Total Synthesis of (–)-Ascochlorin via a Cyclobutenone-Based Benzannulation Strategy

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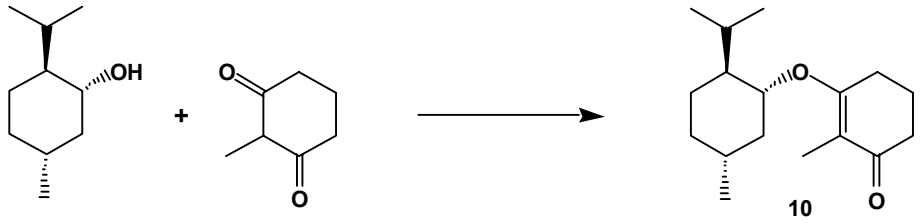
Supporting Information

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon with magnetic stirring. Sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated using a Büchi rotary evaporator at ca. 20 mmHg. Column chromatography was performed on EM Science silica gel 60 (35-75 μm) or Silicycle silica gel 60.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Acetonitrile, benzene, chlorotrimethylsilane, cyclohexane, dichloromethane, diisopropylamine, dimethylformamide, hexamethyldisilazane, hexamethylphosphoric triamide, hexamethylphosphorous triamide, methanesulfonyl chloride, phosphorous oxychloride, tetramethylethylenediamine, toluene, trichloroethylene, and triethylamine were distilled from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from benzophenone ketyl or dianion. Methyl iodide was distilled immediately prior to use. Alkyllithium reagents were titrated in tetrahydrofuran with menthol using 1,10-phenanthroline as the indicator.[1]

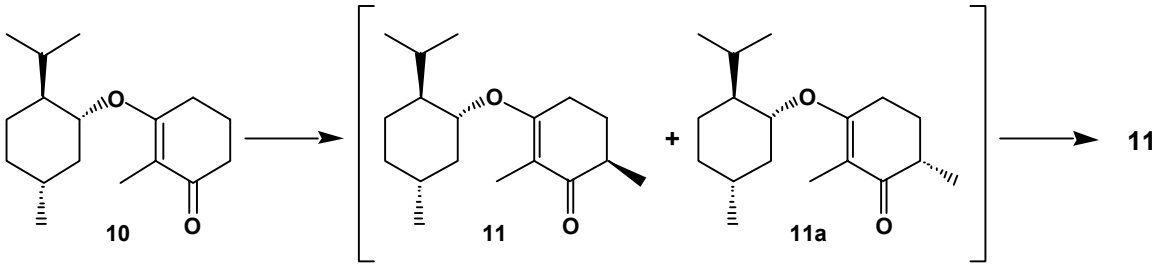
Instrumentation. ^{1}H NMR spectra were recorded on Bruker WM-250 (250 MHz), Varian XL-300 (300 MHz), Varian Unity 300 (300 MHz), and Varian Inova 500 (500 MHz) spectrometers. ^{13}C NMR spectra were recorded on Bruker WM-270 (67.9 MHz), Varian Unity

300 (75 MHz) and Varian Inova 500 (125 MHz) spectrometers. ^{1}H NMR chemical shifts and ^{13}C NMR shifts are expressed in parts per million (δ) relative to $CDCl_3$. Infrared spectra were obtained on a Perkin-Elmer 1320 grating or a Perkin-Elmer 1600 series FTIR spectrophotometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, New Jersey. High resolution mass spectra (HRMS) were measured on a Finnegan MATT-8200 spectrometer. Gas chromatography was performed on a Hewlett–Packard HP6890 GC using a chiral 10% permethylated β-cyclodextrin capillary column, model number: HP19091G–B133 (250 μm by 30 m). Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.



(+)-3-((–)-Menthyloxy)-2-methylcyclohexen-2-one (10). A 1-L, one-necked, round-bottomed flask was fitted with a Claisen adapter equipped with a glass stopper and a Dean–Stark trap with graduated side arm. The Dean–Stark trap was equipped with a reflux condenser and an argon inlet. The flask was then charged with 2-methyl-1,3-cyclohexanedione (25.3 g, 200 mmol, 1.0 equiv), (–)-menthol (31.5 g, 201 mmol, 1.0 equiv), 100 mL of diglyme, 400 mL of toluene, and (+)-camphorsulfonic acid (4.18 g, 18.0 mmol, 0.09 equiv). The resulting suspension was heated to a rapid reflux and within 30 min became a homogeneous, pale yellow solution. After 20 h, approximately 3.6 mL of water (ca. 200 mmol) had collected in the Dean–Stark trap. At this point the trap was opened and 400 mL of the solvent was distilled off. The residue was allowed to cool to room temperature and then was diluted with 200 mL of half-saturated $NaHCO_3$ solution. The resulting mixture was extracted with two 100-mL portions of ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated (rotary evaporator, 45 °C bath; then at 2 mmHg, 45 °C bath) to give 68.0 g of a yellow liquid. This material was dissolved in 50 mL of hot hexanes, allowed to cool to room temperature, and then seeded with a crystal of **10** obtained from a previous experiment.[2] The resulting mixture was allowed to stand at –18 °C for 18 h, and the crystals that formed were filtered, washed with three

portions of cold (–18 °C) hexanes, and dried at 0.1 mmHg to give 30.0 g (57%) of **10** as white prisms. The combined filtrates were concentrated to give 31.2 g of a yellow oil, which was washed with two 50-mL portions of water to remove traces of diglyme. The combined aqueous layers were extracted with 50 mL of hexanes, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 16.0 g of a yellow oil. This material was crystallized as described above from 16 mL of hexanes to provide 7.34 g (14%) of **10** as white prisms. The resulting mother liquor (8.52 g) was partially purified by column chromatography on 85 g of silica gel (elution with 30% ethyl acetate–hexanes) to give 3.0 g of a yellow solid, which was crystallized from 2 mL of hexanes to afford another 2.15 g (4%) of **10** as white prisms. Total yield: 39.0 g (74%) of alkoxy enone **10** as white prisms: mp 67–68 °C; $[\alpha]^{20}_{D}$ +10.7° (*c* = 4.65, $CHCl_3$); IR (CH_2Cl_2) 3053, 2958, 2871, 1638, 1611, 1456, 1422, 1379, 1354, 1256, 1195, 1095, 987, 896 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (td, *J* = 10.5, 4.3 Hz, 1H), 2.29–2.61 (m, 4H), 1.92–2.11 (m, 3H), 1.84–1.91 (m, 1H), 1.68–1.75 (m, 5H), 1.37–1.53 (m, 2H), 0.99–1.15 (m, 2H), 0.86–0.96 (m, 7H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 171.4, 116.1, 77.5, 48.1, 42.6, 36.6, 34.2, 31.6, 26.1, 25.9, 23.6, 22.2, 21.4, 20.9, 16.7, 7.8. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.53; H, 11.06.



3-((–)-Menthyloxy)-2,6-dimethylcyclohexen-2-one (11). A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet, 125-mL pressure-equalizing addition funnel, and a rubber septum was charged with diisopropylamine (14.6 mL, 10.5 g, 104 mmol, 1.04 equiv) and 50 mL of THF. The solution was cooled at –78 °C while *n*-butyllithium (2.45M in hexanes, 42.0 mL, 103 mmol, 1.03 equiv) was added rapidly dropwise via syringe. The resulting cloudy yellow suspension was stirred at 0 °C for 15 min to produce a yellow solution that was then cooled at –78 °C while a solution of ketone **10** (26.4 g, 100 mmol, 1.00 equiv) in 60 mL of THF was added via the addition funnel over 30 min. The resulting yellow solution was stirred at –78 °C for 10 min and at –35 °C for 30 min, and then cooled at –78 °C while methyl iodide (7.5

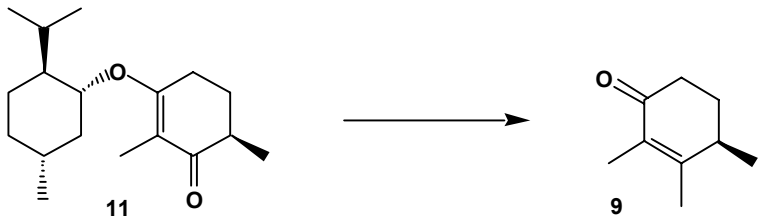
mL, 17 g, 120 mmol, 1.2 equiv) was added in one portion by syringe. The reaction mixture was allowed to warm to room temperature over 14 h, and then was partitioned between 100 mL of half-saturated NH_4Cl solution and 100 mL of ether. The organic layer was separated and washed with 100 mL of saturated NH_4Cl solution and 100 mL of saturated NaCl solution, and the combined aqueous layers were extracted with 100 mL of ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 28.0 g of a mixture of **11** and **11a** as a yellow liquid which solidified upon standing. GC analysis revealed the presence of ca. 4% of a dimethylated by-product. No further effort to purify this material was made prior to recrystallization.

Procedure for separation of (6*R*)-(+)-3-((–)-Menthyloxy)-2,6-dimethylcyclohexen-2-one (11) and recycling of 11a via epimerization. A ca. 50:50 mixture of epimeric ketones **11** and **11a** was dissolved in hot hexanes (ca. 1 mL of hexanes per 2 g of ketones) and allowed to cool to room temperature. A seed crystal[3] obtained from a previous experiment was added, and the mixture was allowed to stand at room temperature for 12 h and then at –3 °C for 12–24 h. The resulting pale yellow prisms (enriched in **11**) were separated by filtration, rinsed with three portions of cold (–18 °C) hexanes, and dried at 0.1 mmHg. The filtrate was concentrated to give an orange liquid (enriched in **11a**), which was then diluted with THF (2 mL per g of product). *tert*-Butyl alcohol (0.6 equiv) and KO*t*-Bu (0.5 equiv) were added, and the resulting brown mixture was stirred for 4 h and then diluted with an equal volume of saturated NH_4Cl solution and stirred for 10 min. The resulting mixture was extracted with ether, and the organic layer was washed with saturated NaCl solution. The combined aqueous layers were extracted with ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation and then at 0.1 mmHg to yield a ca. 50:50 mixture of **11** and **11a** as an amorphous yellow solid.

In this manner, the initial mixture **11** and **11a** (56 g, 96% purity, 190 mmol) afforded, after four cycles, 41.5 g (74%) of pale yellow prisms which by ^{1}H NMR analysis consisted of a ca. 85:15 diastereomeric mixture of **11** and **11a**. These crystals were dissolved in 41 mL of hot hexanes and allowed to cool to room temperature. Introduction of a seed crystal induced immediate crystallization. The mixture was allowed to stand at room temperature for 7 h and the resulting crystals were separated by filtration, rinsed with three portions of cold (–18 °C) hexanes, and dried at 0.1 mmHg to give 29.6 g of **11** as white prisms. This material was

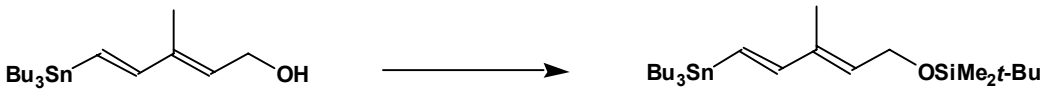
recrystallized as described above from 30 mL of hot hexanes to afford 24.7 g of **11** as colorless prisms. The combined filtrates were concentrated to give 16.5 g of a pale yellow solid, which was recrystallized twice as described above from 16 mL of hot hexanes to provide an additional 7.1 g of white prisms. The combined crystals (31.8 g) were recrystallized from 60 mL of hot hexanes to give 28.4 g (51% overall from **10**) of ketone **11** as colorless prisms: mp 94–95 °C; $[\alpha]^{20}_{D}$ +75.1° (*c* = 1.43, $CHCl_3$); IR (CH_2Cl_2) 3054, 2960, 2929, 2871, 1640, 1614, 1457, 1379, 1354, 1274, 1251, 1218, 1100, 984, 894, 764 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.68 (td, *J* = 10.5, 4.4 Hz, 1H), 2.04–2.16 (m, 5H), 1.88–2.03 (m, 2H), 1.60–1.67 (m, 1H), 1.53–1.60 (m, 1H), 1.43–1.51 (m, 2H), 1.18–1.39 (m, 5H), 1.03–1.17 (m, 1H), 0.92 (dd, *J* = 13.3, 12.3 Hz, 1H), 0.86 (d, *J* = 7.3 Hz, 3H), 0.64–0.82 (m, 8H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 168.7, 116.2, 76.9, 48.4, 42.9, 40.4, 34.7, 31.8, 29.7, 26.7, 25.4, 24.1, 22.6, 21.2, 17.1, 16.4, 9.1. Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.42; H, 11.18.

In addition, 26.4 g (47%) of the epimeric mixture (**11** and **11a**) was recovered as an amorphous yellow-brown solid determined to be 87% pure by GC analysis (contains ca. 9% of the dimethylated by-product and other minor impurities).



(4*R*)-(+)-2,3,4-Trimethylcyclohex-2-enone (9). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet, a 125-mL pressure-equalizing dropping funnel, and a rubber septum was charged with methyllithium (1.4 M in ether, 25.0 mL, 35 mmol, 1.4 equiv) and 50 mL of THF. The septum was replaced with a glass stopper, and the system was cooled at 0 °C while a solution of alkoxy enone **11** (6.96 g, 25.0 mmol, 1.0 equiv) in 50 mL of THF was added via the dropping funnel over 30 min. After 30 min, 70 mL of 1 M HCl solution was added carefully. The resulting mixture was stirred at 0 °C for 10 min and then extracted with two 50-mL portions of ether. Each organic layer was washed separately with 10 mL of saturated $NaHCO_3$ solution and 10 mL of saturated NaCl solution. The combined organic layers were dried over Na_2SO_4 and then briefly over $MgSO_4$, filtered and concentrated by rotary evaporation at 0 °C to give 8.2 g of a colorless liquid consisting primarily of the desired enone and menthol.

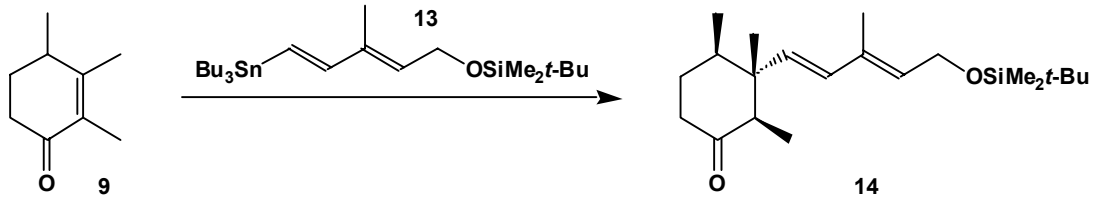
Separation of the enone was facilitated by silylation of the menthol as follows. A solution of the product in 50 mL of CH_2Cl_2 was transferred to a 250-mL, one-necked, round-bottomed flask and triethylamine (5.2 mL, 3.8 g, 37 mmol, 1.5 equiv) was added. The flask was immersed in a tap water bath and chlorotrimethylsilane (4.0 mL, 3.4 g, 32 mmol, 1.3 equiv) was added dropwise over 4 min. The resulting mixture was stirred for 20 min and then diluted with 100 mL of ether, washed with 25 mL of water and 25 mL of saturated NaCl, dried over Na_2SO_4 and then briefly over $MgSO_4$, filtered, and concentrated (rotary evaporator, 0 °C bath temperature) to give 9.71 g of a cloudy white liquid. Purification by column chromatography on 92 g of silica gel (gradient elution with 2.5–20% ether–pentane) provided 3.48 g (100%) of enone **9** as a colorless liquid[4] (200:1 enantiomeric ratio by chiral GC analysis): $[\alpha]^{20}_D$ +131° (*c* = 1.33, $CHCl_3$); IR (thin film) 2962, 2931, 1665, 1628, 1455, 1421, 1376, 1346, 1308, 1193, 1084, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.52 (ddd, *J* = 16.9, 11.4, 4.9 Hz, 1H), 2.37–2.45 (m, 1H), 2.32 (ddd, *J* = 16.9, 6.1, 4.9 Hz, 1H), 2.11 (dddd, *J* = 13.2, 11.4, 4.9, 4.9 Hz, 1H), 1.92 (s, 3H), 1.68–1.76 (m, 4H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 159.3, 130.4, 35.7, 34.1, 29.5, 19.9, 17.8, 11.1. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.29; H, 10.40.



12 **13**

1-Tri-*n*-butylstannyl-5-*t*-butyldimethylsilyloxy-3-methyl-(1*E*,3*E*)-pentadiene (13). A 1-L, one-necked, round-bottomed flask equipped with an argon inlet adapter was charged with a solution of stannyl alcohol **12**[5] (34.0 g, 86.5 mmol) in 500 mL of methylene chloride and triethylamine (12.3 g, 121 mmol), *t*-butyldimethylsilyl chloride (16.9 g, 112 mmol), and 4-dimethylaminopyridine (0.423 g, 3.46 mmol) were then added. The resulting mixture was stirred at room temperature for 2.5 h and then 200 mL of water was added and the methylene chloride was removed under reduced pressure. The two-phase residue was diluted with 500 mL of pentane and an additional 300 mL of water. The aqueous phase was separated and extracted with two 300-mL portions of pentane, and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give 46.1 g of a yellow liquid. Purification by column chromatography on Woelm neutral alumina (activity V, elution with pentane) afforded 42.6 g (98%) of **13** as a pale yellow liquid: IR (thin film) 2970, 2940, 2870, 1570, 1465, 1380,

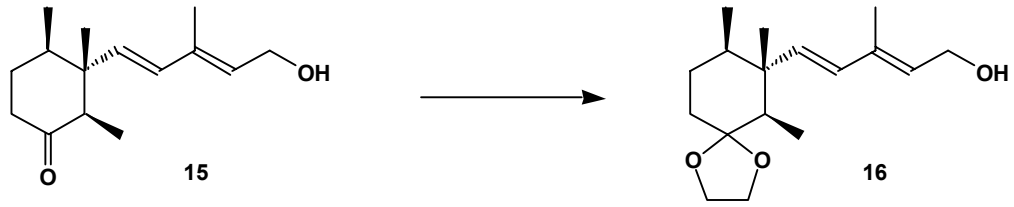
1260, 1110, 1060, 985, 835, 775 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.82 (d with Sn satellites, *J* = 19.3, 1H), 6.35 (d with Sn satellites, *J* = 19.3, 1H), 5.79 (br t, *J* = 6.4, 1H), 4.31 (d, *J* = 6.4, 2H), 1.70 (s, 3H), 1.30–1.66 (m, 12H), 0.83–1.20 (m, 24H), 0.06 (s, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 151.2, 135.9, 132.4, 126.6, 60.6, 29.6, 27.7, 26.1, 18.4, 13.9, 12.1, 9.8, –5.0. HRMS Calcd for $C_{24}H_{50}OSiSn$: 502.265. Found: 502.266.



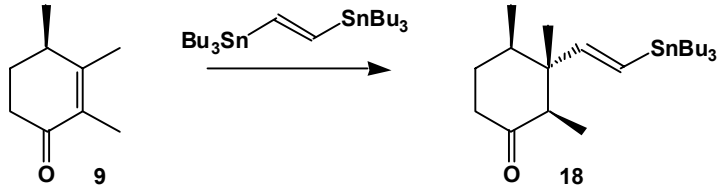
2,3,4-Trimethyl-3-[5'-*t*-butyldimethylsilyloxy-3'-methyl-(1*E*,3*E*)-pentadienyl]-cyclohexanone (14). A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter was charged with vinylstannane **13**[6] (13.7 g, 27.3 mmol) and 100 mL of THF and cooled at –78 °C while a solution of *n*-butyllithium (2.49 M in hexanes, 11.0 mL, 27.3 mmol) was added dropwise over 30 min. The resulting yellow mixture[7] was stirred for 1 h and then a solution of 1-pentynylcopper[8] (4.0 g, 30 mmol) and hexamethylphosphorous triamide (12.4 g, 76.2 mmol) in 20 mL of THF (pre-cooled to –78 °C) was added via cannula over 15 min. The resulting mixture was allowed to warm to –50 °C over 1 h and maintained at that temperature for an additional 2 h. The yellow-orange reaction mixture was then recooled to –78 °C, and BF_3•Et_2O (3.88 g, 27.3 mmol) was added over 10 min via syringe. After 30 min, a solution of enone **9** (1.51 g, 10.9 mmol) in 11 mL of THF (pre-cooled to –78 °C) was added via cannula over 10 min to the yellow cuprate solution. The reaction mixture was allowed to warm to room temperature overnight and then poured into a slurry of 84 g of silica gel in methylene chloride. After removal of the solvent at reduced pressure, the solid was exposed to air for ca. 10 min. The blue-green material was then deposited onto a 250-g column of silica gel and eluted with ethyl acetate–hexane. This initial purification removed the tetrabutyltin by-product, providing 4.3 g of a yellow liquid. Further purification by column chromatography on silica gel (elution with ethyl acetate–hexane) afforded 2.97 g (78%) **14** as a pale yellow oil: IR (thin film) 3040, 2980, 2940, 2860, 1710, 1465, 1455, 1380, 1360, 1330, 1260, 1255, 1105, 1060, 1015, 1005, 970, 835, 775 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.94 (d, *J* = 16.0, 1H), 5.55 (t, *J* = 6.4, 1H), 5.42 (d, *J* = 16.0, 1H), 4.33 (d, *J* = 6.4, 2H), 2.40–2.45 (m, 3H), 1.91–1.97 (m, 3H), 1.76 (s, 3H),

1.59–1.67 (m, 1H), 1.00–1.14 (m, CH_3 of minor epimer), 0.92 (s, 9H), 0.85 (d, J = 6.8, 3H), 0.82 (d, J = 6.6, 3H), 0.74 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$) (for the major epimer only) δ 212.2, 136.7, 133.8, 132.8, 130.4, 60.2, 53.5, 48.4, 41.5, 40.8, 31.1, 26.0, 18.4, 16.2, 12.8, 10.3, 8.8, –5.2. HRMS Calcd for $C_{21}H_{38}O_2Si$: 350.2641. Found: 350.2638.

2,3,4-Trimethyl-3-[5'-hydroxy-3'-methyl-(1*E*,3*E*)-pentadienyl]cyclohexanone (15). A 500-mL, three-necked, round-bottomed flask was equipped with an addition funnel fitted with an argon inlet adapter and charged with TBAF solution (1.0 M in THF, 19.4 mL, 19.4 mmol). The solvent was removed in vacuo, and the remaining salt was dissolved in 95 mL of DMF. The resulting solution was cooled to 0 °C, and a solution of silyl ether **14** (5.68 g, 16.2 mmol) in 65 mL of DMF was added dropwise via addition funnel over 1.5 h. The resulting light brown solution was stirred at 0 °C for 3.5 h and then poured into a mixture of 500 mL of water and 250 mL of ether. The organic phase was separated and washed with two 400-mL portions of water and 400 mL of saturated NaCl solution, and the combined aqueous phases were extracted with three 200-mL portions of ether. The combined organic phases were diluted with pentane, dried over Na_2SO_4, filtered, and concentrated to provide 5.44 g of a yellow oil. Purification by column chromatography on silica gel (elution with ethyl acetate–hexane) provided 3.46 g (90%) of **15** as a pale yellow oil (93:7 ratio of epimers): IR (thin film) 3600–3100, 2960, 2930, 2870, 1705, 1450, 1425, 1385, 1375, 1355, 1330, 1295, 1270, 1230, 1200, 1165, 1105, 1080, 1070, 1000, 975 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.96 (d, J = 16.1, 1H), 5.67 (t, J = 6.8, 1H), 5.49 (d, J = 16.1, 1H), 4.30 (d, J = 6.8, 2H), 2.38–2.46 (m, 3H), 1.90–2.01 (m, 2H), 1.81 (s, 3H), 1.60–1.73 (m, 1H), 1.44 (br s, 1H, exchanges with D_2O), 1.00–1.06 (m, CH_3 of minor epimer), 0.88 (d, J = 6.4, 3H), 0.83 (d, J = 6.4, 3H), 0.75 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 212.4, 137.7, 135.9, 132.5, 128.9, 59.3, 53.4, 48.4, 41.5, 40.7, 31.0, 16.2, 12.8, 10.3, 8.8. HRMS Calcd for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1782.

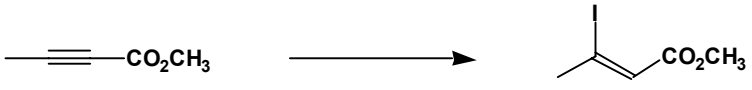


(2*E*,4*E*)-5-[3,3-Ethylenedioxy-1,2,6-trimethylcyclohexyl]-3-methylpenta-2,4-dien-1-ol (16). A 50-mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter and glass stopper was charged with ketone **15** (0.577 g, 2.44 mmol), ethylene glycol (4.40 g, 70.8 mmol), and 20 mL of cyclohexane. To this solution was added calcium sulfate dihydrate (2.50 g, 14.6 mmol; dried by heating in vacuo with a Bunsen burner) and then *p*-TsOH (0.093 g, 0.49 mmol). The resulting slurry was stirred vigorously at room temperature for 3.5 h and then quenched by the addition of 20 mL of saturated $NaHCO_3$ solution. After ca. 10 min, the resulting mixture was combined with the mixtures from five identical runs and filtered through Celite. The filtrate was diluted with 80 mL of ether and 200 mL of saturated $NaHCO_3$ solution, and the organic phase was separated and washed with saturated NaCl solution. The aqueous phases were extracted with three 100-mL portions of ether, and the combined organic phases were diluted with pentane, dried over Na_2SO_4, filtered, and concentrated to give 4.19 g of a yellow oil. Purification by column chromatography on silica gel (elution with ethyl acetate–hexane) provided 3.12 g (76%) of the ketal **16** as a pale yellow oil (for characterization data, see below under alternative procedure).



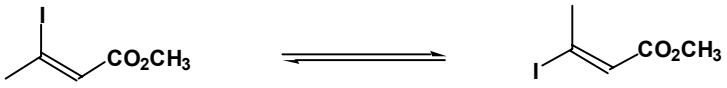
(2*R*,3*S*,4*R*)-(–)-3-[(*E*)-2-(Tri-*n*-butylstannyl)ethenyl]-2,3,4-trimethylcyclohexanone (18). A 250-mL, one-necked, round-bottomed flask equipped with a rubber septum was charged with a solution of bis(tri-*n*-butylstannyl)ethylene[9] (25.5 g, 42.1 mmol, 2.1 equiv) in 50 mL of THF and cooled at –78 °C while *n*-butyllithium (1.56 M in hexanes, 27 mL, 42 mmol, 2.1 equiv) was added dropwise by syringe over 15 min. The resulting yellow solution was stirred at –78 °C for 1 h. A 500-mL, one-necked, round-bottomed flask was charged with 1-pentynylcopper[8] (5.22 g, 40.0 mmol, 2.0 equiv), 50 mL of THF, and hexamethylphosphorous triamide (HMPT)

(14.5 mL, 13.0 g, 79.8 mmol, 4.0 equiv). The resulting mixture was stirred until a homogeneous yellow solution was obtained (10–30 min), and hexamethylphosphoric triamide (HMPA) (21.0 mL, 21.6 g, 121 mmol, 6.0 equiv) was then added in one portion by syringe. The resulting solution was cooled at –40 °C, and the solution of the vinyllithium reagent was added rapidly by cannula. The homogeneous reaction mixture was stirred at –40 °C for 1 h and then cooled at –78 °C while chlorotrimethylsilane (15.2 mL, 13.0 g, 120 mmol, 6.0 equiv) was added dropwise over 10 min. A solution of enone **9** (2.88 g, 20.8 mmol, 1.0 equiv) in 20 mL of THF was added dropwise by cannula over 10 min, the reaction mixture was stirred for 3 h at –78 °C, and then 150 mL of 1M KOH in methanol was added rapidly by cannula. The resulting mixture was allowed to warm to room temperature over 30 min and then added to 250 mL of hexanes and 250 mL of saturated NH_4Cl solution (buffered to pH 8 with NH_4OH) in an open 1-L flask and stirred vigorously for 12 h. The resulting biphasic mixture was filtered through a pad of Celite with the aid of 150 mL of hexanes and the organic phase was separated and washed with 100 mL of water and 100 mL of saturated NaCl solution. The combined aqueous layers were extracted with two 100-mL portions of hexanes and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 33 g of a pale yellow liquid. Purification by column chromatography on 264 g of silica gel (gradient elution with 0–4% ethyl acetate in 1% Et_3N–hexanes) provided 8.51 g (90%)[10] of stannane **18** as a colorless liquid: $[\alpha]^{20}_D$ –17° (*c* = 0.65, $CHCl_3$); IR (thin film) 2955, 2871, 1742, 1715, 1592, 1464, 1375, 1293, 1234, 1184, 1153, 1070, 997, 960, and 874 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (d, *J* = 19.2 Hz, 1H), 5.71 (d, *J* = 19.2 Hz, 1H), 2.33–2.49 (m, 3H), 1.88–1.99 (m, 2H), 1.42–1.68 (m, 7H), 1.24–1.38 (m, 6H), 0.80–1.06 (m, 21H), 0.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 155.9, 125.3, 53.0, 51.6, 41.8, 40.1, 31.5, 29.4, 27.4, 16.4, 13.9, 9.73, 9.70, 9.0. Anal. Calcd for $C_{23}H_{44}OSn$: C, 60.67; H, 9.74. Found: C, 60.33; H, 9.42.



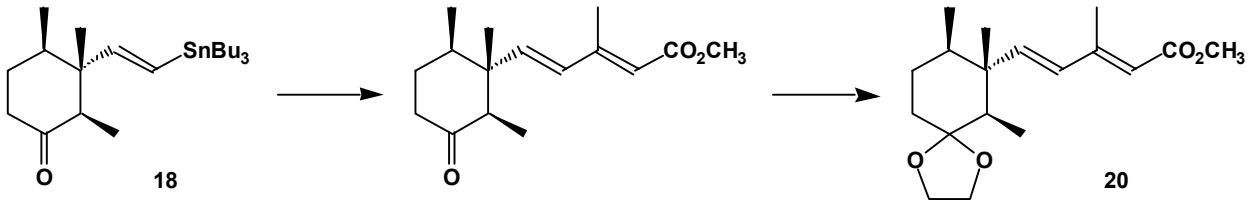
(*Z*)-3-Iodobut-2-enoic acid methyl ester.[11] A 100-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet was charged with methyl tetrolate (9.27 g, 94.5 mmol, 1.0 equiv), NaI (22.66 g, 151.2 mmol, 1.6 equiv), and acetic acid (35 mL, 37 g, 610 mol, 6.4 equiv). The resulting solution was heated at reflux for 90 min,

allowed to cool to room temperature, and partitioned between 150 mL of water and 150 mL of ether. The aqueous layer was separated and extracted with two 50-mL portions of ether. The combined organic layers were washed with two 150-mL portions of saturated $NaHCO_3$ solution, 150 mL of 10% $Na_2S_2O_3$ solution, and 150 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 17 g of a yellow-orange liquid. Short path distillation (bp 50 °C, 0.5 mmHg) provided 15.36 g (72%) of the vinyl iodide as a pale yellow liquid: IR (thin film) 2950, 2839, 2086, 1732, 1633, 1434, 1374, 1312, 1276, 1174, 1080, 1044, 970, 916, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.31 (q, J = 1.5 Hz, 1H), 3.76 (s, 3H), 2.74 (d, J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 125.3, 114.0, 51.7, 36.7.



19

(*E*)-3-Iodobut-2-enoic acid methyl ester (19). A solution of the (*Z*)-vinyl iodide (2.34 g, 10.4 mmol, 1.0 equiv) and iodine (0.027 g, 0.11 mmol, 0.01 equiv) in 21 mL of toluene in a 50-mL, threaded Pyrex tube was purged with argon for 20 minutes, sealed with a threaded Teflon cap, heated at 220 °C for 4 h, and then allowed to cool to room temperature. The resulting mixture was purified by column chromatography on 235 g of silica gel (gradient elution with 0–5% ether–pentane) and mixed fractions were combined and further purified on the same column (elution with 5% ether–pentane) to provide 1.55 g (66%) of the (*E*)-iodide (**19**) as a colorless oil and 0.63 g (27%) of recovered (*Z*)-iodide as a colorless oil which was ca. 90% pure by ^1H NMR analysis and could be recycled in a subsequent step. Spectral data for **19** was consistent with that reported previously:[12] IR (thin film) 2995, 2949, 2839, 1720, 1645, 1433, 1373, 1335, 1271, 1198, 1178, 1074, 1024, 954, 861, 608 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.64 (q, J = 1.5 Hz, 1H), 3.70 (s, 3H), 2.99 (d, J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 131.2, 120.9, 51.7, 31.2.

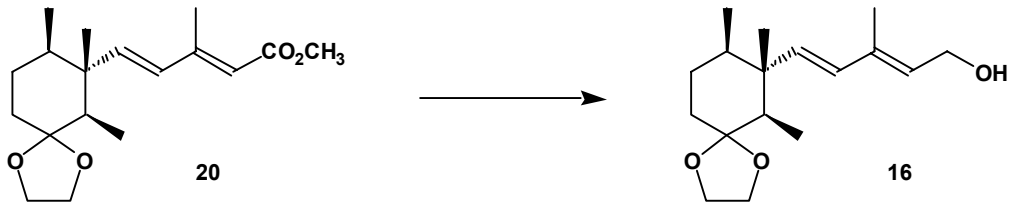


(+)-Methyl (2*E*,4*E*)-5-[(1*R*,2*R*,6*R*)-3,3-ethylenedioxy-1,2,6-trimethylcyclohexyl]-3-methylpenta-2,4-dienoate (20). A 100-mL, one-necked, round-bottomed flask was charged with stannane **18** (4.559 g, 10.01 mmol, 1.0 equiv), iodide **19** (2.72 g, 12.0 mmol, 1.2 equiv), Ph_3As (0.16 g, 0.52 mmol, 0.05 equiv), and 20 mL of NMP. This solution was degassed (three freeze-pump-thaw cycles) and flushed with argon, and $Pd(OAc)_2$ (0.056 g, 0.25 mmol, 0.025 equiv) was then added. The reaction mixture was stirred at 60 °C for 12 h and then 20 mL of 1 M KF solution was added in one portion. The resulting mixture was stirred vigorously while cooling to room temperature over 15 min, and then was filtered through a pad of Celite with the aid of 100 mL of ether. The organic layer was separated and washed with two 25-mL portions of water and 25 mL of saturated NaCl solution, and the combined aqueous layers were extracted with 25 mL of ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 4.69 g of an orange oil, which was used in the next step without further purification.

This compound was observed to undergo partial isomerization during attempted purification. A sample from another run was partially purified by column chromatography on silica gel to provide a sample for characterization: IR (thin film) 2971, 2875, 1714, 1634, 1614, 1434, 1376, 1357, 1274, 1240, 1157, 1019, 974, 918, 859, 792, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (d, J = 16 Hz, 1H), 5.92 (d, J = 16 Hz, 1H), 5.78 (s, 1H), 3.71 (s, 3H), 2.34–2.52 (m, 3H), 2.30 (s, 3H), 1.88–2.06 (m, 2H), 1.66 (apparent qd, J = 13.4, 5.0 Hz, 1H), 0.80–0.92 (m, 6H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 167.7, 152.3, 144.4, 132.3, 118.5, 53.1, 51.2, 49.0, 41.6, 40.7, 31.3, 16.5, 14.2, 10.4, 9.2.

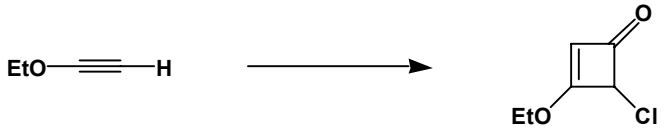
A 250-mL, one-necked, round-bottomed flask was equipped with a Claisen adapter fitted with a glass stopper and Dean–Stark trap. The Dean–Stark trap was equipped with a reflux condenser and an argon inlet. This apparatus was charged with the crude ketone (4.69 g, ≤ 10 mmol), ethylene glycol (5.6 mL, 6.2 g, 100 mmol, ≥ 10 equiv), 100 mL of benzene, and *p*-TsOH•H_2O (1.9 g, 10 mmol, ≥ 1 equiv). The reaction mixture was heated at reflux in an oil bath at ca. 130 °C for 90 min and then allowed to cool to room temperature. Saturated $NaHCO_3$

solution (50 mL) was added, and the resulting mixture was washed with 50 mL of water and 50 mL of saturated NaCl solution (emulsions were broken up with a glass rod). The combined aqueous layers were extracted with 50 mL of ether, and the combined organic phases were dried over $MgSO_4$, filtered through a pad of Celite, and concentrated to give 4.42 g of a yellow solid. This material was deposited onto 9 g of silica gel and purified by column chromatography on 180 g of silica gel (gradient elution with 10–30% ether–pentane) to provide 2.776 g of a cream-colored solid. Recrystallization from 10 mL of hot hexanes provided 1.940 g (63% overall from stannane **18**) of ketal **20** as colorless plates: mp 122 °C; $[\alpha]^{20}_D$ +13.4° (*c* = 1.34, $CHCl_3$); IR (CH_2Cl_2) 3054, 2949, 2881, 1709, 1632, 1611, 1437, 1356, 1244, 1161, 1100, 1070, 1018, 974, 906, 728, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (d, *J* = 16 Hz, 1H), 5.81 (d, *J* = 16 Hz, 1 H), 5.75 (s, 1H), 3.89–4.03 (m, 3H), 3.76–3.83 (m, 1H), 3.70 (s, 3H), 2.28 (s, 3H), 1.79–1.86 (m, 1H), 1.71 (q, *J* = 7 Hz, 1 H), 1.40–1.52 (m, 4H), 0.93 (s, 3H), 0.74 (d, *J* = 7 Hz, 3H), 0.72 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 153.1, 147.8, 132.0, 117.5, 110.4, 65.8, 64.3, 51.2, 47.2, 45.5, 40.8, 35.8, 28.1, 16.8, 14.2, 10.4, 8.5. Anal. Calcd for $C_{18}H_{24}O_4$: C, 70.10; H, 9.15. Found: C, 70.32; H, 9.30.



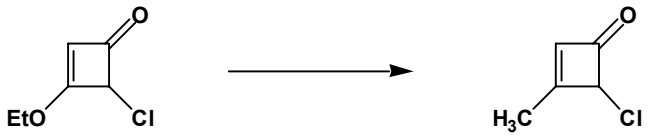
(2*E*,4*E*)-5-[(1*R*,2*R*,6*R*)-3,3-Ethylenedioxy-1,2,6-trimethylcyclohexyl]-3-methylpenta-2,4-dien-1-ol (16). A 50-mL, one-necked, round-bottomed flask was charged with a solution of ester **20** (0.791 g, 2.56 mmol, 1.0 equiv) in 25 mL of ether and cooled in a room temperature water bath while $LiAlH_4$ (1.0 M in THF, 3.1 mL, 3.1 mmol, 1.2 equiv) was added dropwise over 75 sec. The reaction mixture was stirred for 2 min and then water (0.55 mL, 0.55 g, 31 mmol, 12 equiv) was added dropwise by syringe over 30 sec (caution: evolution of gas). The resulting mixture was stirred for 5 min, and then deposited onto 1.4 g of silica gel and purified by column chromatography on 14 g of silica gel (elution with 50% ether–pentane) to provide 0.699 g (97%) of alcohol **16** as a viscous gel: $[\alpha]^{20}_D$ 0° (*c* = 2.22, $CHCl_3$) (lit:[13] $[\alpha]^{22}_D$ –1.4° (*c* = 0.98, $CHCl_3$)). Spectral data for **16** was consistent with that previously reported:[13,14] IR (thin film) 3410, 2930, 2361, 1949, 1844, 1644, 1623, 1455, 1384, 1303, 1276, 1180, 1153, 1066, 904, 876, 793, 734,

676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (d, *J* = 16.2 Hz, 1H), 5.61 (t, *J* = 7.0 Hz, 1H), 5.38 (d, *J* = 16.2 Hz, 1H), 4.28 (apparent t, *J* = 6.3 Hz, 2H), 3.89–4.03 (m, 3H), 3.76–3.82 (m, 1H), 1.78–1.84 (m, 4H), 1.68 (q, *J* = 7.0 Hz, 1H), 1.37–1.52 (m, 5H), 0.90 (s, 3H), 0.75 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 136.6, 132.0, 127.8, 110.5, 65.6, 64.0, 59.3, 47.3, 44.7, 40.8, 35.7, 27.9, 16.6, 12.8, 10.3, 8.3. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.89; H, 10.44.



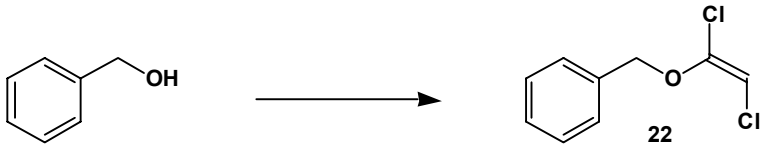
21

4-Chloro-3-ethoxycyclobut-2-enone (21). A 50-mL, one-necked, round-bottomed flask was charged with ethoxyacetylene (46% solution in hexanes, 0.697 g, 4.6 mmol, 1.0 equiv) and cooled to –78 °C. Ether (10 mL) and triethylamine (1.25 mL, 0.908 g, 8.97 mmol, 2.0 equiv) were added, and the resulting solution was stirred for five min (to ensure thorough cooling) and then chloroacetyl chloride (0.71 mL, 1.0 g, 8.9 mmol, 2.0 equiv) was added over 2 min. The resulting white suspension was allowed to warm to room temperature over 14 h and then was filtered through a pad of Celite with the aid of 20 mL of ether. The filtrate was washed with 20 mL of saturated $NaHCO_3$ solution and 20 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated (rotary evaporator, 0 °C bath) to give an orange oil. Purification by column chromatography on 35 g of silica gel (elution with 50% ether–pentane) provided 0.362 g (54%) of cyclobutenone **21** as an orange oil, which as a precaution was stored in CH_2Cl_2 under argon at –78 °C: IR (thin film) 3097, 2987, 2901, 1774, 1585, 1469, 1400, 1324, 1215, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, *J* = 0.9 Hz, 1H), 5.16 (d, *J* = 0.9 Hz, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.52 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 179.7, 110.9, 70.9, 65.9, 14.2. HRMS Calcd for $C_6H_7ClO_2$: 146.0135. Found: 146.0137 ± 0.0004.



21 **4**

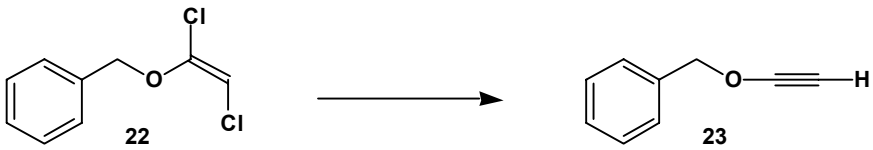
4-Chloro-3-methylcyclobut-2-enone (4). A 50-mL, one-necked, round-bottomed flask was charged with ketone **21** (0.627 g, 4.28 mmol, 1.0 equiv) and 10 mL of THF and the resulting solution was cooled at –78 °C while methyllithium (1.4 M in ether, 3.2 mL, 4.5 mmol, 1.05 equiv) was added dropwise over 3 min. The reaction mixture was maintained at –78 °C for 1 h, and then trifluoroacetic anhydride (0.73 mL, 1.1 g, 5.2 mmol, 1.2 equiv) was added in one portion by syringe. After 4 h, 10 mL of saturated $NaHCO_3$ solution was added in one portion and the resulting mixture was allowed to warm to room temperature over 20 min and then partitioned between 20 mL of water and 20 mL of ether. The organic layer was washed with 10 mL of saturated $NaHCO_3$ solution and 10 mL of saturated NaCl solution, and the combined aqueous layers were then extracted with two 10-mL portions of ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated (rotary evaporator, 0 °C bath) to give 0.940 g of a purple oil. Purification by column chromatography on 25 g of silica gel (elution with 30% ether–pentane) provided 0.377 g (76%) of cyclobutenone **4** as a yellow oil: IR (thin film) 3536, 3084, 2986, 2361, 2099, 1789, 1591, 1428, 1373, 1277, 1219, 1139, 1052, 1022, 960, 862, 811, 617, 588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.17 (apparent s, 1H), 5.21 (apparent s, 1H), 2.34 (apparent s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 178.7, 138.5, 70.2, 14.8. HRMS Calcd for C_5H_5ClO: 116.0029. Found: 116.0031 ± 0.0004.



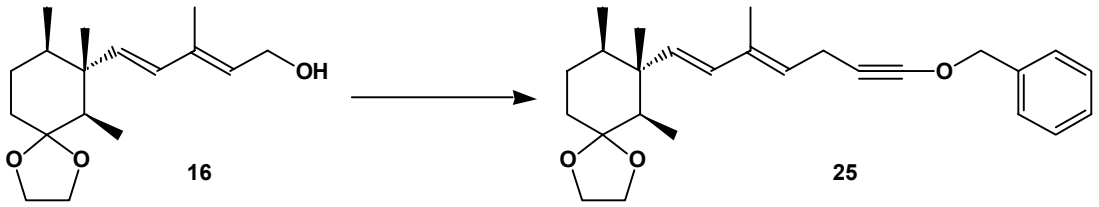
22

Benzyl (1,2-dichlorovinyl) ether (22). A 500-mL, three-necked, round-bottomed flask equipped with a 125-mL pressure-equalizing dropping funnel, mechanical stirrer, and rubber septum was charged with KH (28% by weight in mineral oil, 21.4 g, 150 mmol, 1.5 equiv). The KH was rinsed with three 20-mL portions of hexanes and then suspended in 125 mL of THF. A solution of benzyl alcohol (10.83 g, 100 mmol, 1.0 equiv) in 100 mL of THF was then added dropwise over 20 min to give a thick gray slurry that was stirred for 30 min. This slurry was cooled at –78 °C while a solution of trichloroethylene (15.77 g, 120 mmol, 1.2 equiv) in 60 mL of THF was added dropwise over 10 min. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. Water (10 mL) was added carefully over 2 min to the dark brown mixture, which was then partitioned between 300 mL of water and 250 mL of

pentane. The organic phase was separated and washed with 150 mL of saturated NaCl solution. The combined aqueous layers were extracted with two 100-mL portions of pentane, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give a brown oil. Column chromatography on 200 g of silica gel (elution with pentane) provided 16.83 g of a dark liquid. Short path distillation (bp 69 °C, 0.3 mmHg) furnished 15.48 g (76%) of vinyl ether **22** as a pale yellow liquid: IR (thin film) 3106, 3034, 2948, 2887, 1952, 1876, 1809, 1764, 1625, 1497, 1456, 1376, 1273, 1211, 1086, 1029, 977, 911, 822, 762, 728, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.48 (m, 5H), 5.47 (s, 1H), 5.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 134.7, 128.7, 128.49, 128.48, 98.8, 73.4. Anal. Calcd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97. Found: C, 53.17; H, 3.97.



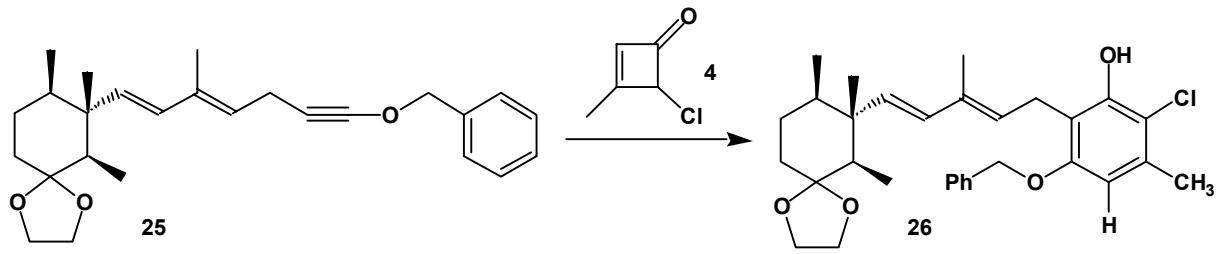
Benzyloxyethyne (23). A 50-mL, one-necked, round-bottomed flask was charged with vinyl ether **22** (1.02 g, 5.02 mmol, 1.0 equiv), 20 mL of ether, and TMEDA (1.5 mL, 1.2 g, 10 mmol, 2.0 equiv) and cooled at –78 °C while *n*-butyllithium (2.30 M in hexanes, 4.4 mL, 10 mmol, 2.0 equiv) was added dropwise over 3 min. The reaction mixture was stirred at –78 °C for 30 min and at –40 °C for 30 min, and then cooled at –78 °C while 6 mL of 10% ethanol–pentane was added. After 5 min, the cold mixture was diluted with 14 mL of pentane and washed with 20 mL of water, 20 mL of half-saturated NaCl solution, 20 mL of water, and 20 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated (rotary evaporator, 0 °C bath) to give a purple oil. Bulb-to-bulb distillation (≤50 °C bath temp, 0.05 mmHg) provided 0.400 g (60%) of benzyloxyethyne as a yellow-orange oil. This compound is unstable to storage at room temperature, and was generally used immediately after preparation or stored in THF at –78 °C: IR (thin film) 3316, 3035, 2955, 2872, 2425, 2148, 1956, 1886, 1813, 1732, 1575, 1497, 1456, 1369, 1246, 1215, 1105, 886, 849, 746, 697 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.03 (apparent s, 5H), 4.50 (s, 2H), 1.47 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 134.9, 129.6, 129.4, 129.0, 91.3, 80.3, 28.5. HRMS Calcd for C_9H_8O: 132.0575. Found: 132.0573 ± 0.0004.



(–)-Benzyl (4*E*,6*E*)-7-[(1*R*,2*R*,6*R*)-3,3-ethylenedioxy-1,2,6-trimethylcyclohexyl]-5-methylhepta-4,6-dien-1-ynyl ether (25). A 100-mL, one-necked, round-bottomed flask was charged with alcohol **16** (1.177 g, 4.20 mmol, 1.0 equiv) and 50 mL of toluene and the solution was concentrated by rotary evaporation to azeotropically remove traces of water. This procedure was repeated twice more and then the flask was equipped with a rubber septum and an inlet needle connected to an argon-vacuum manifold. The residue was concentrated at 0.1 mmHg and then dissolved in 20 mL of THF. The resulting solution was cooled at –78 °C while *n*-butyllithium[15] (1.56 M in hexanes, 2.80 mL, 4.37 mmol, 1.04 equiv) was added dropwise over 3 min to give a yellow-brown solution. After 15 min, methanesulfonyl chloride[15] (0.35 mL, 0.52 g, 4.5 mmol, 1.1 equiv) was added in one portion by syringe, and the resulting clear yellow solution was stirred at –78 °C for 1.5 h. A solution of Li_2CuCl_4[16] (0.1 M in THF, 4.2 mL, 0.42 mmol, 0.1 equiv) was added by syringe over 1 min and the resulting mixture was immediately treated with the Grignard reagent prepared as described below.

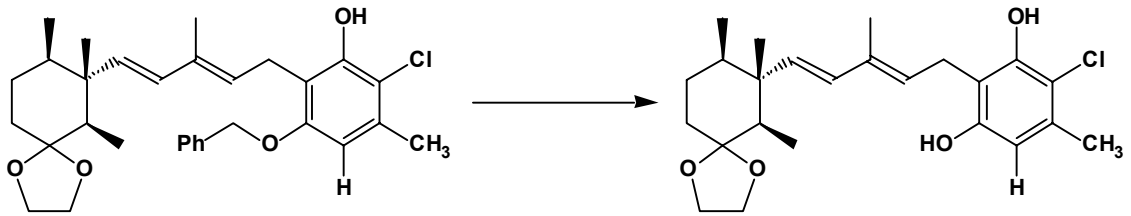
The Grignard derivative of benzyloxyethyne was prepared by adding ethylmagnesium bromide (3.04 M in ether, 4.0 mL, 12 mmol, 2.9 equiv) dropwise by syringe over 3 min to benzyloxyethyne (2.20 g, 16.6 mmol, 4.0 equiv) in 25 mL of THF at 0 °C in a 50-mL, one-necked, pear-shaped flask. The resulting yellow-brown solution was stirred for 1 h and then transferred via cannula over 30 min to the mesylate solution at –78 °C. The resulting orange solution was stirred at 0 °C for 2.5 h, and then excess Grignard reagent was quenched by bubbling CO_2 (passed through a U-tube of $CaSO_4$ to remove water) through the reaction mixture for 20 min while it warmed to room temperature. The resulting purple solution was added to 100 mL of ether and 100 mL of saturated NH_4Cl (buffered to pH 8 with NH_4OH) in an open 500-mL flask and stirred vigorously for 15 min. The organic layer was separated and washed with 100 mL of half-saturated NH_4Cl solution (buffered to pH 8 with NH_4OH), 100 mL of half-saturated $NaHCO_3$ solution, and 100 mL of saturated NaCl solution. The combined aqueous phases were extracted with two 50-mL portions of ether and the combined organic phases were diluted with an equal volume (ca. 400 mL) of pentane, dried over Na_2SO_4, filtered, and concentrated to give

ca. 3 g of a purple oil. Column chromatography on 83 g of silica gel (gradient elution with 0–10% ethyl acetate in 1% Et_3N–hexanes) provided 1.390 g of a yellow oil, which was further purified on 157 g of silica gel (gradient elution with 5–10% ethyl acetate in 1% Et_3N–hexanes) to afford 1.272 g (77%) of acetylene **25** as a yellow oil. This compound is unstable to standing at room temperature but can be stored frozen in benzene at –78 °C for several weeks without detectable decomposition: IR (thin film) 3032, 2940, 2876, 2270, 1955, 1813, 1752, 1456, 1373, 1304, 1275, 1232, 1180, 1152, 1100, 1070, 1016, 1000, 969, 949, 905, 739, 696, 679 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.00–7.17 (m, 5H), 6.07 (d, J = 15.9 Hz, 1H), 5.54 (t, J = 7.0 Hz, 1H), 5.26 (d, J = 15.9 Hz, 1H), 4.59 (s, 2H), 3.41–3.62 (m, 4H), 2.94 (d, J = 7.0 Hz, 2H), 1.75–1.82 (m, 2H), 1.61 (s) and 1.46–1.64 (m, total 5H), 1.33–1.42 (m, 1H), 1.20–1.33 (m, 1H), 1.12 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.6, 135.7, 134.7, 133.2, 129.33, 129.27, 129.0, 128.9, 127.2, 111.0, 90.4, 79.9, 66.0, 64.4, 48.2, 45.3, 41.5, 37.6, 36.5, 28.7, 17.29, 17.26, 12.9, 11.1, 9.0. HRMS Calcd for $C_{26}H_{34}O_3$: 394.2508. Found: 394.2501 ± 0.0012.



(–)-5-Benzyloxy-2-chloro-6-[(2*E*,4*E*)-5-{(1*R*,2*R*,6*R*)-3,3-ethylenedioxy-1,2,6-trimethylcyclohexyl}-3-methylpenta-2,4-dienyl]-3-methylphenol (26). A 20-cm Vycor tube (9-mm outer diameter, 7-mm inner diameter) was charged with acetylene **25** (0.592 g, 1.50 mmol, 1.0 equiv), cyclobutenone **4** (0.211 g, 1.81 mmol, 1.2 equiv) and 2 mL of benzene-d_6 and sealed with a rubber septum. The yellow-orange solution was purged with argon for 30 min, and the tube was then suspended in a large silvered Dewar flask filled with room temperature water. The reaction mixture was irradiated with a 450-watt Hanovia lamp through a Pyrex filter with tap-water cooling for 40 h and then concentrated to give a yellow oil. This oil was dissolved in 10 mL of toluene in a 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet. The resulting solution was heated at reflux for 4 h, and then cooled to room temperature and concentrated. Column chromatography on 80 g of silica gel (gradient elution

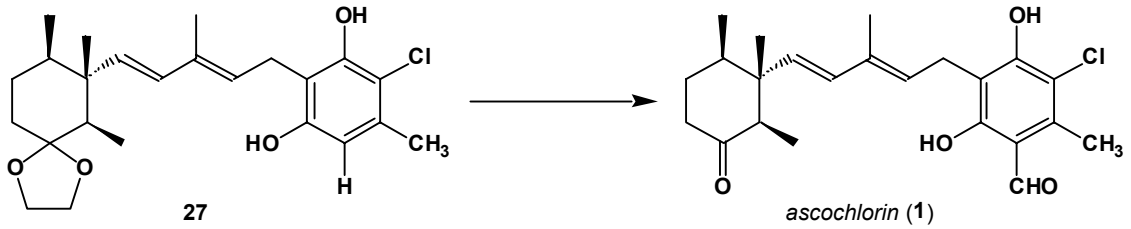
with 10–20% ethyl acetate–hexanes) provided 0.312 g (41%) of phenol **26** as a colorless oil, along with 0.343 g of a yellow oil which is believed to be phenol **26** contaminated with a mixture of esters arising from reaction of **26** with excess vinylketene. This yellow oil was dissolved in 5 mL of THF and 5 mL of 1 M KOH in methanol in a 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet. The solution was heated at reflux for 12 h, cooled to room temperature, and partitioned between 50 mL of ether and 25 mL of saturated NH_4Cl solution. The organic layer was washed with 25 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. Purification of this oil on 40 g of silica gel (elution with 10% ethyl acetate–hexanes) provided an additional 0.185 g (24%) of phenol **26** as a pale yellow oil. The total yield of **26** was 0.497 g (65%). This material is contaminated with a small amount (ca. 5%) of an unidentified by-product. The product is unstable to storage as a neat oil, and was generally stored frozen as a dilute solution in benzene: IR ($CDCl_3$) 3532, 3398, 2936, 1950, 1749, 1606, 1580, 1498, 1454, 1409, 1344, 1275, 1226, 1166, 1064, 970, 922, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29–7.42 (m, 5H), 6.42 (s, 1H), 5.89 (d, J = 15.9 Hz, 1H), 5.69 (s, 1H), 5.48 (t, J = 7.2 Hz, 1H), 5.21 (d, J = 15.9 Hz, 1H), 5.04 (s, 2H), 3.87–4.02 (m, 3H), 3.75–3.82 (m, 1H), 3.55 (d, J = 7.2 Hz, 2H), 2.31 (s, 3H), 1.78–1.82 (m, 4H), 1.65 (q, J = 6.8 Hz, 1H), 1.33–1.50 (m, 4H), 0.85 (s, 3H), 0.70–0.76 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 150.0, 138.3, 137.2, 133.93, 133.89, 133.1, 128.7, 128.05, 128.00, 127.4, 114.9, 113.3, 110.8, 106.6, 70.5, 65.7, 64.2, 47.6, 44.7, 41.1, 35.9, 28.1, 23.4, 20.5, 16.8, 12.8, 10.5, 8.5. HRMS Calcd for $C_{31}H_{39}ClO_4$: 510.2537. Found: 510.2522 ± 0.0015.



26 **27**

(–)-4-Chloro-2-[(2*E*,4*E*)-5-{(1*R*,2*R*,6*R*)-3,3-ethylenedioxy-1,2,6-trimethylcyclohexyl}-3-methylpenta-2,4-dienyl]-5-methylbenzene-1,3-diol (27). A 10-mL, one-necked, pear-shaped flask was charged with $Pd(OAc)_2$ (0.021 g, 0.094 mmol), 0.8 mL of CH_2Cl_2, triethylamine (0.040 mL, 0.029 g, 0.29 mmol), and triethylsilane (0.80 mL, 0.58 g, 5.0 mmol) and stirred at room temperature for 10 min. Approximately half (0.8 mL) of the black mixture was transferred

by syringe in one portion to a solution of benzyl ether **26** (0.127 g, 0.248 mmol) in 1.0 mL of CH_2Cl_2 in a 15-mL, one-necked, pear-shaped flask. The resulting black mixture was stirred at room temperature for 15 h, and then cooled at 0 °C while TBAF (1.0 M in THF, 5 mL, 5 mmol) was added rapidly dropwise. The resulting mixture was stirred at 0 °C for 15 min, and then poured into 25 mL of saturated NH_4Cl solution and filtered through a pad of Celite with the aid of 25 mL of ether. The filtrate was diluted with 25 mL of water, and the aqueous layer was separated and extracted with 25 mL of ether. The combined organic layers were washed with 25 mL of 1 M HCl solution, 25 mL of saturated $NaHCO_3$ solution, and 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.340 g yellow oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 10–30% ethyl acetate–hexanes) provided 0.074 g (70%) of resorcinol **27** as a white foam which was ca. 95% pure by ^{1}H NMR analysis: $[\alpha]^{20}_D$ –20° (*c* = 1.45, benzene); IR (benzene) 3532, 3363, 3090, 3070, 3035, 2977, 2876, 2280, 1960, 1815, 1710, 1615, 1592, 1479, 1456, 1413, 1349, 1276, 1235, 1175, 1100, 1068, 1036, 970, 905, 827, 676 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.10 (d, *J* = 16 Hz, 1H), 5.86 (s, 1H), 5.77 (t, *J* = 7.4 Hz, 1H), 5.60 (s, 1H), 5.31 (d, *J* = 16 Hz, 1H), 4.99 (s, 1H), 3.72 (d, *J* = 7.4 Hz, 2H), 3.40–3.57 (m, 4H), 2.08 (s, 3H), 1.98 (s, 3H), 1.74–1.87 (m, 2H), 1.47–1.61 (m, 2H), 1.33–1.40 (m, 1H), 1.19–1.30 (m, 1H), 1.08 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 154.0, 151.0, 139.1, 134.8, 134.3, 133.8, 128.7, 113.6, 112.8, 111.3, 110.2, 65.9, 64.4, 48.2, 45.3, 41.5, 36.4, 28.7, 24.0, 20.2, 17.3, 13.3, 11.1, 9.0. HRMS Calcd for $C_{24}H_{33}ClO_4$: 420.2067. Found: 420.2076 ± 0.0013.

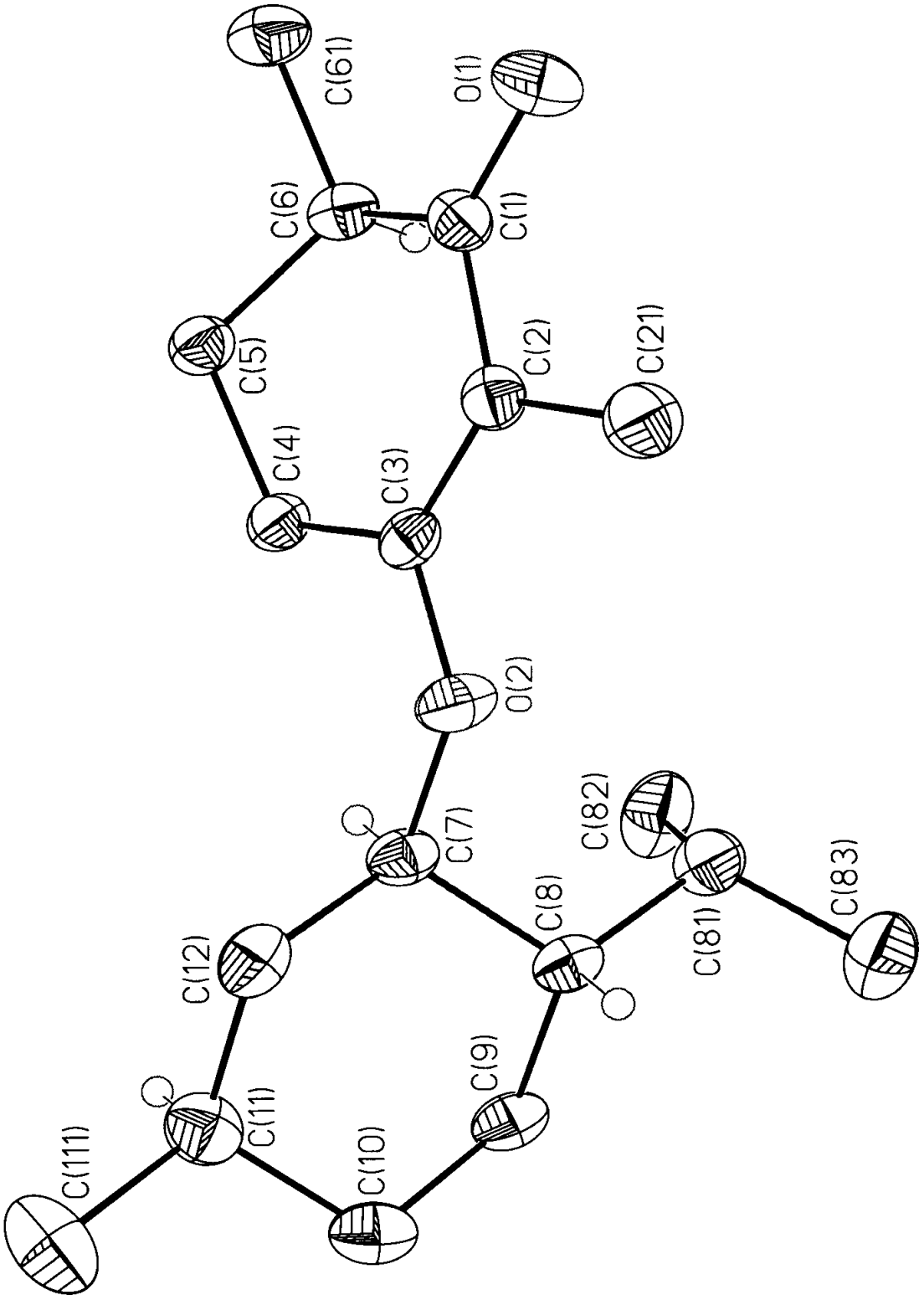


(–)-5-Chloro-2,4-dihydroxy-6-methyl-3-[(2*E*,4*E*)-5-{(1*R*,2*R*,6*R*)-1,2,6-trimethyl-3-oxocyclohexyl}-3-methylpenta-2,4-dienyl]benzaldehyde; (–)-Ascochlorin (1). A 10-mL, one-necked, pear-shaped flask was charged with resorcinol **27** (0.070 g, 0.16 mmol, 1.0 equiv) and 5 mL of toluene and the solution was concentrated by rotary evaporation to azeotropically remove any traces of water. This procedure was repeated twice and the flask was equipped with a rubber septum and an inlet needle connected to an argon-vacuum manifold. The residue was

concentrated at 0.1 mmHg and then dissolved in 2 mL of ether. A solution of ethylmagnesium bromide (0.28 M in ether, 1.45 mL, 0.41 mmol, 2.5 equiv) was added dropwise by syringe over 5 min to produce a white suspension which was stirred at room temperature for 30 min. Triethyl orthoformate (0.27 mL, 0.24 g, 1.6 mmol, 10 equiv) was then added in one portion, the flask was vented with an outlet needle connected to a $CaSO_4$ drying tube, and the solvent was distilled off by heating the reaction mixture to 100 °C over 15 min. The outlet needle was removed and the resulting brown gum was heated further for 10 min at 100 °C, cooled to room temperature, and partitioned between 32 mL of 0.1 M HCl solution and 16 mL of ether. The aqueous layer was separated and extracted with 16 mL of ether, and the combined organic layers were washed with 16 mL of saturated $NaHCO_3$ solution and 16 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.080 g of an orange foam. Column chromatography on 15 g of silica gel (gradient elution with 10–30% ethyl acetate–hexanes) provided 0.075 g of a colorless oil. This material was dissolved in 1 mL of ether in a 10-mL, pear-shaped flask, cooled to 0 °C, and 0.4 mL of 35% $HClO_4$ solution was then added and the biphasic mixture was stirred vigorously for 10 min before being quenched with 2 mL of 10% K_2CO_3 solution and 5 mL of water. The resulting mixture was extracted with 20 mL of ether, and the organic layer was washed with 5 mL of water and 5 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.030 g of a pale yellow solid. Purification by column chromatography on 3 g of silica gel (elution with 20% ethyl acetate–hexanes) provided 0.030 g (45%) of (–)-ascochlorin (**1**) as a pale yellow solid. An analytical sample was obtained by dissolving this material in 1 mL of hot methanol, allowing it to stand at –18 °C for 24 h, and then filtering and washing with three portions of cold (–18 °C) methanol. This provided 0.020 g (30%) of (–)-ascochlorin as a pale yellow, microcrystalline solid: mp 172–174 °C (lit:[17] 172–173 °C); $[\alpha]^{20}_D$ –31° (*c* = 0.49, CH_3OH) (lit:[17] $[\alpha]^{25}_D$ –31° (*c* = 0.99, CH_3OH)) with spectral data consistent with that reported previously:[18] IR (CH_2Cl_2) 3501, 3054, 2977, 2876, 1707, 1633, 1455, 1423, 1375, 1326, 1288, 1272, 1255, 1109, 1011, 972, 896, 792, 770, 694, 590 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.72 (s, 1H), 10.15 (s, 1H), 6.37 (s, 1H), 5.90 (d, *J* = 16 Hz, 1H), 5.52 (t, *J* = 7.4 Hz, 1H), 5.38 (d, *J* = 16 Hz, 1H), 3.54 (d, *J* = 7.4 Hz, 2H), 2.61 (s, 3H), 2.33–2.47 (m, 3H), 1.93 (s, 3H), 1.88–1.98 (m, 2H), 1.62 (qd, *J* = 13.5, 5.2 Hz, 1H), 0.80–0.85 (m, 6H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 193.3, 162.2, 156.2, 137.8, 135.7, 134.1, 133.2, 127.5, 113.8,

113.6, 113.2, 53.6, 48.5, 41.6, 40.8, 31.1, 22.2, 16.3, 14.5, 12.6, 10.3, 8.9. Anal. Calcd for $C_{23}H_{29}ClO_4$: C, 68.22; H, 7.22. Found: C, 67.93; H, 7.38.

X-Ray Crystallographic Data for Compound **11**



X-Ray Crystallographic Data for Compound **11**

Table 1. Crystal data and structure refinement for 1.

Identification code	97134
Empirical formula	$C_{18}H_{30}O_2$
Formula weight	278.42
Temperature	178(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.5620(2) Å alpha = 90° b = 10.9677(3) Å beta = 90° c = 16.2726(4) Å gamma = 90°
Volume, Z	1706.56(7) Å^3, 4
Density (calculated)	1.084 Mg/m^3
Absorption coefficient	0.068 mm^{-1}
F(000)	616
Crystal size	0.39 x 0.18 x 0.18 mm
θ range for data collection	2.24 to 23.26°
Limiting indices	$-9 \le h \le 10$, $-12 \le k \le 12$, $-10 \le l \le 18$
Reflections collected	6872
Independent reflections	2444 (R_{int} = 0.0532)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2444 / 0 / 181
Goodness-of-fit on F^2	1.130
Final R indices [I>2σ(I)]	R1 = 0.0456, wR2 = 0.1031
R indices (all data)	R1 = 0.0509, wR2 = 0.1070
Absolute structure parameter	-1(2)
Largest diff. peak and hole	0.112 and -0.157 eÅ^{-3}

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	1257(2)	-1711(2)	-5351(1)	52(1)
O(2)	-1281(2)	-1143(2)	-7750(1)	42(1)
C(1)	266(2)	-2017(2)	-5783(2)	34(1)
C(2)	12(2)	-1436(2)	-6575(2)	33(1)
C(3)	-1081(2)	-1780(2)	-7044(1)	31(1)
C(4)	-2039(2)	-2813(2)	-6834(2)	35(1)
C(5)	-1383(3)	-3665(2)	-6203(2)	37(1)
C(6)	-772(2)	-2963(2)	-5483(1)	35(1)
C(7)	-2541(2)	-1265(2)	-8249(2)	36(1)
C(8)	-3077(2)	14(2)	-8426(2)	36(1)
C(9)	-4332(3)	-102(3)	-9012(2)	44(1)
C(10)	-3946(3)	-767(3)	-9801(2)	50(1)
C(11)	-3368(3)	-2038(3)	-9636(2)	46(1)
C(12)	-2154(3)	-1950(2)	-9030(2)	43(1)
C(21)	941(3)	-397(2)	-6829(2)	46(1)
C(61)	-160(3)	-3807(3)	-4833(2)	50(1)
C(81)	-3366(3)	759(2)	-7645(2)	46(1)
C(82)	-4585(4)	285(3)	-7138(2)	67(1)
C(83)	-3584(3)	2099(3)	-7835(2)	62(1)
C(111)	-2917(4)	-2675(3)	-10421(2)	71(1)

X-Ray Crystallographic Data for Compound **11**

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.227(3)	O(2)-C(3)	1.358(3)
O(2)-C(7)	1.458(3)	C(1)-C(2)	1.459(3)
C(1)-C(6)	1.516(3)	C(2)-C(3)	1.348(3)
C(2)-C(21)	1.502(3)	C(3)-C(4)	1.496(3)
C(4)-C(5)	1.524(3)	C(5)-C(6)	1.519(3)
C(6)-C(61)	1.523(3)	C(7)-C(8)	1.521(3)
C(7)-C(12)	1.521(4)	C(8)-C(81)	1.536(4)
C(8)-C(9)	1.537(3)	C(9)-C(10)	1.522(4)
C(10)-C(11)	1.524(4)	C(11)-C(111)	1.519(4)
C(11)-C(12)	1.526(4)	C(81)-C(83)	1.517(4)
C(81)-C(82)	1.521(4)		

C(3)-O(2)-C(7)	122.7(2)	O(1)-C(1)-C(2)	121.0(2)
O(1)-C(1)-C(6)	120.6(2)	C(2)-C(1)-C(6)	118.3(2)
C(3)-C(2)-C(1)	120.5(2)	C(3)-C(2)-C(21)	121.0(2)
C(1)-C(2)-C(21)	118.4(2)	C(2)-C(3)-O(2)	116.4(2)
C(2)-C(3)-C(4)	123.9(2)	O(2)-C(3)-C(4)	119.7(2)
C(3)-C(4)-C(5)	111.5(2)	C(6)-C(5)-C(4)	111.5(2)
C(1)-C(6)-C(5)	110.5(2)	C(1)-C(6)-C(61)	112.8(2)
C(5)-C(6)-C(61)	112.0(2)	O(2)-C(7)-C(8)	107.5(2)
O(2)-C(7)-C(12)	108.0(2)	C(8)-C(7)-C(12)	112.2(2)
C(7)-C(8)-C(81)	113.2(2)	C(7)-C(8)-C(9)	107.8(2)
C(81)-C(8)-C(9)	114.6(2)	C(10)-C(9)-C(8)	111.9(2)
C(9)-C(10)-C(11)	112.2(2)	C(111)-C(11)-C(10)	112.1(2)
C(111)-C(11)-C(12)	110.9(2)	C(10)-C(11)-C(12)	109.3(2)
C(7)-C(12)-C(11)	112.7(2)	C(83)-C(81)-C(82)	109.7(2)
C(83)-C(81)-C(8)	111.8(2)	C(82)-C(81)-C(8)	113.9(2)

Symmetry transformations used to generate equivalent atoms:

X-Ray Crystallographic Data for Compound **11**

Table 4. Anisotropic displacement parameters [Å^2 x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

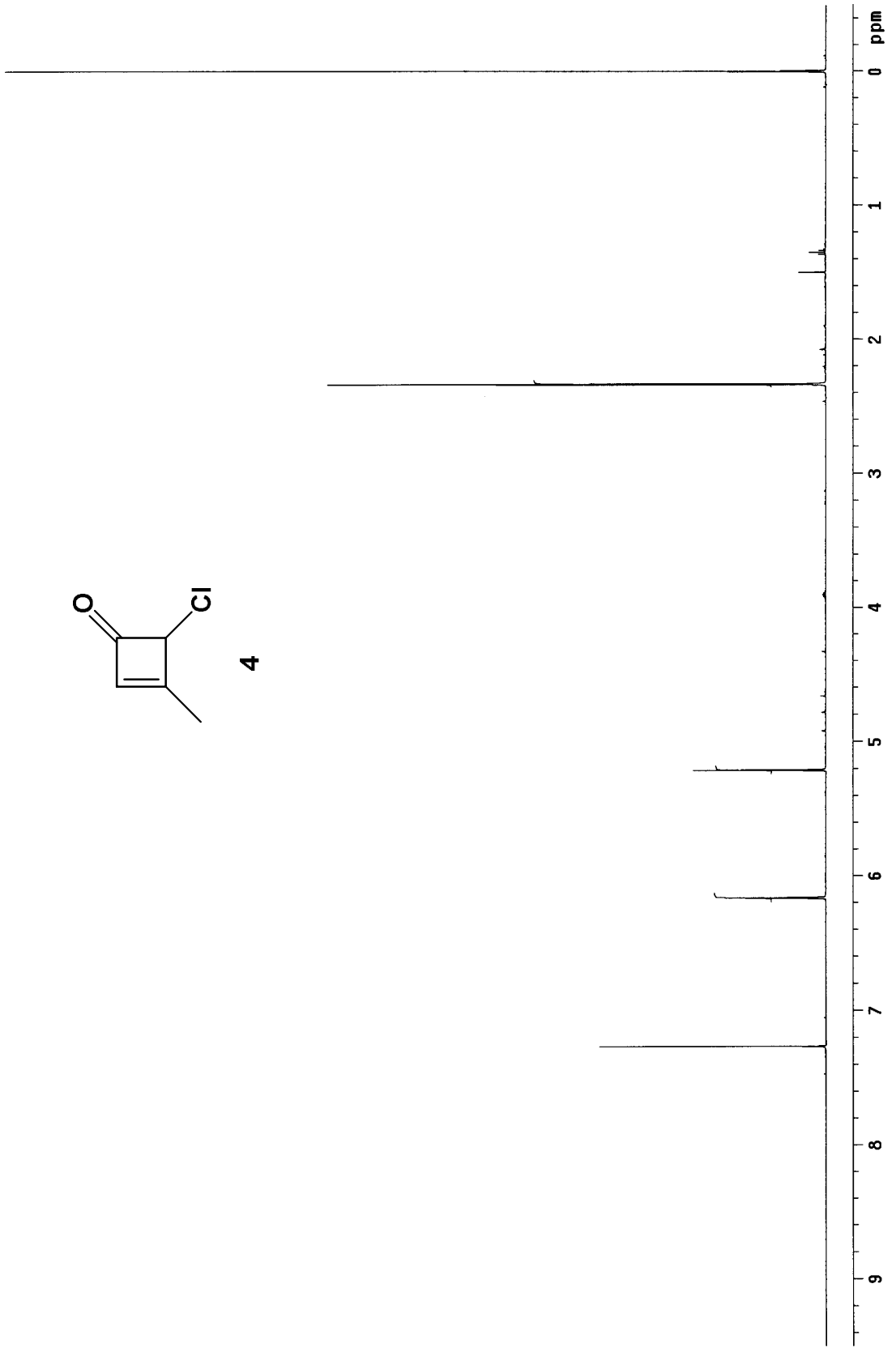
$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
O(1)	39(1)	68(1)	48(1)	0(1)	-12(1)	-5(1)
O(2)	36(1)	46(1)	44(1)	17(1)	-10(1)	-5(1)
C(1)	26(1)	39(1)	37(1)	-8(1)	-2(1)	7(1)
C(2)	27(1)	34(1)	38(1)	-2(1)	0(1)	2(1)
C(3)	29(1)	30(1)	34(1)	3(1)	3(1)	6(1)
C(4)	34(1)	32(1)	39(1)	4(1)	-4(1)	-1(1)
C(5)	39(1)	35(1)	38(1)	5(1)	-3(1)	-1(1)
C(6)	31(1)	44(1)	30(1)	5(1)	4(1)	8(1)
C(7)	27(1)	41(1)	38(1)	8(1)	-5(1)	-2(1)
C(8)	34(1)	39(1)	35(1)	10(1)	0(1)	0(1)
C(9)	38(1)	48(2)	46(2)	12(1)	-7(1)	8(1)
C(10)	46(2)	64(2)	41(2)	9(1)	-10(1)	1(1)
C(11)	42(1)	51(2)	46(2)	-1(1)	-2(1)	-6(1)
C(12)	41(1)	38(1)	52(2)	5(1)	0(1)	5(1)
C(21)	40(1)	45(2)	53(2)	5(1)	-8(1)	-9(1)
C(61)	54(2)	59(2)	38(2)	10(1)	-5(1)	7(2)
C(81)	49(2)	45(2)	44(2)	4(1)	0(1)	3(1)
C(82)	96(3)	48(2)	56(2)	5(2)	32(2)	3(2)
C(83)	72(2)	45(2)	68(2)	3(2)	14(2)	-1(2)
C(111)	68(2)	83(2)	63(2)	-27(2)	1(2)	-3(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(4A)	-2260(2)	-3278(2)	-7339(2)	42
H(4B)	-2926(2)	-2483(2)	-6612(2)	42
H(5A)	-2101(3)	-4240(2)	-5999(2)	45
H(5B)	-634(3)	-4148(2)	-6469(2)	45
H(6A)	-1561(2)	-2511(2)	-5219(1)	42
H(7A)	-3265(2)	-1734(2)	-7938(2)	43
H(8A)	-2323(2)	448(2)	-8735(2)	43
H(9A)	-5094(3)	-550(3)	-8731(2)	53
H(9B)	-4683(3)	723(3)	-9149(2)	53
H(10A)	-3238(3)	-285(3)	-10103(2)	60
H(10B)	-4786(3)	-834(3)	-10154(2)	60
H(11A)	-4125(3)	-2536(3)	-9376(2)	56
H(12A)	-1843(3)	-2782(2)	-8882(2)	52
H(12B)	-1361(3)	-1530(2)	-9299(2)	52
H(21A)	1673(3)	-280(2)	-6415(2)	69
H(21B)	383(3)	349(2)	-6876(2)	69
H(21C)	1371(3)	-583(2)	-7361(2)	69
H(61A)	-871(3)	-4398(3)	-4662(2)	76
H(61B)	139(3)	-3326(3)	-4357(2)	76
H(61C)	647(3)	-4241(3)	-5063(2)	76
H(81A)	-2512(3)	699(2)	-7293(2)	55
H(82A)	-4442(4)	-581(3)	-7016(2)	100
H(82B)	-5456(4)	387(3)	-7447(2)	100
H(82C)	-4644(4)	744(3)	-6622(2)	100
H(83A)	-2797(3)	2402(3)	-8162(2)	93
H(83B)	-3641(3)	2560(3)	-7320(2)	93
H(83C)	-4454(3)	2202(3)	-8145(2)	93
H(11B)	-2553(4)	-3487(3)	-10289(2)	107
H(11C)	-2184(4)	-2195(3)	-10691(2)	107
H(11D)	-3721(4)	-2754(3)	-10791(2)	107

^)/3'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3
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6
7
8
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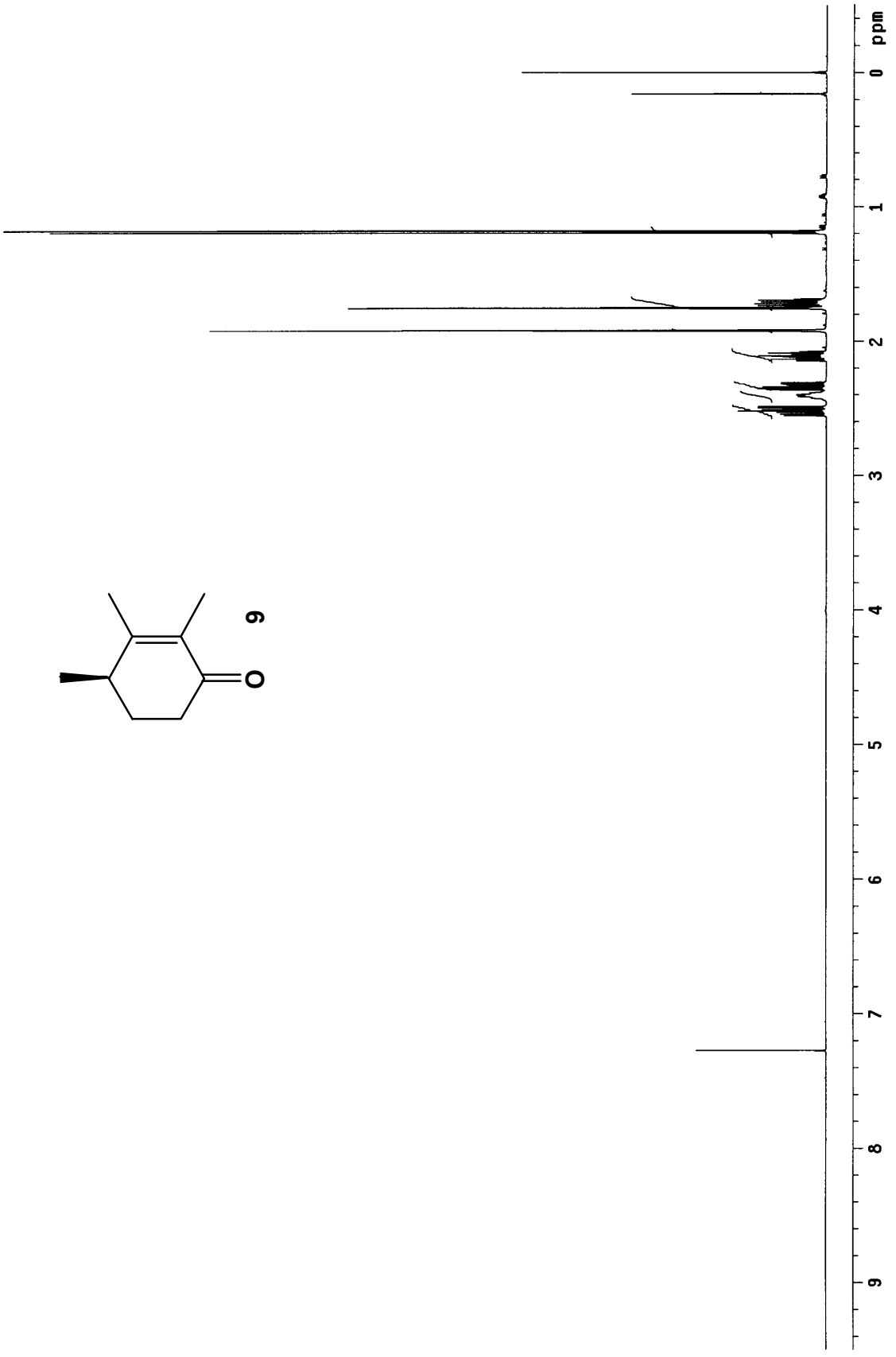
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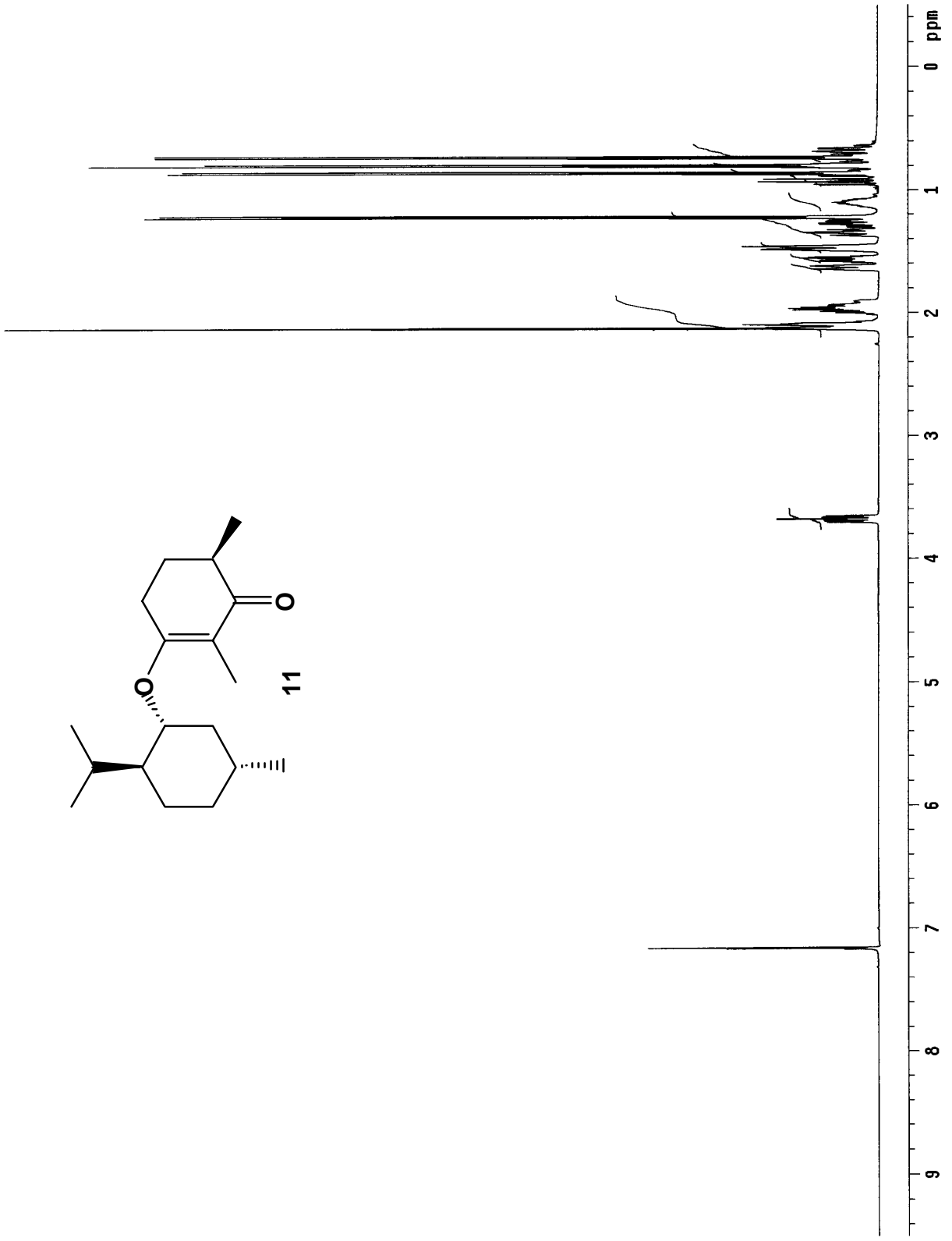
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O
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8
7
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4
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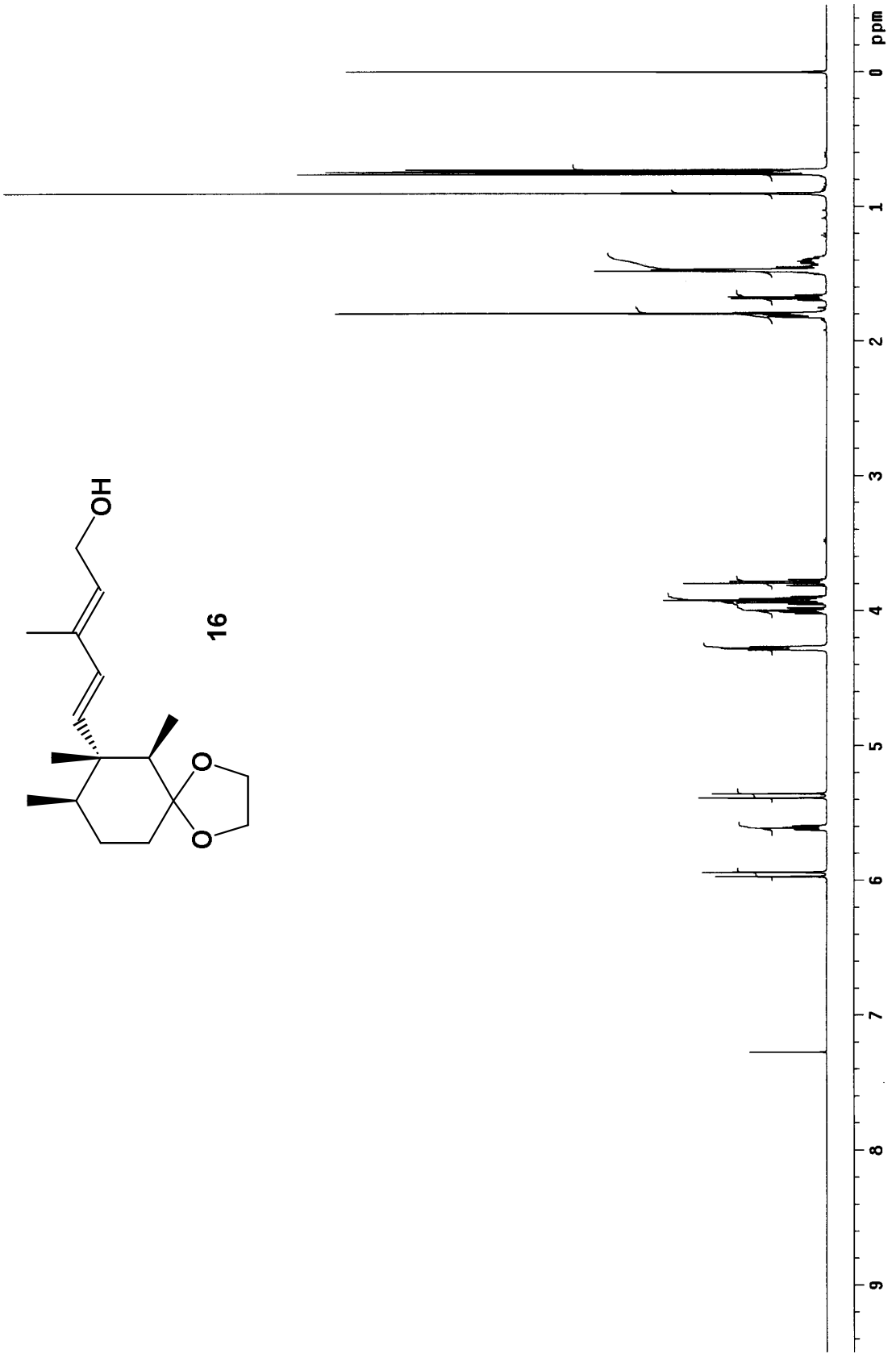
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8
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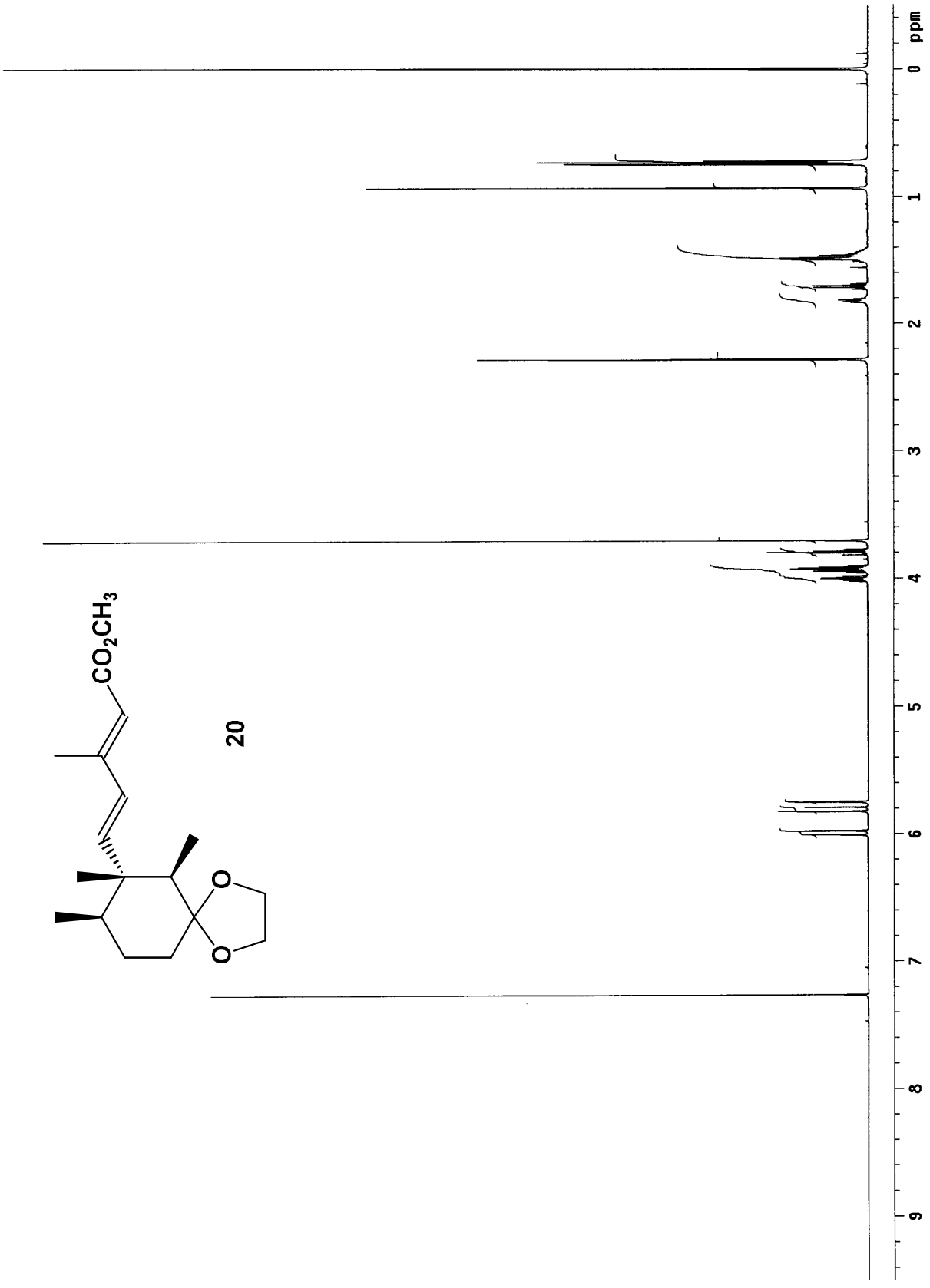
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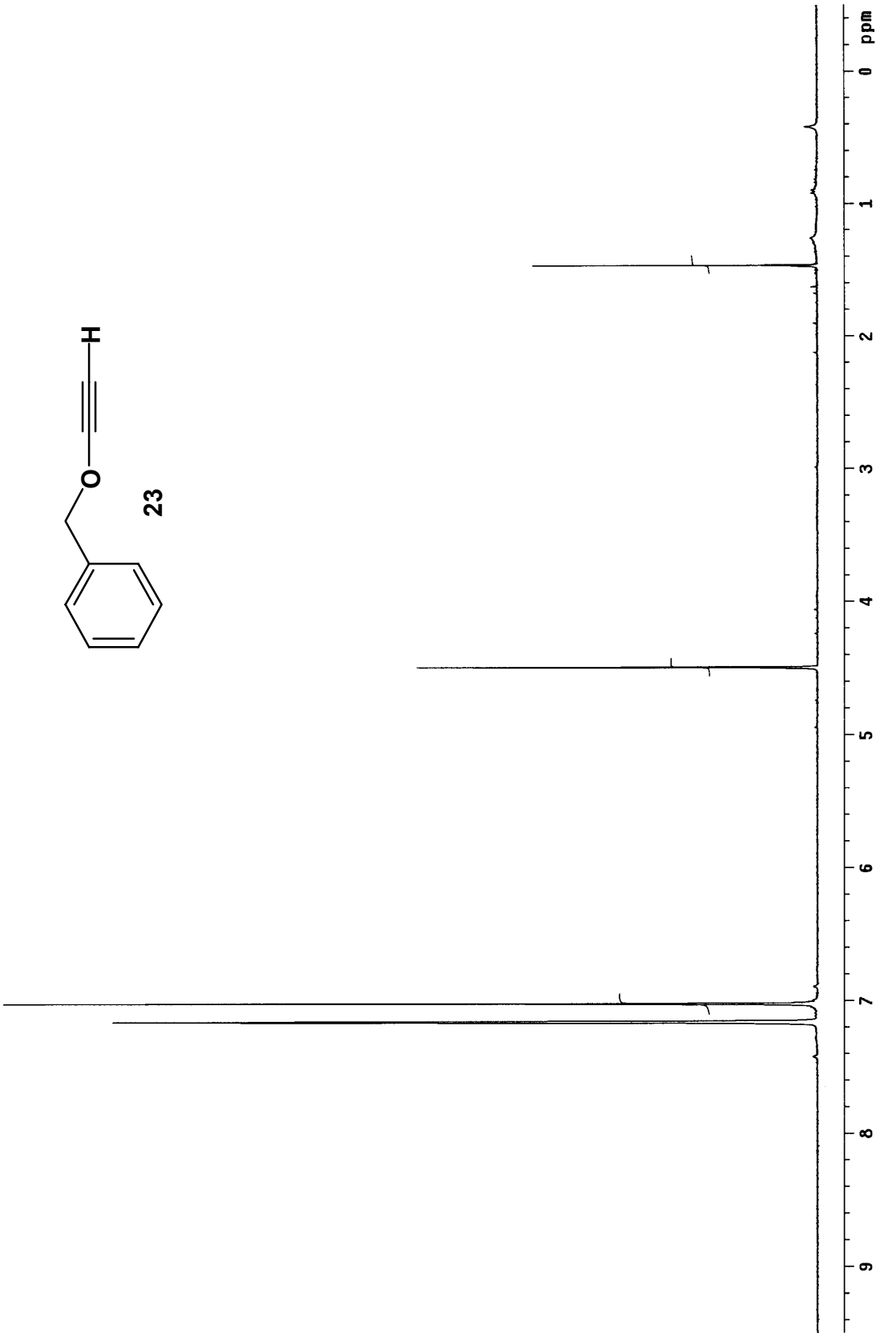
4
5
6
7
8
9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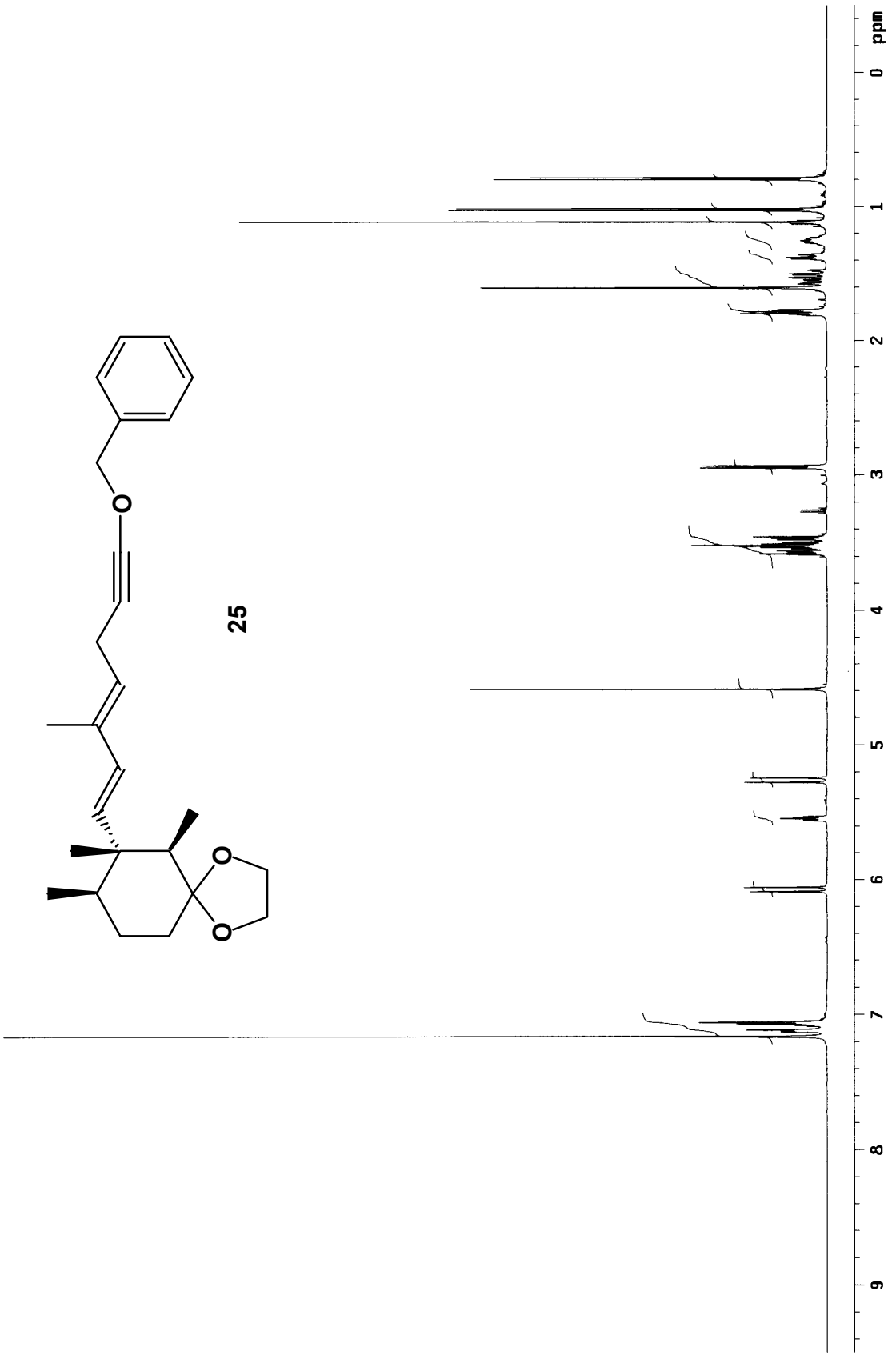
6
7
8
9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1
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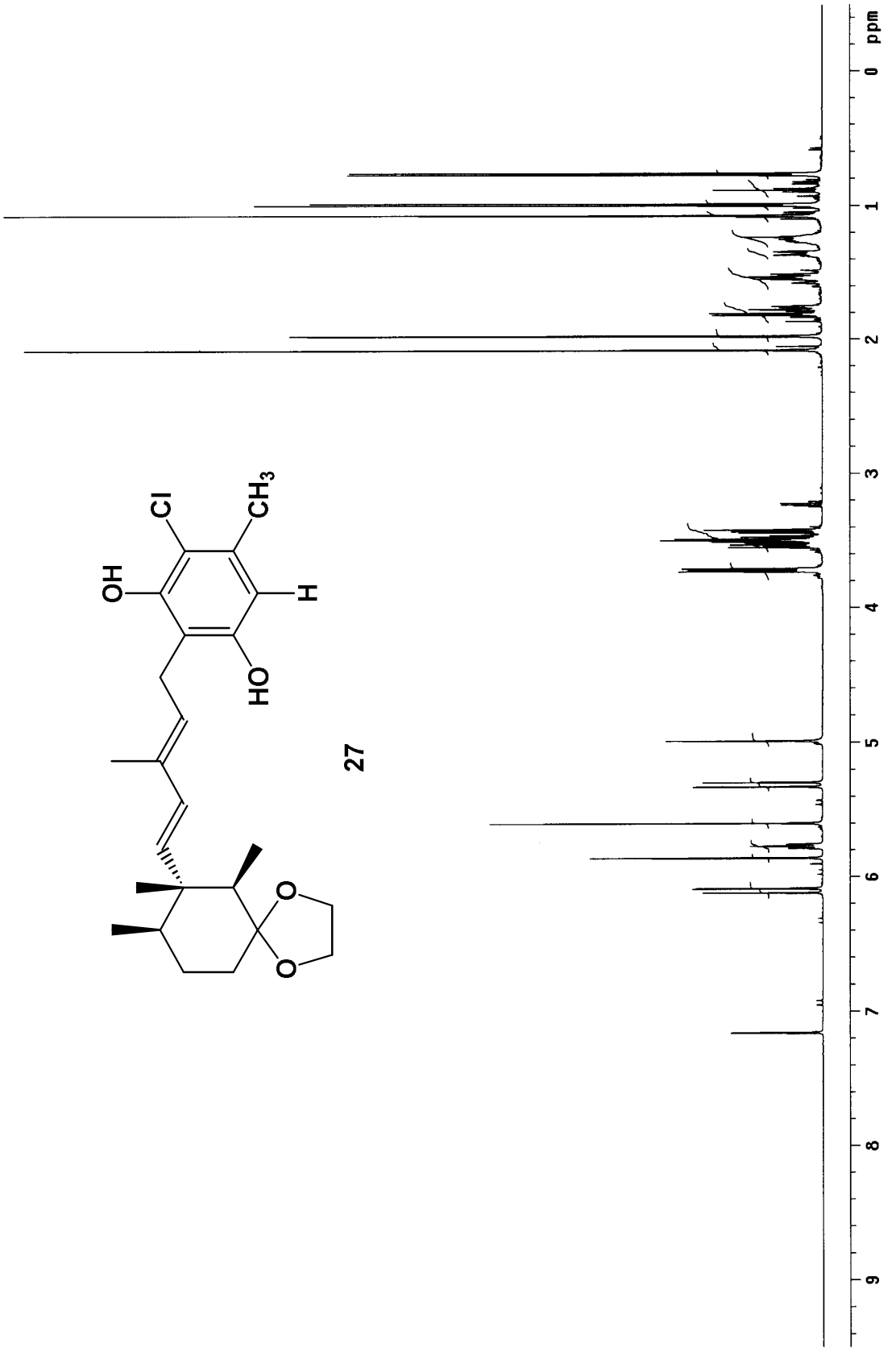
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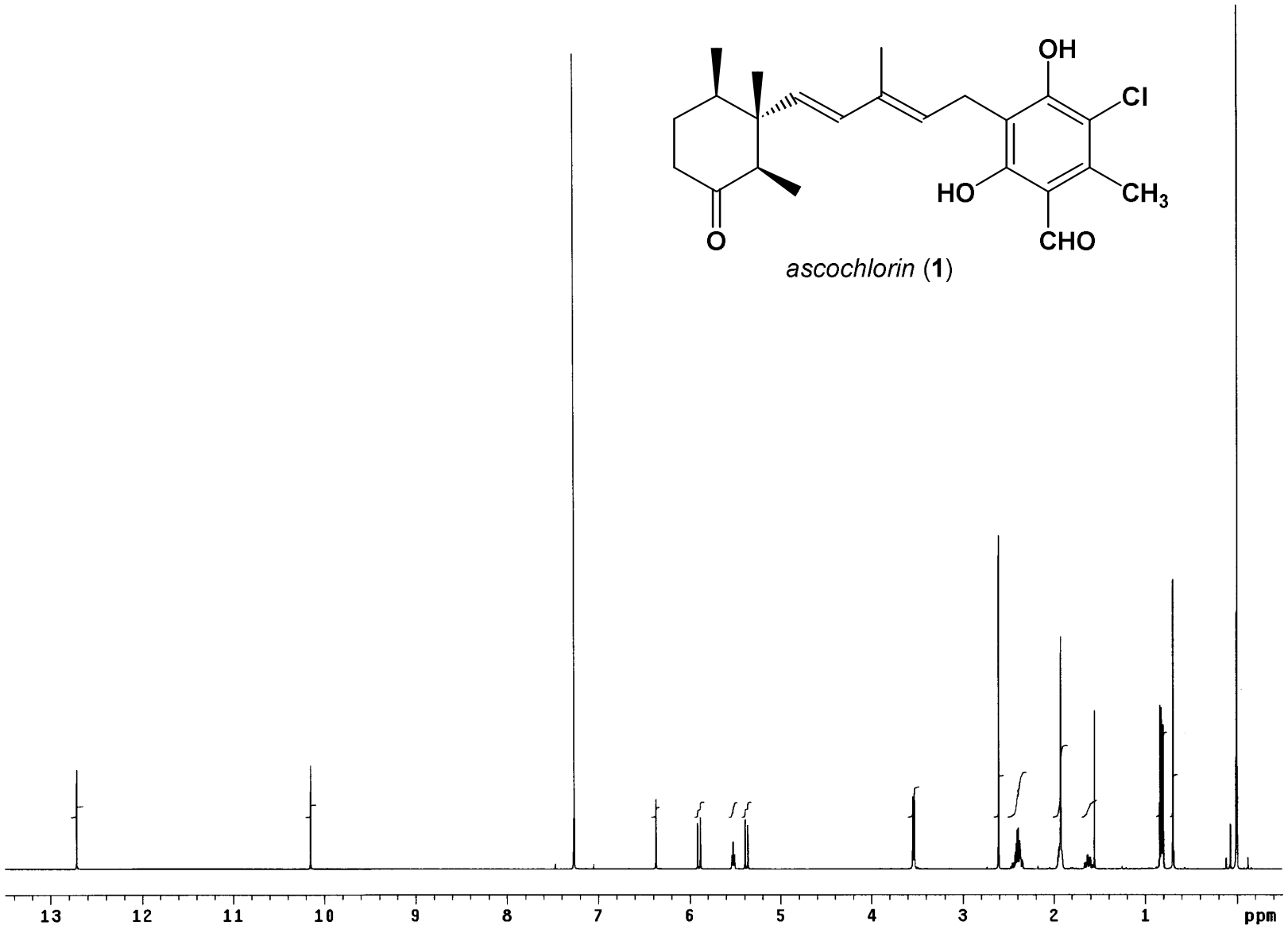
7
8
9



ascochlorin (**1**)

[1] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
[2] In smaller scale experiments, the crude product was purified by column chromatography on silica gel to directly afford crystalline **10**.
[3] The desired diastereomer crystallizes preferentially even in the absence of a seed crystal.
[4] This material was contaminated with ca. 3% of the alkoxy enone (**11**) starting material.
[5] Stannane **12** is available by stannylcupration of the corresponding alkyne, followed by quenching with buffered NH_4Cl solution, as described in: Betzer, J. F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768–7780. The alkyne ((*E*)-3-methyl-pent-2-en-4-yn-1-ol) was generously donated by Hoffmann–LaRoche.
[6] Vinylstannane **13** was purified by column chromatography on Woelm neutral alumina (activity V, elution with pentane) immediately prior to use.
[7] A wide range of colors have been observed for this solution (including yellow, purple, green, and brown) but the color appears to bear no relationship to the relative success of the reaction.
[8] Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078.
[9] Renaldo, A. F.; Labadie, J. W.; Stille, J. K. In *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, pp 268–274.
[10] Enone **9** was contaminated with 3% of ketone **11**. The corrected yield for this experiment based on the purity of enone **9** is therefore 93%.
[11] Prepared by a modification of the procedure reported in: Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488–2501.
[12] Chen, S. H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834–5845.
[13] Mori, K.; Takechi, S. *Tetrahedron* **1985**, *41*, 3049–3062.
[14] Safaryn, J. E.; Chiarello, J.; Chen, K. M.; Joullié, M. M. *Tetrahedron* **1986**, *42*, 2635–2642.
[15] This reaction was found to be particularly sensitive to the quality of the *n*-butyllithium solution and the methanesulfonyl chloride. Best results were obtained using BuLi from a freshly opened bottle.
[16] Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–305.
[17] Ellestad, G. A.; Evans, R. H., Jr., Kunstmann, M. P. *Tetrahedron*, **1969**, *25*, 1323–1334.
[18] (a) Kawagishi, H.; Sato, H.; Sakamura, S.; Kobayashi, K.; Ui, T. *Agric. Biol. Chem.* **1984**, *48*, 1903–1904. (b) Sasaki, H.; Hosokawa, T.; Nawata, Y.; Ando, K. *Agric. Biol. Chem.* **1974**, *38*, 1463–1466. (c) Mori, K.; Takechi, S. *Tetrahedron* **1985**, *41*, 3049–3062.