mechanism toward compound **31a** is shown below. No interconversion occurred between **30a** and **31a** under the cyclization conditions, which implied that those two compounds might be formed through different pathways. And, no cyclization product was obtained using C11-ketone compound **27** as a substrate.

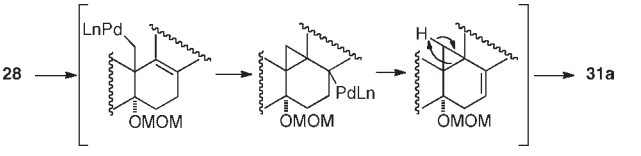
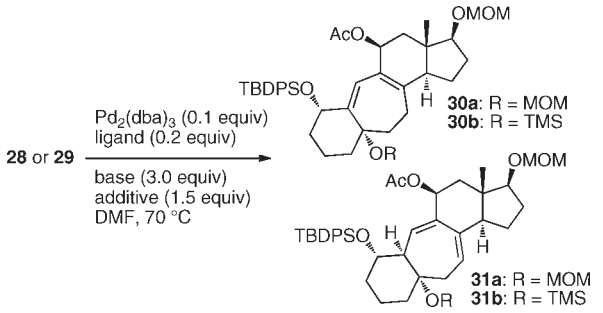


Table 1. Study on Intramolecular Heck Reaction

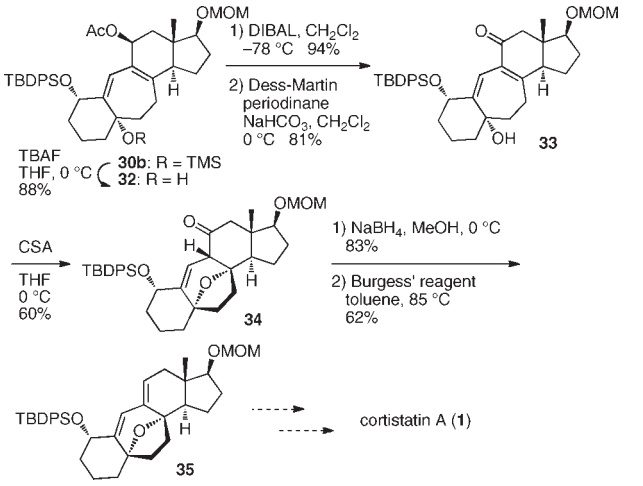


entry	substrate	ligand	base	additive	yield[a]
1	**28**	dppb	KOAc	none	–[b]
2	**28**	dppb	KOAc	TBAB	**30a**: 4%, **31a**: 21% (**28**: 69%)
3	**28**	dppb	CsOAc	TBAB	**30a**: 32%, **31a**: 25% (**28**:30%)
4	**29**	dppp	CsOAc	TBAB	**30b**: 13%, **31b**: 0% (**29**: 73%)
5[c]	**29**	dppp	CsOAc	nBu$_4$NOAc	**30b**: 56%, **31b**: 0% (**29**:12%)

[a] Isolated yield of cyclization products. [b] Not obtained (66% recovery of **28**). [c] 0.7 equiv of $Pd_2(dba)_3$, 1.4 equiv of dppp, and 4.0 equiv of nBu$_4$NOAc were used.

having an objective 8-oxabicyclo[3.2.1]octene structure. Some bases such as K_2CO_3 or Et_3N did not promote this reaction, and surprisingly, CSA treatment in CH_2Cl_2 did not provide **34** and resulted in decomposition. Finally, a 9(11),10(19)-conjugated diene system was elaborated through $NaBH_4$ reduction of the C11 ketone and dehydration using Burgess' reagent, to afford compound **35** possessing the needed core structure of cortistatin A (**1**).

Scheme 3. Synthesis of **35** through Oxy-Michael Reaction



In summary, we achieved a stereoselective synthesis of the core structure of cortistatin A (**1**) through a 7-*endo* intramolecular Heck reaction and subsequent oxy-Michael reaction. Now we are trying to accomplish a total synthesis of **1** and to develop some analogues thereof,[14] which will be presented in due course.

Acknowledgment. This study was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The authors are also grateful to The Uehara Memorial Foundation.

Supporting Information Available. Experimental procedure, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for compounds **12**–**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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