Evolution and Application of Chiral Phosphoric Acid in the Enantioselective 1,3-Dipolar Cycloaddition of Methyleneindolinones and N,N'-Cyclic Azomethine Imines

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Index:

The complete list of authors in references 9i – 9k :

(9i) K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps, S. Wang, *J. Am. Chem. Soc.* **2005,** *127*, 10130.

(9j) S. Shangary, D. Qin, D. McEachern, M. Liu, R. S. Miller, S. Qiu, Z. Nikolovska-Coleska, K. Ding, G. Wang, J. Chen, D. Bernard, J. Zhang, Y. Lu, Q. Gu, R. B. Shah, K. J. Pienta, X. Ling, S. Kang, M. Guo, Y. Sun, D. Yang, S. Wang, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 3933.

(9k) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler, T. T. Diagana, *Science*, **2010,** *329*, 1175.

General methods:

Unless stated otherwise, all reactions were carried out in flame dried glassware. All solvents were purified and dried according to standard methods prior to use. Methyleneindolinones **1** [1], N,N'-cyclic azomethine imines **2** [2] **and** catalysts **3** [3] were prepared according to literature. ^{1}H and ^{13}C NMR spectra were recorded on a Varian instrument (300 MHz and 75 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet or unresolved, coupling constant(s) in Hz, integration). Data for ^{13}C NMR and ^{31}P are reported in terms of chemical shift (δ, ppm). IR spectra were recorded on a FT-IR spectrometer and only major peaks were reported in cm^{-1}. Optical rotations were reported as follows: $[\alpha]_D^{rt}$ (c: g/100 mL, in solvent). High resolution mass spectra (HRMS) were obtained by the ESI ionization sources. The ee value determination was carried out using chiral HPLC with Daicel Chiracel IA column on Waters with a 996 UV-detector.

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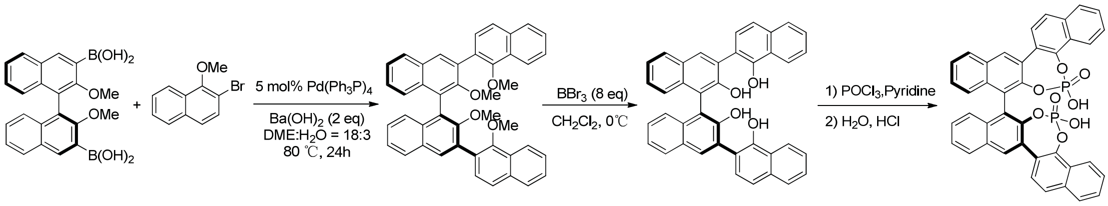
(1) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473.

(2) R. Shintani, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 10778.

(3) (a) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (c) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652.

General procedure and spectral data for the synthesis of catalyst 3l



A B C D 3l

(*S*)-Tetranaphthol **D** was prepared in a modified procedure according to literature [4]: From easily available starting materials **A** and **B**, compound **C** was prepared through typical Suzuki coupling reaction. Subsequent deprotection provided (*S*)-Tetranaphthol **D**.

Spectral data for compound C:

^{1}H NMR (300 MHz, DMSO) δ 8.19 (dd, J = 2.25, 6.9 Hz, 1H), 8.05 (s, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.81 (dd, J = 2.25, 5.49 Hz), 7.61 (s, 2H), 7.49 – 7.41 (m, 2H), 7.35 (dt, J = 1.8, 8.0 Hz, 1H), 7.29 – 7.20 (m, 1H), 3.63 (s, 1H), 3.16 (s, 1H);

^{13}C NMR (75 MHz, DMSO) δ 153.4, 152.5, 133.5, 132.9, 131.1, 130.3, 129.5, 128.2, 127.3, 127.1, 126.8, 126.1, 125.4, 125.3, 125.0, 124.7, 124.4, 123.9, 122.4, 121.7, 60.2, 59.6;

IR: 2935, 1359, 908, 732 cm^{-1};

HRMS (ESI): $C_{44}H_{34}O_4$+Na, Calc: 649.2349, Found: 649.2369.

Spectral data for compound D:

^{1}H NMR (300 MHz, DMSO) δ 7.99 (t, J = 3.3 Hz, 2H), 7.62 – 7.53 (m, 4H), 7.44 (d, J = 7.5 Hz, 1H), 7.41 (s, 2H), 7.19 (t, J = 7.5 Hz, 1H), 6.75 (bs, 1H), 6.61 (t, J = 6.75 Hz, 1H), 5.99 (bs, 1H);

^{13}C NMR (75 MHz, DMSO) δ 150.4, 147.5, 134.1, 132.7, 129.8, 128.7, 128.2, 127.3, 127.1, 126.2, 126.1, 126.0, 125.2, 124.5, 122.5, 121.3, 120.7, 114.0;

IR: 3399, 1251, 906, 732 cm^{-1};

HRMS (ESI): $C_{40}H_{26}O_4$+Na, Calc: 593.1723, Found: 593.1741.

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(4) K. Ishihara, H. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 6920.

D (2.0 mmol, 1.14g) was dissolved in pyridine (15 mL) under N_2 atmosphere in a flame-dried two necked 50-ml round-bottom flask equipped with a magnetic stir bar. To the resulting solution was added phosphorus oxychloride (5.0 equiv.) at room temperature and the reaction mixture was stirred at 70 ℃ for 20 h. Then water (15 mL) was added and the resulting suspension was stirred for additional 12 h. The resulting mixture was diluted with CH_2Cl_2 (100 mL), washed with 6N HCl (3×20 mL) to remove pyridine, and combined organic layers were concentrated under reduced pressure. The resultant solids were dissolved in MeOH (15 mL). To the resulting solution was added conc. HCl (10 mL) at room temperature, and stirred further at this temperature for 1 h. The mixture was extracted with CH_2Cl_2 (3×30 mL), and then, the organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The residual crude product was purified by column chromatography on silica gel with elution by CH_2Cl_2/ MeOH (100:1 - 20:1) to yield a white solid. The product was recrystallized from CH_2Cl_2/hexane to give pure *(S)*-bis-phosphoric acid **3l** as a white solid.

^{1}H NMR (300 MHz, DMSO) δ 8.40 (s, 1H), 8.32 (bs, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.04 (bs, 1H), 7.94 (s, 2H), 7.62 (bs, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 3.43 (bs, 1H);

^{13}C NMR (75 MHz, DMSO) δ 147.2 (d, $J_{P\text{-}C}$= 9.75 Hz), 145.9 (d, $J_{P\text{-}C}$= 8.25 Hz), 134.1, 132.9, 130.4, 130.3, 130.1, 128.3, 127.5, 127.3 (d, $J_{P\text{-}C}$= 2.25 Hz), 126.9, 126.4, 126.3, 126.2, 125.1 (d, $J_{P\text{-}C}$= 2.25 Hz), 124.9, 124.2, 123.5, 123.3, 123.2;

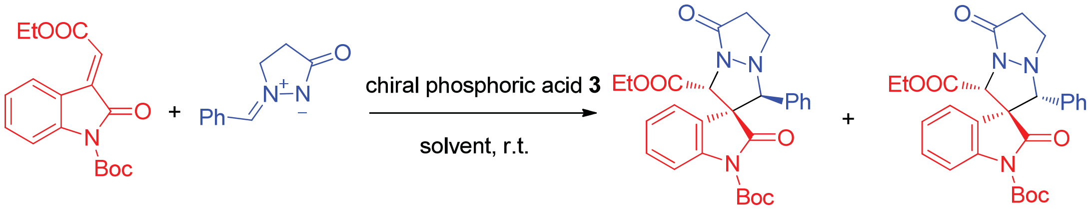
^{31}P NMR (DMSO, 121.5 MHz) δ -3.05;

IR: 3421, 1627, 1255, 1091 cm^{-1};

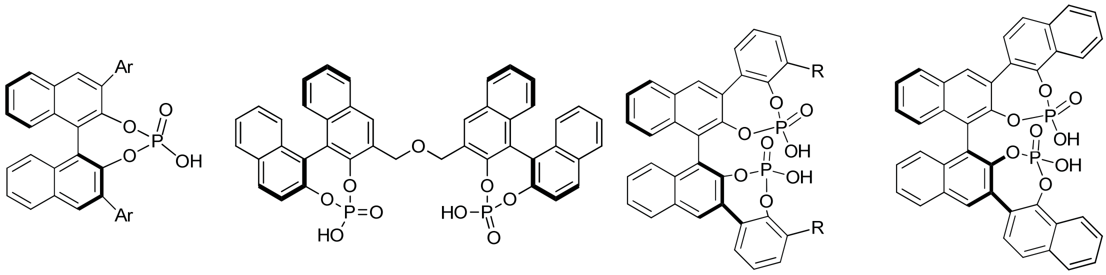
HRMS (ESI): $C_{40}H_{24}O_8P_2$ -H, Calc: 693.0874, Found: 693.0871.

Catalyst screening and evolution:

Table 1.Catalyst Screening and Evolution.[a]

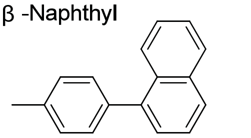


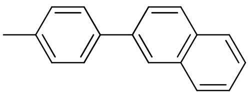
1a **2a** **4aa** **4aa'**



3a - 3g **3h** **3i - 3k** **3l, current work**

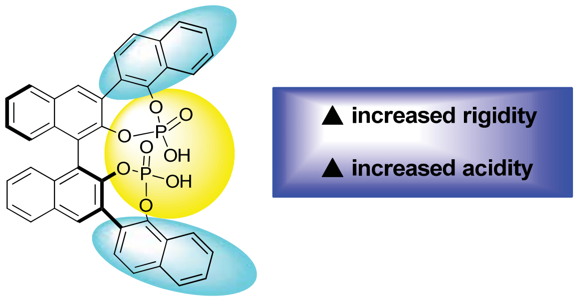
3a: Ar = Ph
3b: Ar = biphenyl
3c: Ar = 3,5-$(CF_3)_2$Ph
3d: Ar = 2,4,6-iPr_3Ph
3e: Ar = β -Naphthyl

3f: Ar = 

3g: Ar = 

3i: R = H; **3j**: R = Me; **3k**: R = Ph

Design of new catalyst



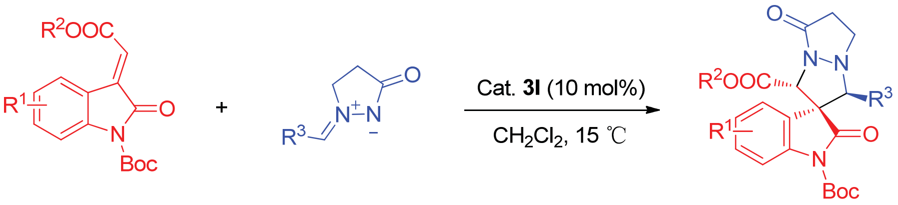
entry	catalyst	solvent	additive	conversion (%)[b]	dr (**4aa** : **4aa'**)[b]	ee of **4aa**(%)[c]
1	**3a**	CH_2Cl_2	-	35	1:1	10
2	**3b**	CH_2Cl_2	-	42	1:1	17
3	**3c**	CH_2Cl_2	-	30	1:1	< 5
4	**3d**	CH_2Cl_2	-	29	1:1	< 5
5	**3e**	CH_2Cl_2	-	32	1:1	5
6	**3f**	CH_2Cl_2	-	30	1:1	11
7	**3g**	CH_2Cl_2	-	28	1:1	11
8	**3b**	Toluene	-	36	1:1	37
9	**3b**	Ether	-	28	1:1	47
10	**3b**	THF	-	34	1:1	rac
11	**3b**	MTBE	-	34	1:1	37

12	**3b**	DME	-	29	1:1	rac
13	**3b**	CPME	-	32	1:1	37
14	**3b**	Hexane	-	15	1:1	rac
15	**3b**	Ether	3A MS	26	1:1	46
16	**3b**	Ether	4A MS	28	1:1	45
17	**3b**	Ether	5A MS	28	1:1	43
18	**3h**	CH_2Cl_2	-	42	1:1	39
19	**3h**	Ether	-	34	1:1	72
20	**3i**	CH_2Cl_2	-	89	1:1	74
21	**3i**	Toluene	-	79	1:1	17
22	**3i**	Ether	-	62	1:1	13
23	**3i**	MTBE	-	70	1:1	rac
24	**3i**	$CHCl_3$	-	87	1:1	56
25	**3i**	DCE	-	89	1:1	66
26	**3i**	Hexane	-	<10	1:1	n.d.
27	**3i**	THF	-	86	1:1	rac
28	**3i**	CH_2Cl_2	3A MS	86	1:1	77
29	**3i**	CH_2Cl_2	4A MS	85	1:1	79
30	**3i**	CH_2Cl_2	5A MS	84	1:1	72
31[d]	**3i**	CH_2Cl_2	-	65	1:1	80
32[e]	**3i**	CH_2Cl_2	-	<15	n.d.	n.d.
33	**3j**	CH_2Cl_2	-	96	2:1	89
34	**3k**	CH_2Cl_2	-	68	1:1	5
35[f]	**3l**	CH_2Cl_2	-	>99	8:1	92
36[f,g]	**3l**	CH_2Cl_2	-	>99	16:1	94
37[f,h]	**3l**	CH_2Cl_2	-	95	8:1	97
38[f,g,i]	**3l**	CH_2Cl_2	-	>99	16:1	92
39[f,g,j]	**3l**	CH_2Cl_2	-	>99 (93)	16:1	98

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.05 mmol), **2a** (0.05 mmol),

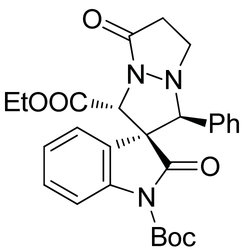
catalyst **3** (0.005 mmol) in solvent (1.0 mL) at room temperature for 72 h. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by chiral HPLC on a Chiralcel IA column. [d]The reaction was was performed at 0 ℃. [e]The reaction was was performed -40 ℃.[f]The reaction was carried out for 4 h. [g] The reaction was performed at 15 ℃. [h]The reaction was performed at 10 ℃. [i]The reaction was carried out in 2 ml CH_2Cl_2. [j]The reaction was carried out in 0.1 M scale with a **1**/**2** = 1:1.3 ratio, the isolated yield is given in the parenthesis.

General procedure and spectral data for the synthesis of 4



In an ordinary vial, methyleneindolinone**1** (0.1 mmol) was added to a stirred mixture of azomethine imine **2** (0.13 mmol) and catalyst **3l** (0.01 mmol) in CH_2Cl_2 (1.0 mL) at 15 ℃. The mixture was stirred at this temperature for 4 h. The reaction mixture was then directly purified by silica gel chromatography (petroleum ether/AcOEt 2:1 - 1:1) without workup and fractions were collected and concentrated in vacuo to provide the pure desired products **4**.

(*1'S,2'S,3'R*)-1-tert-butyl 3'-ethyl 2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'*H*-spiro[indoline-3,2'-pyrazolo[1,2-*a*]pyrazole]-1,3'-dicarboxylate, **4aa**. (Table 2, entry 1)



4aa was isolated by column chromatography in 93% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.35 (td, J = 7.9, 1.3 Hz, 1H), 7.22 (ddd, J = 7.4, 6.3, 1.2 Hz, 2H), 7.13 (t, J = 7.2 Hz, 2H), 6.96 (d, J = 7.2 Hz, 2H), 4.68 (s, 1H), 4.30 - 4.19 (m, 1H), 4.15 – 4.04 (m, 1H), 4.12 (s, 1H), 3.64 (t, J = 8.4 Hz, 1H), 3.34 – 3.15 (m, 1H), 2.99 (dt, J = 13.5, 8.1 Hz, 1H), 2.79 (dd, J = 15.6, 7.5 Hz, 1H), 1.48 (s, 9H), 1.07 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 166.4, 164.8, 148.2, 140.2, 130.2, 130.2, 129.0, 128.2, 127.2, 124.4, 123.7, 121.8, 114.9, 84.3, 77.2, 65.3, 62.2, 59.4, 52.6, 36.3, 27.8, 13.7;

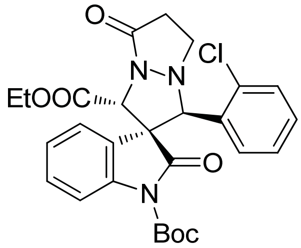
IR: 2982, 2933, 2844, 1767, 1737, 1697, 1605, 1467, 1413, 1353, 1294, 1252, 1152, 1106, 1072, 841, 753, 700 cm^{-1};

$[\alpha]_D^{rt}$ = -17 (c = 0.99, $CHCl_3$);

HRMS (ESI): $C_{27}H_{29}N_3O_6$+H, Calc: 492.2129, Found: 492.2134;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.1, t_{minor} = 9.1, 98% ee.

(1'R,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(2-chlorophenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ab**. (Table 2, entry 2)



4ab was isolated by column chromatography in 89% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 12.4, 4.5 Hz, 1H), 7.14 (t, *J* = 8.2 Hz, 3H), 4.91 (s, 1H), 4.70 (s, 1H), 4.32 – 4.16 (m, 1H), 4.16 – 4.00 (m, 1H), 3.48 (t, *J* = 8.0 Hz, 1H), 3.23 – 3.08 (m, 1H), 3.08 – 2.95 (m, 1H), 2.78 (dd, *J* = 14.4, 6.5 Hz, 1H), 1.52 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 166.2, 165.1, 148.2, 139.7, 134.5, 130.3, 130.1, 130.0, 129.7, 128.1, 126.7, 125.5, 124.2, 120.7, 114.5, 84.4, 71.3, 65.1, 62.1, 60.1, 52.1, 36.3, 27.9, 13.7;

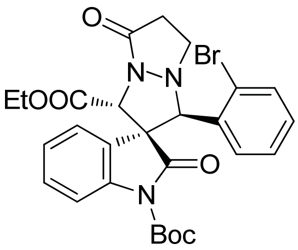
IR: 2982, 29322, 2852, 1792, 1765, 1738, 1707, 1605, 1477, 1412, 1354, 1294, 1252, 1199, 1152, 1108, 1071, 1039, 841, 756 cm^{-1};

$[\alpha]_D^{rt}$ = + 1 (c = 1.02, $CHCl_3$);

HRMS (ESI): $C_{27}H_{28}ClN_3O_6$+H, Calc: 526.1739, Found: 526.1735;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 8.1, t_{minor} = 10.7, 97% ee.

(1'R,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(2-bromophenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ac**. (Table 2, entry 3)



4ac was isolated by column chromatography in 92% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.81 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.23 (m, 1H), 7.20 – 7.05 (m, 2H), 4.93 (d, *J* = 2.6 Hz, 1H), 4.71 (d, *J* = 2.6 Hz, 1H), 4.31 – 4.17 (m, 1H), 4.14 – 4.04 (m, 1H), 3.46 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.26 – 2.96 (m, 2H), 2.90 – 2.72 (m, 1H), 1.54 (d, *J* = 2.9 Hz, 9H), 1.05 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 172.5, 166.1, 165.1, 148.2, 133.1, 130.5, 130.3, 130.4, 130.3, 129.7, 127.3, 125.9, 124.8, 124.1, 120.5, 114.5, 84.4, 73.5, 65.2, 62.1, 60.1, 51.9, 36.2, 27.9, 13.7;

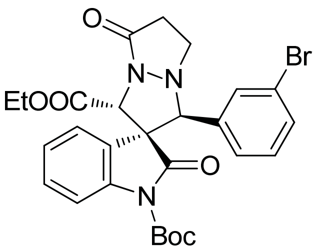
IR: 2981, 2930, 2852, 1765, 1736, 1707, 1605, 1469, 1412, 1367, 1353, 1294, 1251, 1198, 1152, 1107, 1071, 1021, 840, 756 cm^{-1};

$[\alpha]_D^{rt}$ = + 11 (c = 1.03, CHCl$_3$);

HRMS (ESI): $C_{27}H_{28}BrN_3O_6$+H, Calc: 570.1234, Found: 570.1241;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.9, t_{minor} = 10.8, 96% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(3-bromophenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ad**. (Table 2, entry 4)



4ad was isolated by column chromatography in 88% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.73 (d, *J* = 8.6 Hz, 1H), 7.36 (dd, *J* = 13.4, 6.1 Hz, 4H), 7.24 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 4.66 (s, 1H), 4.33 – 4.19 (m, 1H), 4.16 – 3.96 (m, 1H), 4.08 (s, 1H), 3.65 (t, *J* = 8.1 Hz, 1H), 3.24 (td, *J* = 14.7, 8.4 Hz, 1H), 3.06 – 2.91 (m, 1H), 2.79 (dd, J = 15.5, 7.6 Hz, 1H), 1.52 (s, 9H), 1.08 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 166.5, 165.0, 148.2, 140.2, 132.7, 132.2, 130.5, 130.0, 129.7, 126.0, 124.6, 123.7, 122.5, 121.3, 115.1, 84.7, 76.3, 65.3, 62.3, 59.4, 52.7, 36.3, 27.8, 13.8;

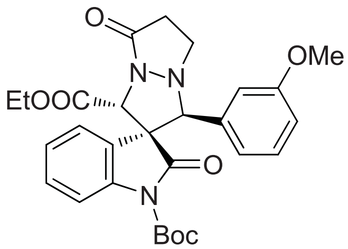
IR: 2980, 2927, 2853, 1767, 1737, 1700, 1603, 1569, 1468, 1413, 1352, 1336, 1294, 1252, 1198, 1151, 1076, 1070, 1011, 841, 795, 760 cm^{-1};

$[\alpha]_D^{rt}$ = - 41 (c = 1.01, $CHCl_3$);

HRMS (ESI): $C_{27}H_{28}BrN_3O_6$+Na, Calc: 592.1054, Found: 592.1048;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.6, t_{minor} = 9.3, 98% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(3-methoxyphenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ae**. (Table 2, entry 5)



4ae was isolated by column chromatography in 82% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 1H), 7.37 (dd, J = 15.8, 7.9 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.9 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.59 (s, 1H), 6.43 (d, J = 7.6 Hz, 1H), 4.67 (s, 1H), 4.33 – 4.22 (m, 1H), 4.19 – 4.01 (m, 1H), 4.09 (s, 1H), 3.66 (t, J = 8.4 Hz, 1H), 3.65 (s, 3H), 3.35 – 3.16 (m, 1H), 3.11 – 2.92 (m, 1H), 2.80 (dd, J = 15.6, 7.7 Hz, 1H), 1.49 (s, 9H), 1.07 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 166.5, 164.9, 159.4, 140.4, 131.7, 130.2, 129.2, 124.5, 123.8, 121.9, 119.6, 115.7, 115.1, 111.4, 84.4, 77.2, 65.4, 62.2, 59.5, 55.1, 52.7, 36.4, 27.8, 13.8;

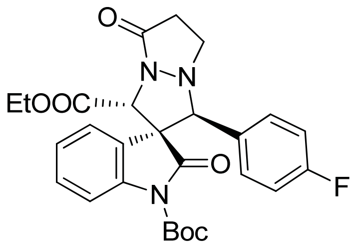
IR: 2925, 2854, 1741, 1699, 1603, 1463, 1414, 1369, 1354, 1294, 1254, 1199, 1153, 1107, 1071, 1043, 842, 801, 759 cm^{-1};

$[\alpha]_D^{rt}$ = - 20 (c = 1.05, $CHCl_3$);

HRMS (ESI): $C_{28}H_{31}N_3O_7$+Na, Calc: 544.2054, Found: 544.2061;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.7, t_{minor} = 8.5, 93% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(4-fluorophenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4af**. (Table 2, entry 6)



4af was isolated by column chromatography in 92% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.1 Hz, 1H), 7.37 (dd, *J* = 11.6, 7.8 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.83 (t, *J* = 8.5 Hz, 2H), 4.67 (s, 1H), 4.34 – 4.17 (m, 1H), 4.17 – 4.01 (m, 1H), 4.11 (s, 1H), 3.62 (t, *J* = 8.4 Hz, 1H), 3.22 (td, *J* = 14.5, 8.4 Hz, 1H), 3.09 – 2.92 (m, 1H), 2.79 (dd, *J* = 15.5, 7.6 Hz, 1H), 1.50 (s, 9H), 1.07 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 172.0, 166.4, 164.9, 163.1 (*J* = 246.75 Hz), 148.1, 140.4, 130.4, 129.0 (*J* = 9.0 Hz), 126.0 (*J* = 3.0 Hz), 124.6, 123.7, 121.6, 115.4, 115.1(*J* = 9.0 Hz), 84.5, 76.4, 65.2, 62.2, 59.4, 52.6, 36.3, 27.8, 13.8;

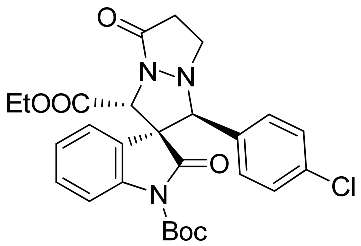
IR: 2980, 2926, 2853, 1792, 1766, 1739, 1696, 1605, 1510, 1466, 1414, 1370, 1351, 1335, 1294, 1252, 1200, 1153, 1105, 1072, 1013, 843, 757 cm^{-1};

$[\alpha]_D^{rt}$ = - 25 (c = 0.96, CHCl$_3$);

HRMS (ESI): $C_{27}H_{28}FN_3O_6$+Na, Calc: 532.1854, Found: 532.1862;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.0, t_{minor} = 11.5, >99% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(4-chlorophenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ag**. (Table 2, entry 7)



4ag was isolated by column chromatography in 93% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.15 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.59 (s, 1H), 4.19 - 4.13 (m, 1H), 4.07 – 3.94 (m, 1H), 4.03 (s, 1H), 3.54 (t, *J* = 8.3 Hz, 1H), 3.27 – 3.04 (m, 1H), 2.92 (dt, *J* = 13.5, 8.0 Hz, 1H), 2.72 (dd, *J* = 15.6, 7.5 Hz, 1H), 1.43 (s, 9H), 0.99 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 166.4, 164.9, 148.0, 140.1, 135.0, 130.4, 128.9, 128.5, 128.4, 124.6, 123.7, 121.5, 115.0, 84.6, 76.3, 65.2, 62.2, 59.4, 52.6, 36.3, 27.8, 13.7;

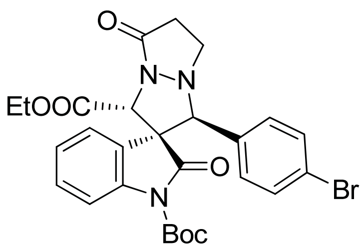
IR: 2981, 2927, 2853, 1793, 1767, 1738, 1708, 1604, 1485, 1466, 1412, 1353, 1294, 1251, 1199, 1152, 1092, 1071, 1014, 840, 761 cm^{-1};

$[\alpha]_D^{rt}$ = - 35 (c = 1.01, $CHCl_3$);

HRMS (ESI): $C_{27}H_{28}ClN_3O_6$+H, Calc: 526.1739, Found: 526.1744;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 8.2, t_{minor} = 13.7, 97% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(4-bromophenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ah**. (Table 2, entry 8)



4ah was isolated by column chromatography in 94% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (td, *J* = 7.8, 1.5 Hz, 1H), 7.36 – 7.08 (m, 5H), 6.77 (dd, *J* = 8.4, 2.7 Hz, 2H), 4.58 (d, *J* = 2.7 Hz, 1H), 4.20 – 4.10 (m, 1H), 4.07 – 3.96 (m, 1H), 4.02 (s, 1H), 3.54 (dt, *J* = 8.1, 2.1 Hz,1H), 3.02 – 2.81 (m, 1H), 2.94 – 2.88 (m, 1H), 2.71 (ddd, *J* = 15.6, 7.6, 3.1 Hz, 1H), 1.43 (d, *J* = 3.5 Hz, 9H), 0.99 (dd, *J* = 8.9, 5.4 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 171.9, 166.4, 164.9, 148.1, 140.2, 131.4, 130.5, 129.4, 128.8, 124.6, 123.7, 123.2, 121.5, 115.1, 84.6, 76.3, 65.2, 62.2, 59.4, 52.6, 36.3, 27.8, 13.7;

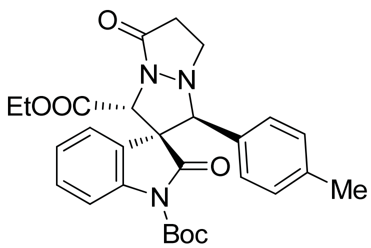
IR: 2981, 293, 2846, 1793, 1767, 1737, 1705, 1604, 1483, 1467, 1412, 1352, 1294, 1251, 1198, 1152, 1104, 1071, 1011, 839, 759 cm^{-1};

$[\alpha]_D^{rt}$ = - 39 (c = 1.00, CHCl$_3$);

HRMS (ESI): $C_{27}H_{28}BrN_3O_6$+Na, Calc: 592.1054, Found: 592.1060;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 9.1, t_{minor} = 15.4, >99% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 2,5'-dioxo-1'-(p-tolyl)-3',5',6',7'-tetrahydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ai**. (Table 2, entry 9)



4ai was isolated by column chromatography in 91% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 7.36 (ddd, J = 9.4, 8.4, 1.1 Hz, 2H), 7.21 (td, J = 7.8, 1.0 Hz, 1H), 6.94 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 8.1 Hz, 2H), 4.67 (s, 1H), 4.29 – 4.18 (m, 1H), 4.17 – 4.02 (m, 1H), 4.19 (s, 1H), 3.62 (t, J = 8.4 Hz, 1H), 3.31 – 3.10 (m, 1H), 2.97 (dt, J = 13.5, 8.1 Hz, 1H), 2.78 (dd, J = 15.6, 7.6 Hz, 1H), 2.23 (s, 3H), 1.49 (s, 9H), 1.06 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 172.3, 166.4, 164.8, 148.3, 140.2, 138.9, 130.2, 128.9, 127.1, 127.0, 124.5, 123.8, 121.9, 115.0, 84.2, 77.2, 65.3, 62.2, 59.4, 52.5, 36.4, 27.8, 21.0, 13.8;

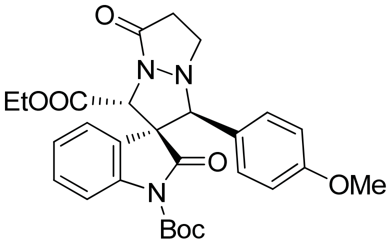
IR: 2925, 2854, 1765, 1738, 1697, 1605, 1513, 1465, 1413, 1370, 1351, 1335, 1294, 1251, 1197, 1152, 1106, 1071, 1013, 840, 757 cm^{-1};

$[\alpha]_D^{rt}$ = - 19 (c = 0.98, CHCl$_3$);

HRMS (ESI): $C_{28}H_{31}N_3O_6$+H, Calc: 506.2286, Found: 506.2285;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.8, t_{minor} = 10.4, 95% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(4-methoxyphenyl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4aj**. (Table 2, entry 10)



4aj was isolated by column chromatography in 86% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.1 Hz, 1H), 7.35 (dt, *J* = 8.1, 4.2 Hz, 2H), 7.20 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 4.67 (s, 1H), 4.26 – 4.18 (m, 1H), 4.15 – 4.03 (m, 1H), 4.07 (s, 1H), 3.71 (s, 3H), 3.61 (t, *J* = 8.4 Hz, 1H), 3.19 (dd, *J* = 14.5, 8.6 Hz, 1H), 2.97 (dt, *J* = 13.4, 8.1 Hz, 1H), 2.78 (dd, *J* = 15.6, 7.6 Hz, 1H), 1.50 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 172.4, 166.5, 164.9, 160.1, 148.3, 140.2, 130.2, 128.5, 124.4, 123.7, 122.0, 121.9, 115.0, 113.6, 84.3, 66.3, 62.1, 59.5, 55.1, 52.5, 36.4, 28.0, 27.9, 13.8;

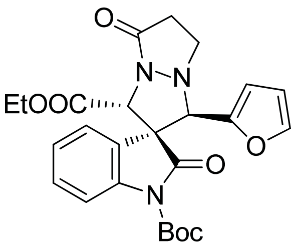
IR: 2956, 2926, 2854, 1792, 1764, 1735, 1699, 1609, 1513, 1464, 1369, 1351, 1295, 1252, 1173, 1152, 1102, 1030, 839, 800, 758 cm^{-1};

$[\alpha]_D^{rt}$ = - 8 (c = 1.04, CHCl$_3$);

HRMS (ESI): $C_{28}H_{31}N_3O_7$+Na, Calc: 544.2054, Found: 544.2060;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 8.4, t_{minor} = 10.4, 94% ee.

(1'R,2'S,3'R)-1-tert-butyl 3'-ethyl 1'-(furan-2-yl)-2,5'-dioxo-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ak**. (Table 2, entry 11)



4ak was isolated by column chromatography in 68% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.35 (dd, *J* =

10.9, 3.8 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 6.30 (s, 2H), 4.99 (s, 1H), 4.25 (s, 1H), 4.09 – 3.79 (m, 2H), 3.36 (t, J = 8.4 Hz 2H), 2.72 (t, J = 6 Hz, 2H), 1.59 (s, 9H), 0.87 (t, J = 7.1 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 166.4, 148.7, 145.5, 143.7, 139.6, 130.0, 124.6, 124.4, 114.9, 114.6, 111.7, 110.6, 84.7, 77.2, 69.7, 62.9, 61.8, 61.5, 34.4, 28.0, 13.5;

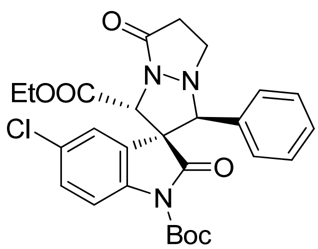
IR: 2955, 2925, 2854, 1744, 1603, 1462, 1416, 1372, 1348, 1296, 1257, 1153, 1096, 1018, 799, 756 cm^{-1};

$[\alpha]_D^{rt}$ = - 8 (c = 1.03, $CHCl_3$);

HRMS (ESI): $C_{25}H_{27}N_3O_7$+Na, Calc: 504.1741, Found: 504.1748;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 6.6, t_{minor} = 8.9, 91% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 5-chloro-2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ba**. (Table 2, entry 12)



4ba was isolated by column chromatography in 84% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.7 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.33 (dd, J = 8.7, 2.1 Hz, 1H), 7.27 (t, J = 8.8 Hz, 1H), 7.16 (t, J = 7.4 Hz, 2H), 7.00 (d, J = 7.2 Hz, 2H), 4.66 (s, 1H), 4.33 – 4.14 (m, 2H), 4.10 (s, 1H), 3.63 (t, J = 8.3 Hz, 1H), 3.32 – 3.12 (m, 1H), 3.00 (dt, J = 13.5, 8.0 Hz, 1H), 2.79 (dd, J = 15.6, 7.5 Hz, 1H), 1.48 (s, 9H), 1.13 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 166.4, 165.0, 148.0, 138.8, 130.3, 130.0, 129.9, 129.3, 128.4, 127.3, 124.0, 123.5, 116.3, 84.7, 77.2, 65.2, 62.5, 59.3, 52.6, 36.3, 27.8, 13.9;

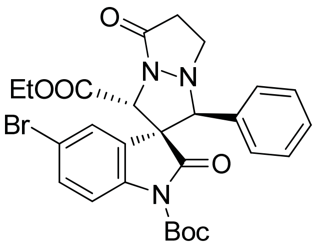
IR: 2925, 2854, 1769, 1739, 1697, 1600, 1469, 1371, 1335, 1293, 1254, 1196, 1153, 1119, 1072, 1025, 827, 757 cm^{-1};

$[\alpha]_D^{rt}$ = -17 (c = 1.05, $CHCl_3$);

HRMS (ESI): $C_{27}H_{28}ClN_3O_6$+Na, Calc: 548.1559, Found: 548.1561;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 8.2, t_{minor} = 14.0, 96% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 5-bromo-2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'H-spiro [indoline -3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ca**. (Table 2, entry 13)



4ca was isolated by column chromatography in 84% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.59 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.47 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.26 (d, *J* = 5.5 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 2H), 7.00 (d, *J* = 7.2 Hz, 2H), 4.66 (s, 1H), 4.37 – 4.15 (m, 2H), 4.10 (s, 1H), 3.63 (t, *J* = 8.4 Hz, 1H), 3.33 – 3.10 (m, 1H), 3.00 (dt, *J* = 13.6, 8.1 Hz, 1H), 2.79 (dd, *J* = 15.5, 7.5 Hz, 1H), 1.47 (s, 9H), 1.14 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 171.3, 166.4, 165.0, 148.0, 139.3, 133.2, 129.9, 129.3, 128.4, 127.3, 126.8, 123.9, 117.4, 116.6, 84.8, 77.2, 65.1, 62.6, 59.4, 52.6, 36.3, 27.8, 13.9;

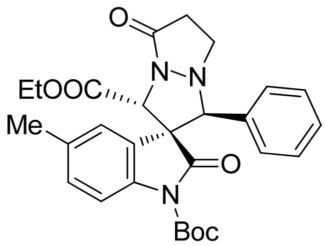
IR: 2980, 2927, 2854, 1770, 1737, 1709, 1601, 1471, 1415, 1369, 1334, 1294, 1253, 1198, 1153, 1120, 1068, 1011, 837, 748, 701 cm^{-1};

$[\alpha]_D^{rt}$ = - 14 (c = 0.99, CHCl$_3$);

HRMS (ESI): $C_{27}H_{28}BrN_3O_6$+Na, Calc: 592.1054, Found: 592.1055;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.7, t_{minor} = 13.2, 98% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 5-methyl-2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4da**. (Table 2, entry 14)



4da was isolated by column chromatography in 93% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 3H), 6.96 (dd, *J* = 8.4, 1.2 Hz, 2H), 4.66 (s, 1H), 4.26 – 4.07 (m, 2H), 4.10 (s, 1H), 3.64 (t, *J* = 8.4 Hz, 1H), 3.34 – 3.13 (m, 1H), 2.99 (dt, *J* = 13.6, 8.1 Hz, 1H), 2.79 (dd, *J* = 15.6, 7.5 Hz, 1H), 2.39 (s, 3H), 1.47 (s, 9H), 1.07 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 166.5, 164.9, 148.2, 137.8, 134.1, 130.7, 130.3, 129.0, 128.2, 127.2, 124.2, 121.7, 114.7, 84.1, 65.4, 62.1, 59.4, 52.6, 36.4, 27.8, 21.1, 13.7;

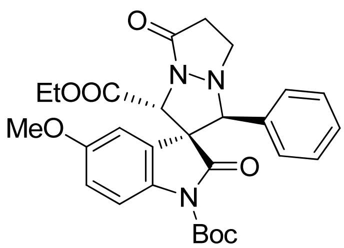
IR: 2980, 2926, 2854, 1768, 1735, 1696, 1598, 1491, 1454, 1414, 1369, 1338, 1284, 1251, 1195, 1155, 1125, 1072, 1030, 1011, 823, 753 cm^{-1};

$[\alpha]_D^{rt}$ = - 26 (c = 0.98, $CHCl_3$);

HRMS (ESI): $C_{28}H_{31}N_3O_6$+H, Calc: 506.2286, Found: 506.2293;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.4, t_{minor} = 9.2, 96% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 5-methoxy-2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ea**. (Table 2, entry 15)



4ea was isolated by column chromatography in 87% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 9.0 Hz, 1H), 7.21 (dd, *J* = 4.9, 3.6 Hz, 1H), 7.18 – 7.11 (m, 2H), 6.98 (m, 3H), 6.86 (dd, *J* = 9.0, 2.7 Hz, 1H), 4.68 (s, 1H), 4.32 – 4.07 (m, 2H), 4.10 (s, 1H), 3.84 (s, 3H), 3.63 (t, *J* = 8.3 Hz, 1H), 3.34 – 3.11 (m, 1H), 2.99 (dt, *J* = 13.5, 8.1 Hz, 1H), 2.79 (dd, *J* = 15.6, 7.5 Hz, 1H), 1.47 (s, 9H), 1.10 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 172.2, 166.4, 164.8, 156.8, 148.3, 133.6, 130.3, 129.1, 128.3, 127.3, 123.0, 115.9, 115.0, 110.0, 84.1, 76.6, 65.6, 62.2, 59.5, 55.7, 52.6, 36.4, 27.9, 13.8.

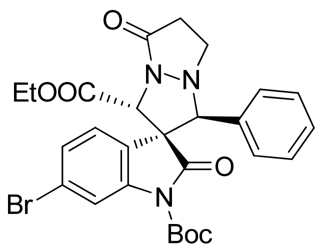
IR: 2926, 2853, 1743, 1599, 1489, 1458, 1415, 1368, 1282, 1251, 1215, 1155, 1070, 1045, 1010, 840, 814, 746, 700 cm^{-1};

$[\alpha]_D^{rt}$ = - 33 (c = 0.94, CHCl$_3$);

HRMS (ESI): $C_{28}H_{31}N_3O_7$+Na, Calc: 544.2054, Found: 544.2061;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 9.4, t_{minor} = 15.9, 99% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-ethyl 6-bromo-2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'H-spiro [indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4fa**. (Table 2, entry 16)



4fa was isolated by column chromatography in 81% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.92 (d, *J* = 1.8 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.26 (dd, *J* = 10.9, 5.1 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 7.3 Hz, 2H), 4.65 (s, 1H), 4.33 – 4.14 (m, 1H), 4.13 – 4.03 (m, 1H), 4.08 (s, 1H), 3.63 (t, *J* = 8.4 Hz, 1H), 3.32 – 3.13 (m, 1H), 2.98 (dt, *J* = 13.5, 8.1 Hz, 1H), 2.79 (dd, *J* = 15.6, 7.7 Hz, 1H), 1.48 (s, 9H), 1.12 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 171.6, 166.4, 164.9, 148.0, 141.3, 129.9, 129.3, 128.4, 127.5, 127.2, 125.1, 124.2, 120.8, 118.5, 84.9, 77.1, 65.1, 62.4, 59.3, 52.6, 36.3, 27.8, 13.9;

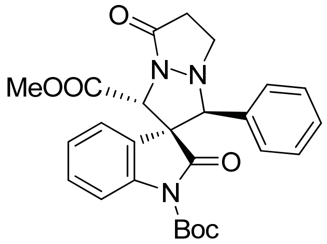
IR: 2981, 2929, 2852, 1770, 1737, 1697, 1600, 1477, 1418, 1368, 1351, 1331, 1285, 1248, 1191, 1151, 1116, 1072, 1021, 981, 841, 754 cm^{-1};

$[\alpha]_D^{rt}$ = - 28 (c = 1.00, CHCl$_3$);

HRMS (ESI): $C_{27}H_{28}BrN_3O_6$+Na, Calc: 592.1054, Found: 592.1062;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.4, t_{minor} = 13.8, 97% ee.

(1'S,2'S,3'R)-1-tert-butyl 3'-methyl 2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ga**. (Table 2, entry 17)



4ga was isolated by column chromatography in 94% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (dd, J = 7.8, 1.2 Hz 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.24 (dd, J = 14.2, 6.7 Hz, 2H), 7.13 (t, J = 7.4 Hz, 2H), 6.95 (d, J = 7.2 Hz, 2H), 4.70 (s, 1H), 4.11 (s, 1H), 3.68 (s, 3H), 3.64 (t, J = 8.1 Hz, 1H), 3.34 – 3.14 (m, 1H), 3.00 (dt, J = 13.6, 8.1 Hz, 1H), 2.80 (dd, J = 15.6, 7.6 Hz, 1H), 1.48 (s, 9H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 172.1, 167.0, 164.9, 148.2, 140.3, 130.3, 130.2, 129.1, 128.3, 127.2, 124.6, 123.5, 121.8, 115.1, 84.4, 77.2, 65.4, 59.3, 52.8, 52.7, 36.4, 27.8;

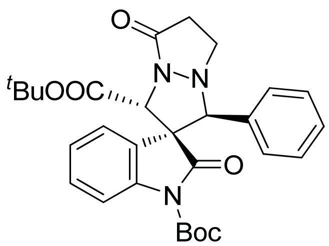
IR: 2925, 2853, 1742, 1696, 1604, 1463, 1414, 1358, 1340, 1295, 1252, 1213, 1153, 1107, 1072, 995, 841, 751 cm^{-1};

$[\alpha]_D^{rt}$ = - 21 (c = 1.02, $CHCl_3$);

HRMS (ESI): $C_{26}H_{27}N_3O_6$+H, Calc: 478.1973, Found: 478.1977;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 7.3, t_{minor} = 12.3, >99% ee.

(1'S,2'S,3'R)-di-tert-butyl 2,5'-dioxo-1'-phenyl-3',5',6',7'-tetrahydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a]pyrazole]-1,3'-dicarboxylate, **4ha**. (Table 2, entry 18)



4ha was isolated by column chromatography in 92% yield;

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (d, J = 7.7 Hz, 1H), 7.57 (dd, J = 7.7, 1.0 Hz, 1H), 7.35 (td, J = 7.9, 1.4 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.13 (dd, J = 8.1, 6.7 Hz, 2H), 7.01 – 6.90 (m, 2H), 4.56

(s, 1H), 4.14 (s, 1H), 3.62 (t, *J* = 8.3 Hz, 1H), 3.29 – 3.11 (m, 1H), 2.98 (dt, *J* = 13.5, 8.1 Hz, 1H), 2.77 (dd, *J* = 15.6, 7.4 Hz, 1H), 1.48 (s, 9H), 1.39 (s, 9H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 165.6, 164.9, 148.3, 140.3, 130.4, 130.2, 129.0, 128.2, 127.3, 125.1, 124.3, 121.8, 114.7, 84.3, 84.2, 77.5, 65.3, 60.3, 52.6, 36.2, 27.9, 27.8;

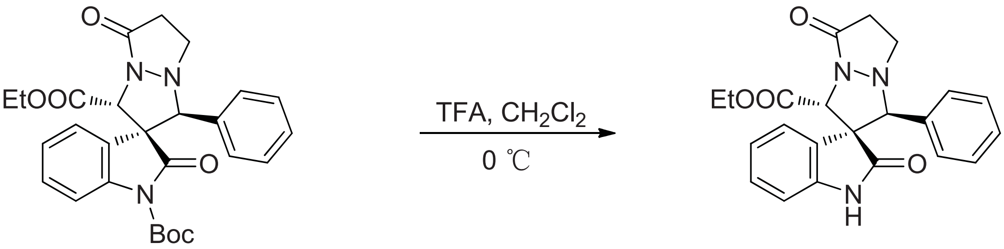
IR: 2980, 2930, 2852, 1767, 1736, 1698, 1605, 1478, 1413, 1365, 1294, 1252, 1221, 1152, 1106, 1072, 843, 755 cm^{-1};

$[\alpha]_D^{rt}$ = - 19 (c = 1.01, $CHCl_3$);

HRMS (ESI): $C_{29}H_{33}N_3O_6$+H, Calc: 520.2442, Found: 520.2446;

HPLC: DAICEL CHIRALCEL IA, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min, retention time: t_{major}= 5.9, t_{minor} = 6.6, 98% ee.

General procedure and spectral data for the synthesis of 5:



4aa **5**

To a stirred solution of **4aa** (0.1 mmol, 49.1mg) was added 0.1 ml TFA slowly under 0 ℃. The reaction mixture was stirred at this temperature and monitored by TLC, and extracted by CH_2Cl_2 after completion in 15 min. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated after filtration and purified by silica gel chromatography (CH_2Cl_2:MeOH 20:1) and fractions were collected and concentrated in vacuo to provide the pure desired products **5** in 94% yield.

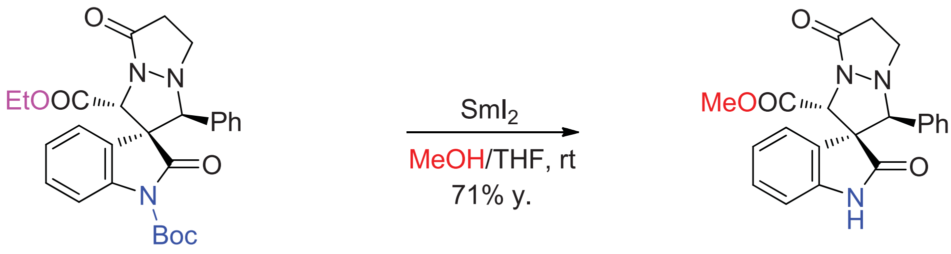
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.19 – 7.06 (m, 3H), 7.01 (d, J = 7.2 Hz, 2H), 6.78 (d, J = 7.5 Hz, 1H), 4.63 (s, 1H), 4.24 (s, 1H), 4.24 – 4.03 (m, 2H), 3.62 (t, J = 8.1 Hz, 1H), 3.20 – 3.02 (m, 1H), 2.96 (dd, J = 13.5, 8.1 Hz, 1H), 2.74 (dd, J = 15.3, 7.2 Hz, 1H), 1.03 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 166.6, 165.4, 141.5, 130.7, 130.1, 128.9, 128.2, 127.3, 124.4, 123.2, 122.6, 110.5, 76.1, 65.0, 62.1, 59.3, 53.0, 36.3, 13.7;

IR: 3239, 1725, 1693, 1620, 1599, 1474, 1413, 1200, 912, 732 cm^{-1};

HRMS (ESI): $C_{22}H_{21}N_3O_4$+Na, Calc: 414.1424, Found: 414.1429.

General procedure and spectral data for the synthesis of 6



4aa **6**

To a stirred solution of **4aa** (0.1 mmol, 49.1mg) in MeOH (0.1 ml) was added a 0.1 M THF solution of SmI_2 (0.4 mmol, 4 ml) at room temperature. After stirring for 10 min at r.t., the reaction solution was poured into saturated $NaHCO_3$ aq. and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2:MeOH 20:1), fractions were collected and concentrated in vacuo to provide the pure desired products **6** in 71% yield.

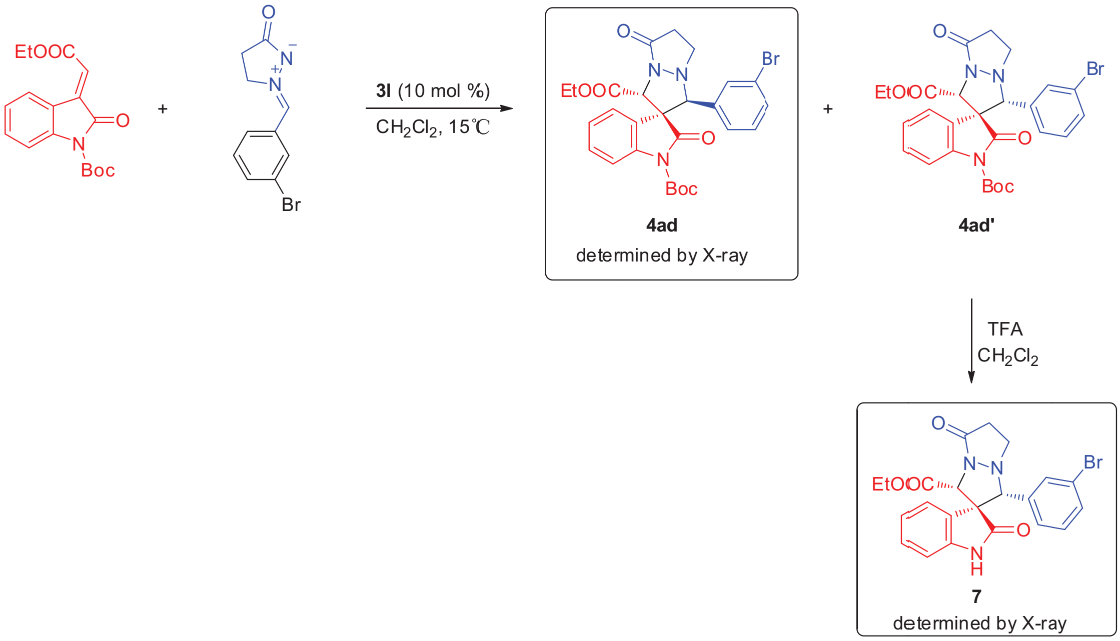
^{1}H NMR (300 MHz, CDCl$_3$) δ 8.19 (s, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.26 (dd, *J* = 11.8, 3.6 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.12 (s, 1H), 7.09 (d, *J* = 5.0 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 2H), 6.75 (d, *J* = 7.8 Hz, 1H), 5.06 (s, 1H), 3.91 (s, 1H), 3.80 (dt, *J* = 10.4, 6.2 Hz, 1H), 3.60 (s, 3H), 3.08 – 2.72 (m, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 175.7, 174.3, 167.9, 141.2, 130.9, 129.7, 128.9, 128.2, 127.6, 127.4, 123.1, 122.7, 110.3, 80.2, 65.6, 62.0, 52.7, 46.4, 30.9;

IR: 3276, 1765, 1724, 1620, 1474, 1337, 1294, 1218, 1107, 1026, 910, 732 cm^{-1};

HRMS (ESI): $C_{21}H_{19}N_3O_4$+Na, Calc: 400.1268, Found: 400.1272.

The absolute configuration determination:

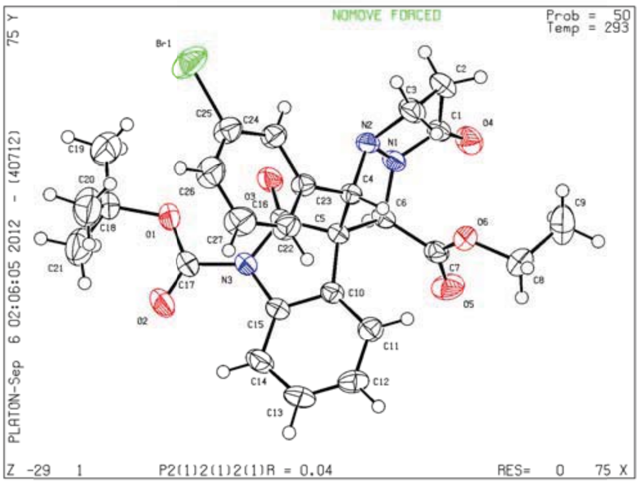


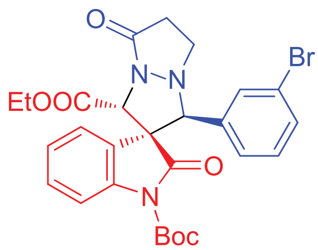
X-ray Structure of **4ad:**

Chirality at C4 *S*

Chirality at C5 *S*

Chirality at C6 *R*





4ad

Datablock:

Bond precision:	C-C = 0.0044 A		Wavelength=0.71073
Cell:	a=9.930(2)	b=11.163(3)	c=24.219(6)
	alpha=90	beta=90	gamma=90
Temperature: 293 K			

	Calculated	Reported
Volume	2684.6(11)	2684.7(11)
Space group	P 21 21 21	P2(1)2(1)2(
Hall group	P 2ac 2ab	?
Moiety formula	C27 H28 Br N3 O6	?
Sum formula	C27 H28 Br N3 O6	C27 H28 Br N3 O6
Mr	570.42	570.43
Dx,g cm-3	1.411	1.411
Z	4	4
Mu (mm-1)	1.577	1.577
F000	1176.0	1176.0
F000'	1175.37	
h,k,lmax	11,13,28	11,13,28
Nref	2698[4733]	4706
Tmin,Tmax	0.610,0.664	0.632,0.685
Tmin'	0.598	

Correction method= MULTI-SCAN

Data completeness= 1.74/0.99 Theta(max)= 25.000

R(reflections)= 0.0356(4096) wR2(reflections)= 0.0923(4706)

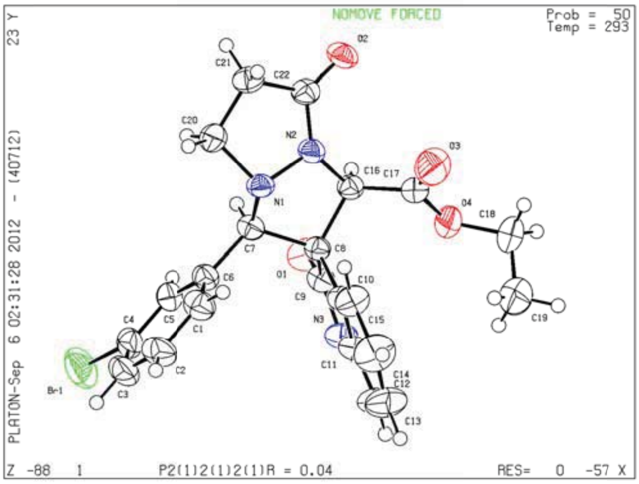
S = 1.051 Npar= 338

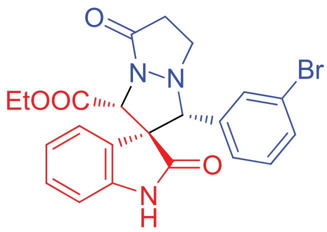
X-ray Structure of **7**:

Chirality at C7 *R*

Chirality at C8 *R*

Chirality at C16 *R*





7

Datablock: 1

Bond precision: C-C = 0.0047 A Wavelength=0.71073

Cell:	a=8.967(3)	b=11.953(4)	c=19.728(6)
	alpha=90	beta=90	gamma=90

Temperature: 293 K

	Calculated	Reported
Volume	2114.5(12)	2114.4(11)
Space group	P 21 21 21	P2(1)2(1)2(1
Hall group	P 2ac 2ab	?
Moiety formula	C22 H19 Br N3 O4	?
Sum formula	C22 H19 Br N3 O4	C22 H19 Br N3 O4
Mr	469.30	469.31

Dx,g cm-3	1.474	1.474
Z	4	4
Mu (mm-1)	1.978	1.978
F000	956.0	956.0
F000'	955.25	
h,k,lmax	11,15,25	11,15,25
Nref	2629[4617]	4552
Tmin,Tmax	0.628,0.673	0.588,0.693
Tmin'	0.547	

Correction method= MULTI-SCAN

Data completeness= 1.73/0.99 Theta(max)= 26.970

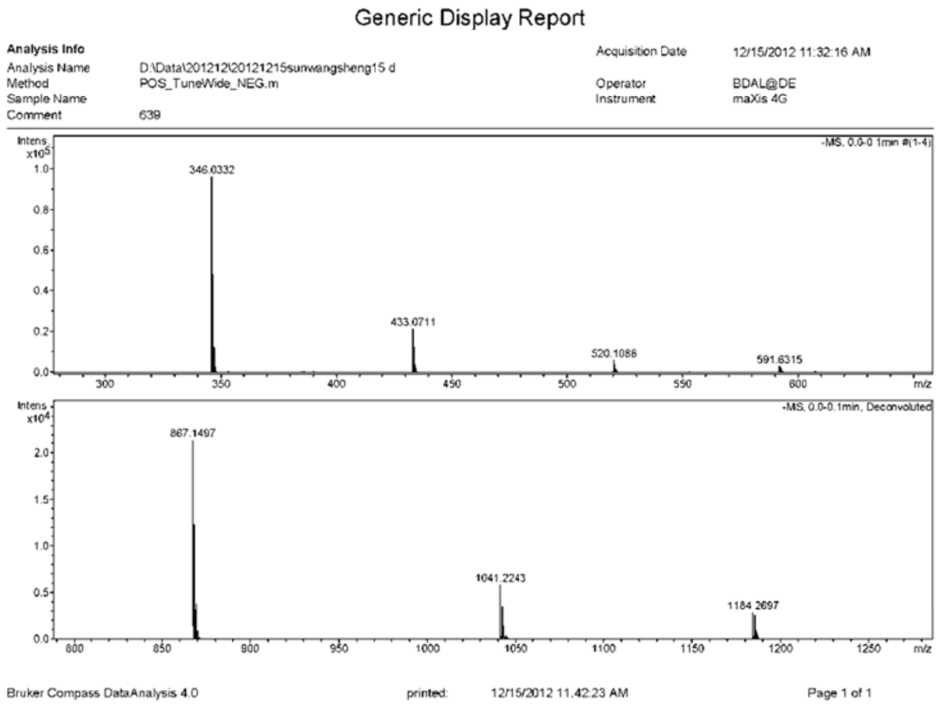
R(reflections)= 0.0398(3277) wR2(reflections)= 0.0979(4552)

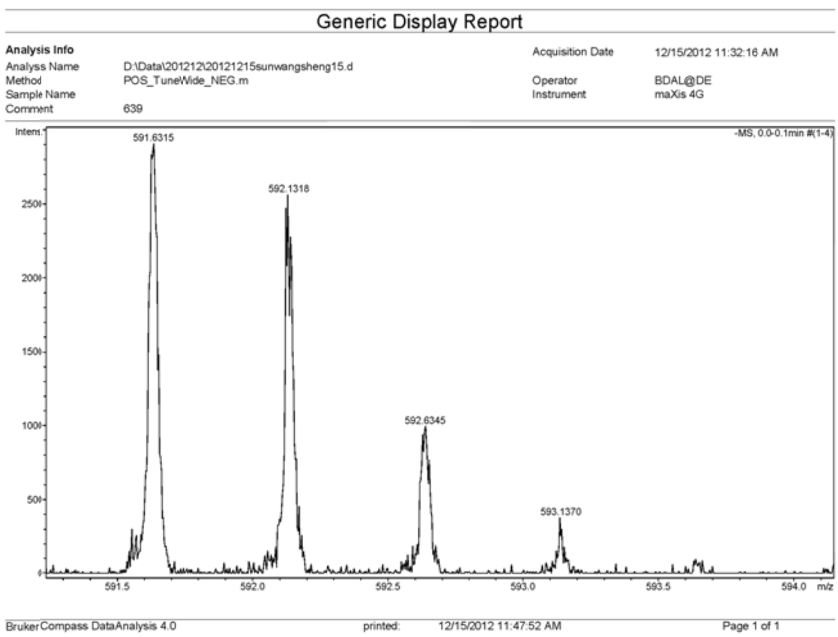
S = 1.005 Npar= 272

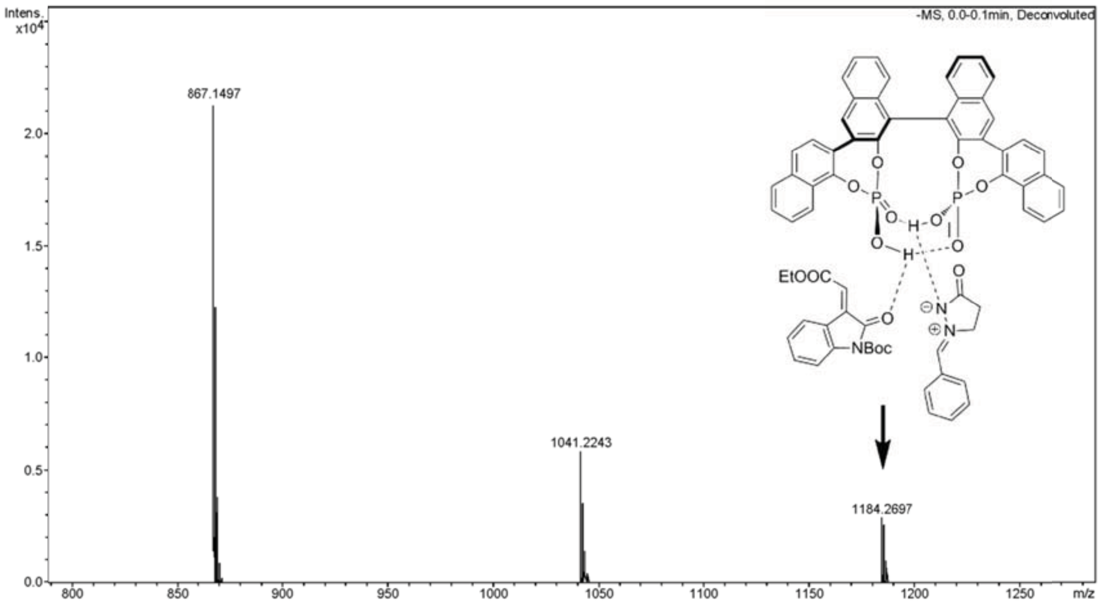
MS experiment

The reaction mixture was monitored by MS (ESI) (negative).

The observed 346.0, 433.11, 520.1 and 591.6 are double charged.

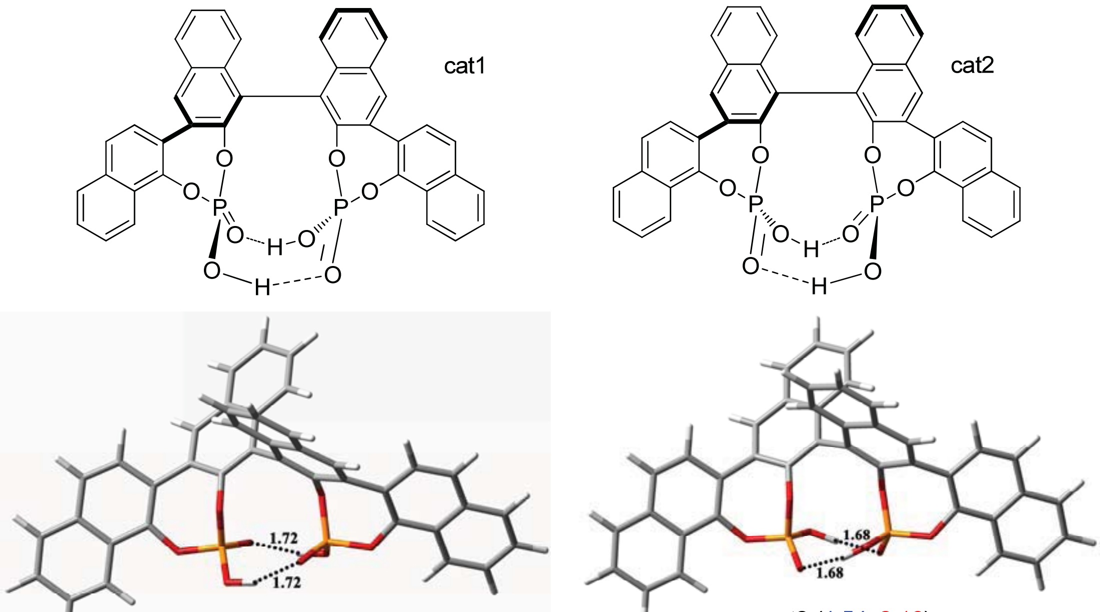





Intens.
x10^4
-MS, 0.0-0.1min, Deconvoluted
867.1497
1041.2243
1184.2697
EtOOC
NBoc
m/z

The DFT Calculation of Intermediates in the Reaction

To gain deeper insight into this asymmetric 1,3-dipolar cycloaddition reaction involving BINOL-derived bisphosphoric acid catalysts, the Gaussian 09 program package[5] was employed and the DFT variant B3LYP[6] was used in conjunction with the 6–31G(d) basis set[7] to optimize all intermediates structures. The geometries of the reaction intermediates were identified using the IRC (intrinsic reaction coordinate) and IRCMAX method.[8] The calculations are carried out without explicit consideration of solvent effects.



cat1 (0.00, 0.00) cat2 (1.54, 2.16)

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(5) M. J. Frisch, *et al.*, Gaussian 03, Revision C. 02, Gaussian, Inc., Wallingford CT, **2004**.

(6) A. D. Backe, *J. Chem. Phys*. **1983**, *98*, 5648.

(7) P. M. W. Gill, B. G. Johnson, J. A. Pople, M. Frisch, *J. Chem. Phys. Lett.* **1992**, *197*, 499.

(8) a) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154;
b) C. Gonzalez, H. B. Schlegel, *J. Phys. Chem*. **1990**, *94*, 5523.

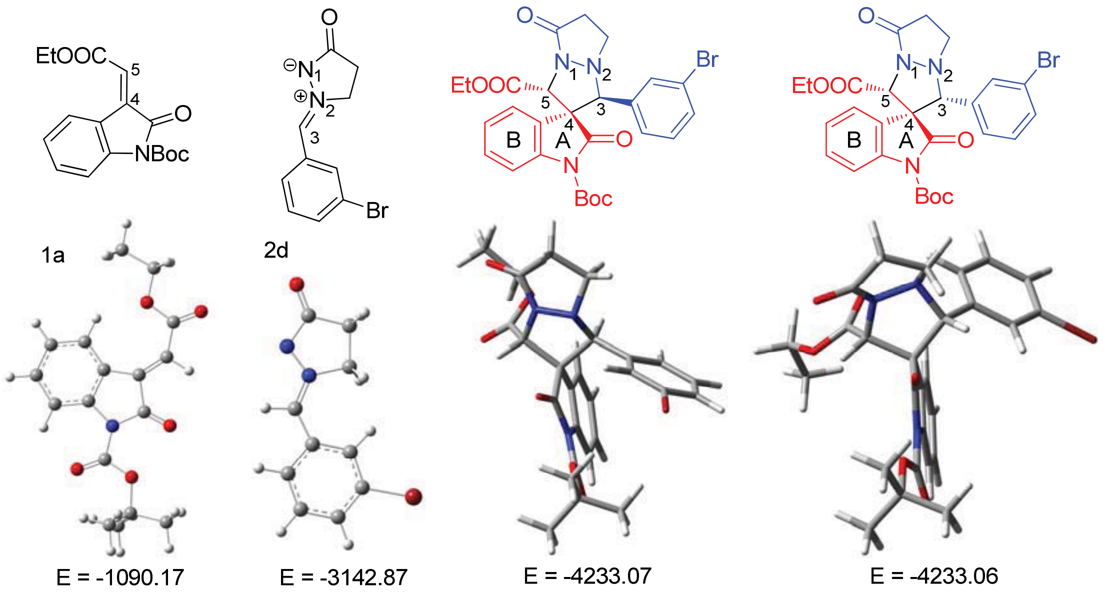


Figure 1. Calculated structures of catalyst, substrates and products relative energies E in Hartree.

The **4ad** have its X-ray structure, the model of **4ad’** determined by X-ray structure of substrates 7, the model of our catalyst originated from X-ray structure of chiral bis-phosphoric acid catalyst.[9] The optimized structures of the catalyst, cat1/cat2, the substrates **1a** and **2d**, the products **4ad** and **4ad’**, are shown in Figure 1.

Because of both substrates can only offer O or N atom as the receptor of hydrogen bond which connected the substrates and catalyst, the two hydrogen atom donors should be provided by the two hydroxyls of phosphoric acid moiety of catalyst in this reaction.

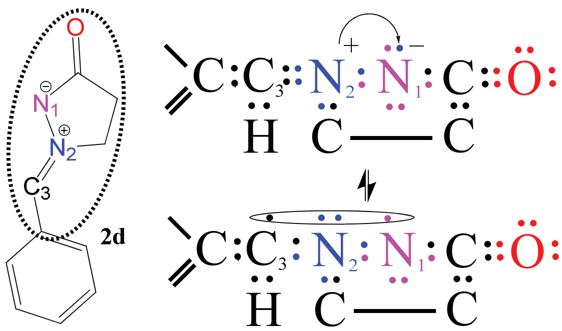


Figure 2. Electron distribution of **2d**, N1 have one set lone pair electrons and O atoms have two set lone pair electrons. So N1 and O can from hydrogen bond with hydrogen atom donors in our catalyst.

(9) N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto, M. Terada, *J Am Chem Soc.* **2011,** *133*, 19294.

In the transition-state structures for the formation of both conformers **4ad** and **4ad'**, two substrates are clearly non-planar. The O atom on the oxo-indole ring of the **1a** connected the hydrogen atom on the hydroxyl of left phosphoric acid moiety, consistent with Gong's study.[10] The N1 atom on the **2d** interact the hydrogen atom on the hydroxyl of right phosphoric acid moiety, by the reason of only N1 and O atoms in **2d** have lone pair electrons can from hydrogen bond with hydrogen atom donors (Figure 2) and our catalyst bond with N1 superior to O. (Figure 3)

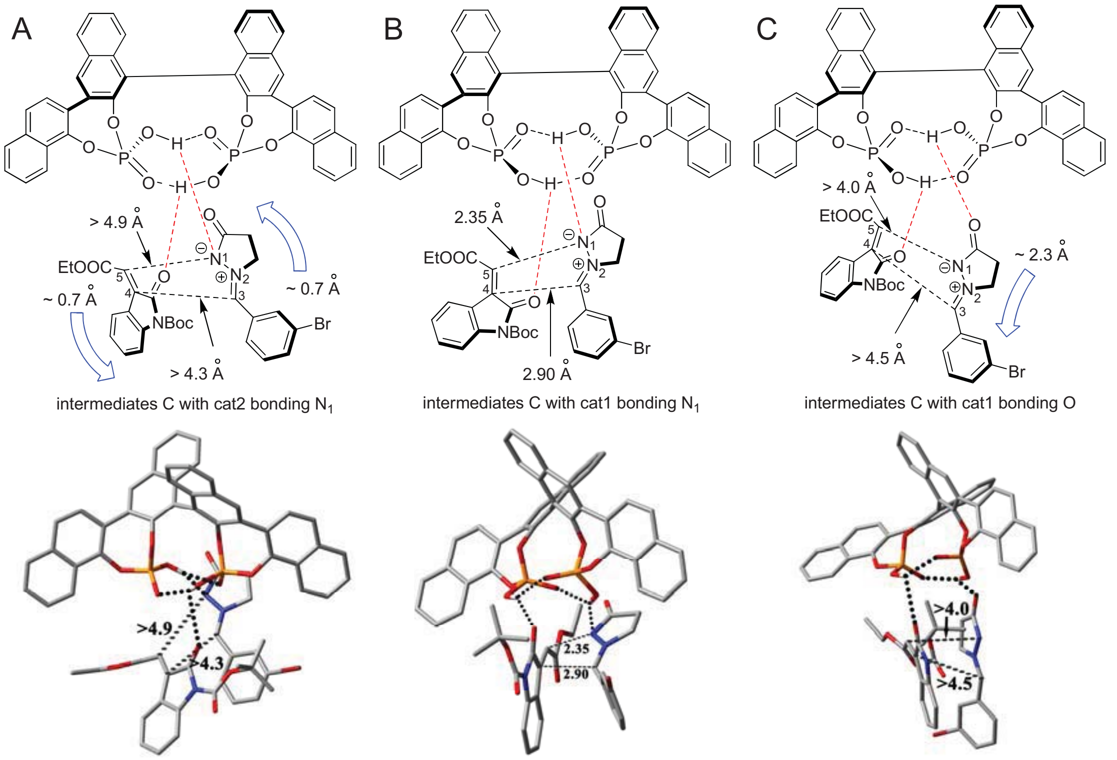


Figure 3. Calculated structures of intermediates C relative distance in angstrom (Å). A is cat2 binding with N1 of 2d, B is cat1 binding with N1 of 2d , C is cat1 binding with O of 2d.

As illustrated in Figure 3B, the best transition structure for the reaction is intermediates C with cat1 bonding with N1 of substrate 2d. In this model, two substrates are tightly aligned, relative the N1- C5 (2.35 Å) and C3-C4 bonds (2.90 Å). The intermediates C with cat2 bonding with N1 of substrate 2d shown in Figure 3A, the relative position of two substrates are dislocated (both ~0.7Å), the bonds of N1-C5 > 4.9 Å and C3-C4 > 4.3Å, the reaction can't happen. In the

(10) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009,** *131*, 13819.

intermediates C with cat1 bonding with O (Figure 3C), the substrate **2d** is about 2.3Å away from its "best location" and hardly attack the substrate 1a (N1-C5 > 4.0 Å and C3-C4 > 4.5Å). In summary, the asymmetric 1,3-dipolar cycloaddition reaction can be best explained by the proposed reaction models of activated intermediate C with cat1 bonding with N1 of substrate **2d**.

Notably, the formation of the stereochemical C3 center might lead to two different final products: **4ad** and **4ad'**. DFT calculations revealed that the 3-bromide-substituted phenyl ring on the **2d** had almost no interactions with the COOEt group (6.27 Å) under a *trans* relationship and had attractive interactions with ring A (3.81 Å) and ring B (4.76 Å) when (*S*)-C3 was formed in product **4ad**. Conversely, in product **4ad'** ((*R*)-C3), this 3-bromide-substituted phenyl ring underwent a steric repulsion with the COOEt group (4.21 Å) under a *cis* relationship and pointed away from ring A (4.60 Å) and ring B (4.76 Å). Compared to compound **4ad'**, the distance of adverse approach is longer (by 2.06 Å) in product **4ad** and the distance of beneficial approach is shorter (by 0.79 Å). Thus, structure **4ad** is more-favorably formed over **4ad'** in keeping with the experimental results (Figure 4).

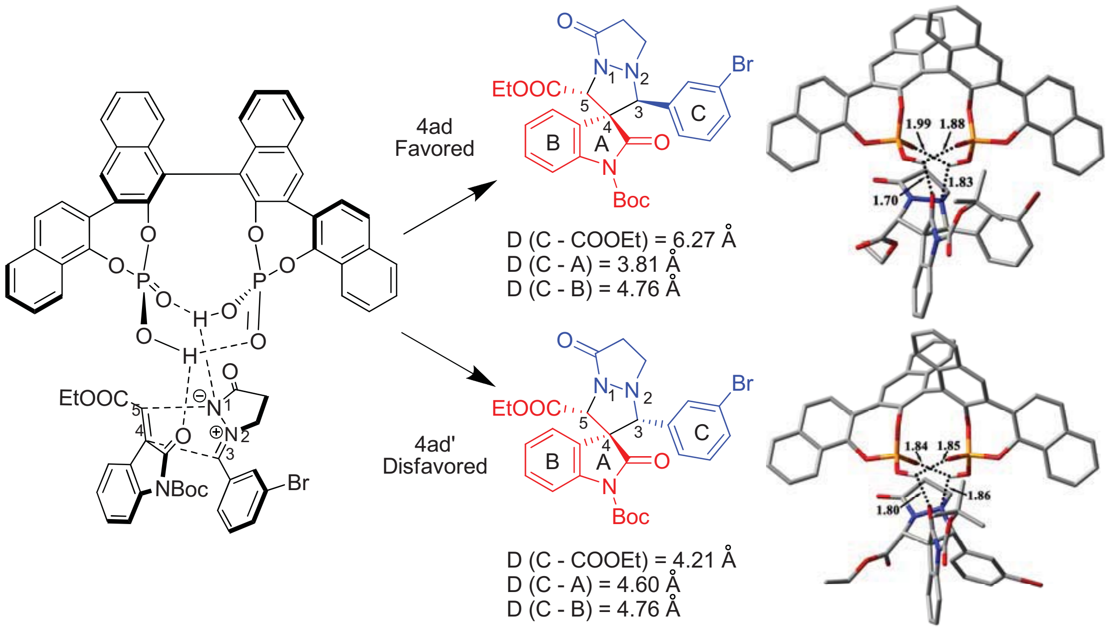
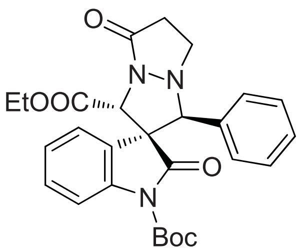
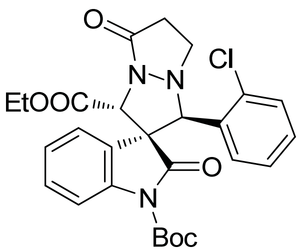
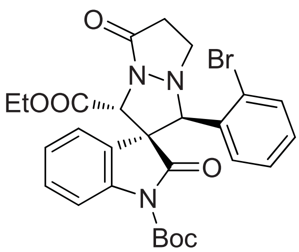
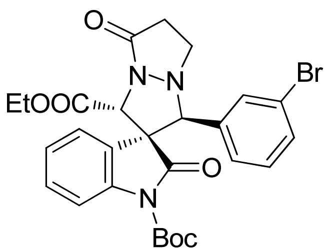
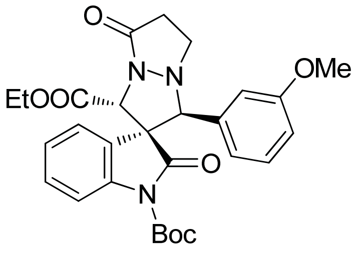
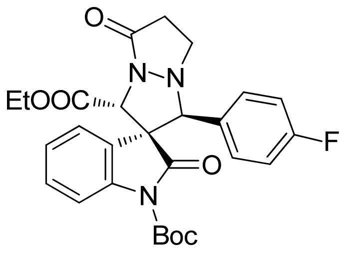
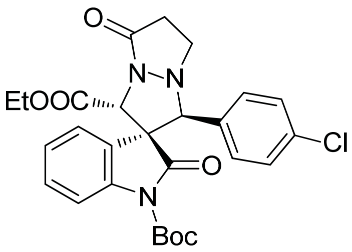
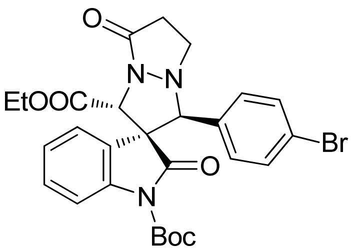
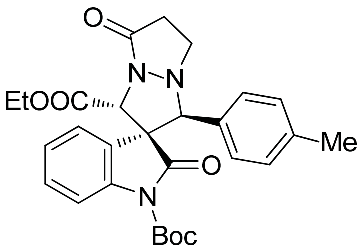


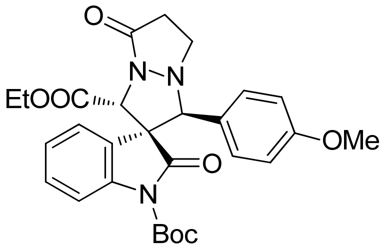
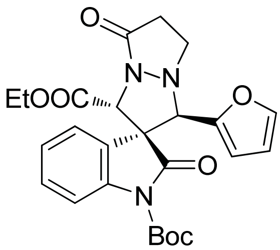
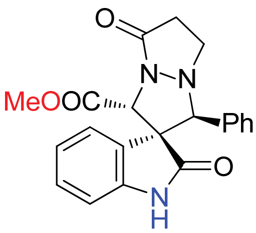
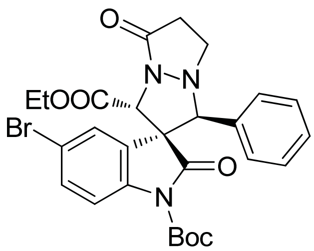
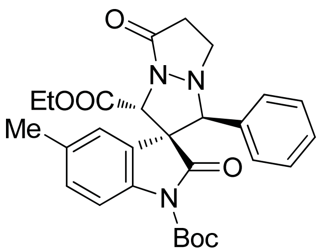
Figure 4. Plausible reaction models for the asymmetric 1,3-DC reaction.

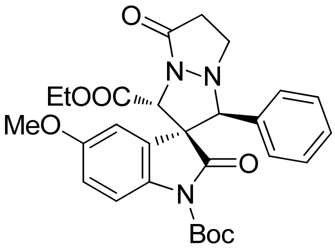
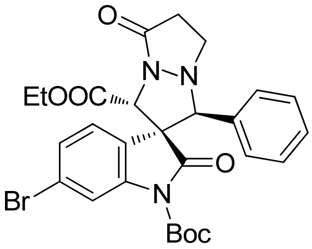
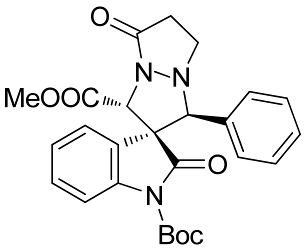
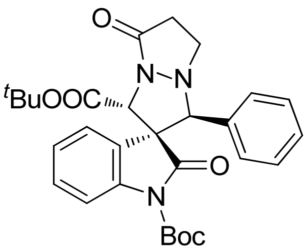
HPLC Analytic Conditions:

Unless otherwise specified, all products are separated by using DAICEL CHIRALCEL IA column, Hexane/iPrOH = 70/30, flow rate = 1.0 mL/min.

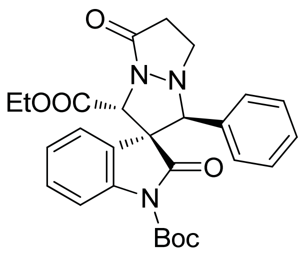
entry	product	Retention time	ee (%)
1	 **4aa**	t_{major} = 7.1 t_{minor} = 9.1	98
2	 **4ab**	t_{major} = 8.1 t_{minor} = 10.7	97
3	 **4ac**	t_{major} = 7.9 t_{minor} = 10.8	96
4	 **4ad**	t_{major} = 7.6 t_{minor} = 9.3	98

5	 **4ae**	t_{major} = 7.7 t_{minor} = 8.5	93
6	 **4af**	t_{major} = 7.0 t_{minor} = 11.5	>99
7	 **4ag**	t_{major} = 8.2 t_{minor} = 13.7	97
8	 **4ah**	t_{major} = 9.1 t_{minor} = 15.4	>99
9	 **4ai**	t_{major} = 7.8 t_{minor} = 10.4	95

10	 **4aj**	t_{major} = 8.4 t_{minor} = 10.4	94
11	 **4ak**	t_{major} = 6.6 t_{minor} = 8.9	91
12	 **6**	t_{major} = 8.2 t_{minor} = 14.0	96
13	 **4ca**	t_{major} = 7.7 t_{minor} = 13.2	98
14	 **4da**	t_{major} = 7.4 t_{minor} = 9.2	96

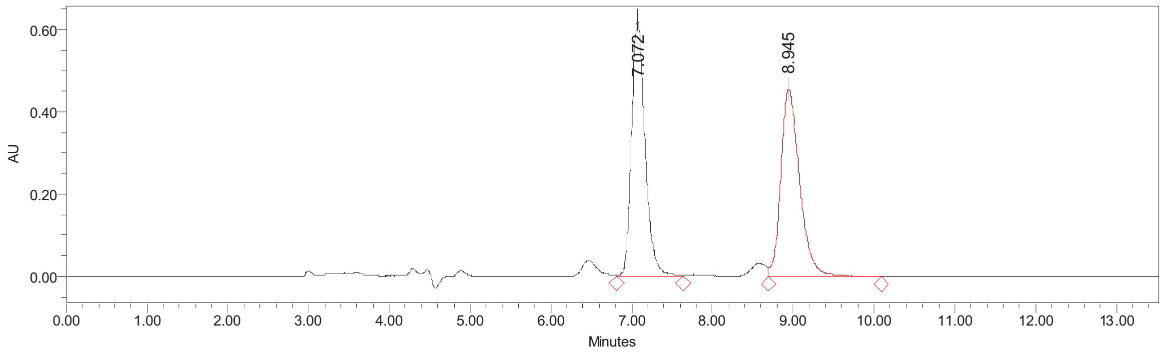
15	 **4ea**	t_{major} = 9.4 t_{minor} = 15.9	99
16	 **4fa**	t_{major} = 7.4 t_{minor} = 13.8	97
17	 **4ga**	t_{major} = 7.3 t_{minor} = 12.3	>99
18	 **4ha**	t_{major} = 5.9 t_{minor} = 6.6	98

4aa (Table 2, entry 1)

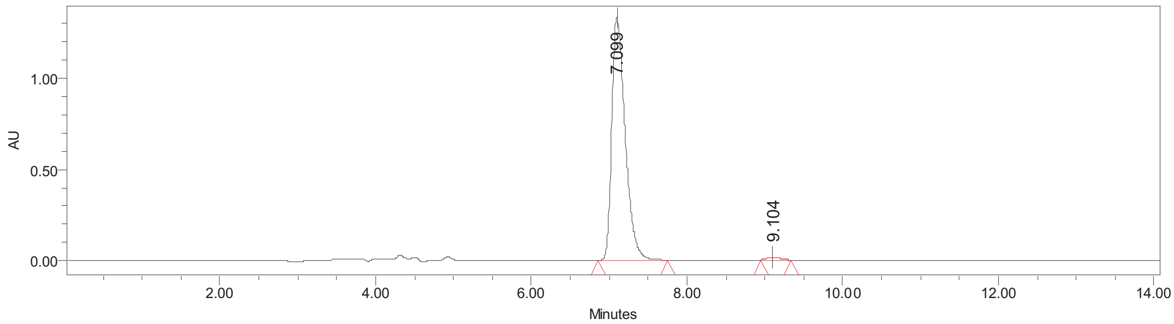


4aa

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min



	Name	Retention time	Area	% Area	Height	Integral type
1		7.072	7269713	49.76	623077	VV
2		8.945	7338760	50.24	454864	VV



	Name	Retention time	Area	% Area	Height	Integral type
1		7.099	15828804	98.97	1328657	bb
2		9.104	165305	1.03	13328	bb

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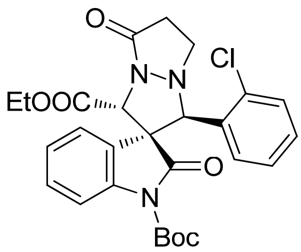
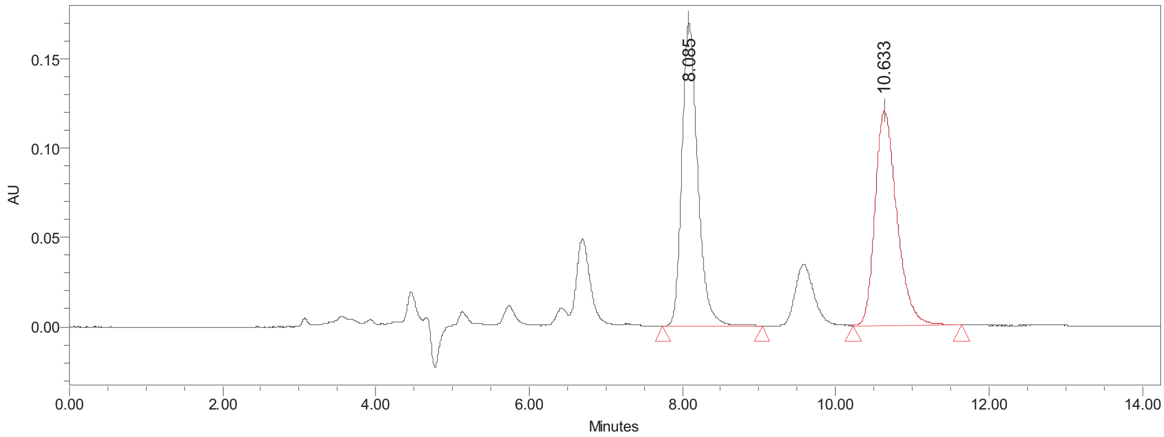
4ab (Table 2, entry 2)

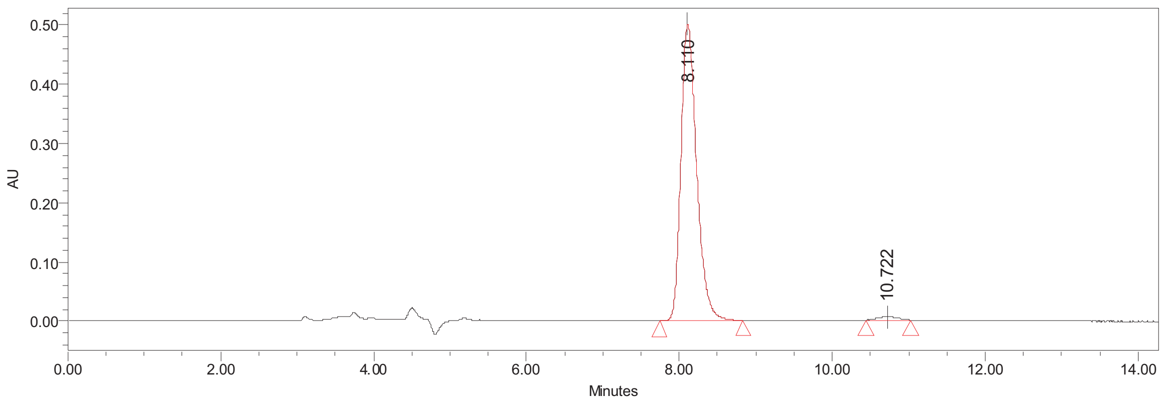


4ab

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

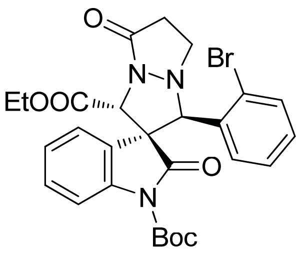


	Name	Retention time	Area	% Area	Height	Integral type
1		8.085	2421415	50.49	169529	bb
2		10.633	2374205	49.51	119984	bb



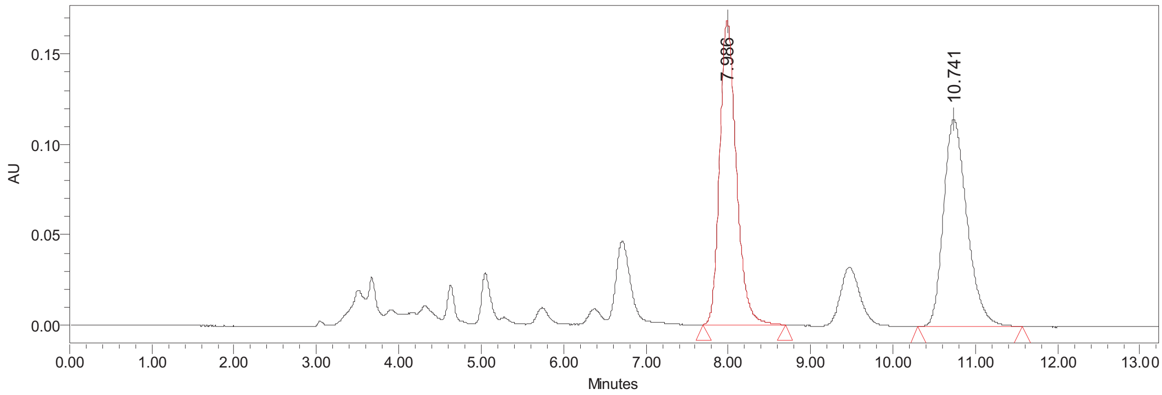
	Name	Retention time	Area	% Area	Height	Integral type
1		8.110	7157306	98.62	501657	bb
2		10.722	100167	1.38	5769	bb

4ac (Table 2, entry 3)

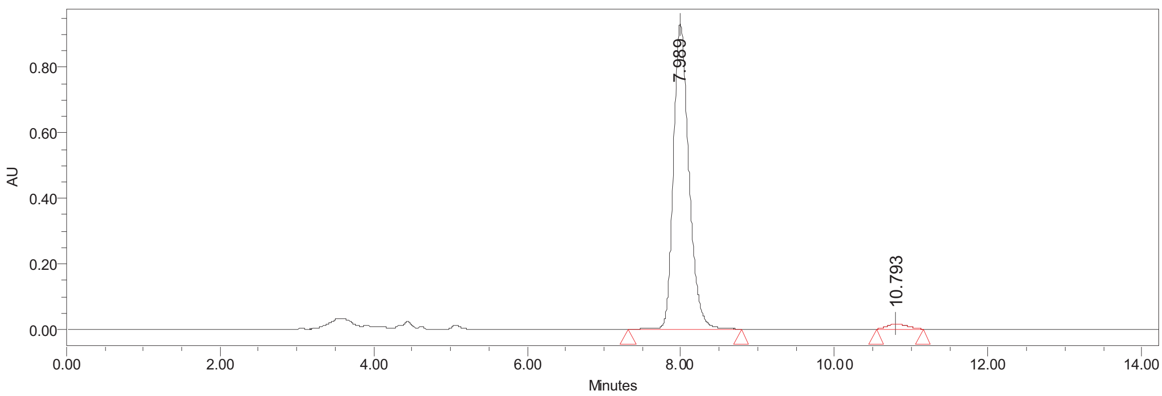


4ac

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

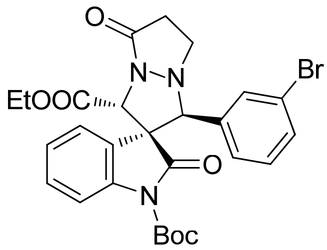


	Name	Retention time	Area	% Area	Height	Integral type
1		7.986	2361180	50.81	168214	bb
2		10.741	2285572	49.19	114658	bb



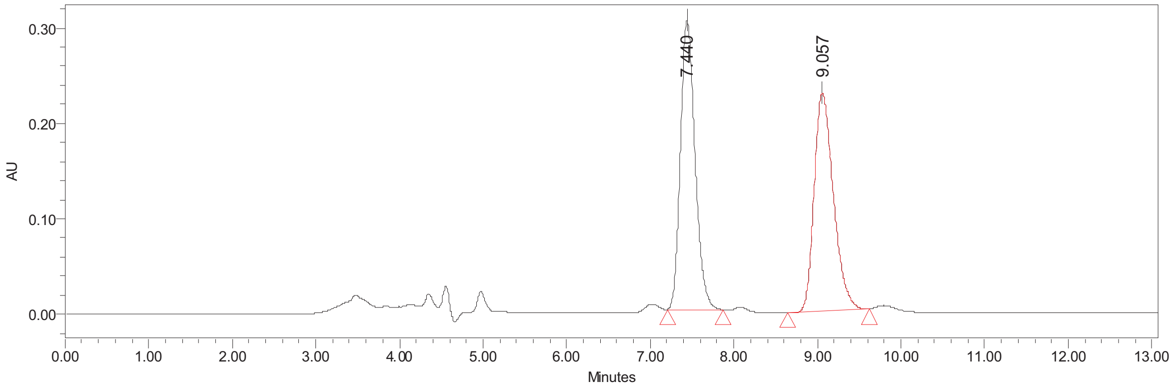
	Name	Retention time	Area	% Area	Height	Integral type
1		7.989	13005704	97.94	928847	bb
2		10.793	273754	2.06	15465	bb

4ad (Table 2, entry 4)

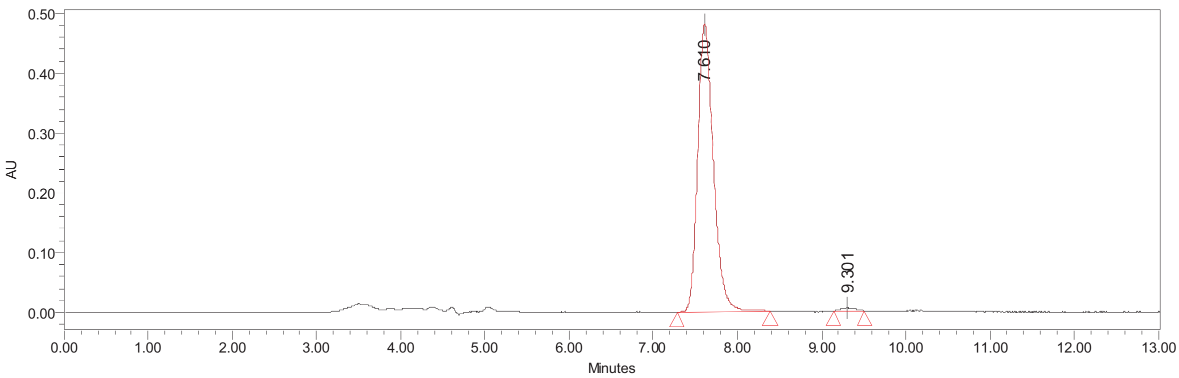


4ad

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min



	Name	Retention time	Area	% Area	Height	Integral type
1		7.440	3693154	50.18	303749	bb
2		9.057	3666155	49.82	228757	bb



	Name	Retention time	Area	% Area	Height	Integral type
1		7.610	6256188	99.07	481125	bb
2		9.301	59026	0.93	4776	bb

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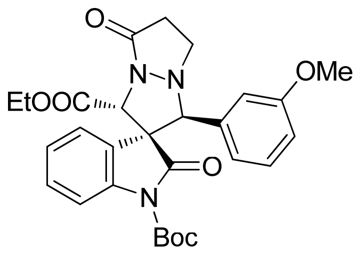
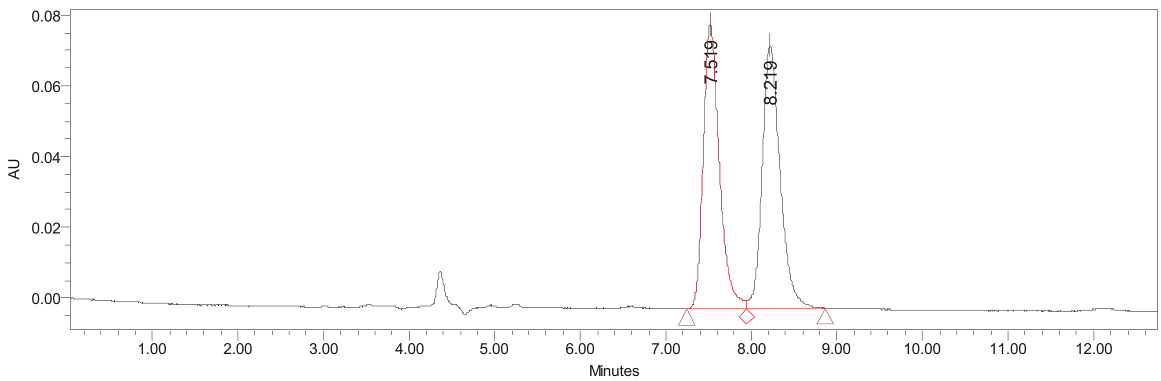
4ae (Table 2, entry 5)

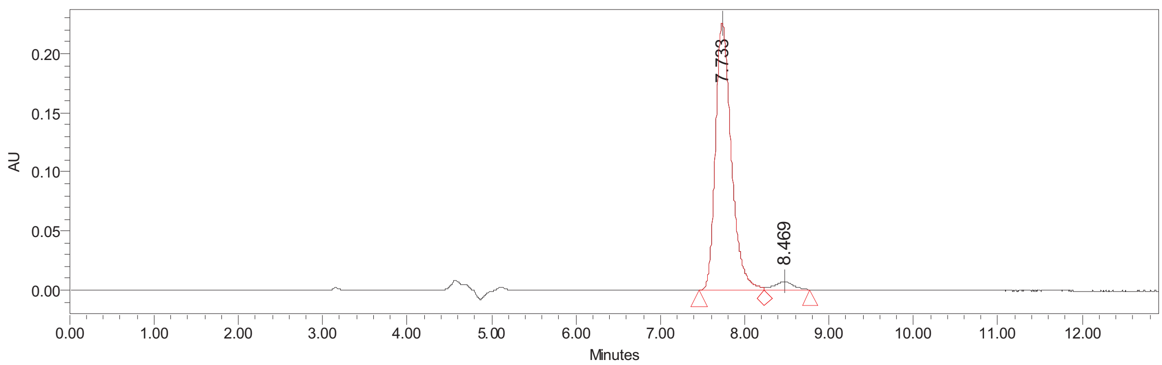


4ae

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

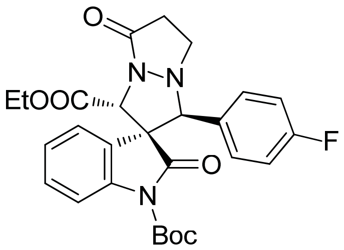


	Name	Retention time	Area	% Area	Height	Integral type
1		7.519	1051713	49.19	80468	BV
2		8.219	1086500	50.81	74534	VB



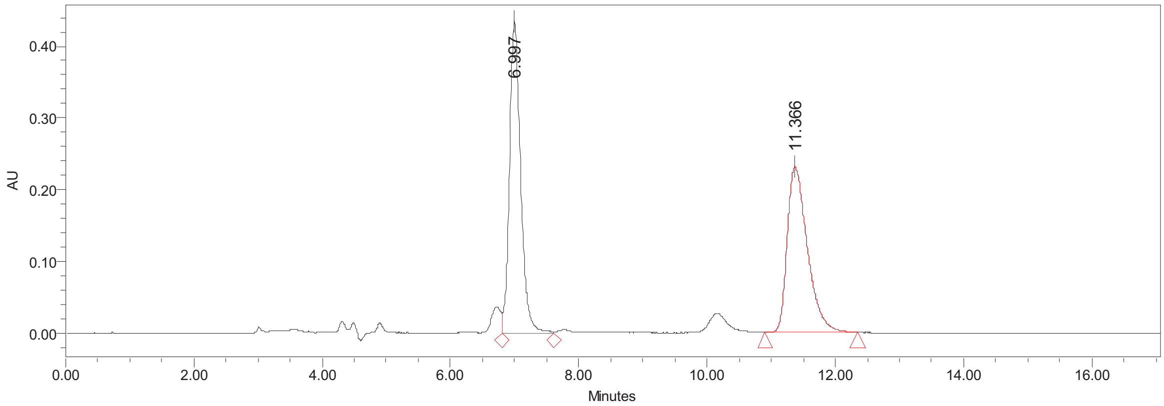
	Name	Retention time	Area	% Area	Height	Integral type
1		7.733	2957377	96.45	225593	BV
2		8.469	108834	3.55	6811	VB

4af (Table 2, entry 6)

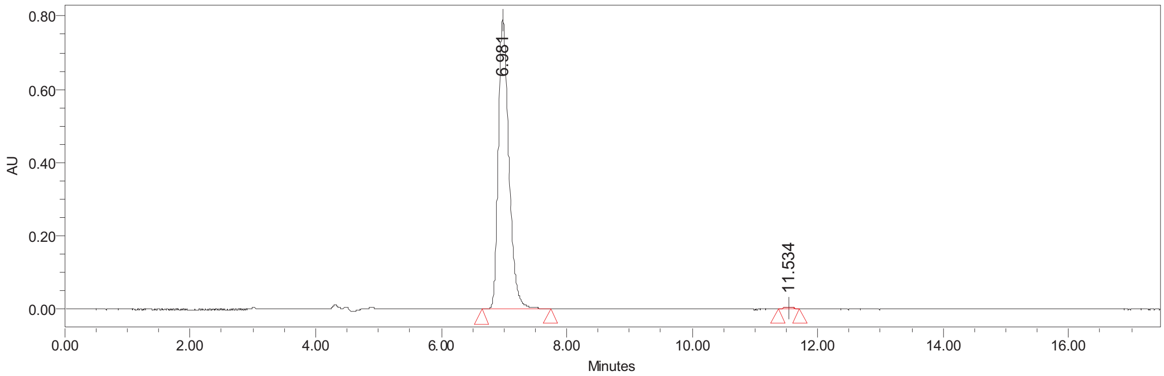


4af

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

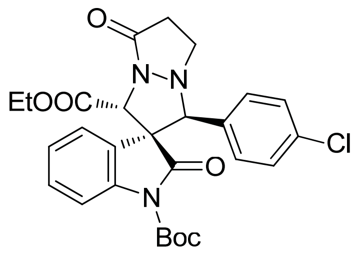


	Name	Retention time	Area	% Area	Height	Integral type
1		6.997	5223725	51.01	435342	VV
2		11.366	5017657	48.99	231359	bb



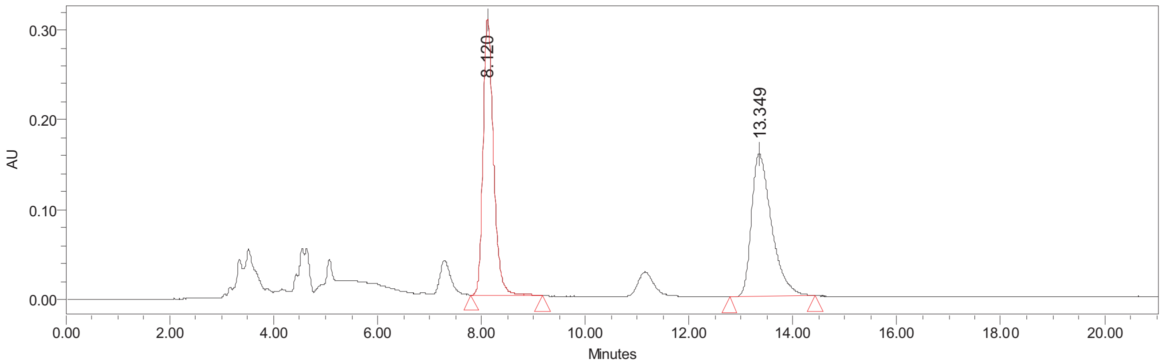
	Name	Retention time	Area	% Area	Height	Integral type
1		6.981	9257452	99.69	789147	bb
2		11.534	28960	0.31	2368	bb

4ag (Table 2, entry 7)

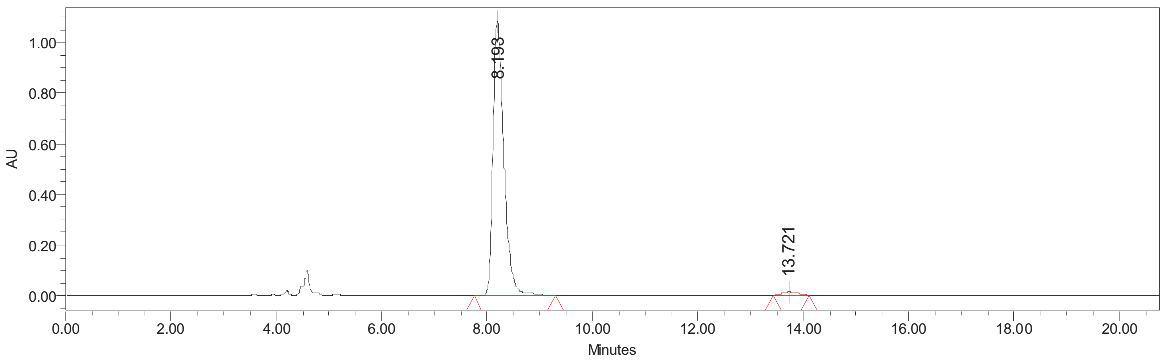


4ag

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

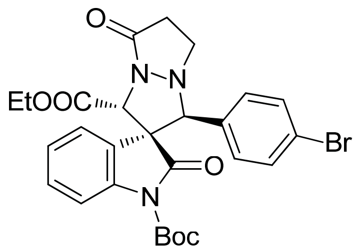


	Name	Retention time	Area	% Area	Height	Integral type
1		8.120	4271995	49.90	306436	bb
2		13.349	4288418	50.10	158720	bb



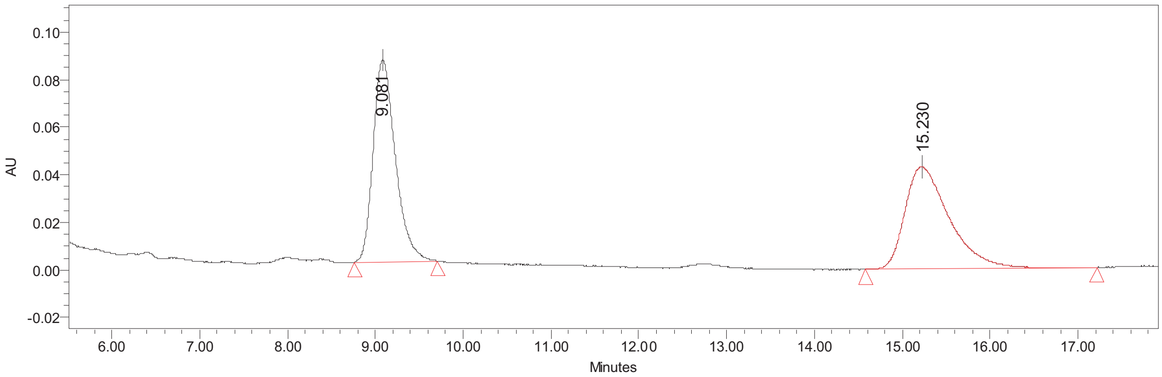
	Name	Retention time	Area	% Area	Height	Integral type
1		8.193	15540033	98.51	1081514	bb
2		13.721	234255	1.49	11487	bb

4ah (Table 2, entry 8)

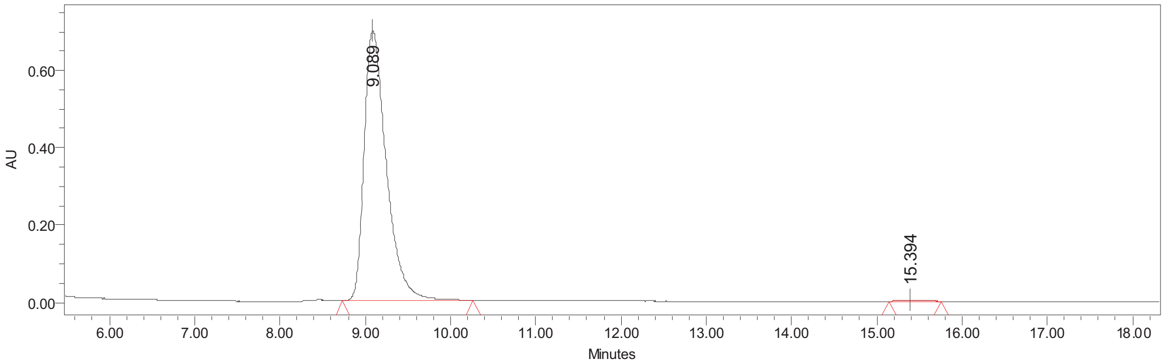


4ah

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

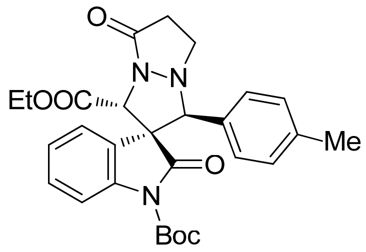


	Name	Retention time	Area	% Area	Height	Integral type
1		9.081	1496376	50.11	84860	bb
2		15.230	1489819	49.89	42809	bb



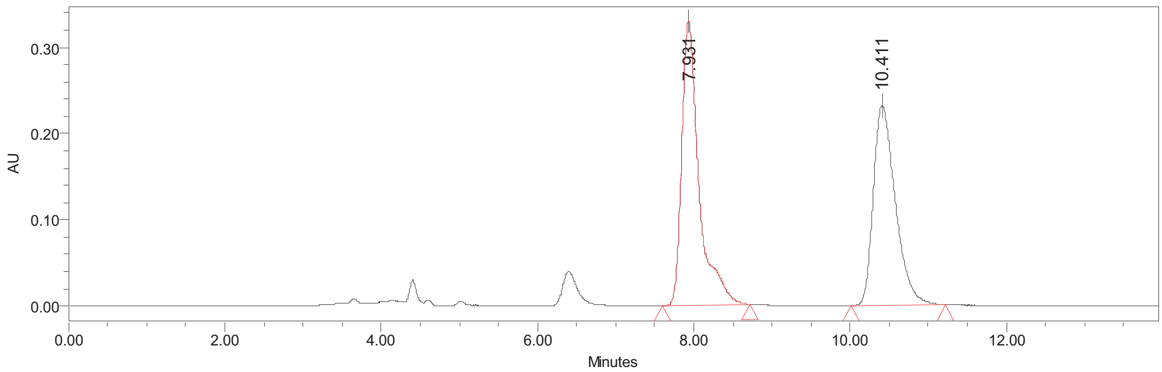
	Name	Retention time	Area	% Area	Height	Integral type
1		9.089	12634095	99.61	698171	bb
2		15.394	49556	0.39	2366	bb

4ai (Table 2, entry 9)

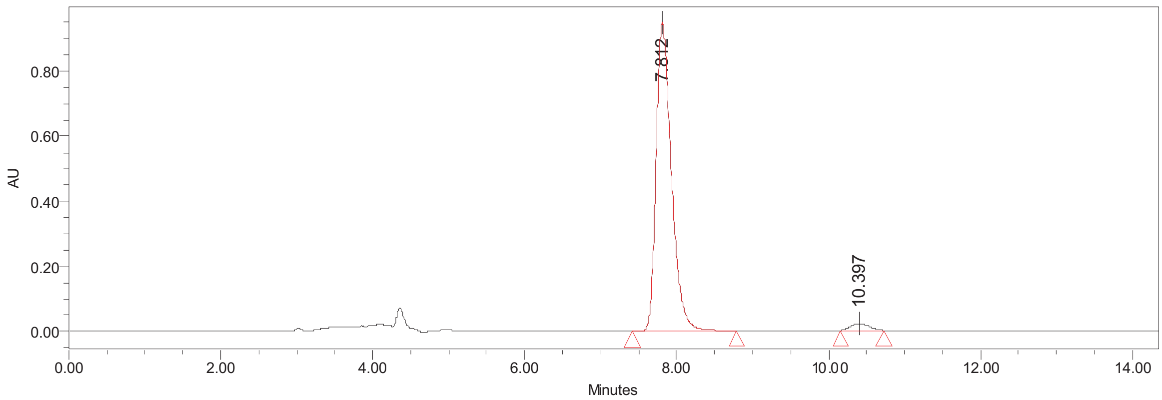


4ai

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

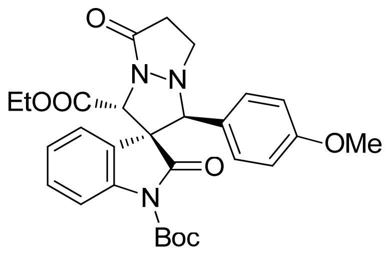


	Name	Retention time	Area	% Area	Height	Integral type
1		7.931	5056673	52.68	329378	bb
2		10.411	4542977	47.32	231652	bb



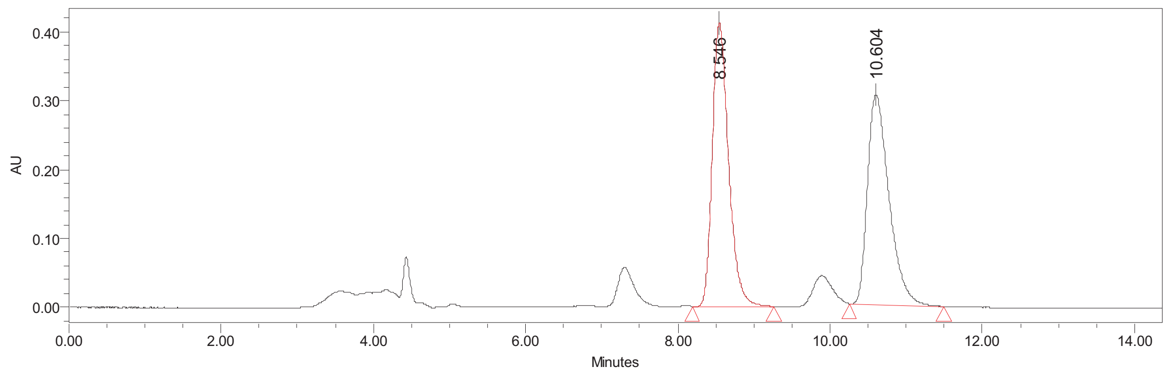
	Name	Retention time	Area	% Area	Height	Integral type
1		7.812	13318845	97.30	948524	bb
2		10.397	369046	2.70	21858	bb

4aj (Table 2, entry 10)

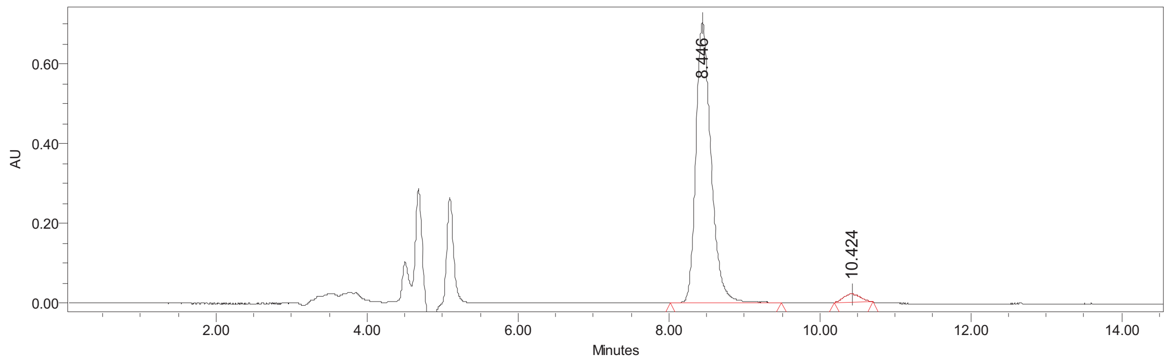


4aj

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

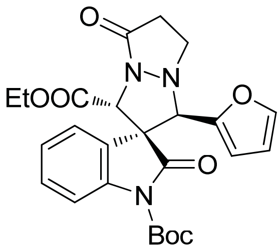


	Name	Retention time	Area	% Area	Height	Integral type
1		8.546	6101557	50.39	411950	bb
2		10.604	6006282	49.61	304965	bb



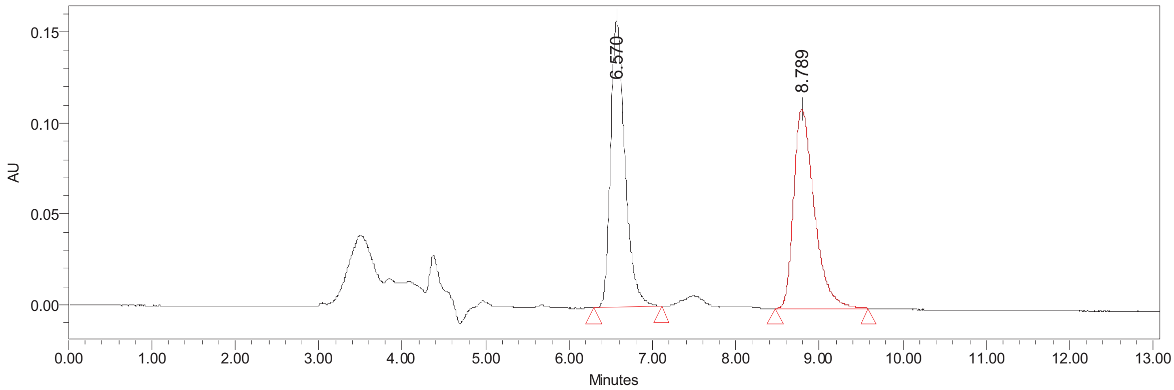
	Name	Retention time	Area	% Area	Height	Integral type
1		8.446	9867510	96.87	702638	bb
2		10.424	319296	3.13	20613	bb

4ak (Table 2, entry 11)

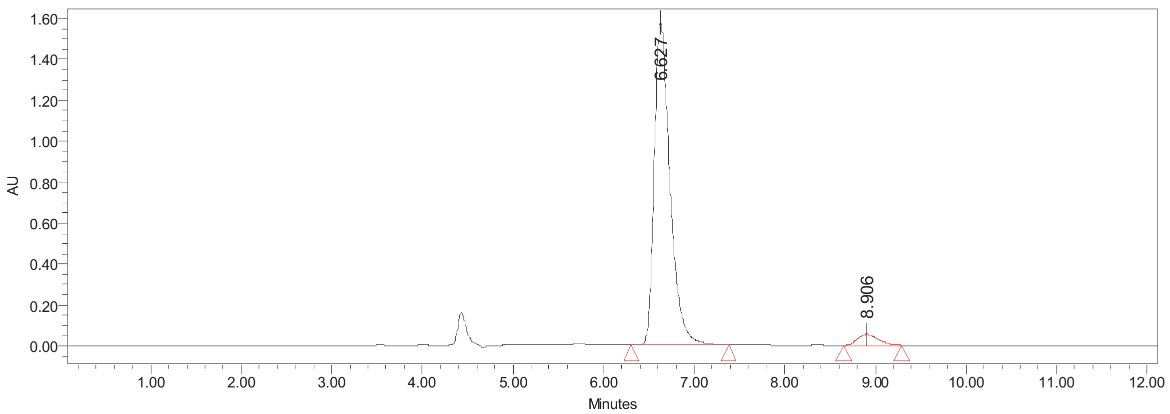


4ak

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

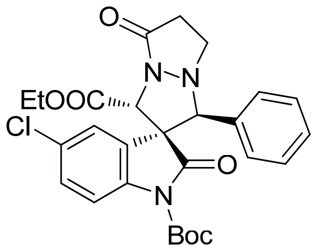


	Name	Retention time	Area	% Area	Height	Integral type
1		6.570	1895159	49.99	157535	bb
2		8.789	1895856	50.01	109888	bb



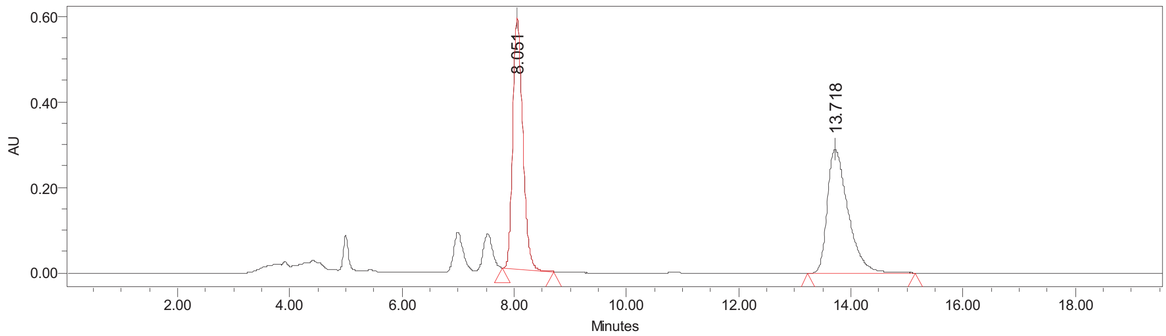
	Name	Retention time	Area	% Area	Height	Integral type
1		6.627	19129580	95.62	1576672	bb
2		8.906	875507	4.38	54373	bb

4ba (Table 2, entry 12)

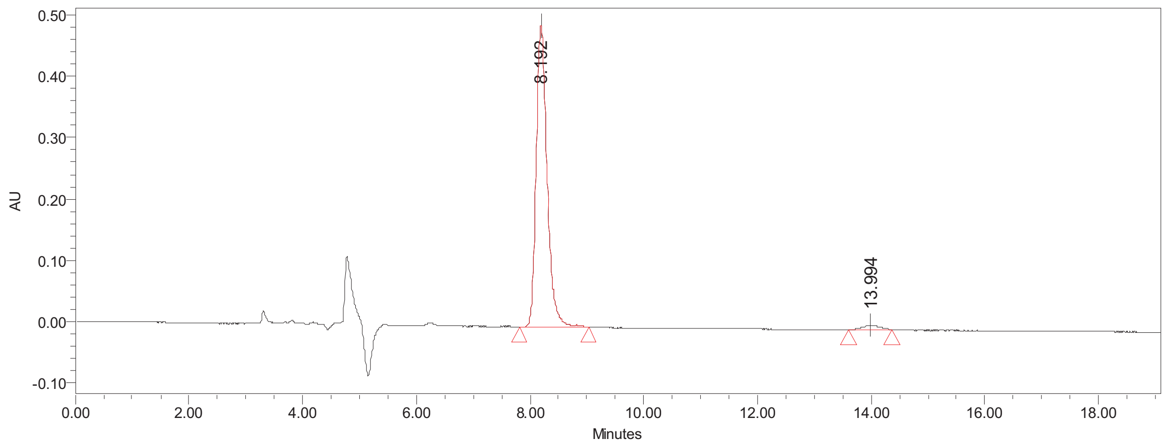


4ba

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

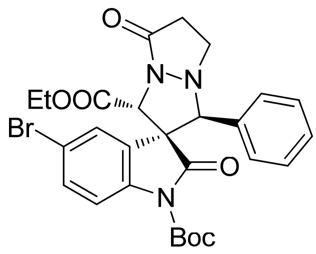


	Name	Retention time	Area	% Area	Height	Integral type
1		8.051	7228904	49.44	587383	bb
2		13.718	7392375	50.56	289400	bb



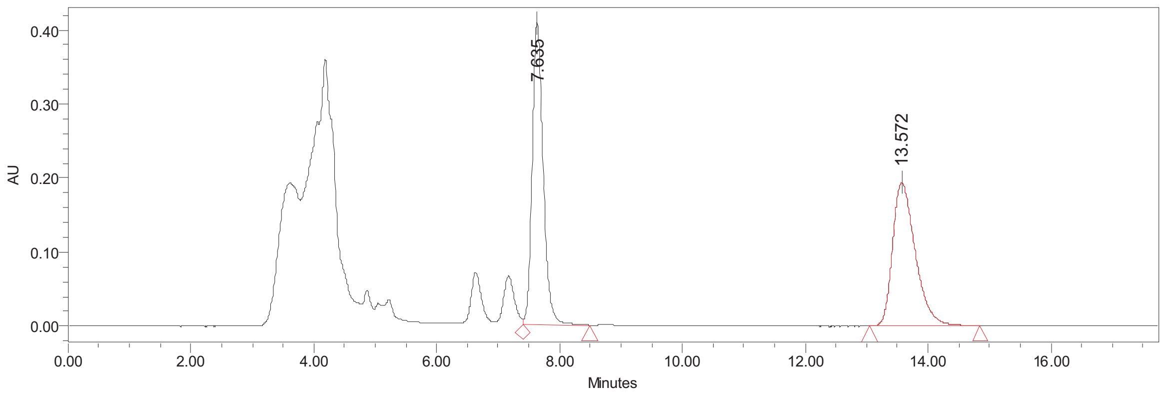
	Name	Retention time	Area	% Area	Height	Integral type
1		8.192	6552697	97.81	491672	bb
2		13.994	146611	2.19	7007	bb

4ca (Table 2, entry 13)

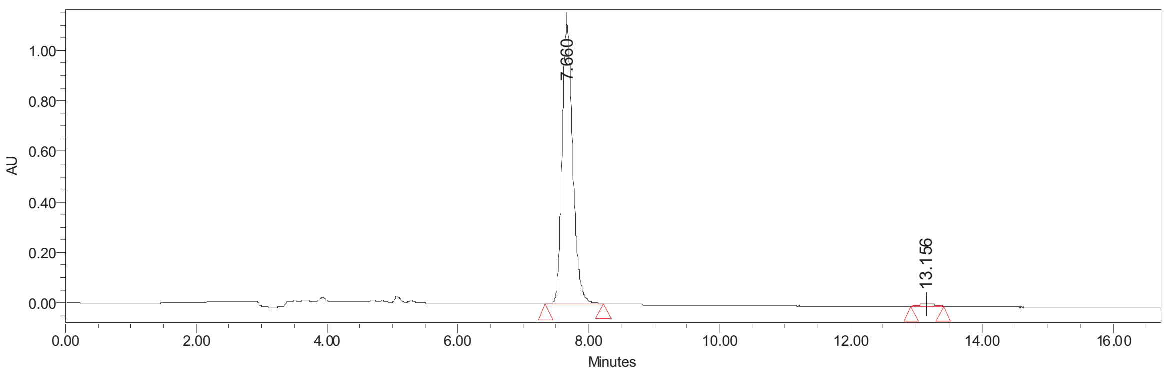


4ca

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

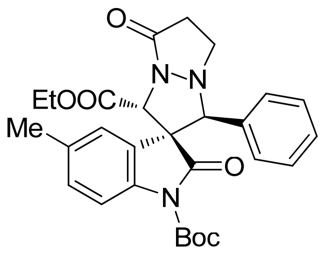


	Name	Retention time	Area	% Area	Height	Integral type
1		7.635	5049104	50.38	407676	VB
2		13.572	4973409	49.62	193953	bb



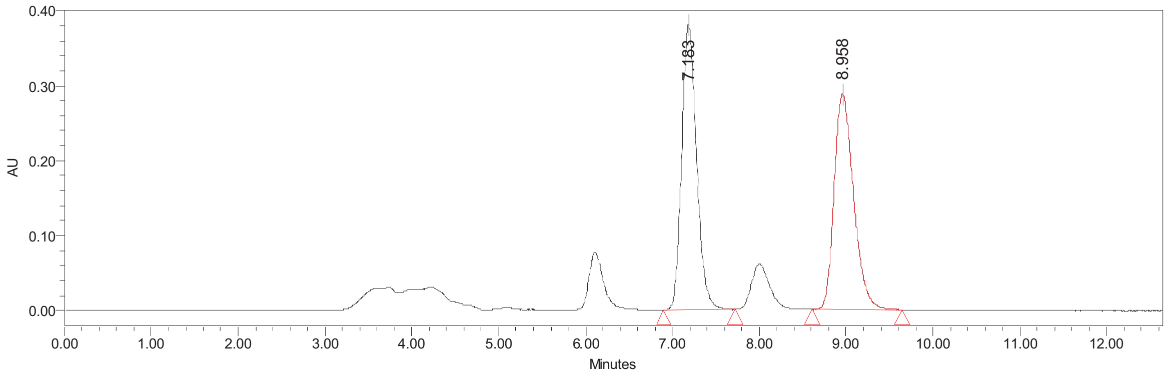
	Name	Retention time	Area	% Area	Height	Integral type
1		7.660	12734229	98.84	1109190	bb
2		13.156	148959	1.16	9024	bb

4da (Table 2, entry 14)

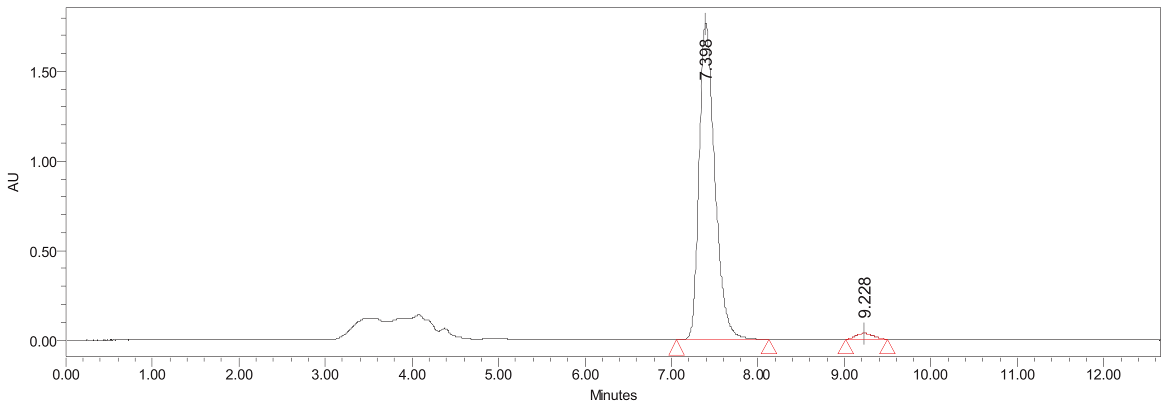


4da

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

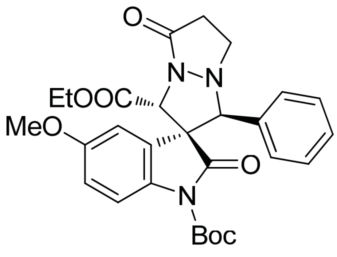


	Name	Retention time	Area	% Area	Height	Integral type
1		7.183	4526589	50.33	380202	bb
2		8.958	4467158	49.67	287334	bb

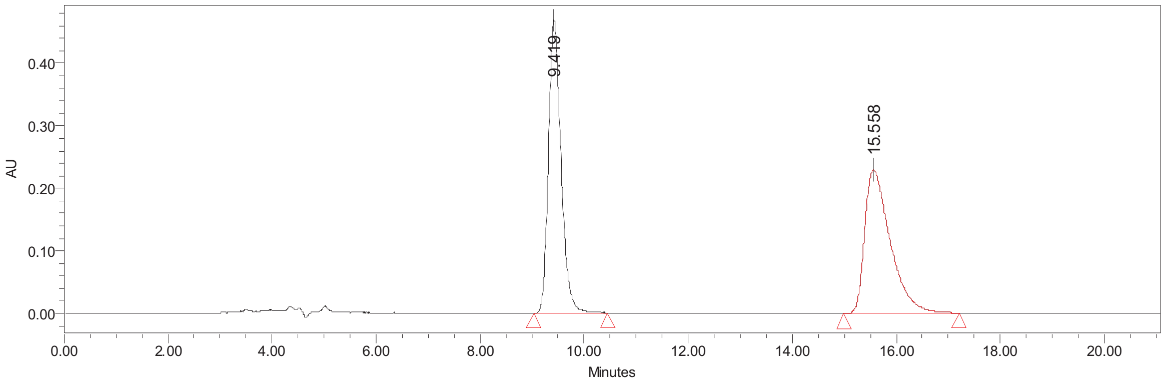


	Name	Retention time	Area	% Area	Height	Integral type
1		7.398	22382356	97.94	1763685	bb
2		9.228	470838	2.06	32693	bb

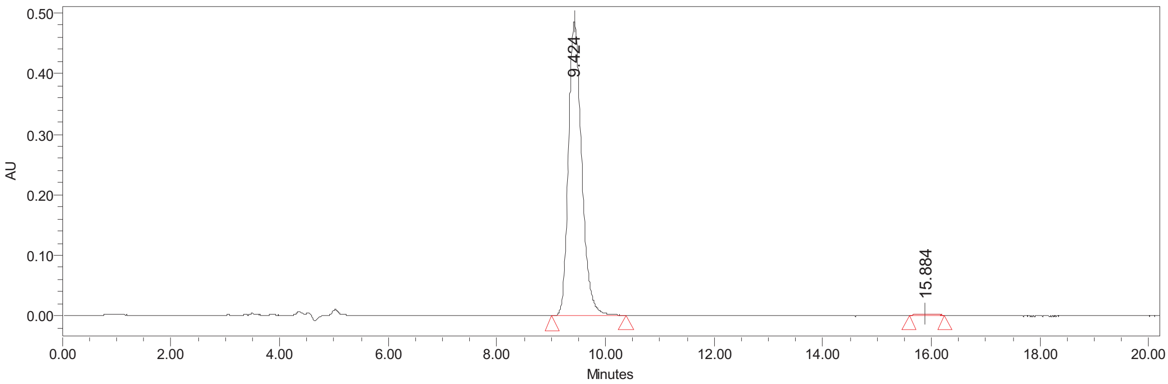
4ea (Table 2, entry 15)



Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

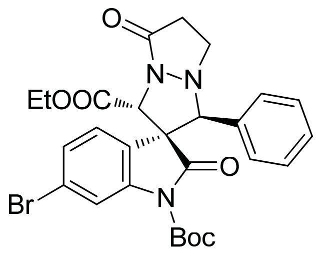


	Name	Retention time	Area	% Area	Height	Integral type
1		9.419	7891394	50.23	468753	bb
2		15.558	7818975	49.77	229824	bb



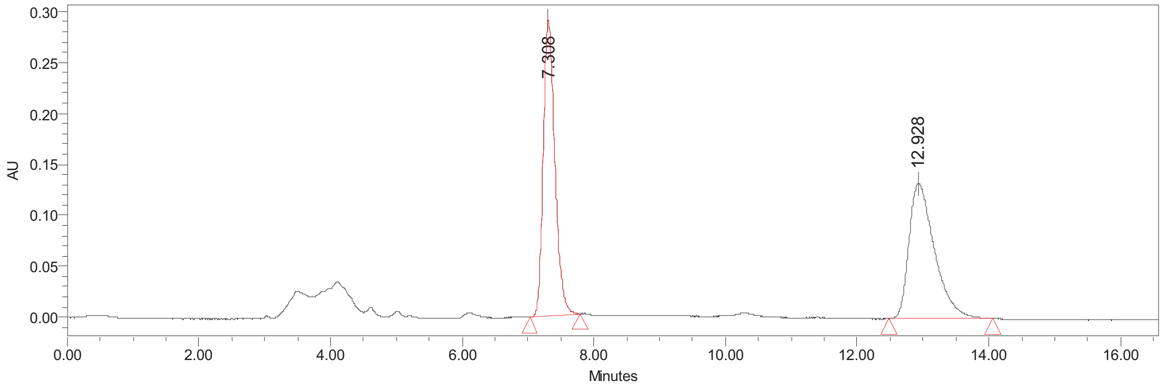
	Name	Retention time	Area	% Area	Height	Integral type
1		9.424	8190993	99.26	485232	bb
2		15.884	61115	0.74	2743	bb

4fa (Table 2, entry 16)

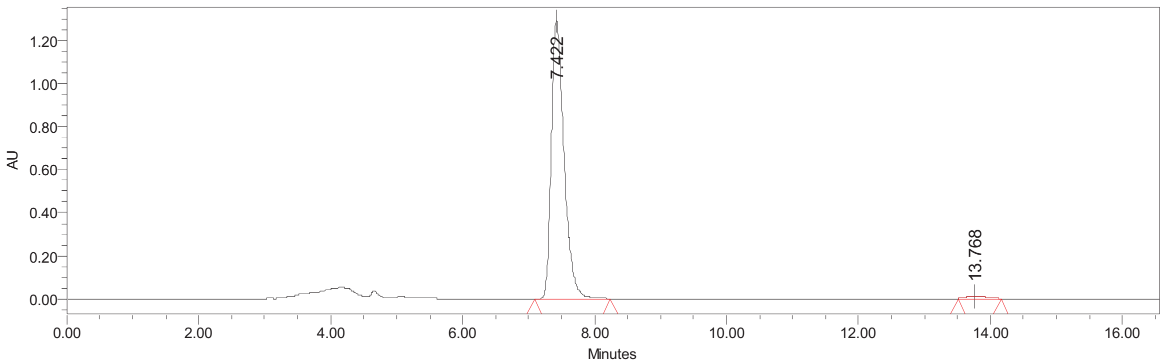


4fa

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min

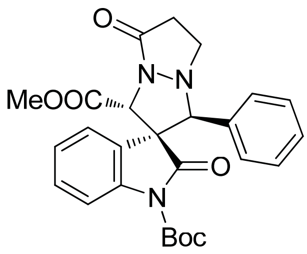


	Name	Retention time	Area	% Area	Height	Integral type
1		7.308	3568736	49.97	290257	bb
2		12.928	3573412	50.03	132443	bb



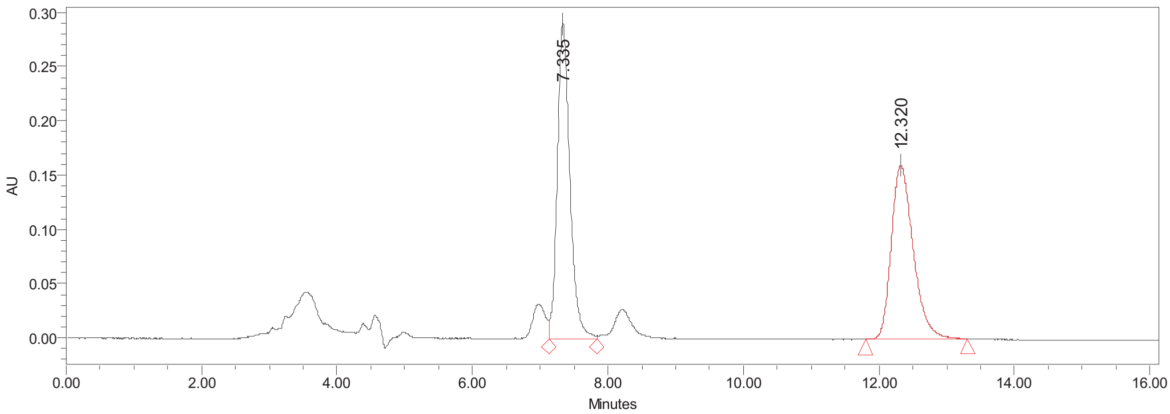
	Name	Retention time	Area	% Area	Height	Integral type
1		7.422	17491517	98.74	1290847	bb
2		13.768	222344	1.26	10405	bb

4ga (Table 2, entry 17)

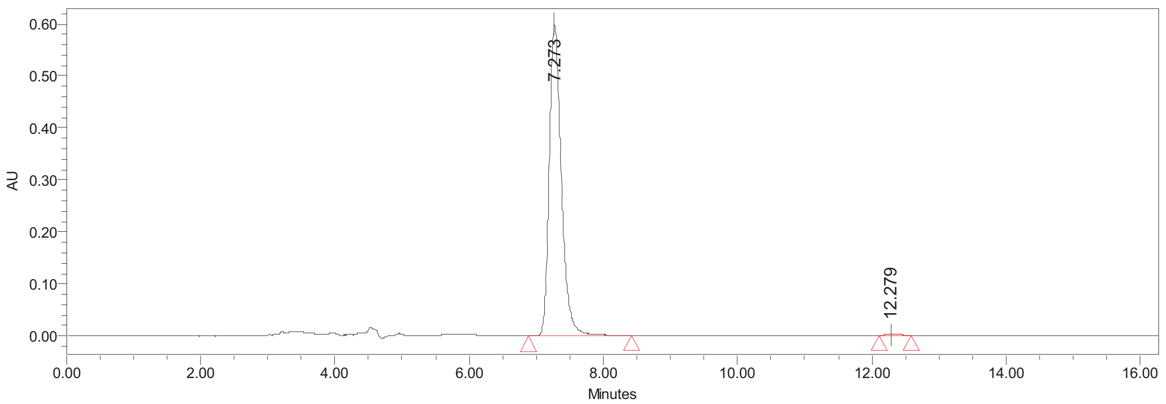


4ga

Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min



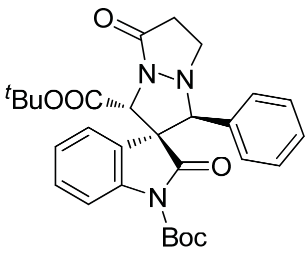
	Name	Retention time	Area	% Area	Height	Integral type
1		7.335	3748475	51.07	290538	VV
2		12.320	3591842	48.93	160000	bb



	Name	Retention time	Area	% Area	Height	Integral type
1		7.273	7537825	99.61	598751	bb
2		12.279	29532	0.39	1952	bb

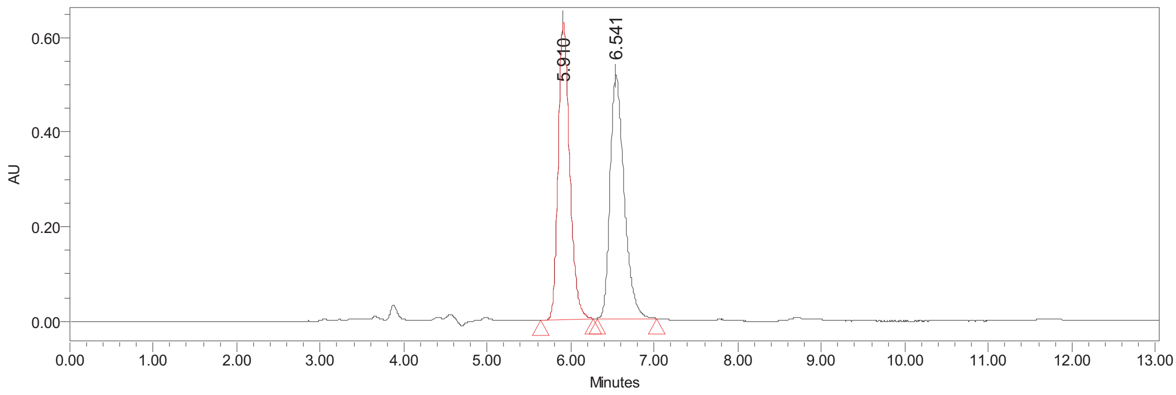
Electronic Supplementary Material (ESI) for Chemical Communications

4ha (Table 2, entry 18)

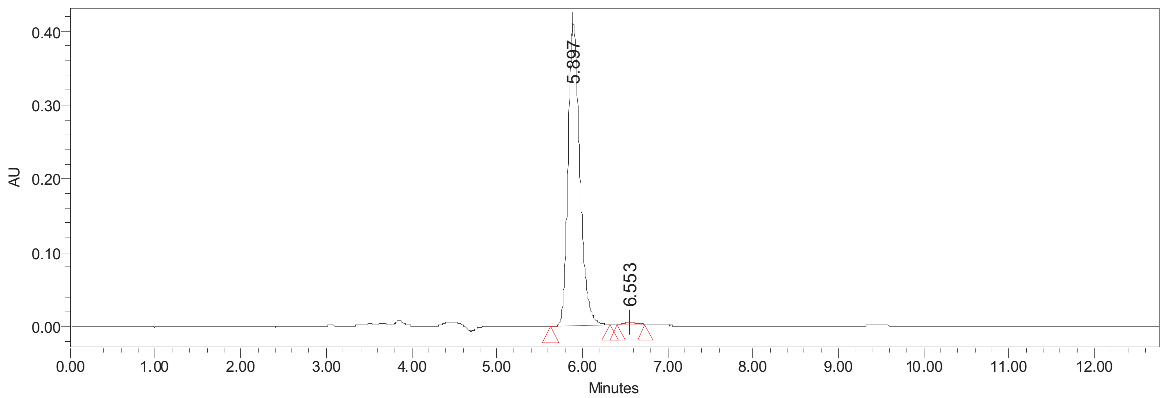


4ha

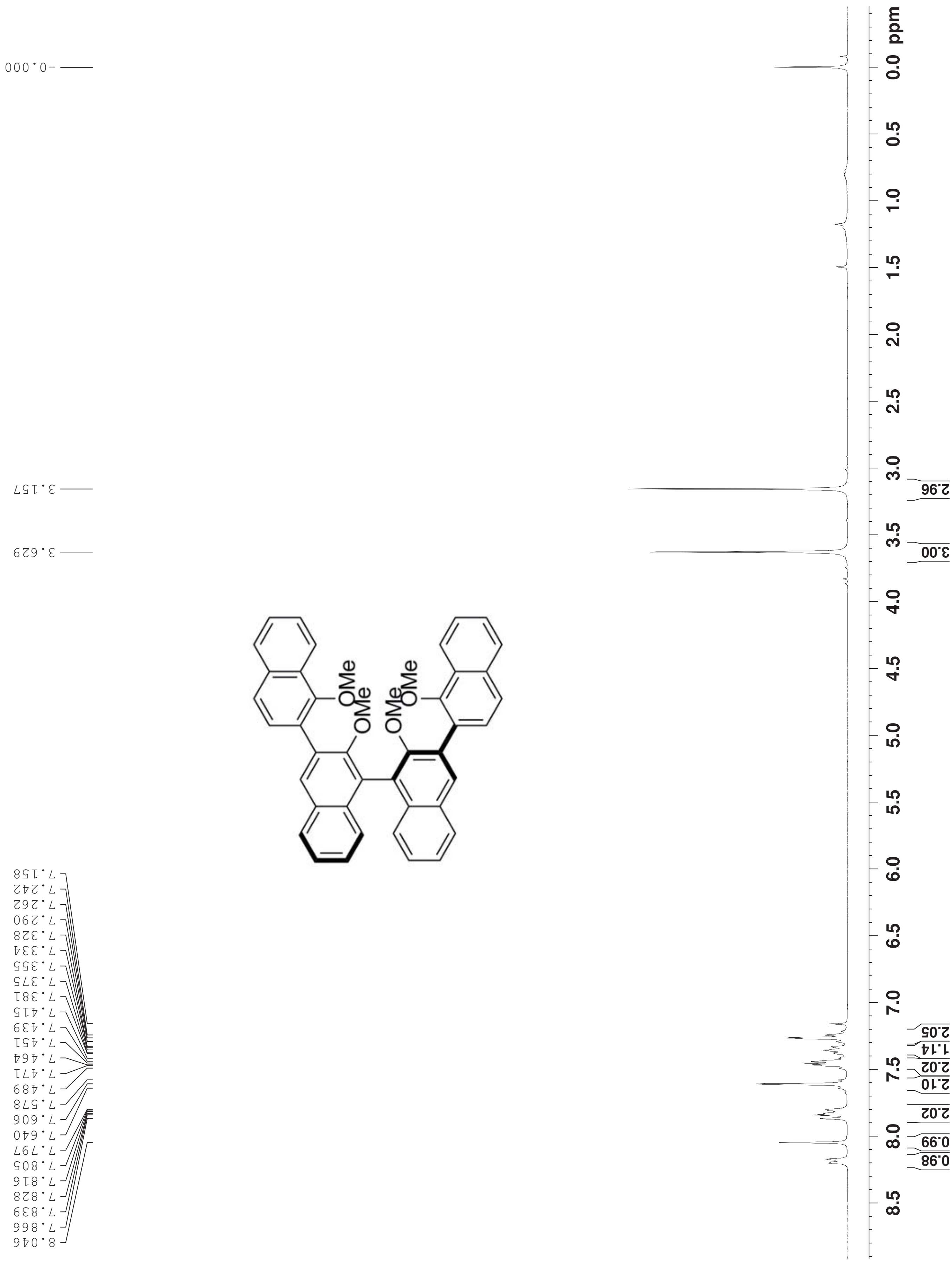
Chiralpak IA column, hexane/iPrOH (70:30), flow rate 1.0 mL/min



	Name	Retention time	Area	% Area	Height	Integral type
1		5.910	6008932	49.96	627254	bb
2		6.541	6019401	50.04	514127	bb



	Name	Retention time	Area	% Area	Height	Integral type
1		5.897	3963121	99.19	409516	bb
2		6.553	32253	0.81	3418	bb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7.415
7.439
7.451
7.464
7.471
7.489
7.578
7.606
7.640
7.797
7.805
7.816
7.828
7.839
7.866
8.046
OMe
OMe
OMe
OMe
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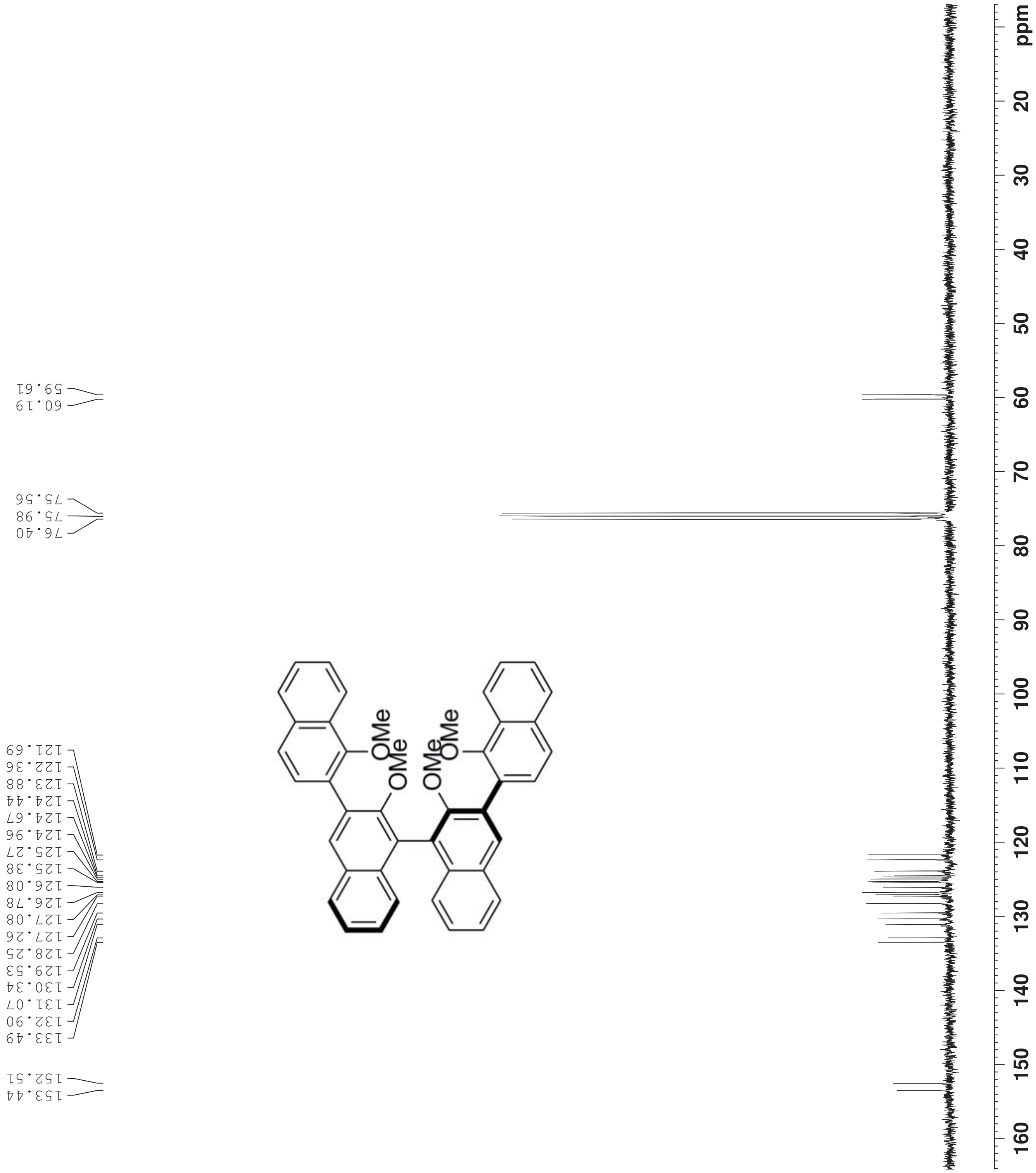
2.10
2.02
0.99
0.98
ppm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123.88
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124.67
124.96
125.27
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126.08
126.78
127.08
127.26
128.25
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131.07
132.90
133.49
152.51
153.44
OMe
OMe
OMe
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ppm
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30
40
50
60
70
80
90
100
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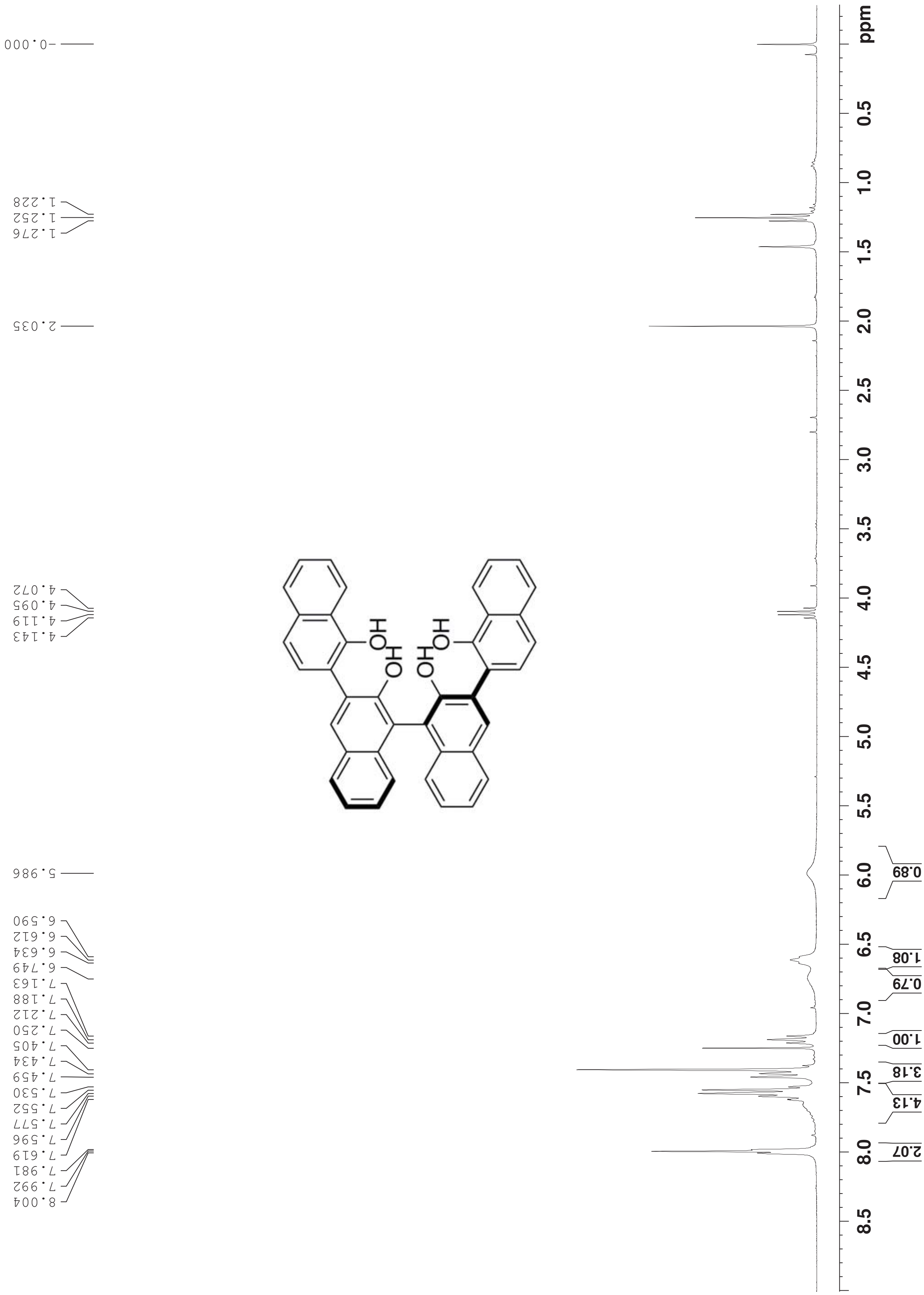
120
130
140
150
160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7.188
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7.250
7.405
7.434
7.459
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7.552
7.577
7.596
7.619
7.981
7.992
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OH
OH
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0.79
1.00
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4.13
2.07
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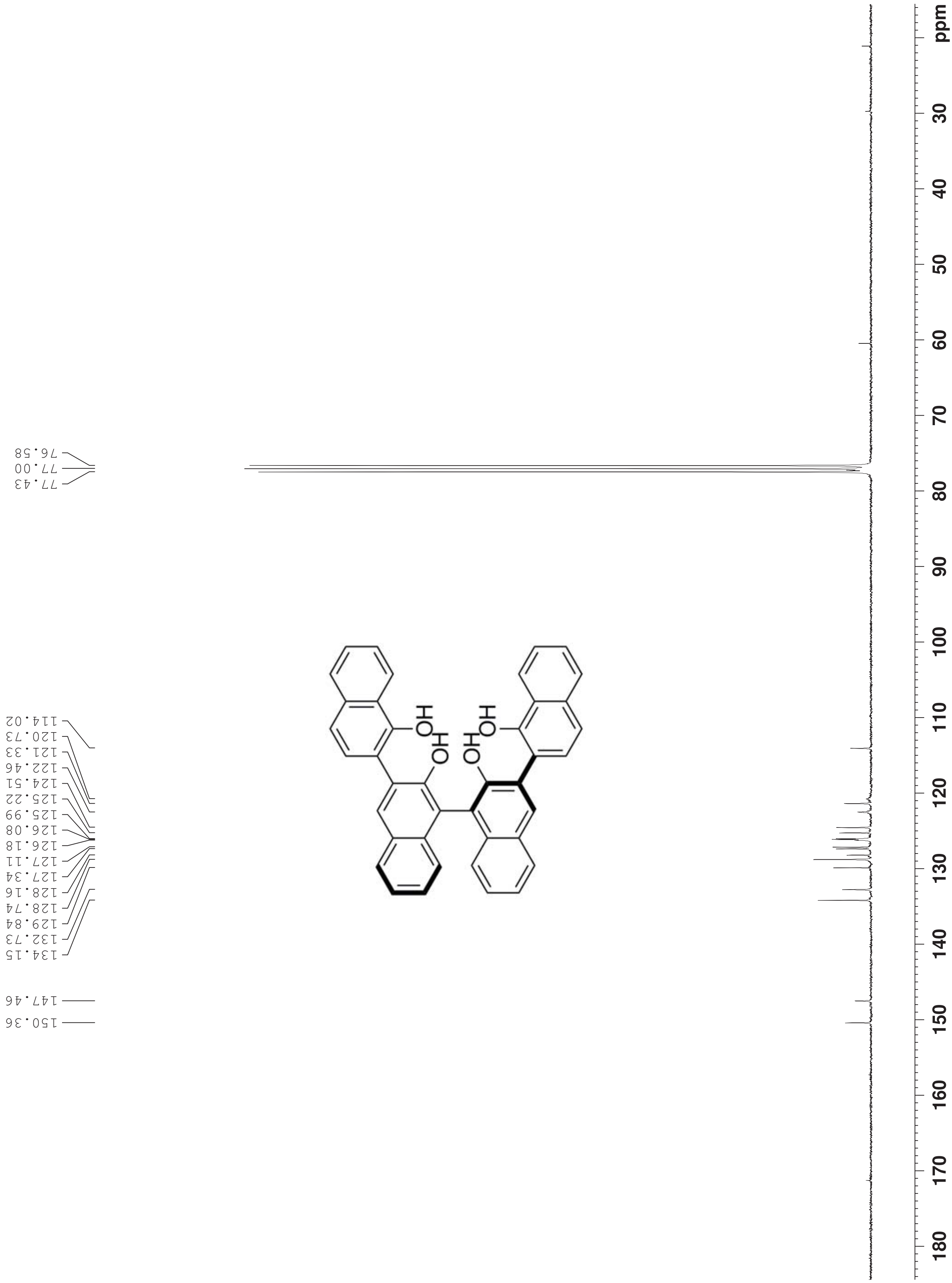
8.5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127.34
128.16
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132.73
134.15
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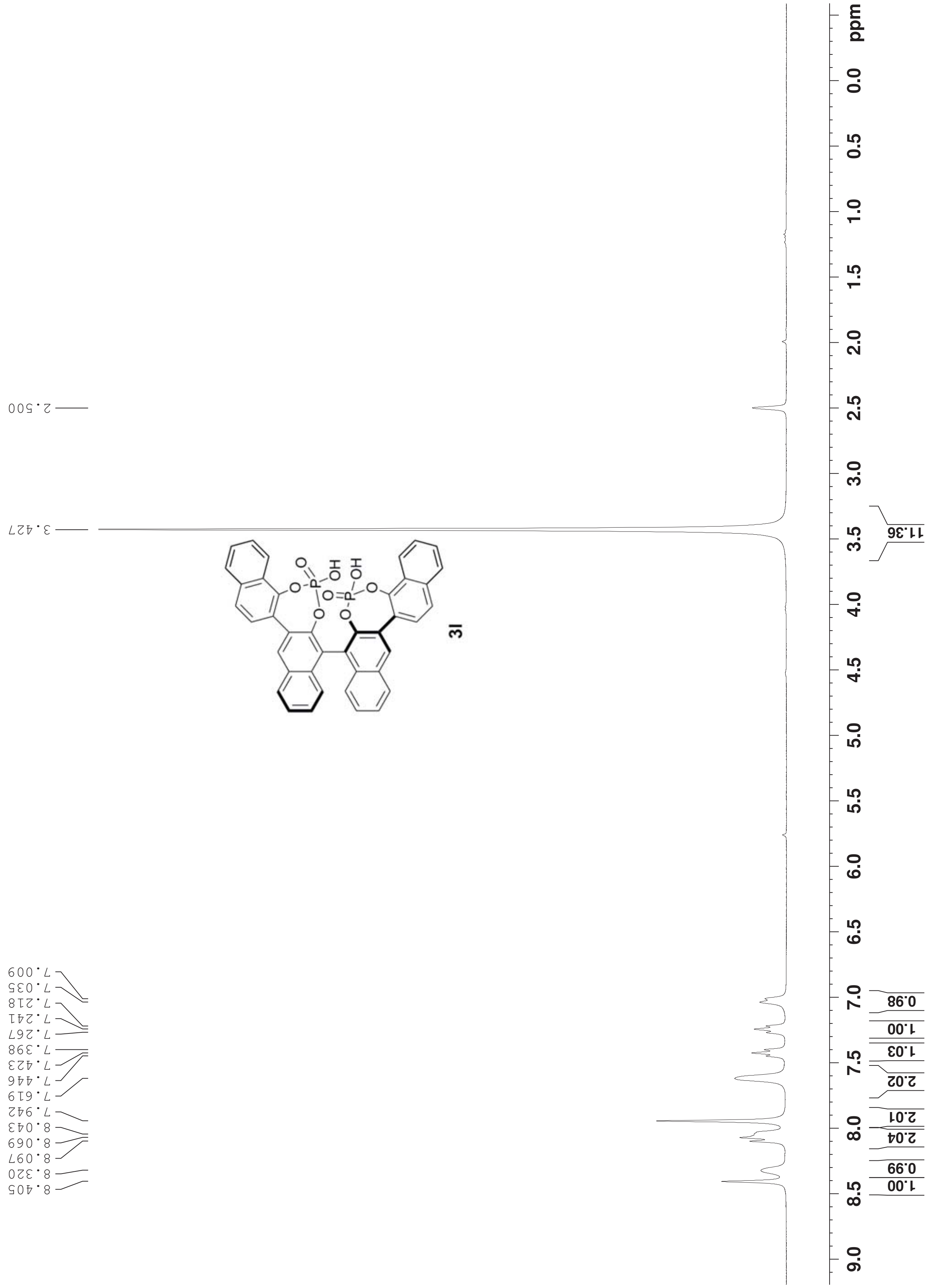
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8.097
8.320
8.405
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6.5
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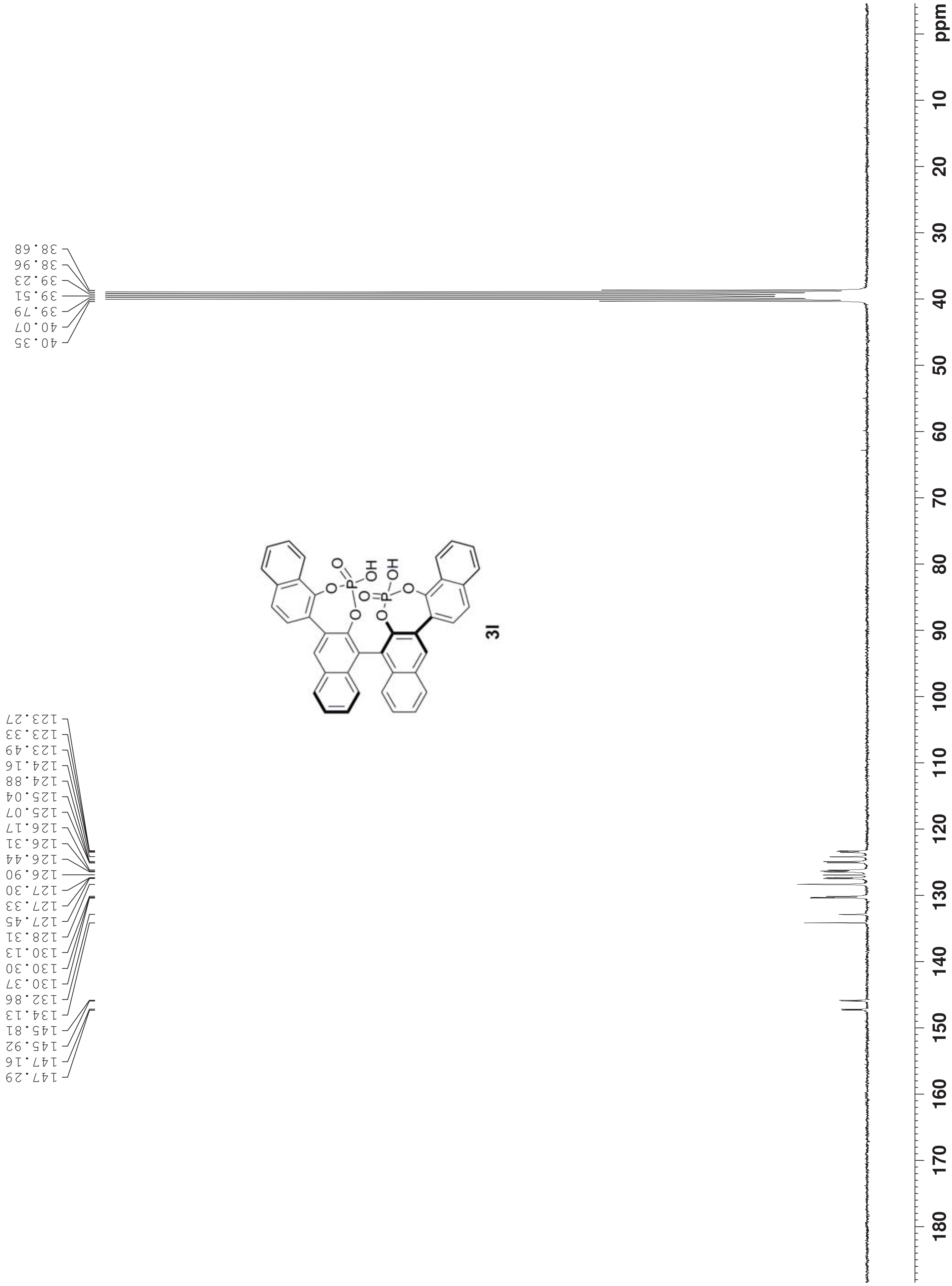
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127.33
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130.30
130.37
132.86
134.13
145.81
145.92
147.16
147.29
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30
40
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150
160
170
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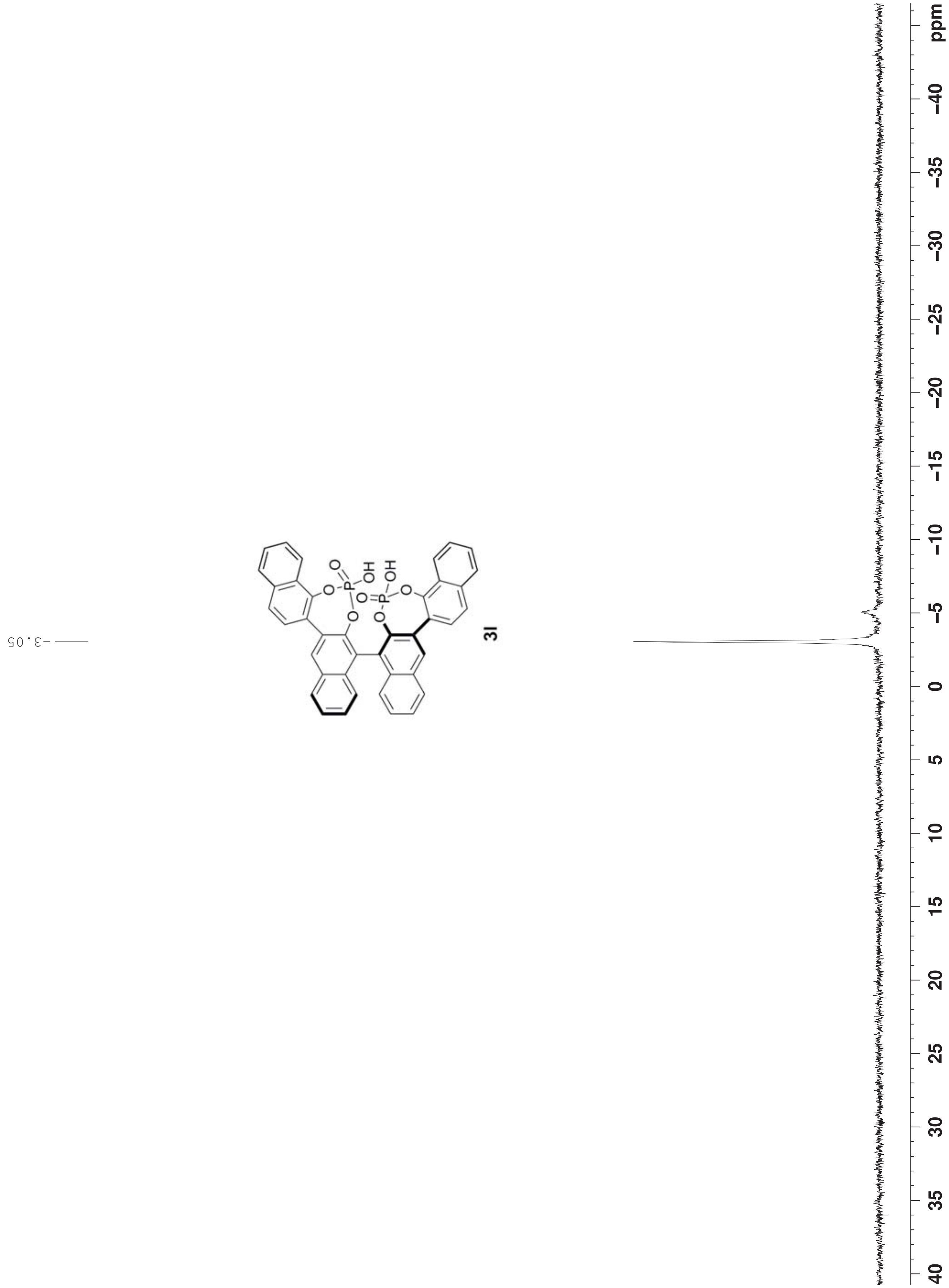
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-10
-5
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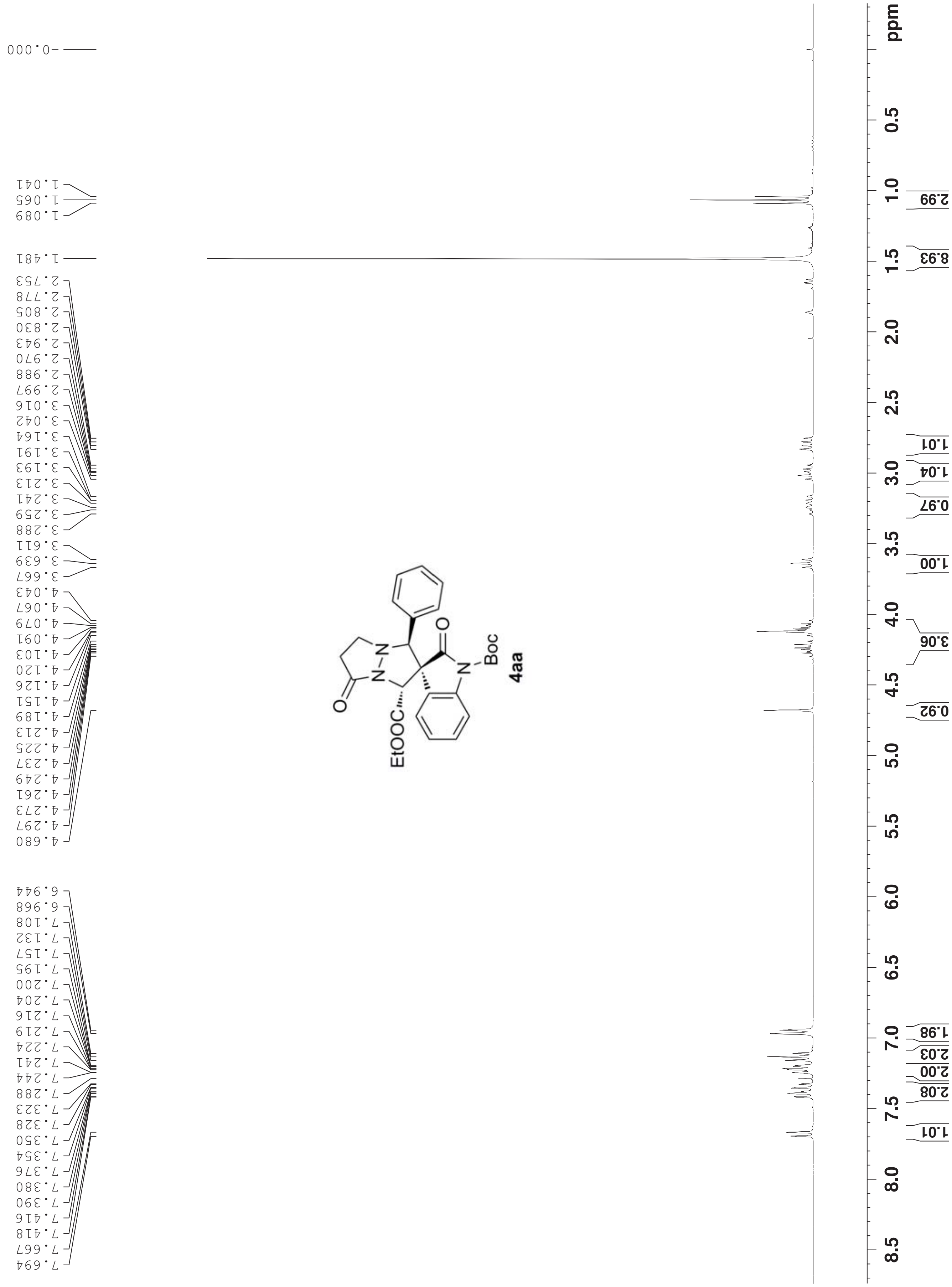
30
35
40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2.00
2.08
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Boc
4aa
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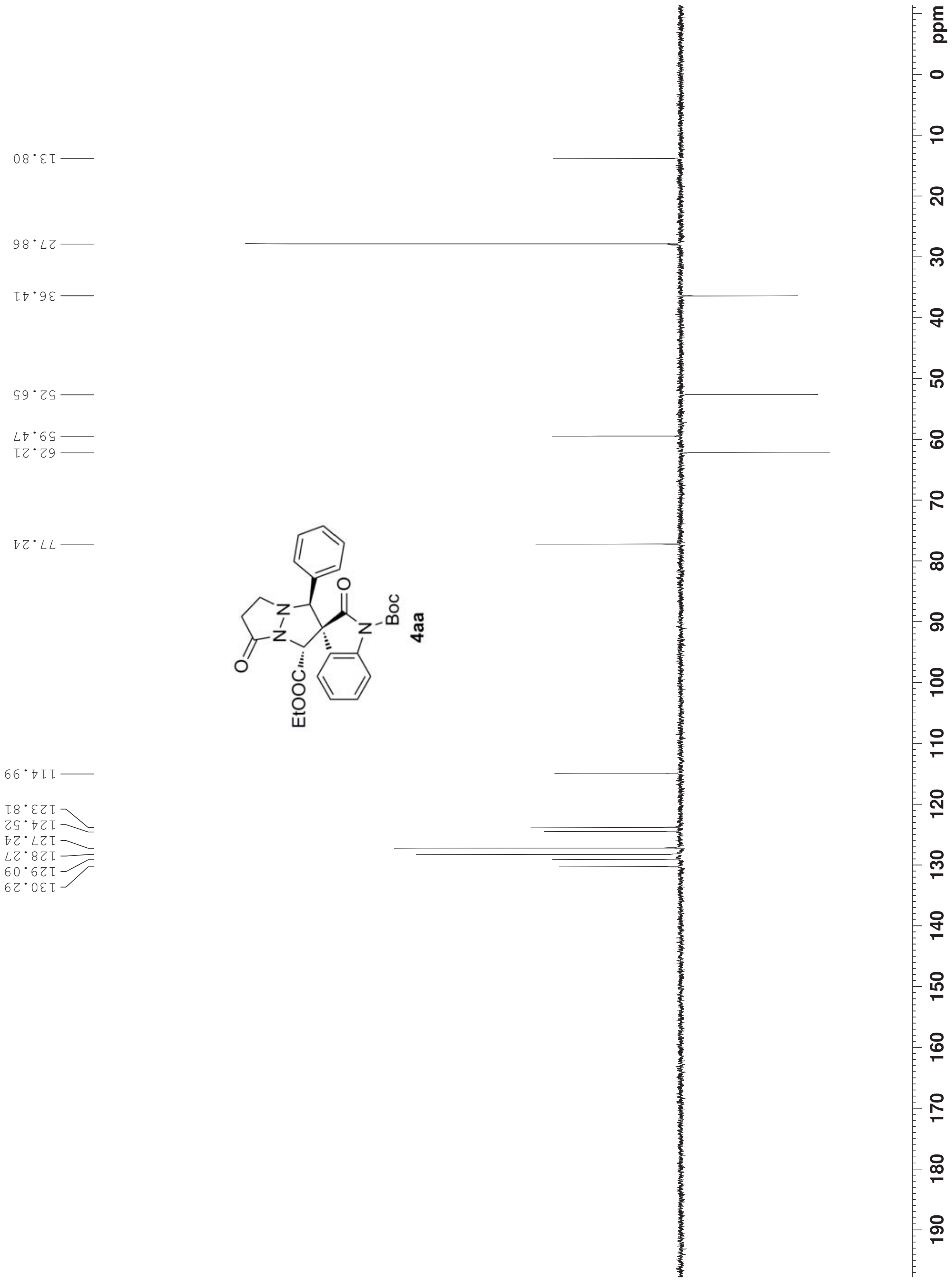
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Boc
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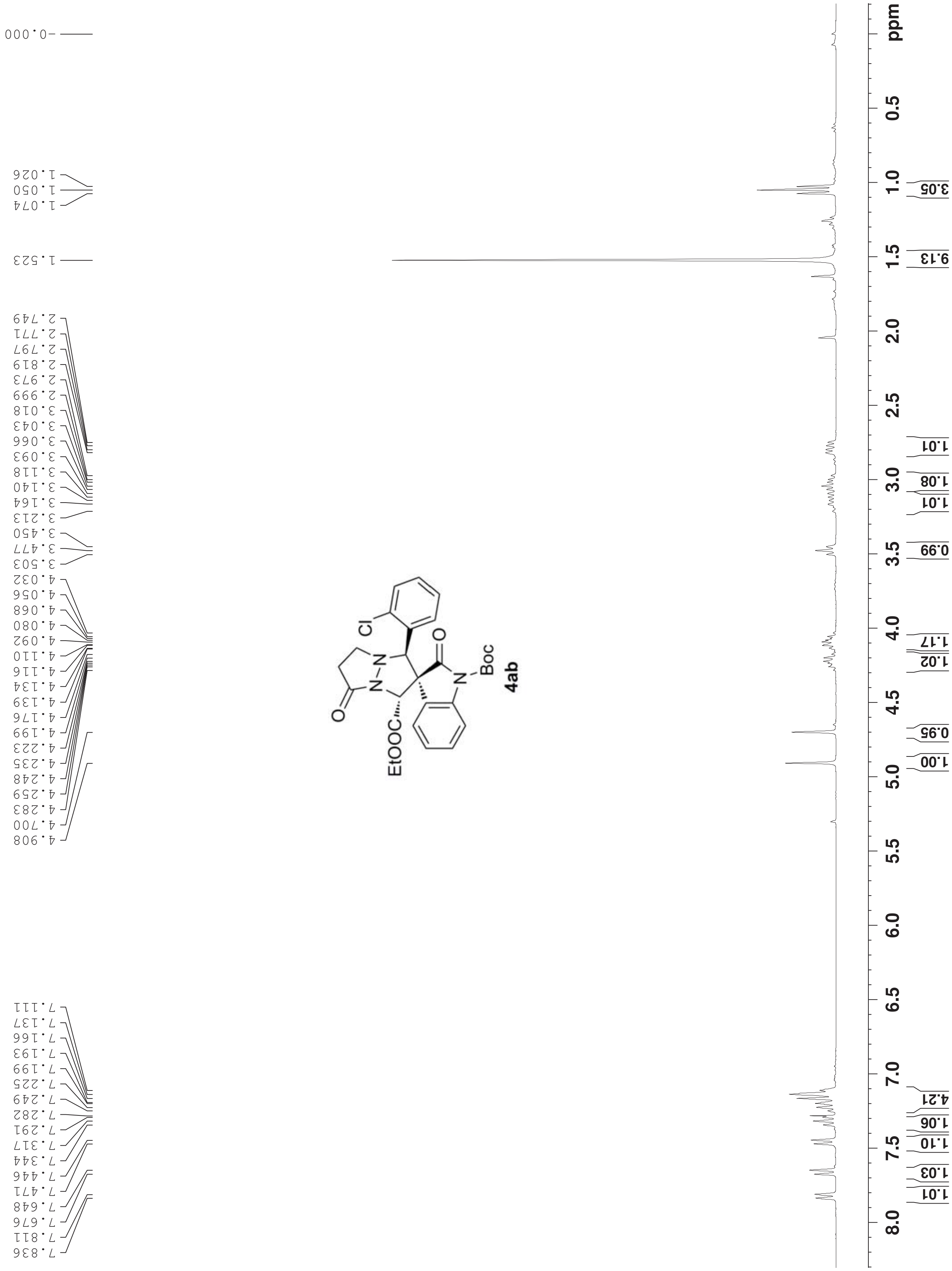
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Boc
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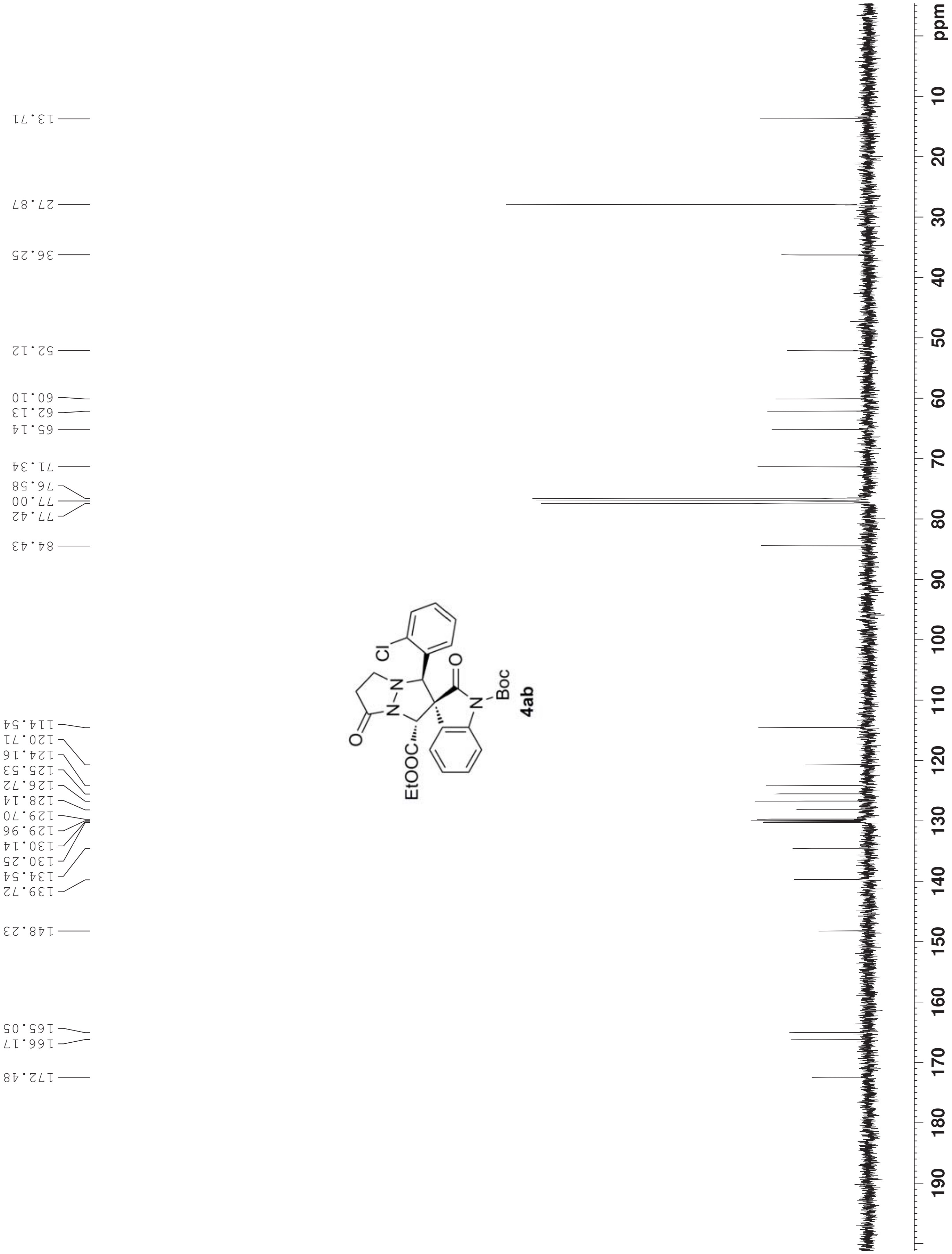
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N
Boc
EtOOC
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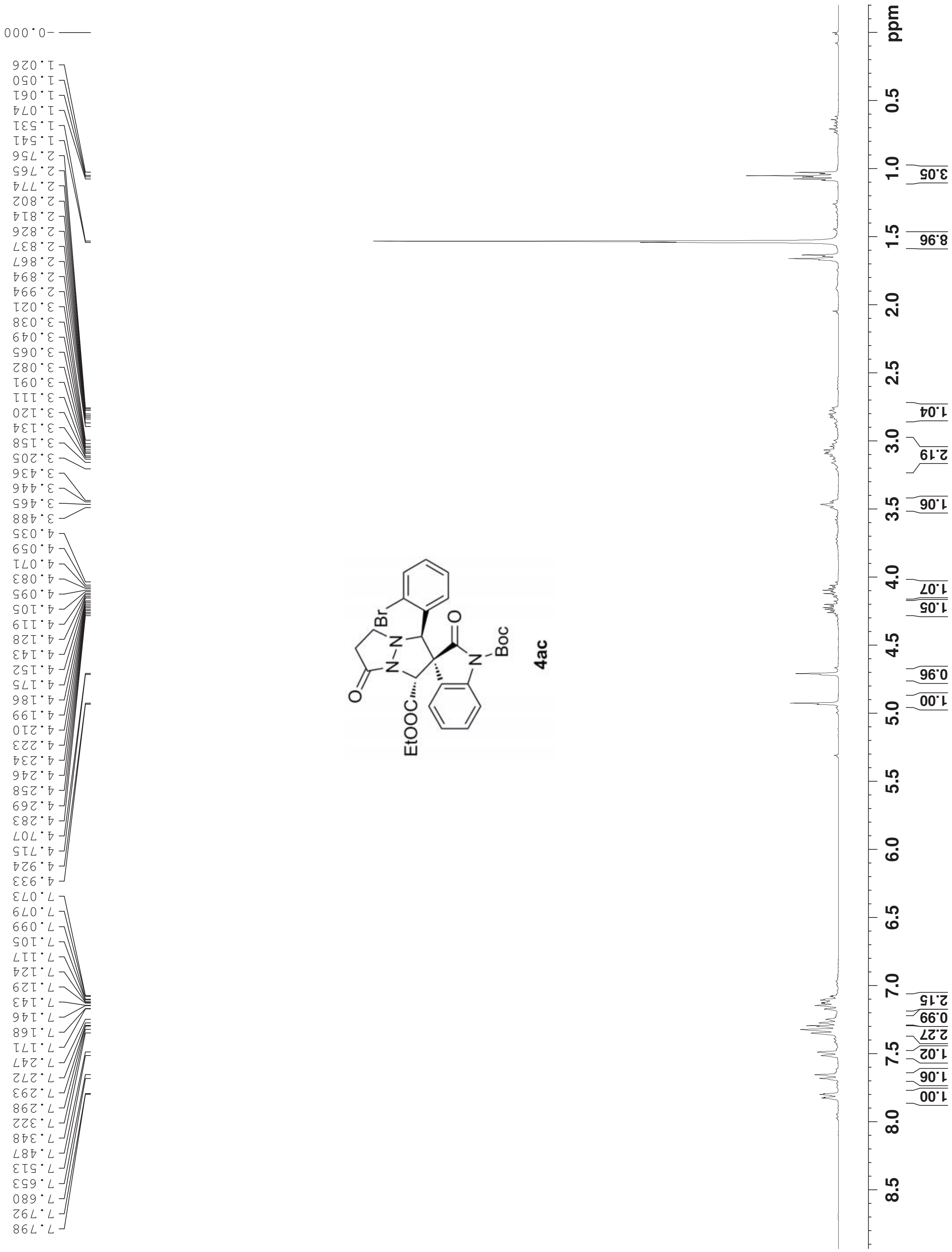
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N
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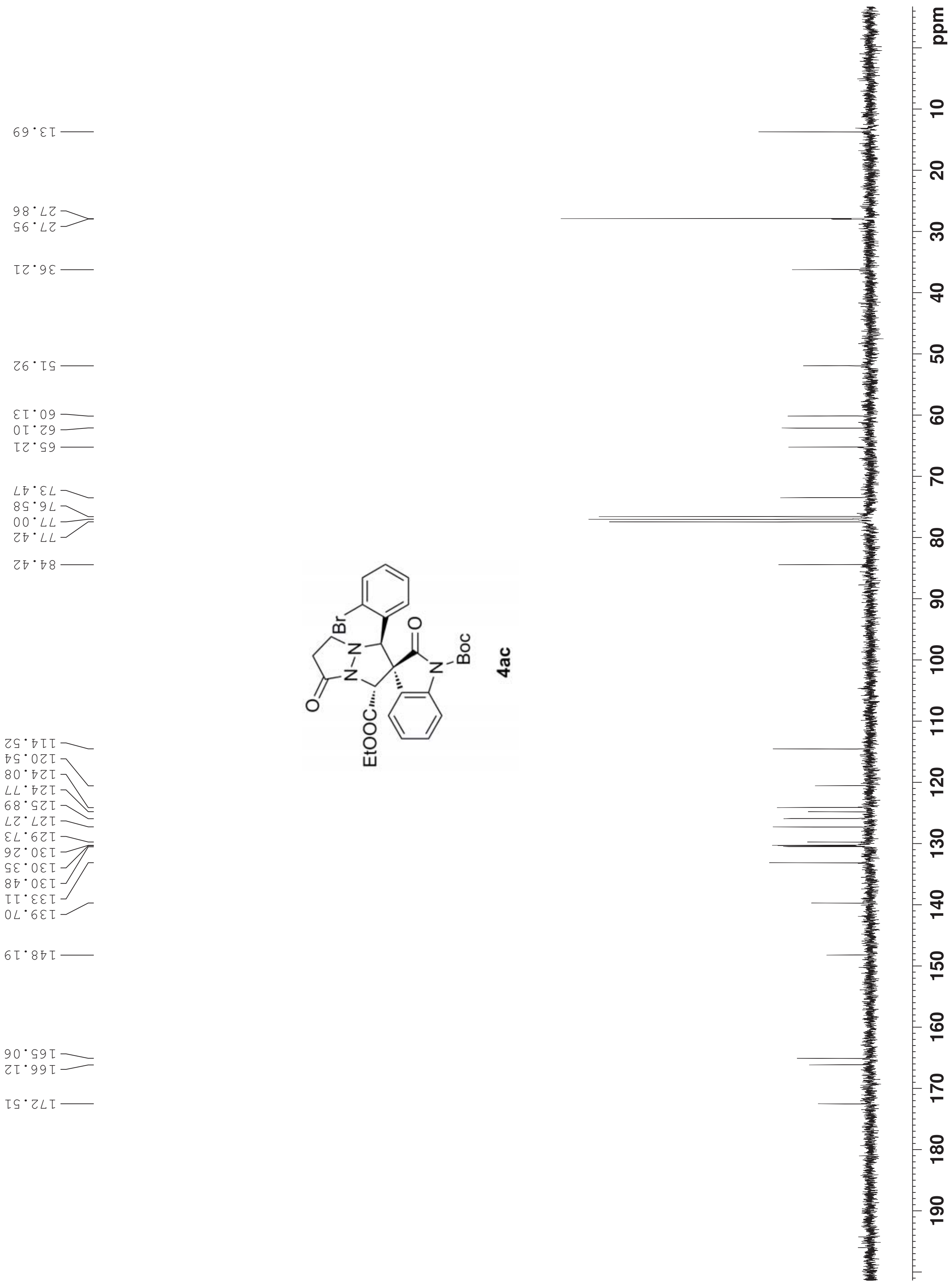
Boc
EtOOC
O
4ac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148.19
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Br
N
N
O
O
N
Boc
EtOOC
4ac
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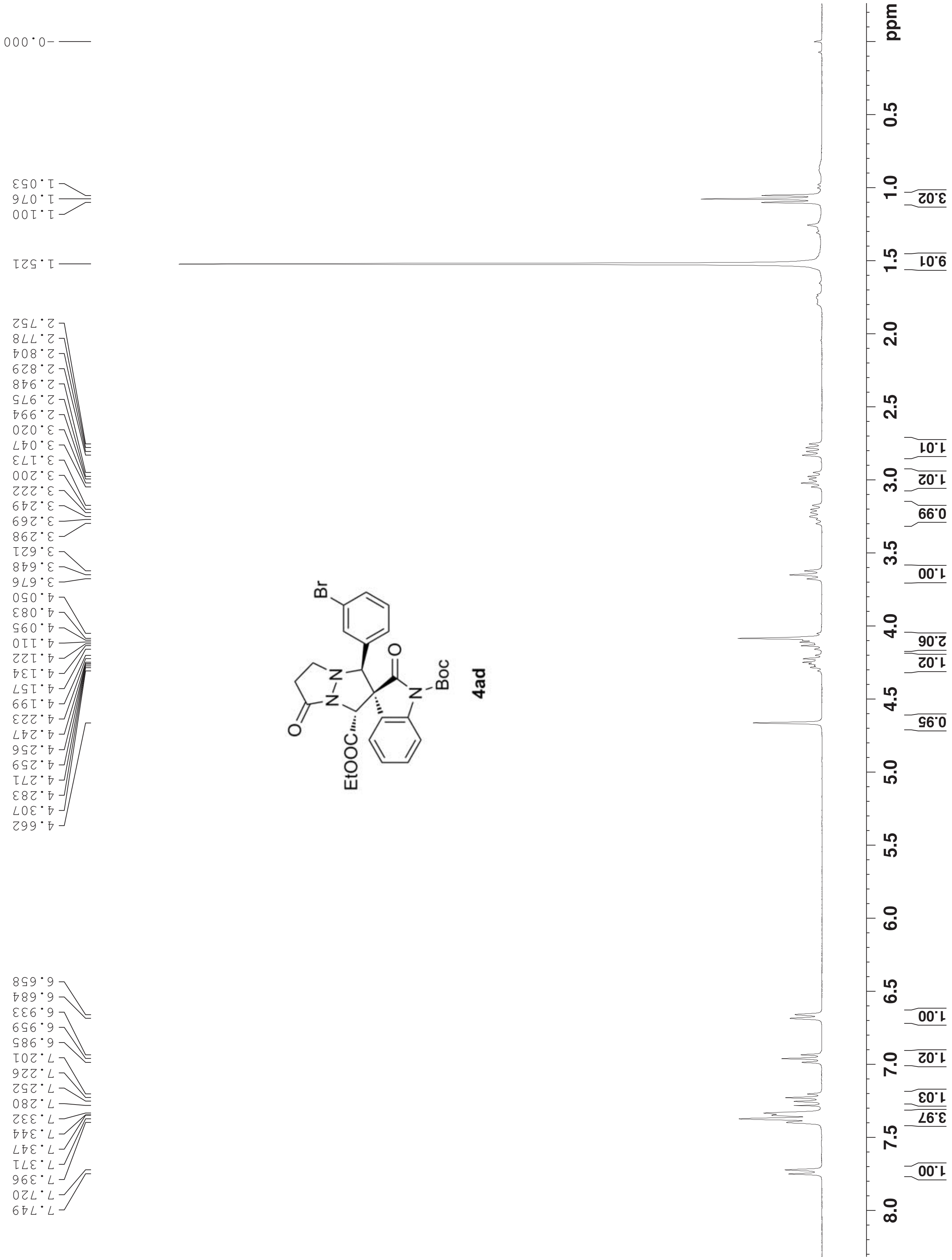
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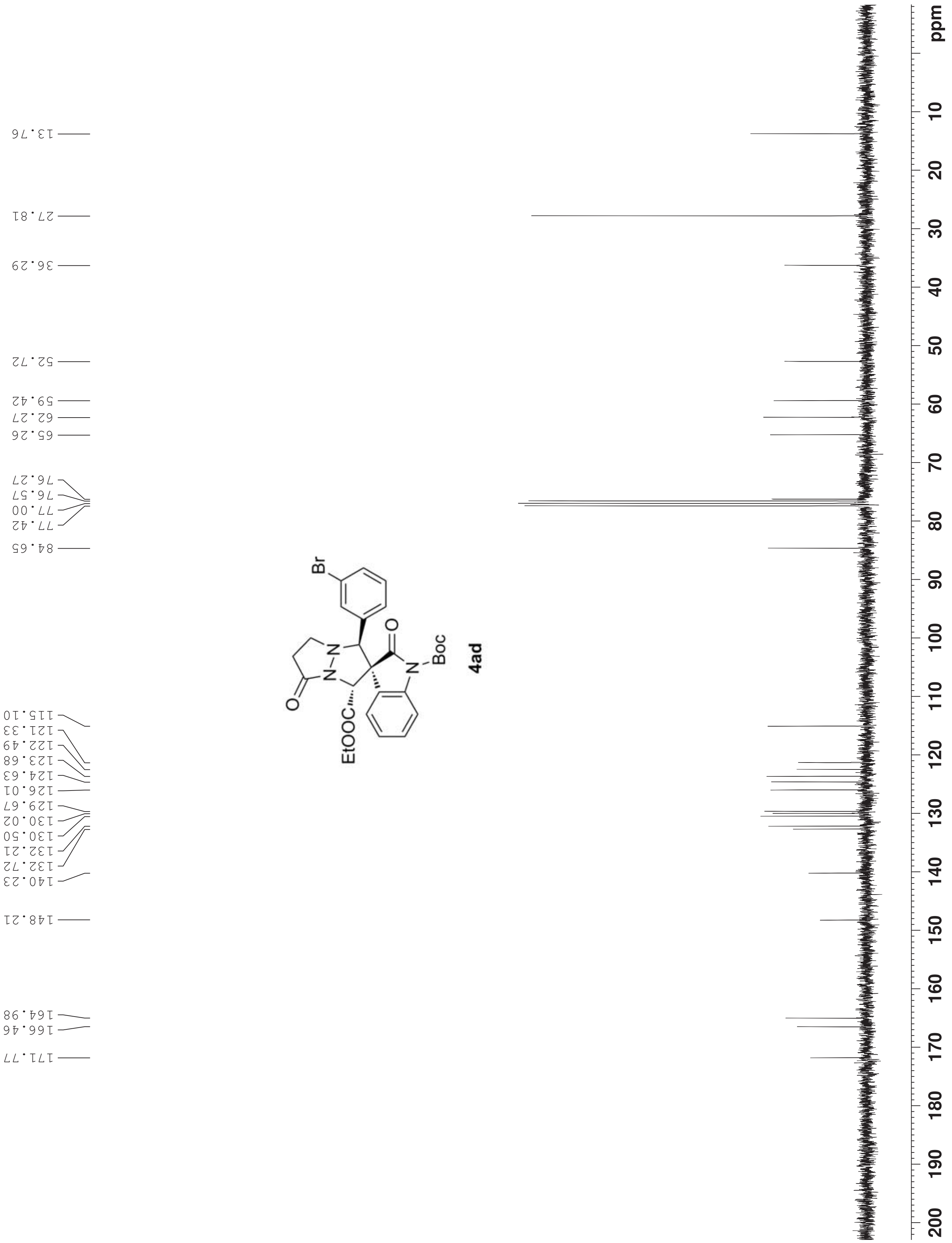
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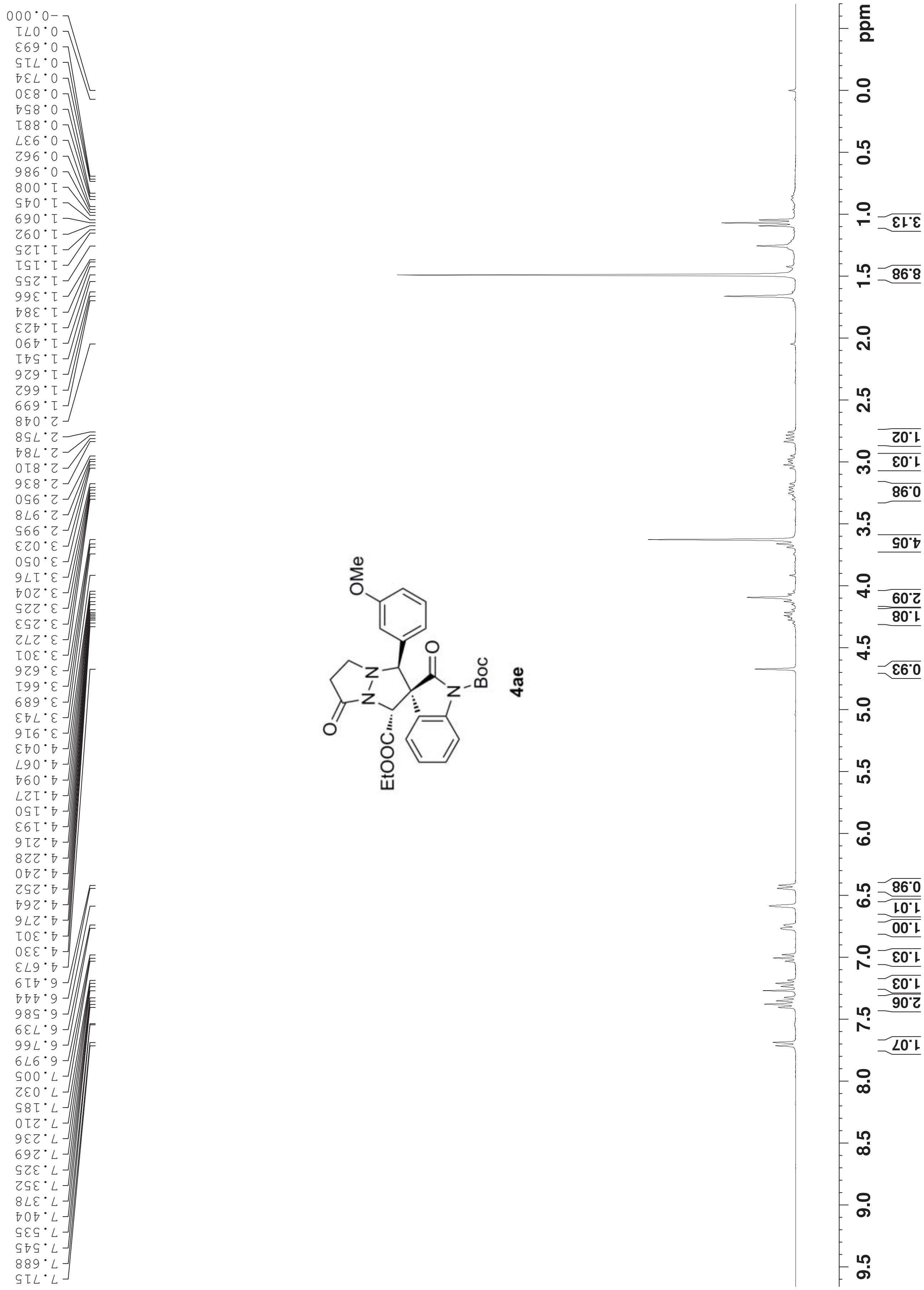
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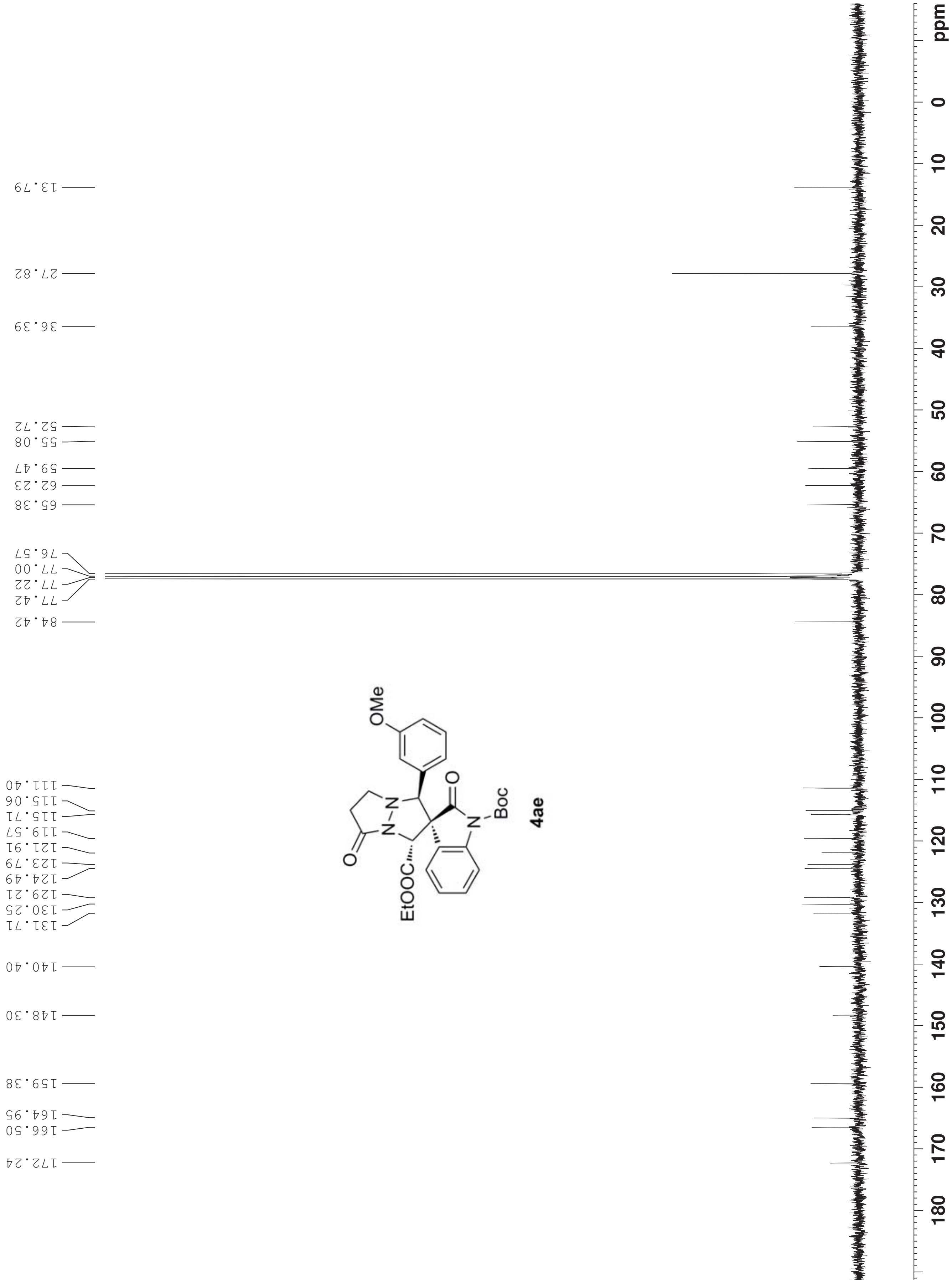
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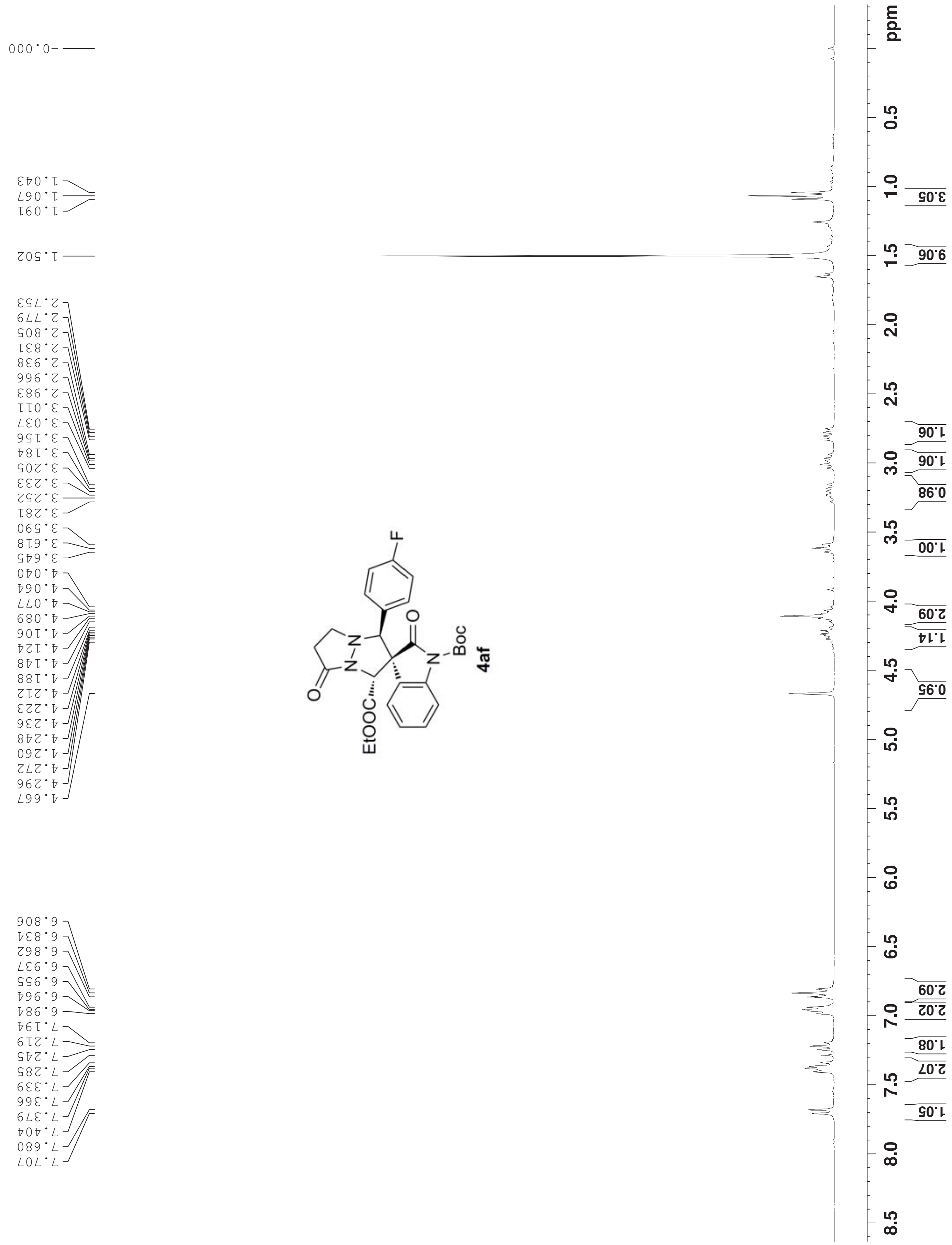
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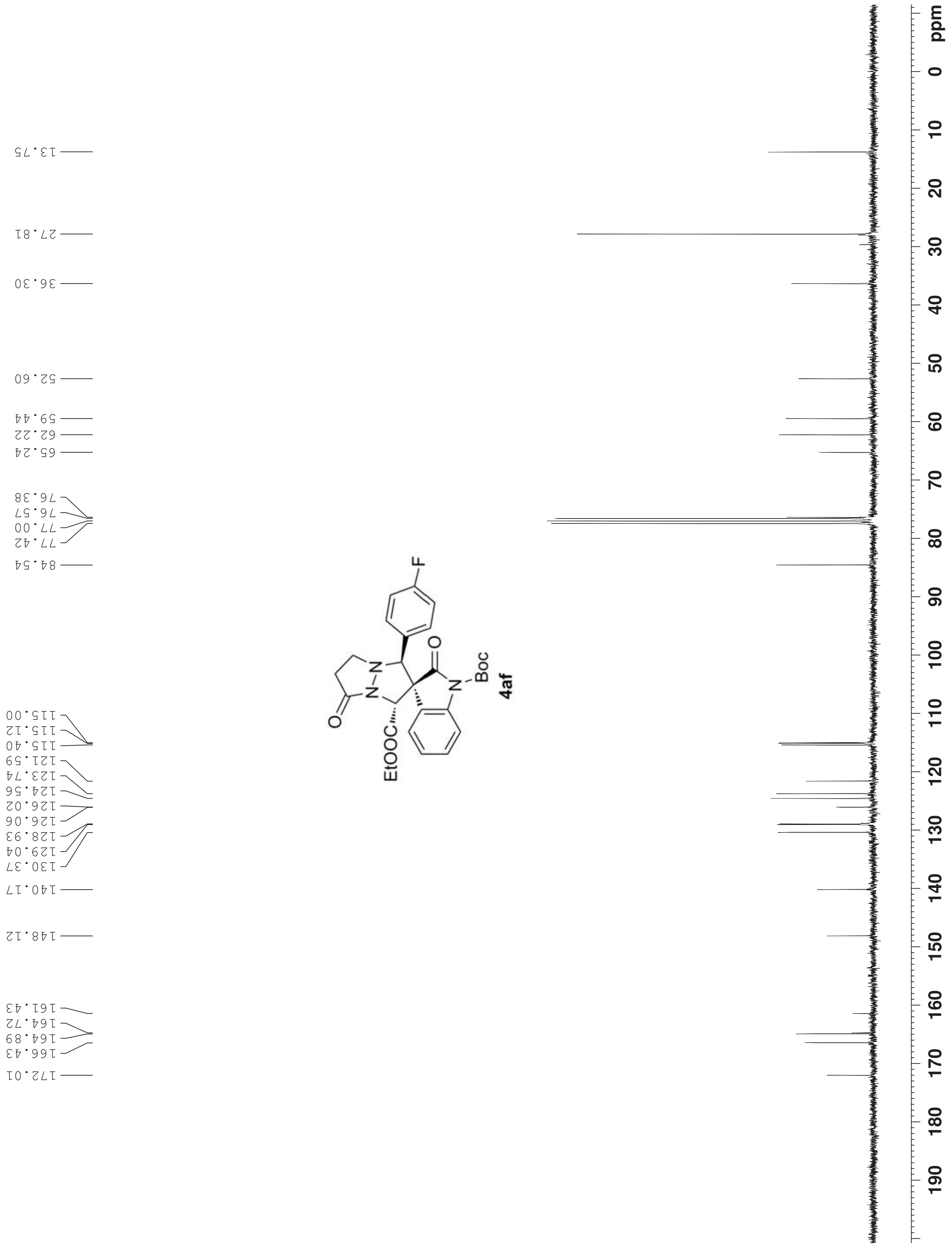
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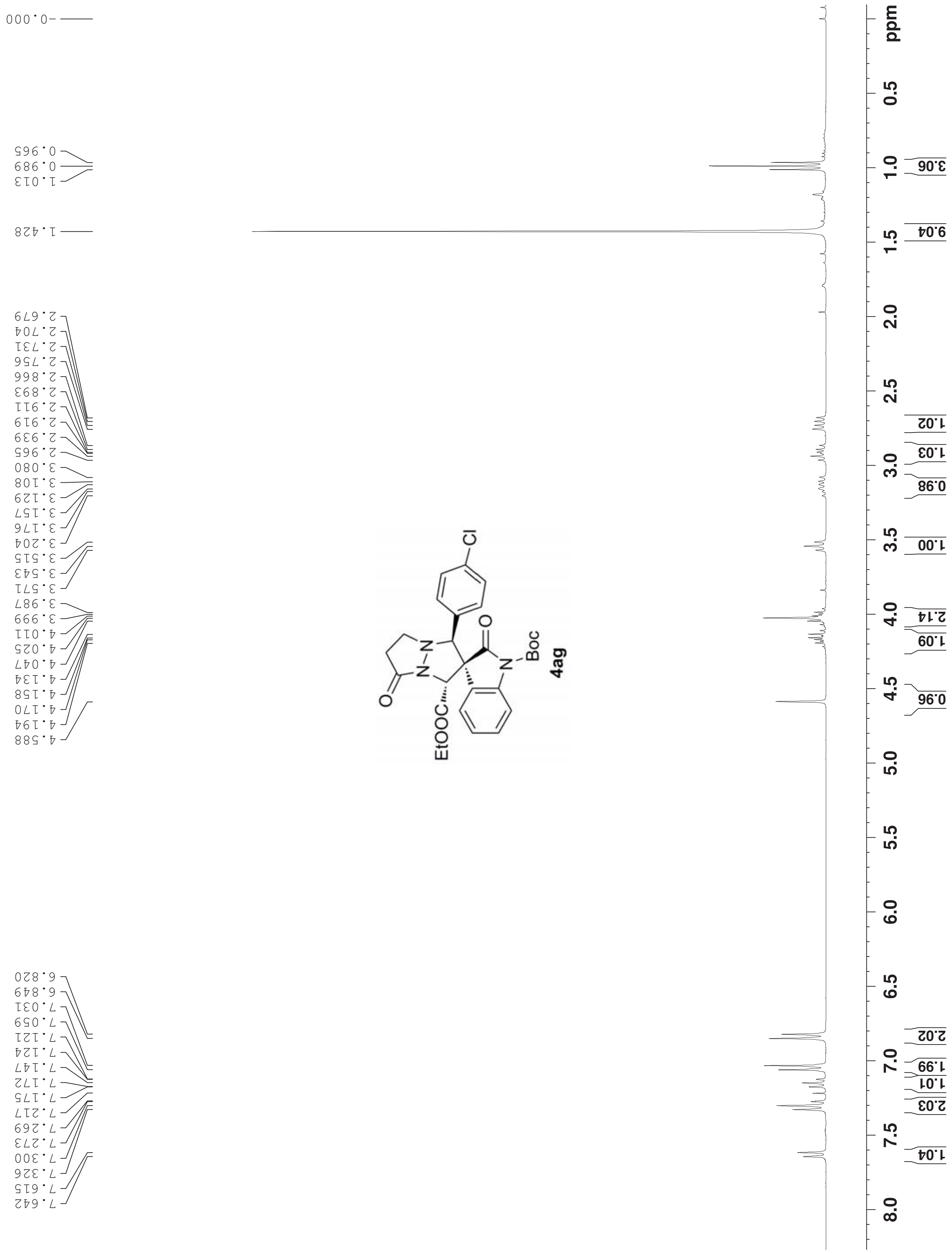
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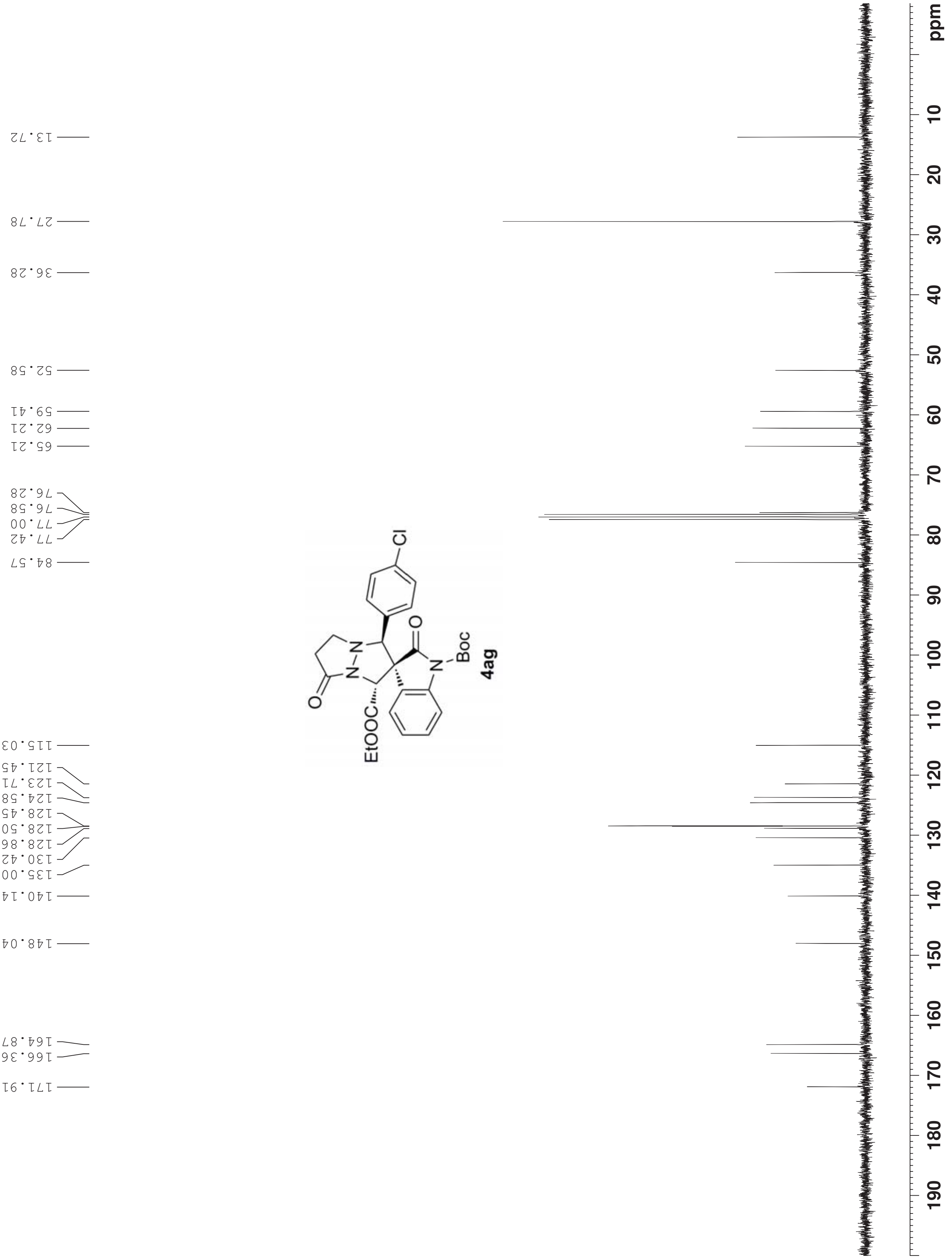
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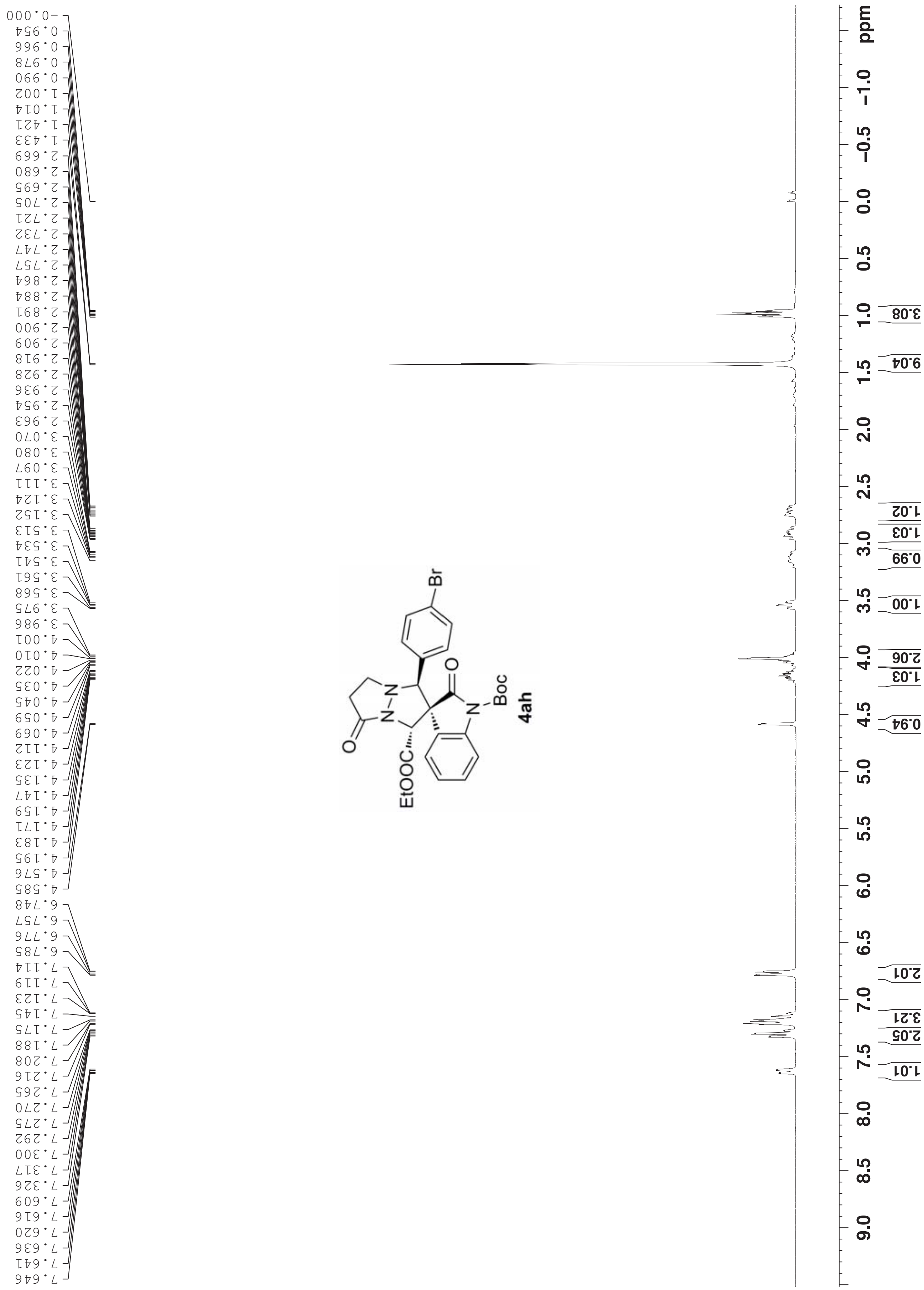
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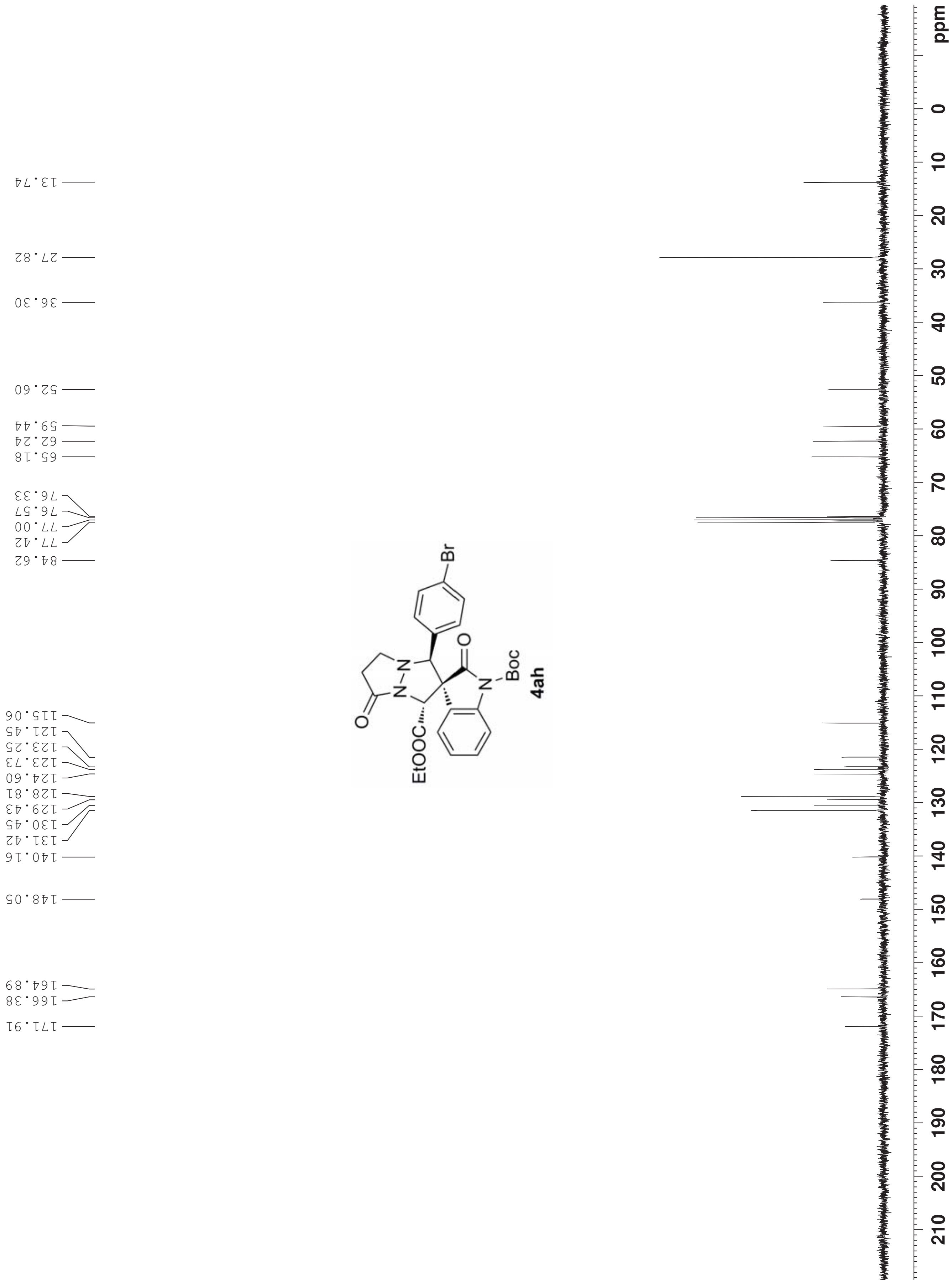
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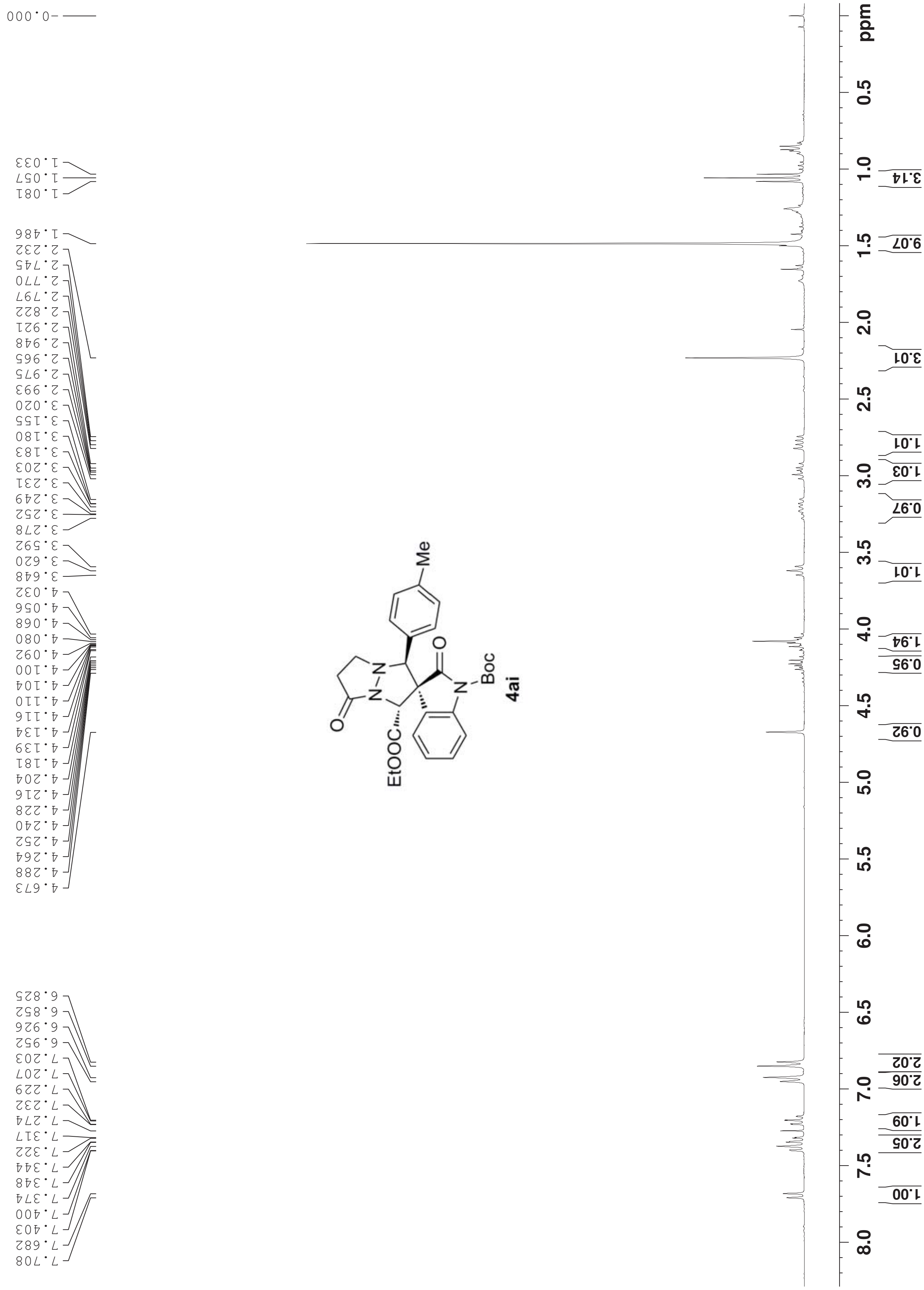
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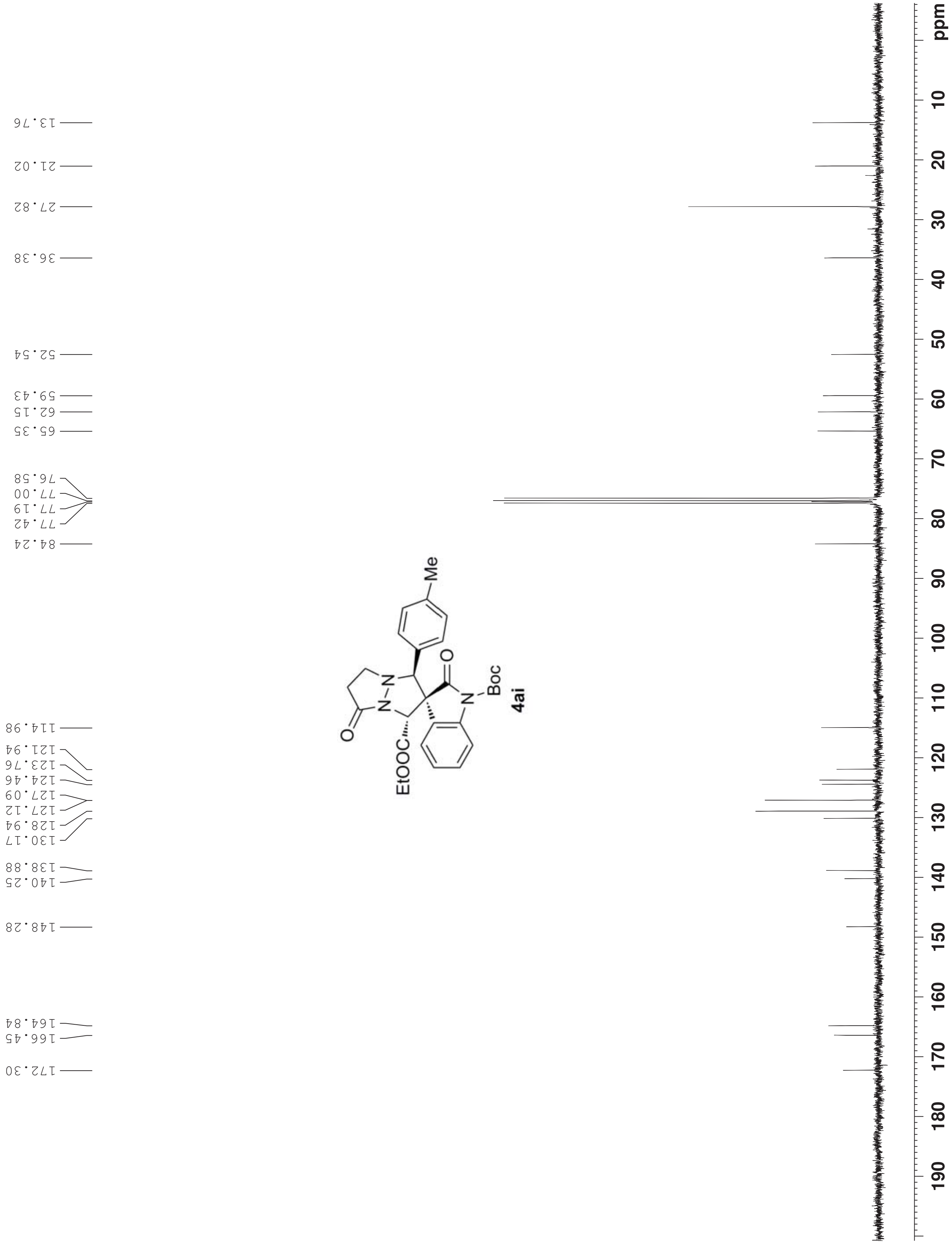
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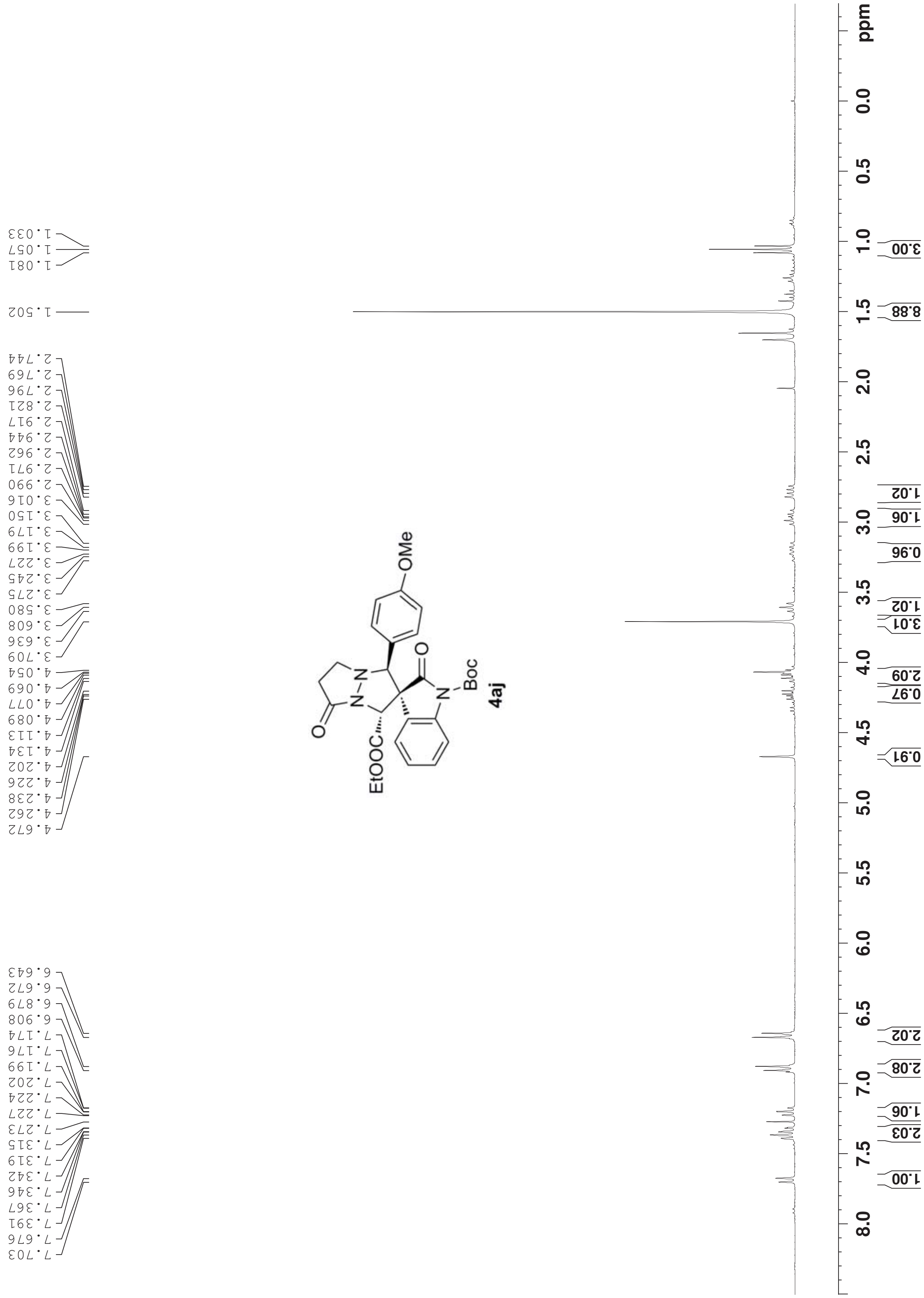
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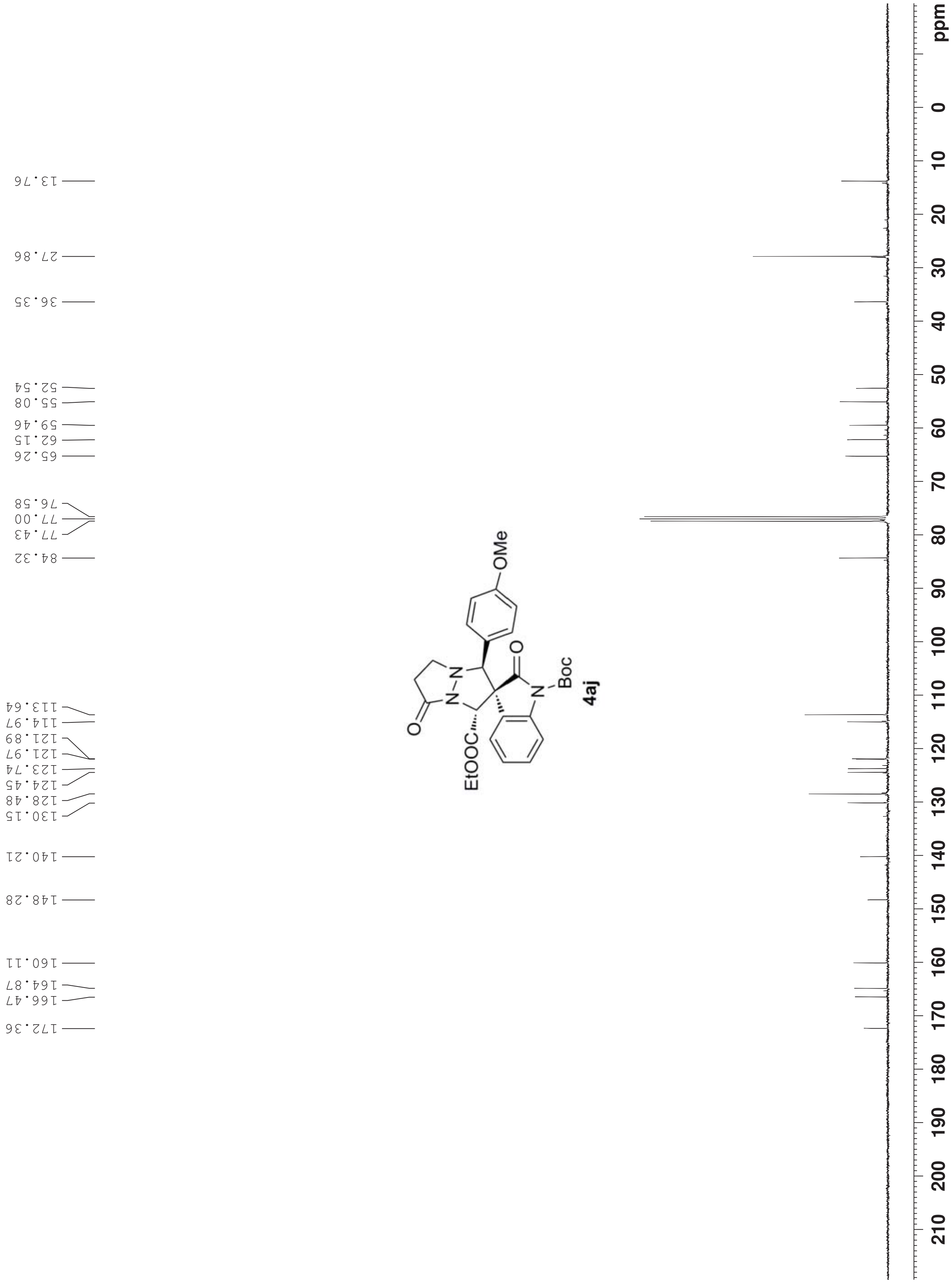
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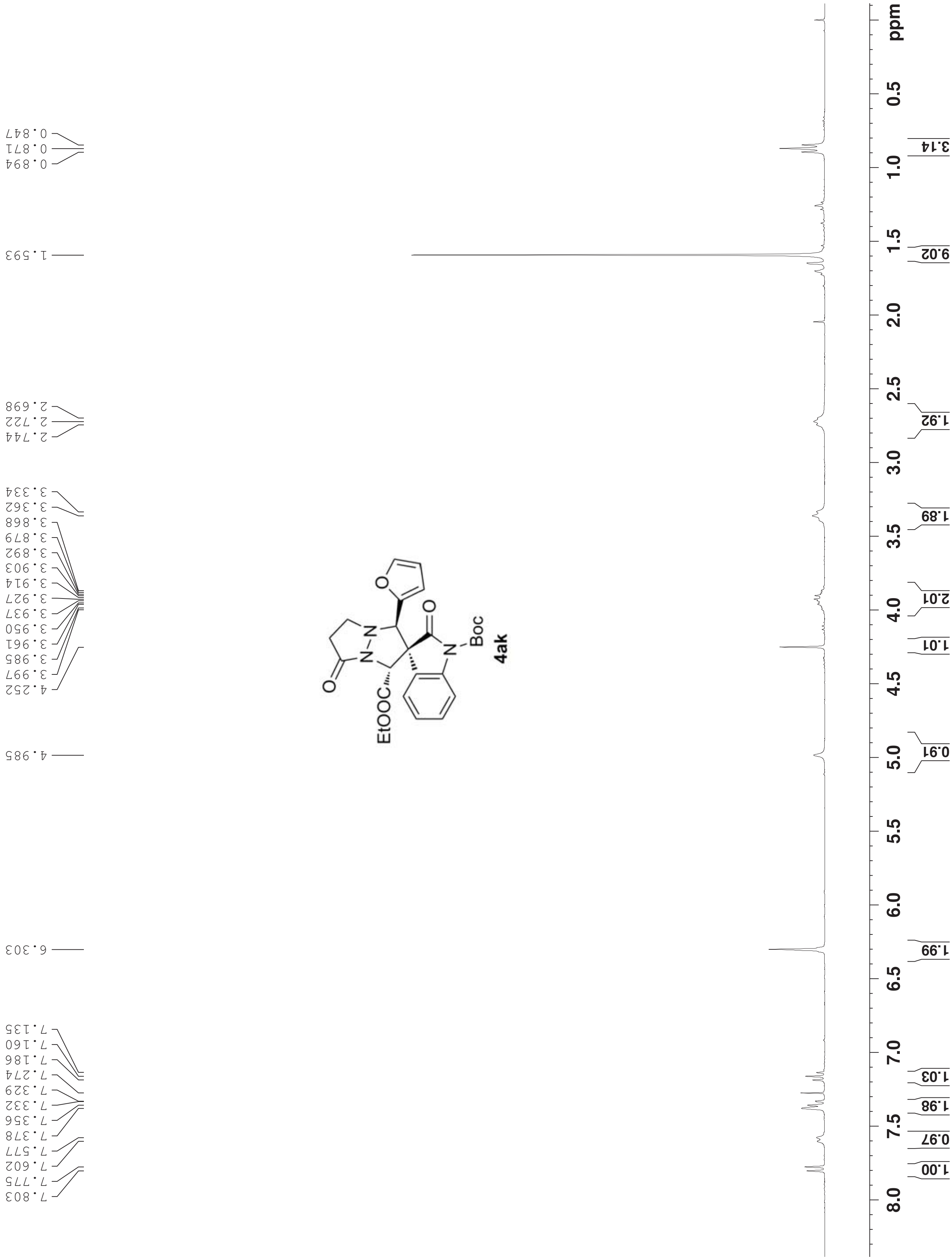
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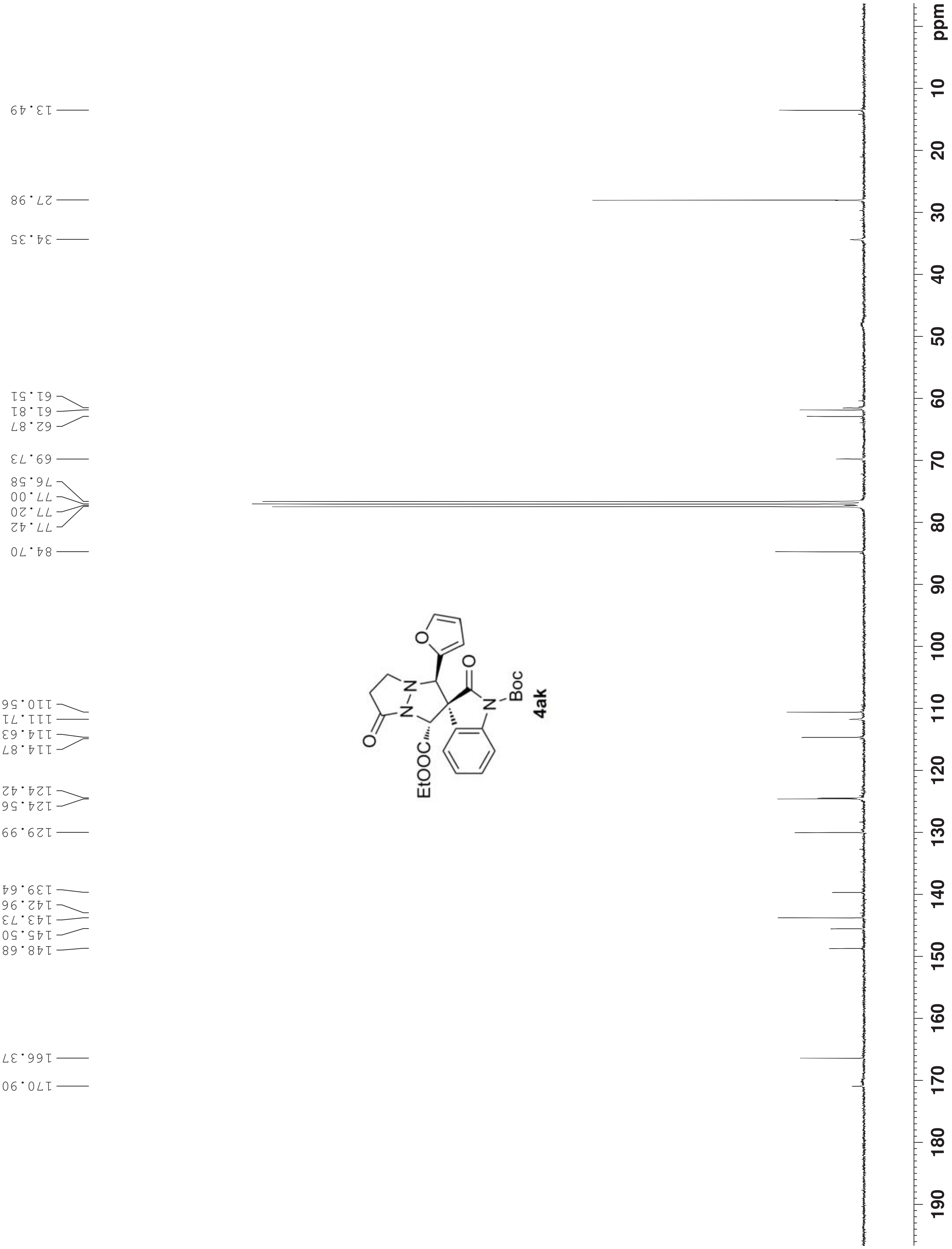
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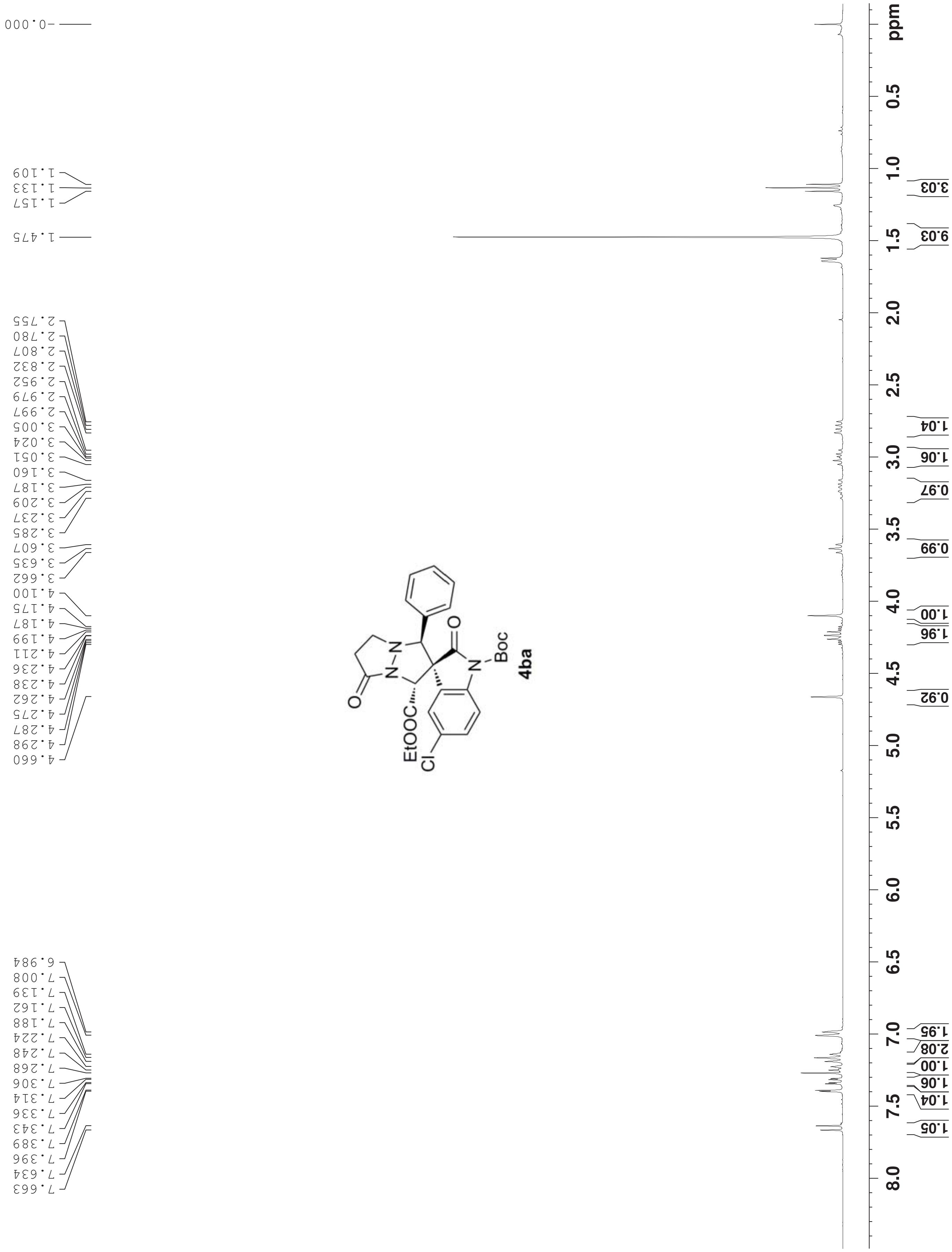
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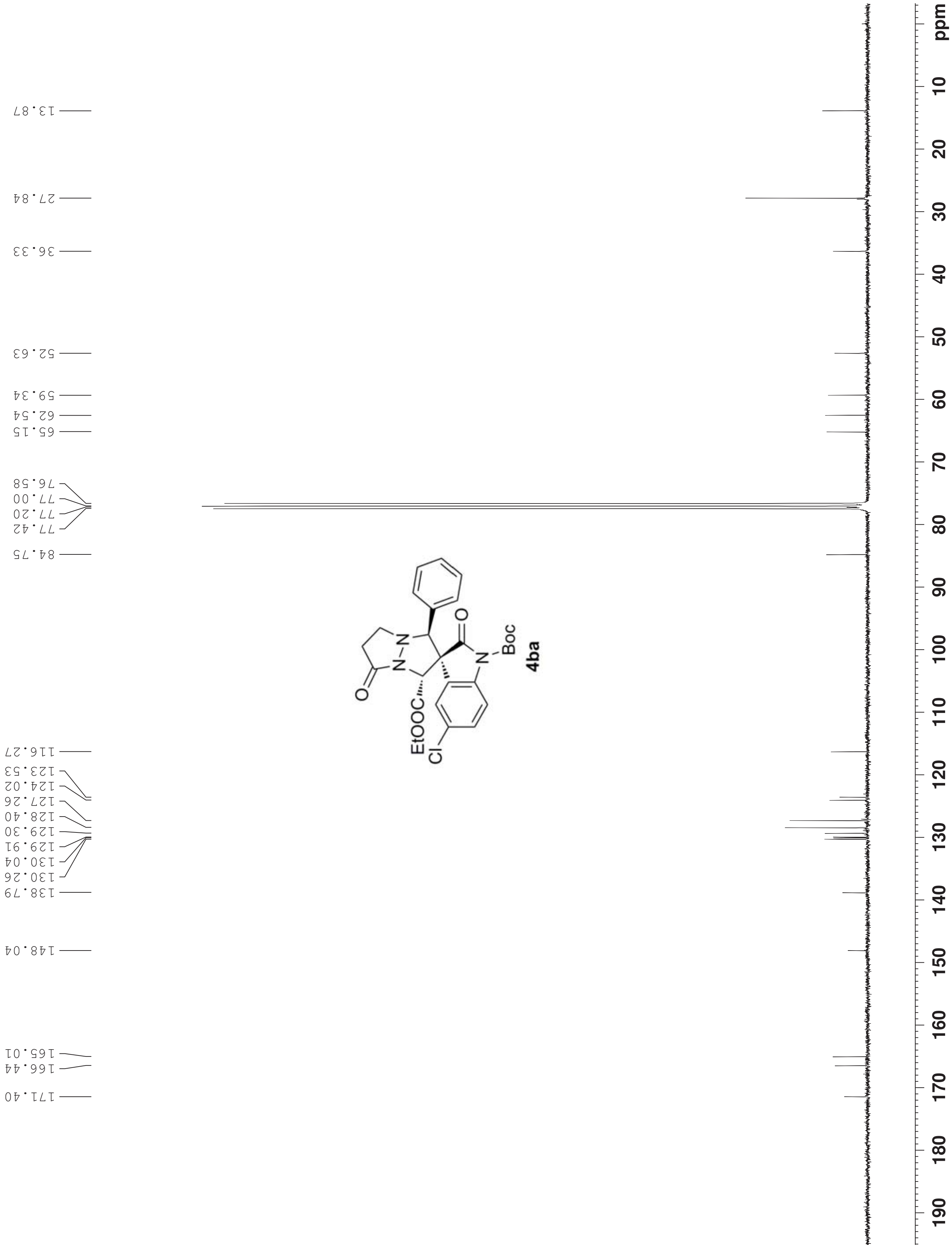
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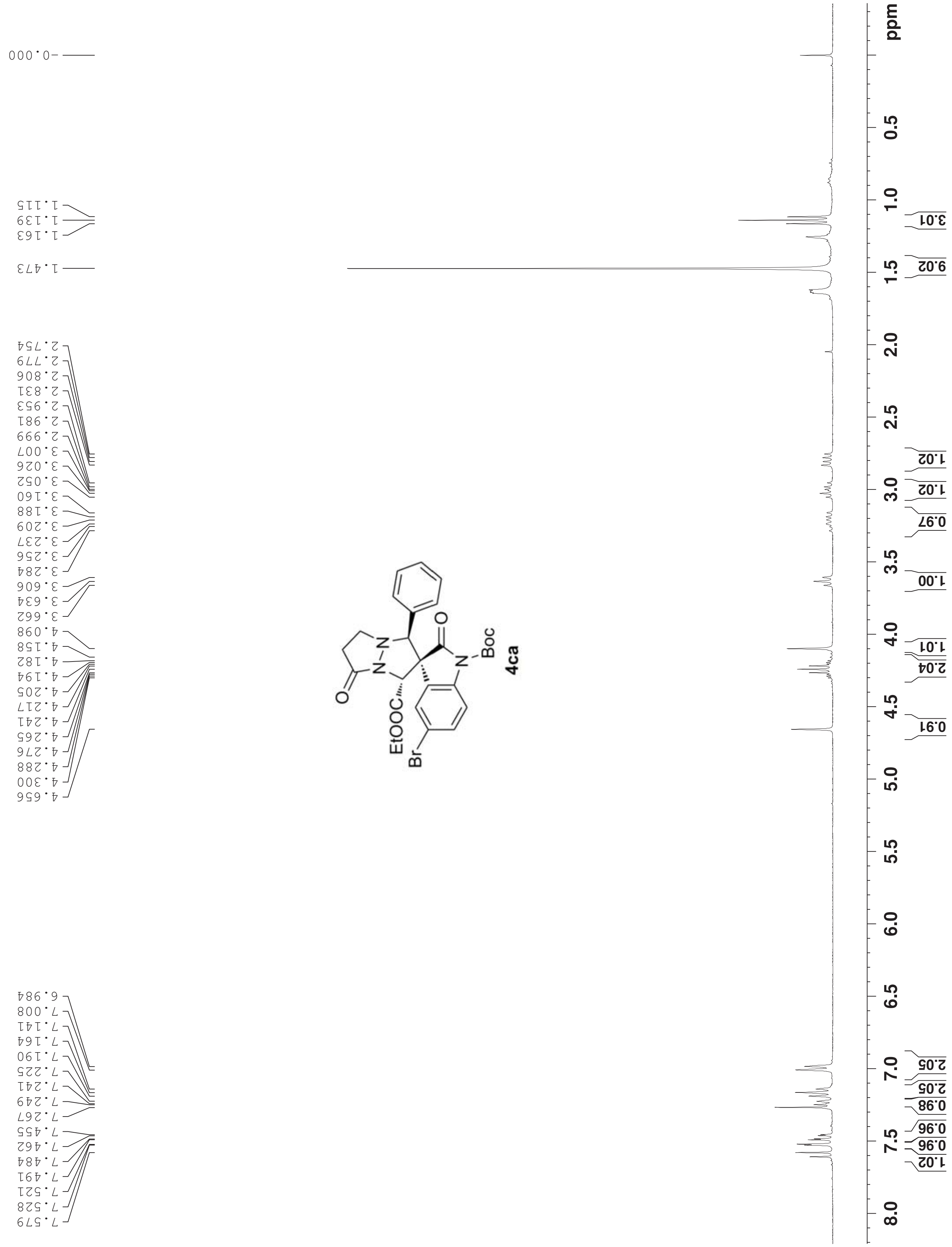
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9.02
1.02
1.02
0.97
1.00
1.01
2.04
0.91
2.05
2.05
0.98
0.96
0.96
1.02
ppm
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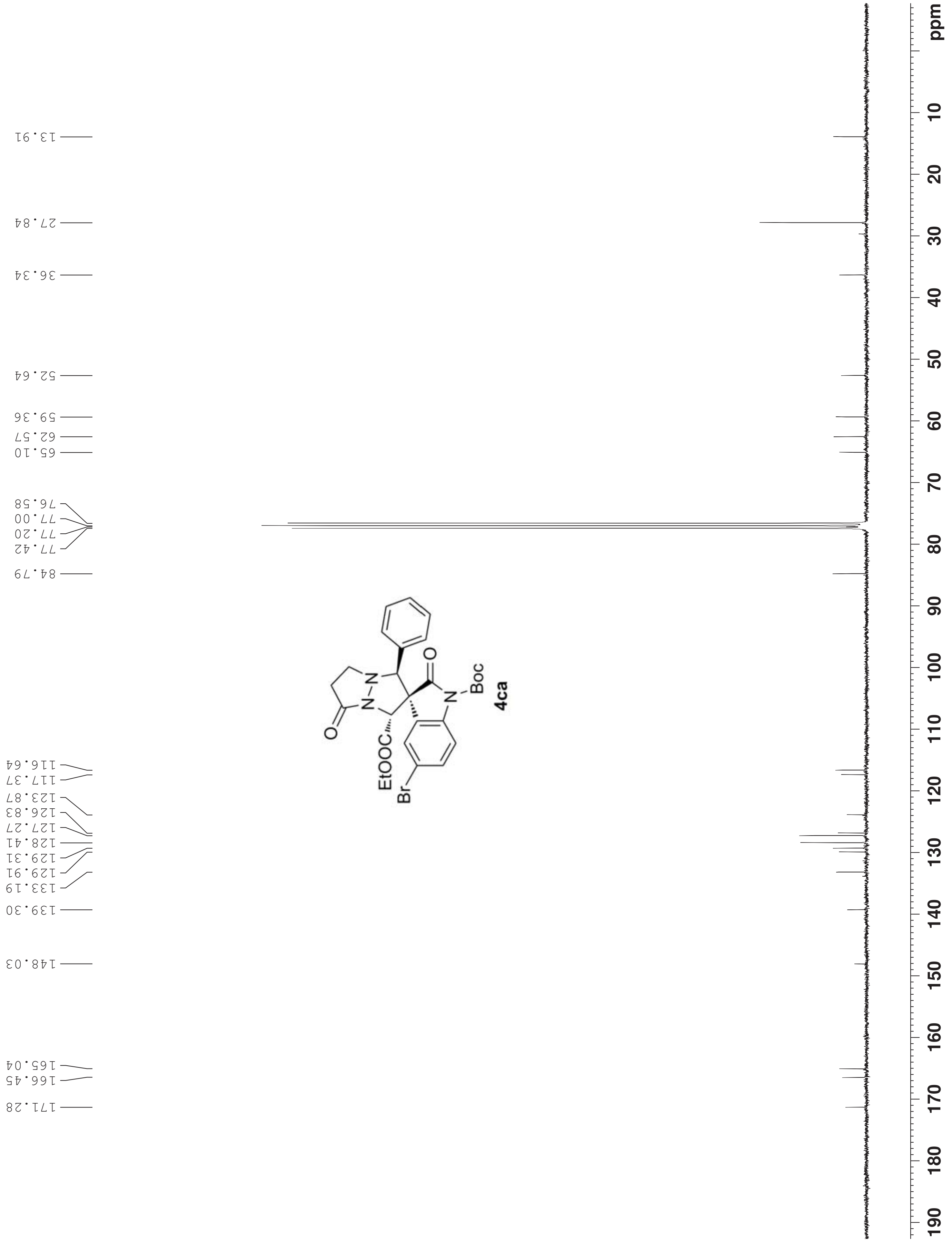
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117.37
123.87
126.83
127.27
128.41
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139.30
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166.45
171.28
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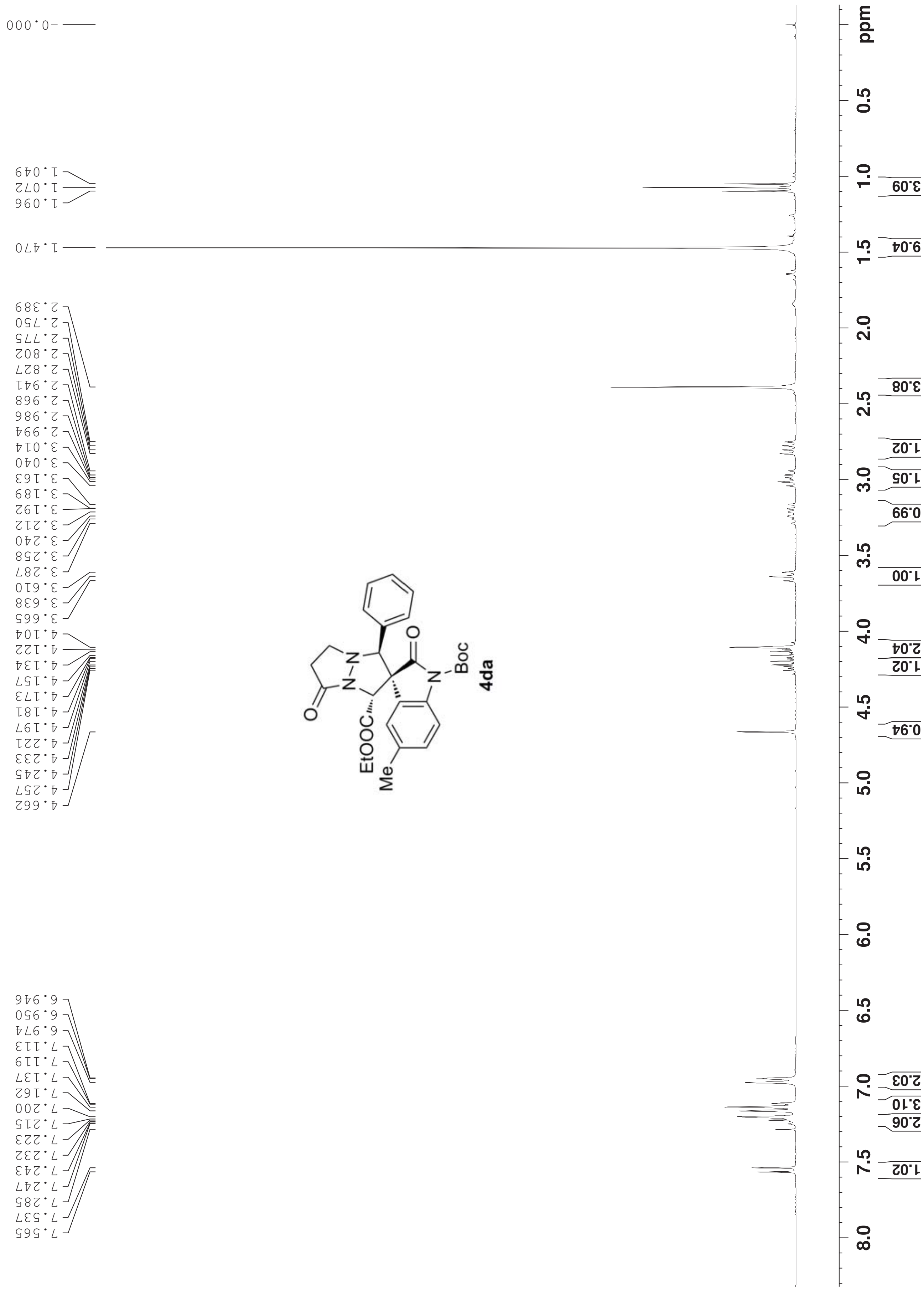
Br
Boc
4ca
ppm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2.994
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3.040
3.163
3.189
3.192
3.212
3.240
3.258
3.287
3.610
3.638
3.665
4.104
4.122
4.134
4.157
4.173
4.181
4.197
4.221
4.233
4.245
4.257
4.662
6.946
6.950
6.974
7.113
7.119
7.137
7.162
7.200
7.215
7.223
7.232
7.243
7.247
7.285
7.537
7.565
EtOOC
Me
Boc
4da
ppm
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9.04
3.08
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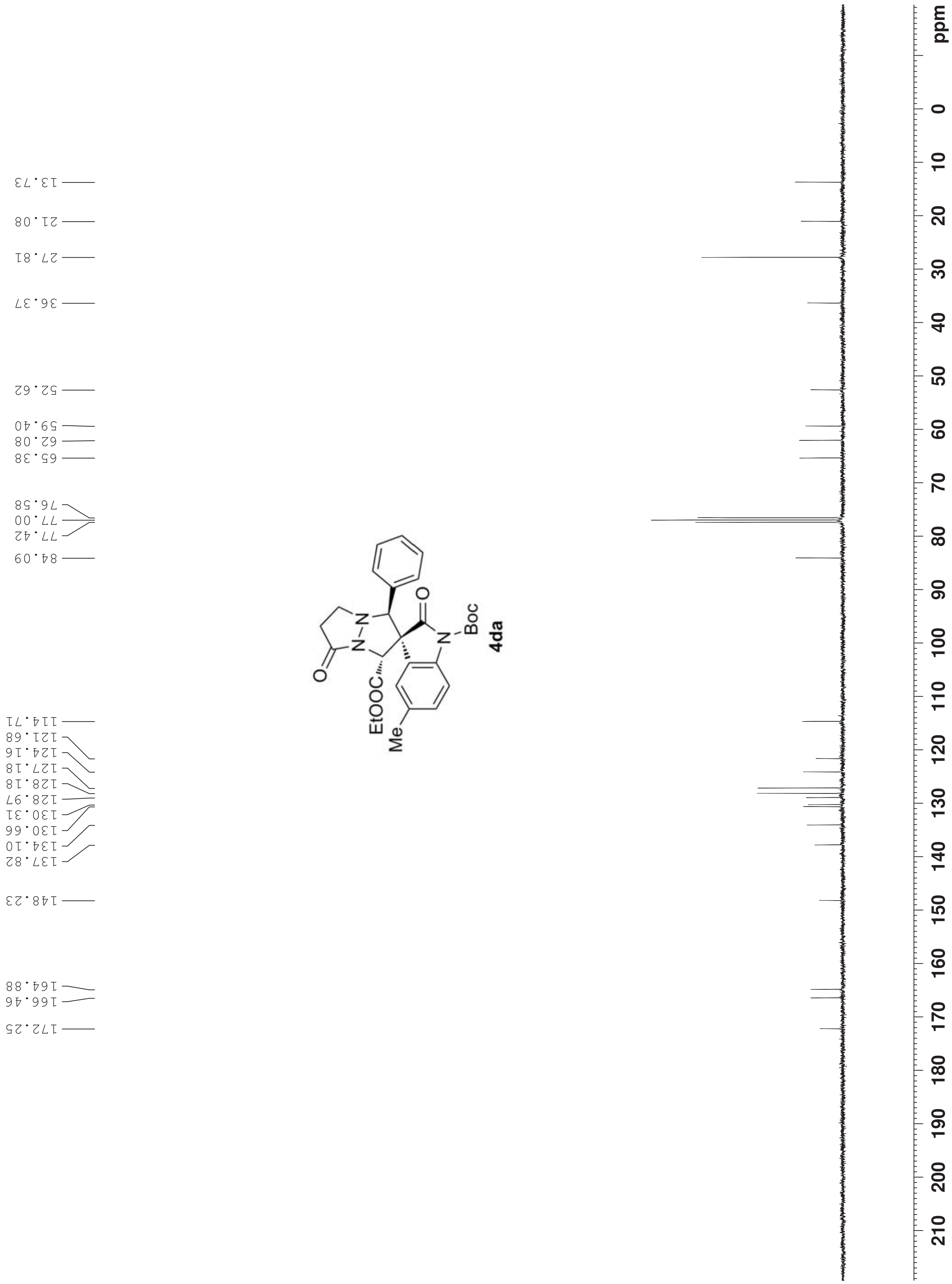
2.06
1.02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121.68
124.16
127.18
128.18
128.97
130.31
130.66
134.10
137.82
148.23
164.88
166.46
172.25
EtOOC
Me
Boc
ppm
0
10
20
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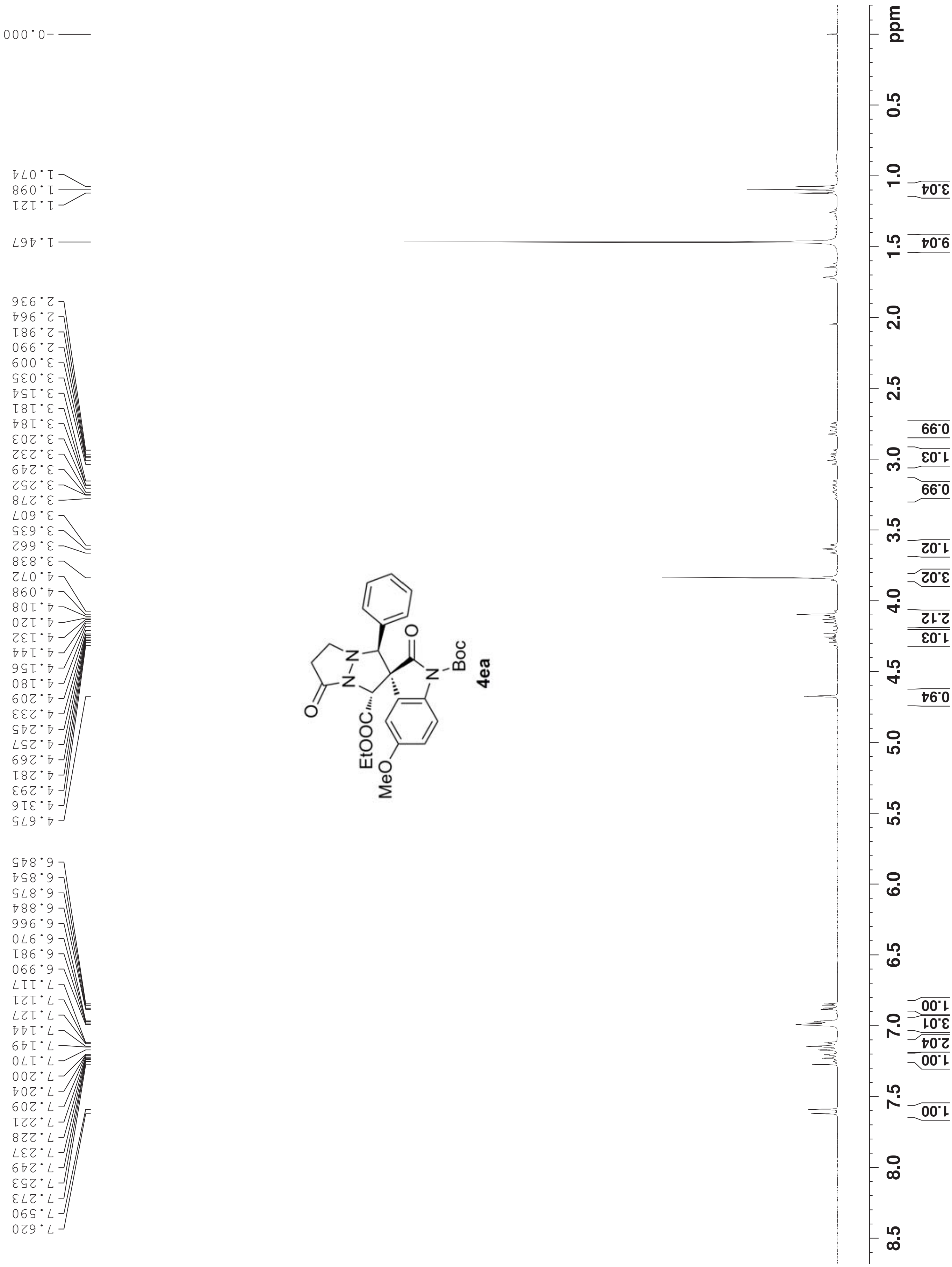
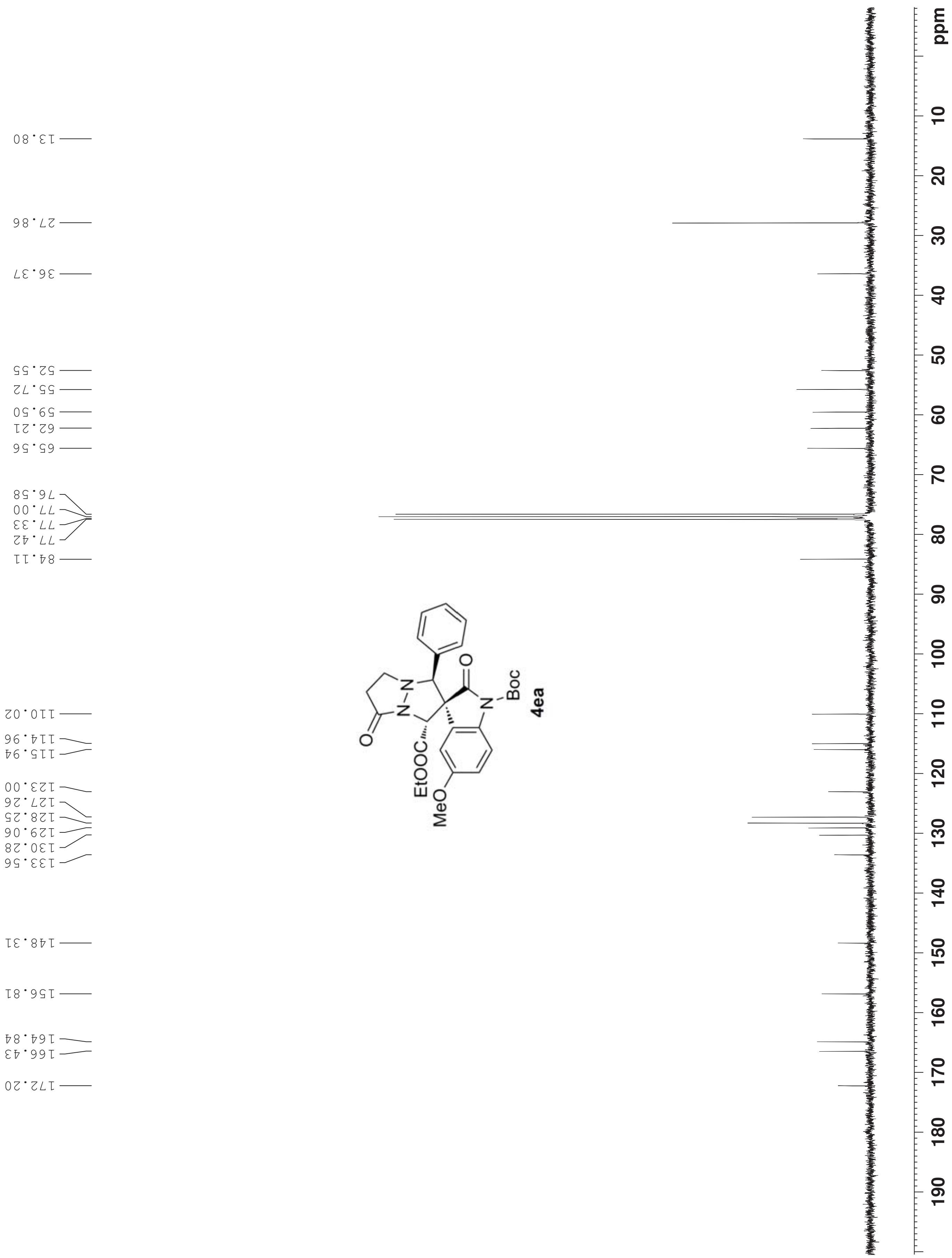
210

4da

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114.96
115.94
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128.25
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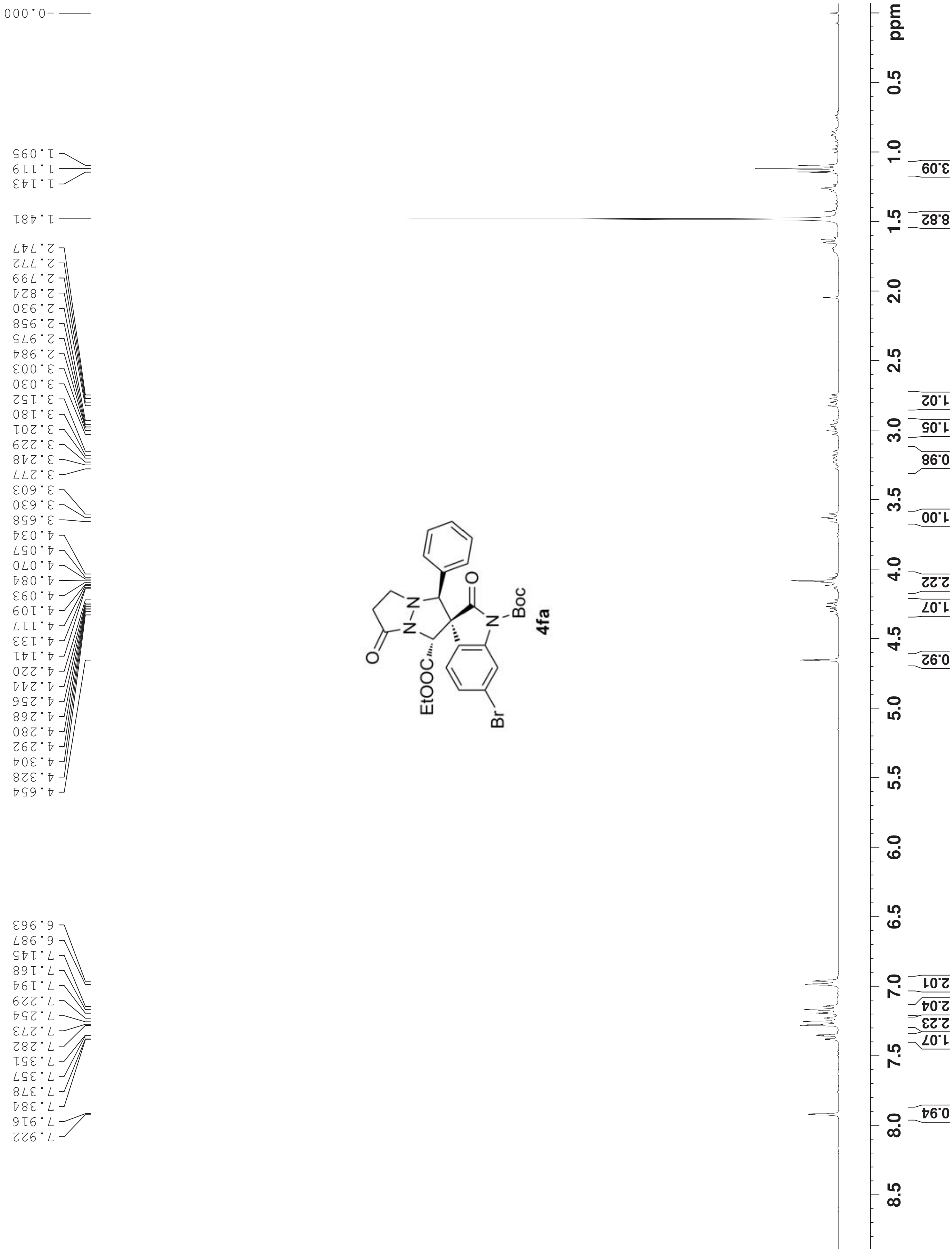
172.20
ppm
4ea
Boc
EtOOC
MeO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2.975
2.984
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3.030
3.152
3.180
3.201
3.229
3.248
3.277
3.603
3.630
3.658
4.034
4.057
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4.084
4.093
4.109
4.117
4.133
4.141
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4.244
4.256
4.268
4.280
4.292
4.304
4.328
4.654
6.963
6.987
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7.194
7.229
7.254
7.273
7.282
7.351
7.357
7.378
7.384
7.916
7.922
ppm
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2.5
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4.0
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5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
3.09
8.82
1.02
1.05
0.98
1.00
2.22
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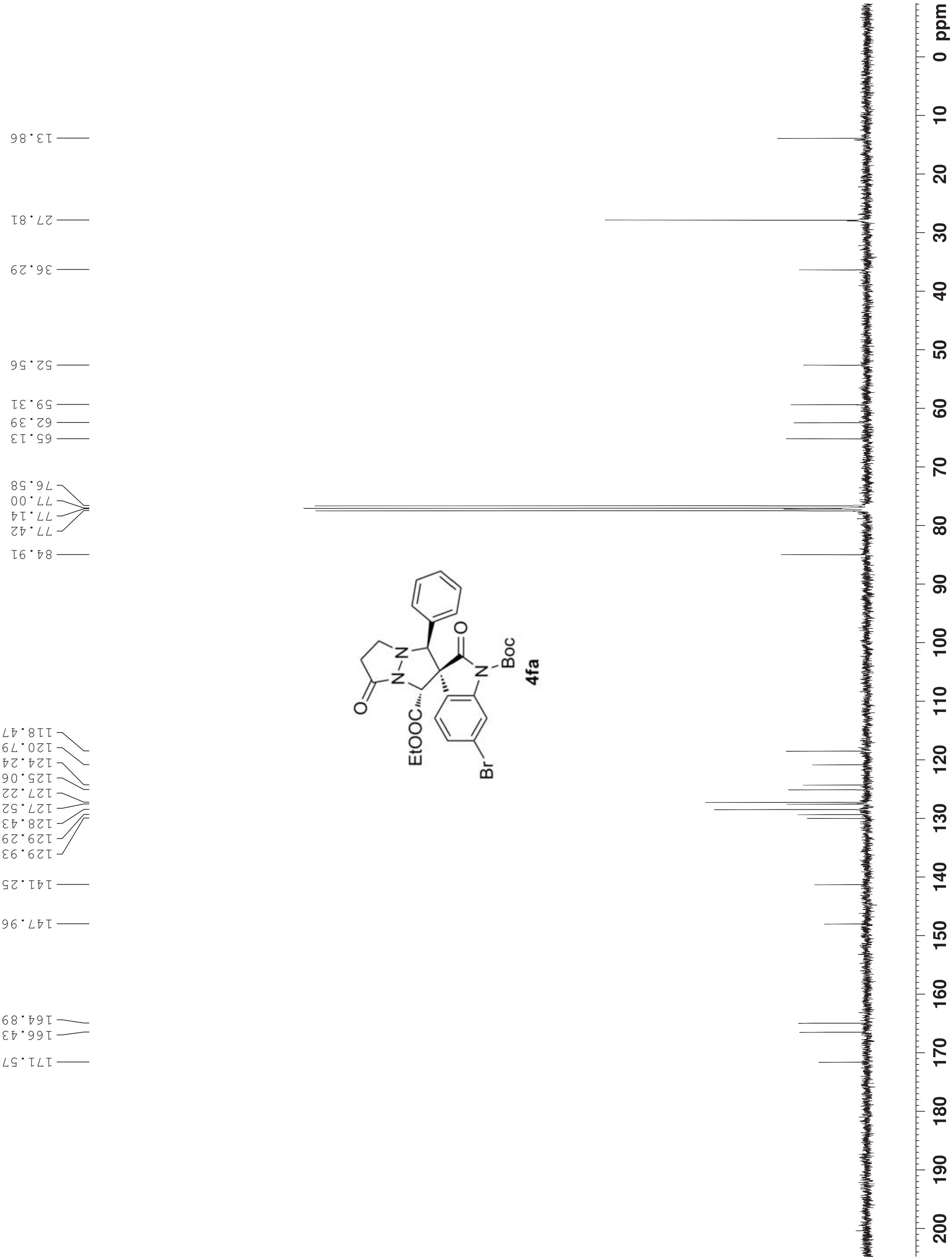
Boc
N
N
EtOOC
Br

4fa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120.79
124.24
125.06
127.22
127.52
128.43
129.29
129.93
141.25
147.96
164.89
166.43
171.57
O
N
N
EtOOC
O
N
Boc
Br
4fa
0 ppm
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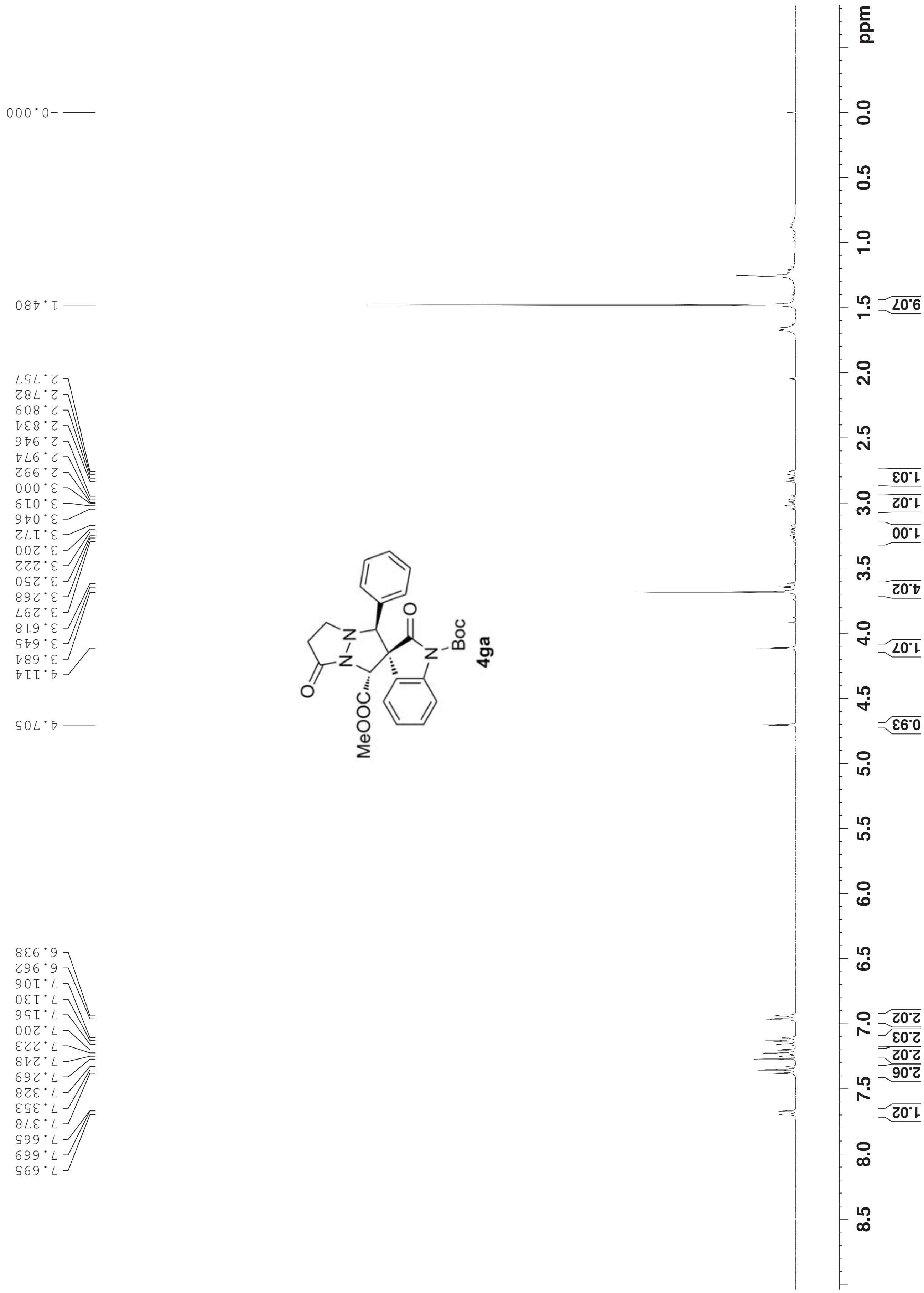
200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3.200
3.222
3.250
3.268
3.297
3.618
3.645
3.684
4.114
4.705
6.938
6.962
7.106
7.130
7.156
7.200
7.223
7.248
7.269
7.328
7.353
7.378
7.665
7.669
7.695
MeOOC
N
N
O
O
N
Boc
4ga
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
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6.0
6.5
7.0
7.5
8.0
8.5
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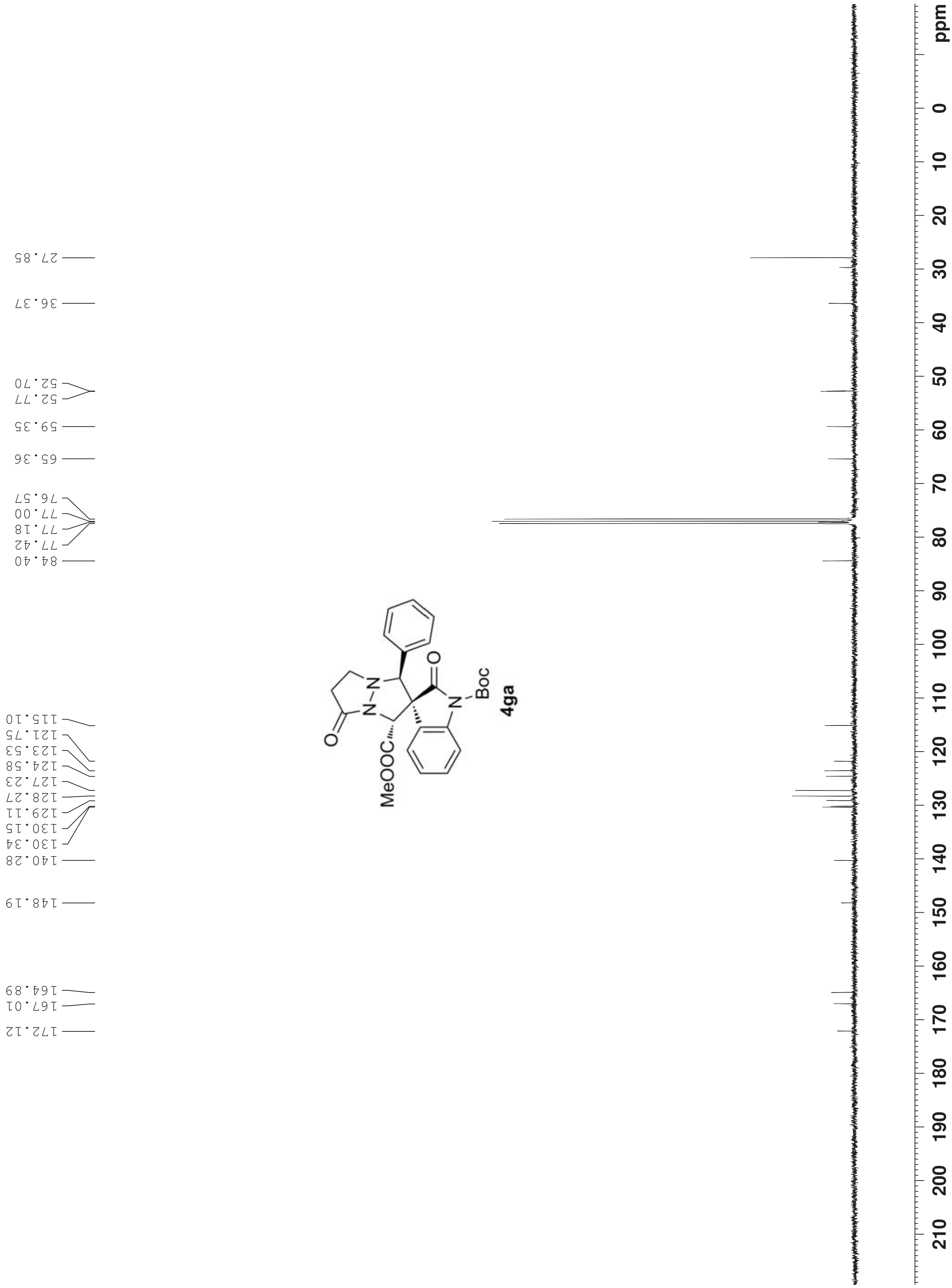
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123.53
124.58
127.23
128.27
129.11
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164.89
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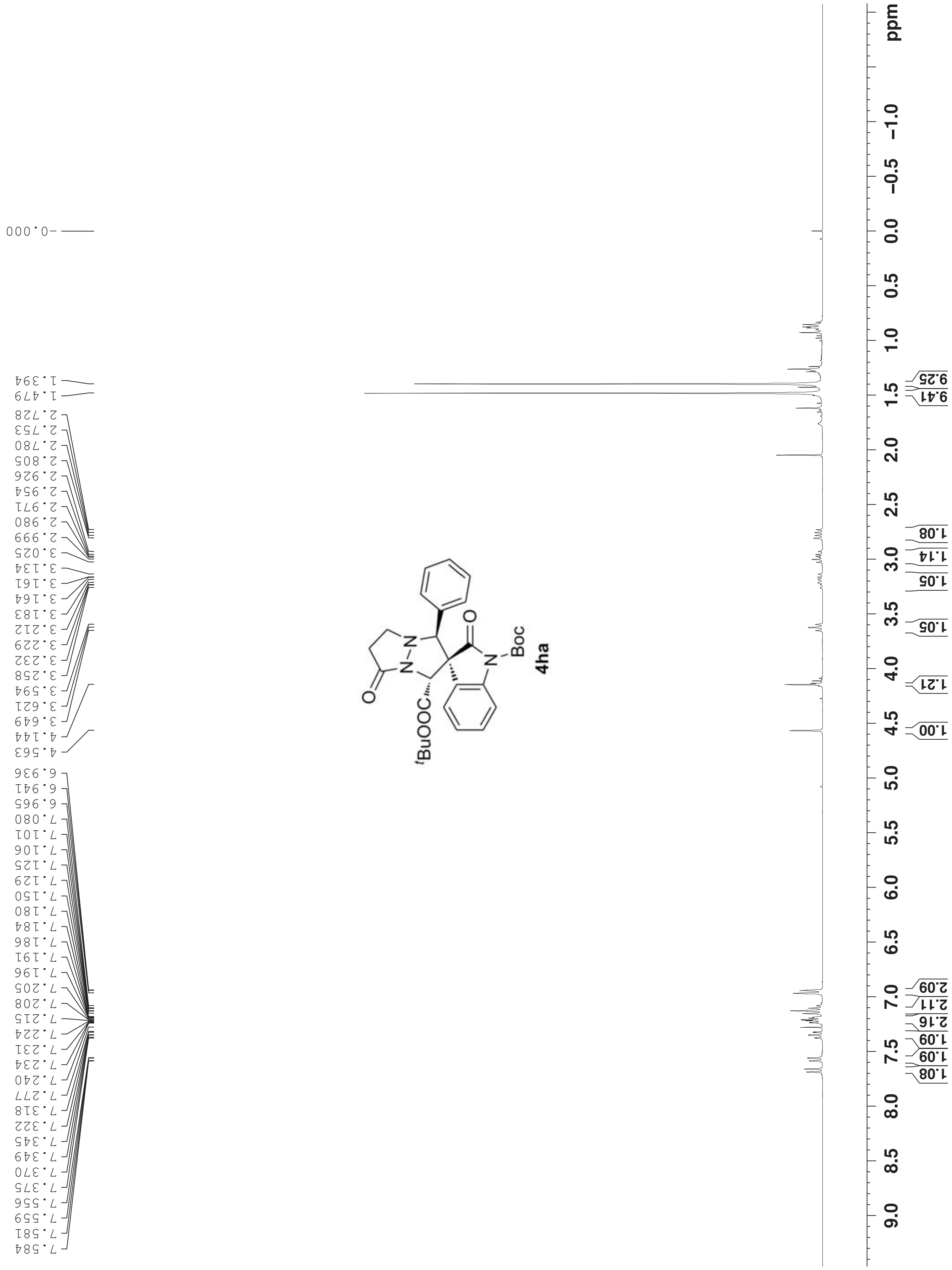
172.12
MeOOC
Boc
4ga
ppm

Electronic Supplementary Material (ESI) for Chemical Communications

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65.28
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77.00
77.42
77.54
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84.25
114.71
121.82
124.34
125.13
127.26
128.19
128.97
130.15
130.45
140.26
148.30
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172.35
ppm
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20
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40
50
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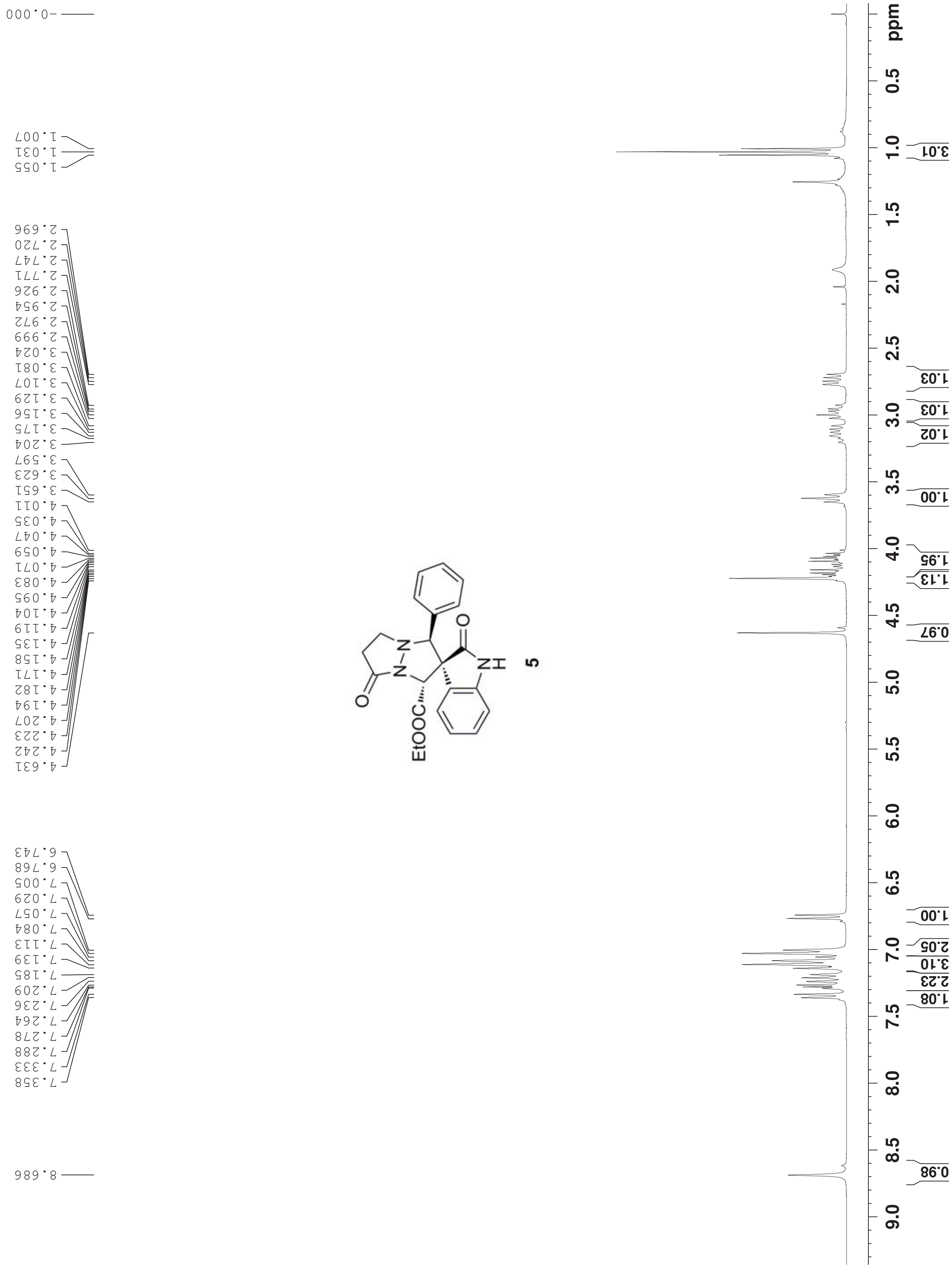
180
190
200
210
Boc
tBuOOC
4ha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3.204
3.597
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4.047
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EtOOC
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O
NH
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5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
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1.03
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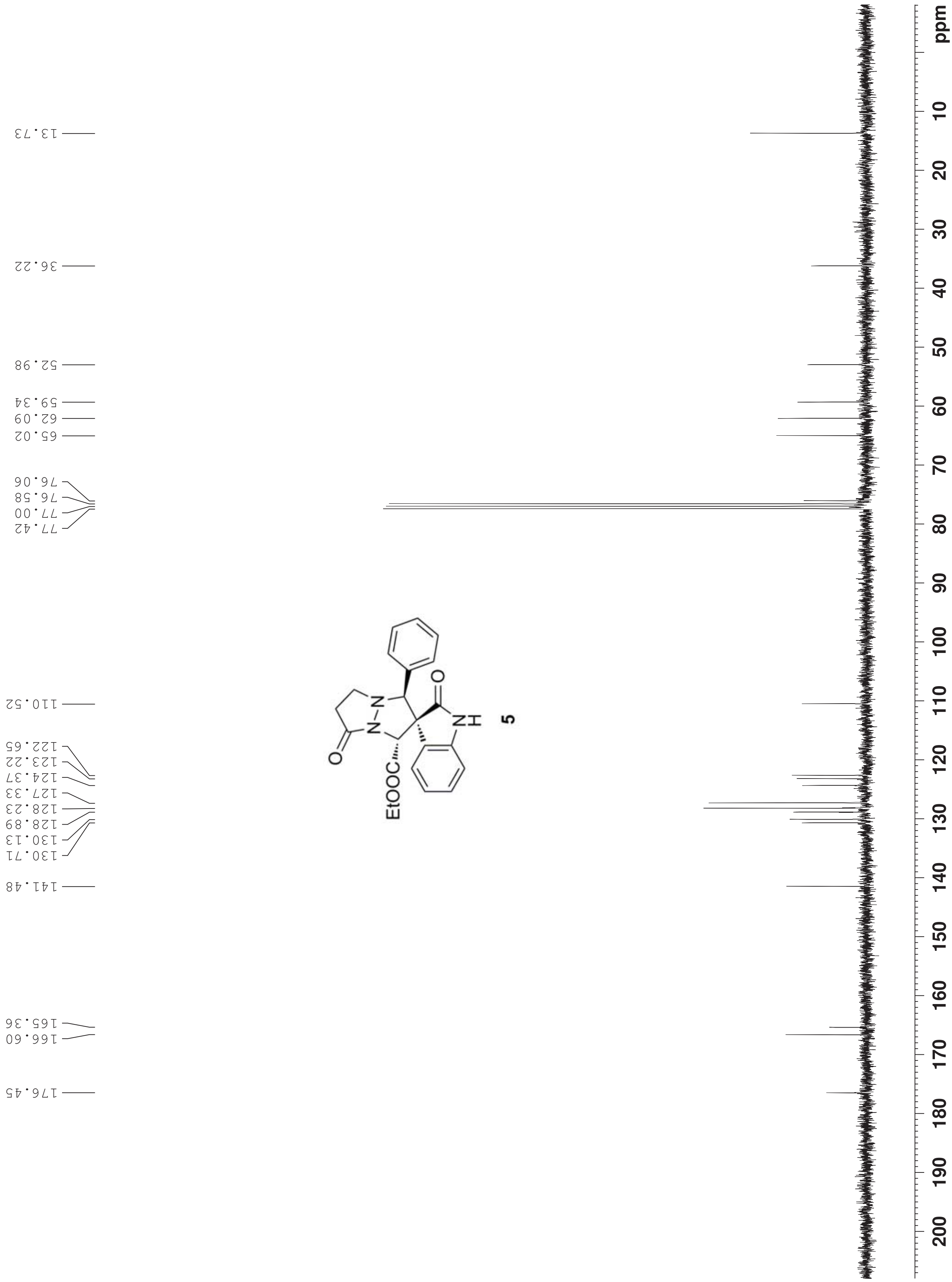
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124.37
127.33
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130.13
130.71
141.48
165.36
166.60
176.45
EtOOC
N
N
O
O
NH
5
ppm
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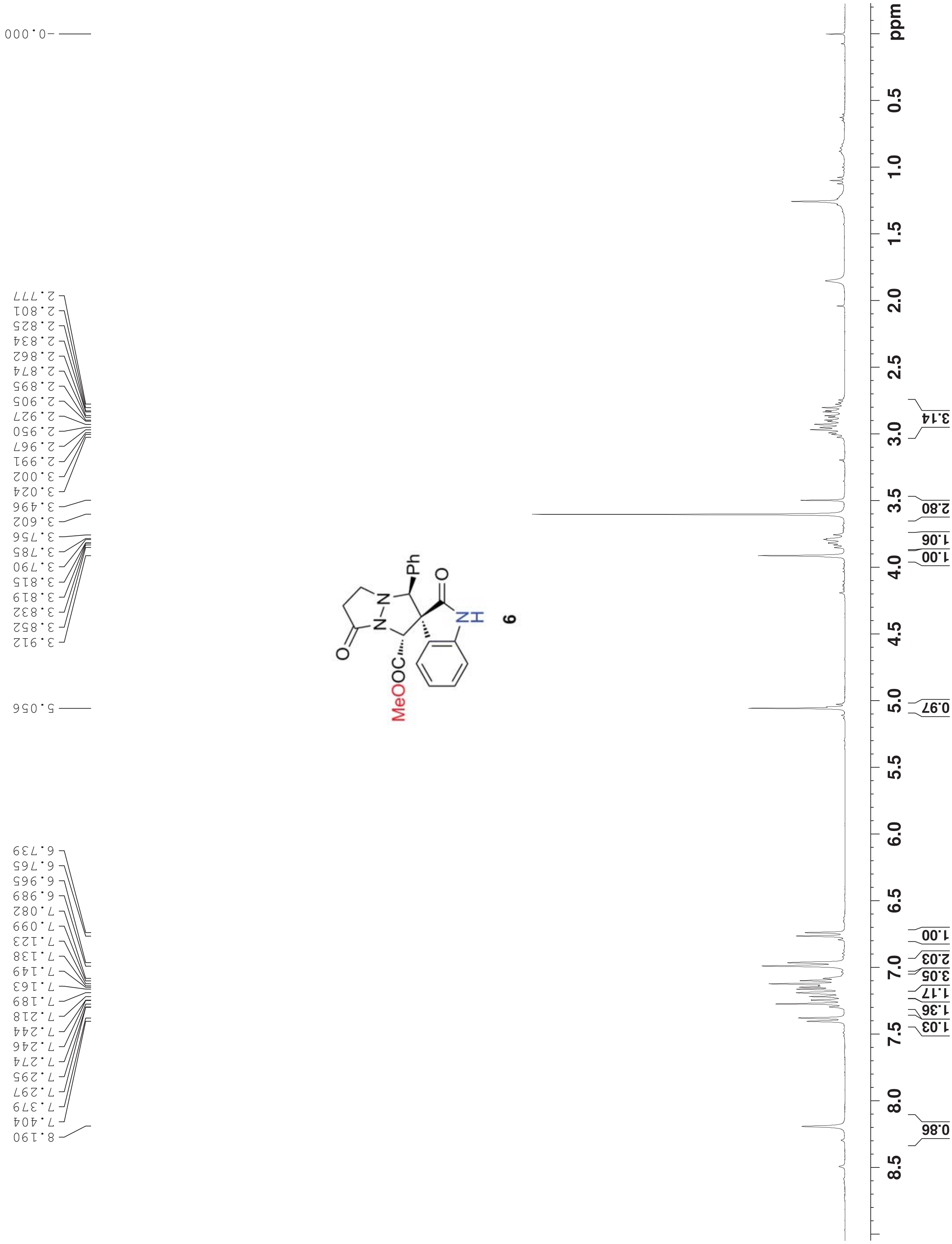
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3.024
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3.602
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3.790
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3.819
3.832
3.852
3.912
5.056
6.739
6.765
6.965
6.989
7.082
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Ph
O
N
N
NH
O
MeOOC
6
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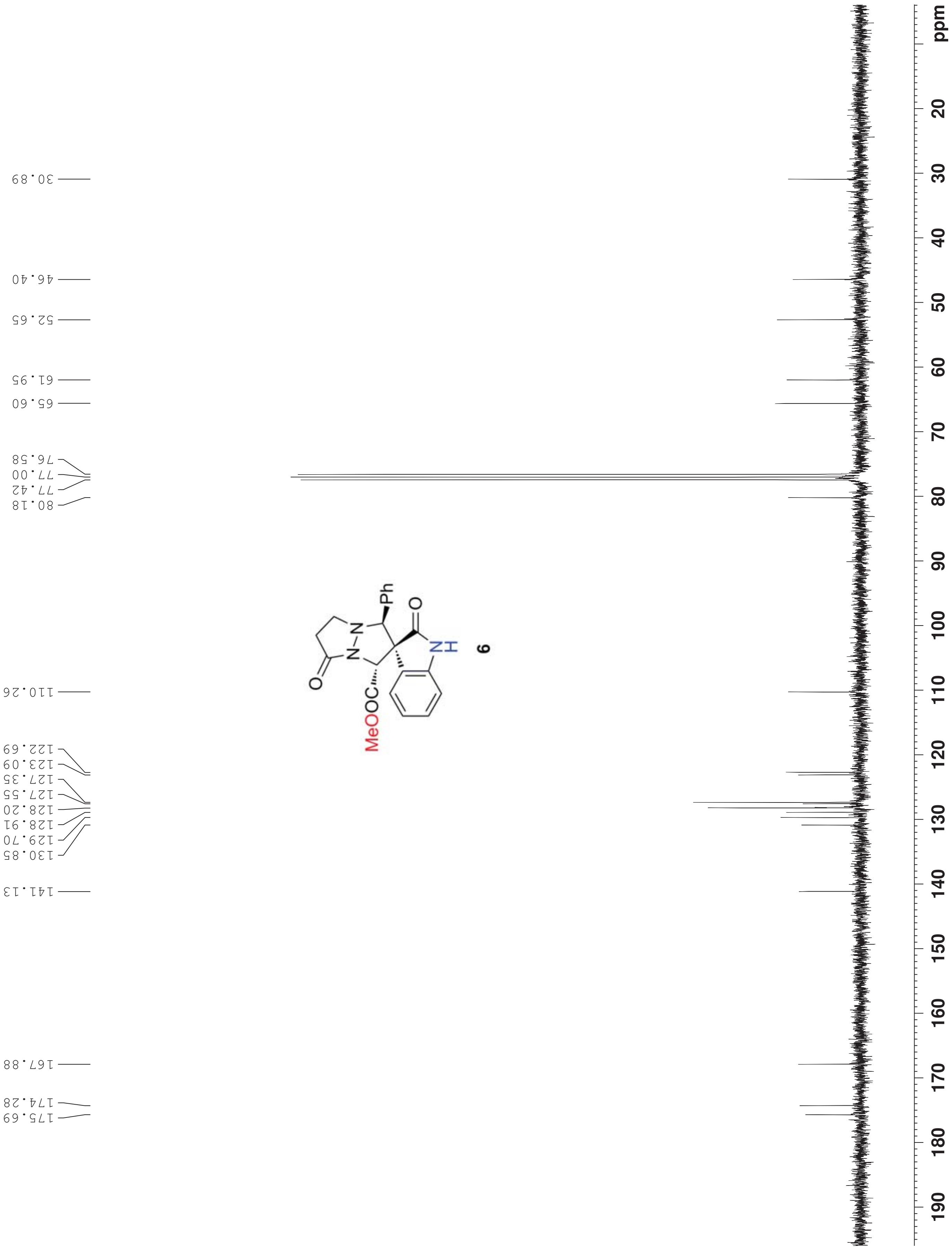
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141.13
167.88
174.28
175.69
MeOOC
Ph
N
N
O
O
NH
6
ppm
20
30
40
50
60
70
80
90
100
110
120
130
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170
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