Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

A Concise Approach to Vinigrol

Thomas J. Maimone, Ana-Florina Voica, and Phil S. Baran*

Contribution from the Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

SUPPORTING INFORMATION

General Procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), triethylamine (TEA), dichloromethane (DCM), and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. $Pd(PPh_3)_4$ was prepared fresh according to standard procedures. Trifluoromethanesulfonic anhydride (Tf_2O) was freshly distilled from P_2O_5 before use. Commercial *m*-CPBA (~ 70%) was purified prior to use (see *JACS*, **2007**, *129*, 12896). LiCl was dried in an oven for 24 hours before use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and *p*-anisaldehyde in ethanol/aqueous H_2SO_4/CH_3CO_2H and heat as developing agents. NMR spectra were recorded on a Bruker DRX 600, DRX 500, or an AMX 400 spectrometer and were calibrated using residual solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR, C_6D_6: 7.16 ppm for ^{1}H NMR and 128.06 ppm for ^{13}C NMR). The following

abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer Spetrum BX spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points (m.p.) are uncorrected and were recorded on a Fisher-Johns 12-144 melting point apparatus. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.

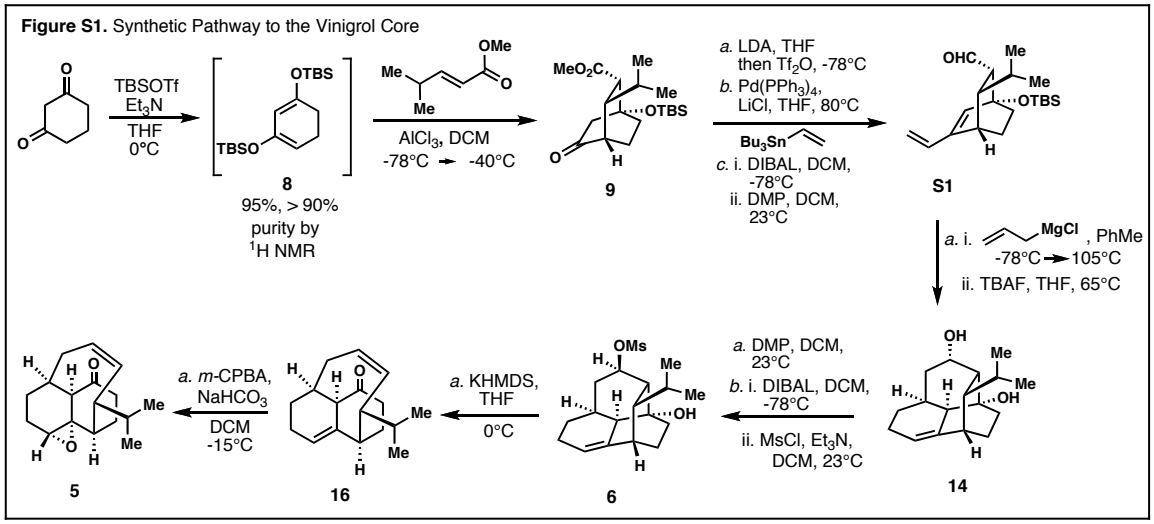


Figure S1. Synthetic Pathway to the Vinigrol Core

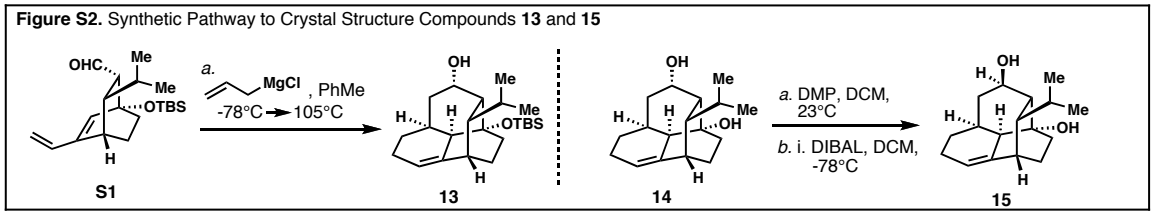
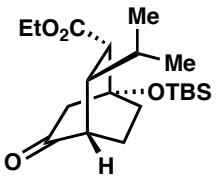


Figure S2. Synthetic Pathway to Crystal Structure Compounds **13** and **15**

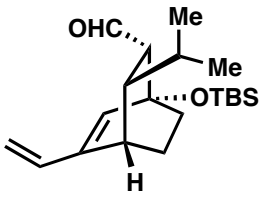


Ketone 9. i. Dry 1,3 cyclohexanedione (1.0 g, 8.9 mmol, 1 equiv) was dissolved in THF (20 ml) and cooled to 0°C. Et_3N (2.6 ml, 18.3 mmol, 2.05 equiv.) was added followed by dropwise addition of TBSOTf (4.1 ml, 17.8 mmol, 2.0 equiv). The mixture was stirred for 2 hours at 0°C, then

concentrated *in vacuo* (at 15°C) to afford a cloudy yellow oil that was redissolved in Et_2O (15 ml) to give a biphasic mixture. Under an atmosphere of N_2, the upper organic layer was transferred to a dry flask. This process was repeated (2X) and the combined organic layers were concentrated *in vacuo* (at 15°C) to give the known diene **8** (2.8 g, purity > 90% by ^{1}H NMR, 95%) as yellow oil which was used in the Diels-Alder reaction without further purification.

ii. A flame dried flask was charged with $AlCl_3$ (447 mg, 3.35 mmol, 1.5 equiv.) in DCM (12.5 ml) and cooled to –78°C. Methyl 4-methyl-2-pentenoate (286 mg, 2.23 mmol, 1 equiv.) in DCM (9 ml) was added dropwise to the stirring suspension, and the resulting mixture stirred at –78°C for 20 minutes. Diene **8** (1.52 g, 4.46 mmol 2 equiv) in DCM (1.1 ml) was added dropwise, followed by a 0.5 ml DCM rinse. The mixture was stirred at –78°C for 1 hour, then warmed to – 45°C and stirred 3 hours. After 3 hours, the reaction mixture was quenched at –45°C with saturated aqueous $NaHCO_3$ (10 ml) and warmed to room temperature. DCM (50 ml) and saturated aqueous Rochelle's salt (75ml) were added and the mixture was vigorously stirred for 8 hours. The layers were partitioned and the aqueous layer was extracted with DCM (50 ml, 2X). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Flash column chromatography (silica gel, 10:1 hexanes:Et_2O) afforded the bicyclic ketone (506 mg, 64%, ~2:1 mixture of *endo:exo*) as a white solid. *Endo isomer:* TLC (hexanes: Et_2O 4:1 v/v): R_F = 0.32; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.14 (dd, *J* = 2.4, 18 Hz, 1 H), 2.52 (d, *J* = 7.2 Hz, 1 H), 2.37 (s, 1 H), 2.20 (d, *J* = 18.5 Hz, 1 H), 1.90 – 1.95 (m, 1 H), 1.71 – 1.79 (m, 3 H), 1.61 – 1.67 (m, 2 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.2,

175.4, 75.2, 56.0, 51.9, 47.1, 45.1, 44.3, 34.8, 31.1, 25.6, 21.1, 20.7, 18.0, 17.7, -1.9, -2.0; IR (film) ν_{max} 2953, 2856, 2359, 2340, 1732, 1473, 1363, 1327, 1253, 1165, 1130, 836, 775 cm^{-1}; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{19}H_{35}O_4Si$, 355. 2299; found, 355. 2311.



Aldehyde S1: A) Ketone **9** (4.0 g, 11.23 mmol, 1 equiv.) was azeotropically dried with benzene and then dissolved in THF. The solution was cooled to –78°C and a 1.0 M LDA solution (13.5 ml, 1.2 equiv.) was added dropwise to the cooled solution. After stirring 30 minutes, freshly distilled Tf_2O (2.5 ml, 14.9 mmol, 1.3 eq.) was slowly added dropwise over 5 minutes. The solution was stirred for 1 hour at –78°C then slowly warmed to 0°C over approximately 1 hour. After stirring 15 minutes at 0°C, the solution was warmed to room temperature and quenched with a saturated aqueous sodium bicarbonate solution (100 ml) and Et_2O (100 ml). The layers were separated and the aqueous phase was extracted with ether (75 ml, 3X). The combined organic layers were washed with 1N HCl, saturated aqueous NH_4Cl, brine, and dried ($MgSO_4$). Concentration *in vacuo* yielded a yellow oil. Flash column chromatography (silica gel, 50:1 hexanes:Et_2O afforded the corresponding vinyl triflate (4.17 g, 76%, 87% BRSM) as a pale yellow oil as well as recovered starting material (490 mg).

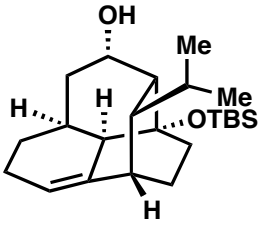
B) Anhydrous LiCl (1.83g, 43.2 mmol, 5 equiv.) was flame dried under high vacuum and allowed to cool under vacuum. The process was repeated three times. $Pd(PPh_3)_4$ (1.0 g, 0.86 mmol, 0.1 equiv.) was then added and the flask was evacuated and then backfilled with argon. The aforementioned vinyl triflate (4.2 g, 8.64 mmol, 1 equiv.) in THF (70 ml), was added, followed by vinyltributyltin (3 ml, 10.27 mmol, 1.2 equiv.). The mixture

was heated to reflux for 3 hours, then cooled to room temperature and partitioned between Et_2O (75 ml) and saturated aqueous NH_4Cl (100 ml). The aqueous layer was extracted with Et_2O (75 ml, 3X) and the combined organic layers were washed with 1N HCL (300 ml, 1X), saturated aqueous $NaHCO_3$ (300 ml, 1X), brine (300 ml, 1X), and dried ($MgSO_4$). The solvent was removed *in vacuo* to give nearly colorless oil. Flash column chromatography (silica gel, gradient from pure hexanes to 50:1 hexanes:Et_2O) gave the corresponding diene (2.83 g, 90%) as a colorless oil.

C) i. The aforementioned diene (2.3 g, 6.07 mmol, 1 equiv.) was azeotropically dried with benzene and then dissolved in DCM (40 ml). The solution was cooled to -78°C and DIBAL (1.5 M solution in toluene, 10ml, 15 mmol, 2.5 equiv.) was added dropwise. After stirring 30 minutes at –78°C the reaction was quenched by dropwise addition of EtOAc (5 ml) followed by saturated aqueous Rochelle's salt (20ml). The mixture was warmed to room temperature, diluted with additional EtOAc (100 ml) and Rochelle's salt solution (100 ml) and stirred for 5 hours. The organic layer was separated and the aqueous layer was thoroughly extracted with EtOAc (50 ml, 3X). The combined organic layers were washed with 1N HCL (250 ml, 1X), saturated aqueous NH_4Cl (250 ml, 1X), brine (250 ml, 1X) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a colorless oil. Flash column chromatography (silica gel, gradient from 30:1 to 10:1 hexanes:Et_2O) gave the corresponding alcohol (1.66 g, 82 %) as a colorless oil which slowly solidified to a waxy solid.

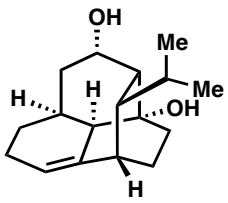
C) ii. The aforementioned alcohol (685 mg, 2.04 mmol, 1 equiv.) was dissolved in wet DCM (20 ml). The Dess-Martin reagent (1.08 g, 2.55 mmol, 1.25 equiv.) was added in one portion to the rapidly stirring solution at room temperature. After TLC analysis

indicated complete consumption of starting material, the mixture was partioned between Et_2O (100 ml) and saturated aqueous $Na_2S_2O_3$ (150 ml) and the aqueous layer was extracted with Et_2O (25 ml, 3X). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (150 ml, 2X), brine (150 ml, 1X), and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow oil. Flash chromatography (silica gel, 20:1 hexanes:Et_2O) gave aldehyde **S1** as a colorless oil (666 mg, 98%); TLC (hexanes:Et_2O, 5:1 v/v): R_F = 0.67; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (d, *J* = 4.0 Hz, 1 H), 6.27 (dd, *J* = 11, 17.5 Hz, 1 H), 6.03 (s, 1 H), 5.27 (d, *J* = 17.5 Hz, 1 H), 5.02 (d, *J* = 10.5 Hz, 1 H), 2.94 (s, 1 H) 2.27 (t, *J* = 4.5 Hz, 1 H), 1.79 – 1.85 (m, 1 H), 1.69 (dt, *J* = 5.0, 11.5 Hz, 1 H), 1.54 (dt, *J* = 4.5, 12.0 Hz, 2 H), 1.24 – 1.27 (m, 1 H), 1.17 – 1.23 (m, 1 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.86 (s, 9 H), 0.11 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 144.4, 134.2, 133.9, 112. 2, 77.9, 66.1, 45.8, 45.8, 35.2, 32.2, 30.2, 25.8, 22.0, 20.9, 20.2, 18.1, -2.0, -2.3; IR (film) ν_{max} 2955, 2358, 1726, 1589, 1471, 1387, 1328, 1251, 1197, 1118, 1085, 1008, 988, 896, 870, 836, 774 cm^{-1}; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{20}H_{35}O_2Si$, 355. 2401; found, 355. 2411.



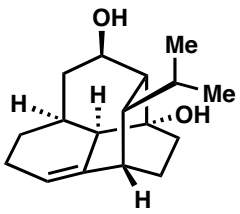
Alcohol 13: Aldehyde **S1** (230 mg, 0.69 mmol, 1.0 equiv.) was dissolved in toluene (6.8 ml) and cooled to –78°C under an atmosphere of argon. Allylmagnesium chloride (1.7 M in THF, 0.41 ml, 0.70 mmol, 1.01 equiv.) was added dropwise at –78°C and the solution was stirred at that temperature for 15 minutes, then warmed to room temperature. After stirring for 5 minutes at ambient temperature, the reaction was heated to 105°C for 90 minutes. Upon cooling, the mixture was partitioned between saturated aqueous NH_4Cl (25 ml) and Et_2O (25 ml) and the aqueous layer was extracted with Et_2O

(15 ml, 3X). The combined organic layers were washed with brine (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a white solid. Flash column chromatography (silica gel, gradient from 25:1 to 15:1 hexanes:Et_2O) afforded the title compound (210 mg, 81%) as a ~ 5:1 mixture of alcohol diastereomers. Preparative thin layer chromatography afforded analytically pure major isomer as a white crystalline solid. Crystallization from cyclohexane yielded white cubes of suitable quality for X–ray diffraction (CCDC# 675356); m.p.: 152-154°C; TLC (hexanes:Et_2O 3:1 v/v): R_F = 0.58; IR (film) ν_{max} 3510, 2929, 2359, 2341, 1471, 1252, 1077, 961, 836 cm^{-1} ; ^1H NMR (600 MHz, $CDCl_3$) δ 5.28 – 5.29 (m, 1 H), 4.54 (d, *J* = 9.6 Hz, 1 H, D_2O exchangeable), 3.54 (d, *J* = 9.6 Hz, 1 H) 2.40 – 2.42 (m, 1 H), 2.09 – 2.18 (m, 3 H), 2.00 – 2.05 (m, 1 H), 1.39 – 1.79 (m, 10 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.91 (s, 9 H), 0.86 (d, *J* = 6.6 Hz, 1 H), 0.63 (d, *J* = 10.8 Hz, 1 H), 0.17 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9, 116.9, 78.8, 74.1, 51.4, 49.5, 44.8, 36.3, 34.2, 32.8, 29.5, 26.2, 26.1, 24.5, 21.6, 21.0, 20.5, 18.4, -1.2, -1.8; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{23}H_{41}O_2Si$, 377.287; found 377.2875.



Diol 14: Aldehyde **S1** (105 mg, 0.31 mmol, 1.0 equiv.) was dissolved in toluene (3.1 ml) and cooled to –78°C under an atmosphere of argon. Allylmagnesium chloride (1.7 M in THF, 0.19 ml, 0.32 mmol, 1.01 equiv.) was added dropwise at –78°C and the solution was stirred at that temperature for 15 minutes, then warmed to room temperature. After stirring for 5 minutes at ambient temperature, the reaction was heated to 105°C for 90 minutes. Upon cooling to 65°C, THF (1 ml) was added followed by TBAF (1.0 M in THF, 1.5 ml, 1.5 mmol, 4.8 equiv.) and the resulting solution was stirred for 45 minutes at 65°C. Upon cooling to room

temperature, the mixture was partitioned between saturated aqueous NH_4Cl (10 ml) and EtOAc (10 ml) and the aqueous layer was extracted with EtOAc (5 ml, 3X). The combined organic layers were washed with 1N HCl (25 ml, 1X), saturated aqueous $NaHCO_3$ (25 ml, 1X), brine (25 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* to give a yellow oil. Flash column chromatography (silica gel, gradient from 2:1 to 1:1 hexanes:Et_2O) afforded the title compound (62 mg, 75%) as a white foam. Major isomer: TLC (hexanes:Et_2O 1:5 v/v): R_F = 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 – 5.30 (m, 1 H), 3.77 (s, 1 H), 3.62 (bs, 1 H), 3.08 (bs, 1 H), 2.44 (bd, *J* = 10 Hz, 1 H), 2.05 – 2.10 (m, 3 H), 1.99 – 2.04 (m, 1 H), 1.70 – 1.82 (m, 3 H), 1.59 – 1.62 (m, 4 H), 1.43 – 1.49 (m, 2 H), 1.35 – 1.37 (bd, *J* = 14.5 Hz, 1 H), 0.94 (d, *J* = 6.0 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.65 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 116.8, 74.7, 73.1, 50.9, 48.4, 45.0, 36.6, 33.7, 32.7, 29.4, 26.0, 23.9, 21.6, 21.1, 21.0, 20.1; IR (film) ν_{max} 3301, 2930, 1468, 1432, 1076, 948 cm^{-1} ; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{17}H_{26}O_2Na$, 285.1825; found, 285.1820.

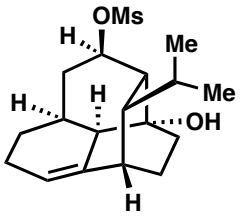


Diol 15: i. Diol **14** (100 mg, 0.38 mmol, 1 equiv.) was dissolved in wet DCM (4 ml) and the Dess-Martin reagent (180 mg, 0.42 mmol, 1.1 equiv) was added at room temperature. After TLC analysis indicated complete consumption of starting material, the mixture was partitioned between Et_2O (25 ml) and saturated aqueous $Na_2S_2O_3$ (25 ml) and the aqueous layer was extracted with Et_2O (10 ml, 3X). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 ml, 2X), brine (50 ml, 1X) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (gradient from

1:1 to 2:1 Et_2O:hexanes) to give the corresponding hydroxyketone (91 mg, 92%) as a white solid.

ii. The aforementioned hydroxyketone (91 mg, 0.35 mmol, 1.0 equiv.) was dissolved in DCM (3.5 ml) and cooled to –78°C. DIBAL (1.5M in toluene, 0.75 ml, 1.13 mmol, 3.2 equiv.) was added dropwise at –78°C and the mixture was stirred for 30 minutes at that temperature. EtOAc (1 ml) was added dropwise followed by saturated aqueous Rochelle's salt (2 ml). The mixture was warmed to room temperature and additional EtOAc (10 ml) and Rochelle's salt (15 ml) were added. The biphasic mixture was vigorously stirred for 3 hours then partitioned and the aqueous layer was extracted with EtOAc (10 ml, 3X). The combined organic layers were washed with 1N HCl (50 ml), brine (50 ml), and dried (Na_2SO_4). The solvent was removed *in vacuo* to give a white foam which was judged to be a ~2.5: 1 mixture of isomers by ^{1}H NMR (nearly analytically pure, quantitative yield). Flash column chromatography (silica gel, gradient from 3:1 to 2:1 hexanes:Et_2O) yielded undesired diol isomer X (26 mg) followed by the title compound (62 mg, 68% of desired, 96% combined yield) as a white crystalline solid. Crystallization from cyclohexane yielded white cubes of suitable quality for X–ray diffraction (CCDC# 675357); m.p.: 161-163°C; TLC (Et_2O:hexanes, 5:1 v/v): R_F = 0.35; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.30 – 5.31 (m, 1 H), 4.21 – 4.24 (m, 1 H), 2.18 – 2.20 (m, 2 H), 2.11 (ddd, J = 1.8, 9.0, 18.0 Hz, 1 H), 2.01 – 2.07 (m, 1 H), 2.00 (m, 1 H), 1.82 – 1.86 (m, 1 H), 1.72 – 1.79 (m, 1 H), 1.67 (m, 1 H), 1.59 – 1.63 (m, 1 H), 1.48 – 1.52 (m, 1 H), 1.41 – 1.43 (m, 2 H), 1.28 (m, 1 H), 1.10 – 1.14 (m, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.7, 116.8, 73.4, 68.2, 49.7, 46.1, 44.1, 36.2, 34.8, 32.1, 30.7, 27.3, 25. 9, 21.9, 21.6, 21.5, 20.6; IR (film) ν_{max} 3361,

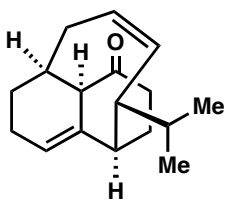
2929, 1470, 1331, 1032, 907, 733 cm^{-1} ; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{17}H_{27}O_2$, 263.2005; found, 263.2004.



Mesylate 6: i. Diol **14** (100 mg, 0.38 mmol, 1 equiv.) was dissolved in wet DCM (4 ml) and the Dess-Martin reagent (180 mg, 0.42 mmol, 1.1 equiv) was added at room temperature. After TLC analysis indicated complete consumption of starting material, the mixture was partitioned between Et_2O (25 ml) and saturated aqueous $Na_2S_2O_3$ (25 ml) and the aqueous layer was extracted with Et_2O (10 ml, 3X). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 ml, 2X), brine (50 ml, 1X) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (gradient from 1:1 to 2:1 Et_2O:hexanes) to give the corresponding hydroxyketone (91 mg, 92%) as a white solid.

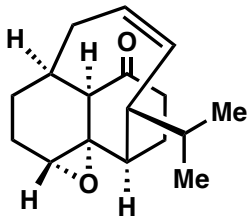
ii. The aforementioned hydroxyketone (25 mg, 0.10 mmol, 1.0 equiv.) was dissolved in DCM (1.0 ml) and cooled to –78°C. DIBAL (1.5M in toluene, 0.2 ml, 0.30 mmol, 3.1 equiv.) was added dropwise at –78°C and the mixture was stirred for 20 minutes at that temperature. EtOAc (0.2 ml) was added followed by saturated aqueous Rochelle's salt (1 ml) and the mixture was warmed to room temperature. Once the mixture had reached room temperature, additional EtOAc (5 ml) and Rochelle's salt solution (2 ml) were added and the biphasic mixture was stirred vigorously for 1 hour. The reaction mixture was then partitioned and the aqueous layer extracted with EtOAc (5 ml, 3X). The combined organic layers were washed with 1N HCl (25 ml), saturated aqueous NH_4Cl (25 ml), brine (25 ml), and dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a

white foam (25 mg) that was re-dissolved in anhydrous DCM (1.0 ml). Et_3N (0.02 ml, 0.14 mmol, 1.5 equiv) was added followed by methanesulfonyl chloride (0.01 ml, 0.12 mmol, 1.25 equiv) and the mixture was stirred for 20 minutes under an atmosphere of N_2. The mixture was partitioned between saturated NH_4Cl (20 ml) and DCM (5 ml) and the aqueous layer was extracted with DCM (5 ml, 3X). The combined organic layers were washed with 1N HCl (25 ml), saturated aqueous $NaHCO_3$ (25 ml), brine (25 ml), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude material purified by flash column chromatography (silica gel, gradient from 3:1 hexanes:Et_2O to 1:1 hexanes:Et_2O) to afford the corresponding mesylate (28.2 mg, 86%, ~2.5:1 mixture of diastereomers). The major isomer is a white solid; TLC (Et_2O:hexanes, 1:5 v/v): R_F = 0.37; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.34 – 5.35 (m, 1 H), 5.22 – 5.26 (m, 1 H), 2.96 (s, 3 H), 2.27 – 2.30 (m, 1 H), 2.23 (m, 1 H), 2.11—2.14 (m, 1 H), 2.01—2.08 (m, 2 H), 1.88 – 1.89 (m, 1 H), 1.84 – 1.86 (m, 1 H), 1.74 – 1.81 (m, 1 H), 1.60—1.71 (m, 4 H), 1.50 – 1.54 (m, 1 H), 1.41 – 1.48 (m, 1 H), 1.22—1.24 (m, 1 H), 1.18 (s, 1 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.0, 117.3, 80.6, 73. 4, 48.4, 46.6, 43.6, 38.5, 35.8, 34.6, 32.0, 28.6, 27.2, 25.5, 21.6, 21.5, 21.4, 20.5; IR (film) ν_{max} 3505, 2934, 1330, 1169, 928 cm^{-1} ; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{18}H_{28}O_4SNa$, 363.160; found 363.1606.



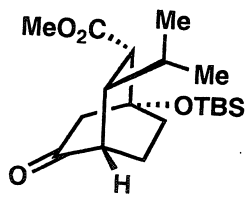
Ketone 16: A flame-dried flask was charged with mesylate **6** (21 mg, 0.06 mmol, 1 equiv.). The flask was evacuated and then back-filled with dry argon. Freshly degassed THF (1.0 ml) was added and the flask cooled to 0°C. KHMDS (0.5M solution in THF, 0.135 ml, 0.068 mmol 1.1 equiv.)

was added dropwise and the solution was stirred for 15 minutes at 0°C, then warmed to room temperature and stirred 5 minutes. While still under an argon atmosphere, glacial acetic acid (0.05 ml) was added and the mixture stirred for 3 minutes, then partitioned between 1N HCl (10 ml) and Et_2O (5 ml). The aqueous layer was extracted with Et_2O (5 ml, 3X) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 ml, 2X), brine (25 ml), and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude material purified by flash column chromatography (silica gel, gradient from 10:1 to 3:1 hexanes Et_2O) to give the title compound (14 mg, 93%) as colorless oil; TLC (Et_2O:hexanes, 1:1 v/v): R_F = 0.52; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 – 5.61 (m, 1 H), 5.40 (dddd, *J* = 1.5, 7.0, 11.0, 18.0 Hz, 1 H), 5.24 (dd, *J* = 7.5, 11.0 Hz, 1 H), 2.96 – 3.00 (m, 1 H), 2.89 (m, 1 H), 2.32 – 2.37 (m, 3 H), 2.19 – 2.27 (m, 1 H), 1.98 – 2.06 (m, 2 H), 1.89 – 1.95 (m, 1 H), 1.81 – 1.88 (m, 3 H), 1.61 – 1.71 (m, 2 H), 1.15 – 1.20 (m, 1 H), 1.00 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 141.0, 137.3, 133.6, 120.4, 53.1, 51.6, 41.5, 36.9, 36.5, 31.5, 31.0, 24.9, 22.1, 21.4, 21.0, 21.0; IR (film) ν_{max} 2934, 2866, 2359, 2341, 1700 cm^{-1} ; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{17}H_{25}O$, 245.190; found 245.1906.



Epoxide 5: To a solution of ketone **16** (8.0 mg, 0.03 mmol, 1 equiv.) in DCM (1 ml) at -15°C was added $NaHCO_3$ (5.5 mg, 0.065 mmol, 2 equiv.). Freshly purified *m*-CPBA (8.5 mg, 0.05 mmol, 1.5 equiv.) was then added in small portions until TLC analysis indicated complete consumption of starting material (~45 minutes). The mixture was then partitioned between saturated aqueous $Na_2S_2O_3$ (5 ml) and Et_2O (5 ml) and the aqueous layer

extracted with Et_2O (5ml, 2X). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 ml), saturated aqueous $NaHCO_3$ (25 ml, 2X), brine (25 ml), and dried ($MgSO_4$). Concentration *in vacuo* yielded the title compound (8.5 mg, 95% purity by ^1H NMR, 95% yield) as a white crystalline solid. [NOTE: The product is somewhat unstable to both acidic and basic conditions and purification often affords product of lower purity than the crude material]). Crystallization from cyclohexane yielded white cubes of suitable quality for X–ray diffraction (CCDC# 675358); m.p.: 117-120°C; TLC (Et_2O:hexanes, 1:1 v/v): R_F = 0.34; ^1H NMR (600 MHz, C_6D_6) δ 5.51 (m, 1 H), 4.98 (dd, J = 7.8, 10.8 Hz, 1 H), 2.84 – 2.88 (m, 1 H), 2.74 (d, J = 4.2 Hz, 1 H), 2.19 – 2.22 (m, 2 H), 1.96 – 2.01 (m, 2 H), 1.78 – 1.86 (m, 2 H), 1.51 – 1.57 (m, 3 H), 1.45 – 1.48 (m, 1 H), 1.20 – 1.29 (m, 3 H), 1.13 – 1.17 (m, 1 H), 0.77 (d, J = 6.6 Hz, 3 H), 0.67 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 207.7, 136.1, 134.3, 61.7, 56.1, 54.8, 46.8, 42.7, 36.3, 34.3, 30.4, 27.5, 24.7, 22.0, 20.7, 19.9, 19.3; IR (film) ν_{max} 2928, 2870, 2359, 2333, 1699, 613 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{17}H_{25}O_2$, 261. 1849; found 261.1852.



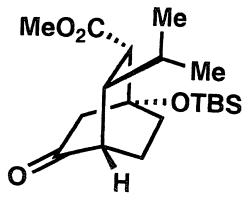
7.5

5.0

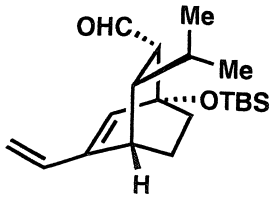
2.5

0.0

ppm (f1)


MeO2C
Me
Me
OTBS
O
H

200
150
100
50
0
ppm (f1)

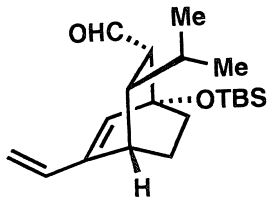


10.0

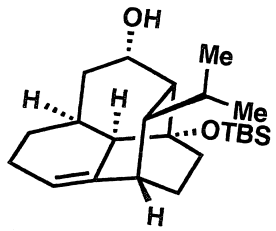
5.0

0.0

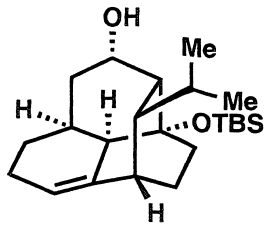
ppm (f1)


OHC
Me
Me
OTBS
H

200
150
100
50
0
ppm (f1)

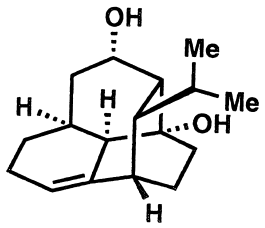

OH
Me
H
H
Me
OTBS
H

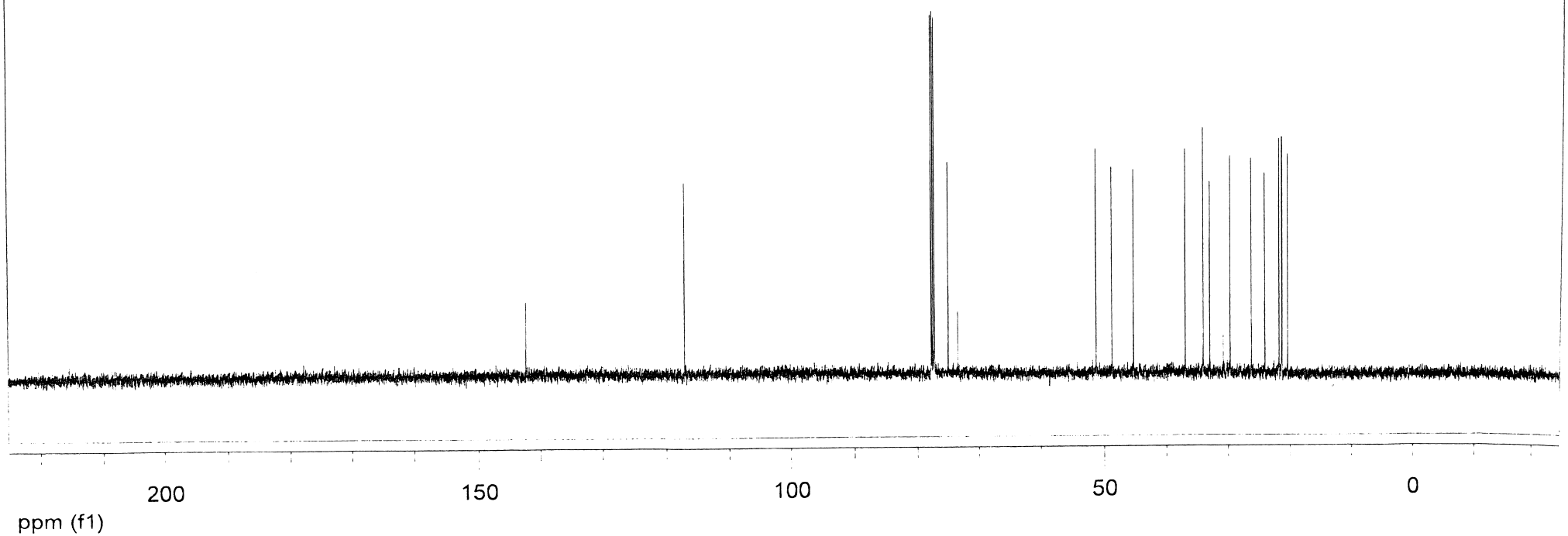
10.0
5.0
0.0
ppm (f1)

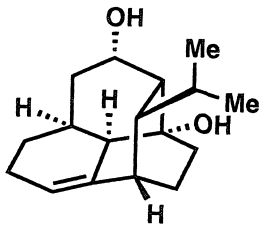


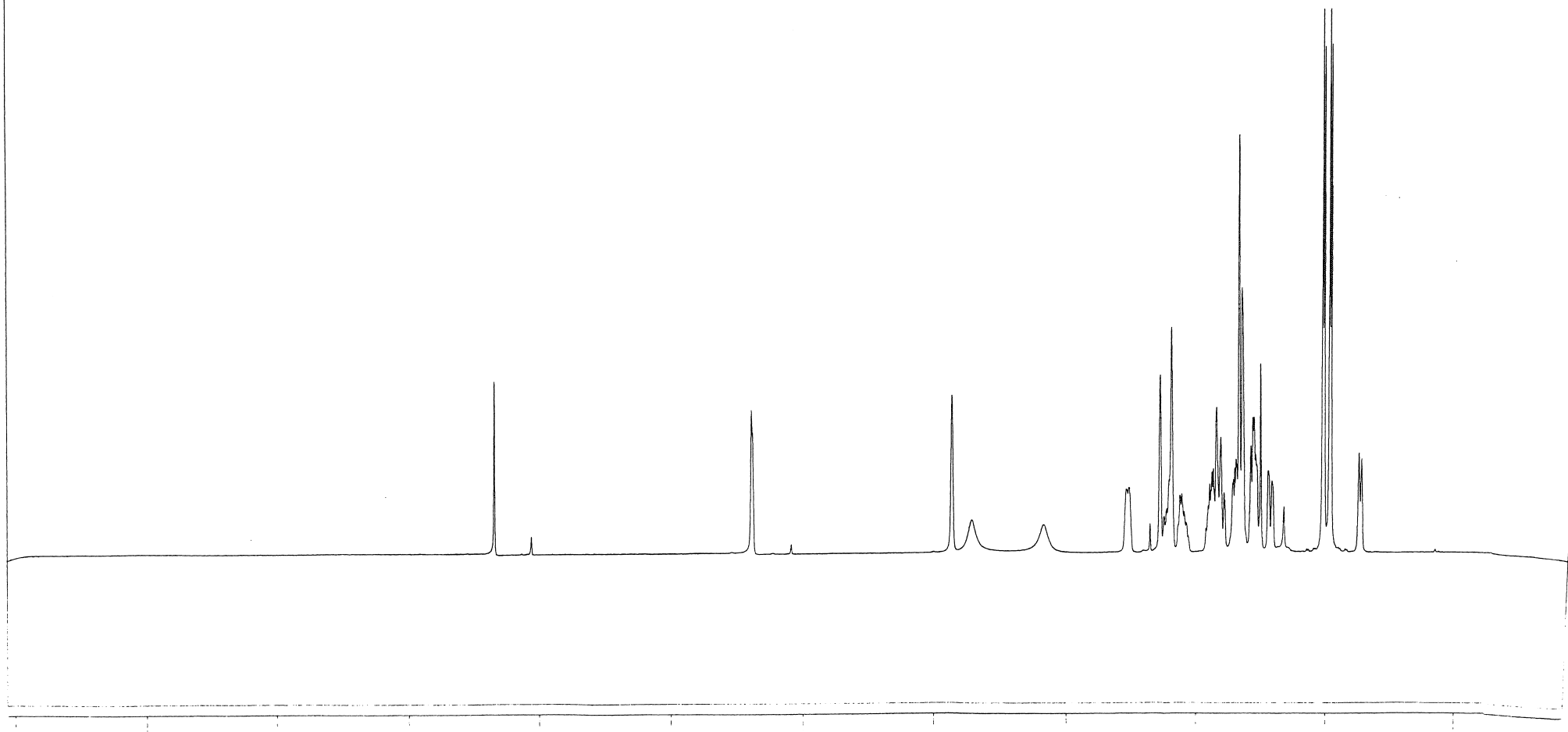
200 150 100 50 0

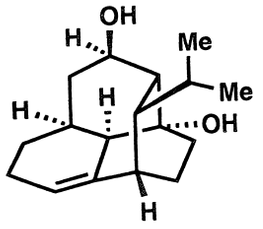
ppm (f1)


OH
Me
H
H
Me
OH
H

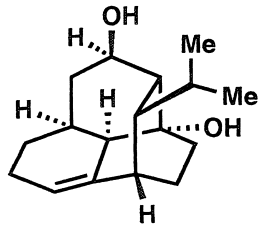

200
150
100
50
0
ppm (f1)


OH
Me
H
H
Me
OH
H

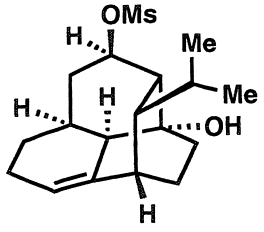

10.0
5.0
0.0


OH
H
Me
Me
H
H
OH
H

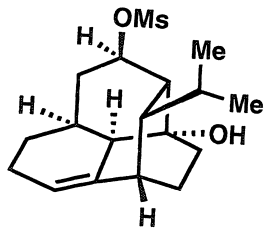
10.0
5.0
0.0
ppm (f1)

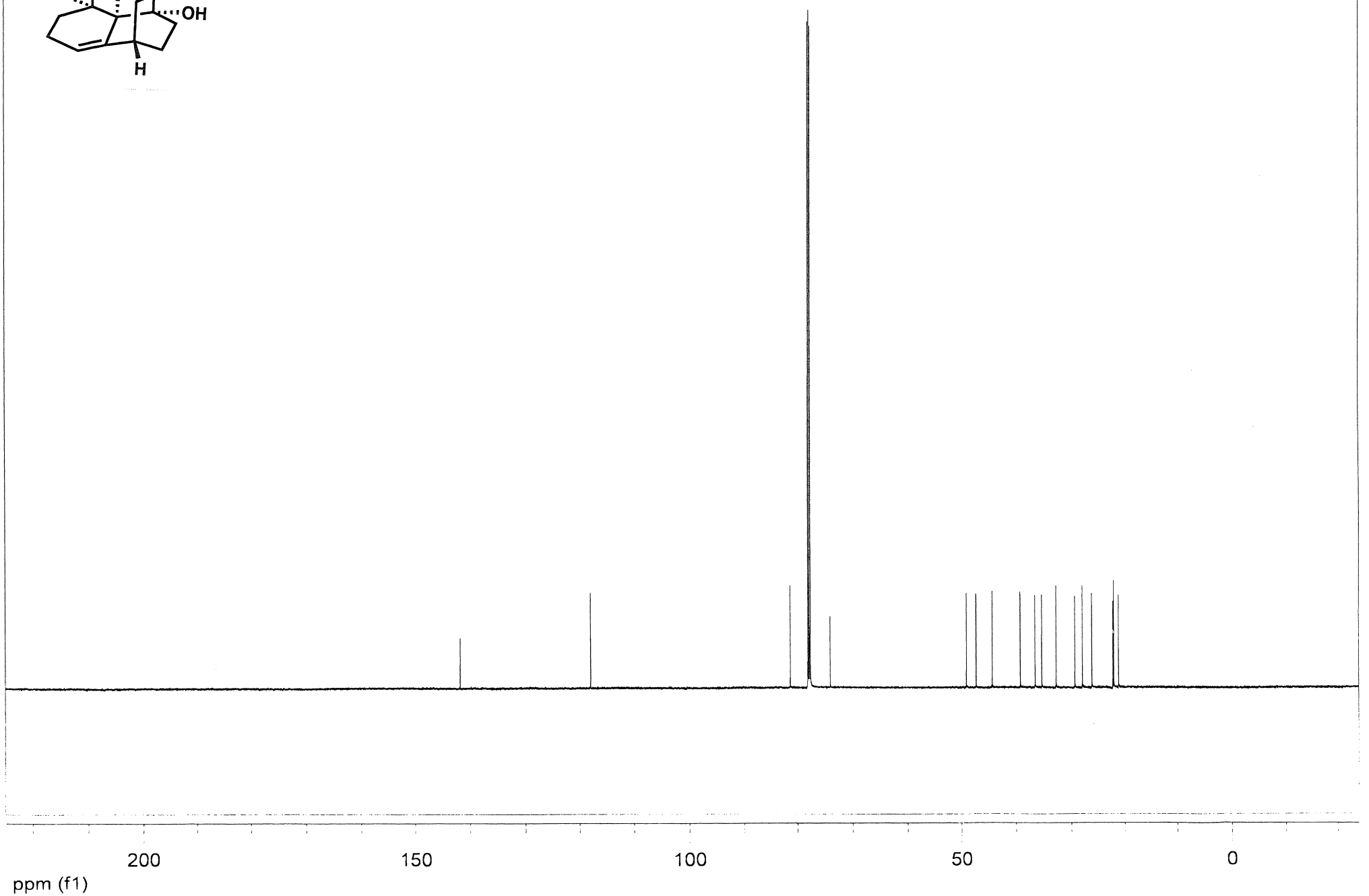

OH
H
Me
H
H
Me
OH
H

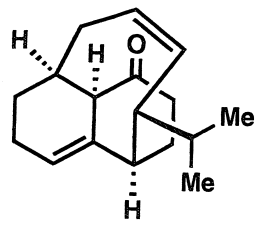
200
150
100
50
0
ppm (f1)

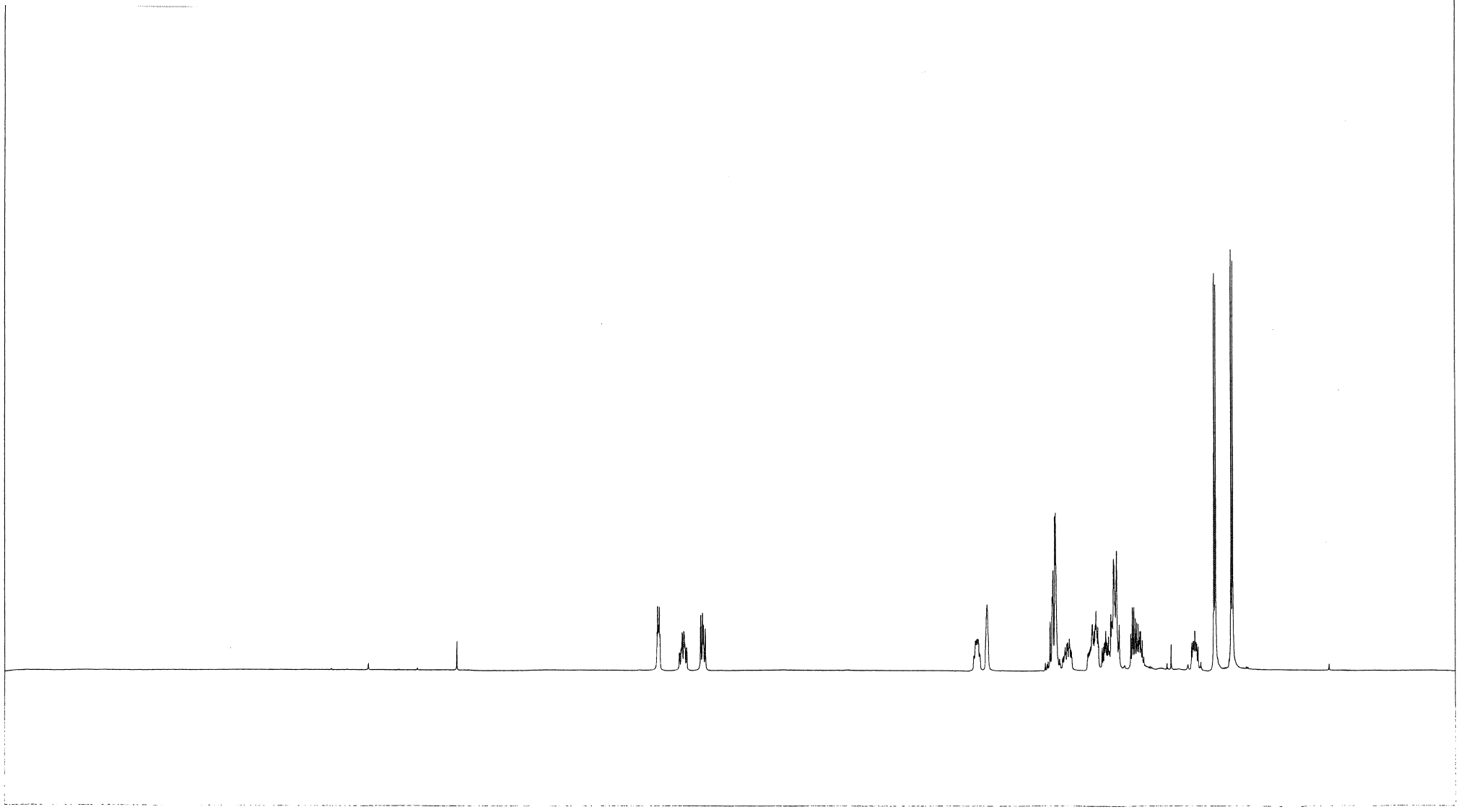

OMs
H
Me
Me
H
H
OH
H

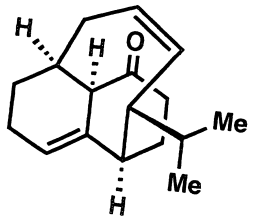
10.0
5.0
0.0
ppm (f1)


OMs
H
Me
H
H
Me
OH
H

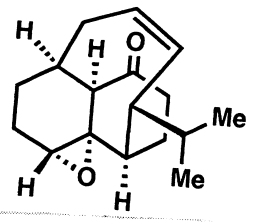

200
150
100
50
0
ppm (f1)

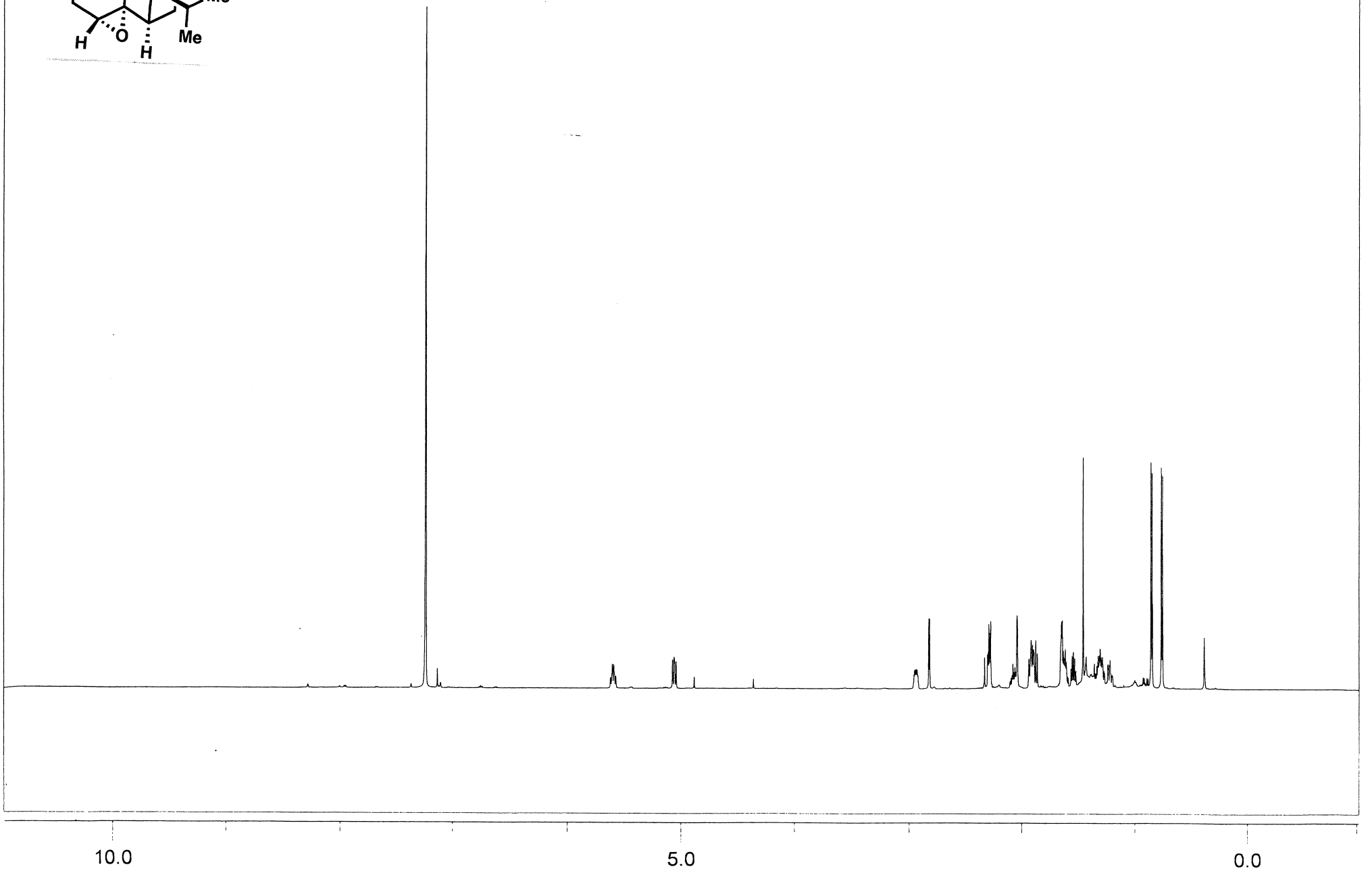

H
H
O
Me
Me
H

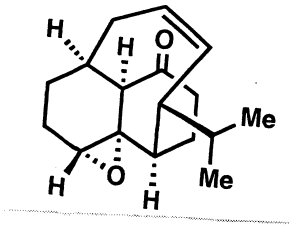

10.0
5.0
0.0
ppm (f1)


H
H
O
Me
Me
H

200
150
100
50
0
ppm (f1)


H
H
O
Me
Me
H
O
H


10.0
5.0
0.0


H
H
O
Me
H
O
Me
H

200
150
100
50
0
ppm (f1)