Synthesis of [Gly-1]RA-VII, [Gly-2]RA-VII and [Gly-4]RA-VII. Glycine-containing Analogues of RA-VII, an Antitumor Bicyclic Hexapeptide from *Rubia* Plants

Yukio Hitotsuyanagi, Tomoyo Hasuda, Takayuki Aihara, Hiroshi Ishikawa, Kentaro Yamaguchi, Hideji Itokawa, and Koichi Takeya*

Supporting Information

Experimental

General. Melting points were recorded uncorrected. NMR spectra were recorded at 300 K unless otherwise specified. ^{1}H Chemical shifts in $CDCl_3$, CD_3OD or C_5D_5N were referenced to the residual $CHCl_3$ (7.26 ppm), CD_2HOD (3.31 ppm) or C_5D_4HN (7.21 ppm); ^{13}C chemical shifts were referenced to the solvent ($CDCl_3$, 77.03 ppm; CD_3OD, 49.0 ppm; C_5D_5N, 135.5 ppm) unless otherwise stated. Preparative HPLC was performed by using a pre-packed ODS column (20 × 250 mm, 10 μm) and a UV detector.

[*N*-Methyl-Ala-2]RA-VII (9). Aqueous NaOH (50%, 3.5 mL) was added to a solution of **1** (1.02 g, 1.32 mmol), iodomethane (0.41 mL, 6.6 mmol) and tetrabutylammonium bromide (85 mg, 0.26 mmol) in dichloromethane (15 mL). After vigorous stirring for 8 h at room temperature, water (20 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The extracts and the organic layer were combined, washed successively with H_2O (5 mL), hydrochloric acid (2 M, 2 × 5 mL) and brine (5 mL), dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo*, and the residue was subjected to column chromatography (silica gel, 15:2:1 $CHCl_3$/EtOAc/MeOH) to give **9**[18,21] (1.01 g, 97%) as a crystalline powder.

Bis(thioamide) 10. Davy-Reagent-Methyl (**7**) (187 mg, 0.658 mmol) was added to a solution of **9** (421 mg, 0.536 mmol) in dioxane (4 mL), and the mixture was stirred at room temperature for 4 days. Saturated aqueous $NaHCO_3$ (10 mL) was added to the mixture, and the whole was stirred at room temperature for 10 min, and then the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ extracts were washed with brine (20 mL), dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. Chromatography of the residue on alumina eluting with 15:2:1 $CHCl_3$/EtOAc/MeOH gave a mixture of thioamides, which was subjected to HPLC (3:1 MeOH/H_2O) to provide **10** (399 mg, 91%) as a crystalline powder: mp >300 °C; $[\alpha]^{23}_D$ –132 (*c* = 0.22, $CHCl_3$); IR (KBr) ν_{max} 3290, 3266, 2999, 2966,

2937, 1663, 1645, 1632, 1513, 1500, 1441, 1413, 1390, 1263, 1245, 1215, 1128, 1092, 1080, 1028, 971, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers) major conformer δ 8.52 (d, 1H, *J* = 7.4 Hz), 8.17 (d, 1H, *J* = 7.0 Hz), 7.45 (dd, 1H, *J* = 8.4, 2.1 Hz), 7.28 (dd, 1H, *J* = 8.4, 2.1 Hz), 7.23 (dd, 1H, *J* = 8.4, 2.4 Hz), 7.07 (d-like, 2H, *J* = 8.6 Hz), 6.88 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.85 (d-like, 2H, *J* = 8.6 Hz), 6.79 (d, 1H, *J* = 8.4 Hz), 6.55 (dd, 1H, *J* = 8.4, 1.8 Hz), 5.42 (dd, 1H, *J* = 11.3, 2.7 Hz), 5.39 (m, 1H), 5.32 (m, 1H), 5.30 (m, 1H), 4.81 (dd, 1H, *J* = 11.8, 3.6 Hz), 4.34 (d, 1H, *J* = 1.8 Hz), 3.94 (s, 3H), 3.84 (dd, 1H, *J* = 13.6, 4.5 Hz), 3.80 (s, 3H), 3.78 (dd, 1H, *J* = 11.2, 4.5 Hz), 3.69 (dd, 1H, *J* = 11.3, 11.3 Hz), 3.53 (dd, 1H, *J* = 13.6, 11.2 Hz), 3.16 (s, 3H), 3.14 (dd, 1H, *J* = 18.3, 11.8 Hz), 3.08 (s, 3H), 2.89 (s, 3H), 2.81 (dd, 1H, *J* = 18.3, 3.6 Hz), 2.78 (s, 3H), 2.61 (dd, 1H, *J* = 11.3, 2.7 Hz), 1.41 (d, 3H, *J* = 7.1 Hz), 1.31 (d, 3H, *J* = 6.7 Hz), 1.09 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of conformers) major conformer δ 202.9, 198.0, 171.8, 171.4, 170.9, 169.3, 158.5, 158.0, 153.1, 146.4, 135.3, 132.6, 131.4, 130.9, 130.4 × 2, 128.3, 126.0, 124.0, 120.7, 114.0 × 2, 113.3, 112.2, 73.5, 63.9, 56.1, 55.3, 54.7, 51.2 × 2, 47.8, 39.9, 38.4, 37.4, 35.9, 30.7, 30.5 × 2, 16.5, 16.4, 14.6; FABMS *m/z* 817 $[M+H]^+$; HR-FABMS *m/z* 817.3389 $[M+H]^+$ (calcd for $C_{42}H_{53}N_6O_7S_2$, 817.3417). Anal. Calcd for $C_{42}H_{52}N_6O_7S_2$, C, 61.74; H, 6.42; N, 10.29. Found C, 61.62; H, 6.44; N, 10.18.

Cycloisodityrosine Thioester 14. Iodomethane (190 μL, 3.05 mmol) and K_2CO_3 (212 mg, 1.53 mmol) were added to a solution of **10** (121.5 mg, 0.149 mmol) in acetone (3 mL), and the mixture was stirred at room temperature for 6 h. $CHCl_3$ (30 mL) was added to the mixture, and the insoluble matter was filtered off. After removal of the solvent under reduced pressure, the resulting residue was dissolved in MeCN (0.25 mL). After addition of hydrochloric acid (6 M, 0.25 mL), the solution was stirred at room temperature for 2 h, and then neutralized with aqueous K_2CO_3 (1 M) at 0 °C, to which phenyl isothiocyanate (210 μL, 1.76 mmol) was added. The solution was stirred at room temperature for 2 h. The solution was extracted with $CHCl_3$ (3 × 10 mL), and the combined $CHCl_3$ extracts were washed with brine (5 mL), dried

over Na_2SO_4 and filtered, and the solvent removed *in vacuo* to give a residue, which was separated from the unreacted phenyl isothiocyanate by silica gel column chromatography eluting with $CHCl_3$. The 12:2:1 $CHCl_3$/EtOAc/MeOH eluate was evaporated to dryness, and the residue was dissolved in MeCN (0.3 mL). Hydrochloric acid (6 M, 0.25 mL) was added to the solution, and the mixture was stirred at room temperature for 5 h. The solution was neutralized with aqueous K_2CO_3 (1 M) at 0 °C, and then di-*tert*-butyl dicarbonate (145 mg, 0.664 mmol) was added to the solution. The solution was stirred at room temperature for 4 h. The solution was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (5 mL), dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 7:7:1 hexane/$CHCl_3$/acetone) and then HPLC (3:2 MeCN/H_2O) to provide **14** (60.0 mg, 78%) as a crystalline powder, which was recrystallized from isopropyl ether/$CHCl_3$ to give colorless prisms: mp 182–184 °C; $[\alpha]^{23}_D$ –239 (c = 0.26, $CHCl_3$); IR (KBr) ν_{max} 2977, 2927, 2835, 1692, 1683, 1643, 1513, 1498, 1438, 1335, 1312, 1265, 1259, 1227, 1206, 1173, 1149, 1126, 1034, 988, 802 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers) major conformer δ 7.47 (dd, 1H, J = 8.4, 2.2 Hz), 7.26 (dd, 1H, J = 8.4, 2.2 Hz), 7.17 (dd, 1H, J = 8.4, 2.2 Hz), 6.88 (dd, 1H, J = 8.4, 2.2 Hz), 6.80 (d, 1H, J = 8.3 Hz), 6.59 (br d, 1H, J = 8 Hz), 4.91 (dd, 1H, J = 11.2, 2.6 Hz), 4.76 (dd, 1H, J = 12.2, 3.7 Hz), 4.36 (br s, 1H), 3.94 (s, 3H), 3.63 (t, 1H, J = 11.2 Hz), 3.33 (dd, 1H, J = 17.8, 3.7 Hz), 2.91 (m, 1H), 2.87 (s, 3H), 2.72 (dd, 1H, J = 11.2, 2.6 Hz), 2.61 (s, 3H), 2.20 (s, 3H), 1.43 (s, 9H); EIMS *m/z* 514 $[M]^+$; HR-EIMS *m/z* 514.2124 $[M]^+$ (calcd for $C_{27}H_{34}N_2O_6S$, 514.2138).

Methyl Ester 15. A mixture of aqueous H_2O_2 (35%, 0.14 mL) and a LiOH solution ($LiOH·H_2O$ 10.1 mg, 0.241 mmol in H_2O 0.3 mL) was slowly added to a cooled (0 °C) solution of **14** (30.9 mg, 0.060 mmol) in a mixture of 3:1 THF/H_2O (1.5 mL), and the solution was stirred at this temperature for 20 min. Saturated aqueous Na_2SO_3 (0.3 mL) was added to the solution, and after stirring at 0 °C for 20 min, aqueous citric acid (10%, 0.75 mL) was added to the mixture, and the mixture was extracted with $CHCl_3$ (3 × 5 mL). The combined $CHCl_3$ extracts were washed with brine (5 mL), dried over Na_2SO_4 and filtered, and the

solvent removed *in vacuo*. The residue was dissolved in a mixture of 10:1 MeCN/MeOH (0.9 mL), to which a solution of (trimethylsilyl)diazomethane in hexanes (2 M, 0.3 mL, 0.6 mmol) was added, and the whole was stirred at room temperature for 3 h. After addition of AcOH (0.28 mL) to the solution, the solvent was removed *in vacuo*. The residue was subjected to MPLC (silica gel, 20:20:1 hexane/$CHCl_3$/MeOH) to provide **15** (28.9 mg, 97%) as a colorless gummy solid: $[\alpha]^{18}_D$ –198 (c = 0.18, $CHCl_3$); IR (film) ν_{max} 2975, 2931, 1747, 1685, 1650, 1585, 1518, 1500, 1445, 1367, 1313, 1266, 1210, 1143, 1130, 1094, 1028, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers) major conformer δ 7.45 (dd, 1H, J = 8.4, 1.9 Hz), 7.26 (dd, 1H, J = 8.4, 1.9 Hz), 7.17 (dd, 1H, J = 8.4, 2.3 Hz), 6.88 (dd, 1H, J = 8.4, 2.3 Hz), 6.80 (d, 1H, J = 8.3 Hz), 6.59 (br d, 1H, J = 8 Hz), 4.90 (dd, 1H, J = 11.2, 2.8 Hz), 4.69 (dd, 1H, J = 12.2, 3.8 Hz), 4.42 (s, 1H), 3.94 (s, 3H), 3.67 (s, 3H), 3.64 (m, 1 H), 3.32 (dd, 1H, J = 18.0, 3.8 Hz), 2.92 (s, 3 H), 2.92 (m, 1 H), 2.72 (dd, 1 H, J =11.3, 2.8 Hz), 2.56 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of conformers) major conformer δ 171.4, 171.0, 157.8, 155.6, 153.0, 146.4, 136.2, 132.7, 131.1, 128.2, 126.0, 124.0, 121.0, 113.5, 112.2, 80.2, 57.2, 56.9, 56.2, 52.6, 37.4, 32.9, 29.8, 28.5 × 3, 28.2; EIMS *m/z* 498 $[M]^+$; HR-EIMS *m/z* 498.2363 $[M]^+$ (calcd for $C_{27}H_{34}N_2O_7$, 498.2366).

Benzyl Ester 16. To a cooled (0 °C) solution of **14** (30.0 mg, 0.0583 mmol) in 3:1 THF/H_2O (1.5 mL) was slowly added a mixture of aqueous H_2O_2 (35%, 0.14 mL) and a LiOH solution (LiOH·H_2O 10.8 mg, 0.257 mmol in H_2O 0.3 mL), and the solution was stirred at this temperature for 20 min. Saturated aqueous Na_2SO_3 (0.3 mL) was added to the solution, and the mixture was stirred at 0 °C for 20 min. Aqueous citric acid (10%, 0.75 mL) was added to the mixture, and the whole was extracted with $CHCl_3$ (3 × 5 mL). The combined $CHCl_3$ extracts were washed with brine (5 mL) dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue, triphenylphosphine (30.7 mg, 0.117 mmol) and benzyl alcohol (15.0 μL, 0.145 mmol) were dissolved in THF (0.9 mL), to which diethyl azodicarboxylate (20.0 μL, 0.127 mmol) was added slowly at 0 °C under an atmosphere of argon, and the solution was stirred at this temperature for 2 h. The solvent was removed *in vacuo*. The residue was subjected to MPLC (silica gel, 60:1 $CHCl_3$/acetone) to provide **16**

(30.2 mg, 90%) as a colorless gummy solid: $[\alpha]^{18}_D$ –202 (c = 0.10, $CHCl_3$); IR (film) ν_{max} 2975, 2932, 1744, 1683, 1651, 1585, 1518, 1500, 1445, 1368, 1314, 1266, 1218, 1163, 1143, 1130, 1093, 1028, 982, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers) major conformer δ 7.46 (dd, 1H, J = 8.3, 1.8 Hz), 7.37–7.23 (m, 6H), 7.18 (dd, 1H, J = 8.3, 2.2 Hz), 6.88 (dd, 1H, J = 8.4, 2.2 Hz), 6.78 (d, 1H, J = 8.3 Hz), 6.56 (br d, 1H, J = 8 Hz), 5.13 (d, 1H, J = 12.3 Hz), 5.02 (d, 1H, J = 12.3 Hz), 4.94 (dd, 1H, J = 11.3, 2.7 Hz), 4.75 (dd, 1H, J = 12.2, 3.6 Hz), 4.42 (s, 1H), 3.93 (s, 3H), 3.63 (t, 1H, J = 11.3 Hz), 3.32 (dd, 1H, J = 17.9, 3.6 Hz), 2.90 (s, 3H), 2.89 (dd, 1H, J = 17.9, 12.2 Hz), 2.73 (dd, 1H, J = 11.3, 2.7 Hz), 2.54 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of conformers) major conformer δ 171.0, 170.8, 157.9, 155.6, 153.0, 146.4, 136.1, 135.3, 132.7, 131.1, 128.6 × 2, 128.4, 128.2, 128.1 × 2, 126.0, 124.1, 121.0, 113.6, 112.2, 80.1, 67.3, 57.3, 56.8, 56.2, 37.4, 32.9, 29.8, 28.6 × 3, 28.3; EIMS m/z 574 $[M]^+$; HR-EIMS m/z 574.2695 $[M]^+$ (calcd for $C_{33}H_{38}N_2O_7$, 574.2679).

Cbz-*N*-Methyl-Tyr-Ala-OMe (18). Cbz-*N*-Methyl-Tyr-OH (**17**)[12a,b] (1.00 g, 3.04 mmol), H-Ala-OMe·HCl (775 mg, 5.55 mmol) and HOBt (585 mg, 4.33 mmol) were dissolved in CH_2Cl_2 (15 mL) to prepare a solution, to which triethylamine (0.78 mL, 5.60 mmol) and a solution of EDC (776 mg, 4.05 mmol) in CH_2Cl_2 (15 mL) were slowly added. The mixture was stirred at room temperature for 16 h, and then hydrochloric acid (1 M, 30 mL) was added. The whole was extracted with $CHCl_3$ (3 × 30 mL), and the combined $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica gel, 2:1 EtOAc/hexane) and then MPLC (silica gel, 2:1 EtOAc/hexane) to afford **18** (894 mg, 71%) as an amorphous solid: $[\alpha]^{28}_D$ –58.0 (c = 1.35, $CHCl_3$); IR (film) ν_{max} 3323, 3017, 2954, 1744, 1669, 1615, 1596, 1518, 1455, 1402, 1311, 1220, 1182, 1147, 1104, 1060, 998, 828, 811, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 297 K, mixture of rotamers) δ 7.37–7.20 (br m, 5H), 7.06–6.90, 6.70–6.58 (each br m, total 4H), 6.30, 6.00 (each br m, total 1H), 5.11 (br s, 2H), 5.10–4.68 (br m, 2H), 4.51 (br quintet, 1H, J = 7 Hz), 3.71 (s, 3H), 3.28–3.18 (m, 1H), 2.97–2.82 (m, 1H), 2.86 (s, 3H), 1.33 (br d, 3H, J = 7 Hz); EIMS m/z 397 $[M-OH]^+$; FABMS m/z 415 $[M+H]^+$; HR-EIMS m/z 397.1749 $[M-OH]^+$

(calcd for $C_{22}H_{25}N_2O_5$, 397.1763).

Cbz-*N,O*-Dimethyl-Tyr-Ala-OMe (19). A solution of **18** (817 mg, 1.97 mmol) in MeOH (5 mL) was treated with diazomethane in diethyl ether solution and was left standing until the reaction completed. The solvent was removed *in vacuo*, and the residue was subjected to column chromatography (silica gel, 1:1 hexane/EtOAc) to afford **19** (844 mg, 100%) as an amorphous solid: $[\alpha]^{29}_D$ –57.7 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 3328, 2953, 2837, 1745, 1675, 1613, 1515, 1455, 1401, 1306, 1249, 1213, 1180, 1146, 1035, 1000, 825, 798, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 297 K, mixture of rotamers) δ 7.37–6.98, 6.83–6.72, 6.55, 6.27 (each br m, total 10H), 5.17–4.85, 4.74 (each br m, total 3H), 4.52 (quintet, 1H, *J* = 7.2 Hz), 3.77 (s, 3H), 3.72 (s, 3H), 3.33–3.20 (br m, 1H), 3.01–2.87 (br m, 1H), 2.84 (s, 3H), 1.34 (br d, 3H, *J* = 7 Hz); EIMS *m/z* 397 $[M-OMe]^+$; HR-EIMS *m/z* 397.1749 $[M-OMe]^+$ (calcd for $C_{22}H_{25}N_2O_5$, 397.1763).

Boc-Ala-*N,O*-dimethyl-Tyr-Ala-OMe (20). A solution of **19** (612 mg, 1.43 mmol) in MeOH (10 mL) was stirred at room temperature under an atmosphere of hydrogen for 2 h in the presence of 10% Pd/C (53 mg) and hydrochloric acid (0.1 mL). The catalyst was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (10 mL) together with Boc-Ala-OH (540 mg, 2.85 mmol) and PyBOP (1.49 g, 2.86 mmol), to which *N,N*-diisopropylethylamine (1.0 mL, 5.74 mmol) was slowly added at –20 °C under an atmosphere of argon. The mixture was stirred at this temperature for 1 h and then at room temperature for 5 days. Aqueous citric acid (10%, 10 mL) was added to the mixture, and the whole was extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 10:10:1, hexane/$CHCl_3$/MeOH) to afford **20** (587 mg, 88%) as a crystalline powder, which was recrystallizd from isopropyl ether to give colorless prisms: mp 127–128 °C; $[\alpha]^{20}_D$ –119 (*c* = 1.01, $CHCl_3$); IR (KBr) ν_{max} 3355, 3295, 2985, 2951, 1746, 1687, 1663, 1535, 1516, 1458, 1366, 1296, 1249, 1214, 1177, 1167, 1087, 1073, 1023, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 8.22 (d, 1H, *J* = 7.3 Hz), 7.02 (d-like, 2H, *J*

= 8.6 Hz), 6.79 (d-like, 2H, J = 8.6 Hz), 4.99 (d, 1H, J = 6.9 Hz), 4.78 (dd, 1H, J = 11.2, 3.4 Hz), 4.53 (quintet, 1H, J = 7.3 Hz), 4.13 (quintet, 1H, J = 6.7 Hz), 3.72 (s, 3H), 3.71 (s, 3H), 3.12 (dd, 1H, J = 14.7, 3.4 Hz), 2.96 (dd, 1H, J = 14.7, 11.2 Hz), 2.87 (s, 3H), 1.38 (d, 3H, J = 7.0 Hz), 1.35 (s, 9H), 0.34 (d, 3H, J = 6.7 Hz); minor rotamer δ 7.08 (d-like, 2H, J = 8.6 Hz), 6.77 (d-like, 2H, J = 8.6 Hz), 6.56 (d, 1H, J = 7.1 Hz), 5.26 (d, 1H, J = 7.9 Hz), 5.14 (t-like, 1H, J = 7.8 Hz), 4.53 (quintet, 1H, J = 7.3 Hz), 4.46 (quintet, 1H, J = 7.2 Hz), 3.73 (s, 3H), 3.68 (s, 3H), 3.23 (dd, 1H, J = 14.5, 7.8 Hz), 2.95 (dd, 1H, J = 14.5, 8.4 Hz), 2.93 (s, 3H), 1.35 (s, 9H), 1.31 (d, 3H, J = 7.1 Hz), 1.21 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 174.1, 172.9, 169.0, 158.6, 156.0, 130.4 × 2, 129.6, 114.3 × 2, 80.3, 62.3, 55.2, 52.1, 48.3, 44.9, 33.1, 29.0, 28.2 × 3, 17.4, 16.4; minor rotamer δ 173.7, 172.7, 169.2, 158.3, 154.9, 129.8 × 2, 128.7, 113.9 × 2, 79.5, 58.6, 55.1, 52.3, 48.0, 46.6, 32.7, 31.6, 28.3 × 3, 18.3, 18.0; EIMS *m/z* 465 $[M]^+$; HR-EIMS *m/z* 465.2460 $[M]^+$ (calcd for $C_{23}H_{35}N_3O_7$, 465.2475). Anal. Calcd for $C_{23}H_{35}N_3O_7$, C, 59.34; H, 7.58; N, 9.03. Found C, 59.14; H, 7.56; N, 8.98.

Boc-Gly-Ala-*N,O*-dimethyl-Tyr-Ala-OMe (21). A solution of **20** (353 mg, 0.758 mmol) in TFA (1.5 mL) was stirred at room temperature for 2 h. TFA was removed *in vacuo*, and the residue was dissolved in $CHCl_3$ (30 mL). The solution was washed successively with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) together with Boc-Gly-OH (201 mg, 1.15 mmol) and HOBt (154 mg, 1.14 mmol), to which EDC (218 mg, 1.14 mmol) was added at –20 °C. The mixture was stirred at this temperature for 1 h, and then at room temperature for 24 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to the solution, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (10 mL), dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 5:5:1 hexane/$CHCl_3$/MeOH) to provide **21** (376 mg, 95%) as an amorphous solid: $[\alpha]^{23}_D$ –103 (c = 1.84, $CHCl_3$); IR (film) ν_{max} 3280, 2980, 2937, 1747, 1711, 1667, 1631, 1540, 1515, 1456, 1367, 1284, 1248, 1175, 1033, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 8.21 (d, 1H, J =

6.7 Hz), 7.45 (br s, 1H), 7.00 (d-like, 2H, J = 8.6 Hz), 6.78 (d-like, 2H, J = 8.6 Hz), 5.46 (br m, 1H), 4.92 (br d, 1H, J = 9 Hz), 4.42 (quintet, 1H, J = 7.2 Hz), 4.35 (quintet, 1H, J = 6.4 Hz), 3.71 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.64 (dd, 1H, J = 17.2, 5.8 Hz), 3.08 (dd, 1H, J = 14.6, 3.2 Hz), 2.95 (dd, 1H, J = 14.6, 11.4 Hz), 2.84 (s, 3H), 1.36 (s, 9H), 1.35 (d, 3H, J = 7.0 Hz), 0.42 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 173.6, 173.1, 170.2, 168.8, 158.7, 155.9, 130.3 × 2, 129.4, 114.3 × 2, 79.8, 62.4, 55.3, 52.2, 48.5, 44.2, 43.1, 33.2, 29.1, 28.2 × 3, 17.2, 16.2; EIMS *m/z* 522 $[M]^+$; FABMS *m/z* 523 $[M+H]^+$; HR-EIMS *m/z* 522.2682 $[M]^+$ (calcd for $C_{25}H_{38}N_4O_8$, 522.2690).

Boc-Gly-Ala-*N*,*O*-dimethyl-Tyr-Ala-OH (22). To a solution of **21** (224 mg, 0.429 mmol) in a mixture of 3:1:1 THF/MeOH/H_2O (4.2 mL) was added $LiOH·H_2O$ (35.9 mg, 0.856 mmol), and the mixture was stirred at room temperature for 3 h. The mixture was acidified with aqueous citric acid (10%, 2 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (10 mL), dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica gel, 5:1 $CHCl_3$/MeOH) to provide **22** (216 mg, 99%) as an amorphous solid: $[\alpha]^{28}_D$ –97.1 (c = 0.15, MeOH); IR (film) ν_{max} 3288, 2980, 2936, 2838, 1708, 1663, 1634, 1514, 1456, 1411, 1367, 1300, 1285, 1249, 1176, 1033, 943, 756 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD, mixture of two rotamers) major rotamer δ 7.14 (d-like, 2H, J = 8.6 Hz), 6.87 (d-like, 2H, J = 8.6 Hz), 5.03 (dd, 1H, J = 11.3, 3.2 Hz), 4.44 (q, 1H, J = 6.8 Hz), 4.34 (q, 1H, J = 7.1 Hz), 3.75 (s, 3H), 3.69 (d, 1H, J = 17.2 Hz), 3.64 (d, 1H, J = 17.2 Hz), 3.15 (dd, 1H, J = 14.5, 3.2 Hz), 2.97 (dd, 1H, J = 14.5, 11.3 Hz), 2.87 (s, 3H), 1.45 (d, 3H, J = 7.1 Hz), 1.42 (s, 9H), 0.47 (d, 3H, J = 6.8 Hz); minor rotamer δ 7.13 (d-like, 2H, J = 8.6 Hz), 6.83 (d-like, 2H, J = 8.6 Hz,), 4.96 (m, 1H), 4.71 (q, 1H, J = 6.8 Hz), 4.32 (q, 1H, J = 7.2 Hz), 3.76 (s, 3H), 3.69 (d, 1H, J = 17.2 Hz), 3.64 (d, 1H, J = 17.2 Hz), 3.26 (dd, 1H, J = 14.5, 5.8 Hz), 3.04 (dd, 1H, J = 14.5, 10.2 Hz), 2.97 (s, 3H), 1.45 (s, 9H), 1.37 (d, 3H, J = 7.2 Hz), 1.24 (d, 3H, J = 6.8 Hz); HR-ESIMS *m/z* 509.2653 $[M+H]^+$ (calcd for $C_{24}H_{37}N_4O_8$, 509.2611).

Boc-Gly-*N,O*-dimethyl-Tyr-Ala-OMe (23). When **19** was treated as described for the preparation of **20** by using Boc-Gly-OH, **23** was obtained in 96% yield as an amorphous solid: $[\alpha]^{20}_D$ –55.7 (*c* = 0.87, $CHCl_3$); IR (film) ν_{max} 3320, 2979, 1744, 1714, 1651, 1515, 1456, 1367, 1250, 1174, 1052, 1034, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 7.08 (d-like, 2H, *J* = 8.6 Hz), 6.79 (d-like, 2H, *J* = 8.6 Hz), 6.54 (d, 1H, *J* = 7.2 Hz), 5.39 (br s, 1H), 5.27 (dd, 1H, *J* = 9.2, 6.9 Hz), 4.47 (quintet, 1H, *J* = 6.2 Hz), 3.92 (dd, 1H, *J* = 17.2, 4.5 Hz), 3.76 (s, 3H), 3.75 (dd, 1H, *J* = 17.2, 4.7 Hz), 3.70 (s, 3H), 3.22 (dd, 1H, *J* = 14.6, 6.9 Hz), 2.93 (dd, 1H, *J* = 14.6, 9.2 Hz), 2.87 (s, 3H), 1.42 (s, 9H), 1.35 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 172.7, 169.8, 169.4, 158.2, 155.6, 129.6 × 2, 128.5, 113.8 × 2, 79.5, 57.9, 55.0, 52.2, 48.0, 42.4, 33.1, 28.2 × 3, 22.7, 17.7; EIMS *m/z* 451 $[M]^+$; HR-EIMS *m/z* 451.2309 $[M]^+$ (calcd for $C_{22}H_{33}N_3O_7$, 451.2319).

Boc-D-Ala-Gly-*N,O*-dimethyl-Tyr-Ala-OMe (24). When **23** was treated as described for the preparation of **21** by using Boc-D-Ala-OH, **24** was obtained in 84% yield as an amorphous solid: $[\alpha]^{23}_D$ –47.1 (*c* = 0.99, $CHCl_3$); IR (film) ν_{max} 3318, 2980, 2936, 2838, 1744, 1646, 1515, 1455, 1367, 1301, 1249, 1217, 1168, 1111, 1032, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 7.06 (d-like, 2H, *J* = 8.6 Hz), 7.03 (br m, 1H), 6.78 (d-like, 2H, *J* = 8.6 Hz), 6.72 (br d, 1H, *J* = 7 Hz), 5.31 (dd, 1H, *J* = 9.5, 6.5 Hz), 5.16 (d, 1H, *J* = 7.5 Hz), 4.49 (quintet, 1H, *J* = 7.2 Hz), 4.26 (br m, 1H), 4.06 (dd, 1H, *J* = 17.7, 4.3 Hz), 3.81 (dd, 1H, *J* = 17.7, 2.7 Hz), 3.76 (s, 3H), 3.70 (s, 3H), 3.22 (dd, 1H, *J* = 14.5, 6.5 Hz), 2.94 (dd, 1H, *J* = 14.5, 9.5 Hz), 2.93 (s, 3H), 1.43 (s, 9H), 1.36 (d, 3H, *J* = 7.1 Hz), 1.34 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 173.0, 172.8, 169.6, 169.3, 158.4, 155.3, 129.7 × 2, 128.6, 114.0 × 2, 80.0, 57.9, 55.2, 52.4, 50.0, 48.1, 41.5, 33.5, 30.5, 28.3 × 3, 19.0, 17.8; EIMS *m/z* 522 $[M]^+$; FABMS *m/z* 523 $[M+H]^+$; HR-EIMS *m/z* 522.2696 $[M]^+$ (calcd for $C_{25}H_{38}N_4O_8$, 522.2690).

Boc-D-Ala-Gly-*N,O*-dimethyl-Tyr-Ala-OH (25). When **24** was processed as described for the preparation of **22**, **25** was obtained in 98% yield as an amorphous solid: $[\alpha]^{28}_D$ –15.7 (*c* = 0.31, MeOH); IR (film) ν_{max} 3320, 2979, 2936, 2838, 1647, 1514, 1456, 1367, 1301, 1249,

1168, 1032, 756 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, mixture of two rotamers) major rotamer δ 7.14 (d-like, 2H, J = 8.6 Hz), 6.82 (d-like, 2H, J = 8.6 Hz), 5.23 (dd, 1H, J = 10.6, 5.5 Hz), 4.37 (q, 1H, J = 7.3 Hz), 4.09 (m, 1H), 4.06 (d, 1H, J = 17.2 Hz), 3.78 (d, 1H, J = 17.2 Hz), 3.75 (s, 3H), 3.25 (dd, 1H, J = 14.5, 5.5 Hz), 2.97 (dd, 1H, J = 14.5, 10.6 Hz), 2.91 (s, 3H), 1.44 (s, 9H), 1.39 (d, 3H, J = 7.3 Hz), 1.31 (d, 3H, J = 7.2 Hz); minor rotamer δ 7.15 (d-like, 2H, J = 8.6 Hz), 6.85 (d-like, 2H, J = 8.6 Hz), 4.65 (m, 1H), 4.40 (q, 1H, J = 7.2 Hz), 4.06 (m, 1H), 4.05 (d, 1H, J = 16.3 Hz), 3.76 (s, 3H), 3.22 (dd, 1H, J = 14.5, 4.1 Hz), 3.10 (br d, 1H, J = 16.3 Hz), 2.97 (dd, 1H, J = 14.5, 10.6 Hz), 2.92 (s, 3H), 1.44 (d, 3H, J = 7.2 Hz), 1.43 (s, 9H), 1.27 (d, 3H, J = 7.2 Hz); HR-ESIMS *m/z* 509.2653 $[M+H]^+$ (calcd for $C_{24}H_{37}N_4O_8$, 509.2611).

Cbz-*N*-Methyl-Tyr-Gly-OMe (26). When **17** was treated as described for the preparation of **18** by using H-Gly-OMe·HCl, **26** was obtained in 79% yield as an amorphous solid: $[\alpha]^{28}_D$ –69.7 (c = 0.98, $CHCl_3$); IR (film) ν_{max} 3341, 3029, 2953, 1752, 1670, 1615, 1596, 1518, 1452, 1403, 1369, 1319, 1217, 1182, 1141, 1028, 971, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.37–7.16, 7.07–6.90, 6.74–6.60, 6.53–6.30 (each br m, total 11H), 5.18–4.76 (br m, 3H), 4.14–3.98 (br m, 1H), 3.96–3.82 (br m, 1H), 3.71 (s, 3H), 3.34–3.21 (br m, 1H), 2.96–2.80 (br m, 1H), 2.89 (s, 3H); FABMS *m/z* 401 $[M+H]^+$; EIMS *m/z* 400 $[M]^+$; HR-EIMS *m/z* 400.1606 $[M]^+$ (calcd for $C_{21}H_{24}N_2O_6$, 400.1634).

Cbz-*N,O*-Dimethyl-Tyr-Gly-OMe (27). When **26** was treated as described for the preparation of **19**, **27** was obtained in 100% yield as an amorphous solid: $[\alpha]^{30}_D$ –68.7 (c = 1.0, $CHCl_3$); IR (film) ν_{max} 3346, 2953, 2837, 1753, 1681, 1613, 1515, 1454, 1402, 1369, 1308, 1248, 1210, 1180, 1140, 1033, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 297 K, mixture of rotamers) δ 7.36–7.00, 6.82–6.73 (each br m, total 9H), 6.44, 6.35 (each br m, total 1H), 5.17–4.94, 4.82 (each br m, total 3H), 4.16–4.00 (m, 1H), 3.88 (dd, 1H, J = 18.1, 4.7 Hz), 3.77 (s, 3H), 3.72 (s, 3H), 3.37–3.25 (m, 1H), 2.98–2.83 (m, 1H), 2.87 (s, 3H); EIMS *m/z* 383 $[M-OMe]^+$; HR-EIMS *m/z* 383.1625 $[M-OMe]^+$ (calcd for $C_{21}H_{23}N_2O_5$, 383.1607).

Boc-Ala-*N,O*-dimethyl-Tyr-Gly-OMe (28). When **27** was treated as described for the

preparation of **20**, **28** was obtained in 73% yield as an amorphous solid: $[\alpha]^{28}_{D}$ –130 (*c* = 0.38, $CHCl_3$); IR (film) ν_{max} 3306, 2979, 2936, 2836, 1754, 1680, 1641, 1514, 1457, 1411, 1367, 1300, 1249, 1208, 1176, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 8.23 (br t, 1H, *J* = 6 Hz), 7.04 (d-like, 2H, *J* = 8.6 Hz), 6.87 (d-like, 2H, *J* = 8.6 Hz), 5.04 (d, 1H, *J* = 7.4 Hz), 4.82 (dd, 1H, *J* = 11.2, 3.5 Hz), 4.19 (dq, 1H, *J* = 7.4, 6.7 Hz), 4.05 (dd, 1H, *J* = 17.5, 6.0 Hz), 3.92 (dd, 1H, *J* = 17.5, 5.8 Hz), 3.74 (s, 3H), 3.70 (s, 3H), 3.15 (dd, 1H, *J* = 14.6, 3.5 Hz), 3.00 (dd, 1H, *J* = 14.6, 11.2 Hz), 2.93 (s, 3H), 1.35 (s, 9H), 0.43 (d, 3H, *J* = 6.7 Hz); minor rotamer δ 7.10 (d-like, 2H, *J* = 8.6 Hz), 6.78 (d-like, 2H, *J* = 8.6 Hz), 6.63 (br t, 1H, *J* = 6 Hz), 5.24 (br d, 1H, *J* = 8 Hz), 5.18 (br t, 1H, *J* = 8 Hz), 4.52 (m, 1H), 4.09 (dd, 1H, *J* = 18.1, 6.5 Hz), 3.78 (dd, 1H, *J* = 18.1, 4.8 Hz), 3.75 (s, 3H), 3.69 (s, 3H), 3.27 (dd, 1H, *J* = 14.4, 7.3 Hz), 2.97 (s, 3H), 2.95 (m, 1H), 1.41 (s, 9H), 1.26 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 174.0, 169.8, 169.8, 158.7, 156.4, 130.3 × 2, 129.5, 114.4 × 2, 80.6, 62.4, 55.3, 52.1, 44.8, 41.1, 33.1, 29.1, 28.2 × 3, 16.6; minor rotamer δ 174.1, 170.1, 169.9, 158.4, 155.1, 129.9 × 2, 128.8, 113.9 × 2, 79.6, 58.6, 55.1, 52.2, 46.7, 41.0, 32.6, 31.7, 28.3 × 3, 18.3; EIMS *m/z* 451 $[M]^+$; HR-EIMS *m/z* 451.2321 $[M]^+$ (calcd for $C_{22}H_{33}N_3O_7$, 451.2319).

Boc-D-Ala-Ala-*N,O*-dimethyl-Tyr-Gly-OMe (29). When **28** was treated as described for the preparation of **21** by using Boc-D-Ala-OH, **29** was obtained in 79% yield as an amorphous solid: $[\alpha]^{23}_{D}$ –96.1 (*c* = 0.90, $CHCl_3$); IR (film) ν_{max} 3298, 2980, 2937, 1755, 1683, 1641, 1515, 1454, 1368, 1301, 1249, 1210, 1177, 1034, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 8.23 (br t, 1H, *J* = 5.3 Hz), 7.04 (d-like, 2H, *J* = 8.6 Hz), 6.81 (d-like, 2H, *J* = 8.6 Hz), 5.31 (br d, 1H, *J* = 6.6 Hz), 4.93 (dd, 1H, *J* = 11.1, 3.5 Hz), 4.34 (quintet, 1H, *J* = 6.6 Hz), 4.14 (br m, 1H), 4.10 (dd, 1H, *J* = 17.7, 5.3 Hz), 3.95 (dd, 1H, *J* = 17.7, 5.3 Hz), 3.74 (s, 3H), 3.71 (s, 3H), 3.14 (dd, 1H, *J* = 14.6, 3.5 Hz), 2.99 (dd, 1H, *J* = 14.6, 11.1 Hz), 2.91 (s, 3H), 1.40 (s, 9H), 1.26 (d, 3H, *J* = 7.1 Hz), 0.48 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two rotamers) major rotamer δ 173.5, 173.2, 170.0, 169.6, 158.7, 155.4, 130.4 × 2, 129.5, 114.4 × 2, 80.2, 62.4, 55.3, 52.1, 49.9, 44.2, 41.4, 33.3, 29.3, 28.3 × 3, 17.8, 16.4; EIMS *m/z* 522 $[M]^+$; FABMS *m/z* 523 $[M+H]^+$; HR-EIMS *m/z*

522.2681 $[M]^+$ (calcd for $C_{25}H_{38}N_4O_8$, 522.2690).

Boc-D-Ala-Ala-*N,O*-dimethyl-Tyr-Gly-OH (30). When **29** was processed as described for the preparation of **22**, **30** was obtained in 93% yield as an amorphous solid: $[\alpha]^{28}_D$ –90.8 (*c* = 1.3, MeOH); IR (film) ν_{max} 3303, 2979, 2936, 2837, 1638, 1514, 1454, 1412, 1367, 1301, 1248, 1176, 1034, 756 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, mixture of two rotamers) major rotamer δ 7.14 (d-like, 2H, *J* = 8.6 Hz), 6.86 (d-like, 2H, *J* = 8.6 Hz), 5.02 (br m, 1H), 4.42 (q, 1H, *J* = 6.8 Hz), 4.04 (m, 1H), 3.92 (d, 1H, *J* = 17.6 Hz), 3.85 (d, 1H, *J* = 17.6 Hz), 3.74 (s, 3H), 3.19 (br d, 1H, *J* = 14 Hz), 2.98 (m, 1H), 2.93 (s, 3H), 1.41 (s, 9H), 1.25 (d, 3H, *J* = 7.4 Hz), 0.50 (br d, 3H, *J* = 6.8 Hz); minor rotamer δ 7.13 (d-like, 2H, *J* = 8.6 Hz), 6.82 (d-like, 2H, *J* = 8.6 Hz), 5.02 (br m, 1H), 4.73 (q, 1H, *J* = 6.9 Hz), 4.05 (d, 1H, *J* = 17.6 Hz), 4.04 (m, 1H), 3.92 (d, 1H, *J* = 17.6 Hz), 3.74 (s, 3H), 3.26 (dd, 1H, *J* = 14.2, 6.2 Hz), 3.00 (m, 1H), 2.98 (s, 3H), 1.44 (s, 9H), 1.26 (d, 3H, *J* = 6.9 Hz), 1.25 (d, 3H, *J* = 7.4 Hz); HR-ESIMS *m/z* 509.2653 $[M+H]^+$ (calcd for $C_{24}H_{37}N_4O_8$, 509.2611).

Hexapeptide 31. A solution of cycloisodityrosine **16** (23.6 mg, 0.0411 mmol) in TFA (0.5 mL) was stirred at room temperature for 3 h. TFA was removed *in vacuo*. $CHCl_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added to the residue, and the whole was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was dissolved in THF (0.5 mL), to which Boc-Gly-Ala-*N,O*-dimethyl-Tyr-Ala-OH (**22**) (39.8 mg, 0.0783 mmol), HOObt (13.4 mg, 0.0821 mmol) and EDC (12.6 mg, 0.0657 mmol) were added, and the solution was stirred at room temperature for 48 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to the solution, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (5 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 10:10:1 hexane/$CHCl_3$/MeOH) to provide **31** (38.4 mg, 97%) as an amorphous solid: $[\alpha]^{24}_D$ –132 (*c* =

0.12, $CHCl_3$); IR (film) ν_{max} 3294, 2979, 2933, 1719, 1641, 1515, 1453, 1412, 1367, 1249, 1220, 1177, 1129, 1094, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 7.83 (br m), 7.54–6.71 (m), 6.61 (m), 6.55 (dd, J = 8.3, 1.8 Hz), 6.49 (d, J = 7.3 Hz), 6.32 (br m), 5.88 (dd, J = 12.0, 4.7 Hz), 5.76 (br m), 5.38 (br m), 5.32 (dd, J = 11.4, 2.2 Hz), 5.23–4.68 (m), 4.65 (dd, J = 12.3, 3.6 Hz), 4.40 (br m), 4.38 (d, J = 1.9 Hz), 4.32 (quintet, J = 7.0 Hz), 3.93 (s), 3.78 (s), 3.76 (s), 3.75–3.57 (m), 3.50–3.41 (m), 3.35–3.14 (m), 3.28 (s), 3.18 (s), 3.08 (s), 3.02 (s), 3.01–2.84 (m), 2.94 (s), 2.89 (s), 2.80 (dd, J = 11.4, 3.1 Hz), 2.74–2.69 (m), 2.56 (s), 2.55 (s), 1.457 (s), 1.453 (s), 1.404 (s), 1.397 (s), 1.348 (s), 1.341 (s), 1.353 (s), 1.33–1.19 (m), 1.16 (d, J = 6.7 Hz), 0.93 (m), 0.61 (d, J = 6.6 Hz), 0.48 (d, J = 6.6 Hz); FABMS *m/z* 965 $[M+H]^+$; HR-ESIMS *m/z* 987.4484 $[M+Na]^+$ (calcd for $C_{52}H_{64}N_6O_{12}Na$, 987.4480).

Hexapeptide 32. A solution of cycloisodityrosine **16** (30.0 mg, 0.0522 mmol) in TFA (0.5 mL) was stirred at room temperature for 3 h. TFA was removed *in vacuo*. $CHCl_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added to the residue, and the whole was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was dissolved in THF (0.5 mL), to which Boc-D-Ala-Gly-*N*,*O*-dimethyl-Tyr-Ala-OH (**25**) (31.3 mg, 0.0615 mmol), HOObt (17.0 mg, 0.104 mmol) and EDC (16.0 mg, 0.0835 mmol) were added, and the solution was stirred at room temperature for 48 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to the solution, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (5 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 10:10:1 hexane/$CHCl_3$/MeOH) to provide **32** (39.6 mg, 79%) as an amorphous solid: $[\alpha]^{24}_D$ –141 (c = 0.13, $CHCl_3$); IR (film) ν_{max} 3307, 2975, 2934, 1742, 1711, 1641, 1515, 1500, 1456, 1412, 1367, 1266, 1249, 1178, 1129, 1094, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of

rotamers) δ 7.56–6.70 (m), 6.63–6.53 (m), 5.88 (dd, J = 12.1, 4.8 Hz), 5.38–4.63 (m), 4.38 (d, J = 2.0 Hz), 4.25–3.82 (m), 3.93 (s), 3.77 (s), 3.74 (s), 3.71 (s), 3.68–3.59 (m), 3.47 (m), 3.37–3.15 (m), 3.20 (s), 3.18 (s), 3.09–2.63 (m), 2.93 (s), 2.85 (s), 2.55 (s), 2.54 (s), 2.53 (s), 1.44 (s), 1.43 (s), 1.38–1.19 (m); FABMS *m/z* 965 $[M+H]^+$; HR-ESIMS *m/z* 987.4484 $[M+Na]^+$ (calcd for $C_{52}H_{64}N_6O_{12}Na$, 987.4480).

Hexapeptide 33. A solution of cycloisodityrosine **16** (9.5 mg, 0.0165 mmol) in TFA (0.5 mL) was stirred at room temperature for 3 h. TFA was removed *in vacuo*. $CHCl_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added to the residue, and the whole was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was dissolved in THF (0.5 mL), to which Boc-D-Ala-Ala-*N*,*O*-dimethyl-Tyr-Gly-OH (**30**) (12.8 mg, 0.0252 mmol), HOAt (5.0 mg, 0.037 mmol) and EDC (6.4 mg, 0.033 mmol) were added, and the solution was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to the solution, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with brine (5 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 10:10:1 hexane/$CHCl_3$/MeOH) to provide **33** (14.7 mg, 92%) as an amorphous solid: $[\alpha]^{24}_D$ –94.6 (c = 0.13, $CHCl_3$); IR (film) ν_{max} 3307, 2976, 2932, 1740, 1711, 1646, 1515, 1454, 1413, 1367, 1265, 1249, 1218, 1178, 1129, 1094, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 7.90 (br m), 7.51–6.52 (m), 5.85 (dd, J = 12.5, 4.4 Hz), 5.37 (br m), 5.31 (dd, J = 11.3, 2.7 Hz), 5.23–4.63 (m), 4.42 (br s), 4.18–4.03 (m), 3.94 (s), 3.93 (s), 3.92–3.74 (m), 3.78 (s), 3.76 (s), 3.62 (t, J = 10 Hz), 3.50 (m), 3.36 (dd, J = 18.3, 3.2 Hz), 3.32–3.13 (m), 3.09–2.72 (m), 3.06 (s), 2.94 (s), 2.84 (s), 2.81 (s), 2.69 (dd, J = 11.2, 2.6 Hz), 2.57 (s), 1.45 (s), 1.43 (s), 1.41–1.23 (m), 1.19 (d, J = 6.7 Hz), 0.62 (d, J = 6.5 Hz), 0.42 (d, J = 6.6 Hz); FABMS *m/z* 965 $[M+H]^+$; HR-ESIMS *m/z* 987.4484 $[M+Na]^+$ (calcd for $C_{52}H_{64}N_6O_{12}Na$,

987.4480).

Amine 34. A solution of **31** (10.0 mg, 0.0104 mmol) in TFA (0.5 mL) was stirred at room temperature for 30 min, and then TFA was removed *in vacuo*. $CHCl_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added to the residue, and the whole was extracted with 97:3 $CHCl_3$/MeOH (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica gel, 10:1 $CHCl_3$/MeOH) to provide **34** (8.5 mg, 95%) as an amorphous solid: $[\alpha]^{24}_D$ –185 (c = 0.16, pyridine); ^{1}H NMR (400 MHz, C_5D_5N, mixture of rotamers) δ 9.02 (d, J = 6.7 Hz), 8.95 (d, J = 6.6 Hz), 8.69 (d, J = 7.3 Hz), 8.63 (d, J = 7.5 Hz), 7.65 (d, J = 7.2 Hz), 7.57 (d, J = 5.7 Hz), 7.50–6.90 (m), 6.88 (d, J = 8.5 Hz), 6.63 (d-like, J = 8.3 Hz), 5.80 (dd, J = 11.4, 3.2 Hz), 5.71–5.64 (m), 5.43 (dd, J = 10.9, 3.4 Hz), 5.35 (d, J = 13 Hz), 5.24 (d, J = 13 Hz), 5.21–5.07 (m), 5.01 (m), 4.81 (m), 4.71 (s), 3.84 (s), 3.75 (t, J = 11.3 Hz), 3.65 (s), 3.62 (m), 3.60 (s), 3.42 (s), 3.37 (s), 3.28 (s), 3.23 (s), 3.21 (s), 3.20–3.00 (m), 2.95–2.87 (m), 2.78 (s), 2.75 (s), 2.66 (dd, J = 11.3, 2.8 Hz), 1.63 (d, J = 7.0 Hz), 1.51 (d, J = 6.8 Hz), 1.36 (d, J = 6.8 Hz), 0.74 (d, J = 6.7 Hz); FABMS m/z 865 $[M+H]^+$.

Amine 35. When **32** was treated in the same manner as described for the preparation of **34**, **35** was obtained in 98% yield as an amorphous solid: $[\alpha]^{24}_D$ –137 (c = 0.29, pyridine); ^{1}H NMR (400 MHz, C_5D_5N, mixture of rotamers) δ 9.11 (d, J = 6.9 Hz), 9.01 (d, J = 7.3 Hz), 8.84 (d, J = 7.0 Hz), 8.79 (br m), 8.59 (br t, J = 4 Hz), 7.63–7.53 (m), 7.51 (d, J = 7.2 Hz), 7.48–7.00 (m), 6.98 (dd, J = 8.4, 2.3 Hz), 6.91 (d, J = 8.4 Hz), 6.86 (d, J = 8.6 Hz), 6.84–6.78 (m), 6.73 (dd, J = 8.1, 1.9 Hz), 6.62 (dd, J = 8.3, 2.0 Hz), 5.89 (dd, J = 9.1, 6.8 Hz), 5.68 (dd, J = 11.4, 3.1 Hz), 5.41–5.07 (m), 5.01 (dd, J = 12.2, 3.8 Hz), 4.71 (d, J = 2.0 Hz), 4.49 (dd, J = 16.2, 4.7 Hz), 4.28 (dd, J = 17.4, 4.6 Hz), 4.15 (dd, J = 17.4, 4.7 Hz), 3.84 (s), 3.78–3.60 (m), 3.59 (s), 3.57 (s), 3.57–3.50 (m), 3.47–3.37 (m), 3.32 (s), 3.29 (s), 3.27–3.20 (m), 3.20 (s), 3.20–3.11 (m), 3.10 (s), 3.10–2.96 (m), 2.87 (s), 2.74 (s), 2.69 (dd, J = 11.4, 3.0 Hz), 1.52 (d, J = 6.8 Hz), 1.50–1.40 (m), 1.43 (d, J = 6.9 Hz), 1.39 (d, J = 6.9 Hz), 1.33 (d, J = 7.0 Hz),

1.32–1.18 (m); FABMS *m/z* 865 $[M+H]^+$.

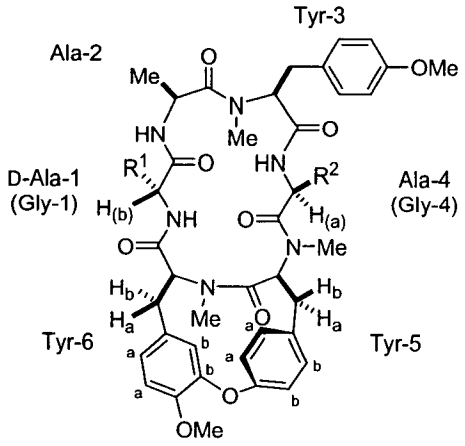
Amine 36. When **33** was treated in the same manner as described for the preparation of **34**, **36** was obtained in 94% yield as an amorphous solid: $[\alpha]^{24}_D$ –169 (*c* = 0.13, pyridine); ^1H NMR (400 MHz, C_5D_5N, mixture of rotamers) δ 8.85 (d, *J* = 5.6 Hz), 8.75 (t, *J* = 5.4 Hz), 8.37 (d, *J* = 7.9 Hz), 8.26–8.07 (m), 7.51 (d, *J* = 7.3 Hz), 7.45 (d, *J* = 7.2 Hz), 7.28–6.87 (m), 6.80 (dd, *J* = 8.8, 2.3 Hz), 6.78–6.65 (m), 6.49–6.42 (m), 5.54–4.80 (m), 4.23–4.10 (m), 4.01–3.90 (m), 3.64 (s), 3.44 (s), 3.41 (s), 3.35–3.20 (m), 3.07 (s), 2.99 (s), 2.92 (s), 2.85 (s), 2.77–2.66 (m), 2.55 (s), 2.54 (s), 2.48–2.39 (m), 1.21 (d, *J* = 6.9 Hz), 1.19 (d, *J* = 6.8 Hz), 1.15 (d, *J* = 6.8 Hz), 0.54 (d, *J* = 6.7 Hz); FABMS *m/z* 865 $[M+H]^+$.

[Gly-1]RA-VII (4). In the presence of 10% Pd/C (12.2 mg), a solution of **34** (8.5 mg, 0.0098 mmol) in EtOH (2.9 mL) was stirred at room temperature under an atmosphere of hydrogen for 25 min. The catalyst was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in DMF (7.6 mL). To this solution were added FDPP (11.3 mg, 0.0294 mmol) and *N,N*-diisopropylethylamine (5.1 μL, 0.029 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 days. The solvent was removed by distillation under reduced pressure. Saturated aqueous $NaHCO_3$ (10 mL) was added to the residue, and the whole was extracted with 97:3 $CHCl_3$/MeOH (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 20:2:1 $CHCl_3$/EtOAc/MeOH) to provide **4** (2.4 mg, 32%) as a crystalline powder, which was recrystallized from MeOH to give white prisms: mp 239–241 °C; $[\alpha]^{26}_D$ –172 (*c* = 0.28, $CHCl_3$); IR (KBr) ν_{max} 3384, 3304, 2996, 2971, 2937, 2840, 1678, 1656, 1648, 1638, 1619, 1542, 1514, 1500, 1443, 1412, 1265, 1248, 1211, 1129, 1096, 1032, 803 cm^{-1}; ^1H and ^{13}C NMR: refer to Tables S1 and S3; FABMS *m/z* 757 $[M+H]^+$; HR-FABMS *m/z* 757.3552 $[M+H]^+$ (calcd for $C_{40}H_{49}N_6O_9$, 757.3561).

[Gly-2]RA-VII (5). In the presence of 10% Pd/C (12.8 mg), a solution of **35** (8.8 mg, 0.0102 mmol) in EtOH (3 mL) was stirred at room temperature under an atmosphere of hydrogen for 40 min. The catalyst was filtered off, and the filtrate was concentrated to give a

residue, which was dissolved in DMF (7.8 mL). To this solution were added HOObt (13.3 mg, 0.0815 mmol) and EDC (15.5 mg, 0.0809 mmol), and the mixture was stirred at room temperature for 4 days. The solvent was removed by distillation under reduced pressure. Water (10 mL) was added to the residue, and the whole was extracted with 97:3 $CHCl_3$/MeOH (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 20:2:1 $CHCl_3$/EtOAc/MeOH) to provide **5** (0.8 mg, 10%) as an amorphous powder, which was recrystallized from MeOH to give a white crystalline powder: mp 263–264 °C; $[\alpha]^{26}_D$ –217 (c = 0.32, $CHCl_3$); IR (KBr) ν_{max} 3387, 3314, 3067, 2934, 2837, 1675, 1664, 1656, 1648, 1638, 1628, 1543, 1514, 1499, 1459, 1448, 1411, 1264, 1249, 1128, 1094, 1032, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, selected data) δ 3.94 (s, 3H), 3.78 (s, 3H), 1.46 (d, 3H, J = 6.9 Hz); FABMS *m/z* 757 $[M+H]^+$; HR-FABMS *m/z* 757.3519 $[M+H]^+$ (calcd for $C_{40}H_{49}N_6O_9$, 757.3561).

[Gly-4]RA-VII (6). A solution of **36** (8.5 mg, 0.0098 mmol) in EtOH (3.4 mL) was stirred in the presence of 10% Pd/C (14.4 mg) at room temperature under an atmosphere of hydrogen for 25 min. The catalyst was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in DMF (7.6 mL), to which were added HOObt (12.8 mg, 0.0785 mmol) and EDC (15.0 mg, 0.0782 mmol), and the mixture was stirred at room temperature for 4 days. The solvent was removed by distillation under reduced pressure. Water (10 mL) was added to the residue, and the whole was extracted with 97:3 $CHCl_3$/MeOH (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered, and the solvent removed *in vacuo*. The residue was subjected to MPLC (silica gel, 20:2:1 $CHCl_3$/EtOAc/MeOH) to provide **6** (4.0 mg, 54%) as an amorphous solid: $[\alpha]^{26}_D$ –150 (c = 0.4, MeOH); IR (film) ν_{max} 3294, 2934, 2837, 1656, 1637, 1513, 1500, 1445, 1411, 1265, 1248, 1216, 1127, 1094, 1031, 753 cm^{-1}; ^1H and ^{13}C NMR: refer to Tables S2 and S3; FABMS *m/z* 757 $[M+H]^+$; HR-FABMS *m/z* 757.3550 $[M+H]^+$ (calcd for $C_{40}H_{49}N_6O_9$, 757.3561).



	R^1	R^2
[Gly-1]RA-VII (**4**)	H_a	Me
[Gly-4]RA-VII (**6**)	Me	H_b

Table S1 ^{1}H NMR Chemical Shifts for [Gly-1]RA-VII (4) in $CDCl_3$ at 300 K

		major conformer	minor conformer
Gly-1	α_a	3.48 (d, 17.7)	3.39 (m)
	α_b	4.29 (dd, 17.7, 7.0)	4.35 (m)
	NH	6.22 (d, 7.0)	6.14 (d, 7.2)
Ala-2	α	4.82 (dq, 8.1, 6.9)	4.85 (m)
	β	1.35 (d, 6.9)	0.98 (d, 6.4)
	NH	6.41 (d, 8.1)	6.43 (*)
Tyr-3	α	3.58 (dd, 10.9, 4.8)	4.68 (m)
	β_a	3.33 (dd, 14.0, 10.9)	2.98–3.07 (m)
	β_b	3.38 (dd, 14.0, 4.8)	2.98–3.07 (m)
	δ	7.04 (d-like, 8.6)	7.09 (d-like, 8.6)
	ε	6.83 (d-like, 8.6)	6.84 (d-like, 8.6)
	NMe	2.87 (s)	2.99 (s)
	OMe	3.79 (s)	3.77 (s)
Ala-4	α	4.75 (dq, 7.6, 6.7)	4.59 (m)
	β	1.13 (d, 6.7)	1.20 (d, 6.8)
	NH	6.76 (d, 7.6)	6.88 (*)
Tyr-5	α	5.44 (dd, 11.4, 3.1)	5.42 (dd, 11.3, 3.0)
	β_a	2.65 (dd, 11.3, 3.1)	2.74 (dd, 11.3, 3.0)
	β_b	3.68 (dd, 11.4, 11.3)	3.70 (dd, 11.3, 11.3)
	δ_a	7.26 (dd, 8.4, 2.2)	7.26 (*)
	δ_b	7.42 (dd, 8.4, 2.2)	7.44 (*)
	ε_a	6.88 (dd, 8.4, 2.4)	6.89 (*)
	ε_b	7.20 (dd, 8.4, 2.4)	7.24 (*)
	NMe	3.13 (s)	3.13 (s)
Tyr-6	α	4.63 (dd, 12.0, 3.8)	4.71 (m)
	β_a	3.11 (dd, 17.8, 12.0)	3.02–3.10 (m)
	β_b	2.98 (dd, 17.8, 3.8)	3.02–3.10 (m)
	δ_a	6.57 (dd, 8.4, 1.9)	6.57 (*)
	δ_b	4.34 (d, 1.9)	4.39 (d, 1.8)
	ε	6.79 (d, 8.4)	6.83 (*)
	NMe	2.67 (s)	2.65 (s)
	OMe	3.93 (s)	3.93 (s)

J-values in parentheses are given in Hz.

* Multiplicity was not determined due to overlapping of the resonances.

Table S2 ^{1}H NMR Chemical Shifts for [Gly-4]RA-VII (6) in CD_3OD at 300 K

		major conformer	minor conformer
D-Ala-1	α	4.14 (q, 7.0)	4.42 (q, 7.0)
	β	1.20 (d, 7.0)	1.28 (d, 7.0)
	NH	*	*
Ala-2	α	4.56 (q, 6.5)	4.54 (q, 6.6)
	β	0.88 (d, 6.5)	1.29 (d, 6.6)
	NH	*	*
Tyr-3	α	4.83 (dd, 11.1, 4.2)	3.96 (br m)
	β_a	3.00 (dd, 14.4, 11.1)	3.25–3.32 (m)
	β_b	3.22 (dd, 14.4, 4.2)	3.25–3.32 (m)
	δ	7.20 (d-like, 8.6)	7.10 (d-like, 8.6)
	ε	6.89 (d-like, 8.6)	6.88 (d-like, 8.6)
	NMe	2.95 (s)	2.90 (s)
	OMe	3.77 (s)	3.77 (s)
Gly-4	α_a	4.12 (d, 17.3)	4.50 (br d, 18)
	α_b	3.80 (d, 17.3)	3.50 (br d, 18)
	NH	*	*
Tyr-5	α	5.35 (dd, 11.3, 3.1)	5.28 (dd, 11.1, 2.8)
	β_a	2.76 (dd, 11.3, 3.1)	2.75 (11.7, 2.8)
	β_b	3.57 (dd, 11.3, 11.3)	3.52 (dd, 11.7, 11.1)
	δ_a	7.23 (dd, 8.4, 2.3)	7.22 (dd, 8.4, 2.3)
	δ_b	7.50 (dd, 8.4, 2.3)	7.50 (dd, 8.4, 2.3)
	ε_a	6.80 (dd, 8.4, 2.4)	6.79 (dd, 8.4, 2.4)
	ε_b	7.26 (dd, 8.4, 2.4)	7.24 (dd, 8.4, 2.4)
	NMe	2.99 (s)	2.95 (s)
Tyr-6	α	4.72 (dd, 12.1, 4.0)	4.65 (m)
	β_a	3.00 (dd, 17.6, 12.1)	2.99–3.07 (m)
	β_b	3.17 (dd, 17.6, 4.0)	2.99–3.07 (m)
	δ_a	6.68 (dd, 8.3, 2.0)	6.67 (dd, 8.3, 2.0)
	δ_b	4.62 (d, 2.0)	4.58 (d, 2.0)
	ε	6.91 (d, 8.3)	6.90 (d, 8.3)
	NMe	2.57 (s)	2.63 (s)
	OMe	3.90 (s)	3.89 (s)

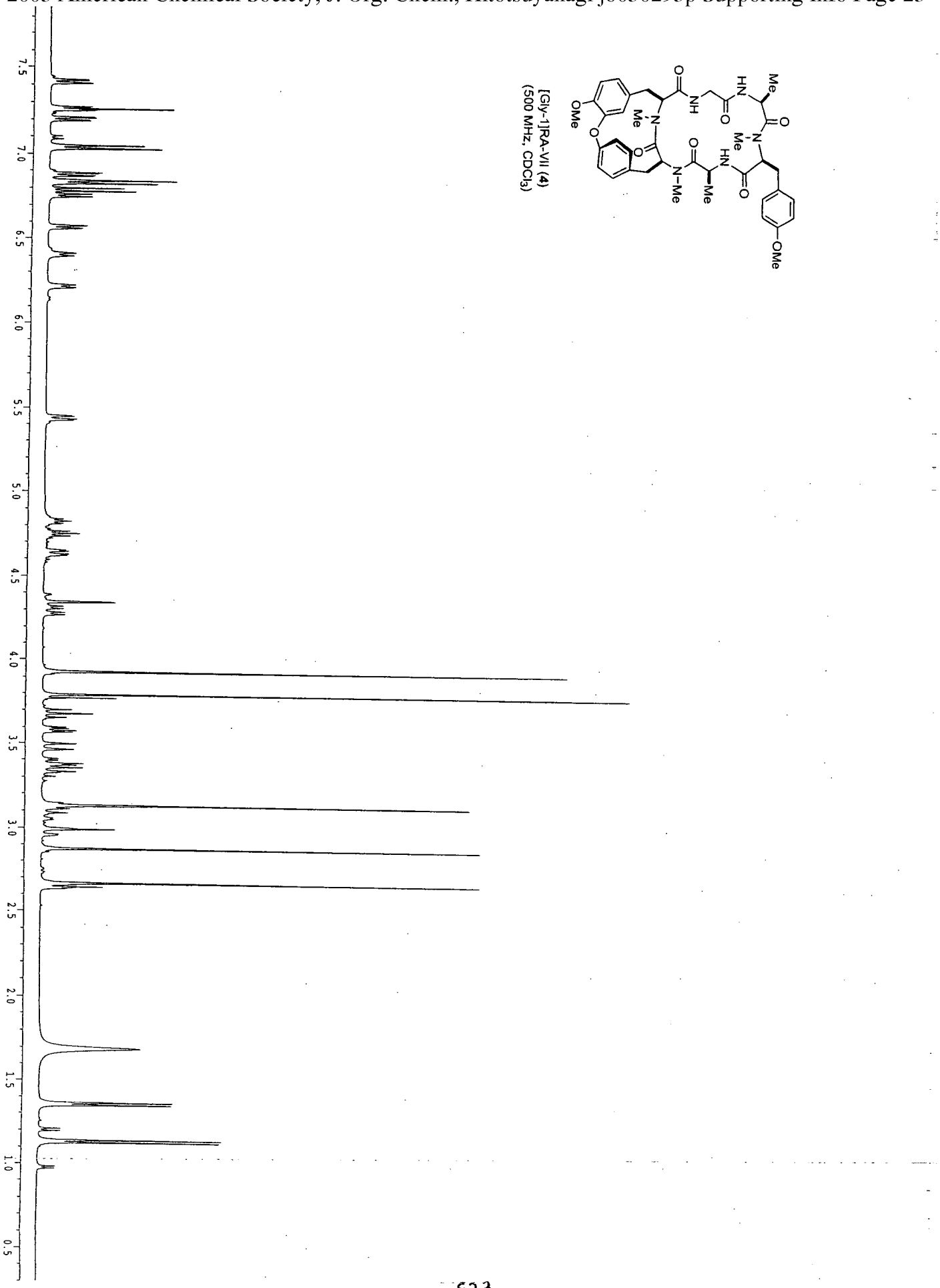
J-values in parentheses are given in Hz.

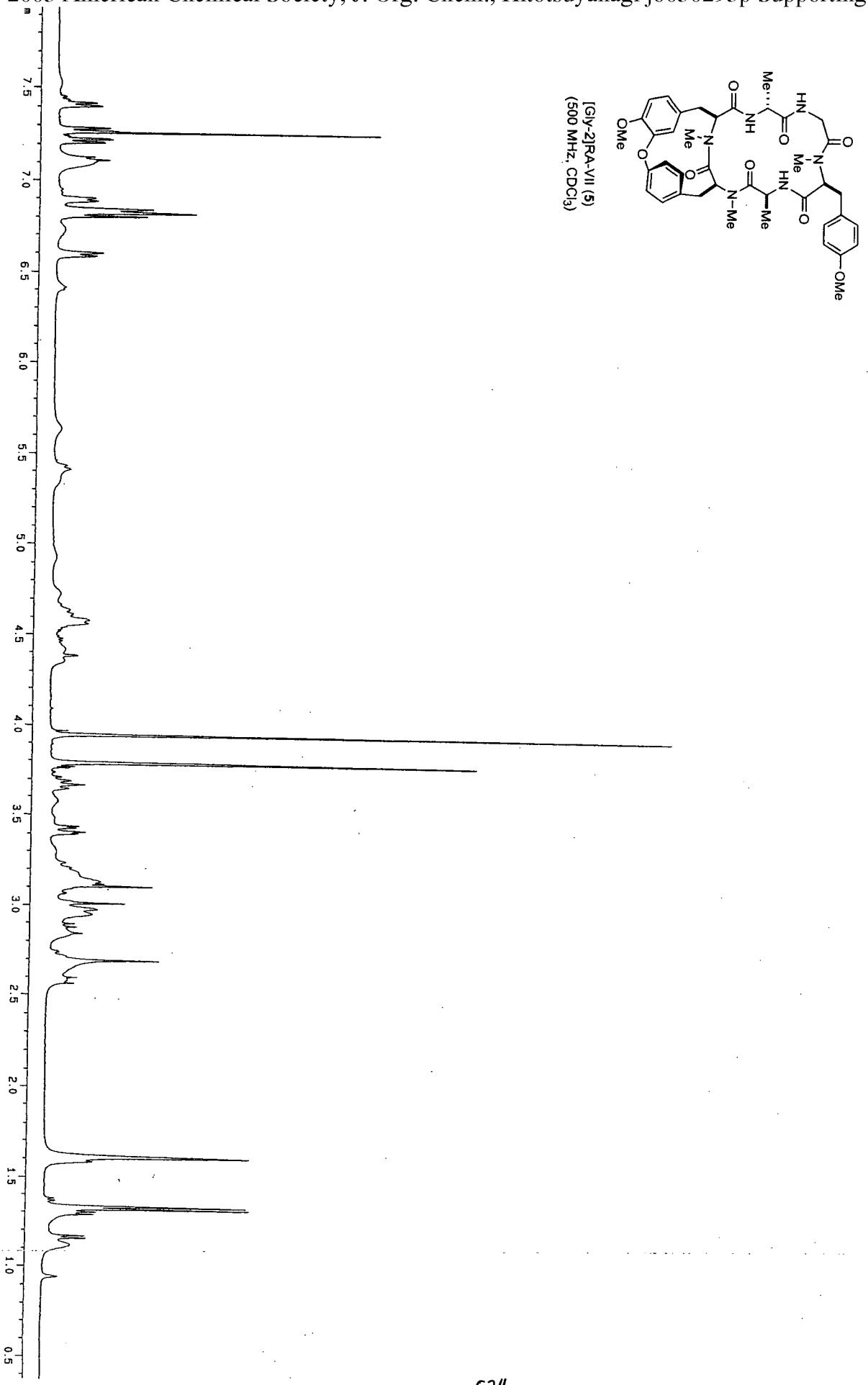
* Not detected due to chemical exchange with deuterium.

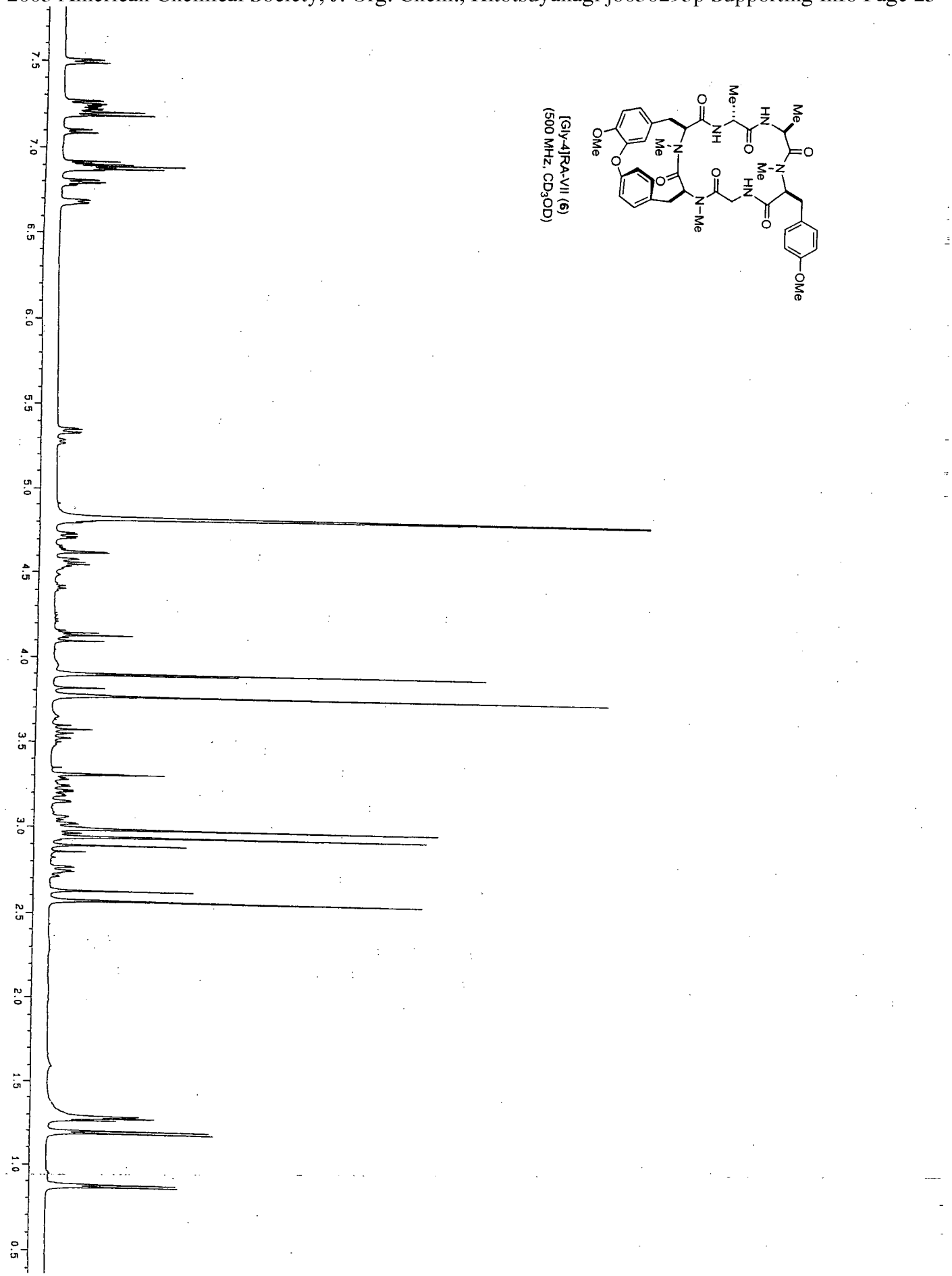
Table S3 ^{13}C NMR Chemical Shifts for [Gly-1]RA-VII (4) and [Gly-4]RA-VII (6) at 300 K

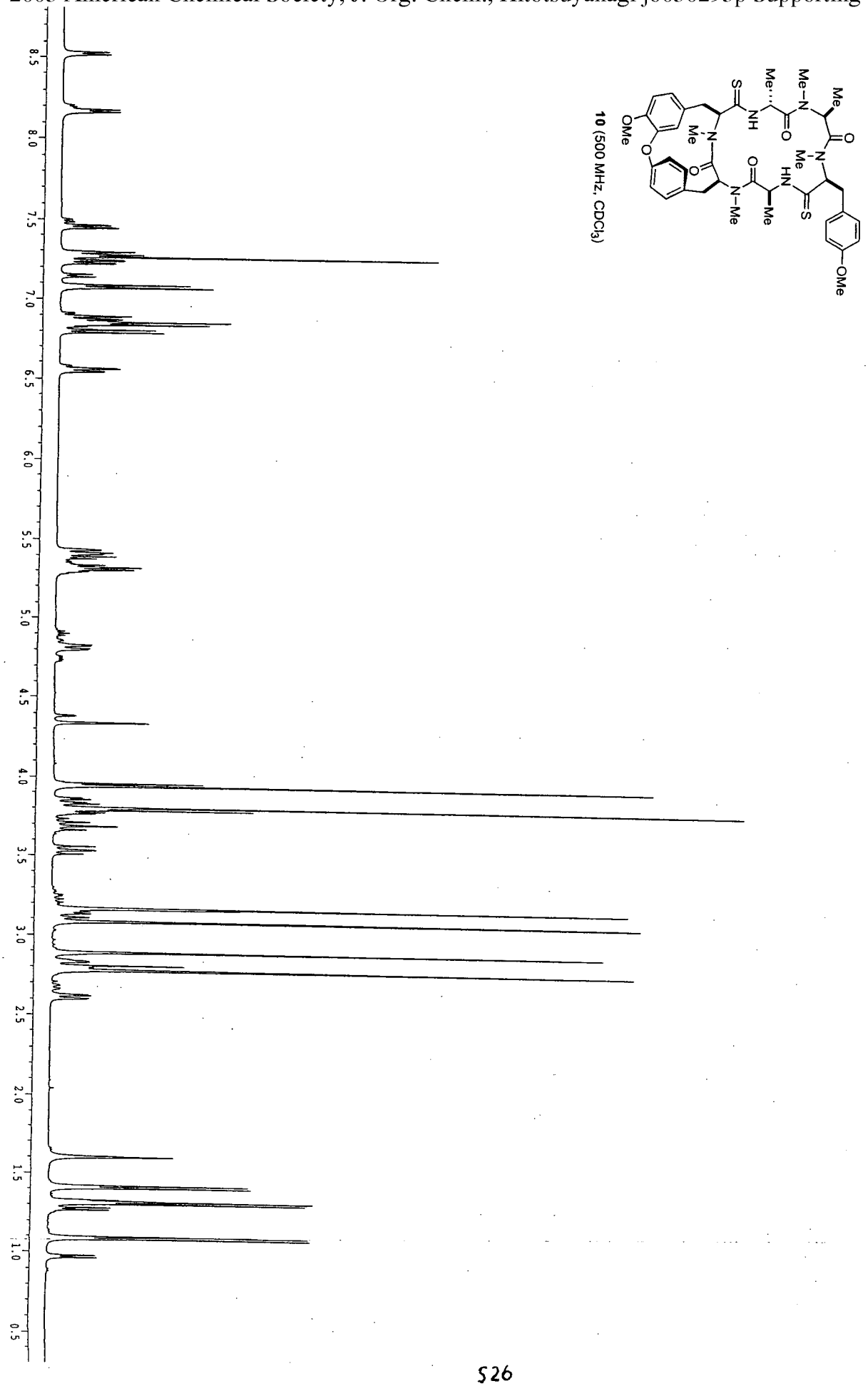
		4[a] major conformer	6[b] major/minor[c]
Gly-1	α	41.4	49.5/*
(D-Ala-1)	β	–	20.6/20.2
	*C*O	168.6	172.8/174.0
Ala-2	α	44.8	45.4/46.8
	β	16.4	17.5/15.9
	*C*O	172.5	173.7/175.6
Tyr-3	α	68.5	63.2/69.0
	β	32.7	35.1/34.1
	γ	130.7	130.2/130.3
	δ	130.3	131.2/131.5
	ε	114.0	115.3/115.0
	ζ	158.4	160.3/160.1
	*C*O	168.1	172.3/172.3[#]
	N*C*H$_3$	39.9	30.9/40.3
	O*C*H$_3$	55.3	55.7/55.7
Ala-4	α	46.5	42.7/42.8
(Gly-4)	β	18.6	–
	*C*O	171.8	169.1/170.1
Tyr-5	α	54.2	56.5/57.4
	β	37.1	37.5/37.6
	γ	135.1	137.3/137.5
	δ$_a$	132.8	134.0/134.0
	δ$_b$	131.0	132.0/132.0
	ε$_a$	124.3	124.9/124.9
	ε$_b$	125.9	127.2/127.2
	ζ	158.3	159.6/159.5
	*C*O	169.6	171.7/171.2
	N*C*H$_3$	30.6	29.9/30.1
Tyr-6	α	57.5	58.9/58.4
	β	35.3	35.8/35.8
	γ	128.1	130.5/130.5
	δ$_a$	121.0	122.6/122.6
	δ$_b$	113.4	115.4/115.2
	ε$_a$	112.2	114.2/114.2
	ε$_b$	153.1	154.4/154.4
	ζ	146.5	148.0/148.0
	*C*O	171.3	172.8/172.2[#]
	N*C*H$_3$	29.2	29.9/30.0
	O*C*H$_3$	56.2	56.9/56.9

[a] Data are recorded in $CDCl_3$. [b] Data are recorded in CD_3OD. [c] Major and minor conformers.
* Not assigned due to overlapping to the solvent resonance. [#] The values may be reversed.

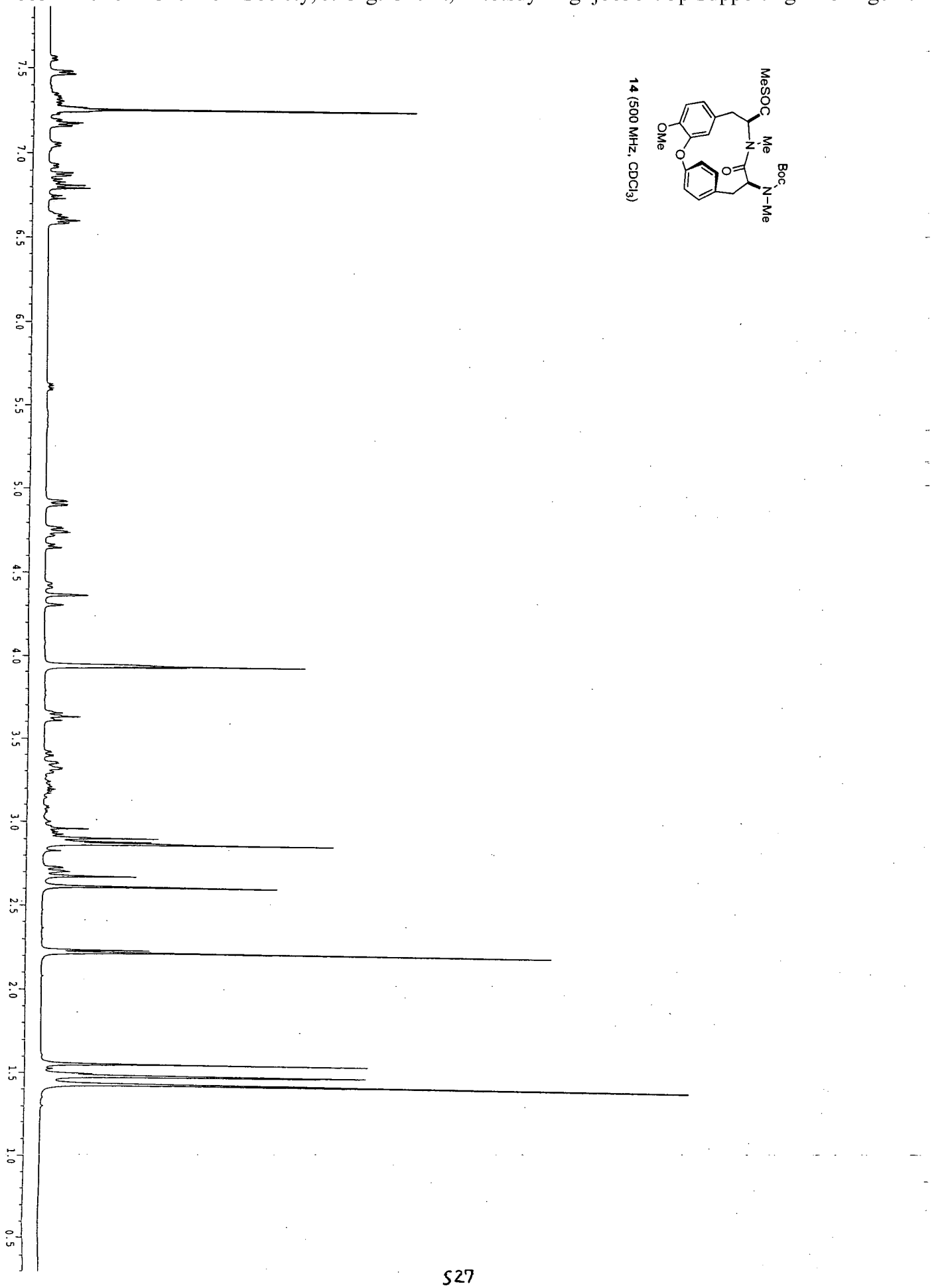


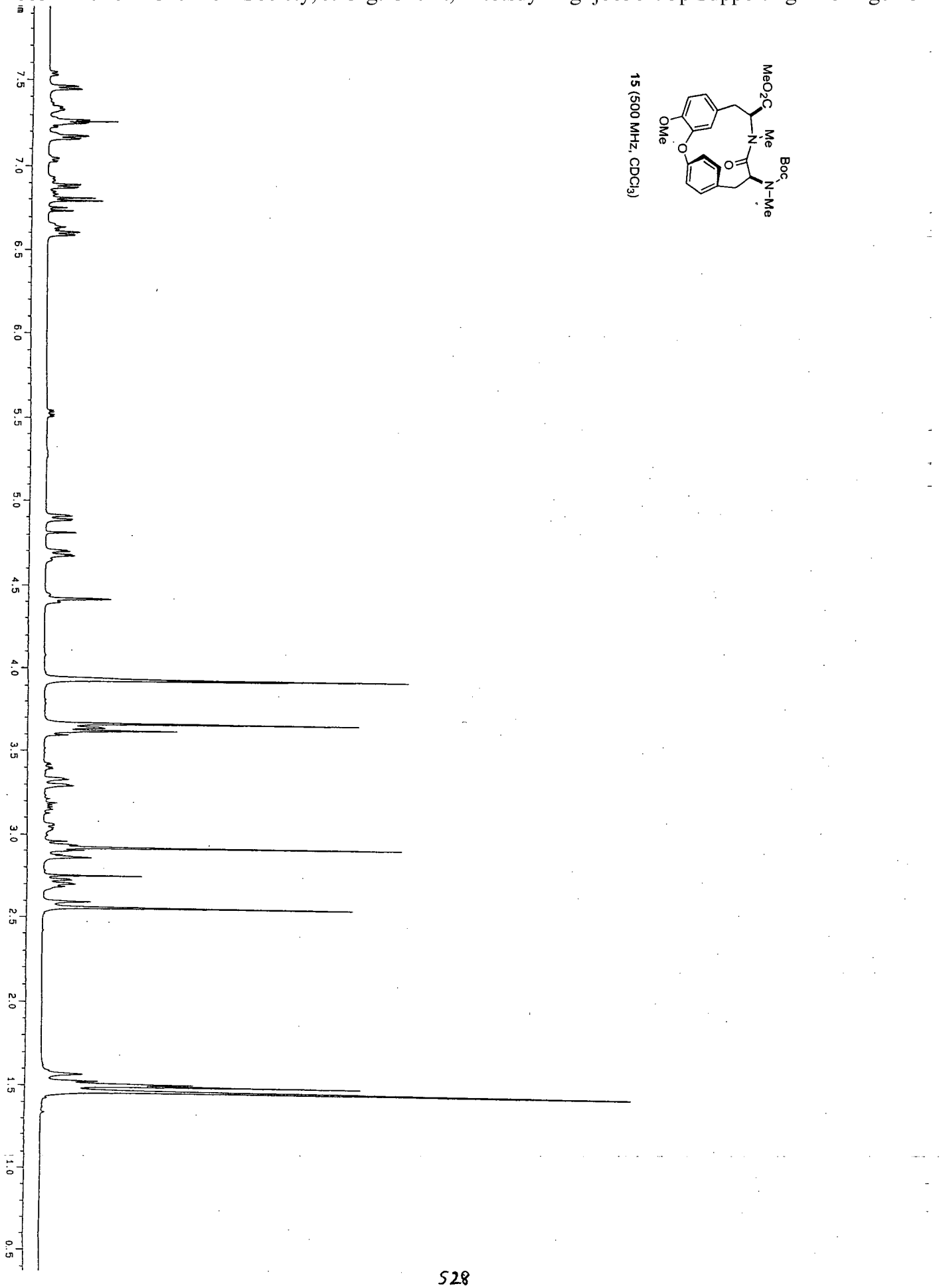


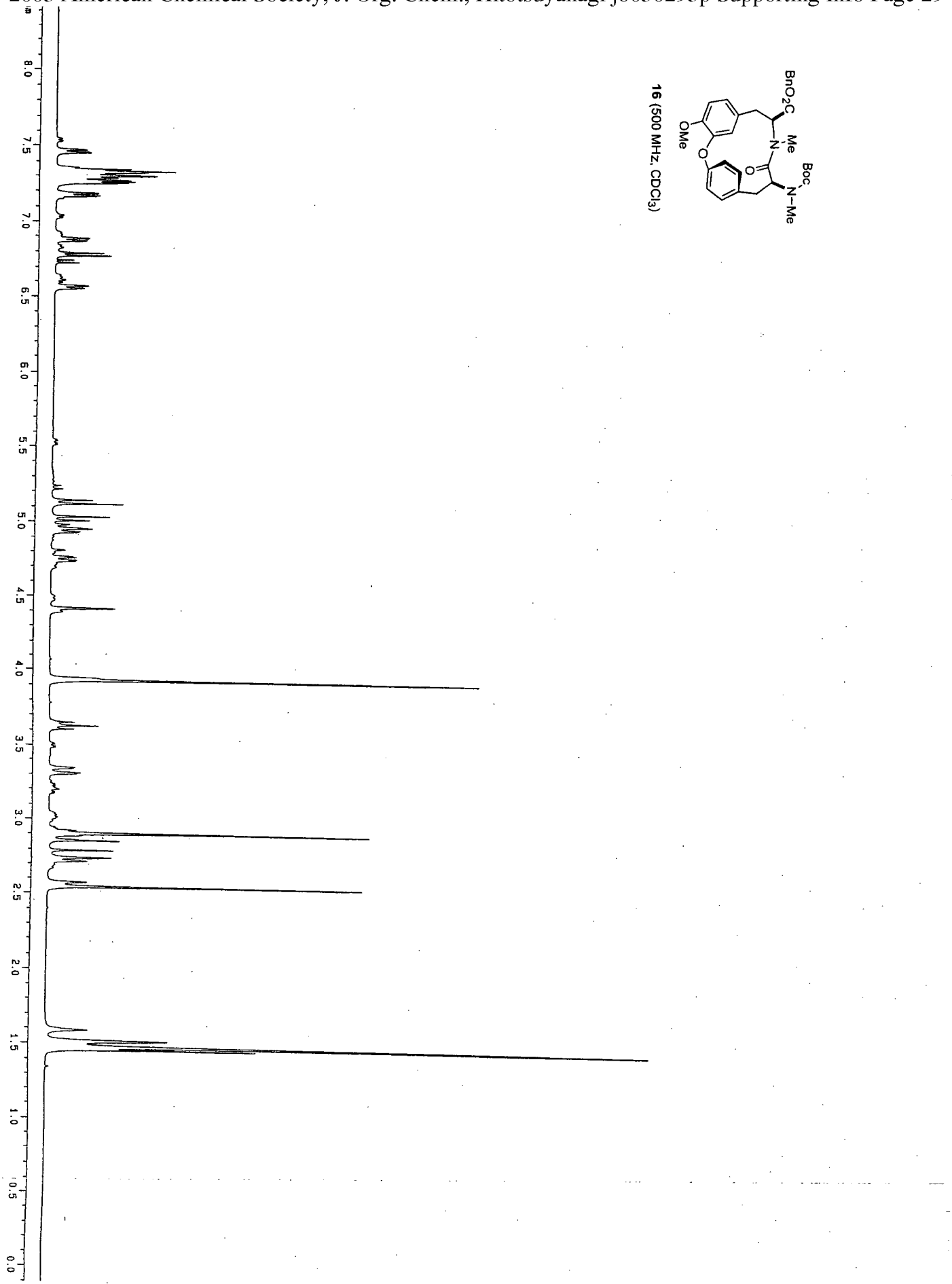




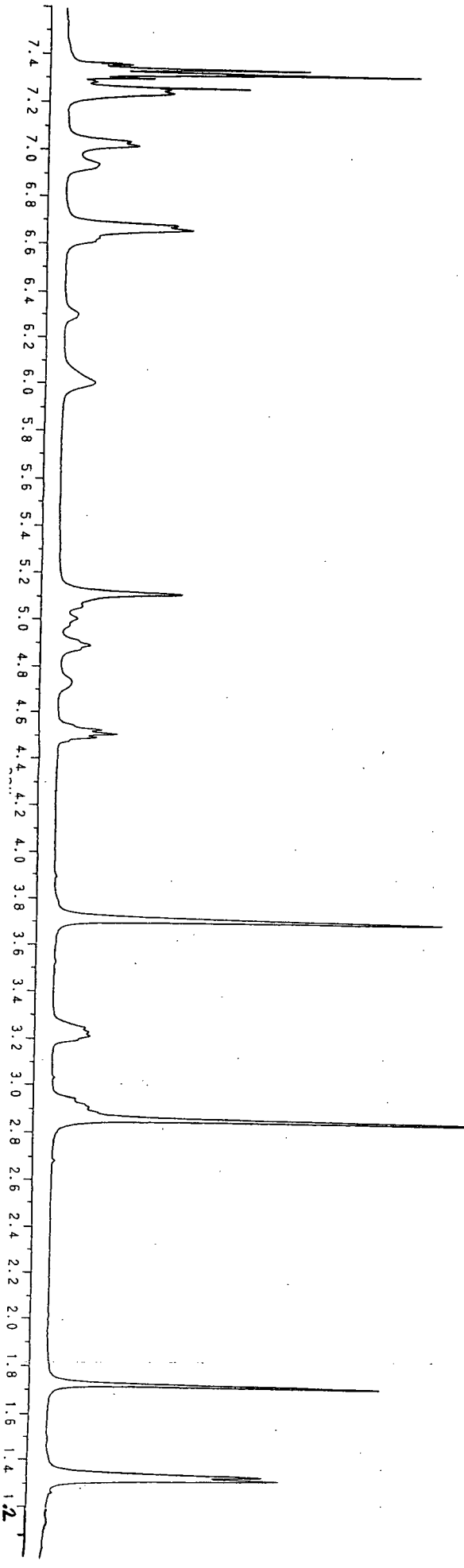
10 (500 MHz, $CDCl_3$)

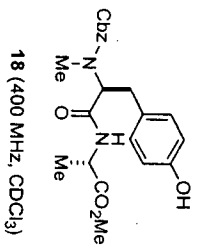




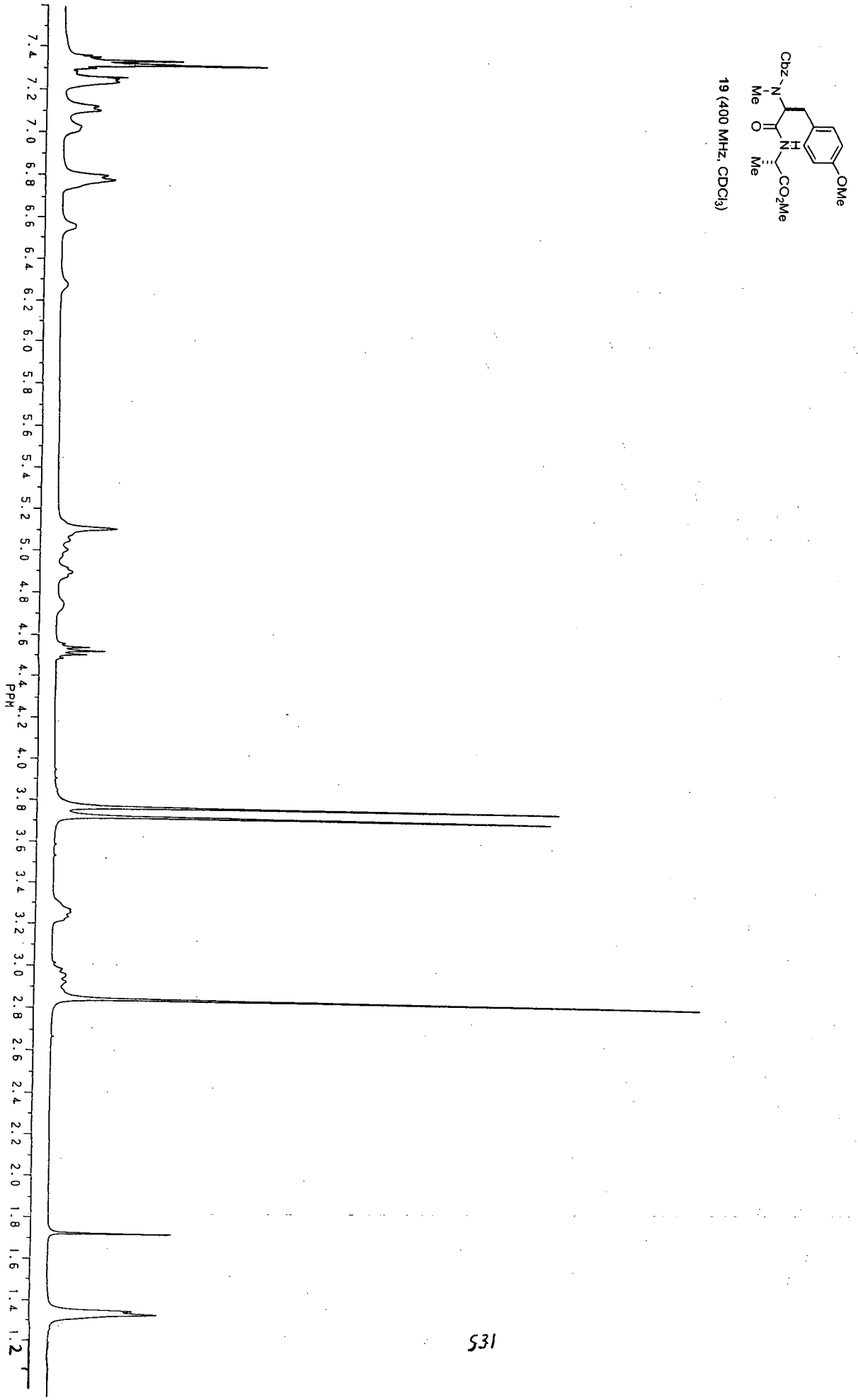


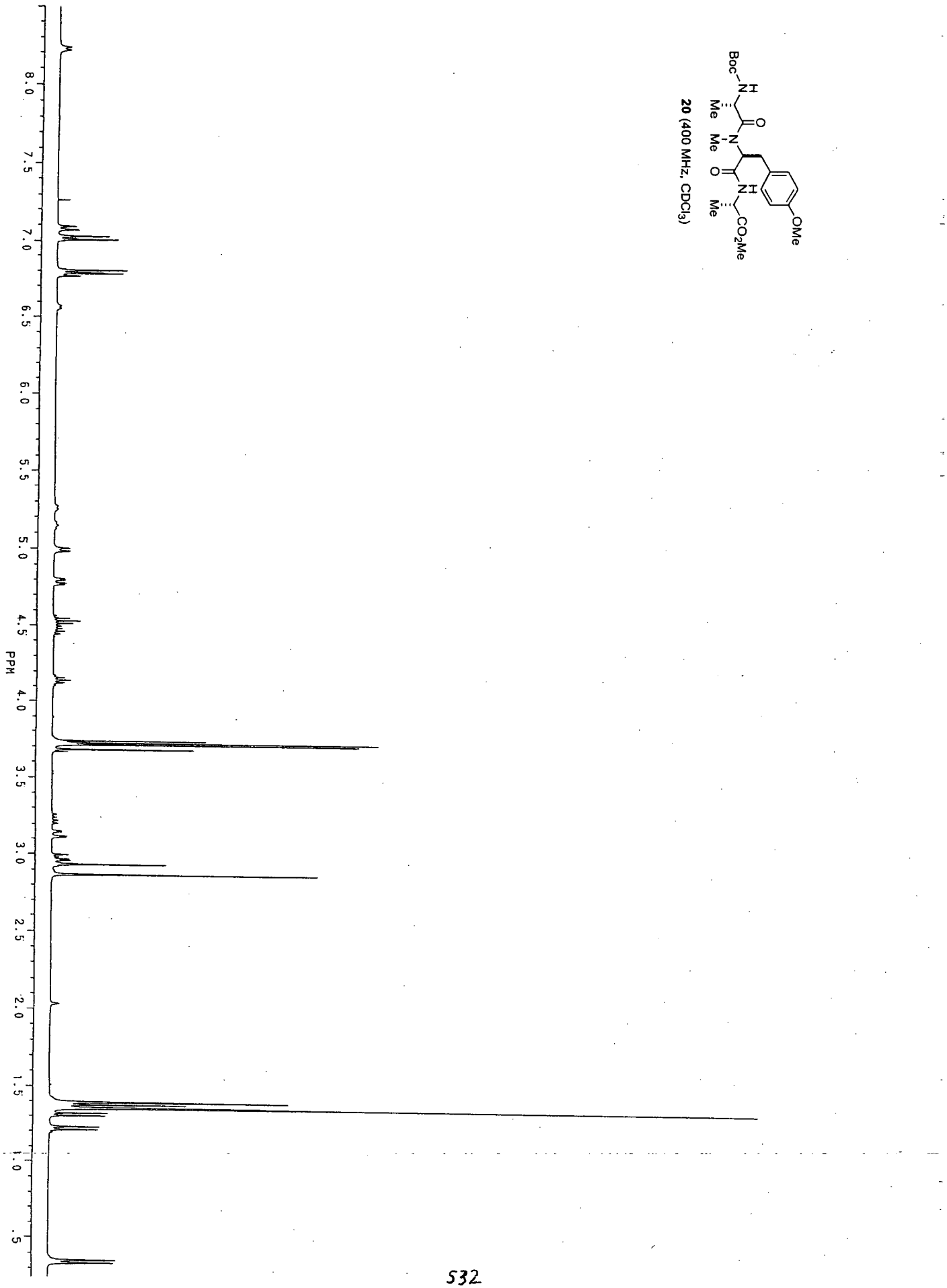
16 (500 MHz, $CDCl_3$)

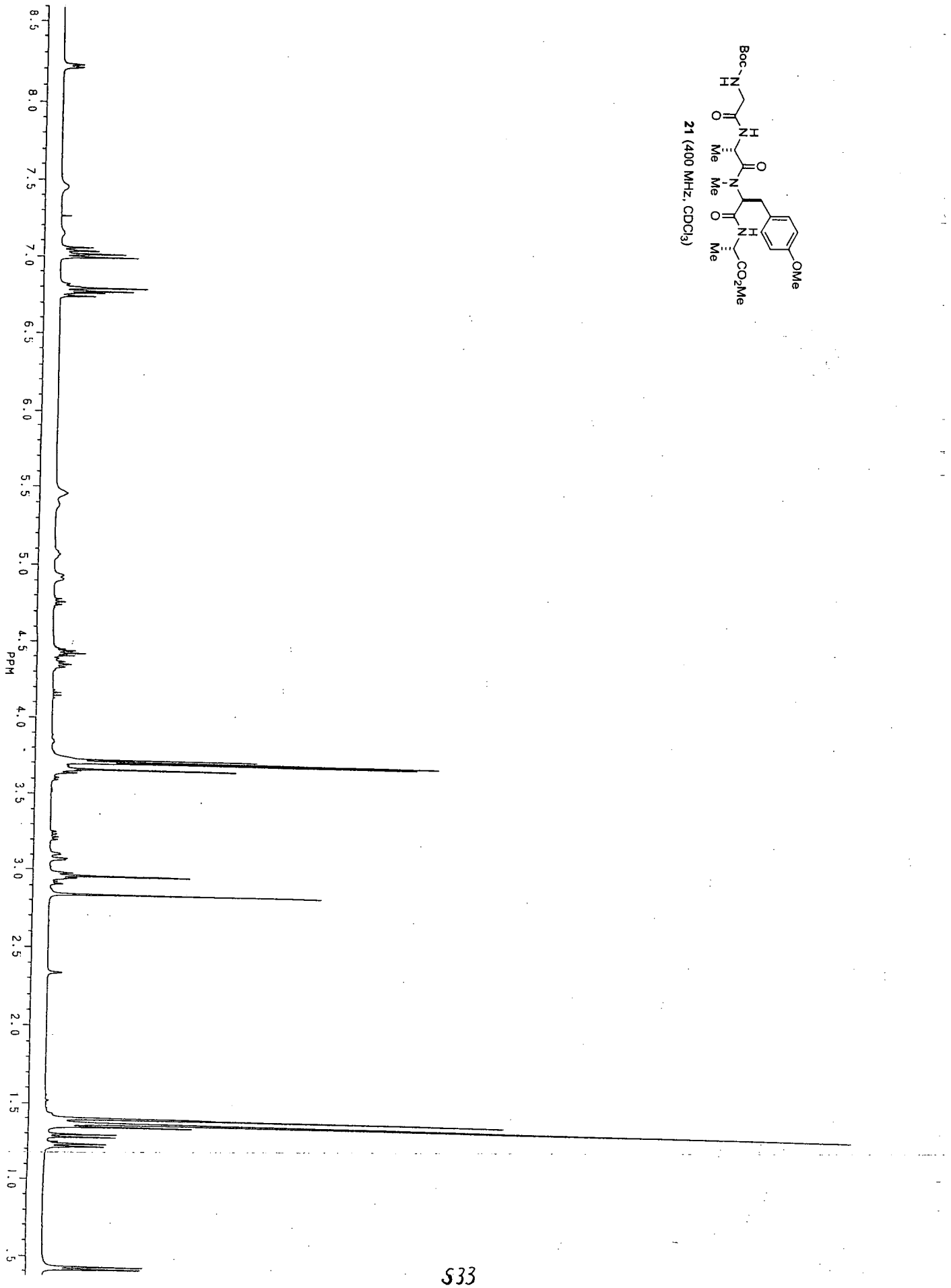


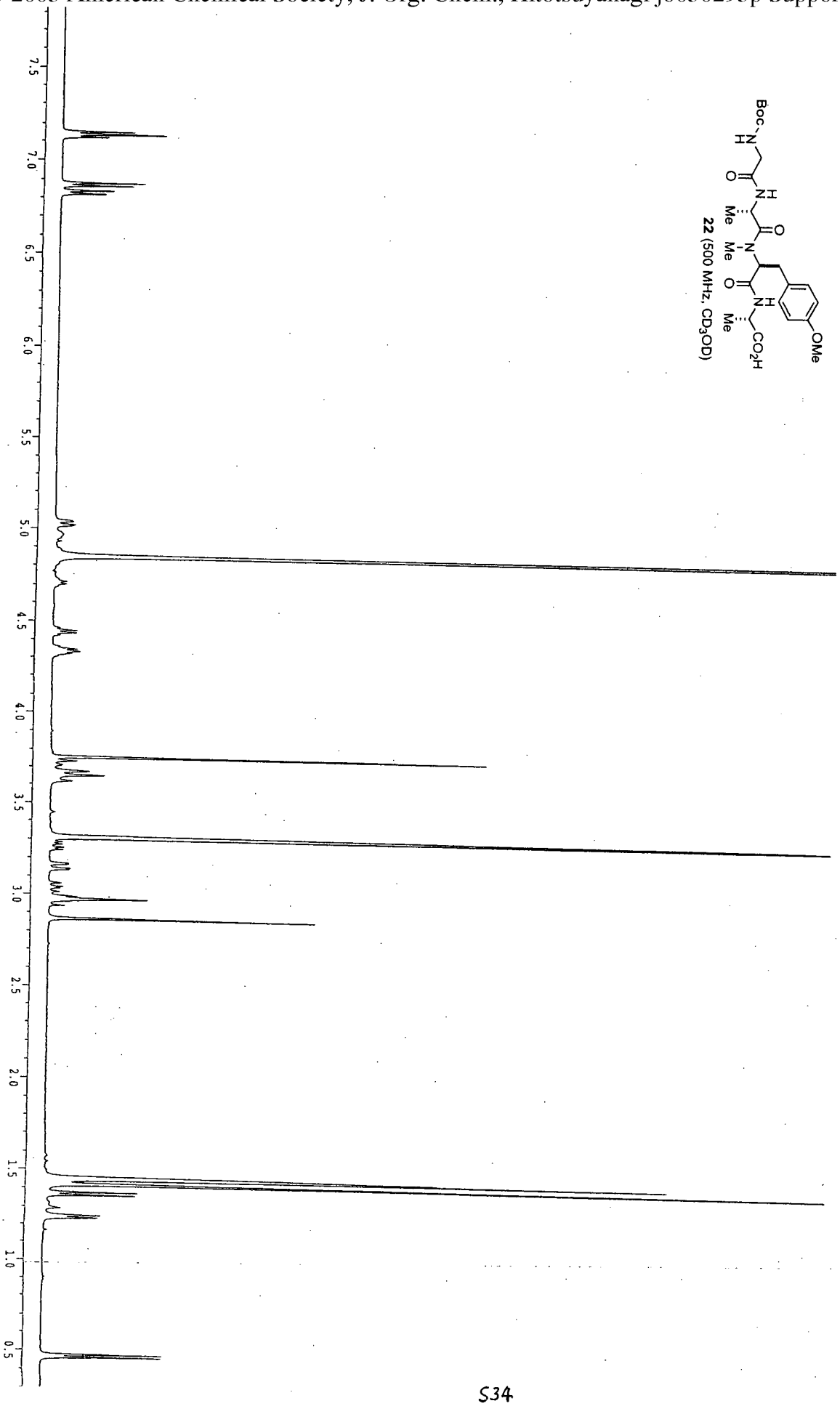


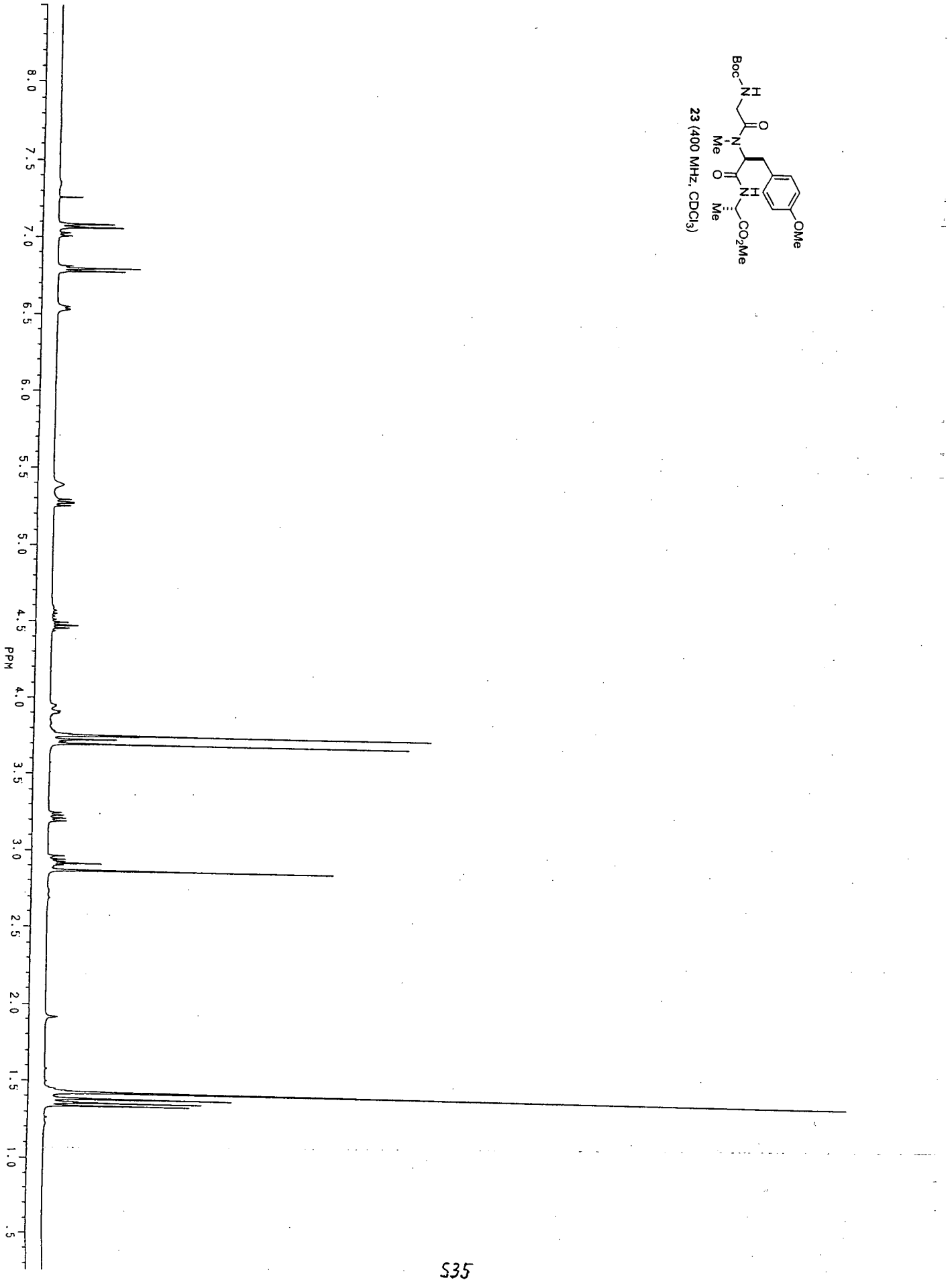
18 (400 MHz, $CDCl_3$)

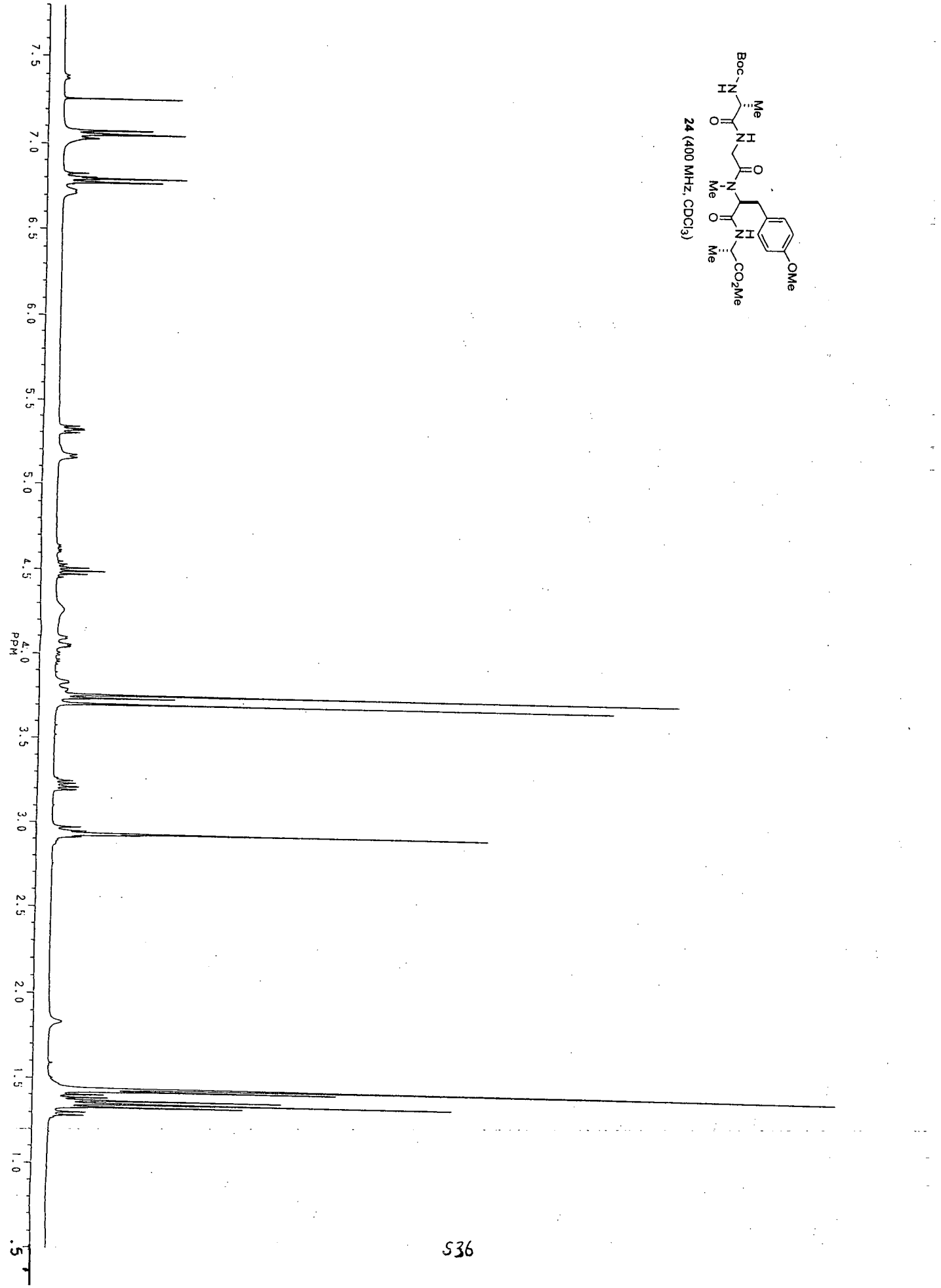





Boc
N
H
O
N
H
Me
O
N
Me
Me
O
N
H
Me
CO2Me
OMe
21 (400 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5







24 (400 MHz, $CDCl_3$)