SUPPLEMENTARY MATERIAL

Electrostatic *vs* Steric Effects in Peptidomimicry. Synthesis and Secondary Structure Analysis of Gramicidin S Analogs with (*E*)-Alkene Peptide Isosteres

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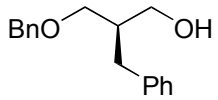
Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra for compounds **2a-b**, **4a-b**, **5a-b**, **7a-b**, **9a-b** and **Cbz$_2$GS**. Crystal information files (CIF) for compounds **5a** and **9b**. Variable temperature ^{1}H NMR shifts for GS, **9a**, and **9b**. NOESY spectra for **9a, 9b** and **Cbz$_2$GS** (600 MHz, DMSO-d$_6$). X-ray crystallographic data for **9b**.

General. All moisture-sensitive reactions were performed using syringe-septum cap techniques under an N_2 atmosphere and all glassware was dried in an oven at 150 ˚C for 2 h prior to use. Reactions carried out at −78 ˚C employed a CO_2−acetone bath. THF was distilled over sodium / benzophenone ketyl; CH_2Cl_2, toluene and Et_3N were distilled from CaH_2. Me_2Zn was purchased from Aldrich Company.

Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a Vaughn's reagent (4.8 g NH_4Mo, 0.2 g $CeSO_4$ in 10 mL conc. H_2SO_4 and 90 mL H_2O). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures.

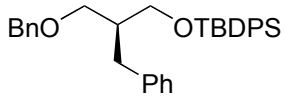
Melting points were determined using a Laboratory Devices Mel-Temp II. Infrared spectra were determined on a Nicolet Avatar 360 FT-IR spectrometer. Circular dichroism spectra were obtained on a JASCO 715 spectrometer at 0.1 mM concentration in EtOH solution. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker Avance 300, 500 or 600 MHz instruments. ^{19}F NMR spectra were obtained on a Bruker Avance 300 instrument. Variable temperature NMR and NOESY spectra were recorded on Bruker Avance 500 or 600 MHz instruments. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), number of protons, and coupling constant(s). Mass spectra were obtained on a Waters Autospec double focusing mass spectrometer (EI) or a Waters Q-Tof mass spectrometer (ESI). A Varian HPLC system equipped with a *semi*-prep C_{18} column (10 mm × 250 mm, 10 μm particle size, 60 Å) and a fraction collector was used for purification.



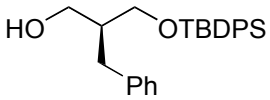
(*R*)-2-Benzyl-3-benzyloxypropan-1-ol (A). Prepared as a colorless oil according to a literature procedure:[1] $[\alpha]^{25}_D$ +32.9 (*c* 1.0, $CHCl_3$); IR (neat) 3415, 3028, 2861, 1495, 1453, 1363, 1088, 1030, 740, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.23 (m, 10

[1] Edmonds, M. K.; Abell, A. D. *J. Org. Chem.* **2001**, *66*, 3747.

H), 4.58, 4.53 (AB, 2 H, J = 11.9 Hz), 3.82-3.69 (m, 2 H), 3.64 (dd, 1 H, J = 9.2, 4.4 Hz), 3.55 (dd, 1 H, J = 9.2, 6.5 Hz), 2.82 (t, 1 H, J = 5.5 Hz), 2.74 (d, 2 H, J = 8.1 Hz), 2.25-2.16 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 138.0, 129.0, 128.3, 128.2, 127.6, 127.5, 125.9, 73.3, 72.2, 64.7, 42.6, 34.4; EIMS *m/z* 256 (M^+, 1.5), 238 (1), 220 (1.3), 208 (2.2), 197 (3.7), 180 (5.3), 165 (3.5), 148 (32), 117 (75), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1456.

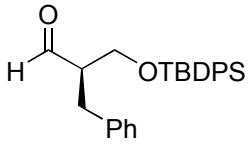


(*S*)-(2-Benzyl-3-benzyloxypropoxy)-*tert*-butyldiphenylsilane (B). A solution of 16.0 g (62.4 mmol) of **A** in 200 mL of dried CH_2Cl_2 was treated at room temperature with 18.0 g (65.5 mmol) of *t*-butylchlorodiphenylsilane. The reaction mixture was cooled to 0 ˚C and treated in one portion with 6.37 g (93.6 mmol) of imidazole followed by 762 mg (6.24 mmol) of DMAP. The resulting mixture was stirred at room temperature overnight. The white precipitate was filtered and washed with cold CH_2Cl_2. The combined organic layers were washed with 1 N HCl and H_2O, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (10 : 1, hexanes/EtOAc) to yield 27.8 g (90%) of **B** as a light yellow oil: $[\alpha]^{25}_D$ +11.2 (*c* 1.0, $CHCl_3$); IR (neat) 3069, 3027, 2950, 2930, 2883, 2857, 1495, 1472, 1428, 1112, 1028, 823, 739, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (t, 4 H, J = 6.3 Hz), 7.59-7.49 (m, 10 H), 7.46-7.33 (m, 6 H), 4.65 (s, 2 H), 3.96 (dd, 1 H, J = 9.9, 4.8 Hz), 3.91 (dd, 1 H, J = 9.8, 5.3 Hz), 3.75-3.70 (m, 2 H), 2.98 (dd, 1 H, J = 13.5, 7.3 Hz), 2.93 (dd, 1 H, J = 14.1, 7.4 Hz), 2.40-2.32 (m, 1 H), 1.29 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 138.7, 135.6, 133.8, 129.5, 129.2, 128.2, 128.2, 127.6, 127.5, 127.3, 125.8, 73.0, 69.8, 63.1, 43.4, 34.3, 26.9, 19.3; EIMS *m/z* 437 ([M- C_4H_9]$^+$, 2), 359 (4), 289 (3.5), 269 (100), 199 (30), 139 (30); HRMS (EI) *m/z* calcd for $C_{29}H_{29}O_2Si$ (M-C_4H_9) 437.1937, found 437.1917.

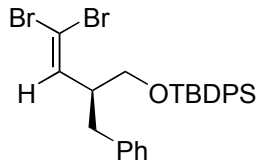


(*S*)-2-Benzyl-3-(*tert*-butyldiphenylsilanyloxy)-propan-1-ol (C). A solution of 10.0 g (20.2 mmol) of **B** in 262 mL of EtOAc was hydrogenated (ballon) with 1.16 g of

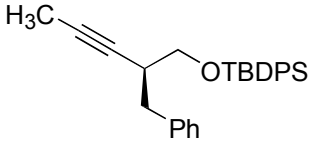
$Pd(OH)_2$ (~20% Pd) at room temperature for 14 h. The mixture was filtered through a thin pad of silica and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (4 : 1, hexanes/EtOAc) to yield 7.70 g (94%) of **C** as a colorless oil: $[\alpha]^{25}_D$ –8.2 (*c* 0.6, $CHCl_3$); IR (neat) 3418, 3070, 3026, 2930, 2889, 2857, 1472, 1428, 1112, 1082, 1049, 823, 789, 740, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 4 H, *J* = 7.5 Hz), 7.50-7.41 (m, 6 H), 7.30-7.20 (m, 3 H), 7.17 (d, 2 H, *J* = 7.0 Hz), 3.84 (dd, 1 H, *J* = 10.2, 4.1 Hz), 3.80 (dd, 1 H, *J* = 9.7, 5.0 Hz), 3.78-3.72 (m, 2 H), 2.68 (d, 2 H, *J* = 7.5 Hz), 2.38 (t, 1 H, *J* = 5.4 Hz), 2.13-2.06 (m, 1 H), 1.14 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 135.6, 133.1, 129.8, 129.0, 128.2, 128.3, 127.8, 125.9, 65.8, 64.7, 44.3, 34.0, 26.9, 19.2; EIMS *m/z* 347 ($[M\text{-}C_4H_9]^+$, 27), 269 (27), 229 (21), 199 (100), 181 (13), 131 (70), 91 (55), 77 (15); HRMS (EI) *m/z* calcd for $C_{22}H_{23}O_2Si$ (M-C_4H_9) 347.1467, found 347.1468.



(*R*)-2-Benzyl-3-(*tert*-butyldiphenylsilanyloxy)-propionaldehyde (D). A solution of 1.08 g (2.66 mmol) of **C** in 20.0 mL of CH_2Cl_2 was treated at 0 ˚C with 1.36 g (3.20 mmol) of Dess-Martin Periodinane. The reaction mixture was stirred at 0 ˚C for 2.5 h, quenched with saturated $Na_2S_2O_3$ in saturated $NaHCO_3$ solution, stirred for 15 min at room temperature, extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10 : 1, hexanes/EtOAc) to yield 960 mg (90%) of **D** as a colorless oil: IR (neat) 3070, 3028, 2956, 2931, 2858, 1728, 1472, 1428, 1112, 1049, 823, 740, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (d, 1 H, *J* = 1.5 Hz), 7.67-7.63 (m, 4 H), 7.50-7.38 (m, 6 H), 7.31-7.20 (m, 3 H), 7.19-7.14 (m, 2 H), 3.98 (dd, 1 H, *J* = 10.5, 4.2 Hz), 3.85 (dd, 1 H, *J* = 10.5, 5.4 Hz), 3.13 (dd, 1 H, *J* = 14.0, 6.3 Hz), 2.89 (dd, 1 H, *J* = 14.0, 8.2 Hz), 2.80-2.73 (m, 1 H), 1.10 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 138.8, 135.6, 133.1, 133.0, 129.9, 129.8, 129.0, 128.5, 127.8, 126.3, 61.6, 55.7, 31.2, 26.8, 19.3; EIMS *m/z* 345 ($[M\text{-}C_4H_9]^+$, 7.4), 315 (6.6), 289 (3.6), 267 (60), 259 (25), 199 (100), 129 (47), 91 (75), 77 (17); HRMS (EI) *m/z* calcd for $C_{22}H_{21}O_2Si$ (M-C_4H_9) 345.1311, found 345.1316.

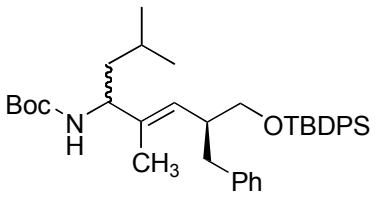


(*S*)-(2-Benzyl-4,4-dibromobut-3-enyloxy)-*tert*-butyldiphenylsilane (E). A solution of 950 mg (2.36 mmol) of **D** in 50.0 mL of dried CH_2Cl_2 was treated at room temperature with 3.13 g (9.44 mmol) of CBr_4, 617 mg (9.44 mmol) of zinc dust and 2.48 g (9.44 mmol) of PPh_3. The reaction mixture was stirred at 25 ˚C for another 1 h, diluted with 100 mL of hexane, filtered through a thin pad of silica gel, washed with hexane, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (50 : 1, hexanes/EtOAc) to yield 1.25 g (95%) of **E** as a colorless oil: $[\alpha]^{25}_D$ +24.8 (*c* 1.0, $CHCl_3$); IR (neat) 3070, 3027, 2999, 2930, 2857, 1495, 1471, 1427, 1112, 1049, 823, 789, 740, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 4 H, *J* = 6.6 Hz), 7.46-7.37 (m, 6 H), 7.30-7.20 (m, 3 H), 7.15 (d, 2 H, *J* = 7.1 Hz), 6.38 (d, 1 H, *J* = 9.3 Hz), 3.62 (dd, 1 H, *J* = 10.1, 5.2 Hz), 3.58 (dd, 1 H, *J* = 10.1, 4.9 Hz), 2.92 (dd, 1 H, *J* = 13.1, 7.0 Hz), 2.88-2.81 (m, 1 H), 2.72 (dd, 1 H, *J* = 13.1, 6.8 Hz), 1.10 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 138.9, 135.6, 133.4, 129.8, 129.2, 128.4, 127.8, 126.3, 89.7, 64.1, 47.8, 36.2, 26.9, 19.3; EIMS *m/z* 499 ($[M\text{-}C_4H_9]^+$, 1.5), 421 (1), 315 (2.7), 263 (10), 199 (8), 159 (10), 121 (100), 91 (27), 77 (10); HRMS (EI) *m/z* calcd for $C_{23}H_{21}{}^{79}Br_2OSi$ ($M\text{-}C_4H_9$) 498.9728, found 498.9727.



(*S*)-(2-Benzylpent-3-ynyloxy)-*tert*-butyldiphenylsilane (2a). A solution of 1.42 g (2.54 mmol) of **E** in 28.0 mL of dried THF was treated at -78 ˚C with 3.50 mL (5.59 mmol) of *n*-BuLi (1.6 M solution in hexane). The reaction mixture was stirred at -78 ˚C for 1 h and at room temperature for an additional 1 h, cooled to -78 ˚C, and treated dropwise with 1.58 mL (25.4 mmol) of CH_3I. The solution was warmed to room temperature, stirred overnight, quenched with H_2O, extracted with ether, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (20 : 1,

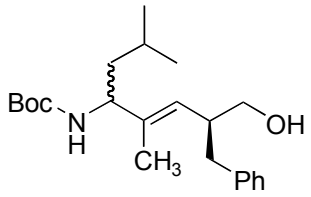
hexanes/EtOAc) to yield 1.02 g (97%) of **2a** as a colorless oil: $[\alpha]^{25}_{D}$ +4.1 (*c* 0.44, $CHCl_3$); IR (neat) 3070, 3028, 2956, 2930, 2857, 1471, 1428, 1112, 823, 740, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72-7.69 (m, 4 H), 7.45-7.38 (m, 6 H), 7.31 (m, 5 H), 3.74 (dd, 1 H, *J* = 9.8, 4.5 Hz), 3.62-3.59 (m, 1 H), 3.11-3.06 (m, 1 H), 2.77-2.71 (m, 2 H), 1.74 (d, 3 H, *J* = 2.0 Hz), 1.11 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 135.6, 133.7, 133.6, 129.6, 129.4, 128.0, 127.6, 126.1, 79.5, 78.4, 65.7, 37.6, 36.7, 26.9, 19.3, 3.5; EIMS *m/z* 411 ($[M-H]^+$, 0.7), 355 (40), 277 (47), 221 (48), 199 (100), 183 (50), 155 (38), 135 (24), 91 (37); HRMS (EI) *m/z* calcd for $C_{28}H_{31}OSi$ (M-H) 411.2144, found 411.2167.



[(4*S*)-Benzyl-5-(*tert*-butyldiphenylsilanyloxy)-1-isobutyl-2-methylpent-(2*E*)-enyl]-carbamic acid *tert*-butyl ester (3a). A solution of 1.20 g (2.91 mmol) of **2a** in 20.0 mL of dried CH_2Cl_2 was treated at room temperature with 1.20 g (4.65 mmol) of Cp_2ZrHCl. The reaction mixture was stirred at room temperature for 20 min, CH_2Cl_2 was removed *in vacuo* and 20.0 mL of toluene was added. The resulting yellow solution was cooled to -78 ˚C, treated over a period of 30 min with 1.45 mL (2.90 mmol) of Me_2Zn (2.0 M solution in toluene), stirred at -78 ˚C for 30 min, warmed to 0 ˚C over a period of 5 min and treated in one portion with 1.08 g (5.82 mmol) of *N*-Boc-isovaleraldimine[2]. The reaction mixture was stirred at 0 ˚C for 4 h, quenched with saturated NH_4Cl, diluted with EtOAc, filtered through a thin pad of Celite, and extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (20 : 1, hexanes/EtOAc) to yield 1.22 g (70%) of **3a** as a colorless, oily 1 : 1.5 mixture of diastereomers: IR (neat) 3442, 3361, 3270, 3069, 2957, 2931, 2860, 1702, 1495, 1472, 1388, 1366, 1248, 1170, 1110, 823, 741, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4 H), 7.43-7.37 (m, 6 H), 7.23-7.11 (m, 5 H), 5.22 (d, 0.4 H, *J* =

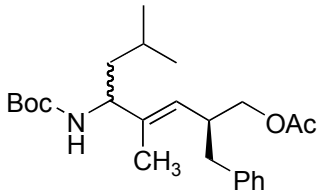
[2] Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem*. **1994**, *59*, 1238.

9.5 Hz), 5.13 (b, 0.6 H), 4.33 (b, 0.6 H), 4.30 (b, 0.4 H), 3.99 (b, 0.6 H), 3.94 (b, 0.4 H), 3.57 (b, 1.2 H), 3.56 (s, 0.8 H), 2.99 (b, 0.4 H), 2.98 (dd, 0.6 H, J = 13.1, 4.6 Hz), 2.80-2.60 (m, 1 H), 2.48-2.40 (m, 1 H), 1.50-1.48 (m, 3 H), 1.45 (s, 5.4 H), 1.41 (s, 3.6 H), 1.27-1.2 (m, 1 H), 1.09 (s, 9 H), 0.99-0.91 (m, 2 H), 0.87 (d, 3 H, J = 5.7 Hz), 0.82 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 140.4, 136.8, 136.5, 135.5, 133.7, 129.5, 129.3, 129.1, 127.8, 127.5, 126.4, 125.5, 78.6, 66.4, 55.5, 42.7, 42.6, 37.9, 28.3, 26.8, 24.7, 24.6, 22.5, 22.4, 19.2, 12.6; EIMS *m/z* 542 ([M-C_4H_9]$^+$, 0.2), 499 (0.8), 486 (3), 442 (55), 425 (37), 364 (14), 199 (100), 135 (42), 91 (44); HRMS (EI) *m/z* calcd for $C_{33}H_{45}NOSi$ (M-$C_5H_8O_2$) 499.3270, found 499.3261.

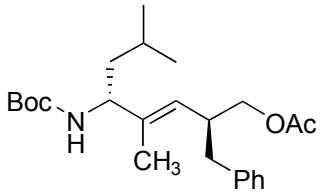


((4*S*)-Benzyl-5-hydroxy-1-isobutyl-2-methylpent-(2*E*)-enyl)-carbamic acid *tert*-butyl ester. A solution of 889 mg (1.48 mmol) of **3a** in 5.00 mL of dried THF was treated at 0 ˚C with 2.22 mL (2.20 mmol) of TBAF (1.0 M solution in THF). The reaction mixture was stirred at room temperature for 7 h, and diluted with EtOAc, washed with brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (4 : 1, hexanes/EtOAc) to yield 375 mg (70%) of ((4*S*)-benzyl-5-hydroxy-1-isobutyl-2-methylpent-(2*E*)-enyl)-carbamic acid *tert*-butyl ester as a colorless, foamy 1 : 1.5 mixture of diastereomers: IR (neat) 3339, 2955, 2930, 1690, 1497, 1366, 1250, 1170, 1045, 1030, 746, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.11 (m, 5 H), 5.18-5.10 (m, 1 H), 4.57 (b, 0.6 H), 4.50 (b, 0.4 H), 4.00-3.85 (m, 1 H), 3.70-3.62 (m, 0.4 H), 3.59 (dd, 0.6 H, J = 10.5, 5.0 Hz), 3.46-3.37 (m, 1 H), 2.95-2.71 (m, 2 H), 2.51-2.38 (m, 1 H), 2.05 (b, 1 H), 1.58-1.49 (m, 1 H), 1.45 (s, 5.4 H), 1.41 (s, 3.6 H), 1.37 (s, 1.8 H), 1.33 (s, 1.2 H), 1.26-1.13 (m, 2 H), 0.89 (d, 3.6 H, J = 6.6 Hz), 0.84 (d, 1.2 H, J = 4.5 Hz), 0.82 (d, 1.2 H, J = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 155.3, 140.1, 140.0, 139.3, 137.5, 129.2, 129.0, 128.0, 125.8, 125.7, 125.2, 79.4, 79.2, 66.0, 57.5, 55.6, 43.1, 42.9, 41.5, 38.0, 37.7, 28.4, 28.3, 24.9, 24.3, 23.0, 22.8, 22.2, 22.0, 13.9, 11.0;

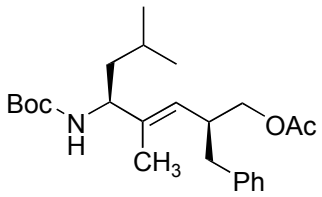
EIMS *m/z* 362 ([M+H]$^+$, 0.2), 331 (8), 304 (8), 275 (25), 248 (22), 214 (85), 130 (60), 91 (79), 57 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{35}NO_3$ 361.2617, found 361.2614.



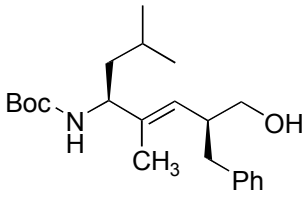
Acetic acid 2-benzyl-(5*S*)-*tert*-butoxycarbonylamino-(*4E*)-7-dimethyloct-3-enyl ester. A solution of 500 mg (1.38 mmol) of ((4*S*)-benzyl-5-hydroxy-1-isobutyl-2-methylpent-(2*E*)-enyl)-carbamic acid *tert*-butyl ester in 15.0 mL of dried CH_2Cl_2 was treated at 0 ˚C with 386 μL (2.77 mmol) of TEA, 522 μL (5.53 mmol) of Ac_2O and 16.8 mg (0.138 □mol) of DMAP. The reaction mixture was stirred at 0 ˚C for 2 h, diluted with EtOAc, and washed with brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (30 : 1, CH_2Cl_2/EtOAc) to yield 273 mg (49%) and 240 mg (43%), respectively, of the two diasteromers of acetic acid 2-benzyl-(5*S*)-*tert*-butoxycarbonylamino-(*4E*)-7-dimethyloct-3-enyl ester.



Acetic acid (2*R*)-benzyl-(5*S*)-*tert*-butoxycarbonylamino-(4*E*)-7-dimethyloct-3-enyl ester (less polar, major epimer): Colorless foam; $[\alpha]^{25}_D$ +35.9 (*c* 1.0, $CHCl_3$); IR (neat) 3370, 2956, 2869, 1742, 1702, 1497, 1366, 1244, 1170, 1038, 748, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.22 (m, 2 H), 7.18-7.11 (m, 3 H), 5.18 (d, 1 H, *J* = 9.0 Hz), 4.42 (b, 1 H), 4.04-3.95 (m, 1 H), 3.98 (d, 2 H, *J* = 6.5 Hz), 2.92-2.83 (m, 1 H), 2.77 (dd, 1 H, *J* = 13.3, 5.6 Hz), 2.53 (dd, 1 H, *J* = 13.0, 8.6 Hz), 2.03 (s, 3 H), 1.50-1.42 (m, 1 H), 1.46 (s, 9 H), 1.28-1.23 (m, 2 H), 1.26 (s, 3 H), 0.88 (d, 3 H, *J* = 6.6 Hz), 0.88 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 155.0, 139.5, 137.8, 129.3, 128.1, 125.9, 125.5, 78.9, 67.1, 55.7, 42.6, 39.3, 38.2, 28.4, 24.8, 22.6, 22.4, 20.8, 12.5; EIMS *m/z* 403 (M$^+$, 0.5), 346 (13), 303 (8), 290 (15), 246 (23), 186 (93), 169 (32), 91 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{37}NO_4$ 403.2723, found 403.2713.

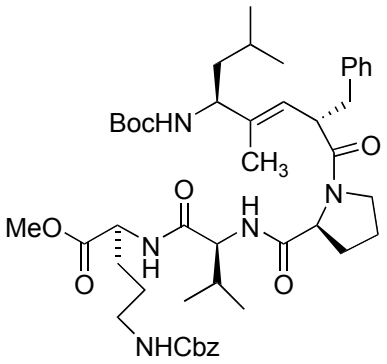


Acetic acid (2*S*)-benzyl-(5*S*)-*tert*-butoxycarbonylamino-(*4E*)-7-dimethyl-oct-3-enyl ester (4a): (more polar, minor epimer): Colorless foam; $[\alpha]^{25}_{D}$ +7.4 (*c* 1.0, $CHCl_3$); IR (neat) 3367, 2956, 2868, 1741, 1701, 1497, 1383, 1366, 1240, 1170, 1033, 747, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2 H), 7.28-7.21 (m, 3 H), 5.23 (d, 1 H, *J* = 8.7 Hz), 4.48 (b, 1 H), 4.13-4.05 (m, 3 H), 3.09-3.02 (m, 1 H), 2.92 (dd, 1 H, *J* = 13.4, 5.5 Hz), 2.59 (dd, 1 H, *J* = 13.4, 8.8 Hz), 2.14 (s, 3 H), 1.53 (s, 9 H), 1.47 (s, 3 H), 1.45-1.36 (m, 1 H), 1.34-1.23 (m, 2 H), 0.93 (d, 6 H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 154.9, 139.5, 137.8, 129.1, 128.1, 126.0, 125.4, 79.0, 67.0, 55.6, 42.6, 39.1, 38.2, 28.4, 24.6, 22.6, 22.5, 20.9, 12.7; EIMS *m/z* 403 (M^+, 0.4), 346 (2.3), 303 (1.5), 290 (3.4), 246 (40), 186 (100), 169 (18), 91 (63); HRMS (EI) *m/z* calcd for $C_{24}H_{37}NO_4$ 403.2723, found 403.2725.



(4*S*)-Benzyl-5-hydroxy-(1*S*)-isobutyl-2-methylpent-(2*E*)-enyl)-carbamic acid *tert*-butyl ester (5a). A solution of 300 mg (0.743 mmol) of **4a** in 25.0 mL of MeOH was treated at 0 ˚C with 51.4 mg (0.372 mmol) of K_2CO_3. The reaction mixture was stirred at 0 ˚C for 2 h and at room temperature for an additional 3 h, diluted with EtOAc, and washed with H_2O. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (4 : 1, hexanes/EtOAc) to yield 242 mg (90%) of **5a** as a colorless solid: Mp 103-105 ˚C (hexanes); $[\alpha]^{25}_{D}$ –4.1 (*c* 0.56, $CHCl_3$); IR (neat) 3331, 3244, 2958, 2923, 2868, 1671, 1551, 1453, 1365, 1065, 1031, 745, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.20 (m, 2 H), 7.15-7.10 (m, 3 H), 5.13 (d, 1 H, *J* = 9.5 Hz), 4.53 (b, 1 H), 3.88 (b, 1 H), 3.63 (b, 1 H), 3.43 (t, 1 H, *J* = 9.7 Hz), 2.88-2.72 (m, 3

H), 2.41 (dd, 1 H, J = 13.2, 9.5 Hz), 1.40 (s, 9 H), 1.31 (s, 3 H), 1.22-1.13 (m, 3 H), 0.82 (d, 3 H, J = 6.3 Hz), 0.81 (d, 3 H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 140.0, 137.2, 129.3, 128.9, 127.9, 125.6, 79.2, 65.9, 57.4, 43.1, 41.3, 37.6, 28.3, 24.2, 23.0, 22.0, 10.9; EIMS *m/z* 331 ([M-CH_2O]$^+$, 11), 304 (5), 275 (30), 248 (25), 214 (100), 187 (19), 130 (75), 91 (80), 57 (97); HRMS (EI) *m/z* calcd for $C_{21}H_{33}NO_2$ (M-CH_2O) 331.2511, found 331.2513.

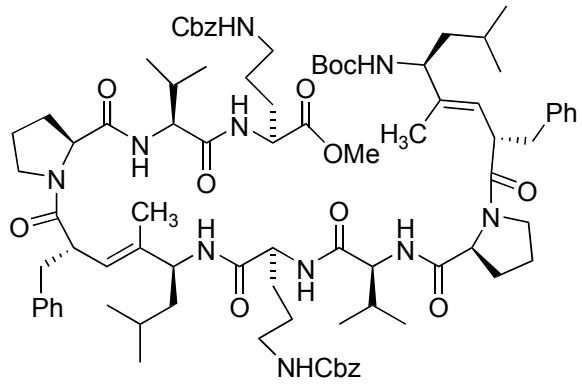


Boc-Leu-ψ[(*E*)-C(CH_3)=CH]-^{D}Phe-Pro-Val-Orn(Cbz)-OMe (7a). A solution of 121 mg (0.335 mmol) of **5a** in 12.0 mL of dried CH_2Cl_2 was treated at 0 ˚C with 284 mg (0.670 mmol) of Dess-Martin Periodinane. The reaction mixture was stirred at 0 ˚C for 3.5 h, quenched with saturated $Na_2S_2O_3$ in saturated $NaHCO_3$ solution, stirred for 30 min at room temperature, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* to give a yellow foam and subsequently dissolved in 10.0 mL of THF, and treated at 0 ˚C with 1.00 mL (2.00 mmol) of 2-methyl-2-butene (2.0 M solution in THF) followed by a solution of 96.3 mg (1.07 mmol) of $NaClO_2$ and 92.5 mg (0.679 mmol) of NaH_2PO_4•H_2O in 10.0 mL of H_2O. The reaction mixture was stirred at 0 ˚C for 1 h and room temperature for an additional 4 h, extracted with EtOAc, and washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to yield crude **6a** as a yellow foam.

A solution of crude **6a** in 10.0 mL of $CHCl_3$ was treated at 0 ˚C with 53.5 mg (0.402 mmol) of HOBt, 70.7 mg (0.396 mmol) of EDC, a solution of 319 mg (0.670 mmol) of H-Pro-Val-Orn(Cbz)-OMe (**10**)[3] in 5.00 mL of $CHCl_3$ and 3.8 mg (0.031 mmol) of DMAP. The reaction mixture was stirred at room temperature for 4 d, diluted with

[3] Tamaki, M.; Akabori, S.; Muramatsu, I. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3113.

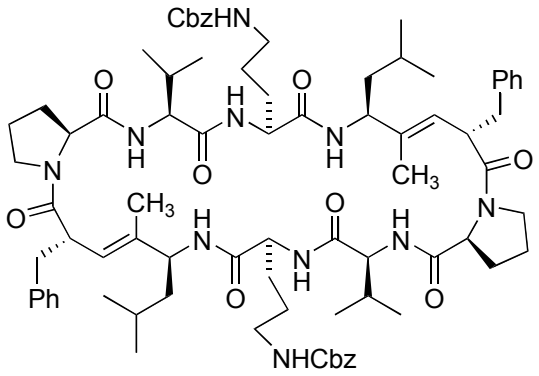
$CHCl_3$, and washed with H_2O. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (2 : 1, hexanes/EtOAc; 50 : 1, $CHCl_3$/MeOH) to yield 263 mg (94%) of **7a** as a colorless foam: $[\alpha]^{25}_D$ –5.8 (*c* 1.0, $CHCl_3$); IR (neat) 3316, 2957, 2871, 1709, 1653, 1522, 1453, 1366, 1253, 1173, 1020, 754, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (b, 1 H), 7.29-7.06 (m, 10 H), 6.62 (d, 1 H, *J* = 8.1 Hz), 6.20 (b, 1 H), 5.86 (d, 1 H, *J* = 8.0 Hz), 5.35 (d, 1 H, *J* = 9.7 Hz), 5.02, 4.99 (AB, 2 H, *J* = 12.7 Hz), 4.63 (b, 1 H), 4.49 (d, 1 H, *J* = 6.5 Hz), 4.40-4.45 (m, 1 H), 4.00-3.90 (m, 1 H), 3.70 (s, 3 H), 3.41 (b, 2 H), 3.24-3.14 (m, 3 H), 3.05 (dd, 1 H, *J* = 13.3, 5.6 Hz), 2.61 (dd, 1 H, *J* = 13.3, 8.3 Hz), 2.08-2.03 (m, 2 H), 1.98-1.80 (m, 4 H), 1.73-1.67 (m, 1 H), 1.63-1.55 (m, 2 H), 1.45 (s, 9 H), 1.39-1.36 (m, 1 H), 1.27 (s, 3 H), 1.24-1.21 (m, 2 H), 0.88 (d, 6 H, *J* = 6.8 Hz), 0.86 (d, 3 H, *J* = 6.6 Hz), 0.83 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 172.2, 171.4, 170.6, 156.7, 155.3, 141.6, 139.2, 136.7, 129.3, 128.2, 128.0, 127.9, 127.6, 125.9, 120.2, 78.4, 66.2, 60.6, 57.6, 54.7, 52.1, 52.0, 51.7, 46.4, 42.8, 40.5, 37.6, 31.4, 29.1, 28.9, 28.3, 28.2, 26.1, 24.9, 24.5, 23.0, 21.6, 18.9, 17.9, 14.3; HRMS (ESI) *m/z* calcd for $C_{46}H_{67}N_5O_9Na$ (M+Na) 856.4836, found 856.4832.



Boc-Leu-ψ[(*E*)-C(CH_3)=CH]-^{D}Phe-Pro-Val-Orn(Cbz)-Leu-ψ[(*E*)-C(CH_3)=CH]-^{D}Phe-Pro-Val-Orn(Cbz)-OMe (8a). A solution of 250 mg (299 μmol) of **7a** in 1.88 mL of MeOH was treated at 0 ˚C with 598 μL (598 μmol) of 1 N NaOH. The reaction mixture was stirred at 0 ˚C for 1 h, at room temperature for an additional 2 h, and treated at 0 ˚C with 598 μL (598 μmol) of 1 N HCl. The solution was extracted with $CHCl_3$ and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give crude acid as a colorless foam.

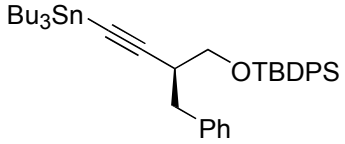
Another solution of 250 mg (299 μmol) of **7a** in 2.07 mL (8.28 mmol) of HCl (4.0 N solution in 1,4-dioxane) was stirred at 0 ˚C for 10 min and at room temperature for an additional 40 min. 1,4-Dioxane was removed *in vacuo* and a solution of the resulting colorless, foamy residue in 50.0 mL of $CHCl_3$ was washed with 5% Na_2CO_3 solution. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude amine as a yellowish foam.

A solution of acid and amine in 3.00 mL of $CHCl_3$ was treated at room temperature with 46.1 mg (341 μmol) of HOBt, 57.3 mg (299 μmol) of EDC and 3.7 mg (30 μmol) of DMAP. The reaction mixture was stirred at 0 ˚C for 1 h and at room temperature for 2 d, diluted with $CHCl_3$, and washed with 5% citric acid, 5% Na_2CO_3 and H_2O. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (2 : 1, hexanes/EtOAc; 50 : 1, $CHCl_3$/MeOH) to yield 445 mg (97%) of **8a** as a colorless foam which was used directly without any further purification.



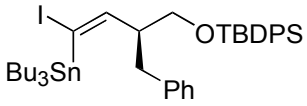
Cyclo[(Val-Orn(Cbz)-Leu-ψ[(*E*)-C(CH$_3$)=CH]-^{D}Phe-Pro)$_2$] (9a). A solution of 68.0 mg (44.3 μmol) of **8a** in 3.61 mL of MeOH was treated at 0 ˚C with 443 μL (443 μmol) of 1 N NaOH. The reaction mixture was stirred at 0 ˚C for 30 min and at room temperature for an additional 8 h. The solvents were removed *in vacuo* and the residue was dissolved at 0 ˚C in 3.61 mL (14.4 mmol) of HCl (4.0 N solution in 1,4-dioxane). The reaction mixture was stirred at 0 ˚C for 5 min and at room temperature for an additional 1 h. 1,4-Dioxane was removed *in vacuo* and the resulting colorless, foamy residue was dissolved in 20.0 mL of benzene, treated at room temperature with 37.2 mg (443 μmol) of $NaHCO_3$, and evaporated to dryness by azeotropic distillation with benzene at 25 ˚C. The solid residue was dissolved in 36.9 mL of $CHCl_3$, and treated at

room temperature with 6.6 mg (48.7 μmol) of HOBt, 10.2 mg (53.2 μmol) of EDC and 5.4 mg (44.2 μmol) of DMAP. The reaction mixture was stirred at room temperature for 2.5 d, diluted with $CHCl_3$, and washed with H_2O. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (3 : 1, hexanes/EtOAc; 10 : 1, $CHCl_3$/MeOH) and repurified by RP-HPLC (C_{18}; 20% H_2O, 80% CH_3CN, 5 mL/min) to yield 26.1 mg (42%) of **9a** as a colorless soild: Mp 105-107 °C ($MeOH/H_2O$); ^1H NMR (600 MHz, DMSO-d_6) δ 9.01 (d, 2 H, *J* = 8.8 Hz), 7.95 (d, 2 H, *J* = 9.4 Hz), 7.27-7.22 (m, 12 H), 7.18-7.11 (m, 10 H), 6.31 (d, 2 H, *J* = 8.5 Hz), 5.24 (d, 2 H, *J* = 10.1 Hz), 4.89, 4.86 (AB, 4 H, *J* = 12.6 Hz), 4.69 (q, 2 H, *J* = 7.9 Hz), 4.61 (dd, 2 H, *J* = 8.2, 4.9 Hz), 4.34 (d, 2 H, *J* = 7.1 Hz), 4.14 (t, 2 H, *J* = 9.8 Hz), 3.60 (q, 2 H, *J* = 8.7 Hz), 3.55-3.49 (m, 2 H), 3.30-3.26 (m, 2 H), 3.11-3.05 (m, 4 H), 2.96 (dd, 2 H, *J* = 13.3, 4.8 Hz), 2.47 (dd, 2 H, *J* = 13.6, 9.1 Hz), 2.07-2.01 (m, 2 H), 1.98-1.90 (m, 2 H), 1.90-1.77 (m, 4 H), 1.73-1.64 (m, 2 H), 1.60-1.53 (m, 2 H), 1.52-1.42 (m, 4 H), 1.38 (t, 2 H, *J* = 11.0 Hz), 1.21 (s, 6 H), 1.17-1.11 (m, 2 H), 0.84-0.77 (m, 4 H), 0.73 (t, 12 H, *J* = 6.7 Hz), 0.71 (d, 12 H, *J* = 6.5 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.7, 170.4, 169.6 (2C), 156.1, 141.4, 139.5, 137.1, 129.4, 128.2, 127.6, 125.6, 118.8, 65.1, 60.0, 55.3, 52.1, 51.7, 45.9, 45.3, 42.1, 40.3, 36.6, 33.3, 30.7, 29.5, 26.1, 24.9, 24.1, 23.1, 20.5, 18.6, 17.6, 15.0; HRMS (ESI) *m/z* calcd for $C_{80}H_{111}N_{10}O_{12}$ (M+H) 1403.8383, found 1403.8369.

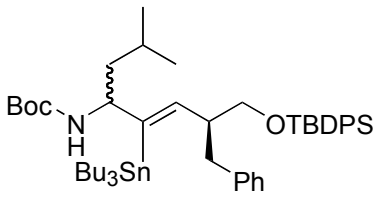


(*S*)-[2-Benzyl-4-(tributylstannanyl)-but-3-ynyloxy]-*tert*-butyldiphenylsilane (2b). A solution of 685 mg (1.23 mmol) of **E** in 10.0 mL of dried THF was treated at -78 °C with 1.69 mL (2.71 mmol) of *n*-BuLi (1.6 M solution in hexane). The mixture was stirred at -78 °C for 1 h and at room temperature for an additional 1 h, cooled to -78 °C and treated dropwise with 0.350 mL (1.29 mmol) of Bu_3SnCl. The solution was warmed to 0 °C, stirred for 30 min, quenched with saturated $NaHCO_3$ solution, extracted with ether, dried (Na_2CO_3) and concentrated *in vacuo* to yield 860 mg (quant) of crude **2b** as a light yellow oil: $[\alpha]^{25}_D$ +11.8 (*c* 1.0, $CHCl_3$); IR (neat) 3070, 3028, 2956, 2929, 2856, 2146, 1463, 1428, 1112, 824, 740, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76-7.72 (m,

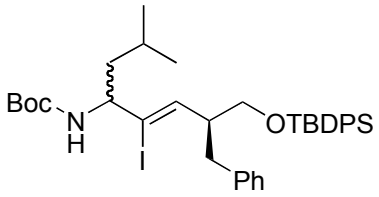
4 H), 7.47-7.41 (m, 6 H), 7.34-7.20 (m, 5 H), 3.80 (dd, 1 H, *J* = 9.8, 4.9 Hz), 3.66 (dd, 1 H, *J* = 9.8, 7.7 Hz), 3.14 (dd, 1 H, *J* = 13.0, 4.9 Hz), 2.94-2.88 (m, 1 H), 2.81 (dd, 1 H, *J* = 13.0, 8.5 Hz), 1.57-1.51 (m, 6 H), 1.38-1.30 (m, 6 H), 1.14 (s, 9 H), 0.98-0.94 (m, 6 H), 0.91 (t, 9 H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 135.6, 135.5, 133.6, 133.5, 129.5, 129.5, 127.8, 127.6, 126.0, 111.4, 84.5, 65.5, 38.0, 37.6, 28.8, 26.9, 26.8, 19.3, 16.3, 13.6, 10.8; EIMS *m/z* 631 ([M-C_4H_9]$^+$, 60), 575 (80), 539 (10), 517 (13), 461 (10), 341 (15), 263 (30), 199 (68), 135 (40), 91 (100); HRMS (EI) *m/z* calcd for $C_{35}H_{47}OSi^{116}Sn$ (M-C_4H_9) 627.2414, found 627.2386.



[(2*S*)-Benzyl-(4*E*)-iodo-4-(tributylstannanyl)-but-3-enyloxy]-*tert*-butyldiphenylsilane. A solution of 1.53 g (2.22 mmol) of **2b** in 15.0 mL of dried THF was treated at room temperature with 802 mg (3.11 mmol) of Cp_2ZrHCl. The reaction mixture was stirred at room temperature for 40 min and treated with a solution of 597 mg (2.35 mmol) of I_2 in 5.0 mL of dried THF. The mixture was stirred at room temperature for 1 h, diluted with Et_2O, and washed with H_2O. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (100 : 1, hexanes/EtOAc) to yield 1.46 g (80%) of [(2*S*)-benzyl-(4*E*)-iodo-4-(tributylstannanyl)-but-3-enyloxy]-*tert*-butyldiphenylsilane as a colorless oil: [α] $^{25}_D$ +29.1 (*c* 1.0, $CHCl_3$); IR (neat) 3070, 3027, 2956, 2929, 2856, 1463, 1427, 1112, 823, 740, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4 H), 7.46-7.37 (m, 6 H), 7.32-7.13 (m, 6 H), 3.54 (d, 2 H, *J* = 5.2 Hz), 2.95 (dd, 1 H, *J* = 13.3, 6.2 Hz), 2.63 (dd, 1 H, *J* = 13.3, 7.7 Hz), 2.36-2.29 (m, 1 H), 1.46-1.37 (m, 6 H), 1.32-1.20 (m, 6 H), 1.10 (s, 9 H), 0.92-0.84 (m, 6 H), 0.86 (t, 9 H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 139.5, 135.7, 133.5, 133.4, 129.7, 129.5, 128.3, 127.8, 127.7, 126.2, 103.3, 65.6, 52.6, 37.3, 28.7, 27.3, 27.0, 19.4, 13.6, 12.6; EIMS *m/z* 815 (M$^+$, 0.13), 759 (25), 631 (40), 361 (100), 305 (32), 263 (35), 199 (62), 135 (47); HRMS (EI) *m/z* calcd for $C_{35}H_{48}IOSi^{120}Sn$ (M-C_4H_9) 759.1541, found 759.1526.

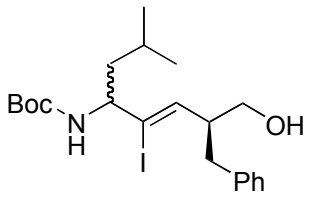


[(4*S*)-Benzyl-5-(*tert*-butyldiphenylsilanyloxy)-1-isobutyl-2-(tributylstannanyl)-pent-(2*E*)-enyl]-carbamic acid *tert*-butyl ester (3b). A solution of 810 mg (0.993 mmol) of [(2*S*)-benzyl-(4*E*)-iodo-4-(tributylstannanyl)-but-3-enyloxy]-*tert*-butyldiphenylsilane in 5.00 mL of dried Et_2O was treated dropwise at -78 ˚C with 1.46 mL (2.48 mmol) of *t*-BuLi (1.7 M solution in pentane). The reaction mixture was stirred at -78 ˚C for 1.5 h and treated at -78 ˚C with 552 mg (2.98 mmol) of *N*-Boc-isovaleraldimine **7**[2]. The reaction mixture was stirred at -78 ˚C for 1 h, quenched with H_2O, and extracted with Et_2O. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (60 : 1, hexanes/EtOAc) to yield 610 mg (70%) of **3b** as a colorless, oily 1 : 1.5 mixture of diastereomers: IR (neat) 3449, 3264, 2956, 2929, 2857, 1718, 1699, 1494, 1472, 1428, 1389, 1356, 1247, 1172, 1112, 1051, 741, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.63 (m, 4 H), 7.46-7.35 (m, 6 H), 7.27-7.15 (m, 5 H), 6.24 (d, 0.4 H, *J* = 9.4 Hz), 6.09 (d, 0.6 H, *J* = 9.1 Hz), 4.35-4.00 (m, 2 H), 3.63-3.40 (m, 2 H), 3.12-3.00 (m, 1 H), 2.71 (dd, 0.4 H, *J* = 12.6, 5.9 Hz), 2.63 (dd, 0.6 H, *J* = 13.1, 7.5 Hz), 2.40 (b, 1 H), 1.68-1.34 (m, 15 H), 1.32-1.21 (m, 9 H), 1.13 (s, 9 H), 0.95-0.79 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 146.9, 146.6, 141.1, 140.0, 135.7, 135.7, 135.7, 133.7, 133.7, 133.6, 133.5, 129.6, 128.1, 127.6, 125.9, 78.6, 66.3, 66.1, 56.9, 56.7, 48.8, 48.6, 45.5, 45.4, 39.9, 38.2, 38.1, 34.8, 29.7, 29.2, 28.5, 27.8, 27.4, 27.0, 26.3, 25.3, 24.9, 24.8, 24.1, 22.8, 22.6, 21.6, 19.4, 13.6, 10.8; EIMS *m/z* 818 ($[M-C_4H_9]^+$, 31), 762 (80), 718 (47), 428 (47), 330 (20), 250 (25), 199 (100), 135 (45); HRMS (EI) *m/z* calcd for $C_{45}H_{68}NO_3Si^{120}Sn$ (M-C_4H_9) 818.3990, found 818.4018.



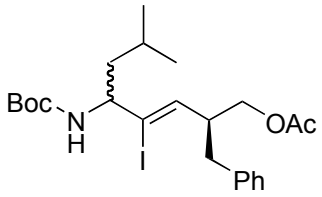
[(4*S*)-Benzyl-5-(*tert*-butyldiphenylsilanyloxy)-(2*Z*)-iodo-1-isobutylpent-2-enyl]-carbamic acid *tert*-butyl ester. A solution of 1.17 g (1.34 mmol) of **3b** in 20.0 mL of

CH_2Cl_2 was treated at 0 ˚C with 391 mg (1.74 mmol) of NIS in one portion. The mixture was rapidly stirred at 0 ˚C for 2 h, quenched with saturated $Na_2S_2O_3$ in saturated $NaHCO_3$ solution and stirred until a clear solution formed. The solution was extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (20 : 1, hexanes/Et_2O) to yield 758 mg (80%) of [(4*S*)-benzyl-5-(*tert*-butyldiphenylsilanyloxy)-(2*Z*)-iodo-1-isobutylpent-2-enyl]-carbamic acid *tert*-butyl ester as a colorless, oily 1 : 1.5 mixture of diastereomers: IR (neat) 3435, 3339, 3070, 3026, 2957, 2931, 2858, 1705, 1494, 1472, 1366, 1244, 1169, 1112, 823, 741, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.64 (m, 4 H), 7.47-7.35 (m, 6 H), 7.25-7.15 (m, 5 H), 5.95 (d, 0.4 H, *J* = 8.4 Hz), 5.74 (d, 0.6 H, *J* = 7.8 Hz), 4.62 (d, 0.4 H, *J* = 9.1 Hz), 4.59 (d, 0.6 H, *J* = 8.7 Hz), 3.90-3.80 (m, 0.4 H), 3.80-3.70 (m, 0.6 H), 3.68-3.60 (m, 2 H), 3.10-2.95 (m, 1.4 H), 2.90-2.82 (m, 0.6 H), 2.76-2.60 (m, 1 H), 1.48 (s, 3.6 H), 1.40 (s, 5.4 H), 1.33-1.26 (m, 2 H), 1.20-1.14 (m, 1 H), 1.11 (s, 5.4 H), 1.09 (s, 3.6 H), 0.93-0.90 (m, 2.4 H), 0.84 (d, 1.8 H, *J* = 6.2 Hz), 0.79 (d, 1.8 H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 154.2, 139.2, 139.0, 137.8, 137.2, 135.5, 133.4, 129.5, 129.3, 129.1, 128.0, 127.6, 125.9, 115.6, 109.3, 79.2, 64.7, 64.6, 57.5, 50.1, 49.9, 44.4, 44.2, 36.6, 36.4, 28.3, 26.8, 26.8, 24.2, 23.9, 23.0, 22.9, 22.1, 21.6, 19.2; EIMS *m/z* 638 ($[M\text{-}OC_4H_9]^+$, 2.3), 598 (50), 554 (59), 520 (36), 476 (33), 349 (31), 198 (100), 135 (55), 91 (71); HRMS (EI) *m/z* calcd for $C_{33}H_{41}INO_2Si$ (M-OC_4H_9) 638.1951, found 638.1975.

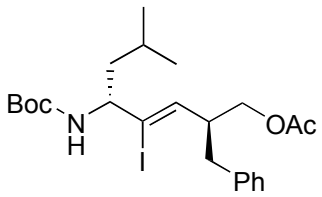


((4*S*)-Benzyl-5-hydroxy-(2*Z*)-iodo-1-isobutylpent-2-enyl)-carbamic acid *tert*-butyl ester. A solution of 600 mg (0.843 mmol) of [(4*S*)-benzyl-5-(*tert*-butyldiphenylsilanyloxy)-(2*Z*)-iodo-1-isobutylpent-2-enyl]-carbamic acid *tert*-butyl ester in 10.0 mL of dried THF was treated at 0 ˚C with 1.69 mL (1.69 mmol) of TBAF (1.0 M solution in THF) and a solution of 96.7 μL (1.69 mmol) of CH_3COOH in 2.00 mL of dried THF. The reaction mixture was stirred at room temperature for 24 h, diluted with EtOAc, and washed with brine. The organic layer was dried (Na_2SO_4), concentrated *in*

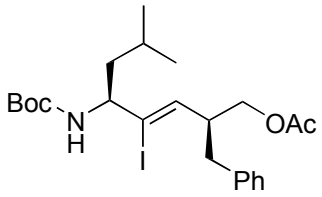
vacuo, and purified by chromatography on SiO_2 (4 : 1, hexanes/EtOAc) to yield 337 mg (84%) of ((4*S*)-benzyl-5-hydroxy-(2*Z*)-iodo-1-isobutylpent-2-enyl)-carbamic acid *tert*-butyl ester as a colorless, oily 1 : 2 mixture of diastereomers: IR (neat) 3411, 3324, 3027, 2956, 2869, 1694, 1496, 1366, 1249, 1167, 1042, 1018, 745, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.16 (m, 5 H), 5.83 (d, 0.33 H, *J* = 8.8 Hz), 5.71 (d, 0.67 H, *J* = 9.3 Hz), 4.66 (d, 0.33 H, *J* = 8.0 Hz), 4.60 (d, 0.67 H, *J* = 6.3 Hz), 3.90-3.81 (m, 0.33 H), 3.75-3.64 (m, 0.67 H), 3.59-3.40 (m, 2 H), 3.17-3.05 (m, 0.67 H), 2.96-2.85 (m, 0.33 H), 2.83-2.73 (m, 1.34 H), 2.61 (dd, 0.66 H, *J* = 13.5, 9.0 Hz), 2.44 (b, 0.33 H), 1.67 (b, 0.67 H), 1.60-1.50 (m, 0.66 H), 1.46 (s, 3 H), 1.42 (s, 6 H), 1.34-1.26 (m, 1.34 H), 1.20-1.08 (m, 1 H), 0.95-0.91 (m, 2 H), 0.84 (d, 2 H, *J* = 6.5 Hz), 0.80 (d, 2 H, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 154.6, 139.0, 138.9, 136.9, 129.3, 129.1, 128.1, 125.9, 116.7, 116.1, 79.9, 79.4, 64.5, 64.0, 58.0, 57.9, 51.1, 50.1, 44.1, 42.9, 36.5, 36.1, 28.3, 24.3, 23.7, 23.1, 22.7, 22.0, 21.5; EIMS *m/z* 473 (M^+, 0.2), 443 (2.9), 316 (43), 290 (76), 272 (16), 260 (50), 246 (35), 229 (20), 91 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{30}INO_2$ (M-CH_2O) 443.1321, found 443.1323.



Acetic acid (2*S*)-benzyl-5-*tert*-butoxycarbonylamino-(4*Z*)-iodo-7-methyloct-3-enyl ester. A solution of 310 mg (0.655 mmol) of ((4*S*)-benzyl-5-hydroxy-(2*Z*)-iodo-1-isobutylpent-2-enyl)-carbamic acid *tert*-butyl ester in 15.0 mL of dried CH_2Cl_2 was treated at 0 ˚C with 183 μL (1.31 mmol) of TEA, 247 μL (2.62 mmol) of Ac_2O and 8.0 mg (65.5 μmol) of DMAP. The reaction mixture was stirred at 0 ˚C for 1 h and at room temperature for an additional 3 h, diluted with EtOAc, and washed with brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (200 : 1, CH_2Cl_2/EtOAc) to yield 98.0 mg (29%) and 236 mg (70%), respectively, of the diastereomers of acetic acid (2*S*)-benzyl-5-*tert*-butoxycarbonylamino-(4*Z*)-iodo-7-methyloct-3-enyl ester.

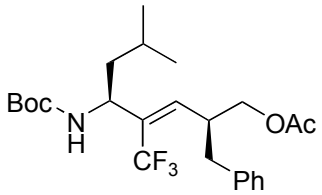


Acetic acid (2*S*)-benzyl-5*R*-*tert*-butoxycarbonylamino-(4*Z*)-iodo-7-methyloct-3-enyl ester (less polar, minor epimer): Colorless oil; $[\alpha]^{25}_{D}$ +26.3 (*c* 1.0, $CHCl_3$); IR (neat) 3365, 3027, 2957, 2927, 2869, 1743, 1713, 1496, 1366, 1245, 1167, 1040, 1018, 748, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2 H), 7.21-7.19 (m, 3 H), 5.83 (d, 1 H, *J* = 8.8 Hz), 4.63 (d, 1 H, *J* = 8.0 Hz), 4.03 (dd, 1 H, *J* = 10.9, 5.2 Hz), 3.98 (dd, 1 H, *J* = 10.9, 7.1 Hz), 3.81 (q, 1 H, *J* = 7.3 Hz), 3.05 (bq, 1 H, *J* = 6.7 Hz), 2.74 (d, 2 H, *J* = 6.7 Hz), 2.03 (s, 3 H), 1.55-1.48 (m, 1 H), 1.46 (s, 9 H), 1.29-1.23 (m, 2 H), 0.93 (d, 3 H, *J* = 6.6 Hz), 0.90 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 154.5, 138.3, 136.6, 129.3, 128.4, 126.3, 116.8, 79.6, 65.4, 57.8, 46.9, 44.2, 36.9, 28.4, 24.4, 23.0, 21.8, 20.8; EIMS *m/z* 458 ($[M-C_4H_9]^+$, 0.5), 443 (2.4), 358 (30), 332 (20), 298 (45), 171 (50), 105 (77), 91 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{25}INO_4$ (M-C_4H_9) 458.0828, found 458.0833.

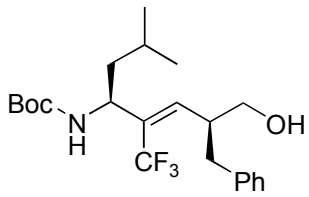


Acetic acid (2*S*)-benzyl-5*S*-*tert*-butoxycarbonylamino-(4*Z*)-iodo-7-methyloct-3-enyl ester (more polar, major epimer): Colorless oil; $[\alpha]^{25}_{D}$ –4.2 (*c* 0.9, $CHCl_3$); IR (neat) 3361, 3027, 2957, 2929, 2869, 1743, 1713, 1496, 1366, 1246, 1168, 1040, 1017, 747, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2 H), 7.02 (d, 1 H, *J* = 7.2 Hz), 7.16 (d, 2 H, *J* = 7.3 Hz), 5.72 (d, 1 H, *J* = 8.8 Hz), 4.60 (d, 1 H, *J* = 7.7 Hz), 4.07 (dd, 1 H, *J* = 10.7, 5.8 Hz), 4.01 (dd, 1 H, *J* = 10.8, 6.5 Hz), 3.75-3.65 (bm, 1 H), 3.25-3.10 (bm, 1 H), 2.84 (dd, 1 H, *J* = 13.7, 6.5 Hz), 2.66 (dd, 1 H, *J* = 13.7, 8.3 Hz), 2.06 (s, 3 H), 1.43 (s, 9 H), 1.35-1.28 (m, 1 H), 1.18-1.12 (m, 2 H), 0.83 (d, 3 H, *J* = 6.1 Hz), 0.78 (d, 3 H, *J* = 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 154.4, 138.4, 136.4, 129.1, 128.3, 126.3, 117.2, 79.6, 65.4, 57.6, 46.6, 44.0, 37.0, 28.3, 24.0, 23.1, 21.7, 20.9; EIMS *m/z* 458 ([M-

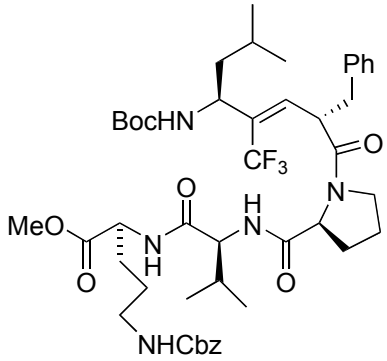
$C_4H_9]^+$, 0.6), 442 (3.7), 358 (34), 332 (22), 298 (50), 171 (57), 129 (27), 91 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{25}INO_4$ (M-C_4H_9) 458.0828, found 458.0842.



Acetic acid (2*S*)-benzyl-(5*S*)-*tert*-butoxycarbonylamino-7-methyl-(4*Z*)-trifluoromethyloct-3-enyl ester (4b). A solution of 10.0 mg (19.4 μmol) of acetic acid (2*S*)-benzyl-5*S*-*tert*-butoxycarbonylamino-(4*Z*)-iodo-7-methyloct-3-enyl ester in 0.80 mL of DMF was treated at room temperature with 20.3 mg (107 μmol) of CuI and 42.4 μL (243 μmol) of HMPA followed by 24.7 μL (194 μmol) of methyl-2,2-difluoro-2-(fluorosulfonyl)-acetate. The reaction mixture was warmed to 70-80 ˚C for 24 h, cooled to room temperature, diluted with EtOAc, washed with saturated NH_4Cl solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (2 : 1, hexanes/Et_2O) to yield 8.2 mg (92%) of **4b** as a colorless oil: $[\alpha]^{25}_D$ +2.0 (*c* 0.5, $CHCl_3$); IR (neat) 3368, 3029, 2960, 2932, 2871, 1745, 1705, 1497, 1455, 1383, 1367, 1245, 1160, 1119, 1041, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2 H), 7.24-7.21 (m, 1 H), 7.14 (d, 2 H, *J* = 7.3 Hz), 5.80 (d, 1 H, *J* = 11.0 Hz), 4.62 (d, 1 H, *J* = 8.5 Hz), 4.13 (q, 1 H, *J* = 7.3 Hz), 4.09 (dd, 1 H, *J* = 10.8, 5.3 Hz), 4.02 (dd, 1 H, *J* = 10.4, 7.3 Hz), 3.33-3.25 (m, 1 H), 2.80 (dd, 1 H, *J* = 13.5, 6.9 Hz), 2.68 (dd, 1 H, *J* = 13.5, 7.2 Hz), 2.05 (s, 3 H), 1.50-1.44 (m, 1 H), 1.47 (s, 9 H), 1.40-1.29 (m, 2 H), 0.90 (t, 6 H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 154.6, 138.6, 137.8, 132.5 (q, *J* = 27.5 Hz), 129.0, 128.4, 126.5, 124.0 (q, *J* = 243 Hz), 79.5, 65.6, 51.9, 43.4, 39.5, 37.8, 28.3, 24.8, 22.6, 22.1, 20.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ –55.7 (s); EIMS *m/z* 400 ([M-$C_4H_9]^+$, 0.8), 300 (15), 240 (75), 223 (7), 130 (15), 91 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{25}F_3NO_4$ (M-C_4H_9) 400.1736, found 400.1732.



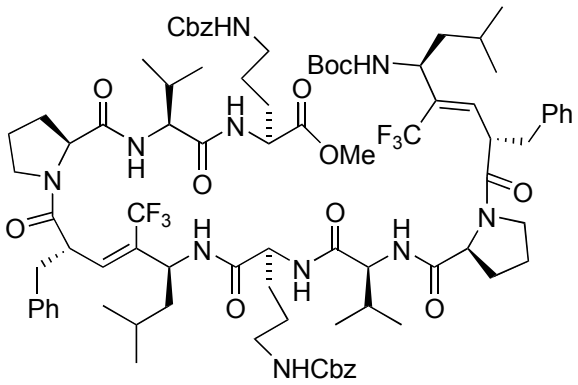
((4*S*)-Benzyl-5-hydroxy-(1*S*)-isobutyl-(2*Z*)-trifluoromethylpent-2-enyl)-carbamic acid *tert*-butyl ester (5b). A solution of 80.5 mg (0.176 mmol) of **4b** in 3.00 mL of MeOH was treated at 0 ˚C with 9.8 mg (0.352 mmol) of K_2CO_3. The reaction mixture was stirred at 0 ˚C for 2 h and at room temperature for an additional 2 h, diluted with EtOAc, and washed with brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (1 : 1, hexanes/EtOAc) to yield 74.0 mg (quant) of **5b** as a colorless foam: $[\alpha]^{25}_D$ +26.0 (*c* 1.0, $CHCl_3$); IR (neat) 3416, 3344, 3064, 3028, 2960, 2871, 1697, 1497, 1392, 1368, 1253, 1158, 1120, 1044, 1022, 748, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2 H), 7.20-7.17 (m, 1 H), 7.13 (d, 2 H, *J* = 7.3 Hz), 5.84 (d, 1 H, *J* = 11.2 Hz), 4.69 (d, 1 H, *J* = 7.9 Hz), 4.17 (q, 1 H, *J* = 7.5 Hz), 3.65 (dd, 1 H, *J* = 10.8, 4.2 Hz), 3.54 (dd, 1 H, *J* = 10.9, 6.7 Hz), 3.15-3.05 (m, 1 H), 2.81 (dd, 1 H, *J* = 13.5, 6.7 Hz), 2.62 (dd, 1 H, *J* = 13.4, 7.8 Hz), 1.44-1.35 (m, 3 H), 1.42 (s, 9 H), 0.87 (t, 6 H, *J* = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 142.3, 138.7, 131.0 (q, *J* = 26.3 Hz), 129.1, 128.3, 126.2, 124.0 (q, *J* = 276 Hz), 80.0, 64.9, 54.4, 43.3, 42.4, 37.4, 28.3, 24.8, 22.4, 22.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −54.9 (s); EIMS *m/z* 385 ([M-CH_2O]$^+$, 0.5), 329 (10), 309 (21), 147 (27), 130 (61), 91 (100); HRMS (ESI) *m/z* calcd for $C_{22}H_{32}F_3NO_3Na$ (M+Na) 438.2232, found 438.2244.



Boc-Leu-ψ[(*E*)-C(CF_3)=CH]-^{D}Phe-Pro-Val-Orn(Cbz)-OMe (7b). A solution of 47.0 mg (0.113 mmol) of **5b** in 5.00 mL of dried CH_2Cl_2 was treated at 0 ˚C with 27.6

mg (0.119 mmol) of trichloroisocyanuric acid followed by 1.8 mg (0.012 mmol) of TEMPO. The reaction mixture was stirred at 0 ˚C for 15 min, diluted with CH_2Cl_2, filtered through a pad of celite, and washed with H_2O. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* to give a colorless oil and subsequently dissolved in 6.00 mL of THF, treated at 0 ˚C with 0.70 mL (1.40 mmol) of 2-methyl-2-butene (2.0 M solution in THF) followed by a solution of 30.7 mg (0.339 mmol) of $NaClO_2$ and 31.2 mg (0.226 mmol) of $NaH_2PO_4 \bullet H_2O$ in 6.00 mL of H_2O. The reaction mixture was stirred at 0 ˚C for 2 h and at room temperature for an additional 5 h, extracted with EtOAc, and washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to yield **6b** as a crude colorless foam.

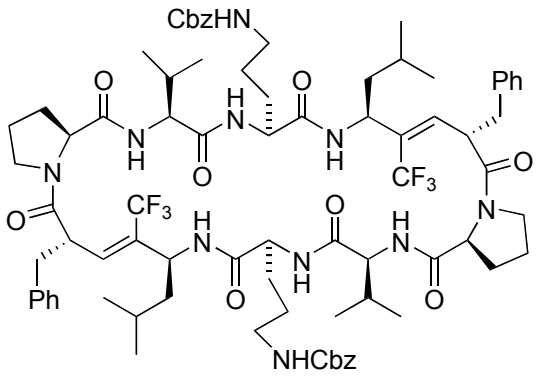
A solution of crude **6b** in 5.00 mL of $CHCl_3$ was treated at 0 ˚C with 16.5 mg (0.122 mmol) of HOBt, 22.8 mg (0.119 mmol) of EDC, followed by a solution of 118 mg (0.226 mmol) of H-Pro-Val-Orn(Cbz)-OMe (**10**) in 1.00 mL of $CHCl_3$ and 1.5 mg (0.012 mmol) of DMAP. The reaction mixture was stirred at room temperature for 24 h, diluted with $CHCl_3$, and washed with brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (1 : 1, CH_2Cl_2/Et_2O) to yield 77.5 mg (77%) of **7b** as a colorless foam: $[\alpha]^{25}_D$ –56.4 (*c* 1.0, $CHCl_3$); IR (neat) 3411, 3320, 3065, 2960, 2873, 1716, 1653, 1526, 1454, 1367, 1256, 1159, 1116, 1023, 755, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5 H), 7.23-7.11 (m, 5 H), 6.75 (d, 1 H, *J* = 8.0 Hz), 6.65 (d, 1 H, *J* = 8.5 Hz), 6.10 (d, 1 H, *J* = 10.5 Hz), 5.92 (b, 1 H), 5.73 (d, 1 H, *J* = 8.5 Hz), 5.12-5.00 (m, 2 H), 4.64 (b, 1 H), 4.55-4.45 (m, 1 H), 4.42 (b, 1 H), 4.17 (t, 1 H, *J* = 7.8 Hz), 4.00-3.90 (m, 1 H), 3.75 (s, 3 H), 3.43-3.35 (m, 1 H), 3.35-3.20 (m, 2 H), 3.11 (t, 1 H, *J* = 11.7 Hz), 2.83-2.75 (m, 1 H), 2.65 (d, 1 H, *J* = 9.9 Hz), 2.10-1.95 (m, 3 H), 1.80-1.60 (m, 6 H), 1.50-1.40 (m, 1 H), 1.48 (s, 9 H), 1.39 (t, 2 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.4 Hz), 0.89-0.87 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 172.2, 171.1, 170.8, 156.8, 155.2, 138.5, 136.6, 135.2 (q, *J* = 26.3 Hz), 132.7, 129.0, 128.4, 128.3, 128.2, 127.9, 126.6, 124.0 (q, *J* = 275 Hz), 79.4, 66.5, 60.7, 57.8, 52.3, 51.8, 49.6, 47.0, 46.7, 44.1, 40.5, 38.5, 31.3, 29.3, 28.6, 28.3, 26.1, 25.1, 24.4, 23.3, 21.1, 19.0, 18.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ –56.5 (s); HRMS (ESI) *m/z* calcd for $C_{46}H_{64}F_3N_5O_9Na$ (M+Na) 910.4554, found 910.4544.



Boc-Leu-ψ[(*E*)-C(CF$_3$)=CH]-^{D}Phe-Pro-Val-Orn(Cbz)-Leu-ψ[(*E*)-C(CF$_3$)=CH]-^{D}Phe-Pro-Val-Orn(Cbz)-OMe (8b). A solution of 20.0 mg (22.5 μmol) of **7b** in 0.60 mL of MeOH was treated at room temperature with 225 μL (225 μmol) of NaOH (1.0 N solution in H_2O). The reaction mixture was stirred at room temperature for 7 h, treated with 225 μL (225 μmol) of 1 N HCl and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the acid as a colorless foam.

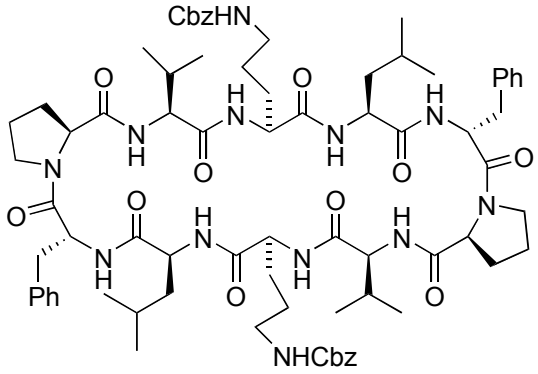
Another solution of 20.0 mg (22.5 μmol) of **7b** in 600 μL (2.40 mmol) of HCl (4.0 N solution in 1,4-dioxane) was stirred at 0 ˚C for 5 min and at room temperature for an additional 40 min. 1,4-Dioxane was removed *in vacuo* and the colorless, foamy residue was dissolved in 6.00 mL of $CHCl_3$ and washed with 5% Na_2CO_3 solution. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the amine as a light yellowish foam.

A solution of acid and amine in 4.70 mL of $CHCl_3$ was treated at room temperature with 3.4 mg (25 μmol) of HOBt, 5.2 mg (27 μmol) of EDC and 1.0 mg (8.2 μmol) of DMAP. The reaction mixture was stirred at room temperature for 2.5 d, diluted with $CHCl_3$, and washed with brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (2 : 1, hexanes/EtOAc; 20 : 1, $CHCl_3$/MeOH) to yield 31.4 mg (85%) of **8b** as a colorless foam that was used directly without any further purification.



Cyclo[(Val-Orn(Cbz)-Leu-ψ[(*E*)-C(CF$_3$)=CH]-^{D}Phe-Pro)$_2$] (9b). A solution of 31.4 mg (19.1 μmol) of **8b** in 1.57 mL of MeOH was treated at room temperature with 191 μL (191 μmol) of 1 N NaOH. The reaction mixture was stirred at room temperature for 9 h. Solvents were removed *in vacuo* and 1.57 mL (6.28 mmol) of HCl (4.0 N solution in 1,4-dioxane) was added at 0 ˚C. The solution was stirred at 0 ˚C for 5 min and at room temperature for an additional 40 min. 1,4-Dioxane was removed *in vacuo* and the colorless, foamy residue was dissolved in 8.37 mL of benzene, treated at room temperature with 16.2 mg (191 μmol) of $NaHCO_3$, and evaporated to dryness by azeotropic distillation with benzene at 25 ˚C. The solid residue was diluted with 15.9 mL of $CHCl_3$ and treated at room temperature with 2.8 mg (21.0 μmol) of HOBt, 4.4 mg (22.9 μmol) of EDC 1.0 mg (8.2 μmol) of DMAP. The reaction mixture was stirred at room temperature for 2.5 d, diluted with $CHCl_3$, and washed with H_2O. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (1 : 1, hexanes/EtOAc; 20 : 1, $CHCl_3$/MeOH) and repurified by RP-HPLC (C_{18}; 100% CH_3CN, 5 mL/min) to yield 12.0 mg (42%) of **9b** as a colorless solid: Mp 232 ˚C (decomp., MeOH/H_2O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.18 (d, 2 H, J = 8.9 Hz), 8.10 (d, 2 H, J = 8.8 Hz), 7.28-7.09 (m, 22 H), 6.14 (d, 2 H, J = 8.8 Hz), 6.01 (d, 2 H, J = 10.5 Hz), 4.90, 4.86 (AB, 4 H, J = 12.6 Hz), 4.70-4.64 (m, 4 H), 4.62 (q, 2 H, J = 6.8 Hz), 4.26 (dd, 2 H, J = 9.4, 6.2 Hz), 3.91 (b, 2 H), 3.49-3.30 (m, 4 H), 3.16 (dd, 2 H, J = 13.9, 9.1 Hz), 3.13-3.08 (m, 4 H), 2.50-2.48 (m, 2 H), 1.90-1.60 (m, 10 H), 1.55-1.38 (m, 12 H), 1.28-1.22 (m, 2 H), 0.86-0.73 (m, 24 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.4, 170.3, 169.8, 169.6, 156.1, 138.6, 137.1, 134.3 (q, J = 25.5 Hz), 132.6, 128.8, 128.2, 128.1, 127.6, 126.2, 123.5 (q, J = 275 Hz), 65.1, 60.7, 55.4, 51.9, 46.3, 45.9, 43.2, 36.7, 33.2, 30.6, 30.5, 29.3, 25.9, 24.8, 24.2, 22.9, 20.1, 18.6, 17.7; ^{19}F NMR (282 MHz, DMSO-d_6)

δ -58.0 (s); HRMS (ESI) *m/z* calcd for $C_{80}H_{105}F_6N_{10}O_{12}$ (M+H) 1511.7818, found 1511.7858.



Cyclo[(Val-Orn(Cbz)-Leu-^{D}Phe-Pro)$_2$] (Cbz$_2$GS).[3] A colorless solid: Mp 52-53 °C (hexanes/Et_2O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.94 (d, 2 H, *J* = 3.2 Hz), 8.58 (d, 2 H, *J* = 9.1 Hz), 8.38 (d, 2 H, *J* = 8.9 Hz), 7.34-7.27 (m, 12 H), 7.20-7.16 (m, 8 H), 7.13-7.10 (m, 4 H), 4.99, 4.96 (AB, 4 H, *J* = 12.6 Hz), 4.80-4.75 (m, 2 H), 4.57 (q, 2 H, *J* = 7.9 Hz), 4.42 (dd, 2 H, *J* = 9.1, 7.2 Hz), 3.35 (d, 2 H, *J* = 8.1 Hz), 4.33-4.30 (m, 2 H), 3.51 (bt, 2 H, *J* = 9.3 Hz), 3.00-2.90 (m, 6 H), 2.83 (t, 2 H, *J* = 11.4 Hz), 2.39 (q, 2 H, *J* = 8.8 Hz), 2.05-1.95 (m, 2 H), 1.95-1.87 (m, 2 H), 1.75-1.65 (m, 2 H), 1.50-1.35 (m, 12 H), 1.35-1.20 (m, 6 H), 0.79 (d, 12 H, *J* = 6.6 Hz), 0.78 (d, 6 H, *J* = 6.7 Hz), 0.75 (d, 6 H, *J* = 6.7 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.7, 170.7, 170.5, 170.4, 169.6, 155.9, 137.2, 136.3, 129.2, 128.3, 128.1, 127.7, 127.6, 126.7, 65.2, 59.7, 56.6, 53.7, 51.3, 49.5, 45.7, 41.0, 40.2, 35.7, 31.3, 29.9, 25.2, 24.0, 23.0, 22.7, 22.5, 19.0, 18.0; HRMS (ESI) *m/z* calcd for $C_{76}H_{104}N_{12}O_{14}Na$ (M+Na) 1431.7693, found 1431.7726.

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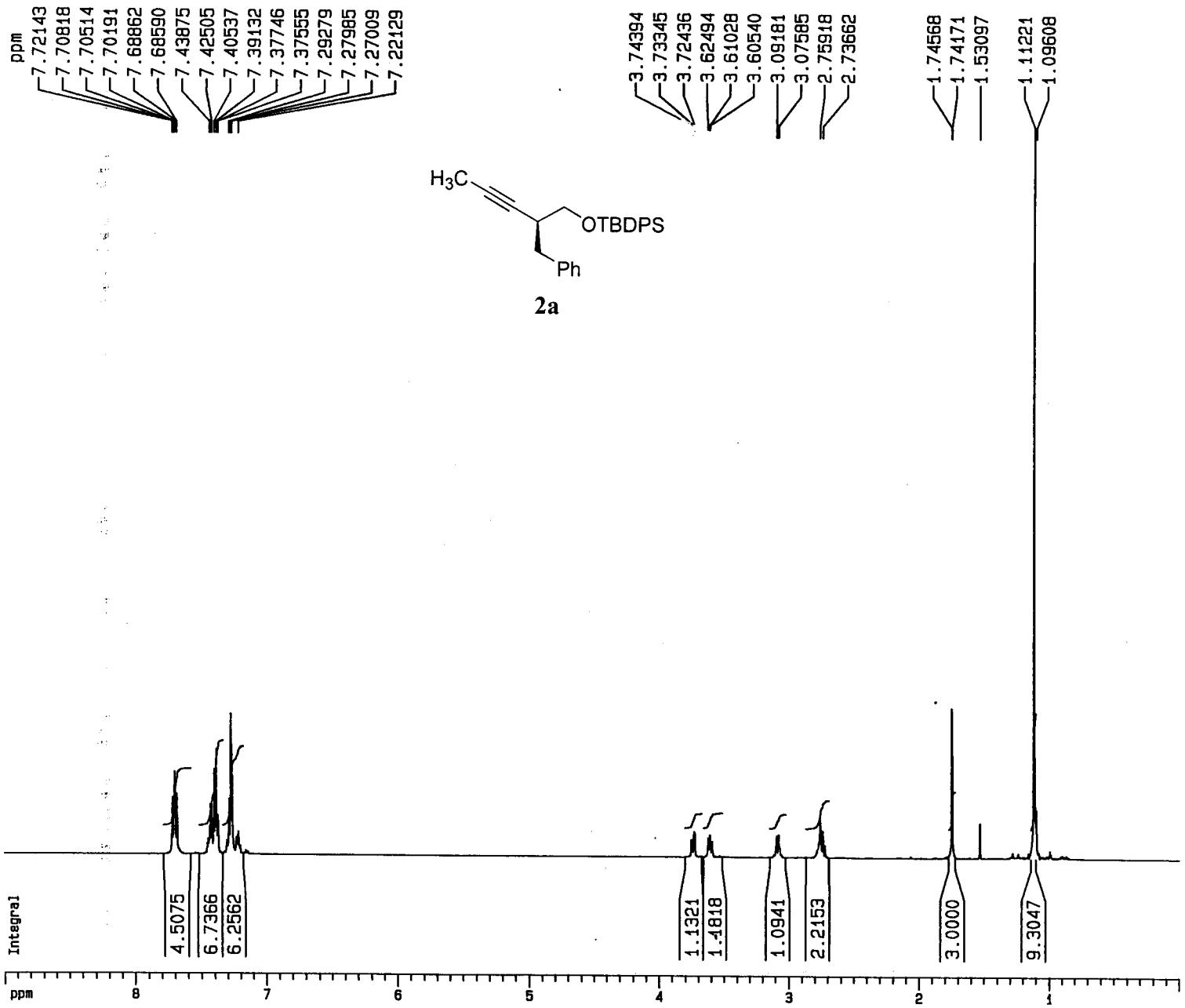

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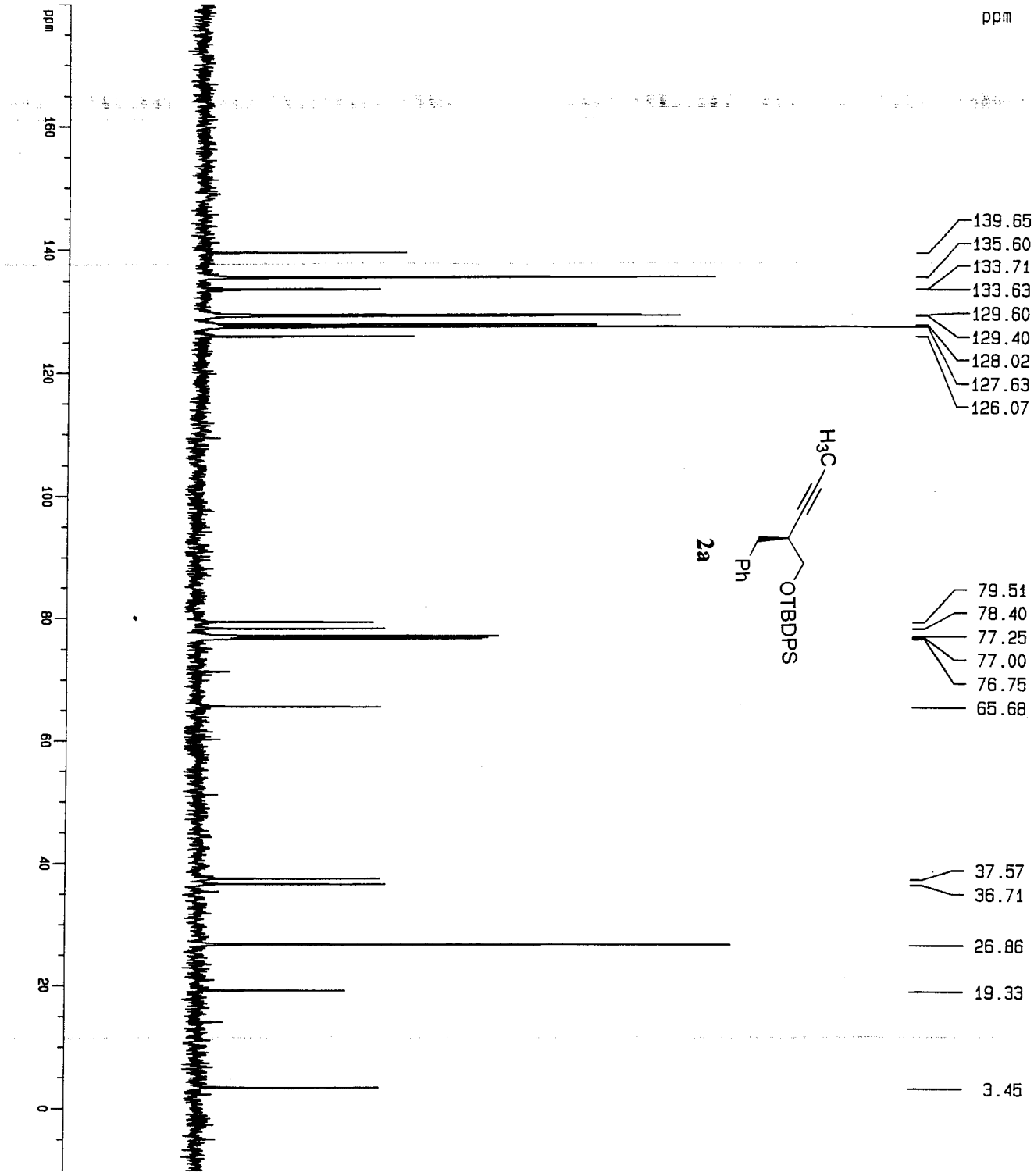


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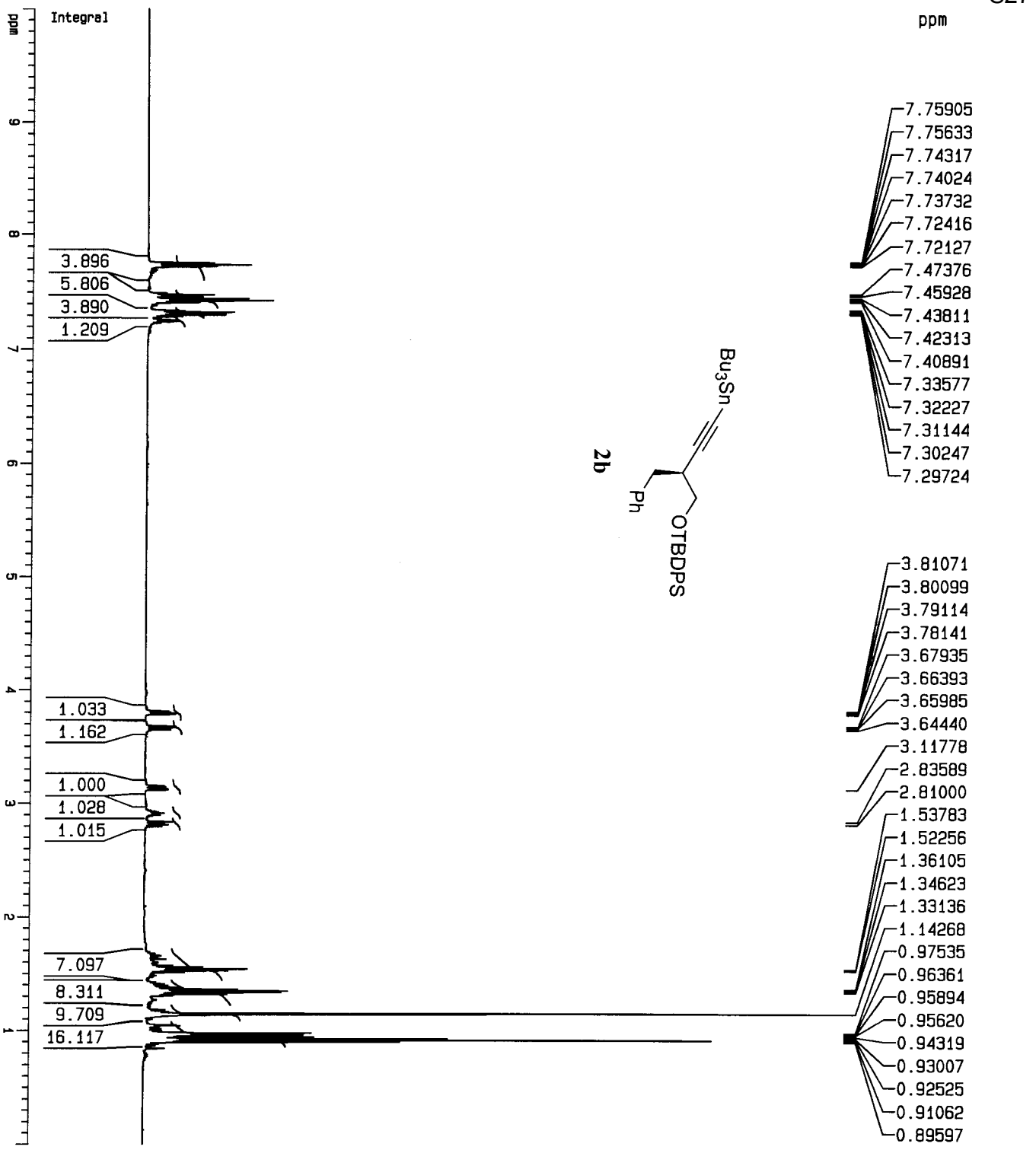


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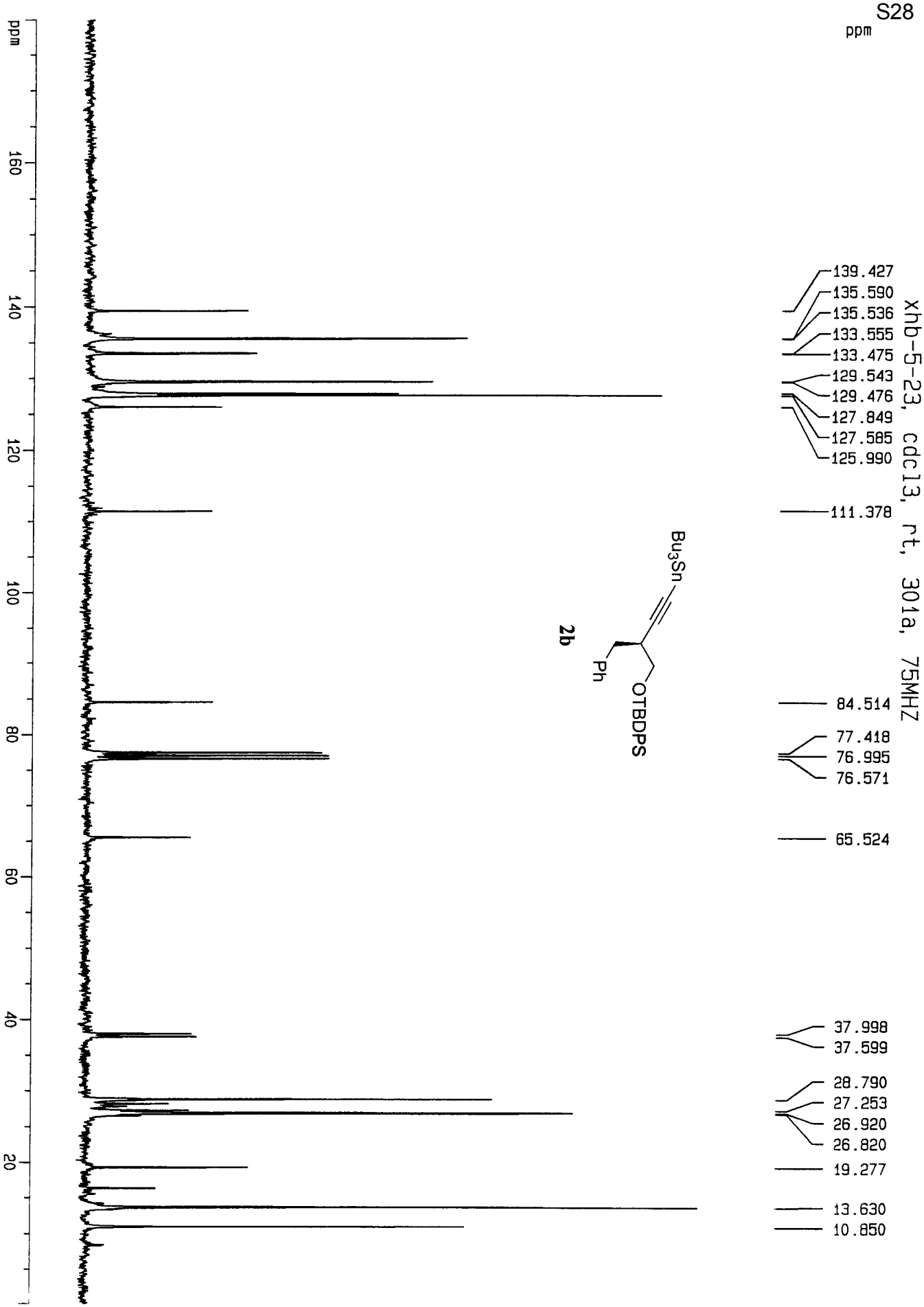
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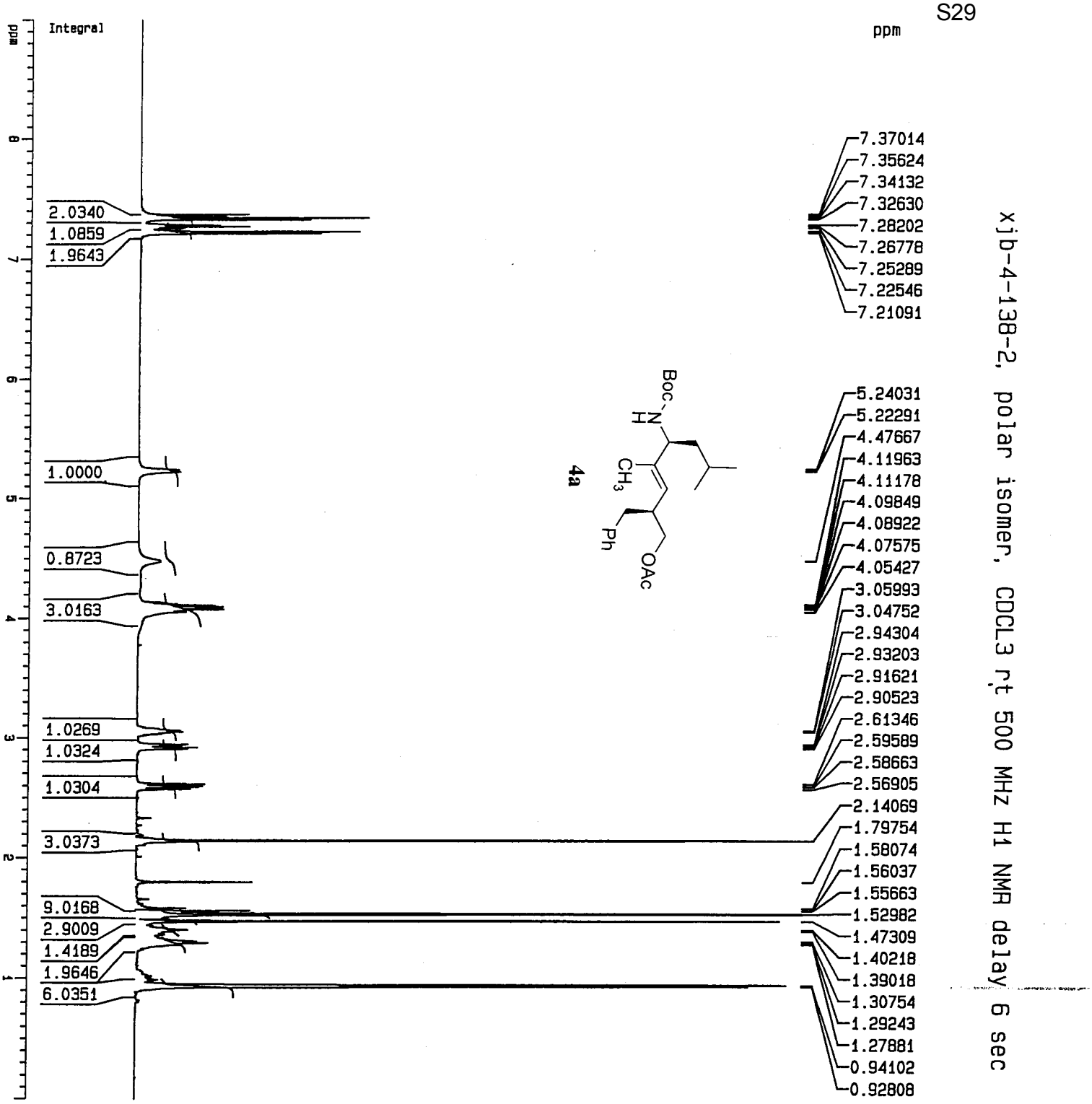
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S30

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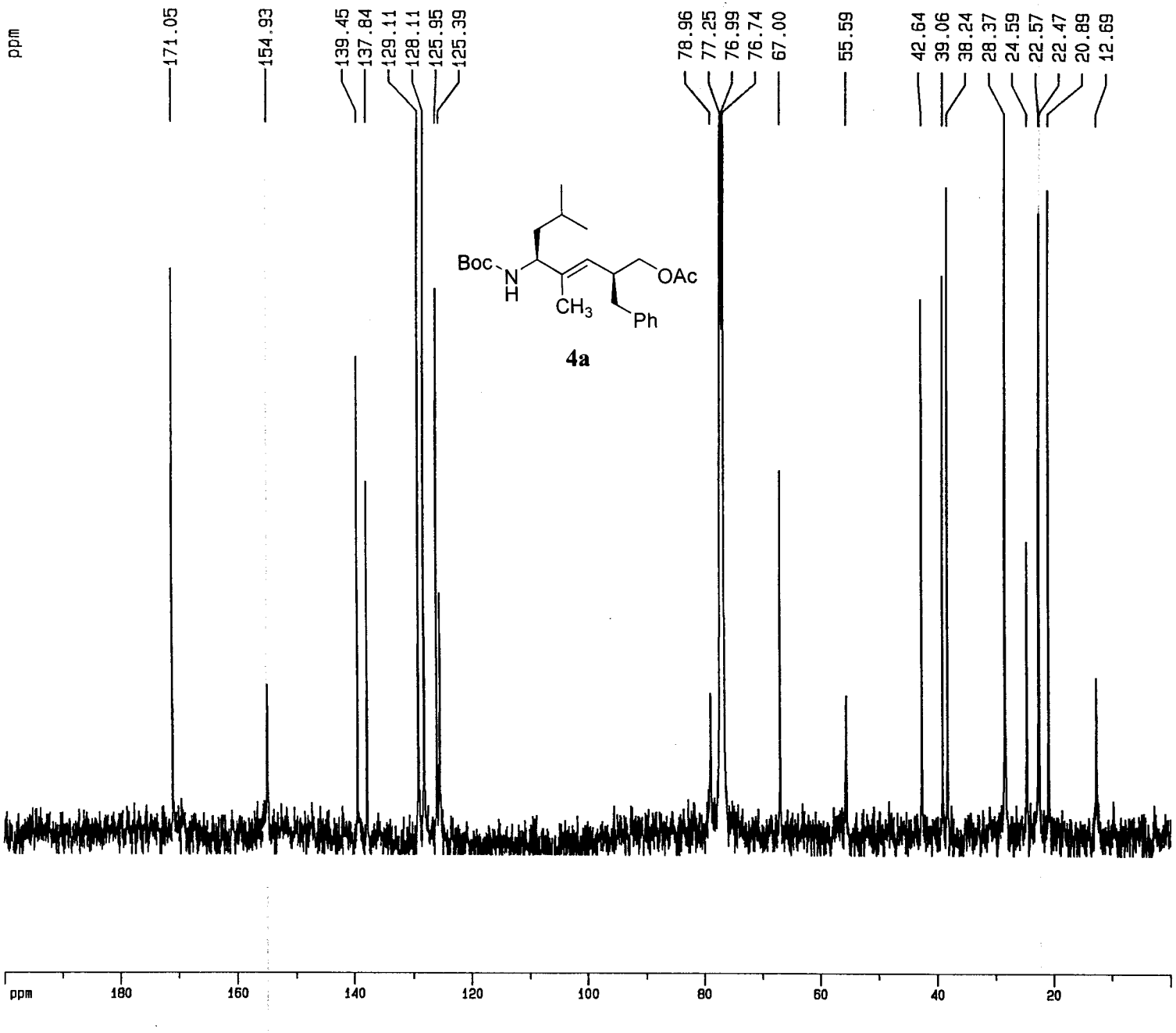

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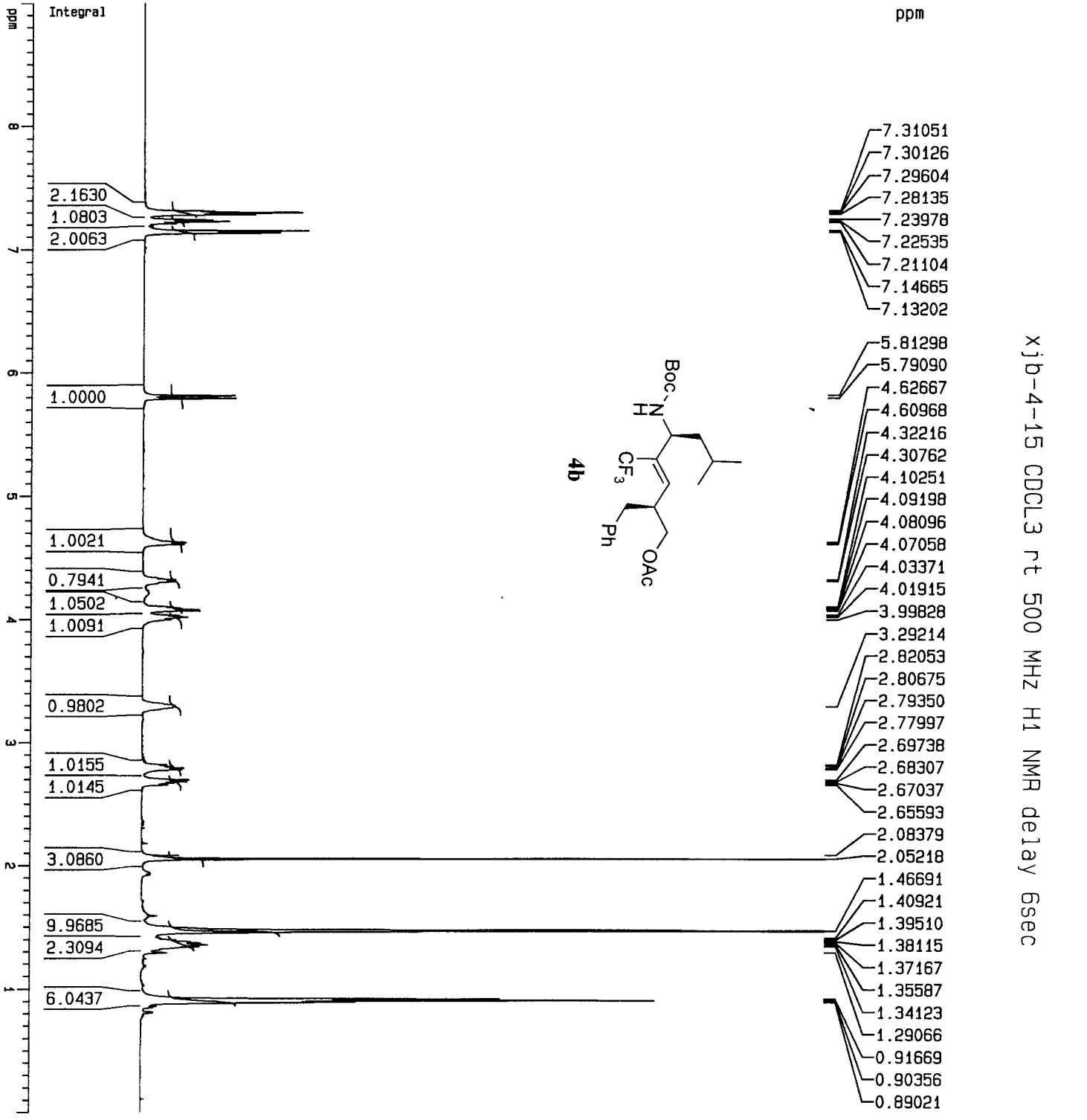

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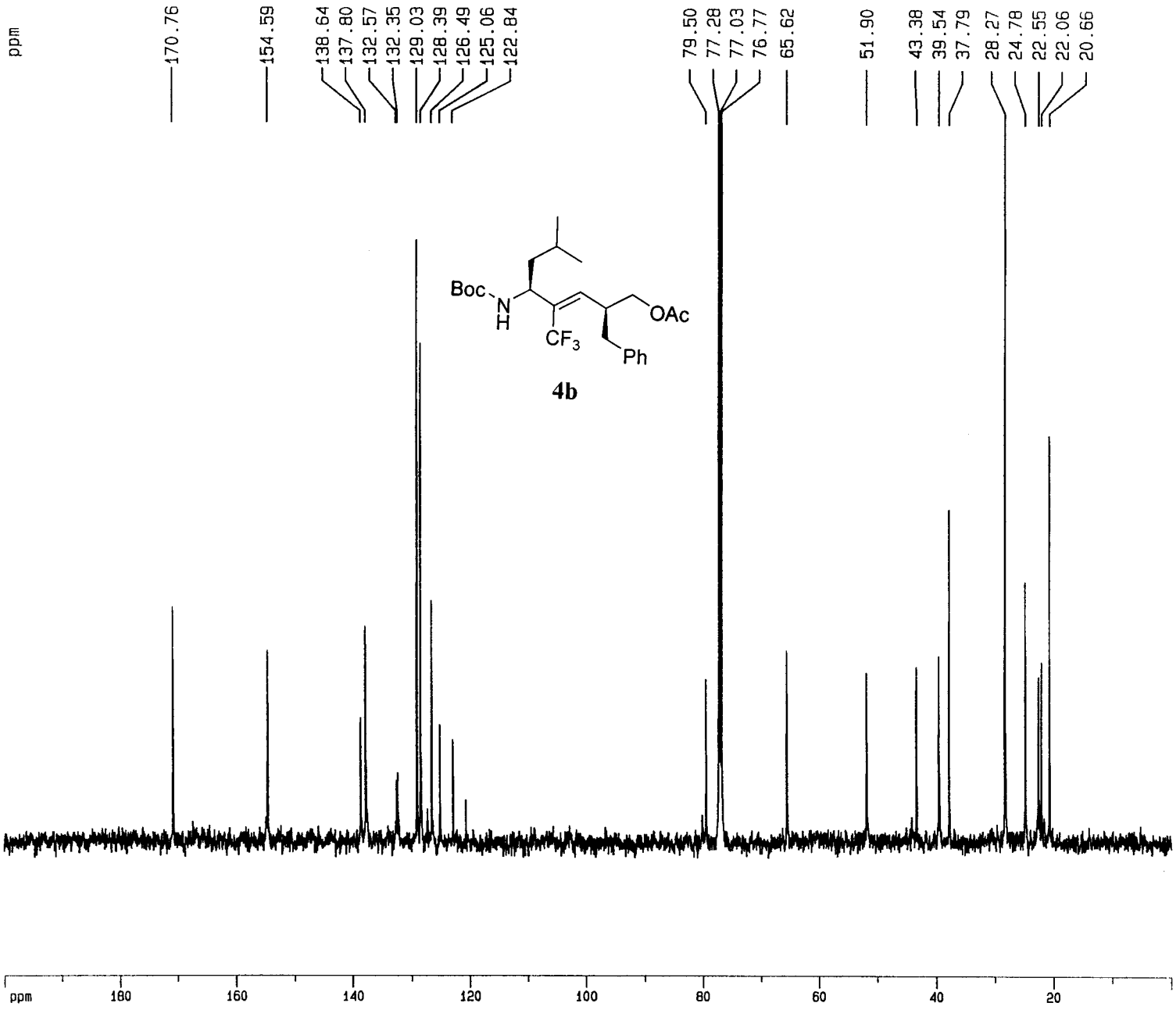

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D1	12.00000000 sec
CPDPRG2	waltz16
PCPD2	100.00 usec
SFO2	500.1330008 MHz
NUC2	1H
PL2	120.00 dB
P1	17.00 usec
DE	6.00 usec
SFO1	125.7715724 MHz
NUC1	13C
PL1	0.00 dB

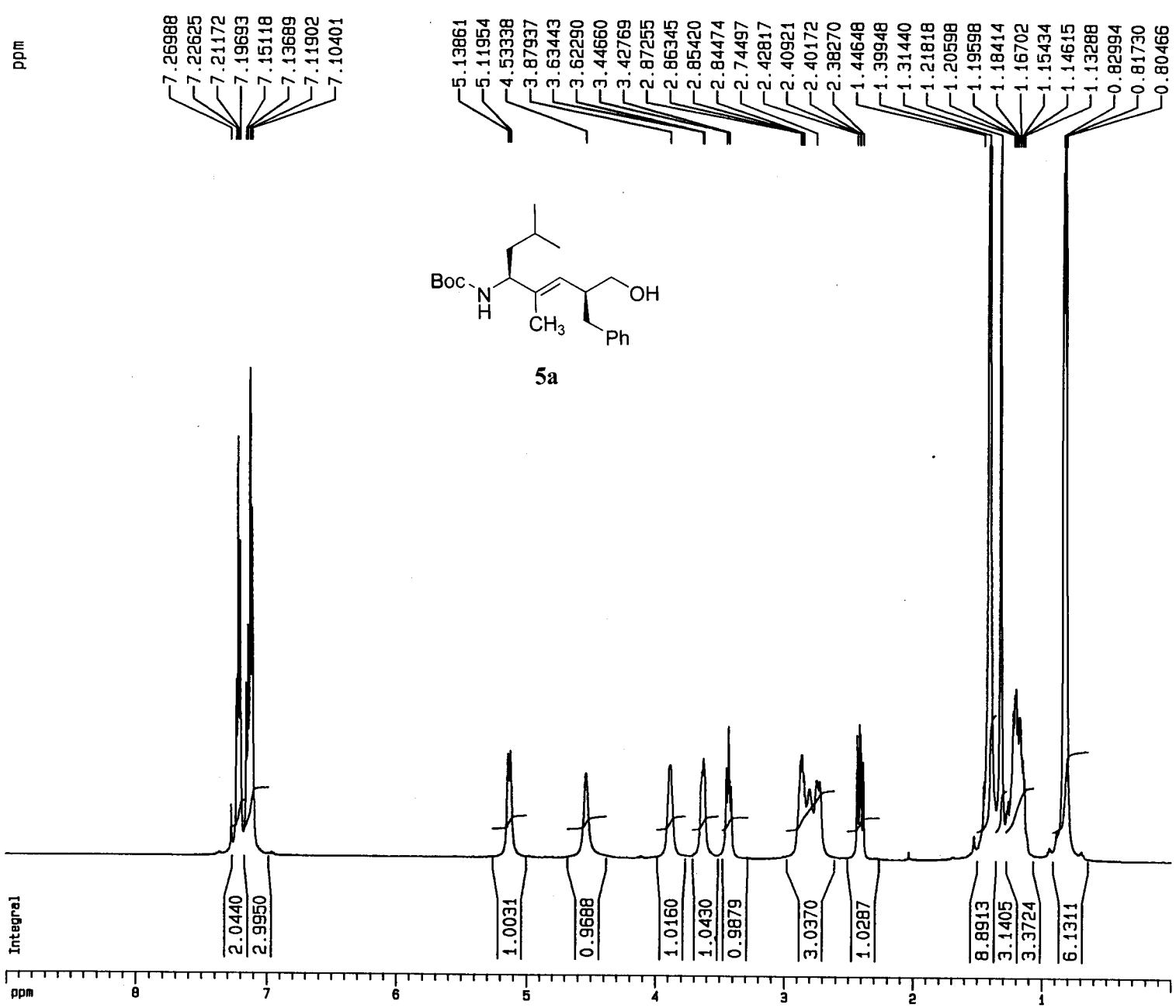
F2 - Processing parameters

SI	8192
SF	125.7578003 MHz
WDW	EM
SSB	0
LB	4.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	200.000 ppm
F1	25151.56 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	10.00000 ppm/cm
HZCM	1257.57800 Hz/cm

xjb-4-197 CDCL3 rt 500 MHz H1 NMR delay 8



5a

Current Data Parameters

NAME	xjb-4-197
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	21.02
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	zg
TD	32768
SOLVENT	CDC13
NS	10
DS	0
SWH	7507.507 Hz
FIDRES	0.229111 Hz
AQ	2.1823988 sec
RG	1
DW	66.600 usec
DE	6.00 usec
TE	290.0 K
D1	8.00000000 sec
P1	11.00 usec
DE	6.00 usec
SFO1	500.1330008 MHz
NUC1	1H
PL1	0.00 dB

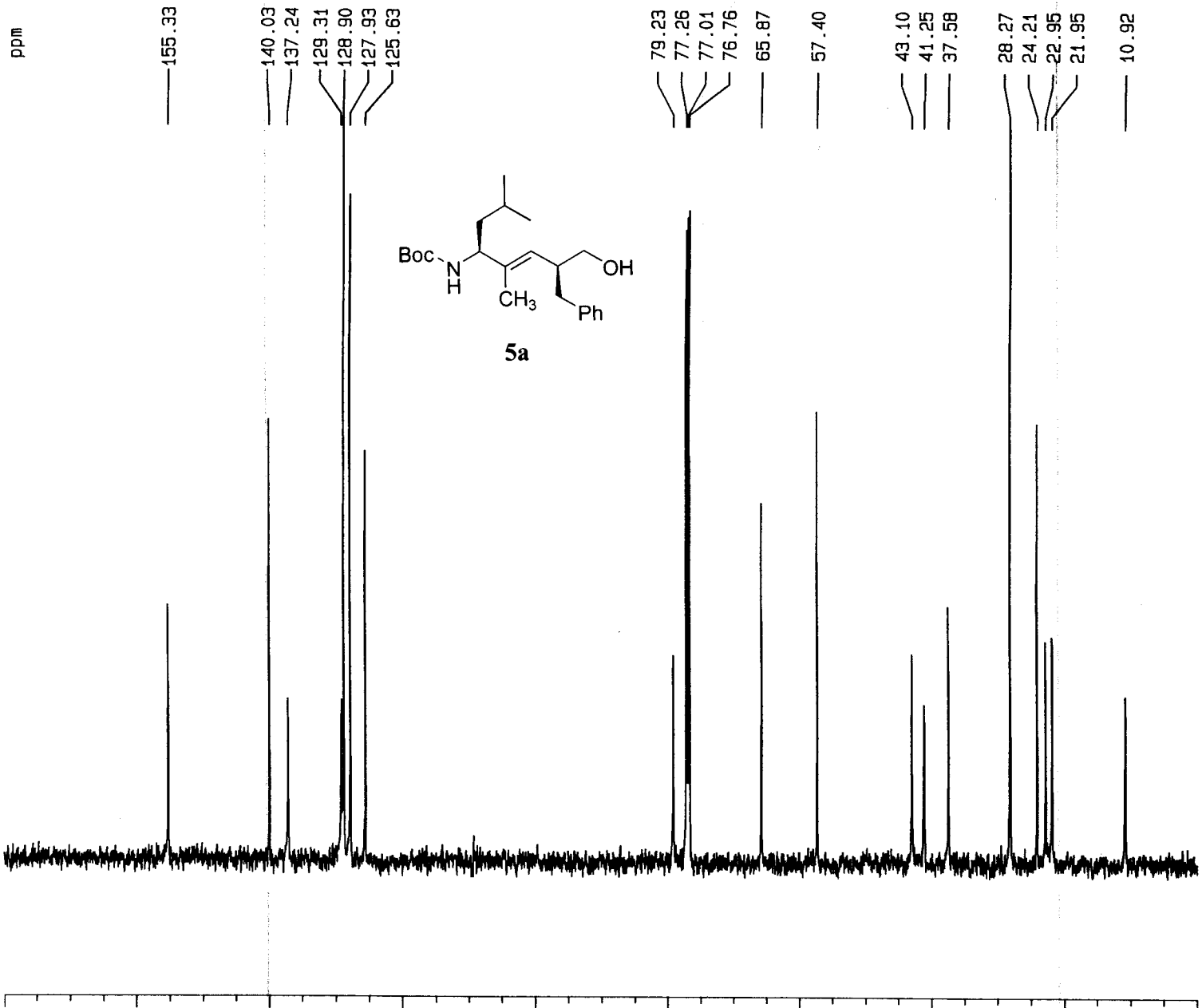
F2 - Processing parameters

SI	32768
SF	500.1300231 MHz
WDW	EM
SSB	0
LB	0.40 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	9.000 ppm
F1	4501.17 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.45000 ppm/cm
HZCM	225.05852 Hz/cm

xjb-4-197, cdcl3, rt, 125MHz C13 d1 = 10 sec



5a

Current Data Parameters

NAME	xjb-4-197
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	20.10
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	c13wonoe
TD	32768
SOLVENT	CDCl3
NS	311
DS	2
SWH	32679.738 Hz
FIDRES	0.997306 Hz
AQ	0.5014004 sec
RG	32768
DW	15.300 usec
DE	6.00 usec
TE	290.0 K
D3	0.00100000 sec
PL12	6.00 dB
D1	10.00000000 sec
CPDPRG2	waltz16
PCPD2	100.00 usec
SFO2	500.1330008 MHz
NUC2	1H
PL2	120.00 dB
P1	17.00 usec
DE	6.00 usec
SFO1	125.7715724 MHz
NUC1	13C
PL1	0.00 dB

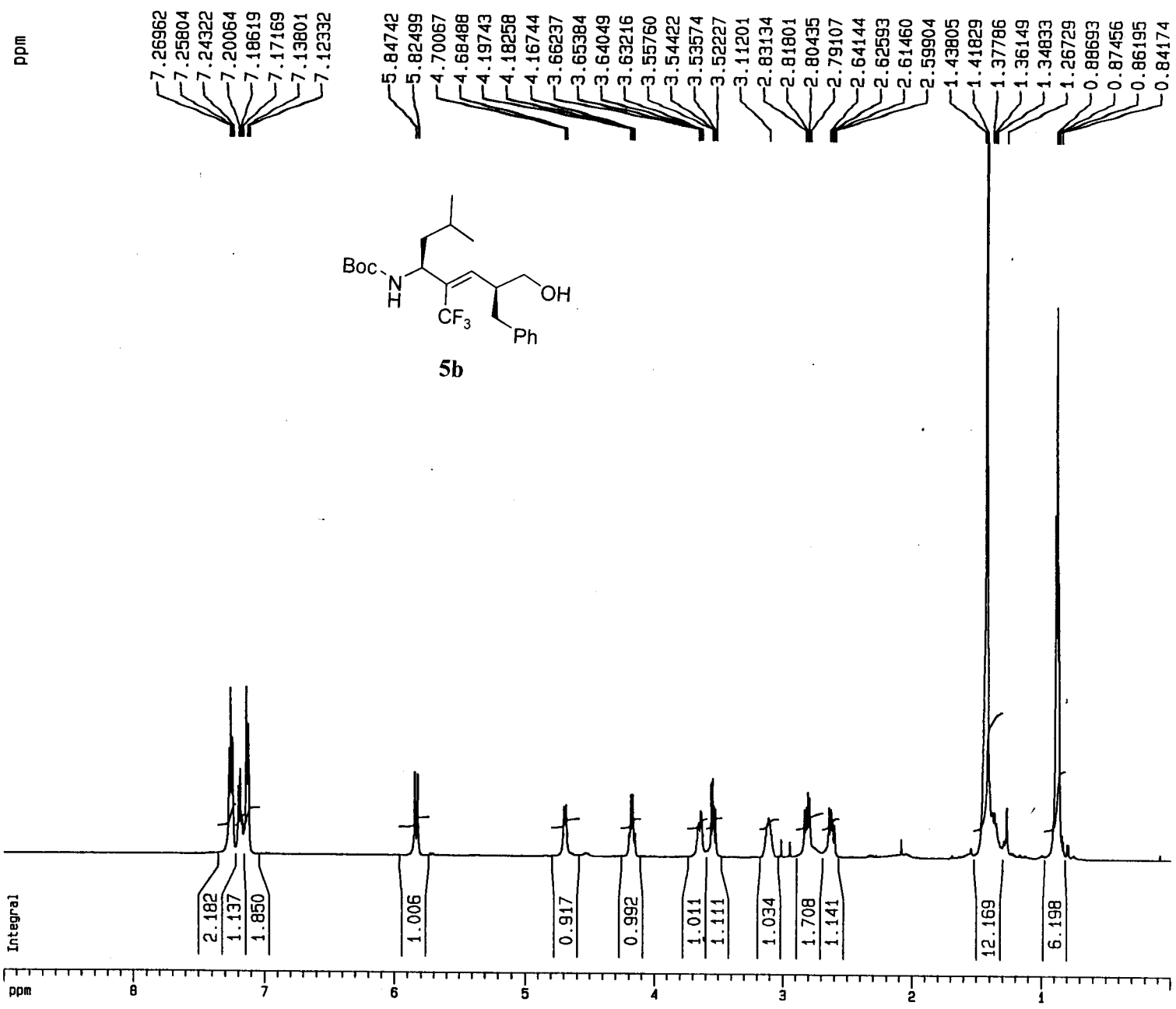
F2 - Processing parameters

SI	8192
SF	125.7578080 MHz
WDW	EM
SSB	0
LB	4.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	180.000 ppm
F1	22636.40 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	9.00000 ppm/cm
HZCM	1131.82019 Hz/cm

xjb-4-16 CDCL3 rt 500 MHz H1 NMR delay 6sec



Current Data Parameters

NAME	xjb-4-16-500
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	14.46
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	43
DS	0
SWH	7507.507 Hz
FIDRES	0.229111 Hz
AQ	2.1823988 sec
RG	9
DW	66.600 usec
DE	6.00 usec
TE	290.0 K
D1	6.00000000 sec
P1	11.00 usec
DE	6.00 usec
SFO1	500.1330008 MHz
NUC1	1H
PL1	0.00 dB

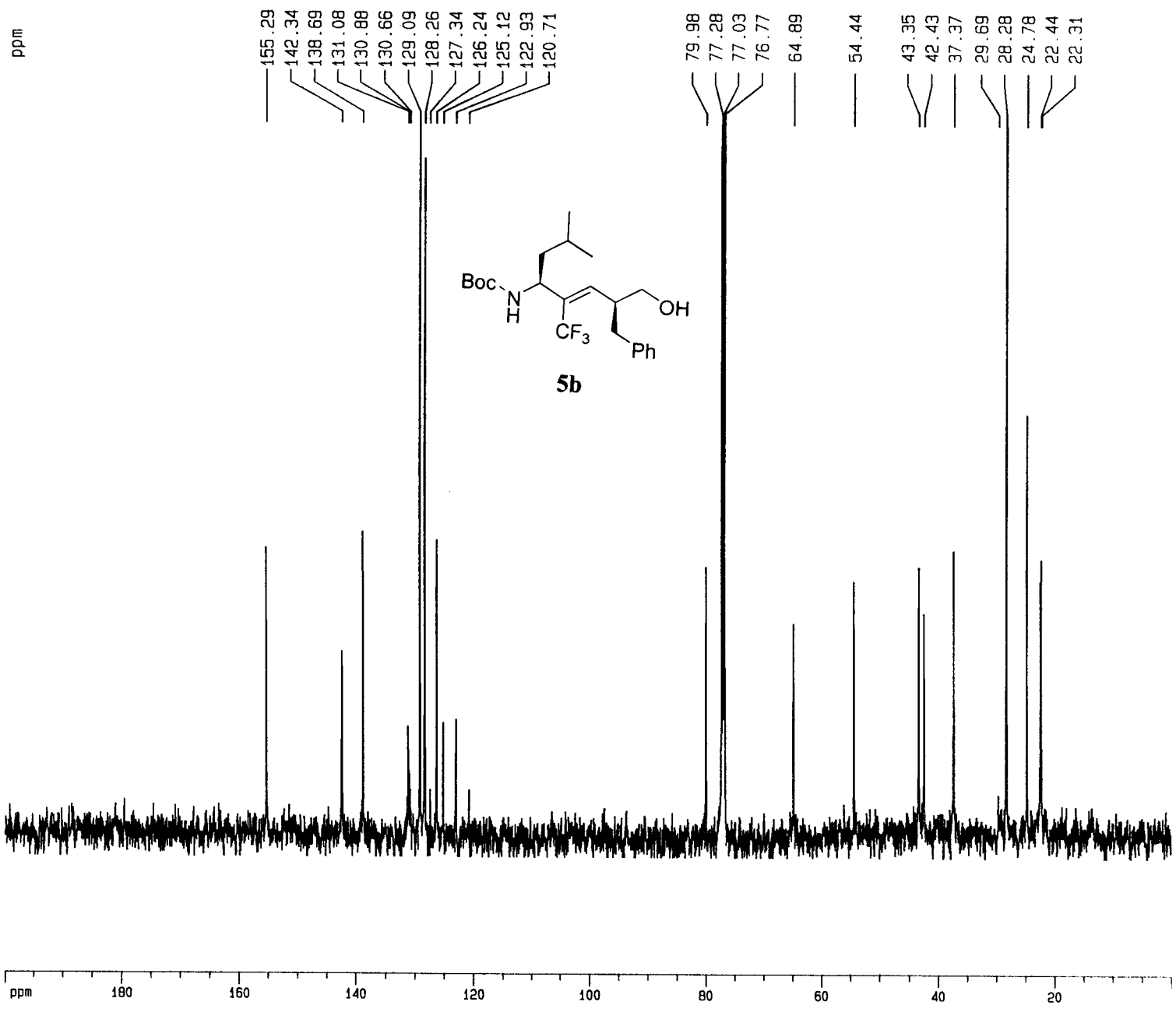
F2 - Processing parameters

SI	32768
SF	500.1300235 MHz
WDW	EM
SSB	0
LB	0.40 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	9.000 ppm
F1	4501.17 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.45000 ppm/cm
HZCM	225.05852 Hz/cm

xjb-4-16, cdcl3, rt, 125MHz, d1 = 8 sec



5b

Current Data Parameters

NAME	xjb-4-16-500
EXPNO	13
PROCNO	1

F2 - Acquisition Parameters

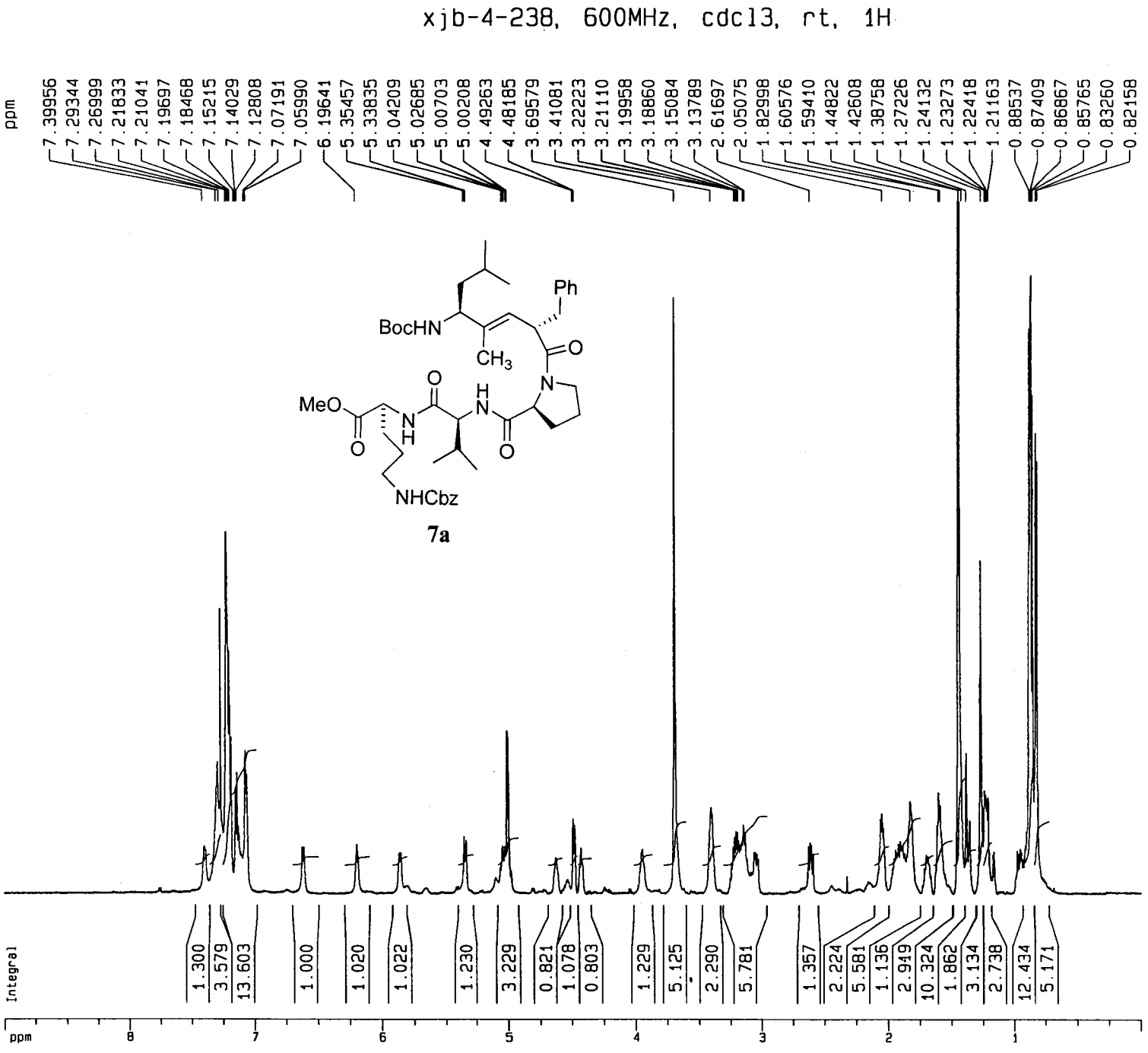
Date_	500000
Time	13.2?
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	c13wonoe
TD	32768
SOLVENT	CDCl3
NS	525
DS	2
SWH	32679.738 Hz
FIDRES	0.997306 Hz
AQ	0.5014004 sec
RG	32768
DW	15.300 usec
DE	6.00 usec
TE	290.0 K
D3	0.00100000 sec
PL12	6.00 dB
D1	8.00000000 sec
CPDPRG2	waltz16
PCPD2	100.00 usec
SFO2	500.1330008 MHz
NUC2	1H
PL2	120.00 dB
P1	17.00 usec
DE	6.00 usec
SFO1	125.7715724 MHz
NUC1	13C
PL1	0.00 dB

F2 - Processing parameters

SI	8192
SF	125.7577963 MHz
WDW	EM
SSB	0
LB	4.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	200.000 ppm
F1	25151.56 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	10.00000 ppm/cm
HZCM	1257.57800 Hz/cm



7a

Current Data Parameters

NAME	xjb-4-238-600
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040301
Time	21.49
INSTRUM	spect
PROBHD	5 mm TBI 1H/
PULPROG	zg
TD	65536
SOLVENT	CD2Cl2
NS	10
DS	0
SWH	8992.806 Hz
FIDRES	0.137219 Hz
AQ	3.6438515 sec
RG	1
DW	55.600 use
DE	6.00 use
TE	290.0 K
D1	6.00000000 sec

========== CHANNEL f1 ===

NUC1	1H
P1	9.00 use
PL1	0.00 dB
SFO1	600.8336050 MHz

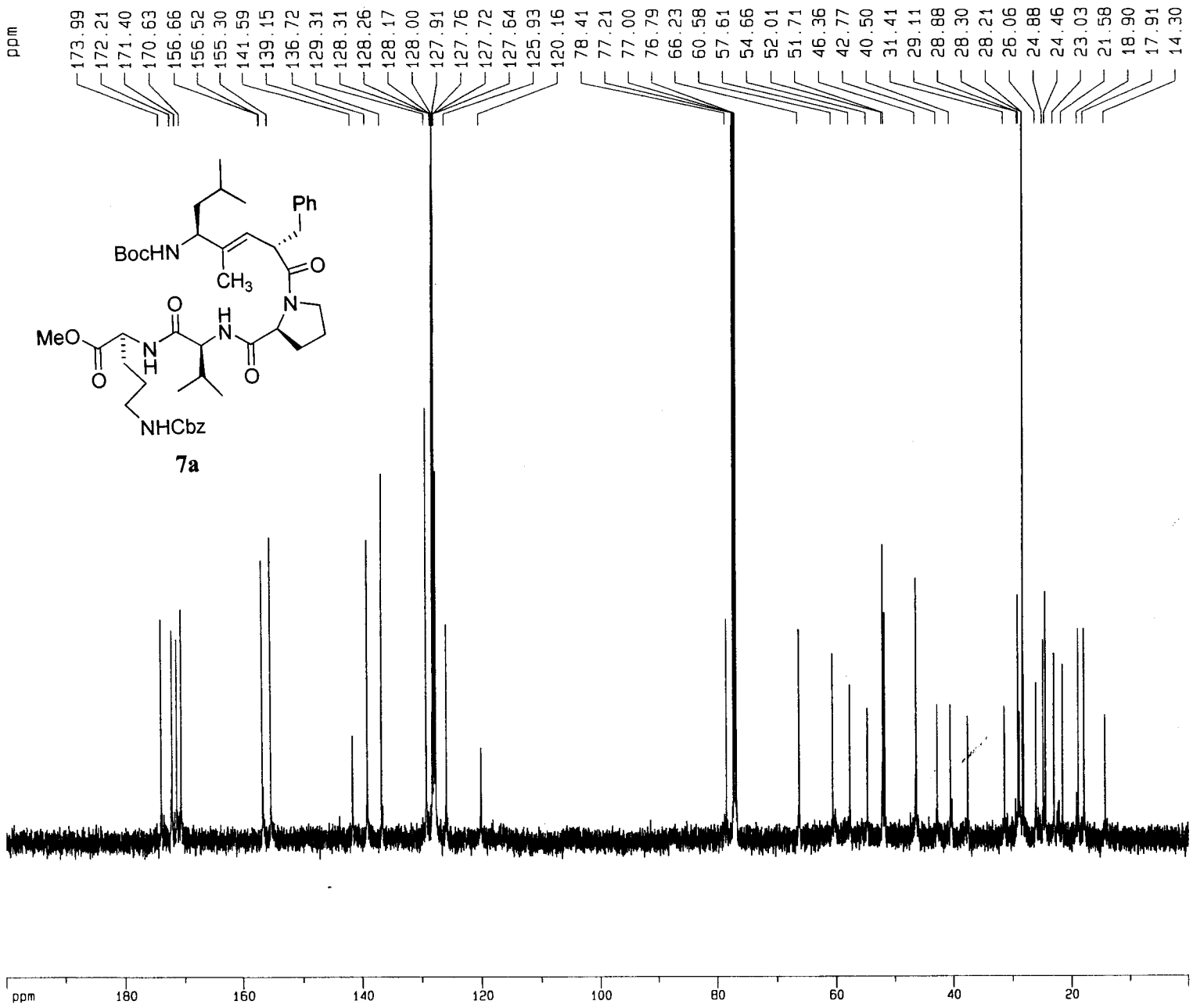
F2 - Processing parameters

SI	65536
SF	600.8300264 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

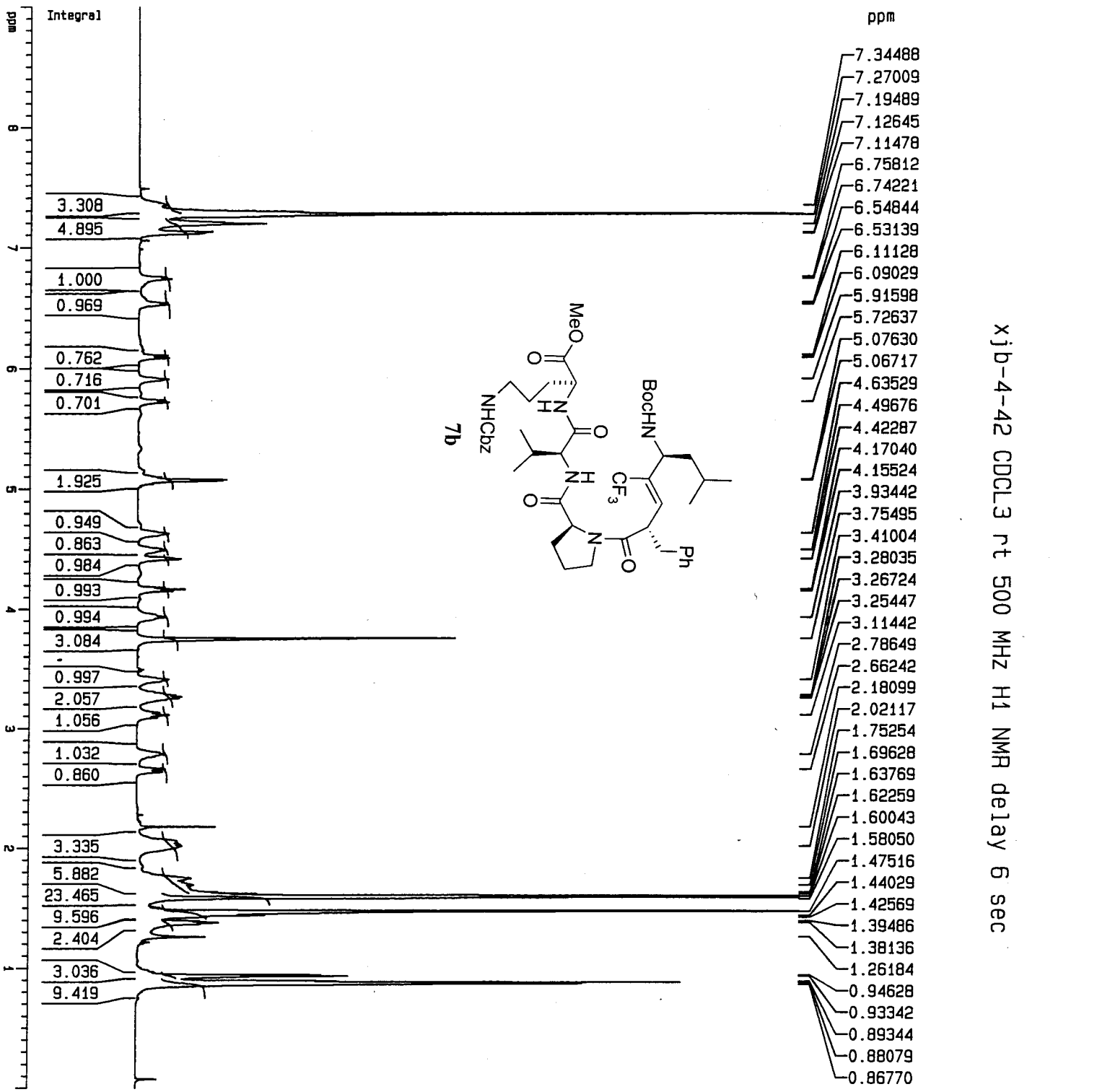
CX	20.00 cm
F1P	9.000 ppm
F1	5407.47 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.45000 ppm
HZCM	270.37350 Hz/

xjb-4-238, cdcl3, rt, 150Mhz, C13

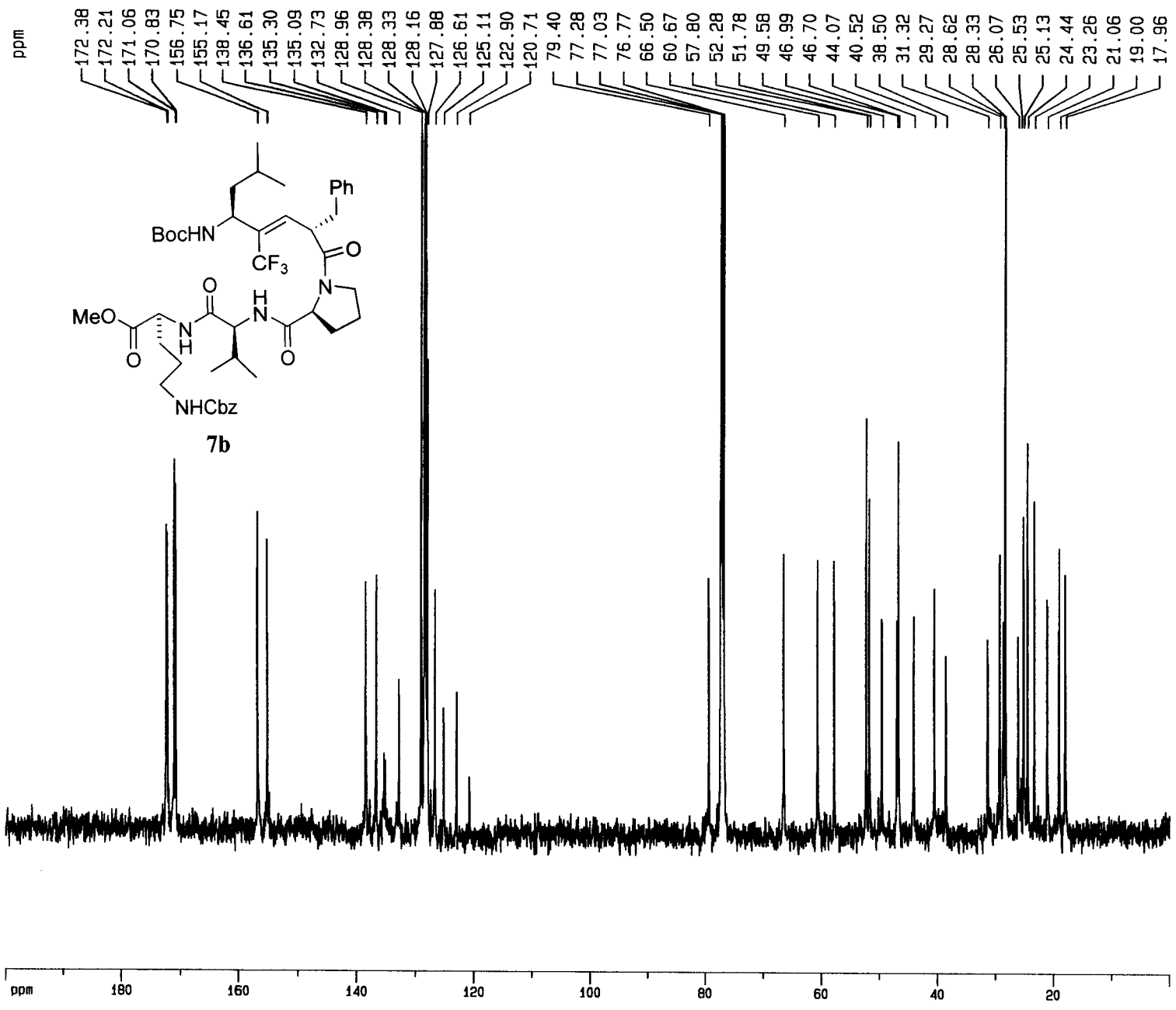


7a

```
Current Data Parameters
NAME        xjb-4-238-600
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20040302
Time                13.24
INSTRUM             spect
PROBHD      5 mm TBI 1H/
PULPROG          c13wonoe
TD                 65536
SOLVENT            CDCl3
NS                   884
DS                     0
SWH          37878.789 Hz
FIDRES       0.577984 Hz
AQ           0.8651252 sec
RG                 32768
DW              13.200 usec
DE               6.00 usec
TE               290.0 K
D1           8.00000000 sec
D3           0.00100000 sec

============ CHANNEL f1 ======
NUC1                13C
P1              13.50 usec
PL1              0.00 dB
SFO1       151.0953827 MHz

============ CHANNEL f2 ======
CPDPRG2         waltz16
NUC2                1H
PCPD2           100.00 usec
PL2              0.00 dB
PL12            12.00 dB
SFO2       600.8336050 MHz

F2 - Processing parameters
SI                 65536
SF         151.0788512 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.00

1D NMR plot parameters
CX               20.00 cm
F1P             200.000 ppm
F1             30215.77 Hz
F2P              0.000 ppm
F2               0.00 Hz
PPMCM          10.00000 ppm/cm
HZCM         1510.78857 Hz/cm
```


xjb-4-42 CDCL3 rt 500 MHz H1 NMR delay 6 sec
ppm
Integral
7.34488
7.27009
7.19489
7.12645
7.11478
6.75812
6.74221
6.54844
6.53139
6.11128
6.09029
5.91598
5.72637
5.07630
5.06717
4.63529
4.49676
4.42287
4.17040
4.15524
3.93442
3.75495
3.41004
3.28035
3.26724
3.25447
3.11442
2.78649
2.66242
2.18099
2.02117
1.75254
1.69628
1.63769
1.62259
1.60043
1.58050
1.47516
1.44029
1.42569
1.39486
1.38136
1.26184
0.94628
0.93342
0.89344
0.88079
0.86770
3.308
4.895
1.000
0.969
0.762
0.716
0.701
1.925
0.949
0.863
0.984
0.993
0.994
3.084
0.997
2.057
1.056
1.032
0.860
3.335
5.882
23.465
9.596
2.404
3.036
9.419
MeO
NHCbz
BocHN
Ph
7b
Current Data Parameters
NAME xjb-4-42-500
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 21.09
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg
TD 32768
SOLVENT CDC13
NS 100
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 71.8
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 6.00000000 sec
P1 11.00 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
F2 - Processing parameters
SI 32768
SF 500.1300235 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 9.000 ppm
F1 4501.17 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45000 ppm/cm
HZCM 225.05852 Hz/cm

xjb-4-42, cdcl3, rt, 125MHz



7b

Current Data Parameters

NAME	xjb-4-42-500
EXPNO	132
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	14.03
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	c13wonoe
TD	32768
SOLVENT	CDCl3
NS	3634
DS	2
SWH	32679.738 Hz
FIDRES	0.997306 Hz
AQ	0.5014004 sec
RG	32768
DW	15.300 usec
DE	6.00 usec
TE	290.0 K
D3	0.00100000 sec
PL12	6.00 dB
D1	6.00000000 sec
CPDPRG2	waltz16
PCPD2	100.00 usec
SFO2	500.1330008 MHz
NUC2	1H
PL2	120.00 dB
P1	17.00 usec
DE	6.00 usec
SFO1	125.7715724 MHz
NUC1	13C
PL1	0.00 dB

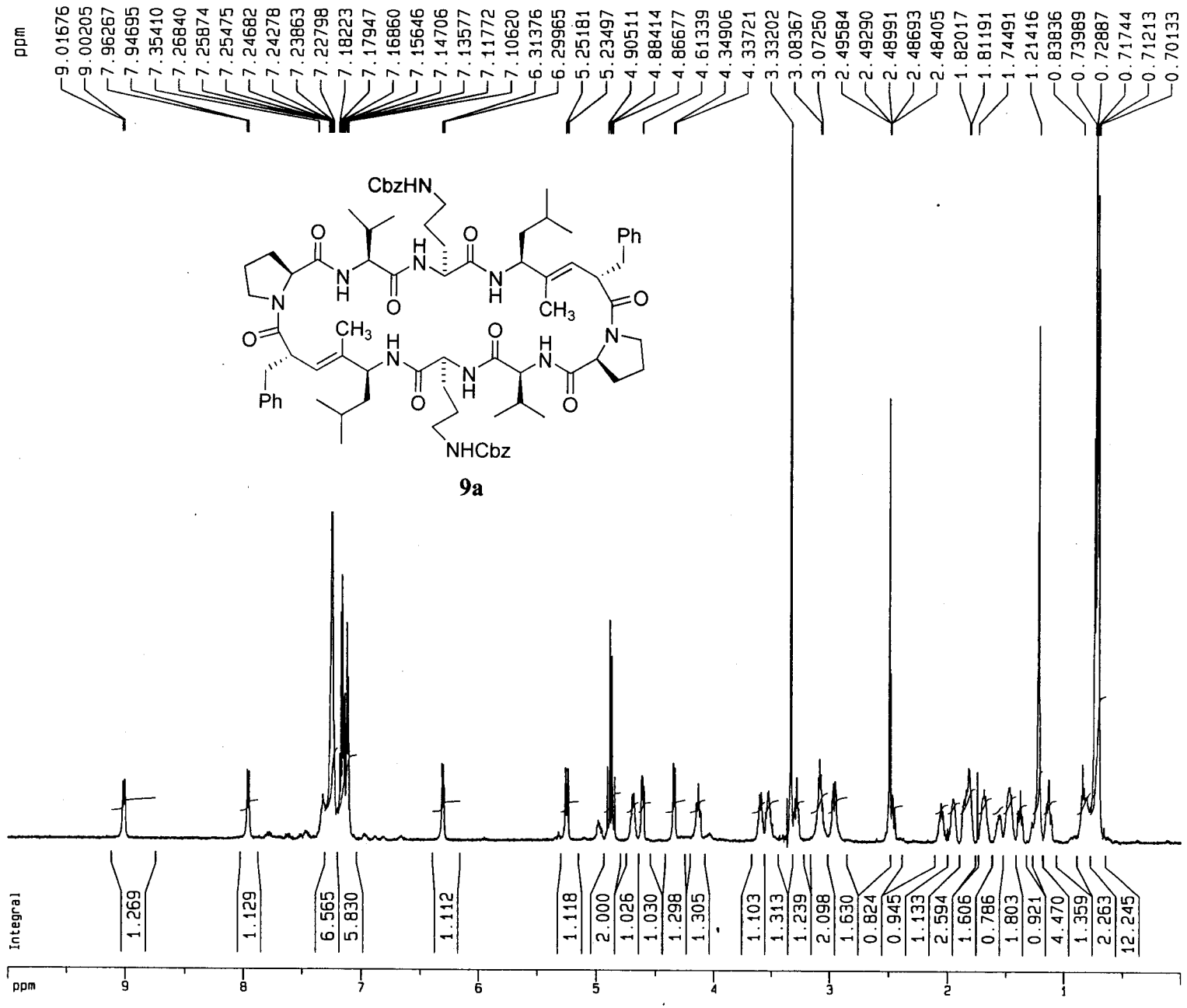
F2 - Processing parameters

SI	8192
SF	125.7578003 MHz
WDW	EM
SSB	0
LB	4.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	200.000 ppm
F1	25151.56 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	10.00000 ppm/cm
HZCM	1257.57800 Hz/cm

xjb-4-257, DMSO-d6, rt, 600MHz, CH3-GS



9a

Current Data Parameters

NAME	xjb-4-257-600
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040328
Time	22.11
INSTRUM	spect
PROBHD	5 mm TBI 1H/
PULPROG	zg
TD	65536
SOLVENT	DMSO
NS	30
DS	0
SWH	8992.806 Hz
FIDRES	0.137219 Hz
AQ	3.6438515 sec
RG	1
DW	55.600 use
DE	6.00 use
TE	290.0 K
D1	6.00000000 sec

========== CHANNEL f1 ===

NUC1	1H
P1	9.00 use
PL1	0.00 dB
SFO1	600.8336050 MHz

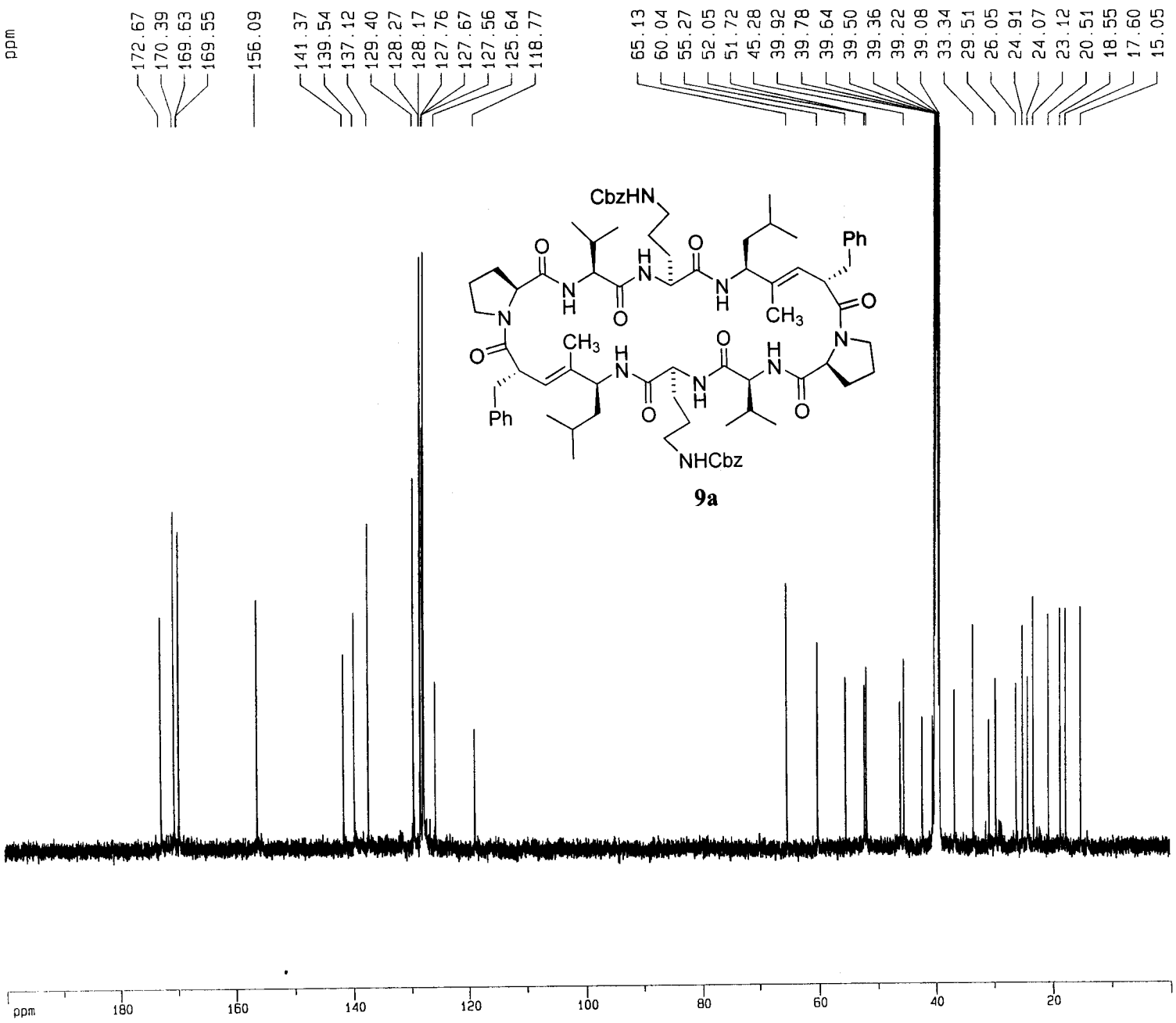
F2 - Processing parameters

SI	65536
SF	600.8300115 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.000 ppm
F1	6008.30 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.50000 ppm
HZCM	300.41501 Hz/

xjb-4-257, DMSO-d6, 150MHz, C13, rt, CH3-GS



9a

Current Data Parameters

NAME	xjb-4-257-600
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20040328
Time	22.02
INSTRUM	spect
PROBHD	5 mm TBI 1H/
PULPROG	c13wonoe
TD	65536
SOLVENT	CDCl3
NS	9005
DS	0
SWH	37878.789 Hz
FIDRES	0.577984 Hz
AQ	0.8651252 sec
RG	32768
DW	13.200 usec
DE	6.00 usec
TE	290.0 K
D1	8.00000000 sec
D3	0.00100000 sec

========== CHANNEL f1 ======

NUC1	13C
P1	13.50 usec
PL1	0.00 dB
SFO1	151.0953827 MHz

========== CHANNEL f2 ======

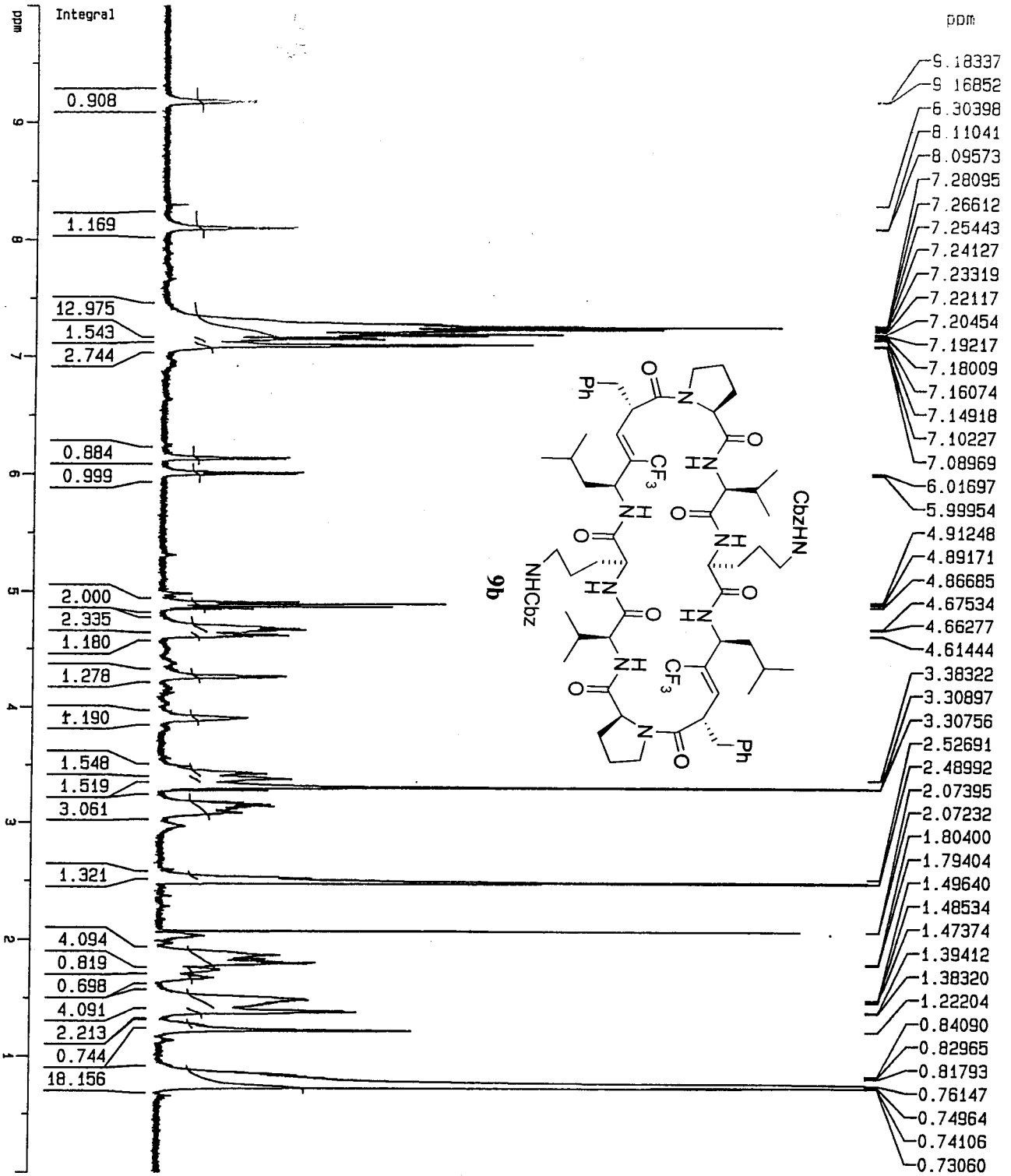
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	0.00 dB
PL12	12.00 dB
SFO2	600.8336050 MHz

F2 - Processing parameters

SI	65536
SF	151.0788998 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

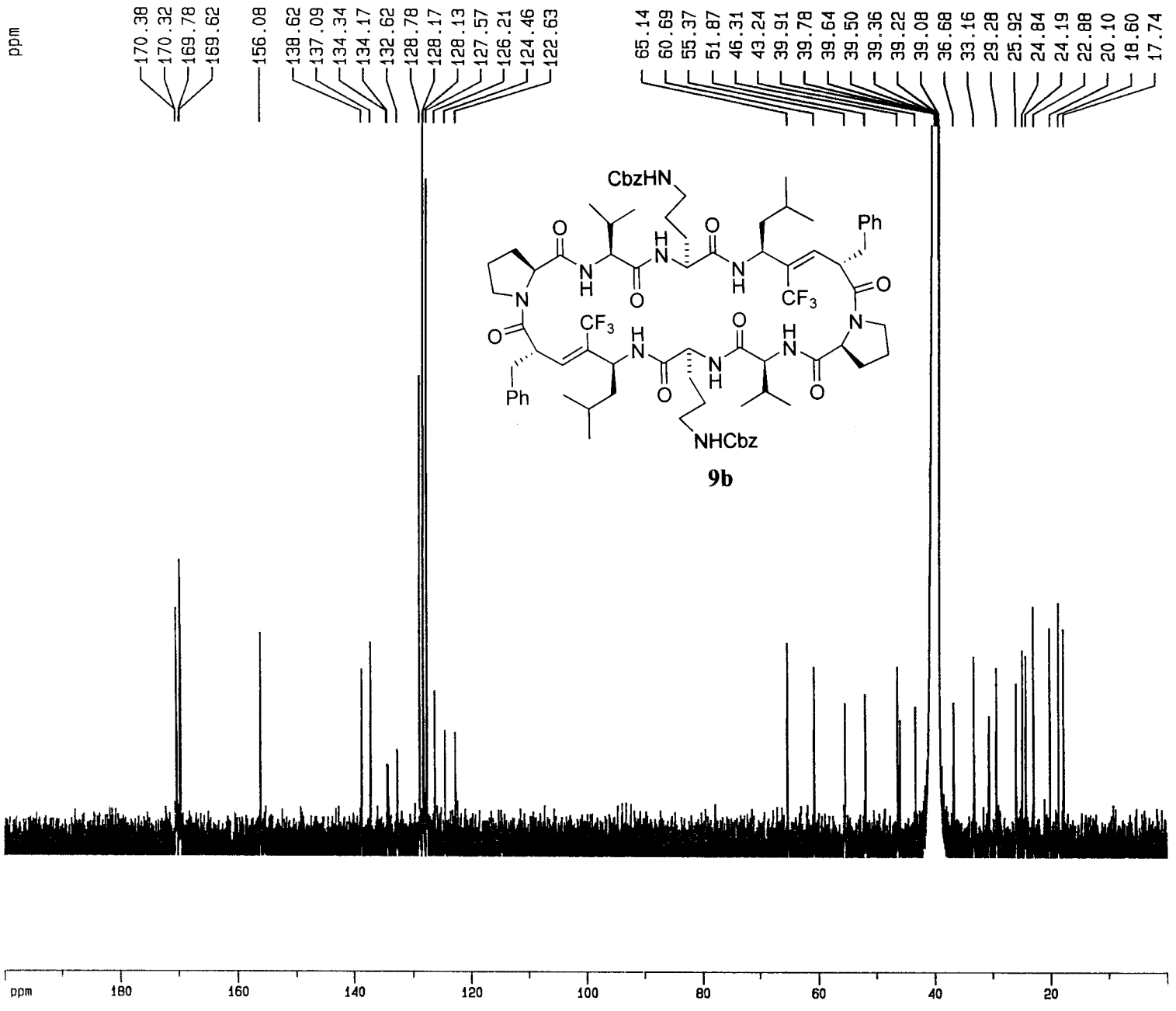
1D NMR plot parameters

CX	20.00 cm
F1P	200.000 ppm
F1	30215.78 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	10.00000 ppm/cm
HZCM	1510.78906 Hz/cm



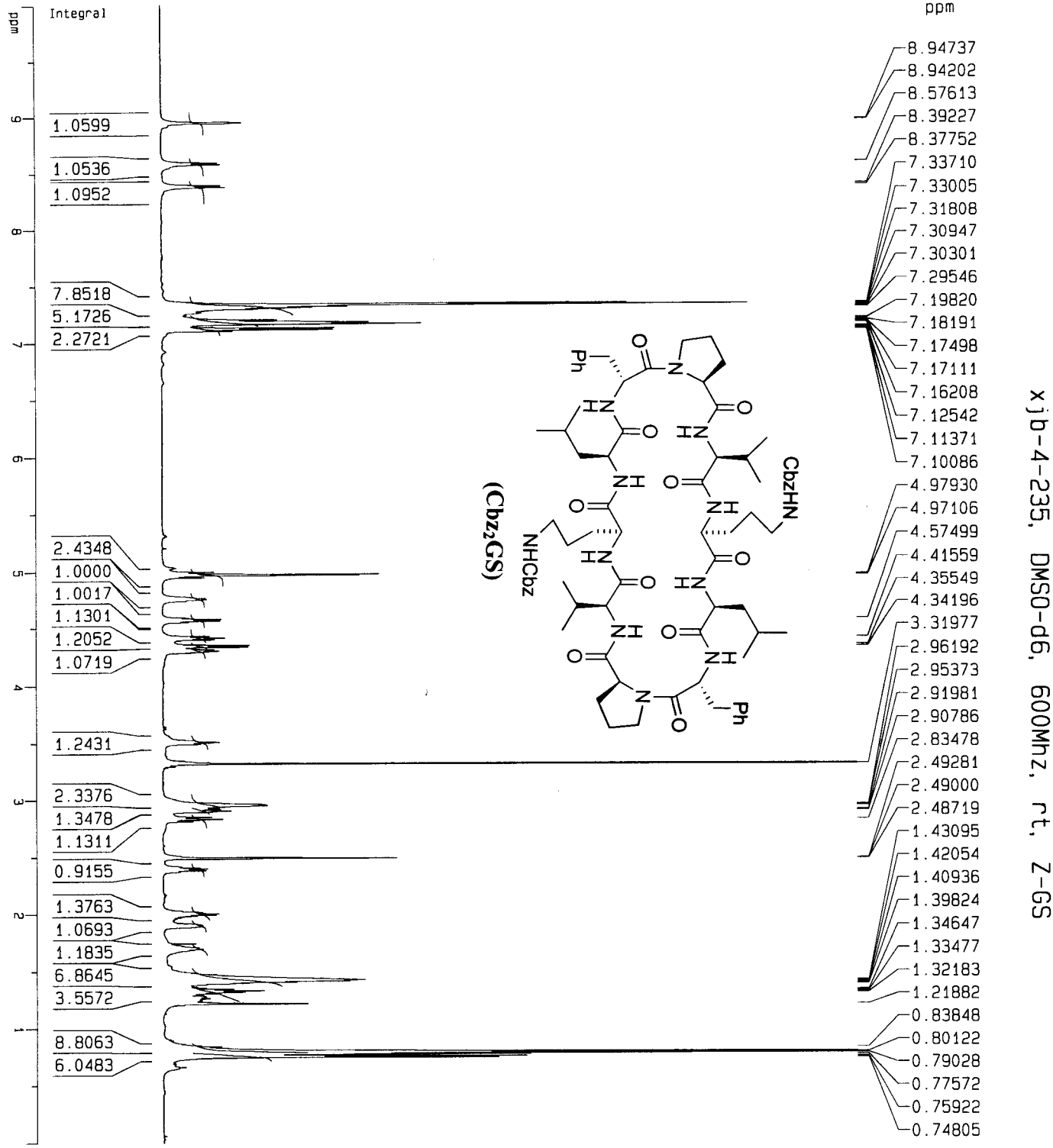

```
Current Data Parameters
NAME                  xjb462-600-ft1
EXPNO                              1
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20031208
Time                            8.33
INSTRUM                         spect
PROBHD     5 mm TBI 1H/
PULPROG                         zg
TD                              65536
SOLVENT                         CD2Cl2
NS                                 41
DS                                  0
SWH                          8992.806 Hz
FIDRES                       0.137219 Hz
AQ                           3.6438515 sec
RG                                  2
DW                           55.600 usec
DE                            6.00 usec
TE                            290.0 K
D1                           12.00000000 sec
======== CHANNEL f1 ========
NUC1                               1H
P1                            9.00 usec
PL1                           0.00 dB
SFO1                         600.8336050 MHz

F2 - Processing parameters
SI                                 65536
SF                           600.8300108 MHz
WDW                                EM
SSB                                 0
LB                            0.10 Hz
GB                                  0
PC                                1.00

1D NMR plot parameters
CX                           20.00 cm
F1P                          10.000 ppm
F1                           6008.30 Hz
F2P                          0.000 ppm
F2                           0.00 Hz
PPMCM                        0.50000 ppm/cm
HZCM                         300.41501 Hz/cm
```

xjb-4-62-600 dmso-d6 298K 151MHz 13C 1H decp delay 8sec 12/8/03 ftl



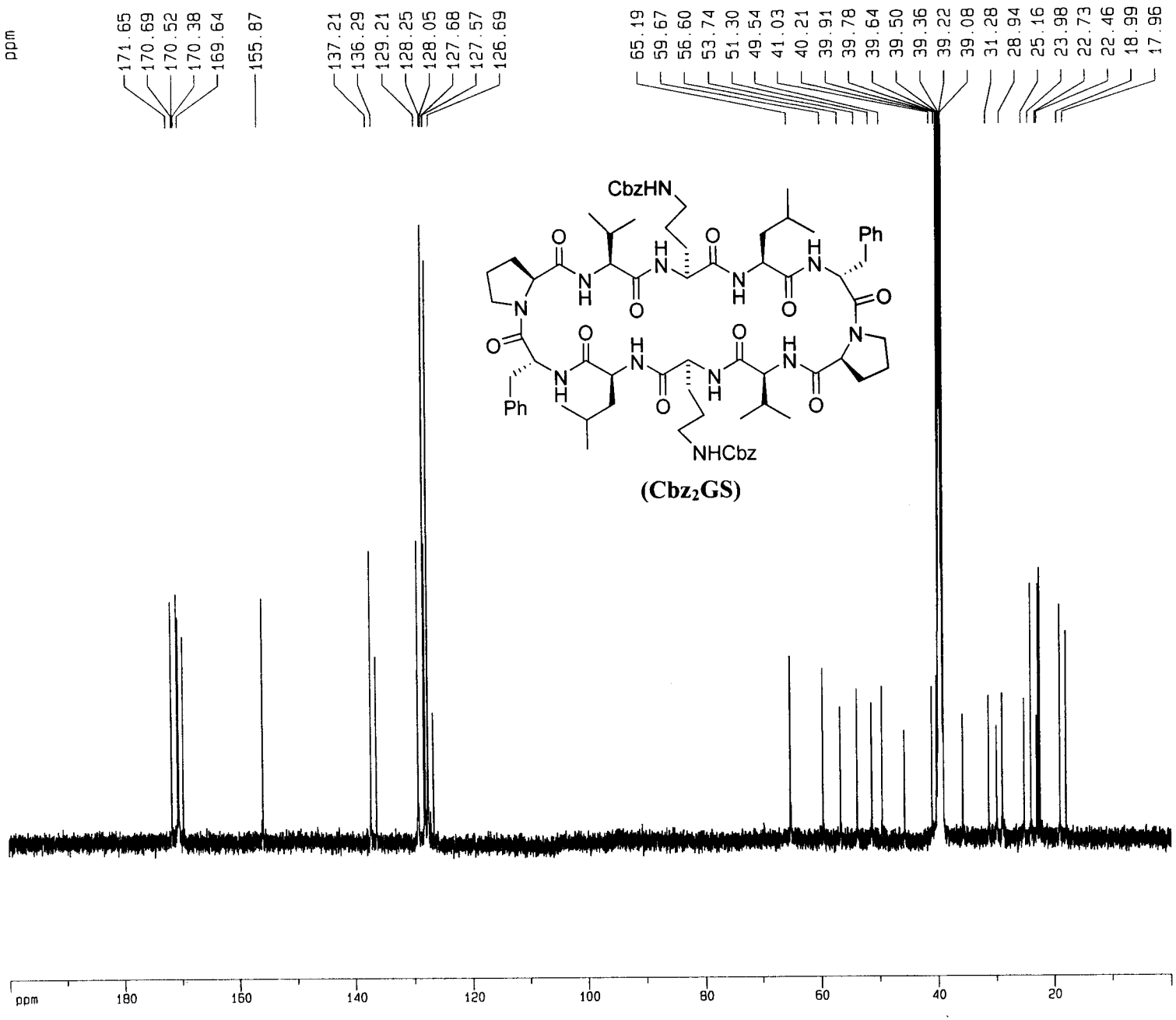
9b

```
Current Data Parameters
NAME      xjb462-600-ftl
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20031208
Time               8.25
INSTRUM           spect
PROBHD     5 mm TBI 1H/
PULPROG        c13wonoe
TD                65536
SOLVENT           CDCl3
NS                13540
DS                    0
SWH          37878.789 Hz
FIDRES       0.577984 Hz
AQ           0.8651252 sec
RG                32768
DW             13.200 usec
DE              6.00 usec
TE             290.0 K
D1          8.00000000 sec
D3          0.00100000 sec

========== CHANNEL f1 ==========
NUC1                13C
P1             13.50 usec
PL1             0.00 dB
SFO1       151.0953827 MHz

========== CHANNEL f2 ==========
CPDPRG2         waltz16
NUC2                1H
PCPD2          100.00 usec
PL2             0.00 dB
PL12           12.00 dB
SFO2       600.8336050 MHz

F2 - Processing parameters
SI                65536
SF         151.0789015 MHz
WDW                EM
SSB                   0
LB             1.00 Hz
GB                    0
PC             1.00

1D NMR plot parameters
CX             20.00 cm
F1P           200.000 ppm
F1          30215.78 Hz
F2P            0.000 ppm
F2             0.00 Hz
PPMCM         10.00000 ppm/cm
HZCM       1510.78906 Hz/cm
```




```
Current Data Parameters
NAME                  xjb-4-235-600
EXPNO                            3
PROCNO                           1

F2 - Acquisition Parameters
Date_                     20040303
Time                         17.09
INSTRUM                       spect
PROBHD     5 mm TBI 1H/
PULPROG                         zg
TD                           65536
SOLVENT                     CD2Cl2
NS                              100
DS                                0
SWH                        8992.806 Hz
FIDRES                     0.137219 Hz
AQ                         3.6438515 sec
RG                               2
DW                          55.600 use
DE                           6.00 use
TE                          290.0 K
D1                          6.00000000 sec
============== CHANNEL f1 ===
NUC1                             1H
P1                           9.00 use
PL1                          0.00 dB
SFO1                       600.8336050 MHz

F2 - Processing parameters
SI                           65536
SF                         600.8300108 MHz
WDW                             EM
SSB                              0
LB                           0.10 Hz
GB                               0
PC                           1.00

1D NMR plot parameters
CX                           20.00 cm
F1P                       10.000 ppm
F1                        6008.30 Hz
F2P                        0.000 ppm
F2                           0.00 Hz
PPMCM                     0.50000 ppm
HZCM                    300.41501 Hz/
```

xjb-4-235, DMSO-d6, 150MHz, C13, Z-GS



(Cbz_2GS)

Current Data Parameters

NAME	xjb-4-235-600
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20040303
Time	8.36
INSTRUM	spect
PROBHD	5 mm TBI 1H/
PULPROG	c13wonoe
TD	65536
SOLVENT	CDCl3
NS	3533
DS	0
SWH	37878.789 Hz
FIDRES	0.577984 Hz
AQ	0.8651252 sec
RG	32768
DW	13.200 usec
DE	6.00 usec
TE	290.0 K
D1	8.00000000 sec
D3	0.00100000 sec

========== CHANNEL f1 ======

NUC1	13C
P1	13.50 usec
PL1	0.00 dB
SFO1	151.0953827 MHz

========== CHANNEL f2 ======

CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	0.00 dB
PL12	12.00 dB
SFO2	600.8336050 MHz

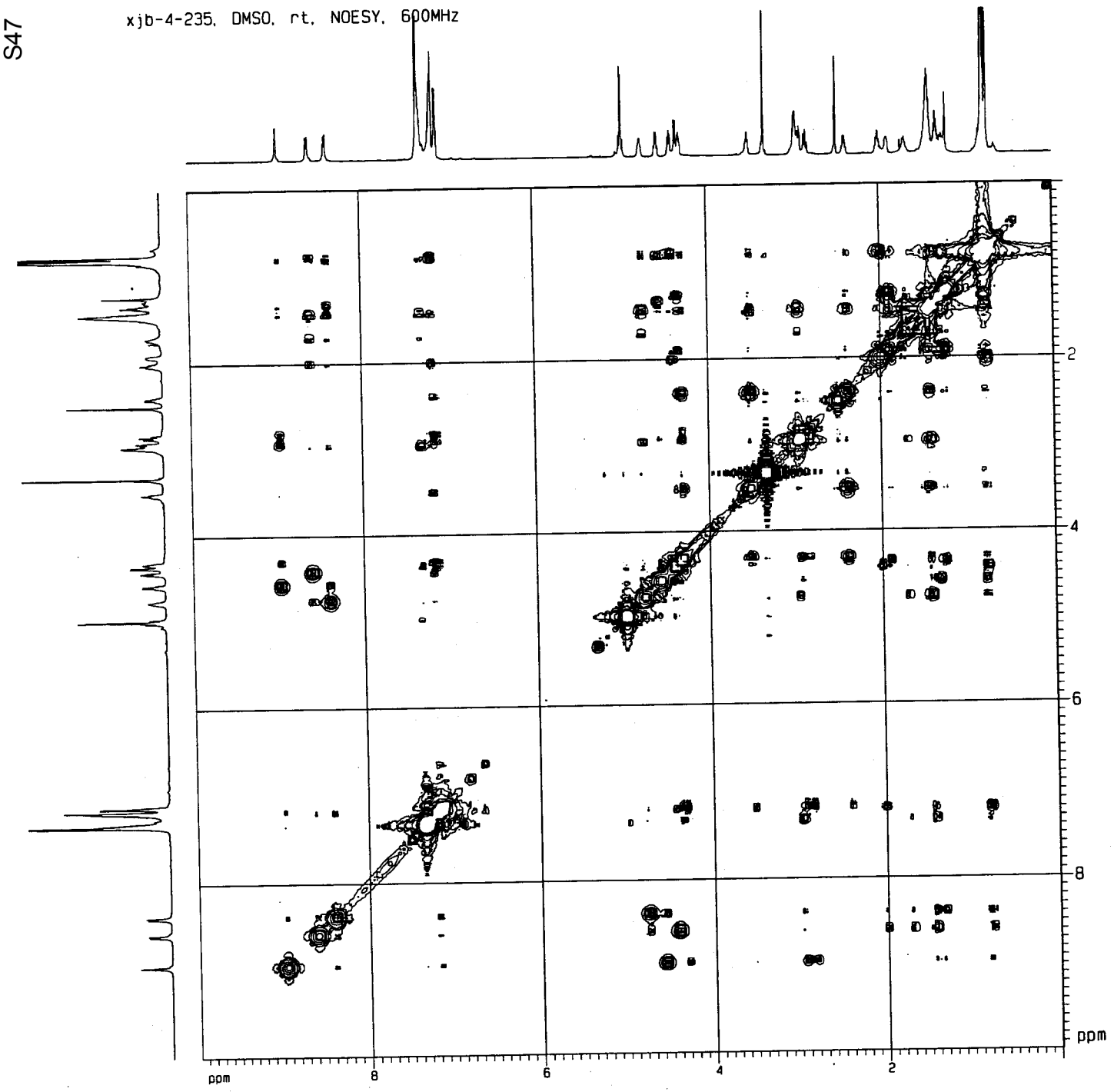
F2 - Processing parameters

SI	65536
SF	151.0789009 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	200.000 ppm
F1	30215.78 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	10.00000 ppm/cm
HZCM	1510.78906 Hz/cm

xjb-4-235, DMSO, rt, NOESY, 600MHz



Current Data Parameters

NAME	xjb-4-235-600
EXPNO	1111
PROCNO	1

F2 - Acquisition Parameters

Date_	20040303
Time	18.01
INSTRUM	spect
PROBHD	5 mm TBI 1H/
PULPROG	noesytp
TD	4096
NOC	8
NS	64
SFO1	600.8300 MHz
FIDRES	23.475060 Hz
SW	10.002 ppm

F2 - Processing parameters

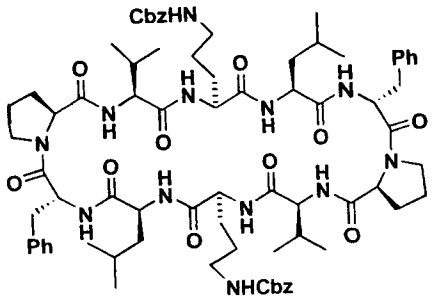
SI	1024
SF	600.8300055 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	600.8300058 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

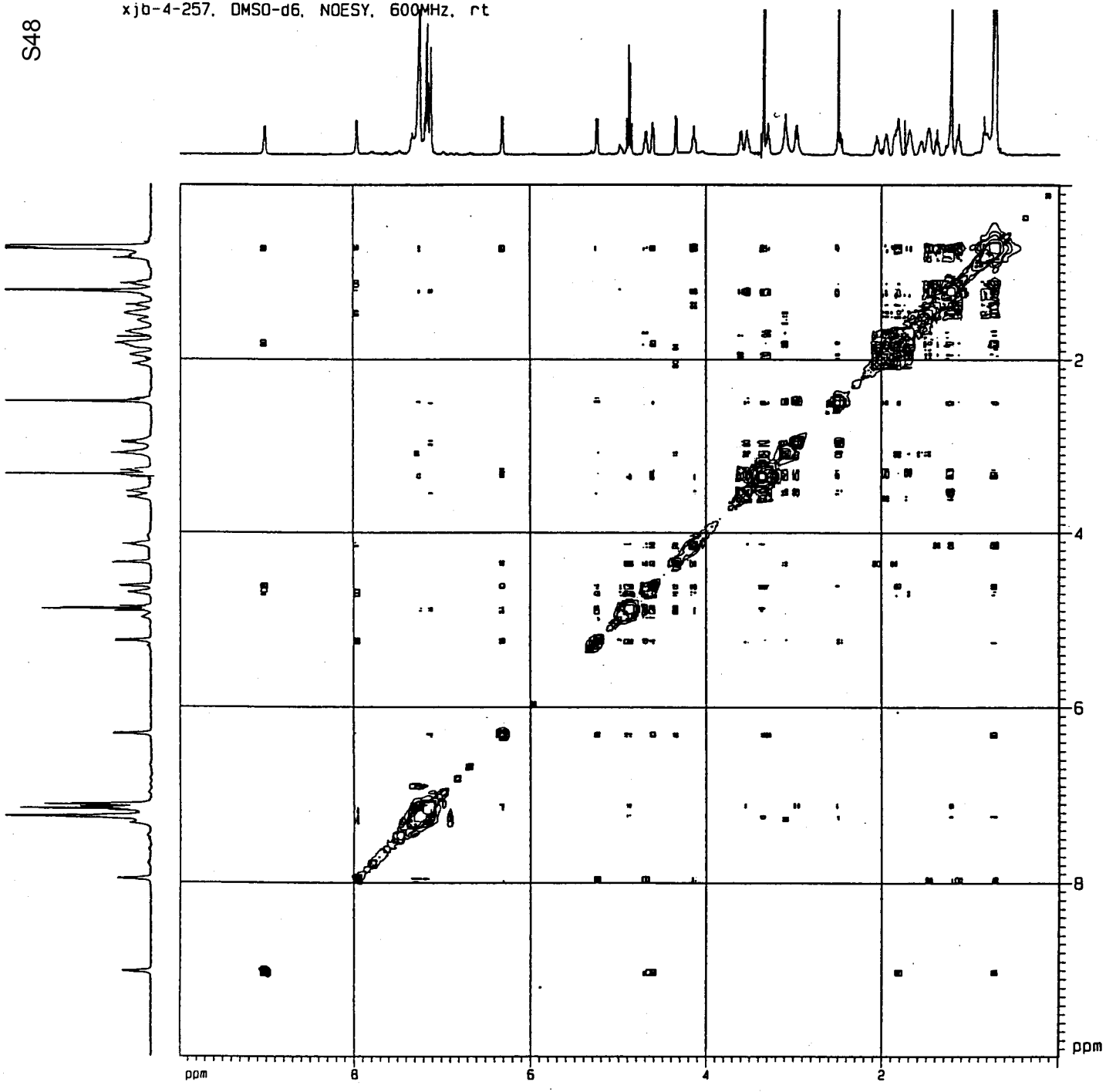
2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	9.992 ppm
F2LO	6003.46 Hz
F2PHI	-0.010 ppm
F2HI	-6.16 Hz
F1PLO	9.992 ppm
F1LO	6003.21 Hz
F1PHI	-0.011 ppm
F1HI	-6.41 Hz
F2PPMCM	0.66681 ppm/cm
F2HZCM	400.64105 Hz/cm
F1PPMCM	0.66681 ppm/cm
F1HZCM	400.64105 Hz/cm



$(Cbz)_2GS$

xjb-4-257, DMSO-d6, NOESY, 600MHz, rt

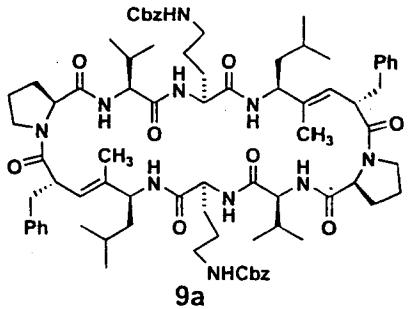


Current Data Parameters

NAME	xjb-4-257-600
EXPNO	1111
PROCNO	1

F2 - Acquisition Parameters

Date_	20040328
Time	22.17
INSTRUM	spect
PROBHD	5 mm TBI 1H/
PULPROG	noesytp
TD	1024
SOLVENT	CDCl3
NS	16



9a

F1 - Acquisition parameters

NDO	2
TD	256
SFO1	600.833 MHz
FIDRES	23.475060 Hz
SW	10.002 ppm

F2 - Processing parameters

SI	1024
SF	600.8300065 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

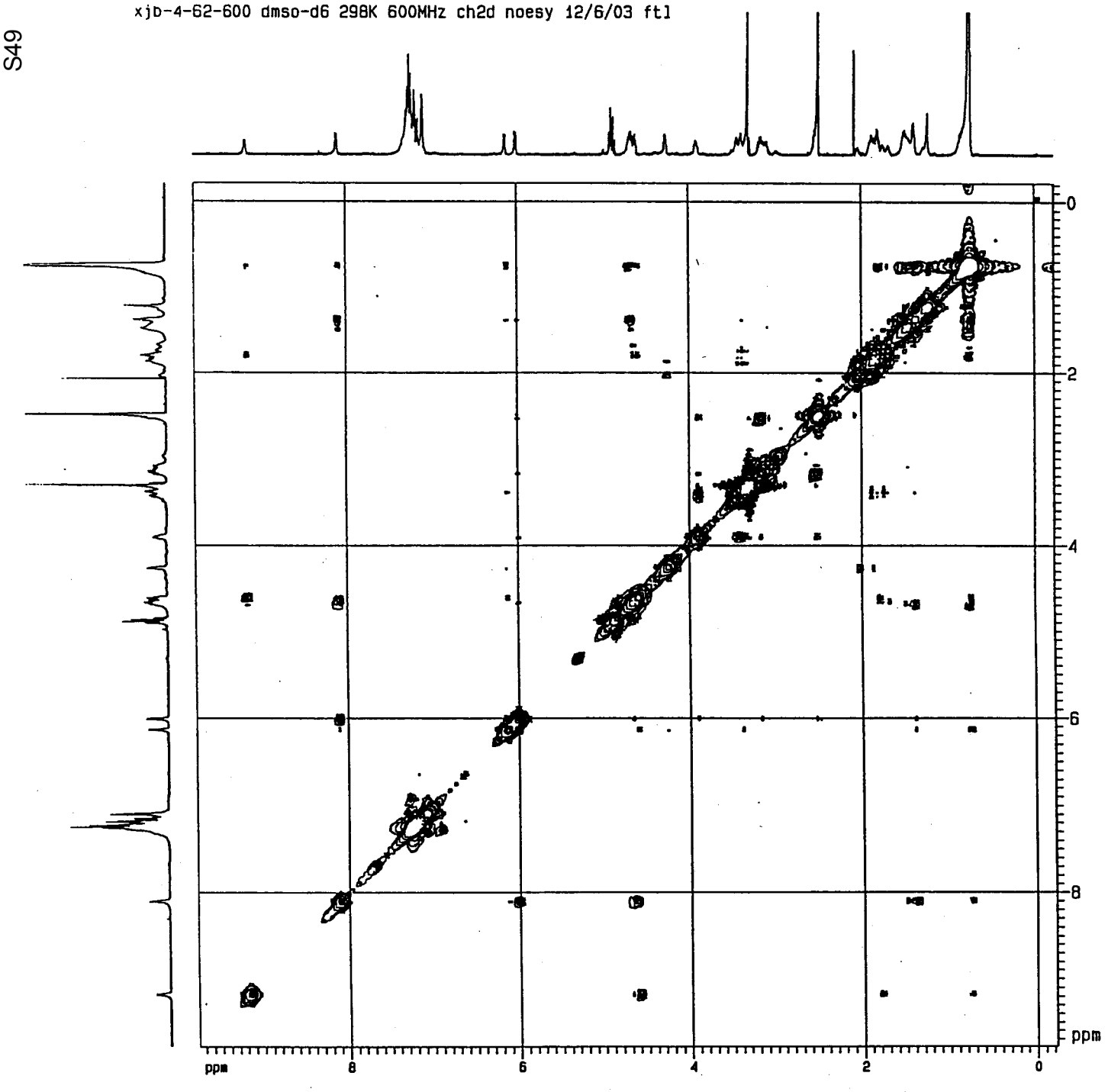
F1 - Processing parameters

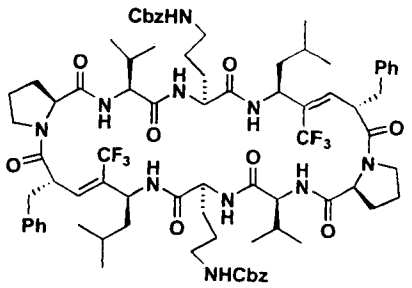
SI	1024
MC2	TPPI
SF	600.8300079 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	9.990 ppm
F2LO	6002.47 Hz
F2PHI	-0.012 ppm
F2HI	-7.14 Hz
F1PLO	9.988 ppm
F1LO	6001.11 Hz
F1PHI	-0.014 ppm
F1HI	-8.51 Hz
F2PPMCM	0.66681 ppm/cm
F2HZCM	400.64105 Hz/cm
F1PPMCM	0.66681 ppm/cm
F1HZCM	400.64105 Hz/cm

xjb-4-62-600 dmso-d6 298K 600MHz ch2d noesy 12/6/03 ft1





9b

Current Data Parameters

NAME	xjb462-600-ft1
EXPNO	1111
PROCNO	1

F2 - Acquisition Parameters

Date_	20031205
Time	12.22
INSTRUM	spect
PROBHD	5 mm TBI 1H/
PL1	0.00 dB
SF01	600.8328840 MHz

F1 - Acquisition parameters

NDO	2
TD	256
SFO1	600.8329 MHz
FIDRES	23.475060 Hz
SW	10.002 ppm

F2 - Processing parameters

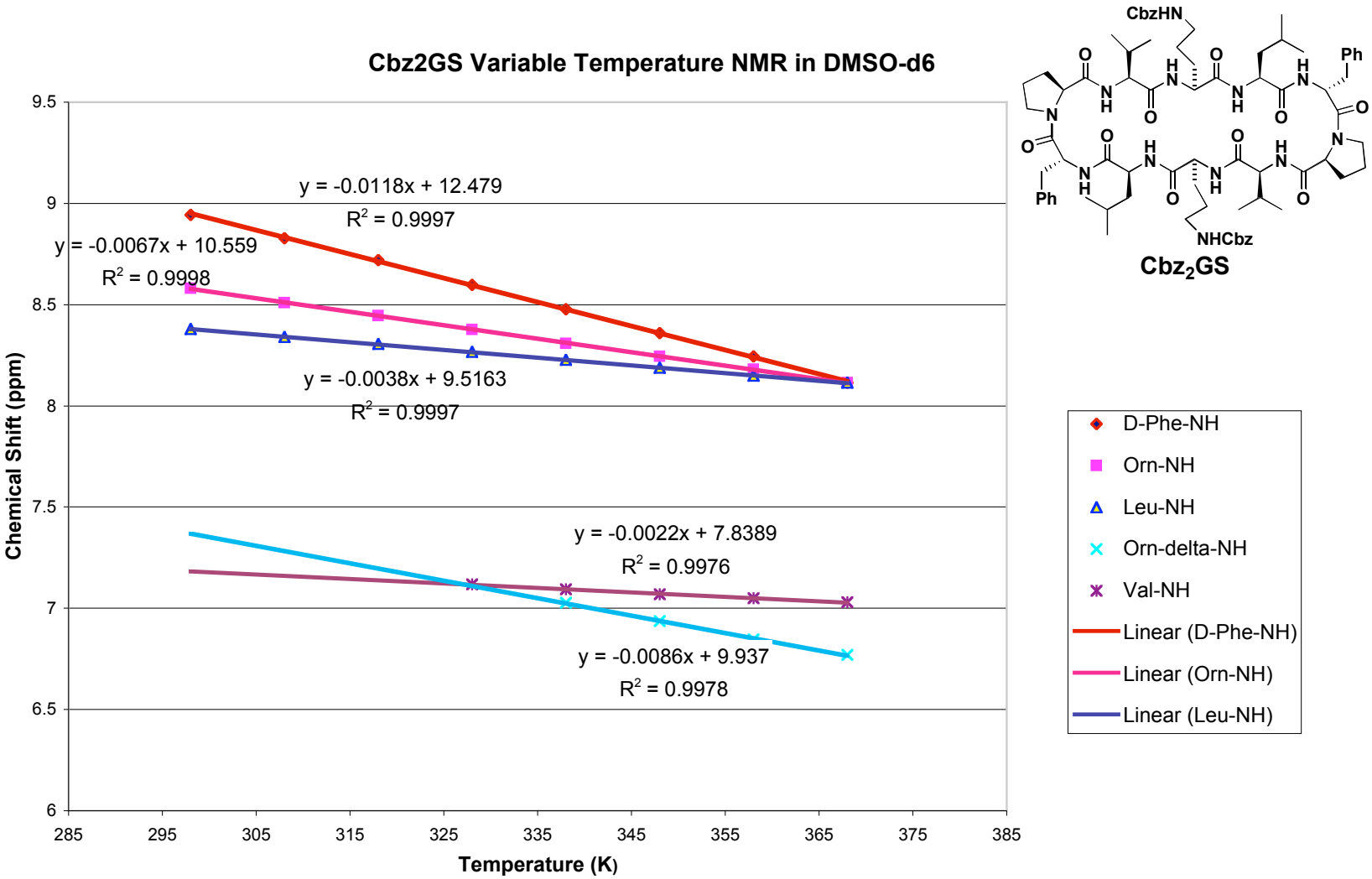
SI	1024
SF	600.8300120 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

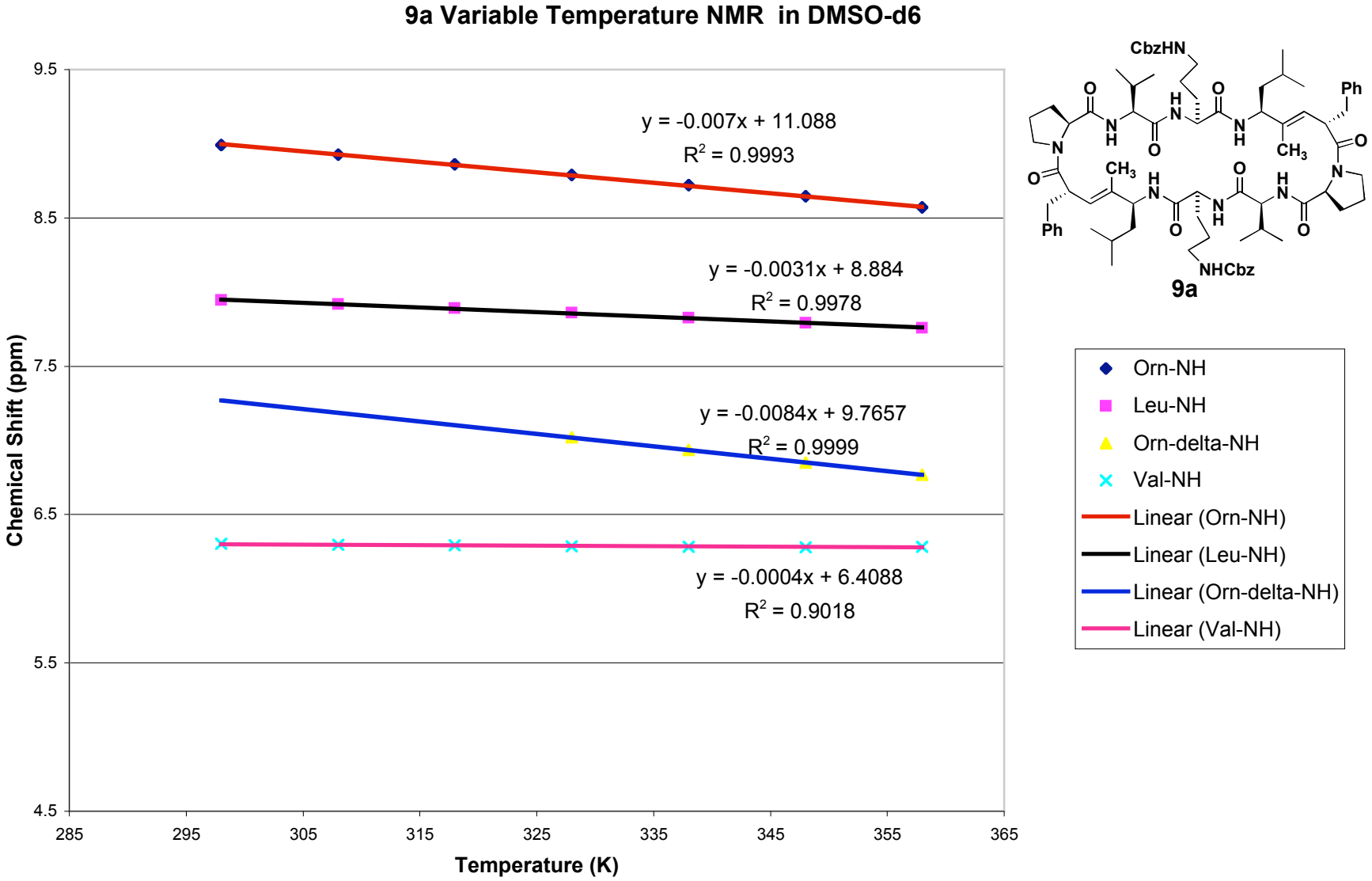
F1 - Processing parameters

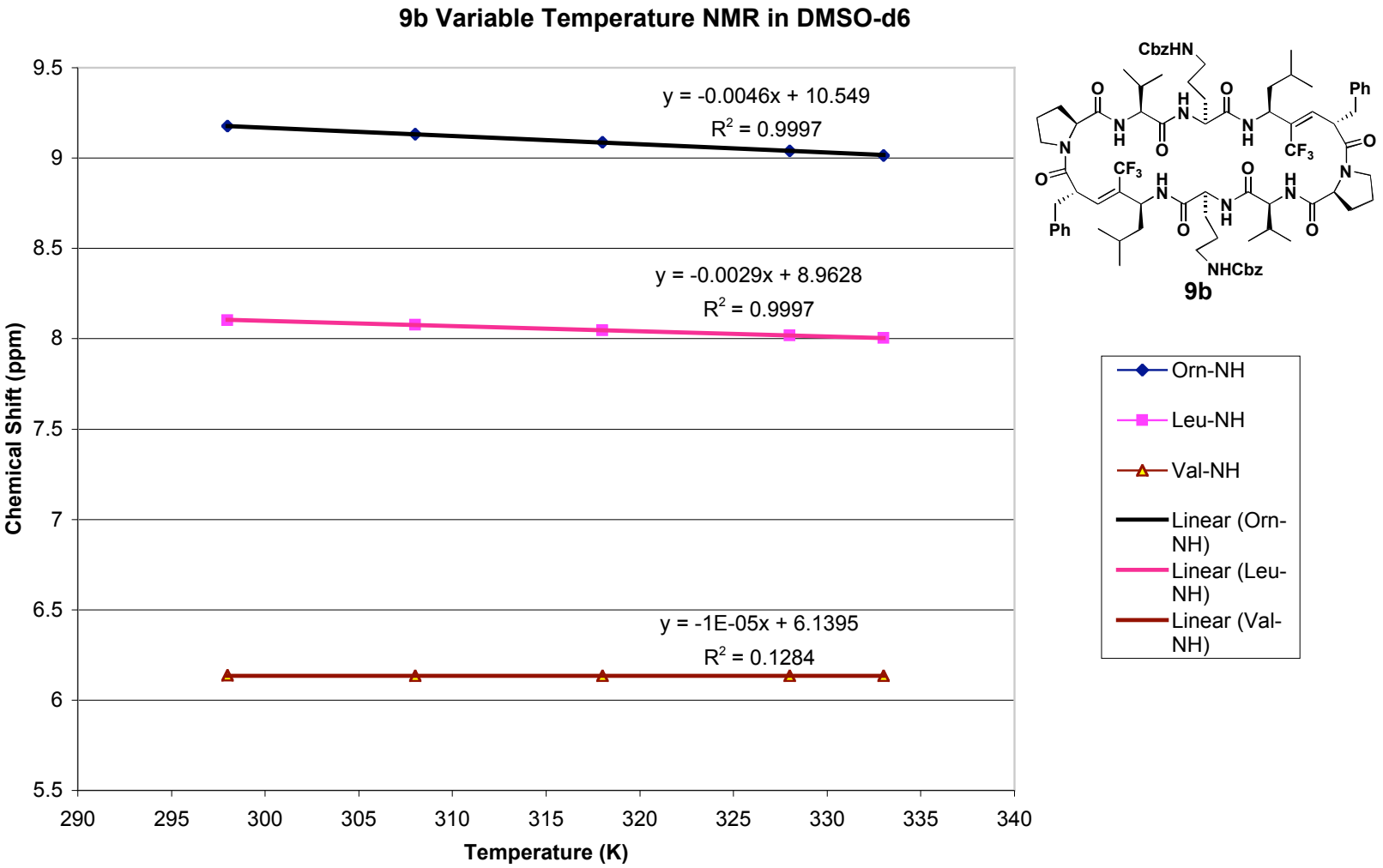
SI	1024
MC2	TPPI
SF	600.8300119 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

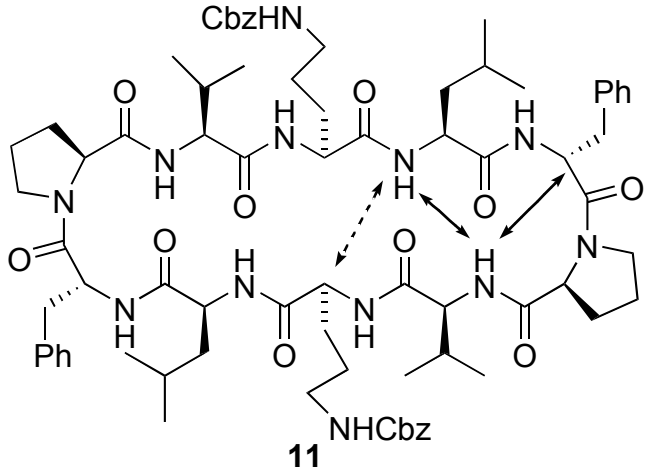
CX2	15.00 cm
CX1	15.00 cm
F2PLO	9.781 ppm
F2LO	5876.81 Hz
F2PHI	-0.221 ppm
F2HI	-132.81 Hz
F1PLO	9.781 ppm
F1LO	5876.86 Hz
F1PHI	-0.221 ppm
F1HI	-132.76 Hz
F2PPMCM	0.66681 ppm/cm
F2HZCM	400.64105 Hz/cm
F1PPMCM	0.66681 ppm/cm
F1HZCM	400.64105 Hz/cm


Cbz2GS Variable Temperature NMR in DMSO-d6
Chemical Shift (ppm)
Temperature (K)
y = -0.0118x + 12.479
R2 = 0.9997
y = -0.0067x + 10.559
R2 = 0.9998
y = -0.0038x + 9.5163
R2 = 0.9997
y = -0.0022x + 7.8389
R2 = 0.9976
y = -0.0086x + 9.937
R2 = 0.9978
D-Phe-NH
Orn-NH
Leu-NH
Orn-delta-NH
Val-NH
Linear (D-Phe-NH)
Linear (Orn-NH)
Linear (Leu-NH)
CbzHN
NHCbz
Ph
Cbz2GS

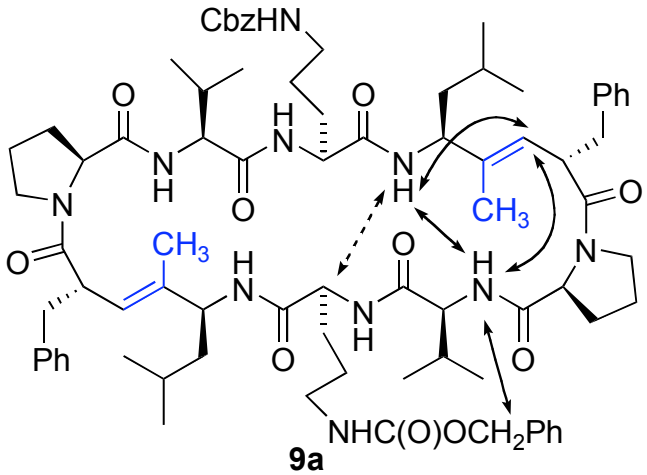

9a Variable Temperature NMR in DMSO-d6
Chemical Shift (ppm)
Temperature (K)
9.5
8.5
7.5
6.5
5.5
4.5
285
295
305
315
325
335
345
355
365
y = -0.007x + 11.088
R2 = 0.9993
y = -0.0031x + 8.884
R2 = 0.9978
y = -0.0084x + 9.7657
R2 = 0.9999
y = -0.0004x + 6.4088
R2 = 0.9018
Orn-NH
Leu-NH
Orn-delta-NH
Val-NH
Linear (Orn-NH)
Linear (Leu-NH)
Linear (Orn-delta-NH)
Linear (Val-NH)
CbzHN
NHCbz
Ph
Ph
CH3
CH3
9a


9b Variable Temperature NMR in DMSO-d6
y = -0.0046x + 10.549
R2 = 0.9997
y = -0.0029x + 8.9628
R2 = 0.9997
y = -1E-05x + 6.1395
R2 = 0.1284
Chemical Shift (ppm)
Temperature (K)
9.5
9
8.5
8
7.5
7
6.5
6
5.5
290
295
300
305
310
315
320
325
330
335
340
Orn-NH
Leu-NH
Val-NH
Linear (Orn-NH)
Linear (Leu-NH)
Linear (Val-NH)
CbzHN
Ph
CF3
NHCbz
9b

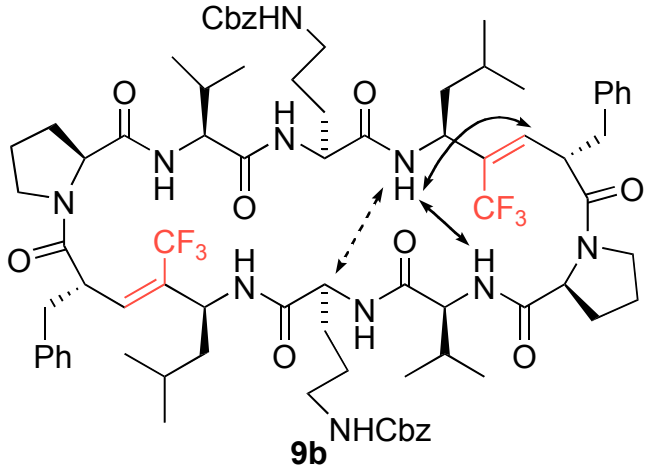
Selected Observed nOes for **9a, 9b** and **Cbz$_2$GS** (600 MHz, DMSO-d$_6$).



11



9a



9b

X-ray crystallographic data for **9b** (crystallized from MeOH/H_2O):

Table 1. Crystal data and structure refinement for **9b**.

Identification code	pitt1	
Empirical formula	C80 H104 F6 N10 O12 – 3(H_2O)	
Formula weight	1559.73	
Temperature	100.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P $2_12_12_1$	
Unit cell dimensions	a = 9.6390(9) Å	α= 90°.
	b = 23.908(2) Å	β= 90°.
	c = 38.807(4) Å	γ = 90°.
Volume	8943.3(14) $Å^3$	
Z	4	
Density (calculated)	1.158 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	3312	
Crystal size	0.29 x 0.06 x 0.06 mm^3	
Theta range for data collection	1.35 to 25.00°.	
Index ranges	-9<=h<=11, -28<=k<=28, -46<=l<=46	
Reflections collected	42826	
Independent reflections	15549 [R(int) = 0.0760]	

Completeness to theta = 25.00°	99.7 %
Max. and min. transmission	0.9947 and 0.9748
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15549 / 0 / 988
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0999, wR2 = 0.2574
R indices (all data)	R1 = 0.1567, wR2 = 0.2868
Absolute structure parameter	-0.1(13)
Largest diff. peak and hole	1.593 and -0.439 e.$Å^{-3}$