# Supporting Information

# Non-Racemic Bicyclic Lactam Lactones Via Regio- and cis-Diastereocontrolled C–H insertion. Asymmetric Synthesis of (8S,8aS)-octahydroindolizidin-8-ol and (1S,8aS)-octahydroindolizidin-1-ol.

*Andrew G.H. Wee*, Gao-Jun Fan and Hypolite M. Bayirinoba*

Department of Chemistry and Biochemistry

University of Regina, Regina

Saskatchewan, S4S 0A2, Canada

CONTENTS

Preparation and characterization of **2a**,**b;** (*S*)-**3**; (*R*)-**3**; (*S*)-**4**; (*R*)-**4**; (*S*)-**6**; (*S*)-**7**; (*S*)-**8** SI-1 – SI-7

Data for (*S*,*S*)-**11**; **12a**,**b**; (*S*,*S*)-**14**, **15** SI-7 – SI-8

Spectral data for compounds (S)-**2a**, (S)-**2b**, (*S*)-**3**, (*R*)-**3**, (*S*)-**4**, (*R*)-**4**, (*S*)-**6**, (*S*)-**7**, (*S*)-**8**, **9a**, **10a**, (*S*,*S*)-**11**, **12a**(5*S*), **9b**, **10b**, **12b**(5*R*), **13**, **14***E*, **14***Z*, **15**, **19**, **20**(*Z*/*E*), **18**, **21a**, **21b**, **17**·$BH_3$, **17**·HCl, **25**, **26a**, **26c**, **24**, **23**, **27a**, **27b**, **22**. SI-9 – SI-87

**(S)-1-Benzyl-5-(*t*-butyldimethylsilyloxy)piperidin-2-one (2a)**: A solution of lactam alcohol (*S*)-**1**[15a] (2.52 g, ca. 22 mmol), TBSCl (4.62g, 30.7 mmol), imidazole (3.0 g, 44 mmol) and DMAP (268 mg, 2.2 mmol) in DMF (20 mL) was stirred at 40 $^{o}$C overnight. Upon cooling, it was diluted with diethyl ether (100 mL) and washed with brine. Aqueous layer was extracted twice with diethyl ether, the combined organic layers were dried, filtered and evaporated to give a crude oil. The crude oil was purified by chromatography (EtOAc and then 10:1 EtOAc:MeOH) to afford 4.14 g of white solid: mp: 43-44 $^{o}$C; $^{1}$H NMR (300 MHz) δ 6.27 (brs, 1 H) 4.04–4.11 (m, 1 H), 3.38 (ddd, *J* = 2.0, 3.9, 12.1 Hz, 1 H), 3.18 (ddd, *J* = 2.4, 5.0, 12.1 Hz, 1 H), 2.57 (dt, *J* = 7.4, 7.4, 17.7 Hz, 1 H), 2.31 (dt, *J* = 6.2, 6.2, 17.7 Hz, 1 H), 1.80–1.92 (m, 2 H), 0.86 (s, 9 H), 0.07 (s, 6 H); HRMS calcd for $C_{10}H_{20}NO_2$ ($[M\text{-}Me]^+$) 214.1263, found 214.1268.

Sodium hydride (0.84 g, 60% in mineral oil) was washed with hexane, dried in vacuo and then suspended in DMF (20 mL). Lactam TBS ether (4.0 g, 17.4 mmol) was added followed by benzyl bromide (2.5 mL, 20.9 mmol). The mixture was stirred at rt overnight, then diluted with ether (100 mL) and washed with brine. The ethereal layer was dried, filtered and concentrated. The crude oil was purified by chromatography (1:1 pet. ether:EtOAc) to give 5.17 g of (*S*)-**2a** as a light yellow oil in 93% yield: $[\alpha]^{22}_{D}$ +19.0$^{o}$ (*c* 27.1, $CHCl_3$); IR $\nu_{max}$: 2943, 2920, 1643, 1249 cm$^{-1}$; $^{1}$H NMR (300 MHz) δ 7.24-7.40 (m, 5 H), 4.86 (d, *J* = 14.9 Hz, 1 H), 4.38 (d, *J* = 14.9 Hz, 1 H), 4.07-4.15 (m, 1 H), 3.33 (dd, *J* = 3.7, 12.3 Hz, 1 H), 3.14 (ddd, *J* = 1.1, 4.5, 12.4 Hz, 1 H), 2.77 (ddd, *J* = 9.0, 9.2, 17.7 Hz, 1 H), 2.46 (dt, *J* = 5.6, 17.6 Hz, 1 H), 1.84-2.02 (m, 2 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR (75 MHz) δ 169.4, 136.8, 128.5, 127.8, 127.2, 64.5, 54.1, 49.6, 29.1, 27.9, 25.6, 17.8, -4.9, -5.0.

**(S)-1-Benzyl-5-(benzyloxy)piperidin-2-one (2b)**: Powdered KOH (11.2 g , 0.173 mol, 86%) was added to dry DMSO (30 mL) and the suspension was stirred for 15 mins, under Ar. The suspension assumed a pale yellow color. The solution of the alcohol (S)-1 (2.5 g, 21.6 mmol) in dry DMSO (5 mL) was transferred, via cannula (5 mL DMSO rinse), to the KOH suspension and the mixture was stirred under Ar for 35 min. A brown mixture was formed. Benzyl bromide (10.2 mL, 86.4 mmol) was added,

via syringe, and the brown color of the mixture slowly lightened and eventually a light yellow color was formed. The mixture was stirred for 40 min and a fine white KBr precipitate was formed. The mixture was diluted with $CH_2Cl_2$ (60 mL), filtered through a glass-wool plug to remove the KBr/KOH. The residue was washed thoroughly with $CH_2Cl_2$, the organic filtrate was washed with brine, dried, filtered and concentrated. The crude product was purified by chromatography (4:1 pet. ether:EtOAc and then 2:1 pet. ether:EtOAc) to afford 4.6 g (71%) of dibenzylated lactam (*S*)-**2b** as a thick oil. $[\alpha]^{25}_D$ = + 29.8$^o$ (*c* 1.68, $CH_2Cl_2$). $^1$H NMR (300 MHz) δ 7.20-7.40 (m, 10H), 4.62 (d, *J* = 14.8 Hz, 1H), 4.51 (d, *J* = 14.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.74-3.82 (m, 1H), 3.32 (d, *J* = 14.2 Hz, 1H), 3.26 (d, *J* = 14.2 Hz, 1H), 2.69 (ddd, *J* = 17.6, 9.5, 6.5 Hz, 1H), 2.43 (dt, *J* = 17.6, 5.8, 5.8 Hz, 1H), 1.90-2.10 (m. 2H); $^{13}$C NMR (75 MHz) δ 169.3, 137.9, 136.8, 128.5, 128.3, 127.9, 127.6, 127.3, 127.2, 70.4, 70.2, 50.6, 49.8, 28.0, 25.7.

**(*S*)-1-Benzyl-5-hydroxypiperidin-2-one, (*S*)-3:** From (*S*)-**2a**: A solution of TBS ether **2a** (1.36 g, 4.26 mmol) in 1 M HCl methanolic solution (16 mL) was stirred at rt for 4.5 h. Reaction was quenched by carefully addition of solid sodium bicarbonate. After drying over sodium sulfate and filtering through a pad of Celite, solvent was removed under reduced pressure. Recrystalization from pet. ether-EtOAc afforded 0.73 g of colorless crystal. The remaining residue was purified by chromatography (10:1 EtOAc:MeOH) to give additional 0.13 g of white power. The combined yield was 0.86 g (98%) yield: mp: 136-137 $^o$C, $[\alpha]^{22}_D$ –16.7$^o$ (*c* 3.30, $CHCl_3$); IR $\nu_{max}$: 3354 (br), 1613 cm$^{-1}$; $^1$H NMR (300 MHz) δ 7.10-7.40 (m, 5 H), 4.58 (d, *J* = 14.7 Hz, 1 H), 4.48 (d, *J* = 14.7, 1 H), 4.05 (m, 1 H), 3.32 (dd, *J* = 4.2, 12.6 Hz, 1 H), 3.10 (dd, *J* = 5.1, 12.3 Hz, 1 H), 2.64 (ddd, *J* = 6.6, 8.1, 16.2 Hz, 1 H), 2.39 (ddd, J = 6.6, 6.4, 18.0 Hz, 1 H), 1.80-2.00 (m, 2 H); $^{13}$C NMR (75 MHz) δ 169.4, 136.7, 128.6, 127.7, 127.4, 63.9, 53.6, 49.0, 28.7, 28.1.

From (*S*)-**2b**: The dibenzylated compound (*S*)-**2b** (3.69 g) was dissolved in freshly dried and distilled EtOH (96 mL). 20% $Pd(OH)_2$ (2.45 g) was added, under Ar, followed by redistilled cyclohexene (48 mL). The mixture was refluxed under Ar and reaction progress was monitored by tlc. After 5 h, the

mixture was cooled to rt and filtered through Celite® and the residue was washed thoroughly with 95% EtOH. The combined filtrate was concentrated and the residual thick oil was dissolved in $CH_2Cl_2$, filtered and concentrated. Trituration of the residual oil with 2:1 pet. ether-EtOAc caused crystallization. The crystals were filtered off to yield (*S*)-**3** (2.42 g, 94%), which has identical spectroscopic data to that reported above.

The e.e. of (*S*)-**3** ($t_R$ = 66.1 min) was assessed by HPLC (UV detection, λ = 254 nm; hexane:2-propanol (97:3 v/v); flow rate of 1.0 mL/min) using a Chiralcel® OD column (1.5 mm x 250 mm) and was found to be >99%.

**(*R*)-1-Benzyl-5-hydroxypiperidin-2-one, (*R*)-3:** Compound (*S*)-**3** (329 mg, 1.6 mmol), $Ph_3P$ (755 mg, 2.9 mmol) and $ClCH_2CO_2H$ (273 mg, 2.9 mmol) were dissolved in dry $CH_2Cl_2$ (15 mL). DEAD (0.46 mL, 2.9 mmol) was added dropwise to the solution and the resulting pale yellow solution was stirred at rt for 4 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (1:1 pet. ether:EtOAc and then EtOAc) to give a mixture of chloroacetate contaminated with trace amounts of $Ph_3PO$. The chloroacetate was hydrolyzed using $K_2CO_3$ (662 mg, 4.8 mmol) in methanol (15 mL). Methanol was evaporated and $CH_2Cl_2$ was added to the residue. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude product was purified by chromatography (10:1 EtOAc:MeOH) to give (*R*)-**3** (230 mg, 70%) as a colorless crystals. mp (pet. ether:EtOAc): 136-137 $^oC$, $[\alpha]^{22}_D$ +17.4$^o$ (*c* 3.30, $CHCl_3$); IR $\nu_{max}$: 3284 (br), 1607, 1272 $cm^{-1}$; $^1H$ NMR (200 MHz) δ 7.10-7.40 (m, 5 H), 4.56 (s, 2 H), 4.02-4.15 (m, 1 H), 3.40 (dd, *J* = 3.8, 12.5 Hz, 1 H), 3.10 (ddd, *J* = 0.9, 5.1, 12.5 Hz, 1 H), 2.60 (dt, *J* = 7.7, 17.7 Hz, 1 H), 2.45 (dt, *J* = 6.4, 17.7 Hz, 1 H), 1.80-2.05 (m, 2 H); $^{13}C$ NMR (50 MHz) δ 169.3, 136.7, 128.6, 128.0, 127.4, 63.9, 53.6, 50.0, 28.7, 28.1; HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1101.

The e.e. of (*R*)-**3** ($t_R$ = 68.9 min) was assessed by HPLC (UV detection, λ = 254 nm; hexane:2-propanol (97:3 v/v); flow rate of 1.0 mL/min) using a Chiralcel® OD column (1.5 mm x 250 mm) and was found to be >99%.

**(S)-1-Benzyl-5-(α-diazoacetoxy)piperidin-2-one, (*S*)-4.** Compound (*S*)-**3** (1.0 g, 4.87 mmol) and (tosylhydrazone)acetyl chloride (1.9 g, 7.3 mmol) were dissolved in dry $CH_2Cl_2$ and the solution was cooled to 0 °C in an ice-water bath. *N*,*N*-Dimethylaniline (0.93 mL, 7.3 mmol) was added dropwise via syringe. After the mixture was stirred at 0 °C for 20 min, *i*-$Pr_2NEt$ (4.2 mL) was added. After stirring at 0 °C for 50 min, the reaction mixture was washed with saturated aqueous citric acid solution, brine and then saturated aqueous $NaHCO_3$ solution. The organic layer was dried, filtered, concentrated and the residue was purified by chromatography (1:1 pet. ether:EtOAc and then EtOAc) to yield (*S*)-**4** (1.28 g, 98%) as a red oil. $[\alpha]^{25}_D$ +25.0° (*c* 5.90, $CHCl_3$); IR $\nu_{max}$: 2097, 1690, 1637, 1378, 1173 $cm^{-1}$; $^1H$ NMR (300 MHz) δ 7.18-7.36 (m, 5 H), 5.20 (sextet, *J* = 3.6, 8.7 Hz, 1 H), 4.72 (d, *J* = 12.6 Hz, 1 H), 4.70 (s, 1 H), 4.47 (d, *J* = 14.4 Hz, 1 H), 3.44 (dd, *J* = 3.6, 13.2 Hz, 1 H), 3.29 (ddd, *J* = 1.5, 3.6, 13.5 Hz, 1 H), 2.40-2.70 (m, 2 H), 1.95-2.15 (m, 2 H); $^{13}C$ NMR (75 MHz) δ 168.4, 165.7, 136.3, 128.3, 127.6, 127.2, 66.4, 50.4, 49.4, 46.1, 27.4, 25.3; HRMS calcd for $C_{14}H_{15}N_3O_3$ 273.1113, found 273.1120.

**(*R*)-1-Benzyl-5-(α-diazoacetoxy)piperidin-2-one, (*R*)-4.** (prepared as described for (*S*)-**4**): Red oil; $[\alpha]^{25}_D$ –22.0° (*c* 5.90, $CHCl_3$); IR $\nu_{max}$: 2954, 2108, 1689, 1637, 1490, 1384, 1178 $cm^{-1}$; $^1H$ NMR (200 MHz) δ 7.14-7.34 (m, 5 H), 5.17 (six, *J* = 3.5, 8.2 Hz, 1 H), 4.71 (s, 1 H), 4.70 (d, *J* = 14.2 Hz, 1 H), 4.42 (d, *J* = 14.7 Hz, 1 H), 3.43 (dd, *J* = 3.8, 13.4 Hz, 1 H), 3.25 (ddd, *J* = 0.9, 3.4, 13.4 Hz, 1 H), 2.30-2.70 (m, 2 H), 1.85-2.15 (m, 2 H); $^{13}C$ NMR (50 MHz) δ 168.4, 165.7, 136.3, 128.4, 127.7, 127.3, 66.4, 50.5, 49.5, 46.3, 27.5, 25.4; HRMS calcd for $C_{14}H_{15}N_3O_3$ 273.1113, found 273.1118.

**(S)-1-Benzyl-4-(*t*-butyldimethylsilyloxy)pyrrolidin-2-one (S)-6**. A solution of (*S*)-(–)-4-hydroxypyrrolidin-2-one (505 mg, 5 mmol), TBSCl (1.05 g, 7 mmol), imidazole (680 mg, 10 mmol) and DMAP (61 mg, 0.5 mmol) in DMF (5 mL) was stirred at 40 °C overnight. The solution was diluted with ether, and the mixture was washed with water, brine, dried, filtered and concentrated. The crude product was purified by chromatography (EtOAc and then 10:1 EtOAc:MeOH) to give 1.07 g (100%) of the γ-lactam TBS ether. mp: 74.5-75.0 °C; $[\alpha]^{22}_D$ –7.40° (*c* 1.30, $CHCl_3$); IR $\nu_{max}$: 3425 (br), 3178,

2931, 1660 $cm^{-1}$; $^1H$ NMR (200 MHz): δ 5.90 (br. s), 4.40-4.60 (m, 1 H), 3.58 (dd, *J* = 6.0, 10.0 Hz, 1 H), 3.20 (dd, *J* = 3.5, 10.0 Hz, 1 H), 2.50 (dd, *J* = 6.8, 16.9 Hz, 1 H), 2.25 (dd, *J* = 4.2, 16.9 Hz, 1 H), 0.85 (s, 9 H), 0.05 (s, 6 H); $^{13}C$ NMR (50 MHz): δ 176.6, 67.8, 51.7, 40.5, 25.6, 17.9, -4.9; HRMS calcd for $C_9H_{18}NO_2Si$ ($[M-Me]^+$) 200.1107, found 200.1105.

A solution of γ-lactam TBS ether (770 mg, 3.58 mmol) in THF (30 mL) containing a few crystals of 2,2'-bipyridine indicator was cooled to –15 °C. Butyl lithium (1.4 mL, 3.58 mmol, 2.5M) was added dropwise until the solution became red. After 10 min, dry DMF (6 mL) was added to the red solution followed by benzyl bromide (0.55 mL, 4.6 mmol). An orange colored solution developed almost immediately. The solution was gradually warmed to 0 °C over 5 h. The reaction mixture was diluted with ether, then washed once with water and brine. The ethereal layer was dried, filtered, concentrated and the crude product purified by column chromatography (1:1 pet. ether:EtOAc and then EtOAc) to give 200 mg of starting material and 678 mg (84% based on recovered starting material) of (*S*)-**6**[19b-d] as a light yellow oil: $[\alpha]^{22}_D$ –3.33° (*c* 2.20, $CHCl_3$); IR $\nu_{max}$: 2913, 1690 $cm^{-1}$; $^1H$ NMR (200 MHz): δ7.10-7.40 (m, 5 H), 4.60 (d, *J* = 14.9 Hz, 1 H), 4.30-4.50 (m, 1 H), 4.35 (d, *J* = 14.9 Hz, 1 H), 3.44 (dd, *J* = 5.7, 10.3 Hz, 1 H), 3.12 (dd, *J* = 2.7, 10.3 Hz, 1 H), 2.68 (dd, *J* = 6.4, 16.9 Hz, 1 H), 2.40 (dd, *J* = 3.3, 16.9 Hz, 1 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H); $^{13}C$ NMR (50 MHz): δ172.6, 136.1, 128.5, 127.7, 127.4, 65.2, 55.8, 45.9, 41.4, 25.6, 17.9, -4.8, -4.9; HRMS calcd for $C_{17}H_{27}NO_2Si$ 305.1811, found 305.1815.

**(S)-1-Benzyl-4-hydroxypyrrolidin-2-one, (S)-7**. (*S*)-**6** (612 mg, 2.04 mmol) was stirred in 1 M methanolic HCl (10 mL) for 2 h. Solid $NaHCO_3$ was carefully added to the reaction mixture at 0 °C and then the mixture was evaporated. The residue was extracted toroughly with $CH_2Cl_2$ and the combined $CH_2Cl_2$ layers were dried, filtered and concentrated. The residue was purified by chromatography (10:1 EtOAc:MeOH) to afford 376 mg (98%) of (*S*)-**7**[19b-d] as a white solid. mp: 107.5-108 °C, lit.[19b] 1075-109 °C; $[\alpha]^{22}_D$ –33.7° (*c* 2.20, $CHCl_3$), lit.[19b] $[\alpha]^{20}D$ –35.2° (*c* 1.3, $CHCl_3$); IR $\nu_{max}$:

3287, 1656 $cm^{-1}$; $^1H$ NMR (200 MHz): δ 7.10-7.40 (m, 5 H), 4.45 (d, *J* = 14.9 Hz, 1 H), 4.40 (m, 1 H), 4.32 (d, *J* = 14.9 Hz, 1 H), 3.59 (br s, 1 H), 3.42 (dd, *J* = 5.6, 10.8 Hz, 1 H), 3.12 (dd, *J* = 2.0, 10.8 Hz, 1 H), 2.63 (dd, *J* = 6.5, 17.3 Hz, 1 H), 2.35 (dd, *J* = 2.4, 17.3 Hz, 1 H); $^{13}C$ NMR (50 MHz): δ 173.1, 135.9, 128.7, 127.9, 127.5, 64.1, 55.8, 46.3, 41.1; HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0948.

**(S)-1-Benzyl-4-(α-diazoacetoxy)pyrrolidin-2-one, (*S*)-8**. (prepared as described for (*S*)-**4** in 98% yield): Yellow oil; IR $\nu_{max}$: 2105, 1686, 1380, 1181 $cm^{-1}$; $^1H$ NMR (200 MHz) δ 7.10-7.40 (m, 5 H), 5.30-5.40 (m, 1 H), 4.74 (s, 1 H), 4.48 (dd, *J* = 14.8 Hz, 2 H), 3.61 (dd, *J* = 5.8, 11.6 Hz, 1 H), 3.26 (dd, *J* = 1.8, 11.7 Hz, 1 H), 2.82 (dd, *J* = 6.9, 17.8 Hz, 1 H), 2.55 (dd, *J* = 2.2, 17.8 Hz, 1 H); $^{13}C$ NMR (50 MHz) δ 171.3, 165.7, 135.5, 128.5, 127.7, 127.5, 67.2, 52.7, 46.3, 46.0, 37.7; HRMS calcd for $C_{13}H_{13}N_3O_3$ 259.0957, found 259.0955.

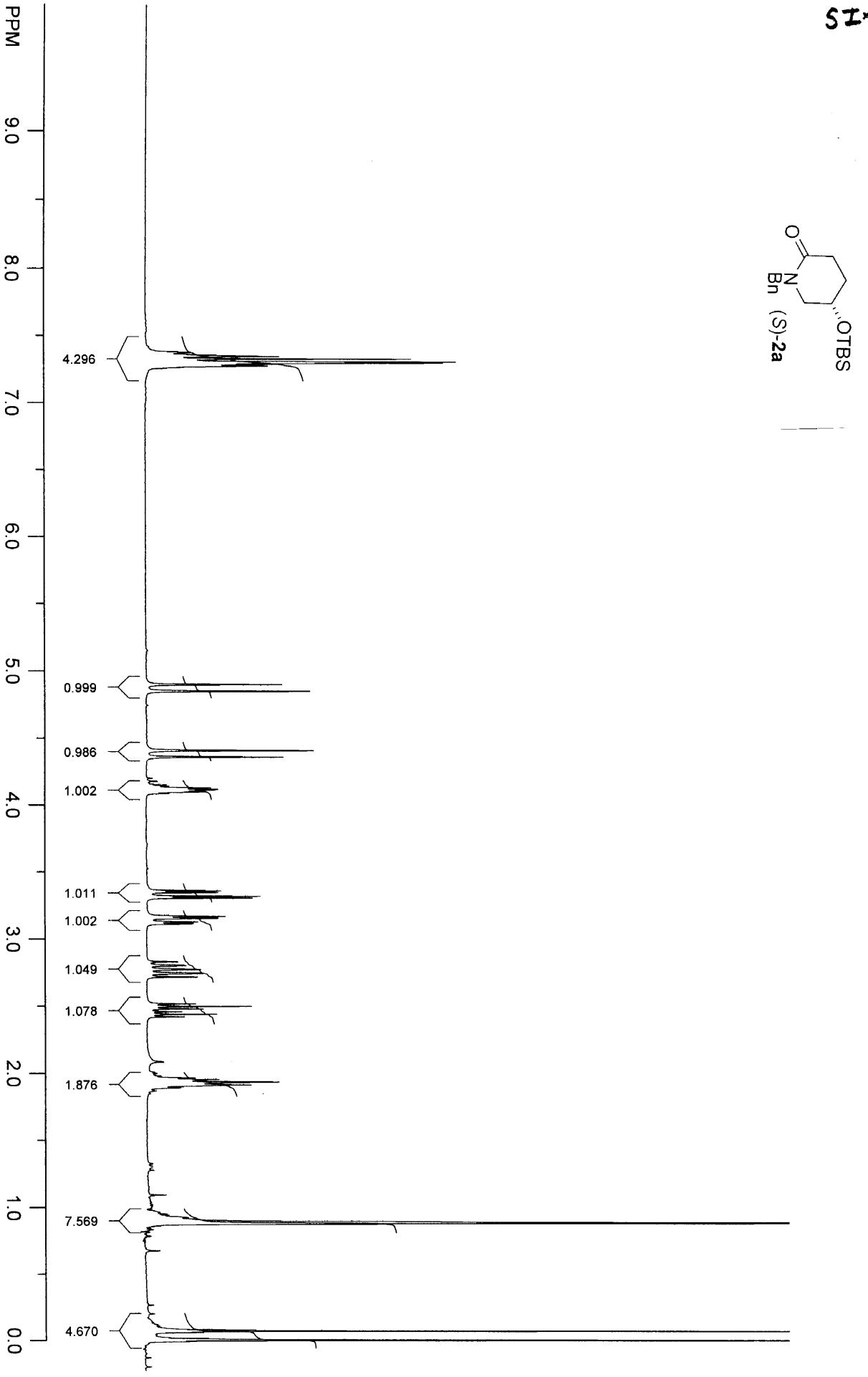
**Alkene (*S,S*)-11** (*E*/*Z* mixture)**:** colorless oil: $[\alpha]^{23}_D$ +8.3° (*c* 2.10, $CHCl_3$); IR $\nu_{max}$: 1724, 1635, 1494 $cm^{-1}$; $^1H$ NMR (300 MHz) δ: 7.09-7.30 (m, 26 H), 6.64 (s, 2 H), 6.12 (s, 3.2 H), 5.10-5.20 (m, 5.2 H), 4.63 (d, *J* = 14.7 Hz, 2 H), 4.60 (d, *J* = 14.7 Hz, 3.2 H), 4.45 (d, *J* = 14.7 Hz, 2 H), 4.42 (d, *J* = 14.7 Hz, 3.2 Hz), 3.42 (dd, *J* = 3.8, 13.4 Hz, 3.2 Hz), 3.35 (dd, *J* = 4.2, 8.1 Hz, 2 H), 3.15-3.32 (m, 5.2 H), 2.30-2.70 (m, 10.4 H), 1.80-2.15 (m, 10.4 H); $^{13}C$ NMR (75 MHz) δ 168.6, 168.4, 164.2, 163.6, 136.4, 136.3, 133.5, 129.9, 128.6 (x2), 128.0 (x2), 127.6, 127.5, 67.5, 67.3, 50.3, 50.2, 49.9, 49.8, 27.7, 27.6, 25.4, 25.2; HRMS calcd for $C_{28}H_{30}N_2O_6$ 490.2104, found 490.2112.

**Ether dimer 12a:** red oil, $[\alpha]^{23}_D$ +53.3° (*c* 1.50, $CHCl_3$); IR $\nu_{max}$: 2919, 1748, 1643, 1490, 1202, 1137 $cm^{-1}$; $^1H$ NMR (300 MHz) δ 7.19-7.36 (m, 10 H), 5.19-5.26 (m, 2 H), 4.68 (d, *J* = 14.6 Hz, 2 H), 4.48 (d, *J* = 14.6 Hz, 2 H), 4.13 (d, *J* = 16.6 Hz, 2 H), 4.03 (d, *J* = 16.6 Hz, 2 H), 3.46 (dd, *J* = 3.8, 13.4 Hz, 2 H), 3.29 (dd, *J* = 3.2, 13.5 Hz, 2 H), 2.44-2.70 (m, 4 H), 2.00-2.14 (m, 4 H); $^{13}C$ NMR (50 MHz) δ 168.7, 168.4, 136.4, 128.6, 128.0, 127.6, 67.9, 67.1, 50.3, 49.8, 27.3, 25.5; HRMS calcd for $C_{28}H_{32}N_2O_7$ 508.2210, found 508.2210.

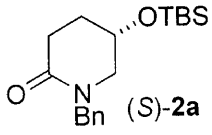
**Ether dimer 12b:** red oil, $[\alpha]^{22}_D$ -53.0° (*c* 1.50, $CHCl_3$); IR $\nu_{max}$: 1748, 1644, 1490 $cm^{-1}$; $^1H$ NMR (300 MHz) δ 7.19-7.36 (m, 10 H), 5.20-5.28 (m, 2 H), 4.72 (d, *J* = 14.7 Hz, 2 H), 4.46 (d, *J* = 14.7 Hz, 2 H), 4.13 (d, *J* = 17.3 Hz, 2 H), 4.03 (d, *J* = 17.3 Hz, 2 H), 3.46 (dd, *J* = 3.8, 13.4 Hz, 2 H), 3.30 (dd, *J* = 3.5, 13.4 Hz, 2 H), 2.40-2.70 (m, 4 H), 2.00-2.15 (m, 4 H).

**Alkene (*S,S*)-14:** IR $\nu_{max}$: 1719, 1690, 1255, 1155 $cm^{-1}$; <u>*E*-diastereomer</u>: $[\alpha]^{22}_D$ +16.7° (*c* 0.30, $CHCl_3$);$^1H$ NMR (300 MHz) δ 7.20-7.38 (m, 10 H), 6.77 (s, 2 H), 5.35-5.42 (m, 2 H), 4.53 (d, *J* = 14.7 Hz, 2 H), 4.47 (d, *J* = 14.7 Hz, 2 H), 3.66 (dd, *J* = 5.9, 11.7 Hz), 3.28 (dd, *J* = 1.9, 11.7 Hz, 2 H), 2.88 (dd, *J* = 7.0, 17.9 Hz, 2 H), 2.58 (dd, *J* = 2.3, 17.9 Hz, 2 H) ; $^{13}C$ NMR (75 MHz) δ 171.2, 164.0, 135.6, 133.6, 128.8, 128.1, 127.9, 68.1, 52.6, 46.3, 37.7; <u>*Z*-diastereomer</u>: $^1H$ NMR (300 MHz) δ 7.18-7.36 (m, 10 H), 6.23 (s, 2 H), 5.29-5.36 (m, 2 H), 4.52 (d, *J* = 14.7 Hz, 2 H), 4.39 (d, *J* = 14.7 Hz, 2 H), 3.61 (dd, *J* = 5.8, 11.8 Hz), 3.31 (dd, *J* = 1.8, 11.7 Hz, 2 H), 2.82 (dd, *J* = 7.0, 17.8 Hz, 2 H), 2.58 (dd, *J* = 1.0, 17.5 Hz, 2 H) ; $^{13}C$ NMR (75 MHz) δ 171.3, 164.4, 135.7, 130.0, 128.8, 128.1, 127.8, 67.9, 52.5, 46.3, 37.4.

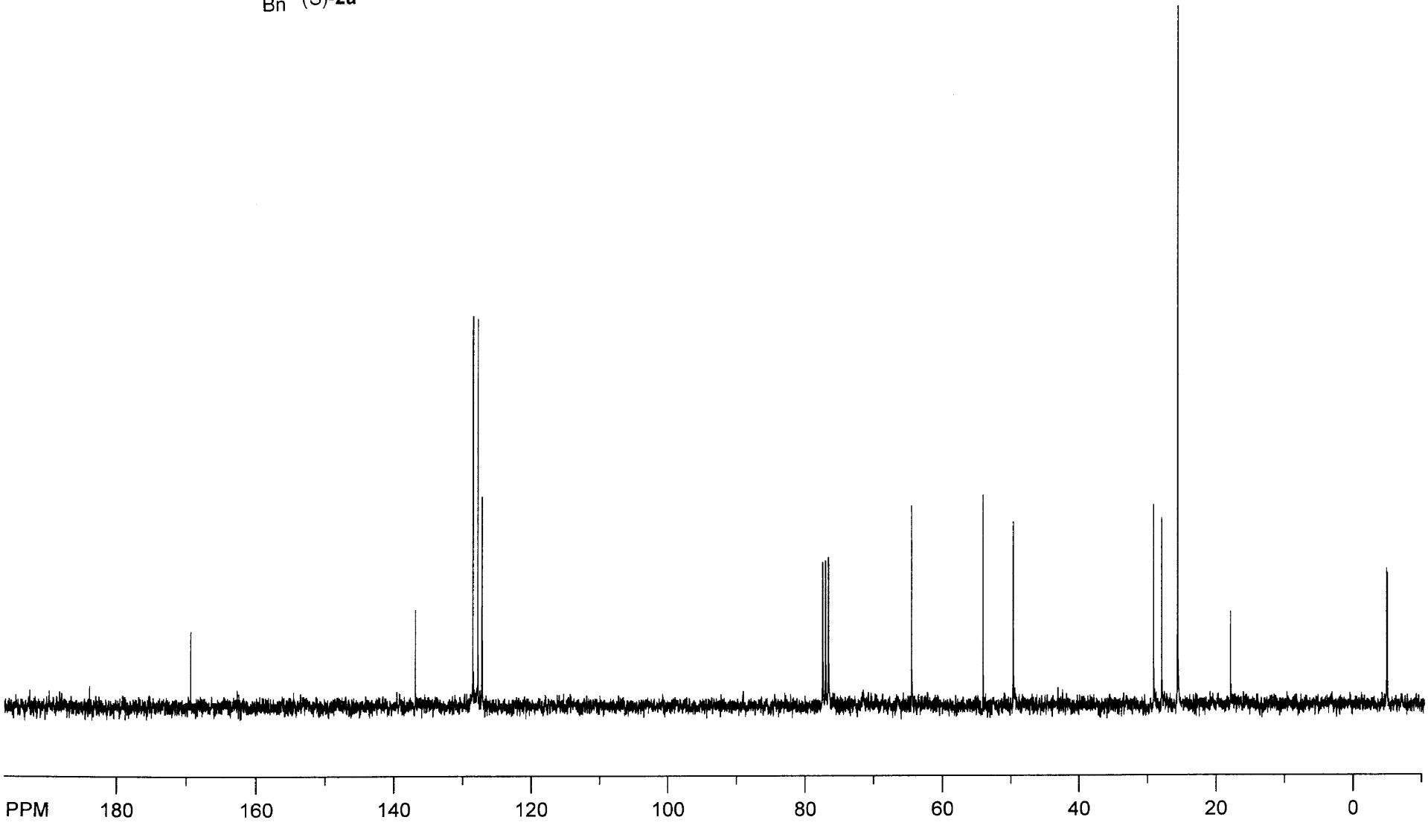
**Ether dimer 15:** $[\alpha]^{22}_D$ –13.6° (*c* 1.10, $CHCl_3$); IR $\nu_{max}$: 1752, 1686, 1195, 1135 $cm^{-1}$; $^1H$ NMR (200 MHz) δ 7.18-7.38 (m, 10 H), 5.30-5.40 (m, 2 H), 4.50 (d, *J* = 14.8 Hz, 2 H), 4.44 (d, *J* = 14.8 Hz, 2 H), 4.10 (s, 4 H), 3.63 (dd, *J* = 5.9, 11.7 Hz), 3.24 (dd, *J* = 1.9, 11.7 Hz, 2 H), 2.85 (dd, *J* = 7.0, 17.9 Hz, 2 H), 2.55 (dd, *J* = 2.3, 17.9 Hz, 2 H) ; $^{13}C$ NMR (50 MHz) δ 171.1, 168.9, 135.5, 128.7, 127.9, 127.8, 67.9, 67.7, 52.5, 46.2, 37.6; HRMS calcd for $C_{26}H_{28}N_2O_7$ 480.1897, found 480.1904.


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
4.296
0.999
0.986
1.002
1.011
1.002
1.049
1.078
1.876
7.569
4.670
O
N
Bn
OTBS
(S)-2a

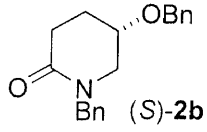
S1-10



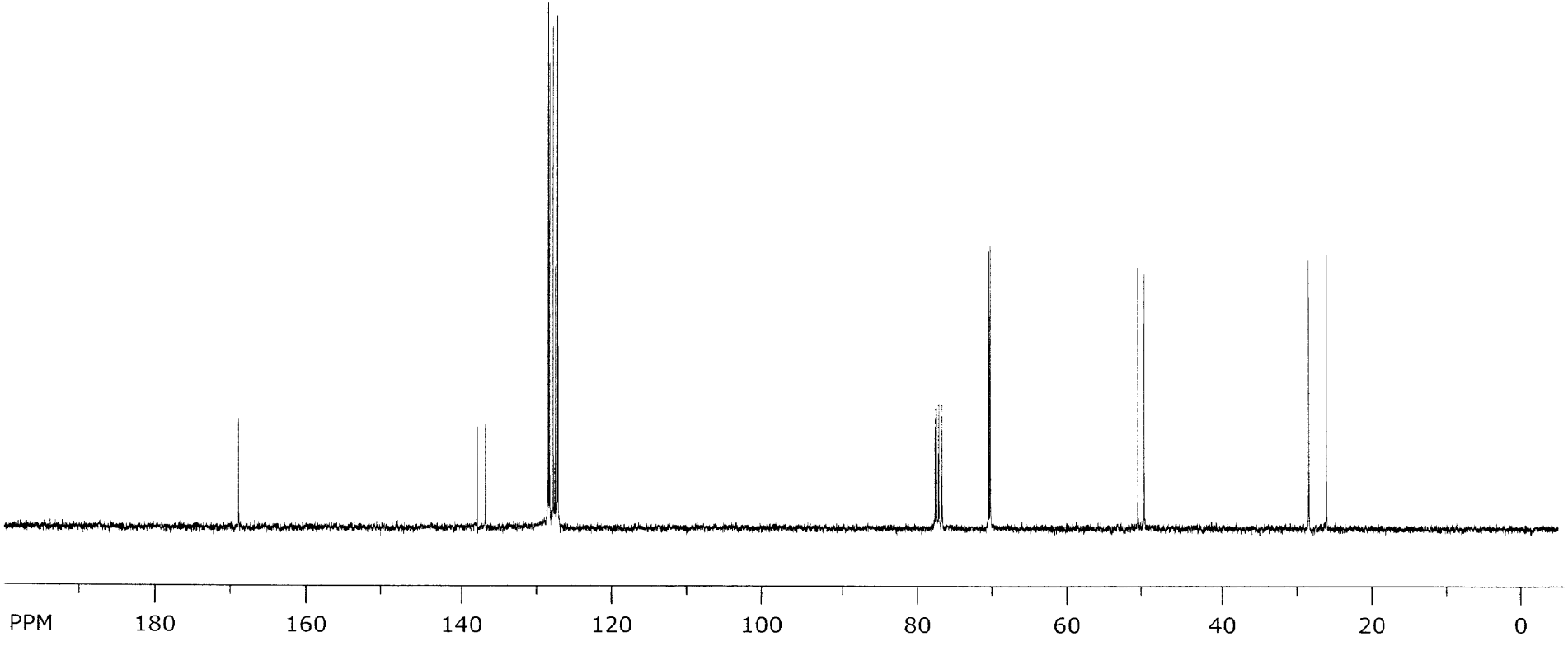

(*S*)-**2a**

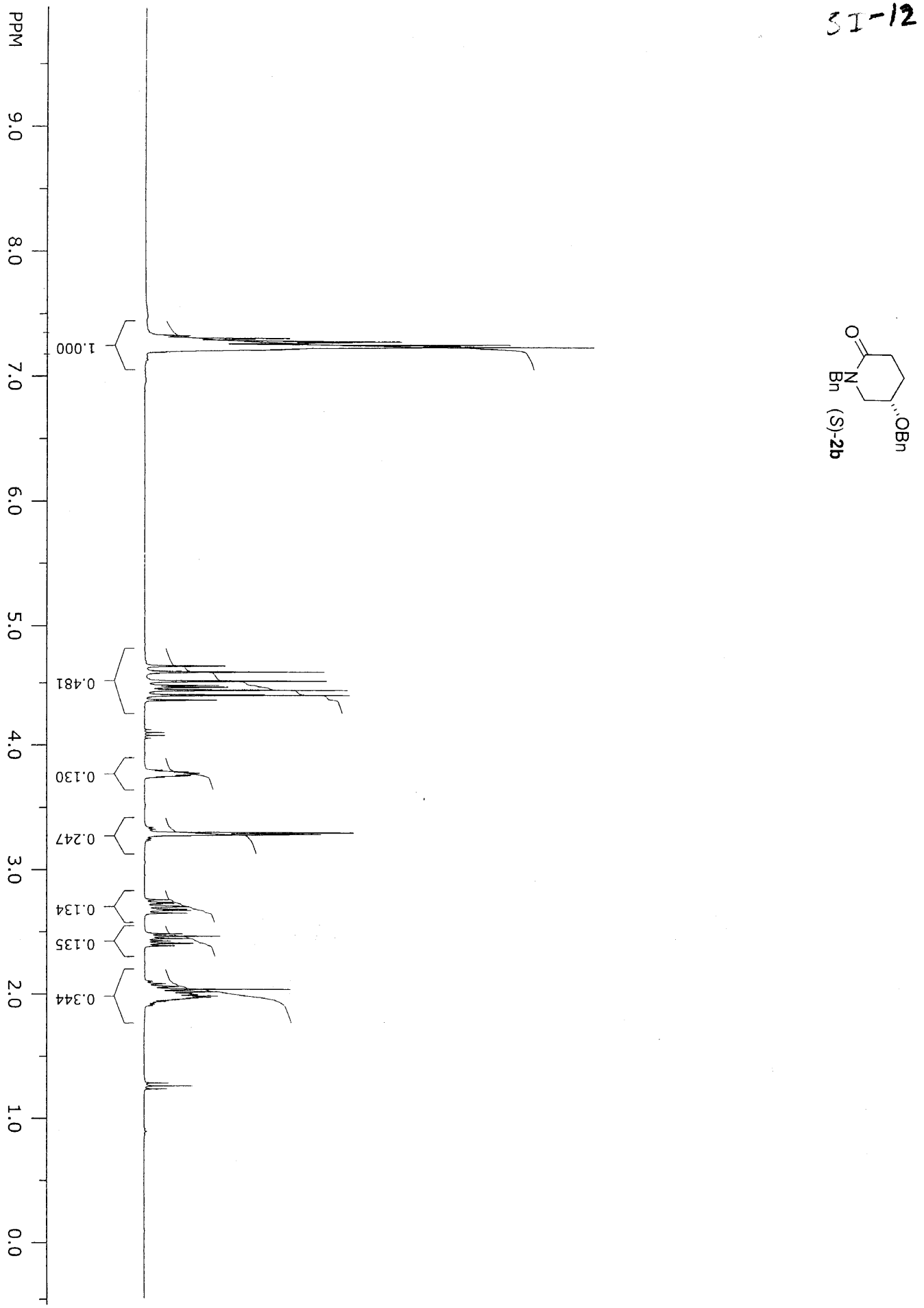


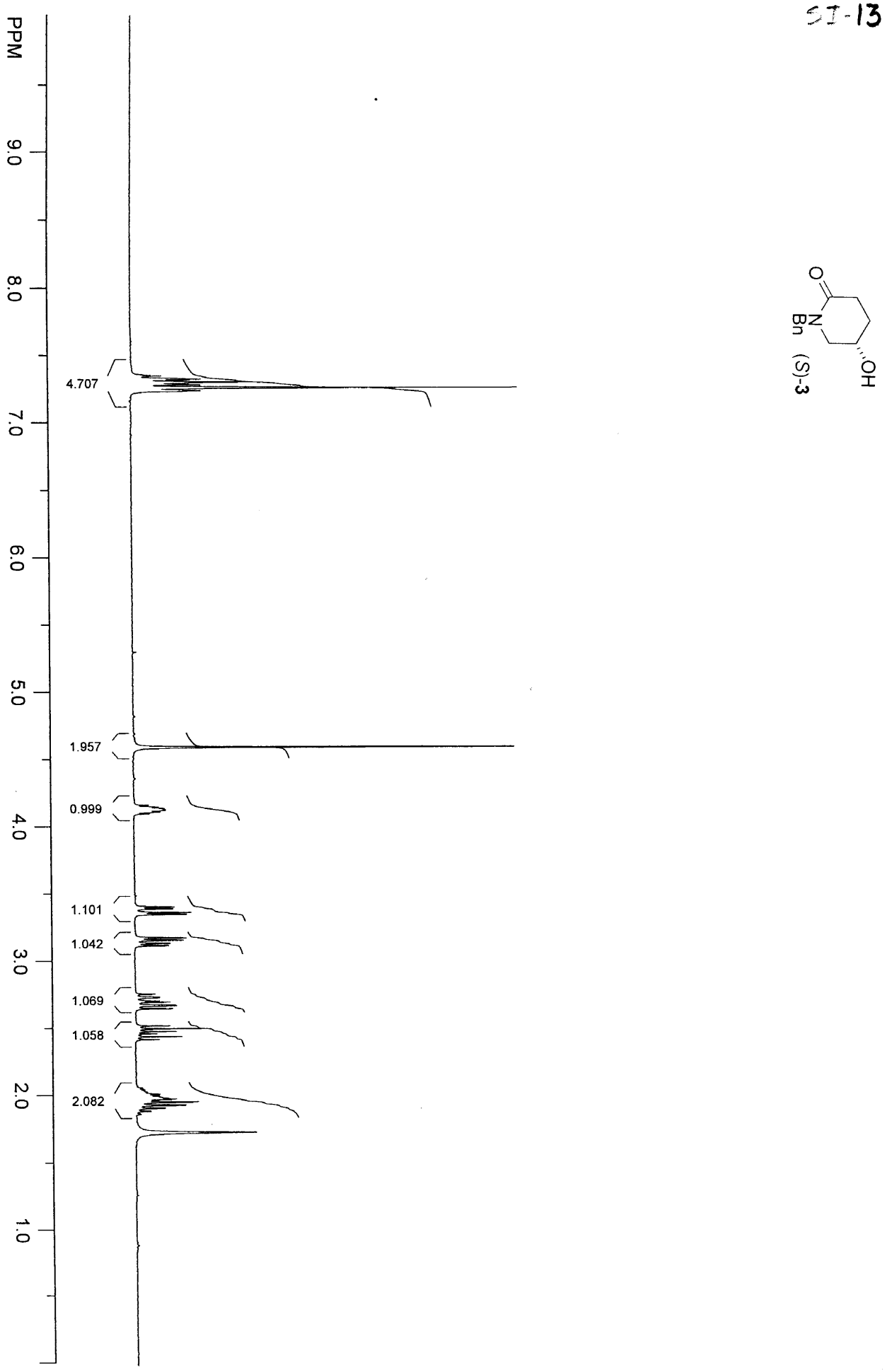
S-11




(*S*)-**2b**

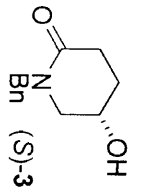



PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.000
0.481
0.130
0.247
0.134
0.135
0.344
O
N
Bn
OBn
(S)-2b

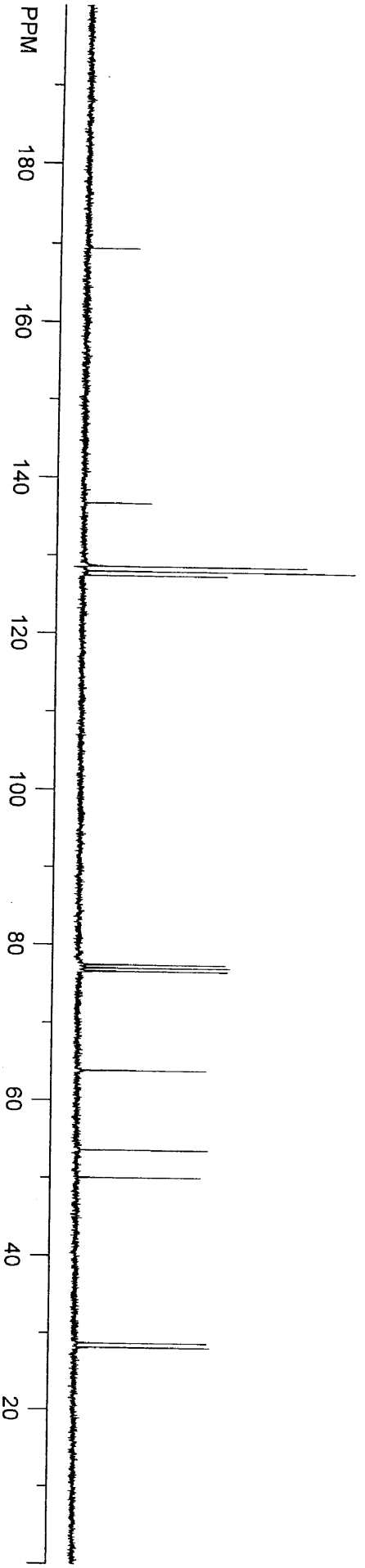

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
4.707
1.957
0.999
1.101
1.042
1.069
1.058
2.082

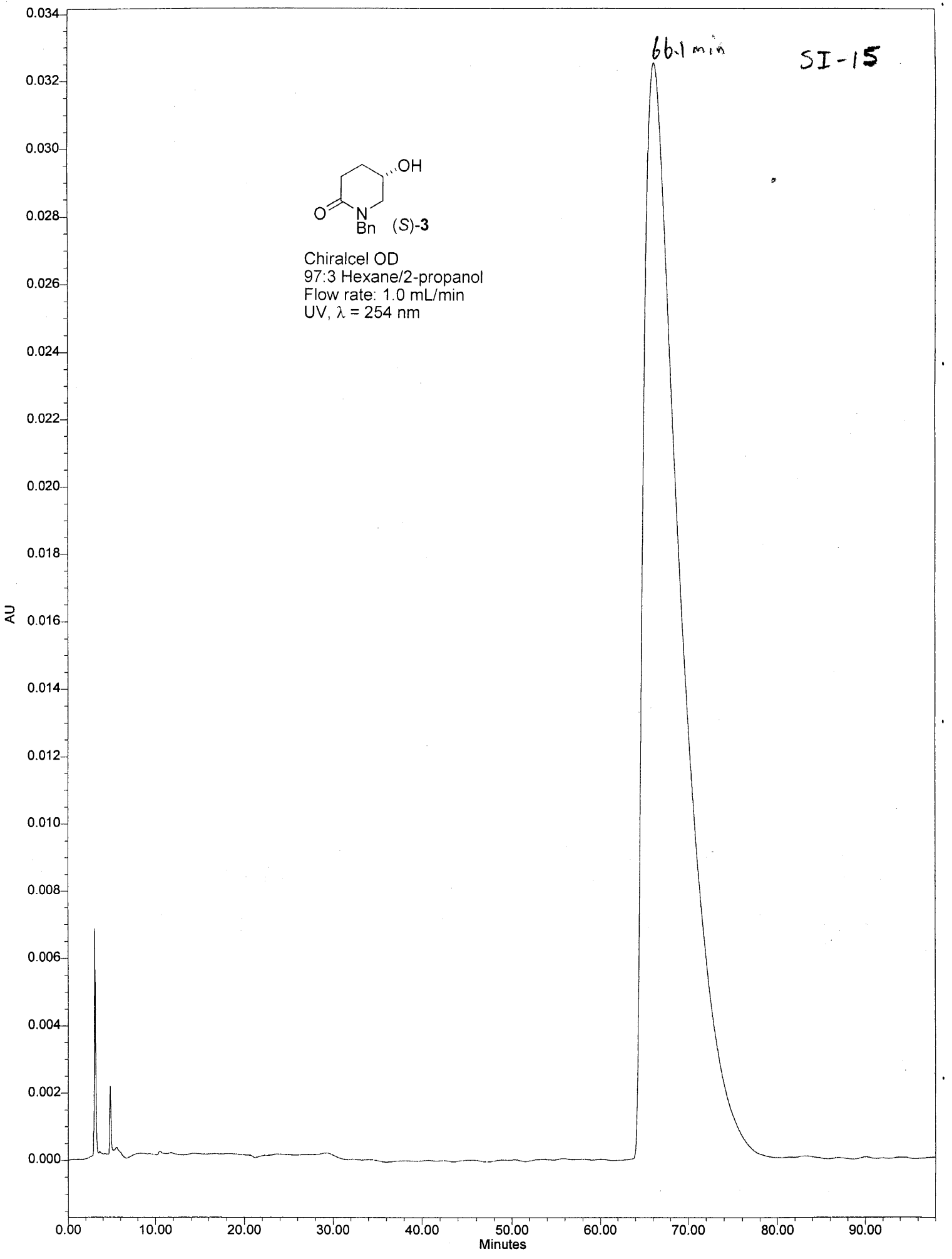

O
N
Bn
OH

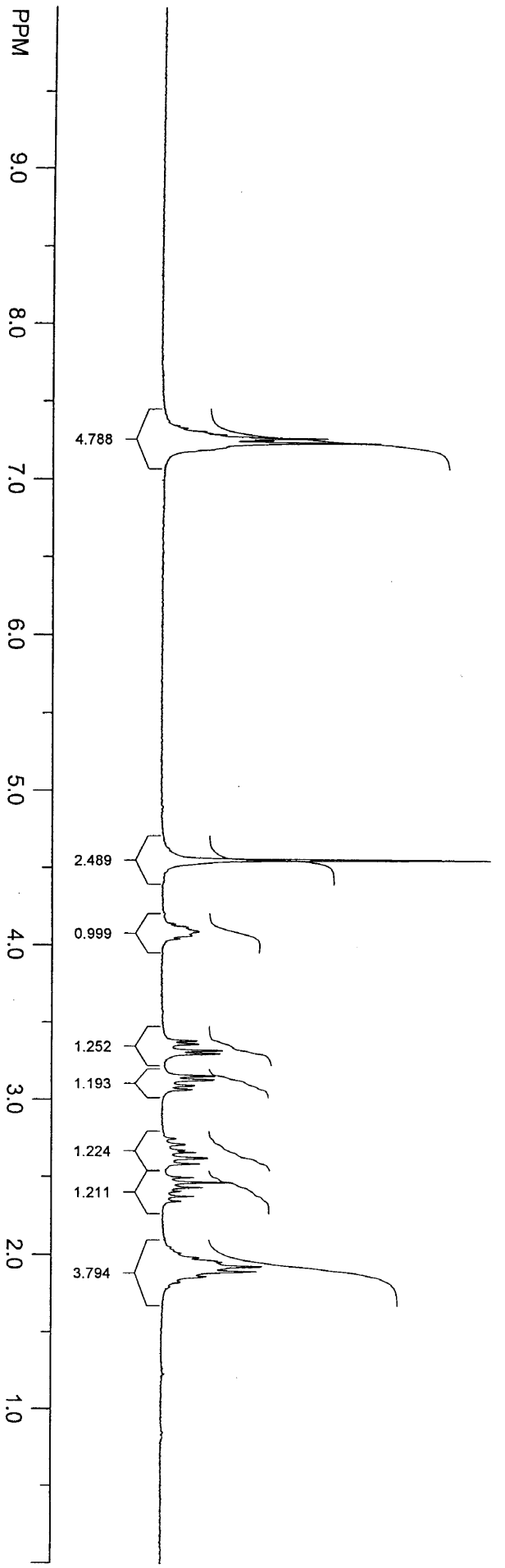
(S)-3

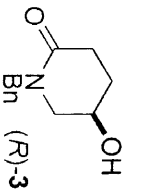



(S)-3

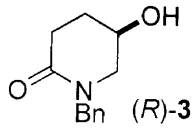



66.1 min
SI-15
OH
O
N
Bn
(S)-3
Chiralcel OD
97:3 Hexane/2-propanol
Flow rate: 1.0 mL/min
UV, λ = 254 nm
AU
0.034
0.032
0.030
0.028
0.026
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
90.00
Minutes

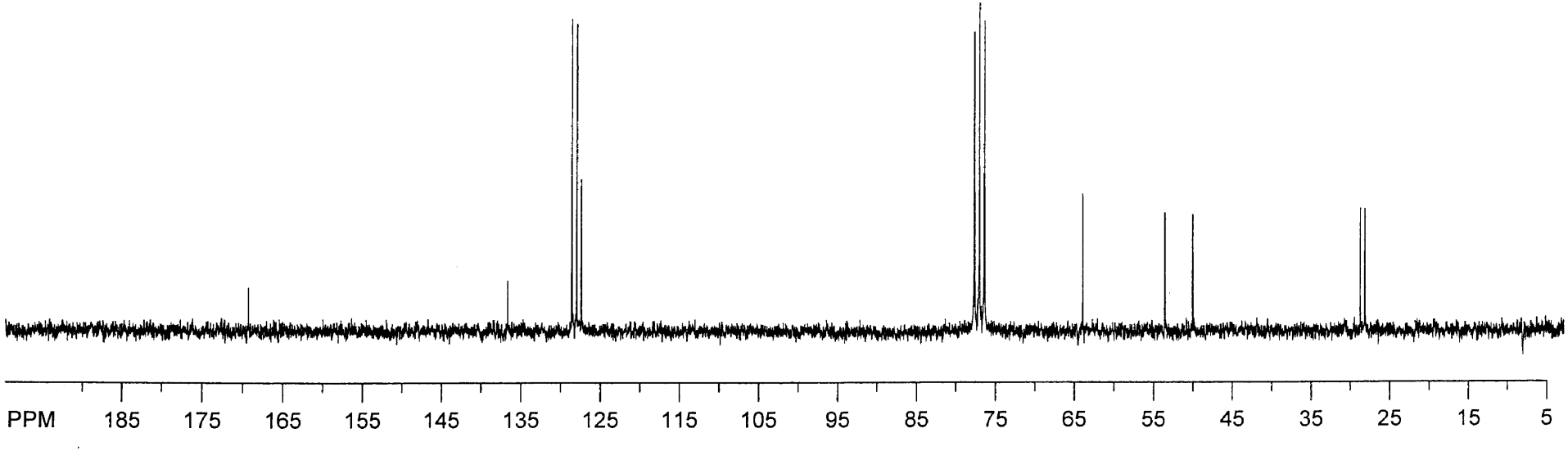

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
4.788
2.489
0.999
1.252
1.193
1.224
1.211
3.794

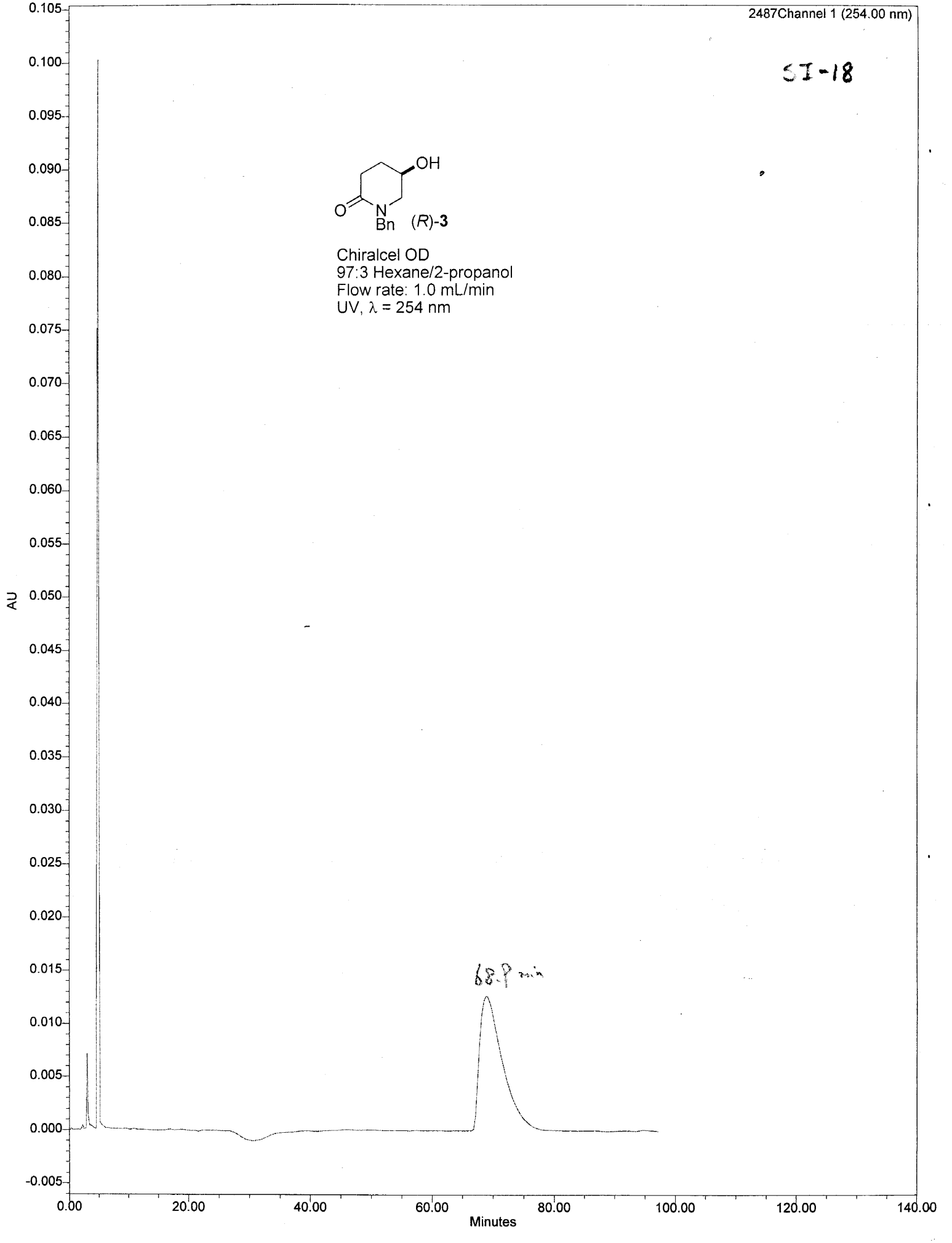

O
N
Bn
OH

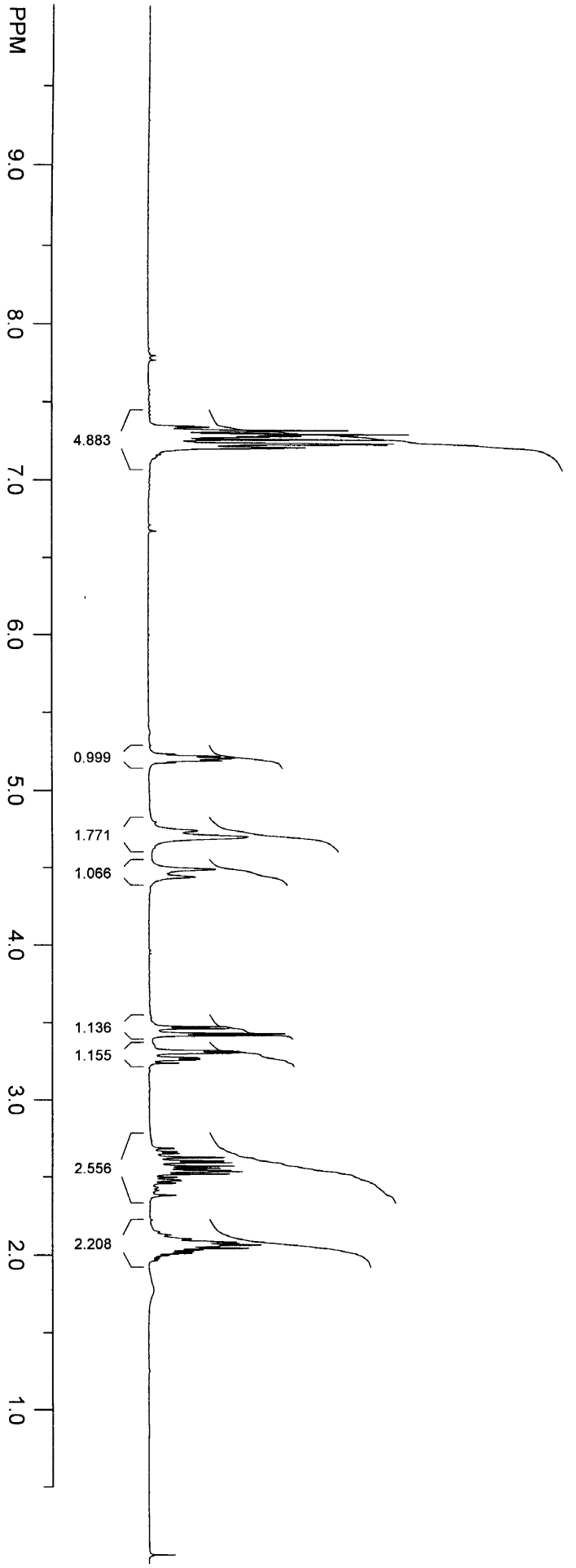
(*R*)-**3**

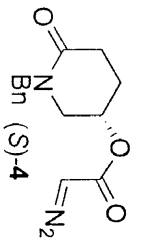

OH
O
N
Bn

(*R*)-**3**

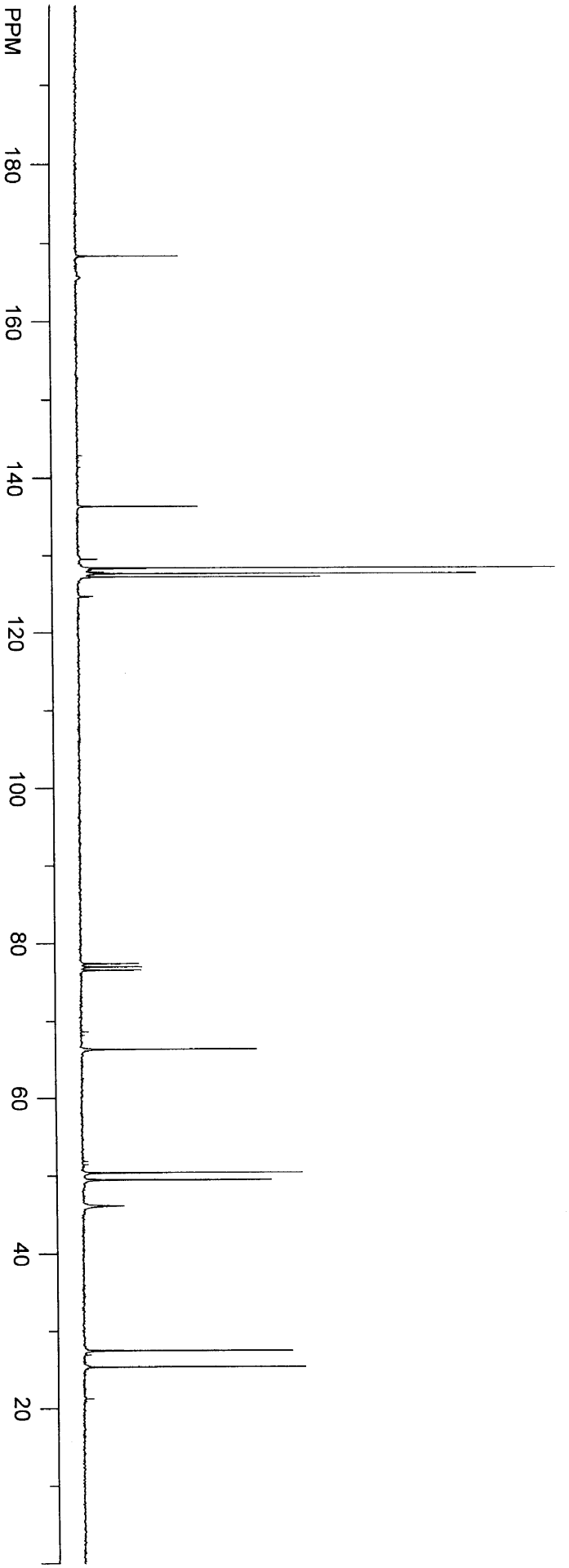

PPM
185
175
165
155
145
135
125
115
105
95
85
75
65
55
45
35
25
15
5

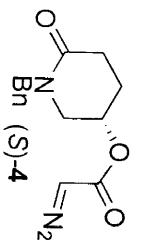

2487Channel 1 (254.00 nm)
SI-18
OH
O
N
Bn
(R)-3
Chiralcel OD
97:3 Hexane/2-propanol
Flow rate: 1.0 mL/min
UV, λ = 254 nm
68.9 min
AU
0.105
0.100
0.095
0.090
0.085
0.080
0.075
0.070
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
-0.005
0.00
20.00
40.00
60.00
80.00
100.00
120.00
140.00
Minutes


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
4.883
0.999
1.771
1.066
1.136
1.155
2.556
2.208


O
N
Bn
O
O
O
N2

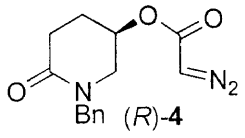
(S)-**4**



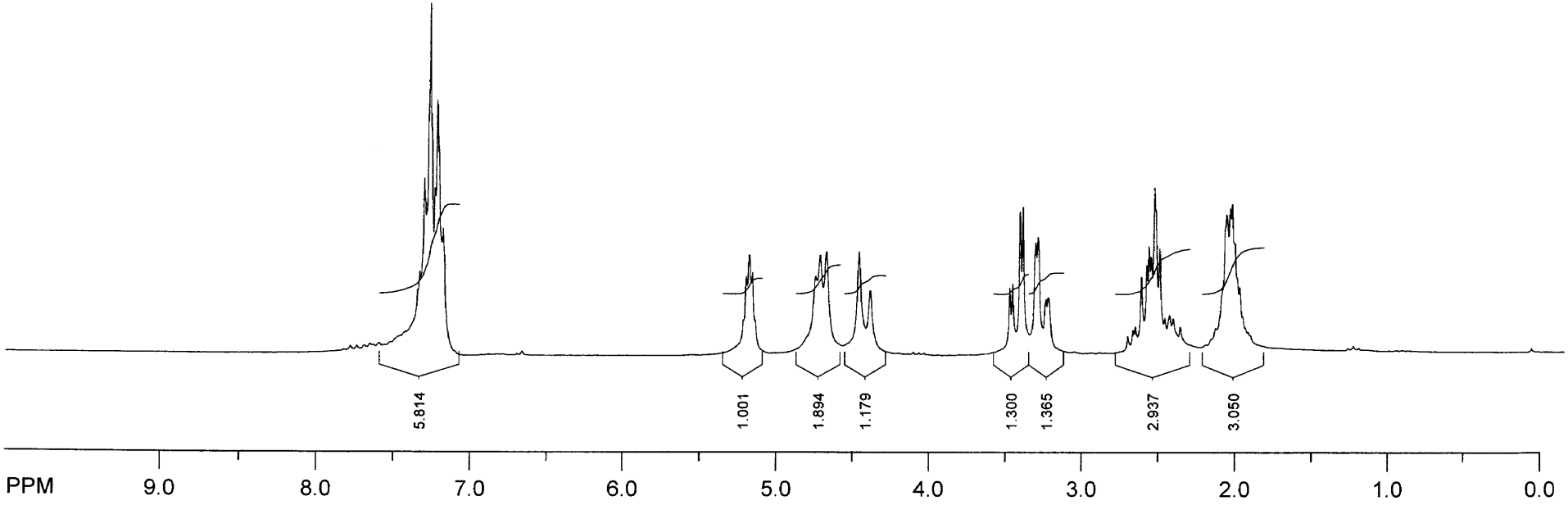




(S)-**4**

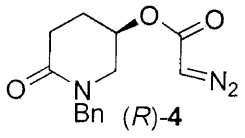
ST-21


O
O
O
N
N2
Bn

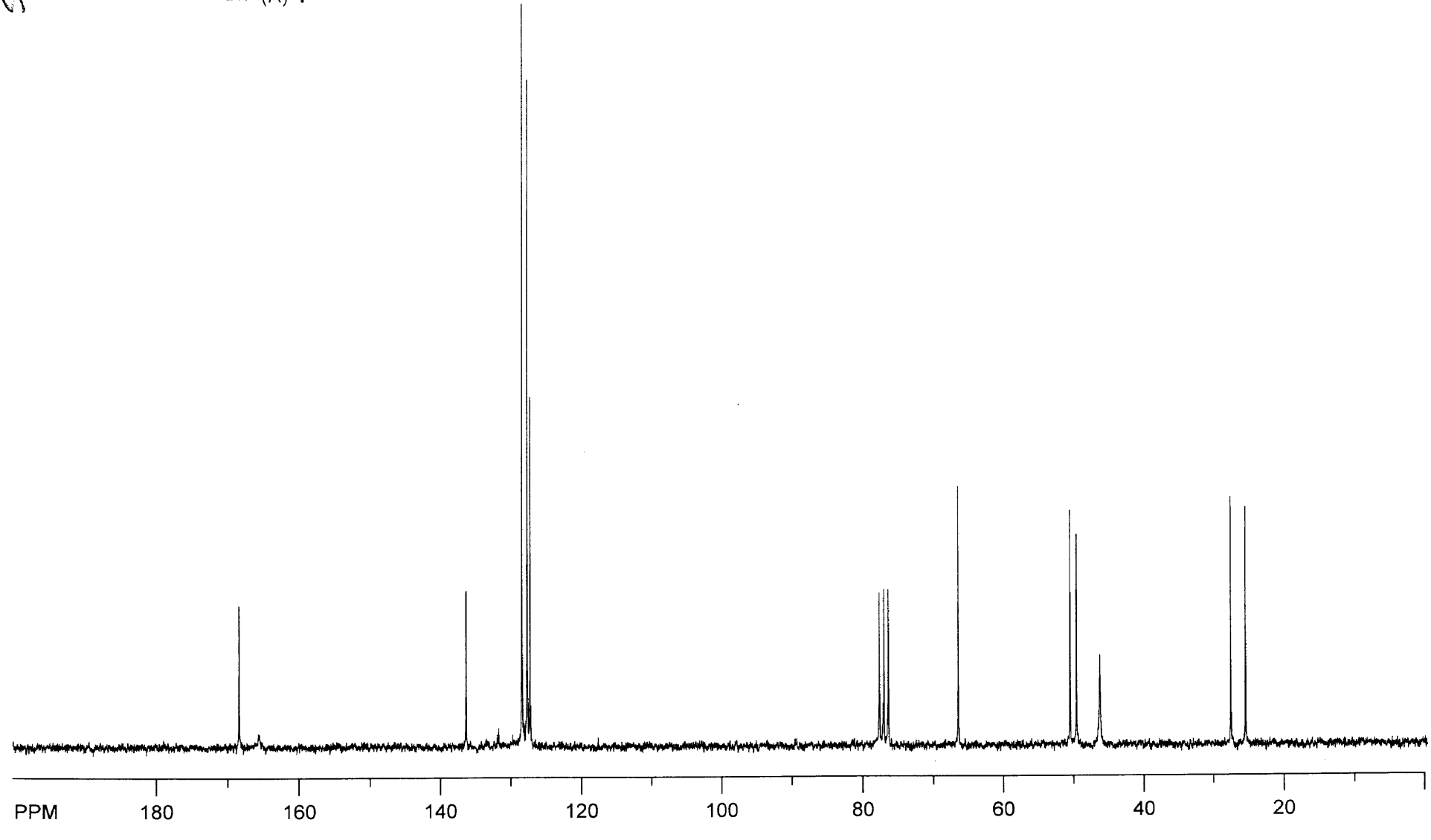
(*R*)-**4**


5.814
1.001
1.894
1.179
1.300
1.365
2.937
3.050
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

ST-22



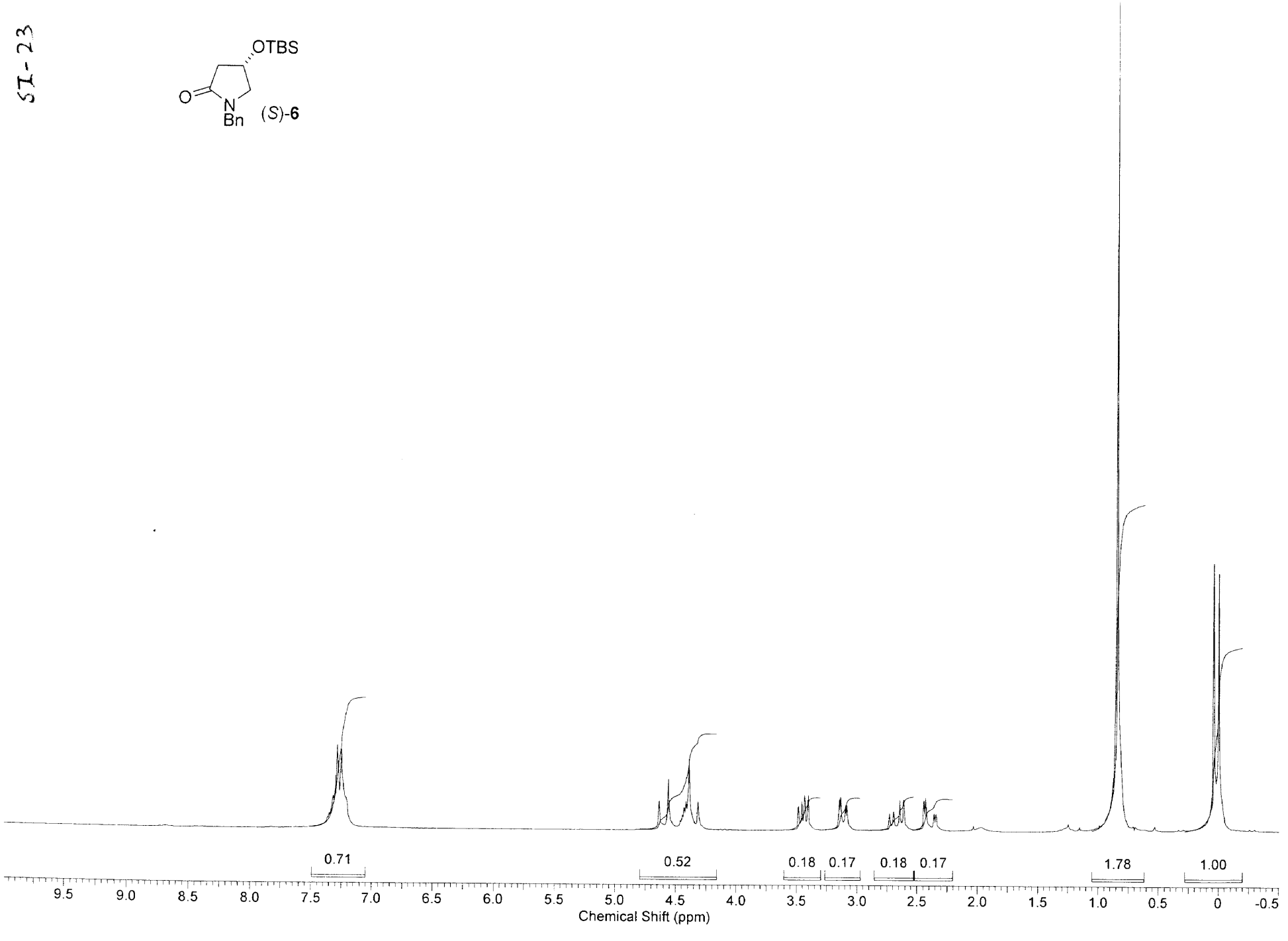

(*R*)-**4**



SI-23


OTBS
O
N
Bn

(*S*)-**6**

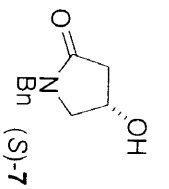

0.71
0.52
0.18
0.17
0.18
0.17
1.78
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

CT-24

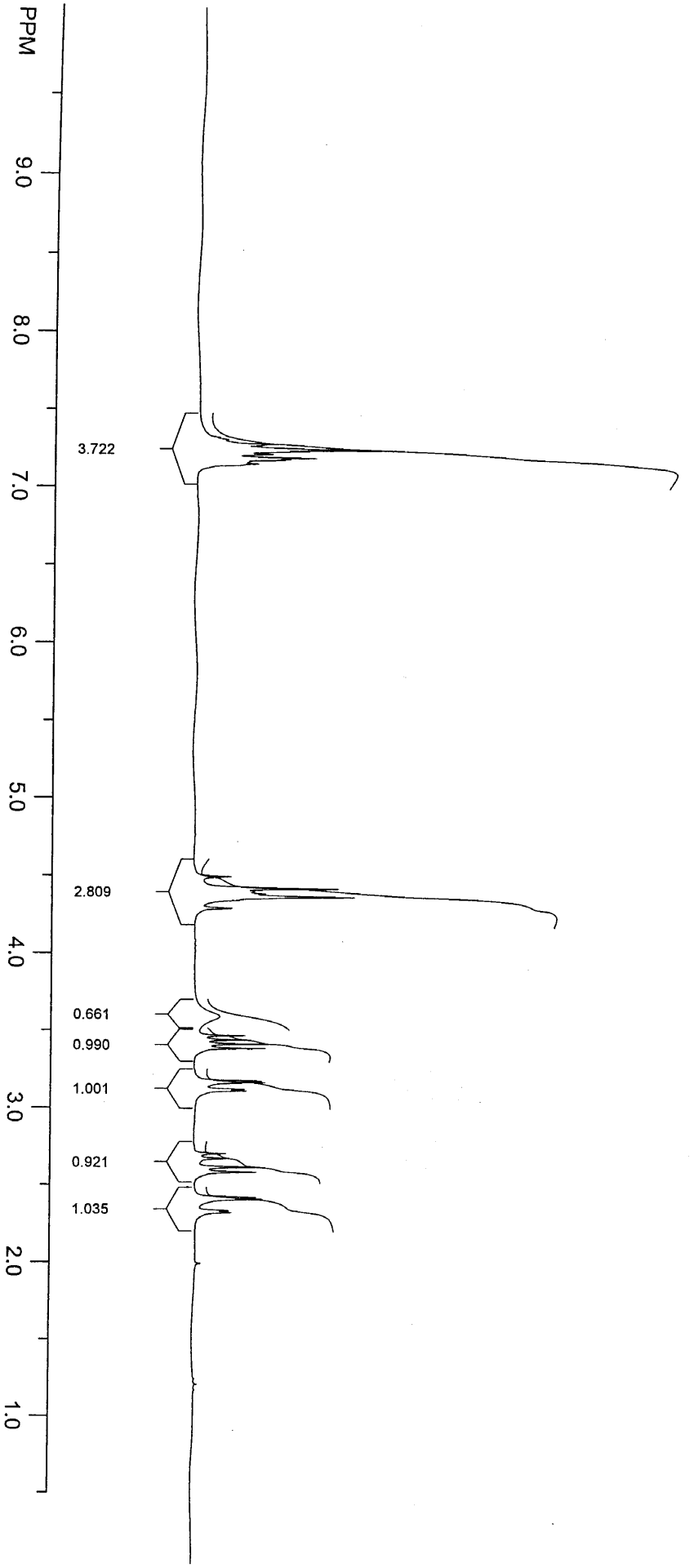

O
N
Bn
OTBS

(S)-**6**


192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)

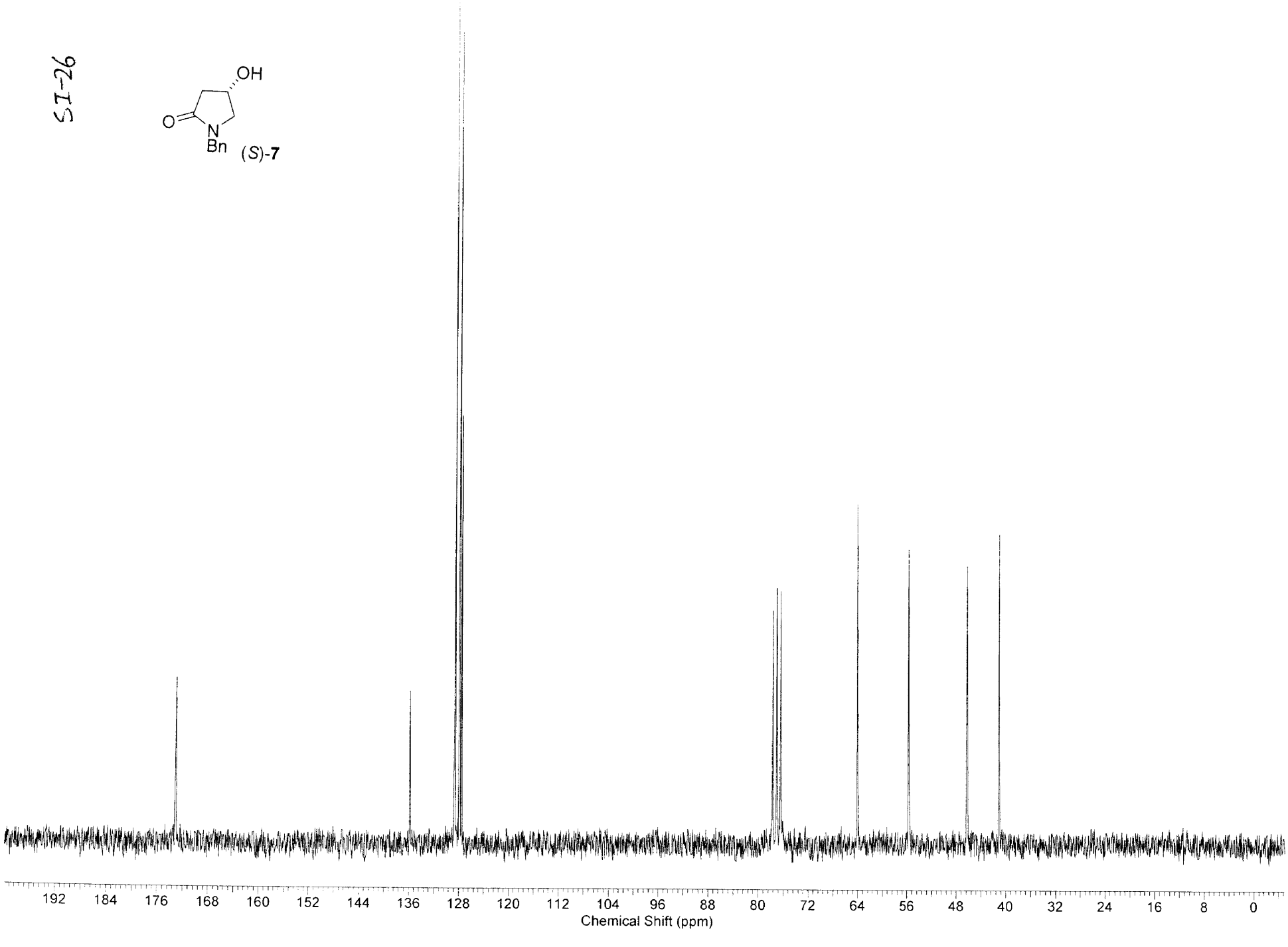

O
N
Bn
OH

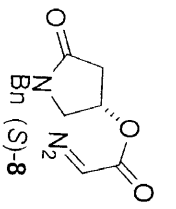
(S)-**7**

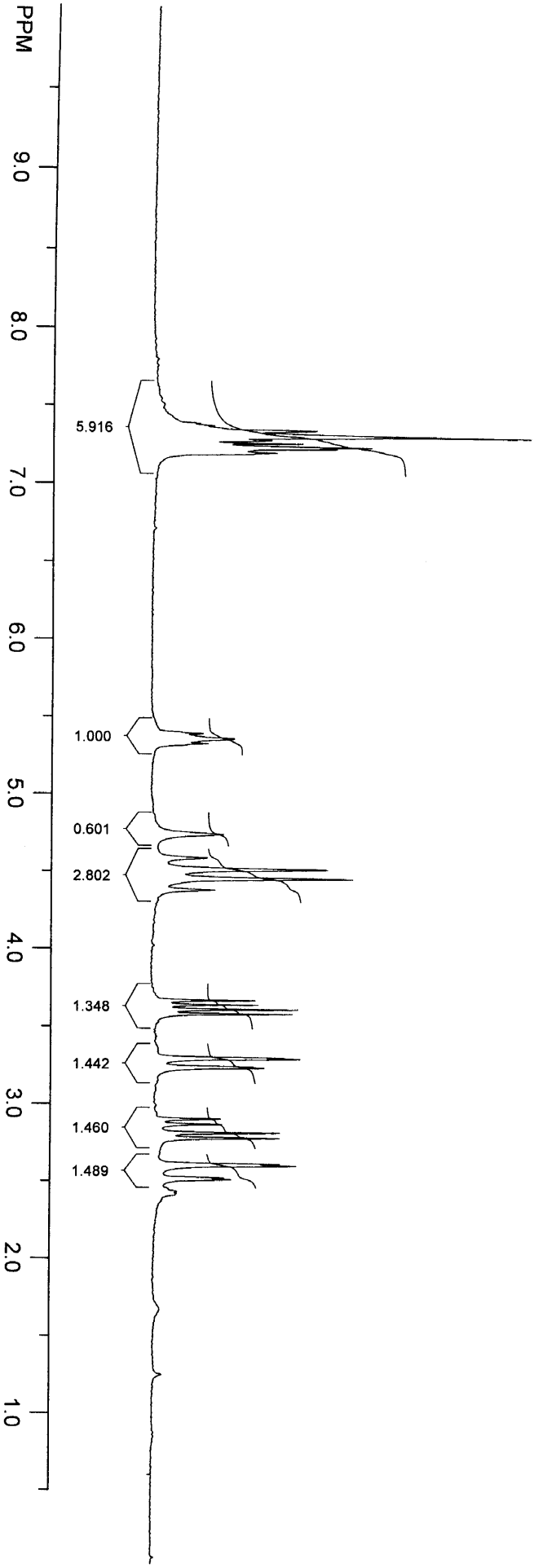

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
3.722
2.809
0.661
0.990
1.001
0.921
1.035

OH
O
N
Bn

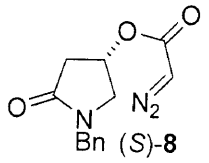
(*S*)-**7**


192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

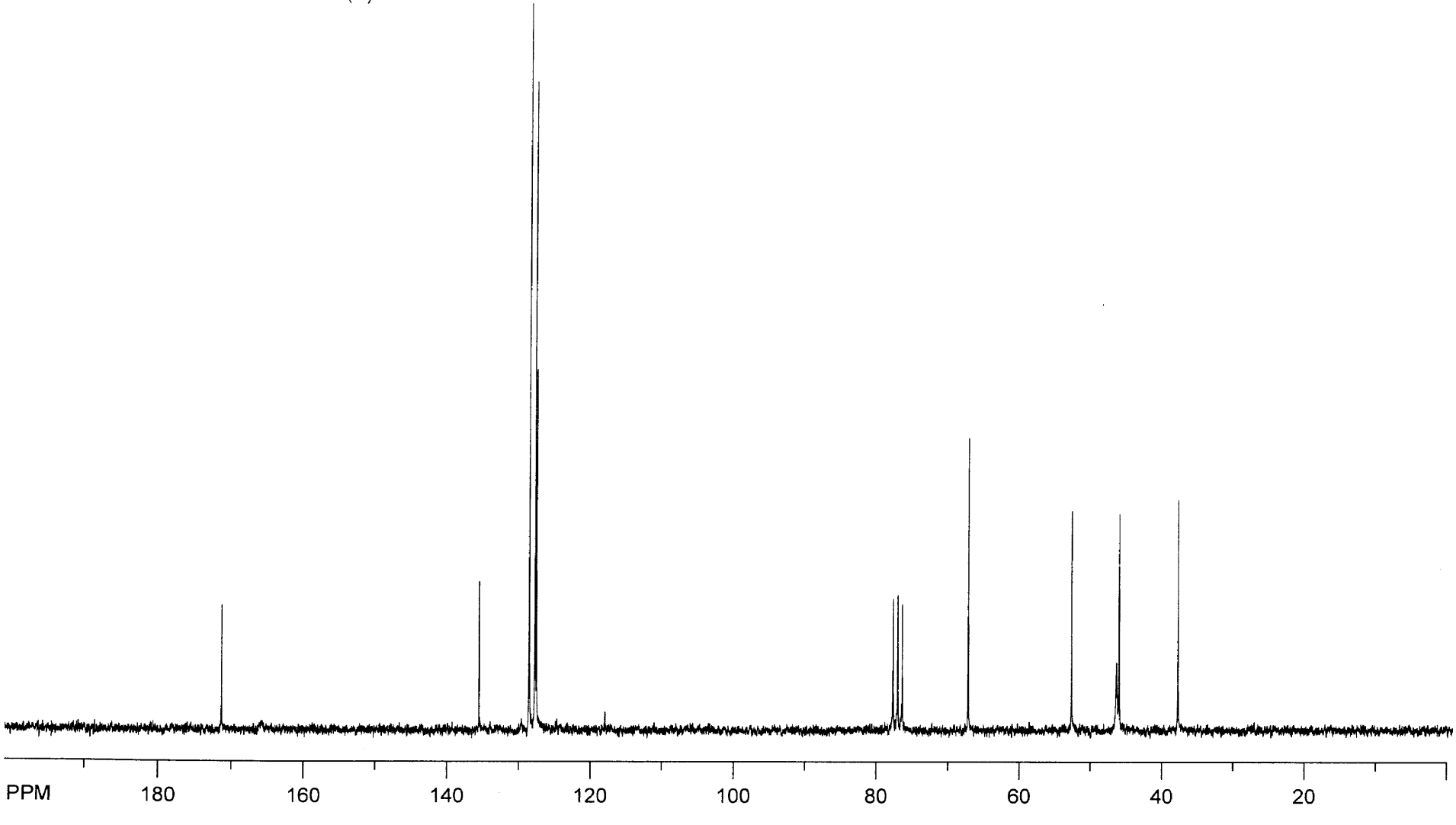

O
N
Bn
(S)-8
O
N2
O

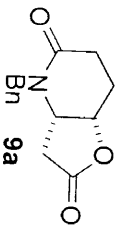

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
5.916
1.000
0.601
2.802
1.348
1.442
1.460
1.489

SI-28

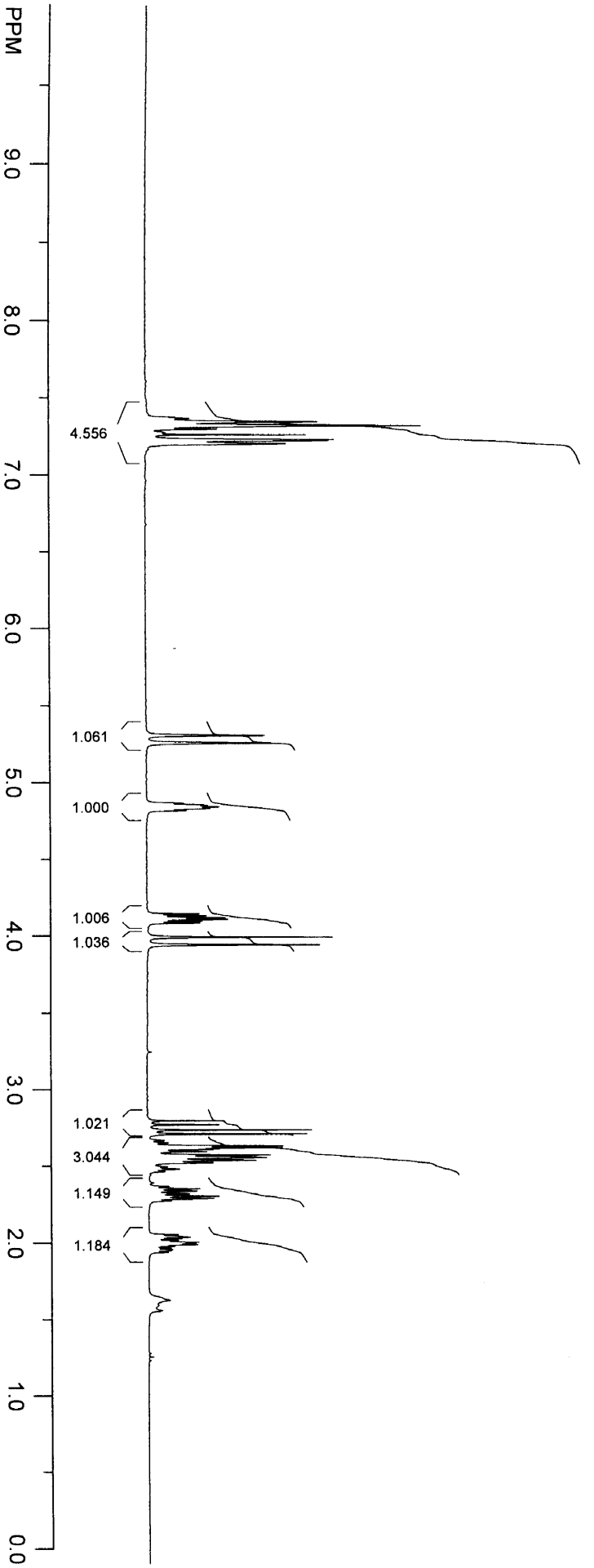



(*S*)-**8**

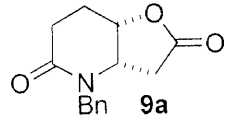



O
N
Bn
O
O
O

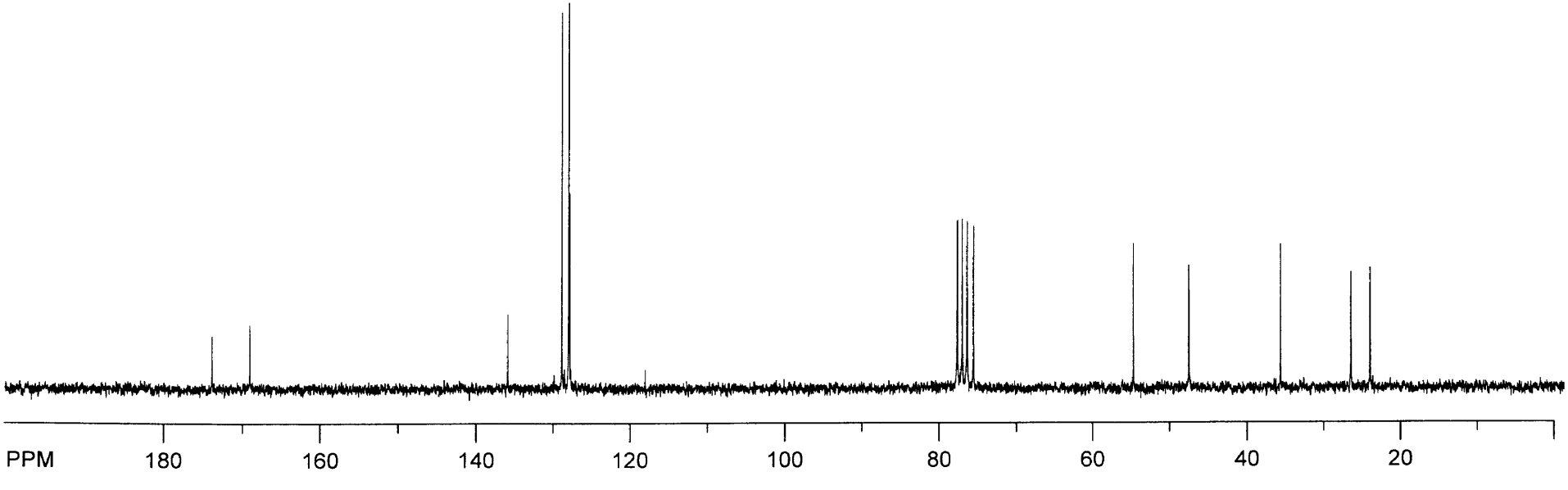
9a


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
4.556
1.061
1.000
1.006
1.036
1.021
3.044
1.149
1.184

SI-30

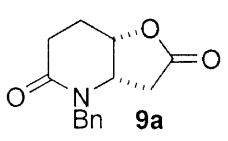



**9a**

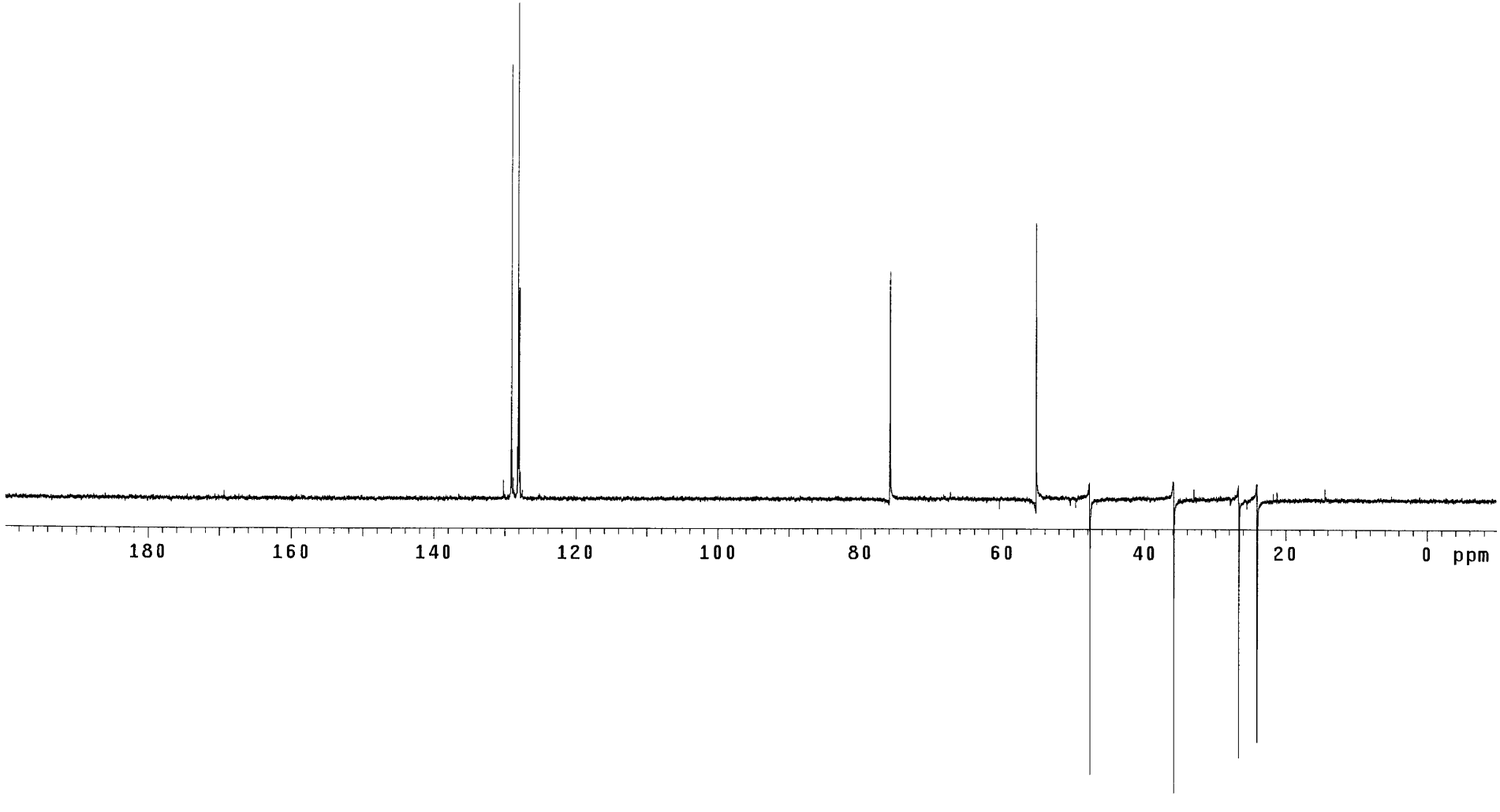


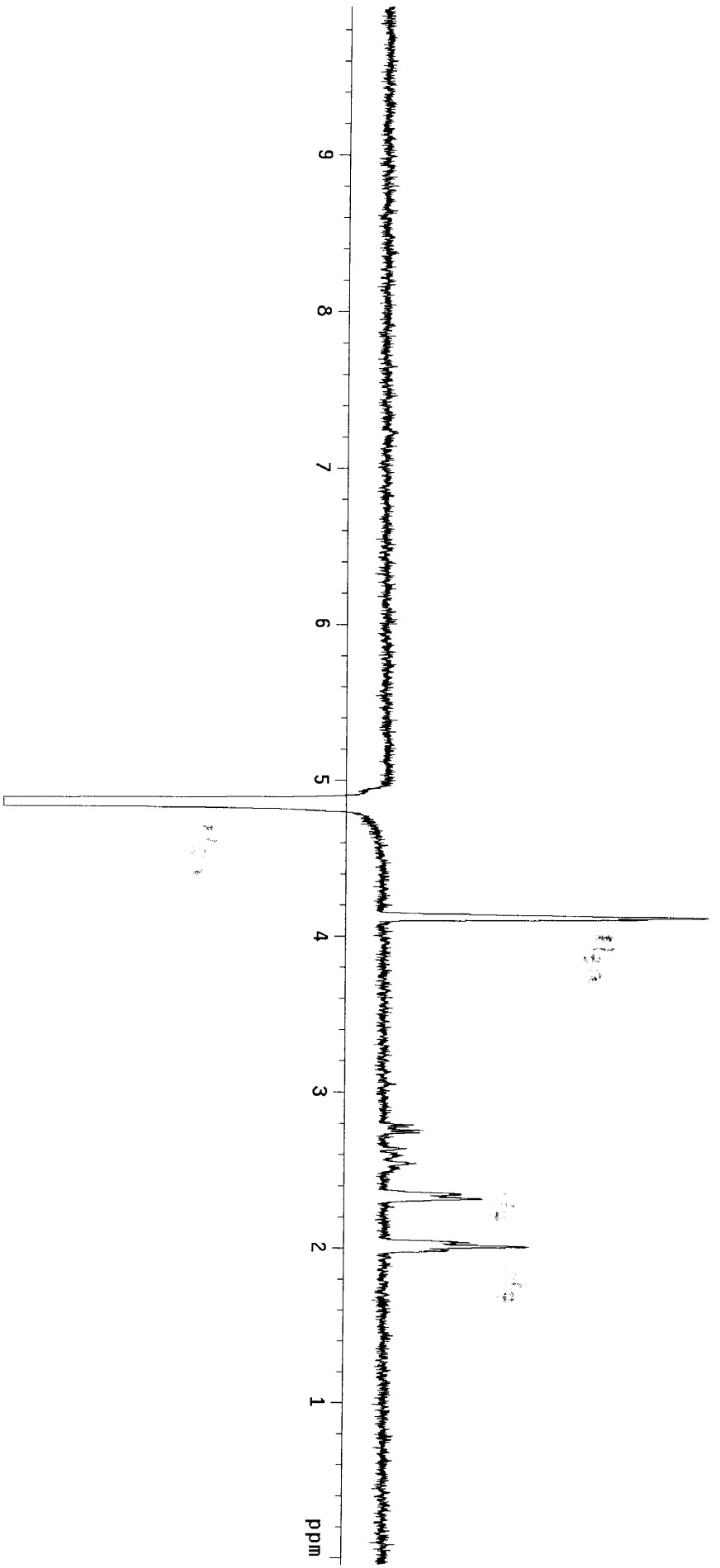
S15

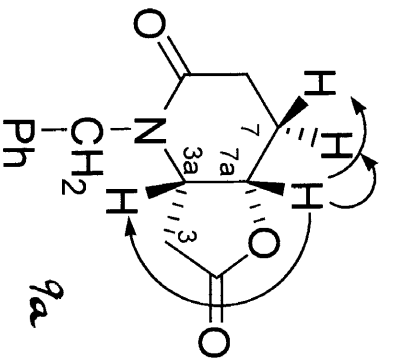
DEPT-135



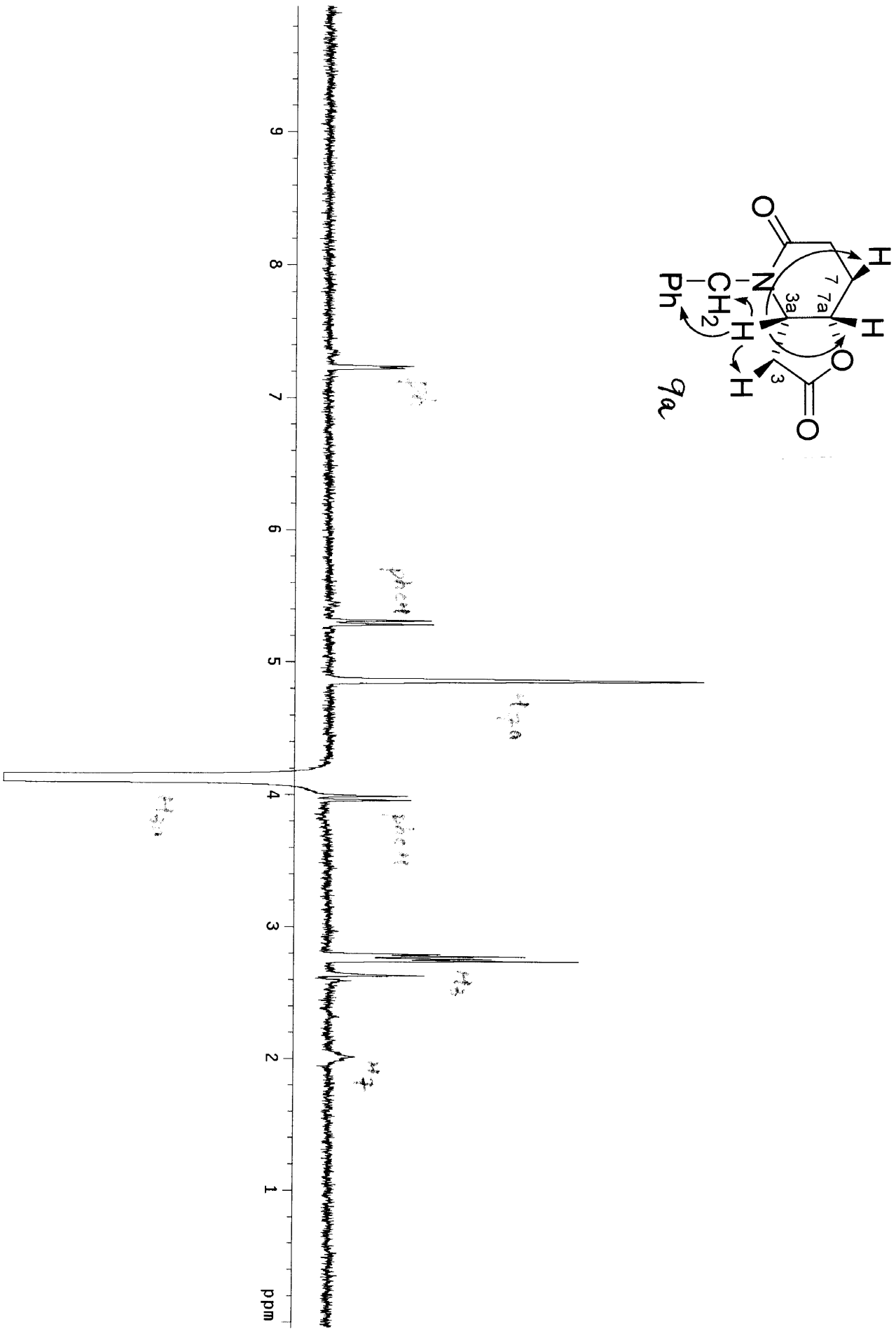

9a



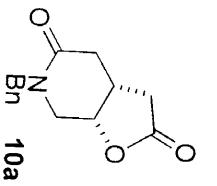


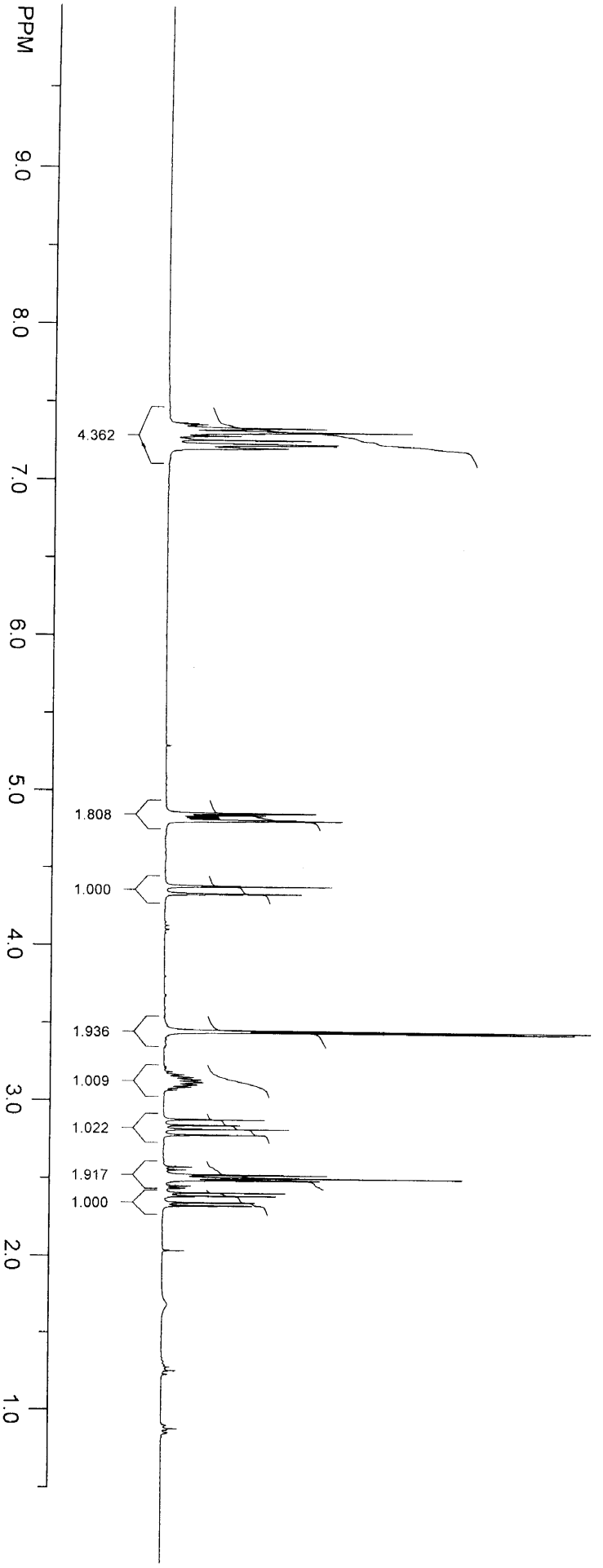

9a



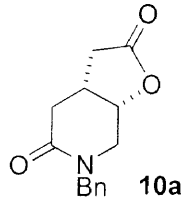

9a


O
N
Bn
O
O

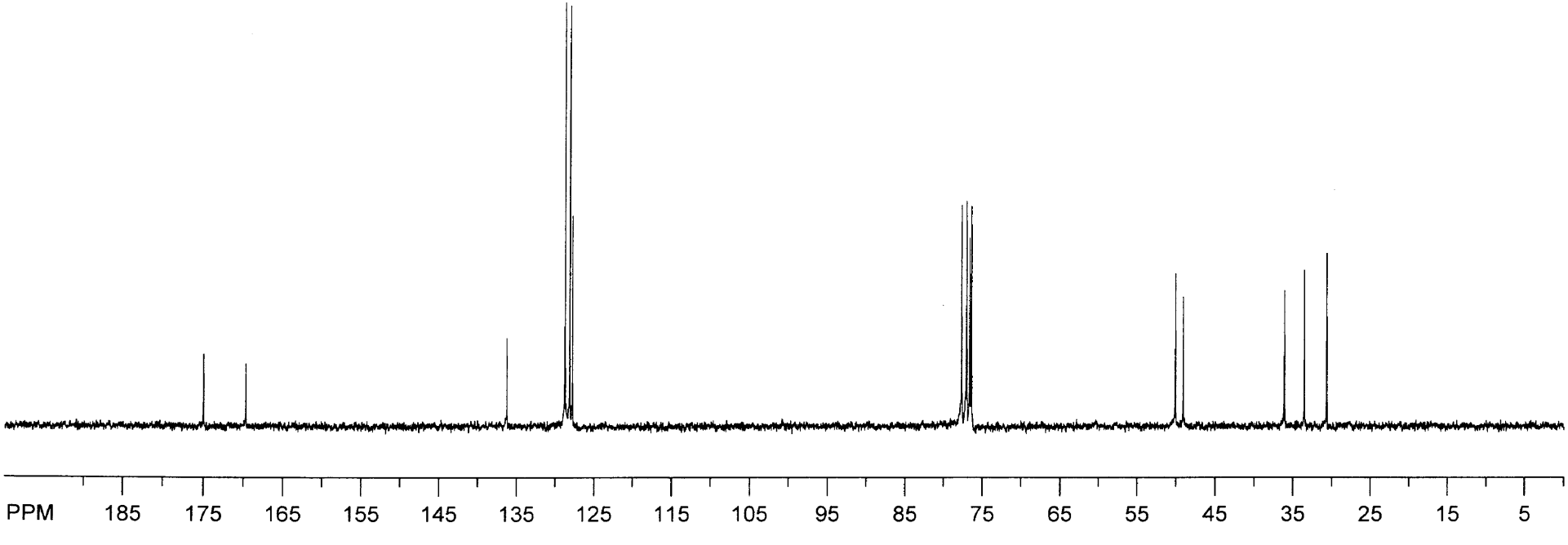
**10a**


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
4.362
1.808
1.000
1.936
1.009
1.022
1.917
1.000

ST-35

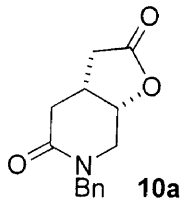

O
O
O
N
Bn

**10a**

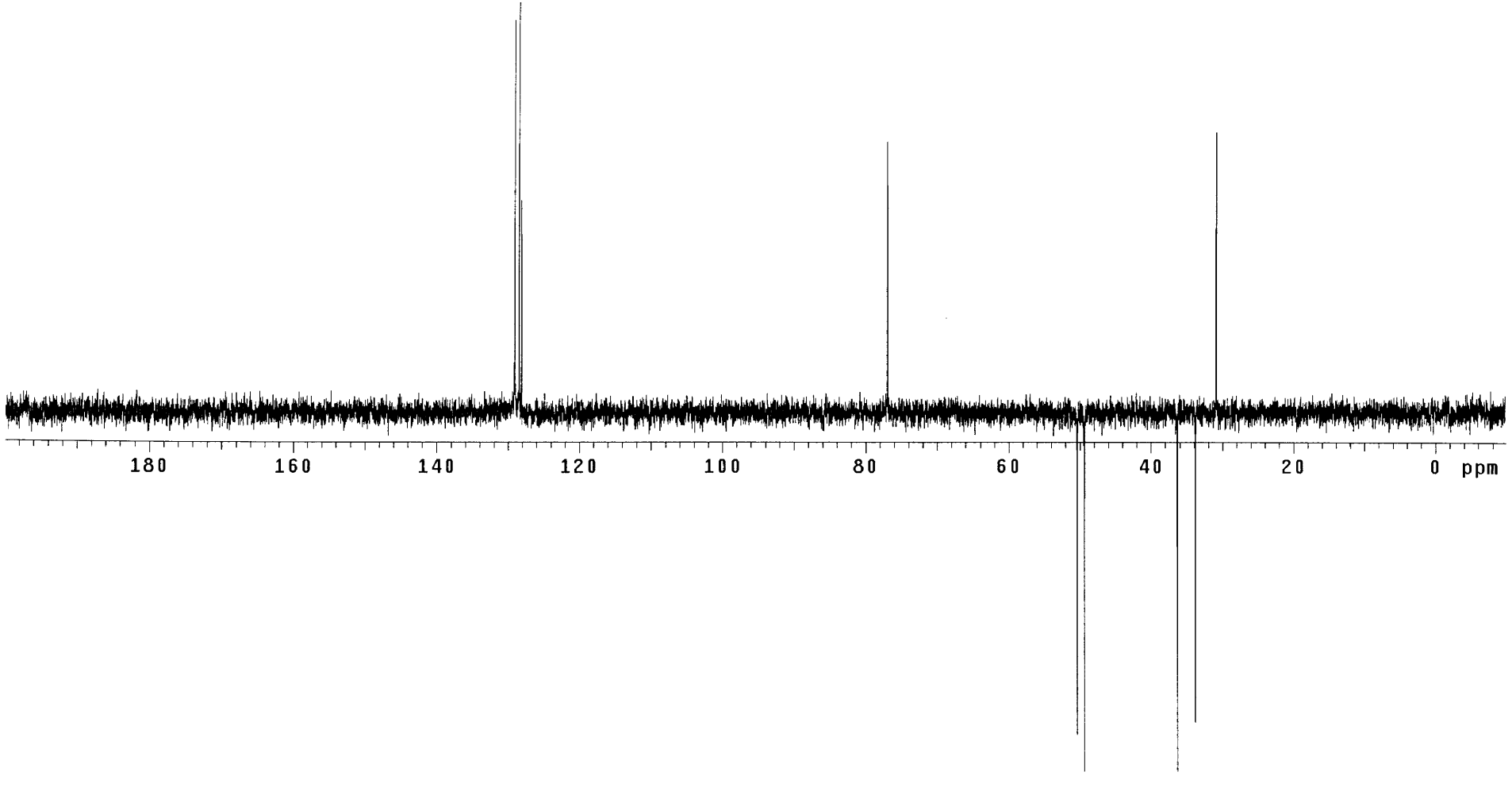

PPM
185
175
165
155
145
135
125
115
105
95
85
75
65
55
45
35
25
15
5

SI-36

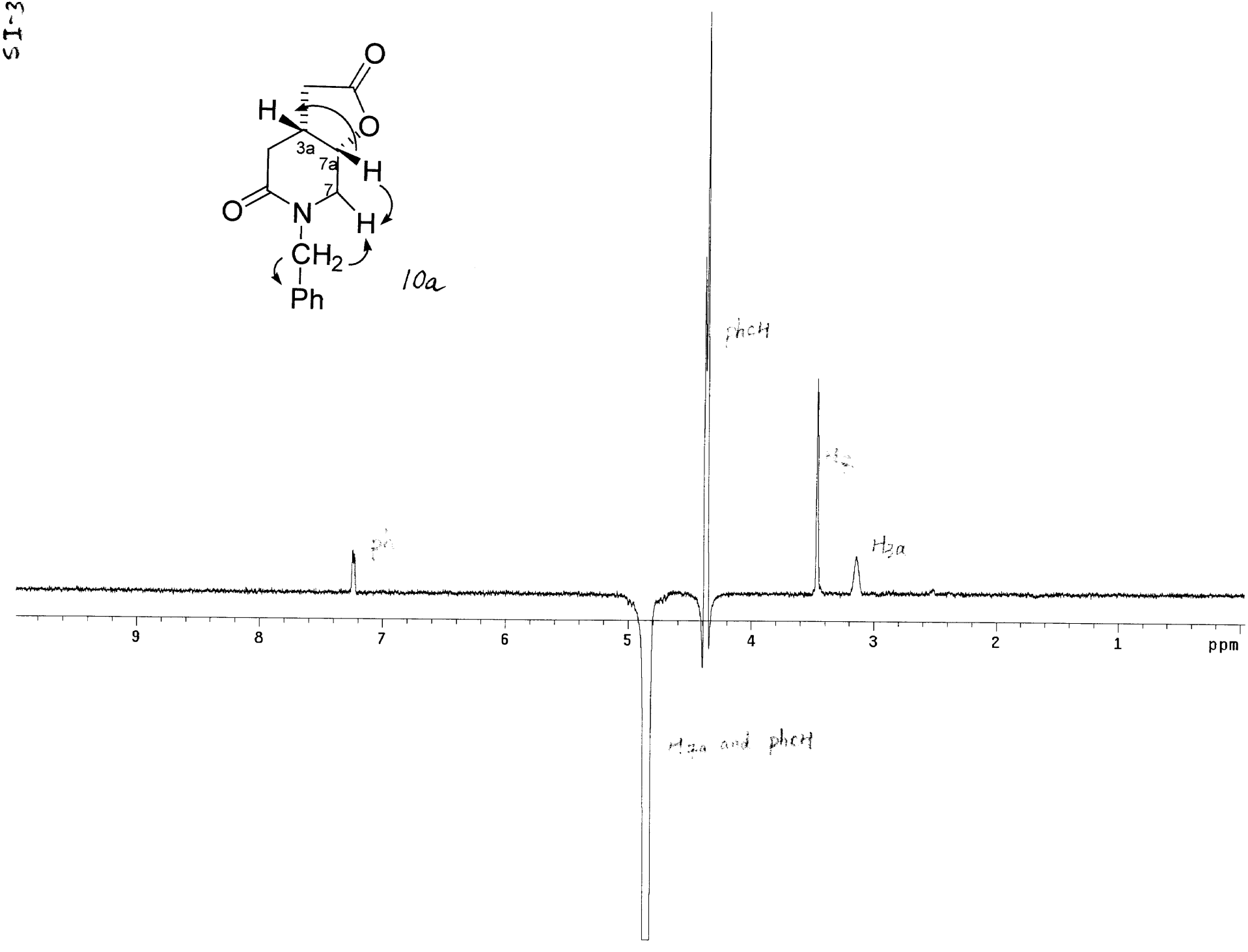
DEPT-135

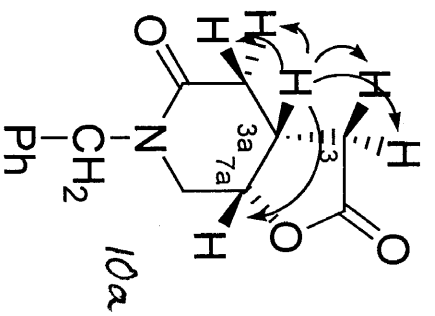



**10a**

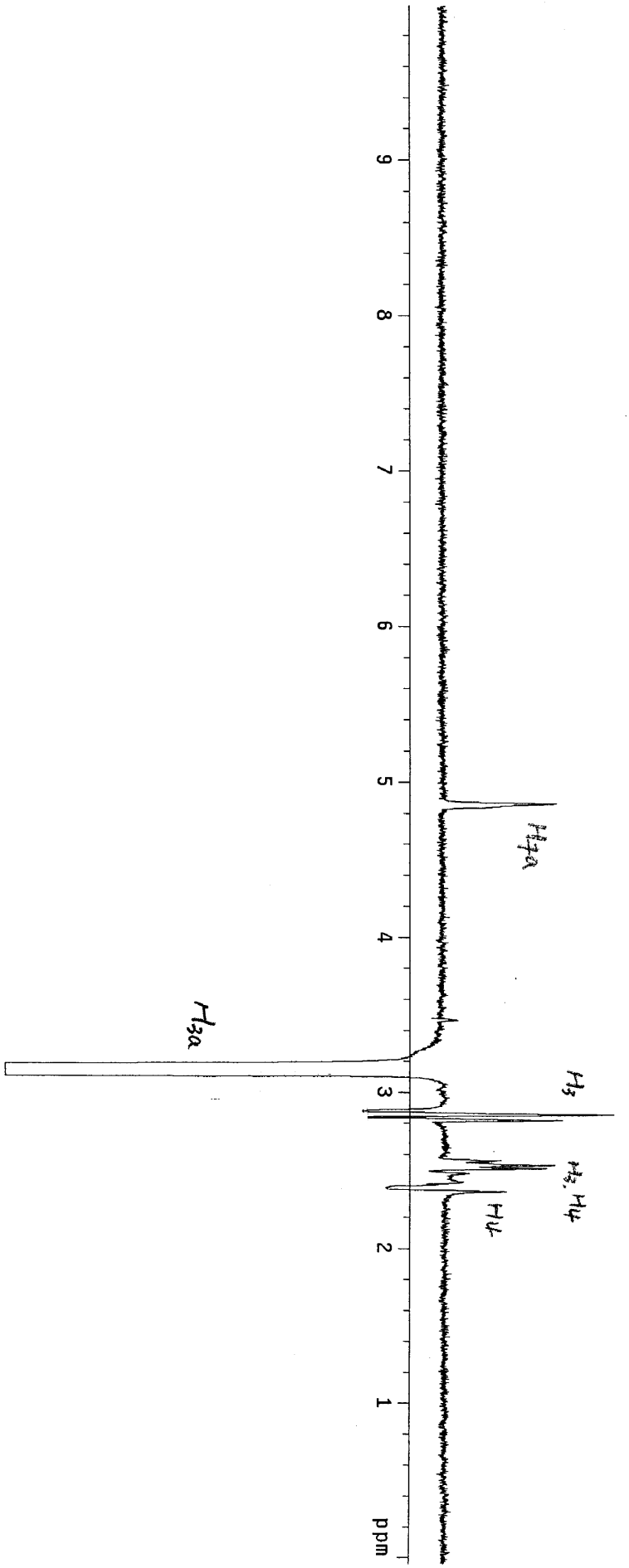


10a

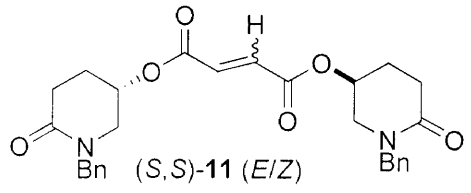




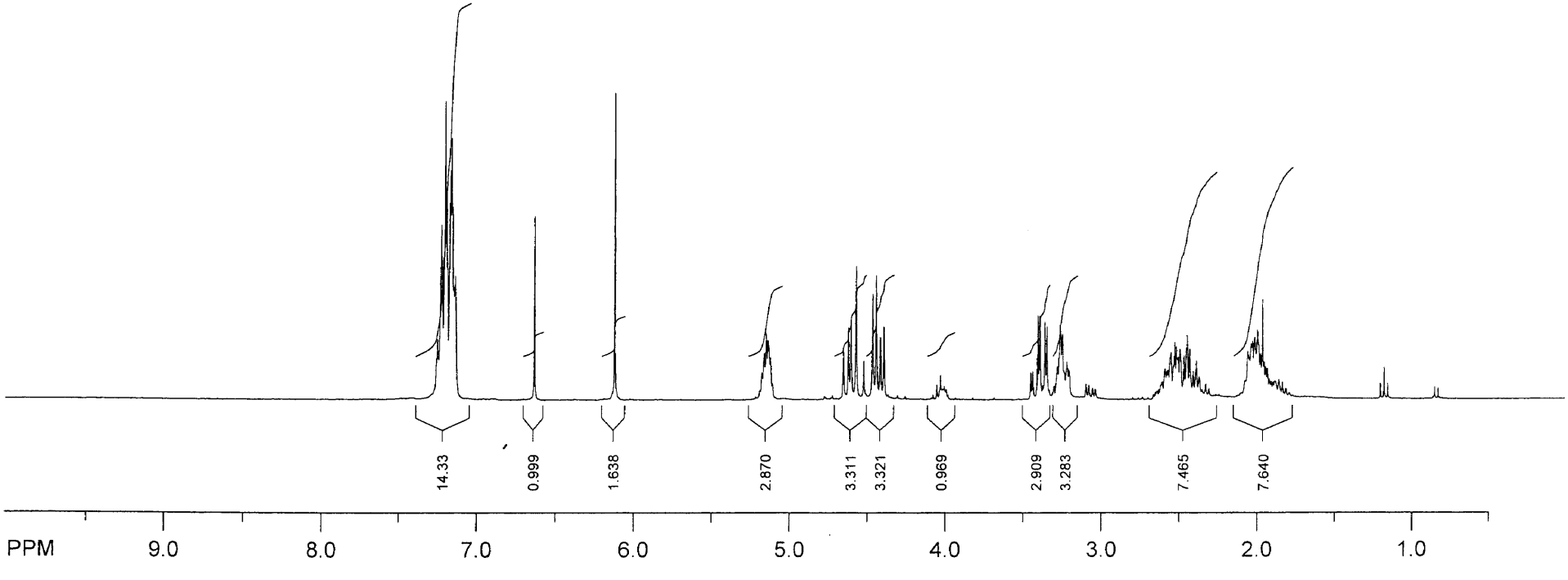

10a

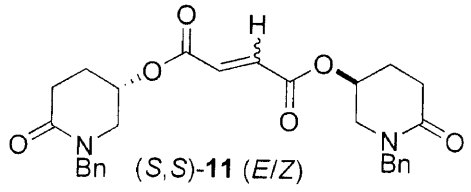


S1-39

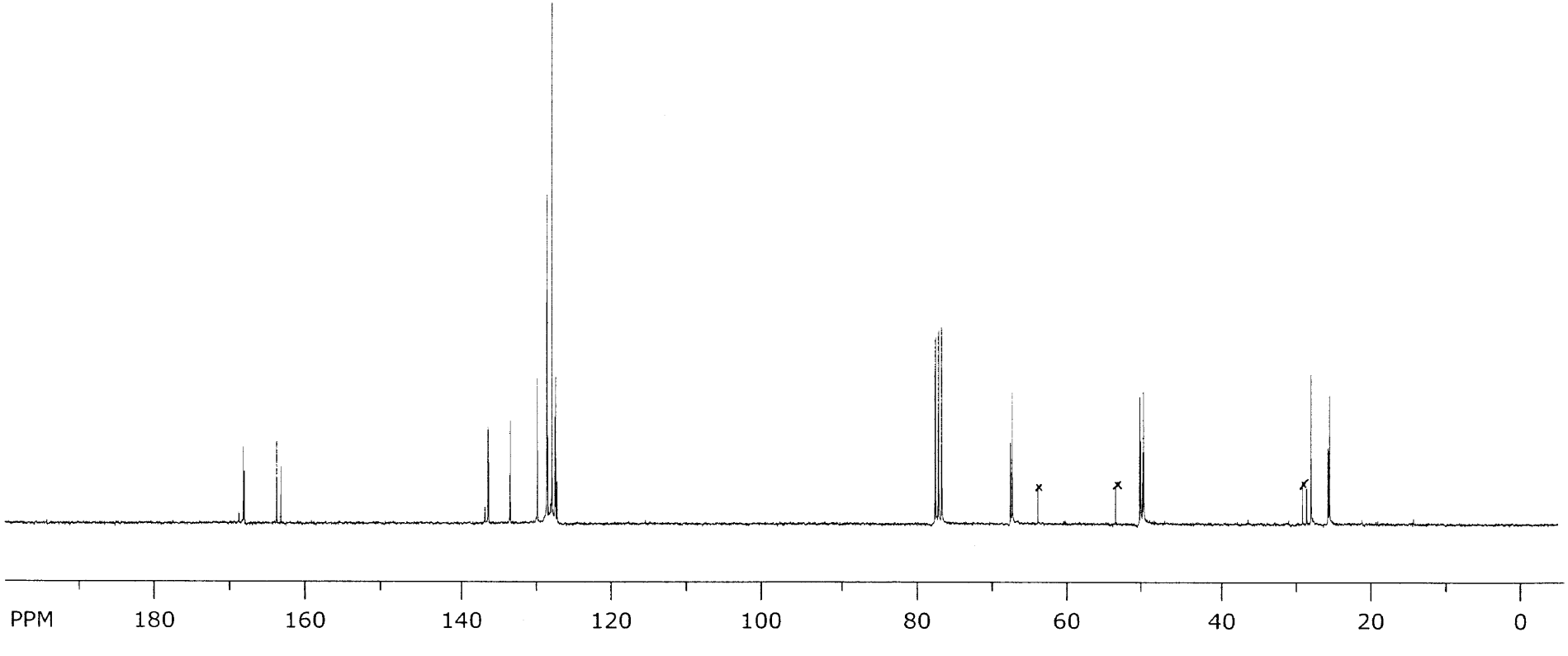

O
H
O
O
O
O
N
Bn
N
Bn
O
O

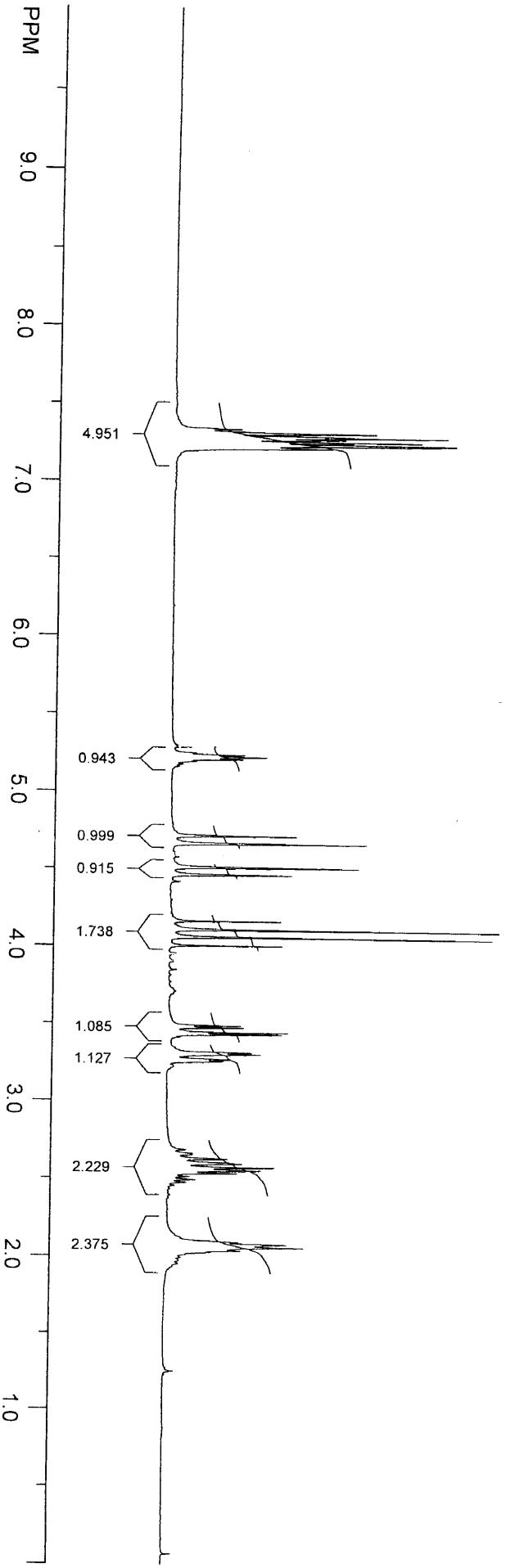
(*S*,*S*)-**11** (*E*/*Z*)

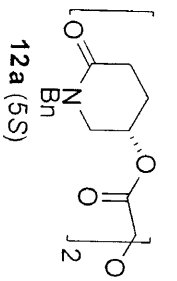

14.33
0.999
1.638
2.870
3.311
3.321
0.969
2.909
3.283
7.465
7.640
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0




(*S*,*S*)-**11** (*E*/*Z*)



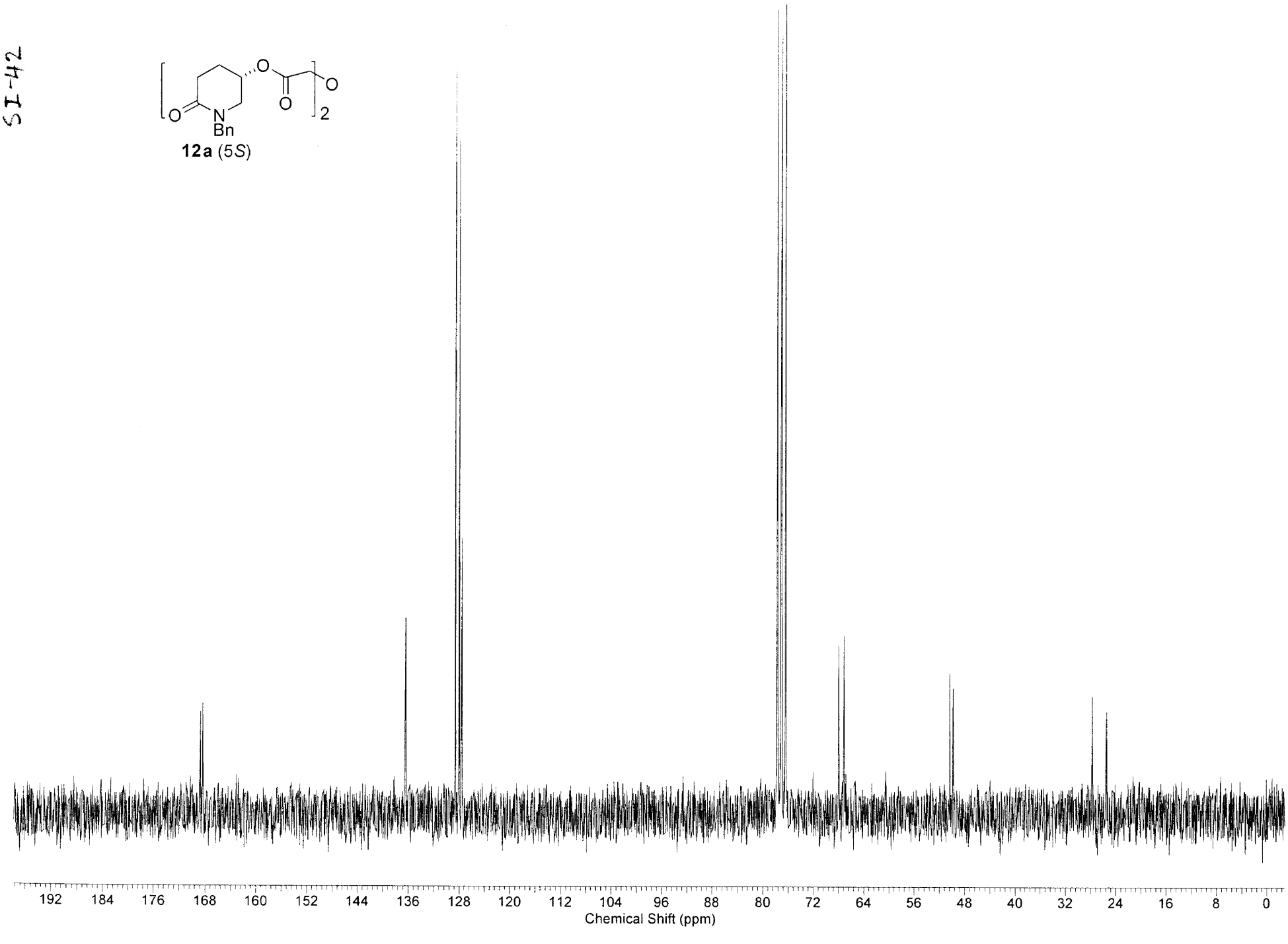

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
4.951
0.943
0.999
0.915
1.738
1.085
1.127
2.229
2.375

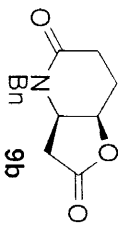

O
N
Bn
O
O
O
2

**12a** (5S)

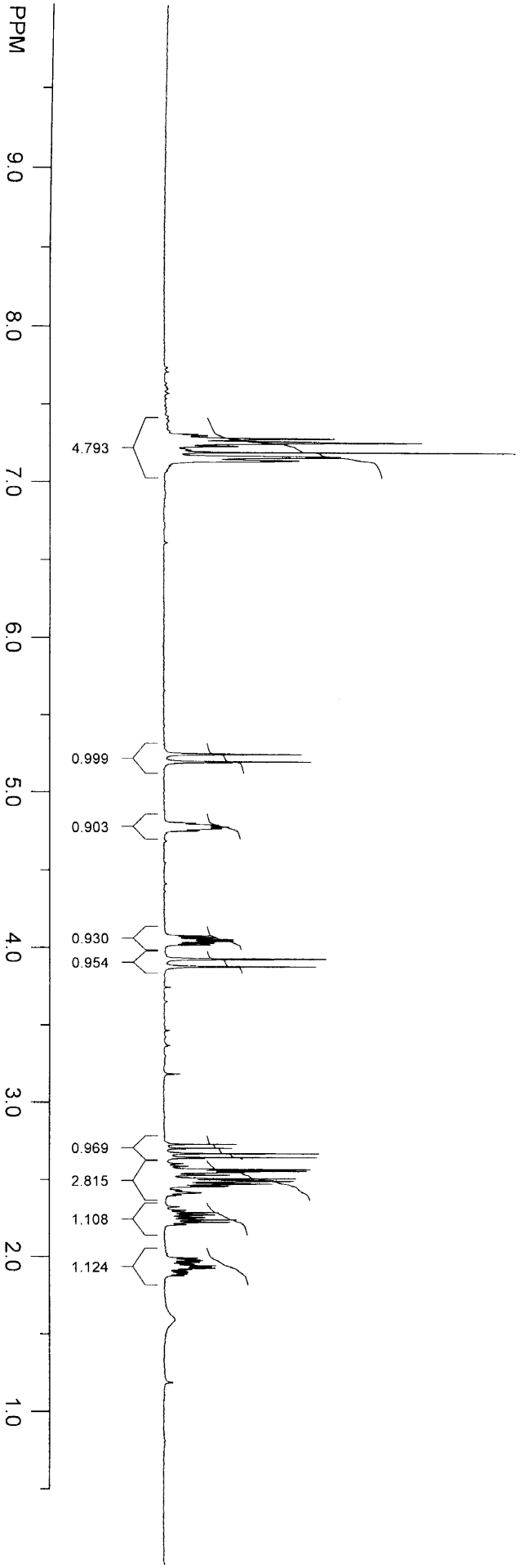
O
O
O
O
N
Bn
2

**12a** (5*S*)

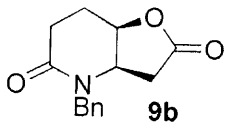

192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


O
N
Bn
O
O
O

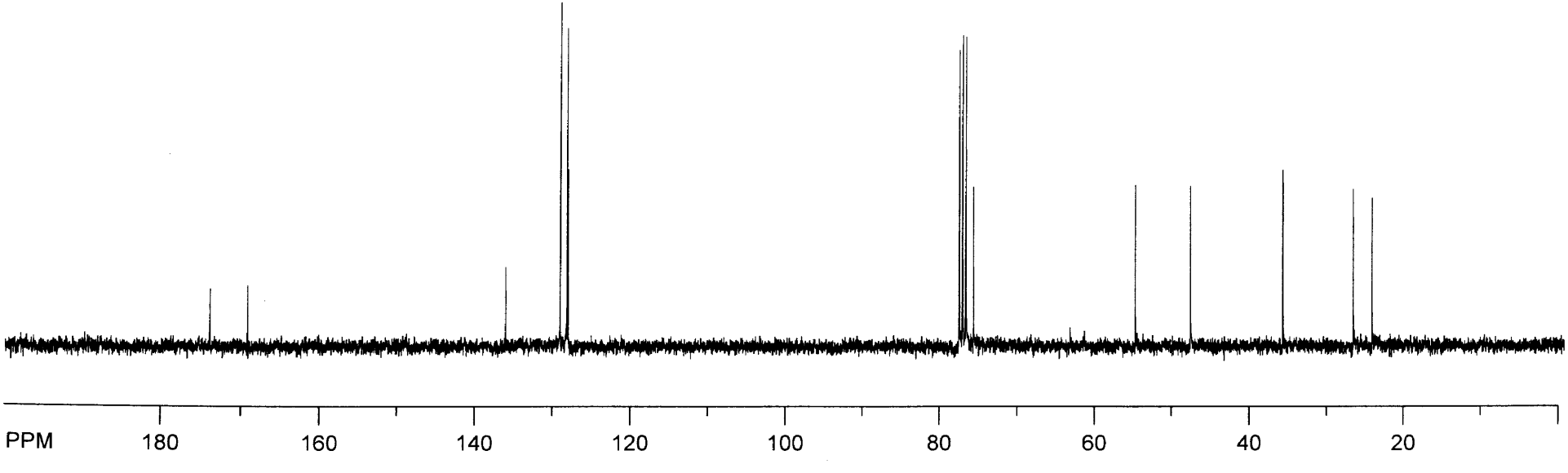
**9b**

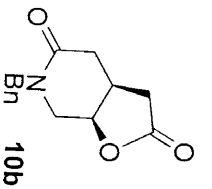

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
4.793
0.999
0.903
0.930
0.954
0.969
2.815
1.108
1.124

ST-444

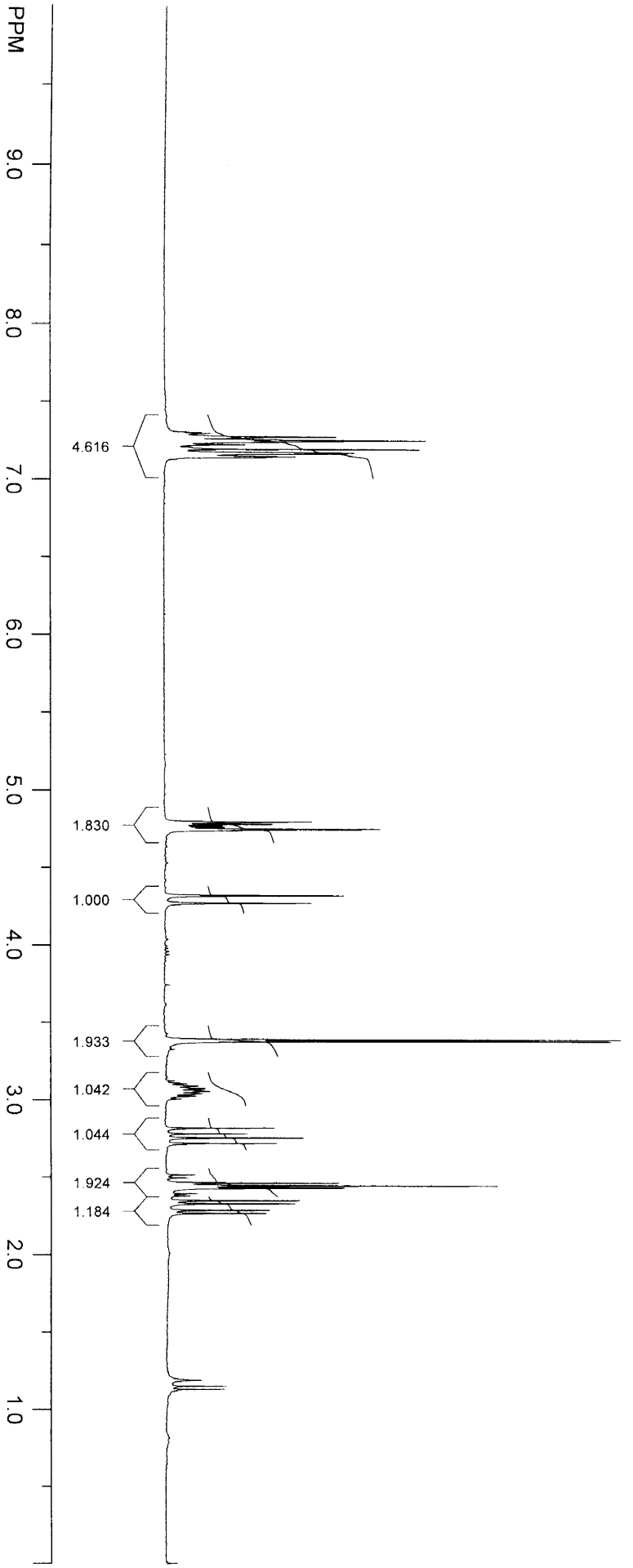


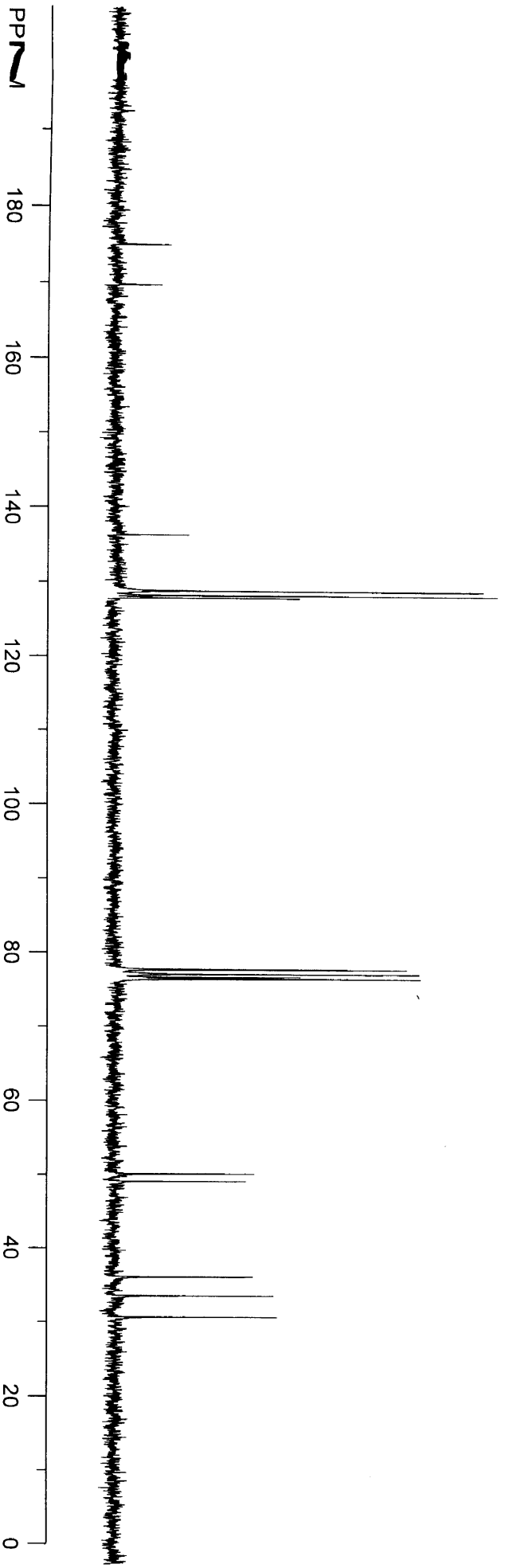

**9b**

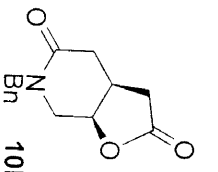



O
N
Bn
O
O

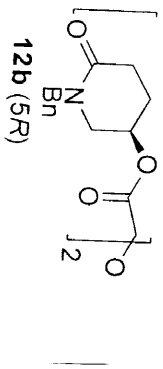
**10b**


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
4.616
1.830
1.000
1.933
1.042
1.044
1.924
1.184

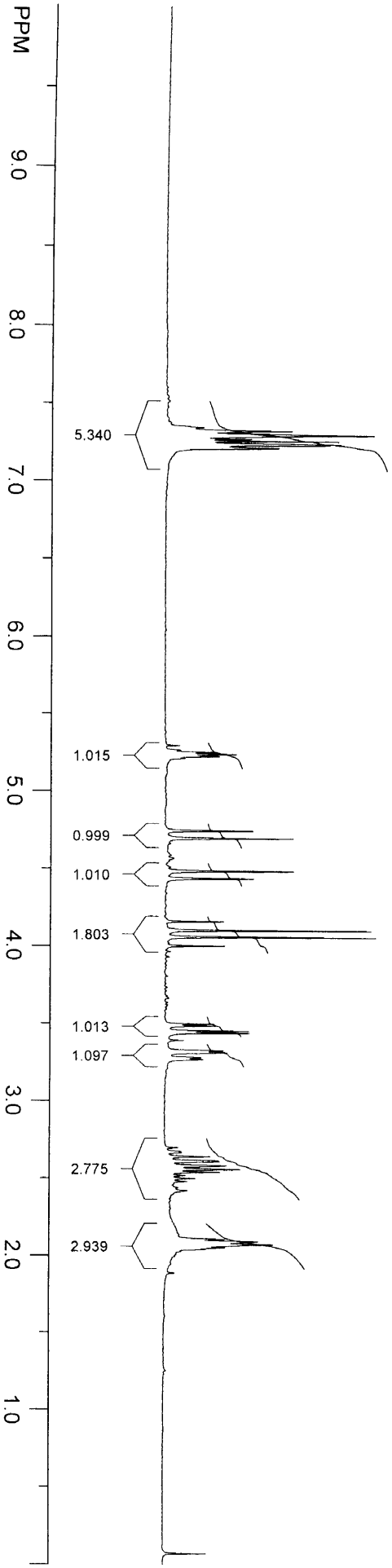


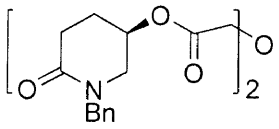

10b


O
N
Bn
O
O
O
O
2

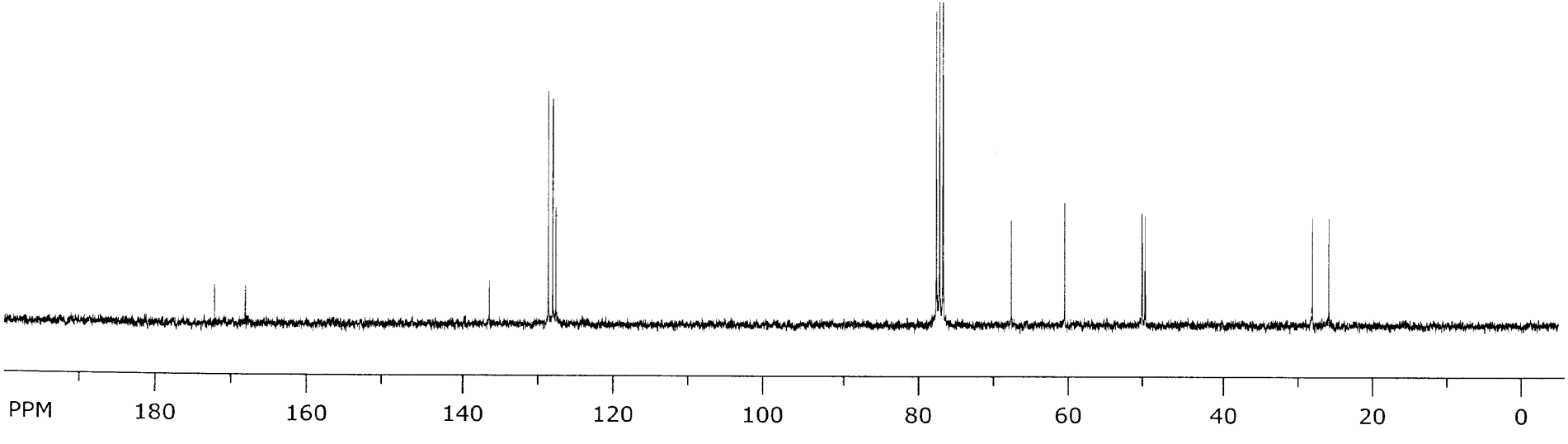
**12b** (5*R*)

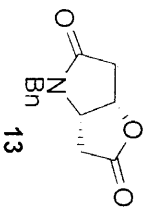

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
5.340
1.015
0.999
1.010
1.803
1.013
1.097
2.775
2.939

S1-48

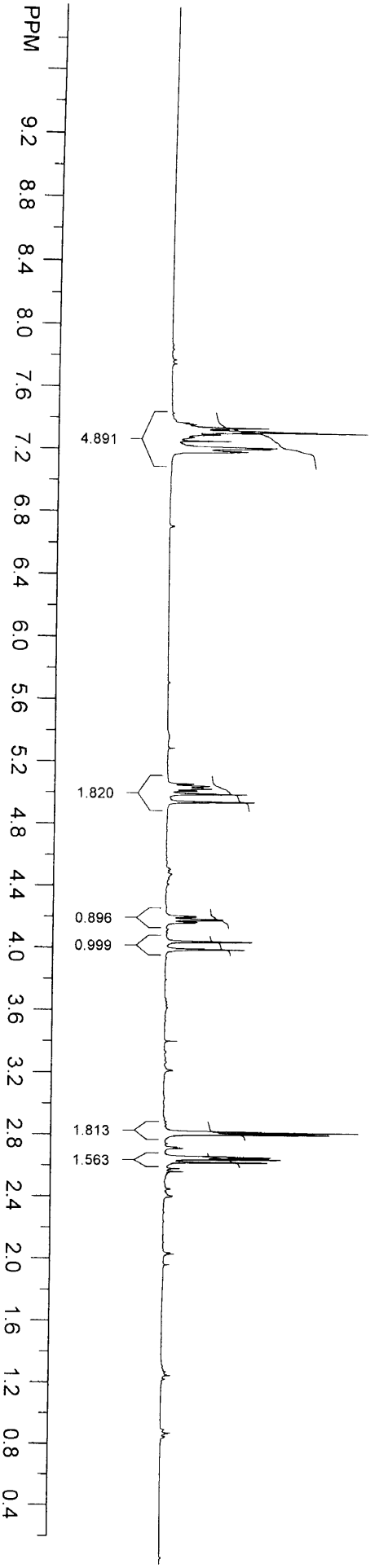



**12b** (5*R*)

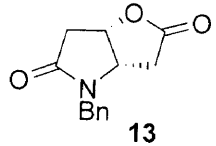



O
N
Bn
O
O

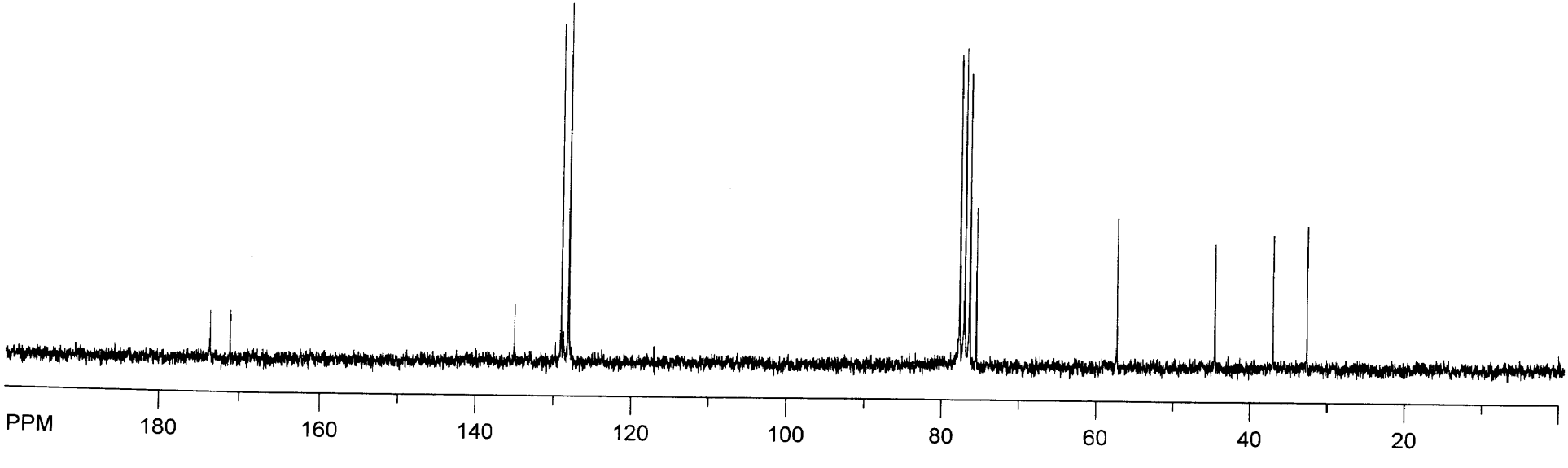
13


PPM
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
4.891
1.820
0.896
0.999
1.813
1.563

SI-50

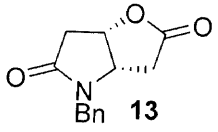



13

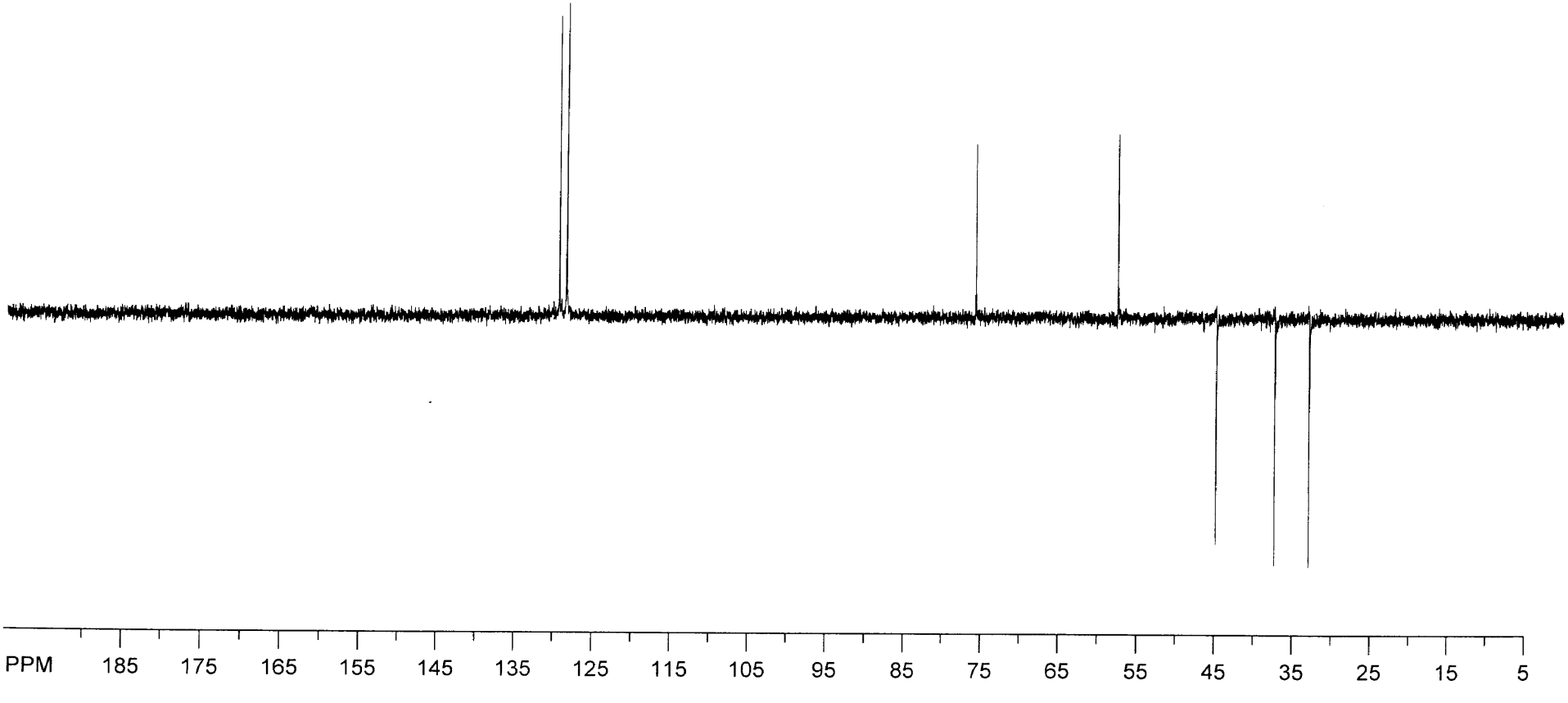


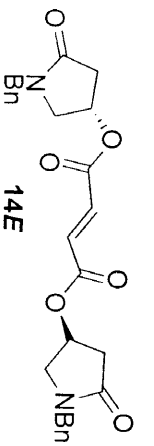
DEPT-135

ST-51

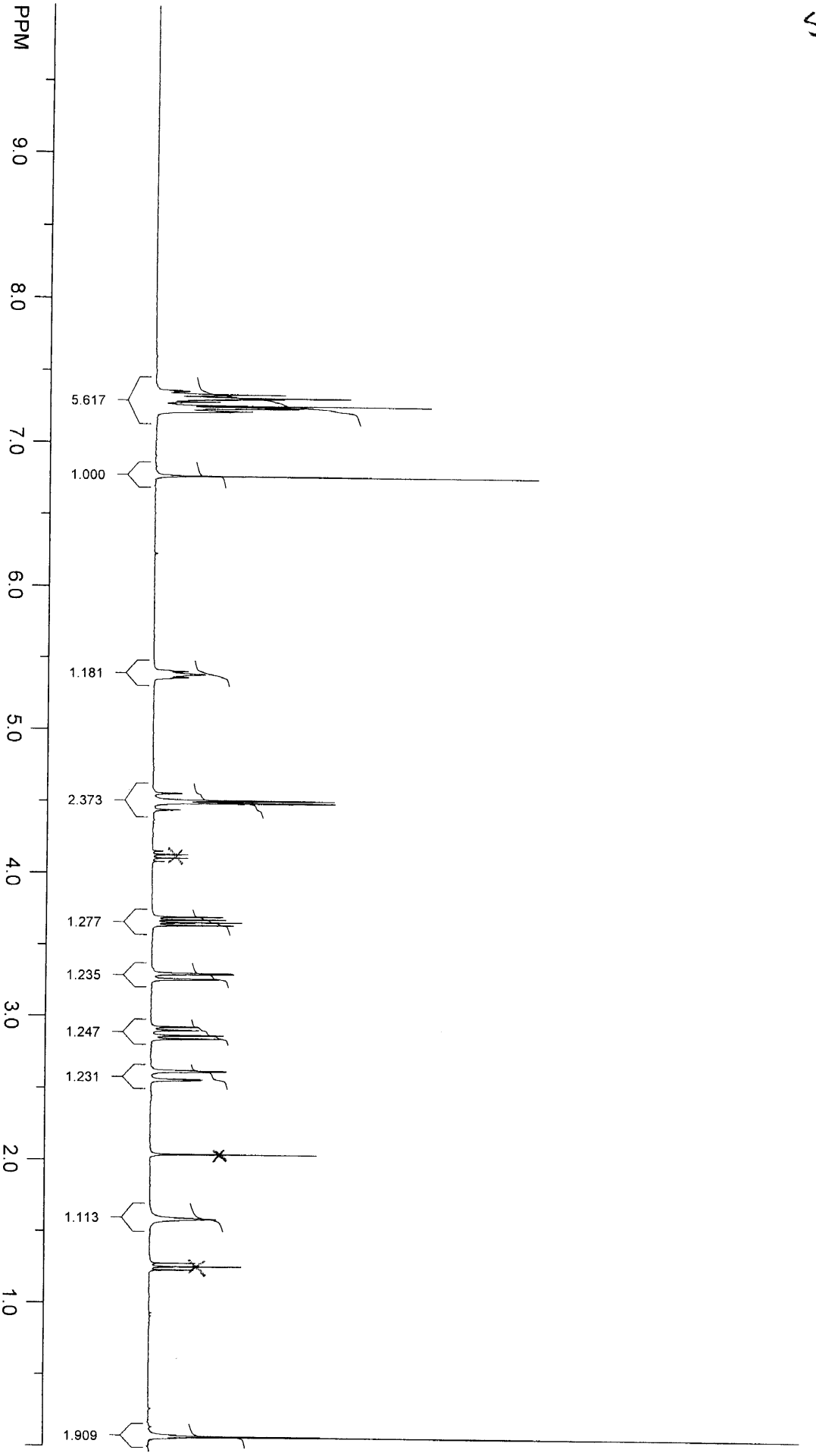


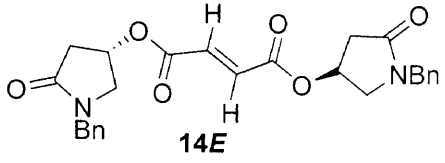

13



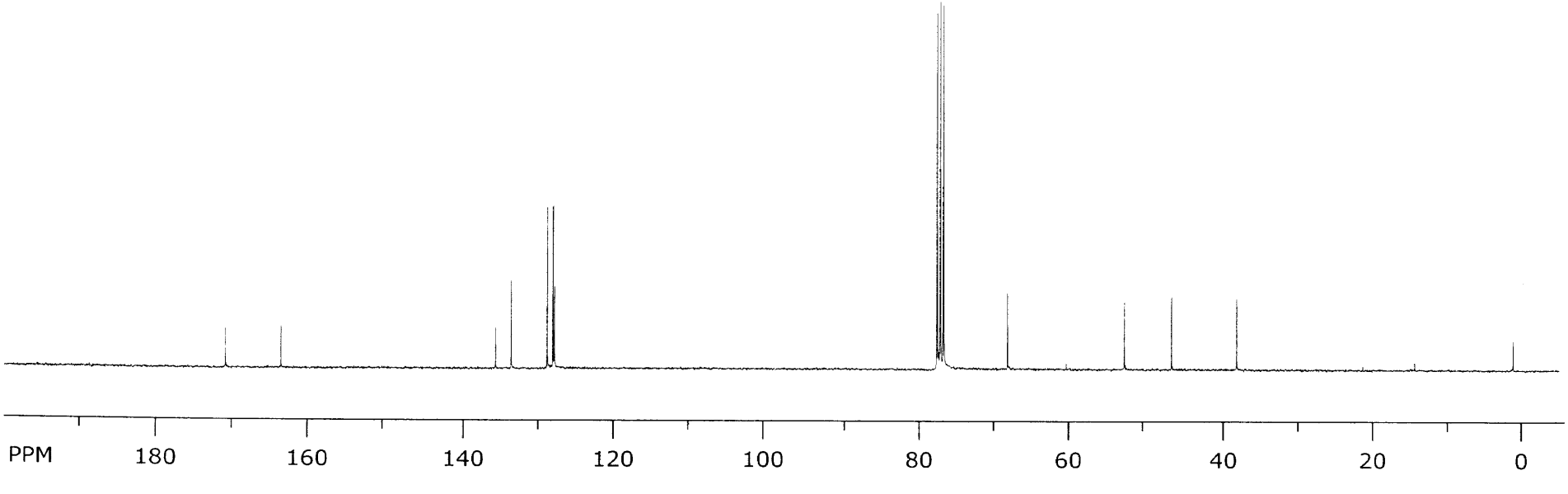

O
N
Bn
O
O
O
O
O
O
NBn
O

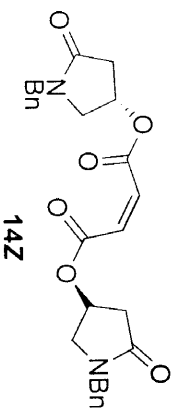
**14E**


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
5.617
1.000
1.181
2.373
1.277
1.235
1.247
1.231
1.113
1.909

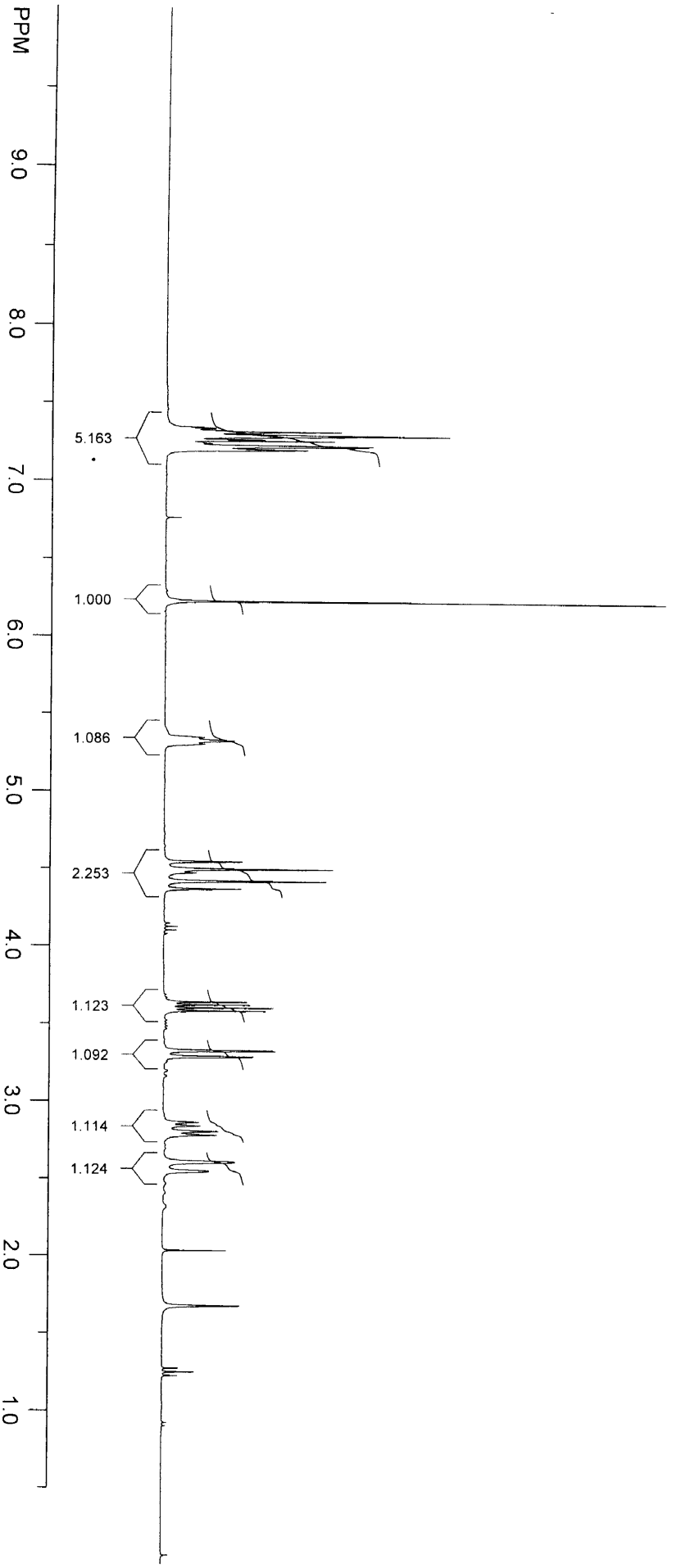



**14*E***

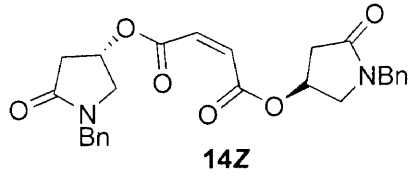



O
N
Bn
O
O
O
O
O
NBn
O

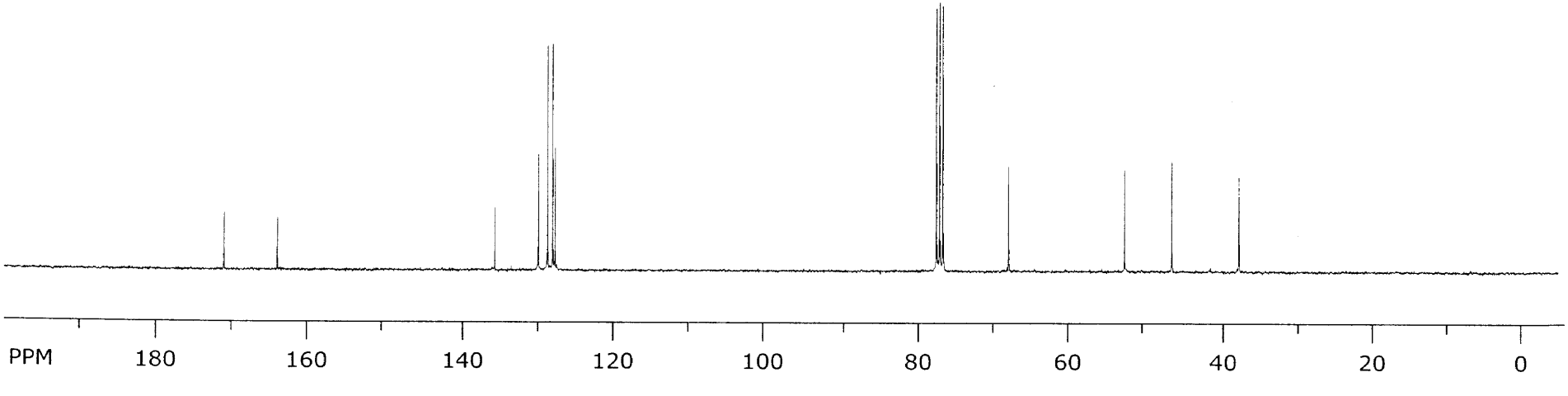
14Z

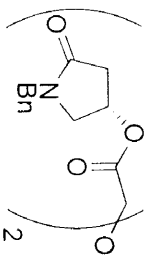

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
5.163
1.000
1.086
2.253
1.123
1.092
1.114
1.124

SI-55

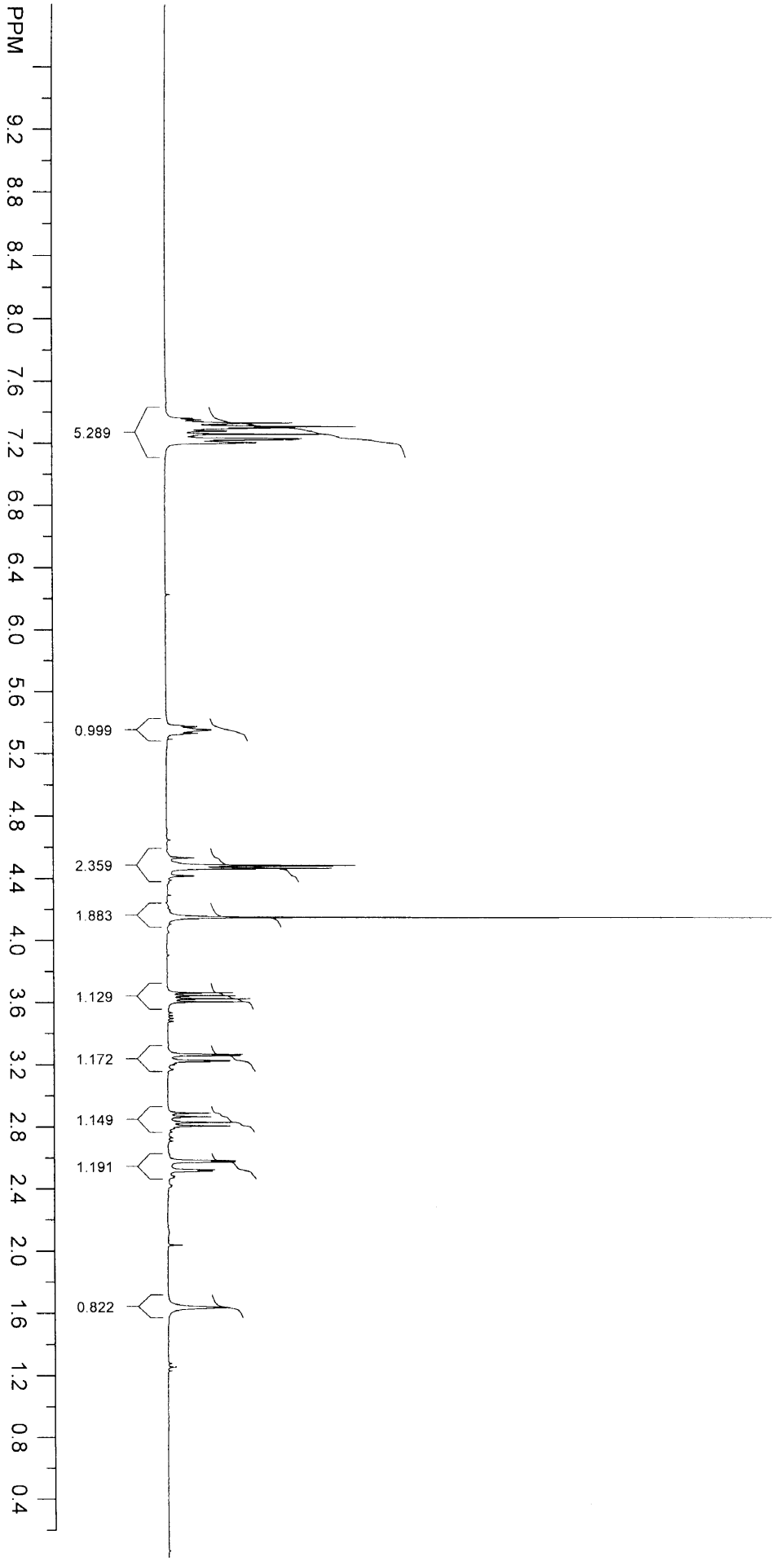



**14Z**




O
N
Bn
O
O
O
O
2

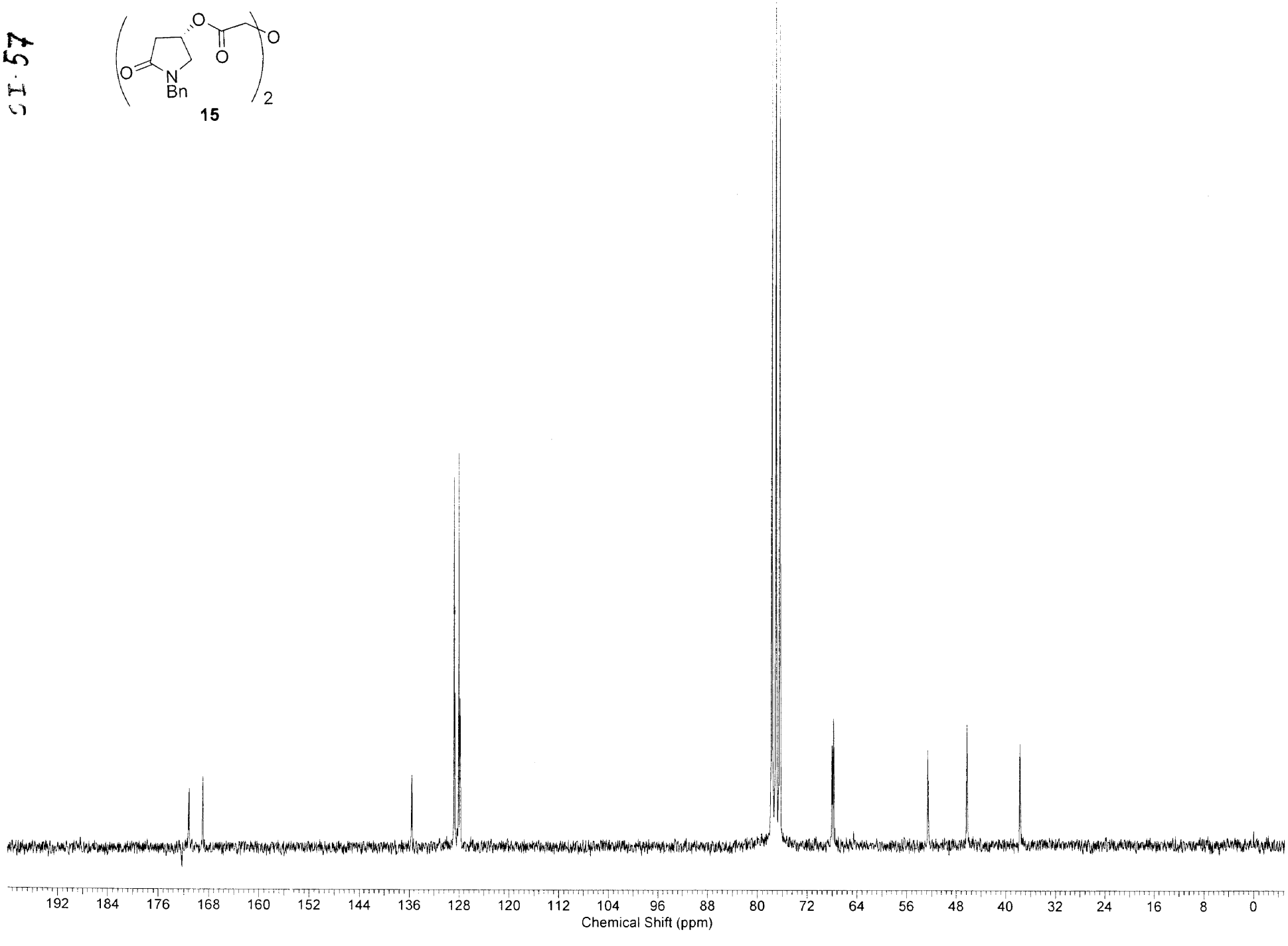
15

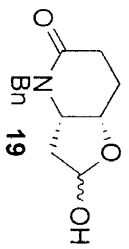

PPM
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
5.289
0.999
2.359
1.883
1.129
1.172
1.149
1.191
0.822

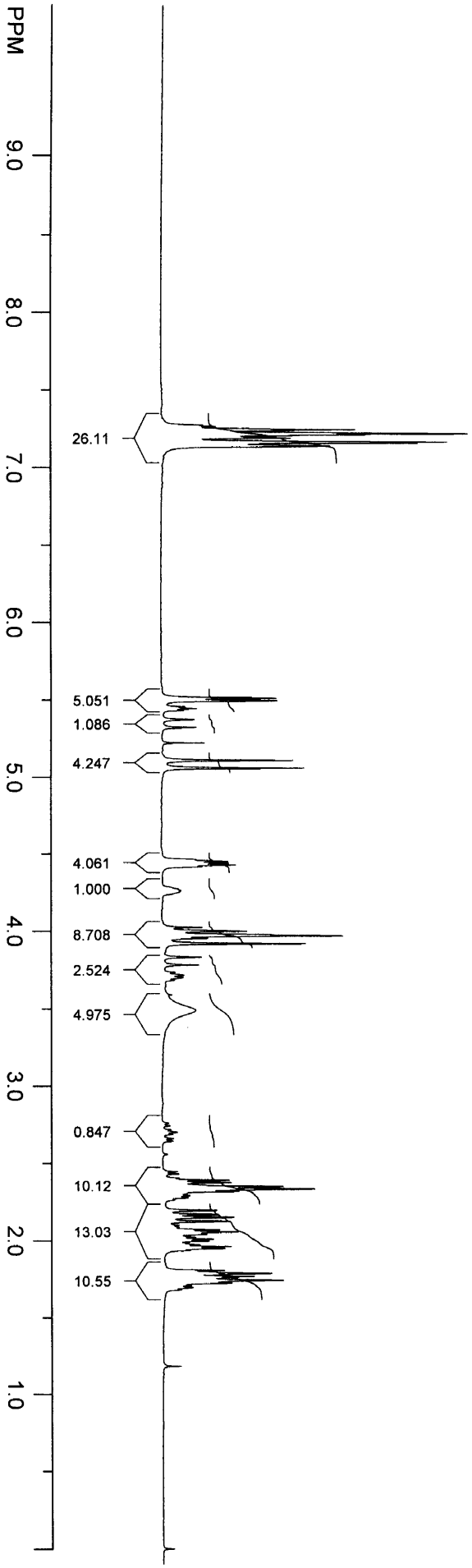
S1.57


O
O
O
O
N
Bn
2

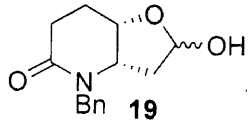
**15**


192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

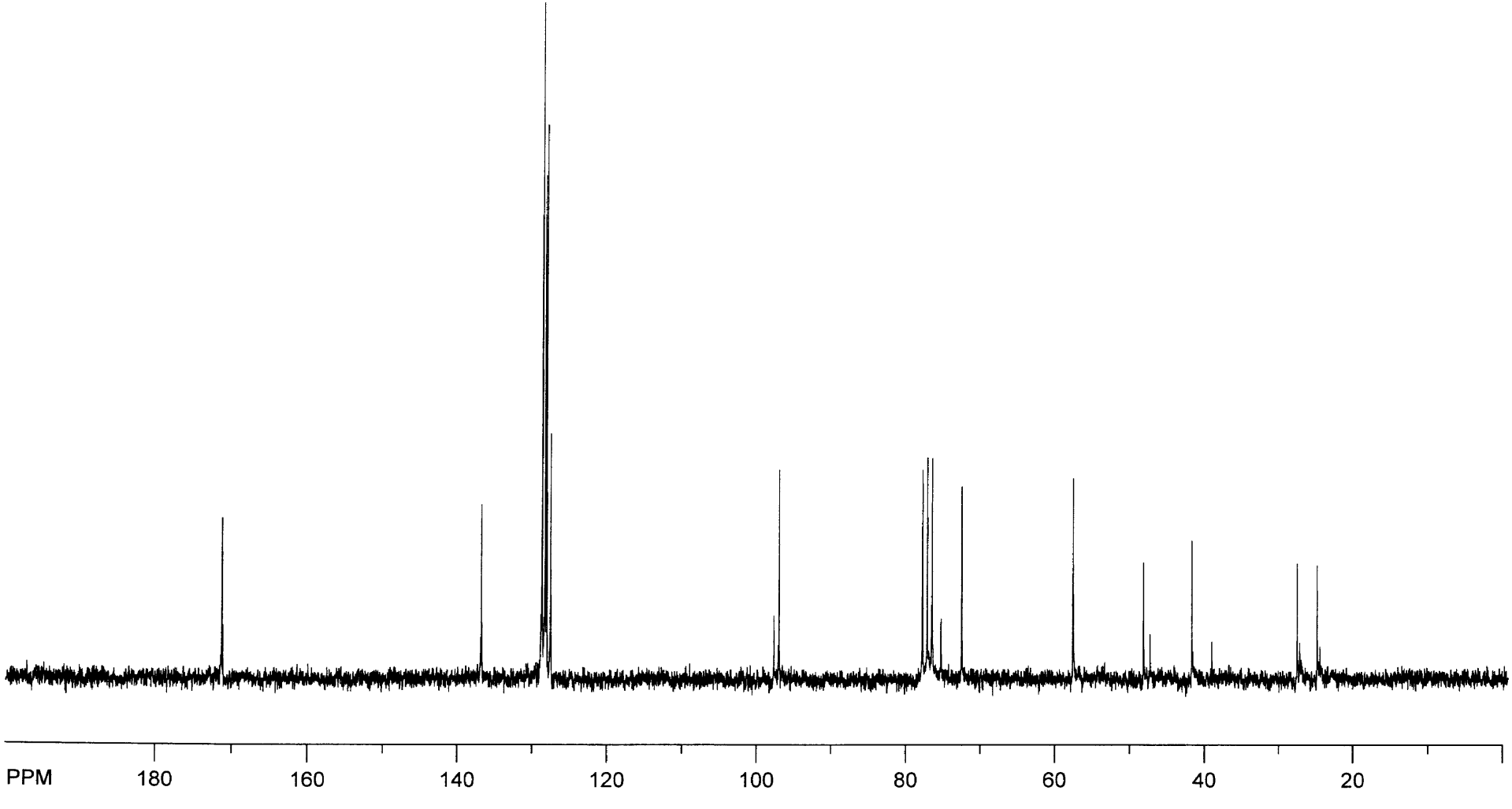

O
N
Bn
19
O
OH

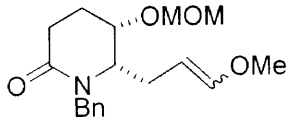

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
26.11
5.051
1.086
4.247
4.061
1.000
8.708
2.524
4.975
0.847
10.12
13.03
10.55

SI-59

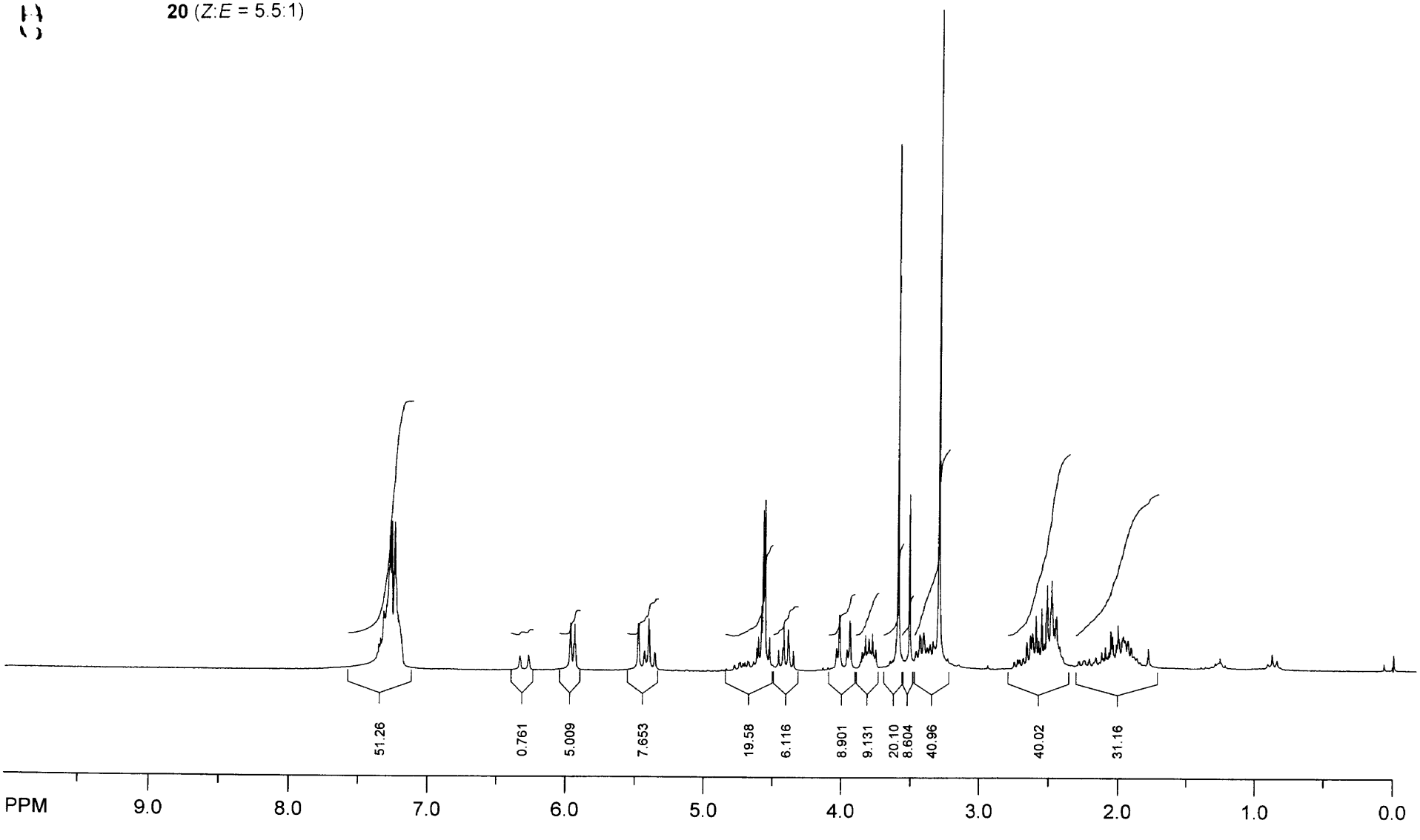


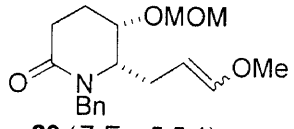

**19**



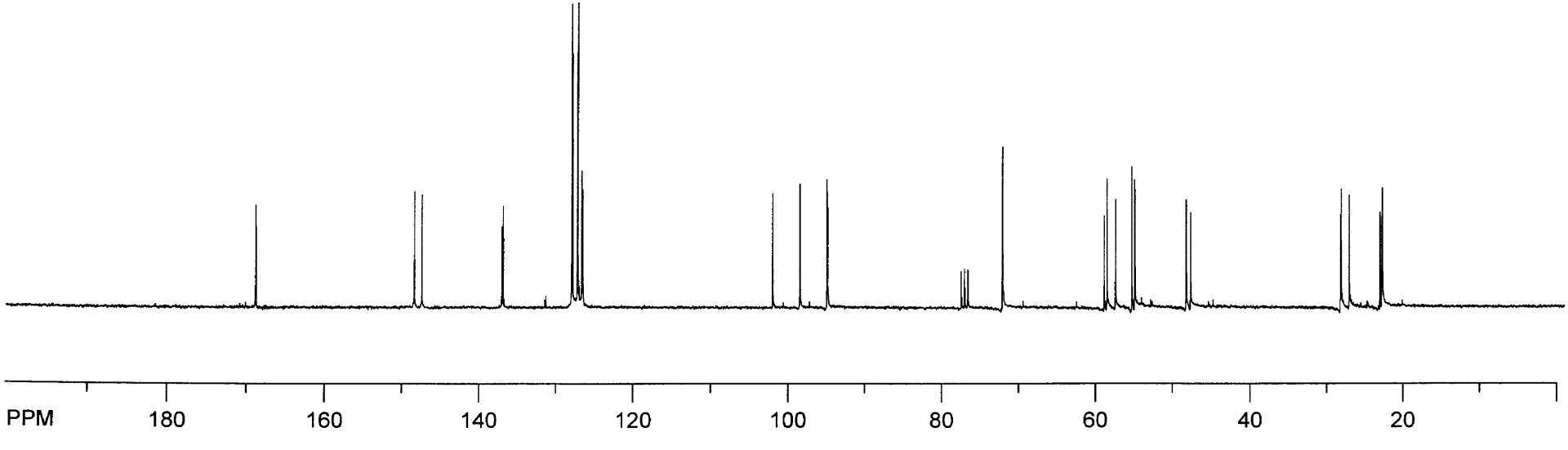

OMOM
OMe
O
N
Bn

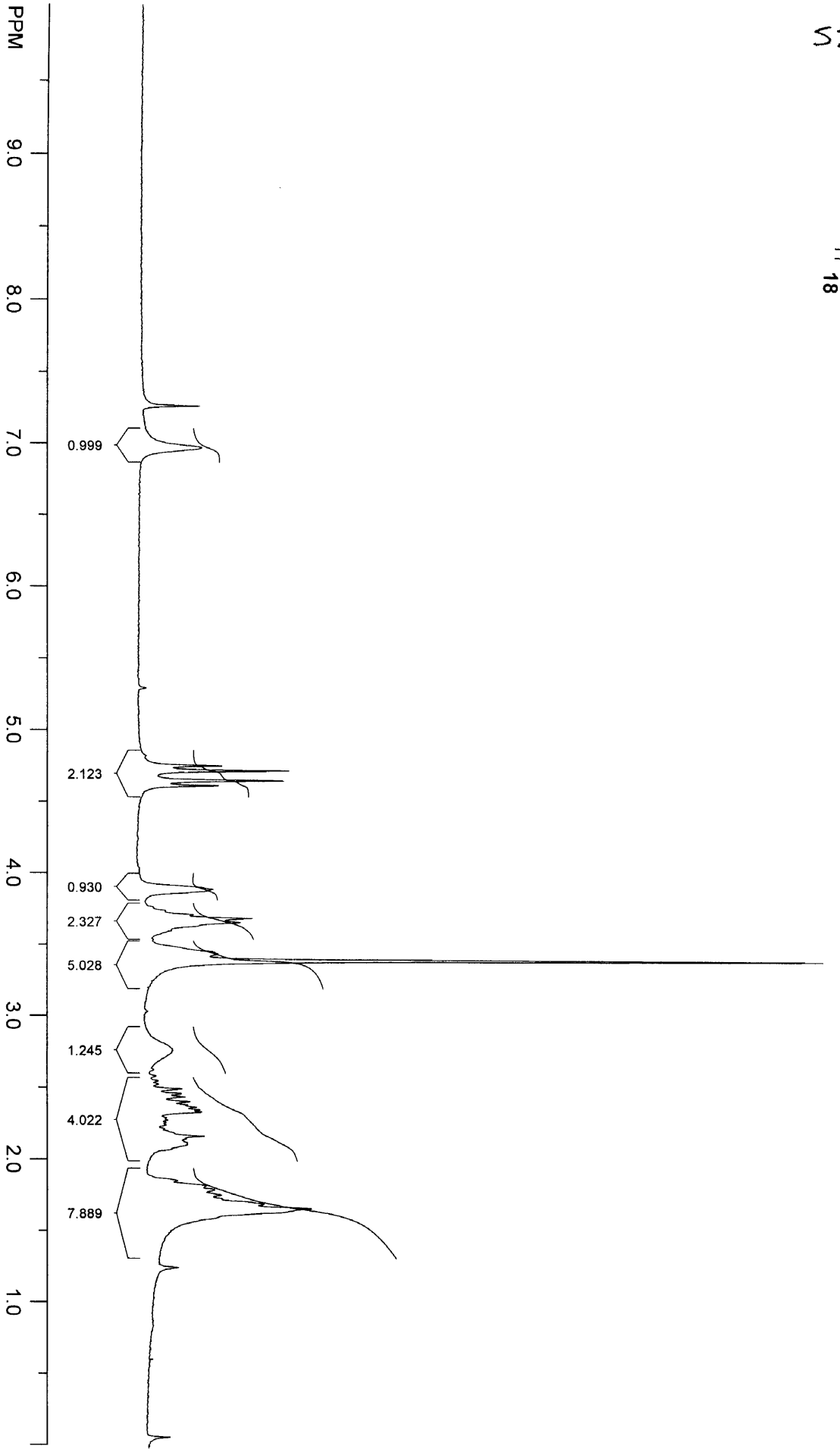
**20** (*Z*:*E* = 5.5:1)

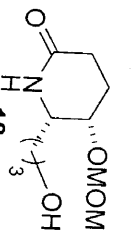

51.26
0.761
5.009
7.653
19.58
6.116
8.901
9.131
20.10
8.604
40.96
40.02
31.16
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0




**20** (*Z*:*E* = 5.5:1)

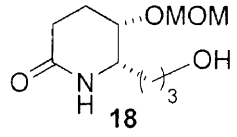



PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.999
2.123
0.930
2.327
5.028
1.245
4.022
7.889

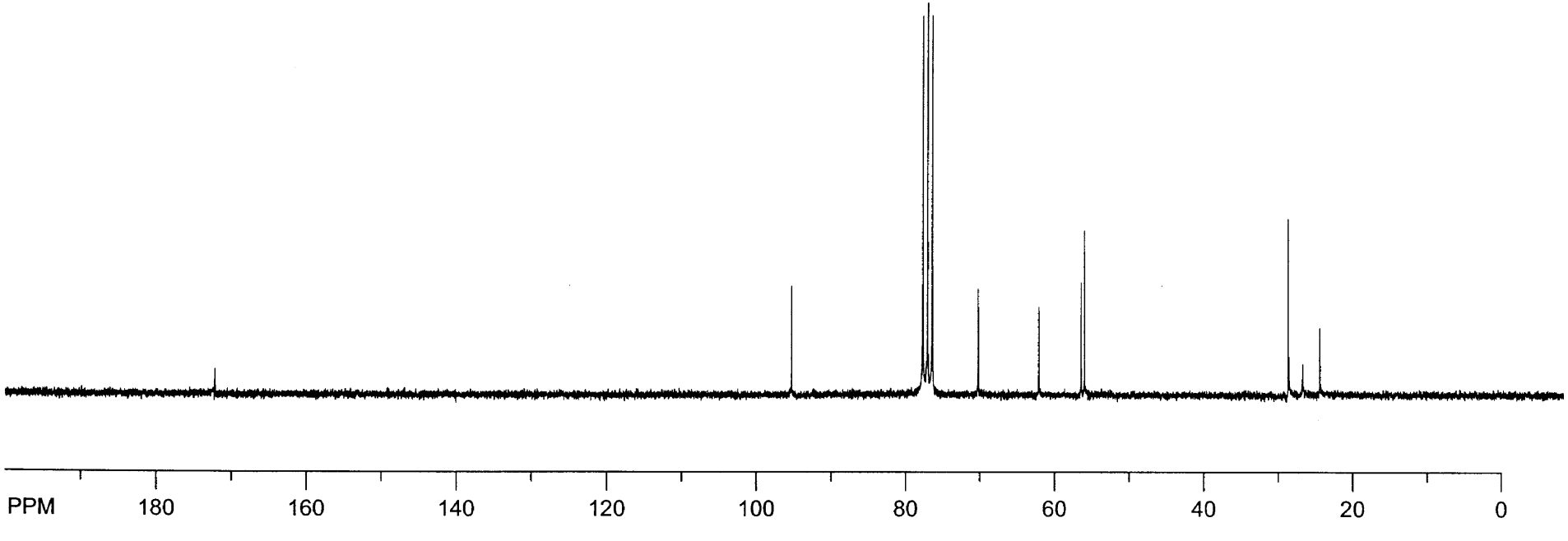

O
N
H
OMOM
OH
3

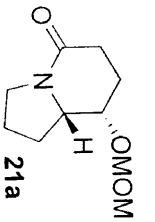
18

ST-63

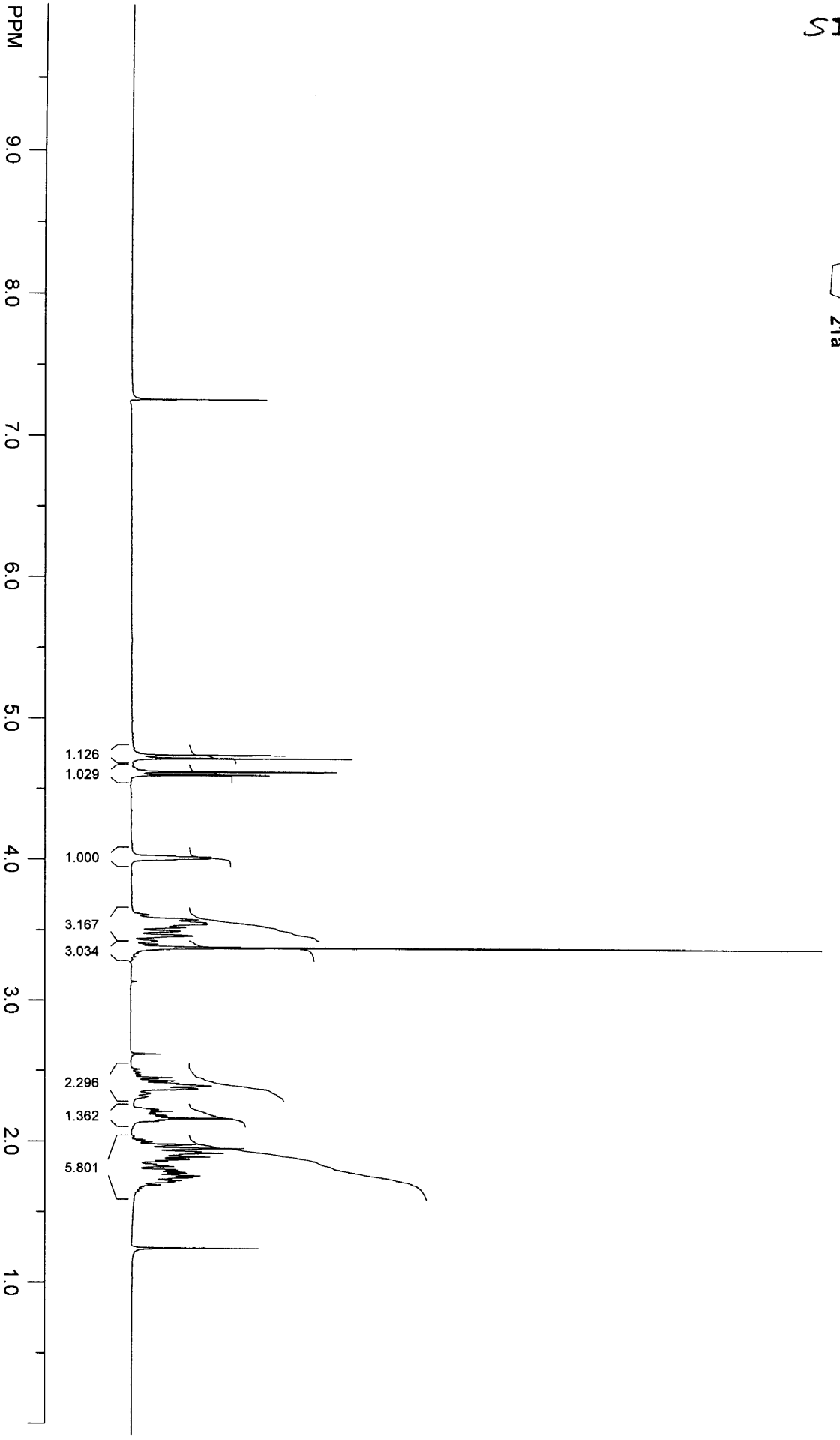



18

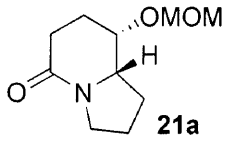



O
N
H
OMOM

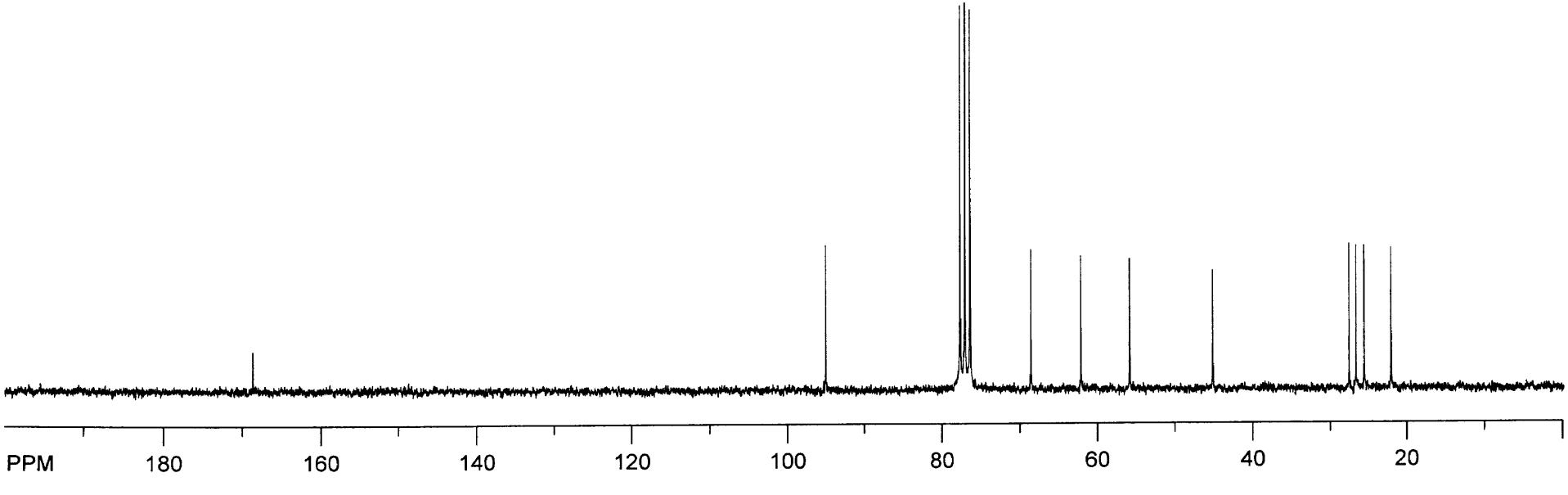
21a

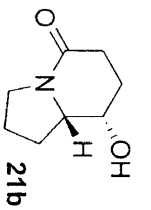

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
1.126
1.029
1.000
3.167
3.034
2.296
1.362
5.801

SI-65

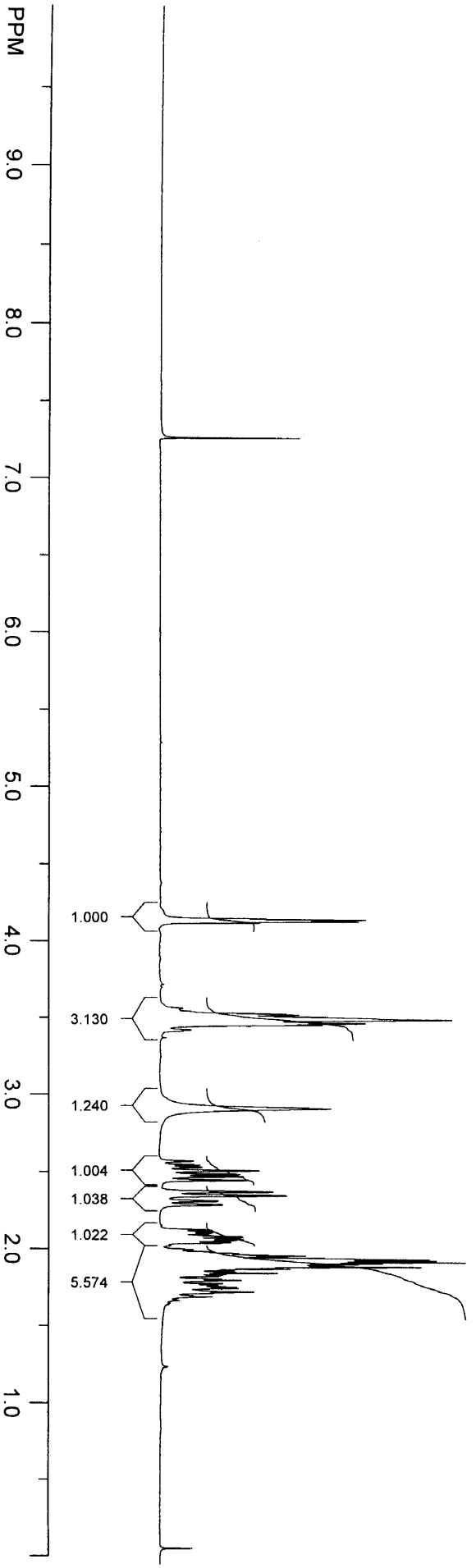


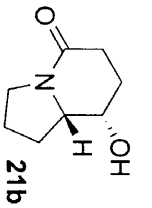

**21a**



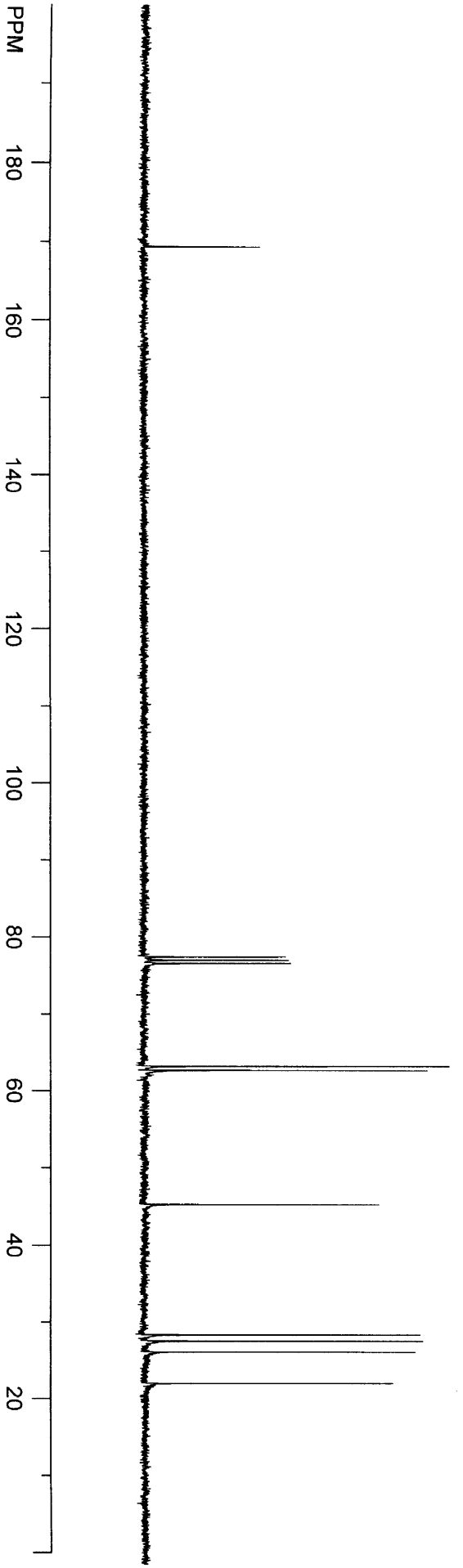

O
N
H
OH

21b

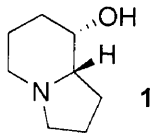

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
1.000
3.130
1.240
1.004
1.038
1.022
5.574




21b

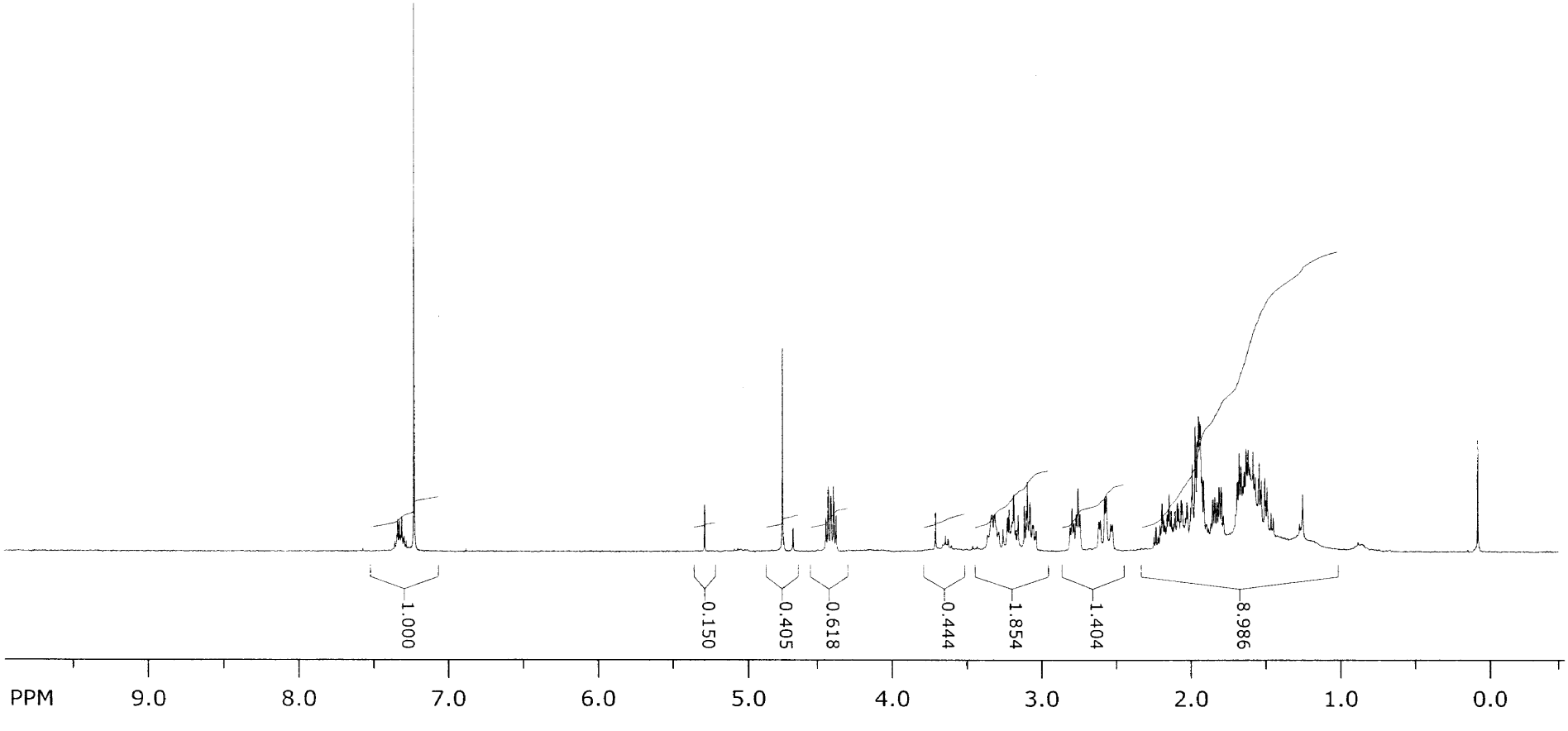


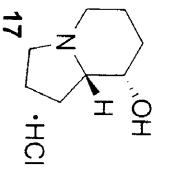
89-15

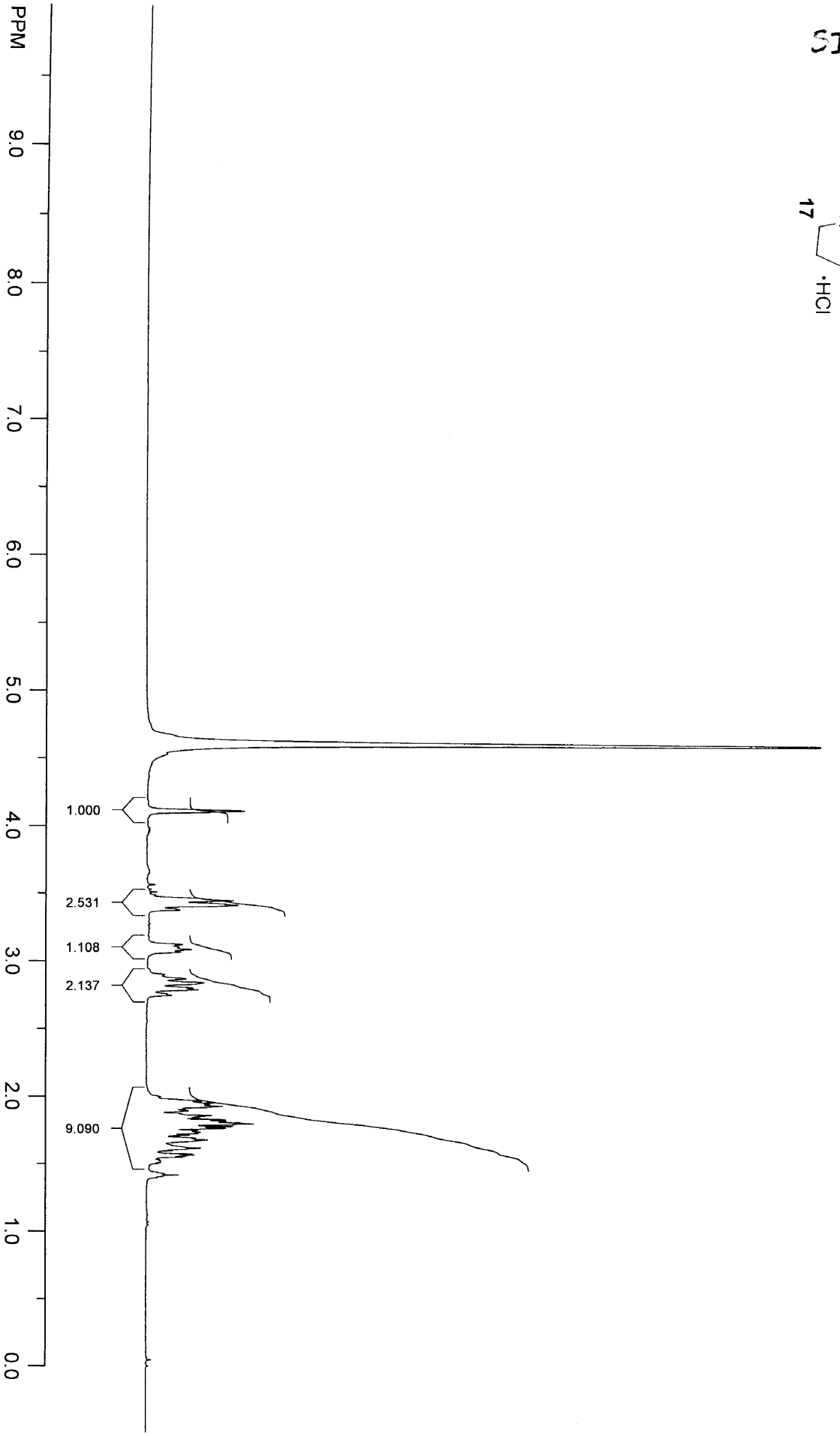



**17·$BH_3$**

Borane complex




17
N
H
OH
·HCl

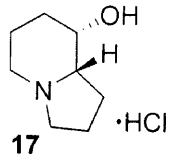

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.000
2.531
1.108
2.137
9.090

17
N
H
OH
·HCl

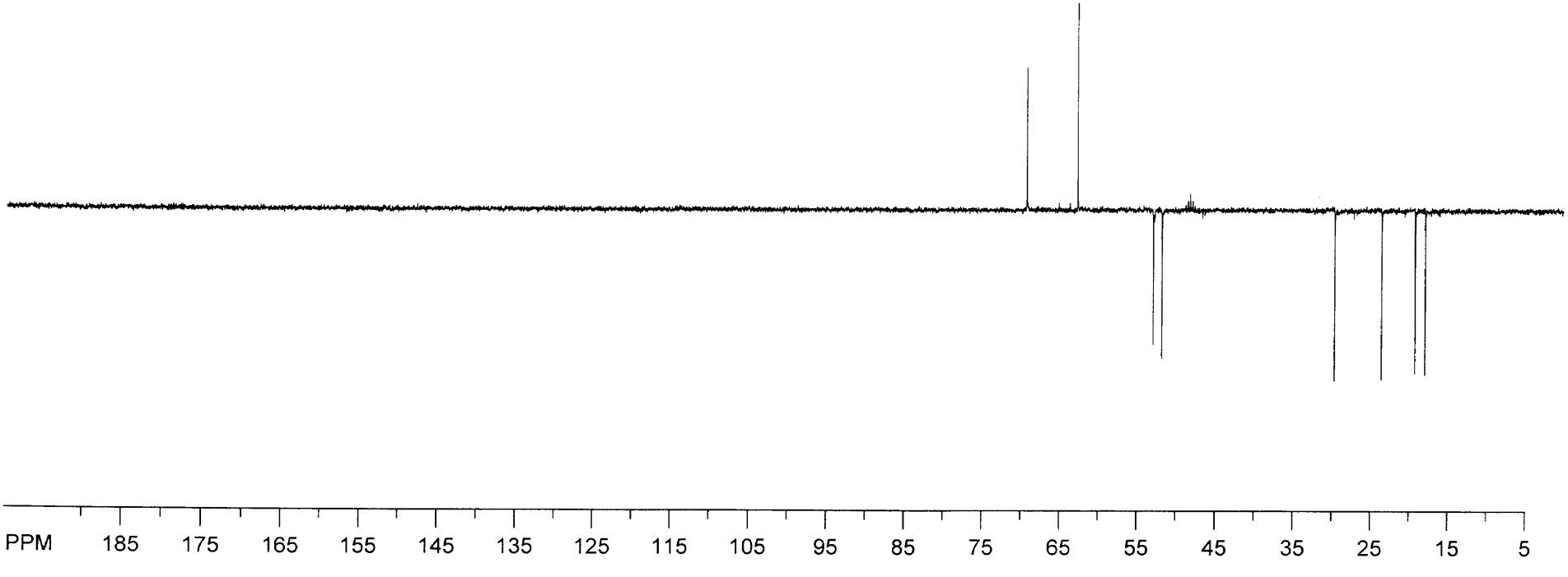

PPM
180
160
140
120
100
80
60
40
20

SI-71

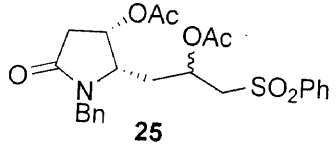
DEPT-135



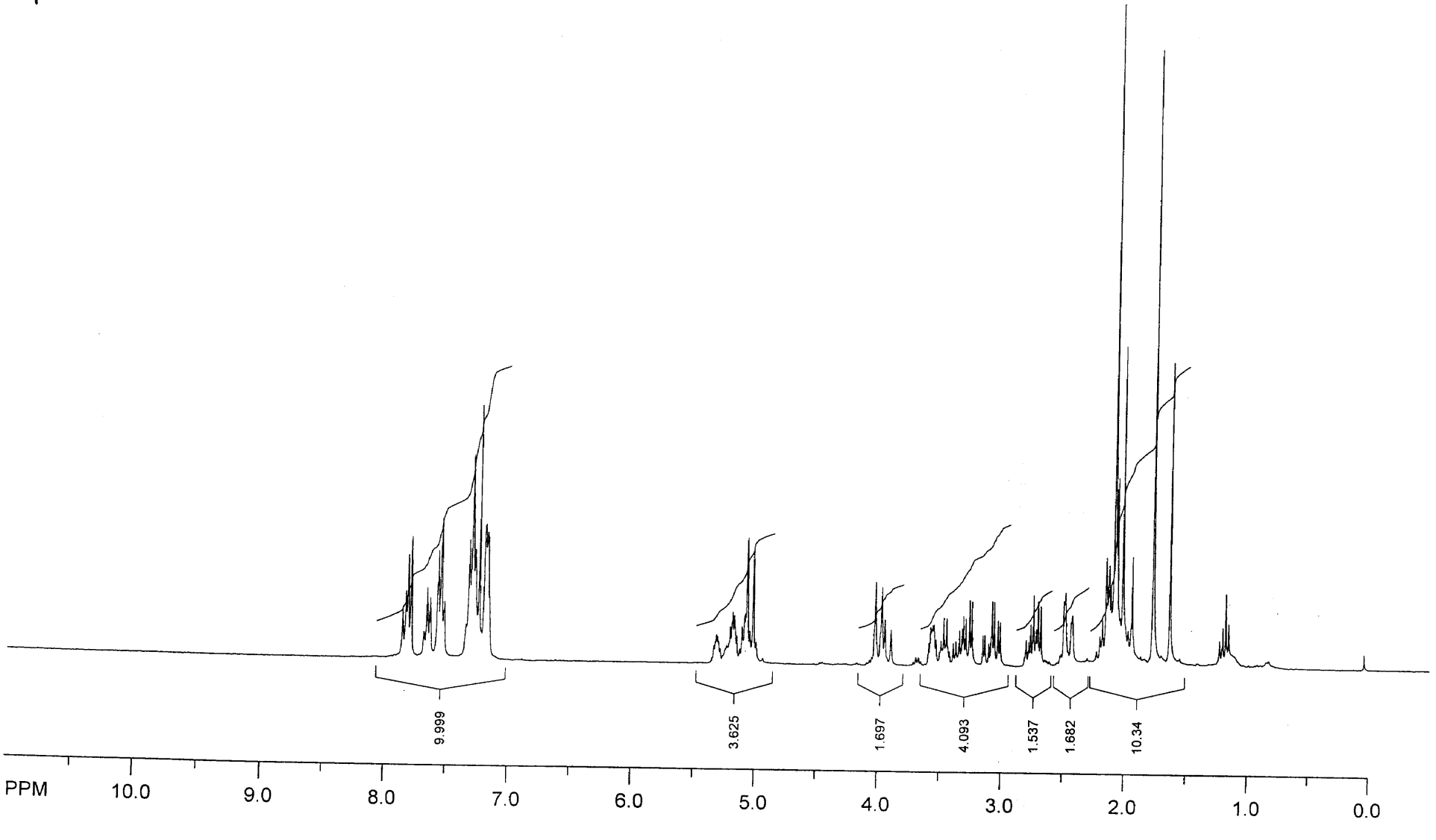

17



SI-72

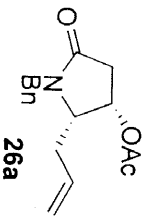

OAc
OAc
O
N
Bn
SO2Ph

**25**

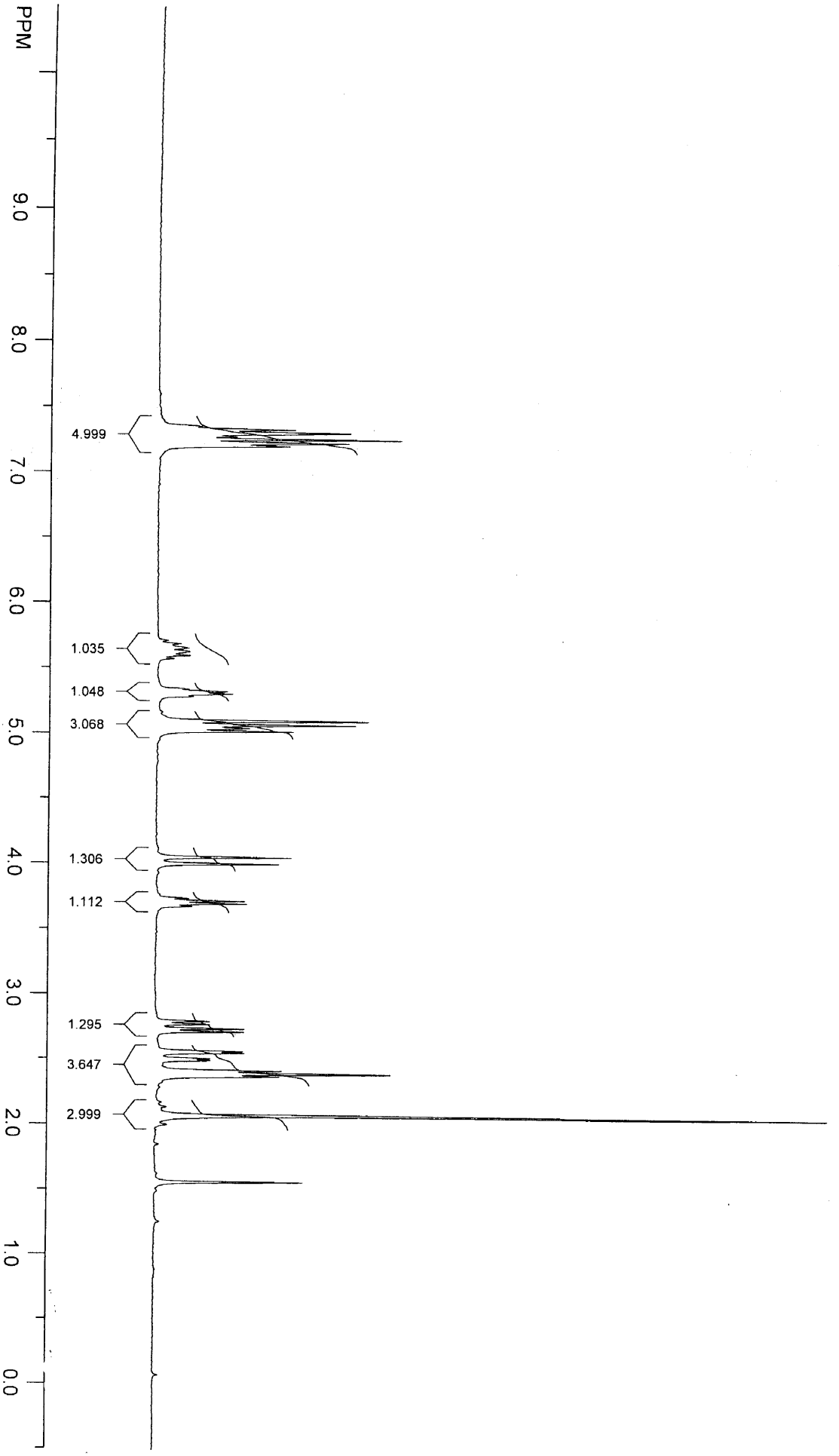

9.999
3.625
1.697
4.093
1.537
1.682
10.34
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

O
N
Bn
OAc
OAc
SO2Ph
25

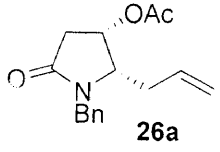

PPM
180
160
140
120
100
80
60
40
20
0


O
N
Bn
OAc

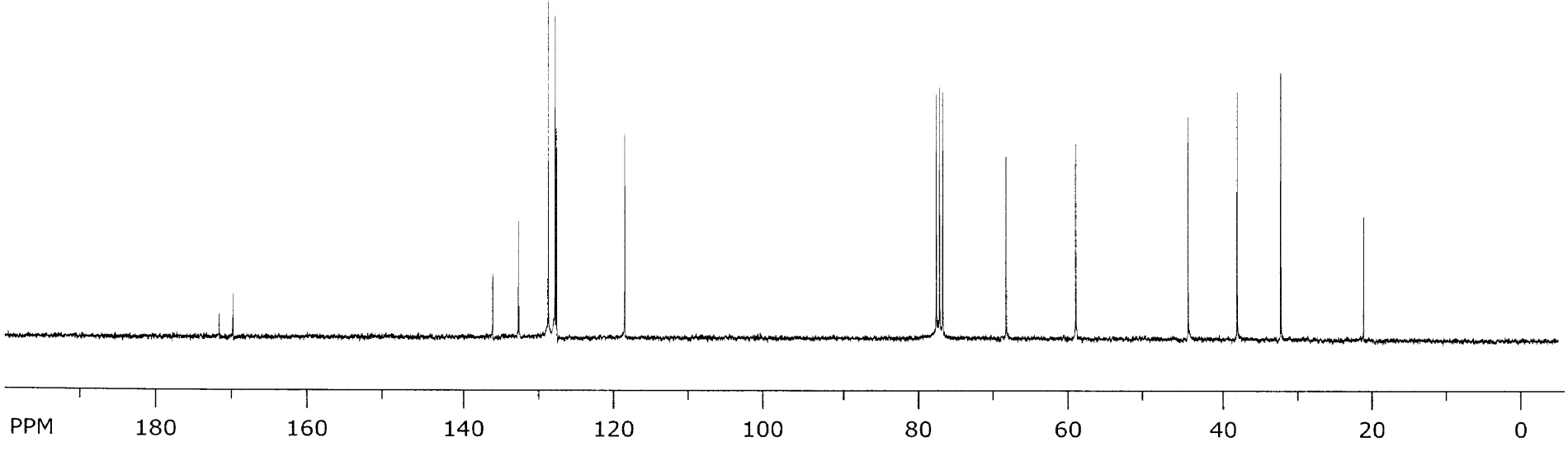
**26a**

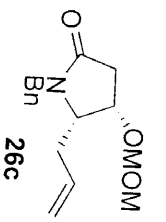

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
4.999
1.035
1.048
3.068
1.306
1.112
1.295
3.647
2.999

54-75

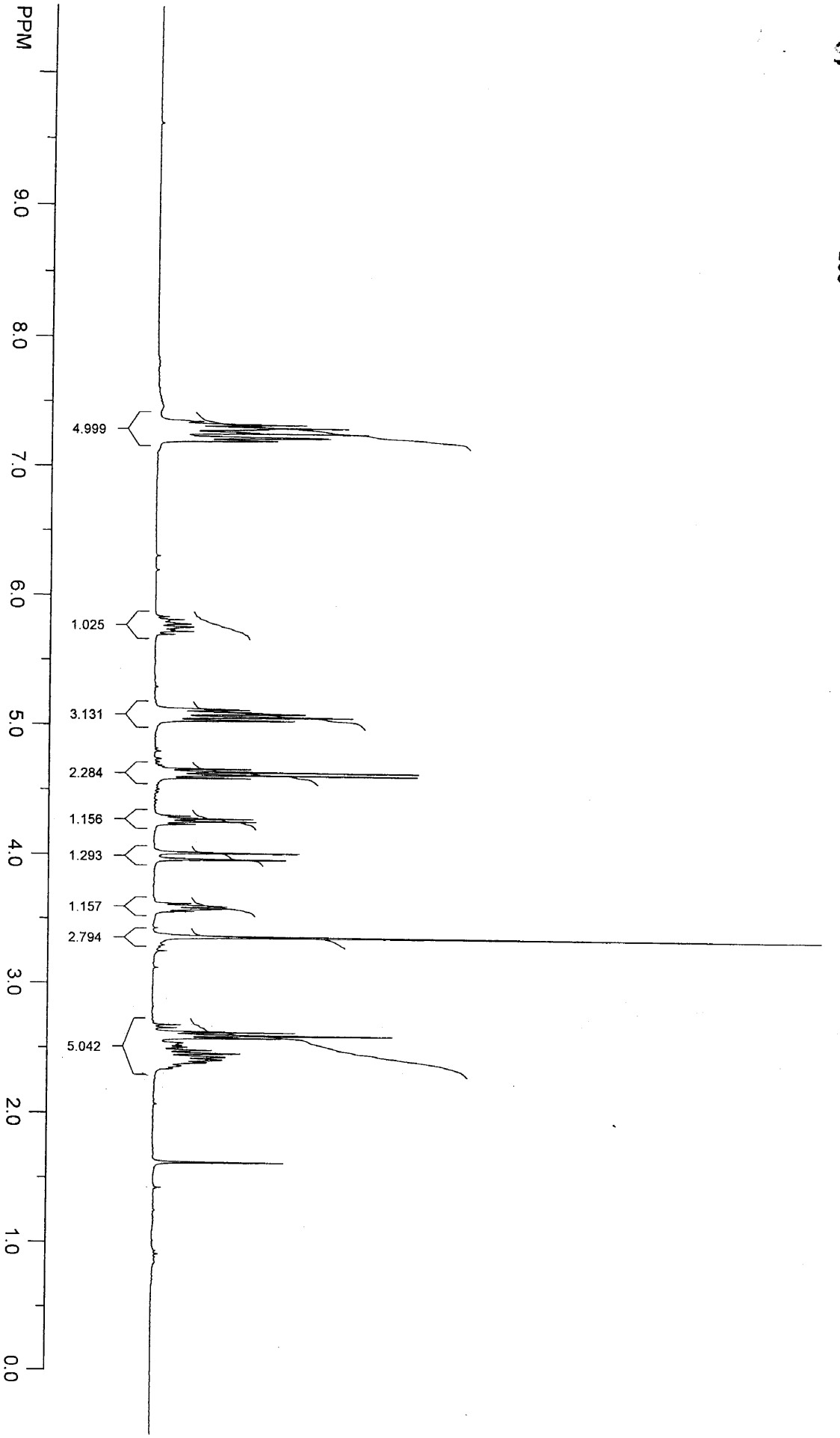


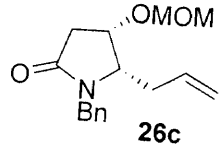

**26a**



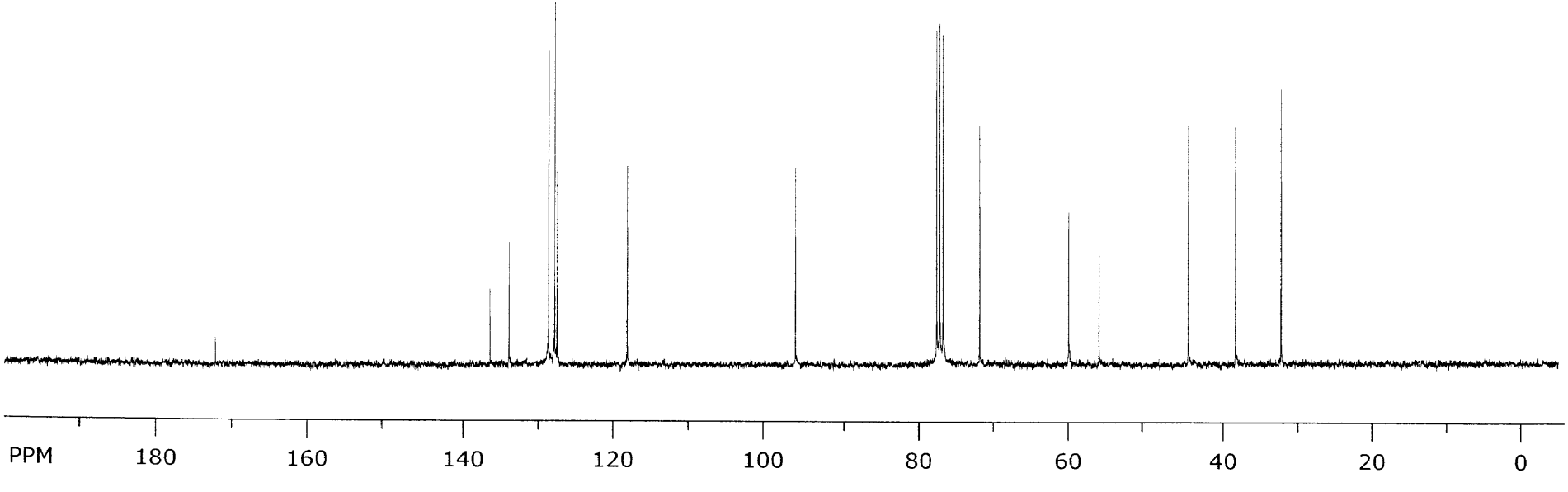

O
N
Bn
OMOM

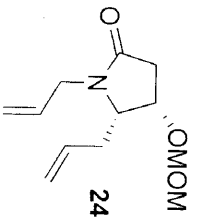
26c


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
4.999
1.025
3.131
2.284
1.156
1.293
1.157
2.794
5.042

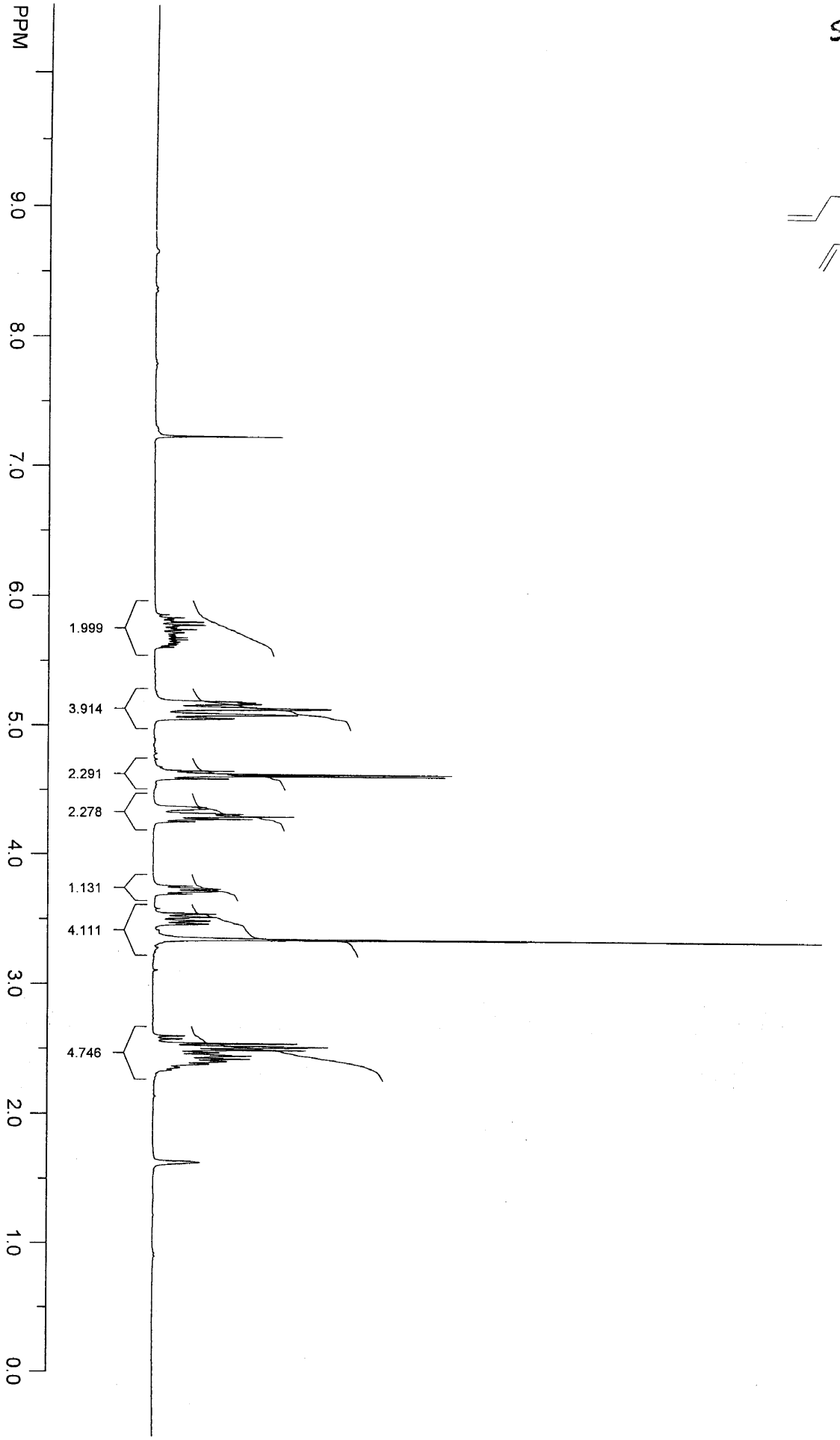


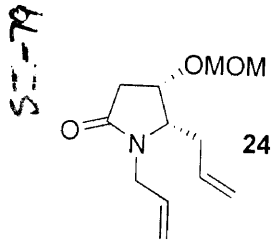

**26c**

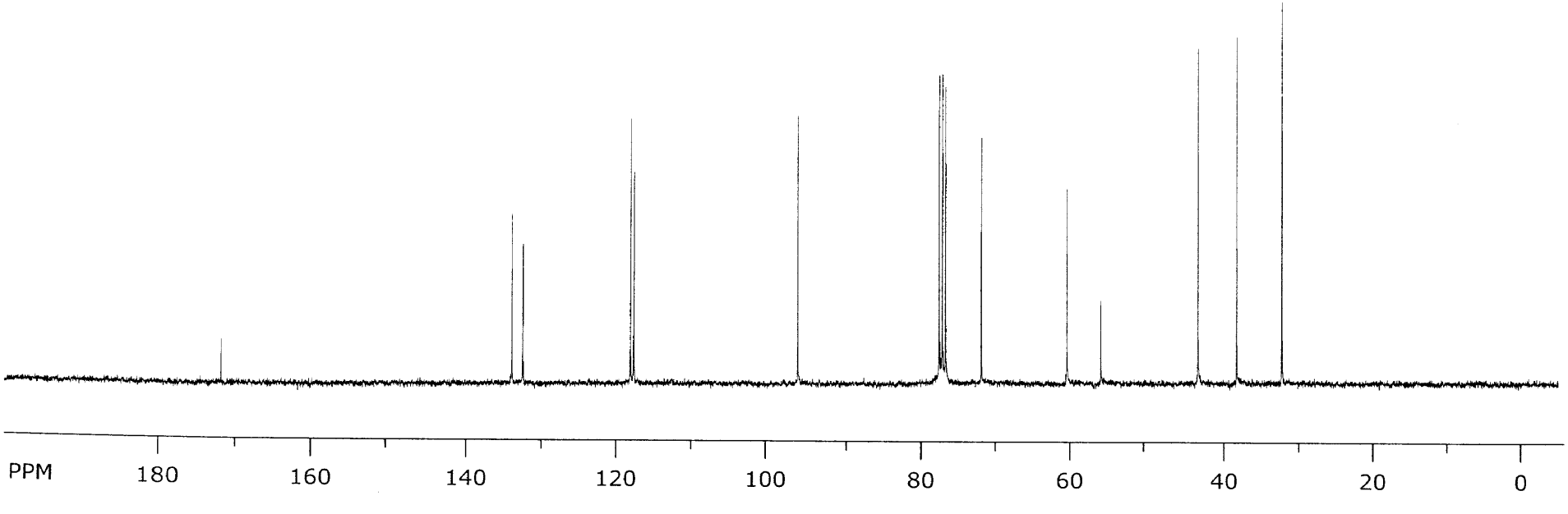


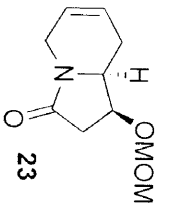

O
N
OMOM

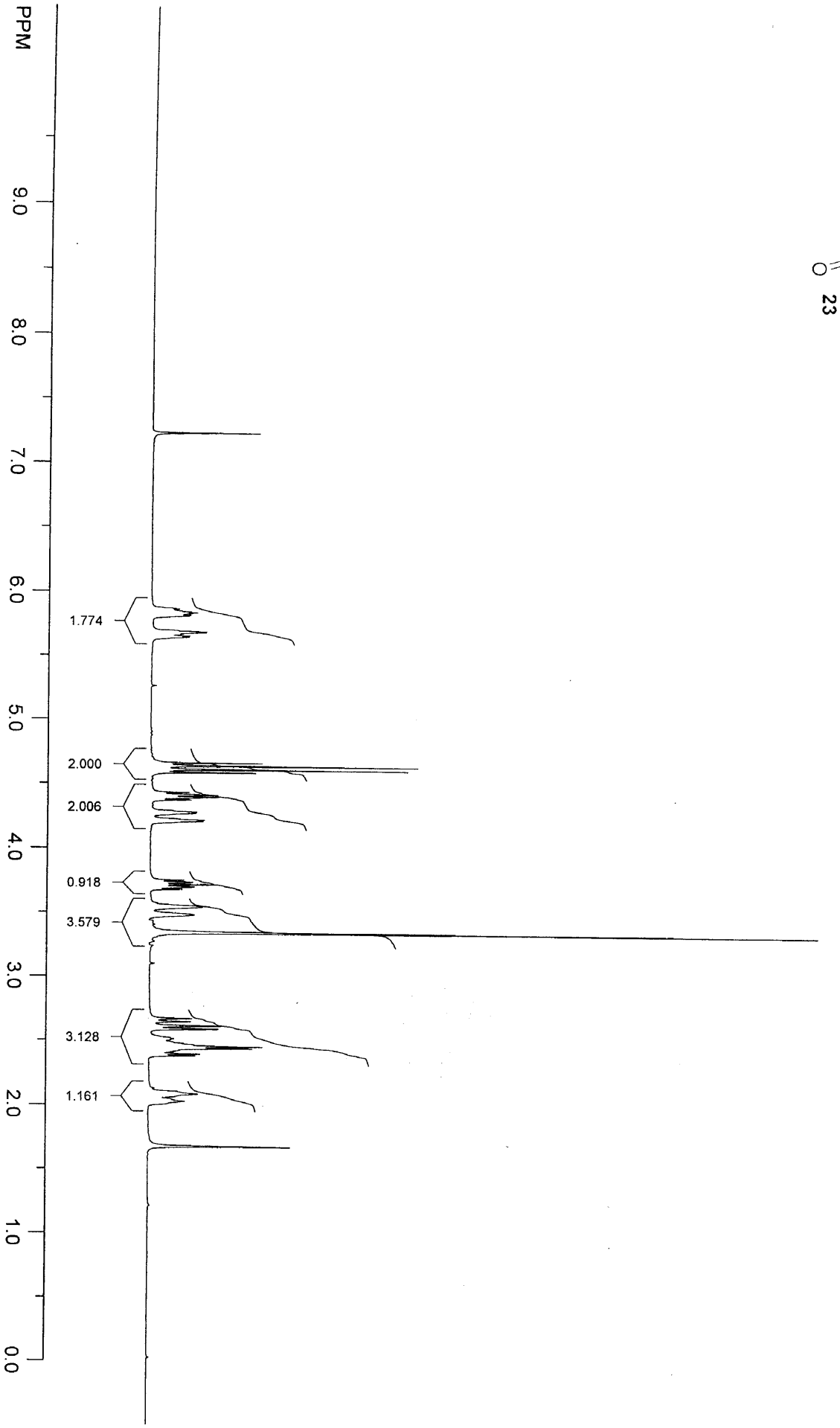
24


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.999
3.914
2.291
2.278
1.131
4.111
4.746

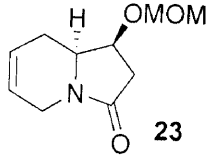

OMOM
O
N
24


PPM
180
160
140
120
100
80
60
40
20
0

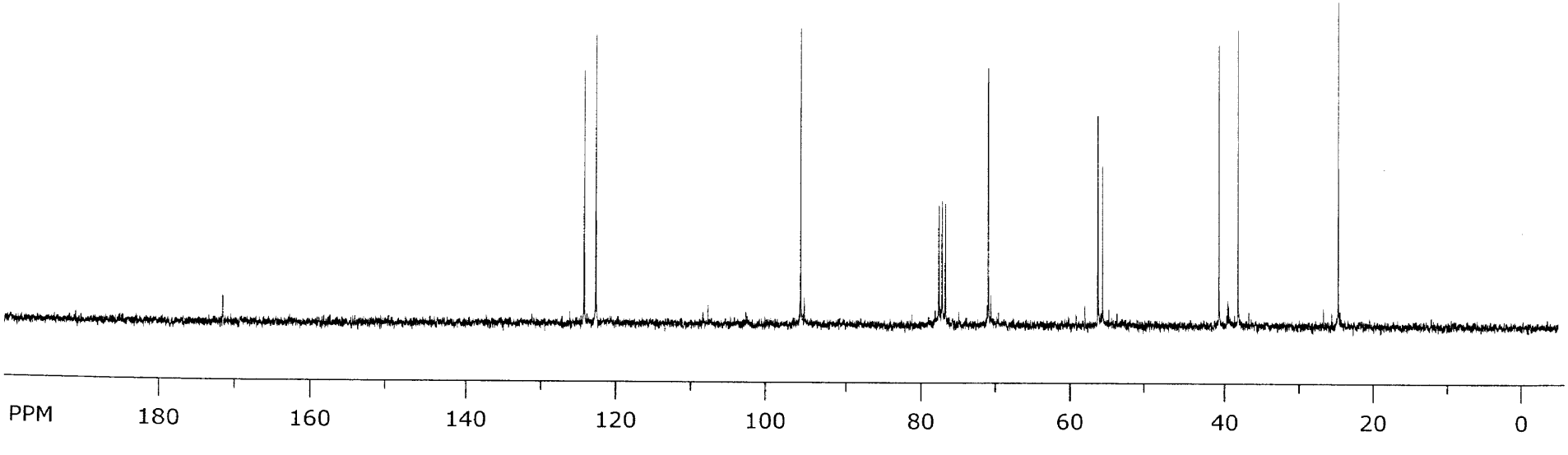

N
H
O
OMOM
23

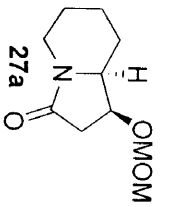

PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.774
2.000
2.006
0.918
3.579
3.128
1.161

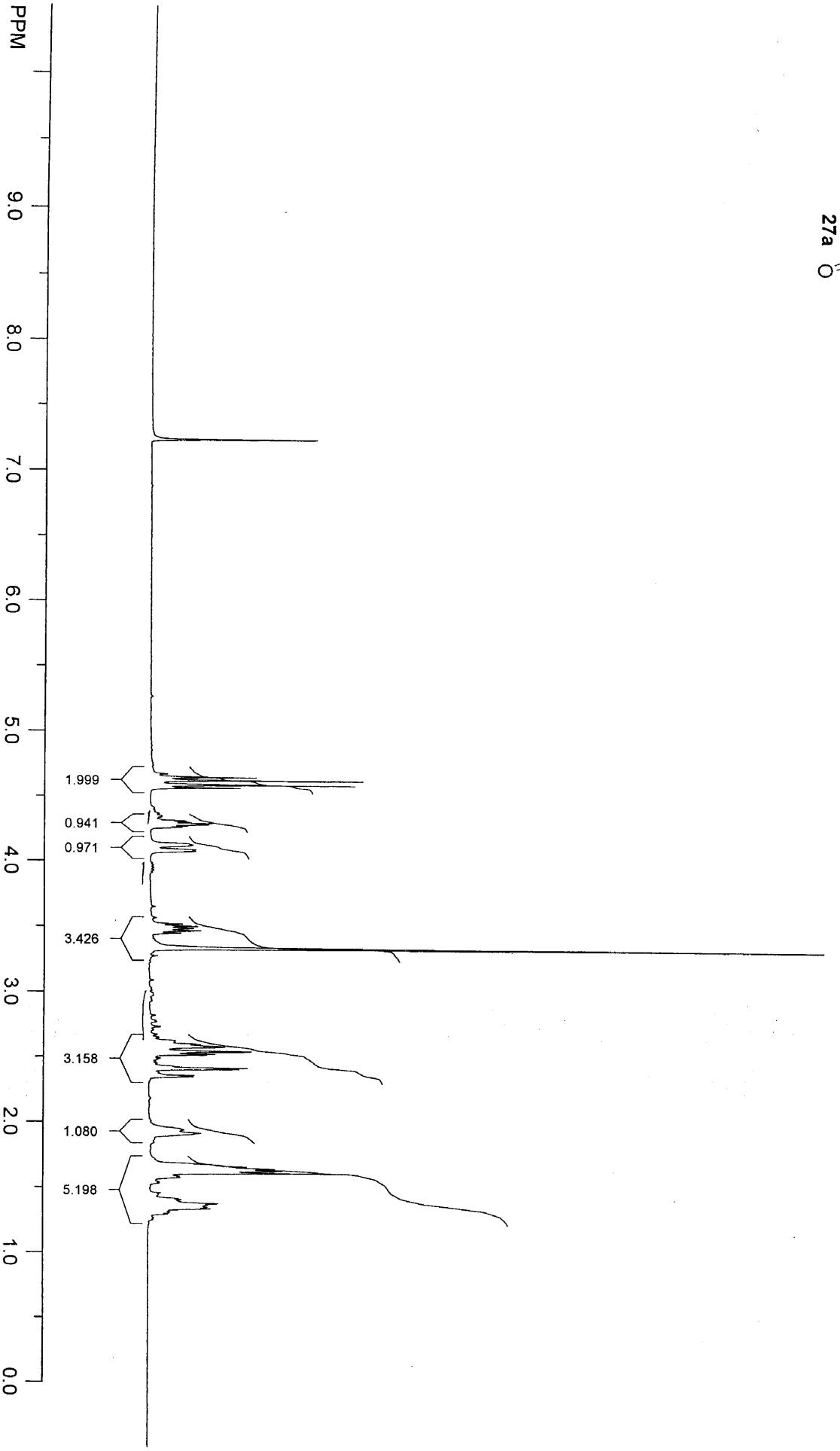
SI-81

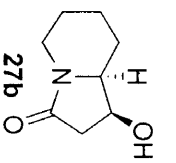


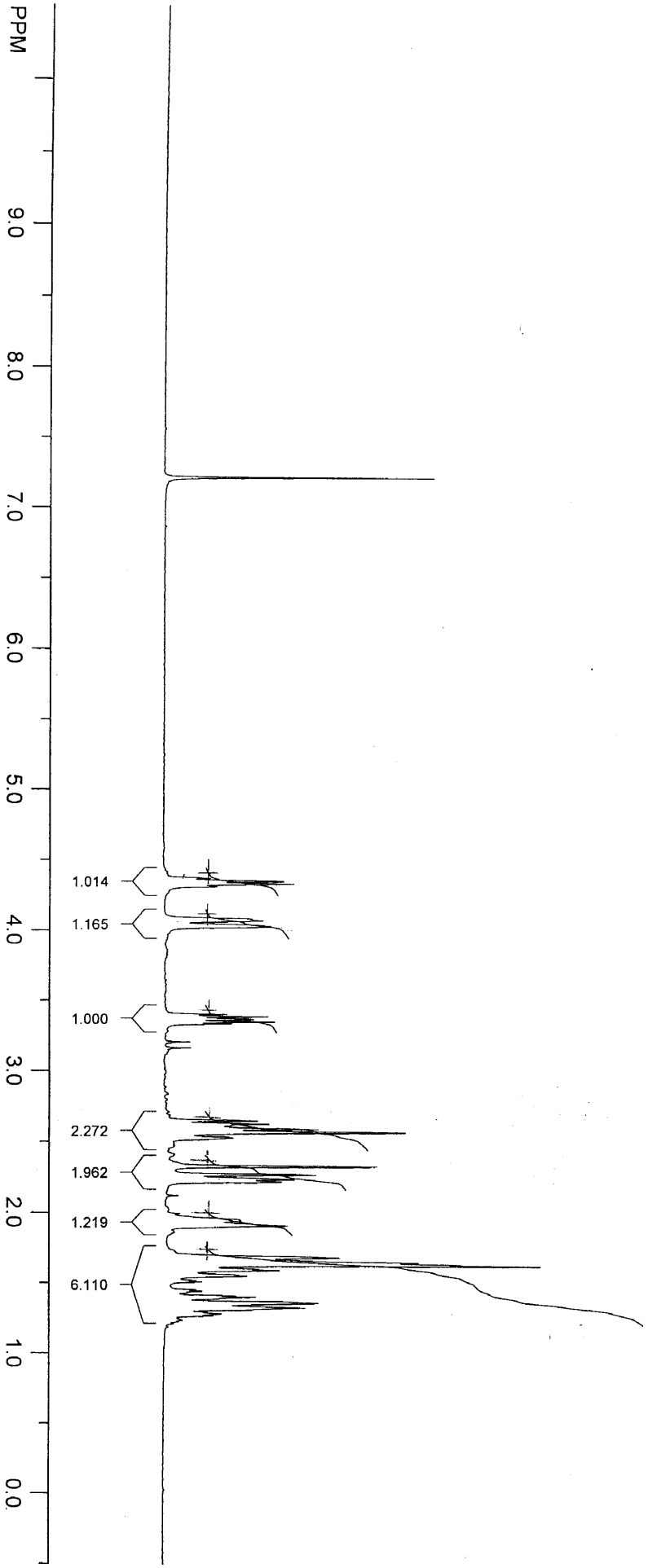

23



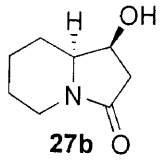

27a
N
O
H
OMOM


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.999
0.941
0.971
3.426
3.158
1.080
5.198

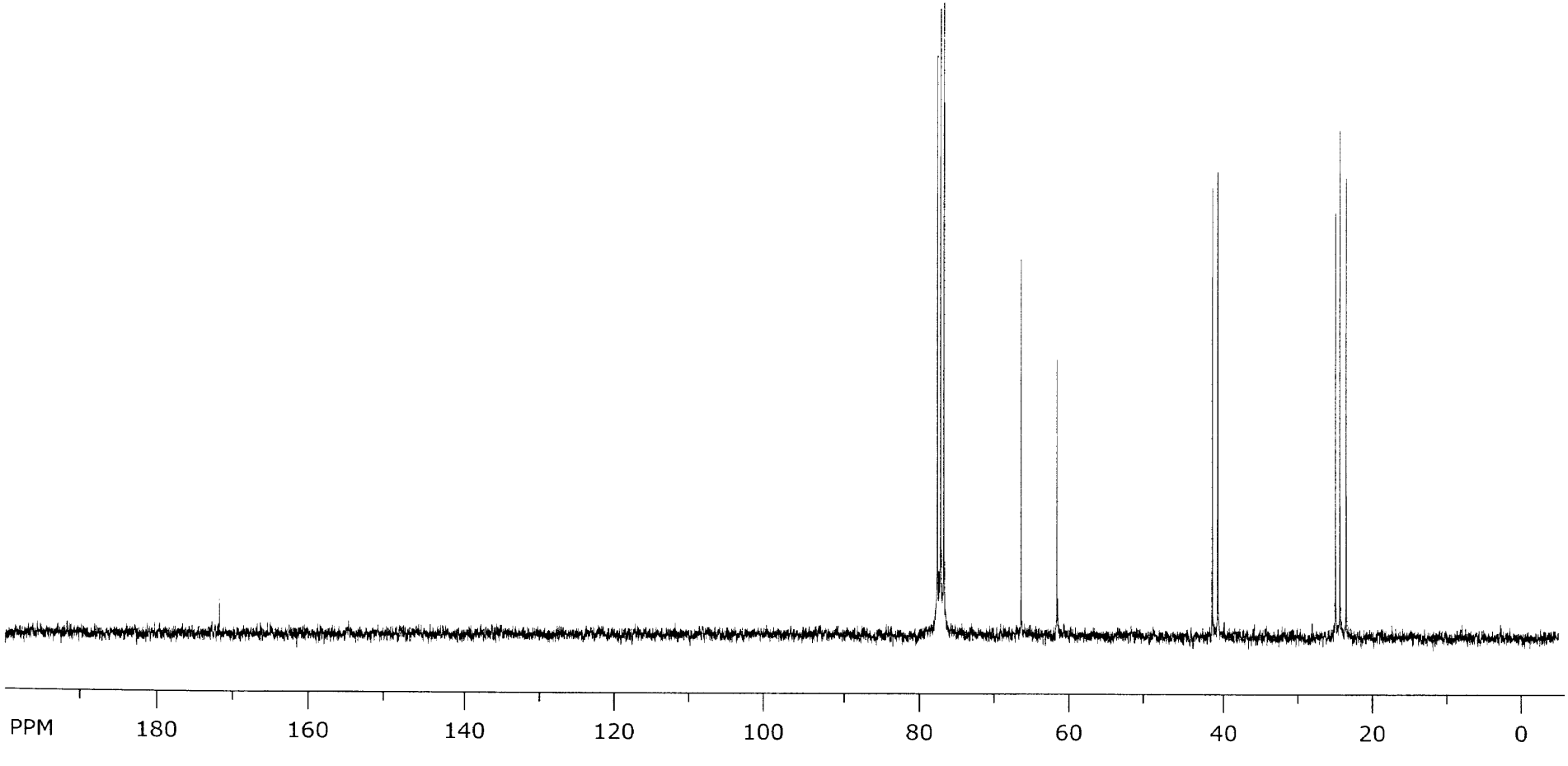

27b
N
H
O
OH


PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.014
1.165
1.000
2.272
1.962
1.219
6.110

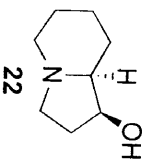
SI-84



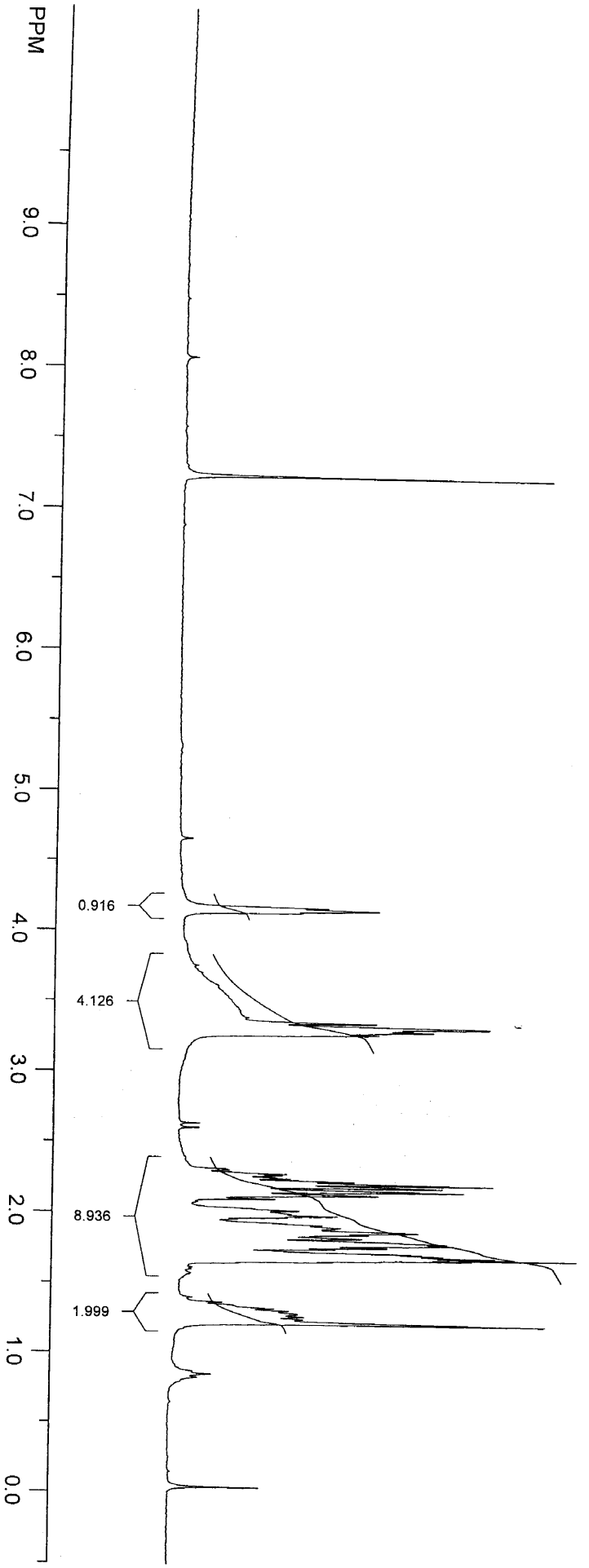

**27b**



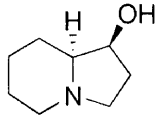
SI-85



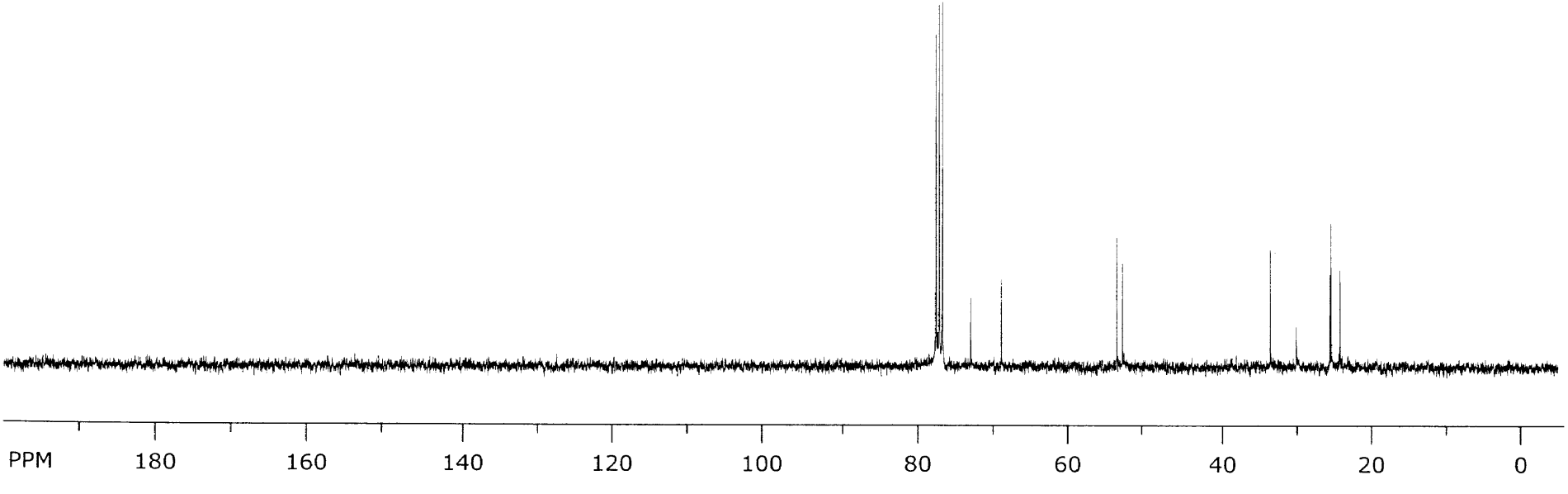

22



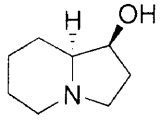
SI-26




**22**



SI-87




**22**; $D_2O$ exchange