Supporting information

Total Synthesis of (±)-Chamobtusin A

Hikaru Suzuki and Sakae Aoyagi*

School of Pharmacy, Tokyo University of Pharmacy & Life Sciences
Horinouchi, Hachioji, Tokyo 192-0392, Japan
aoyagis@toyaku.ac.jp

General Methods. Reported melting points are uncorrected. Unless otherwise stated $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ or CD$_3$OD, on a 400 MHz instrument. Proton chemical shifts are given in $\delta$ (ppm) relative to internal CHCl$_3$ (7.26 ppm) or CD$_3$OH (4.78 ppm). Carbon chemical shifts are given relative to CDCl$_3$ (77.05 ppm) or CD$_3$OD (49.3 ppm). Analytical TLC was carried out with precoated silica gel 60F$_{254}$ plates (Merck). Flash column chromatography was performed on Silica gel 60N (spherical, neutral, 40-50 mm, Kanto Chemical Co., Inc.).

Methyl (1$´$S*,4a$´$S*,8a$´$S*)-5$,5$´$,8a$´$-Trimethyloctahydro-1$´$H-spiro[1,3]dioxolane-2,2$´$-naphthalene-1$´$-carboxylate. Ethylene glycol (1.1 mL, 19.6 mmol) and trimethylsilyl chloride (2.1 mL, 15.7 mmol) were added to a solution of 4 (990 mg, 3.92 mmol) in dry CH$_2$Cl$_2$ (8.0 mL) at room temperature. The mixture was heated at reflux for 23 h. After cooling, the reaction was quenched with saturated aqueous NaHCO$_3$ (8.0 mL) at 0 °C, and the resulting mixture was extracted with Et$_2$O (3 x 8.0 mL). The combined extracts were washed with brine, then dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 10:1) to give the title compound (1.14 g, 98%) as white crystals. mp 78-79 °C (from hexane); IR (KBr) 1735 cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 0.66 (3H, s), 0.82 (3H, s), 0.99-1.02 (1H, m), 1.14 (3H, s), 1.02-1.09 (1H, m), 1.34-1.41 (3H, m), 1.47 (1H, td, $J$ = 13.6, 4.0 Hz), 1.57-1.73 (3H, m), 2.13 (1H, dd, $J$ = 12.5, 2.38 Hz), 2.25 (1H, td, $J$ = 13.8, 5.78 Hz), 2.44 (1H, d, $J$ = 1.78
Hz), 3.66 (3H, s), 3.86-3.99 (4H, m); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 18.5 (CH$_2$), 19.7 (CH$_2$), 21.4 (CH$_3$), 21.9 (CH$_3$), 33.1 (C), 33.4 (CH$_2$), 33.5 (CH$_3$), 38.2 (C), 38.5 (CH$_2$), 41.8 (CH$_2$), 45.3 (CH), 51.1 (CH), 62.6 (CH$_3$), 63.9 (CH$_3$), 64.5 (CH$_2$), 109.1 (C) 172.6 (C); HRMS (ESI) calcd for C$_{17}$H$_{29}$O$_4$ [M+H]$^+$ 297.2066, found 297.2063. Anal. Calcd for C$_{17}$H$_{28}$O$_4$: C, 68.89; H, 9.52. Found: C, 68.92; H, 9.54.

2-((1$^R$*,$^{4a}S$*,$^{8a}S$*)-5$^5$-5$^5$,$^{8a}$-Trimethyloctahydro-1$^1$H-spiro[1,3]dioxolane-2,2$^2$-naphthalene]-1$^1$-yl)methanol (5). A solution of the above ester (9.20 g, 31.0 mmol) in dry Et$_2$O (30 mL) was added to a stirred suspension of lithium aluminium hydride (3.53 g, 93.0 mmol) in dry Et$_2$O (280 mL) at 0 °C under argon, and stirring was continued for 19 h at room temperature. The reaction was quenched with successive addition of water (3.5 mL), 4M aqueous sodium hydroxide (3.5 mL), and water (7.0 mL). The suspension was filtrated through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/AcOEt 2:1) to give 5 (8.20 g, 99%) as white crystals. mp 77-79 °C (from hexane); IR (KBr) 3330 cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) δ 0.81 (3H, s), 0.85 (3H, s), 0.94 (1H, dd, $J = 12.3$, 3.11 Hz), 1.08-1.16 (1H, m), 1.16 (3H, s), 1.22-1.27 (1H, m), 1.37-1.77 (9H, m), 3.29 (1H, dd, $J = 10.0$, 2.41 Hz), 3.76-4.01 (6H, m); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 18.7 (CH$_2$), 20.4 (CH$_3$), 22.1 (CH$_3$), 22.6 (CH$_3$), 33.1 (CH$_2$), 33.4 (C), 33.5 (CH$_3$), 37.3 (CH$_3$), 38.5 (C), 42.4 (CH$_2$), 48.2 (CH), 57.2 (CH), 61.2 (CH$_2$), 63.5 (CH$_3$), 64.2 (CH$_3$), 113.1 (C); HRMS (ESI) calcd for C$_{16}$H$_{28}$O$_3$ [M+H]$^+$ 269.2117, found 269.2113. Anal. Calcd for C$_{16}$H$_{28}$O$_3$: C, 71.60; H, 10.52. Found: C, 71.50; H, 10.49.
naphthalene]-1'-yl)acetonitrile (6). p-Toluenesulfonyl chloride (12.3 g, 61.2 mmol) was added to a solution of 5 (8.20 g, 30.6 mmol) in pyridine (31.0 mL) at 0 °C under argon. After stirring for 2 h at 0 °C, the reaction was quenched with a saturated aqueous solution of copper (II) sulfate penta hydrate (30 mL), and the resulting mixture was extracted with Et₂O (3 x 50 mL). The combined extracts were washed with brine, then dried over MgSO₄ and concentrated under reduced pressure to afford a yellow oil, which was used in the next step without further purification. KCN (4.98 g, 76.5 mmol) and 18-crown-6 (5.65 g, 30.6 mmol) were added to a solution of the above residue in MeCN (61.0 mL) at room temperature. The mixture was heated at reflux for 4 h. After cooling, the reaction was diluted with a saturated aqueous solution of NaHCO₃ (30 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 60 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 4:1) to give 6 (6.44 g, 76% from 5) as a yellow oil. IR (neat) 2242 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.83 (3H, s), 0.89 (3H, s), 0.89-1.18 (1H, m), 1.20 (3H, s), 1.38-1.56 (8H, m), 1.68-1.71 (3H, m), 1.37-1.58 (8H, m), 1.68-1.71 (3H, m), 2.64 (1H, dd, J = 17.3, 7.3 Hz), 2.65 (1H, dd, J = 17.3, 3.69 Hz), 3.87-4.03 (4H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 15.1 (CH₂), 18.5 (CH₂), 19.8 (CH₃), 21.8 (CH₃), 22.3 (CH₃), 33.1 (C), 33.2 (CH₂), 33.5 (CH₃), 37.8 (CH₂), 38.6 (C), 42.2 (CH₃), 46.3 (CH), 52.9 (CH), 63.6 (CH₂), 64.9 (CH₂), 109.9 (C), 121.5 (C); HRMS (ESI) calcd for C₁₇H₂₈NO₂ [M+H]+ 278.2120, found 278.2125. Anal. Calcd for C₁₇H₂₇NO₂: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.46; H, 9.72; N, 5.16.

![chemical structure](image)

2-(1'S*,4a'S*,8a'S*)-5'S,5`8a'-'Trimethyloctahydro-1'H-spiro[1,3]dioxolane-2,2'-naphthalene]-1'-yl)ethanamine. A solution of 6 (6.44 g, 23.2 mmol) in dry Et₂O (10 mL) was added to a stirred suspension of lithium aluminium hydride (2.64 g, 69.6 mmol) in dry Et₂O (220 mL) at 0 °C under argon, and stirring was continued for 2 h at 0 °C. The reaction was quenched with successive addition of water (2.5 mL), 4M aqueous sodium hydroxide (2.5 mL), and water (5.0 mL). The suspension was filtrated through a Celite pad and the
filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CHCl₃/MeOH/NH₄OH 100:9:1) to give the title compound (6.26 g, 96%) as a colorless oil. IR (neat) 3372 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.80 (3H, s), 1.02-1.06 (3H, m), 1.13 (3H, s), 1.35-1.38 (4H, m), 1.38-1.62 (9H, m), 2.59-2.64 (2H, m), 3.78-4.11 (4H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.5 (CH₂), 20.2 (CH₂), 21.6 (CH₃), 22.8 (CH₂), 32.7 (C), 32.9 (CH₂), 33.3 (CH₂), 33.4 (CH₂), 36.4 (CH₂), 38.8 (C), 42.3 (CH₂), 44.7 (CH₂), 46.3 (CH), 52.9 (CH), 63.3 (CH₂), 64.5 (CH₂). 112.3 (C); HRMS (ESI) calcd for C₁₇H₃₂NO₂ [M+H]⁺ 282.2433, found 282.2435.

Anal. Calcd for C₁₇H₃₁NO₂: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.33; H, 10.84; N, 5.02.

2-Nitro-N-((2-((1′S*,4a′S*,8a′S*)-5′,5′,8a′-trimethyloctahydro-1′H-spiro[1,3]-dioxolane-2,2′-naphthalene]-1′-yl)ethyl)benzenesulfonamide (7). Triethylamine (1.66 mL, 11.9 mmol) and o-NsCl (791mg, 3.57 mmol) were added to a stirred solution of the above amine in dry CH₂Cl₂ (24 mL) at 0 °C under argon. After 5 min, the reaction was quenched with a saturated aqueous solution of NaHCO₃ (30 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 40 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 2:1) to give 7 (1.11 g, 100%) as an amorphous solid. IR (KBr) 3334, 1541 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.79 (3H, s), 0.83 (3H, s), 0.88-0.90 (1H, m), 0.98-1.09 (2H, m), 1.10 (3H, s), 1.14-1.15 (1H, m), 1.22-1.48 (7H, m), 1.59-1.67 (3H, m), 2.96-3.04 (1H, m), 3.10-3.16 (1H, m), 3.83-3.98 (4H, m), 5.74 (1H, t, J = 4.75 Hz), 7.71-7.74 (2H, m), 7.84-7.86 (1H, m), 8.10-8.13 (1H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.4 (CH₂), 20.6 (CH₂), 21.5 (CH₃), 22.6 (CH₃), 27.0 (CH₂), 32.90 (C), 32.91 (CH₂), 33.4 (CH₂), 36.0 (CH₂), 38.9 (C), 42.3 (CH₂), 45.5 (CH₂), 46.4 (CH), 53.3 (CH), 63.2 (CH₂), 64.8 (CH₂), 111.8 (C), 125.3 (CH), 131.1 (CH), 132.6 (CH), 133.3 (CH), 133.9 (C), 148.1 (C); HRMS (ESI) calcd for C₂₅H₃₅N₂O₆S[M+H]⁺ 467.2216, found 467.2200.
2-Nitro-N-(2-(((1’S*,4a´S*,8a´S*)-5´,5´,8a´-trimethyl-2-oxodecahydronaphtalene-1-yl)ethyl)benzenesulfonamide. An aqueous 5% HCl solution (0.98 mL, 1.35 mmol) was added to a stirred solution of 7 (126 mg, 0.27 mmol) in dry THF (2.7 mL) at 0 °C under argon. After stirring for 8 h at 0 °C, the reaction was quenched with saturated aqueous NaHCO₃ (3.0 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 10 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 3:1) to give the title compound (101 mg, 89%) as white crystals. mp 135-136 °C; IR (KBr) 3300, 1687, 1541 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.85 (3H, s), 0.90 (3H, s), 0.95 (3H, s), 1.01-1.05 (1H, m), 1.14-1.22 (1H, m), 1.41-1.63 (6H, m), 1.70-1.80 (2H, m), 1.90-2.01 (2H, m), 2.31-2.37 (2H, m), 2.81-2.88 (1H, m), 3.00-3.08 (1H, m), 5.56 (1H, t, J = 6.21 Hz), 7.70-7.74 (2H, m), 7.84-7.86 (1H, m), 8.07-8.10 (1H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.5 (CH₂), 22.0 (CH₃), 22.1 (CH₃), 23.1 (CH₃), 27.8 (CH₃), 33.3 (C), 33.4 (CH₃), 36.3 (CH₂), 38.4 (CH₂), 39.7 (C), 42.0 (CH₂), 42.2 (CH₂), 44.8 (CH), 61.9 (CH), 125.4 (CH), 131.0 (CH), 132.8 (CH), 133.6 (CH), 133.7 (C), 140.1 (C), 215.2 (C); HRMS (ESI) calcd for C₂₁H₃₀N₂O₅S [M+H]⁺ 423.1954, found 423.1977. Anal. Calcd for C₂₁H₃₀N₂O₅S: C, 59.69; H, 7.16; N, 6.63. Found: C, 59.67 H, 7.04; N, 6.67.

N-Benzyl-2-nitro-N-(2-(((1’S*,4a´S*,8a´S*)-5´,5´,8a´-trimethyl-2-oxodecahydronaphthalene-1-yl)ethyl)benzenesulfonamide (8). Benzyl alcohol (72.0 µL, 0.69 mmol) and triphenyl phosphine (157 mg, 0.60 mmol) were added to a stirred solution of the above ketone (195 mg, 0.46 mmol) in dry toluene (4.6 mL) at room temperature under argon. And then, diethyl azodicarboxylate (40% in toluene, 0.27 mL, 0.60 mmol) was added to the above
mixture at 0 °C. After stirring for 10 min at room temperature, the mixture was directly purified by silica gel flash column chromatography (hexane/EtOAc 2:1) to give 8 (236 mg, 100%) as white crystals. mp 137-138 °C; IR (KBr) 1702, 1543 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.79 (3H, s), 0.80 (3H, s), 0.90 (3H, s), 1.05-1.30 (3H, m), 1.37-1.51 (7H, m), 1.70-1.85 (2H, m), 2.09-2.14 (2H, m), 2.93-3.06 (2H, m), 4.45 (1H, d, J = 14.9 Hz), 4.51 (1H, d, J = 14.9 Hz), 7.29-7.32 (5H, m), 7.63-7.70 (3H, m), 7.91-7.94 (1H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.5 (CH₂), 21.7 (CH₃), 22.0 (CH₃), 23.1 (CH₂), 26.7 (CH₃), 33.2 (C), 33.3 (CH₃), 36.1 (CH₂), 38.0 (CH₂), 39.8 (C), 42.1 (CH₂), 44.6 (CH), 47.0 (CH₂), 53.1 (CH₂), 62.3 (CH), 124.3 (CH), 128.3 (CH), 128.7 (CH, 2 carbons), 128.8 (CH, 2 carbons), 130.1 (CH), 131.7 (CH), 133.1 (C), 133.5 (CH), 135.9 (C), 148.2 (C), 214.8 (C); HRMS (ESI) calcd for C₂₈H₃₅N₂O₅S [M+H]⁺ 513.2423, found 513.2437. Anal. Calcd for C₂₈H₃₆N₂O₅S: C, 65.60; H, 7.08; N, 5.46. Found: C, 65.63 H, 7.00; N, 5.49.

N-Benzyl-N-((1R*,4aS*,8aS*)-2-(cyanomethylene)-5’,5’,8a’-trimethyl-2-oxodecahydronaphthalene-1-yl)ethyl-2-nitrobenzenesulfonamide (9). n-BuLi (1.6 M solution in hexane, 12.0 mL, 19.2 mmol) was added dropwise to a stirred solution of diethyl cyanomethylphosphonate (3.89 mL, 23.0 mmol) in dry THF (60 mL) at 0 °C under argon, and stirring was continued for 1 h at room temperature. A solution of 8 (3.93 g, 7.67 mmol) in dry THF (20 mL) was added dropwise to the above mixture at 0 °C. After stirring for 24 h at room temperature, the reaction was quenched with water (30 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 100 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 4:1) to give 9 (as an E/Z mixture in the ratio of 1:1) (3.78 g, 92%) as a yellow oil. IR (neat) 2214, 1545 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.74-0.85 (9H, m), 0.85-0.95 (1H, m), 1.05-1.58 (10H, m), 1.65-1.67 (3H, m), 2.00-2.11 (1H, m), 2.14-2.20 (0.5H, m), 2.65-2.75 (0.5H, m), 2.80-3.14 (2H, m), 4.40 (1H, t, J = 14.1 Hz), 4.55 (1H, d, J = 14.6 Hz), 4.86 (0.5H, d, J = 1.46 Hz), 5.07 (0.5H, d, J = 1.84 Hz), 7.27-7.34 (5H, m), 7.64-7.71 (3H, m), 7.92-8.00 (1H, m); ¹³C NMR
(100.6 MHz, CDCl$_3$) δ 18.7 (CH$_2$, 2 carbons), 21.2 (CH$_3$), 21.9 (CH$_3$, 3 carbons), 23.2 (CH$_2$), 23.6 (CH$_2$), 26.2 (CH$_2$), 27.4 (CH$_2$), 29.3 (CH$_2$), 32.2 (CH$_2$), 33.17 (C, 2 carbons), 33.2 (CH$_3$), 33.27 (CH$_3$), 36.08 (CH$_2$), 36.12 (CH$_2$), 39.20 (C), 39.29 (C), 42.1 (CH$_2$, 2 carbons), 45.2 (CH), 45.3 (CH), 47.0 (CH$_2$), 47.4 (CH$_2$), 52.5 (CH$_2$), 53.1 (CH), 53.3 (CH$_2$), 56.2 (CH), 94.1 (CH), 94.2 (CH), 116.5 (C), 117.0 (C), 124.2 (CH), 124.3 (CH), 128.2 (CH), 128.3 (CH), 128.66 (CH, 2 carbons), 128.79 (CH, 2 carbons), 128.83 (CH, 2 carbons), 128.86 (CH, 2 carbons), 130.7 (CH), 130.9 (CH), 131.7 (CH), 131.8 (CH), 133.0 (C), 133.1 (C), 133.5 (CH), 133.7 (CH), 135.6 (C), 136.0 (C), 148.1 (C), 148.2 (C), 168.9 (C), 169.5 (C); HRMS (ESI) calcd for C$_{30}$H$_{38}$N$_3$O$_4$S [M+H]$^+$ 536.2583, found 536.2562.

2-((1R*,4aS*,8aS*)-1-(2-(Benzylationo)ethyl)-5,5,8,1-trimethylhexahydronaphthalene-2(1H)-yldene)acetonitrile (3). Thiophenol (0.31 mL, 2.96 mmol) and 5 M aqueous KOH (0.30 mL, 1.48 mmol) were added dropwise to a stirred solution of 9 (396 mg, 0.739 mmol) in MeCN (4.0 mL) at 0 °C under argon. After stirring for 4 h at room temperature, the mixture was directly purified by silica gel flash column chromatography (CHCl$_3$/MeOH 20:1) to give 3 (236 mg, 91%) as a yellow oil. IR (neat) 3313, 2214 cm$^{-1}$; $^1$H NMR (major diastereomer, 400MHz, CDCl$_3$) δ 0.81 (3H, s), 0.88 (3H, s), 0.95 (3H, s), 1.15-1.19 (2H, m), 1.38-1.75 (9H, m), 1.90-2.00 (1H, m), 2.26-2.30 (2H, m), 3.68 (1H, d, J = 13.0 Hz), 3.75 (1H, d, J = 12.9 Hz), 5.12 (1H, s), 7.22-7.37 (5H, m); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 18.8 (CH$_2$), 21.5 (CH$_2$), 22.0 (CH$_3$), 23.9 (CH$_3$), 28.1 (CH$_2$), 32.5 (CH$_2$), 33.3 (C), 33.4 (CH$_3$), 36.4 (CH$_2$), 39.5 (C), 42.3 (CH$_2$), 45.4 (CH), 47.9 (CH$_2$), 53.5 (CH), 54.3 (CH$_2$), 94.0 (CH), 117.3 (C), 126.9 (CH), 128.2 (CH, 2 carbons), 128.4 (CH, 2 carbons), 140.3 (C), 170.1 (C); HRMS (ESI) calcd for C$_{24}$H$_{35}$N$_2$ [M+H]$^+$ 351.2800, found 351.2794.
2-((3aS*,5aS*,9aS*)-6,6,9a-trimethylperhydro-1H-benzo[e]indol-3a-yl)acetonitrile (2). N,N-Diisopropylethylamine (0.36 mL, 2.18 mmol) was added to a stirred solution of 3 (153 mg, 0.436 mmol) in EtOH (4.4 mL) at room temperature under argon. The mixture was heated at reflux for 24 h. After cooling, the reaction was quenched with saturated aqueous NH₄Cl (5.0 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 10 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/EtOAc 5:1) to give 2 (123 mg, 80%) as white crystals. mp 154-156 °C; IR (KBr) 2243 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.83 (3H,s), 0.90 (3H, s), 1.10-1.20 (3H, m), 1.23 (3H, s), 1.23-1.29 (2H, m), 1.50-1.70 (3H, m), 1.78-1.81 (2H, m), 2.14 (1H, t, J = 10.2 Hz), 2.25-2.31 (1H, m), 2.65 (1H, d, J = 17.4 Hz), 2.92-2.97 (1H, m), 2.99 (1H, d, J = 17.4 Hz), 3.14 (1H, d, J = 13.2 Hz), 3.91 (1H, d, J = 13.2 Hz), 7.12-7.73 (5H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.2 (CH₂), 19.5 (CH₂), 21.6 (CH₃), 22.7 (CH₃), 23.7 (CH₂), 26.6 (CH₂), 28.3 (CH₂), 32.9 (C), 33.4 (CH₂), 36.3 (C), 37.3 (CH₂), 42.2 (CH₂), 46.5 (CH), 48.9 (CH₂), 52.0 (CH₂), 55.6 (CH), 62.3 (C), 118.6 (C), 126.9 (CH), 128.3 (CH, 2 carbons), 128.4 (CH, 2 carbons), 139.6 (C); HRMS (ESI) calcd for C₂₄H₃₅N₂ [M+H]⁺ 351.2800, found 351.2812. Anal. Calcd for C₂₄H₃₄N₂: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.08 H, 9.86; N, 7.98.

2-((3aS*,5aS*,9aS*)-6,6,9a-Trimethylperhydro-1H-benzo[e]indol-3a-yl)acetonitrile (10). Celium(IV) ammonium nitrate (64.0 mg, 0.116 mmol) was added to a stirred solution of 2 (13.5 mg, 38.5 µmol) in (MeCN/CH₂Cl₂/H₂O 4:1:1, 0.5 mL) at 0 °C under argon. After stirring for 3.5 h at room temperature, the reaction was quenched with saturated aqueous
NaHCO₃ (1.0 mL) at 0 °C, and the resulting mixture was extracted with CHCl₃ (3 x 10 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CHCl₃/MeOH 20:1) to give 10 (8.5 mg, 85%) as white crystals. mp 87-89 °C; IR (KBr) 3435, 2240 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.81 (3H, s), 0.88 (3H, s), 1.11 (3H, s), 1.18-1.30 (5H, m), 1.74 (1H, t, J = 10.1 Hz), 1.89-1.92 (2H, m), 1.98 (1H, br s), 2.69 (1H, d, J = 16.7 Hz), 2.70 (1H, d, J = 16.7 Hz), 2.97-3.02 (2H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.3 (CH₂), 19.9 (CH₂), 21.7 (CH₃), 22.7 (CH₂), 27.8 (CH₂), 29.5 (CH₃), 32.9 (C), 33.4 (CH₃), 34.9 (CH₂), 36.0 (C) 38.2 (CH₂), 46.5 (CH); 57.0 (CH), 60.4 (C), 118.5 (C); HRMS (ESI) calcd for C₁₇H₂₉N₂ [M+H]⁺ 261.2331, found 261.2333. Anal. Calcd for C₁₇H₂₈N₂: C, 78.41; H, 10.84; N, 10.76. Found: C, 78.23 H, 10.63; N, 10.63.

2-((3aS*,5aS*,9aS*)-6,6,9a-Trimethyl-3-(2-nitrobenzenesulfonyl)perhydro-1H-benzo[e]indol-3a-yl)acetonitrile (11). Triethylamine (0.28 mL, 2.00 mmol) and α-NsCl (221 mg, 0.988 mmol) were added to a stirred solution of 10 (104 mg, 0.399 mmol) in CH₂Cl₂ (4.0 mL) at 0 °C under argon. After stirring for 8 h at room temperature, the reaction was quenched with saturated aqueous NaHCO₃ (4.0 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 15 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 2:1) to give 11 (147 mg, 83%) as white crystals. mp 221-224 °C; IR (KBr) 2246, 1545 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.80 (3H, s), 0.88 (3H, s), 1.11-1.23 (3H, m), 1.21 (3H, s), 1.30-1.33 (2H, m), 1.41-1.47 (2H, m), 1.56-1.63 (2H, m), 1.94-1.98 (2H, m), 2.01-2.15 (1H, m), 2.26 (1H, dd, J = 12.98, 6.35 Hz), 2.37 (1H, d, J = 13.9 Hz), 3.05 (1H, d, J = 17.8 Hz), 3.13 (1H, td, J = 10.7, 6.89 Hz), 3.74 (1H, d, J = 17.9 Hz), 3.79 (1H, t, J = 9.27 Hz), 7.56-7.59 (1H, m), 7.67-7.72 (2H, m), 8.11-8.13 (1H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.2 (CH₃), 20.0 (CH₂), 21.6 (CH₃), 22.4 (CH₃), 25.2 (CH₂), 27.4 (CH₂), 32.9 (C), 33.3 (CH₃), 36.4 (CH₂), 38.1 (CH₂), 41.9 (CH₂), 46.8
(CH), 47.6 (CH₂), 57.2 (CH), 69.1 (C), 118.3 (C), 124.0 (CH), 130.3 (CH), 131.8 (CH), 133.0 (C), 133.8 (CH), 148.6 (C); HRMS (ESI) calcd for C₂₃H₃₃N₃O₄S [M+H]+ 446.2114, found 446.2118. Anal. Calcd for C₂₃H₃₂N₃O₄S: C, 62.00; H, 7.01; N, 9.42. Found: C, 61.93; H, 7.04; N, 9.45.

2-((3aS*,5aS*,9aS*)-6,6,9a-Trimethyl-3-(2-nitrobenzenesulfonyl)perhydro-1H-benzo[e]indol-3a-yl)acetalddehyde (12). DIBAL-H (1.01 M in toluene, 0.65 mL, 0.66 mmol) was added dropwise to a stirred solution of 11 (147 mg, 0.33 mmol) in CH₂Cl₂ (3.3 mL) at −78 °C under argon. After stirring for 30 min at −78 °C, 1M HCl (1.0 mL) was added to the mixture. After warming to room temperature very slowly, the reaction was quenched with saturated aqueous NaHCO₃ (4.0 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 15 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 2:1) to give 12 (125 mg, 85%) as white crystals. mp 201-203 °C; IR (KBr) 1720, 1543 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.77 (3H, s), 0.86 (3H, s), 1.08 (3H, s), 1.13-1.28 (5H, m), 1.38-1.45 (2H, m), 1.52-1.68 (2H, m), 1.66 (1H, td, J = 13.1, 4.22 Hz), 1.90 (1H, dd, J = 12.1, 6.06), 1.94-2.07 (1H, m), 2.16 (1H, dd, J = 13.1, 6.14), 2.21-2.25 (1H, br d, J = 13.7 Hz), 3.06 (1H, dd, J = 18.2, 3.13 Hz), 3.27 (1H, td, J = 10.11, 6.6 Hz), 3.54 (1H, d, J = 18.2 Hz), 3.78 (1H, d, J = 9.08 Hz), 9.74 (1H, d, J = 2.96 Hz); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.3 (CH₂), 20.0 (CH₂), 21.7 (CH₃), 23.1 (CH₃), 25.3 (CH₂), 32.9 (C), 33.3 (CH₃), 36.9 (C), 37.7 (CH₂), 38.2 (CH₂), 42.0 (CH₂), 46.9 (CH), 48.3 (CH₂), 48.8 (CH₂), 56.5 (CH), 68.8 (C), 123.9 (CH), 130.1 (CH), 131.5 (CH), 133.6 (CH), 134.1 (CH), 148.3 (C), 201.8 (CH); HRMS (ESI) calcd for C₂₅H₃₂N₂O₅S [M+H]+ 449.2110, found 449.2102. Anal. Calcd for C₂₅H₃₂N₂O₅S: C, 61.58; H, 7.19; N, 6.24. Found: C, 61.43; H, 7.23; N, 6.32.

-S10-
(3aS*,5aS*,9aS*)-6,6,9a-Trimethyl-3a-(3-methylbut-2-enyl)-3-(2-nitrobenzenesulfonyl)-perhydro-1H-benzo[e]indole (13). n-BuLi (1.6 M solution in hexane, 33.0 µL, 53.0 µmol) was added dropwise to a stirred suspension of isopropyltriphenylphosphonium iodide (24.0 mg, 54.4 µmol) in dry THF (300 µL) at 0 °C under argon, and stirring was continued for 30 min at the same temperature. A solution of 12 (6.10 mg, 13.6 µmol) in dry THF (300 µL) was added dropwise to the above mixture at 0 °C. After stirring for 15 h at room temperature, the reaction was quenched with saturated aqueous NH₄Cl (1.0 mL) at 0 °C, and the resulting mixture was extracted with Et₂O (3 x 10 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 4;1) to give 13 (4.50 mg, 70%) as yellow crystals. mp 141-143 °C; IR (KBr) 1543 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.78 (3H, s), 0.87 (3H, s), 1.00 (3H, s), 1.10-1.41 (7H, m), 1.48 (6H, s), 1.48-1.70 (2H, m), 1.80-1.95 (4H, m), 2.32 (1H, dt, J = 13.7, 3.06 Hz), 2.65-2.85 (2H, m), 3.23-3.28 (1H, m), 3.81-3.85 (1H, m), 4.79-4.81 (1H, br s), 7.48-7.50 (1H, m), 7.50-7.61 (2H, m), 7.98-8.10 (1H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.4 (CH₂), 18.4 (CH₂), 20.4 (CH₃), 21.8 (CH₃), 22.1 (CH₃), 25.1 (CH₃), 25.8 (CH₃), 32.9 (CH₃), 33.4 (C), 34.5 (CH₂), 36.6 (C), 38.4 (CH₂), 38.5 (CH₂), 42.2 (CH₂), 47.1 (CH), 48.5 (CH₂), 55.0 (CH), 71.3 (C), 120.0 (CH), 123.4 (CH), 130.7 (CH), 131.0 (CH), 132.8 (CH), 135.1 (C), 148.4 (C); HRMS (ESI) calcd for C₂₆H₃₉N₂O₄S [M+H]⁺ 475.2631, found 475.2652. Anal. Calcd for C₂₆H₃₈N₂O₄S: C, 65.79; H, 8.07; N, 5.90. Found: C, 65.69 H, 8.03; N, 5.95.

3-Hydroxy-3-methyl-1-((3aS*,5aS*,9aS*,9bS*)-6,6,9a-trimethyl-3-(2-nitrobenzenesulfonyl)perhydro-1H-benzo[e]indol-3-yl)butan-2-one (14). N-Methylmorpholine N-oxide (78.0 mg, 0.632 mmol) and osmium(IV) tetroxide (0.20 mL, 31.6 µmol) was added to a
stirred solution of 13 (150 mg, 0.316 mmol) in (MeCN/H$_2$O 4:1, 3.2 mL) at room temperature under argon. After stirring for 17 h at room temperature, the reaction was quenched with saturated aqueous Na$_2$S$_2$O$_3$ (4.0 mL) at 0 °C, and the resulting mixture was extracted with Et$_2$O (3 x 10 mL). The combined extracts were washed with brine, then dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was roughly purified by silica gel flash column chromatography (hexane/EtOAc 4:1) to afford a yellow oil, which was used in the next step without further purification. N-Methylmorpholine N-oxide (57.0 mg, 0.474 mmol) and MS4A were added to a stirred solution of the above residue in MeCN (2.7 mL) at room temperature under argon. After stirring for 15 min, a solution of TPAP (5.70 mg, 15.8 µmol) in MeCN (0.5 mL) was added dropwise to the above mixture. After stirring for 1 h, the solvent was removed under reduced pressure. The residue was diluted with CHCl$_3$ and through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/AcOEt 2:1) to give 14 (115 mg, 72% from 13) as a yellow oil. IR (neat) 3493, 1713, 1545 cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) δ 0.77 (3H, s), 0.85 (3H, s), 1.02 (3H, s), 1.13-1.28 (5H, m), 1.34 (6H, s), 1.34-1.41 (2H, m), 1.55-1.77 (2H, m), 1.78 (1H, td, $J$ = 13.6, 4.1 Hz), 1.87-2.03 (2H, m), 2.17-2.20 (1H, m), 2.67 (1H, dd, $J$ = 12.9, 6.35 Hz), 3.40-3.47 (3H, m), 3.73-3.81 (1H, m) 7.51-7.53 (1H, m), 7.61-7.64 (2H, m), 7.85-7.87 (1H, m); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 18.3 (CH$_2$), 20.1 (CH$_2$), 21.7 (CH$_2$), 23.4 (CH$_2$), 25.7 (CH$_2$), 27.1 (CH$_3$, 2 carbons), 32.9 (C), 33.3 (CH$_3$), 36.5 (C), 38.2 (CH$_2$), 38.7 (CH$_2$), 41.3 (CH$_2$), 42.0 (CH$_2$), 47.1 (CH), 48.7 (CH$_2$), 54.5 (CH), 68.2 (C), 123.9 (CH), 130.1 (CH), 131.4 (CH), 133.2 (CH), 134.7 (C), 148.3 (C), 213.1 (C); HRMS (ESI) calcd for C$_{26}$H$_{39}$N$_2$O$_6$S [M+H]$^+$ 507.2529, found 507.2503.

3-Hydroxy-3-methyl-1-((3aS*,5aS*,9aS*,9bS*)-6,6,9a-trimethylperhydro-1H-benzo[e]indol-3a-yl)butan-2-one (15). Thiophenol (56.0 µL, 0.109 mmol) and 5 M aqueous KOH (87.0 µL, 0.436 mmol) were added dropwise to a stirred solution of 14 (55.2 mg, 0.109 mmol) in MeCN (1.1 mL) at 0 °C under argon. After stirring for 17 h at room temperature, the mixture was directly purified by silica gel flash column chromatography.
(CHCl₃/MeOH/NH₄OH 100:9:1) to give 15 (25.6 mg, 73%) as a yellow oil. IR (neat) 3314, 1702 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.81 (3H, s), 0.88 (3H, s), 1.12 (3H, s), 1.14-1.18 (2H, m), 1.23 (3H, s), 1.26 (3H, s), 1.28-1.42 (6H, m), 1.50-1.60 (1H, m), 1.60-1.76 (1H, m), 1.76-1.90 (3H, m), 1.98-2.05 (1H, m), 2.71 (1H, d, J = 11.5 Hz), 2.76-2.83 (1H, m), 3.01-3.06 (1H, m) 3.22 (1H, d, J = 11.5 Hz); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.4 (CH₃), 20.0 (CH₃), 21.8 (CH₃), 23.0 (CH₃), 26.5 (CH₃), 26.8 (CH₃), 27.8 (CH₃), 33.0 (C), 33.5 (CH₃), 36.1 (C), 37.0 (CH₃), 38.7 (CH₃), 42.2 (CH₂), 43.1 (CH₂), 46.6 (CH₃), 47.4 (CH), 59.2 (CH), 62.5 (C), 76.2 (C), 216.6 (C); HRMS (ESI) calcd for C₂₀H₃₂NO₂[M+H]+ 322.2746, found 322.2726.

(3aS*,5aS*,9aS*,9bS*)-3a-(3-Hydroxy-3-methyl-2-oxobutyl)-6,6,9a-trimethyl-3a,4,5,5a,6,7,8,9,9b-decahydro-1H-benzo[e]indole 3-oxide (16). Na₂WO₄·2H₂O (14.4 mg, 43.6 µmol) was added to a stirred solution of 15 (28.0 mg, 87.1 µmol) in MeOH (870 µL) at room temperature under argon. After cooling at 0 °C, 30% H₂O₂ (30.0 µL, 0.261 mmol) was added dropwise to the mixture. The resulting mixture was gradually warmed to room temperature over 30 min. After stirring for an additional 1 h at room temperature, the reaction was extracted with CHCl₃ (3 x 10 mL). The combined extracts were washed with brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was roughly purified by silica gel flash column chromatography (CHCl₃/MeOH 40:1) to afford 16 (25.2 mg, 86%) as a yellow oil. IR (neat) 3348, 1714 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.93 (3H, s), 1.13 (3H, s), 1.13-1.25 (2H, m), 1.27 (3H, s), 1.27-1.35 (2H, m), 1.37 (3H, s), 1.43-1.55 (2H, m), 1.63-1.70 (4H, m), 2.50-2.60 (4H, m), 3.07 (1H, d, J = 14.4 Hz), 3.24 (1H, d, J = 14.5 Hz), 5.04 (1H, s), 6.81 (1H, t, J = 2.34 Hz); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.0 (CH₃), 18.2 (CH₃), 21.9 (CH₃), 23.0 (CH₃), 26.3 (CH₃), 26.5 (CH₃), 28.7 (CH₂), 32.9 (C), 33.4 (CH₃), 35.8 (C), 35.9 (CH₂), 36.9 (CH₃), 38.7 (CH₂), 42.0 (CH₂), 48.4 (CH), 53.6 (CH), 53.6 (C), 78.5 (C), 133.4 (CH), 214.2 (C); HRMS (ESI) calcd for C₂₀H₃₄NO₄[M+H]+ 336.2539, found 336.2545.

-S13-
(±)-Chamobtusin A (1). Benzoyl chloride (1.71 µL, 14.7 µmol) was added to a stirred, refluxing solution of 16 (4.50 mg, 13.4 µmol) in pyridine (600 µL) under argon. After stirring for 1h at reflux, the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (CHCl₃/MeOH 20:1) to give (±)-chamobtusin A (1) (2.30 mg, 54%) as a yellow solid. IR (neat) 3334, 2929, 1710, 1604, 1518, 1464, 1374, 1236 cm⁻¹; ¹H NMR (400MHz, CD₃OD) δ 0.61-0.70 (2H, m), 0.83 (3H, s), 0.92 (3H, s), 1.10 (3H, s), 1.15 (3H, s), 1.16 (3H, s), 1.39-1.79 (9H, m), 2.54-2.58 (1H, m), 3.32 (1H, d, J = 17.8 Hz), 3.47 (1H, d, J = 17.8 Hz), 6.03 (1H, s), 7.90 (1H, s); ¹³C NMR (100.6 MHz, CD₃OD) δ 17.6 (CH₃), 19.8 (CH₃), 20.6 (CH₂), 22.4 (CH₃), 27.1 (CH₃, 2 carbons), 34.5 (CH₃), 35.2 (C), 39.1 (CH₂), 41.8 (C), 42.4 (CH₂), 42.8 (CH₂), 43.5 (CH₂), 59.9 (CH), 78.2 (C), 81.1 (C), 118.4 (CH), 166.0 (CH), 184.8 (C), 213.9 (C); HRMS (ESI) calcd for C₂₉H₃₂NO₂ [M+H]^+ 318.2433, found 318.2447.
Electronic Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2011