

Research Article

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Double [3 + 2] cycloadditions for diastereoselective synthesis of spirooxindole-pyrrolizidines

Supplementary material

S1 General information

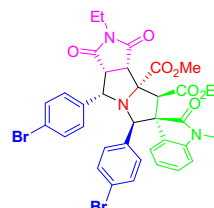
All solvents were used as received from commercial sources without further purification. ^1H -NMR and ^{13}C -NMR spectra were detected on Agilent NMR spectrometers (400 and 106 MHz, respectively) instruments internally referenced to SiMe_4 , chloroform, and dimethyl sulfoxide signals. Low resolution mass spectra on an Agilent 2100 LC were recorded in APCI (atmospheric pressure chemical ionization). The high-resolution mass spectra were obtained on a Waters Micromass GCT Premier. All products were purified on Agela Flash System with Venusil PrepG C18 column (10 μm , 120 $\text{\AA}$, 21.2 mm $\times$ 250 mm).

S2 General procedure for products 1 and 7

To a solution of TEA (1.25 mmol), glycine ester hydrochloride **2** (1.2 mmol), and aldehydes **4** (1.1 mmol) in

5 mL of MeCN was added maleimides **3** (1.0 mmol). The reaction solution was stirred at 125°C for 15 min under microwave heating. Upon the completion of the reaction as monitored by LC-MS. To the reaction solution were added aldehydes **4** or **4b'** (1.1 mmol), olefinic oxindoles **6** (1.0 mmol) and TFA (1.0 mmol), and then heated under conventional heating in the sealed vessels at 125°C for 18 h. The reaction mixture was evaporated to remove solvents, and the concentrated residue was isolated by Agela Flash System to give product **1** and **7**.

S3 Characterization of products



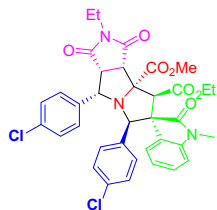
Compound 1a: white solid (62% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.29 (m, 1H), 7.20–7.09 (m, 5H), 7.04 (dt, J = 7.6, 1.1 Hz, 1H), 6.98–6.93 (m, 2H), 6.89–6.84 (m, 1H), 6.80 (d, J = 7.9 Hz, 2H), 5.28 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 11.4 Hz, 1H), 4.26 (dd, J = 8.0, 1.0 Hz, 1H), 4.03 (dd, J = 12.2, 1.0 Hz, 1H), 3.62–3.54 (m, 2H), 3.50 (dd, J = 7.9, 1.0 Hz, 1H), 3.33 (s, 3H), 3.21 (s, 3H), 3.15–3.08 (m, 1H), 2.99–2.91 (m, 1H), 0.77–0.71 (m, 3 t, J = 7.2 Hz, 3H), 0.63–0.58 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.4, 174.2, 173.4, 168.6, 168.2, 143.1, 138.4, 133.1, 130.8, 130.6, 130.3, 129.3, 129.1, 128.6, 123.6, 122.6, 122.1, 121.1, 108.0, 84.9, 67.2, 65.4, 63.9, 60.7, 54.4, 54.0, 51.0, 50.5, 33.7, 27.0, 13.4, 12.3. HRMS (ESI-TOF, m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{33}\text{Br}_2\text{N}_3\text{O}_7$ 778.0764, found: 778.0759.

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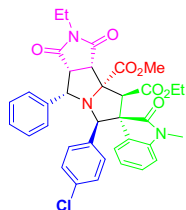
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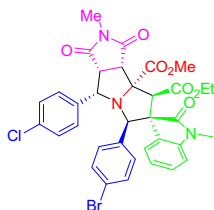


The chemical structure of compound 6 is shown. It features a central nitrogen atom (N) bonded to several groups: an ethyl ester group (-CO₂Et), two methoxyphenyl rings (one at the top left and one at the bottom left), and a dimethylamino group (-NMe₂) at the bottom right. The structure also includes a carbonyl group (=O) and a methyl ester group (-CO₂Me).

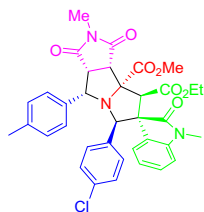
Compound 7a: white solid (66% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.30 (tt, J = 7.8, 1.1 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.11–7.07 (m, 2H), 7.06–6.92 (m, 6H), 6.87 (d, J = 8.3 Hz, 3H), 5.35 (d, J = 12.2 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.26 (dd, J = 11.4, 7.9 Hz, 1H), 4.07 (d, J = 12.2 Hz, 1H), 3.62–3.56 (m, 2H), 3.53 (d, J = 0.8 Hz, 1H), 3.33 (s, 3H), 3.21 (s, 3H), 3.15–3.09 (m, 1H), 2.92 (dd, J = 13.6, 7.0 Hz, 1H), 0.69 (t, J = 7.2 Hz, 3H), 0.63 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.5, 174.4, 173.53, 168.7, 168.3, 143.0, 138.1, 133.9, 132.6, 128.9, 128.8, 127.9, 127.7, 127.4, 123.8, 122.5, 107.9, 84.9, 67.8, 65.2, 64.0, 60.5, 54.5, 54.2, 50.9, 50.6, 33.6, 27.0, 13.4, 12.3. HRMS (ESI-TOF, m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{34}\text{ClN}_3\text{O}_7$ 656.2164, found: 656.2168.



Compound 7b: off-white solid (62% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.27 (m, 1H), 7.19 (ddd, $J = 7.7$, 1.3, 0.5 Hz, 1H), 7.06–6.97 (m, 6H), 6.94–6.84 (m, 5H), 5.34–5.29 (m, 1H), 4.50 (d, $J = 11.4$ Hz, 1H), 4.31–4.24 (m, 1H), 4.07 (d, $J = 12.2$ Hz, 1H), 3.62–3.55 (m, 2H), 3.49 (d, $J = 7.9$ Hz, 1H), 3.33 (s, 3H), 3.21 (s, 3H), 3.13 (dd, $J = 13.4$, 7.2 Hz, 1H), 2.95–2.88 (m, 1H), 0.71 (t, $J = 7.2$ Hz, 3H), 0.61 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.5, 174.5, 173.6, 168.7, 168.3, 143.1, 139.2, 133.6, 132.7, 130.1, 129.0, 128.8, 127.7, 127.6, 127.5, 127.1, 123.7, 122.5, 107.9, 85.0, 67.3, 66.0, 64.1, 60.6, 54.5, 54.1, 50.9, 50.6, 33.7, 27.0, 13.4, 12.3. HRMS (ESI-TOF, m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{34}\text{ClN}_3\text{O}_7$ 656.2164, found: 656.2163.

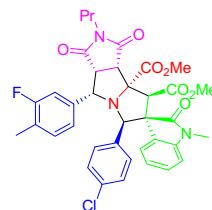


Compound 7c: white solid (69% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.28 (m, 1H), 7.17 (d, $J = 7.8$ Hz, 1H), 7.13–7.09 (m, 2H), 7.01 (tt, $J = 7.5$, 1.1 Hz, 3H), 6.97–6.92 (m, 2H), 6.87 (d, $J = 7.8$ Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 2H), 5.29 (d, $J = 12.2$ Hz, 1H), 4.46 (d, $J = 11.4$ Hz, 1H), 4.28 (dd, $J = 11.3$, 7.8 Hz, 1H), 4.05 (d, $J = 12.2$ Hz, 1H), 3.62–3.55 (m, 2H), 3.51 (d, $J = 7.7$ Hz, 1H), 3.33 (s, 3H), 3.21 (s, 3H), 2.46 (s, 3H), 0.61 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.4, 174.6, 173.7, 168.6, 168.2, 143.1, 138.1, 133.2, 133.0, 130.8, 130.3, 129.1, 128.6, 128.6, 127.7, 123.7, 122.6, 122.1, 108.0, 85.0, 67.2, 65.6, 63.9, 60.7, 54.3, 54.0, 51.0, 50.8, 27.1, 24.4, 13.4. HRMS (ESI-TOF, m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{35}\text{H}_{31}\text{ClBrN}_3\text{O}_7$ 720.1112, found: 720.1109.

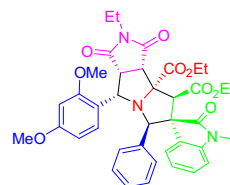


Compound 7d: white solid (60% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.27 (m, 1H), 7.18 (d, $J = 7.7$ Hz, 1H), 7.04–6.97

(m, 3H), 6.92–6.84 (m, 3H), 6.81 (d, $J = 7.6$ Hz, 2H), 6.67 (d, $J = 7.7$ Hz, 2H), 5.31 (d, $J = 12.1$ Hz, 1H), 4.44 (d, $J = 11.5$ Hz, 1H), 4.27 (dd, $J = 11.6$, 7.9 Hz, 1H), 4.06 (d, $J = 12.2$ Hz, 1H), 3.59 (dt, $J = 7.2$, 5.4, 3.0 Hz, 2H), 3.49 (d, $J = 8.1$ Hz, 1H), 3.32 (s, 3H), 3.20 (s, 3H), 2.44 (s, 3H), 2.20 (s, 3H), 0.60 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.5, 174.8, 174.0, 168.7, 168.4, 143.1, 136.7, 136.3, 133.5, 132.8, 130.0, 129.0, 128.7, 128.2, 127.7, 127.0, 123.8, 122.5, 107.9, 85.1, 67.3, 66.2, 64.0, 60.6, 54.4, 54.1, 50.9, 50.9, 27.0, 24.3, 21.0, 13.4. HRMS (ESI-TOF, m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{38}\text{H}_{34}\text{ClN}_2\text{O}_3$ 656.2164, found: 656.2164.

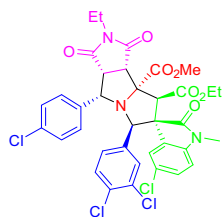


Compound 7e: white solid (59% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.27 (m, 1H), 7.18–7.13 (m, 1H), 7.06–7.00 (m, 3H), 6.97–6.91 (m, 2H), 6.90–6.85 (m, 1H), 6.79 (dd, $J = 8.4$, 7.3 Hz, 1H), 6.62 (d, $J = 10.7$ Hz, 1H), 6.51–6.43 (m, 1H), 5.32 (d, $J = 12.2$ Hz, 1H), 4.46 (d, $J = 11.4$ Hz, 1H), 4.22 (dd, $J = 11.4$, 8.0 Hz, 1H), 4.10 (d, $J = 12.2$ Hz, 1H), 3.49–3.47 (m, 1H), 3.34 (s, 3H), 3.22 (s, 3H), 3.13–3.03 (m, 4H), 2.86 (ddd, $J = 13.2$, 9.3, 6.1 Hz, 1H), 2.13 (s, 3H), 1.29–1.19 (m, 1H), 1.15–1.05 (m, 1H), 0.70 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.5, 174.5, 173.7, 168.9, 168.5, 142.9, 133.8, 132.6, 130.4, 130.3, 130.1, 129.0, 128.6, 127.8, 123.6, 123.5, 123.4, 122.9, 122.9, 122.5, 114.1, 113.9, 108.1, 85.0, 67.1, 65.4, 65.4, 64.1, 54.1, 54.1, 51.7, 50.9, 50.4, 40.4, 27.0, 20.5, 11.3. HRMS (ESI-TOF, m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{37}\text{H}_{35}\text{ClN}_3\text{O}_7$ 688.2226, found: 688.222.



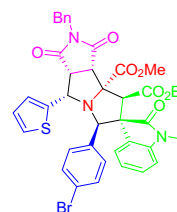
Compound 7f: white solid (61% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.23 (m, 2H), 7.19–7.09 (m, 3H), 7.05–6.95 (m, 4H), 6.86 (dd, $J = 7.8$, 1.0 Hz, 1H), 6.49 (dd, $J = 8.8$, 3.2 Hz, 1H), 6.36 (d, $J = 8.8$ Hz, 1H), 5.32 (d, $J = 12.2$ Hz, 1H), 5.03 (d, $J = 11.3$ Hz, 1H), 4.29 (dd, $J = 11.3$, 7.9 Hz, 1H), 4.15 (d, $J = 12.2$ Hz, 1H), 3.96 (dd, $J = 10.5$, 7.2 Hz, 1H), 3.68 (s, 3H), 3.57 (dd, $J = 7.5$, 2.7 Hz, 3H), 3.51–3.44 (m, 4H), 3.34 (s, 3H), 3.12 (dd, $J = 13.5$, 7.1 Hz, 1H), 2.95 (dd, $J = 13.5$, 7.0 Hz, 1H), 0.74–0.58 (m, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.6, 174.5, 173.7, 168.6, 168.5,

153.0, 150.5, 143.3, 134.3, 129.3, 129.2, 128.9, 128.8, 127.5, 127.3, 123.9, 122.5, 114.3, 113.5, 110.9, 107.7, 84.9, 68.0, 60.4, 60.4, 56.0, 55.7, 54.6, 54.6, 49.8, 33.5, 27.0, 13.4, 13.1, 12.3.



Compound 7g: white solid (55% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.32 (ddd, $J = 8.3, 2.1, 0.7$ Hz, 1H), 7.16 (d, $J = 2.0$ Hz, 1H), 7.14 (d, $J = 2.0$ Hz, 1H), 7.07 (d, $J = 8.2$ Hz, 1H), 7.02 (dd, $J = 8.7, 0.7$ Hz, 2H), 6.93–6.88 (m, 1H), 6.83 (dd, $J = 11.6, 8.1$ Hz, 3H), 5.23 (d, $J = 12.2$ Hz, 1H), 4.45 (d, $J = 11.4$ Hz, 1H), 4.20 (dd, $J = 11.4, 8.0$ Hz, 1H), 4.05 (d, $J = 12.2$ Hz, 1H), 3.71–3.64 (m, 2H), 3.43 (dd, $J = 8.0, 0.6$ Hz, 1H), 3.33 (d, $J = 5.1$ Hz, 6H), 3.19 (dd, $J = 13.5, 7.1$ Hz, 1H), 3.01 (dd, $J = 13.5, 7.1$ Hz, 1H), 0.79 (t, $J = 7.2$ Hz, 3H), 0.70 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) 176.0, 174.0, 173.2, 168.1, 167.9, 141.6, 137.5, 133.9, 133.3, 132.3, 132.1, 130.2, 129.6, 129.0, 128.8, 128.1, 127.8,

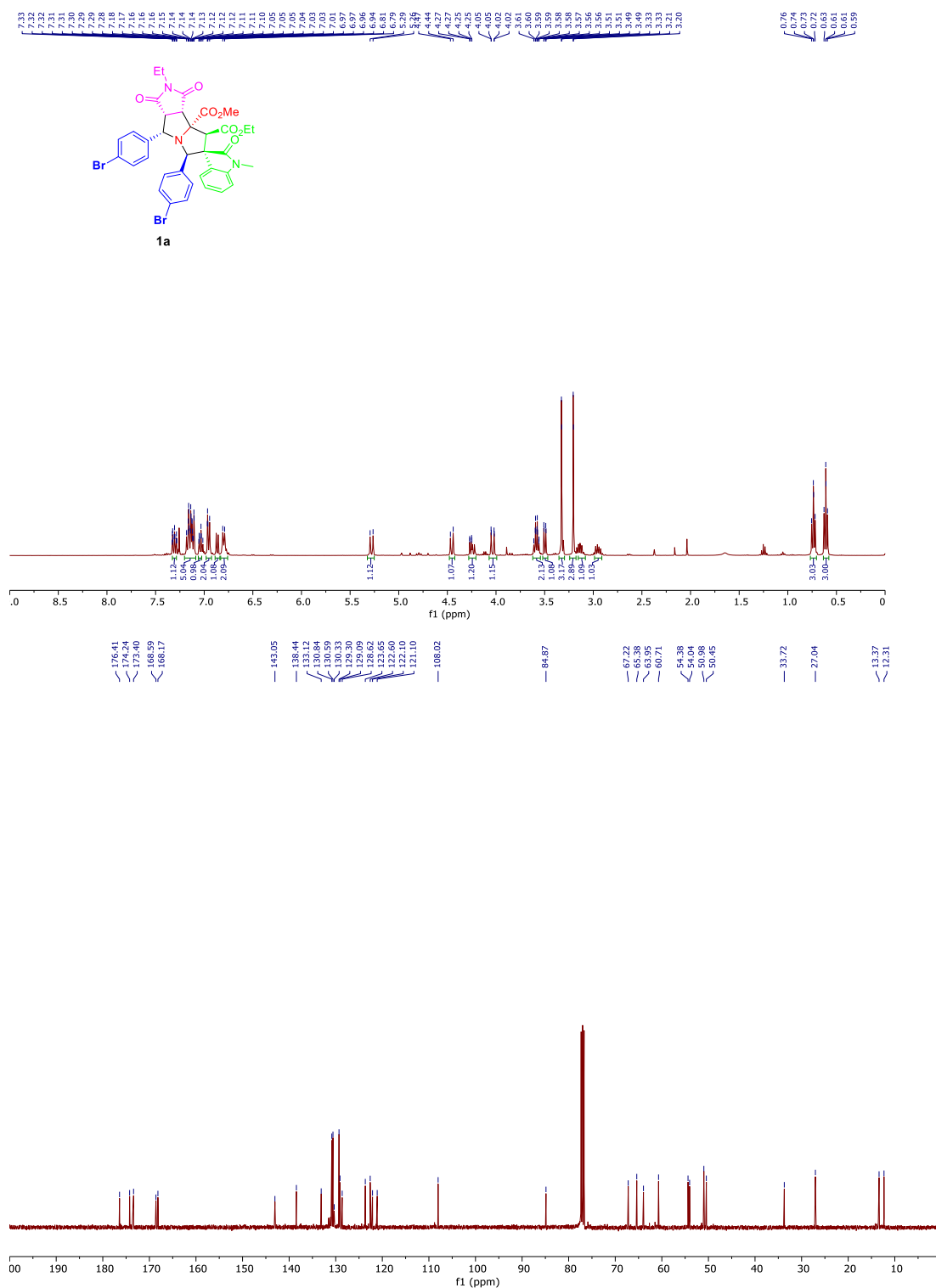
124.0, 109.0, 85.2, 66.7, 65.5, 64.1, 61.1, 54.0, 53.9, 51.2, 50.2, 33.9, 27.2, 13.4, 12.4.

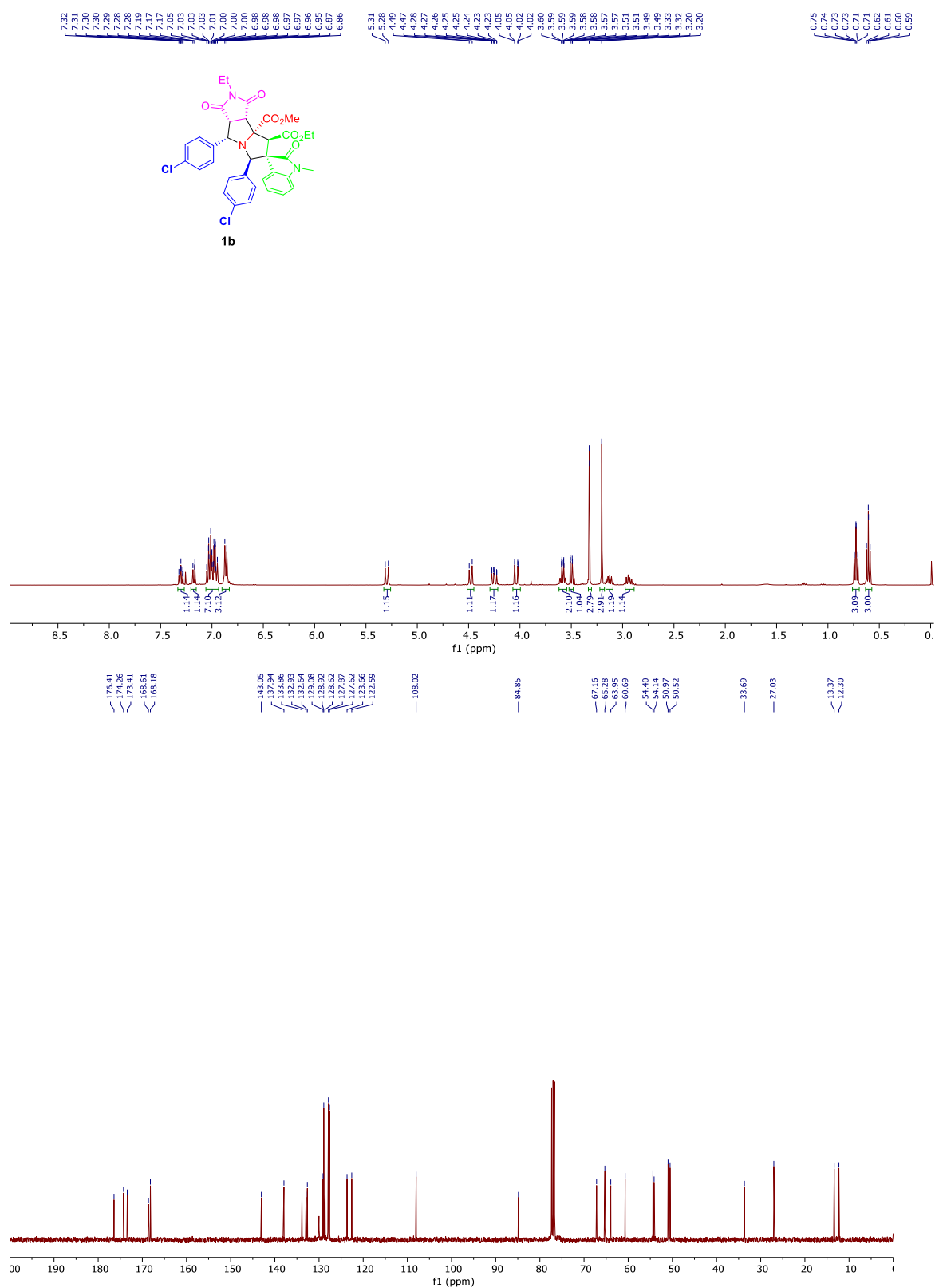


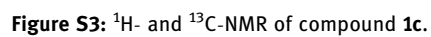
Compound 7h: white solid (49% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.26 (m, 1H), 7.22–7.11 (m, 8H), 7.10–7.06 (m, 2H), 7.02 (td, $J = 7.6, 1.0$ Hz, 1H), 6.93 (dd, $J = 5.1, 1.2$ Hz, 1H), 6.84 (d, $J = 7.5$ Hz, 1H), 6.58 (dd, $J = 5.1, 3.6$ Hz, 1H), 6.31 (d, $J = 3.3$ Hz, 1H), 5.29 (s, 1H), 4.80 (d, $J = 11.0$ Hz, 1H), 4.30–4.25 (m, 1H), 4.06–3.98 (m, 2H), 3.58 (dq, $J = 7.1, 3.6$ Hz, 2H), 3.48 (d, $J = 0.7$ Hz, 2H), 3.29 (s, 3H), 3.19 (s, 3H), 0.59 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.4, 173.8, 173.1, 168.1, 144.1, 143.1, 135.3, 133.1, 130.7, 129.1, 128.9, 128.4, 127.7, 126.2, 125.0, 124.7, 123.7, 122.6, 122.0, 107.9, 84.5, 67.3, 63.8, 61.7, 60.7, 54.2, 54.0, 51.0, 50.9, 42.2, 27.0, 13.4.

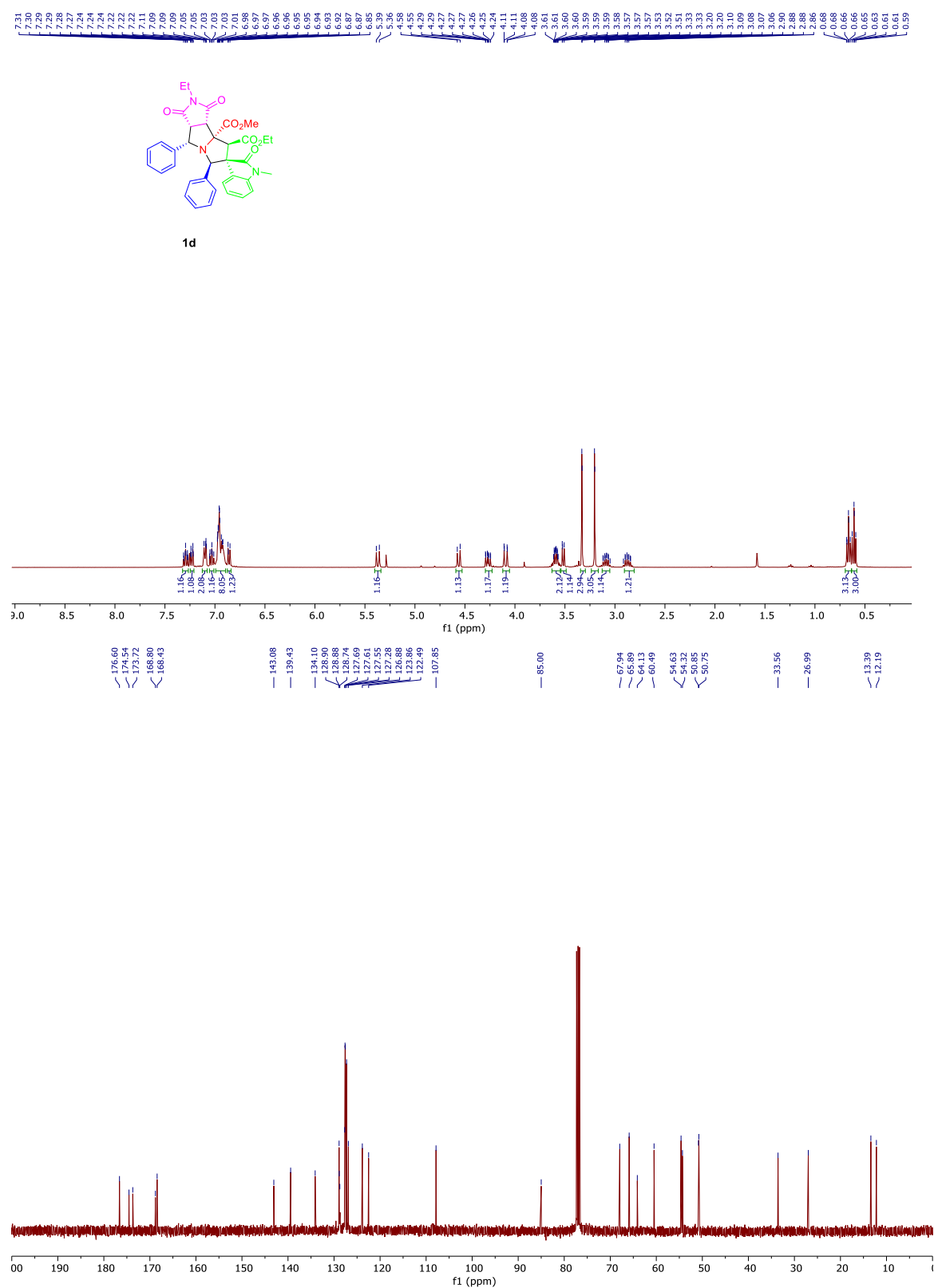
S4 NMR spectra of products

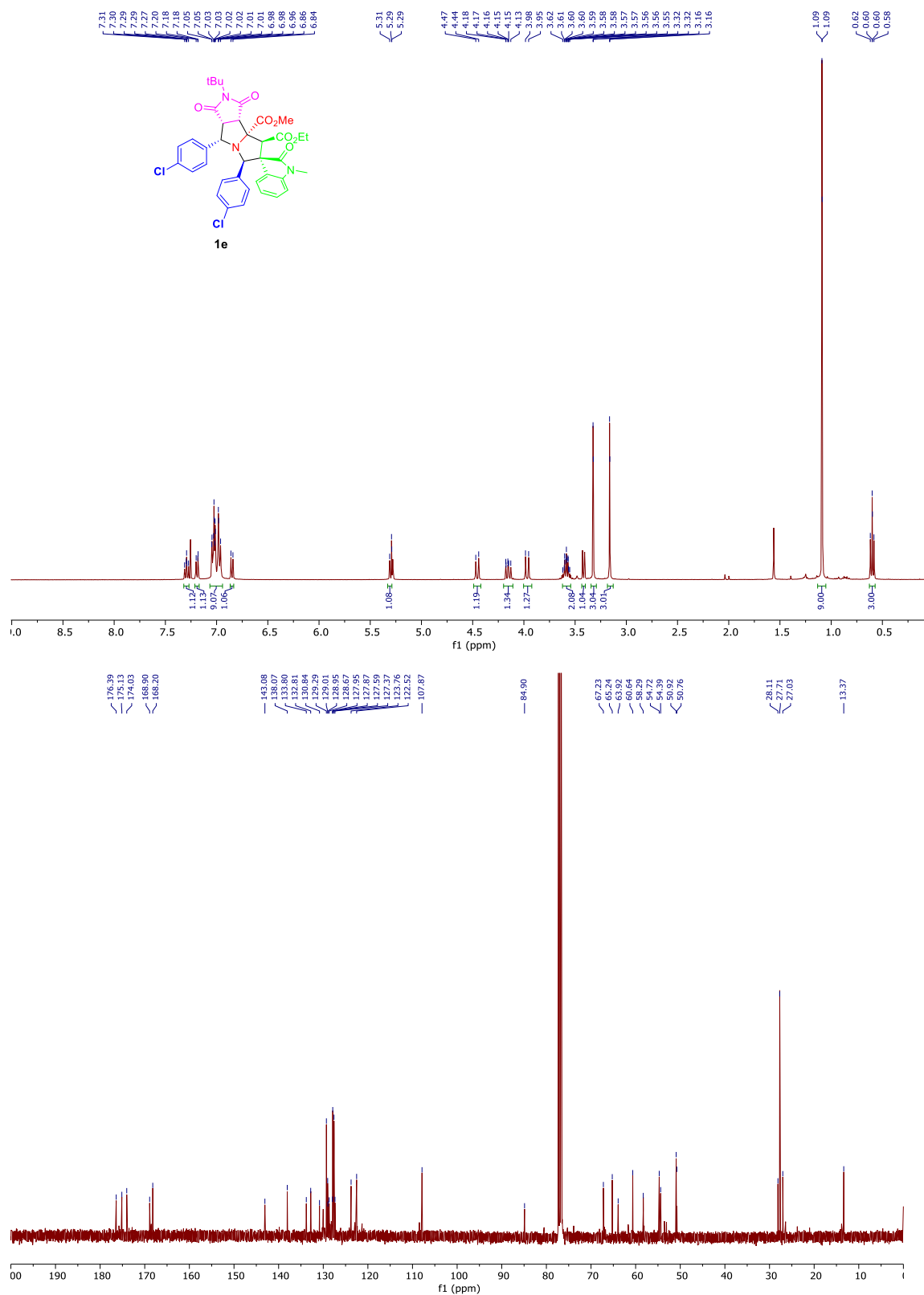
S4 NMR spectra of products

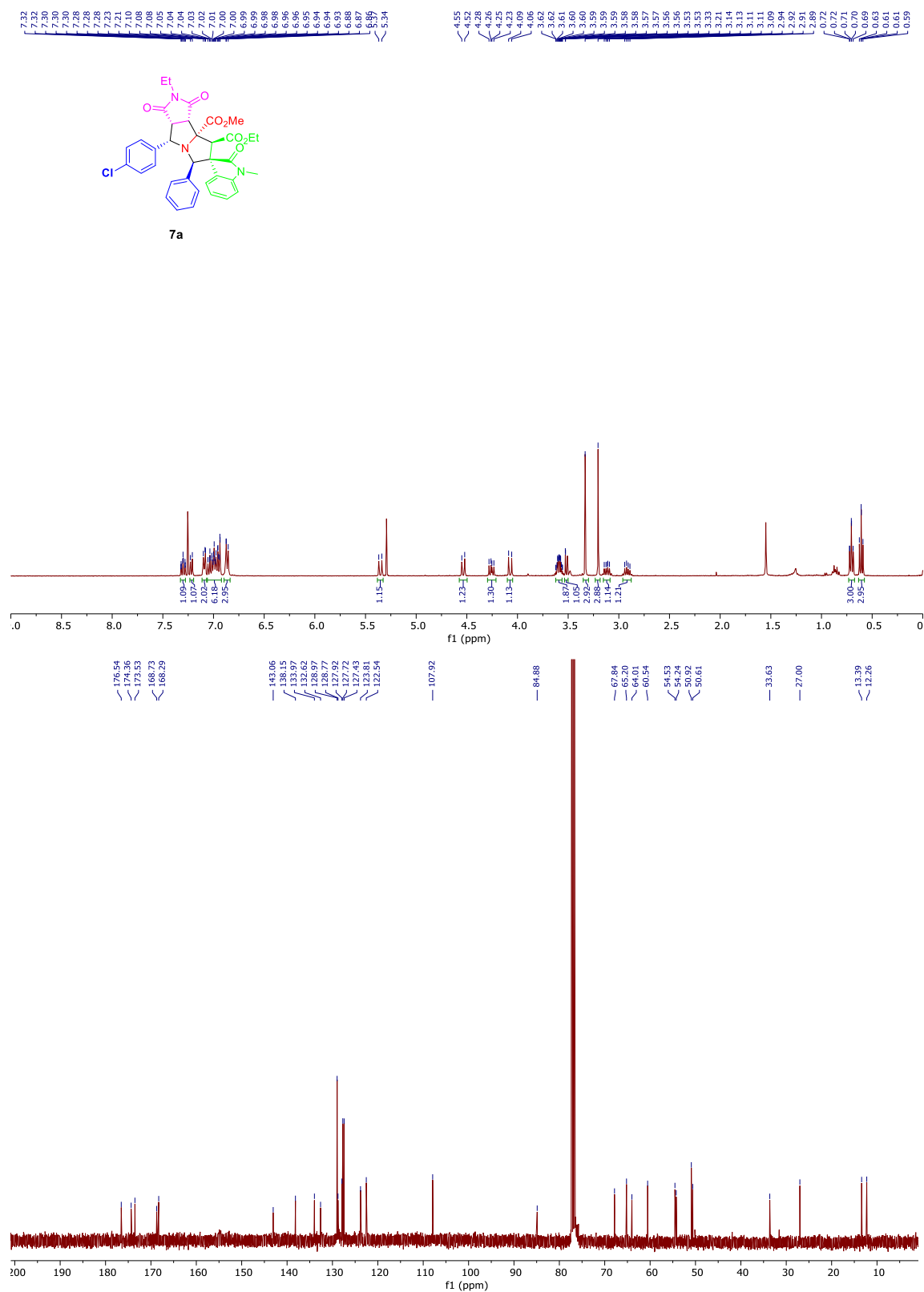
Figure S1: ¹H- and ¹³C-NMR of compound **1a**.

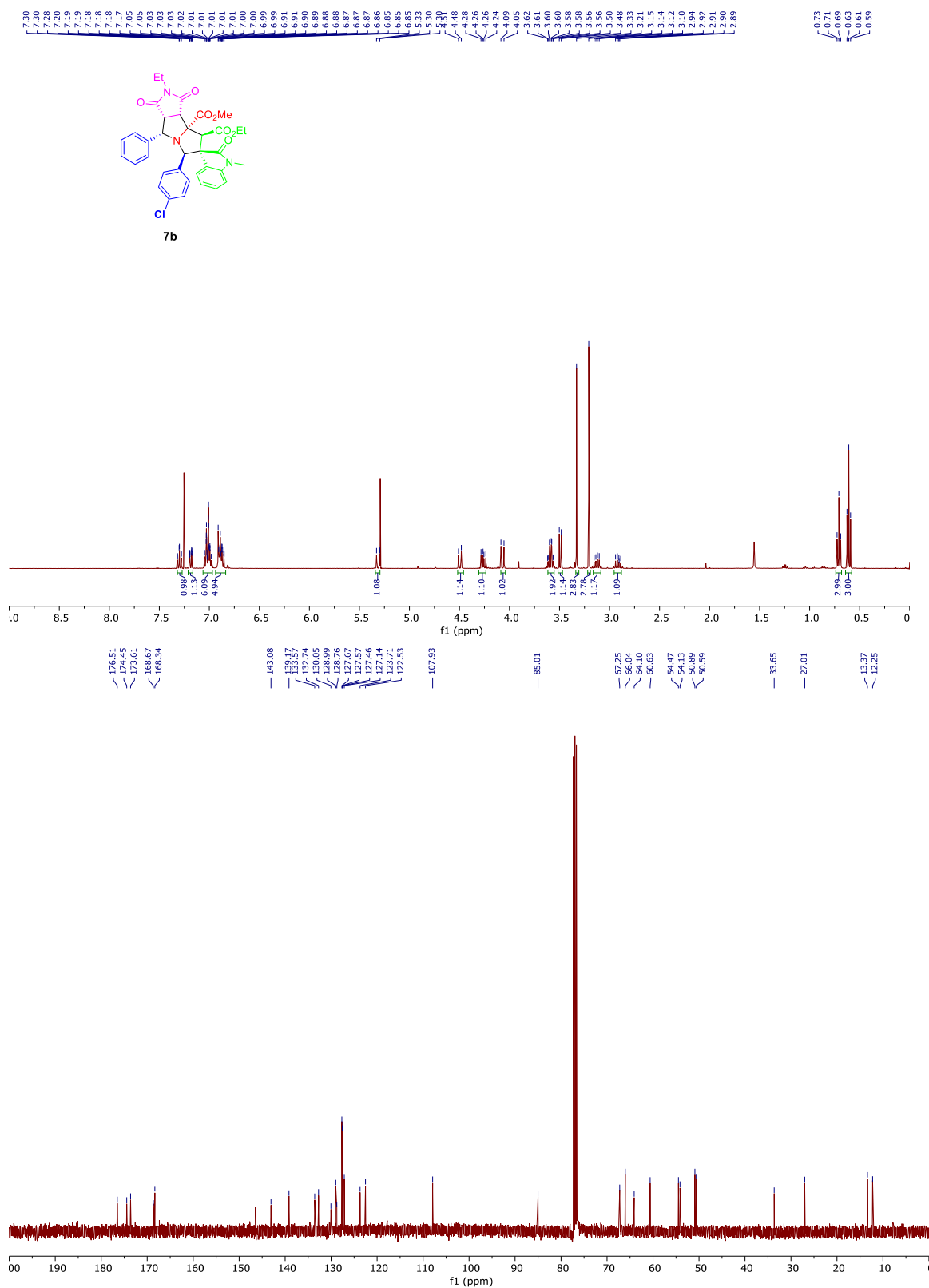
Figure S2: ¹H- and ¹³C-NMR of compound 1b.

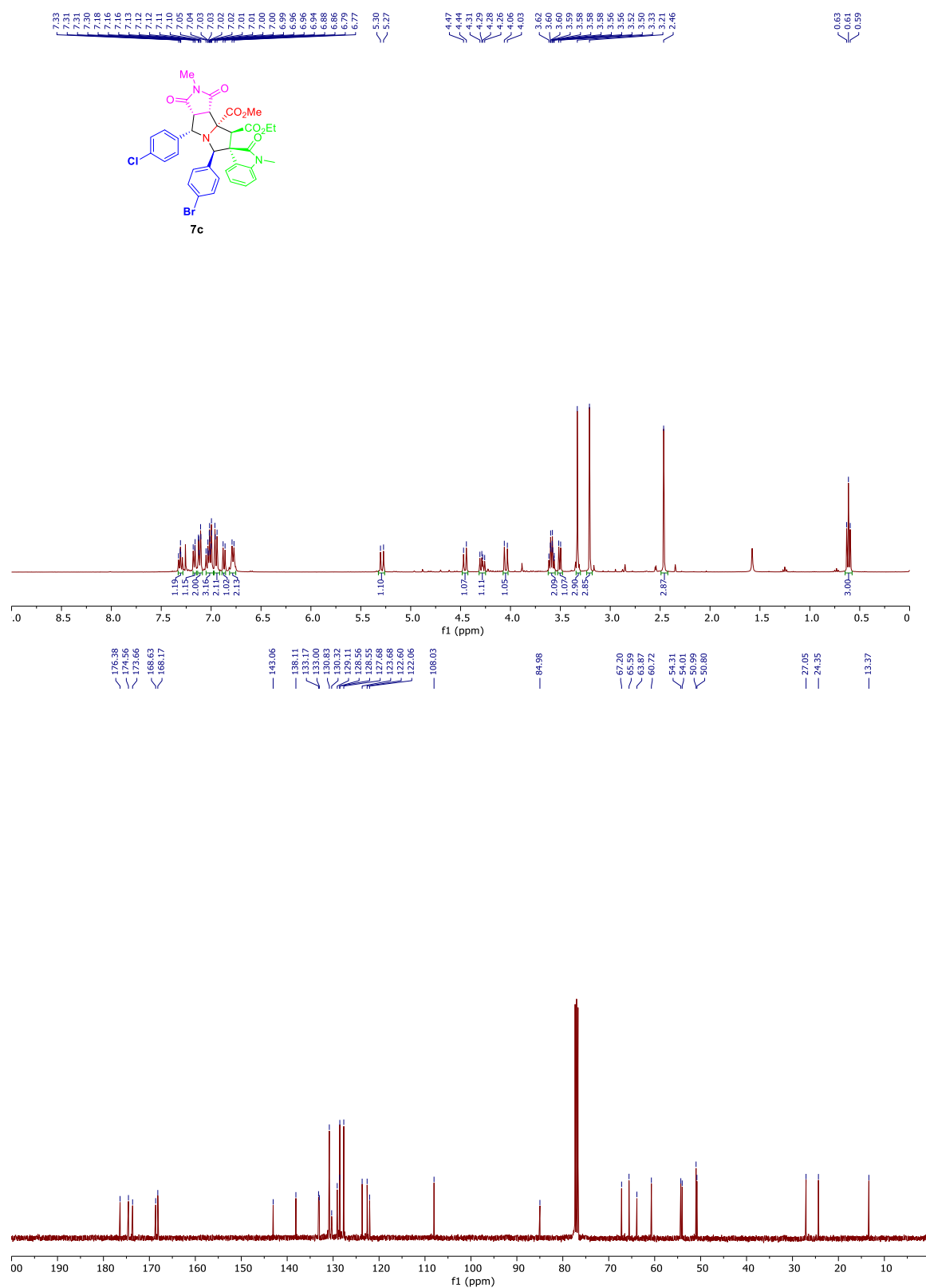


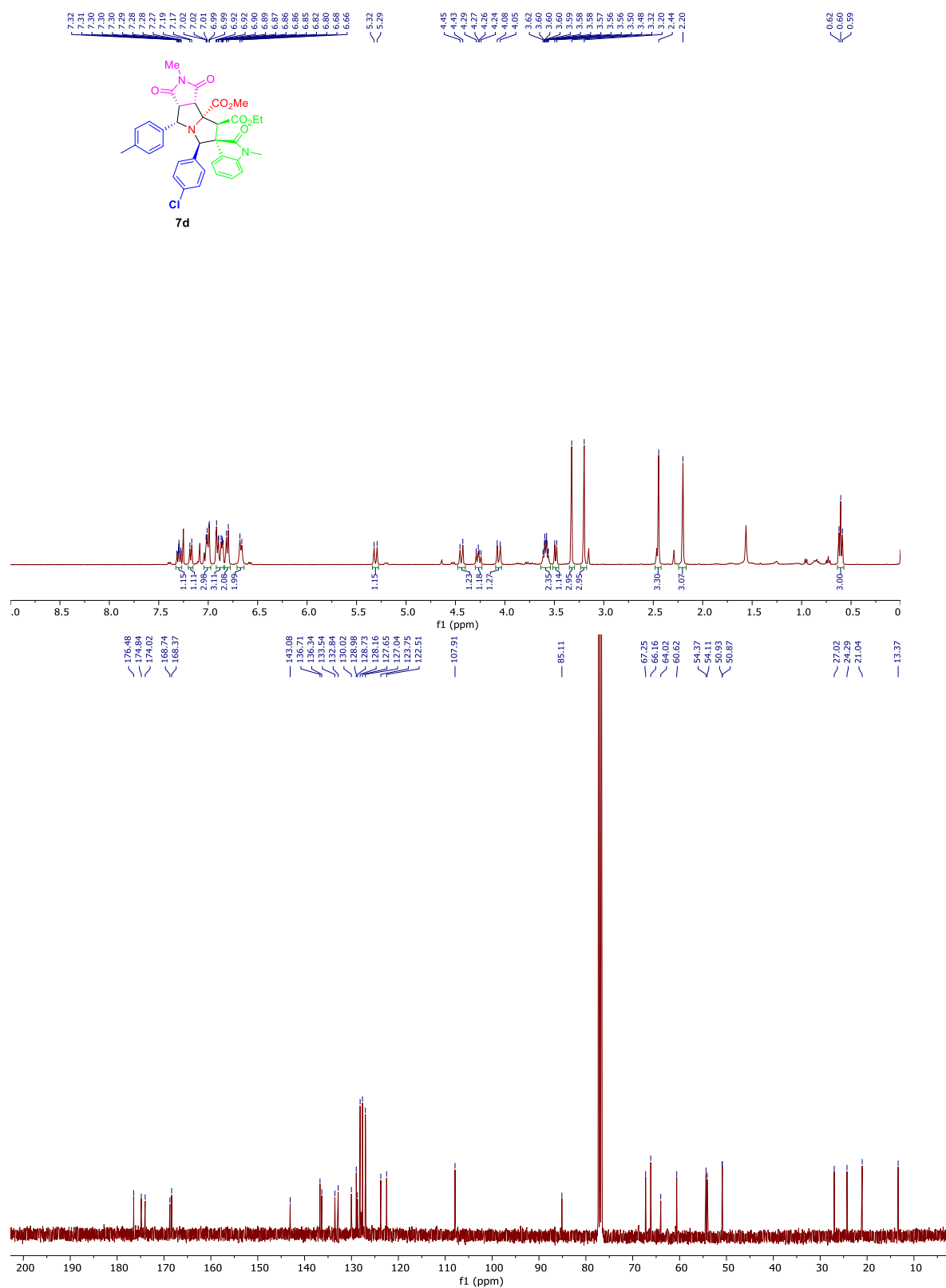
Figure S4: ^1H - and ^{13}C -NMR of compound **1d**.

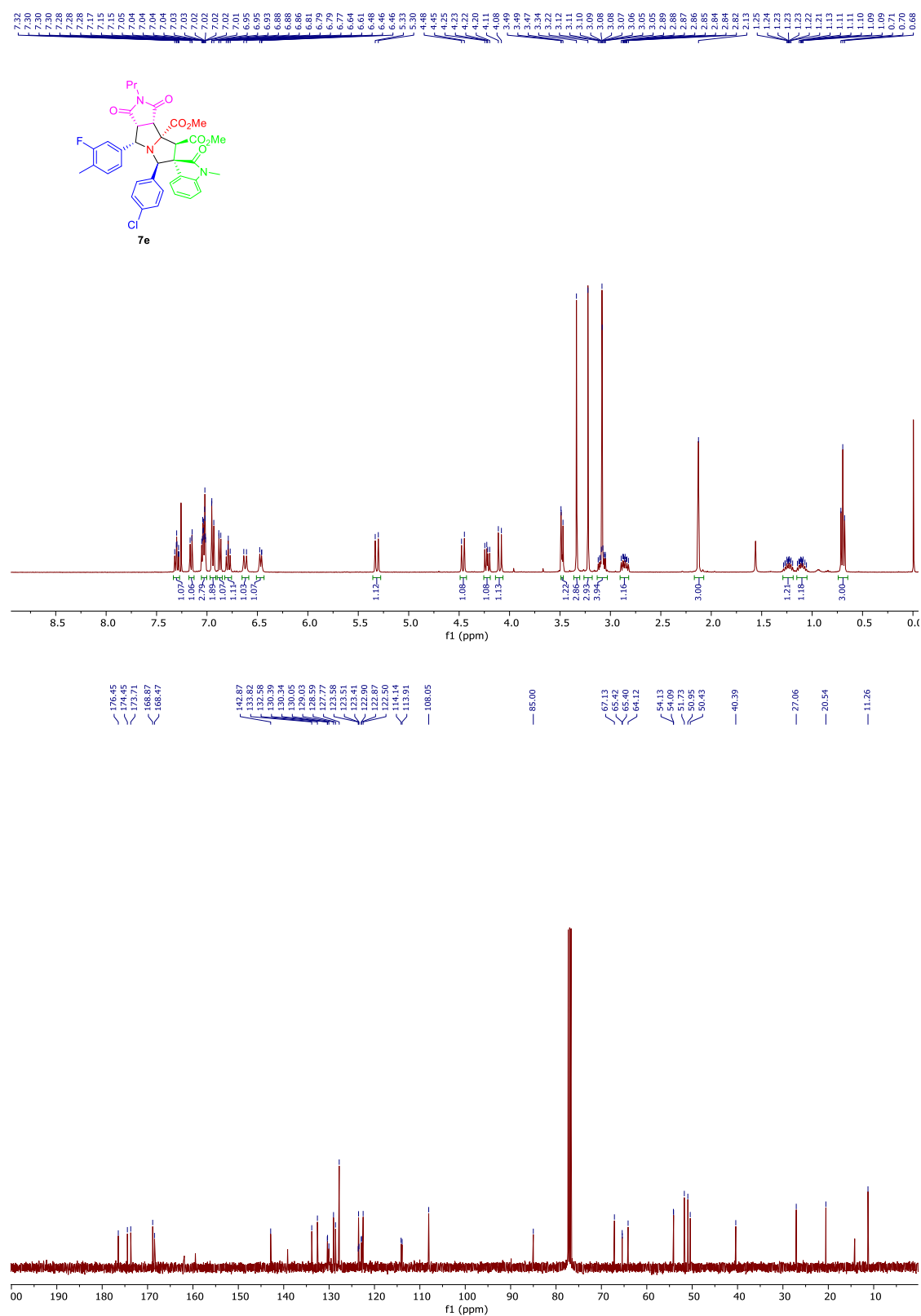
Figure S5: ¹H- and ¹³C-NMR of compound 1e.

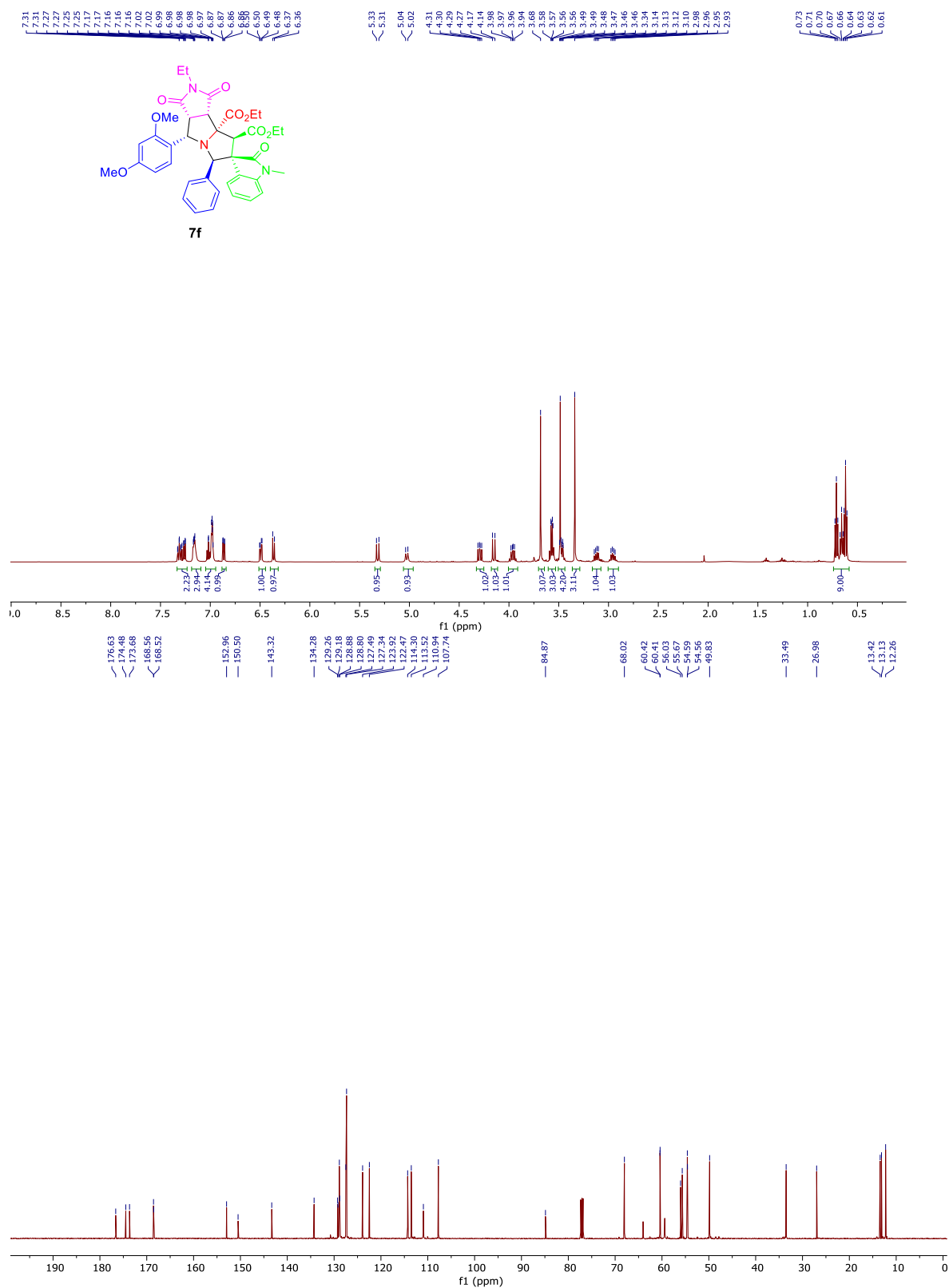
Figure S6: ^1H - and ^{13}C -NMR of compound **7a**.

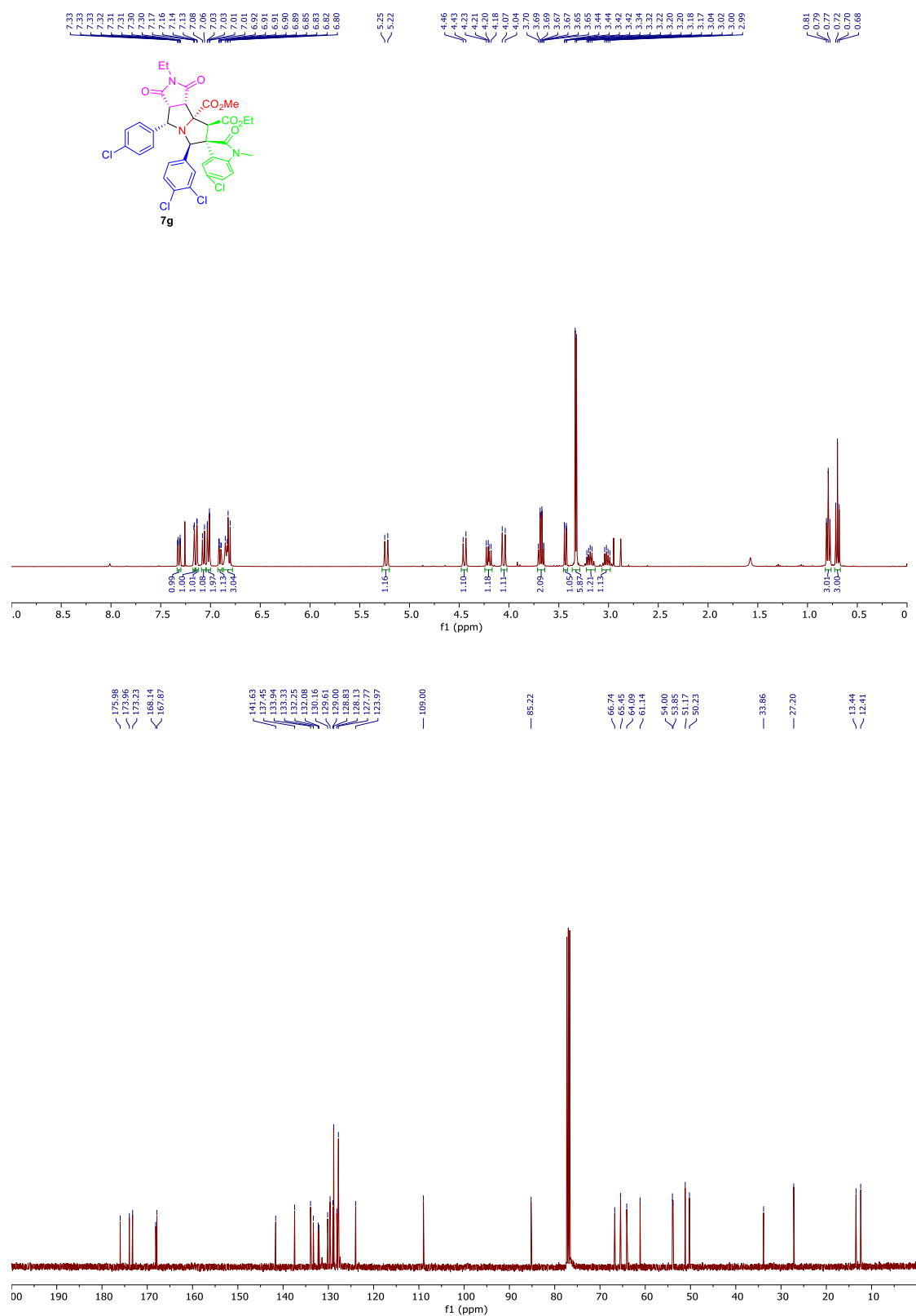
Figure S7: ^1H - and ^{13}C -NMR of compound **7b**.

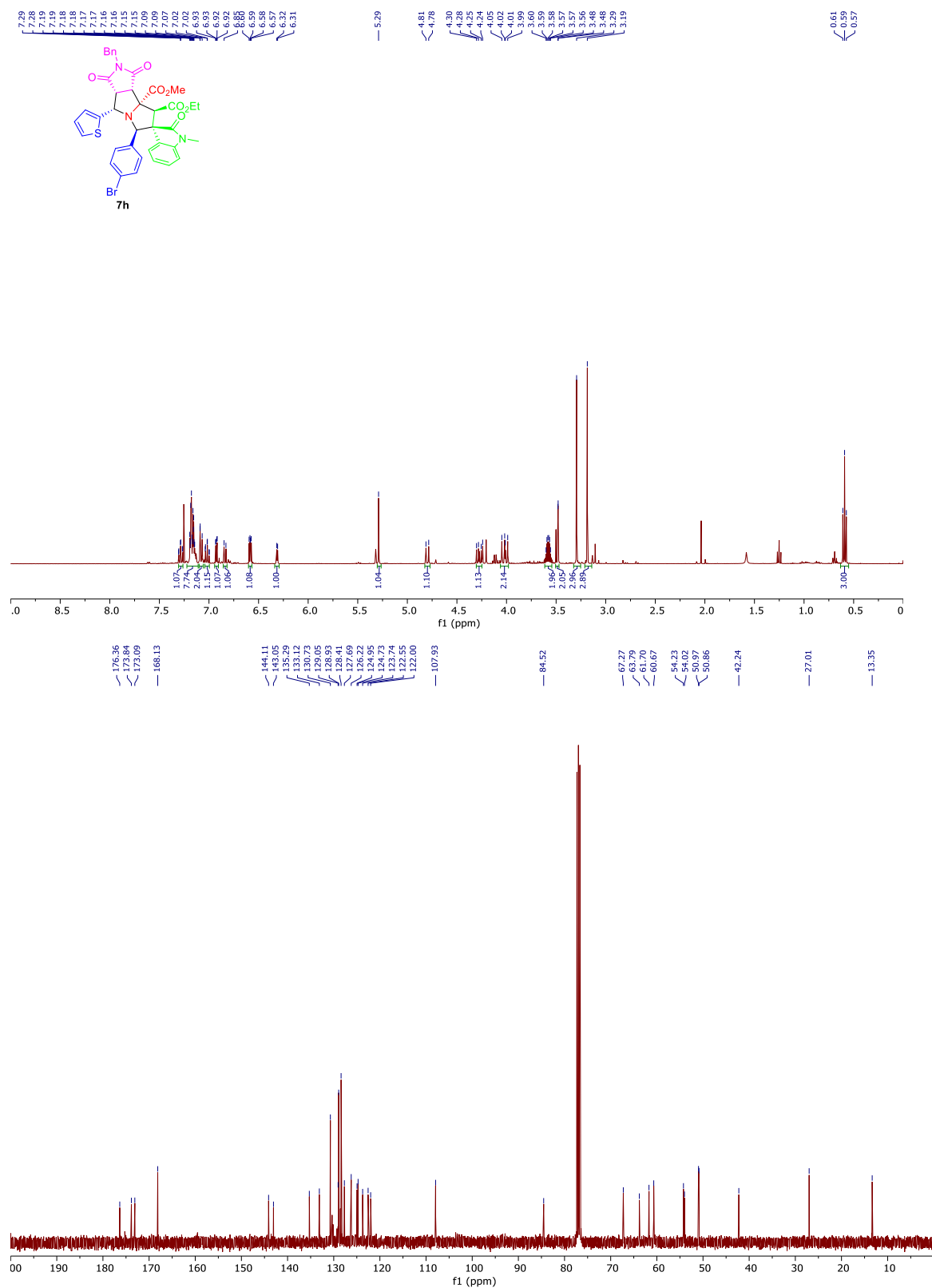
Figure S8: ¹H- and ¹³C-NMR of compound 7c.

Figure S9: ¹H- and ¹³C-NMR of compound **7d**.

Figure S10: ¹H- and ¹³C-NMR of compound 7e.

Figure S11: ^1H - and ^{13}C -NMR of compound **7f**.

Figure S12: ¹H- and ¹³C-NMR of compound 7g.

Figure S13: ^1H - and ^{13}C -NMR of compound **7h**.