A Four-Step Synthesis of the Hydroazulene Core of Guanacastepene

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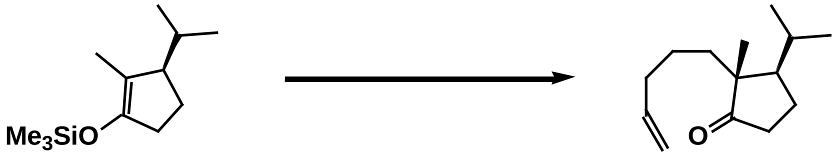
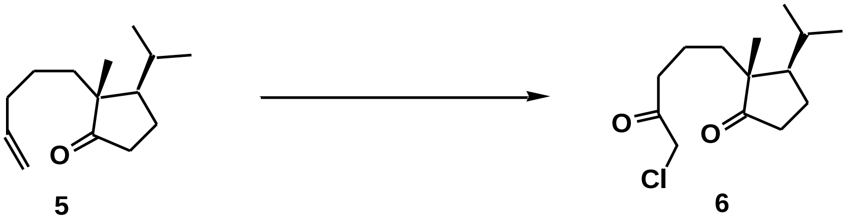
Supporting Information

General Procedures. All reactions were performed in oven-dried glassware with magnetic stirring. Commercial grade reagents and anhydrous solvents were used without further purification expect for chlorotrimethylsilane (TMSCl) and hexamethylphosphoramide (HMPA), which were distilled from calcium hydride, and perdeuterated tetrahydrofuran (THF-d_8), which was distilled from $LiAlH_4$.

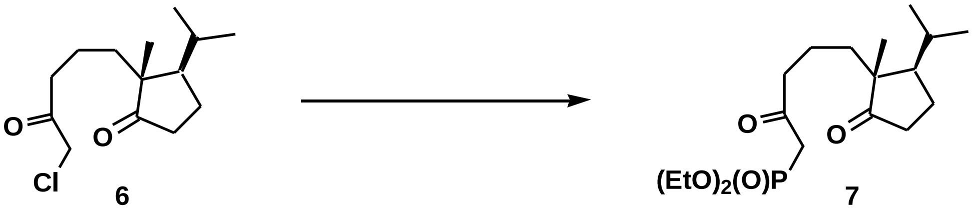


4 **5**

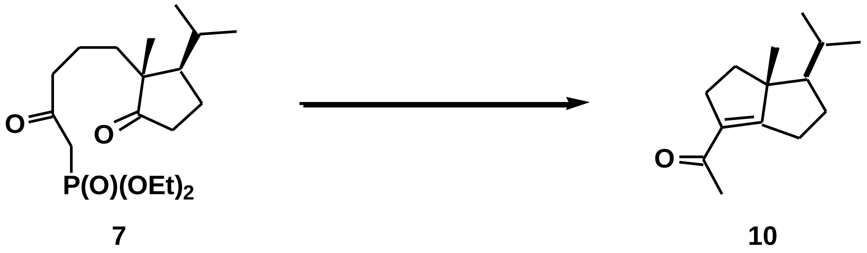
Keto-olefin 5. A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with a solution of **4** (0.429 g, 2.0 mmol) in 15 mL of THF and cooled at 0 °C while a solution of methyllithium–lithium iodide (1.0 M in ether, 2.1 mL, 2.1 mmol) was added rapidly dropwise by syringe. The resulting solution was stirred for 1 h, then cooled at –78 °C while a solution of 5-iodo-1-pentene (0.98 g, 5.0 mmol) in 5 mL of hexamethylphosphoramide (HMPA) was added rapidly by syringe. The resulting slurry was allowed to stir overnight (17 h) with gradual warming to room temperature to give a yellow solution, which was diluted with 45 mL of ether and washed with three 10-mL portions of water and 10 mL of saturated NaCl solution. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to give 0.93 g of a faintly yellow liquid. Purification by column chromatography on 42 g of silica gel (elution with 5% ether in pentane) provided 0.267 g (63%) of **5** as a colorless oil. Spectral data for **5** was consistent with that reported previously for this compound.[1]



α**-Chloro ketone 6**. A 15-mL, one-necked, pear-shaped flask was charged with a mixture of **5** (0.104 g, 0.50 mmol), water (0.5 mL), chloramine-T (0.282 g, 1.0 mmol), and 0.5 mL of acetone. Sulfuric acid (3.0 M in water, 0.25 mL, 0.75 mmol) was added dropwise, and the resulting mixture was heated at 50 °C for 30 min, then cooled to room temperature and diluted with 2.5 mL of acetone. A mixture of CrO_3 (0.50 g, 5.0 mmol) and H_2SO_4 (3.0 M in water, 2.5 mL, 7.5 mmol) (Jones reagent) was then added, and the resulting orange–brown mixture was stirred for 30 min at room temperature before isopropanol (1.0 mL, 13 mmol) was added. After an additional 30 min, the reaction mixture was diluted with 20 mL of water and extracted with three 10-mL portions of ethyl acetate. The combined organic layers were washed with 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and deposited onto 0.39 g of silica gel. Purification by column chromatography on 13 g of silica gel (elution with 10% ethyl acetate in hexanes) provided 82 mg (63%) of a colorless oil: IR (thin film) 2962, 1734, 1458, 1405, 1170, 1087, and 956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 2H), 2.53–2.61 (m, 2H), 2.33–2.40 (m, 1H), 2.00–2.14 (m, 2H), 1.64–1.81 (m, 4H), 1.43–1.57 (m, 2H), 1.14–1.22 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), and 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 224.1, 202.3, 52.0, 48.1, 48.0, 40.0, 37.5, 36.5, 29.4, 23.7, 22.0, 21.4, 18.9, and 18.2. HRMS Calcd for $C_{14}H_{23}ClO_2$: 258.1387. Found: 259.1466 ($M+H^+$).

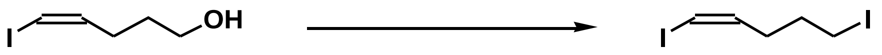


β-Ketophosphonate 7. A 15-mL, one-necked, pear-shaped flask equipped with an argon inlet was charged with a solution of **6** (55 mg, 0.21 mmol) in 2 mL of acetone, and NaI (95 mg, 0.63 mmol) was added. The resulting mixture was stirred in the dark for 15 min, then was partitioned between 10 mL of ether and 2 mL of water. The organic layer was washed with 2-mL portions of 1 M $Na_2S_2O_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated (protected from light) to give 75 mg colorless oil, which was immediately dissolved in 5 mL of benzene in 25-mL, one-necked, pear-shaped flask equipped with a reflux condenser with an argon inlet. Triethyl phosphite (55 μL, 0.32 mmol) was added, and the resulting solution was heated at reflux for 5 h in the dark and then cooled to room temperature and concentrated to give 89 mg of a colorless oil. Purification by column chromatography on 8 g of silica gel (gradient elution with 50–100% ethyl acetate in hexanes) provided 56 mg (74%) of **7** as a colorless oil: IR (thin film) 3476, 2963, 1732, 1460, 1406, 1369, 1256, 1164, 1025, 967, and 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (apparent quint, *J* = 7.0 Hz, 4H), 3.05 (d, $J_{H\text{-}P}$ = 22.7 Hz, 2H), 2.51–2.63 (m, 2H), 2.31–2.40 (m, 1H), 2.00–2.12 (m, 2H), 1.78–1.84 (m, 1H), 1.62–1.72 (m, 3H), 1.42–1.50 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.13–1.20 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H), and 0.88 (s, 3H); ^{13}C NMR δ 224.2, 201.7 (d, $J_{C\text{-}P}$ = 6.1 Hz), 62.5 (m), 52.0, 48.0, 44.3, 42.3 (d, $J_{C\text{-}P}$ = 127.3 Hz), 37.6, 36.6, 29.4, 23.7, 22.0, 21.5, 18.8, 18.2, and 16.3 (d, $J_{C\text{-}P}$ = 6.1 Hz); ESIMS *m/z* 361.4 ($M+H^+$, $C_{18}H_{33}O_5P$ requires 361.4).



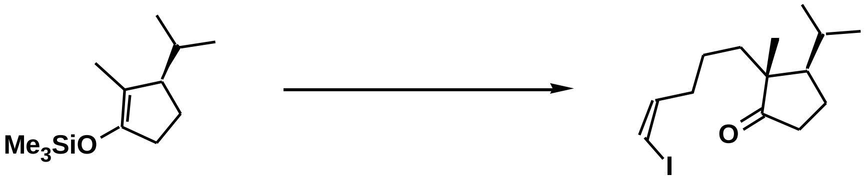
[5,5]-Bicyclic enone 10. A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser with an argon inlet was charged with **7** (42 mg, 0.11 mmol), Cs_2CO_3 (0.19 g, 0.58 mmol), and 22 mL of toluene, and the resulting mixture was heated at reflux for 12 h, then cooled to room temperature. The liquid was decanted, washed with 5 mL of water and 5 mL of saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated. Purification by column chromatography on 5 g of silica gel (elution with

10% ethyl acetate in hexanes) provided 21 mg (83%) of **10** as a colorless oil. Spectral data for **10** was consistent with that reported previously for this compound.[1]



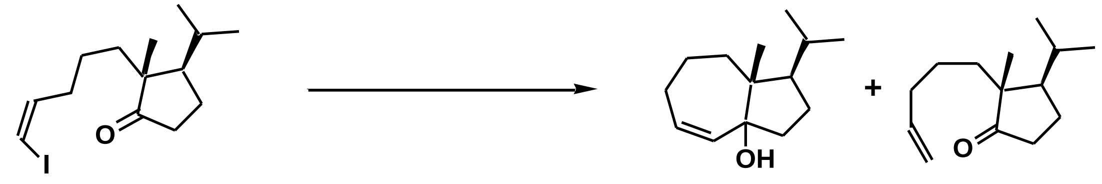
11 **12**

Diiodide 12. A 500-mL, one-necked, round-bottomed flask equipped with an argon inlet was charged with a mixture of triphenylphosphine (14.69 g, 56 mmol), imidazole (3.81 g, 56 mmol), and 150 mL of CH_2Cl_2 and immersed in a room temperature water bath. The stirred mixture became homogeneous within 5 min, at which time iodine (14.21 g, 56 mmol) was added. After an additional 10 min, a solution of **11** (7.9 g, 37 mmol) in 35 mL of CH_2Cl_2 was added. The resulting mixture was stirred for 1 h in the dark, then diluted with 185 mL of hexanes, filtered through Celite with the aid of three 50-mL portions of hexanes, and concentrated. Purification by column chromatography on 60 g of silica gel (elution with hexanes) provided 11.0 g (92%) of **12** as a colorless liquid: IR (thin film) 3062, 2934, 2835, 1608, 1425, 1305, 1280, 1263, 1198, 1164, and 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (d, *J* = 7.4 Hz, 1H), 6.18 (apparent q, *J* = 7.1 Hz, 1H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.27 (apparent q, *J* = 7.2 Hz, 2H), and 1.98 (apparent quint, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 84.0, 35.6, 31.8, and 5.4.



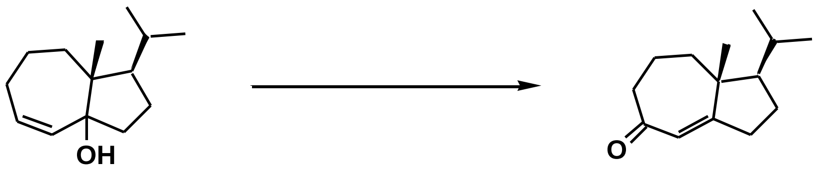
4 **13**

Vinyl iodide 13. A 200-mL, one-necked, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with a solution of **4** (1.91 g, 9.0 mmol) in 66 mL of THF and cooled at 0 °C while a solution of methyllithium–lithium iodide (0.93 M in ether, 9.8 mL, 9.1 mmol) was added rapidly dropwise by syringe. The resulting solution was stirred for 1 h, then cooled at –78 °C while a solution of **12** (7.22 g, 22 mmol) in 22 mL of hexamethylphosphoramide (HMPA) was added rapidly by syringe. The resulting slurry was allowed to stir overnight (14 h) with gradual warming to room temperature to give a yellow solution, which was diluted with 200 mL of ether and washed with three 40-mL portions of water and 40 mL of saturated NaCl solution. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Purification by column chromatography on 75 g of silica gel (gradient elution with 2–5% ethyl acetate in hexanes) provided ca. 4.5 g of unreacted **12**, followed by 2.28 g (76%) of **13** as a colorless oil: IR (thin film) 2959, 2870, 1736, 1608, 1458, 1406, 1386, 1373, 1281, 1231, and 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 7.4 Hz, 1H), 6.14 (apparent q, *J* = 6.8 Hz, 1H), 2.32–2.40 (m, 1H), 2.01–2.13 (m, 4H), 1.65–1.82 (m, 3H), 1.42–1.58 (m, 3H), 1.00–1.15 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), and 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 224.1, 140.8, 82.7, 52.0, 48.2, 37.6, 36.9, 35.0, 29.4, 23.7, 23.3, 22.1, 21.5, and 18.3. HRMS Calcd for $C_{14}H_{23}IO$: 334.0794. Found: 335.0875 ($M+H^+$).



13 **14** **5**

Allylic alcohol 14. A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet, a 250-mL pressure equalizing dropping funnel, and a rubber septum was charged with 150 mL of THF and cooled in a 0 °C bath. A solution of *n*-butyllithium (2.5 M in hexanes, 9.0 mL, 22.5 mmol) was added, followed immediately by dropwise addition of a solution of **13** (1.50 g, 4.5 mmol) in 150 mL of THF over 40 min. The resulting solution was stirred for 30 min, then was diluted with 50 mL of water and washed with two 50-mL portions of saturated NaCl solution. The combined aqueous solutions were extracted with 50 mL of ether, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give a wet orange oil. Purification by column chromatography on 93 g of silica gel (gradient elution with 2.5–10% ethyl acetate in hexanes) provided 0.15 g (16%) of **5**, followed by 0.580 g (62%) of **14** as a yellow oil: IR (thin film) 3616, 3468, 2956, 2879, 1458, 1376, 1013, and 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59–5.69 (m, 2H), 2.23–2.42 (m, 1H), 2.03–2.18 (m, 2H), 1.65–1.82 (m, 4H), 1.32–1.62 (m, 6H), 0.99 (s, 3H), 0.93 (d, $J = 6.5$ Hz, 3H), and 0.86 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 132.0, 83.3, 53.9, 49.1, 40.1, 39.7, 30.4, 30.2, 24.8, 23.0, 22.3, 19.4, and 17.5. HRMS Calcd for $C_{14}H_{24}0$: 208.1827. Found: 208.1818.



14 **2**

Hydroazulene 2. A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet was charged with 4.84 g of oven-dried, powdered 3Å molecular sieves, PCC (2.42 g, 11.2 mmol), and 19 mL of CH_2Cl_2. To this vigorously stirred suspension was added a solution of **14** (0.78 g, 3.7 mmol) in 18 mL of CH_2Cl_2, and the resulting brown mixture was stirred for 30 min at room temperature and then deposited onto 9.7 g of silica gel. Purification on 77 g of silica gel (elution with 10% ethyl acetate in hexanes) provided 0.550 g (71%) of **2** as a colorless oil: IR (thin film) 2956, 2870, 1652, 1464, 1426, 1366, 1336, 1260, 1191, 970, and 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (apparent t, *J* = 1.7 Hz, 1H), 2.37–2.71 (m, 4H), 2.12 (ddd, *J* = 13.9, 7.2, and 3.5 Hz, 1H), 1.91–2.03 (m, 1H), 1.78–1.90 (m, 2H), 1.61–1.75 (m, 2H), 1.43–1.57 (m, 2H), 1.05 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), and 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 171.9, 123.8, 58.6, 50.0, 44.2, 38.8, 32.9, 27.9, 25.6, 24.1, 22.0, 21.0, and 20.7. HRMS Calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1666.

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[1] Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569.