Nitrenium Ion Azaspirocyclization-Cyclohexadienone Cleavage: A New Synthetic Strategy for the Stereocontrolled Preparation of Highly Substituted Lactams and *N*-Hydroxy Lactams

Duncan J. Wardrop and Matthew S. Burge*

Department of Chemistry, University of Illinois at Chicago,

845 West Taylor Street, Chicago, IL 60607.

E-mail: wardropd@uic.edu

Supporting Information

Table of Contents

1. 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[1] using silica gel 60 (mesh 230-400) supplied by Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

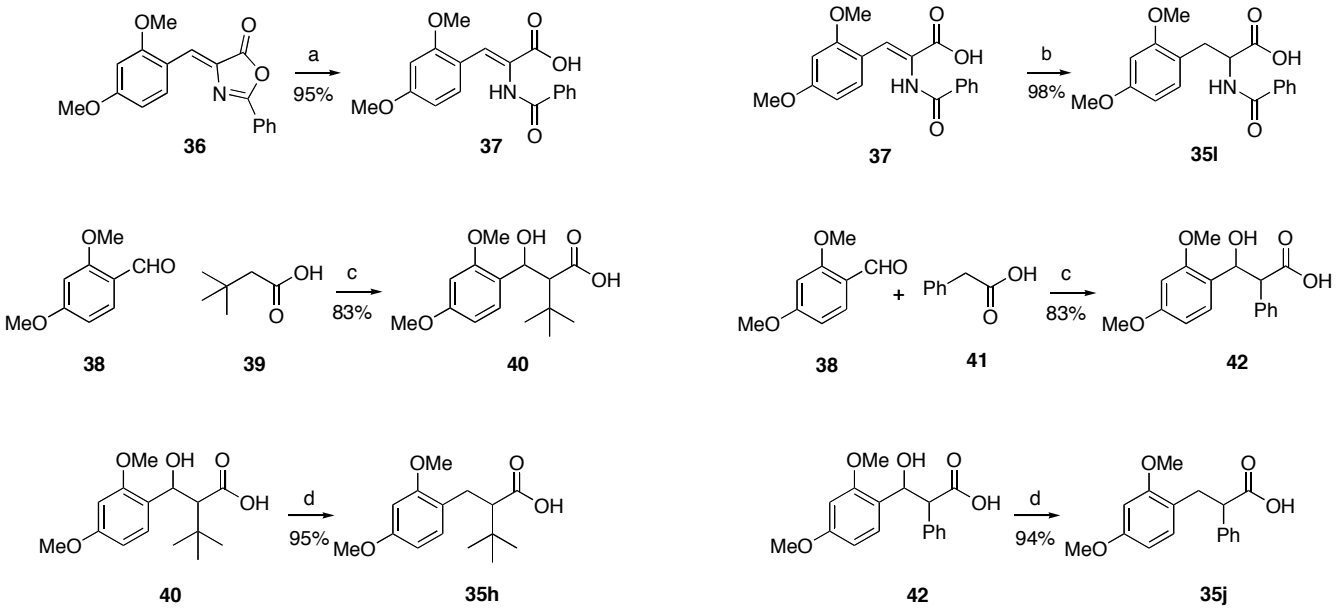
2. Materials

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. Dichloromethane (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride, under an atmosphere of dry nitrogen. Phenyliodine(III) bis(trifluoroacetate) (PIFA) was prepared following the procedure reported by Loudon.[2] (*Z*)-4-(2,4-Dimethoxybenzylidene)-2-phenyl-4*H*-oxazol-5-one (**36**) was prepared using an adaptation of the method reported by Buck.[3] All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

3. Instrumentation

All melting points were determined in open Pyrex capillaries and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates or in compressed discs of potassium bromide. 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), appt (apparent) 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 are reported as follows: $[\alpha]_{\text{wavelength}}^{\text{temperature}}$ (*c*, solvent); $[\alpha]_D$ is reported in 10^{-1} deg $cm^{-2}g^{-1}$; concentration (*c*) is g in per 100 ml).

4. **Scheme S1**:[a] Preparation of Carboxylic Acids **35l**, **35h** and **35j**



[a]***Reagents and General Procedures.*** (a) NaOH, H_2O, reflux, 3h; (b) H_2 (50 psi), 10% Pd/C, EtOAc, MeOH, rt, 12 h; (c) **39** or **41**, LDA (2 equiv), THF, 0 °C, 1 h, then **38**, 0 °C→rt, 16 h; (d) H_2 (50 psi), 2 M aq. HCl, EtOAc, THF, 48 h.

5. Preparation of Carboxylic Acids 35l, 35h, 35j

(*Z*)-2-Benzoylamino-3-(2,4-dimethoxyphenyl)acrylic acid (37). Azalactone **36**[3] (2.13 g, 6.89 mmol) was heated at reflux in aqueous NaOH (0.05 M, 34 ml) for 3 h, whereupon the solution was cooled to rt and acidified with aqueous HCl (2 M, 100 ml). The reaction mixture was then extracted with EtOAc (4 x 50 ml), the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was recrystallized (EtOAc/hexanes) to provide **37** (2.13 g, 95%): white solid; mp 216-218 °C; R_f 0.28 (EtOAc); FTIR (film) υ_{max} 3254 (br), 1687, 1651, 1603, 1479, 1274, 1209, 1030, 711 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.90-7.88 (m, 3 H), 7.60 (d, J = 8.7 Hz, 1 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 2 H), 6.51 (d, J = 2.3 Hz, 1 H), 6.43 (dd, J = 2.3, 8.7 Hz, 1 H), 3.82 (s, 3 H), 3.74 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.3, 167.3, 162.7, 159.5, 133.7, 131.7, 130.1, 129.9, 128.3, 127.3, 123.1, 115.0, 105.0, 97.7, 54.9, 54.5; HRMS-ESI calcd for $C_{18}H_{17}NO_5Na$ $[M+Na]^+$ 350.1004, found 350.1003.

(±)-2-Benzoylamino-3-(2,4-dimethoxyphenyl)propionic acid (35l). A 50 ml, glass reaction bottle, charged with 10% Pd/C (45 mg) and a solution of **37** (1.35 g, 4.13 mmol) in EtOAc and MeOH (1:1, 17 ml) was connected to a Parr type, shaker hydrogenation apparatus. The reaction vessel was flushed with N_2 and then placed under an atmosphere of H_2 (50 psi) and sealed. After shaking at rt for 12 h, the vessel was flushed with N_2, the reaction mixture filtered through a plug of Celite and the filter cake washed with MeOH (3 x 10 ml). The combined filtrates were concentrated under reduced pressure and the resulting residue recrystallized (EtOAc/hexanes) to provide **35l** (1.33 g, 98%): white crystals; mp 165-167 ºC; R_f 0.29 (EtOAc); FTIR (film) υ_{max} 3309 (br), 1708, 1651, 1533, 1508, 1289, 1209, 1119, 1032, 693 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.65-7.63 (m, 2 H), 7.45-7.41 (m, 1 H), 7.37-7.33 (m, 2 H), 7.04 (d, J = 8.3 Hz, 1 H), 6.40 (d, J = 2.4 Hz, 1 H), 6.34 (dd, J = 2.4, 8.3 Hz, 1 H), 4.68 (dd, J = 4.7, 9.2 Hz, 1 H), 3.69 (s, 3 H), 3.66 (s, 3 H), 3.24 (dd, J = 4.7, 13.7 Hz, 1 H), 2.93 (dd, J = 9.2, 13.7 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.3, 169.7 161.6, 160.1, 135.9, 132.7 (2 C), 129.6, 128.3, 119.6, 105.6, 99.3, 56.5, 56.0, 55.8, 33.1; HRMS-ESI calcd for $C_{18}H_{19}NO_5Na$ $[M+Na]^+$ 352.1161, found 352.1155.

General Procedure H (Aldol Reaction of Carboxylic Acid Dianion with Aldehyde 38). (±)-3-(2,4-Dimethoxyphenyl)-3-hydroxy-2-phenylpropionic Acid (42). To a solution of LDA in THF (90 ml) (prepared from *i*-Pr_2NH (11.3 ml, 80.8 mmol) and *n*-BuLi (30.9 ml, 2.5 M in hexanes, 77.3 mmol)), under an atmosphere of nitrogen at 0 °C, was added a solution of phenylacetic acid (**41**) (5.0 g, 36.7 mmol) in THF (10 ml) via syringe. After stirring for 1 h, 2,4-dimethoxybenzaldehyde (**38**) (6.41 g, 38.6 mmol) in THF (10 ml) was added via syringe and the solution then allowed to warm to rt. After stirring for 16 h, the reaction was quenched with aqueous HCl (3 M, 20 ml) and the volatiles removed under reduced pressure. The aqueous concentrate was extracted with CH_2Cl_2 (4 x 40 ml) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting colorless residue was recrystallized (EtOAc/hexanes) to provide **42** (9.25 g, 83%) as a mixture (18:1) of diastereomers: yellow solid; mp 113-115 ºC; R_f 0.74 (EtOAc); FTIR (film) υ_{max} 3454 (br), 1709, 1508, 1293, 1209, 1158, 1035, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18-7.16 (m, 5 H), 6.92 (d, J = 8.4 Hz, 1 H), 6.32 (d, J = 2.2 Hz, 1 H), 6.28 (dd, J = 2.2, 8.4 Hz, 1 H), 5.31 (d, J = 9.3 Hz, 1 H), 4.16 (d, J = 9.3 Hz, 1 H), 3.71 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 160.3, 157.7, 135.4, 129.3, 128.5, 128.3, 127.4, 120.8, 104.1, 98.5, 73.6, 58.2, 55.2 (2 C); HRMS-ESI calcd for $C_{17}H_{18}O_5Na$ $[M+Na]^+$ 325.1052, found 325.1048.

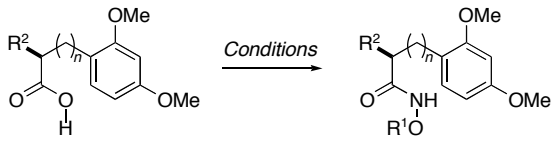
(±)-2-[(2,4-Dimethoxyphenyl)-hydroxymethyl]-3,3-dimethylbutyric acid (40). Following general procedure H, reaction of 2,4-dimethoxybenzaldehyde (**38**) (4.51 g, 27.1 mmol) with the lithium dianion derived from *tert*-butylacetic acid (**39**) (3.00 g, 25.8 mmol) provided a colorless oil, which was recrystallized (EtOAc/hexanes) to provide **40** (6.02 g, 83%) as a single diastereomer: white solid; mp 150-154 ºC; R_f 0.44 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3319 (br), 1680, 1616, 1504, 1461, 1209, 1032, 852 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.24 (d, *J* = 9.1 Hz, 1 H), 6.51-6.49 (m, 2 H), 5.26 (d, *J* = 5.7 Hz, 1 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 2.70 (d, *J* = 5.7 Hz, 1 H), 1.00 (s, 9 H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.6, 160.5, 157.0, 127.7, 124.0, 104.1, 97.8, 66.9, 60.1, 54.3 (2 C), 32.1, 27.9; HRMS-ESI calcd for $C_{15}H_{22}O_5Na$ $[M+Na]^+$ 305.1365, found 305.1366.

General Procedure I (Hydrogenolysis of Aldol Products). (±)-3-(2,4-Dimethoxyphenyl)-2-phenylpropionic acid (35j). A 500 ml, glass reaction bottle, charged with 10% Pd/C (72 mg), aqueous HCl (2 M, 5 ml) and a solution of **42** (2.04 g, 6.76 mmol) in EtOAc and MeOH (10:1, 68 ml) was connected to a Parr Shaker hydrogenation apparatus. The reaction vessel was flushed with N_2 and then placed under an atmosphere of H_2 (50 psi) and sealed. After shaking at rt for 48 h, the vessel was flushed with N_2 and the reaction mixture filtered through a plug of Celite and the filter cake washed with MeOH (3 x 20 ml). The combined filtrates were concentrated under reduced pressure and the resulting residue recrystallized (EtOAc/hexanes) to provide **35j** (1.81 g, 94%): white crystals; mp 119–124 ºC; R_f 0.39 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3026 (br), 1704, 1506, 1459, 1290, 1208, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5 H), 6.90 (d, *J* = 8.3 Hz, 1 H), 6.42 (d, *J* = 2.4 Hz, 1 H), 6.31 (dd, *J* = 2.4, 8.3 Hz, 1 H), 3.95 (dd, *J* = 6.6, 8.5 Hz, 1 H), 3.77 (s, 6 H), 3.31 (dd, *J* = 8.5, 13.7 Hz, 1 H), 2.99 (dd, *J* = 6.6, 13.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 159.6, 158.4, 138.7, 131.1, 128.5, 128.1, 127.3, 119.4, 103.7, 98.3, 55.3, 55.2, 51.4, 33.9; HRMS-ESI calcd for $C_{17}H_{19}O_4[M+H]^+$ 287.1283, found 287.1295.

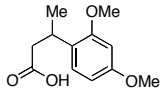
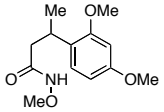
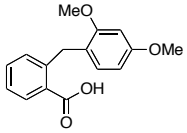
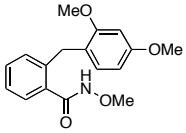
(±)-2-(2,4-Dimethoxybenzyl)-3,3-dimethylbutyric acid (35h). Following general procedure I, acid-catalyzed hydrogenolysis of **40** (3.04 g, 10.77 mmol) gave a colorless oil, which was recrystallized (EtOAc/hexanes) to afford **35h** (2.72 g, 95%): white crystals; mp 119-120 ºC; R_f 0.70 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3083 (br), 1702, 1614, 1507, 1465, 1289, 1209, 1156, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.2 Hz, 1 H), 6.43 (d, *J* = 2.1 Hz, 1 H), 6.35 (dd, *J* = 2.1, 8.2 Hz, 1 H), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H), 2.94 (dd, *J* = 2.1, 13.1 Hz, 1 H), 2.70 (t, *J* = 12.5 Hz, 1 H), 2.59 (dd, *J* = 2.1,

11.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 159.5, 158.3, 130.4, 120.7, 103.7, 98.4, 56.4, 55.2, 55.1, 33.0, 28.3, 27.7; HRMS-ESI calcd for $C_{15}H_{22}NaO_4$ $[M+Na]^+$ 289.1416, found 289.1424. Anal Calcd for $C_{15}H_{22}O_4$; C, 67.64; H, 8.33. Found: C, 67.87; H 8.61.

6. **Table S1:** Synthesis of *O*-Alkyl Hydroxamates **10**.



35 **10**

entry	substrate	*n*	R^1	R^2	method[a]	yield (%)[b]	
1	**35a**	0	Me	H	A	**10a**	93
2	**35b**	0	Bn	H	B	**10b**	95
3	**35c**	1	Me	H	A	**10c**	95
4	**35d**	1	Bn	H	B	**10d**	97
5	**35e**	2	Me	H	A	**10e**	92
6	**35f**	2	Bn	H	B	**10f**	88
7	**35g**	1	Me	Me	A	**10g**	100
8	**35h**	1	Me	*t*-Bu	A	**10h**	85
9	**35i**	1	Me	Bn	A	**10i**	85
10	**35j**	1	Me	Ph	A	**10j**	85
11	**35k**	1	Me	OTIPS	C	**10k**	88
12	**35l**	1	Me	NHBz	A	**10l**	89
13	 **35m**	-	-	-	A	 **10m**	97
14	 **35n**	-	-	-	A	 **10n**	99

[a] Method A: $MeONH_2$•HCl, EDC, Et_3N, CH_2Cl_2, rt. Method B: $BnONH_2$•HCl, EDC, Et_3N, CH_2Cl_2, rt. Method C: *i*-BuOCOCl, Et_3N, CH_2Cl_2, then $MeONH_2$•HCl. [b] Isolated yield, after purification by flash chromatography.

7. Synthesis of *O*-Alkyl Hydroxamates 10

Coupling Method A (Preparation of *O*-Methyl Hydroxamates via EDC Coupling). *O*-Methyl 2-(2,4-dimethoxyphenyl)acetohydroxamate (10a) (Entry 1, Table S1). To a stirred solution of **35a** (2.00 g, 10.19 mmol) and Et_3N (1.05 ml, 7.77 mmol) in CH_2Cl_2 (20 ml) was added EDC (2.15 g, 11.21 mmol) and H_2NOMe•HCl (979 mg, 11.72 mmol). After stirring for 9 h, the reaction mixture was quenched with aqueous HCl (2 M, 40 ml) and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 ml) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, EtOAc) to provide **10a** (2.13 g, 93%): colorless crystals; mp 94-97 ºC (EtOAc/hexanes); R_f 0.43 (EtOAc); FTIR (film) ν_{max} 3172, 1678, 1650, 1614, 1508, 1293, 1207, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.64 (br s, 1 H, NH), 7.11 (d, J = 8.2 Hz, 2 H), 6.45-6.43 (m, 3 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.69 (s, 3 H), 3.40 (br s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (C-1), 160.9, 158.3, 131.9, 115.2, 105.1, 99.2, 64.7, 55.9, 55.8, 35.8 (C-2); HRMS-ESI calcd for $C_{11}H_{15}NO_4Na$ $[M+Na]^+$ 248.0899, found 248.0910. Anal Calcd for $C_{11}H_{15}NO_4$; C, 58.66; H, 6.71; N, 6.22. Found: C, 58.65; H 6.53; N, 6.31.

***O*-Methyl 3-(2,4-dimethoxyphenyl)propiohydroxamate (10c) (Entry 3, Table S1).** Following Coupling Method A, **35c** (4.00 g, 19.04 mmol) was coupled with $MeONH_2$•HCl to provide **10c** (4.35 g, 95%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 64-66 °C (EtOAc/hexanes); R_f 0.46 (EtOAc); FTIR (film) υ_{max} 3188 (br), 1662, 1614, 1507, 1206, 1155, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.97 (d, J = 8.2 Hz, 1 H), 6.46 (d, J = 2.2 Hz, 1 H), 6.38 (dd, J = 2.2, 8.2 Hz, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.56 (s, 3 H), 2.80 (t, J = 7.5 Hz, 2 H), 2.25 (t, J = 7.5 Hz, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.2, 162.3, 160.7, 132.3, 122.8, 106.1, 100.2, 65.2, 56.7 (2 C), 35.2, 28.0; HRMS-ESI calcd for $C_{12}H_{17}NO_4Na$ $[M+Na]^+$ 262.1055, found 262.1053.

***O*-Methyl 4-(2,4-dimethoxyphenyl)butyrohydroxamate (10e) (Entry 5, Table S1).** Following Coupling Method A, **34e** (2.00 g, 7.87 mmol) was coupled with $MeONH_2$•HCl to provide **10e** (2.05 g, 92%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 64-66 °C (EtOAc/hexanes); R_f 0.51 (EtOAc); FTIR (film) υ_{max} 3172 (br), 1655, 1614, 1506, 1288, 1206, 1153, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.96 (d, J = 8.2 Hz, 1 H), 6.46 (d, J = 2.3 Hz, 1 H), 6.40 (dd, J = 2.3, 8.2 Hz, 1 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.64 (s, 3 H), 2.53 (t, J = 7.4 Hz, 2 H), 2.02 (t, J = 7.4 Hz, 2

H), 1.84-1.76 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.3, 159.5, 158.3, 129.8, 121.5, 103.8, 97.8, 62.9, 54.3 (2 C), 32.0, 28.6, 25.7; HRMS-ESI calcd for $C_{13}H_{19}NO_4Na$ $[M+Na]^+$ 276.1212, found 276.1210.

***O*-Methyl (±)-3-(2,4-dimethoxyphenyl)-2-methylpropiohydroxamate (10g) (Entry 7, Table S1).** Following Coupling Method A, **34g** (1.92 g, 8.56 mmol) was coupled with $MeONH_2$•HCl to provide **10g** (2.16 g, 100%), after flash chromatography (SiO_2, EtOAc/hexanes, 1:1): white crystals; mp 69-72 °C (EtOAc/hexanes); R_f 0.20 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3201 (br), 1658, 1508, 1208, 1158, 1039, 832 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (br s, 1 H), 7.00 (d, *J* = 8.2 Hz, 1 H), 6.42-6.36 (m, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.58 (s, 3 H), 2.80-2.72 (m, 1 H,), 2.68 (dd, *J* = 6.3, 13.3 Hz, 1 H), 2.39-2.32 (m, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 160.0, 158.6, 131.8, 120.4, 104.2, 98.9, 64.6, 55.74, 55.67, 38.7, 34.8, 17.6; HRMS-CI calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$ 254.1387, found 254.1369. Anal. Calcd for $C_{13}H_{19}NO_4$; C, 61.64; H, 7.56; N, 5.53. Found: C, 61.33; H, 7.41; N, 5.53.

***O*-Methyl (±)-2-(2,4-dimethoxybenzyl)-3,3-dimethylbutyriohydroxamate (10h) (Entry 8, Table S1).** Following Coupling Method A, **35h** (457 mg, 1.72 mmol) was coupled with $MeONH_2$•HCl to provide **10h** (438 mg, 85%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 138-140 ºC (EtOAc/hexanes); R_f 0.30 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3168 (br), 1651, 1506, 1463, 1288, 1209, 1155, 1041 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (br s, 1 H, NH), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 6.35 (dd, *J* = 2.4, 8.2 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.50 (s, 3 H), 2.95 (appt d, *J* = 12.9 Hz, 1 H), 2.72 (appt t, *J* = 12.3 Hz, 1 H), 1.87 (appt d, *J* = 10.7 Hz, 1 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 159.5, 158.1, 131.3, 120.7, 103.7, 98.5, 64.1, 55.3, 55.2, 54.3, 33.3, 28.1, 27.8; HRMS-ESI calcd for $C_{16}H_{25}NO_4Na$ $[M+Na]^+$ 318.1681, found 318.1667.

***O*-Methyl (±)-2-(2,4-dimethoxybenzyl)-2-benzylpropiohydroxamate (10i) (Entry 9, Table S1).** Following Coulpling Method A, **35i** (362 mg, 1.21 mmol) was coupled with $MeONH_2$•HCl to provide **10i** (338 mg, 85%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:1): colorless oil; R_f 0.60 (EtOAc); FTIR (film) υ_{max} 3159 (br), 1673, 1613, 1587, 1505, 1459, 1288, 1206, 1160, 1037 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.26-7.22 (m, 2 H), 7.18-7.15 (m, 3 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.41 (d, *J* = 2.1 Hz, 1 H), 6.32 (dd, *J* = 2.1, 8.2 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.36 (s, 3 H), 3.00 (dd, *J* = 10.1,

13.3 Hz), 2.88-2.81 (m, 2 H), 2.76 (dd, J = 5.0, 13.3 Hz, 1 H), 2.52-2.43 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 159.7, 158.2, 139.6, 131.4, 129.0 (2 C), 128.4 (2 C), 126.3, 119.7, 103.8, 98.5, 64.0, 55.3 (2 C), 46.7, 38.4, 33.1; HRMS-CI calcd for $C_{19}H_{24}NO_4$ $[M+H]^+$ 330.1705, found 330.1714.

***O*-Methyl (±)-3-(2,4-dimethoxyphenyl)-2-phenylpropiohydroxamate (10j) (Entry 10, Table S1).** Following Coupling Method A, **35j** (1.43 g, 4.99 mmol) was coupled with $MeONH_2$·HCl to provide **10j** (1.34 g, 85%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 134-135 ºC (EtOAc/hexanes); R_f 0.39 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3172 (br), 1655, 1614, 1505, 1458, 1288, 1207, 1155, 1036 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.32-7.12 (m, 5 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.44 (d, *J* = 2.4 Hz, 1 H), 6.30 (dd, *J* = 2.4, 8.2 Hz, 1 H), 3.77 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.55 (dd, *J* = 5.7, 9.5 Hz, 1 H), 3.42 (s, 3 H, OCH_3), 3.13 (dd, *J* = 9.5, 13.2 Hz, 1 H), 2.95 (dd, *J* = 5.7, 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.1, 159.9, 158.4, 139.7, 130.8, 128.0, 127.4, 126.7, 119.1, 103.5, 97.8, 62.7, 54.3 (2 C), 49.0, 33.4; HRMS-ESI calcd for $C_{18}H_{21}NO_4Na$ $[M+Na]^+$ 338.1368, found 338.1367.

(±)-*N*-[2-(2,4-Dimethoxyphenyl)-1-methoxycarbamoylethyl]-benzamide (10l) (Entry 12, Table S1). Following Coupling Method A, **35l** (1.57 g, 4.77 mmol) was coupled with $MeONH_2$•HCl to provide **10l** (1.52 g, 89%), after purification by flash chromatography (SiO_2, EtOAc): yellow crystals; mp 172-176 ºC (EtOAc/hexanes); R_f 0.39 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3218 (br), 1677, 1641, 1537, 1511, 1459, 1292, 1209, 1157, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (br s, 1 H, NH), 7.68 (d, *J* = 7.6 Hz, 2 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.31 (d, *J* = 6.0 Hz, 1 H, NH), 7.11 (d, *J* = 8.9 Hz, 1 H), 6.41 (m, 2 H), 4.67-4.65 (m, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.69 (s, 3 H), 3.29 (dd, *J* = 9.1, 13.8 Hz, 1 H), 3.03 (dd, *J* = 5.9, 13.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 167.8, 160.1, 158.3, 133.4, 131.9, 131.8, 128.6, 127.0, 117.2, 104.6, 98.7, 64.2, 55.5, 55.3, 52.7, 31.2; HRMS-ESI calcd for $C_{19}H_{22}N_2O_5Na$ $[M+Na]^+$ 381.1426, found 381.1428.

***O*-Methyl (±)-3-(2,4-dimethoxyphenyl)-3-methylpropiohydroxamate (10m) (Entry 13, Table S1).** Following Coupling Method A, **35m** (383 mg, 1.71 mmol) was coupled with $MeONH_2$•HCl to provide **10m** (430 mg, 99%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:1): white crystals; mp 110-112 °C (EtOAc/hexanes); R_f 0.15 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 3181 (br), 1666, 1506, 1208, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCL_3$) δ 8.64 (br s, 1 H, NH), 7.04 (d, *J* = 8.0 Hz, 1 H), 6.43-6.41 (m, 2 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.61 (s, 3 H), 3.54-3.52 (m, 1 H), 2.47-2.42 (m ,1 H),

2.30-2.25(m, 1 H), 1.25 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 159.3, 157.8, 127.7, 125.7, 104.2, 98.7, 64.1, 55.3 (2 C), 40.7, 30.2, 20.2; HRMS-ESI calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$ 253.13086, found 253.13078.

***O*-Methyl 2-(2,4-dimethoxybenzyl)benzohydroxamate (10n) (Entry 14, Table S1).** Following Coupling Method A, **35n** (1.09 g, 4.00 mmol) was coupled with $MeONH_2$•HCl to provide **10n** (1.17 g, 97%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:5): white powder; mp 144-145 °C (EtOAc/hexanes); R_f 0.68 (EtOAc); FTIR (film) υ_{max} 3179 (br), 1653, 1613, 1506, 1291, 1208, 1157, 1036, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (br s, 1 H, NH), 7.40 (d, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.7 Hz, 1 H), 7.22-7.15 (m, 2 H), 7.00 (d, J = 8.1 Hz, 1 H), 6.44-6.42 (m, 2 H), 4.04 (s, 2 H), 3.82 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 159.7, 158.0, 139.3, 132.7, 131.0, 130.5, 130.4, 127.9, 126.0 (2 C), 121.3, 104.1, 98.8, 64.4, 55.4, 32.5; HRMS-ESI calcd for $C_{17}H_{19}NO_4Na$ $[M+Na]^+$ 324.1212, found 324.1221.

Coupling Method B (Preparation of *O*-Benzyl Hydroxamates via EDC Coupling). *O*-Benzyl 2-(2,4-dimethoxyphenyl)acetohydroxamate (10b) (Entry 2, Table S1). To a stirred solution of **35b** (2.00 g, 10.19 mmol) and Et_3N (1.50 ml, 10.70 mmol) in CH_2Cl_2 (20 ml) was added, EDC•HCl (2.15 g, 11.21 mmol) and $BnONH_2$•HCl (1.87 g, 11.72 mmol). After stirring for 16 h, the reaction was quenched with aqueous HCl (2 M, 40 ml) and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, EtOAc) to provide **10b** (2.91 g, 95%): white solid; mp 92-94 °C (EtOAc/hexanes) R_f 0.60 (EtOAc); FTIR (film) υ_{max} 3195 (br), 1662, 1614, 1587, 1507, 1208, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1 H, NH), 7.33-7.26 (m, 5 H), 7.12 (d, J = 8.2 Hz, 1 H), 6.48 (d, J = 8.2 Hz, 1 H), 6.37 (s, 1H), 4.83 (s, 2 H), 3.80 (s, 3 H), 3.62 (s, 3 H), 3.39 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 160.4, 157.5, 135.3, 131.5 (2 C), 129.2, 128.5, 114.8, 104.6, 98.8, 55.4, 55.3, 77.8, 35.6; HRMS-ESI calcd for $C_{17}H_{19}NO_4Na$ $[M+Na]^+$ 324.1212, found 324.1217.

***O*-Benzyl 3-(2,4-dimethoxyphenyl)propiohydroxamate (10d) (Entry 4, Table S1).** Following Coupling Method B, **35d** (936 mg, 4.45 mmol) was coupled with $BnONH_2$•HCl to provide **10d** (1.36 g, 97%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 77-79 °C (EtOAc/hexanes); R_f 0.68 (EtOAc); FTIR (film) υ_{max} 3187 (br), 1654, 1614, 1505, 1206, 1038 cm^{-1}; ^{1}H

NMR (400 MHz, CD_3OD) δ 7.35-7.22 (m, 5 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 6.47 (d, *J* = 2.3 Hz, 1 H), 6.39 (dd, *J* = 2.3, 8.2 Hz, 1 H), 4.67 (s, 2 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 2.79 (t, *J* = 7.4 Hz, 2 H), 2.23 (t, *J* = 7.4 Hz, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.0, 159.9, 158.3, 135.5, 130.1, 129.0, 128.1, 128.0, 120.4, 103.7, 97.9, 77.6, 54.3 (2 C), 32.7, 25.6; HRMS-ESI calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$ 316.1549, found 316.1542.

***O*-Benzyl 4-(2,4-dimethoxyphenyl)butyrohydroxamate (10f) (Entry 6, Table S1).** Following Coupling Method B, **35f** (1.53 g, 6.82 mmol) was coupled with $BnONH_2$•HCl to provide **10f** (1.98 g, 88%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 72-74 °C (EtOAc/hexanes); R_f 0.64 (EtOAc); FTIR (film) υ_{max} 3197 (br), 1656, 1619, 1512, 1288, 1207, 1159, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.39-7.30 (m, 5 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.44 (d, *J* = 2.3 Hz, 1 H), 6.37 (dd, *J* = 2.3, 8.2 Hz, 1 H), 4.80 (s, 2 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 2.48 (t, *J* = 7.4 Hz, 2 H), 2.00 (t, *J* = 7.4 Hz, 2 H), 1.81-1.74 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.5, 159.5, 158.3, 135.6, 129.8, 128.9, 128.2, 128.1, 121.6, 103.8, 97.9, 77.5, 54.3 (2 C), 32.0, 28.6, 25.7; HRMS-ESI calcd for $C_{19}H_{23}NO_4Na$ $[M+Na]^+$ 352.1525, found 352.1536.

Coupling Method C (Preparation of *O*-Methyl Hydroxamates via Intermediacy of Mixed Anhydride). *O*-Methyl 2(*S*)-3-(2,4-dimethoxyphenyl)-2-triisopropylsilanyloxypropiohydroxamate (10k) (Entry 11, Table S1). To a solution of **35k**[4] (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 rt 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 **10k** (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}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (br s, 1 H), 7.05 (d, *J* = 8.1 Hz, 1 H), 6.41-6.38 (m, 2 H, H-5'), 4.55 (t, *J* = 5.9 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.05 (dd, *J* = 13.7, 5.8 Hz, 1 H), 2.99 (dd, *J* = 13.7, 6.1 Hz, 1 H), 1.05-1.03 (m,

21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 160.4, 159.1, 132.6, 117.3, 104.1, 98.6, 74.1, 64.7, 55.8, 55.4, 36.6, 18.3, 12.5; HRMS-FAB calcd for $C_{21}H_{38}NO_5Si$ $[M+H]^+$ 412.2519, found 412.2510.

8. Synthesis of Spirodienones 12

(±)-1-Benzyloxy-5-methoxy-1-azaspiro[3.5]nona-5,8-diene-2,7-dione (12b) (Entry 3, Table 1). Following general procedure A, cyclization of **10b** (100 mg, 0.33 mmol) and purification of the crude product by flash chromatography (SiO_2, EtOAc/hexanes, 1:3) afforded **12b** (82 mg, 86%): white crystals; mp 101-102 ºC (EtOAc/hexanes); R_f 0.68 (EtOAc); FTIR (film) υ_{max} 1786, 1662, 1600, 1222, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5 H), 6.29 (d, J = 9.9 Hz, 1 H), 6.01 (d, J = 9.9 Hz, 1 H), 5.58 (s, 1 H), 4.83 (s, 2 H), 3.72 (s, 3 H), 3.07 (d, J = 13.8 Hz, 1 H), 2.73 (d, J = 13.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 169.2, 164.8, 141.6, 135.4, 131.1, 129.5, 129.4 (2 C), 129.1, 105.4, 79.4, 61.4, 56.5, 43.8; HRMS-ESI calcd for $C_{16}H_{15}NO_4Na$ $[M+Na]^+$ 308.0899, found 308.0892. Anal. Calcd for $C_{16}H_{15}NO_4$; C, 67.36; H, 5.30; N, 4.91. Found: C, 67.23; H, 5.44; N, 4.86.

(±)-1,5-Dimethoxy-1-azaspiro[3.5]nona-5,8-diene-2,7-dione (12a) and (±)-1,5,9-Trimethoxy-1-azaspiro[3.5]non-5-ene-2,7-dione (20) (Entry 1, Table 1 and Footnote 31). Following general procedure B, cyclization of **10a** (300 mg, 1.33 mmol) and purification of the crude product by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) afforded **12a** (148 mg, 53%) and **20** (73 mg, 26%). Analytical data for **20**: colorless oil; R_f 0.25 (EtOAc); FTIR (film) υ_{max} 1780, 1660, 1615, 1224 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 1 H), 3.87-3.84 (m, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.48 (s, 3 H), 3.03, (d, J = 13.0 Hz, 1 H), 2.81-2.76 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 170.3, 163.4, 106.3, 77.7, 66.2, 65.3, 57.8, 57.3, 39.8, 39.5; HRMS-ESI Calcd for $C_{11}H_{16}NO_5$ $[M+H]^+$ 242.1028, found 242.1024.

(±)-1-Benzyloxy-6-methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (12d) (Entry 5, Table 1). Following general procedure B, cyclization of **10d** (50 mg, 0.16 mmol) and purification of the crude product by flash chromatography (SiO_2, EtOAc) afforded **12d** (46 mg, 98%): white crystals; mp 142-143 °C (EtOAc/hexanes); R_f 0.39 (EtOAc); FTIR (film) υ_{max} 1723, 1662, 1598, 1367, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 5 H), 6.17 (d, J = 9.9 Hz, 1 H), 6.09 (d, J = 9.9 Hz, 1 H), 5.56 (s, 1 H), 4.93 (s, 2 H), 3.73 (s, 3 H), 2.67-2.57 (m, 1 H), 2.49-2.42 (m, 1 H), 2.22-2.16 (m, 1 H), 2.10-2.02 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 173.7, 172.9, 144.4, 134.8, 129.9, 129.8 (2 C), 128.9, 128.4 (2 C), 103.0, 78.4, 62.9, 56.2, 27.4, 26.3; HRMS-ESI Calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$ 300.1236, found 300.1240. Anal. Calcd for $C_{17}H_{17}NO_4$; C, 68.21; H, 5.89; N, 4.68. Found: C, 68.11; H, 4.89; N, 4.73.

(±)-1,7-Dimethoxy-1-azaspiro[5.5]undeca-7,10-diene-2,9-dione (12e) (Entry 6, Table 1). Following general procedure B, cyclization of **10e** (491 mg, 1.94 mmol) and purification of the crude

product by flash chromatography (SiO_2, EtOAc) afforded **12e** (422 mg, 92%): white crystals; mp 142-143 °C (EtOAc/hexanes); R_f 0.20 (EtOAc); FTIR (film) υ_{max} 1702, 1598, 1364, 1223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 9.9 Hz, 1 H), 6.19 (dd, *J* = 1.7, 9.9 Hz, 1 H), 5.56 (d, *J* = 1.7 Hz, 1 H), 3.75 (s, 3 H), 3.64 (s, 3 H), 2.54-2.51 (m, 2 H), 2.16-2.11 (m, 1 H), 2.03-1.98 (m, 2 H), 1.85-1.79 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 173.9, 170.1, 145.8, 129.1, 103.4, 65.7, 64.1, 56.5, 35.7, 33.6, 18.3; HRMS-ESI calcd for $C_{12}H_{15}NO_4Na$ $[M+Na]^+$ 260.0899, found 260.0889.

(±)-1-Benzyloxy-7-methoxy-1-azaspiro[5.5]undeca-7,10-diene-2,9-dione (12f) (Entry 7, Table 1). Following general procedure B, cyclization of **10f** (260 mg, 0.79 mmol) and purification of the crude product by flash chromatography (SiO_2, EtOAc) afforded **12f** (206 mg, 83%): white crystals; mp 175-177 °C (EtOAc/hexanes); R_f 0.44 (EtOAc); FTIR (film) υ_{max} 1664, 1630, 1598, 1365, 1222 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.21 (m, 5 H), 6.51 (d, *J* = 9.9 Hz, 1 H), 6.12 (dd, *J* = 1.6, 9.9 Hz, 1 H), 5.56 (d, *J* = 1.6 Hz, 1 H), 4.84 (s, 2 H), 3.73 (s, 3 H), 2.58 (t, *J* = 6.3 Hz, 2 H), 2.15-2.11 (m, 1 H), 2.04-2.01 (m, 2 H), 1.84-1.81 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.0, 174.3, 170.9, 146.2, 135.1, 129.7 (2 C), 129.1, 128.9, 128.8 (2 C), 103.3, 78.1, 65.8, 56.7, 35.8, 33.6, 18.3; HRMS-ESI calcd for $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ 336.1236, found 336.1230. Anal. Calcd for $C_{18}H_{19}NO_4$; C, 68.99; H, 6.11; N, 4.47. Found: C, 68.95; H, 6.19; N, 4.49.

(3*S,5*R**)-1,6-Dimethoxy-3-methyl-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (*anti*-12 g) (Entry 8, Table 1).** Following general procedure B, cyclization of **10g** (100 mg, 0.39 mmol) gave a chromatographically inseparable mixture of spirodienone diastereomers [*anti*-**12g**/*syn*-**12g**, 92:8; diastereoisomeric ratio determined by integration of the peaks at δ_H (major diastereomer) = 5.61 (d, *J* = 1.7 Hz, C(OCH_3)C*H*CO) and δ_H (minor) = 5.68 (d, *J* = 1.6 Hz, C(OCH_3)C*H*CO) in the crude ^1H NMR] which upon recrystallization (EtOAc/hexanes) yielded *anti*-**12g** (80 mg, 85%): white crystals; mp 146-148 °C (EtOAc/hexanes); R_f 0.30 (EtOAc); FTIR (film) υ_{max} 1717, 1662, 1606, 1457, 1227 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (d, *J* = 9.9 Hz, 1 H), 6.30 (dd, *J* = 1.7, 9.9 Hz, 1 H), 5.61 (d, *J* = 1.7 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.84-2.74 (m, 1 H), 2.42 (dd, *J* = 9.5, 13.3 Hz, 1 H), 1.7 5 (dd, *J* = 9.2, 13.3 Hz, 1 H), 1.29 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 175.9, 172.9, 144.9, 130.4, 103.0, 64.7, 62.0, 56.2, 36.7, 32.5, 17.3; HRMS-ESI calcd for $C_{12}H_{16}NO_4$ $[M+H]^+$ 238.1079, found 238.1080. Anal. Calcd for $C_{12}H_{15}NO_4$; C, 60.75; H, 6.37; N, 5.90. Found: C, 60.47; H, 6.25; N, 5.87.

(3*R,5*R**)-3-*tert*-Butyl-1,6-dimethoxy-1-aza-spiro[4.5]deca-6,9-diene-2,8-dione (*anti*-12h) (Entry 9, Table 1).** Following general procedure B, cyclization of **10h** (200 mg, 0.68 mmol) gave a mixture of spirodienone diastereomers [*anti*-**12h**/*syn*-**12h**, 87:13; diastereoisomeric ratio determined by integration of the peaks at δ_H (major diastereomer) = 5.56 (s, 1 H, C*H*COCHCH) and δ_H (minor) = 5.70 (s, 1 H, C(OCH$_3$)C*H*CO) in the crude ^{1}H NMR], which was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) and recrystallized (EtOAc/hexanes) to provide *anti*-**12h** (155 mg, 82%): white needles; mp 150-152 °C (EtOAc/hexanes); R_f 0.30 (EtOAc); FTIR (film) υ_{max} 1722, 1666, 1603, 1365, 1224, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, *J* = 9.9 Hz, 1 H), 6.29 (dd, *J* = 1.5, 9.9 Hz, 1 H), 5.59 (d, *J* = 1.5 Hz, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 2.53 (t, *J* = 9.6 Hz, 1 H), 2.15 (dd, *J* = 9.8, 13.5 Hz, 1 H), 1.90 (dd, *J* = 9.3, 13.5 Hz, 1 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 174.7, 173.3, 145.0, 130.3, 102.9, 64.7, 61.1, 56.2, 46.6, 32.7, 30.9, 26.8; HRMS-ESI calcd for $C_{15}H_{22}NO_4$ $[M+H]^+$ 280.1549, found 280.1556.

(3*S,5*RS**)-3-Benzyl-1,6-dimethoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (*anti*/*syn*-12i) (Entry 10, Table 1).** Following general procedure B, cyclization of **12i** (100 mg, 0.30 mmol) gave a mixture of spirodienone diastereomers [*anti*-**12i**/*syn*-**12i** 92:8; diastereoisomeric ratio determined by integration of the peaks at δ_H (major diastereomer) = 5.53 (s, 1 H, C(OCH$_3$)C*H*CO) and δ_H (minor) = 5.63 (s, 1 H, C(OCH$_3$)C*H*CO) in the crude ^{1}H NMR] which was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) to provide a 92:8 mixture of *anti*-**12i** and *syn*-**12i** (93 mg, 98%): colorless oil; R_f 0.17 (EtOAc/hexanes, 1:1); FTIR (film) υ_{max} 1720, 1664, 1631, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (major diastereomer) 7.31-7.16 (m, 5 H), 6.23-6.17 (m, 2 H), 5.55 (s, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.18 (dd, *J* = 4.1, 13.8 Hz, 1 H), 3.06-3.00 (m, 1 H), 2.84 (dd, *J* = 8.6, 13.8 Hz, 1 H), 2.17 (dd, *J* = 9.7, 13.5 Hz, 1 H), 1.84 (dd, *J* = 8.6, 13.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major diastereomer) 186.7, 174.6, 173.1, 145.0, 138.0, 130.6, 129.6 (2 C), 129.0 (2 C), 127.3, 103.4, 65.1, 62.3, 56.6, 39.4, 37.7, 33.7; HRMS-ESI calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1392, found 314.1397.

(3*R,5*RS**)-1,6-Dimethoxy-3-phenyl-1-aza-spiro[4.5]deca-6,9-diene-2,8-dione (*anti*/*syn*-12j) (Entry 11, Table 1).** Following general procedure B, cyclization of **10j** (200 mg, 0.63 mmol) gave a mixture of spirodienone diastereomers [*anti*-**12j**/*syn*-**12j**, 91:9; diastereoisomeric ratio determined by integration of the peaks at δ_H (major diastereomer) = 5.66 (d, *J* = 1.6 Hz, 1 H, C(OCH$_3$)C*H*CO) and δ_H (minor) = 5.74 (d, *J* = 1.6 Hz, 1 H, C(OCH$_3$)C*H*CO) in the crude ^{1}H NMR], which was purified by flash

chromatography (SiO_2, EtOAc/hexanes, 1:1) to provide a 93:7 mixture of *anti*-**12j** and *syn*-**12j** (162 mg, 85%): pale yellow solid; R_f 0.55 (EtOAc); mp 129-130 ºC; FTIR (film) υ_{max} 1726, 1664, 1603, 1367, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (major diastereomer) 7.39-7.26 (m, 5 H), 6.67 (d, *J* = 9.9 Hz, 1 H), 6.34 (dd, *J* = 1.6, 9.9 Hz, 1 H), 5.66 (d, *J* = 1.6 Hz, 1 H), 3.67 (t, *J* = 9.7 Hz, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 2.68 (dd, *J* = 10.0, 13.5 Hz, 1 H), 2.18 (dd, *J* = 9.4, 13.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major diastereomer) 186.2, 173.7, 172.6, 144.3, 138.6, 130.7, 129.1 (2 C), 127.7 (3 C), 103.3, 64.9, 61.9, 56.3, 43.7, 37.3; HRMS-ESI calcd for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$ 322.1055, found 322.1065.

(3*S*,5*RS*)-1,6-Dimethoxy-3-(triisopropylsilanyloxy)-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (*anti*/*syn*-12k) (Entry 12, Table 1). Following general procedure B, cyclization of **10k** (878 mg, 2.00 mmol) gave a mixture of spirodienone diastereomers [*anti*-**12k**/*syn*-**12k**, 90:10; diastereoisomeric ratio assigned by integration of the peaks at δ_H (major diastereomer) = 5.64 (d, *J* = 1.6 Hz, 1 H, $C(OCH_3)CHCO$) and δ_H (minor) = 5.69 (d, *J* = 1.6 Hz, 1 H, $C(OCH_3)CHCO$) in the ^1H NMR spectrum], which was purified by flash chromatography (SiO_2, EtOAc/hexanes, 3:1) to provide a 90:10 mixture of *anti*-**12k** and *syn*-**12k** (672 mg, 99%): 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}; ^1H NMR (500 MHz, $CDCl_3$) δ (major diastereomer) 6.68 (d, *J* = 9.9 Hz, 1 H), 6.30 (dd, *J* = 9.9, 1.6 Hz, 1 H), 5.64 (d, *J* = 1.6 Hz, 1 H), 4.59 (dd, *J* = 8.4, 6.6 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 2.58 (dd, *J* = 13.2, 8.4 Hz, 1 H), 2.03 (dd, *J* = 13.2, 6.6 Hz, 1 H), 1.11-1.06 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major diastereomer) 186.6, 172.0, 171.0, 144.7, 130.7, 104.2, 67.1 , 65.0 , 61.6, 56.6, 39.6, 18.2, 12.5; HRMS-ESI calcd for $C_{20}H_{34}NO_5Si$ $[M+H]^+$ 396.2206, found 396.2193.

1,6-Dimethoxy-4-methyl-1-aza-spiro[4.5]deca-6,9-diene-2,8-dione (*anti*-12m) (Entry 14, Table 1) Following general procedure B, cyclization of **10m** (101 mg, 0.40 mmol) gave a mixture of spirodienone diastereomers [*anti*-**12m**/*syn*-**12m**, 80:20; diastereoisomeric ratio determined by integration of the peaks at δ_H (major) = 5.72 (d, *J* = 1.6 Hz, $CHCOCHCH$) and δ_H (minor) = 5.70 (*J* = 1.6 Hz, $CHCOCHCH$) in the crude ^1H NMR] which were separated by radial chromatography over silica gel (2 mm, EtOAc/hexanes, 1:1) to provide *syn*-**12m** (17 mg, 18%) and *anti*-**12m** (68 mg, 72%): white crystals; mp 134-136 °C (EtOAc/hexanes); R_f 0.37 (EtOAc); FTIR (film) υ_{max} 1725, 1665, 1631, 1601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 10.1 Hz, 1 H), 6.38 (dd, *J* = 1.6, 10.1 Hz, 1 H), 5.72 (d, *J* = 1.6 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 2.81-2.70 (m, 2 H), 2.17-2.11 (m, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 186.0, 171.9, 171.2, 141.6, 131.0, 104.8, 67.1, 64.2, 56.0, 34.9, 34.0, 15.8; HRMS-CI calcd for $C_{12}H_{16}NO_4$ $[M+H]^+$ 238.1074, found 238.1067. Anal. Calcd for $C_{12}H_{15}NO_4$; C, 60.75; H, 6.37; N, 5.90. Found: C, 60.83; H, 6.56; N, 5.87.

(±)-1-Oxo-2-methoxy-3,4-dihydro-2*H*-isoquinoline-3-spiro-1′-(cyclohexa-2′-methoxy-2′,5′dien-4′-one (12n) (Entry 15, Table 1). Following general procedure B, cyclization of **10n** (150 mg, 0.50 mmol) and purification of the crude product by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) afforded **12n** (134 mg, 94%): yellow solid; mp 130-131 °C (EtOAc/hexanes); R_f 0.67 (EtOAc); FTIR (film) υ_{max} 1684, 1668, 1603, 1459, 1365, 1226, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.5 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 7.5 Hz, 1 H), 7.13 (d, *J* = 7.5 Hz, 1 H), 6.72 (d, *J* = 10.0 Hz, 1 H), 6.26 (dd, *J* = 1.2, 10.0 Hz, 1 H), 5.65 (d, *J* = 1.2 Hz, 1 H), 3.88 (s, 3 H), 3.74 (s, 3 H), 3.68 (d, *J* = 16.5 Hz, 1 H), 3.20 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 172.0, 165.3, 143.7, 134.0, 133.0, 129.6, 128.1, 127.5, 127.4, 127.2, 103.2, 65.2, 64.2, 56.0, 38.8; HRMS-ESI Calcd for $C_{16}H_{15}NO_4Na$ $[M+Na]^+$ 308.0899, found 308.0908.

(3*S,5*R**)-*N*-(1,6-Dimethoxy-2,8-dioxo-1-aza-spiro[4.5]deca-6,9-dien-3-yl)-benzamide (*anti*-12l) (Entry 13, Table 1).** To a suspension of phenyliodine(III) bis(trifluoroacetate) (PIFA) (363 mg, 0.84 mmol, 1.2 equiv) in MeOH (3 mL), under an atmosphere of N_2 at –78 °C, was added a cold (-78 °C) solution of **10l** (252 mg, 0.70 mmol) in CH_2Cl_2 (6 mL) and MeOH (3 mL) via cannula. The reaction mixture was then allowed to warm to –55 °C (internal temperature) over 15 min whereupon H_2O (3 mL) was added and the cooling bath removed. After stirring for 10 min, the biphasic mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated under reduced pressure [*anti*-**12l**/*syn*-**12l**, 91:9; diastereoisomeric ratio determined by integration of the peaks at δ_H (major) = 5.64 (d, *J* = 1.4 Hz, C*H*COCHCH) and δ_H (minor) = 5.69 (d, *J* = 1.2 Hz, C*H*COCHCH) in the crude ^1H NMR]. Purification of the residue by flash chromatography over silica gel (EtOAc) then afforded a 91:9 mixture of *anti*-**12l** and *syn*-**12l** (238 mg, 99%): white solid; mp 198-200 °C (EtOAc/hexanes); R_f 0.30 (EtOAc); FTIR (film) υ_{max} 3340, 1728, 1665, 1604, 1533, 1369, 1225, 1001, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (m, 2 H), 7.60 (d, *J* = 6.4 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 1 H), 7.35 (t, *J* = 7.7 Hz, 2 H), 6.73 (d, *J* = 9.9 Hz, 1 H), 6.27 (dd, *J* = 1.4, 9.9 Hz, 1 H), 5.64 (d, *J* = 1.4 Hz, 1 H), 4.82-4.76 (m, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 2.72 (dd, *J* = 9.5, 13.2 Hz, 1 H), 2.31

(dd, J = 9.0, 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 171.8, 169.7, 167.6, 143.6, 132.8, 132.0, 130.5, 128.5 (2 C), 127.1 (2 C), 103.4, 64.6, 61.4, 56.3, 48.0, 35.9; HRMS-ESI calcd for $C_{18}H_{18}N_2O_5Na$ $[M+Na]^+$ 365.1113, found 365.1098.

9. Ozonolysis of Spirodienones 12

Methyl (±)-2-Hydroxymethyl-1-benzyloxy-4-oxo-azetidine-2-carboxylate (30b) (Entry 2, Table 2). Following general procedure C, ozonolysis of **12b** (50 mg, 0.18 mmol) for 25 min and sequential reduction with thiourea and $NaBH(OAc)_3$ gave **30b** (38 mg, 82%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:3): colorless oil; R_f 0.76 (EtOAc); FTIR (film) ν_{max} 3457 (br), 1780, 1747, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.33 (m, 5 H), 5.04 (s, 2 H), 4.03 (d, J = 12.3 Hz, 1 H), 3.93 (d, J = 12.3 Hz, 1 H), 3.76 (s, 3 H), 2.90 (d, J = 13.8 Hz, 1 H) 2.84 (d, J = 13.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 165.8, 135.8, 129.3 (2 C), 128.8, 128.5 (2 C), 78.8, 68.8, 59.4, 52.3, 19.9; HRMS-ESI calcd for $C_{13}H_{15}NO_5Na$ $[M+Na]^+$ 288.0848, found 288.0835.

Methyl (±)-2-Hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30c) (Entry 3, Table 2). Following general procedure C, ozonolysis of **12c** (500 mg, 2.24 mmol) for 1 h and sequential reduction with thiourea and $NaBH(OAc)_3$ gave **30c** (369 mg, 81%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:1).

Methyl (±)-2-Hydroxymethyl-1-benzyloxy-5-oxo-pyrrolidine-2-carboxylate (30d) (Entry 4, Table 2). Following general procedure C, ozonolysis of **12d** (50 mg, 0.15 mmol) for 1 h and sequential reduction with thiourea and $NaBH(OAc)_3$ gave **30d** (41 mg, 98%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 111-113 °C (EtOAc/hexanes); R_f 0.51 (EtOAc); FTIR (film) υ_{max} 3357 (br), 1750, 1688, 1234, 1096, 1058, 747 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (m, 5 H), 5.10 (s, 2 H), 4.00 (d, J = 11.8 Hz, 1 H), 3.85 (d, J = 11.8 Hz, 1 H), 3.74 (s, 3 H), 2.43-2.37 (m, 2 H), 2.36-2.29 (m, 1 H), 2.18-2.13 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.1, 171.4, 135.0, 129.1 (2 C), 128.4, 128.0 (2 C), 77.7, 70.3, 60.4, 51.8, 26.0, 22.9; HRMS-ESI calcd for $C_{14}H_{17}NO_5Na$ $[M]^+$ 302.1004, found 302.0992.

Methyl (2*S,4*S**)-2-Hydroxymethyl-1-methoxy-4-methyl-5-oxo-pyrrolidine-2-carboxylate (30g) (Entry 7, Table 2).** Following general procedure C, ozonolysis of **12g** (100 mg, 0.42 mmol) for 1 h and sequential reduction with thiourea and $NaBH(OAc)_3$, gave **30g** (48 mg, 53%), after purification by

flash chromatography (SiO_2, EtOAc): white solid; mp 66-64 °C (EtOAc/hexanes); R_f 0.56 (EtOAc); IR (film) υ_{max} 3429 (br), 1739, 1703, 1444, 1284, 1213, 1063, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (d, *J* = 11.9 Hz, 1 H), 3.95 (d, *J* = 11.9 Hz, 1 H), 3.91 (s, 3 H), 3.80 (s, 3 H), 2.65-2.55 (m, 1 H), 2.34 (dd, *J* = 9.3, 13.3 Hz, 1 H), 2.29 (br s, 1 H), 1.83 (dd, *J* = 9.3, 13.3 Hz, 1 H), 1.25 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 172.2, 68.0, 64.1, 63.8, 52.9, 32.6, 32.0, 16.3; HRMS-ESI calcd for $C_9H_{15}NO_5Na$ $[M+Na]^+$ 240.0848, found 240.0852.

Methyl (2*S,4*S*)-4-*tert*-Butyl-2-hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30h) (Entry 8, Table 2).** Following general procedure C, ozonolysis of **12h** (200 mg, 0.72 mmol) for 1 h and sequential reduction with thiourea and $NaBH(OAc)_3$ gave **30h** (110 mg, 59%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:1): white crystals; mp 112-115 ºC (EtOAc/hexanes); R_f 0.37 (EtOAc); FTIR (film) υ_{max} 3384, 1739, 1682, 1367, 1068, 1011, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (d, *J* = 11.7 Hz, 1 H), 3.93 (d, *J* = 11.7 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 2.38 (t, *J* = 9.8 Hz, 1 H), 2.12-1.98 (m, 2 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 172.5, 66.9, 64.2, 64.0, 52.9, 46.3, 32.5, 26.9 (4 C); HRMS-ESI calcd for $C_{12}H_{21}NO_5Na$ $[M+Na]^+$ 282.1317, found 282.1328.

Methyl (2*S,4*S**)-4-Benzyl-2-hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30i) (Entry 9, Table 2).** Following general procedure C, ozonolysis of **12i** (318 mg, 1.01 mmol) for 1 h and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30i** (250 mg, 84%; 91% based upon cleavage of *anti*-**12i**), after purification by flash chromatography (SiO_2, EtOAc): colorless oil; R_f 0.63 (EtOAc); FTIR (film) υ_{max} 3417 (br), 1738, 1703, 1444, 1068, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5 H), 3.89 (s, 3 H), 3.85 (br s, 2 H), 3.75 (s, 3 H), 3.25 (dd, *J* = 3.9, 13.7 Hz, 1 H), 2.84 (dddd, *J* = 3.9, 9.2, 9.6, 9.9 Hz, 1 H), 2.70 (dd, *J* = 9.9, 13.7 Hz, 1 H), 2.35 (br s, 1 H), 2.08 (dd, *J* = 9.6, 13.5 Hz, 1 H), 1.93 (dd, *J* = 9.2, 13.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 172.4, 138.6, 129.5 (2 C), 129.0 (2 C), 127.1, 68.5, 64.5, 63.8, 53.3, 39.2, 37.3, 30.2; HRMS-ESI calcd for $C_{15}H_{19}NO_5$ $[M+Na]^+$ 316.1161, found 316.1162.

Methyl (2*S,4*S**)-2-Hydroxymethyl-1-methoxy-5-oxo-4-phenyl-pyrrolidine-2-carboxylate (30j) (Entry 10, Table 2).** Following general procedure C, ozonolysis of **12j** (36 mg, 0.12 mmol) for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided *anti*-**30j** (25 mg, 75%; 81% based upon cleavage of *anti*-**12j**), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:1): white

solid; mp 145-147 °C (EtOAc/hexanes); R_f 0.80 (EtOAc); FTIR (film) υ_{max} 3425 (br), 1741, 1707, 1055, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5 H), 4.04 (br s, 2 H), 3.94 (s, 3 H), 3.84 (s, 3 H), 3.79 (t, *J* = 9.9 Hz, 1 H), 2.57 (dd, *J* = 9.9, 13.5 Hz, 1 H), 2.34 (dd, *J* = 10.0, 13.5 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.1, 172.0, 138.2, 128.9 (2 C), 128.0 (2 C), 127.6, 67.7, 64.3, 63.2, 53.1, 43.5, 33.0; HRMS-ESI calcd for $C_{14}H_{18}NO_5$ $[M+H]^+$ 280.1185, found 280.1179.

Methyl (2*S*,4*RS)-2-Hydroxymethyl-1-methoxy-5-oxo-4-(triisopropylsilanyloxy)-pyrrolidine-2-carboxylate (30k) (Entry 11, Table 2).** Following general procedure C, ozonolysis of **12k** (525 mg, 1.33 mmol) for 1 h and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30k** as a 91:9 mixture of *anti*-**30k** and *syn*-**30k** (454 mg, 91%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:3): 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, $CDCl_3$) δ 4.47 (dd, *J* = 8.4, 6.8 Hz, 1 H), 4.00-3.98 (m, 2 H), 3.97 (s, 3 H), 3.80 (s, 3 H), 2.61 (br s, 1 H), 2.53 (dd, *J* = 13.4, 8.4 Hz, 1 H), 2.11 (dd, *J* = 13.4, 6.8 Hz, 1 H), 1.09-1.07 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 170.5, 67.8, 67.0, 64.4, 64.1, 53.4, 36.1, 18.2, 12.5; HRMS-ESI calcd for $C_{17}H_{33}NO_6SiNa$ $[M+Na]^+$ 398.1975, found 398.1958.

Methyl (2*S,4*S**)-4-Benzoylamino-2-hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30l) (Entry 12, Table 2).** Following general procedure C, ozonolysis of **12l** (100 mg, 0.29 mmol) for 1 h and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30l** (43 mg, 46%), after purification by flash chromatography (SiO_2, EtOAc): colorless oil; R_f 0.37 (EtOAc); FTIR (film) υ_{max} 3346 (br), 1734, 1717, 1646, 1540, 1435, 1059, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.3 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 4.90 (dd, *J* = 7.6, 16.9 Hz, 1 H), 4.10 (dd, *J* = 5.6, 12.0 Hz, 1 H), 3.89-3.84 (m, 4 H), 3.80 (s, 3 H), 3.70 (t, *J* = 6.1 Hz, 1 H), 2.79 (dd, *J* = 9.8, 13.5 Hz, 1 H), 2.29 (dd, *J* = 7.3, 13.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.2, 167.6, 133.0, 131.8, 128.5, 127.2, 68.6, 63.9, 61.3, 53.1, 46.7, 32.4; HRMS-ESI calcd for $C_{15}H_{19}N_2O_6$ $[M+H]^+$ 323.1243, found 323.1245.

Methyl (±)-3-Hydroxymethyl-2-methoxy-1-oxo-1.2.3.4-tetrahydroisoquinoline-3-carboxylate (30n) (Entry 14, Table 2). Following general procedure C, ozonolysis of **12n** (105 mg, 0.37 mmol) for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ gave **30n** (82 mg, 84%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 179-180 °C; R_f 0.46 (EtOAc); FTIR (film) ν_{max}

3411 (br), 1725, 1654, 1224, 1029, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.7 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 7.5 Hz, 1 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 4.23 (dd, *J* = 4.3, 11.9 Hz, 1 H), 4.06-4.01 (m, 4 H), 3.69 (s, 3 H), 3.51, (d, *J* = 16.3 Hz, 1 H), 3.38 (d, *J* = 16.3 Hz, 1 H), 2.72 (dd, *J* = 4.3, 9.7 Hz, 1 H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 165.3, 133.9, 132.9, 128.3, 127.6 (2 C), 127.4, 72.2, 65.0, 64.6, 53.1, 35.4; HRMS-ESI calcd for $C_{13}H_{15}NO_5Na$ $[M+Na]^+$ 288.0848, found 288.0842.

Methyl (±)-2-Acetoxymethyl-1-benzyloxy-6-oxo-piperidine-2-carboxylate (30f) (Entry 6, Table 2). Following general procedure D, ozonolysis of **12f** (50 mg, 0.16 mmol) for 3 h, sequential reduction with thiourea and $NaBH(OAc)_3$ then acetylation of the crude product gave **30f** (30 mg, 56%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 111-113 °C (EtOAc/hexanes); R_f 0.62 (EtOAc); IR (film) υ_{max} 1746, 1683, 1235 cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5 H), 5.13 (d, *J* = 9.6 Hz, 1 H), 4.87 (d, *J* = 9.6 Hz, 1 H), 4.57 (d, *J* = 11.9 Hz, 1 H), 4.53 (d, *J* = 11.9 Hz, 1 H), 3.77 (s, 3 H), 2.63-2.51 (m, 2 H), 2.22-2.12 (m, 2 H), 2.11 (s, 3 H), 1.87-1.83 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.4, 170.3, 135.1, 129.2 (2 C), 128.5, 128.4 (2 C), 77.4, 70.4, 63.6, 53.1, 33.2, 30.9, 21.0, 17.7; HRMS-ESI calcd for $C_{17}H_{21}NO_6Na$ $[M+Na]^+$ 358.1267, found 358.1273.

Methyl (±)-2-Hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30c) (Entry 3, Table 2). Following general procedure E, Luche reduction of **12c** (98 mg, 0.44 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30c** (68 mg, 76%), after purfication by flash chromatography (SiO_2, EtOAc).

Methyl (±)-2-Hydroxymethyl-1-benzyloxy-5-oxo-pyrrolidine-2-carboxylate (30d) (Entry 4, Table 2). Following general procedure E, Luche reduction of **12d** (165 mg, 0.55 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30d** (145 mg, 94%), after purification by flash chromatography (SiO_2, EtOAc).

Methyl (±)-2-Hydoxymethyl-1-methoxy-6-oxo-piperidine-2-carboxylate (30e) (Entry 5, Table 2). Following general procedure E, Luche reduction of **12e** (148 mg, 0.62 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30e** (95 mg, 70%), after purification by flash chromatography (SiO_2, EtOAc): white crystals; mp 95-97 °C (EtOAc/hexanes); R_f 0.33 (EtOAc); IR (film) υ_{max} 3406, 1739, 1655, 1367, 1242, 1068, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (d, *J* = 11.7 Hz, 1 H), 3.97 (d, *J* = 11.7 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H),

2.57-2.43 (m, 3 H), 2.27-2.19 (m, 1 H), 2.16-2.10 (m, 1 H), 1.84-1.74 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 170.2, 72.2, 64.3, 63.5, 52.9, 33.1, 30.5, 17.5; HRMS-ESI calcd for $C_9H_{15}NO_5Na$ $[M+Na]^+$ 240.0848, found 240.0855.

Methyl (±)-2-Hydoxymethyl-1-benzyloxy-6-oxo-piperidine-2-carboxylate (30f) (Entry 6, Table 2). Following general procedure E, Luche reduction of **12f** (108 mg, 0.34 mmol) and ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30f** (66 mg, 65%), after purification by flash chromatography (SiO_2, EtOAc): yellow solid; mp 120-122 °C (EtOAc/hexanes); R_f 0.38 (EtOAc); IR (film) υ_{max} 3406, 1739, 1658, 1371, 1242, 1065, 752 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 5 H), 5.12 (d, J = 9.9 Hz, 1 H), 5.07 (d, J = 9.9 Hz, 1 H), 3.92 (d, J = 11.9 Hz, 1 H), 3.89 (d, J = 11.9 Hz, 1 H), 3.79 (s, 3 H), 2.57-2.49 (m, 2 H), 2.25-2.04 (m, 3 H), 1.87-1.72 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.4, 135.1, 129.5, 128.8, 128.6, 77.4, 72.4, 64.2, 52.9, 33.2, 30.6, 17.6; HRMS-ESI calcd for $C_{15}H_{19}NO_5Na$ $[M+Na]^+$ 316.1161, found 316.1149.

Methyl (2*S,4*S**)-2-Hydroxymethyl-1-methoxy-4-methyl-5-oxo-pyrrolidine-2-carboxylate (30g) (Entry 7, Table 2).** Following general procedure E, Luche reduction of **12g** (122 mg, 0.51 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30g** (75 mg, 67%), after purfication by flash chromatography (SiO_2, EtOAc).

Methyl (2*S,4*S*)-4-*tert*-Butyl-2-hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30h) (Entry 8, Table 2).** Following general procedure E, Luche reduction of **12h** (49 mg, 0.18 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30h** (38 mg, 84%), after purfication by flash chromatography (SiO_2, EtOAc).

Methyl (2*S,4*S**)-4-Benzyl-2-hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30i) (Entry 9, Table 2).** Following general procedure E, Luche reduction of **12i** (111 mg, 0.35 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30i** (87 mg, 84%), after purfication by flash chromatography (SiO_2, EtOAc).

Methyl (2*S,4*S**)-2-Hydroxymethyl-1-methoxy-5-oxo-4-(triisopropylsilanyloxy)-pyrrolidine-2-carboxylate (30k) (Entry 11, Table 2).** Following general procedure E, Luche reduction of **12k** (133 mg, 0.34 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30k** (112 mg, 89%), after purfication by flash chromatography (SiO_2, EtOAc/hexanes, 1:1).

Methyl (2*S,4*S**)-4-Benzoylamino-2-hydroxymethyl-1-methoxy-5-oxo-pyrrolidine-2-carboxylate (30l) (Entry 12, Table 2).** Following general procedure E, Luche reduction of **12l** (82 mg, 0.24 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30l** (65 mg, 84%), after purfication by flash chromatography (SiO_2, EtOAc).

Methyl (*2S,3*R**)-*2*-Acetoxymethyl-1-methoxy-3-methyl-5-oxo-pyrrolidine-2-carboxylate (30m) (Entry 13, Table 2).** Following general procedure E, Luche reduction **12m** (148 mg, 0.62 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided the crude product. This material was dissolved in a mixture of pyridine (1.5 mL) and Ac_2O (1 mL) and stirred at room temperature for 12 h. The reaction mixture was then concentrated under reduced pressure and the resulting oil purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) to provide **30m** (50 mg, 31%): colorless oil; R_f 0.57 (EtOAc); IR (film) υ_{max} 1749, 1733, 1253, 1229, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (d, *J* = 12.2 Hz, 1 H), 4.37 (d, *J* = 12.2 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 2.63-2.51 (m, 2 H), 2.12-2.07 (m, 1 H), 2.04 (s, 3 H), 1.18 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 170.5, 170.0, 70.9, 63.9, 60.3, 53.0, 35.2, 32.3, 20.8, 14.5; HRMS-ESI calcd for $C_{11}H_{18}NO_6$ $[M+H]^+$ 260.1134, found 260.1132.

Methyl (±)-3-Hydroxymethyl-2-methoxy-1-oxo-1.2.3.4-tetrahydroisoquinoline-3-carboxylate (30n) (Entry 14, Table 2). Following general procedure E, Luche reduction **12n** (84 mg, 0.29 mmol), ozonolysis of the resulting dienylic alcohols for 30 min and sequential reduction with thiourea and $NaBH(OAc)_3$ provided **30n** (30 mg, 38%), after purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:1).

10. Reductive Cleavage of *N*-Alkoxy Lactams

Methyl (±)-2-Hydroxymethyl-5-oxo-pyrrolidine-2-carboxylate (32c) (Entry 2, Table 4). Following general procedure F, reduction of **30c** (65 mg, 0.32 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **32c** (57 mg, 88%): white crystals; mp 133-135 ºC (EtOAc/hexanes); R_f 0.17 (EtOAc); FTIR (film) ν_{max} 3324 (br), 1735, 1688, 1228, 1050 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 3.84 (d, *J* = 11.2 Hz, 1 H), 3.77 (s, 3 H), 3.64 (d, *J* = 11.2 Hz, 1 H), 2.38-2.35 (m, 2 H), 2.31-2.26 (m, 1 H), 2.17-2.11 (m, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 179.4, 173.6, 68.1, 66.6, 52.1, 29.8, 27.0; HRMS-ESI calcd for $C_7H_{11}NO_4Na$ $[M+Na]^+$ 196.0586, found 196.0593.

Methyl (2*S,4*S**)-2-Hydroxymethyl-4-methyl-5-oxo-pyrrolidine-2-carboxylate (32g) (Entry 3, Table 4).** Following general procedure F, reduction of **30g** (63 mg, 0.29 mmol) and purfication by flash chromatography (SiO_2, EtOAc) provided **32g** (40 mg, 70%): colorless oil; R_f 0.19 (EtOAc); FTIR (film) ν_{max} 3357 (br), 1739, 1691, 1452, 1228, 1099, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 4.56 (br s, 1 H), 3.99 (d, *J* = 11.4 Hz, 1 H), 3.77 (s, 3 H), 3.59 (d, *J* = 11.4 Hz, 1 H), 2.58-2.46 (m, 2 H), 1.70-1.61 (m, 1 H), 1.16 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 180.6, 173.6, 67.7, 66.2, 52.9, 35.8, 35.4, 15.7; HRMS-ESI calcd for $C_8H_{13}NO_4Na$ $[M+Na]^+$ 210.0742, found 210.0743.

Methyl (2*S,4*S**)-4-*tert*-Butyl-2-hydroxymethyl-5-oxo-pyrrolidine-2-carboxylate (32h) (Entry 4, Table 4).** Following general procedure F, reduction of **30h** (39 mg, 0.15 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **32h** (20 mg, 59%): white crystals; mp 108-110 ºC (EtOAc/hexanes); R_f 0.35 (EtOAc); FTIR (film) υ_{max} 3342 (br), 1738, 1695, 1365, 1223, 1062, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (br s, 1 H), 4.02 (dd, *J* = 6.5, 11.2 Hz, 1 H), 3.82 (t, *J* = 6.5 Hz, 1 H), 3.78 (s, 3 H), 3.59 (dd, *J* = 6.5, 11.2 Hz, 1 H), 2.39-2.25 (m, 2 H), 1.81 (dd, *J* = 10.6, 12.8 Hz, 1 H), 1.01 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 174.0, 67.6, 64.5, 52.9, 49.5, 32.0, 30.5, 27.1; HRMS-ESI calcd for $C_{11}H_{19}NO_4Na$ $[M+Na]^+$ 252.1212, found 252.1217 .

Methyl (2*S,4*S**)-4-Benzyl-2-hydroxymethyl-5-oxo-pyrrolidine-2-carboxylate (32i) (Entry 5, Table 4).** Following general procedure F, reduction of **30i** (89 mg, 0.30 mmol) and purification product by flash chromatography (SiO_2, EtOAc) provided **32i** (58 mg, 73%): white crystals; mp 130-132 ºC (EtOAc/hexanes); R_f 0.21 (EtOAc); FTIR (film) υ_{max} 3357 (br), 1741, 1697, 1685, 1456, 1228, 1045, 752 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.29-7.17 (m, 5 H), 3.76 (d, *J* = 11.1 Hz, 1 H), 3.71 (s, 3 H), 3.36 (d, *J* = 11.1 Hz, 1 H), 3.12 (dd, *J* = 4.0, 13.6 Hz, 1 H), 2.83-2.75 (m, 1 H), 2.67 (dd, *J* = 9.5, 13.6 Hz, 1 H), 2.23 (dd, *J* = 9.0, 13.5 Hz, 1 H), 1.79 (dd, *J* = 9.7, 13.5 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 179.5, 173.4, 138.8, 128.7, 128.2, 126.1, 66.3, 65.8, 51.8, 42.3, 36.0, 32.3; HRMS-ESI calcd for $C_{14}H_{17}NO_4Na$ $[M+Na]^+$ 286.1055, found 286.1058.

Methyl (2*S,4*S**)-2-Hydroxymethyl-5-oxo-4-phenyl-pyrrolidine-2-carboxylate (32j) (Entry 6, Table 4).** Following general procedure F, reduction of **30j** (146 mg, 0.52 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **32j** (85 mg, 65%): white crystals; mp 136-138 ºC (EtOAc/hexanes); R_f 0.24 (EtOAc); FTIR (film) υ_{max} 3343 (br), 1736, 1697, 1231, 1049, 755, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.21 (m, 6 H), 3.97-3.96 (m, 1 H), 3.80 (s, 3 H), 3.59-3.56 (m, 2 H), 2.75

(dd, J = 9.4, 13.3 Hz, 1 H), 2.18 (dd, J = 11.0, 13.3 Hz, 1 H), 1.87 (br s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 173.4, 138.1, 128.9, 128.2, 127.4, 67.3, 65.6, 53.1, 46.9, 36.7; HRMS-ESI calcd for $C_{13}H_{16}NO_4$ $[M+H]^+$ 250.1079, found 250.1070.

Methyl (2*S*,4*S)-2-Hydroxymethyl-5-oxo-4-(triisopropylsilanyloxy)-pyrrolidine-2-carboxylate (32k) (Entry 7, Table 4).** Following general procedure F, reduction of **30k** (250 mg, 067 mmol) and purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:3) provided **32k** (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}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (br s, 1 H), 4.45 (t, J = 7.5 Hz, 1 H), 3.99 (d, J = 11.3 Hz, 1 H), 3.79 (s, 3 H), 3.69 (d, J = 11.3 Hz, 1 H), 3.47 (br s, 1 H), 2.60 (dd, J = 13.4, 8.0 Hz, 1 H), 1.99 (dd, J = 13.4, 7.0 Hz, 1 H), 1.17-1.06 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 173.4, 69.9, 68.1, 64.6, 53.4, 38.4, 18.2, 12.5; HRMS-ESI calcd for $C_{16}H_{31}NO_5SiNa$ $[M+Na]^+$ 368.1869, found 368.1869.

Methyl (2*S,4*S**)-4-Benzoylamino-2-hydroxymethyl-5-oxo-pyrrolidine-2-carboxylate (32l) (Entry 8, Table 4).** Following general procedure F, reduction of **30l** (85 mg, 0.26 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **32l** (60 mg, 77%): white solid; mp 82-83 ºC (EtOAc/hexanes); R_f 0.07 (EtOAc); FTIR (film) ν_{max} 3317 (br), 1734, 1716, 1645, 1541, 1309, 1055, 912 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1 H), 7.77 (d, J = 7.6 Hz, 2 H), 7.73 (d, J = 7.3 Hz, 1 H), 7.43 (t, J = 7.3 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 4.78 (dd, J = 8.9, 16.8 Hz, 1 H, 4.58 (br s, 1 H), 3.93 (dd, J = 5.4, 11.6 Hz, 1 H), 3.73-3.67 (m, 4 H), 2.75 (dd, J = 9.3, 13.3 Hz, 1 H), 2.14 (dd, J = 9.3, 13.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 173.0, 167.8, 133.0, 131.9, 128.5, 127.2, 66.0, 65.3, 53.1, 50.5, 34.2; HRMS-ESI calcd for $C_{14}H_{16}N_2O_5Na$ $[M+Na]^+$ 315.0957, found 315.0956.

Methyl (±)-2-Acetoxymethyl-6-oxo-piperidine-2-carboxylate (32e) (Entry 9, Table 4). Following general procedure F, reduction of **30e** (24 mg, 0.09 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **32e** (16 mg, 76%): white crystals; mp 54-56 ºC (EtOAc/hexanes); R_f 0.20 (EtOAc); FTIR (film) ν_{max} 3243 (br), 1742, 1672, 1237, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (br s, 1 H), 4.47 (d, J = 10.9 Hz, 1 H), 4.04 (d, J = 10.9 Hz, 1 H), 3.79 (s, 3 H), 2.46-2.35 (m, 2 H), 2.20-2.16 (m, 1 H), 2.07 (s, 3 H), 1.91-1.85 (m, 1 H), 1.81-1.67 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.2, 170.0, 69.1, 62.3, 53.2, 31.0, 27.8, 20.6, 17.8; HRMS-ESI calcd for $C_{10}H_{15}NO_5$ $[M+Na]^+$ 252.0848, found 252.0845.

Methyl (2*S,3*S**)-2-Acetoxymethyl-3-methyl-5-oxo-pyrrolidine-2-carboxylate (32m) (Entry 10, Table 4).** Following general procedure F, reduction of **30m** (24 mg, 0.09 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **32m** (18 mg, 86%): colorless oil; R_f 0.24 (EtOAc); FTIR (film) ν_{max} 3235 (br), 1744, 1706, 1236, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.11 (br s, 1 H), 4.52 (d, *J* = 11.1 Hz, 1 H), 4.14 (d, *J* = 11.1 Hz, 1 H), 3.81 (s, 3 H), 2.75-2.67 (m, 1 H), 2.54 (dd, *J* = 8.7, 16.8 Hz, 1 H), 2.15 (dd, *J* = 9.5, 16.8 Hz, 1 H), 2.08 (s, 3 H), 1.25 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 171.8, 170.3, 66.4, 65.5, 53.1, 37.9, 36.5, 20.7, 14.4; HRMS-ESI calcd for $C_{10}H_{15}NaNO_5$ $[M+Na]^+$ 252.0848, found 252.0847.

Methyl (±)-3-Hydroxymethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (32n) (Entry 11, Table 4). Following general procedure F, reduction of **30n** (29 mg, 0.11 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **32n** (19 mg, 74%): white crystals; mp 131-133 ºC (EtOAc/hexanes); R_f 0.29 (EtOAc); FTIR (film) ν_{max} 3332 (br), 1739, 1660, 1465, 1205, 1085, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 1 H), 7.63 (s, 1 H, NH), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.20 (d, *J* = 7.5 Hz, 1 H), 4.07, (dd, *J* = 9.7, 13.3 Hz, 1 H), 3.90-3.85 (m, 2 H), 3.71 (s, 3 H), 3.28 (d, *J* = 16.0 Hz, 1 H), 3.16 (d, *J* = 16.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 166.3, 135.2, 132.9, 128.1, 127.7, 127.6 (2 C), 67.6, 64.1, 53.2, 33.0; HRMS-ESI calcd for $C_{12}H_{13}NO_4Na$ $[M+Na]^+$ 258.0742, found 258.0745.

Methyl (±)-2-(2-Ethoxycarbonylvinyl)-5-oxo-pyrrolidine-2-carboxylate (33) (Entry 12, Table 4). Following general procedure F, reduction of **27** (87 mg, 0.32 mmol) and purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) provided **33** (56 mg, 73%): colorless oil; R_f 0.34 (EtOAc); FTIR (film) ν_{max} 3220 (br), 1716, 1655, 1313, 1259, 1184, 1034, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 15.7 Hz, 1 H), 7.08 (br s, 1 H, NH), 6.06 (d, *J* = 15.7 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.81 (s, 3 H), 2.63-2.55 (m, 1 H), 2.41-2.38 (m, 2 H), 2.27-2.20 (m, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 171.3, 165.5, 145.6, 121.4, 66.2, 60.9, 53.4, 32.0, 29.0, 14.2; HRMS-ESI calcd for $C_{11}H_{16}NO_5$ $[M+H]^+$ 242.1028, found 242.1021.

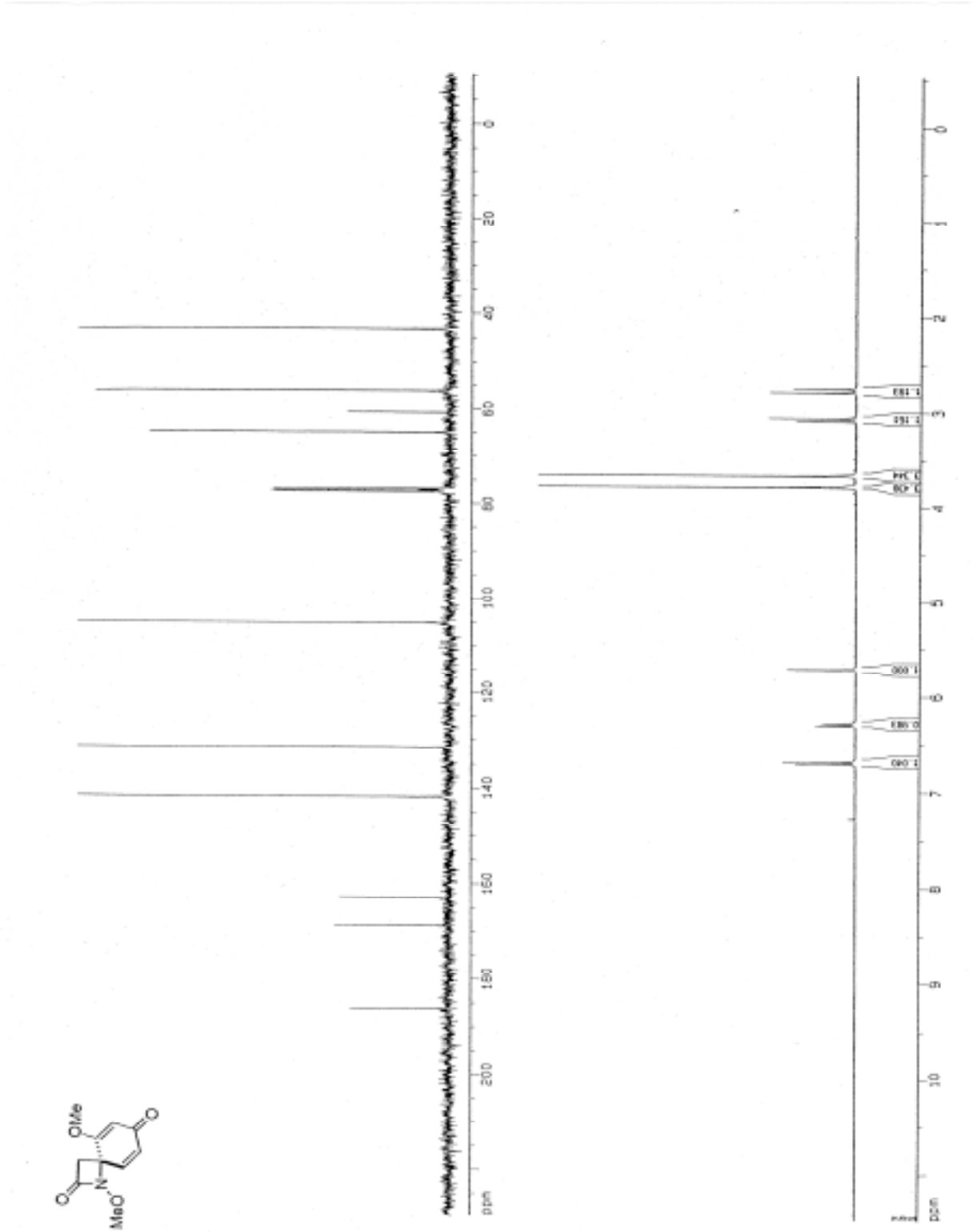
Methyl (±)-1-Hydroxy-2-hydroxymethyl-5-oxo-pyrrolidine-2-carboxylate (34d) (Entry 2, Table 5). Following general procedure G, hydrogenolysis of **30d** (32 mg, 0.11 mmol) and purification by flash chromatography over silica gel (EtOAc) provided **34d** (20 mg, 90%): colorless oil; R_f 0.03 (EtOAc); FTIR (film) ν_{max} 3352 (br), 1737, 1689, 1252, 1076 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 3.96 (d, *J* =

11.9 Hz 1 H), 3.89 (d, J = 11.9 Hz, 1 H), 3.74 (s, 3 H), 2.40-2.37 (m, 2 H), 2.32-2.27 (m, 1 H), 2.14-2.10 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.0, 171.9, 70.8, 60.7, 52.1, 26.6, 22.9; HRMS-ESI calcd for $C_7H_{11}NO_5Na$ $[M+Na]^+$ 212.0535, found 212.0539.

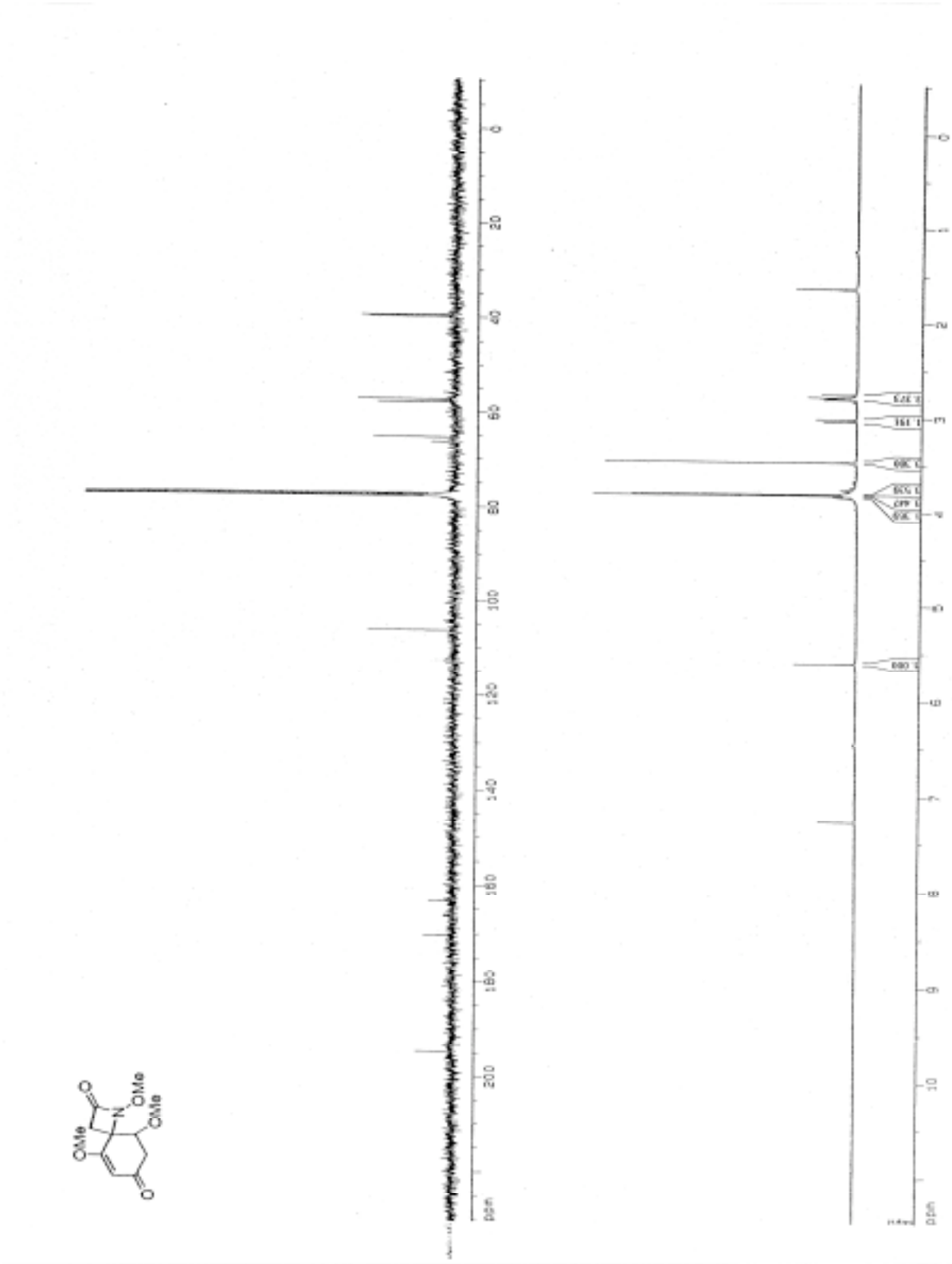
Methyl (±)-2-Acetoxymethyl-1-hydroxy-6-oxo-piperidine-2-carboxylate (34f) (Entry 3, Table 5). Following general procedure G, hydrogenolysis of **30f** (20 mg, 0.06 mmol) and purification by flash chromatography (SiO_2, EtOAc) provided **34f** (15 mg, 99%): colorless oil; R_f 0.59 (EtOAc); FTIR (film) ν_{max} 3194 (br), 1744, 1641, 1236, 1053 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (d, J = 11.8 Hz, 1 H), 4.46 (d, J = 11.8 Hz, 1 H), 3.82 (s, 3 H), 2.60-2.57 (m, 1 H), 2.53-2.46 (m, 1 H), 2.28-2.22 (m, 1 H), 2.16-2.12 (m, 1 H), 2.11 (s, 3 H), 1.87-1.81 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 170.7, 168.4, 69.2, 63.6, 53.6, 31.2, 30.4, 21.3, 17.8; HRMS-ESI calcd for $C_{10}H_{16}NO_6$ $[M+H]^+$ 246.0978, found 246.0975.

11. ^{1}H and ^{13}C NMR Spectra for Compounds 12a-34f

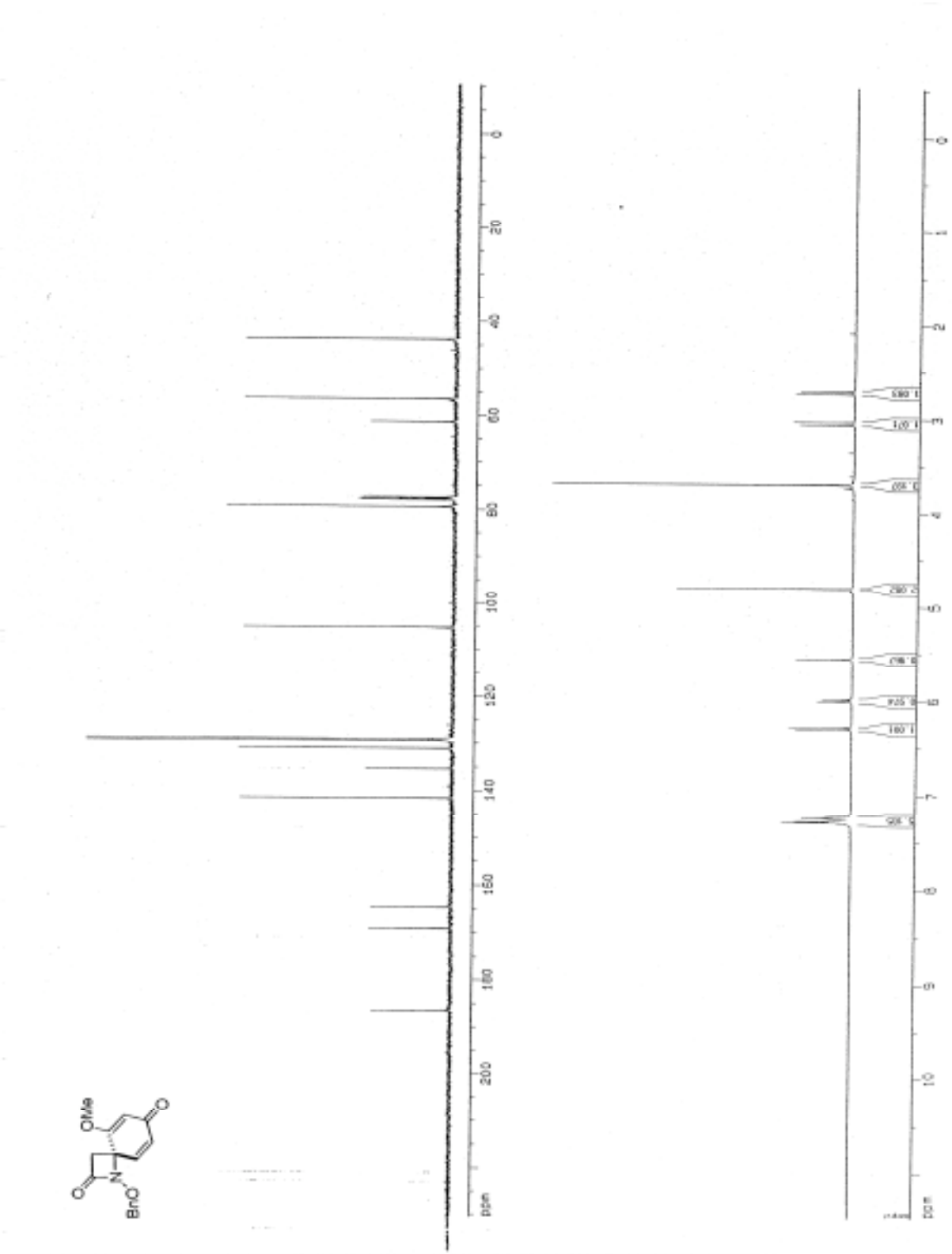
Compound 12a



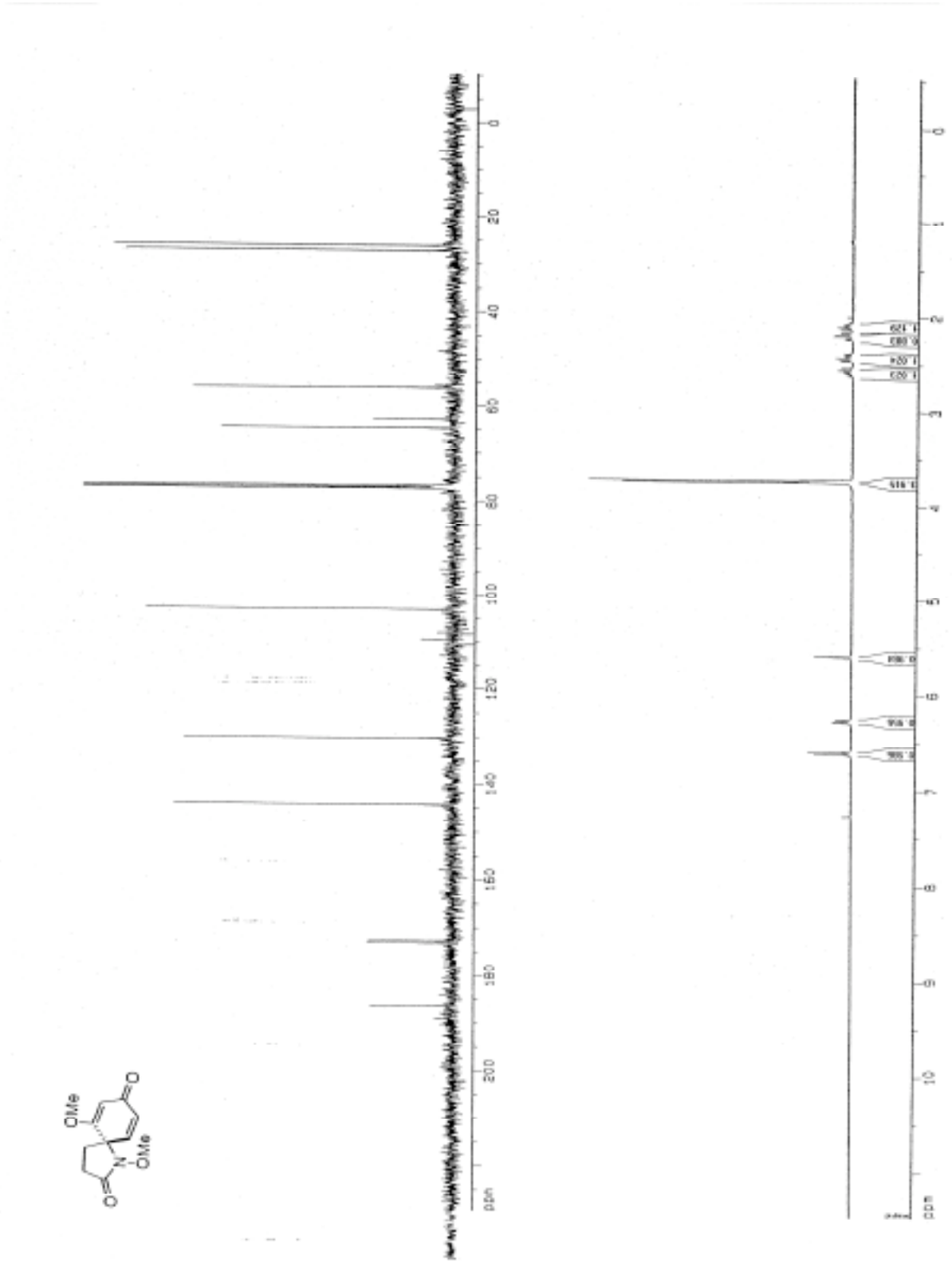
Compound 20



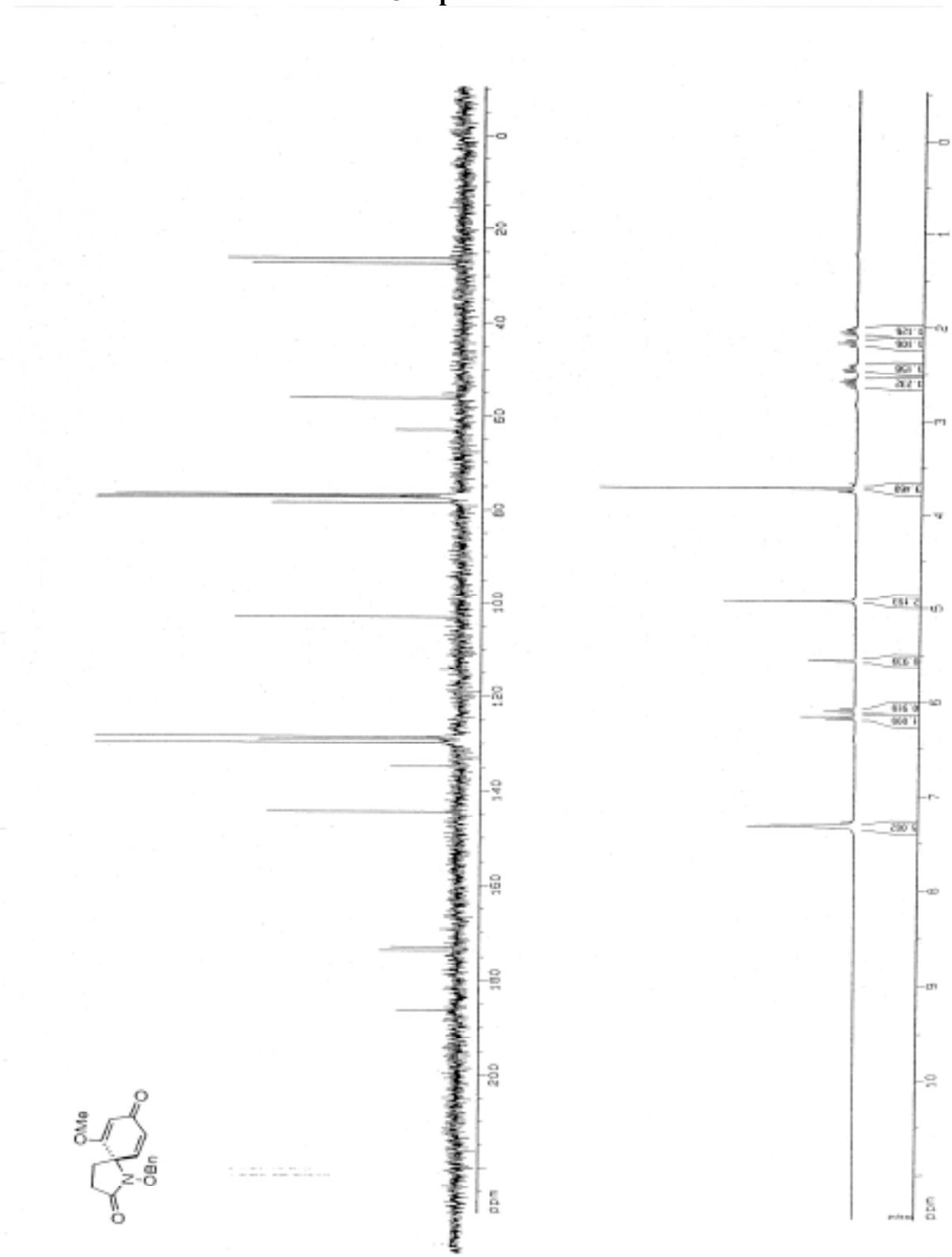
Compound 12b



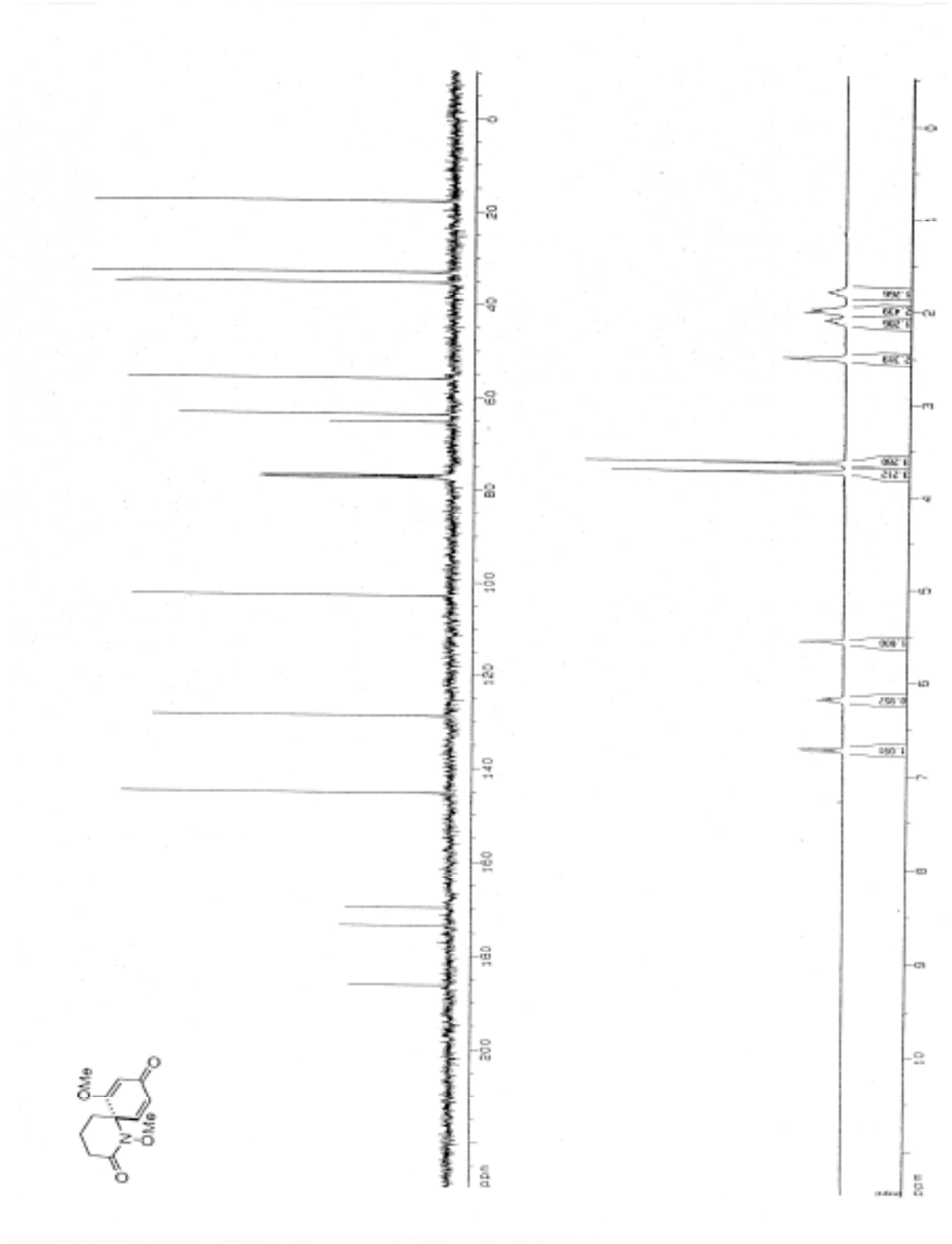
Compound 12c



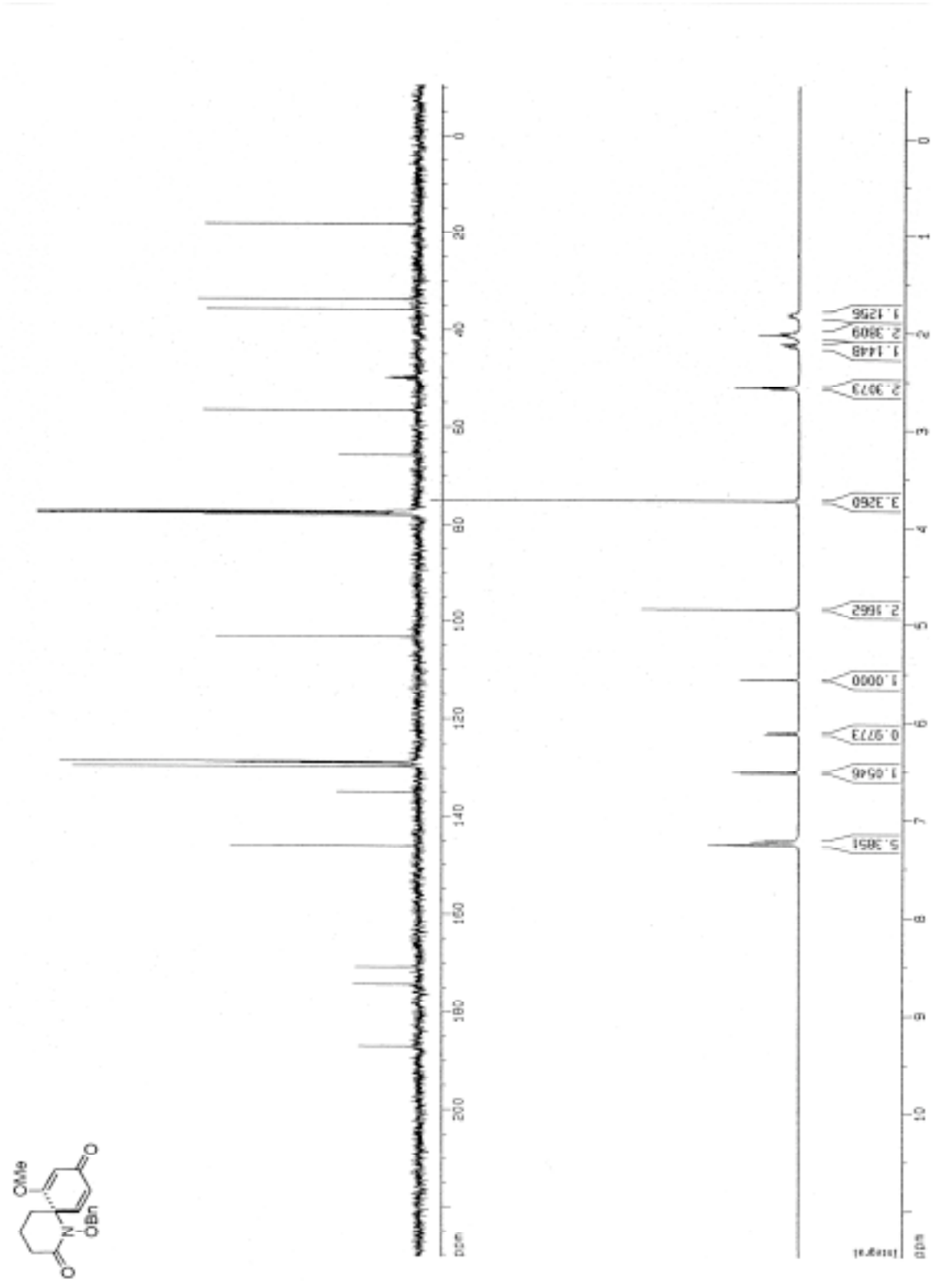
Compound 12d



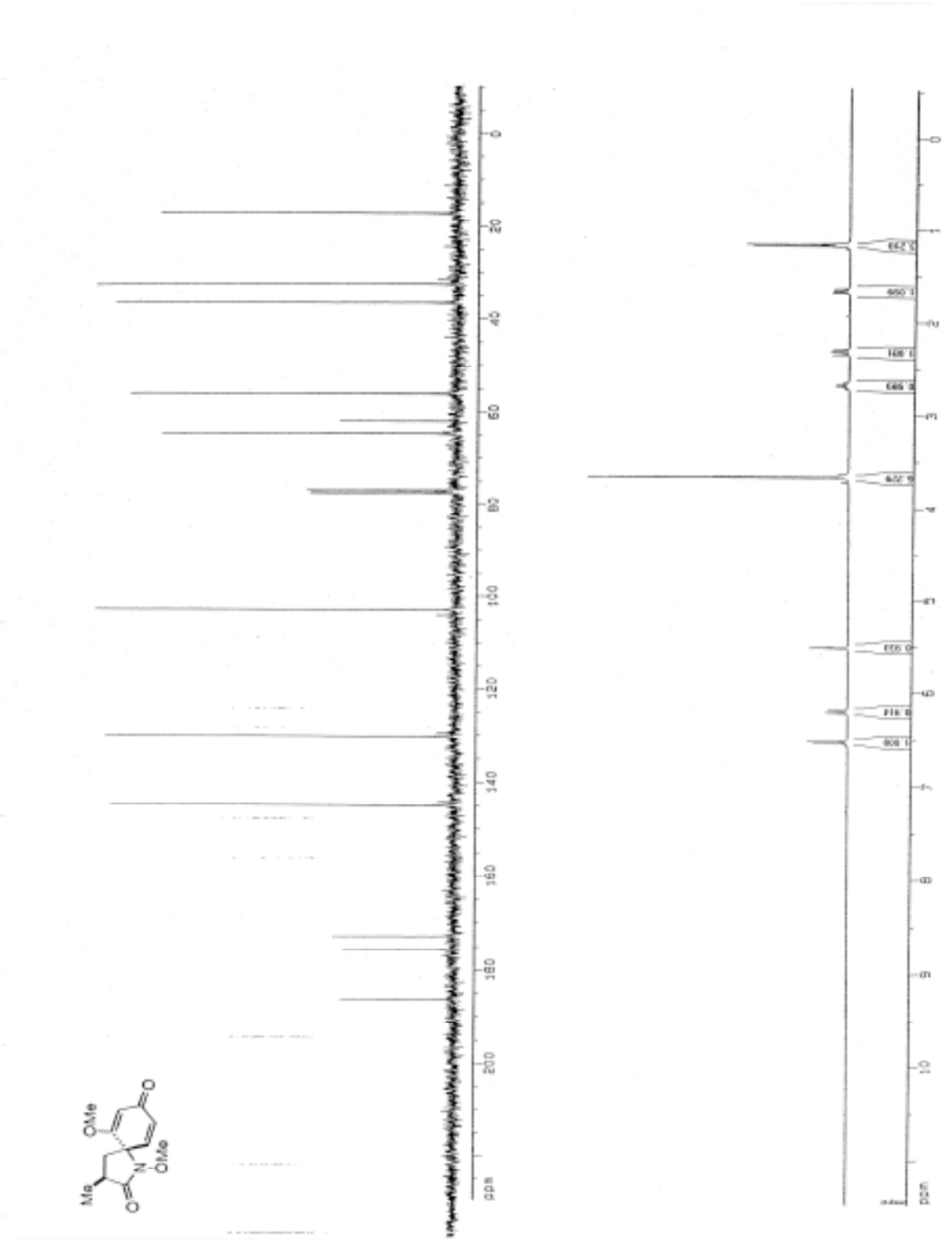
Compound 12e



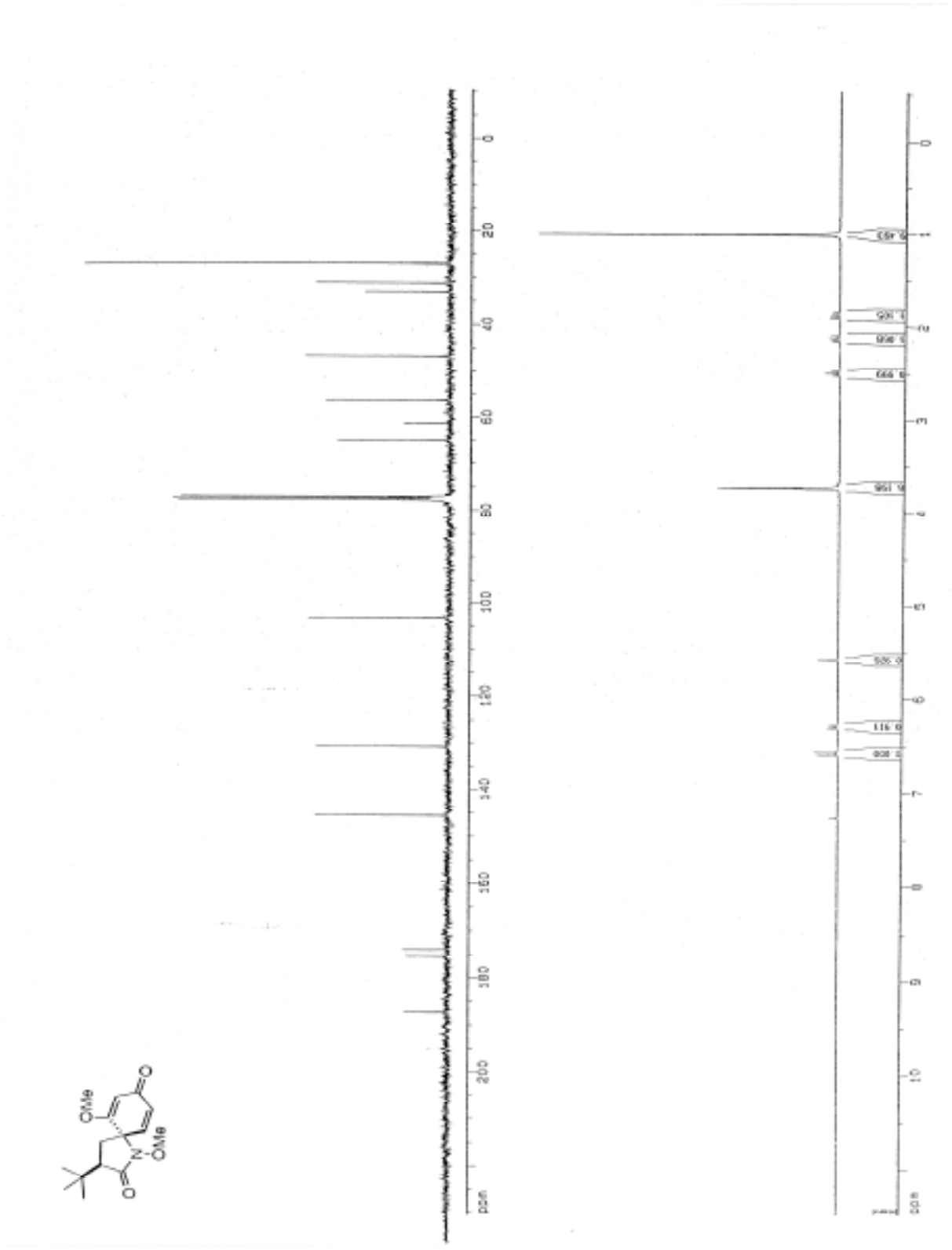
Compound 12f



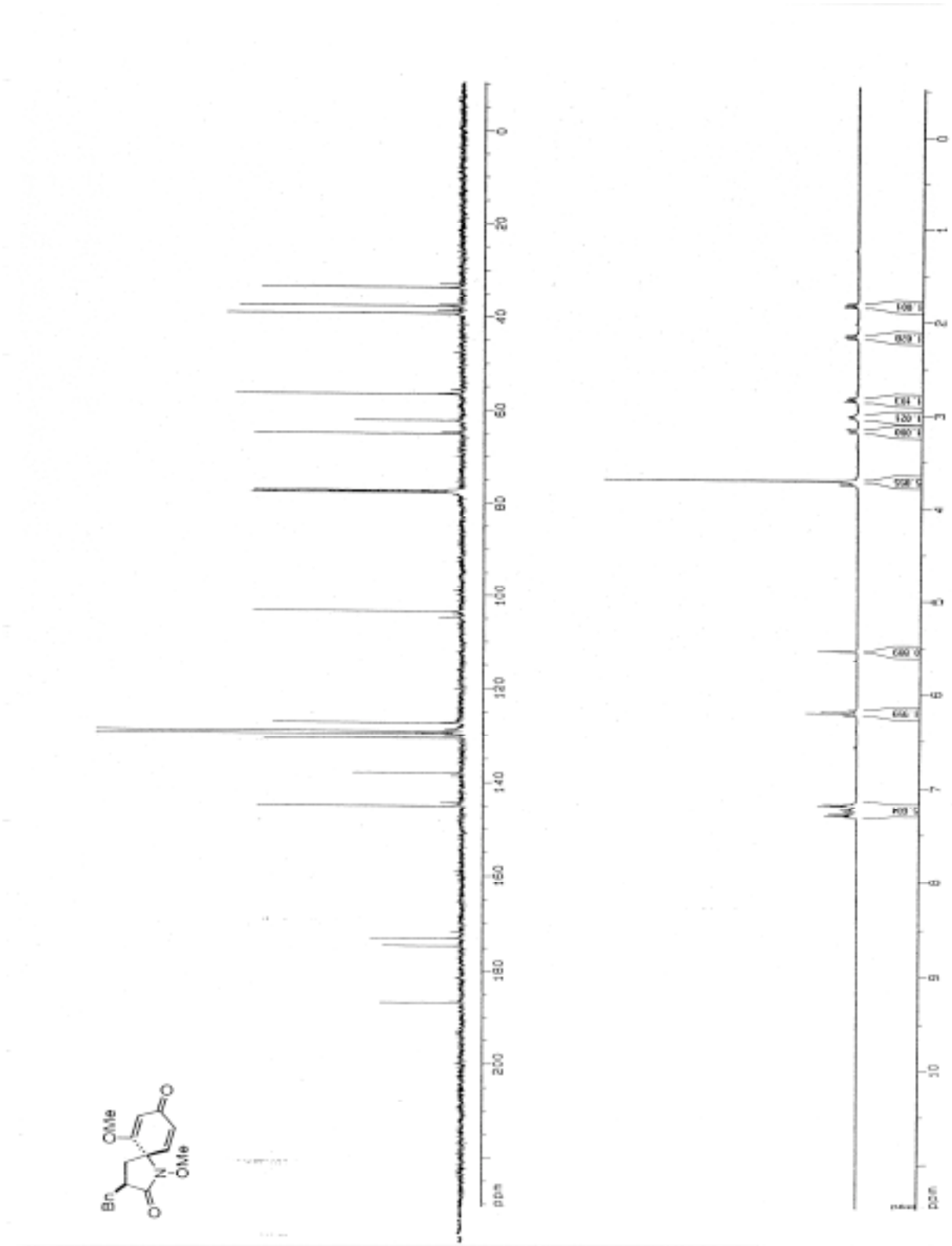
Compound 12g



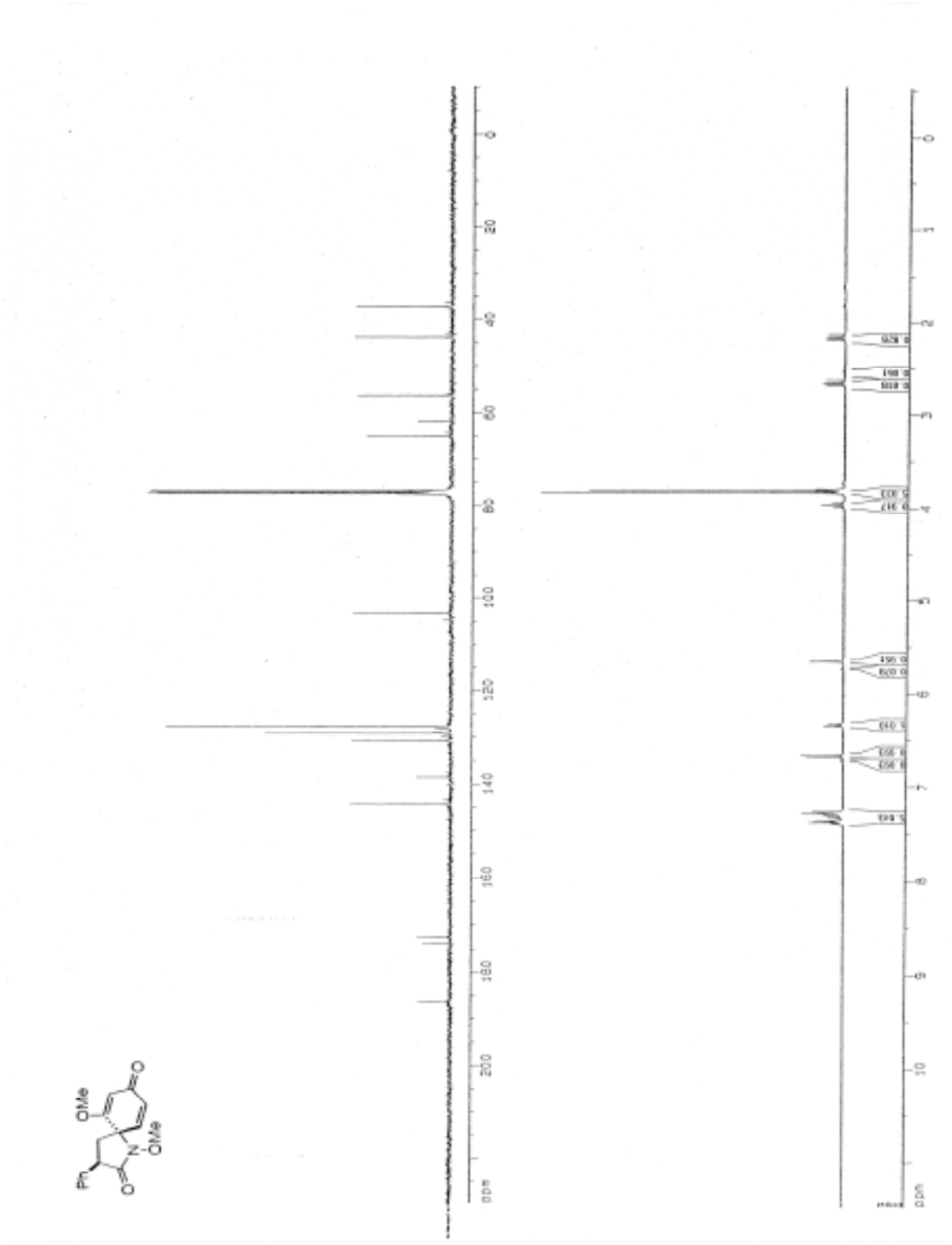
Compound 12h



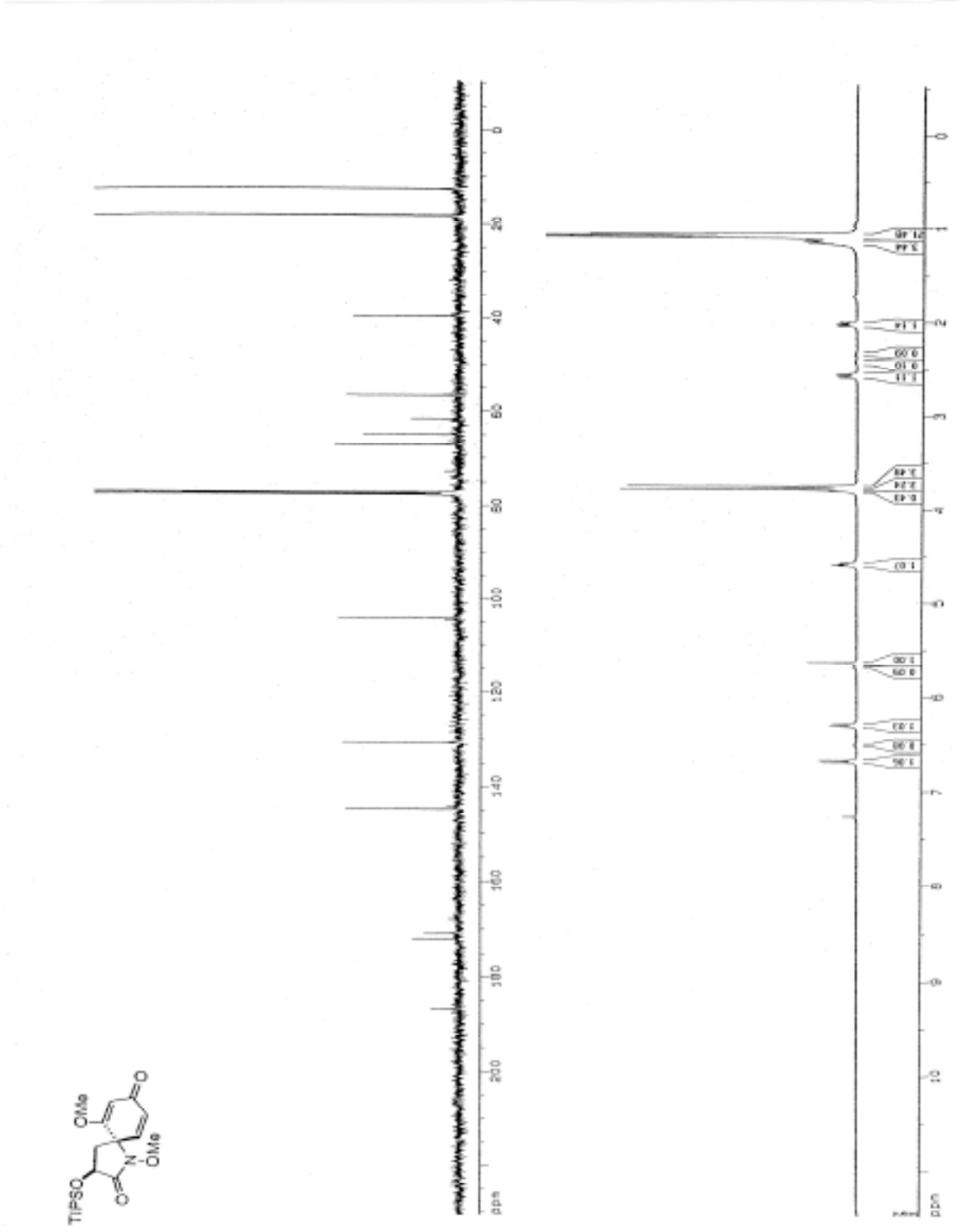
Compound 12i



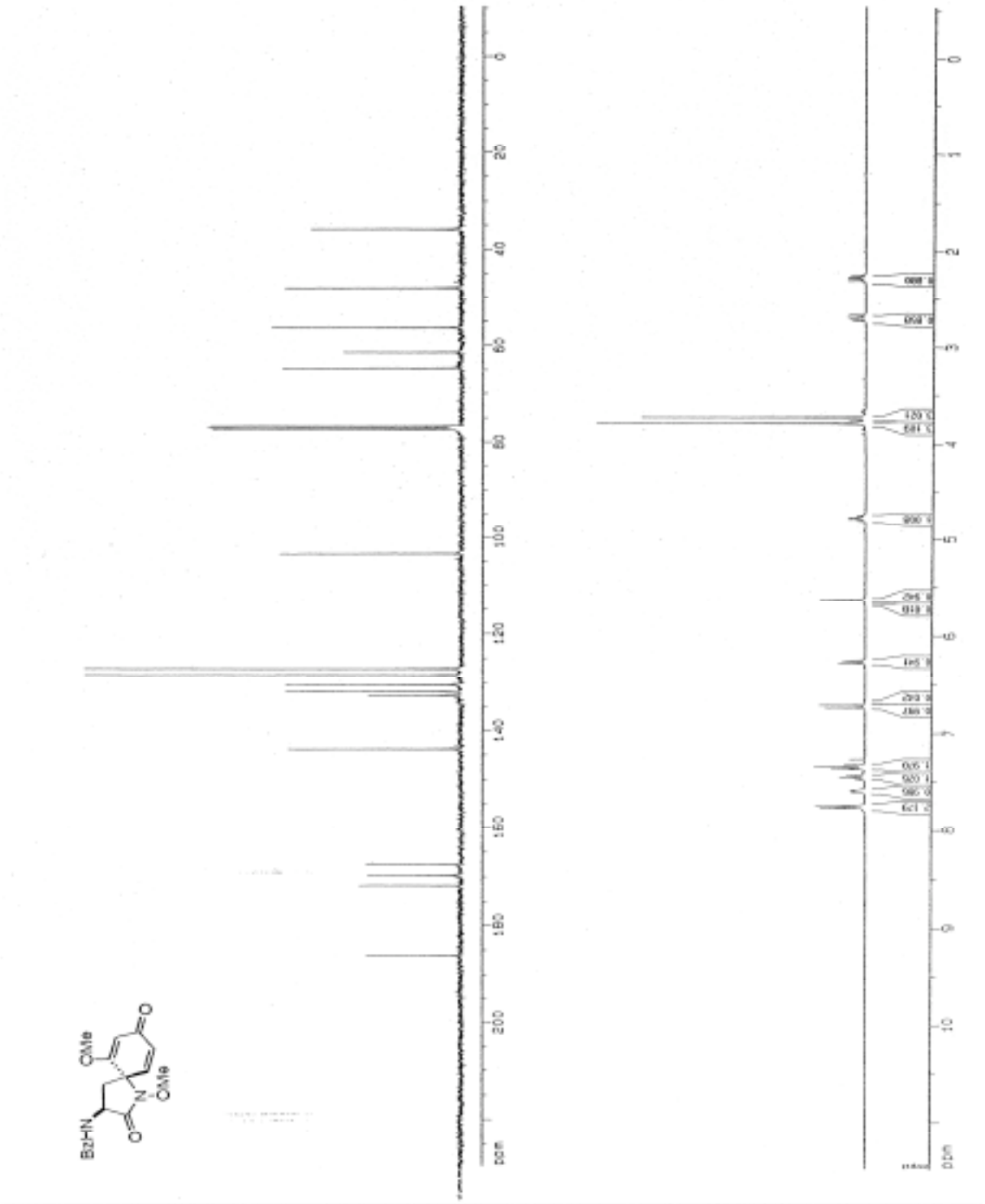
Compound 12j



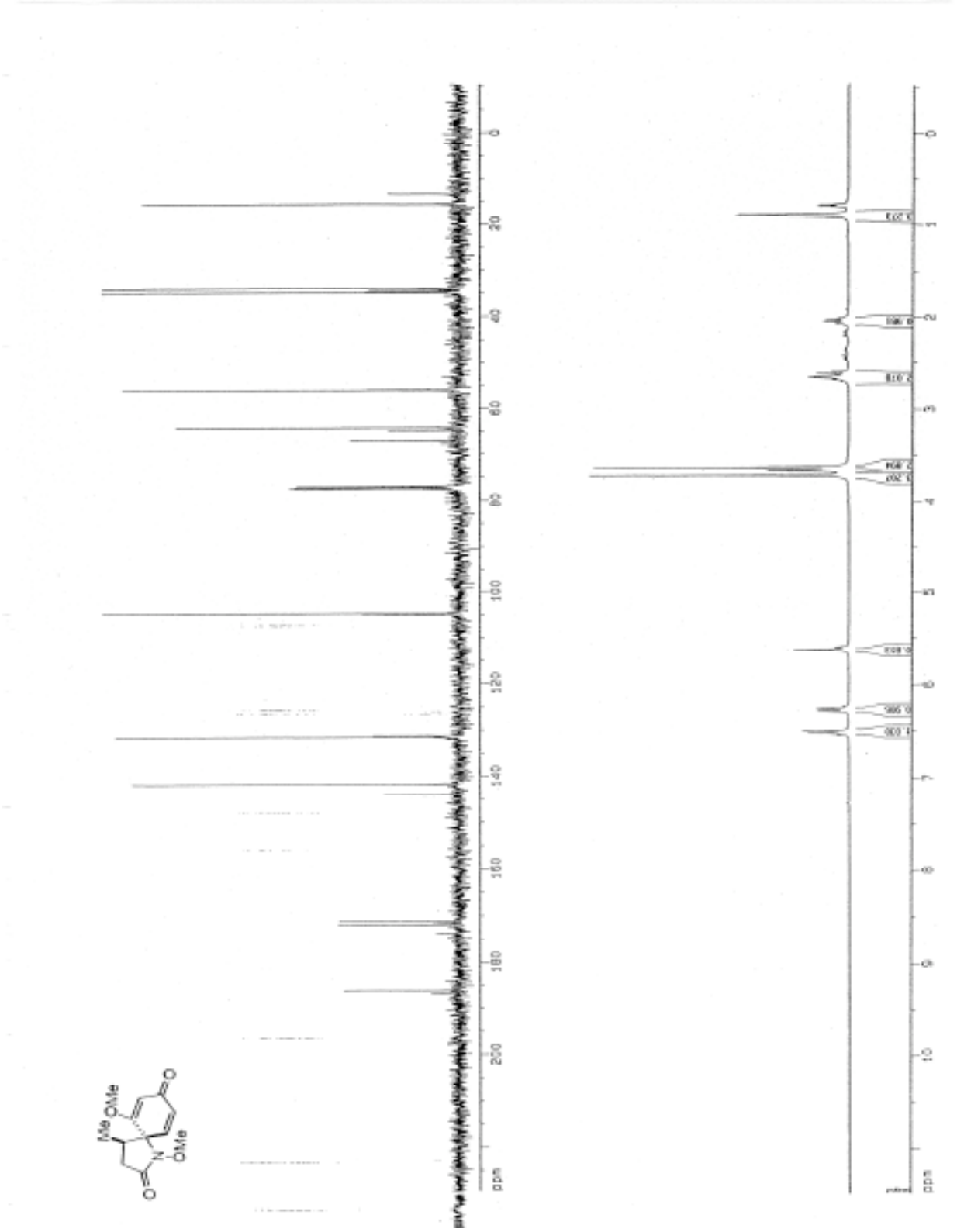
Compound 12k



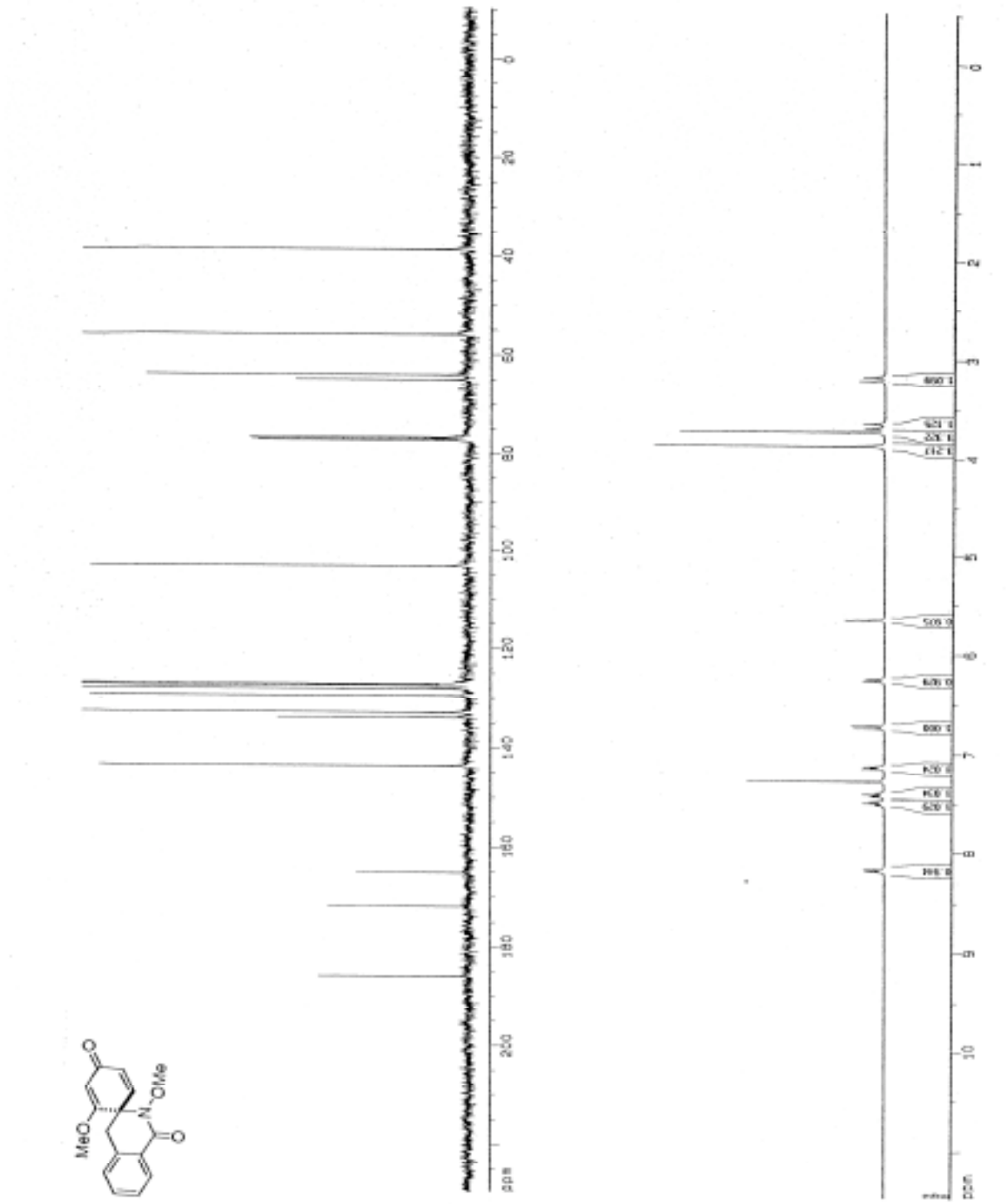
Compound 12l



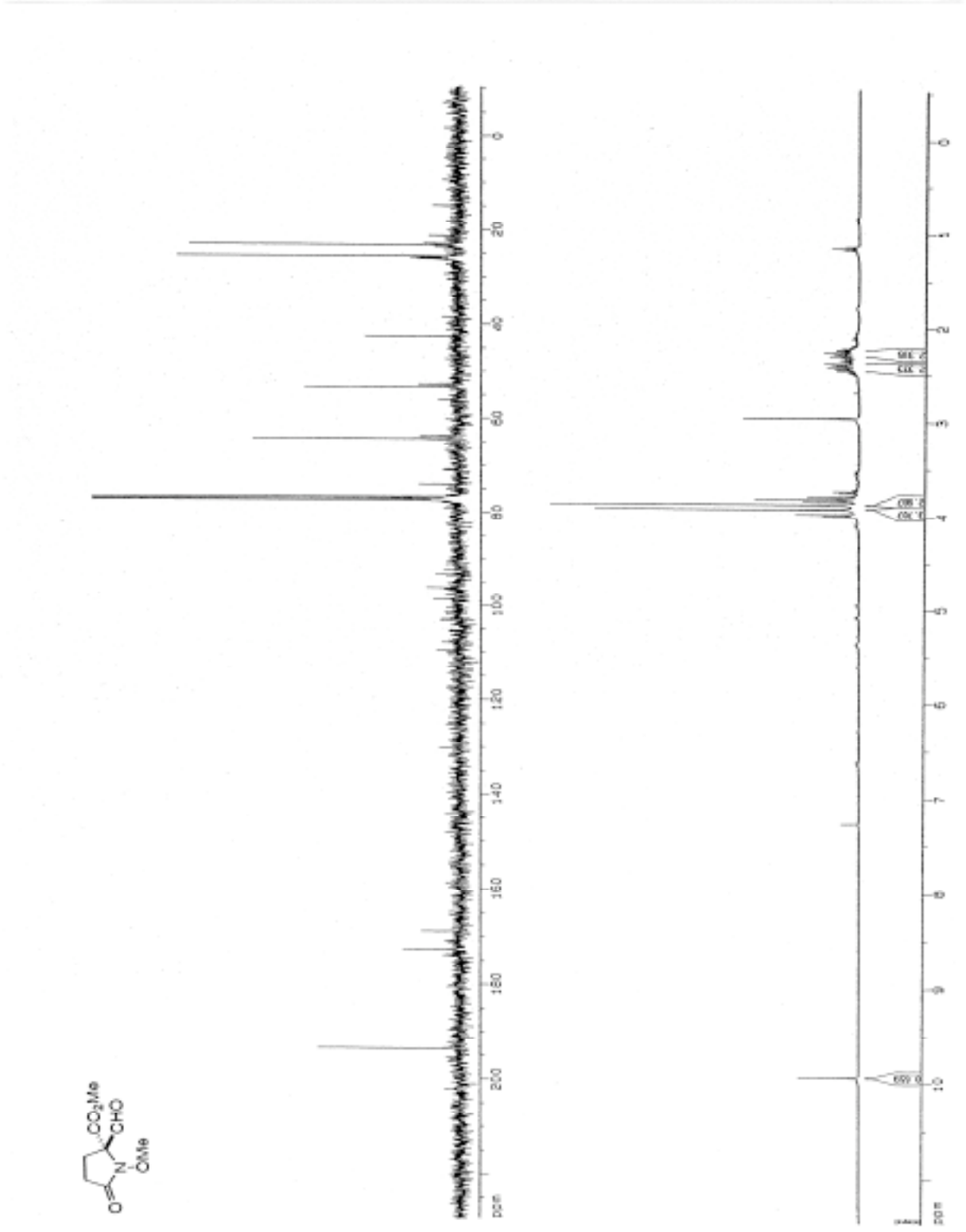
Compound 12m



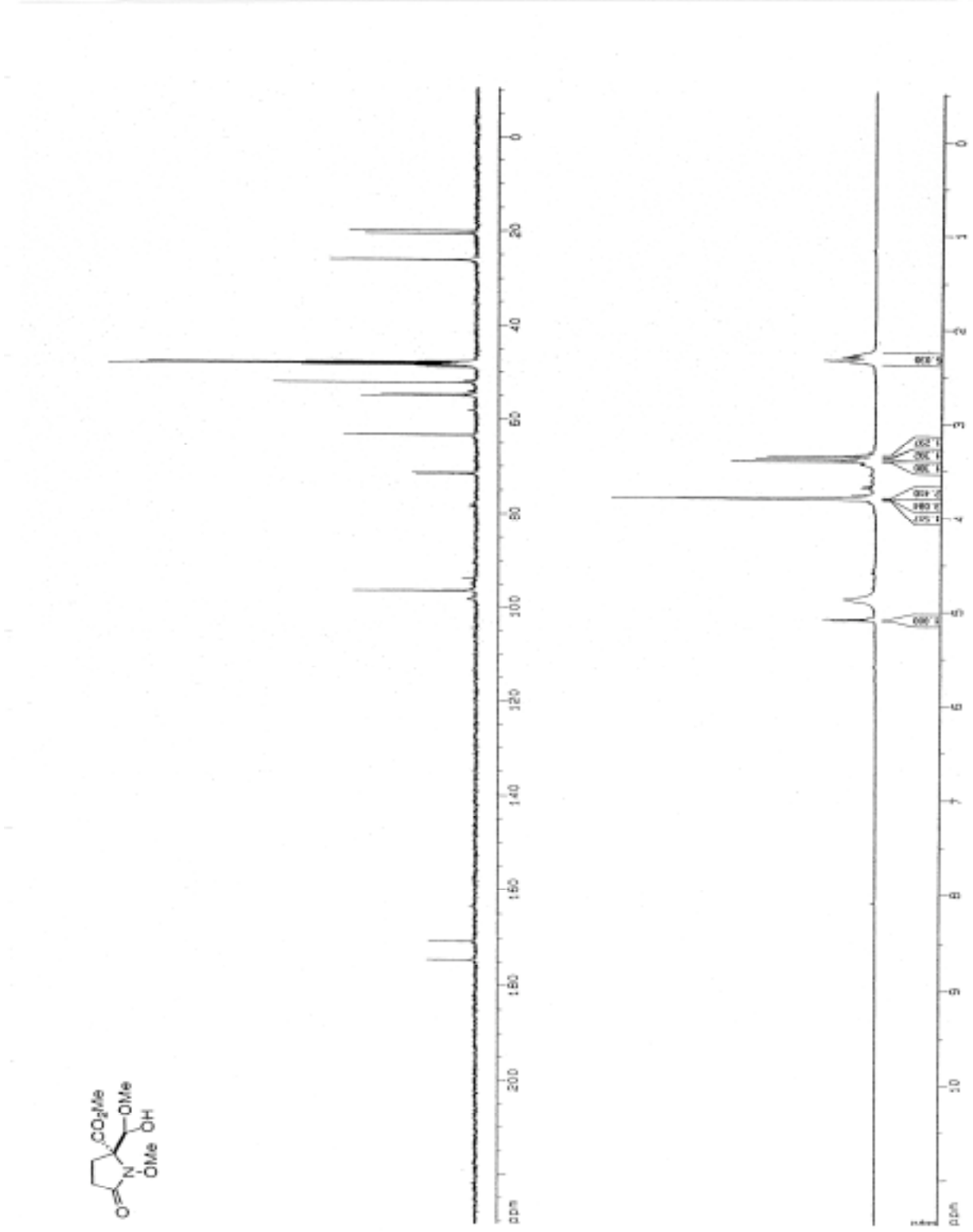
Compound 12n



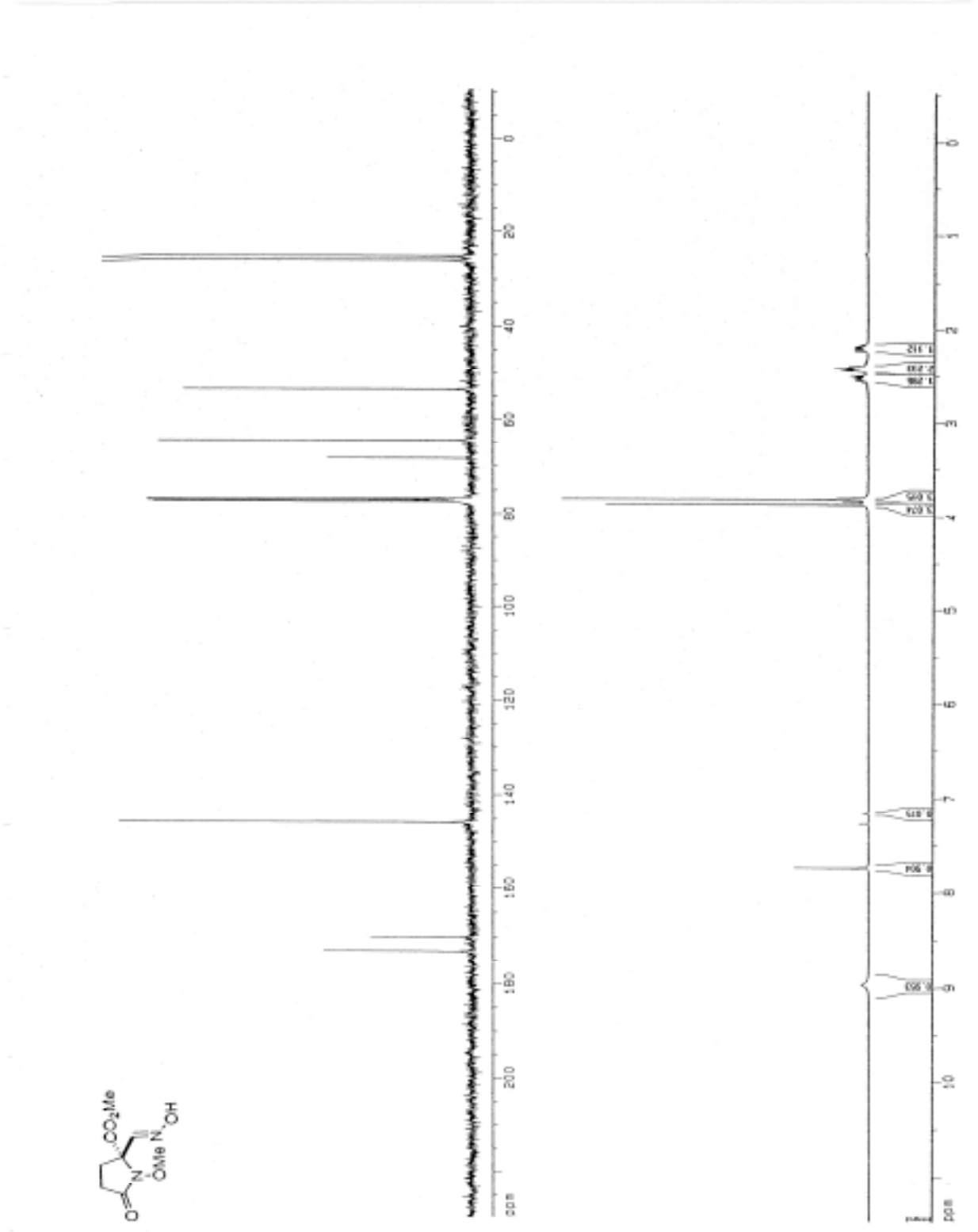
Compound 21



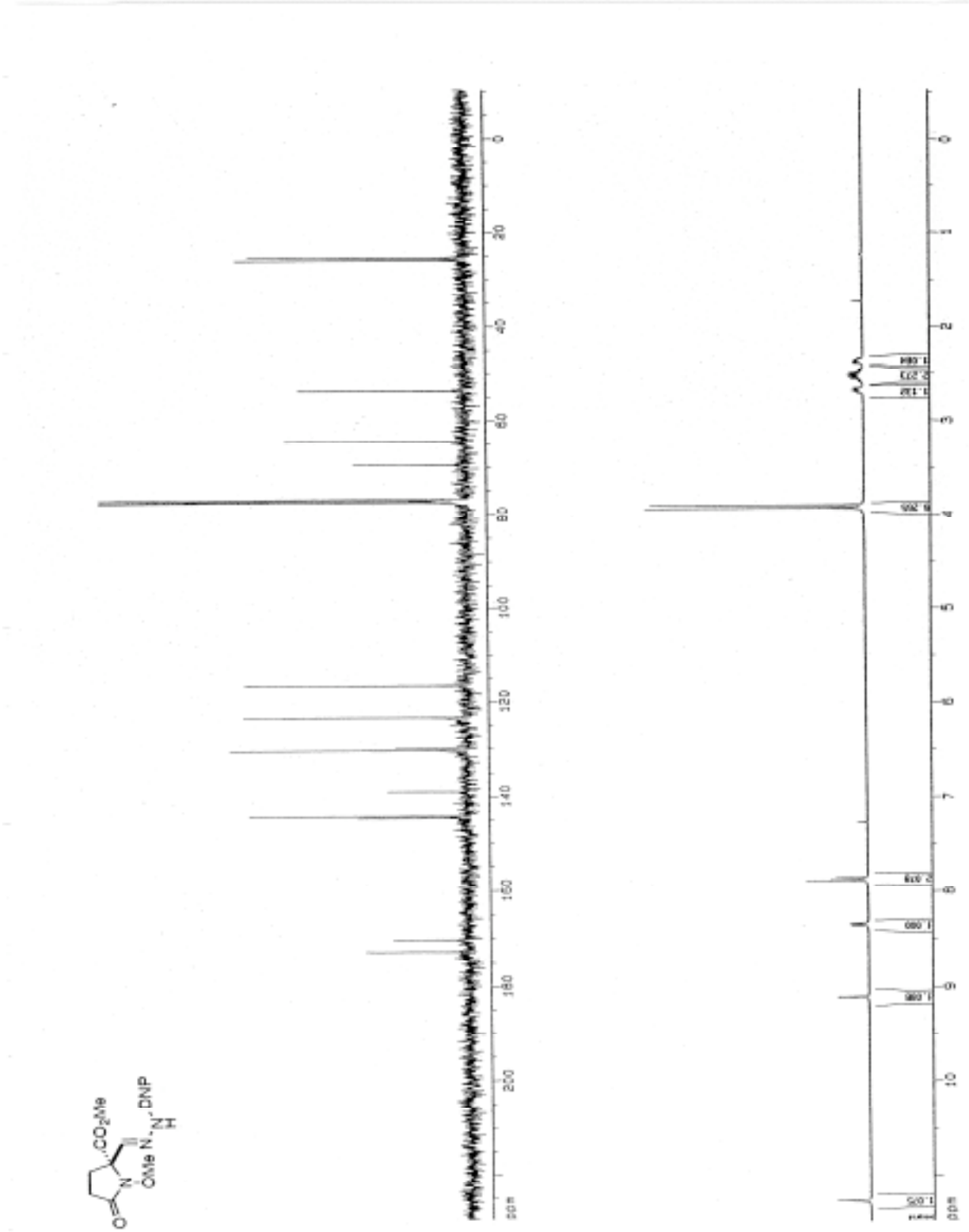
Compound 22



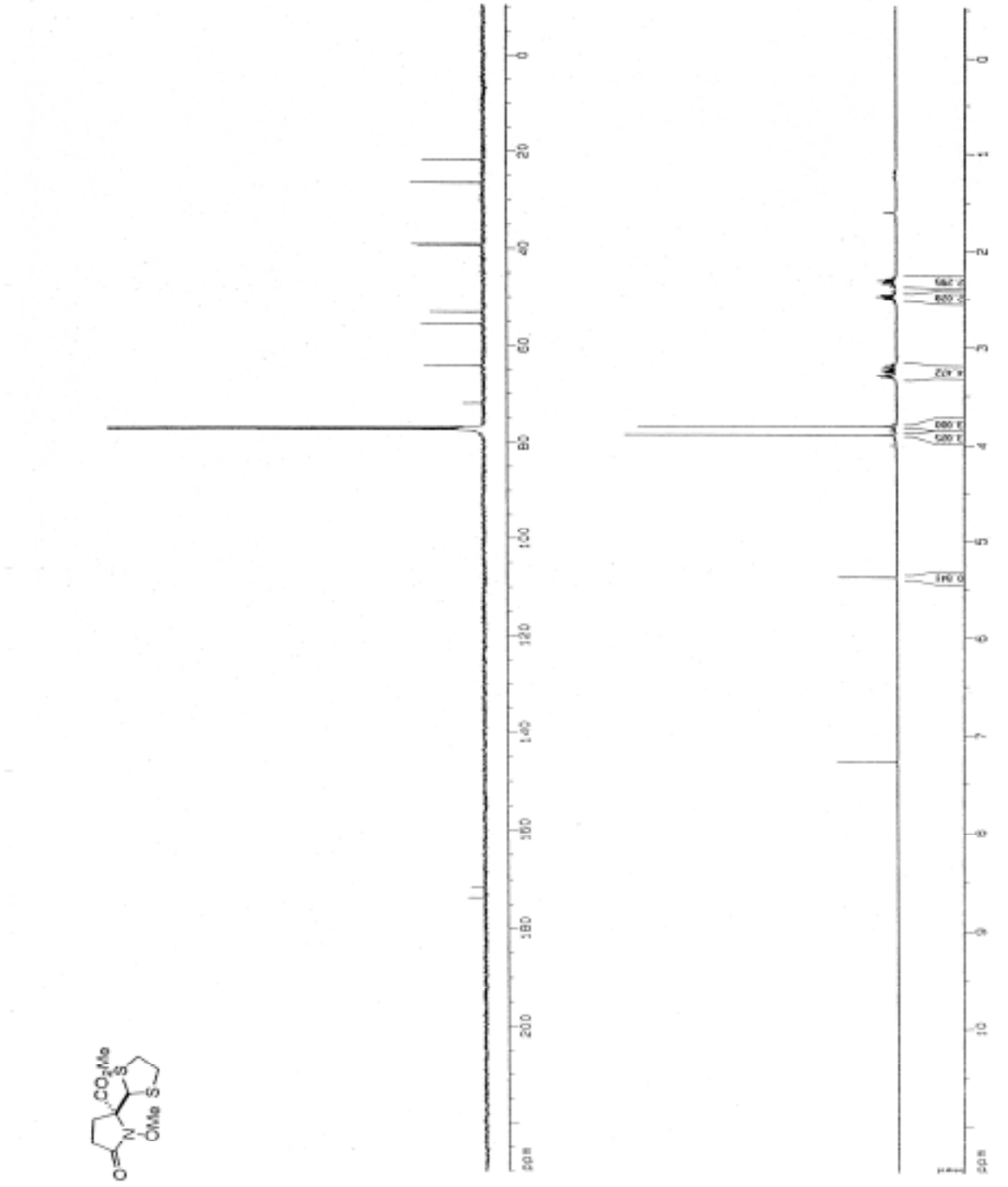
Compound 23



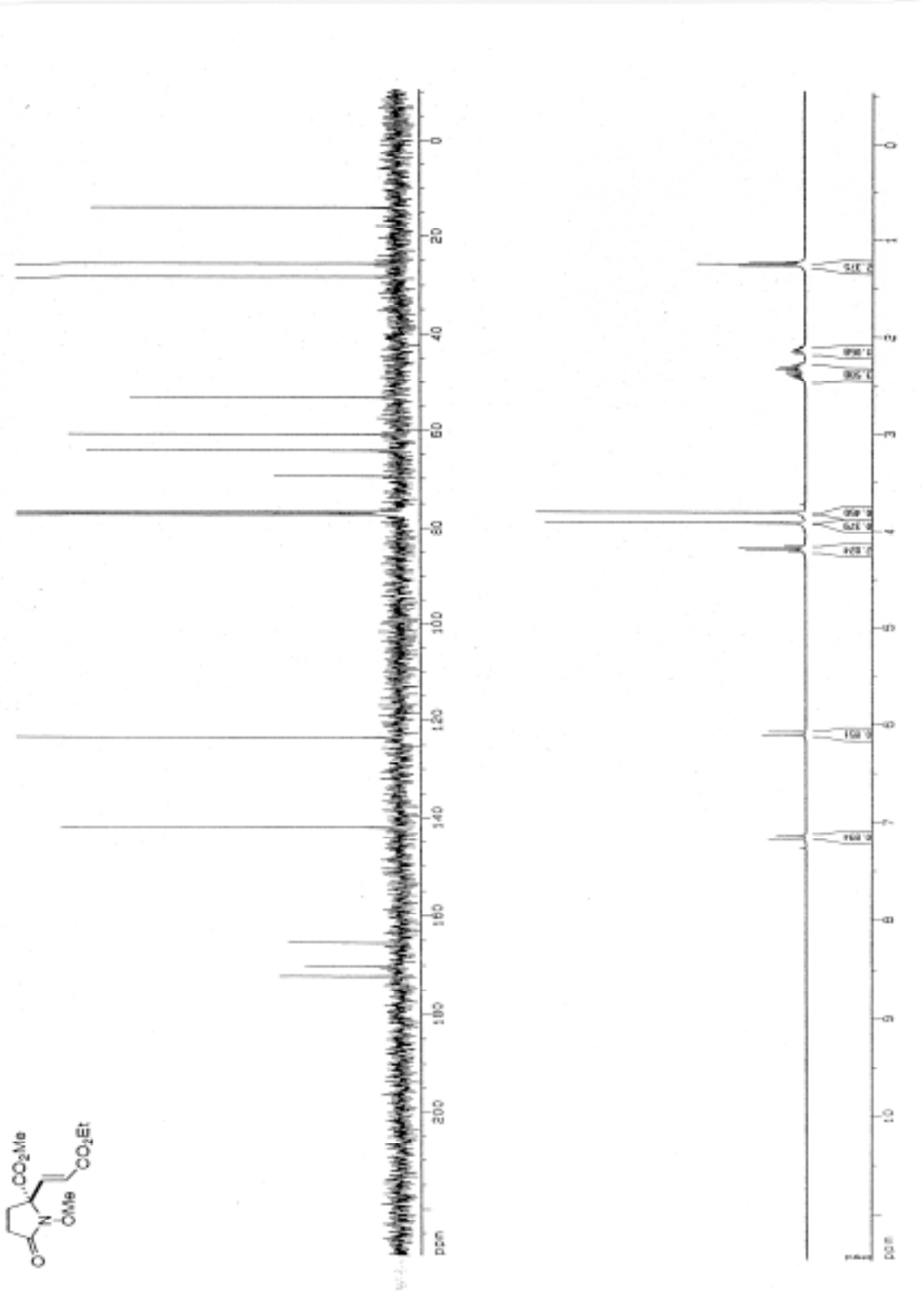
Compound 24



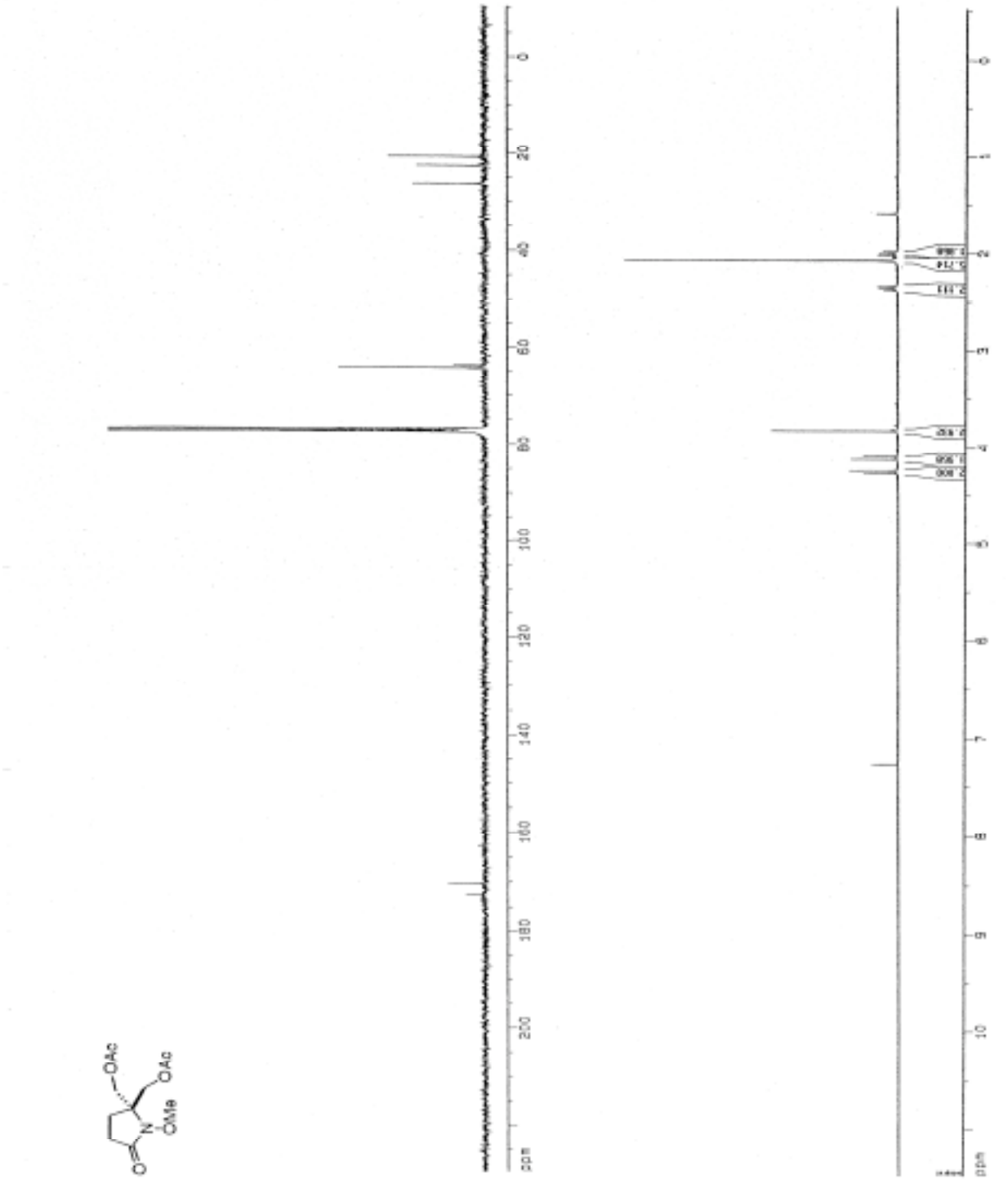
Compound 26



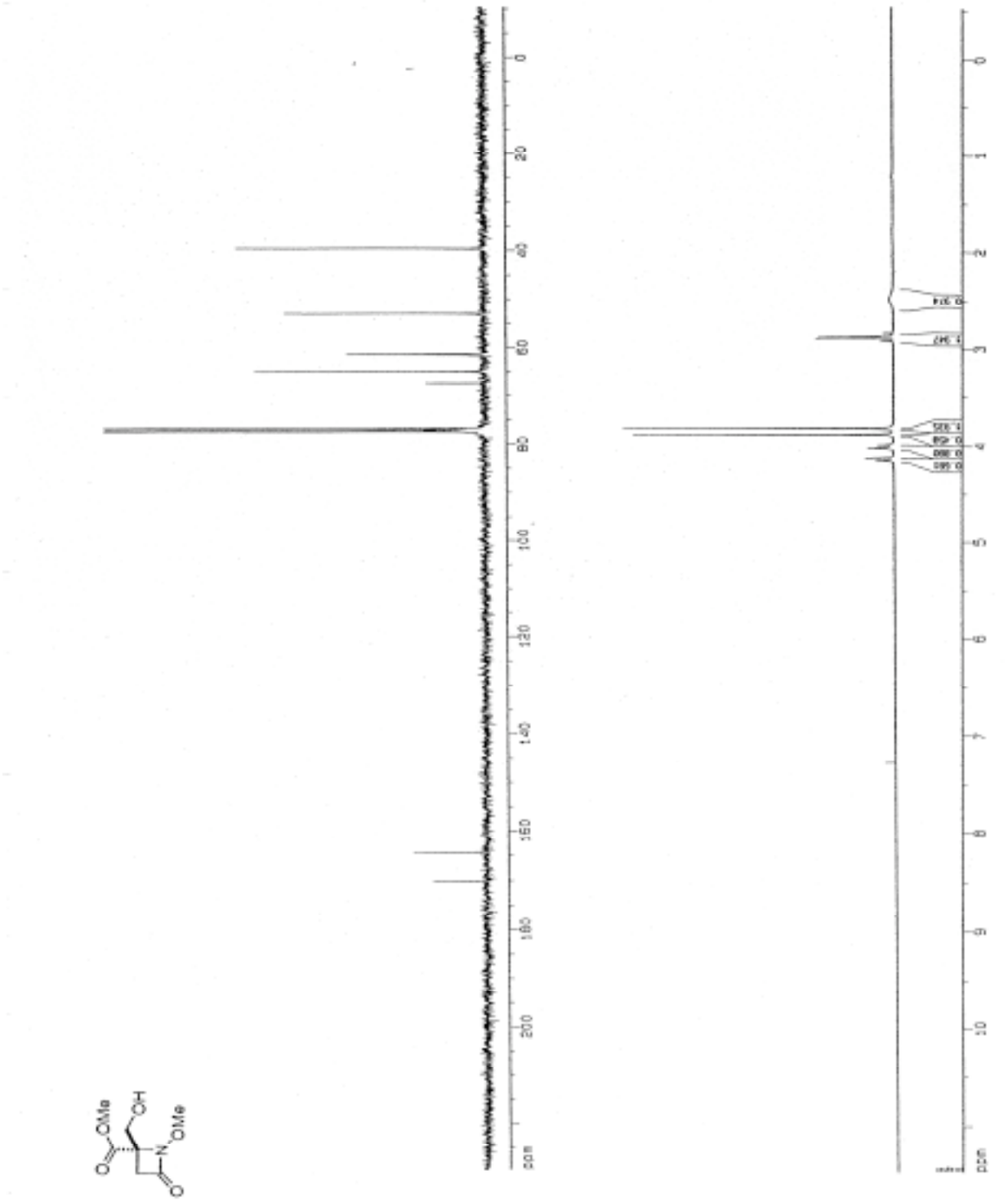
Compound 27



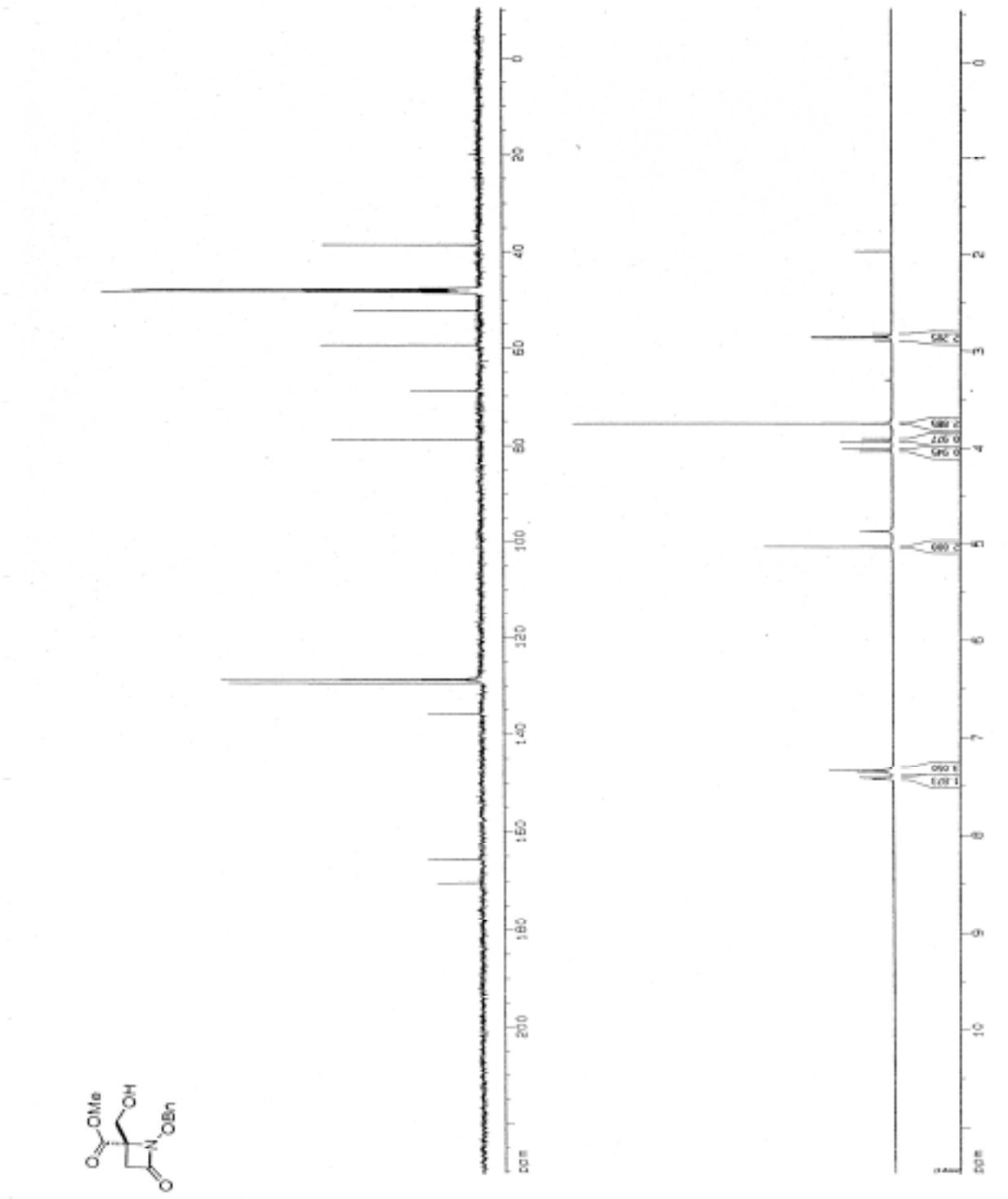
Compound 29


OAc
OAc
OMe
N
O
O
0
20
40
60
80
100
120
140
160
180
200
ppm
0
1
2
3
4
5
6
7
8
9
10
ppm

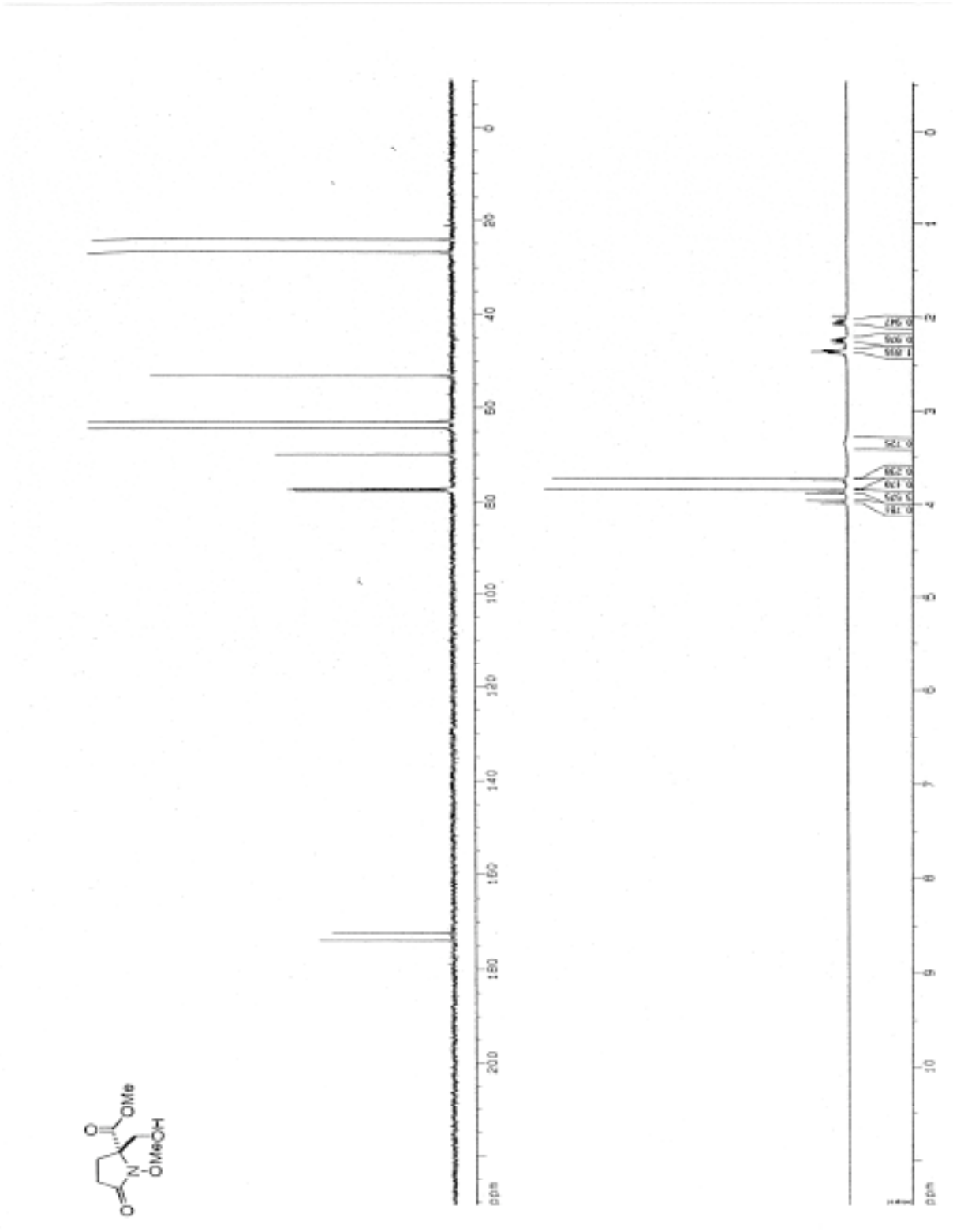
Compound 30a



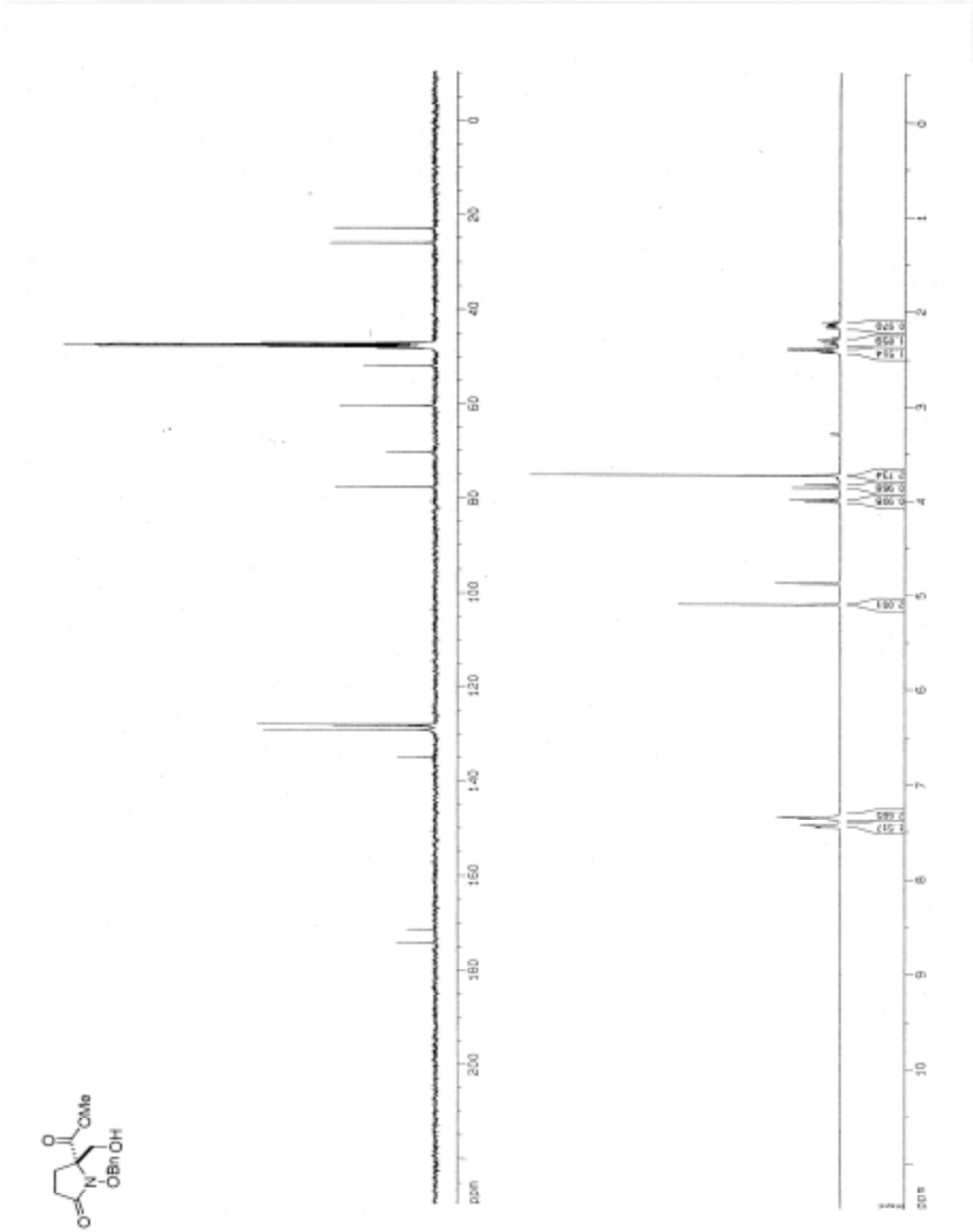
Compound 30b



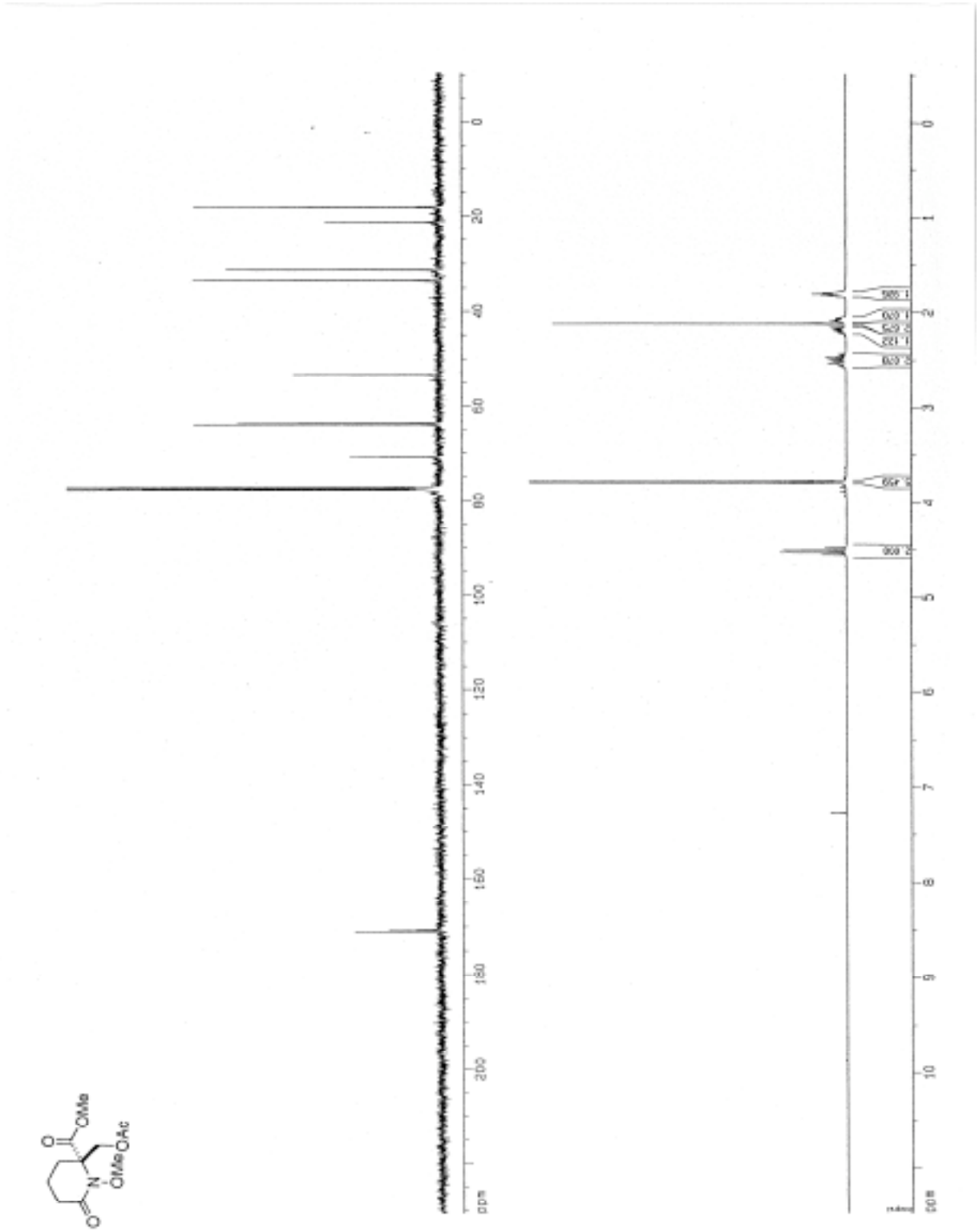
Compound 30c



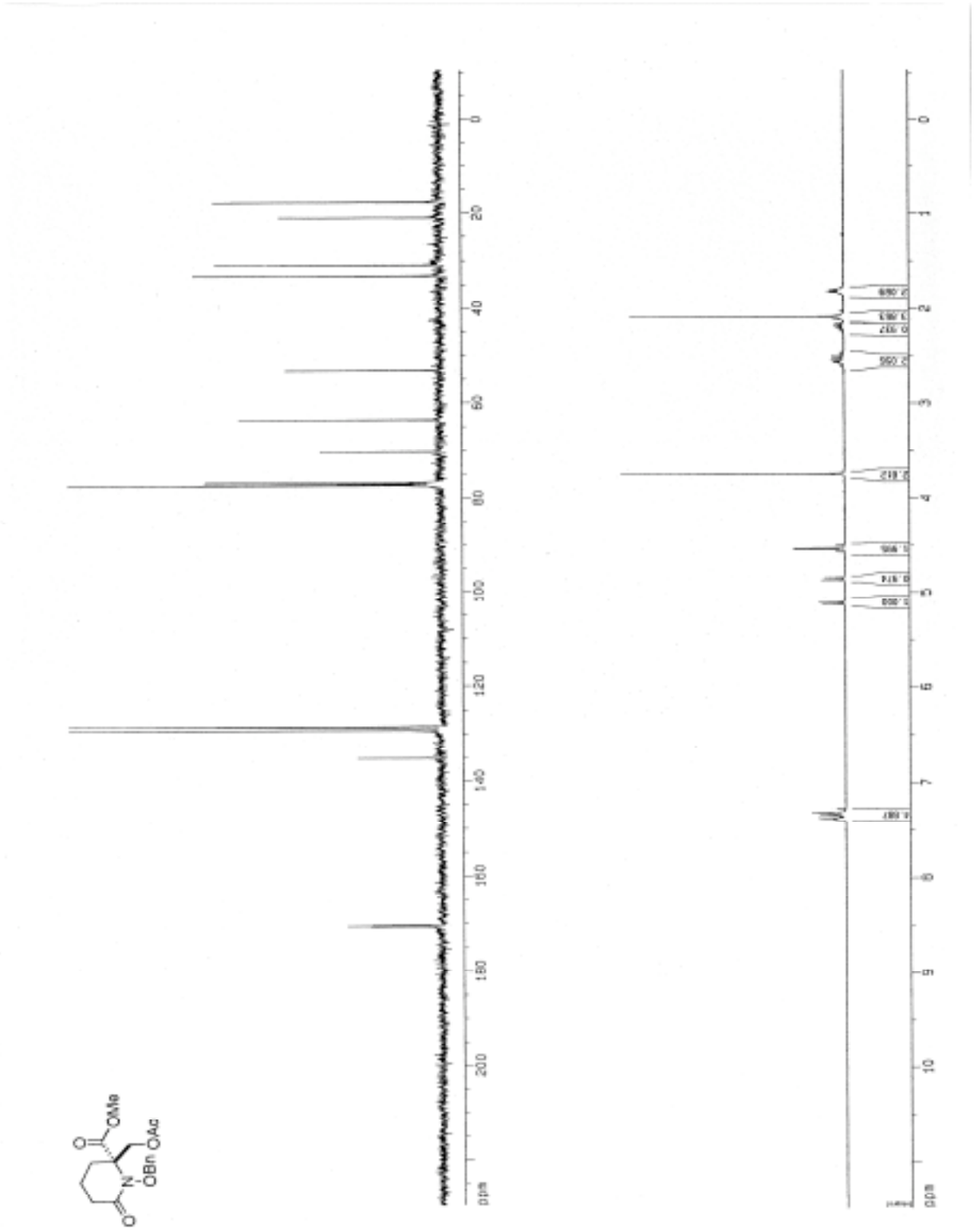
Compound 30d



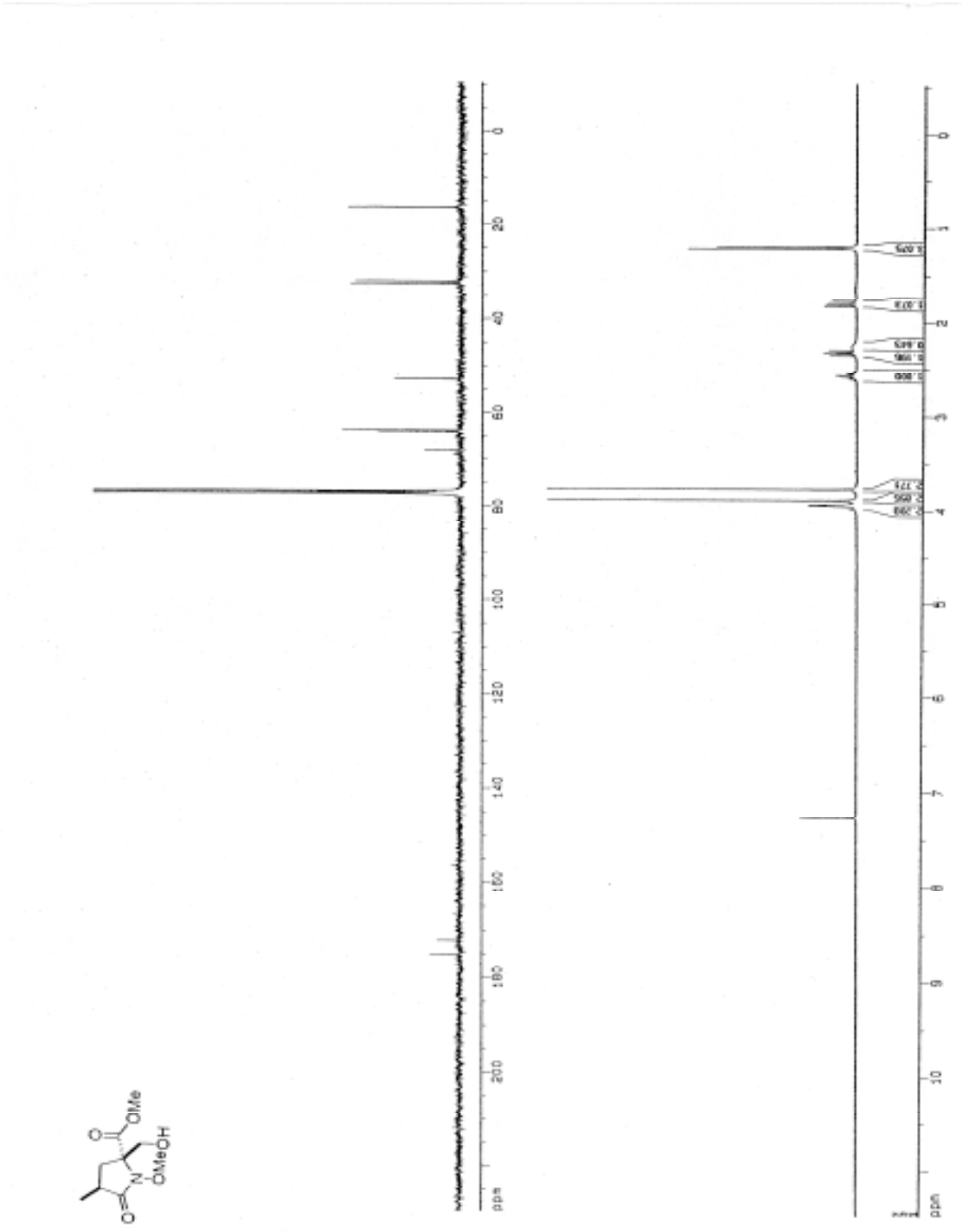
Compound 30e



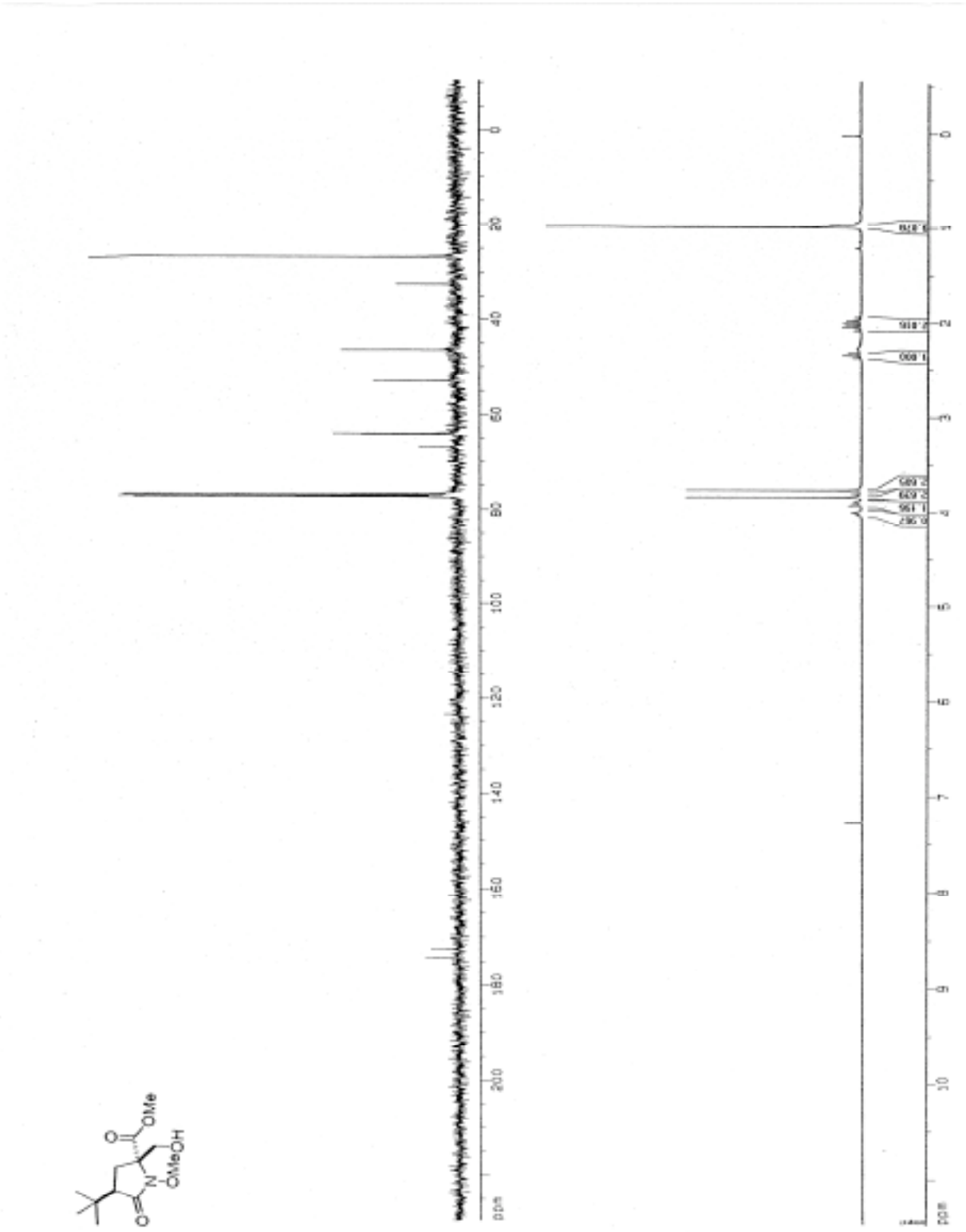
Compound 30f



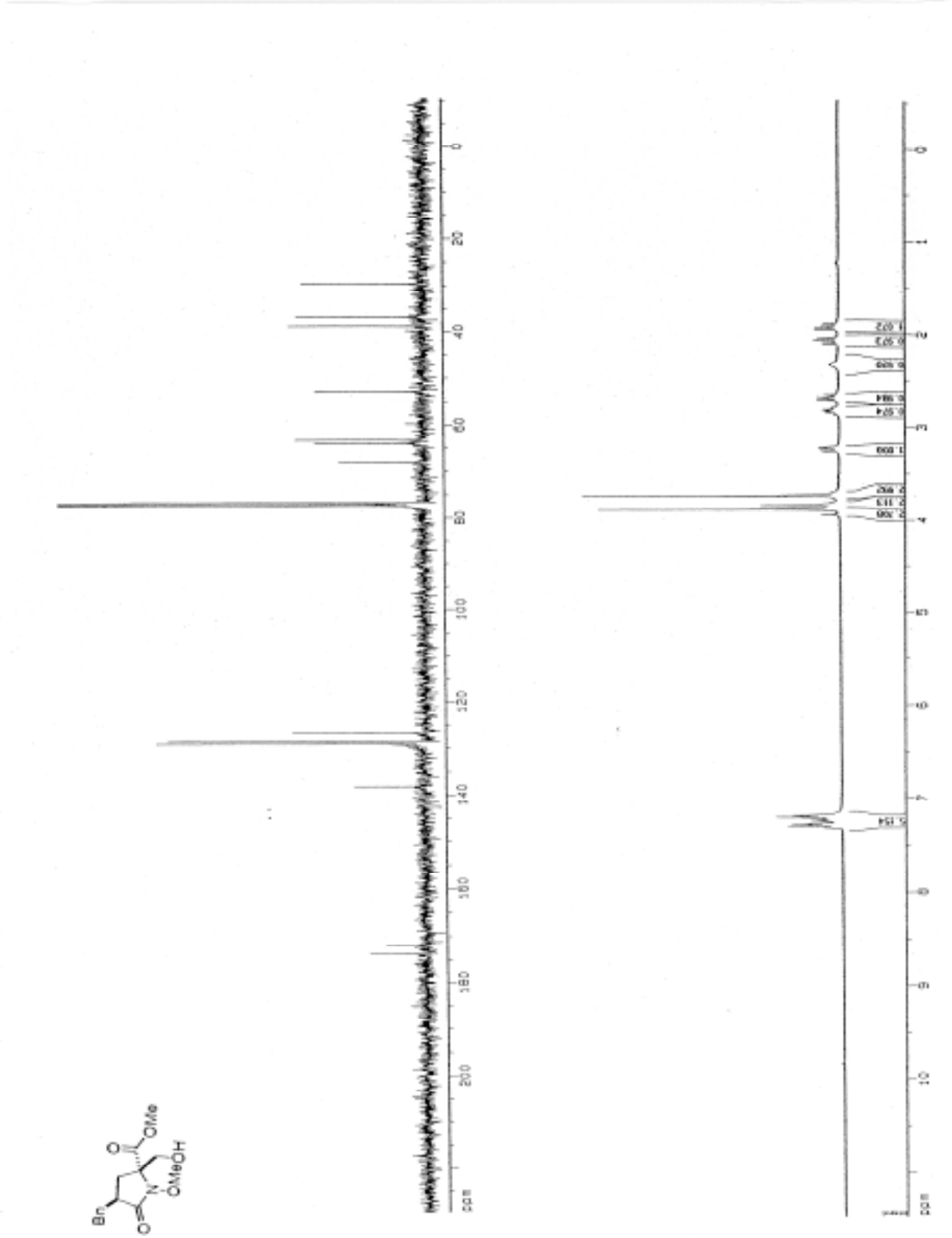
Compound 30g



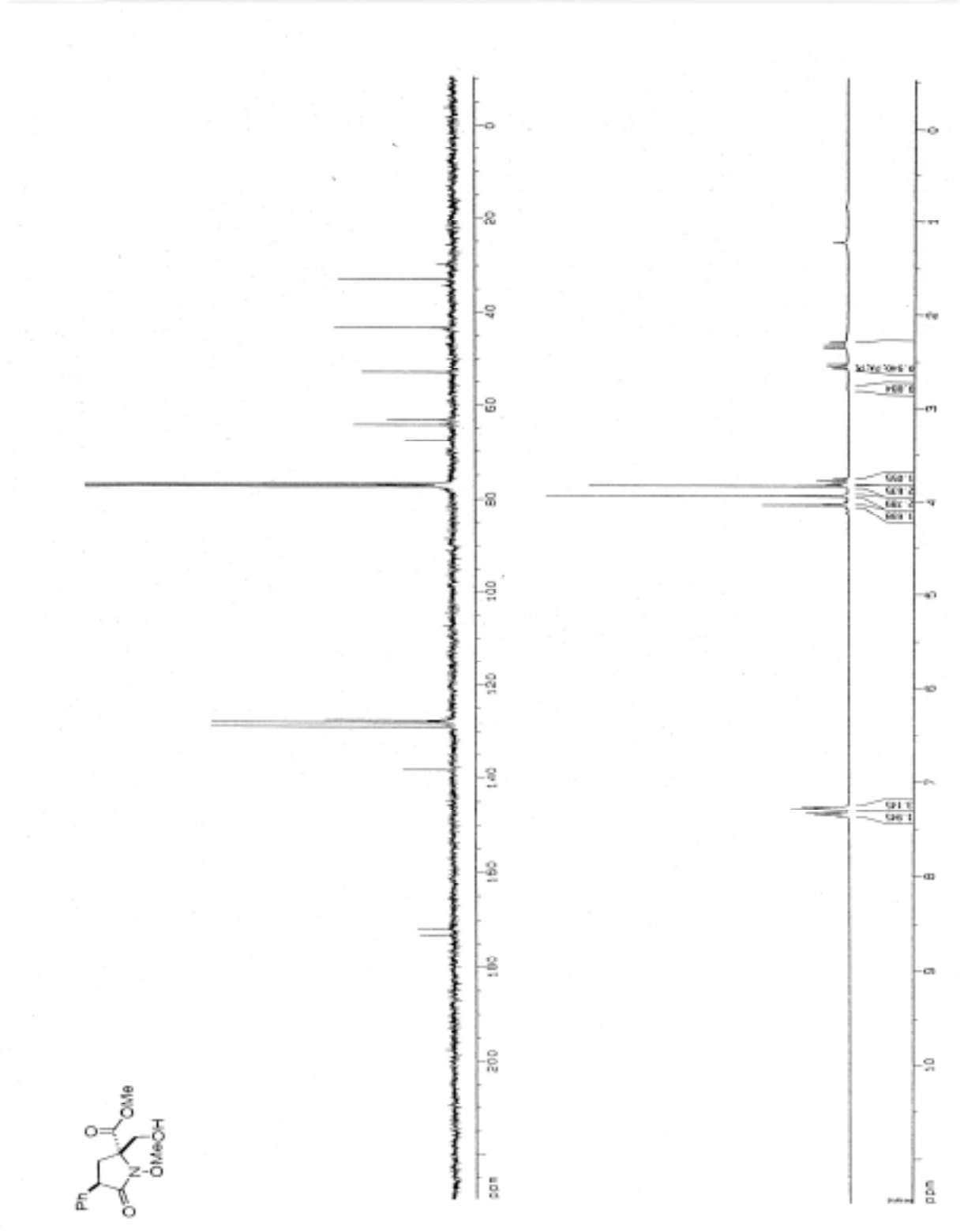
Compound 30h



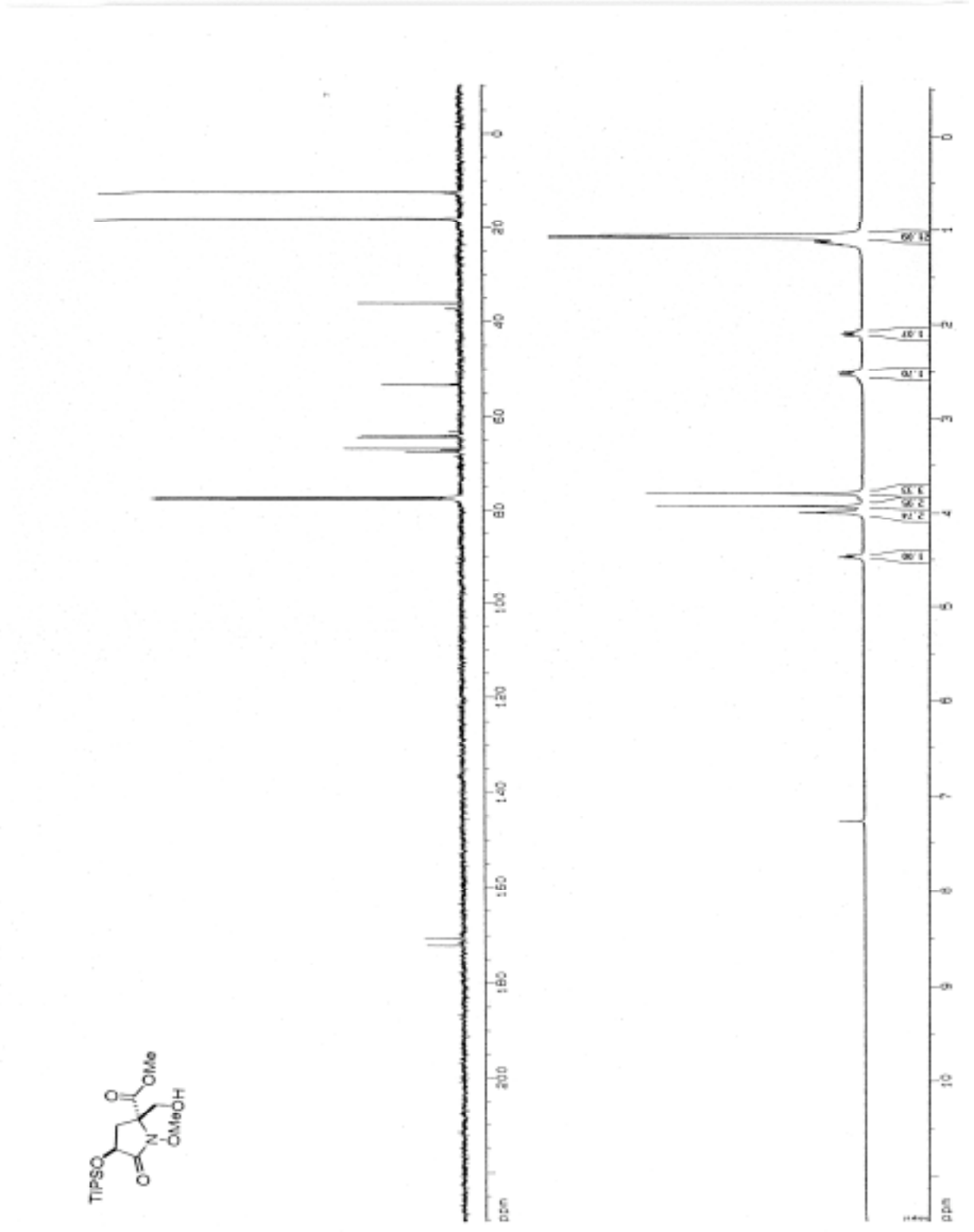
Compound 30i



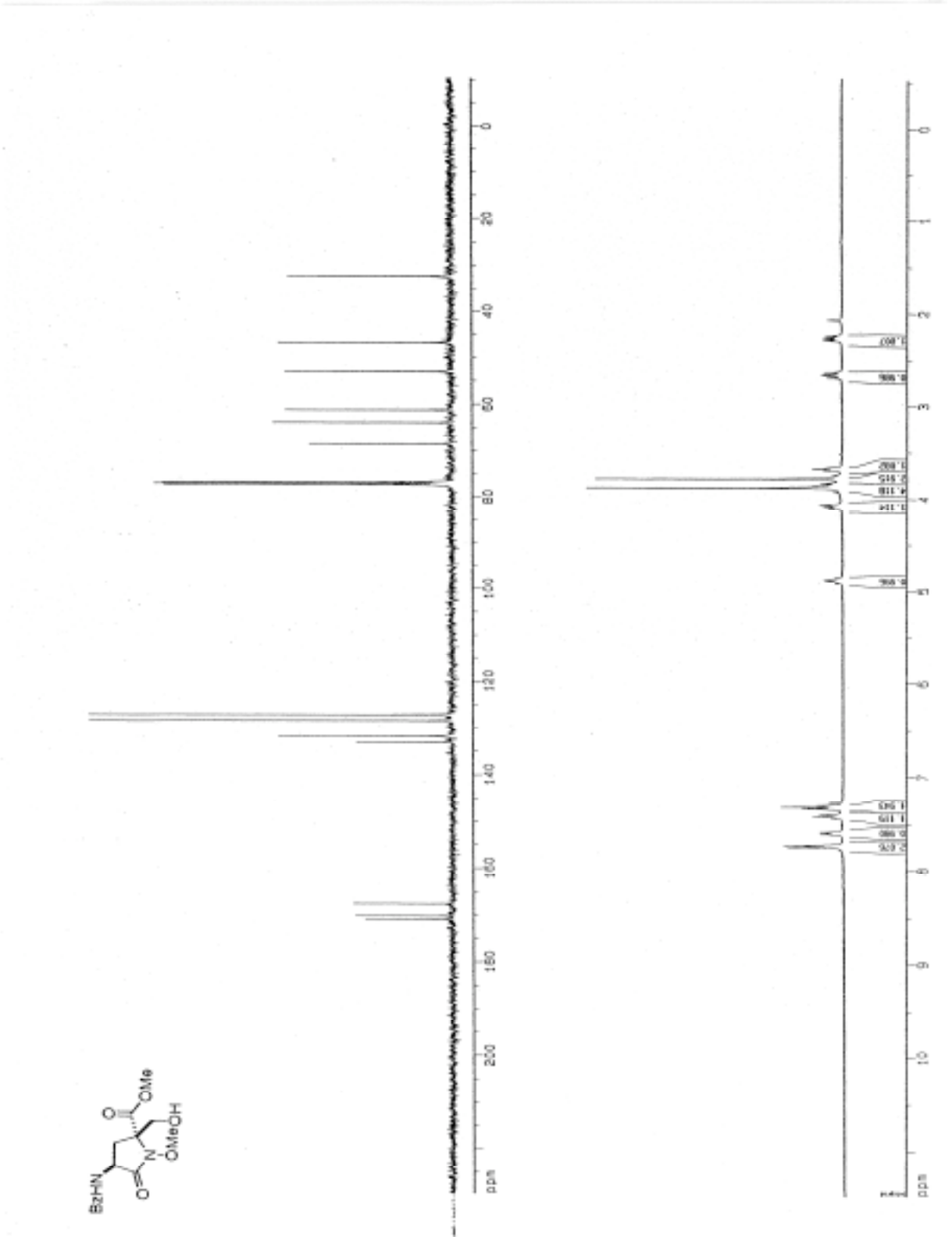
Compound 30j



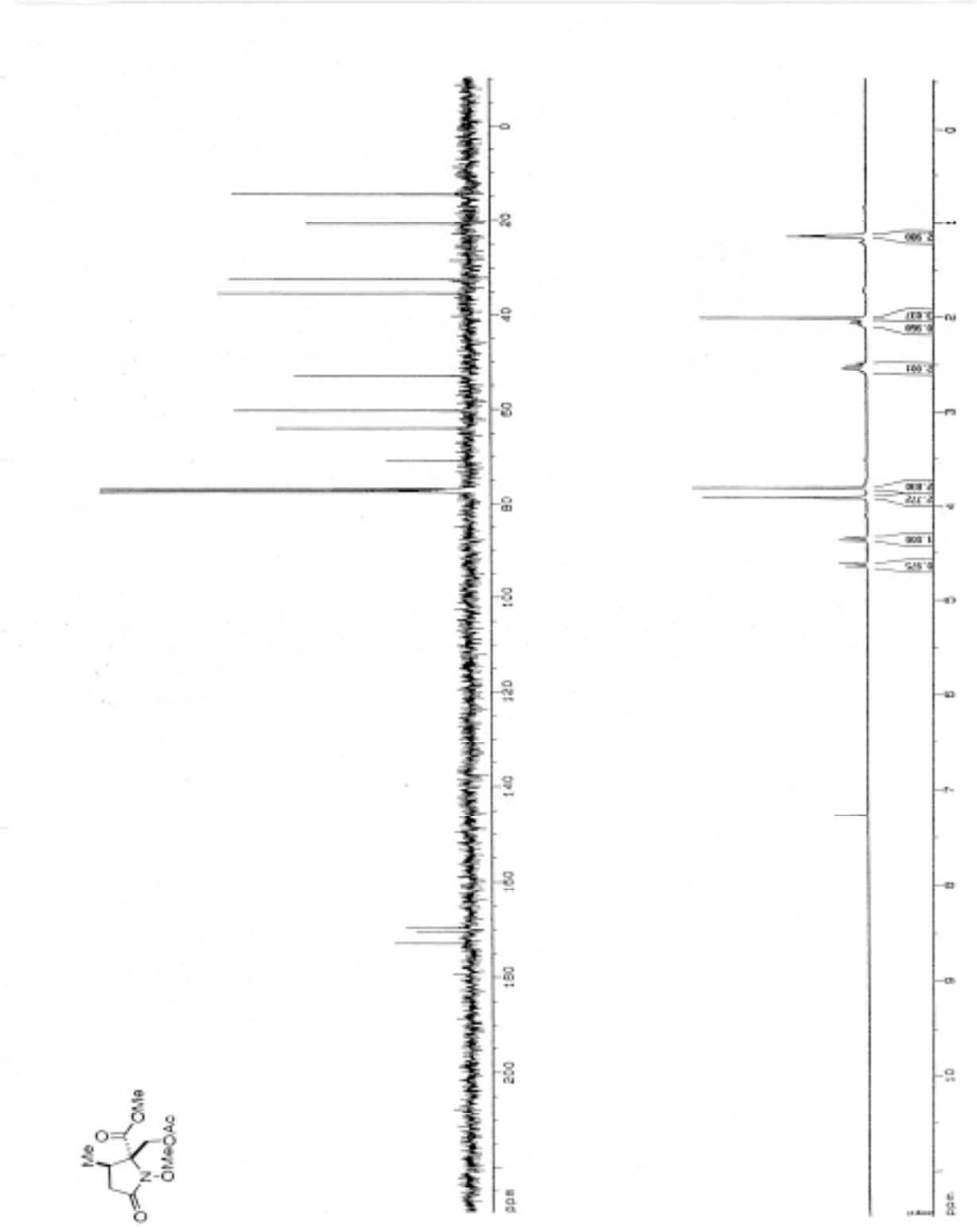
Compound 30k



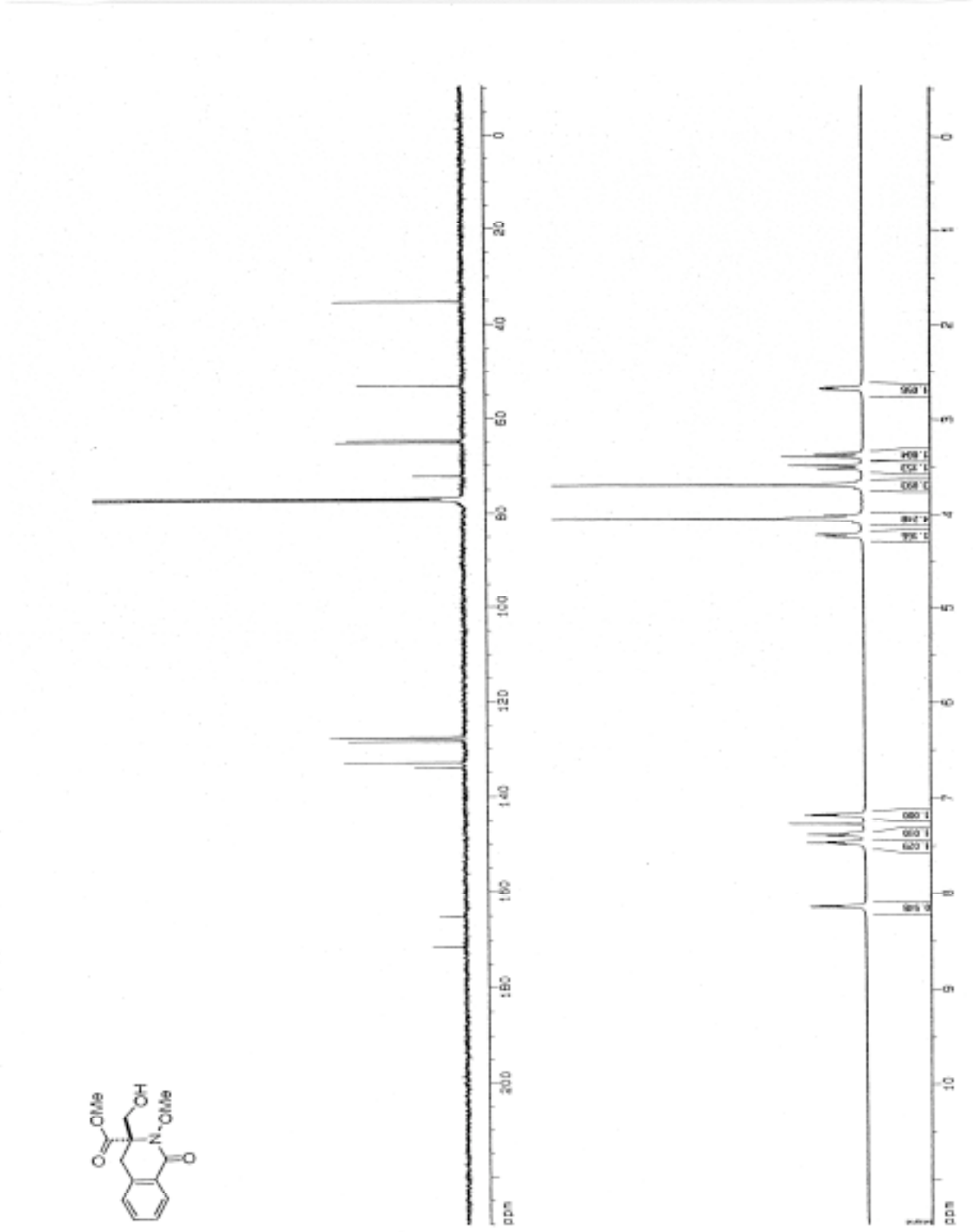
Compound 30l



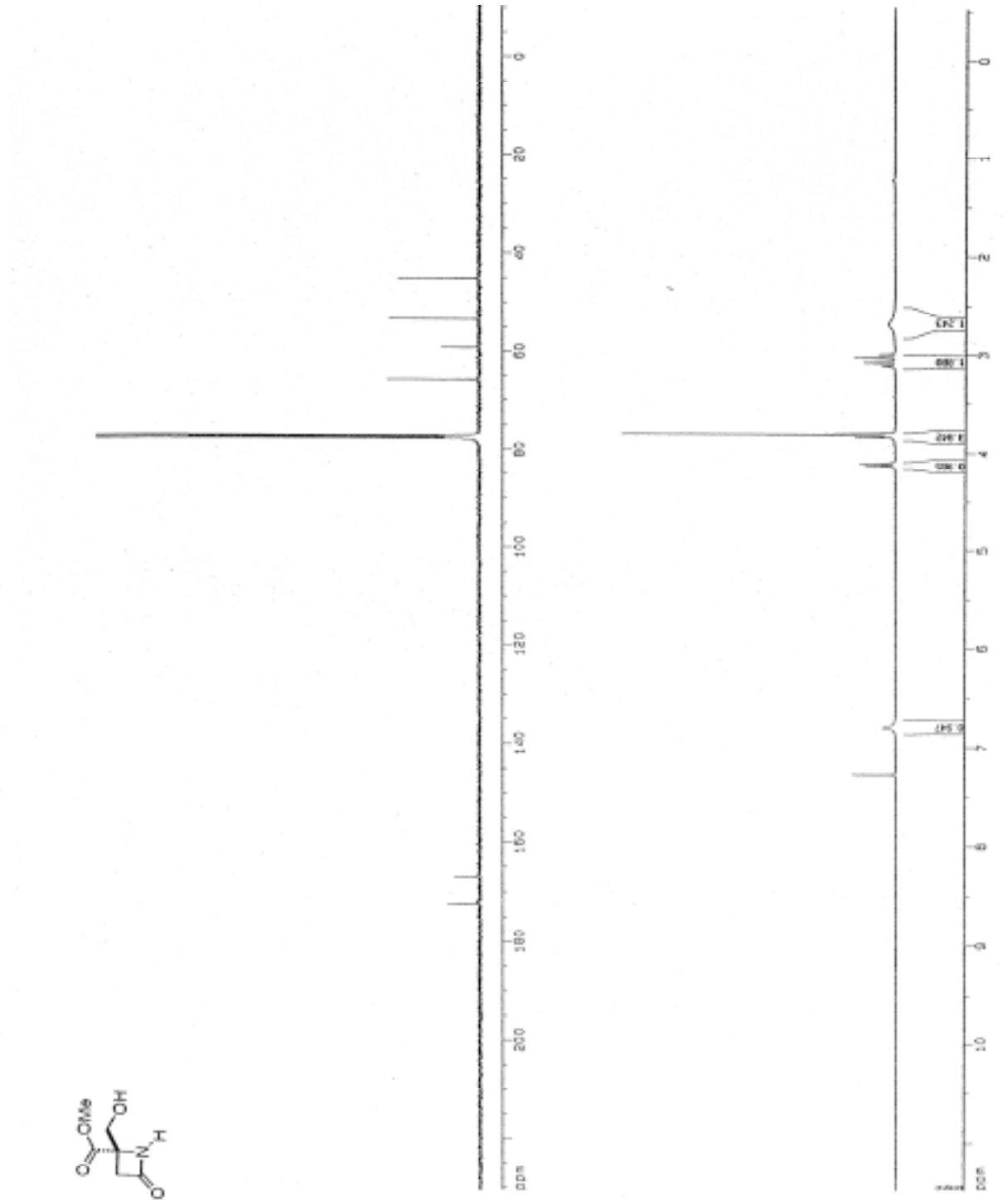
Compound 30m



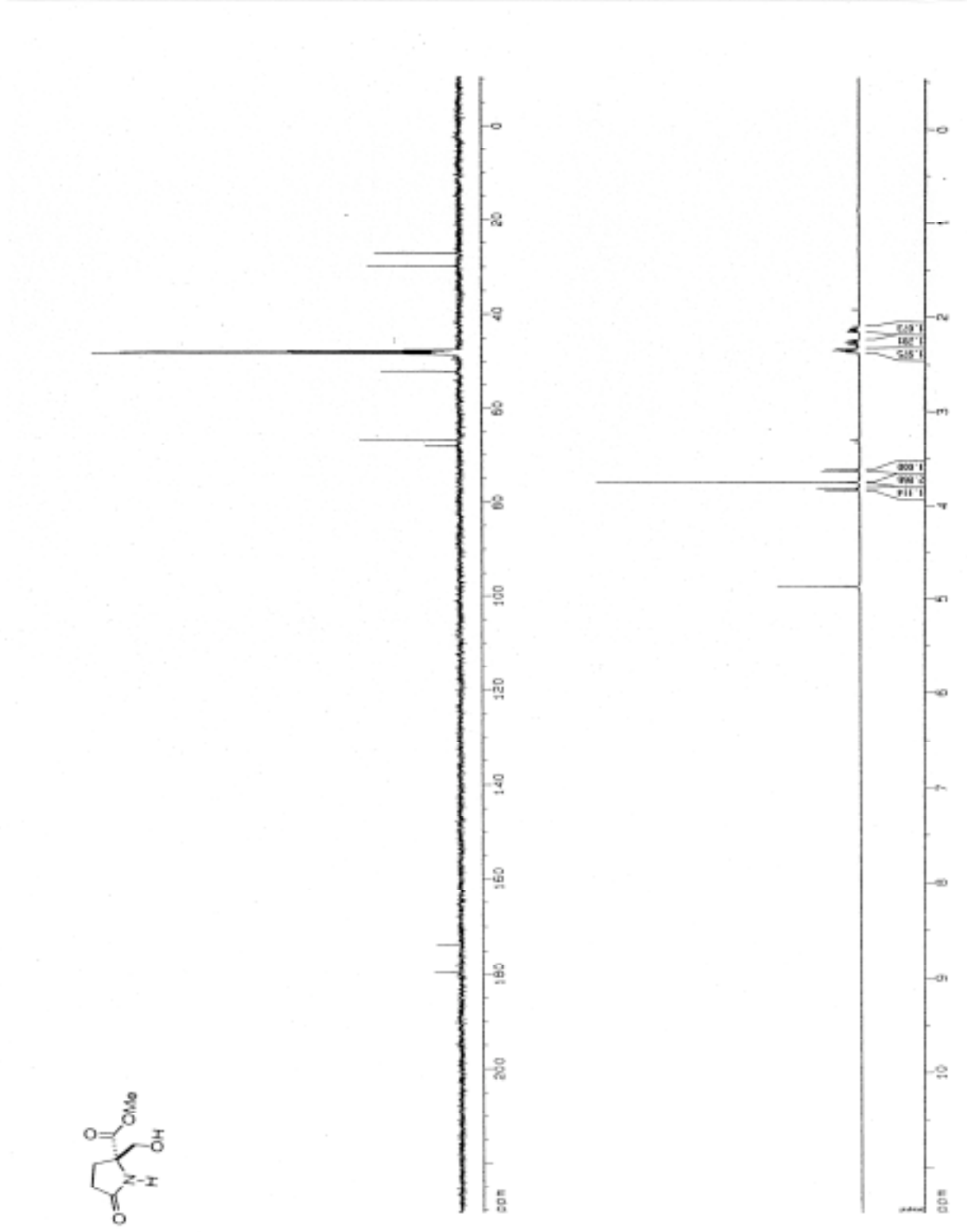
Compound 30n



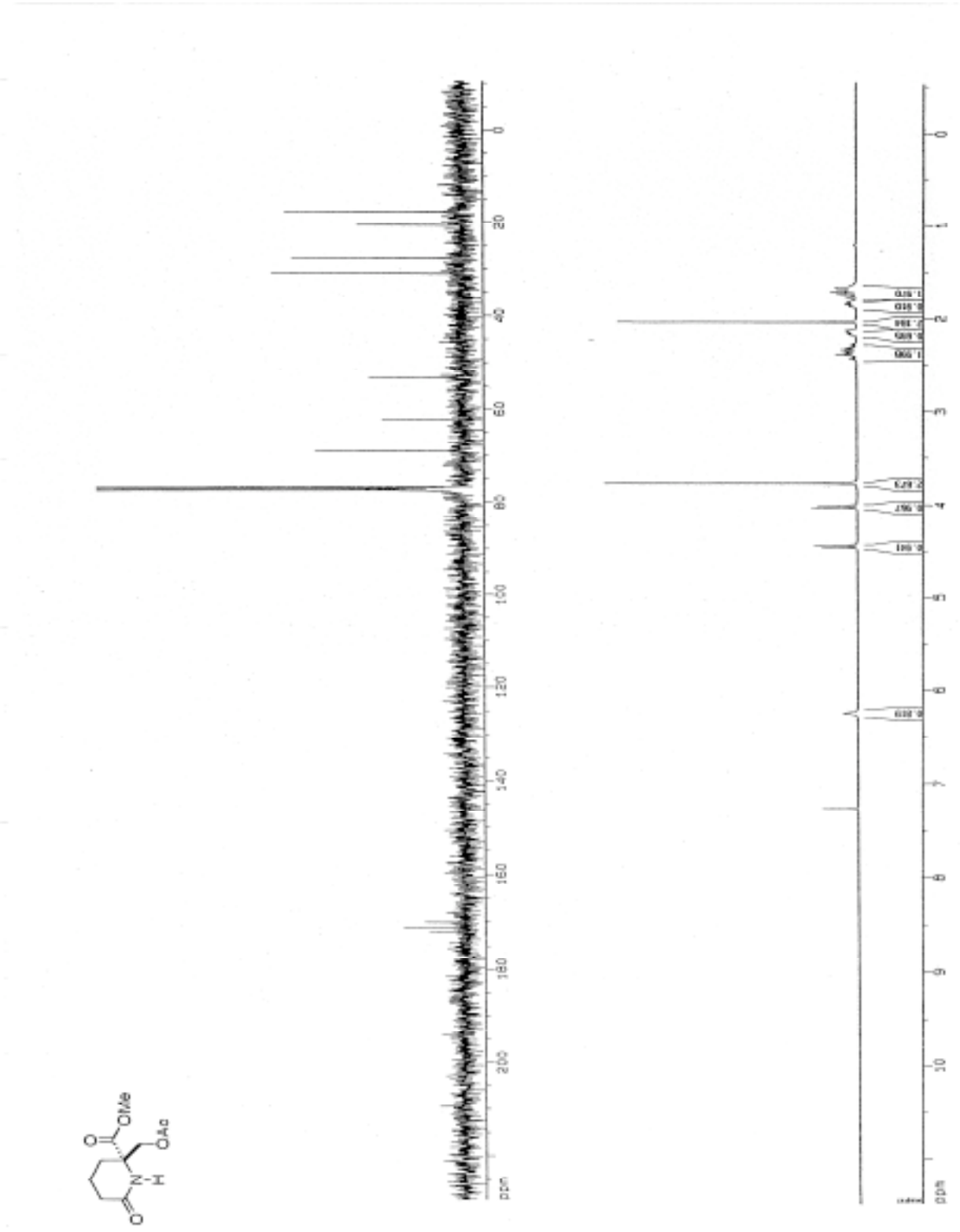
Compound 32a



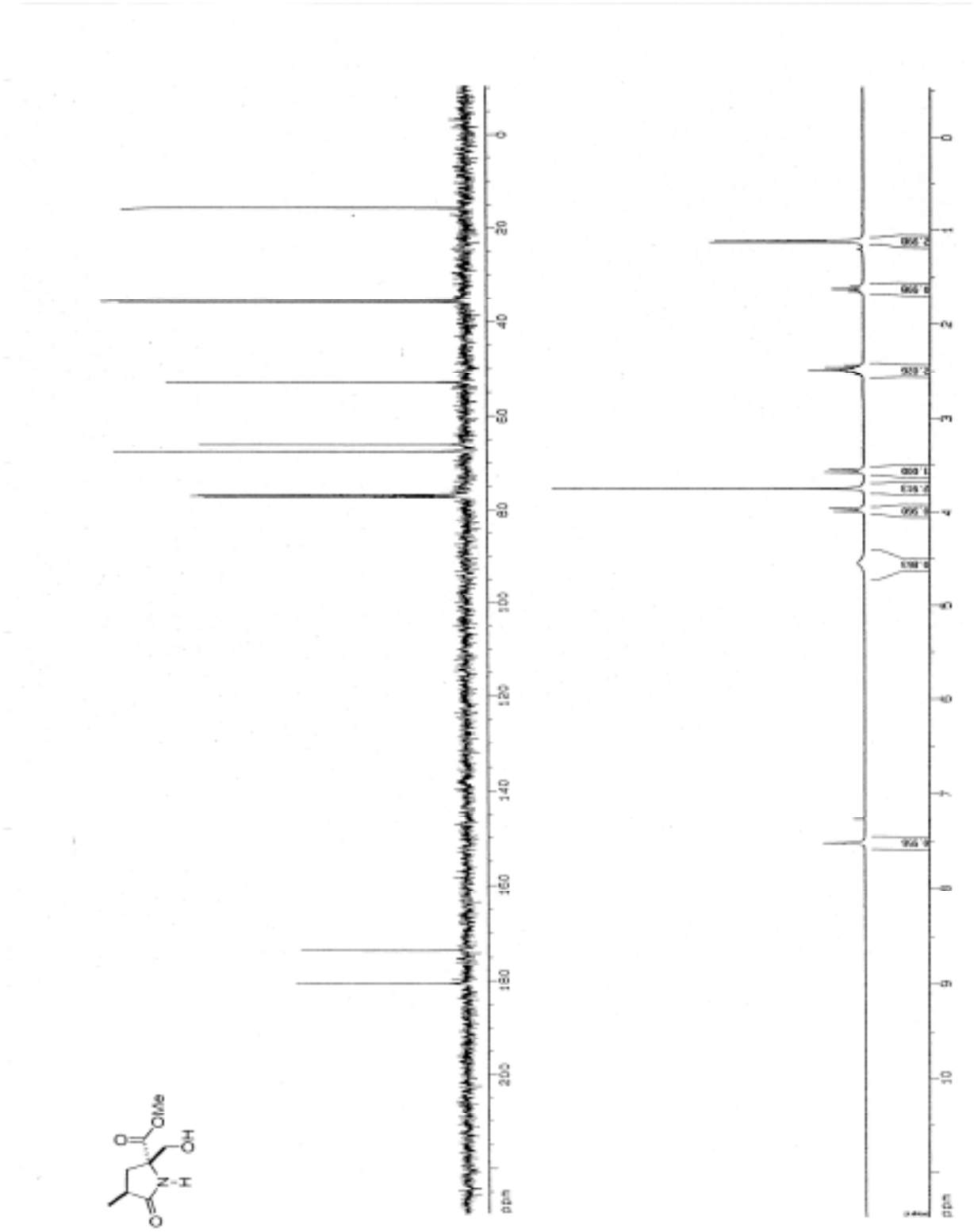
Compound 32c



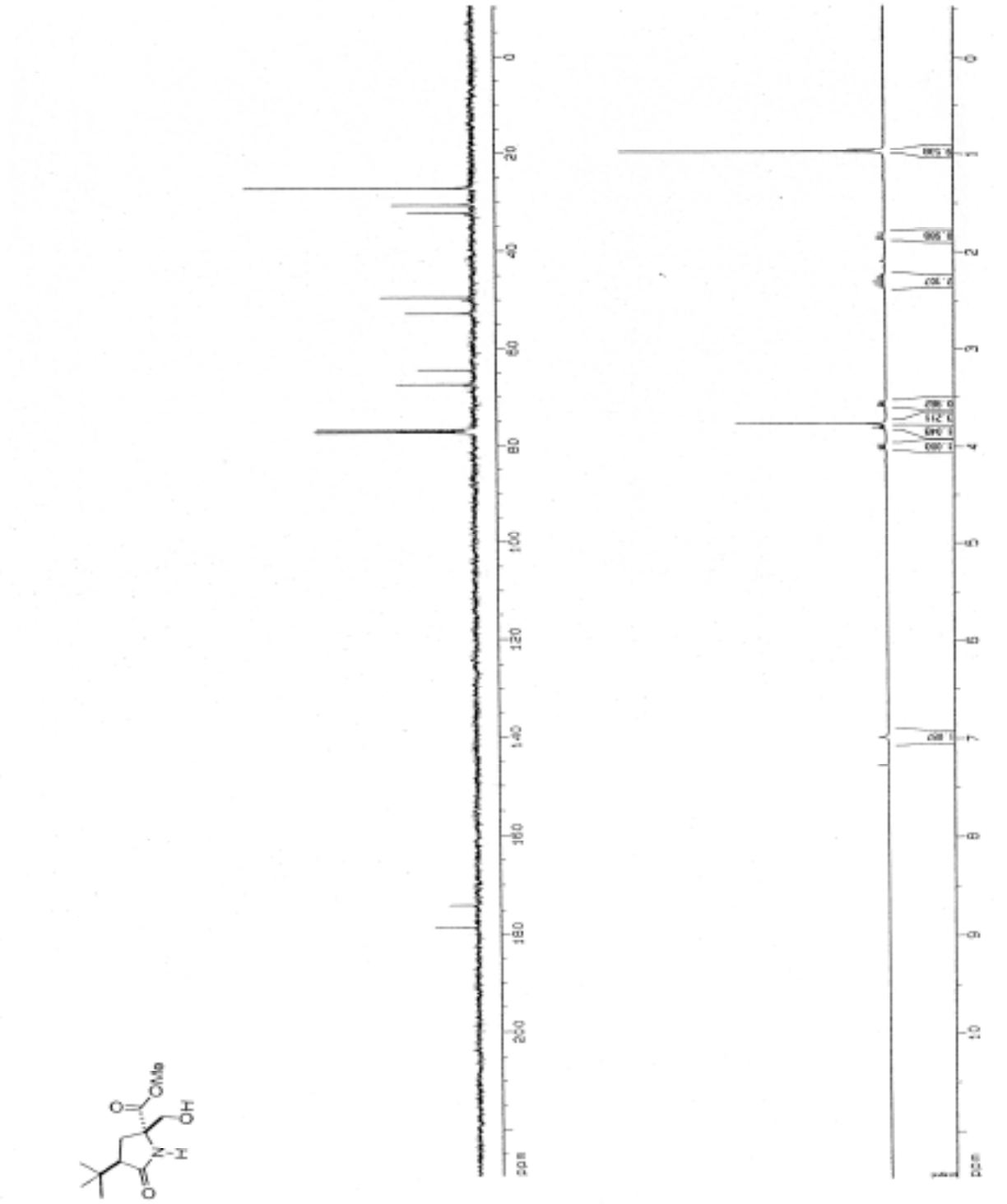
Compound 32e



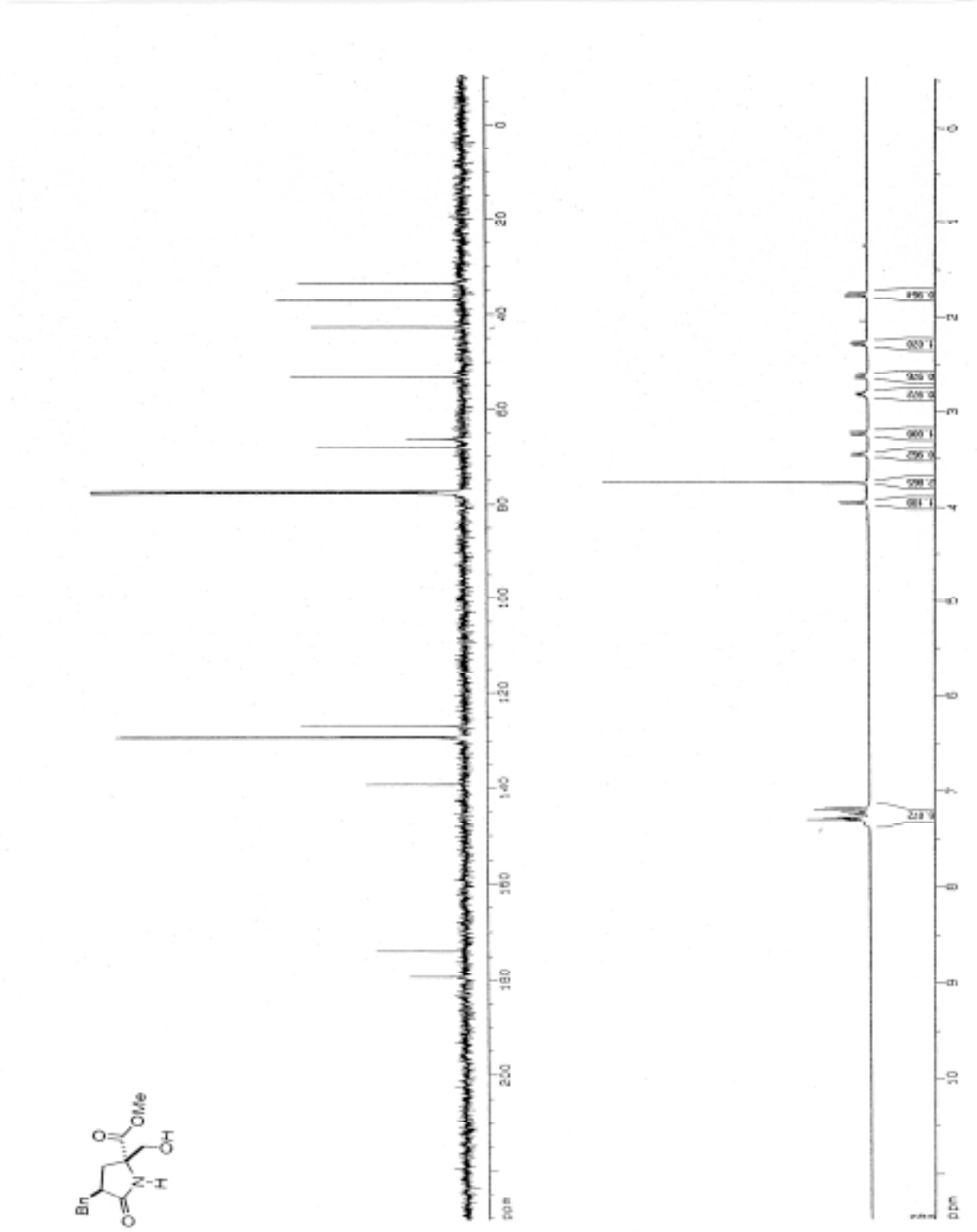
Compound 32g



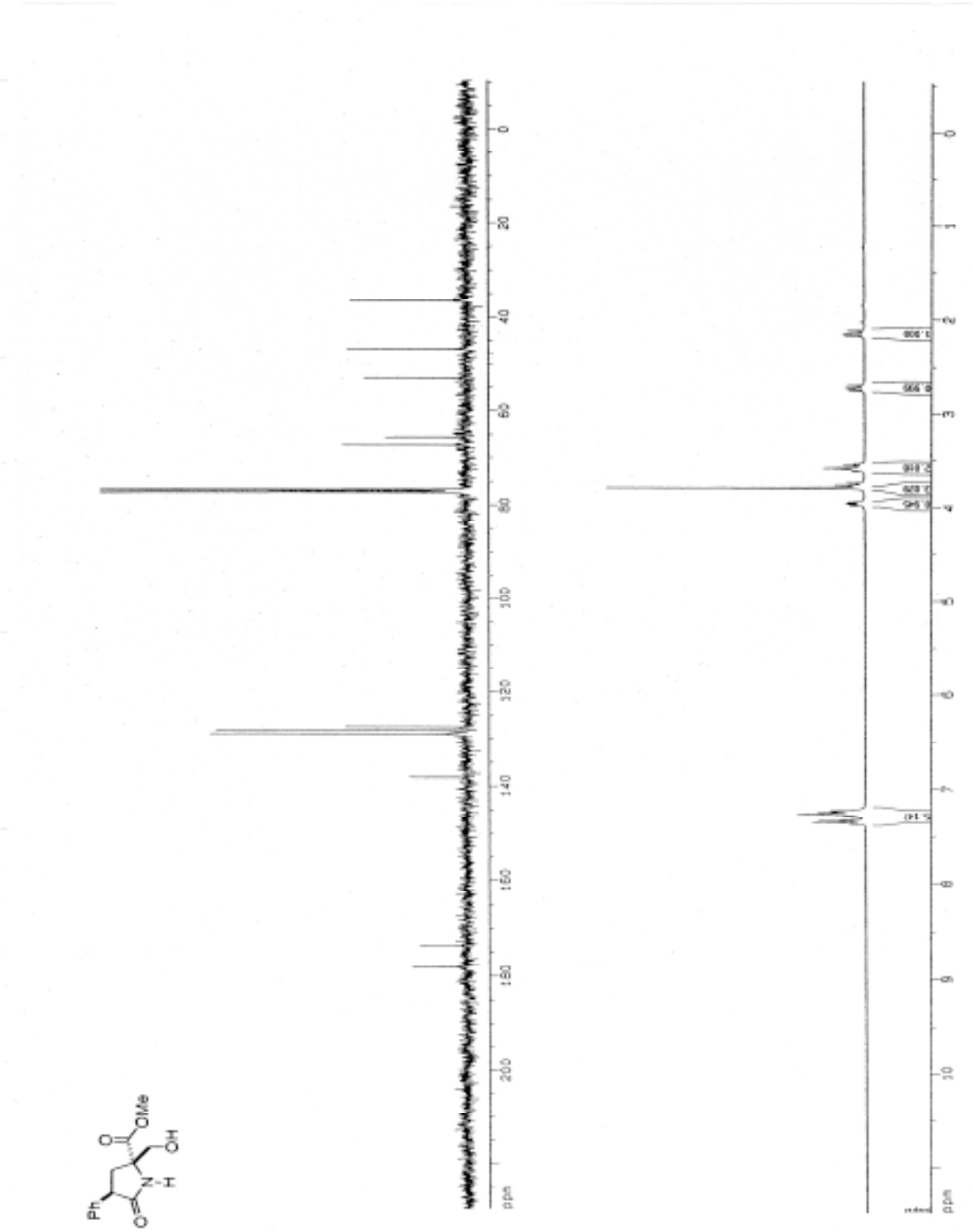
Compound 32h



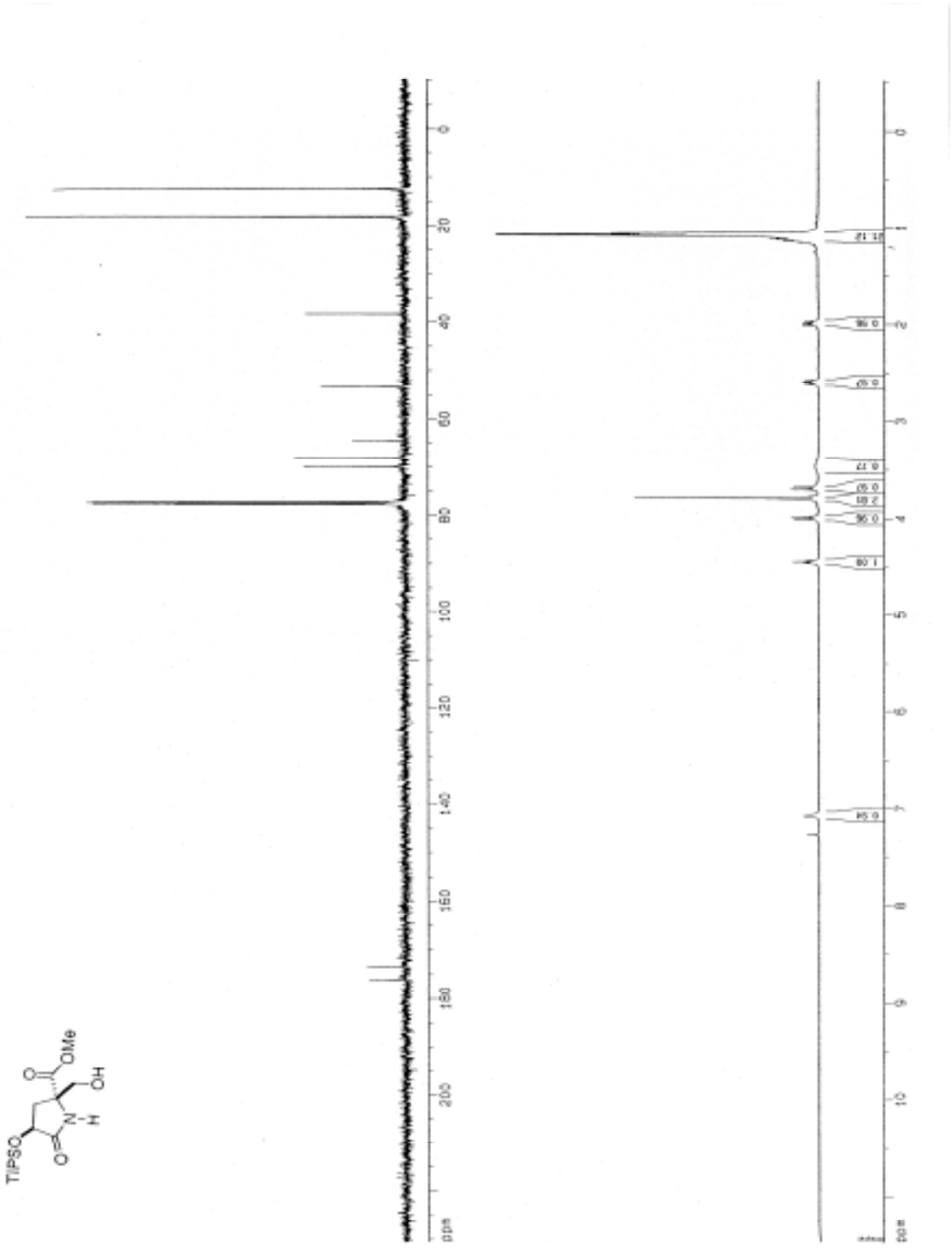
Compound 32i



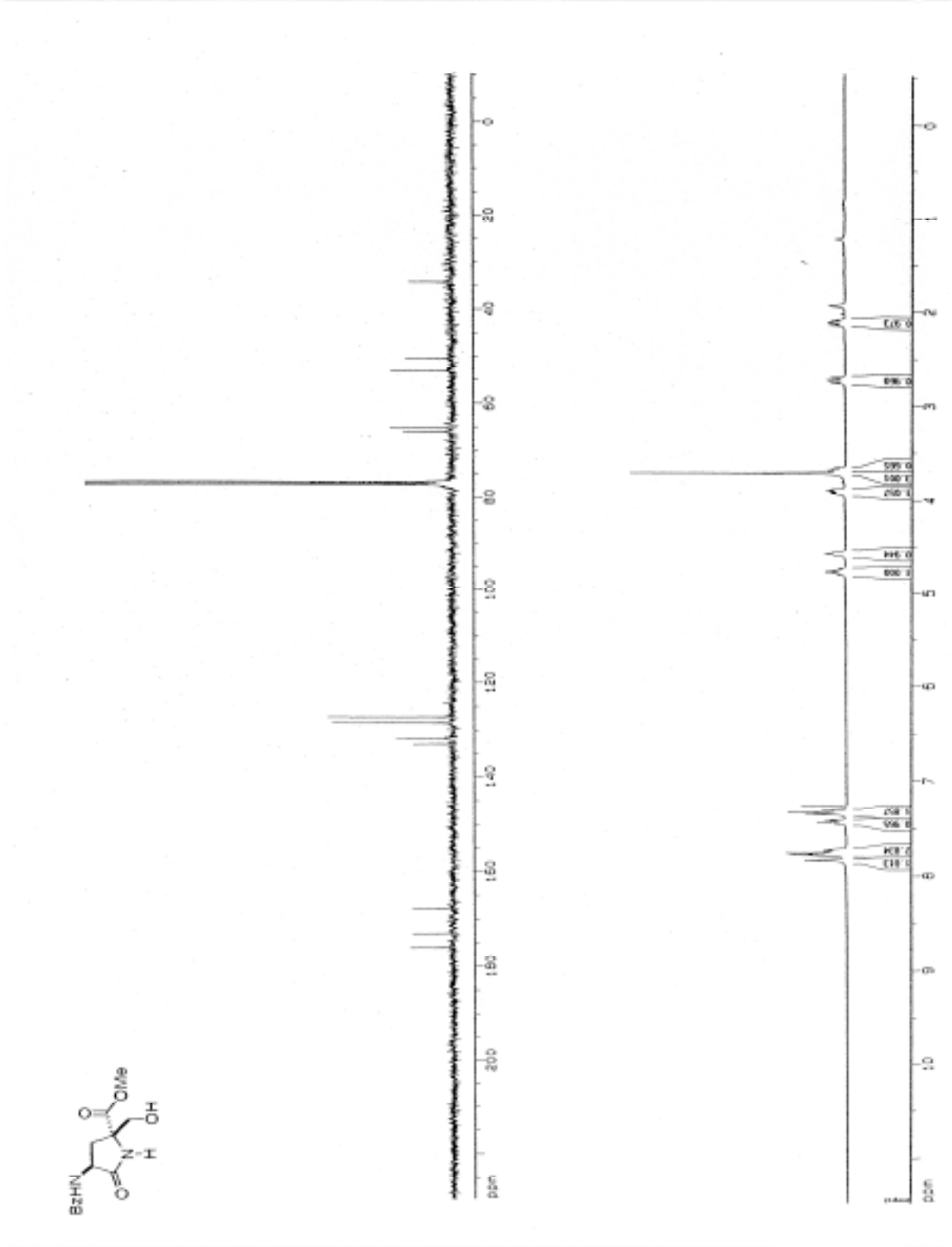
Compound 32j



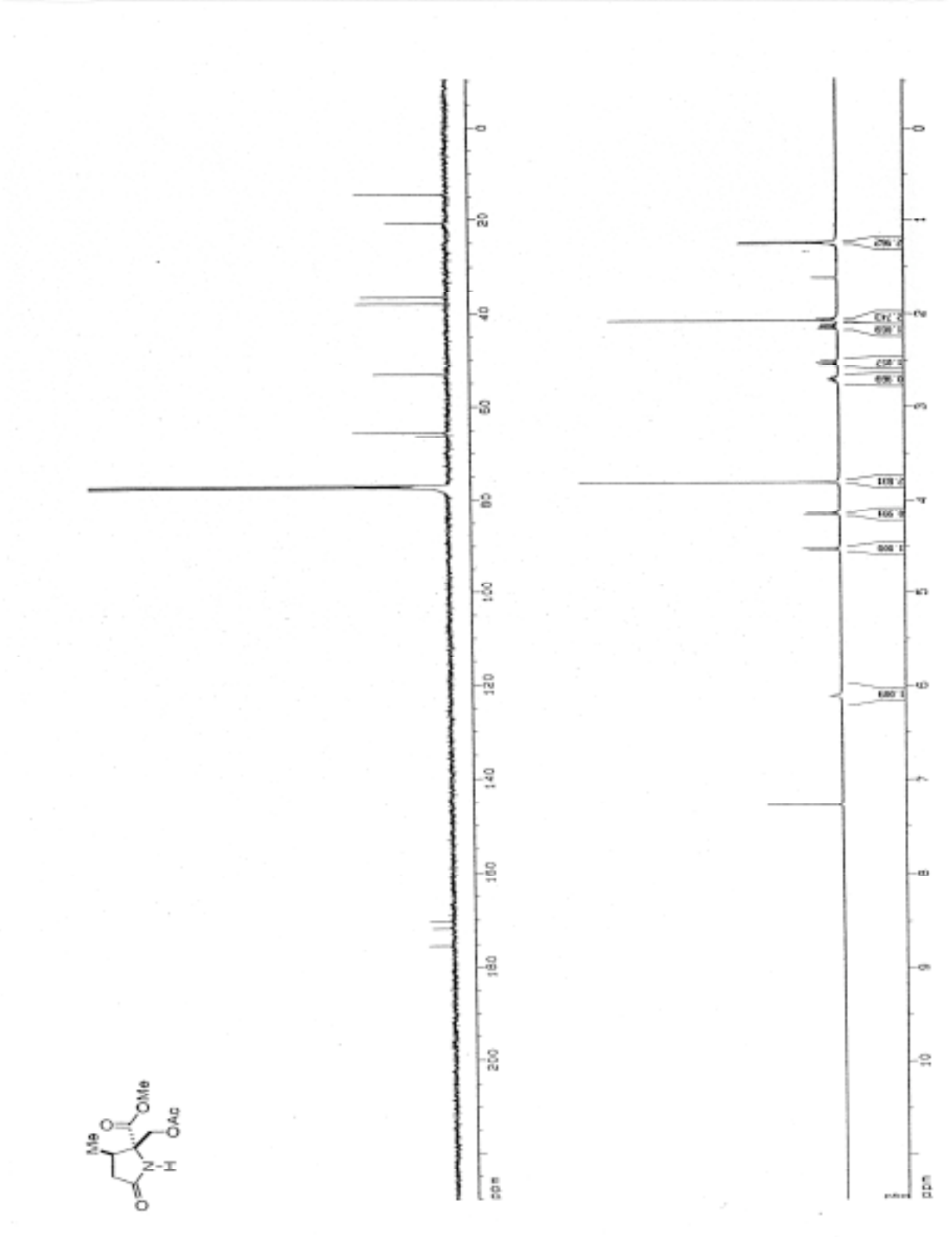
Compound 32k



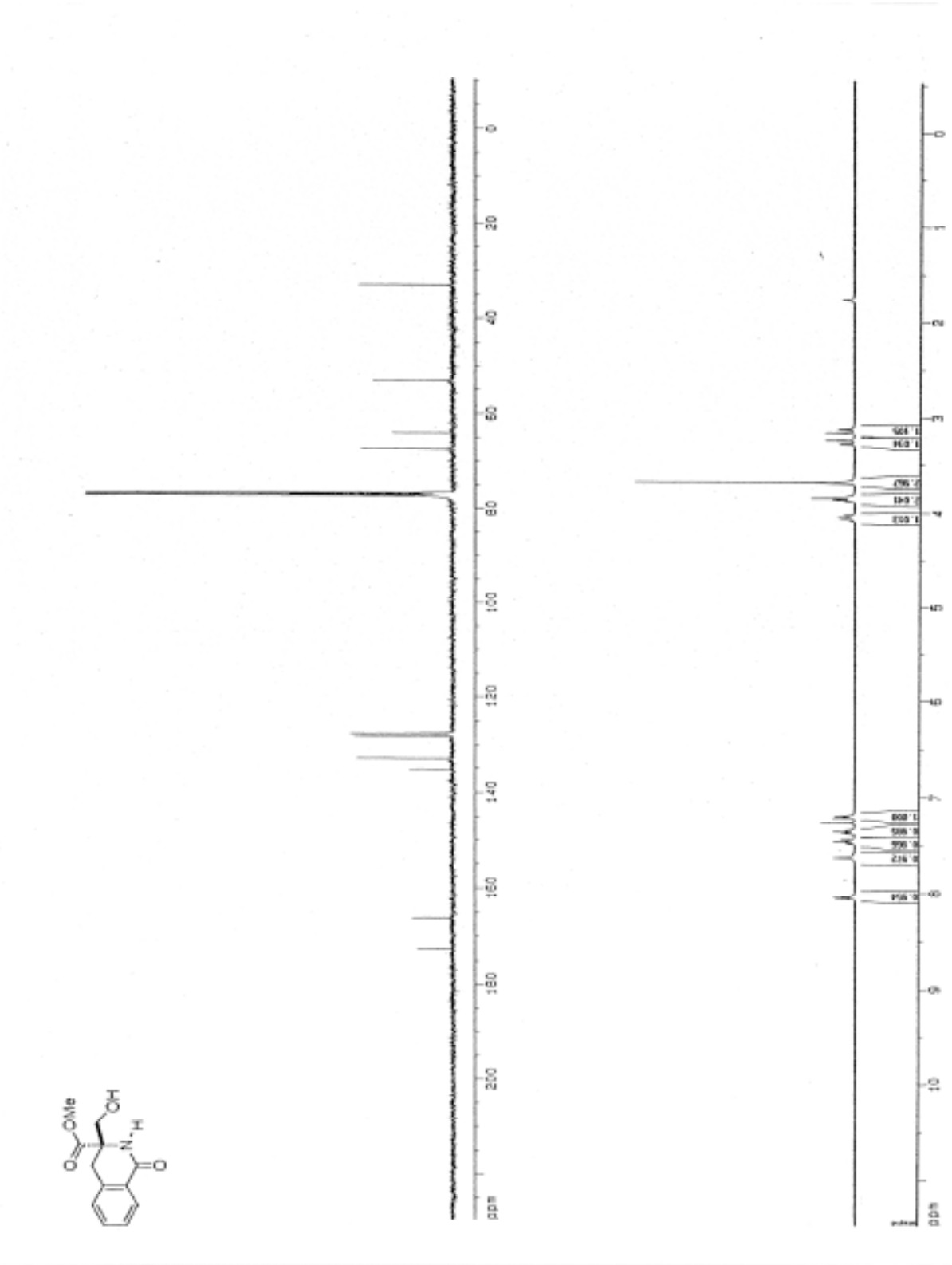
Compound 32l



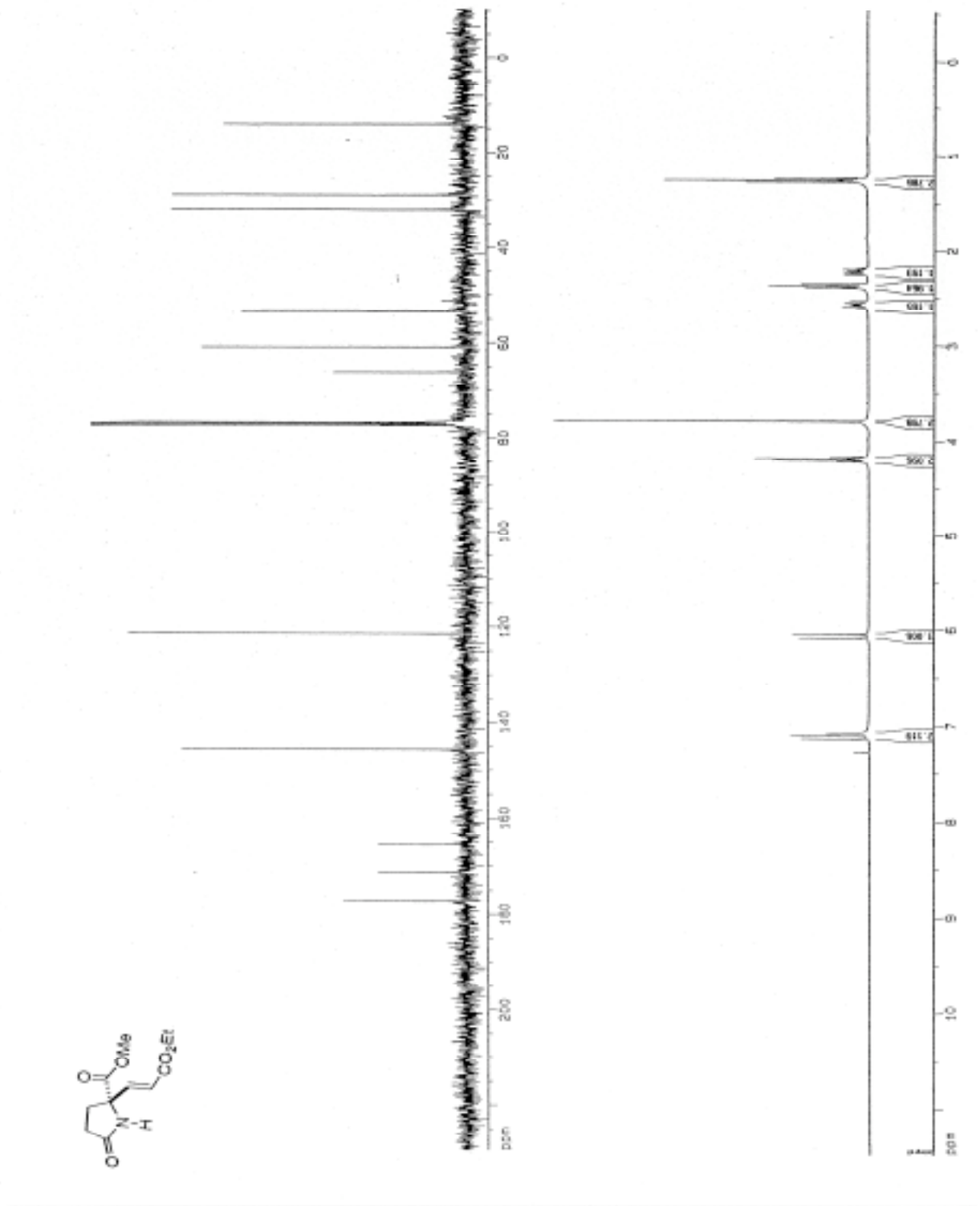
Compound 32m



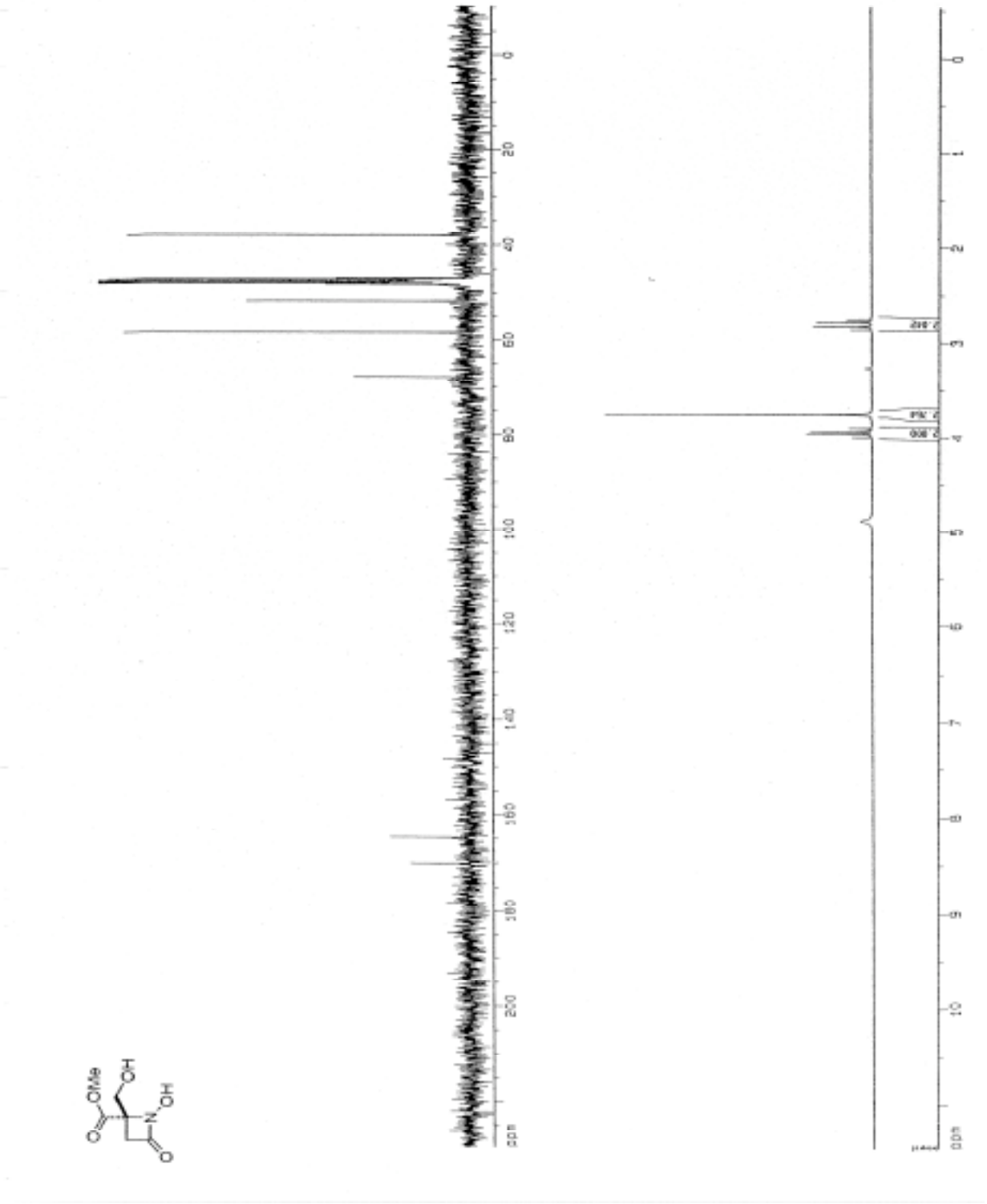
Compound 32n



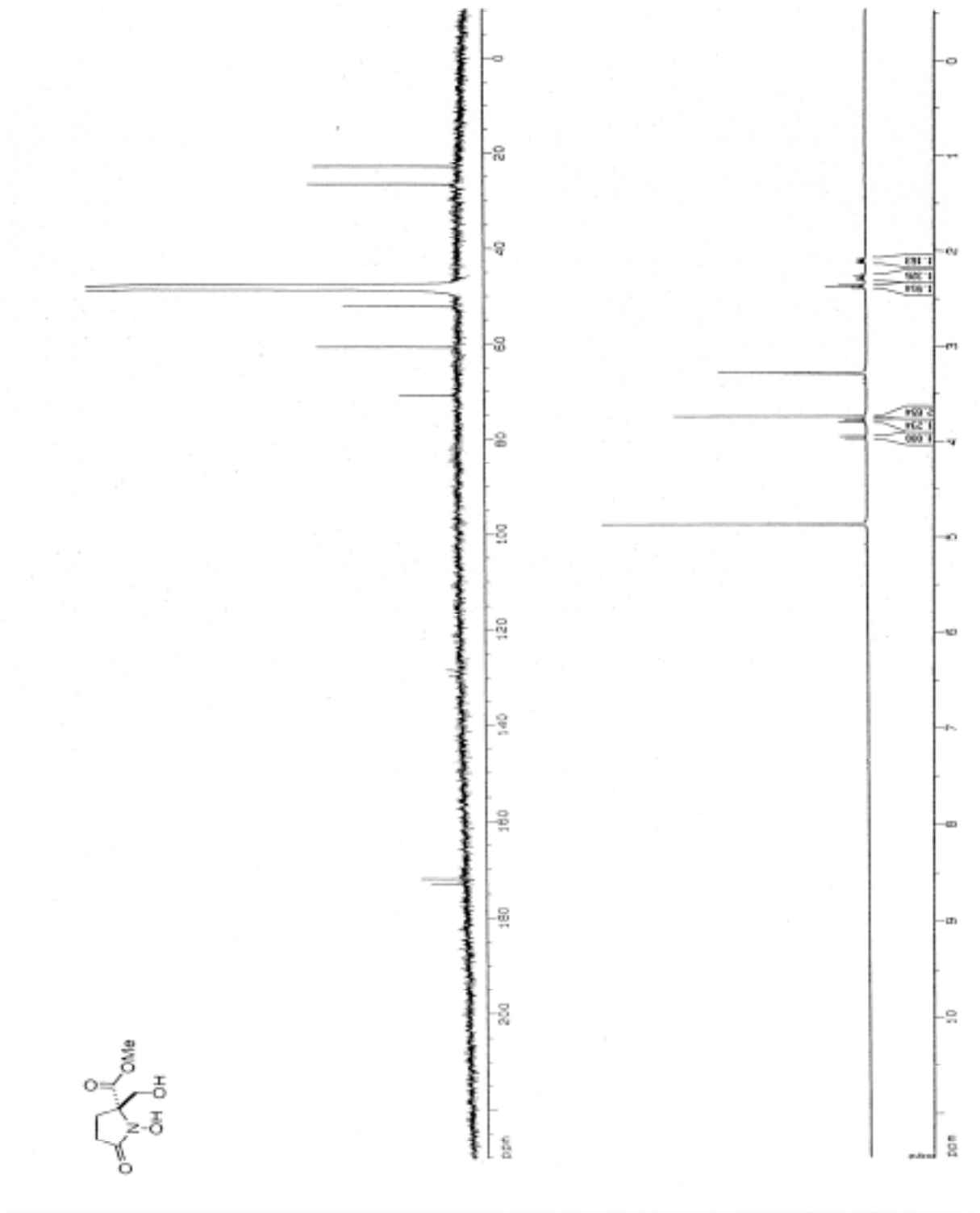
Compound 33



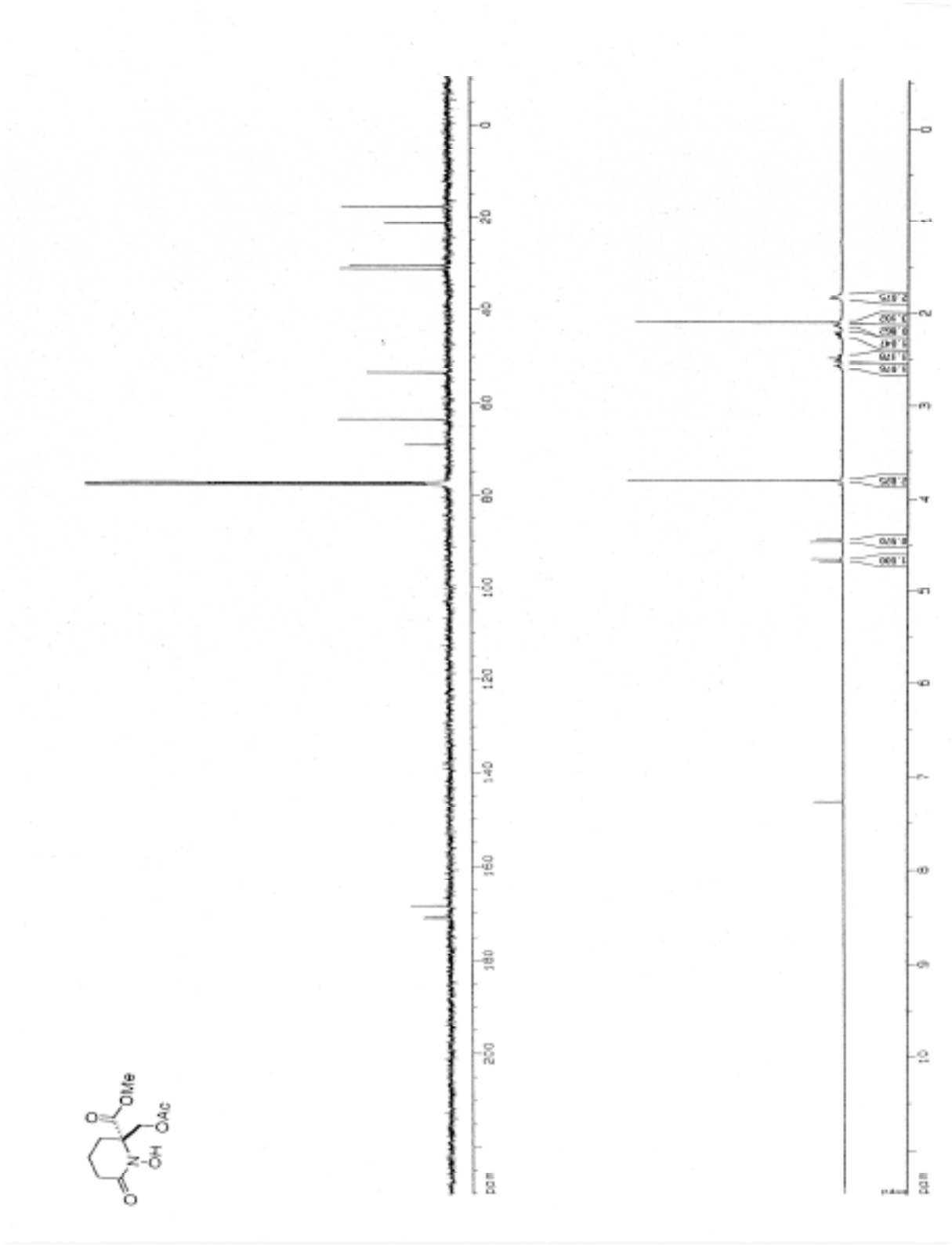
Compound 34b



Compound 34d



Compound 34f



12. References

(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(2) G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett, R. H. Boutin, *J. Org. Chem.,* **1984**, *49*, 4272.

(3) (a) Buck, J. S.; Ide, W. S. *Org. Syn., Coll. Vol. II,* 55. (b) Barua, A. K.; Chakrabarty, M.; Datta, P. K.; Ray, S. *Phytochemistry*, **1988**, *27*, 3259.

(4) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230