ORGANIC LETTERS

2006
Vol. 8, No. 10
2039−2042

Synthetic Studies on (+)-Ophiobolin A: Asymmetric Synthesis of the Spirocyclic CD-Ring Moiety

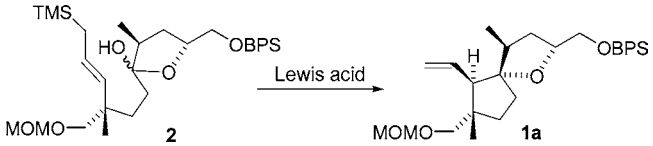
Naoyoshi Noguchi and Masahisa Nakada*

Department of Chemistry, Faculty of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

mnakada@waseda.jp

Received February 19, 2006

ABSTRACT



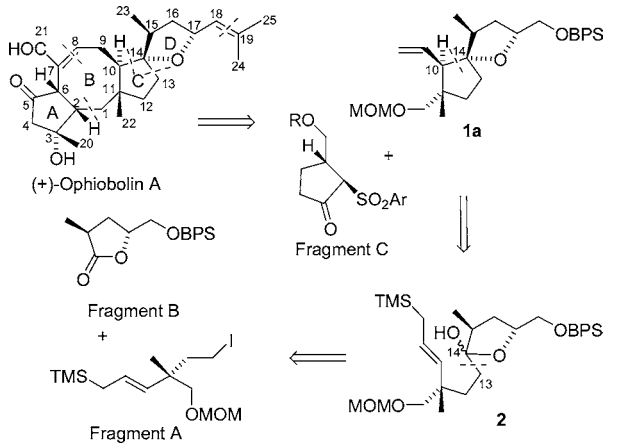
Asymmetric synthesis of the spirocyclic CD-ring moiety of (+)-ophiobolin A is described. Fragment A, which was prepared via pig liver esterase (PLE)-mediated kinetic resolution, and fragment B, which was prepared via diastereoselective allylation and subsequent kinetic iodolactonization, were coupled to afford the allylsilane 2, which was successfully cyclized to the desired spirocyclic CD-ring moiety 1a in the presence of a Lewis acid.

(+)-Ophiobolin A (Scheme 1) was first isolated as a metabolite from the culture broth of the pathogenic plant fungus *Ophiobolus miyabeanus*,[1a] and from its absolute structure proof, the first naturally occurring sesterterpene was identified.[1b] Since then, several congeners, including ophiobolin B,[1c] C,[1d] D,[1e,f] F,[1g] G,[1h] H,[1h] I,[2] J,[2b] K,[3a] L,[3b] M,[3c] 6-epi-ophiobolin G,[3d] and 6-epi-ophiobolin N,[3d] have been isolated.[4a]

(+)-Ophiobolin A shows a broad spectrum of bioactivity against nematodes, fungi, and bacteria.[4a] It was reported to inhibit calmodulin-activated cyclic nucleotide phosphodiesterase[4b] and also to induce apoptotic cell death in the L1210 cell line.[4c] Recent studies disclosed that (+)-ophiobolin A is cytotoxic to the cancer cell lines A-549, Mel-20, and P-335 with IC_{50} values ranging from 62.5 to 125 nM.[4d]

(+)-Ophiobolin A possesses eight stereogenic centers on the unique tricyclic 5-8-5-5 ring system. The five-membered A-ring incorporates three successive stereogenic centers including a chiral tertiary alcohol and two contiguous stereogenic centers at the cis-fused AB-ring juncture. The CD-ring is a spirocyclic ether, possessing a total of five

Scheme 1. Retrosynthetic Analysis of (+)-Ophiobolin A



(1) (a) Ishibashi, K.; Nakamura, R. *J. Agric. Chem. Soc. Jpn.* **1958**, *32*, 739−744. (b) Nozoe, S.; Morisaki, M.; Tsuda, K.; Iitaka, Y.; Tokahashi, N.; Tamura, S.; Ishibashi, K.; Shirasaka, M. *J. Am. Chem. Soc.* **1965**, *87*, 4968−4970. (c) Canonica, L.; Friecchi, A.; Galli Kienle, U.; Scala, A. *Tetrahedron Lett.* **1966**, *7*, 1329−1333. (d) Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1966**, *7*, 2211−2216. (e) Itai, A.; Nozoe, S.; Tsuda, K.; Okuda, S.; Iitaka, Y.; Nakayama, Y. *Tetrahedron Lett.* **1967**, *8*, 4111−4112. (f) Nozoe, S.; Itai, A.; Tsuda, K.; Okuda, S. *Tetrahedron Lett.* **1967**, *8*, 4113−4117. (g) Nozoe, S.; Morisaki, K.; Fukushima, K.; Okuda, S. *Tetrahedron Lett.* **1968**, *9*, 4457−4458. (h) Culter, H. G.; Crumley, F. G.; Cox, R. H.; Springer, J. P.; Arrendale, R. F.; Cole, R. J.; Cole, P. D. *J. Agric. Food Chem.* **1984**, *32*, 778−782.

10.1021/ol060437x CCC: $33.50
Published on Web 04/13/2006

stereogenic centers, four of which are successive, as well as a quaternary stereogenic center at the trans-fused BC-ring juncture.

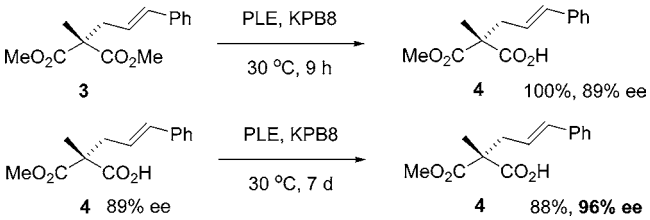
Total synthesis of (+)-ophiobolin A has not been achieved nor have synthetic studies on the spirocyclic CD-ring moiety been reported.[5,6] Recent studies on its potent bioactivity[4] as well as on its complex structural features led us to commence synthetic studies on (+)-ophiobolin A.

We envisioned that (+)-ophiobolin A could be synthesized from the CD-ring moiety **1a** and fragment C, which we expected to derive from the chiral building block we had reported earlier.[7] Consequently, we first examined the synthesis of **1a** and report herein the asymmetric synthesis of the spirocyclic CD-ring moiety of (+)-ophiobolin A.

As outlined in Scheme 1, we selected a Lewis acid promoted cyclization reaction of **2** to construct **1a** because this reaction[8] would simultaneously construct the 1-oxaspiro-[4.4]nonane framework as well as the two requisite stereogenic centers at C10 and C14. Because this cyclization proceeds via an oxonium ion, the allylsilane was expected to react at the C14 position from the less-hindered side to afford **1a** as a major product. A coupling reaction of fragments A and B would provide **2**. Consequently, we first prepared these two fragments.

We selected pig liver esterase (PLE)-mediated asymmetric hydrolysis of **3** to prepare **4** for the synthesis of fragment A (Scheme 2) because fragment A possesses a quaternary

Scheme 2. Kinetic Resolution of **4** with PLE



stereogenic center, which could not be derived from a commercially available compound. PLE-mediated asymmetric hydrolysis of **3** in 0.01 M KPB8 (pH 8, potassium phosphate buffer) successfully generated **4** with 96% ee via kinetic resolution. Specifically, monoester **4**, prepared with 89% ee via PLE-mediated asymmetric hydrolysis in the initial 9 h reaction, was again treated with PLE, and after a week, **4** was recovered in 88% yield. HPLC analysis of the corresponding anilide revealed that the ee of **4** was increased from 89 to 96% ee.[9]

The synthesis of fragment A began with the conversion of chiral starting material **4** to the corresponding acid chloride (Scheme 3), which was then reduced with $NaBH_4$ to afford **5** (86%).[10] Alcohol **5** was protected as a MOM ether, followed by reduction with $LiAlH_4$ (99%) to produce **6**, which was acetylated and subjected to ozonolysis followed by reductive workup affording **7** (100%). Protection of **7** as an ethoxyethyl ether, removal of the acetyl group, and Swern oxidation gave aldehyde **8** (84%). Horner−Wadsworth−Emmons reaction of **8**, followed by DIBAL-H reduction, and treatment of the resulting allylic alcohol with lithium chloride and methanesulfonyl chloride[11] afforded **9** (97%). Still's protocol successfully introduced the allyltrimethylsilane,[12] and the following removal of the ethoxyethyl group and subsequent conversion furnished fragment A (81%).

(2) (a) Sugawara, F.; Strobel, G.; Strange, R. N.; Siedow, J. N.; Duyne, G. D. V.; Clardy, J. *Proc. Natl. Acad. Sci.* **1987**, *84*, 3081−3085. (b) Sugawara, F.; Takahashi, N.; Strobel, G.; Yun, C.; Gray, G.; Fu, Y.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 2170−2172.

(3) (a) Singh, S. B.; Smith, J. L.; Sabnis, G. S.; Dombrowski, A. W.; Schaeffer, J. M.; Goetz, M. A.; Bills, G. F. *Tetrahedron* **1991**, *47*, 6931−6938. (b) Li, E.; Clark, A. M.; Rotella, D. P.; Hufford, C. D. *J. Nat. Prod.* **1995**, *58*, 74−81. (c) Tsipouras, A.; Adefarati, A. A.; Tkacz, J. S.; Frazier, E. G.; Rohrer, S. P.; Birzin, E.; Rosegay, A.; Zink, D. L.; Geotz, M. A.; Singh, S. B.; Schaeffer, J. M. *Bioorg. Med. Chem.* **1996**, *4*, 531−536. (d) Wei, H.; Itoh, T.; Kinoshita, M.; Nakai, Y.; Kurotaki, M.; Kobayashi, M. *Tetrahedron* **2004**, *60*, 6015−6019.

(4) (a) Au, T. K.; Chick, Wallace S. H.; Leung, P. C. *Life Sci.* **2000**, *67*, 733−742. (b) Fujiwara, H.; Matsunaga, K.; Kumagai, H.; Ishizuka, M.; Ohizumi, Y. *Pharm. Pharmacol. Commun.* **2000**, *6*, 427−431. (c) Leung, P. C.; Taylor, W. A.; Wang, J. H.; Tipton, C. L. *J. Biol. Chem.* **1984**, *259*, 2742−2747. (d) Shen, X.; Krasnoff, S. B.; Lu, S.-W.; Dunbar, C. D.; O'Neal, J.; Turgeon, B. G.; Yoder, O. C.; Gibson, D. M.; Hamann, M. T. *J. Nat. Prod.* **1999**, *62*, 895−897.

(5) Several research groups reported synthetic studies on ophiobolins. See: (a) Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977**, *42*, 922−923. (b) Das, T. K.; Dutta, P. C.; Kartha, G.; Bernassau, J. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1287−95. (c) Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1977**, *42*, 3630−3633. (d) Paquette, L. A.; Andrews, D. R.; Springer, J. P. *J. Org. Chem.* **1983**, *48*, 1147−1149. (e) Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201−205. (f) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541−3557. (g) Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319−1321. (h) Umehara, M.; Hishida, S.; Okumoto, S.; Ohba, S.; Ito, M.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4474−4476. (i) Rigby, J. H.; Senanayake, C. *J. Org. Chem.* **1987**, *52*, 4634−4635. (j) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909−4912. (k) Dauben, W. G.; Warshawsky, A. M. *J. Org. Chem.* **1990**, *55*, 3075−3087. (l) Paquette, L. A.; Liang, S.; Galatsis, P. *Synlett* **1990**, 663−665. (m) Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615−3626. (n) Rigby, J. H.; McGuire, T.; Senanayake, C.; Khemani, K. *J. Chem. Soc., Perkin Trans.1* **1994**, 3449−3457. (o) Paquette, L. A.; Liang, S.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 3268−3279. (p) Blake, A. J.; Highton, A. J.; Majid, T. N.; Simpkins, N. S. *Org. Lett.* **1999**, *1*, 1787−1789. (q) McGee, K. F., Jr.; Al-Tel, T. H.; Sieburth, S. M. *Synthesis* **2001**, 1185−1196. (r) Ruprah, P. K.; Cros, J.-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145−3152. (s) Salem, B.; Suffert, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2826−2830.

(6) For the total synthesis of ophiobolin C, see: (a) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735−2737. For the total synthesis of (+)-albolic acid and (+)-ceroplastol II, see: (b) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354−356. (c) Kato, N.; Takeshita, H.; Kataoka, H.; Ohbuchi, S.; Tanaka, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 165−174. For the total synthesis of (±)-ceroplastol I, see: (d) Boeckman, R. K., Jr.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737−2739. For the total synthesis of (+)-ceroplastol I, see: (e) Paquette, L. A.; Wang, T. Z.; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676−1683.

(7) (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860−2861. (b) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897−4900. (c) Miyamoto, H.; Iwamoto, M.; Nakada, M. *Heterocycles* **2005**, *66*, 61−68.

(8) For oxonium ion mediated cyclizations using dihydropyrans, see: Paquette, L. A.; Tae, J. *J. Org. Chem.* **1996**, *61*, 7860−7866. For a recent review of allylsilane chemistry, see: (a) Fleming, I.; Barbero, A.; Walter, W. *Chem. Rev.* **1997**, *97*, 2063−2192. (b) Hosomi, A.; Miura, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835−851. (c) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173−3199.

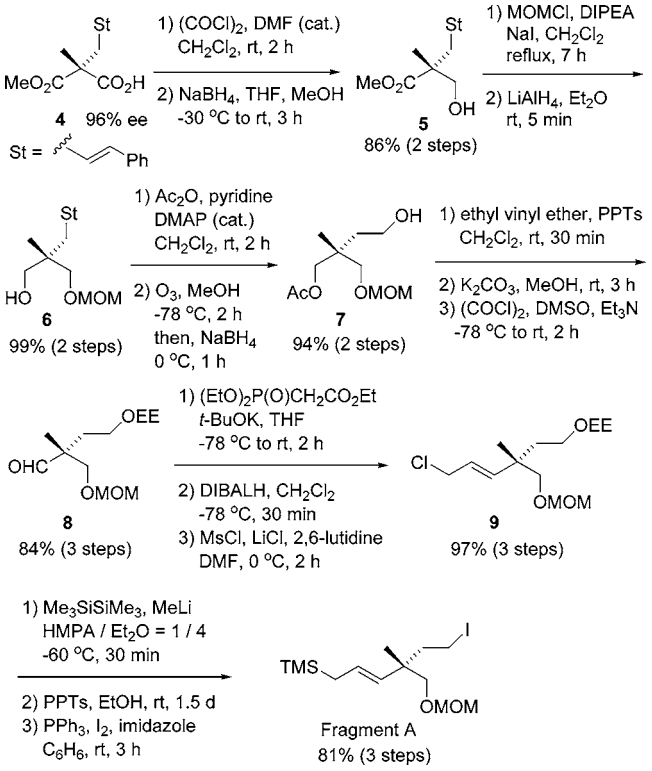
(9) To the best of our knowledge, this kinetic resolution of monoester has never been reported. For details, see Supporting Information.

(10) Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* **1987**, 647−648.

(11) Meyers, A. I.; Collington, E. W. *J. Org. Chem.* **1971**, *36*, 3044−3045.

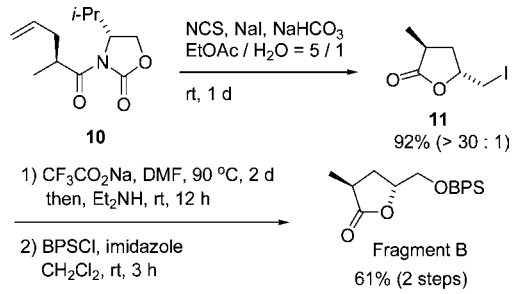
(12) (a) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063−3064. (b) Smith, J. G.; Drozda, S. E.; Petraglia, S. P.; Quinn, N. R.; Rice, E. M.; Taylor, B. S.; Viswanathan, M. *J. Org. Chem.* **1984**, *49*, 4112−4120.

Scheme 3. Synthesis of Fragment A



The synthesis of fragment B was initiated from **10** (Scheme 4), which had been stereoselectively prepared.[13]

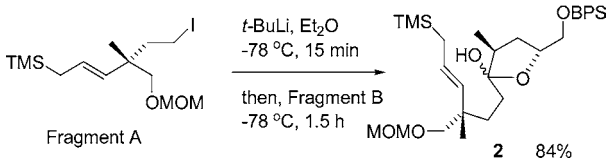
Scheme 4. Synthesis of Fragment B



Iodolactonization of **10** under the optimized conditions[14] cleanly afforded iodolactone **11** as the sole product (92%). Compound **11** was converted to the corresponding trifluoroacetate, followed by removal of the trifluoroacetate with diethylamine and subsequent protection of the resulting alcohol with BPSCl to generate fragment B (61%).[15]

To couple fragments A and B (Scheme 5), fragment A was treated with *t*-BuLi in Et_2O at −78 °C to generate the corresponding organolithium intermediate, which was then reacted with fragment B at the same temperature, successfully affording **2** in 84% yield as a mixture of two diastereomers.

Scheme 5. Coupling of Fragment A with Fragment B



Now, the stage was set for the Lewis acid promoted cyclization reaction of **2**. Table 1 compares the effect of several Lewis acids on the generation of **1a** as well as three other possible products. $EtAlCl_2$ generated three products, **1a**, **1b**, and **1c**, in 20, 40, and 40% yields, respectively. Less acidic Et_2AlCl required an elevated temperature to produce **1a**, **1b**, and **1c** with yields of 25, 36, and 36%, respectively. $SnCl_4$ similarly afforded a mixture of the same three products, but the ratio of **1c** was slightly higher, representing 49% of the product yield. Although $TiCl_4$ merely decomposed **2** because of its strong acidity, $TiCl_3(O^iPr)$ afforded **1a**, **1b**, and **1c** in 29, 31, and 40% yields, respectively. $TiCl_2(O^iPr)_2$ gave rather different results, however, producing **1a** and **1c** in 18 and 19% yields, respectively, and a major new product, **1d**, which formed in 57% yield. Interestingly, **1d** was the sole product (84% yield) when the less acidic $TiCl(O^iPr)_3$ was used. The acidity of $Ti(O^iPr)_4$ was too weak to promote this reaction. In contrast to the above results, $BF_3{\cdot}OEt_2$ produced **1a** in 45% yield.

X-ray crystallographic analysis of the crystalline derivative of **1a** confirmed the whole structure of **1a** as the desired product shown in Table 1.[16] Products **1b**, **1c**, and their derivatives were not suitable for the X-ray crystallographic analysis; however, NMR studies including NOESY experiments of their derivatives successfully elucidated their structures.[16]

X-ray crystallographic analysis of **1d** disclosed that it was an unexpected product because the configuration of the C15 stereogenic center was clearly reversed. Because no epimerization at the C15 position can occur except in the spiroether formation step, the oxonium ion derived from **2** or the hydroxyl ketone which arose from **2** must have epimerized under the reaction conditions, and the epimerized oxonium ion, which was more reactive than the sterically hindered, unepimerized species, reacted with the allylsilane from the less-hindered side to afford **1d**. This key epimerization to form **1d** occurs only under the reaction conditions in entries 6 and 7 of Table 1, and the isopropoxy ligand of the employed titanium catalysts could play a crucial role in this reaction.

Admittedly, the yields of the desired precursor **1a** were relatively low in several of the reactions in Table 1. However, stereogenic centers generated at C10 in **1b** and at C14 in **1c**

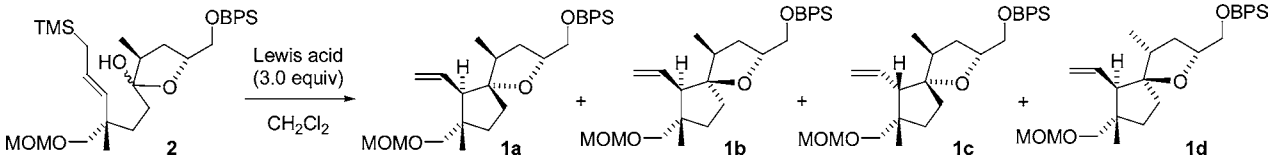
(13) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

(14) (a) Moon, H.-S.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504−6505. (b) Maligres, P. E.; Upadhyay, V.; Rossen, K.; Cianciosi, S. J.; Purick, R. M.; Eng, K. K.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 2195−2198. (c) Williams, D. R.; Cortez, G. S. *Tetrahedron Lett.* **1998**, *39*, 2675−2678.

(15) For the alternate approach to fragment B, see: Herdeis, C.; Luetsch, K. *Tetrahedron: Asymmetry* **1993**, *4*, 121−131.

(16) For details, see Supporting Information.

Table 1. Intramolecular Cyclization Reaction of **2**



entry	Lewis acid	temp (°C)	time (h)[a]	yield (%)[b] 1a	1b	1c	1d
1	$EtAlCl_2$	−78	6	20	40	40	0
2	Et_2AlCl	−78, −50, −20	5, 8, 12	25	36	36	0
3	$SnCl_4$	−78	2	25	24	49	0
4	$TiCl_3(O^iPr)$	−78	4	29	31	40	0
5	$TiCl_2(O^iPr)_2$	−78, −50	4, 1.5	18	0	19	57
6	$TiCl(O^iPr)_3$	−78, −50, −20	2, 2, 12	0	0	0	84
7	$BF_3{\cdot}OEt_2$	−78	4	45	25	27	0

[a] Time at the corresponding reaction temperature. [b] Isolated yields.

are correct, suggesting that further optimization of the cyclization reaction of **2** would improve the diastereoselectivity, and the transformations from **1b** and **1c** to the compounds possessing correct stereochemistry could be possible.

In conclusion, the spiro CD-ring moiety **1a** possessing the correct stereochemistry has been successfully constructed via a Lewis acid promoted cyclization reaction of **2**, which had been prepared by the coupling of fragments A and B in a convergent manner. Further studies toward the asymmetric total synthesis of (+)-ophiobolin A, which include efficient access to fragment A, and the improved stereoselectivity in the cyclization of **2** are now in progress.

Acknowledgment. We thank Dr. Motoo Shiro of Rigaku X-ray Research Laboratory for the X-ray crystal structure determination of compound **1d**. This work was financially supported in part by a Waseda University Grant for Special Research Projects and a Grant-in-Aid for Scientific Research on Priority Areas (Creation of Biologically Functional Molecules (No. 17035082)) from The Ministry of Education, Culture, Sports, Science, Sports and Technology (MEXT), Japan. We are also indebted to 21COE Practical Nano-Chemistry.

Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060437X