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Unprecedented synergistic effects between weak Lewis and Brønsted acids in Prins Cyclization

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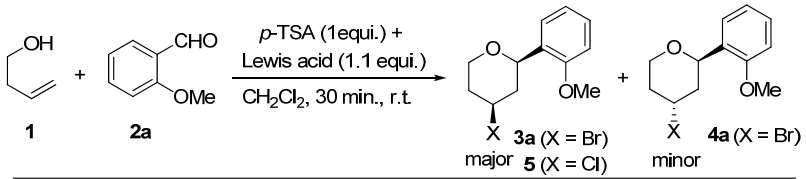
1. General

Dichloroethane was dried over CaH_2 and then distilled under nitrogen atmosphere. Reactions were performed in oven-dried round bottom flask, the flasks were fitted with rubber septa and reactions were conducted under nitrogen atmosphere. Glass syringes were used to transfer solvent. Crude products were purified by flash column chromatography using silica gel of 230–400 mesh. Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to methanolic acidic solution of p-anisaldehyde (anis) followed by heating (<1 min) on a hot plate. Organic solutions were concentrated on rotary evaporator at 35–40°C. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300, 400 or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (*J*) are quoted in hertz (Hz). Mass spectra were recorded on mass spectrometer by Electro Spray Ionization (ESI) and Atmospheric Solids Analysis Probe (ASAP) techniques.

2. Synergistic effects between Lewis acids and Ts-OH

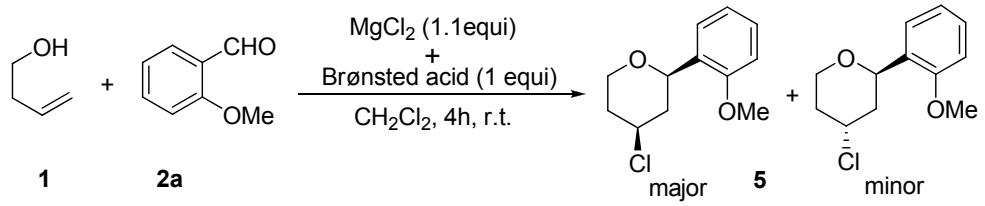
Table S-1. Synergistic effects between various Lewis acids and Ts-OH in Prins cyclization



Entry	Lewis Acid	Conversion (%)			
		No Ts-OH	dia. ratio	1 equi. Ts-OH	dia. ratio
1	$InBr_3$	70	80 : 20	96	75 : 25
2	$ZnBr_2$	22	100 : 00	94	96 : 4
3	$NiBr_2$	—	—	56	93 : 7
4	LiBr	—	—	35	75 : 25
5	$InCl_3$	55	98 : 2	95	95 : 2
6	$ZnCl_2$	20	98 : 2	90	96 : 4
7	$SnCl_2$	15	98 : 2	88	98 : 2
8	$MgCl_2$	—	—	45	98 : 2
9	$LaCl_3$	—	—	45	98 : 2
10	$NiCl_2$	—	—	34	98 : 2
11	LiCl	—	—	30	95 : 5

3. Synergistic effects between $MgCl_2$ and Brønsted acids

Table S-2. Synergistic effects between $MgCl_2$ and various Brønsted acids in Prins cyclization



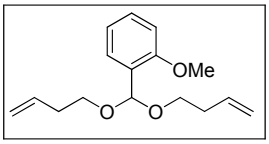
1 **2a**

Entry	Brønsted acid	Conversion (%)	Diastereomeric ratio
1	---	0	----
2	*p*-Toluenesulphonic acid	86	96 : 4
3	Camphorsulphonic acid	68	92 : 8
4	4-Nitrobenzoic acid	40	95 : 5
5	2-Iodobenzoic acid	38	96 : 4
6	Acetic acid	32	94 : 6
7	Benzoic acid	26	98 : 2
8	4-Hydroxybenzoic acid	20	96 : 4

During our study, we performed the Prins cyclization between 3-buten-1-ol and 2-methoxybenzaldehyde with a combination of $MgCl_2$ (1.1 equiv.) and various Brønsted acids (1 equiv.) in dichloromethane and the results are summarized in table S-2. Here also we observed synergistic effect between $MgCl_2$ and various Brønsted acids. Such a combination of non reactive Lewis acid and non reactive Brønsted acid was able to perform the reaction very well. Among the several Brønsted acids tested for this conversion in combination with $MgCl_2$, Ts-OH gave the best result in terms of reaction time and conversion (entry 2, table S-2). From the table S-2, it seems that strength of synergistic effect is a direct function of the *p*Ka of Brønsted acid but even weak acids, such as acetic or benzoic acids show this synergistic effect.

4. Experimental Procedures

A. Procedure for Synthesis of 1-(bis(but-3-enyloxy)methyl)-2-methoxybenzene (6)



2-Methoxybenzaldehyde (2 g, 14.7 mmol) and 3-buten-1-ol (3.17 g, 44.1 mmol) were added to a 100 mL round bottom flask at 0 °C, which contained 55 mL of dry tetrahydrofuran (THF) and 4 g vacuum-dried 4Å molecular sieves.[1] Ts-OH (0.28 g, 1.47 mmol) was added to this solution, and the mixture was stirred at room temperature for 12h, quenched with triethylamine, filtered, extracted with dichloromethane and purified by flash column chromatography (silica gel of 230–400 mesh) using EtOAc/*n*-pentane/triethylamine (1: 95 : 4 %) as the eluent, affording corresponding acetal **6** with a yield of 43%. Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 7.6 and 1.7 Hz, 1H), 7.33-7.26 (m, 1H), 6.96 (dt, *J* = 7.4 and 1.0 Hz, 1H), 6.88 (dd, *J* = 8.3 and 1.0 Hz, 1H), 5.91-5.74 (m, 2H), 5.83 (s, 1H), 5.12-5.08 (m, 1H), 5.07-5.02 (m, 2H), 5.01-4.98 (m, 1H), 3.84 (s, 3H), 3.66-3.49 (m, 4H), 2.40-2.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.0, 135.4, 129.5, 127.4, 126.8, 120.2, 116.2, 110.6, 97.2, 65.5, 55.5, 34.2; ESI-MS: *m/z* 285 $(M+Na)^+$; HRMS (ESI) calculated for $C_{16}H_{22}O_3Na$: 285.14666 $(M+Na)^+$, Found 285.1466.

Reference: 1. S. D. Khaja, S. lee and N. Murthy, *Biomacromolecules*, 2007, **8**, 1391.

B. General Procedure for Prins cyclization with Lewis acids alone (Table 1)

To a stirred solution of 3-buten-1-ol (1 mmol) and 2-Methoxybenzaldehyde (**2a)** (1.2 mmol) in dry dichloromethane (10 mL) under nitrogen atmosphere was added Lewis acid (1. 1 mmol) at specified temperature as mentioned in table 1. The reaction mixture was stirred at same temperature for 2h and then quenched with saturated aqueous $NaHCO_3$ solution (1-2 mL) and extracted with dichloromethane (2x10 mL). The organic phases were combined, washed with brine (2x4 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The

resulting crude product was purified by purified by flash column chromatography (silica gel of 230–400 mesh) using ethyl acetate/*n*-pentane as eluent to afford pure product **3a or 5** (Table 1).

C. General Procedure for Prins cyclization with a combination of Lewis acid and Brønsted acid (Table 2 and table S-1, S-2)

To a stirred solution of 3-buten-1-ol (1 mmol) and 2-Methoxybenzaldehyde (**2a)** (1.2 mmol) in dry dichloromethane (10 mL) under nitrogen atmosphere were added Lewis acid (1. 1 mmol) and Brønsted acid (1 mmol) at room temperature as mentioned in table 2 and table S-1, S-2. The reaction mixture was stirred at same temperature for specified time and then quenched with saturated aqueous $NaHCO_3$ solution (4-5 mL) and extracted with dichloromethane (2x10 mL). The organic phases were combined, washed with brine (2x4 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product **3a** or **5** was analysed on the basis of ^1H NMR spectra for percentage reaction conversion and diastereomeric ratio in each case (Table 2 and Table S-1, S-2).

D. General Procedure for Prins cyclization with homoallyllic alcohol and carbonyl compound with a combination of $MgBr_2$ and Ts-OH (Table 3).

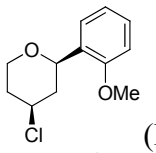
To a stirred solution of homoallylic alcohol (**1**) (1 mmol) and carbonyl compound (**2)** (1.2 mmol) in dry dichloromethane (10 mL) under nitrogen atmosphere were added $MgBr_2$ (1. 1 mmol) and Ts-OH (1 mmol) at room temperature. The reaction mixture was stirred at same temperature for specified time (Table 3) and after completion (indicated by TLC), quenched with saturated aqueous $NaHCO_3$ solution (4-5 mL) and extracted with dichloromethane (2x10 mL). The organic phases were combined, washed with brine (2x4 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel of 230–400 mesh) using ethyl acetate/*n*-pentane as eluent to afford pure product **3** and **4** (Table 3).

E. General Procedure for Prins cyclization of acetal i.e. 1-(bis(but-3-enyloxy)methyl)-2-methoxybenzene (6) (Table 4).

To a stirred solution of 1-(bis(but-3-enyloxy)methyl)-2-methoxybenzene (**6**) (0.5 mmol) in dry dichloromethane (5 mL) under nitrogen atmosphere was added Lewis acid (0.5 mmol) alone or Brønsted acid (0.5 mmol) and tetrabutyl ammonium bromide (1 mmol) at room temperature. The reaction mixture was stirred at same temperature for 30 minutes (Table 4) and quenched with excess of triethylamine, diluted with water and extracted with dichloromethane (2x10 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product **3a** or **5** was analysed on the basis of ^{1}H NMR spectra for percentage reaction conversion and diastereomeric ratio in each case (Table 4).

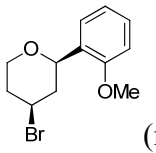
5. Characterization data of products (5, 3a-3l).

(2*R,4*S**)-4-chloro-2-(2-methoxyphenyl)tetrahydro-2*H*-pyran** (**5**):



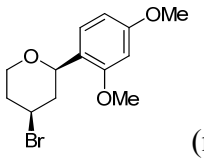
(Major, diastereomeric ratio = 96 : 4)
Yield, 85% (with $MgCl_2$ and Ts-OH); Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.6 and 1.7 Hz, 1H), 7.24 (dt, *J* = 8.3 and 1.7 Hz, 1H), 6.97 (dt, *J* = 7.6 and 1.0 Hz, 1H), 6.84 (dd, *J* = 8.3 and 1.0 Hz, 1H), 4.70 (dd, *J* = 10.9 and 1.9 Hz, 1H), 4.24-4.11 (m, 2H), 3.81 (s, 3H), 3.59 (dt, *J* = 12.3 and 2.3 Hz, 1H), 2.44 (tdd, *J* = 12.8, 4.3 and 2.1 Hz, 1H), 2.19-2.09 (m, 1H), 1.98 (dq, *J* = 12.3 and 4.7 Hz, 1H), 1.72 (td, *J* = 12.5 and 11.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 129.7, 128.4, 126.0, 120.8, 110.1, 73.6, 67.3, 56.0, 55.2, 43.4, 37.0; ESI-MS: *m/z* 249 $(M+Na)^+$; HRMS (ESI) calculated for $C_{12}H_{15}O_2ClNa$: 249.06583 $(M+Na)^+$, Found 249.0658.

(2*R,4*S**)-4-bromo-2-(2-methoxyphenyl)tetrahydro-2*H*-pyran** (**3a**, Table 3, entry a):



(major)
The reaction afforded a 92:8 mixture of two diastereomers **3a** and **4a**. The two diastereomers were partially separable by flash column chromatography.Yield of major diastereomer, 84%; White solid, m.p. 68-70 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.6 and 1.5 Hz, 1H), 7.25 (dt, *J* = 8.1 and 1.5 Hz, 1H), 6.98 (dt, *J* = 7.6 and 0.7 Hz, 1H), 6.85 (dd, *J* = 8.1 and 0.7 Hz, 1H), 4.72 (dd, *J* = 10.9 and 1.8 Hz, 1H), 4.32 (tt, *J* = 11.9 and 4.5 Hz, 1H), 4.15 (ddd, *J* = 11.9, 4.8 and 1.8 Hz, 1H), 3.82 (s, 3H), 3.61 (dt, *J* = 12.0 and 2.4 Hz, 1H), 2.56 (tdd, *J* = 12.9, 4.2 and 2.0 Hz, 1H), 2.29-2.21 (m, 1H), 2.17 (dq, *J* = 11.9 and 4.8 Hz, 1H), 1.91 (td, *J* = 12.1 and 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 129.6, 128.3, 126.0, 120.7, 110.0, 74.3, 68.1, 55.2, 46.9, 44.3, 37.8; ESI-MS: *m/z* 293 $(M+Na)^+$; HRMS (ESI) calculated for $C_{12}H_{15}O_2BrNa$: 293.01531 $(M+Na)^+$, Found 293.0153.

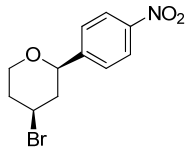
(2*R,4*S**)-4-bromo-2-(2,4-dimethoxyphenyl)tetrahydro-2*H*-pyran** (**3b**, Table 3, entry b):



(major)

The reaction afforded a 82:18 mixture of two diastereomers **3b** and **4b**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 71%; Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.4 Hz, 1H), 6.50 (dd, *J* = 8.4 and 2.3 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 4.63 (dd, *J* = 10.9 and 2.0 Hz, 1H), 4.30 (tt, *J* = 11.8 and 4.5 Hz, 1H), 4.13 (ddd, *J* = 11.8, 4.5 and 2.0 Hz, 1H), 3.80 (s, 6H), 3.59 (dt, *J* = 11.8 and 2.5 Hz, 1H), 2.49 (tdd, *J* = 12.9, 4.5 and 2.0 Hz, 1H), 2.28-2.09 (m, 2H), 1.95 (td, *J* = 12.3 and 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 156.6, 126.9, 122.3, 104.4, 98.2, 74.2, 68.3, 55.4, 55.3, 47. 1, 44.5, 37.9; ESI-MS: *m/z* 323 $(M+Na)^+$; HRMS (ESI) calculated for $C_{13}H_{17}O_3BrNa$: 323.02588 $(M+Na)^+$, Found 323.0263.

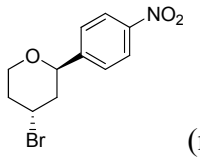
(2*R,4*S**)-4-bromo-2-(4-nitrophenyl)tetrahydro-2*H*-pyran** (**3c**, Table 3, entry c):



(major)

The reaction afforded a 65:35 mixture of two diastereomers **3c** and **4c**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 60%; White solid, m.p. 96-98 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23-8.16 (m, 2H), 7.53-7.46 (m, 2H), 4.43 (dd, *J* = 11.3 and 1.9 Hz, 1H), 4.29 (tt, *J* = 11.9 and 4.4 Hz, 1H), 4.17 (ddd, *J* = 12.0, 4.8 and 1.6 Hz, 1H), 3.61 (dt, *J* = 12.2 and 2.2 Hz, 1H), 2.50 (tdd, *J* = 13.0, 4.3 and 2.0 Hz, 1H), 2.31-2.25 (m, 1H), 2.15 (dq, *J* = 12.2 and 4.8 Hz, 1H), 1.95 (td, *J* = 12.8 and 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 147.3, 126.3, 123.6, 78.7, 68.0, 45.3, 45.2, 37.2; ESI/ASAP-MS: *m/z* 286 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_{11}H_{13}NO_3Br$: 286.00788 $(M+H)^+$, Found 286.0079.

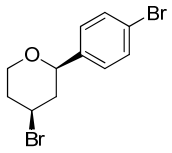
(2*R,4*R**)-4-bromo-2-(4-nitrophenyl)tetrahydro-2*H*-pyran** (**4c**, Table 3, entry c):



(minor)

Minor diastereomer, Yield, 32%; White solid, m.p. 118-120 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21-8.17 (m, 2H), 7.55-7.49 (m, 2H), 4.99 (dd, *J* = 11.0 and 1.8 Hz, 1H), 4.81-4.77 (m, 1H), 4.16 (dt, *J* = 11.9 and 2.1 Hz, 1H), 4.09-4.03 (m, 1H), 2.27-2.18 (m, 2H), 2.04-1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4, 147.3, 126.5, 123.6, 73.3, 63.4, 49.4, 41.8, 33.6; ESI-MS: *m/z* 308 $(M+Na)^+$; HRMS (ESI) calculated for $C_{11}H_{12}NO_3BrNa$: 307.98982 $(M+Na)^+$, Found 307.9897.

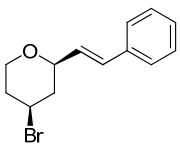
(2*R,4*S**)-4-bromo-2-(4-bromophenyl)tetrahydro-2*H*-pyran** (**3d**, Table 3, entry d):



(major)

The reaction afforded a 86:14 mixture of two diastereomers **3d** and **4d**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 76%; White solid, m.p. 58-60 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.44 (m, 2H), 7.24-7.17 (m, 2H), 4.34-4.20 (m, 2H), 4.15 (ddd, *J* = 12.1, 4.9 and 1.9 Hz, 1H), 3.58 (dt, *J* = 12.1 and 2.4 Hz, 1H), 2.45 (tdd, *J* = 13.0, 4.3 and 2.0 Hz, 1H), 2.31-2.07 (m, 2H), 2.01 (td, *J* = 12.8 and 11.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2, 131.5, 127.4, 121.6, 79.3, 68.1, 45.9, 45.4, 37.5; ESI/ASAP-MS: *m/z* 318.9 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_{11}H_{13}OBr_2$: 318.93331 $(M+H)^+$, Found 318.9341.

(2*R,4*S**)-4-bromo-2-styryltetrahydro-2*H*-pyran** (**3e**, Table 3, entry e):

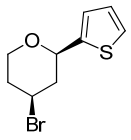


(major)

The reaction afforded a 88:12 mixture of two diastereomers **3e** and **4e**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 83%; Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.33 (m, 2H), 7.32-7.27 (m, 2H), 7.26-7.20 (m, 1H), 6.60 (dd, *J* = 16.0 and 1.1 Hz, 1H), 6.14 (dd, *J* = 16.0 and

5.9 Hz, 1H), 4.19 (tt, *J* = 11.8 and 4.5 Hz, 1H), 4.06 (ddd, *J* = 12.1, 4.7 and 2.0 Hz, 1H), 3.96 (tdd, *J* = 10.9, 5.9 and 1.7 Hz, 1H), 3.50 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.38 (tdd, *J* = 12.9, 4.5 and 2.0 Hz, 1H), 2.23-2.16 (m, 1H), 2.09 (dq, *J* = 12.1 and 4.8 Hz, 1H), 1.95 (td, *J* = 12.3 and 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 130.9, 128.5, 127.8, 126.5, 78.3, 67.8, 46.0, 43.7, 37.6; ESI/ASAP-MS: *m/z* 267 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_{13}H_{16}OBr$: 267.03845 $(M+H)^+$, Found 267.0379.

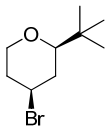
(2*R,4*S**)-4-bromo-2-(thiophen-2-yl)tetrahydro-2*H*-pyran** (**3f**, Table 3, entry f):



(major)

The reaction afforded a 90:10 mixture of two diastereomers **3f** and **4f**. The two diastereomers were inseparated by flash column chromatography. Yield, 88%; Semisolid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.24 (m, 1H), 7.00-6.94 (m, 2H), 4.59 (dd, *J* = 11.3 and 2.3 Hz, 1H), 4.24 (tt, *J* = 11.9 and 4.5 Hz, 1H), 4.12 (ddd, *J* = 12.1, 4.7 and 1.9 Hz, 1H), 3.60 (dt, *J* = 12.1 and 2.6 Hz, 1H), 2.61 (tdd, *J* = 12.8, 4.3 and 2.1 Hz, 1H), 2.29-2.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 126.5, 124.9, 123.8, 75.7, 68.2, 45.5, 45.1, 37.4; ESI/ASAP-MS: *m/z* 247 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_9H_{12}OBrS$: 246.97922 $(M+H)^+$, Found 246.9787.

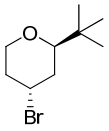
(2*R,4*S**)-4-bromo-2-tert-butyltetrahydro-2*H*-pyran** (**3g**, Table 3, entry g):



(major)

The reaction afforded a 65:35 mixture of two diastereomers **3g** and **4g**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 56%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (tt, *J* = 11.9 and 4.5 Hz, 1H), 3.99 (ddd, *J* = 11.7, 4.9 and 1.7 Hz, 1H), 3.35 (dt, *J* = 11.9 and 2.3 Hz, 1H), 2.86 (dd, *J* = 11.1 and 1.7 Hz, 1H), 2.24 (tdd, *J* = 12.7, 4.3 and 1.9 Hz, 1H), 2.18-2.09 (m, 1H), 2.00 (dq, *J* = 11.9 and 4.7 Hz, 1H), 1.75 (td, *J* = 12.1 and 11.7 Hz, 1H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.0, 68.1, 48.5, 38.4, 38.1, 34.2, 25.9; ESI/ASAP-MS: *m/z* 221 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_9H_{18}OBr$: 221.05410 $(M+H)^+$, Found 221.0544.

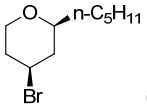
(2*R,4*R**)-4-bromo-2-tert-butyltetrahydro-2*H*-pyran** (**4g**, Table 3, entry g):



(minor)

Minor diastereomer, Yield, 29%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.82-4.75 (m, 1H), 3.98-3.83 (m, 2H), 3.44 (dd, *J* = 11.0 and 1.7 Hz, 1H), 2.12-1.92 (m, 2H), 1.90-1.73 (m, 2H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 79.6, 63.3, 51.8, 34.3, 34.2, 33.6, 25.9; ESI/ASAP-MS: *m/z* 221 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_9H_{18}OBr$: 221.05410 $(M+H)^+$, Found 221.0544.

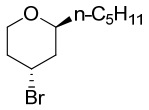
(2*R,4*S**)-4-bromo-2-pentyltetrahydro-2*H*-pyran** (**3h**, Table 3, entry h):



(major)

The reaction afforded a 68:32 mixture of two diastereomers **3h** and **4h**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 58%; Liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (tt, *J* = 12.1 and 4.5 Hz, 1H), 3.96 (ddd, *J* = 11.8, 4.8 and 1.7 Hz, 1H), 3.38 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.27-2.19 (m, 1H), 2.22 (tdd, *J* = 12.6, 4.5 and 2.0 Hz, 1H), 2.18-2.10 (m, 1H), 2.02 (dq, *J* = 12.1 and 4.8 Hz, 1H), 1.73 (td, *J* = 12.2 and 11.5 Hz, 1H), 1.57-1.46 (m, 1H), 1.45-1.18 (m, 7H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.2, 67.9, 47.0, 43.7, 38.0, 35.9, 31.8, 25.0, 22.5, 14.0; ESI/ASAP-MS: *m/z* 235 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_{10}H_{20}OBr$: 235.06975 $(M+H)^+$, Found 235.0694.

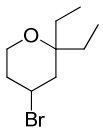
(2*R,4*R**)-4-bromo-2-pentyltetrahydro-2*H*-pyran** (**4h**, Table 3, entry h):



(minor)

Minor diastereomer, Yield, 26%; Liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73-4.67 (m, 1H), 3.93 (dt, *J* = 11.8 and 2.3 Hz, 1H), 3.87-3.74 (m, 2H), 2.13-2.02 (m, 1H), 2.00-1.92 (m, 1H), 1.91-1.83 (m, 1H), 1.80-1.70 (m, 1H), 1.56-1.20 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 72.1, 62.9, 50.6, 39.9, 35.6, 34.3, 31.8, 25.0, 22.6, 14.0; ESI/ASAP-MS: *m/z* 235 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_{10}H_{20}OBr$: 235.06975 $(M+H)^+$, Found 235.0699.

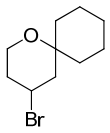
4-bromo-2,2-diethyltetrahydro-2*H*-pyran (**3i**, Table 3, entry i):



(single product)

Yield, 72%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34 (tt, *J* = 12.1 and 4.5 Hz, 1H), 3.71 (ddd, *J* = 12.1, 5.3 and 1.9 Hz, 1H), 3.56 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.19-2.09 (m, 2H), 1.98 (dq, *J* = 12.1 and 5.3 Hz, 1H), 1.88-1.65 (m, 2H), 1.59-1.33 (m, 3H), 0.83 (t, *J* = 7.6 Hz, 3H), 0.79 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.9, 61.0, 45.7, 44.4, 37.8, 31.5, 22.8, 7.3, 6.8; ESI/ASAP-MS: *m/z* 221 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_9H_{18}OBr$: 221.05410 $(M+H)^+$, Found 221.0544.

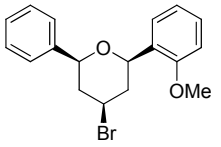
4-bromo-1-oxaspiro[5.5]undecane (**3j**, Table 3, entry j):



(single product)

Yield, 80%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34 (tt, *J* = 12.1 and 4.5 Hz, 1H), 3.73 (ddd, *J* = 12.3, 5.3 and 1.9 Hz, 1H), 3.60 (dt, *J* = 12.1 and 2.5 Hz, 1H), 2.24-2.12 (m, 2H), 2.09-1.86 (m, 2H), 1.78 (t, *J* = 12.3 Hz, 1H), 1.72-1.19 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.5, 60.6, 47.4, 45.2, 39.5, 38.0, 29.6, 25.8, 21.4, 21.0; ESI/ASAP-MS: *m/z* 233 $(M+H)^+$; HRMS (ESI/ASAP) calculated for $C_{10}H_{18}OBr$: 233.0541 $(M+H)^+$, Found 233.0539.

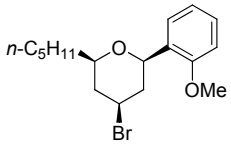
(2*R,4*S**,6*S**)-4-bromo-2-(2-methoxyphenyl)-6-phenyltetrahydro-2*H*-pyran** (**3k**, Table 3, entry k):



(major)

The reaction afforded a 88:12 mixture of two diastereomers **3k** and **4k**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 75%; Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 7.5 and 1.5 Hz, 1H), 7.45-7.39 (m, 2H), 7.38-7.19 (m, 4H), 6.98 (dt, *J* = 7.5 and 1.0 Hz, 1H), 6.83 (dd, *J* = 8.3 and 1.0 Hz, 1H), 4.93 (dd, *J* = 11.0 and 1.7 Hz, 1H), 4.58 (dd, *J* = 11.3 and 2.1 Hz, 1H), 4.47 (tt, *J* = 12.1 and 4.4 Hz, 1H), 3.81 (s, 3H), 2.65 (tdd, *J* = 12.7, 4.4 and 1.9 Hz, 1H), 2.55 (tdd, *J* = 12.8, 4.3 and 2.1 Hz, 1H), 2.12 (td, *J* = 12.3 and 11.9 Hz, 1H), 1.93 (td, *J* = 12.3 and 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 141.5, 129.8, 128.4, 128.3, 127.6, 126.2, 125.8, 120.8, 110.0, 79.7, 74.1, 55.2, 46.7, 45.3, 43.8; ESI-MS: *m/z* 369 $(M+Na)^+$; HRMS (ESI) calculated for $C_{18}H_{19}O_2BrNa$: 369.04661 $(M+Na)^+$, Found 369.0468.

(2*R,4*S**,6*R**)-4-bromo-2-(2-methoxyphenyl)-6-pentyltetrahydro-2*H*-pyran** (**3l**, Table 3, entry l):

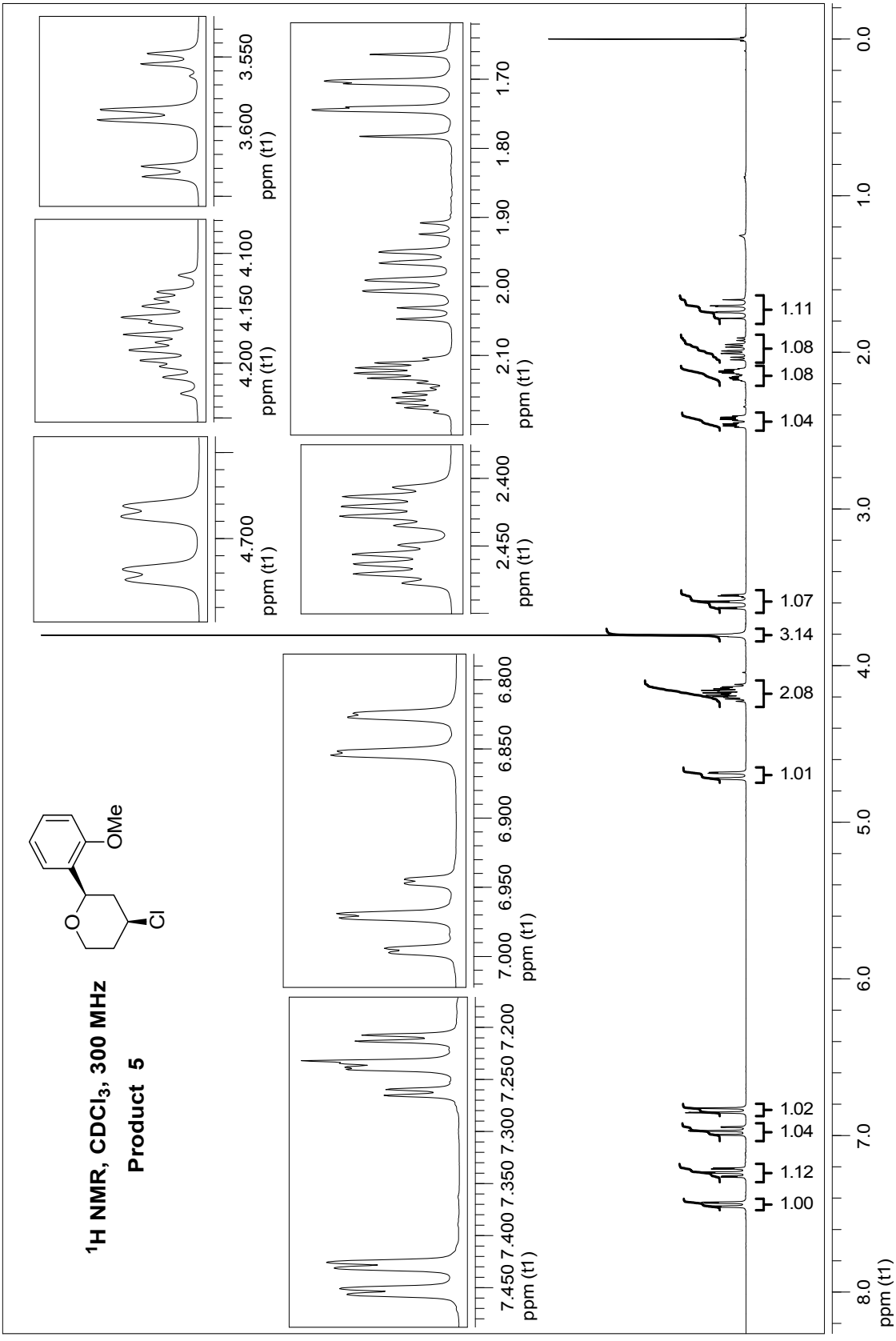


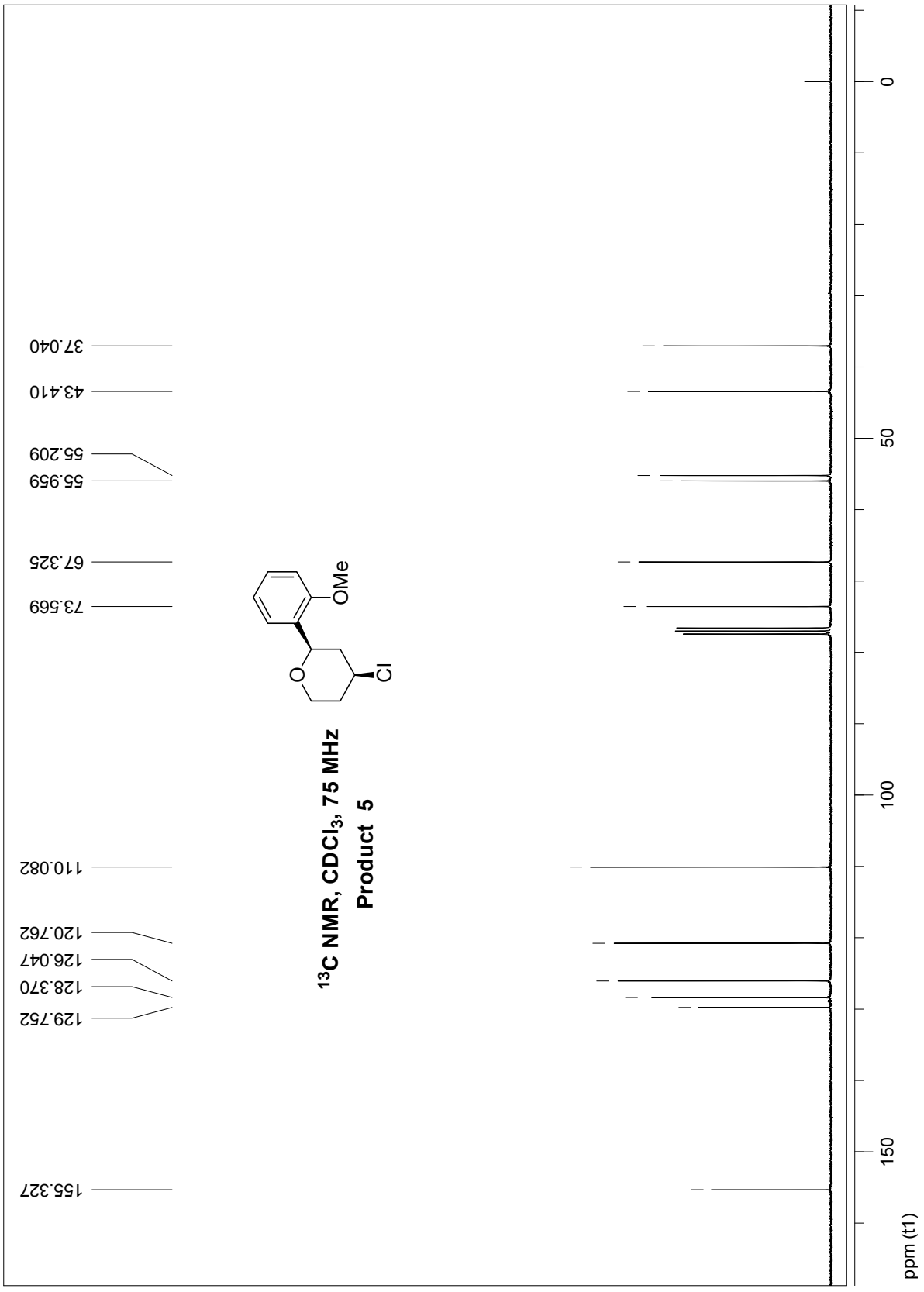
(major)

The reaction afforded a 90:12 mixture of two diastereomers **3l** and **4l**. The two diastereomers could be easily separated by flash column chromatography. Yield of major diastereomer, 78%; Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 7.6 and 1.7 Hz, 1H), 7.26 (dt, *J* = 8.1 and 1.9 Hz, 1H), 7.00 (dt, *J* = 7.6 and 1.0 Hz, 1H), 6.86 (dd, *J* = 8.1 and 1.0 Hz, 1H), 4.73 (dd, *J* = 11.0 and 1.7 Hz, 1H), 4.35 (tt, *J* = 12.1 and 4.3 Hz, 1H), 3.83 (s, 3H), 3.56-3.45 (m, 1H), 2.60 (tdd, *J* = 12.7, 4.3 and 1.7 Hz, 1H), 2.32 (tdd, *J* = 12.7, 4.5 and 1.9 Hz, 1H), 1.91-1.23 (m, 10H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 130.2, 128.1, 126.1, 120.7, 109.9, 77.8, 73.7, 55.2, 47.4, 44.1, 43.2, 35.9, 31.8, 24.9, 22.5, 14.0; ESI-MS: *m/z* 363 $(M+Na)^+$; HRMS (ESI) calculated for $C_{17}H_{25}O_2BrNa$: 363.09356 $(M+Na)^+$, Found 363.0936.

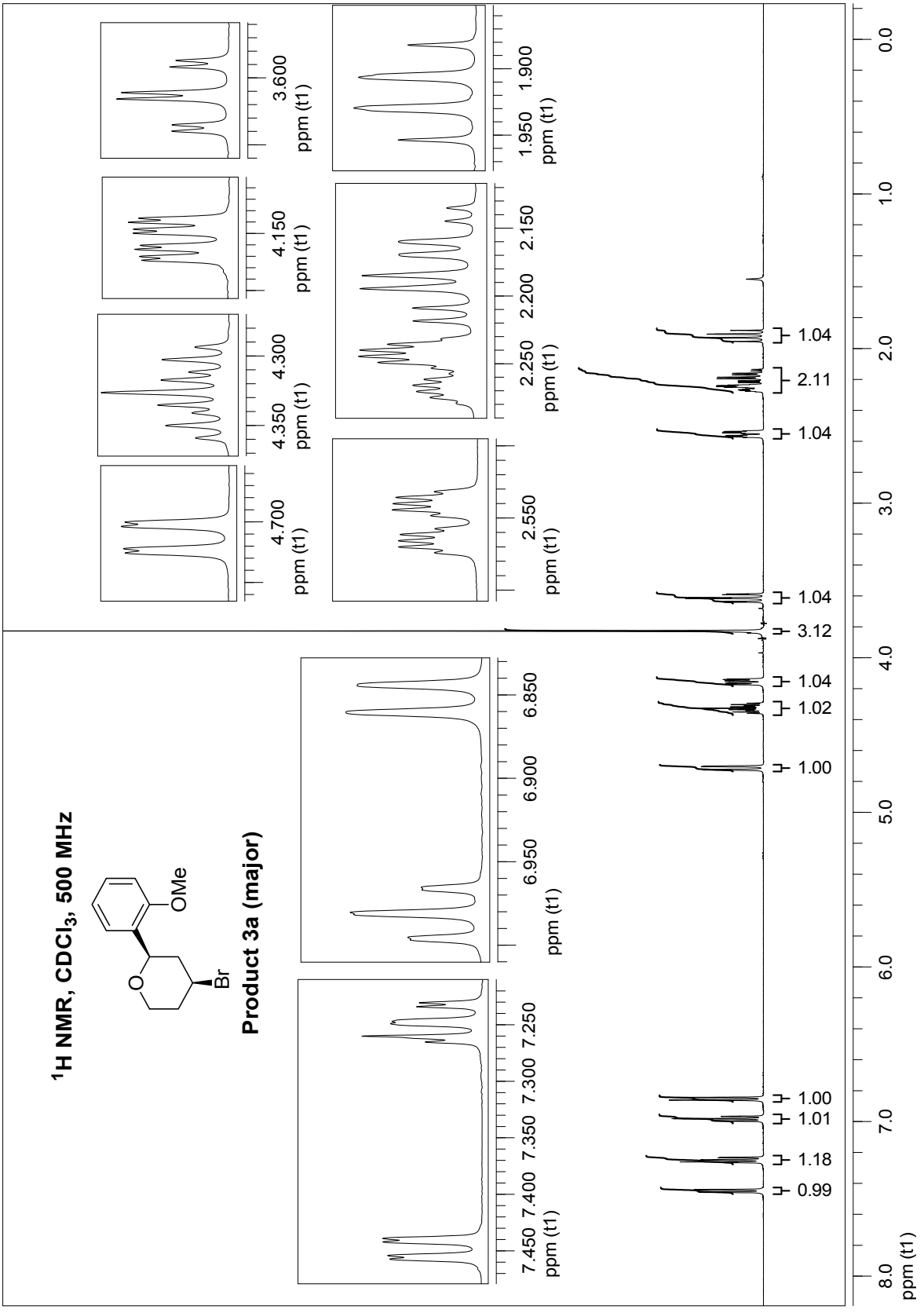
6. Copies of ^{1}H and ^{13}C NMR spectra of products (5, 3a-3l, 4c, 4g, 4h and 6).

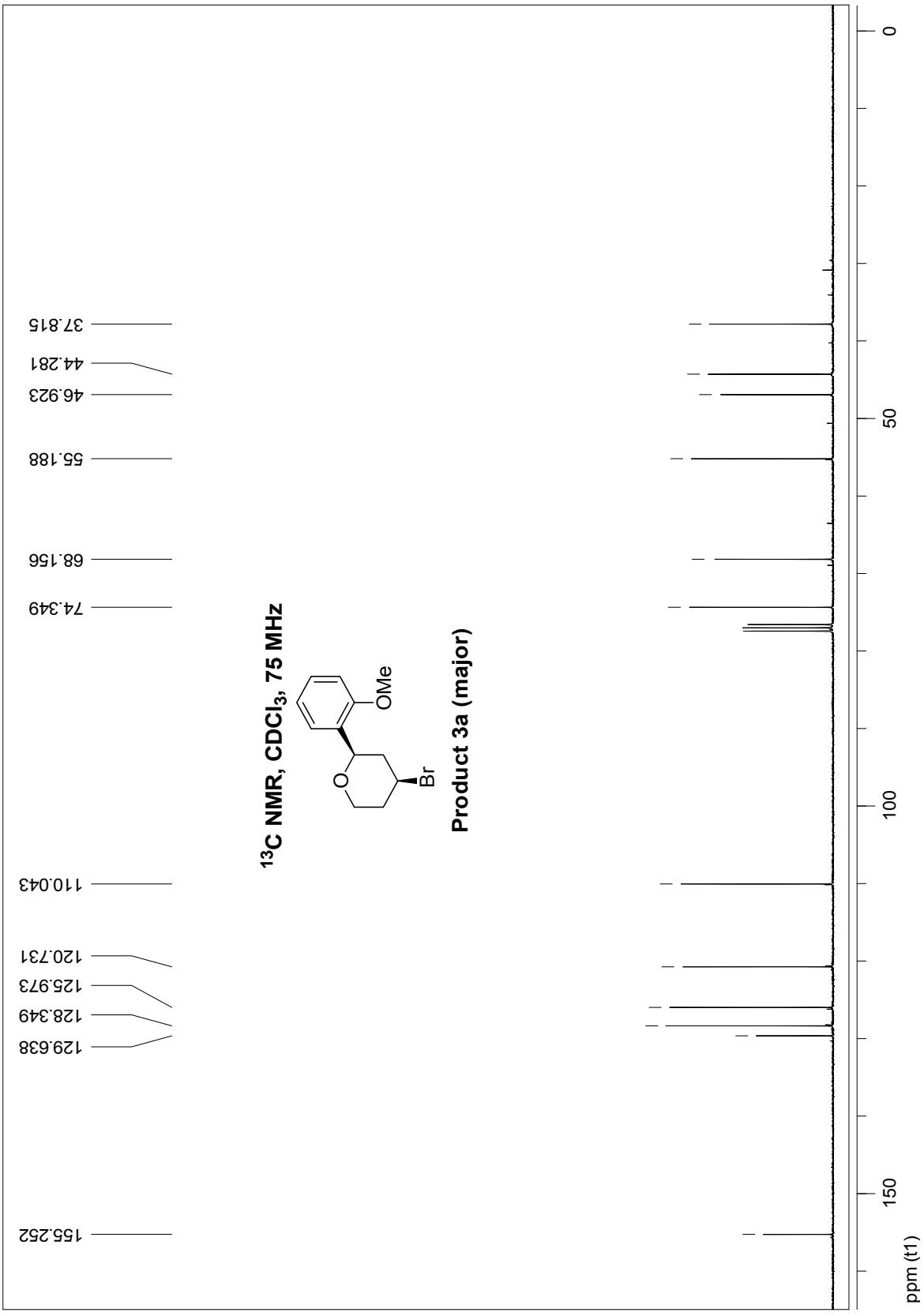
Product **5**:



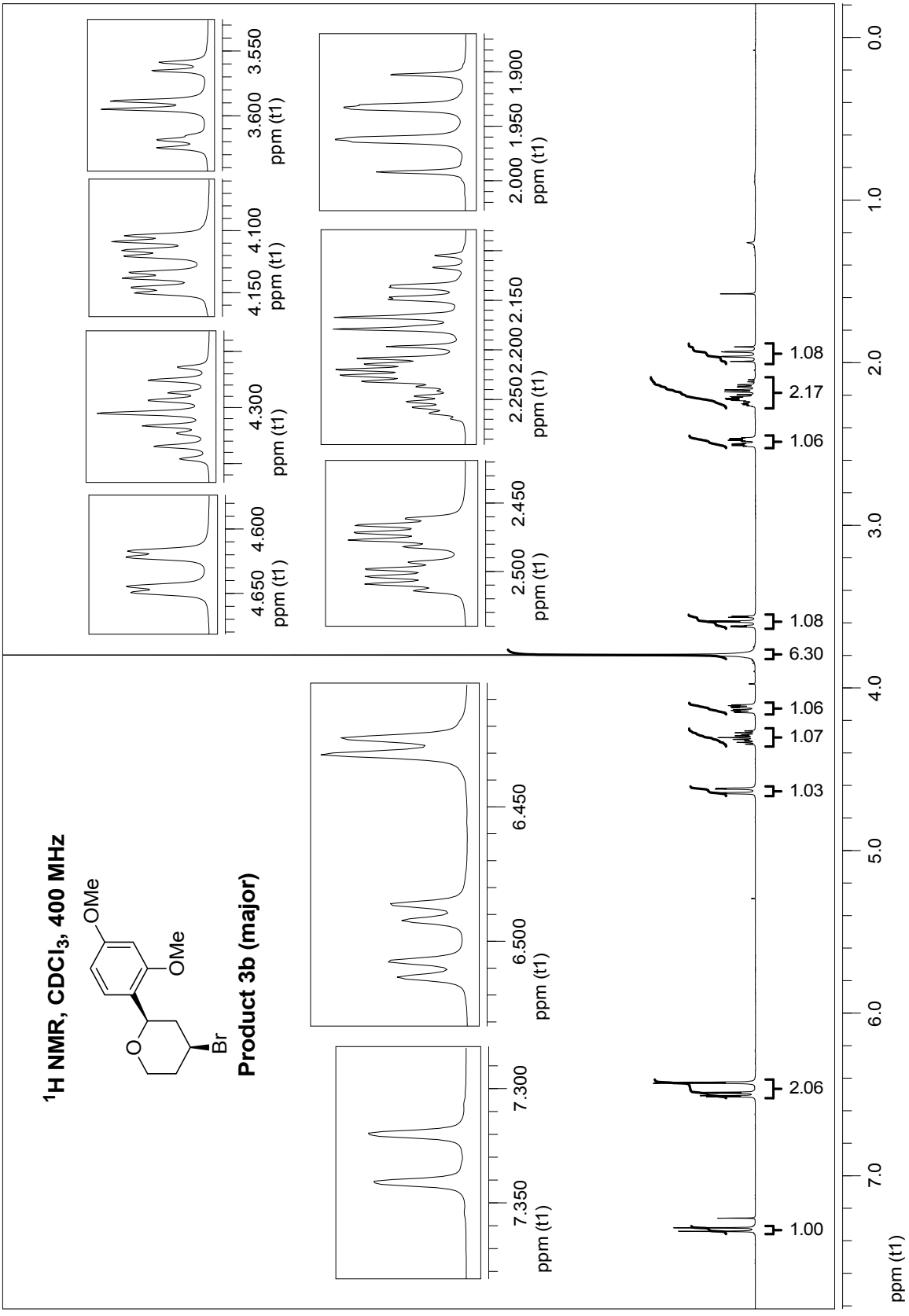


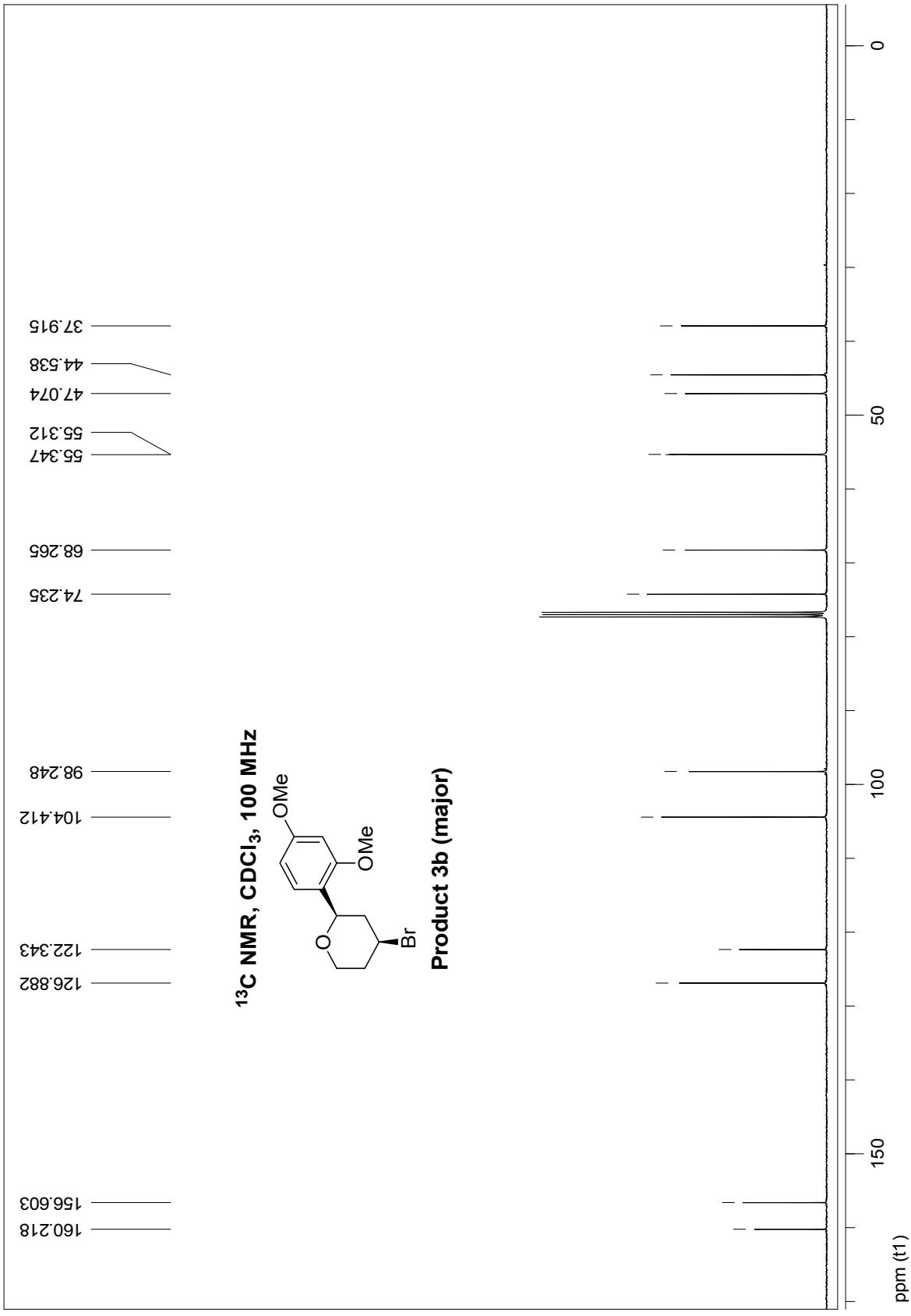
Product **3a** (Table 3, Entry **a**):



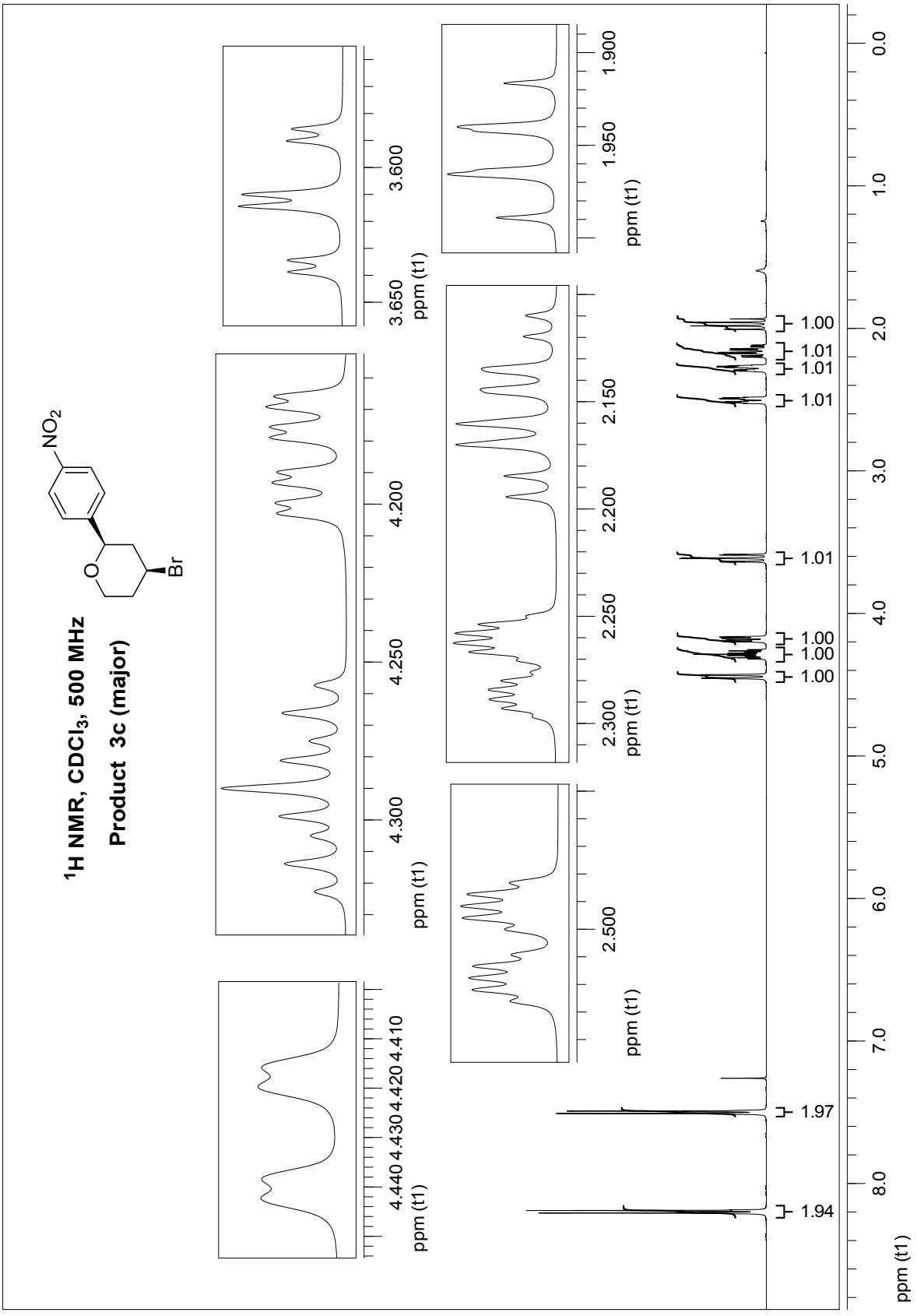

155.252
129.638
128.349
125.973
120.731
110.043
74.349
68.156
55.188
46.923
44.281
37.815
^{13}C NMR, CDCl$_3$, 75 MHz
Product 3a (major)
OMe
O
Br
0
50
100
150
ppm (t1)

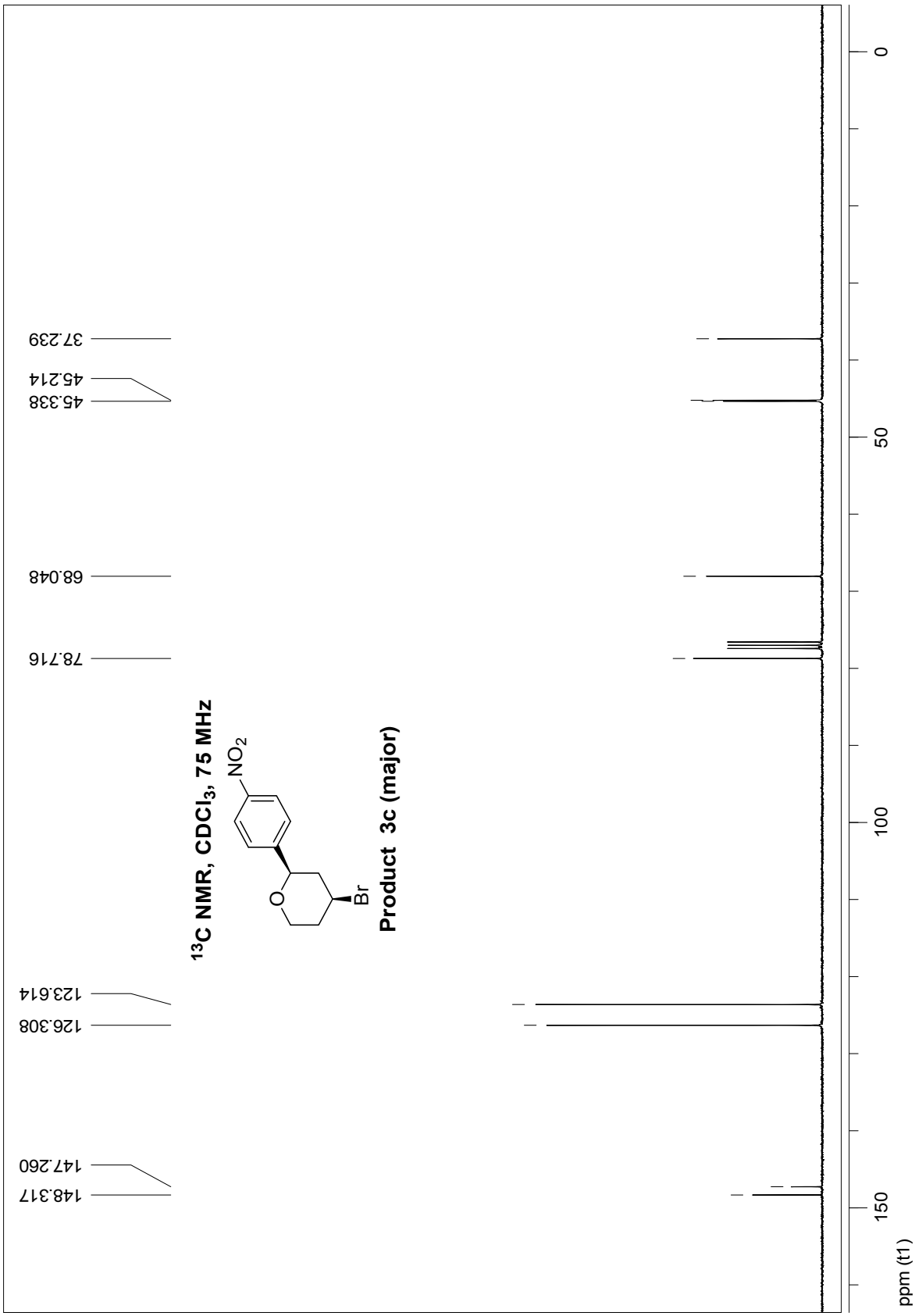
Product **3b** (Table 3, Entry **b**):



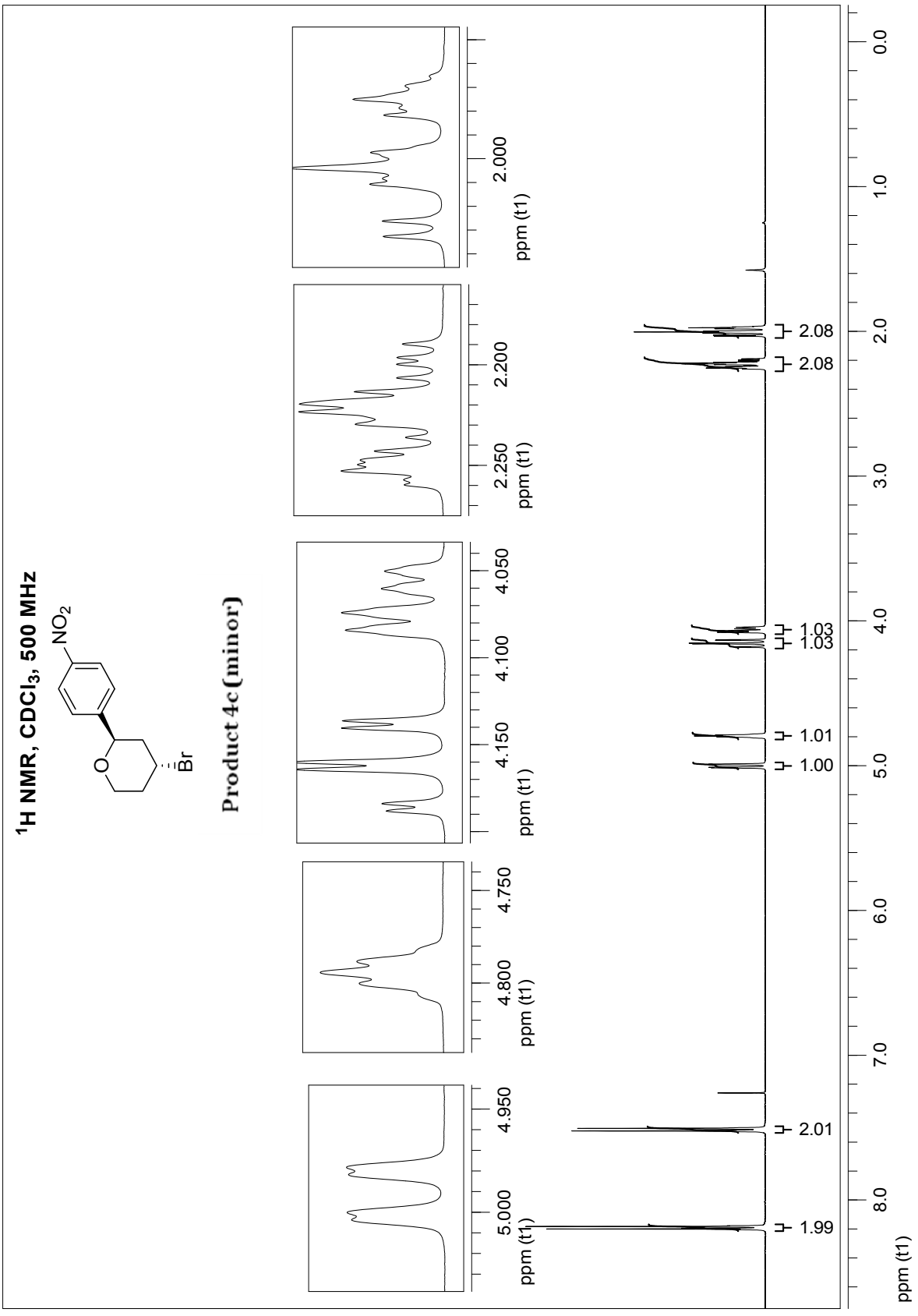


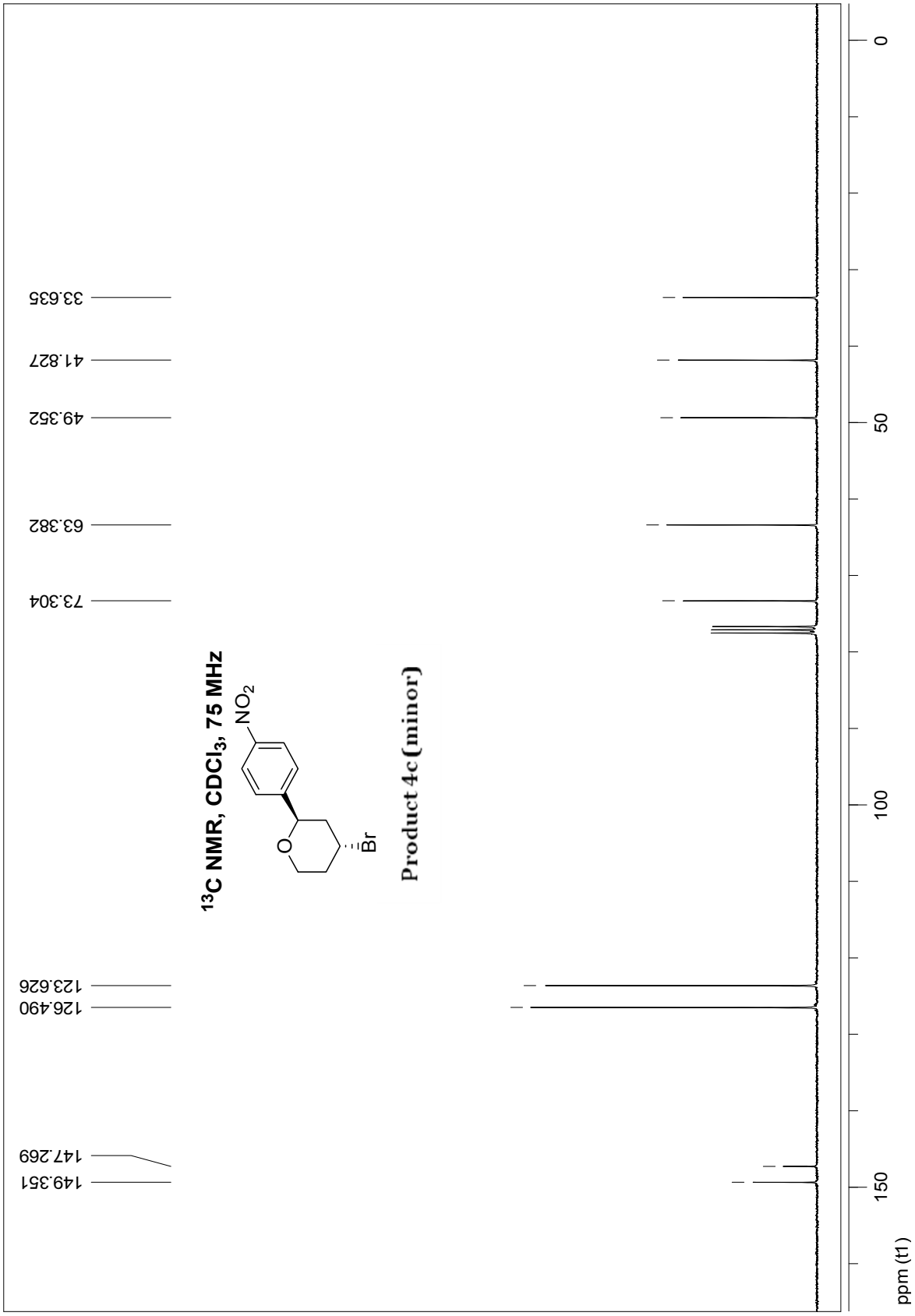
Product **3c** (Table 3, Entry **c**):



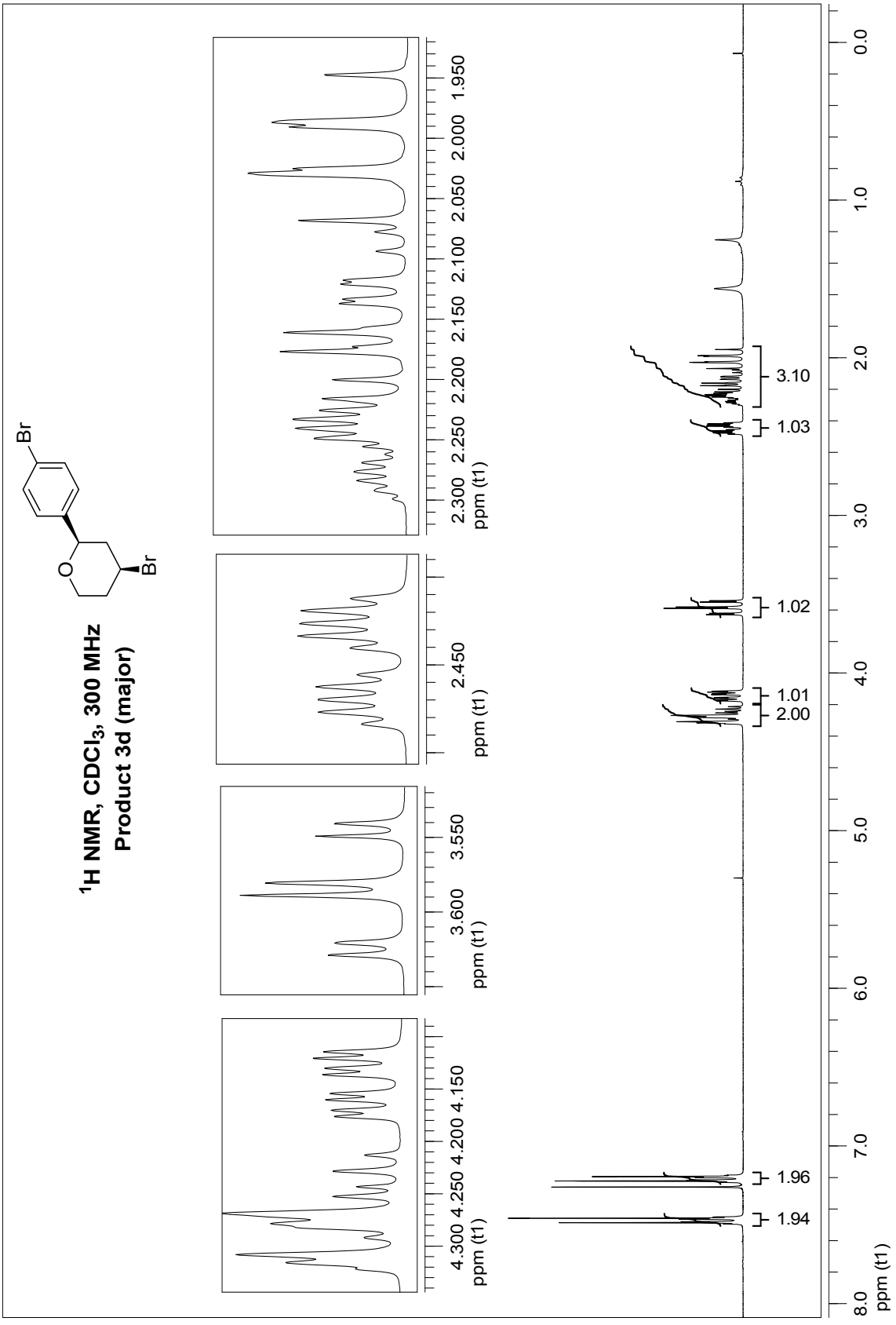

37.239
45.214
45.338
68.048
78.716
123.614
126.308
147.260
148.317
^{13}C NMR, $CDCl_3$, 75 MHz
NO_2
O
Br
Product 3c (major)
0
50
100
150
ppm (t1)

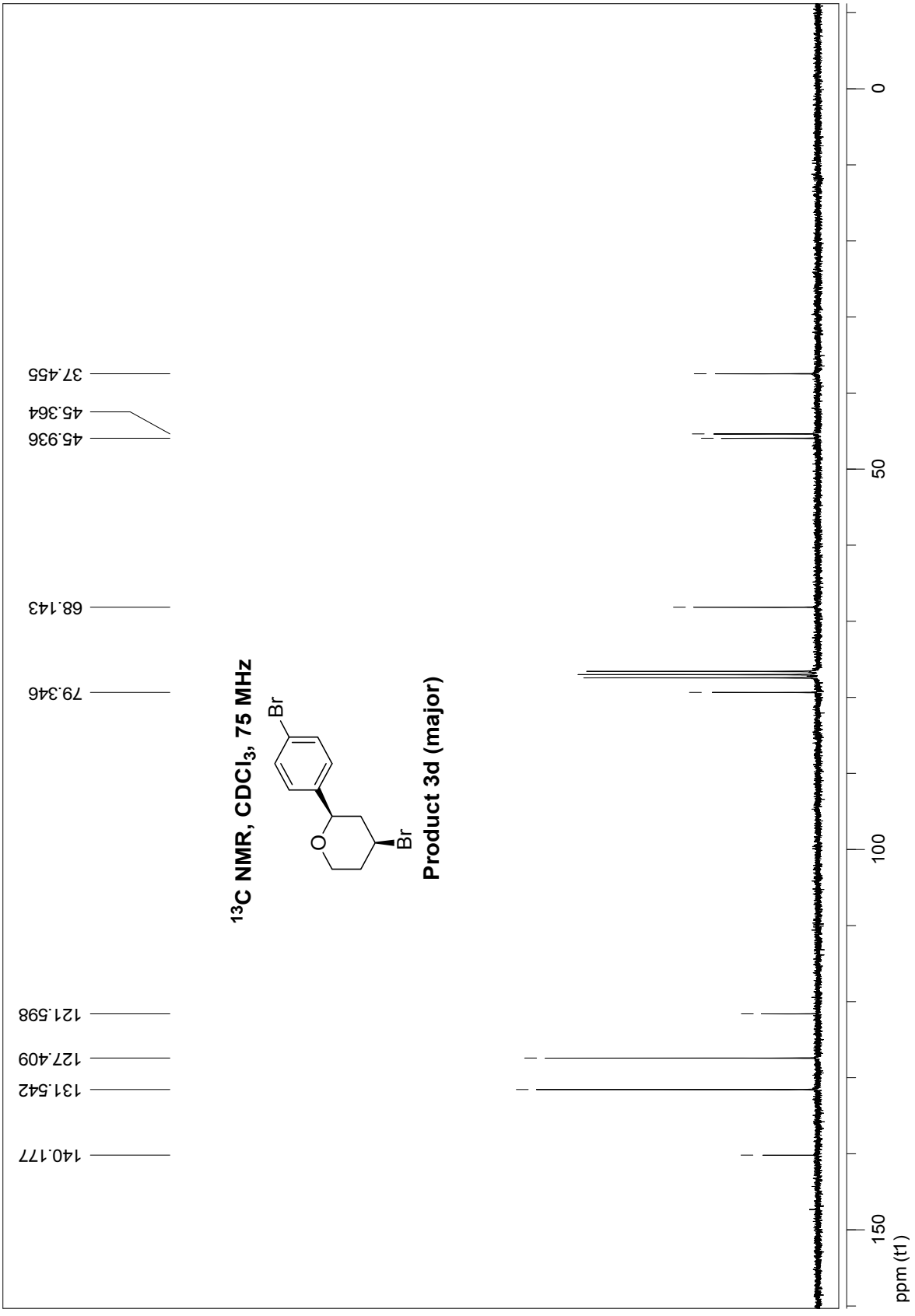
Product **4c** (Table 3, Entry **c**):



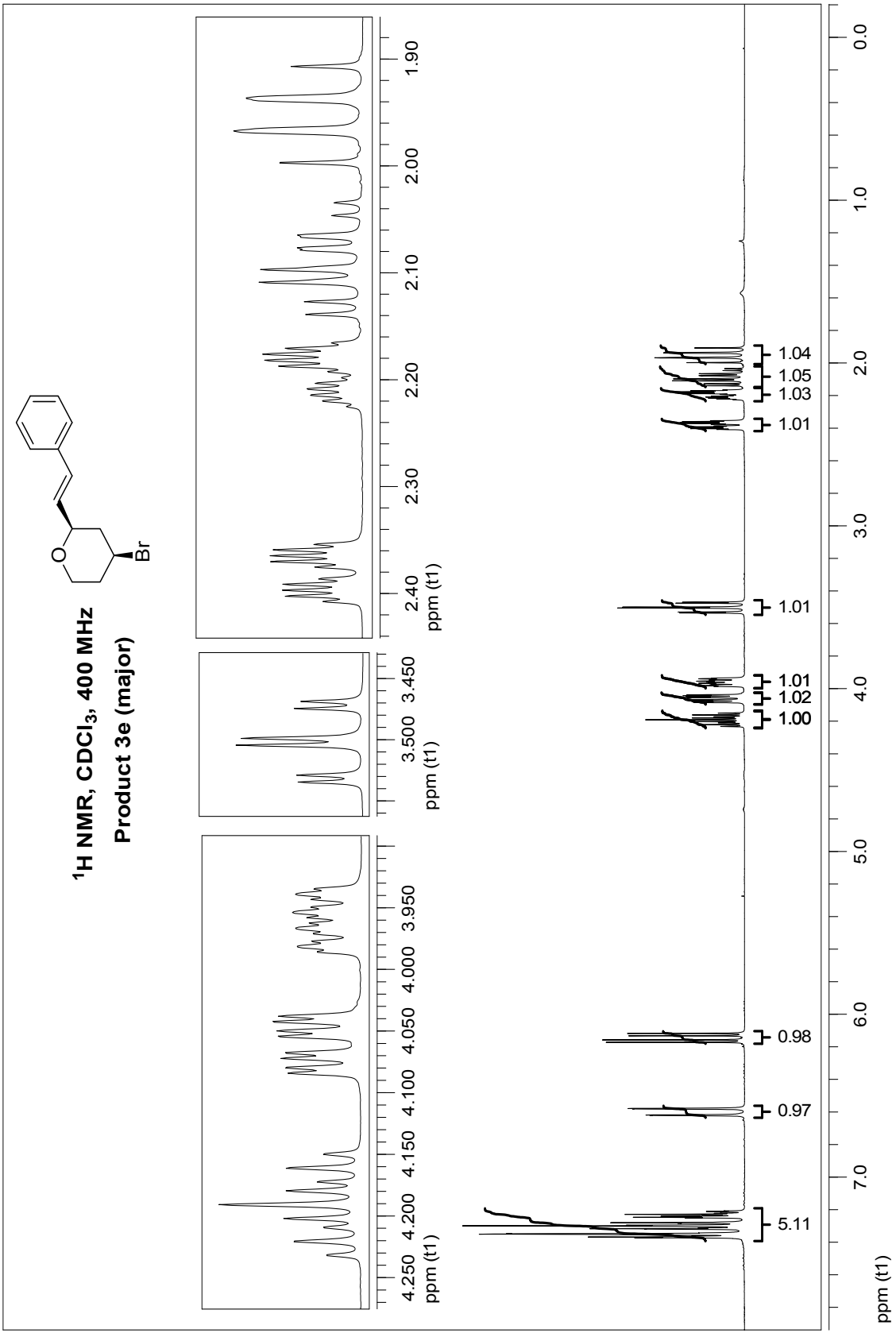


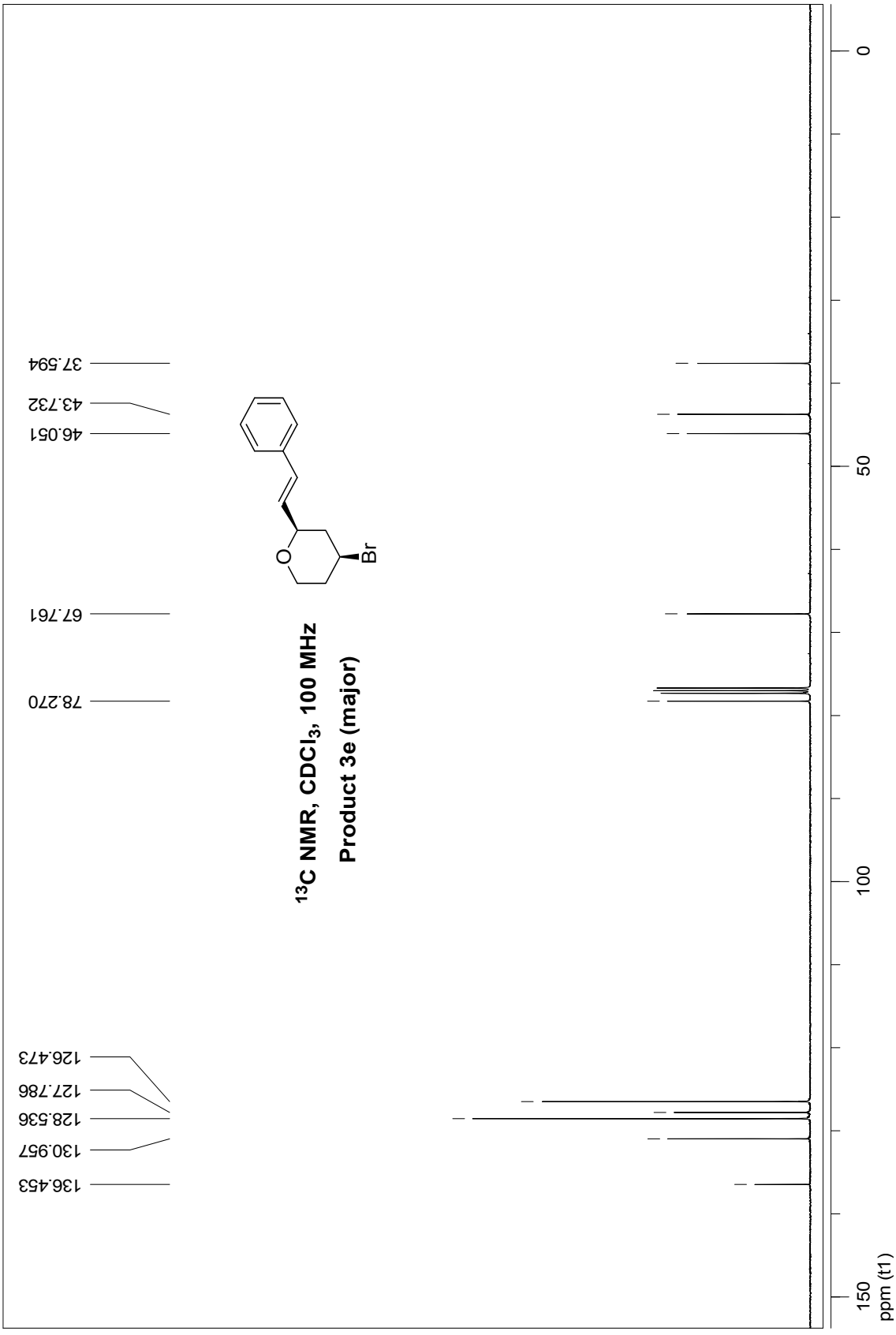
Product **3d** (Table 3, Entry **d**):



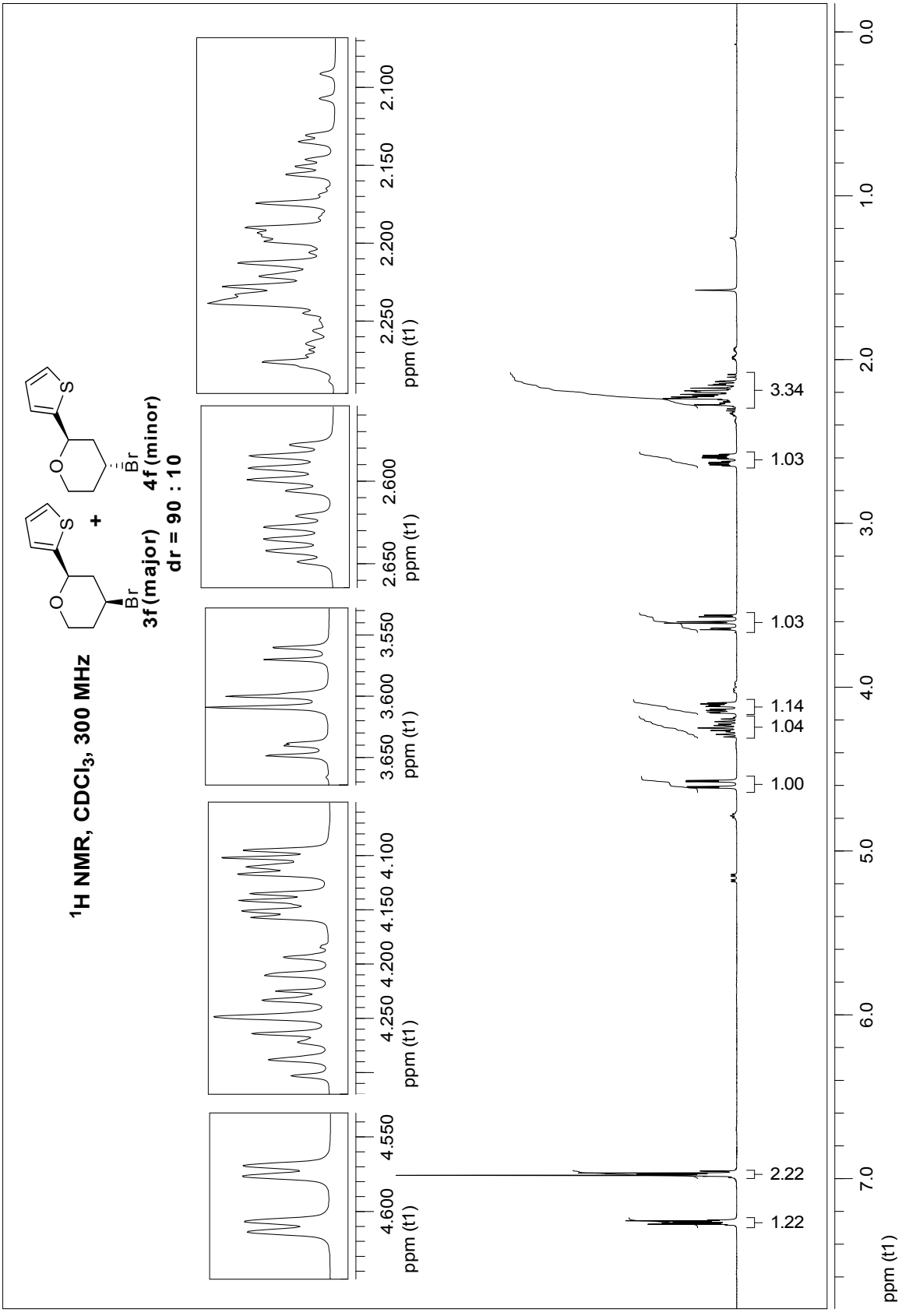


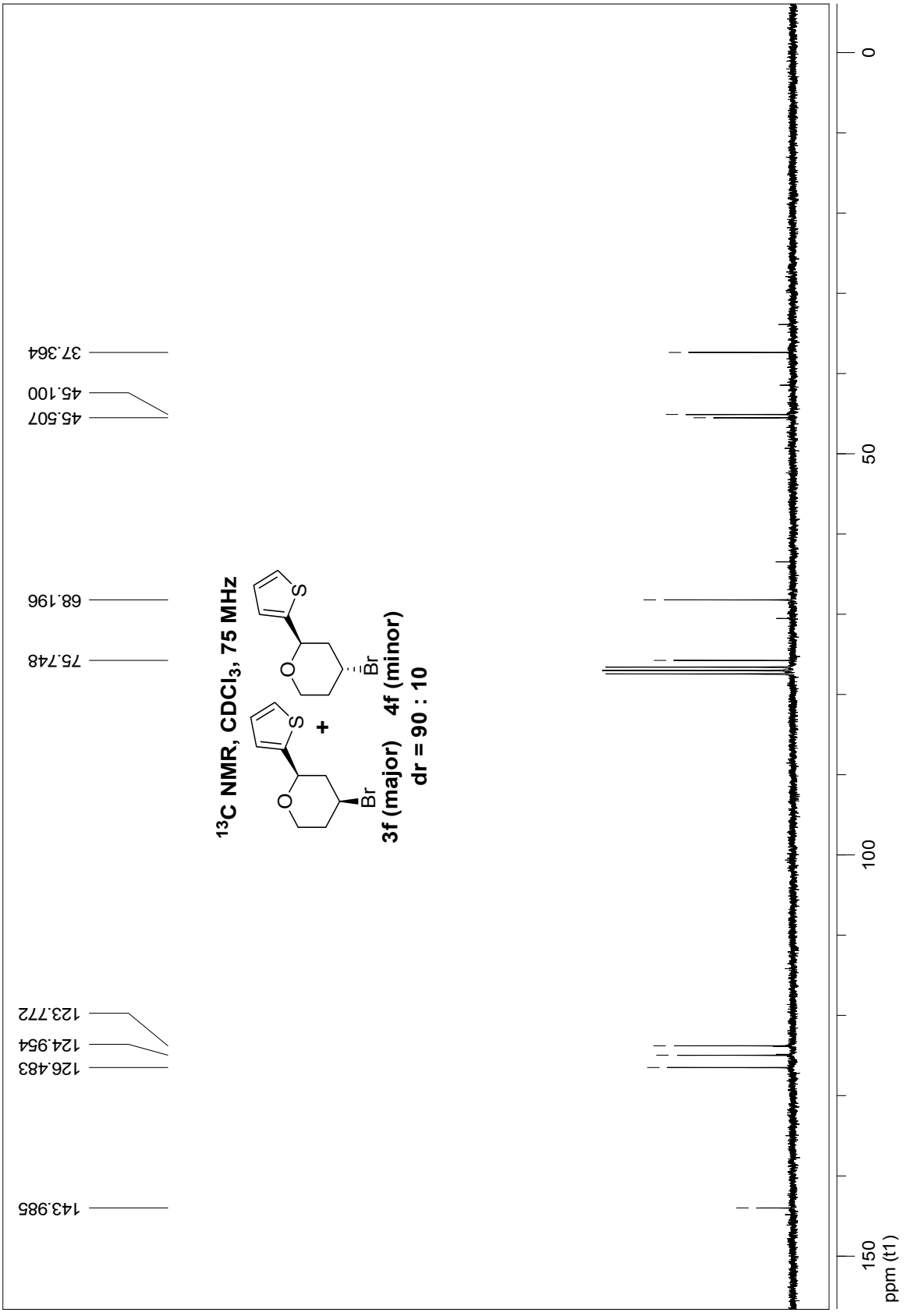
Product **3e** (Table 3, Entry **e**):



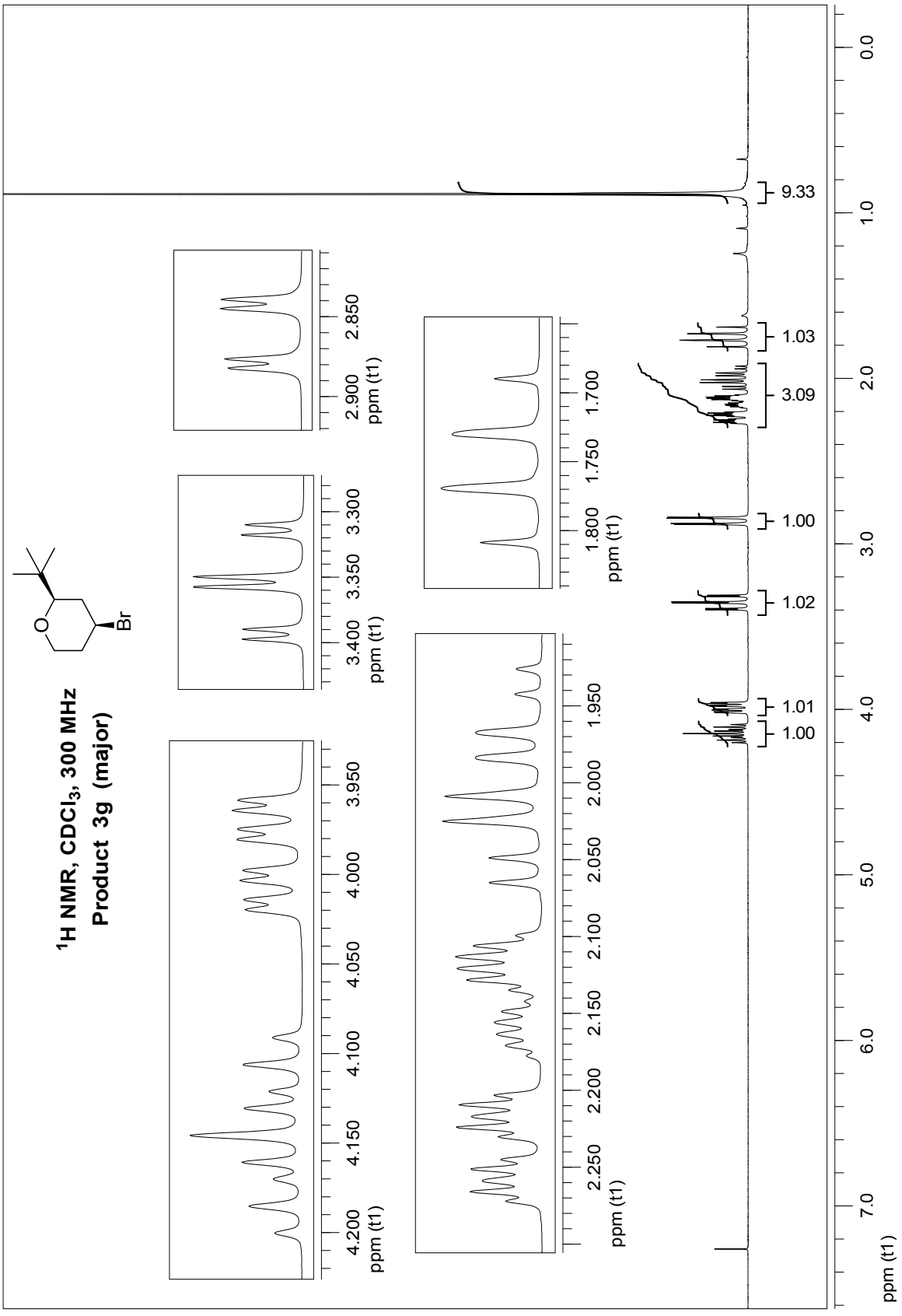

37.594
43.732
46.051
67.761
78.270
126.473
127.786
128.536
130.957
136.453
0
50
100
150
ppm (t1)
Br
O
^{13}C NMR, $CDCl_3$, 100 MHz
Product 3e (major)

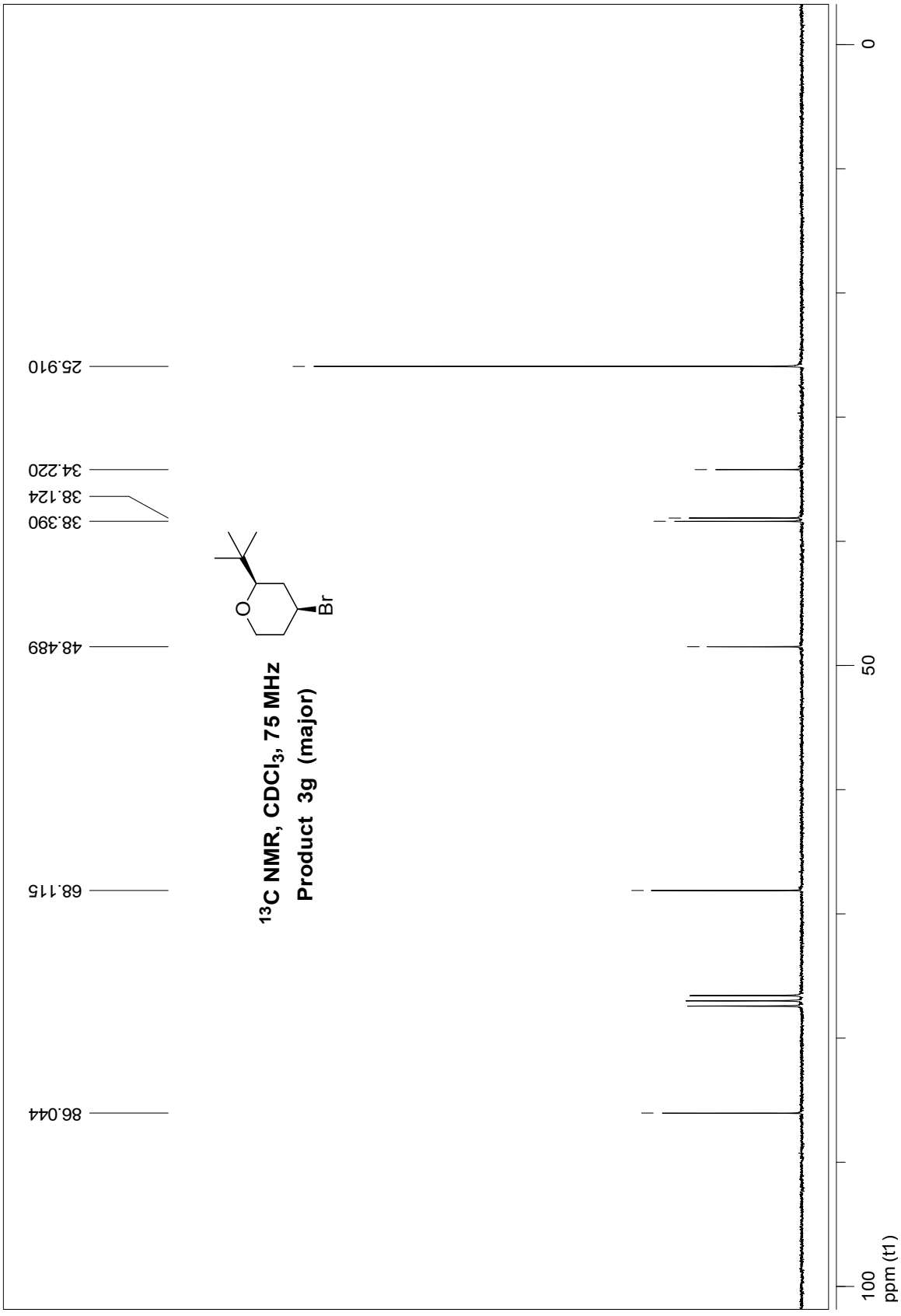
Product **3f** (Table 3, Entry **f**):



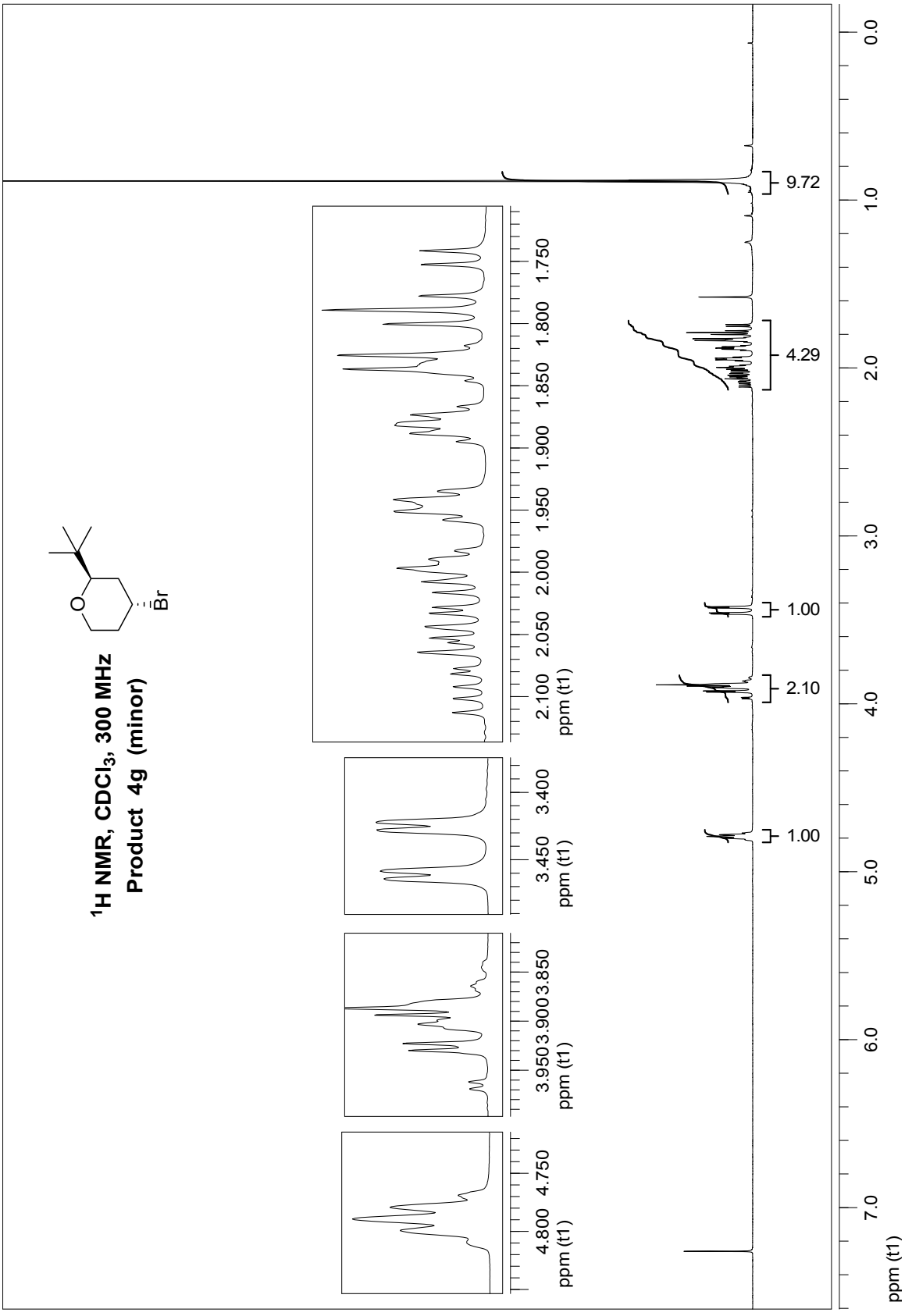

143.985
126.483
124.954
123.772
68.196
75.748
37.364
45.100
45.507
^{13}C NMR, $CDCl_3$, 75 MHz
3f (major) 4f (minor)
dr = 90 : 10
Br
Br
S
O
+
150
100
50
0
ppm (t1)

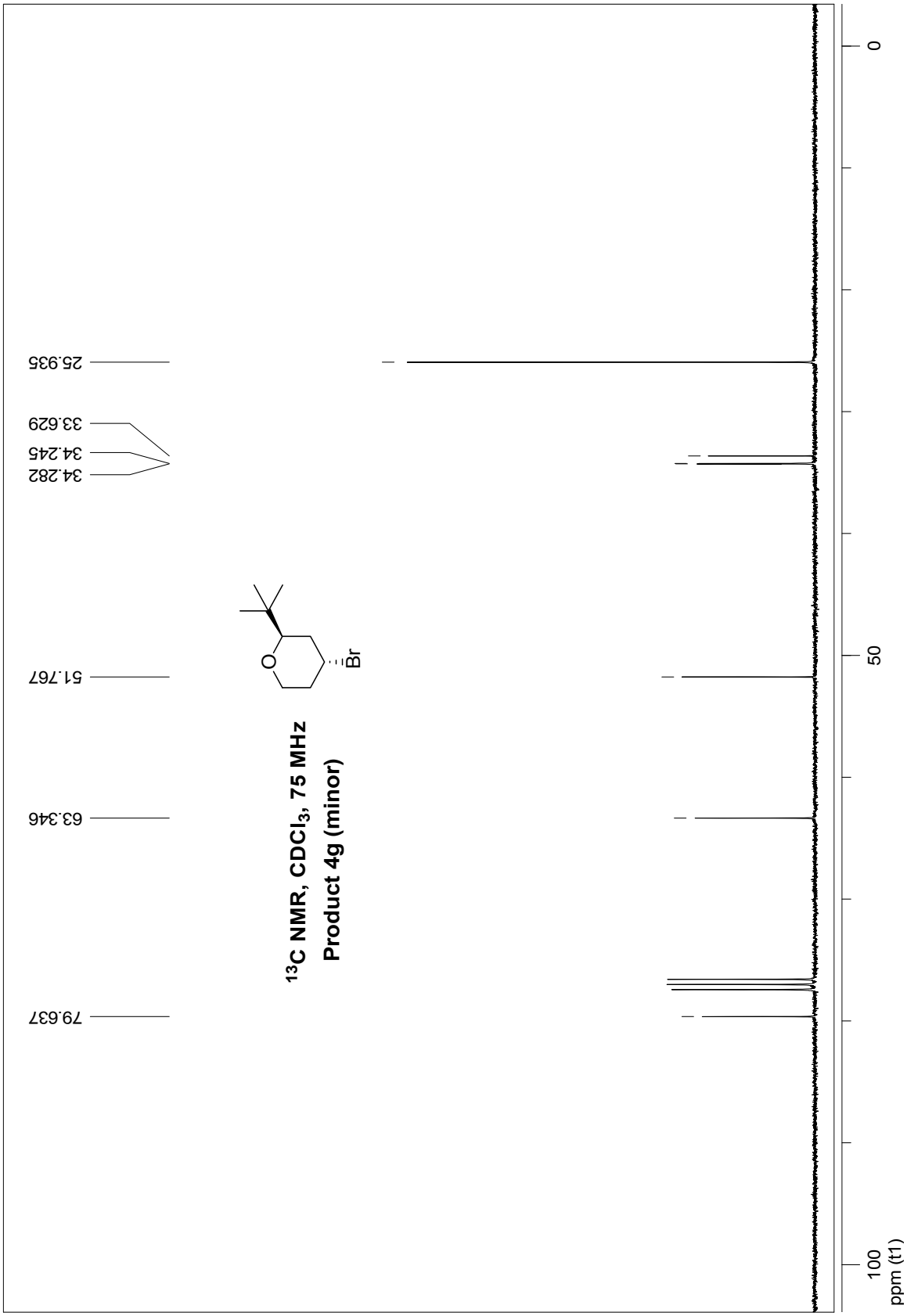
Product **3g** (Table 3, Entry **g**):



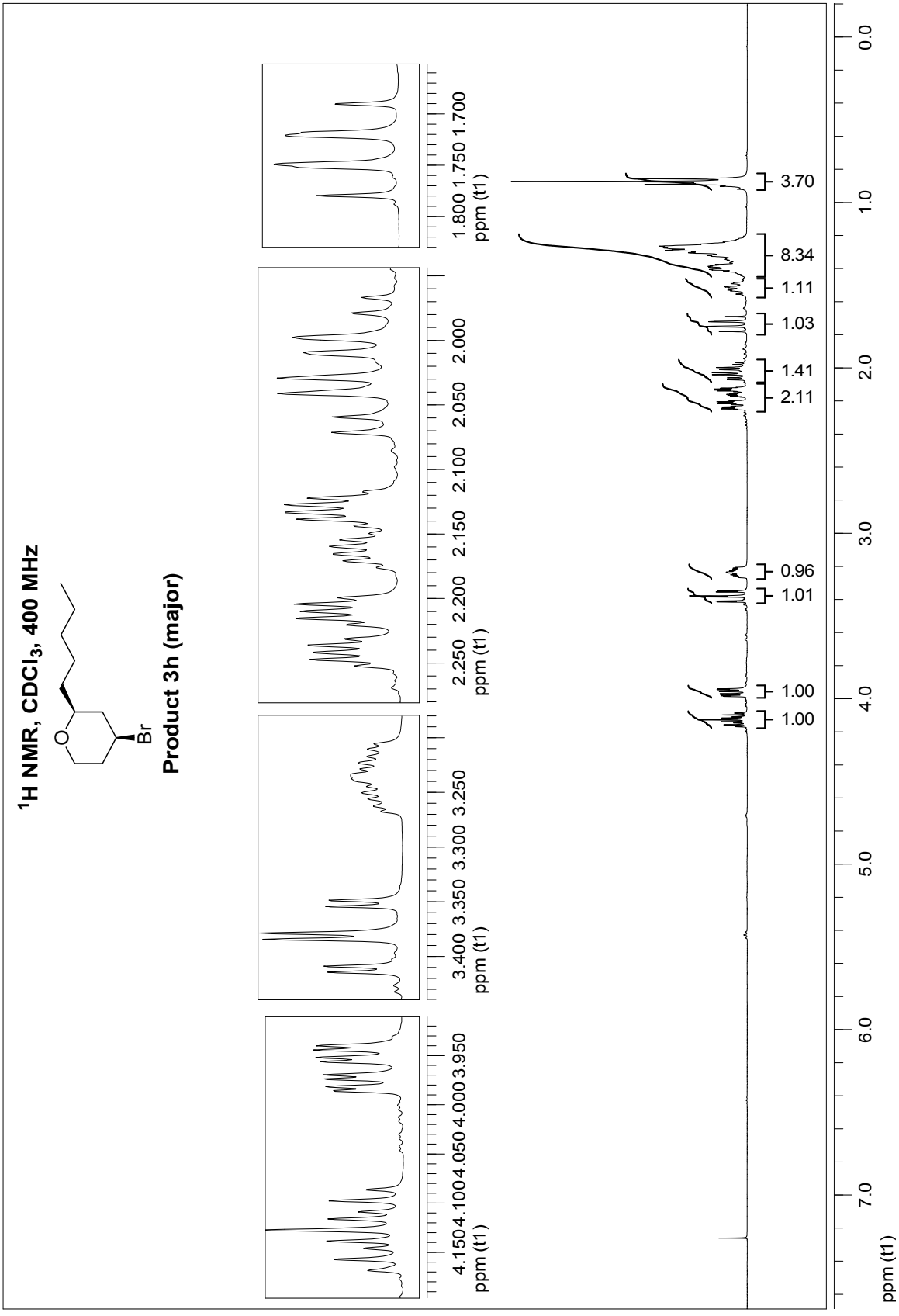


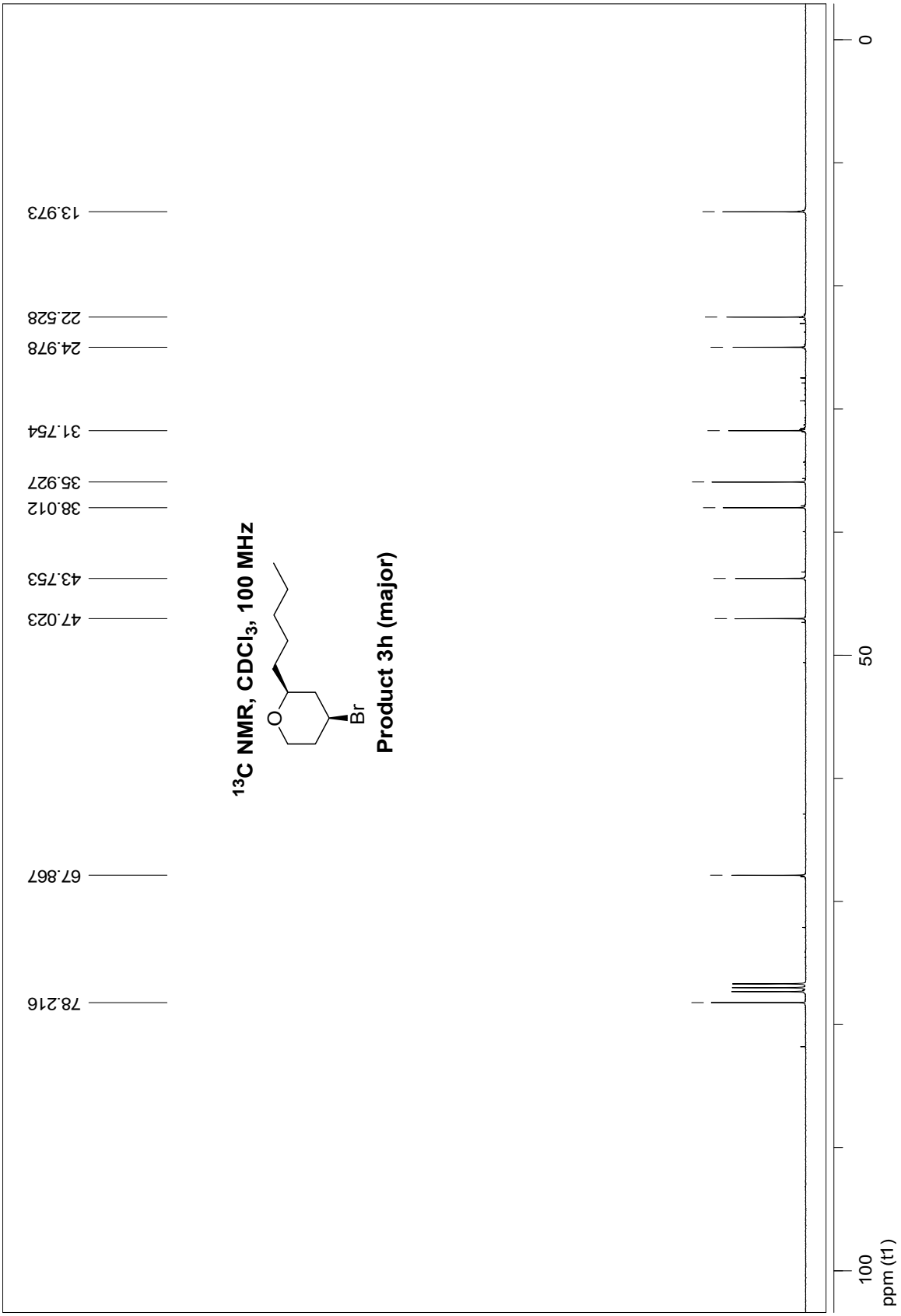
Product **4g** (Table 3, Entry **g**):



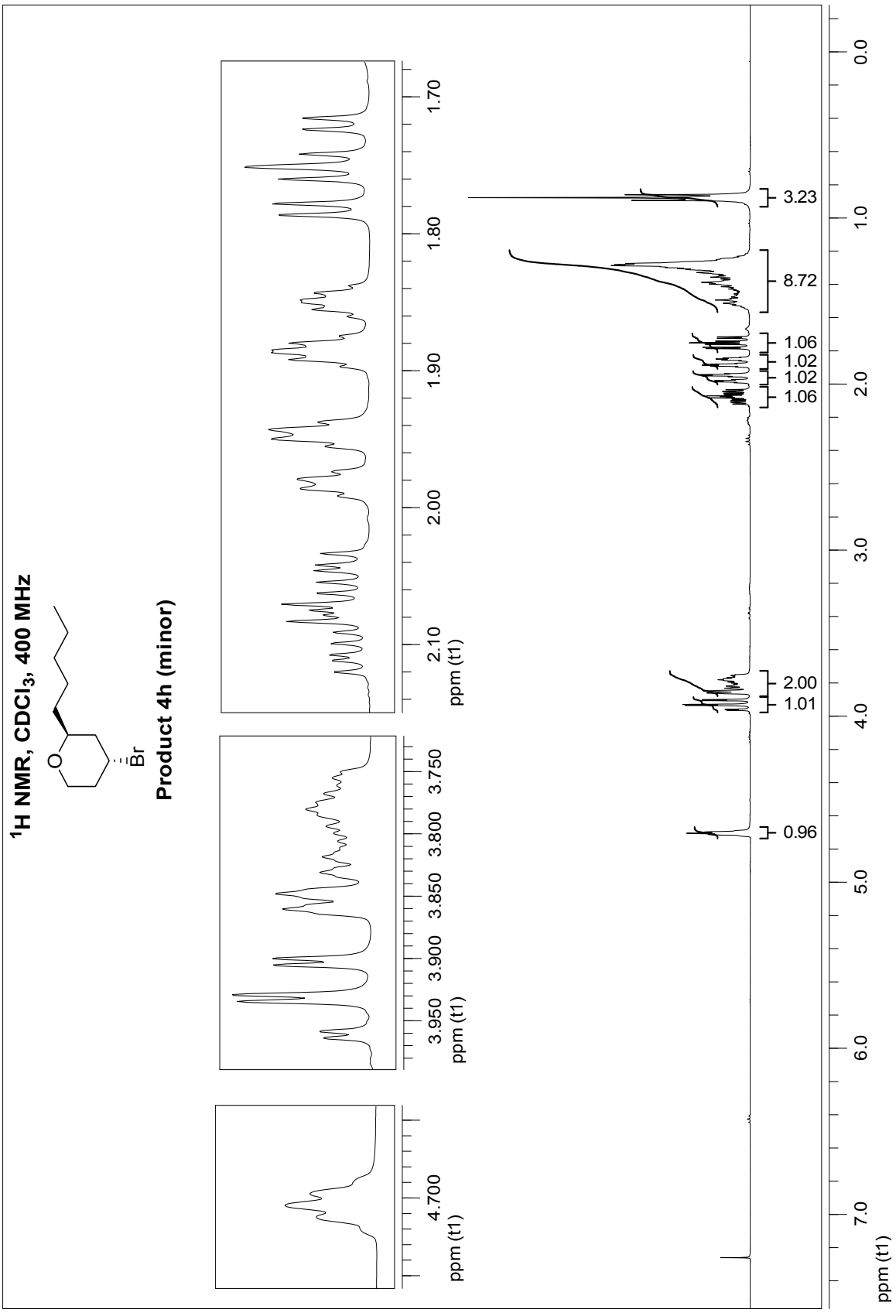


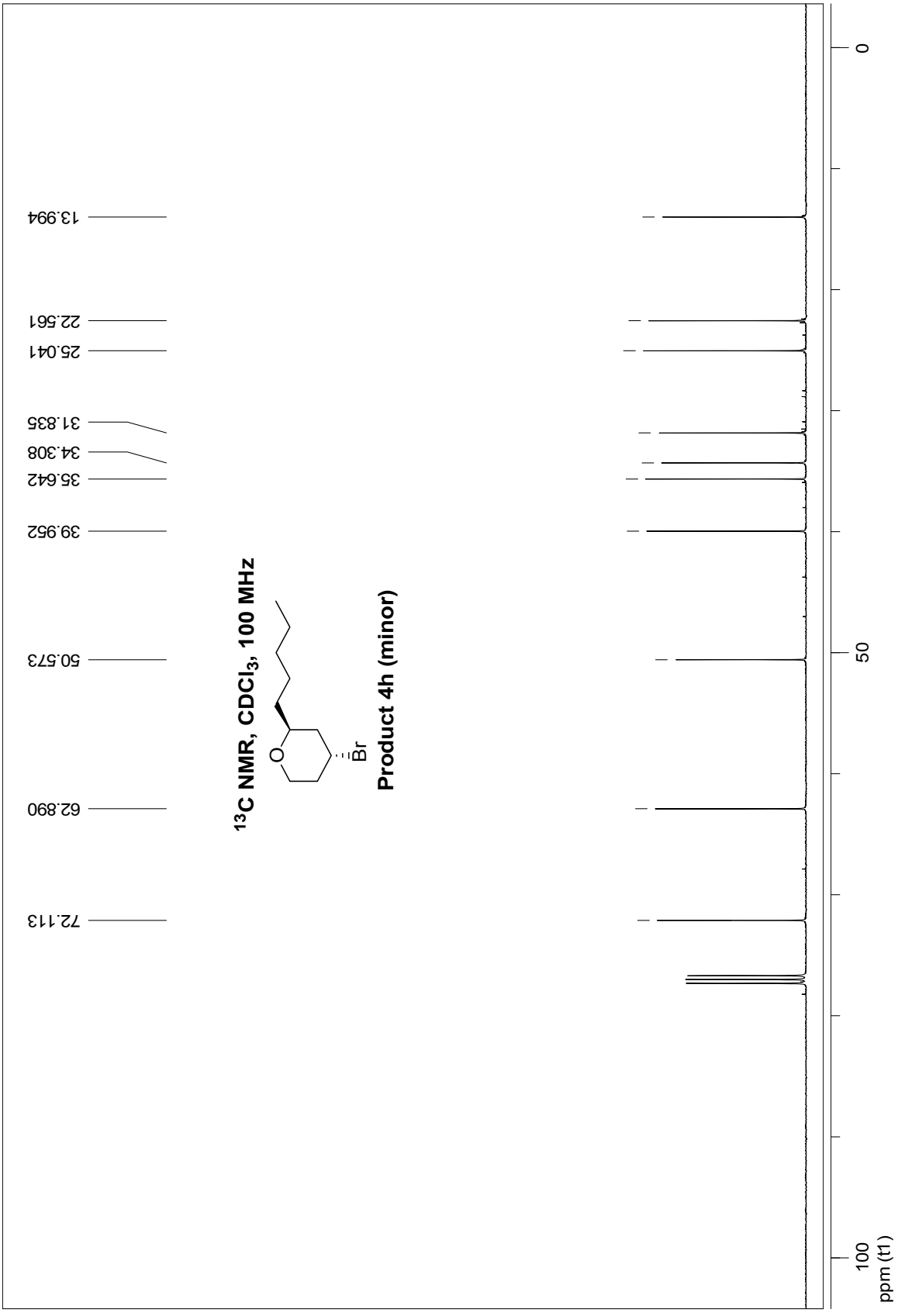
Product **3h** (Table 3, Entry **h**):



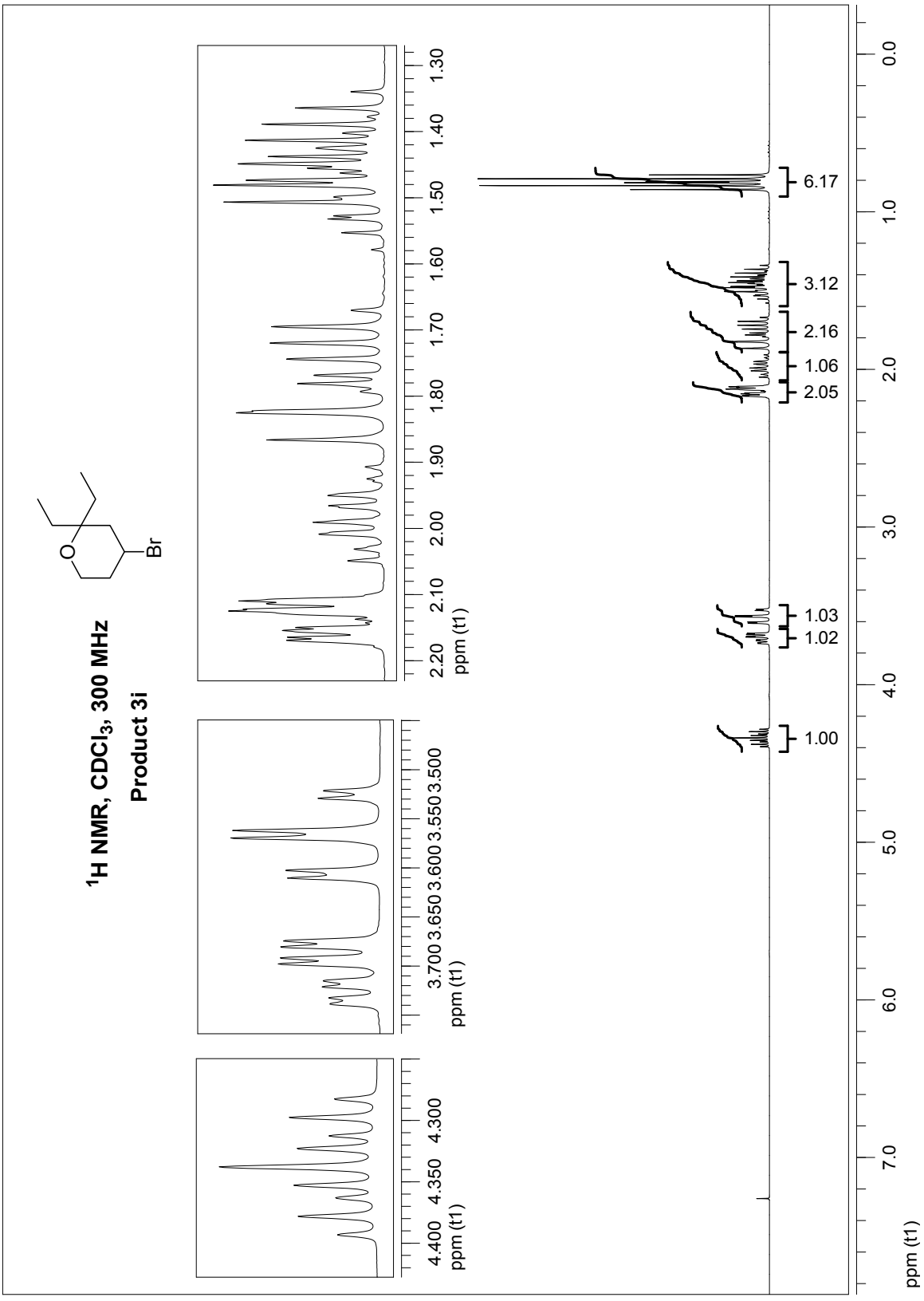


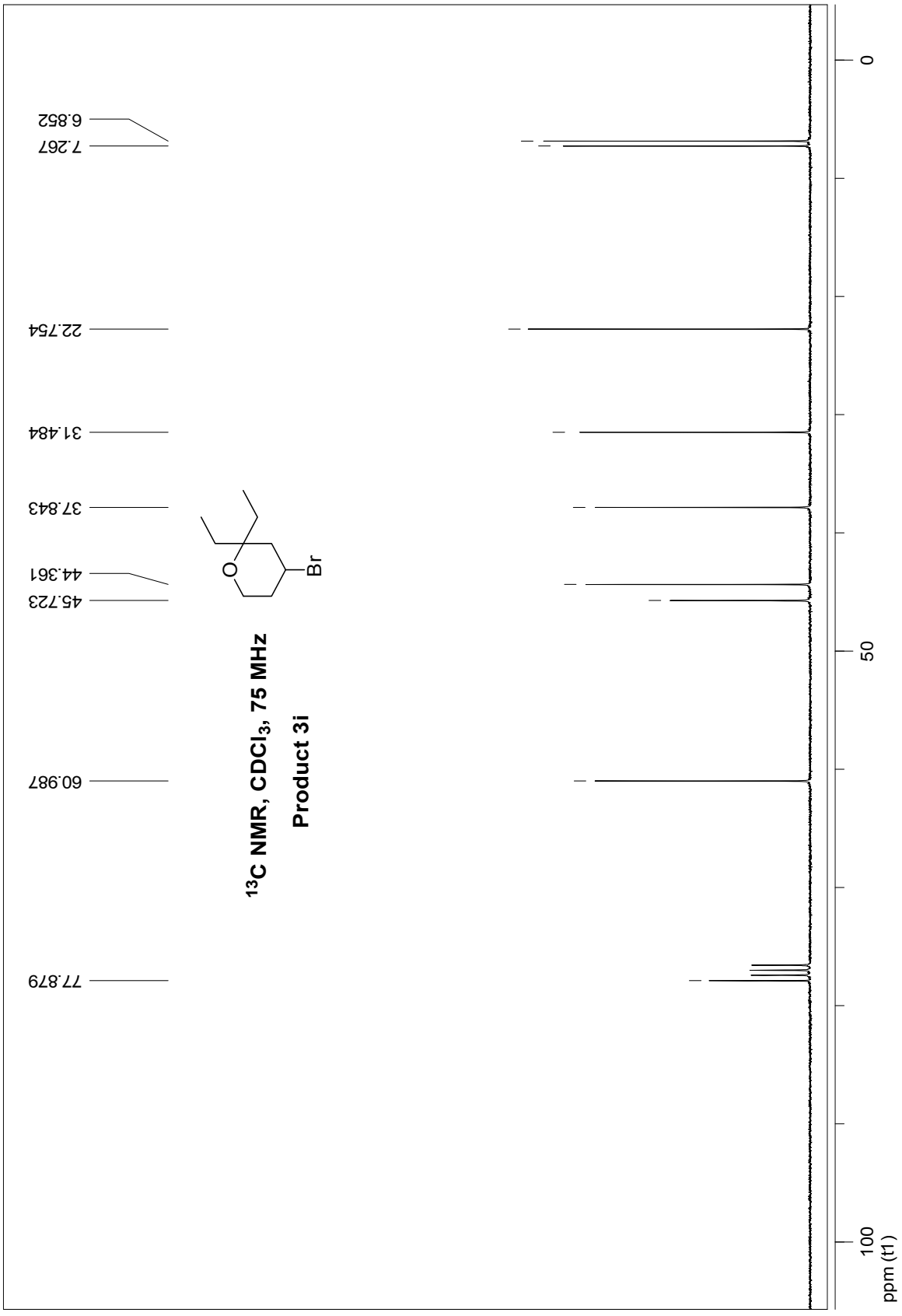
Product **4h** (Table 3, Entry **h**):



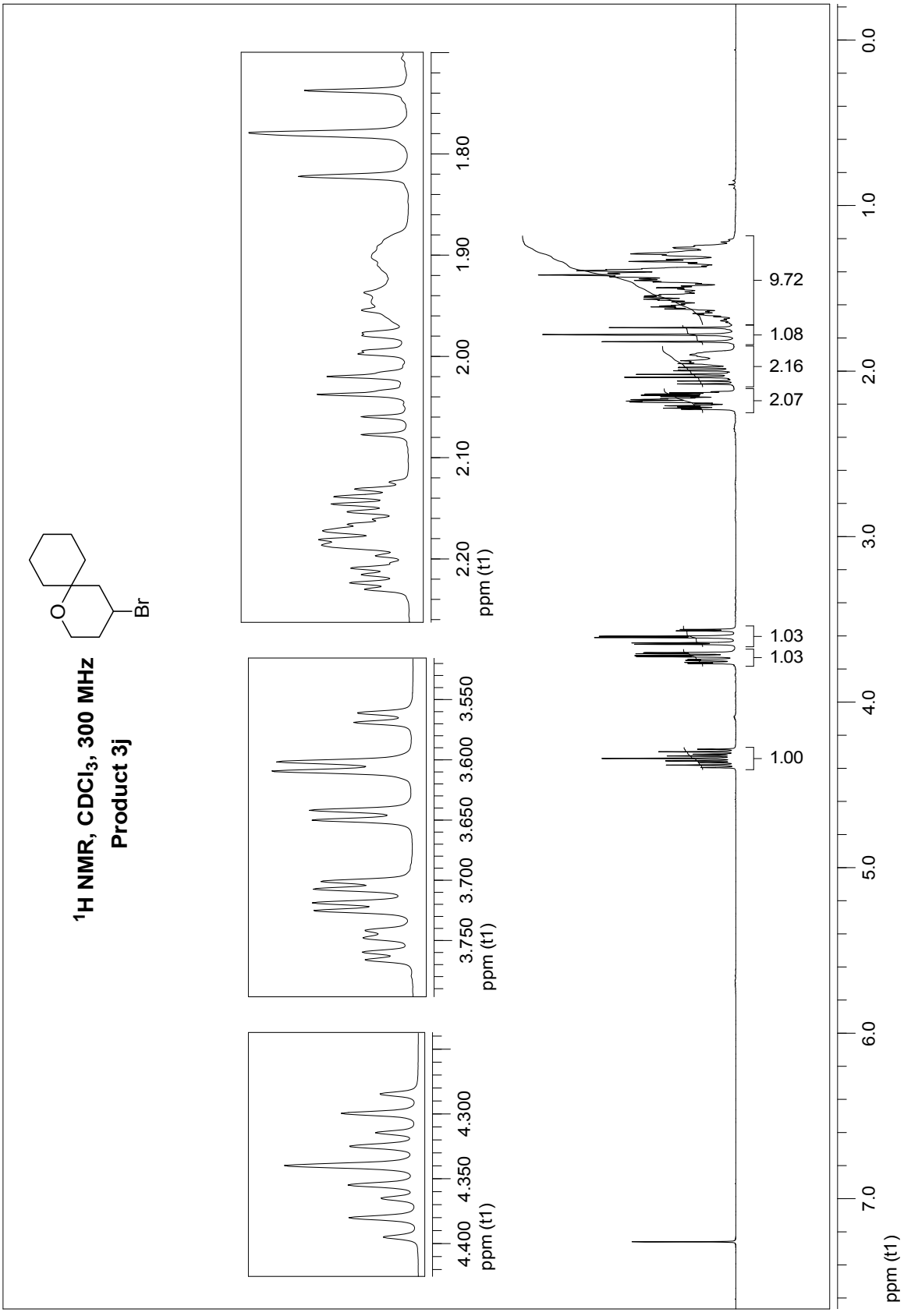

13.994
22.561
25.041
31.835
34.308
35.642
39.952
50.573
62.890
72.113
^{13}C NMR, $CDCl_3$, 100 MHz
Br
Product 4h (minor)
0
50
100
ppm (t1)

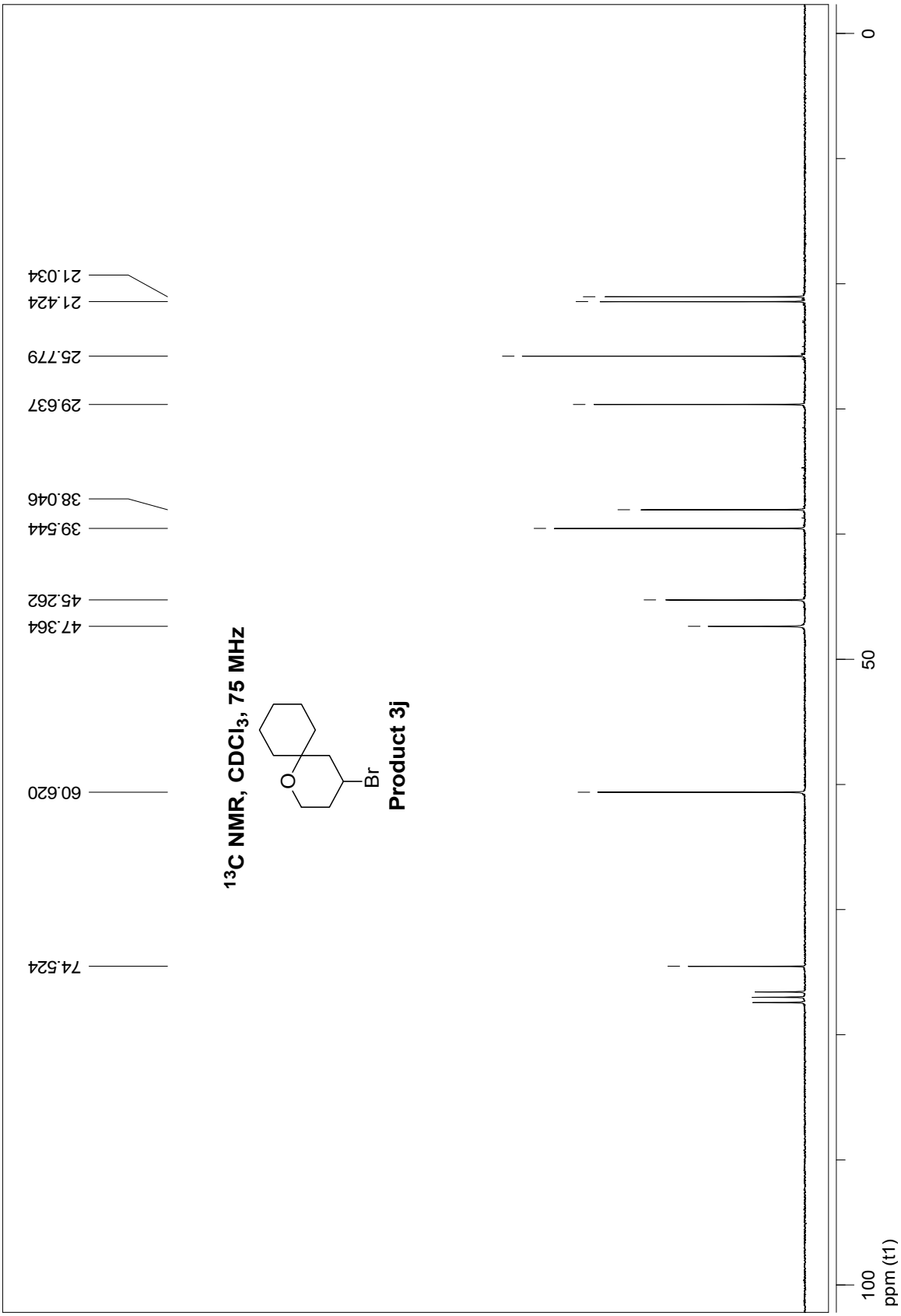
Product **3i** (Table 3, Entry **i**):



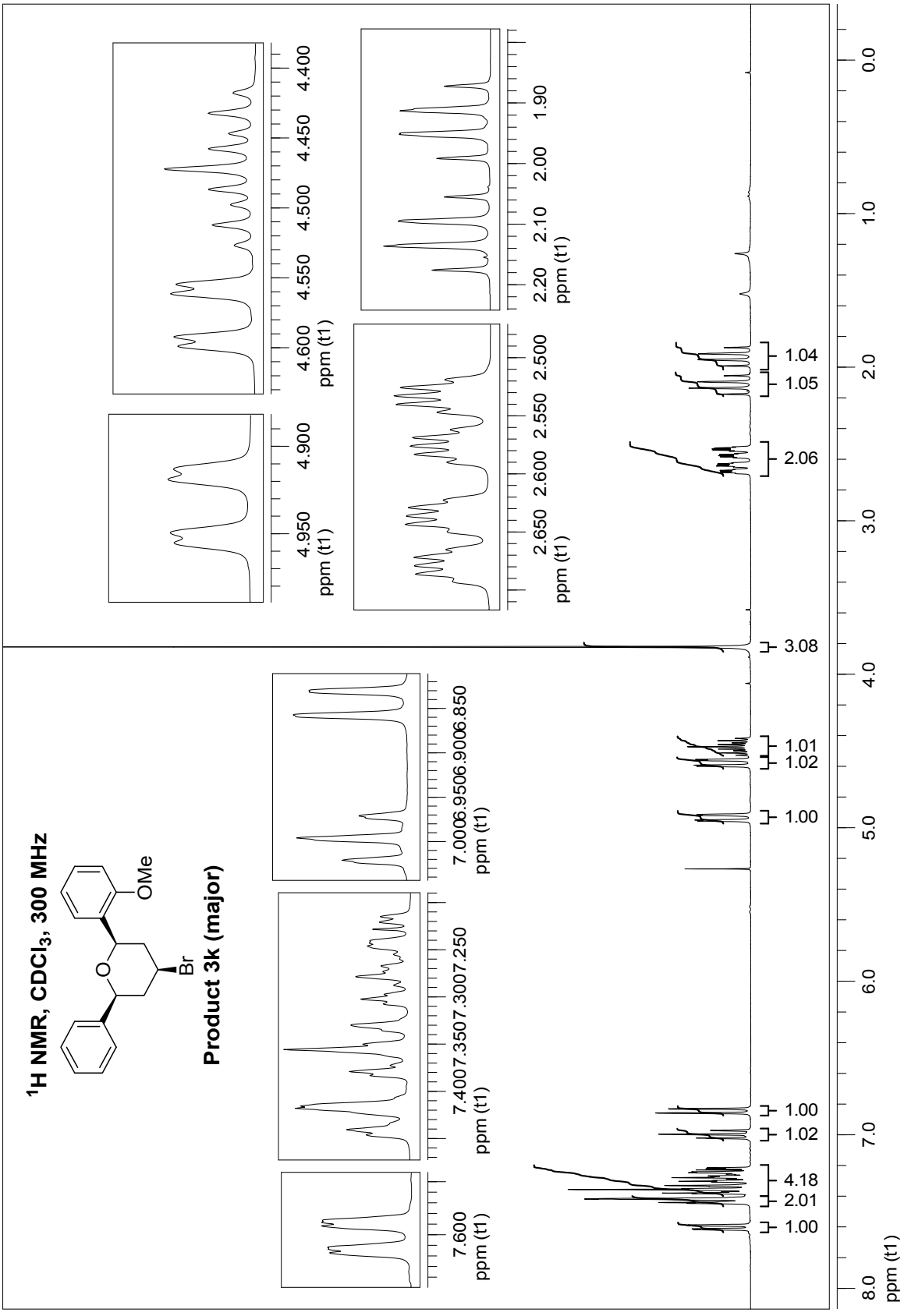


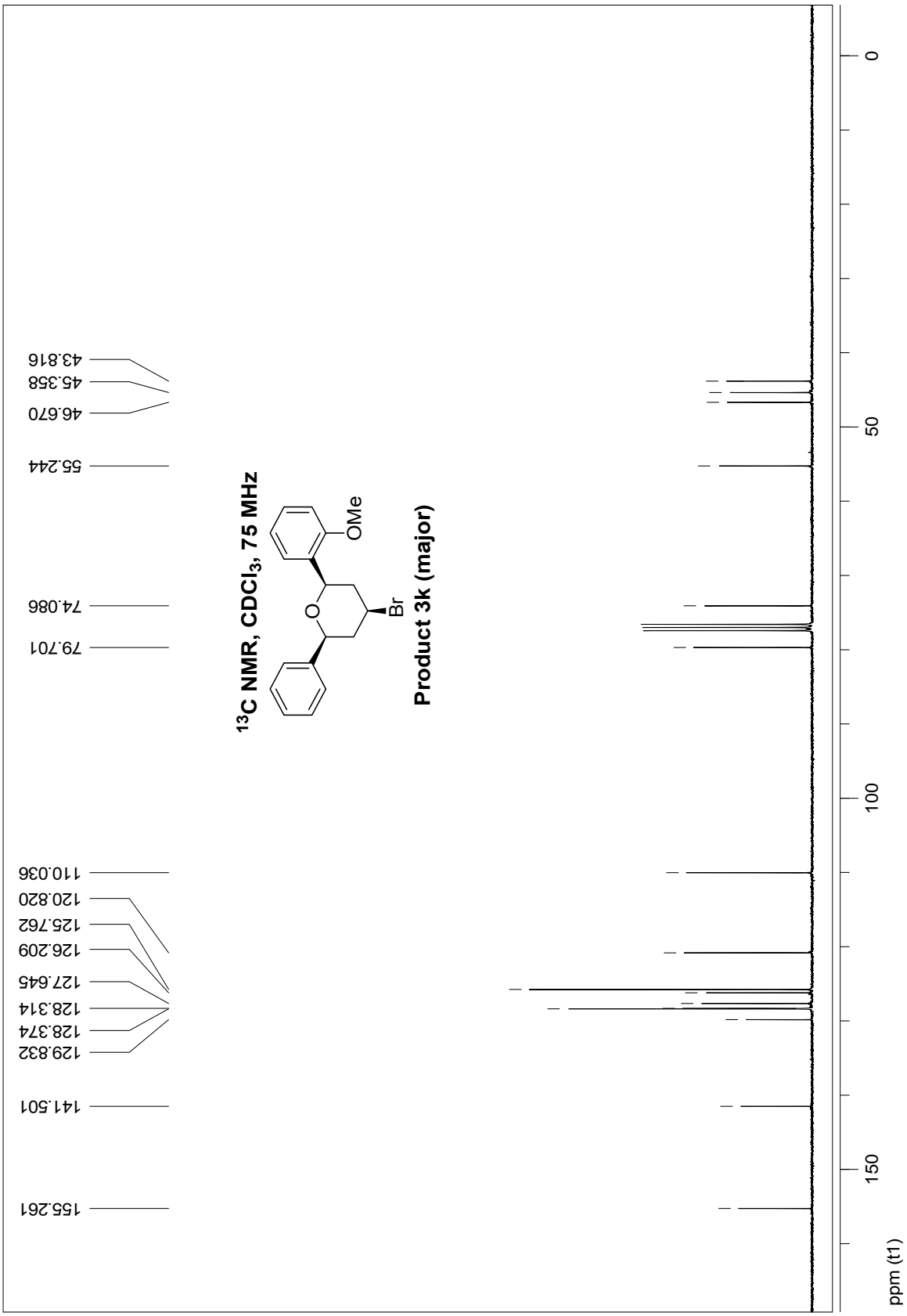
Product **3j** (Table 3, Entry **j**):



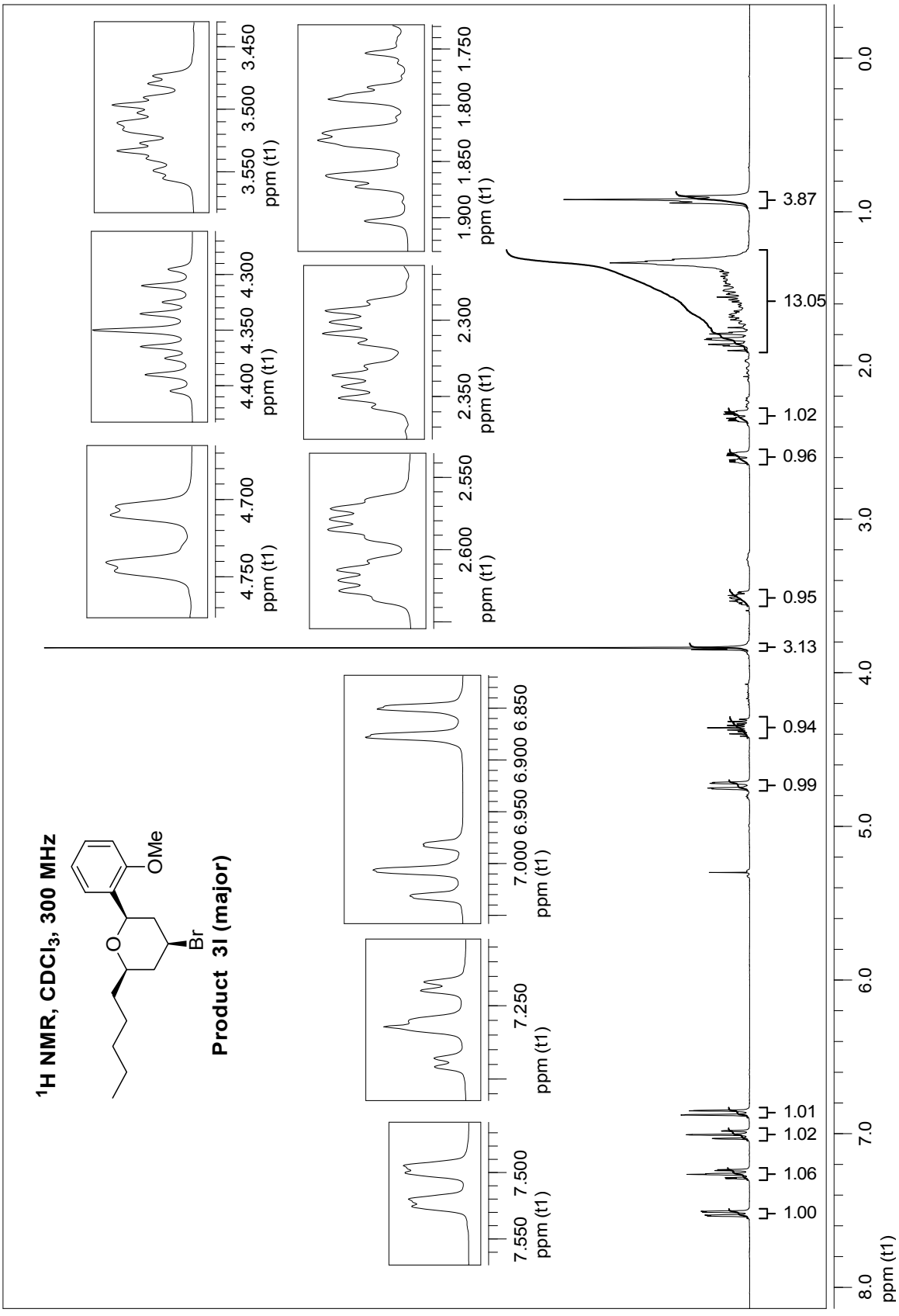


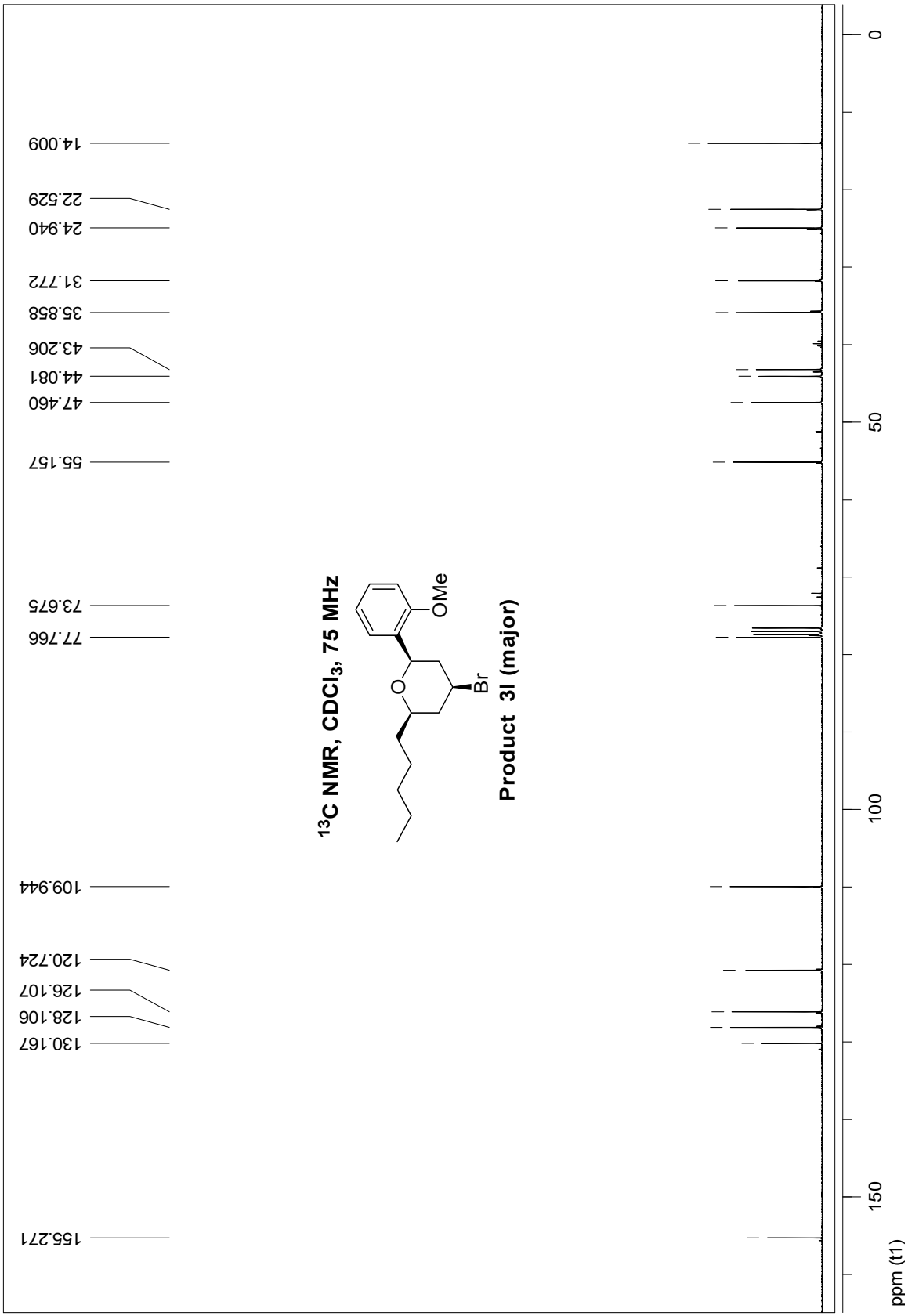
Product **3k** (Table 3, Entry **k**):



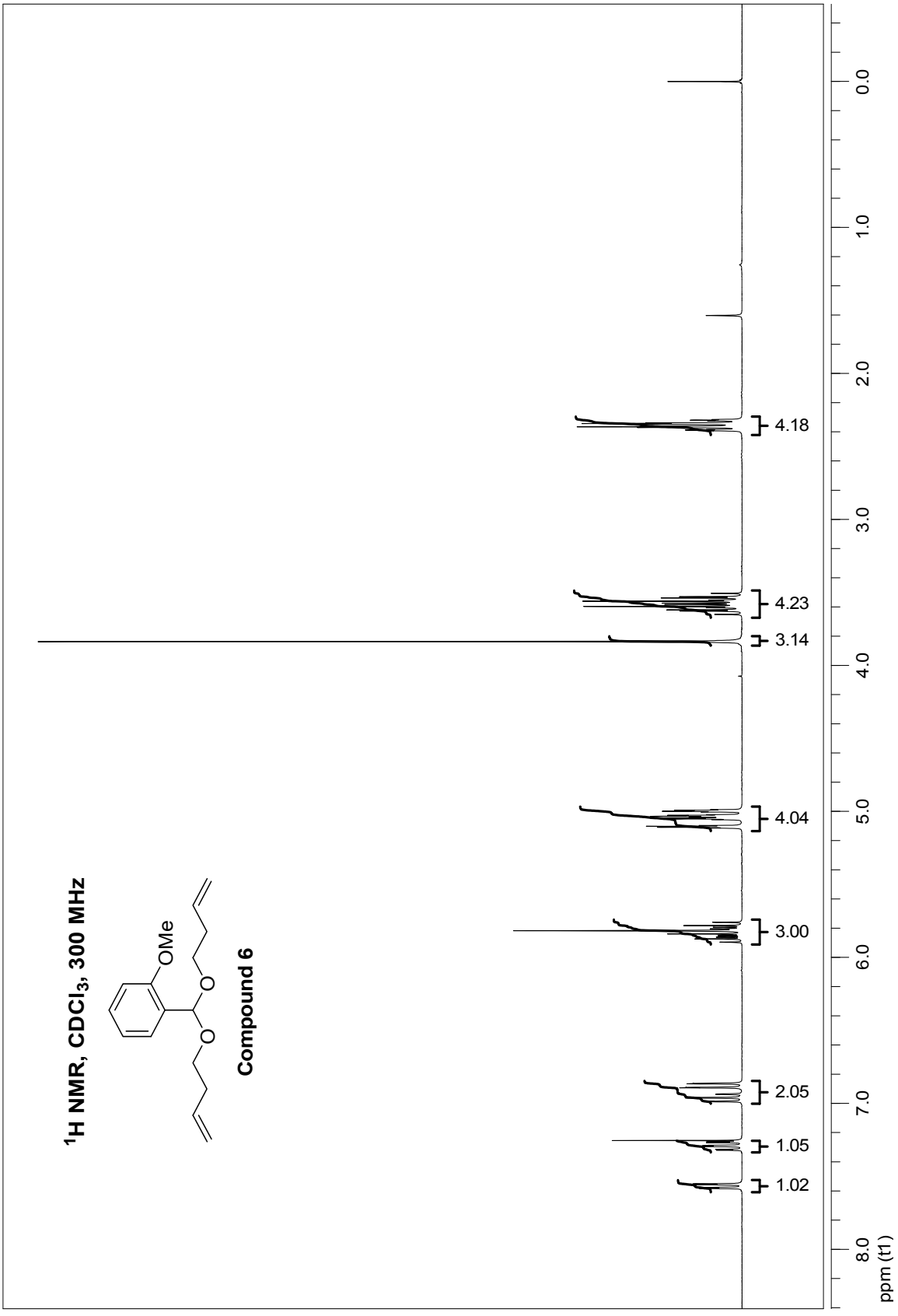

^{13}C NMR, $CDCl_3$, 75 MHz
Product 3k (major)
OMe
Br
O
43.816
45.358
46.670
55.244
74.086
79.701
110.036
120.820
125.762
126.209
127.645
128.314
128.374
129.832
141.501
155.261
0
50
100
150
ppm (t1)

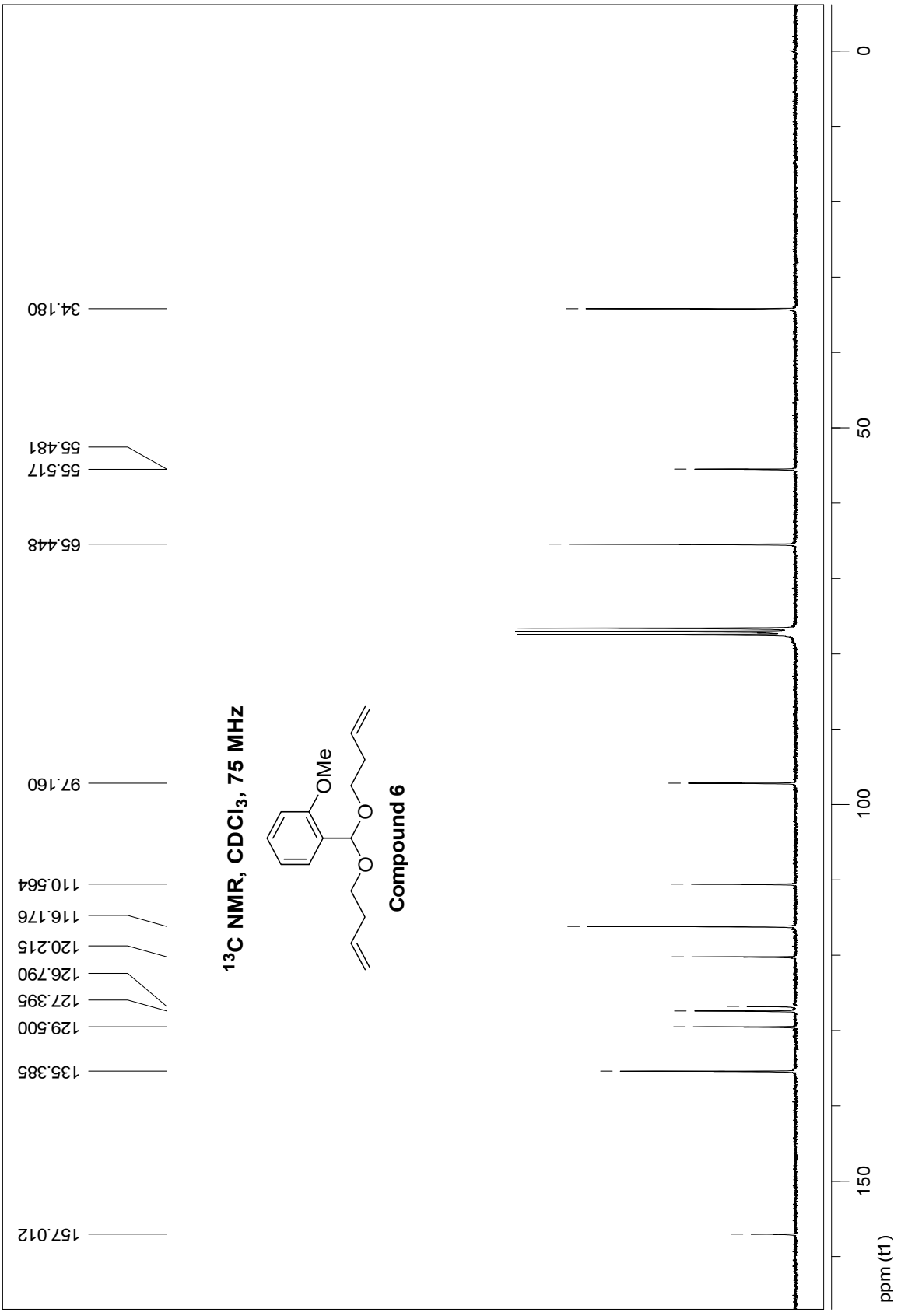
Product **3l** (Table 3, Entry **l**):




14.009
22.529
24.940
31.772
35.858
43.206
44.081
47.460
55.157
73.675
77.766
109.944
120.724
126.107
128.106
130.167
155.271
0
50
100
150
ppm (t1)
^{13}C NMR, CDCl$_3$, 75 MHz
OMe
O
Br
Product 3l (major)

Compound **6** (Table 4)




157.012
135.385
129.500
127.395
126.790
120.215
116.176
110.564
97.160
65.448
55.517
55.481
34.180
^{13}C NMR, $CDCl_3$, 75 MHz
OMe
O
O
Compound 6
0
50
100
150
ppm (t1)