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

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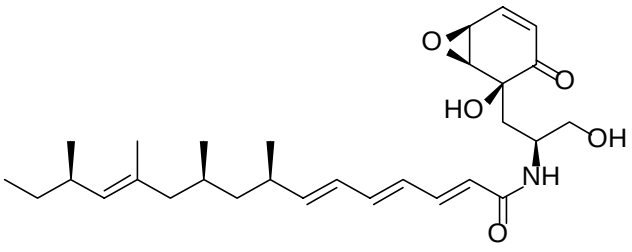
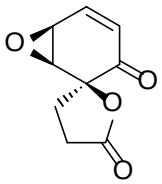
Abstract – An analogue of the hydrophilic moiety of scyphostatin was synthesized *via* π-facial selective Diels-Alder reaction of a 2,5-cyclohexadien-1-one bearing a spirolactone with cyclopentadiene.

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 sphingomyerinase (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.



Scyphostatin (**1**)



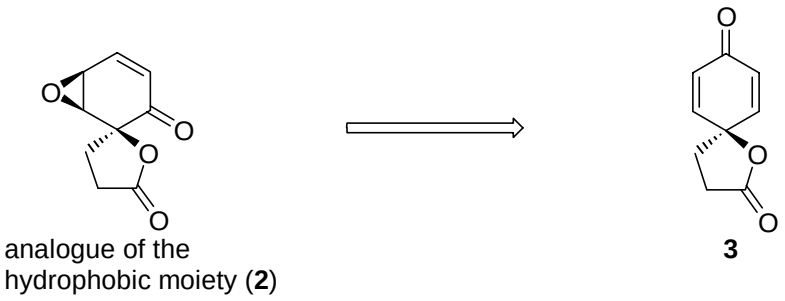
analogue of the hydrophilic moiety of scyphostatin (**2**)

Figure 1.

RESULTS AND DISCUSSION

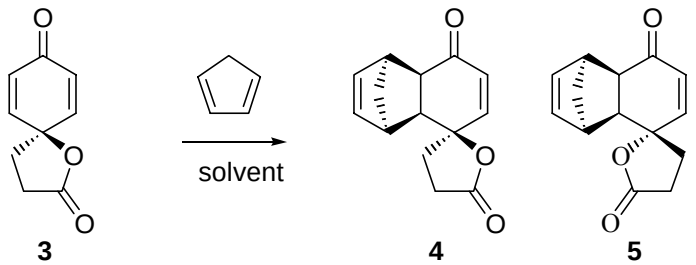
This paper is dedicated to Dr. Pierre Potier on the occasionof his 70th birthday.

We selected 2,5-cyclohexadien-1-one bearing a spirolactone (**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 derivative[7] proceeded with high π-facial selectivity.



Scheme 1.

Application of this highly π-facial selective reaction to spirolactone (**3**) seemed to be attractive for the synthesis of **2**, an analogue of the hydrophilic moiety. To this end, the Diels-Alder reaction of spirolactone (**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 CF_3CH_2OH 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]



solvent	conditions	**4**	:	**5**	yields (%)
CH_2Cl_2	25 °C, 3 days	96	:	4	99
CH_3CN	35 °C, 3 days	91	:	9	72
CF_3CH_2OH	37 °C, 4 h	96	:	4	87

Scheme 2.

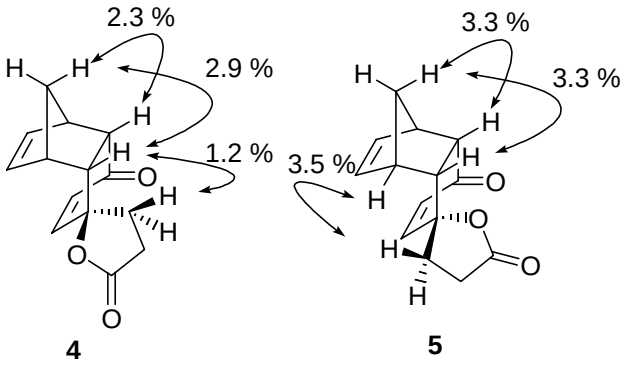


Figure 2.

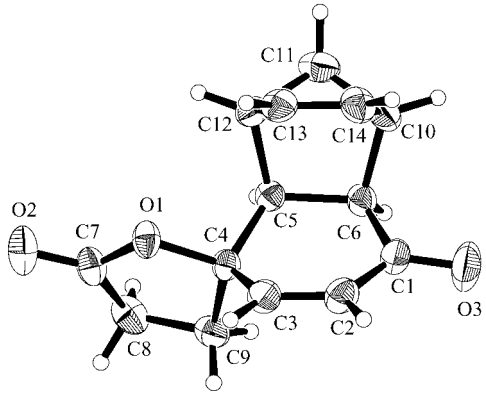
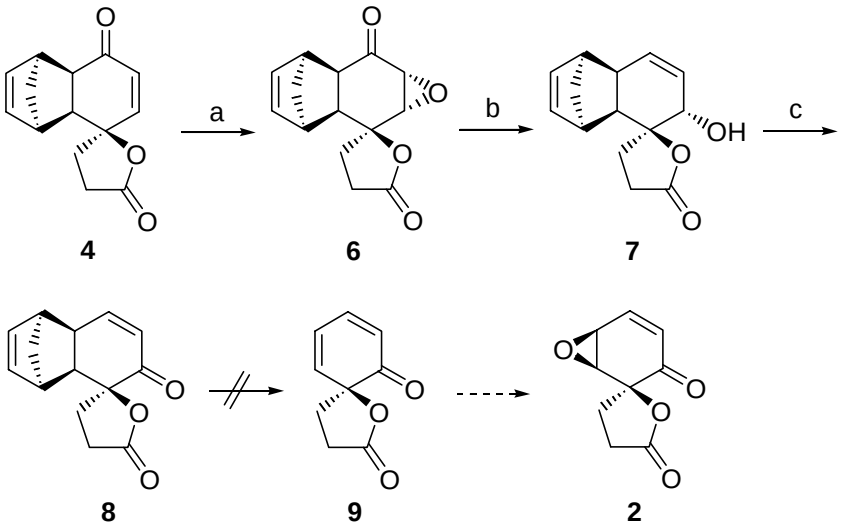


Figure 3. ORTEP drawing of **4**.

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 H_2O_2/LiOH, followed by reclosure to the lactone ring with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSCI) 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*-$Cl_2C_6H_4$, 250 °C; Ph_2O, maleic anhydride, 250 °C; $CHCl_3$, $BF_3 \cdot Et_2O$, 70 °C; CH_2Cl_2, $BF_3 \cdot Et_2O$, 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) $NH_2NH_2 \cdot H_2O$, AcOH, CF_3CH_2OH, 25 °C, 74%; (c) IBX, DMSO, 25 °C, then WSCI, CH_2Cl_2, 25 °C, 85% (two steps).

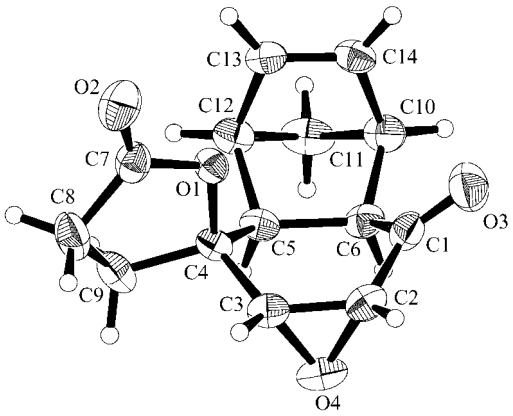
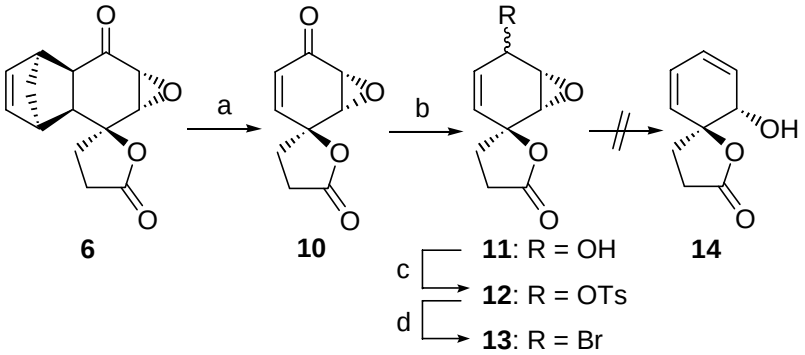


Figure 4. ORTEP drawing of **6.**

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 Zn(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%.

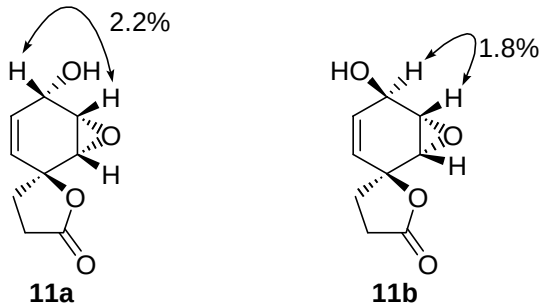
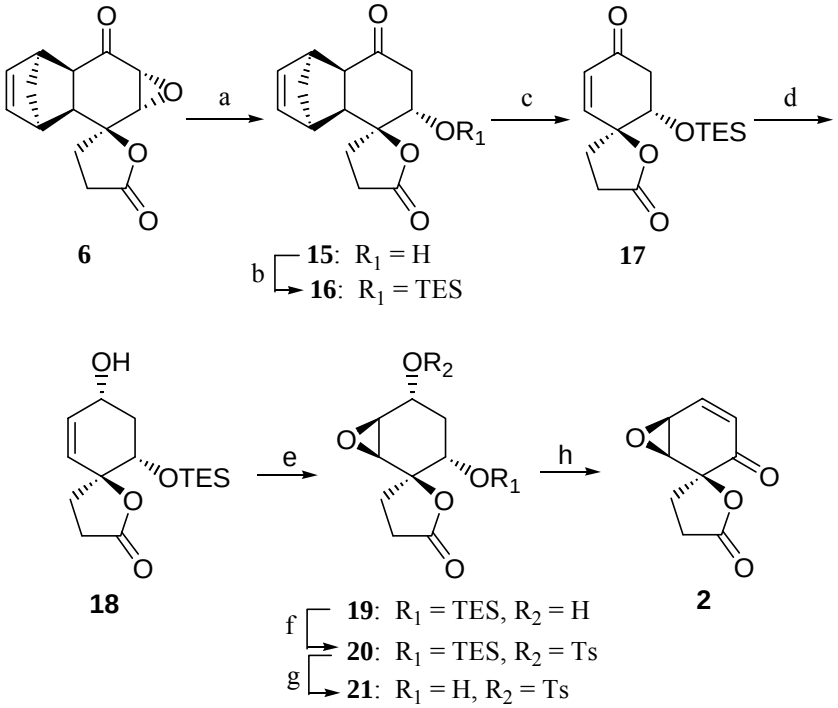


Figure 5. Determination of the relative stereochemistry of adducts (**11a**) and (**11b**).



Scheme 5. *Reagents and conditions*: (a) SmI_2, MeOH, THF, -78 °C, 89%; (b) TESCl, imidazole, CH_2Cl_2, 25 °C, quant; (c) maleic anhydride, Ph_2O, 230 °C, 96%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, THF, *i*-PrOH, 0 °C, 99%; (e) *m*CPBA, CH_2Cl_2, 25 °C, 95%; (f) TsCl, DABCO, CH_2Cl_2, 25 °C, 79%; (g) TBAF, AcOH, THF, 25 °C, 75%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °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 ($J_{H1\text{-}H2ax}$, $J_{H2ax\text{-}H3}$) and NOE experiments in ^1H NMR (Figure 6).

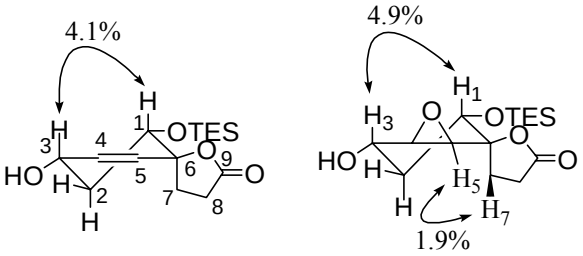


Figure 6. Determination of the relative stereochemistry of **18** and **19**.

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 ^{1}H 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**).

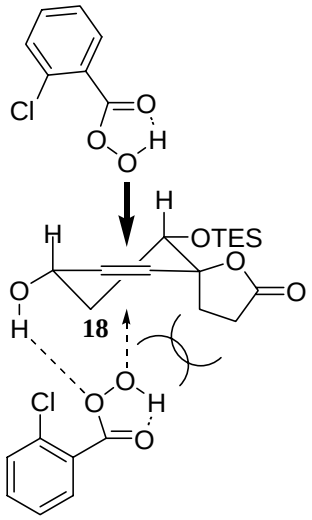


Figure 7. Stereoselectivity in epoxidation of **18** with *m*CPBA.

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 $60F_{254}$ (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 ^{1}H 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(8*H*)-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*endo*), 1.48 (1 H, d, *J* = 8.7 Hz, H9*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 $C_{14}H_{14}O_3$ [M^+] 230.0943. Found 230.0940; Anal. Cacld for $C_{14}H_{14}O_3$: 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*endo*), 1.57 (1 H, dt, *J* = 1.6, 8.6 Hz, H9*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 $C_{14}H_{15}O_3$ [M+H] 231.1021. Found 231.1015.

6,7-Epoxy-1,3',4,4',4a,6,7,8a-octahydrospiro[furan-2'(5'*H*),5(8*H*)-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 (WSCI) (153.8 mg, 0.80 mmol) was added to a solution of the residue in CH_2Cl_2 (2.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 14 h. After diluting with H_2O, 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 **6** (89.7 mg, 66%) as a colorless crystal: mp 167-169 °C ($CHCl_3$/hexane); IR (thin film): 2974, 1778, 1716, 1188 cm^{-1}; R_f (hexane/EtOAc 1:1) 0.5; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{14}O_4$ [M^+] 246.0892. Found 246.0889; Anal. Cacld for $C_{14}H_{14}O_4$: 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(6*H*)-1,4-methanonaphthalene]-5',8-dione (7)

$NH_2NH_2 \cdot H_2O$ (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 CF_3CH_2OH (4.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. After diluting with CH_2Cl_2 followed by quenching with sat. $NaHCO_3$, 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, CH_2Cl_2) to give **7** (139.7 mg, 74%) as a colorless crystal: mp 141-143 °C ($CHCl_3$/hexane); IR (thin film): 3464, 2981, 2893, 1759, 1269, 1212 cm^{-1}; R_f (CH_2Cl_2) 0.25; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{16}O_3$ [M^+] 232.1099. Found 232.1091.

1,3',4,4',4a,7,8a-Heptahydrospiro[furan-2'(5'*H*),5(6*H*)-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 H_2O, brine and dried over Na_2SO_4. WSCI (29.6 mg, 0.16 mmol) was added to a solution of the residue in CH_2Cl_2 (1.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 24 h. After addition of 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 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 ($CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{14}O_3$ [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 Ph_2O (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 Ph_2O. 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 ($CHCl_3$/hexane); IR (thin film): 1782, 1689, 1184 cm^{-1}; R_f (hexane/EtOAc 1:1) 0.5 ; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_9H_8O_4$ [M^+] 180.0423. Found 180.0415; Anal. Cacld for $C_{15}H_{24}O_4Si$: 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)

$NaBH_4$ (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. 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*. The residue was purified by column chromatography (silica gel, CH_2Cl_2/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, CH_2Cl_2/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 $C_9H_{10}O_4$ [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 $C_9H_{10}O_4$ [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, $C_6H_4C\mathbf{H}_3$), 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, $C_6\mathbf{H}_4CH_3$), 7.84 (d, *J* = 8.2 Hz, minor-$C_6\mathbf{H}_4CH_3$), 7.85 (d, *J* = 8.8 Hz, major-$C_6\mathbf{H}_4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6 (major-$C_6H_4\mathbf{C}H_3$), 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-$\mathbf{C}_6H_4CH_3$), 128.7 (major-C6), 130.1 (x2, major-$\mathbf{C}_6H_4CH_3$), 133.4 (major-*ipso*-$\mathbf{C}_6H_4CH_3$), 145.4 (major-*ipso*-$\mathbf{C}_6H_4CH_3$), 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 H_2O, 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 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, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_9H_9O_3{}^{79}Br$ [M^+] 243.9735. Found 243.9729.

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

CH_2I_2 (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 H_2O, 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, CH_2Cl_2/MeOH 30:1) to give **15** (893 mg, 89%) as a colorless crystal: mp 143-145 °C ($CHCl_3$/hexane); IR (thin film): 3425, 2970, 1770, 1701, 1188 cm^{-1}; R_f (hexane/EtOAc 1:1) 0.1; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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. Cacld 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(8*H*)-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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (6 H, q, *J* = 7.7 Hz, SiC**H**$_2$CH$_3$), 0.93 (9 H, t, *J* = 7.7 Hz, SiCH$_2$C**H**$_3$), 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, Si**C**H$_2$CH$_3$), 6.7 (x3, SiCH$_2$**C**H$_3$), 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}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (6 H, q, *J* = 7.9 Hz, SiC**H**$_2$CH$_3$), 0.95 (9 H, t, *J* = 7.9 Hz, SiCH$_2$C**H**$_3$), 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, Si**C**H$_2$CH$_3$), 6.6 (x3, SiCH$_2$**C**H$_3$), 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)

$NaBH_4$ (38.1 mg, 1.01 mmol) was added to a solution of **17** (292.4 mg, 0.99 mmol) and $CeCl_3 \cdot 7H_2O$ (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. 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*. The residue was purified by column chromatography (silica gel, CH_2Cl_2/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, $CDCl_3$) δ 0.63 (6 H, q, *J* = 7.9 Hz, $SiC\mathbf{H}_2CH_3$), 0.96 (9 H, t, *J* = 7.9 Hz, $SiCH_2C\mathbf{H}_3$), 1.66 (1 H, td, *J* = 9.4, 12.4 Hz, H9*ax*), 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, H9*eq*), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.6 (x3, $Si\mathbf{C}H_2CH_3$), 6.6 (x3, $SiCH_2\mathbf{C}H_3$), 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 $C_{15}H_{25}O_4Si$ [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 CH_2Cl_2 (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. $NaHSO_3$ and sat. $NaHCO_3$, 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*. 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, $CDCl_3$) δ 0.60 (6 H, q, *J* = 7.9 Hz, $SiC\mathbf{H}_2CH_3$), 0.94 (9 H, t, *J* = 7.9 Hz, $SiCH_2C\mathbf{H}_3$), 1.45 (1 H, td, *J* = 11.0, 12.6 Hz, H9*ax*), 1.66-1.78 (1 H, br s, OH), 1.84 (1 H, ddd, *J* = 3.3, 5.2, 12.6 Hz, H9*eq*), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.7 (x3, $Si\mathbf{C}H_2CH_3$), 6.6 (x3, $SiCH_2\mathbf{C}H_3$), 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 $C_{13}H_{21}O_5Si$ [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-diazabicycolo[2.2.2]octane (DABCO) (104.6 mg, 0.86 mmol) in CH_2Cl_2 (3.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 18 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 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, $SiC\mathbf{H}_2CH_3$), 0.89 (9 H, t, *J* = 7.9 Hz, $SiCH_2C\mathbf{H}_3$), 1.59-1.71 (2 H, m, H9 x2), 2.21-2.29 (1 H, m, H4), 2.39-2.45 (1 H, m, H4), 2.46 (3 H, s, CH_3), 2.47-2.63 (2 H, m, H3 x2), 3.26 (1 H, d, *J* = 3.7 Hz, H6), 3.39 (1 H, br s, H7), 3.58 (1 H, dd, *J* = 4.9, 11.0 Hz, H10), 4.95 (1 H, ddd, *J* = 1.7, 7.0, 10.4 Hz, H8), 7.38 (2 H, d, *J* = 8.2 Hz, $C_6\mathbf{H}_4CH_3$), 7.84 (2 H, d, *J* = 8.2 Hz, $C_6\mathbf{H}_4CH_3$); ^{13}C NMR (125 MHz,$CDCl_3$) δ 4.5 (x3, $Si\mathbf{C}H_2CH_3$), 6.4 (x3, $SiCH_2\mathbf{C}H_3$), 21.5 (CH_3), 23.3 (C4), 28.6 (C9), 29.3 (C3), 54.6 (C7), 58.2 (C6), 71.3 (C10), 76.0 (C8), 83.6 (C5), 127.6 (x2, $\mathbf{C}_6H_4CH_3$), 129.9 (x2, $\mathbf{C}_6H_4CH_3$), 133.6 ($\mathbf{C}_6H_4CH_3$), 145.2 ($\mathbf{C}_6H_4CH_3$), 176.5 (C2); HRMS (EI) calcd for $C_{20}H_{27}O_7SSi$ [M-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, H9), 1.89 (1 H, dddd, *J* = 0.9, 3.1, 6.1, 12.8 Hz, H9), 2.27-2.36 (1 H, m, H4), 2.45-2.36 (1 H, m, H4), 2.45-2.55 (1 H, m, H3), 2.46 (3 H, s, CH_3), 2.66-2.75 (1 H, m, H3), 2.81-2.95 (1 H, br s, OH), 3.28 (1 H, d, *J* = 3.4 Hz, H6), 3.42 (1 H, br s, H7), 3.69 (1 H, dd, *J* = 3.1, 12.8 Hz, H10), 5.02 (1 H, ddd, *J* = 1.8, 6.1, 10.5 Hz, H8), 7.37 (2 H, d, *J* = 8.1 Hz, $C_6\mathbf{H}_4CH_3$), 7.83 (2 H, d, *J* = 8.1 Hz, $C_6\mathbf{H}_4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7 (CH_3), 23.7 (C4), 28.7 (C9), 29.0 (C3), 54.8 (C7), 58.2 (C6), 70.3 (C8), 75.6 (C10), 83.8 (C5), 127.7 (x2, $\mathbf{C}_6H_4CH_3$), 130.1 (x2, $\mathbf{C}_6H_4CH_3$), 133.6 ($\mathbf{C}_6H_4CH_3$), 145.3 ($\mathbf{C}_6H_4CH_3$), 177.2 (C2); HRMS (EI) calcd for $C_{16}H_{18}O_7S$ 354.0793. Found 354.0789; Anal. Calcd for $C_{16}H_{18}O_7S$: 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 $(COCl)_2$ (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

Na_2SO_4. 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, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_9H_8O_4$ [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 180º 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 $P12_1/c$, a = 6.5700(3) Å, b = 18.2680(8) Å, c = 9.9190(4) Å, V = 1162.69(9) $Å^3$, 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 $I>3\sigma(I)$. Goodness of fit = 1.549. for **6**: monoclinic system, space group $P12_1/c$, a = 7.8340(3) Å, b = 11.1270(5) Å, c = 13.8110(6) Å, V = 1168.69(9) $Å^3$, 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 $I>3\sigma(I)$. 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.

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