

Supporting Information for

Ti(III)-Catalyzed radical cyclization of epoxy enones. Total synthesis of (+)-paeonisuffrone.

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GENERAL METHODS

Deoxygenated solvents were used for all reactions promoted or catalysed by Cp_2TiCl . THF was freshly distilled from Na and benzophenone ketyl and was degassed before use; ethyl acetate and methylene chloride were freshly distilled from CaH_2 . Methanol was distilled from Mg under argon. All reactions were conducted under a positive pressure of argon, using standard bench-top techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel 50 (eluents are given in parentheses). R_f values refer to TLC carried out on 0.25 mm silica gel plates with the same eluent as indicated for the flash column chromatography unless otherwise indicated. Reported yields refer to chromatographically pure isolated products. IR were recorded using a FTIR spectrometer and optical rotations were measured on a digital polarimeter. NMR spectra were recorded either on a 200 MHz or a 400 MHz spectrometer in CDCl_3 and referenced to TMS (^1H) or the solvent used (^{13}C), except where stated otherwise. Low-resolution electron impact mass spectrum data (MS-EI) were obtained at 70 eV, unless otherwise stated. HRMS were recorded on a quadrupole spectrometer, with positive electrospray ionization (3.5 kV). The preparation of epoxy enones **6** and **7a-b** was achieved by trivial manipulations of the allylic alcohol **5**.¹⁵ In all cases, the epoxydation step led to mixtures of diastereomers at C-8. (Only the major isomers are described in the supporting information).

EXPERIMENTAL PROCEDURES

(+)-(5S)-8,9-epoxy-10-hydroxy-carvone **6**

A solution of **5**¹⁵ (1g, 6 mmol) in 35 mL of dichloromethane was placed in a two-necked 250 mL round-bottomed flask equipped with a magnetic stirrer under argon atmosphere. Then, Na_2CO_3 (1g, 9 mmol) and mCPBA (1.6g, 9.0 mmol) were added and the reaction mixture was vigorously stirred for 24h. The solids were filtered and washed with dichloromethane (3x25 mL) and the filtrate was washed with NaHSO_3 (10%), NaHCO_3 (sat.) and NaCl (sat.). The organic phase was dried with anhydrous Na_2SO_4 and the solvent was removed at reduced pressure to afford a residue, which was fractionated by flash column chromatography. By elution with hexane-ethyl acetate (1: 3), the epoxy alcohol **6** was obtained (0.65g, 60%) as a yellow oil. R_f = 0.20 (hexane-ethyl acetate 6:4); $[\alpha]_D^{20}$ 49.2 (c = 1.5, CHCl_3); IR (neat) ν : 3472, 2926, 2891, 1738, 1713, 1672, 1433, 1370, 1165, 1109, 1049 cm^{-1} . ^1H NMR (CDCl_3) δ : 1.73 (s, 3H), 2.00-2.75 (m, 5H); 2.80-3.00 (m, 2H), 3.52-4.00 (m, 2H); 6.70 (s, 1H) ppm. ^{13}C NMR (CDCl_3) δ = 15.4, 28.0, 36.8, 39.3, 48.5, 60.6, 62.2, 135.5, 143.8, 198.4 ppm. MS (EI) (m/z , %): 182 (M^+ , 2); 164

(3.5), 151 (10); 108 (100), 82 (64); 67 (17). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91, H, 7.74. Found C, 65.76, H, 7.92.

Preparation of epoxy enone **7a**

A solution of **6** (0.5g, 2.75 mmol) in 3 mL of freshly distilled tetrahydrofuran was placed in a two-necked 100 mL round-bottomed flask equipped with a magnetic stirrer under argon atmosphere. Then, the addition of diisopropylethylamine (0.85 mL, 4.85 mmol) was followed by dropwise addition of benzylchloromethyl (BOM) ether (0.6 mL, 4.12 mmol) and tetrabutyl ammonium iodide (0.1g, 0.3 mmol). The reaction mixture was stirred for four days at room temperature. Methanol (2 mL) was added and stirring was continued for one hour. Then, 10 mL of mixture of ethyl: acetate (1:1) was added and the organic layer was washed with $NaHSO_3$ (5%), sodium phosphate buffer (pH: 7) and sodium chloride (sat.). The organic phase was dried with Na_2SO_4 and the solvent evaporated at reduced pressure to afford a crude which was fractionated by flash column chromatography on silicagel. By elution with hexane-ethyl acetate (6:4) **7a** was obtained (0.518 g, 62%) as a yellow oil. R_f = 0.50 hexane-ethyl acetate (1:1); $[\alpha]_D^{20}$ -13.7 (c = 1.27, $CHCl_3$); IR ν (film) = 3445, 2930, 1665, 1439, 1378, 1107, 1042, 829, 740 cm^{-1} . 1H NMR δ ($CDCl_3$): 1.77 (s, 3H), 2.10-2.70 (m, 5H), 2.71 (m, 2H), 3.50-3.80 (m, 2H), 4.60 (s, 2H), 4.67 (d, J=14.5Hz, 1H), 4.79 (d, J=14.5Hz, 1H), 6.73 (s, 1H), 7.34 (m, 5H) ppm. ^{13}C NMR δ ($CDCl_3$): 15.6, 26.5, 38.0, 38.7, 46.1, 69.1, 70.3, 74.0, 95.5, 127.1, 128.1, 128.6, 135.4, 141.2, 144.7, 199.5 ppm. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50, H, 7.33. Found C, 71.26, H, 7.58. HRMS-EI ($M^+ + Na$) calcd for $C_{18}H_{22}O_4Na$: 325.1410. Found: 325.1408.

Preparation of epoxy enone **7b**

A solution of **6** (0.364 g, 2 mmol) and pyridine (0.2 mL, 2.4 mmol) in 2 mL of dichloromethane was placed in a two-necked 50 mL round bottomed flask equipped with a magnetic stirrer under argon atmosphere. Then, pivaloyl chloride (0.3 mL, 2.3 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred under an argon atmosphere at room temperature for 20h. The reaction mixture was diluted by the addition of dichloromethane, and the organic phase was washed with 0.5M HCl, $NaHCO_3$ (sat.), dried with Na_2SO_4 , and evaporated under reduced pressure to afford a crude, which was fractionated by flash column chromatography on silica gel. By elution with hexane-ethyl acetate (1:1) led to the isolation of **7b** (0.266 g, 50%) as a colorless oil. R_f = 0.50 hexane-ethyl acetate (1: 1); $[\alpha]_D^{20}$ -17.63 (c 1.7, $CHCl_3$); IR ν = 3460, 2974, 1733, 1674, 1482, 1281, 1154, 1037, 906, 757 cm^{-1} . 1H NMR δ

CDCl₃: 1.22 (s, 9H), 1.78 (s, 3H), 2.3-2.6 (m, 5H), 3.60 (m, 2H); 4.00-4.35 (m, 2H), 6.65 (s, 1H) ppm. ¹³CNMR δ (CDCl₃): 15.4, 26.1, 27.0 (3x), 38.0, 38.7, 46.4, 58.3, 64.3, 73.8, 135.2, 144.2 (d), 178.3, 198.9 ppm. Anal. Calcd for C₁₅H₂₂O₄: C, 67.64, H, 8.33. Found C, 67.87, H, 8.62. HRMS-EI: (M⁺ Na) Calcd for C₁₅H₂₂O₄Na: 289.1410. Found: 289.1419.

Synthesis of diols **8a** and **9a**.

The experimental procedure described in the Experimental Part for the preparation of **8b** and **9b**, was followed.

Method A: Starting from **7a** (0.150 g, 0.50 mmol), a crude product was obtained, which was fractionated by flash column chromatography on silica gel. After evaporation of the solvent, elution with hexane-ethyl acetate (7:3) yielded, **8a** (39.5 mg, 26%) and **9a** (36.0 mg, 24%).

Method B: Starting from **7a** (160 mg, 0.53 mmol), a crude product was obtained, which was fractionated by flash column chromatography on silica gel. After evaporation of the solvent, elution with hexane-ethyl acetate (8:2) yielded, **8a** (40 mg, 23.5%) and **9a** (39 mg, 23.5%).

Diol 8a *R*_f = 0.50 hexane-ethyl acetate (1: 1); [α]_D²⁰ +8.7 (c= 0.825, CHCl₃); IR (film) ν: 3417, 2940, 2885, 1713, 1454, 1379, 1213, 1167, 1109. 1041 cm⁻¹. ¹HNMR (CDCl₃) δ= 1.68 (d, J= 8.6 Hz, 1H); 1.81 (s, 3H); 2.0-2.3 (m, 5H), 2.33 (t, J= 8.6 Hz, 1H); 3.68 (d, J= 11Hz, 1H); 3.81 (d, J= 11Hz, 1H); 4.07 (d, J= 10Hz, 1H); 4.21 (d, J= 10Hz, 1H); 4.63 (m, 2H); 4.83 (m, 2H); 5.28 (s, 1H); 7.35 (m, 5H) ppm. ¹³CNMR (CDCl₃) δ= 16.9, 30.3, 30.7, 39.6, 50.0, 62.6, 70.0, 71.5, 77.5, 95.2, 117.2, 127.8, 127.9, 128.5, 137.4, 145.9 (s) ppm. Anal. Calcd for C₁₈H₂₄O₄: C, 71.03, H, 7.95. Found C, 71.38, H, 8.14. HRMS-EI (M⁺ + Na) Calcd for C₁₈H₂₄O₄Na: 327.1567. Found: 327.1561.

Diol 9a *R*_f = 0.25 hexane-ethyl acetate (1: 1); [α]_D²⁰ +15.16 (c= 0.31, CHCl₃); IR (film) ν: 3416, 2924, 2853, 1714, 1454, 1379, 1238, 1210, 1167, 1107, 1040, 740, 699 cm⁻¹. ¹HNMR (CDCl₃) δ= 1.68 (d, J= 7 Hz, 1H), 1.80 (s, 3H); 1.9-2.3 (m, 5H); 2.45 (t, J= 7Hz, 1H); 3.6 (d, J= 10 Hz, 1H); 4.0 (d, J= 10 Hz, 1H); 4.15 (d, J= 12 Hz, 1H); 4.27 (d, J= 12 Hz, 1H); 4.57 (d, J= 12 Hz, 1H); 4.61 (d, J= 12 Hz, 1H); 4.59 (d, J= 6Hz, 1H); 4.61 (d, J= 6Hz, 1H); 5.26 (s, 1H); 7.4 (m, 5H). ppm. ¹³CNMR (CDCl₃) δ= 17.0, 30.3, 30.9, 40.3, 48.3, 67.8, 69.7, 69.8, 78.1, 95.2, 117.1, 127.8, 127.8, 128.5, 137.5, 146.0 ppm. Anal.

Calcd for $C_{18}H_{24}O_4$: C, 71.03, H, 7.95. Found C, 71.28, H, 8.06. HRMS-EI ($M^+ + Na$) Calcd for $C_{18}H_{24}O_4Na$: 327.1567. Found: 327.1562.

Cyclization of **7a** and **7b** with the addition of TEA:

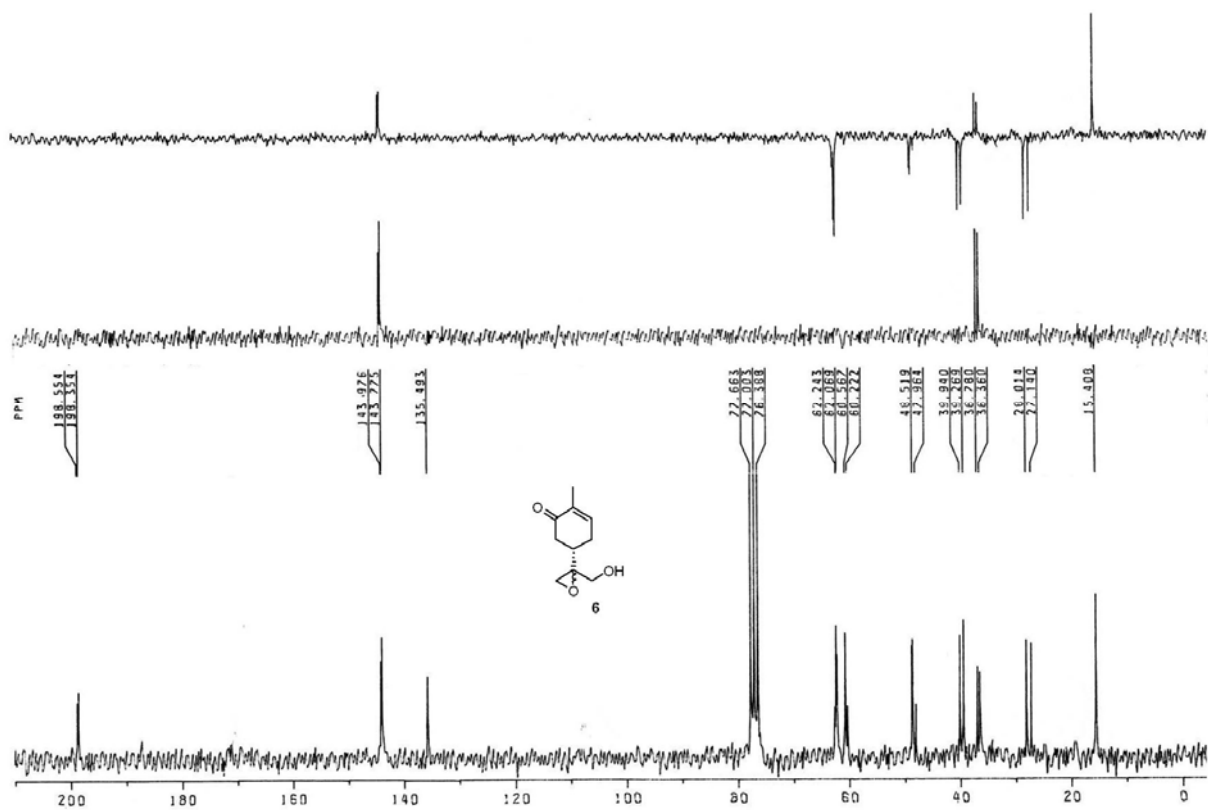
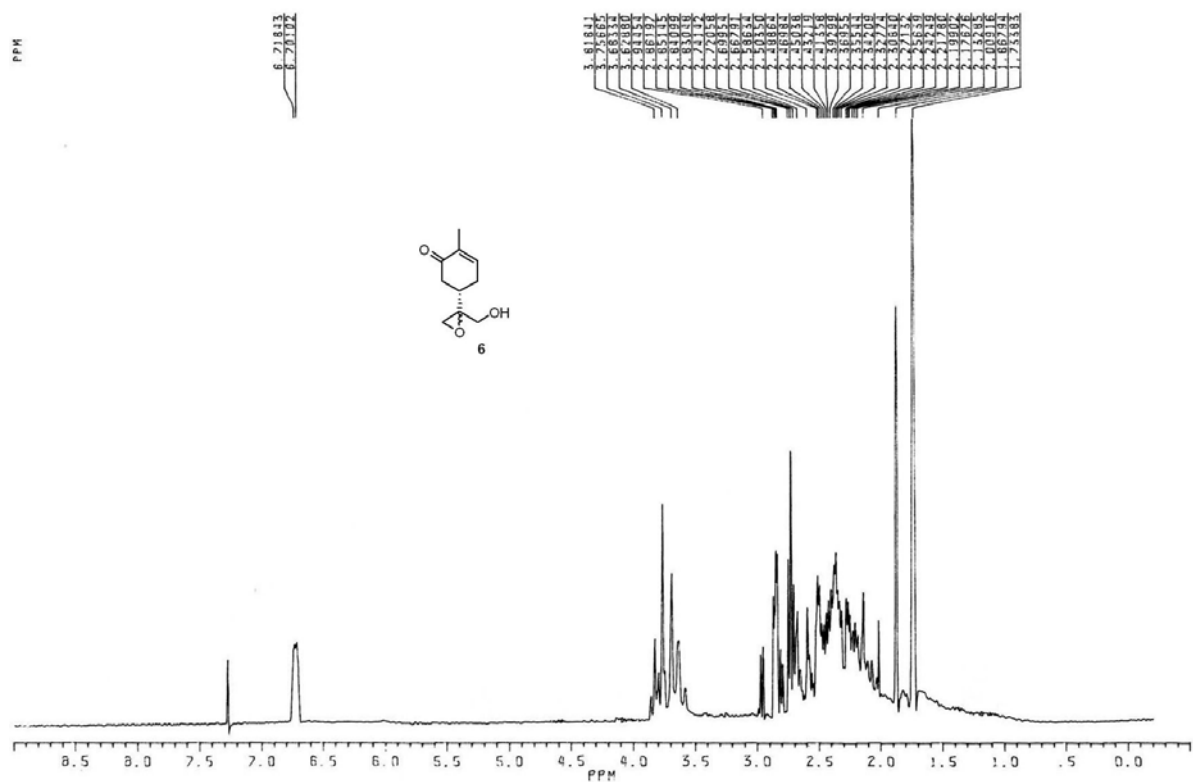
Method A was followed. Solution B was prepared as described in the *General Procedure* (Experimental Part), except that triethylamine (0.5 ml, 3 mmol) was added dropwise before the addition of solution A to solution B. Starting from **7a** (150 mg, 0.5 mmol), a crude product was obtained, which was fractionated by flash column chromatography on silica gel. After evaporation of the solvent, elution with hexane-ethyl acetate (8:2) yielded, **8a** (33.5 mg, 22.5%) and **9a** (33.5 mg, 22.5%). Starting from **7b** (250 mg, 0.94 mmol), a crude product was obtained, which was fractionated by flash column chromatography on silica gel. After evaporation of the solvent, elution with hexane-ethyl acetate (9:1) yielded, **8b** (93 mg, 37%) and **9b** (53.5 mg, 21%).

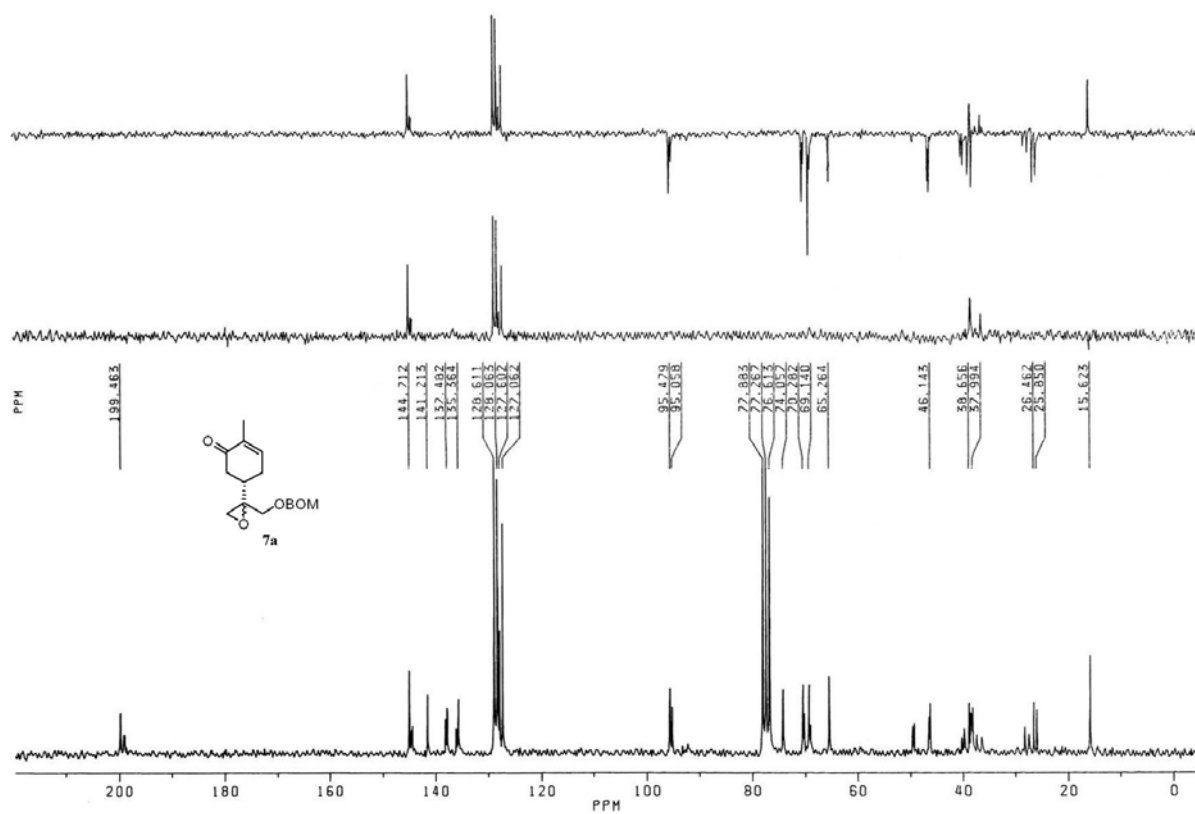
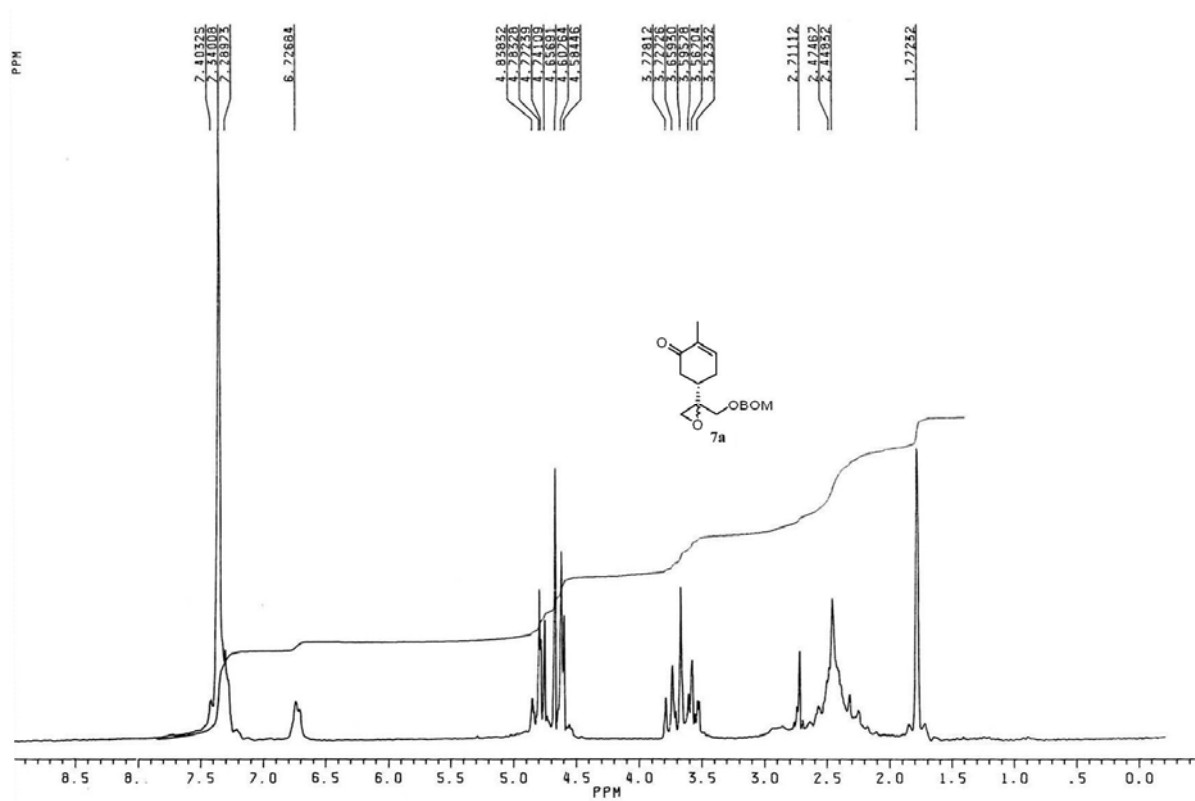
Ti-catalyzed cyclization of **7a** and **7b**

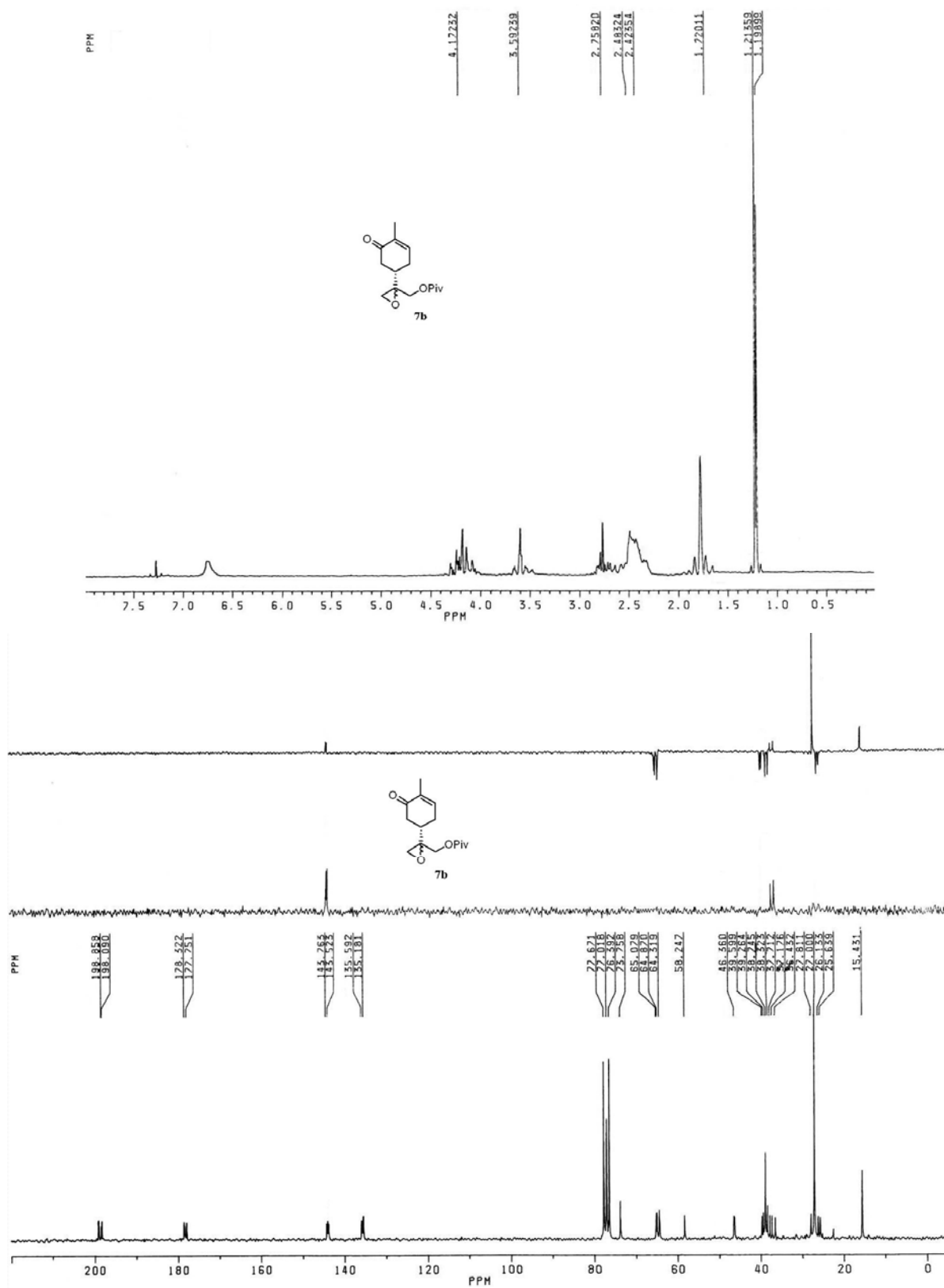
Deoxygenated THF (10mL) was added to a mixture of Cp_2TiCl_2 (50 mg, 0.2 mmol) and Mn dust (440 mg, 8 mmol) under an argon atmosphere, and the reaction mixture was stirred at room temperature until it turned green (15 min). A solution of epoxy pivalate (1 mmol) and 2,4,6-collidine hydrochloride (945 mg, 6 mmol) in THF (2.5 mL) was added, and the reaction mixture was stirred at room temperature for 20h (**7a**) and 24h (**7b**). Brine was added and the mixture was extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield a crude, which was subjected to flash column chromatography on silica gel. Starting from **7a** (0.302g, 1 mmol), the elution of the crude reaction product with hexane-ethyl acetate (8:2) yielded **8a** (75 mg, 25%) and **9a** (62 mg, 20%). Starting from **7b** (266 mg, 1 mmol), the elution of the crude reaction product with hexane-ethyl acetate (9:1) yielded **8b** (124 mg, 46%) and **9b** (50 mg, 19%).

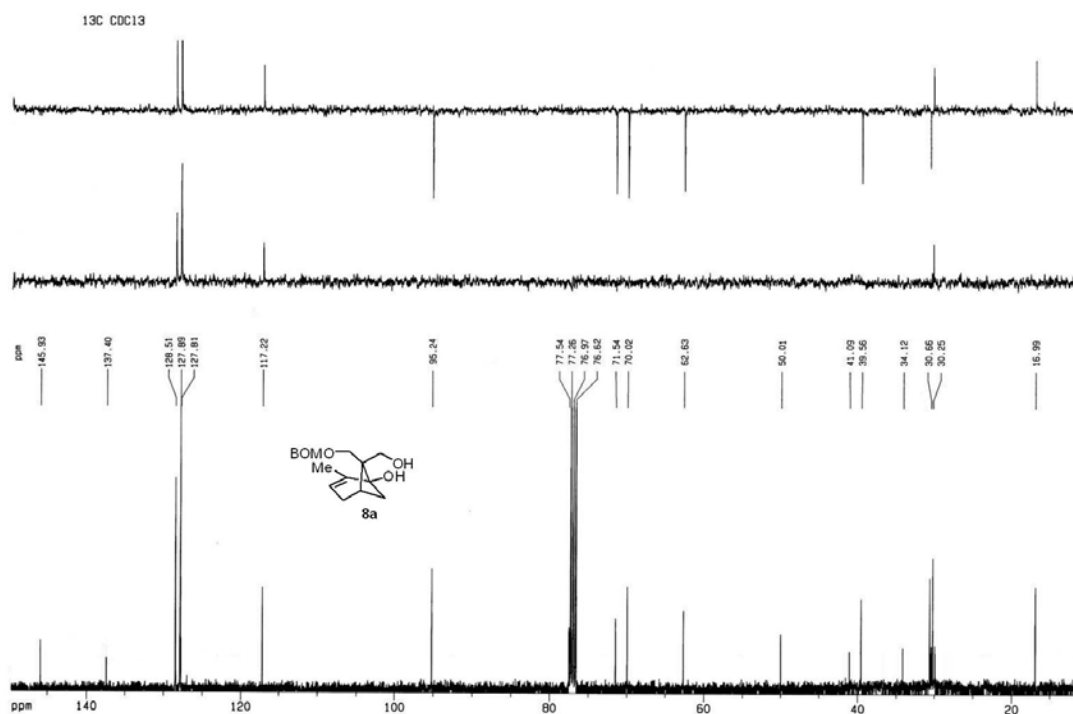
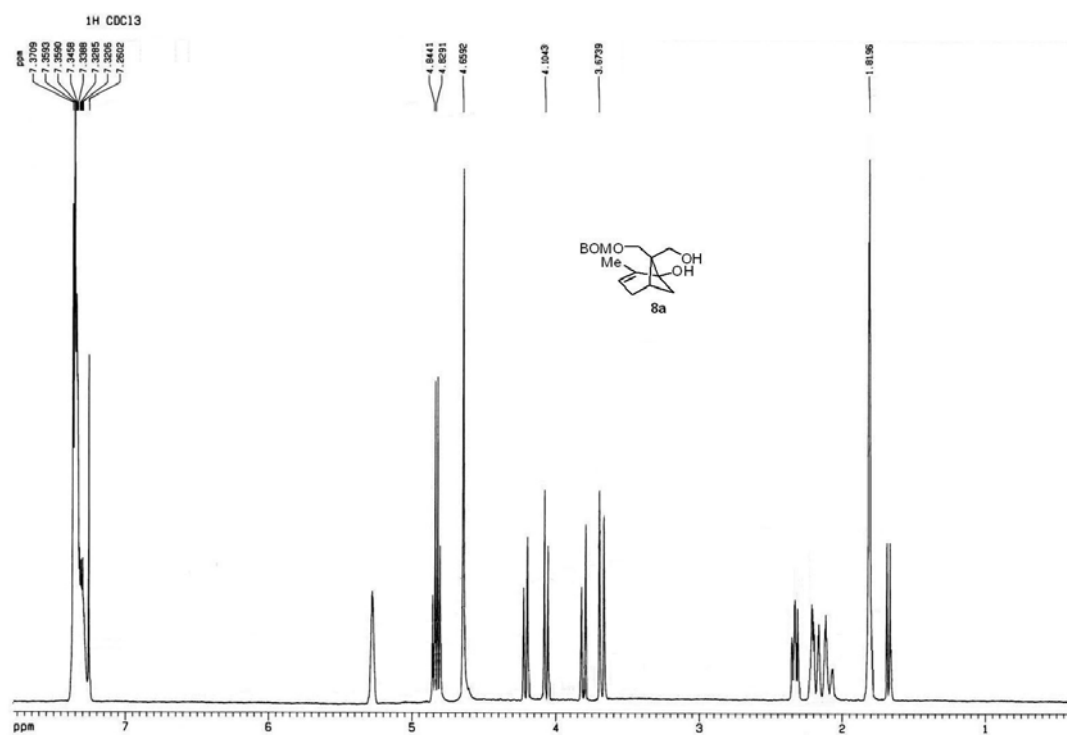
SPECTRAL DATA

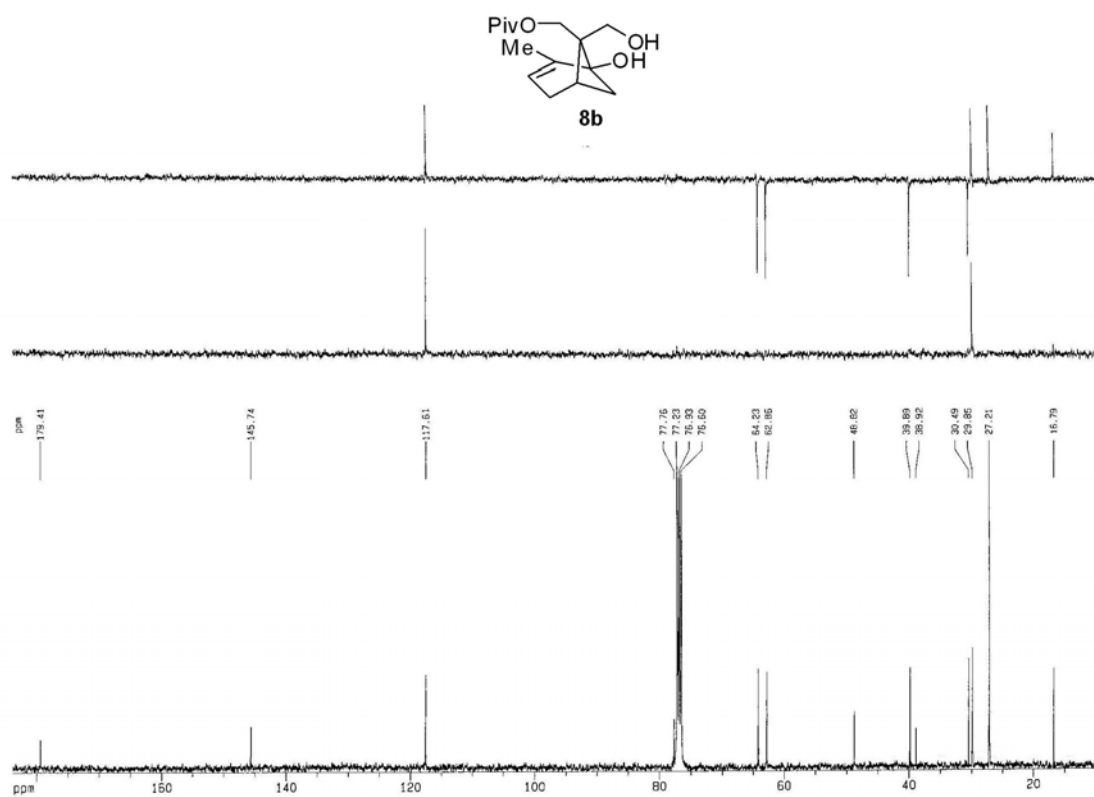
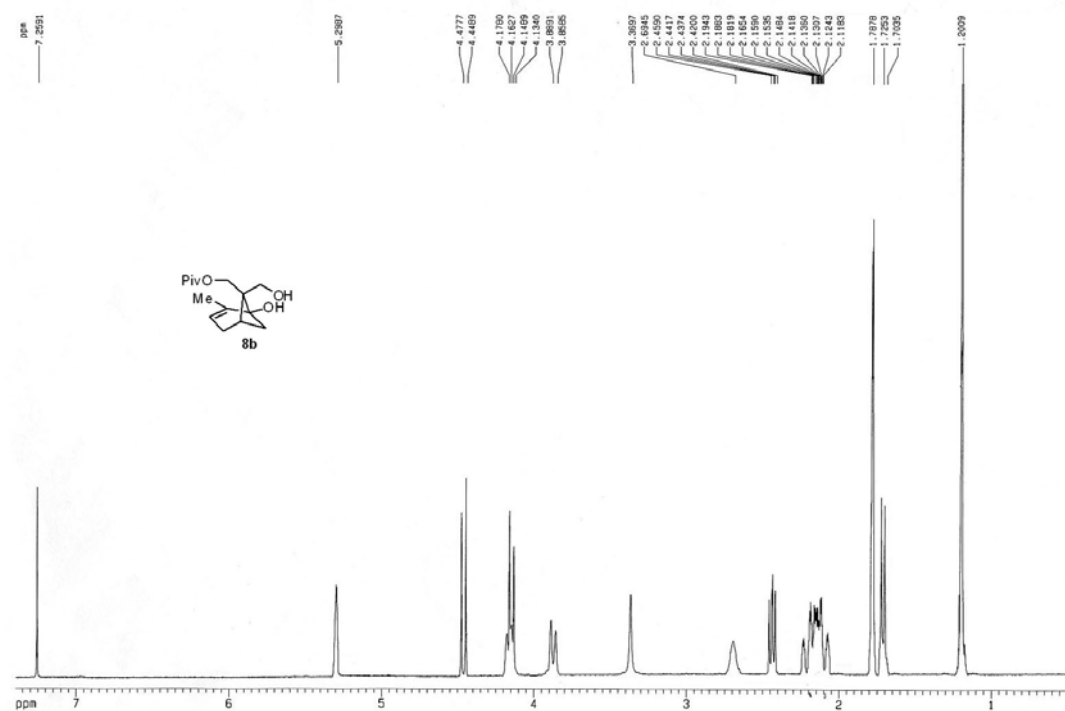
Spectral data for mixtures of diastereomers **6**, **7a**, **7b**, and products **8a**, **9a**, **8b**, **9b**, **10**, **11**, **12**, **13** **14** and **4** are given (17 pages).

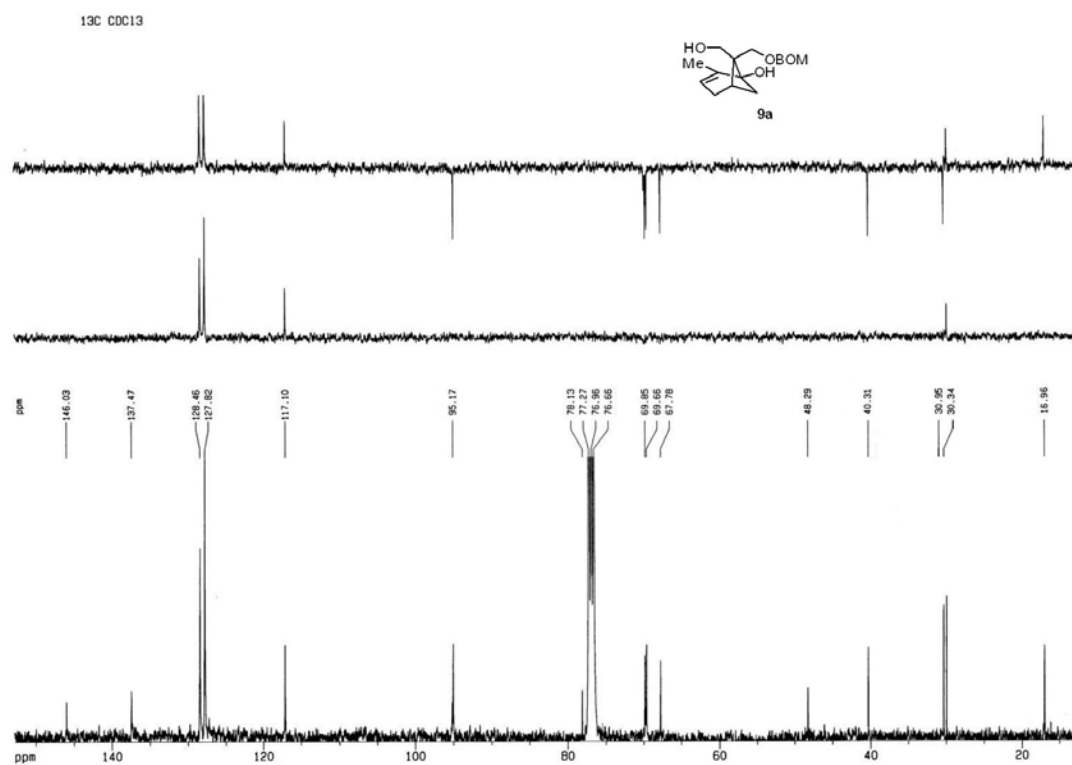
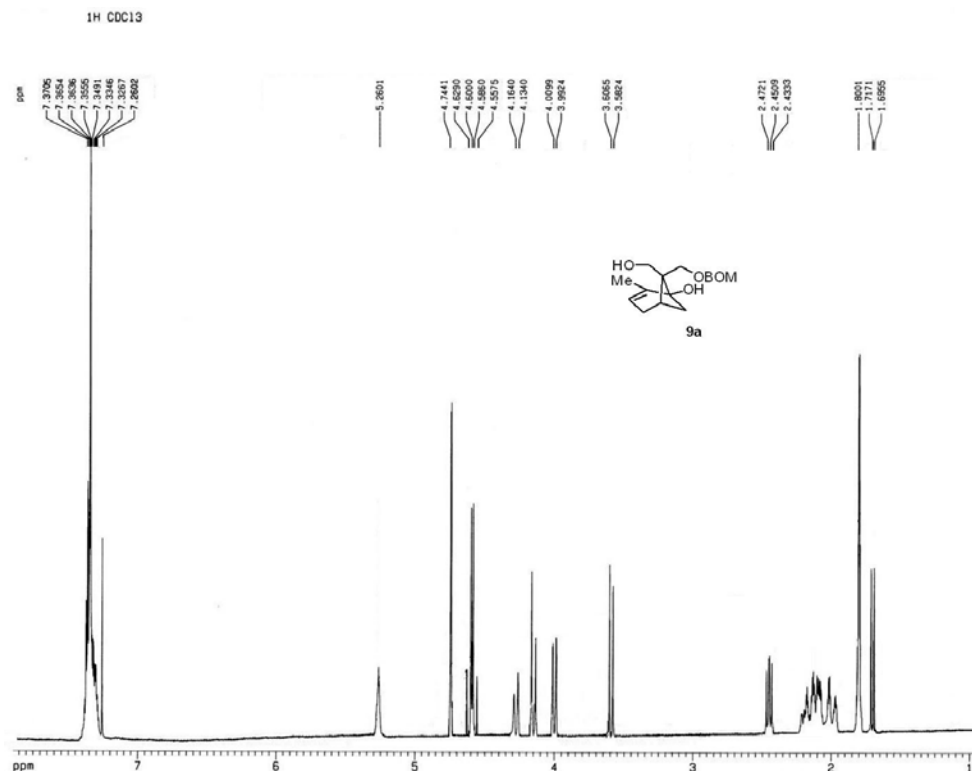


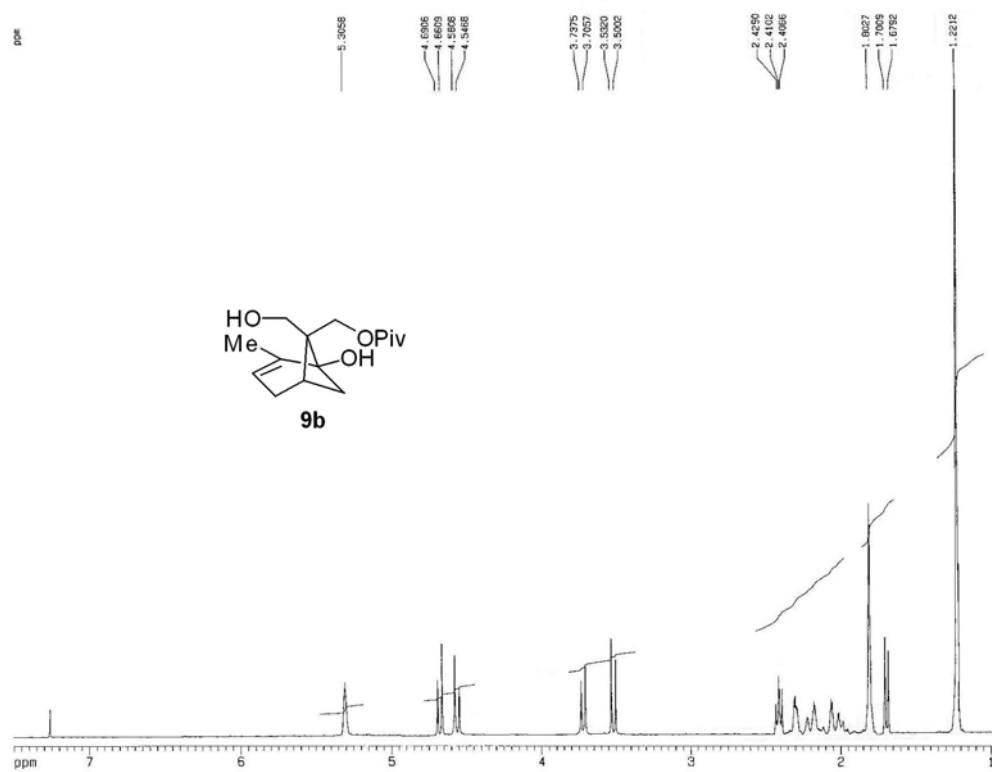




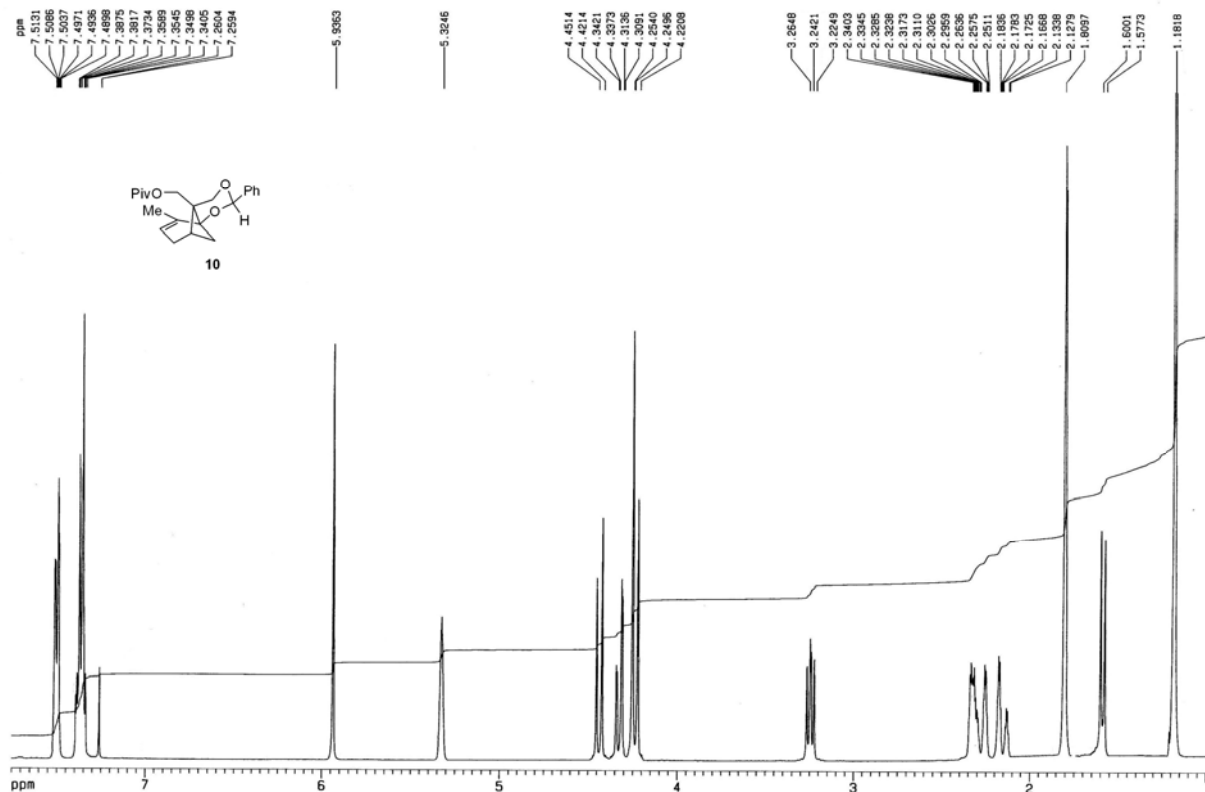




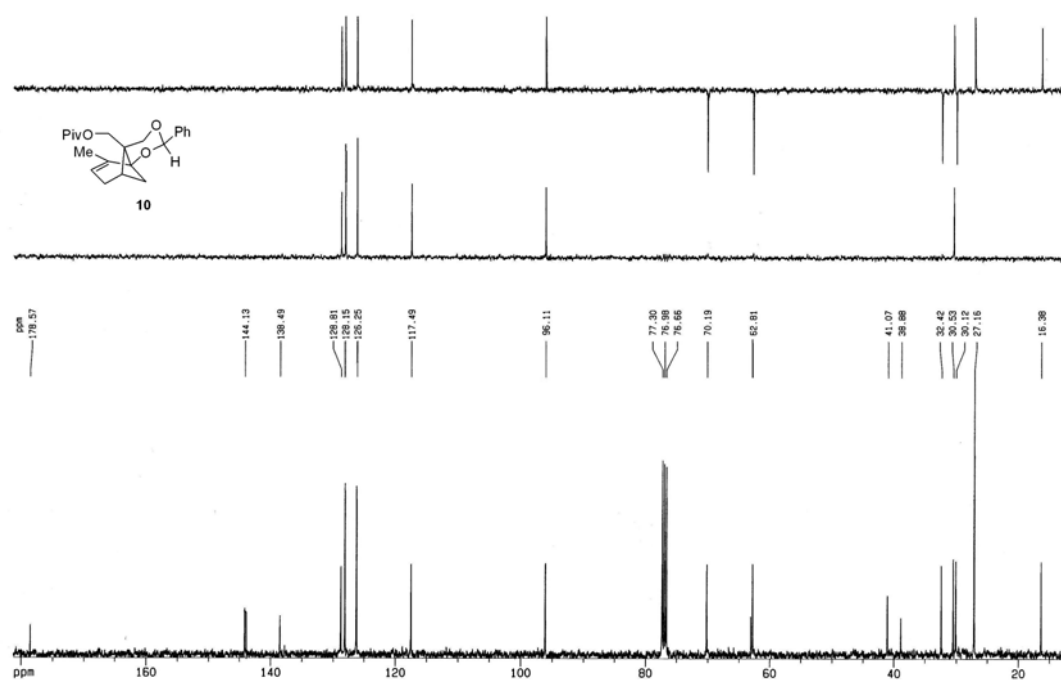




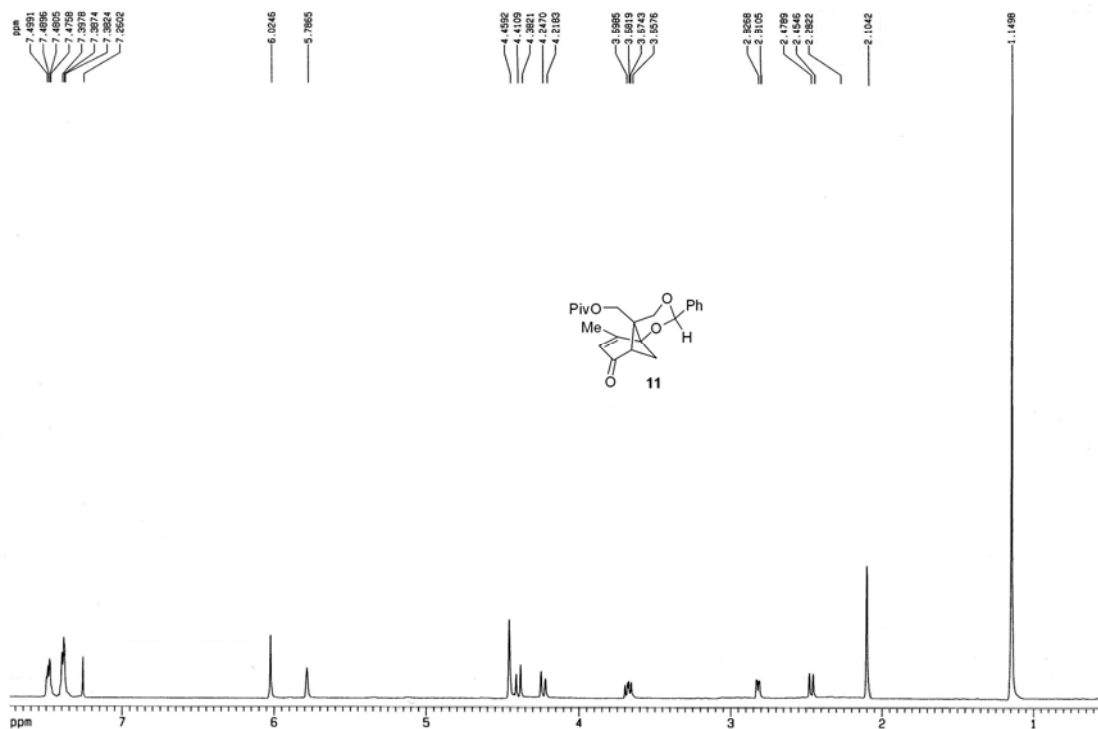
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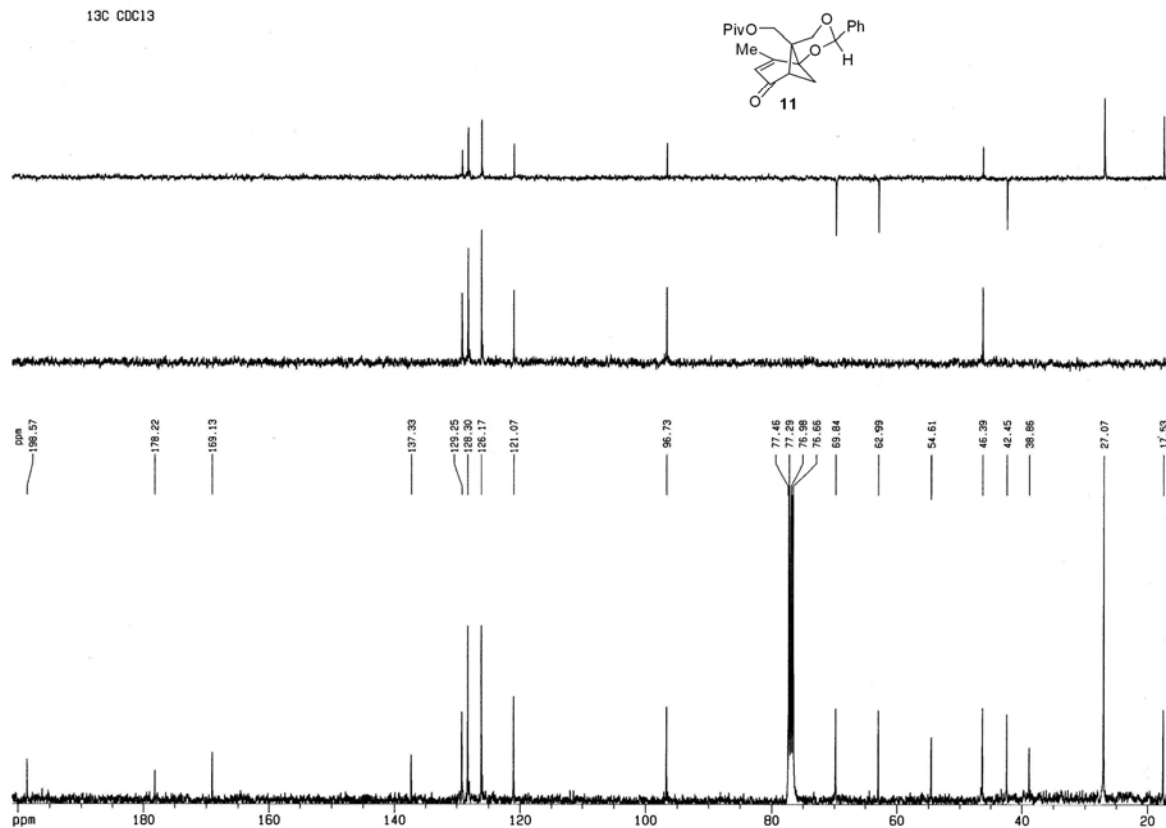
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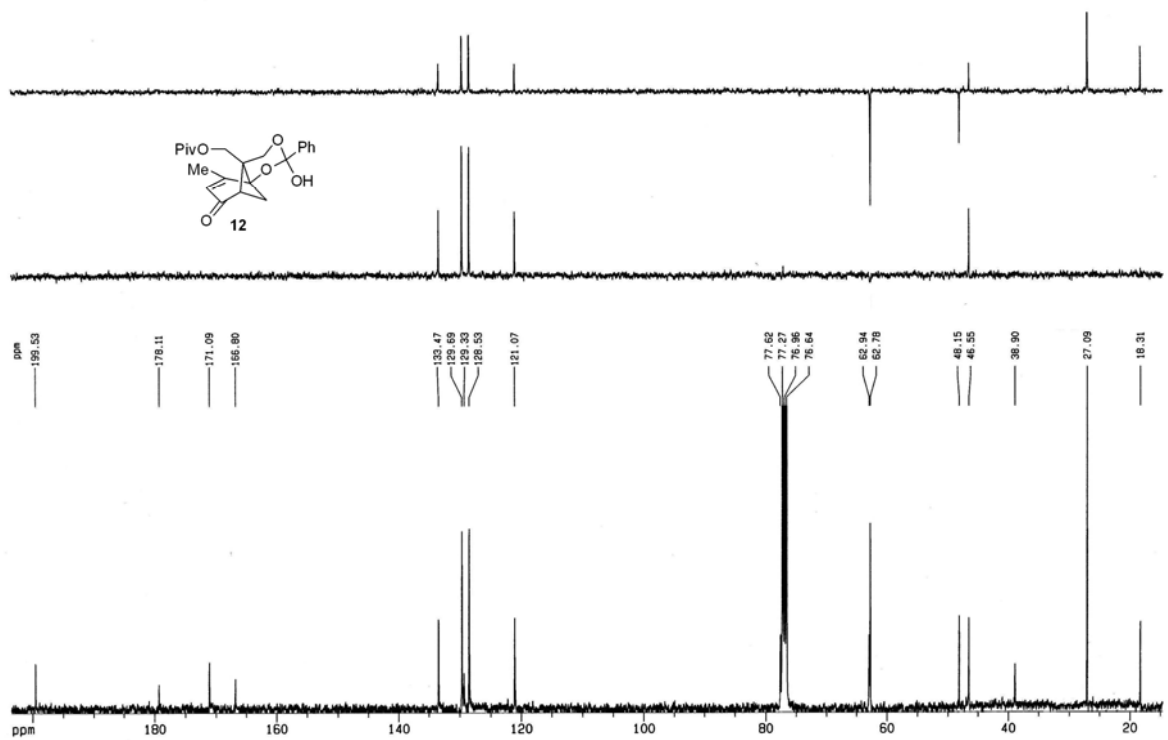
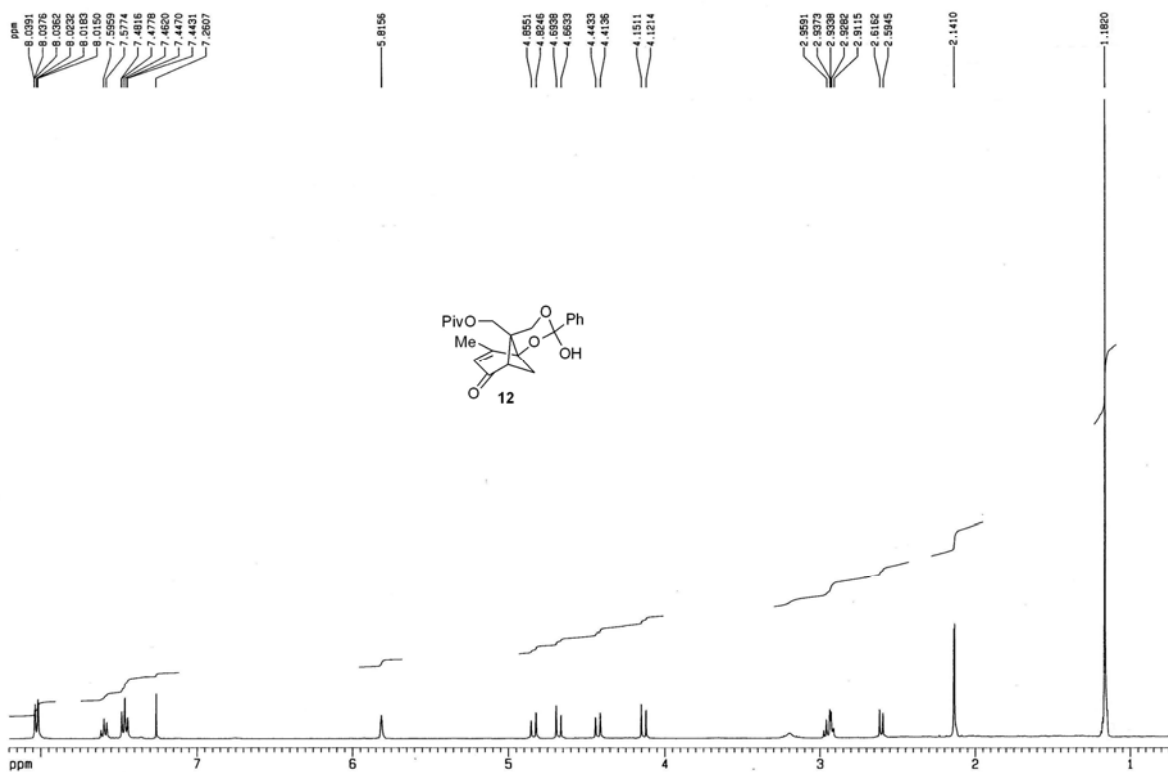
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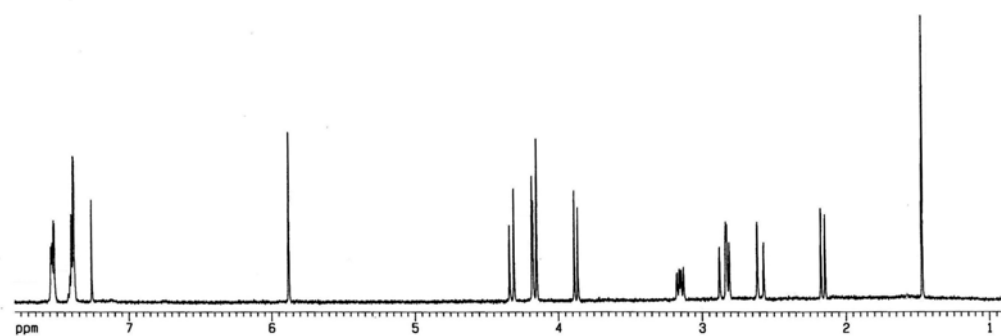
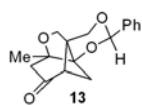
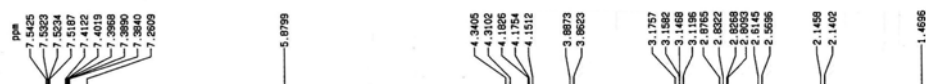
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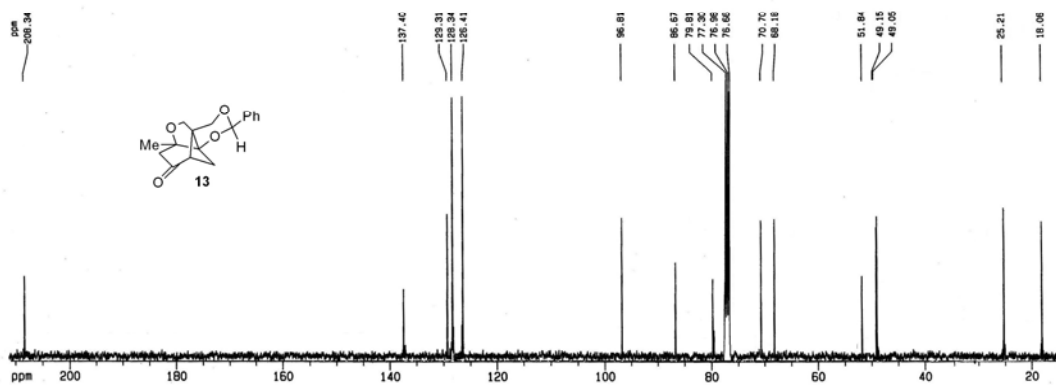
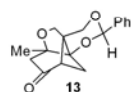
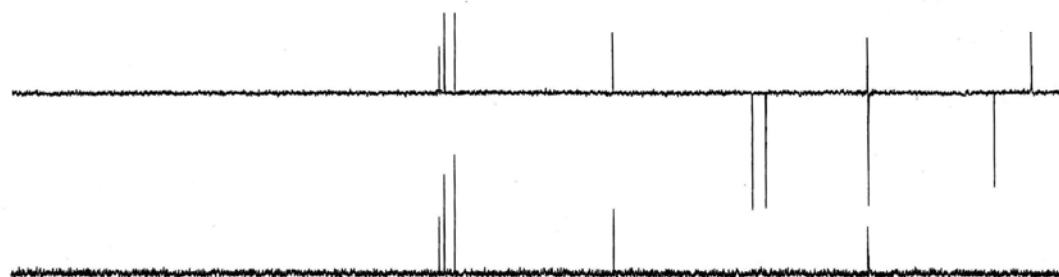
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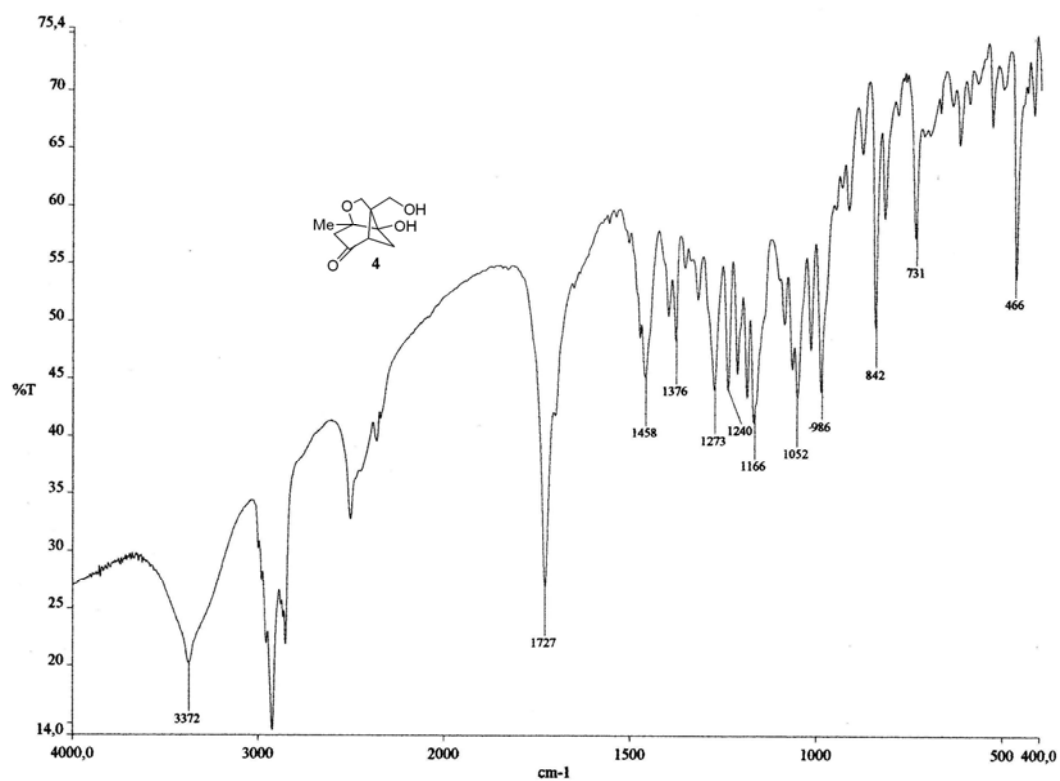


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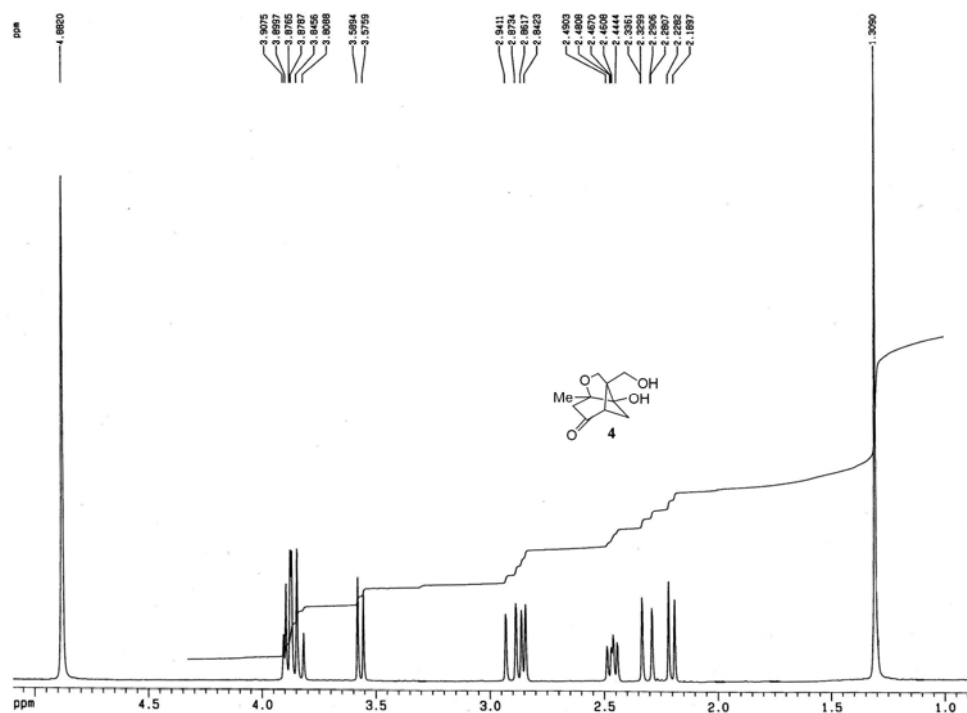


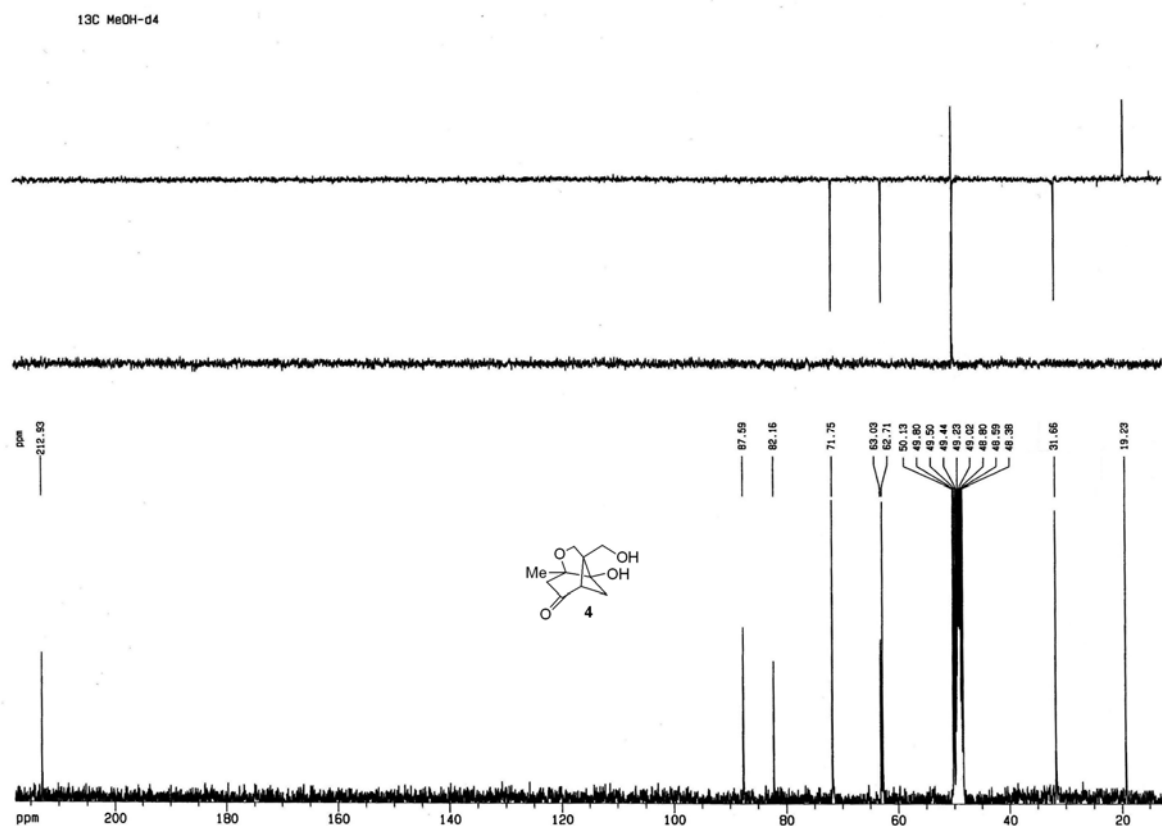
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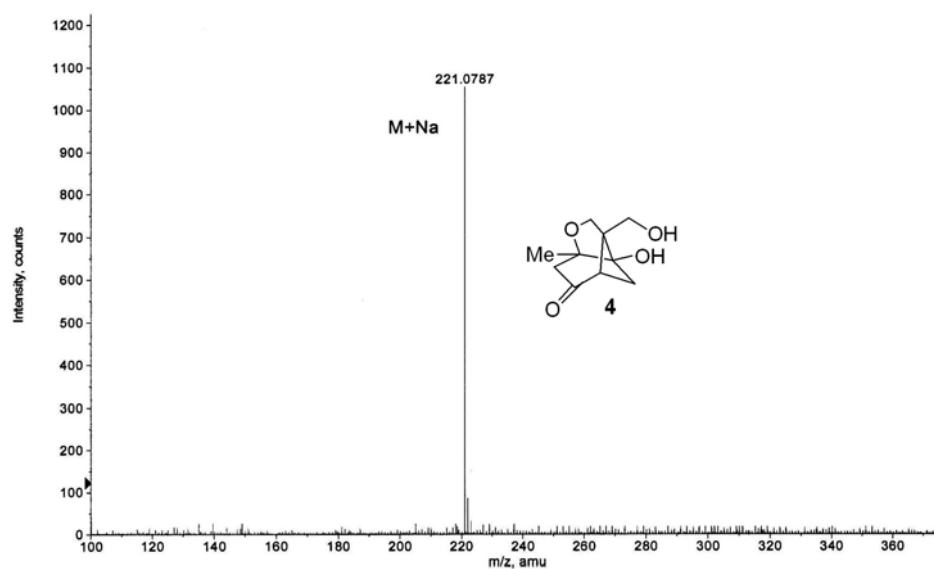
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