Supporting Information for
Biomimetic Synthesis of Acid-sensitive (–)-Caparrapi Oxide and
(+)-8-Epicaparrapi Oxide Induced by Artificial Cyclases

Muhammet Uyanik,[†] Hideaki Ishibashi,[†] Kazuaki Ishihara,^{,†} and Hisashi Yamamoto^{*,‡}*

[†]Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan

[‡]Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, Illinois 60637, USA

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ¹H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), integration, and assignment. ¹³C NMR spectra were measured on Varian Gemini-2000 (75 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuteriochloroform at 77.00 ppm). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm x 25 cm) or Daicel CHIRALPAK AD-H (4.6 mm x 25 cm). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. GC analysis was performed with Shimadzu 17A instruments using PEG (0.25 mm x 25 m). All experiments were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄ 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether and tetrahydrofuran (THF) were purchased from Aldrich or Wako as the “anhydrous” and stored over 4A molecular sieves. Hexane, toluene, 1-chloropropane, and dichloromethane were freshly distilled from calcium hydride. Tin(IV) chloride was distilled under nitrogen. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of Chiral Catechol Derivatives (Chiral BA of (*S*)-4 and (*R*)-4):¹ Chiral catechols (*S*)- and (*R*)-4 were prepared from (*R*)-BINOL and (*S*)-BINOL, respectively.

Diastereoselective Cyclization of *trans*-Nerolidol Induced by Chiral LBA 4·SnCl₄ (Table 1): To a solution of chiral catechol (*R*)-4 (154 mg, 0.30 mmol) or 2-methoxyphenol (**5**, 33 μ L, 0.30 mmol) in toluene or CH₂Cl₂ (6 mL) was added a 1 *M* solution of tin(IV) chloride in hexane (for toluene as reaction solvent) or CH₂Cl₂ (for CH₂Cl₂ as reaction solvent) (300 μ L, 0.30 mmol) under N₂ at room temperature, and the mixture was stirred for 5 min. After the solution was cooled to -78 °C, *trans*-nerolidol (85 μ L, 0.30 mmol) was added dropwise. The reaction mixture was stirred for 1 day, quenched with saturated aqueous NaHCO₃, and extracted with ether. The combined organic layers were dried over anhydrous MgSO₄ and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 50:1~30:1) to give bicyclic compounds contained a small amount of unknown products. **1** and **2** could not be separated by column chromatography on silica gel (see, reference 6 on the paper). See Table 1 on the paper for yield of bicyclic compounds.

Total Synthesis of (5*S*,8*S*,10*S*)-(-)-Caparrapi Oxide (1**) and (5*R*,8*S*,10*R*)-(+)-Epicaparrapi Oxide (**2**) from Farnesol (**9**).**

(2*S*,3*S*)-(-)-Epoxyfarnesol (10**):**² A mixture of powdered, activated 4A molecular sieves (20 mg) and CH₂Cl₂ (1 mL) was cooled to -20 °C. L-(+)-Diisopropyl tartrate (L-(+)-DIPT, 18 mg, 0.075 mmol, Aldrich) and Ti(O*i*-Pr)₄ (14 mg, 15 μ L, 0.05 mmol, distilled) were added sequentially. After the mixture was cooled to -50 °C, TBHP (400 μ L, 1.50 mmol, 3.74 *M* in toluene) was added and the resulting mixture was stirred for 30 min, whereupon freshly distilled *trans*, *trans*-farnesol (222 mg, 1.00 mmol) was added. Stirring was maintained for 2 h at -50 ~ -45 ° C. Diluted with 10% aqueous tartaric acid solution (5 mL) and stirred at same temperature for further 30 min, and the reaction mixture was allowed to warm to room temperature and the stirring was continued for 1 h. Extracted with CH₂Cl₂ (3 $\times$ 10 mL) and washed with water, dried over anhydrous Na₂SO₄ and concentrated. To a residual oil in ether (10 mL) was added aqueous 1 *M* NaOH (3 mL) and the mixture was stirred at 0 °C for 30 min. Extracted with ether (3 $\times$ 10 mL), washed with NH₄Cl

and brine, dried over anhydrous MgSO_4 and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 4:1) to give **10** (226 mg, 0.95 mmol, 95% yield with 90% ee). TLC (hexane-EtOAc, 2:1) R_f = 0.40; ^1H NMR (CDCl_3 , 300 MHz) δ 1.31 (s, 3H), 1.45–1.75 (m, 2H), 1.61 (s, 6H), 1.68 (s, 3H), 1.95–2.14 (m, 7H), 2.99 (dd, J = 4.5, 6.6 Hz, 1H), 3.69 (ddd, J = 4.8, 6.6, 11.7 Hz, 1H), 3.81 (ddd, J = 4.5, 7.5, 11.7 Hz, 1H), 5.05–5.13 (m, 2H). Determination of the ee value of **10** via Mosher ester: A mixture of 4-(dimethylamino)pyridine (DMAP, 5 mg, 0.04 mmol) and Et_3N (27 μL) in CH_2Cl_2 (140 μL) was treated with **10** (9.8 mg, 0.04 mmol). Immediately, (+)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (MTPACl, 8 μL) was added. After 30 min, quenched with water, dried, and concentrated. The residue was through pipette column on silica gel to give MTPA ester of epoxyfarnesol (90% ee). TLC (hexane-EtOAc, 4:1) R_f = 0.46; ^1H NMR analysis focused on the M or AB part of the ABM pattern, ^1H NMR (C_6D_6 , 300 MHz) δ 0.97 (s, 3H), 1.22–1.45 (m, 2H), 1.50 (s, 3H), 1.56 (s, 3H), 1.68 (s, 3H), 1.90–2.20 (m, 8H), 2.74 (dd, J = 4.5, 7.2 Hz, 1H, M part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 2.84), 3.43 (s, 3H), 4.04 (dd, J = 7.2, 12.0 Hz, 1H, A part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 3.87), 4.18 (dd, J = 4.5, 12.0 Hz, 1H, B part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 3.91), 5.08 (t, J = 7.2 Hz, 1H), 5.21 (t, J = 7.2 Hz, 1H), 7.00–7.13 (m, 3H), 7.71 (d, J = 7.8 Hz, 2H).

(S)-3,7,11-Trimethyl-6,10-dodecadiene-1,3-diol (6a):³ A 100-mL flask was charged with (–)-**10** (1.458 g, 6.12 mmol) and dry toluene (17 mL). The mixture was stirred under N_2 at 0 °C during the addition of Red-Al[®] (Kanto, 65% sodium bis(2-methoxyethoxy)aluminum hydride in toluene, 1.95 mL, 6.50 mmol). The reaction was allowed to warm to room temperature, over 3 h, at which time TLC analysis of an acidified sample disclosed the formation of single polar product. The reaction was cooled to 0 °C and quenched by addition of 2-propanol (2 mL). Acidification with 5% aqueous HCl was followed by phase separation and washing the organic layer with water and brine and drying over anhydrous MgSO_4 . The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 2:1) to give **6a** (1.440 g, 5.99 mmol, 98% yield) as colorless oil. TLC (hexane-EtOAc, 1:1) R_f = 0.16; IR (film) 3550–3150, 2973, 2929, 2858, 1436, 1379, 1110, 1049 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.26 (s, 3H), 1.54–1.71 (m, 3H), 1.60 (s, 3H), 1.63 (s, 3H), 1.68 (s, 3H), 1.81 (ddd, J = 4.8, 7.5, 15.0 Hz, 1H), 1.97–2.14 (m, 6H),

2.34 (brs, 1H), 2.78 (brs, 1H), 3.86–3.95 (m, 2H), 5.08 (t, $J = 7.0$ Hz, 1H), 5.15 (t, $J = 7.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 15.6, 17.3, 22.3, 25.3, 26.1, 26.3, 39.4, 41.3, 42.0, 58.8, 72.9, 123.9, 124.0, 130.7, 134.6; $[\alpha]^{22.3}_{\text{D}} = 0.80$ (c 2.0, CHCl_3) for 90% ee; HRMS (FAB) m/z calcd for $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}$) 263.1987, found 263.1980.

Selective Silylation or Acylation of 1-Hydroxy Group of **6a**.⁴

(±)-1-*t*-Butyldimethylsiloxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (6b): To a solution of **6a** (1.010g, 4.20 mmol) and imidazole (572 mg, 8.4 mmol) in *N,N*-dimethylformamide (DMF, 8 mL) was added slowly *tert*-butylchlorodiphenylsilane (1.196 mL, 4.60 mmol) in DMF (2 mL) at room temperature. After stirring 3 h at rt, quenched with water, extracted with hexane, washed with brine, dried over anhydrous MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **6b** (2.01 g, 4.20 mmol, 100% yield) as colorless oil. TLC (hexane-EtOAc, 4:1) $R_f = 0.44$; ^1H NMR (CDCl_3 , 300 MHz) δ 1.06 (s, 9H), 1.24 (s, 3H), 1.50–1.85 (m, 4H), 1.60 (s, 6H), 1.68 (s, 3H), 1.94–2.12 (m, 6H), 3.71 (s, OH), 3.92 (t, $J = 7.2$ Hz, 2H), 5.08–5.16 (m, 2H), 7.37–7.44 (m, 6H), 7.68–7.71 (m, 4H).

(±)-1-Isovaleryloxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (6c): To a solution of **6a** (159 mg, 0.66 mmol), 2,4,6-collidine (114 μL , 0.86 mmol) in CH_2Cl_2 (1.3 mL) at -78°C under N_2 was added isovaleryl chloride (105 μL , 0.86 mmol) dropwise and stirred for 5 h at -78°C . Then 1 *M* HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **6c** (204 mg, 0.63 mmol, 95% yield) as colorless oil. TLC (hexane-EtOAc, 4:1) $R_f = 0.30$; IR (film) 3600–3250 (br, OH), 2968, 2930, 2872, 1726 (C=O), 1523, 1436, 1385, 1296, 1120, 1049 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.79 (d, $J = 6.3$ Hz, 3H), 1.06 (s, 3H), 1.34–1.39 (m, 2H), 1.44 (s, 3H), 1.46 (s, 3H), 1.52 (s, 3H), 1.67 (dt, $J = 1.5, 6.9$ Hz, 2H), 1.80–2.03 (m, 9H), 4.08 (t, $J = 6.9$ Hz, 2H), 4.90–5.01 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 15.9, 17.6, 22.3 (2C), 22.5, 25.6 (2C), 26.5, 26.8, 39.6, 39.7, 42.1, 43.4, 60.9, 71.7, 123.9, 124.1, 131.3, 135.4, 173.1; HRMS (FAB) m/z calcd for $\text{C}_{20}\text{H}_{36}\text{O}_3\text{Na}$ ($\text{M} + \text{Na}$) 347.2562, found 347.2572.

(±)-1-(3-Phenylpropionyloxy)-3,7,11-trimethyl-6,10-dodecadiene-3-ol (6d): To a solution of **6a** (180 mg, 0.75 mmol), 2,4,6-collidine (130 μL , 0.98 mmol) in CH_2Cl_2 (1.5 mL) at -78°C under N_2 was added hydrocinnamoyl chloride (146 μL , 0.98 mmol) dropwise and stirred for 5 h at

–78 °C. Then 1 M HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 8:1) to give **6d** (265 mg, 0.71 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) *R*_f = 0.28; IR (film) 3600–3250 (br, OH), 2972, 2928, 2863, 1728 (C=O), 1454, 1383, 1046, 929 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 1.18 (s, 3H), 1.46–1.52 (m, 2H), 1.59 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.78 (dt, *J* = 2.1, 7.2 Hz, 2H), 1.96–2.07 (m, 7H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.93 (t, *J* = 7.8 Hz, 2H), 4.23 (t, *J* = 6.9 Hz, 2H), 5.06–5.14 (m, 2H), 7.16–7.20 (m, 3H), 7.24–7.29 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 15.9, 17.5, 22.4, 25.6 (2C), 26.5, 26.7, 30.8, 35.8, 39.5, 42.0, 61.2, 71.6, 123.9, 124.1, 126.1, 128.1 (2C), 128.3 (2C), 131.2, 135.3, 140.2, 172.8; HRMS (FAB) *m/z* calcd for C₂₄H₃₆O₃Na (M + Na) 395.2562, found 395.2576.

(±)-1-Benzoxo-3,7,11-trimethyl-6,10-dodecadiene-3-ol (6e): To a solution of **6a** (240 mg, 1.0 mmol), pyridine (105 µL, 1.3 mmol) in CH₂Cl₂ (2 mL) at –78 °C under N₂ was added benzoyl chloride (151 µL, 1.3 mmol) drop wise and stirred for 10 h at –78 °C. Then 1 M HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **6e** (327 mg, 0.95 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) *R*_f = 0.23; IR (film) 3600–3250 (br, OH), 2972, 2928, 2858, 1714 (C=O), 1452, 1279, 1114 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (s, 3H), 1.50–1.70 (m, 2H), 1.60 (s, 3H), 1.62 (s, 3H), 1.68 (s, 3H), 1.79 (s, 1H), 1.96–2.15 (m, 8H), 4.50 (t, *J* = 7.0 Hz, 2H), 5.08 (t, *J* = 7.0 Hz, 1H), 5.14 (t, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 16.0, 17.7, 22.5, 25.7, 26.6, 27.0, 39.6, 39.8, 42.2, 61.7, 71.9, 123.9, 124.1, 128.3 (2C), 129.5 (2C), 130.2, 131.5, 132.9, 135.6, 166.6; HRMS (FAB) *m/z* calcd for C₂₂H₃₂O₃Na (M + Na) 367.2249, found 367.2245.

(S)-1-Phenylacetoxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (6f): To a solution of **6a** (841 mg, 3.50 mmol), 2,4,6-collidine (604 µL, 4.55 mmol) in CH₂Cl₂ (7 mL) at –78 °C under N₂ was added phenyl acetyl chloride (602 µL, 4.55 mmol) dropwise and stirred for 5 h at –78 °C. Then 1 M HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **6f** (1.23 mg, 3.43 mmol, 98% yield) as

colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.22; HPLC (two linear OD-H columns, hexane–*i*-PrOH = 40:1, flow rate=0.5 mL/min) t_R =20.2 min for (*S*)-**6f**, 21.2 min for (*R*)-**6f**; IR (film) 3650–3150 (br, OH), 2968, 2925, 2855, 1734 (C=O), 1454, 1257, 1142, 757 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.17 (s, 3H), 1.45–1.53 (m, 2H), 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.81 (t, J = 6.9 Hz, 2H), 1.95–2.08 (m, 7H), 3.62 (s, 2H), 4.26 (t, J = 6.9 Hz, 2H), 5.05–5.14 (m, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 15.9, 17.5, 22.4, 25.6, 26.5, 26.6, 39.5 (2C), 41.3, 41.9, 61.6, 71.5, 123.9, 124.1, 127.0, 128.4 (2C), 129.1 (2C), 131.2, 133.7, 135.3, 171.4; $[\alpha]_D^{22.3}$ = –1.70 (*c* 2.0, CHCl_3) for 90% ee; HRMS (FAB) m/z calcd for $\text{C}_{23}\text{H}_{34}\text{O}_3\text{Na}$ ($M + \text{Na}$) 381.2406, found 381.2409.

General Procedure for the Diastereoselective Cyclization of **6 Induced by Chiral LBA **4**· SnCl_4 (Table 2):** To a solution of chiral catechol (*R*)-**4** (103 mg, 0.20 mmol) in toluene or CH_2Cl_2 or *n*-PrCl (2 mL) was added a 1 *M* solution of tin(IV) chloride in hexane (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 or *n*-PrCl as reaction solvent) (200 μL , 0.20 mmol) at room temperature, and the mixture was stirred for 5 min. After the solution was cooled to –78 °C, 1.0 *M* solution of **6** in toluene (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 or *n*-PrCl as reaction solvent) (100 μL , 0.10 mmol) was added dropwise. The reaction mixture was stirred for 1 day, quenched with saturated aqueous NaHCO_3 , and extracted with ether. The combined organic phases were dried over anhydrous MgSO_4 and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1 → 5:1 → 2:1) to give bicyclic compounds, chiral catechol and monocyclic compounds. Further column chromatography (see below for conditions of each compound) of bicyclics gave **7** and **8**. Yields, ratio and enantioselectivity of bicyclics are described in Table 2 on the paper.

(2*S*,4*aS*,8*aS*)-(–)-2-(2,5,5,8*a*-Tetramethyloctahydrochromen-2-yl)ethyl

3-Phenylpropionate (7d): TLC (hexane–EtOAc, 4:1) R_f = 0.68; column chromatography, hexane– Et_2O = 20:1; HPLC (two linear AD-H columns, hexane–*i*-PrOH = 250:1, flow rate = 0.5 mL/min) t_R =45.1 min for (+)-**7d**, 47.2 min for (–)-**7d**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 54.3 min; IR (film) 2992, 2938, 2868, 1725 (C=O), 1455, 1377, 1134, 1101, 976 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.75 (s, 3H), 0.88 (s, 3H), 1.13–1.82 (m, 10H), 1.24 (s, 3H), 1.25 (s, 3H), 2.61 (t, J = 7.8 Hz, 2H), 2.94 (t, J = 7.8 Hz, 2H), 4.18 (ddd, J = 6.3, 8.4, 11.1 Hz, 1H), 4.25 (ddd, J = 6.3, 8.7, 11.1 Hz, 1H), 7.19–7.21 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 16.2, 20.0, 20.8, 23.5, 28.1, 30.9, 32.2, 33.4, 36.0, 36.9, 41.4, 41.5, 43.5, 54.1, 61.5, 72.1, 74.9, 126.2, 128.3

(2C), 128.4 (2C), 140.6, 173.1; HRMS (FAB) m/z calcd for $C_{24}H_{36}O_3Na$ (M + Na) 395.2562, found 395.2576.

(2S,4aS,8aS)-(-)-2-(2,5,5,8a-Tetramethyloctahydrochromen-2-yl)ethyl Benzoate (7e):

TLC (hexane–EtOAc, 12:1) R_f = 0.40; column chromatography, hexane–Et₂O = 25:1 ~ 20:1; HPLC (AD-H column, hexane–*i*-PrOH = 200:1, flow rate = 1.0 mL/min) t_R = 7.9 min for (+)-**7e**, 8.7 min for (–)-**7e**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 31.6 min; ¹H NMR (CDCl₃, 300 MHz) δ 0.77 (s, 3H), 0.89 (s, 3H), 1.16–1.71 (m, 11H), 1.28 (s, 3H), 1.31 (s, 3H), 1.83 (ddd, J = 6.0, 8.4, 13.8 Hz, 1H), 1.94 (ddd, J = 6.0, 8.1, 13.2 Hz, 1H), 4.44 (ddd, J = 2.4, 6.0, 11.1 Hz, 1H), 4.50 (ddd, J = 1.8, 8.1, 11.1 Hz, 1H), 7.43 (t, J = 1.5, 7.5 Hz, 2H), 7.55 (dd, J = 1.5, 7.5 Hz, 1H), 8.03 (dd, J = 1.5, 7.5 Hz, 2H).

(2S,4aS,8aS)-(-)-2-(2,5,5,8a-Tetramethyloctahydrochromen-2-yl)ethyl Phenylacetate (7f):

TLC (hexane–EtOAc–CH₂Cl₂, 4:1:1) R_f = 0.62; column chromatography, hexane–Et₂O = 15:1; HPLC (two linear AD-H columns, hexane–*i*-PrOH = 250:1, flow rate = 0.5 mL/min) t_R = 39.7 min for (+)-**7f**, 41.2 min for (–)-**7f**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 39.0 min; IR (film) 2975, 2936, 1726, 1523, 1426, 1045 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 0.75 (s, 3H), 0.87 (s, 3H), 1.07–1.60 (m, 11H), 1.22 (s, 3H), 1.24 (s, 3H), 1.66 (ddd, J = 6.3, 8.4, 13.8 Hz, 1H), 1.78 (ddd, J = 6.3, 8.4, 13.8 Hz, 1H), 3.60 (s, 2H), 4.20 (ddd, J = 6.3, 8.4, 11.1 Hz, 1H), 4.26 (ddd, J = 6.3, 8.7, 11.1 Hz, 1H), 7.23–7.24 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 16.1, 20.7 (2C), 23.4, 28.0, 32.0 (2C), 36.7 (2C), 41.4 (2C), 43.3, 54.0, 61.8, 72.0, 74.6, 126.9, 128.4 (2C), 129.7 (2C), 134.1, 171.7; $[\alpha]_D^{22.8}$ = –8.21 (c 1.0, CHCl₃) for >99% ee; HRMS (FAB) m/z calcd for $C_{23}H_{34}O_3Na$ (M + Na) 381.2406, found 381.2409.

(2S,4aR,8aR)-(+)-2-(2,5,5,8a-Tetramethyloctahydrochromen-2-yl)ethyl

3-Phenylpropionate (8d): TLC (hexane–EtOAc, 4:1) R_f = 0.66; column chromatography, hexane–Et₂O = 15:1; HPLC (AD-H column, hexane–*i*-PrOH = 250:1, flow rate = 1.0 mL/min) t_R = 9.8 min for (–)-**8d**, 14.0 min for (+)-**8d**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 56.8 min; IR (film) 2982, 2938, 2870, 1726 (C=O), 1456, 1375, 1180, 1100, 974 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 0.77 (s, 3H), 0.89 (s, 3H), 1.14 (s, 3H), 1.17–1.80 (m, 19H), 1.25 (s, 3H), 2.05 ((quintet, J = 7.5 Hz, 1H), 2.61 (t, J = 7.8 Hz, 2H), 2.95 (t, J = 7.8 Hz, 2H), 4.15–4.27 (m, 2H), 7.19–7.21 (m, 3H), 7.28–7.32 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 16.2, 20.2, 20.8, 23.1, 30.5, 31.0, 32.2, 33.5, 36.0, 38.1, 39.4, 41.4, 42.0, 53.5, 61.9, 72.3, 75.3, 126.2, 128.3 (2C), 128.5 (2C), 140.5, 173.0;

HRMS (FAB) m/z calcd for $C_{24}H_{36}O_3SeNa$ ($M + Na$) 395.2562, found 395.2576.

(2*S*,4*aR*,8*aR*)-(+)-2-(2,5,5,8a-Tetramethyloctahydrochromen-2-yl)ethyl Benzoate (8e):

TLC (hexane–Et₂O–CH₂Cl₂, 12:1) R_f = 0.32; column chromatography, hexane–Et₂O = 20:1 ~ 15:1; HPLC (AD-H column, hexane–*i*-PrOH = 200:1, flow rate = 1.0 mL/min) t_R = 8.1 min for (–)-**8e**, 9.5 min for (+)-**8e**; GC (PEG, column temp. 210 °C, 210 kPa) t_R = 34.4 min; ¹H NMR (CDCl₃, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.12–1.70 (m, 10H), 1.23 (s, 3H), 1.32 (s, 3H), 1.84–1.95 (m, 2H), 2.17–2.30 (m, 1H), 4.40–4.51 (m, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 8.04 (dd, J = 1.5, 7.5 Hz, 2H).

(2*S*,4*aR*,8*aR*)-(+)-2-(2,5,5,8a-Tetramethyloctahydrochromen-2-yl)ethyl Phenylacetate (8f):

TLC (hexane–Et₂O–CH₂Cl₂, 4:1:1) R_f = 0.60; column chromatography, hexane–Et₂O = 15:1 ~ 10:1; HPLC (AD-H column, hexane–*i*-PrOH = 250:1, flow rate = 1.0 mL/min) t_R = 9.4 min for (–)-**8f**, 12.8 min for (+)-**8f**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 40.1 min; IR (film) 2976, 2936, 1727, 1523, 1426, 1045 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 0.76 (s, 3H), 0.88 (s, 3H), 1.11 (s, 3H), 1.12–1.82 (m, 12H), 1.24 (s, 3H), 2.05 (dd, J = 5.7, 8.1 Hz, 1H), 2.09 (dd, J = 6.0, 7.5 Hz, 1H), 3.60 (s, 2H), 4.15 (ddd, J = 6.6, 8.1, 11.1 Hz, 1H), 4.25 (ddd, J = 6.0, 8.4, 11.1 Hz, 1H), 7.24–7.35 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 16.1, 20.1, 20.8, 23.1, 30.5, 32.2, 33.4, 37.9, 39.3, 41.4, 41.5, 42.0, 53.3, 62.3, 72.2, 75.2, 127.0, 128.5 (2C), 129.3 (2C), 134.1, 171.6; $[\alpha]^{23.4}_D$ = 23.4 (c 1.0, CHCl₃) for 98% ee; HRMS (FAB) m/z calcd for $C_{23}H_{34}O_3Na$ ($M + Na$) 381.2406, found 381.2409.

(2*S*,4*aS*,8*aS*)-(–)-2-(2,5,5,8a-Tetramethyloctahydrochromen-2-yl)ethanol (7a):

To a solution of **7f** (100 mg, 0.58 mmol) in methanol (2 mL) at 0 °C was added 1 *M* aqueous LiOH (870 μ L, 0.87 mmol). After stirring for an additional 1 h poured into brine and extracted with ether (twice). The combined organic phases were dried over anhydrous MgSO₄ and concentrated. The crude product was through pipette column on silica gel to give **7a** (139 mg, 0.58 mmol, 100% yield) as colorless oil. TLC (hexane–EtOAc, 2.5:1) R_f = 0.37; IR (film) 3550–3250 (br, OH), 2975, 2941, 2872, 1711, 1523, 1427, 1046, 929 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 1.21–1.75 (m, 13H), 1.29 (s, 3H), 1.32 (s, 3H), 3.72–3.88 (m, 2H), 4.04 (t, J = 5.0 Hz, OH); ¹³C NMR (CDCl₃, 75 MHz) δ 16.1, 20.0, 20.8, 23.3, 27.6, 32.1, 33.4, 37.3, 41.3, 41.7, 45.8, 54.2, 59.7, 76.0, 76.1; $[\alpha]^{23.4}_D$ = –6.41 (c 1.0, CHCl₃) for >99% ee; HRMS (FAB) m/z calcd for $C_{15}H_{28}O_2Na$ ($M + Na$) 263.1987, found 263.1980.

(2*S*,4*aS*,8*aS*)-(-)-*o*-Nitrophenyl-2-(2,5,5,8*a*-tetramethyloctahydrochromen-2-yl)ethylselenide (11):

To a stirring solution of **7a** (166 mg, 0.69 mmol) and *o*-nitrophenyl selenocyanate (384 mg, 1.73 mmol) in dry THF (3 mL) under N₂ at room temperature was added tri-*n*-butylphosphine (427 μ L, 1.73 mmol). After stirring for 3 h, quenched with ethanol and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 15:1) to give **11** (282 mg, 0.66 mmol, 96% yield) as yellow oil. TLC (hexane–EtOAc, 4:1) R_f = 0.54; HPLC (OD-H column, hexane–*i*-PrOH = 80:1, flow rate = 1.0 mL/min) t_R = 6.7 min for (+)-**11**, 8.0 min for (–)-**12**; IR (film) 2976, 2932, 1515, 1426, 1335, 1046, 929 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.16–1.73 (m, 11H), 1.28 (s, 3H), 1.30 (s, 3H), 1.78 (ddd, J = 5.7, 10.8, 13.4 Hz, 1H), 1.87 (ddd, J = 5.7, 11.1, 13.4 Hz, 1H), 2.97 (dt, J = 5.8, 12.4 Hz, 1H), 3.06 (dt, J = 5.8, 12.4 Hz, 1H), 7.30 (ddd, J = 1.2, 7.2, 8.2 Hz, 1H), 7.52 (ddd, J = 1.2, 7.2, 8.2 Hz, 1H), 7.74 (dd, J = 1.2, 8.2 Hz, 1H), 8.30 (dd, J = 1.2, 8.2 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 16.3, 20.1, 20.5, 20.8, 23.5, 27.4, 32.3, 33.5, 36.8, 41.5, 41.7, 44.5, 54.3, 73.2, 75.0, 125.0, 126.4, 129.2, 133.5, 134.4; $[\alpha]^{23.7}_D$ = –8.97 (c 1.0, CHCl₃) for >99% ee; HRMS (FAB) m/z calcd for C₂₁H₃₁O₃SeNa (M + Na) 448.1367, found 443.1383.

(5*S*,8*S*,10*S*)-(-)-Caparrapi Oxide (1):⁵

To a solution of **11** (276 mg, 0.65 mmol) in THF (15 mL) was slowly added 30% aqueous hydrogen peroxide (592 μ L) at 0 °C. Stirring was maintained for 1 day at room temperature. Water was added, extracted with ether (twice), washed with water, dried over anhydrous MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **1** (139 mg, 0.625 mmol, 96% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.45; GC (PEG, column temp. 60 °C, 60 kPa) t_R = 109.8 min; GC (β -DM column, column temp. 70 °C, 70 kPa) t_R = 104.9 min for (+)-**1**, t_R = 108.6 min for (–)-**1**; ¹H NMR (CDCl₃, 300 MHz) δ 0.79 (s, 3H), 0.86 (s, 3H), 1.15–1.84 (m, 11H), 1.29 (s, 3H), 1.30 (s, 3H), 4.92 (dd, J = 1.5, 10.7 Hz, 1H), 5.15 (dd, J = 1.5, 17.4 Hz, 1H), 5.89 (dd, J = 10.7, 17.4 Hz, 1H); $[\alpha]^{22.7}_D$ = –18.5 (c 0.065, CHCl₃) for >99% ee.

(2*S*,4*aR*,8*aR*)-(+)-2-(2,5,5,8*a*-Tetramethyloctahydrochromen-2-yl)ethanol (8a):

To a solution of **8f** (22 mg, 0.061 mmol) in methanol (1 mL) at 0 °C was added 1 *M* aqueous LiOH (92 μ L, 0.092 mmol). After stirring for an additional 1 h poured into brine and extracted with ether (twice). The combined organic phases were dried over anhydrous MgSO₄ and concentrated. The crude product was through pipette column on silica gel to give **8a** (14.6 mg, 0.061 mmol, 100%

yield) as colorless oil. TLC (hexane–EtOAc, 2.5:1) R_f = 0.20; IR (film) 3550–3250 (br, OH), 2976, 2941, 2872, 1523, 1427, 1046, 926 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.67 (s, 3H), 0.74 (s, 3H), 1.00–1.60 (m, 11H), 1.11 (s, 3H), 1.17 (s, 3H), 1.76–1.90 (m, 2H), 3.23 (brs, OH), 3.60 (quintet, J = 5.1 Hz, 1H), 3.79 (ddd, J = 4.8, 9.0, 11.1 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 15.6, 20.0, 20.5, 24.0, 28.8, 31.9, 33.7, 35.1, 41.5, 42.3, 44.0, 50.0, 60.0, 74.6, 75.5; $[\alpha]^{23.1}_{\text{D}}$ = 28.8 (c 1.0, CHCl_3) for 98% ee; HRMS (FAB) m/z calcd for $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Na}$ ($M + \text{Na}$) 263.1987, found 263.1978.

(2*S*,4*aR*,8*aR*)-(+)-*o*-Nitrophenyl-2-(2,5,5,8*a*-tetramethyloctahydrochromen-2-yl)ethylselenide (12): To a stirring solution of **8a** (19.2 mg, 0.080 mmol) and *o*-nitrophenyl selenocyanate (44.4 mg, 0.200 mmol) in dry THF (1 mL) under N_2 at room temperature was added tri-*n*-butylphosphine (49 μL , 0.200 mmol). After stirring for 3 h, quenched with ethanol and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **12** (32.4 mg, 0.076 mmol, 95% yield) as yellow oil. TLC (hexane–EtOAc, 4:1) R_f = 0.48; IR (film) 2977, 2932, 1520, 1425, 1335, 1046, 929 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.18–1.90 (m, 12H), 1.24 (s, 3H), 1.28 (s, 3H), 2.19 (ddd, J = 4.2, 12.0, 14.1 Hz, 1H), 2.96 (dt, J = 5.1, 10.6 Hz, 1H), 3.06 (dt, J = 3.9, 10.6 Hz, 1H), 7.31 (ddd, J = 1.5, 6.9, 9.5 Hz, 1H), 7.52 (ddd, J = 1.5, 6.9, 9.5 Hz, 1H), 7.59 (dd, J = 1.5, 8.4 Hz, 1H), 8.31 (dd, J = 1.5, 8.4 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 16.1, 20.2, 20.8, 21.3, 22.9, 30.0, 32.2, 33.5, 37.9, 38.9, 41.4, 42.1, 53.3, 73.4, 75.4, 125.2, 126.4, 129.2, 133.6, 134.4; $[\alpha]^{23.7}_{\text{D}}$ = 28.7 (c 1.0, CHCl_3) for 98% ee; HRMS (FAB) m/z calcd for $\text{C}_{21}\text{H}_{31}\text{O}_3\text{SeNa}$ ($M + \text{Na}$) 448.1367, found 448.1367.

(5*R*,8*S*,10*R*)-(+)-Epicaparrapi Oxide (2):^{5c,6} To a solution of **12** (21.3 mg, 0.050 mmol) in THF (1 mL) was slowly added 30% aqueous hydrogen peroxide (46 μL) at 0 °C. Stirring was maintained for 1 day at room temperature. Water was added, extracted with ether (twice), washed with water, dried over anhydrous MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **2** (10.6 mg, 0.048 mmol, 96% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.45; GC (PEG, column temp. 60 °C, 60 kPa) t_R = 114.4 min; GC (β -DM column, column temp. 80 °C, 100 kPa) t_R = 61.1 min for (+)-**2**, t_R = 66.6 min for (–)-**2**; ^1H NMR (CDCl_3 , 300 MHz) δ 0.73 (s, 3H), 0.89 (s, 3H), 1.18–1.67 (m, 10H), 1.14 (s, 3H), 1.22 (s, 3H), 2.18–2.28 (m, 1H), 4.91 (dd, J = 1.0, 11.1 Hz, 1H), 4.97 (dd, J = 1.0, 18.0 Hz, 1H), 6.02 (dd, J = 11.1, 18.0 Hz, 1H); $[\alpha]^{23.0}_{\text{D}}$ = 43.0 (c 1.1, EtOH) and $[\alpha]^{22.5}_{\text{D}}$ = 47.7 (c 1.0,

CHCl₃) for 98% ee.

References

1. H. Ishibashi, K. Ishihara, H. Yamamoto *J. Am. Chem. Soc.* **2004**, *126*, 1122–1123.
2. H. Kigoshi, M. Ojika, Y. Shizuri, H. Niwa, K. Yamada *Tetrahedron* **1986**, *42*, 3789–3792. b) D. C. Dittmer, R. P. Discordia, Y. Zhang, C. K. Murphy, A. Kumar, A. S. Pepito, Y. Wang *J. Org. Chem.* **1993**, *58*, 718–731.
3. a) S. M. Viti *Tetrahedron Lett.* **1982**, *23*, 4541–4544. b) J. A. Hyatt, G. S. Kottas, J. Effler *Org. Process Res. Dev.* **2002**, *6*, 782–787.
4. K. Ishihara, H. Kurihara, H. Yamamoto *J. Org. Chem.* **1993**, *58*, 3791–3793.
5. a) C. J. W. Brooks, M. M. Campbell *Phytochemistry* **1969**, *8*, 215–218. b) Y.-C. Shen, P.-W. Hsieh *Chin. Pharm. J.* **1999**, *51*, 213–218. c) P. Lomardi, R. C. Cookson *Helv. Chim. Acta* **1976**, *59*, 1158–1168.
6. D. J. Faulkner *Phytochemistry* **1976**, *15*, 1993–1994.