Synthesis of the Hydroazulene Ring System of Guanacastepene

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Supporting Material

General Procedures. NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated, chemical shifts are reported in δ, coupling constants in Hz, and IR spectra in cm^{-1}.

5-Iodo-1-pentene (10). 5-Bromo-1-pentene (0.8 mL, 6.71 mmol) was added to a solution of NaI (2.0g, 13.3 mmol) in acetone (22 mL). The reaction mixture was heated at 60 ºC for 2 h. The mixture was cooled to rt, diluted with water (100 mL), and extracted with pentane. The pentane layers were combined, washed with brine, dried over Na_2SO_4 and concentrated to give 1.27 g (96%) of 5-iodo-1-pentene (**10**): ^{1}H NMR 5.73 (tdd, 1, J = 6.4, 10.4, 17.2), 5.06 (dd, 1, J = 1.6, 17.2), 5.00 (dd, 1, J = 1.6, 10.4), 3.17 (t, 2, J = 6.8), 2.17-2.11 (m, 2), 1.89 (dt, 2, J = 7.6, 6.8).

2-Methyl-3-methylene-8-penten-4-ol (11). *t*-BuLi (8.25 mL, 14.03 mmol of a 1.7 M solution in pentane) was added dropwise to a solution of 5-iodo-1-pentene (1.31 g, 6.68 mmol) in Et_2O (33.4 mL) at -78 °C. The reaction mixture was stirred for 5 min at -78 ºC and then warmed to rt for 1 h. The resulting solution was added dropwise to a solution of 2-isopropylacrolein[9] (662 mg, 6.35 mmol) in Et_2O (20 mL) at -78 ºC. The reaction mixture was warmed to rt and allowed to stir at rt for 1 h. The mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. The Et_2O extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated providing 961 mg (89%) of alcohol **11**, which was used without further purification. An analytical sample was prepared by flash chromatography on silica gel (4:0.05 hexane/EtOAc): ^{1}H NMR 5.78 (tdd, 1, *J* = 6.8, 10.4, 17.2), 5.01 (s, 1), 4.94 (dd, 1, *J* = 2.0, 17.2), 4.93 (dd, 1, *J* = 2.0, 10.4), 4.80 (s, 1), 4.09-4.05 (m, 1), 2.24 (qq, 1, *J* = 6.8, 6.8), 2.11-2.01 (m, 2), 1.67-1.35 (m, 4), 1.06 (d, 3, *J* = 6.8), 1.03 (d, 3, *J* = 6.8); ^{13}C NMR 159.2, 138.7, 114.6, 106.9, 74.3, 35.6, 33.6, 30.2, 25.1, 23.2, 22.7; HRMS (CI/CH_4/NH_3) calcd for $C_{11}H_{22}N$ [$(M+NH_4-H_2O)^+$] 168.1752, found 168.1744.

2-Methyl-3-methylene-8-penten-4-yl Acetoacetate (12). Diketene (0.5 mL, 6.51 mmol) was added to a solution of **11** (961 mg, 5.71 mmol) and DMAP (6 mg, 0.051 mmol) in Et_2O (19 mL) at -15 ºC. The solution was warmed to rt and stirred overnight. The mixture was washed with 0.01 M NaOH until the dark orange color of the Et_2O layer was removed resulting in a pale yellow Et_2O layer. The Et_2O layer was washed with brine, dried over Na_2SO_4, and concentrated to give 1.32 g (92%) of **12** as an orange oil which was used without further purification: ^{1}H NMR 5.75 (tdd, 1, *J* = 6.8, 10.4, 17.2), 5.23 (t, 1, *J* = 6.4), 4.99 (s, 1), 4.98 (dd, 1, *J* = 2.0, 17.2), 4.96 (dd, 1, *J* = 2.0, 10.4), 4.93 (s, 1), 3.43 (s, 2), 2.24 (s, 3), 2.26-2.21 (m,1), 2.07-2.01 (m, 2), 1.67-1.61 (m, 2), 1.40-1.33 (m, 2), 1.06 (d, 3, *J* = 6.8), 1.03 (d, 3, *J* = 6.8).

5-(1-Methylethyl)-5*E*,10-undecadien-2-one (13). *n*-BuLi (21.14 mL, 0.053 mol) was added to (*i*-Pr)$_2$NH (7.85 mL, 0.056 mol) in THF (53.0 mL) at 0 ºC. The resulting solution was stirred for 30 min. and then cooled to –78 ºC. Acetoacetate **12** (4.44 g, 0.018 mol) in THF (20 mL) was added dropwise to the LDA solution at –78 ºC. The reaction mixture was warmed to rt and stirred for 4 h at rt, heated at reflux for 1 h cooled to rt, concentrated *without heating*, and taken up in water. The water layer was then washed with Et_2O. The Et_2O layer was further washed with 0.01 M NaOH. The combined aqueous layers were diluted with CH_2Cl_2. 1 M HCl was added slowly to this H_2O/CH_2Cl_2 mixture with rapid stirring. Upon complete acidification, the two layers separated. The CH_2Cl_2 layer was separated and the water layer was further extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried over Na_2SO_4, and concentrated *without heating*. The residue was dissolved in toluene (20 mL) and heated at 80 ºC for an hour. The solution was concentrated and purified by flash chromatography on silica gel (4:0.05 hexane/EtOAc) to give 2.25 g (60%) of **13** (from 2-isopropylacrolein): ^{1}H NMR 5.78 (tdd, 1, *J* = 6.8, 10.4, 17.2), 5.00-4.98 (m, 1), 4.96-4.91 (m, 2), 2.81 (sp, 1, *J* = 6.8), 2.52 (t, 2, *J* = 8.0), 2.18 (t, 2, *J* = 8.0), 2.13 (s, 3), 2.05-1.97 (m, 4), 1.42-1.35 (m, 2), 0.95 (d, 6, *J* = 6.8); ^{13}C NMR 208.7, 143.1, 138.8, 112.9, 114.3, 43.1, 33.3, 29.8, 29.3, 28.3, 26.6, 24.5, 21.0 (2); HRMS (DEI) calcd for $C_{14}H_{25}O$ (MH^+) 209.1954, found 209.1896.

(2α,3β)-2-Methyl-3-(1-methylethyl)-2-(4-pentenyl)cyclopentanone (14). A solution of **13** (272 mg, 1.31 mmol) in dry CH_2Cl_2 (26.2 mL) was cooled to 0 ºC and evacuated under vacuum for 1-2 min and then purged with N_2. $EtAlCl_2$ (1.97 mL, 1.97 mmol, 1 M in heptane) was added dropwise to the solution of **13** at 0 ºC. The mixture was stirred at 0 ºC for 30 min and then warmed to rt and stirred for 24 h. The reaction mixture was then poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 were combined washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel deactivated with 1% water (4:0.05 hexane/EtOAc) gave 185 mg (69%) of **14**: ^{1}H NMR 5.73 (tdd, 1, *J* = 6.8, 10.4, 17.2), 4.96 (dd, 1, *J* = 1.2, 17.2), 4.91 (d, 1, *J* = 1.2, 10.4), 2.36-2.28 (m, 2), 2.06-1.93 (m, 4), 1.79-1.63 (m, 3), 1.48-1.33 (m, 3), 0.98 (d, 3, *J* = 6.8), 0.91 (d, 3, *J* = 6.8), 0.86 (s, 3); ^{13}C NMR 224.3, 138.5, 114.6, 52.0, 48.3, 37.7, 37.1, 34.2, 29.4, 24.3, 23.6, 22.1, 21.4, 18.3; IR (neat) 2933, 2871, 1738; HRMS (DEI) calcd for $C_{14}H_{25}O$ (MH^+) 209.1905, found 209.1910; MS *M/Z* (%) 209 (5, MH^+), 193 (3), 191 (6), 140 (18), 109 (13), 97 (100).

(2α,3β)-2-Methyl-3-(1-methylethyl)-2-(4-Oxopentyl)cyclopentanone (15). A solution of cyclopentanone **14** (114 mg, 0.582 mmol), $PdCl_2$ (10 mg, 0.0582 mmol), $Cu(OAc)_2{\cdot}H_2O$ (23 mg, 0.1164 mmol), DMF (1.7 mL), and H_2O (0.23 mL) was evacuated under vacuum at rt. The flask was then placed under oxygen (1 atm) and stirred at rt for 2 d. The mixture was then diluted with Et_2O and filtered through a plug of Celite. The filtrate was washed with water and brine, dried over Na_2SO_4 and concentrated to give 115 mg (88%) of **15**: ^{1}H NMR 2.42-2.28 (m, 2), 2.08 (s, 3), 2.05-1.96 (m, 2), 1.79-1.58 (m, 5), 1.47-1.39 (m, 3), 0.98 (d, 3, *J* = 6.8), 0.92 (d, 3, *J* = 6.8), 0.86 (s, 3); ^{13}C NMR 224.2, 208.6, 52.0, 48.1, 44.0, 37.6, 36.8, 29.8, 29.4, 23.7, 22.0, 21.4, 19.2, 18.3.

((6α,6aα)-1,2,4,5,6,6a-Hexahydro-6a-methyl-6-(1-methylethyl)-3-pentalenyl)-1-ethanone (16). Diketone **15** (20 mg, 0.089 mmol) in dry THF (3 mL) was added dropwise to a solution of LDA (0.19 mL, 0.188 mmol) at 0 ºC. The mixture was allowed to warm to rt and stirred for 24 h. The mixture was then quenched with NH_4Cl solution and extracted with Et_2O. The Et_2O layers were washed with brine, dried over Na_2SO_4 and concentrated to afford a 1:1

mixture of diketone **15** and bicyclic ketone **16**. Purification by flash chromatography (2:0.2 hexane/EtOAc) gave 8 mg (40%) of recovered **15** preceded by 8 mg (42%) of **16**: ^{1}H NMR 2.93-2.83 (m, 1), 2.75 (dd, 1, *J* = 8.8, 15.6), 2.56-2.43 (m, 2), 2.20 (s, 3), 1.99 (ddd, 2, *J* = 3.2, 8.8, 16.0), 1.82-1.76 (m, 2), 1.73-1.63 (m, 2), 1.50 (sp, 1, *J* = 6.8), 1.29-1.22 (m, 1), 0.95 (s, 3), 0.87 (d, 6, *J* = 6.8).

(4α,5β)-5-Methyl-4-(1-methylethyl)-5-(4-pentenyl)-1-cyclopenten-1-yl Trifluoromethanesulfonate (17). Tf_2O (0.81 mL, 0.481 mmol) was added to a solution of **14** (50 mg, 0.240 mmol), Proton Sponge (70 mg, 0.323 mmol), and dry CH_2Cl_2 (5 mL) at -78 ºC. The mixture was warmed to rt and stirred for 1 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The CH_2Cl_2 layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The crude triflate was purified by flash chromatography on silica gel deactivated with 1% water (hexane) to afford 70 mg (86%) of unstable triflate **17**: ^{1}H NMR 5.76 (tdd, 1, *J* = 6.8, 10.4, 17.2), 5.53 (t, 1, *J* = 3.2), 4.99 (dd, 1, *J* = 1.2, 17.2), 4.94 (dd, 1, *J* = 1.2, 10.4), 2.35 (ddd, 1, *J* = 3.2, 8.0, 15.2), 2.04-1.95 (m, 3), 1.87-1.81 (m, 1), 1.74-1.65 (m, 1), 1.51-1.42 (m, 2), 1.24-1.17 (m, 2), 1.02 (s, 3), 0.94 (d, 3, *J* = 6.8), 0.86 (d, 3, *J* = 6.8); ^{13}C NMR 153.7, 138.4, 118.5 (q, 1, $J_{C\text{-}F}$ = 319), 114.7, 111.9, 48.6, 48.0, 36.5, 34.0, 30.9, 29.2, 23.9, 22.2, 21.4, 18.9.

(4α,5β)-1-Ethenyl-5-methyl-4-(1-methylethyl)-5-(4-pentenyl)-1-cyclopentene (21). Vinylmagnesium bromide (2.3 mL, 1.88 mmol, 0.8-1 M in THF) was added to a solution of **17** (128 mg, 0.375 mmol) in dry THF (5 mL) at 0 ºC. The solution was warmed to rt and Pd_2dba_3 (6.9 mg, 0.0075 mmol) and tri-(*o*-furyl)phosphine (6.9 mg, 0.03 mmol) were added simultaneously. The solution turned dark blue and faded to a dark yellow color over 12 h. The mixture was quenched with sat NH_4Cl solution and extracted with Et_2O. The Et_2O layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The residue was filtered through a plug of silica gel deactivated with 1% water (hexane) to provide 66 mg (80%) of unstable triene **21**: ^{1}H NMR 6.10 (dd, 1, *J* = 11.6, 17.7), 5.79 (tdd, 1, *J* = 6.8, 10.4, 17.2), 5.76 (br s, 1), 5.35 (d, 1, *J* = 17.2), 4.99-4.89 (m, 3), 2.31 (ddd, 1, *J* = 2.8, 8.0, 16.6), 2.01-1.92 (m, 3),

1.84-1.77 (m, 1), 1.75-1.66 (m, 1), 1.58-149 (m, 2), 1.46-1.34 (m, 1), 1.89-1.08 (m, 1), 0.96 (d, 3, *J* = 6.0), 0.95 (s, 3), 0.86 (d, 3, *J* = 6.0); ^{13}C NMR 149.2, 139.1, 131.9, 126.2, 114.2, 113.5, 50.9, 50.2, 37.9, 35.0, 34.5, 29.3, 24.0, 22.8, 22.5, 20.6.

(1α,8aα)-1,2,6,7,8,8a-Hexahydro-8a-methyl-1-(1-methylethyl)azulene (20). A solution of bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Grubbs' catalyst) (9 mg, 0.011 mmol) in dry CH_2Cl_2 (1 mL) was added to **21** (48 mg, 0.220 mmol) in dry CH_2Cl_2 (2 mL) at rt. The solution was stirred for 1 h. Another portion (9 mg, 0.011 mmol) of catalyst was added and stirring was continued for 1 h. The reaction was monitored using 20% impregnated $AgNO_3$ silica gel TLC plates (4:0.05 hexanes/EtOAc). The reaction mixture was concentrated and purified using flash chromatography on 20% impregnated $AgNO_3$ silica gel (hexane) to give 33 mg (80%) of unstable diene **20**: ^{1}H NMR 6.00 (d, 1, *J* = 12.0), 5.52 (ddd, 1, *J* = 3.2, 6.2, 12.0), 5.43 (br s, 1), 2.39-2.67 (m, 2), 2.17-1.96 (m, 3), 1.79-1.57 (m, 4), 1.51-1.44 (m, 1), 0.98 (d, 3, *J* = 6.4), 0.94 (s, 3), 0.89 (d, 3, *J* = 6.4); ^{13}C NMR 152.0, 129.4, 127.6, 125.5, 58.6, 50.5, 41.3, 35.7, 31.9, 29.3, 23.5, 22.9, 22.0, 18.6.

(1α,3β,3aβ,8aα)-3,3a-Epoxy-1,2,3,3a,6,7,8,8a-octahydro-8a-methyl-1-(1-methylethyl)azulene (22). *m*-CPBA (50 mg, 0.221 mmol) was added to a biphasic mixture of **20** (42 mg, 0.221 mmol), CH_2Cl_2 (2.2 mL), and saturated aqueous sodium bicarbonate (2.2 mL) at 0 °C. The heterogeneous mixture was stirred vigorously for 30 min and then quenched with saturated sodium sulfite solution and warmed to rt. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 layers were combined and washed with saturated Na_2SO_3, saturated $NaHCO_3$, and brine. The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated to give 45 mg (98%) of crude unstable epoxide **22** that was carried on without purification: ^{1}H NMR 6.09 (dt, 1, *J* = 10.8, 5.6), 5.50 (d, 1, *J* = 10.8), 3.26 (s, 1), 2.35-2.16 (m, 2), 2.09-2.04 (m, 1), 1.83-1.19 (m, 7), 0.90 (s, 3), 0.89 (d, 3, *J* = 6.8), 0.82 (d, 3, *J* = 6.8); ^{13}C NMR 139.9, 125.4, 69.7, 62.9, 52.1, 44.4, 39.9, 32.2, 30.1, 29.2, 24.2, 23.0, 22.6, 18.0.

(1α,3β,8aα)-5-Acetoxy-1,2,3,5,6,7,8,8a-octahydro-8a-methyl-1-(1-methylethyl)azulen-3-ol. (23). Crude epoxide **22** (13 mg, 0.063 mmol) in dry THF (1 mL) was added to a solution of

Pd_2dba_3 (0.5 mg, 0.0063 mmol), dppb (0.47 mg, 0.011 mmol), AcOH (6.6 μL, 0.116 mmol), and dry THF (1 mL) at 0 °C. The solution was stirred at rt for 30 min and then heated at 60 ºC for 1.5 h. Additional portions of Pd_2dba_3 (0.5 mg, 0.0063 mmol) and dppb (0.47 mg, 0.011 mmol) were added when the dark orange color of the solution faded (3 times at 30 min intervals) until the reaction was complete by TLC. The mixture was concentrated and purified by flash chromatography on silica gel using gradient elution. The residue was first eluted with CH_2Cl_2 until the eluent came off colorless. The solvent was then changed to 4:1 hexanes/EtOAc, followed by 2:1 hexanes/EtOAc, to afford 8.0 mg (50%) of **23** as a 1:1 mixture of isomers: ^{1}H NMR 5.88 (d, 0.5 × 1, *J* = 6.8), 5.67 (br, 0.5 × 1), 5.52 (ddd, 0.5 × 1, *J* = 12.0, 3.6, 3.6), 5.26 (ddd, 0.5 × 1, *J* = 6.8, 6.8, 1.9), 4.36 (d, 0.5 × 1, *J* = 4.8), 4.28 (d, 0.5 × 1, *J* = 5.2), 2.03 (s, 0.5 × 3), 2.025 (s, 0.5 × 3), 1.91-1.45 (m, 7), 1.36-1.22 (m, 3), 1.02 (s, 0.5 × 3), 0.96 (d, 0.5 × 3, *J* = 6.8), 0.95 (d, 0.5 × 3, *J* = 6.8), 0.94 (s, 0.5 × 3), 0.88 (d, 3, *J* = 6.8); ^{13}C NMR (170.9, 170.4), (167.8, 167.3), (129.3, 123.4), (74.4, 74.1), (73.1, 70.3), (55.1, 54.7), (48.2, 47.5), (39.6, 39.0), (36.2, 36.0), (34.1, 32.6), 27.7, (24.2, 24.0), (22.3, 22.1), 21.4, (19.6, 19.1), 16.7.

(1α,3β,8aα)-5-Acetoxy-1,2,3,5,6,7,8,8a-octahydro-8a-methyl-1-(1-methylethyl) 3-(trimethylacetoxy)azulene (24). DMAP (3 mg, 0.0226 mmol) and pyridine (22 μL) were added to a solution of **23** (6 mg, 0.0226 mmol), CH_2Cl_2 (2 mL), and PivCl (3 μL, 0.0237 mmol) at 0 °C. The mixture was stirred overnight at rt and the quenched with water and was extracted with CH_2Cl_2. The CH_2Cl_2 layers were washed with saturated copper sulfate solution, and brine. The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated to give crude **24** that was carried on without further purification: ^{1}H NMR 5.77 (d, 0.5 × 1, *J* = 6.0), 5.76 (br, 0.5 × 1), 5.52 (dd, 0.5 × 1, *J* = 3.2, 3.2, 11.6), 5.38 (d, 0.5 × 1, *J* = 5.6), 5.34 (d, 0.5 × 1, *J* = 4.8), 5.25 (dd, 0.5 × 1, 6.0, 6.0), 2.02 (s, 3), 1.96-1.53 (m, 10), 1.15-0.84 (m, 18).

(1α,3β,8aα)-1,2,3,5,6,7,8,8a-octahydro-8a-methyl-1-(1-methylethyl) 3-(trimethylacetoxy)azulene-5-ol (25). K_2CO_3 (15.6 mg, 0.113 mmol) and $NaHCO_3$ (18.9 mg, 0.226 mmol) were added to a solution of crude **24** and MeOH (2 mL). The mixture was stirred at rt for 4 h. The mixture was then concentrated to remove the MeOH and the residue was taken

up in CH_2Cl_2 and washed with water, saturated NH_4Cl solution, and brine. The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (2:1 hexane/EtOAc) gave 7 mg (86%) of **25** from **23** as a 1:1 mixture of isomers: ^{1}H NMR 5.84 (s, 0.5 × 1), 5.77 (d, 0.5 × 1, *J* = 4.8), 5.40 (d, 0.5 × 1, *J* = 6.8), 5.32 (d, 0.5 × 1, *J* = 4.0), 4.54 (br d, 0.5 × 1, *J* = 11.0), 4.34 (br, 0.5 × 1), 2.01-1.25 (m, 10), 1.16-0.84 (m, 18).

(1α,3β,8aα)-2,3,6,7,8,8a-Hexahydro-8a-methyl-1-(1-methylethyl) 3-(trimethylacetoxy)-5(1*H*)-azulenone (26). Dess-Martin reagent (11 mg, 0.025 mmol) was added to **25** (7 mg, 0.023 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred at rt for 45 min and then quenched with 10% sodium thiosulfate solution. The solution stirred for an additional 30 min until the layers appeared clear. The layers were separated and the CH_2C_2 layers were combined and washed with saturated bicarbonate solution and brine. The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated to give 7 mg (99%) of enone **26** (>95% pure) as a single isomer: ^{1}H NMR 5.90 (s, 1), 5.51 (d, 1, *J* = 7.2), 2.65 (ddd, 1, *J* = 4.4, 7.6, 15.4), 2.52 (ddd, 1, *J* = 4.8, 9.2, 15.4), 2.12 (ddd, 1, *J* = 3.2, 6.8, 13.6), 2.01-1.61 (m, 7), 1.17 (s, 9), 1.04 (s, 3), 0.98 (d, 3, *J* = 6.4), 0.89 (d, 3, *J* = 6.4); ^{13}C NMR 167.7, 165.9, 126.4, 74.8, 55.4, 49.4, 44.4, 39.3, 38.7, 34.0, 28.1, 27.1 (3 C), 23.7, 21.9, 21.3, 20.6. (The enone carbonyl carbon was not observed)