

Direct synthesis of sensitive selenocysteine peptides by the Ugi reaction

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General: Chemicals and solvents were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica 60 (230–400 mesh, 0.040–0.063 mm) from Merck. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ plates (250 µm layer thickness; aluminium sheets; particle size: 0.040–0.063 mm). Compounds were visualized by UV ($\lambda = 254$ nm), or by dipping the plates into a CerMOP-TLC reagent followed by heating. CerMOP-TLC reagent was prepared by dissolving 12.5 g molybdato-phosphoric acid, 5.0 g Ce(SO₄)₂·H₂O and 30 mL of concentrated sulfuric acid in 470 mL of water. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300 and 75.5 MHz, respectively. The chemical shifts (δ) are given in ppm downfield from TMS ($\delta = 0$ ppm, ¹H) and CDCl₃ ($\delta = 77.0$ ppm, ¹³C), respectively. Coupling constants *J* values are given in Hz. For multiplets the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet or unresolved signal), br (broad). The high resolution ESI mass spectra were obtained from a Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer (Bruker Daltonics, Billerica, USA) equipped with an InfinityTM cell, a 7.0 Tesla superconducting magnet (Bruker, Karlsruhe, Germany), an RF-only hexapole ion guide and an APOLLO electrospray ion source (Agilent, off axis spray). Nitrogen was used as drying gas at 150°C. The sample solutions were introduced continuously via a syringe pump with a flow rate of 120 µL h⁻¹.

Experimental Section:

Diselenide **1a**, **1b** and the isonitrile **5a** were synthesized as reported in the literature.¹

Table S1. Selenopeptides directly synthesized by Ugi-4CR with ammonium carbonate as ammonia source in trifluorethanol

Aldehydes	Acids	Isocyanides
$\text{R}-\text{Se}-\text{CH}_2-\text{CHO}$		
R =		
Me	3a BOC-Gly-OH	4a $\text{BnO}_2\text{C}(\text{H}_2\text{C})_5-\text{N}^{\oplus}\equiv\text{C}^{\ominus}$ 5a
2-Nitrobenzyl (NBn)	3b Fmoc-Ser-OH	4b
4-Methoxy benzyl (PMB)	3c BOC-Phe-OH	$\text{c-Hex}-\text{N}^{\oplus}\equiv\text{C}^{\ominus}$ 5b
Allyl	3d BOC-Phg-OH	4d
Benzyl (Bn)	3e BOC-Gly-Gly-Gly-OH	$t\text{-Bu}-\text{N}^{\oplus}\equiv\text{C}^{\ominus}$ 5c
Phenyl (Ph)	3f	

<p>from 3a, 4a, 5a 25% yield</p> <p>6</p>	<p>from 3b, 4a, 5b 85% yield</p> <p>7</p>
<p>from 3b, 4c, 5b 62% yield</p> <p>8</p>	<p>from 3b, 4e, 5b 61% yield</p> <p>9</p>
<p>from 3b, 4d, 5b 58% yield</p> <p>10</p>	<p>from 3d, 4a, 5b 62% yield</p> <p>11</p>
<p>from 3c, 4a, 5c 60% yield</p> <p>12</p>	<p>from 3a, 4b, 5a 49% yield</p> <p>13</p>
<p>from 3a, 4c, 5b 40% yield</p> <p>14</p>	<p>from 3e, 4a, 5b 35% yield</p> <p>15</p>

General procedure for selenoaldehyde synthesis, 3a–3e: A diselenide **1a** or **1b** (15 mmol) was dissolved in 100 ml ethanol at 0°C. To the solution NaBH₄ (40 mmol) was slowly added in portions (30 min) until the solution turns clear or slightly yellow. The reaction mixture was warmed to 25°C for 30 min and then cooled to 0°C. Then alkylhalide (28 mmol) was added and reaction mixture was stirred at room temperature for 2 h. Afterwards, the solution was filtered, the solvent was evaporated, intermediate (**2a–2e**) was dissolved in water and extracted with diethylether. The organic layer was dried over Na₂SO₄ and then the solvent was evaporated. The residue is chromatographed on silica gel (petrol ether : ethyl acetate = 10 : 1). To the obtained acetal 1M HCOOH (40 mL) was added and heated to 40–50°C for 4 h. After cooling to room temperature product was extracted with ether and concentrated at 40°C and 5 mbar for 2 h yielding a yellow oil (**3a–3e**) which was directly used for the further reactions without purification.

General procedure for Ugi-4CR, 6–15: To TFE (4–5 mL) at 0°C (ice-water cooling bath) selenenylaldehyde (1.5 mmol) and (NH₄)₂CO₃ (1.2 mmol) are added and stirred for 10 min. Then, amino acid (1 mmol) and isonitrile (1.5 mmol) are added and the reaction mixture is stirred for 1 h and then at room temperature for 8 h. The solvent is removed in vacuum and the gummy product is purified by column chromatography on silica.

6: Eluent dichloromethane : methanol : triethylamine (20 : 1 : 0.1). R_f = 0.35. ¹H NMR (CDCl₃, 300 MHz): 7.38–7.31 (m, 5H), 7.22–7.17 (m, 1H), 6.97 (br s, 1H), 5.51–5.47 (m, 1H), 5.10 (s, 2H), 4.67–4.60 (m, 1H), 3.81–3.79 (m, 2H), 3.31–3.02 (m, 3H), 2.84–2.77 (m, 1H), 2.39–2.77 (m, 1H), 2.39–2.34 (m, 2H), 2.01 (s, 3H), 1.70–1.30 (m, 15H) ppm. ¹³C NMR (CDCl₃, 75.5 MHz): 173.2 (s), 169.7 (s), 156.2 (s), 135.7 (s), 128.4 (d, 2C), 128.0 (d), 127.9 (d, 2C), 80.5 (s), 66.1 (t), 52.4 (d), 44.5 (t), 39.5 (t), 34.1 (t), 28.9 (t), 28.3 (q, 3C), 27.1 (t), 26.3 (t), 24.4 (t), 5.2 (q) ppm. HRMS (ESI): Exact mass calculated for C₂₄H₃₇N₃O₆SeNa⁺: 566.1740. Found: 566.1736.

7: Eluent dichloromethane : methanol (20 : 1). R_f = 0.40. ¹H NMR (CDCl₃, 300 MHz): 8.07–8.03 (m, 1H), 7.60–7.48 (m, 2H), 7.44–7.37 (m, 1H), 7.22–7.17 (m, 1H), 6.75–6.68 (m, 1H), 5.50–5.43 (m, 1H), 4.68–4.58 (m, 1H), 4.22–4.02 (m, 2H), 3.84–3.65 (m, 2H), 3.13–3.04 (m, 1H), 2.78–2.70 (m, 1H), 1.93–1.54 (m, 5H), 1.46 (s, 9H), 1.41–1.10 (m, 6H) ppm. ¹³C NMR (CDCl₃, 75.5 MHz): 169.1 (s), 168.6 (s), 156.1 (s), 147.4 (s), 135.5 (s), 133.4 (d), 132.0 (d), 128.0 (d), 125.6 (d), 80.4 (s), 52.5 (d), 48.8 (d), 44.5 (t), 32.7 (t, 2C), 28.3 (q, 3C), 26.1 (t),

25.4 (t), 24.8 (t, 3C) ppm. HRMS (ESI): Exact mass calculated for $C_{23}H_{34}N_4O_6SeNa^+$: 565.1536. Found: 565.1533.

8: Eluent petrol ether : ethyl acetate (7 : 3). $R_f = 0.15$. 1H NMR (CD_3OD , 300 MHz): 8.03–7.99 (m, 1H), 7.62–7.41 (m, 3H), 7.28–7.17 (m, 5H), 4.53–4.47 (m, 1H), 4.31–4.26 (m, 1H), 4.12 (br s, 2H), 3.62–3.56 (m, 1H), 3.32–3.29 (m, 1H), 3.13–2.98 (m, 1H), 2.89–2.74 (m, 2H), 1.87–1.57 (m, 5H), 1.43–1.12 (m, 14H) ppm. ^{13}C NMR (CD_3OD , 75.5 MHz): 173.8 (s), 170.8 (s), 157.3 (s), 149.1 (s), 138.3 (s), 137.0 (s), 134.4 (d), 133.1 (d), 130.2 (d), 129.4 (d), 129.3 (d, 2C), 129.1 (d), 127.6 (d), 126.5 (d) 80.8 (s), 57.6 (d), 54.6 (d), 50.1 (d), 38.9 (t), 33.6 (t, 2C), 28.7 (q, 3C), 26.6 (t), 26.3 (t), 26.1 (t, 2C), 25.2 (t) ppm. HRMS (ESI): Exact mass calculated for $C_{30}H_{40}N_4O_6SeNa^+$: 655.2005. Found: 655.1993.

9: Eluent dichloromethane : methanol (20 : 1). $R_f = 0.35$. 1H NMR ($CDCl_3$, 300 MHz): 7.95 (d, $J = 10$ Hz, 1H), 7.50–7.40 (m, 1H), 7.38–7.27 (m, 2H), 5.30 (s, 1H), 5.15 (br s, 1H), 4.51 (q, 2H), 4.41–4.14 (m, 4H), 3.85–3.83 ('d', 2H), 3.75 (s, 1H), 2.92 (s, 2H), 2.13 (s, 1H), 1.93–1.65 (m, 5H), 1.44 (s, 9H), 1.28–1.21 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): 173.1 (s), 172.1 (s), 171.0 (s), 170.9 (s), 158.3 (s), 148.9 (d), 136.7 (s), 134.3 (d), 133.0 (d), 129.0 (d), 126.4 (d), 80.8 (s), 54.8 (d), 50.0 (d), 44.8 (t), 43.8 (t), 43.5 (t), 33.5 (t), 33.4 (t) 28.7 (q, 3C), 26.5 (t), 26.3 (t), 24.0 (t, 2C), 25.2 (t) ppm. HRMS (ESI): Exact mass calculated for $C_{27}H_{40}N_6O_8SeNa^+$: 679.1965. Found: 679.1950.

10: Eluent petrol ether : ethyl acetate (7 : 3). $R_f = 0.35$. 1H NMR ($CDCl_3$, 300 MHz): 8.06–7.98 (m, 1H), 7.55–7.26 (m, 9H), 6.80–6.46 (m, 1H), 5.93–5.68 (m, 1H), 4.70–4.58 (m, 1H), 4.21–3.94 (m, 2H), 3.76–3.57 (m, 1H), 2.84–2.59 (m, 1H), 1.88–1.55 (m, 5H), 1.43 (s, 9H), 1.35–0.99 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): 169.8 (s), 168.5 (s), 155.2 (s), 147.3 (s), 135.4 (s), 133.4 (s), 133.4 (d), 132.0 (d), 128.9 (d, 2C), 128.7 (d), 127.9 (d), 127.0 (d), 126.9 (d), 125.5 (d) 80.4 (s), 59.3 (d), 52.6 (d), 48.6 (d), 32.7 (t), 32.6 (t) 32.5 (t), 28.3 (q, 3C), 25.9 (t), 25.4 (t), 24.7 (t, 2C), 24.6 (t) ppm. HRMS (ESI): Exact mass calculated for $C_{29}H_{38}N_4O_6SeNa^+$: 641.1849. Found: 641.1843.

11: Eluent dichloromethane : methanol (5 : 0.1). $R_f = 0.10$. 1H NMR (pyridine- d_5 , 300 MHz): 9.18–9.14 (m, 1H), 8.63–8.52 (m, 1H), 8.15–8.10 (m, 1H), 5.95–5.80 (m, 1H), 5.33–4.90 (m, 4H), 4.28–3.93 (m, 3H), 3.28–3.05 (m, 4H), 2.10–1.89 (m, 2H), 1.69–1.10 (m, 16H) ppm. ^{13}C NMR (pyridine- d_5 , 75.5 MHz): 170.1 (s), 170.0 (s), 157.0 (s), 135.2 (t), 116.6 (d), 78.9 (s),

53.9 (d), 49.0 (d), 33.4 (t), 33.2 (t), 28.6 (q, 3C), 25.9 (t), 25.7 (t), 25.5 (t, 2C) ppm. HRMS (ESI): Exact mass calculated for $C_{19}H_{33}N_3O_4SeNa^+$: 470.1528. Found: 470.1525.

12: Eluent petrol ether : ethyl acetate (6 : 4). $R_f = 0.55$. 1H NMR ($CDCl_3$, 300 MHz): 7.27–7.19 (m, 3H), 6.84–6.79 (m, 2H), 6.50 (br s, 1H), 5.60 (br s, 1H), 4.60–4.48 (m, 1H), 3.80–3.71 (br s 6H), 2.98–2.65 (m, 3H), 1.43 (s, 9H) 1.32 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): 169.1 (s), 169.0 (s, 2C), 158.1 (s), 130.8 (s), 129.8 (d, 2C), 113.7 (d, 2C), 79.9 (s), 55.1 (d), 53.0 (d), 51.5 (s), 44.2 (t), 28.5 (q, 3C), 28.2 (q, 3C), 25.7 (t) ppm. HRMS (ESI): Exact mass calculated for $C_{22}H_{35}N_3O_5SeNa^+$: 524.1634. Found: 524.1631.

13: Eluent dichloromethane : methanol (20 : 1). $R_f = 0.30$. 1H NMR ($CDCl_3$, 300 MHz): 7.75–7.22 (m, 14H), 7.16–7.11 (m, 1H), 6.49–6.29 (m, 1H), 5.10–5.06 (m, 2H), 4.73–4.62 (m, 1H), 4.45–4.31 (m, 3H), 4.20–4.13 (m, 1H), 4.05–3.94 (m, 1H), 3.84–3.67 (m, 1H), 3.29–3.05 (m, 2H), 3.02–2.81 (m, 2H), 2.38–2.25 (m, 2H), 2.08–1.96 (m, 1H), 1.93 (s, 3H), 1.69–1.20 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): 173.3 (s), 170.7 (s), 170.1 (s), 156.3 (s), 143.4 (s), 140.9 (s, 3C), 135.6 (s), 128.3 (d, 3C), 128.0 (d), 127.9 (d, 2C), 127.5 (d, 2C), 126.8 (d, 2C), 124.8 (d), 119.7 (d, 2C), 67.3 (t), 66.1 (t), 62.8 (t), 56.3 (d), 52.2 (d), 46.9 (d), 39.5 (t) 33.9 (t), 28.7 (t), 26.9 (t), 22.2 (t), 24.3 (t), 5.1 (q) ppm. HRMS (ESI): Exact mass calculated for $C_{35}H_{41}N_3O_7SeNa^+$: 718.2002. Found: 718.2000.

14: Eluent petrol ether : ethyl acetate (7 : 3). $R_f = 0.50$. 1H NMR (CD_3OD , 300 MHz): 7.31–7.17 (m, 5H), 4.55–4.47 (m, 1H), 4.36–4.25 (m, 1H), 3.69–3.56 (m, 1H), 3.18–3.03 (m, 1H), 2.93–2.70 (m, 3H), 2.11–1.57 (m, 8H), 1.45–1.14 (m, 14H) ppm. ^{13}C NMR (CD_3OD , 75.5 MHz): 173.6 (s), 171.0 (s), 157.4 (s), 138.2 (s), 130.2 (d, 2C), 129.3 (d, 2C), 127.6 (d), 80.6 (s), 57.8 (d), 54.3 (d), 50.0 (d), 38.9 (t), 33.6 (t, 2C), 28.8 (q, 3C), 27.4 (t), 26.6 (t), 26.0 (t, 2C), 4.8 (q) ppm. MS (ESI) calcd for $C_{24}H_{37}N_3O_4Se$: 511.19; found $[M+H]^+$: 512.5. HRMS (ESI): Exact mass calculated for $C_{24}H_{37}N_3O_4SeNa^+$: 534.1841. Found: 534.1834.

15: Eluent petrol ether : ethyl acetate (6 : 4). $R_f = 0.25$. 1H NMR (CD_3OD , 300 MHz): 7.52–7.14 (m, 5H), 4.60–4.52 (m, 1H), 3.81 (s, 2H), 3.71–3.55 (m, 3H), 2.89–2.70 (m, 1H), 1.89–1.54 (m, 5H), 1.44 (s, 9H), 1.37–1.09 (m, 5H) ppm. ^{13}C NMR (CD_3OD , 75.5 MHz): 171.9 (s), 171.2 (s), 158.2 (s), 140.3 (s), 129.8 (d, 2C), 129.3 (d, 2C), 121.6 (d), 80.7 (s), 54.3 (d), 50.1 (d), 44.8 (t), 33.7 (t), 33.6 (t), 28.8 (q, 3C), 26.2 (t), 26.6 (t), 26.1 (t, 2C), 26.0 (t) ppm. MS

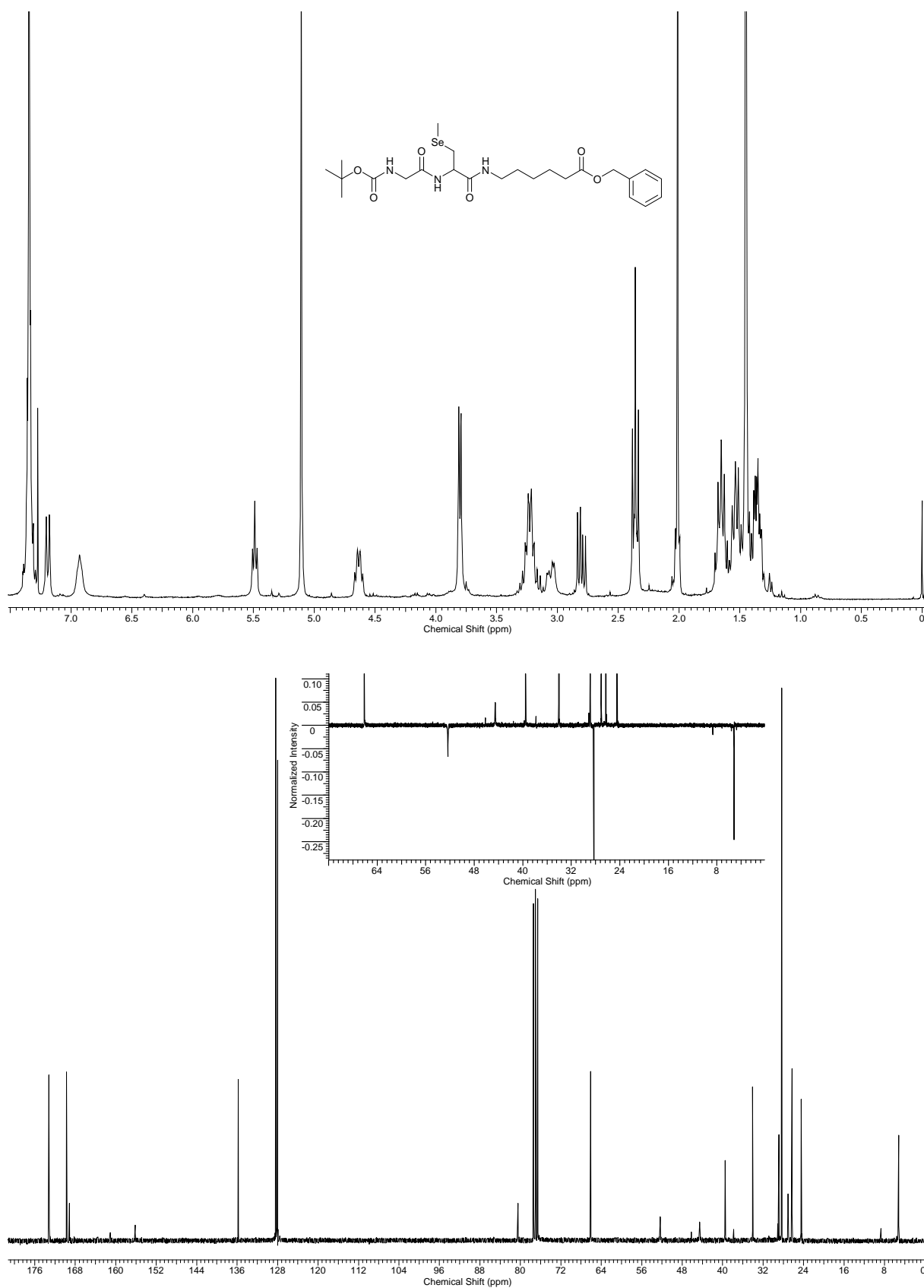
(ESI) calcd. for $C_{23}H_{35}N_3O_4Se$: 497.18; found $[M+H]^+$: 498.6. HRMS (ESI): Exact mass calculated for $C_{23}H_{35}N_3O_4SeNa^+$: 520.1685. Found: 520.1679.

16: Precipitated with dichloromethane and then filtered to give light yellow solid. 1H NMR (pyridine- d_5 , 300 MHz): 10.5 (d, 1H), 9.37 (d, 2H), 8.95–8.71 (m, 2H), 8.63 (d, 2H), 8.02 ('t', 2H), 7.45–7.12 (m, 2H), 4.72–4.51 (m, 1H), 4.62 (d, 4H), 3.97–3.18 (m, 8H), 1.98 (s, 1H) 1.98–1.78 (m, 5H), 1.48 (s, 9H), 1.62–1.21 (m, 6H), 1.20–0.89 (m, 4H) ppm. ^{13}C NMR (pyridine- d_5 , 75.5 MHz): 171.0 (s), 169.8 (s), 156.9 (s), 78.9 (s), 54.6 (d), 49.0 (d), 44.6 (d), 32.9 (t), 32.7 (t), 28.4 (q), 25.6 (t, 3C), 25.2 (t, 3C) ppm. MS (ESI) calcd. for $C_{32}H_{56}N_6O_8Se_2$: 812.25; found $[M+Na]^+$: 833.6. HRMS (ESI): Exact mass calculated for $C_{32}H_{56}N_6O_8Se_2Na^+$: 835.2382. Found: 835.2364.

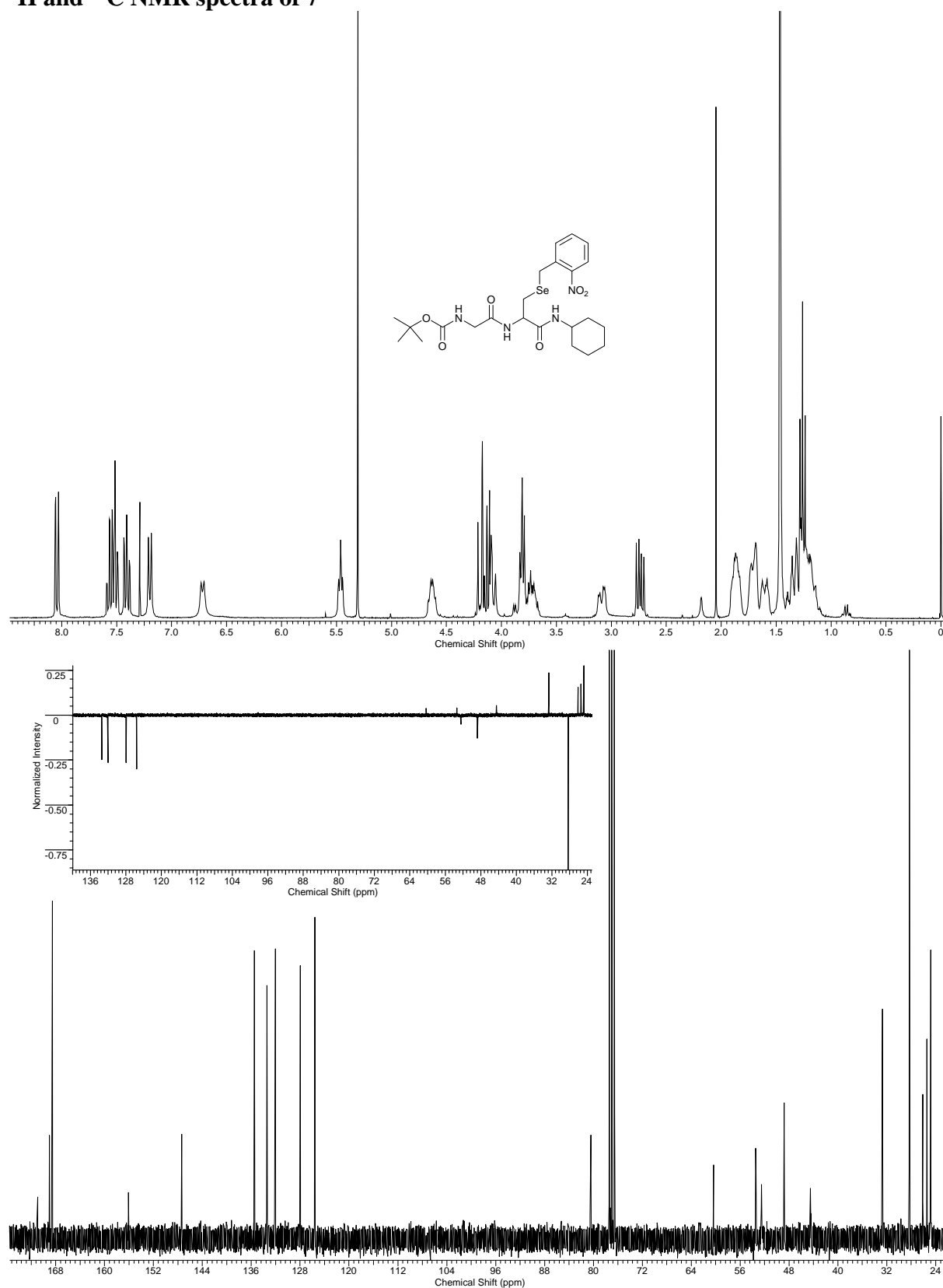
24: Eluent dichloromethane : methanol (5 : 0.1). R_f = 0.30. 1H NMR ($CDCl_3$, 300 MHz): 5.16–5.15 (m, 1H), 5.05–5.00 (m, 1H), 4.89–4.82 (m, 1H), 4.58 (br s, 1H), 3.89–3.69 (m, 2H), 3.61–3.00 (m, 6H), 1.96–1.80 (m, 16H), 1.76–1.54 (m, 8H), 1.47–1.33 (m, 32H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): 171.0 (s), 168.9 (s, 2C), 155.2 (s), 152.1 (s), 138.1 (s), 98.4 (s, 2C), 80.8 (s), 80.2 (s), 74.2 (s), 73.8 (s), 68.9 (d), 66.6 (d), 54.7 (d), 54.1 (d) 49.4 (d), 48.8 (d), 32.8 (t), 32.6 (t, 2C), 32.5 (t, 2C), 32.3 (t), 29.2 (q), 28.8 (q), 28.3 (q, 3C), 28.2 (q, 3C), 28.0 (q), 27.4 (q), 25.4 (t, 3C), 24.8 (t, 3C), 24.6 (t) ppm. MS (ESI) calcd. for $C_{40}H_{68}N_6O_8S_2Se_2$: 984.29; found $[M+H]^+$: 985.3. HRMS (ESI): Exact mass calculated for $C_{40}H_{69}N_6O_8S_2Se_2^+$: 985.2943. Found: 985.2909.

26: Eluent dichloromethane : methanol (5 : 0.1). R_f = 0.40. 1H NMR ($CDCl_3$, 300 MHz): 6.64–6.61 (m, 1H), 4.89–4.86 (m, 1H), 4.49–4.43 (m, 1H), 3.82–3.66 (m, 2H), 3.53–3.43 (m, 2H), 3.17–3.10 (m, 1H), 1.94–1.81 (m, 8H), 1.78–1.12 (m, 9H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): 173.8 (s), 169.1 (s), 167.4 (s), 74.7 (s), 66.5 (d), 57.4 (d), 48.8 (d), 32.8 (t), 28.6 (q), 26.6 (q), 26.8 (t, 2C), 25.4 (t, 2C), 24.7 (t, 2C), ppm. MS (ESI) calcd. for $C_{16}H_{25}N_3O_3SSe$: 419.08; found $[M+H]^+$: 420.2. HRMS (ESI): Exact mass calculated for $C_{16}H_{26}N_3O_3SSe^+$: 420.0855. Found: 420.0852.

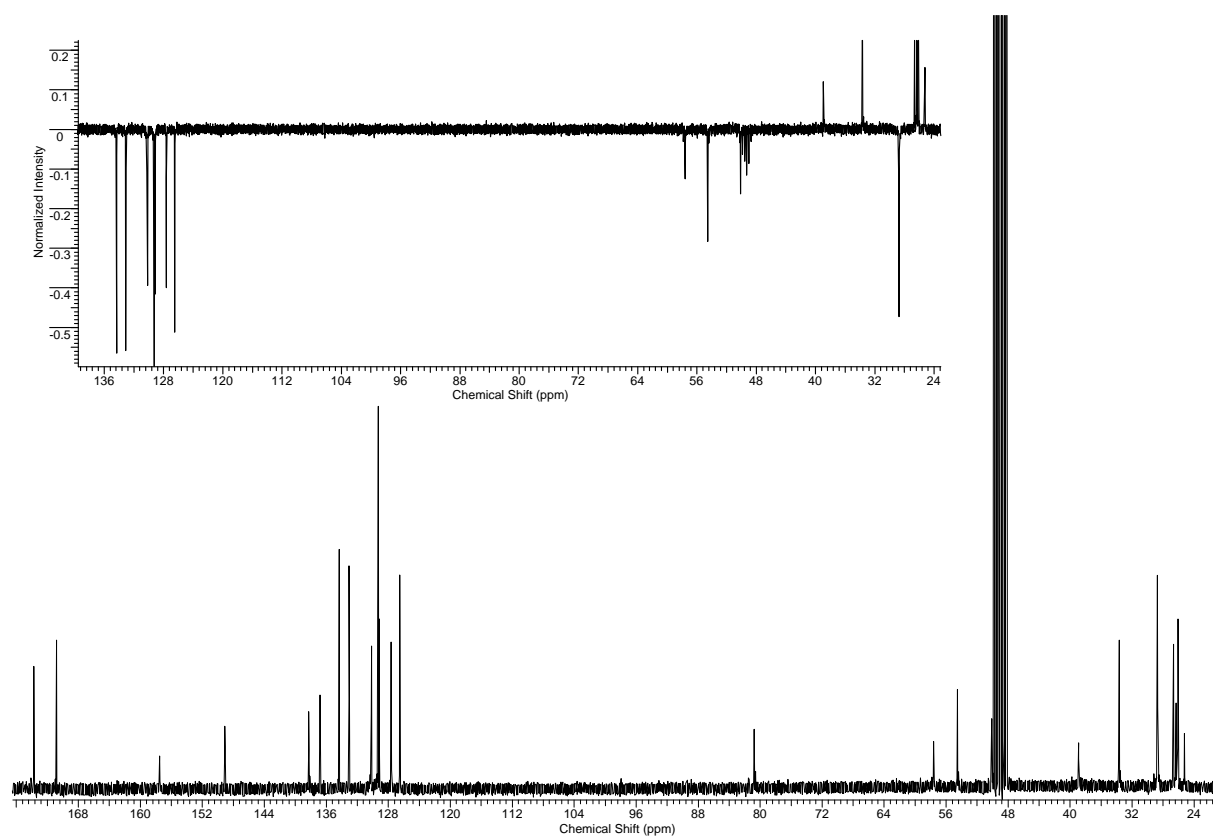
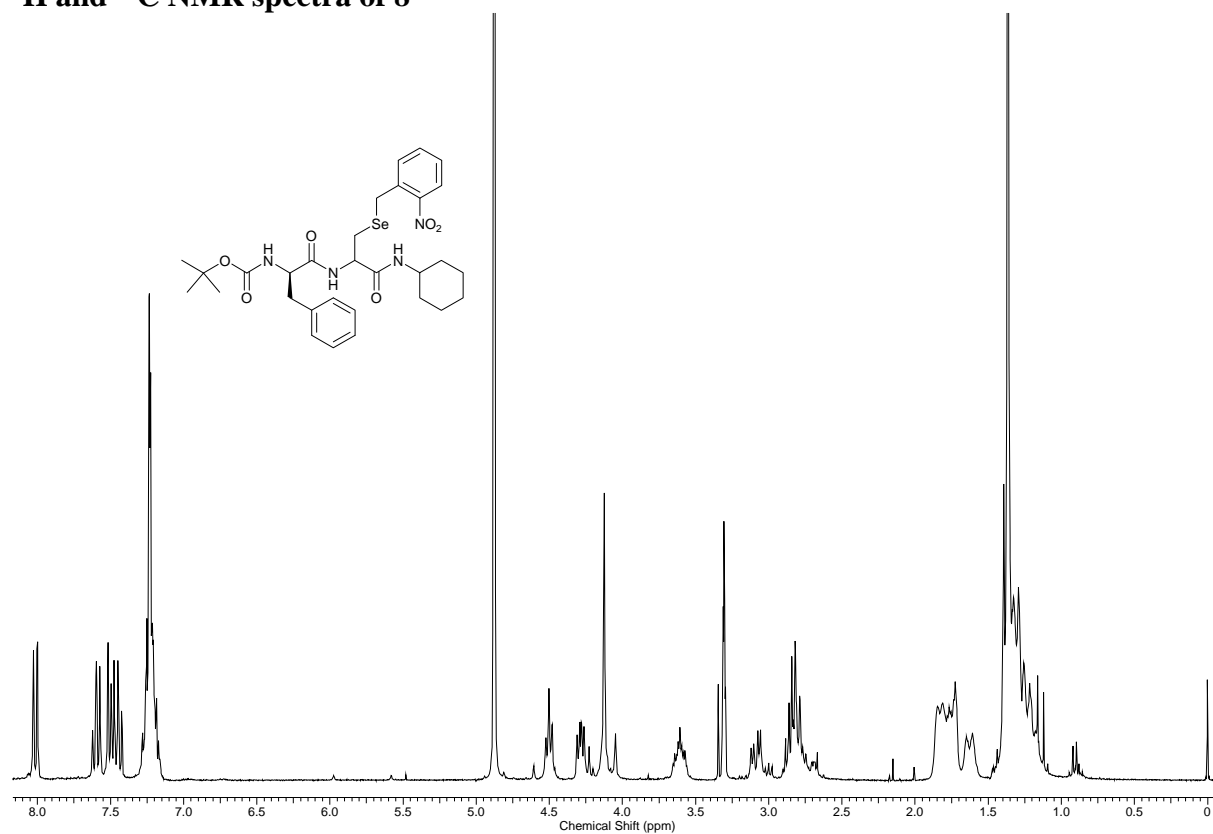
^1H and ^{13}C NMR spectra of **6**



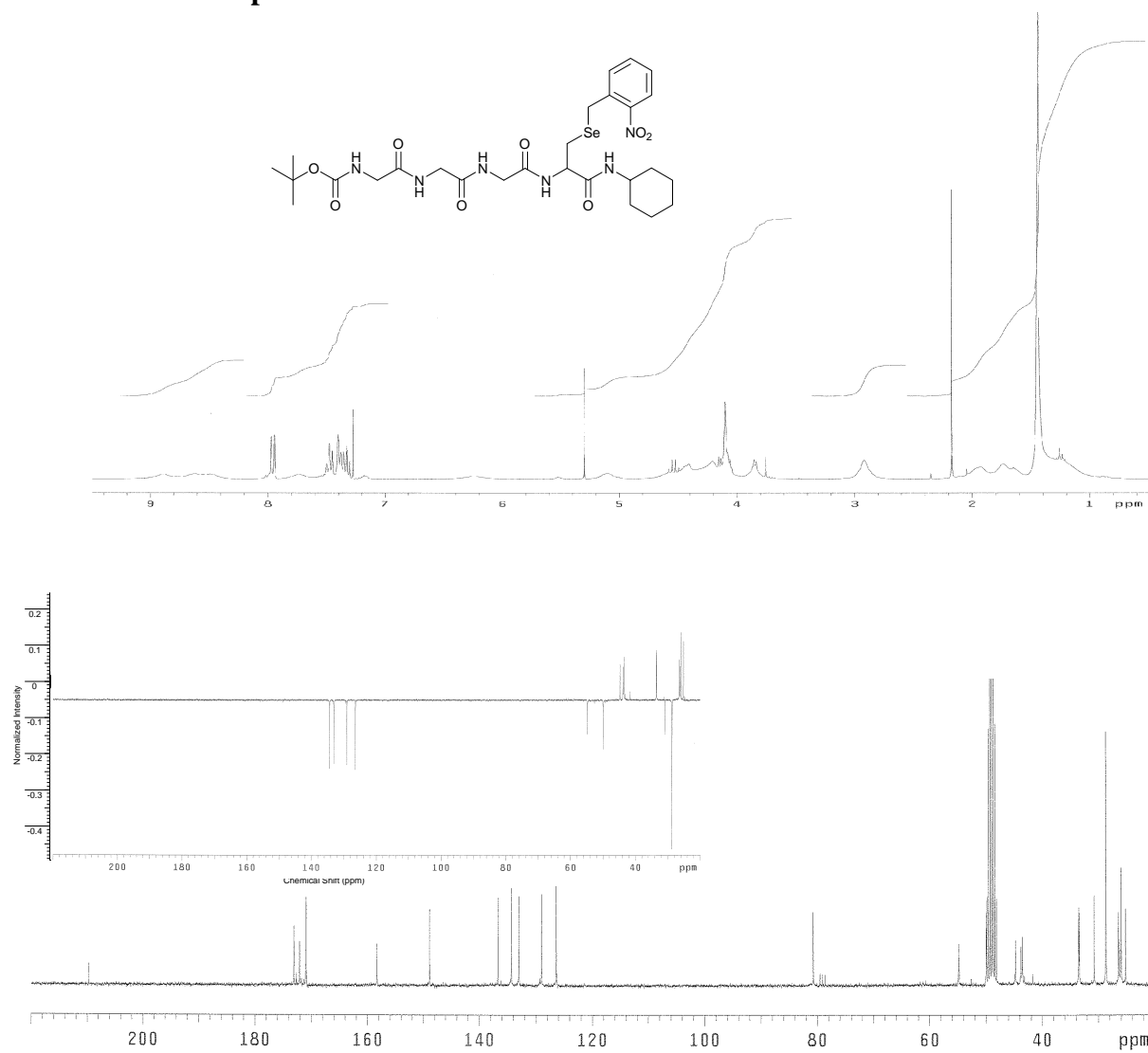
^1H and ^{13}C NMR spectra of **7**



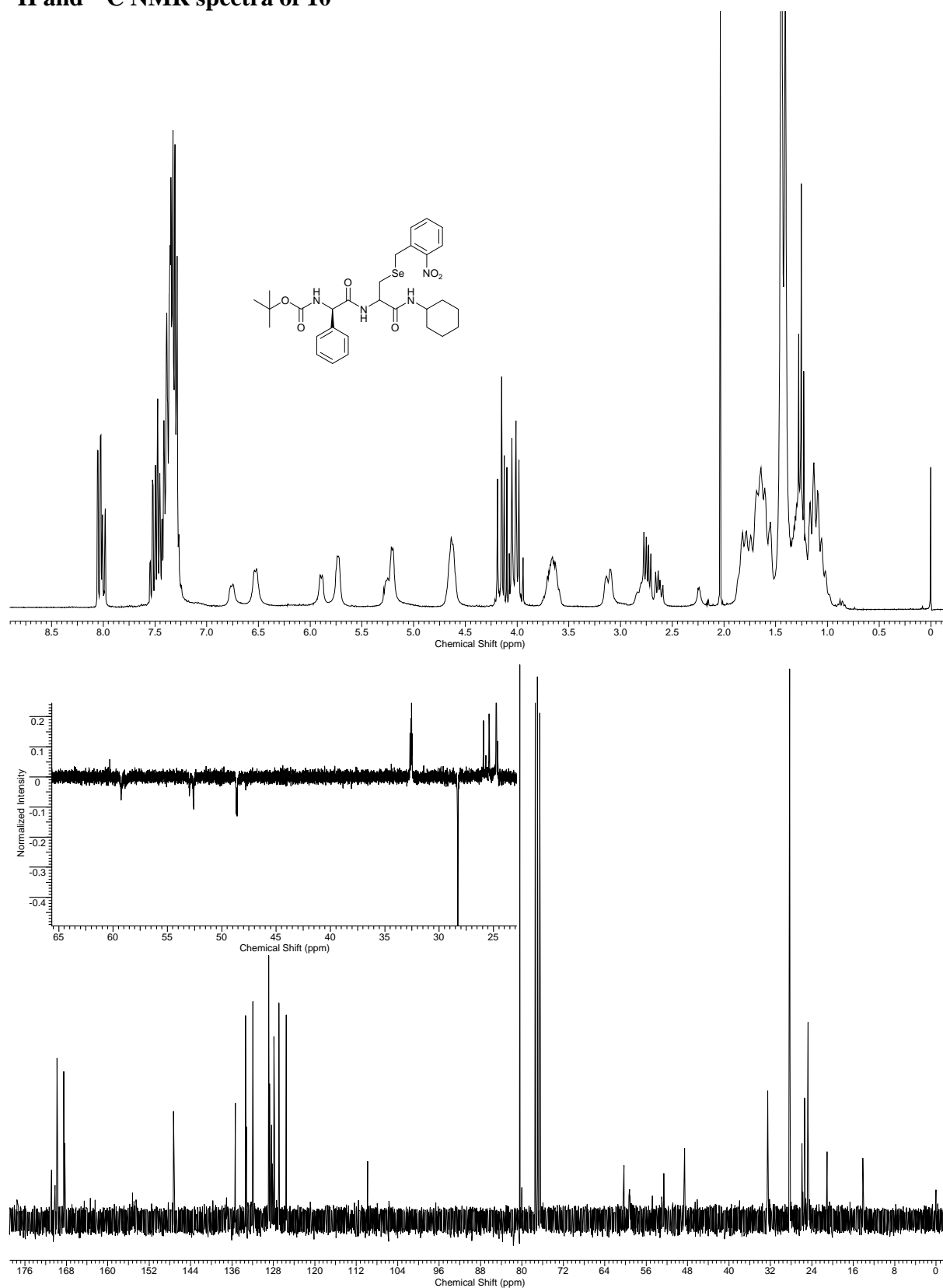
^1H and ^{13}C NMR spectra of **8**



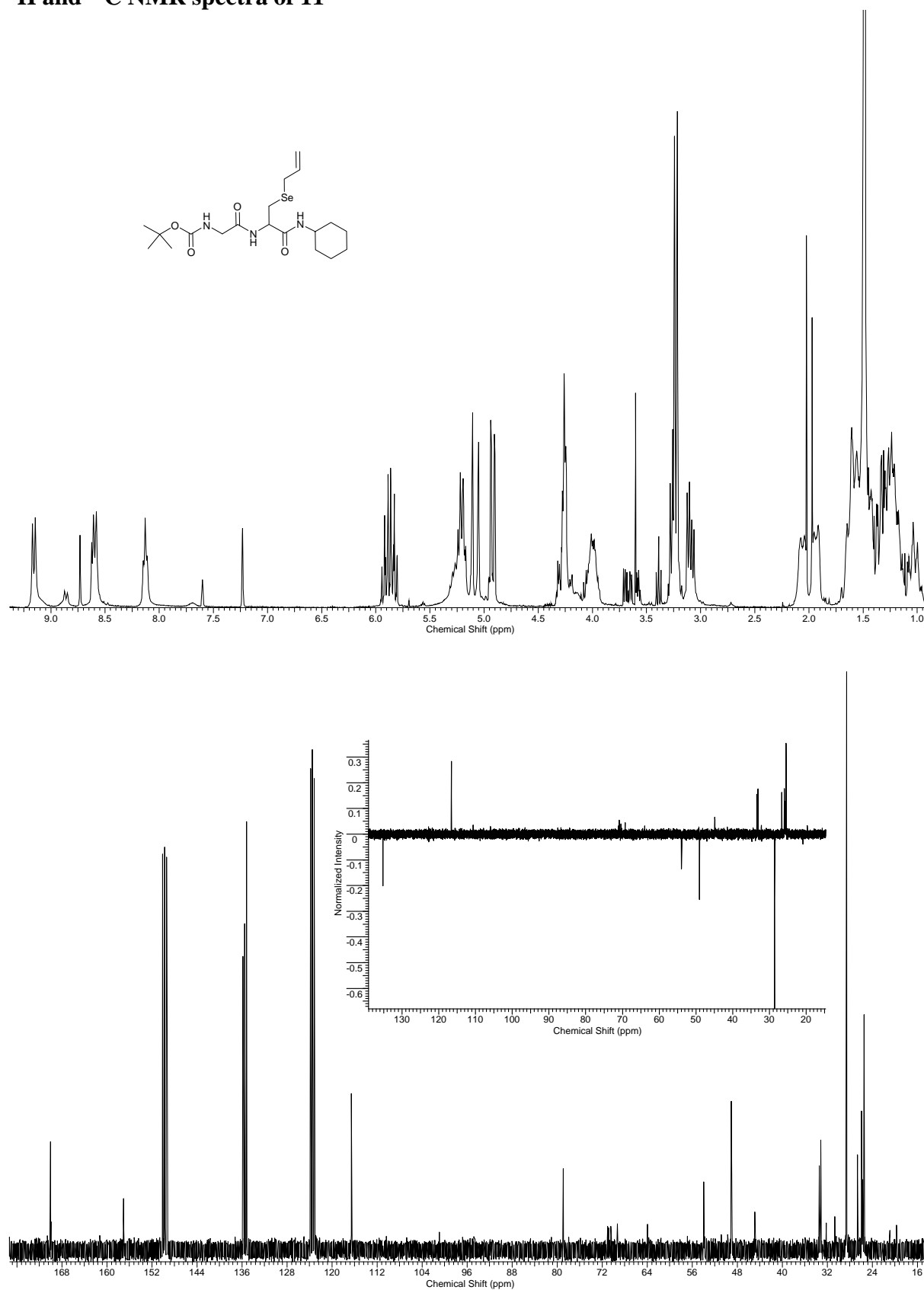
^1H and ^{13}C NMR spectra of **9**



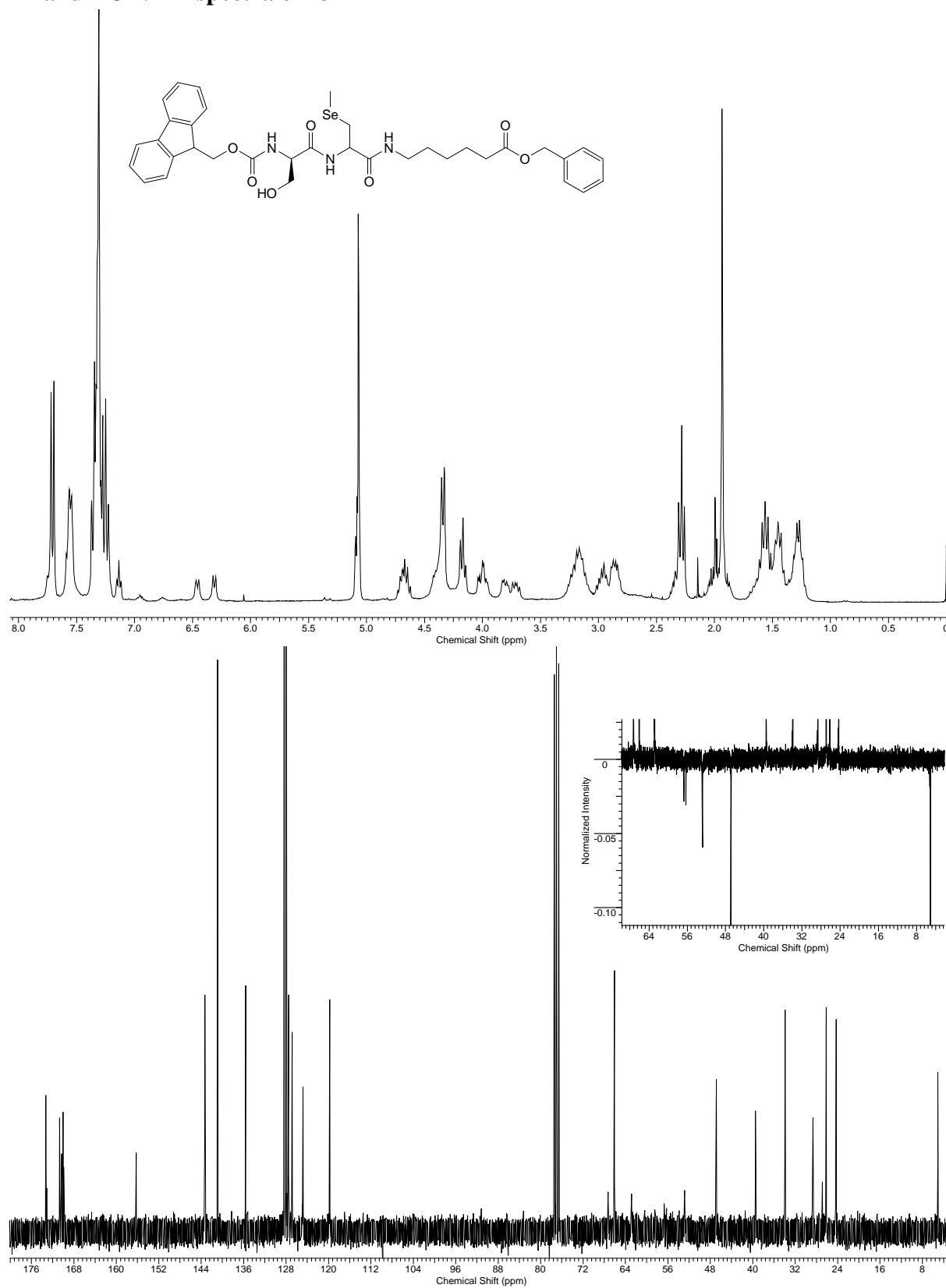
^1H and ^{13}C NMR spectra of 10



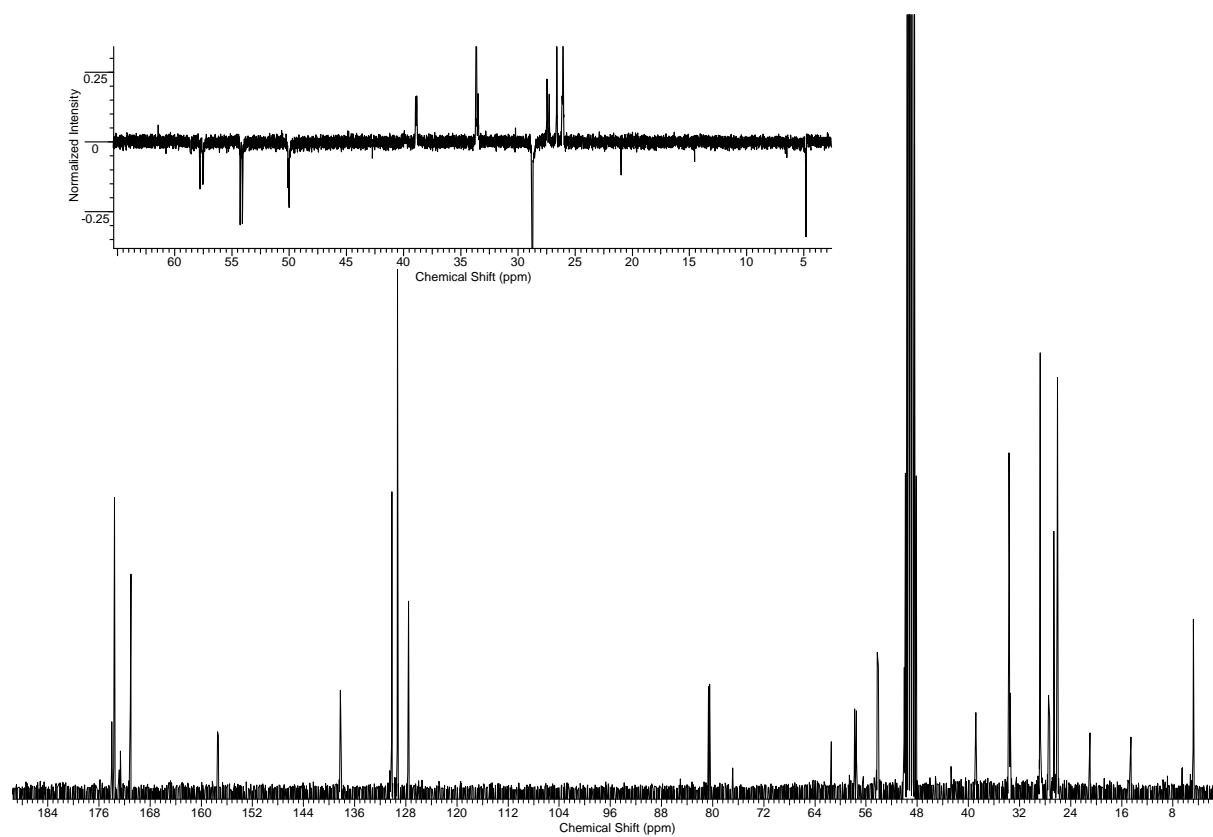
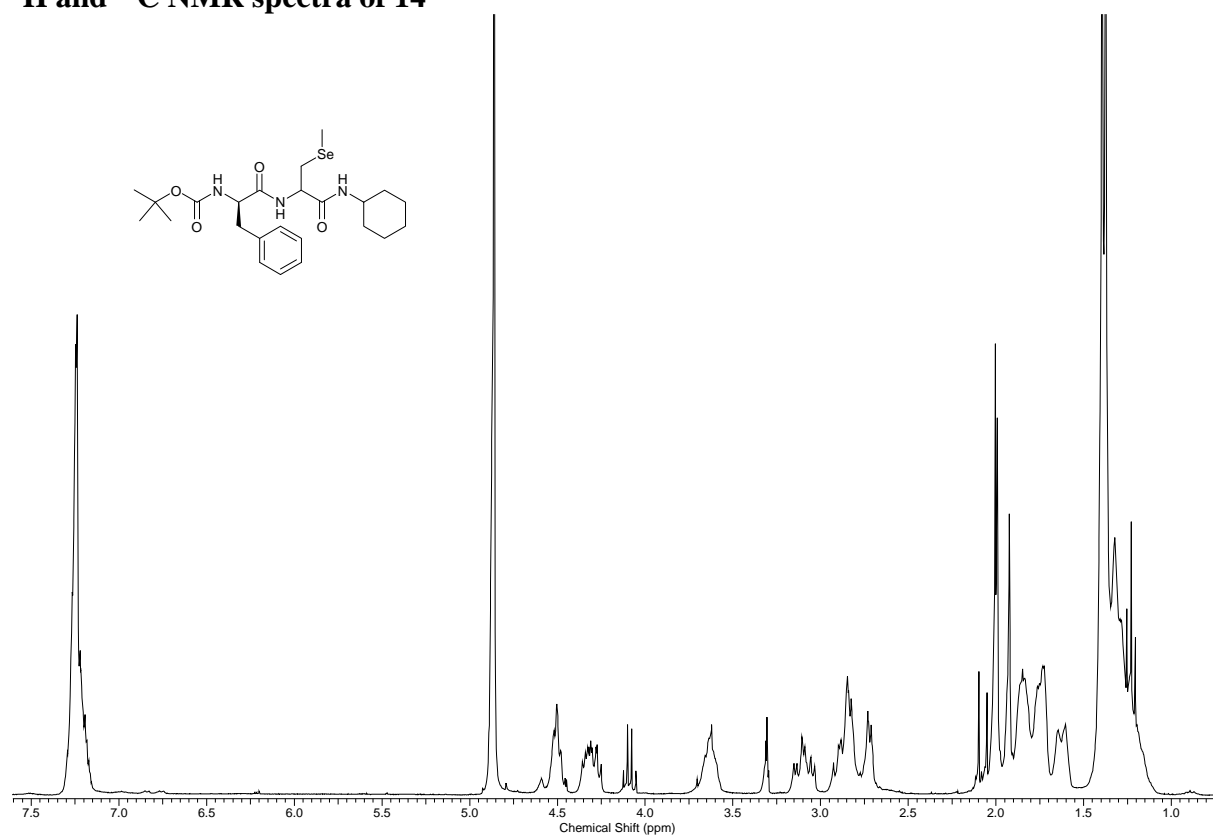
^1H and ^{13}C NMR spectra of 11



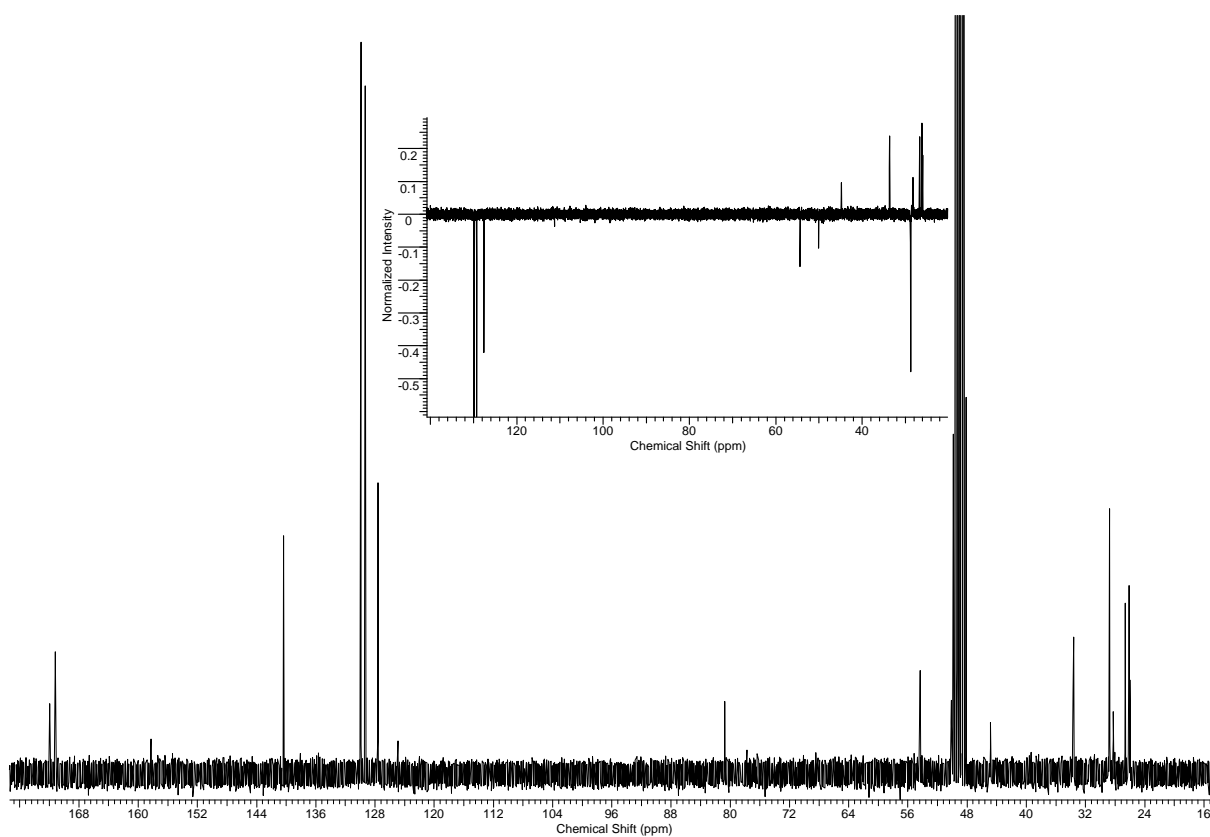
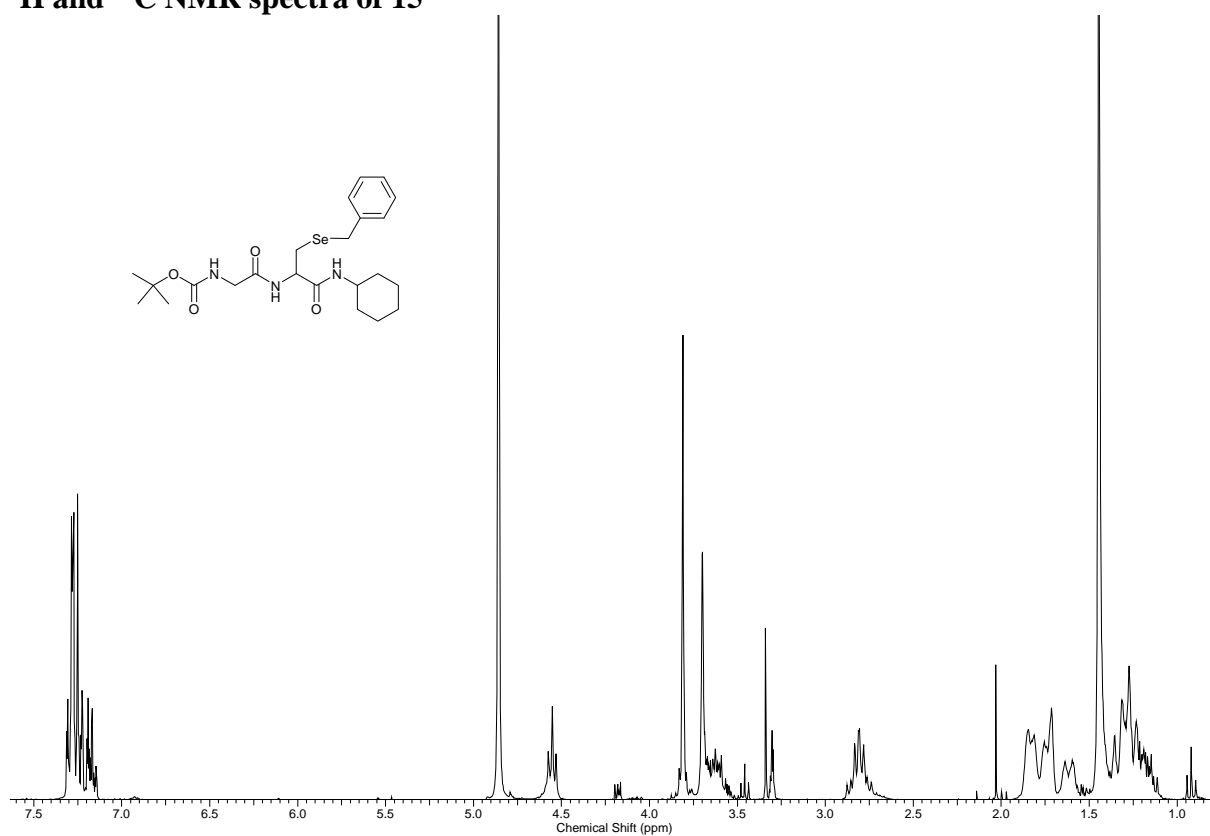
^1H and ^{13}C NMR spectra of 13



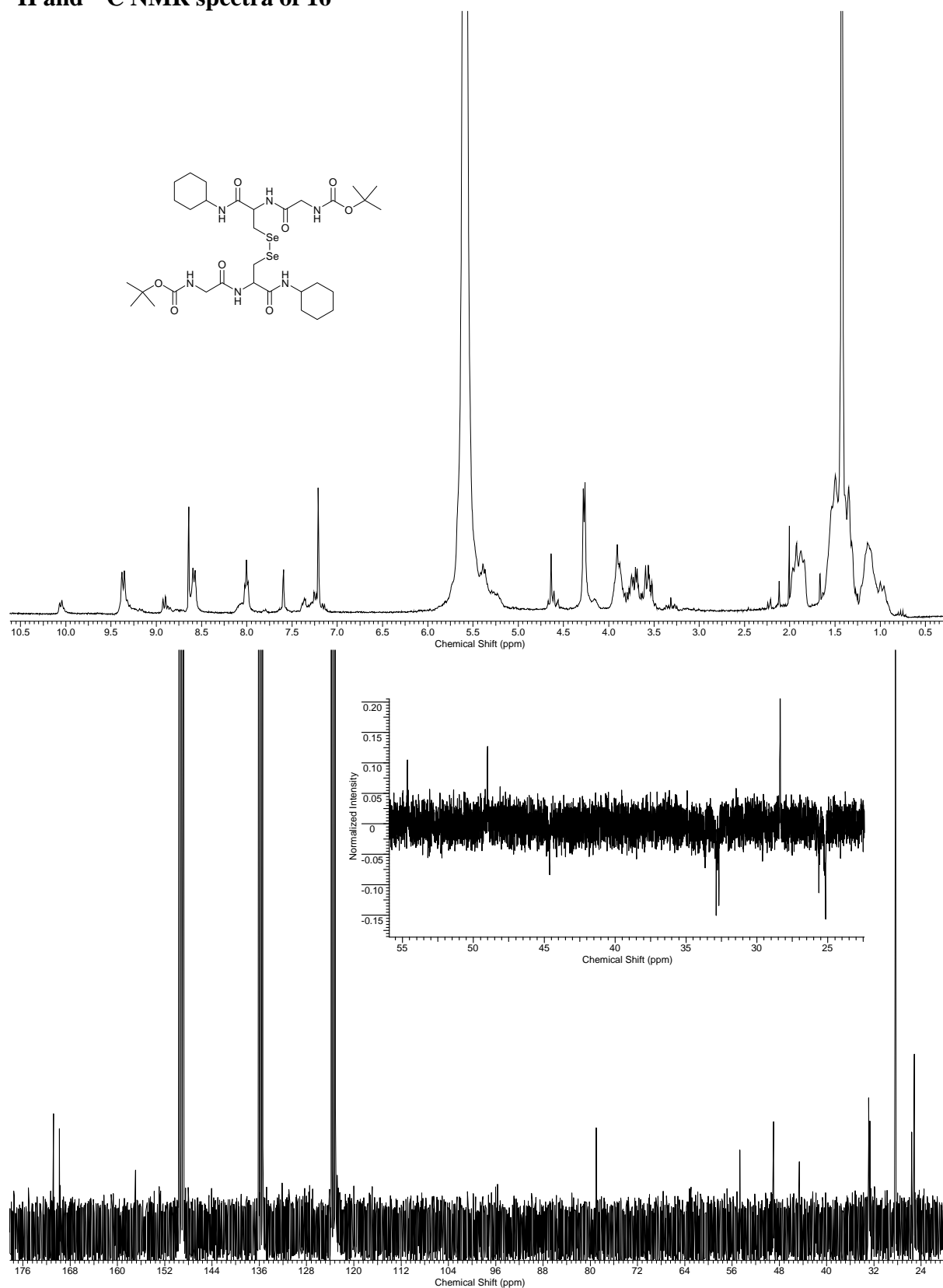
^1H and ^{13}C NMR spectra of 14



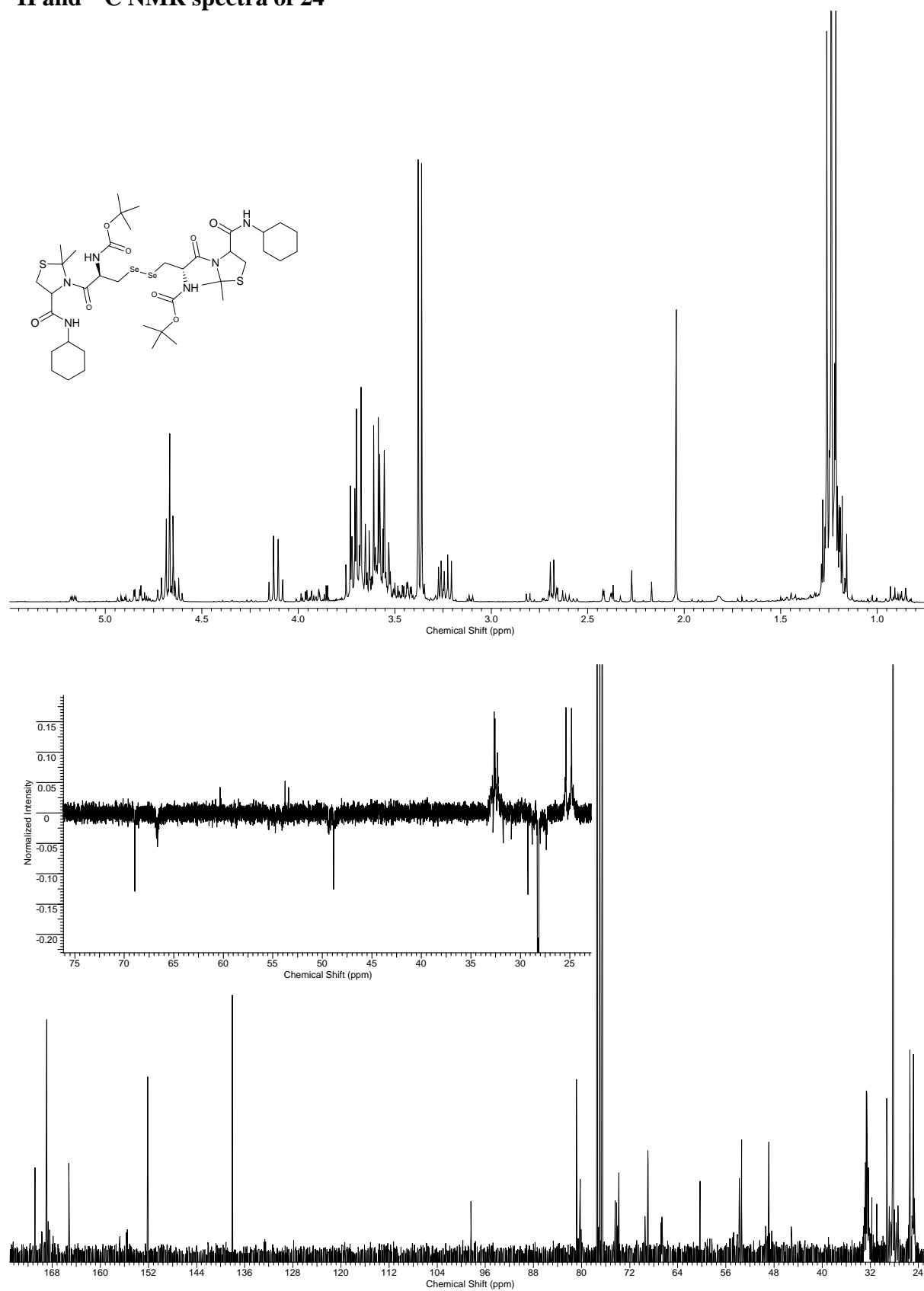
^1H and ^{13}C NMR spectra of 15



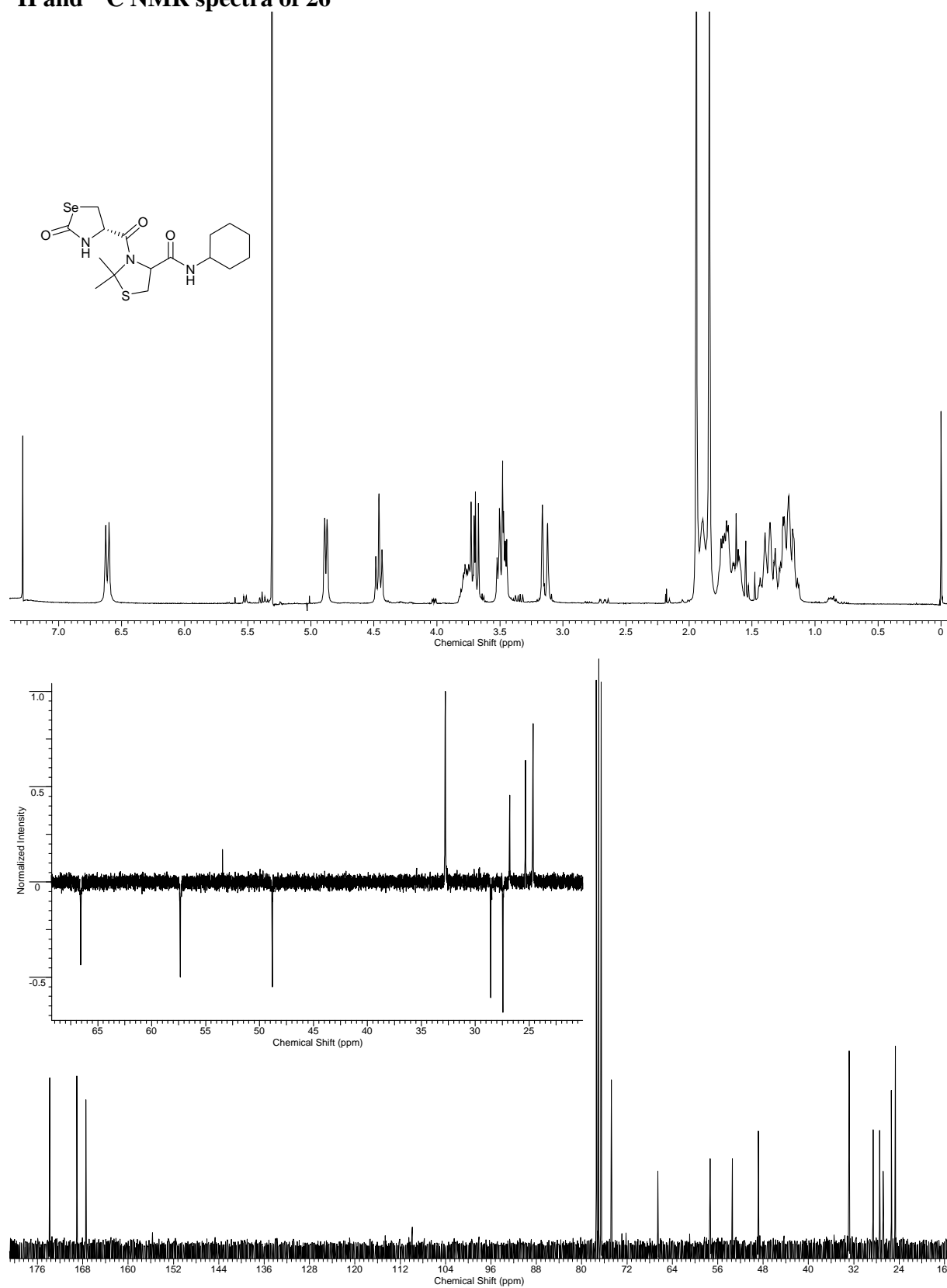
^1H and ^{13}C NMR spectra of 16



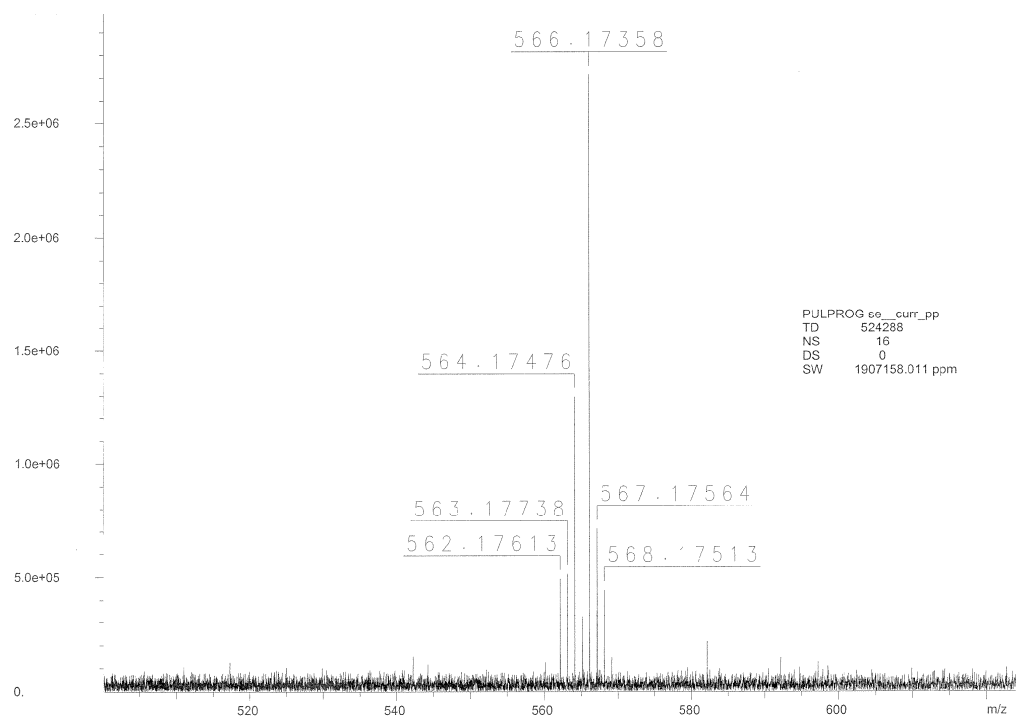
^1H and ^{13}C NMR spectra of 24



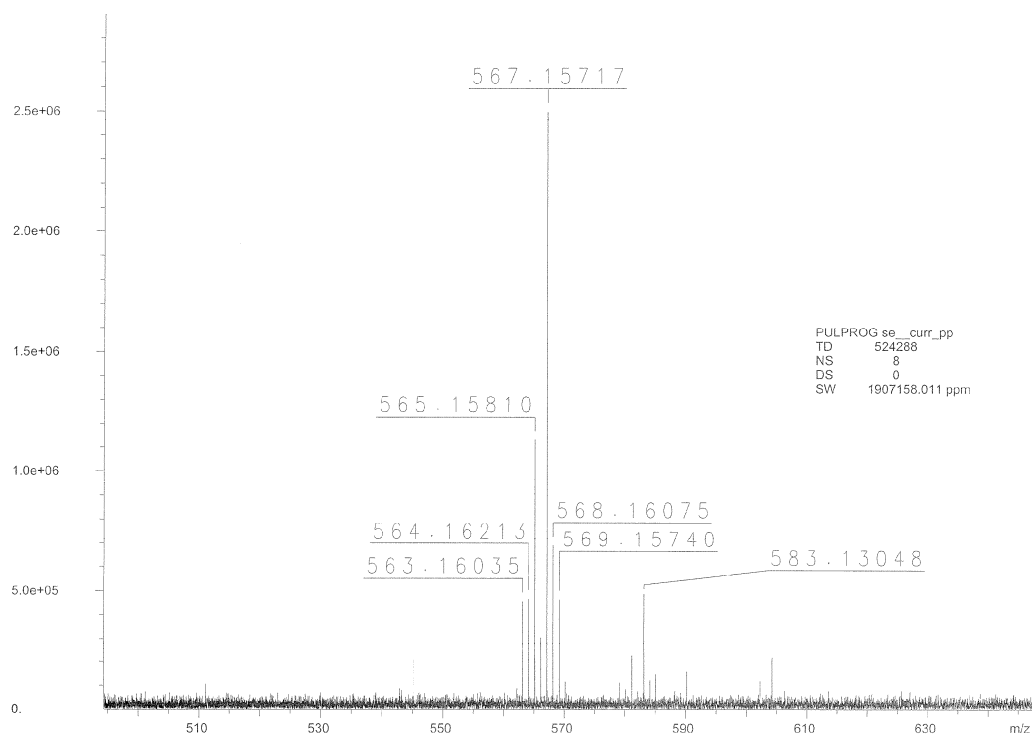
^1H and ^{13}C NMR spectra of 26



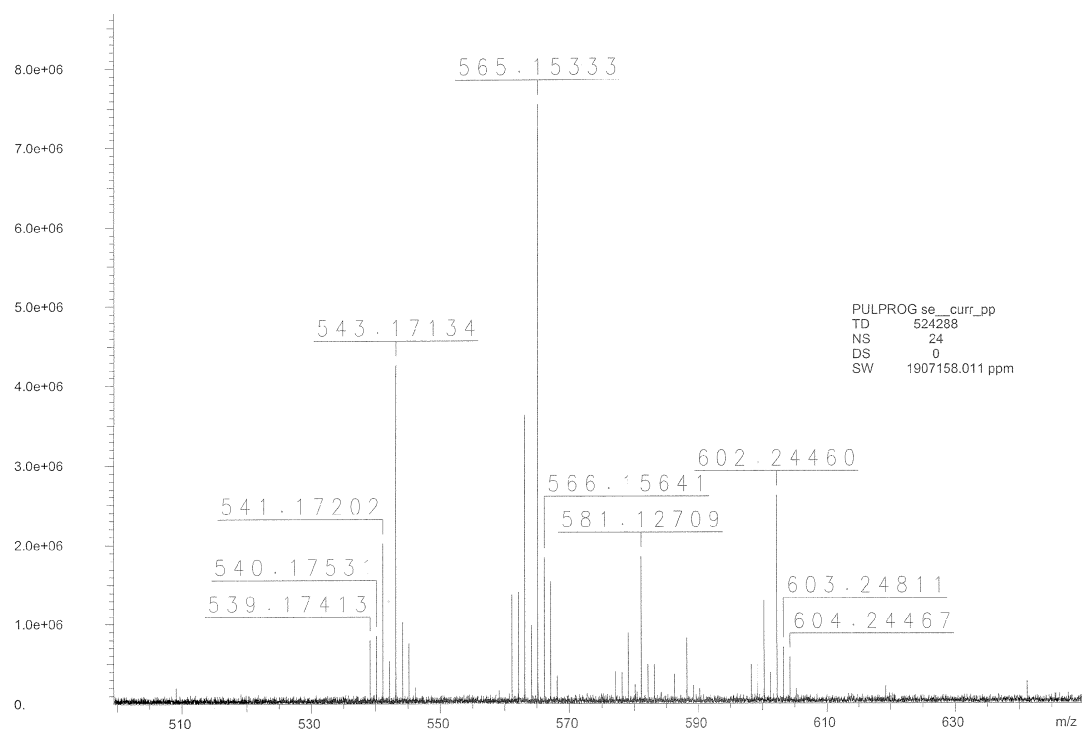
HRMS (ESI) spectrum of 6



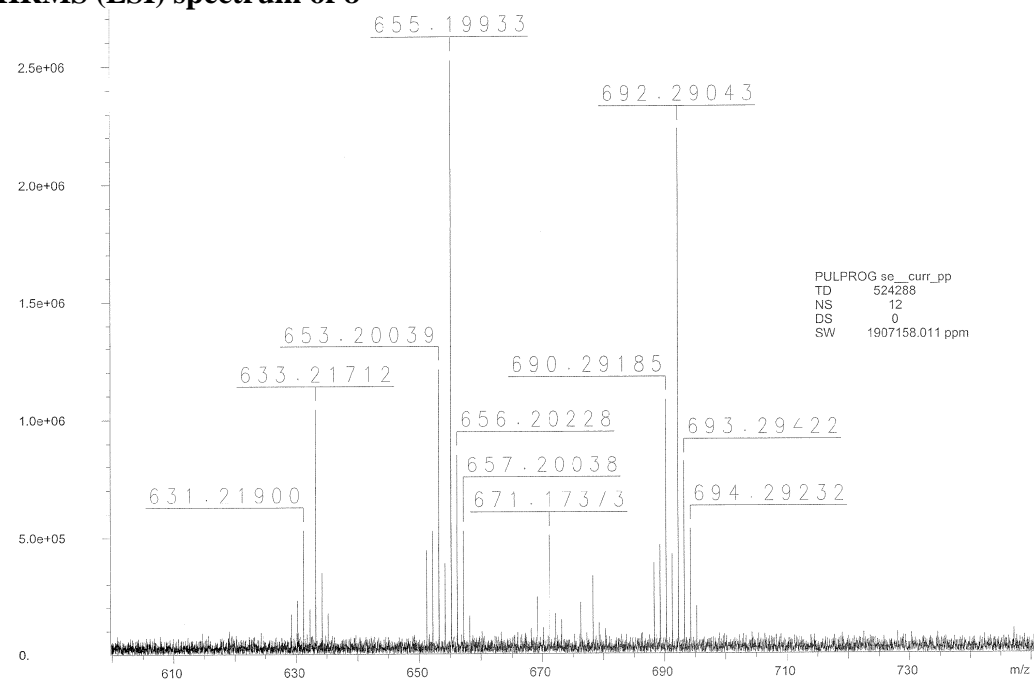
HRMS (ESI) spectrum of 6a



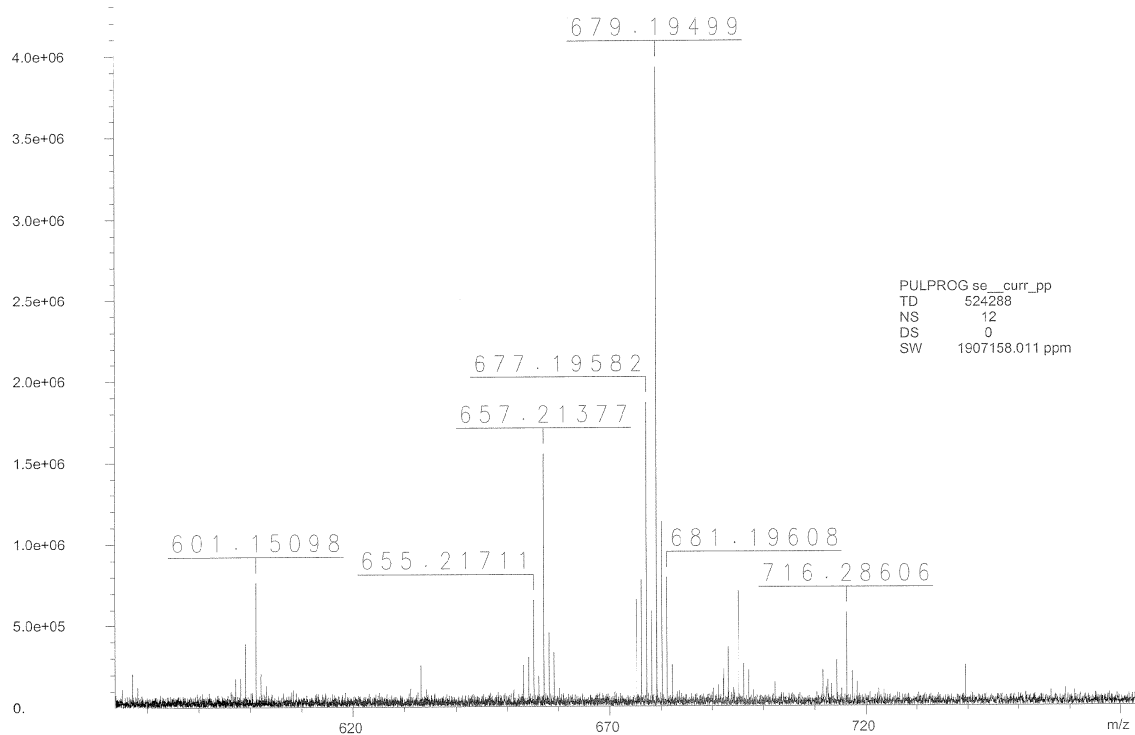
HRMS (ESI) spectrum of 7



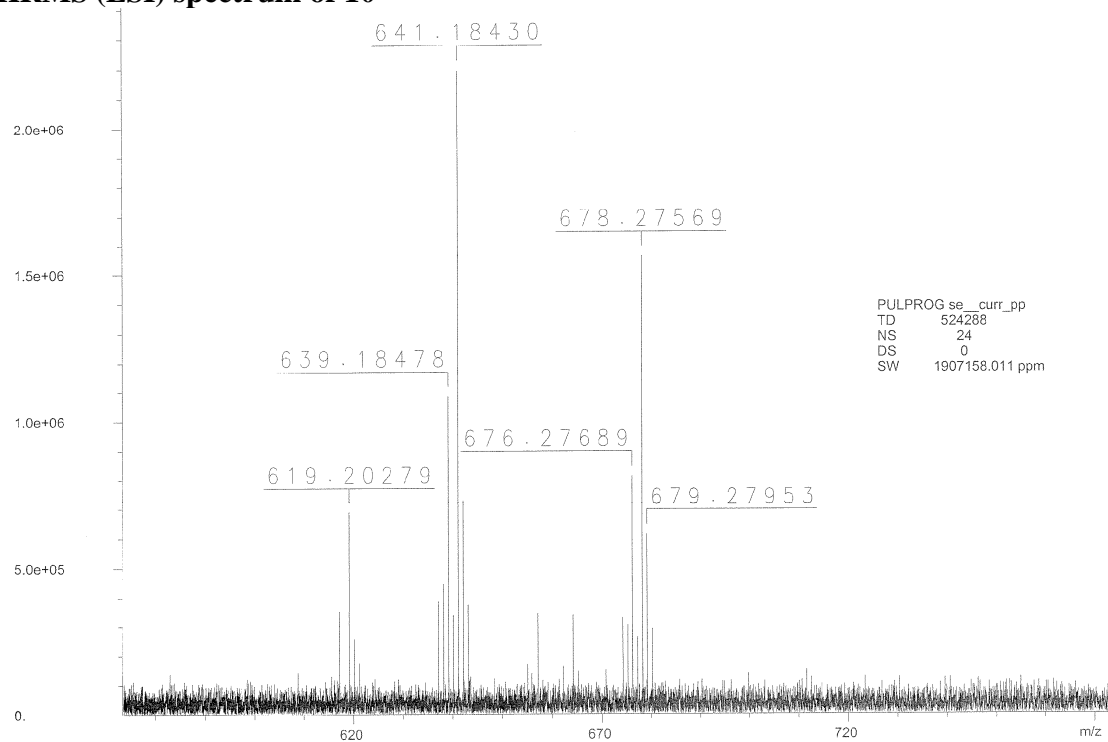
HRMS (ESI) spectrum of 8



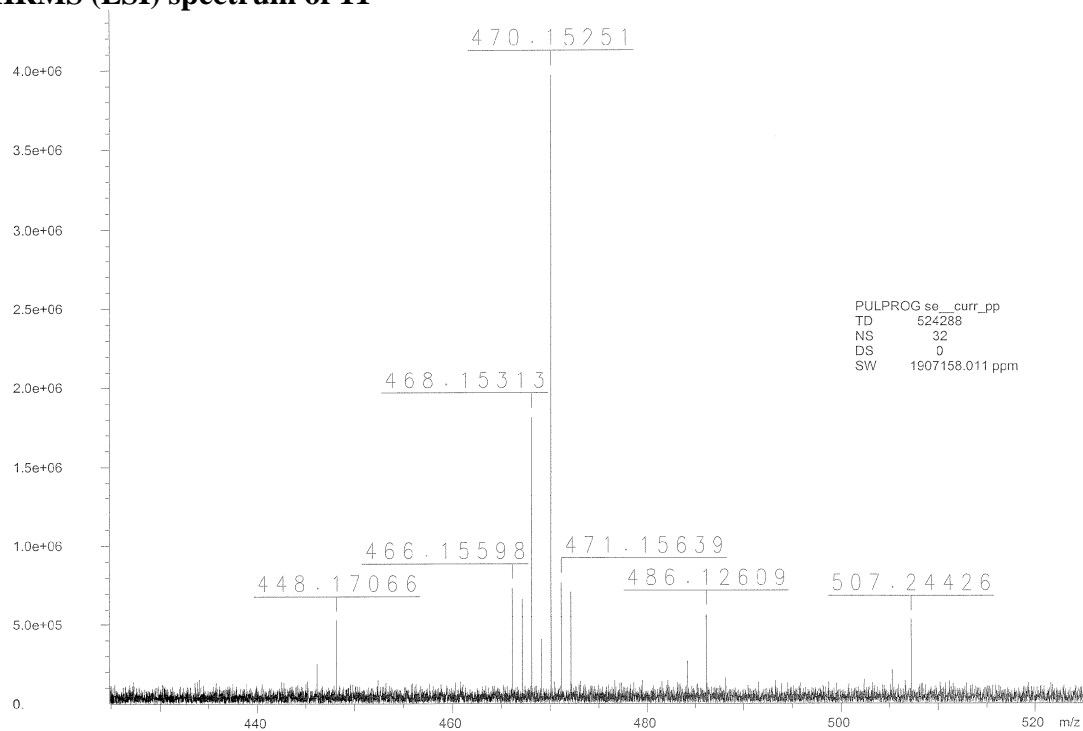
HRMS (ESI) spectrum of 9



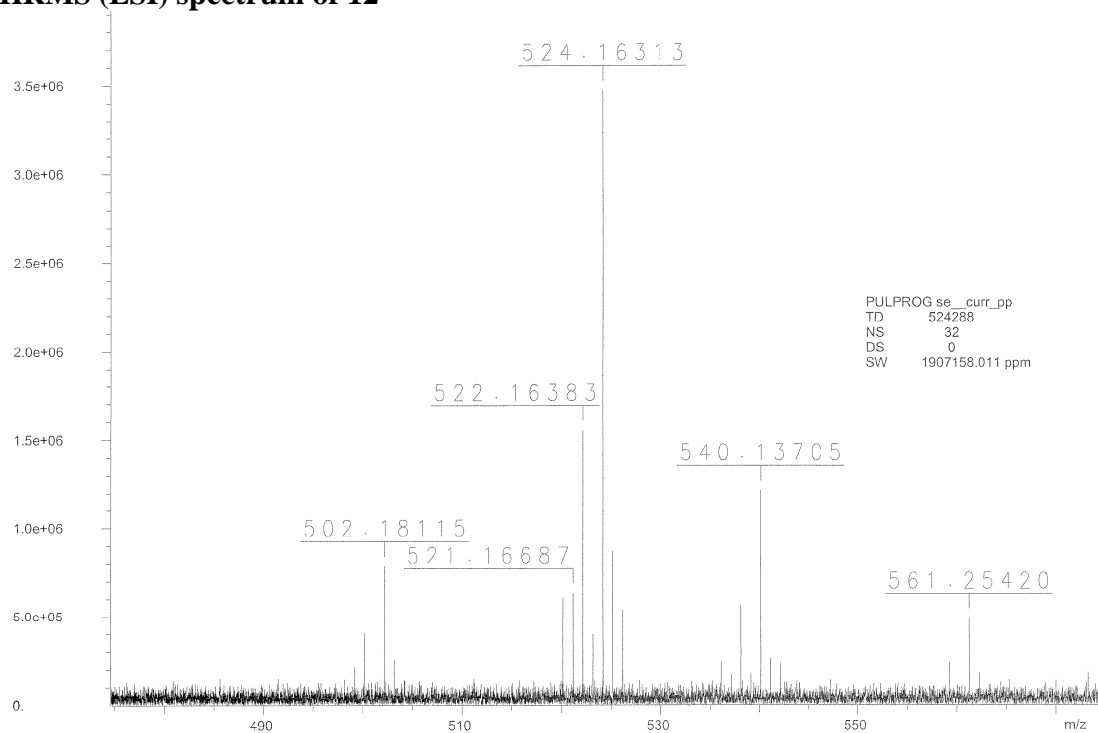
HRMS (ESI) spectrum of 10



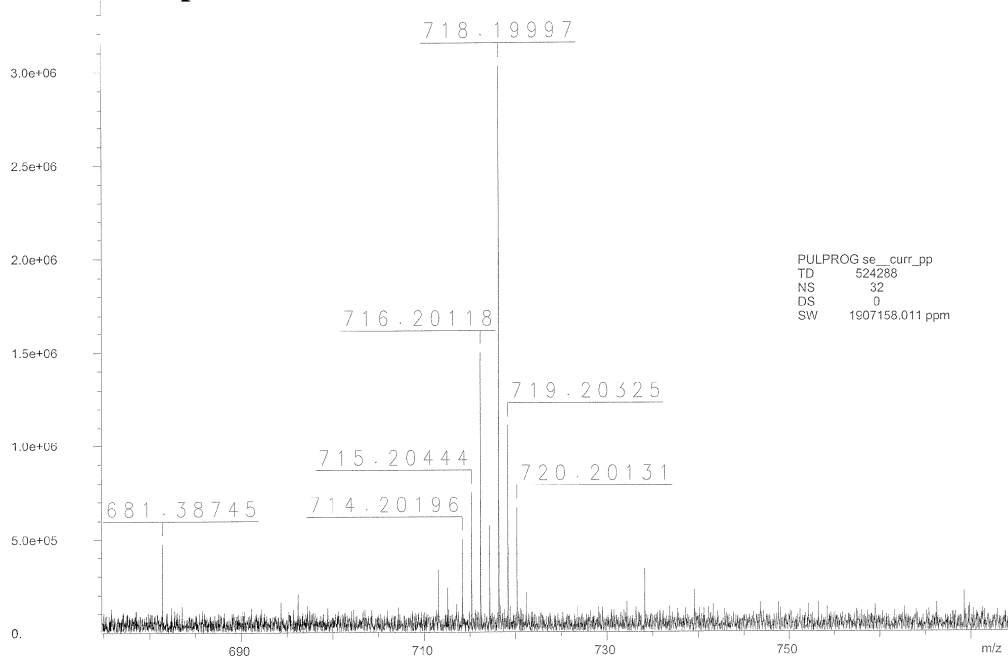
HRMS (ESI) spectrum of 11



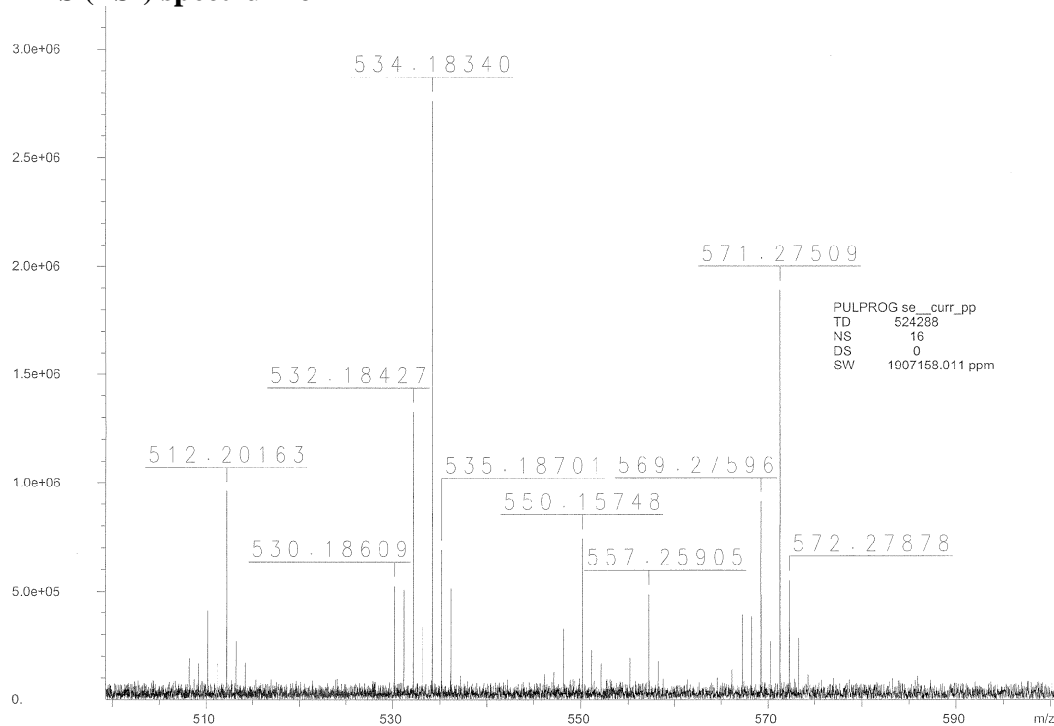
HRMS (ESI) spectrum of 12



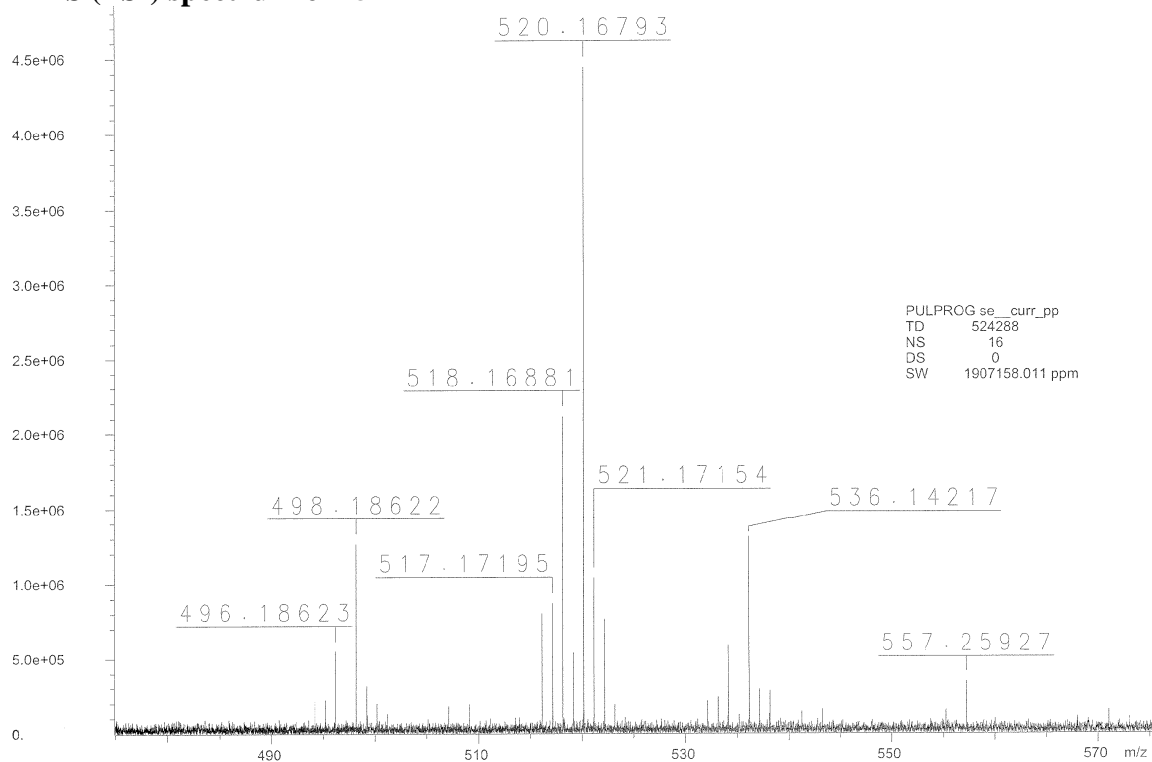
HRMS (ESI) spectrum of 13



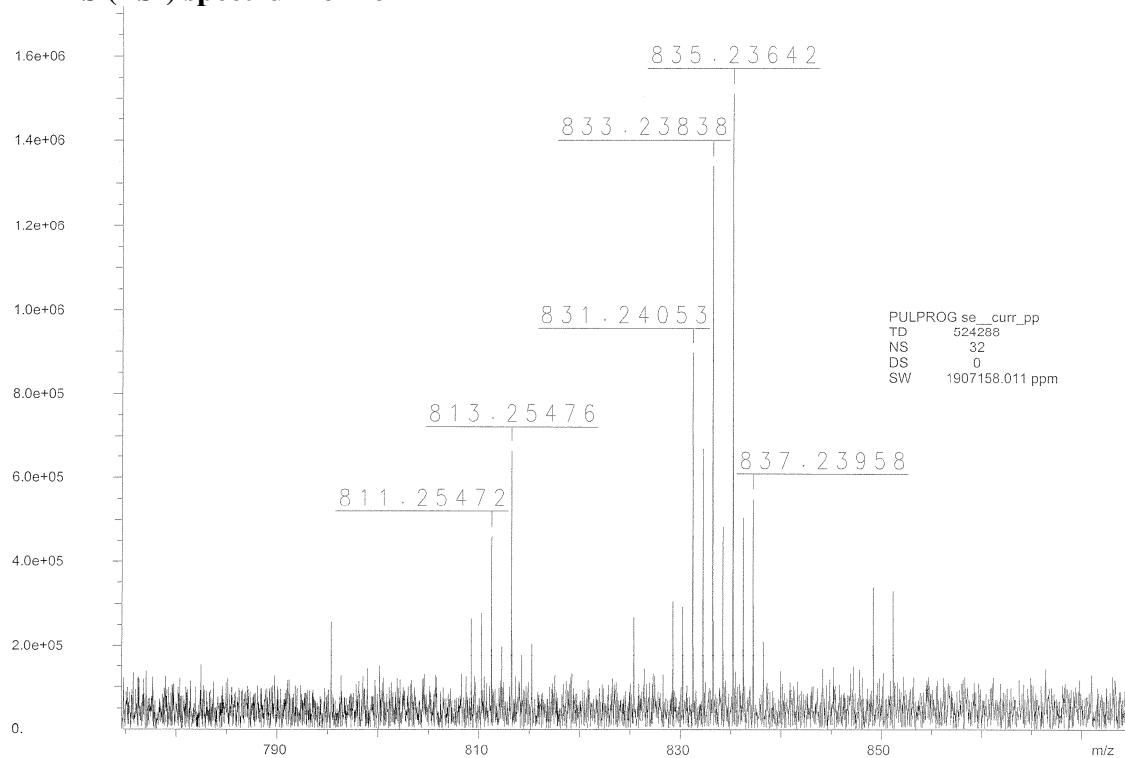
HRMS (ESI) spectrum of 14



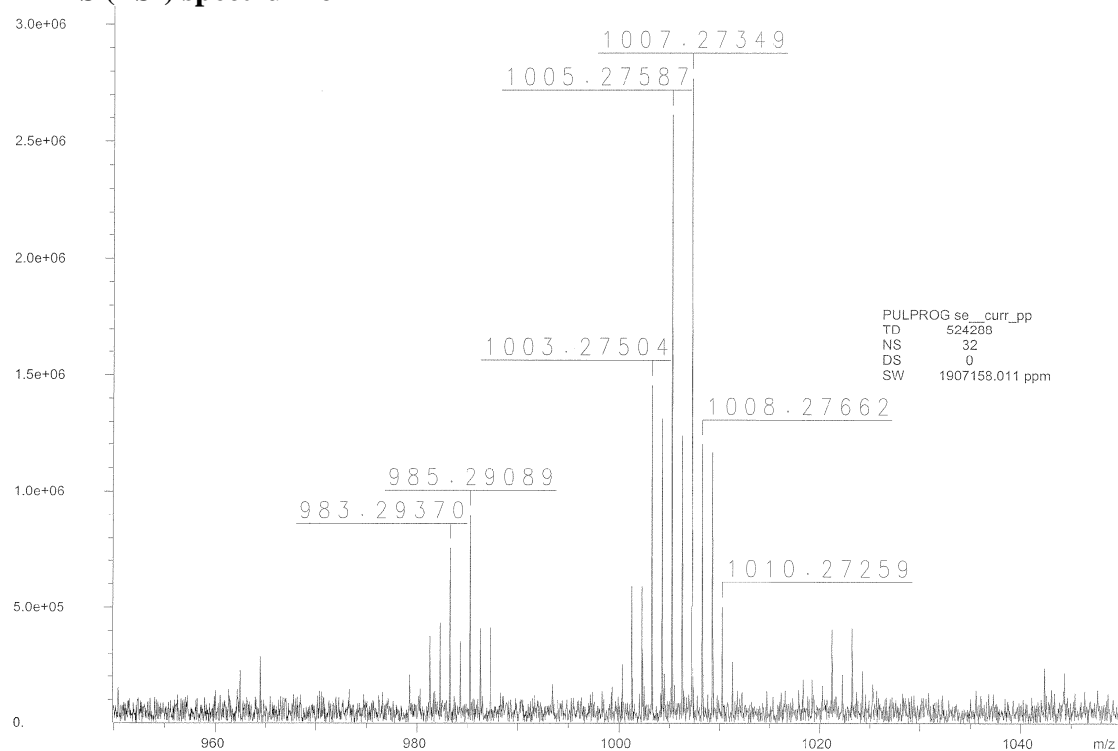
HRMS (ESI) spectrum of 15



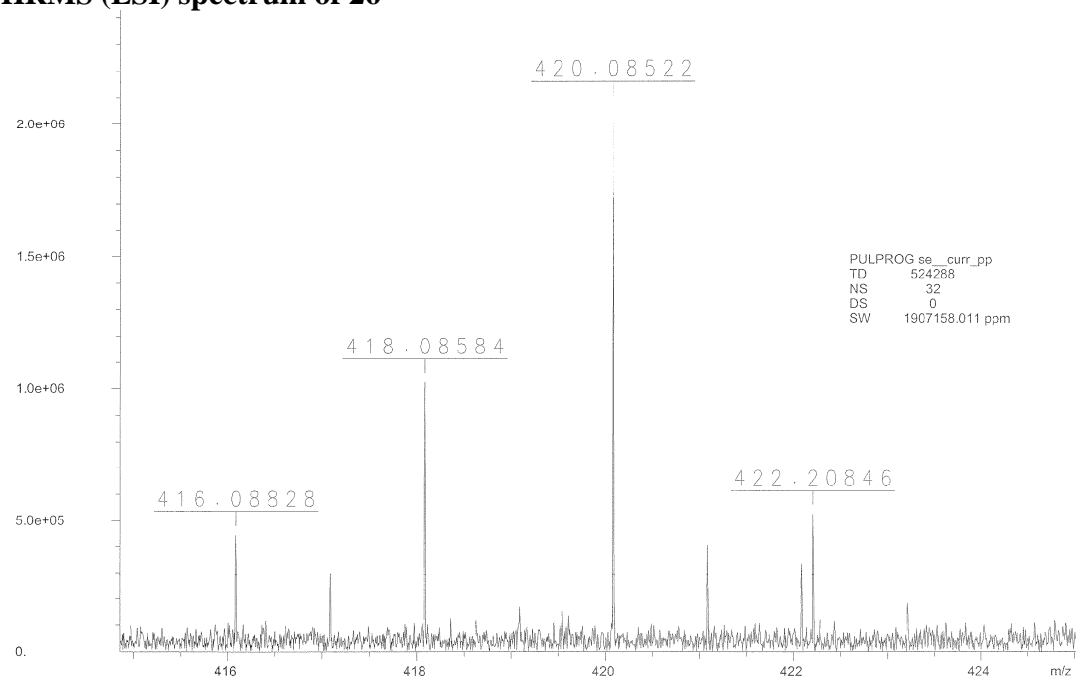
HRMS (ESI) spectrum of 16



HRMS (ESI) spectrum of 24



HRMS (ESI) spectrum of 26



References:

1. M. Abbas, J. Bethke and L. A. Wessjohann, *Chem. Commun.* 2006, 541.