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Enantioselective Total Synthesis of Reveromycin B

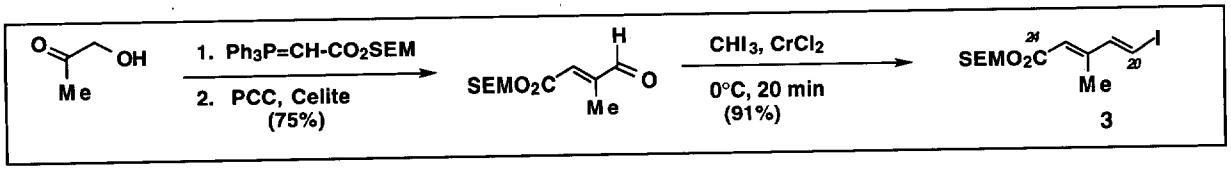
Keith E. Drouet and Emmanuel A. Theodorakis*

Contribution from the Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0358

Supporting Information

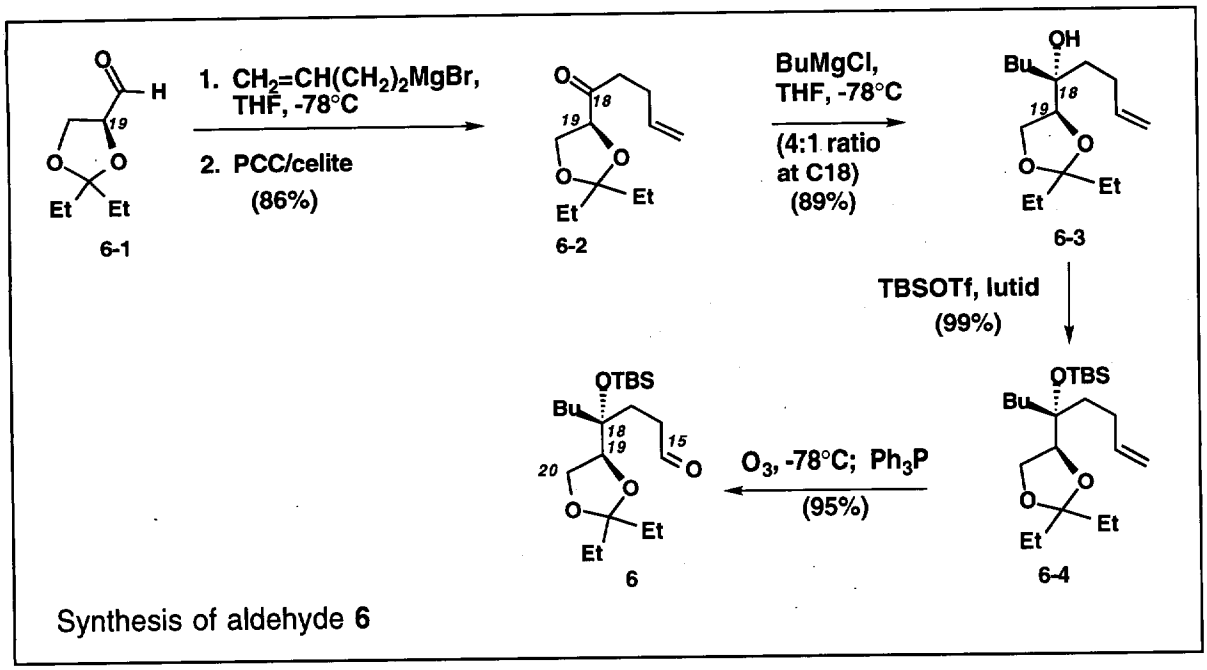
General techniques. All reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone; dichloromethane (CH_2Cl_2) and toluene from calcium hydride; and benzene from potassium. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on a Varian 400 and/or 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. 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 Model 781 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points (mp) are uncorrected, and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

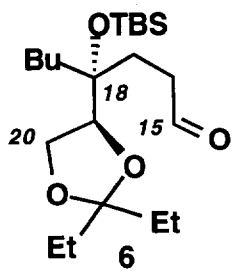


Vinyl iodide 3. **3**: colorless liquid; R_f = 0.4 (silica, 5% ether in hexanes); IR (film) ν_{max} 2957, 1719, 1619, 1243, 1154, 1055, 951, 836; ^{1}H NMR (400 MHz, C_6D_6) δ 6.75 (d, 1H, J= 14.5 Hz), 6.28 (d, 1H, J= 14.8 Hz), 5.57 (s, 1H), 4.21-4.17 (m, 2H), 2.01 (s, 3H), 0.89 (t, 2H, J= 8.5 Hz), -0.96 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.1, 150.9, 148.2, 120.9, 85.0, 62.3, 17.9, 13.5, -1.0; HRMS, calcd for $C_{11}H_{19}I_1O_2Si_1$ (M+Cs$^+$) 470.9251, found 470.9270.

Synthesis of aldehyde 6 (complete scheme).

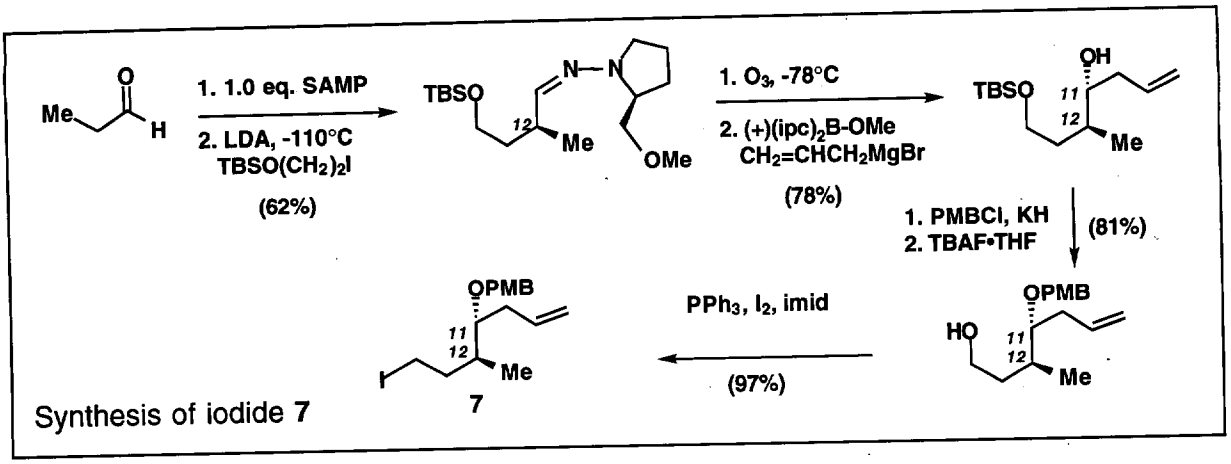


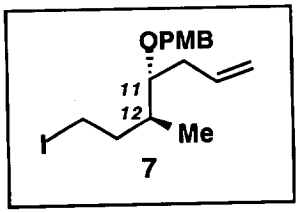
Synthesis of aldehyde **6**



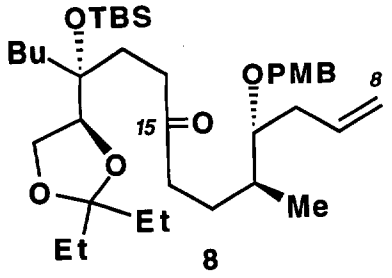
Aldehyde 6. A solution of the C15 alkene (12.0 g, 31.21 mmol) in CH_2Cl_2 (100 ml) was cooled at -78 °C and treated with ozone for 20 min. The excess ozone was then removed, triphenylphosphine (16.4 g, 62.5 mmol) was added and the reaction mixture was allowed to warm to 25 °C over 1 h. The solution was concentrated and subjected to flash chromatography (silica, 0-10% ether in hexanes) to afford aldehyde **6** (11.46 g, 29.69 mmol, 95%). **6**: colorless liquid; R_f = 0.60 (silica, 25% ether in hexanes); $[\alpha]^{25}_D$: -3.1 (c=1.1, CH_2Cl_2); IR (film) ν_{max} 2956, 2858, 1728, 1462, 1252, 1082, 835, 774; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 4.05 (t, 1H, J= 7.5 Hz), 3.92 (t, 1H, J= 7.5 Hz) 3.75 (t, 1H, J= 7.5 Hz), 2.62-2.49 (m, 2H), 1.97-1.91 (m, 1H), 1.76-1.56 (m, 5H), 1.40-1.22 (m, 6H), 0.92-0.86 (m, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 113.2, 80.7, 77.2, 65.7, 38.7, 35.8, 29.1, 28.5, 27.9, 26.0, 25.9, 23.3, 18.5, 13.9, 8.3, 8.2, -2.2, -2.3; HRMS, calcd for $C_{21}H_{42}O_4Si$ ($M+Cs^+$) 519.1907, found 519.1929.

Synthesis of iodide 7 (complete scheme).



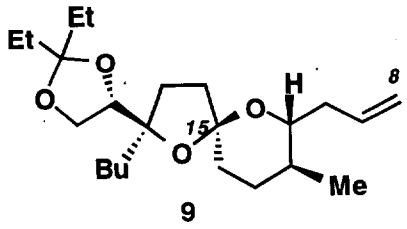


Iodide 7. To a solution of the C14 alcohol (7.05 g, 26.66 mmol) in THF (120 ml) was added imidazole (4.36 g, 64.12 mmol) followed by triphenylphosphine (8.40 g, 32.06 mmol) and the mixture was stirred at 0 °C for 10 min. The flask was then protected from the light with alumina foil and the mixture was treated with iodine (8.14 g, 32.06 mmol) introduced slowly (over 5 min). After stirring at 0 to 25 °C for 30 min, the reaction mixture was diluted with ether (200 ml) and washed with aqueous saturated sodium thiosulfate (2 x 100 ml) and aqueous saturated sodium bicarbonate (2 x 100 ml). The organic layer was dried ($MgSO_4$), concentrated and subjected to flash chromatography (silica, 0-10% ether in hexanes) to yield iodide **7** (9.67 g, 25.85 mmol, 97%). **7**: colorless liquid; R_f = 0.7 (silica, 10% ether in hexanes); $[\alpha]^{25}_D$: -7.8 (c= 1.3, CH_2Cl_2); IR (film) ν_{max} 2936, 2852, 1614, 1510, 1249, 1181, 1097, 1040, 825; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, 2H, J= 8.0 Hz), 6.88 (d, 2H, J= 8.0 Hz), 5.85-5.80 (m, 1H), 5.11 (d, 1H, J= 17 Hz), 5.07 (d, 1H, J= 10 Hz), 4.50 (d, 1H, J= 10 Hz), 4.43 (d, 1H, J= 10 Hz), 3.80 (s, 3H), 3.31-3.20 (m, 2H), 3.14-3.1 (m, 1H), 2.3 -2.2 (m, 2H), 2.1-2.0 (m, 1H), 1.9-1.8 (m, 1H), 1.7-1.6 (m, 1H), 0.90 (d, 3H, J= 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 135.5, 130.8, 129.3, 116.9, 113.7, 81.7, 80.8, 71.2, 55.2, 36.7, 36.3, 35.2, 14.6; HRMS, calcd for $C_{16}H_{23}IO_2$ ($M+Cs^+$) 506.9797, found 506.9817.



8

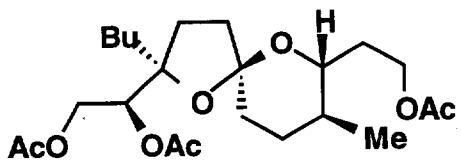
Ketone 8: colorless liquid; R_f = 0.5 (silica, 30% ether in hexanes); $[\alpha]^{25}_D$: -7.8 (c= 1.3, CH_2Cl_2); IR (film) ν_{max} 2956, 1714, 1613, 1514, 1462, 1248, 1082, 835; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, 2H, J= 8.0 Hz), 6.87 (d, 2H, J= 8.0 Hz), 5.85-5.80 (m, 1H), 5.11 (d, 1H, J= 17 Hz), 5.07 (d, 1H, J= 10 Hz), 4.50 (d, 1H, J= 10 Hz), 4.43 (d, 1H, J= 10 Hz), 4.02 (t, 1H, J= 7.0 Hz), 3.90 (t, 1H, J= 7.5 Hz), 3.79 (s, 3H), 3.76 (t, 1H, J= 8.0 Hz), 3.26-3.23 (m, 1H), 2.49-2.27 (m, 6H), 1.90-1.55 (m, 10H), 1.42-1.25 (m, 6H), 0.92-0.85 (m, 20H), 0.10 (s, 3H), 0.098 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 159.2, 135.6, 131.0, 129.3, 116.6, 113.7, 113.0, 82.4, 80.7, 71.2, 65.7, 55.2, 40.9, 37.0, 35.9, 35.2, 34.7, 30.3, 29.2, 28.0, 26.5, 26.0, 25.6, 23.3, 18.6, 14.9, 13.9, 8.3, 8.2, -2.1, -2.3; HRMS, calcd for $C_{37}H_{64}O_6Si$ ($M+Cs^+$) 765.3527, found 765.3557.



9

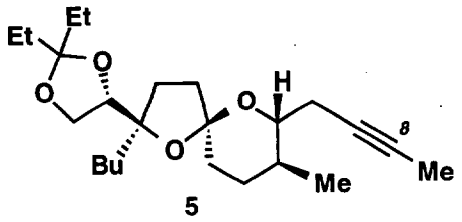
Spiroketal 9. A solution of ketone **8** (7.66 g, 12.12 mmol) in THF (20 ml) and tetra-*n*-butylammonium fluoride (18.2 ml of a 1.0 M solution in THF, 18.2 mmol) was stirred at 50 °C for 2 h. The reaction mixture was diluted with ether (100 ml) and washed with aqueous saturated ammonium chloride (2 x 50 ml) and brine (2 x 50 ml). The organic layer was dried and concentrated under reduced pressure. The crude lactol was redissolved in CH_2Cl_2 (80 ml) containing H_2O (2 ml) and treated with 2,3-dichloro-5,6 dicyano-benzoquinone (4.14 g, 18.22 mmol) at 25 °C for 15 min. The reaction mixture was quenched with aqueous saturated sodium bicarbonate (20 ml), filtered through a short pad of celite, diluted with CH_2Cl_2 (100 ml) and extracted with water (2 x 20 ml). The organic layer was dried ($MgSO_4$), concentrated and subjected to flash chromatography to produce spiroketal **9**

(4.02 g, 10.58 mmol, 87 %). **9:** colorless liquid; R_f = 0.7 (silica, 15% ether in hexanes); $[\alpha]^{25}_D$: +28.1 (c= 1.25, CH_2Cl_2); IR (film) ν_{max} 2938, 2880, 1461, 1377, 1174, 1083, 993, 923; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95-5.88 (m, 1H), 5.07 (d, 1H, J= 17.0 Hz), 5.01 (d, 1H, J= 10.0 Hz), 4.18 (t, 1H, J= 7.0 Hz), 3.94-3.89 (m, 2H), 3.37-3.34 (m, 1H), 2.37-2.32 (m, 1H), 2.13-1.85 (m, 5H), 1.77-1.45 (m, 10H), 1.34-1.23 (m, 6H), 1.93-0.81 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 116.0, 112.7, 106.6, 86.9, 81.4, 75.7, 66.0, 38.6, 37.7, 34.4, 34.2, 33.9, 32.0, 29.2, 29.1, 28.5, 25.7, 23.3, 17.5, 14.0, 8.3, 7.9; HRMS, calcd for $C_{23}H_{40}O_4$ ($M+Cs^+$) 513.1979, found 513.1991.



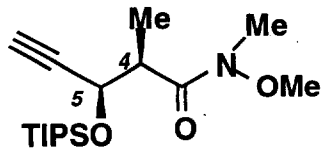
10

Triacetate 10. A solution of the C9 alcohol (20 mg, 50 μmol) in CH_2Cl_2 (2 ml) was treated with pyridine (12 μl, 0.15 mmol) and acetic anhydride (7 μl, 77 μmol) at 25 °C for 15 min. The reaction mixture was diluted with ether (20 ml) and washed with ammonium chloride (2 x 10 ml) and brine (2 x 10 ml). The organic layer was dried ($MgSO_4$), concentrated and the residue chromatographed (silica, 0-25% ether in hexanes) to afford triacetate **11** (21.4 mg, 47.5 μmol, 97%). **11**: colorless liquid; R_f = 0.45 (silica, 30% ether in hexanes); $[\alpha]^{25}_D$: +37.5 (c= 1.0, $CHCl_3$); IR (film) ν_{max} 2931, 2868, 1745, 1463, 1369, 1238, 1050, 1083, 993, 923; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (dd, 1H, J= 9.0, 2.5 Hz), 4.52 (dd, 1H, J= 12.0, 2.0 Hz), 4.34-4.26 (m, 1H), 4.24 (dd, 1H, J= 12.0, 8.5 Hz), 4.18-4.13 (m, 1H), 3.49 (ddd, 1H, J= 10.8, 8.0, 2.8 Hz), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.96-1.50 (m, 11H), 1.31-1.25 (m, 6H), 0.91 (t, 3H, J= 7 Hz), 0.87 (d, 3H, J= 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.27, 171.25, 170.4, 107.0, 86.2, 73.6, 63.9, 61.7, 38.4, 34.5, 34.4, 34.2, 32.1, 31.3, 29.6, 29.0, 25.4, 23.1, 21.0, 20.9, 20.7, 17.6, 14.0; HRMS, calcd for $C_{23}H_{38}O_8$ ($M+Cs^+$) 575.1619, found 575.1632.



5

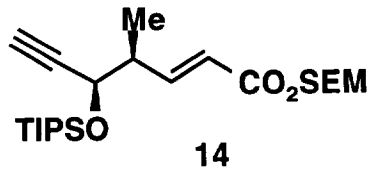
Alkyne 5. A solution of the dibromoalkene (104 mg, 0.19 mmol) in THF (3 ml) was cooled at - 78 °C and treated with *n*-butyllithium (254 µl of a 1.6 M solution in hexanes, 0.40 mmol). Stirring was continued for 20 min at -78 °C and for 20 min at - 20 °C. The reaction mixture was then cooled at - 78 °C, treated with freshly distilled iodomethane (60 µl, 0.96 mmol) and subsequently allowed to warm to 0 °C where it was stirred for a period of 1 h. The solution was then quenched with water (1 ml), diluted with ether (30 ml) and washed with brine (2 x 20 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated and chromatographed (silica, 0-15% ether in hexanes) to give alkyne **5** (72 mg, 18.4 µmol, 95%). **5**: colorless liquid; R_f = 0.65 (silica, 15% ether in hexanes); $[\alpha]^{25}_D$: +2.14 (c= 0.84, CH_2Cl_2); IR (film) ν_{max} 2957, 2931, 2878, 1463, 1087, 930; ^1H NMR (500 MHz, $CDCl_3$) δ 4.25 (t, 1H, J= 7.5 Hz), 3.98-3.95 (m, 2H), 3.47-3.42 (m, 1H), 2.41-2.37 (m, 1H), 2.30-2.28 (m, 1H), 2.05-2.00 (m, 2H), 1.79-1.42 (m, 14H), 1.34-1.25 (m, 6H), 0.94-0.82 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.8, 106.7, 87.1, 81.0, 76.1, 74.4, 66.0, 38.3, 34.53, 34.5, 33.8, 31.6, 29.1, 29.0, 28.6, 25.9, 23.6, 23.3, 17.5, 14.0, 8.4, 7.9, 3.5; HRMS, calcd for $C_{24}H_{40}O_4$ (M^+) 393.3005, found 393.3017.



13

Amide 13. A solution of the C5 alcohol (2.22 g, 13.0 mmol) and 2,6-lutidine (3.7 ml, 39 mmol) in CH_2Cl_2 (20 ml) was treated at 0 °C with triisopropylsilyl trifluoromethanesulfonate (6.50 ml, 19.5 mmol). After stirring at 25 °C for 15 min, the mixture was diluted with ether (100 ml) and washed with aqueous saturated sodium bicarbonate (3 x 30 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated and subjected to flash chromatography (silica, 10-40% ether in hexanes) to give amide **13** (4.12 g, 12.6 mmol, 97%). **13**: colorless liquid; R_f = 0.3 (silica, 30%

ether in hexanes); $[\alpha]^{25}_D$: +48.0 (c=1.2, CH_2Cl_2); IR (film) ν_{max} 2939, 2869, 1651, 1460, 1418, 1390, 1115, 1064, 994, 882; ^1H NMR (500 MHz, $CDCl_3$) δ 4.63 (dd, 1H, J= 7.5, 1.5 Hz), 3.70 (s, 3H), 3.16 (s, 3H), 3.16 (m, 1H), 2.36 (d, 1H, J= 2 Hz), 1.22 (d, 3H, J= 6.5 Hz), 1.14-1.02 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 97.2, 84.6, 73.0, 64.5, 61.4, 44.0, 17.9, 13.9, 12.2; HRMS, calcd for $C_{17}H_{33}O_3NSi$ ($M+Cs^+$) 460.1282, found 460.1298.



14

Ester 14. A solution of amide **13** (1.55 g, 4.74 mmol) in THF (30 ml) was cooled at -78 °C and treated with DIBALH (7.9 ml of a 1.5 M solution in toluene, 11.8 mmol). After stirring for 30 min at -78 °C, the reaction mixture was quenched with methanol (3 ml), diluted with ethyl acetate (50 ml), allowed to warm to 25 °C and stirred for 30 min with a saturated solution of Rochelle salt (100 ml). The mixture was extracted with ethyl acetate (3 x 50 ml) and the organic layer was dried ($MgSO_4$) and concentrated to produce the crude aldehyde, that was used for the next step without any purification. A solution of the above aldehyde in CH_2Cl_2 (10 ml) was treated with Ph_3P=CH-CO_2SEM (5.07 g, 11.85 mmol) for 15 h, at 25 °C. The reaction mixture was then concentrated and subjected to flash chromatography (silica, 0-5% ether in hexanes) to afford ester **14** (1.76 g, 4.31 mmol, 91%). **14**: colorless liquid; R_f = 0.65 (silica, 15% ether in hexanes); $[\alpha]^{25}_D$: +10.6 (c=0.5, CH_2Cl_2); IR (film) ν_{max} 2946, 2863, 1719, 1466, 1253, 1175, 860, 836; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (dd, 1H, J= 16, 7.5 Hz), 5.86 (d, 1H, J= 16.5 Hz), 4.46 (dd, 1H, J= 5.0, 2.0 Hz); 4.22 (t, 2H, J= 8.0 Hz), 2.60 (q, 1H, J= 6.0 Hz), 2.40 (d, 1H, J= 2.0 Hz), 1.14 (d, 3H, J= 6.5 Hz), 1.07-0.99 (m, 23H), 0.026 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 149.5, 122.3, 83.1, 73.9, 66.4, 62.3, 43.6, 17.92, 17.90, 17.1, 14.6, 12.1, -1.6; HRMS, calcd for $C_{22}H_{42}O_3Si_2$ ($M+Cs^+$) 543.1725, found 543.1739.

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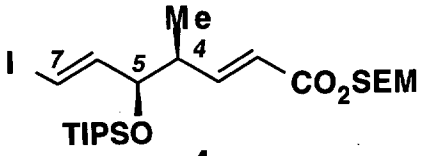
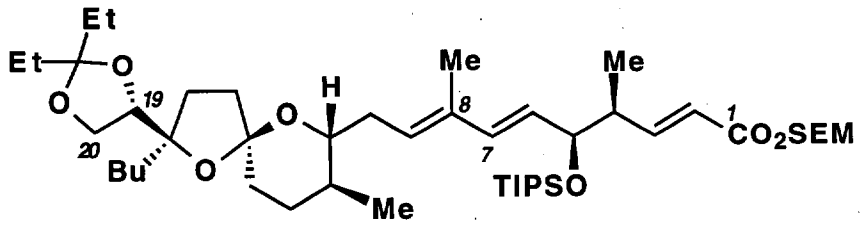


4

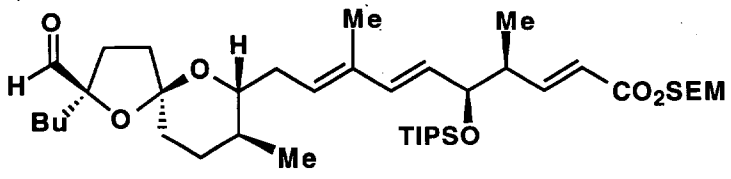
Vinyl iodide 4. A solution of the starting vinyl stannane (202 mg, 0.29 mmol) in dichloromethane (3 ml) was cooled to 0 °C and titrated with a saturated solution of iodine in dichloromethane, until the iodine color persisted. The solution was then stirred for 5 minutes and partitioned between a solution of dichloromethane (20 ml) and aqueous saturated sodium thiosulfate (20 ml). The organic layer was collected, dried ($MgSO_4$), filtered, concentrated and chromatographed (silica, 0-10% ether in hexanes) to afford compound **4** (140 mg, 0.26 mmol, 90 %). **4**: colorless liquid; R_f = 0.65 (silica, 10% ether in hexanes); $[\alpha]^{25}_D$: +39.6 (c=1.0, CH_2Cl_2); IR (film) ν_{max} 2951, 2863, 1719, 1651, 1463, 1254, 1175, 862, 841; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, 1H, J= 16.0, 7.0 Hz), 6.46 (dd, 1H, J= 14.5, 7.0 Hz), 6.26 (d, 1H, J= 15.0 Hz), 5.80 (d, 1H, J= 15.5 Hz), 4.23 (t, 2H, J= 8.0 Hz), 4.17 (dd, 1H, J= 5.0, 7.5 Hz), 2.53 (m, 1H), 1.04-1.03 (m, 26H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 149.4, 146.3, 122.1, 78.9, 77.8, 62.4, 42.8, 18.0, 17.9, 17.2, 14.3, 12.2, -1.6. HRMS, calcd for $C_{22}H_{43}O_3Si_2I$ (M+Cs^+) 671.0849, found 671.0859.



15

Ester 15. A solution of alkyne **5** (99 mg, 0.25 mmol) and bis(cyclopentadienyl)zirconium-chloride-hydride (131 mg, 0.51 mmol) in tetrahydrofuran (1 ml) was stirred at 50 °C under argon for 2 hrs in the dark. The resulted yellow solution was allowed to cool to 25 °C and treated with a solution of

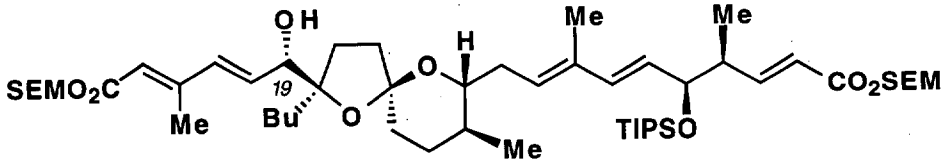
anhydrous zinc chloride (104 mg, 0.76 mmol) in tetrahydrofuran (1.5 ml), added via cannula. The reaction mixture was stirred for 5 minutes and subsequently treated with a solution of vinyl iodide **4** (165 mg, 0.31 mmol) and palladium tetrakis triphenyl phosphine (15 mg, 0.012 mmol) in tetrahydrofuran (2 ml). The reaction was stirred for 2 h, then diluted with 10 ml of water, and extracted with ethyl ether (3 x 30 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated and chromatographed (silica, 0-5% ether in hexanes) to afford compound **15** (168 mg, 0.21 mmol, 84 %). **15**: colorless liquid; R_f = 0.45 (silica, 10% ether in hexanes); $[\alpha]^{25}_D$: +12.1 (c= 0.93, CH_2Cl_2); IR (film) ν_{max} 2936, 2863, 1719, 1651, 1463, 1254, 1170, 1087; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, 1H, J= 7.0, 16.0 Hz), 6.08 (d, 1H, J= 16.0 Hz), 5.76 (d, 1H, J= 16.0 Hz), 5.56 (t, 1H, J= 7.5 Hz), 5.42 (dd, 1H, J= 8.5, 15.5, Hz), 4.23-4.14 (m, 4H), 3.93-3.89 (m, 2H), 3.48-3.44 (m, 1H), 2.56-2.53 (m, 1H), 2.41-2.37 (m, 1H), 2.26-2.21 (m, 1H), 1.92-1.89 (m, 1H), 1.81-1.24 (m, 21H), 1.02-.98 (m, 21H), 0.93-0.87 (m, 14H), 0.81 (d, 3H, J= 6.5 Hz), 2.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 151.2, 136.4, 134.0, 129.3, 126.9, 121.3, 112.7, 106.5, 86.9, 81.0, 77.8, 77.2, 75.4, 65.9, 62.2, 43.9, 38.3, 34.7, 34.2, 32.1, 31.4, 29.2, 29.18, 28.8, 26.0, 23.3, 18.1, 18.0, 17.7, 17.1, 14.2, 14.1, 12.6, 12.3, 8.4, 7.9, -1.6; HRMS, calcd for $C_{46}H_{84}O_7Si_2$ ($M+Cs^+$) 937.4810, found 937.4835.



16

Aldehyde 16: colorless liquid; R_f = 0.4 (silica, 5% ether in hexanes); $[\alpha]^{25}_D$: +40.3 (c=0.65, CH_2Cl_2); IR (film) ν_{max} 2962, 2863, 1719, 1651, 1463, 1249, 1175, 1066, 862, 841; ^1H NMR (500 MHz, C_6D_6) δ 9.67 (s, 1H), 7.48 (dd, 1H, J= 7.5, 16.5 Hz), 6.36

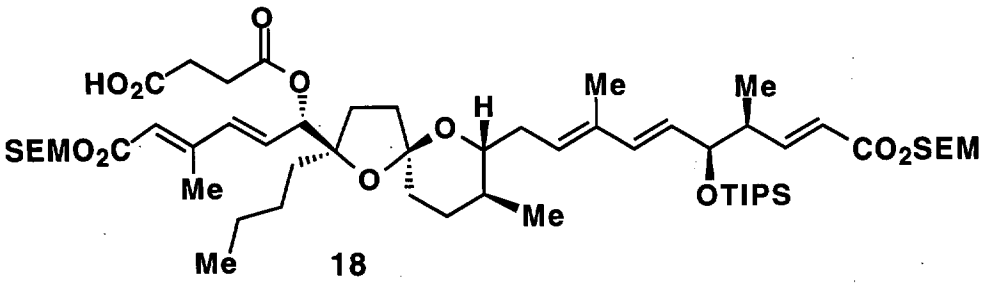
(d, 1H, J= 15.5 Hz), 6.09 (d, 1H, J= 15.5 Hz), 5.73 (t, 1H, J= 6.5 Hz), 5.66 (dd, 1H, J=7.5, 15.5 Hz), 4.31 (dd, 1H, J= 4.0, 8.0 Hz), 4.27-4.23 (m, 2H), 3.61-3.57 (m, 1H), 2.57-2.55 (m, 1H), 2.37-2.32 (m, 1H), 2.14-2.11 (m, 1H), 1.92-1.80 (m, 1H), 1.67 (s, 3H), 1.95-1.61 (m, 13H), 1.16-1.12 (m, 21H), 1.04 (d, 3H, J= 6.5 Hz), 0.91 (t, 2H, J= 8.0 Hz), 0.80 (t, 3H, J= 7 Hz), 0.67 (d, 3H, J= 6.5 Hz), -0.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.4, 166.4, 150.9, 136.9, 134.3, 129.8, 127.5, 122.2, 107.2, 90.4, 78.2, 76.9, 62.0, 44.3, 38.1, 35.0, 34.5, 33.8, 31.9, 29.4, 29.3, 25.5, 23.2, 18.3, 18.2, 17.5, 17.3, 14.6, 13.9, 12.6, 12.5, -1.7; HRMS, calcd for $C_{40}H_{72}O_5Si_2$ (M+ Cs^+) 821.3973, found 821.3992.



17

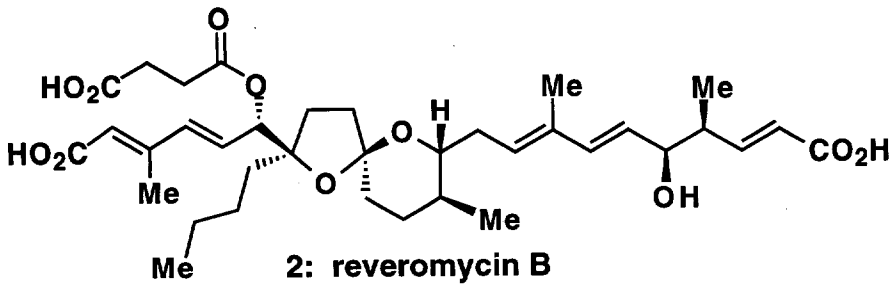
Alcohol 17. A solution of aldehyde **16** (64 mg, 93 μmol) and vinyl iodide **3** (123 mg, 0.363 mmol) in dry DMF (3 ml) was treated under Argon with chromium (II) chloride (274 mg, 2.2 mmol) and nickel (II) chloride (1.4 mg, 0.01 mmol). After stirring for 2 h at 25 °C, the reaction mixture was diluted with water (10 ml) and extracted with ethyl ether (3 x 10 ml). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated and chromatographed (preparative silica gel plate, 15% ether in hexanes) to yield alcohol **17** (55.2 mg, 60 μmol, 65%) as a 1.2:1 mixture of diastereomers at C19. The minor diastereomer was shown to have the desired stereochemistry -S- at the C19 carbon center (NOE studies). Major diastereomer (R stereochemistry at C19), (30.1 mg, 32.7 μmol, 35%): colorless liquid; R_f = 0.4 (silica, 15% ether in hexanes); $[\alpha]^{25}_D$: -24.5 (c= 0.4, CH_2Cl_2); IR (film) ν_{max} 3843, 2953, 2867, 1722, 1463, 1260, 1162, 860, 842; ^1H NMR (500 MHz, C_6D_6) δ 7.48 (dd, 1H, J=

7.0, 16.0 Hz), 6.70 (d, 1H, J= 16.0 Hz), 6.35 (d, 1H, J= 15.5 Hz), 6.14 (dd, 1H, J= 5.5, 15.5 Hz), 6.10-6.04 (m, 2H), 5.89 (t, 2H, J= 7.5 Hz), 5.64 (dd, 1H, J= 7.5, 15.5 Hz), 4.46 (d, 1H, J= 6.0 Hz), 4.27-4.22 (m, 5H), 3.71-3.67 (m, 1H), 3.61 (bs, 1H), 2.57-2.44 (m, 1H), 2.47 (s, 3H), 2.42-2.36 (m, 1H), 2.35-2.21 (m, 1H), 2.06-1.98 (m, 1H), 1.70 (s, 3H), 1.58-1.20 (m, 15H), 1.13-1.08 (m, 21H), 1.01 (d, 3H, J= 7.0 Hz), 0.10-0.92 (m, 4H), 0.88 (t, 3H, J= 6.5 Hz), 0.65 (d, 3H, J= 6.5 Hz), -0.08 (s, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.9, 166.5, 151.8, 150.9, 136.8, 135.1, 135.0, 134.8, 128.9, 127.7, 122.2, 120.2, 107.2, 91.6, 78.1, 77.3, 76.5, 62.1, 62.6, 44.2, 39.4, 37.5, 35.1, 34.1, 32.0, 29.2, 27.9, 27.7, 25.7, 23.4, 18.3, 18.2, 17.5, 17.4, 17.3, 14.6, 14.1, 13.9, 12.6, -1.74, -1.75; HRMS, calcd for $C_{51}H_{92}O_8Si_3$ (M+ Cs^+) 1049.5154, found 1049.5189. Minor diastereomer **17** (S stereochemistry at C19), (25.1 mg, 27.3 μmol, 30%): colorless liquid; R_f = 0.38 (silica, 15% ether in hexanes); $[\alpha]^{25}_D$: -25.5 (c= 0.4, CH_2Cl_2); IR (film) ν_{max} 3843, 2953, 2867, 1722, 1463, 1260, 1162, 860, 842; ^1H NMR (400 MHz, C_6D_6) δ 7.45 (dd, 1H, J= 7.2, 15.6 Hz), 6.60 (d, 1H, J= 16.0 Hz), 6.34-6.25 (m, 2H), 6.08-6.03 (m, 2H), 5.86 (t, 1H, J= 7.0 Hz), 5.65 (dd, 1H, J= 8.0, 16.0 Hz), 4.29-4.25 (m, 4H), 4.19-4.17 (m, 1H), 3.72-3.69 (m, 1H), 3.62-3.57 (m, 1H), 2.53-2.50 (m, 1H), 2.47 (s, 3H), 2.42-2.21 (m, 1H), 2.04-1.99 (m, 1H), 1.72 (s, 3H), 1.60-1.20 (m, 15H), 1.13-1.08 (m, 21H), 1.02 (d, 3H, J= 7.2 Hz), 0.91-0.88 (m, 4H), 0.87 (t, 3H, J= 6.4 Hz), 0.66 (d, 3H, J= 6.4 Hz), -0.07 (s, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.9, 166.4, 151.8, 150.9, 136.7, 135.3, 135.0, 134.9, 129.0, 127.6, 122.2, 120.2, 107.2, 90.8, 78.1, 77.9, 77.4, 62.0, 61.6, 44.2, 39.5, 34.8, 34.1, 32.1, 30.1, 30.0, 29.2, 26.1, 23.4, 18.3, 18.2, 17.5, 17.4, 17.3, 14.4, 14.1, 13.9, 12.7, -1.7; HRMS, calcd for $C_{51}H_{92}O_8Si_3$ (M+ Cs^+) 1049.5154, found 1049.5172.



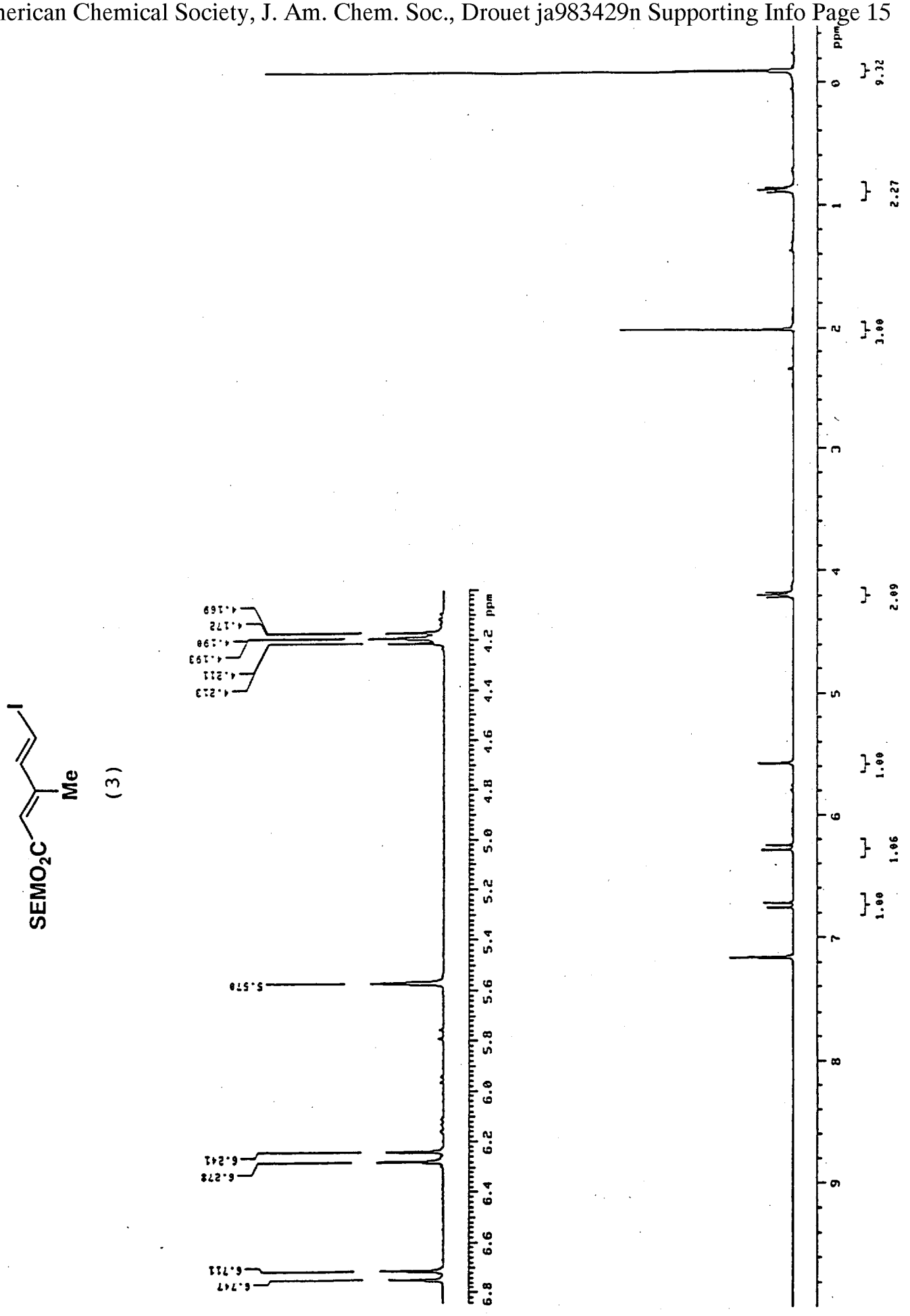
18

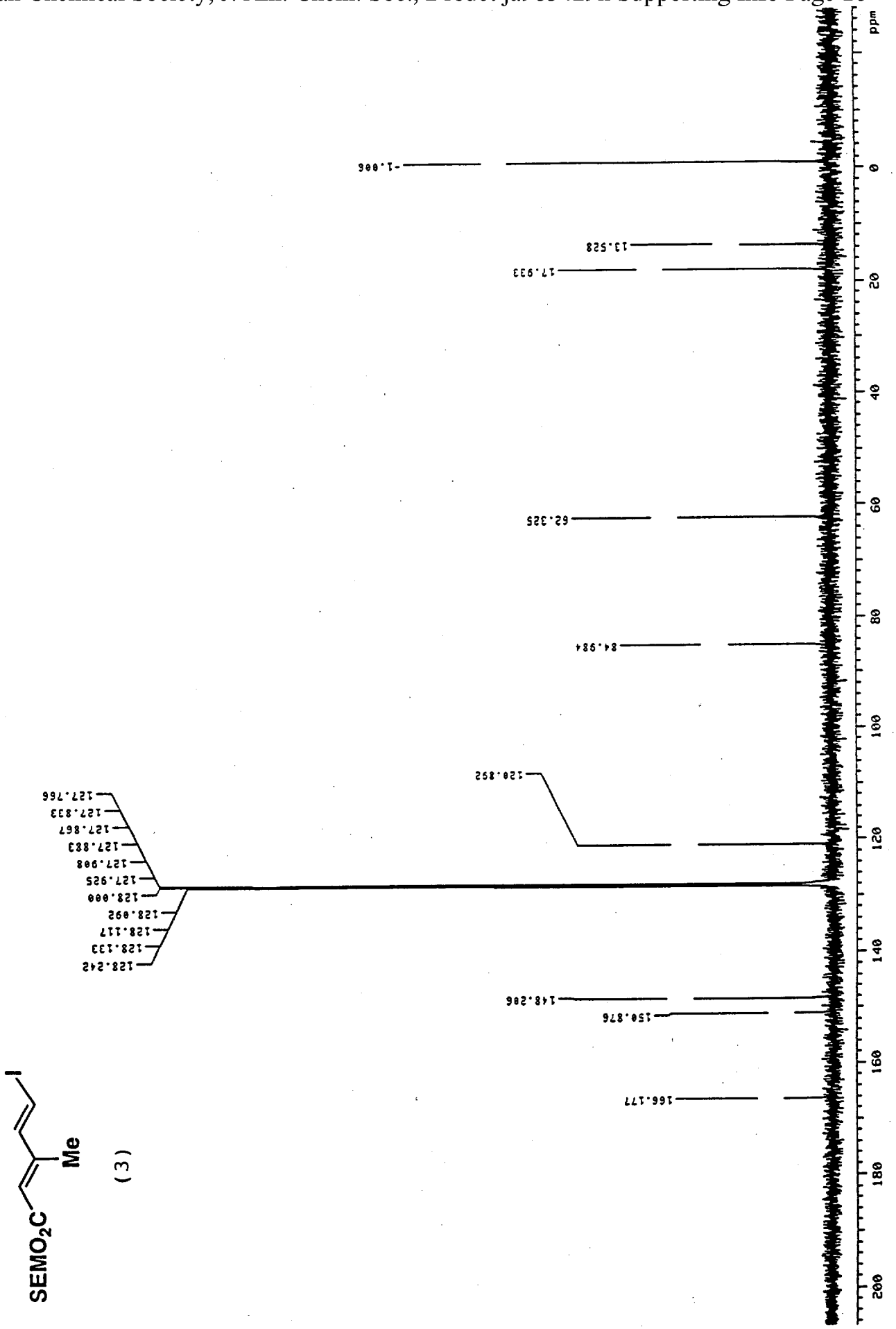
Acid 18. To a solution of alcohol **17** (11 mg, 12 μmol) in methylene chloride (1 ml) was added succinic anhydride (12 mg, 120 μmol) and *N*-dimethylaminopyridine (17 mg, 144 μmol) and the reaction mixture was stirred 3 h at 25 °C. Upon completion of the reaction, the mixture was diluted with aqueous saturated ammonium chloride (5 ml) and extracted with methylene chloride (5 x 5 ml). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated and chromatographed on a preparative silica plate (2% MeOH in ethyl acetate) to yield acid **18** (10.3 mg, 10 μmol, 85%). **18**: colorless solid; R_f = 0.5 (silica, 10% methanol in methylene chloride); $[\alpha]^{25}_D$: -19.7 (c= 0.12, CH_2Cl_2); IR (film) ν_{max} 3409, 2960, 2923, 1716, 1648, 1470, 1248, 1156; ^{1}H NMR (500 MHz, C_6D_6) δ 7.60 (dd, 1H, J= 6.5, 15.5 Hz), 6.78 (d, 1H, J= 15.5 Hz), 6.70 (d, 1H, J= 16.0 Hz), 6.41 (dd, 1H, J= 4.5, 16.0 Hz), 6.26 (t, 1H, J= 6.5 Hz), 6.19 (d, 1H, J= 16.0 Hz), 6.17 (s, 1H), 5.91 (d, 1H, J= 3.5 Hz), 5.80 (dd, 1H, J= 16.0, 8.5 Hz), 4.60-4.58 (m, 1H), 4.29-4.18 (m, 4H), 3.60-3.56 (m, 1H), 2.79-2.55 (m, 5H), 2.40 (s, 3H), 2.38-2.04 (m, 3H) 1.81 (s, 3H), 1.76-1.58 (m, 6H), 1.39-1.21 (m, 8H), 1.17-1.02 (m, 22H), 0.95-0.82 (m, 10H), 0.73 (d, 3H, J= 7.0 Hz), -0.80 (s, 9H), -0.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.5, 168.6, 167.0, 154.3, 151.5, 137.3, 135.5, 133.8, 131.3, 130.8, 127.5, 120.9, 120.8, 107.6, 88.0, 79.3, 78.3, 78.2, 62.7, 61.6, 44.7, 39.1, 34.8, 34.6, 34.5, 32.1, 31.9, 30.0, 29.9, 29.5, 25.7, 23.4, 18.3, 17.8, 17.5, 17.3, 14.2, 13.6, 12.7, 12.4, -1.7; HRMS, calcd for $C_{55}H_{96}O_{11}Si_3$ ($M+Cs^+$) 1149.5315, found 1149.5342.



2: reveromycin B

Reveromycin B (2). A solution of acid **18** (3.1 mg, 3 μmol) in THF (0.1 ml) was treated with tetra *n*-butylammonium fluoride (30 μl of a 1M solution in THF, 30 μmol) at 25 °C for 2 h. The reaction mixture was then diluted with aqueous saturated ammonium chloride (2 ml), the pH was adjusted to 3 with dilute HCl and the mixture was extracted with ethyl acetate (5 x 5 ml). The organic layer was dried, concentrated and chromatographed on a preparative silica gel plate (10% MeOH in methylene chloride) to yield reveromycin B (**2**) (1.4 mg, 2.1 μmol, 69%). **2:** white solid, R_f = 0.25 (silica, 15% methanol in methylene chloride); $[\alpha]^{25}_D$: -61 (c=0.1, MeOH); IR (film) ν_{max} 3427, 2960, 2923, 2861, 1740, 1568, 1414, 1377, 1260, 1162; ^{1}H NMR (400 MHz, CD_3OD) δ 6.94 (dd, 1H, J= 15.6, 7.6 Hz), 6.38 (d, 1H, J= 15.6 Hz), 6.25 (d, 1H, J= 16.0 Hz), 6.19 (dd, 1H, J= 4.4, 16.0 Hz), 5.80 (d, 1H, J= 15.6 Hz), 5.78 (s, 1H), 5.75 (t, 1H, J= 6.8 Hz), 5.55 (d, 1H, J= 4.4 Hz), 5.50 (dd, 1H, J= 15.6, 7.6 Hz), 4.11 (m, 1H), 3.39 (m, 1H), 2.65-2.45 (m, 5H), 2.25-2.15 (m, 5H), 2.01-1.30 (m, 18H), 1.01 (d, 3H, J= 6.4 Hz), 0.91 (t, 3H, J= 7.2 Hz), 0.83 (d, 3H, J= 7.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 177.9, 173.4, 171.7, 171.1, 152.0, 151.3, 138.6, 136.3, 135.3, 132.0, 131.0, 127.5, 123.6, 122.7, 108.7, 88.9, 80.5, 78.7, 77.4, 44.2, 39.7, 35.9, 35.6, 35.4, 33.0, 32.9, 31.4, 30.8, 30.3, 26.7, 24.4, 18.3, 15.3, 14.7, 14.1, 12.9; HRMS, calcd for $C_{36}H_{52}O_{11}$ ($M+Na^+$) 683.3407, found 683.3388.





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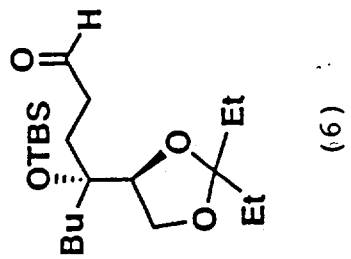

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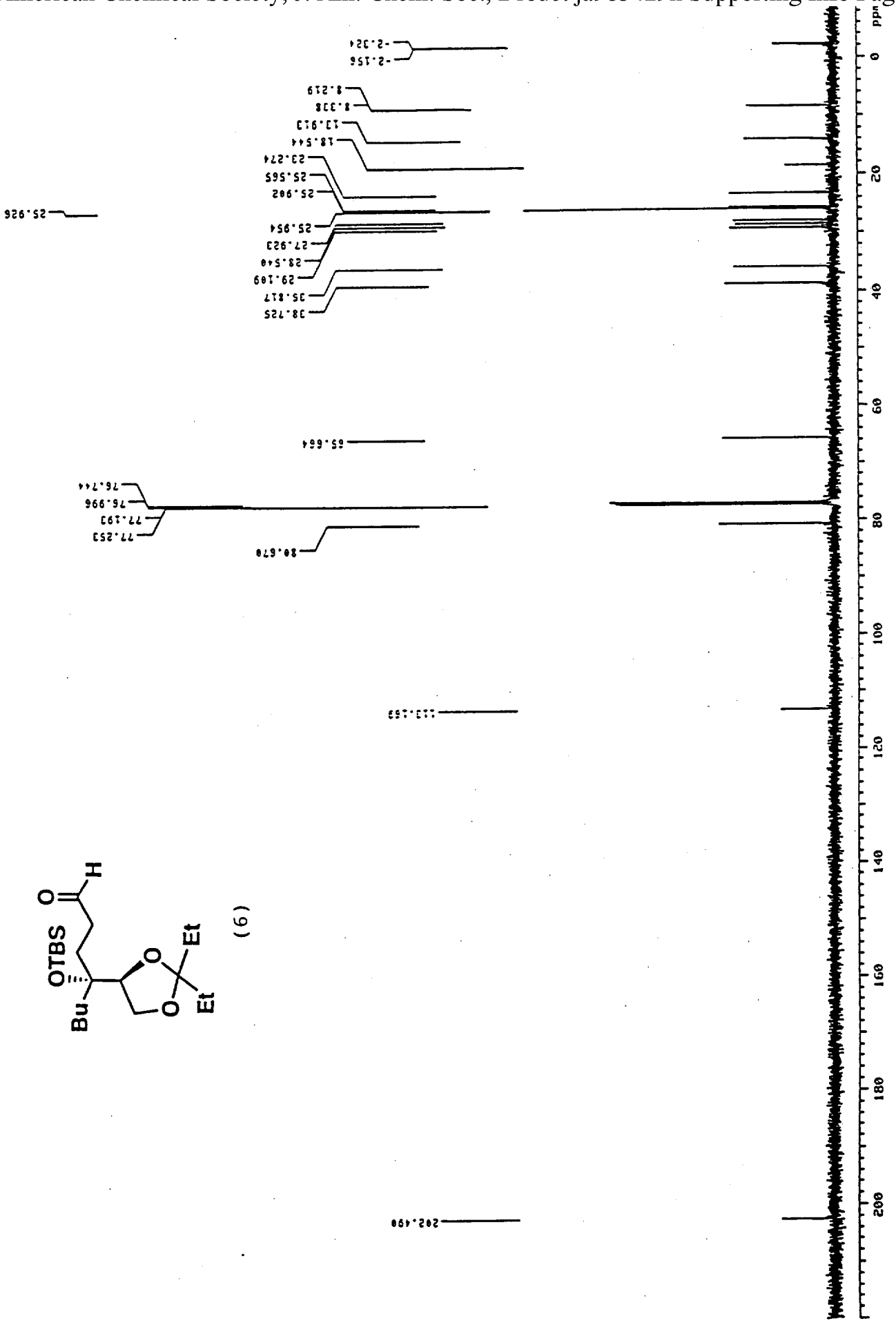

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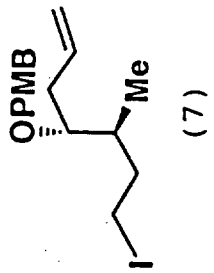

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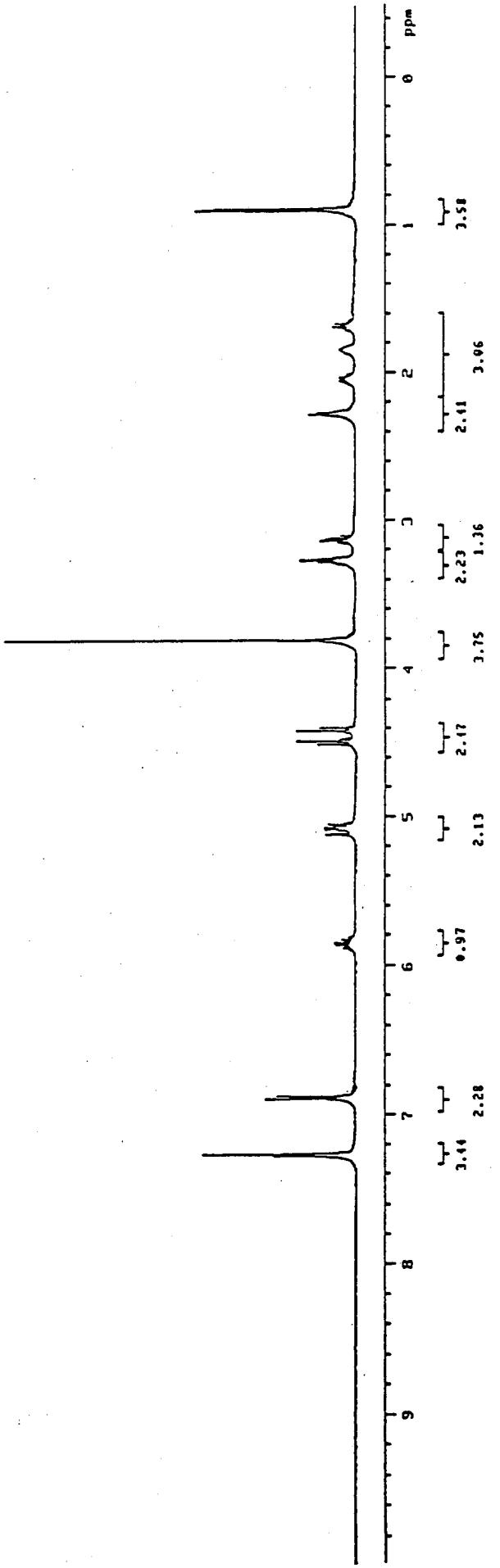

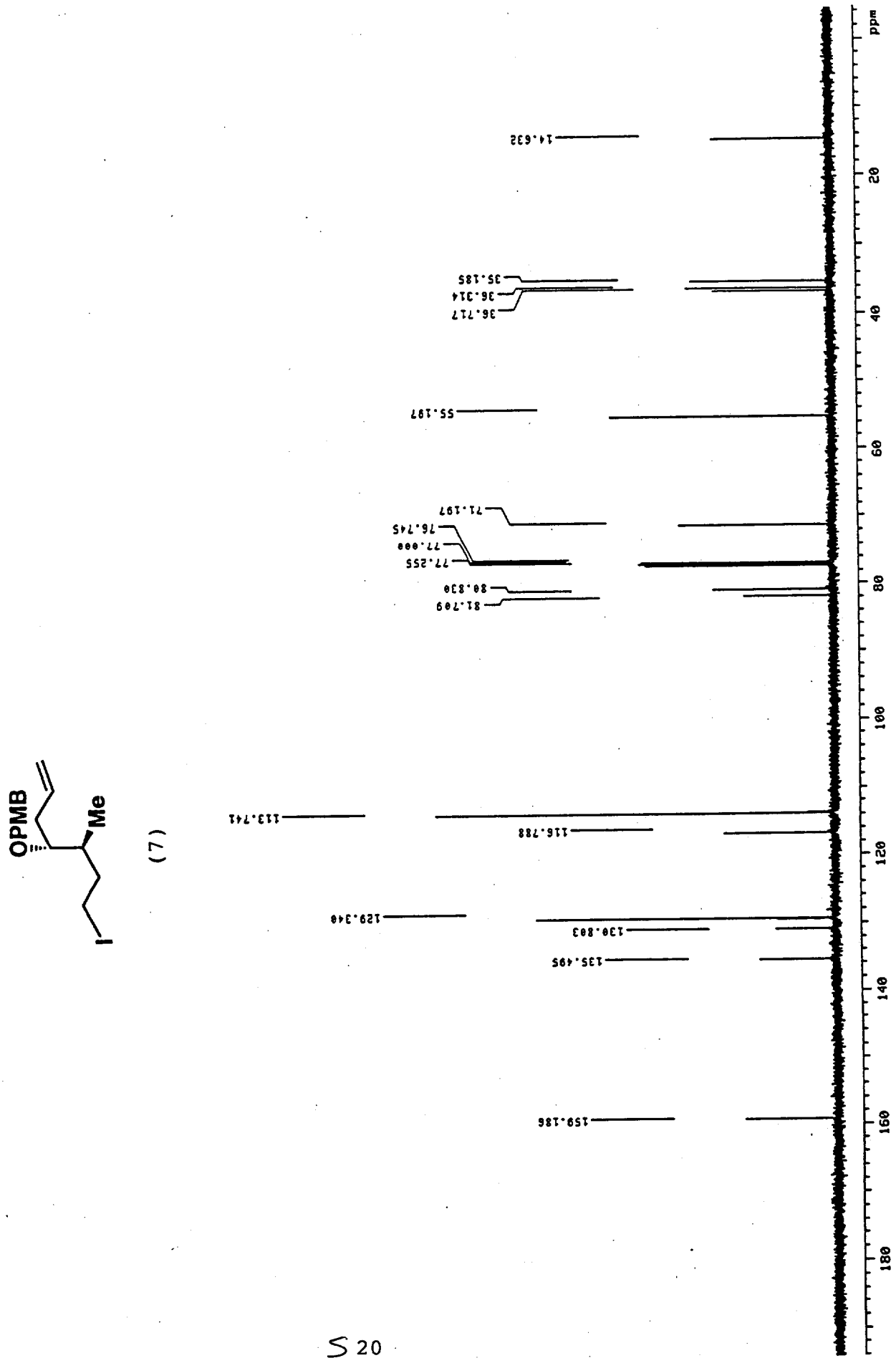

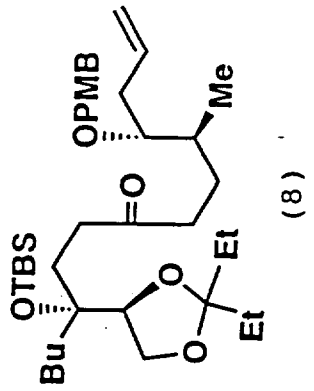

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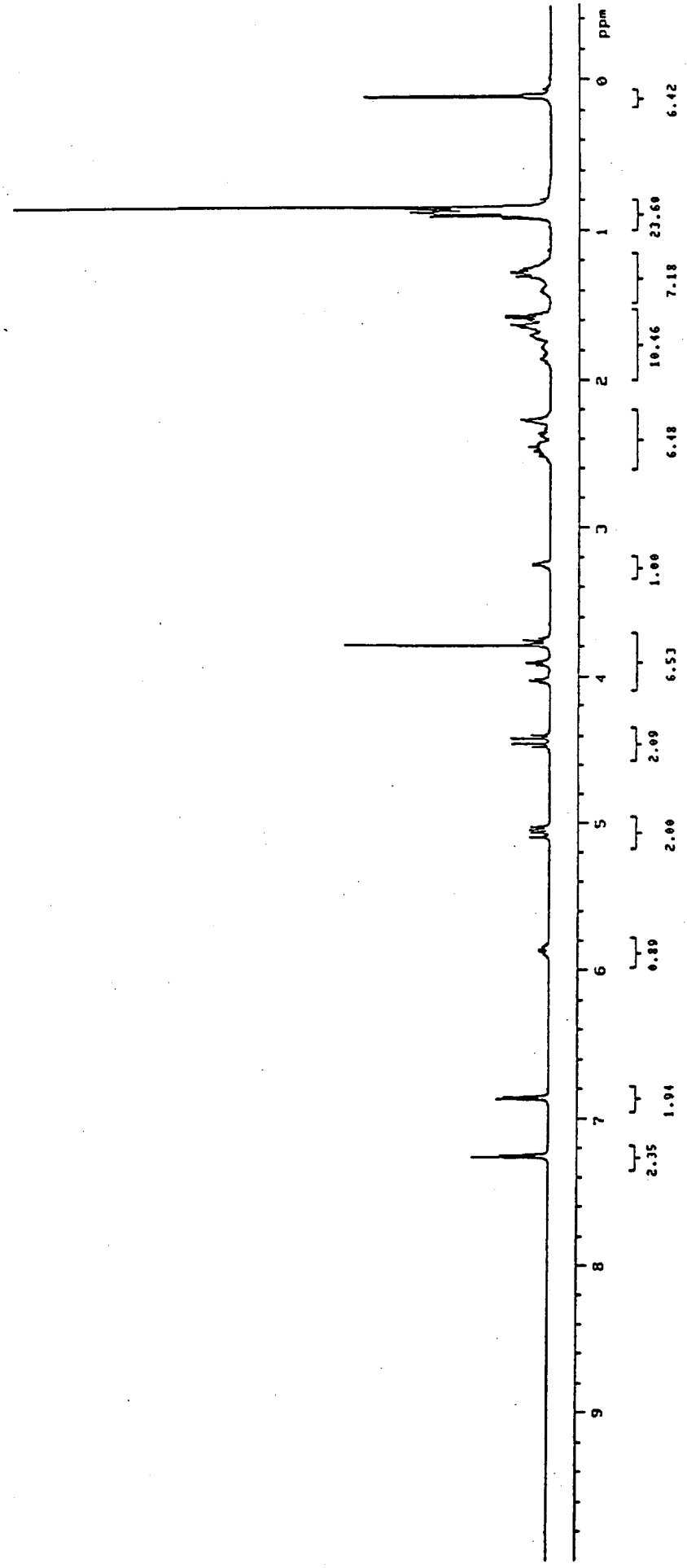

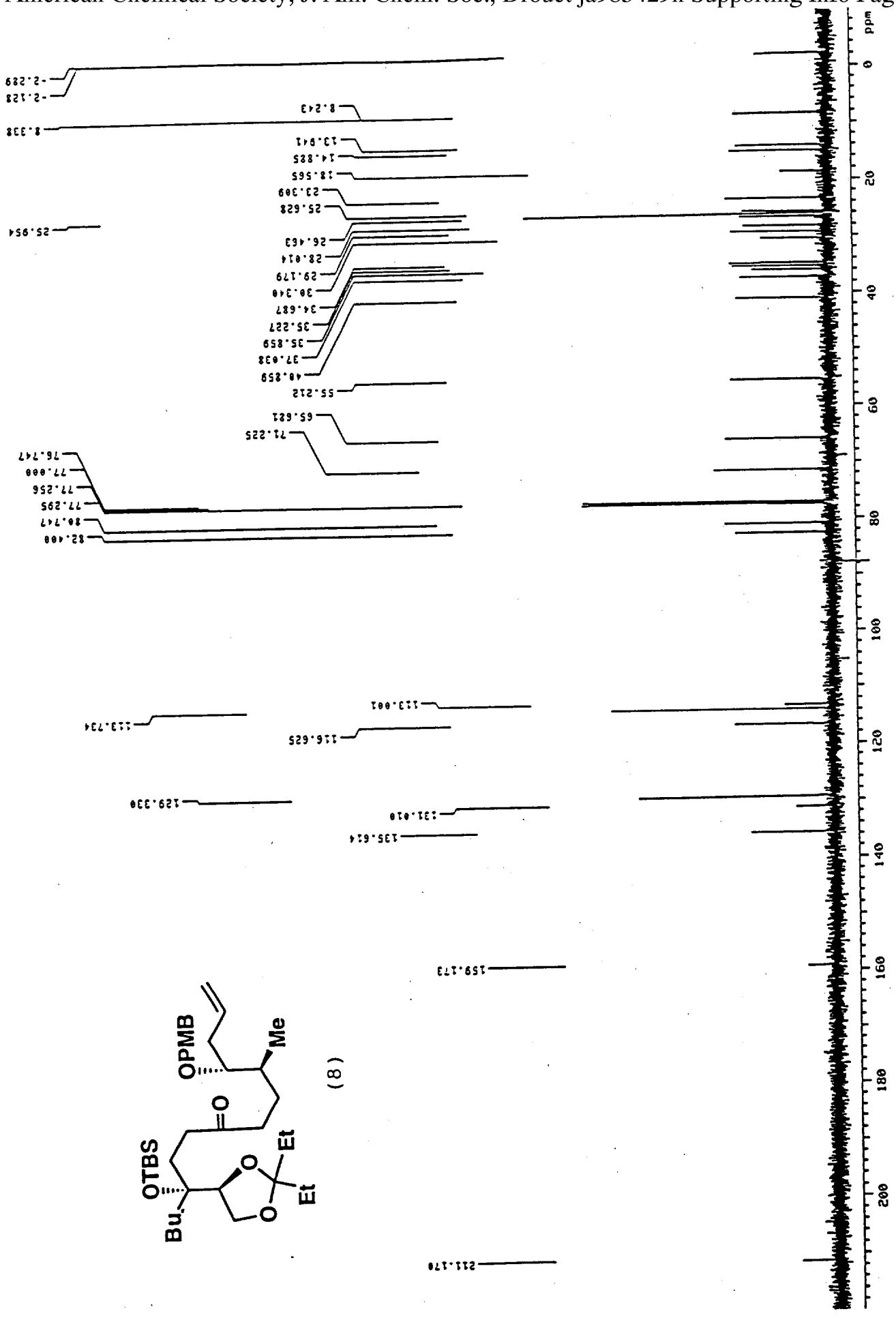

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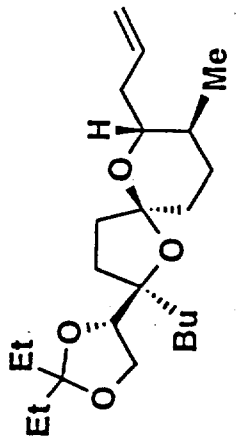

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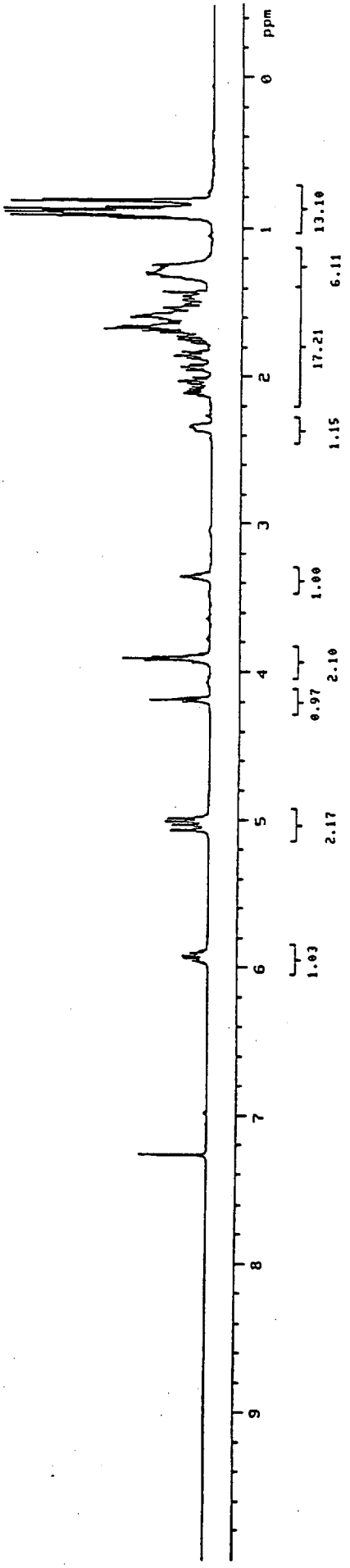

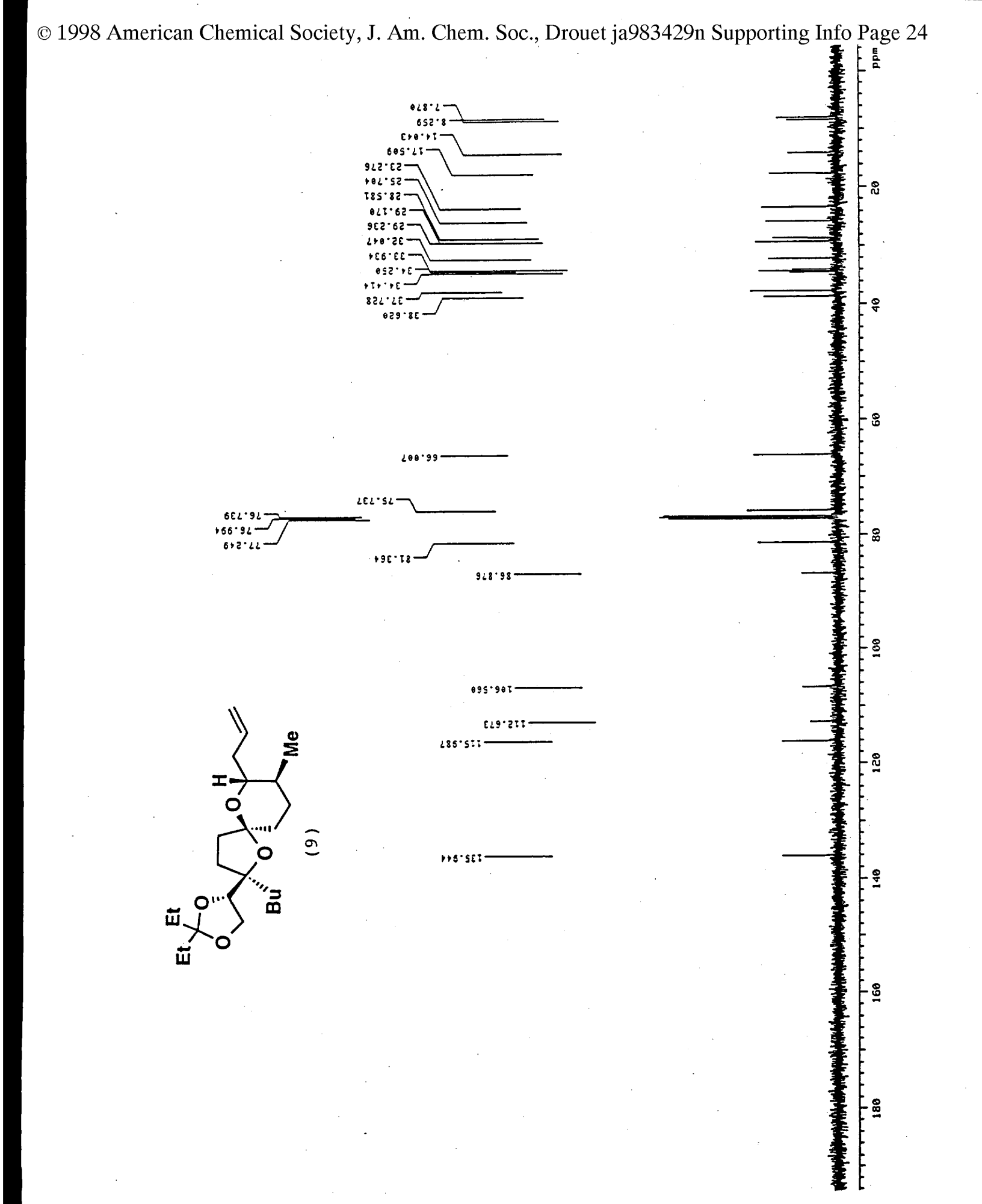

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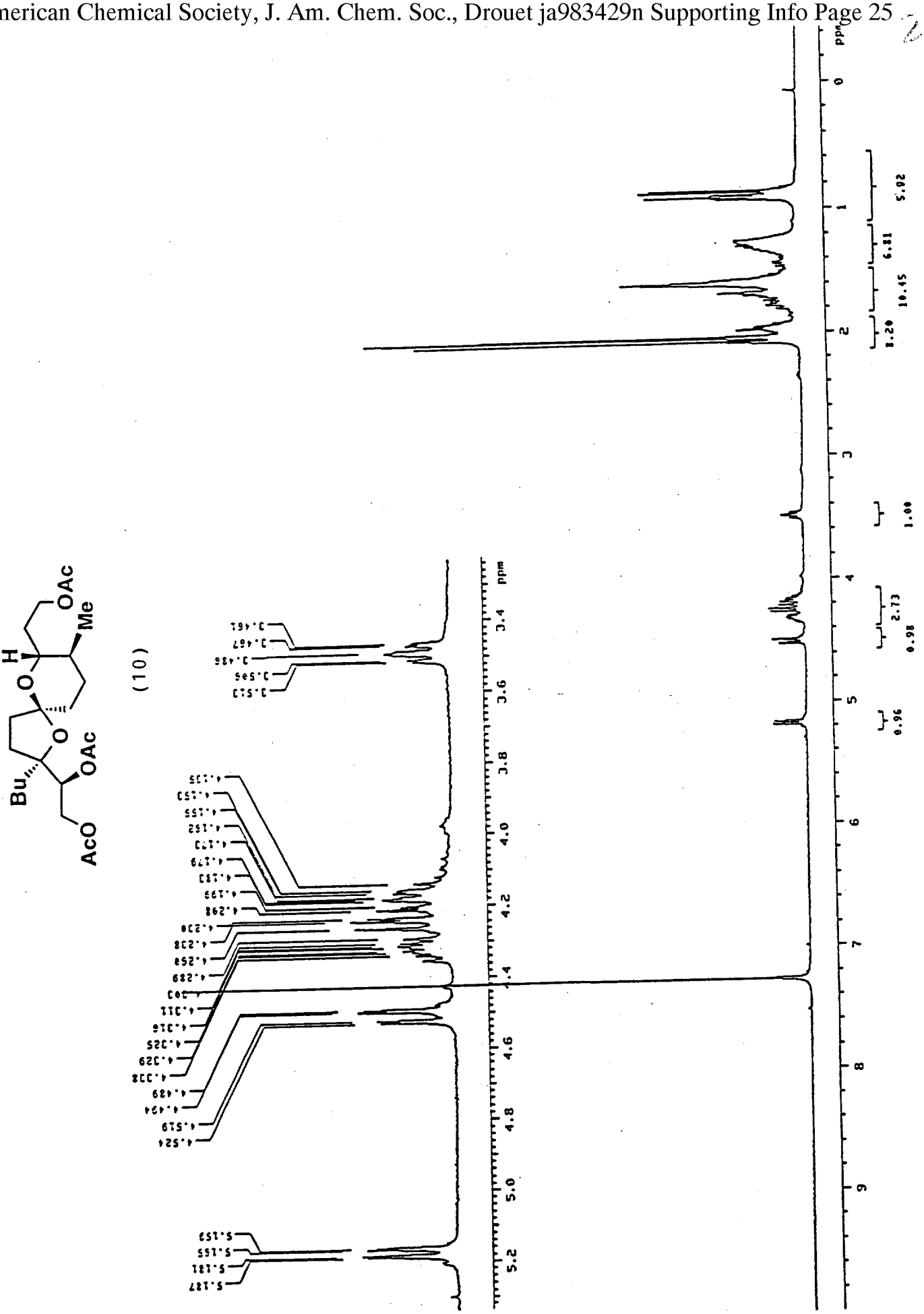

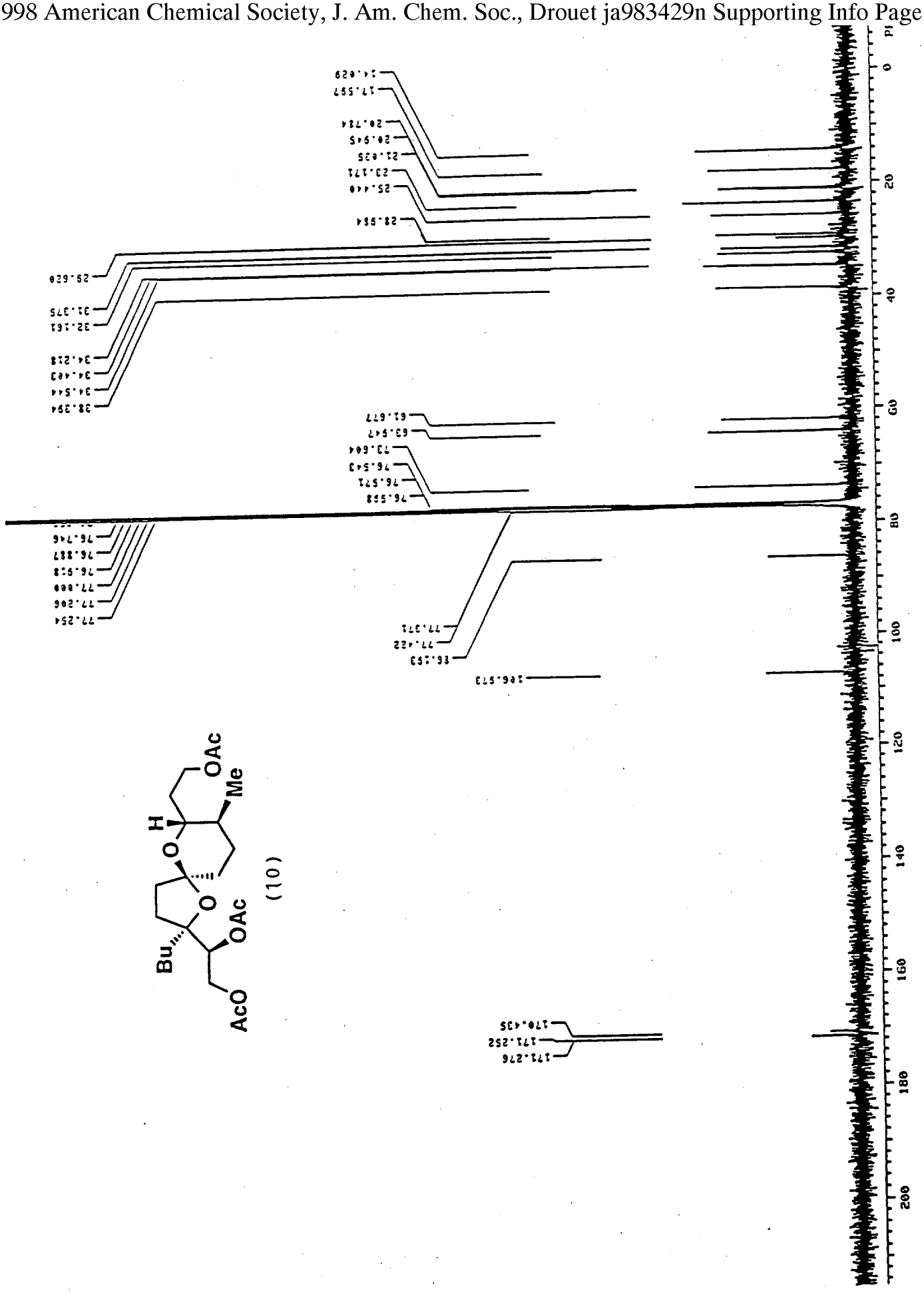

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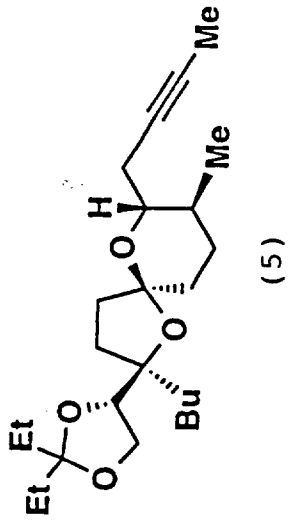

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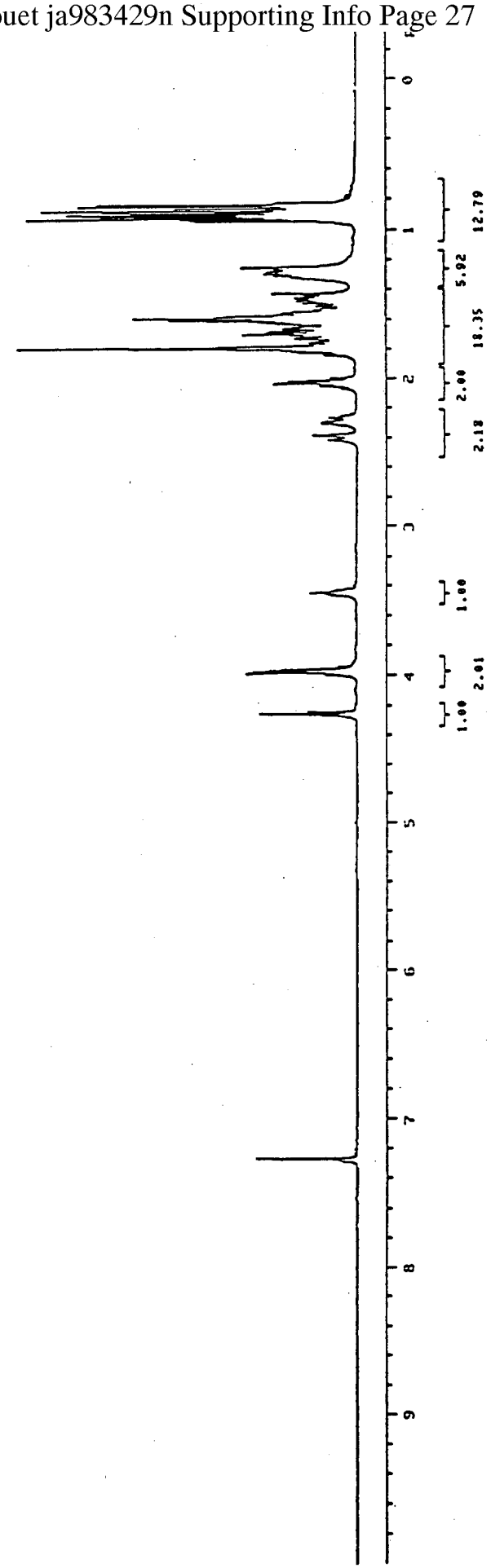

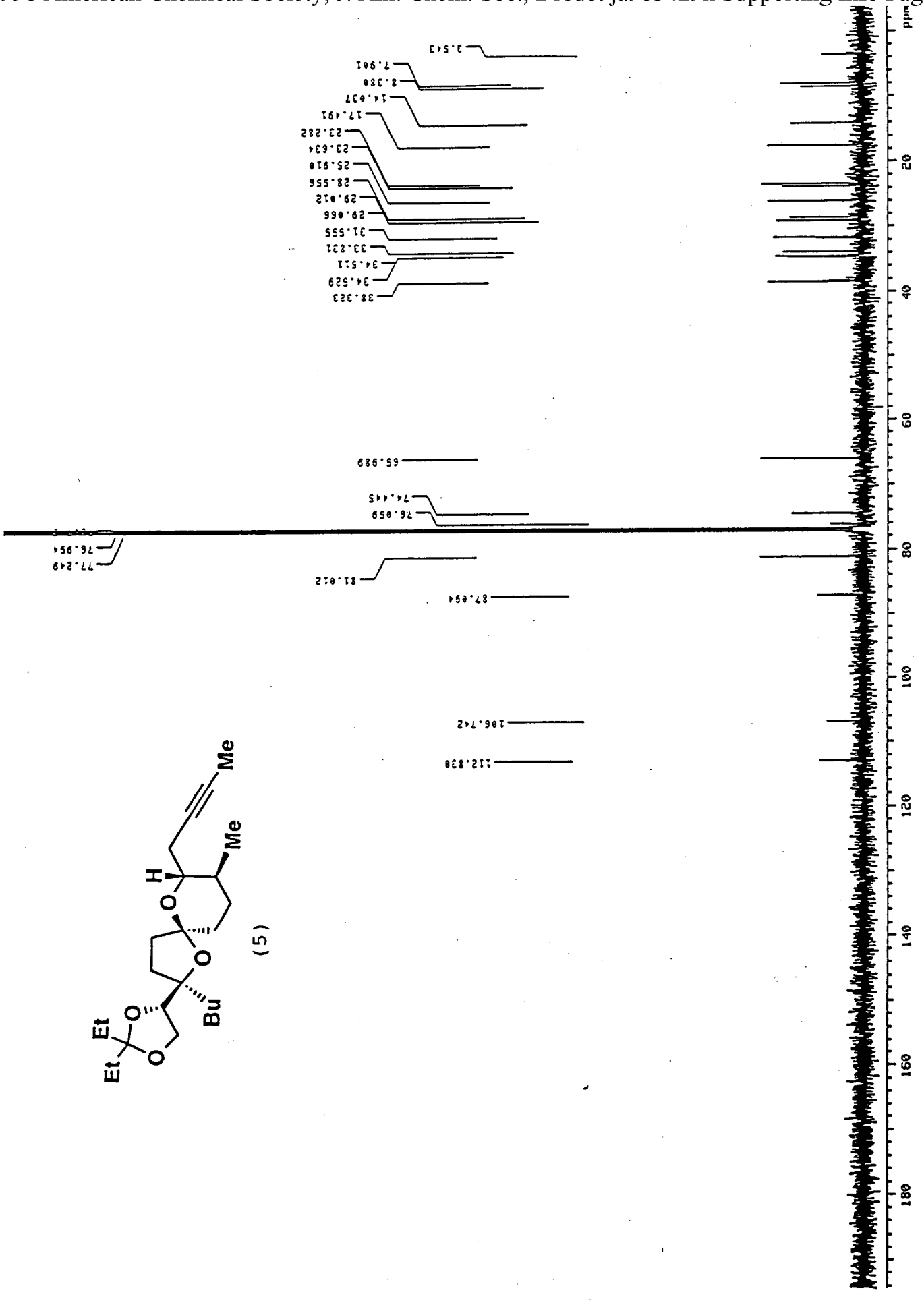

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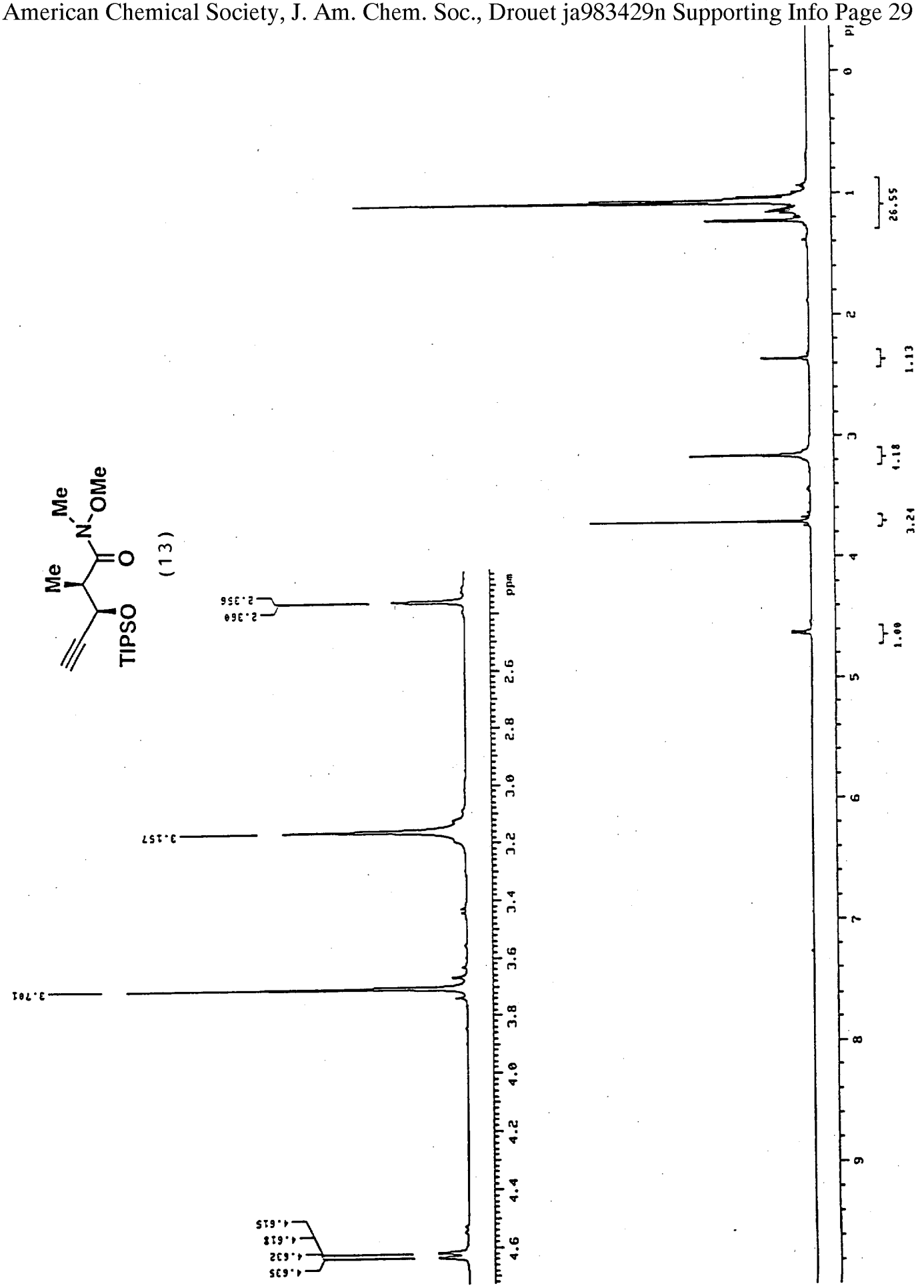

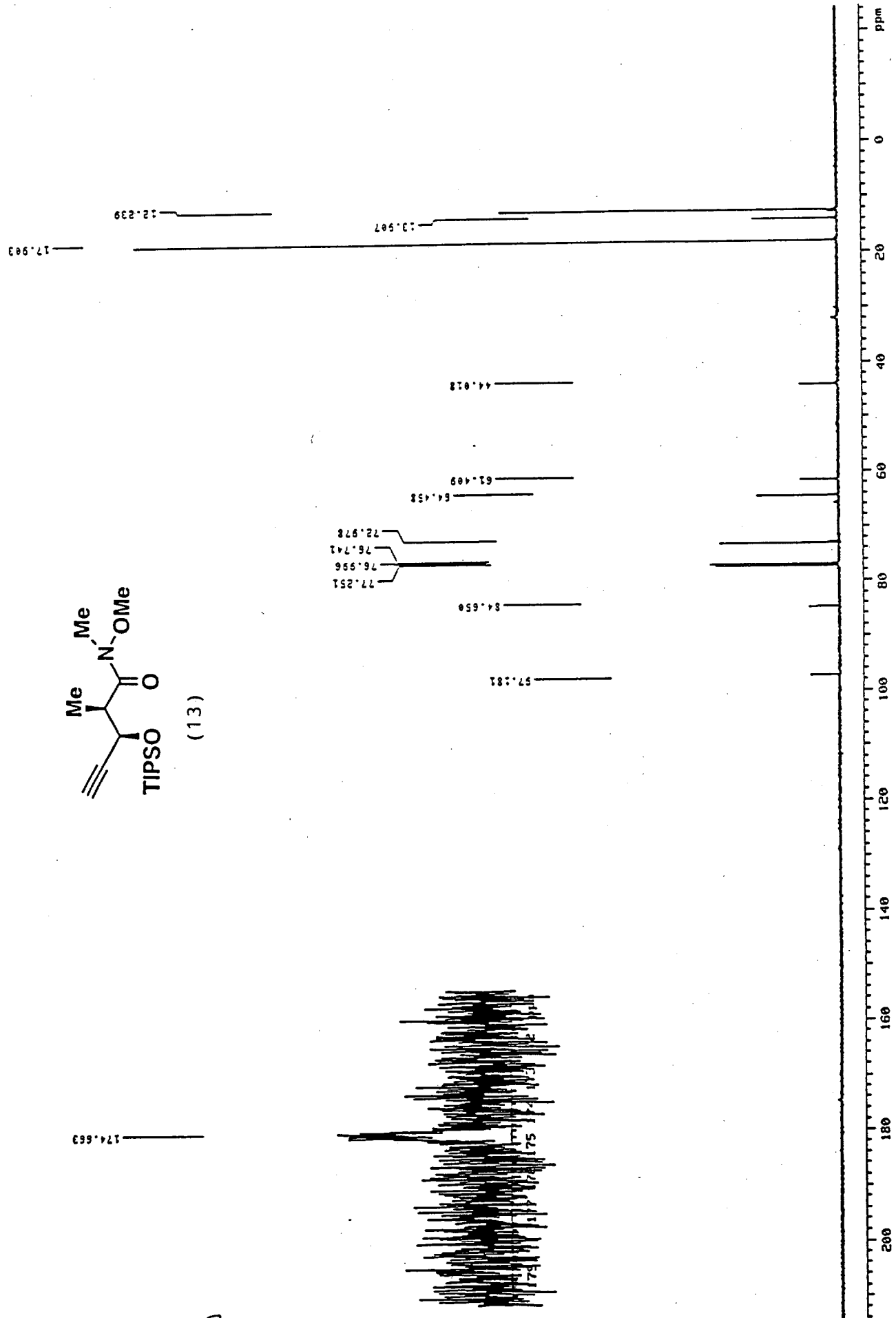

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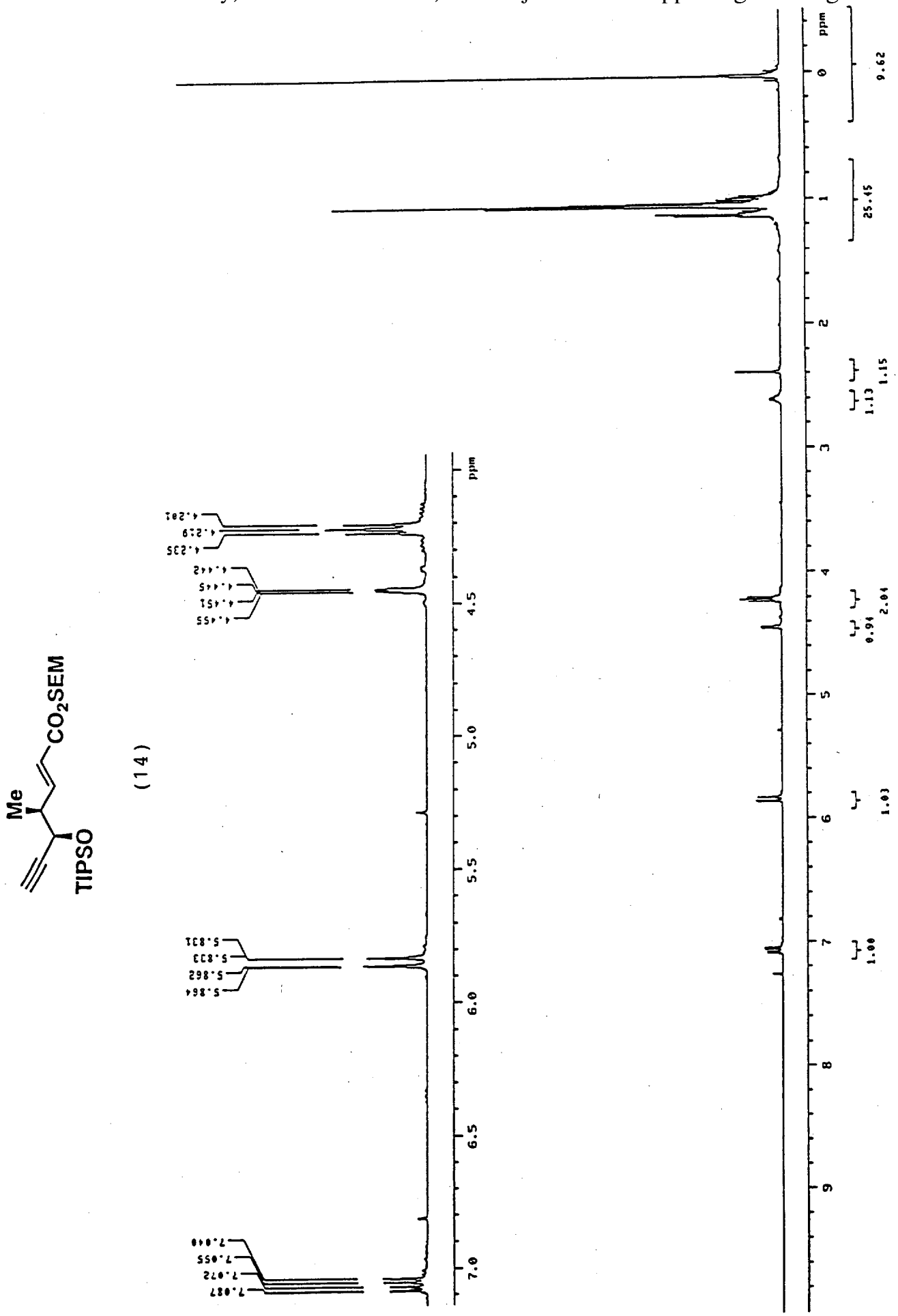

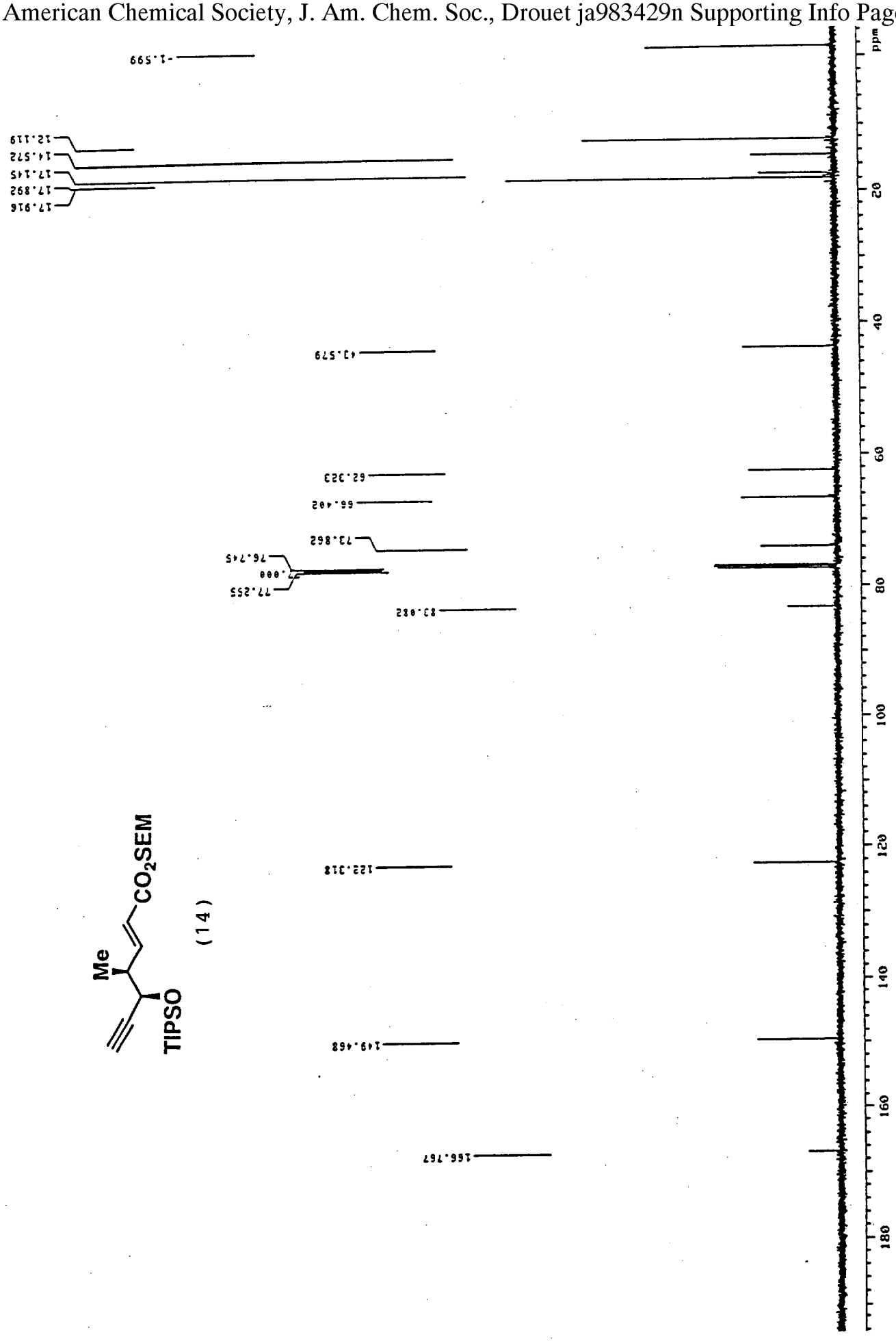

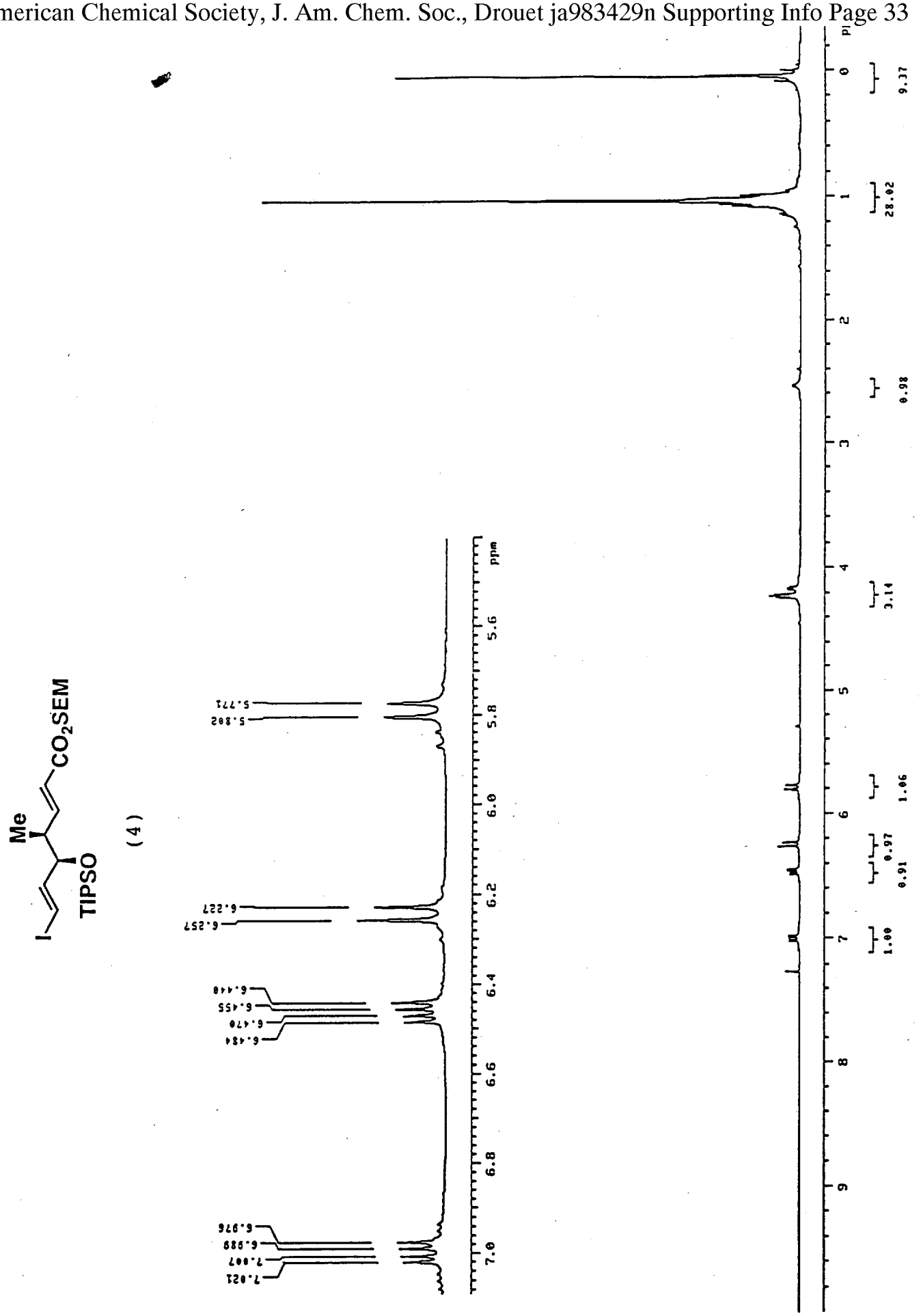

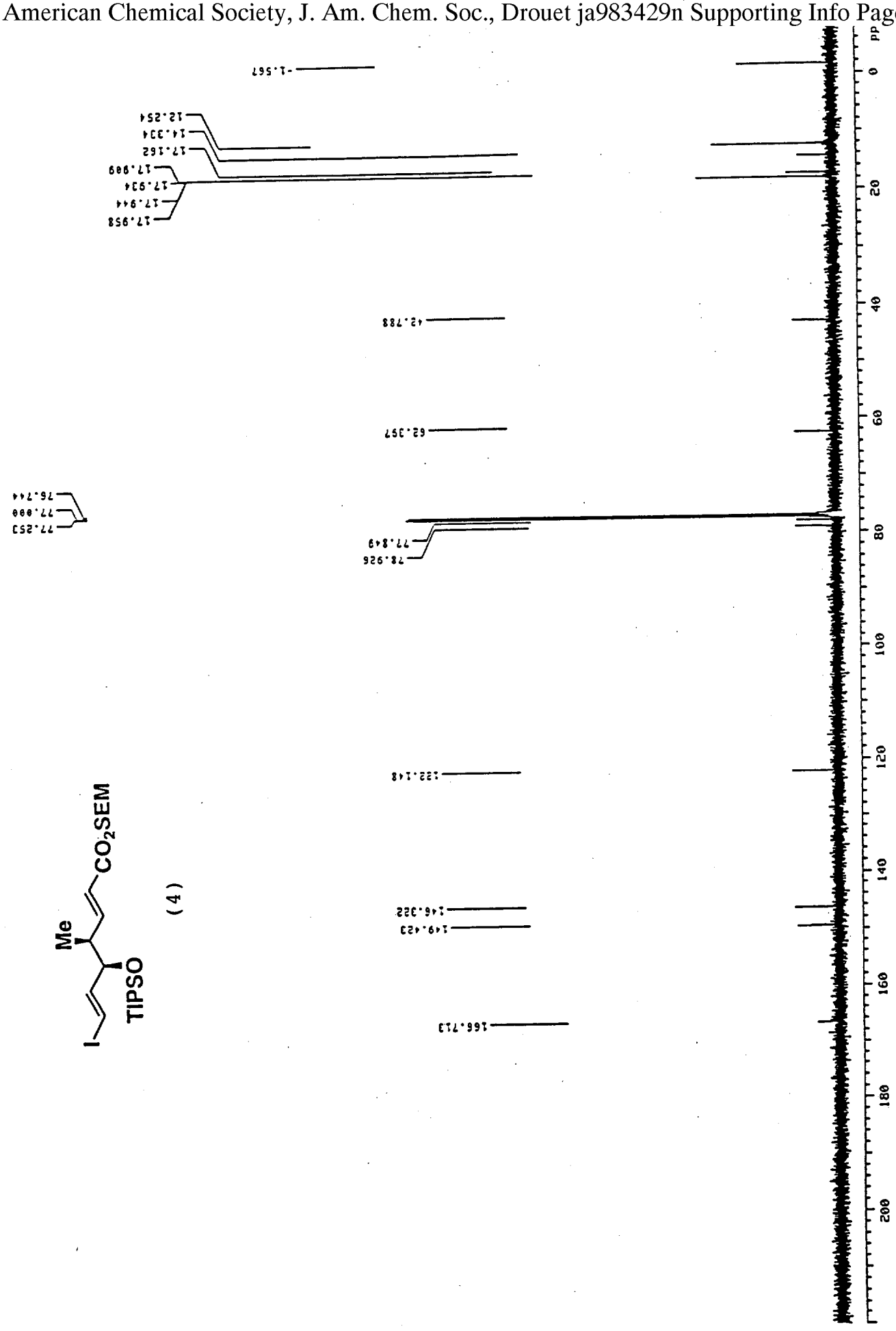

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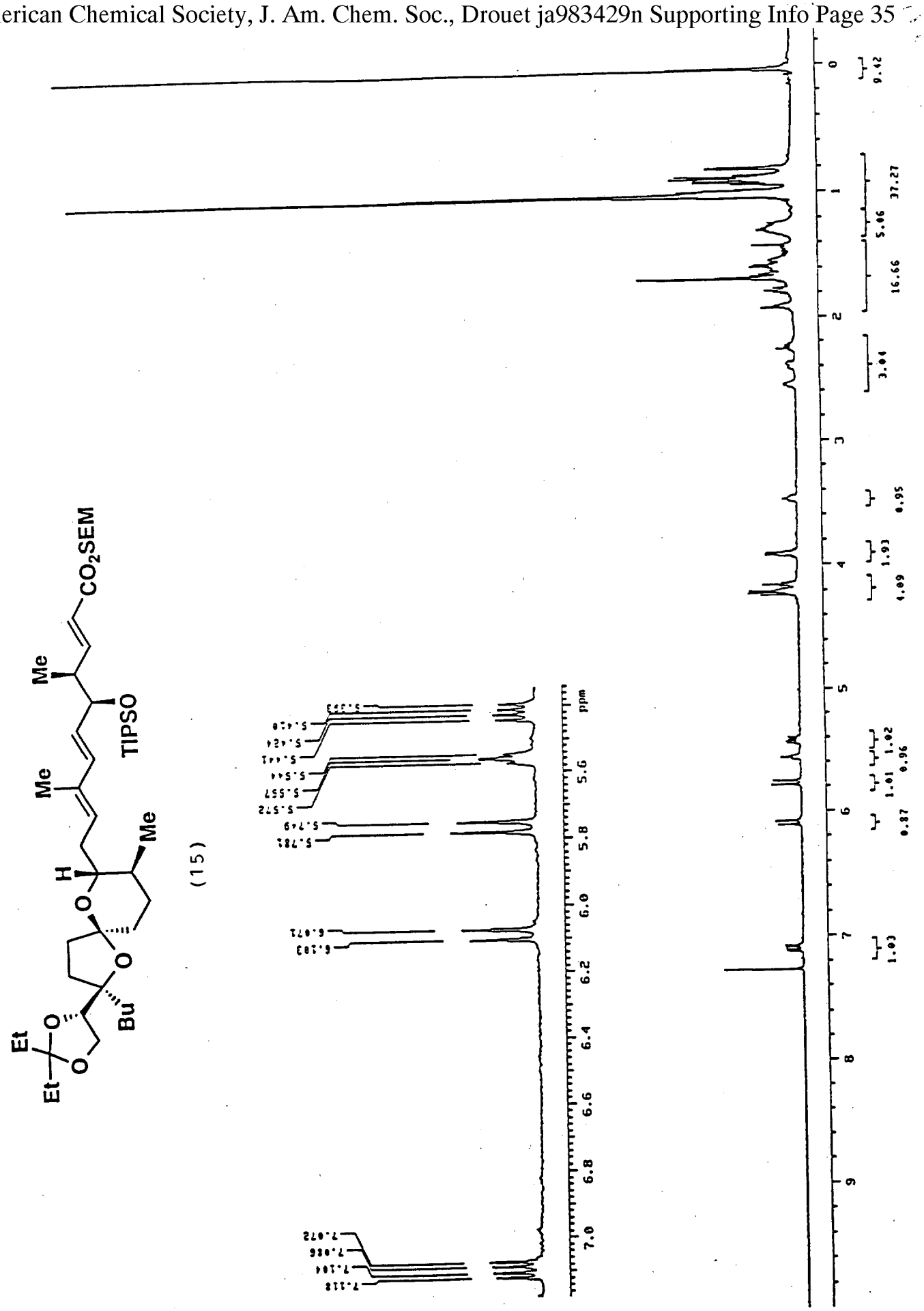

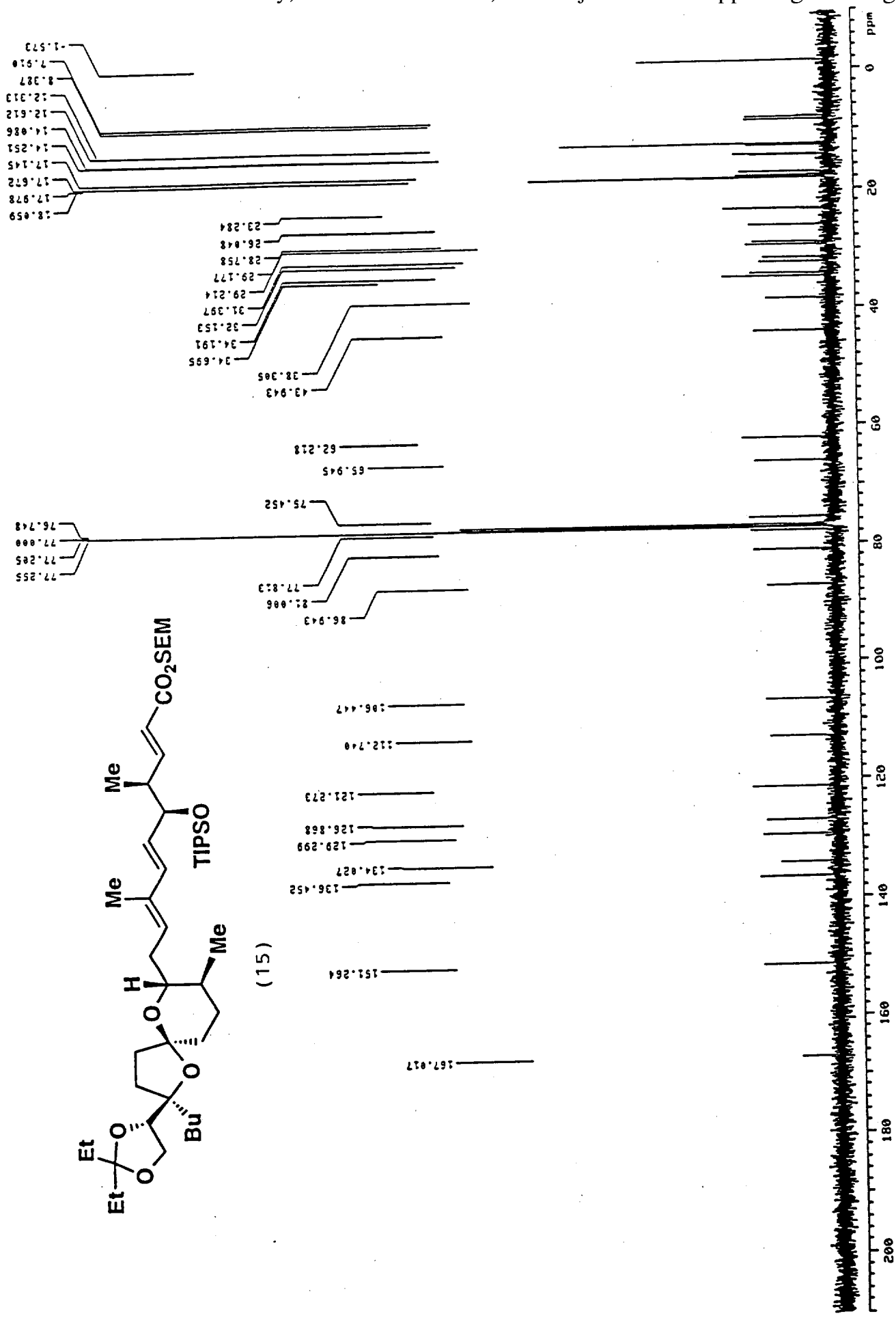

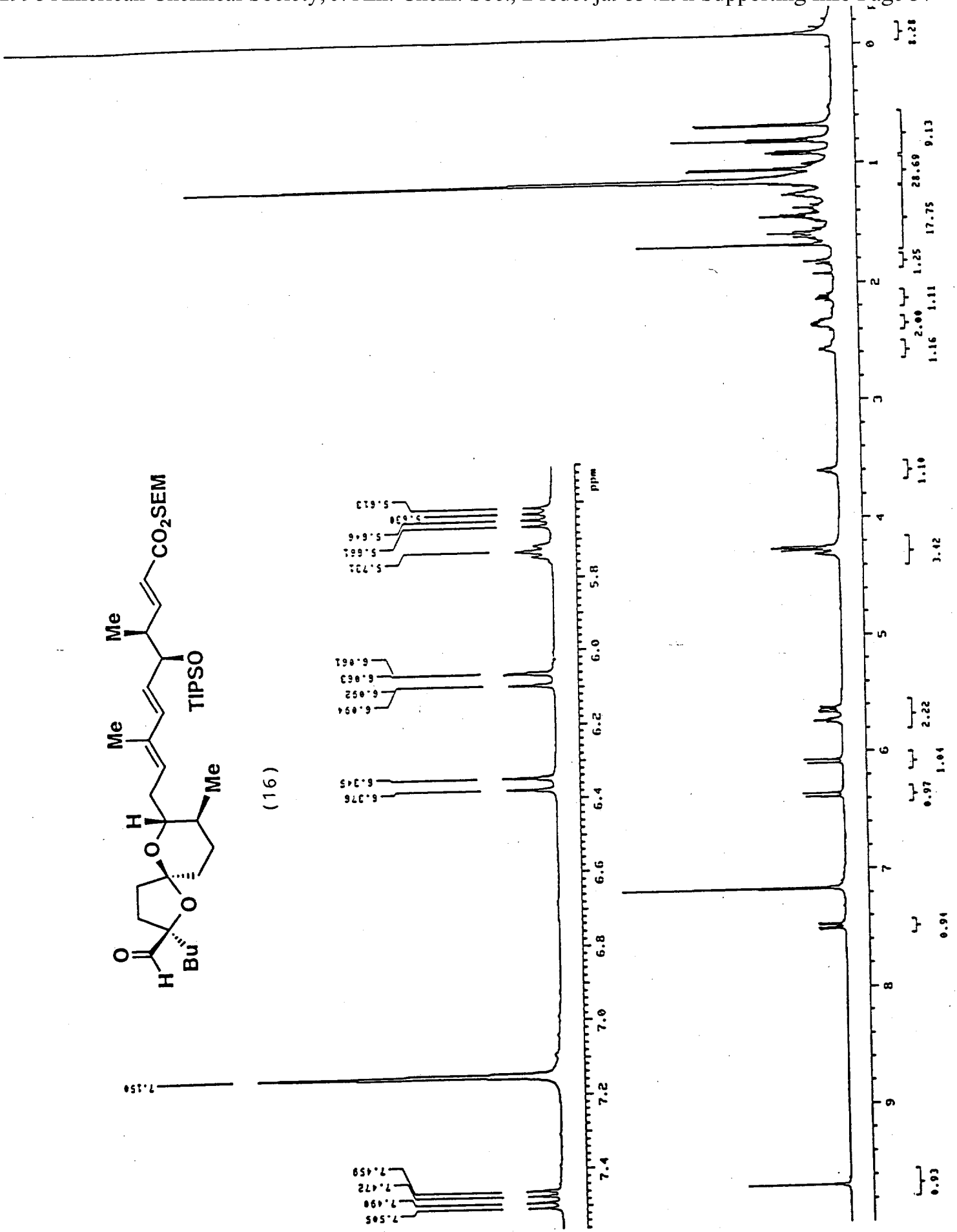

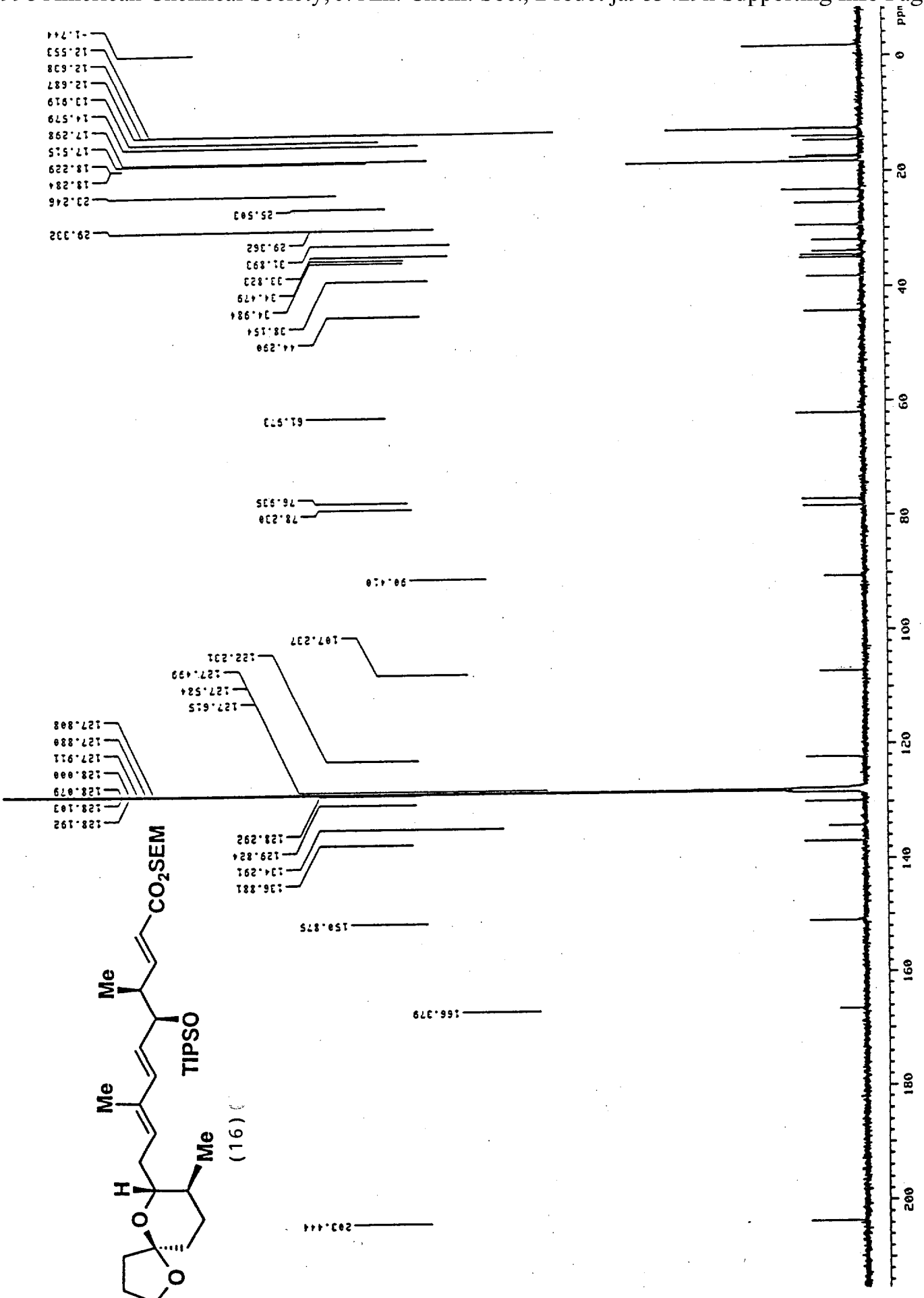

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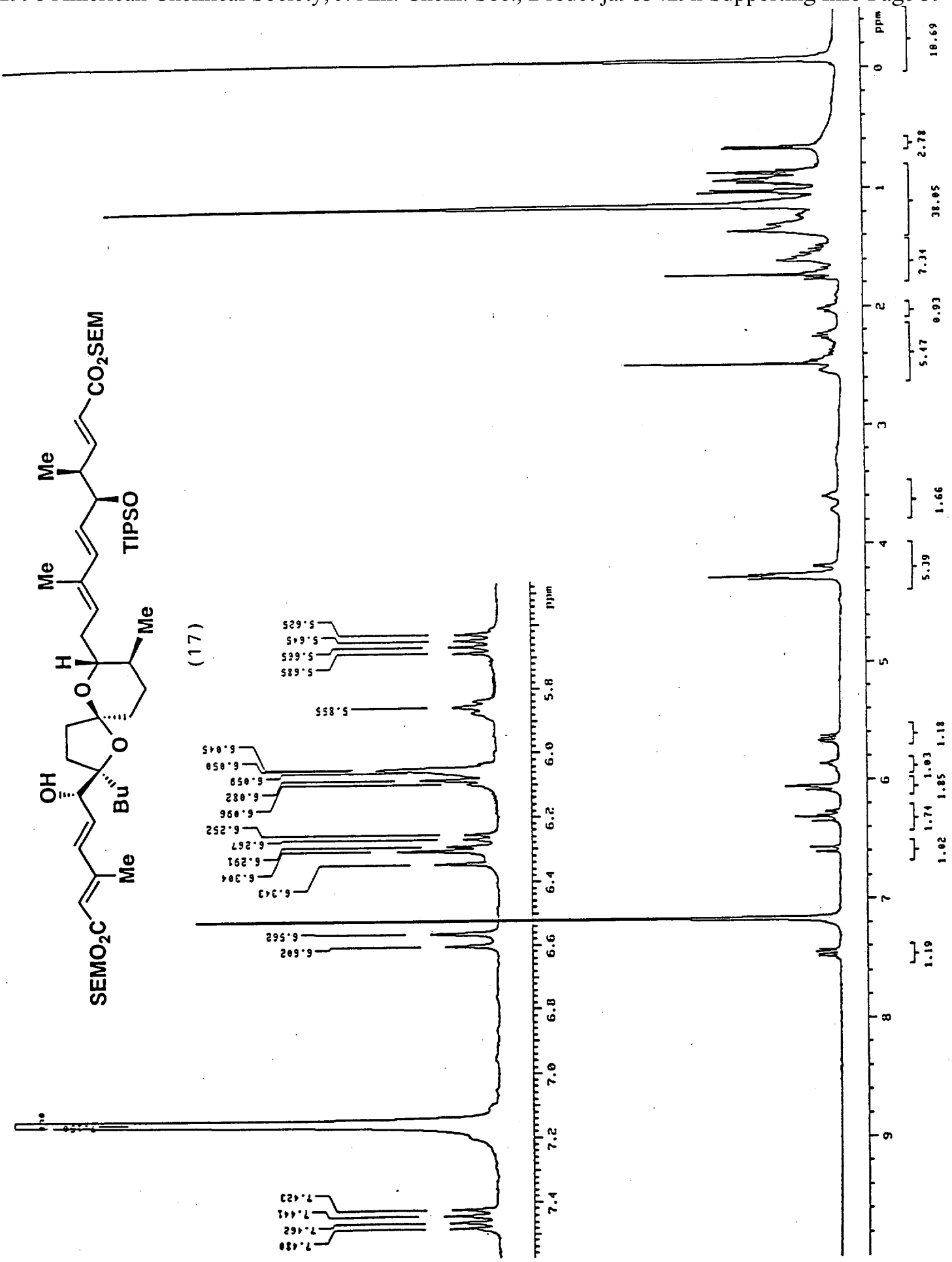

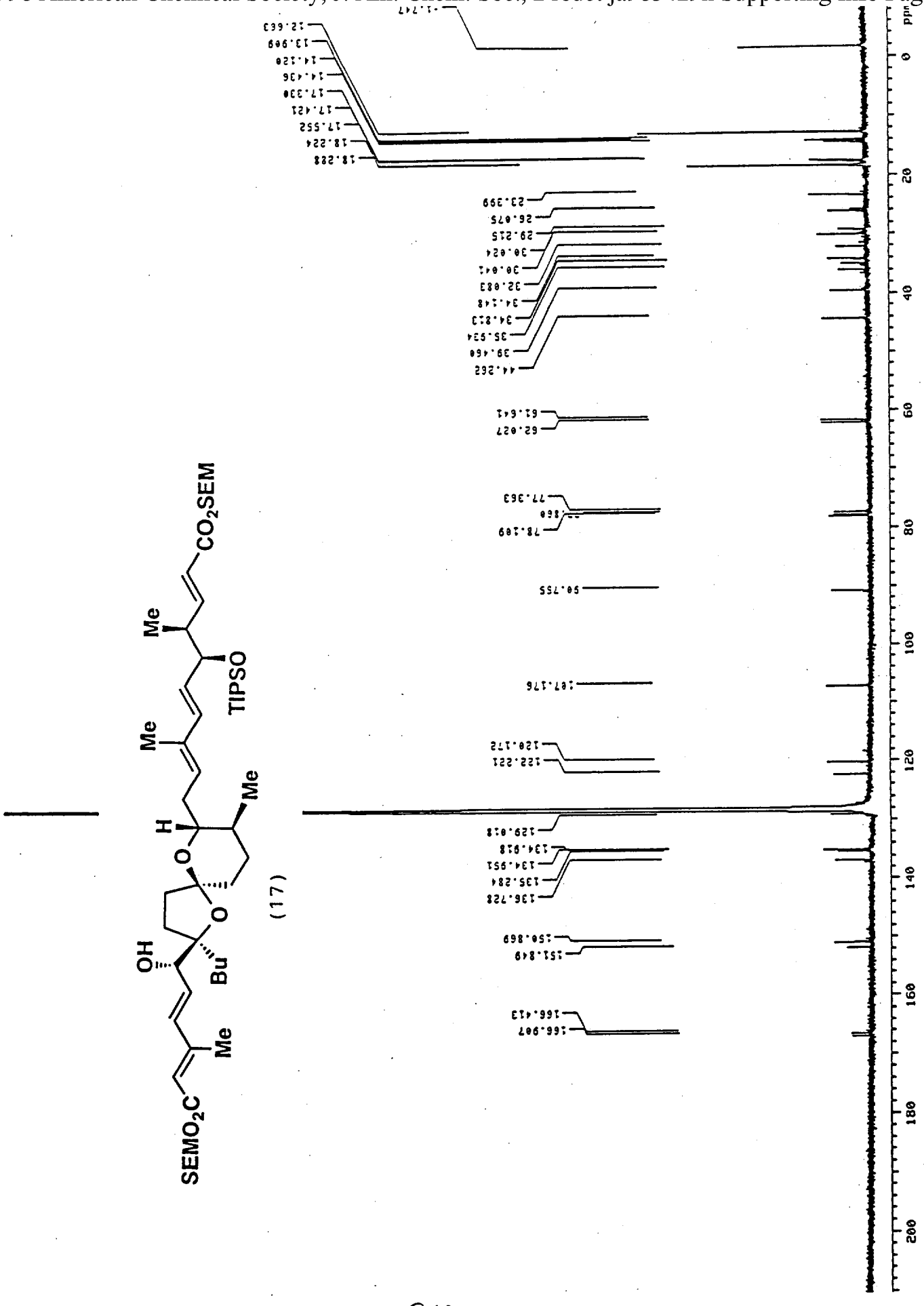

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