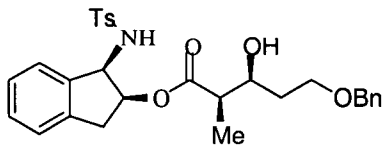
Supporting Information

Enantioselective Total Synthesis of (+)-Amphidinolide T1

Arun K. Ghosh,* and Chunfeng Liu

Department of Chemistry, University of Illinois at Chicago,
845 West Taylor Street, Chicago, Illinois 60607

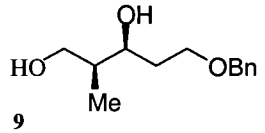
All moisture sensitive reactions were carried out under nitrogen or argon atmosphere. Anhydrous solvents were obtained as follows: THF, diethyl ether, distilled from sodium and benzophenone; dichloromethane, distilled from P_2O_5; pyridine, toluene, benzene, and diisopropylethylamine, distilled from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240-400 mesh silica gel under low pressure of 5-10 psi. TLC was carried out with E. Merck silica gel 60-F-254 plates. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 and 500 spectrometers. Infrared spectra were recorded on a Mattson Genesis II FTIR instrument. Optical rotations were measured using a Perkin-Elmer 341 polarimeter.



8

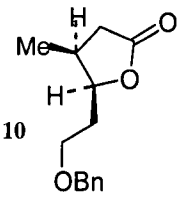
5-Benzyloxy-3-hydroxy-2-methyl-pentanoic acid 1-(toluene-4-sulfonylamino)-indan-2-yl ester (8). To a solution of propionate ester **7** (5.00 g, 13.9 mmol) in dry dichloromethane (200 mL) at 0 °C under nitrogen were added neat $TiCl_4$ (1.83 mL, 16.7 mmol) and diisopropylethylamine (9.70 mL, 55.6 mmol). The reaction mixture was allowed to warm to 23°C and stirred for 2 h. To the resulting brown solution at –78 °C were added neat $TiCl_4$ (4.59 mL, 41.7 mmol) and benzyloxypropionaldehyde (4.30 mL, 27.8 mmol) in dry dichloromethane (20 mL) slowly. The dark brown solution was stirred at this temperature for 2 h, quenched by addition of saturated aqueous NH_4Cl solution and warmed to 23°C. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to provide crude product. Flash chromatography afforded **8** (6.56 g, 90%) as a colorless foam (m.p 89-90 °C). *Rf* = 0.32 (40% EtOAc in hexanes);

$[\alpha]^{23}_{D}$ +50° (c 0.6, $CHCl_3$); IR (neat): 3484, 3274, 1732, 1454, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, 2 H, *J* = 8.2 Hz), 7.18-7.35 (m, 1 H), 6.12 (br, 1 H), 5.36 (t, 1 H, *J* = 4.5 Hz), 4.95 (dd, 1 H, *J* = 5.1, 9.9 Hz), 4.52 (s, 2 H), 4.05 (d, 1 H, *J* = 9.5 Hz), 3.64 (m, 2 H), 3.38 (s, 1 H), 3.11 (dd, 1 H, *J* = 4.7, 17.1 Hz), 2.90 (d, 1 H, *J* = 17.1 Hz), 2.46 (s, 3 H), 2.44-2.46 (m, 1 H), 1.77 (m, 1 H), 1.63 (m, 1 H), 1.04 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 143.9, 140.5, 138.9, 138.5, 138.1, 130.2, 128.9, 128.8, 128.3, 128.2, 127.8, 127.5, 125.0, 124.8, 73.8, 72.2, 69.0, 60.1, 45.8, 37.7, 34.1, 22.0, 10.9; MS (CI) *m/z* 522 $[M-H]^+$.



9

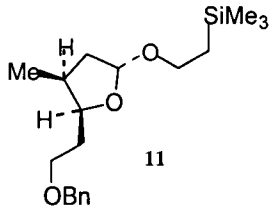
5-Benzyloxy-2-methyl-pentane-1,3-diol (9). To a solution of aldol adduct **8** (9.87 g, 18.8 mmol) in THF (200 mL) was added LAH (2.15 g, 56.6 mmol) portionwise at 0 °C. After 10 min, the reaction mixture was warmed to 23°C and stirred for 2 h. Then to the reaction were added 2 M HCl at 0 °C and anhydrous Na_2SO_4 and the mixture was warmed to r.t and stirred for 2 h. The organic layer was separated and the remaining solid was washed with EtOAc three times. The combined organic layers were concentrated *in vacuo*. The residue was crystallized with chloroform/hexanes (5:1) and the white solid was separated by filtration and washed with chloroform/hexanes (10:1) three times. The resulting white needles are recovered pure chiral auxiliary (5.04 g, 88%). The combined filtrate was concentrated under reduced pressure and purified by flash chromatography to provide pure diol **9** (3.85 g, 91%) as a colorless oil. *Rf* = 0.21 (60% EtOAc in hexanes); $[\alpha]^{23}_{D}$ +5.5° (c 13.4, $CHCl_3$); IR (neat) 3399, 1496, 1454, 1364, 1098, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 4.52 (s, 2 H), 4.02 (tt, 1 H, *J* = 2.6, 10.0 Hz), 3.74 (m, 1 H), 3.63-3.69 (m, 3 H), 3.07 (br, 2 H), 1.80-1.87 (m, 2 H), 1.60-1.67 (m, 1 H), 0.89 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 128.9, 128.3, 128.1, 73.9, 70.3, 67.1, 39.9, 33.2, 11.3; HRMS (ESI) $[M+Na]^+$ calcd for $C_{13}H_{20}O_3Na$: 247.1310, found: 247.1300.



10

5-(2-Benzyloxy-ethyl)-4-methyl-dihydro-furan-2-one (10). The nitrile (2.32 g, 9.94 mmol) was treated with 0.4 M HCl (75.4 mL) at 70 °C for 48 h. The solvent

was removed under reduced pressure and the residue was redissolved in EtOAc (100 mL). The organic solution was washed with 10% aqueous $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to provide the crude product. The light yellow oil was purified by flash chromatography to afford the lactone **10** (2.30 g, 98% yield) as a colorless oil. *Rf* = 0.55 (40% EtOAc in hexanes); $[\alpha]^{23}_D$ –65° (c 50.0, $CHCl_3$); IR (neat) 1776, 1454, 1364, 1208, 1167, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 4.69 (dd, 1 H, *J* = 6.1, 13.5 Hz), 4.52 (ABq, 2 H, *J* = 11.8, 16.5 Hz), 3.65 (m, 2 H), 2.71 (dd, 1 H, *J* = 7.7, 16.9 Hz), 2.61 (m, 1 H), 2.20 (dd, 1 H, *J* = 4.0, 16.9 Hz), 1.88 (m, 2 H), 1.06 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 138.1, 128.4, 127.7, 80.3, 73.3, 66.7, 37.4, 33.0, 30.5, 14.1; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{18}O_3Na$: 257.1154, found: 257.1147.

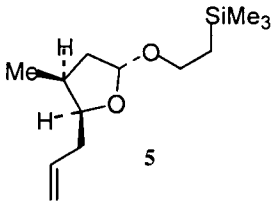


11

{2-[5-(2-Benzyloxy-ethyl)-4-methyl-tetrahydro-furan-2-yloxy]-ethyl}-trimethyl-silane (11). The lactone **10** (2.30 g, 9.83 mmol) in dry toluene (60 mL) was treated with Dibal-H (11.8 mL of a 1.0 M solution in hexanes, 11.8 mmol) at –78 °C for 3 h. The reaction was diluted by addition of diethyl ether and quenched with methanol (2 mL) and 20% potassium sodium tartrate solution (20 mL). The resulting mixture was warmed to 23°C and stirred for 2 h. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to provide the crude product. The light yellow oil (2.23 g) was used directly without further purification.

To the above crude compound in dry dichloromethane (60 mL) were added trimethylsilylethanol (2.71 mL, 18.9 mmol), anhydrous $MgSO_4$ (2.27 g, 18.9 mmol), and p-toluenesulfonic acid (0.36 g, 1.89 mmol). The resulting mixture was stirred at r.t for 12 h and quenched with 5% aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to provide the crude product. The light yellow oil (2.23 g) was purified by flash chromatography to afford **11** (3.02 g, 91% yield in two steps) as a colorless oil (α:β = 3:1). *Rf* = 0.74 (30% EtOAc in hexanes); IR (neat) 1454, 1361, 1248, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major) δ 7.27-7.35 (m, 5 H), 5.10 (dd, 0.66 H, *J* = 2.8, 5.6 Hz), 5.06 (m, 0.34 H), 4.54 (s, 0.68 H),

4.53 (s, 1.32 H), 4.16 (q, 0.66 H, J = 6.1, 13.3 Hz), 4.12 (m, 0.34 H), 3.77 (m, 1 H), 3.58-3.66 (m, 2 H), 3.42-3.48 (m, 1 H), 2.33 (m, 1 H), 2.29 (m, 1 H), 1.99 (m, 1 H), 1.75 (m, 3 H), 1.02 (d, 1.32 H, J = 6.8 Hz), 0.92 (d, 0.68 H, J = 8.3 Hz), 0.88 (d, 3 H, J = 7.1 Hz), 0.0079 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.5, 128.4, 127.6, 127.5, 103.9, 102.5, 79.1, 73.1, 73.1, 68.2, 68.2, 66.2, 64.8, 41.2, 40.2, 35.2, 34.4, 31.4, 301.0, 18.2, 18.2, 14.9, 14.6, -1.4; HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{32}O_3NaSi$: 359.2018, found: 359.2001.



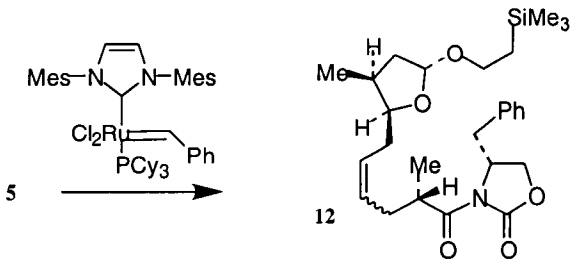
5

[2-(5-Allyl-4-methyl-tetrahydro-furan-2-yloxy)-ethyl]-trimethyl-silane (5). To a solution of benzyl ether (2.91 g, 8.65 mmol) in EtOAc (60 mL) was added 10% Pd/C (2.50 g) at 23°C. The mixture was hydrogenated under a hydrogen atmosphere for 12 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography to afford the alcohol (1.96 g, 92%). For the *trans* isomer: $[\alpha]^{23}_D$ +2.4° (c 2.5, $CHCl_3$); IR (neat) 3432, 1445, 1342, 1248, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd,1 H, J = 2.5, 5.5 Hz), 4.20 (m, 1 H), 3.77 (m, 3 H), 3.45 (m, 1 H), 2.40 (m, 1 H), 1.98 (m, 1 H), 1.73 (m, 2 H), 1.60 (m, 1 H), 0.90 (d, 3 H, J = 7.0 Hz), 0.90 (t, 2 H, J = 8.2 Hz), 0.0052 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.7, 80.5, 65.0, 62.2, 40.8, 34.7, 32.6, 30.9, 18.1, 14.8.

The alcohol (1.36 g, 5.53 mmol) was oxidized under standard Swern condition to afford the corresponding aldehyde. The crude aldehyde was used directly for the next step without further purification.

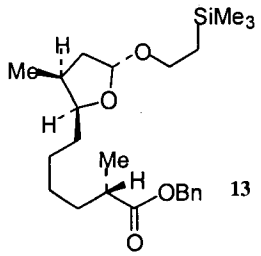
To a solution of CH_3PPh_3Br (2.96 g, 8.29 mmol) in THF (60 mL) at 0 °C was added *n*-BuLi (4.49 mL of 1.6 M solution in hexanes, 7.18 mmol) dropwise. After the resulting yellow mixture was stirred at this temperature for 20 min, the crude aldehyde in THF (10 mL) was added. The reaction was stirred at 0 °C for 2 h and quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to provide crude product. The crude product was purified by flash chromatography to afford pure product **5** (1.12 g, 84% yield in two steps) as a colorless oil. *Rf* = 0.83 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ –106° (c 2.1, $CHCl_3$); IR (neat) 1642, 1445, 1340, 1248, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (m,

1 H), 5.11 (m, 2 H), 5.06 (dd, 1 H, J = 10.5 Hz), 4.08 (dd, 1 H, J = 5.9, 13.6 Hz), 3.80 (dd, 1 H, J = 8.8, 17.5 Hz), 3.46 (dd, 1 H, J = 8.7, 17.2 Hz), 2.27-2.36 (m, 2 H), 2.22 (m, 2 H), 1.99 (m, 1 H), 1.77 (m, 1 H), 0.91 (t, 2 H, J = 8.0 Hz), 0.90 (d, 3 H, J = 7.1 Hz), 0.0040 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 116.4, 102.6, 79.2, 64.9, 41.3, 34.8, 34.2, 18.2, 14.8, -1.4; MS $[M+Na]^+$ (ESI) *m/z* 265.1.



4-Benzyl-3-{2-methyl-6-[3-methyl-5-(2-trimethylsilanyl-ethoxy)-tetrahydro-furan-2-yl]-hex-4-enoyl}-oxazolidin-2-one (12). To a solution of alkene **5** (248 mg, 1.03 mmol) and alkene **6** (560 mg, 2.05 mmol) in dichloromethane (20 mL) was added the second generation Grubbs's catalyst (43.5 mg, 0.051 mmol). The resulting mixture was heated at 40 °C for 36 h. The dark reaction mixture was concentrated and directly purified by flash chromatography to afford the cross-coupling product **12** (345 mg) as a colorless oil.

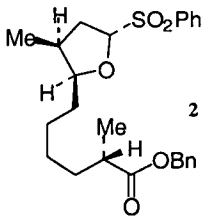
To a solution of the recovered materials from the above reaction (dimer and monomer of the alkene **5**, 90 mg, and the dimer of alkene **6,** 400 mg) in dry dichloromethane (20 mL) was added the second generation Grubbs's catalyst (16.4 mg). The resulting mixture was heated at 40 °C for 36 h. The dark reaction mixture was concentrated and directly purified by flash chromatography to afford the cross-coupling product **12** (124 mg) as a colorless oil, *Rf* = 0.44 (20% EtOAc in hexanes). Overall two reaction cycles afforded **12** (479 mg, 96%) and the dimer of alkene **6** (280 mg, quantitative), which could be reused for a new cross metathesis cycle. IR (neat) 3029, 1782, 1699, 1455, 1384, 1349, 1243, 1210 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5 H), 5.54 (m, 2 H), 4.98-5.12 (m, 1 H), 4.65-4.70 (m, 1 H), 4.13-4.20 (m, 2 H), 4.04 (m, 1 H), 3.72-3.86 (m, 2 H), 3.39-3.46 (m, 1 H), 3.28 (m, 1 H), 2.70 (m, 1 H), 2.48 (m, 1 H), 2.16-2.33 (m, 4 H), 1.97 (m, 1 H), 1.76(m, 1 H), 1.17 (m, 3 H), 0.87-1.03 (m, 5 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 153.5, 135.8, 130.1, 129.8, 129.3, 129.1, 127.7, 103.0, 80.0, 66.4, 65.3, 55.8, 41.7, 38.5, 38.0, 37.3, 34.6, 34.0, 18.6, 16.7, 15.2, -0.9. MS $[M+Na]^+$ (ESI) *m/z* 510.4; HRMS (ESI) $[M+Na]^+$ calcd for $C_{27}H_{41}O_5NaSi$: 510.2652, found: 510.2638.



13

2-Methyl-6-[3-methyl-5-(2-trimethylsilanyl-ethoxy)-tetrahydro-furan-2-yl]-hexanoic acid benzyl ester (13). To a solution of alkene **12** (440 mg) in ethyl acetate was added 10% Pd/C (264 mg) at 23°C. The mixture was stirred under a hydrogen atmosphere for 4 h. The mixture was filtered, concentrated and the residue was used in the next step without further identification.

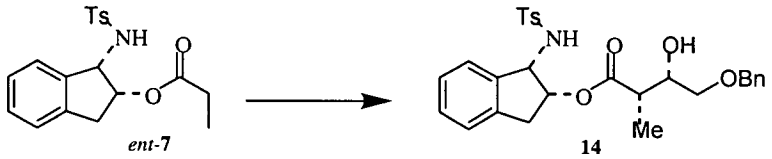
To a solution of freshly distilled benzyl alcohol (292 mg, 0.28 mmol) in THF (20 mL) at -20 °C was added phenyllithium (1.35 mL of 2.0 M solution in 70/30 cyclohexane/ether, 2.70 mmol) dropwise. The resulting mixture was stirred at the same temperature for 15 min. At this time the above compound (440 mg, 0.094 mmol) in THF (5 mL) was added through a cannula. The reaction was stirred at -20 °C for 3 h, then 0 °C for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to provide crude product, which was purified by flash chromatography to afford the pure product (320 mg, 85% in two steps) as a colorless oil. *Rf* = 0.78 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ –54.1° (c .6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.08-5.11 (m, 3 H), 3.94 (m, 1 H), 3.78 (dd, 1 H, *J* = 8.5, 17.9 Hz), 3.44 (dd, 1 H, *J* = 8.2, 17.6 Hz), 2.49 (m, 1 H), 2.27 (m, 1 H), 1.98 (m, 1 H), 1.75 (m, 1 H), 1.37-1.46 (m, 4 H), 1.28-1.35 (m, 4 H), 1.16 (d, 3 H, *J* = 7.0 Hz), 0.92 (t, 2 H, *J* = 8.2 Hz), 0.85 (d, 3 H, *J* = 7.0 Hz), 0.01 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 136.2, 128.5, 128.1, 128.1, 102.5, 79.9, 66.0, 64.9, 41.4, 39.5, 34.3, 33.7, 30.2, 27.4, 26.6, 18.2, 17.0, 14.8, -1.4. MS $[M+Na]^+$ (ESI) *m/z* 443.3; HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{40}O_4NaSi$: 443.2594, found: 443.2578.



2

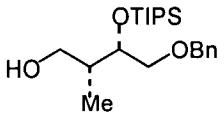
6-(5-Benzenesulfonyl-3-methyl-tetrahydro-furan-2-yl)-2-methyl-hexanoic acid benzyl ester (2). To a solution of compound **13** (250 mg, 0.6 mmol) and benzenesulphinic acid (256 mg, 1.80 mmol) in dry dichloromethane (30 mL) was

added $CaCl_2$ (333 mg, 3 mmol) at 23°C. The resulting mixture was stirred at 23°C for 4 h, filtered through Celite®, and the filter cake was washed with dichloromethane three times. The filtrate was concentrated *in vacuo* to provide a pale yellow residue, which was purified by flash chromatography to afford **2** (252 mg, 95%) as a pale yellow oil. *Rf* = 0.54 (32% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 2 H, *J* = 7.4 Hz), 7.64 (t, 1 H, *J* = 7.4 Hz), 7.55 (t, 2 H, *J* = 7.6 Hz), 7.35 (m, 5 H), 5.11 (s, 2 H), 4.89 (t, 1 H, *J* = 7.2 Hz), 4.15 (m, 1 H), 2.78 (m, 1 H), 2.42-2.50 (m, 1 H), 2.37-2.41(m, 1 H), 1.99-2.06 (m, 1 H), 1.62-1.70 (m, 1 H), 1.26-1.44 (m, 7 H), 1.16 (d, 3 H, *J* = 6.9 Hz), 0.85 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 137.2, 136.2, 133.8, 129.2, 129.0, 128.5, 128.1, 128.1, 92.4, 84.4, 66.0, 39.5, 35.2, 33.6, 33.5, 29.8, 27.2, 26.4, 17.1, 14.2. MS $[M+Na]^+$ (ESI) *m/z* 467.2; HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{32}O_5NaS$: 467.1868, found: 467.1978.



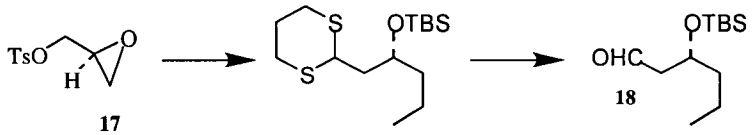
4-Benzyloxy-3-hydroxy-2-methyl-butyric acid 1-(toluene-4-sulfonylamino)-indan-2-yl ester (14). To a solution of the propionate ester *ent*-**7** (4.00 g, 11.1 mmol) in dry dichloromethane (150 mL) under nitrogen at 0 °C were added neat $TiCl_4$ (1.47 mL, 13.4 mmol) and diisopropylethylamine (7.75 mL, 44.5 mmol). The reaction mixture was allowed to warm to 23°C and stirred for 2 h. Then to the resulting brown solution at –78 °C was added neat $TiCl_4$ (3.68 mL, 33.4 mmol) and benzyloxyacetaldehyde (3.13 mL, 22.3 mmol) in dry dichloromethane (20 mL) slowly. The dark brown solution was stirred at this temperature for 2 h, quenched by addition of saturated aqueous NH_4Cl solution and warmed to 23°C. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to provide a brown liquid, which was purified by flash chromatography to afford the pure product (5.27 g, 93%) as a colorless foam. *Rf* = 0.24 (40% EtOAc in hexanes); $[\alpha]^{23}_D$ –27.9° (c 3.31, $CHCl_3$); IR (neat) 3495, 3280, 1733, 1336, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2 H, *J* = 8.2 Hz), 7.22-7.34 (m, 1 H), 5.76 (br, 1 H), 5.28 (q, 1 H, *J* = 4.8 Hz), 4.94 (dd, 1 H, *J* = 5.1, 9.8 Hz), 4.42 (ABq, 2 H, *J* = 11.8, 16.8 Hz), 4.01 (tt, 1 H, *J* = 4.5, 6.8 Hz), 3.37 (dddd, 2 H, *J* = 4.4, 9.5, 6.9, 9.5 Hz), 3.06 (dd, 1 H, *J* = 4.9, 17.2 Hz), 2.86 (d, 1 H, *J* = 17.2 Hz), 2.57 (dd, 1 H, *J* = 4.3, 7.1 Hz), 2.44 (s, 3 H), 1.04 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 143.7, 139.8, 138.5, 137.9, 137.6, 129.8, 128.6, 128.5, 127.9, 127.8, 127.4, 127.1, 124.9, 124.4, 75.2, 73.4, 71.3,

70.8, 59.6, 42.2, 37.2, 21.6, 10.8; MS (CI) *m/z* 508 (M^+-H); Anal. Calc'd. For $C_{28}H_{31}NO_6S$ C, 65.99, H, 6.13, N, 2.75, Found: C, 65.80, H, 6.22, N, 2.52.



15

4-Benzyloxy-2-methyl-3-triisopropylsilanyloxy-butan-1-ol (15). To a solution of the silyl ether (7.47 g, 11.2 mmoL) in dichloromethane (100 mL) at –40 °C was added Dibal-H (39.3 mL of 1.0 M solution in Hexanes, 39.3 mmoL) dropwise. The resulting solution was stirred for 1 h at the same temperature and quenched with methanol (2 mL) and 20% potassium sodium tartrate aqueous solution (30 mL). The cloudy mixture was warmed to 23°C and stirred for 2 h. The clear layers were separated and the aqueous layer was extracted with ethyl acetate/hexanes two times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to provide the alcohol (3.75 g, 91%) as a light yellow oil. *Rf* = 0.38 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ –8.7° (c 2.4, $CHCl_3$); IR (neat) 3435, 1463, 1384, 1248, 1103, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 4.53 (s, 2 H), 4.09 (dd, 1 H, *J* = 5.0, 8.9 Hz), 3.61-3.69 (m, 2 H), 3.55 (d, 2 H, *J* = 5.3 Hz), 1.06 (m, 21 H), 0.91 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 128.3, 127.7, 127.7, 74.3, 73.5, 71.8, 65.2, 39.6, 18.1, 18.1, 12.6, 12.1; HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{38}O_3NaSi$: 389.2488, found: 389.2485.



17 18

3-(tert-Butyl-dimethyl-silanyloxy)-hexanal (18).). To a solution of 1,3-Dithiane (2.86 g, 23.8 mmol) in THF (40 mL) at –10 °C was added *n*-BuLi (15.6 mL of 1.6 M solution in hexanes, 24.9 mmol) and stirred at the same temperature for 2 h, then cooled to –78 °C. A solution of (*S*)-glycidyl tosylate **17** (5.16 g, 22.6 mmol) in THF (10 mL) was added by a cannula, and the solution was maintained at –78 °C for 4 h and allowed to r.t over 2 h. At this time saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with diethyl ether twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to afford the

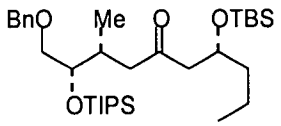
corresponding epoxide (2.65 g) as a light yellow oil, which was directly employed in the next step.

To a solution of the above epoxide (2.65 g, 15.0 mmol) in THF (80 mL) at –40 °C was added CuI (0.57 g, 3 mmol) and stirred at the same temperature for 15 min. At this time the precooled ethyl magnesium bromide (15.0 mL of 3 M solution in THF, 45.1 mmol, ~20 °C) was added by a cannula. The resulting mixture was stirred at –40 °C for 2 h and quenched by addition of aqueous NH_4Cl solution and warmed to 23°C. The layers were separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to provide the crude product. Flash chromatography afforded the pure product (3.0 g, 64% yield in two steps) as a colorless oil: IR (neat) 3417, 1422, 1275, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.26 (t, 1 H, J = 7.2 Hz), 3.90-3.95 (m, 1 H), 2.81-2.95 (m, 4 H), 2.10-2.13 (m, 1 H), 1.83-1.92 (m, 4 H), 1.34-1.46 (m, 4 H), 0.93 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.9, 44.8, 43.1, 40.1, 30.8, 30.5, 26.4, 19.2, 14.4.

To a solution of the above alcohol (2.79 g, 13.5 mmol) in dichloromethane (40 mL) at 0 °C were added diisopropylethylamine (5.87 mL, 33.8 mmol) and TBSOTf (4.04 mL, 17.6 mmol) dropwise. The resulting mixture was stirred at the same temperature for 30 min, quenched by addition of aqueous NH_4Cl solution and warmed to 23°C. The layers were separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Flash chromatography of the yellow residue afforded the above TBS-ether (4.24 g, 98%) as a colorless oil: IR (neat) 1471, 1463, 1423, 1254, 1067 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10 (dd, 1 H, J = 5.8, 8.8 Hz), 3.95 (m, 1 H), 2.89 (m, 1 H), 2.82 (m, 3 H), 2.11 (m, 1 H), 1.88 (m, 1 H), 1.81 (m, 2 H), 1.44 (m, 2 H), 1.33 (m, 2 H), 0.89 (m, 12 H), 0.083 (d, 6 H, J = 15.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.8, 44.6, 43.0, 40.2, 31.0, 30.5, 26.5, 26.3, 18.5, 18.4, 14.7, -4.0, -4.1.

To a solution of above TBS-ether (3.70 g, 11.5 mmol) in CH_3CN/H_2O (9:1, 40 mL) were added $CaCO_3$ (11.6 g, 115 mmol) and MeI (6.46 mL, 104 mmol) dropwise. The resulting mixture was stirred at 40 °C for 15 h, filtered through a pad of Celite®, and the filtrate was concentrated. Flash chromatography of the yellow residue afforded **18** (2.0 g, 75%) as a colorless oil. Rf = 0.62 (12% EtOAc in hexanes); $[\alpha]^{23}_D$ –1.5° (c 3.4, $CHCl_3$); IR (neat) 1727, 1471, 1464, 1362, 1255, 1099, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, 1 H, J = 2.4 Hz), 4.19 (m, 1 H), 2.51 (dd, 2 H, J = 2.4, 5.8 Hz), 1.46-1.57 (m, 2 H), 1.29-1.38 (m, 2 H), 0.92 (t, 3 H, J = 7.3 Hz), 0.87 (s, 9 H), 0.06 (d, 6 H, J = 6.7 Hz); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 202.6, 68.1, 50.8, 40.0, 25.8, 18.4, 18.0, 14.1, -4.4, -4.7; HRMS (ESI) $[M+Na]^+$ calcd for $C_{12}H_{26}O_2NaSi$: 253.1600, found: 253.1590.



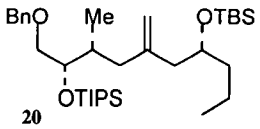
19

1-Benzyloxy-7-(tert-butyl-dimethyl-silanyloxy)-3-methyl-2-triisopropylsilany - loxy-decan-5-one (19). To a solution of the alcohol **15** (1.36 g, 3.70 mmol) in diethyl ether/dichloromethane (8:2, 100 mL) were added imidazole (0.504 g, 7.40 mmol), Ph_3P (1.45 g, 5.55 mmol) and iodine (1.41 g, 5.55 mmol). The resulting mixture was protected from light and stirred for 2 h at 23°C. The mixture was filtered and the yellow solid was washed with diethyl ether three times. The combined organic solution was washed with 10% aqueous $Na_2S_2O_3$ (30 mL) solution two times, saturated aqueous $NaHCO_3$ (30 mL) solution, and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography to afford iodide **16** (1.63 g, 90%) as a pale yellow oil. The iodide was used for the next reaction without further purification (NMR showed the product containing ~5% PPh_3).

To a solution of the above iodide **16** in anhydrous diethyl ether (60 mL) at –78 °C was added 4 Å molecular sieves and *t*-BuLi (4.4 mL of 1.7 M solution in pentane, 7.48 mL). The mixture was stirred at –78 °C for 10 min, and then warmed to r.t and stirred for 20 min. After the resulting yellow mixture was cooled to –78 °C, a solution of aldehyde (0.787 g, 3.42 mmol) in diethyl ether (10 mL) was added and the mixture was stirred at this temperature for 2 h and warmed to 23°C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate two times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to provide the alcohol (1.65 g, 80%) as a colorless oil.

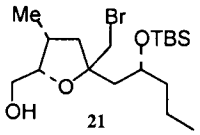
To a solution of the above alcohol (1.30 g, 2.2 mmol) and NMO (0.524 g, 4.5 mmol) in dry dichloromethane (40 mL) at 0 °C under argon were added 4 Å molecular sieves and TPAP (39.3 mg, 0.11 mmol). The resulting mixture was warmed to 23°C and stirred for 1 h. The solvent was removed and the residue was purified by flash chromatography to give the ketone **19** (1.29 g, 99%) as a colorless oil. *Rf* = 0.76 (8% EtOAc in hexanes; $[\alpha]^{23}_D$ –7.5° (c 2.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 4.49 (ABq, 2 H, *J* = 11.9, 17.9 Hz), 4.17 (m, 1 H), 3.95 (m, 1 H), 3.44 (dd, 1 H, *J* = 5.5, 9.7 Hz), 3.39 (dd, 1 H, *J* = 5.8, 9.5 Hz), 2.71 (dd, 1 H, *J* = 3.4, 16.0 Hz), 2.57 (dd, 1 H, *J* = 6.8, 15.4 Hz), 2.41 (dd, 1 H, *J* = 5.4,

15.4 Hz), 2.32 (m, 1 H), 2.26 (dd, 1 H, J = 9.2, 16.1 Hz), 1.39 (m, 2 H), 1.31 (m, 2 H), 1.03 (m, 21 H), 0.83-0.92 (m, 15 H), 0.03 (d, 6 H, J = 16.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 138.2, 128.3, 127.7, 127.5, 74.3, 73.2, 72.5, 68.7, 50.5, 47.6, 39.9, 32.8, 25.8, 18.2, 14.5, 14.2, 12.7, -4.6, -4.7; HRMS (ESI) $[M+Na]^+$ $C_{33}H_{62}N_3O_4Si_2Na$: 601.4084, found: 601.4098.



20

{5-[2-(tert-Butyl-dimethyl-silanyloxy)-pentyl]-3-methyl-2-triisopropylsilany - loxy-hex-5-enyloxymethyl}-benzene (20). To a solution of ketone **19** (560 mg, 0.967 mmol) in THF (20 ml) was added Cp_2TiMe_2 (7.2 mL of 0.4 M solution in toluene, 2.90 mmol) and stirred for 16 h at 75 °C under N_2 in the dark. Then the mixture was concentrated *in vacuo*. The crude slurry was dissolved in diethyl ether (50 ml) and silica gel was added slowly. The solid was filtered and rinsed with diethyl ether. The filtrate was concentrated *in vacuo*. The dark yellow residue was purified by flash chromatography to give a light yellow oil (470 mg, 84%). *Rf* = 0.86 (8% EtOAc in hexanes); $[\alpha]^{23}_D$ −7° (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (m, 5 H), 4.79 (s, 1 H), 4.77 (s, 1 H), 4.49 (ABq, 2 H, J = 11.9, 19.3 Hz), 3.96 (ddd, 1 H, J = 2.4, 6.0 Hz), 3.78 (m, 1 H), 3.43 (dd, 2 H, J = 1.2, 5.9 Hz), 2.20 (ddd, 2 H, J = 3.7, 4.7, 5.7 Hz), 2.10 (dd, 1 H, J = 7.6, 13.8 Hz), 1.97 (m, 1 H), 1.88 (dd, 1 H, J = 10.0, 13.5 Hz), 1.40 (m, 2 H), 1.30 (m, 2 H), 1.05 (d, 18 H, J = 2.3 Hz), 0.98-1.00 (m, 3 H), 0.87 (s, 9 H), 0.86-0.90 (m, 3 H), 0.82 (d, 3 H, J = 6.5 Hz), 0.026 (d, 6 H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.4, 128.2, 127.6, 127.5, 112.8, 74.6, 73.2, 72.8, 71.0, 44.3, 40.3, 39.0, 34.3, 25.9, 18.5, 18.3, 18.2, 18.1, 14.3, 12.8, -4.4, -4.6; HRMS (ESI) $[M+Na]^+$ calcd for $C_{34}H_{64}O_3NaSi_2$: 599.4292, found: 599.4274.



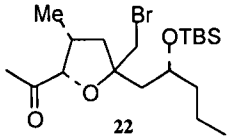
21

{5-Bromomethyl-5-[2-(tert-butyl-dimethyl-silanyloxy)-pentyl]-3-methyl-tetrahydro-furan-2-yl}-methanol (21). To a solution of lithium (23.2 mg, 3.63 mmol) in liquid ammonia (30 mL) was added benzyl ether (524 mg, 0.908 mmol) in THF (4 mL). The resulting dark blue mixture was stirred for 3 h. Solid NH_4Cl was then added until the blue color disappeared. After the liquid was evaporated at 23°C, water and dichloromethane were added. The layers were separated and the

aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The light yellow residue was used directly in the next step without further purification.

To a solution of the above light yellow residue in THF (20 mL) was added LAH (90 mg, 2.4 mmol) portionwise at 0 °C. After 5 min, the mixture was warmed to r.t and stirred for 3 h. Then to the reaction were added saturated aqueous NH_4Cl (3 mL) at 0 °C and anhydrous Na_2SO_4. The mixture was warmed to 23°C and stirred for 2 h. The organic layer was separated and the filter cake was washed with ethyl acetate three times. The combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography to provide the pure diol (265 mg, 90% yield in two steps) as a colorless oil: $[\alpha]^{23}_D$ +1.8° (c 0.8, $CHCl_3$); IR (neat) 3363, 1643, 1462, 1254, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1 H), 4.81 (s, 1 H), 3.78 (m, 1 H), 3.55-3.67 (m, 3 H), 2.05-2.21 (m, 3 H), 1.99 (br, 2 H), 1.88 (dd, 1 H, *J* = 8.7, 13.5 Hz), 1.74-1.82 (m, 1 H), 1.29-1.45 (m, 4 H), 0.88 (s, 9 H), 0.87-0.90 (m, 6 H), 0.04 (d, 6 H, *J* = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 114.0, 74.9, 70.9, 65.2, 43.5, 40.3, 39.0, 33.4, 25.9, 18.6, 18.1, 12.2, 14.2, -4.4, -4.6.

To a solution of the diol (783 mg, 2.4 mmol) in dry dichlormethane (30 mL) at -78 °C was added NBS (634 mg, 3.6 mmol). The reaction was gradually warmed to 23°C and stirred for 12 h, additional NBS (500 mg) was added, and stirred for 12 h. The reaction was quenched by addition of water (50 mL). The organic layers were separated and the aqueous layer was extracted with dichloromethane two times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to provide the bromide **21** (889 mg, 91%) as a light yellow oil. *Rf* = 0.39 (16% EtOAc in hexanes); IR (neat) 3459, 1463, 1255, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06-4.11 (m, 1 H), 3.82-3.91 (m, 0.2 H), 3.78-3.84 (m, 0.8 H), 3.50-3.64 (m, 3.6 H), 3.37-3.46 (m, 0.4 H), 2.52-2.59 (m, 1 H), 1.95-2.00 (m, 1 H), 1.89-1.93 (m, 0.5 H), 1.85-1.87 (m, 1.5 H), 1.79 (m, 1 H), 1.44-1.52 (m, 2 H), 1.31-1.38 (m, 2 H), 1.06 (d, 2.4 H, *J* = 7.0 Hz), 1.00 (d, 0.6 H, *J* = 7.0 Hz), 0.88-0.93 (m, 12 H), 0.086 (d, 1.2 H, *J* = 2.2 Hz), 0.06 (d, 4.8 H, *J* = 4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.1, 81.5, 81.0, 69.4, 69.2, 62.8, 45.8, 44.6, 44.5, 41.9, 41.6, 40.8, 40.6, 38.5, 35.0, 34.6, 26.0, 25.9, 18.3, 18.1, 18.0, 14.2, 13.6, 13.3 -4.1, -4.4; HRMS (ESI) $[M+Na]^+$ calcd for $C_{18}H_{37}O_3BrNaSi$: 431.1593, found: 431.1584.

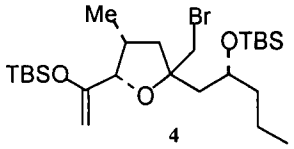


22

1-{5-Bromomethyl-5-[2-(tert-butyl-dimethyl-silanyloxy)-pentyl]-3-methyl-tetrahydro-furan-2-yl}-ethanone (22). Alcohol **21** (128 mg, 0.3 mmoL) was oxidized under standard Swern conditions to afford the corresponding crude aldehyde in quantitative yield. The aldehyde was directly used in the next step without further purification and identification.

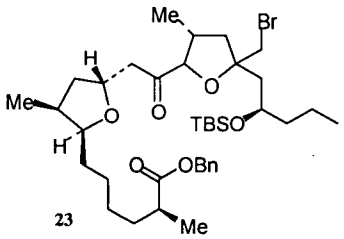
To a solution of the above aldehyde in THF (20 mL) at –78 °C was added methyl magnesium chloride (0.2 mL of 3.0 M solution in diethyl ether, 0.62 mmol). The reaction was stirred at –78 °C for 30 min and warmed to 23°C for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to provide the crude product. The alcohol was directly used in the next step without further purification and identification.

To a solution of the above alcohol and NMO (68 mg, 0.6 mmol) in dry dichloromethane (15 mL) at 0 °C under argon were added 4 Å molecular sieves and TPAP (5.1 mg, 0.01 mmol). The resulting mixture was warmed to 23°C and stirred for 1 h. The solvent was removed and the residue was purified by flash chromatography to give the ketone **22** (79 mg, 60% three steps) as a colorless oil. *Rf* = 0.69 (12% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (d, 0.5 H, *J* = 8.3 Hz), 4.42 (d, 0.5 H, *J* = 7.6 Hz), 3.95 (m, 0.5 H), 3.83 (m, 0.5 H), 3.68 (ABq, 1 H, *J* = 10.4, 27 Hz), 3.46 (ABq, 1 H, *J* = 10.5, 34.4 Hz), 2.71 (m, 1 H), 2.34 (dd, 0.5 H, *J* = 7.7, 21.0 Hz), 2.18 (d, 3 H, *J* = 8.5 Hz), 2.15 (d, 0.5 H, *J* = 7.7, 21.0 Hz), 2.04 (d, 1 H, *J* = 6.3 Hz), 1.80 (d, 1 H, *J* = 5.5 Hz), 1.70 (m, 1 H), 1.45-1.56 (m, 2 H), 1.35 (m, 2 H), 0.99 (d, 1.5 H, *J* = 7.1 Hz), 0.94 (d, 1.5 H, *J* = 7.1 Hz), 0.91 (q, 3 H, *J* = 7.3, 14.8 Hz), 0.88 (d, 9 H, *J* = 6.9 Hz), 0.08 (d, 3 H, *J* = 4.5 Hz), 0.05 (d, 3 H, *J* = 4.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 210.3, 86.9, 86.7, 85.1, 84.9, 69.5, 45.6, 44.8, 43.1, 43.1, 41.2, 41.1, 40.6, 38.8, 37.1, 37.1, 29.3, 29.0, 26.4, 26.3, 18.6, 18.4, 16.1, 16.0, 14.7, -3.6, -3.7, -3.8, -3.9; HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{37}O_3BrNaSi$: 443.1593, found: 443.1604.



4

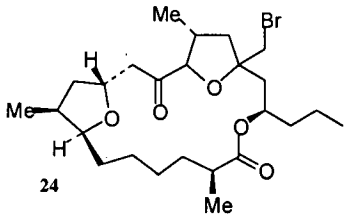
Enol ether 4. To a solution of ketone **22** (150 mg, 0.36 mmol) in THF (20 mL) at –78 °C was added LiHMDS (1.1 mL of 1.0 M solution in THF, 1.1 mmol) dropwise. After stirring at the same temperature for 15 min, TBSCl (187 mg, 1.2 mmol) in HMPA (0.6 mL) were added through a cannula. The resulting reaction mixture was stirred at the same temperature for 30 min, warmed to 23°C for 30 min, quenched by addition of 5% aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the residue afforded semi-pure vinyl silyl ether **4** (185 mg) as pale yellow oil, which was used directly for the next coupling without further purification (NMR showed the silyl ether containing ~5% ketone).



23

7-[5-(2-{5-Bromomethyl-5-[2-(tert-butyl-dimethyl-silanyloxy)-pentyl]-3-methyl-tetrahydro-furan-2-yl}-2-oxo-ethyl)-3-methyl-tetrahydro-furan-2-yl]-2-methyl-heptanoic acid benzyl ester (23). To a solution of the above silyl ether **4** (185 mg), sulfone **2** (110 mg, 0.26 mmol), and DTBMP (58.4 mg, 0.28 mmol) in dry dichloromethane (20 mL) at –78 °C was added $AlCl_3$ (206 mg, 1.55 mmol). The reaction mixture was stirred at the same temperature for 10 min, warmed to –35°C and stirred for 3 h, and quenched by addition of saturated aqueous potassium sodium tartrate solution. The mixture was then warmed to 23°C and stirred until the layers were clear. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the residue afforded the pure product **23** (130 mg, 73%) as a colorless oil. *Rf* = 0.63 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35(m, 5 H), 5.11 (s, 2 H), 4.42-4.49 (m, 2 H), 3.76-3.85 (m, 2 H), 3.73 (d, 1 H, *J* = 8.2 Hz), 3.63 (d, 1 H, *J* = 8.2 Hz), 2.93 (dd, 1 H, *J* = 4.7, 13.9 Hz), 2.64-2.75 (m, 1 H), 2.52 (dd, 1 H, *J* = 5.5, 14.0 Hz), 2.47 (dd, 1 H, *J* = 5.6, 11.2 Hz), 2.15-2.20 (m, 1 H), 2.13 (dd, 1 H, *J* = 6.0, 10.3 Hz), 1.88 (m, 3 H), 1.70 (m, 3 H), 1.20-1.51 (m, 12 H), 1.15 (d, 3 H, *J*

= 5.6 Hz), 0.99 (d, 3 H, J = 5.7 Hz), 0.87-0.91 (m, 15 H), 0.05 (d, 6 H, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 177.0, 136.7, 128.9, 128.5, 128.5, 86.6, 85.1, 81.5, 72.3, 69.5, 66.4, 48.7, 43.9, 43.2, 41.2, 40.6, 40.5, 39.9, 37.4, 36.3, 34.2, 30.6, 27.8, 26.9, 26.3, 18.6, 18.4, 17.4, 15.9, 14.7, 14.3, -3.7, -3.9; MS $[M+Na]^+$ (ESI) *m/z* 745.2; HRMS (ESI) $[M+Na]^+$ calcd for $C_{38}H_{63}O_6BrNaSi$: 745.3475, found: 745.3474.

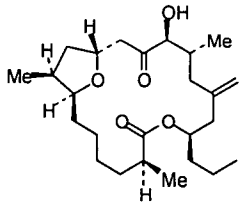


7-Bromomethyl-5,12,18-trimethyl-9-propyl-10,20,21-trioxatricyclo-[15.2.1.14,7] heneicosane-3,11-dione (24). To the compound **23** (52 mg, 0.07 mmol) in dry THF (5 mL) were added pyridine (1 mL) and HF·Py (1.2 mL) at 23°C. The resulting mixture was stirred at 23°C for 12 h and quenched by addition of 5% aqueous $NaHCO_3$ solution slowly at 0 °C. The layers were separated and the aqueous layer was extracted by EtOAc twice. The combined organic layers were dried, concentrated *in vacuo* to provide a residue, which was purified by flash chromatography to afford the pure product (38 mg, 87%) as a pale yellow oil.

To a solution of the above alcohol (26 mg, 0.04 mmol) in EtOH (10 mL) was added 10% Pd/C (26 mg). The mixture was stirred under a hydrogen atmosphere for 2 h. The resulting reaction mixture was filtered through Celite® and washed with EtOAc three times. The combined organic solvent was evaporated and azetropically dried with benzene. The resulting pale yellow oil (24 mg) was used for the next step without further purification.

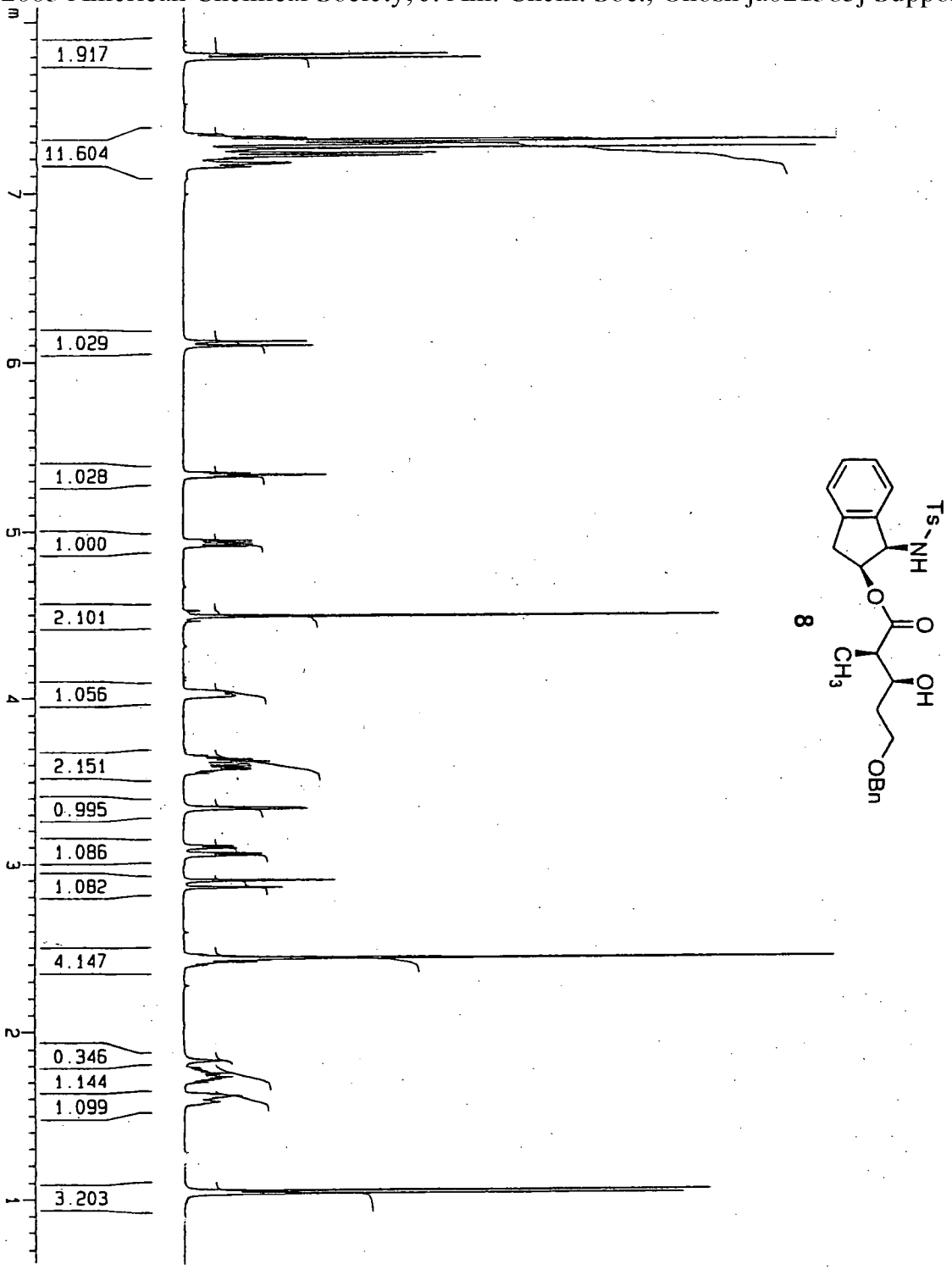
To a solution of the above hydroxy acid (24 mg, 0.05 mmol) in dry toluene (5 mL) were added trichlorobenzoylchloride (0.2 mL, 1.15 mmol) and diisopropylethylamine (0.4 mL) at 23°C. The resulting reaction mixture was stirred for 15 h at 23°C. The solution was diluted by addition of dry toluene (5 mL) and was added by syringe pump slowly to a solution of DMAP (170 mg, 1.38 mmol) in dry toluene (100 mL) at 50 °C over 10 h. The reaction was stirred an additional 24 h at the same temperature and quenched by addition of saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted by EtOAc twice. The combined organic layers were dried and concentrated *in vacuo* to provide a yellow residue, which was purified by flash chromatography to afford the pure product (15 mg, 71%) as a pale yellow oil. Rf = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (m, 1 H), 4.81 (d, 1 H, J = 8.2 Hz),

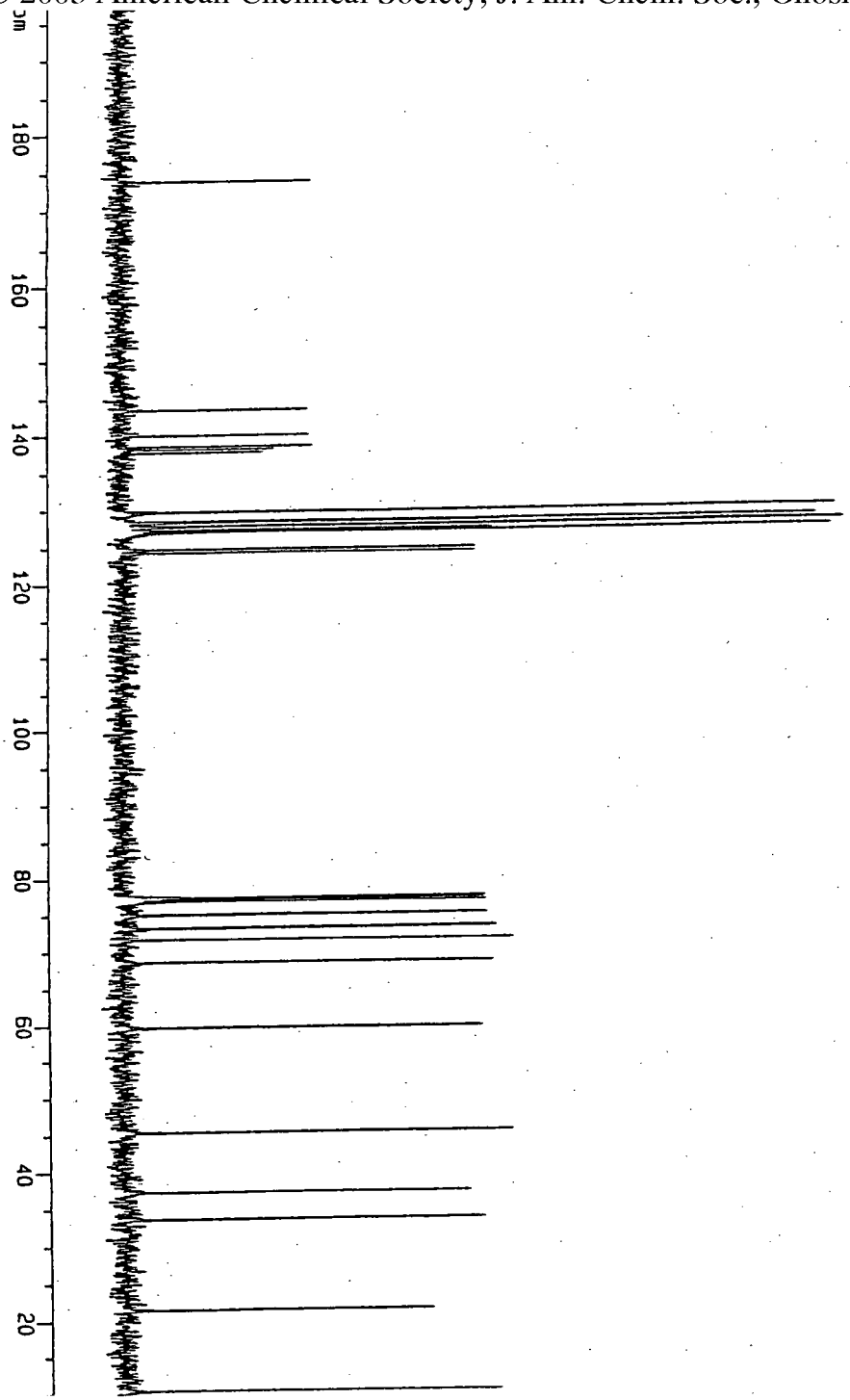
4.41 (m, 1 H), 3.94 (d, 1 H, J = 10.0 Hz), 3.75 (d, 1 H, J = 10.0 Hz), 3.63 (m, 1 H), 2.79 (dd, 1 H, J = 7.7, 12.6 Hz), 2.72 (m, 1 H), 2.37 (m, 1 H), 2.29 (dd, 1 H, J = 6.6, 12.6 Hz), 2.11 (m, 2 H), 1.91 (m, 2 H), 1.72 (m, 2 H), 1.64 (m, 2 H), 1.46 (m, 4 H), 1.30-1.43 (m, 8 H), 0.1.12 (d, 3 H, J = 6.9 Hz), 1.03 (d, 3 H, J = 7.0 Hz), 0.91 (t, 3 H, J = 7.2 Hz), 0.83 (d, 1 H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 175.6, 128.2, 88.4, 84.4, 79.1, 73.8, 69.5, 45.4, 44.9, 42.0, 41.0, 38.3, 37.6, 37.4, 36.9, 36.7, 34.5, 30.1, 29.7, 26.6, 26.3, 18.0, 17.9, 15.3, 14.0, 13.9; MS $[M+Na]^+$ (ESI) m/z 523.3; HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{41}O_5BrNa$: 523.2035, found: 523.2042.

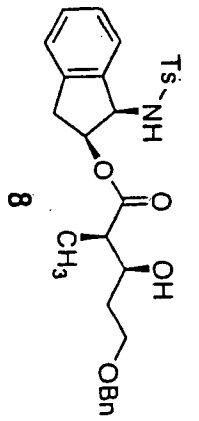


(+)-1
(Amphidinolide T1)

(+)-Amphidinolide T1 (1). To a solution of the macrolactone (12 mg, 0.02 mmol) in 95% ethanol (10 mL) were added Zn dust (47 mg, 0.72 mmol) and solid NH_4Cl (47 mg). The mixture was stirred at 80°C for 4 h. The solvent was evaporated under reduced pressure. The solid was diluted with EtOAc and filtered through a cintered funnel and washed with EtOAc three times. The combined organic layers were dried, concentrated *in vacuo* and purified by flash chromatography to afford the pure product **1** (6.2 mg, 61%) as a colorless oil. *Rf* = 0.36 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ +16° (c 0.1, $CHCl_3$); IR (neat) 3492, 1722 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.43 (m, 1 H), 5.22 (s, 1 H), 5.00 (s, 1 H), 4.58 (m, 1 H), 4.39 (dd, 1 H, J = 1.6, 5.7 Hz), 3.73 (dddd, 1 H, J = 2.6, 2.4, 4.5, 10.8 Hz), 3.69 (d, 1 H, J = 5.7 Hz), 2.62 (dd, 1 H, J = 10.3, 13.4 Hz), 2.49-2.56 (m, 3 H), 2.31-2.42 (m, 3 H), 1.98 (dd, 1 H, J = 2.7, 14.2 Hz), 1.78 (m, 1 H), 1.57-1.69 (m, 4 H), 1.42-1.54 (m, 2 H), 1.30-1.41 (m, 5 H), 1.22 (m, 1 H), 1.17 (d, 3 H, J = 7.0 Hz), 1.15 (m, 1 H), 1.13 (d, 3 H, J = 6.5 Hz), 0.95 (d, 3 H, J = 7.3 Hz), 0.71 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 212.3, 175.2, 143.8, 116.4, 78.7, 78.4, 73.9, 72.0, 45.3, 42.0, 41.5, 40.0, 36.7, 35.9, 32.2, 29.9, 27.1, 26.5, 19.3, 18.3, 14.2, 14.2, 14.0; MS $[M]^+$ (EI) m/z 422.3; HRMS (EI) $[M]^+$ calcd for $C_{25}H_{42}O_5$: 422.3032, found: 422.3035.







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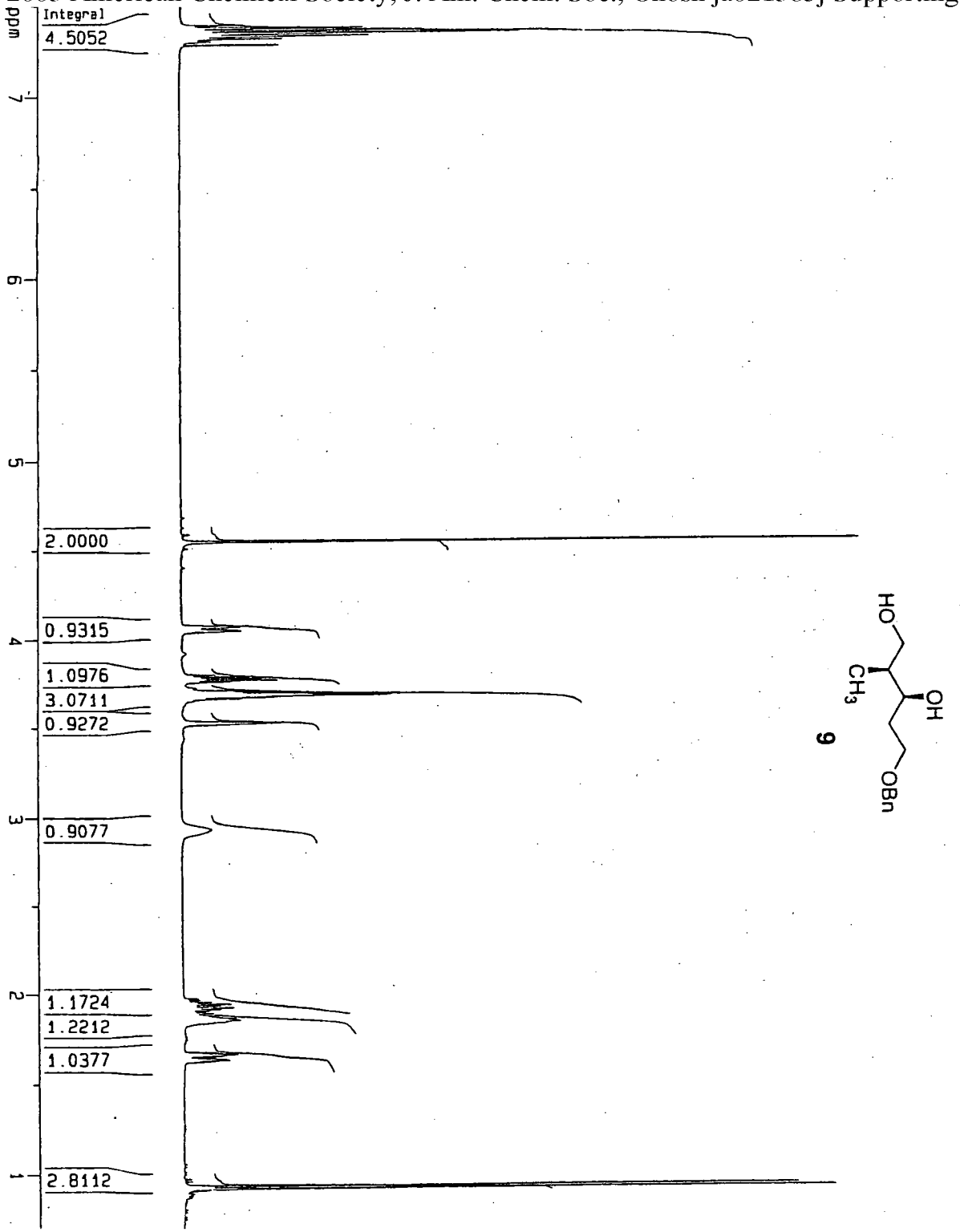

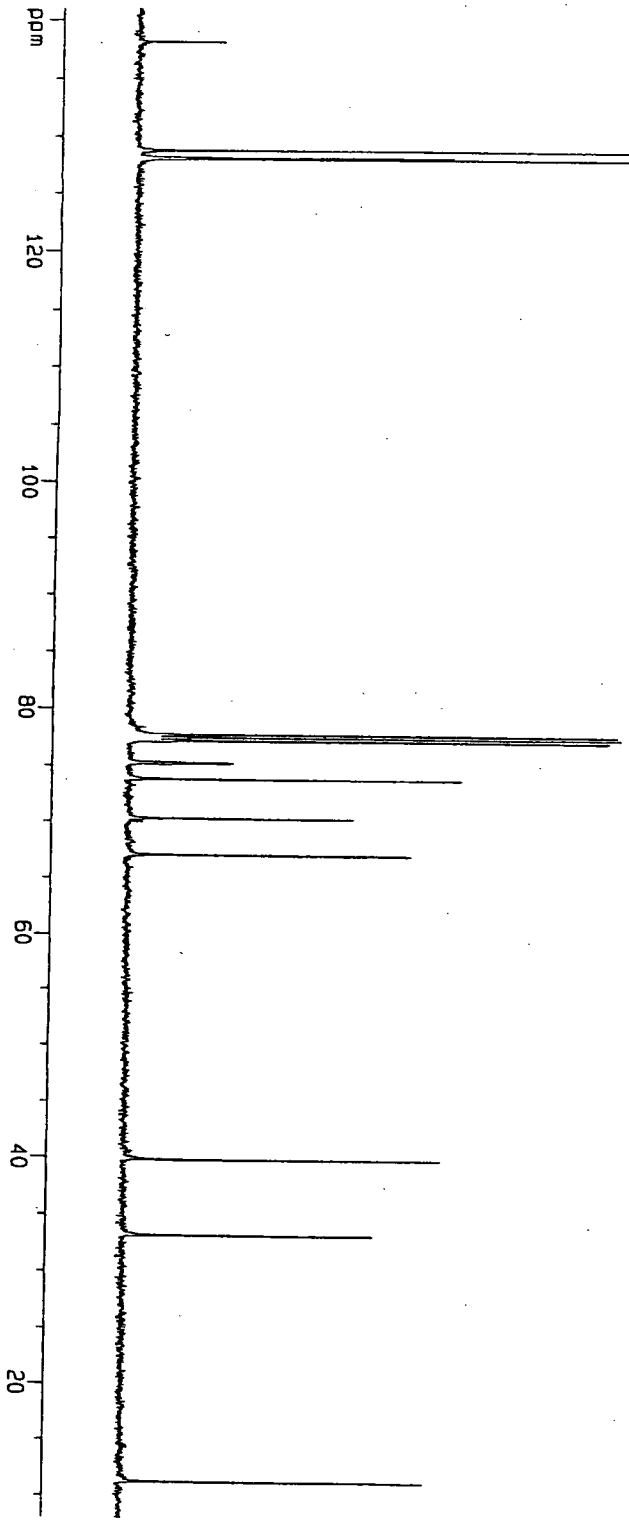

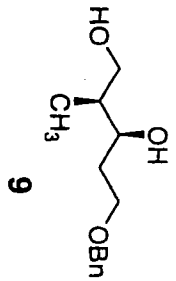

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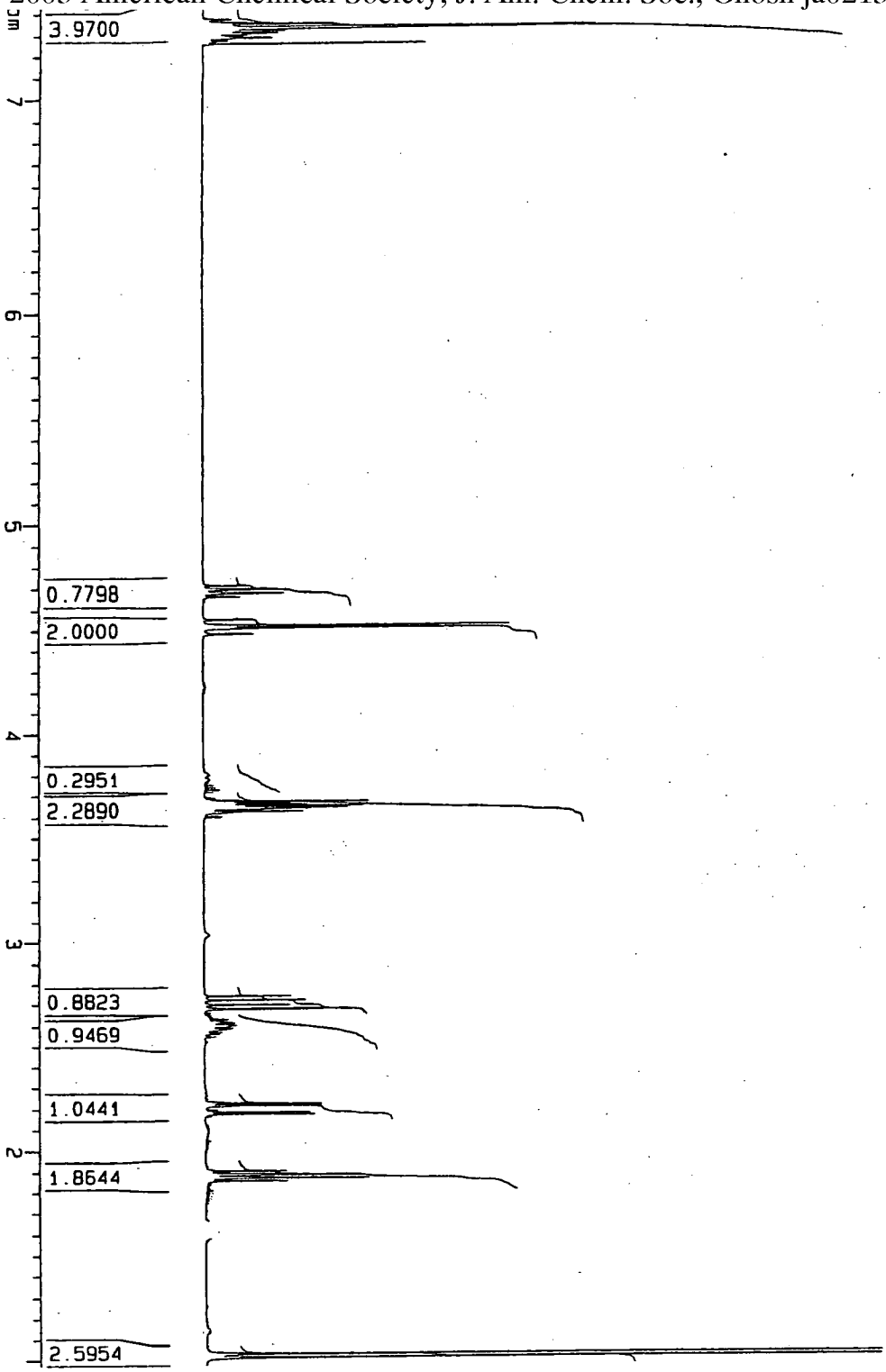

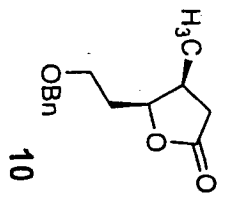

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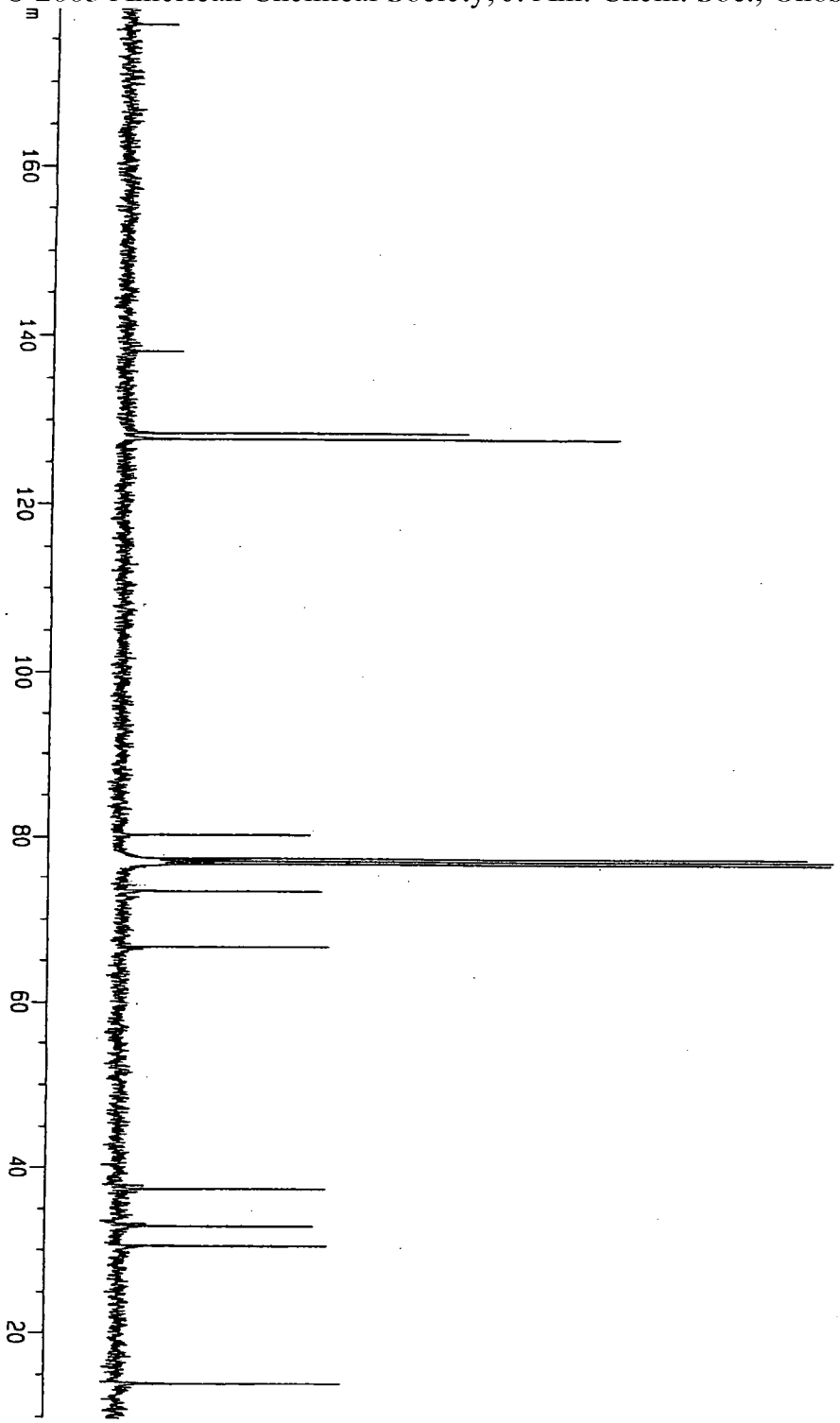

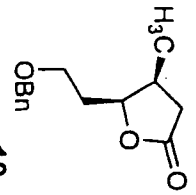

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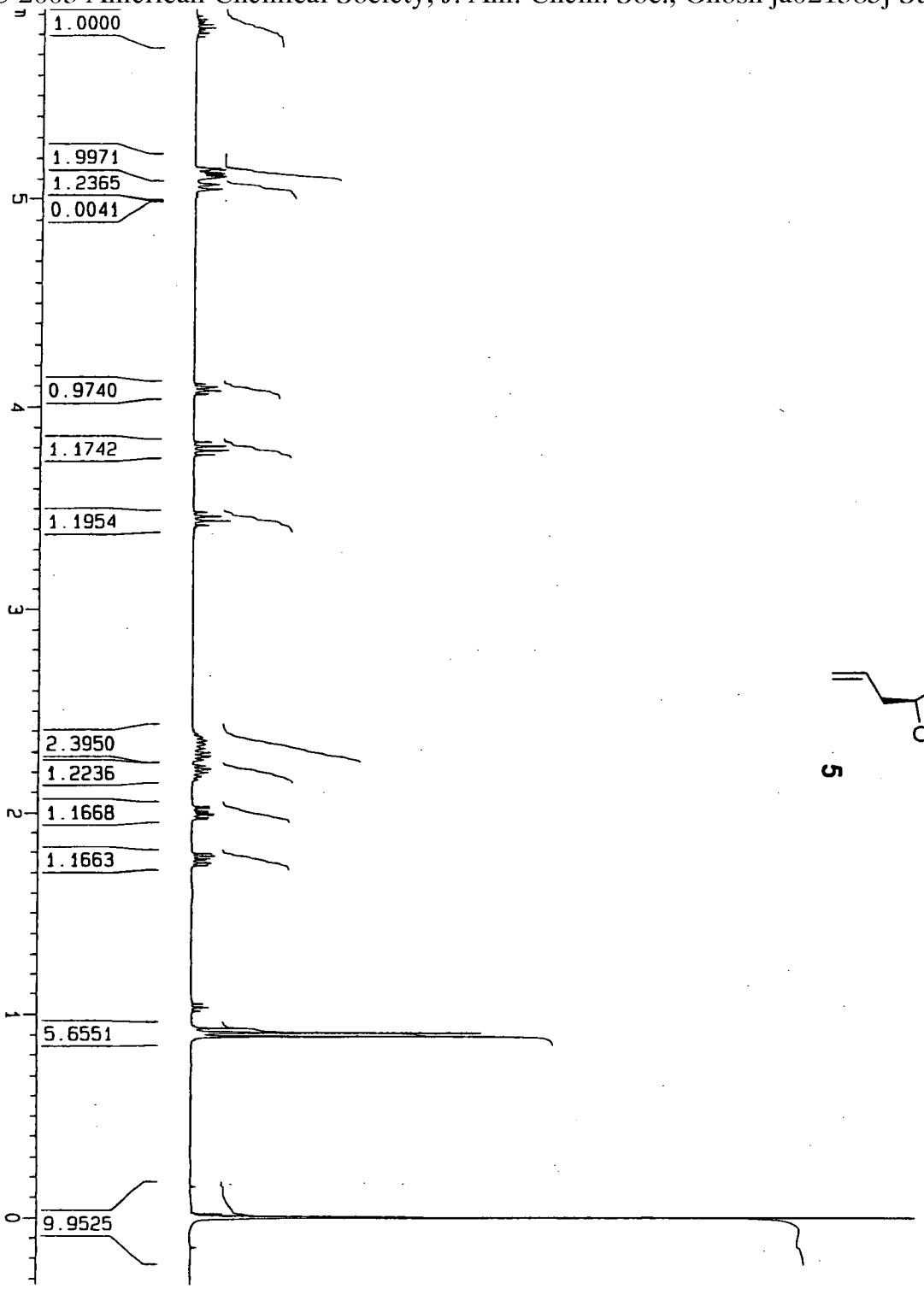

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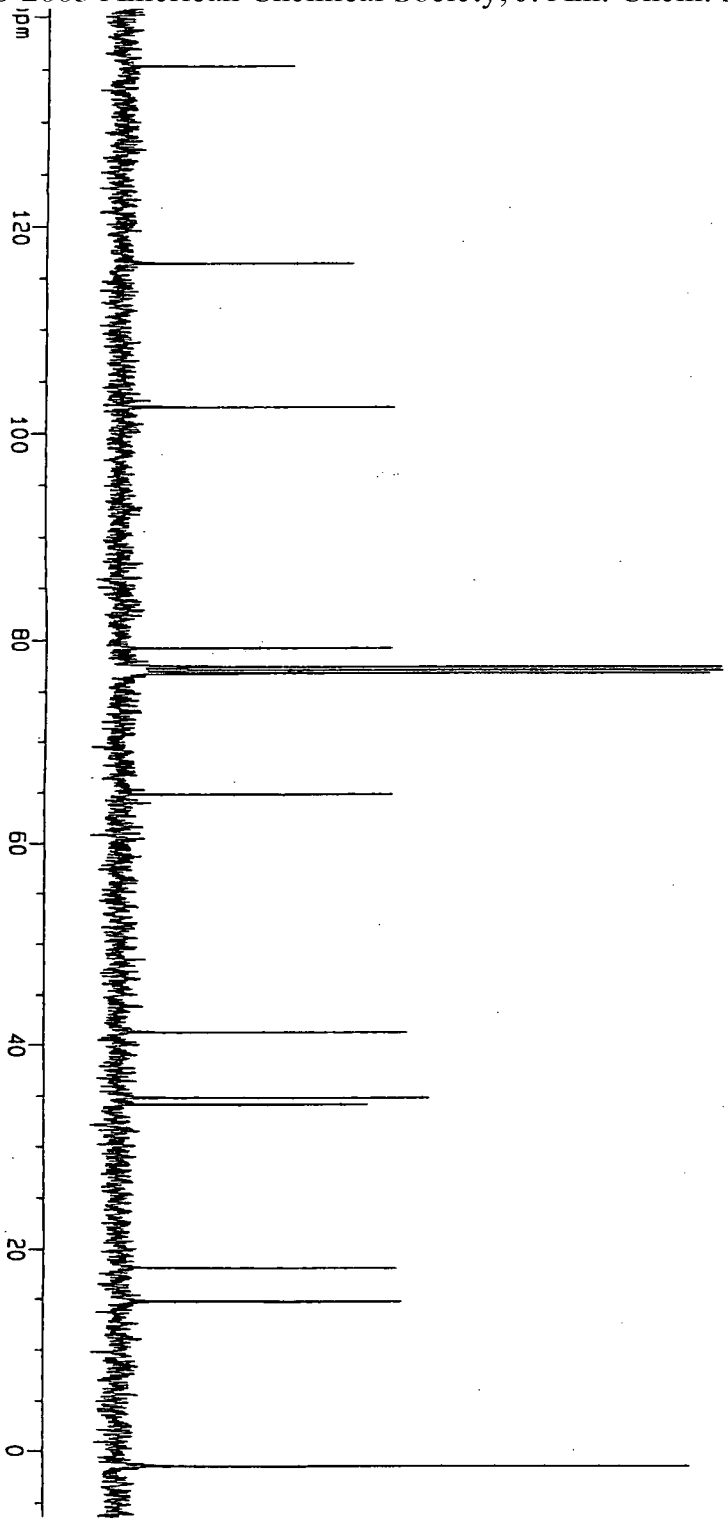

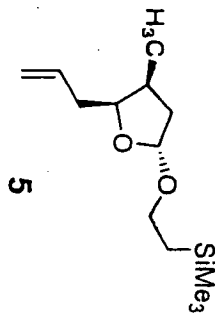

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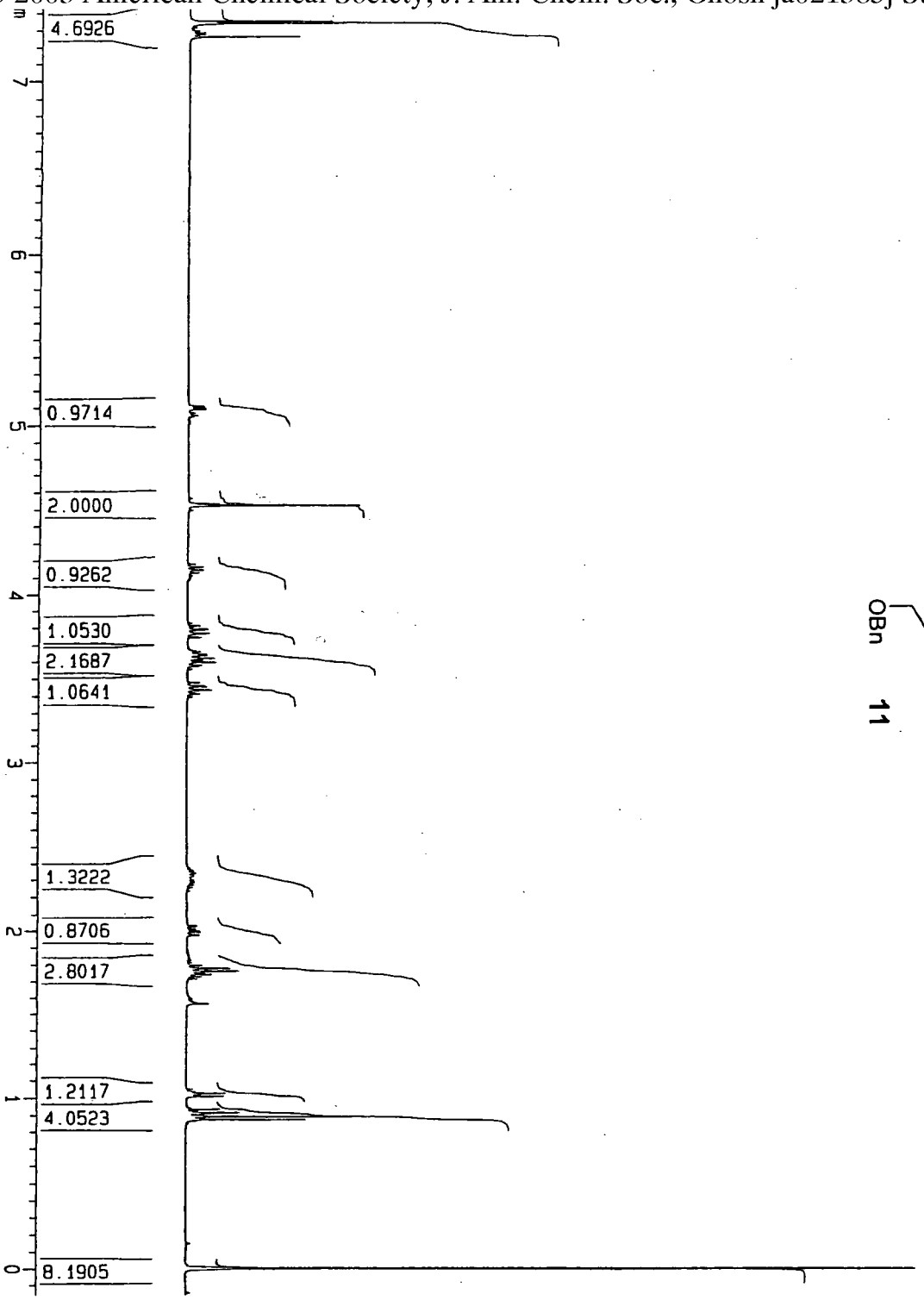

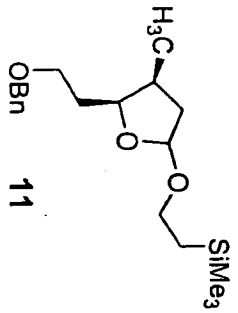

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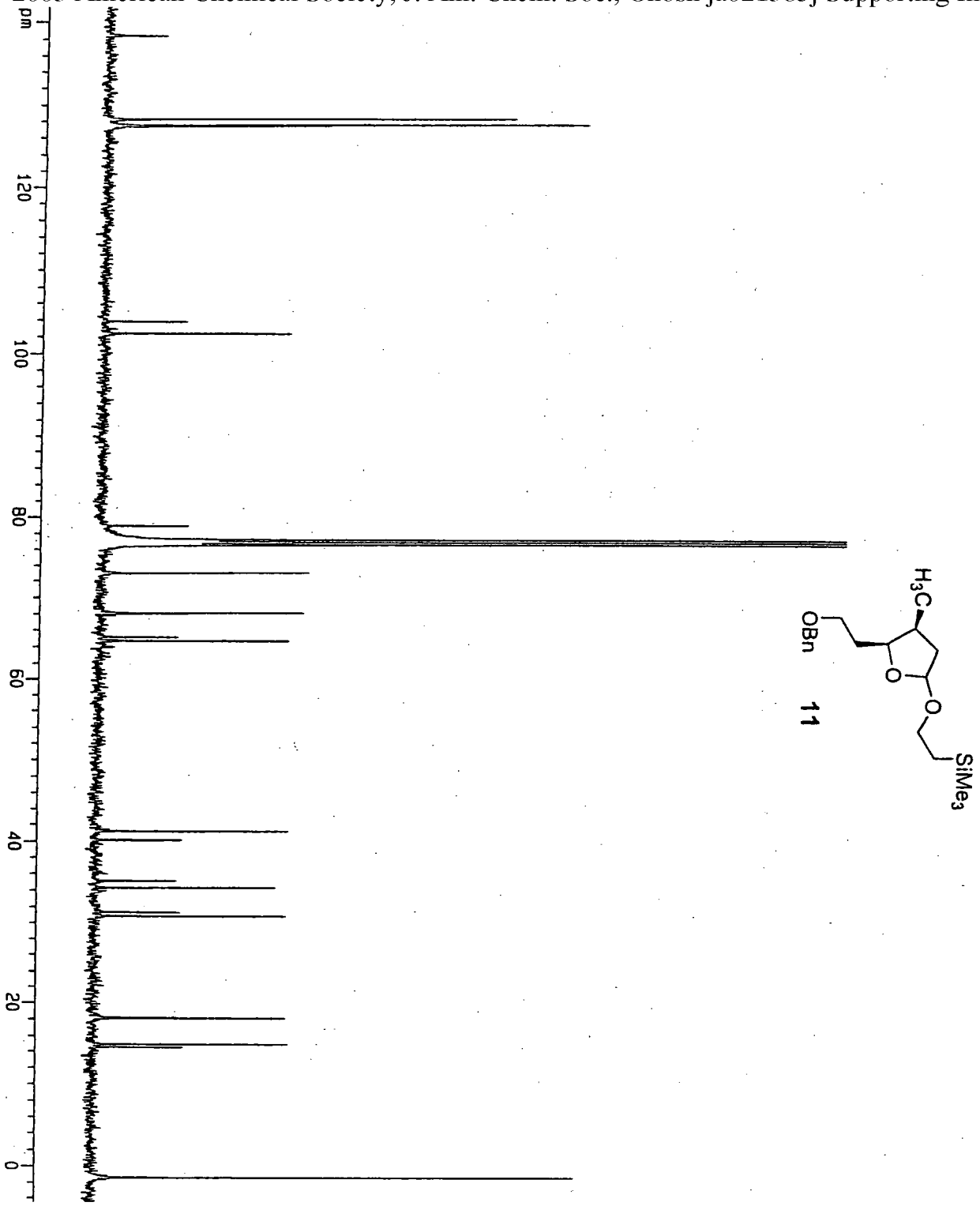

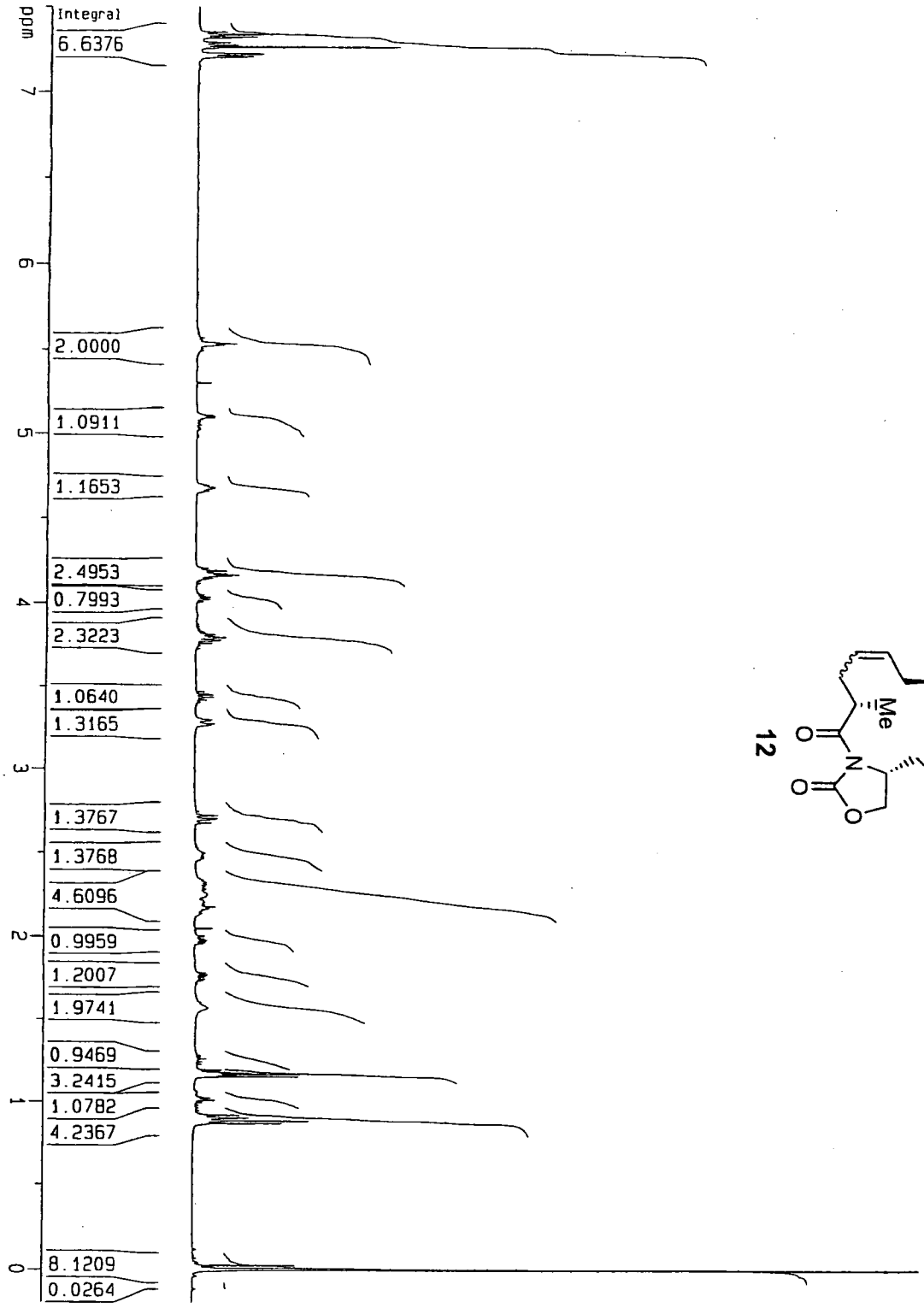

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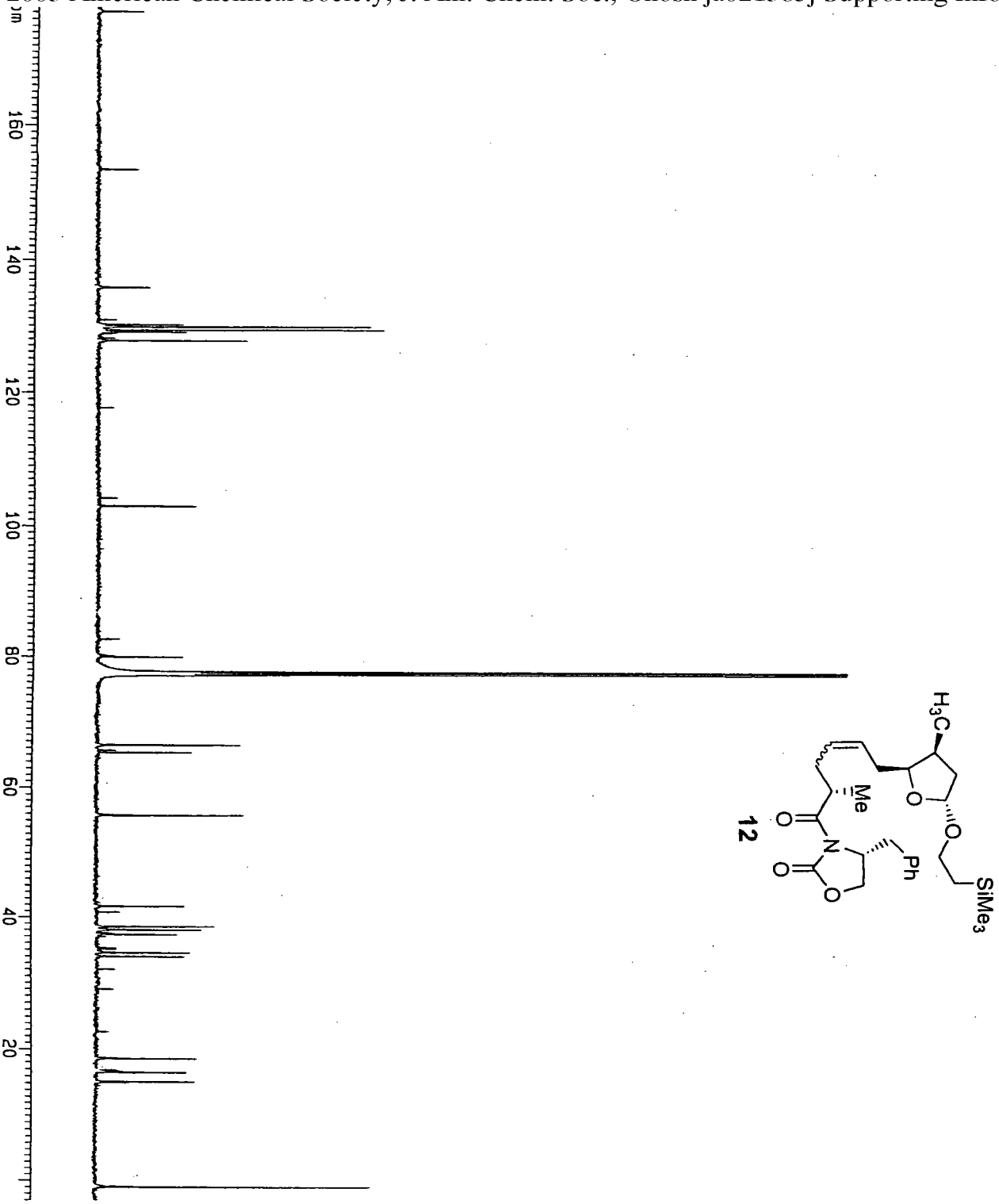

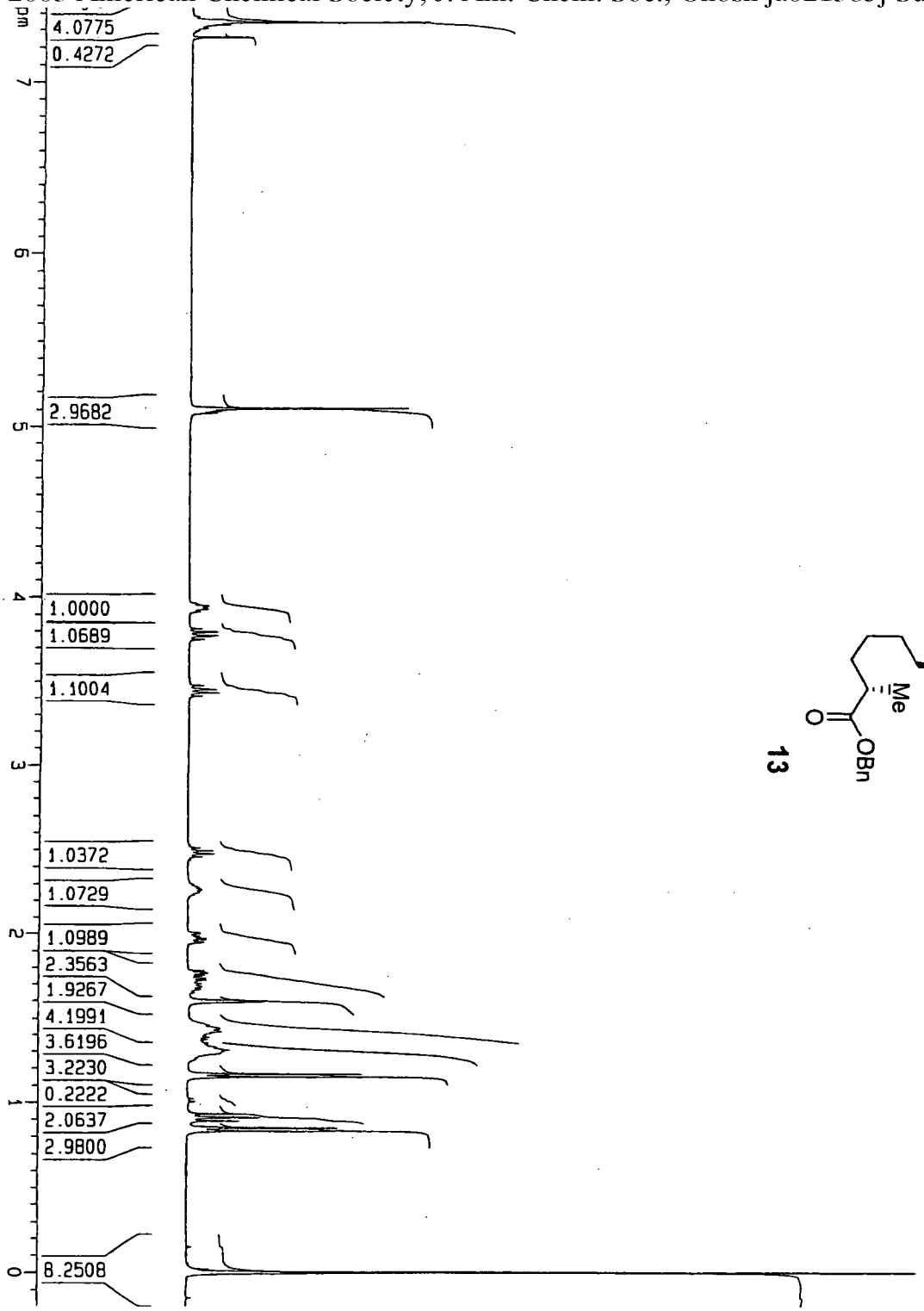

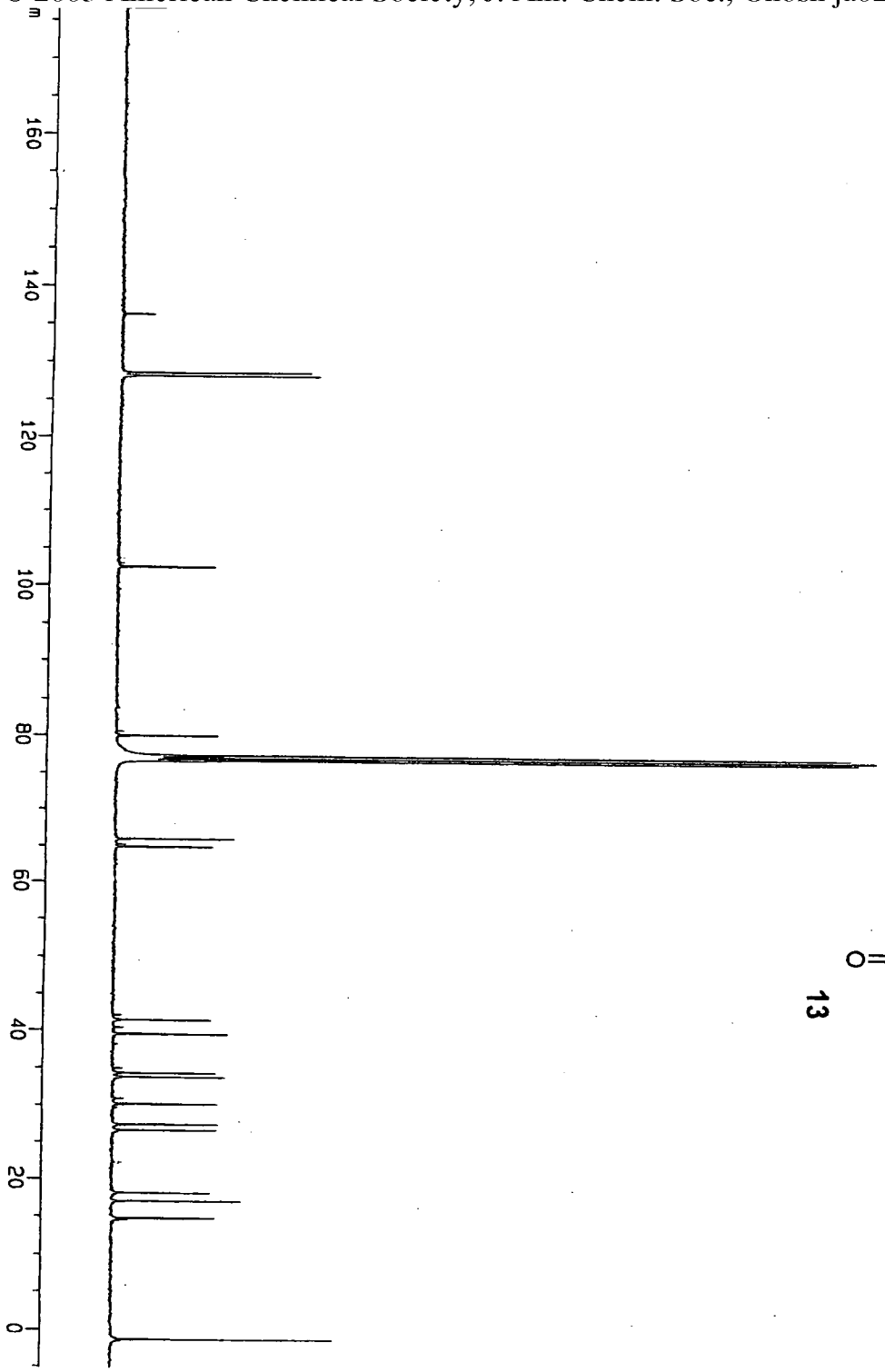

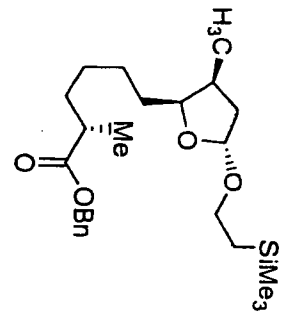

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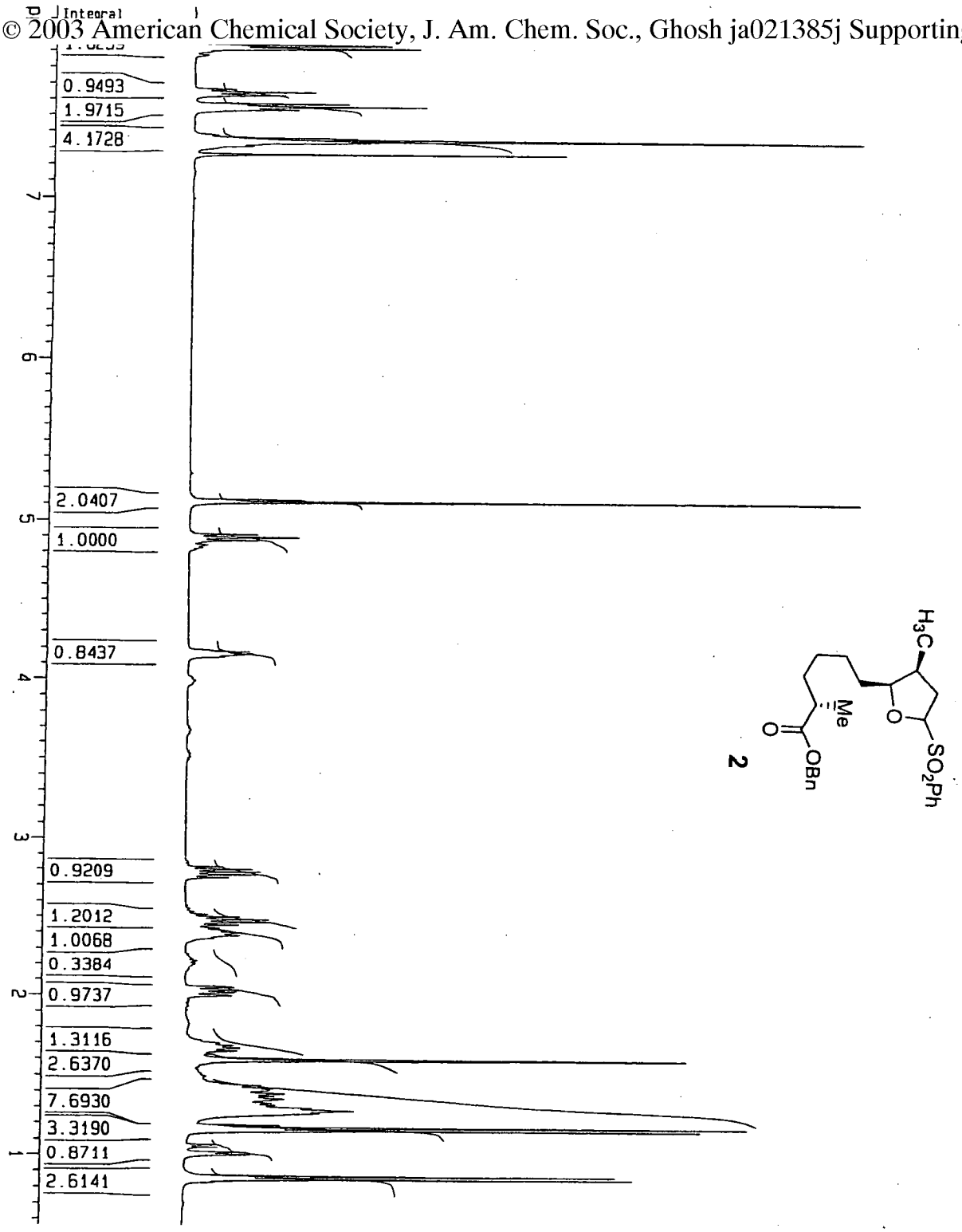

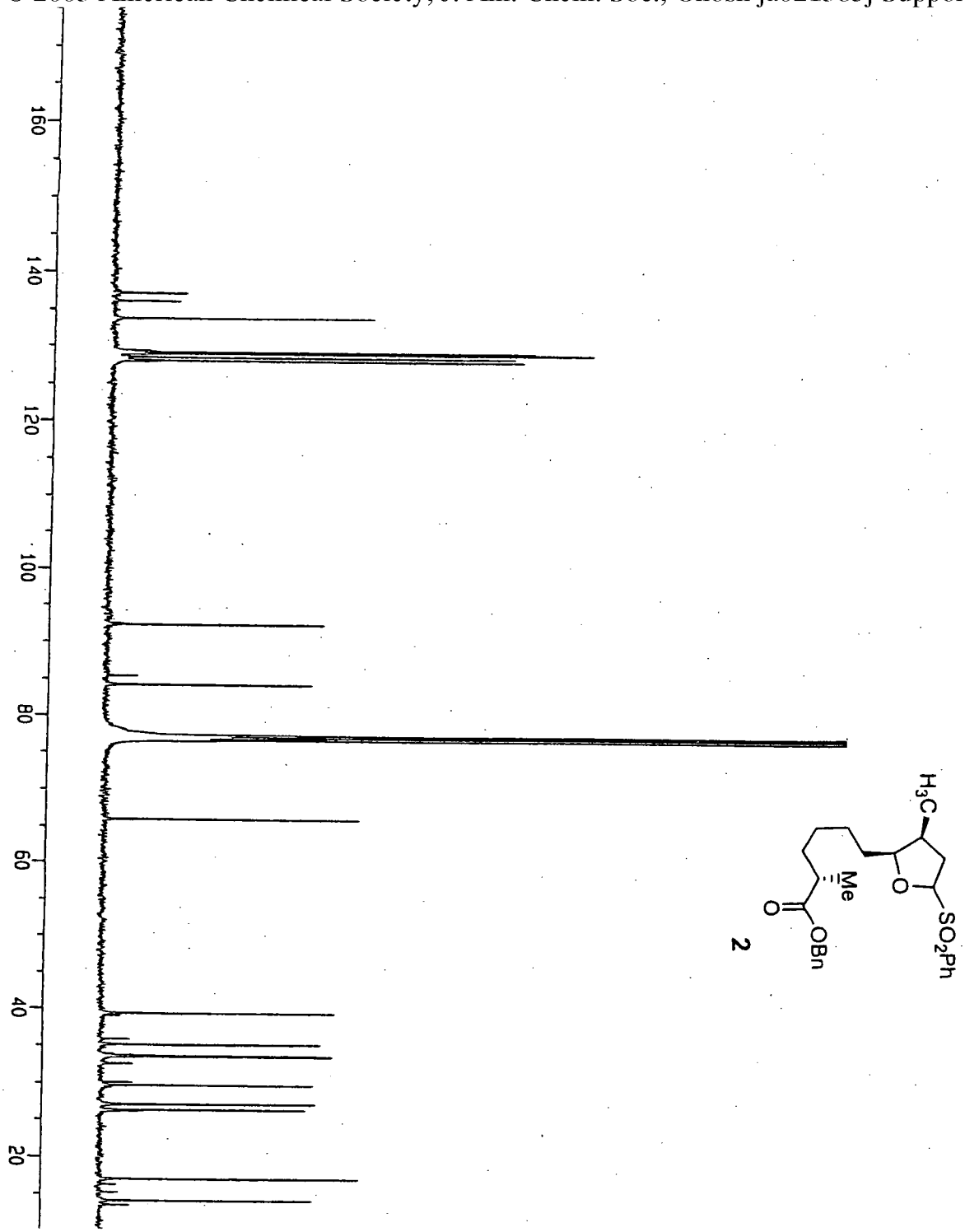

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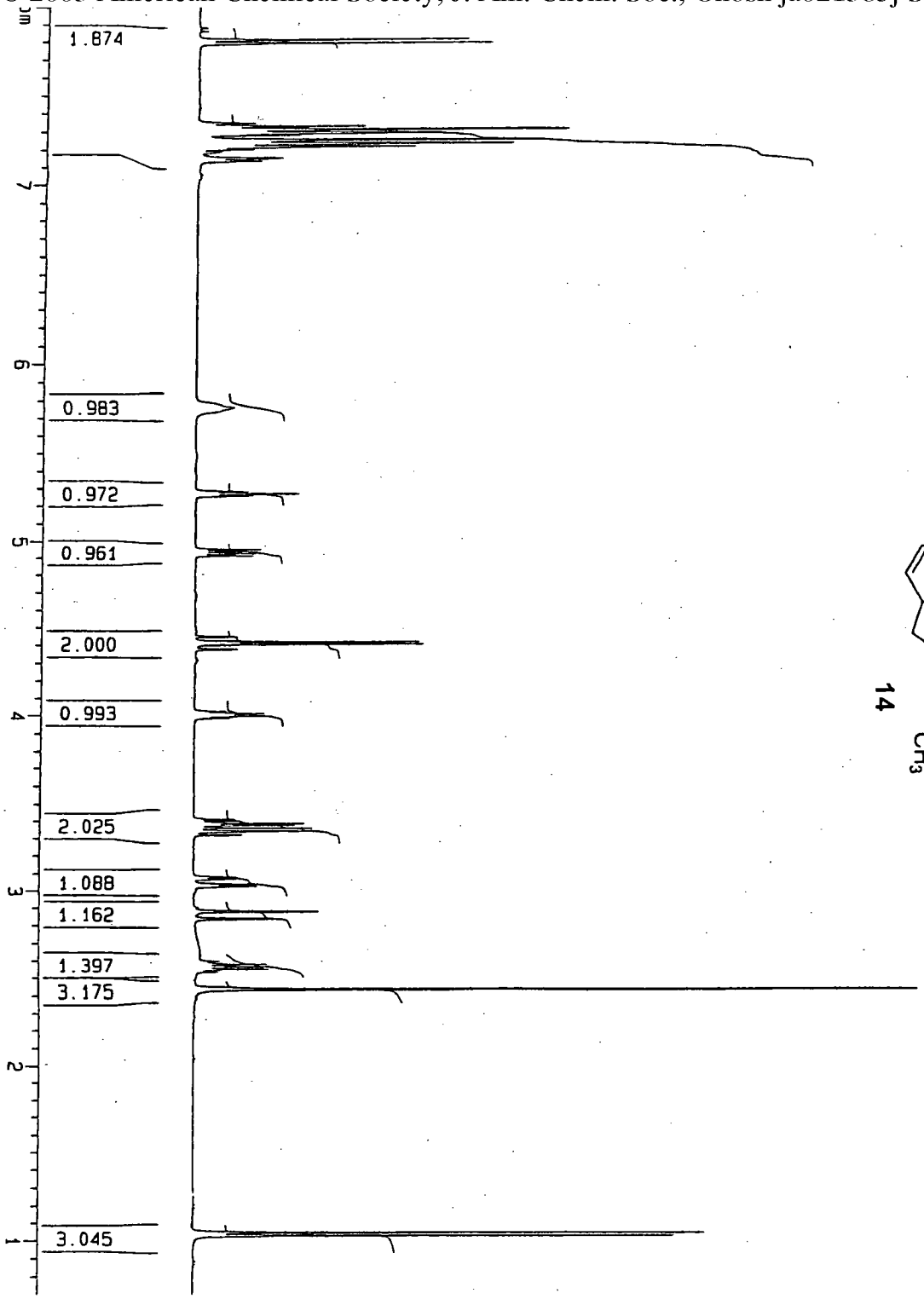

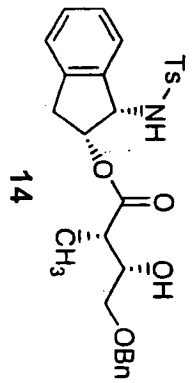

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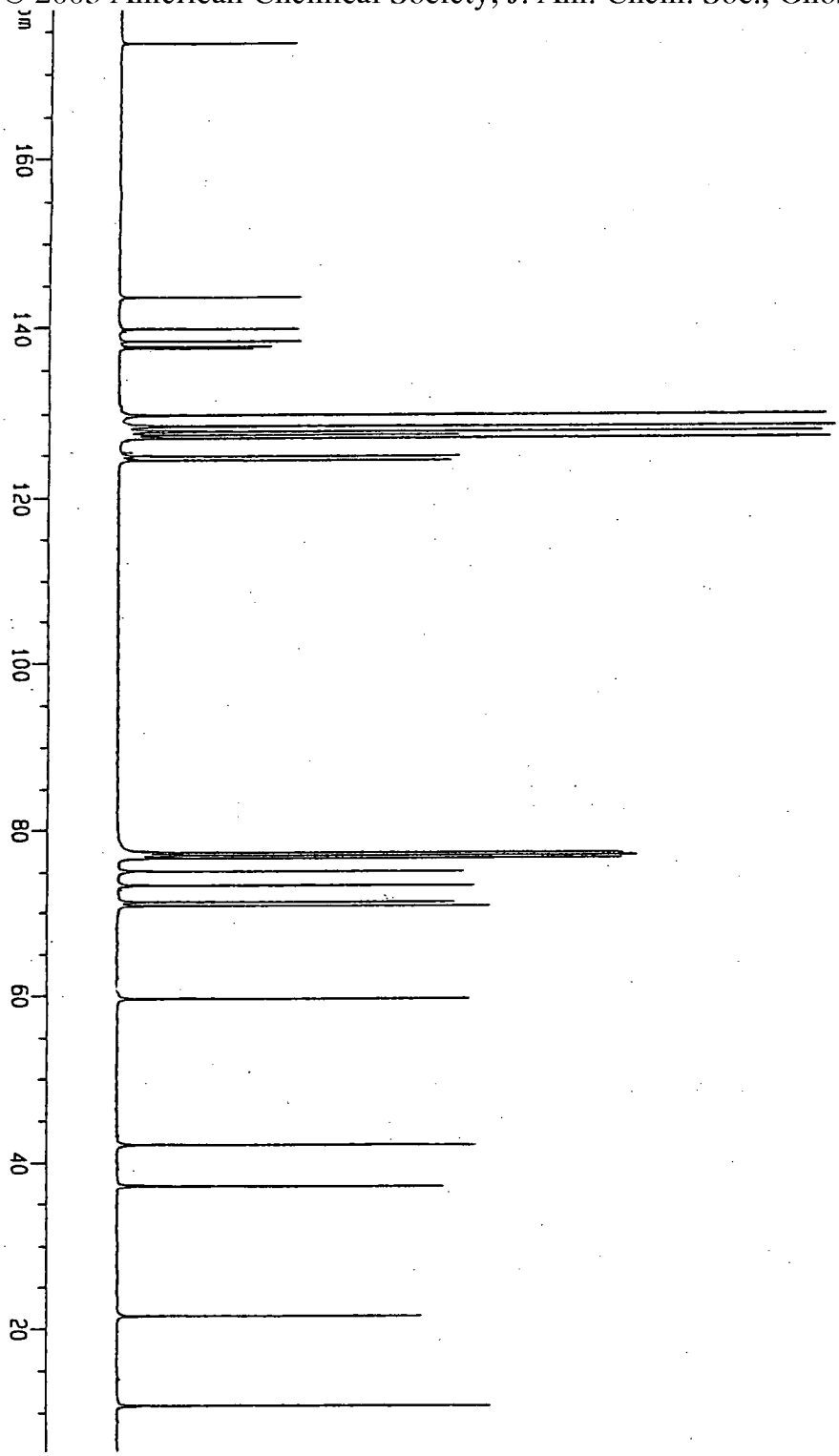

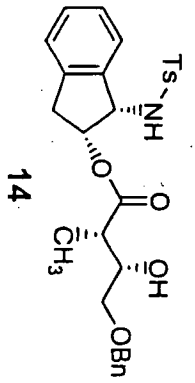

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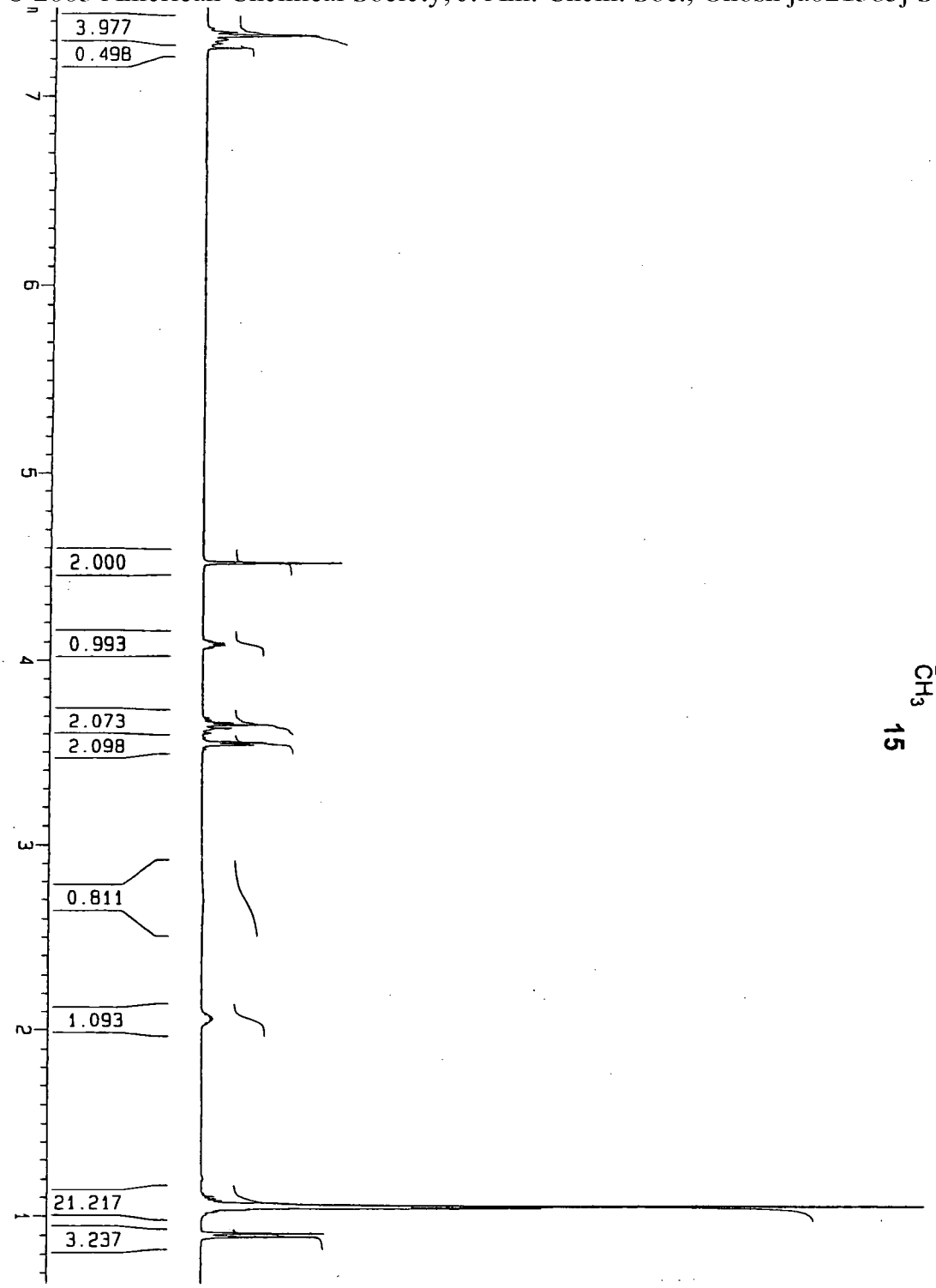

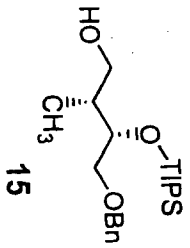

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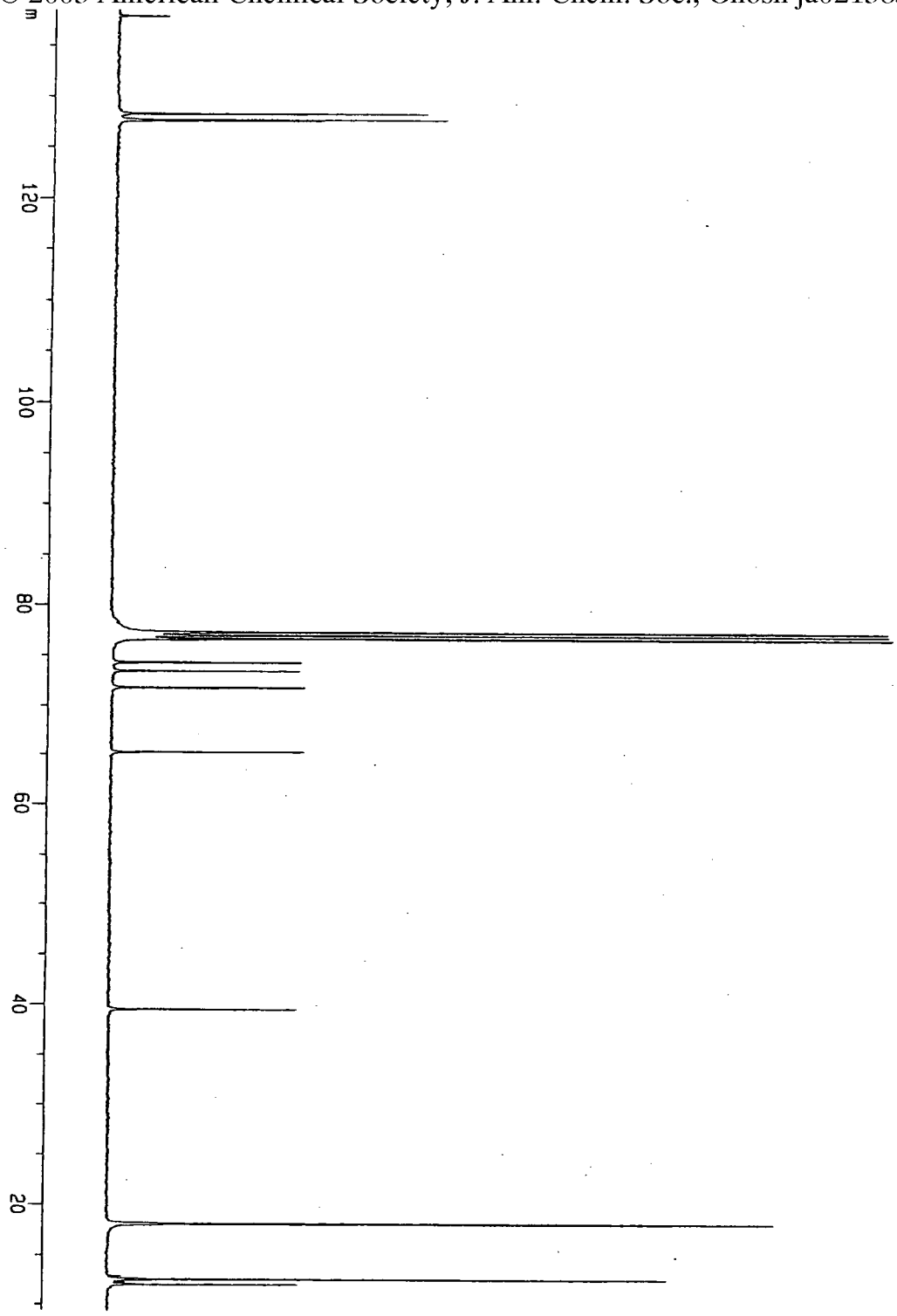

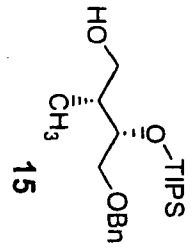

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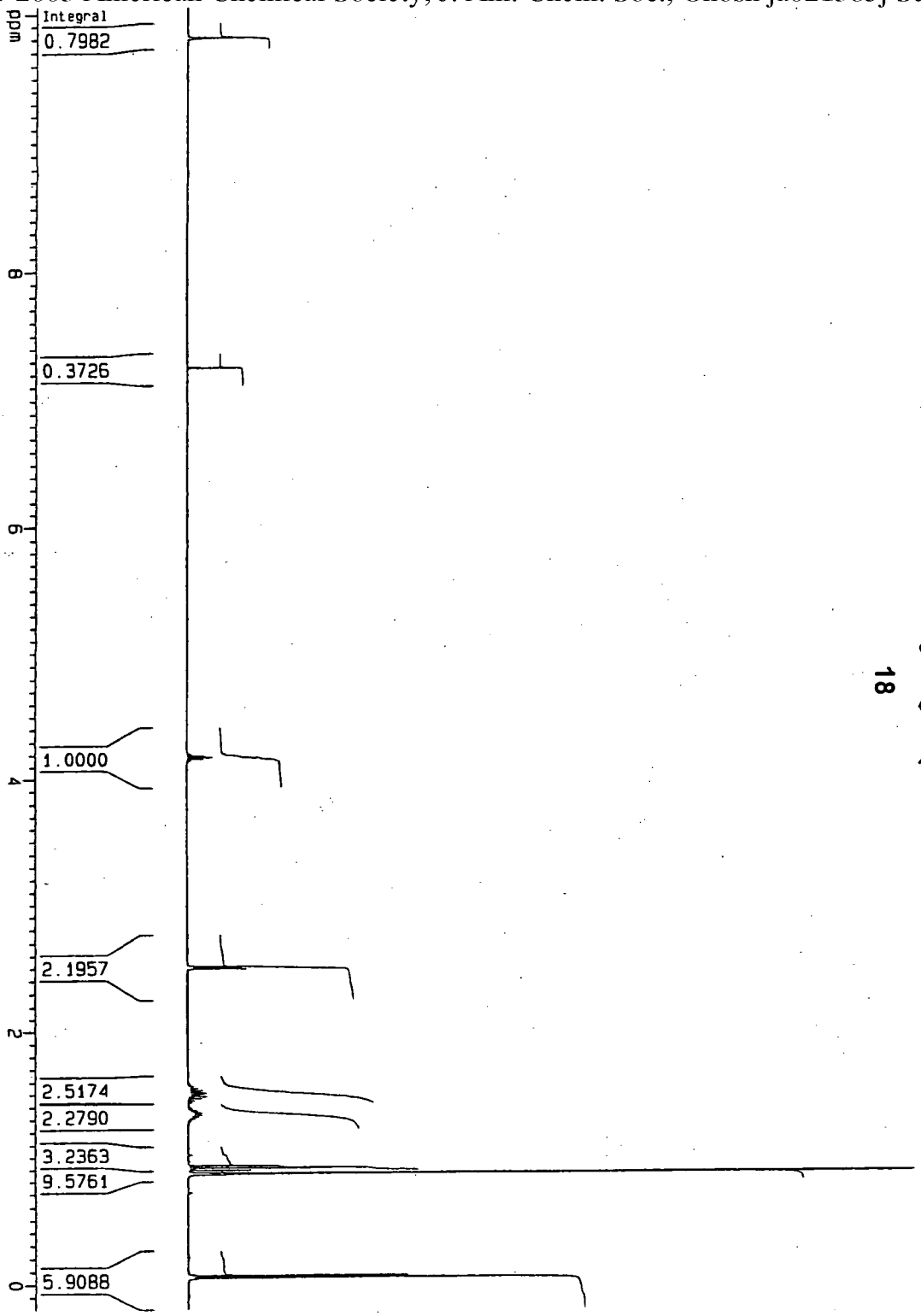

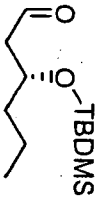

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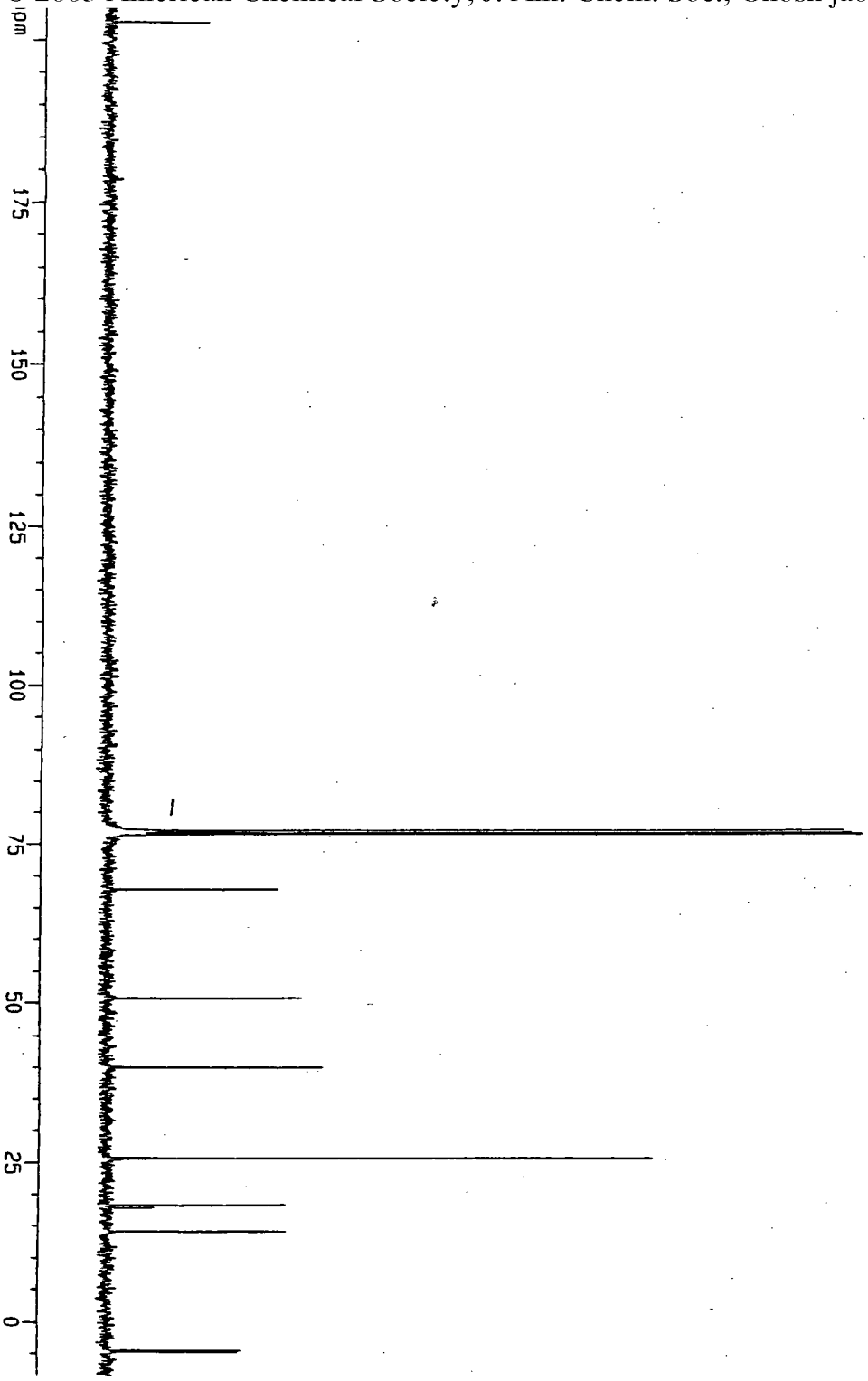

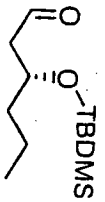

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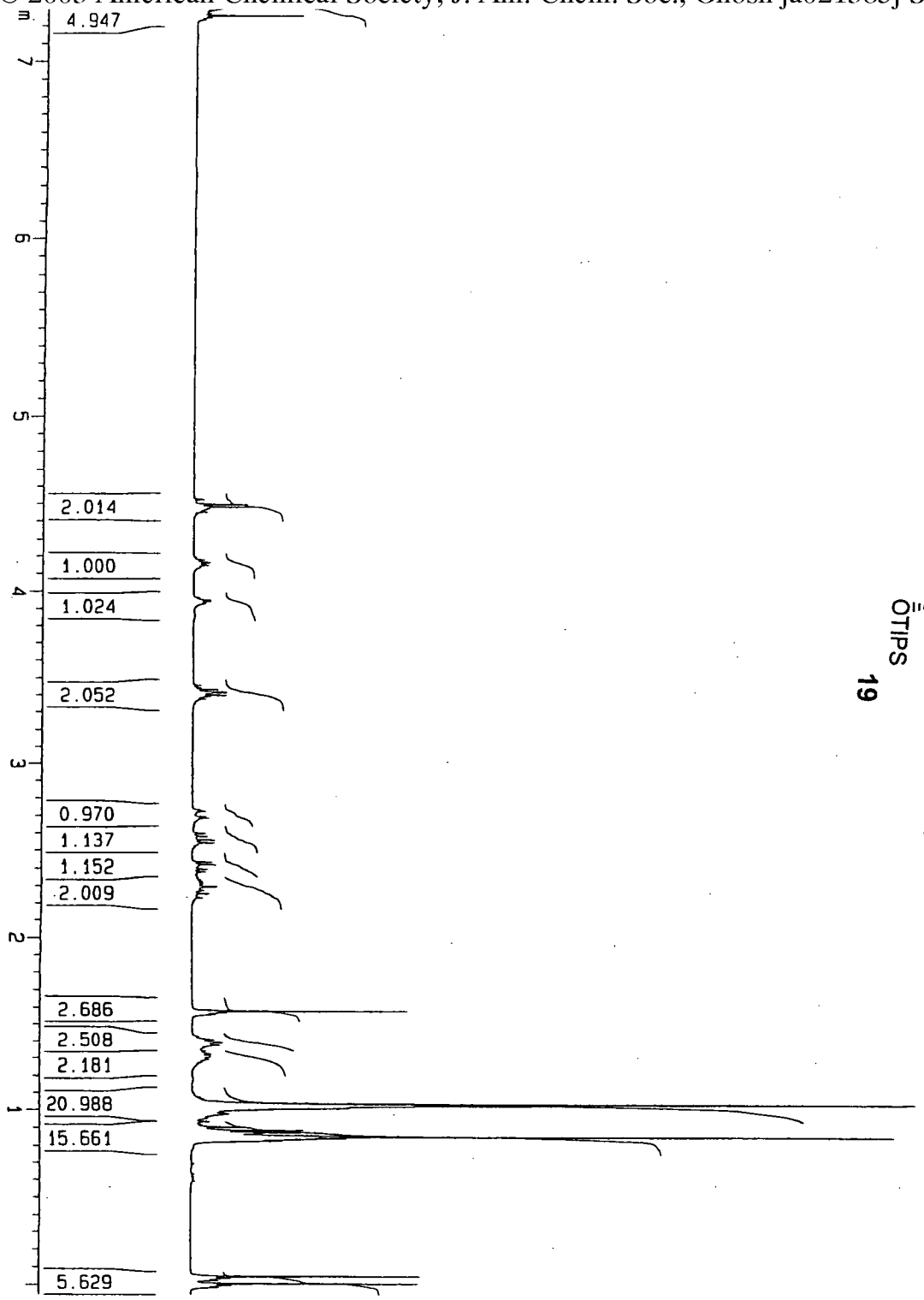

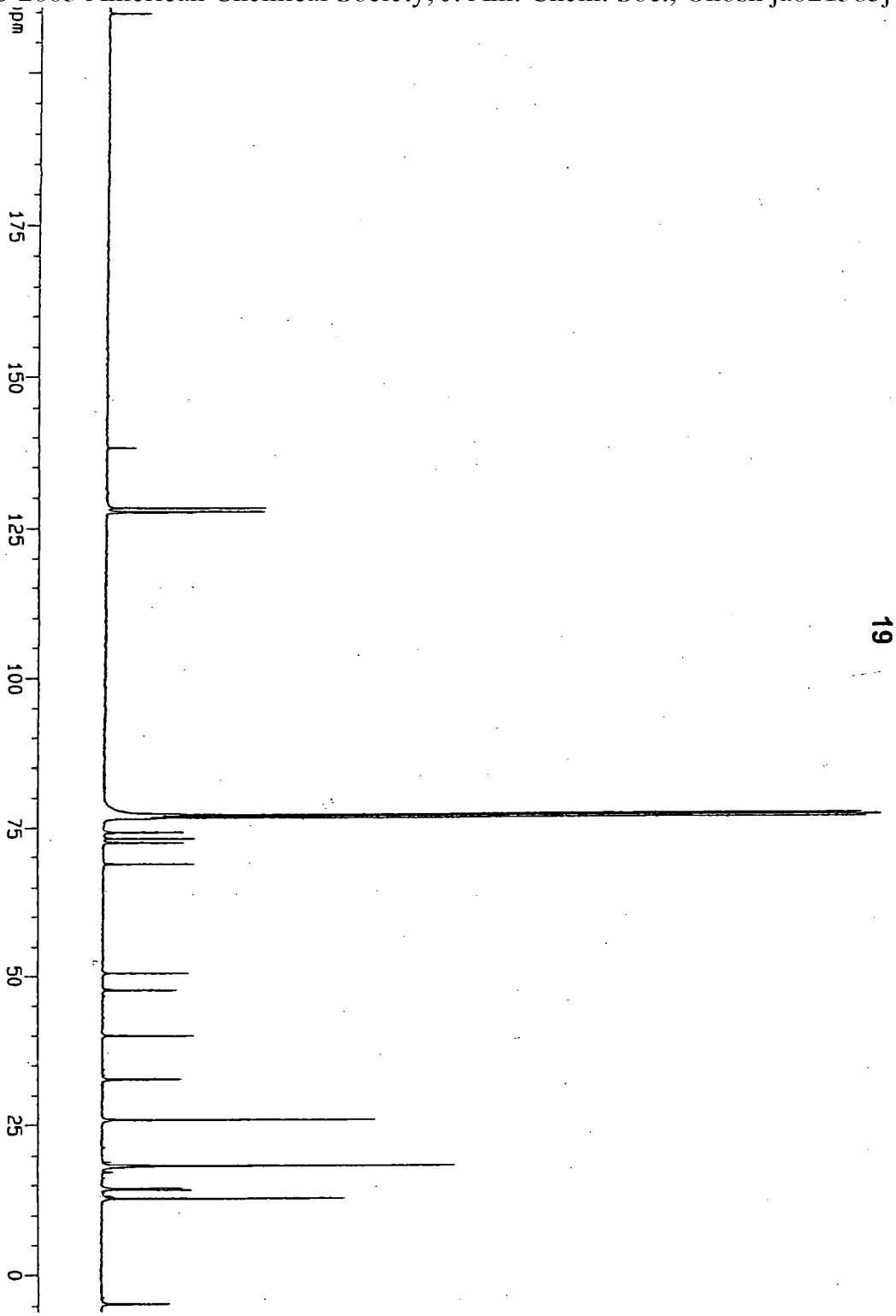
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