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PATERSON
3623-3624

Substrate-Controlled Aldol Reactions of Chiral Ethyl Ketones: Application to the Total Synthesis of Oleandomycin

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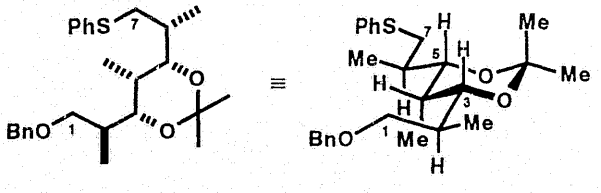
SUPPLEMENTARY MATERIAL (16 Pages)

General. ^{1}H nuclear magnetic resonance spectra were recorded at 400 MHz on a Bruker AM 400 spectrometer at ambient temperature using an internal deuterium lock, and all chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane (TMS, $\delta_{TMS} = 0$). The following abbreviations for splitting patterns are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C nuclear magnetic resonance APT spectra were recorded at 100.6 MHz on a Bruker AM 400 spectrometer at ambient temperature using an internal deuterium lock, and all chemical shift values are reported in parts per million (δ) downfield relative to tetramethylsilane (TMS, $\delta_{TMS} = 0$).

Infra-red spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer using 0.1 mm sodium chloride solution cells. Absorbance bands are reported in wavenumbers (cm^{-1}), and the following abbreviations are used to describe their appearance: w, weak; m, medium; s, strong; vs, very strong; br, broad.

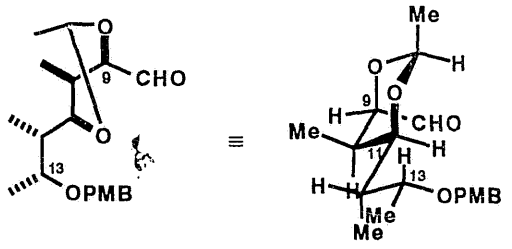
High and low resolution mass spectra were carried out by the SERC Mass Spectrometry Service Centre, Swansea, UK, using chemical ionisation (CI). Analytical thin-layer chromatography was carried out using Merck Kieselgel 60 F_{254} plates. Flash chromatography[1] was carried out on Merck Kieselgel 60 (230-400 mesh) using distilled solvents.

(2*S*,3*R*,4*S*,5*R*,6*R*)-1-Benzyloxy-3,5-isopropylidenedioxy-2,4,6-trimethyl-7-phenylthioheptane (immediate precursor to sulphoxide 14).



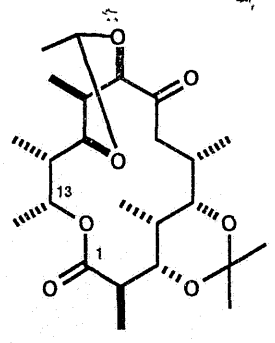
TLC R_f 0.55 (3% Et_2O in CH_2Cl_2); $[\alpha]_D^{20} = -13.9$ (*c* 3.6, $CHCl_3$); IR (thin film) 1590 (m), 1490 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.10 (10H, m, ArH), 4.54 (1H, d, *J*=12.2 Hz, benzyl CH), 4.45 (1H, d, *J*=12.2 Hz, benzyl CH), 3.65 (1H, dd, *J*=9.6, 1.9 Hz, H_3), 3.59 (1H, dd, *J*=9.9, 2.0 Hz, H_5), 3.42 (1H, dd, *J*=12.8, 2.6 Hz, H_{7a}), 3.36 (2H, m, H_{1a}, H_{1b}), 2.72 (1H, dd, *J*=12.8, 8.3 Hz, H_{7b}), 2.00-1.85 (2H, m, H_2, H_6), 1.57 (1H, qdd, *J*=6.8, 2.0, 1.9 Hz, H_4), 1.42 (3H, s, acetonide Me), 1.38 (3H, s, acetonide Me), 1.07 (3H, d, *J*=6.7 Hz, Me), 0.93 (3H, d, *J*=6.8 Hz, Me), 0.82 (3H, d, *J*=6.7 Hz, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 138.4, 137.9, 128.7, 127.8, 127.5, 125.0, 99.0, 76.3, 76.0, 73.1, 71.5, 37.0, 34.9, 31.1, 29.9, 19.6, 14.8, 14.0, 5.0; m/z ($CI^+(NH_3)$) 429($[M+H]^+$ 13), 428($[M]^+$ 27), 371(100), 353(52), 263(59), 91(25%); HRMS calculated for $C_{26}H_{36}O_3S$ $[M]^+$ requires 428.2385, found 428.2385.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2,4-(*S*)-Ethylidenedioxy-6-*p*-methoxybenzyloxy-3,5-dimethylheptanal (9).



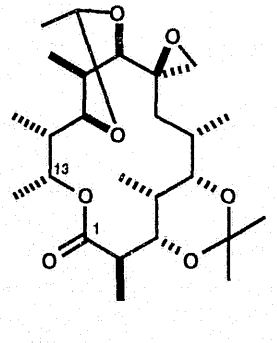
TLC R_f 0.15 (30% Et_2O in hexane); $[\alpha]_D^{20}$ = –118.5 (*c* 3.2, $CHCl_3$); IR (thin film) 1730 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.85 (1H, s, H_8), 7.16 (2H, d, *J*=8.5 Hz, ArH), 6.84 (2H, d, *J*=8.5 Hz, ArH), 4.49 (1H, d, *J*=12.0 Hz, benzyl CH), 4.45 (1H, q, *J*=5.0 Hz, ethylidene CH), 4.17 (1H, d, *J*=12.0 Hz, benzyl CH), 4.02 (1H, br s, H_9), 3.80 (1H, qd, *J*=6.4,1.8 Hz, H_{13}), 3.79 (3H, s, MeOAr), 3.28 (1H, dd, *J*=10.1,2.1 Hz, H_{11}), 2.15 (1H, m, H_{10}), 1.40 (1H, dqd, *J*=10.1, 7.0, 1.8 Hz, H_{12}), 1.19 (3H, d, *J*=5.0 Hz, ethylidene Me), 1.12 (3H, d, *J*=6.4 Hz, Me), 1.09 (3H, d, *J*=7.0 Hz, Me), 0.78 (3H, d, *J*=7.0 Hz, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 204.0, 159.0, 131.2, 129.6, 113.5, 96.9, 85.0, 76.7, 70.0, 69.8, 55.2, 40.1, 28.9, 21.0, 16.8, 11.2, 7.0; m/z ($CI^+(NH_3)$) 354 ($[M+NH_4]^+$ 15), 337($[M+H]^+$ 85), 309(50), 295(20), 280(95), 263(100), 121(100); HRMS calculated for $C_{19}H_{32}O_5N$ $[M+NH_4]^+$ requires 354.2280, found 354.2280.

***(2R,3S,4R,5S,6S,9R,10R,11S,12S,13R)*-9,11-(*S*)-Ethylidenedioxy-3,5-isopropylidenedioxy-2,4,6,10,12,13-hexamethyl-8-oxotetradecanolide (20).**



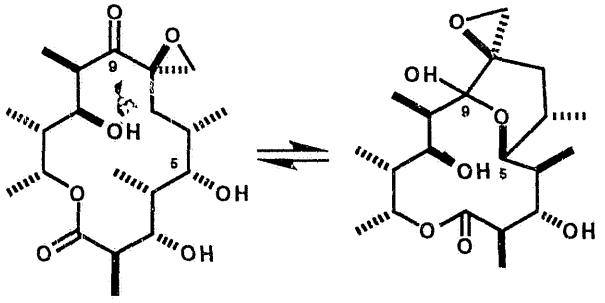
TLC R_f 0.50 (40% EtOAc in hexane); $[\alpha]_D^{20}$ = –46.8° (*c* 2.7, $CHCl_3$); IR (thin film) 1719 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.53 (1H, qd, *J*=6.7, 1.0 Hz, H_{13}), 4.95 (1H, q, *J*=5.0 Hz, ethylidene CH), 4.34 (1H, br d, *J*=4.1 Hz, H_5), 4.15 (1H, br s, H_9), 3.66 (1H, dd, *J*=10.7, 1.5 Hz, H_3), 3.10 (1H, dd, *J*=9.8, 1.6 Hz, H_{11}), 2.70-2.60 (2H, m, H_6, H_{7a}), 2.62 (1H, dq, *J*=10.7, 6.6 Hz, H_2), 2.31 (1H, br d, *J*=16.7 Hz, H_{7b}), 2.22 (1H, br q, *J*=6.4 Hz, H_{10}), 1.55 (1H, dqd, *J*=9.7, 7.2, 1.1 Hz, H_{12}), 1.45 (3H, s, acetonide Me), 1.41 (3H, s, acetonide Me), 1.35 (3H, d, *J*=5.0 Hz, ethylidene Me), 1.3-1.2 (1H, buried m, H_4), 1.23 (3H, d, *J*=6.7 Hz, Me), 1.21 (3H, d, *J*= 6.7 Hz, Me), 1.11 (3H, d, *J*=6.6 Hz, Me), 0.99 (3H, d, *J*=8 Hz, Me), 0.97 (3H, d, *J*=6.7 Hz, Me), 0.89 (3H, d, *J*=7.2 Hz, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 206.6, 174.7, 100.4, 97.0, 84.8, 77.2, 76.8, 71.4, 69.2, 41.7, 41.4, 39.9, 32.7, 32.2, 30.6, 29.7, 20.9, 20.0, 18.3, 14.9, 13.4, 11.5, 7.6, 7.2; m/z ($CI^+(NH_3)$) 441 ($[M+H]^+$ 5), 400 (21), 383(100), 365(15), 339(42), 321(15), 125(10%); HRMS calculated for $C_{24}H_{41}O_7$ $[M+H]^+$ requires 441.2852, found 441.2852.

***(2R,3S,4R,5S,6S,9R,10R,11S,12S,13R)*-9,11-(*S*)-Ethylidenedioxy-8-(*R*)-epoxy-3,5-isopropylidenedioxy-2,4,6,10,12,13-hexamethyltetradecanolide (21).**



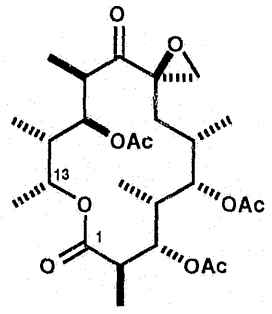
TLC R_f 0.43 (30% EtOAc in hexane); $[\alpha]_D^{20}$ = +3.9 (*c* 3.1, $CHCl_3$); IR (thin film) 1728 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.53 (1H, q, *J*=6.6 Hz, H_{13}), 5.50 (1H, q, *J*=5.0 Hz, ethylidene CH), 4.23 (1H, d, *J*=6.9 Hz, H_5), 3.84 (1H, s, H_9), 3.77 (1H, d, *J*=10.7 Hz, H_3), 3.66 (1H, d, *J*=9.4 Hz, H_{11}), 2.84 (1H, d, *J*=5.3 Hz, $H_{8'a}$), 2.66 (1H, dq, *J*=10.7, 6.6 Hz, H_2), 2.64 (1H, d, *J*=5.3 Hz, $H_{8'b}$), 2.11 (1H, q, *J*=6.5 Hz, H_4), 1.98 (1H, dd, *J*=14.3, 12.3 Hz, H_{7a}), 1.91 (1H, m, H_6), 1.75 (1H, dd, *J*=14.3, 0.8 Hz, H_{7b}), 1.73 (1H, m, H_{10} or H_{12}), 1.52 (1H, m, H_{10} or H_{12}), 1.41 (3H, s, acetonide Me), 1.40 (3H, s, acetonide Me), 1.23 (3H, d, *J*=6.7 Hz, Me), 1.19 (3H, d, *J*=5.0 Hz, ethylidene Me), 1.16 (3H, d, *J*=6.5 Hz, Me), 1.15 (3H, d, *J*=6.5 Hz, Me), 1.02 (3H, d, *J*=6.6 Hz, Me), 0.96 (3H, d, *J*=6.7 Hz, Me), 0.95 (3H, d, *J*=7.3 Hz, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 174.8, 100.3, 97.1, 77.2, 76.8, 75.2, 73.1, 70.2, 59.5, 43.1, 41.6, 40.5, 32.6, 32.3, 31.3, 29.8, 29.0, 21.5, 20.1, 18.7, 16.0, 13.5, 12.1, 7.9, 7.4; m/z ($CI^+(NH_3)$) 455 ($[M+H]^+$ 10), 414(20), 397(100), 353(100), 335(32), 283(15), 239(23), 125(15%); HRMS calculated for $C_{25}H_{43}O_7$ $[M+H]^+$ requires 455.3009, found 455.3009.

(*2R,3S,4R,5S,6S,10R,11S,12S,13R*)-8-(*R*)-epoxy-2,4,6,10,12,13-hexamethyl-9-oxo-3,5,11-trihydroxy-tetradecanolide, oleandolide (2).



TLC R_f 0.20 (70% EtOAc in hexane); $[\alpha]_D^{20}$ = –14.3 (*c* 1.05, $CHCl_3$) lit[2] $[\alpha]_D^{20}$ = -13.0 (*c* 1.0, $CHCl_3$); IR (thin film) 3500 (br s), 1725 (s); ^1H NMR ($CDCl_3$, 400 MHz) 5,9-hemiacetal form δ 4.99 (1H, qd, *J*=6.4, 2.2 Hz, H_{13}), 4.02 (2H, m, H_5, H_{11}), 3.34 (1H, dd, *J*=10.3, 1.8 Hz, H_3), 2.97 (1H, d, *J*=4.6 Hz, $H_{8'a}$), 2.71 (1H, d, *J*=4.6 Hz, $H_{8'b}$), 2.53 (1H, qd, *J*=7.2, 0.9 Hz, H_2), 2.26 (1H, q, *J*=6.9 Hz, H_{10}), 2.10 (1H, m, H_4), 1.92 (1H, dd, *J*=14.0, 12.3 Hz, H_{7a}), 1.69 (2H, m, H_6, H_{12}), 1.41 (1H, dd, *J*=14.0,4.2 Hz, H_{7b}), 1.32 (3H, d, *J*=6.5Hz, Me), 1.13 (3H, d, *J*=7.1 Hz, Me), 1.01 (3H, d, *J*=6.9 Hz, Me), 0.99 (3H, d, *J*=7.3 Hz, Me), 0.94 (3H, d, *J*=6.9 Hz, Me), 0.83 (3H, d, *J*=6.6 Hz, Me); 9-keto form (minor tautomer, some peaks obscured) δ 5.65 (1H, qd, *J*=6.7, 1.3 Hz, H_{13}), 3.88 (1H, dd, *J*=10.4,1.8 Hz, H_3), 3.79 (2H, m, H_5, H_{11}), 3.05 (1H, d, *J*=4.5 Hz, $H_{8'a}$), 3.03 (1H, qd, *J*=6.7,1.8 Hz, H_{10}), 2.77 (1H, d, *J*=4.5 Hz, $H_{8'b}$), 2.72 (1H, m, H_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 5,9-hemiacetal form δ 177.8, 98.9, 76.0, 71.1, 70.0, 58.5, 52.2, 43.7, 43.5, 40.2, 36.5, 34.6, 29.9, 17.8, 16.6, 9.7, 9.0, 8.9, 8.65; 9-keto form (minor tautomer) δ 207.0, 176.1, 77.3, 76.4, 69.8, 69.2, 62.2, 52.2, 45.0, 43.9, 41.7, 39.1, 32.2, 31.0, 18.6, 18.5, 14.3, 8.9, 7.5, 6.4; m/z ($CI^+(NH_3)$) 404($[M+NH_4]^+$ 55), 387($[M+H]^+$ 50), 369(100), 351(40), 226(40), 138(70), 124(45), 104(50%); HRMS calculated for $C_{20}H_{35}O_7$ $[M+H]^+$ requires 387.2383, found 387.2383.

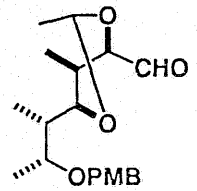
(*2R,3S,4R,5S,6S,10R,11S,12S,13R*)-3,5,11-triacetoxy-8-(*R*)-epoxy-2,4,6,10,12,13-hexamethyl-9-oxo tetradecanolide, oleandolide triacetate (25).



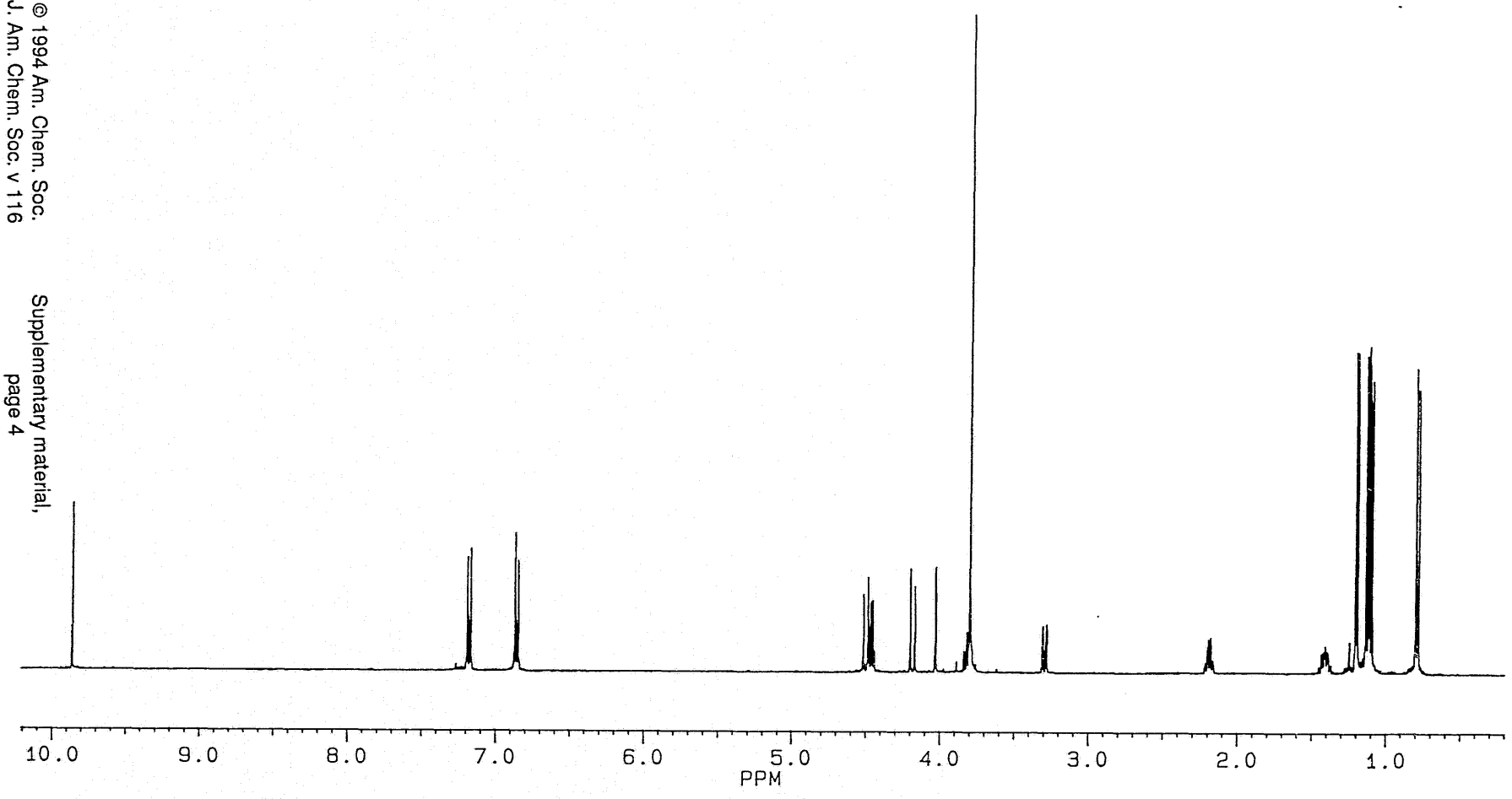
TLC R_f 0.43 (70% EtOAc in hexane); $[\alpha]_D^{20}$ = +39.7 (*c* 0.61, $CHCl_3$), lit[2] $[\alpha]_D^{20}$ = +43 (*c* 1.0, $CHCl_3$); IR (thin film) 1737 (vs); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.22 (1H, dd, *J*=10.0, 1.6 Hz, H_3), 5.19 (1H, qd, *J*=6.6, 1.0 Hz, H_{13}), 4.99 (1H, dd, *J*=9.8, 1.4 Hz, H_{11}), 4.74 (1H, d, *J*=4.9 Hz, H_5), 3.18 (1H, qd, *J*=5.0, 1.5 Hz, H_{10}), 2.75 (1H, dq, *J*=10.0, 6.8 Hz, H_2), 2.62 (1H, ABq, *J*=5.7 Hz, $H_{8'a}$), 2.59 (2H, obscured m, H_4, H_6), 2.57 (1H, ABq, *J*=5.7 Hz, $H_{8'b}$), 2.31 (1H, m, H_{12}), 2.08 (6H, s, 2 x MeCO), 2.03 (3H, s, MeCO), 1.86 (1H, m, H_{7a}), 1.36 (1H, dd, *J*=15.0, 11.9 Hz, H_{7b}), 1.25 (3H, d, *J*=6.5 Hz, Me), 1.08-0.98 (15H, m, 5 x Me groups, all overlapping); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 206.2, 172.4, 170.7, 170.1, 170.0, 78.1, 74.1, 70.4, 68.8, 63.6, 51.2, 42.2, 41.7, 39.8, 39.4, 35.1, 31.5, 20.8, 20.7, 20.6, 18.8, 18.3, 13.5, 9.7, 9.0; m/z ($CI^+(NH_3)$) 530 ($[M+NH4]^+$ 100), 514(10), 453(10), 393(10), 96(10%); HRMS calculated for $C_{26}H_{44}NO_{10}$ $[M+NH_4]^+$ requires 530.2964, found 530.2970.

1) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

2) Tatsuta K.; Kobayashi, Y.; Gunji, H.; Musuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975.



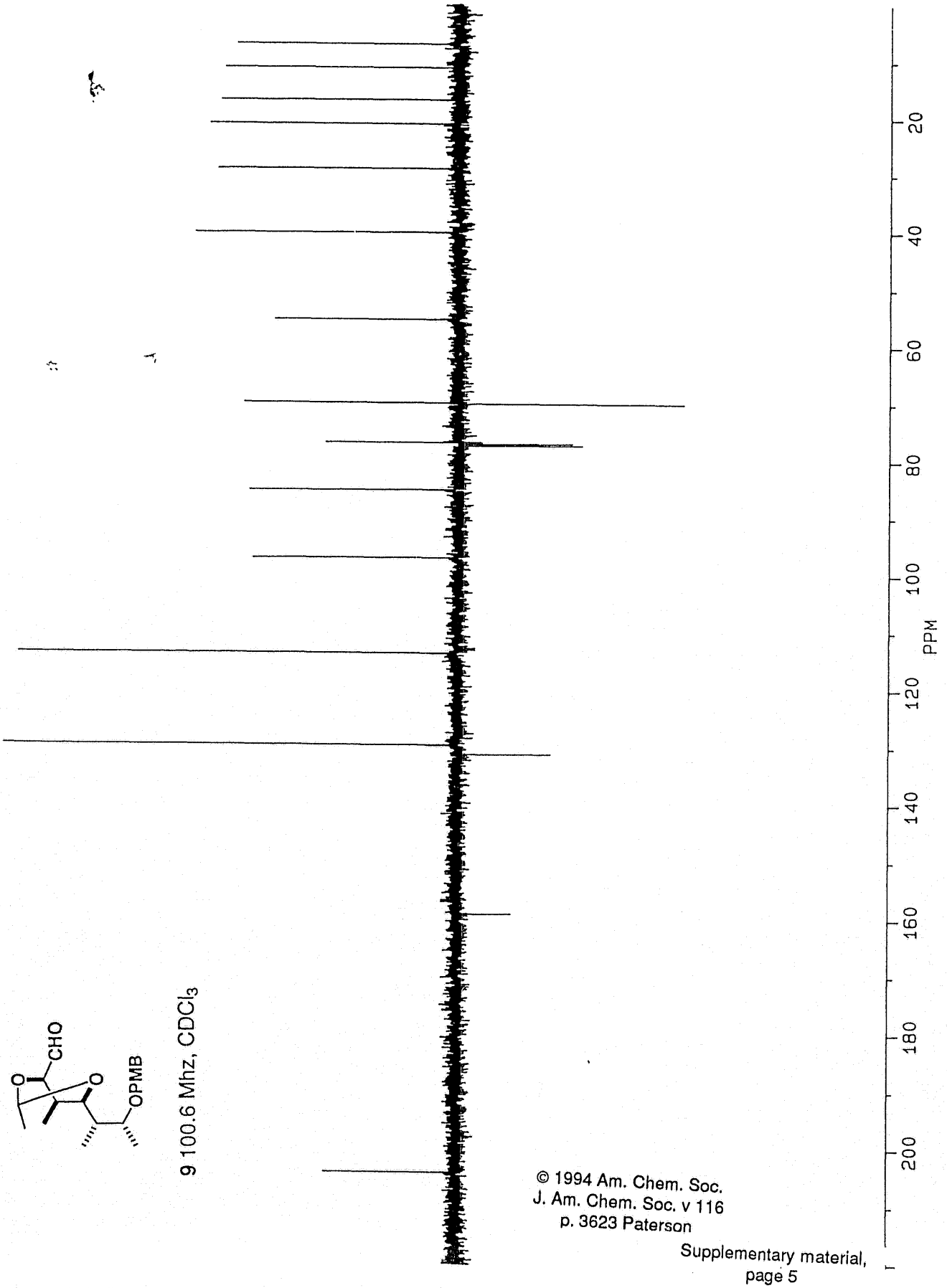
9 400 Mhz, $CDCl_3$

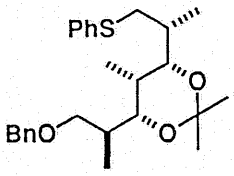


J. Am. Chem. Soc. v 116
p. 3623 Paterson

J-3624-mm4

J-3624-m5





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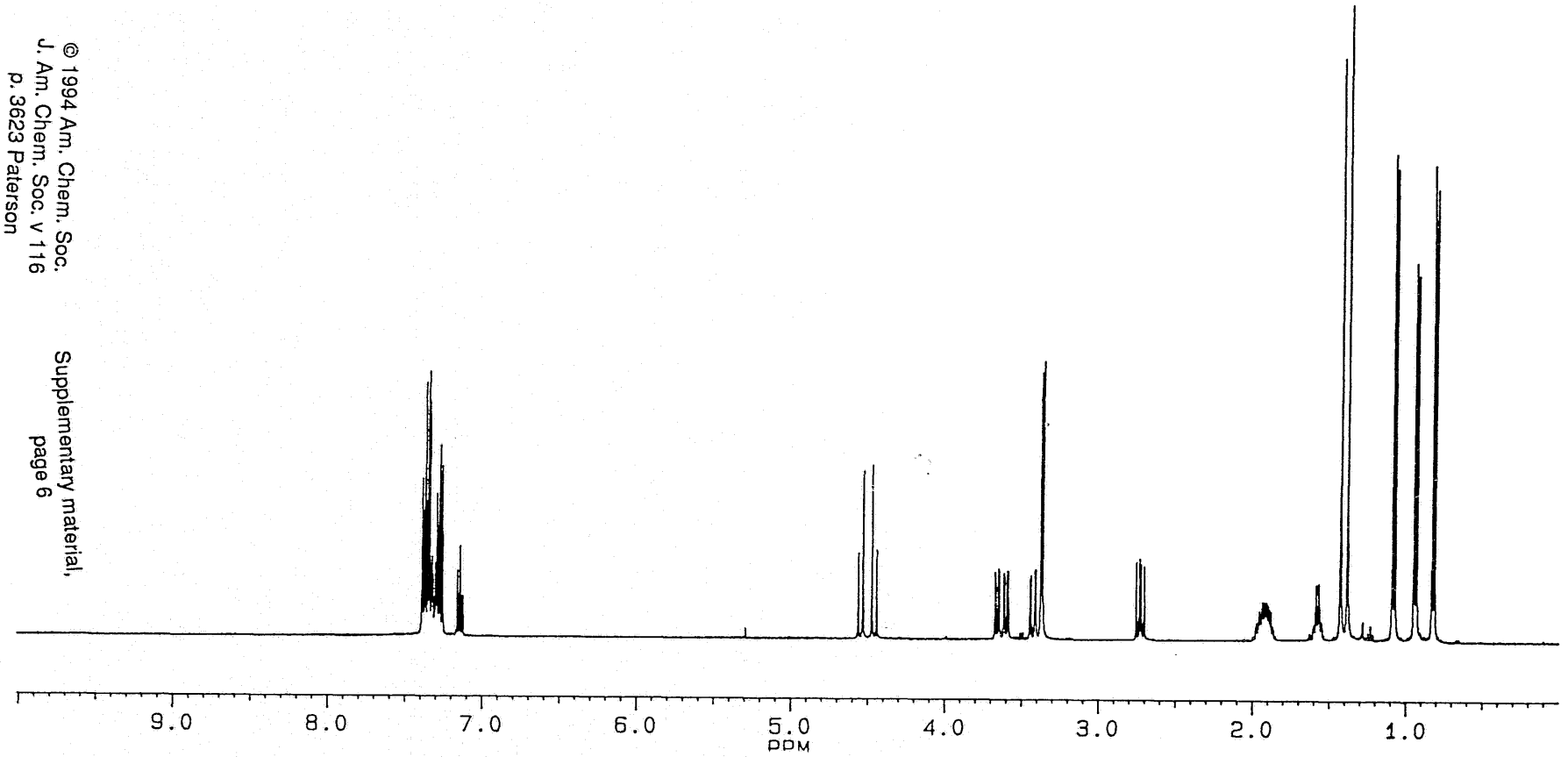
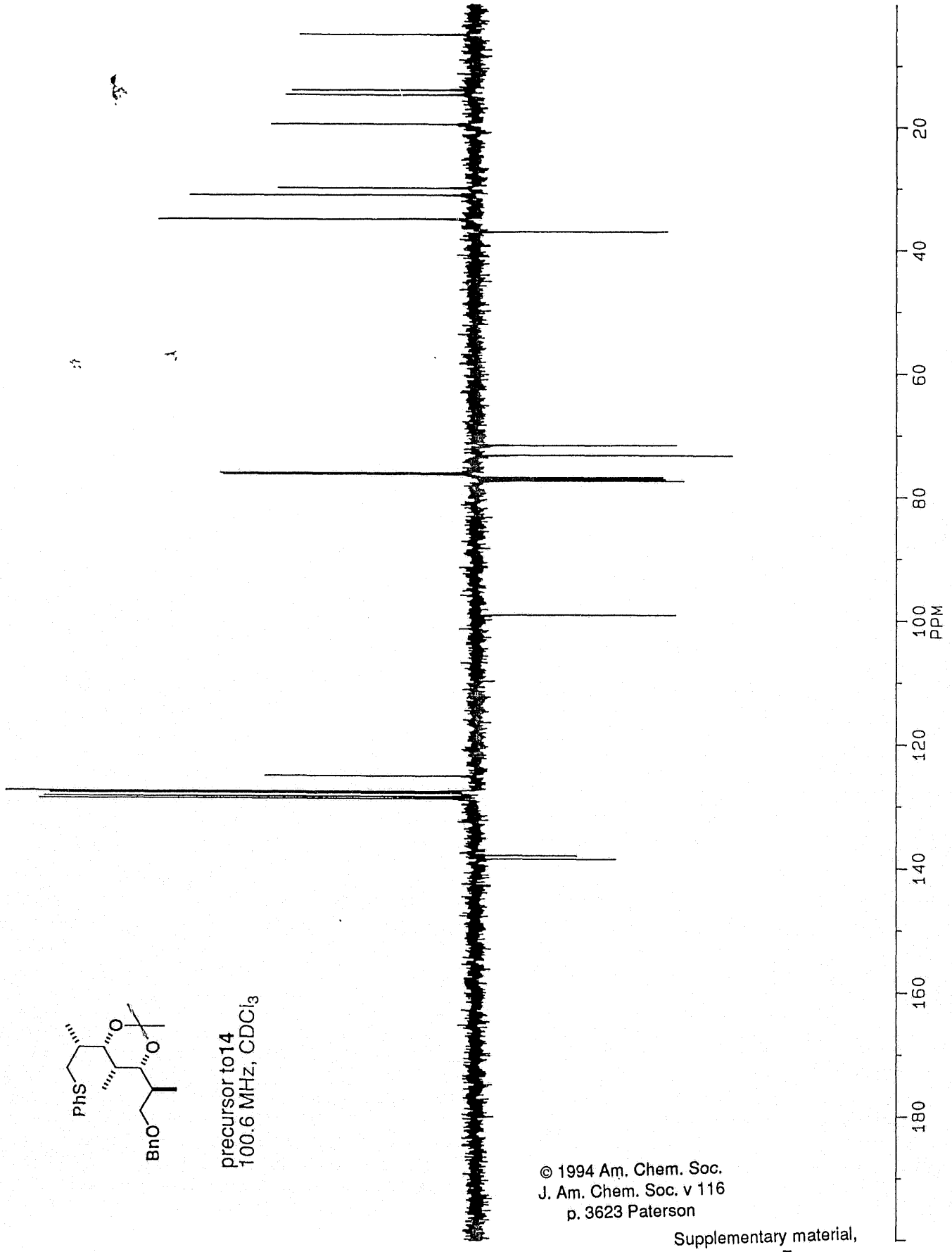
400 MHz, $CDCl_3$



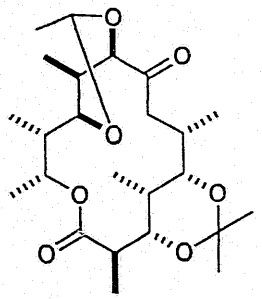
J-3624-mo

J-3624-M7

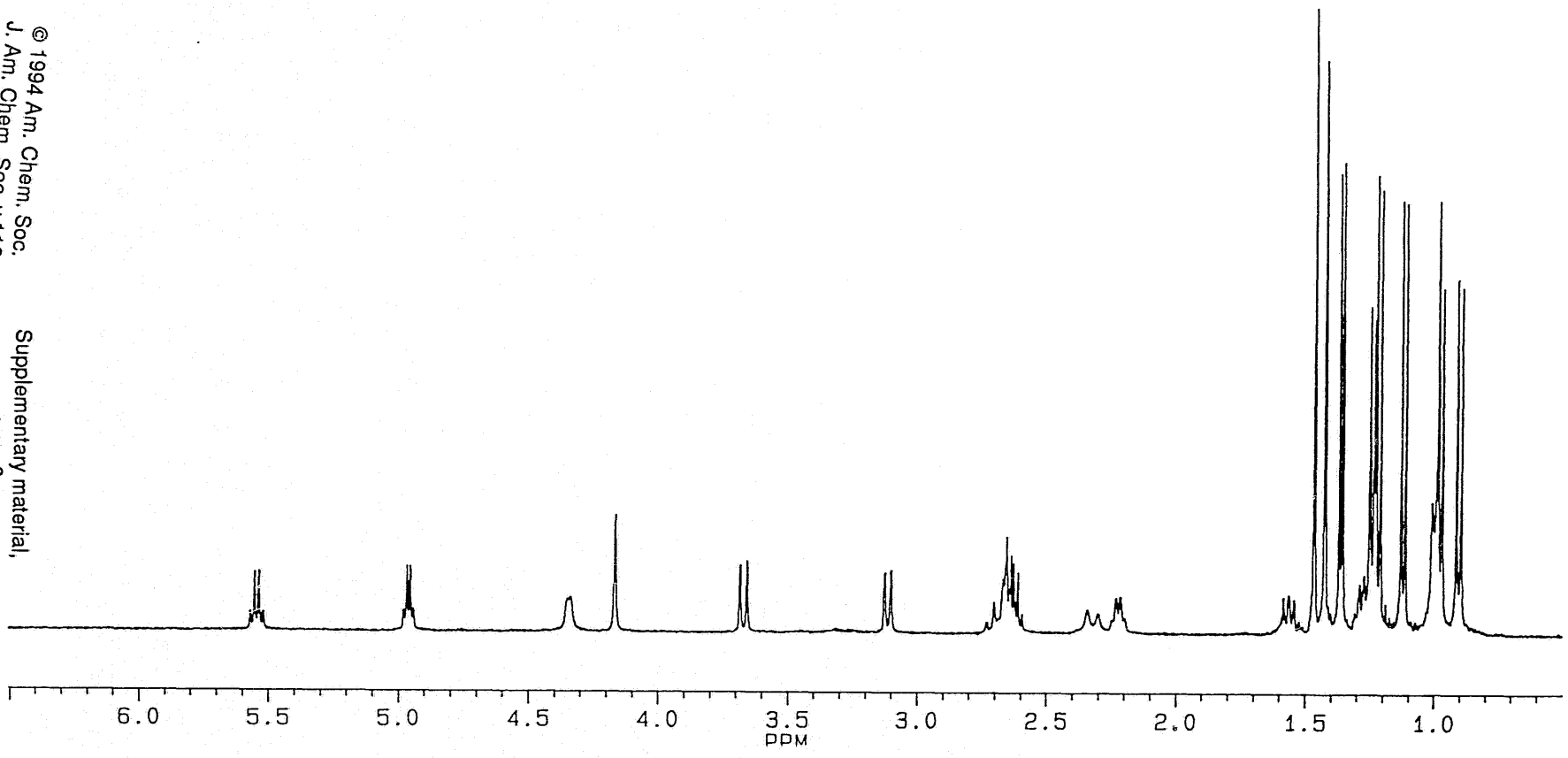


precursor to **14**
100.6 MHz, $CDCl_3$

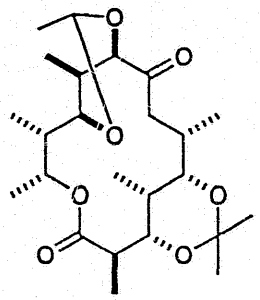
J. Am. Chem. Soc. v 116
p. 3623 Paterson



20 400 MHz, $CDCl_3$



J-3623

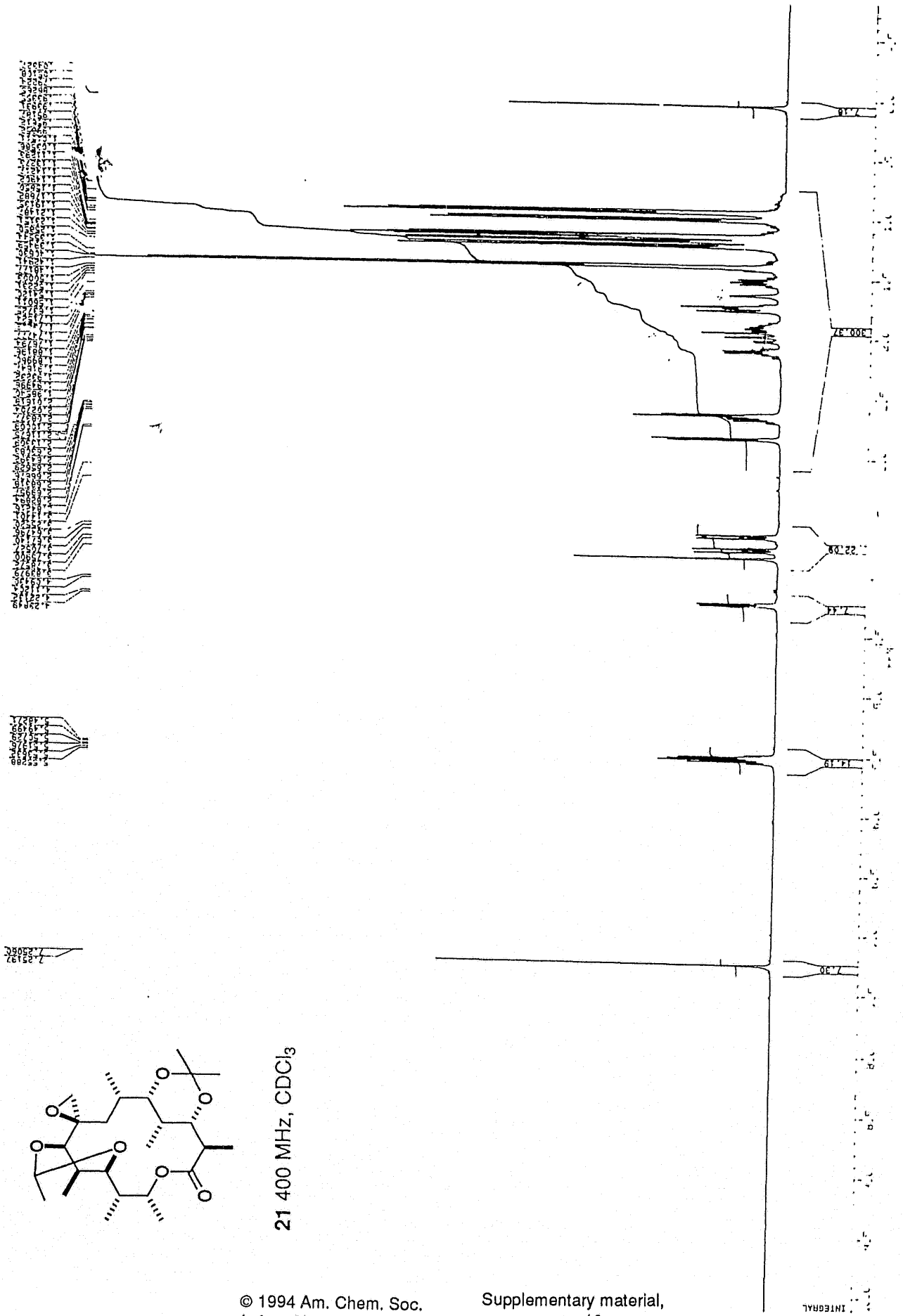


20 100.6 MHz, $CDCl_3$

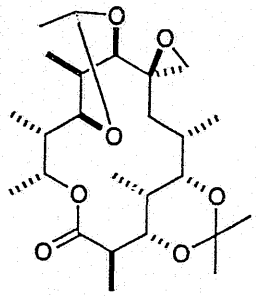
200 180 160 140 120 100 80 60 40 20
PPM

J-3624-M9

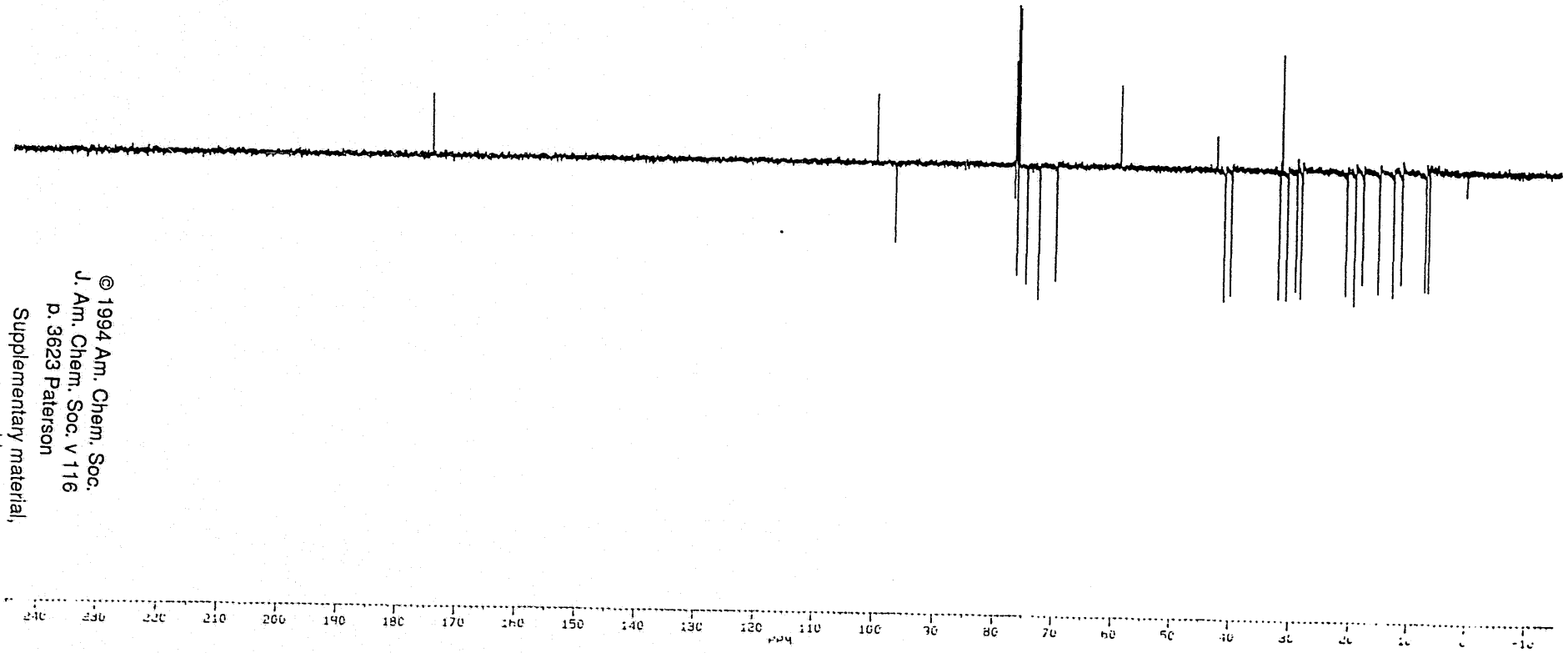
J-3624-m10



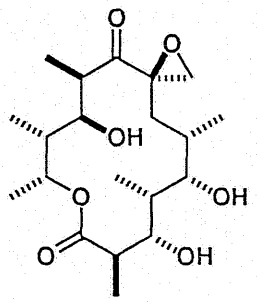
21 400 MHz, $CDCl_3$



21 100.6 MHz, $CDCl_3$

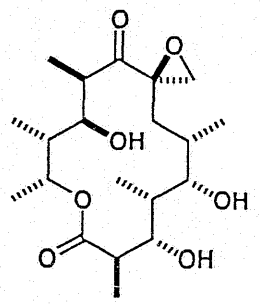


J-3623-m11

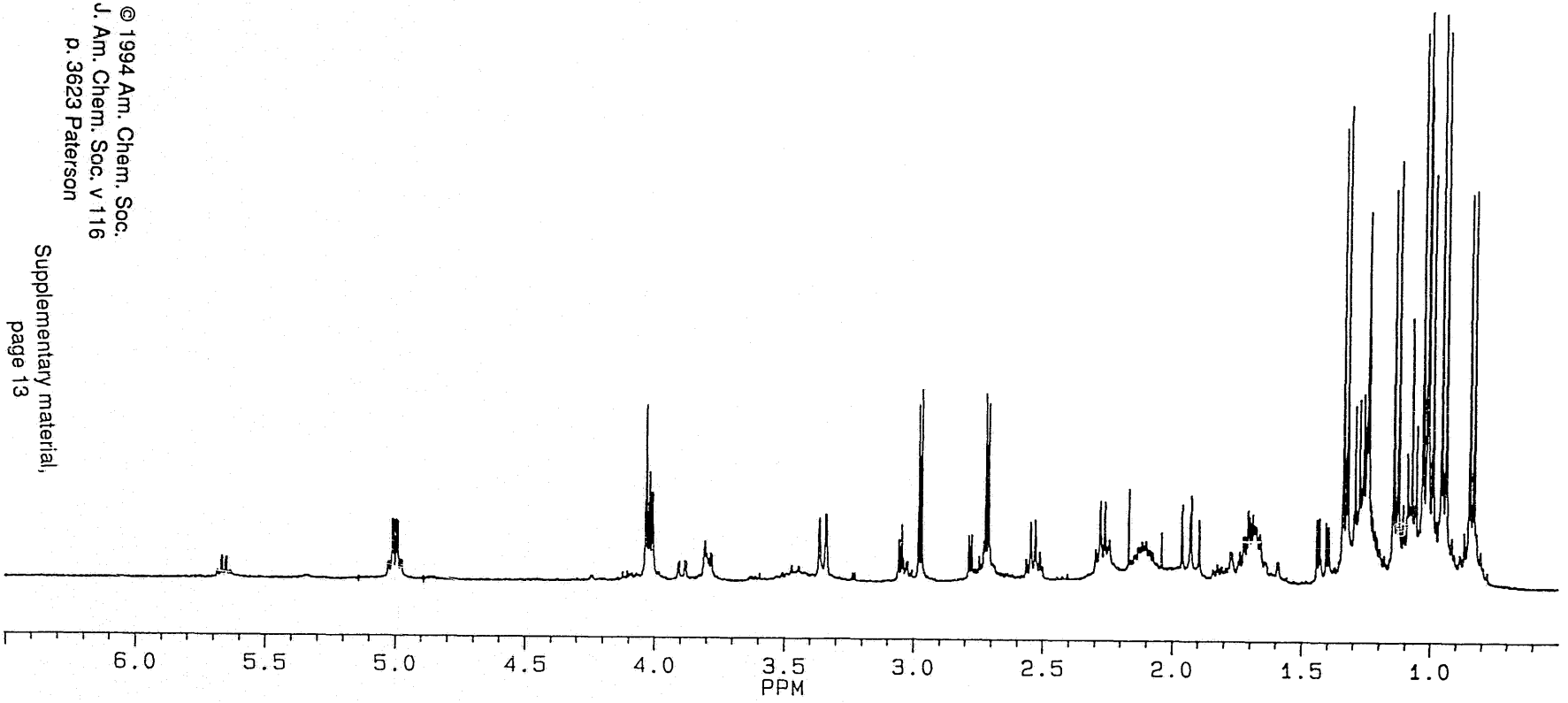


2 400 MHz, CD_3OD

J-3624-m12

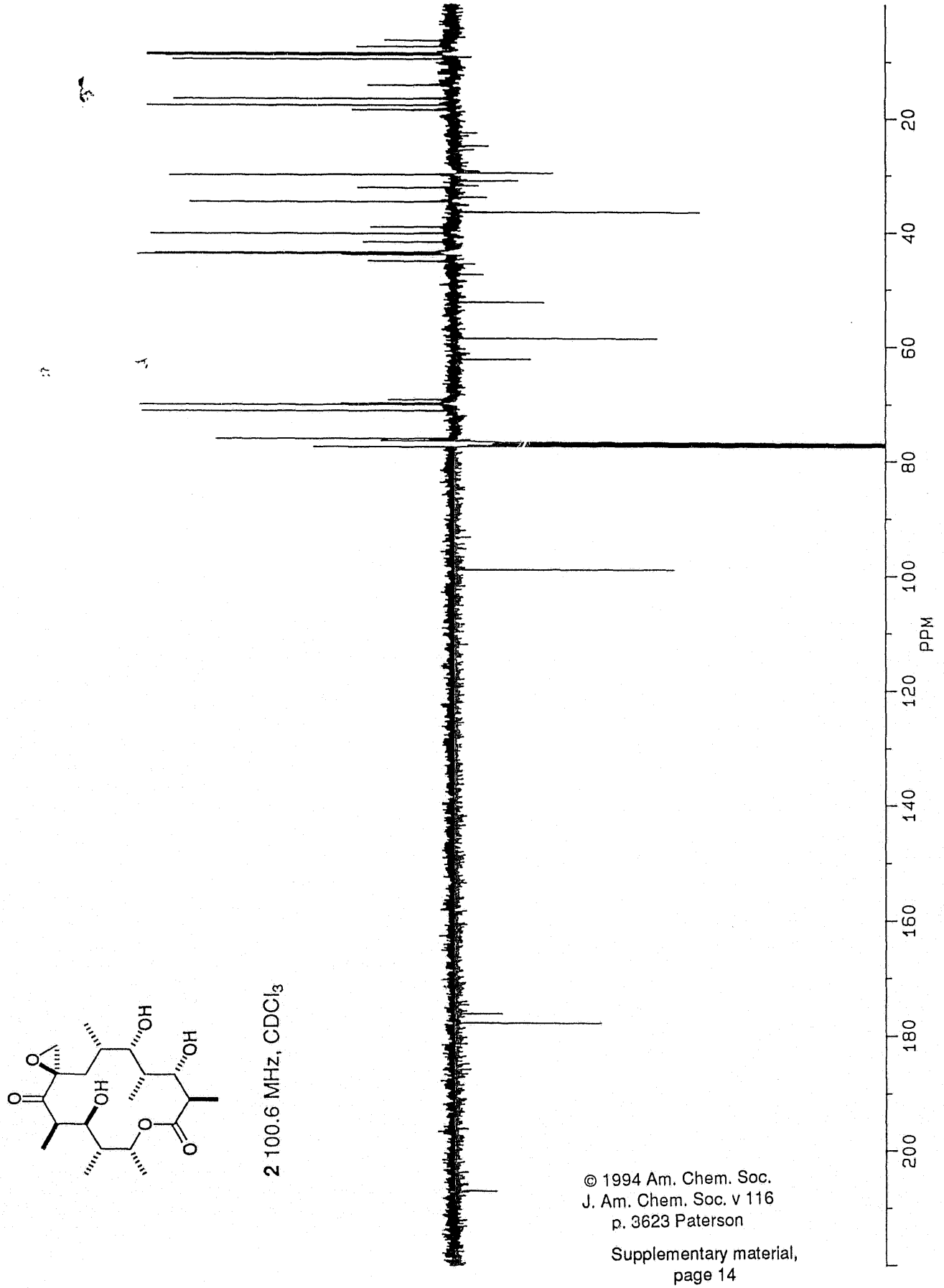


2 400 MHz, $CDCl_3$



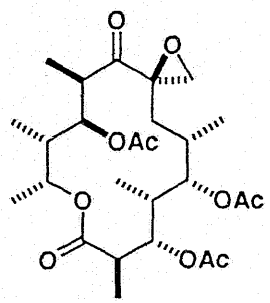
J-3604-nm13

J-3624-mf



2 100.6 MHz, $CDCl_3$

J. Am. Chem. Soc. v 116
p. 3623 Paterson



25 400 MHz, $CDCl_3$

J-3624-m15

J-3624-m16