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Electronic Supplementary Information

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

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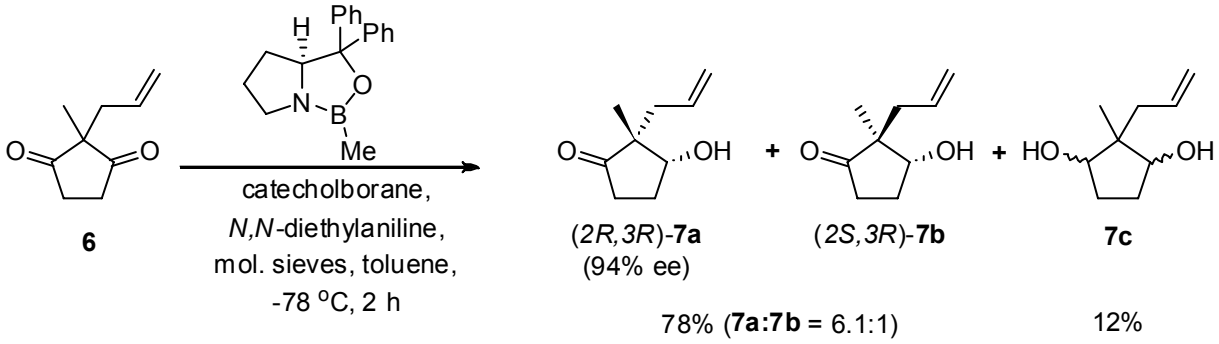
Contents

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 chromatrography 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 Spectrophotomer from 4000 cm^{-1} to 400 cm^{-1}. Mass spectra were recorded on a Finnigan MAT 95 mass spectrometer or API QSTAR PULSAR *i*LC/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 (2*R*,3*R*)-2-allyl-3-hydroxy-2-methylcyclopentanone (**7a**)



6

(*2R,3R*)-**7a** (94% ee)

(*2S,3R*)-**7b**

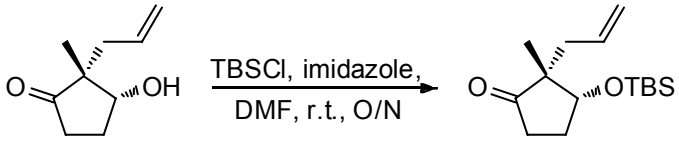
7c

78% (**7a:7b** = 6.1:1)

12%

(*S*)-CBS-*B*-Me-was prepared according to the literature,[1] 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 $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using 35%-85% EtOAc in hexane to afford (2*R*,3*R*)-**7a** (288.0 mg, 67% yield) as a colorless oil, (2*S*,3*R*)-**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. (2*R*,3*R*)-**7a**: R_f = 0.40 (35% EtOAc in hexane); $[\alpha]_D^{20}$ = –79.5 ° (c = 0.95, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 (2*R*,3*R*)-**7a** in the literature.[2,3] (2*S*,3*R*)-**7b**: R_f = 0.33 (35% EtOAc in hexane); $[\alpha]_D^{20}$ = +76.7° (c = 0.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (dddd, *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 (dddd, *J* = 12.3, 8.7, 7.6, 7.0 Hz, 1H), 1.63 (s, 1H), 1.01 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 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 (2*S*,3*R*)-**7b** in the literature.[2]

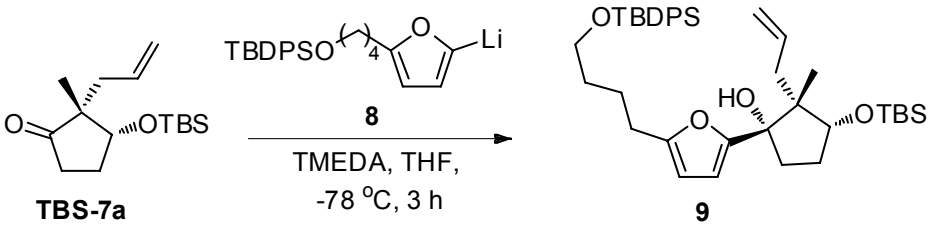
Preparation of (2*R*,3*R*)-2-allyl-3-(*tert*-butyldimethylsiloxy)-2-methylcyclopentanone **(TBS-7a)**



7a quantitative **TBS-7a**

To a solution of (2*R*,3*R*)-**7a** (632.6 mg, 4.102 mmol) in DMF (2.0 mL) was added imidazole (854.1 mg, 12.54 mmol), TBSCl (1.225 g, 8.130 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with saturated NH_4Cl. 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 5% EtOAc in hexane to afford **TBS-7a** (1.100 g, 100% yield) as a colorless oil. **TBS-7a**: R_f = 0.87 (35% EtOAc in hexane); $[\alpha]_D^{20}$ = –37.8 ° (c = 0.23, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.5, 134.4, 117.8, 78.2, 53.5, 35.5, 34.4, 28.4, 25.9, 19.7, 18.1, –4.2, –4.8 ppm; IR (CH_2Cl_2) 3070, 2955, 2862, 1736, 1636, 1466, 1381, 1088 cm^{-1}; LRMS (EI, 20 eV) m/z 211 ($M^+ - C_4H_9$, 100), 193 (5), 143 (3), 119 (7); HRMS (EI, 20 eV) Calculated for $C_{11}H_{19}O_2Si$ ($M^+ - C_4H_9$) 211.1149, Found 211.1151.

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



TBS-7a **9**

45%
81% b.o.r.s.m.

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 NH_4Cl. 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 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); $[\alpha]_D^{20}$ = –33.4 ° (c = 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ7.80-7.74 (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, C_6D_6) 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 (CH_2Cl_2) 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 $C_{39}H_{58}O_4Si_2$ (M^+) 646.3874, Found 646.3841.

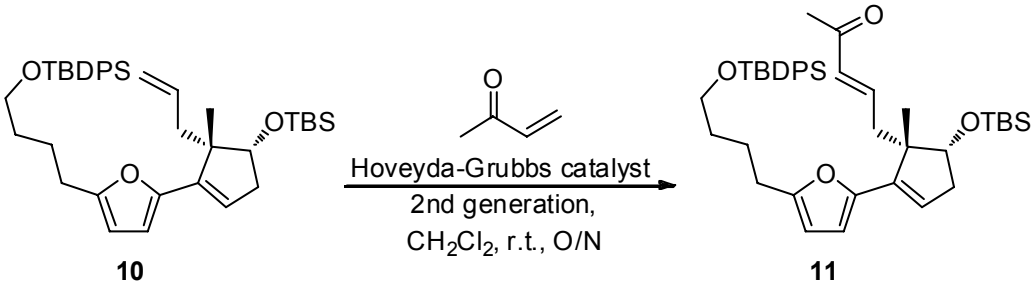
Preparation of (((1*R*,2*S*)-2-allyl-3-(5-(4-(*tert*-butyldiphenylsiloxy)butyl)furan-2-yl)-2-methyl-cyclopent-3-en-1-yl)oxy)(*tert*-butyl)dimethylsilane **(10)**

9 68% 88% b.o.r.s.m. **10**

To a solution of **9** (483.5 mg, 0.7472 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (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 NH_4Cl. The reaction mixture was extracted with ether (10 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 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); $[\alpha]_D^{20}$ = –24.1 ° (c = 0.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 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,

2H), 1.81-1.70 (m, 2H), 1.69-1.59 (m, 2H), 1.24 (s, 3H), 1.07 (s, 9H), 0.95 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 150.0, 138.4, 137.0, 135.7, 134.2, 129.7, 127.7, 121.3, 116.1, 106.9, 106.2, 81.9, 63.7, 51.2, 39.6, 39.2, 32.2, 27.9, 27.0, 26.0, 25.1, 24.5, 19.4, 18.2, –4.3, –4.8 ppm; IR (CH_2Cl_2) 3086, 3030, 2988, 2856, 1699, 1653, 1623, 1472, 1429, 1265 cm^{-1}; LRMS (EI, 20 eV) m/z 628 (M^+, 1), 603 (8), 628 (35), 613 (58), 587 (15); HRMS (EI, 20 eV) Calculated for $C_{39}H_{56}O_3Si_2$ (M^+) 628.3716, Found 628.3763.

Preparation of (*E*)-5-((1*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-(5-(4-(*tert*-butyldiphenylsiloxy)-butyl)furan-2-yl)-1-methylcyclopent-2-en-1-yl)pent-3-en-2-one **(11)**

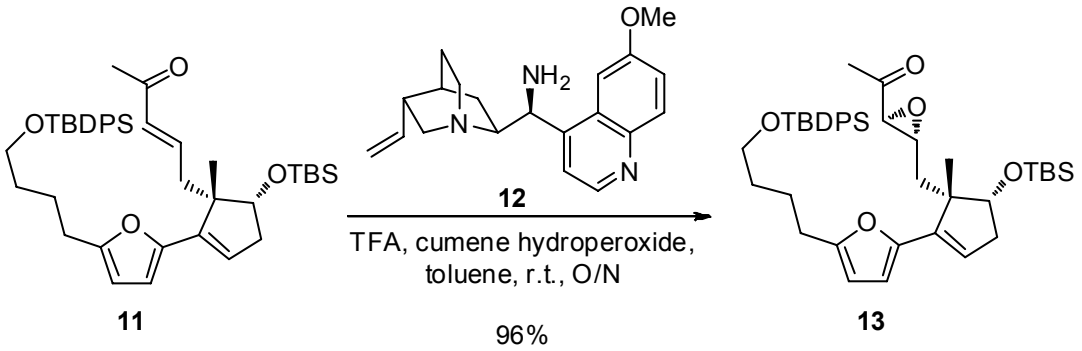


10 **11**

83%

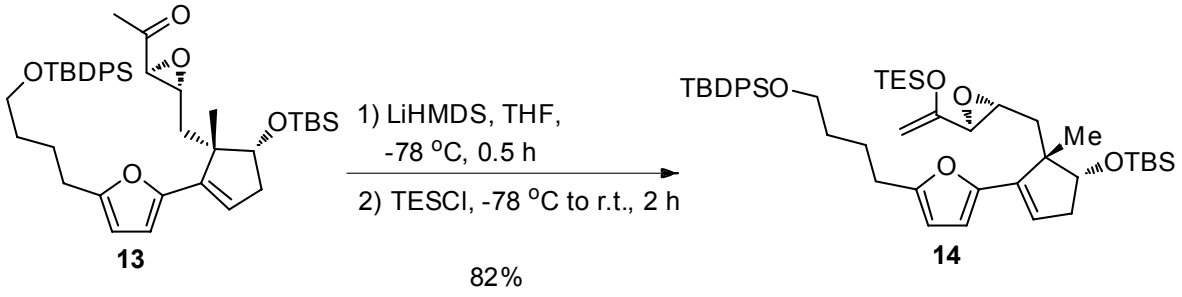
To a solution of **10** (321.4 mg, 0.5109 mmol) in degassed CH_2Cl_2 (10.5 mL) was added 3-buten-2-one (0.13 mL, 1.6 mmol) and the Hoveyda-Grubbs catalyst 2nd generation (16.3 mg, 0.0260 mmol) at room temperature. The resulting mixture was stirred overnight at room temperature. After filtered through 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**: R_f = 0.60 (10% EtOAc in hexane); $[\alpha]_D^{20}$ = –18.1 ° (c = 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 155.8, 149.5, 147.7, 137.8, 135.7, 134.2, 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 (CH_2Cl_2) 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 $C_{41}H_{58}O_4Si_2$ (M^+) 670.3874, Found 670.3849.

Preparation of 1-((2*S*,3*R*)-3-(((1*S*,5*R*)-5-((*tert*-butyldimethylsiloxy)-2-(5-(4-(*tert*-butyldiphenyl-siloxy)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.[4] 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 in 10% ether hexane to afford **13** (271.1 mg, 96% yield) as a colorless oil. **13**: R_f = 0.5 (10% EtOAc in hexane); $[\alpha]_D^{20}$ = –23.0 ° (c = 0.2, CH_2Cl_2); ^{1}H 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; ^{13}C 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 $C_{37}H_{49}O_5Si_2$ ($M^+ - C_4H_9$) 629.3113, Found 629.3055.

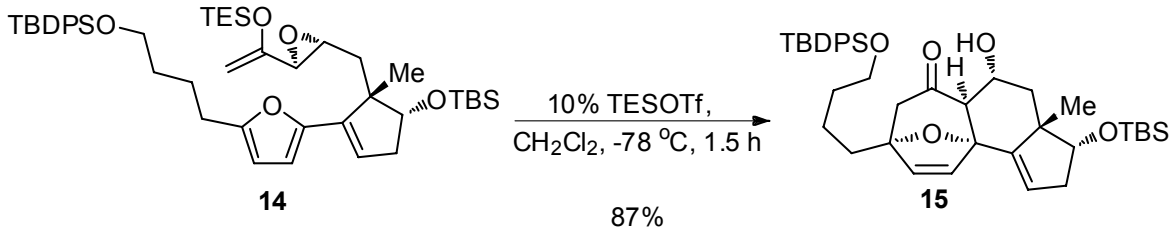
Preparation of *tert*-butyl(4-(5-((4*R*,5*S*)-4-(*tert*-butyldimethylsiloxy)-5-methyl-5-(((2*R*,3*S*)-3-(1-(triethylsiloxy)vinyl)oxiran-2-yl)methyl)cyclopent-1-en-1-yl)furan-2-yl)butoxy)diphenylsilane **(14)**



13 82% **14**

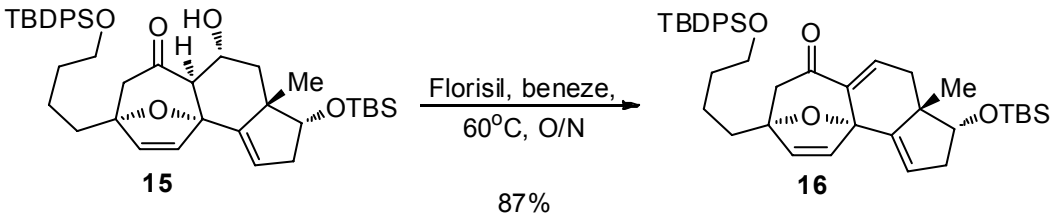
LiHMDS was prepared from adding a solution of *n*-BuLi (2.1 M in hexane, 330 μL, 0.69 mmol) to HMDS (290 μL, 1.4 mmol) in THF (5 mL) at 0°C and stirring for 1 h at 0 °C. Then the solution of LiHMDS was added to **13** (95.2 mg, 0.138 mmol) in THF (10 mL) via cannula at -78 °C. The resulting mixture was 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 NH_4Cl. The reaction mixture was extracted with ether (10 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 5% ether and 1% Et_3N in hexane to afford **14** (91.5 mg, 82% yield) as a colorless oil. **14**: R_f = 0.73 (10% EtOAc in hexane); $[\alpha]_D^{20}$ = +20.0 ° (c= 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) 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; ^{13}C NMR (100 MHz, C_6D_6) 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 (CH_2Cl_2) 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 $C_{47}H_{72}O_5Si_3$ (M^+) 800.4682, Found 800.4591.

Preparation of (3R,3aS,5R,5aS,8R,10aR)-3-(*tert*-butyldimethylsiloxy)-8-(4-(*tert*-butyldiphenyl-siloxy)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_2Cl_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); $[\alpha]_D^{20}$ = −105.0 ° (c = 0.06, CH_2Cl_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 ($M^+ - H_2O$, 0.53), 611 (61), 595 (26), 479 (46), 461 (34), 401 (48); HRMS (EI, 20 eV) Calculated for $C_{41}H_{56}O_4Si_2$ ($M^+ - H_2O$) 668.3712, Found 668.3700.

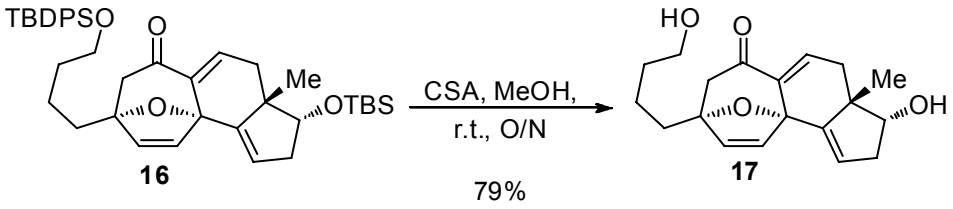
Preparation of (3R,3aS,8R,10aS)-3-(*tert*-butyldimethylsiloxy)-8-(4-(*tert*-butyldiphenylsiloxy)butyl-3a-methyl-3a, 4,7,8-tetrahydro-2H-8,10a-epoxycyclohepta[e]inden-6(3H)-one **(16)**



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**: R_f = 0.52 (10% EtOAc in hexane); $[\alpha]_D^{20}$ = –16.0 ° (c = 0.01, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) 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, 9H), –0.01 (s, 3H), –0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, C_6D_6) 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 (CH_2Cl_2) 3053, 3005, 2997, 2968, 1695, 1688, 1632, 1622, 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 $C_{41}H_{56}O_4Si_2$ (M^+) 668.3712, Found 668.3707.

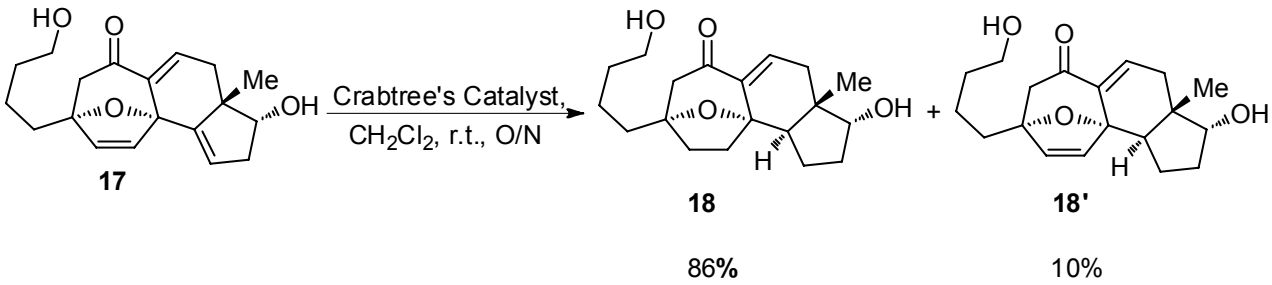
Preparation of (3R,3aS,8R,10aS)-3-hydroxy-8-(4-hydroxybutyl)-3a-methyl-3a,4,7,8-tetrahydro-2H-8,10a-epoxycyclohepta[e]inden-6(3H)-one **(17)**



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 $NaHCO_3$ (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**: R_f = 0.21 (70% EtOAc in hexane); $[\alpha]_D^{20}$ = –65.4 ° (c = 0.48, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) 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; ^{13}C NMR (125 MHz, C_6D_6) 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 (CH_2Cl_2) 3051, 3032, 3016, 2953, 1697, 1637, 1522, 1421, 1225 cm^{-1}; LRMS (EI, 20

eV) m/z 316 (M^+ , 18), 275 (20), 274 (100), 257 (25), 241 (29); HRMS (EI, 20 eV) Calculated for $C_{19}H_{24}O_4$ (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)**



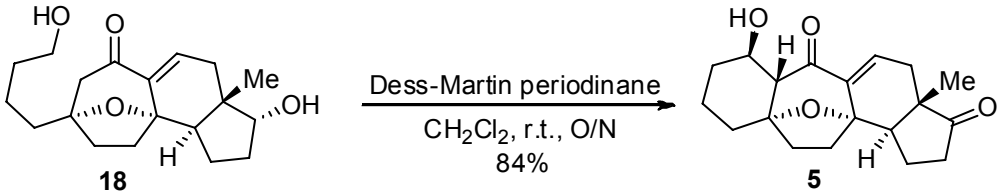
17 **18** **18'**

86% 10%

To a solution of **17** (9.9 mg, 0.031 mmol) in degassed CH_2Cl_2 (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 CH_2Cl_2 to afford **18** (8.6 mg, 86% yield) as a colorless oil and **18'** (1.0 mg, 10% yield) as a colorless oil. **18**: R_f = 0.23 (70% EtOAc in hexane); $[\alpha]_D^{20}$ = +5 ° (c = 0.12, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) 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; ^{13}C NMR (125 MHz, C_6D_6) 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 (CH_2Cl_2) 3819, 3055, 2986, 2939, 1690, 1620, 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 $C_{19}H_{28}O_4$ (M^+) 320.1982, Found 320.1983. **18'**: R_f = 0.23 (70% EtOAc in hexane); $[\alpha]_D^{20}$ = +31 ° (c = 0.01, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ6.72 (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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2Cl_2) 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 $C_{19}H_{26}O_4$ (M^+) 318.1826, Found 318.1834.

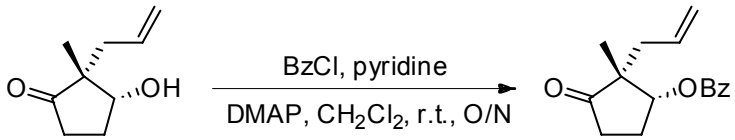
Preparation of

(3aS,6aS,7R,10aS,12aS,12bR)-7-hydroxy-3a-methyl-1,3a,4,7,8,9,10,11,12,12b-decahydro-10a,12a-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 CH_2Cl_2 (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% Et_3N, 55% EtOAc in hexane to afford **5** (4.9 mg, 84% yield) as a colorless oil. R_f = 0.63 (70% EtOAc in hexane); $[\alpha]_D^{20}$ = +232 ° (c = 0.05, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) 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; ^{13}C NMR (125 MHz, C_6D_6) 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 (CH_2Cl_2) 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 $C_{19}H_{24}O_4$ (M^+) 316.1669, Found 316.1670.

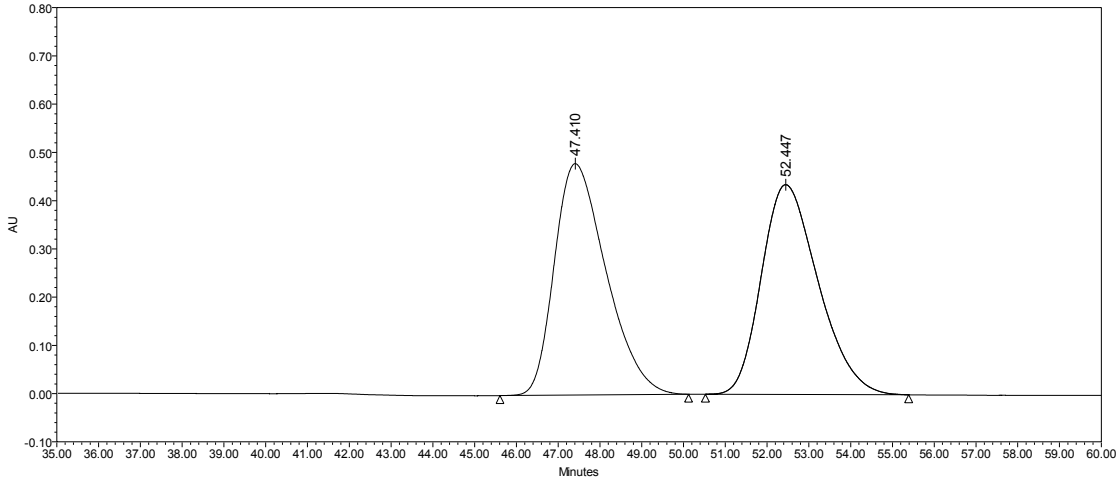
Determination of ee of **7a**



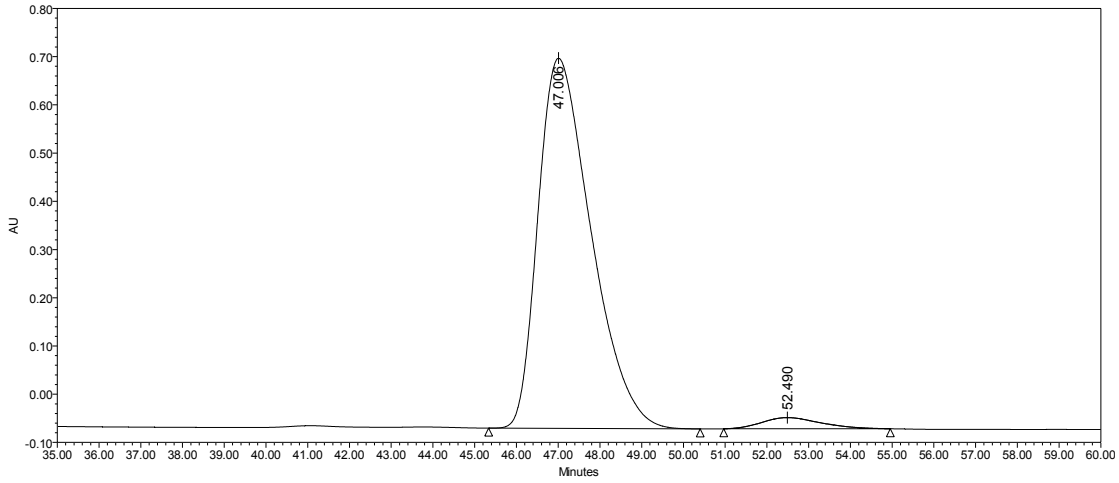
7a **Bz-7a**

To a solution of **7a** (3.4 mg, 0.022 mmol) in CH_2Cl_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_2Cl_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_2Cl_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).

Sample	rac-**Bz-7a/ Bz-7a**
Column	CHIRALCEL OD
Mobile phase	n-Hexane/2-Propanol = 99/1 (v/v)
Flow rate	0.1 mL/min
Detection	UV 210 nm



	Retention Time/ min	Area	% Area	Height
1	47.410	41253198	50.08	479817
2	52.447	41113343	49.92	434952



	Retention Time/ min	Area	%Area	Height
1	47.006	67743602	96.76	767842
2	52.490	2267514	3.24	23143

References

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