Electronic Supplementary Information

An Expeditious Asymmetric Synthesis of the Pentacyclic Core of the Cortistatins by an Intramolecular (4+3) Cycloaddition

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General Experimental

All reactions were performed in oven-dried flasks under an atmosphere of dry argon. All solvents were freshly distilled over granular calcium hydride before use. Air- and moisture-sensitive compounds were introduced via syringes or cannulae using standard inert atmosphere techniques. TLC was performed with E. Merck 0.2 mm pre-coated silica gel plates (Kieselgel 60 F_{254}) and are visualized with a short-wavelength UV light and/or anisaldehyde or potassium permanganate followed by heating. Flash column chromatography was performed with E. Merck silica gel 60 (230-400 mesh ASTM). All $^1$H and $^{13}$C NMR spectra were in CDCl$_3$, unless otherwise stated, with TMS as an internal standard at ambient temperature on Bruker DPX 300, 400, 500 MHz Fourier Transform Spectrometers operating at 300 MHz, 400 MHz, 500 MHz or 600 Mhz for $^1$H NMR or at 75 MHz, 100 MHz, 125 MHz, or 150 MHz for $^{13}$C NMR. IR spectroscopy was performed with a Bio-Rad Fourier Transform 165 Spectrophotometer from 4000 cm$^{-1}$ to 400 cm$^{-1}$. Mass spectra were recorded on a Finnigan MAT 95 mass spectrometer or API QSTAR PULSAR iLC/MS/TOF System. Optical rotations were recorded on a Perkin Elmer 343 Polarimeter. Analytic scale HPLC was carried out on a Waters 2707 autosampler with 1525 Binary Pump system on a Breeze 2 software. Chiral column and a variable wavelength Waters 2498 UV detector were used for ee determination.
Preparation of (2R,3R)-2-allyl-3-hydroxy-2-methylcyclopentanone (7a)

(S)-CBS-B-Me was prepared according to the literature, except that methylboronic acid was used instead of n-butylboronic acid. To the freshly prepared (S)-CBS-B-Me catalyst (20 mol%) in toluene (4.0 mL) was added dried molecular sieves, 2-allyl-2-methyl-1,3-cyclopentanedione (6) (421.7 mg, 2.771 mmol), and N,N-diethylaniline (176 μL, 1.11 mmol). The resulting solution was stirred at room temperature for 10 min and then cooled to −78 °C. A pre-cooled (−78 °C) solution of 1.0 M catecholborane in toluene (3.1 mL, 3.0 mmol) was added to the reaction mixture via cannula over 5 min. After the addition, the resulting solution was stirred for 2 h, then quenched with 1 M NaOH solution. The mixture was extracted with ethyl acetate (10 mL x 3) and washed with brine. The combined extracts were dried over anhydrous MgSO4 and concentrated in vacuo. The residue was purified by flash column chromatography using 35%-85% EtOAc in hexane to afford (2R,3R)-7a (288.0 mg, 67% yield) as a colorless oil, (2S,3R)-7b (47.0 mg, 11% yield) as a colorless oil, and 7c as a mixture of diastereomers (53.5 mg, 12%) in the form of a colorless oil.

(2R,3R)-7a: Rf = 0.40 (35% EtOAc in hexane); [α]D 20 = −79.5 ° (c = 0.95, CH2Cl2); 1H NMR (500 MHz, CDCl3) δ 5.88 (tdd, J = 17.2, 10.1, 7.4 Hz, 1H), 5.15 (ddd, J = 17.5, 3.4, 1.6 Hz, 1H), 5.14-5.09 (m, 1H), 4.14-4.09 (m, 1H), 2.47 (td, J = 18.7, 9.2 Hz, 1H), 2.39-2.24 (m, 3H), 2.23-2.15 (m, 1H), 1.97 (tdd, J = 13.4, 9.6, 3.5 Hz, 1H), 1.86 (s, 1H), 1.00 (s, 3H) ppm; 13C NMR (125 MHz, CDCl3) δ 220.6, 134.5, 118.3, 77.6, 53.3, 35.6, 34.1, 27.9, 19.8 ppm. The NMR data corresponded to those of (2R,3R)-7a in the literature.

(2S,3R)-7b: Rf = 0.33 (35% EtOAc in hexane); [α]D 20 = +76.7 ° (c = 0.03, CHCl3); 1H NMR (500 MHz, CDCl3) δ 5.76 (ddddd, J = 15.0, 11.9, 9.1, 7.5 Hz, 1H), 5.12 (s, 1H), 5.11-5.08 (m, 1H), 4.22 (t, J = 5.8 Hz, 1H), 2.47 (ddd, J = 19.0, 9.3, 4.3 Hz, 1H), 2.30-2.11 (m, 4H), 1.86 (ddddd, J = 12.3, 8.7, 7.6, 7.0 Hz, 1H), 1.63 (s, 1H), 1.01 (s, 3H) ppm; 13C NMR (125 MHz, CDCl3) δ 219.9, 133.7, 118.9, 75.6, 53.1, 40.0, 35.0, 27.6, 15.1 ppm. The NMR data corresponded to those of (2S,3R)-7b in the literature.

Preparation of (2R,3R)-2-allyl-3-(tert-butyldimethylsiloxy)-2-methylcyclopentanone (TBS-7a)
To a solution of (2R,3R)-7a (632.6 mg, 4.102 mmol) in DMF (2.0 mL) was added imidazole (854.1 mg, 12.54 mmol), TBSCI (1.225 g, 8.130 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with saturated NH₄Cl. The reaction mixture was extracted with ether (5 mL x 3) and washed with brine. The combined extracts were dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography using 5% EtOAc in hexane to afford TBS-7a (1.100 g, 100% yield) as a colorless oil. TBS-7a: Rf = 0.87 (35% EtOAc in hexane); [α]₂₀ ᵃ⁻ = −37.8 ° (c = 0.23, CH₂Cl₂); ^1H NMR (400 MHz, CDCl₃) δ 5.82–5.70 (m, 1H), 5.07–5.03 (m, 1H), 5.02 (t, J = 1.1 Hz, 1H), 4.02 (t, J = 5.1 Hz, 1H), 2.39 (ddd, J = 18.7, 9.6, 6.9 Hz, 1H), 2.29 (tdd, J = 14.0, 6.8, 1.2 Hz, 1H), 2.23 (dd, J = 9.0, 5.7 Hz, 1H), 2.21-2.05 (m, 3H), 1.90 (tdd, J = 13.2, 9.8, 5.4 Hz, 1H), 0.93 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H) ppm; ^13C NMR (100 MHz, CDCl₃) δ 220.5, 134.4, 117.8, 78.2, 53.5, 34.4, 28.4, 25.9, 19.7, 18.1, −4.2, −4.8 ppm; IR (CH₂Cl₂) 3070, 2955, 2862, 1736, 1636, 1466, 1381, 1088 cm⁻¹; LRMS (EI, 20 eV) m/z 211 (M⁺ – C₄H₉, 100), 193 (5), 143 (3), 119 (7); HRMS (EI, 20 eV) Calculated for C₁₁H₁₉O₂Si (M⁺ – C₄H₉) 211.1149, Found 211.1151.

Preparation of (1S,2R,3R)-2-allyl-3-(tert-butyldimethylsiloxy)-1-((5-(4-(tert-butyldiphenylsiloxy)-butyl)furan-2-yl)-2-methylcyclopentanol (9)

To a solution of TBS-7a (179.9 mg, 0.6701 mmol) in THF (6.0 mL), was added 8 (prepared from n-BuLi (2.29 M in hexane, 901 μL, 2.06 mmol), tert-butyl(4-(furan-2-yl)butoxy)diphenylsilane (0.7809 g, 2.063 mmol), TMEDA (309 μL, 2.06 mmol) in THF (4.0 mL) at 0 °C) via cannula at −78 °C. The reaction was stirred at −78 °C for 3 h and then quenched with saturated NH₄Cl. The reaction mixture was extracted with ether (5 mL x 3) and washed with brine. The combined
extracts were dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography using 5% ether in hexane to afford 9 (195.2 mg, 45% yield) as a colorless oil, and recovered TBS-7a (79.9 mg, 44%). 9: \(R_f = 0.40\) (5% EtOAc in hexane); \(\left[\alpha\right]_{D}^{20} = -33.4^\circ\) (c = 1.02, CH₂Cl₂); \(^1\)H NMR (400 MHz, C₆D₆) δ 7.80-7.74 (m, 4H), 7.27-7.21 (m, 6H), 6.51 (d, \(J = 3.0\) Hz, 1H), 5.93-5.80 (m, 2H), 5.07 (d, \(J = 8.4\) Hz, 1H), 5.03 (s, 1H), 4.47 (s, 1H), 3.86 (d, \(J = 5.0\) Hz, 1H), 3.62 (t, \(J = 6.3\) Hz, 2H), 3.04 (dd, \(J = 14.1, 5.8\) Hz, 1H), 2.79 (ddd, \(J = 14.3, 12.0, 5.2\) Hz, 1H), 2.48 (dt, \(J = 7.3, 2.8\) Hz, 2H), 2.40 (dd, \(J = 14.2, 8.8\) Hz, 1H), 2.29 (ddd, \(J = 14.6, 9.9, 5.2\) Hz, 1H), 1.93 (tdd, \(J = 14.6, 11.8, 5.2\) Hz, 1H), 1.79-1.64 (m, 3H), 1.57-1.49 (m, 2H), 1.17 (s, 9H), 0.88 (s, 9H), 0.77 (s, 3H), −0.01 (s, 3H), −0.02 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, C₆D₆) δ 155.1, 154.8, 136.4, 136.0, 134.4, 129.9, 128.1, 117.1, 108.3, 106.2, 84.6, 82.1, 63.9, 53.5, 36.6, 34.7, 32.3, 31.2, 28.2, 27.2, 25.9, 24.9, 20.9, 19.5, 18.0, −4.2, −5.1 ppm; IR (CH₂Cl₂) 3919, 3163, , 3047, 1939, 2855, 1435, 1389, 1252, 1111 cm⁻¹; LRMS (EI, 20 eV) m/z 646 (M⁺, 0.11), 629 (18), 628 (35), 613 (58), 589 (9); HRMS (EI, 20 eV) Calculated for C₃₉H₅₈O₄Si₂ (M⁺) 646.3874, Found 646.3841.

Preparation of (((1R,2S)-2-allyl-3-(5-(4-(tert-butyldiphenylsiloxy)butyl)furan-2-yl)-2-methyl-cyclopent-3-en-1-yl)oxy)(tert-butyldimethylsilane (10)

\[
\text{OTBDPS} \quad \text{HO} \quad \text{OTBS} \quad \text{OTBDPS} \quad \text{OTBS}
\]

\[
\text{9} \quad \text{MsCl, Et₃N, CH₂Cl₂, r.t., O/N} \quad \text{68%} \quad \text{88% b.o.r.s.m.} \quad \text{10}
\]

To a solution of 9 (483.5 mg, 0.7472 mmol) in CH₂Cl₂ (20 mL) was added Et₃N (0.63 mL, 4.5 mmol) and MsCl (0.18 mL, 2.3 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 8h before quenching with saturated NH₄Cl. The reaction mixture was extracted with ether (10 mL x 3) and washed with brine. The combined extracts were dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography using 5% ether in hexane to afford 10 (319.3 mg, 68% yield) as a colorless oil and recovered 9 (112.1 mg, 23%). 10: \(R_f = 0.81\) (5% EtOAc in hexane); \(\left[\alpha\right]_{D}^{20} = -24.1^\circ\) (c = 0.29, CH₂Cl₂); \(^1\)H NMR (400 MHz, CDCl₃) δ 7.71-7.65 (m, 4H), 7.44-7.36 (m, 6H), 6.18 (d, \(J = 3.2\) Hz, 1H), 5.99-5.83 (m, 2H), 4.97-4.86 (m, 2H), 4.10 (t, \(J = 8.0\) Hz, 1H), 3.70 (t, \(J = 6.2\) Hz, 2H), 2.61 (t, \(J = 7.4\) Hz, 2H), 2.51 (ddd, \(J = 16.5, 7.8, 3.4\) Hz, 1H), 2.42 (dd, \(J = 13.6, 7.0\) Hz, 1H), 2.34-2.23 (m,
Preparation of (E)-5-((1S,5R)-5-(tert-butyldimethylsilyloxy)-2-(5-(4-(tert-butyldiphenylsiloxy)-butyl)furan-2-yl)-1-methylcyclopent-2-en-1-yl)pent-3-en-2-one (11)

To a solution of 10 (321.4 mg, 0.5109 mmol) in degassed CH2Cl2 (10.5 mL) was added 3-buten-2-one (0.13 mL, 1.6 mmol) and the Hoveyda-Grubbs catalyst 2nd generation (16.3 mg, 0.0260 mmol) at room temperature. The resulting mixture was stirred overnight at room temperature. After filtered through a short pad of silica gel, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography using 10% ether in hexane to afford 11 (285.9 mg, 83% yield) as a colorless oil. 11: Rf = 0.60 (10% EtOAc in hexane); [α]D 20 = −18.1 ° (c = 0.16, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 7.70-7.64 (m, 4H), 7.45-7.35 (m, 6H), 6.88 (td, J = 15.7, 7.7 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 5.99-5.90 (m, 3H), 4.13 (t, J = 7.9 Hz, 1H), 3.69 (t, J = 6.2 Hz, 2H), 2.64-2.48 (m, 4H), 2.43 (ddd, J = 13.7, 7.9, 1.1 Hz, 1H), 2.21 (ddd, J = 16.9, 8.1, 2.1 Hz, 1H), 2.14 (s, 3H), 1.80-1.69 (m, 2H), 1.68-1.58 (m, 2H), 1.28 (s, 3H), 1.06 (s, 9H), 0.94 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 199.0, 155.8, 149.5, 147.7, 137.8, 133.0, 129.7, 127.7, 121.7, 107.2, 106.3, 81.7, 63.7, 51.7, 39.3, 38.3, 32.2, 27.9, 27.0, 26.5, 26.0, 25.2, 24.4, 19.4, 18.2, −4.3, −4.8 ppm; IR (CH2Cl2) 3040, 2932, 2862, 1666, 1620, 1427, 1366, 987 cm⁻¹; LRMS (EI, 20 eV) m/z 670(M⁺, 0.7), 645 (7), 629 (5), 613 (4); HRMS (EI, 20 eV) Calculated for C41H58O4Si2 (M⁺) 670.3874, Found 670.3849.
Preparation of 1-((2S,3R)-3-(((1S,5R)-5-((tert-butyldimethylsiloxy)butyl)furan-2-yl)-1-methylcyclopent-2-en-1-yl)methyl)oxiran-2-yl)ethanone (13)

Amine 12 was prepared according to the literature procedure. To a solution of 11 (275.2 mg, 0.4101 mmol) in toluene (0.4 mL) was added chiral amine (0.0132 g, 0.0408 mmol), TFA (6 μL, 0.08 mmol), and 85% cumene hydroperoxide (100 μL, 0.5 mmol). The resulting solution was stirred overnight at room temperature. Then the reaction mixture was directly purified by flash column chromatography using 10% ether hexane to afford 13 (271.1 mg, 96% yield) as a colorless oil. 13: R_f = 0.5 (10% EtOAc in hexane); [α]_D^20 = −23.0° (c = 0.2, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 7.81-7.71 (m, 4H), 7.28-7.20 (m, 6H), 6.21 (d, J = 3.1 Hz, 1H), 5.99 (t, J = 2.6 Hz, 1H), 5.86 (d, J = 3.1 Hz, 1H), 3.95 (t, J = 8.1 Hz, 1H), 3.61 (t, J = 6.2 Hz, 2H), 3.27 (d, J = 1.6 Hz, 1H), 3.17 (ddd, J = 6.7, 4.9, 1.5 Hz, 1H), 2.47 (t, J = 7.4 Hz, 2H), 2.42-2.20 (m, 2H), 2.06 (dd, J = 14.1, 4.9 Hz, 1H), 1.83-1.62 (m, 3H), 1.59 (s, 3H), 1.57-1.45 (m, 2H), 1.30 (s, 3H), 1.17 (s, 9H), 0.94 (s, 9H), 0.04 (s, 3H), −0.01 (s, 3H) ppm; ^13C NMR (75 MHz, C_6D_6) δ 204.7, 156.0, 149.9, 138.2, 136.0, 134.4, 130.0, 128.1, 121.8, 107.7, 106.8, 82.1, 63.8, 61.4, 55.9, 50.1, 38.7, 37.2, 32.3, 28.1, 27.2, 26.1, 25.3, 24.7, 23.5, 19.5, 18.3, −4.3, −4.9 ppm; IR (CH_2Cl_2) 3055, 3024, 2954, 2862, 1712, 1427, 1365, 1096 cm⁻¹; LRMS (EI, 20 eV) m/z 629 (M⁺ − C_4H_9, 7), 627 (11), 589 (4), 583 (8), 567 (7); HRMS (EI, 20 eV) Calculated for C_37H_49O_5Si_2 (M⁺ − C_4H_9) 629.3113, Found 629.3055.

Preparation of tert-butyl(4-(5-((4R,5S)-4-(tert-butyldimethylsiloxy)-5-methyl-5-(((2R,3S)-3-(1-(triethylsiloxy)vinyl)oxiran-2-yl)methyl)cyclopent-1-en-1-yl)furan-2-yl)butoxy)diphenylsilane (14)
LiHMDS was prepared from adding a solution of n-BuLi (2.1 M in hexane, 330 μL, 0.69 mmol) to HMDS (290 μL, 1.4 mmol) in THF (5 mL) at 0°C and stirring for 1 h at 0°C. Then the solution of LiHMDS was added to 13 (95.2 mg, 0.138 mmol) in THF (10 mL) via cannula at -78°C. The resulting mixture was stirred at -78°C for 1 h followed by adding of TESCl (80 μL, 0.5 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h before quenching with saturated NH₄Cl. The reaction mixture was extracted with ether (10 mL x 3) and washed with brine. The combined extracts were dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography using 5% ether and 1% Et₃N in hexane to afford 14 (91.5 mg, 82% yield) as a colorless oil. 14: Rᵣ = 0.73 (10% EtOAc in hexane); [α]₂⁰ = +20.0 ° (c= 0.1, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.80-7.74 (m, 4H), 7.27-7.22 (m, 6H), 6.33 (d, J = 3.2 Hz, 1H), 6.08 (t, J = 2.7 Hz, 1H), 5.90 (d, J = 3.1 Hz, 1H), 4.50 (d, J = 0.7 Hz, 1H), 4.32 (d, J = 0.7 Hz, 1H), 4.01 (t, J = 8.1 Hz, 1H), 3.62 (t, J = 6.3 Hz, 2H), 3.40 (ddd, J = 7.0, 5.5, 1.8 Hz, 1H), 3.25 (d, J = 1.8 Hz, 1H), 2.48 (t, J = 7.4, 7.4 Hz, 2H), 2.45-2.34 (m, 2H), 2.11 (dd, J = 14.0, 5.4 Hz, 1H), 1.91 (dd, J = 14.0, 6.8 Hz, 1H), 1.75-1.64 (m, 2H), 1.59-1.48 (m, 2H), 1.39 (s, 3H), 1.18 (s, 9H), 1.02-0.94 (m, 18H), 0.66 (q, J = 7.5 Hz, 6H), 0.02 (s, 6H) ppm; ¹³C NMR (100 MHz, C₆D₆) δ 155.8, 155.7, 150.1, 138.6, 136.0, 134.4, 130.0, 128.1, 121.5, 107.7, 106.8, 93.0, 82.2, 63.8, 59.1, 55.8, 50.3, 38.9, 37.3, 32.4, 28.1, 27.2, 26.2, 25.7, 24.7, 19.5, 18.3, 6.9, 5.2, −4.3, −4.8 ppm; IR (CH₂Cl₂) 3079, 3056, 3022, 2954, 2885, 1535, 1458, 1420, 1111 cm⁻¹; LRMS (EI, 20 eV) m/z 800 (M⁺, 1), 759 (6), 741 (3), 643 (3); HRMS (EI, 20 eV) Calculated for C₄₇H₇₂O₅Si₃ (M⁺) 800.4682, Found 800.4591.

Preparation of (3R,3aS,5R,5aS,8R,10aR)-3-(tert-butyldimethylsiloxy)-8-(4-(tert-butyldiphenylsiloxy)butyl-5-hydroxy-3a-methyl-3a,4,5,5a,7,8-hexahydro-2H-8,10a-epoxycyclohepta[e]inden-6(3H)-one (15)
To a solution of 14 (114.0 mg, 1.423 mmol) in CH$_2$Cl$_2$ (3 mL) was added TESOTf (3.2 μL, 0.14 mmol) at −78 °C. The resulting mixture was stirred for 1.5 h before quenching with saturated NaHCO$_3$. The reaction mixture was extracted with ether (5 mL x 3) and washed with brine. The combined extracts were dried over anhydrous MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography using 15% EtOAc in hexane to afford 15 (85.3 mg, 87% yield) as a colorless oil. 15: R$_f$ = 0.53 (20% EtOAc in hexane); [α]$_D^{23}$ = −105.0 ° (c = 0.06, CH$_2$Cl$_2$); $^{1}$H NMR (500 MHz, CDCl$_3$) δ 7.67-7.64 (m, 4H), 7.44-7.34 (m, 6H), 6.07 (d, $J$ = 5.9 Hz, 1H), 6.06 (d, $J$ = 6.1 Hz, 1H), 5.68-5.64 (m, 1H), 4.08 (dt, $J$ = 11.4, 4.2 Hz, 1H), 4.04 (d, $J$ = 0.9 Hz, 1H), 3.97 (d, $J$ = 5.1 Hz, 1H), 3.68 (t, $J$ = 5.9 Hz, 2H), 2.75 (ddd, $J$ = 17.1, 5.2, 1.7 Hz, 1H), 2.57 (d, $J$ = 14.7 Hz, 1H), 2.45 (d, $J$ = 10.4 Hz, 1H), 2.33 (d, $J$ = 14.7 Hz, 1H), 2.19 (dd, $J$ = 17.1, 3.0 Hz, 1H), 1.99 (t, $J$ = 12.3 Hz, 1H), 1.86-1.69 (m, 2H), 1.68-1.55 (m, 4H), 1.47-1.38 (m, 1H), 1.13 (s, 3H), 1.04 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$) δ 210.3, 143.8, 136.4, 135.7, 134.5, 134.2, 129.7, 127.8, 120.9, 86.8, 86.2, 81.7, 66.6, 65.3, 63.8, 51.2, 50.6, 40.9, 38.0, 35.8, 32.8, 27.0, 26.1, 25.6, 20.6, 19.4, 18.4, −4.6, −4.7 ppm; IR (CHCl$_3$) 3593, 3036, 3005, 2997, 1732, 1472, 1373, 1256, 1194, 1047 cm$^{-1}$; LRMS (EI, 20 eV) m/z 668 (M$^+$ − H$_2$O, 0.53), 611 (61), 595 (26), 479 (46), 461 (34), 401 (48); HRMS (EI, 20 eV) Calculated for C$_{41}$H$_{56}$O$_4$Si$_2$ (M$^+$ − H$_2$O) 668.3712, Found 668.3700.

Preparation of (3R,3aS,8R,10aS)-3-(tert-butyldimethylsiloxy)-8-(4-(tert-butyldiphenylsiloxy)butyl-3a-methyl-3a, 4,7,8-tetrahydro-2H-8,10a-epoxycyclohepta[e]inden-6(3H)-one (16)

To a solution of 15 (22.7 mg, 0.0330 mmol) in benzene (1 mL) was added activated Florisil (0.165 g, 1.65 mmol). The resulting mixture was warmed to 60 °C and stirred overnight. After cooled to room temperature, the reaction mixture was filtered through a short pad of celite and washed with
EtOAc. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography using 10% EtOAc in hexane to afford 16 (19.3 mg, 87% yield) as a colorless oil.

16: 
- Rf = 0.52 (10% EtOAc in hexane); 
- [α]D20 = −16.0 ° (c = 0.01, CH2Cl2); 
- 1H NMR (400 MHz, C6D6) δ 7.85-7.74 (m, 4H), 7.28-7.21 (m, 6H), 6.81 (dd, J = 5.2, 2.5 Hz, 1H), 6.05 (d, J = 5.7 Hz, 1H), 5.83 (t, J = 2.1 Hz, 1H), 5.63 (d, J = 5.7 Hz, 1H), 4.01 (dd, J = 7.1, 4.9 Hz, 1H), 3.67 (t, J = 6.0 Hz, 2H), 2.68 (dd, J = 19.4, 2.2 Hz, 1H), 2.52 (ddd, J = 16.7, 7.2, 2.1 Hz, 1H), 2.42 (d, J = 17.4 Hz, 1H), 2.27 (d, J = 17.4 Hz, 1H), 2.15 (ddd, J = 16.7, 4.8, 2.4 Hz, 1H), 1.72 (dd, J = 19.4, 5.3 Hz, 1H), 1.65-1.48 (m, 4H), 1.46-1.28 (m, 2H), 1.20 (s, 9H), 0.98 (s, 3H), 0.92 (s, 3H), −0.01 (s, 3H), −0.02 (s, 3H) ppm; 
- 13C NMR (100 MHz, C6D6) δ 194.8, 143.8, 138.0, 136.1, 135.2, 134.5, 132.8, 130.0, 128.1, 120.5, 84.9, 84.2, 81.0, 64.0, 50.3, 48.5, 40.8, 36.5, 33.5, 33.2, 27.2, 26.1, 26.0, 20.5, 19.5, 18.3, −4.4, −4.8 ppm; 
- IR (CH2Cl2) 3053, 3005, 2997, 2968, 1695, 1688, 1632, 1474, 1364, 1236 cm−1; 
- LRMS (EI, 20 eV) m/z 668 (M+, 0.32), 653 (2), 626 (3), 614 (4), 611 (69); 
- HRMS (EI, 20 eV) Calculated for C41H56O4Si2 (M+) 668.3712, Found 668.3707.

Preparation of (3R,3aS,8R,10aS)-3-hydroxy-8-(4-hydroxybutyl)-3a-methyl-3a,4,7,8-tetrahydro-2H-8,10a-epoxycyclohepta[e]inden-6(3H)-one (17)

To a solution of 16 (36.1 mg, 0.0540 mmol) in MeOH (2 mL) was added camphorsulfonic acid (0.0255 g, 0.110 mmol). The resulting mixture was stirred overnight at room temperature before NaHCO3 (9.3 mg, 0.11 mmol) added. Then the resulting solution was concentrated in vacuo and the residue was purified by flash column chromatography using EtOAc to afford 17 (13.5 mg, 79% yield) as a colorless oil.

17: 
- Rf = 0.21 (70% EtOAc in hexane); 
- [α]D20 = −65.4 ° (c = 0.48, CH2Cl2); 
- 1H NMR (500 MHz, C6D6) δ 6.82 (dd, J = 5.1, 2.8 Hz, 1H), 5.91 (d, J = 5.7 Hz, 1H), 5.78 (t, J = 2.2 Hz, 1H), 5.57 (d, J = 5.7 Hz, 1H), 3.72 (dd, J = 6.4, 3.2 Hz, 1H), 3.35 (t, J = 6.2 Hz, 2H), 2.67 (dd, J = 19.8, 2.7 Hz, 1H), 2.49 (ddd, J = 17.2, 6.5, 2.0 Hz, 1H), 2.44 (d, J = 17.4 Hz, 1H), 2.27 (d, J = 17.4 Hz, 1H), 1.99 (td, J = 17.2, 2.9 Hz, 1H), 1.64 (dd, J = 19.8, 5.1 Hz, 1H), 1.58-1.24 (m, 7H), 0.99 (broad, 1H), 0.84 (s, 3H) ppm; 
- 13C NMR (125 MHz, C6D6) δ 194.8, 144.0, 137.1, 136.1, 134.8, 132.9, 121.1, 85.1, 83.6, 80.0, 62.4, 50.0, 48.5, 40.5, 36.5, 33.2, 32.0, 25.9, 20.5 ppm; 
- IR (CH2Cl2) 3051, 3032, 3016, 2953, 1697, 1637, 1522, 1421, 1225 cm−1; 
- LRMS (EI, 20 eV) Calculated for C41H56O4Si2 (M+) 668.3712, Found 668.3707.
eV) m/z 316 (M⁺, 18), 275 (20), 274 (100), 257 (25), 241 (29); HRMS (EI, 20 eV) Calculated for C₁₉H₂₄O₄ (M⁺) 316.1669, Found 316.1677.

Preparation of (3R,3aS,8S,10aS,10bR)-3-hydroxy-8-(4-hydroxybutyl)-3a-methyl-2,3,3a,4,7,8,9,10-octahydro-1H-8,10a-epoxycyclohepta[e]inden-6(10bH)-one (18)

To a solution of 17 (9.9 mg, 0.031 mmol) in degassed CH₂Cl₂ (0.3 mL) was added Crabtree’s catalyst (1.3 mg, 0.0016 mmol). The resulting mixture was stirred under hydrogen overnight at room temperature. After filtered through a short pad of silica gel, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography using 30% acetone in CH₂Cl₂ to afford 18 (8.6 mg, 86% yield) as a colorless oil and 18’ (1.0 mg, 10% yield) as a colorless oil. 18: Rf = 0.23 (70% EtOAc in hexane); [α]D²⁰ = +5 ° (c = 0.12, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 6.76 (dd, J = 5.1, 2.6 Hz, 1H), 3.36-3.26 (m, 3H), 2.69 (dd, J = 11.6, 7.9 Hz, 1H), 2.52 (dd, J = 19.3, 2.3 Hz, 1H), 2.45 (d, J = 17.2 Hz, 1H), 2.36 (d, J = 17.2 Hz, 1H), 1.93-1.75 (m, 2H), 1.57-1.50 (m, 3H), 1.48-1.21 (m, 12H), 0.37 (s, 3H) ppm; ¹³C NMR (125 MHz, C₆D₆) δ 196.5, 141.7, 132.5, 83.4, 80.0, 79.0, 62.4, 52.2, 45.5, 39.8, 35.8, 33.4, 33.4, 32.4, 31.4, 26.3, 20.5, 20.4, 20.0 ppm; IR (CH₂Cl₂) 3819, 3055, 2986, 2939, 1690, 1427, 1273, 1258, 1041 cm⁻¹; LRMS (EI, 20 eV) m/z 320 (M⁺, 1), 302 (3), 292 (59), 274 (28); HRMS (EI, 20 eV) Calculated for C₁₉H₂₈O₄ (M⁺) 320.1982, Found 320.1983. 18’: Rf = 0.23 (70% EtOAc in hexane); [α]D²² = +31 ° (c = 0.01, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.72 (dd, J = 5.3, 2.5 Hz, 1H), 6.21 (d, J = 5.9 Hz, 1H), 6.10 (d, J = 5.9 Hz, 1H), 3.83 (d, J = 5.5 Hz, 1H), 3.66 (t, J = 6.3 Hz, 2H), 2.69 (dd, J = 19.1, 1.9 Hz, 1H), 2.51 (d, J = 17.6 Hz, 1H), 2.44 (dd, J = 11.5, 8.2 Hz, 1H), 2.38 (d, J = 17.5 Hz, 1H), 2.25 (s, 1H), 2.05-1.92 (m, 2H), 1.78-1.73 (m, 2H), 1.67-1.37 (m, 6H), 0.81 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 197.2, 138.5, 137.1, 133.6, 133.4, 87.6, 84.2, 79.2, 62.8, 48.3, 46.2, 44.4, 36.3, 33.2, 32.9, 32.7, 21.2, 20.1, 20.0 ppm; IR (CH₂Cl₂) 3425, 3055, 2986, 2924, 2862, 1690, 1628, 1427, 1265, 1049 cm⁻¹; LRMS (EI, 20 eV) m/z 318 (M⁺, 4), 300 (6), 285 (7), 282 (5); HRMS (EI, 20 eV) Calculated for C₁₉H₂₆O₄ (M⁺) 318.1826, Found 318.1834.
Preparation of
(3aS,6aS,7R,10aS,12aS,12bR)-7-hydroxy-3a-methyl-1,3a,4,7,8,9,10,11,12,12b-decahydro-10a,12 a-epoxybenzo[4,5]cyclohepta[1,2-e]indene-3,6(2H,6aH)-dione (5)

To a solution of 18 (5.9 mg, 0.018 mmol) in CH₂Cl₂ (2 mL) was added Dess-Martin periodinane (23 mg, 0.055 mmol). The resulting mixture was stirred for 6.5 h at room temperature. After filtered through a short pad of silica gel, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography using 1% Et₃N, 55% EtOAc in hexane to afford 5 (4.9 mg, 84% yield) as a colorless oil. Rᵢ = 0.63 (70% EtOAc in hexane); [α]₂⁰° = +232 ° (c = 0.05, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 6.51 (t, J = 3.8 Hz, 1H), 3.87 (ddd, J = 10.8, 10.0, 4.6 Hz, 1H), 2.20-2.12 (m, 1H), 2.07-2.01 (m, 1H), 2.00-1.95 (m, 2H), 1.92 (d, J = 3.8 Hz, 2H), 1.77-1.64 (m, 3H), 1.61-1.49 (m, 2H), 1.44-1.36 (m, 3H), 1.31-1.19 (m, 3H), 1.09 (dt, J = 13.9, 4.4 Hz, 1H), 0.43 (s, 3H) ppm; ¹³C NMR (125 MHz, C₆D₆) δ 216.8, 200.0, 140.2, 134.3, 83.3, 79.7, 69.3, 64.9, 47.7, 46.6, 37.9, 35.4, 35.4, 34.8, 33.5, 31.3, 20.7, 18.8, 16.9 ppm; IR (CH₂Cl₂) 3834, 3047, 2986, 2924, 1744, 1682, 1612, 1427, 1242, 1034 cm⁻¹; LRMS (EI, 20 eV) m/z 316(M⁺, 8), 298 (12), 280 (9), 270 (11), 197 (10); HRMS (EI, 20 eV) Calculated for C₁₉H₂₄O₄ (M⁺) 316.1669, Found 316.1670.
Determination of ee of 7a

To a solution of 7a (3.4 mg, 0.022 mmol) in CH$_2$Cl$_2$ (300 µL) was added pyridine (15 µL, 0.11 mmol), benzoyl chloride (8 µL, 0.07 mmol), and DMAP (2.7 mg, 0.022 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was directly purified by flash column chromatography using 10% EtOAc in hexane to afford Bz-7a (5.4 mg, 95% yield, 94% ee) as a colorless oil. Bz-7a: R$_f$ = 0.70 (20% EtOAc in hexane); [$\alpha$]$^D_{20}$ = −41.5 ° (c = 0.2, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.03-7.98 (m, 2H), 7.61-7.55 (m, 1H), 7.48-7.42 (m, 2H), 5.74 (tdd, J = 15.7, 11.2, 7.5 Hz, 1H), 5.38 (dd, J = 4.3, 3.0 Hz, 1H), 5.04 (s, 1H), 5.03-4.99 (m, 1H), 2.51-2.30 (m, 5H), 2.23-2.13 (m, 1H), 1.10 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 219.3, 165.7, 133.4, 133.2, 130.0, 129.7, 128.7, 118.9, 79.6, 52.4, 35.9, 34.2, 25.9, 20.0 ppm; IR (CH$_2$Cl$_2$) 3038, 3018, 2986, 1734, 1717, 1452, 1112 cm$^{-1}$; LRMS (EI, 20 eV) m/z 258 (M$^+$, 0.15), 136 (13), 121 (4); HRMS (EI, 20 eV) Calculated for C$_{16}$H$_{18}$O$_3$ (M$^+$) 258.1250, Found 258.1251; enantiomeric excess was determined by HPLC analysis (Chiralcel OD 0.1 mL/ min, 1% IPA in hexane); retention times: 47.4 min (major), 52.4 min (minor).
Table 1: Chromatographic Data

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