

# Biomimetic Syntheses of the Neurotrophic Natural Products Caryolanemagnolol and Clovanemagnolol

Xu Cheng, Nicole L. Harzdorf, Travis Shaw, and Dionicio Siegel\*

*Department of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station, Austin TX 78712*

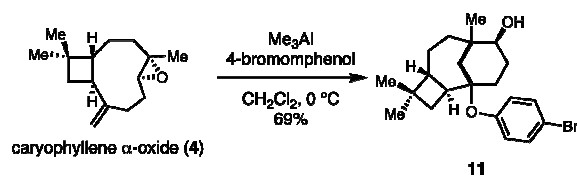
*dsiegel@cm.utexas.edu*

## Supporting Information

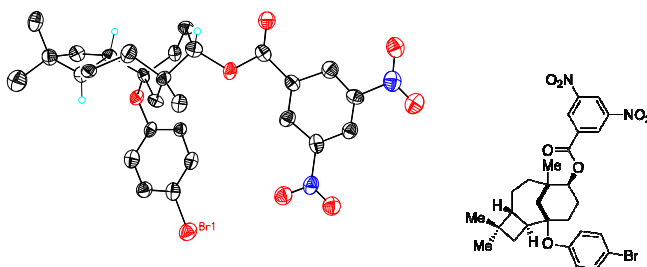
**General Procedures.** All reactions were performed in flame dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or canula. Where necessary (so noted), solutions were deoxygenated by alternative freeze (liquid N<sub>2</sub>)/evacuation/thaw cycles ( $\geq$  three iterations). Organic solutions were concentrated by rotary evaporation at ~20 Torr. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or exposure to an acidic solution of *p*-anisaldehyde or ceric ammonium molybdate solution followed by heating on a hot plate.

**Materials.** Dichloromethane, tetrahydrofuran, toluene, and benzene were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). All commercial reagents were used directly, without further purification unless otherwise noted.

**Instrumentation.** Nuclear magnetic resonance spectra (<sup>1</sup>H NMR and <sup>13</sup>C NMR) were recorded with a Varian Gemini (400 MHz) or Varian (300MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) downfield of tetramethylsilane and referenced relative to residual protium in NMR solvents (CHCl<sub>3</sub>:  $\delta$  7.26 ppm, C<sub>6</sub>D<sub>5</sub>H:  $\delta$  7.15 ppm; D<sub>2</sub>HCO:  $\delta$  3.31 ppm). Chemical shifts for carbon are reported in ppm downfield of tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl<sub>3</sub>  $\delta$  77.0, C<sub>6</sub>D<sub>6</sub>  $\delta$  128.0, D<sub>3</sub>CO:  $\delta$  44.9). Infrared spectra (IR) were recorded on a Nicolet 380 FTIR using thin film (neat). Optical rotations were measured on an ATAGO AP-300 automatic polarimeter with a path length of 100 mm. Melting points were measured on a MEL-TEMP device without correction. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 at the UT Mass Spectrometry Facility.

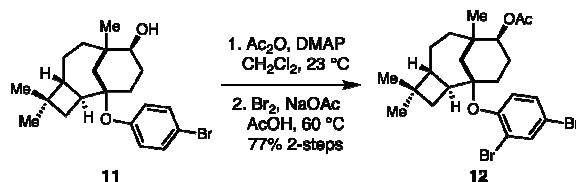


To a solution of *p*-bromophenol (1.93 g, 11.2 mmol, 1.5 eq) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0 °C was added a solution of AlMe<sub>3</sub> in hexane (1 M, 3.72 mL, 3.72 mmol, 0.5 eq) over 5 minutes, followed by stirring at 0 °C for 30 minutes, warmed to 23 °C, and stirred for 1 hour then the solution was concentrated and *p*-bromophenol (1.93 g, 11.2 mmol, 1.5 eq) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added at 0 °C dropwise. After stirring for 10 minutes a solution of caryophyllene oxide (1.64 g (2.2:1 ratio of epoxides), 5.1 mmol of **4**, 1 eq of **4**) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added over 30 minutes. The mixture was stirred at 0 °C for an additional 2 hours then the solvent was removed and the residue was suspended with hexane (200 mL). The organic layer was washed with 2 N HCl (50 mL), 1 NaOH (50 mL), and brine (30 mL). The organic extract was dried over MgSO<sub>4</sub>, filtered, and concentrated to provide a viscous residue. The residue was purified by silica gel chromatography (hexane/EtOAc = 9:1 as eluent) to give **11** as a clear oil (1.37 g, yield 69% from **4**. TLC R<sub>f</sub> = 0.24, hexane/EtOAc = 85:15. [α]<sub>D</sub><sup>26</sup> = 90.3°, (*c* 1.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.00 (s, 3H), 1.14-1.21 (m, 1H), 1.37-1.87 (m, 10H), 1.96-2.06 (m, 2H), 2.34 (ddd, *J* = 2.1, 3.4, 18.2 Hz, 1H), 3.49 (dd, *J* = 3.0, 4.6 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 20.8, 21.1, 26.4, 28.3, 30.3, 30.5, 34.7, 36.0, 37.5, 39.2, 40.3, 41.9, 44.8, 71.6, 80.7, 114.0, 123.2, 131.5, 154.7; FTIR: 3394, 1638, 1493, 1232 cm<sup>-1</sup>; HRMS (ESI<sup>+</sup>) calculated for C<sub>21</sub>H<sub>29</sub>BrO<sub>2</sub>Na 415.1249, found 415.1243.



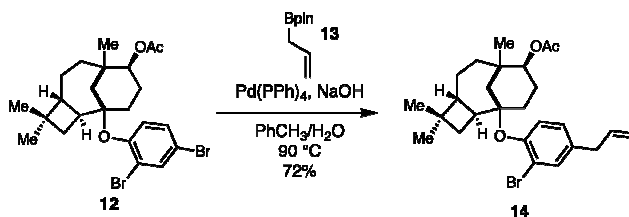
To a solution of **11** (50 mg, 0.127 mmol, 1 eq) and 4-dimethylaminopyridine (31.1 mg, 0.254 mmol, 2 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at 0 °C was added a solution of 3,5-dinitrobenzoyl chloride (58.6 mg, 0.254 mmol, 2eq) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The mixture was stirred at 23 °C for 4 hours, then the solution was washed with 1 N NaOH (10 mL), and 2 N HCl (10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 90:10 as eluent) provided the 3,5-dinitrobenzoate of **11** as a light yellow solid (58 mg, 78%). The solid was readily recrystallized from ethanol to provide crystals suitable for X-ray analysis. TLC R<sub>f</sub> = 0.55, hexane/EtOAc = 80:20; Mp 177-178 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.98 (s, 3H), 1.03 (s, 3H), 1.06 (s, 3H), 1.32-1.37 (m, 1H), 1.47-1.54 (m, 1H), 1.58-1.76 (m, 6H), 1.89 (dd, *J* = 1.4, 13.3 Hz, 1H), 1.97-2.22 (m, 4H), 2.41 (ddd, *J* = 2.8, 9.0 and 12.0 Hz, 1H), 5.11 (t, *J* = 4.0 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 9.04 (d, *J* = 2.1 Hz, 2H), 9.22 (t, *J* = 2.1 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 20.8, 21.2, 25.7, 26.9, 30.3, 31.2, 34.8, 35.8, 37.4, 38.8, 40.6, 43.2, 44.9, 79.9, 114.6, 122.4, 123.2, 129.2, 131.8, 134.1, 148.7, 154.4,

161.8; FTIR: 3104, 1734, 1540  $\text{cm}^{-1}$ ; HRMS (CI<sup>+</sup>), calculated for  $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_7\text{Br}$  586.1315, found 586.1326.



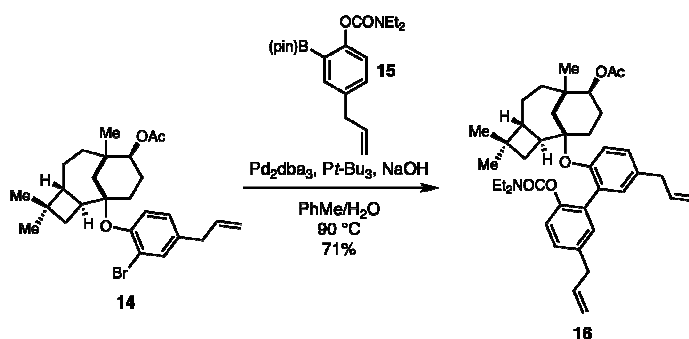
To a solution of **11** (1.23 g, 3.13 mmol, 1 eq), triethylamine (0.87 mL, 6.25 mmol, 2 eq), and 4-dimethylaminopyridine (0.382 g, 3.13 mmol, 1 eq) in  $\text{CH}_2\text{Cl}_2$  (40 mL) at 0 °C was added the acetic anhydride (0.443 mL, 4.69 mmol, 1.5 eq). The solution was stirred at 23 °C for 20 minutes then the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and washed with 2 N HCl (30 mL), 1 N NaOH (20 mL), and brine (10 mL). The organic extract was dried over  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 95:5 as eluent) to yield the acetate of **11** as colorless oil (1.14 g, 84%). TLC  $R_f$  = 0.28, hexane/EtOAc = 95:5;  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.87 (s, 3H), 0.99 (s, 3H), 1.01 (s, 3H), 1.20-1.28 (m, 1H), 1.39-2.06 (m, 9H), 1.91-2.06 (m, 3H), 2.01 (s, 3H), 2.36 (ddd,  $J$  = 1.3, 10.2, 11.7 Hz, 1H), 4.71 (t,  $J$  = 3.7 Hz, 1H), 6.73 (d,  $J$  = 8.9 Hz, 2H), 7.29 (d,  $J$  = 8.9 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.8, 21.1, 21.2, 25.7, 26.6, 30.3, 34.7, 35.9, 37.8, 38.3, 40.2, 43.1, 44.9, 73.6, 80.4, 113.8, 122.7, 131.6, 154.7, 170.6. FTIR: 1734, 1486, 1245  $\text{cm}^{-1}$ ; HRMS (ESI<sup>+</sup>), calculated for  $\text{C}_{23}\text{H}_{31}\text{BrO}_3\text{Na}$  458.1349, found 457.1349.

To a reaction flask charge with the acetate of **11** (0.832 g, 1.91 mmol, 1 eq) and sodium acetate (0.314 g, 3.82 mmol, 2 eq) in acetic acid (10 mL) was added bromine (0.404 mL, 7.64 mmol, 4 eq) dissolved in acetic acid (5 mL) in a single portion. The reaction was heated to 60 °C for 4 hour the reaction was diluted with hexane (100 mL) and washed with water (100 mL X 3), 1 N NaOH (20 mL X 3), and then brine (30 mL). The organic extract was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 95:5) provided **12** as colorless oil (0.902 g, 92%). TLC  $R_f$  = 0.28, hexane/EtOAc = 95:5;  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.89 (s, 3H), 1.01 (s, 3H), 1.02 (s, 3H), 1.23-1.29 (m, 1H), 1.39-2.01 (m, 11H), 2.03 (s, 3H), 2.13 (m, 1H), 2.29-2.43 (m, 1H), 4.71 (t,  $J$  = 3.2 Hz, 1H), 6.78 (d,  $J$  = 8.8 Hz, 1H), 7.24 (dd,  $J$  = 2.4, 8.8 Hz, 1H), 7.65 (d,  $J$  = 2.4 Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.8, 21.0, 21.2, 25.7, 26.7, 30.3, 30.9, 34.8, 35.8, 37.7, 38.4, 40.3, 42.4, 44.7, 73.6, 83.0, 114.0, 117.9, 122.5, 130.2, 135.4, 152.1, 170.6. FTIR: 1738, 1467, 1040, 1017  $\text{cm}^{-1}$ ; HRMS (ESI<sup>+</sup>), calculated for  $\text{C}_{23}\text{H}_{30}\text{Br}_2\text{O}_3\text{Na}$  535.0455, found 535.0454.

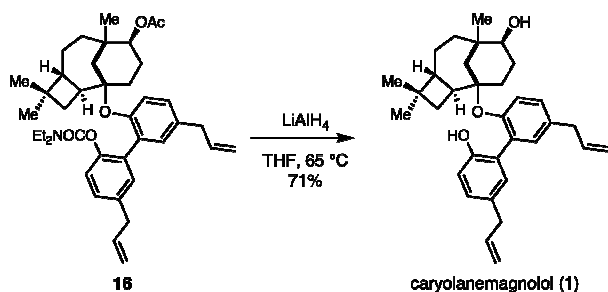


To a mixture of **12** (640 mg, 1.24 mmol, 1 eq),  $\text{Pd}(\text{PPh}_3)_4$  (288 mg, 0.249 mmol, 0.2 eq), and NaOH (0.995 g, 24.9 mmol, 20 eq) was added toluene (18 mL), water (9 mL), and pinacol allylboronate **13** (4.0 mL, 16.0 mmol, 13 eq) followed by vigorous stirring (1200

rpm) at 90 °C for 55 minutes. The organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL). The combined the organic extracts were combined with silica gel (1 g) and the sample was concentrated to dryness. The sample was purified by silica gel chromatography (hexane/EtOAc = 95:5 as eluent) to provide **14** as colorless oil (430 mg, 72%). TLC  $R_f$  = 0.30, hexane/EtOAc = 95:5;  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.88 (s, 3H), 1.01 (s, 3H), 1.02 (s, 3H), 1.21-1.27 (m, 1H), 1.39-1.65 (m, 4H), 1.73 (dd,  $J$  = 8.0, 9.6 Hz, 1H), 1.88-1.91 (m, 5H), 1.95-2.00 (m, 1H), 2.02 (s, 3H), 2.16 (m, 1H), 2.37 (ddd,  $J$  = 1.7, 3.6, 18.2 Hz, 1H), 3.28 (d,  $J$  = 6.7 Hz, 2H), 4.70 (t,  $J$  = 3.0 Hz, 1H), 5.03-5.06 (m, 1H), 5.08-5.09 (m, 1H), 5.86-5.96 (m, 1H), 6.83 (d,  $J$  = 8.4 Hz, 1H), 6.94 (dd,  $J$  = 2.2, 8.4 Hz, 1H), 7.34 (d,  $J$  = 2.2 Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.8, 21.0, 21.2, 25.7, 26.7, 30.3, 30.8, 34.8, 35.8, 37.5, 38.4, 39.0, 40.3, 42.4, 44.6, 73.8, 82.2, 116.1, 117.1, 121.7, 127.4, 133.1, 134.8, 136.9, 150.9, 170.6; FTIR: 1737, 1486, 1247  $\text{cm}^{-1}$ ; HRMS (ESI+), calculated for  $\text{C}_{26}\text{H}_{35}\text{BrO}_3\text{Na}$  497.1665, found 497.1662.

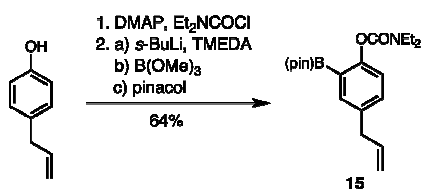


To a flask charged with **14** (330 mg, 0.694 mmol, 1 eq), borate ester **15** (997 mg, 2.78 mmol, 4 eq), and NaOH (333 mg, 8.33 mmol, 12 eq) followed by addition of toluene (7mL) and water (5 mL, sparged with argon for 5 minutes). A solution of  $\text{Pd}_2(\text{dba})_3$  (39.9 mg, 0.069 mmol, 0.1 eq) and *t*-Bu<sub>3</sub>P (51  $\mu\text{L}$ , 0.208 mmol, 0.3 eq) in toluene (3 mL) was then added. The mixture was immediately placed in a 90 °C oil bath and stirred at 1200 rpm for 30 minute (color transition of red to yellow to brown to dark brown). After cooling the mixture was diluted with EtOAc (50 mL) and water (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 90:10 as eluent) provided **16** as colorless oil (308 mg, 71%). TLC  $R_f$  = 0.42, hexane/EtOAc = 80:20;  $^1\text{H}$ NMR (300 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  0.72 (s, 3H), 0.77 (t,  $J$  = 7.2 Hz, 3H), 0.82-0.87 (m, 3H), 0.91 (s, 3H), 0.99 (s, 3H), 1.03-1.60 (m, 10H), 1.66 (s, 3H), 1.68-1.82 (m, 2H), 1.88 (t,  $J$  = 9.7 Hz, 1H), 2.09 (dd,  $J$  = 8.8, 20.8 Hz, 1H), 2.90-3.12 (m, 4H), 3.21 (t,  $J$  = 8.0 Hz, 4H), 4.23 (bs, 1H), 4.91-5.03 (m, 4H), 5.82-5.96 (m, 2H), 6.87 (d,  $J$  = 8.3 Hz, 1H), 6.97 (dd,  $J$  = 1.9, 8.5 Hz, 2H), 7.20 (d,  $J$  = 1.9 Hz, 2H), 7.32 (d,  $J$  = 8.3 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  13.4, 14.0, 20.6, 20.9, 24.8, 25.9, 26.7, 30.3, 30.7, 34.6, 35.8, 36.7, 38.3, 39.7, 39.9, 40.3, 41.5, 41.9, 42.0, 44.2, 73.5, 80.8, 115.5, 115.7, 122.5, 123.3, 131.9, 132.4, 132.8, 133.1, 133.3, 135.8, 136.7, 137.6, 137.7, 137.8, 148.1, 151.7, 153.8, 169.5. FTIR: 1737, 1486, 1247  $\text{cm}^{-1}$ ; HRMS (CI+), calculated for  $\text{C}_{40}\text{H}_{53}\text{NO}_5$  627.3924, found 627.3921.



To the solution of **16** (80 mg, 0.127 mmol, 1 eq) in tetrahydrofuran (2 mL) was added LiAlH<sub>4</sub> solution in tetrahydrofuran (1M, 2.55 mL, 2.55 mmol, 20 eq) dropwise at 23 °C. The mixture was heated to reflux for 2 hours and then cooled to 23 °C and cautiously quenched !! with water (5 mL). The mixture was diluted with diethyl ether (10 mL) and 2 N HCl (5 mL). The organic layer was collected and washed with brine (20 mL). The organic phase was concentrated and the residue purified by silica gel chromatography (hexane/EtOAc = 85:15) to provide caryolanemagnolol (**1**) as colorless pasty oil (44mg, 71%). TLC R<sub>f</sub> = 0.25, hexane/EtOAc = 80:20; [α]<sub>D</sub><sup>26</sup> = 61.6°, (c 2.1, CHCl<sub>3</sub>); <sup>1</sup>HNMR (400 MHz, C<sub>6</sub>D<sub>6</sub>): δ 0.60 (s, 3H), 0.80 (dt, *J* = 4.2, 14.7 Hz, 1H), 0.88 (s, 3H), 1.08 (s, 3H), 1.12-1.41 (m, 6H), 1.44-1.59 (m, 2H), 1.64-1.82 (m, 2H), 1.91-2.03 (m, 2H), 2.16 (ddd, *J* = 1.9, 10.2, 20.1 Hz, 1H), 2.90 (t, *J* = 3.0 Hz, 1H), 3.16 (d, *J* = 6.8 Hz, 2H), 3.24 (d, *J* = 6.6 Hz, 2H), 4.94-5.04 (m, 4H), 5.82 (ddt, *J* = 6.8, 10.1, 16.8 Hz, 1H), 5.94 (ddt, *J* = 6.6, 10.2, 20.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.97 (dd, *J* = 2.2, 8.3 Hz, 1H), 7.03 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 7.22 (d, *J* = 2.2 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>): δ 20.2, 20.5, 26.3, 28.4, 29.2, 30.0, 34.6, 35.3, 36.1, 38.7, 39.2, 39.41, 39.44, 39.5, 43.8, 71.0, 84.1, 115.0, 118.4, 123.7, 128.2, 128.7, 129.4, 131.3, 132.0, 133.5, 135.6, 137.2, 138.1, 149.4, 153.0; FTIR: 3361, 1638, 1491, 1209, 1045, 938, 822 cm<sup>-1</sup>. MS (ESI): M+Na<sup>+</sup> 509. HRMS (ESI+), calculated for C<sub>33</sub>H<sub>41</sub>O<sub>3</sub> (M-H) 485.3060, found 485.3061.

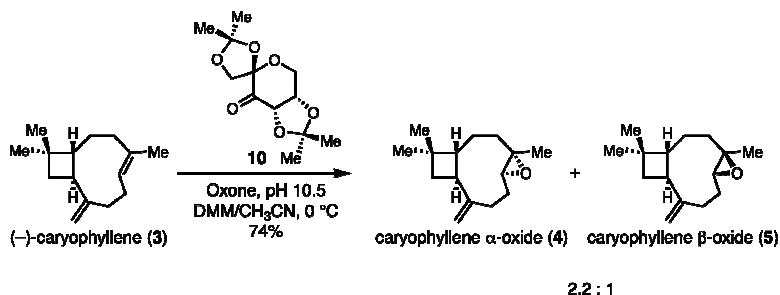
Note: reported optical rotations [α]<sub>D</sub><sup>23.5</sup> = 11.2° synthetic material [α]<sub>D</sub><sup>26</sup> = 61.6° see reference 2.



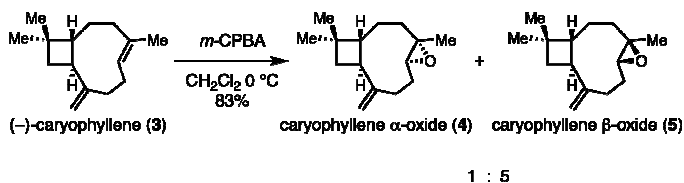
To a solution of 4-allylphenol (2g, 14.9 mmol, 1 eq) and 4-dimethylamino pyridine (3.64 g, 29.8 mmol, 2 eq) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added a solution of diethyl chlorocarbamate (3.77 mL, 29.8 mmol, 2 eq) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0 °C. The solution was stirred at 0 °C for 2 hours and 23 °C for 4 hours and then diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and washed with 1NaOH (100 mL), 2 N HCl (100 mL), and brine (50 mL). The organic extract was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification of the residue by silica gel chromatography (hexane/EtOAc = 85:15 as eluent) provided the carbamate as a yellow oil (2.7 g, 78% yield). TLC R<sub>f</sub> = 0.45, hexane/EtOAc = 80:20.

To THF (40 mL) under argon at -78 °C was added *s*-BuLi (1.21 M, 12.75 mL, 15.4 mmol, 1.2 eq) followed by TMEDA (2.33 mL, 15.4 mmol, 1.2 eq) providing a light yellow solution. After 30 minutes, a solution of the carbamate prepared above (3 g, 12.9 mmol) in THF (10 mL) was added over 10 minutes. The yellow solution was stirred for 2 hours at -78

°C then trimethyl borate (2.87 mL, 25.7 mmol, 2 eq) was added followed by warming to 23 °C over 1 hour (color fade upon addition of trimethyl borate). A solution of 0.1 N HCl (100 mL) was added and the aqueous phase was extracted with ether (20 mL X 3). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The oily residue was dissolved in methanol (40 mL) and pinacol (4.56 g, 38.6 mmol, 3 eq) was added as a solid. The solution was stirred at 23 °C for 1 hour and the mixture was concentrated. The viscous residue was dissolved in EtOAc (30 mL) and washed with water (20 mL X 3). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Silica gel chromatography (hexane/EtOAc = 90:10 as eluent) yielded the borate **15** as colorless oil (3.8 g, 82% yield). TLC R<sub>f</sub> = 0.37, hexane/EtOAc = 80:20; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.19 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.30 (s, 12H), 3.37 (q, *J* = 7.2 Hz, 2H), 3.37 (d, *J* = 8.0 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 2H), 5.03-5.09 (m, 2H), 5.95 (ddt, *J* = 6.7, 10.1, 16.8 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 2.3, 8.3 Hz, 1H), 7.57 (d, *J* = 2.3 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.4, 14.1, 24.9, 39.5, 41.6, 41.9, 83.4, 115.7, 122.2, 132.3, 136.2, 136.3, 137.5, 154.5, 154.9; FTIR: 1720, 1510 cm<sup>-1</sup>; HRMS (CI+), calculated for C<sub>20</sub>H<sub>31</sub>O<sub>4</sub>NB 360.2348, found 360.2346.

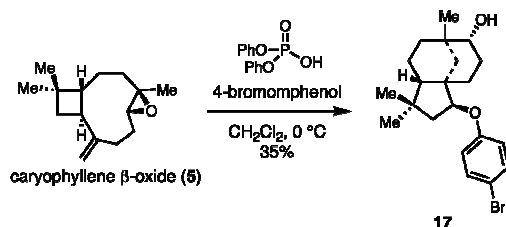


To a solution of (β)-caryophyllene (2.27 g (90%), 10 mmol, 1 eq) in acetonitrile (50 mL) and dimethoxymethane (100 mL) was added a buffer solution (100 mL, 0.05 M Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4X10<sup>-4</sup> M Na<sub>2</sub>(EDTA)), *n*-Bu<sub>4</sub>HSO<sub>4</sub> (140 mg, 0.4 mmol, 0.04 eq), L-Shi catalyst **10** (2.58 g, 10 mmol, 1 eq), and cooled to 0 °C. Addition of Oxone® (8.5 g, 13.8 mmol, 1.38 eq) in buffer aqueous solution (65 mL, 4X10<sup>-4</sup> M Na<sub>2</sub>EDTA aqueous solution) and K<sub>2</sub>CO<sub>3</sub> aqueous solution (9.3 g, 67.3 mmol, 6.73 eq in water (65 mL)) in separate syringes over 1.5 hours using a syringe pump. After complete addition, the reaction mixture was extracted with hexane (100 mL X 3). The combined organic extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude oil was purified by silica gel chromatography (hexane/EtOAc = 95:5 as eluent) to give a light yellow oil, 1.64 g, yield 74%. TLC R<sub>f</sub> = 0.24, Hex/EA = 95:5. <sup>1</sup>H NMR showed a 2.2:1 ratio of diastereomers **4** and **5** respectively with the desired epoxide as the major isomer. NMR data matches that reported.<sup>1</sup>

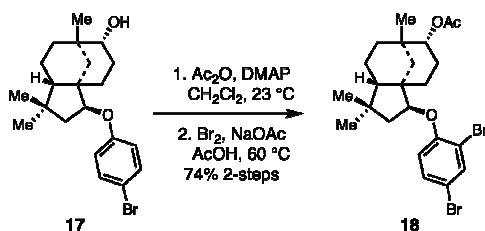


To a solution of (β)-caryophyllene (5.6 g (90%), 24.7 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) under argon at 0 °C was added *m*-CPBA (4.51 g, 25.9 mmol, 1.05 eq) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) over 30 minutes via syringe pump, the reaction mixture became heterogeneous after 15

minutes. After stirring for an additional hour at 0 °C the mixture was filtered through cotton. The filtrate was concentrated, diluted with hexane (40 mL), and washed with 1N NaOH (30 mL X 2). The organic extract was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 95:5 as eluent) provided a colorless oil (4.5 g, 83%). TLC R<sub>f</sub> = 0.24, Hex/EA = 95:5. <sup>1</sup>H NMR showed a 1:5 ratio of diastereomers **4** and **5** respectively. NMR data matches that reported.<sup>1</sup>



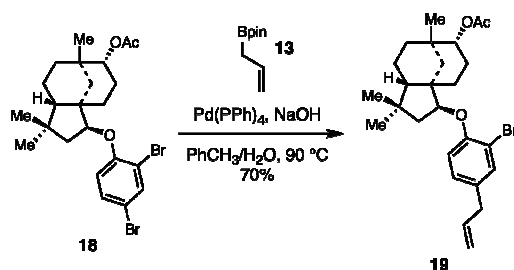
To a solution of β-caryophyllene β-oxide (recrystallized from benzene)<sup>3</sup> (5 g, 21.6 mmol, 1 eq) and *p*-bromophenol (11.9 g, 64.7 mmol, 3 eq) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL) at 0 °C was added a solution of diphenylphosphate (2.70 g, 10.8 mmol, 0.5 eq) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) over 30 minutes. The gray solution was stirred at 0 °C for 4 hours then the solvent was removed under vacuum. The residue was diluted with hexane (300 mL) and washed with 1 M NaOH (50mL X 3). The organic layer was washed with brine (10 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 90:10 as eluent) to give 3.08 g of **17** as a white solid (yield 35%). TLC R<sub>f</sub>: 0.34 hexane/EtOAc = 85:15; Mp 114-116 °C; [α]<sub>D</sub><sup>26</sup> = 93.1°, (*c* 1.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.94 (s, 3H), 0.95 (s, 3H), 0.96-1.04 (m, 2H), 1.06 (s, 3H), 1.09-1.21 (m, 1H), 1.32-1.43 (m, 3H), 1.48-1.68 (m, 6H), 1.79 (dt, *J* = 4.7, 13.6 Hz, 1H), 1.85 (dd, *J* = 5.4, 12.7 Hz, 1H), 1.98-2.07 (m, 1H), 3.34 (bs, 1H), 4.19 (dd, *J* = 5.4, 7.9 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 20.9, 25.7, 26.6, 27.2, 28.3, 31.6, 33.1, 34.7, 36.0, 38.3, 43.8, 45.3, 50.0, 74.9, 86.5, 112.3, 117.5, 132.1, 158.1; FTIR: 3416, 1486, 1243 cm<sup>-1</sup>; HRMS (ESI+), calculated for C<sub>21</sub>H<sub>28</sub>BrO (M-H<sub>2</sub>O) 375.1323, found 375.1318.



To a solution of compound **17** (2.6 g, 6.38 mmol, 1 eq) and 4-dimethylaminopyridine (0.78 g, 6.38 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at 0 °C was added triethylamine (1.78 mL, 12.8 mmol, 2 eq). Subsequently, acetic anhydride (1.21 mL, 12.8 mmol, 2 eq) was added dropwise over 10 minutes. The solution was stirred at 0 °C for 1 hour then diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) washed with 1 N NaOH (30 mL), 2 N HCl (30 mL) and brine (20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 95:5) to provide the acetate of **17** as colorless oil (2.50 g yield 87%). TLC R<sub>f</sub> = 0.32, hexane/EtOAc = 95:5; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.85 (s, 3H), 0.94 (s, 3H), 1.05 (s, 3H), 1.09 (d, *J* = 12.6 Hz, 1H), 1.21-1.28 (m, 1H), 1.33-1.74 (m, 9H), 1.85 (d, *J* = 5.4, 12.8 Hz, 1H), 1.93-1.99 (m, 1H), 2.02 (s, 3H), 4.20 (dd, *J* = 1.9, 7.4 Hz, 1H), 4.57 (b, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz,

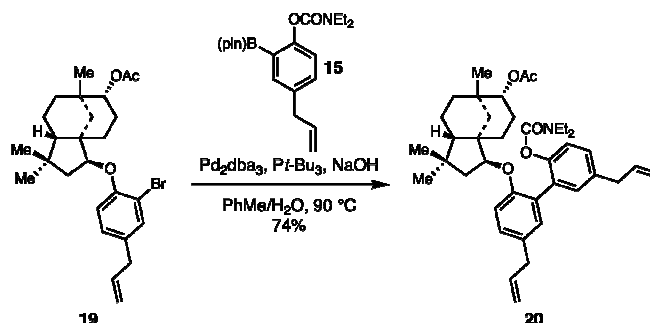
CDCl<sub>3</sub>):  $\delta$  20.8, 21.3, 24.1, 25.8, 27.8, 28.1, 31.7, 32.8, 33.6, 36.9, 38.5, 43.7, 45.3, 50.0, 86.5, 112.4, 117.6, 132.1, 157.9, 170.8; FTIR: 1733, 1486 cm<sup>-1</sup>; HRMS (ESI+), calculated for C<sub>23</sub>H<sub>31</sub>BrO<sub>3</sub>Na 457.1356, found 457.1349.

To a solution of the acetate of **17** (2.00 g, 4.45 mmol, 1 eq) and sodium acetate (0.73 g, 8.9 mmol, 2 eq) in acetic acid (30 mL) was added a solution of bromine (0.918 mL, 17.8 mmol, 4 eq) in acetic acid (10 mL) over 1 minute. The flask was stirred at 60 °C for 4 hours the mixture was diluted with hexane (200 mL) and washed with water (100 mL X 3), 1 N NaOH (3 X 100 mL), and brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification by silica gel chromatography (hexane/EtOAc = 95:5 as eluent) gave **18** as colorless oil (2.01 g, 85%). TLC R<sub>f</sub> = 0.32, hexane/EtOAc = 95:5; <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.87 (s, 3H), 0.96 (s, 3H), 1.08 (s, 3H), 1.10 (d, *J* = 13.2 Hz, 1H), 1.24-1.31 (m, 1H), 1.35-1.48 (m, 1H), 1.53-1.85 (m, 7H), 1.88 (dd, *J* = 5.3, 13.0 Hz, 1H), 1.96-2.01 (m, 1H), 2.03 (s, 3H), 4.21 (dd, *J* = 0.9, 6.5 Hz, 1H), 4.58 (bs, 1H), 6.73 (d, *J* = 8.9 Hz, 1H), 7.32 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.64 (d, *J* = 2.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  20.8, 21.3, 24.3, 25.9, 27.9, 28.1, 31.8, 32.8, 33.6, 36.8, 39.0, 43.7, 45.9, 49.9, 87.9, 112.3, 114.0, 115.4, 130.9, 135.5, 154.4, 170.8; FTIR: 1735, 1246, 1042 cm<sup>-1</sup>; HRMS (ESI+), calculated for C<sub>23</sub>H<sub>30</sub>Br<sub>2</sub>O<sub>3</sub>Na 535.0455, found 535.0454.

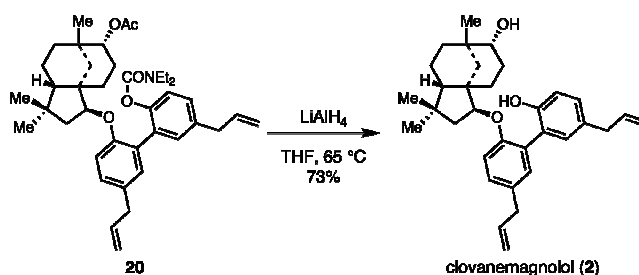


To a flask charged with substrate **18** (0.4875 g, 0.948 mmol, 1 eq), NaOH (0.758 g, 17.0 mmol, 18 eq), and tetrakis(triphenylphosphine)palladium (0.219 g, 0.190 mmol, 0.2 eq) under argon was added toluene (10 mL), water (5 mL, sparged with argon for 5 minutes), and allyl pinacol borate **13** (3.05 mL, 15.17 mmol, 16 eq). The biphasic mixture was stirred at 1200 rpm at 90 °C for 50 minutes where upon TLC (hexane/EtOAc = 97:3) showed full conversion. Then the mixture was cooled to 23 °C and extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 97:3 as eluent) to provide **19** as colorless oil (0.316 g, yield 70%). TLC R<sub>f</sub> = 0.33, hexane/EtOAc = 95:5; <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.87 (s, 3H), 0.95 (s, 3H), 1.09 (s, 3H), 1.10 (d, *J* = 7.2 Hz, 1H), 1.25-1.48 (m, 4H), 1.53-1.78 (m, 5H), 1.88 (dd, *J* = 5.3, 12.9 Hz, 2H), 1.96-2.01 (m, 1H), 2.03 (s, 3H), 3.29 (d, *J* = 6.7 Hz, 2H), 4.22 (dd, *J* = 5.4, 7.0 Hz, 1H), 4.58 (b, 1H), 5.04-5.07 (m, 1H), 5.07-5.09 (m, 1H), 5.86-5.96 (m, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 2.2, 8.3 Hz, 1H), 7.35 (d, *J* = 2.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  20.8, 21.3, 24.2, 25.8, 27.9, 28.1, 31.8, 32.8, 33.6, 36.8, 38.8, 38.9, 43.9, 45.7, 49.9, 87.7, 113.0, 114.4, 116.0, 128.2, 133.2, 133.3, 137.1, 153.5, 170.9; FTIR: 1735, 1248 cm<sup>-1</sup>; HRMS (ESI+), calculated for C<sub>26</sub>H<sub>35</sub>BrO<sub>3</sub>Na 497.1665, found 497.1662.





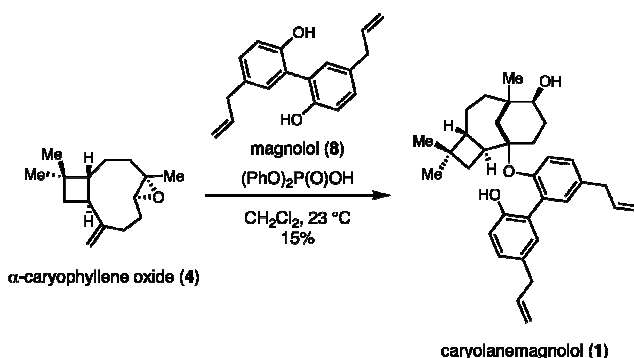
To a flask charged with **19** (200 mg, 0.421 mmol, 1 eq), the borate **15** (604 mg, 1.683 mmol, 4 eq), and NaOH (202 mg, 5.05 mmol, 12 eq) under argon was added toluene (6 mL), water (4 mL, sparged with argon for 5 minutes) and a solution of Pd(dba)<sub>3</sub> (24.2 mg, 0.042 mmol, 0.1 eq), and *t*-Bu<sub>3</sub>P (31  $\mu$ L, 0.126 mmol, 0.3 eq) solution in toluene (2 mL, stirring for 10 minutes before addition). The mixture was immediately placed in a 90 °C oil bath and stirred at 1200 rpm for 30 minutes (red to yellow to brown to dark brown color sequence) then the reaction was diluted with EtOAc (30 mL) and water (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. Silica gel chromatography (hexane/EtOAc = 90:10 as eluent) provided **20** as colorless pasty oil (196 mg, 74%). TLC R<sub>f</sub> = 0.40, hexane/EtOAc = 80:20; <sup>1</sup>HNMR (400 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  0.70 (s, 3H), 0.81 (s, 3H), 0.86 (s, 3H), 0.71-0.90 (m, 8H), 0.95-1.24 (m, 5H), 1.44 (d, *J* = 12.7 Hz, 1H), 1.50-1.70 (m, 5H), 1.80 (s, 3H), 2.91 (d, *J* = 5.4 Hz, 2H), 3.00 (d, *J* = 5.6 Hz, 2H), 3.18 (t, *J* = 7.5 Hz, 4H), 4.01 (dd, *J* = 5.8, 15.6 Hz, 1H), 4.68 (b, 1H), 4.93-5.02 (m, 4H), 5.80-6.00 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.01 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.20 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.31 (d, *J* = 8.3 Hz, 1H, Ar-H); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  13.1, 13.7, 18.1, 20.6, 24.2, 25.5, 27.8, 28.0, 31.4, 32.7, 33.3, 36.6, 38.2, 39.4, 39.6, 41.3, 41.7, 43.7, 45.4, 49.7, 76.3, 87.2, 115.0, 115.1, 115.4, 122.9, 129.1, 131.7, 131.8, 132.1, 135.7, 137.4, 137.8, 148.0, 153.5, 154.7, 169.4; FTIR: 1720, 1246, cm<sup>-1</sup>; HRMS (CI<sup>+</sup>), calculated for C<sub>40</sub>H<sub>54</sub>O<sub>5</sub>N 628.4002, found 628.3986.



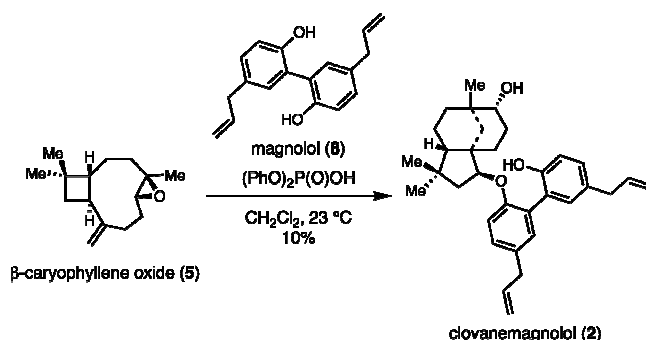
To the solution of **20** (100 mg, 0.159 mmol, 1 eq) in tetrahydrofuran (4 mL) was added LiAlH<sub>4</sub> solution in tetrahydrofuran (1M, 3.19 mL, 3.19 mmol, 20 eq) dropwise at 23 °C. The mixture was heated to reflux for 2 hours and then cooled to 23 °C and excess LiAlH<sub>4</sub> was carefully quenched !! with water (10 mL). The mixture diluted with Et<sub>2</sub>O (40 mL) and 2N HCl (20 mL). The organic layer was collected and washed with brine (10 mL). The concentrated organic phase was purified by silica gel chromatography with hexane/EtOAc = 85:15 to provide the clovanemagnolol **2** as colorless oil (57 mg, 73%). TLC R<sub>f</sub> = 0.22, hexane/EtOAc = 80:20; [ $\alpha$ ]<sub>D</sub><sup>26</sup> = 96.0°, (*c* 1.5, CHCl<sub>3</sub>); <sup>1</sup>HNMR (400 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  0.64 (s, 3H), 0.70 (d, *J* = 12.8 Hz, 1H), 0.83 (s, 3H), 0.83 (m, 1H), 0.92 (s, 3H), 0.98-1.18 (m, 4H), 1.26 (dd, *J* = 5.5, 11.4 Hz, 1H), 1.35 (m, 1H), 1.50-1.71 (m, 4H), 1.79 (dt, *J* = 3.7, 13.3 Hz,

1H), 3.04 (s, 1H), 3.18 (d,  $J = 6.8$  Hz, 2H), 3.23 (d,  $J = 6.6$  Hz, 2H), 4.10 (dd,  $J = 5.7, 8.5$  Hz, 1H), 4.96-5.01 (m, 3H), 5.03 (dd,  $J = 1.7, 3.4$  Hz, 1H), 5.81-5.98 (m, 2H), 6.58 (b, 1H), 6.94 (d,  $J = 8.4$  Hz, 1H), 7.02 (dd,  $J = 2.3, 8.2$  Hz, 1H), 7.04 (dd,  $J = 2.3, 8.4$  Hz, 1H), 7.16 (d,  $J = 2.3$  Hz, 1H), 7.17 (d,  $J = 2.3$  Hz, 1H), 7.19 (d,  $J = 8.3$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  20.6, 25.1, 26.5, 26.7, 28.3, 30.9, 32.8, 34.4, 35.4, 37.4, 39.3, 39.4, 44.2, 45.0, 49.9, 74.3, 89.4, 115.0, 115.4, 115.9, 117.4, 127.1, 128.9, 129.2, 129.4, 131.2, 131.8, 132.5, 133.8, 137.4, 138.0, 152.8, 154.2; FTIR: 3394, 1638, 1232, 822  $\text{cm}^{-1}$ ; HRMS (CI+), calculated for  $\text{C}_{33}\text{H}_{42}\text{O}_3$  486.3131, found 486.3134.

Note: reported optical rotations  $[\alpha]_{\text{D}}^{25} = 21.0^\circ$  synthetic material  $[\alpha]_{\text{D}}^{26} = 96.0^\circ$  see reference 2.



To a solution of  $\beta$ -caryophyllene  $\alpha$ -oxide **4** (40 mg, 2.2:1 ratio of  $\alpha$ -oxide **4** to  $\beta$ -oxide **5**, 0.125 mmol of **4**, 1 eq of **4**) and magnolol (**8**) (49.3 mg, 0.185 mmol, 1.5 equiv.) in dichloromethane (2 mL) at  $23^\circ\text{C}$  was added a solution of diphenylphosphate (15.4 mg, 0.062 mmol, 0.5 eq) in dichloromethane (1 mL) over 3 minutes. Then the orange solution was stirred at  $38^\circ\text{C}$  for 2.5 hours the solvent was removed and the residue was diluted with hexane (50 mL). The hexane solution was washed with phosphate buffer (pH 7.4, 2 X 10 mL) and 1 N NaOH (3 X 10 mL (to recover the magnolol)). The organic layer was washed with brine (10 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The solution was concentrated and the residue purified by silica gel chromatography (hexane/EtOAc = 85:15 as eluent) to yield a mixture of clovanemagnolol **1** and caryolanemagnolol **2**. The mixture was purified by a second round of silica gel chromatography (100% dichloromethane as eluent) to provide pure caryolanemagnolol **2** as colorless oil (9.1 mg, 15% yield).



To a solution of recrystallized  $\beta$ -caryophyllene  $\beta$ -oxide **5** (60 mg, 0.259 mmol, 1 eq) and magnolol (**8**) (103 mg, 0.388 mmol, 1.5 eq) in dichloromethane (2 mL) was added a solution of diphenylphosphate (32.4 mg, 0.129 mmol, 0.5 eq) in dichloromethane (1 mL) over 3 minutes. The orange solution was stirred at  $38^\circ\text{C}$  for 2.5 hours then the solvent was removed. The residue was diluted with hexane (50 mL) and washed with phosphate buffer (pH 7.4, 2 X 10 mL) and 1 M NaOH (3 X 10 mL (to recover the magnolol)). The organic layer was washed with brine (10 mL) and dried over  $\text{Na}_2\text{SO}_4$  and then concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 85:15 as eluent) to yield 12 mg of clovanemagnolol (**2**) a colorless oil (12 mg, 9.5% yield).

#### References:

1. A. F. Barrero, J. Molina, J. E. Oltra, J. Altarejos, A. Barragan, A. Lars, M. Segura, *Tetrahedron* **1995**, *51*, 3813.
2. a) Y. Fukuyama, Y. Otoshi, M. Kodama, *Tetrahedron Lett.* **1990**, *31*, 4477. b) Y. Fukuyama, Y. Otoshi, K. Miyoshi, K. Nakamura, M. Kodama, M. Nagasawa, T. Hasegawa, H. Okazaki, M. Sugawara, *Tetrahedron* **1992**, *48*, 377.
3. Recrystallization of  $\beta$ -caryophyllene  $\beta$ -oxide can also be accomplished using methanol, see a) G. R. Ramage, R. Whitehead, *J. Chem. Soc.* **1954**, 4336. b) Armarego, W. L. F; Chai, C. L. L. In *Purification of Laboratory Chemicals*. 5<sup>th</sup> ed.; Elsevier, Butterworth-Heinemann: Great Britain, Bodmin, Cornwall, 2003; p. 157.

## Spectra of Isolated and Synthetic Caryolanemagnolol

