Supplementary Material:

Total Synthesis of Antitumor Depsipeptide (-)-Doliculide

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All the moisture sensitive reactions were carried out under nitrogen atmosphere. Anhydrous solvents were obtained as follows: THF, distilled from sodium and benzophenone; dichloromethane, distilled from P_2O_5; pyridine, toluene and benzene, 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. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60-F-254 plates. ^1H and ^{13}C NMR spectra were recorded on Varian 300 (300 MHz), Bruker AM 400 (400 MHz), Avance 400 (400 MHz) and Avance 500 (500 MHz) spectrometers.

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Allylic alcohol 5: To a solution of nitrile **4** (10.7 g, 56 mmol) in CH_2Cl_2 (100 mL) at 0 ^{0}C was added diisobutylaluminum hydride in hexanes (84 mL, 84 mmol) dropwise. After stirring at the same temperature for 30 min, the reaction mixture was quenched with MeOH (2 mL) and Rochelle salts (100 mL), then warmed to 23 °C and stirred for 2 h. The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, concentrated and flash chromatographed to afford the aldehyde (9.17g, 85% yield): $[\alpha]_D^{23}$ -9.1 ^{0} (c 0.66, $CHCl_3$); IR (neat) 3029, 1723, 1494, 1453, 1362, 1096 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 9.76 (t, J=2.3 Hz, 1H), 7.32 (m, 5H), 4.49 (s, 2H), 3.42 (dd, J=4.8, 9.3 Hz, 1H), 3.25 (dd, J=7.6, 8.9 Hz, 1H), 2.56 (m, 1H), 0.99 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 202.4, 138.4, 128.3, 127.5, 74.8, 73.0, 48.4, 29.0, 17.0.

To a mixture of NaH (3.13 g, 78 mmol) in THF (100 mL) at 0 ^{0}C was added triethylphosphonoacetate (17.52 g, 78 mmol) in THF (10 mL) dropwise. The resulting mixture was warmed to 23 °C and stirred for 1 h. The mixture was cooled to 0 ^{0}C, the above aldehyde (7.5 g, 39 mmol) in THF (10 mL) was added dropwise, the mixture was warmed to 23 °C and stirred for 3 h. The reaction was quenched

with saturated aqueous NH_4Cl, extracted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed to afford the ester (8.6 g, 84% yield); $[\alpha]_D^{23}$ +0.6 ^{0} (c 2.44, $CHCl_3$); IR (neat) 3029, 1719, 1653, 1454, 1366, 1314, 1267, 1177, 1098 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 6.94 (tt, J=7.5, 15.2 Hz, 1H), 5.82 (d, J=15.6 Hz, 1H), 4.50 (s, 2H), 4.18 (q, J=7.2 Hz, 2H), 3.31 (dd, J=2.6, 6.2 Hz, 2H), 2.39 (m, 1H), 1.91-2.12 (m, 2H), 1.29 (t, J=6.91 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.5, 147.5, 138.4, 128.3, 127.5, 122.6, 74.8, 73.0, 60.1, 36.3, 33.0, 16.7, 14.2.

To a solution of the above ester (8.6 g, 33 mmol) in CH_2Cl_2 (100 mL) at -40 ^{0}C was added diisobutylaluminum hydride in hexanes (69 mL, 69 mmol) dropwise. After stirring at the same temperature for 30 min, the reaction mixture was quenched with MeOH (2 mL), Rochelle salts (100 mL), then warmed to 23 °C and stirred for 2 h. The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was flash chromatographed to afford the allylic alcohol **5** (6.75 g, 93% yield): $[\alpha]_D^{23}$ +1.0 ^{0} (c

1.0, $CHCl_3$); IR (neat) 3385, 3029, 1495, 1454, 1364, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26-7.34 (m, 5H), 5.64 (m, 2H), 4.50 (s, 2H), 4.07 (d, J=3.8 Hz, 2H), 3.32 (dd, J=6.4, 9.0 Hz, 1H), 3.28 (dd, J=6.2, 9.0 Hz, 1H), 2.21 (m, 1H), 1.91 (m, 2H), 1.47 (br, 1H), 0.93 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.6, 131.0, 130.5, 128.2, 127.5, 127.4, 75.1, 72.9, 63.6, 36.3, 33.4, 16.7; MS (APCI) $[M+H-H_2O]^+$ 203.1.

Dioxaborolane 6: To a solution of (+)-N,N,N',N'-tetramethyltartaric acid diamide (7.42 g, 36 mmol) in anhydrous toluene (50 mL) was added 1-butaneboronic acid (4.8 g, 47 mmol). The mixture was heated under reflux for 18 h (Dean-Stark). The reaction mixture was cooled to 40 ^0C and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, filtered to remove excess 1-butaneboronic acid and concentrated to produce the dioxoborolane **6** (9 g, 92% yield): ^1H NMR ($CDCl_3$) δ 5.46 (s, 2H), 3.13 (s, 6H), 2.92 (s, 6H), 1.23-1.33 (m, 4H), 0.77-0.83 (m, 5h); ^{13}C NMR ($CDCl_3$) δ 168.4, 75.7, 37.1, 36.0, 25.8, 25.2, 13.8, 9.9.

Cyclopropane 7: To a solution of $ZnEt_2$ (8.9 mL, 87 mmol) in CH_2Cl_2 (100 mL) and freshly distilled ethylene glycol dimethyl ether (9.2 mL, 87 mmol) at –15 ^{0}C was added diiodomethane (14 mL, 0.17 mol) at a rate to keep the internal temperature below –10 ^{0}C. The $Zn(CH_2I)_2$•DME complex solution in CH_2Cl_2 so produced was used directly in the next reaction.

To a mixture of dioxoborolane **6** (4.68 g, 17 mmol), allylic alcohol **5** (3.2 g, 15 mmol) and 4Å molecular sieves (800 mg) in CH_2Cl_2 (100 mL) at –15 ^{0}C was added the above prepared solution of $Zn(CH_2I)_2$•DME complex at a rate to keep the internal temperature below –10 ^{0}C. The resulting mixture was stirred at this temperature for 8 h. Saturated aqueous NH_4Cl was added and the layers were separated. The aqueous layer was washed with diethyl ether three times. The combined organic layers were treated with 5 M NaOH and stirred vigorously for 12 h, and the layers were separated. The organic layer was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water, brine and concentrated under reduced pressure. The residue was chromatographed over silica gel to afford the product **7** (3.51 g, 99% yield) of a colorless oil: $[\alpha]_D^{23}$ 16.2 ^{0} (c 0.18, $CHCl_3$);

IR (neat) 3387, 3028, 1495, 1454, 1364, 1095, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5H), 4.51 (s, 2H), 3.37-3.34 (m, 3H), 3.32 (dd, J=6.2, 9.1 Hz, 1H), 2.21 (br, 1H), 1.87-1.95 (m, 1H), 1.37 (m, 1H), 1.20 (m, 1H), 0.99 (d, J=6.8 Hz, 3H), 0.82 (m, 1H), 0.61 (m, 1H), 0.38 (m, 1H), 0.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.6, 128.3, 127.5, 127.4, 75.4, 72.9, 66.8, 37.7, 34.1, 21.0, 17.4, 14.9, 10.3; MS (APCI) $[M+H]^+$ 235.1.

Olefin 8: To triphenylphosphine (3.54 g, 13.47 mmol) in CH_2Cl_2 (40 mL), imidazole (0.92 g, 13.47 mmol) and iodine (3.42 g, 13.47 mmol) were added. After the iodine was completely dissolved, a solution of alcohol **7** (2.63 g, 11.22 mmol) was added and the resulting mixture was stirred at 23 °C for 1 h. After this period, the reaction mixture was concentrated under reduced pressure, diluted with ether and filtered. The filtrate was concentrated and purified by flash chromatography to provide the iodide (3.1 g, 80% yield). The compound was used in the next step without further identification. The iodide (2.8 g, 8 mmol) in anhydrous diethyl ether (80 mL) was cooled to -78 ^{0}C, 4Å molecular sieves (1.4 g), TMEDA (1.85

mL, 16 mmol) and n-BuLi (10 mL, 16 mmol) were added. The resulting mixture was stirred at -78 ^{0}C for 30 min, and water was added. The cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. Ether was then added and the organic layer was successively washed with 10% aqueous HCl (20 mL), saturated aqueous $NaHCO_3$, water and brine. After concentration under reduced pressure, the residue was chromatographed over silica gel to afford the product **8** (1.6 g, 90% yield): $[\alpha]_D^{23}$ -4.6 ^{0} (c 1.3, $CHCl_3$); IR (neat) 3030, 1641, 1495, 1454, 1363, 1098 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.56-5.64 (m, 1H), 4.95 (m, 2H), 4.50 (s, 2H), 3.29-3.32 (dd, J=6.0, 9.0 Hz, 1H), 3.22-3.26 (dd, J=6.7, 9.0 Hz, 1H), 2.24 (m, 1H), 1.82 (m, 1H), 1.37-1.44 (m, 1H), 1.06-1.09 (m, 1H), 0.98 (d, J=6.5 Hz, 3H), 0.93 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.4, 138.8, 128.2, 127.4, 127.3, 112.7, 76.2, 72.8, 40.7, 35.4, 31.0, 21.3, 16.9; MS (EI) M^+ 218, HRMS (EI) Calcd for $C_{15}H_{22}O$ 218.1671, Found 218.1662.

Cyclopropane derivative 9: A solution of **8** (1.76 g, 8.1 mmol) in THF (20 mL) was allowed to react with 9-BBN (40.4 mL, 20.2 mmol) at 23 ^{0}C for 10 h. The

reaction mixture was cooled to 0 ^{0}C and quenched with 3 M NaOH (8.07 mL, 24.2 mmol) and 30% H_2O_2 (8.1 mL, 76 mmol). The resulting mixture was stirred at 0 ^{0}C for 1 h and then diluted with diethyl ether (100 mL). The organic layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give the alcohol (1.52 g, 80% yield).

To a solution of oxalyl chloride (1.4 g, 10.9 mmol) in CH_2Cl_2 (10mL) was added DMSO (0.85 g, 10.9 mmol) at –78 ^{0}C. After 5 min, alcohol (1.72 g, 7.3 mmol) in CH_2Cl_2 (10 mL) was added to the solution and stirred at –78 ^{0}C for 45 min. To the reaction mixture triethylamine (2.2 g, 21.9 mmol) was added and the resulting mixture was stirred at the same temperature for 45 min, then 23 ^{0}C for 30 min. Saturated aqueous NH_4Cl was added to the mixture and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude aldehyde was used in the next reaction without further purification.

The ester was obtained in the same Horner-Emmons olefination as that described for **5** as a colorless oil (1.77 g, 80% overall yield in two steps).

The allylic alcohol was obtained using the same Dibal-H reduction as that described for **5** as a colorless oil (1.38 g, 90% yield) from the above ester (1.77 g, 5.86 mmol).

Cyclopropane **9** was obtained in the same manner as that described for **5** as an oil (1.2 g, 96% yield) from the above alcohol (1.2 g, 4.55 mmol): de 91% (by ^{1}H NMR and ^{13}C NMR); $[\alpha]_D^{23}$ 12.0 ^{0} (c 5.5, $CHCl_3$); IR (neat) 3383, 3028, 1455, 1374, 1099, 1030 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 4.50 (AB, J=12.3, 16.5 Hz, 2H), 3.42 (dd, J=5.6, 11.4 Hz, 2H), 3.31-3.35 (dd, J=5.3, 9.1 Hz, 1H), 3.22-3.26 (dd, J=6.9, 9.1 Hz, 1H), 1.80-1.86 (m, 1H), 1.58-1.64 (m, 2H), 1.41-1.50 (m, 2H), 1.12-1.16 (m, 2H), 0.94 (m, 6H), 0.75-0.78 (m, 1H). 0.58-0.62 (m, 1H), 0.35-0.40 (m, 1H), 0.27-0.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.7, 128.2, 127.5, 127.4, 75.8, 72.9, 67.0, 41.1, 40.6, 31.0, 30.9, 21.1, 20.6, 18.0, 15.1, 10.3; MS (APCI) $[M+H]^+$ 277.1.

Olefin derivative 10 : Olefin **10** was obtained in the same manner as that described for **8** as a colorless oil (1.66 g, 74% overall yield in two steps) from **9** (2.4 g, 8.7 mmol): $[\alpha]_D^{23}$ -4.7 ^{0} (c 1.3, $CHCl_3$); IR (neat) 3029, 1640, 1495, 1455, 1374, 1101 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.56-5.64 (m, 1H), 4.88-4.98 (m, 1H), 4.50 (AB, J=12.1, 16.6 Hz, 2H), 3.31-3.34 (dd, J=5.3, 9.1 Hz, 1H), 3.18-3.22 (dd, J=7.0, 9.0 Hz, 1H), 2.18-2.27 (m, 1H), 1.82-1.90 (m, 1H), 1.51-1.56 (m, 1H), 1.24-1.33 (m, 4H), 0.96 (d, J=6.7 Hz, 3H), 0.92 (d, J=6.7 Hz, 3H). 0.86 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.7, 138.9, 128.3, 127.5, 127.4, 112.7, 76.2, 73.0, 44.2, 42.2, 35.7, 30.9, 27.7, 21.6, 20.3, 18.0; HRMS (EI) Calcd for $C_{18}H_{28}O$ 260.2140, Found 260.2146.

Allylic alcohol 11: Olefin **10** (900 mg, 3.44 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to –78 ^{0}C. Ozone was passed through the solution until a faint blue color appeared. Triphenylphosphine (948 mg, 3.61 mmol) in dry CH_2Cl_2 (10 mL) was added at –78 ^{0}C, then slowly warmed to 23 ^{0}C and stirred for 4 h. The

reaction mixture was concentrated, diluted by 5% ethyl acetate/hexanes and filtered. After removing the solvent, the crude product was used in the same Horner-Emmons olefination as that described for **5** to give the ester (747 mg, 65% overall yield in two steps).

Allylic alcohol **11** was obtained in the same Dibal-H reduction as that described for **5** as an oil (582 mg, 90% yield) from the above ester (740 mg, 2.23 mmol): $[\alpha]_D^{23}$ -8.2 ^{0} (c 1.5, $CHCl_3$); IR (neat) 3357, 3028, 1602, 1454, 1374, 1094 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.56-5.62 (tt, J=5.9, 9.4 Hz, 1H), 5.44-5.50 (dd, J=8.1, 15.3 Hz, 1H), 4.50 (AB, J=12.2, 15.0 Hz, 2H), 4.07 (t, J=5.8 Hz, 2H), 3.30-3.34 (dd, J=5.3, 9.0 Hz, 1H), 3.18-3.22 (dd, J=6.7, 9.0 Hz, 1H), 2.25 (m, 1H), 1.85 (m, 1H), 1.50 (m, 1H), 1.24-1.33 (m, 3H), 0.99 (m, 1H), 0.96 (d, J=6.9 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H), 0.85 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 139.0, 138.3, 128.3, 127.5, 127.4, 76.1, 73.0, 63.9, 44.2, 42.0, 34.1, 30.9, 27.7, 21.6, 20.3, 17.9, MS (ESI) $[M+H-H_2O]^+$ 273.0.

Epoxide 12: To a flask charged with 4Å molecular sieves (400 mg) in CH_2Cl_2 (20 mL) at –23 ^{0}C were added (-)-DET (127.8 mg, 0.62 mmol) and $Ti(O^iPr)_4$ (146.7 mg, 0.52 mmol). The resulting mixture was continued to stir at –23 °C. After 5 min, TBHP (1.29 mL, 6.45 mmol) was added dropwise. The mixture was stirred at –23 ^{0}C for 30 min. Allylic alcohol **11** (748.4 mg, 2.58 mmol) in CH_2Cl_2 (5 mL) was then added dropwise and the resulting mixture was kept at –23 ^{0}C for 20 h. The reaction mixture was quenched with 15% aqueous NaOH saturated with NaCl. The mixture was warmed to 0 ^{0}C and stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel to afford the product **12** (0.7 g, 90% yield) as a colorless oil: $[\alpha]_D^{23}$ 16.2 ^{0} (c 1.9, $CHCl_3$); IR (neat) 3438, 1525, 1454, 1215, 1098 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 4.50 (AB, J=12.0, 15.9 Hz, 2H), 3.81-3.86 (dd, J=2.5, 12.4 Hz, 1H), 3.50-3.56 (dd, J=4.8, 12.4 Hz, 1H), 3.28-3.33 (dd, J=5.4, 9.0 Hz, 1H), 3.15-3.21 (dd, J=6.9, 9.0 Hz, 1H), 2.83-2.86 (m, J=2.4 Hz, 1H), 2.65-2.68 (dd, J=2.4, 7.2 Hz,

1H), 1.90-1.97 (m, 2H), 1.85 (m, 1H), 1.13-1.28 (m, 4H), 1.05 (m, 1H), 0.92 (d, J=6.6 Hz, 3H), 0.87 (d, J=5.6 Hz, 3H), 0.85 (d, J=4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 75.9, 73.0, 62.0, 60.9, 56.6, 42.9, 41.6, 32.8, 30.9, 27.8, 20.9, 18.2, 16.8; MS (APCI) $[M+H]^+$ 307.1

Ethyl ester 13: Alcohol **12** (0.584 g, 1.91 mmol) was oxidized in the same Swern oxidation as that described for **9** to give the crude aldehyde, which was not further purified and treated with carbethoxylidenetriphenylphosphorane (1.11 g, 3.05 mmol) at 80 ^{0}C for 15 h. Most of the solvent was removed and diluted with 5% ethyl acetate/hexanes. The precipitate was filtered off and thoroughly washed with 5% ethyl acetate/hexanes. The filtrate was concentrated and the residue was purified to give the product **13** (0.6 g, 81% overall yield in two steps): $[\alpha]_D^{23}$ 11.8 ^{0} (c 1.2, $CHCl_3$); IR (neat) 1713, 1558, 1455, 1367, 1245, 1101 cm $^{-1}$; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H), 6.34 (dd, J=1.3, 8.7 Hz, 1H), 4.52 (AB, J=12.1, 18 Hz, 2H), 4.22 (q, J=7.1 Hz, 2H), 3.36-3.39 (m, 2H), 3.25 (dd, J=6.9, 9.0 Hz, 1H), 2.74 (dd, J=2.0, 7.4 Hz, 1H), 2.02 (d, J=1.2 Hz, 3H), 1.90 (m, 1H), 1.77 (m, 1H), 1.50-

1.60 (m, 2H), 1.35-1.40 (m, 1H), 1.31 (t, J=7.1 Hz, 3H), 1.10-1.15 (m, 1H), 1.03 (m, 1H), 0.99 (d, J=6.7 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.94 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.6, 139.2, 138.7, 132.4, 128.7, 127.9, 127.8, 76.2, 73.4, 65.6, 61.2, 53.2, 43.2, 42.0, 33.8, 31.4, 28.2, 21.3, 18.5, 17.3, 14.6, 13.2; HRMS (EI) Calcd for $C_{24}H_{36}O_4$ 388.2614, Found 388.2582.

Alcohol 14: To a mixture of $Pd_2(dba)_3 \bullet CHCl_3$ (77.3 mg, 0.075 mmol) in dioxane (5 mL) were added n-Bu_3P (22.4 μl, 0.09 mmol), a solution of formic acid (413 mg, 9 mmol) and triethylamine (302 mg, 3 mmol) in dioxane (2 mL) at 23 °C. The resulting mixture was stirred for 5 min. The alkenyloxirane **13** (580 mg, 1.5 mmol) in dioxane (5 mL) was added to the solution, and the mixture was stirred for 10 h. The solution was passed over a short pad of silica gel, and the filtrate was concentrated. The residue was purified over flash silica gel to give the product **14** (524.7 mg, 90% yield): $[\alpha]_D^{23}$ 1.0 ^{0} (c 0.98, $CHCl_3$); IR (neat) 3483, 1708, 1454, 1367, 1278, 1251, 1097 cm $^{-1}$; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H), 6.87 (td, J=1.3, 7.4 Hz, 1H), 4.52 (AB, J=12.1, 17.5 Hz, 2H), 4.21 (q, J=7.1 Hz, 2H), 3.63 (m, 1H),

3.38 (dd, J=4.9, 9.0 Hz, 1H), 3.24 (dd, J=6.9, 9.0 Hz, 1H), 2.32 (t, J=6.9 Hz, 2H), 1.88 (d, J=0.8 Hz, 3H), 1.73 (m, 1H), 1.67 (s,, 1H), 1.6 (m, 1H), 1.52 (m, 1H), 1.33-1.42 (m, 2H), 1.32 (t, J=7.1 Hz, 3H), 0.98 (d, J=7.2 Hz, 3H), 0.94 (t, J=5.9, 6.4 Hz, 6H), 0.85-0.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.4, 139.2, 139.2, 130.3, 128.7, 127.9, 127.8, 76.0, 75.4, 73.4, 61.0, 41.5, 40.7, 36.6, 33.0, 31.4, 28.4, 21.7, 19.1, 16.1, 14.7, 13.1; MS (APCI) $[M+H]^+$ 391.1.

Epoxide 15: To a solution of **14** (240 mg, 0.61 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (0.26mL, 1.84 mmol) and *tert* -butyldimethylsilyl triflate (0.25 mL, 1.1 mmol) at 0 ^0C. After 15 min, the reaction was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give a yellow oil, which without further purification, was reduced by Dibal-H as described for **5** to give the corresponding allylic alcohol (0.23 g, 80% overall yield in two steps).

The epoxide **15** was obtained in the same manner as that described for **12** as a colorless oil (151 mg, 91% yield) from the above allylic alcohol (160 mg, 0.36

mmol) and (+)-DET: $[\alpha]_D^{23}$ -25.6 ^{0} (c1.3, $CHCl_3$); IR (neat) 3455, 1461, 1379, 1254, 1070 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 4.50 (AB, J=12.1, 14.5 Hz, 2H), 3.82 (tt, J=3.2, 9.8 Hz, 1H), 3.68 (dd, J=4.1, 12.2 Hz, 1H), 3.55 (dd, J=8.3, 12.2 Hz, 1H), 3.33 (dd, J=5.3, 8.9 Hz, 1H), 3.17-3.24 (m, 2H), 1.80-1.87 (m, 3H), 1.63-1.66(m, 1H), 1.55-1.56 (m, 1H), 1.42-1.47 (m, 1H), 1.32 (s, 3H), 1.18-1.32 (m, 1H), 0.95 (d, J=5.7 Hz, 3H), 0.86 (d, J=6.7 Hz, 3H), 0.90 (s, 9H), 0.86-0.96 (m, 5H), 0.07 (d, J=2.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 138.2, 128.3, 127.4, 127.4, 76.0, 73.0, 72.8, 65.3, 61.3, 58.3, 41.7, 40.9, 36.3, 31.0, 29.7, 27.7, 25.9, 21.2, 18.3, 18.1, 14.6, 14.4; MS (ESI) $[M+H]^+$ 479.1.

TBS ether 16: To the epoxy alcohol **15** (351 mg, 0.73 mmol) in CH_2Cl_2 (10 mL) at –78 ^{0}C were added triethylamine (0.51 mL, 3.5 mmol), methanesulfonic chloride (0.17 mL, 2.2 mmol) and DMAP (9 mg, 0.073 mmol). The resulting mixture was warmed to 0 ^{0}C and stirred for 2 h. The reaction was quenched with water, diluted with diethyl ether (50 mL), washed with 10% aqueous $CuSO_4$ and brine. The

organic layer was separated, dried over anhydrous Na_2SO_4, concentrated to give a yellow residue which was used in the next step without further identification.

To the above crude mesylate in butanone (20 mL) were added NaI (1.1 g, 7.3 mmol) and 2 drops of diisopropylethylamine. The mixture was heated at 85 ^{0}C for 15 h. The solvent was removed, the residue was redissolved in ethyl acetate, washed with water, 10% aqueous $Na_2S_2O_3$, water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give a yellow oil. The crude iodide was used directly in the next step without further purification.

16 was obtained in the same manner as that described for opening cyclopropane (from **7** to **8**) as a colorless oil (285 mg, 84% overall yield in three steps): $[\alpha]_D^{23}$ -13 ^{0} (c 2.0, $CHCl_3$); IR (neat) 3472, 1650, 1496, 1461, 1377, 1254, 1076 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 4.99 (d, J=1.0 Hz, 1H), 4.81 (s, 1H), 4.50 (AB, J=12.1, 14.1 Hz, 2H), 4.23 (d, J=9.5 Hz, 1H), 3.86 (m, 1H), 3.68 (dd, J=4.1, 12.2 Hz, 1H), 3.35 (dd, J=5.1, 9.0 Hz, 1H), 3.20 (dd, J=7.0, 8.9 Hz, 1H), 2.27 (d, J=3.4 Hz, 1H), 1.78-1.90 (m, 2H), 1.71 (s, 3H), 1.55-1.63 (m, 3H), 1.41-1.48 (m, 1H), 1.31-1.38 (m, 1H), 1.22-1.29 (m, 2H), 0.96 (d, J=6.6 Hz, 3H), 0.84 (d, J=6.7 Hz,

3H), 0.91 (s, 9H), 0.89-0.92 (m, 3H), 0.09 (d, J=8.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 148.9, 139.3, 128.7, 127.9, 127.8, 110.0, 76.3, 73.4, 73.1, 72.7, 42.0, 41.8, 36.8, 36.2, 31.4, 28.1, 26.3, 21.7, 18.8, 18.5, 14.8, -3.8, -4.2; MS (ESI) $[M+H]^+$ 463.0.

Polyketide fragment 2 : The mixture of alkene **16** (210 mg, 0.45 mmol) in THF (15 mL) and Pd/C (10%, 30 mg) was treated with H_2 at 23 °C for 6 h. The reaction mixture was then filtered over a short pad of Celite and the filtrate was purified to give diol (143 mg, 84%) as a colorless oil.

To the above diol (143 mg, 0.38 mmol) in CH_2Cl_2 (10 mL), 4Å molecular sieves (200 mg), NMO (42 mg, 0.36 mmol) and TPAP (10.7 mg, 0.03 mmol) were added. After stirring at 23 °C for 1 h, the reaction mixture was passed over a short silica gel column and eluted with 5% and 12% ethyl acetate/hexanes, successively. The fractions containing the aldehyde were concentrated to give a yellow oil (105 mg), which was dissolved in a mixture (5:1) of t-BuOH and water (10 mL). To the resulting solution were added 2-methyl-2-butene (0.3 mL, 2.8 mmol), $NaClO_2$ (152.5 mg, 1.7 mmol) and NaH_2PO_4 (77.6 mg, 0.56 mmol). After stirring

overnight at 23 °C, the reaction mixture was quenched by phosphate buffer solution (pH 3.5, 10 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude acid, which was used in the next reaction without further purification.

To a solution of the above acid in *t*-BuOH (5 mL) were added BOC_2O (122.7 mg, 0.56 mmol) and DMAP (10.3 mg, 0.084 mmol). The resulting solution was stirred at 30^{0}C for 15 h. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to provide **2** (96.6 mg, 51% overall yield in 4 steps) as a colorless oil: $[\alpha]_D^{23}$ 6.4 ^{0} (c 0.7, $CHCl_3$); IR (neat) 3521, 1730, 1462, 1368, 1255, 1152, 1070 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 3.76 (m, 1H), 3.61 (m, 1H), 2.44 (m, 1H), 1.84 (m, 1H), 1.69-1.75 (m, 1H), 1.55-1.65 (m, 3H), 1.44 (s, 10H), 1.26-1.40 (m, 2H), 1.10 (d, J=8.2 Hz, 3H), 0.89-0.96 (m, 21H), 0.82 (d, J=8.5 Hz, 3H), 0.083 (d, J=11.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 176.8, 80.17, 74.6, 73.8, 42.2, 41.3, 38.9, 35.7, 35.2, 34.5, 28.7, 28.5, 26.3, 21.1, 19.0, 18.9, 18.4, 18.2, 14.9, -4.0, -4.0.

Tyrosine derivative 18: To the ester **17** (2.3 g, 5.46 mmol) in DMF (30 mL) at 0^0C, imidazole (1.12 g, 16.4 mmol) and triisopropylchlorosilane (1.37 g, 7.1 mmol) were added. The solution was then warmed to 23 °C and stirred for 2 h. The reaction mixture was diluted with Et_2O (100 mL) and washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by flash chromatography to give the corresponding TIPS ether (3.1 g, 98%): $[\alpha]_D^{23}$ 35.1 ^{0} (c 9.6, $CHCl_3$); IR (neat) 3372, 1745, 1719, 1597, 1487, 1390, 1366, 1287, 1169, 1016 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1H), 6.96 (dd, J=2.0, 8.3 Hz, 1H), 6.76 (d, J=8.3 Hz, 1H), 5.02 (d, J=8.0 Hz, 1H), 4.53 (dd, J=6.2, 13.8 Hz, 1H), 3.72 (s, 3H), 3.00-3.04 (dd, J=5.8, 13.9 Hz, 1H), 2.91-2.95 (dd, J=6.2, 13.9 Hz, 1H), 1.45 (s, 9H), 1.31-1.36 (m, 3H), 1.14 (d, J=7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 172.6, 155.4, 155.0, 140.6, 130.5, 130.4, 118.3, 90.7, 80.4, 54.9, 52.6, 37.4, 28.7, 18.5, 13.5.

To the above ester (2.86 g, 4.95 mmol) in a mixture (10:1) of THF and DMF (44 mL), MeI (1.4 mL, 24.8 mmol) and NaH (0.23 g, 5.7 mmol) were added. The solution was heated at 60 ^{0}C for 20 h. After this period, the mixture was cooled

and then diluted with Et_2O. The solution was washed with saturated aqueous NH_4Cl, 20% aqueous $Na_2S_2O_3$ and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give the product **18** (2.93 g) which was used in the next reaction without further purification.

Diepetide 19:

To a stirred solution of the above **18** in CH_2Cl_2 (20 mL) at 0 ^{0}C, TFA (7.7 mL) was added. The solution was warmed to 23 °C and stirred for 3 h. The reaction mixture was washed with 5% $NaHCO_3$ and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by flash chromatography to give the corresponding amine (1.22 g, 50% yield from **17**).

To the above amine (0.6 g, 1.22 mmol) and BOC-Glycine (0.3 g, 1.71 mmol) in DMF at 0 ^{0}C were added EDC (0.33 g, 1.71 mmol) and HOBT (0.26 g, 1.95 mmol). The resulting solution was warmed to 23 °C and stirred for 20 h. The solution was quenched with saturated aqueous NH_4Cl, diluted with ethyl acetate,

washed with 5% HCl, 5% $NaHCO_3$ and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give a solid which was purified by flash chromatography to give the dipeptide **19** (0.71 g, 90% yield): $[\alpha]_D^{23}$ 15.9 ^{0} (c 2.0, $CHCl_3$); IR (neat) 3421, 1742, 1716, 1661, 1487, 1285, 1170 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J=1.8 Hz, 1H), 6.96 (dd, J=2.1, 8.4 Hz, 1H), 6.74 (d, J=7.8 Hz, 1H), 5.41 (br, 1H), 5.10 (dd, J=5.4, 10.5 Hz, 1H), 3.93 (dd, J=3.9, 17.1 Hz, 1H), 3.76 (dd-like, J=3.9, 18.3 Hz, 1H), 3.72 (s, 3H), 3.24 (dd, J=5.7, 14.4 Hz, 1H), 2.92 (dd, J=11.2, 14.0 Hz, 1H), 2.77 (s, 3H), 1.43 (s, 9H), 1.24-1.36 (m, 3H), 1.11 (d, J=6.9 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 170.6, 169.0, 155.5, 154.4, 139.6, 130.7, 129.4, 118.2, 118.0, 90.2, 79.5, 58.9, 52.3, 42.3, 33.2, 31.9, 28.3, 18.0, 12.9; MS (ESI) $[M+H]^+$ 648.7.

***t*-Butyl ester 20:** To the dipeptide **19** (0.23 g, 0.35 mmol) in a mixture (2:1) of THF and H_2O (12 mL) was added LiOH (36.6 mg, 0.87 mmol) at 0 ^{0}C. The resulting mixture was stirred for 1 h and then acidified to pH 3.5 with aqueous $NaHSO_4$ solution. The mixture was extracted with Et_2O (2 x 25 mL). The

combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give the crude acid which was used in the next reaction without further purification.

To the stirred solution of above acid (160 mg, 0.26 mmol) and the alcohol **2** (30 mg. 0.07 mmol) in CH_2Cl_2 (20 mL) at -20 ^{0}C, DCC (64.3 mg, 0.31 mmol) and DMAP (9.9 mg, 0.08 mmol) were added. The resulting mixture was stirred at the same temperature for 20 h. After this period, the mixture was filtered over a short silica gel column and eluted with 10% EtOAc/Hexanes. The organic solution was concentrated and purified by flash chromatography to give the ester **20** (70 mg, 98%) as an oil: $[\alpha]_D^{23}$ 3.1 ^{0} (c 1.1, $CHCl_3$); IR (neat) 3424, 1725, 1663, 1487, 1463, 1366, 1285, 1252, 1169, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J=2.1 Hz, 1H), 7.0 (dd, J=2.1, 8.2 Hz, 1H), 6.73 (d, J=8.2 Hz, 1H), 5.45 (br, 1H), 5.17 (br, 1H), 4.93 (m, 1H), 3.87 (dd, J=3.6, 17.2 Hz, 1H), 3.78 (dd, J=3.9, 17.3 Hz, 1H), 3.49 (m, 1H), 3.26 (dd, J=5.2, 14.7 Hz, 1H), 2.92 (dd, J=10.8, 14.9 Hz, 1H), 2.79 (s, 3H), 2.40 (m, 1H), 1.88-1.93 (m, 1H), 1.62-1.70 (m, 2H), 1.43 (s, 19H), 1.29 (m, 4H), 1.10 (m, 23H), 0.79-0.92 (m, 24H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 176.6, 170.3,

169.2, 156.0, 154.8, 140.0, 131.4, 129.8, 118.5, 90.7, 80.1, 79.9, 79.1, 78.4, 72.9, 59.3, 42.8, 41.6, 41.4, 38.8, 36.6, 33.6, 32.5, 32.1, 28.9, 28.8, 28.5, 26.3, 21.1, 18.9, 18.5, 18.1, 17.9, 13.9, 13.5, -3.6, -4.4.

Cycloamide 21: To a stirred solution of the ester **20** (45 mg, 0.042 mmol) in CH_2Cl_2 (1 mL) at 0 °C, TFA (1 mL) was added. The resulting mixture was stirred at 0°C to 23°C for 3 h. After this period, the yellow solution was concentrated and azeotropically dried with benzene to give the crude amino acid.

To the above crude amino acid in CH_2Cl_2 (90 mL) at 0 ^{0}C were added BOP reagent (90 mg, 0.2 mmol) and DMAP (45 mg, 0.37 mmol). The solution was stirred at 0 ^{0}C for 4 h, then allowed to warm to 23 °C and stirred for 20 h. The reaction mixture was washed with dilute HCl and brine. The organic layers were dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by flash chromatography to provide cycloamide **21** (25.4 mg, 82% yield) and trifluoroacetate derivative **22** (3.5 mg, 10% yield). Compound **22** (crude) was redissolved in methanol (1 mL) and treated with aqueous ammonia (2 drops) and

stirred at 23 °C for 1 h. The solvent was removed and the residue was purified by chromatography to give **21** (2.7 mg, 88% yield): $[\alpha]_D^{23}$ -33.9 ^{0} (c 0.3, $CHCl_3$); IR (neat) 3352, 1727, 1652, 1487, 1463, 1286, 1254, 1037 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J=2.1 Hz, 1H), 7.02 (dd, J=2.3, 8.4 Hz, 1H), 6.77 (d, J=8.3 Hz, 1H), 6.18 (d, J=8.3 Hz, 1H), 5.44 (dd, J=4.4, 12.4 Hz, 1H), 5.06 (dd,dd, J=1.8, 5.2, 2.0, 5.2 Hz, 1H), 4.80 (dd, J=8.8, 16.9 Hz, 1H), 3.59 (dd J=13.6 Hz, 1H), 3.45 (dd, J=4.4, 15.5 Hz, 1H), 3.30 (dd, J=1.5, 16.9 Hz, 1H), 2.94 (s, 3H), 2.89 (dd, J=12.5, 15.5 Hz, 1H), 2.80-2.93 (m, 1H), 2.43 (m, 1H), 2.06 (m, 1H), 1.88 (m, 1H), 1.43-1.56 (m, 3H), 1.28-1.39 (m, 7H), 1.14 (d, J=7.5 Hz, 24H), 1.03-1.12 (m, 4H), 0.99 (d, J=5.6 Hz, 3H), 0.98 (d-like, J=1.2 Hz, 3H), 0.96 (d-like, J=1.3 Hz, 3H), 0.86 (d, J=8.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.1, 172.4, 172.0, 155.0, 139.5, 130.8, 129.2, 118.6, 90.9, 66.0, 58.6, 45.4, 43.4, 40.2, 39.6, 34.7, 33.2, 31.1, 30.8, 27.4, 19.4, 18.7, 18.5, 18.4, 18.1, 14.8, 13.5.

Doliculide 1: To the TIPS ether **21** (20 mg, 0.027 mmol) in THF (1 mL) at 0 ^{0}C was added TBAF (41 μL, 0.041 mmol). The resulting mixture was stirred for 15

min. After this period, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by flash chromatography to provide synthetic **1** (16.5 mg, 98%): mp 173-174 ^{0}C; $[\alpha]_D^{23}$ -25.4 ^{0} (c 0.28, MeOH); IR (neat) 3395, 3324, 1729, 1644, 1506, 1459, 1416, 1290, 1256, 1035, 998 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J=2.0 Hz, 1H), 7.09 (dd, J=2.0, 8.3 Hz, 1H), 6.90 (d, J=8.3 Hz, 1H), 6.25 (d, J=8.7 Hz, 1H), 6.06 (br s, 1H), 5.50 (dd, J=4.4, 12.4 Hz, 1H), 5.07 (dd,dd, J=1.7, 5.1 Hz, 1H), 4.82 (dd, J=8.9, 16.9 Hz, 1H), 3.60 (dd, J=11.3 Hz, 1H), 3.47 (dd, J=4.4, 15.7 Hz, 1H), 3.28 (dd, J=1.8, 16.8 Hz, 1H), 2.97 (s, 3H), 2.90 (dd, J=12.4, 15.5 Hz, 1H), 2.45 (m, 1H), 2.05 (m, 1H), 1.89 (m, 1H), 1.72 (br s, 1H), 1.46 (t, J=12.4 Hz, 1H), 1.44 (ddd, J=1.9, 11.8, 13.9 Hz, 1H), 1.31 (ddd, J=2.4, 11.8, 13.9 Hz, 1H), 1.19 (m, 1H), 1.15 (d, J=6.6 Hz, 3H), 1.03-1.11 (m, 3H), 0.99 (d, J=6.3 Hz, 3H), 0.97 (d, J=7.2 Hz, 6H), 0.86 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.2, 172.3, 172.1, 154.5, 138.3, 130.8, 130.1, 115.6, 86.0,

77.8, 66.1, 58.5, 45.4, 43.5, 40.1, 39.6, 34.7, 33.2, 32.8, 31.2, 30.6, 27.4, 19.3, 18.8, 18.5, 18.1, 14.8; MS (EI) (M^+) 616.

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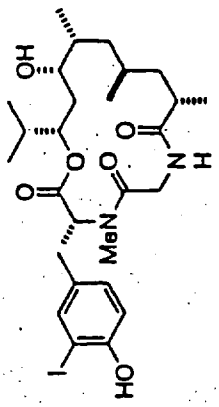
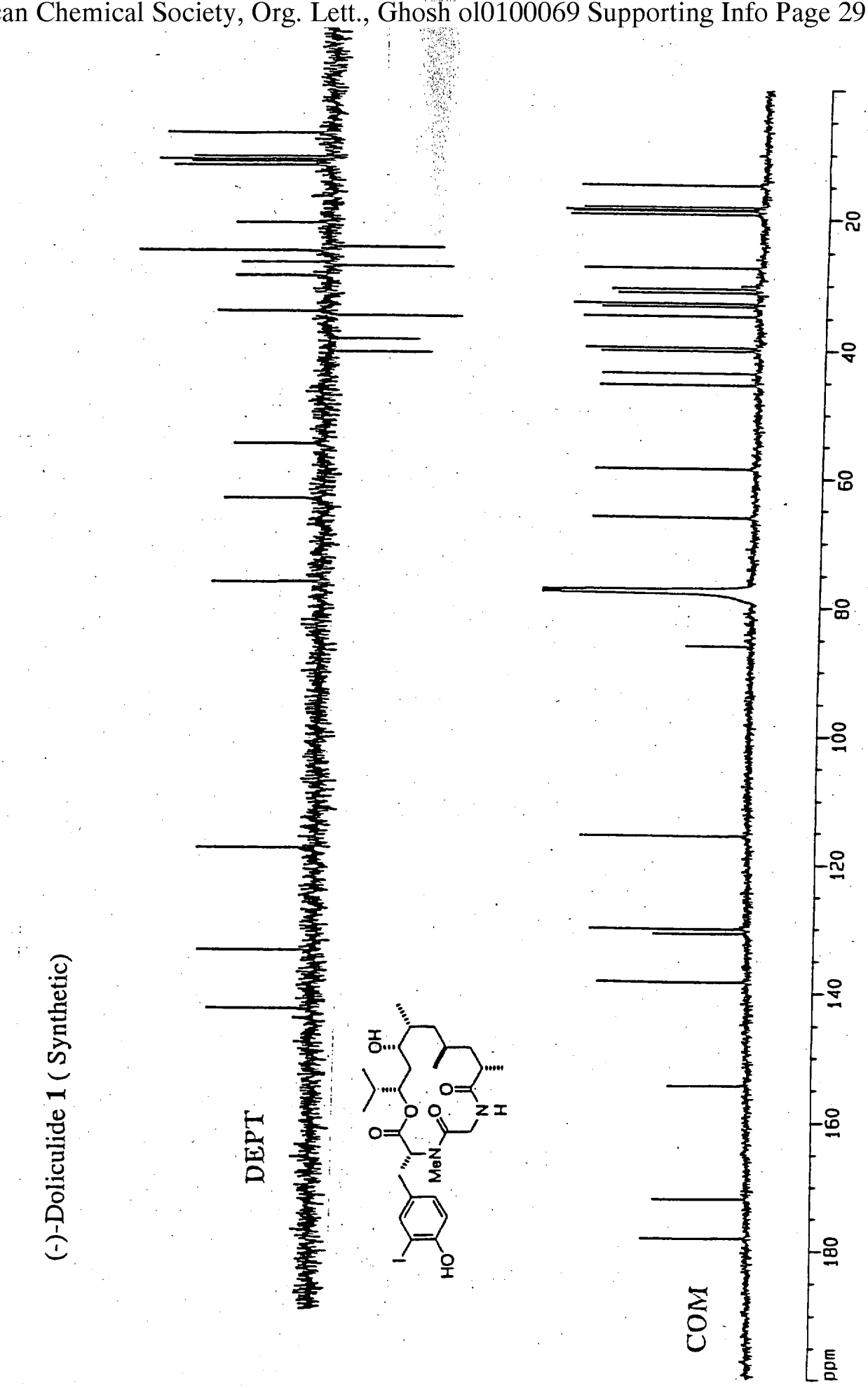
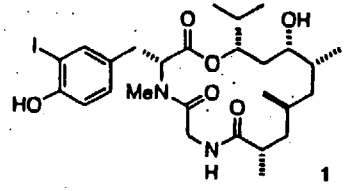




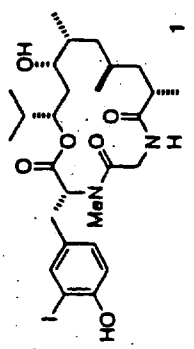
(-)-Doliculide (Natural Product) (Ref. Spectrum)



1

From: Ishiwata, H.; Nemoto, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4710.

(-)-Doliculide (Natural Product) (Ref. Spectrum)



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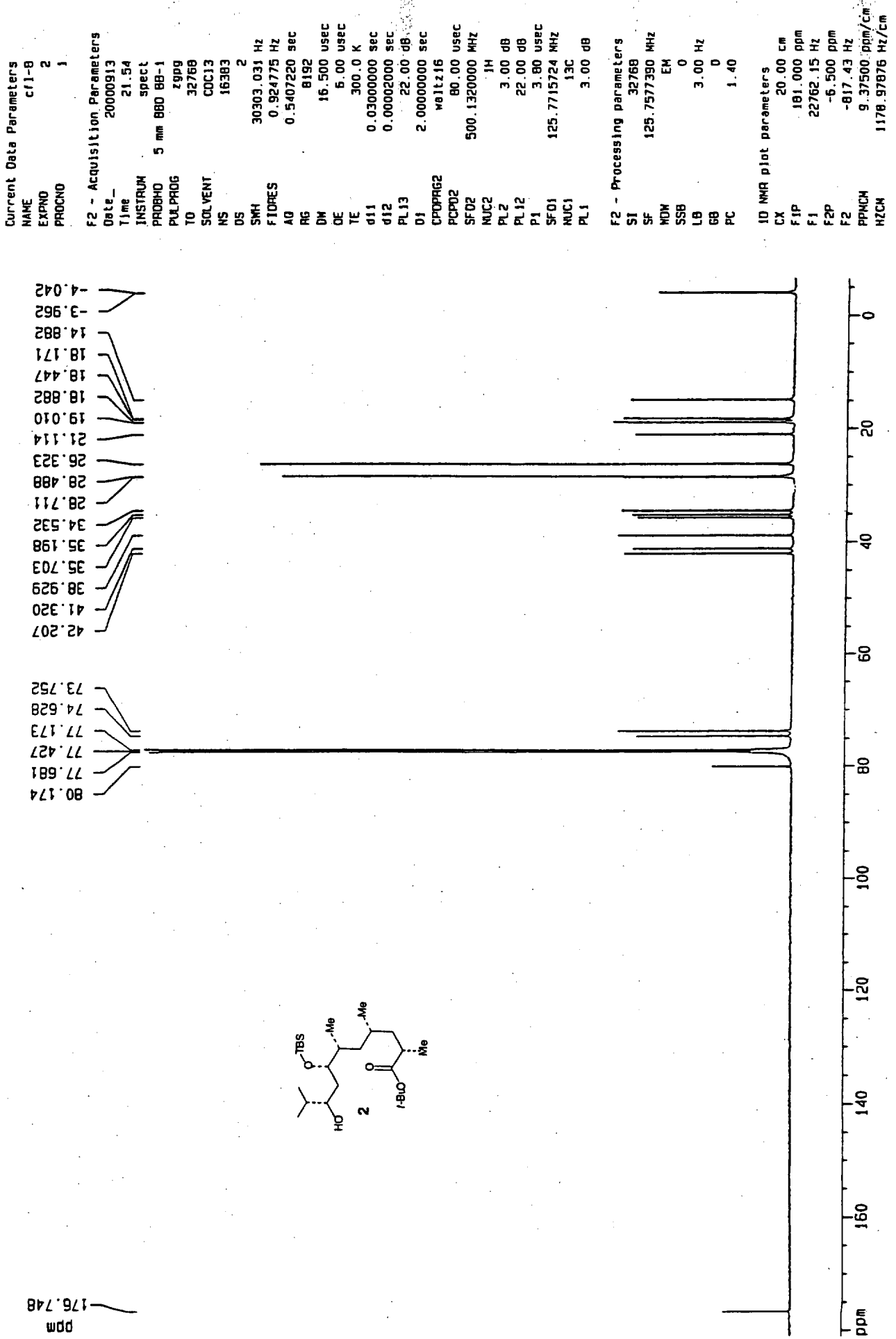
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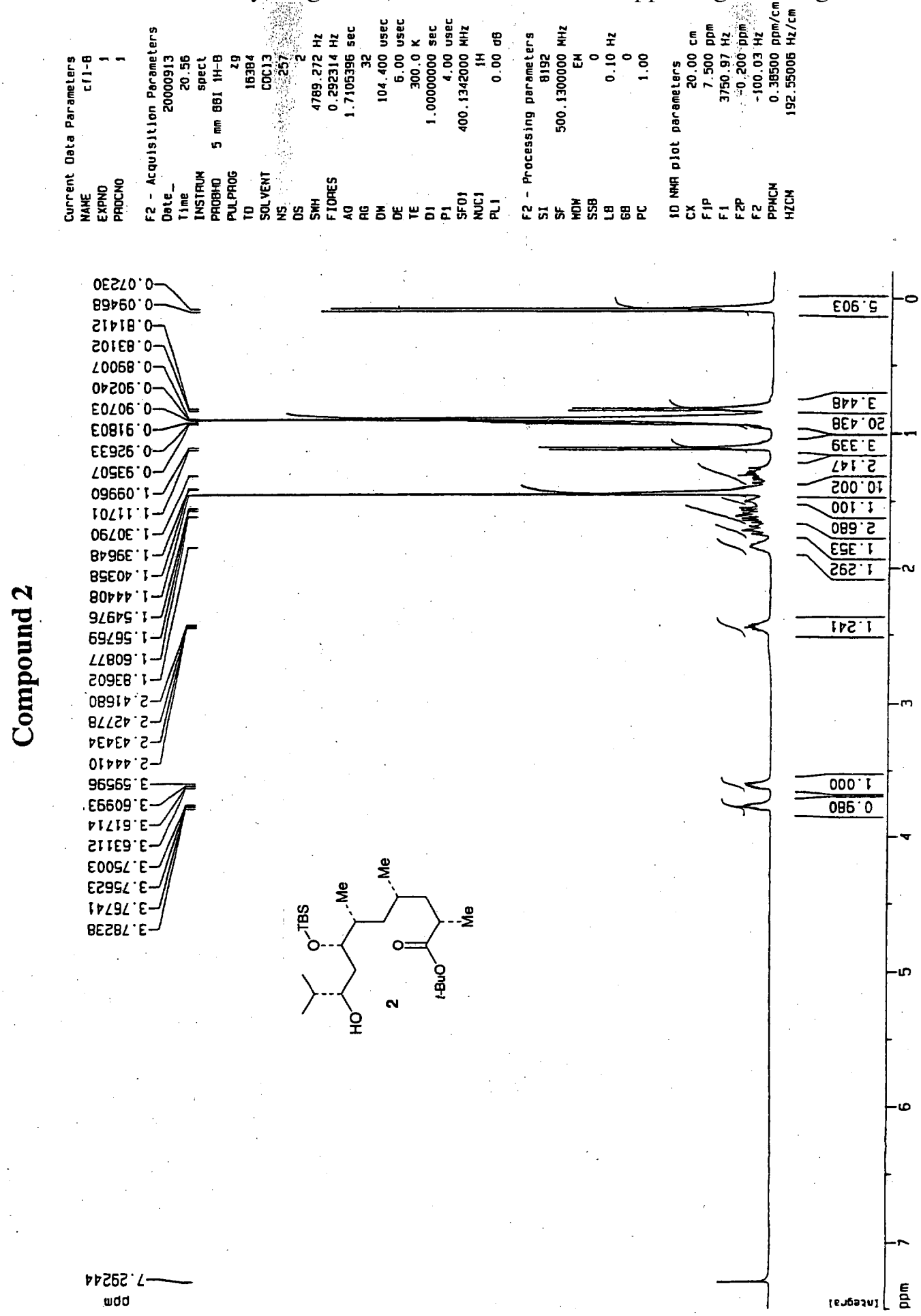

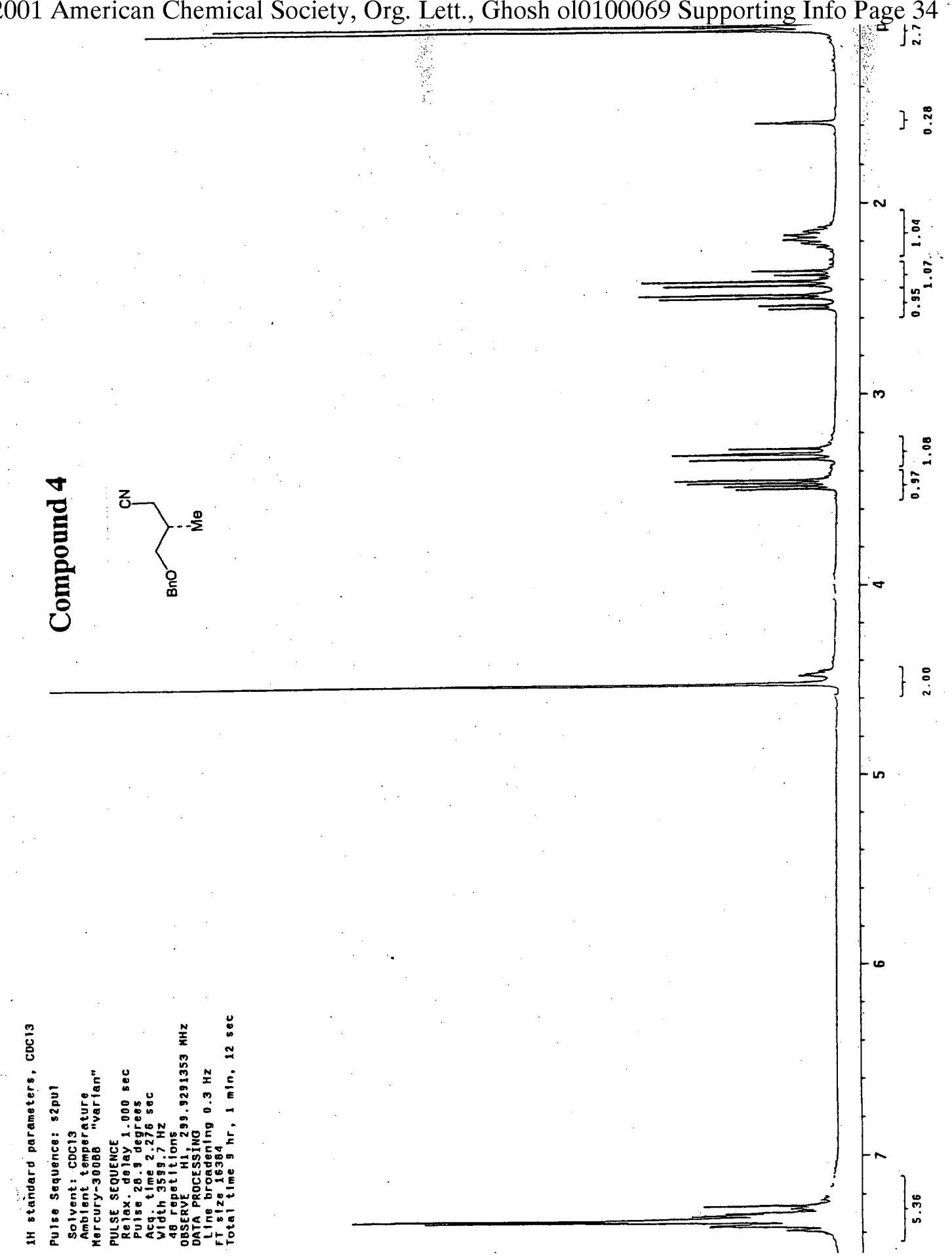
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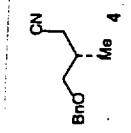
2

Compound 4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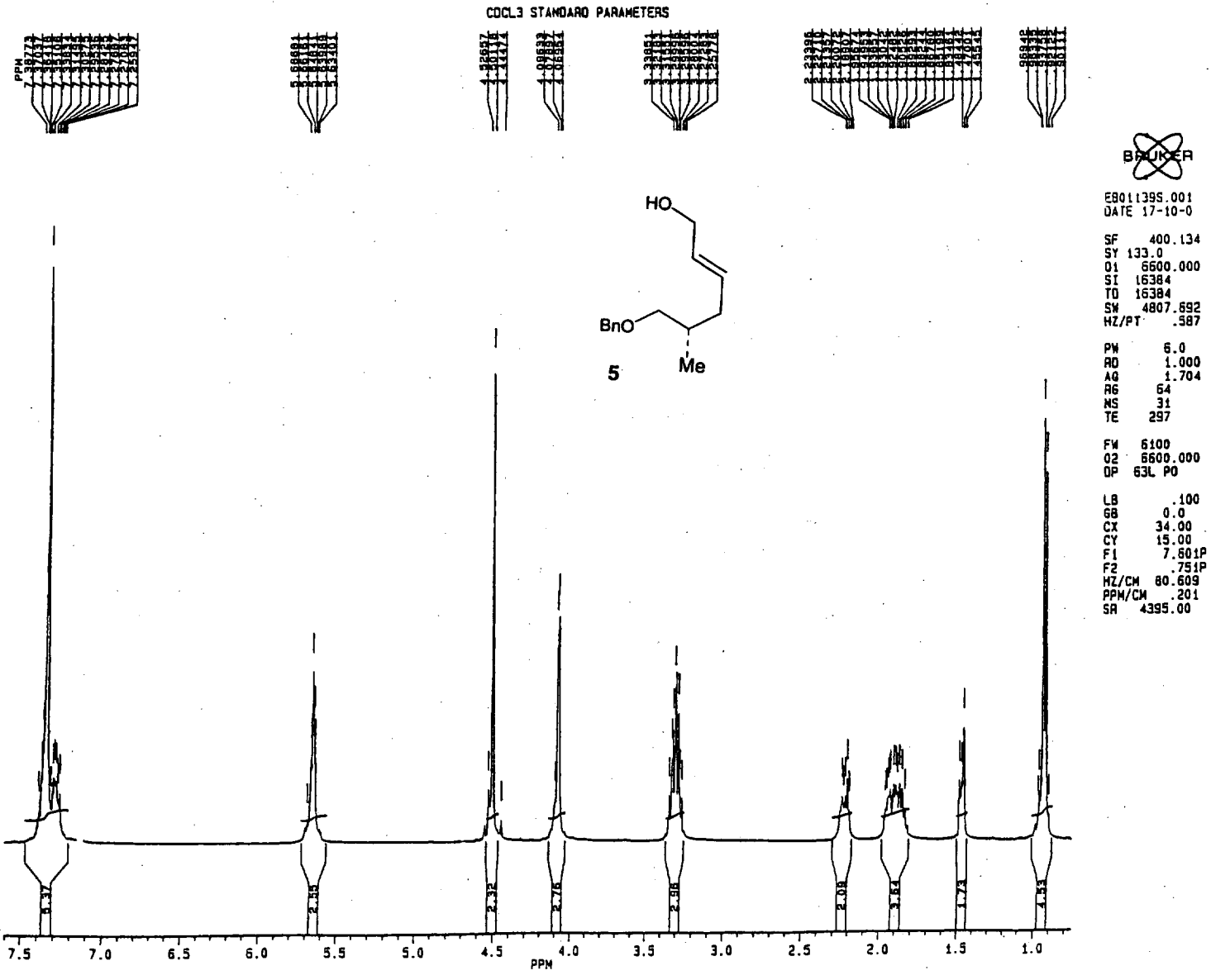
Compound 5



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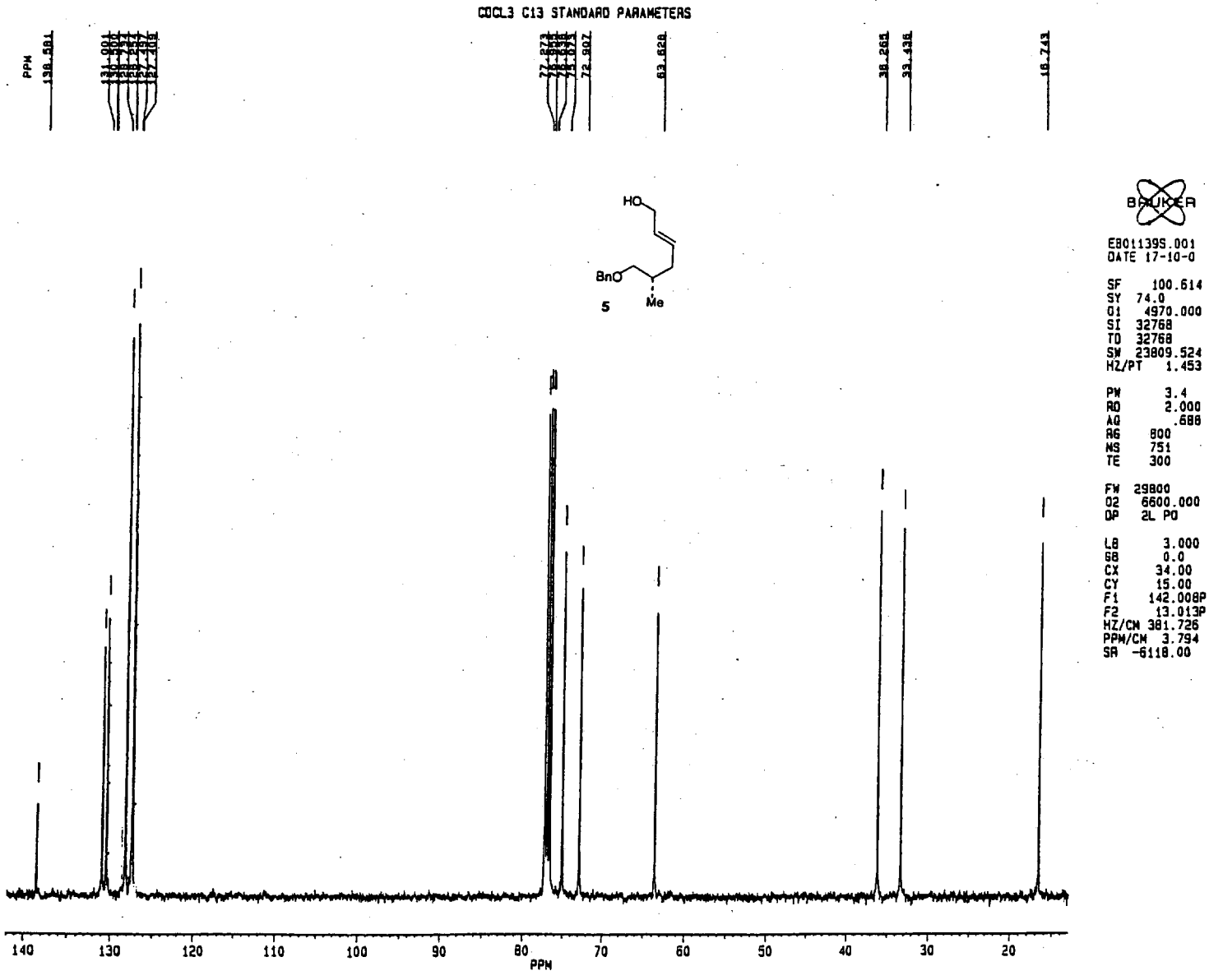

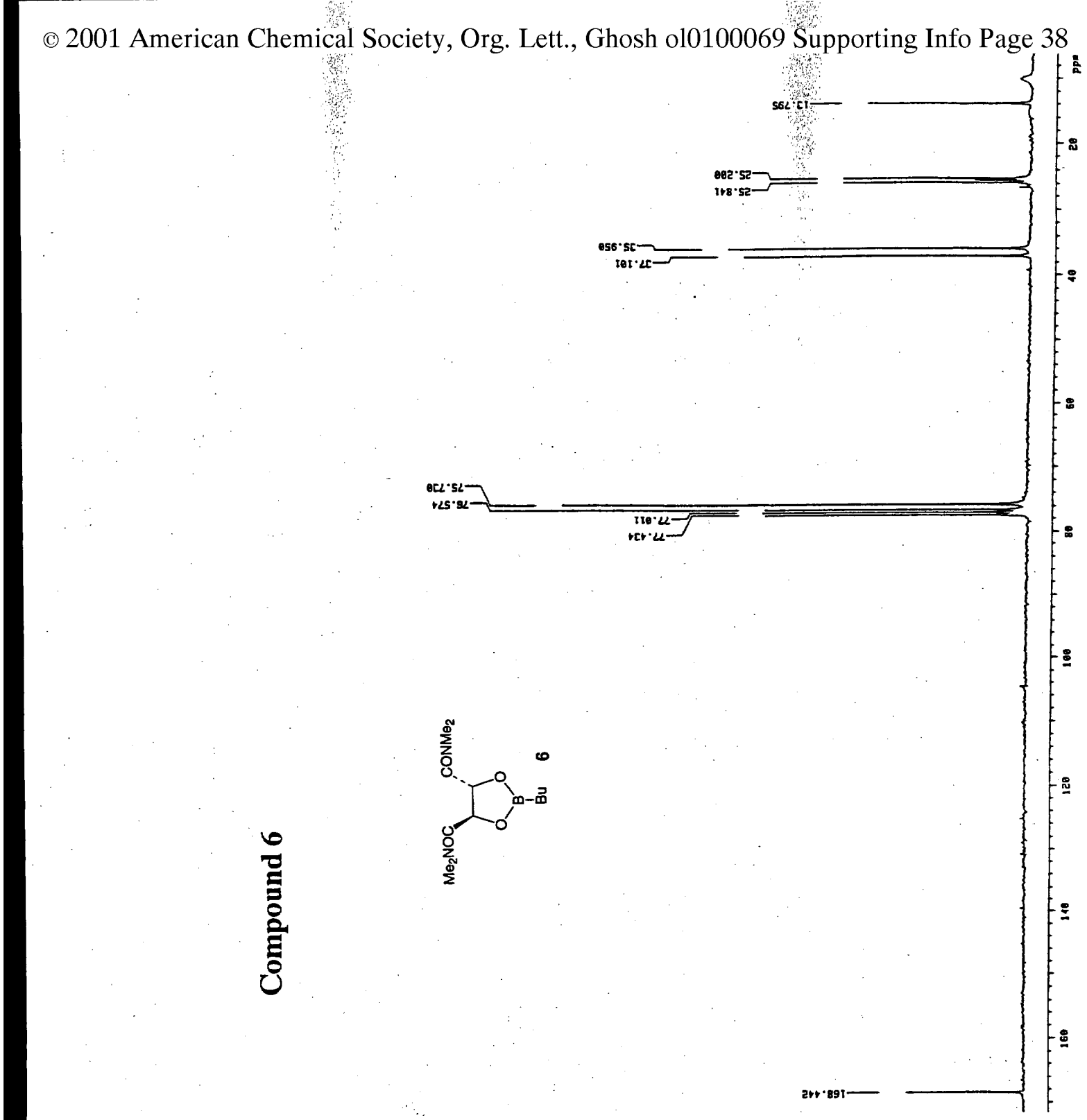

Compound 6

CDCl3 standard parameters, 3D probe

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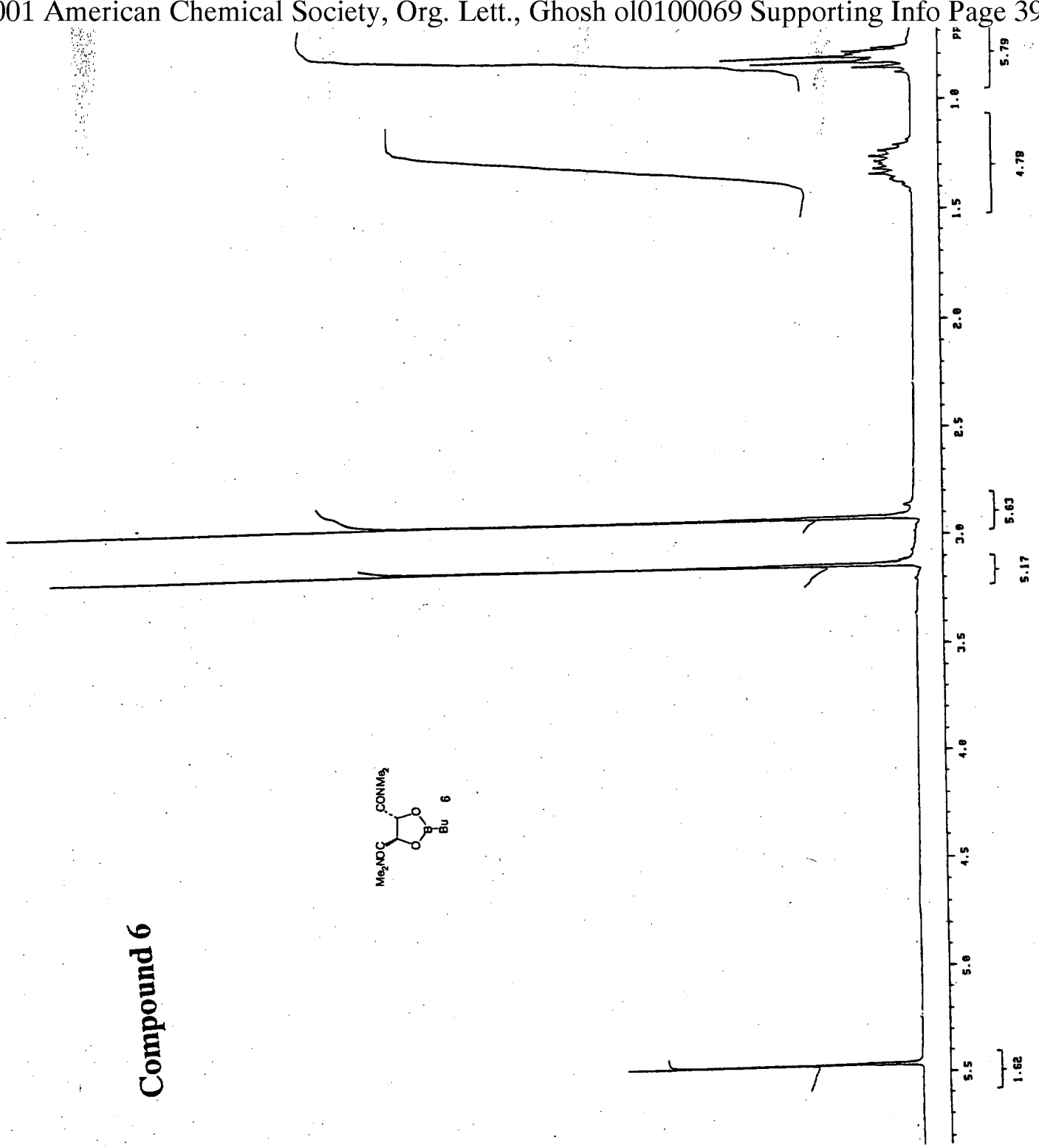
FT SIZE 32768
TOTAL ACQUISITION TIME 9.0 hours



CDCl3 standard parameters, BB probe

OBSERVE H1
FREQUENCY 299.949 MHz
SPECTRAL WIDTH 3780.0 Hz
ACQUISITION TIME 2.214 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 7.0 usec
TEMPERATURE 23.0 deg. C.
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 0.1 Hz
FT SIZE 16384
TOTAL ACQUISITION TIME 1 minutes

Compound 7