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Claisen Rearrangement Based Methodology for the Spiroannulation of a Cyclopentane Ring. Formal Total Synthesis of (±)-Acorone and Isoacorones

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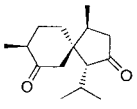
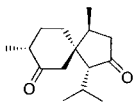
Abstract—A Claisen rearrangement based methodology for spiroannulation of a cyclopentane ring to cyclic precursors and its application in the formal total synthesis of acorones **1** is described. Thus, Claisen rearrangement of 2-cycloalkylideneethanols **12** with 2-methoxypropene and a catalytic amount of mercuric acetate generates 4,4-substituted hex-5-en-2-ones **13**. Ozonolytic cleavage of the terminal olefin in the enones **13** and intramolecular aldol condensation of the resulting keto-aldehydes **14** furnishes the spiroannulated compounds **15**. © 2000 Elsevier Science Ltd. All rights reserved.

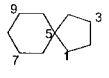
Sorm and coworkers, in 1948, reported the isolation of two epimeric sesquiterpene ketones, acorone **1a** and isoacorone **1b** from the oil of Sweet Flag, *Acorus calamus L.* Presence of the novel spiro[4.5]decane carbon framework in acorones **1** was established in 1958 based on the interpretation of extensive degradation experiments on acorones by Sorm et al.[1] The absolute stereochemistry of acorones **1** was established by correlation with cedrene, a tricyclic sesquiterpene isolated along with acorones from the same source, and was finally confirmed by the single crystal X-ray analysis of a derivative of acorone. Further phytochemical investigations led to the characterisation of a number of acorane derivatives.[2]



Acorone **1a**

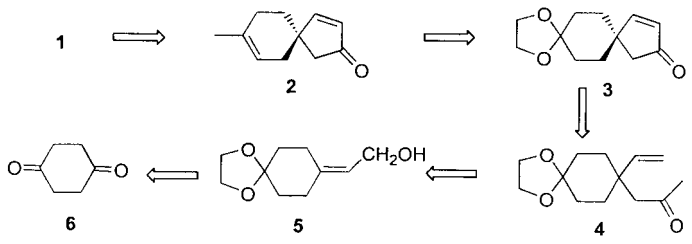


Isoacorone **1b**



spiro[4.5]decane

The most important aspect in the synthesis of acorones **1** is the stereocontrolled construction of the spirocyclic carbon skeleton.[3] A successful synthesis of these spiro sesquiterpenes depends critically, therefore, upon the generation of a quaternary carbon centre which is suitably substituted for the annulation to form a functionalised spiro[4.5]decane. Since the discovery of acoranes, several research groups have reported the synthesis of a variety of acoranes.[4] We wished to develop general methodology for spiroannulation of a five-membered ring to an existing ring, and a synthesis of (±)-acorones **1** was conceived as the test case.[5] The retrosynthetic strategy for acorones **1** via a prochiral precursor is depicted in Scheme 1. The dienone **2**, a precursor employed by Dolby and McCrae;[3b] and Martin and Chou[3c] in their syntheses of (±)-acorone and isoacorones **1**, was identified as the target molecule for achieving the formal total synthesis. The prochiral monoprotected spiroenedione **3** was visualised as a precursor of the dienone **2**. It was anticipated that the cyclopentenone **3** could be obtained from the enone **4** via oxidative cleavage of the terminal olefin followed by an intramolecular aldol condensation of the resulting



Scheme 1.

Keywords: spiro compounds; annulation; Claisen rearrangement; ozonolysis.

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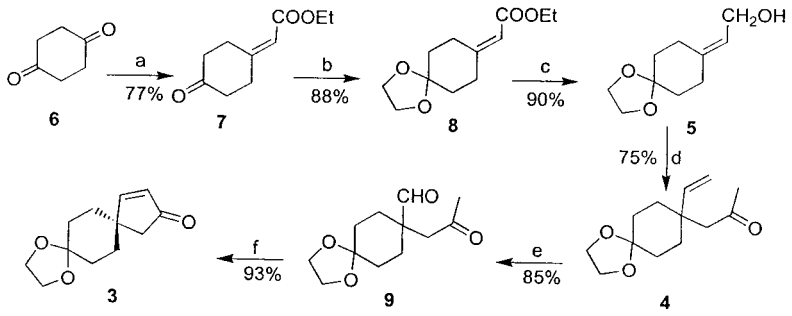
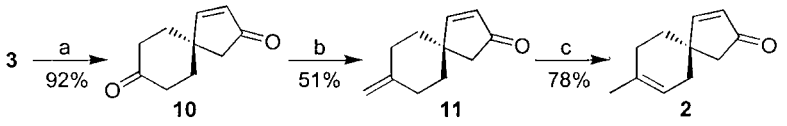


Scheme 2. *Reagents:* (a) NaH, $(EtO)_2POCH_2COOEt$; (b) $(CH_2OH)_2$, *p*-TSA; (c) $LiAlH_4$; (d) $CH_2{=}C(Me)OMe$, EtCOOH; (e) (i) O_3/O_2; (ii) PPh_3; (f) KOH.

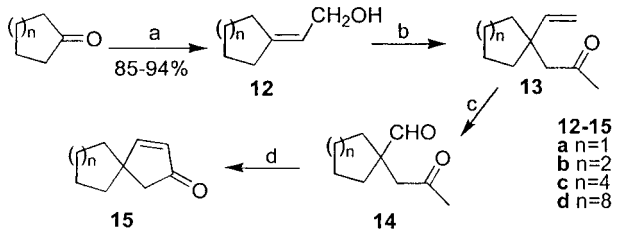
keto-aldehyde. The vinyl ketone **4**, being a γ,δ-unsaturated ketone, could be obtained by a Claisen rearrangement, and the allyl alcohol **5** was readily recognised as the requisite precursor, which could be obtained from cyclohexane-1,4-dione (**6**).

First attention was focussed on the synthesis of the allyl alcohol **5** starting from the readily available cyclohexane-1,4-dione (**6**), for which a controlled Wittig–Horner–Emmons reaction, protection of the ketone and regiochemical reduction protocol was conceived. Thus, treatment of cyclohexane-1,4-dione (**6**) with 1.1 equiv. of the anion derived from triethyl phosphonoacetate and sodium hydride in dry THF at −70°C for 10 min, furnished the keto ester **7** in 77% yield.[6] Protection of the ketone in the keto ester **7** with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) using a Dean–Stark water separator furnished the ketal **8** in 88% yield. Low temperature (−70°C) reduction of the ester **8** with lithium aluminium hydride in ether furnished the allyl alcohol **5** in 90% yield. For the generation of the quaternary centre, which is required to generate the spiro system, a one-pot Claisen rearrangement[7] was employed. Thus, thermal activation of the allyl alcohol **5** with 2-methoxypropene in the presence of a catalytic amount of propionic acid in a sealed tube first at 100°C and then at 170°C furnished the Claisen rearrangement product, the γ,δ-unsaturated ketone **4** in 75% yield (see Scheme 2). Ozonolysis of the enone **4** in methylene chloride and methanol in the presence of a catalytic amount of sodium bicarbonate followed by reductive work-up using triphenylphosphine furnished the keto-aldehyde **9**. Intramolecular aldol condensation of the keto-aldehyde **9** with 1N methanolic potassium hydroxide in THF furnished the spiroenone **3**, in 93% yield. The structure of the spiroenone **3** was established on the basis of the spectral data, in particular, the presence of two doublets at δ 7.56 and 6.08 due to the β and α olefinic protons, respectively, in the ^1H NMR spectrum, and the nine lines ^{13}C NMR spectrum with diagnostic resonances, a singlet at δ 209.1 due to the carbonyl carbon and two doublets at 172.3 and 131.9 due to the β and α olefinic carbons, respectively, of a cyclopentenone. After successful completion of the spiroannulation of the cyclopentenone ring, attention was turned to the conversion of spiroenone **3** into the target molecule spirodienone **2**. Thus, two-phase hydrolysis of the ketal moiety in the spiroenone **3** in methylene chloride and 3N hydrochloric acid furnished the enedione **10** in 92% yield. A Wittig reaction based methodology was adopted for the conversion of the end-dione **10** into the dienone **2**. Thus, regioselective Wittig reaction with methylenetriphenylphosphorane in benzene cleanly transformed the enedione **2** into the dienone **11** in 51% yield along with 33% of unreacted starting material. Finally, isomerisation of the exomethylene group in the dienone **11** in the presence of a catalytic amount of *p*-toluenesulphonic acid in refluxing benzene furnished the spirodienone **2**, whose structure was confirmed by comparison of the spectral data with that reported by Martin and Chou. Since, Dolby and McCrae[3b] and Martin and Chou[3c] have already converted the spirodienone **2** into (±)-acorone **1a** and isoacorone **1b**, employing an aldol-cuprate-hydroboration-oxidation protocol, the present synthesis of the spirodienone **2** constitutes a formal total synthesis of (±)-acorone and isoacorones. It is worth noting that in the present sequence, the spirodienone **2** was obtained via prochiral precursors **3** and **11**, and hence has the potential to serve as precursors for chiral acorones (Scheme 3).

Even though many methodologies have been developed for cyclopentannulation over the last two decades employing novel and innovative strategies,[8] comparatively, not much attention was focussed on the development of methods for the annulation of spirofused cyclopentanes.[9] After successfully accomplishing the formal total synthesis of acorones, to establish the generality of the Claisen rearrangement based spiroannulation of cyclopentanes, **5→3**, the sequence was carried out with a few other cyclic ketones. Thus, the requisite allyl alcohols **12a–d** were prepared from the corresponding cyclic ketones employing Horner–Wadsworth–Emmons reaction followed by regioselective reduction of the resulting α,β-unsaturated esters with lithium aluminium hydride at low temperature. One-pot Claisen rearrangement of the allyl alcohols **12a–d** with 2-methoxypropene and a catalytic amount of mercuric acetate in a sealed tube



Scheme 3. *Reagents:* (a) H_3O^+; (b) $Ph_3P{=}CH_2$; (c) *p*-TSA.



	% yield of 13	14	15
a	52	72	89
b	76	89	75
c	58	83	70
d	56	73	85

Scheme 4. *Reagents:* (a) (i) NaH, $(EtO)_2POCH_2COOEt$; (ii) $LiAlH_4$; (b) $CH_2{=}C(Me)OMe$, $Hg(OAc)_2$; (c) (i) O_3/O_2; (ii) PPh_3; (d) KOH.

furnished the 4,4-disubstituted hex-5-en-2-ones **13a–d**, respectively. Ozonolysis of the enones **13a–d** in methanol, methylene chloride and a catalytic amount of sodium bicarbonate followed by reduction of the resulting ozonides with triphenylphosphine furnished the keto aldehydes **14a–d**, respectively. Finally, intramolecular aldol condensation of the keto aldehydes **14a–d** with methanolic potassium hydroxide at room temperature, furnished the spiroenones **15a–d** in 70–80% yield.[10] The structures of all the compounds **12a–d** to **15a–d** were established from their interrelated spectral data (Scheme 4).

In conclusion, we have developed a convenient method for the spiroannulation of a cyclopentenone ring to cyclic ketones based on the Claisen rearrangement, and it has been applied in the formal total synthesis of the spirosesquiterpenes, acorones.

Experimental

Ethyl 2-(4-oxocyclohexylidene)acetate (7). A suspension of sodium hydride (60% in oil, 43 mg, 1.1 mmol) in hexanes under a nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free sodium hydride was then suspended in dry THF (5 mL) and cooled in an ice bath. Triethyl phosphonoacetate (0.23 mL, 1.16 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred for 30 min at RT. It was then cooled to −70°C and a solution of cyclohexane-1,4-dione (**6**, 100 mg, 0.89 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 10 min at the same temperature. It was then diluted with water (5 mL) and extracted with ethyl acetate (2×5 mL). The combined organic layer was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using hexanes as eluent furnished the unsaturated ester[6] **7** (125 mg, 77%) as an oil. IR (neat): ν_{max} 1710, 1640 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.82 (1H, t, J=1.4 Hz, C=C*H*), 4.14 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 3.20–3.10 (2H, m), 2.65–2.60 (2H, m), 2.55–2.40 (4H, m), 1.26 (3H, t, J=7.0 Hz, OCH$_2$CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 208.5 (s, C=O), 165.0 (s, O–C=O), 156.8 (s, *C*=CH), 115.0 (d, C=*C*H), 58.8 (t, O–*C*H$_2$CH$_3$), 38.5 (t), 38.0 (t), 32.9 (t), 25.9 (t), 13.5 (q, CH$_2$*C*H$_3$). Mass: *m/z* 182 (M^+, 94%), 137 (100), 126 (40), 109 (78), 108 (50). HRMS: *m/z* For $C_{10}H_{14}O_3$, Calcd.: 182.0943. Found: 182.0936.

Ethyl 2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetate (8). A magnetically stirred solution of the keto ester **7** (960 mg, 5.27 mmol), ethylene glycol (0.38 mL, 6.86 mmol) and a catalytic amount of *p*-TSA in dry benzene (60 mL) was refluxed using Dean–Stark water separator for 4 h. Benzene was distilled off, saturated aq. $NaHCO_3$ (5 mL) was added to the reaction mixture and extracted with ether (2×10 mL). The ether layer was washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the product on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the ketal **8** (1.05 g, 88%) as an oil. IR (neat): ν_{max} 1710, 1650 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.67 (1H, s, olefinic H), 4.20 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 3.98 (4H, s, OCH_2CH_2O), 3.00 (2H, t, J=6.3 Hz), 2.38 (2H, t, J=6.3 Hz), 1.85–1.70 (4H, m), 1.28 (3H, t, J=7.1 Hz, OCH$_2$CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 165.7 (s, O–C=O), 159.7 (s, *C*=CH), 113.8 (d, C=*C*H), 107.4 (s, O–C–O), 64.0 (2C, t, OCH_2CH_2O), 59.0 (t, OCH_2CH$_3$), 35.4 (t), 34.6 (t), 34.2 (t), 25.5 (t), 13.8 (q, OCH$_2$CH_3). Mass: *m/z* 226 (M^+, 88%), 197 (95), 181 (84), 180 (55), 153 (100), 135 (38). HRMS: *m/z* For $C_{12}H_{18}O_4$, Calcd.: 226.1217. Found: 226.1205.

8-(2-Hydroxyethylidene)-1,4-dioxaspiro[4.5]decane (5). To a cold (−70°C), magnetically stirred solution of the ester **8** (1.0 g, 4.46 mmol) in dry ether (10 mL) was added $LiAlH_4$ (85 mg, 2.2 mmol) in one portion. The reaction mixture was stirred at −70°C for 2 h and allowed to warm up to −20°C over a period of 30 min. Ethyl acetate (1 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 mL). It was then filtered through a sintered funnel and the residue washed thoroughly with ether (3×10 mL). The ether layer was washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified on a silica gel column using ethyl acetate–hexane (1:10) as eluent to furnish the allyl alcohol **5** (740 mg, 90%) as an oil. IR (neat): ν_{max} 3390 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.43 (1H, t, J=7.1 Hz, olefinic H), 4.16 (2H, d, J=7.1 Hz, CH_2OH), 3.97 (4H, s, OCH_2CH_2O), 2.40–2.25 (4H, m), 1.75–1.50 (4H, m). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 139.4 (s, *C*=CH), 121.6 (d, C=*C*H), 108.1 (s, O–C–O), 63.6 (2C, t, OCH_2CH_2O), 57.5 (t, *C*H$_2$OH), 35.3 (t), 34.6 (t), 32.8 (t), 24.5 (t). Mass: *m/z* 184 (M^+, 5%), 99 (65), 87 (100), 86 (100). HRMS: *m/z* For $C_{10}H_{16}O_3$, Calcd.: 184.1099. Found: 184.1092.

8-(2-Oxopropyl)-8-vinyl-1,4-dioxaspiro[4.5]decane (4). A solution of the allyl alcohol **5** (270 mg, 1.47 mmol), 2-methoxypropene (1 mL, 9.8 mmol) and a catalytic amount of propionic acid was heated first at 100°C for 12 h and then at 170°C for 36 h in a Carius tube under nitrogen atmosphere. The reaction mixture was then cooled, diluted with ether, washed with aqueous $NaHCO_3$ solution 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 (1:20) as eluent furnished the enone **4** (250 mg, 75% yield) as an oil. IR (neat): ν_{max} 1700, 940 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.83 (1H, dd, J=17.6 and 10.9 Hz, C*H*=CH_2), 5.17 (1H, dd, J=10.9 and 1.0 Hz) and 5.05 (1H, dd, J=17.6 and 1.0 Hz) [CH=CH_2], 3.92 (4H, s, OCH_2CH_2O), 2.45 (2H, s, CH_2C=O), 2.08 (3H, s, CH_3C=O), 1.90–1.50 (8H, m). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 206.5 (s, C=O), 143.0 (d, *C*H=CH_2), 113.3 (t, CH=*C*H_2), 107.9 (s, O–C–O), 63.4 (2C, t, OCH_2CH_2O), 53.2 (t, *C*H_2C=O), 38.1 (s), 32.2 (2C, t), 31.7 (q, *C*H_3C=O), 30.4 (2C, t). Mass: *m/z* 224 (M^+, 3%), 196 (12), 167 (32), 153 (43), 100 (50), 99 (100). HRMS: *m/z* For $C_{13}H_{20}O_3$, Calcd.: 224.1412. Found: 224.1418.

8-(2-Oxopropyl)-1,4-dioxaspiro[4.5]decane-8-aldehyde (9). Through a cold (−90°C) solution of the enone **4** (175 mg, 0.78 mmol) and a catalytic amount of $NaHCO_3$ in methanol (1 mL) and CH_2Cl_2 (4 mL) was passed a precooled (−80°C) mixture of ozone in oxygen until the colour of the solution becomes blue. The excess ozone was flushed off with a stream of oxygen and triphenylphosphine (245 mg, 0.94 mmol) was added to the reaction mixture. It was then slowly warmed up to RT and magnetically stirred for 8 h. Evaporation of the solvent under reduced pressure and purification on a silica gel column using ethyl acetate–hexane (1:5 to 1:2.5) as eluent furnished the keto aldehyde **9** (150 mg, 85%) as an oil. IR (neat): ν_{max} 2700, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.76 (1H, s, H–C=O), 3.93 (4H, s, OCH_2CH_2O), 2.77 (2H, s, CH_2C=O), 2.12 (3H, s, CH_3C=O), 2.10–1.50 (8H, m). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 206.0 (s, C=O), 205.2 (d, H–C=O), 107.3 (s, O–C–O), 63.7 (2C, t, OCH_2CH_2O), 49.8 (t, *C*H_2C=O), 45.9 (s), 30.4 (2C), 29.9 (q, *C*H_3C=O), 28.2 (2C, t). Mass: *m/z* 226 (M^+, 2%), 198 (13), 155 (70), 99 (90), 86 (100). HRMS: *m/z* For $C_{12}H_{18}O_4$, Calcd.: 226.1205. Found: 226.1211.

9,12-Dioxadispiro[4.2;4.2]tetradec-3-en-2-one (3). To a solution of the keto aldehyde **9** (140 mg, 0.62 mmol) in THF (8 mL) was added 1N methanolic KOH solution (0.6 mL, 0.6 mmol). The reaction mixture was stirred at RT for 8 h and the solvent was removed under reduced pressure. It was then taken in ether (10 mL) and washed with brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:49 to 1:20) as eluent furnished the spiroenone **3** (120 mg, 93%) as an oil.[3c] IR (neat): ν_{max} 1710, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (1H, d, J=5.7 Hz, C*H*=CHC=O), 6.08 (1H, d, J=5.7 Hz, CH=C*H*C=O), 3.92 (4H, s, OCH_2CH_2O), 2.28 (2H, s, CH_2C=O), 1.90–1.50 (8H, m). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ 209.1 (C, C=O), 172.3 (CH, *C*H=CHC=O), 131.9 (CH, CH=*C*HC=O), 107.7 (C, O–C–O), 64.3 (2C, CH_2, OCH_2CH_2O), 46.1 (CH_2), 45.0 (C), 34.0 (2C, CH_2), 32.2 (2C, CH_2). Mass: *m/z* 208 (M^+, 10%), 99 (100), 86 (100).

Spiro[4.5]dec-3-ene-2,8-dione (10). A solution of the dispiroenone **3** (275 mg, 1.32 mmol) in CH_2Cl_2 (4 mL) and 3N aq. HCl (3 mL) was stirred for 30 min at room temperature. The reaction mixture was extracted with ether (2×10 mL), washed with water, saturated $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:5 to 2:5) as eluent furnished the spirodione **10** (200 mg, 92%) as an oil. IR (neat): ν_{max} 1700, 1670, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, d, J=5.7 Hz, H-4), 6.19 (1H, d, J=5.7 Hz, H-3), 2.55–2.40 (6H, m), 2.05–1.85 (4H, m). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 209.1 (C-2), 207.4 (C-8), 170.1 (C-4), 132.2 (C-3), 45.2, 44.6, 38.2 (2 C), 36.1 (2 C). Mass: *m/z* 164 (M^+, 100%), 136 (25), 108 (22), 107 (20), 94 (42). HRMS: *m/z* For $C_{10}H_{12}O_2$, Calcd.: 164.0837. Found: 164.0832.

8-Methylspiro[4.5]dec-3,7-diene-2-one (2). To a cold (0°C), magnetically stirred solution of methyltriphenylphosphonium iodide (236 mg, 0.59 mmol) in benzene (1 mL) was added potassium *tert*-amyloxide (0.59 mmol) [prepared from potassium (23 mg, 0.59 mmol) and 0.8 mL *tert*-amyl alcohol] in benzene (1 mL) and the resultant yellow reaction mixture was stirred at RT for 20 min. To the methylenetriphenylphosphorane thus formed, was added a solution of the enedione **10** (80 mg, 0.49 mmol) in benzene (1 mL) and stirred at RT for 1.5 h. The reaction mixture was then quenched with water (1 mL) and extracted with ether (2×5 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:20 to 1:5) as eluent furnished the dienone **11** (40 mg, 51%) as an oil. [IR (neat): ν_{max} 1710, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.51 (1H, d, J=5.6 Hz, H-4), 6.07 (1H, d, J=5.6 Hz, H-3), 4.70 (2H, s, C=CH_2), 2.30 (2H, s, CH_2C=O), 2.50–2.00 (4H, m), 1.80–1.50 (4H, m). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ 209.2 (C, C=O), 172.3 (CH, C-4), 146.9 (C, C-8), 131.8 (CH, C-3), 108.2 (CH_2, C=*C*H_2), 46.4 (CH_2, C-1), 45.8 (C, spiro C), 37.7 (2C, CH_2), 31.9 (2C, CH_2)]. Further elution of the column furnished the unreacted starting dione **10** (27 mg, 33%).

A catalytic amount of *p*-TSA was added to a magnetically stirred solution of the dienone **11** (9 mg, 0.06 mmol) in dry benzene (1.5 mL) and the reaction mixture was refluxed for 2 h. Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate–hexane (1:5 to 2:5) as eluent furnished the dienone **2** (7 mg, 78%) as an oil.[3b,c] IR (neat): ν_{max} 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.52 (1H, d, J=5.7 Hz, H-4), 6.06 (1H, d, J=5.4 Hz, H-3), 5.39 (1H, br s, H-7), 2.21 and 2.14 (2H, AB quartet, J=18.3 Hz, CH_2C=O), 1.71 (3H, s, olefinic CH_3), 2.30–1.60 (6H, m). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$+CCl_4): δ 208.6 (C, C=O), 171.3 (CH, C-4), 134.0 (C, C-8), 132.3 (CH, C-3), 119.2 (CH, C-7), 47.5 (CH_2, C-1), 43.6 (C, C-5), 36.7 (CH_2), 33.0 (CH_2), 28.2 (CH_2), 23.6 (CH_3). Mass: *m/z* 162 (M^+, 100%).

2-Cyclopentylideneethanol (29). A suspension of sodium hydride (60% in oil, 568 mg, 14.2 mmol) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free sodium hydride was then suspended in dry THF (10 mL) and cooled in an ice bath. Triethyl phosphonoacetate (3.0 mL,

15 mmol) in dry THF (20 mL) was added dropwise and the reaction mixture was stirred for 30 min at room temperature. It was then cooled in an ice bath and a solution of cyclopentanone (1.0 g, 11.9 mmol) in dry THF (2 mL) was added dropwise and stirred for 8 h at room temperature. It was then quenched by careful addition of saturated aq. NH_4Cl solution and extracted with ether (2×15 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished ethyl cyclopentylideneacetate (1.7 g, 92%) as an oil.[11] IR (neat): ν_{max} 1710, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.74 (1H, br s), 4.10 (2H, q, J=7.0 Hz), 2.74 (2H, t, J=7.5 Hz), 2.40 (2H, t, J=7.2 Hz), 1.80–1.50 (4H, m), 1.24 (3H, t, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9 (C), 166.8 (C), 111.6 (CH), 59.3 (CH_2), 35.9 (CH_2), 32.5 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 14.3 (CH_3). To a cold (−70°C), magnetically stirred solution of ethyl cyclopentylideneacetate (1.7 g, 11 mmol) in dry ether (10 mL) was added LAH (209 mg, 5.5 mmol) in one portion. The reaction mixture was stirred at −70°C for 2 h and allowed to warm up to −20°C over a period of 30 min. Ethyl acetate (2 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 mL). The solution was filtered through a sintered funnel and the residue thoroughly washed with ether (2×20 mL). The ether layer was separated, washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the allyl alcohol **12a** (1.15 g, 93.5%) as an oil.[11] IR (neat): ν_{max} 3300 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.50–5.40 (1H, m), 4.06 (2H, d, J=7.2 Hz), 2.30–2.18 (4H, m), 2.00 (1H, br s), 1.70–1.50 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5 (C), 119.0 (CH), 60.7 (CH_2), 33.6 (CH_2), 28.5 (CH_2), 26.2 (CH_2), 25.9 (CH_2).

2-Cyclohexylideneethanol (12b). Horner–Wadsworth–Emmons reaction of cyclohexanone (1.0 g, 10.2 mmol) using sodium hydride (60% in oil, 480 mg, 12 mmol) and triethyl phosphonoacetate (3.0 mL, 15 mmol) in dry THF (8 mL) for 8 h and purification of the product over a silica gel column using ethyl acetate–hexane (1:40) as eluent furnished ethyl cyclohexylideneacetate (1.6 g, 94%) as an oil.[11] IR (neat): ν_{max} 1720, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.47 (1H, br s), 4.06 (2H, q, J=7.2 Hz), 2.78 (2H, t), 2.15 (2H, t), 1.58 (6H, br s), 1.23 (3H, t, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (C), 162.8 (C), 113.2 (CH), 59.2 (CH_2), 38.0 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 26.4 (CH_2), 14.4 (CH_3). Regioselective reduction of ethyl cyclohexylideneacetate (1.6 g, 9.52 mmol) in dry ether (20 mL) using LAH (180 mg, 4.73 mmol) for 2 h and purification of the product over a silica gel column using ethyl acetate–hexane (1:20 to 1:10) as eluent furnished the allyl alcohol **12b** (1.1 g, 92%) as an oil.[11] IR (neat): ν_{max} 3300, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.32 (1H, t, J=7.2 Hz), 4.08 (2H, d, J=7.2 Hz), 2.20–2.00 (4H, m), 1.50 (7H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1 (C), 120.2 (CH), 58.3 (CH_2), 36.9 (CH_2), 28.7 (CH_2), 28.3 (CH_2), 27.7 (CH_2), 26.6 (CH_2).

2-(Cyclooctylidene)ethanol (12c). Horner–Wardsworth–Emmons reaction of cyclooctanone (1.26 g, 10 mmol) using sodium hydride (60% in oil, 520 mg, 13 mmol) and triethyl phosphonoacetate (3.0 mL, 15 mmol) in dry THF (5 mL) for 8 h and purification of the product over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished ethyl cyclooctylideneacetate (1.85 g, 94%) as an oil.[11] IR (neat): ν_{max} 1730, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.72 (1H, s), 4.13 (2H, q, J=7.0 Hz), 2.76 (2H, t, J=6.0 Hz), 2.31 (2H, t, J=6.0 Hz), 1.80–1.70 (4H, m), 1.50–1.45 (6H, m), 1.27 (3H, t, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4 (C), 166.3 (C), 115.5 (CH), 59.2 (CH_2), 38.7 (CH_2), 30.6 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 14.3 (CH_3). Regioselective reduction of ethyl cyclooctylideneacetate (1.0 g, 5.1 mmol) in dry ether (15 mL) using LAH (97 mg, 2.55 mmol) for 2 h and purification of the product over a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the allyl alcohol **12c** (780 g, 99%) as an oil.[11] IR (neat): ν_{max} 3300, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.43 (1H, t, J=7.0 Hz), 4.17 (2H, d, J=7.0 Hz), 2.23 (2H, t, J=6.0 Hz), 2.19 (2H, t, J=6.0 Hz), 1.70–1.40 (11H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9 (C), 123.9 (CH), 59.3 (CH_2), 37.6 (CH_2), 29.0 (CH_2), 28.0 (CH_2), 27.3 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 25.8 (CH_2).

2-Cyclododecylideneethanol (12d). Wittig–Horner–Emmons reaction of cyclododecanone (2.0 g, 11 mmol) using sodium hydride (60% in oil, 560 mg, 14 mmol) and triethyl phosphonoacetate (3.2 mL, 16 mmol) in dry THF (30 mL) for 8 h and purification of the product on a silica gel column using ethyl acetate and hexane (1:19) as eluent furnished ethyl cyclododecylideneacetate (2.65 g, 96%) as an oil.[11] IR (neat): ν_{max} 1720, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (1 H, s), 4.14 (2H, q, J=7.0 Hz), 2.72 (2H, t, J=6.6 Hz), 2.21 (2H, t, J=6.6 Hz), 1.70–1.20 (21H, m), ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C), 163.0 (C), 116.2 (CH), 59.4 (CH_2), 32.8 (CH_2), 29.8 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 24.1 (CH_2), 24.0 (2C, CH_2), 23.7 (CH_2), 23.4 (CH_2), 22.9 (CH_2), 22.1 (CH_2), 14.3 (CH_3). Regioselective reduction of ethyl cyclododecylideneacetate (1.0 g, 3.97 mmol) in dry ether (10 mL) with LAH (76 mg, 2.0 mmol) for 30 min and purification of the product on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the allyl alcohol **12d** (820 mg, 99%) as an oil.[11] IR (neat): ν_{max} 3300, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.50 (1H, t, J=7.2 Hz), 4.18 (2H, d, J=7.2 Hz), 2.13–2.06 (4H, m), 1.70–1.20 (19H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1 (C), 124.0 (CH), 59.3 (CH_2), 31.5 (CH_2), 28.9 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 24.1 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 23.2 (CH_2), 23.0 (CH_2), 22.1 (CH_2).

Spiro[4.4]non-3-en-2-one (15a). A solution of the allyl alcohol **12a** (1.0 g, 8.92 mmol), 2-methoxypropene (3.22 g, 44.6 mmol) and a catalytic amount of mercuric acetate was heated first at 100°C and then at 180°C for 36 h in Carius tube under nitrogen atmosphere. The reaction mixture was then cooled, diluted with ether, washed with aqueous $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate–hexane (1:20 to 1:9) as eluent furnished the ketone **13a** (700 mg, 52%) as an oil. IR (neat): ν_{max} 1710, 1635, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.86 (1H, dd, J=17.1 and 10.5 Hz, C*H*=CH_2), 4.96 (1H, d,

J=10.5 Hz) and 4.92 (1H, d, J=17.1 Hz) [CH=CH_2], 2.50 (2H, s, CH_2C=O), 2.05 (3H, s, CH_3C=O), 1.90–1.45 (8H, m). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$+CCl_4): δ 207.0 (C, C=O), 144.8 (CH, *C*H=CH_2), 112.1 (CH_2, CH=*C*H_2), 53.7 (CH_2, *C*H_2C=O), 47.7 (C), 37.2 (2 C, CH_2), 28.8 (CH_3, *C*H_3C=O), 23.5 (2C, CH_2). Mass: *m/z* 152 (M^+, 10%), 135 (15), 109 (50), 95 (100), 94 (80). Ozonolysis of the ketone **13a** (152 mg, 1 mmol) in methanol (0.2 mL) and CH_2Cl_2 (4 mL) and reductive work up with triphenylphosphine (314 mg, 1.2 mmol) followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished the keto aldehyde **14a** (120 mg, 72%) as an oil. IR (neat): ν_{max} 2720, 1720 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 9.58 (1H, s, *H*–C=O), 2.81 (2H, s, CH_2C=O), 2.10 (3H, s, CH_3C=O), 1.80–1.40 (8H, m). Intramolecular aldol condensation reaction of the keto aldehyde **14a** (50 mg, 0.3 mmol) with 1 M methanolic KOH solution (0.3 mL, 0.3 mmol) in THF (4.0 mL) for 8 h followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the spiroenone **15a** (40 mg, 89%).[10a] IR (neat): ν_{max} 1720, 1580 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.48 (1H, d, J=6.0 Hz, H-4), 6.01 (1H, d, J=6.0 Hz, H-3), 2.22 (2H, s, H-1), 1.80–1.50 (8H, m).

Spiro[4.5]dec-3-en-2-one (15b). One-pot Claisen rearrangement of the allyl alcohol **12b** (1.1 g, 8.73 mmol) with 2-methoxypropene (3.14 g, 43.6 mmol) and a catalytic amount of mercuric acetate at 180°C for 36 h and purification of the product on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished ketone **13b** (1.1 g, 76%) as an oil. IR (neat): ν_{max} 1710, 1630, 910 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (1H, dd, J=17.7 and 11.1 Hz, C*H*=CH_2), 5.12 (1H, d, J=11.1 Hz) and 5.00 (1H, d, J=17.7 Hz) [CH=CH_2], 2.44 (2H, s, CH_2C=O), 2.08 (3H, s, CH_3C=O), 1.70–1.60 (4H, m), 1.46 (6H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.6 (C=O), 145.3 (*C*H=CH_2), 113.5 (CH=*C*H_2), 54.6, 39.7, 35.8 (2C), 32.8, 26.2, 22.1 (2C). Mass: *m/z* 166 (M^+, 10%), 151 (15), 123 (50), 108 (45). Ozonolysis of the enone **13b** (200 mg, 1.2 mmol) in methanol (0.2 mL, mmol) and CH_2Cl_2 (5 mL) at −78°C and reductive work up with triphenylphosphine (378 mg, 1.45 mmol) followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished the keto aldehyde **14b** (180 mg, 89%), which was found to decompose on standing. IR (neat): ν_{max} 2700, 1715 cm^{-1}. Intramolecular aldol condensation of the keto aldehyde **14b** (180 mg, 1.07 mmol) in THF (15 mL) with 1 M methanolic KOH solution (1 mL, 1 mmol) at RT for 8 h followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:20 to 1:10) as eluent furnished the spiroenone **15b** (120 mg, 75%).[10b–e] IR (neat): ν_{max} 1710, 1590 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (1H, d, J=5.5 Hz, H-4), 5.99 (1H, d, J=5.5 Hz, H-3), 2.17 (2H, s, H-1), 1.80–1.20 (10H, m). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$+CCl_4): δ 208.4 (C, C=O), 172.5 (CH, C-4), 131.6 (CH, C-3), 46.9 (CH_2, C-1), 46.0 (C, C-5), 36.8 (2C, CH_2, C-6 and 10), 25.5 (CH_2, C-8), 21.4 (2C, CH_2, C-7 and 9). Mass: *m/z* 150 (M^+, 75%), 107 (75), 95 (100).

Spiro[4.7]dodec-3-en-2-one (15c). A one-pot Claisen rearrangement of the allyl alcohol **12c** (550 mg, 3.57 mmol) with 2-methoxypropene (1.54 g, 21.5 mmol) and a catalytic amount of mercuric acetate at 180°C for 36 h followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the enone **13c** (400 mg, 58% yield) as an oil. IR (neat): ν_{max} 1700, 1630, 910 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.79 (1H, dd, J=17.5 and 11.0 Hz, C*H*=CH_2), 5.06 (1H, d, J=11.0 Hz) and 4.95 (1H, d, J=17.5 Hz) [CH=CH_2], 2.40 (2H, s, CH_2C=O), 2.07 (3H, s, CH_3C=O), 1.70–1.40 (14H, m). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ 208.7 (C, C=O), 146.4 (CH, C*H*=CH_2), 112.6 (CH_2, CH=CH_2), 53.7 (CH_2, *C*H_2C=O), 42.9 (C), 32.6 (CH_3, *C*H_3C=O), 32.3 (2C, CH_2), 28.5 (2C, CH_2), 25.2 (CH_2), 22.5 (2C, CH_2). Mass: *m/z* 194 (M^+, 12%), 136 (50), 121 (30), 110 (20), 108 (32), 95 (50), 43 (100). Ozonolysis of the enone **13c** (240 mg, 1.23 mmol) and reductive workup with triphenylphosphine (388 mg, 1.48 mmol) for 8 h followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished the keto aldehyde **14c** (200 mg, 83%), which was found to form hydrate on standing. IR (neat): ν_{max} 1720 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.56 (1H, s, *H*–C=O), 2.73 (2H, s, CH_2C=O), 2.12 (3H, s, CH_3C=O), 1.90–1.50 (14H, m). Intramolecular aldol condensation of the keto aldehyde **14c** (16 mg, 0.08 mmol) in THF (1.1 mL) with 10% methanolic KOH solution (0.08 mL, 0.08 mmol) for 8 h followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the spiroenone **15c** (10 mg, 70%). IR (neat): ν_{max} 1710, 1670 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (1H, d, J=5.7 Hz, H-4), 6.00 (1H, d, J=5.5 Hz, H-3), 2.19 (2H, s, H-1), 1.70–1.60 (14H, m). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 209.4 (s, C=O), 172.6 (d, C-4), 130.7 (d, C-3), 49.0 (t, C-1), 48.5 (s, C-5), 34.7 (2C, t, C-6 and 12), 28.1 (2C, t, C-8 and 10), 24.4 (t, C-9), 23.3 (2C, t, C-7 and 11). Mass: *m/z* 178 (M^+, 35%), 135 (43), 121 (43), 107 (43), 95 (80), 94 (100). HRMS: For $C_{12}H_{18}O$, Calcd.: 178.1358. Found: 178.1361.

Spiro[4.11]hexadec-3-en-2-one (15d). One-pot Claisen rearrangement of the allyl alcohol **12d** (600 mg, 2.9 mmol) with 2-methoxypropene (1.03 g, 14.3 mmol) and a catalytic amount of mercuric acetate at 180°C for 36 h followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the ketone **13d** (450 mg, 56%) as an oil. IR (neat): ν_{max} 1700, 1640, 910 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.83 (1H, dd, J=17.6 and 11.0 Hz, C*H*=CH_2), 5.05 (1H, d, J=11.0 Hz) and 4.95 (1H, d, J=17.6 Hz) [CH=CH_2], 2.40 (2H, s, H-1), 2.08 (3H, s, CH_3C=O), 1.60–1.20 (22H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4 (C, C=O), 145.8 (CH, *C*H=CH_2), 112.5 (CH_2, CH=*C*H_2), 52.9 (CH_2, *C*H_2C=O), 41.9 (C, C-1′), 32.4 (CH_3, *C*H_3C=O), 31.4 (CH_2), 26.6 (2C, CH_2), 26.1 (2C, CH_2), 22.6 (2C, CH_2), 22.1 (2C, CH_2), 19.0 (2C, CH_2). Mass: *m/z* 250 (M^+, 15%), 193 (28), 123 (20), 110 (35), 95 (36), 81 (30), 68 (30), 55 (38), 43 (100). Ozonolysis of the ketone **13d** (300 mg, 1.2 mmol) in methanol (0.2 mL) and CH_2Cl_2 (4 mL) and reductive work up with triphenylphosphine (367 mg, 1.4 mmol) at RT for 8 h followed by purification of the product on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished the keto aldehyde **14d** (220 mg, 73%) as an oil. IR (neat): ν_{max} 1720 cm^{-1}. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 9.67 (1H, s, H–C═O), 2.70 (2H, s, CH_2C═O), 2.10 (3H, s, CH_3C═O), 1.60–1.40 (4H, m), 1.26 (18H, br s). Intramolecular aldol condensation reaction of the keto aldehyde **14d** (50 mg, 0.2 mmol) in THF (3.5 mL) with 1 M methanolic KOH solution (0.16 mL, 0.16 mmol) at RT for 8 h followed by purification of the residue on a silica gel column using ethyl acetate–hexane (1:20 to 1:9) as eluent furnished the spiroenone **15d** (40 mg, 85%) as a solid. IR (neat): ν_{max} 1710, 1580 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.60 (1H, d, J=5.6 Hz, H-4), 6.02 (1H, d, J=5.7 Hz, H-3), 2.17 (2H, s, H-1), 1.50–1.30 (22H, m, H-6 to 16). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 208.9 (s, C═O), 172.0 (d, C-4), 131.1 (d, C-3), 47.8 (t, CH_2C═O), 33.4 (2C, t, C-6 and 16), 32.2 (s, C-5), 26.3 (2C, t), 25.7 (t), 22.3 (2C, t), 21.8 (2C, t), 19.9 (2C, t). Mass: m/z 234 (M^+, 40%), 109 (70), 96 (100), 95 (80). HRMS: For $C_{16}H_{26}O$, Calcd.: 234.1983. Found: 234.1981.

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