JOC*Note*

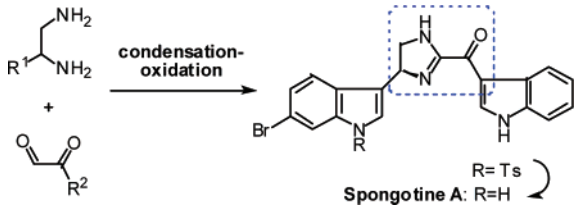
Concise Total Synthesis of (−)-Spongotine A

Kenichi Murai,† Maiko Morishita, Ryo Nakatani, Ozora Kubo, Hiromichi Fujioka,* and Yasuyuki Kita*

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

fujioka@phs.osaka-u.ac.jp; kita@phs.osaka-u.ac.jp

Received July 30, 2007

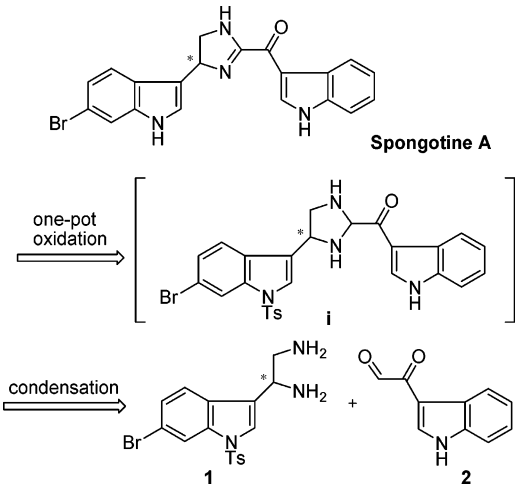


The first asymmetric total synthesis of spongotine A is described. The oxidative synthesis of the imidazoline/ketone unit from keto aldehyde and diamine is a key step in this synthesis. The absolute stereochemistry of the asymmetric center of natural spongotine A is revealed as the (*S*)-configuration.

Bisindole alkaloids, isolated from marine sponges, such as topsentines,[1] nortopsentines,[2] dragmacidines,[3] and hamacanthines[4] are very attractive compounds because they have potent and diverse bioactivities such as cytotoxic, antitumor, antiviral, antifungal, antibacterial, and anti-inflammatory activities.[2,3a,4a,c,5] They have unique structures with the two indole units linked through imidazole or piperazine derivatives. Many synthetic studies have been reported for the synthesis of members of the family.[6] Recently, Jung et al. reported a new class of bisindole alkaloids, spongotines A−C, which have the imidazoline/ketone structure as a linker from the marine sponge *Spongosrites* sp.,[7] but their absolute configurations were not determined.

For the synthesis of spongotines, the construction of the imidazoline/ketone structures is an important issue. Very recently, Denis et al. described the first synthesis of spongotine B.[8] They made the imidazoline/ketone structures by condensation between the α-ketothioimidate salts and diamines. However, the preparation of α-ketothioimidate salts needed several steps including a low-yielding step in the conversion of an acyl chloride to a thioamide. Furthermore, they synthesized the racemic spongotine B, and asymmetric synthesis was not accomplished.

SCHEME 1. Strategy



Recently, we developed an efficient method for the synthesis of imidazolines from aldehydes and diamines.[9] Thus, aldehydes and diamines were condensed and oxidized by NBS to give imidazolines in a one-pot operation. This reaction was the first method to synthesize imidazolines from aldehydes in high yields under mild conditions and was applied to a variety of aromatic and aliphatic aldehydes. We thought that this reaction could be applied to the construction of imidazoline/ketone structures and total synthesis of spongotine A could be accomplished by one-pot oxidation of aminal **i** generated from the condensation of indole diamine **1** and indole keto aldehyde **2** (Scheme 1). However, it was not clear that our reaction could work for the keto aldehydes. Since the keto aldehyde compounds have two reactive carbonyl functions, it could be possible for a diamine to react with both the aldehyde and the ketone. For example, Stolz et al. reported an aminoamide reacted with both carbonyl groups in a similar keto aldehyde to give a pyrazone ring in their study of dragmacidine D.[6a]

† JSPS Research Fellow.

(1) (a) Bartik, K.; Braekman, J. C.; Daloze, D.; Stoller, C.; Huysecom, J.; Vandevyver, G.; Ottinger, R. *Can. J. Chem.* **1987**, *65*, 2118. (b) Tsujii, S.; Rinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446.

(2) Sakemi, S.; Sun, H. H. *J. Org. Chem.* **1991**, *56*, 4304.

(3) (a) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772. (b) Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carroll, A. R. *J. Nat. Prod.* **1998**, *61*, 660.

(4) (a) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. J. *J. Nat. Prod.* **1994**, *57*, 1437. (b) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. *J. Nat. Prod.* **2000**, *63*, 447. (c) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C. O.; Sim, C. J.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **2005**, *68*, 711.

(5) For examples see: (a) Sato, H.; Tsuda, M.; Watanabe, K.; Kobayashi, J. *Tetrahedron* **1998**, *54*, 8687. (b) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J. R.; Sim, C. J. *J. Nat. Prod.* **1999**, *62*, 647. (c) Morris, S. A.; Andersen, R. J. *Tetrahedron* **1990**, *46*, 715. (d) Jacobs, R. S.; Pomponi, S.; Gunasekera, S.; Wright, A. PCT Int. Appl. WO 9818466, May 7, 1998.

(6) For examples see: (a) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (b) Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem*, **2001**, *66*, 4865. (c) Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem*, **2002**, *67*, 1396. (d) Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B. *Tetrahedron*: *Asymmetry* **2002**, *13*, 383. (e) Kawasaki, T.; Ohno, K.; Enoki, H.; Umemoto, Y.; Sakamoto, M. *Tetrahedron Lett.* **2002**, *43*, 4245. (f) Kouko, T.; Matsumura, K.; Kawasaki, T. *Tetrahedron* **2005**, *61*, 2309. (g) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121. (h) Tonsiengsom, F.; Miyake, F. K.; Yakushijin, K.; Horne, D. A. *Synthesis* **2006**, 49. (i) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2002**, *4*, 941. (j) Fresneda, P. M.; Molina, P.; Sanz, M. A. *Synlett* **2000**, 1190. (k) Achab, S. *Tetrahedron Lett.* **1996**, *37*, 5503 and references cited therin.

(7) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Cho, H. Y.; Jung, J. H. *J. Nat. Prod.* **2007**, *70*, 2.

(8) Guinchard, X.; Vallée, Y.; Denis, J.-N. *J. Org. Chem.* **2007**, *72*, 3972.

(9) (a) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46*, 2197. (b) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63*, 638.

10.1021/jo701668s CCC: $37.00
Published on Web 10/12/2007

SCHEME 2. Total Synthesis of Spongotine A

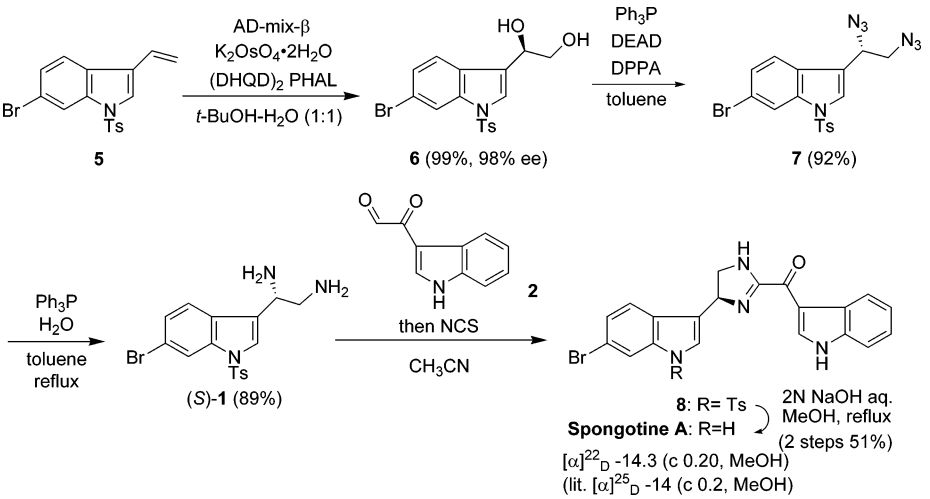
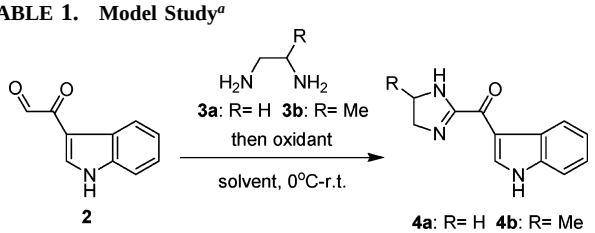


TABLE 1. Model Study[a]



entry	solvent	oxidant	diamine	yield %
1	CH_2Cl_2−CH_3CN (1:1)	NBS	**3a**	69[b]
2	CH_3CN	NBS	**3a**	*c*
3	acetone	NBS	**3a**	*c*
4	CH_2Cl_2−CH_3CN (1:1)	NCS	**3a**	42
5	CH_2Cl_2	NCS	**3a**	no reaction
6	CH_3CN	NCS	**3a**	88
7	MeOH	NCS	**3a**	75
8	acetone	NCS	**3a**	*c*
9	CH_3CN	*t*-BuOCl	**3a**	34
10	CH_3CN	NCS	**3b**	57
11	MeOH	NCS	**3b**	51

[a] Conditions: 1.0 equiv of **2**, 1.1 equiv of **3**, and oxidant in 0.1 M solution. [b] Containing a small amount of unidentified compound. [c] Containing a large amount of unidentified compound.

We then first examined the reaction of the indole keto aldehyde **2** with the simple 1,2-diamines as a model reaction. According to the literature, keto aldehyde **2** was prepared from indole in 2 steps by the condensation with oxalyl chloride and the reduction with tributyltin hydride.[6a] The reaction of ethylenediamine **3a** and indole keto aldehyde **2** followed by NBS oxidation in CH_3CN−CH_2Cl_2 (1:1) gave compound **4a** in 69% yield (entry 1). Although compound **4a** was obtained by filtration, due to its low solubility, further purification was difficult and the product contained a small amount of unidentified compounds determined by ^{1}H NMR.[10] To obtain a pure product by only filtration, other solvents and oxidants were examined. The oxidation reaction with NBS in CH_3CN or acetone did not produce a pure product (entries 2 and 3 in Table 1). On the other hand, when NCS was used as an oxidant the sole product was obtained (entries 4, 6, and 7 in Table 1). The best result (88% yield) was obtained in CH_3CN. Due to the low solubility of keto aldehyde **2** in CH_2Cl_2 the reaction did not proceed (entry 5). The reaction in acetone gave a poor result (entry 8). The reaction with *t*-BuOCl in CH_3CN resulted in a low yield (entry 9). Besides ethylenediamine **3a**, the reaction was also applied with use of 1,2-propanediamine **3b** to give moderate yields of **4b** (entries 10 and 11 in Table 1).

Since it was revealed that the indole keto aldehyde **2** reacted with 1,2-diamines to give the condensed imidazoline products in good yields, the total synthesis of spongotine A was studied (Scheme 2). First, the chiral indole diamine **1** was synthesized. Vinyl indole **5**[6b] was prepared from 6-bromoindole by formylation, tosylation, and the Wittig olefination reaction. The asymmetric dihydroxylation of vinyl indole **5** with use of the Sharpless AD reaction[11] was already reported by Jiang et al.[6b,c] Although the stereochemistry of spongotine A was not described, the (*S*)-configuration was selected for the first asymmetric synthesis. The chiral diol **6**, which has the (*R*)-configuration, was prepared by using AD-mix-β in 98% ee.[12] The diol **6** was then converted into diazide **7** by the Mitsunobu reaction with diphenylphosphoryl azide (DPPA) in 92% yield. The hydrogenation of indole diazide **7** by the Lindlar catalyst gave a complex mixture, while the reduction by triphenylphosphine in refluxing toluene with water succeeded in producing indole diamine (*S*)-**1** in excellent yield.

The condensation of diamine (*S*)-**1** and keto aldehyde **2** followed by NCS oxidation in CH_3CN proceeded smoothly and compound **8**, which has the imidazoline/ketone moiety, was obtained. Compound **8** was unstable under purification by SiO_2. Then crude **8** was directly deprotected by NaOH in refluxing MeOH to give spongotine A in 51% yield over 2 steps. All spectral data were identical with those reported for the natural spongotine A. The optical rotation, the signal and value, of synthetic spongotine A agreed with that of the natural spongotine A and its absolute stereochemistry was determined to be the (*S*)-configuration.

In summary, we demonstrated that our imidazoline synthetic method in which aldehydes and diamines are condensed and oxidized in a one-pot operation could be applied to the indole keto aldehyde **2**, and the first asymmetric total synthesis of

(10) For experimental details, see the Supporting Information

(11) (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. (b) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(12) Jiang et al. used only AD-mix for asymmetric dihydroxylation of vinyl indole **5**; however, additional K_2OsO_4·$2H_2O$ and $(DHQD)_2PHAL$ were needed for high yield and ee in our hand.

spongitine A was accomplished in 41% yield over 5 steps from the known vinyl indole **5**. The absolute stereochemistry of the naturally obtained spongotine A was also determined. Further studies about the generality of our coupling reaction and the application to other heterocycles are also underway in our laboratory.

Experimental Section

Typical Procedure of Experiment in Table 1. Diamine **3** (1.1 mmol) was added to a solution of keto aldehyde **2** (1 mmol) in solvent (20 mL) at 0 °C under N_2 atmosphere and stirred for 20 min. Oxidant (1.1 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by sat. $Na_2S_2O_3$ aq and solvent was evaporated in vacuo. Saturated $NaHCO_3$ aq (20 mL) was added to the residue and the mixture was stirred for 30 min. The solid was filtered, washed with cold H_2O and cold Et_2O, and dried in vacuo to give compound **4**.

Compound 4a: brown solid; mp 166−168 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.1 (br s, 1H), 8.84 (s, 1H), 8.24−8.21 (m, 1H), 7.51−7.48 (m, 1H), 7.26−7.18 (m, 2H), 6.96 (br s, 1H), 3.63 ppm (br s, 4H); ^{13}C NMR (67.8 MHz, DMSO-d_6 + TFA (ca. 1%)) δ 179.6, 163.2, 138.1, 136.2, 126.0, 123.0, 122.2, 121.2, 113.5, 112.3, 44.3 ppm; IR (KBr) 3348, 3152, 1622, 1589, 1495, 1441 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{12}N_3O$ [M + H]$^+$ 214.0980, found 214.0981.

Compound 4b:[13] brown solid; mp 121−122 °C; ^{1}H NMR (300 MHz, DMSO-d_6 + TFA (ca. 1%)) δ 12.85 (br s, 1H), 10.97 (br s, 1H), 10.84 (b s, 1H), 8.55 (d, 1H, J = 3.6 Hz), 8.16−8.14 (m, 1H), 7.62−7.60 (m, 1H), 7.40−7.31 (m, 2H), 4.54−4.50 (m, 1H), 4.17 (t, 1H, J = 8.7 Hz), 3.64 (dd, 1H, J = 8.7, 2.7 Hz), 1.38 ppm (d, 3H, J = 6.6 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6 + TFA (ca. 1%)) δ 173.6, 161.5, 139.7, 136.9, 124.9, 124.3, 123.4, 121.0, 113.1, 113.0, 54.0, 52.2, 20.5 ppm; IR (KBr) 3069, 1705, 1583, 1516, 1435, 1238, 750 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{14}N_3O$ [M + H]$^+$ 228.1137, found 228.1142.

Total Synthesis of (−)-Spongotine A. Diazide 7. To a solution of diol **6** (200 mg, 0.478 mmol) in dry toluene (5.0 mL) was added triphenylphosphine (384 mg, 1.46 mmol), diethyl azodicarboxylate (40% solution in toluene, 0.64 mL, 1.46 mmol), and diphenylphosphoryl azide (0.31 mL, 1.46 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. Solvent was evaporated in vacuo and the residue was purified by SiO_2 column chromatography (hexane/AcOEt = 9/1) to give diazide **7** (207 mg, 92%) as a colorless oil. $[\alpha]^{23}_D$ +23.5 (c 0.20, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 1H, J = 1.8 Hz), 7.77 (d, 2H, J = 8.1 Hz), 7.62 (s, 1H), 7.46−7.37 (m, 2H), 7.27 (d, 2H, J = 8.1 Hz), 4.84−4.80 (m, 1H), 3.68−3.60 (m, 2H), 2.36 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.8, 135.9, 134.6, 130.2, 127.1, 127.0, 126.9, 125.1, 120.8, 119.3, 117.4, 117.1, 58.1, 54.5, 21.6 ppm; IR (KBr) 2251, 2170, 2104 1597, 1487 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{14}BrN_7NaO_2S$ [M + Na]$^+$ 482.0011, found 482.0014. (**Caution**: Diazide compounds are potentially explosive.)

Diamine (*S*)-1. A solution of diazide **7** (625 mg, 1.36 mmol) and triphenylphosphine (891 mg, 3.39 mmol) in toluene (9.0 mL) was heated under reflux for 15 min and cooled to room temperature. H_2O (0.6 mL) was added to the reaction mixture, which was then heated under reflux overnight. The reaction mixture was cooled to room temperature and extracted by 0.5% HCl aq. The aqueous phase was washed with Et_2O, treated with 5% NaOH aq, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated in vacuo to give diamine (*S*)-**1** (495 mg, 89%) as a colorless solid: mp 124 °C; $[\alpha]^{22}_D$ +27.8 (c 0.20, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 1H, J = 1.5 Hz), 7.77 (d, 2H, J = 8.1 Hz), 7.49 (s, 1H), 7.46 (d, 1H, J = 8.7 Hz), 7.34 (dd, 1H, J = 8.4, 1.5 Hz), 7.25 (d, 2H, J = 7.8 Hz), 4.16 (dd, 1H, J = 6.9, 4.5 Hz), 3.03 (dd, 1H, J = 12.6, 4.5 Hz), 2.83 (dd, 1H, J = 12.6, 6.9 Hz), 2.36 ppm (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 145.1, 136.0, 134.8, 129.9, 128.0, 126.7, 126.3, 125.3, 123.1, 121.0, 118.4, 116.8, 50.7, 48.2, 21.7 ppm; IR (KBr) 3099, 1596 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{18}BrN_3NaO_2S$ [M + Na]$^+$ 430.0201, found 430.0180.

(−)-Spongotine A.[13] Diamine (*S*)-**1** (100 mg, 0.245 mmol) was added to a solution of keto aldehyde **2** (38.6 mg, 0.223 mmol) in CH_3CN (4.5 mL) at 0 °C under N_2 atmosphere and the mixture was stirred for 20 min. NCS (32.7 mg, 0.245mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by sat. $Na_2S_2O_3$ aq and solvent was evaporated in vacuo. Saturated $NaHCO_3$ aq (10 mL) was added to the residue and the mixture was stirred for 30 min. The solid was filtered, washed with cold H_2O and cold Et_2O, and dried in vacuo to give crude compound **8** (133.0 mg). HRMS (EI) calcd for $C_{27}H_{21}N_4O_3SBr$ [M$^+$] 560.0517, found 560.0512. Crude compound **8** (30.0 mg) in MeOH (1.0 mL) and 2 N NaOH (0.7 mL) was heated under reflux for 15 min. The reaction mixture was cooled to room temperature and solvent was removed in vacuo. H_2O and AcOEt were added to the residue and the organic phase was extracted with AcOEt. The organic phase was dried over Na_2SO_4 and evaporated in vacuo. Residue was purified by SiO_2 column chromatography (AcOEt) to give spongotine A (11.0 mg, 51%) as a pale yellow solid: mp 229 °C; $[\alpha]^{22}_D$ −14.3 (c 0.20, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6 + TFA (ca. 1%)) δ 12.87 (br s, 1H), 11.51 (br s, 1H), 11.35 (br s, 1H), 11.16 (br s, 1H), 8.57 (d, 1H, J = 3.3 Hz), 8.19−8.16 (m, 1H), 7.67 (m, 2H), 7.64−7.61 (m, 1H), 7.56 (d, 1H, J = 8.4 Hz), 7.38 (t, 1H, J = 7.2 Hz), 7.35 (t, 1H, J = 6.9 Hz), 7.25 (d, 1H, J = 8.4 Hz), 5.88 (dd, 1H, J = 12.0, 9.3 Hz), 4.52 (t, 1H, J = 12.0 Hz), 4.09 ppm (t, 1H, J = 9.3 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6 + TFA (ca. 1%)) δ 172.8, 161.4, 139.9, 137.5, 137.0, 125.7, 124.7, 124.6, 123.8, 123.6, 122.2, 121.0, 119.9, 114.6, 114.5, 113.2, 113.1, 112.4, 54.4, 51.2 ppm; IR (KBr) 2361, 2341, 1615, 1582, 1447 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{16}BrN_4O$ [M + H]$^+$ 407.0507, found 407.0514.

Acknowledgment. This work was financially supported by Grant-in-Aid for Scientific Research (A) and Grant-in-Aid for Scientific Research for Exploratory Research from the Japan Society for the Promotion of Science and by Grant-in-Aid for Scientific Research on Priority Areas (17035047) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. K. M. thanks the Japan Society for the Promotion of Science (JSPS) for a Research Fellowship for Young Scientists.

Supporting Information Available: Experimental details and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701668S

(13) Jung et al. mentioned broadening or doubling of the ^{1}H NMR signals of spongotine A was observed in neutral solution (DMSO-d_6), and the NMR spectrum was measured with TFA in DMSO-d_6 in ref 7. So the NMR spectra of compound **4b** and spongotine A were measured with TFA in DMSO-d_6.