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Total synthesis of (±)-β-chamigrene and (±)-laurencenone C via Ireland ester Claisen rearrangement and an intramolecular type II carbonyl ene reaction sequence

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ABSTRACT

A combination of Ireland ester Claisen rearrangement and intramolecular type II carbonyl ene reactions were exploited for the total synthesis of chamigrenes containing a quaternary carbon atom next to the spirocentre in spiro[5.5]undecane.

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1. Introduction

Chamigrenes, containing a spiro[5.5]undecane carbon framework incorporating two vicinal quaternary carbon atoms, are interesting sesquiterpene natural products isolated from plant, liverwort as well as marine sources. Chamigrenes appear to be the more generalized metabolites in algae from the genus *Laurencia*, and most of these are characterized by the predominant incorporation of chlorine and bromine atoms.[1] Isolation of β-chamigrene **1** was first reported by Ito and co-workers[2] in 1967 from the leaf oil of *Chamaecyparis taiwanensis*, whereas the isolation of α-chamigrene **2** was reported by Ohta and Hirose[3] from the oil of the fruits of *Schisandra chinensis* almost at the same time. Subsequently, a variety of chlorine and bromine containing chamigrenes were isolated from marine sources. Over 120 chamigrenes were isolated from *Laurencia* species and sea hares grazing on them. Thomson and co-workers reported[4] the isolation of laurencenones A–D **3**–**6** from *Laurencia obtusa* containing an enone functionality in the A-ring of chamigrenes. Several of the halogenated chamigrenes were shown to exhibit cytostatic activity and remarkable antimicrobial activity on both Gram positive and Gram negative bacteria.[5] Recently, Cueto and co-workers reported the isolation of several halogenated chamigrenes from *Aplysia dactylomela* from Canary islands, some of which were shown to exhibit cytotoxic activity against HeLa and Hep-2 cancer cell lines.[6]

Synthesis of chamigrenes is challenging owing to the presence of a quaternary carbon adjacent to the spirocentre.[5,7,8] Herein, we report a methodology for the synthesis of (±)-β-chamigrene **1** and (±)-laurencenone C **5** employing a combination of Ireland ester Claisen rearrangement and intramolecular type II carbonyl ene reactions for the construction of a spiro[5.5]undecane containing a quaternary carbon atom adjacent to the spirocentre.

2. Results and discussion

The retrosynthetic sequence is depicted in Scheme 1. It was conceived that intramolecular type II carbonyl ene reaction[9] of the aldehyde **7** would generate the spiro alcohol **8**, which could be converted to laurencenone C **5** or β-chamigrene **1** by oxidation or reductive deoxygenation, respectively. The aldehyde **7** could be generated from the ester **9**. Ireland ester Claisen rearrangement[10] of the allyl ester **10** was contemplated for the generation of the ester **9** containing two vicinal quaternary carbon atoms.

The synthetic sequence starting from cyclohexane-1,4-dione **11** is depicted in Scheme 2. Controlled Horner–Wadsworth–Emmons reaction of the dione **11** with sodium hydride and triethyl phosphonopropionate generated the keto ester **12** in 82% yield. Prior to the reduction of the α,β-unsaturated ester in the keto ester **12** into an allyl alcohol, the keto group was protected as ethylene ketal by refluxing with 1,2-ethanediol and a catalytic amount of *p*-toluenesulfonic acid (PTSA) in benzene using a Dean–Stark water trap to furnish the ketal ester **13** in 96% yield. Regioselective reduction with lithium aluminum hydride (LAH) in ether at low temperature transformed the ester **13** into the allyl alcohol **14** in 97% yield.[11] Coupling of the allyl alcohol **14** with isobutyric acid in methylene chloride in the presence of dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*-dimethylaminopyridine (DMAP) produced the ester **15**. Ireland-Claisen rearrangement of the ester **15** was then explored via the corresponding trimethylsilyl (TMS) enol ether **16** for the generation of the requisite two vicinal quaternary carbon atoms. Thus, generation of the TMS enol ether **16** of the ester **15** with LDA, trimethylsilyl chloride, and triethylamine in THF at −70 °C followed

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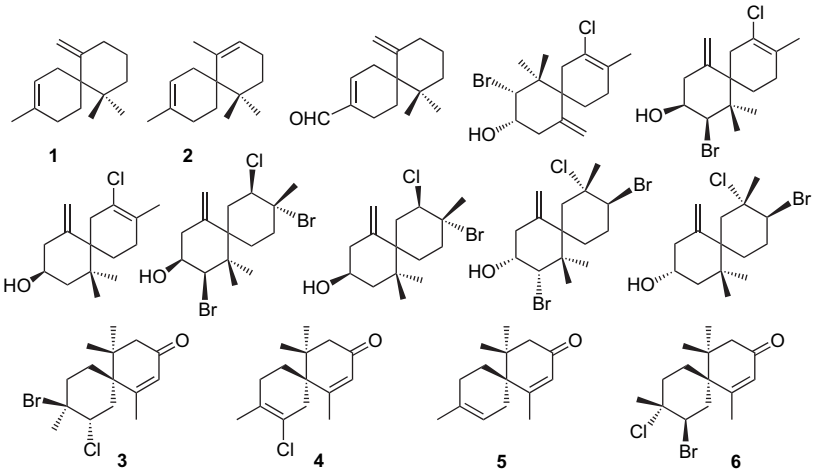
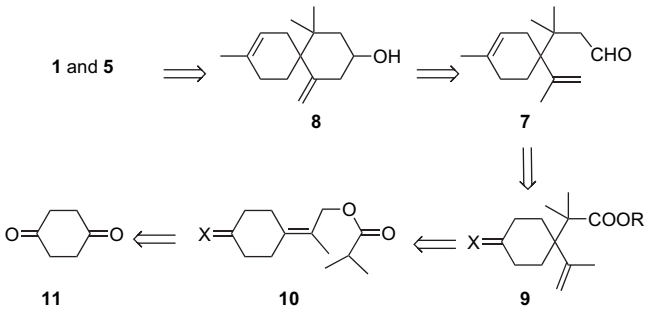


by refluxing the reaction mixture for 4 h resulted in the Ireland ester Claisen rearrangement. Hydrolysis of the reaction mixture with dilute hydrochloric acid, which also led to the deprotection of the ketal moiety, followed by esterification with ethereal diazomethane furnished the keto ester **17**. Next, construction of the second ring via an intramolecular ene reaction was investigated. In order to avoid regiochemical problems, cyclohexanone in **17** was converted into a methylcyclohexene moiety by employing a Wittig reaction followed by olefin isomerization. Thus, reaction of the keto ester **17** with methylenetriphenylphosphorane in benzene furnished the methylene compound **18**, which on isomerization with PTSA in methylene chloride furnished the cyclohexene **19**. For the conversion of the ester **19** into the homologated aldehyde **7**, a Wittig reaction based methodology was contemplated. First, the ester **19** was converted in to the aldehyde **20** employing a two-step protocol, via reduction with lithium aluminum hydride (LAH) in ether, followed by oxidation of the resultant primary alcohol **21** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride. Wittig reaction of the aldehyde **20** with methoxymethylenetriphenylphosphorane furnished the enol ether **22**. Attempted hydrolysis of the enol ether **22** under a variety of acid conditions directly generated the spiro[5.5]undecanes **8** and **23** in varying proportions[12] instead of the aldehyde **7**. It is interesting to note that the enol ether **22** underwent competitive cyclization leading to the methoxy spiro compound **23**, even before the hydrolysis to the aldehyde **7**. It was found that the best results were obtained on treatment of the enol ether **22** with 10 mol % of trifluoroacetic acid in 2:1 acetic acid and water at 70 °C leading to the formation of a 11:6 mixture of hydroxy-β-chamigrene **8** and methoxy-β-chamigrene **23** in 87% yield, which were separated by column chromatography on silica gel, and their structures were established from their spectral data. Formation of the spiro compounds **8** and **23** could be explained as depicted in Scheme 3. Acid catalyzed hydrolysis of the enol ether **22** to the aldehyde **7** followed by an intramolecular type II carbonyl ene reaction generates the alcohol **8**. Whereas, initial protonation of the enol ether **22** generates the oxonium ion **24**, which on cyclization generates the methoxy compound **23**.



Scheme 1.

Barton's free radical mediated deoxygenation[13] was employed for the conversion of the alcohol **8** into β-chamigrene **1**. Thus, treatment of the alcohol **8** with sodium hydride, carbon disulfide, and methyl iodide in the presence of imidazole furnished the dithiocarbonate **25**. Reaction of the dithiocarbonate **25** with tributyltin hydride and a catalytic amount of azobisisobutyronitrile (AIBN) in refluxing benzene furnished β-chamigrene **1** in 76% yield. On the other hand oxidation of the spiro alcohol **8** with PCC and silica gel in methylene chloride for 1 h furnished the β,γ-unsaturated enone **26**. Isomerization of the *exo*-methylene group in **26** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride at rt for 2.5 h furnished laurencenone C **5**. Both β-chamigrene **1** and laurencenone C **5** exhibited spectral data identical to those of the authentic compounds reported[5,7] in the literature. Conversion of either β-chamigrene **1** or laurencenone C **5** into α-chamigrene **2** has already been reported in the literature.

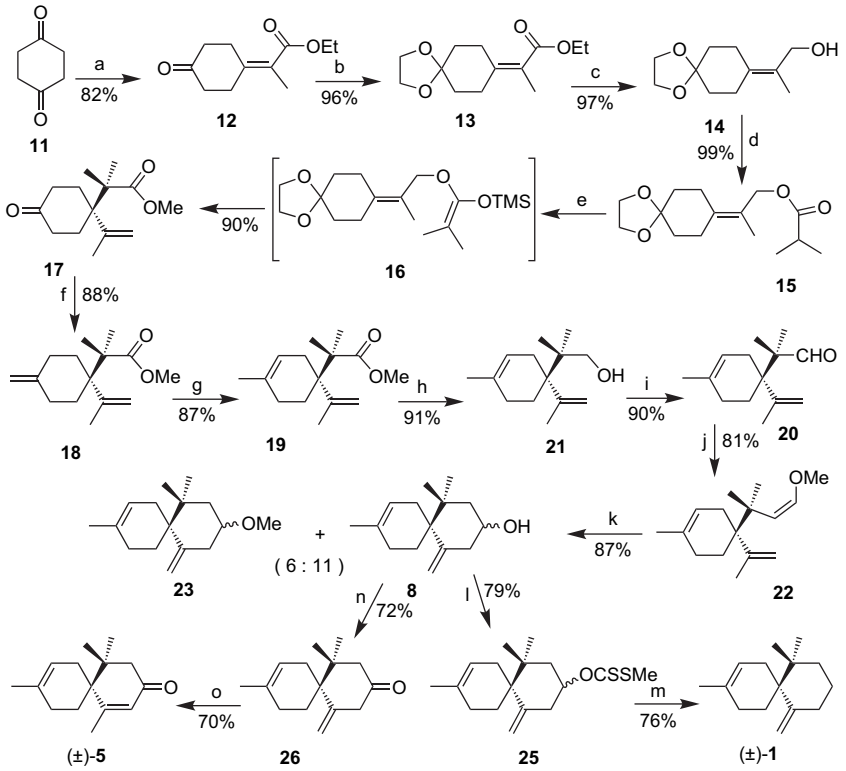
3. Conclusions

In summary, we have accomplished total syntheses of (±)-laurencenone C **5** and (±)-β-chamigrene **1**. A combination of Ireland ester Claisen rearrangement and an intramolecular type II carbonyl ene reactions were employed for the efficient construction of the requisite two vicinal quaternary carbon atoms.

4. Experimental section

4.1. General

Melting points are recorded using Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Jasco FTIR 410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JNM λ-300 spectrometer. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Elemental analyses were carried out using Carlo Erba 1106 CHN analyzer at the Department of Organic Chemistry, Indian Institute of Science, Bangalore. Thin-layer chromatographies



Scheme 2. Reagents: (a) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF; (b) $(CH_2OH)_2$, PTSA, C_6H_6; (c) $LiAlH_4$, Et_2O; (d) DCC, DMAP (catalytic), $Me_2CHCOOH$, CH_2Cl_2; (e) (i) LDA, THF, TMSCl, NEt_3; (ii) dil HCl; (iii) CH_2N_2, Et_2O; (f) $Ph_3P{=}CH_2$, C_6H_6; (g) PTSA, CH_2Cl_2; (h) $LiAlH_4$, Et_2O; (i) PCC, silica gel, CH_2Cl_2; (j) $Ph_3P{=}CHOMe$, THF; (k) TFA, AcOH, H_2O; (l) NaH, CS_2, MeI, THF, imidazole; (m) $^nBu_3SnH$, AIBN, C_6H_6; (n) PCC, silica gel, CH_2Cl_2; (o) DBU, CH_2Cl_2.

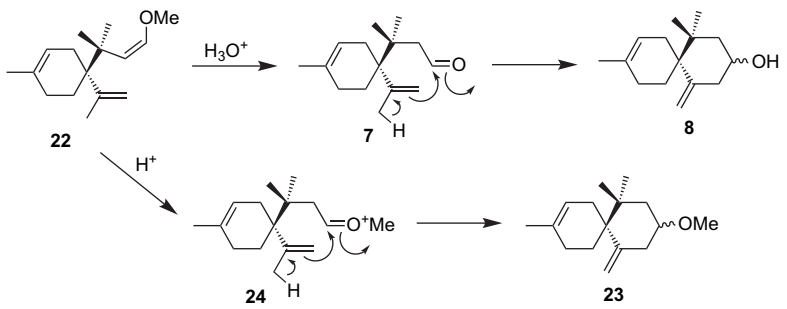
(TLC) were performed on glass plates (7.5×2.5 cm and 7.5×5.0 cm) coated with Acme's silica gel G containing 13% calcium sulfate as binder and various combinations of ethyl acetate, methylene chloride, and hexane were used as eluent. Visualization of spots was accomplished by exposure to iodine vapor or anisaldehyde–H_2SO_4 or MeOH–H_2SO_4 spray followed by heating. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product).

4.1.1. *Ethyl 2-(4-oxocyclohex-1-ylidene)propionate* ***12***

A suspension of sodium hydride (392 mg, 60% dispersion in oil, 9.81 mmol) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free NaH was then suspended in dry THF (8 mL) and cooled in an ice bath. Triethyl phosphonopropionate (2.3 mL, 10.7 mmol) was added dropwise and the reaction mixture was stirred for 30 min at rt. The above reagent was transferred to a pressure equalizer funnel and added dropwise to a solution of cyclohexane-1,4-dione **11** (1.0 g, 8.92 mmol) in dry THF (2 mL) at ice temperature over a period of 15 min and stirred for 3 h at ice temperature. The reaction was then quenched by careful addition of saturated aq NH_4Cl (2 mL) solution and extracted with ether (3×5 mL). The combined ether extract was washed with brine (2 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:6) as eluent furnished the keto ester **12** (1.43 g, 82%) as oil. R_f (1:6 EtOAc–hexane) 0.4; IR (liquid film): ν_{max}/cm^{-1} 2980, 2906, 1716, 1628, 1446, 1304, 1284, 1246, 1204, 1105, 1022, 774; ^1H NMR (300 MHz, $CDCl_3$): δ 4.18 (2H, q, *J* 6.9 Hz, OCH_2CH_3), 2.95 (2H, t, *J* 6.3 Hz), 2.64 (2H, t, *J* 6.3 Hz), 2.60–2.30 (4H, m), 1.90 (3H, s, olefinic-CH_3), 1.32 (3H, t, *J* 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.7 (C, C=O), 168.3 (C, OC=O), 144.0 (C, C-1′), 123.2 (C, C-2), 60.0 (CH_2, OCH_2), 38.9 (CH_2), 38.5 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 15.3 (CH_3, C-3), 14.3 (CH_3, OCH_2CH_3); HRMS: *m*/*z* calcd for $C_{11}H_{16}O_3Na$ (M+Na): 219.0997, found: 219.0998.

4.1.2. *Ethyl 2-(4,4-ethylenedioxycyclohexylidene)propionate* ***13***

A magnetically stirred solution of the keto ester **12** (1.0 g, 5.1 mmol), ethylene glycol (0.85 mL, 15.3 mmol), and PTSA (70 mg,



Scheme 3.

10 mol %) in 10 mL of dry benzene was refluxed using a Dean–Stark water separator for 4 h. Benzene was distilled off, saturated aq $NaHCO_3$ (5 mL) solution was added to the residue and extracted with ether (3×5 mL). The ether layer was washed with water (5 mL) and brine (4 mL), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the ketal ester **13** (1.18 g, 96%) as oil. R_f (1:9 EtOAc–hexane) 0.4; IR (liquid film): ν_{max}/cm^{-1} 2952, 2883, 1714, 1636, 1446, 1366, 1312, 1283, 1206, 1126, 1095, 1034, 945, 913, 886, 775, 752, 693; ^1H NMR (300 MHz, $CDCl_3$): δ 4.17 (2H, q, J 7.2 Hz, OCH_2CH_3), 3.94 (4H, s, 2×OCH_2), 2.59 (2H, t, J 6.3 Hz), 2.37 (2H, t, J 6.3 Hz), 1.87 (3H, s, olefinic-CH_3), 1.90–1.65 (4H, m), 1.30 (3H, t, J 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 (C, OC=O), 144.9 (C), 121.1 (C), 108.3 (C), 64.3 (2C, CH_2, OCH_2CH_2O), 60.0 (CH_2, OCH_2CH_3), 35.6 (CH_2), 35.3 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 15.4 (CH_3, C-3), 14.4 (CH_3, OCH_2CH_3); HRMS: m/z calcd for $C_{13}H_{20}O_4Na$ (M+Na): 263.1259, found: 263.1250.

4.1.3. 2-(4,4-Ethylenedioxycyclohexylidene)propanol **14**

To a cold (−50 °C) magnetically stirred solution of the keto ester **13** (600 mg, 2.5 mmol) in dry ether (4 mL) was added LAH (143 mg, 3.75 mmol) and stirred at the same temperature for 2 h. Ethyl acetate (0.5 mL) was added to the reaction to consume the excess LAH. The reaction was then quenched with water (5 mL) and extracted with ether (3×5 mL). The combined ether extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the alcohol **14** (481 mg, 97%) as oil. R_f (1:3 EtOAc–hexane) 0.5; IR (liquid film): ν_{max}/cm^{-1} 3423 (OH), 2946, 2882, 1663, 1444, 1367, 1281, 1237, 1125, 1105, 1064, 1033, 944, 909, 864; ^1H NMR (300 MHz, $CDCl_3$): δ 3.99 (2H, s, CH_2OH), 3.86 (4H, s, OCH_2CH_2O), 2.44 (1H, br s), 2.30–2.15 (4H, m), 1.69 (3H, s, olefinic-CH_3), 1.60–1.50 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0 (C), 125.9 (C), 108.6 (C, C-4′), 64.0 (2C, CH_2, OCH_2CH_2O), 62.7 (CH_2, CH_2OH), 35.8 (CH_2), 35.3 (CH_2), 27.0 (CH_2), 26.3 (CH_2), 16.2 (CH_3). HRMS: m/z calcd for $C_{11}H_{18}O_3Na$ (M+Na): 221.1154, found: 221.1158.

4.1.4. 2′-[4,4-Ethylenedioxycyclohexylidene]propyl 2-methylpropanoate **15**

To a magnetically stirred solution of isobutyric acid (0.2 mL, 2.20 mmol) in dry CH_2Cl_2 (3 mL) were added a solution of the alcohol **14** (250 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (2 mL), DCC (390 mg, 1.89 mmol), and a catalytic amount of DMAP and stirred at rt for 5 h. The reaction mixture was then concentrated under reduced pressure and filtered through a short silica gel column using ethyl acetate. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the ester **15** (335 mg, 99%) as oil. R_f (1:19 EtOAc–hexane) 0.6; IR (liquid film): ν_{max}/cm^{-1} 2973, 2947, 2879, 1732, 1471, 1388, 1367, 1343, 1273, 1251, 1190, 1155, 1107, 1069, 1035, 945, 912; ^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (2H, s, H-1′), 3.94 (4H, s, OCH_2CH_2O), 2.53 (1H, sep, J 6.9 Hz, H-2), 2.45–2.25 (4H, m), 1.73 (3H, s, olefinic-CH_3), 1.70–1.55 (4H, m), 1.16 (6H, d, J 6.9 Hz, $HC(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6 (C, OC=O), 137.0 (C), 121.3 (C), 108.4 (C, C-4″), 64.8 (CH_2, C-1′), 64.1 (2C, CH_2, OCH_2CH_2O), 35.8 (CH_2), 35.4 (CH_2), 33.9 (CH, C-2), 27.2 (CH_2), 26.8 (CH_2), 19.0 (2C, CH_3, $HC(CH_3)_2$), 16.5 (CH_3); HRMS: m/z calcd for $C_{15}H_{24}O_4Na$ (M+Na): 291.1572, found: 291.1572.

4.1.5. Methyl 2-[1-isopropenyl-4-oxocyclohexyl]-2-methylpropanoate **17**

To a cold (−70 °C) magnetically stirred solution of diisopropylamine (1.2 mL, 8.58 mmol) in anhydrous THF (8 mL) was added a solution of ^{n}BuLi (2.4 M in hexane, 3.1 mL, 7.46 mmol) and stirred for 10 min. To LDA thus formed were added dropwise a solution of the ester **15** (1.0 g, 3.73 mmol) in anhydrous THF (1 mL), TMSCl (1.1 mL, 8.58 mmol), and NEt_3 (0.5 mL), and stirred the reaction mixture for 30 min at the same temperature. It was further stirred at rt for 4 h and then refluxed for 4 h. The reaction mixture was then cooled, diluted with ether (2 mL), and 3 N HCl (3 mL) was added and stirred for 45 min. The resulting biphasic mixture was separated and the aqueous layer was extracted with ether (3×3 mL). The ether extract was dried (Na_2SO_4). Evaporation of the solvent furnished the acid, which was taken in dry ether (2 mL), added dropwise to a cold (0 °C) solution of diazomethane (excess, prepared from 2 g of *N*-nitroso-*N*-methylurea and 20 mL of 60% aq KOH solution and 10 mL of ether) and the reaction mixture was stirred at rt for 30 min. Evaporation of the solvent on water bath and purification of the residue over a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the ester **17** (797 mg, 90%) as oil. R_f (1:7 EtOAc–hexane) 0.55; IR (liquid film): ν_{max}/cm^{-1} 3086, 2974, 2954, 1721, 1631, 1457, 1433, 1391, 1340, 1266, 1190, 1142, 1104, 1015, 995, 961, 900, 828, 776, 759; ^1H NMR (300 MHz, $CDCl_3$): δ 5.38 (1H, s) and 4.98 (1H, s) [C=CH_2], 3.65 (3H, s, OCH_3), 2.50–2.15 (6H, m), 2.00–1.75 (2H, m), 1.86 (3H, br s), 1.22 (6H, s, 2×*tert*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.7 (C, C=O), 176.8 (C, OC=O), 142.0 (C, C=CH_2), 118.1 (CH_2, C=CH_2), 51.5 (CH_3, OCH_3), 48.8 (C), 46.7 (C), 38.1 (2C, CH_2, C-3′ and C-5′), 30.2 (2C, CH_2, C-2′ and C-6′), 22.2 (2C, CH_3), 21.4 (CH_3, olefinic-CH_3); HRMS: m/z calcd for $C_{14}H_{22}O_3Na$ (M+Na): 261.1467, found: 261.1454.

4.1.6. Methyl 2-(1-isopropenyl-4-methylenecyclohexyl)-2-methylpropanoate **18**

To a freshly prepared ^{t}AmOK [from potassium (100 mg, 2.52 mmol) and ^{t}AmOH (3 mL) followed by evaporation of ^{t}AmOH under vacuum] in dry benzene (10 mL) was added methyltriphenylphosphonium bromide (1.125 g, 3.15 mmol) and the resulting yellow solution was stirred for 30 min at rt. The solution was allowed to settle for 30 min. The dark yellow solution of methylenetriphenylphosphorane was added to a magnetically stirred solution of the keto ester **17** (300 mg, 1.26 mmol) in dry benzene (1 mL) at rt and stirred for 1 h. Saturated aq NH_4Cl solution (2 mL) was added to the reaction mixture and extracted with ether (3×4 mL). The combined ether extract was washed with brine (3 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using methylene chloride–hexane (1:9) as eluent furnished the ester **18** (262 mg, 88%) as oil. R_f (1:4 CH_2Cl_2–hexane) 0.4; IR (liquid film): ν_{max}/cm^{-1} 3071, 2976, 2949, 2847, 1727, 1651, 1630, 1470, 1449, 1434, 1389, 1377, 1261, 1219, 1191, 1140, 1111, 1095, 993, 886, 826; ^1H NMR (300 MHz, $CDCl_3$): δ 5.20 (1H, s), 4.82 (1H, s), 4.48 (2H, s), 3.57 (3H, s, OCH_3), 2.25–1.98 (6H, m), 1.72 (3H, s, olefinic-CH_3), 1.50–1.30 (2H, m), 1.11 (6H, s, 2×*tert*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1 (C, OC=O), 148.7 (C), 143.3 (C), 117.2 (CH_2), 106.2 (CH_2), 51.3 (CH_3, OCH_3), 49.1 (C), 47.4 (C), 31.7 (2C, CH_2), 31.5 (2C, CH_2), 22.3 (2C, CH_3), 21.9 (CH_3); HRMS: m/z calcd for $C_{15}H_{24}O_2Na$ (M+Na): 259.1674, found: 259.1668.

4.1.7. Methyl 2-(1-isopropenyl-4-methylcyclohex-3-enyl)-2-methylpropanoate **19**

To a magnetically stirred solution of the compound **18** (60 mg, 0.254 mmol) in CH_2Cl_2 (1.5 mL) was added PTSA (25 mg, 50 mol %) and the reaction mixture was stirred for 3.5 h at rt. It was neutralized with saturated aq $NaHCO_3$ solution (2 mL) and extracted with CH_2Cl_2 (3×4 mL). The organic layer was washed with brine (4 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using methylene chloride–hexane (1:9) as eluent furnished the isomerized ester **19** (52 mg, 87%) as oil. R_f (1:4 CH_2Cl_2–hexane) 0.45; IR (liquid film): ν_{max}/cm^{-1} 3084, 3002, 2964, 2909, 2838, 1727, 1629, 1473, 1448,

1434, 1389, 1372, 1258, 1192, 1160, 1085, 1068, 1029, 1010, 988, 900, 840, 805, 775, 744, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29 (1H, d, *J* 5.1 Hz, H-3′), 5.10 (1H, s) and 4.72 (1H, s) [C=CH_2], 3.62 (3H, s, OCH_3), 2.45–1.50 (6H, m), 1.74 (3H, s) and 1.57 (3H, s) [2×olefinic-CH_3], 1.18 (3H, s) and 1.17 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3 (C), 144.5 (C, *C*=CH_2), 133.9 (C), 120.2 (CH, C-3′), 115.9 (CH_2, C=CH_2), 51.3 (CH_3, OCH_3), 49.2 (C), 45.8 (C), 30.0 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 23.2 (CH_3), 22.9 (CH_3), 22.4 (CH_3), 22.0 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{24}O_2Na$ (M+Na): 259.1674, found: 259.1674.

4.1.8. 2-(1-Isopropenyl-4-methylcyclohex-3-enyl)-2-methylpropanol *21*

To a magnetically stirred solution of the ester **19** (60 mg, 0.254 mmol) in dry ether (2 mL) was added LAH (20 mg, 0.51 mmol) in one portion. The reaction mixture was stirred at rt for 45 min. Ethyl acetate (0.2 mL) was added to consume excess LAH and the reaction was then quenched with water (2 mL) and extracted with ether (3×4 mL). The ether extract was washed with brine (2 mL) and dried (Na_2SO_4). Evaporation of solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the primary alcohol **21** (48 mg, 91%) as oil. R_f (1:7 EtOAc–hexane) 0.5; IR (liquid film): ν_{max}/cm^{-1} 3378, 3081, 2962, 2925, 1626, 1476, 1476, 1446, 1372, 1158, 1031, 897, 804; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.28 (1H, d, *J* 5.1 Hz, H-3′), 5.14 (1H, s) and 4.79 (1H, s) [C=CH_2], 3.52 and 3.40 (2H, 2×d, *J* 11.1 Hz, C*H*$_2$OH), 2.45–1.00 (7H, m), 1.83 (3H, s) and 1.56 (3H, s) [2×olefinic-CH_3], 0.93 (3H, s) and 0.90 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.9 (C, *C*=CH_2), 133.7 (C, C-4′), 120.6 (CH, C-3′), 115.6 (CH_2, C=*C*H_2), 69.4 (CH_2, CH_2OH), 45.4 (C), 41.1 (C), 29.6 (CH_2), 28.4 (CH_2), 27.0 (CH_2), 23.7 (CH_3), 23.2 (CH_3), 21.3 (CH_3), 21.2 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{24}ONa$ (M+Na): 231.1725, found: 231.1734.

4.1.9. 2-(1-Isopropenyl-4-methylcyclohex-3-enyl)-2-methylpropanal *20*

To a magnetically stirred solution of the primary alcohol **21** (200 mg, 0.96 mmol) in anhydrous CH_2Cl_2 (1 mL) was added a homogeneous mixture of PCC (415 mg, 1.92 mmol) and silica gel (415 mg), and stirred at rt for 45 min. The reaction mixture was then filtered through a small silica gel column using CH_2Cl_2 as eluent. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the aldehyde **20** (168 mg, 90%) as oil. R_f (1:4 CH_2Cl_2–hexane) 0.5; IR (liquid film): ν_{max}/cm^{-1} 3084, 2964, 2717, 1723, 1629, 1468, 1447, 1373, 899, 804; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (1H, s, H-1), 5.29 (1H, d, *J* 5.1 Hz, H-3′), 5.16 (1H, s) and 4.76 (1H, s) [C=CH_2], 2.40–1.50 (6H, m), 1.77 (3H, s) and 1.58 (3H, s) [2×olefinic-CH_3], 1.07 (3H, s) and 1.04 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6 (C, C=O), 144.3 (C, *C*=CH_2), 134.1 (C, C-4′), 119.7 (CH, C-3′), 116.4 (CH_2, C=*C*H_2), 50.6 (C, C-2), 45.6 (C, C-1′), 29.7 (CH_2), 28.0 (CH_2), 27.2 (CH_2), 23.2 (2C, CH_3), 18.9 (CH_3), 18.7 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{22}ONa$ (M+Na): 229.1568, found: 229.1578.

4.1.10. 3-[(1-Isopropenyl)-4-methylcyclohex-3-enyl]-1-methoxy-3-methylbut-1-ene *22*

To a magnetically stirred solution of methoxymethyltriphenylphosphonium chloride (454 mg, 1.33 mmol) in THF (2 mL) was added ^{n}BuLi (2.4 M, 0.4 mL, 1.07 mmol) at 0 °C, and the resulting wine red colored solution was stirred for 25 min at rt. The Wittig reagent thus formed was added to a magnetically stirred solution of the aldehyde **20** (110 mg, 0.53 mmol) in dry THF (1 mL) and stirred at rt for 30 min. Saturated aq NH_4Cl solution (2 mL) was added to the reaction mixture and extracted with ether (2×5 mL). The combined organic layer was washed with brine (4 mL) and dried on Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using hexanes as eluent furnished the enol ether **22** (100 mg, 81%) as oil. R_f (hexane) 0.65; IR (liquid film): ν_{max}/cm^{-1} 3082, 2961, 2927, 2865, 1657, 1626, 1453, 1435, 1396, 1378, 1299, 1102, 895, 744, 696; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.69 (1H, d, *J* 7.2 Hz, H-1), 5.30 (1H, d, *J* 5.1 Hz, H-3′), 5.08 (1H, s) and 4.68 (1H, s) [C=CH_2], 4.10 (1H, d, *J* 7.2 Hz, H-2), 3.49 (3H, s, OCH_3), 2.40–1.00 (6H, m), 1.78 (3H, s) and 1.56 (3H, s) [2×olefinic-CH_3], 1.09 (3H, s) and 1.07 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5 (C, C-1″), 145.1 (CH, C-1), 133.5 (C, C-4′), 121.2 (CH, C-3′), 115.0 (CH_2, C=CH_2), 114.5 (CH, C-2), 59.5 (CH_3, OCH_3), 47.5 (C), 41.7 (C), 29.8 (CH_2), 28.7 (CH_2), 27.1 (CH_2), 25.4 (CH_3), 25.2 (CH_3), 24.0 (CH_3), 23.4 (CH_3); HRMS: *m*/*z* calcd for $C_{16}H_{26}ONa$ (M+Na): 257.1881, found: 257.1883.

4.1.11. 3-Methoxy-1-methylene-5,5,9-trimethylspiro[5.5]undec-8-ene *23* and 1-methylene-5,5,9-trimethylspiro[5.5]undec-8-en-3-ol *8*

A solution of the enol ether **22** (158 mg, 0.67 mmol) in CH_3CO_2H–H_2O (2:1, 3 mL) and TFA (8 mg, 10 mol %) was magnetically stirred at 70 °C for 2 h. The reaction mixture was diluted with water (4 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was washed with aq $NaHCO_3$ (3 mL) and brine (4 mL), and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished a diastereomeric mixture of methoxy β-chamigrene **23** (48 mg, 31%) as oil. R_f (1:19 EtOAc–hexane) 0.5; IR (liquid film): ν_{max}/cm^{-1} 3085, 2945, 2875, 2824, 1652, 1465, 1455, 1386, 1371, 1190, 1118, 1094, 974, 890; ^{1}H NMR (300 MHz, $CDCl_3$, ~1:1 mixture of epimers): δ 5.29 (1H, br s, H-8), 4.96 and 4.95 (1H, s) and 4.68 and 4.61 (1H, s) [C=CH_2], 3.50–3.20 (1H, m), 3.33 and 3.28 (3H, s, OCH_3), 2.60–1.00 (10H, m), 1.58 (3H, s, olefinic-CH_3), 0.94 and 0.92 (3H, s) and 0.86 and 0.82 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$, ~1:1 mixture of epimers): δ 146.6 and 145.8 (C), 132.6 and 132.5 (C), 119.9 and 119.8 (CH, C-8), 113.3 and 112.9 (CH_2, C=*C*H_2), 76.7 and 76.6 (CH, C-3), 55.7 and 55.6 (CH_3, OCH_3), 44.5 (C), 42.7 and 39.7 (CH_2), 38.1 and 36.7 (CH_2), 37.4 and 37.2 (C), 28.9 and 28.8 (CH_2), 28.2 and 27.9 (CH_2), 26.1 and 25.9 (CH_2), 25.3 and 25.2 (CH_3), 25.1 (CH_3), 24.1 (CH_3), 23.3 (CH_3); HRMS: *m*/*z* calcd for $C_{16}H_{26}ONa$ (M+Na): 257.1881, found: 257.1870.

Further elution of the column with ethyl acetate–hexane (1:4) as eluent furnished an epimeric mixture of hydroxy-β-chamigrene **8** (83 mg, 56%) as a white solid. Mp: 77–79 °C; [found: C, 81.61; H, 11.03. $C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%]; R_f (1:7 EtOAc–hexane) 0.45; IR (liquid film): ν_{max}/cm^{-1} 3374, 3087, 2956, 2922, 2878, 1637, 1460, 1438, 1387, 1367, 1046, 1024, 897, 887, 817, 803; ^{1}H NMR (400 MHz, $CDCl_3$, ~1:3 mixture of epimers): δ 5.25 (1H, br s, H-8), 4.99 and 4.94 (1H, s), 4.73 and 4.58 (1H, s) [C=CH_2], 4.00–3.90 and 3.80–3.60 (1H, m, C*H*OH), 2.58 and 2.38 (1H, dd, *J* 12.4 and 4 Hz), 2.25–1.00 (10H, m), 1.56 (3H, s, olefinic-CH_3), 0.95 and 0.90 (3H, s) and 0.86 and 0.80 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$, signals due to the major isomer): δ 145.8 (C, C-1), 132.7 (C, C-9), 119.9 (CH, C-8), 113.4 (CH_2, C=*C*H_2), 67.9 (CH, C-3), 46.2 (CH_2), 44.0 (C), 41.9 (CH_2), 37.6 (C), 28.9 (CH_2), 27.9 (CH_2), 26.3 and 26.2 (CH_2), 25.1 (CH_3), 24.1 (CH_3), 23.4 (CH_3).

4.1.12. Methyl 3-(1-methylene-5,5,9-trimethylspiro[5.5]undec-8-enyl)dithiocarbonate *25*

To a magnetically stirred suspension of NaH (60% in oil, 14 mg, 0.36 mmol, washed with hexane) in dry THF (2 mL) was added a solution of the alcohol **8** (53 mg, 0.24 mmol) in dry THF (0.5 mL) followed by a catalytic amount of imidazole (4 mg). The reaction mixture was heated to 60 °C for 15 min. It was cooled to rt, CS_2 (0.02 mL, 0.36 mmol) was added and refluxed for 15 min. It was recooled to rt, MeI (0.06 mL, 0.96 mmol) was added and refluxed for 4 h. It was then cooled to rt, diluted with water (2 mL), and extracted with ether (3×4 mL). The combined organic layer was

washed with brine (2 mL) and dried (Na_2SO_4). Evaporation of the solvent and rapid purification of the residue on a silica gel column using hexane as eluent furnished the dithiocarbonate **25** (59 mg, 79%) as yellow oil. R_f (hexane) 0.45; IR (liquid film): ν_{max}/cm^{-1} 3089, 2959, 2831, 1639, 1439, 1390, 1371, 1224, 1163, 1128, 1054, 963, 899, 804; ^1H NMR (300 MHz, $CDCl_3$, mixture of epimers): δ 5.76 and 5.70 (1H, m), 5.29 (1H, br s, H-8), 5.05 and 5.00 (1H, s), 4.70 and 4.73 (1H, s), 2.80–2.30 (2H, m), 2.54 and 2.51 (3H, s, SCH_3), 2.25–1.40 (8H, m), 1.58 (3H, s, olefinic-CH_3), 0.94 (3H, s) and 0.91 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$, mixture of epimers): δ 214.9, 144.3, 143.5, 132.8, 132.7, 119.7, 114.9, 114.4, 80.8, 80.5, 44.6, 44.3, 41.1, 39.8, 38.1, 37.1, 36.0, 28.9, 28.8, 28.2, 27.9, 26.1, 25.4, 25.1, 24.9, 23.7, 23.3, 18.9, 18.6; HRMS: *m*/*z* calcd for $C_{17}H_{26}OS_2Na$ (M+Na): 333.1323, found: 333.1329.

4.1.13. 1-Methylene-5,5,9-trimethylspiro[5.5]undec-8-ene (β-chamigrene **1**)

A solution of the dithiocarbonate **25** (51 mg, 0.173 mmol), $^nBu_3SnH$ (0.1 mL, 0.346 mmol), and a catalytic amount of AIBN (5 mg, 20 mol %) in dry benzene (1 mL) was refluxed for 2 h. The reaction mixture was cooled, diluted with ether (5 mL), washed successively with 1% aq NH_4OH solution (2×3 mL), water (2 mL), and brine (3 mL), and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using hexane as eluent furnished β-chamigrene **1** (27 mg, 76%) as colorless oil. R_f (hexane) 0.95; IR (liquid film): ν_{max}/cm^{-1} 3086, 2951, 2930, 2868, 1636, 1452, 1384, 1367, 1157, 1129, 890; ^1H NMR (300 MHz, $CDCl_3$): δ 5.30 (1H, br s, H-8), 4.86 (1H, s) and 4.50 (1H, s) [C=CH_2], 2.24 (1H, td, *J* 12.6 and 5.4 Hz), 2.20–2.00 (2H, m), 2.00–1.90 (2H, m), 1.85–1.65 (4H, m), 1.58 (3H, s, olefinic-CH_3), 1.60–1.30 (2H, m), 1.15 (1H, m of d, *J* 13.5 Hz), 0.87 (3H, s) and 0.82 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1 (C, C-1), 132.7 (C, C-9), 119.9 (CH, C-8), 110.5 (CH_2, C=CH_2), 44.7 (C, C-6), 37.2 (C, C-5), 37.0 (CH_2), 32.2 (CH_2), 28.9 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 25.0 (CH_3), 23.8 (CH_2, C-3), 23.2 (CH_3), 23.0 (CH_3).

4.1.14. 1-Methylene-5,5,9-trimethylspiro[5.5]undec-8-en-3-one **26**

To a magnetically stirred solution of the spiro alcohol **8** (30 mg, 0.136 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added a homogeneous mixture of PCC (147 mg, 0.68 mmol) and silica gel (147 mg), and stirred for 45 min at rt. The reaction mixture was then filtered through a small silica gel column using CH_2Cl_2 as eluent. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the ketone **26** (26 mg, 88%) as oil. R_f (1:9 EtOAc–hexane) 0.6; IR (liquid film): ν_{max}/cm^{-1} 3070, 2946, 2853, 1720, 1651, 1635, 1452, 1373, 1306, 1261, 1230, 1054, 886; ^1H NMR (300 MHz, $CDCl_3$): δ 5.34 (1H, br s, H-8), 4.96 (1H, s) and 4.70 (1H, s) [C=CH_2], 3.27 and 2.92 (2H, 2×d, *J* 15.3 Hz), 2.68 (1H, d, *J* 14.7 Hz), 2.40–1.00 (7H, m), 1.61 (3H, s), 1.02 (3H, s) and 0.81 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.6 (C, C=O), 143.5 (C), 132.7 (C), 119.4 (CH, C-8), 114.4 (CH_2, C=CH_2), 52.5 (CH_2), 49.0 (CH_2), 44.3 (C), 39.3 (C), 28.8 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 24.2 (CH_3), 24.1 (CH_3), 23.3 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{22}ONa$ (M+Na): 241.1568, found: 241.1560.

4.1.15. 1,5,5,9-Tetramethylspiro[5.5]undeca-1,8-dien-3-one (laurencenone C **5**)

To a magnetically stirred solution of the enone **26** (15 mg, 0.068 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added a catalytic amount of DBU (ca. 50 μL) and stirred for 2.5 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (5 mL), washed with 1 N aq HCl, and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished laurencenone C **5** (8.5 mg, 53%) as oil. R_f (1:5 EtOAc–hexane) 0.55; IR (liquid film): ν_{max}/cm^{-1} 3016, 2962, 2927, 2876, 2855, 1667, 1610, 1447, 1390, 1376, 1320, 1282, 1257, 1021; ^1H NMR (300 MHz, $CDCl_3$): δ 5.87 (1H, s, H-2), 5.51 (1H, s, H-8), 2.62 (1H, br d, *J* 18.3 Hz), 2.24 (1H, br d, *J* 18.3 Hz), 2.10–1.70 (6H, m), 1.98 (3H, s, C_1-CH_3), 1.68 (3H, s, C_9-CH_3), 1.03 (3H, s) and 0.95 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7 (C, C=O), 170.5 (C, C-1), 134.2 (C, C-9), 127.0 (CH, C-3), 121.6 (CH, C-8), 49.0 (CH_2, C-4), 43.4 (C, C-6), 40.4 (C, C-5), 28.2 (2C, CH_2), 28.0 (CH_2), 24.8 (CH_3), 24.3 (CH_3), 23.9 (CH_3), 23.3 (CH_3).

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