Enantioselective Syntheses of Georgyone, Arborone and Structural Relatives; Relevance to the Molecular-Level Understanding of Olfaction

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Supplementary Materials

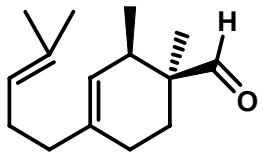
Materials and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Flash chromatography was performed using Baker silica gel (40 μm particle size). NMR spectra were recorded on Varian Innova-500, or Mercury-400 instruments and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on Avatar 360 FT-IR spectrometer. Low-resolution and high-resolution mass spectral analyses were performed at the Harvard University Mass Spectrometry Center. Analytical high performance liquid chromatography (HPLC) was performed on Isco 2350 Series or Waters 626 HPLC using the indicated chiral column. Gas chromatography (GC) analyses were performed on Hewlett-Packard 6850 Series GC System equipped with flame ionization detector using a J & W Scientific Cyclosil-B column (30 m x 0.25 mm). Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane was distilled from calcium hydride. Toluene was distilled from sodium.

General Procedure for the Preparation and Use of Chiral Diels-Alder Catalysts. A 100-mL, two-necked, round-bottomed flask equipped with a stir bar, a glass stopper and a 50-mL pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 4A molecular sieves,[1] and functioning as a Soxhlet extractor) fitted on top with a reflux condenser and a nitrogen inlet adaptor was charged with (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (82.0 mg, 0.324 mmol, from Lancaster), tri-*o*-tolylboroxine[2] (38.0 mg, 0.107 mmol) and 25 mL of toluene.

[1] Molecular sieves (pellets) were dried *in vacuo* at *ca.* 200 °C with a gas burner for 10 min prior to use.
[2] Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3803.

The resulting solution was heated to reflux (bath temperature ~ 145 °C). After 3 h, the reaction mixture was cooled to *ca.* 60 °C and the addition funnel and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated by distillation (air-cooling) to a volume of *ca.* 5 mL. This distillation protocol was repeated three times by re-charging with 3 x 5 mL of toluene. The solution was then allowed to cool to room temperature and the distillation head was quickly replaced with a vacuum adaptor. Concentration *in vacuo* (*ca*. 0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as clear oil, which can then be dissolved in CH_2Cl_2 and used in two Diels-Alder experiments. To an aliquot of the oxazaborolidine precursor (0.160 mmol, theoretical) in 1.0mL of CH_2Cl_2 at –25 °C was added trifluoromethanesulfonimide (0.20 M solution in CH_2Cl_2, freshly prepared, 667 μL, 0.133 mmol) dropwise. After 10 min at –25 °C, a colorless homogeneous catalyst solution was ready for use in the Diels-Alder reactions.

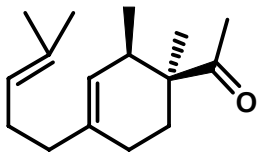
Part I. Synthesis of Georgyone (1).



6

(-)-1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enecarbaldehyde (6). To a CH_2Cl_2 solution of 0.2 equiv of the freshly prepared catalyst **5** were successively added a solution of homomyrcene **(4)** (612 mg, 4.08 mmol) in CH_2Cl_2 (5 mL) and methacrolein (235 mg, 4.08 mmol) at -95 ^oC. The reaction mixture was stirred at -95 °C for 2 h and then quenched by addition of 100 μL of Et_3N. After the mixture had warmed to room temperature, the residue was concentrated *in vacuo* and purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to give the desired aldehyde **6** (799 mg, 89%) as a colorless oil: $[\alpha]_D^{25}$ -55.1 (*c* 0.5, $CHCl_3$, 96% ee, 6:1 de); IR (film) 2966, 2919, 1725, 1453, 1376, 833 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 9.65 (1H, s), 5.30 (1H, s), 5.01 (1H, t, *J* = 6.5 Hz), 2.20 (1H, br s), 2.11-1.79 (7H, m), 1.67 (3H, s), 1.60 (3H, s), 1.58-1.49 (1H, m), 1.05 (3H, s), 0.97 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 136.9, 131.9, 125.3, 124.3, 47.4, 37.5, 37.2, 28.2, 26.6, 25.9, 25.6, 20.2, 17.9, 17.4. Diastereoselectivity (*endo/exo* ratio) was determined by ^{1}H NMR (500 MHz, $CDCl_3$) analysis of the crude mixture: δ 9.65 (s, *endo* major), δ 9.45 (s, *exo* minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, $CDCl_3$): δ 4.19 (H, d, *J* = 10.8 Hz minor), 4.15 (H, d, *J* = 12.0 Hz major).

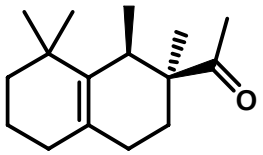


7

(-)-1-[1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enyl]-ethanone (7). To a solution of the above aldehyde **6** (410 mg, 1.86 mmol) in THF (10 mL) was added methylmagnesium bromide (0.93 mL, 2.79 mmol, 3.0 M solution in ether) dropwise at 0 ^{o}C. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (5 mL) was carefully added. The mixture was diluted with water (10 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, 15:1) to afford alcohol (381 mg, 87%) as a colorless oil.

To a solution of the above alcohol (381 mg, 1.62 mmol) in CH_2Cl_2 (8 mL) was added Dess-Martin periodinane (755 mg, 1.78 mmol) at 0 ^{o}C. The resulting solution was stirred at rt for 1 h, and then saturated aqueous $NaHCO_3$ (20 mL) was carefully added. The two-phase mixture

which formed was diluted with water (10 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford methylketone **7** (343 mg, 91%) as a yellow oil: $[\alpha]_D^{25}$ -104.3 (*c* 1.0, $CHCl_3$); IR (film) 2966, 2929, 1704, 1453, 1376, 1355, 1086, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.31 (1H, s), 5.01 (1H, t, *J* = 6.4 Hz), 2.21-2.15 (1H, m), 2.12 (3H, s), 2.10-1.79 (6H, m), 1.67 (3H, s), 1.60 (3H, s), 1.58-1.51-1.44 (2H, m), 1.11 (3H, s), 0.80 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 135.3, 131.5, 126.1, 124.8, 124.4, 49.2, 37.5, 37.4, 26.6, 25.8, 25.6, 24.0, 21.3, 18.3, 17.8; HRMS (ES+) calcd for $C_{16}H_{27}O$ (MH^+) 235.2062, found 235.2063.

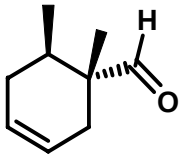


1

(-)-Georgyone (1). To a solution of methylketone **7** (181 mg, 0.77 mmol) in toluene (6 mL) was added dropwise methylaluminum dichloride (1.93 mL, 1.93 mmol, 1.0 M solution in hexanes) at 0 °C. The resulting solution was heated to 65 °C for 4 h. After cooling the mixture, the residue was diluted with saturated aqueous NH_4Cl (5 mL) and extracted with hexanes (2 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc:hexanes, 1:25) to give **(-)**-Georgyone **(1)** (151 mg, 83%) as a colorless oil: $[\alpha]_D^{25}$ -18.1 (*c* 0.5, $CHCl_3$); IR (film) 2929, 1702, 1459, 1358, 1221, 1196, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (1H, q, *J* = 6.9 Hz), 2.15 (3H, s), 2.14-1.23 (10H, m), 1.06 (3H, s), 1.01 (3H, s), 0.99 (3H, s), 0.85 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 137.3, 126.2, 51.1, 40.5, 35.7, 34.4, 31.1, 29.8,

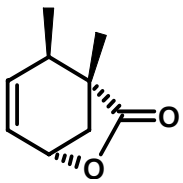
28.8, 28.0, 25.2, 22.9, 21.4, 20.0, 19.5; HRMS (ES+) calcd for $C_{16}H_{27}O$ (MH^+) 235.2062, found 235.2064.

Part II. Synthesis of Arborone (2).



8

1,6-Dimethyl-cyclohex-3-enecarbaldehyde (8). To a CH_2Cl_2 (3 mL) solution of 0.2 equiv of the freshly prepared catalyst **5** were successively added a solution of 1.3-butadiene (2 mL) and tiglic aldehyde (412 mg, 4.89 mmol) at -78 ^oC. The Pyrex bottle was sealed with a screw cap and was stirred at rt for 21 h and then quenched by addition of 100 μL of Et_3N. The residue was concentrated *in vacuo* and purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to give the desired aldehyde **8** (567 mg, 84%) as a colorless oil: $[\alpha]_D^{25}$ +26.7 (*c* 0.8, $CHCl_3$, 88% ee); IR (film) 2962, 2887, 2690, 1727, 1455, 903, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (1H, s), 2.33-1.69 (5H, m), 0.96 (3H, s), 0.86 (3H, d, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 126.1, 123.6, 48.2, 31.6, 30.9, 30.5, 16.2, 14.0. Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^{19}F NMR integration (376.2 MHz, $CDCl_3$): δ -71.8 (s, CF_3, minor), -71.9 (s, CF_3, major).



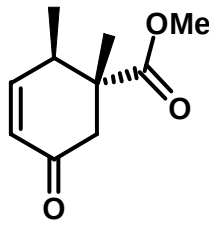
9

5-Hydroxy-1,2-dimethyl-cyclohex-3-enecarboxylic Acid Lactone (9). Jones' reagent (3.58 mmol) was added dropwise to a stirred solution of aldehyde **8** (413 mg, 2.99 mmol) in acetone (10 mL) at 0 °C. The reaction mixture was stirred for 1 h and then saturated aqueous $NaHCO_3$ (10 mL) was carefully added. The mixture was diluted with water (10 mL) and extracted with ether (3 × 40 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:7) to afford acid (399 mg, 87%) as a yellow oil: $[\alpha]_D^{25}$ +15.4 (*c* 1.0, $CHCl_3$); IR (film) 2962, 2887, 2690, 1727, 1455, 903, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.38 (1H, br s), 5.61 (2H, s), 2.62-1.64 (5H, m), 1.07 (3H, s), 0.89 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 125.8, 124.3, 45.0, 35.7, 33.1, 30.9, 16.6, 15.6.

To a solution of the above acid (399 mg, 2.61 mmol) in THF (7 mL) were added $NaHCO_3$ (247 mg, 2.96 mmol), water (7 mL), potassium iodide (1.59 g, 9.6 mmol) and iodine (811 mg, 3.19 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 6 h and then saturated aqueous sodium thiosulfate (10 mL) was carefully added. The mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide iodo lactone (598 mg, 82%).

The above iodo lactone (521 mg, 1.86 mmol) in THF (10 mL) was treated with DBU (0.37 mL, 2.44 mmol). The resulting solution was heated at reflux for 12 h. After cooling the mixture, the mixture was diluted with saturated aqueous NH_4Cl (7 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (7 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, gradient 1:15) to afford lactone **9** (268 mg, 95%): $[\alpha]_D^{25}$ -70.3 (*c* 0.8, $CHCl_3$); IR (film) 2979, 2877, 1767, 1090, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (1H, m), 5.68

(1H, ddd, J = 9.2, 3.6, 0.8 Hz), 4.62 (1H, t, J = 4.8 Hz), 2.38-2.24 (1H, m), 2.06-2.02 (2H, m), 1.18 (3H, s), 0.98 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 137.8, 128.3, 72.3, 44.6, 37.8, 36.8, 19.6, 14.6; LRMS (ES+) calcd for $C_9H_{13}O_2$ (MH^+) 153.1, found 153.1.

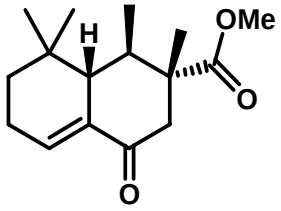


10

1,2-Dimethyl-5-oxo-cyclohex-3-enecarboxylic Acid Methyl Ester (10). Sodium methoxide (142 mg, 2.64 mmol) was added to a solution of lactone **9** (268 mg, 1.76 mmol) in methanol (6 mL) and the resulting solution was stirred for 3 h at rt. The methanol was removed *in vacuo* and the resulting aqueous was diluted with saturated aqueous NH_4Cl (7 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford allylic alcohol (271 mg, 84%) as a colorless oil: $[\alpha]_D^{25}$ +3.8 (*c* 0.5, $CHCl_3$); IR (film) 3377, 2954, 1727, 1455, 1239, 1034, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62-5.58 (1H, m), 5.49-5.46 (1H, m), 4.15-4.10 (1H, m), 3.62 (3H, s), 3.00 (1H, s), 2.70-2.64 (1H, m), 1.95 (1H, dd, J = 12.8, 5.6 Hz), 1.84 (1H, dd, J = 13.2, 7.0 Hz), 1.05 (3H, s), 0.84 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 133.1, 128.8, 64.8, 52.3, 45.8, 40.3, 35.7, 17.8, 15.9; LRMS (ES+) calcd for $C_{10}H_{15}O_3$ (MH^+) 185.1, found 185.1.

To a solution of the above alcohol (271 mg, 1.47 mmol) in CH_2Cl_2 (10 mL) was added PCC (349 mg, 1.62 mmol) at 0 ^{o}C. The resulting solution was stirred at rt for 1 h, and was filtered through a short plug of Celite eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 15:1 to 10:1) to afford

enone **10** (251 mg, 94%) as a colorless oil: $[\alpha]_D^{25}$ +74.5 (*c* 0.7, $CHCl_3$); IR (film) 2973, 2883, 1729, 1681, 1453, 1245, 1196, 1111, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, dd, *J* = 10.0, 4.0 Hz), 5.90 (1H, dd, *J* = 10.0, 1.6 Hz), 3.65 (3H, s), 3.09-3.01 (1H, m), 2.75 and 2.35 (2H, AB_q, J_{AB} = 16.4 Hz), 1.17 (3H, s), 1.06 (3H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 176.2, 153.3, 127.8, 52.3, 47.7, 44.8, 36.6, 19.2, 14.4; LRMS (ES+) calcd for $C_{10}H_{15}O_3$ (MH^+) 183.1, found 183.1.



13

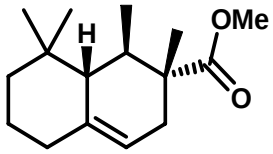
1,2,8,8-Tetramethyl-4-oxo-1,2,3,4,6,7,8,8a-octahydro-naphthalene-2-carboxylic Acid Methyl Ester (13) A chloride **11** (392 mg, 2.68 mmol) was added dropwise to a preformed solution of LDBB (2.76 mmol) in THF (10 mL) at -78 ^oC. The color of the solution changed from a dark-blue to a dark-red after all the chloride was added. After 10 min, CuCN (240 mg, 2.68 mmol) was added and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was then treated with TMSCl (1 mL) and enone **10** (241 mg, 1.32 mmol) consecutively. After stirring for further 1 h at -78 ^oC, the reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL). The two-phase mixture formed was diluted with water (10 mL) and extracted with ether (3 × 70 mL). The combined extracts were washed with 2 N HCl (2 x 10 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, gradient 1:20 to 1:10) to provide the desired ketone (281 mg, 76%) as a colorless oil: $[\alpha]_D^{25}$ +29.6 (*c* 0.8, $CHCl_3$); IR (film) 2952, 1717, 1434,

1260, 1156, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (1H, m), 4.98 (1H, dd, *J* = 17.0, 2.0 Hz), 4.92 (1H, d, *J* = 10.5 Hz), 3.68 (3H, s), 2.70 and 2.16 (2H, AB_q, J_{AB} = 17.5 Hz), 2.44-2.40 (1H, m), 2.24 (1H, dd, *J* = 16.0, 5.5 Hz), 2.12-1.92 (3H, m), 1.48-1.27 (3H, m), 1.17 (3H, s), 0.99 (3H, d, *J* = 7.0 Hz), 0.91 (3H, s), 0.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 178.2, 139.2, 114.5, 52.5, 47.6, 47.5, 45.1, 39.6, 39.5, 36.5, 34.8, 28.4, 25.4, 24.8, 22.6, 19.1; HRMS (ES+) calcd for $C_{17}H_{29}O_3$ (MH^+) 281.2116, found 281.2114.

A solution of the above olefin (262 mg, 0.94 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 ^oC and was exposed to ozone gas with efficient stirring for 10 min. While still at -78 ^oC, the solution was flushed with argon. After 10 min, dimethyl sulfide (1.5 mL) was added and the resulting solution was gradually warmed to rt. After being stirred overnight, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL). The two-phase mixture formed was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to produce the desired crude aldehyde **12** (239 mg, 91%) suitable for use in the next step without purification:

A solution of above aldehyde **12** (226 mg, 0.81 mmol) and *p*-TSA (30 mg) in benzene was heated at reflux with removal of water through a Dean-Stark apparatus for 14 h. After cooling the mixture to rt, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL). The two-phase mixture formed was extracted with ether (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:15) to afford enone **13** (197 mg, 81%) as a colorless oil: $[\alpha]_D^{25}$ +27.2 (*c* 0.6, $CHCl_3$); IR (film) 2950, 1731, 1696, 1621, 1250, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, m), 3.59 (3H, s), 2.59 (1H, d, *J* = 16.4 Hz), 2.44-1.98 (5H, m), 1.39-1.35 (2H, m), 1.15 (3H, s), 1.08 (3H, d, *J* = 6.8 Hz), 1.04 (3H, s), 0.80 (3H, s); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 200.2, 177.4, 136.6, 136.4, 52.2, 50.0, 46.7, 44.8, 37.4, 34.9, 32.8, 30.2, 23.6, 22.0, 20.6, 19.5; LRMS (ES+) calcd for $C_{16}H_{25}O_3$ (MH^+) 265.2, found 265.1.

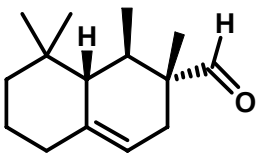


14

1,2,8,8-Tetramethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalene-2-carboxylic Acid Methy Ester (14). Tosyl hydrazine (25 mg, 0.13 mmol) was added to a solution of enone **13** (25 mg, 0.10 mmol) in EtOH (4 mL). A drop of conc. HCl was added and the reaction mixture was then heated at reflux for 1.5 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (hexanes:EtOAc, gradient 15:1 to 10:1) to afford the tosylhydrazone of **13** (36 mg, 83%).

The above tosylhydrazone (36.1 mg, 0.084 mmol) in $CHCl_3$ (3 mL) was first degassed by N_2 bubbling for 5 min. The solution was then cooled to 0 °C as catecholborane (0.11 mL, 1 M in THF, 0.110 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C and warmed to room temperature. $NaOAc{\cdot}3H_2O$ (18 mg, 0.138 mmol) was added, and the mixture was then heated at 65 °C for 12 h, cooled to room temperature, and diluted with ether (30 mL). After the mixture was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 15:1 to 10:1) to afford ester **14** (19.2 mg, 82%) as a colorless oil: $[\alpha]_D^{25}$ +26.7 (*c* 0.4, $CHCl_3$); IR (film) 2927, 2842, 1729, 1233, 1104, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, d, *J* = 7.5 Hz), 3.68 (3H, s), 2.25-2.18 (3H, m), 1.85-1.81 (2H, m), 1.56-1.38 (5H, m), 1.03 (3H, s), 1.02 (3H, s), 0.94 (3H, d, *J* = 6.5 Hz), 0.83 (3H, s); ^{13}C

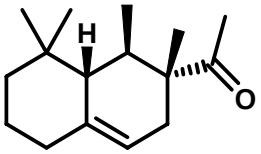
NMR (100 MHz, $CDCl_3$) δ 179.7, 140.6, 117.3, 53.7, 52.0, 47.5, 43.5, 37.8, 36.4, 35.0, 32.0, 24.2, 20.5, 20.3, 16.1; HRMS (ES+) calcd for $C_{16}H_{27}O_2$ (MH^+) 251.2012, found 251.2015.



15

1,2,8,8-Tetramethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalene-2-carboxaldehyde (15). To a solution of ester **14** (17.1 mg, 0.068 mmol) in CH_2Cl_2 (3 mL) at -78 ^oC was added DIBALH (136 μL, 0.136 mmol, 1.0 M solution in CH_2Cl_2). After the mixture was stirred for 50 min at the same temperature, saturated aqueous NH_4Cl (0.15 mL) was carefully added. The reaction mixture was stirred for 1 h at rt and was filtered through a short plug of Celite eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give the colorless crude alcohol suitable for use in the next step without purification.

To a solution of the above alcohol (13.6 mg, 0.061 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (35 mg, 0.089 mmol) at 0 ^oC. The resulting solution was stirred at rt for 1 h, and was filtered through a short plug of Celite eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo* and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford aldehyde **15** (12.2 mg, 82% for 2 steps) as a colorless oil: $[\alpha]_D^{25}$ +30.1 (*c* 0.3, $CHCl_3$); IR (film) 2927, 2842, 1727, 1455, 910, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (1H, s), 5.45 (1H, d, *J* = 5.2 Hz), 2.22-2.18 (1H, m), 2.08-1.82 (3H, m), 1.62-1.21 (6H, m), 1.05 (3H, s), 0.94 (3H, s), 0.92 (3H, *J* = 6.4 Hz), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 141.0, 115.9, 53.0, 50.6, 43.4, 37.8, 36.4, 32.1, 31.9, 24.2, 20.4, 20.1, 13.9; LRMS (ES+) calcd for $C_{15}H_{25}O$ (MH^+) 221.2, found 221.2.



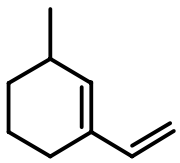
2

1-(1,2,8,8-Tetramethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-yl)-ethanone (2). To a solution of the above aldehyde **15** (10.1 mg, 0.046 mmol) in THF (3 mL) was added methylmagnesium bromide (23 μL, 0.069 mmol, 3.0 M solution in ether) dropwise at 0 ^{o}C. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (1 mL) was carefully added. The mixture was diluted with water (2 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the colorless crude alcohol suitable for use in the next step without purification.

To a solution of the above alcohol in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (26 mg, 0.060 mmol) at 0 ^{o}C. The resulting solution was stirred at rt for 1 h, and then saturated aqueous $NaHCO_3$ (5 mL) was carefully added. The two-phase mixture which formed was diluted with water (2 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford methylketone **2** (9.4 mg, 88% for 2 steps) as a colorless oil: $[\alpha]_D^{25}$ +30.8 (*c* 0.3, $CHCl_3$); IR (film) 2925, 2865, 1702, 1457, 1383, 1219, 1082 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.43 (1H, d, *J* = 7.5 Hz), 2.26-2.20 (2H, m), 2.15 (3H, s), 2.10-2.07 (1H, m), 1.90-1.82 (1H, m), 1.71 (1H, dd, *J* = 15.5, 7.0 Hz), 1.57-1.47 (3H, m), 1.44-1.39 (2H, m), 1.05 (3H, s), 1.01 (3H, s), 0.89 (3H, d, *J* = 6.5 Hz), 0.84 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3, 141.0, 116.8, 53.8, 52.7, 43.4, 37.9, 36.4, 35.6,

33.7, 31.9, 25.9, 24.3, 20.5, 20.3, 16.0; HRMS (ES+) calcd for $C_{16}H_{27}O$ (MH^+) 235.2062, found 235.2054.

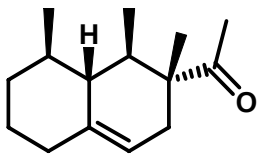
Part III. Synthesis of 20.



17

3-Methyl-1-vinyl-cyclohexene (17). To a suspension of methyltriphenylphosphonium iodide (6.12 g, 15.11 mmol) in dry THF (30 mL) was slowly added a 2.5 M solution of *n*-BuLi in hexane (5.7 mL, 14.34 mmol). The suspension was stirred for 1 h at 0 °C. A solution of aldehyde **16**[3] (1.58 g, 12.75 mmol) in THF (25 mL) was added to the mixture at 0 °C. The reaction mixture was slowly warmed to rt, stirred for 2 h and then saturated aqueous NH_4Cl (20 mL) was carefully added. The two-phase mixture which formed was diluted with water (20 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1) to afford diene **17** (1.41 g, 91%) as a yellow oil: IR (film) 2925, 2869, 1640, 1455, 987, 891, 853 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (1H, dd, *J* = 10.5 Hz, *J* = 17.5 Hz), 5.61 (1H, s), 5.09 (1H, d, *J* = 18.0 Hz), 4.92 (1H, d, *J* = 11.0 Hz), 2.30 (1H, br s), 2.21-2.01 (2H, m), 1.85-1.71 (2H, m), 1.58-1.54 (2H, m), 1.02 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 136.2, 135.5, 110.3, 31.5, 31.1, 24.0,21.8, 21.6.

[3] This aldehyde was prepared by modification of a procedure of outlined by Matsui. Kawanobe, T.; Kogami, K.; Hayashi, K.; Matsui, M. *Agric. Biol.Chem.* **1984**, *48*, 461.



20

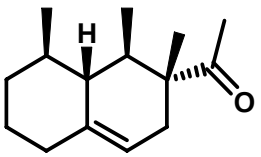
1-(1,2,8-Trimethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-yl)-ethanone (20). To a CH_2Cl_2 solution of 0.2 equiv of the freshly prepared catalyst **5** were successively added a solution of diene **17** (540 mg, 4.42 mmol) in CH_2Cl_2 and tiglic aldehyde (259 mg, 4.42 mmol) at -78 ^oC. The reaction mixture was stirred at -20 ^oC overnight and then quenched by addition of 100 μL of Et_3N. After the mixture had warmed to room temperature, the residue was concentrated *in vacuo* and purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to provide an inseparable 1:2.2 mixture of aldehyde **18** and **19** (838 mg, 85%) as a yellow oil.

To a solution of the above mixture of aldehyde **18** and **19** (821 mg, 3.98 mmol) in THF (13 mL) was added methylmagnesium bromide (14.2 mL, 4.73 mmol, 3.0 M solution in ether) dropwise at 0 ^oC. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (10 mL) was carefully added. The mixture was diluted with water (10 mL) and extracted with ether (3 × 40 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford alcohol **18a** (548 mg) and **19a** (289 mg, 91%).

18a: IR (film) 3469, 2923, 1453, 1378, 1084, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (1H, s), 4.12-4.02 (1H, m), 2.24-2.18 (2H, m), 2.08-1.33 (10H, m), 1.20 (3H, d, J = 6.0 Hz), 1.12 (3H, d, J = 6.0 Hz), 1.06 (3H, s), 0.86 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 118.9, 70.8, 51.5, 42.5, 37.2, 36.2, 34.5, 29.9, 25.3, 25.1, 21.0, 20.3, 16.4.

To a solution of the alcohol **18a** (221 mg, 0.99 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (454 mg, 1.08 mmol) at 0 ^oC. The resulting solution was stirred at rt for 1 h, and

then saturated aqueous $NaHCO_3$ (10 mL) was carefully added. The two-phase mixture which formed was diluted with water (10 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford methyl ketone **20** (204 mg, 93%) as a colorless oil: $[\alpha]_D^{25}$ -91.6 (*c* 1.0, $CHCl_3$, 92% ee); IR (film) 2927, 1702, 1453, 1380, 1355, 1082, 957 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, s), 2.23-2.18 (1H, m), 2.18 (3H, s), 2.08-1.33 (9H, m), 1.20 (3H, s), 1.18-1.08 (1H, m), 0.87 (3H, d, J = 7.0 Hz), 0.82 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 139.5, 117.7, 53.6, 53.0, 36.5, 36.4, 35.0, 31.5, 31.3, 28.5, 26.0, 22.4, 21.2, 16.5; HRMS (EI+) calcd for $C_{15}H_{25}O$ (MH^+) 221.1906 found 221.1904. Enantioselectivity was determined by GC analysis (gamma-TA 125 °C, 22 psi); retention times: 33.94 min (enantiomer), 34.51 min (major).



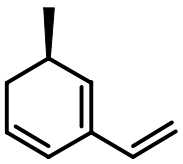
20

For the preparation of 20 in a large scale: 1-(1,2,8-Trimethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-yl)-ethanone (20). To a CH_2Cl_2 (5 mL) solution of 0.2 equiv of the freshly prepared catalyst **5** were successively added a solution of diene **17** (3.21 g, 26.27 mmol) in CH_2Cl_2 (10 mL) and tiglic aldehyde (2.11 mL, 21.86 mmol) at -78 °C. The reaction mixture was stirred at -20 °C for 2 days and then quenched by addition of 1 mL of Et_3N. After the mixture had warmed to room temperature, the residue was concentrated *in vacuo* and purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to provide an inseparable 1:2.3 mixture of aldehyde **18** and **19** (3.74 g, 83%) as a yellow oil.

To a solution of the above mixture of aldehyde **18** and **19** (3.72 g, 18.04 mmol) in THF (40 mL) was added methylmagnesium bromide (7.8 mL, 23.41 mmol, 3.0 M solution in ether) dropwise at 0 ^{o}C. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (40 mL) was carefully added. The mixture was diluted with water (20 mL) and extracted with ether (3 × 100 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford alcohol **18a** (1.09 g, 87%).

To a solution of the alcohol **18a** (1.08 g, 4.87 mmol) in CH_2Cl_2 (30 mL) was added Dess-Martin periodinane (2.21 g, 5.31 mmol) at 0 ^{o}C. The resulting solution was stirred at rt for 1 h, and then saturated aqueous $NaHCO_3$ (40 mL) was carefully added. The two-phase mixture which formed was diluted with water (30 mL) and extracted with ether (3 × 100 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford methyl ketone **20** (0.92 g, 85%) as a colorless oil: $[\alpha]_D^{25}$ -91.6 (*c* 1.0, $CHCl_3$, 92% ee); IR (film) 2927, 1702, 1453, 1380, 1355, 1082, 957 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, s), 2.23-2.18 (1H, m), 2.18 (3H, s), 2.08-1.33 (9H, m), 1.20 (3H, s), 1.18-1.08 (1H, m), 0.87 (3H, d, *J* = 7.0 Hz), 0.82 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 139.5, 117.7, 53.6, 53.0, 36.5, 36.4, 35.0, 31.5, 31.3, 28.5, 26.0, 22.4, 21.2, 16.5; HRMS (EI+) calcd for $C_{15}H_{25}O$ (MH^+) 221.1906 found 221.1904. Enantioselectivity was determined by GC analysis (gamma-TA 125 ^{o}C, 22 psi); retention times: 33.94 min (enantiomer), 34.51 min (major).

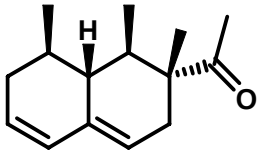
Part IV. Synthesis of 25.



22

6-Methyl-2-vinyl-cyclohexa-1,3-diene (22). To a solution of LDA (8.95 mmol) in THF (15 mL) cyclohexenone **21** (1.01 g, 13.1 mmol) in THF (20 mL) was added dropwise, and the reaction mixture was stirred for 40 min at -78 ^{o}C. A solution of Tf_2NPh (3.14 g, 8.95 mmol) dissolved in THF (15 mL) was then added. After complete addition, the reaction mixture was warmed to 0 ^{o}C. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (5 mL) was carefully added. The mixture was diluted with water (10 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:20) to afford enol triflate (1.68 g, 76%) as a yellow oil.

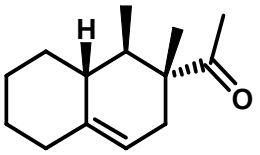
To a slurry of $Pd(PPh_3)_4$ (132 mg, 115 μmol), LiCl (448 mg, 10.61 mmol) in THF (15 mL) were added a solution of the above enol triflate (546 mg, 2.26 mmol) and tributyl(vinyl)tin (734 mg, 2.33 mmol). The Pyrex bottle was sealed with a screw cap and heated at reflux for 8 h. After cooling the mixture to rt, the reaction mixture was diluted with water (10 mL) and was extracted with hexanes (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:50) to afford triene **22** (219 mg, 81%) as a colorless oil: IR (film) 2957, 2924, 1615, 987, 891, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34-6.24 (2H, m), 5.95-5.91 (1H, m), 5.62 (1H, d, J = 4.0 Hz), 5.26 (1H, d, J = 17.6 Hz), 4.98 (1H, d, J = 10.8 Hz), 2.59-2.43 (1H, m), 2.32-2.25 (1H, m), 1.98-1.88 (1H, m), 1.07 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.3, 131.4, 127.0, 120.8, 111.2, 31.3, 28.8, 20.2.



25

1-(1,2,8-Trimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-2-yl)-ethanone (25). The methyl ketone **25** was prepared in an analogue manner of methyl ketone **20**. Purification by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 20:1) to afford methyl ketone **25** (47 mg) as a colorless oil: $[\alpha]_D^{25}$ -89.1 (*c* 1.0, $CHCl_3$), IR (film) 2964, 2894, 1698, 1459, 1338, 1358, 1096, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (1H, dd, *J* = 2.5 Hz, *J* = 9.5 Hz), 5.59-5.54 (2H, m), 2.98 (1H, s), 2.36-2.34 (1H, m), 2.16 (3H, s), 2.11-1.85 (5H, m), 1.03 (3H, s), 0.91 (3H, d, *J* = 7.0 Hz), 0.74 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 133.8, 130.1, 124.5, 124.3, 55.1, 47.7, 37.8, 37.1, 31.7, 29.2, 26.0, 16.8, 16.0, 10.2; HRMS (ES+) calcd for $C_{15}H_{23}O$ (MH^+) 219.1750 found 219.1747. Enantioselectivity was determined by GC analysis (gamma-TA 125 °C, 22 psi); retention times: 31.42 min (enantiomer), 32.79 min (major).

Part V. Synthesis of 29.



29

1-(1,2-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-yl)-ethanone (29). To a CH_2Cl_2 (3 mL) solution of 0.2 equiv of the freshly prepared catalyst **5** were successively added a solution of diene **26** (79.1 mg, 0.73 mmol) and tiglic aldehyde (74 μL, 0.73 mmol) at -78 °C. The reaction

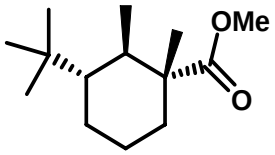
mixture was stirred at 0 °C for 1 day and then quenched by addition of 0.2 mL of Et_3N. After the mixture had warmed to room temperature, the residue was concentrated *in vacuo* and purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to provide an inseparable 2:3.3 mixture of aldehyde **27** and **28** (120.7 mg, 86%) as a yellow oil.

To a solution of the above mixture of aldehyde **27** and **28** (120.7 mg, 0.63 mmol) in THF (4 mL) was added methylmagnesium bromide (0.42 mL, 1.26 mmol, 3.0 M solution in ether) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (5 mL) was carefully added. The mixture was diluted with water (3 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford alcohol **27a** (40.1 mg, 88%).

To a solution of the alcohol **27a** (40.1 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (97.5 mg, 0.23 mmol) at 0 °C. The resulting solution was stirred at rt for 1 h, and then saturated aqueous $NaHCO_3$ (5 mL) was carefully added. The two-phase mixture which formed was diluted with water (5 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 20:1) to afford methyl ketone **29** (36.1 mg, 91%) as a colorless oil: $[\alpha]_D^{25}$ -145.3 (*c* 0.6, $CHCl_3$, 90% ee); IR (film) 2927, 2856, 1708, 1453, 1380, 1353, 1082, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, br s), 2.26-2.15 (2H, m), 2.10 (3H, s), 2.04-1.60 (6H, m), 1.12 (3H, s), 1.38-1.16 (4H, m), 0.82 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 139.7, 117.0, 53.3, 48.7, 37.5, 32.1, 31.7, 30.0, 27.8, 27.8, 27.5, 17.2, 16.8; HRMS (ES+) calcd for $C_{14}H_{23}O$ (MH^+) 207.1749 found

207.1749. Enantioselectivity was determined by GC analysis (gamma-TA 115 ^{o}C, 22 psi); retention times: 35.54 min (major), 36.42 min (enantiomer).

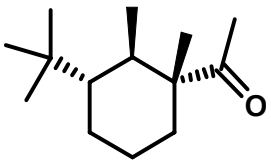
Part VI. Synthesis of 32.



30

3-tert-Butyl-1,2-dimethyl-cyclohexanecarboxylic Acid Methyl Ester (30) *t*-BuLi (1.98 mL, 3.36 mmol, 1.7 M solution in pentane) was added dropwise to a solution of CuCN (302 mg, 3.36 mmol) in THF (7 mL) at -78 ^{o}C. After 1 h, the reaction mixture was then treated with TMSCl (0.5 mL) and enone **10** (122 mg, 0.67 mmol) consecutively. After stirring for further 2 h at -78 ^{o}C, the reaction mixture was diluted with saturated aqueous NH_4Cl (5 mL). The two-phase mixture formed was diluted with water (5 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with 2 N HCl (2 x 5 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, gradient 1:20 to 1:10) to provide the desired ketone (143 mg, 89%) as a colorless oil: IR (film) 2958, 2861, 1731, 1466, 1258, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s), 2.71-2.64 (1H, m), 2.42-2.01 (4H, m), 1.38-1.28 (1H, m), 1.12 (3H, s), 0.99 (3H, d, *J* = 7.2 Hz), 0.89 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 178.2, 52.5, 49.5, 47.7, 45.3, 40.1, 35.2, 34.1, 30.5, 28.1, 22.3, 19.1; HRMS (ES+) calcd for $C_{14}H_{25}O_3$ (MH^+) 241.2, found 241.2.

To a solution of the above enone (41.5 mg, 0.17 mmol), tosyl hydrazide (43.1 mg, 0.22 mmol), and *p*-TsOH (5 mg) in 4 mL of DMF and sulfolane (1:1) was added sodium cyanoborohydride (59.1 mg, 0.93 mmol). The resulting solution was stirred at 100 ^{o}C for 2 h, and then saturated aqueous $NaHCO_3$ (5 mL) was carefully added. The two-phase mixture which formed was diluted with water (2 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford ester **30** (26.2 mg, 68%) as a colorless oil: IR (film) 2953, 1729, 1457, 1186, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, d, *J* = 7.5 Hz), 3.68 (3H, s), 2.25-2.18 (3H, m), 1.85-1.81 (2H, m), 1.56-1.38 (5H, m), 1.03 (3H, s), 1.02 (3H, s), 0.94 (3H, d, *J* = 6.5 Hz), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 54.4, 52.3, 46.1, 37.6, 36.1, 29.4, 28.3, 24.3, 21.8, 19.5, 15.6; LRMS (ES+) calcd for $C_{14}H_{27}O_2$ (MH^+) 227.2, found 227.2.



32

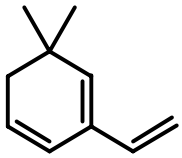
1-(3-tert-Butyl-1,2-dimethyl-cyclohexyl)-ethanone (32). To a solution of ester **30** (22.4 mg, 0.0985 mmol) in CH_2Cl_2 (3 mL) at -78 ^{o}C was added DIBALH (121 μL, 0.121 mmol, 1.0 M solution in CH_2Cl_2). After the mixture was stirred for 1 h at the same temperature, saturated aqueous NH_4Cl (0.15 mL) was carefully added. The reaction mixture was stirred for 1 h at rt and was filtered through a short plug of Celite eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give the colorless crude alcohol. To a solution of this alcohol in CH_2Cl_2 (5 mL) was added PCC (34.2 mg, 0.162 mmol) at 0 ^{o}C. The resulting solution was stirred at rt for 1 h, and

was filtered through a short plug of Celite eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give the colorless crude aldehyde (15.6 mg, 81% for 2 steps) suitable for use in the next step without purification.

To a solution of the above aldehyde **31** (15.6 mg, 0.079 mmol) in THF (3 mL) was added methylmagnesium bromide (34 μL, 0.104 mmol, 3.0 M solution in ether) dropwise at 0 ^oC. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (1 mL) was carefully added. The mixture was diluted with water (2 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the colorless crude alcohol suitable for use in the next step without purification.

To a solution of the above alcohol in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (39 mg, 0.091 mmol) at 0 ^oC. The resulting solution was stirred at rt for 1 h, and then saturated aqueous $NaHCO_3$ (5 mL) was carefully added. The two-phase mixture which formed was diluted with water (2 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford methylketone **32** (14.5 mg, 87% for 2 steps) as a colorless oil: IR (film) 2927, 2867, 1702, 1461, 1366, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.14 (3H, s), 1.99-1.82 (2H, m), 1.64-1.10 (5H, m), 1.06 (3H, s), 0.94 (9H, s), 0.93-0.86 (1H, m), 0.82 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 54.5, 47.1, 38.6, 36.3, 29.8, 28.7, 25.3, 21.9, 19.4, 15.2; LRMS (ES+) calcd for $C_{14}H_{27}O$ (MH^+) 211.2, found 211.2.

Part VII. Synthesis of 40.



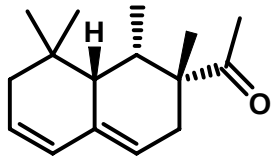
37

6,6-Dimethyl-2-vinyl-cyclohexa-1,3-diene (37). To a solution of LDA (8.95 mmol) in THF (15 mL) cyclohexenone **35**[4] (1.01 g, 13.1 mmol) in THF (20 mL) was added dropwise, and the reaction mixture was stirred for 40 min at -78 ^{o}C. A solution of Tf_2NPh (3.14 g, 8.95 mmol) dissolved in THF (15 mL) was then added. After complete addition, the reaction mixture was warmed to 0 ^{o}C. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (5 mL) was carefully added. The mixture was diluted with water (10 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:20) to afford enol triflate **36** (1.69 g, 82%) as a yellow oil.

To a slurry of $Pd(PPh_3)_4$ (143 mg, 125 μmol), LiCl (498 mg, 11.79 mmol) in THF (15 mL) were added a solution of the above enol triflate **36** (642 mg, 2.51 mmol) and tributyl(vinyl)tin (798 mg, 2.53 mmol). The Pyrex bottle was sealed with a screw cap and heated at reflux for 8 h. After cooling the mixture to rt, the reaction mixture was diluted with water (10 mL) and was extracted with hexanes (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:50) to afford triene **37** (272 mg, 81%) as a colorless oil: IR (film) 2956, 2923,

[4] Yates, P.; Burnell, D. J.; Freer, V. J.; Sawyer, J. F. *Can. J. Chem.* **1987**, *65*, 69.

1466, 1358, 1000, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.31-6.22 (2H, m), 5.89-5.84 (1H, m), 5.47 (1H, br s), 5.26 (1H, d, *J* = 17.6 Hz), 4.99 (1H, d, *J* = 10.8 Hz), 2.11 (1H, dd, *J* = 1.6 Hz, *J* = 2.8 Hz), 1.02 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.3, 131.4, 127.0, 120.8, 111.2, 38.2, 31.6, 28.1.

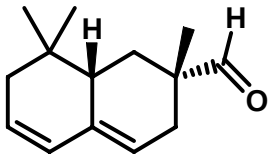


40

1-(1,2,8,8-Tetramethyl-1,2,3,7,8,8a-hexahydro-naphthalen-2-yl)-ethanone (40). To a solution of the 1: 2 mixture of aldehyde **38** and **39** (574 mg, 2.63 mmol) in THF (15 mL) was added methylmagnesium bromide (0.44 mL, 1.32 mmol, 3.0 M solution in ether) dropwise at 0 ^oC. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (10 mL) was carefully added. The mixture was diluted with water (10 mL) and extracted with ether (3 × 40 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford alcohol **38a** (188 mg, 92%) along with unreacted aldehyde **39** (372 mg). aldehyde **39**: $[\alpha]_D^{25}$ +62.8 (*c* 0.9, $CHCl_3$); IR (film) 2964, 2933, 2877, 1725, 1455, 1368, 905, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (1 H, s), 6.04 (1H, dd, *J* = 2.8 Hz, *J* = 9.6 Hz), 5.63-5.56 (2H, m), 2.74 (1H, br s), 2.19 (1H, d, *J* = 17.2 Hz), 2.08-1.87 (3H, m), 1.68 (1H, dd, *J* = 6.3 Hz, *J* = 17.6 Hz), 1.02 (3H, s), 0.91 (3H, s), 0.90 (H, s), 0.72 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 134.9, 130.8, 125.3, 125.1, 52.5, 50.6, 46.7, 35.4, 34.0, 30.6, 30.2, 23.0, 15.6, 9.2; LRMS (EI+) calcd for $C_{15}H_{22}O$ (MH^+) 219.2, found 219.2.

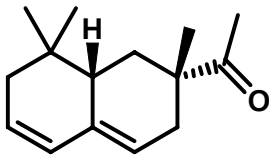
To a solution of the above alcohol **38a** (188 mg, 0.81 mmol) in CH_2Cl_2 (8 mL) was added Dess-Martin periodinane (378 mg, 0.89 mmol) at 0 ^oC. The resulting solution was stirred at rt for 1 h, and then saturated aqueous $NaHCO_3$ (10 mL) was carefully added. The two-phase mixture which formed was diluted with water (10 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford methylketone **40** (168 mg, 89%): $[\alpha]_D^{25}$ -68.9 (*c* 1.0, $CHCl_3$, 94% ee); IR (film) 2964, 2904, 1702, 1366, 1355, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (1H, dd, *J* = 2.8 Hz, *J* = 9.2 Hz), 5.57 (1H, t, *J* = 8.0 Hz), 5.49 (1H, br s), 2.55 (1H, d, *J* = 19.6 Hz), 2.34 (1H, br s), 2.13 (3H, s), 2.16-1.73 (4H, m), 1.09 (3H, s), 1.04 (3H, s), 0.92 (3H, s), 0.73 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 133.7, 130.2, 125.4, 122.8, 52.4, 46.4, 45.1, 34.7, 33.6, 28.8, 28.1, 24.7, 23.3, 22.8, 14.4; HRMS (ES+) calcd for $C_{16}H_{25}O$ (MH^+) 233.1905 found 233.1901. Enantioselectivity was determined by GC analysis (gamma-TA 130 ^oC, 22 psi); retention times: 107.97 min (major), 109.74 min (enantiomer). The absolute configuration of **40** determined by single crystal X-ray diffraction analysis of the *p*-toluenesulfonylhydrazone derivative.

Part VIII. Synthesis of 43.



42

2,8,8-Trimethyl-1,2,3,7,8,8a-hexahydro-naphthalene-2-carbaldehyde (42). To a CH_2Cl_2 solution of 0.2 equiv of the freshly prepared catalyst **5** were successively added a solution of triene **37** (272 mg, 2.03 mmol) in CH_2Cl_2 (3mL) and methacrolein (117 mg, 2.03 mmol) at -78 ^oC. The reaction mixture was stirred at -78 ^oC for 2 h and then quenched by addition of 80 μL of Et_3N. After the mixture had warmed to room temperature, the residue was concentrated *in vacuo* and purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 20:1) to give the desired aldehyde **42** (377 mg, 91%): $[\alpha]_D^{25}$ -142.2 (*c* 0.35, $CHCl_3$); IR (film) 2962, 2931, 2869, 1727, 1459, 1366, 910, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (1H, s), 6.00 (1H, dd, *J* = 2.5 Hz, *J* = 9.5 Hz), 5.60 (1H, t, *J* = 7.5 Hz), 5.52 (1H, br s), 2.40 (1H, d, *J* = 18.0 Hz), 2.16-1.54 (5H, m), 1.36 (1H, t, *J* = 12 Hz), 1.10 (3H, s), 0.98 (3H, s), 0.75 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 135.5, 129.1, 126.0, 121.7, 45.1, 42.7, 40.4, 32.9, 31.1, 28.6, 28.2, 20.2, 18.3; LRMS (ES+) calcd for $C_{14}H_{21}O$ (MH^+) 205.2, found 205.2.



43

1-(2,8,8-Trimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-2-yl)-ethanone (43). To a solution of the aldehyde **42** (238 mg, 1.17 mmol) in THF (10 mL) was added methylmagnesium bromide (0.58 mL, 1.75 mmol, 3.0 M solution in ether) dropwise at 0 ^oC. The reaction mixture was stirred at the same temperature for 1 h and then saturated aqueous NH_4Cl (5 mL) was carefully added. The mixture was diluted with water (10 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

The residue was purified by flash column chromatography (hexanes:EtOAc, 15:1) to afford alcohol (213 mg, 83%) as a colorless oil.

To a solution of the above alcohol (188 mg, 0.81 mmol) in CH_2Cl_2 (8 mL) was added Dess-Martin periodinane (378 mg, 0.89 mmol) at 0 ^oC. The resulting solution was stirred at rt for 1 h, and then saturated aqueous $NaHCO_3$ (10 mL) was carefully added. The two-phase mixture which formed was diluted with water (10 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc, gradient 30:1 to 15:1) to afford methylketone **43** (168 mg, 89%) as a colorless oil: $[\alpha]_D^{25}$ -130.9 (*c* 1.0, $CHCl_3$, 93% ee); IR (film) 2960, 2871, 1702, 1364, 1102, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (1H, dd, *J* = 3.0 Hz, *J* = 10.0 Hz), 5.59 (1H, t, *J* = 7.5 Hz), 5.50 (1H, br s), 2.43 (1H, d, *J* = 18.0 Hz), 2.17 (3H, s), 2.16-1.71 (5H, m), 1.37 (1H, t, *J* = 12 Hz), 1.14 (3H, s), 0.98 (3H, s), 0.74 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 135.2, 129.1, 125.9, 122.7, 46.8, 42.8, 41.3, 33.6, 32.9, 30.2, 28.6, 25.0, 20.8, 20.2; LRMS (ES+) calcd for $C_{15}H_{23}O$ (MH^+) 219.2, found 219.2. Enantioselectivity was determined by GC analysis (gamma-TA 120 ^oC, 22 psi); retention times: 32.92 min (enantiomer), 33.48 min (major).

Part IX. X-ray Structure.

X-ray Structure of *p*-toluenesulfonylhydrazone derivative of Compound 40