Total Synthesis of (-)-Dysibetaine via a Nitrenium Ion Cyclization-Dienone Cleavage Strategy

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Supporting Information

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^{1}H NMR for (-)-Dysibetaine

Synthetic (500 MHz, D_2O)	$\Delta\delta_H$	Literature[1] (400 MHz, D_2O)
4.20 (dd, *J* = 7.8, 5.4 Hz, 1 H)	0.03	4.23 (dd, *J* = 8.0, 5.5 Hz, 1 H)
3.89 (d, *J* = 13.9 Hz, 1 H)	0.03	3.92 (d, *J* = 14.0 Hz, 1 H)
3.59 (d, *J* = 13.9 Hz, 1 H)	0.03	3.62 (d, *J* = 14.0 Hz, 1 H)
3.05 (s, 9 H)	0.04	3.09 (s, 9 H)
2.51 (dd, *J* = 14.0, 7.8 Hz, 1 H)	0.04	2.55 (dd, *J* = 13.9, 8.0 Hz, 1 H)
1.85 (dd, *J* = 14.0, 5.4 Hz, 1 H)	0.03	1.88 (dd, *J* = 13.9, 5.5 Hz, 1 H)

^{13}C NMR for (-)-Dysibetaine

Synthetic (125 MHz, CD_3OD/D_2O)	$\Delta\delta_C$	Literature[1] (100 MHz, CD_3OD/D_2O)
179.6	0.1	179.5
176.8	0.0	176.8
73.1	0.2	72.9
69.1	0.2	68.9
64.1	0.0	64.1[a]
55.6 (NMe_3)	0.1	55.5 (NMe_3)
42.4	0.1	42.3

[a]As a result of a typographical error by Sakai,[1] this resonance was originally reported as appearing at δ 66.0. Snider[2] and Sakai has subsequently clarified that the quaternary carbon actually absorbs at δ 64.1.

1. R. Sakai, C. Oiwa, K. Takaishi, H. Kamiya and M. Tagawa, *Tetrahedron Lett*., 1999, **40**, 6941.
2. B. B. Snider and Y. Gu, *Org. Lett*., 2001, **3**, 1761.

General Procedures.
All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry argon or nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light and/or potassium permanganate solution. Flash column chromatography was performed according to the method of Still[3] using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted. Mosher (MTPA) esters were prepared using method reported by Ward.[4]

Materials.
Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl under an atmosphere of dry argon. Methanol (MeOH) was dried from magnesium methoxide, prepared from magnesium turnings and iodine. Acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and triethylamine (Et_3N) were distilled from calcium hydride, under an atmosphere of dry nitrogen. Deionized H_2O was obtained from a High Q series 103S all-glass water still. Phenyliodine(III) bis(trifluoroacetate) (PIFA) was prepared according to Loudon.[5] Methyl (*E*)-2,4-dimethoxycinnamate (**5**) was prepared through Fischer esterification of commercially available (*E*)-2,4-dimethoxycinnamic acid. All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

Instrumentation.
All melting points were determined in open Pyrex capillaries using a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates or in compressed discs of potassium bromide using an ATI Mattson genesis series FTIR spectrometer. Hydrogenation reactions at medium pressure were preformed in a Parr, series 3911 hydrogenator. Mixtures of oxygen and oxone were generated using an Ozonology series L-50 apparatus. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C), a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C, 470 MHz ^{19}F), or a Bruker AM-400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^{1}H; δ 77.23 ppm for ^{13}C), residual water (δ 4.65 ppm for ^{1}H) and residual methanol (δ 4.87 ppm for ^{1}H; δ 49.0 ppm for ^{13}C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), m (multiplet) and br (broad). DEPT 135 and two-dimensional (COSY, HMQC, HMBC, NOESY) NMR experiments were employed, where appropriate, to aid in the assignment of signals in the ^{1}H NMR spectra. Optical rotations were measured with a Autopol III polarimeter and reported as follows: $[\alpha]^{\text{temperature}}_{\text{wavelength}}$ (*c*, solvent); $[\alpha]_D$ is reported in 10^{-1} deg $cm^{-2}g^{-1}$; concentration (*c*) is g in per 100 mL). High-resolution electron impact mass spectra (HRMS-EI), high-resolution chemical ionization mass spectra (HRMS-CI) and high-resolution fast atom bombardment mass spectra (HRMS-FAB) were obtained on a

3. W. C. Still, M. Kahn and A. Mitra *J. Org. Chem.,* 1978, **43**, 2923.
4. D. E. Ward and C. K. Rhee *Tetrahedron Lett.*, 1991, **32**, 7165
5. G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett, R. H. Boutin, *J. Org. Chem.,* 1984, **49**, 4272.

JEOL GCMate II at the University of Illinois Research Resources Center. High-resolution electron spray ionization mass spectra (HRMS-ESI) were obtained on a Micromass QTOF 2, at the University of Illinois Research Resources Center. Elemental combustion analyses were performed by Midwestern Microlab, Indianapolis, IN.

Methyl (2*S*,3*R*)-3-(2,4-dimethoxyphenyl)-2,3-dihydroxypropionate (not shown in Scheme 3). A solution of methylsulfonamide (5.54 g, 58.2 mmol) and AD-mix-β (81.5 g) in *tert*-BuOH (291 mL) and H_2O (291 mL) was cooled to 0 °C and **9** (13.0 g, 58.2 mmol) was added. The solution was stirred for 24 h at 0 ºC, whereupon solid Na_2SO_3 (87 g) was added, and the reaction mixture allowed to stir at room temperature for 1 h. EtOAc (200 mL) was then added and the organic layer separated. The aqueous layer was extracted with EtOAc (5 x 50 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting white powder was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:1) to yield the title compound (13.5 g, 91%): white solid; mp 69-72 °C (EtOAc/hexanes); R_f 0.52 (EtOAc); $[\alpha]_D^{24}$ –9.9 (*c* 1.47, $CHCl_3$); FTIR (film) υ_{max} 3417 (br), 1737, 1612, 1505, 1290, 1212, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 1 H, H-6′), 6.52 (dd, *J* = 8.5, 2.3 Hz, 1 H, H-5′), 6.46 (d, *J* = 2.3 Hz, 1 H, H-3′), 5.23 (dd, *J* = 7.5, 3.0 Hz, 1 H, H-3), 4.43 (dd, *J* = 6.3, 3.0 Hz, 1 H, H-2), 3.82 (s, 3 H, OCH_3), 3.81 (s, 6 H, 2 x OCH_3), 3.17 (d, *J* = 6.3 Hz, 1 H, OH), 3.04 (d, *J* = 7.5 Hz, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C-1), 160.5, 157.1, 128.0 (C-6′), 120.4 (C-1′), 104.1 (C-5′), 98.3 (C-3′), 73.6, 70.2, 55.3 (2 x OCH_3), 52.6 (OCH_3); HRMS-CI calcd for $C_{12}H_{20}NO_6$ $[M+NH_4]^+$ 274.1291, found 274.1296.

Methyl (2*S*)-3-(2,4-Dimethoxyphenyl)-2-hydroxypropionate (10). To a solution of methyl (2*S*,3*R*)-3-(2,4-dimethoxyphenyl)-2,3-dihydroxypropionate (2.71 g, 10.6 mmol) and Et_3SiH (22.0 mL, 137.5 mmol) in CH_2Cl_2 (35 mL) at 0 °C, was added trifluoroacetic acid (11.4 mL, 148.1 mmol) via syringe. After 10 min, saturated aqueous $KHCO_3$ was cautiously added. After the evolution of gas had abated, the biphasic mixture was separated and the aqueous portion extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The remaining colorless oil was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:3) to provide **10** (2.13 g, 84%): white solid; mp 69-72 °C; R_f 0.44 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ –0.6 (*c* 2.00, $CHCl_3$); FTIR (film) υ_{max} 3479 (br), 1739, 1612, 1587, 1509, 1459, 1287, 1208, 1156, 1122, 1036, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 8.0 Hz, 1 H, H-6′), 6.46-6.42 (m, 2 H, H-5′, H-3′), 4.43 (dd, *J* = 7.5, 4.8 Hz, 1 H, H-2), 3.80 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.10 (dd, *J* = 13.9, 4.8 Hz, 1 H, H-3), 2.92 (dd, *J* = 13.9, 7.5 Hz, 1 H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (C-1), 160.5, 158.8, 132.2 (C-6′), 117.4 (C-1′), 104.6 (C-5′), 99.0 (C-3′), 71.2 (C-2), 55.8 (OCH_3), 55.7 (OCH_3), 52.6 (OCH_3), 35.6 (C-3); HRMS-EI calcd for $C_{12}H_{16}O_5$ $[M]^+$ 240.0998, found 240.1004. Anal. calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71, found: C, 60.26; H, 6.74.

Determination of the enantiomeric excess of compound 10. Preparation of the (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate ester derivative of methyl (2*S*)-3-(2,4-dimethoxyphenyl)-2-hydroxypropionate.[4] To a solution of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) (146 mg, 0.62 mmol) and DMF (48 µL, 0.62 mmol) in hexanes (10 mL) was added oxalyl chloride (103 µL, 1.19 mmol) at room

temperature. After 1 h, the reaction mixture was filtered through a glass frit under an atmosphere of N_2 and the filtrate concentrated under reduced pressure. To the resulting residue was added, at room temperature via cannula, a solution of **10** (50 mg, 0.21 mmol), Et_3N (88 μL, 0.62 mmol) and DMAP (2 crystals) in $CDCl_3$ (2 mL). After stirring for 16 h, the reaction mixture was concentrated under reduced pressure to provide the MTPA ester (256 mg). Analysis of this unpurified material by ^{19}F and ^{1}H NMR spectroscopy indicated the presence of a single diastereomer. Purification was subsequently accomplished by flash chromatography on silica gel (EtOAc/hexanes, 1:9): colorless oil; R_f 0.71 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 1753, 1604, 1452, 1279, 1194, 1032, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.26 (m, 5 H, Ph), 6.83 (d, J = 8.2 Hz, 1 H), 6.37 (d, J = 2.1 Hz, 1 H), 6.23 (dd, J = 8.2, 2.1 Hz, 1 H), 5.48 (dd, J = 9.3, 4.4 Hz, 1 H), 3.77 (s, 6 H, 2 x OCH_3), 3.76 (s, 3 H, OCH_3) 3.55 (s, 3 H, OCH_3), 3.26 (dd, J = 14.2, 4.4 Hz, 1 H), 2.98 (dd, J = 14.2, 9.3 Hz, 1 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1 (CO), 166.7 (CO), 160.6, 158.7, 132.5 (Ph), 132.1, 129.7, 128.6 (Ph), 127.7 (Ph), 124.7 (CF_3), 122.4, 116.0, 104.3, 98.6, 73.9, 56.0 (OMe), 55.7 (2 x OMe), 52.8 (OMe), 32.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -73.4; HRMS-FAB calcd for $C_{22}H_{23}F_3O_7Na$ $[M+Na]^+$ 479.1294, found 479.1300.

Methyl (2*S*)-3-(2,4-dimethoxyphenyl)-2-triisopropylsilanyloxypropionate (not shown in Scheme 3). To a solution of **10** (3.00 g, 12.5 mmol), DMAP (485 mg, 3.8 mmol) and imidazole (2.98 g, 43.7 mmol) in DMF (31 mL) was added TIPS-Cl (2.64 g, 13.7 mmol). After stirring for 36 h at room temperature, the reaction was concentrated under reduced pressure, the remaining oil diluted with CH_2Cl_2 (25 mL) and this solution washed with 1 M aqueous HCl (75 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:1) to provide the title compound (4.94 g, 99%): colorless oil; R_f 0.62 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ +2.8 (*c* 1.44, $CHCl_3$), FTIR (film) υ_{max} 1767, 1619, 1506, 1462, 1207, 1126 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 8.2 Hz, 1 H, H-6′), 6.41 (d, J = 2.3 Hz, 1 H, H-3′), 6.38 (dd, J = 8.2, 2.3 Hz, 1 H, H-5′), 4.56 (t, J = 7.0 Hz, 1 H, H-2), 3.78 (s, 6 H, 2 x OCH_3), 3.61 (s, 3 H, OCH_3), 3.01-2.93 (m, 2 H, H-3), 1.02-0.98 (m, 21 H, Si(*i*-Pr)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3 (C-1), 160.3, 159.0, 132.3 (C-6′), 117.7 (C-1′), 104.2 (C-5′), 98.6 (C-3′), 72.7 (OCH_3), 55.7 (OCH_3), 55.4 (OCH_3), 51.7 (C-2), 37.1 (C-3), 18.1 (Si(*i*-Pr)$_3$), 12.6 (Si(*i*-Pr)$_3$); HRMS-FAB calcd for $C_{21}H_{37}O_5Si$ $[M+H]^+$ 397.2410, found 397.2396.

(2*S*)-3-(2,4-Dimethoxyphenyl)-2-triisopropylsilanyloxypropionic acid (not shown in Scheme 3). Methyl (2*S*)-3-(2,4-dimethoxyphenyl)-2-triisopropylsilanyloxypropionate (2.00 g, 5.0 mmol) was heated in a solution of KOH in methanol (1 M, 60 mL) for 16 h, cooled to room temperature and concentrated under reduced pressure. The resulting residue was diluted with CH_2Cl_2 (50 mL) and washed with 2 M aqueous HCl (150 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (5 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel (*i*-PrOH/hexanes, 7:93) to yield the title compound (1.89 g, 98%): colorless oil; R_f 0.24 (EtOAc/hexanes, 1:3); $[\alpha]_D^{24}$ +0.5 (*c* 1.63, $CHCl_3$), FTIR (film) υ_{max} 3023 (br), 1719, 1506, 1460, 1209, 1151, 1124 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 8.2

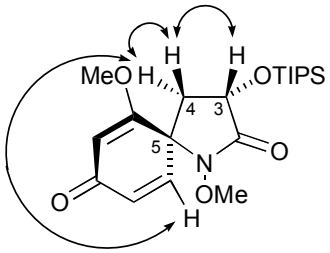
Hz, 1 H, H-6′), 6.42 (d, *J* = 2.4 Hz, 1 H, H-3′), 6.40 (dd, *J* = 8.2, 2.4 Hz, 1 H, H-5′), 4.62-4.59 (m, 1 H, H-2), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.05-2.95 (m, 2 H, H-3), 1.07-1.01 (m, 21 H, Si(*i*-Pr)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5 (C-1), 160.5, 159.0, 132.4 (C-6′), 117.0 (C-1′), 104.2 (C-5′), 98.7 (C-3′), 72.7 (C-2), 55.8 (OCH_3), 55.4 (OCH_3), 36.7 (C-3), 18.2 (Si(*i*-Pr)$_3$), 12.6 (Si(*i*-Pr)$_3$); HRMS-FAB calcd for $C_{20}H_{35}O_5Si$ $[M+H]^+$ 383.2254, found 383.2259.

(2*S*)-*N*-Methoxy-3-(2,4-dimethoxyphenyl)-2-triisopropylsilanyloxypropionamide (8). To a solution of (2*S*)-3-(2,4-dimethoxyphenyl)-2-triisopropylsilanyloxypropionic acid (376 mg, 0.98 mmol) in CH_2Cl_2 (6.0 mL) at –20 °C, was sequentially added Et_3N (207 μL, 1.47 mmol) and *i*-BuOCOCl (178 μL, 1.38 mmol) via syringe. The reaction mixture was then allowed to warm to room temperature over 1 h and a solution of $MeONH_2$•HCl (123 mg, 1.47 mmol) and Et_3N (207 μL, 1.47 mmol) in CH_2Cl_2 (3.0 mL) added via cannula. After stirring for 16 h, the reaction was diluted with CH_2Cl_2 (5 mL), quenched with 1 M aqueous HCl (15 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:1) to afford **8** (358 mg, 88%): white crystals; mp 93-95 °C (EtOAc/hexanes); R_f 0.13 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ -29.6 (*c* 1.63, $CHCl_3$); FTIR (film) υ_{max} 3158 (br), 1668, 1612, 1506, 1460, 1206, 1156, 1117, 1039, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (br s, 1 H, NH), 7.05 (d, *J* = 8.1 Hz, 1 H, H-6′), 6.41-6.38 (m, 2 H, H-5', H-3′), 4.55 (t, *J* = 5.9 Hz, 1 H, H-2), 3.78 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.05 (dd, *J* = 13.7, 5.8 Hz, 1 H, H-3), 2.99 (dd, *J* = 13.7, 6.1 Hz, 1 H, H-3), 1.05-1.03 (m, 21 H, Si(*i*-Pr)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C-1), 160.4, 159.1, 132.6 (C-6′), 117.3 (C-1′), 104.1 (C-5′), 98.6 (C-3′), 74.1 (C-2), 64.7 (OCH_3), 55.8 (OCH_3), 55.4 (OCH_3), 36.6 (C-3), 18.3 (Si(*i*-Pr)$_3$), 12.5 (Si(*i*-Pr)$_3$); HRMS-FAB calcd for $C_{21}H_{38}NO_5Si$ $[M+H]^+$ 412.2519, found 412.2510.

(3*S*,5*SR*)-1,6-Dimethoxy-3-(triisopropylsilanyloxy)-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (7). To a stirred suspension of phenyliodine(III) bistrifluoroacetate (PIFA) (878 mg, 2.0 mmol) in MeOH (6.8 mL), was added a cold (-78 °C) solution of **8** (700 mg, 1.7 mmol) in CH_2Cl_2 (6.8 mL) via cannula. The reaction mixture was allowed to warm to –30 °C (internal temperature) over 1 h, whereupon H_2O (4.0 mL) was added and the cooling bath removed. After 10 min, the biphasic mixture was concentrated under reduced pressure and the aqueous concentrate partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $KHCO_3$ (10 mL). After separation of the organic phase, the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide **3**, an oil, as a mixture of C-5 epimers [*anti*/*syn*, 90:10; diastereoisomeric ratio assigned by integration of the peaks at δ_H (major) = 5.64 (d, *J* = 1.6 Hz, 1 H, 7-H) and δ_H (minor) = 5.69 (d, *J* = 1.6 Hz, 1 H, 7-H) in the ^{1}H NMR spectrum]. Purification by flash chromatography over silica gel (EtOAc/hexanes, 3:1) afforded **7** (672 mg, 99%), as an inseparable mixture of C-5 epimers [*anti*/*syn*, 90:10; measured by ^{1}H NMR spectroscopy]: pale yellow oil; R_f 0.27 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$–44.0 (*c* 1.75, $CHCl_3$); FTIR (film) υ_{max} 1736, 1666, 1635, 1604 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (major) 6.68 (d, *J* = 9.9 Hz, 1 H, H-10), 6.30 (dd, *J* = 9.9, 1.6 Hz, 1 H, H-9), 5.64 (d, *J* = 1.6 Hz, 1 H, H-7), 4.59 (dd, *J* = 8.4, 6.6

Hz, 1 H, H-3), 3.79 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.58 (dd, J = 13.2, 8.4 Hz, 1 H, H_β-4), 2.03 (dd, J = 13.2, 6.6 Hz, 1 H, H_α-4), 1.11-1.06 (m, 21 H, $SiC(i\text{-}Pr)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 186.6 (C-8), 172.0 (C-2), 171.0 (C-6), 144.7 (C-10), 130.7 (C-9), 104.2 (C-7), 67.1 (OCH_3), 65.0 (OCH_3), 61.6 (C-5), 56.6 (C-3), 39.6 (C-4), 18.2 ($SiC(i\text{-}Pr)_3$), 12.5 ($SiC(i\text{-}Pr)_3$); HRMS-ESI calcd for $C_{20}H_{34}NO_5Si$ $[M+H]^+$ 396.2206, found 396.2193.

The relative stereochemistry of compound **7** was determined through recourse to a NOESY experiment. The salient correlations are shown below.



7

Methyl (3*S*, 5*S*)-5-hydroxymethyl-1-methoxy-2-oxo-3-triisopropylsilanyloxy-5-pyrrolidine carboxylate (11).

1. Preparation of $NaBH(OAc)_3$. AcOH (5 mL) was cooled to 0 ºC and $NaBH_4$ (206 mg, 5.31 mmol) added portionwise. The cooling bath was removed and the mixture stirred until the evolution of gas abated (30 min).

2. Ozonolysis-Reduction. A stream of ozone-oxygen was passed through a solution of **7** (525 mg, 1.33 mmol) in MeOH (3 mL) at –78 °C for 1 h. The blue solution was then purged with a stream of O_2 for 10 min, thiourea (51 mg, 0.66 mmol) was added in one portion and the solution then allowed to warm to room temperature over 30 min. After stirring for a additional 30 min, the reaction was concentrated under reduced pressure, the residue taken up in AcOH (500 μL) and this mixture added to the solution of $NaBH(OAc)_3$. After stirring for 4 h at room temperature, the reaction was concentrated under reduced pressure, the residual oil diluted with CH_2Cl_2 (10 mL) and 2 M aqueous HCl (5 mL) added. After standing for 20 min, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were concentrated under reduced pressure and the resulting oil purified by flash chromatography over silica gel (EtOAc/hexanes, 1:3) to provide **11** (454 mg, 91%): pale yellow oil; R_f 0.56 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ –30.3 (*c* 1.63, $CHCl_3$); FTIR (film) υ_{max} 3444 (br), 1739, 1462, 1175, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4.47 (dd, J = 8.4, 6.8 Hz, 1 H, H-3), 4.00-3.98 (m, 2 H, H-6), 3.97 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 2.61 (br s, 1 H, OH), 2.53 (dd, J = 13.4, 8.4 Hz, 1 H, H-4), 2.11 (dd, J = 13.4, 6.8 Hz, 1 H, H-4), 1.09-1.07 (m, 21 H, $SiC(i\text{-}Pr)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ172.1 (CO), 170.5 (CO), 67.8 (C-5), 67.0 (C-3), 64.4 (OCH_3), 64.1 (C-6), 53.4 (OCH_3), 36.1 (C-4), 18.2 ($SiC(i\text{-}Pr)_3$), 12.5 ($SiC(i\text{-}Pr)_3$); HRMS-ESI calcd for $C_{17}H_{33}NO_6SiNa$ $[M+Na]^+$ 398.1975, found 398.1958.

Methyl (3*S*,5*S*)-5-hydroxymethyl-2-oxo-3-triisopropylsilanyloxy-5-pyrrolidine carboxylate (12). A solution of **11** (250 mg, 0.67 mmol) and $Mo(CO)_6$ (212 mg, 0.80

mmol) in a mixture of CH_3CN and deionized H_2O (15:1, 3 mL) was heated at reflux for 24 h under an atmosphere of N_2. The reaction was cooled to room temperature, the condensor removed and the black mixture stirred for an additional 24 h. The reaction was then concentrated under reduced pressure and the residue purified by flash chromatography over silica gel (EtOAc/hexanes, 1:3) to provide **12** (205 mg, 90%): colorless oil; R_f 0.33 (EtOAc); $[\alpha]_D^{24}$ –28.2 (*c* 1.00, $CHCl_3$); FTIR (film) υ_{max} 3336 (br), 1720, 1463, 1163, 883, 685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (br s, 1 H, NH), 4.45 (t, *J* = 7.5 Hz, 1 H, H-3), 3.99 (d, *J* = 11.3 Hz, 1 H, H-6), 3.79 (s, 3 H, OCH_3), 3.69 (d, *J* = 11.3 Hz, 1 H, H-6), 3.47 (br s, 1 H, OH), 2.60 (dd, *J* = 13.4, 8.0 Hz, 1 H, H-4), 1.99 (dd, *J* = 13.4, 7.0 Hz, 1 H, H-4), 1.17-1.06 (m, 21 H, SiC(*i*-Pr)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1 (CO), 173.4 (CO), 69.9 (C-3), 68.1 (C-6), 64.6 (C-5), 53.4 (OCH_3), 38.4 (C-4), 18.2 (SiC(*i*-Pr)$_3$), 12.5 (SiC(*i*-Pr)$_3$); HRMS-ESI calcd for $C_{16}H_{31}NO_5SiNa$ $[M+Na]^+$ 368.1869, found 368.1869.

Methyl (3*S*,5*S*)-5-methanesulfonyloxymethyl-2-oxo-3-triisopropylsilanyloxy-5-pyrrolidine carboxylate (not shown in Scheme 3). . Methanesulfonyl chloride (86 μL, 1.11 mmol) was added to a solution of **12** (175 mg, 0.51 mmol) and Et_3N (78 μL, 0.56 mmol) in CH_2Cl_2 (17 mL) at 0 ºC. After stirring for 3 h, the reaction quenched with saturated aqueous $NaHCO_3$ (20 mL), the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:3) to provide the title compound (187 mg, 87%): white crystals; mp 87-89 ºC (EtOAc/hexanes); R_f 0.58 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ –4.8 (*c* 1.0, $CHCl_3$); FTIR (film) υ_{max} 3349, 1732, 1362, 1177, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (br s, 1 H, NH), 4.63 (d, *J* = 9.9 Hz, 1 H, H-6), 4.41 (dd, *J* = 7.3, 5.3 Hz, 1 H, H-3), 4.38 (d, *J* = 9.9 Hz, 1 H, H-6), 3.83 (s, 3 H, OCH_3), 3.05 (s, 3 H, SO_2CH_3), 2.61 (dd, *J* = 13.7, 7.3 Hz, 1 H, H-3), 2.05 (dd, *J* = 13.7, 5.3 Hz, 1 H, H-3), 1.19-1.07 (m, 21 H, SiC(*i*-Pr)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9 (CO), 171.4 (CO), 72.9 (C-6), 69.6 (C-3), 62.4 (C-5), 53.9 (OCH_3), 38.7 (C-4), 38.0 (SO_2CH_3), 18.2 (SiC(*i*-Pr)$_3$), 12.4 (SiC(*i*-Pr)$_3$); HRMS-ESI calcd for $C_{17}H_{33}NO_7SiSNa$ $[M+Na]^+$ 446.1645, found 446.1636.

Methyl (3*S* , 5*S*)-5-azidomethyl-2-oxo-3-triisopropylsilanyloxy-5-pyrrolidine carboxylate (13). A solution of methyl (3*S*,5*S*)-5-methanesulfonyloxymethyl-2-oxo-3-triisopropylsilanyloxy-5-pyrrolidine carboxylate (98 mg, 0.23 mmol) and sodium azide (152 mg, 2.34 mmol) in anhydrous DMF (1.3 mL) was heated behind a safety screen (CAUTION!), at 80 ºC for 24 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (EtOAc/hexanes, 1:3) to yield **13** (51 mg, 63%): white crystals; mp 50-53 ºC; R_f 0.65 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ +6.0 (*c* 1.0, $CHCl_3$); FTIR (film) υ_{max} 3234 (br), 2108, 1727, 1462, 1274, 1153, 883, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (br s, 1 H, NH), 4.40 (dd, *J* = 7.5, 5.8 Hz, 1 H, H-3), 3.89 (d, *J* = 11.9 Hz, 1 H, H-6), 3.81 (s, 3 H, OCH_3), 3.62 (d, *J* = 11.9 Hz, 1 H, H-6), 2.60 (dd, *J* = 13.6, 7.5 Hz, 1 H, H-4), 2.02 (dd, *J* = 13.6, 5.8 Hz, 1 H, H-4), 1.19-1.06 (m, 21 H, SiC(*i*-Pr)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (CO), 171.9 (CO), 69.4 (C-3), 62.5 (C-5), 58.4 (C-6), 53.3 (OCH_3), 39.3 (C-4), 17.8 (SiC(*i*-Pr)$_3$), 12.0 (SiC(*i*-Pr)$_3$); HRMS-ESI calcd for $C_{16}H_{30}N_4O_4SiNa$ $[M+Na]^+$ 393.1931, found 393.1931.

Methyl (3*S*,5*S*)-5-azidomethyl-3-hydroxy-2-oxo-5-pyrrolidine carboxylate (not shown in Scheme 3). A mixture of **13** (104 mg, 0.3 mmol), CH_3CN (500 μL) and 48% aqueous HF (1 mL) was stirred for 4 h, at room temperature, then poured into aqueous 2 M HCl (20 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide the title compound (55 mg, 91%), which required no further purification: white solid; $[\alpha]_D^{24}$–15.1 (*c* 0.4, MeOH); FTIR (film) υ_{max} 3322 (br), 2112, 1709, 1445, 1282, 1112 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.43 (t, *J* = 8.5 Hz, 1 H, H-3), 3.91 (d, *J* = 12.9 Hz, 1 H, H-6), 3.74 (s, 3 H, OCH_3), 3.54 (d, *J* = 12.9 Hz, 1 H, H-6), 2.74 (dd, *J* = 13.7, 8.5 Hz, 1 H, H-4), 1.97 (dd, *J* = 13.7, 8.5 Hz, 1 H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0 (CO), 173.9 (CO), 68.5 (C-3), 63.3 (C-5), 56.5 (C-6), 54.0 (OCH_3), 37.0 (C-4); HRMS-ESI calcd for $C_7H_{10}N_4O_4Na$ $[M+Na]^+$ 237.0600, found 237.0600.

Methyl (3*S*, 5*S*)-5-aminomethyl-3-hydroxy-2-oxo-5-pyrrolidine carboxylate hydrochloride (14). A round-bottomed flask was charged with methyl (3*S*,5*S*)-5-azidomethyl-3-hydroxy-2-oxo-5-pyrrolidine carboxylate (36 mg, 0.20 mmol), aqueous 2 M HCl (285 μL, 0.6 mmol), MeOH (1.7 mL) and 10% Pd/C (3 mg), flushed with H_2, placed under an atmosphere of H_2 and stirred at room temperature for 1.5 h. The flask was then flushed with N_2 and the contents filtered through a plug of Celite, which was then washed with MeOH (3 x 10 mL). The combined filtrates were concentrated under reduced pressure to provide **14** (30 mg, 79%), which was used without fur ther purification: pale yellow solid; $[\alpha]_D^{24}$–54.6 (*c* 1.4, MeOH); FTIR (KBr) υ_{max} 3435 (br), 1718, 1707 cm^{-1}; ^1H NMR (500 MHz, CD_3OD/D_2O, 2:5 (v/v)) δ 4.15 (t, *J* = 8.2 Hz, 1 H, H-3), 3.49 (s, 3 H, OCH_3), 3.31 (s, 2 H, H-6), 2.50 (dd, *J* = 13.8, 8.2 Hz, 1 H, H-4), 1.76 (dd, *J* = 13.8, 8.2 Hz, 1 H, H-4); ^{13}C NMR (100 MHz, CD_3OD) δ 179.7 (CO), 173.1 (CO), 69.1 (C-3), 61.5 (C-5), 54.9 (OCH_3), 44.9 (C-6), 38.4 (C-4); HRMS-ESI calcd for $C_7H_{13}N_2O_4$ $[M\text{-}Cl^-]^+$ 189.0875, found 189.0877.

Three-Step Conversion of Compound 14 to (-)-Dysibetaine (5)

Step 1

Methyl (3*S*, 5*S*)-5-*N*,*N*-dimethylaminomethyl-3-hydroxy-2-oxo-5-pyrrolidine carboxylate hydrochloride (not shown in Scheme 3). A glass pressure bottle was charged with **14** (28 mg, 0.12 mmol), 37% aqueous formaldehyde (21 μL, 0.26 mmol), deionized H_2O (1.6 mL) and 10% Pd/C (2 mg), placed under 50 psi of H_2 and sealed. The mixture was shaken at room temperature for 36 h. The flask was then flushed with N_2, the contents filtered through a plug of Celite and the combined filtrates concentrated under reduced pressure to provide the unstable title compound (30 mg), which was immediately submitted to the following procedure without further purification: clear oil; $[\alpha]_D^{24}$–46.2 (*c* 1.3, MeOH); FTIR (KBr) υ_{max} 3427 (br), 1714, 1651, 1455, 1088 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.46 (t, *J* = 8.1 Hz, 1 H, H-3), 3.69 (s, 3 H, OCH_3), 3.63 (d, *J* = 14.0 Hz, 1 H, H-6), 3.57 (d, *J* = 14.0 Hz, 1 H, H-6), 2.83 (m, 7 H, NMe_2, H-4), 2.04 (dd, *J* = 13.8, 7.7 Hz, 1 H, H-4); ^{13}C NMR (125 MHz, CD_3OD/D_2O, 1:7 (v/v)) δ 179.4 (CO),

172.5 (CO), 68.0 (C-3), 62.3 (C-6), 60.7 (C-5), 54.5 (OCH_3), 45.8 (br, NMe_2), 38.7 (C-4); HRMS-ESI calcd for $C_9H_{17}N_2O_4$ $[M\text{-}Cl^-]^+$ 217.1188, found 217.1187.

Step 2

(-)-(3*S*,5*S*)-5-Methoxycarbonyl-5-(*N*,*N*,*N*-trimethylmethyl)-3-hydroxy-2-oxo-5-pyrrolidinemethanaminium iodide (not shown in Scheme 3). Saturated aqueous $NaHCO_3$ (8 drops) was added to a solution of methyl (3*S*, 5*S*)-5-*N*,*N*-dimethylaminomethyl-3-hydroxy-2-oxo-5-pyrrolidine carboxylate hydrochloride (20 mg) in MeOH (2 mL). The solution was concentrated under reduced pressure and the resulting solid stirred with $CHCl_3$ (6 mL) for 30 min. The solution was then filtered and concentrated under reduced pressure to provide the amine (10 mg), which was taken up in THF (1 mL). Methyl iodide MeI (76 μL, 1.38 mmol) was then added, and the mixture was stirred at room temperature for 36 h. The reaction mixture was then concentrated under reduced pressure to provide the title compound (13 mg, 45% over two steps from **14**), which was submitted to the following procedure without further purification: oily solid; $[\alpha]_D^{24}$ –24.7 (*c* 0.3, MeOH); FTIR (KBr) υ_{max} 3438 (br), 1734, 1716, 1473, 1086 cm^{-1}; ^1H NMR (500 MHz, H_2O) δ 4.26 (dd, *J* = 7.9, 5.7 Hz, 1 H, H-3), 4.05 (d, *J* = 14.3 Hz, 1 H, H-6), 3.78 (d, *J* = 14.3 Hz, 1 H, H-6), 3.72 (s, OCH_3), 3.06 (s, 9 H, NMe_3), 2.75 (dd, *J* = 14.2, 7.9 Hz, 1 H, H-4), 2.02 (dd, *J* = 14.2, 5.7 Hz, 1 H, H-4); ^{13}C NMR (125 MHz, CD_3OD/D_2O (1:7, v/v)) δ 179.8 (CO), 173.0 (CO), 71.5 (C-3), 68.4 (C-6), 62.4 (C-5), 55.7 (NMe_3), 55.3 (OCH_3), 42.3 (C-4); HRMS-ESI calcd for $C_{10}H_{19}N_2O_4$ $[M\text{-}I^-]^+$ 231.1345, found 231.1337.

Step 3

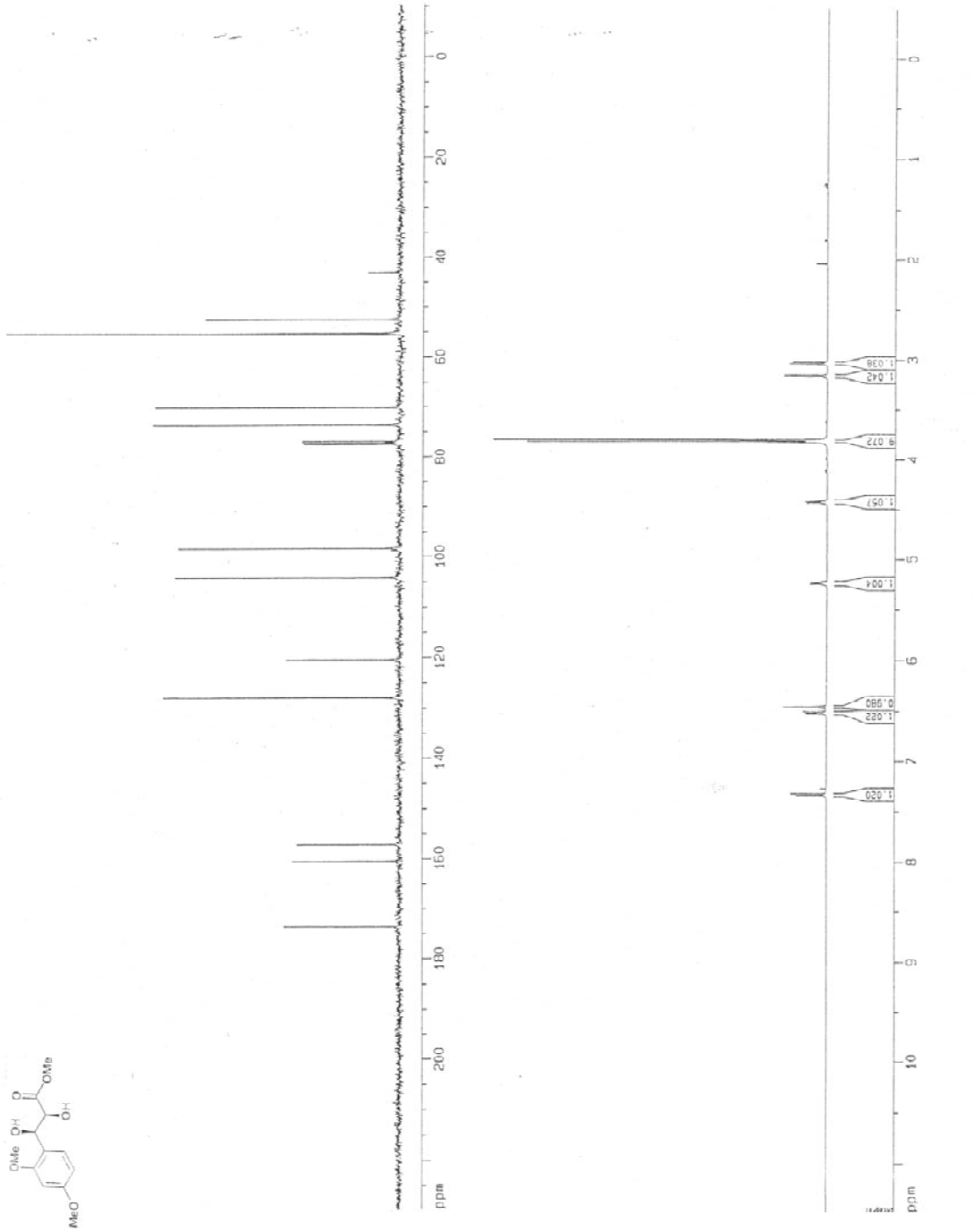
(-)-Dysibetaine (5) [(-)-(3*S*,5*S*)-5-(*N*,*N*,*N*-trimethylaminomethyl)-3-hydroxy-2-oxo-5-pyrrolidine carboxylate].

1. Preparation of Dowex 550A. Dowex 550A resin (5 g) was sequentially washed with 20% aqueous NaOH (100 mL) and H_2O (25 mL). The resin was then heated in MeOH (20 mL) at 60 ºC for 24 h, cooled to room temperature and filtered. The resin was washed with MeOH (20 mL) and allowed to air dry.

2. Hydrolysis. A mixture of Dowex 550A (200 mg) and (-)-(3*S*,5*S*)-5-methoxycarbonyl-5-(*N,N,N*-trimethylmethyl)-3-hydroxy-2-oxo-5-pyrrolidinemethanaminium iodide (7.0 mg, 0.02 mmol) in MeOH (2 mL) was heated at 55 ºC for 24 h then cooled to room temperature and filtered through a glass frit. The resin was washed with MeOH (2 x 10 mL) and the combined filtrates concentrated under reduced pressure to provide (-)-dysibetaine (**5**) (4 mg, 95%; 43% over three steps from **14**): white powder; $[\alpha]_D^{24}$ -8.0 (*c* 0.30, H_2O); FTIR (KBr) υ_{max} 3428 (br), 1691, 1614, 1338, 1103 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.20 (dd, *J* = 7.8, 5.4 Hz, 1 H, H-3), 3.89 (d, *J* = 13.9 Hz, 1 H, H-6), 3.59 (d, *J* = 13.9 Hz, 1 H, H-6), 3.05 (s, 9 H, NMe_3), 2.51 (dd, *J* = 14.0, 7.8 Hz, 1 H, H-4), 1.85 (dd, *J* = 14.0, 5.4 Hz, 1 H, H-4) ; ^{13}C NMR (125 MHz, (CD_3OD/D_2O, 1:7 (v/v)) δ 179.6 (CO), 176.8 (CO), 73.1 (C-3), 69.1 (C-6), 64.1 (C-5), 55.6 (NMe_3), 42.4 (C-4); HRMS-ESI calcd for $C_9H_{16}N_2NaO_4$ $[M+Na]^+$ 239.1008, found 239.1010.

Analytical Data for Natural (-)-Dysibetaine (Sakai):[1] $[\alpha]_D^{20}$ -7.3 (*c* 0.26, H_2O); FTIR υ_{max} 3400, 1705, 1605 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.23 (dd, *J* = 8.0, 5.5 Hz, 1 H, H-3), 3.92 (d, *J* = 14.0 Hz, 1 H, H-6), 3.62 (d, *J* = 14.0 Hz, 1 H, H-6), 3.09 (s, 9 H, NMe_3), 2.55 (dd, *J* = 13.9, 8.0 Hz, 1 H, H-4), 1.88 (dd, *J* = 13.9, 5.5 Hz, 1 H, H-4) ; ^{13}C NMR (100 MHz, CD_3OD/D_2O) δ 179.5 (CO), 176.8 (CO), 72.9 (C-3), 68.9 (C-6), 64.1 (C-5), 55.5 (NMe_3), 42.3 (C-4); HRMS-FAB calcd for $C_9H_{17}N_2O_4$ $[M+H]^+$ 217.1188, found 217.1191.

Analytical Data for Synthetic (-)-Dysibetaine (Snider):[2] $[\alpha]_D$ -7.1 (*c* 0.26, H_2O); FTIR υ_{max} 3361, 1713, 1626 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.21 (dd, *J* = 8.0, 5.5 Hz, 1 H, H-3), 3.90 (d, *J* = 14.0 Hz, 1 H, H-6), 3.60 (d, *J* = 14.0 Hz, 1 H, H-6), 3.07 (s, 9 H, NMe_3), 2.53 (dd, *J* = 13.9, 8.0 Hz, 1 H, H-4), 1.86 (dd, *J* = 13.9, 5.5 Hz, 1 H, H-4) ; ^{13}C NMR (100 MHz, CD_3OD/D_2O) δ 179.5 (CO), 176.8 (CO), 73.1 (C-3), 69.1 (C-6), 64.1 (C-5), 55.6 (NMe_3), 42.4 (C-4); HRMS-FAB calcd for $C_9H_{17}N_2O_4$ $[M+H]^+$ 217.1188, found 217.1190.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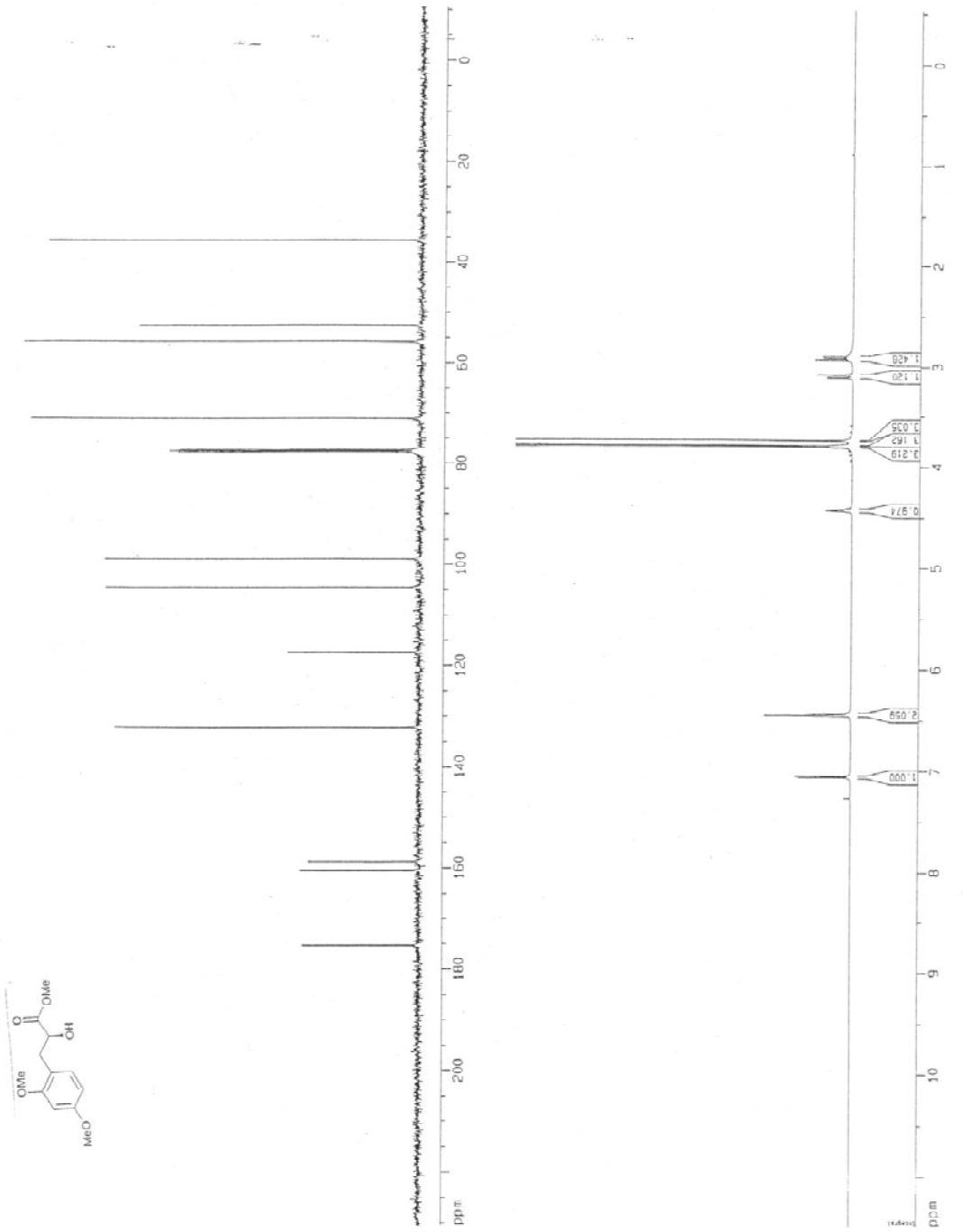
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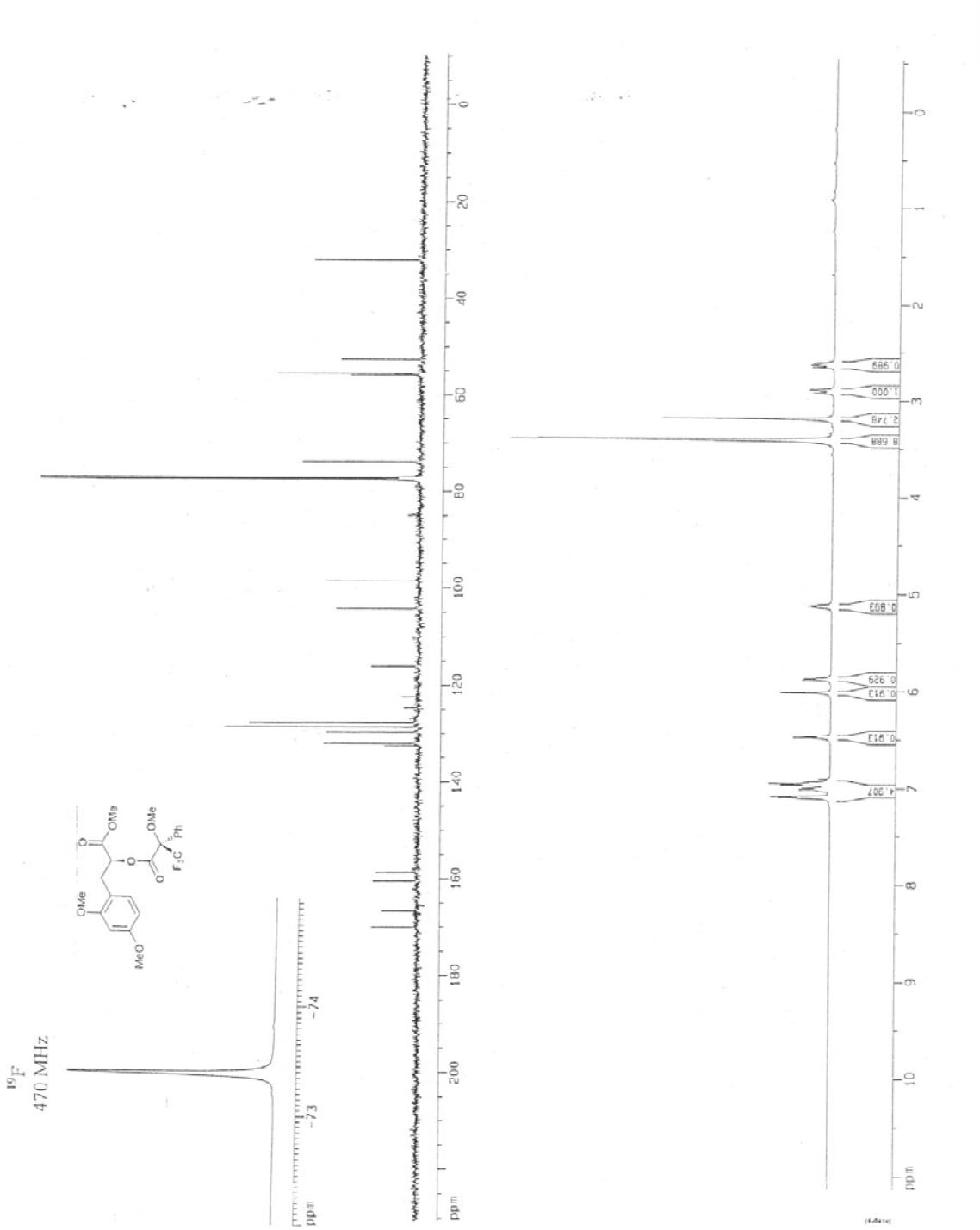
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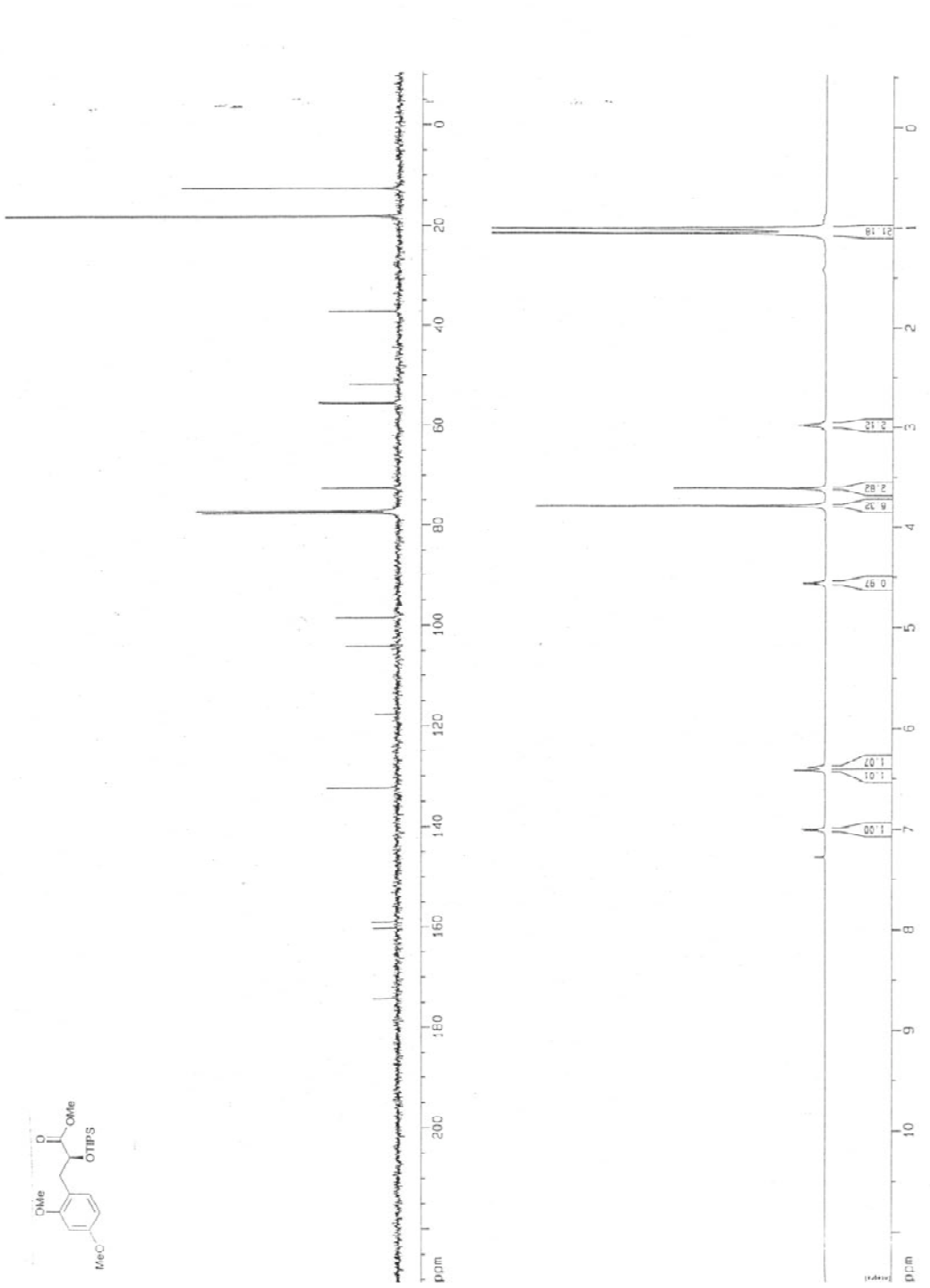
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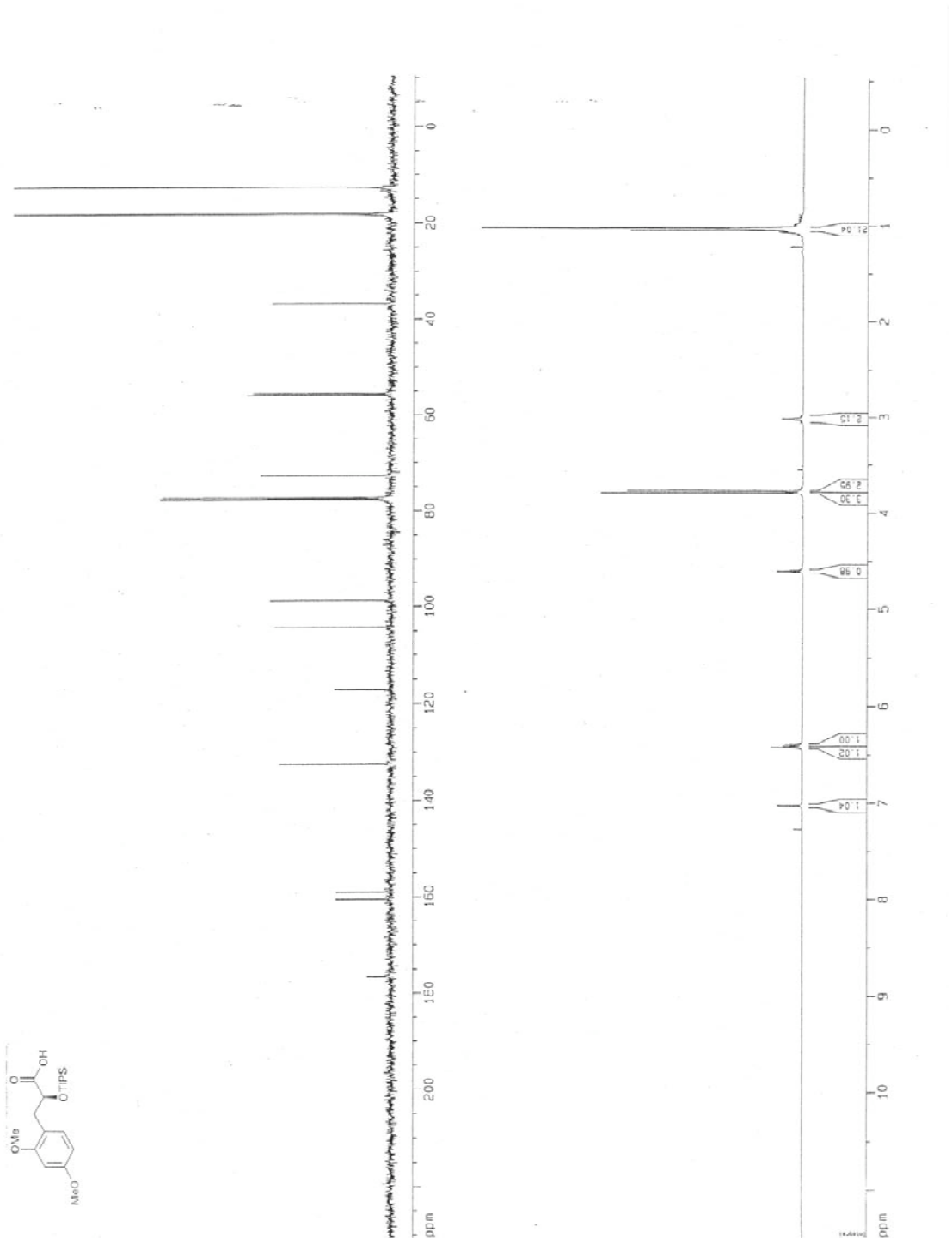
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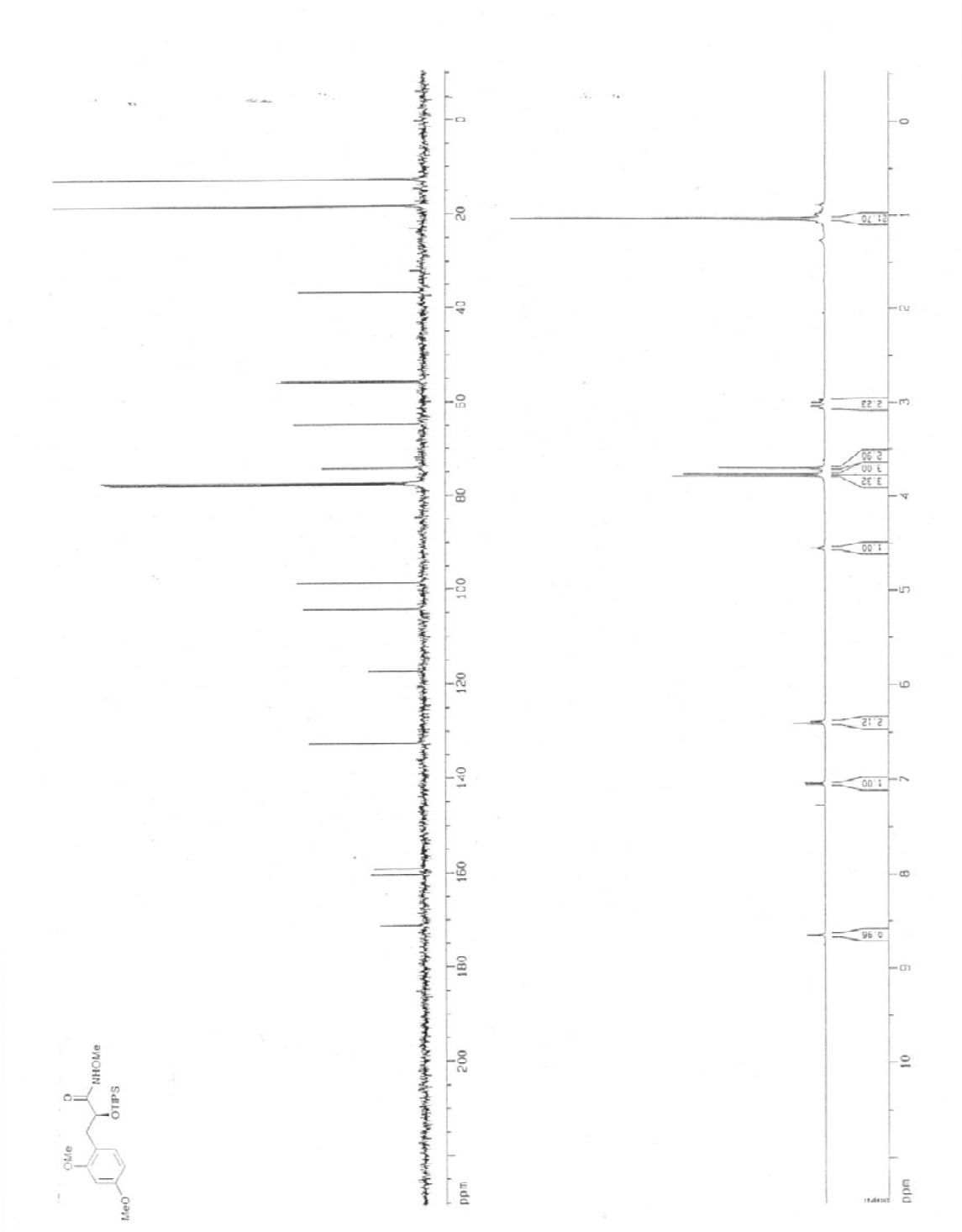
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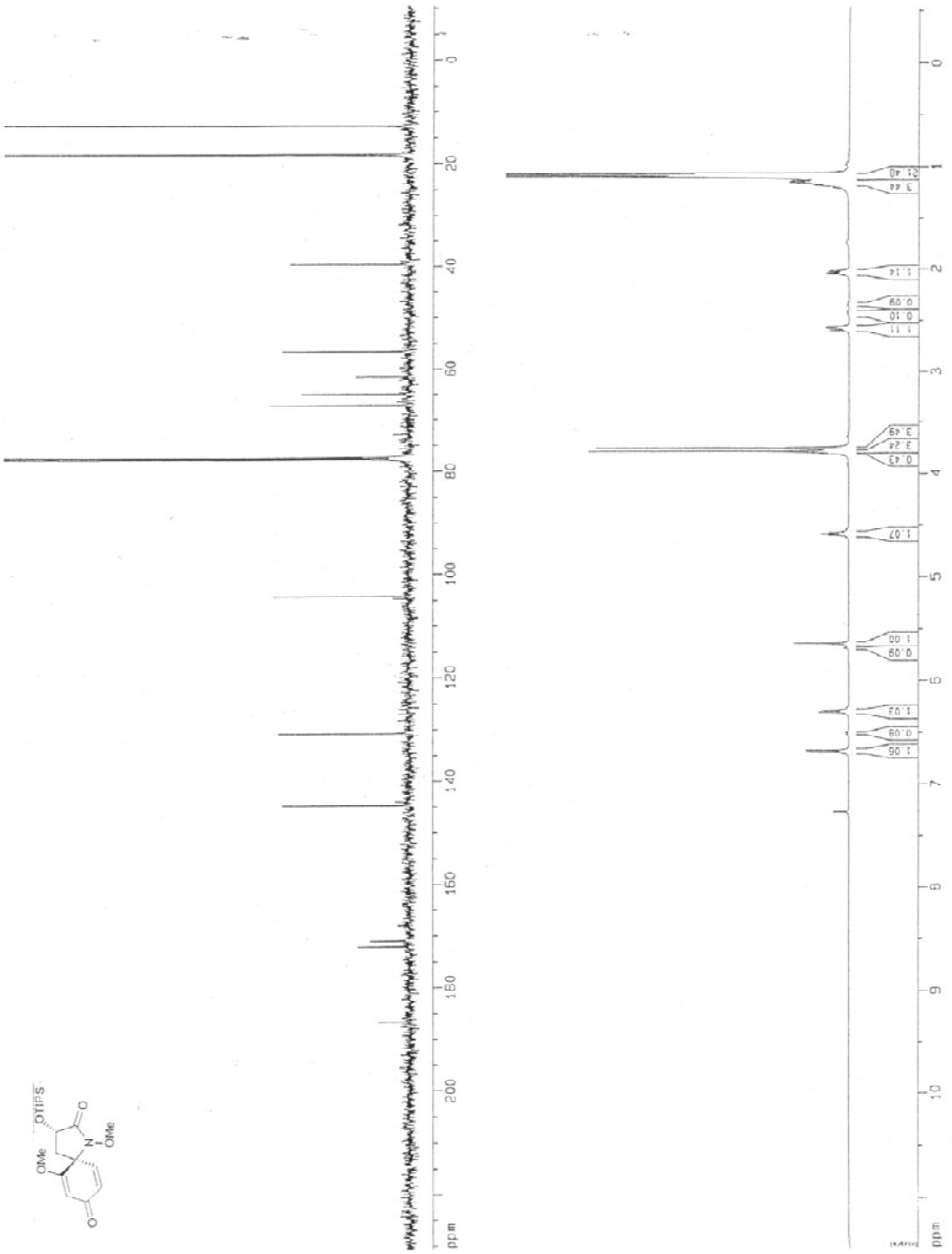
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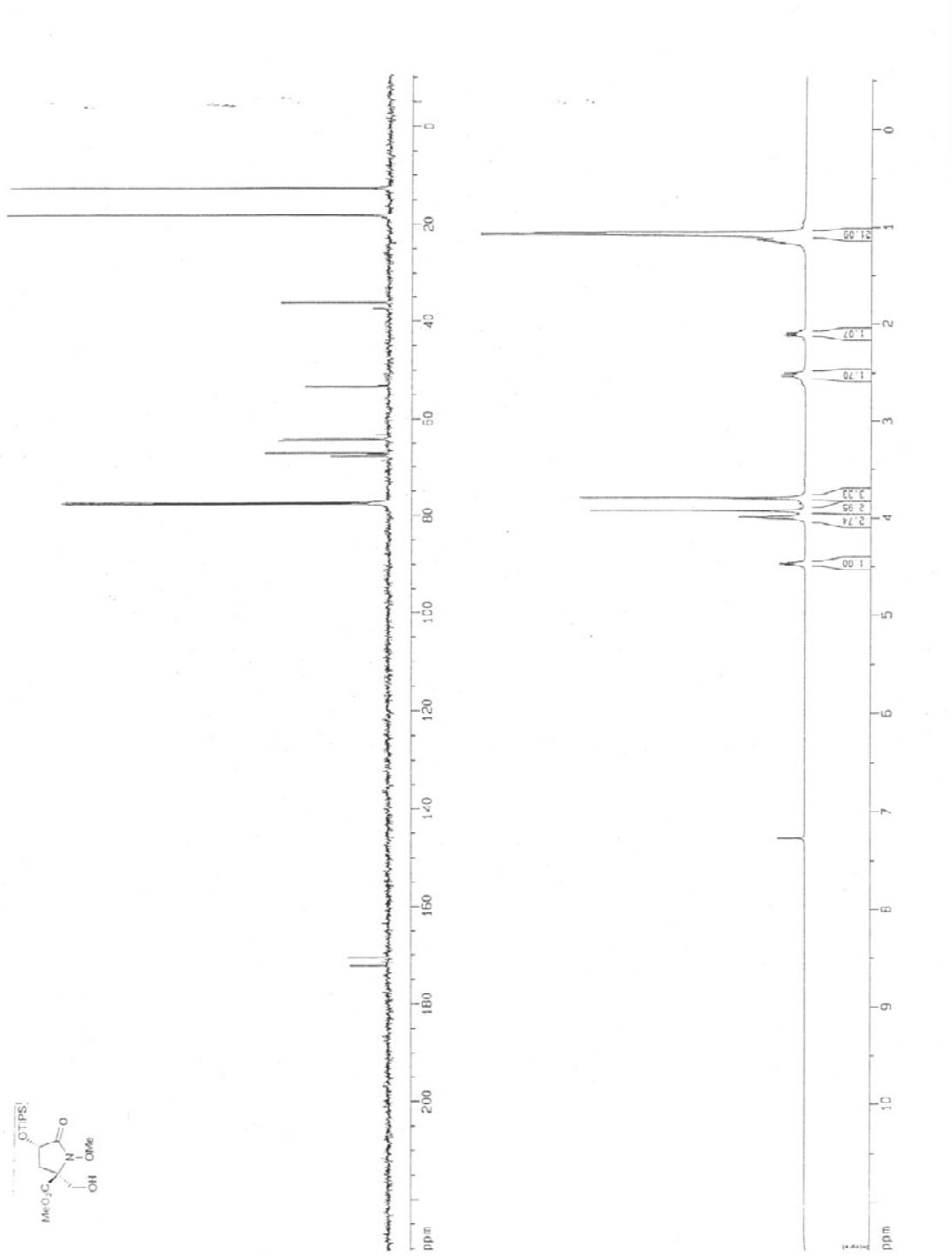
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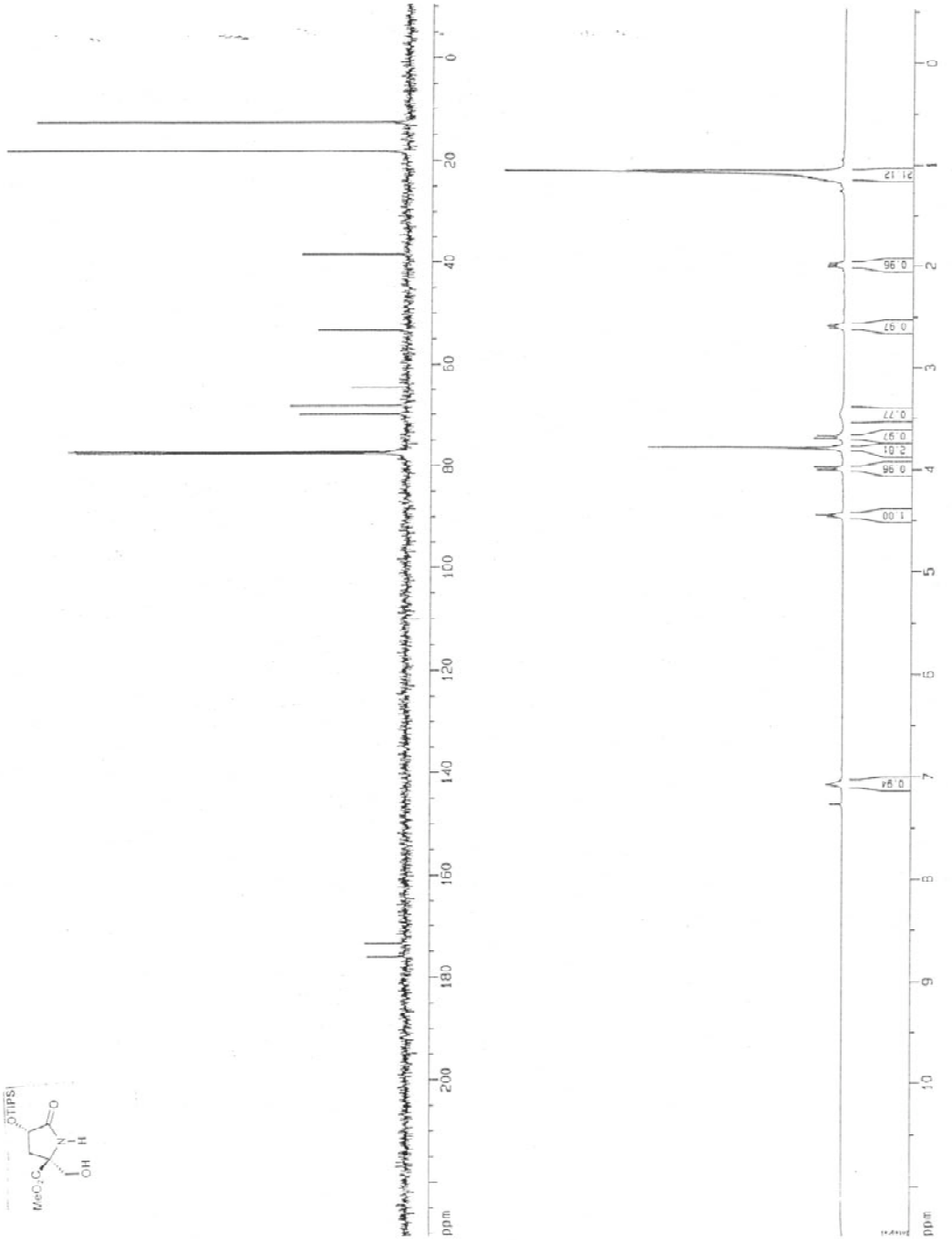
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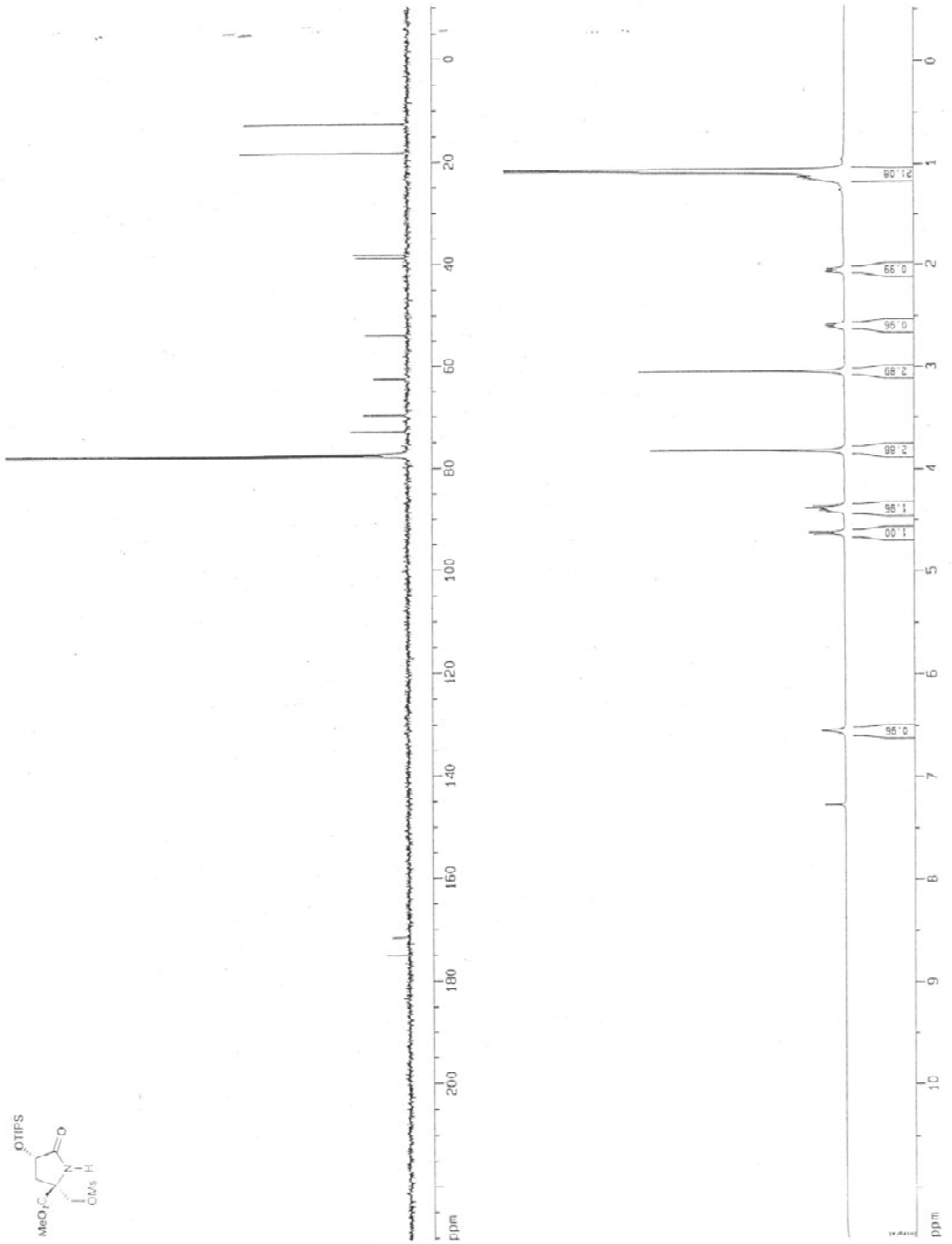
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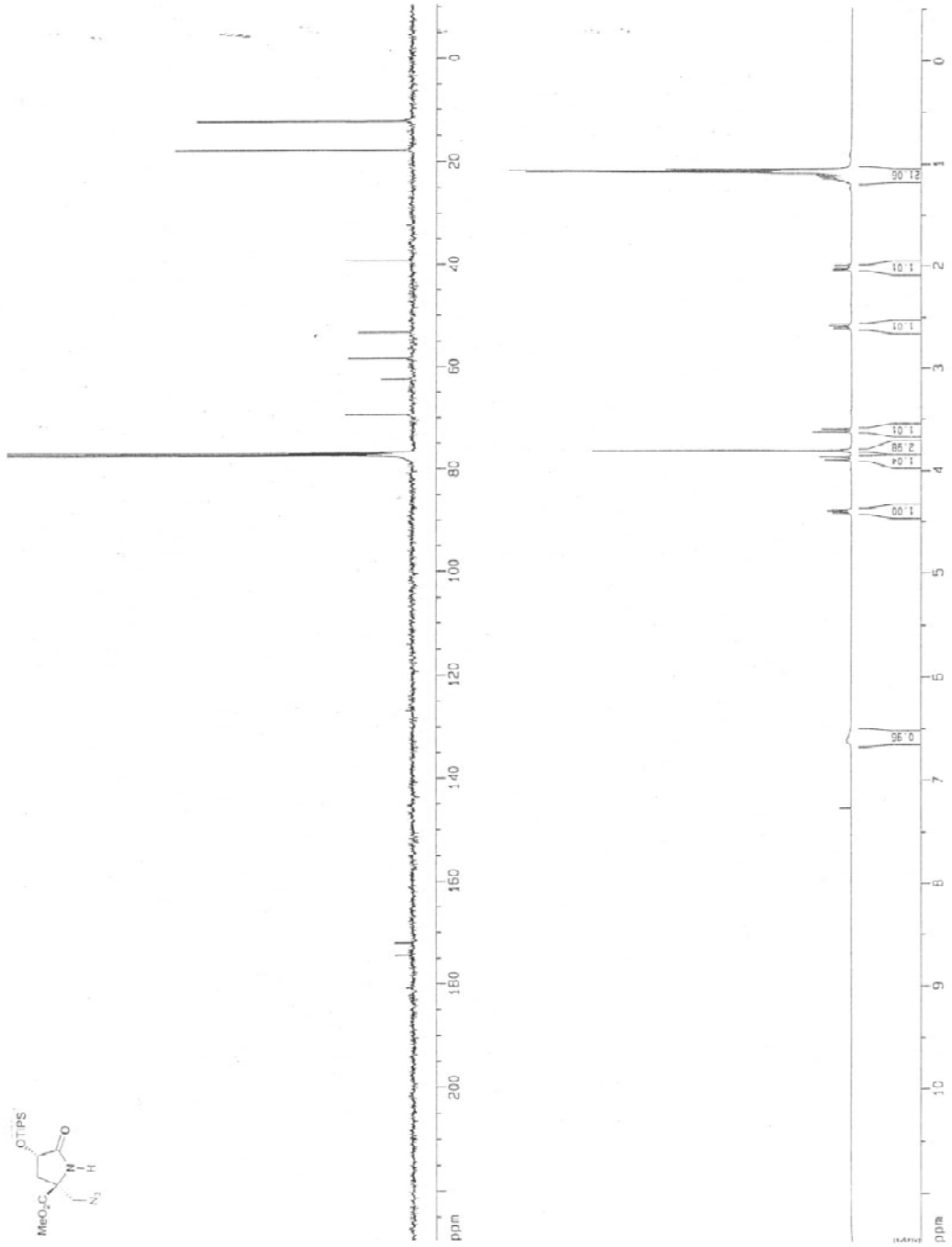
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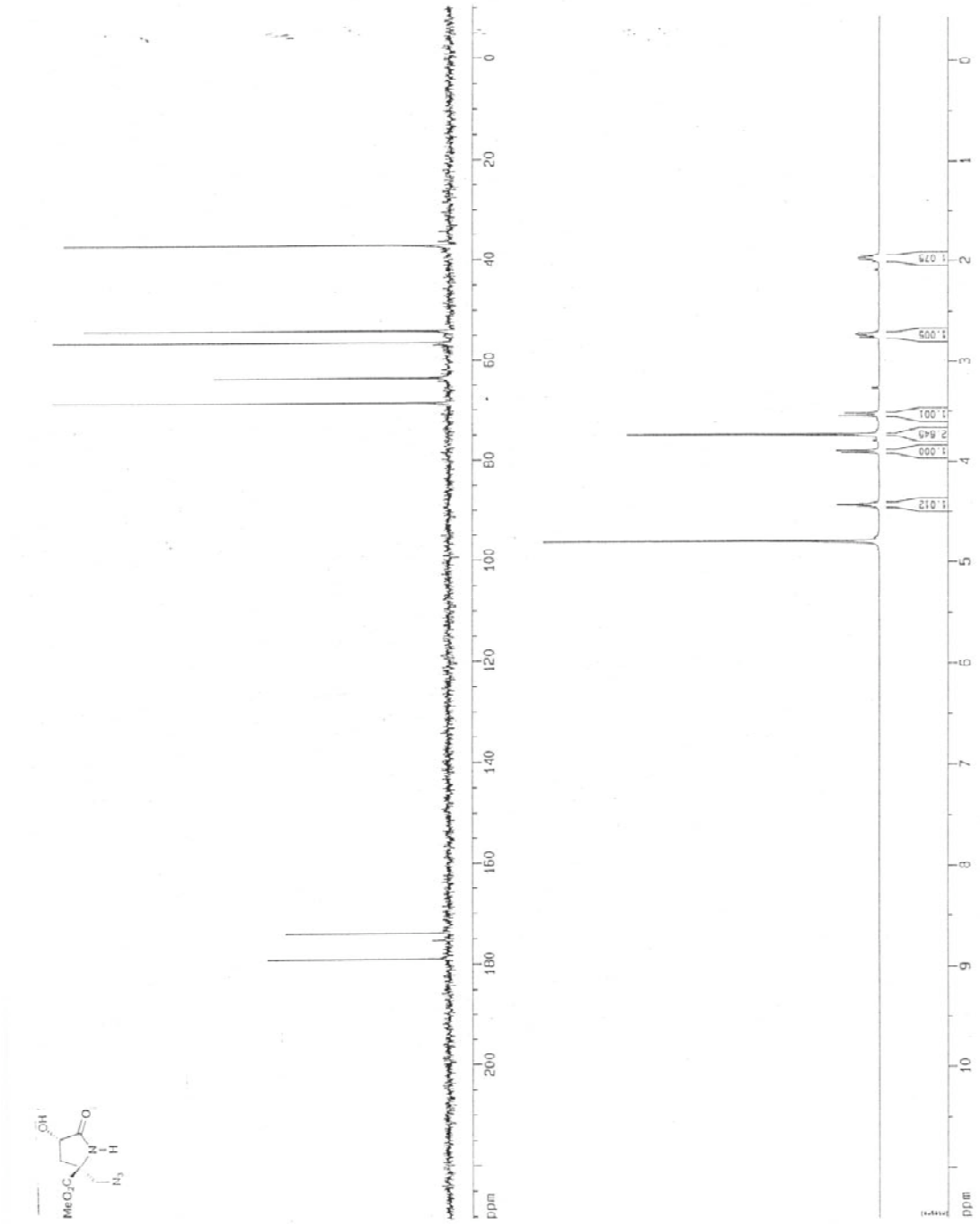
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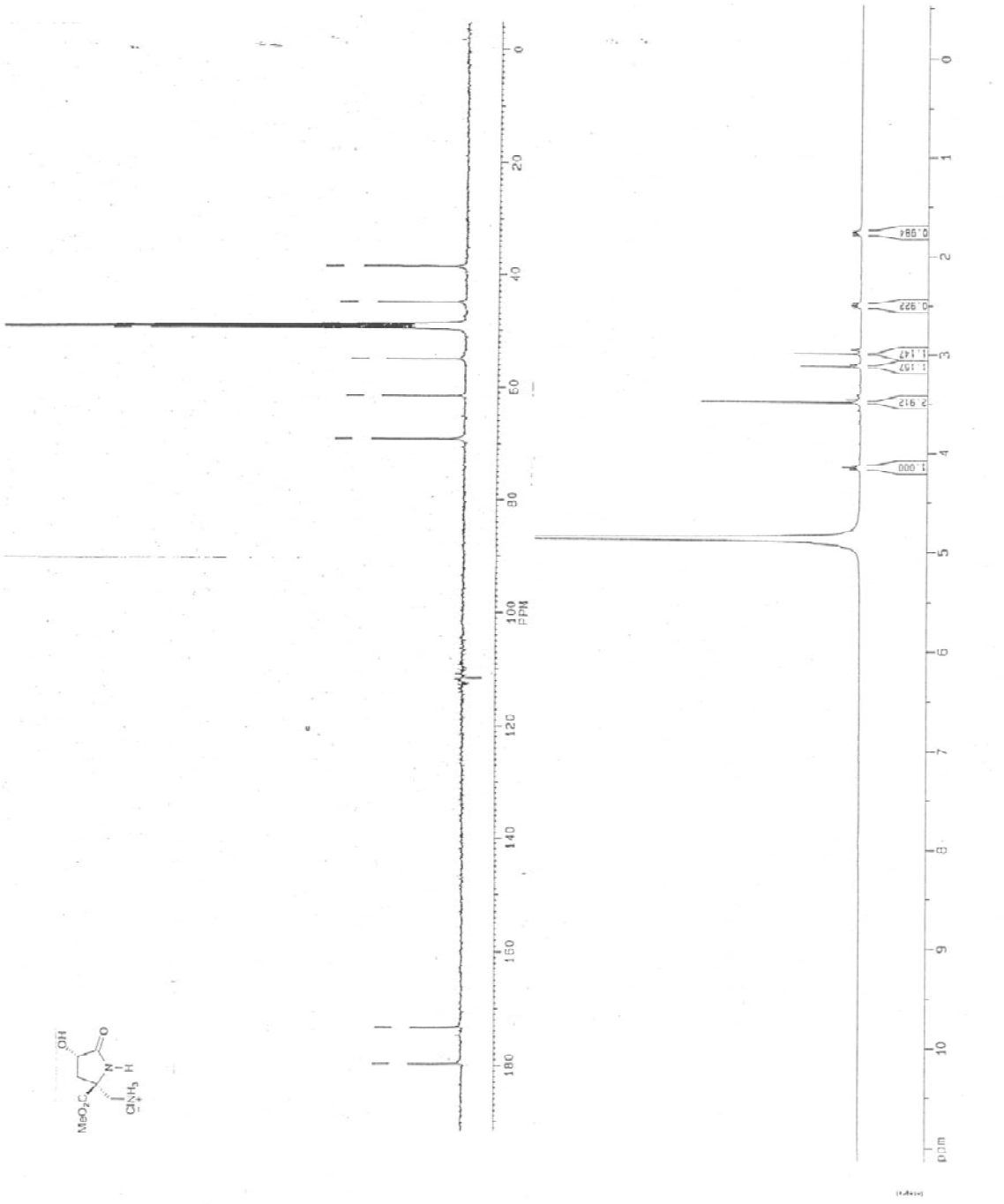
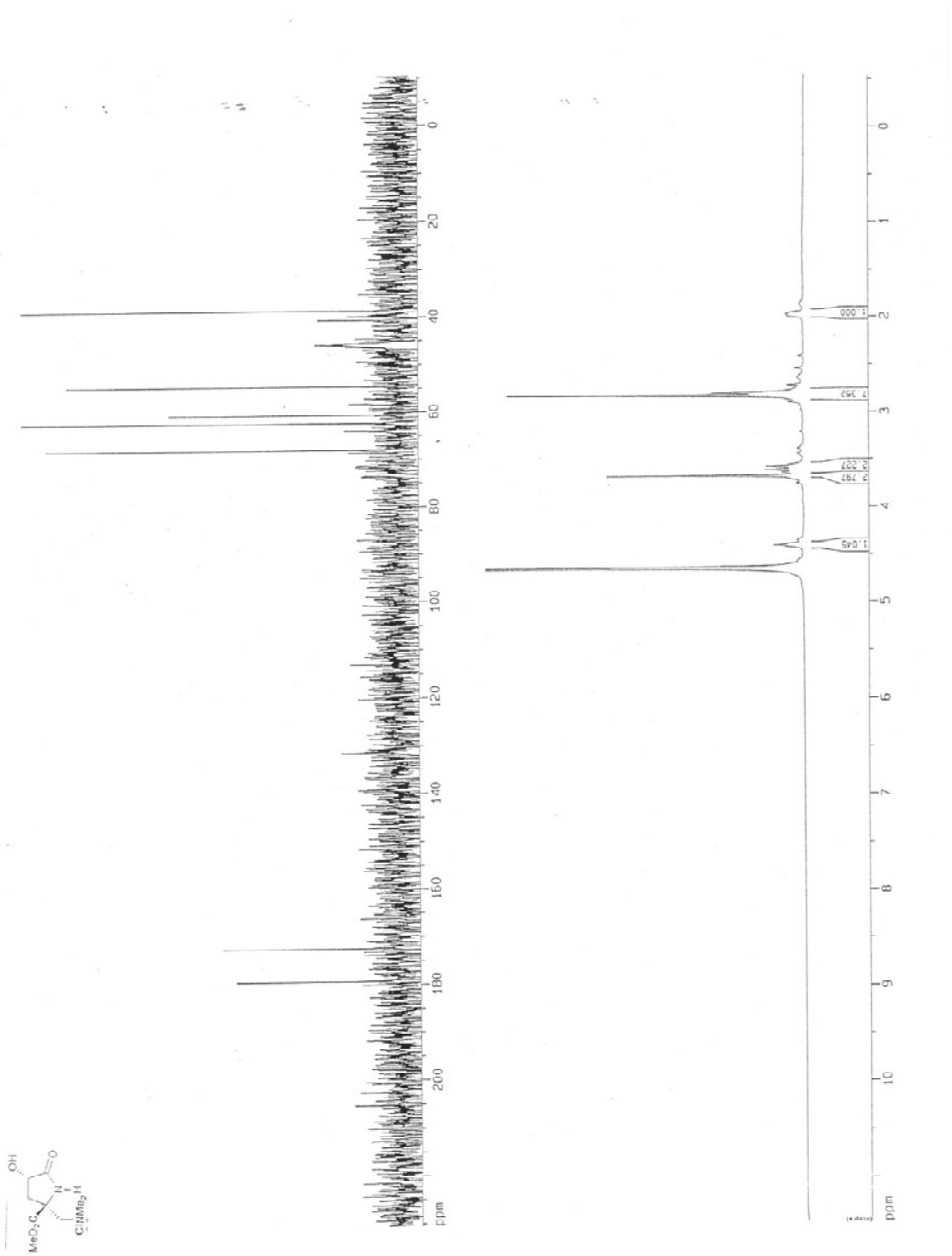
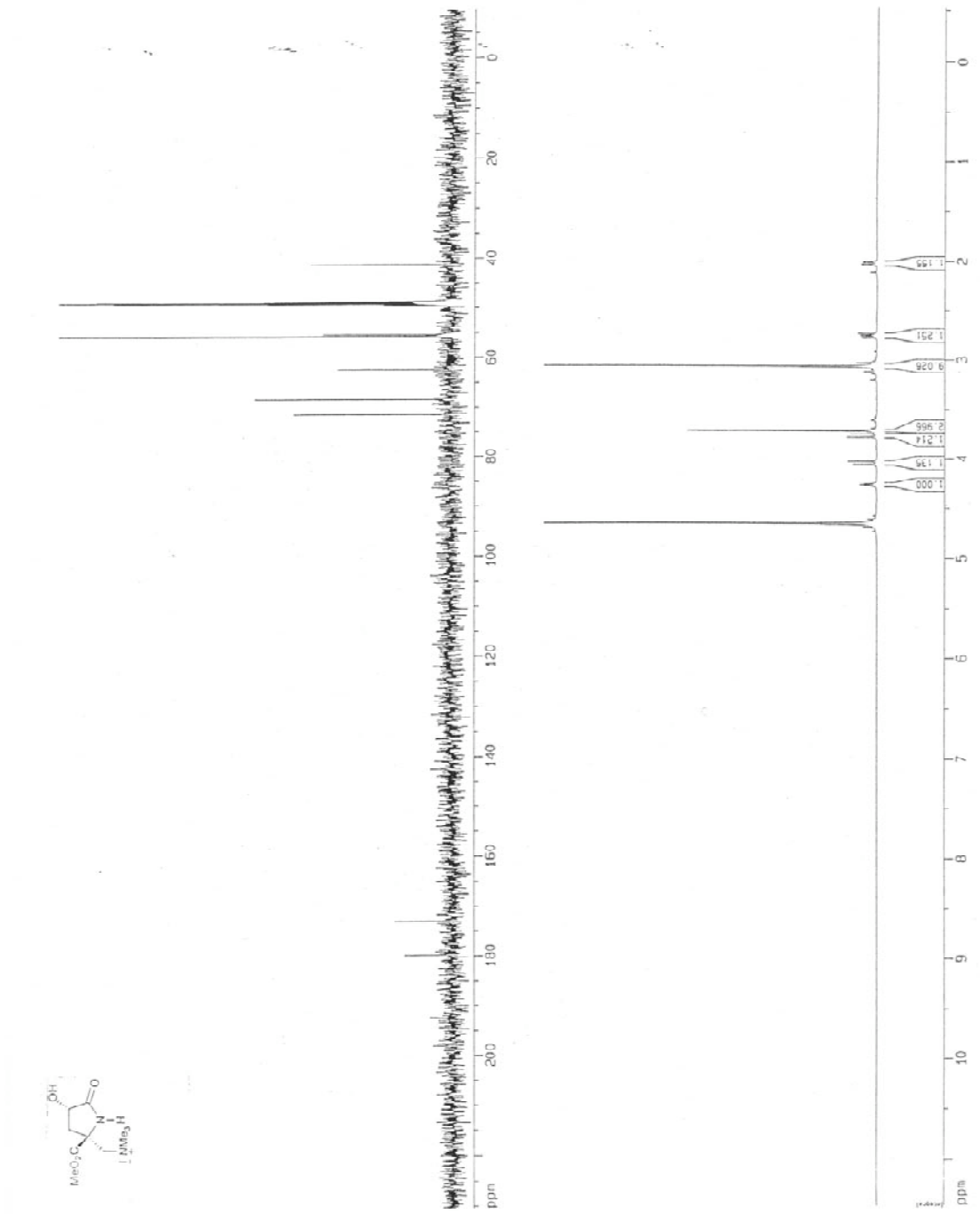
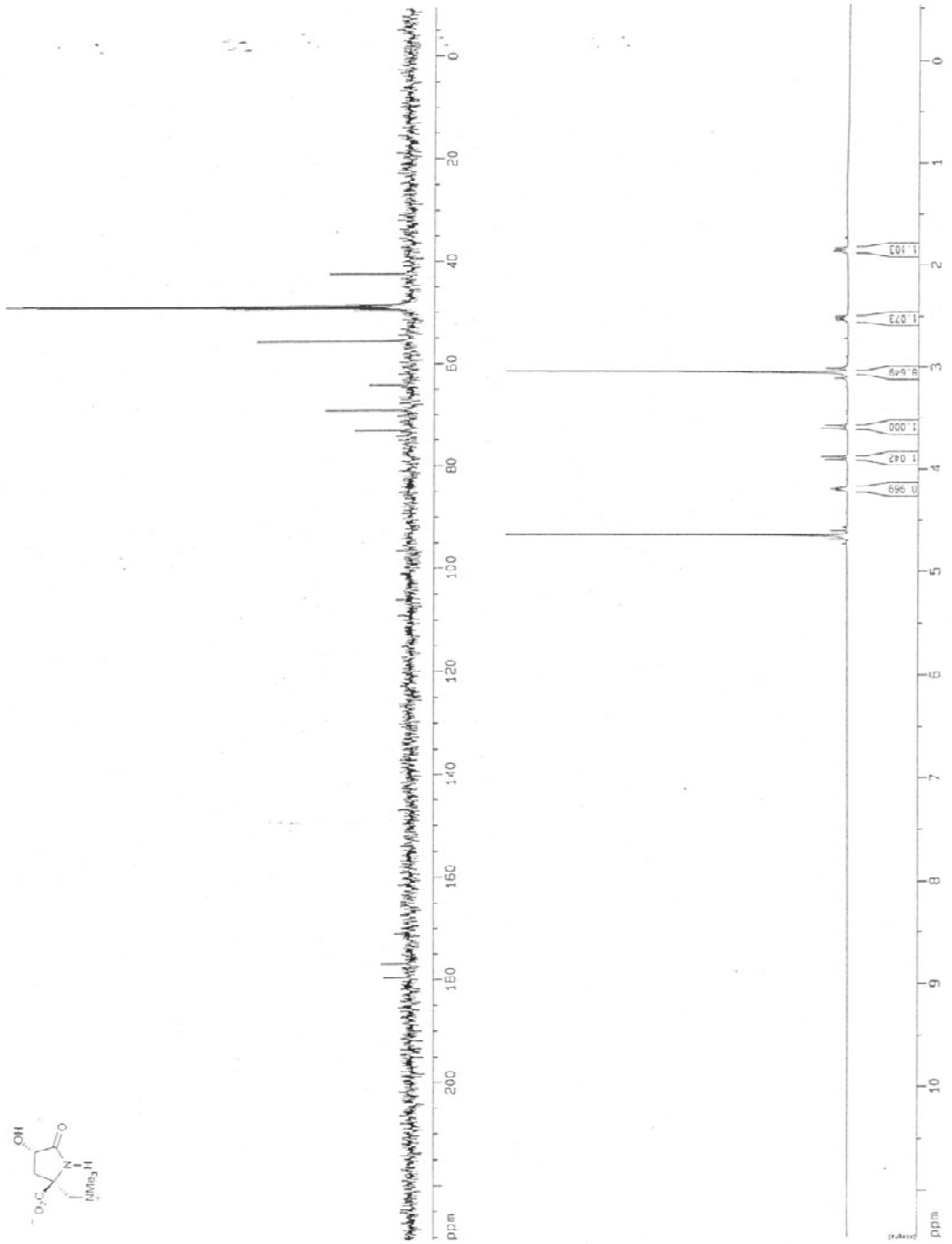

OH
O
N
H
CNH3
MeO2C
0.984
0.922
1.147
1.157
2.912
1.000
PPM


OH
O
N
H
MeO2C
CH2NMe2H
ppm
1.000
7.352
2.797
2.027
1.045
ppm


ppm
ppm


OH
O
N
H
NMe3+
O2C
200
180
160
140
120
100
80
60
40
20
0
ppm
1.103
1.073
8.649
1.000
1.042
0.969
10
9
8
7
6
5
4
3
2
1
0
ppm