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Supporting Information

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“Intramolecular Organocatalytic [3+2] Dipolar Cycloaddition: Stereospecific Cycloaddition and The Total Synthesis of (±)-Hirsutene”

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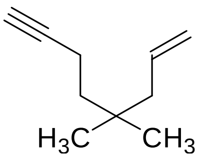
I. Experimental Procedure and Spectroscopic Data for Selected Compounds

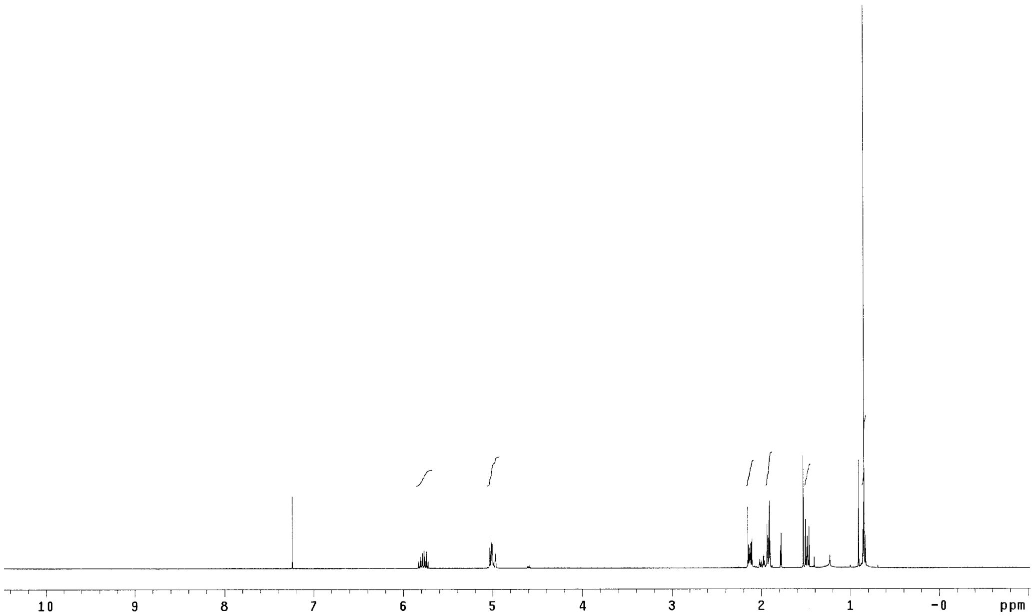
General: Ethyl acetate was degassed with Ar prior to use. Anhydrous solvents were transferred by an oven-dried syringe. Tributylphosphine was distilled from CaH_2 prior to use. All reactions were performed under Ar atmosphere unless otherwise noted. Chemical reagents were purchased from Aldrich chemical companies and used without further purification, unless otherwise noted. Deuterated solvents were used as received from Cambridge Isotope Laboratories. Analytical TLC was performed on EM Reagents 0.25 mm silica gel 60-F plates, and visualized under UV light. Flash chromatography was performed on silica gel 60 (200-400 mesh). NMR spectra were recorded on a Varian UNITY+ spectrometer. ^{1}H NMR spectra were obtained at Mercury 400 MHz spectrometer. ^{13}C NMR spectra were obtained at Mercury 100 MHz spectrometer. nOe spectra were recorded with a Varian Gemini (500 MHz) spectrometer. FT-IR spectra were obtained using a Nicolet Impact 410 spectrometer. Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected.



4,4-Dimethyl-oct-1-en-7-yne (2): A solution of the previously reported tosylate of 3,3 dimethyl-hex-5-en-1-ol **1** (8.4 g, 29.8 mmol, 100 mol%) in DMSO (25 mL, 1.2 M) was added to a solution of of lithium acetylide ethylenediamine complex (7.2 g, 77.5 mmol, 260 mol%) in DMSO (50 mL, 1.6 M) at 5 °C. The resulting dark brown solution was stirred for 1.5h and then cooled to 0 °C, at which point 20 mL of 5% aqueous hydrochloric acid was added dropwise. The mixture was partitioned between water and ether. The ethereal layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by flash chromatography (SiO_2: pentane) to provide **2** as a clear liquid (2.8 g, 20.2 mmol) in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (s, 6H), 1.49 (m, 2H), 1.90~1.94 (m, 3H), 2.13 (m, 2H), 5.00 (m, 2H). 5.78 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): 13.5, 26.5, 33.1, 40.6, 46.2, 67.8, 85.4, 117.1, 135.1. **HRMS**: Calcd [M+1] for $C_{10}H_{17}$: 137.1330; Found: 137.1334.

(**^{1}H** and **^{13}C NMR** Spectra on following page)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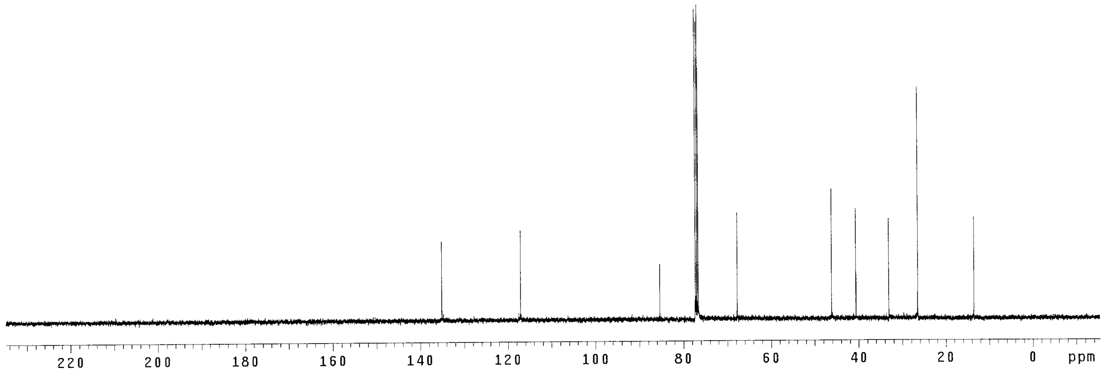
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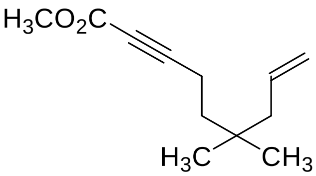
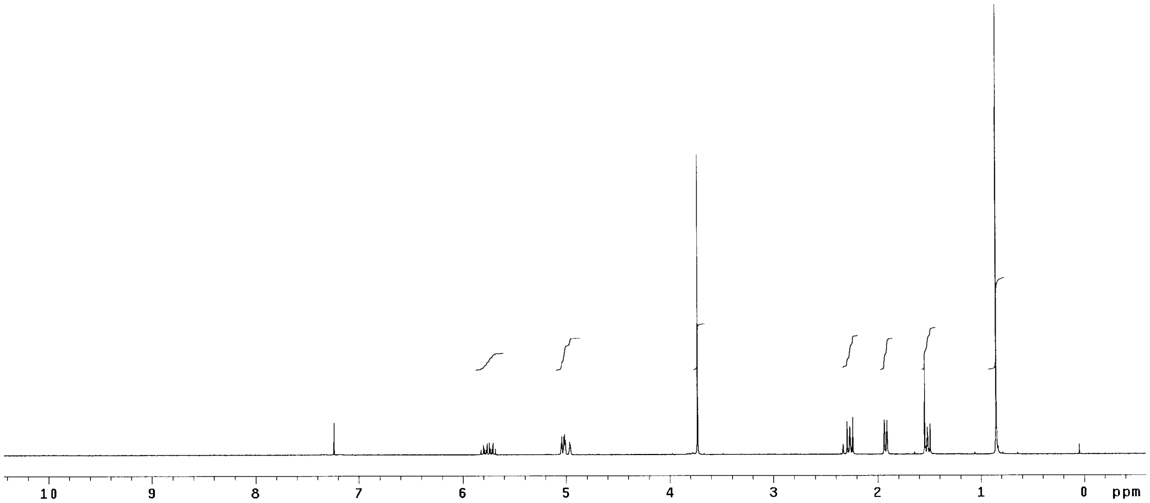


6,6-Dimethyl-non-8-en-2-ynoic acid methyl ester (3): Methylithium (24.3 mL, 38.8 mmol, 110 mol%) was added dropwise to a solution of **2** (4.8 g, 35.3 mmol, 100 mol%) in THF (150 mL, 0.36 M) at -78 °C. The reaction mixture was stirred at -78 °C for 2h, at which point methyl chloroformate (4.0 g, 42.4 mmol, 120 mmol%) was added and the reaction temperature was increased to -30 °C and the reaction mixture was allowed to stir for 1h at -30 °C. The cooling batch was removed and the reaction was stirred at ambient temperature for 8h, at which point water (50 mL) was added. The mixture was extracted with ether and the combined ethereal layers were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by flash chromatography (SiO_2: 5% ethyl acetate in hexanes) to provide **3** as a clear liquid (5.7 g, 29.2 mmol) in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (s, 6H), 1.50 (m, 2H), 1.90 (dt, *J* = 1.4, 7.2 Hz, 2H), 2.24 (m, 2H), 3.71 (s, 3H), 4.98 (m, 2H), 5.73 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): 13.7, 26.4, 33.0, 39.3, 46.0, 52.4, 72.5, 90.3, 117.3, 134.6, 154.2. **HRMS**: Calcd [M+1] for $C_{12}H_{18}O_2$: 195.1385; Found: 195.1381. **FTIR** (film): 3412, 3081, 2961, 2237, 1715, 1431, 1248, 1061, 902, 705 cm^{-1}.

(**^{1}H** and **^{13}C NMR** Spectra on following page)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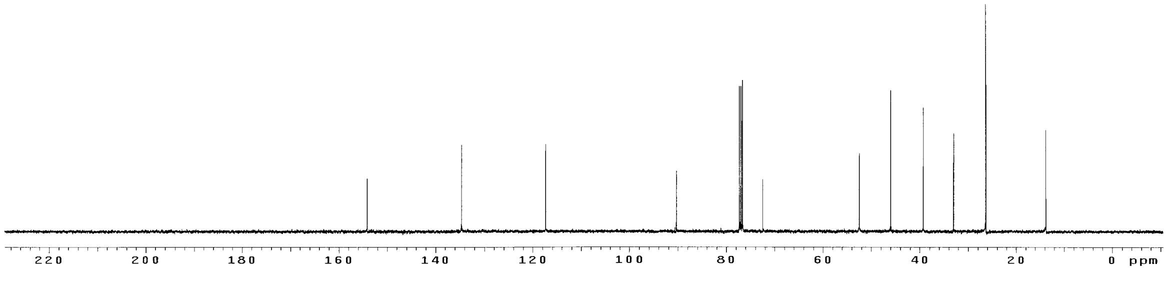
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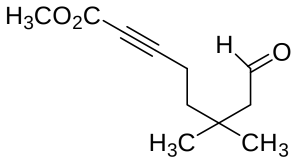
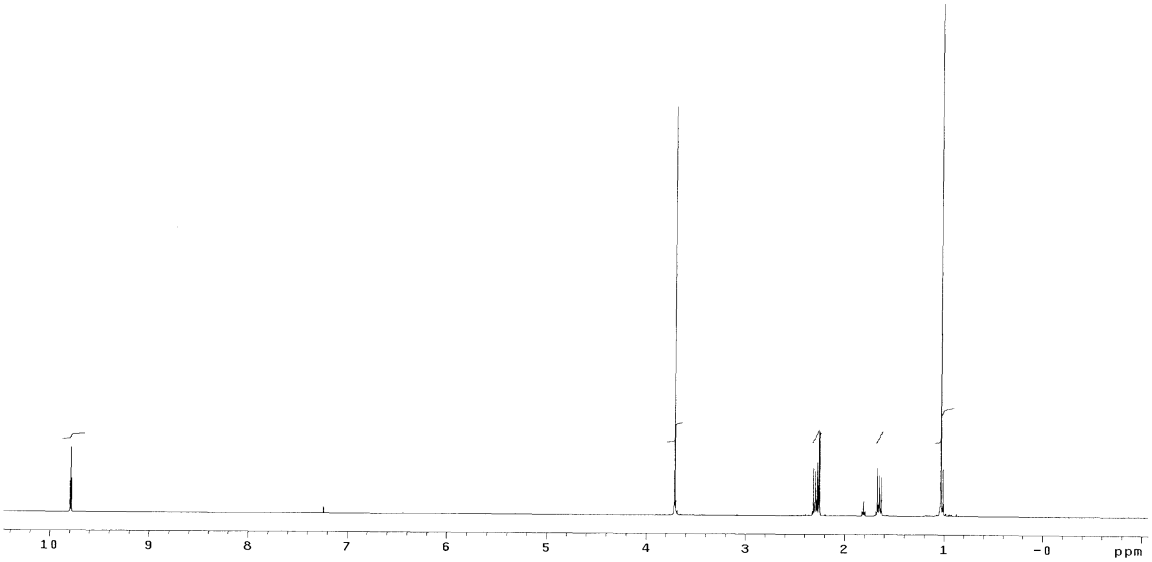


6,6-Dimethyl-8-oxo-oct-2-ynoic acid methyl ester (4): A stirred solution of **3** (4.7 g, 24.0 mmol, 100% mol) in dichloromethane (60 mL, 0.4 M) was treated at -78 °C with a stream of ozone until a blue color persisted. The excess ozone was purged from the solution with a stream of argon, and triphenylphosphine (6.2 g, 23.5 mmol, 98% mol) was added to the solution. The mixture was allowed to warm slowly to ambient temperature, at which point it was diluted with CH_2Cl_2 and washed with brine. The combined brine washes were extracted with CH_2Cl_2 and the combined organics were dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by flash chromatography (SiO_2: 10% ethyl acetate in hexanes) to provide **4** as a clear liquid (4.0 g, 20.2 mmol) in 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 6H), 1.64 (m, 2H), 2.26 (d, *J* = 2.7 Hz, 2H), 2.30 (m, 2H), 9.79 (t, *J* = 3.1 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): 13.8, 26.9, 33.3, 39.9, 52.6, 54.2, 73.0, 89.3, 154.1, 202.4. **HRMS**: Calcd [M+1] for $C_{11}H_{17}O_3$: 197.1178; Found: 197.1177. **FTIR** (film): 2957, 2864, 2245, 1719, 1439, 1260, 1069, 754 cm^{-1}.

(**^{1}H** and **^{13}C NMR** Spectra on following page)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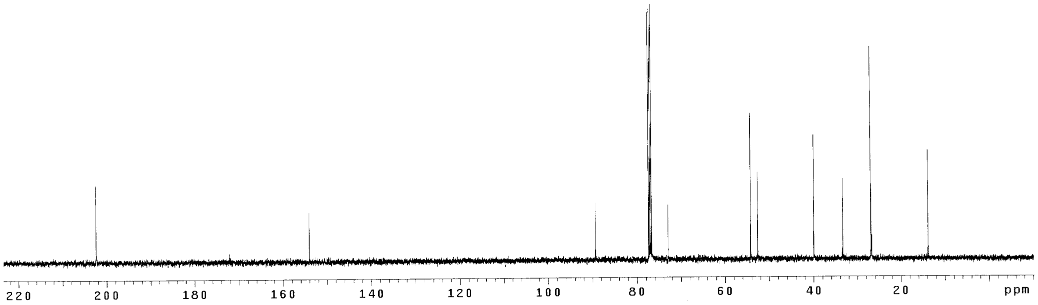
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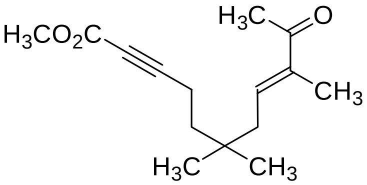
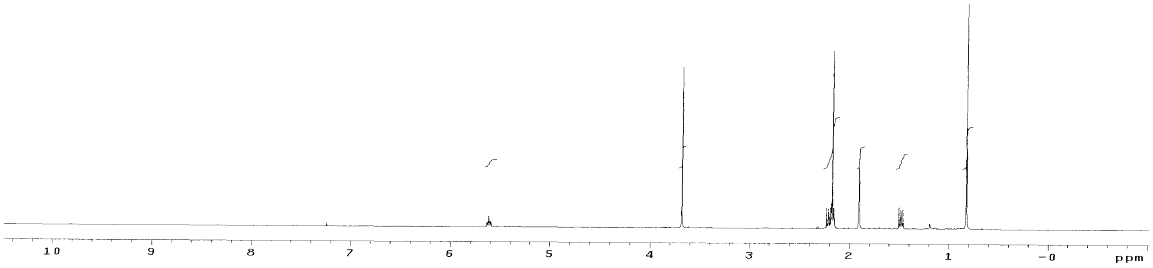


<u>**(E)-6,6,9-Trimethyl-10-oxo-undec-8-en-2-ynoic acid methyl ester (*E*)-5:**</u> To a solution of sodium hydride (115.0 mg, 4.8 mmol, 110% mol) in dry THF (50 mL, 0.1 M) was added to 3-diethylphosphono-2-butanone (997.0 mg, 4.8 mmol, 110% mol) in dry THF (10 mL, 0.5 M) at such a rate that the temperature did not exceed 20 °C. The mixture was stirred until the sodium hydride had completely dissolved, at which point a solution of **4** (863.0 mg 4.4 mmol, 100% mol) in dry ether (10 mL, 0.4 M) was added dropwise. The mixture was stirred at 35 °C for 8h, cooled, quenched with water, and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by flash chromatography (SiO_2: 5% ethyl acetate in hexanes) to provide a colorless liquid **5** (655 mg, 2.6 mmol) as a 5.5:1 ratio of E:Z isomers in 60% yield

<u>Spectral Data for (*E*)-**5**</u>
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 6H), 1.58 (m, 2H), 1.74 (d, *J* = 1.4 Hz, 4H), 2.14 (dd, *J* = 0.7, 7.5 Hz, 2H), 2.27~ 2.31 (m, 5H), 3.77 (s, 3H), 6.63 (tq, *J* = 1.4, 6.5 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): 11.4, 14.0, 25.6, 26.5, 32.3, 39.6, 40.9, 52.6, 72.8, 89.8, 139.2, 139.4, 154.1, 199.7. **HRMS**: Calcd [M+1] for $C_{15}H_{23}O_3$: 251.1647; Found: 251.1645. **FTIR** (film): 2953, 2240, 1715, 1601, 1431, 1256, 1069, 906, 754 cm^{-1}.

(**^{1}H** and **^{13}C NMR** Spectra on following page)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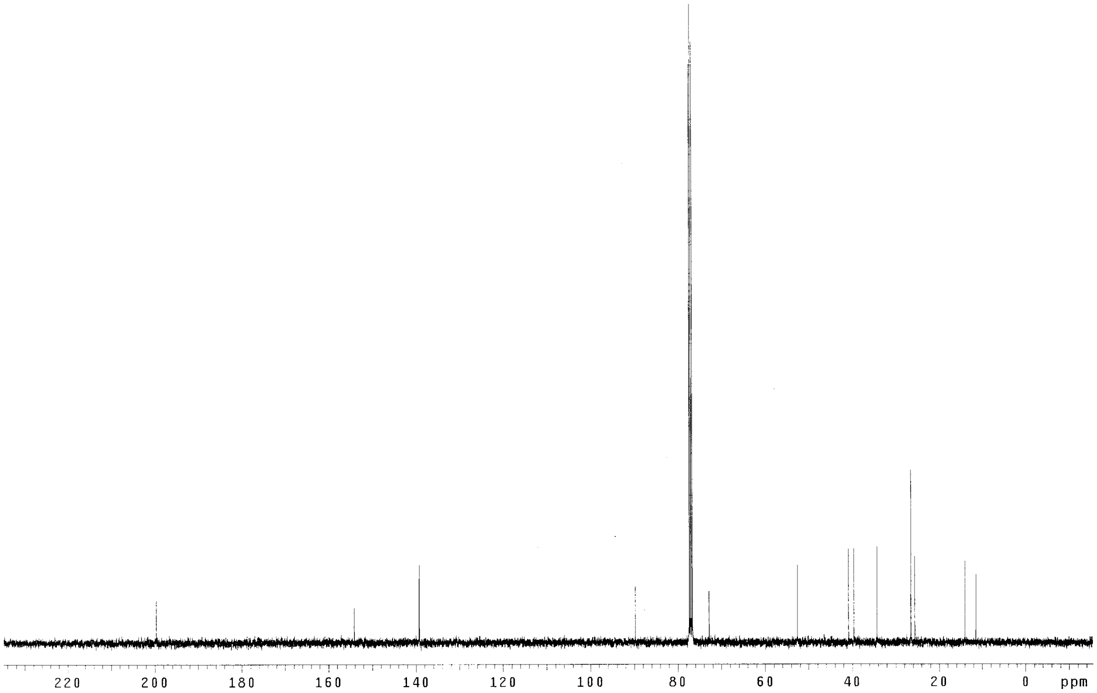
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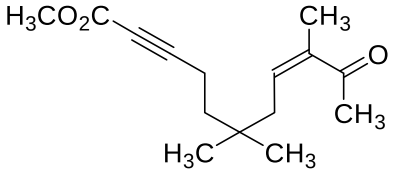

<u>Spectral Data for (*Z*)-**5:**</u>

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.83 (s, 6H), 1.48 (m, 2H), 1.90 (d, *J* = 1.7 Hz, 3H), 2.15~2.23 (m, 7H), 3.68 (s, 3H), 5.62 (dq, *J* = 1.7, 7.5 Hz, 1H). **^{13}C NMR** (100 MHz, CDCl$_3$): 13.8, 21.2, 26.4, 29.8, 33.5, 39.2, 40.2, 52.4, 72.5, 90.2, 133.9, 137.1, 154.1, 203.1. **HRMS**: Calcd [M+1] for $C_{15}H_{23}O_3$: 251.1647; Found: 251.1651. **FTIR** (film): 3439, 2953, 2867, 2361, 2237, 1719, 1630, 1431, 1365, 1260, 1073, 750 cm^{-1}.

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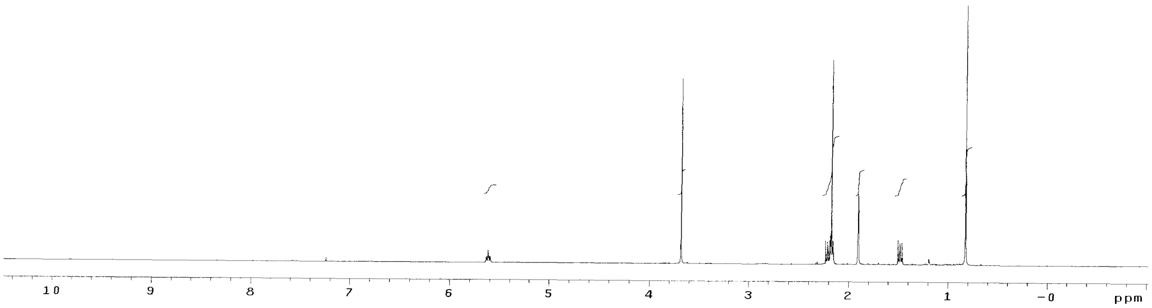
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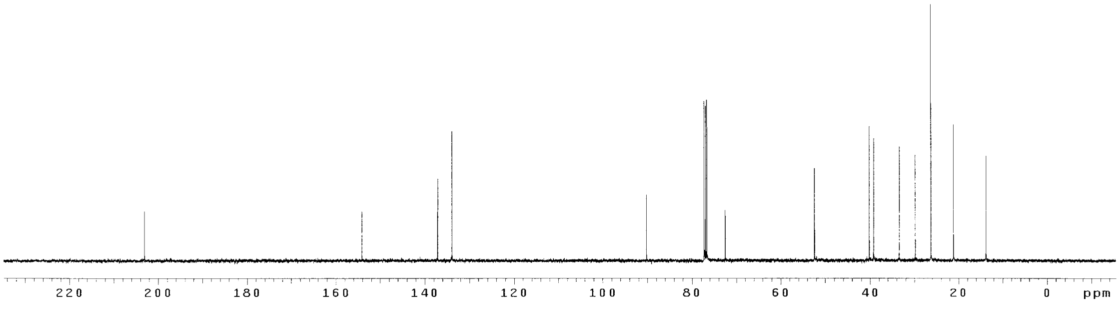
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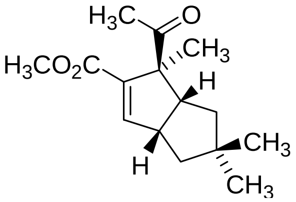
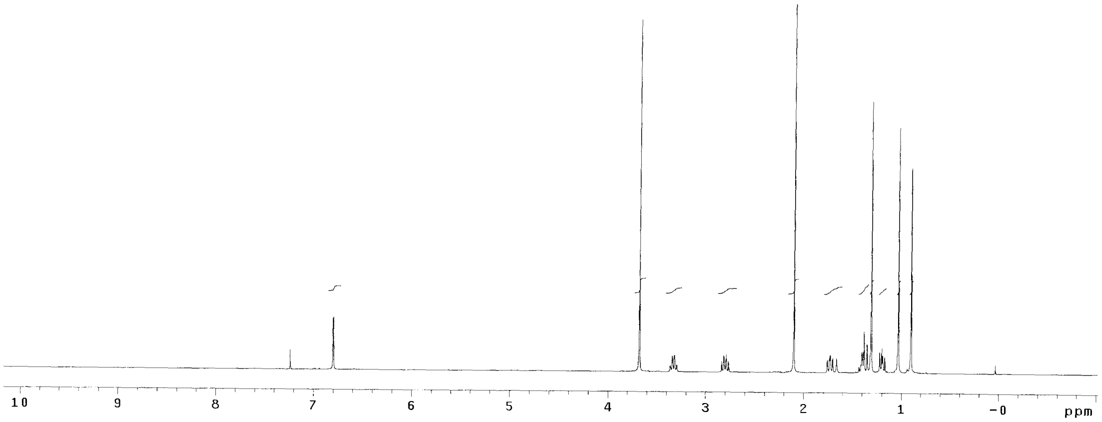


(±)-1-Acetyl-1,5,5-trimethyl-1,3a,4,5,6,6a-hexahydro-pentalene-2-carboxylic acid methyl ester (6): Tributylphosphine (24.2 mg, 0.12 mmol, 10 mol%) was added to a solution of (*E*)-**5** (300 mg, 1.2 mmol, 100 mol%) in ethyl acetate (12 mL, 0.1 M) and the reaction was allowed to stir at 110 °C in a sealed tube until complete consumption of starting material was observed, at which point the reaction mixture was evaporated onto silica and purified by flash chromatography (SiO_2: 5% ethyl acetate in hexanes) to provide **6** as a colorless liquid (264.0 mg, 1.1 mmol) in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 1.03 (s, 3H), 1.20 (dd, *J* = 8.3, 12.3 Hz, 1H), 1.31 (s, 3H), 1.40 (m, 2H), 1.71 (m, 1H), 2.10 (s, 3H), 2.80 (dt, *J* = 8.3, 10.6 Hz, 1H), 3.33 (dq, *J* = 2.4, 8.9 Hz, 1H), 3.68 (s, 3H), 6.81 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): 17.4, 25.6, 26.8, 28.9, 40.5, 42.2, 44.8, 48.7, 49.9, 51.5, 61.9, 137.0, 149.7, 165.0, 210.7. **HRMS**: Calcd [M+1] for $C_{15}H_{23}O_3$: 251.1647; Found: 251.1644. **FTIR** (film): 2961, 2864, 2369, 1715, 1260, 1058, 766 cm^{-1}.

(**^{1}H** and **^{13}C NMR** Spectra on following page)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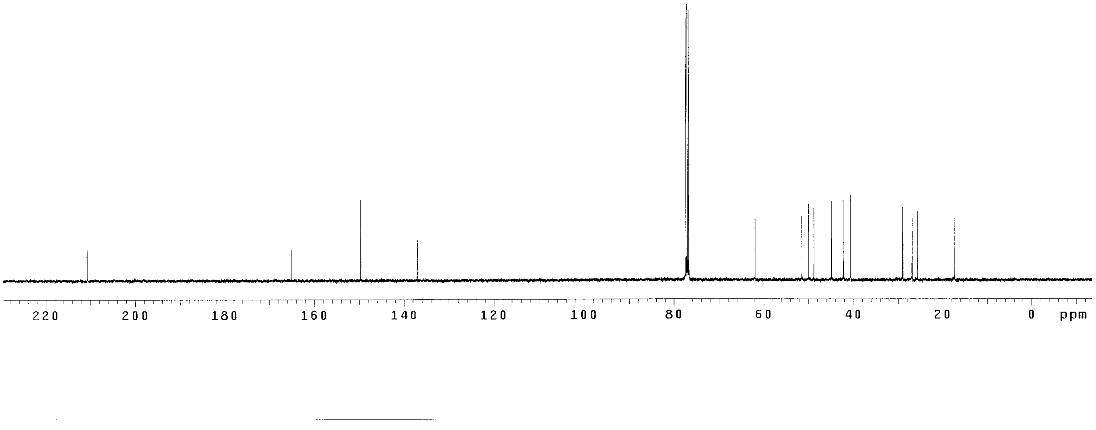
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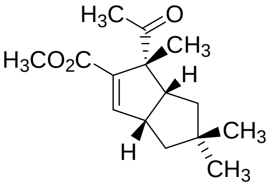
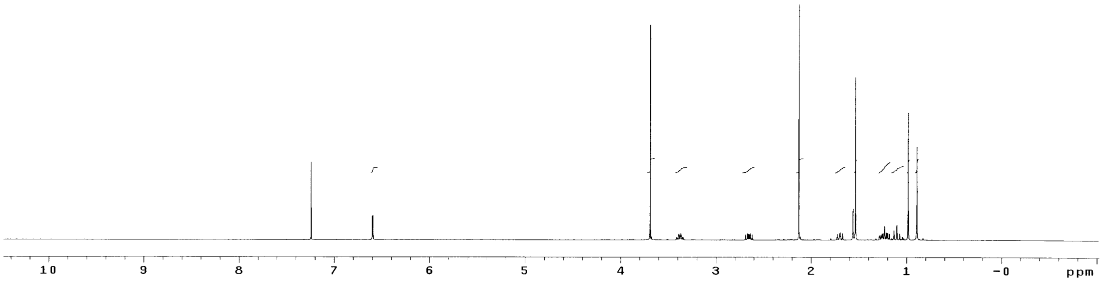


(±)-1-Acetyl-1,5,5-trimethyl-1,3a,4,5,6,6a-hexahydro-pentalene-2-carboxylic acid methyl ester *epi*-(6): Tributylphosphine (2.4 mg, 0.012 mmol, 10 mol%) was added to a solution of (*Z*)-**5** (30 mg, 0.12 mmol 100 mol%) in ethyl acetate (1.2 mL, 0.1 M) and the reaction was allowed to stir at 110 °C in a sealed tube until complete consumption of starting material was observed, at which point the reaction mixture was evaporated onto silica and purified by flash chromatography (SiO_2: 5% ethyl acetate in hexanes) to provide ***epi*-6** as a colorless liquid (22.0 mg, 0.09 mmol) in 73% yield.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.89 (s, 3H), 0.98 (s, 3H), 1.08 (dd, *J* = 4.1, 11.9 Hz, 1H), 1.18~1.29 (m, 3H), 1.53 (s, 3H), 1.69 (ddd, *J* = 2.1, 9.6, 12.7 Hz, 1H), 2.12 (s, 3H), 2.65 (dt, *J* = 7.1 Hz, 1H), 3.37 (dq, *J* = 2.4, 8.2, Hz 1H), 3.67 (s, 1H), 6.59 (d, *J* = 2.4 Hz, 1H). ^{13}**C NMR** (100 MHz, $CDCl_3$): 24.8, 27.0, 27.9, 28.7, 40.8, 42.5, 43.7, 48.0, 51.4, 53.5, 62.8, 137.4, 147.4, 165.3, 209.3. **HRMS**: Calcd [M+1] for $C_{15}H_{23}O_3$: 251.1647; Found: 251.1654. **FTIR** (film): 2961, 2864, 2369, 1715, 1260, 1058, 766 cm^{-1}.

(^{1}**H** and ^{13}**C NMR** Spectra on following page)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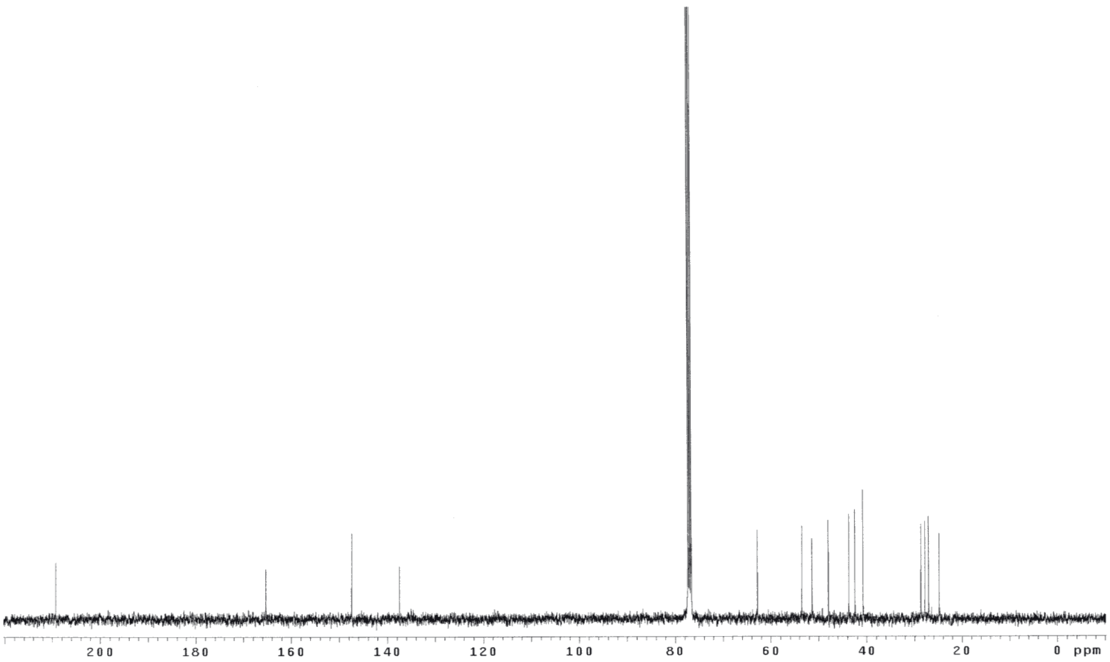
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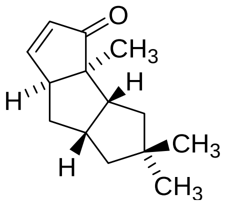
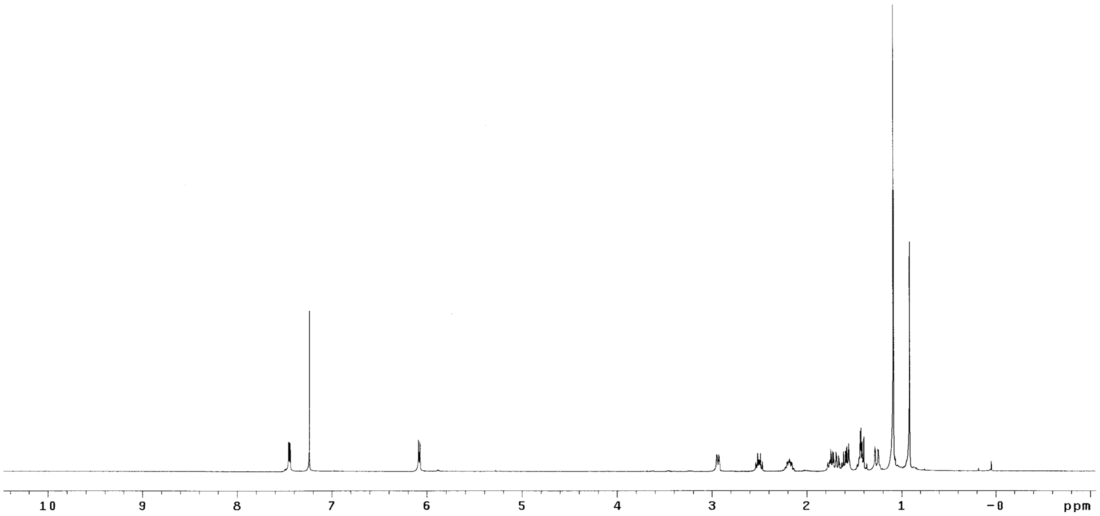


(±)-3a,5,5-Trimethyl-3a,3b,4,5,6,6a,7,7a-octahydro-cyclopenta[a]pentalen-3-one (8): To a biphasic mixture of 5% aqueous KOH (1.4 mL, 1.3 mmol, 1400 mol%), THF (2.8 mL) and 40% aqueous n-Bn_4NOH (3 drops) was added to a solution of keto-aldhyde (20 mg 0.09 mmol, 100% mol), which was prepared through oxidation of diol **7**, in ether (1.4 mL, 0.06 M). The mixture was vigorously stirred and heated at reflux overnight. The reaction was cooled to room temperature, poured into water, and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by flash chromatography (SiO_2: 5% ethyl acetate in hexanes) to provide **8** (17.5 mg, 0.09 mmol) as a pale yellow solid in 95% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.08 (s, 6H), 1.26 (dd, *J* = 2.4, 13.3 Hz, 1H), 1.43 (m, 2H), 1.59 (dd, *J* = 8.0, 13.5 Hz, 1H), 1.68 (ddd, *J* = 9.6, 11.6, 13.1 Hz 1H), 1.75 (ddd, *J* = 1.5, 7.7, 10.1 Hz, 1H), 2.18 (ddq, *J* = 2.4, 7.6, 11.2 Hz, 1H), 2.50 (dt, *J* = 7.5, 12.0 Hz, 1H), 2.93 (dq, *J* = 1.7, 9.2, Hz, 1H), 6.08 (dd, *J* = 1.7, 5.5 Hz, 1H), 7.45 (dd, *J* = 2.7, 5.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): 18.5, 30.3, 31.6, 36.2, 40.5, 42.1, 42.3, 45.5, 51.0, 55.7, 56.4, 131.8, 166.7, 216.4. **HRMS**: Calcd [M+1] for $C_{13}H_{18}O$: 205.1592; Found: 205.1583. **FTIR** (film): 2930, 2856, 1703, 1641 cm^{-1}. **MP:** 69-70 °C.

(**^{1}H** and **^{13}C NMR** Spectra on following page)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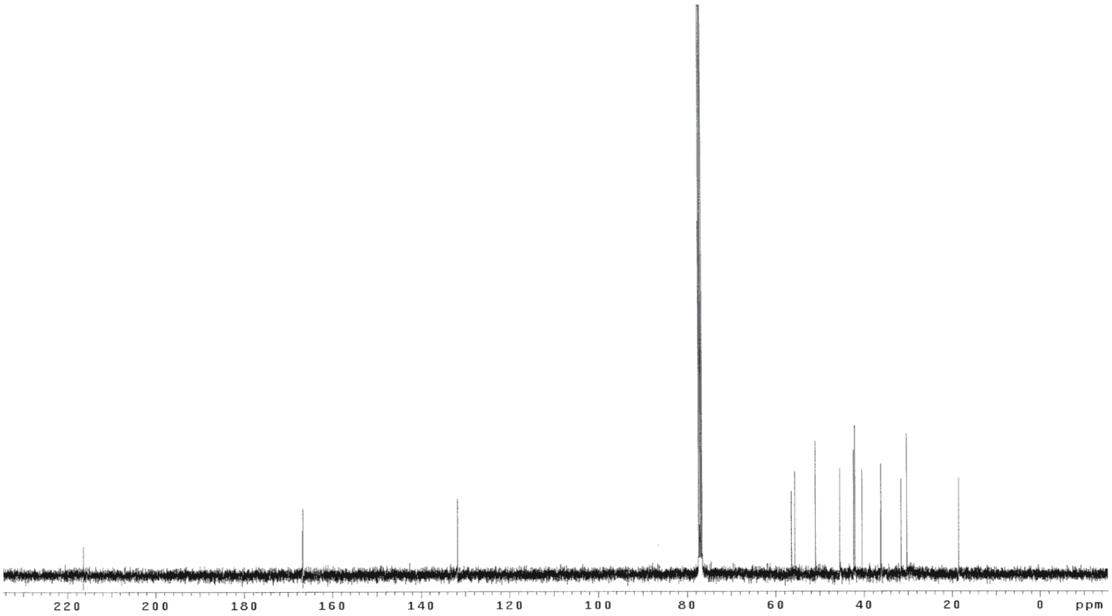
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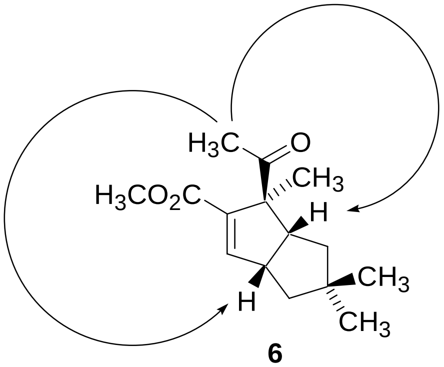
II. Determination of Cycloadduct Stereochemistry.

The stereochemistry of **6** is established by its conversion to the known enone **8**. To further corroborate our stereochemical assignment, **6** and ***epi*-6** were subjected to GOESY analysis. The results are shown below.



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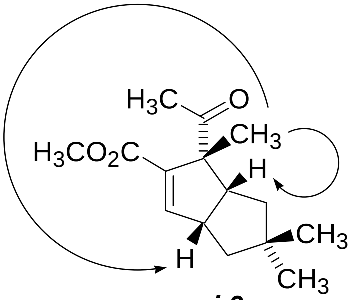

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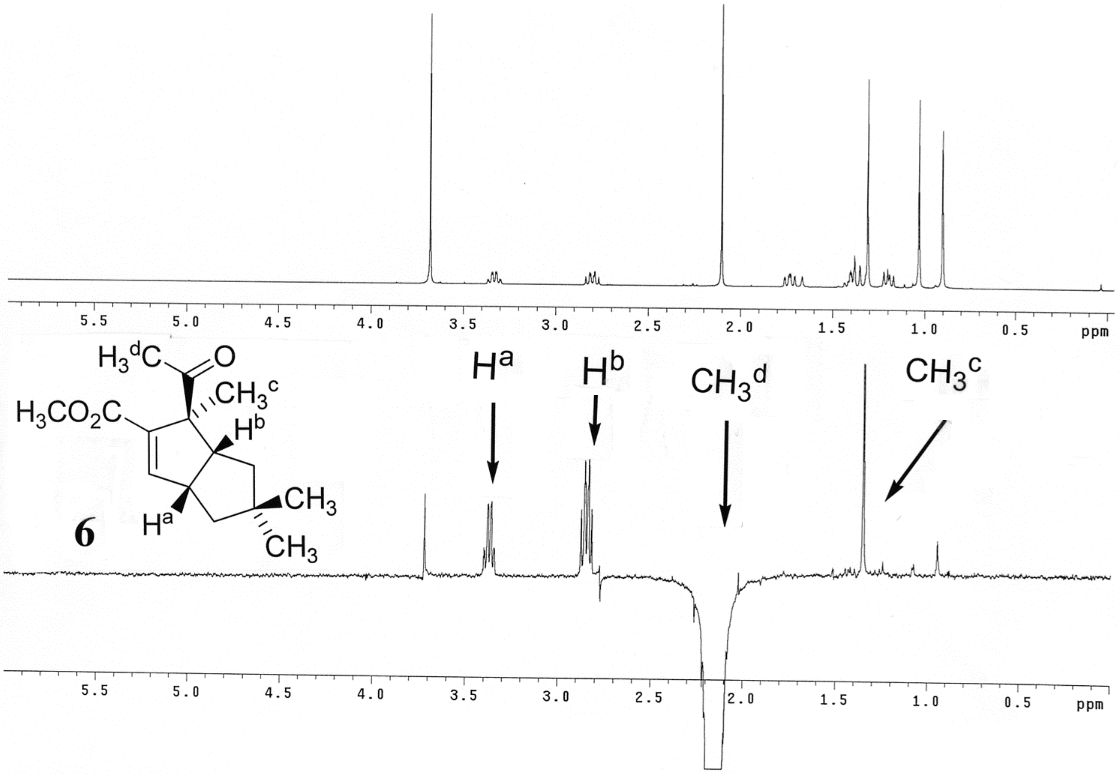

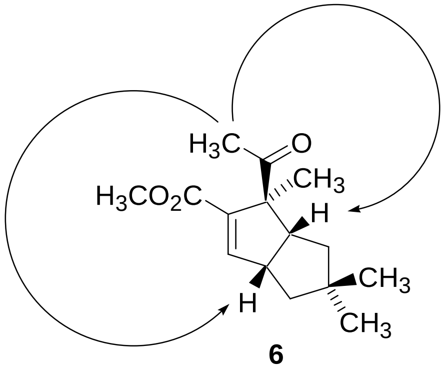

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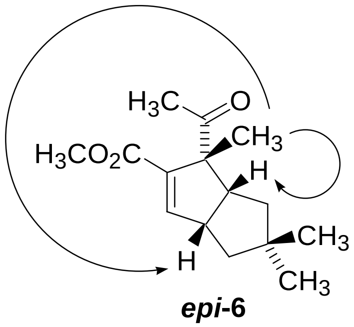

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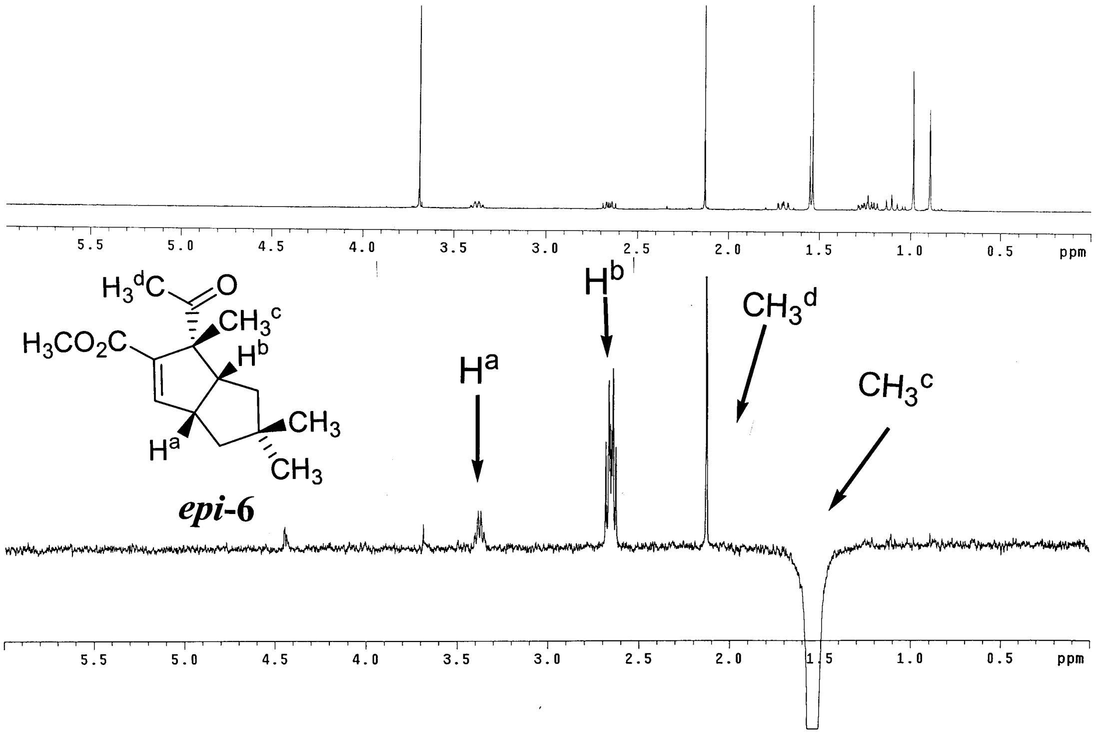
H
CH3

***epi*-6**



5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
H3dC
O
CH3c
H3CO2C
Hb
Ha
CH3
CH3
epi-6
Hb
Ha
CH3d
CH3c
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm