

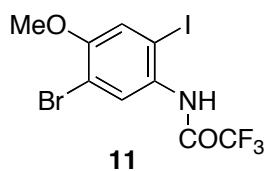
Stereocontrolled Total Synthesis of (–)-Eudistomin C

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General. All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dichloromethane, toluene, and benzene were distilled from calcium hydride. Dehydrated tetrahydrofuran, diethyl ether, acetonitrile, *N,N*-dimethylformamide, methanol, and ethanol were purchased from Kanto Chemical Co., Inc. and stored over molecular sieves 3A or 4A. All other reagents were commercially available and used without further purification. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40–100 μ m) purchased from Kanto Chemical Co., Inc. 1 H and 13 C NMR were recorded on a JEOL LA-400 MHz spectrometer. All 1 H NMR spectra are reported in δ units, ppm downfield from tetramethylsilane internal standard. All 13 C NMR spectra are reported in ppm relative to the central line of the triplet for CDCl_3 at 77.0 ppm. Infrared spectra (IR) were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer. High resolution mass spectra were obtained on a JEOL JMS-GCmate MS-DIP20 quadrupole at 70 eV using direct probe insertion at temperatures of 70 to 330 °C. Fast atom bombardment (FAB) mass spectra were obtained with 3-nitrobenzyl alcohol and polyethylene glycol 200 or 400 or 600 as the matrix. Optical rotations were measured on a JASCO DIP-1000 Digital Polarimeter at room temperature, using the sodium D line. Melting points, determined on a Yanaco Micro Melting Point Apparatus, are uncorrected.

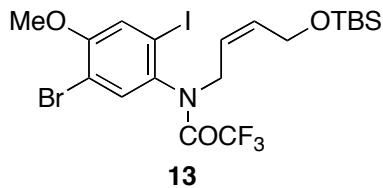
***N*-(5-Bromo-2-iodo-4-methoxy-phenyl)-2,2,2-trifluoro-acetamide (11)**



To a solution of 4-bromo-5-methoxy-2-nitrobenzenamine (**10**)¹ (7.00 g, 28.3 mmol) and H_2SO_4 (7.00 g) in CH_3CN (250 ml) was added NaNO_2 (3.91 g, 56.7 mmol) in H_2O (25 ml) at 0 °C. After stirring for 15 minutes, KI (18.8 g, 115 mmol) in H_2O (25 ml) was added to the reaction mixture at 0 °C. The reaction mixture was then allowed to warm up to room temperature and was stirred for 15 minutes. The mixture was poured into sat. $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with EtOAc . The extracts were washed with brine, dried over MgSO_4 , filtrated, and evaporated. The residue was dissolved EtOH

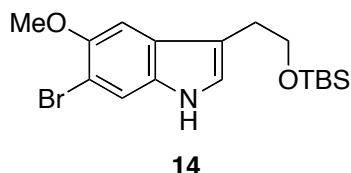
(75 ml) and to the solution were added Fe powder (15.9 g, 283 mmol), FeCl_2 (8.23 g, 28.3 mmol), and 1 N HCl (15 ml). The reaction mixture was heated at 80 °C for 2 hours. After cooling to room temperature, the mixture was filtrated and the filtration was poured into sat. NaHCO_3 and extracted with EtOAc . The extracts were washed with brine, dried over MgSO_4 , filtered, and evaporated. The residue was dissolved in CH_2Cl_2 (75 ml) and to the solution were added pyridine (4.6 ml, 56.8 mmol) and TFAA (4.0 ml, 28.4 mmol) at 0 °C. The reaction mixture was poured into sat. NaHCO_3 and extracted with CH_2Cl_2 . The extracts were washed with brine, dried over MgSO_4 . Filtration and evaporation afforded a crude product as brown solid, which was washed with Et_2O to give **11** (7.50 g, 62%) as a white solid. IR (film, cm^{-1}) 3356, 1700, 1530, 1163, 1061, 873, 794 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.31 (s, 1 H), 8.05 (br s, 1 H), 7.28 (s, 1 H), 3.90 (s, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 154.8, 129.9, 127.1, 121.6, 117.2, 114.4, 112.8, 89.4, 56.9; HRMS (FAB): calcd for $\text{C}_9\text{H}_6\text{BrF}_3\text{INO}_2$ 422.8579, found 422.8576.

N-(5-Bromo-2-iodo-4-methoxy-phenyl)-N-[4-(*tert*-butyl-dimethyl-silanyloxy)-but-2-enyl]-2,2,2-trifluoro-acetamide (13)



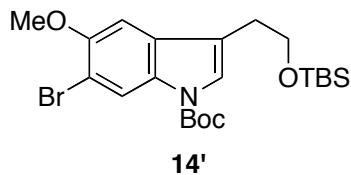
To a solution of **11** (4.38 g, 10.4 mmol), alcohol **12** (2.51 g, 12.5 mmol) and PPh_3 (4.09 g, 15.6 mmol) in benzene (30 ml) was added DEAD (40% in toluene) (7.1 ml, 15.6 mmol) at 5 °C under an argon atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 15 minutes. After removal of solvent on a rotary evaporator, the residue was purified by flash column chromatography on silica gel (5-10% EtOAc in hexane, gradient elution) to give **13** (5.65 g, 90%). IR (film) 2954, 2856, 1707, 1485, 1205, 1069, 838, 778 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.35 (br s, 2 H), 5.79-5.69 (m, 1 H), 5.53-5.45 (m, 1 H), 4.87 (dd, J = 6.6, 14.7 Hz, 1 H), 4.09 (dd, J = 5.6, 13.5 Hz, 1 H), 4.01 (ddd, J = 5.6, 13.5 Hz, 1 H), 3.80 (dd, J = 8.3, 14.7 Hz, 1 H), 0.85 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 156.7, 135.9, 134.6, 134.3, 122.1, 121.9, 117.5, 114.6, 111.6, 98.5, 59.4, 56.9, 47.5, 26.0, 18.4, -5.2; HRMS (FAB): calcd for $\text{C}_{19}\text{H}_{26}\text{BrF}_3\text{INO}_3\text{Si}$ 606.9862, found 606.9861.

6-Bromo-3-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-5-methoxy-1*H*-indole (14)



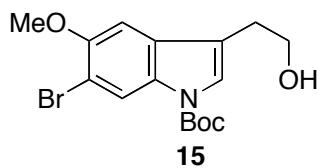
To a solution of **13** (5.32 g, 8.75 mmol), benzyltriethylammonium chloride (1.99 g, 8.75 mmol), and Et₃N (3.7 ml, 26.3 mmol) in DMF (30 ml) was added Pd(OAc)₂ (197 mg, 0.875 mmol) at room temperature under an argon atmosphere. The mixture was heated at 80 °C for 30 minutes. After cooled to room temperature, the mixture was diluted with EtOAc, washed with brine three times, and dried over MgSO₄. Filtration and concentration on a rotary evaporator afforded a crude product. The crude product was purified by flash column chromatography on silica gel (5-20% EtOAc in hexane, gradient elution) to give **14** (2.22 g, 66%). IR (film) 3418, 2952, 2929, 1472, 1093, 835, 777 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.92 (br s, 1 H), 7.49 (s, 1 H), 7.03 (s, 1 H), 6.97 (s, 1 H), 3.89 (s, 3 H), 3.84 (t, *J* = 7.1 Hz, 2 H), 2.91 (t, *J* = 7.1 Hz, 2 H), 0.87 (s, 9 H), 0.03 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 149.8, 131.4, 127.5, 123.3, 115.5, 113.1, 107.2, 101.0, 63.7, 56.8, 25.9, 18.4, 5.28, -28.9; HRMS (FAB): calcd for C₁₇H₂₆BrNO₂Si 383.0916, found 383.0900.

6-Bromo-3-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-5-methoxy-indole-1-carboxylic acid *tert*-butyl ester (14')



To a solution of **14** (2.11 g, 5.49 mmol) in CH₂Cl₂ (15 ml) were added Boc₂O (1.80 g, 8.23 mmol) and DMAP (67 mg, 0.549 mmol) at room temperature. After stirring for 20 minutes, the reaction mixture was diluted with CH₂Cl₂, washed with sat. NH₄Cl, brine, and dried over MgSO₄. Filtration and concentration on a rotary evaporator afforded a crude product. The crude product was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give Boc protected indole derivative **14'** (2.66 g, quant.). IR (film) 2954, 1733, 1469, 1281, 1086, 833, 775 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.38 (br s, 1 H), 7.39 (s, 1 H), 6.98 (s, 1 H), 3.94 (s, 3 H), 3.88 (t, *J* = 6.8 Hz, 2 H), 2.86 (t, *J* = 6.8 Hz, 2 H), 1.66 (s, 9 H), 0.90 (s, 9 H), 0.03 (s, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ 151.9, 149.4, 130.8, 130.1, 124.1, 119.9, 117.6, 108.9, 101.1, 83.7, 62.8, 56.6, 28.4, 28.2, 25.9, 18.4, -5.3; HRMS (FAB): calcd for C₂₂H₃₄BrNO₄Si 483.1440, found 483.1441.

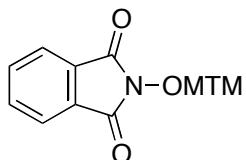
6-Bromo-3-(2-hydroxy-ethyl)-5-methoxy-indole-1-carboxylic acid *tert*-butyl ester (15)



To a solution of **14'** (4.43 g, 9.15 mmol) in MeOH (50 ml)-CH₂Cl₂ (20 ml) was added CSA (425 mg, 1.83 mmol) at room temperature. After stirring for 30 minutes, Et₃N (0.18 ml, 1.24 mmol) was

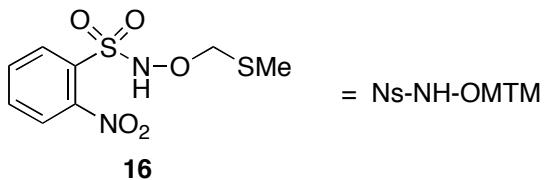
added to the reaction mixture and solvent was removed on a rotary evaporator to afford a crude product. The crude product was purified by flash column chromatography on silica gel (40-60% EtOAc in hexane, gradient elution) to give **15** (3.27 g, 97%). IR (film) 2988, 2940, 1730, 1469, 1384, 1281, 1151, 1085, 1048 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.36 (br s, 1 H), 7.42 (s, 1 H), 6.98 (s, 1 H), 3.93 (s, 3 H), 3.92-3.88 (br s, 2 H), 2.92 (t, *J* = 7.4 Hz, 2 H), 1.66 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 152.1, 149.4, 130.5, 130.4, 124.3, 120.1, 116.9, 109.3, 101.1, 84.0, 62.1, 56.7, 28.4, 28.2; HRMS (FAB): calcd for C₁₆H₂₀BrNO₄ 369.0576, found 369.0572.

2-Methylsulfanylmethoxy-isoindole-1,3-dione



To a stirred solution of *N*-hydroxyphthalimide (9.74 g, 59.7 mmol) in DMF (140 ml) was added NaH (2.39 g, 59.7 mmol) at 0 °C under an argon atmosphere. After stirring for 15 minutes, NaI (8.95 g, 59.7 mmol) and chloromethyl methyl sulfide (5.0 ml, 59.7 mmol) were added to the reaction mixture at 0 °C. After stirring for 30 minutes at 60 °C, the reaction mixture was poured into sat. NH₄Cl, and extracted with EtOAc. The extracts were washed with brine, dried over MgSO₄, filtrated and evaporated under reduced pressure. The crude solid was washed with Et₂O to afford MTM protected *N*-hydroxyphthalimide (12.7 g, 95%) as white solid. IR (film) 2925, 1796, 1730, 1371, 1183, 1081, 966, 876, 775 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.85 (dd, *J* = 2.9, 5.4 Hz, 2 H), 7.76 (dd, *J* = 2.9, 5.4 Hz, 1H), 5.29 (s, 2 H), 2.39 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.7, 134.5, 128.9, 123.6, 82.5, 15.0; HRMS (FAB): calcd for C₁₀H₉NO₃S 223.0303, found 223.0300.

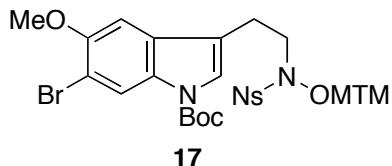
N-Methylsulfanylmethoxy-2-nitro-benzenesulfonamide (**16**)



To a solution of the MTM protected *N*-hydroxyphthalimide (6.47 g, 29.0 mmol) in THF (100 ml) was added H₂NNH₂·H₂O (1.73 ml, 31.9 mmol) at room temperature under an argon atmosphere. After stirring for 30 minutes, pyridine (4.7 ml, 58.0 mmol) and *o*-nitrobenzenesulfonyl chloride (6.43 g, 29.0 mmol) were added and the resulting solution was stirred for an hour. The reaction mixture was then poured into sat. NH₄Cl and extracted with EtOAc. The extracts were dried over MgSO₄, filtrated, and evaporated under reduced pressure. Compound **16** (4.00 g, 50%) was obtained by recrystallization (CH₂Cl₂-hexane). Mp 131-133 °C; IR (film) 3231, 1593, 1545, 1363,

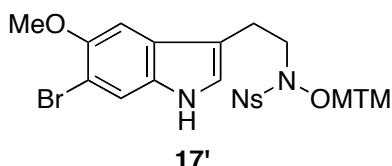
1174, 783, 738 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.27 (br s, 1 H), 8.22 (dd, J = 1.7, 6.4 Hz, 1 H), 7.92 (dd, J = 1.7, 6.4 Hz, 1 H), 7.85 (ddd, J = 1.7, 6.4, 9.3 Hz, 1 H), 7.82 (ddd, J = 1.7, 6.4, 9.3, 1 H), 5.11 (s, 2 H), 2.61 (s, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 148.5, 134.9, 133.6, 132.9, 130.3, 125.7, 82.6, 15.7; HRMS (FAB): calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3\text{S}$ 278.0031, found 278.0036; Anal. calcd for C, 34.53; H, 3.62; N, 10.07. Found, C, 34.40; H, 3.58; N, 9.81.

6-Bromo-5-methoxy-3-{2-[methylsulfanylmethoxy-(2-nitro-benzenesulfonyl)-amino]-ethyl}-indole-1-carboxylic acid *tert*-butyl ester (17)



To a solution of indole derivative **15** (3.27 g, 8.83 mmol), **16** (2.71 g, 9.72 mmol) and PPh_3 (3.01 g, 13.2 mmol) in benzene (30 ml) was added DEAD (40% in toluene) (5.2 ml, 13.2 mmol) at 5 °C under an argon atmosphere. After stirring for 15 minutes at room temperature, solvent was removed on a rotary evaporator and the residue was purified by flash column chromatography on silica gel (50-100% CH_2Cl_2 in hexane, gradient elution) to give **17** (5.57 g, quant.). IR (film) 2979, 1732, 1375, 1281, 1177, 1090, 851, 751 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.35 (br s, 1 H), 8.04 (dd, J = 1.5, 7.8 Hz, 1 H), 7.78 (ddd, J = 1.5, 7.8 Hz, 1 H), 7.73 (ddd, J = 1.5, 7.8, 9.0 Hz, 1 H), 7.59 (dd, J = 1.5, 7.8 Hz, 1 H), 7.43 (s, 1 H), 6.96 (s, 1 H), 5.13 (s, 2 H), 3.94 (s, 3 H), 3.51 (br s, 2 H), 3.09 (t, J = 7.6 Hz, 2 H), 2.29 (s, 3 H), 1.66 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 152.0, 149.6, 149.2, 135.2, 132.6, 132.4, 131.2, 130.0, 125.9, 124.1, 123.8, 123.7, 120.0, 116.3, 109.2, 100.8, 84.0, 82.7, 56.6, 52.9, 28.1, 23.1, 16.1; HRMS (FAB): calcd for $\text{C}_{24}\text{H}_{28}\text{BrN}_3\text{O}_8\text{S}_2$ 629.0501, found 629.0487.

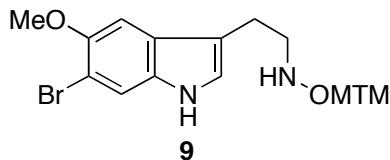
***N*-[2-(6-Bromo-5-methoxy-1*H*-indol-3-yl)-ethyl]-*N*-methylsulfanylmethoxy-2-nitro-benzenesulfonamide (17')**



To a solution of Boc-protected indole derivative **17** (1.00 g, 1.59 mmol) and dimethyl sulfide (1.2 ml, 15.9 mmol) in CH_2Cl_2 (5 ml) was added TFA (5 ml) at room temperature under an argon atmosphere. After stirring for 30 minutes, the reaction mixture was poured into sat. NaHCO_3 , and extracted with CH_2Cl_2 twice. The extracts were washed with brine, dried over MgSO_4 , filtered, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (40-60% EtOAc in hexane, gradient elution) afforded **17'** (817 mg, 97%). IR (film) 3432, 2925,

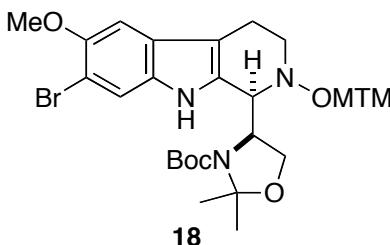
1547, 1374, 1176, 1042, 851, 750 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.03 (dd, J = 1.5, 7.8 Hz, 1 H), 8.00 (br s, 1 H), 7.77 (ddd, J = 1.5, 7.8, 9.0 Hz, 1 H), 7.70 (ddd, J = 1.5, 7.8, 9.0 Hz, 1 H), 7.55 (dd, J = 1.5, 7.8 Hz, 1 H), 7.53 (s, 1 H), 7.06 (s, 1 H), 7.01 (s, 1 H), 5.09 (s, 2 H), 3.92 (s, 3 H), 3.52 (br s, 2 H), 3.13 (t, J = 7.6 Hz, 2 H), 2.27 (s, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 150.1, 149.6, 135.1, 132.3, 131.4, 131.2, 126.9, 126.0, 123.7, 123.4, 115.7, 111.9, 107.6, 100.6, 82.6, 56.8, 53.5, 23.1, 16.0; HRMS (FAB): calcd for $\text{C}_{19}\text{H}_{20}\text{BrN}_3\text{O}_6\text{S}_2$ 528.9977, found 528.9982.

***N*-[2-(6-Bromo-5-methoxy-1*H*-indol-3-yl)-ethyl]-*O*-methylsulfanylmethyl-hydroxylamine (9)**



To a solution of indole derivative **17'** (4.04 g, 7.63 mmol) and pulverized K_2CO_3 (3.17 g, 22.9 mmol) in DMF (20 ml) was added PhSH (1.2 ml, 11.4 mmol) at room temperature under an argon atmosphere. After stirring for 45 minutes at ambient temperature, the reaction mixture was poured into brine and extracted with EtOAc. The extracts were washed with brine twice, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (30-60% EtOAc in hexane, gradient elution) afforded the indole segment **9** (2.47 g, 94%). IR (film) 3418, 2920, 2856, 1473, 1234, 1043, 831, 772 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.00 (br s, 1 H), 7.54 (s, 1 H), 7.07 (s, 1 H), 7.01 (s, 1 H), 4.84 (s, 2 H), 3.93 (s, 3 H), 3.29 (t, J = 6.8 Hz, 2 H), 2.97 (t, J = 6.8 Hz, 2 H), 2.21 (s, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 149.9, 131.6, 127.2, 123.3, 115.6, 113.2, 107.5, 100.9, 78.9, 56.9, 52.0, 22.9, 14.7; HRMS (FAB): calcd for $\text{C}_{13}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S}$ 344.0194, found 344.0189.

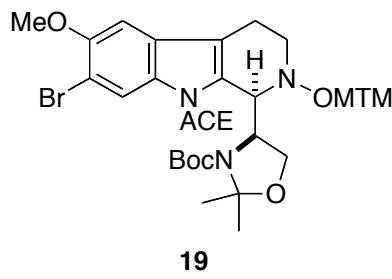
(4*S*)-4-[(1*S*)-7-Bromo-6-methoxy-2-methylsulfanylmethoxy-2,3,4,9-tetrahydro-1*H*- β -carbolin-1-yl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (18)



To a solution of the indole fragment **9** (1.00 g, 2.91 mmol) and the Garner aldehyde **8²** (858 mg, 3.49 mmol) in toluene (15 ml) was added dichloroacetic acid (24 μl , 0.291 mmol) at 0 °C under an argon atmosphere. After stirring for 15 minutes at 0 °C, the reaction mixture was diluted with EtOAc, washed with sat. NaHCO_3 , and dried over MgSO_4 . Filtration and concentration on a rotary evaporator afforded a crude product (dr = 11 : 1, determined by ^1H NMR). The crude product was

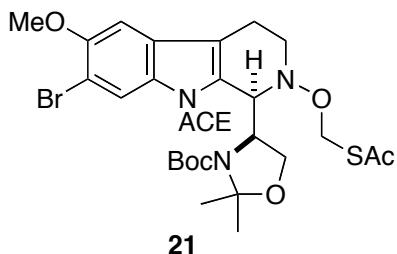
purified by flash column chromatography on silica gel (15% Et₂O in hexane) to give **18** (1.62 g, quant.). $[\alpha]_D^{24} +5.48^\circ$ (c 0.76, CHCl₃); IR (film) 3469, 3359, 2978, 2981, 1699, 1366, 1171, 852, 759 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.26 (br s, 1 H), 7.50 (s, 1 H), 6.94 (s, 1 H), 4.85 (d, *J* = 11.6 Hz, 1 H), 4.81 (d, *J* = 11.6 Hz, 1 H), 4.70-4.64 (m, 1 H), 4.63-4.57 (m, 1 H), 4.15-4.06 (m, 1 H), 3.91 (s, 3 H), 3.83-3.77 (m, 1 H), 3.76-3.67 (m, 1 H), 3.16-3.04 (m, 1 H), 2.96-2.84 (m, 1 H), 2.82-2.72 (m, 1 H), 2.26 (s, 3 H), 1.54 (s, 9 H), 1.50 (s, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ 150.1, 131.8, 131.5, 126.1, 115.3, 110.2, 106.8, 100.6, 95.1, 81.2, 77.9, 64.9, 64.7, 63.8, 56.8, 52.1, 28.4, 26.9, 19.8, 15.6; HRMS (FAB): calcd for C₂₄H₃₅BrN₃O₅S ([M+H]⁺) 556.1480, found 556.1485.

(1S)-7-Bromo-1-[(4S)-3-*tert*-butoxycarbonyl-2,2-dimethyl-oxazolidin-4-yl]-6-methoxy-2-methylsulfanylmethoxy-1,2,3,4-tetrahydro- β -carboline-9-carboxylic acid 1-chloro-ethyl ester (19)



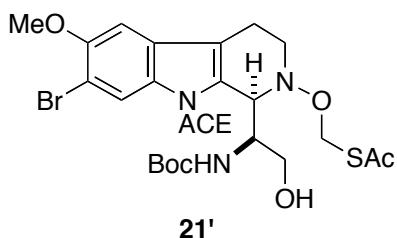
To a solution of **18** (2.01 g, 3.62 mmol) in THF (20 ml) was added *n*-BuLi (3.0 ml, 1.56 M hexane solution) at -78 °C under an argon atmosphere. After stirring for 15 minutes, α -chloroethyl chloroformate (0.58 ml, 5.43 mmol) was added to the reaction mixture at -78 °C and the resulting mixture was allowed to warm up to room temperature. After stirring for 30 minutes at room temperature, the reaction mixture was poured into sat. NH₄Cl and extracted with EtOAc. The extracts were washed with brine, dried over MgSO₄, filtrated, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (15-30% EtOAc in hexane, gradient elution) gave ACE-protected compound **19** (2.13 g, 89%). $[\alpha]_D^{23} +4.28^\circ$ (c 0.36, CHCl₃); IR (film) 2978, 2936, 1743, 1697, 1468, 1377, 1083, 855, 756 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.27 (br s, 1 H), 6.88 (s, 1 H), 6.78-6.76 (m, 1 H), 4.89 (d, *J* = 11.5 Hz, 1 H), 4.84 (d, *J* = 11.5 Hz, 1 H), 4.58-4.55 (m, 1 H), 4.45-4.40 (m, 1 H), 4.33-4.03 (m, 2 H), 3.94 (s, 3 H), 3.73-3.63 (m, 1 H), 3.53-3.45 (m, 1 H), 3.01-2.89 (m, 1 H), 2.48 (dd, *J* = 6.0, 16.4 Hz, 1 H), 2.21 (s, 3 H), 2.03 (d, *J* = 5.6 Hz, 3 H), 1.55-1.45 (m, 15 H); ¹³C NMR (CDCl₃, 100 MHz) δ 153.1, 152.6, 148.9, 131.7, 129.8, 120.8, 116.9, 108.6, 100.1, 83.3, 81.0, 79.8, 77.8, 64.8, 58.7, 56.7, 56.5, 53.4, 28.3, 27.7, 25.3, 16.8, 14.9; HRMS (FAB) calcd for C₂₇H₃₈BrClN₃O₇S ([M+H]⁺) 662.1302, found 662.1310.

(1S)-2-Acetylsulfanylmethoxy-7-bromo-1-[(4S)-3-*tert*-butoxycarbonyl-2,2-dimethyl-oxazolidin-4-yl]-6-methoxy-1,2,3,4-tetrahydro- β -carboline-9-carboxylic acid 1-chloro-ethyl ester (21)



To a solution of compound **19** (1.67 g, 2.52 mmol) in CH_2Cl_2 (20 ml) was added sulfonyl chloride (0.11 ml, 1.26 mmol) over 5 minutes at -78°C under an argon atmosphere. After stirring for 15 minutes at -78°C , the reaction mixture was allowed to warm up to room temperature and stirred for 15 minutes at that temperature. After removal of solvent on a rotary evaporator, the residue containing compound **20** was dissolved in CH_2Cl_2 (20 ml), to which were added *i*-Pr₂NEt (1.8 ml, 10.1 mmol) and AcSH (0.36 ml, 5.05 mmol) at room temperature and stirred. The mixture was then poured into sat. NaHCO_3 and extracted with CH_2Cl_2 . The extracts were washed with brine, dried over MgSO_4 , filtrated, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (20-40% EtOAc in hexane, gradient elution) afforded thiol acetate **21** (1.65 g, 95%). $[\alpha]_D^{23} -0.10^\circ$ (c 0.32, CHCl_3); IR (film) 2979, 2934, 1742, 1700, 1468, 1249, 1138, 1083, 856, 756 cm^{-1} ; ¹H NMR (CDCl_3 , 400 MHz) δ 8.22 (br s, 1 H), 5.85 (s, 1 H), 6.76 (q, *J* = 5.9 Hz, 1 H), 5.28 (d, *J* = 11.2 Hz, 1 H), 5.22 (d, *J* = 11.2 Hz, 1 H), 4.56 (d, *J* = 6.8 Hz, 1 H), 4.39-4.20 (m, 2 H), 4.19-4.06 (m, 1 H), 3.94 (s, 1 H), 3.74-3.61 (m, 1 H), 3.49-3.33 (m, 1 H), 2.98-2.84 (m, 1 H), 2.47-2.41 (m, 1 H), 2.04 (d, *J* = 5.9 Hz, 3 H), 1.59-1.43 (m, 12 H); ¹³C NMR (CDCl_3 , 100 MHz) δ 194.5, 153.1, 152.8, 149.1, 129.9, 120.9, 116.9, 115.3, 108.7, 100.6, 100.1, 83.4, 80.2, 79.9, 71.6, 70.8, 64.7, 58.9, 56.8, 56.6, 31.1, 28.4, 27.7, 25.4, 16.7; HRMS (FAB) calcd for $\text{C}_{28}\text{H}_{38}\text{BrClN}_3\text{O}_8\text{S}$ ($[\text{M}+\text{H}]^+$) 690.1251, found 690.1252.

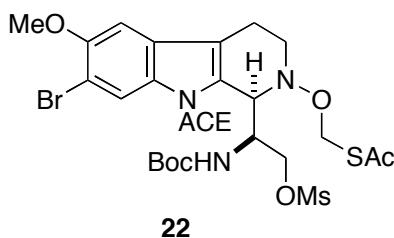
(1S)-2-Acetylsulfanylmethoxy-7-bromo-1-[(4S)-1-*tert*-butoxycarbonylamino-2-hydroxy-ethyl]-6-methoxy-1,2,3,4-tetrahydro- β -carboline-9-carboxylic acid 1-chloro-ethyl ester (21')



Acetonide **21** (1.98 g, 2.86 mmol) was dissolved in a mixture of AcOH (10 ml), THF (5 ml), and H_2O (2.5 ml) and the mixture was heated at 80°C . After stirring for 15 minutes at that temperature, the mixture was cooled to room temperature and diluted with toluene. Removal of solvent and purification by flash column chromatography on silica gel (50-80% EtOAc in hexane, gradient

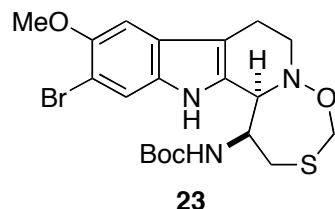
elution) gave alcohol **21'** (1.14 g, 61%). $[\alpha]_D^{24} -58.8^\circ$ (c 0.83, CHCl_3); IR (film) 3403, 2976, 2940, 1742, 1699, 1468, 1138, 1044, 871, 755 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.31 (br s, 1 H), 6.84 (s, 1 H), 6.83-6.73 (m, 1 H), 5.27 (br s, 2 H), 5.06-4.91 (m, 1 H), 3.85-3.78 (m, 1 H), 3.65 (dd, $J = 6.1, 14.6$ Hz, 1 H), 3.61-3.23 (m, 1 H), 3.01-2.85 (m, 1 H), 2.62-2.52 (m, 1 H), 2.44 (s, 3 H), 2.04 (d, $J = 5.9$ Hz, 3 H), 1.19-0.88 (m, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 194.6, 154.9, 152.6, 148.9, 129.3, 120.9, 120.8, 117.0, 116.9, 109.1, 100.0, 83.4, 79.3, 71.5, 65.7, 64.7, 56.6, 52.6, 47.3, 31.1, 27.8, 25.4, 16.5; HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{34}\text{BrClN}_3\text{O}_8\text{S}$ ($[\text{M}+\text{H}]^+$) 650.0938, found 650.0946.

(1*S*)-2-Acetylsulfanylmethoxy-7-bromo-1-[(4*S*)-1-*tert*-butoxycarbonylamino-2-methanesulfonyloxy-ethyl]-6-methoxy-1,2,3,4-tetrahydro- β -carboline-9-carboxylic acid 1-chloro-ethyl ester (22)



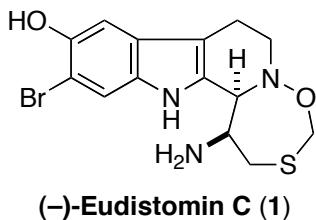
To a solution of alcohol **21'** (1.09 g, 1.68 mmol) and *i*-Pr₂NEt (0.59 ml, 3.36 mmol) in CH_2Cl_2 (20 ml) was added methanesulfonyl chloride (0.20 ml, 2.52 mmol) and the mixture was stirred at 0 °C for five minutes. The reaction mixture was then diluted with CH_2Cl_2 , washed with sat. NaHCO_3 , and dried over MgSO_4 . Filtration and concentration on a rotary evaporator afforded a crude product. The crude product was purified by flash column chromatography on silica gel (60% EtOAc in hexane) to give mesylate **22** (1.19 g, 98%). $[\alpha]_D^{24} -4.90^\circ$ (c 0.27, CHCl_3); IR (film) 3389, 2978, 1742, 1700, 1468, 1362, 1175, 1043, 834, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.27 (br s, 1 H), 6.86 (s, 1 H), 6.83-6.73 (m, 1 H), 5.24 (d, $J = 11.2$ Hz, 1 H), 5.20 (d, $J = 11.2$ Hz, 1 H), 4.98-4.79 (m, 1 H), 4.71-4.51 (m, 2 H), 4.50-4.38 (m, 1 H), 3.93 (s, 3 H), 3.59-3.59 (m, 1 H), 3.33-3.17 (m, 1 H), 3.08 (s, 3 H), 2.98-2.85 (m, 1 H), 2.57 (dd, $J = 4.4, 16.4$ Hz, 1 H), 2.43 (s, 3 H), 2.06 (d, $J = 5.6$ Hz, 3 H), 1.17-1.07 (m, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 194.3, 154.9, 152.8, 148.9, 129.3, 120.9, 120.8, 118.2, 109.3, 109.1, 100.3, 83.6, 80.1, 71.4, 69.6, 62.9, 56.6, 53.5, 52.0, 37.8, 31.1, 27.9, 25.4, 16.8; HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{36}\text{BrClN}_3\text{O}_{10}\text{S}_2$ ($[\text{M}+\text{H}]^+$) 728.0713, found 728.0733.

(-)-10-*N*-*tert*-Butoxycarbonyl-*O*-methyl-eudistomin C (23)



To a solution of mesylate **22** (1.15 g, 1.58 mmol) in MeOH (10 ml) was added pulverized K_2CO_3 (1.09 g, 7.90 mmol) at room temperature under an argon atmosphere and the reaction mixture was heated at 80 °C for 15 minutes. The mixture was then cooled to room temperature, diluted with sat. NH_4Cl , and extracted with CH_2Cl_2 . The extracts were washed with brine, dried over MgSO_4 , filtration, and concentration on a rotary evaporator afforded a crude product. The crude product was purified by flash column chromatography on silica gel (50-60% EtOAc in hexane, gradient elution) to give 10-Boc-*O*-methyl-eudistomin C (**23**) (498 mg, 65%). $[\alpha]_D^{23} -85.8^\circ$ (c 0.31, CHCl_3); IR (film) 3338, 1685, 1497, 1164, 1040, 829, 757 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.58 (br s, 1 H), 7.46 (s, 1 H), 6.89 (s, 1 H), 4.93 (d, $J = 8.8$ Hz, 1 H), 4.79 (d, $J = 8.8$ Hz, 1 H), 4.67-4.59 (m, 1 H), 4.10 (br s, 1 H), 3.90 (s, 1 H), 3.63-3.56 (m, 1 H), 3.30 (d, $J = 14.4$ Hz, 1 H), 3.19-3.06 (m, 1 H), 3.00-2.88 (m, 1 H), 2.85-2.72 (m, 2 H), 1.19 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 156.1, 149.8, 132.4, 132.1, 125.9, 115.7, 109.3, 106.7, 100.3, 80.1, 70.9, 69.5, 56.7, 54.8, 48.5, 32.4, 28.0, 20.7; HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{26}\text{BrN}_3\text{O}_4\text{S}$ 483.0827, found 483.0825.

(-)-Eudistomin C (**1**)



To a solution of **23** (27.0 mg, 0.0557 mmol) in CH_2Cl_2 (5 ml) was added BBr_3 (1.0 M CH_2Cl_2 solution, 0.28 ml) at -78 °C under an argon atmosphere. After stirring for 30 minutes at -78 °C, the mixture was warmed to room temperature and stirred for additional 2 hours. The solution was cooled to -78 °C, quenched with 5% aq. Na_2CO_3 , and extracted with CHCl_3 . The extracts were dried over Na_2SO_4 , filtrated, and evaporated to give (-)-eudistomin C (**1**) (16.1 mg, 78%). $[\alpha]_D^{25} -51.7^\circ$ (c 0.43, MeOH); IR (film) 3208, 2921, 2850, 1455, 1266, 1137, 1038, 854, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 8.18 (br s, 1 H), 7.44 (s, 12 H), 6.97 (s, 1 H), 4.91 (d, $J = 8.8$ Hz, 1 H), 4.77 (d, $J = 8.8$ Hz, 1 H), 4.06 (br s, 1 H), 3.65-3.59 (m, 1 H), 3.57-3.51 (m, 1 H), 3.29 (d, $J = 14.4$ Hz, 1 H), 3.15-3.04 (m, 1 H), 2.92-2.80 (m, 1 H), 2.77-2.66 (m, 2 H), 2.43 (br s, 2 H); ^{13}C NMR (CD_3OD , 100 MHz) δ 148.3, 134.2, 132.7, 127.9, 115.9, 110.8, 106.8, 104.5, 71.9, 70.3, 54.9, 51.1, 33.3, 21.5; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{17}\text{BrN}_3\text{O}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 370.0224, found 370.0234.

References

- (1) Kauffman, J. M.; Litak, P. T. *J. Heterocyclic Chem.* **1995**, 32, 1541.
- (2) The Garner aldehyde was prepared according to the literature method from (R)-serine. (a) Garner, P.; Park, J. M. *Org. Synth.* **1992**, 70, 18. (b) Dondoni, A.; Perrone, D. *Org. Synth.* **1999**, 77, 64.