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Synthesis of CD-ring structure of cortistatin A, an anti-angiogenic steroidal alkaloid from marine sponge

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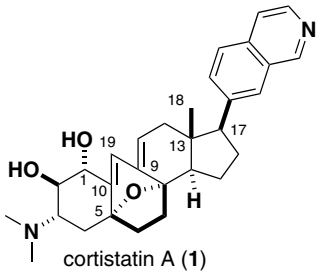
ABSTRACT

Stereoselective synthesis of the CD-ring structure of cortistatin A (**1**), a novel anti-angiogenic steroidal alkaloid from Indonesian marine sponge, was achieved. The stereogenic tertiary carbon center bearing the isoquinoline moiety was constructed by 1,3-chiral transfer method using Johnson–Claisen rearrangement of the chiral allylic alcohol **5**. Subsequent intramolecular Michael-aldol reaction afforded the targeted *trans*-hydrindane skeleton with moderate stereoselectivity.

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. In addition, the new blood vessels provide a way for tumor cells to enter in the circulation and to metastasize to another organ. Therefore, substances that inhibit angiogenesis have a 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 anti-angiogenic substances and isolated cortistatins,[2] a family of novel *abeo*-9(10-19)-androstane-type steroidal alkaloids, from the Indonesian marine sponge of *Corticium simplex*. We found that cortistatin A (**1**, Fig. 1), a major active constituent having unique chemical structure, showed highly selective anti-proliferative activity against HUVECs and also inhibited migration and tubular formation of HUVECs induced by VEGF or bFGF. [2] The scarcity of natural supply prompted us to engage in synthetic study of **1** for further biological evaluation. Some synthetic studies of **1** including two completed total syntheses have recently been reported.[3,4] As both the total syntheses utilized palladium-catalyzed cross-coupling reaction and hydrogenation for introduction of isoquinoline moiety, an essential component for potent anti-angiogenic activity of **1**, in moderate yields, another synthetic method is desirable.Here, we present a synthesis of the CD-ring structure of cortistatin A (**1**) through 1,3-chiral transfer method and Michael-aldol double cyclization.[5]



cortistatin A (**1**)

Figure 1. Chemical structure of cortistatin A (**1**).

Our strategy for the total synthesis of cortistatin A (**1**) is illustrated in Figure 2. The core structure was divided into two fragments, that is, A-ring fragment (**2**) and CD-ring fragment (**3**). These two fragments could be coupled by using B-alkyl Suzuki–Miyaura coupling,[6] and subsequent intramolecular cyclization would afford an oxygen-bridged 7-membered B-ring moiety. The *trans*-hydrindane skeleton of the CD-ring fragment could be elaborated by Michael-aldol double cyclization. The stereogenic carbon center bearing the isoquinoline moiety of **4** would be created through 1,3-chiral transfer method from an optically active (*E*)-allylic alcohol (**5**).

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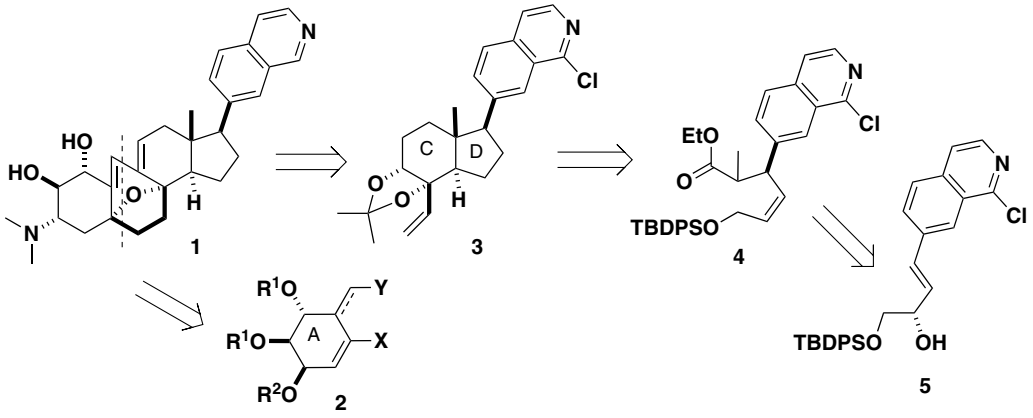
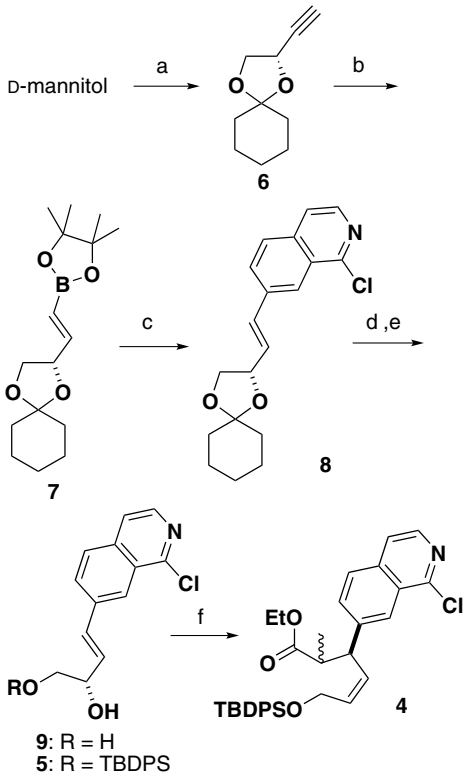


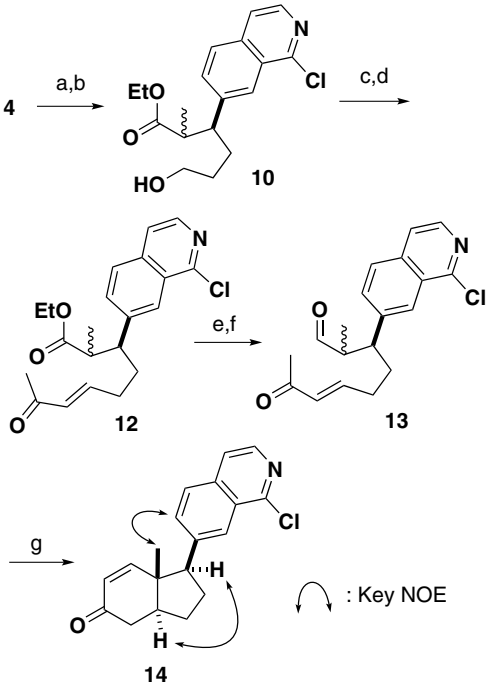
Figure 2. Retrosynthetic analysis.



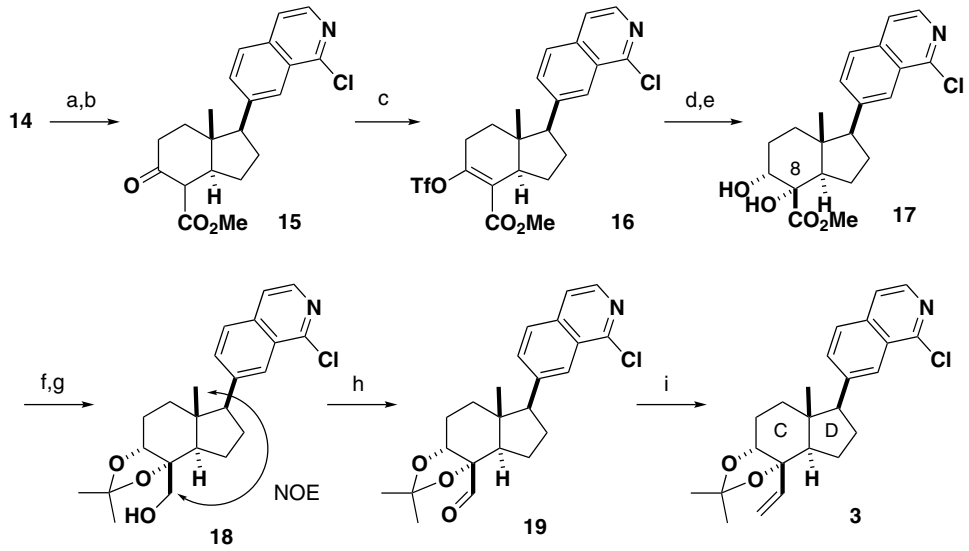
Scheme 1. Reagents and conditions: (a) Ref. 8; (b) pinacolborane, Cp_2ZrHCl, Et_3N, 92%; (c) 7-bromo-1-chloroisoquinoline, $Pd(dppf)Cl_2$, K_2CO_3, 1,4-dioxane, 82%; (d) 80% TFA; (e) TBDPSCl, imidazole, DMF, 57% (two steps); (f) $CH_3CH_2C(OEt)_3$, propionic acid, toluene, reflux, 99%.

Access to the chiral allylic alcohol (**5**) was as follows (Scheme 1). Zirconium-catalyzed regioselective hydroboration[7] to the known chiral alkyne **6**, easily obtained in three steps from D-mannitol,[8] gave an (*E*)-alkenyl borate **7** in good yield and stereoselectively. Subsequent Suzuki–Miyaura cross-coupling with commercially available 7-bromo-1-chloroisoquinoline proceeded selectively at the bromide position to give a coupling product **8**. Cleavage of the cyclohexylidene group and following TBDPS protection of the primary hydroxyl group of **9** afforded a desired allylic alcohol **5**. Optical purity of the product was ascertained by NMR analysis of its MTPA ester. Successful Johnson–Claisen rearrangement[9] reaction was achieved by the treatment of the chiral allylic alcohol **5** with triethyl orthopropionate in the presence of catalytic amount of propionic acid in refluxing toluene, to give an ester **4** as a 1:1 diastereomixture at the tertiary carbon center bearing methyl group. The absolute configuration of the newly generated stereogenic carbon center bearing the isoquinoline moiety in **4** was ascertained by X-ray crystallographic analysis of its derivative.[10]

Cleavage of the TBDPS group of **4** with tetrabutylammonium fluoride (TBAF) and subsequent hydrogenation of the allyl alcohol moiety, using platinum oxide (PtO_2) as a catalyst, gave an alcohol **10**. Hydrogenation using Pd–C resulted in concomitant reduction of isoquinoline ring. Following Swern oxidation and Wittig reaction with phosphorane **11** smoothly proceeded to give a keto-ester **12** with high *E*-selectivity. The desired keto-aldehyde **13**, a precursor of Michael-aldol cyclization, was obtained by reduction of **12**



Scheme 2. Reagents and conditions: (a) TBAF, THF, 96%; (b) H_2/PtO_2, AcOEt, 93%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 79%; (d) $Ph_3P{=}CHCOCH_3$ (**11**), THF, 60 °C, 97%; (e) DIBAL-H, THF, 87%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 83%; (g) NaOMe, THF, rt to 70 °C, 69%.



Scheme 3. Reagents and conditions: (a) NaHMDS, $NCCO_2Me$, THF, −78 °C, 89%; (b) H_2/PtO_2, AcOEt, 95%; (c) $PhNTf_2$, NaH, THF, 79%; (d) $Pd(OAc)_2$, HCOOH, PPh_3, Et_3N, THF, 70 °C; (e) OsO_4, NMO, acetone/H_2O, 77% (two steps); (f) 2,2-dimethoxypropane, *p*-TsOH, acetone, 40 °C, 74%; (g) $LiAlH_4$, THF, 93% (brsm); (h) Dess–Martin periodinane, CH_2Cl_2, 83%; (i) CH_3PPh_3Br, NaHMDS, THF, quant.

with diisobutylaluminum hydride (DIBAL-H) and subsequent Swern oxidation.

According to the Stork's work,[5] Michael-aldol double cyclization of **13** was investigated, using several metal alkoxides. In the use of sodium methoxide as a base, the desired double-cyclized product **14** with hydrindane skeleton was obtained in moderate yield (31%) and trans/cis selectivity (5:1, determined by NMR). Elevated reaction temperature improved yield, up to 69%, with the same diastereoselectivity. The use of $Mg(OEt)_2$ gave in low yield with a little better selectivity (6:1), and zirconium tetra-*n*-propoxide, designated as a best reagent in the literature, did not give cyclization product at all. The relative stereochemistry of the product was determined by NOE experiment (Scheme 2).

Generation of the stereogenic center at C-8 was further investigated. Sodium enolate of the ketone **14** reacted with methyl cyanoformate, and following hydrogenation catalyzed by PtO_2 gave a β-keto ester **15**. Then, **15** was converted to an enol triflate **16** by the treatment with NaH and *N*-phenyltriflimide. Palladium-catalyzed reduction of **16** gave an α,β-unsaturated ester, which was subjected to dihydroxylation for generating a stereogenic center corresponding to C-8 of cortistatin A (**1**). To our delight, dihydroxylation occurred stereoselectively from α-face of the hydrindane ring to give a diol **17**, due to steric repulsion of both the methyl and isoquinoline groups on the β-face of the molecule. The product **17** was further converted to an alcohol **18**, by protection of the diol moiety as acetonide and subsequent treatment with $LiAlH_4$. An NOE correlation between the angular methyl proton and the methylene proton of the hydroxymethyl group was observed in the NOESY spectrum of **18**, confirming stereochemistry of the tertiary alcohol moiety corresponding to the C-8 stereogenic center of **1**. Treatment of **18** with Dess–Martin periodinane gave an aldehyde **19**, and subsequent Wittig reaction afforded the targeted compound **3** having vinyl moiety. The compound **3** possesses almost all the required functional groups and stereochemistry corresponding to the CD-ring part of cortistatin A (**1**) (Scheme 3).[11]

In summary, we achieved the stereoselective synthesis of the CD-ring structure of cortistatin A (**1**) utilizing 1,3-chiral transfer method and intramolecular Michael-aldol cyclization reaction. Coupling reaction with the A-ring fragment and construction of the B-ring structure leading to the total synthesis of cortistatin A (**1**) are now in progress.

Acknowledgments

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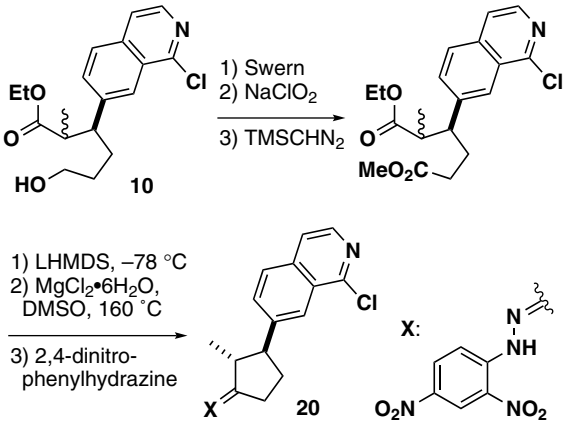
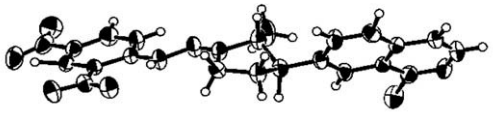
References and notes

1. Carmeliet, P.; Jain, R. K. *Nature* **2000**, *407*, 249.
2. (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; (d) 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. For the total synthesis 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; (b) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310.
4. For studies towards the synthesis of cortistatins, see: (a) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413; (b) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650; (c) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931; (d) Dai, M.; Danishefsky, S. J. *Heterocycles*; published online, April 17th, 2008. COM-08-S(F)6; (e) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**. doi:10.1016/j.tetlet.2008.09.018; (f) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**. doi:10.1016/j.tetlet. 2008. 09.019.
5. (a) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310; (b) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767.
6. Review Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.
7. Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777.
8. (a) Sugiyama, T.; Sugawara, H.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem.* **1984**, *48*, 1841; (b) Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503.
9. (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741; (b) Takano, S.; Sugihara, T.; Samizu, K.; Akiyama, M.; Ogasawara, K. *Chem. Lett.* **1989**, 1781; (c) Lee, J.; Hong, J. *J. Org. Chem.* **2004**, *69*, 6433.
10. The stereochemistry of the tertiary carbon center bearing isoquinoline moiety was ascertained by X-ray crystallographic analysis of the hydrazone **20**, which was obtained in six steps from the alcohol **10**, depicted below. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 699923. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).





11. *Data for* **3**: IR (KBr): 1549, 1732, 2926 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.54 (3H, s), 1.39–1.57 (5H, m), 1.62–1.99 (4H, m), 3.01 (1H, t, J = 9.8 Hz), 4.00 (1H, s), 5.23 (1H, dd, J = 1.5, 11.0 Hz), 5.52 (1H, dd, J = 2.0, 17.0 Hz), 6.02 (1H, dd, J = 11.0, 17.0 Hz), 7.56–7.62 (2H, m), 7.77 (1H, d, J = 8.4 Hz), 8.11 (1H, s), 8.22 (1H, d, J = 5.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.1, 20.7, 24.0, 25.3, 26.5, 28.6, 32.4, 45.0, 54.2, 57.9, 78.4, 83.9, 107.3, 116.0, 120.4, 125.2, 126.1, 126.8, 132.9, 136.6, 136.9, 140.9, 141.5, 151.3. ESI MS: m/z 424 $(M+Na)^+$. Anal. Calcd for $C_{24}H_{28}ClNO_2$: C, 72.44; H, 7.09; N, 3.52; Cl, 8.91. Found: C, 72.33; H, 7.25; N, 3.42; Cl, 8.62.