

Atroposelective Formation of Dibenz[*c*,*e*]azepines via Intramolecular Direct Arylation with Centre-axis Chirality Transfer

Caroline A. Cheetham, Richard S. Massey, Silvain L. Pira, Robin G. Pritchard and Timothy W. Wallace*

School of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK

*Corresponding author; e-mail: tim.wallace@manchester.ac.uk; fax +44 (0) 161 275 4939

Supplementary Information

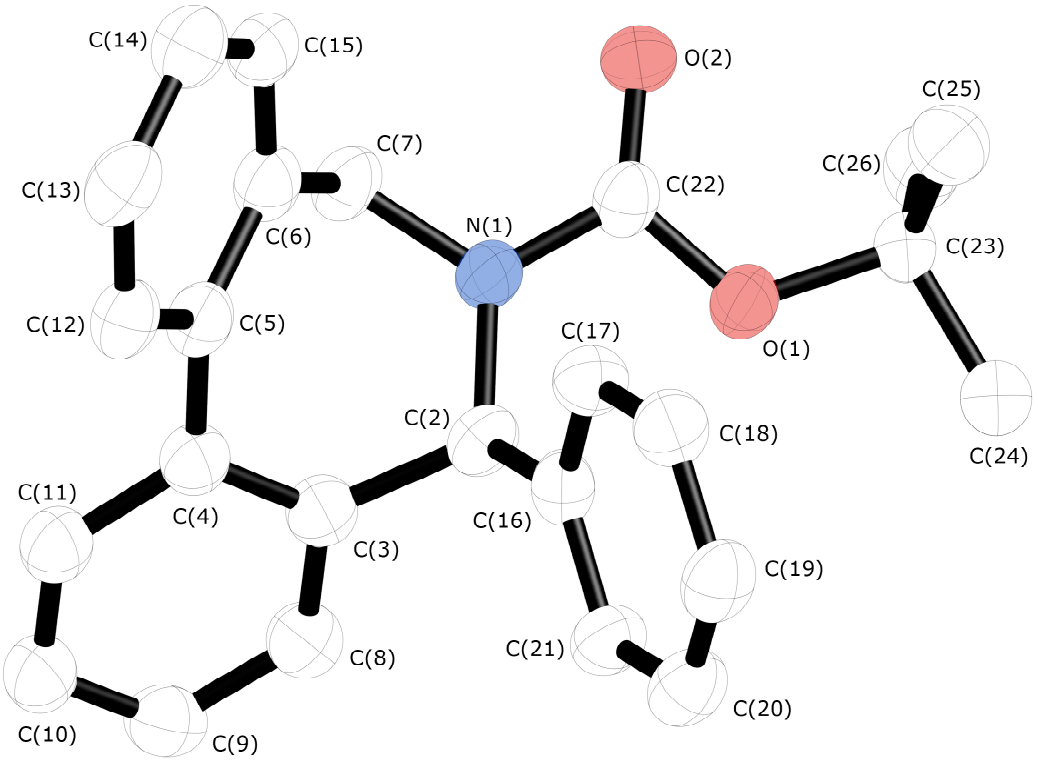
Contents

Page

Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Crystal structure data tables for the carbamate (±)-21

CCDC deposition number 793197



X-ray crystal structure of carbamate **21** generated using *CrystalMaker* (thermal ellipsoids 50%)

Table 1. Crystal data and structure refinement for (±)-**21**.

CCDC deposition number	CCDC 793197	
Empirical formula	$C_{25}H_{25}NO_2$	
Formula weight	371.46	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.4053(3) Å	α = 90°.
	b = 9.7021(4) Å	β = 92.978(2)°.
	c = 21.9587(10) Å	γ = 90°.
Volume	2001.05(14) $Å^3$	
Z	4	
Density (calculated)	1.233 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	792	
Crystal size	0.10 x 0.15 x 0.25 mm^3	
Theta range for data collection	3.02 to 25.50°.	
Index ranges	0<=h<=11, 0<=k<=11, –26<=l<=26	
Reflections collected	14457	
Independent reflections	3710 [R(int) = 0.096]	
Completeness to theta = 25.50°	99.7 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3710 / 0 / 354	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0861, wR2 = 0.1660	
R indices (all data)	R1 = 0.1888, wR2 = 0.2154	
Extinction coefficient	0.0046(12)	
Largest diff. peak and hole	0.411 and –0.405 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **21**. U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(2)	2371(5)	4060(6)	3587(2)	39(1)
C(3)	2725(5)	3353(6)	4194(2)	42(1)
C(4)	2799(5)	4054(6)	4758(2)	42(1)
C(5)	2357(5)	5505(5)	4827(2)	41(1)
C(6)	1092(5)	5978(6)	4533(2)	43(1)
C(7)	249(5)	5034(6)	4105(2)	42(1)
C(8)	3096(5)	1958(6)	4174(2)	45(1)
C(9)	3559(5)	1252(6)	4697(3)	49(1)
C(10)	3676(5)	1943(6)	5257(2)	49(1)
C(11)	3304(5)	3332(6)	5280(2)	46(1)
C(12)	3139(5)	6386(6)	5230(2)	44(1)
C(13)	2667(6)	7722(7)	5318(2)	51(2)
C(14)	1403(6)	8204(6)	5029(2)	49(1)
C(15)	639(6)	7315(6)	4632(2)	46(1)
C(16)	3619(5)	4960(5)	3395(2)	38(1)
C(17)	3552(5)	6404(6)	3392(2)	42(1)
C(18)	4680(5)	7155(6)	3182(2)	46(1)
C(19)	5902(5)	6498(6)	3001(2)	48(1)
C(20)	5983(5)	5070(6)	3019(2)	49(1)
C(21)	4853(5)	4315(6)	3223(2)	44(1)
C(22)	391(5)	5226(5)	3010(2)	40(1)
C(23)	730(5)	5193(6)	1910(2)	42(1)
C(24)	1872(6)	4512(7)	1548(2)	49(1)
C(25)	786(7)	6747(6)	1855(3)	56(2)
C(26)	-721(6)	4601(7)	1728(3)	54(2)
N(1)	1001(4)	4773(4)	3552(2)	40(1)
O(1)	1154(3)	4798(4)	2542(1)	44(1)
O(2)	-699(3)	5902(4)	2960(2)	47(1)

Table 3. Bond lengths [Å] and angles [°] for **21**.

C(2)-N(1)	1.461(6)
C(2)-C(3)	1.521(7)
C(2)-C(16)	1.539(6)
C(3)-C(8)	1.399(7)
C(3)-C(4)	1.410(7)
C(4)-C(11)	1.406(7)
C(4)-C(5)	1.479(7)
C(5)-C(6)	1.401(7)
C(5)-C(12)	1.408(7)
C(6)-C(15)	1.386(7)
C(6)-C(7)	1.508(7)
C(7)-N(1)	1.459(6)
C(8)-C(9)	1.388(7)
C(9)-C(10)	1.399(8)
C(10)-C(11)	1.395(8)
C(12)-C(13)	1.388(8)
C(13)-C(14)	1.398(8)
C(14)-C(15)	1.398(7)
C(16)-C(21)	1.389(7)
C(16)-C(17)	1.402(7)
C(17)-C(18)	1.387(7)
C(18)-C(19)	1.389(7)
C(19)-C(20)	1.388(8)
C(20)-C(21)	1.384(7)
C(22)-O(2)	1.217(6)
C(22)-O(1)	1.348(5)
C(22)-N(1)	1.367(6)
C(23)-O(1)	1.475(5)
C(23)-C(25)	1.513(8)
C(23)-C(26)	1.515(7)
C(23)-C(24)	1.519(7)
N(1)-C(2)-C(3)	114.3(4)
N(1)-C(2)-C(16)	113.6(4)
C(3)-C(2)-C(16)	111.1(4)
C(8)-C(3)-C(4)	119.5(5)

C(8)-C(3)-C(2)	116.9(5)
C(4)-C(3)-C(2)	123.4(5)
C(11)-C(4)-C(3)	118.4(5)
C(11)-C(4)-C(5)	118.3(5)
C(3)-C(4)-C(5)	123.2(5)
C(6)-C(5)-C(12)	119.6(5)
C(6)-C(5)-C(4)	120.0(5)
C(12)-C(5)-C(4)	120.1(5)
C(15)-C(6)-C(5)	119.7(5)
C(15)-C(6)-C(7)	120.6(5)
C(5)-C(6)-C(7)	119.7(5)
N(1)-C(7)-C(6)	111.3(4)
C(9)-C(8)-C(3)	121.3(5)
C(8)-C(9)-C(10)	119.8(6)
C(11)-C(10)-C(9)	119.2(5)
C(10)-C(11)-C(4)	121.7(5)
C(13)-C(12)-C(5)	119.6(5)
C(12)-C(13)-C(14)	121.3(6)
C(13)-C(14)-C(15)	118.3(6)
C(6)-C(15)-C(14)	121.5(5)
C(21)-C(16)-C(17)	119.1(5)
C(21)-C(16)-C(2)	118.6(5)
C(17)-C(16)-C(2)	122.3(4)
C(18)-C(17)-C(16)	119.5(5)
C(17)-C(18)-C(19)	120.8(5)
C(20)-C(19)-C(18)	119.7(5)
C(21)-C(20)-C(19)	119.7(5)
C(20)-C(21)-C(16)	121.1(5)
O(2)-C(22)-O(1)	125.2(4)
O(2)-C(22)-N(1)	124.4(4)
O(1)-C(22)-N(1)	110.4(4)
O(1)-C(23)-C(25)	109.0(4)
O(1)-C(23)-C(26)	110.2(4)
C(25)-C(23)-C(26)	113.1(5)
O(1)-C(23)-C(24)	102.4(4)
C(25)-C(23)-C(24)	111.3(5)
C(26)-C(23)-C(24)	110.4(5)
C(22)-N(1)-C(7)	118.0(4)

C(22)-N(1)-C(2)	121.8(4)
C(7)-N(1)-C(2)	120.2(4)
C(22)-O(1)-C(23)	120.6(4)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **21**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(2)	35(3)	43(3)	41(3)	-3(3)	8(2)	-1(2)
C(3)	33(2)	50(4)	43(3)	5(3)	5(2)	-3(2)
C(4)	37(3)	49(3)	40(3)	2(3)	4(2)	0(2)
C(5)	39(3)	50(3)	35(3)	-3(2)	5(2)	-4(2)
C(6)	37(3)	56(4)	37(3)	1(3)	6(2)	-3(3)
C(7)	33(3)	56(4)	38(3)	-6(3)	6(2)	0(3)
C(8)	40(3)	46(3)	49(3)	5(3)	5(2)	-5(3)
C(9)	46(3)	43(4)	59(3)	8(3)	7(3)	3(3)
C(10)	45(3)	58(4)	45(3)	8(3)	5(2)	-3(3)
C(11)	41(3)	53(4)	43(3)	2(3)	5(2)	-2(3)
C(12)	41(3)	52(4)	40(3)	0(3)	10(2)	-5(3)
C(13)	49(3)	61(4)	44(3)	-13(3)	8(3)	-6(3)
C(14)	47(3)	54(4)	47(3)	-3(3)	8(2)	-3(3)
C(15)	40(3)	56(4)	41(3)	0(3)	8(2)	2(3)
C(16)	35(3)	47(3)	32(2)	2(2)	1(2)	-6(2)
C(17)	37(3)	45(3)	46(3)	0(3)	3(2)	1(2)
C(18)	44(3)	49(4)	46(3)	2(3)	2(2)	-2(3)
C(19)	37(3)	62(4)	46(3)	0(3)	9(2)	-9(3)
C(20)	38(3)	60(4)	48(3)	-9(3)	5(2)	0(3)
C(21)	37(3)	51(4)	46(3)	-2(3)	7(2)	3(3)
C(22)	35(3)	49(3)	36(3)	0(2)	6(2)	-6(2)
C(23)	42(3)	52(3)	31(2)	4(2)	3(2)	7(3)
C(24)	50(3)	56(4)	41(3)	3(3)	4(2)	8(3)
C(25)	65(4)	45(4)	58(4)	12(3)	12(3)	10(3)
C(26)	44(3)	73(5)	43(3)	-6(3)	-4(3)	2(3)
N(1)	34(2)	52(3)	36(2)	0(2)	5(2)	3(2)
O(1)	40(2)	54(2)	38(2)	0(2)	6(1)	1(2)
O(2)	33(2)	60(2)	47(2)	4(2)	4(2)	6(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **21**.

	x	y	z	U(eq)
H(2)	2250(40)	3320(50)	3281(19)	30(12)
H(7A)	60(50)	4040(60)	4350(20)	64(16)
H(7B)	-630(40)	5480(40)	3980(17)	21(10)
H(8)	3000(50)	1410(50)	3710(20)	61(15)
H(9)	3770(40)	250(50)	4664(18)	31(12)
H(10)	4110(40)	1490(50)	5670(20)	38(12)
H(11)	3320(50)	3780(50)	5660(20)	52(15)
H(12)	4100(50)	6050(50)	5450(19)	37(12)
H(13)	3130(50)	8320(50)	5610(20)	53(16)
H(14)	1140(60)	9310(70)	5100(30)	90(20)
H(15)	-290(50)	7690(50)	4440(20)	55(15)
H(17)	2540(50)	6840(50)	3520(20)	47(13)
H(18)	4650(50)	8250(50)	3180(20)	41(13)
H(19)	6630(60)	6960(60)	2810(30)	77(19)
H(20)	6970(50)	4620(50)	2857(19)	43(13)
H(21)	4820(40)	3270(50)	3188(17)	22(11)
H(24A)	1830(50)	3430(60)	1590(20)	54(15)
H(24B)	2870(40)	4890(40)	1658(17)	22(10)
H(24C)	1660(40)	4770(50)	1050(20)	42(13)
H(25A)	1840(70)	7160(70)	1930(30)	90(20)
H(25B)	120(60)	7230(60)	2100(20)	67(18)
H(25C)	620(60)	6970(70)	1410(30)	90(20)
H(26A)	-710(60)	3470(70)	1840(30)	78(19)
H(26B)	-1530(50)	5020(50)	2000(20)	45(13)
H(26C)	-920(50)	4730(50)	1280(20)	54(15)

NMR Spectra

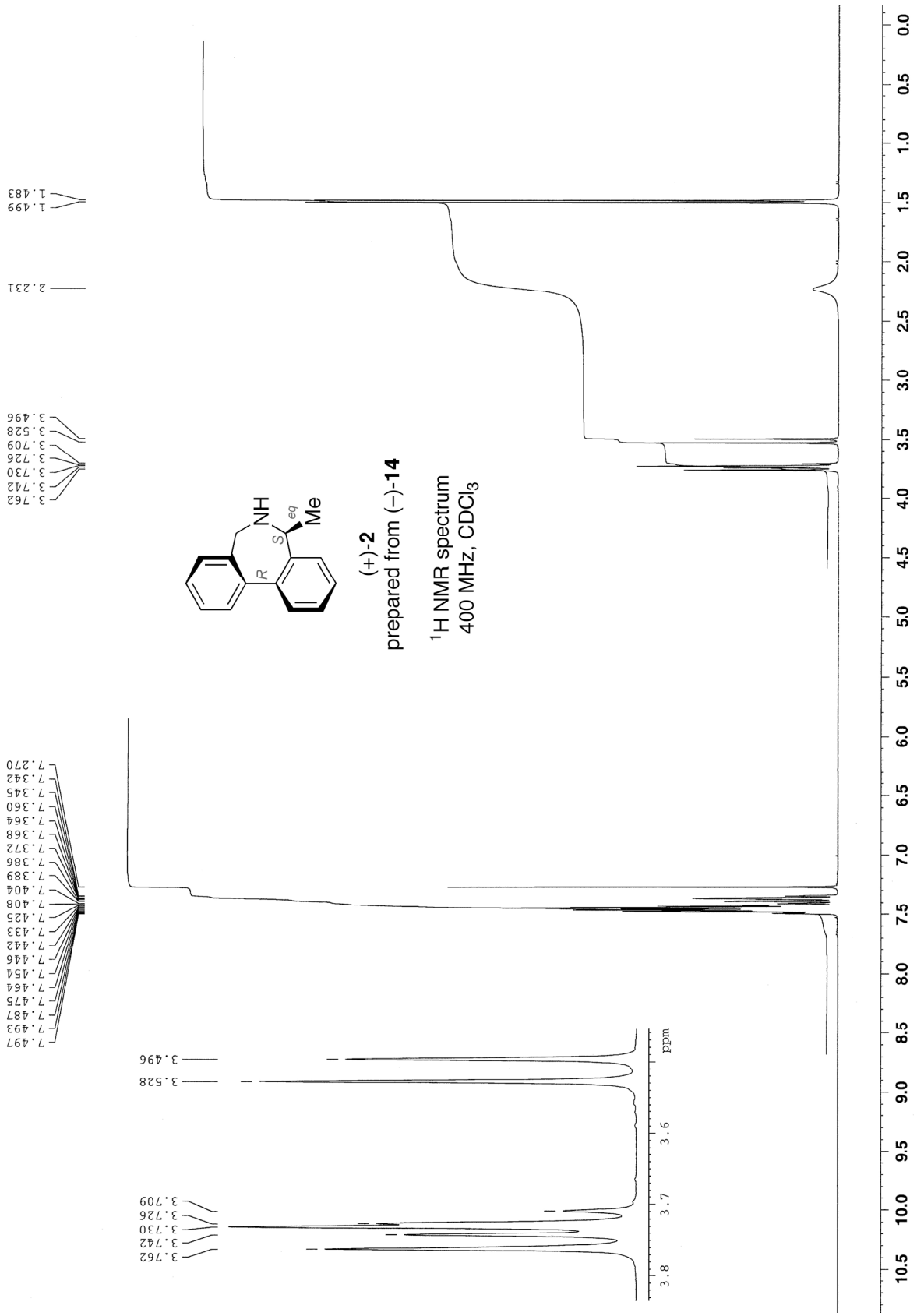
^{1}H and ^{13}C NMR spectra of **2**, **4**, **10**, **11**, **12**, **14**, **15**, **16**, **18**, **19**, **20**, **21** and **22**. ^{19}F NMR spectra of **12** and **15**.

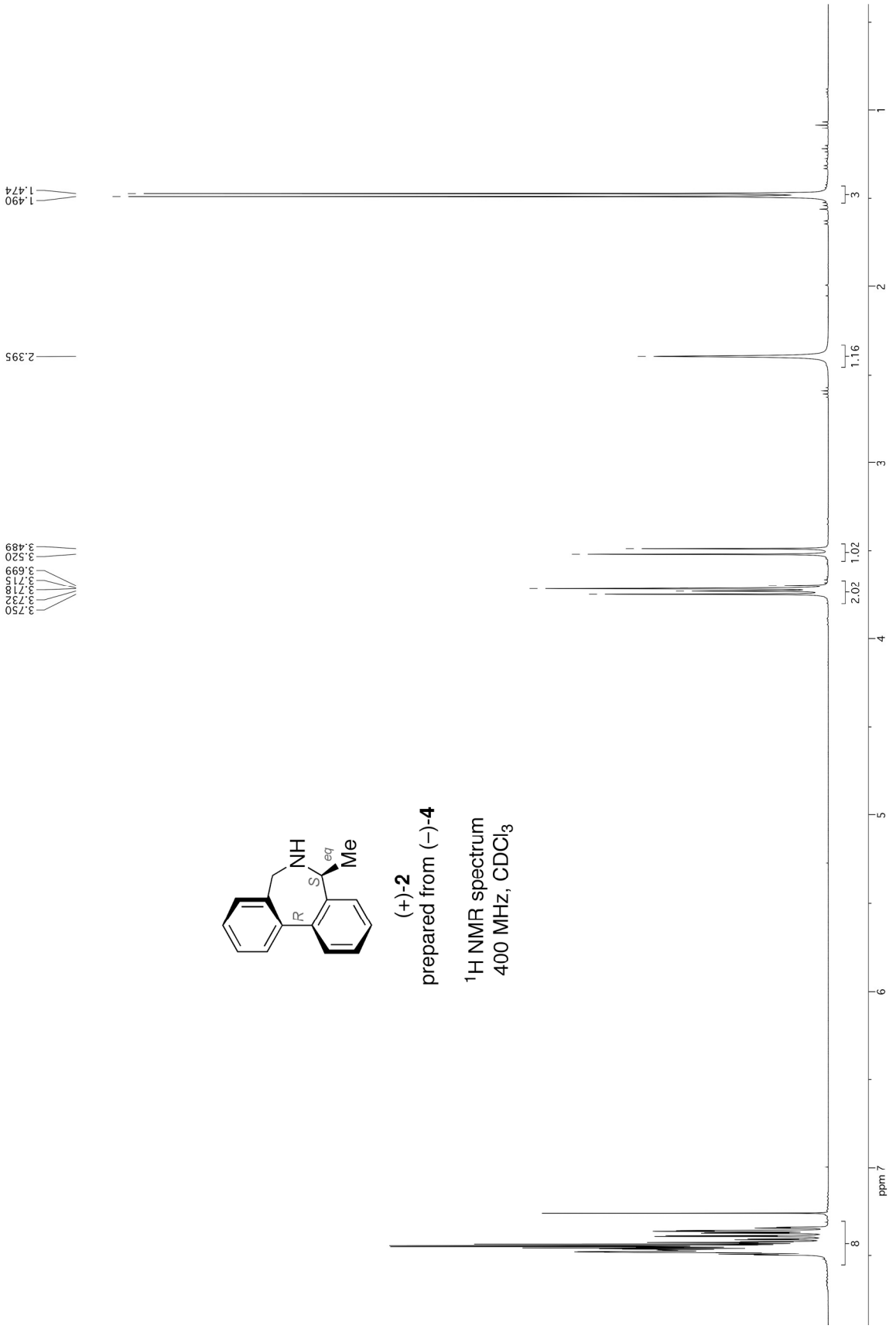
NMR spectra were recorded on a Bruker Avance 400 spectrometer and calibrated internally by reference to signals from the solvent ($CDCl_3$ at 77.16 ppm for ^{13}C spectra; $CHCl_3$ at 7.26 ppm for ^{1}H spectra)[1] or externally (referenced to $CFCl_3$ at 0 ppm for ^{19}F spectra).

Reference

1. H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512–7515.

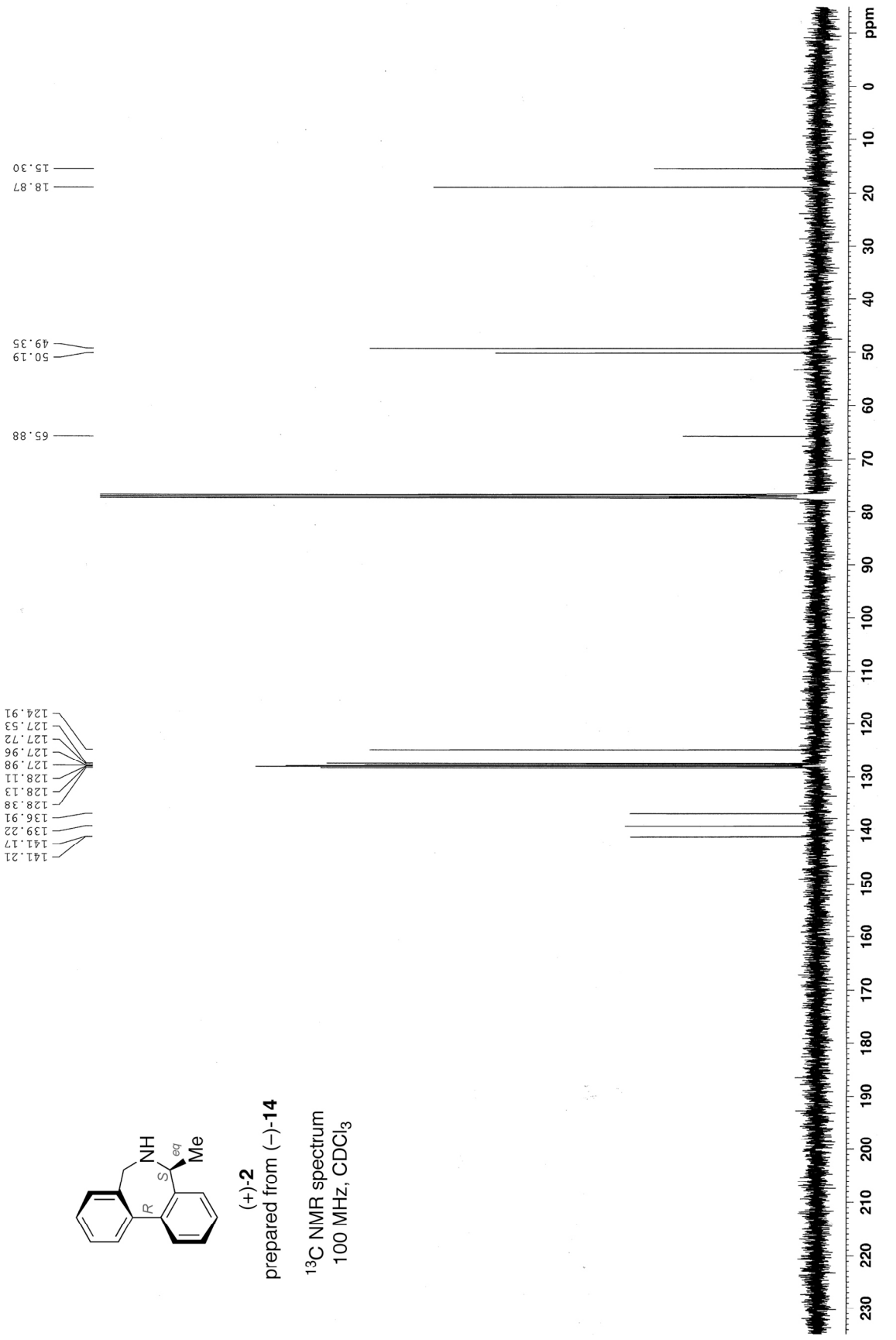
Supplementary Material (ESI) for Organic & Biomolecular Chemistry

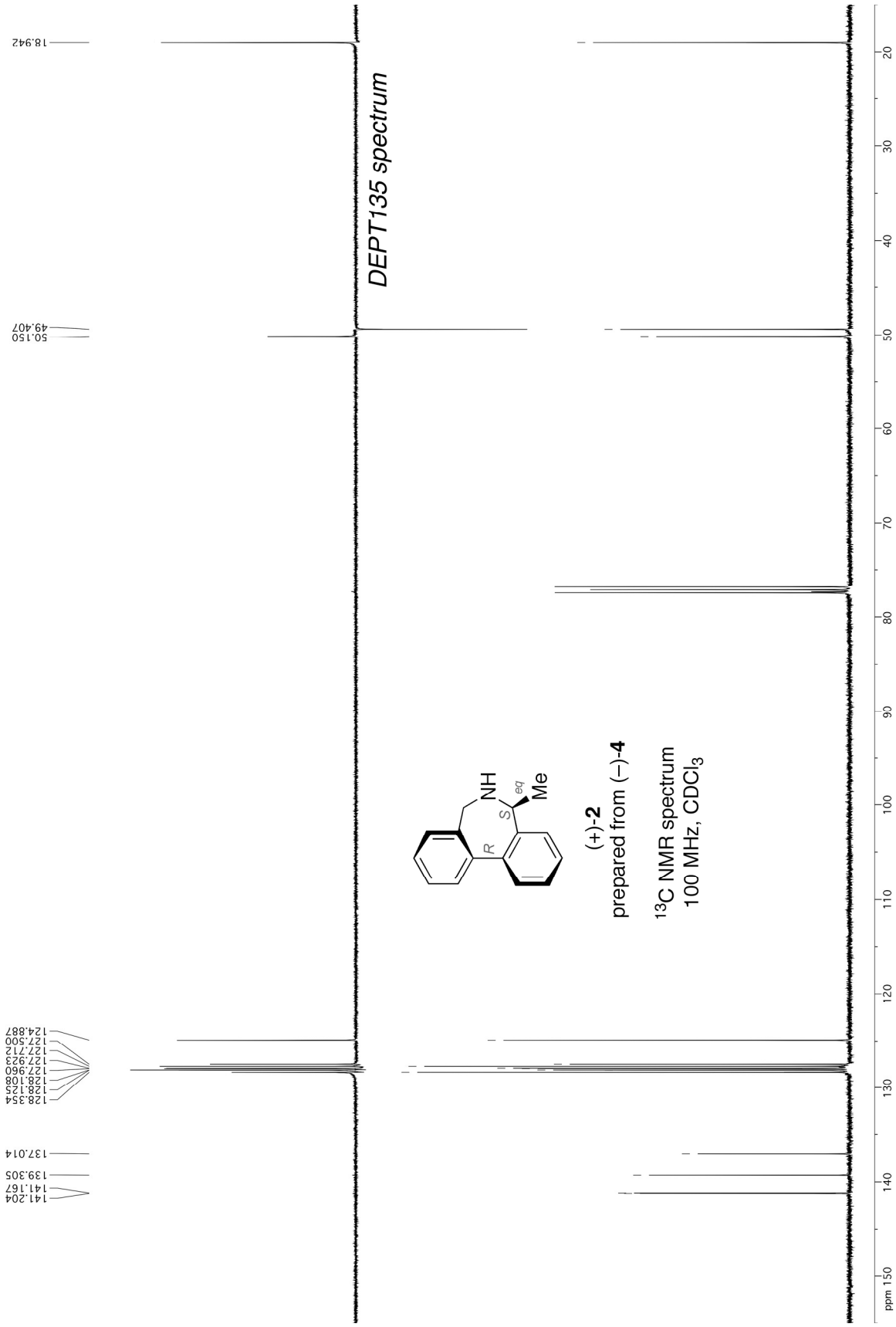


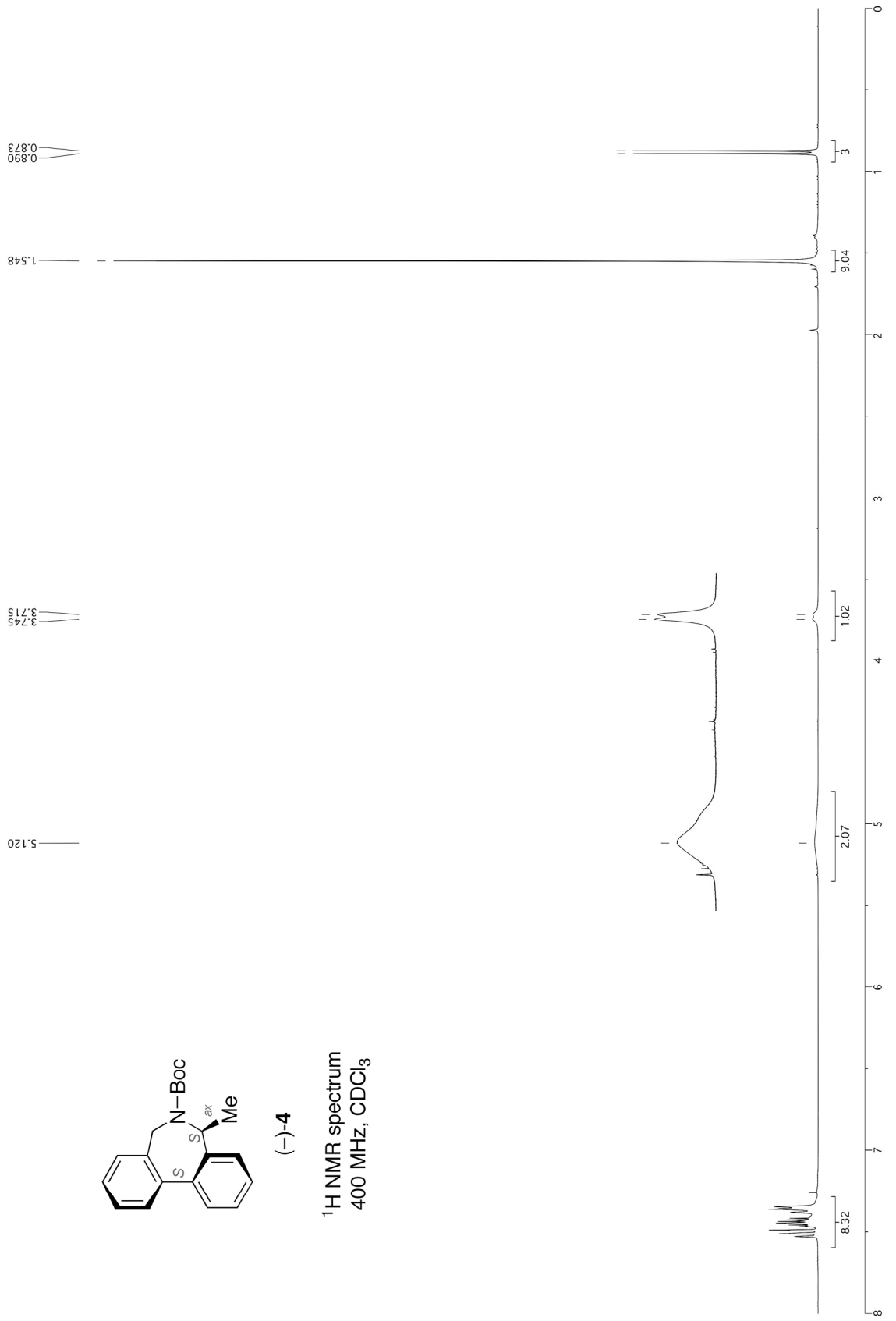


(+)-**2**
prepared from (–)-**4**

^{1}H NMR spectrum
400 MHz, $CDCl_3$

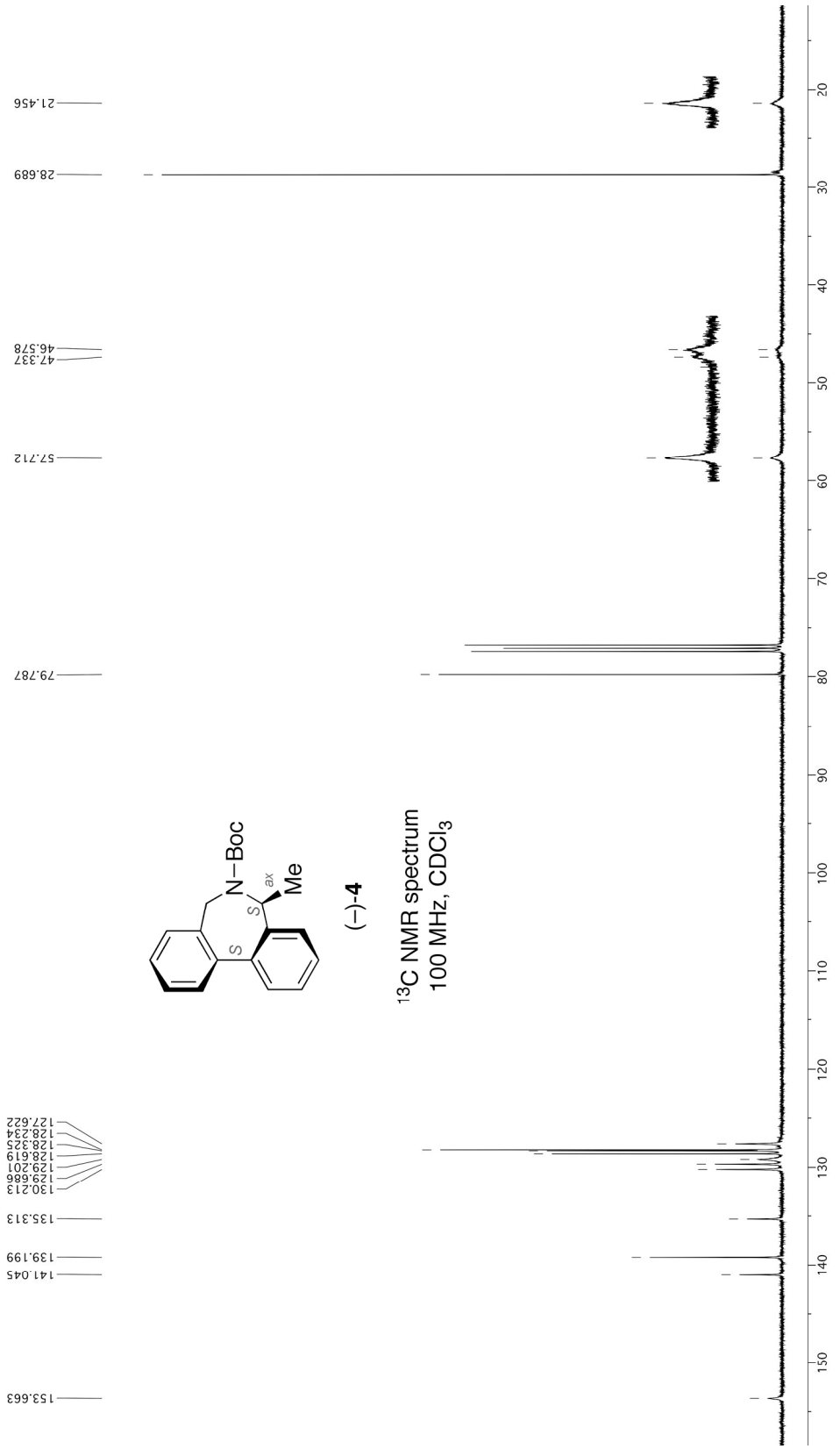


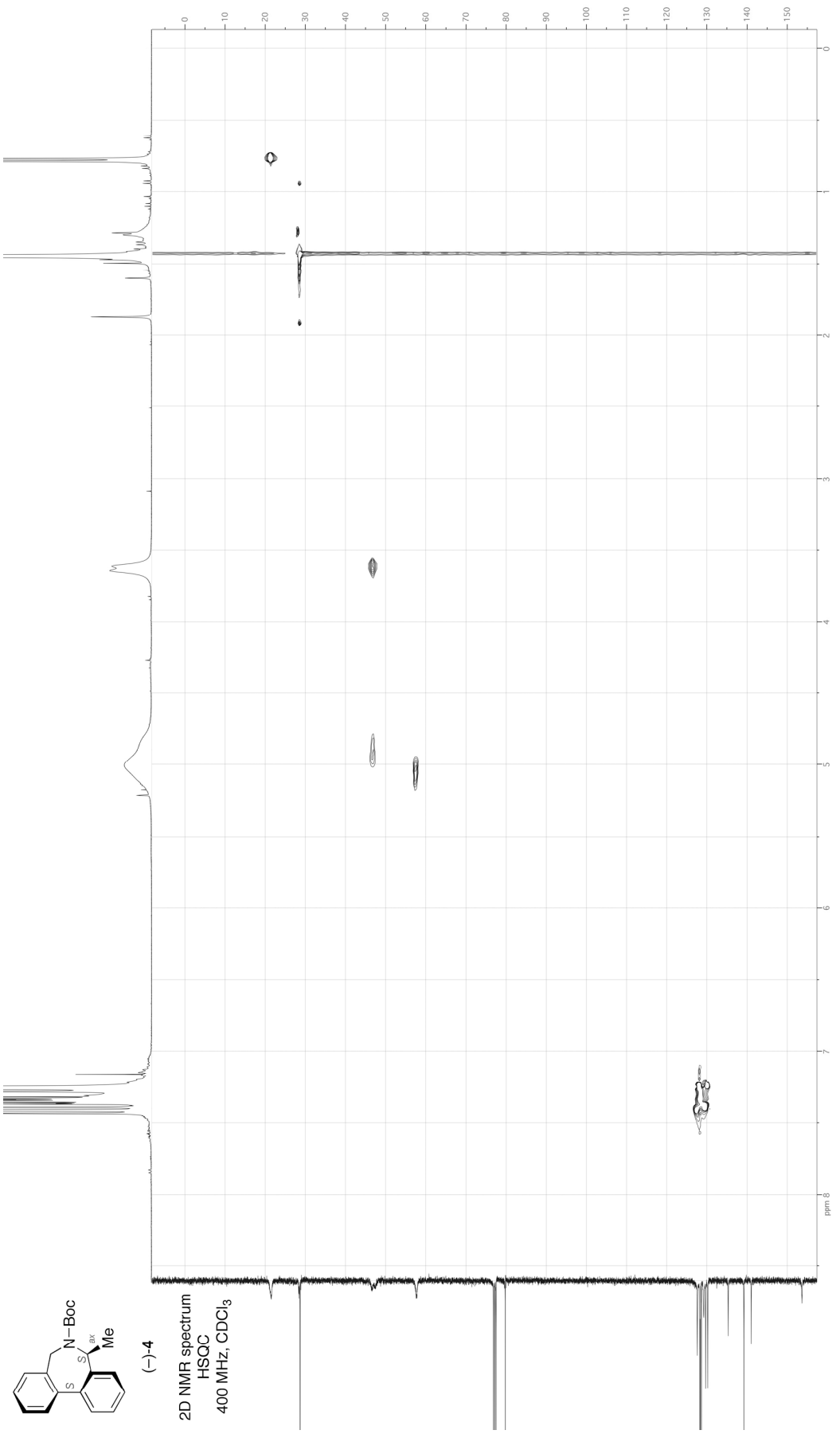


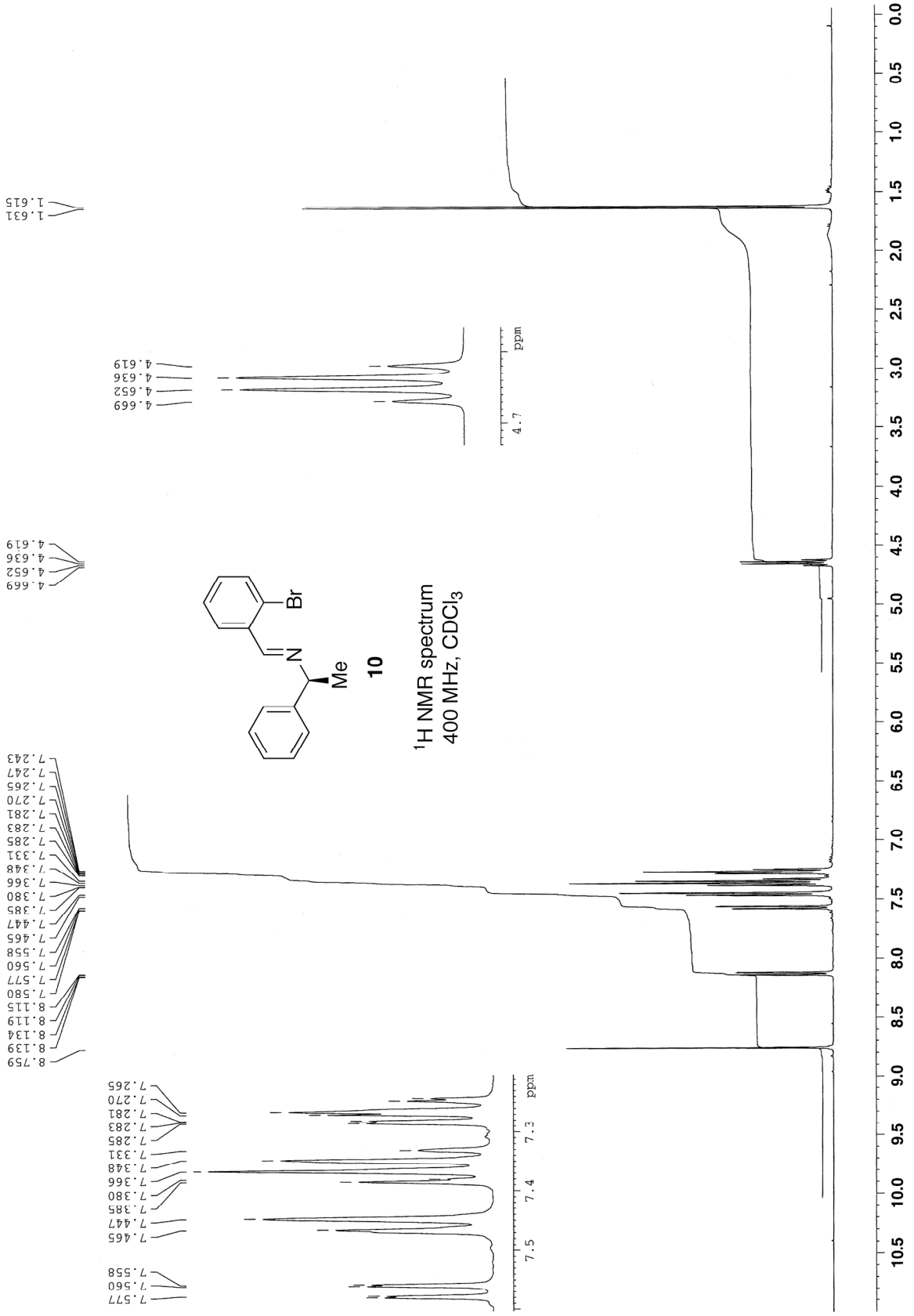


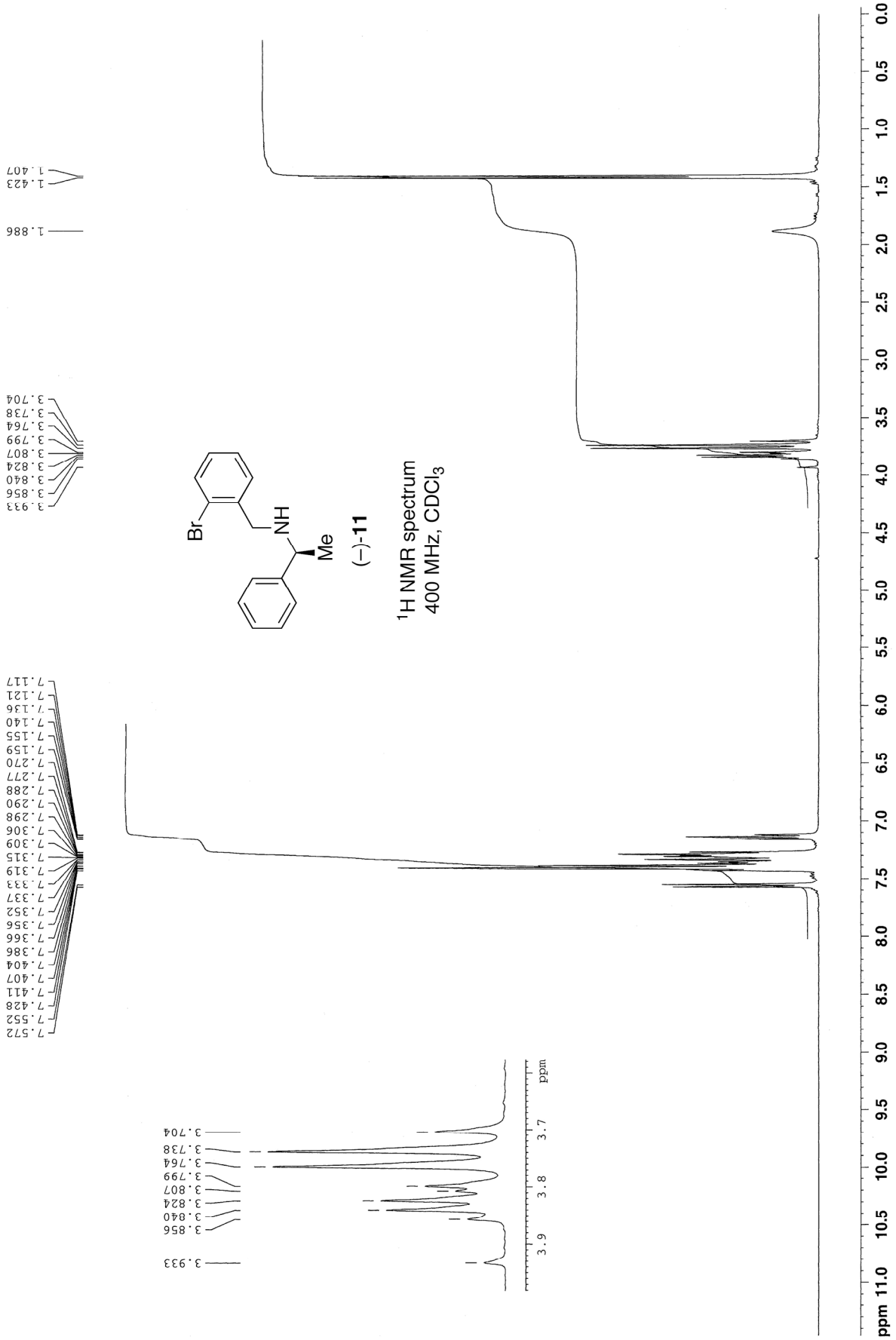
(–)-**4**

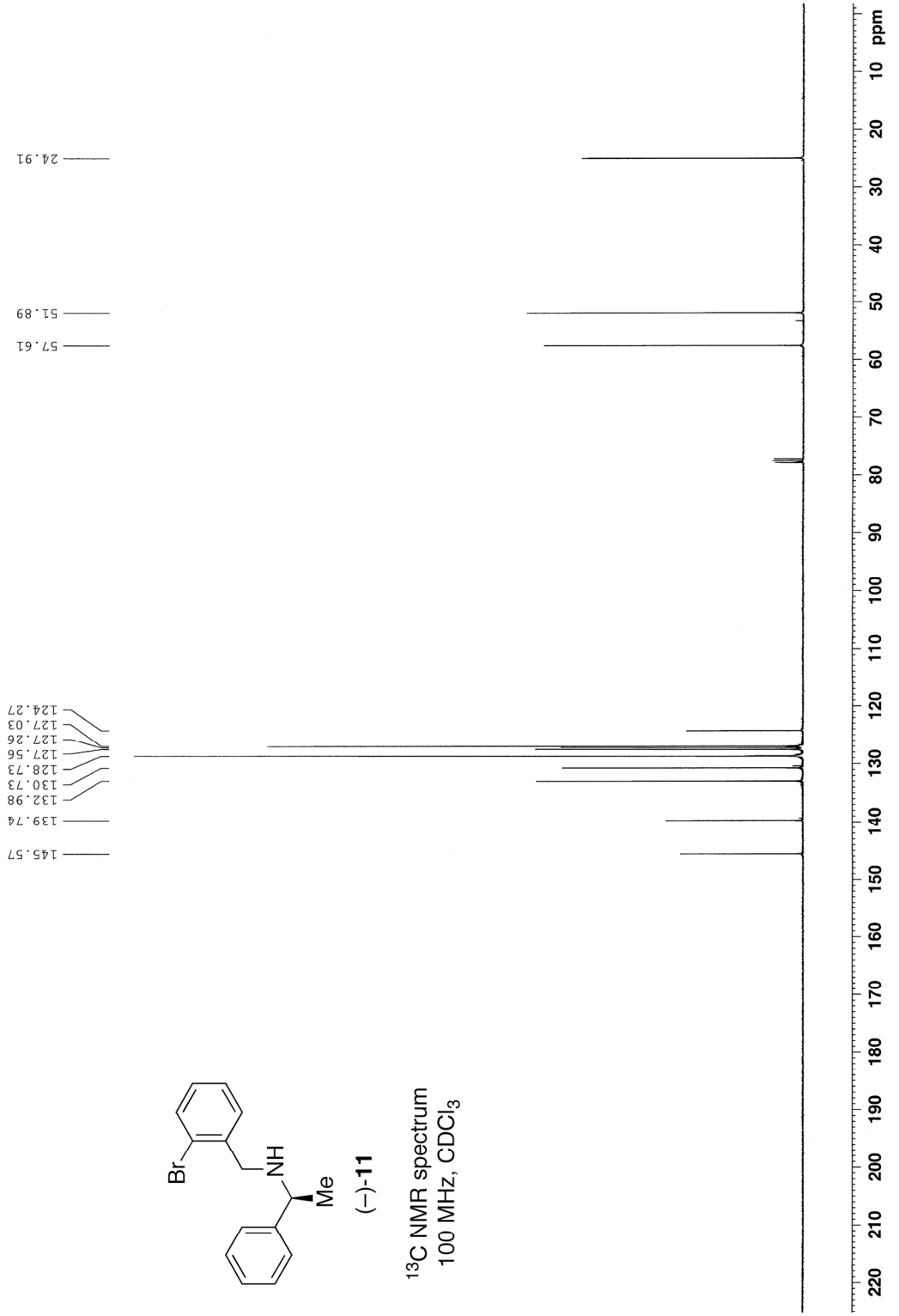
^{1}H NMR spectrum
400 MHz, $CDCl_3$

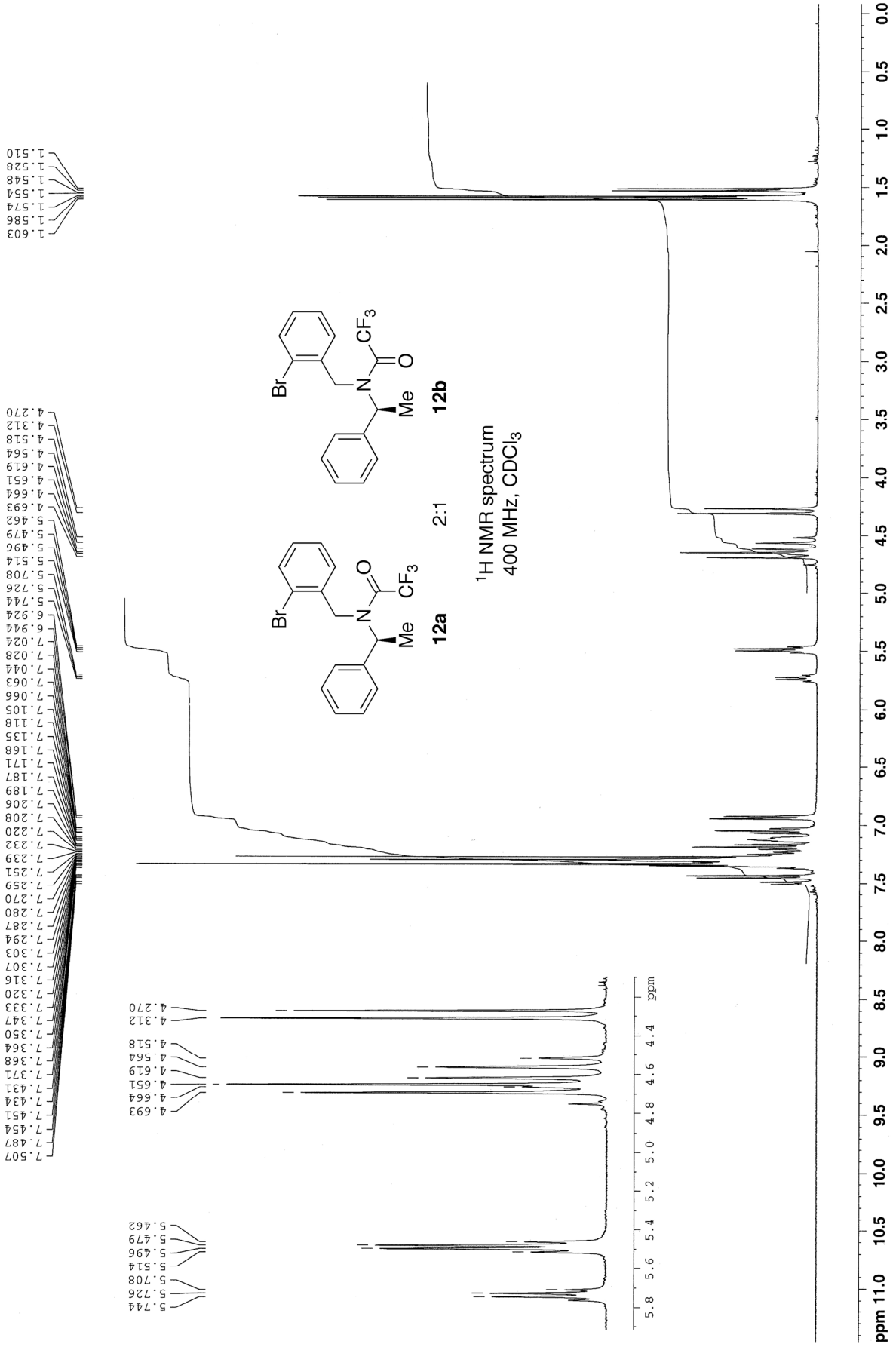


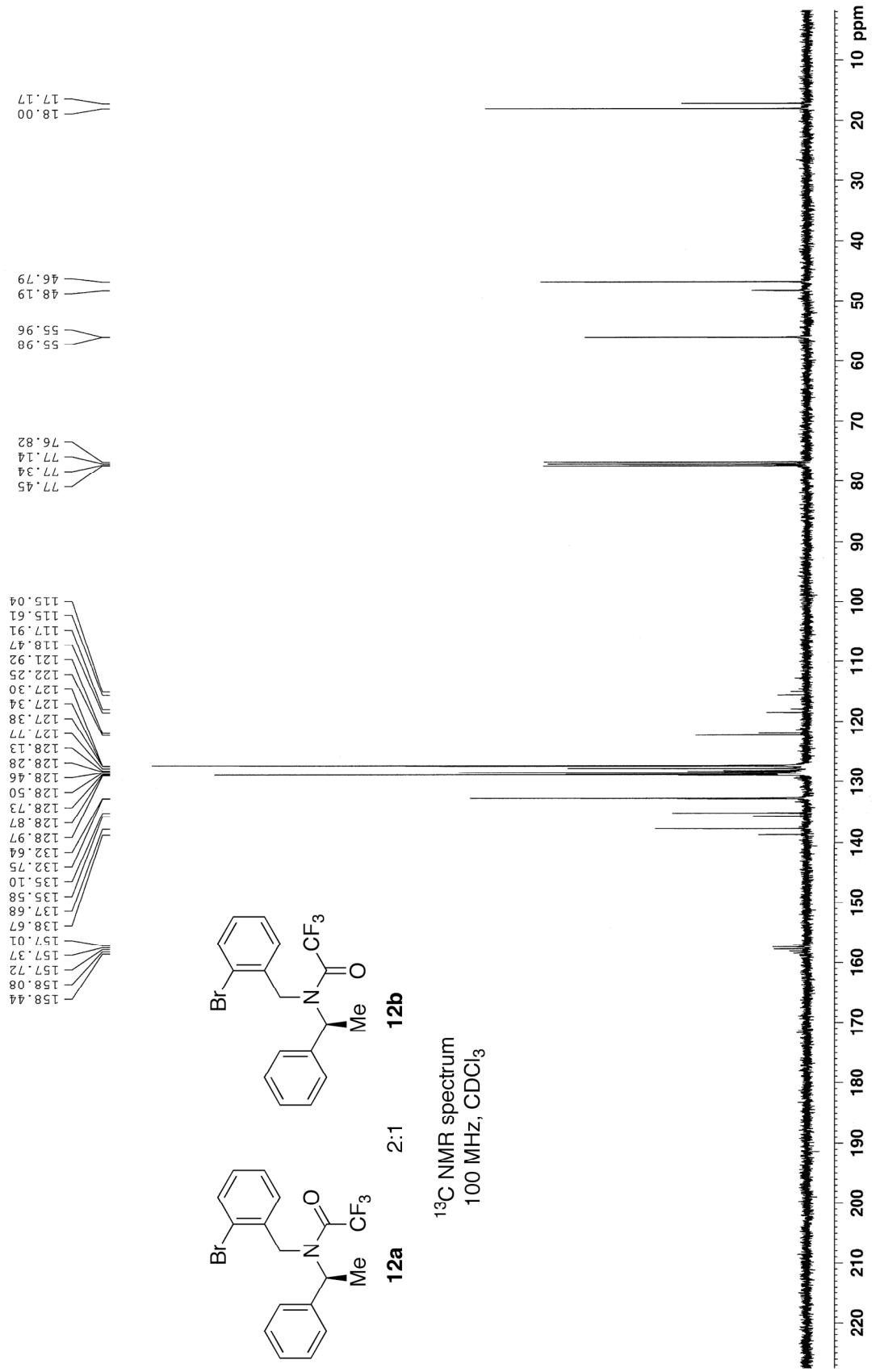


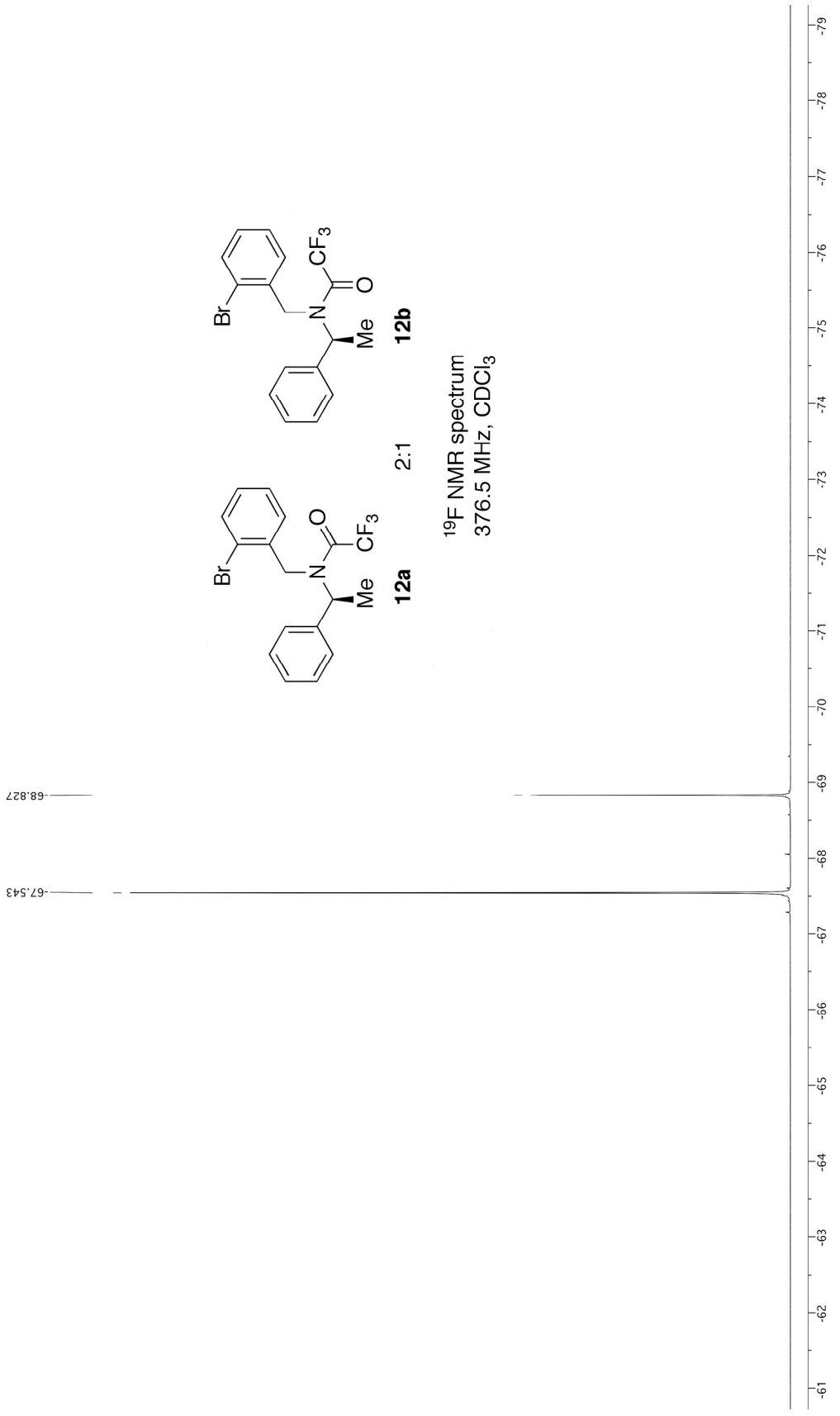


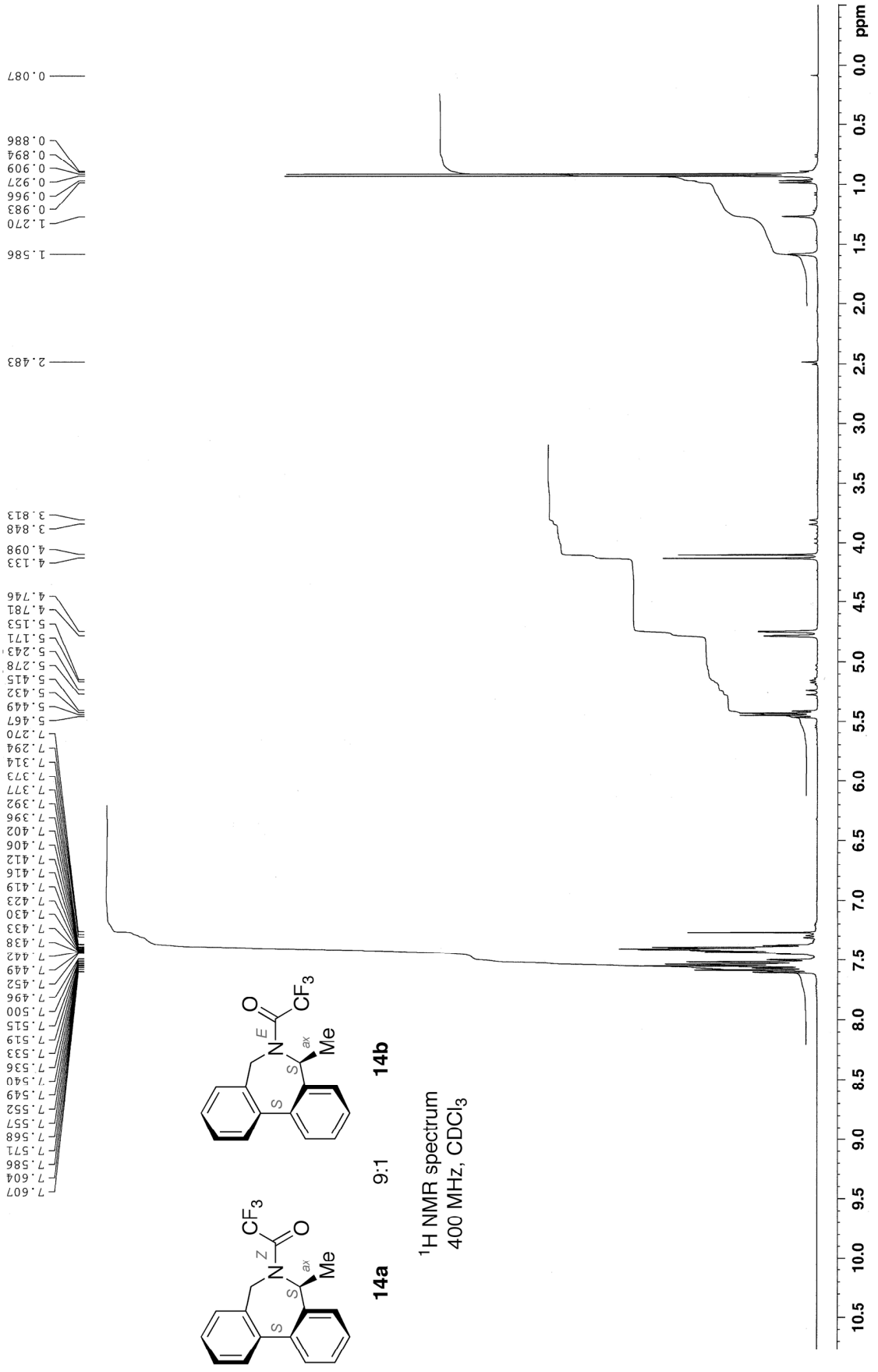

1.407
1.423
1.886
3.704
3.738
3.764
3.799
3.807
3.824
3.840
3.856
3.933
7.117
7.121
7.136
7.140
7.155
7.159
7.270
7.277
7.288
7.290
7.298
7.306
7.309
7.315
7.319
7.333
7.337
7.352
7.356
7.366
7.386
7.404
7.407
7.411
7.428
7.552
7.572
Br
NH
Me
(−)-11
^{1}H NMR spectrum
400 MHz, CDCl$_3$
ppm

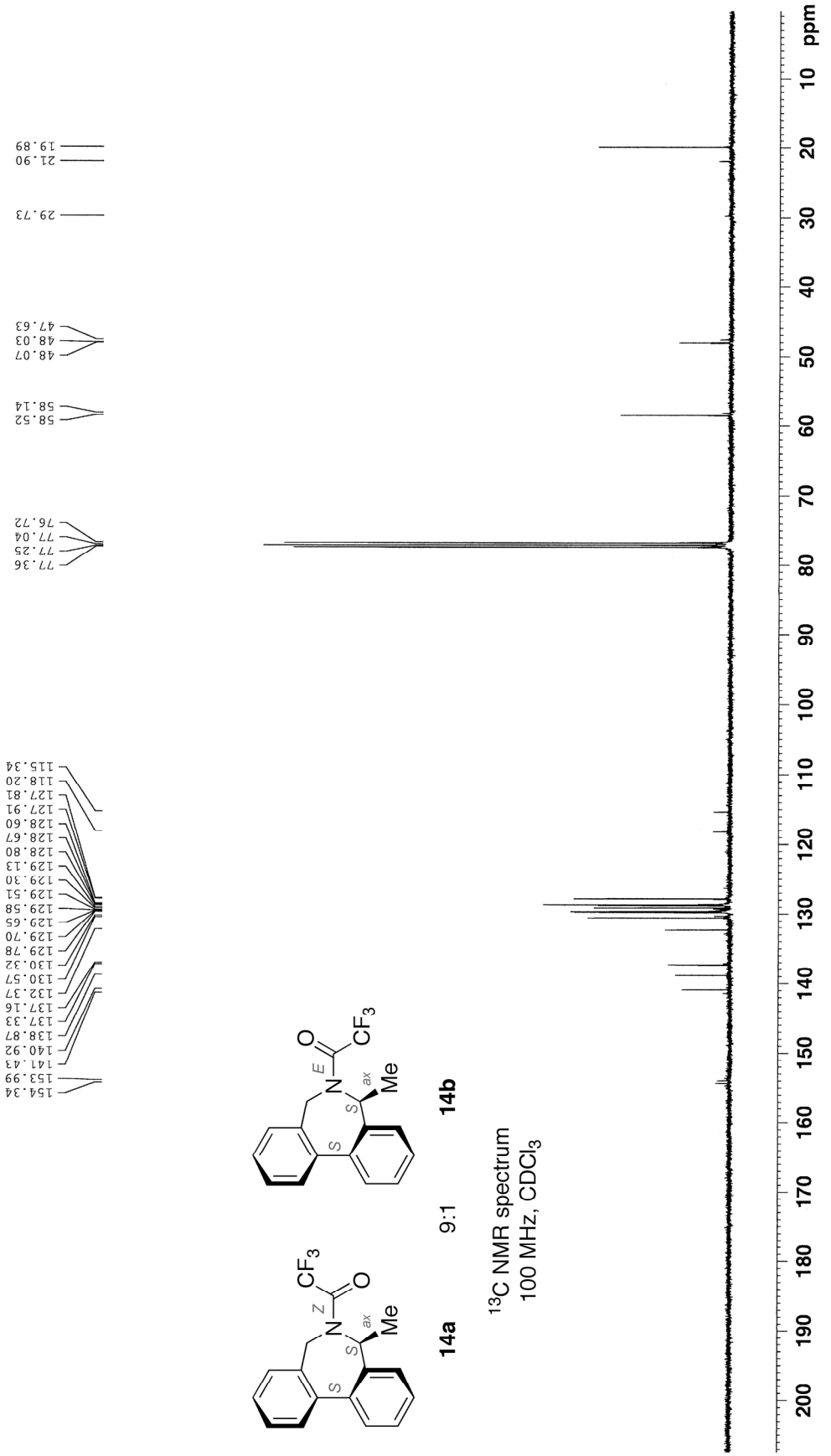


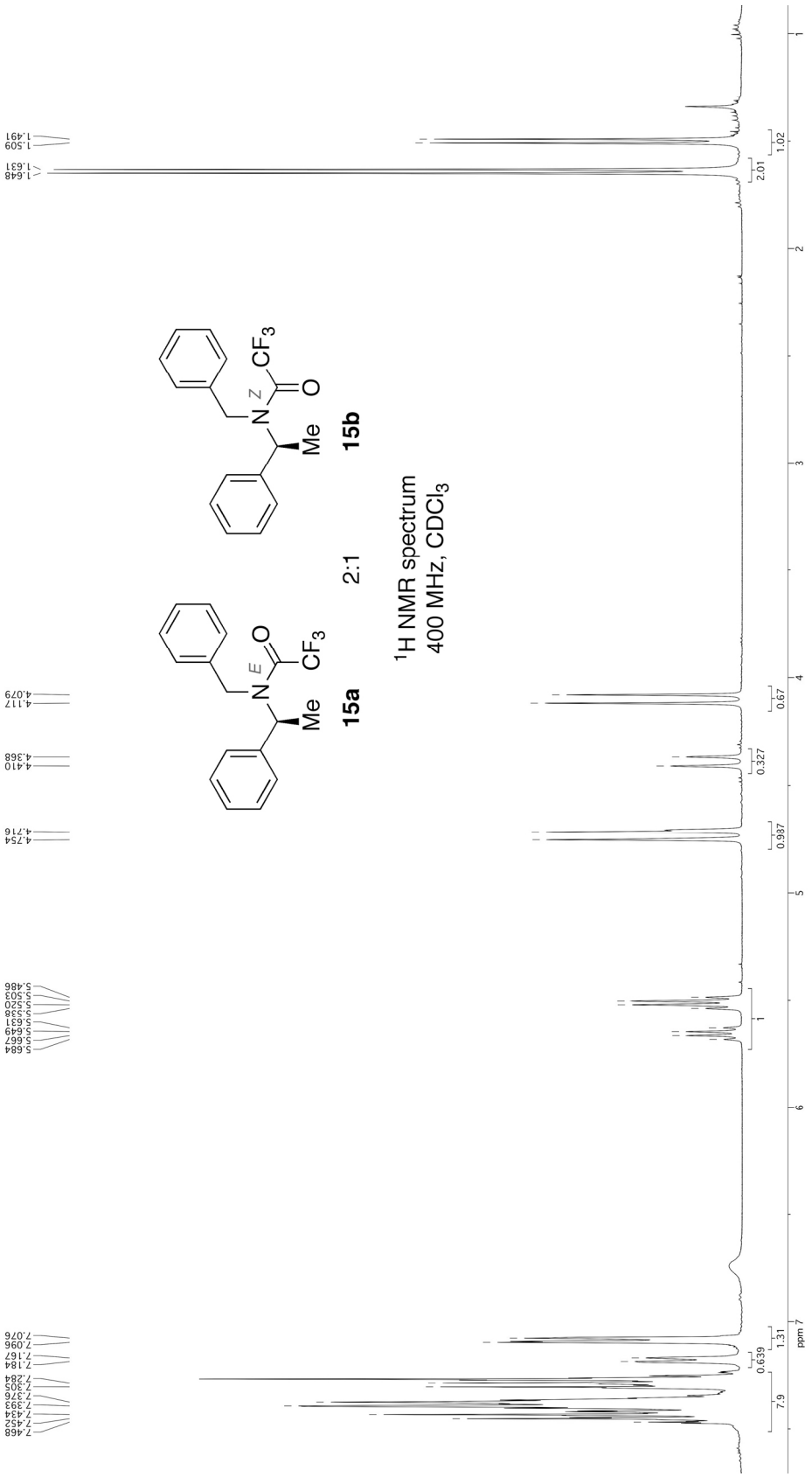


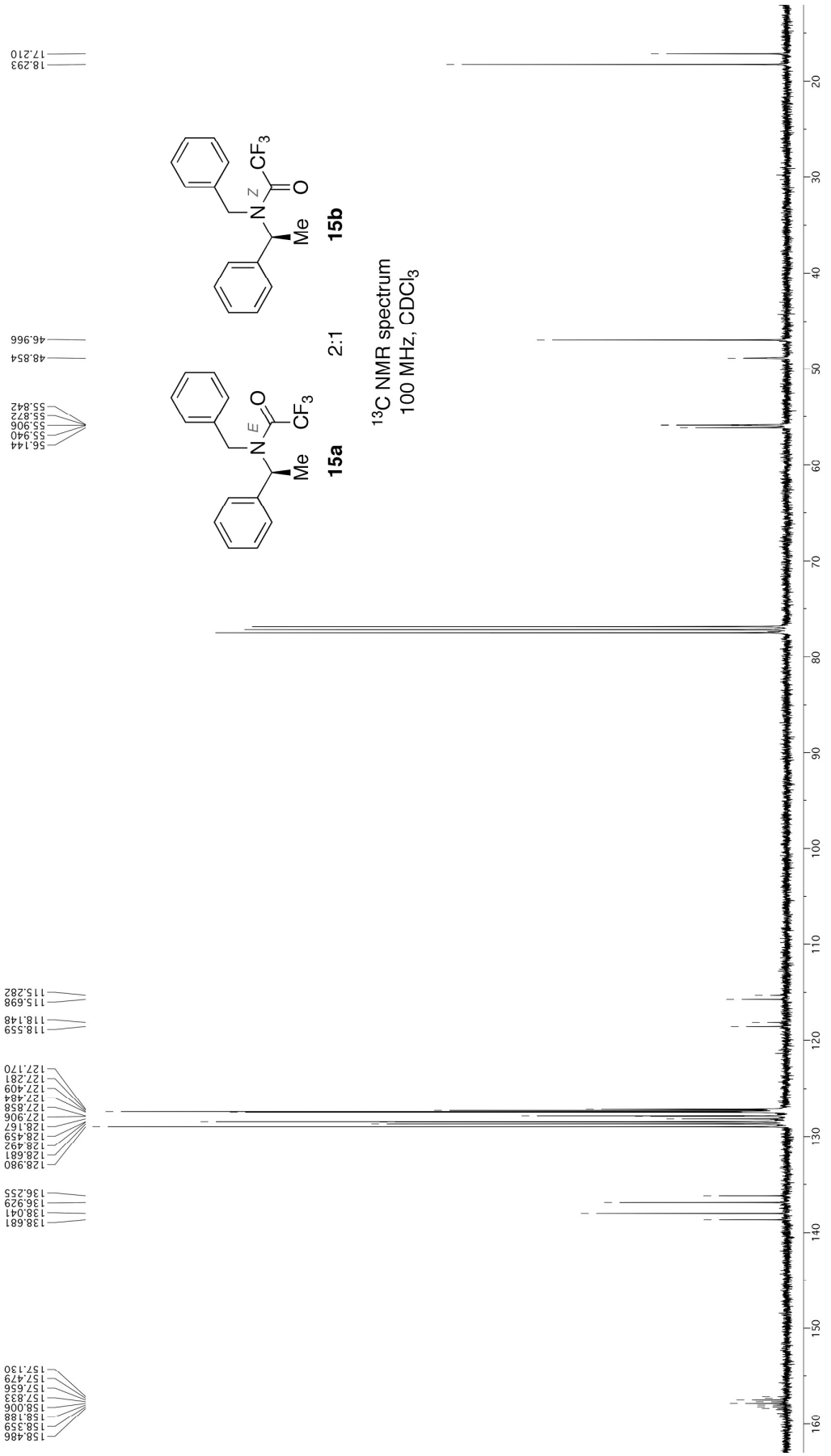

158.44
157.72
157.37
157.01
138.67
137.68
135.58
135.10
132.75
132.64
128.97
128.87
128.73
128.50
128.46
128.28
128.13
127.77
127.38
127.34
127.30
122.25
121.92
118.47
117.91
115.61
115.04
77.45
77.34
77.14
76.82
55.98
55.96
48.19
46.79
18.00
17.17
10 ppm
Br
N
O
CF3
Me
12a
2:1
12b
13C NMR spectrum
100 MHz, CDCl3

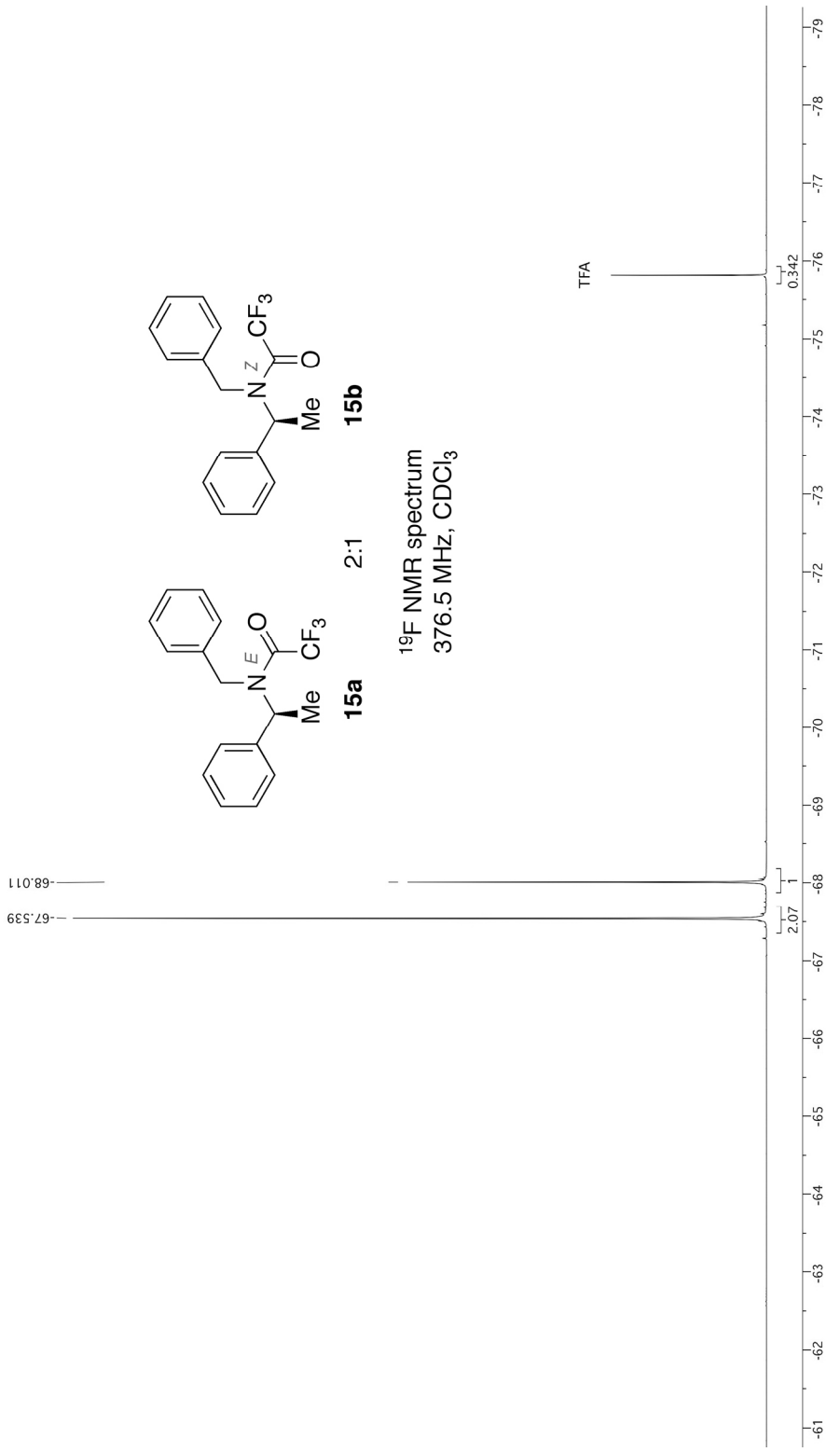


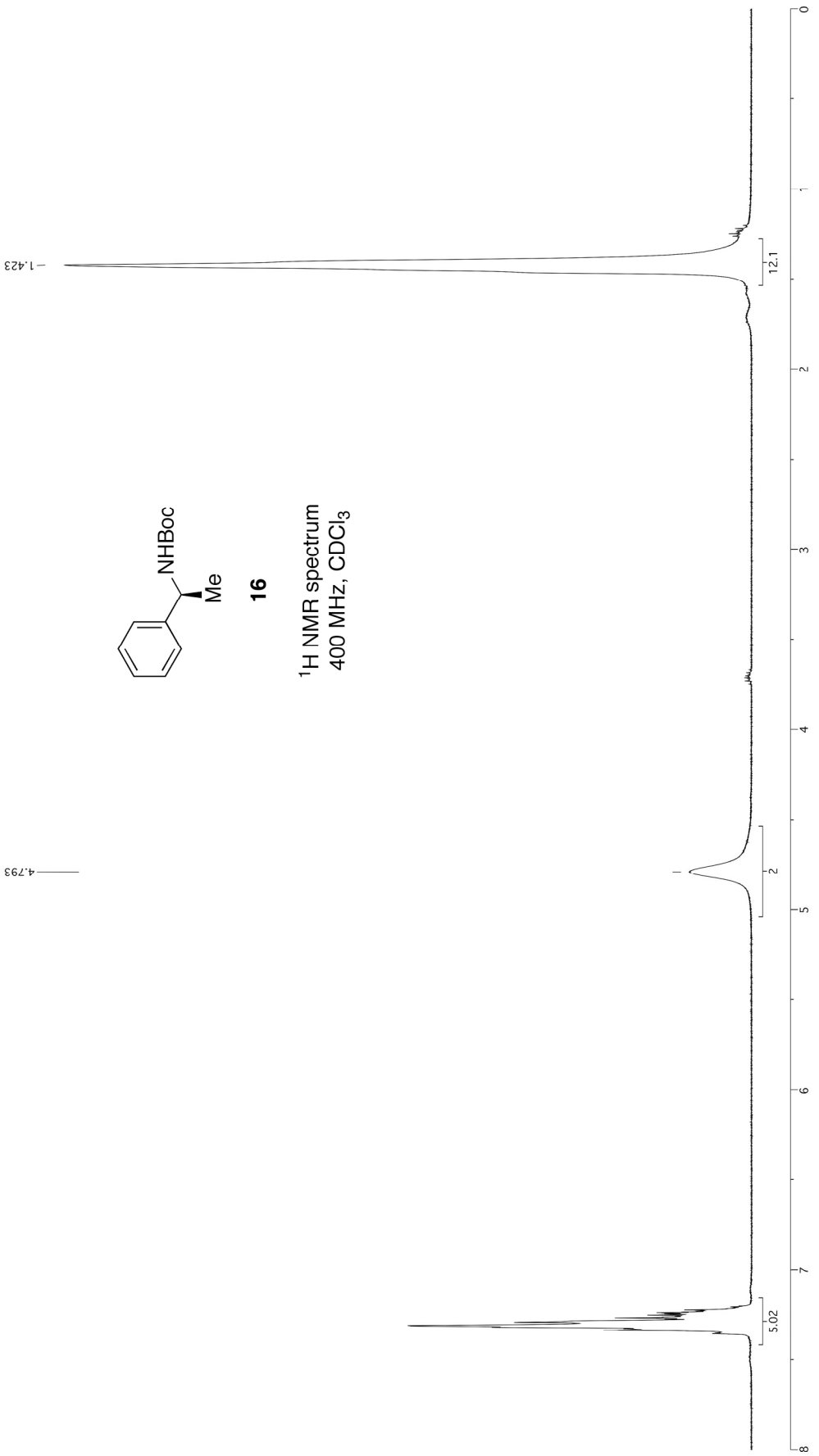


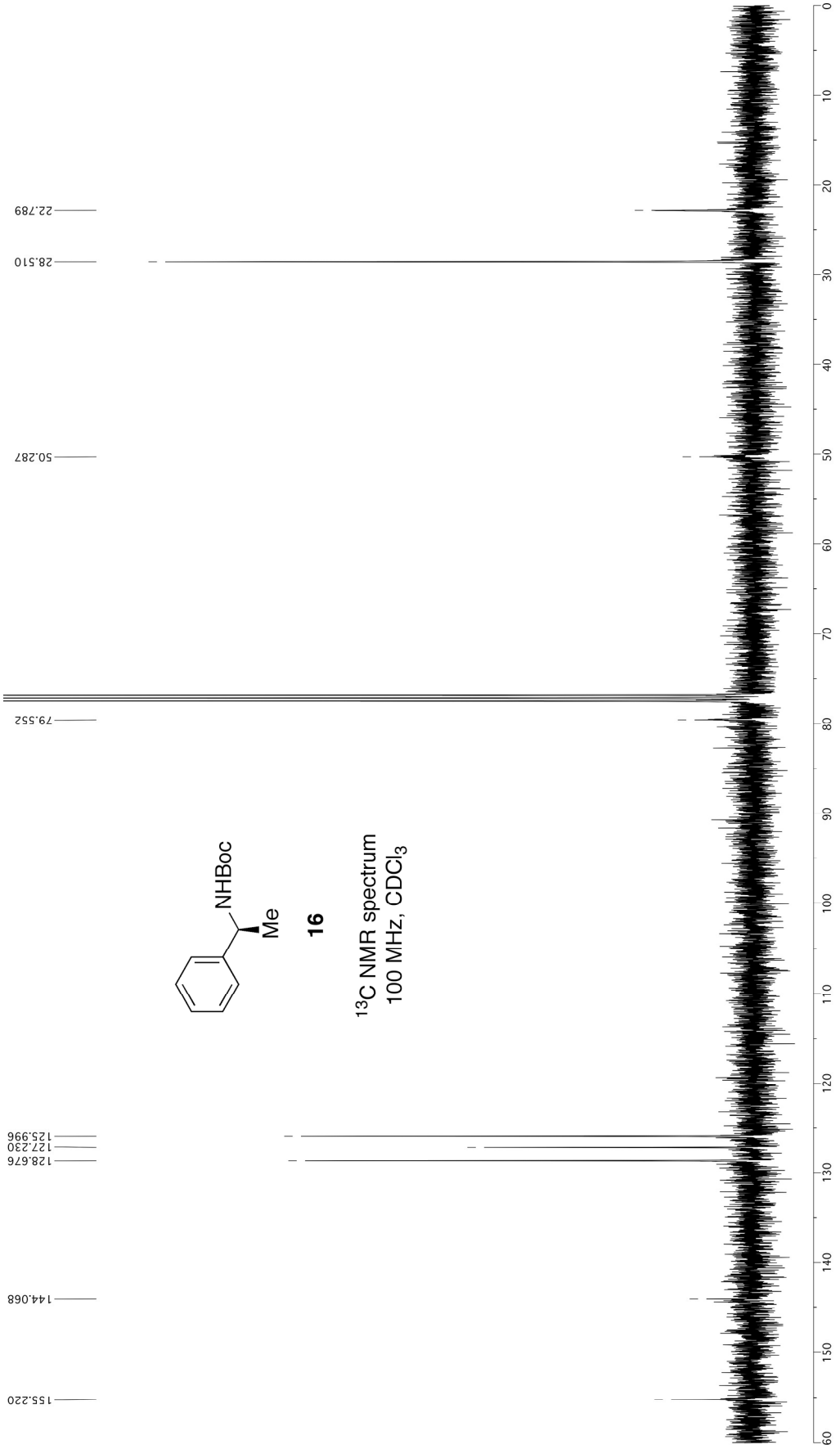


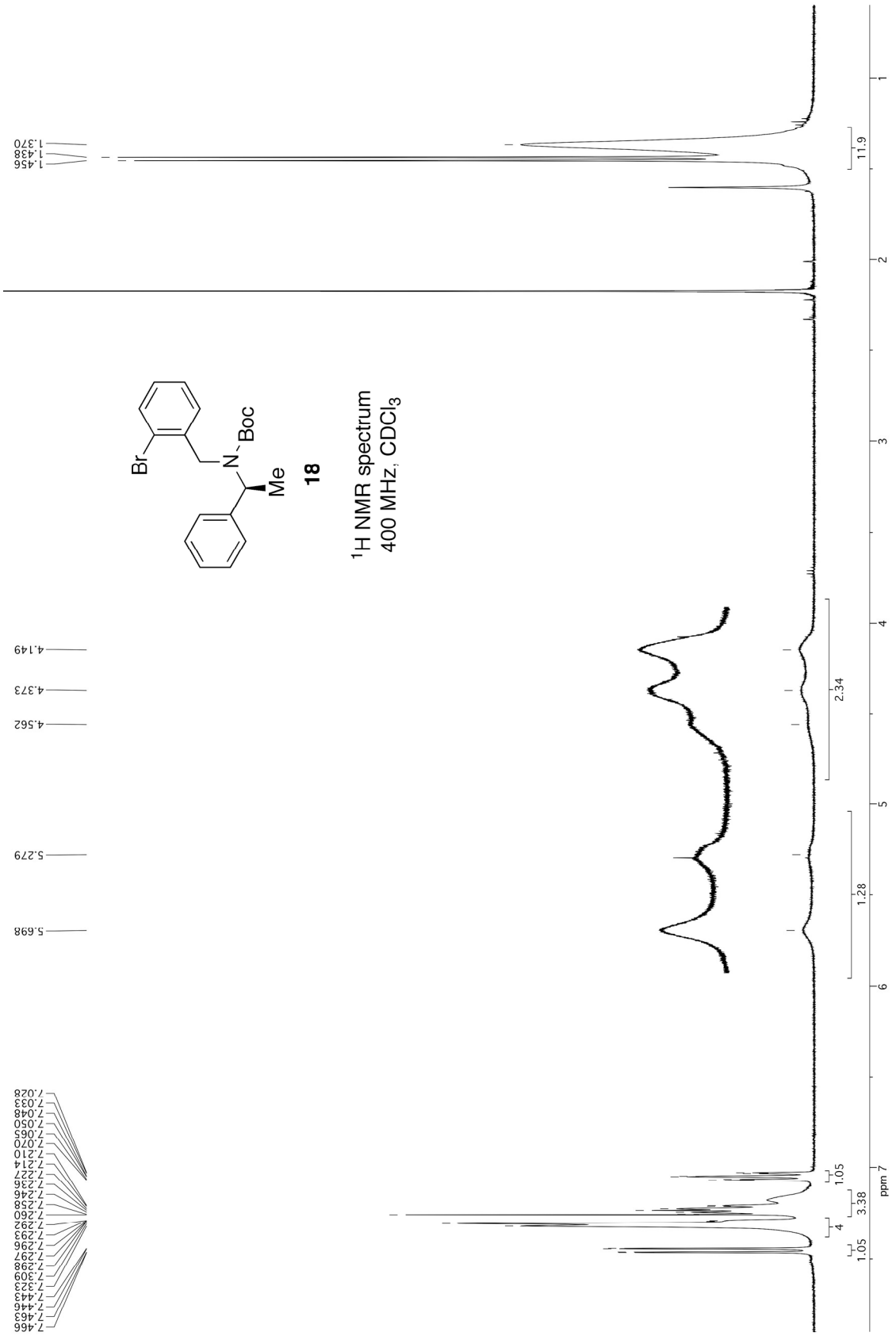


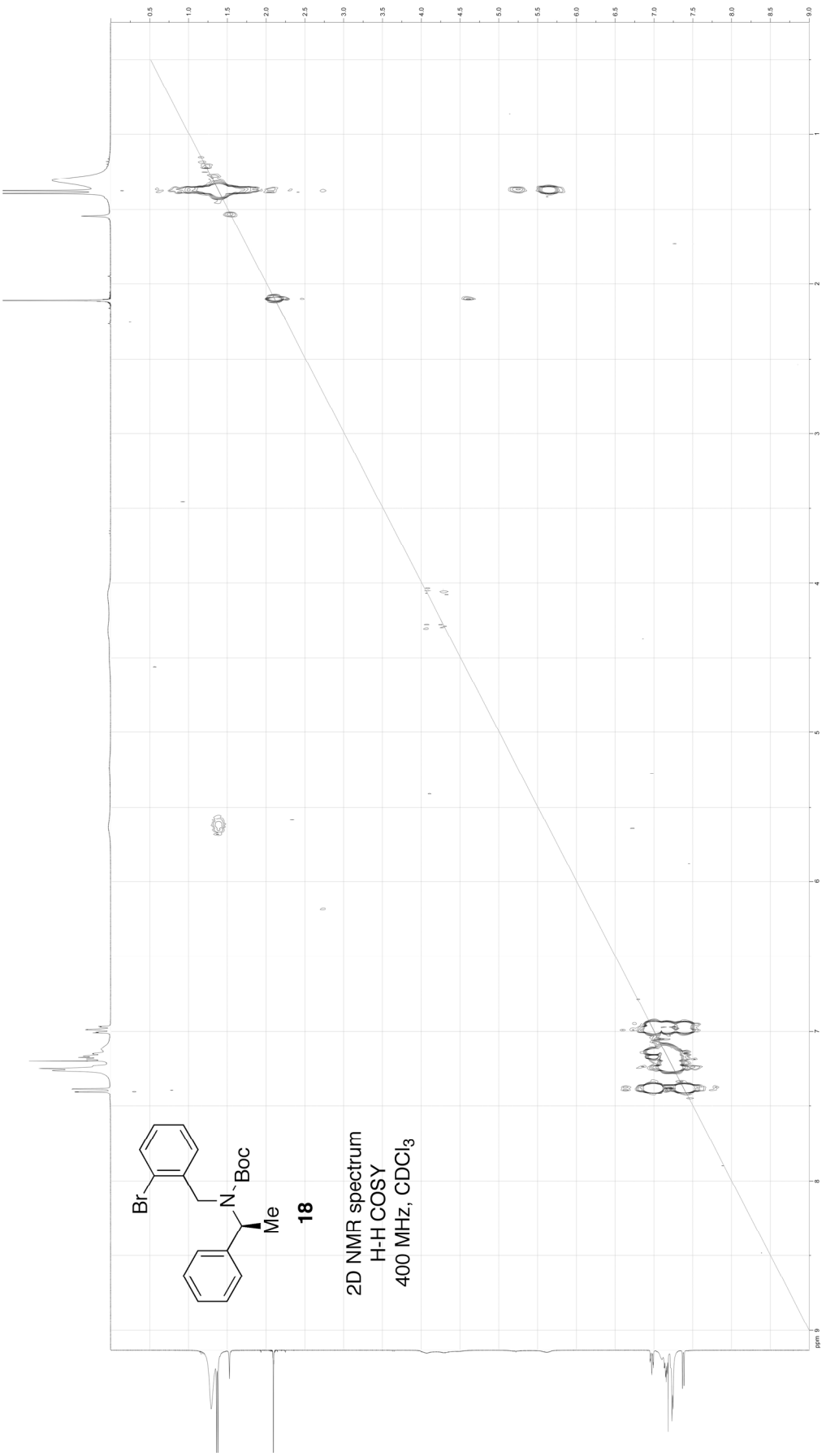


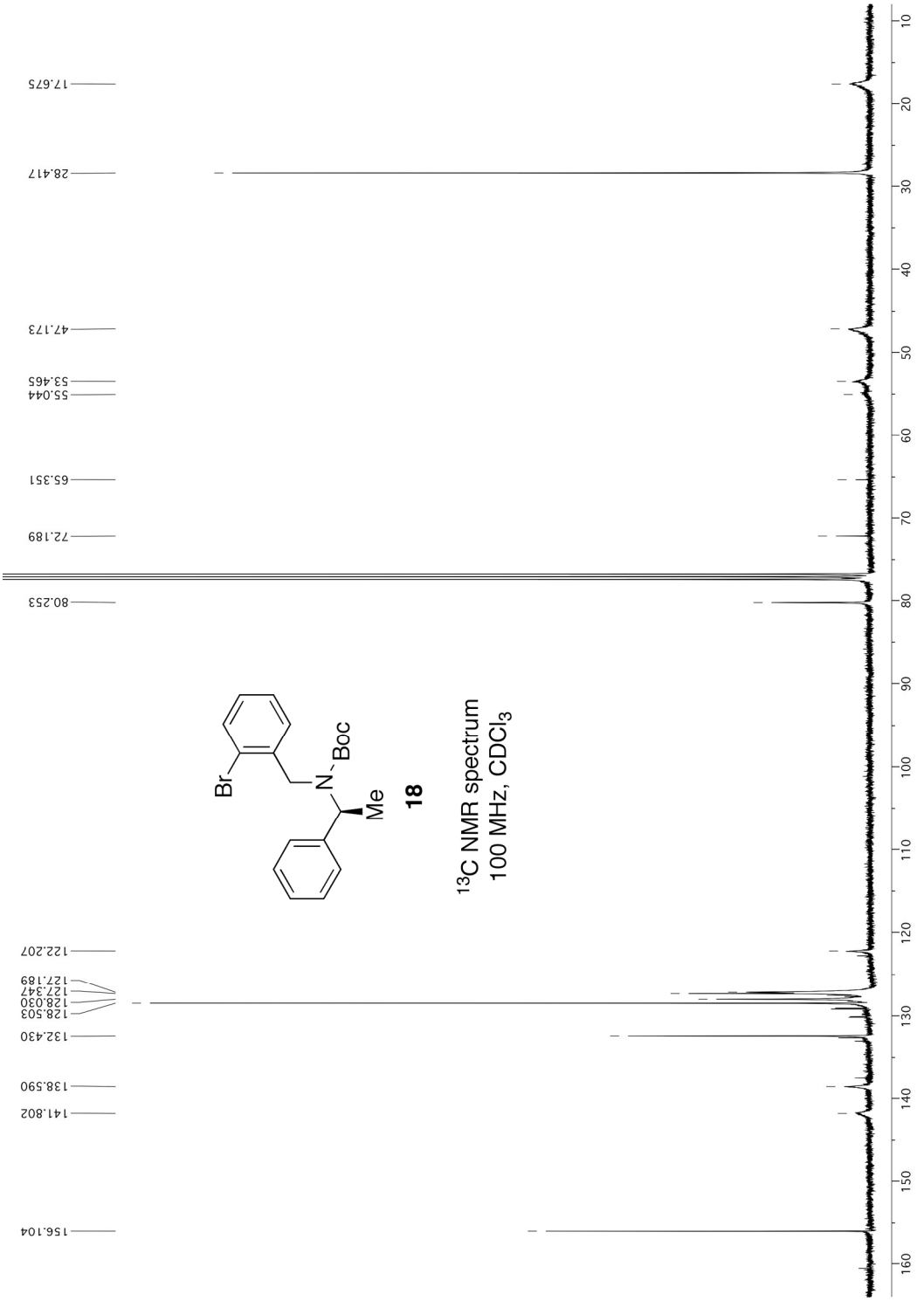

^{19}F NMR spectrum
376.5 MHz, $CDCl_3$
2:1
15a
15b
Me
CF_3
O
N
E
Z
TFA
0.342
1
2.07
-67.539
-68.011
-61
-62
-63
-64
-65
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79

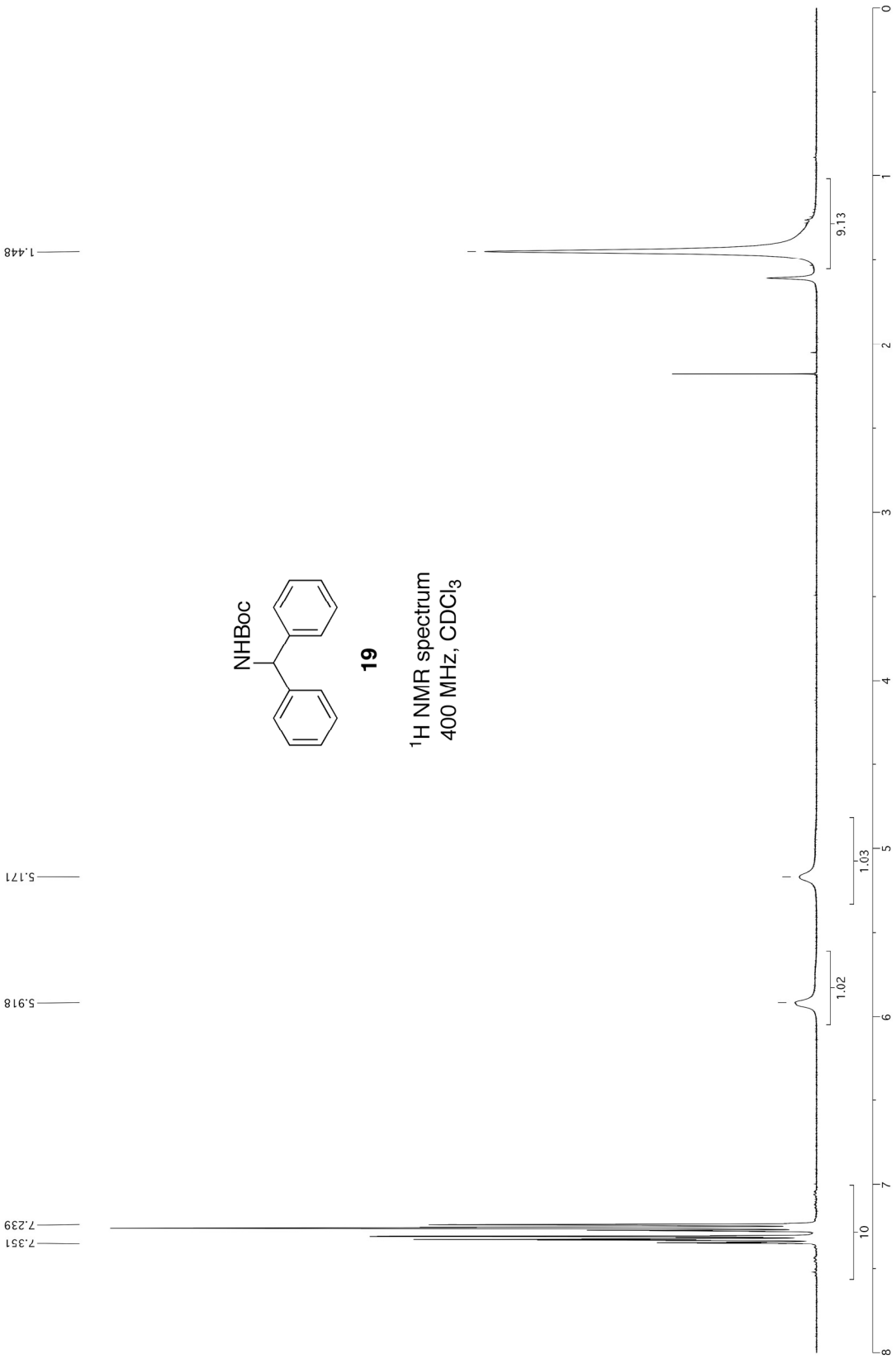


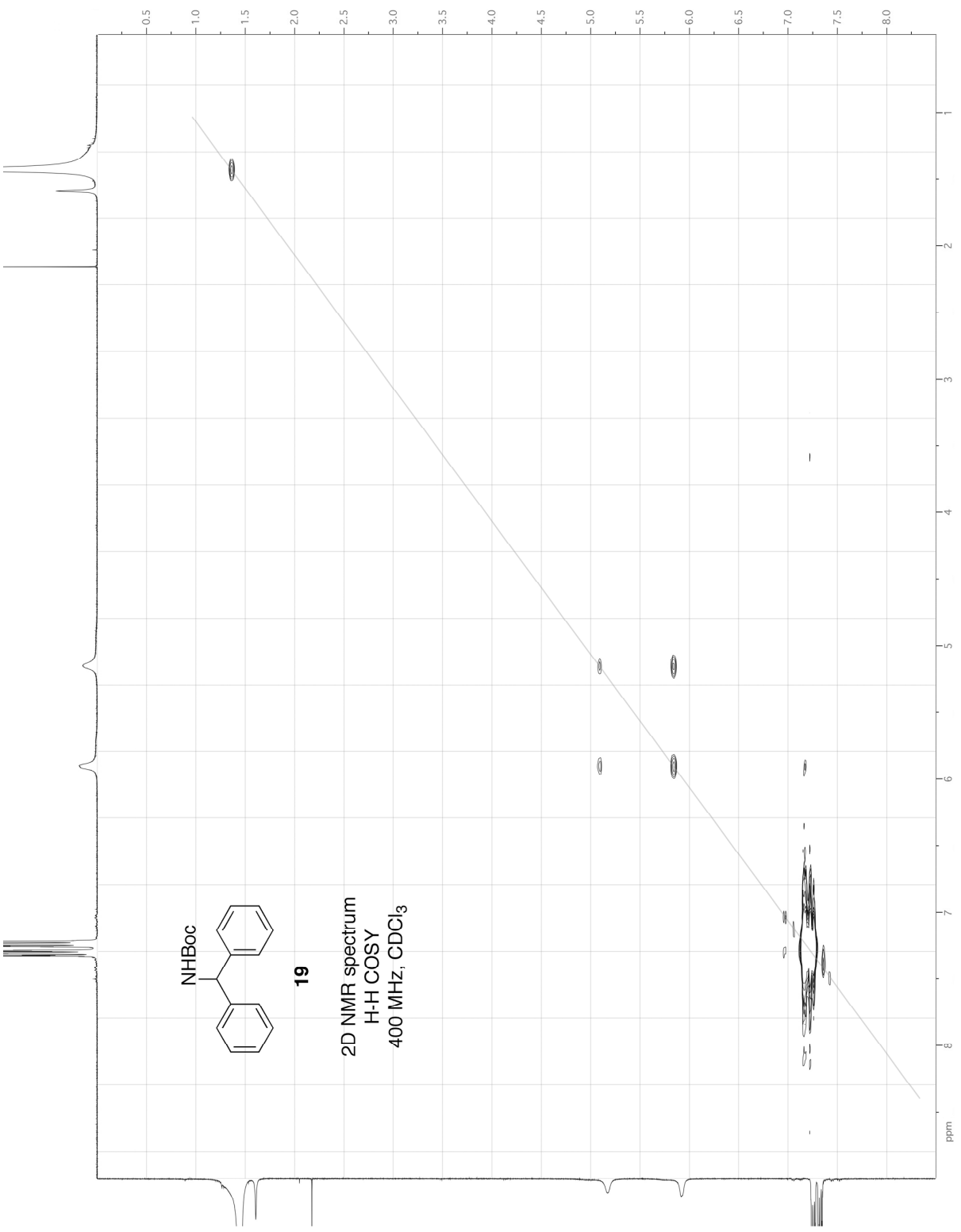


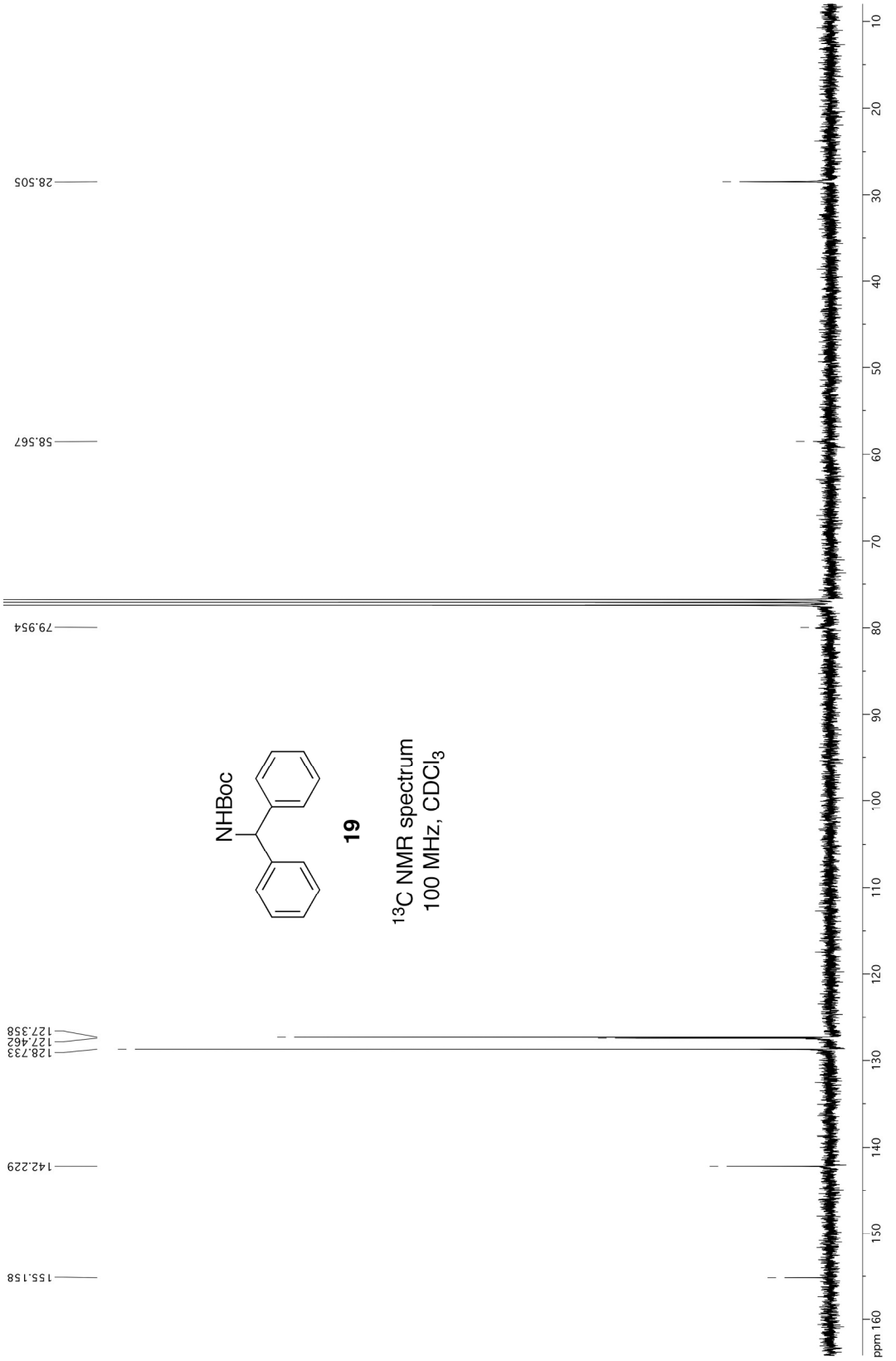


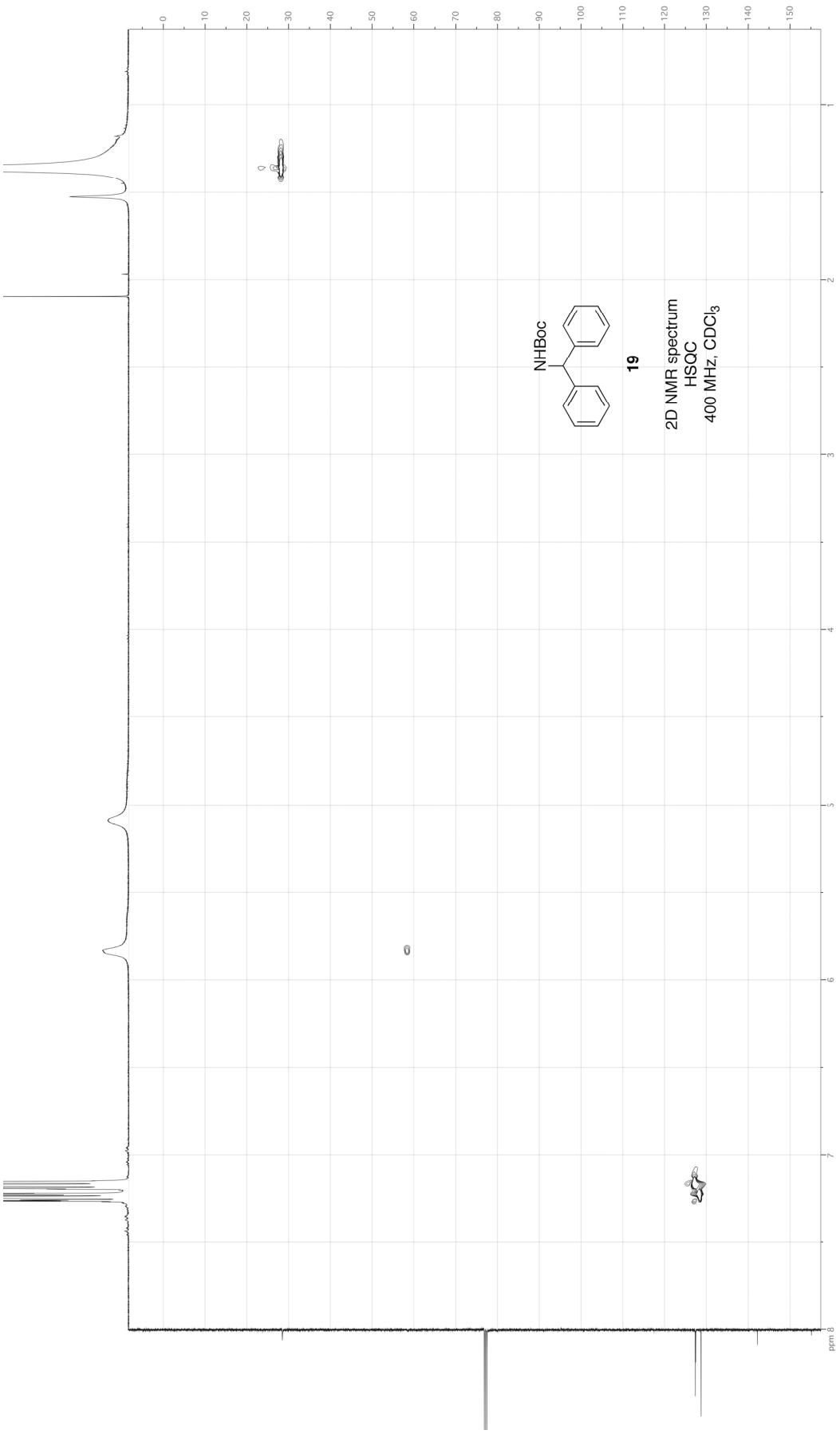


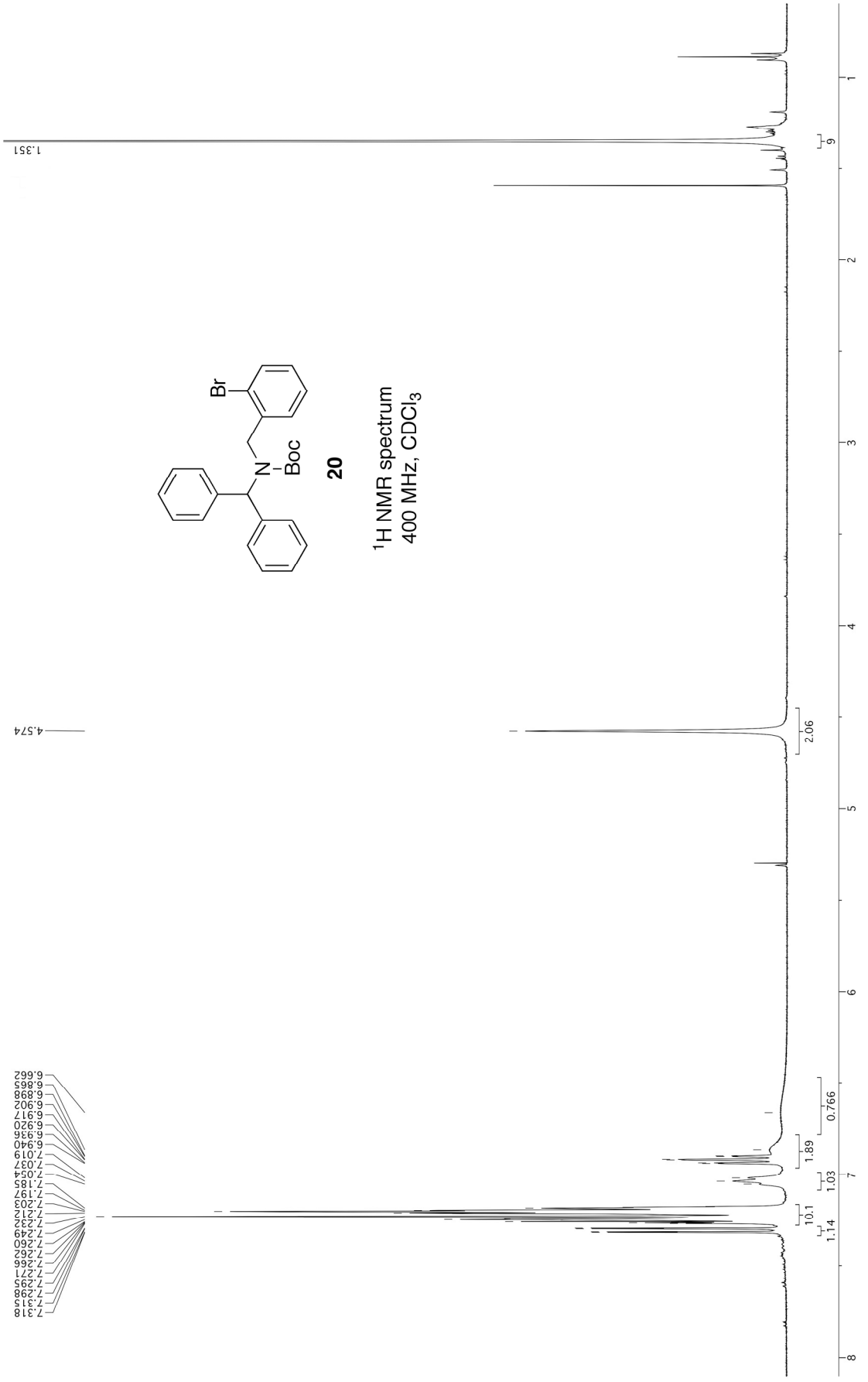


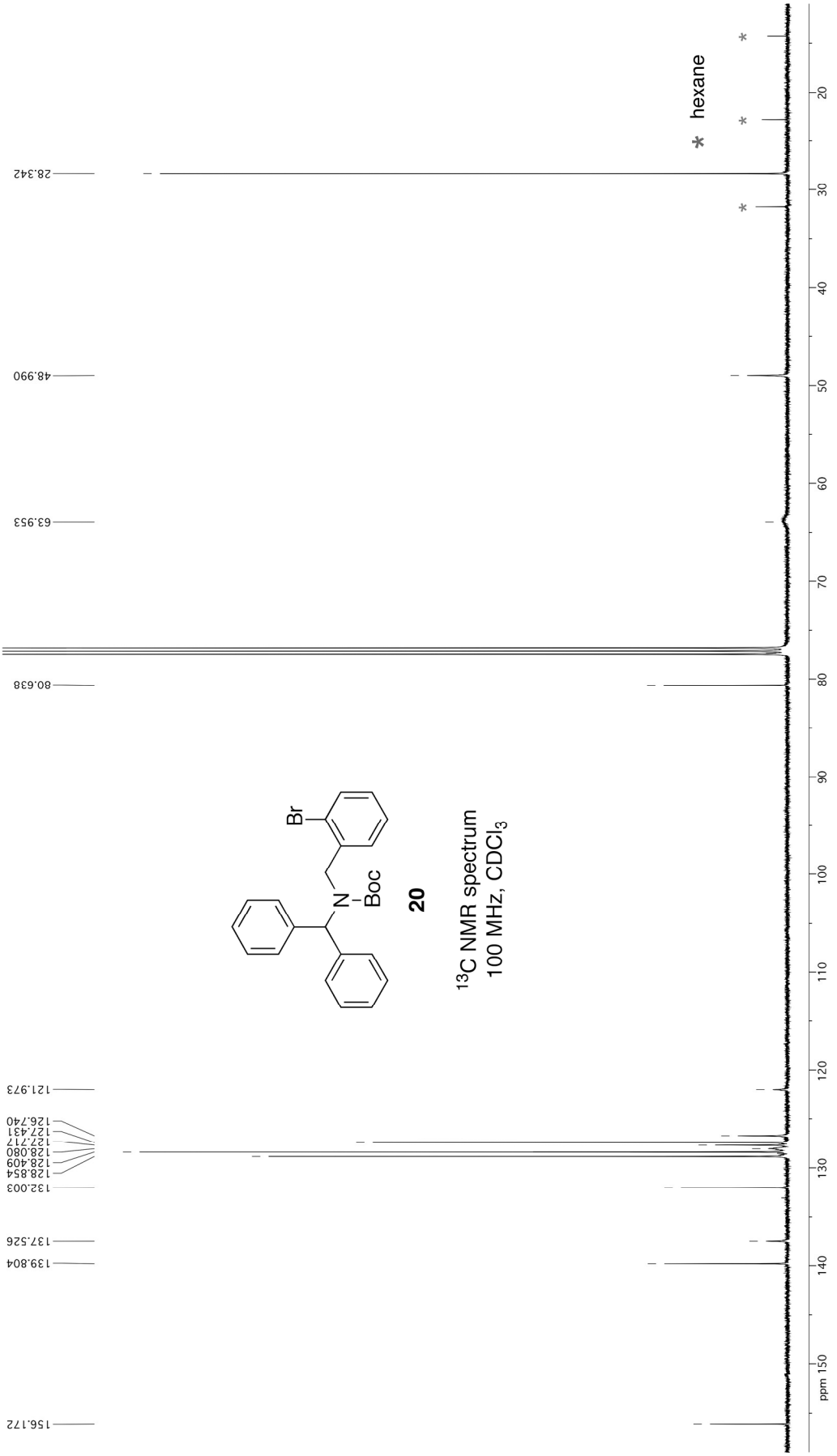


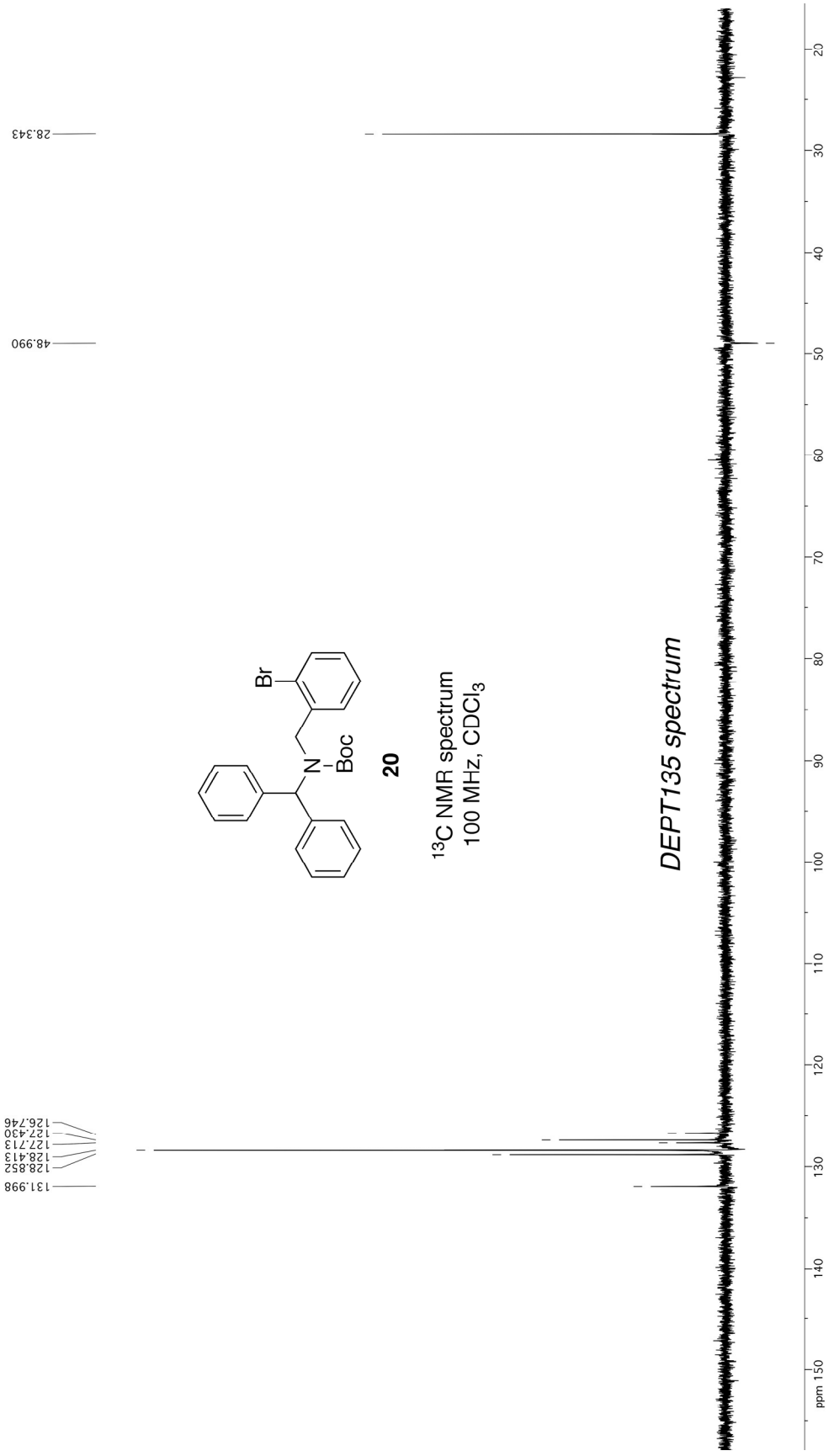

NHBoc
19
2D NMR spectrum
H-H COSY
400 MHz, $CDCl_3$
ppm

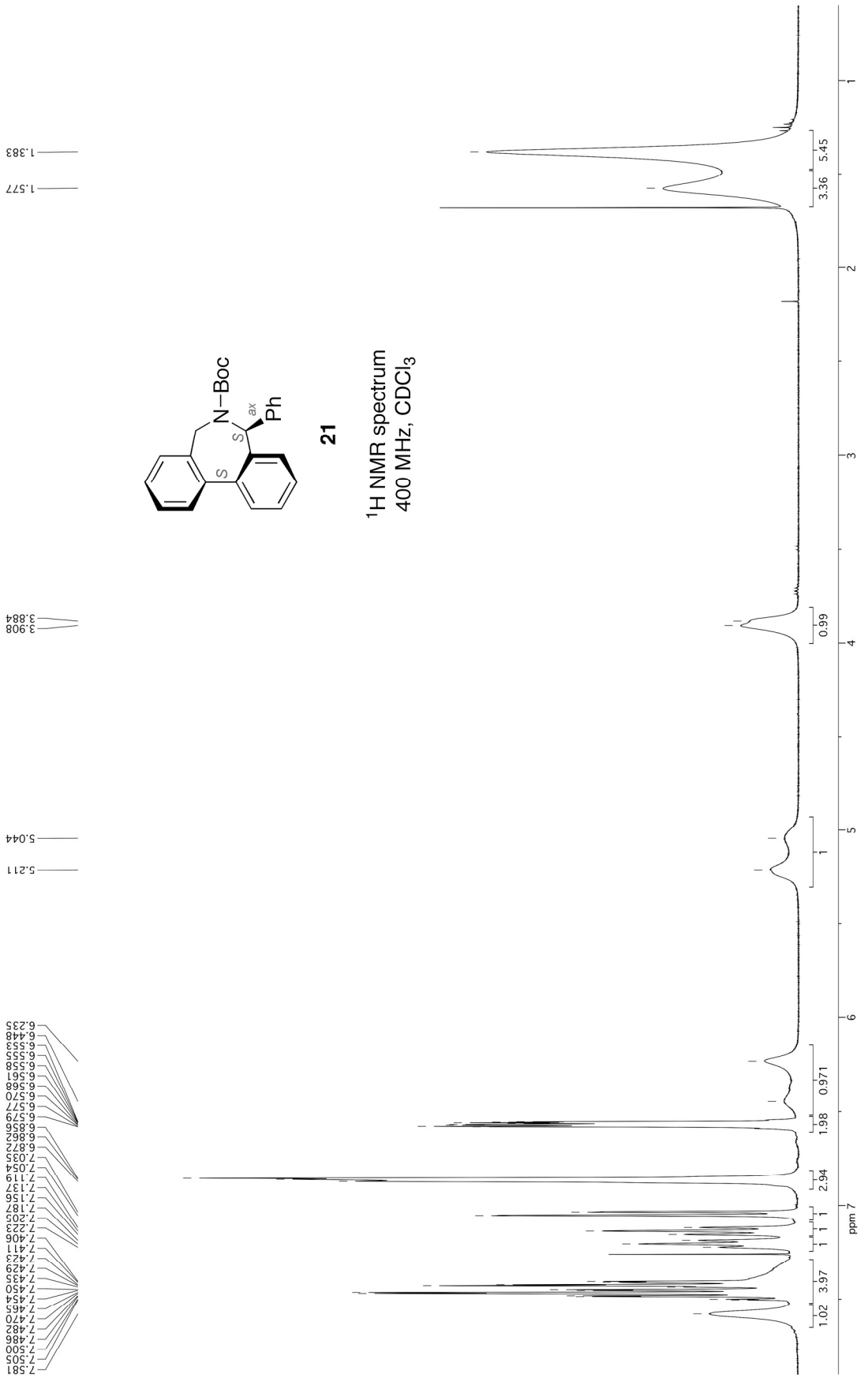


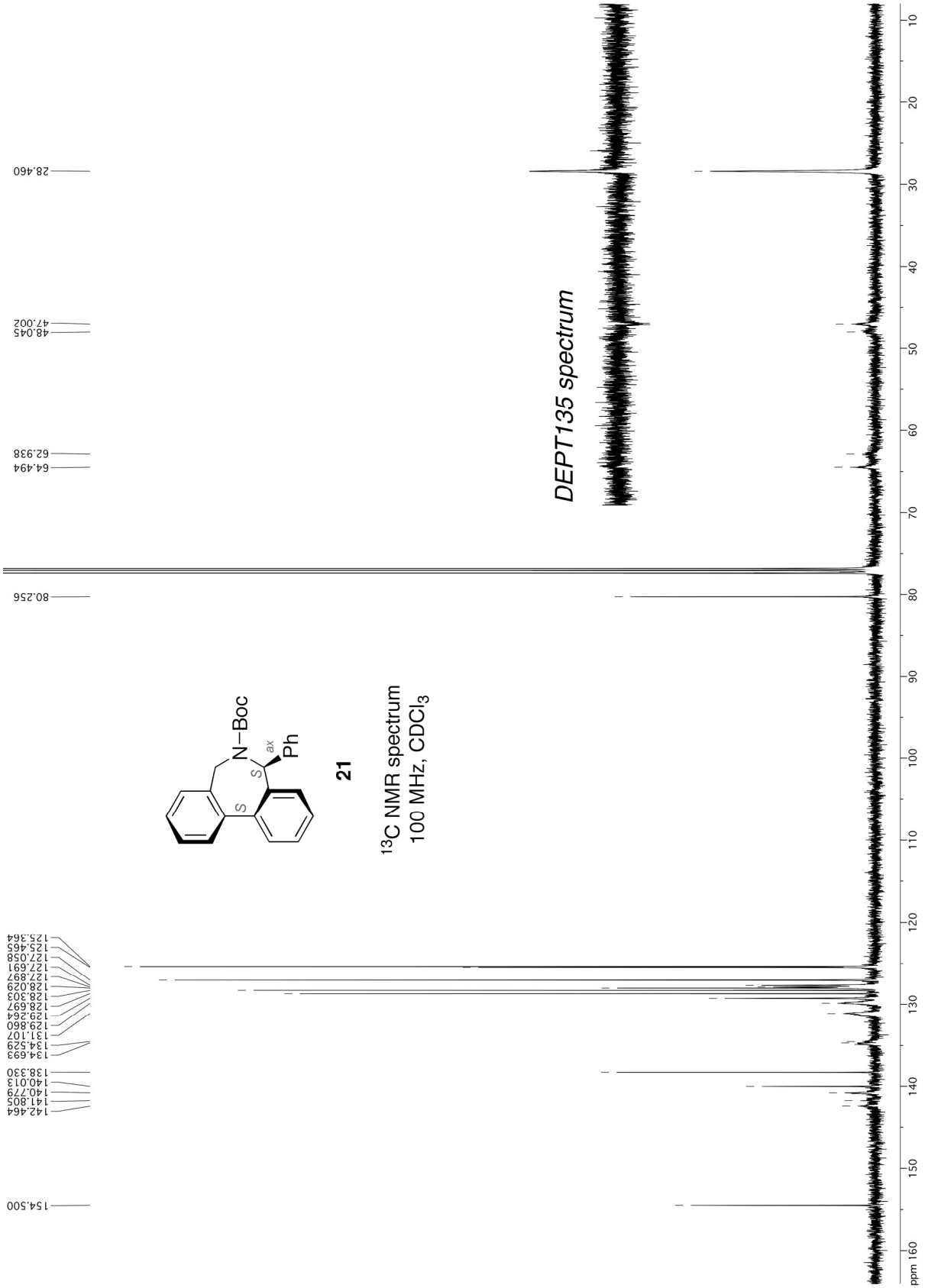

NHBoc
19
2D NMR spectrum
HSQC
400 MHz, $CDCl_3$
ppm

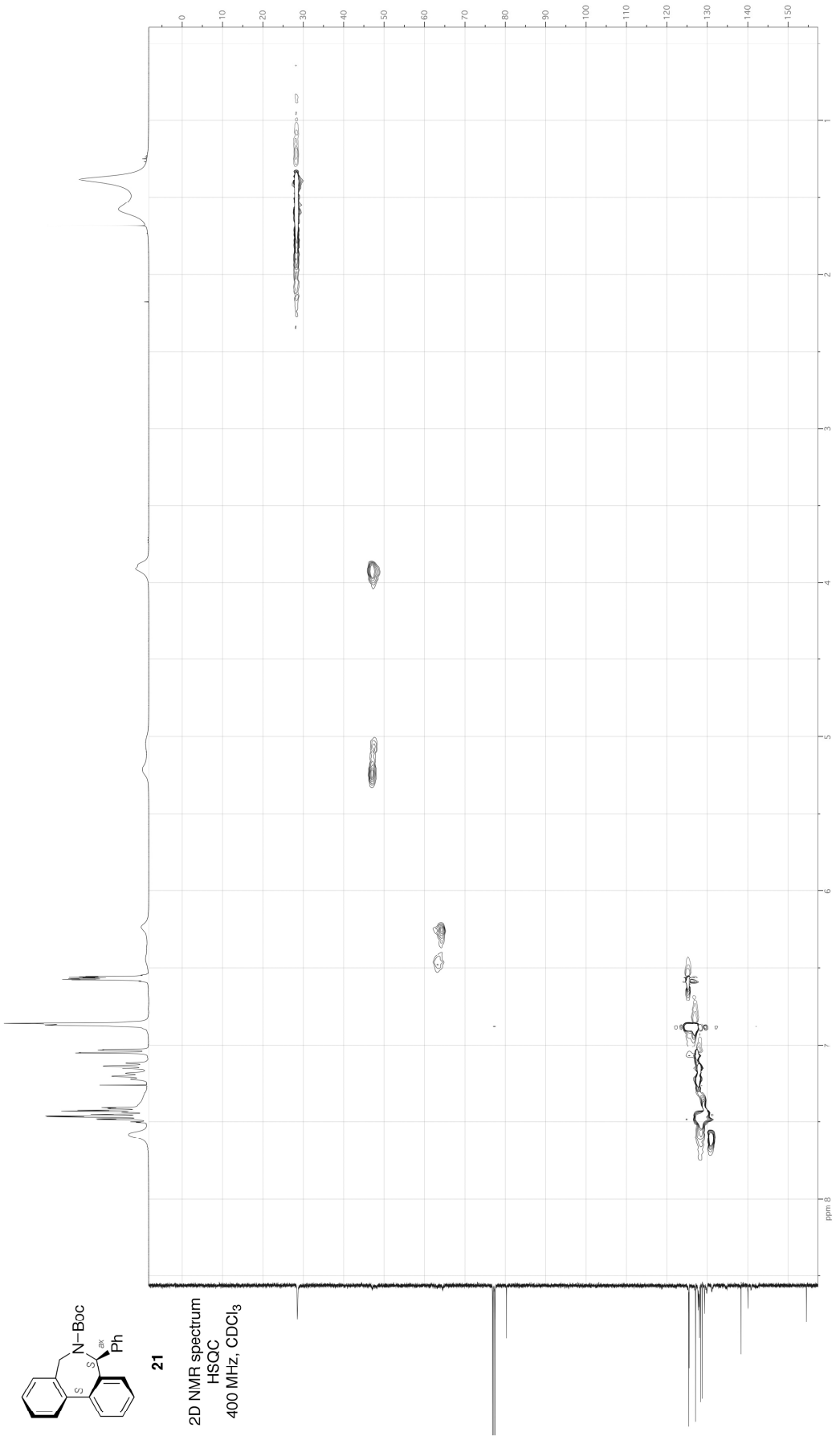


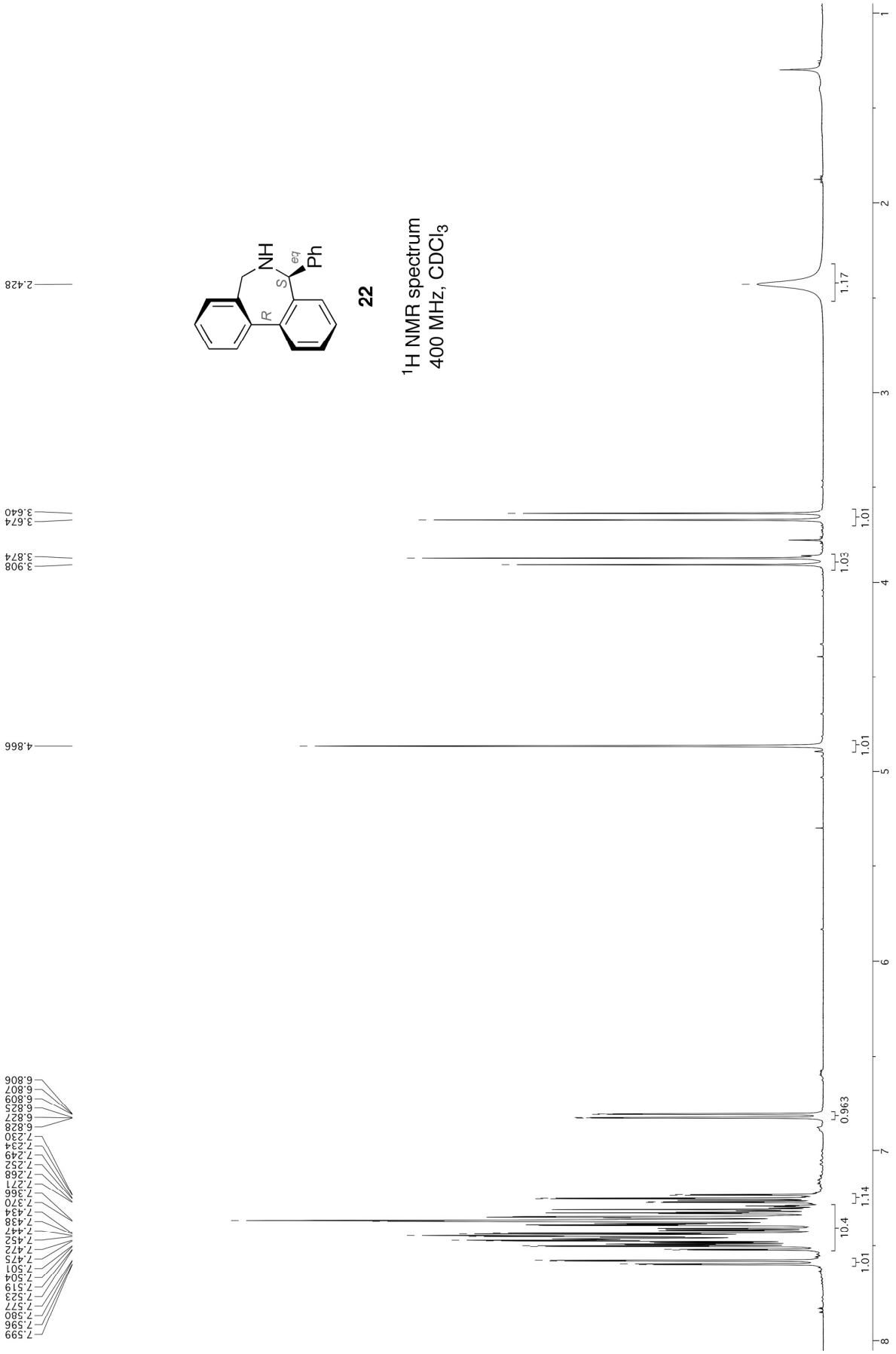


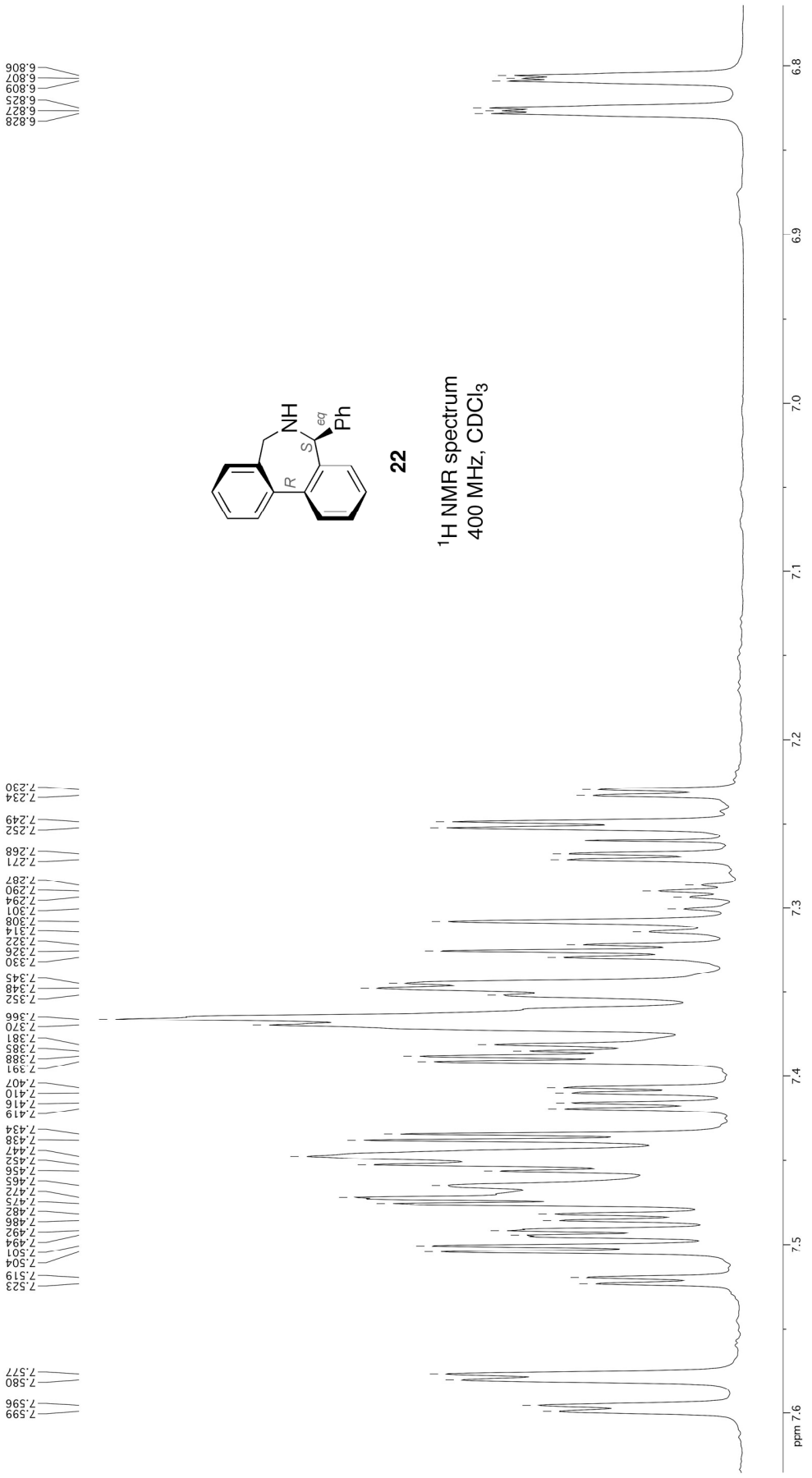


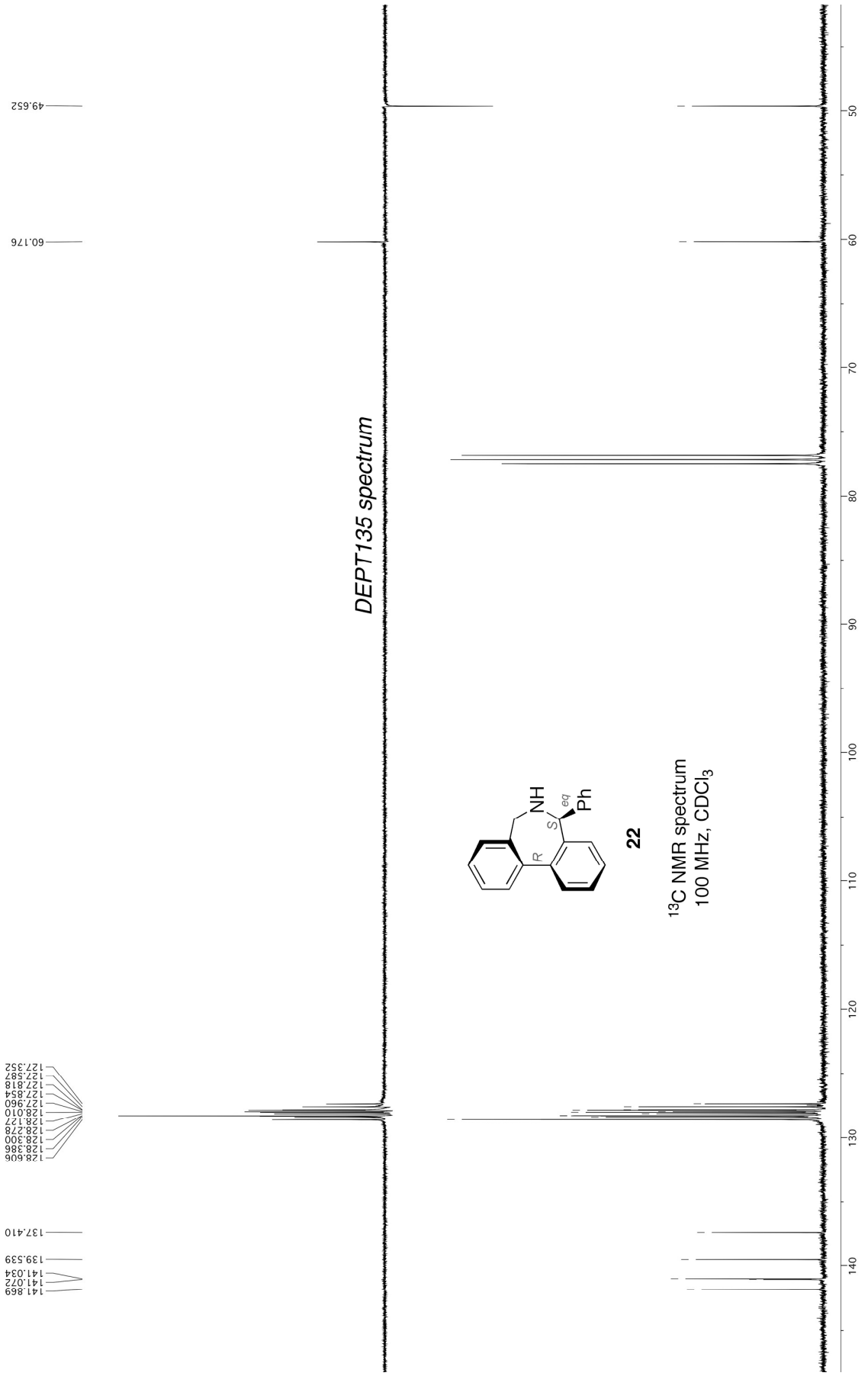







NH
S
eq
Ph
R
22
^{1}H NMR spectrum
400 MHz, CDCl$_3$
2.428
3.640
3.674
3.874
3.908
4.866
6.806
6.807
6.809
6.825
6.827
6.828
7.230
7.234
7.249
7.252
7.268
7.271
7.366
7.370
7.434
7.438
7.447
7.452
7.472
7.475
7.501
7.504
7.519
7.523
7.577
7.580
7.596
7.599
1.17
1.01
1.03
1.01
0.963
1.14
10.4
1.01





Molecular mechanics calculations

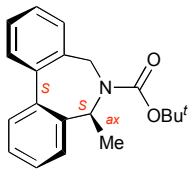
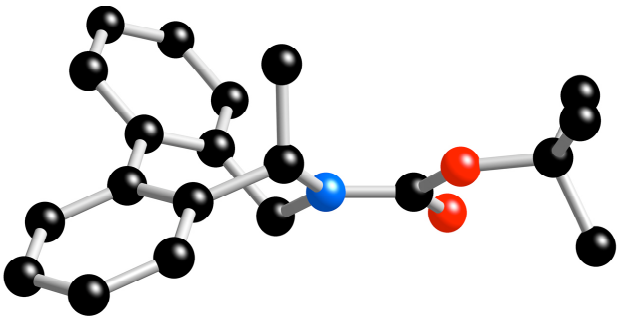
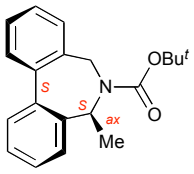
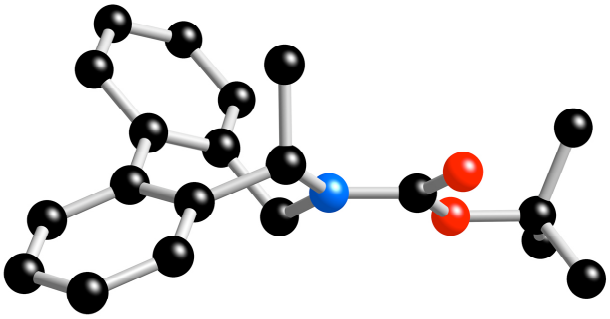
Minimised steric energy (MSE) structures for the 5*S* stereoisomers of compounds **4**, **14**, **21** and **22** were calculated on a Mac Mini 2.6 GHz Intel Core 2 Duo running Linux (Fedora Core 12, x86 64-bit), using *MacroModel* v. 8.0 (*Maestro* v. 9.0.211 interface) with the MM3 force field and Monte Carlo conformational search (*csearch*) method (1000 iterations). The *csearch* parameters were: no solvent; PRCG method; convergence on gradient; max. number of iterations 3000; convergence threshold 0.0200.

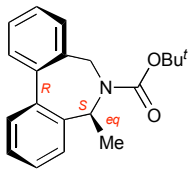
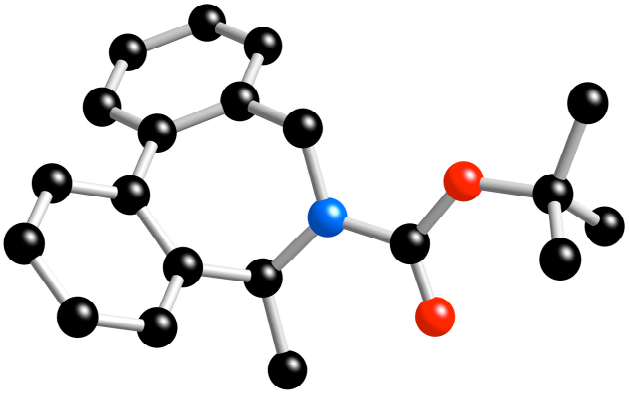
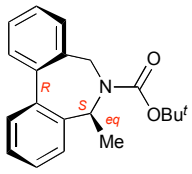
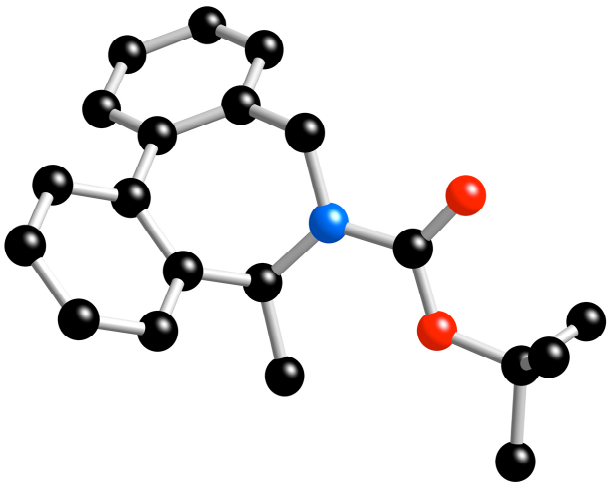
This procedure returned multiple repeats of the same global MSE structure, which is shown first for each compound listed below. The MSE values indicated are relative to the global MSE structure for that compound.

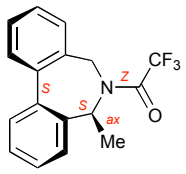
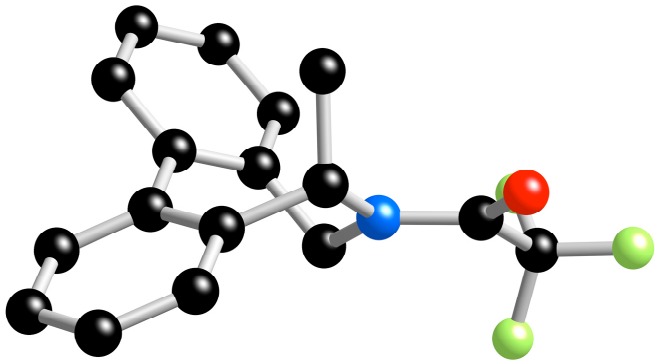
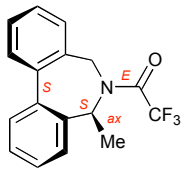
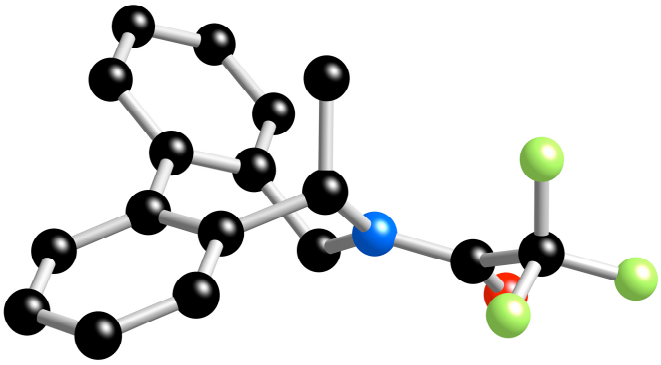
For the amine **22**, the difference in steric energy, ΔE, between the two diastereoisomers was converted into the equilibrium population at 25 ˚C indicated in the table using the equation:

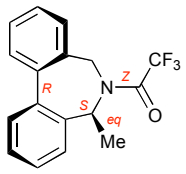
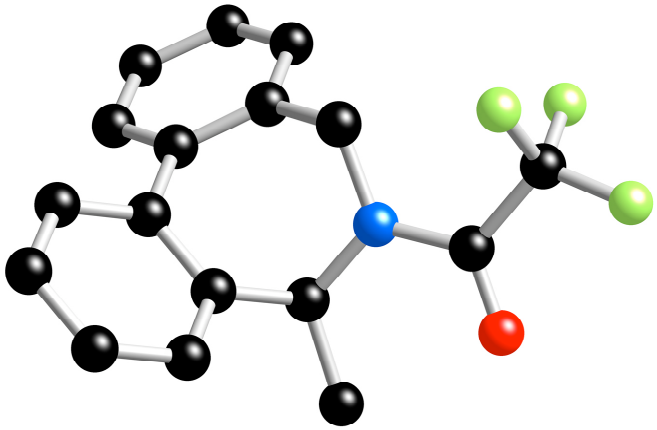
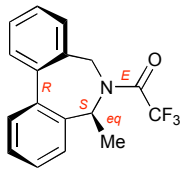
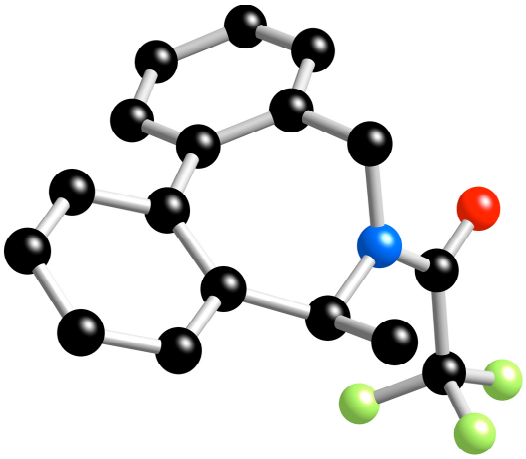
$$\Delta E = -\mathrm{R}T \ln K$$

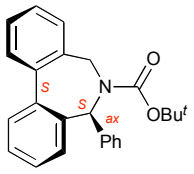
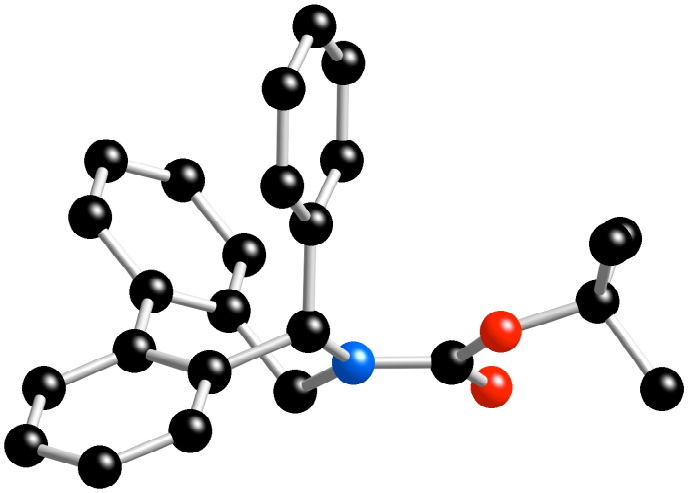
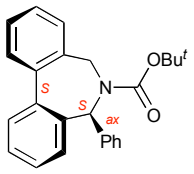
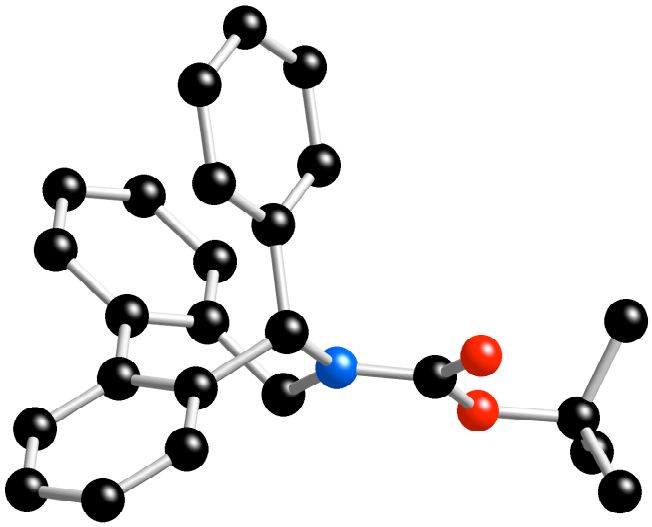
where K is the stereoisomer ratio and T is 298.15 K.

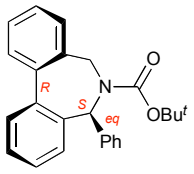
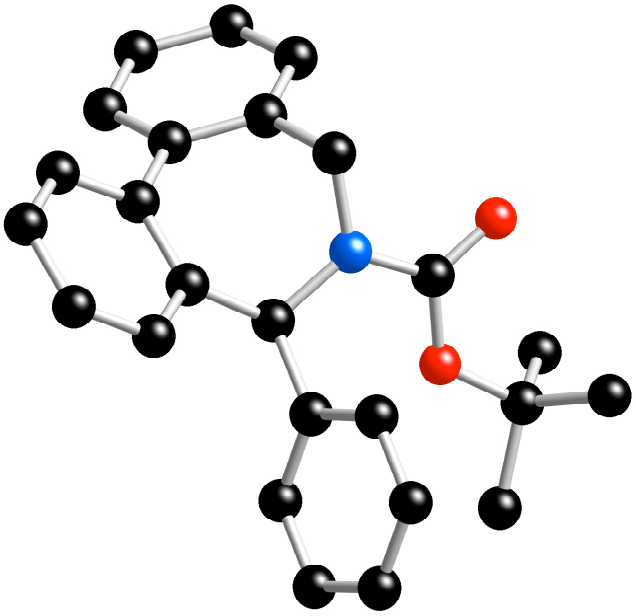
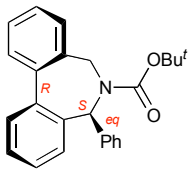
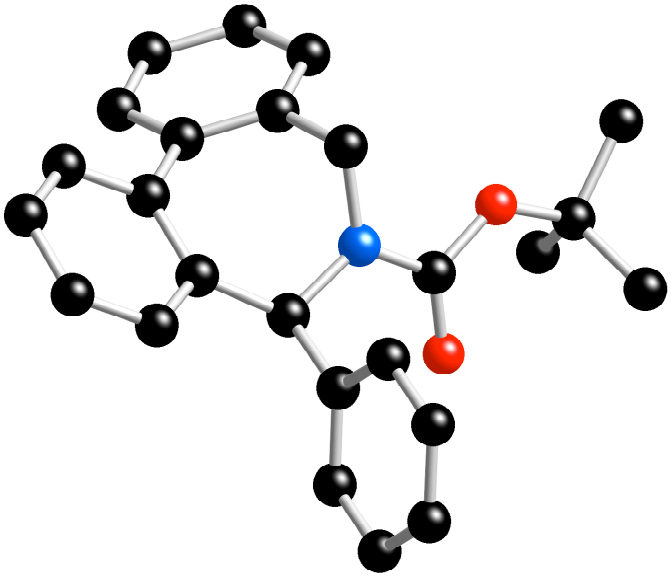
Compound	MSE structure
 (5*S*,a*S*)-**4** MSE = 0.0 kJ mol^{-1}	
 (5*S*,a*S*)-**4** MSE = +0.7 kJ mol^{-1}	

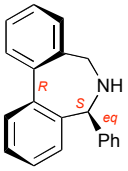
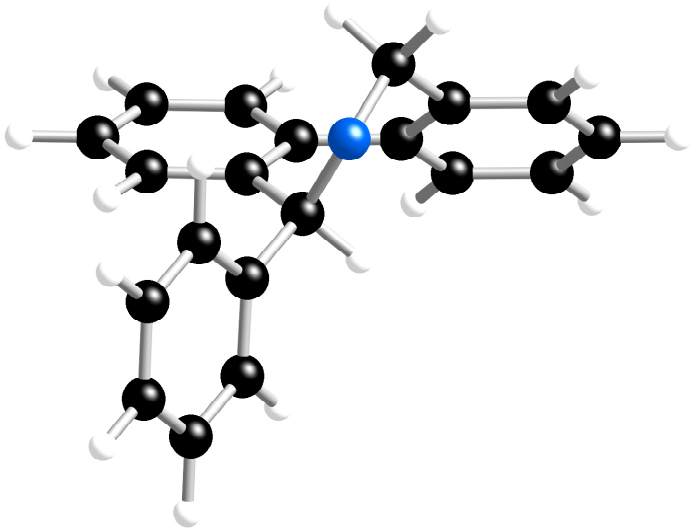
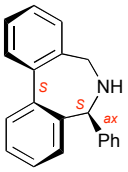
Compound	MSE structure
 (5*S*,a*R*)-**4** MSE = +19.2 kJ mol^{-1}	
 (5*S*,a*R*)-**4** MSE = +21.6 kJ mol^{-1}	

Compound	MSE structure
 (5*S*,a*S*)-**14a** MSE = 0.0 kJ mol^{-1}	
 (5*S*,a*S*)-**14b** MSE = +5.0 kJ mol^{-1}	

Compound	MSE structure
 (5*S*,a*R*)-**14a** MSE = +20.1 kJ mol^{-1}	
 (5*S*,a*R*)-**14b** MSE = +30.1 kJ mol^{-1}	

Compound	MSE structure
 (5*S*,a*S*)-**21** MSE = 0.0 kJ mol^{-1}	
 (5*S*,a*S*)-**21** MSE = +3.9 kJ mol^{-1}	

Compound	MSE structure
 (5*S*,a*R*)-**21** MSE = +12.0 kJ mol^{-1}	
 (5*S*,a*R*)-**21** MSE = +20.7 kJ mol^{-1}	

Compound	MSE structure
 (5*S*,a*R*)-**22** MSE = 0.0 kJ mol^{-1} (a*R*):(a*S*) = 86:14	
 (5*S*,a*S*)-**22** MSE = +4.4 kJ mol^{-1}