

HETEROCYCLES, Vol. 64, 2004, 75 - 91

Received, 4th December, 2003, Accepted, 22nd January, 2004, Published online, 26th January, 2004

SYNTHETIC STUDY OF AN ANALOGUE OF THE HYDROPHILIC MOIETY OF SCYPHOSTATIN VIA π -FACIAL SELECTIVE DIELS-ALDER REACTION

Wataru Miyanaga, Ryukichi Takagi, and Katsuo Ohkata*

Department of Chemistry, Graduate School of Science, Hiroshima University,
1-3-1 Kagamiyama, Higashi-Hiroshima, 739-8526, Japan

E-mail: ohkata@sci.hiroshima-u.ac.jp

Abstract – An analogue of the hydrophilic moiety of scyphostatin was synthesized *via* π -facial selective Diels-Alder reaction of a 2,5-cyclohexadien-1-one bearing a spirolactone with cyclopentadiene.

INTRODUCTION

Our research group has been interested in biphilic natural products for the reason of both their biological activities and their attractive structures.¹ Scyphostatin (**1**), the first isolated small molecule found to be a potent inhibitor of neutral sphingomyelinase (N-SMase), is also an attractive biphilic natural product (Figure 1).² Several synthetic studies toward total synthesis have been reported to date,³ and quite recently Katoh *et al.* reported the first total synthesis of scyphostatin starting from D-arabinose.⁴ In this paper, our synthetic study on an analogue (**2**) of the hydrophilic moiety of scyphostatin *via* a Diels-Alder reaction with high π -facial selectivity is detailed.

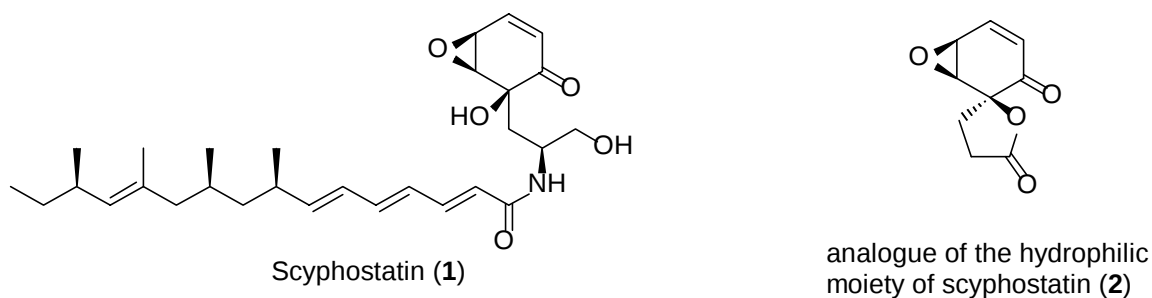
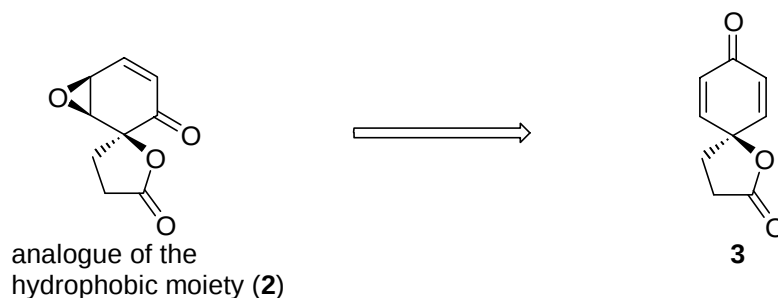


Figure 1.

RESULTS AND DISCUSSION

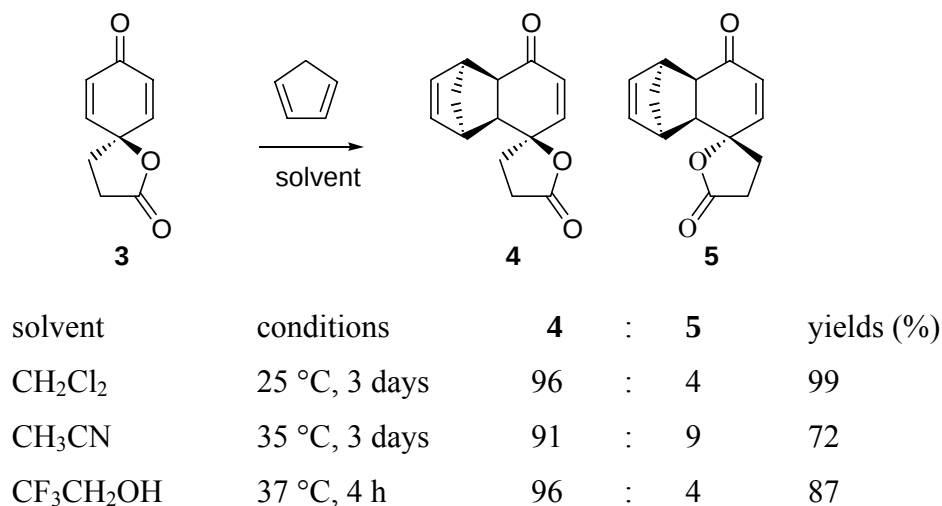
This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

We selected 2,5-cyclohexadien-1-one bearing a spiro lactone (**3**)⁵ as a key synthetic intermediate (Scheme 1). It has been reported that reaction of **3** with nucleophiles (MeMgBr etc.)⁶ and a sterically hindered chiral cyclopentadiene derivative⁷ proceeded with high π -facial selectivity.



Scheme 1.

Application of this highly π -facial selective reaction to spiro lactone (**3**) seemed to be attractive for the synthesis of **2**, an analogue of the hydrophilic moiety. To this end, the Diels-Alder reaction of spiro lactone (**3**) with cyclopentadiene was examined (Scheme 2),⁸ and it was found that the reaction proceeded with high π -facial selectivity to preferentially afforded the adduct (**4**) under mild reaction conditions even though the diene component was not sterically demanding as in the reported case.⁷ Furthermore, when $\text{CF}_3\text{CH}_2\text{OH}$ was used as the solvent, the Diels-Alder reaction of **3** was accelerated. The stereochemistry of the adducts (**4**) and (**5**) was assigned by ^1H NMR NOE experiments and/or X-Ray structural analysis (Figures 2, 3). The high π -facial selectivity in the Diels-Alder reaction of spiro compound (**3**) can be rationalized in terms of the Cieplak model.^{8b} Paquette *et al.* independently reported that the Diels-Alder reaction of 1-oxaspiro[4.5]deca-6,9-dien-8-one with diphenylisobenzofuran and 9,10-dihydro-11,12-dimethylene-9,10-ethanoanthracene also proceeded with high π -facial selectivity.⁹



Scheme 2.

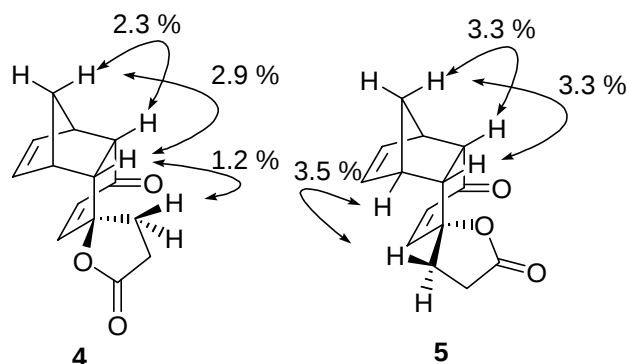


Figure 2.

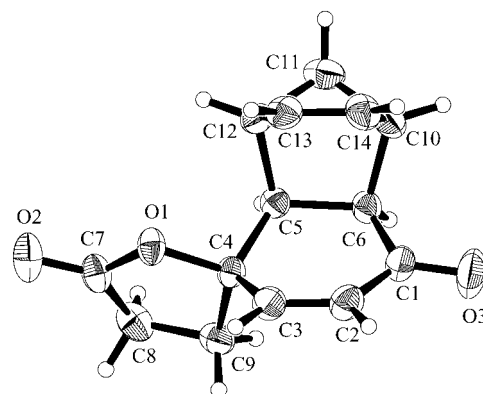
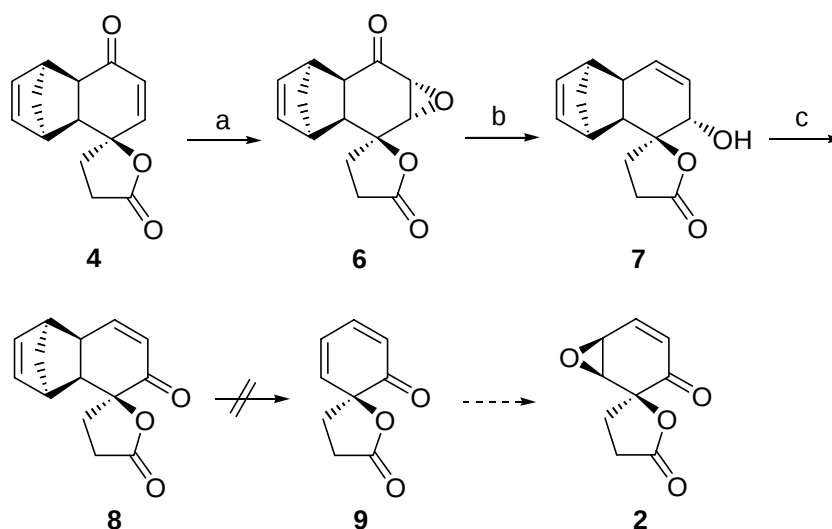


Figure 3. ORTEP drawing of 4.

The high π -facial selectivity in the Diels-Alder reaction of spirolactone (**3**) with cyclopentadiene prompted us to use it for the synthesis of **2**. As the initial strategy, epoxidation of dienone (**9**) at the final step was planned for introduction of the epoxy functional group (Scheme 3).¹⁰ Treatment of **4** with $\text{H}_2\text{O}_2/\text{LiOH}$, followed by reclosure to the lactone ring with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSCl) gave epoxide (**6**) (66%, two steps). The stereochemistry of **6** was confirmed by X-Ray structural analysis (Figure 4). The epoxide (**6**) was converted to allyl alcohol (**7**) by Wharton rearrangement (74%).¹¹ Oxidation of the allyl alcohol (**7**) by *o*-iodoxybenzoic acid (IBX) gave an α,β -unsaturated ketone, in which hydrolysis of the lactone ring accompanied; therefore, WSCI treatment was necessary to obtain **8** (85%, two steps). Retro-Diels-Alder reaction of **8** did not proceed in spite of several attempts (*o*- $\text{Cl}_2\text{C}_6\text{H}_4$, 250 °C; Ph_2O , maleic anhydride, 250 °C; CHCl_3 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 70 °C; CH_2Cl_2 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, maleic anhydride, 60 °C).



Scheme 3. Reagents and conditions: (a) 30% H_2O_2 , LiOH , THF, 0 °C, then WSCI, CH_2Cl_2 , 25 °C, 66% (two steps); (b) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, AcOH , $\text{CF}_3\text{CH}_2\text{OH}$, 25 °C, 74%; (c) IBX, DMSO, 25 °C, then WSCI, CH_2Cl_2 , 25 °C, 85% (two steps).

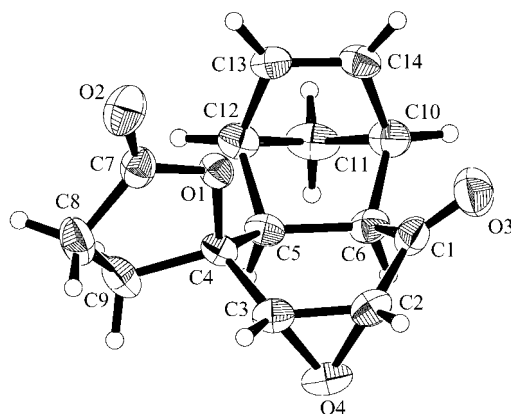
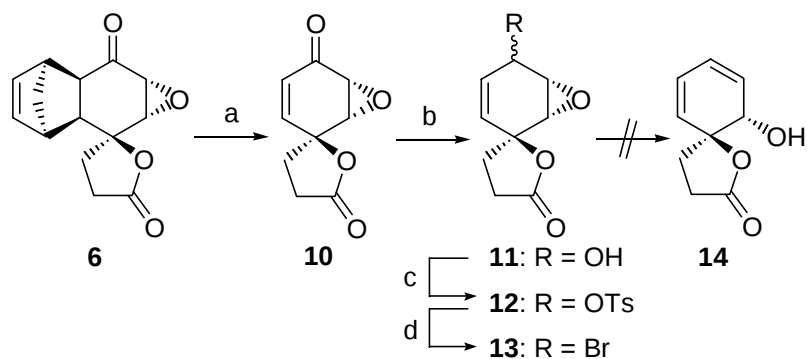


Figure 4. ORTEP drawing of **6**.

Next, we investigated a synthetic path, in which the retro-Diels-Alder reaction was to be carried out at an earlier step and epoxidation of dienone (**9**) was to be performed at the final step (Scheme 4). Heating of **6** in the presence of maleic anhydride gave retro-Diels-Alder product (**10**) (quant). Treatment of **10** with NaBH_4 afforded the alcohol (**11**) (72%, **11a** : **11b** = 2 : 1). The relative stereochemistry of **11a** and **11b** was determined by ^1H NMR NOE experiments (Figure 5). The diastereomeric mixture of **11** was used for the next reaction. Bromide (**13**) was obtained by tosylation of **11** followed by bromination with NaBr (50%, two steps). However, Wharton-type reaction of **13** with $\text{Zn}(\text{Cu})$ was not successful.



Scheme 4. Reagents and conditions: (a) maleic anhydride, Ph_2O , 250 °C, quant; (b) NaBH_4 , *i*-PrOH, THF, -20 °C, 72%; (c) TsCl , DMAP, Et_3N , THF, 25 °C, 78%; (d) NaBr , CH_3CN , 50 °C, 64%.

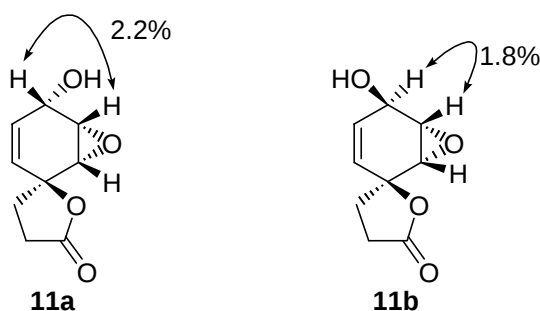
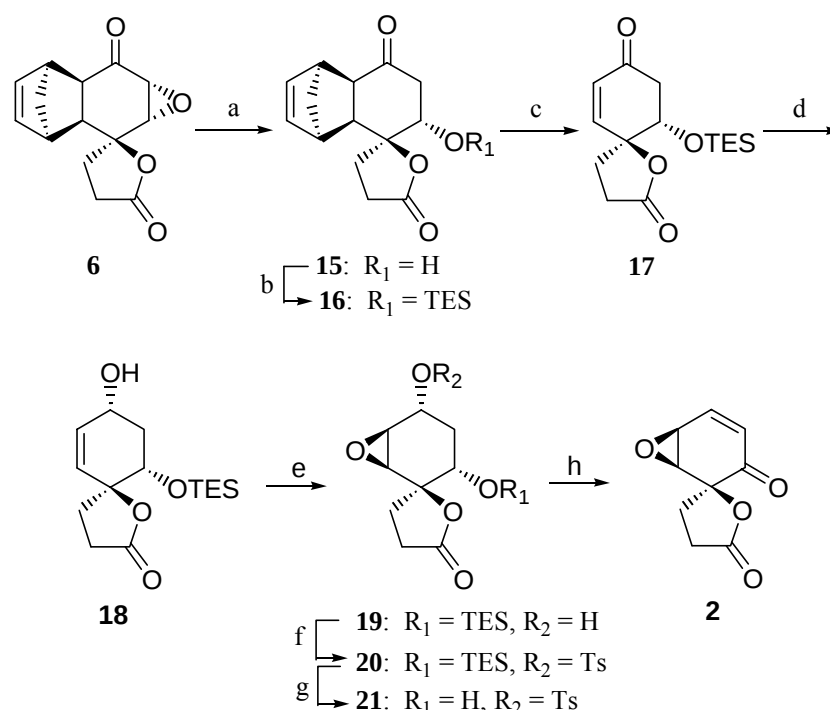


Figure 5. Determination of the relative stereochemistry of adducts (**11a**) and (**11b**).



Scheme 5. Reagents and conditions: (a) SmI_2 , MeOH, THF, $-78^\circ C$, 89%; (b) TESC1, imidazole, CH_2Cl_2 , $25^\circ C$, quant; (c) maleic anhydride, Ph_2O , $230^\circ C$, 96%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, THF, $i\text{-}PrOH$, $0^\circ C$, 99%; (e) $mCPBA$, CH_2Cl_2 , $25^\circ C$, 95%; (f) $TsCl$, DABCO, CH_2Cl_2 , $25^\circ C$, 79%; (g) TBAF, AcOH, THF, $25^\circ C$, 75%; (h) $(COCl)_2$, DMSO, CH_2Cl_2 , $-60^\circ C$, 75%.

As the third strategy, we planned a path *via* epoxidation of allyl alcohol (**18**) for introduction of the epoxy functional group (Scheme 5). Treatment of **6** with SmI_2 afforded **15** (89%).¹² When **10** was subjected to the reductive cleavage reaction using SmI_2 , a complex mixture was obtained. Alcohol (**15**) was protected with a triethyl silyl group (TES) and the retro-Diels-Alder reaction of **16** afforded **17** (96%, two steps). α,β -Unsaturated ketone (**17**) was stereoselectively converted to allyl alcohol (**18**) by reduction with $NaBH_4/CeCl_3$ (99%). The relative stereochemistry was assigned by coupling constants ($J_{H1-H2ax}$, $J_{H2ax-H3}$) and NOE experiments in 1H NMR (Figure 6).

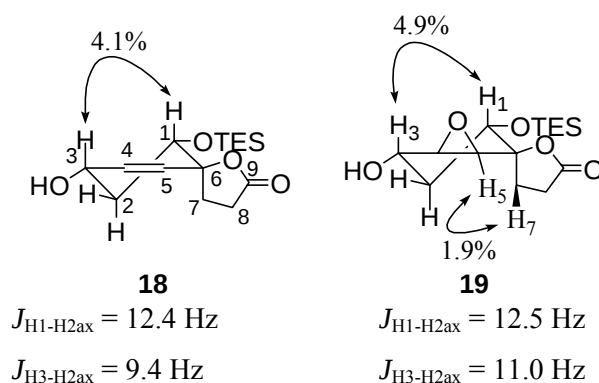


Figure 6. Determination of the relative stereochemistry of **18** and **19**.

With allyl alcohol (**18**) in hand, epoxidation with 3-chloroperoxybenzoic acid (*m*CPBA) was performed and epoxide (**19**) was obtained as a single isomer (95%). The relative stereochemistry of **19** was determined by both ^1H NMR NOE experiments and coupling constants to be contrary to our expectations that the reaction would occur from the side of the hydroxy group (Figure 6).¹³ Reasoning for the observed facial selectivity in the epoxidation reaction is that the peracid attacked the face opposite to the lactone CH_2 group in order to avoid steric repulsion (Figure 7). Treatment of **19** with TsCl gave tosylate (**20**) (79%). The TES group of **20** was removed by TBAF and epoxide (**21**) was obtained (75%). Upon reaction of epoxide (**21**) under Swern oxidation conditions, concomitant extrusion of the TsO group occurred to yield 4,5-epoxy-2-cyclohexen-1-one (75%) bearing a spirolactone (**2**), which can be considered to be an analogue of the hydrophilic moiety of scyphostatin (**1**).

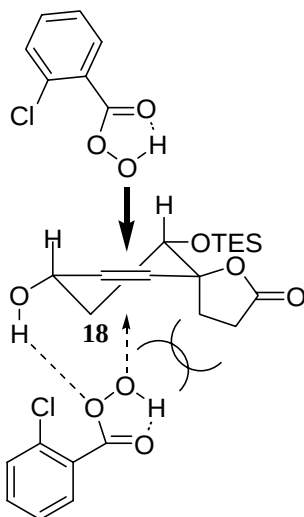


Figure 7. Stereoselectivity in epoxidation of **18** with *m*CPBA.

In summary, an analogue (**2**) of the hydrophilic moiety of scyphostatin was synthesized in a short and efficient manner. Featured were a highly π -facial selective Diels-Alder reaction of **3**, and completely selective sequence of reductive oxirane ring opening, 1,2-enone reduction, and epoxidation. In order to achieve the total synthesis of scyphostatin (**1**), application of this convenient strategy to a spirolactone prepared from L-tyrosine is now in progress.

EXPERIMENTAL

General experimental

All reactions were carried out under N_2 . THF was distilled after refluxing over Na-benzophenone prior to use. CH_2Cl_2 was distilled over CaH_2 before use. Silica gel 60F₂₅₄ (Merck) was used for preparative thin layer chromatography (PTLC). NMR spectra were recorded on JEOL JNM-GSX270 or JNM-LA500 instruments. The internal reference for ^1H NMR spectra was Me_4Si (TMS) (0.0 ppm) for CDCl_3 .

Chemical shifts for ^{13}C NMR spectra were referenced to CDCl_3 (77.0 ppm). MS spectra were recorded on a JEOL JMS-SX102A instrument under electron ionization (EI) conditions (70 eV). Melting points were recorded on a Yanaco melting point apparatus. IR spectra were recorded on a HORIBA FT-IR720. Elemental analyses were carried out on a Perkin-Elmer 2400II analyzer.

1,3',4,4',4a,8a-Hexahydrospiro[furan-2'(5'H),5(8H)-1,4-methanonaphthalene]-5',8-dione (4)

To a solution of spirolactone (**3**)⁵ (48.3 mg, 0.29 mmol) in CH_2Cl_2 (3.0 mL), was added cyclopentadiene (201.3 mg, 3.04 mmol). The solution was shielded from a light and stirred at 25 °C. After 72 h, the volatiles were removed under reduced pressure. The residue was purified by preparative TLC (SiO_2 , hexane/EtOAc 1:1) and a mixture of **4** and **5** (67.0 mg, 99%) was obtained as a white solid. The isomers were separated by high performance liquid chromatography (Wako Sil-II, hexane/*i*-PrOH 10:1): **4**: mp 129-131 °C (CHCl_3 /hexane); IR (thin film): 2985, 2943, 1774, 1666, 1176 cm^{-1} ; R_f (hexane/EtOAc 1:1) 0.4; ^1H NMR (CDCl_3 , 500 MHz) δ 1.35 (1 H, d, J = 8.7 Hz, H9 $_{\text{endo}}$), 1.48 (1 H, d, J = 8.7 Hz, H9 $_{\text{exo}}$), 2.15-2.27 (2 H, m, H3'), 2.62 (1 H, ddd, J = 3.7, 8.5, 17.9 Hz, H4'), 2.78 (1 H, ddd, J = 9.2, 10.8, 17.9 Hz, H4'), 2.88 (1 H, ddd, J = 1.2, 3.3, 8.7 Hz, H4a), 3.04 (1 H, dd, J = 4.4, 8.7 Hz, H8a), 3.18 (1 H, m, H1), 3.39 (1 H, m, H4), 5.85 (1 H, dd, J = 1.1, 9.2 Hz, H7), 5.87 (1 H, dd, J = 1.1, 10.0 Hz, H3), 6.14 (1 H, dd, J = 2.5, 10.0 Hz, H2), 6.52 (1 H, dd, J = 2.5, 9.2 Hz, H6); ^{13}C NMR (CDCl_3 , 125 MHz) δ 27.5 (C4'), 38.6 (C3'), 45.2 (C4a), 47.5 (C8a), 47.4 (C1), 48.7 (C9), 50.8 (C4), 83.0 (C5), 130.7 (C7), 134.8 (C3), 135.4 (C2), 148.9 (C6), 175.9 (C5), 199.1 (C8); HRMS (EI) calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$ [M^+] 230.0943. Found 230.0940; Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$: C, 73.03; H, 6.13. Found: C, 73.11; H, 6.04; **5**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.47 (1 H, d, J = 8.6 Hz, H9 $_{\text{endo}}$), 1.57 (1 H, dt, J = 1.6, 8.6 Hz, H9 $_{\text{exo}}$), 2.17 (1 H, ddd, J = 4.6, 13.1, 15.4 Hz, H3'), 2.60 (1 H, ddd, J = 9.0, 10.4, 13.1 Hz, H3'), 2.71-2.78 (2 H, m, H4'), 3.02 (1 H, ddd, J = 1.3, 3.2, 8.4 Hz, H4a), 3.19 (1 H, dd, J = 4.4, 8.4 Hz, H8a), 3.24 (1 H, s, H4), 3.44 (1 H, s, H1), 5.96-6.01 (2 H, m, H12, H2), 6.07 (1 H, d, J = 10.2 Hz, H7), 6.45 (1 H, dd, J = 1.3, 10.2 Hz, H6); ^{13}C NMR (125 MHz, CDCl_3) δ 28.6 (C4'), 31.9 (C3'), 46.4 (C4), 46.5 (C4a), 47.0 (C8a), 49.4 (C9), 49.9 (C1), 82.2 (C5), 132.9 (C3), 134.1 (C7), 136.2 (C2), 143.0 (C6), 174.8 (C5'), 199.1 (C8); HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{15}\text{O}_3$ [$\text{M}+\text{H}$] 231.1021. Found 231.1015.

6,7-Epoxy-1,3',4,4',4a,6,7,8a-octahydrospiro[furan-2'(5'H),5(8H)-1,4-methanonaphthalene]-5',8-dione (6)

A mixture of 30% H_2O_2 (177.8 mg, 1.57 mmol) and 0.5N LiOH (0.55 mL, 0.28 mmol) was added to a solution of **4** (127.6 mg, 0.55 mmol) in THF (1.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After quenching with sat. NaHSO_3 and sat. NH_4Cl , the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4 . The solvent was removed *in*

vacuo. 1-(3-Diemthylaminopropyl)-3-ethylcarbodiimide (WSCl) (153.8 mg, 0.80 mmol) was added to a solution of the residue in CH₂Cl₂ (2.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 14 h. After diluting with H₂O, the mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to give **6** (89.7 mg, 66%) as a colorless crystal: mp 167-169 °C (CHCl₃/hexane); IR (thin film): 2974, 1778, 1716, 1188 cm⁻¹; *R*_f (hexane/EtOAc 1:1) 0.5; ¹H NMR (500 MHz, CDCl₃) δ 1.29 (1 H, d, *J* = 8.4 Hz, H9_{endo}), 1.48 (1 H, dt, *J* = 1.5, 8.4 Hz, H9_{exo}), 2.49 (1 H, dt, *J* = 9.7, 13.1 Hz, H4'), 2.65 (1 H, ddd, *J* = 4.0, 9.1, 13.1 Hz, H4'), 2.68-2.79 (2 H, m, H3'), 2.87 (1 H, dd, *J* = 3.0, 10.1 Hz, H8a), 2.99 (1 H, br s, H1), 3.14 (1 H, dd, *J* = 3.4, 10.1 Hz, H4a), 3.15 (1 H, br s, H4), 3.35 (1 H, d, *J* = 4.2 Hz, H6), 3.40 (1 H, d, *J* = 4.2 Hz, H7), 5.99 (1 H, dd, *J* = 2.8, 5.7 Hz, H2), 6.14 (1 H, dd, *J* = 2.8, 5.7 Hz, H3); ¹³C NMR (125 MHz, CDCl₃) δ 27.9 (C4'), 32.5 (C3'), 42.7 (C4), 43.9 (C1), 48.8 (x2, C8a, C9), 49.9 (C4a), 55.2 (C6), 59.7 (C7), 83.8 (C5), 134.1 (C2), 135.4 (C3), 174.8 (C5'), 205.2 (C8); HRMS (EI) calcd for C₁₄H₁₄O₄ [M⁺] 246.0892. Found 246.0889; Anal. Calcd for C₁₄H₁₄O₄: C, 68.28; H, 5.73. Found: C, 68.17; H, 5.79.

6-Hydroxy-1,3',4,4',4a,7,8a-heptahydrospiro[furan-2'(5'H),5(6H)-1,4-methanonaphthalene]-5',8-dione (7)

NH₂NH₂·H₂O (0.20 mL, 4.07 mmol) and AcOH (0.23 mL, 4.07 mmol) were added to a solution of **6** (200.3 mg, 0.81 mmol) in CF₃CH₂OH (4.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. After diluting with CH₂Cl₂ followed by quenching with sat. NaHCO₃, the mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, CH₂Cl₂) to give **7** (139.7 mg, 74%) as a colorless crystal: mp 141-143 °C (CHCl₃/hexane); IR (thin film): 3464, 2981, 2893, 1759, 1269, 1212 cm⁻¹; *R*_f (CH₂Cl₂) 0.25; ¹H NMR (500 MHz, CDCl₃) δ 1.35 (1 H, d, *J* = 8.4 Hz, H9_{endo}), 1.52 (1 H, dt, *J* = 1.8, 8.4 Hz, H9_{exo}), 1.74 (1 H, ddd, *J* = 6.2, 10.1, 11.8 Hz, H3'), 2.52 (1 H, ddd, *J* = 6.6, 10.9, 11.8 Hz, H3'), 2.57-2.72 (3 H, m, H4' x2, H8a), 2.82-2.86 (1 H, m, H4a), 2.86-2.89 (1 H, m, H4), 3.19 (1 H, br s, H1), 4.28 (1 H, br s, H8), 5.42 (1 H, dt, *J* = 1.3, 10.3 Hz, H8), 5.74 (1 H, ddd, *J* = 2.9, 4.1, 10.3 Hz, H7), 6.03 (1 H, dd, *J* = 2.8, 5.6 Hz, H3), 6.09 (1 H, dd, *J* = 2.8, 5.6 Hz, H2); ¹³C NMR (125 MHz, CDCl₃) δ 29.1 (C4'), 30.4 (C3'), 42.0 (C4a), 45.5 (C4), 46.3 (C1), 50.2 (C8a), 50.3 (C9), 69.1 (C6), 92.4 (C5), 128.8 (C8), 131.1 (C7), 135.0 (C2), 136.2 (C3), 178.2 (C5'); HRMS (EI) Calcd for C₁₄H₁₆O₃ [M⁺] 232.1099. Found 232.1091.

1,3',4,4',4a,7,8a-Heptahydrospiro[furan-2'(5'H),5(6H)-1,4-methanonaphthalene]-5',6,8-trione (8)

o-Iodoxybenzoic acid (IBX) (38.4 mg, 0.14 mmol) was added to a solution of **7** (23.9 mg, 0.10 mmol) in DMSO (1.0 mL) at 25 °C. The reaction mixture was stirred for 20 h. After diluting with EtOAc, the mixture was filtered. The residue was washed with EtOAc, and the combined organic layer was washed with H₂O, brine and dried over Na₂SO₄. WSCI (29.6 mg, 0.16 mmol) was added to a solution of the residue in CH₂Cl₂ (1.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 24 h. After addition of sat. NH₄Cl, the mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **8** (20.3 mg, 85%) as a colorless oil: *R*_f (hexane/EtOAc 2:1) 0.45; IR (thin film): 2947, 1786, 1732, 1196 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.86 (1 H, dt, *J* = 9.6, 13.4 Hz, H9_{endo}), 1.96-2.03 (1 H, m, H9_{exo}), 2.25 (1 H, ddd, *J* = 4.3, 10.3, 12.8 Hz, H3'), 2.51-2.64 (2 H, m, H3', H4'), 2.81 (1 H, ddd, *J* = 9.3, 10.2, 18.0 Hz, H4'), 3.02-3.06 (1 H, m, H4), 3.10-3.16 (1 H, m, H4a), 3.27-3.33 (2 H, m, H1, H8a), 5.42-5.45 (1 H, m, H7), 5.69-5.73 (1 H, m, H8), 6.13 (1 H, t, *J* = 7.0 Hz, H2), 6.31 (1 H, t, *J* = 7.3 Hz, H3); ¹³C NMR (125 MHz, CDCl₃) δ 28.6 (C4'), 31.3 (C3'), 34.2 (C4a), 38.3 (C4), 48.2 (C1), 50.0 (C8a), 51.5 (C9), 83.1 (C5), 129.4 (C7), 129.8 (C8), 131.1 (C2), 133.6 (C3), 176.4 (C5'), 207.0 (C6); HRMS (EI) calcd for C₁₄H₁₄O₃ [M⁺] 230.0943. Found 230.0943.

9,10-Epoxy-1-oxaspiro[4.5]dec-6-ene-2,8-dione (**10**)

Maleic anhydride (576.3 mg, 5.88 mmol) was added to a solution of **6** (493.5 mg, 2.00 mmol) in Ph₂O (25 mL) at 25 °C. The reaction mixture was heated at 230 °C for 1 h. After cooling to rt, the mixture was subjected to the flash column chromatography (silica gel, hexane/EtOAc 10:1 to EtOAc) to remove Ph₂O. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to give **10** (375.6 mg, 100%) as a white solid: mp 114-116 °C (CHCl₃/hexane); IR (thin film): 1782, 1689, 1184 cm⁻¹; *R*_f (hexane/EtOAc 1:1) 0.5; ¹H NMR (500 MHz, CDCl₃) δ 2.36 (1 H, ddd, *J* = 7.9, 9.2, 13.1 Hz, H4), 2.69-2.77 (1 H, m, H4), 2.78-2.89 (2 H, m, H3 x2), 3.60 (1 H, dd, *J* = 1.7, 3.3 Hz, H9), 3.72 (1 H, dd, *J* = 2.9, 3.3 Hz, H10), 6.08 (1 H, dd, *J* = 1.7, 10.5 Hz, H7), 6.40 (1 H, dd, *J* = 2.9, 10.5 Hz, H6); ¹³C NMR (125 MHz, CDCl₃) δ 27.5 (C3), 31.0 (C4), 53.4 (C9), 58.1 (C10), 78.2 (C5), 128.0 (C7), 142.1 (C6), 174.8 (C2), 191.2 (C8); HRMS (EI) calcd for C₉H₈O₄ [M⁺] 180.0423. Found 180.0415; Anal. Calcd for C₁₅H₂₄O₄Si: C, 60.78; H, 8.16. Found: C, 60.64; H, 8.10.

9,10-Epoxy-8-hydroxy-1-oxaspiro[4.5]dec-6-en-2-one (**11**)

NaBH₄ (7.42 mg, 0.20 mmol) was added to a solution of **10** (25.1 mg, 0.14 mmol) in *i*-PrOH (1.4 mL) and THF (0.5 mL) at -20 °C. The reaction mixture was stirred at -20 °C for 40 min. After dilution with EtOAc followed by addition of sat. NH₄Cl, the mixture was extracted with EtOAc. The combined organic

layer was washed with brine and dried over Na_2SO_4 . The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1) to give a mixture of **11a** and **11b** (18.3 mg, 72%) as colorless oil. The mixture of **11a** and **11b** was separated by preparative TLC (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1): **11a**: R_f (hexane/EtOAc 1:1) 0.25; IR (thin film): 3348, 2927, 1770, 1234, 1192 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.19 (1 H, ddd, $J = 8.2, 9.0, 13.4$ Hz, H3), 2.57 (1 H, ddd, $J = 6.3, 9.8, 13.4$ Hz, H3), 2.66-2.79 (2 H, m, H4 x2), 3.41 (1 H, dd, $J = 2.4, 3.7$ Hz, H10), 3.67 (1 H, ddd, $J = 2.0, 3.2, 3.7$ Hz, H9), 4.55 (1 H, br s, H8), 5.52 (1 H, dt, $J = 2.4, 10.4$ Hz, H6), 5.78 (1 H, dt, $J = 2.0, 10.4$ Hz, H7); ^{13}C NMR (125 MHz, CDCl_3) δ 27.9 (C3), 31.3 (C4), 54.7 (C10), 56.5 (C8), 63.8 (C9), 78.8 (C5), 125.9 (C7), 130.7 (C6), 175.6 (C2); HRMS (EI) calcd for $\text{C}_9\text{H}_{10}\text{O}_4$ [M^+] 182.0579. Found 182.0575. **11b**: R_f (hexane/EtOAc 1:1) 0.30; IR (thin film): 3413, 2923, 1774, 1238, 1192 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.17 (1 H, ddd, $J = 8.2, 9.2, 13.4$ Hz, H3), 2.56 (1 H, ddd, $J = 6.1, 10.1, 13.4$ Hz, H3), 2.67-2.81 (2 H, m, H4 x2), 3.31 (1 H, dd, $J = 2.1, 3.2$ Hz, H10), 3.51 (1 H, dt, $J = 1.8, 3.2$ Hz, H9), 4.43 (1 H, br s, H8), 5.58 (1 H, dd, $J = 2.1, 10.4$ Hz, H6), 5.96 (1 H, dd, $J = 1.8, 10.4$ Hz, H7); ^{13}C NMR (125 MHz, CDCl_3) δ 27.7 (C3), 32.1 (C4), 53.8 (C10), 54.1 (C8), 61.8 (C9), 78.9 (C5), 126.2 (C7), 129.1 (C6), 175.6 (C2); HRMS (EI) calcd for $\text{C}_9\text{H}_{10}\text{O}_4$ [M^+] 182.0579. Found 182.0578.

9,10-Epoxy-8-toluenesulfoxy-1-oxaspiro[4.5]dec-6-en-2-one (**12**)

TsCl (13.7 mg, 0.072 mmol) and Et_3N (0.01 mL, 0.075 mmol) were added to a solution of **11** (a mixture of **11a** and **11b**, **11a** : **11b** = 2 : 1, 9.74 mg, 0.054 mmol) and *N,N*-dimethylaminopyridine (1.50 mg, 0.012 mmol) in THF (0.5 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was stirred at 25 °C for 19 h. After quenching with sat. NH_4Cl , the mixture was extracted with CH_2Cl_2 . The combined organic layer was washed with brine and dried over Na_2SO_4 . The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to give **12** (diastereomer ratio = 2 : 1, 14.2 mg, 78%) as a colorless oil; R_f (hexane/EtOAc 1:1) 0.4; IR (thin film): 2954, 1782, 1365, 1176, 1138 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.11 (ddd, $J = 8.0, 9.6, 13.7$ Hz, minor-H3), 2.20 (ddd, $J = 8.4, 9.1, 13.4$ Hz, major-H3), 2.47 (3 H, s, $\text{C}_6\text{H}_4\text{CH}_3$), 2.51 (ddd, $J = 6.2, 9.9, 13.7$ Hz, minor-H3), 2.56 (ddd, $J = 6.6, 9.6, 13.4$ Hz, major-H3), 2.63-2.77 (2 H, m, H4 x2), 3.30-3.32 (m, minor-H10), 3.34 (dd, $J = 1.8, 3.7$ Hz, major-H10), 3.49-3.51 (m, minor-H9), 3.56-3.59 (m, major-H9), 5.19-5.20 (m, minor-H6), 5.37-5.39 (m, major-H6), 5.59-5.61 (m, H8, minor-H7), 5.64-5.66 (m, major-H7), 7.38 (2 H, d, $J = 7.9$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$), 7.84 (d, $J = 8.2$ Hz, minor- $\text{C}_6\text{H}_4\text{CH}_3$), 7.85 (d, $J = 8.8$ Hz, major- $\text{C}_6\text{H}_4\text{CH}_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 21.6 (major- $\text{C}_6\text{H}_4\text{CH}_3$), 27.6 (major-C3), 31.1 (major-C4), 51.9 (major-C10), 55.3 (major-C8), 73.2 (maor-C9), 78.3 (major-C5), 125.9 (major-C7), 127.8 (x2, major- $\text{C}_6\text{H}_4\text{CH}_3$), 128.7 (major-C6), 130.1 (x2, major- $\text{C}_6\text{H}_4\text{CH}_3$), 133.4 (major-*ipso*- $\text{C}_6\text{H}_4\text{CH}_3$), 145.4 (major-*ipso*- $\text{C}_6\text{H}_4\text{CH}_3$), 175.3 (major-C2).

8-Bromo-9,10-epoxy-1-oxaspiro[4.5]dec-6-en-2-one (13)

NaBr (28.4 mg, 0.28 mmol) was added to a solution of **12** (diastereomer ratio = 2 : 1, 42.8 mg, 0.13 mmol) in MeCN (1.5 mL) at 25 °C. The reaction mixture was stirred at 50 °C for 5 h. After diluting with EtOAc followed by quenching with H₂O, the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 3:2) to give **13** (diastereomer ratio = 2 : 1, 21.7 mg, 70%) as a white amorphous: *R_f* (hexane/EtOAc 1:1) 0.5; IR (thin film): 2958, 1770, 1200, 1184 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.18 (ddd, *J* = 8.1, 9.1, 13.5 Hz, minor-H3), 2.23 (ddd, *J* = 8.4, 9.0, 13.3 Hz, major-H3), 2.57 (ddd, *J* = 6.0, 9.7, 13.5 Hz, minor-H3), 2.63 (ddd, *J* = 6.0, 10.0, 13.3 Hz, major-H3), 2.67-2.80 (2 H, m, H₄ x2), 3.39-3.41 (br s, minor-H10), 3.58 (dd, *J* = 2.8, 3.2 Hz, major-H10), 3.72 (dt, *J* = 2.2, 3.2 Hz, major-H9), 3.80 (dt, *J* = 1.8, 3.7 Hz, minor-H9), 4.74 (d, *J* = 4.7 Hz, minor-H8), 4.99 (dd, *J* = 2.2, 5.2 Hz, major-H8), 5.50 (dd, *J* = 2.0, 10.1 Hz, minor-H6), 5.53 (dt, *J* = 2.2, 10.5 Hz, major-H6), 5.91 (dt, *J* = 2.3, 10.5 Hz, major-H7), 5.97 (ddd, *J* = 1.8, 4.7, 10.1 Hz, minor-H7); ¹³C NMR (125 MHz, CDCl₃) δ 27.7 (major-C3), 31.4 (major-C4), 42.3 (major-C8), 54.7 (major-C10), 60.0 (major-C9), 78.2 (major-C5), 126.8 (major-C7), 128.9 (major-C6), 175.4 (major-C2); HRMS (EI) calcd for C₉H₉O₃⁷⁹Br [M⁺] 243.9735. Found 243.9729.

6-Hydroxy-1,3',4,4',4a,6,7,8a-octahydrospiro[furan-2'(5'H),5(8H)-1,4-methanonaphthalene]-5',8-dione (15)

CH₂I₂ (4.9 g, 18.3 mmol) was added to a suspension of samarium metal (2.9 g, 19.2 mmol) in THF (190 mL). The mixture was stirred at 25 °C for 5 h. The resulting deep blue solution was cooled to -78 °C and added dropwise to a solution of **6** (1.0 g, 4.06 mmol) in MeOH (1.6 mL, 40.6 mmol) and THF (10 mL) at -78 °C for 30 min. The reaction mixture was stirred at -78 °C for 1 h. After quenching with H₂O, the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, CH₂Cl₂/MeOH 30:1) to give **15** (893 mg, 89%) as a colorless crystal: mp 143-145 °C (CHCl₃/hexane); IR (thin film): 3425, 2970, 1770, 1701, 1188 cm⁻¹; *R_f* (hexane/EtOAc 1:1) 0.1; ¹H NMR (500 MHz, CDCl₃) δ 1.40 (1 H, dt, *J* = 1.4, 8.5 Hz, H9_{endo}), 1.54 (1 H, dt, *J* = 1.8, 8.5 Hz, H9_{exo}), 1.70-1.79 (1 H, br s, OH), 2.35 (1 H, ddd, *J* = 0.8, 8.2, 18.6 Hz, H7), 2.56 (1 H, ddd, *J* = 0.6, 5.3, 18.6 Hz, H7), 2.65-2.78 (4 H, m, H3' x2, H4' x2), 2.90 (1 H, dd, *J* = 3.2, 9.7 Hz, H4a), 3.05 (1 H, dd, *J* = 4.4, 9.7 Hz, H8a), 3.20 (1 H, br s, H4), 3.38 (1 H, br s, H1), 4.14 (1 H, dd, *J* = 3.2, 8.2 Hz, H6), 6.15 (1 H, dd, *J* = 2.8, 5.7 Hz, H2), 6.23 (1 H, dd, *J* = 3.0, 5.7 Hz, H3); ¹³C NMR (125 MHz, CDCl₃) δ 28.5 (C4'), 29.3 (C3'), 44.4 (C7), 45.4 (C4), 47.2 (C8), 48.0 (C4a), 50.2 (C9), 51.9 (C8a), 67.9 (C6), 87.8 (C5), 135.6

(C2), 136.3 (C3), 176.5 (C9), 210.4 (C1); HRMS (EI) calcd for $C_{14}H_{16}O_4$ [M^+] 248.1049. Found 248.1058; Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.71; H, 6.59.

6-Triethylsilyloxy-1,3',4,4',4a,6,7,8a-octahydrospiro[furan-2'(5'H),5(8H)-1,4-methanonaphthalene]-5',8-dione (16)

TESCl (0.41 mL, 2.42 mmol) was added to a solution of **15** (502.5 mg, 2.02 mmol) and imidazole (414.4 mg, 6.09 mmol) in CH_2Cl_2 (20 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. After quenching with H_2O , the mixture was extracted with CH_2Cl_2 . The organic layer was washed with brine and dried over Na_2SO_4 . The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **16** (791.2 mg, 100%) as a colorless crystal: mp 88-90 °C ($CHCl_3$ /hexane); IR (thin film): 2954, 1774, 1704, 1184, 1095 cm^{-1} ; R_f (hexane/EtOAc 2:1) 0.33; 1H NMR (500 MHz, $CDCl_3$) δ 0.59 (6 H, q, $J = 7.7$ Hz, $SiCH_2CH_3$), 0.93 (9 H, t, $J = 7.7$ Hz, $SiCH_2CH_3$), 1.36 (1 H, d, $J = 8.4$ Hz, H9*endo*), 1.50 (1 H, dt, $J = 1.8, 8.4$ Hz, H9*exo*), 2.03-2.12 (1 H, m, H3'), 2.30 (1 H, dd, $J = 6.8, 18.3$ Hz, H7), 2.43 (1 H, dd, $J = 4.4, 18.3$ Hz, H7), 2.53-2.70 (3 H, m, H3', H4' x2), 2.83 (1 H, dd, $J = 3.3, 10.1$ Hz, H4a), 2.96 (1 H, dd, $J = 4.3, 10.1$ Hz, H8a), 3.15 (1 H, br s, H4), 3.33 (1 H, br s, H1), 3.99 (1 H, dd, $J = 4.4, 6.8$ Hz, H6), 6.10 (1 H, dd, $J = 2.9, 5.8$ Hz, H2), 6.17 (1 H, dd, $J = 2.7, 5.8$ Hz, H3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.8 (x3, $SiCH_2CH_3$), 6.7 (x3, $SiCH_2CH_3$), 28.7 (C4'), 30.2 (C3'), 45.2 (C7), 45.4 (C4), 46.7 (C1), 48.4 (C4a), 50.0 (C9), 51.7 (C8a), 69.7 (C6), 87.2 (C13), 135.2 (C2), 136.3 (C3), 176.0 (C5'), 210.4 (C8); HRMS (EI) calcd for $C_{20}H_{30}O_4Si$ [M^+] 362.1913. Found 362.1900; Anal. Calcd for $C_{20}H_{30}O_4Si$: C, 66.26; H, 8.34. Found: C, 66.21; H, 8.45.

10-Triethylsilyloxy-1-oxaspiro[4.5]dec-6-ene-2,8-dione (17)

Maleic anhydride (101.6 mg, 2.08 mmol) and **16** (376.2 mg, 1.04 mmol) were dissolved in Ph_2O (51 mL). The reaction mixture was heated at 230 °C for 1.5 h. The reaction mixture was subjected to flash column chromatography (silica gel, hexane/EtOAc 10:1) to remove Ph_2O . The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **17** (295.4 mg, 96%) as a yellow oil: R_f (hexane/EtOAc 2:1) 0.33; IR (thin film): 2924, 1774, 1678, 1230, 1203, 1161 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 0.62 (6 H, q, $J = 7.9$ Hz, $SiCH_2CH_3$), 0.95 (9 H, t, $J = 7.9$ Hz, $SiCH_2CH_3$), 1.94-2.03 (1 H, m, H5), 2.52 (1 H, dd, $J = 12.0, 14.8$ Hz, H9), 2.58 (1 H, dd, $J = 3.5, 13.2$ Hz, H9), 2.68-2.79 (3 H, m, H5, H3 x2), 4.33 (1 H, dd, $J = 3.5, 12.0$ Hz, H10), 6.00 (1 H, d, $J = 10.2$ Hz, H7), 6.83 (1 H, d, $J = 10.2$ Hz, H6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.6 (x3, $SiCH_2CH_3$), 6.6 (x3, $SiCH_2CH_3$), 25.4 (C3), 28.9 (C4), 43.9 (C9), 72.2 (C10), 85.9 (C5), 129.1 (C7), 149.8 (C6), 176.2 (C2), 196.1 (C8); HRMS (EI) calcd for $C_{15}H_{24}O_4Si$ [M^+] 296.1444. Found 296.1444.

8-Hydroxy-10-triethylsilyloxy-1-oxaspiro[4.5]dec-6-en-2-one (18)

NaBH₄ (38.1 mg, 1.01 mmol) was added to a solution of **17** (292.4 mg, 0.99 mmol) and CeCl₃·7H₂O (367.5 mg, 0.99 mmol) in *i*-PrOH (4.5 mL) and THF (4.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After quenching with sat. NH₄Cl, the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, CH₂Cl₂/MeOH 20:1) to give **18** (269.3 mg, 99%) as a yellow oil: *R*_f(hexane/EtOAc 1:1) 0.6; IR (thin film): 3440, 2951, 1755, 1242, 1207 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.63 (6 H, q, *J* = 7.9 Hz, SiCH₂CH₃), 0.96 (9 H, t, *J* = 7.9 Hz, SiCH₂CH₃), 1.66 (1 H, td, *J* = 9.4, 12.4 Hz, H_{9ax}), 1.72-1.82 (1 H, br s, OH), 1.87-1.95 (1 H, m, H₄), 2.26 (1 H, dddd, *J* = 1.2, 3.3, 5.9, 12.8 Hz, H_{9eq}), 2.50-2.60 (2 H, m, H₃, H₄), 2.63-2.72 (1 H, m, H₃), 3.97 (1 H, dd, *J* = 3.3, 12.4 Hz, H₁₀), 4.39 (1 H, br s, H₈), 5.66 (1 H, dd, *J* = 1.8, 10.1 Hz, H₆), 5.80 (1 H, dt, *J* = 1.2, 10.1 Hz, H₇); ¹³C NMR (125 MHz, CDCl₃) δ 4.6 (x3, SiCH₂CH₃), 6.6 (x3, SiCH₂CH₃), 27.8 (C₄), 29.5 (C₃), 39.0 (C₉), 66.2 (C₈), 71.8 (C₁₀), 87.6 (C₅), 129.9 (C₆), 133.1 (C₇), 177.5 (C₂); HRMS (EI) calcd for C₁₅H₂₅O₄Si [M-H] 297.1522. Found 297.1521.

6,7-Epoxy-8-hydroxy-10-triethylsilyloxy-1-oxaspiro[4.5]dec-6-en-2-one (19)

3-Chloroperoxybenzoic acid (*m*CPBA) (36.8 mg, 0.21 mmol) was added to a solution of **18** (29.2 mg, 0.098 mmol) in CH₂Cl₂ (1.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C. After 24 h, *m*CPBA (35.7 mg, 0.21 mmol) was added to the reaction mixture at 25 °C and the mixture was stirred for 24 h. After quenching with sat. NaHSO₃ and sat. NaHCO₃, the mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. Epoxide (**19**) (29.3 mg, 95%) was obtained as a white amorphous: *R*_f(hexane/EtOAc 1:1) 0.6; IR (thin film): 3413, 1751, 1242, 1053 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.60 (6 H, q, *J* = 7.9 Hz, SiCH₂CH₃), 0.94 (9 H, t, *J* = 7.9 Hz, SiCH₂CH₃), 1.45 (1 H, td, *J* = 11.0, 12.6 Hz, H_{9ax}), 1.66-1.78 (1 H, br s, OH), 1.84 (1 H, ddd, *J* = 3.3, 5.2, 12.6 Hz, H_{9eq}), 2.24-2.33 (1 H, m, H₄), 2.45-2.54 (1 H, m, H₄), 2.54-2.67 (2 H, m, H₃ x2), 3.33 (1 H, d, *J* = 3.7 Hz, H₆), 3.45 (1 H, br s, H₇), 3.66 (1 H, dd, *J* = 3.3, 12.6 Hz, H₁₀), 4.18 (1 H, dd, *J* = 5.2, 8.8 Hz, H₈); ¹³C NMR (125 MHz, CDCl₃) δ 4.7 (x3, SiCH₂CH₃), 6.6 (x3, SiCH₂CH₃), 23.5 (C₄), 28.9 (C₉), 32.4 (C₃), 57.4 (C₇), 59.0 (C₆), 67.2 (C₈), 71.8 (C₁₀), 84.5 (C₅), 177.2 (C₂); HRMS (EI) calcd for C₁₃H₂₁O₅Si [M-Et] 285.1158. Found 285.1167.

6,7-Epoxy-8-toluenesulfoxy-10-triethylsilyloxy-1-oxaspiro[4.5]dec-6-en-2-one (20)

p-Toluenesulfonyl chloride (TsCl) (69.8 mg, 0.37 mmol) was added to a solution of **19** (90.6 mg, 0.29 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (104.6 mg, 0.86 mmol) in CH₂Cl₂ (3.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 18 h. After quenching with sat. NH₄Cl, the mixture

was extracted with CH_2Cl_2 . The combined organic layer was washed with brine and dried over Na_2SO_4 . The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **20** (106.8 mg, 79%) as a colorless oil: R_f (hexane/EtOAc 1:1) 0.7; IR (thin film): 1774, 1362, 1238, 1176, 1149 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.52 (6 H, q, $J = 7.9$ Hz, SiCH_2CH_3), 0.89 (9 H, t, $J = 7.9$ Hz, SiCH_2CH_3), 1.59-1.71 (2 H, m, $\text{H}_9 \times 2$), 2.21-2.29 (1 H, m, H_4), 2.39-2.45 (1 H, m, H_4), 2.46 (3 H, s, CH_3), 2.47-2.63 (2 H, m, $\text{H}_3 \times 2$), 3.26 (1 H, d, $J = 3.7$ Hz, H_6), 3.39 (1 H, br s, H_7), 3.58 (1 H, dd, $J = 4.9, 11.0$ Hz, H_{10}), 4.95 (1 H, ddd, $J = 1.7, 7.0, 10.4$ Hz, H_8), 7.38 (2 H, d, $J = 8.2$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$), 7.84 (2 H, d, $J = 8.2$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 4.5 ($\times 3$, SiCH_2CH_3), 6.4 ($\times 3$, SiCH_2CH_3), 21.5 (CH_3), 23.3 (C_4), 28.6 (C_9), 29.3 (C_3), 54.6 (C_7), 58.2 (C_6), 71.3 (C_{10}), 76.0 (C_8), 83.6 (C_5), 127.6 ($\times 2$, $\text{C}_6\text{H}_4\text{CH}_3$), 129.9 ($\times 2$, $\text{C}_6\text{H}_4\text{CH}_3$), 133.6 ($\text{C}_6\text{H}_4\text{CH}_3$), 145.2 ($\text{C}_6\text{H}_4\text{CH}_3$), 176.5 (C_2); HRMS (EI) calcd for $\text{C}_{20}\text{H}_{27}\text{O}_7\text{SSi}$ [$\text{M}-\text{Et}$] 439.1247. Found 439.1255.

6,7-Epoxy-10-hydroxy-8-toluenesulfoxy-1-oxaspiro[4.5]dec-6-en-2-one (**21**)

AcOH (0.013 mL, 0.23 mmol) and TBAF (0.1 M in THF, 0.23 mL, 0.23 mmol) were added to a solution of **20** (30.1 mg, 0.064 mmol) in THF (1.8 mL) at 25 °C and the reaction mixture was stirred for 30 min. After quenching with sat. NaHCO_3 , the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4 . The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to give **21** (17.0 mg, 75%) as a white solid: mp 150-152 °C (CHCl_3 /hexane); R_f (hexane/EtOAc 1:1) 0.2; IR (thin film): 3413, 1774, 1362, 1176 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.73 (1 H, td, $J = 10.5, 12.8$ Hz, H_9), 1.89 (1 H, dddd, $J = 0.9, 3.1, 6.1, 12.8$ Hz, H_9), 2.27-2.36 (1 H, m, H_4), 2.45-2.36 (1 H, m, H_4), 2.45-2.55 (1 H, m, H_3), 2.46 (3 H, s, CH_3), 2.66-2.75 (1 H, m, H_3), 2.81-2.95 (1 H, br s, OH), 3.28 (1 H, d, $J = 3.4$ Hz, H_6), 3.42 (1 H, br s, H_7), 3.69 (1 H, dd, $J = 3.1, 12.8$ Hz, H_{10}), 5.02 (1 H, ddd, $J = 1.8, 6.1, 10.5$ Hz, H_8), 7.37 (2 H, d, $J = 8.1$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$), 7.83 (2 H, d, $J = 8.1$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 21.7 (CH_3), 23.7 (C_4), 28.7 (C_9), 29.0 (C_3), 54.8 (C_7), 58.2 (C_6), 70.3 (C_8), 75.6 (C_{10}), 83.8 (C_5), 127.7 ($\times 2$, $\text{C}_6\text{H}_4\text{CH}_3$), 130.1 ($\times 2$, $\text{C}_6\text{H}_4\text{CH}_3$), 133.6 ($\text{C}_6\text{H}_4\text{CH}_3$), 145.3 ($\text{C}_6\text{H}_4\text{CH}_3$), 177.2 (C_2); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{18}\text{O}_7\text{S}$ 354.0793. Found 354.0789; Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_7\text{S}$: C, 54.23; H, 5.12. Found: C, 54.21; H, 5.24.

6,7-Epoxy-1-oxaspiro[4.5]dec-6,8-diene-2,10-dione (**2**)

A solution of $(\text{COCl})_2$ (0.015 mL, 0.18 mmol) and DMSO (0.025 mL, 0.35 mmol) in CH_2Cl_2 (0.5 mL) was stirred at -60 °C for 30 min, followed by addition of a solution of **21** (12.6 mg, 0.035 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at -60 °C for 30 min. After addition of Et_3N (0.12 mL, 0.87 mmol), the reaction mixture was stirred at -60 °C for 5 h. After quenching with sat. NH_4Cl , the mixture was extracted with CH_2Cl_2 . The combined organic layer was washed with brine and dried over

Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to give **2** (4.7 mg, 75%) as a colorless oil: *R_f* (hexane/EtOAc 1:1) 0.45; IR (thin film): 1786, 1685, 1176, 1122 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.38 (1 H, dt, *J* = 9.1, 13.2 Hz, H4), 2.70 (1 H, ddd, *J* = 3.8, 9.1, 17.5 Hz, H3), 2.78 (1 H, ddd, *J* = 3.8, 9.2, 13.2 Hz, H4), 2.94 (1 H, ddd, *J* = 9.1, 9.2, 17.5 Hz, H3), 3.64 (1 H, dd, *J* = 3.4, 4.0 Hz, H7), 3.79 (1 H, d, *J* = 3.4 Hz, H6), 6.20 (1 H, d, *J* = 10.2 Hz, H9), 7.26 (1 H, dd, *J* = 4.0, 10.2 Hz, H8); ¹³C NMR (125 MHz, CDCl₃) δ 28.1 (C4), 28.2 (C3), 47.3 (C7), 58.7 (C6), 80.1 (C5), 130.8 (C9), 145.0 (C8), 175.6 (C2), 191.1 (C10); HRMS (EI) calcd for C₉H₈O₄ [M⁺] 180.0423. Found 180.0430.

X-Ray Structure Determination

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-193077 (for **4**) and CCDC-224012 (for **6**). A Copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2, 1EZ, U.K. (fax: (+44)1223-336-033; e-mail: deposit@ccdc.ac.uk).

A crystal suitable for X-Ray structure determination was mounted on a Mac Science DIP2030 imaging plate equipped with graphite-monochromated Mo-Kα radiation (λ=0.71073 Å). Unit cell parameters were determined by autoindexing several images in each data set separately with the DENZO program.¹⁴ For each data set, rotation images were collected in 3° increments with a total rotation of 180° about φ. Data were processed by using the SCALEPACK program. The structures were solved by a direct method and refined by full-matrix least-squares methods with the TeXsan (Rigaku) program.¹⁵ Crystallographic data: for **4**: monoclinic system, space group *P*12₁/*c*, *a* = 6.5700(3) Å, *b* = 18.2680(8) Å, *c* = 9.9190(4) Å, *V* = 1162.69(9) Å³, *Z* = 4, ρ_{calc} = 1.315 g cm⁻³, *F*(000) = 440, *R* = 0.0556 (*R_w* = 0.1045) for 2088 reflections out of 2753 collected (154 parameters) with *I* > 3σ(*I*). Goodness of fit = 1.549. for **6**: monoclinic system, space group *P*12₁/*c*, *a* = 7.8340(3) Å, *b* = 11.1270(5) Å, *c* = 13.8110(6) Å, *V* = 1168.69(9) Å³, *Z* = 4, ρ_{calc} = 1.400 g cm⁻³, *F*(000) = 520, *R* = 0.0680 (*R_w* = 0.1286) for 2448 reflections out of 2745 collected (163 parameters) with *I* > 3σ(*I*). Goodness of fit = 1.290.

ACKNOWLEDGEMENTS

NMR and MS spectra, and elemental analysis were made using JEOL JMN-LA500, JEOL SX-102A, and Perkin Elmer 2400II, respectively, at the Natural Science Centre for Basic Research and Development (N-BARD), Hiroshima University. We thank Dr. Yoshikazu Hiraga for measurements of NMR (JEOL JMN-LA500) at the Hiroshima Prefectural Institute of Science and Technology. We thank Dr. Satoshi Kojima for X-Ray analysis. Financial support of this work through Grants-in-Aid for Scientific Research

(nos.11740355 and 14740349) provided by the Japan Society for the Promotion of Science are heartily acknowledged.

REFERENCES AND NOTES

1. (a) R. Takagi, A. Sasaoka, H. Nishitani, S. Kojima, Y. Hiraga, and K. Ohkata, *J. Chem. Soc., Perkin Trans. 1*, 1998, 925. (b) H. Nishitani, A. Sasaoka, M. Tokumasu, and K. Ohkata, *Heterocycles*, 1999, **50**, 35. (c) M. Tokumasu, H. Ando, Y. Hiraga, S. Kojima, and K. Ohkata, *J. Chem. Soc., Perkin Trans. 1*, 1999, 489. (d) Y. Hiraga, M. Ago, M. Tokumasu, K. Kaku, and K. Ohkata, *Aust. J. Chem.*, 2000, **53**, 909. (e) N. Ohmori, *J. Chem. Soc., Perkin Trans. 1*, 2002, 755.
2. (a) M. Tanaka, F. Nara, K. Suzuki-Konagai, T. Hosoya, and T. Ogita, *J. Am. Chem. Soc.*, 1997, **119**, 7871. (b) F. Nara, M. Tanaka, T. Hosoya, K. Suzuki-Konagai, and T. Ogita, *J. Antibiot.*, 1999, **52**, 525. (c) F. Nara, M. Tanaka, S. Masuda-Inoue, Y. Yamasato, H. Doi-Yoshioka, K. Suzuki-Konagai, S. Kumakura, and T. Ogita, *J. Antibiot.*, 1999, **52**, 531. (d) S. Saito, N. Tanaka, K. Fujimoto, and H. Kogen, *Org. Lett.*, 2000, **2**, 505.
3. Synthetic studies on the hydrophilic moiety of scyphostatin (**1**) and related compounds: (a) M. K. Gurjar and S. Hotha, *Heterocycles*, 2000, **53**, 1885. (b) T. Katoh and T. Izuhara, *Tetrahedron Lett.*, 2000, **41**, 7651. (c) T. Izuhara and T. Katoh, *Org. Lett.*, 2001, **3**, 1653. (d) K. A. Runcie and R. J. K. Taylor, *Org. Lett.*, 2001, **3**, 3237. (e) H. Fujioka, N. Kotoku, Y. Sawama, Y. Nagatomi, and Y. Kita, *Tetrahedron Lett.*, 2002, **43**, 4825. (f) L. M. Murray, P. O'Brien, and R. J. K. Taylor, *Org. Lett.*, 2003, **5**, 1943. (g) M. Eipert, C. Maichle-Mössmer, and M. E. Maier, *Tetrahedron*, 2003, **59**, 7949. Synthetic studies on the hydrophobic moiety of scyphostatin (**1**): (h) T. R. Hoye and M. A. Tennakoon, *Org. Lett.*, 2000, **2**, 1481.
4. M. Inoue, W. Yokota, M. G. Murugesu, T. Izuhara, T. Katoh, *45th Symposium on the Chemistry of Natural Products* (Oct. 6-8, Kyoto, Japan), *Abstracts*, 2003, pp. 49-54.
5. P. Wipf and Y. Kim, *J. Org. Chem.*, 1993, **58**, 1649.
6. For a review: P. Wipf and J.-K. Jung, *Chem. Rev.*, 1999, **99**, 1469.
7. (a) P. G. Jones, H. Weinmann, and E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 448. (b) E. Winterfeldt, C. Borm, and F. Nerenz, *In Advances in Asymmetric Synthesis*; JAI Press Inc, 1997, Vol. 2, p. 1. (c) K. Goldenstein, T. Fendert, P. Proksch, and E. Winterfeldt, *Tetrahedron*, 2000, **56**, 4173.
8. (a) R. Takagi, W. Miyanaga, Y. Tamura, and K. Ohkata, *Chem. Commun.*, 2002, 2096. (b) R. Takagi, W. Miyanaga, Y. Tamura, S. Kojima, and K. Ohkata, *Heterocycles*, 2003, **60**, 785.
9. L. A. Paquette, B. B. Shetuni, and J. C. Gallucci, *Org. Lett.*, 2003, **5**, 2539.
10. (a) A. Khodabocus, T. K. M. Shig, J. K. Sutherland, and J. G. Williams, *J. Chem. Soc., Chem.*

- Commun.*, 1989, 783. (b) S. J. Danishefsky, J. J. Masters, W. B. Young, T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, and M. J. D. Grandi, *J. Am. Chem. Soc.*, 1996, **118**, 2843. (c) S.-P. Hong and M. C. McIntosh, *Org. Lett.*, 2002, **4**, 19. (d) Y. Chen, J. B. Evarts, Jr., E. Torres, and P. L. Fuchs, *Org. Lett.*, 2002, **4**, 3571.
11. C. Dupuy and J. L. Luche, *Tetrahedron*, 1989, **45**, 3447.
 12. G. A. Molander and G. J. Hahn, *J. Org. Chem.*, 1986, **51**, 2596.
 13. (a) T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *J. Am. Chem. Soc.*, 1979, **101**, 159. (b) R. B. Dehnell and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1979, 953.
 14. Z. Otwinowsky, W. Minor, DENZO and SCALEPAK. *In Processing of X-Ray Diffraction Data Collected in Oscillation Mode, Methods in Enzymology, Vol 276, Macromolecular Crystallography, Part A*, ed. by C. W. Carter, Jr. and R. M. Sweet, Academic Press, New York, 1997, pp. 307-326. The program is available from Mac Science Co.
 15. TeXsan: Single-Crystal Analysis Software, version 1.9; Molecular Structure Corporation: The Woodlands, Texas 77381, USA, 1998. The program is available from Mac Science Co.