Supporting Information

Stereoselective Total Synthesis of (+)-Scyphostatin *via* a π -Facially Selective Diels-Alder Reaction and Revision of the Stereochemical Assignment in our Model Study

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Table of Contents

General Methods.....	S2
Experimental Procedures and/or	
Characterization Data of 13-18 , 23-26 , 32 and 36	S2-S12
Table S1.....	S13
NMR Spectra of 8-18 , 23-36 and 1	S14-S136

General Method

All reactions involving air- and moisture-sensitive reagents were carried out under N₂. CH₂Cl₂ was distilled over CaH₂ before use. Tetrahydrofuran (THF) was distilled after refluxing over Na-benzophenone before use. Merck silica gel 60F₂₅₄ TLC aluminum sheets were used for routine monitoring of reactions. Column chromatography was performed on Merck silica gel 60 (70-230 mesh, ASTM) or Kanto Chemical Silica Gel 60N (spherical, neutral 40-50 μm). Merck silica gel 60F₂₅₄ was used for preparative thin-layer chromatography.

Internal references for ¹H NMR spectra were 0.0 ppm (Me₄Si) for CDCl₃, 3.30 ppm for CD₃OD, and 7.55 ppm for C₅D₅N. Chemical shifts for ¹³C NMR spectra were referenced to CDCl₃ (77.0 ppm), CD₃OD (49.0 ppm), and C₅D₅N (135.5 ppm). MS were recorded under electron ionization (EI; 70eV) or FAB conditions. FAB spectra were measured by using glycerol or *m*-nitrobenzyl alcohol (NBA) as the matrix.

(3S,5S,6R,7R,8R10S)-3-Benzyloxycarbonylamino-6,7-epoxy-8-hydroxy-10-triethylsilyloxy-1-oxaspiro[4.5]decan-2-one (13). *m*CPBA (256 mg, 1.49 mmol) was added to a solution of **12** (433 mg, 0.97 mmol) in CH₂Cl₂ (10 mL) at room temperature. After stirring at room temperature for 24 h, additional *m*CPBA (265 mg, 1.54 mmol) was added to the reaction mixture at room temperature and the reaction mixture was stirred at room temperature for another 24 h. After diluting with CH₂Cl₂, the reaction mixture was quenched with sat. NaHSO₃. The mixture was extracted with CH₂Cl₂. The organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed in *vacuo*. **13** (445 mg, 99%) was obtained as a white crystal: m.p. 85-88 °C (hexane:CHCl₃); [α]_D²⁷ -5.0 (*c* 0.70, CHCl₃); IR (thin film) 3406, 1782, 1709, 1523, 1053 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.60 (q, *J* = 7.6 Hz, 6 H), 0.95 (t, *J* = 7.6 Hz, 9 H), 1.47 (dt, *J* = 11.3, 12.1 Hz, 1 H), 1.78-1.92 (m, 2 H), 2.35 (dd, *J* = 10.3, 12.1

Hz, 1 H), 2.86 (dd, $J = 11.0, 12.1$ Hz, 1 H), 3.43 (bs, 2 H), 3.64 (d, $J = 12.1$ Hz, 1 H), 4.18 (m, 1 H), 4.46 (dd, $J = 10.3, 11.0$ Hz, 1 H), 5.12 (d, $J = 12.1$ Hz, 1 H), 5.16 (d, $J = 12.1$ Hz, 1 H), 5.30 (bs, 1 H), 7.30-7.40 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 4.7 (x3), 6.6 (x3), 31.6, 32.6, 51.2, 57.3, 59.0, 67.2, 67.3, 72.1, 82.4, 128.1, 128.3, 128.6 (x3), 135.9, 155.7, 174.5; EI-HRMS: m/z Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_7\text{Si}$ [M^+] 463.2026, Found 463.2049; Anal. Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_7\text{Si}$; C, 59.59; H, 7.17; N, 3.02. Found: C, 59.66; H, 7.36; N, 2.89.

(3S,5S,6R,7S,8R,10S)-3-Benzyloxycarbonylamino-6,7-epoxy-8-(4-methylbenzenesulfonyl)-10-triethylsilyloxy-1-oxaspiro[4.5]decan-2-one (14). *p*-Toluenesulfonyl chloride (TsCl) (222 mg, 1.16 mmol) was added to a solution of **13** (446 mg, 0.96 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (353 mg, 2.89 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 7 h. After quenching with sat. NH_4Cl , 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 **14** (537 mg, 90%) as a colorless oil: $[\alpha]_D^{27} +0.48$ (c 0.79, CHCl_3); IR (thin film) 3425, 1790, 1720, 1520, 1369, 1176 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.53 (q, $J = 7.6$ Hz, 6 H), 0.89 (t, $J = 7.6$ Hz, 9 H), 1.63-1.71 (m, 2 H), 2.33 (dd, $J = 10.7, 12.4$ Hz, 1 H), 2.46 (s, 3 H), 2.77 (dd, $J = 11.3, 12.4$ Hz, 1 H), 3.33-3.42 (m, 2 H), 3.55 (dd, $J = 7.3, 8.2$ Hz, 1 H), 4.38 (ddd, $J = 6.1, 10.7, 11.3$ Hz, 1 H), 4.93 (dd, $J = 7.3, 8.2$ Hz, 1 H), 5.09 (d, $J = 12.2$ Hz, 1 H), 5.13 (d, $J = 12.2$ Hz, 1 H), 5.43 (d, $J = 6.1$ Hz, 1 H), 7.29-7.36 (m, 5 H), 7.38 (d, $J = 8.3$ Hz, 2 H), 7.83 (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 4.6 (x3), 6.5 (x3), 21.6, 29.3, 31.2, 51.0, 54.5, 58.1, 67.2, 71.5, 75.9, 81.7, 127.7 (x2), 128.0, 128.2, 128.5 (x2), 130.0 (x2), 133.7, 135.8, 145.3 (x2), 155.7, 174.3; EI-HRMS: m/z Calcd for $\text{C}_{30}\text{H}_{39}\text{NO}_9\text{Si}$ [M^+]

617.2115, Found 617.2119; Anal. Calcd for C₃₀H₃₉NO₉Si: C, 58.32; H, 6.36; N, 2.27. Found C, 58.27; H, 6.44; N, 2.39.

(1R,2R,2'S,3S,4R,6S)-1-(2'-Benzyloxycarbonylamino-3'-tert-butyldiphenylsilyloxypropyl)-2,3-epoxy-6-hydroxy-4-(4-methylbenzenesulfonyl)cyclohexan-1-ol (15). NaBH₄ (18.0 mg, 0.48 mmol) was added to a solution of **14** (147 mg, 0.24 mmol) in EtOH (1.2 mL) and THF (1.2 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred at room temperature for 5 h. After quenched with sat. NH₄Cl, the mixture was extracted with EtOAc. The 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 the diol (147 mg, 99%) as a colorless oil: [α]_D²⁷ +18.0 (*c* 0.797, CHCl₃); IR (thin film) 3375, 1689, 1523, 1365, 1176 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.53 (q, *J* = 7.6 Hz, 6 H), 0.88 (t, *J* = 7.6 Hz, 9 H), 1.47-1.58 (m, 2 H), 1.86-1.90 (m, 2 H), 1.99 (t, *J* = 5.4 Hz, 1 H), 2.45 (s, 3 H), 3.16 (d, *J* = 3.4 Hz, 1 H), 3.30 (bs, *J* = 1.9, 3.4 Hz, 1 H), 3.39 (dd, *J* = 3.7, 12.5 Hz, 1 H), 3.70 (m, 1 H), 3.83 (m, 1 H), 3.96 (m, 1 H), 4.64 (bs, 1H), 4.93 (ddd, *J* = 1.8, 6.1, 10.7 Hz, 1 H), 5.08 (d, *J* = 12.2 Hz, 1 H), 5.11 (d, *J* = 12.2 Hz, 1 H), 5.50 (bs, 1 H), 7.30-7.35 (m, 7 H), 7.82 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 4.6 (x3), 6.7 (x3), 21.6, 29.6, 30.3, 54.6, 58.9, 60.4, 65.3, 67.0, 71.6, 74.0, 77.1, 127.7 (x2), 128.0, 128.2, 128.5 (x2), 129.9 (x2), 133.9, 136.1, 145.1 (x2), 157.3; EI-HRMS: *m/z* Calcd for C₂₈H₃₈NO₉Si [M⁺-Et] 592.2037, Found 592.2059; Anal. Calcd for C₃₀H₄₃NO₉Si: C, 57.95; H, 6.97; N, 2.25. Found: C, 57.66; H, 7.22; N, 2.05.

TBAF (1.0 M solution in THF, 0.24 mL, 0.24 mmol) was added to a solution of the diol (147 mg, 0.24 mmol) in THF (2.4 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 min. After diluting with H₂O, the mixture was extracted with EtOAc. The 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 the triol (120 mg, 99%) as a colorless oil: $[\alpha]_D^{27} +24.7$ (*c* 0.356, CHCl₃); IR (thin film) 3375, 1693, 1527, 1354, 1176 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.75-1.81 (m, 2 H), 1.88 (dd, *J* = 4.3, 14.8 Hz, 1 H), 1.98 (dd, *J* = 8.0, 14.8 Hz, 1 H), 2.45 (s, 3 H), 3.17 (bs, 1 H), 3.29 (bs, 1 H), 3.51 (dd, *J* = 3.1, 12.2 Hz, 1 H), 3.68 (dd, *J* = 4.6, 11.1 Hz, 1 H), 3.74 (dd, *J* = 3.1, 11.1 Hz, 1 H), 4.03 (m, 1 H), 4.96 (dddd, *J* = 0.6, 1.5, 5.8, 9.4 Hz, 1 H), 5.06 (d, *J* = 12.2 Hz, 1 H), 5.11 (d, *J* = 12.2 Hz, 1 H), 6.15 (bs, 1 H), 7.27-7.37 (m, 5 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 7.81 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 21.6, 29.2, 33.8, 49.3, 54.4, 59.2, 65.3, 67.1, 71.5, 73.1, 76.6, 127.7 (x2), 127.9, 128.2, 128.5 (x2), 130.0 (x2), 133.5, 136.0, 145.2 (x2), 157.3; EI-HRMS: *m/z* Calcd for C₂₄H₂₉NO₉S [M⁺] 507.1563. Found 507.1540, Anal. Calcd for C₂₄H₂₉NO₉S: C, 56.79; H, 5.76; N, 2.76. Found: C, 56.68; H, 6.00; N, 2.77.

tert-Butyldiphenylsilyl chloride (TBDPSCI) (14.7 mg, 97.5 μ mol) was added to a solution of the triol (38.1 mg, 75.0 μ mol) and imidazole (16.0 mg, 0.24 mmol) in DMF (0.75 mL). The reaction mixture was stirred at room temperature for 24 h. After diluting with EtOAc, the mixture was washed with H₂O and brine. The organic layer was 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** (57.2 mg, 96%) as a colorless oil: $[\alpha]_D^{27} +12.5$ (*c* 1.24, CHCl₃); IR (thin film) 3386, 1693, 1520, 1362, 1176 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.05 (s, 9 H), 1.50 (ddd, *J* = 9.8, 10.1, 12.2 Hz, 1 H), 1.78 (ddd, *J* = 2.7, 6.1, 12.2 Hz, 1 H), 1.81-1.90 (m, 2 H), 2.44 (s, 3 H), 2.70 (bs, 1 H), 2.96 (d, *J* = 4.0 Hz, 1 H), 3.22 (bs, 1 H), 3.36 (ddd, *J* = 2.5, 3.9, 11.7 Hz, 1 H), 3.70 (dd, *J* = 5.8, 10.4 Hz, 1 H), 3.80-3.95 (m, 2 H), 4.93 (ddd, *J* = 2.5, 6.2, 9.4 Hz, 1 H), 5.03 (d, *J* = 12.2 Hz, 1 H), 5.12 (d, *J* = 12.2 Hz, 1 H), 5.42 (bs, 1 H), 7.26-7.44 (m, 14 H), 7.62 (dt, *J* = 1.2, 7.9 Hz, 4 H), 7.81 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 19.2, 21.6, 26.9 (x3), 28.8, 36.5, 53.4, 54.3, 58.9, 66.4, 67.2, 71.1, 72.9, 76.6, 127.6 (x2), 127.7 (x2), 127.8 (x4), 128.0, 128.3, 128.5, 129.9, 132.7, 132.9, 133.9, 134.8, 135.6 (x4), 136.0, 145.0 (x4), 162.3; EI-HRMS: *m/z* Calcd for C₄₀H₄₆NO₉SSi [M⁺-H] 744.2663, Found 744.2689; Anal. Calcd for C₄₀H₄₇NO₉SSi: C, 64.40; H, 6.35; N, 1.88. Found: C, 64.28; H, 6.55; N, 1.88.

(1*R*,2*R*,2'*S*,2''*E*,3*S*,4*R*,4''*E*,6*S*,6''*E*,8''*R*,10''*S*,12''*E*,14''*R*)-1-[3'-*tert*-Butyldiphenylsilyloxy-2'-(8'',10'',12'',14''-tetramethylhexadeca-2'',4'',6'',12''-tetraenoylamino)propyl]-2,3-epoxy-6-hydroxy-4-(4-methylbenzenesulfonyl)cyclohexan-1-ol (16). PtO₂ (8.8 wt%, 2.03 mg) was added to a solution of **15** (23.1 mg, 31.0 μmol) and 1*N*-HCl (0.08 mL, 24.8 μmol) in MeOH (0.62 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h under a hydrogen atmosphere. The reaction mixture was filtered and the insoluble material was washed with MeOH. The solvent was removed *in vacuo*. The residue was diluted with EtOAc and sat. NaHCO₃ and extracted with EtOAc. The organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was used in the next reaction without further purification: ¹H NMR (500 MHz, CDCl₃) δ 1.07 (s, 9 H), 1.51 (q, *J* = 11.8 Hz, 1 H), 1.61 (dd, *J* = 2.1, 13.5 Hz, 1 H), 1.65 (t, *J* = 13.5 Hz, 1 H), 1.76 (ddd, *J* = 2.6, 6.0, 11.8 Hz, 1 H), 2.45 (s, 3 H), 3.18 (d, *J* = 3.7 Hz, 1 H), 3.29-3.36 (m, 3 H), 3.46 (dd, *J* = 6.1, 10.1 Hz, 1 H), 3.65 (dd, *J* = 4.0, 10.1 Hz, 1 H), 4.97 (ddd, *J* = 1.9, 6.0, 11.8 Hz, 1 H), 7.30-7.47 (m, 8 H), 7.61-7.65 (m, 4 H), 7.82 (d, *J* = 8.5 Hz, 2 H).

EDCI (9.08 mg, 0.05 mmol) was added to a solution of the residue and the hydrophilic moiety **2** (11.0 mg, 0.04 mmol) in CH₂Cl₂ (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 14 h. Then it was quenched with sat. NH₄Cl, and extracted with CH₂Cl₂. The organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by preparative TLC (silica gel, CH₂Cl₂/MeOH 30:1) to give **16** (17.9 mg, 64%) as a colorless oil: [α]_D²⁷ +42.3 (*c* 0.251, CDCl₃); IR (thin film) 3371, 1647, 1597, 1365, 1176, 1111 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.81 (d, *J* = 6.4 Hz, 3 H), 0.84 (t, *J* = 7.5 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.98-1.02 (m, 1 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.09 (s, 9 H), 1.16-1.24 (m, 1 H), 1.27-1.37 (m, 2 H),

1.43-1.52 (m, 1 H), 1.53 (d, $J = 1.3$ Hz, 3 H), 1.73-1.95 (m, 6 H), 2.19-2.28 (m, 1 H), 2.29-2.40 (m, 1 H), 2.41 (d, $J = 5.2$ Hz, 1 H), 2.45 (s, 3 H), 2.98 (d, $J = 7.0$ Hz, 1 H), 3.24 (dd, $J = 1.8, 3.7$ Hz, 1 H), 3.37 (ddd, $J = 3.4, 4.0, 10.1$ Hz, 1 H), 3.84 (dd, $J = 6.1, 10.7$ Hz, 1 H), 3.96 (dd, $J = 3.5, 10.7$ Hz, 1 H), 3.98-4.03 (m, 1 H), 4.84 (dd, $J = 0.6, 9.5$ Hz, 1 H), 4.92 (ddd, $J = 1.8, 6.1, 10.1$ Hz, 1 H), 5.62 (d, $J = 14.9$ Hz, 1 H), 5.73 (dd, $J = 8.5, 15.2$ Hz, 1 H), 6.10 (dd, $J = 10.7, 15.2$ Hz, 1 H), 6.11 (d, $J = 6.4$ Hz, 1 H), 6.18 (dd, $J = 11.6, 14.6$ Hz, 1 H), 6.18 (s, 1 H), 6.49 (dd, $J = 11.0, 14.9$ Hz, 1 H), 7.21 (dd, $J = 11.6, 14.9$ Hz, 1 H), 7.32-7.48 (m, 8 H), 7.61-7.67 (m, 4 H), 7.82 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 12.0, 16.2, 19.3, 19.5, 21.0, 21.3, 21.6, 26.9 (x3), 28.3, 28.7, 30.5, 34.1, 34.9, 35.8, 44.0, 47.8, 48.3, 54.5, 59.1, 66.3, 70.8, 72.8, 76.8, 121.1, 127.4, 127.8 (x2), 127.92 (x3), 128.0 (x2), 128.2, 129.9 (x2), 130.0, 130.1, 132.1, 132.8, 133.0, 133.1, 133.9, 135.6 (x3), 141.2, 142.5, 145.0, 146.2, 167.6; FAB+-HRMS: m/z Calcd for $\text{C}_{52}\text{H}_{72}\text{NO}_8\text{SSi}$ $[\text{M}+\text{H}]$ 898.4748. Found 898.4789.

(2'S,2''E,4R,4'E,5R,6S,6'E,8'R,10'S,12'E,14'R)-4,5-Epoxy-6-hydroxy-6-[2'-(8'',10'',12'',14''-tetramethylhexadeca-2'',4'',6'',12''-tetraenoylamino)-3'-tert-butyl diphenylsilyloxypropyl]-2-cyclohexen-1-one (17). A solution of $(\text{COCl})_2$ (14.0 μL , 158 μmol) and DMSO (18.0 μL , 793 μmol) in CH_2Cl_2 (1.0 mL) was stirred at -78°C for 30 min, followed by addition of a solution of **16** (57.0 mg, 63.4 μmol) in CH_2Cl_2 (0.6 mL). The reaction mixture was stirred at -78°C for 40 min. To the solution was added Et_3N (0.11 mL, 0.79 mmol) at -78°C . After stirring at -78°C for 1 h, the reaction mixture was quenched with sat. NH_4Cl , warmed to room temperature, and 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, CH_2Cl_2) to give crude product. The crude product was treated with silica gel for 1 h. After eluting with EtOAc , the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **17** (32.9 mg, 71%) as a

colorless oil: $[\alpha]_D^{27} +11.2$ (c 0.212, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.81 (d, $J = 6.7$ Hz, 3 H), 0.84 (t, $J = 7.3$ Hz, 3 H), 0.91 (d, $J = 6.7$ Hz, 3 H), 1.00 (d, $J = 6.7$ Hz, 3 H), 0.98-1.03 (m, 1 H), 1.06-1.10 (m, 1 H), 1.09 (s, 9 H), 1.15-1.25 (m, 1 H), 1.27-1.38 (m, 1 H), 1.48-1.49 (m, 1 H), 1.53 (d, $J = 1.2$ Hz, 3 H), 1.77 (dd, $J = 7.0, 13.2$ Hz, 1 H), 1.85 (dd, $J = 4.0, 15.4$ Hz, 1 H), 1.89 (d, $J = 7.0, 13.2$ Hz, 1 H), 2.18-2.28 (m, 1 H), 2.30-2.38 (m, 1 H), 2.44 (dd, $J = 6.1, 15.4$ Hz, 1 H), 3.42 (dd, $J = 0.6, 3.7$ Hz, 1 H), 3.43 (dd, $J = 1.2, 3.7$ Hz, 1 H), 3.78 (dd, $J = 6.1, 11.0$ Hz, 1 H), 3.85 (dd, $J = 4.0, 11.0$ Hz, 1 H), 4.15-4.23 (m, 1 H), 4.84 (d, $J = 8.8$ Hz, 1 H), 5.66 (d, $J = 14.4$ Hz, 1 H), 5.72 (dd, $J = 8.5, 15.2$ Hz, 1 H), 6.06-6.07 (m, 1 H), 6.07 (dd, $J = 1.2, 10.1$ Hz, 1 H), 6.10 (dd, $J = 11.0, 15.2$ Hz, 1 H), 6.19 (dd, $J = 11.6, 14.6$ Hz, 1 H), 6.49 (dd, $J = 11.0, 14.6$ Hz, 1 H), 7.06 (ddd, $J = 0.9, 3.7, 10.1$ Hz, 1 H), 7.22 (dd, $J = 11.6, 14.4$ Hz, 1 H), 7.24-7.49 (m, 6 H), 7.62-7.68 (m, 4 H).

(2'S,2''E,4R,4'E,5R,6S,6'E,8'R,10'S,12'E,14'R)-4,5-Epoxy-6-hydroxy-6-[2'-(8'',10'',12'',14''-tetramethylhexadeca-2'',4'',6'',12''-tetraenoylamino)-3'-tert-butylphenylsilyloxypropyl]-2-cyclohexen-1-one (18). Tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) (2.5 mg, 9.0 μmol) was added to a solution of **17** (5.9 mg, 8.1 μmol) in pyridine (0.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h. Then it was quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layer was washed with sat. NH_4Cl and brine, dried over Na_2SO_4 , and evaporated. The residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 30:1) to give **18** (2.8 mg, 70%) as a colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 0.80 (d, $J = 6.4$ Hz, 3 H), 0.84 (t, $J = 7.3$ Hz, 3 H), 0.90 (d, $J = 6.6$ Hz, 3 H), 0.95-1.07 (m, 1 H), 1.00 (d, $J = 6.6$ Hz, 3 H), 1.13-1.23 (m, 1 H), 1.23-1.36 (m, 2 H), 1.53 (d, $J = 1.0$ Hz, 3 H), 1.40-1.55 (m, 1 H), 1.76 (dd, $J = 7.3, 13.1$ Hz, 1 H), 1.88 (dd, $J = 7.1, 13.1$ Hz, 1 H), 2.09 (dd, $J = 5.3, 15.1$ Hz, 1 H), 2.16-2.40 (m, 2 H), 2.26 (dd, $J = 8.0, 15.1$ Hz, 1 H), 3.54 (ddd, $J = 1.2, 3.6, 3.8$ Hz, 1 H), 3.75 (d, $J = 3.6$ Hz, 1 H), 3.71-3.84 (m, 2 H), 4.25-4.35 (m, 1 H), 4.84 (d, $J =$

S8

8.9 Hz, 1 H), 5.44 (s, 1 H), 5.71 (dd, $J = 8.7, 15.2$ Hz, 1 H), 5.84 (d, $J = 14.9$ Hz, 1 H), 6.09 (dd, $J = 10.8, 15.2$ Hz, 1 H), 6.12 (dd, $J = 1.2, 10.1$ Hz, 1 H), 6.19 (dd, $J = 11.2, 15.1$ Hz, 1 H), 6.46 (d, $J = 6.2$ Hz, 1 H), 6.50 (dd, $J = 10.8, 15.1$ Hz, 1 H), 7.12 (dd, $J = 3.7, 10.1$ Hz, 1 H), 7.25 (dd, $J = 11.2, 14.9$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 12.0, 16.2, 19.5, 21.0, 21.3, 28.3, 30.5, 34.1, 35.0, 37.1, 44.0, 47.2, 48.2, 48.3, 59.2, 65.7, 72.2, 121.6, 127.6, 128.3, 130.7, 132.1, 133.1, 141.1, 142.4, 143.5, 146.0, 167.6, 196.2; EI-HRMS: m/z Calcd. for $\text{C}_{29}\text{H}_{43}\text{NO}_5$ [M^+] 485.3141, Found 485.3117.

6-Bromo-1-oxaspiro[4.5]dec-7-ene-2,6-dione (23). A mixture of *cis*- and *trans*-isomers; ^1H NMR (500 MHz, CDCl_3) δ 1.88-1.94 (m, *trans*-H2), 2.55-2.73 (m, *trans*-H2, *trans*-H3 x2, *cis*-H2 x2, *cis*-H3 x3), 3.15 (bs, *cis*-OH), 3.35 (d, $J = 3.6$ Hz, *trans*-OH), 4.40 (t, $J = 4.2$ Hz, *cis*-H9), 4.49 (dd, $J = 3.6, 8.7$ Hz, *trans*-H9), 4.74 (dt, $J = 2.4, 8.7$ Hz, *trans*-H8), 5.12 (t, $J = 4.2$ Hz, *cis*-H8), 6.08 (dd, $J = 2.3, 10.3$ Hz, *trans*-H6), 6.13 (d, $J = 10.0$ Hz, *cis*-H6), 7.03 (dd, $J = 4.2, 10.0$ Hz, *cis*-H7), 7.06 (dd, $J = 2.4, 10.3$ Hz, *trans*-H7); EI-HRMS: m/z Calcd for $\text{C}_9\text{H}_9\text{O}_4^{79}\text{Br}$ [M^+] 259.9684. Found: 259.9674.

9,10-Epoxy-1-oxaspiro[4.5]dec-7-ene-2,6-dione (24). Colorless oil; IR (thin film) 2975, 1786, 1685, 1176, 1122 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 2.38 (ddd, $J = 9.4, 9.8, 13.1$ Hz, 1 H), 2.66-2.81 (m, 2 H), 2.94 (ddd, $J = 9.4, 9.8, 18.0$ Hz, 1 H), 3.64 (dt, $J = 1.2, 3.7$ Hz, 1 H), 3.79 (d, $J = 3.7$ Hz, 1 H), 6.20 (dd, $J = 1.2, 10.1$ Hz, 1 H), 7.28 (dd, $J = 4.0, 10.1$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.1, 28.2, 47.3, 58.7, 80.1, 130.8, 145.0, 175.6, 191.1; EI-HRMS: m/z Calcd. for $\text{C}_9\text{H}_8\text{O}_4$ [M^+] 180.0423, Found 180.0424.

(3*S*,5*S*,6*S*,7*R*,10*S*)-3-Benzyloxycarbonylamino-6,7-epoxy-10-triethylsilyloxy-1-oxaspiro[4.5]deca-2,8-dione (25). To a solution of **11** (63.4 mg, 0.142 mmol) in THF (0.7 mL) at 0 °C was added dropwise a mixture of 30%-H₂O₂ (0.08 mL, 0.7 mmol) and 0.5*N*-LiOH (0.14 mL, 0.07 mmol) chilled at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. After quenching with sat. Na₂S₂O₃ and sat. NH₄Cl, the reaction mixture was extracted with EtOAc and washed with brine. The organic layer was dried over Na₂SO₄ and evaporated. The resulting residue was purified by preparative TLC (silica gel, hexane/EtOAc 2:1) to give **25** (50.6 mg, 77%): Colorless oil; ¹H NMR (CDCl₃, 500 MHz) δ 0.60 (q, *J* = 7.9 Hz, 6 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 2.19 (t, *J* = 11.3 Hz, 1 H), 2.30 (dd, *J* = 9.4, 19.2 Hz, 1 H), 2.69 (t, *J* = 11.3 Hz, 1 H), 2.84 (dd, *J* = 7.6, 19.2 Hz, 1 H), 3.43 (d, *J* = 3.0 Hz, 1 H), 3.80 (d, *J* = 3.0 Hz, 1 H), 4.41 (dt, *J* = 6.7, 9.8 Hz, 1 H), 4.47 (t, *J* = 7.6 Hz, 1 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 5.14 (d, *J* = 12.2 Hz, 1 H), 5.43 (d, *J* = 5.5 Hz, 1 H), 7.32-7.37 (m, 5 H); ¹³C NMR (125 MHz, CDCl₃) δ 4.6 (x3), 6.6 (x3), 30.4, 43.6, 51.3, 55.7, 58.4, 66.3, 67.4, 84.1, 128.1 (x2), 128.4, 128.6 (x2), 135.7, 155.8, 173.8, 201.0; EI-HRMS: *m/z* Calcd. for C₂₃H₃₁NO₇Si [*M*⁺] 461.1870, Found 461.1883.

(3*S*,5*S*,6*S*,7*S*,10*S*)-3-Benzyloxycarbonylamino-6,7-epoxy-8-hydroxy-10-triethylsilyloxy-1-oxaspiro[4.5]deca-2-one (26). To a solution of **25** (26.2 mg, 56.7 μmol) in MeOH (0.6 mL) at $\bar{20}$ °C was added NaBH₄ (2.56 mg, 67.7 μmol). After stirring for 5 h, the reaction mixture was quenched with sat. NH₄Cl and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated. The residue was purified by preparative TLC (silica gel, CH₂Cl₂/MeOH 20:1) to give a

S10

mixture of **26a** (6.51 mg, 25 %) and **26b** (5.00 mg, 19%): **26a**: colorless oil; ^1H NMR (500 MHz, $\text{C}_5\text{D}_5\text{N}$) δ 0.52 (q, $J = 7.9$ Hz, 6 H), 0.88 (t, $J = 7.9$ Hz, 9 H), 2.02 (ddd, $J = 6.7, 11.9, 14.3$ Hz, 1 H), 2.13 (dd, $J = 4.6, 14.3$ Hz, 1 H), 2.38 (dd, $J = 10.1, 12.8$ Hz, 1 H), 2.92 (dd, $J = 10.4, 12.8$ Hz, 1 H), 3.61 (t, $J = 4.0$ Hz, 1 H), 3.67 (d, $J = 4.0$ Hz, 1 H), 4.45-4.49 (m, 1 H), 4.69 (dd, $J = 4.6, 11.9$ Hz, 1 H), 5.00-5.06 (m, 1 H), 5.30 (s, 2 H), 7.23-7.32 (m, 3 H), 7.42 (d, $J = 7.3$ Hz, 2 H), 9.26 (bd, $J = 7.6$ Hz, 1 H); ^{13}C NMR (125 MHz, $\text{C}_5\text{D}_5\text{N}$) δ 4.9 (x3), 6.9 (x3), 31.1, 39.8, 52.0, 57.3, 59.8, 63.9, 66.8, 68.8, 86.2, 128.2 (x2), 128.3, 128.8 (x2), 137.5, 157.2, 175.5. **26b**: colorless oil; ^1H NMR (500 MHz, $\text{C}_5\text{D}_5\text{N}$) δ 0.57 (q, $J = 7.9$ Hz, 6 H), 0.90 (t, $J = 7.9$ Hz, 9 H), 2.03 (dt, $J = 10.4, 12.8$ Hz, 1 H), 2.40 (dd, $J = 10.1, 12.8$ Hz, 1 H), 2.38-2.44 (m, 1 H), 3.06 (dd, $J = 10.7, 12.5$ Hz, 1 H), 3.62 (d, $J = 3.4$ Hz, 1 H), 3.67 (d, $J = 3.4$ Hz, 1 H), 4.34 (dd, $J = 3.7, 12.8$ Hz, 1 H), 4.55-4.61 (m, 1 H), 4.99-5.04 (m, 1 H), 5.29 (s, 2 H), 7.23-7.43 (m, 5 H), 9.25 (bd, $J = 7.9$ Hz, 1 H); ^{13}C NMR (125 MHz, $\text{C}_5\text{D}_5\text{N}$) δ 4.9 (x3), 6.9 (x3), 31.3, 39.8, 52.0, 59.8, 60.2, 64.6, 66.8, 68.7, 86.2, 128.2 (x3), 128.8 (x2), 137.5, 157.1, 175.6.

(1S,2'S,4R,6S)-4-Acetoxy-1-(2'-benzyloxycarbonylamino-3'-hydroxypropyl)-2,3-epoxy-6-triethylsilyloxycyclohexan-1-ol (32). (2S,3S)-**32** (major product): colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 0.60 (q, $J = 7.9$ Hz, 6 H), 0.94 (t, $J = 7.9$ Hz, 9 H), 1.56 (ddd, $J = 8.5, 11.6, 13.7$ Hz, 1 H), 1.91 (dd, $J = 5.2, 15.5$ Hz, 1 H), 2.03-2.11 (m, 2 H), 2.10 (s, 3 H), 2.61 (bs, 1 H), 3.11 (bs, 1 H), 3.22 (d, $J = 3.4$ Hz, 1 H), 3.34 (d, $J = 3.4$ Hz, 1 H), 3.72 (dd, $J = 4.0, 11.6$ Hz, 1 H), 3.69-3.74 (m, 1 H), 3.78 (d, $J = 4.9, 11.3$ Hz, 1 H), 3.99-4.06 (m, 1 H), 5.09 (d, $J = 12.2$ Hz, 1 H), 5.10-5.14 (m, 2 H), 5.84 (bs, 1 H), 7.31-7.37 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 4.8 (x3), 6.8 (x3), 21.0, 32.7, 50.4, 57.0 (x2), 59.6, 66.5, 67.0, 70.2, 73.6, 128.1 (x2), 128.2, 12.5 (x2), 136.3, 156.9, 170.0. (2R,3R)-**32** (minor product): a colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 0.61 (q, $J = 7.9$ Hz, 6 H), 0.94 (t, $J = 7.9$ Hz, 9 H), 1.51 (dt,

$J = 11.0, 12.8$ Hz, 1 H), 1.69 (dddd, $J = 0.9, 3.4, 5.8, 12.5$ Hz, 1 H), 1.93-1.96 (m, 2 H), 2.06-2.12 (m, 1 H), 2.10 (s, 3 H), 3.21 (d, $J = 3.7$ Hz, 1 H), 3.40 (d, $J = 3.7$ Hz, 1 H), 3.54 (dd, $J = 3.4, 12.8$ Hz, 1 H), 3.71-3.77 (m, 1 H), 3.84-3.90 (m, 1 H), 4.01-4.07 (m, 1 H), 5.07-5.13 (m, 1 H), 5.12 (s, 2 H), 5.26 (ddd, $J = 1.8, 5.8, 11.0$ Hz, 1 H), 5.56 (bs, 1 H), 7.33-7.37 (m, 5 H).

(2*S*,3*aS*,4*S*,6*R*,7*R*,7*aR*)-6-Acetoxy-2-*tert*-butyldiphenylsilyloxymethyl-3*a*,4,7-trihydroxy-

2,3,3*a*,4,5,6,7,7*a*-octahydroindole (36). ^1H NMR (500 MHz, CD_3OD) δ 1.07 (s, 9 H), 1.50 (q, $J = 12.2$ Hz, 1 H), 1.70 (ddd, $J = 1.2, 3.7, 14.6$ Hz, 1 H), 2.06 (s, 3 H), 2.11 (dt, $J = 4.9, 12.5$ Hz, 1 H), 2.20 (dd, $J = 10.1, 14.6$ Hz, 1 H), 2.83 (dd, $J = 0.9, 9.8$ Hz, 1 H), 3.36 (t, $J = 9.8$ Hz, 1 H), 3.56-3.61 (m, 1 H), 3.74 (dd, $J = 5.5, 10.1$ Hz, 1 H), 3.78 (dd, $J = 5.8, 10.1$ Hz, 1 H), 3.88 (dd, $J = 4.9, 12.2$ Hz, 1 H), 4.66 (ddd, $J = 4.3, 10.1, 11.9$ Hz, 1 H), 7.38-7.46 (m, 6 H), 7.68-7.71 (m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.1, 21.1, 27.4 (x3), 35.0, 35.3, 57.8, 68.5, 71.5, 72.4, 73.2, 73.5, 84.4, 128.9 (x4), 131.0, 134.4 (x2), 136.8 (x4), 172.4; EI-HRMS: m/z Calcd for $\text{C}_{27}\text{H}_{37}\text{NO}_6\text{Si}$ [M^+] 499.2390, Found 499.2366.

Table S1. Comparison of the NMR Data of natural and synthetic scyphostatin, and 18 (in CD₃OD)^a

δ_H				δ_C			
pos.	natural	synthetic	18	pos.	natural	synthetic	
1	3.45	3.46	3.56	1	65.6	66.1	
	3.52	3.52	3.56		48.5	48.5	
2	4.05	4.05	4.23	2	40.3	40.3	
3	1.89	1.89	2.16	3	78.0	78.0	
	2.08	2.08	2.25		58.7	58.7	
4				4	49.8	49.7	
5	3.67	3.67	3.75	5	146.6	146.4	
6	3.59	3.59	3.55	6	132.5	132.6	
7	7.15	7.14	7.23	7	201.0	200.1	
8	6.07	6.08	6.05	8	169.0	169.1	
9				9	124.3	124.3	
1'				1'	142.9	142.9	
2'	5.89	5.90	5.78	2'	129.9	129.9	
3'	7.15	7.14	7.16	3'	141.9	141.9	
4'	6.25	6.26	6.27	4'	130.4	130.5	
5'	6.53	6.54	6.53	5'	146.4	146.7	
6'	6.15	6.15	6.15	6'	36.7	36.8	
7'	5.70	5.71	5.71	7'	45.7	45.7	
8'	2.35	2.35	2.35	8'	30.0	30.0	
9'	1.10	1.03	1.03	9'	50.1	50.1	
	1.33	1.34	1.34		134	134.1	
10'	1.59	1.59	1.59	10'	134.7	134.7	
11'	1.79	1.79	1.79	11'	35.9	35.9	
	1.89	1.89	1.90		32.6	32.2	
12'				12'	13.0	13.0	
13'	4.84	4.85	4.85	13'	22.0	22.0	
14'	2.27	2.26	2.26	14'	16.9	16.9	
15'	1.19	1.19	1.19	15'	20.4	20.4	
	1.33	1.34	1.34		22.4	22.4	
16'	0.86	0.86	0.86	16'			
17'	0.91	0.92	0.92	17'			
18'	1.54	1.54	1.54	18'			
19'	0.83	0.83	0.83	19'			
20'	1.00	1.00	1.00	20'			

^a Chemical shifts are referenced to $\delta = 3.31$ for ^1H NMR and $\delta = 49.49$ for ^{13}C NMR.

13

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16

17

24

8.5
 8.2
 7.8
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26a

100

1000

100

100

100

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