Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

New selenosteroids as antiproliferative agents

Alma G. Fuentes-Aguilar,[a,#] Laura L. Romero-Hernández,[a,#] Ailed V. Arenas-González,[a,#] Penélope Merino-Montiel,[a,*] Sara Montiel-Smith,[a] Socorro Meza-Reyes,[a] José Luis Vega-Báez,[a] Gabriela G. Plata,[b] José M. Padrón,[b] Óscar López,[c,*] José G. Fernández-Bolaños[c]

[a]*Facultad de Ciencias Químicas, Ciudad Universitaria, Benemérita Universidad Autónoma de Puebla, 72570 Puebla, PUE, Mexico. e-mail: penelope.merino@correo.buap.mx; Tel: +52 222 2295500-7382*

[b]*BioLab, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Universidad de La Laguna, c/ Astrofísico Francisco Sánchez 2, E-38206 La Laguna, Spain.*

[c]*Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 1203, E-41071, Seville, Spain. e-mail: osc-lopez@us.es; Fax: +34 954624960; Tel: +34 954 559997*

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To a solution of amines **2**, **5** or **6** (0.22 mmol) in dry CH_2Cl_2 (7 mL) were added a solution of freshly-prepared chloroselenyl derivative **8** (1.6 equiv.) in dry CH_2Cl_2 (1 mL) and Et_3N (1.9 equiv.). The corresponding solution was stirred at rt and under Ar for 2 h. Then, it was diluted with CH_2Cl_2 (12 mL) and washed with H_2O (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness. The residue was purified by column chromatography using the eluant indicated in each case.

1.1. (25*R*)-3α-(3'-Oxobenzo[*d*][1,2]selenazol-2'(3*H*)-yl)-5β-spirostane (10). Yield: 71 mg, 54%. $[\alpha]_D^{26}$ –49 (c 0.20, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.04 (m, 1H, H-1''), 7.60 (brd, 1H, $J_{3'',4''}$ = 7.9 Hz, H-4''), 7.56 (td, 1H, $J_{2'',3''}$ = 6.9 Hz, $J_{2'',4''}$= 1.1 Hz, H-2''), 7.40 (dd, 1H, $J_{1'',3''}$= 0.9 Hz, H-3''), 4.94 (brs, 1H, H-3), 4.40 (m, 1H, H-16), 3.47 (ddd, 1H, $J_{26ax,26eq}$ = 10.9 Hz, $J_{25,26eq}$ = 8.3 Hz, $J_{24,26eq}$ = 4.2 Hz, H-26eq), 3.37 (t, 1H, $J_{25,26ax}$ = 10.9 Hz, H-26ax), 2.30 (td, 1H, $J_{4a,4b}$= 14.8 Hz, $J_{H,H}$= 5.7 Hz, H-4a), 1.78 (dd, 1H, $J_{16,17}$= 8.5 Hz, $J_{17,20}$= 6.9 Hz, H-17), 2.04–1.91 (m, 2H, H-6a, H-15a), 1.87–1.85 (m, 4H, H-2a, H-2b, H-5, H-20), 1.72 (brdd, 1H, $J_{H,H}$= 2.6 Hz, $J_{12a,12b}$= 12.4 Hz, H-12a), 1.69–1.57 (m, 7H, H-1a, H-4b, H-8, H-23a, H-23b, H-24a, H-25), 1.45–1.31 (m, 5H, H7a, H-9, H-11a, H-11b, H-24b), 1.31-1.13 (m, 5H, H-1b, H-6b, H-12b, H-14, H-15b), 1.09 (brdd, 1H, $J_{H,H}$= 3.0 Hz, $J_{7a,7b}$= 13.3 Hz, H-7b), 1.05 (s, 3H,

CH_3-19), 0.97 (d, 3H, $J_{20,21}$ = 6.9 Hz, CH_3-21), 0.77 (d, 3H, $J_{25,27}$ = 6.4 Hz, CH_3-27), 0.79 (s, 3H, CH_3-18) ppm; ^{13}C-NMR ($CDCl_3$, 125.7 MHz) δ 167.5 (CO), 138.3 (C-4'), 131.8 (C-2''), 128.6 (C-1''), 127.6 (C-5'), 126.2 (C-3''), 123.4 (C-4''), 109.4 (C-22), 81.0 (C-16), 67.0 (C-26), 62.4 (C-17), 56.5 (C-14), 51.3 (C-3), 41.8 (C-20), 40.9 (C-13), 40.8 (C-9), 40.3 (C-12), 39.0 (C-5), 35.3 (C-10), 35.0 (C-8), 32.5 (C-1), 31.9 (C-15), 31.5 (C-23), 31.2 (C-4), 30.4 (C-25), 28.9 (C-24), 26.6, 26.5 (C-6, C-7), 25.6 (C-2), 24.2 (C-19), 21.0 (C-11), 17.3 (C-27), 16.6 (C-18), 14.6 (C-21) ppm; HRESI-MS *m/z* calcd for $C_{34}H_{47}NNaO_3{}^{80}Se$ ($[M+Na]^+$): 620.2613, found: 620.2598.

1.2. **(25*R*)-3α-(3'-Oxobenzo[*d*][1,2]selenazol-2'(3*H*)-yl)-5α-spirostan-12-one (11)**. Yield: 43 mg, 23%. $[\alpha]_D^{26}$ +37 (*c* 0.19, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, 1H, $J_{1'',2''}$ = 7.7 Hz, H-1''), 7.60–7.58 (m, 2H, H-4'', H-2''), 7.41 (td, 1H, $J_{1'',3''}$= 1.3 Hz, H-3''), 4.88 (brs, 1H, H-3), 4.37–4.30 (m, 1H, H-16), 3.48 (m, 1H, H-26eq), 3.34 (t, 1H, $J_{25,26ax} = J_{26ax,26eq}$= 10.9 Hz, H-26ax), 2.52 (dd, 1H, $J_{16,17}$= 6.9 Hz, $J_{17,20}$= 8.6 Hz, H-17), 2.42 (t, 1H, $J_{9,11\alpha}$= $J_{11\alpha,11\beta}$= 13.8 Hz, H-11α), 2.26 (dd, 1H, $J_{9,11\beta}$= 4.8 Hz, H-11β), 2.11 (m, 1H, H-15a), 2.07–1.85 (m, 4H, H-2a, H-4, H-7a, H-8), 1.82–1.27 (m, 16H, H-1a, H-1b, H-2b, H-5, H-6a, H-6b, H-7b, H-9, H-14, H-15b, H-20, H-23a, H-23b, H-24a, H-24b, H-25), 1.07 (d, 3H, $J_{20,21}$ = 6.8 Hz, CH_3-21), 1.06 (s, 3H, CH_3-18), 0.94 (s, 3H, CH_3-19), 0.78 (d, 3H, $J_{25,27}$ = 6.3 Hz, CH_3-27) ppm; ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 213.5 (C-12), 167.5 (CO), 138.1 (C-4'), 131.9 (C-2''), 128.6 (C-1''), 127.4 (C-5'), 126.3 (C-3''), 123.6 (C-4''), 109.4 (C-22), 79.3 (C-16), 67.0 (C-26), 56.1, 56.0 (C-9, C-14), 55.2 (C-13), 53.6 (C-17), 50.3 (C-3), 42.3 (C-20), 41.1 (C-5), 37.5 (C-11), 36.5 (C-10), 34.5 (C-1), 34.4 (C-8), 33.3 (C-4), 31.5 (C-7), 31.2 (C-15), 30.3 (C-23), 29.8 (C-25), 28.9 (C-24), 28.2 (C-6), 26.3 (C-2), 17.2 (C-27), 16.1 (C-18), 13.4 (C-21), 11.2 (C-19) ppm; HRESI-MS *m/z* calcd for $C_{34}H_{45}NNaO_4{}^{80}Se$ ($[M+Na]^+$): 634.2406, found: 634.2380.

2. General procedure for the preparation of selenosemicarbazones 16–18

To a solution of 5α-spirostan-3-one **12** or hecogenin **4** (0.23 mmol) in EtOH (22 mL) was dropwise added glacial AcOH up to pH 5, and then, the corresponding selenosemicarbazide (1.3 equiv.). The mixture was stirred at 70 ºC in the dark and under

Ar overnight; then, it was concentrated to dryness and the residue was purified by column chromatography (75:1 CH_2Cl_2–MeOH) to give compounds **16**–**18**.

2.1. **(25'*R*)-1-(5'α-Spirostan-3'-ylidene)-4-*p*-tolyl-3-selenosemicarbazone (16, 1:1 *E*/*Z*)**. Yield: 43 mg, 30%; mp 132-135 ºC (dec.); $[\alpha]_D^{25}$ –36 (*c*, 0.35, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.39 (brs, 1H, NHPh), 8.98, 8.97 (2brs, 1H each, N-NH *E*/*Z*), 7.47 (m, 2H, Ar-H-*o*), 7.17 (m, 2H, Ar-H-*m*), 4.39 (m, 1H, H-16'), 3.46 (ddd, 1H, $J_{26'ax,26'eq}$= 11.0 Hz, $J_{H,H}$= 1.7 Hz, $J_{H,H}$ = 4.0 Hz, H-26'eq), 3.36 (t, 1H, $J_{25',26'ax}$= 11.0 Hz, H-26'ax), 2.34 (s, 3H, CH_3-Ar), 2.16–1.25 (m, 23H, H-1'a, H-2'a, H-2'b, H-4'a, H-4'b, H-6'a, H-6'b, H-7'a, H-7'b, H-8', H-11'a, H-11'b, H-12'a, H-15'a, H-15'b, H-17', H-20', H-23'a, H-23'b, H-24'a, H-24'b, H-25'), 1.17–1.10 (m, 3H, H-1'b, H-12'b, H-14'), 0.96 (d, 3H, $J_{20',21'}$ = 6.9 Hz, CH_3-21'), 0.94 (s, 3H, CH_3-19'), 0.78 (s, 3H, CH_3-18'), 0.79 (m, 3H, CH_3-27'), 0.72 (m, 1H, H-9') ppm; ^{13}C-NMR ($CDCl_3$, 125.7 MHz) δ 175.2, 175.0 (CSe *E*/*Z*), 157.0, 156.9 (C-3' *E*/*Z*), 136.6 (Ar-C-*p*), 136.1 (Ar-C-*ipso*), 129.4 (Ar-C-*m*), 125.3 (x2) (Ar-C-*o*, *E*/*Z*), 109.3 (C-22'), 80.8 (C-16'), 67.0 (C-26'), 62.3 (C-17'), 56.2 (x2) (C-14' *E*/*Z*), 54.0, 53.8 (C-9' *E*/*Z*), 46.9, 45.8 (C-5' *E*/*Z*), 41.7 (C-20'), 40.7, 40.6 (C-13' *E*/*Z*), 40.0 (x2) (C-12' *E*/*Z*), 38.5 (C-1' or C-4'), 37.8, 37.6 (C-1' or C-4' *E*/*Z*), 36.4, 36.3 (C-10' *E*/*Z*), 35.1 (C8'), 32.0, 31.9, 31.8 (C-2', C-7', C-15'), 31.5 (C-23'), 30.4 (C-25'), 29.8 (C-6'), 28.9 (C-24'), 21.2 (C-11', *C*H_3-Ar), 17.2 (C-27'), 16.6 (C-18'), 14.6 (C-21'), 11.8, 11.5 (C-19' *E*/*Z*) ppm; HRESI-MS *m/z* calcd for $C_{35}H_{52}N_3O_2{}^{80}Se$ ($[M+H]^+$) : 626.3219, found: 626.3203.

2.2. **(25'*R*)-1-(3'-β-Hydroxy-5'α-spirostan-12'-ylidene)-4-*p*-tolyl-3-selenosemicarbazone (17, 5.2:1 *E*/*Z*).** Yield: 22.5 mg, 15%. $[\alpha]_D^{27}$ +13 (*c*, 0.21, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.45 (brs, 1H, NHPh), 9.08 (brs, 1H, NHCSe), 7.45 (m, 2H, Ar-H-*o*), 7.44 (m, 2H, Ar-H-*o*, *Z*), 7.15 (m, 2H, Ar-H-*p*), 7.02 (m, 2H, Ar-H-*p*, *Z*), 4.38 (m, 1H, H-16'), 3.60 (m, 1H, H-3'), 3.46 (ddd, 1H, $J_{26'ax,26'eq}$ = 11.1 Hz, $J_{25',26'eq}$ = 3.1 Hz, $J_{24',26'eq}$ = 1.8 Hz, H-26'eq), 3.34 (t, 1H, $J_{25',26'ax}$ = 11.1 Hz, H-26'ax), 2.68–2.64 (m, 2H, H-2'a, H-17'), 2.10 (m, 1H, H-23'a), 2.33 (s, 3H, CH_3-Ar), 1.93–1.82 (m, 3H, H-2'b, H-8', H-15'a), 1.79–1.67 (m, 3H, H-1'a, H-4'a, H-7'a),

1.65–1.57 (m, 4H, H-7'b, H-11'a, H-24'a, H-25'), 1.47–1.30 (m, 9H, H-6'a, H-6'b, H-11'b, H-14', H-15'b, H-20', H-23'b, H-24'b), 1.13 (d, 3H, $J_{20',21'}$ = 6.9 Hz, CH_3-21'), 1.09–1.03 (m, 2H, H-1'b, H-5'), 1.00 (s, 3H, CH_3-18'), 0.97–0.92 (m, 2H, H-4'b, H-9'), 0.91 (s, 3H, CH_3-19'), 0.78 (d, 3H, $J_{25',27'}$ = 6.3 Hz, CH_3-27') ppm; ^{13}C-NMR ($CDCl_3$, 125.7 MHz) δ 175.3 (CSe), 161.5 (C-12'), 136.5 (Ar-C-*p*), 135.9 (Ar-C-*ipso*), 129.4 (Ar-C-*m*), 124.9 (Ar-C-*o*), 109.5 (C-22'), 79.7 (C-16'), 70.9 (C-3'), 70.0 (C-26'), 56.2 (C-14'), 55.6 (C-17'), 54.3 (C-9'), 49.5 (C-13'), 44.8 (C-5'), 42.2 (C-20'), 37.9 (C-11'), 37.0 (C-1'), 36.3 (C-10'), 34.5 (C-8'), 31.7 (C-4'), 31.8 (C-7'), 31.3 (C-15'), 31.2 (C-23'), 30.3 (C-25'), 28.8 (C-24'), 28.3 (C-6'), 23.4 (C-2'), 21.2 (*C*H_3-Ar), 17.7 (C-18'), 17.2 (C-27'), 14.7 (C-21'), 12.2 (C-19') ppm; HRESI-MS *m/z* calcd for $C_{35}H_{52}N_3O_3{}^{80}Se$ ($[M+H]^+$): 642.3168, found: 642.152.

3. General procedure for the preparation of 2-aminobenzoxazoles 24, 25

To a solution of 2-amino-3-hydroxyestra-1,3,5(10)-trien-17-one **22** (50.4 mg, 0.18 mmol) in THF (10 mL) was added the corresponding isoselenocyanate (5.0 equiv.), and the resulting mixture was refluxed during the time indicated in each case. After that, it was concentrated to dryness, and the residue was purified by column chromatography (cyclohexane→9:1 cyclohexane–EtOAc).

3.1. 2´-(Phenylamino)estra-1,3,5(10)-trieno[2,3-*d*]oxazol-17-one (24). Phenyl isoselenocyanate (161.4 mg, 0.89 mmol) was used, and the reaction took place during 24 h. Yield: 36.4 mg, 43%; mp > 250 ºC; $[\alpha]_D^{25}$ +126 (*c* 1.01, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.13 (brs, 1H, NH), 7.60 (m, 2H, Ar-H-*o*), 7.43 (s, 1H, H-4), 7.38 (m, 2H, Ar-H-*m*), 7.09 (t, 1H, $J_{m,p}$= 7.4 Hz, Ar-H-*p*), 7.07 (s, 1H, H-1), 2.99 (m, 2H, H-6a, H-6b), 2.51 (dd, 1H, $J_{15,16a}$= 8.6 Hz, $J_{16a,16b}$= 18.8 Hz, H-16a), 2.44 (m, 1H, H-11a), 2.36 (td, 1H, $J_{8,9}$=$J_{9,11\beta}$=10.9 Hz, $J_{9,11\alpha}$=4.2 Hz, H-9), 2.15 (dt, 1H, $J_{15a,16b}$=$J_{15b,16b}$=8.9 Hz, H-16b), 2.07 (m, 1H, H-15a), 2.03 (m, 1H, H-7a), 1.99 (dt, 1H, $J_{11a,12a}$=$J_{11b,12a}$= 2.9 Hz, $J_{12a,12b}$= 12.6 Hz, H-12a), 1.64 (m, 1H, H-15b), 1.62 (m, 1H, H-8), 1.60 (m, 1H, H-11b), 1.56 (m, 1H, H-14), 1.53 (m, 1H, H-12b), 1.45 (m, 1H, H-7b), 0.93 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 220.9 (C-17), 158.2 (C-2´), 146.5 (C-3), 140.5 (C-10), 138.2 (Ar-C-*ipso*), 136.2 (C-2), 130.8 (C-5), 129.4 (Ar-C-*m*), 123.2 (Ar-C-*p*), 118.4 (Ar-C-*o*), 113.8 (C-4), 108.9 (C-1), 50.7 (C-14), 48.1 (C-13), 44.6 (C-9),

38.4 (C-8), 36.0 (C-16), 31.8 (C-12), 29.9 (C-6), 26.7 (C-7), 26.3 (C-11), 21.8 (C-15), 14.0 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2067, found: 387.2058.

3.2. **2´-[(*p*-Bromophenyl)amino]estra-1,3,5(10)-trieno[2,3-*d*]oxazol-17-one (25).** *p*-Bromophenyl isoselenocyanate (230.4 mg, 0.88 mmol) was used, and the reaction took place during 14 h. Yield: 68.5 mg, 82%; mp > 250 ºC; $[\alpha]_D^{25}$ +89 (*c* 1.06, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.53–7.47 (m, 4H, Ar-H), 7.44 (s, 1H, H-4), 7.06 (s, 1H, H-1), 2.99 (m, 2H, H-6a, H-6b), 2.51 (dd, 1H, $J_{15,16a}$= 8.7 Hz, $J_{16a,16b}$ = 19.0 Hz, 1H, H-16a), 2.46 (m, 1H, H-11a), 2.37 (m, 1H, td, 1H, $J_{8,9}$=$J_{9,11\beta}$=11.3 Hz, $J_{9,11\alpha}$=3.7 Hz, H-9), 2.15 (dt, 1H, $J_{15a,16b}$=$J_{15b,16b}$=8.8 Hz, H-16b), 2.08 (m, 1H, H-15a), 2.04 (m, 1H, H-7a), 2.00 (dt, 1H, $J_{11a,12a}$=$J_{11b,12a}$= 3.0 Hz, $J_{12a,12b}$= 12.7 Hz, H-12a), 1.64 (m, 1H, H-15b), 1.62 (m, 1H, H-8), 1.61 (m, 1H, H-11b), 1.55 (m, 1H, H-14), 1.53 (m, 1H, H-12b), 1.50 (m, 1H, H-7b), 0.93 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 220.8 (C-17), 157.3 (C-2´), 146.4 (C-3), 140.6 (C-10), 137.2 (Ar-C-*ipso*), 136.5 (C-2), 132.4 (Ar-C-*m*), 131.4 (C-5), 119.8 (Ar-C-*o*), 115.7 (Ar-C-*p*), 114.2 (C-4), 108.9 (C-1), 50.8 (C-14), 48.1 (C-13), 44.7 (C-9), 38.4 (C-8), 36.0 (C-16), 31.8 (C-12), 30.0 (C-6), 26.7 (C-7), 26.3 (C-11), 21.8 (C-15), 14.0 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{25}H_{26}{}^{79}BrN_2O_2$ $[M+H]^+$: 465.1172, found: 465.1163.

4. General procedure for the preparation of selenoureas 28–32

To a solution of 2-amino-3-methoxyestra-1,3,5(10)-trien-17-one **26** (100 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) was added the corresponding isoselenocyanate (3.0 equiv.), and the resulting mixture was stirred at rt, under Ar and in the dark during the time indicated in each case. Then, it was concentrated to dryness and the residue was purified by column chromatography (3:2 cyclohexane–CH_2Cl_2).

4.1. 3-Methoxy-2-[3´-(*p*-tolyl)selenoureido]estra-1,3,5(10)-trien-17-one (29). *p*-Tolyl isoselenocyanate (196.1 mg, 1.00 mmol) was used, and the reaction took place during

13.5 h. Yield: 98.1 mg, 60%; mp 125 ºC (dec.); $[\alpha]_D^{28}$ +72 (*c* 1.01, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 2H, NH, H-1), 8.09 (brs, 1H, NH), 7.23 (m, 4H, Ar-H), 6.62 (s, 1H, H-4), 3.77 (s, 3H, OMe), 2.88 (m, 2H, H-6a, H-6b), 2.50 (dd, 1H, $J_{15,16a}$= 8.6 Hz, $J_{16a,16b}$ = 18.8 Hz, H-16a), 2.40 (m, 1H, H-11a), 2.36 (s, 3H, CH_3-Ar), 2.29 (m, 1H, H-9), 2.15 (dt, 1H $J_{15a,16b}$=$J_{15b,16b}$=8.6 Hz, H-16b), 2.06 (m, 1H, H-15a), 2.02 (m, 1H, H-7a), 1.97 (m, 1H, H-12a), 1.63 (m, 1H, H-15b), 1.58 (m, 1H, H-8), 1.52 (m, 1H, H-14), 1.50 (m, 3H, H-11b, H-12b, H-7b), 0.91 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 220.8 (C-17), 177.8 (CSe), 149.9 (C-3), 137.7 (C-10), 136.0 (Ar-C-*p*), 134.6 (Ar-C-*ipso*), 132.2 (C-5), 130.4 (Ar-C-*o*), 125.6 (Ar-C-*m*), 124.5 (C-2), 122.6 (C-1), 111.7 (C-4), 56.0 (OMe), 50.5 (C-14), 48.1 (C-13), 44.1 (C-9), 38.3 (C-8), 36.0 (C-16), 31.7 (C-12), 29.7 (C-6), 26.6 (C-7), 26.1 (C-11), 21.7 (C-15), 21.2 (*C*H_3-Ar), 14.0 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{27}H_{33}N_2O_3{}^{80}Se$ $[M+H]^+$: 513.1651, found: 513.1634.

4.2. **3-Methoxy-2-[3´-(*p*-methoxyphenyl)selenoureido]estra-1,3,5(10)-trien-17-one (30).** *p*-Methoxyphenyl isoselenocyanate (212.5 mg, 1.00 mmol) was used, and the reaction took place during 15.5 h. Yield: 120.2 mg, 71%; mp 186-190 ºC (dec.); $[\alpha]_D^{28}$ +92 (*c* 1.04, CH_2Cl_2); ^{1}H-NMR (500 MHz, CDCl3) δ 8.36 (brs, 1H, NH), 8.19 (s, 1H, H-1), 8.0 (brs, 1H, NH), 7.28 (m, 2H, Ar-H-*o*), 6.93 (m, 2H, Ar-H-*m*), 6.62 (s, 1H, H-4), 3.81 (s, 3H, OMe), 3.76 (s, 3H, Ar-OMe), 2.88 (m, 2H, H-6a, H-6b), 2.50 (dd, 1H, $J_{15,16a}$=8.7 Hz, $J_{16a,16b}$ = 19.2 Hz, H-16a), 2.40 (m, 1H, H-11a), 2.27 (td, 1H, $J_{8,9}$=$J_{9,11\beta}$=11.2 Hz, $J_{9,11\alpha}$=3.6 Hz, H-9), 2.14 (dt, 1H $J_{15a,16b}$=$J_{15b,16b}$=8.9 Hz, H-16b), 2.08–2.00 (m, 2H, H-15a, H-7a), 1.96 (m, 1H, H-12a), 1.67-1.46 (m, 6H, H-15b, H-8, H-14, H-12b, H-11b, H-7b), 0.90 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 220.7 (C-17), 177.7 (CSe), 158.9 (Ar-C-*p*), 149.8 (C-3), 135.9 (Ar-C-*ipso*), 132.0 (C-10), 129.8 (C-5), 127.6 (Ar-C-*o*), 124.5 (C-5), 122.6 (C-1), 114.8 (Ar-C-*m*), 111.5 (C-4), 55.9 (OMe), 55.5 (Ar-OMe), 50.4 (C-14), 48.0 (C-13), 44.0 (C-9), 38.2 (C-8), 35.9 (C-16), 31.5 (C-12), 29.4 (C-6), 26.5 (C-7), 26.0 (C-11), 21.6 (C-15), 13.9 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{27}H_{33}N_2O_2{}^{80}Se$ $[M+H]^+$: 497.1702, found: 497.1679.

4.3. **3-Methoxy-2-[3´-(*p*-chlorophenyl)selenoureido]estra-1,3,5(10)-trien-17-one (31).** *p*-Chlorophenyl isoselenocyanate (216.5 mg, 1.00 mmol) was used, and the reaction took place during 7.5 h. Yield: 64.7 mg, 38%. $[\alpha]_D^{29}$ +79 (*c* 1.01, CH_2Cl_2); ^{1}H-NMR (500 MHz, CDCl3) δ 8.15 (s, 1H, NH), 7.99 (s, 1H, NH), 7.75 (s, 1H, H-1), 7.35 (m, 4H, Ar-H), 6.66 (s, 1H, H-4), 3.81 (s, 3H, OMe), 2.90 (m, 2H, H-6a, H-6b), 2.51 (dd, 1H, $J_{15,16a}$= 8.3 Hz, $J_{16a,16b}$ = 18.5 Hz, H-16a), 2.35 (m, 1H, H-11a), 2.27 (m, 1H, H-9), 2.15 (dt, 1H, $J_{15a,16b}$= $J_{15b,16b}$=8.6 Hz, H-16b), 2.07–1.95 (m, 3H, H-15a, H-7a, H-12a), 1.66–14.0 (m, 6H, H-15b, H-8, H-14, H-12b, H-11b, H-7b), 0.91 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 220.7 (C-17), 177.8 (CSe), 150.2 (C-3), 136.8 (Ar-C-*ipso*), 136.4 (Ar-C-*p*), 132.5 (C-10), 132.4 (C-5), 129.4 (Ar-C-*o*), 126.8 (Ar-C-*m*), 123.5 (C-2), 122.9 (C-1), 111.9 (C-4), 55.9 (OMe), 50.3 (C-14), 47.9 (C-13), 43.9 (C-9), 38.1 (C-8), 35.8 (C-16), 31.5 (C-12), 29.6 (C-6), 26.4 (C-7), 25.9 (C-11), 21.5 (C-15), 13.9 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{26}H_{30}{}^{35}ClN_2O_2{}^{80}Se$ ($[M]^+$): 517.1156, found: 517.1139.

4.4. **2-[3´-(*p*-Bromophenyl)selenoureido]-3-methoxyestra-1,3,5(10)-trien-17-one (32).** *p*-Bromophenyl isoselenocyanate (261.4 mg, 1.00 mmol) was used, and the reaction took place during 7 h. Yield: 148 mg, 80%; mp 140-145 ºC (dec.); $[\alpha]_D^{28}$ +91 (*c* 1.03, CH_2Cl_2); ^{1}H-NMR (300 MHz,$CDCl_3$) δ 8.22 (s, 1H, NH), 8.11 (s, 1H, NH), 7.73 (s, 1H, H.1), 7.50 (m, 2H, Ar-H-*o*), 7.28 (m, 2H, Ar-H-*m*), 6.66 (s, 1H, H-4), 3.80 (s, 3H, OMe), 2.89 (m, 2H, H-6a, H-6b), 2.50 (dd, 1H, $J_{15,16a}$= 8.3 Hz, $J_{16a,16b}$ = 18.5 Hz, 1H, H-16a), 2.34 (m, 1H, H-11a), 2.26 (m, 1H, H-9), 2.15 (dt, 1H, $J_{15a,16b}$=$J_{15b,16b}$=8.9 Hz, H-16b), 2.07–1.94 (m, 3H, H-15a, H-7a, H-12a), 1.68–1.40 (m, 6H, H-15b, H-8, H-14, H-12b, H-11b, H-7b), 0.90 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 220.6 (C-17), 177.8 (CSe), 150.2 (C-3), 136.9 (C-10, Ar-C-*ipso*), 132.4 (Ar-C-*m*, C-10), 127.0 (Ar-C-*o*), 123.5 (C-2), 123.0 (C-1), 120.5 (Ar-C-*p*), 112.0 (C-4), 55.9 (OMe), 50.3 (C-14), 48.0 (C-13), 43.9 (C-9), 38.1 (C-8), 35.9 (C-16), 31.5 (C-12), 29.6 (C-6), 26.4 (C-7), 26.0 (C-11), 21.6 (C-15), 13.9 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{26}H_{30}{}^{77}BrN_2O_2{}^{80}Se$ ($[M+H]^+$): 561.0650, found: 561.0627.

5. **3-(2'-Azidoethoxy)estra-1,3,5(10)-trien-17-one (37).** To a solution of 3-(2'-bromoethoxy)estra-1,3,5(10)-trien-17-one **33** (99.7 mg, 0.26 mmol) in dry DMF (15 mL) was added NaN_3 (48.4 mg, 0.79 mmol, 3.0 equiv.), and the corresponding mixture was stirred at 70 ºC and under Ar for 2 h. Then, it was concentrated to dryness, and the residue was partitioned between CH_2Cl_2 (10 mL) and brine (10 mL). The organic layer was washed with H_2O (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness to give pure **37**, without any further purification. Yield: 109.6 mg, quant. $[\alpha]_D^{27}$ +71 (*c* 1.32, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.20 (d, 1H, $J_{1,2}$= 8.6 Hz, H-1), 6.73 (dd, 1H, $J_{2,4}$= 2.8 Hz, H-2), 6.66 (d, 1H, H-4), 4.36 (t, 2H, $J_{H,H}$=5.1 Hz, CH_2O), 3.56 (t, 2H, CH_2N), 2.88 (m, 2H, H-6a, H-6b), 2.49 (dd, 1H, $J_{15,16a}$= 8.6 Hz, $J_{16a,16b}$= 19.1 Hz, 1H, H-16a), 2.39 (m, 1H, H-11a), 2.25 (td, 1H, $J_{8,9}$=$J_{9,11\beta}$=10.3 Hz, $J_{9,11\alpha}$=4.1 Hz, H-9), 2.13 (dt, 1H, $J_{15a,16b}$=$J_{15b,16b}$=8.9 Hz, H-16b), 2.07–1.93 (m, 3H, H-15a, H-7a, H-12a), 1.66-1.39 (m, 6H, H-15b, H-8, H-14, H-12b, H-11b, H-7b), 0.90 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 221.1 (C-17), 156.4 (C-3), 138.1 (C-5), 133.0 (C-10), 126.6 (C-1), 115.0 (C-4), 112.3 (C-2), 67.1 (CH_2O), 50.6 (C-14), 50.4 (CH_2N), 48.3 (C-13), 44.1 (C-9), 38.5 (C-8), 36.0 (C-16), 31.7 (C-12), 29.8 (C-6), 26.7 (C-7), 26.1 (C-11), 21.7 (C-15), 14.0 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{20}H_{25}N_3NaO_2$ ($[M+Na]^+$): 362.1839, found: 362.1834.

6. General procedure for the preparation of selenoureas 39, 40

To a solution of 3-(2'-aminoethoxy)estra-1,3,5(10)-trien-17-one **38** (60.0 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was added the corresponding isoselenocyanate (3.0 equiv.), and the reaction was kept at rt, under Ar and in the dark during the time indicated in each case. After that, it was concentrated to dryness, and the residue was purified by column chromatography (4:1 cyclohexane–EtOAc).

6.1. 3-[2´-(3´´-*p*-Chlorophenylselenoureido)ethoxy]estra-1,3,5(10)-trien-17-one (40). *p*-Chlorophenyl isoselenocyanate (124.3 mg, 0.56 mmol) was used, and the reaction took place for 2h. Yield: 30.3 mg, 30%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H, NH), 7.39 (m, 2H, Ar-H-*m*), 7.20 (d, 1H, $J_{1,2}$ = 8.6 Hz, H-1), 7.14 (m, 2H, Ar-H-*o*), 6.77 (s, 1H, NH), 6.63 (dd, 1H, $J_{2,4}$ = 2.7 Hz, 1H, H-2), 6.55 (d, 1H, H-4), 4.14 (m, 4H, H-1´, H-2´), 2.88 (m, 2H, H-6a, H-6b), 2.51 (dd, 1H, $J_{15,16a}$ = 8.4 Hz, $J_{16a,16b}$ = 18.3 Hz, H-

16a), 2.39 (m, 1H, H-11a), 2.25 (m, 1H, H-9), 2.13 (m, 1H, H-16b), 2.06 (m, 1H, H-15a), 2.02 (m, 1H, H-7a), 1.96 (m, 1H, H-12a), 1.63 (m, 1H, H-15b), 1.57 (m, 1H, H-8), 1.52 (m, 1H, H-14), 1.50 (m, 2H, H-11b, H-12b), 1.44 (m, 1H, H-7b), 0.91 (s, 3H, CH_3-18) ppm; ^{13}C-NMR (500 MHz, $CDCl_3$) δ 220.9 (C-17), 179.6 (CSe), 156.3 (C-3), 138.3 (C-5), 130.7 (Ar-C-*m*), 129.0 (Ar-C-*ipso*), 127.4 (C-10), 132.5 (Ar-C-*p*), 126.7 (C-1), 126.5 (Ar-C-*o*), 114.5 (C-4), 112.3 (C-2), 66.3 (C-1´), 50.5 (C-14), 48.1 (C-13), 47.8 (C-2´), 44.1 (C-9), 38.5 (C-8), 36.0 (C-16), 31.7 (C-12), 29.8 (C-6), 26.6 (C-7), 26.1 (C-11), 21.7 (C-15), 14.0 (C-18) ppm. HRESI-MS *m/z* calcd for $C_{27}H_{31}{}^{35}ClN_2NaO_2{}^{80}Se$ ($[M+Na]^+$): 553.1131, found: 553.1114.

7. **3-(2'-Formamidoethoxy)estra-1,3,5(10)-trien-17-one (41).** To a vigorously stirred solution of 3-(2'-aminoethoxy)estra-1,3,5(10)-trien-17-one **38** (30 mg, 95.7 μmol) in a 1:1 CH_2Cl_2-sat. aq. $NaHCO_3$ mixture (20 mL) at 0 ºC was added AFA (0.1 mL). Stirring was kept at rt for 3 h, and then, both layers were separated. The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness. The residue was purified by column chromatography (100:1 CH_2Cl_2–MeOH). Yield: 17.1 mg, 52%. $[\alpha]_D^{27}$ +70 (*c* 0.84, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.22 (brs, 1H, CHO), 7.20 (d, 1H, $J_{1,2}$= 8.7 Hz, H-1), 6.70 (dd, 1H, $J_{2,4}$= 2.8 Hz, H-2), 6.63 (d, 1H, H-4), 6.02 (brs, 1H, NH), 4.04 (t, 2H, $J_{H,H}$=5.1 Hz, CH_2O), 3.71 (q, 2H, $J_{H,NH}$=5.1 Hz, CH_2N), 2.89 (m, 2H, H-6a, H-6b), 2.50 (dd, 1H, $J_{15,16a}$= 8.3 Hz, $J_{16a,16b}$= 18.4 Hz, H-16a), 2.39 (m, 1H, H-11a), 2.25 (td, 1H, $J_{8,9}$=$J_{9,11\beta}$=10.8 Hz, $J_{9,11\alpha}$=4.4 Hz, H-9), 2.14 (dt, 1H, $J_{15a,16b}$=$J_{15b,16b}$=9.0 Hz, H-16b), 2.08–1.99 (m, 2H, H-15a, H-7a), 1.97–1.94 (m, 1H, H-12a), 1.66–1.39 (m, 6H, H-15b, H-8, H-14, H-11b, H-12b, H-7b), 0.91 (s, 3H, CH_3-18); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 221.0 (C-17), 161.3 (CHO), 156.5 (C-3), 138.1 (C-5), 132.9 (C-10), 126.7 (C-1), 114.6 (C-4), 112.3 (C-2), 66.7 (CH_2O), 50.5 (C-14), 48.1 (C-13), 44.1 (C-9), 38.5 (C-8), 37.7 (CH_2N), 36.0 (C-16), 31.7 (C-12), 29.8 (C-6), 26.6 (C-7), 26.1 (C-11), 21.7 (C-15), 14.0 (C-18) ppm; HRESI-MS *m/z* calcd for $C_{21}H_{27}NNaO_3$ ($[M+Na]^+$): 364.1883, found: 364.1870.

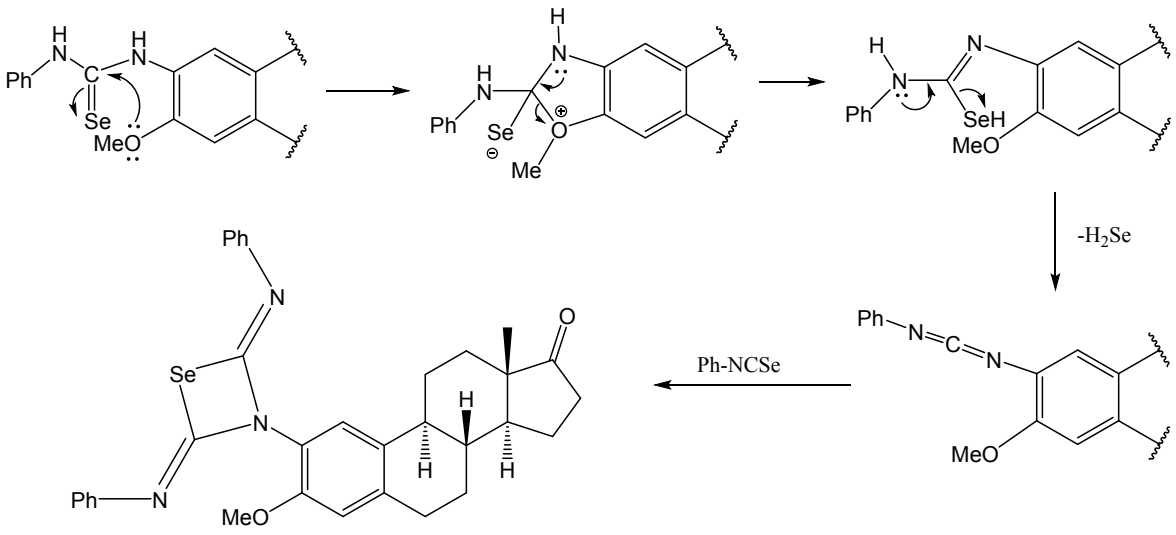
8. **(25*R*)-3β-*tert*-Butyldiphenylsilyloxy-26-hydroxy-22-oxocholest-5-en-16β-yl acetate (44).** To a cooled solution of **43** (2.8 g, 4.29 mmol) in dry CH_2Cl_2 (30 mL) were dropwise added Ac_2O (7 mL, 74.0 mmol) and $BF_3{\cdot}OEt_2$ (5.6 mL, 45.37 mmol) under Ar. The mixture was stirred at 0 °C for 10 min, poured into iced water and stirred overnight. The organic layer was separated, washed several times with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtrated, and the filtrate was concentrated to dryness. The residue was purified by column chromatography (4:1 hexane-EtOAc) to give **44** as a white foam. Yield: 1.59 g, 52%. $[\alpha]_D^{20}$ –5 (*c* 0.1, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ar-H-*m*), 7.41 (m, 2H, Ar-H-*p*), 7.35 (m, 4H, Ar-H-*o*), 5.10 (m, 1H, H-6), 4.95 (td, 1H, $J_{16,17}$= $J_{16,15eq}$= 7.9 Hz, $J_{16,15ax}$= 4.8 Hz, H-16), 3.52 (m, 1H, H-3), 3.41 (d, 2H, $J_{25,26}$= 5.9 Hz, H-26), 2.94 (dq, 1H, $J_{20,17}$ = 11.0 Hz, $J_{20,21}$ = 7.1 Hz, H-20), 2.62 (ddd, 1H, $J_{23a,24a}$= 8.5 Hz, $J_{23a,24b}$= 6.6 Hz, $J_{23a,23b}$= 18.1 Hz, H-23a), 2.38 (ddd, 1H, $J_{23b,24b}$= 8.6 Hz, $J_{23b,24a}$= 5.8 Hz, H-23b), 2.36 (m, 1H, H-15a), 2.31 (m, 1H, H-4a), 2.12 (ddd, 1H, $J_{3,4b}$= 5.0 Hz, $J_{4b,6}$= 1.9 Hz, $J_{4a,4b}$= 13.4 Hz, H-4b), 1.95 (s, 3H, OAc), 1.89 (m, 1H, H-12eq), 1.87 (m, 1H, H-17), 1.86 (m, 1H, H-7a), 1.68 (m, 1H, H-1a), 1.68 (m, 1H, H-24a), 1.67 (m, 1H, H-2a), 1.59 (m, 1H, H-2b), 1.56 (m 1H, H-25), 1.45 (m, 1H, H-8), 1.45 (m, 1H, H-11a), 1.42 (m, 1H, H-11b), 1.42 (m, 1H, H-7b), 1.33 (m, 1H, H-24b), 1.20 (ddd, 1H, $J_{11eq,12ax}$= 4.8 Hz, $J_{11ax,12ax}$=$J_{12a,12b}$=12.5 Hz, H-12ax), 1.12 (d, 3H, $J_{20,21}$ = 7.1 Hz, CH_3-21), 1.05 (s, 9H, -C(CH_3)$_3$), 0.99 (m, 1H, H-15b), 0.98 (s, 3H, CH_3-19), 0.94 (m, 1H, H-14), 0.90 (d, 3H, $J_{25,27}$= 6.8 Hz, CH_3-27), 0.84 (m, 5H, H-9, H-1b, CH_3-18) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 213.9 (C-22), 170.0 (O*C*(O)CH_3), 141.3 (C-5), 135.9, 135.8 (Ar-C-*m*), 134.8, 134.8 (Ar-C-*ipso*), 129.6, 129.5 (Ar-C-*p*), 127.6, 127.6 (Ar-C-*o*), 120.9 (C-6), 75.8 (C-16), 73.2 (C-3), 67.5 (C-26), 55.1 (C-17), 54.1 (C-14), 49.9 (C-9), 43.6 (C-20), 42.5 (C-4), 42.0 (C-13), 39.7 (C-12), 38.6 (C-23), 37.2 (C-1), 36.5 (C-10), 35.5 (C-25), 34.9 (C-15), 31.9 (C-2), 31.7 (C-7), 31.3 (C-8), 27.1 (C(*C*H_3)$_3$), 26.3 (C-24), 21.3 (OAc), 20.8 (C-11), 19.5 (C-19), 19.2 (*C*(CH_3)$_3$), 17.0 (C-21), 16.7 (C-27), 13.3 (C-18) ppm; HRESI-MS calcd for $C_{45}H_{64}NaO_5Si$ ([M+Na]$^+$): 735.4415, found: 735.4402.

9. **(25*R*)-3β-*tert*-Butyldiphenylsilyloxy-26-mesyloxy-22-oxocholest-5-en-16β-yl acetate (45).** To a cooled solution of **44** (0.2 g, 0.28 mmol) in dry CH_2Cl_2 (2 mL) were dropwise added MsCl (90 µL, 1.12 mmol) and Et_3N (0.35 mL, 2.52 mmol) under Ar. The mixture was stirred at 0 °C for 1 h, and then, washed with aq. 5% HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. Column chromatography (17:3 hexane–EtOAc) afforded **45** as a white foam. Yield: 0.2 g, 90%. $[\alpha]_D^{20}$ –22 (*c* 0.3, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4H, Ar-H-*m*), 7.41 (m, 2H, Ar-H-*p*), 7.36 (m, 4H, Ar-H-*o*), 5.10 (m, 1H, H-6), 4.95 (td, 1H, $J_{16,17}$=$J_{15eq,16}$= 7.8 Hz, $J_{15ax,16}$= 4.8 Hz, H-16), 4.05 (dd, 1H, $J_{26a,25}$ = 6.0 Hz, $J_{26a,26b}$= 9.7 Hz, H-26a), 4.03 (dd, 1H, $J_{25,26b}$= 6.2 Hz, H-26b), 3.52 (m, 1H, H-3), 3.01 (s, 3H, SO_2CH_3), 2.92 (dq, 1H, $J_{17,20}$= 11.2 Hz, $J_{20,21}$ = 7.1 Hz, H-20), 2.64 (ddd, 1H, $J_{23a,24a}$= 9.4 Hz, $J_{23a,24b}$= 6.3 Hz, $J_{23a,23b}$= 17.9 Hz, H-23a), 2.35 (m, 1H, H-15a), 2.34 (m, 1H, H-23b), 2.30 (m, 1H, H-4a), 2.12 (ddd, 1H, $J_{3,4b}$ = 4.7 Hz, $J_{4b,6}$ = 1.6 Hz, $J_{4a,4b}$ = 13.3 Hz, H-4b), 1.95 (s, 3H, $COCH_3$), 1.88 (m, 1H, H-12eq), 1.87 (m, 1H, H-17), 1.85 (m, 1H, H-25), 1.85 (m, 1H, H-7a), 1.70 (m, 1H, H-24a), 1.68 (m, 1H, H-1a), 1.67 (m, 1H, H-2a), 1.58 (m, 1H, H-2b), 1.45 (m, 1H, H-11a), 1.45 (m, 1H, H-8), 1.42 (m, 1H, H-7b), 1.41 (m, 1H, H-11b), 1.38 (m, 1H, H-24b), 1.20 (ddd, 1H, $J_{11eq,12ax}$= 4.7 Hz, $J_{12ax,12eq}$=$J_{12ax,11ax}$= 12.4 Hz, H-12ax), 1.11 (d, 3H, $J_{20,21}$ = 7.1 Hz, CH_3-21), 1.05 (s, 9H, $C(CH_3)_3$), 0.98 (m, 1H, H-15b), 0.98 (s, 3H, CH_3-19), 0.97 (d, 3H, $J_{25,27}$ = 7.0 Hz, CH_3-27), 0.94 (m, 1H, H-14), 0.84 (m, 1H, H-1b), 0.84 (m, 1H, H-9), 0.84 (s, 3H, CH_3-18). ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 212.6 (C-22), 169.9 (O*C*(O)CH_3), 141.3 (C-5), 135.9, 135.8 (Ar-C-*m*), 134.8 (x2) (Ar-C-*ipso*), 129.6, 129.5 (Ar-C-*p*), 127.6, 127.6 (Ar-C-*o*), 120.9 (C-6), 75.8 (C-16), 74.2 (C-26), 73.2 (C-3), 55.1 (C-17), 54.1 (C-14), 49.9 (C-9), 43.7 (C-20), 42.5 (C-4), 42.0 (C-13), 39.7 (C-12), 38.1 (C-23), 37.4 (SO_2CH_3), 37.2 (C-1), 36.5 (C-10), 34.9 (C-15), 32.7 (C-25), 31.9 (C-2), 31.7 (C-7), 31.3 (C-8), 27.1 ($C(CH_3)_3$), 26.4 (C-24), 21.3 (OAc), 20.8 (C-11), 19.5 (C-19), 19.2 ($C(CH_3)_3$), 16.8 (C-21), 16.4 (C-27), 13.3 (C-18); HRESI-MS calcd for $C_{46}H_{66}NaO_7SSi$ ($[M+Na]^+$): 813.4191, found: 813.4163.

10. **(25*R*)-3β-*tert*-Butyldiphenylsilyloxy-22-oxo-26-selenocyanatocholest-5-en-16β-yl acetate (46).** KSeCN (0.8 g, 5.55 mmol) was added to a solution of **45** (0.88 g, 1.11 mmol) in dry THF (40 mL) under Ar. The mixture was refluxed in the dark for 10 h. After that, it was concentrated to dryness and the residue was purified by column chromatography (17:3 hexane-EtOAc) to give **46** as a white foam. Yield: 0.84 g, 94%. $[\alpha]_D^{20}$ +1 (*c* 1.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ar-H-*m*), 7.41 (m, 2H, Ar-H-*p*), 7.36 (m, 4H, Ar-C-*o*), 5.10 (m, 1H, H-6), 4.96 (td, 1H, $J_{16,17}$=$J_{15eq,16}$= 7.9 Hz, $J_{15ax,16}$= 4.8 Hz, H-16), 3.52 (m, 1H, H-3), 3.09 (dd, 1H, $J_{25,26a}$ = 5.4 Hz, $J_{26a,26b}$= 12.1 Hz, H-26a), 2.93 (dq, 1H, $J_{17,20}$ = 11.1 Hz, $J_{20,21}$= 7.1 1H, H-20), 2.91 (dd, 1H, $J_{25,26b}$= 7.1 Hz, H-26b), 2.65 (ddd, 1H, $J_{23a,24a}$= 9.0 Hz, $J_{23a,24b}$= 6.4 Hz, $J_{23a,23b}$= 18.1 Hz, H-23a), 2.36 (m, 1H, H-15a), 2.36 (m, 1H, H-23b), 2.32 (m, 1H, H-4a), 2.12 (ddd, 1H, $J_{3,4b}$= 4.9 Hz, $J_{4b,6}$= 1.8 Hz, $J_{4a,4b}$= 13.4 Hz, H-4b), 1.96 (s, 3H, $COCH_3$), 1.89 (m, 1H, H-12eq), 1.88 (m, 1H, H-17), 1.87 (m, 1H, H-25), 1.86 (m, 1H, H-7a), 1.75 (m, 1H, H-24a), 1.69 (m, 1H, H-1a), 1.68 (m, 1H, H-2a), 1.59 (m, 1H, H-2b), 1.47 (m, 1H, H-8), 1.46 (m, 1H, H-11a), 1.43 (m, 1H, H-24b), 1.42 (m, 1H, H-11b), 1.42 (m, 1H, H-7b), 1.21 (ddd, 1H, $J_{11eq,12ax}$= 4.2 Hz, $J_{11ax,12ax}$= $J_{12ax,12eq}$= 11.8 Hz,, H-12ax), 1.12 (d, 3H, $J_{20,21}$= 7.1 Hz, CH_3-21), 1.06 (s, 9H, $C(CH_3)_3$), 1.05 (d, 3H, CH_3-27), 1.0 (m, 1H, H-15b), 0.99 (s, 3H, CH_3-19), 0.96 (m, 1H, H-14), 0.85 (m, 1H, H-1b), 0.85 (m, 1H, H-9), 0.84 (s, 3H, CH_3-18); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 212.5 (C-22), 169.8 ($OC(O)CH_3$), 141.3 (C-5), 135.8, 135.8 (Ar-C-*m*), 134.8, 134.8 (Ar-C-*ipso*), 129.6, 129.5 (Ar-C-*p*), 127.6, 127.5 (Ar-C-*o*), 120.8 (C-6), 102.3 (SeCN), 75.8 (C-16), 73.2 (C-3), 55.1 (C-17), 54.0 (C-14), 49.8 (C-9), 43.6 (C-20), 42.5 (C-4), 41.9 (C-13), 39.7 (C-12), 38.4 (C-23), 37.6 (C-26), 37.2 (C-1), 36.5 (C-10), 34.9 (C-15), 34.0 (C-25), 31.9 (C-2), 31.6 (C-7), 31.3 (C-8), 29.2 (C-24), 27.1 ($C(CH_3)_3$), 21.3 ($OC(O)CH_3$), 20.8 (C-11), 19.5 (C-19), 19.3 (C-27), 19.2 ($C(CH_3)_3$), 16.9 (C-21), 13.3 (C-18); HRESI-MS calcd for $C_{46}H_{63}NNaO_4{}^{80}SeSi$ ($[M+Na]^+$): 824.3584, found: 824.3557.

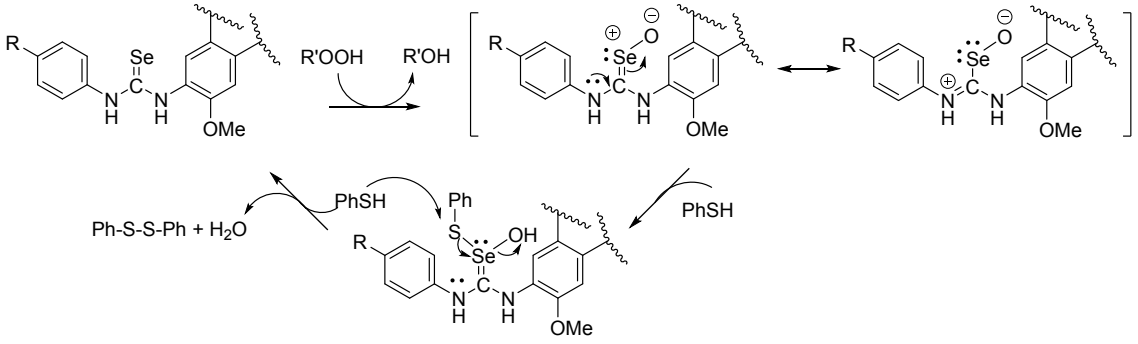
11. **Bis[(25*R*)-16β-Acetoxy-3β-*tert*-butyldiphenylsilyloxy-22-oxo-cholest-5-en-26-yl]diselenide (47).** $NaBH_4$ (6.0 mg, 0.16 mmol) was added, under Ar, to a solution of **46** (0.25 g, 0.31 mmol) in a dry 5:3 MeOH–THF mixture (8 mL). The mixture was stirred at rt for 30 min, and after that, the solvent was removed *in vacuo*. The

residue was partitioned between H_2O and CH_2Cl_2; the organic layer was dried over $MgSO_4$, filtrated, and the filtrate was concentrated to dryness. Column chromatography of the residue (19:1 hexane-EtOAc) afforded **47** as a yellow foam. Yield: 0.16 g, 68%. $[\alpha]_D^{22}$ +11 (*c* 0.2, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ar-H-*m*), 7.41 (m, 2H, Ar-H-*p*), 7.36 (m, 4H, Ar-H-*o*), 5.10 (m, 1H, H-6), 4.93 (ddd, 1H, $J_{16,17}$= $J_{15eq,16}$= 7.9 Hz, $J_{15ax,16}$= 4.8 Hz, H-16), 3.51 (m, 1H, H-3), 2.96 (dd, 1H, $J_{25,26a}$= 5.3 Hz, $J_{26a,26b}$= 12.0 Hz, H-26a), 2.93 (dq, 1H, $J_{17,20}$= 11.0 Hz, $J_{20,21}$= 7.1 Hz, H-20), 2.80 (dd, 1H, $J_{26b,25}$= 7.3 Hz, H-26b), 2.61 (ddd, 1H, $J_{23a,24a}$= 10.4 Hz, $J_{23a,24b}$= 5.4 Hz, $J_{23a,23b}$= 17.8 Hz, H-23a), 2.36 (m, 1H, H-15a), 2.34 (m, 1H, H-23b), 2.31 (m, 1H, H-4a), 2.11 (ddd, 1H, $J_{3,4b}$= 4.8 Hz, $J_{4b,6}$ = 1.8 Hz, $J_{4a,4b}$= 13.4 Hz, H-4b), 1.95 (s, 3H, $COCH_3$), 1.89 (m, 1H, H-12eq), 1.87 (m, 1H, H-17), 1.85 (m, 1H, H-7a), 1.71 (m, 1H, H-24a), 1.71 (m, 1H, H-25), 1.68 (m, 1H, H-1a), 1.67 (m, 1H, H-2a), 1.59 (m, 1H, H-2b), 1.45 (m, 1H, H-11a), 1.44 (m, 1H, H-8), 1.41 (m, 1H, H-7b), 1.41 (m, 1H, H-11b), 1.37 (m, 1H, H-24b), 1.19 (td, 1H, $J_{11eq,12ax}$= 4.8 Hz, $J_{12ax,12eq}$=$J_{11ax,12ax}$= 12.5 Hz, H-12ax), 1.11 (d, 3H, $J_{20,21}$= 7.1 Hz, CH_3-21), 1.05 (s, 9H, $C(CH_3)_3$), 0.98 (s, 3H, CH_3-19), 0.98 (m, 1H, H-15b), 0.97 (d, 3H, $J_{25,27}$= 5.6 Hz, CH_3-27), 0.94 (m, 1H, H-14), 0.84 (m, 1H, H-9), 0.83 (m, 1H, H-1b), 0.83 (s, 3H, CH_3-18). ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 213.0 (C-22), 169.9 (O*C*(O)CH_3), 141.3 (C-5), 135.9, 135.9 (Ar-C-*m*), 134.8 (x2) (Ar-C-*ipso*), 129.6 (x2) (Ar-C-*p*), 127.6 (x2) (Ar-C-*o*), 120.9 (C-6), 75.9 (C-16), 73.2 (C-3), 55.0 (C-17), 54.0 (C-14), 49.8 (C-9), 43.6 (C-20), 42.5 (C-4), 41.9 (C-13), 39.7 (C-12), 38.9 (C-26), 38.8 (C-23), 37.2 (C-1), 36.5 (C-10), 34.9 (C-15), 34.0 (C-25), 31.9 (C-2), 31.7 (C-7), 31.3 (C-8), 29.9 (C-24), 27.1 (C(*C*H_3)$_3$), 21.4 (OC(O)*C*H_3), 20.8 (C-11), 19.6 (C-19), 19.5 (C-27), 19.3 (*C*$(CH_3)_3$), 16.9 (C-21), 13.3 (C-18); HRESI-MS calcd for $C_{90}H_{126}NaO_8{}^{80}Se_2Si_2$ ($[M+Na]^+$): 1573.7214, found: 1573.7217.



27

Scheme S1. Plausible mechanism for the synthesis of 27

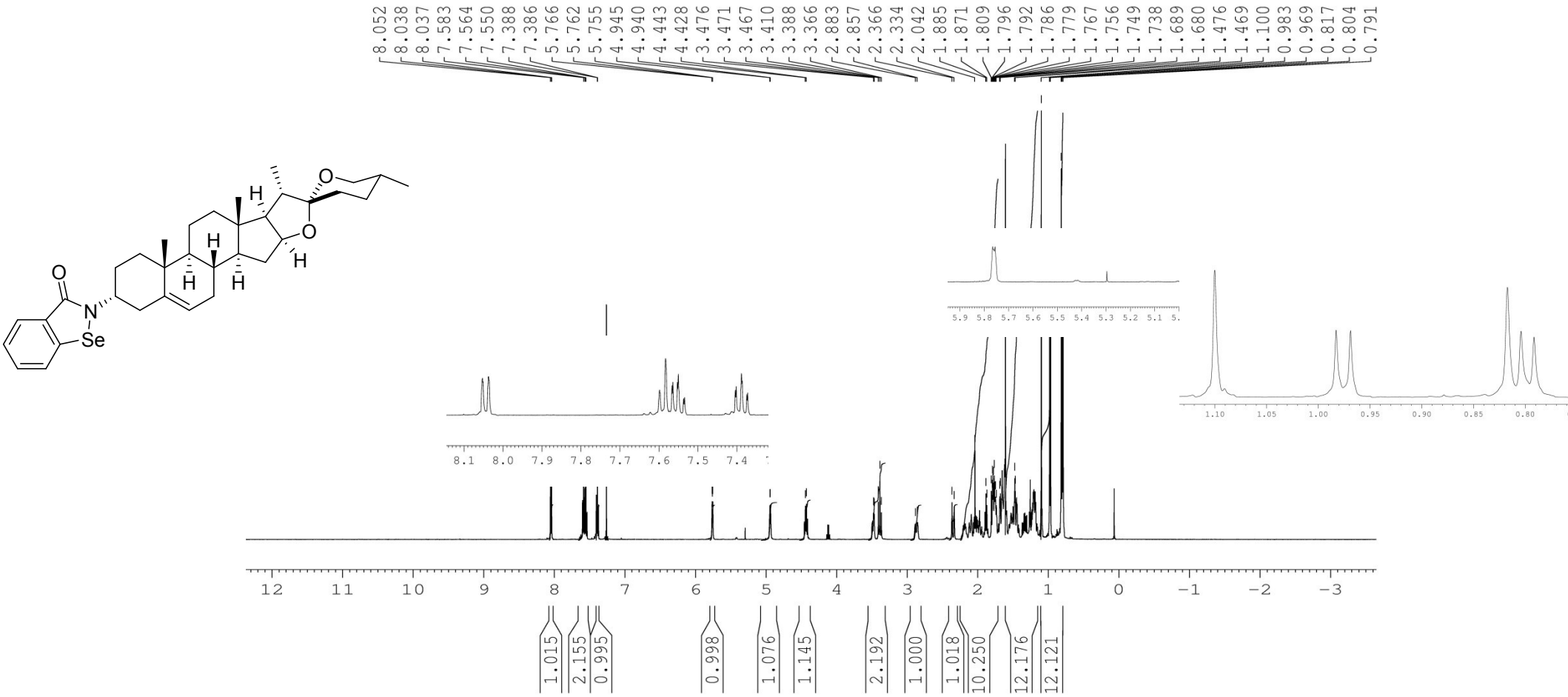


Scheme S2. Mechanism for the GPx-like activity of estrone selenoureas (PhSH method)

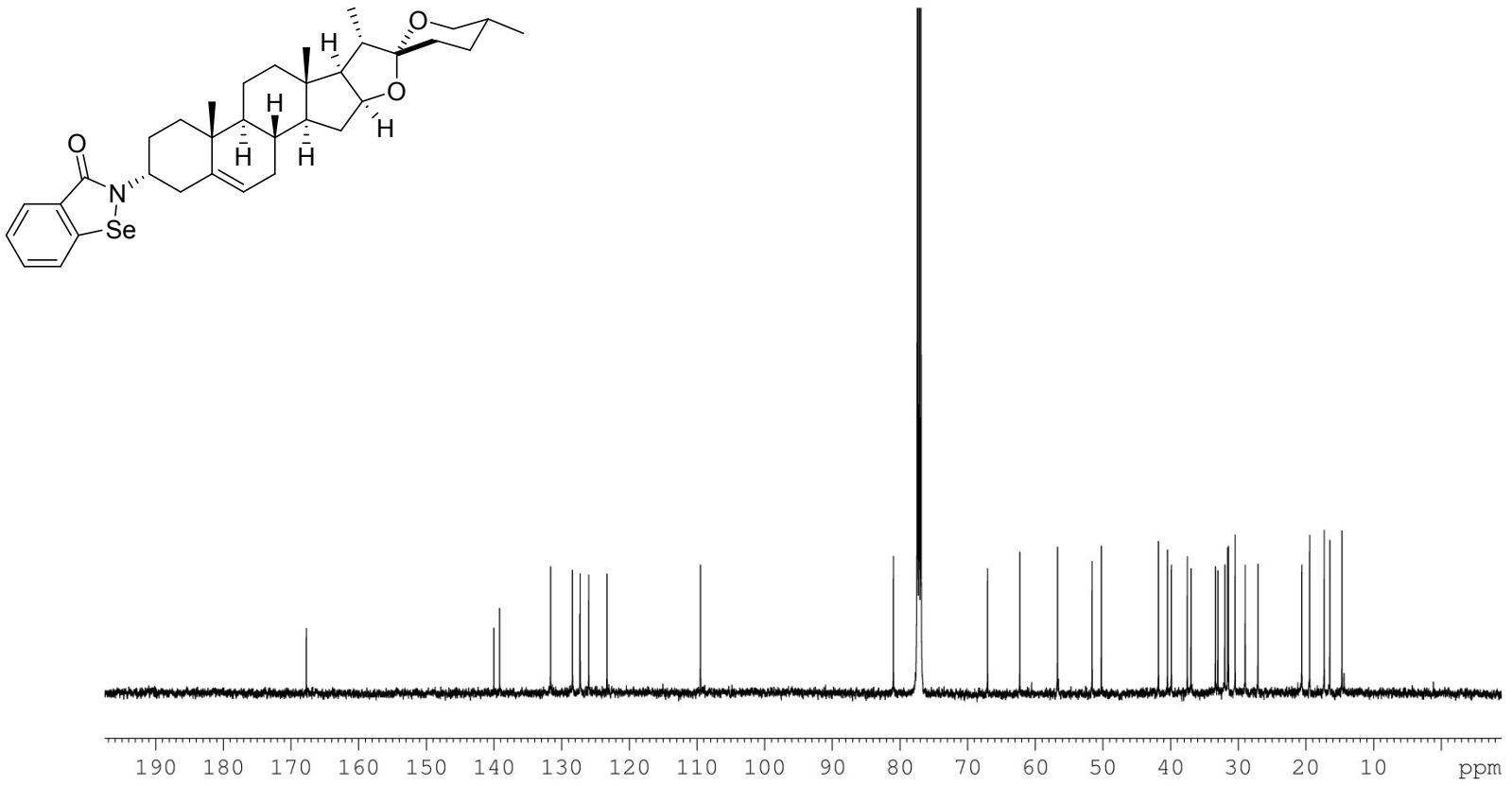
Table S1. Antiproliferative activity (GI_{50}, μM) of selenosteroids against human solid tumour cells

Compound	Cell lines					
	A549	**HBL-100**	**SW1573**	**HeLa**	**T-47D**	**WiDr**
9	>100	38±11	33.0±4.0	32.0±2.6	>100	>100
10				[a]		
11	35.0±6.2	45.0±6.8	27.0±0.7	32.0±3.2	83±23	88±17
16	69±12	89±19	89±20	86±20	83±23	>100
17	**3.7±0.9**	**3.8±1.0**	**3.3±1.5**	**2.9±0.5**	13.0±1.7	**8.1±0.3**
18	**4.6±1.1**	33±14	**4.9±1.6**	**4.5±1.6**	58±28	31±15
24	**2.8±0.8**	12.0±2.3	**6.4±2.7**	**4.5±1.7**	**4.0±1.7**	**0.3±0.1**
25	**3.1±1.2**	**7.6±0.8**	**3.6±0.2**	**4.2±0.4**	**4.1±0.1**	**2.4±1.1**
27	>100	>100	>100	>100	>100	>100
28	**2.2±0.2**	**2.5±0.3**	**4.1±0.4**	**2.1±0.4**	**3.9±0.6**	**3.6±0.4**
29	**2.4±0.4**	**2.4±0.1**	**2.9±0.6**	**2.1±0.3**	**3.0±0.8**	**2.8±0.7**
30	**2.7±0.3**	**2.3±0.4**	**3.3±0.6**	**2.3±0.5**	**3.2±1.0**	**3.3±1.0**
31	**2.5±0.2**	**2.3±0.2**	**3.5±0.1**	**2.0±0.4**	**3.5±0.7**	**3.4±0.6**
32	**2.0±0.4**	**2.2±0.1**	**3.8±0.7**	**2.0±0.5**	**2.8±0.5**	**3.3±1.7**
34	24.0±1.7	94±10	>100	80±34	39.0±1.9	10.0±0.6
35	**4.1±0.7**	22.0±3.4	**4.5±1.0**	15.0±0.1	19.0±1.7	22.0±1.3
36	>100	>100	>100	>100	96	83
39	**6.0±1.1**	>100	93±13	61±16	**7.9±1.4**	**7.3±0.2**
40	**4.4±1.4**	50.0±6.8	30±3.4	31.0±6.1	76±23	64±15
42	37.0±3.8	38.0±9.2	34.0±4.1	29.0±0.1	44±10	31.0±0.1
48	>100	>100	53±13	>100	>100	>100
51	**1.7±0.5**	**2.2±0.2**	**2.2±0.5**	**3.3±0.4**	**3.2±0.8**	**5.5±1.4**
Ebselen	25±9	13±3	26±8	28±4	90±15	>100
5-Fluorouracil	---[b]	5.5±2.3	15±4.7	4.3±1.6	47±18	49±6.7
Cisplatin	4.9±0.2	1.9±0.2	2.0±0.3	3.4±0.7	15±2.3	26±5.6

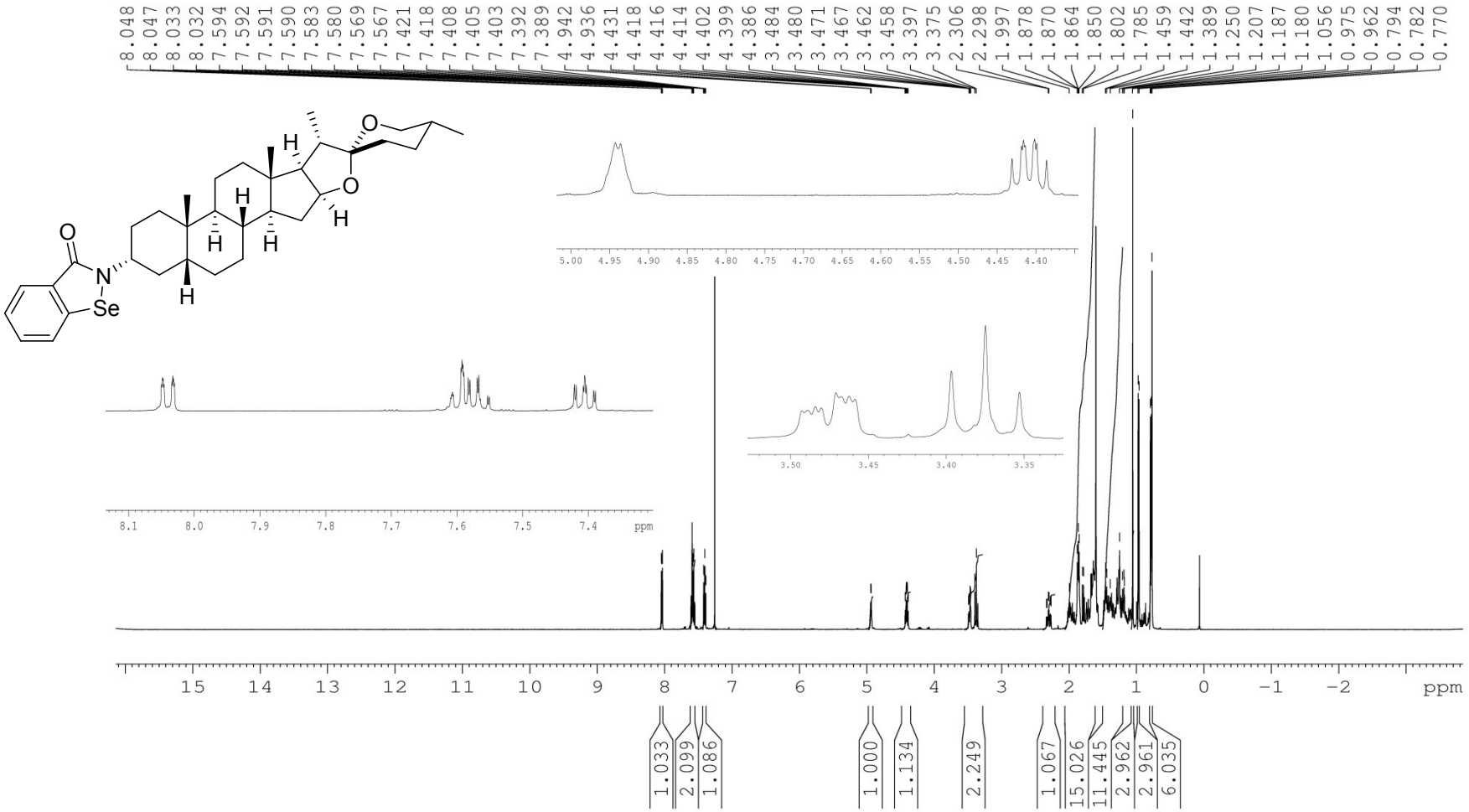
[a] Not soluble under the assay conditions; [b] Not tested



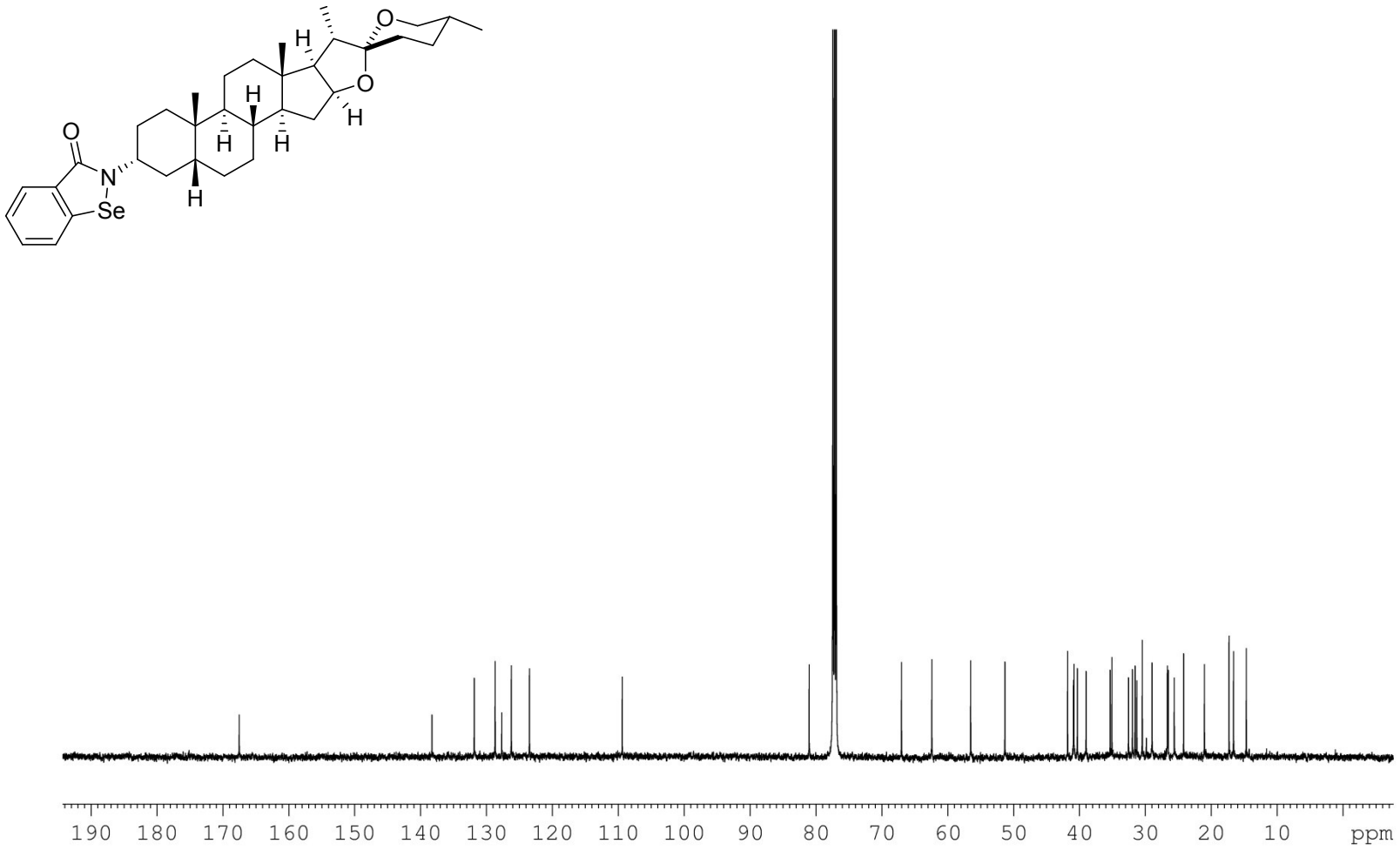
^{1}H-NMR (500 MHz, $CDCl_3$) of **9**



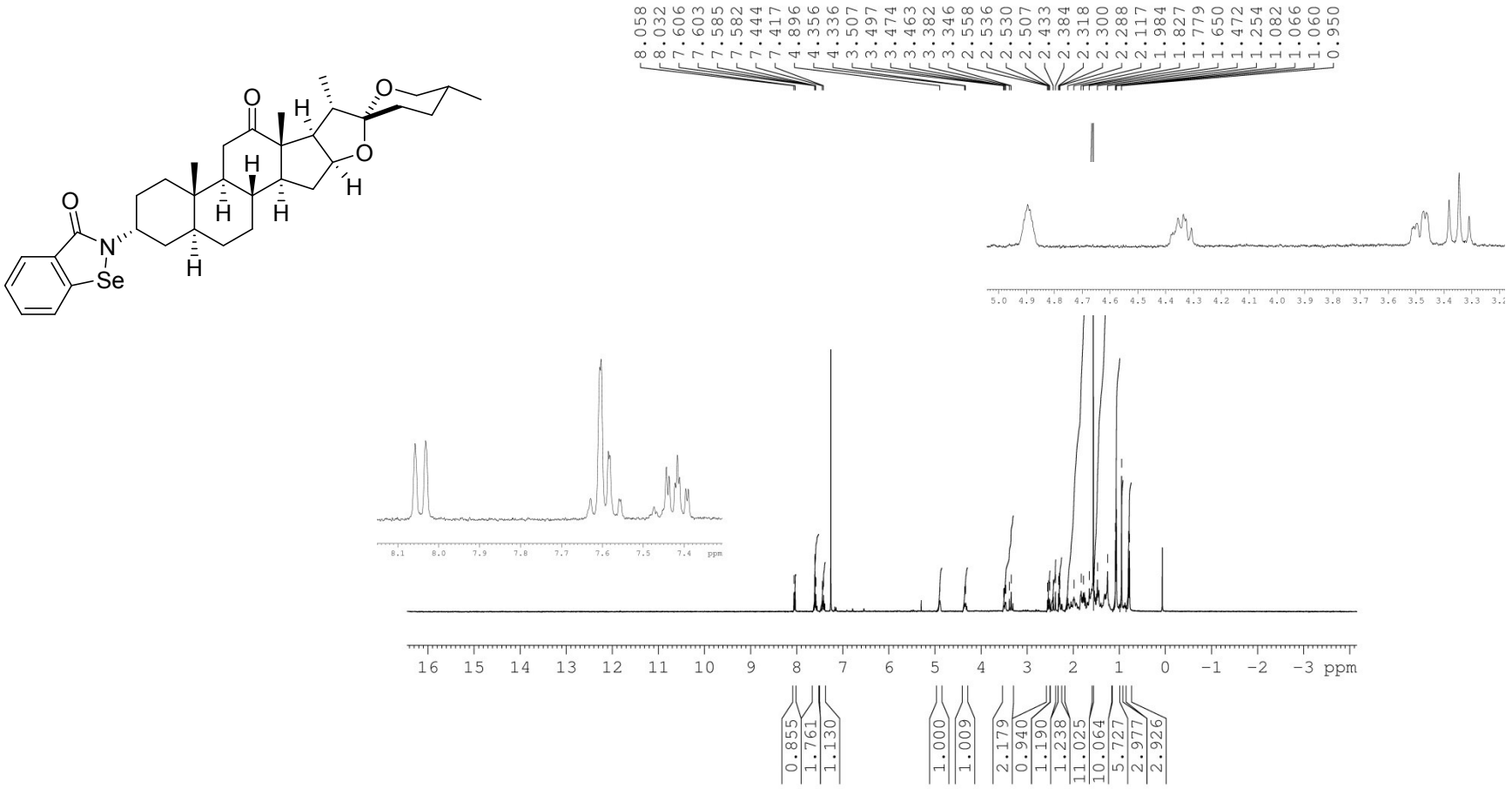
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **9**



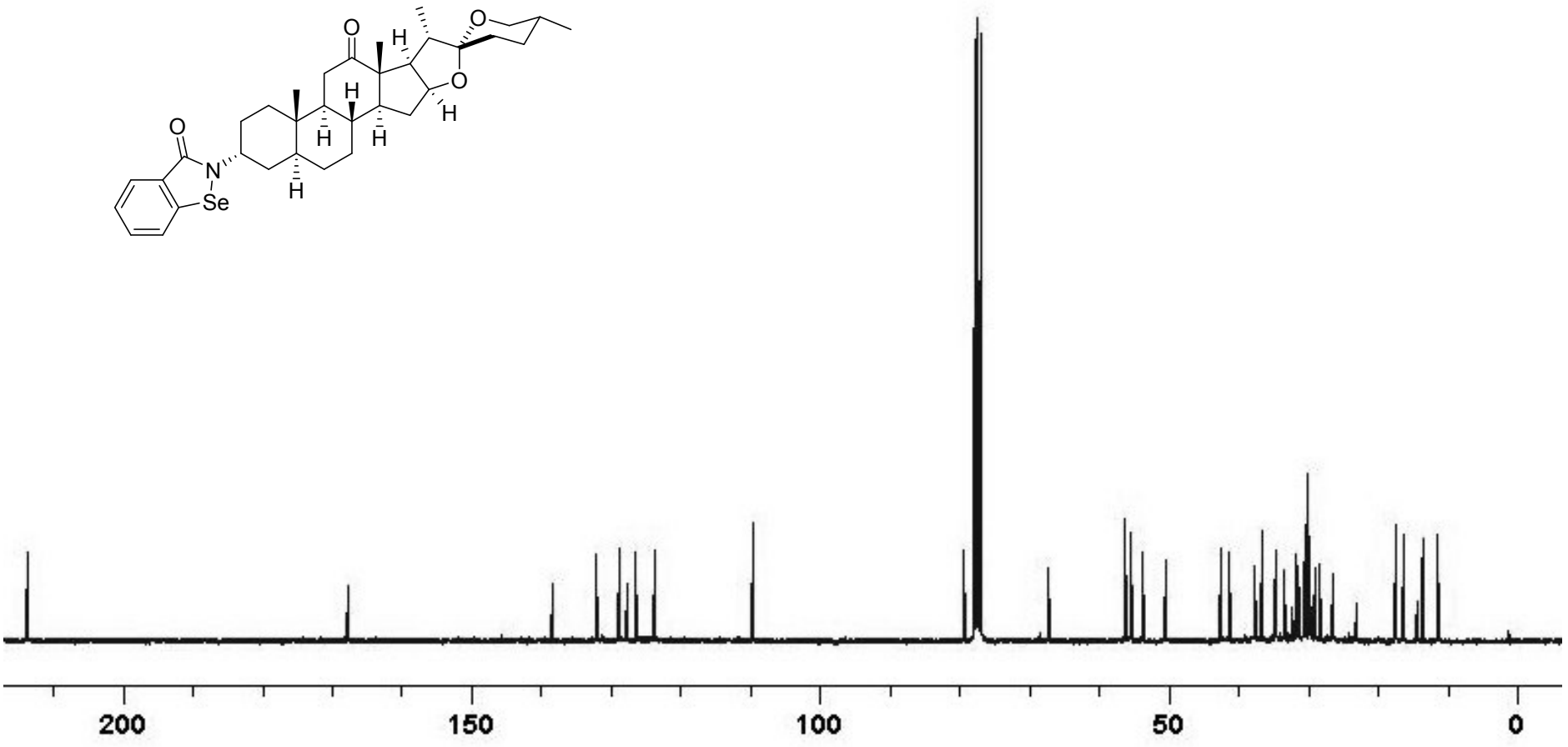
^{1}H-NMR (500 MHz, $CDCl_3$) of **10**



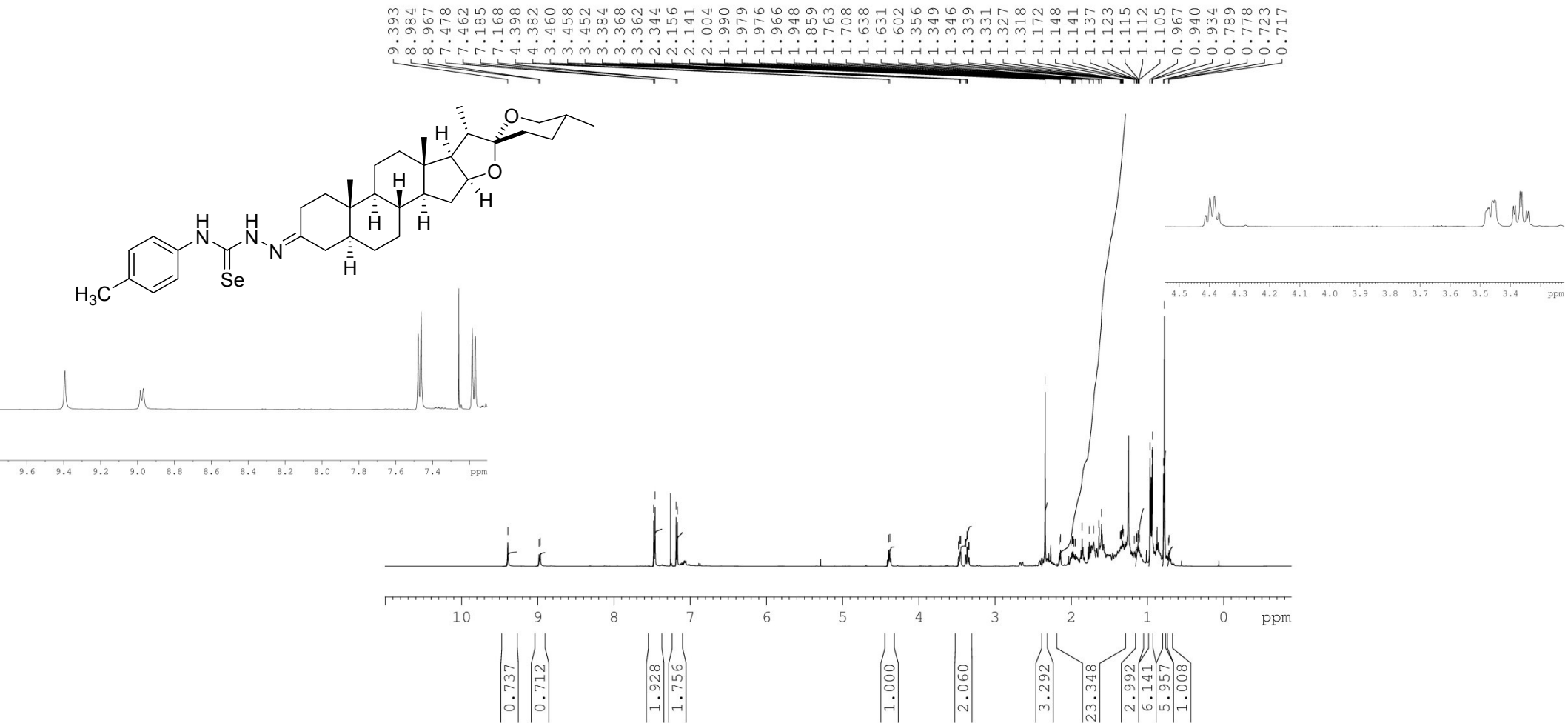
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **10**



^{1}H-NMR (300 MHz, $CDCl_3$) of **11**



^{13}C-NMR (75.5 MHz, $CDCl_3$) of **11**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8.984
8.967
7.478
7.462
7.185
7.168
4.398
4.382
3.460
3.458
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3.384
3.368
3.362
3.344
2.156
2.141
2.004
1.990
1.979
1.976
1.966
1.948
1.859
1.763
1.708
1.638
1.631
1.602
1.356
1.349
1.346
1.339
1.331
1.327
1.318
1.172
1.148
1.141
1.137
1.123
1.115
1.112
1.105
0.967
0.940
0.934
0.789
0.778
0.723
0.717
H
O
O
H
H
H
H
H
H
N
N
N
Se
H_3C
10
9
8
7
6
5
4
3
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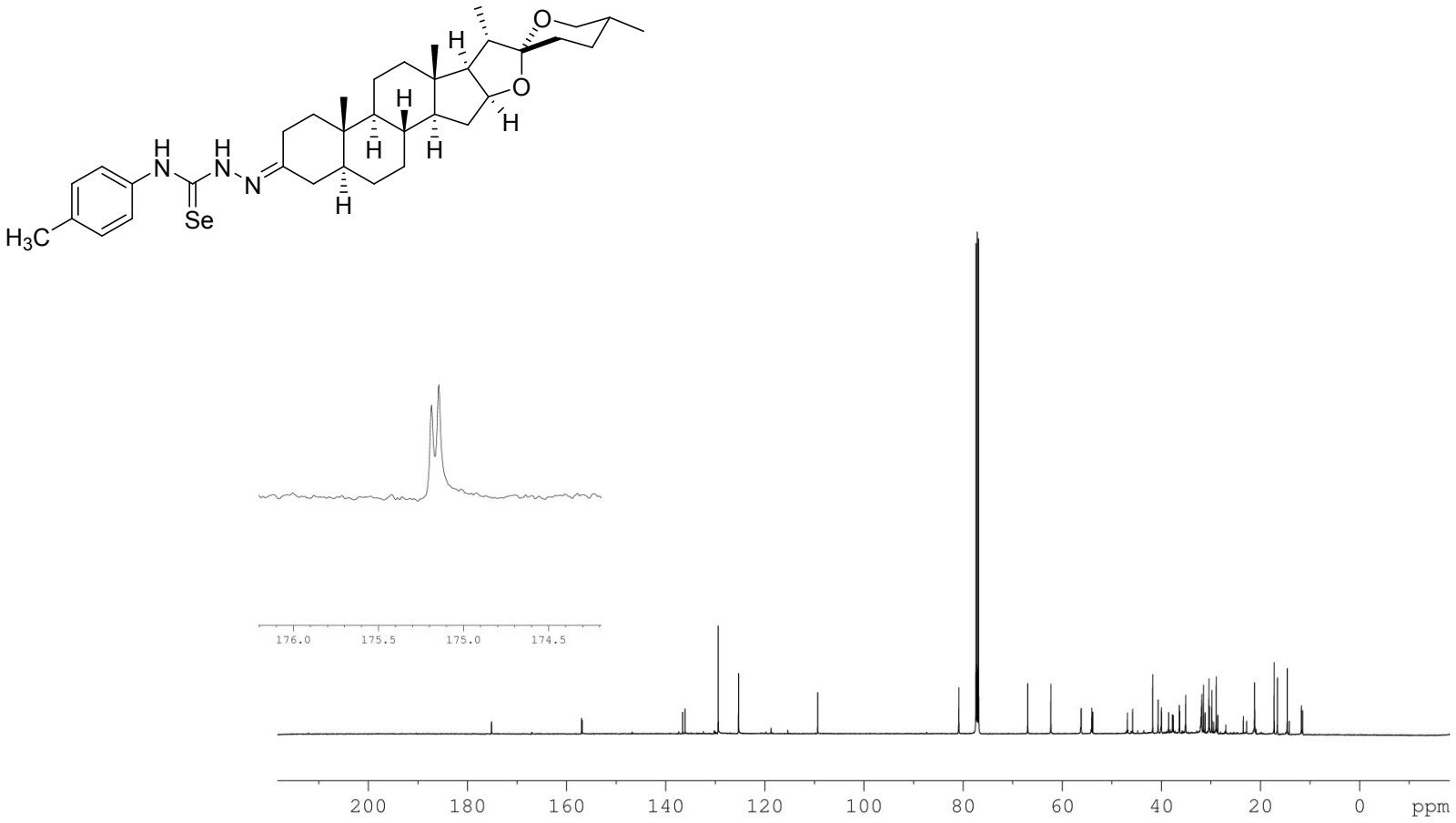
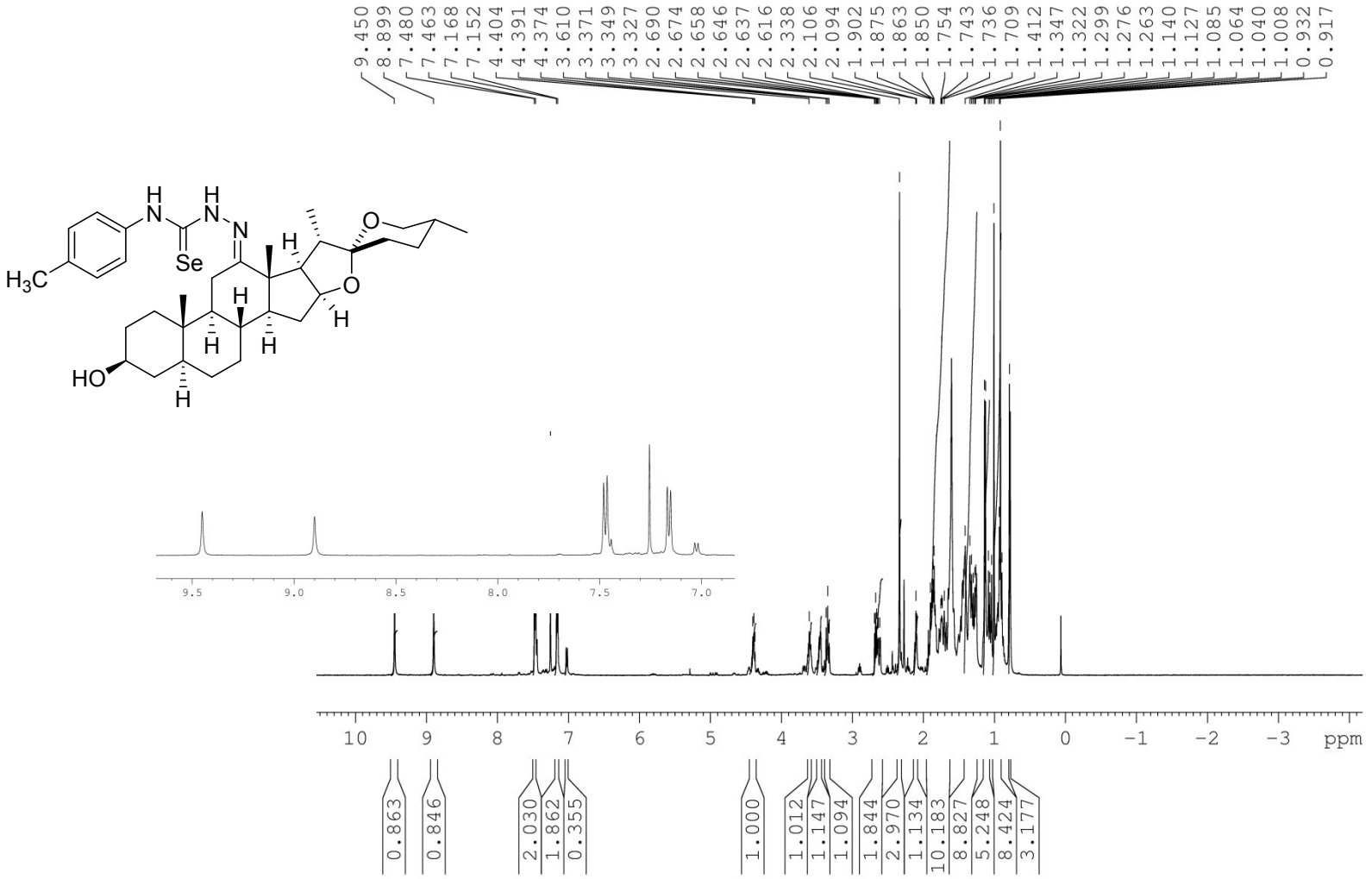
23.348
2.992
6.141
5.957
1.008

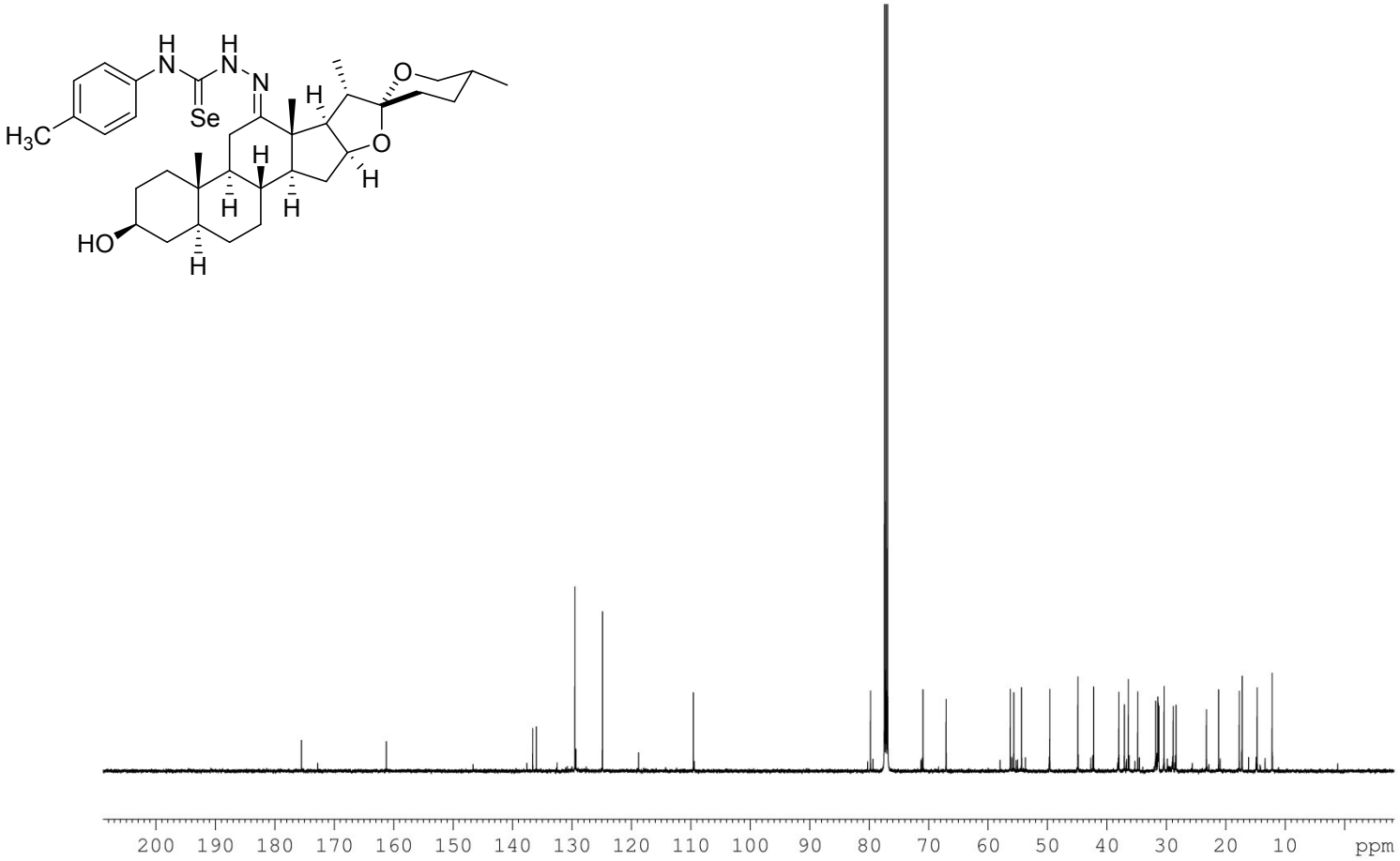
^{1}H-NMR (500 MHz, $CDCl_3$) of **16**



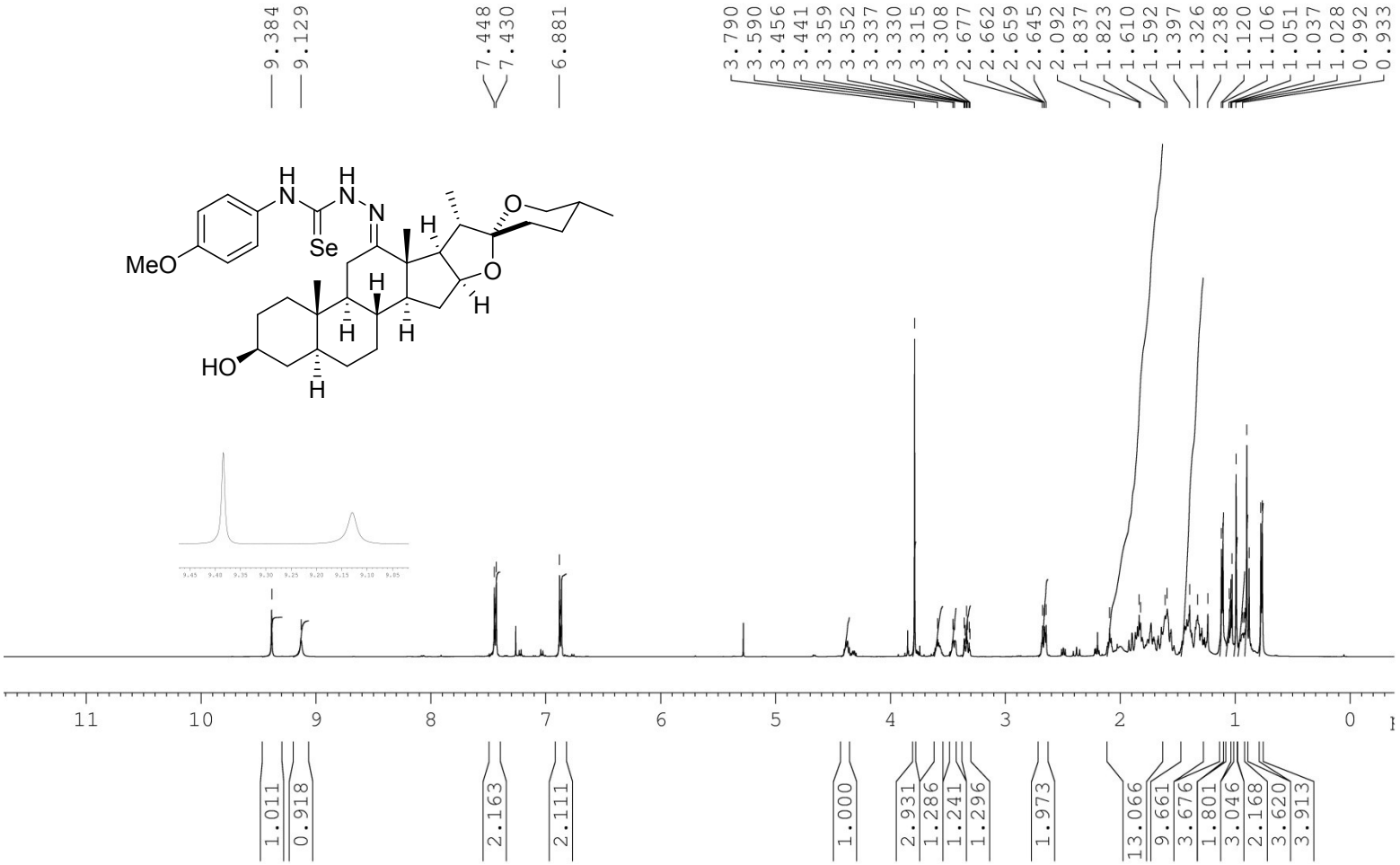
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **16**



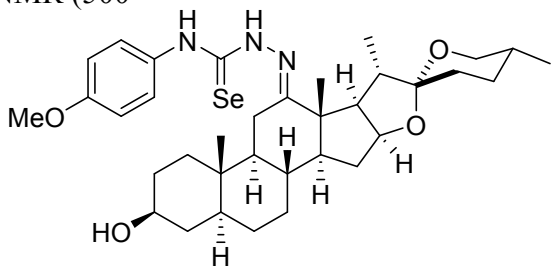
^{1}H-NMR (500 MHz, $CDCl_3$) of **17**

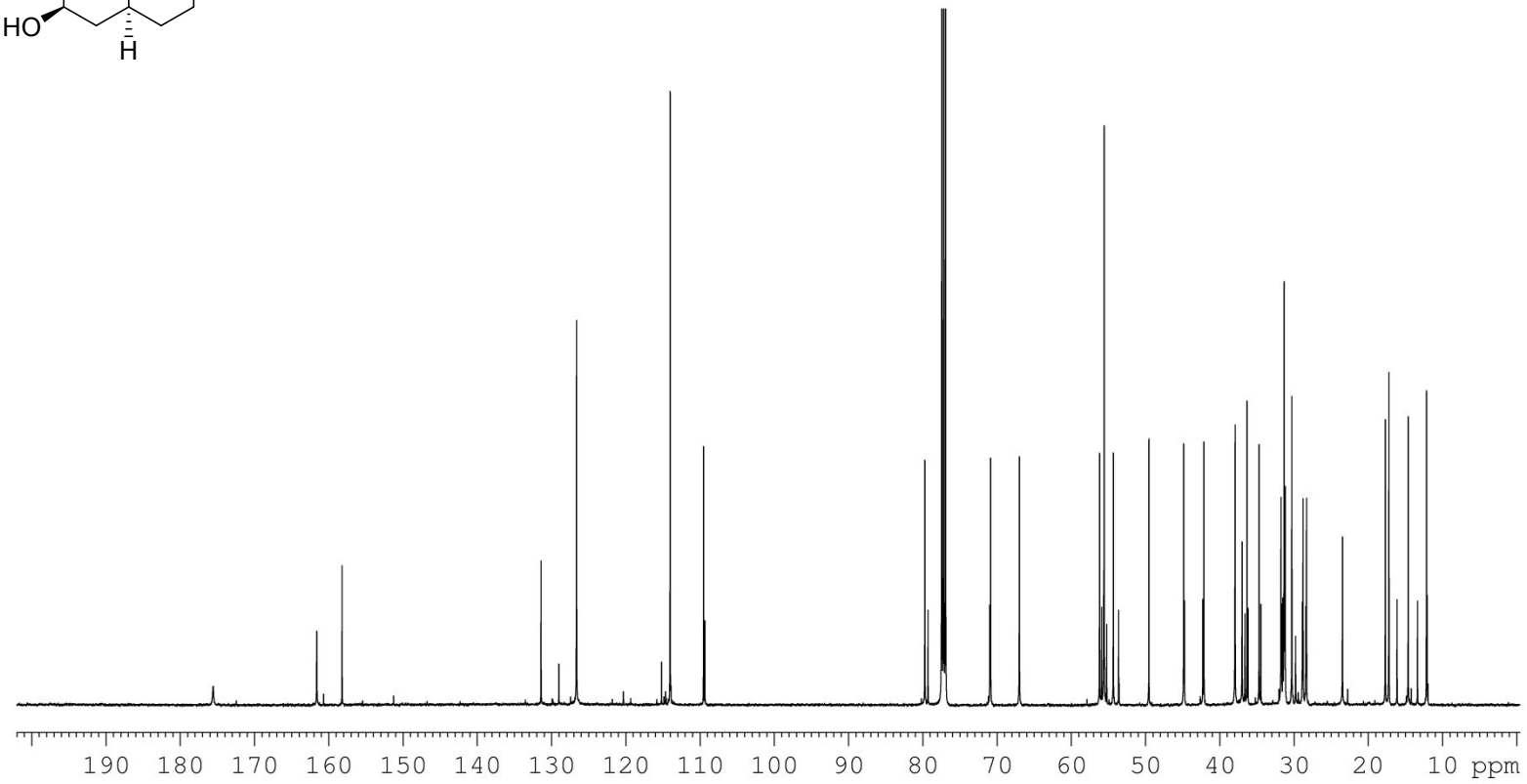


^{13}C-NMR (125.7 MHz, $CDCl_3$) of **17**

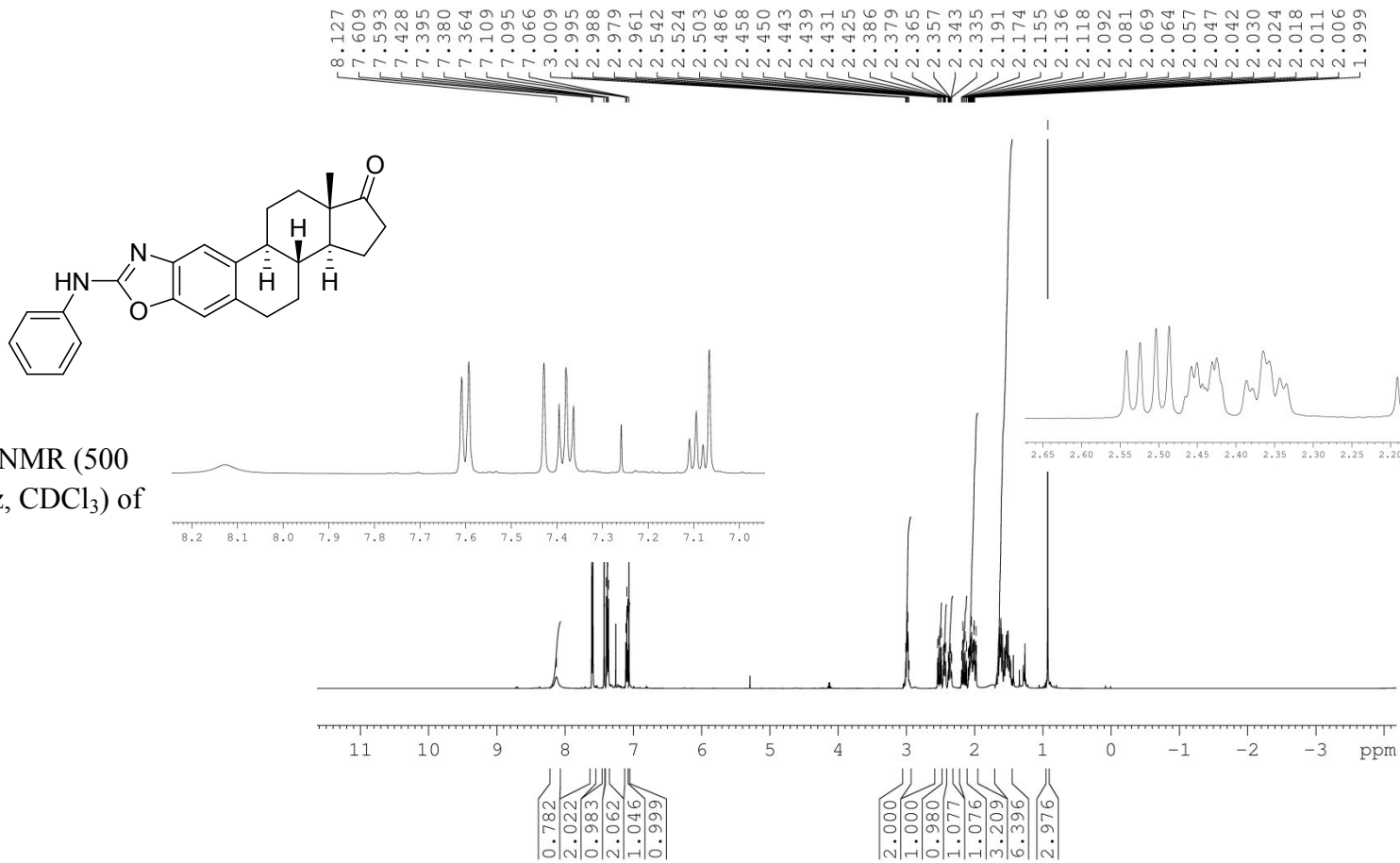


^{1}H-NMR (500 MHz, $CDCl_3$) of **18**

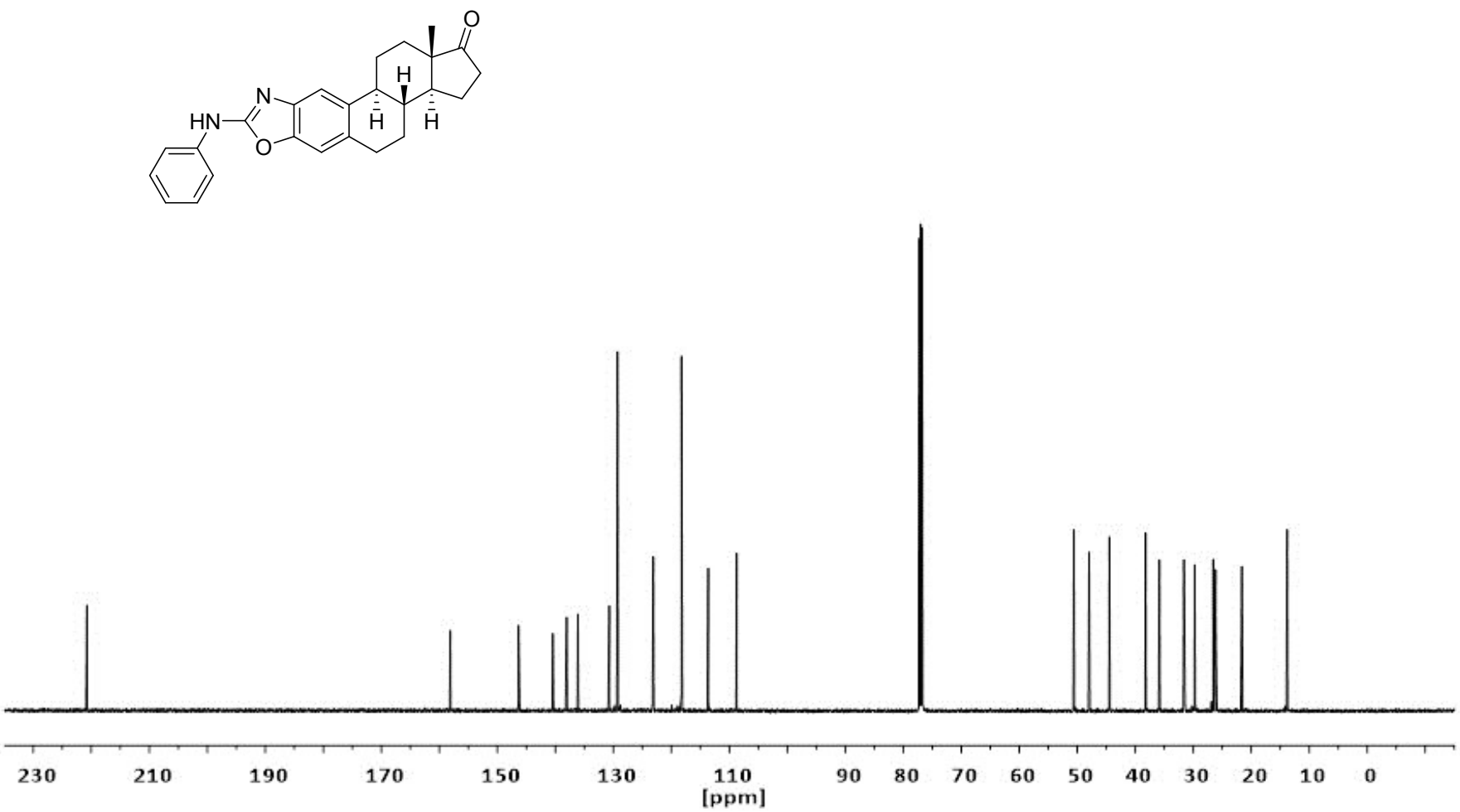




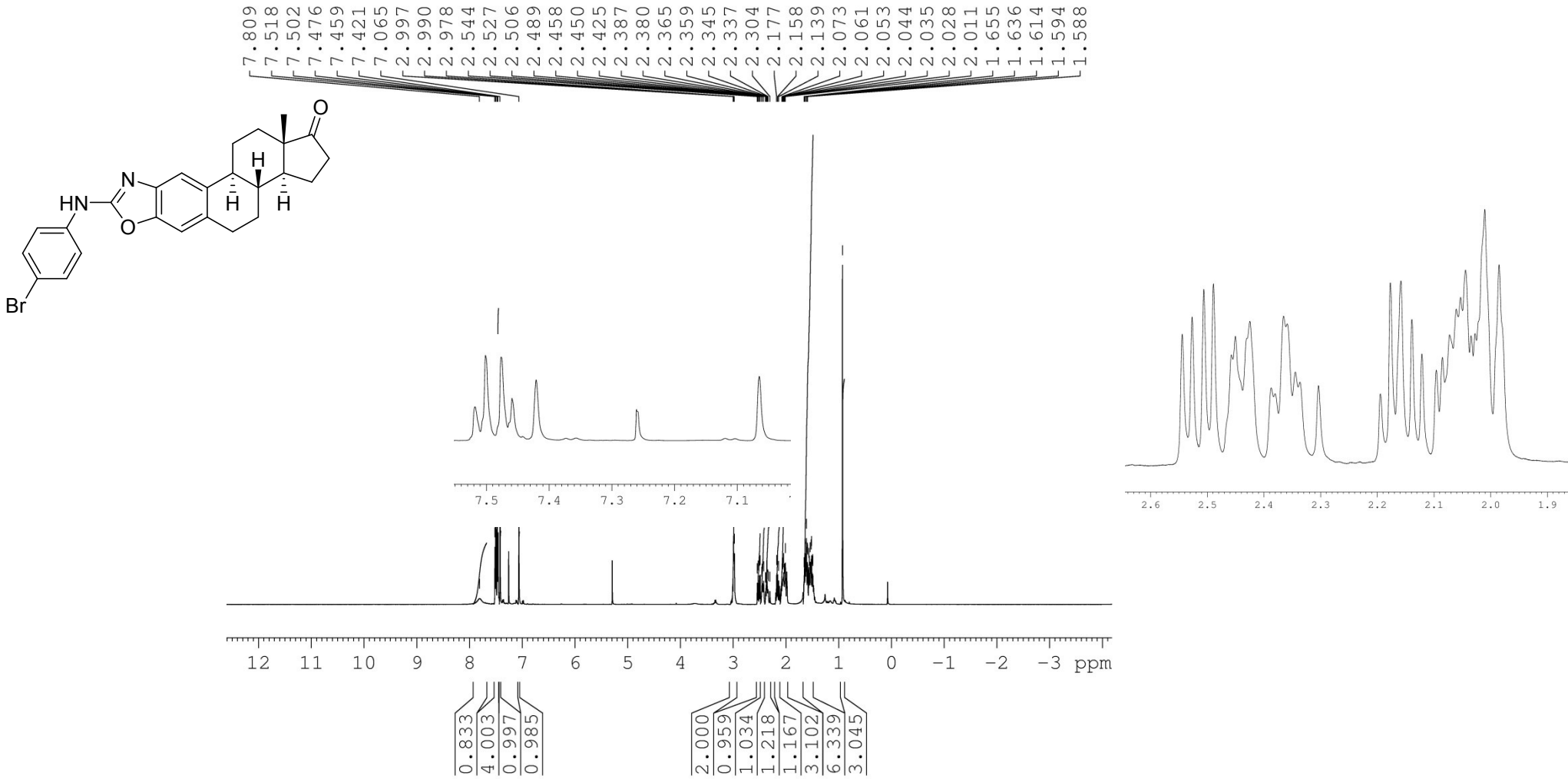
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **18**



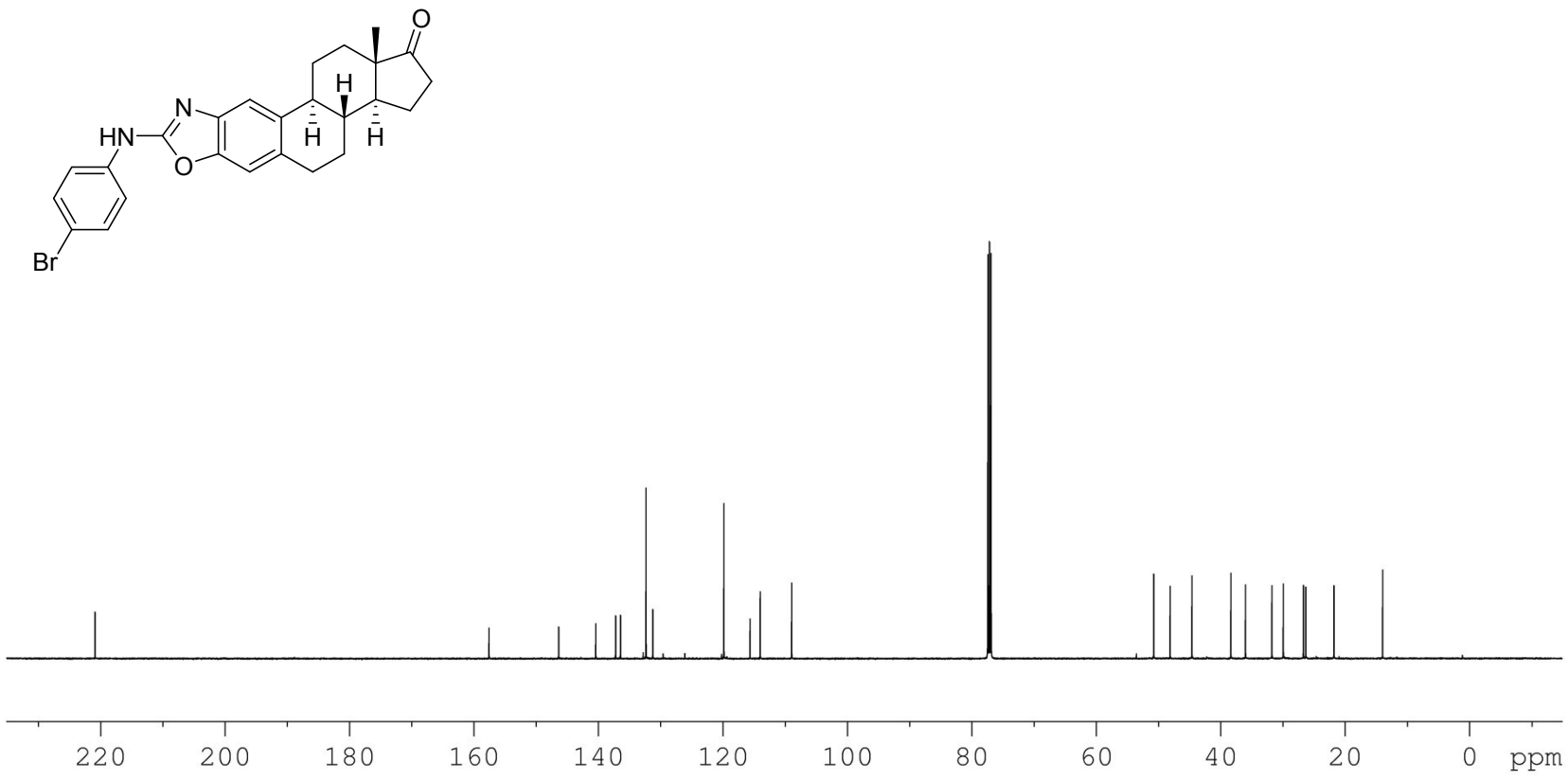
^{1}H-NMR (500 MHz, $CDCl_3$) of **24**



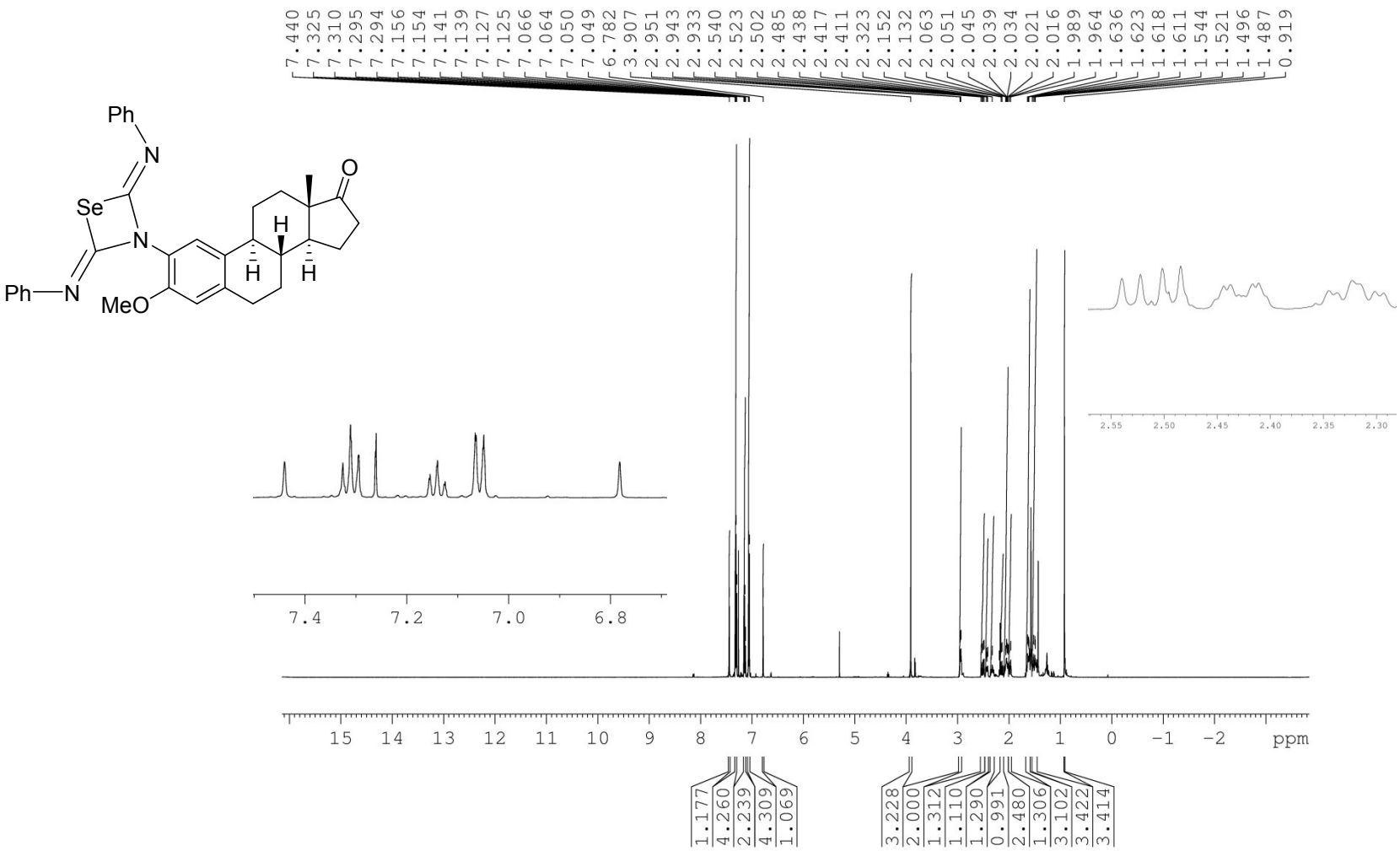
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **24**



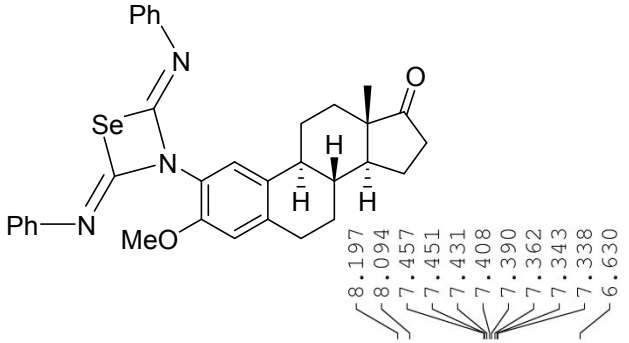
^{1}H-NMR (500 MHz, $CDCl_3$) of **25**

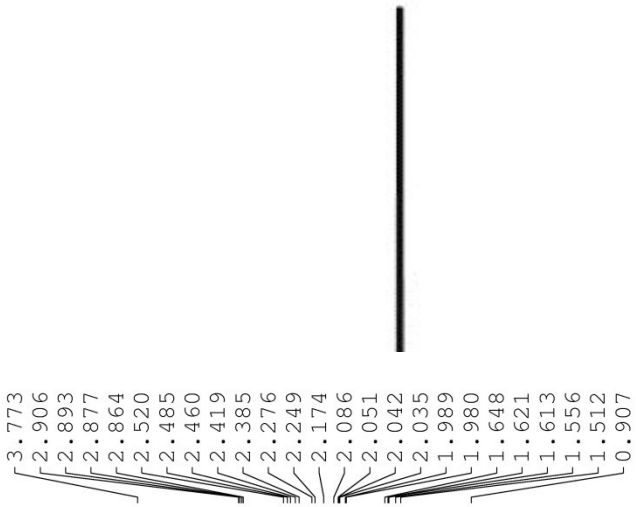


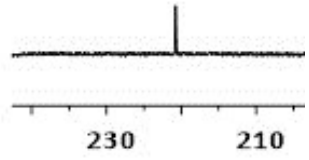
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **25**

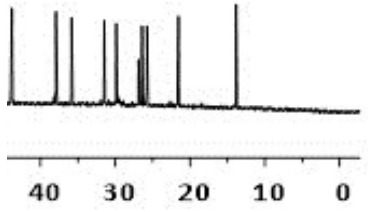


^{1}H-NMR (500 MHz, $CDCl_3$) of **27**

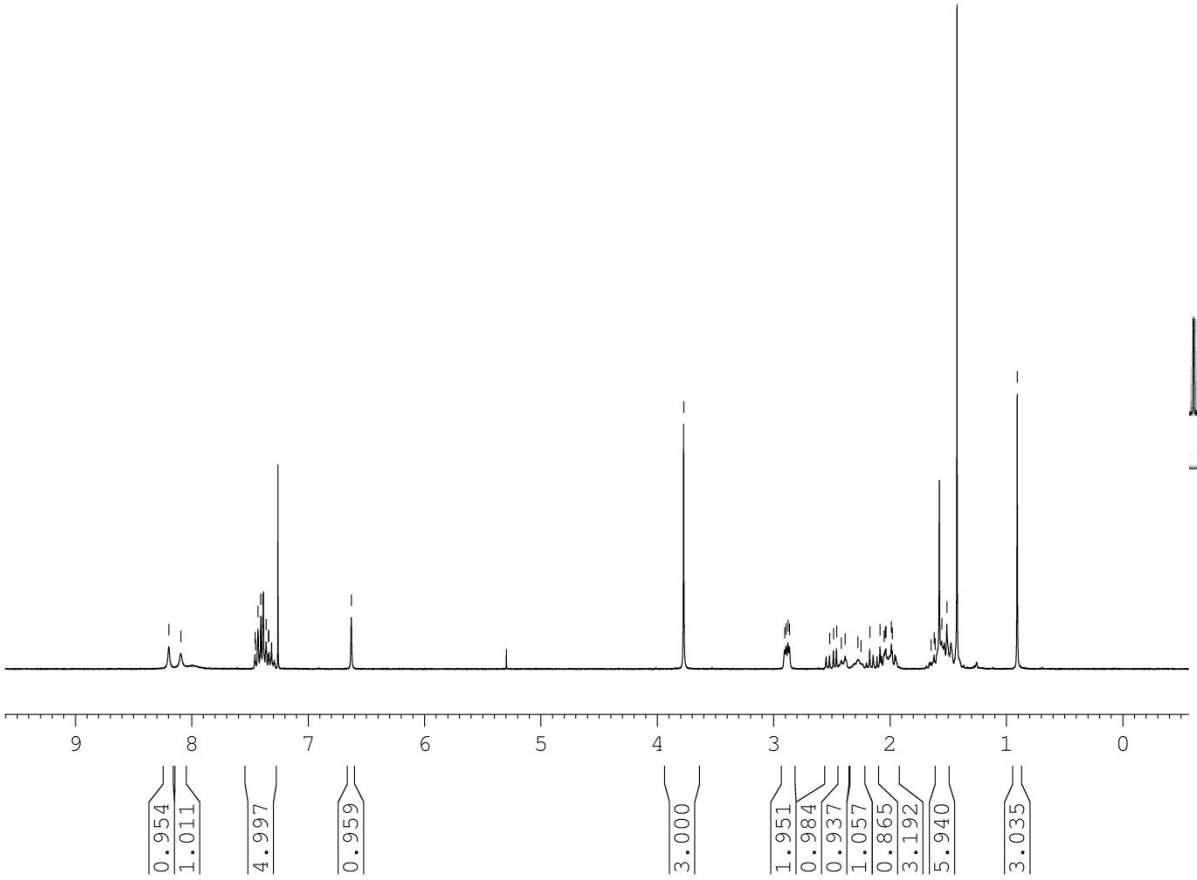


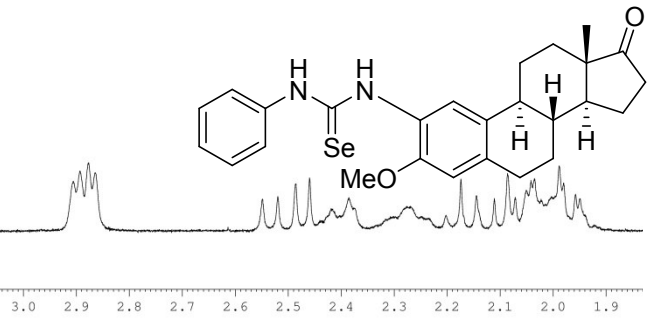


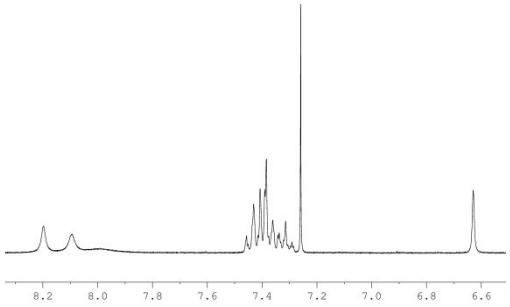




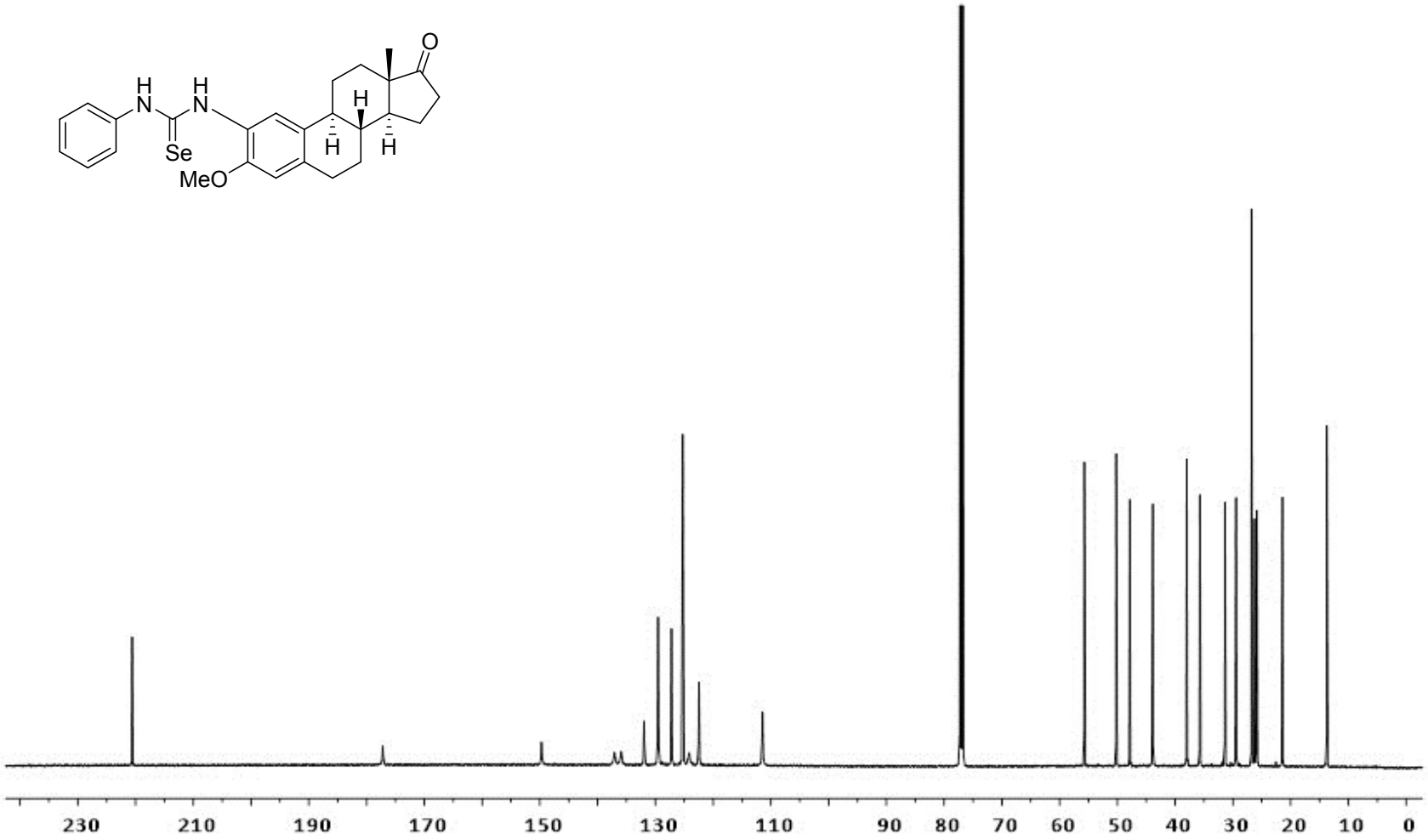
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **27**



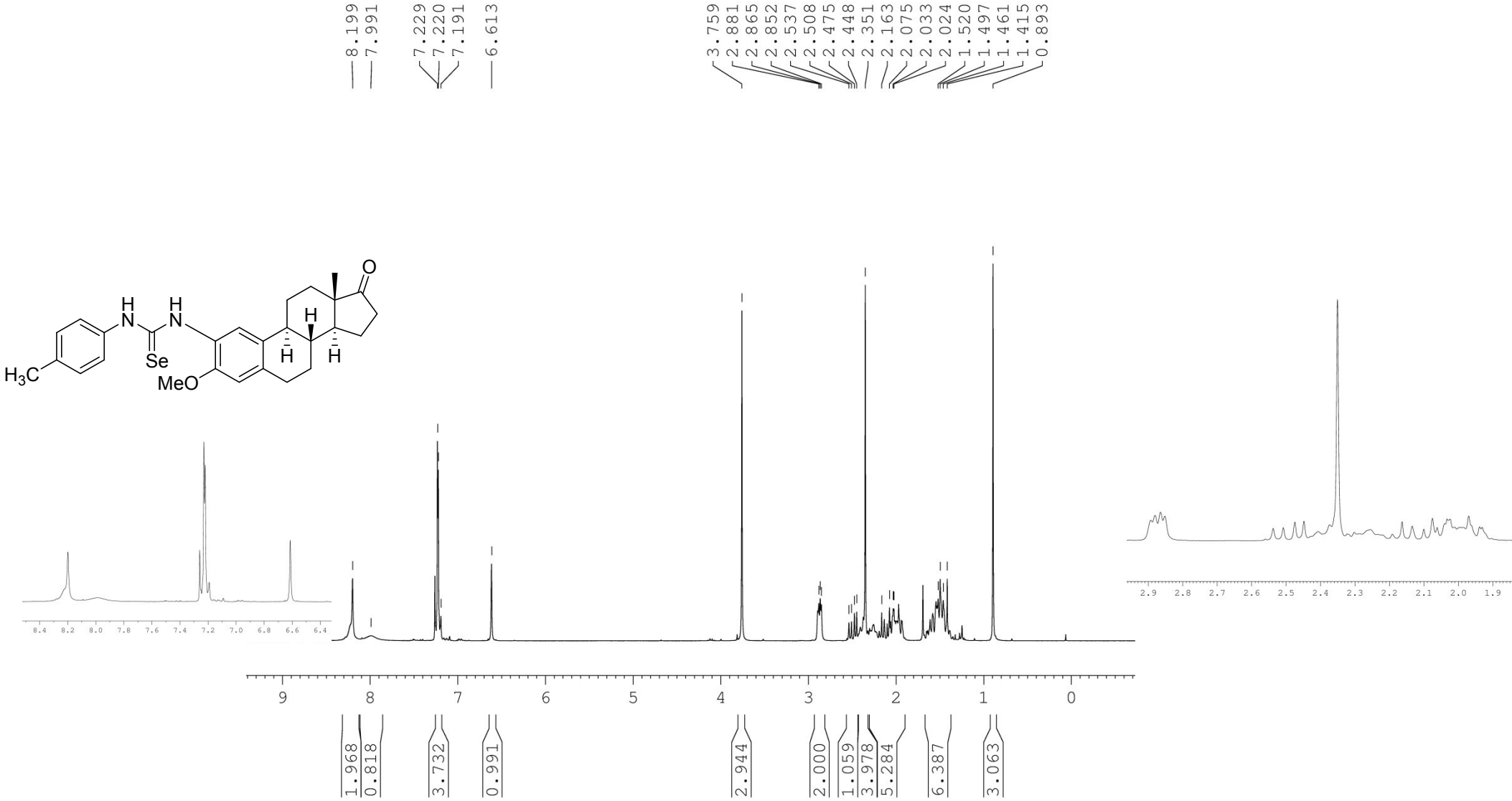




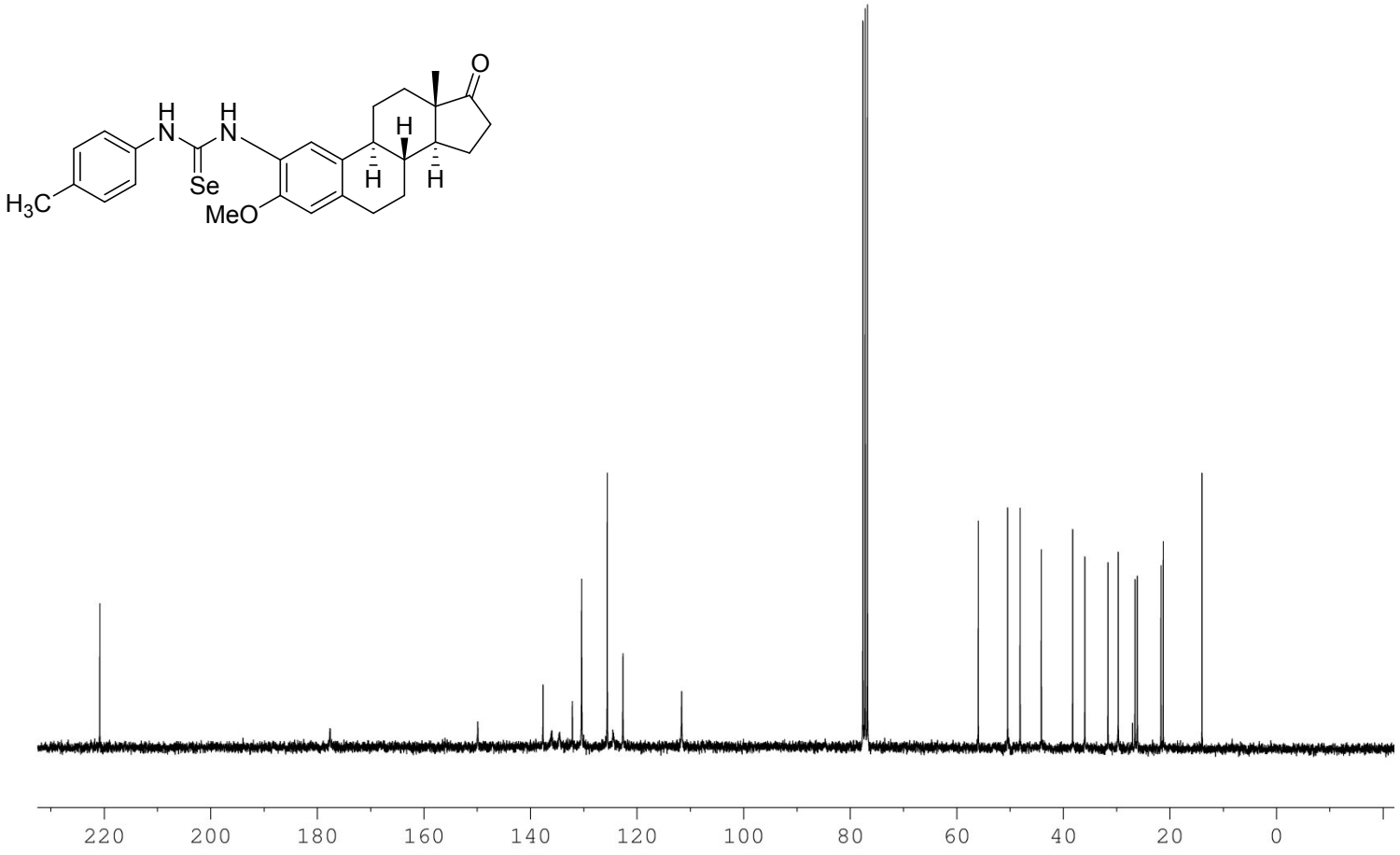
^{1}H-NMR (300 MHz, $CDCl_3$) of **28**



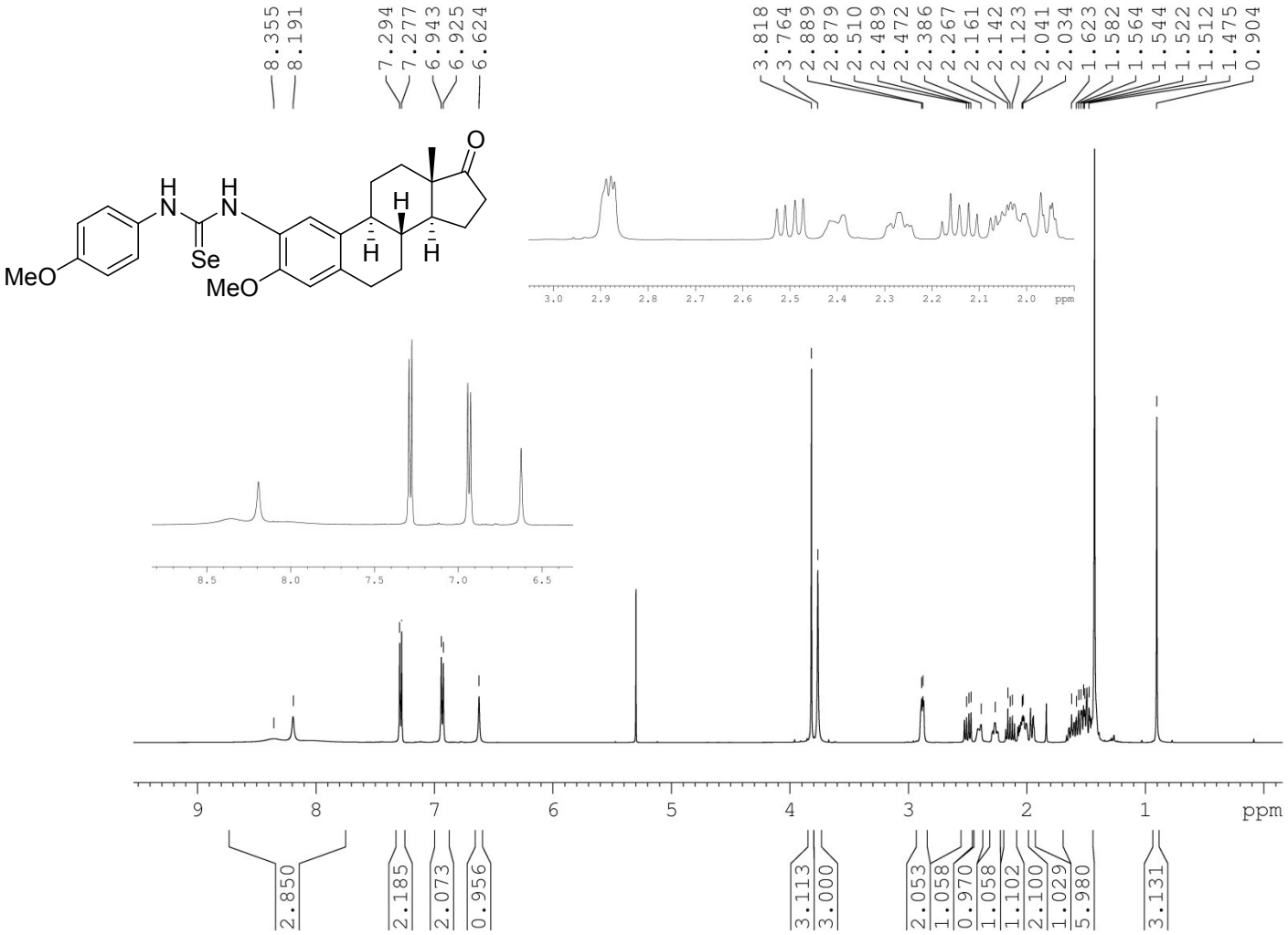
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **28**



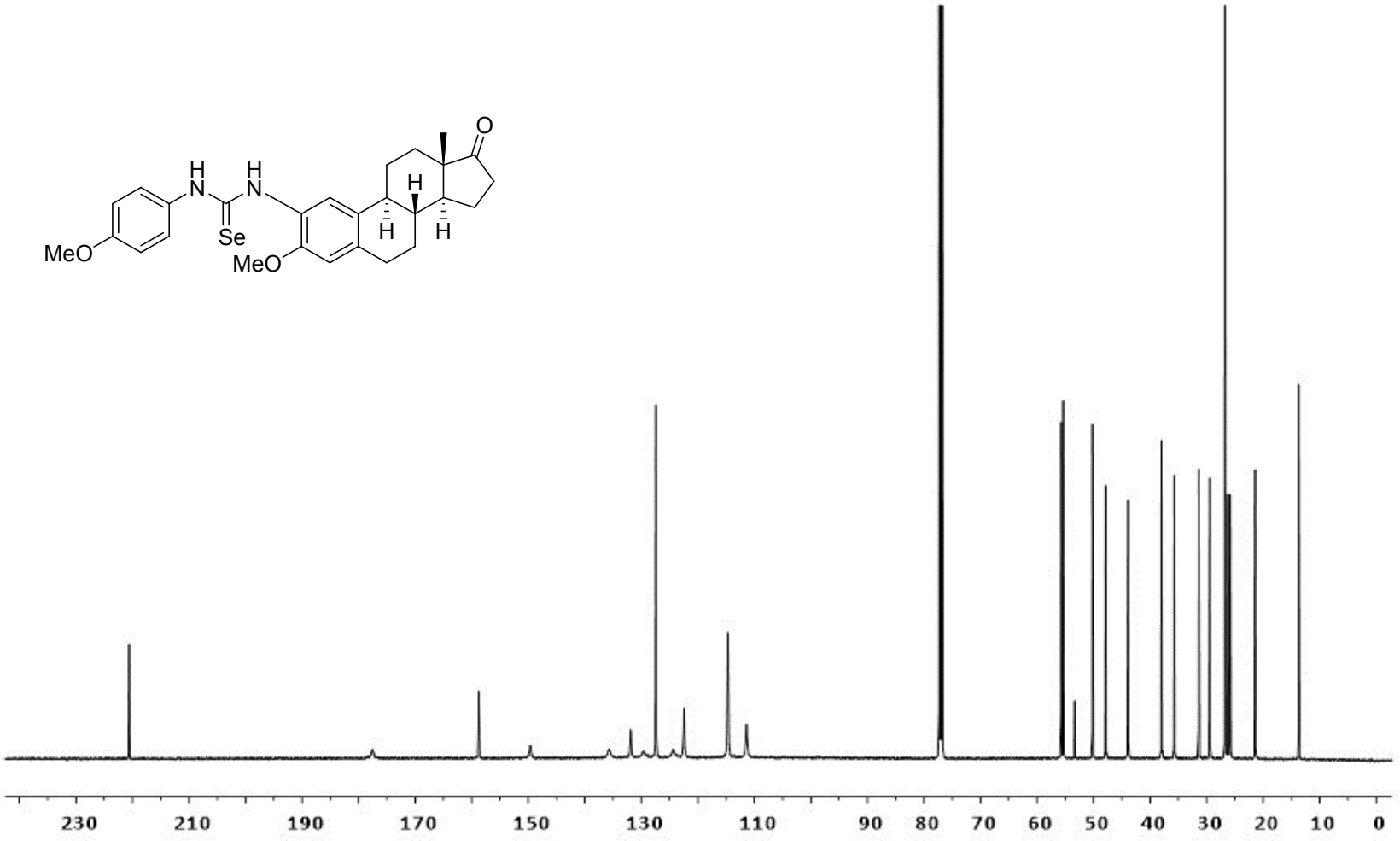
^{1}H-NMR (300 MHz, $CDCl_3$) of **29**



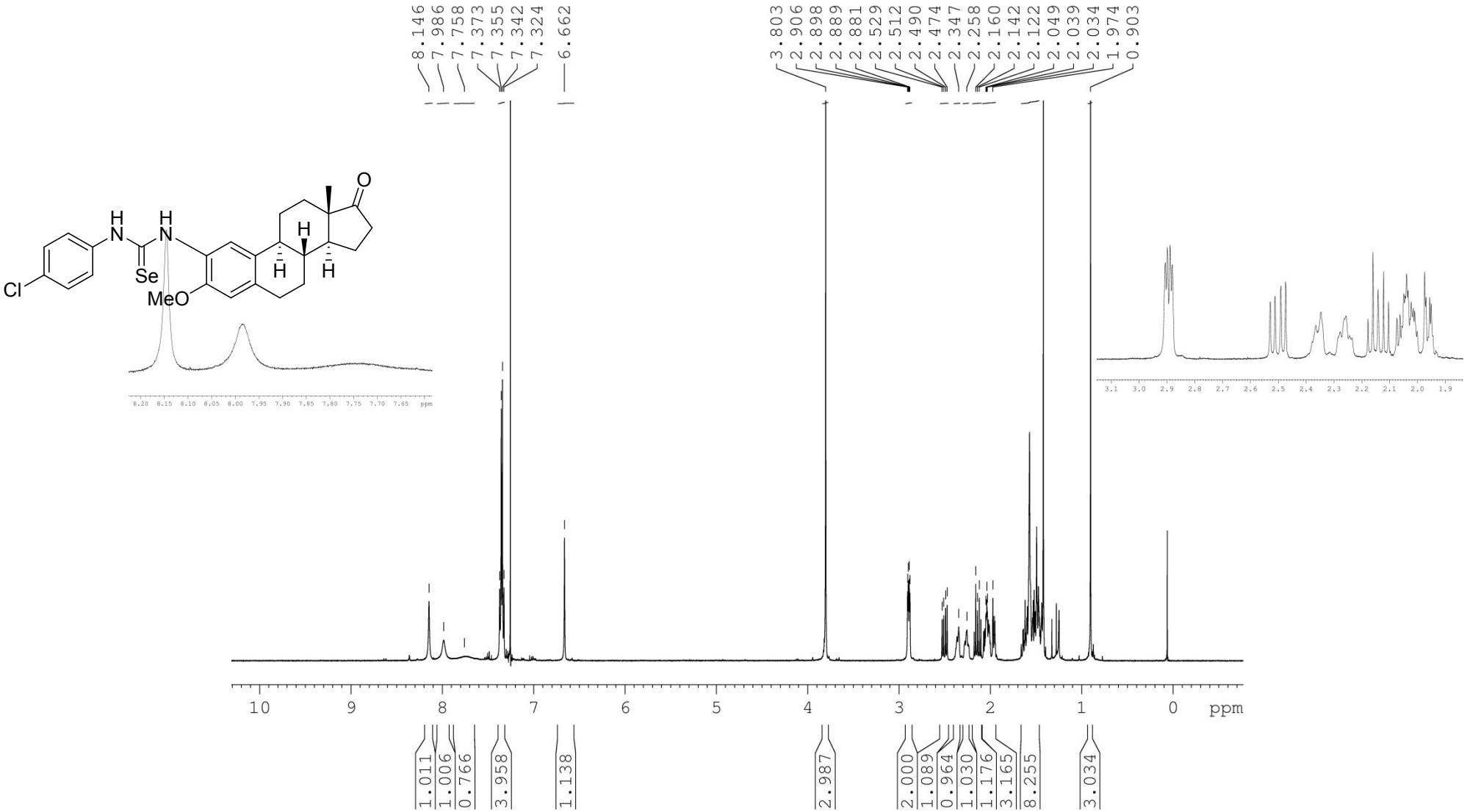
^{13}C-NMR (75.5 MHz, $CDCl_3$) of **29**



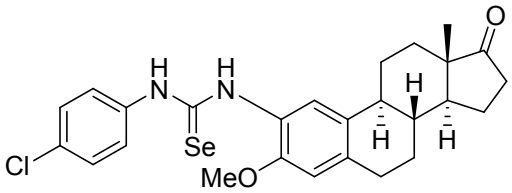
^{1}H-NMR (500 MHz, CDCl3) of **30**

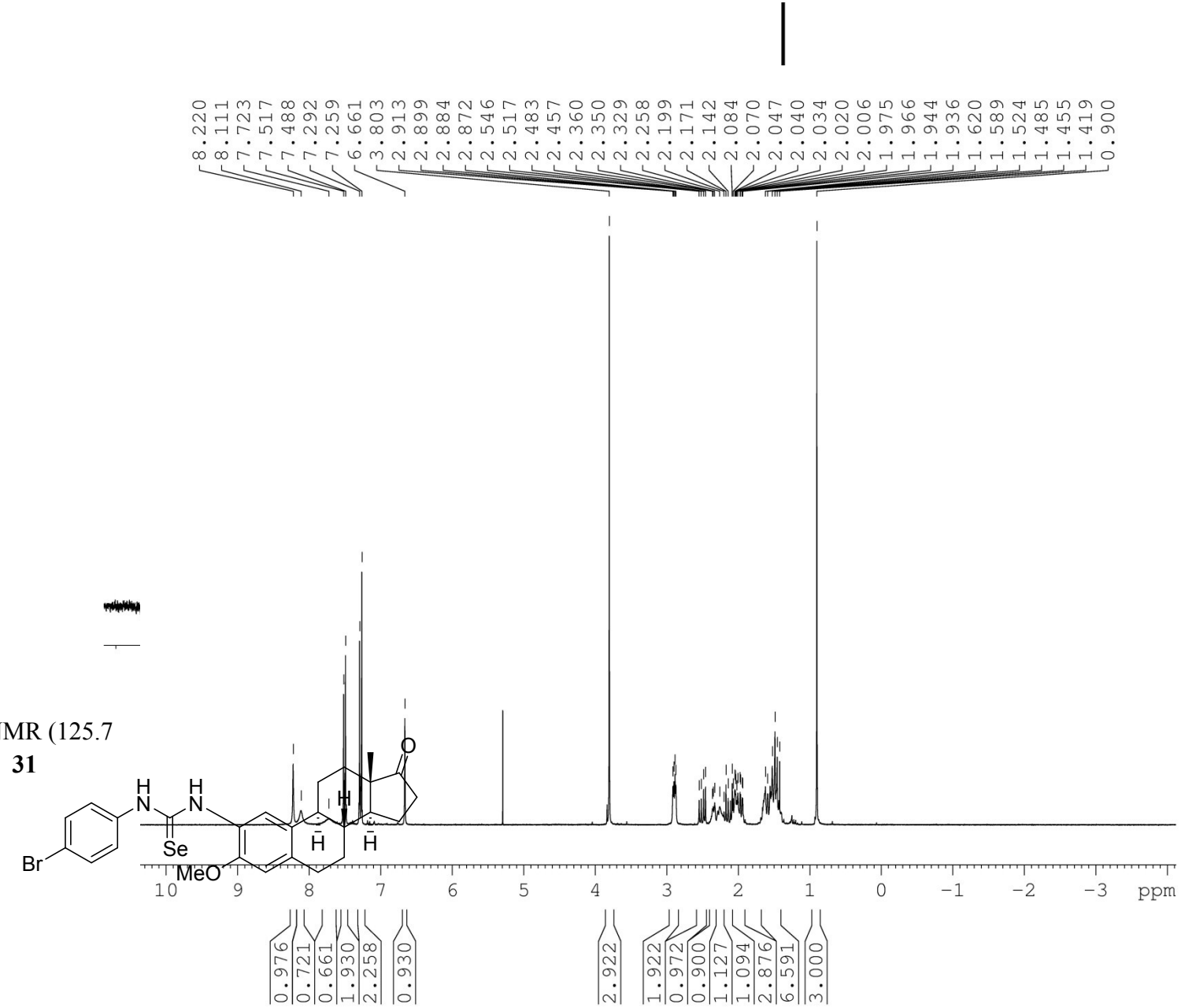


^{13}C-NMR (125.7 MHz, $CDCl_3$) of **30**

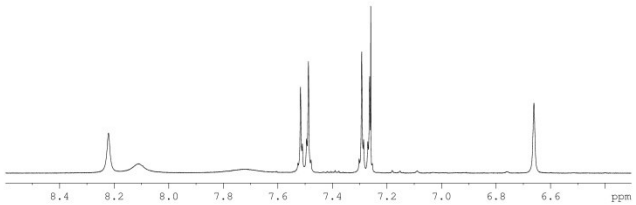


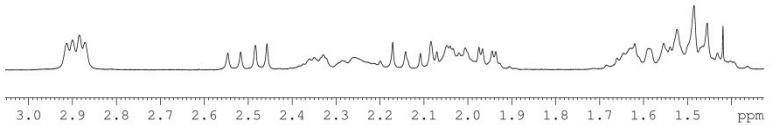
^{1}H-NMR (500 MHz, CDCl3) of **31**



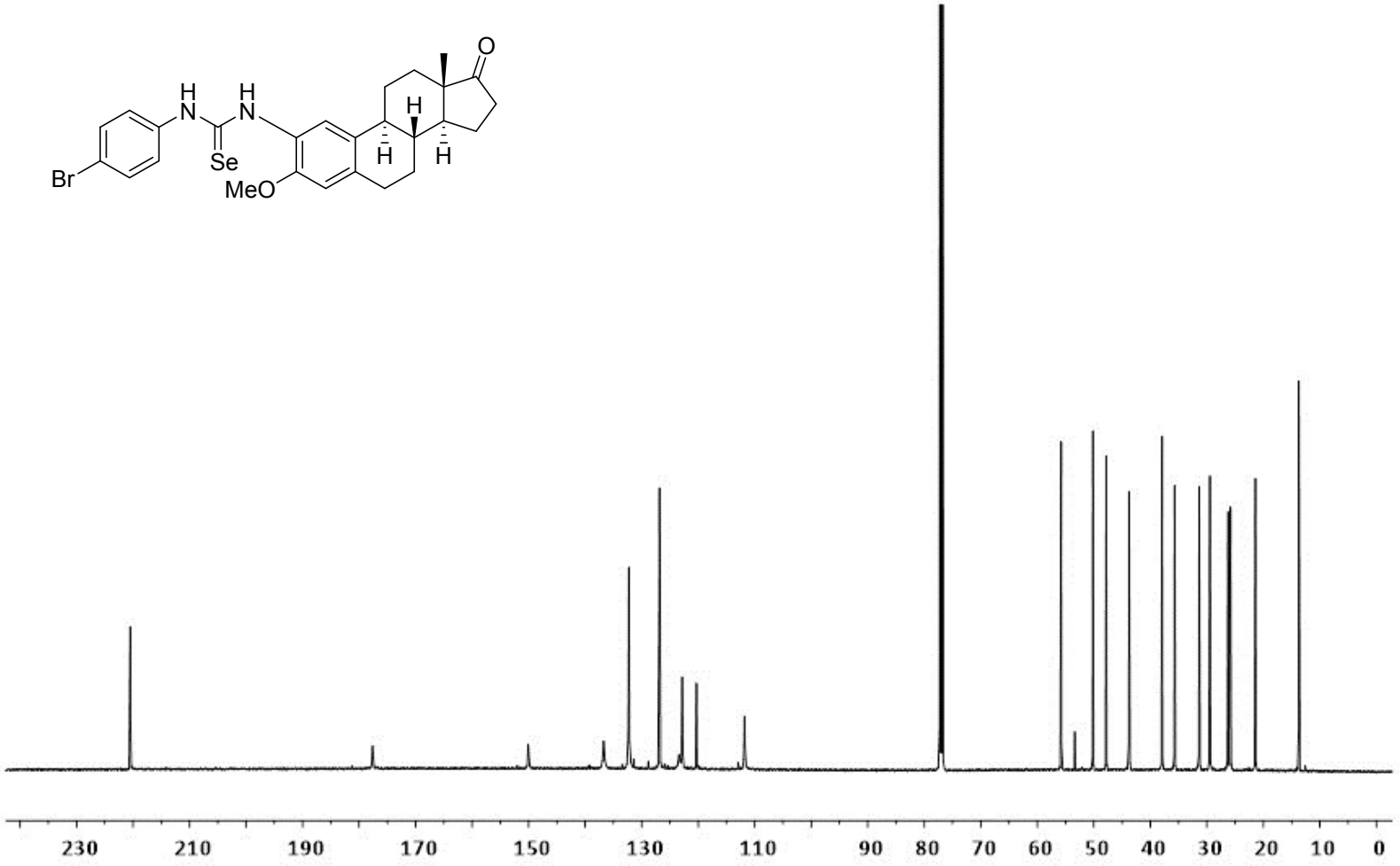


^{13}C-NMR (125.7 MHz, $CDCl_3$) of **31**

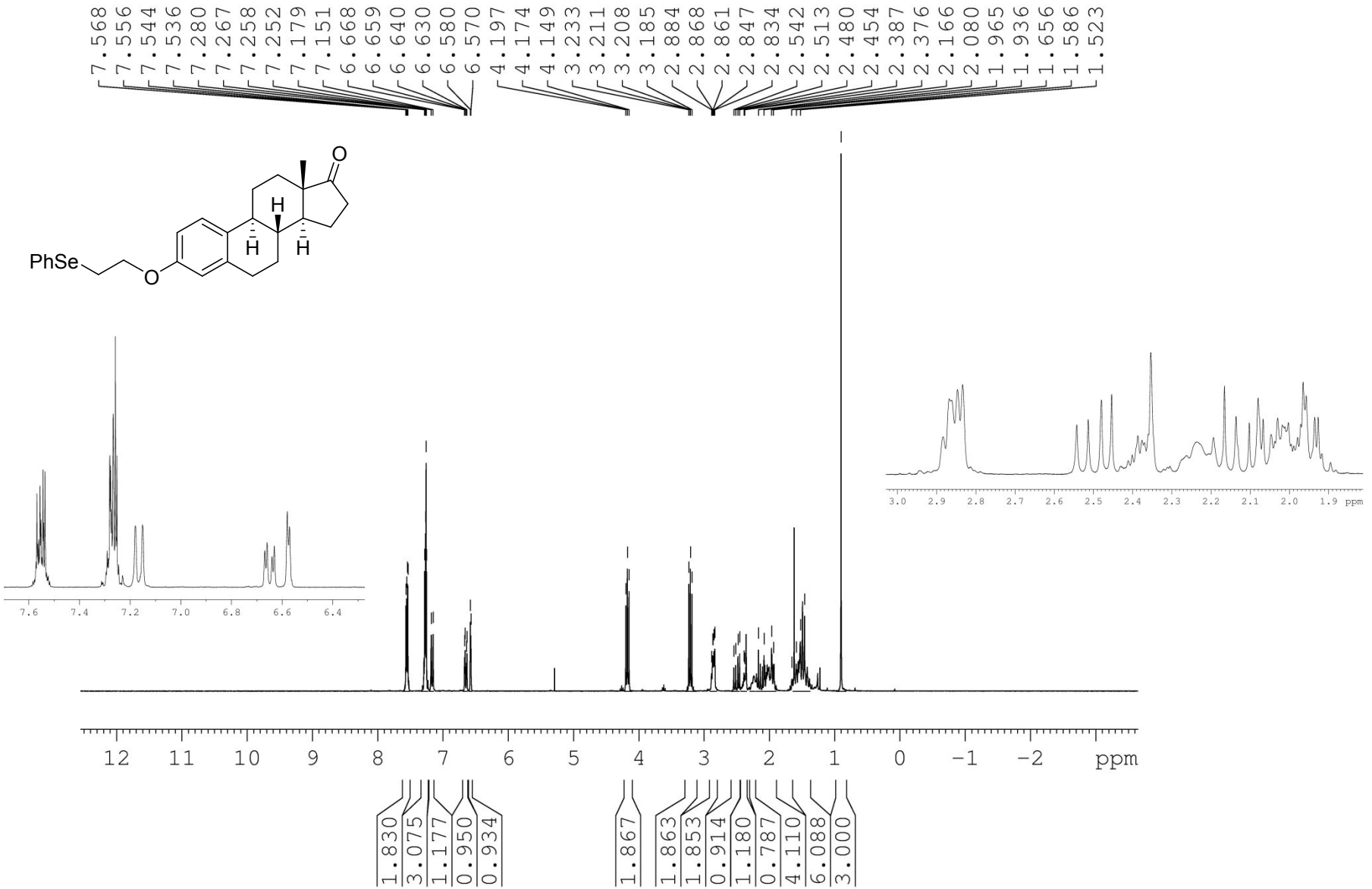




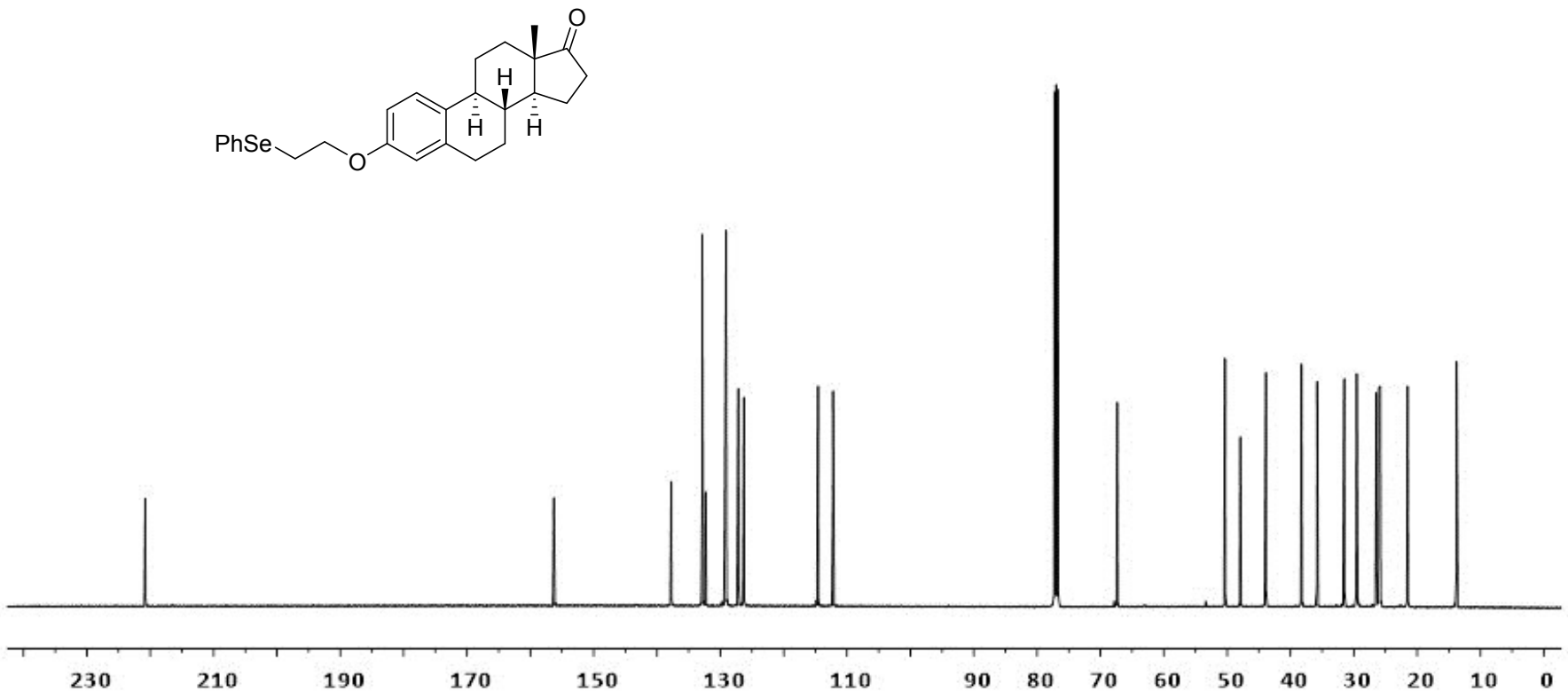
^{1}H-NMR (300 MHz,$CDCl_3$) of **32**



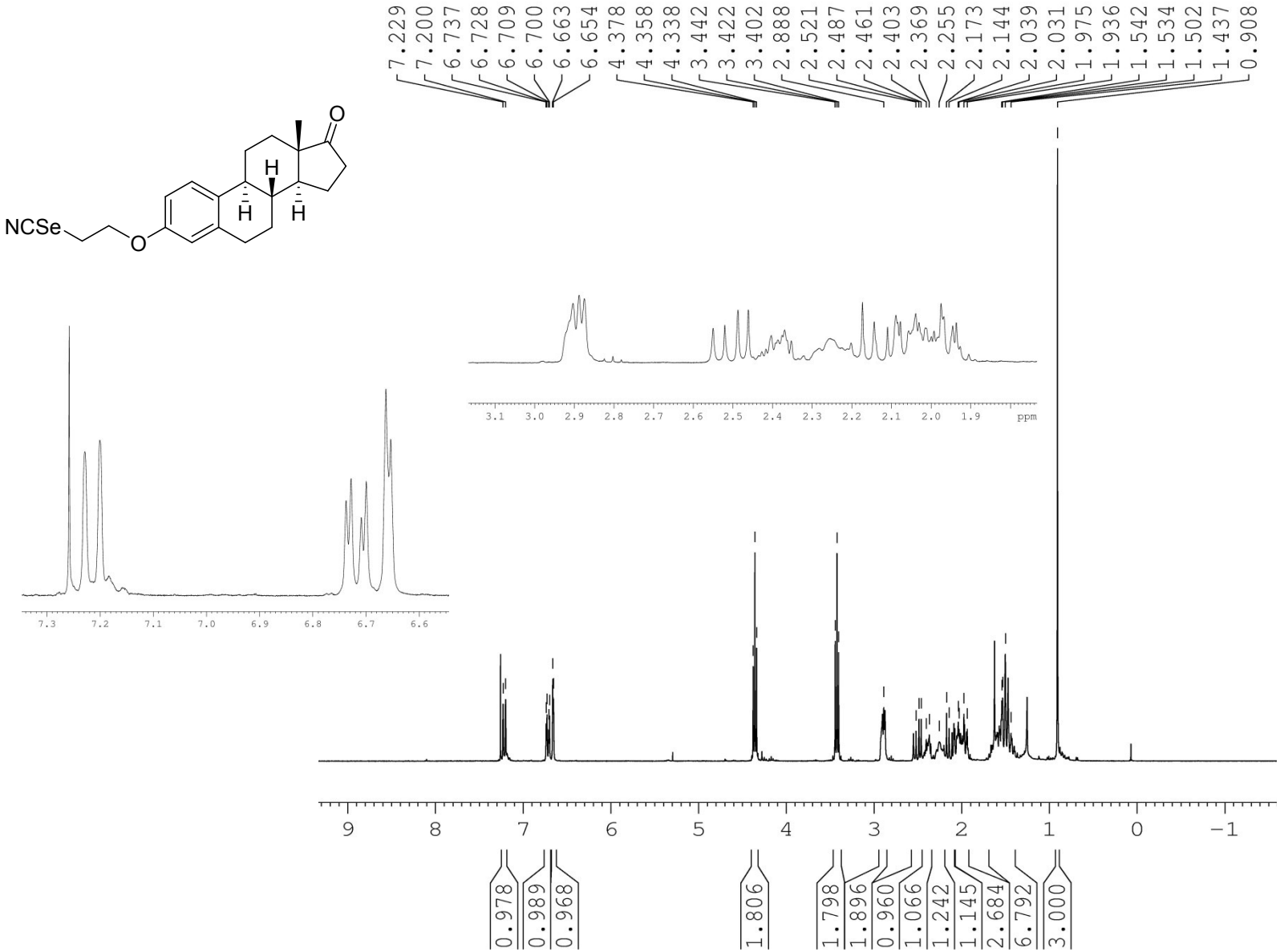
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **32**



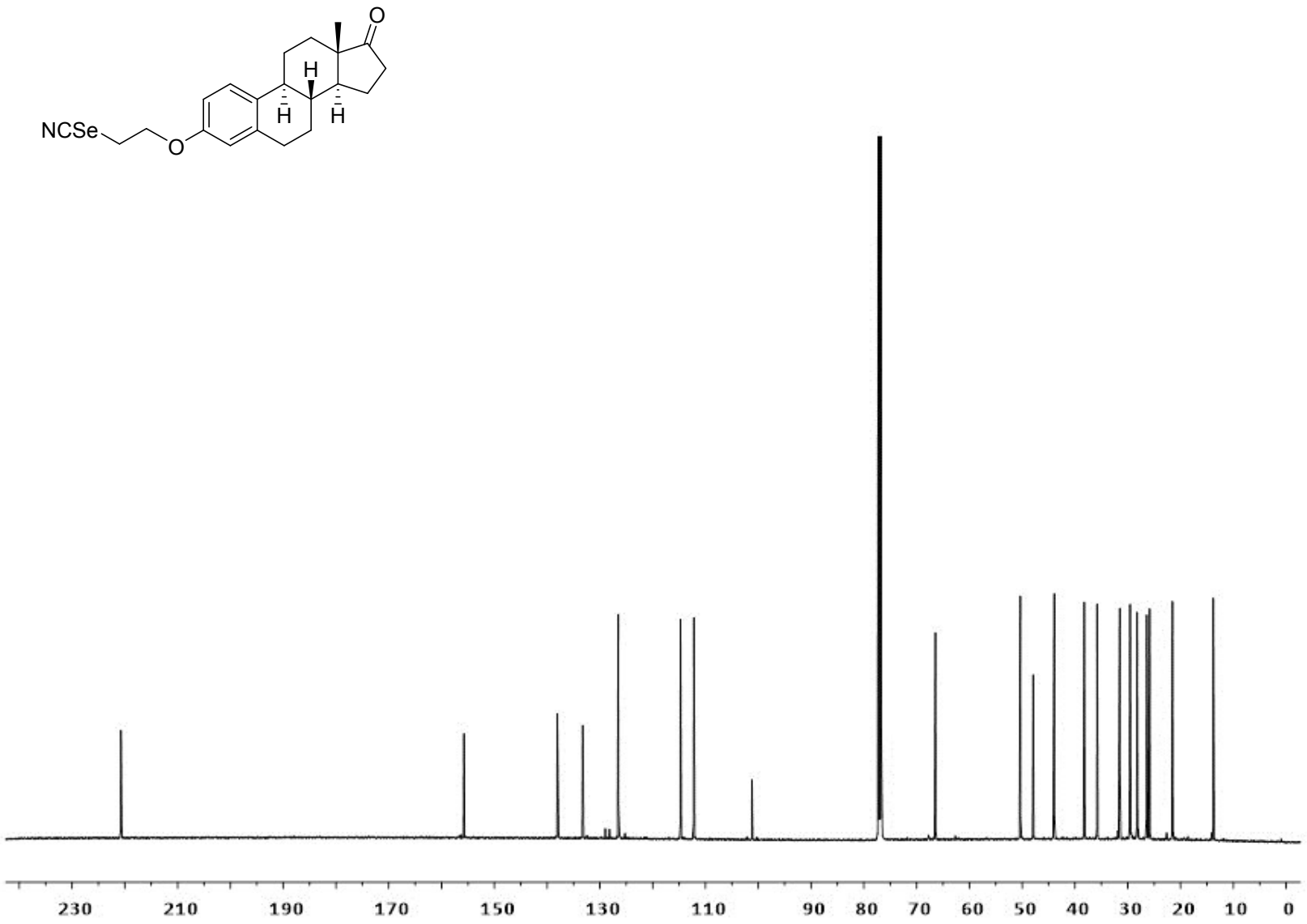
^{1}H-NMR (300 MHz, CDCl3) of **34**



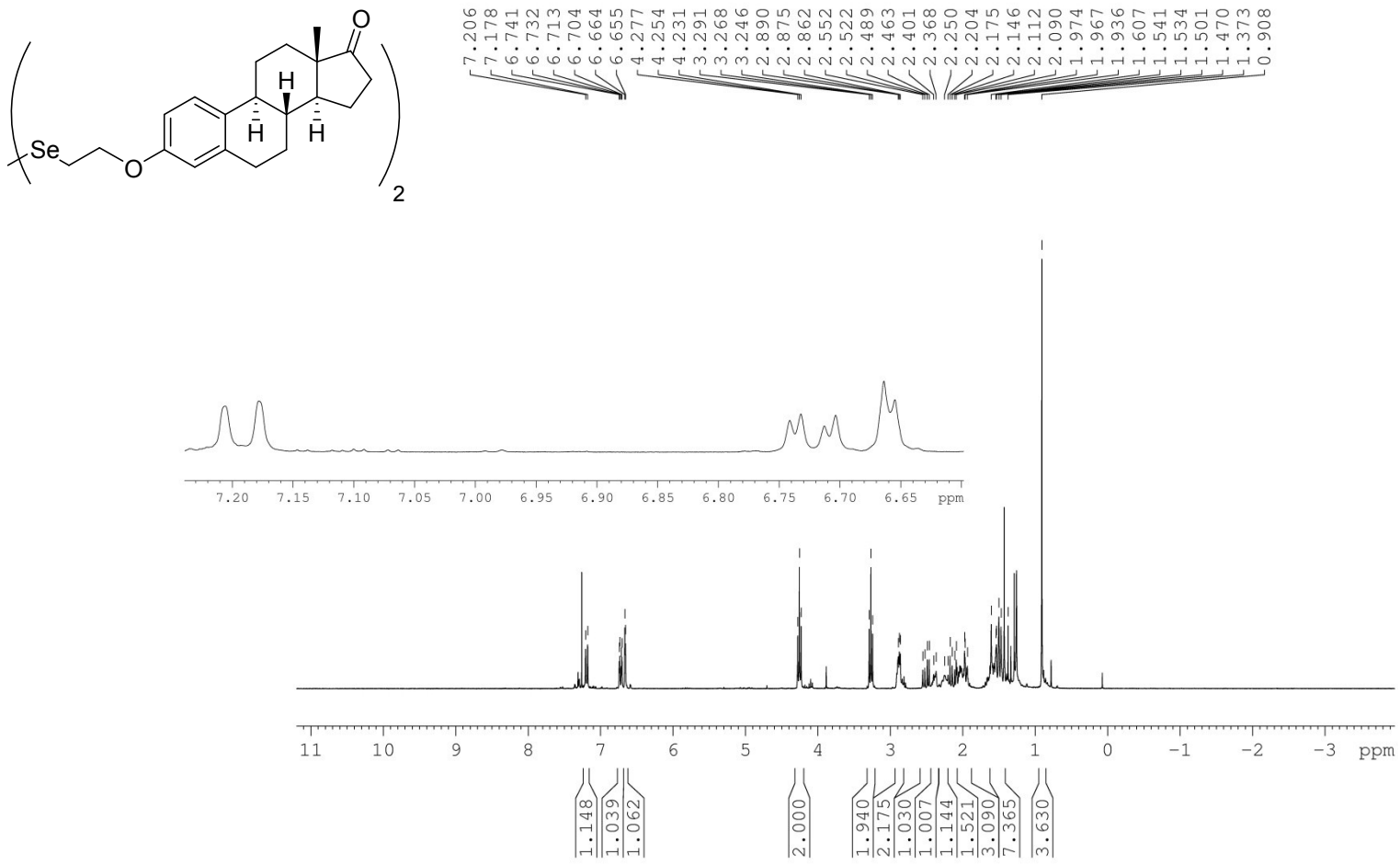
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **34**



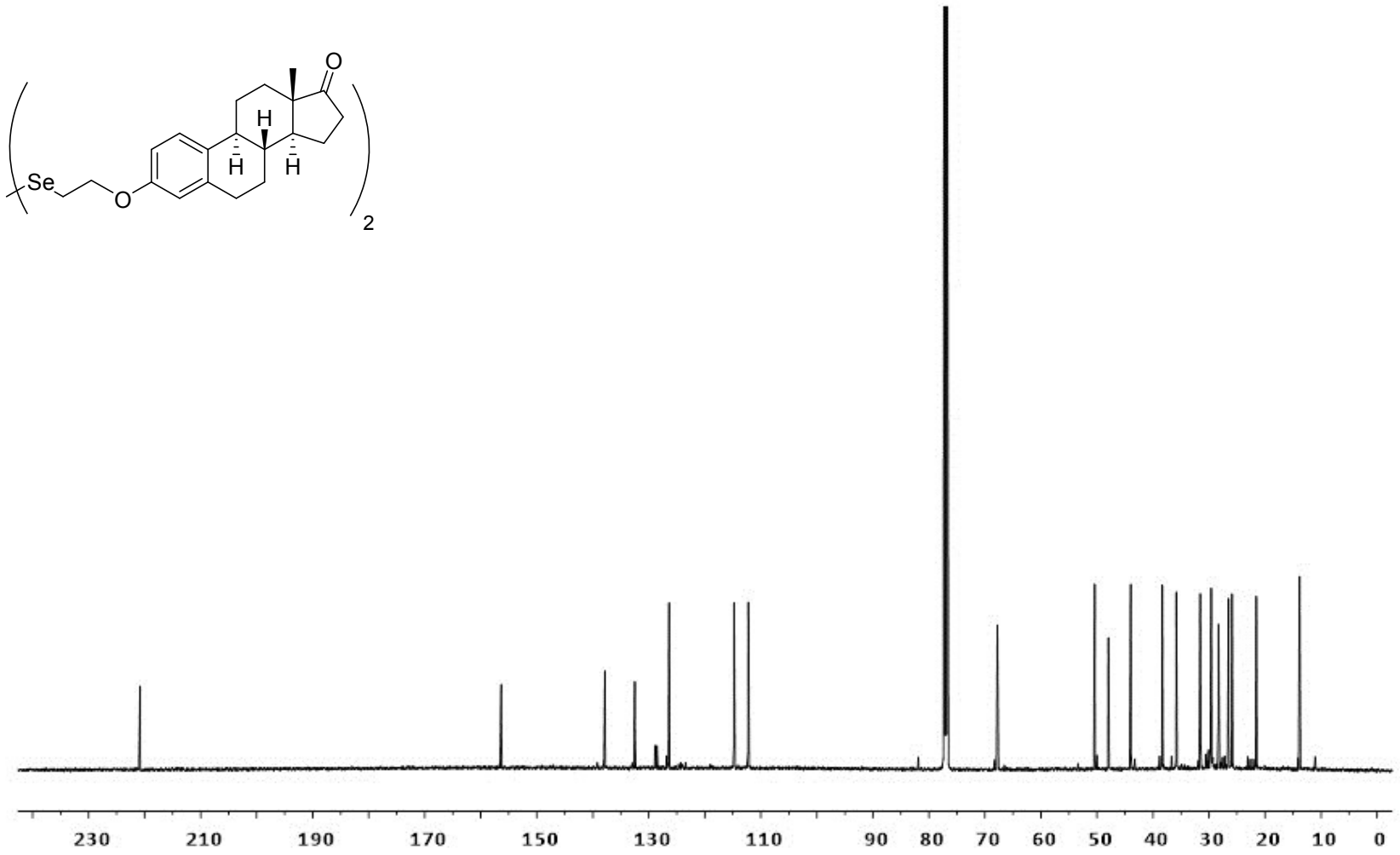
^{1}H-NMR (300 MHz, $CDCl_3$) of **35**



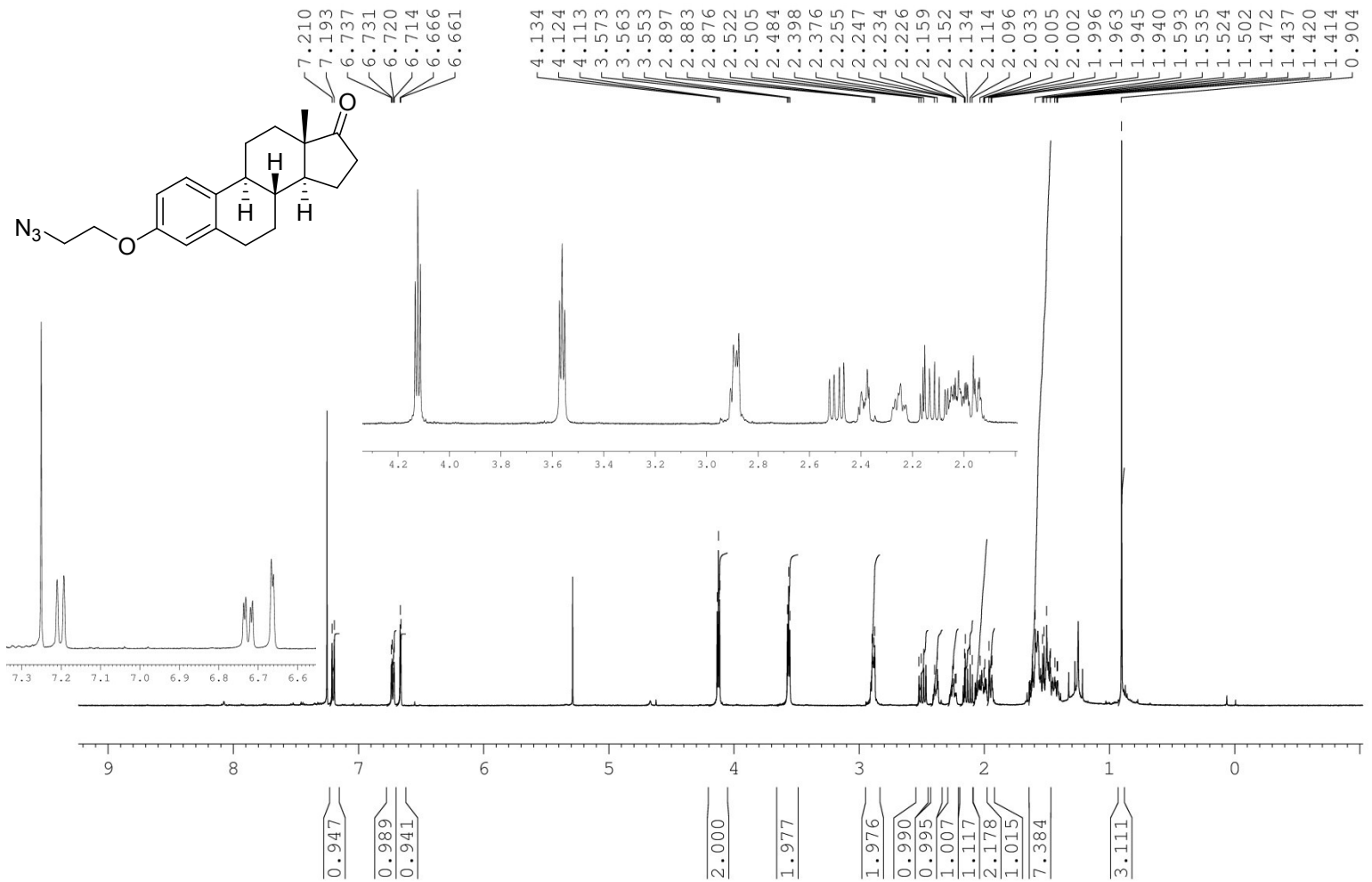
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **35**



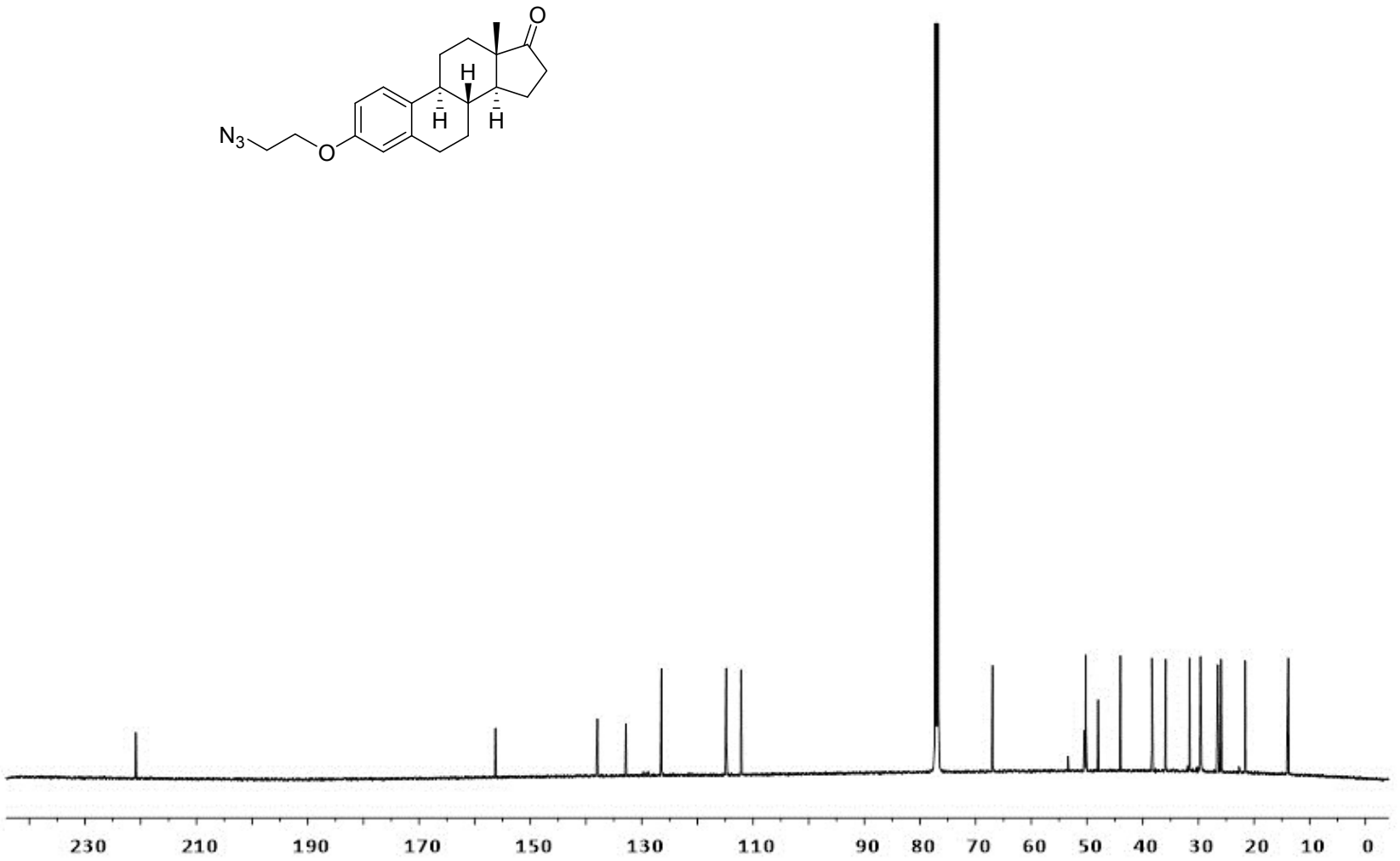
^{1}H-NMR (300 MHz, $CDCl_3$) of **36**



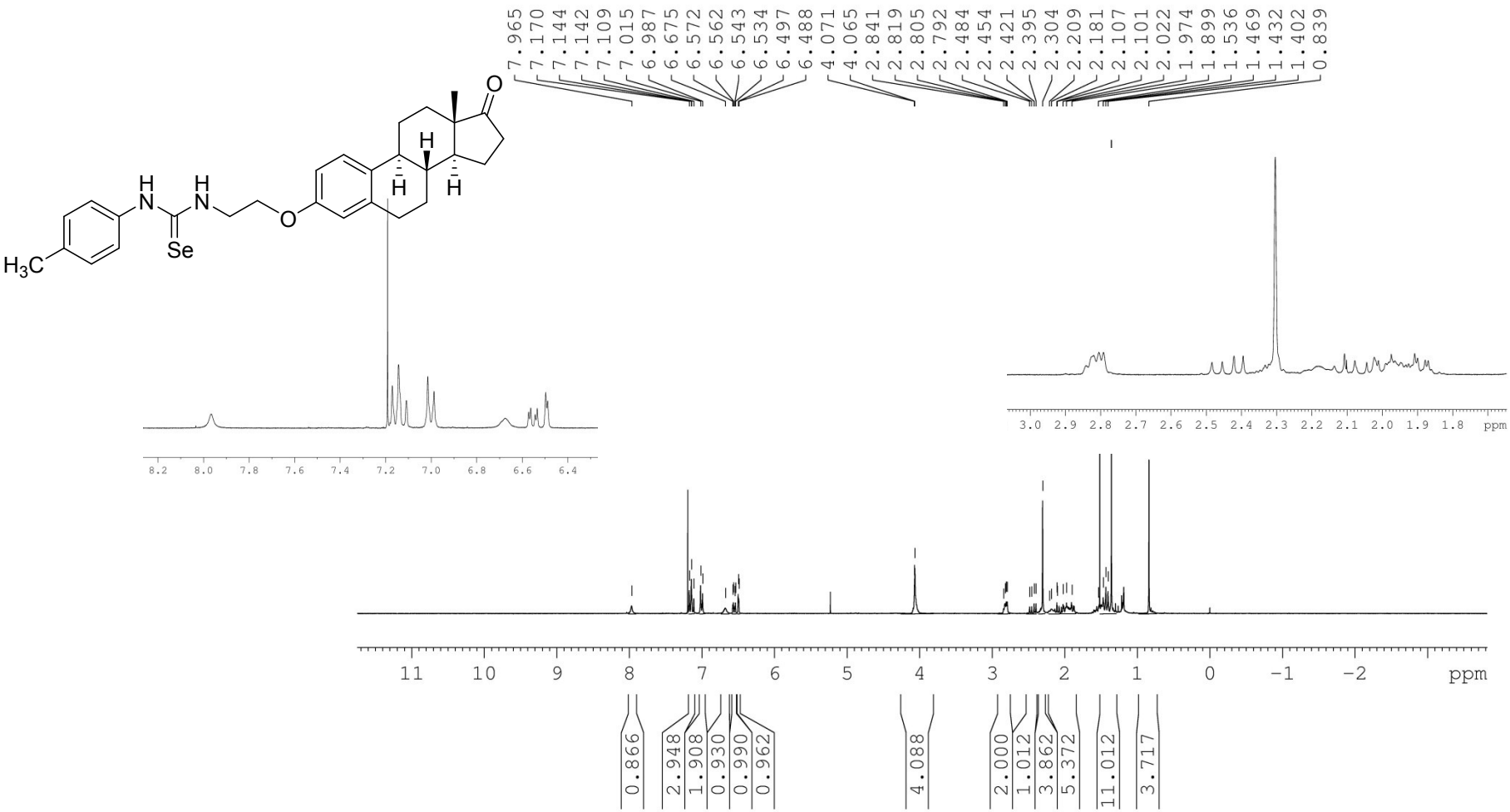
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **36**



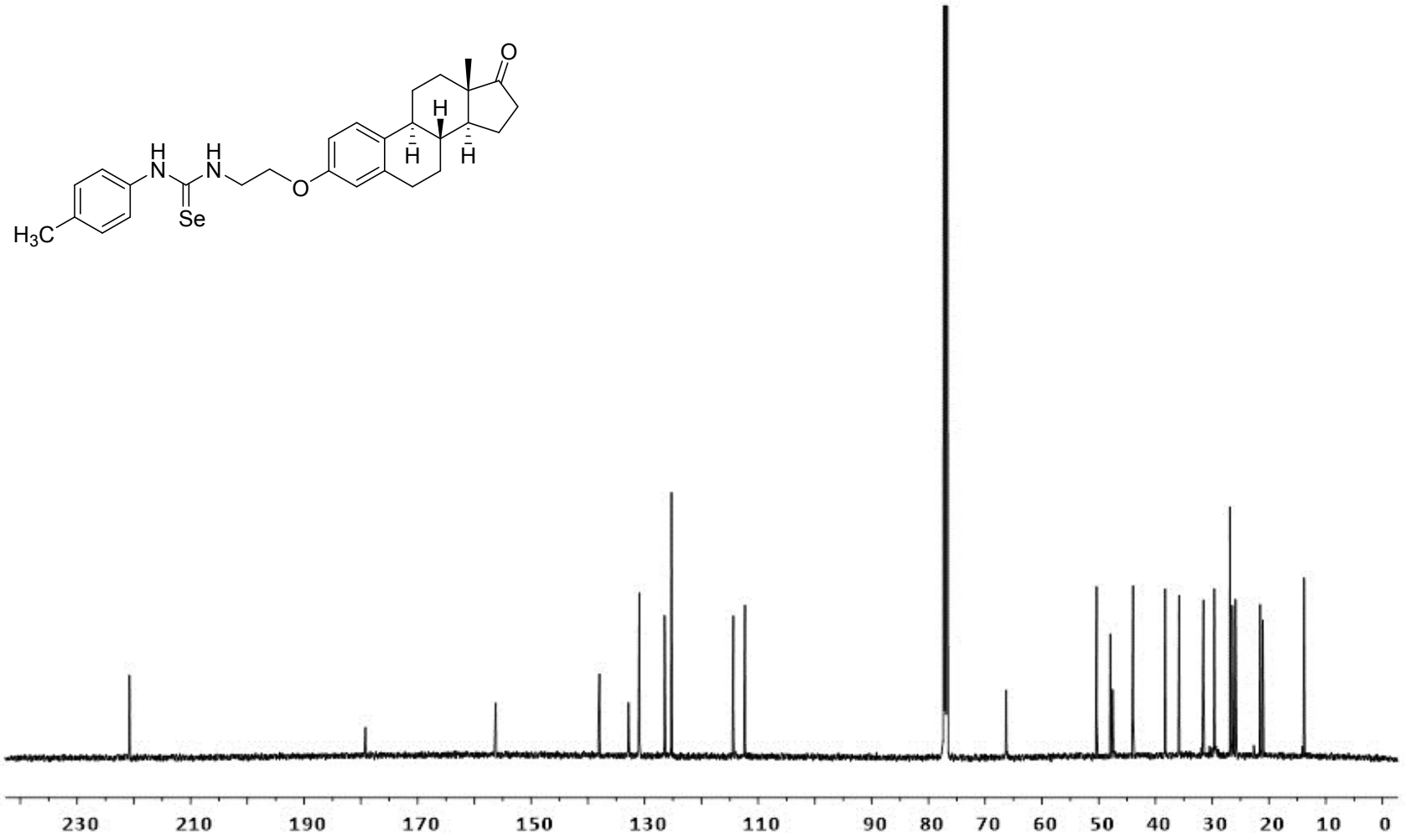
^{1}H-NMR (500 MHz, $CDCl_3$) of **37**



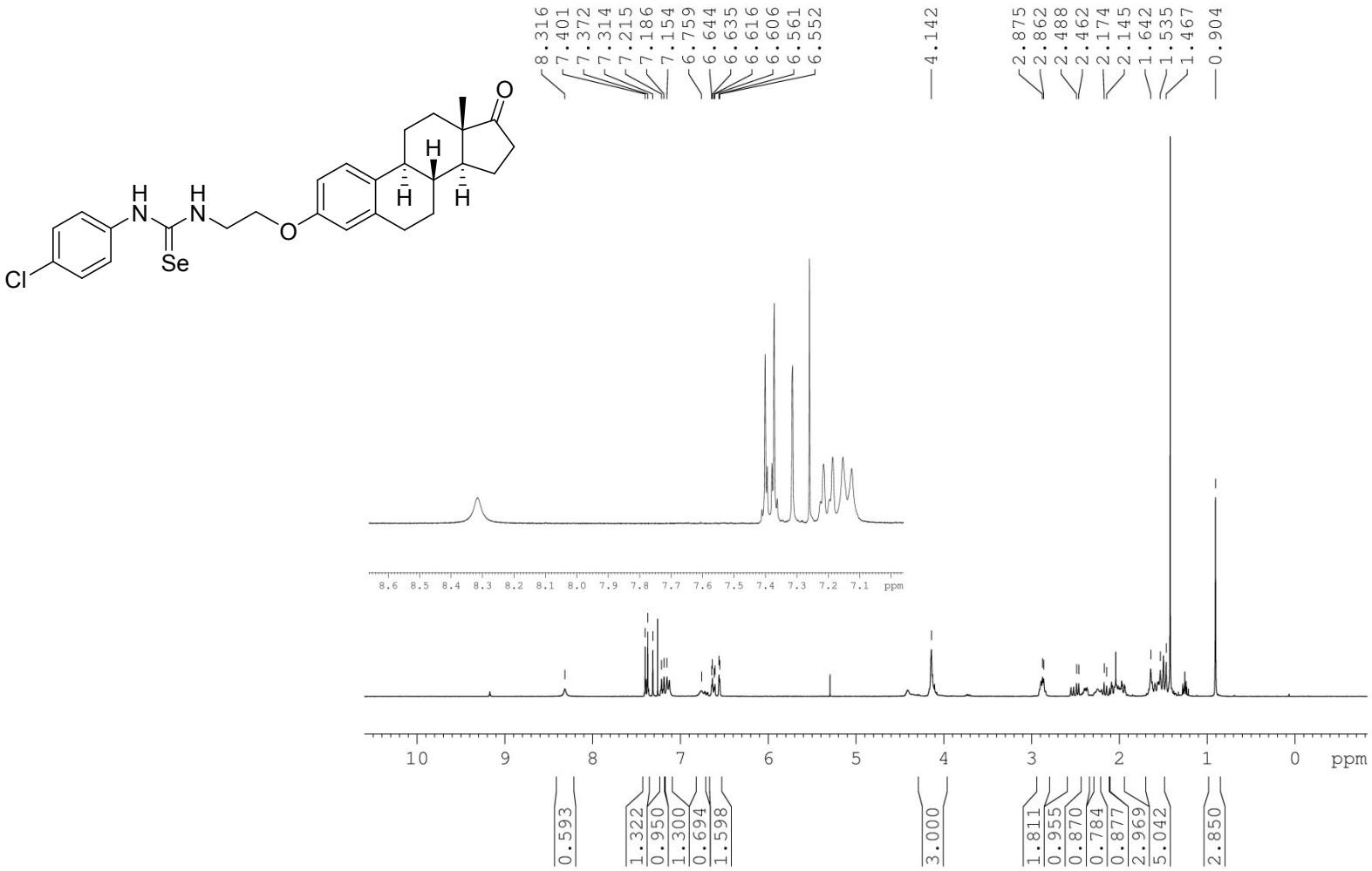
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **37**



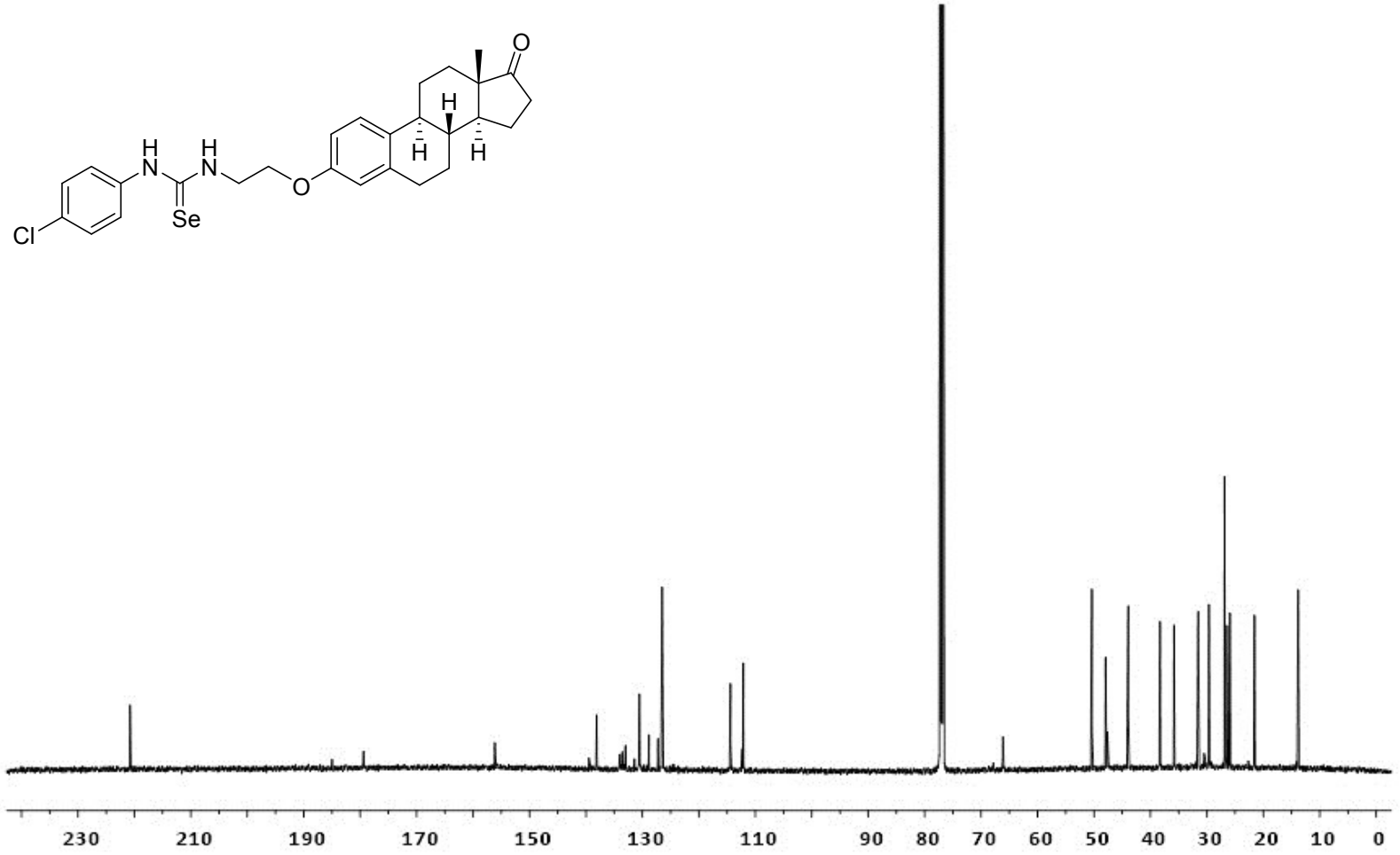
^{1}H-NMR (300 MHz, $CDCl_3$) of **39**



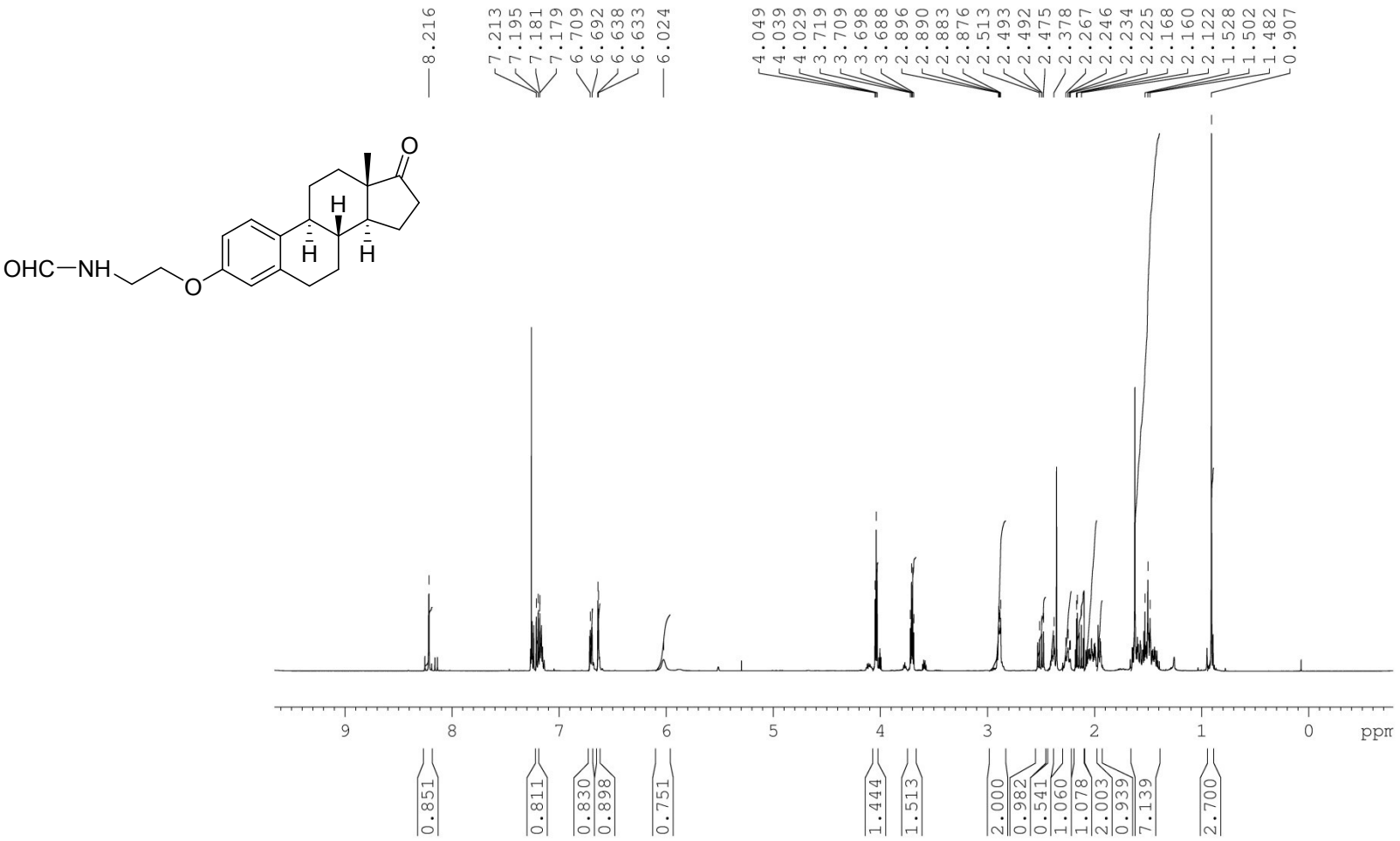
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **39**



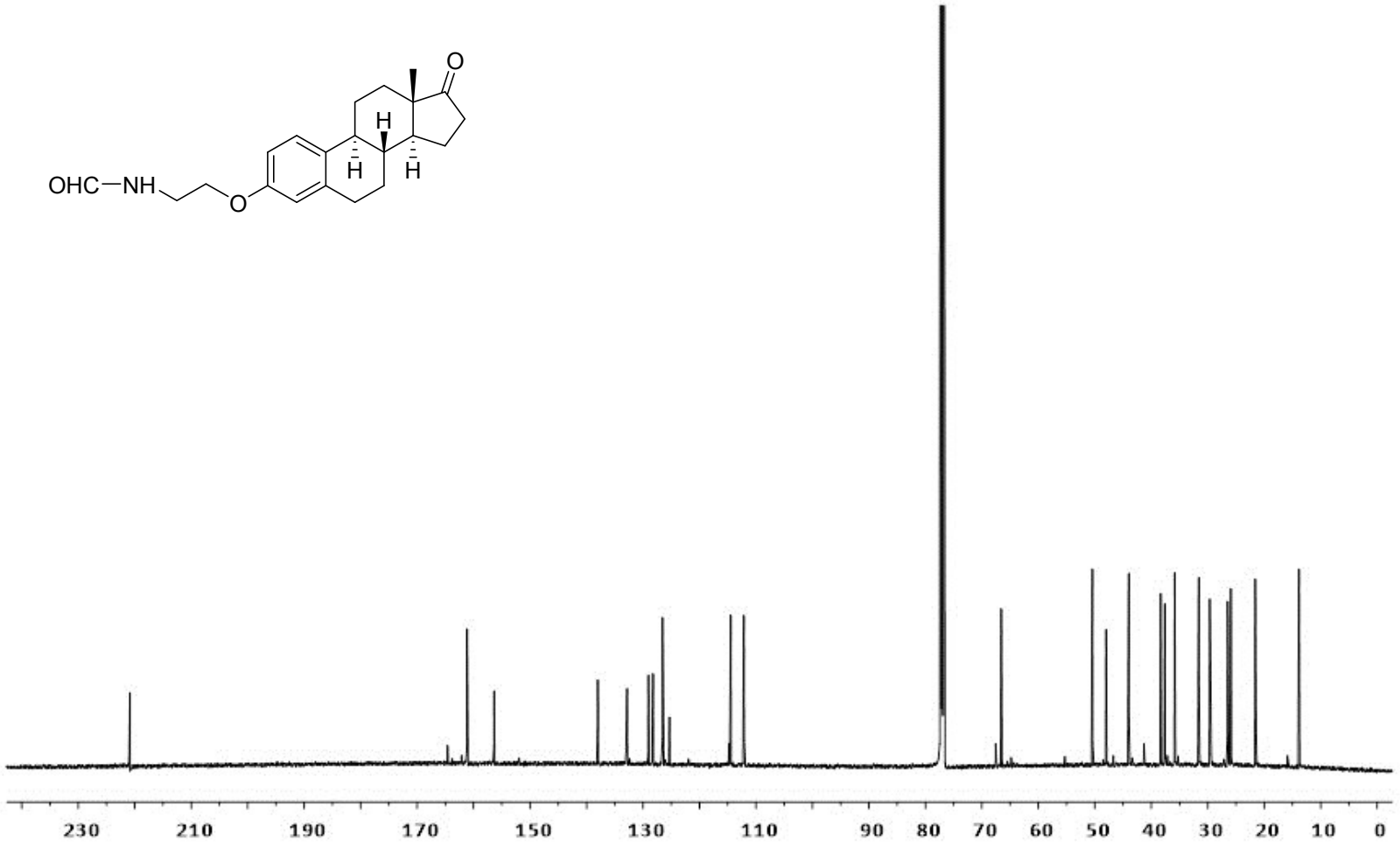
^{1}H-NMR (300 MHz, $CDCl_3$) of **40**



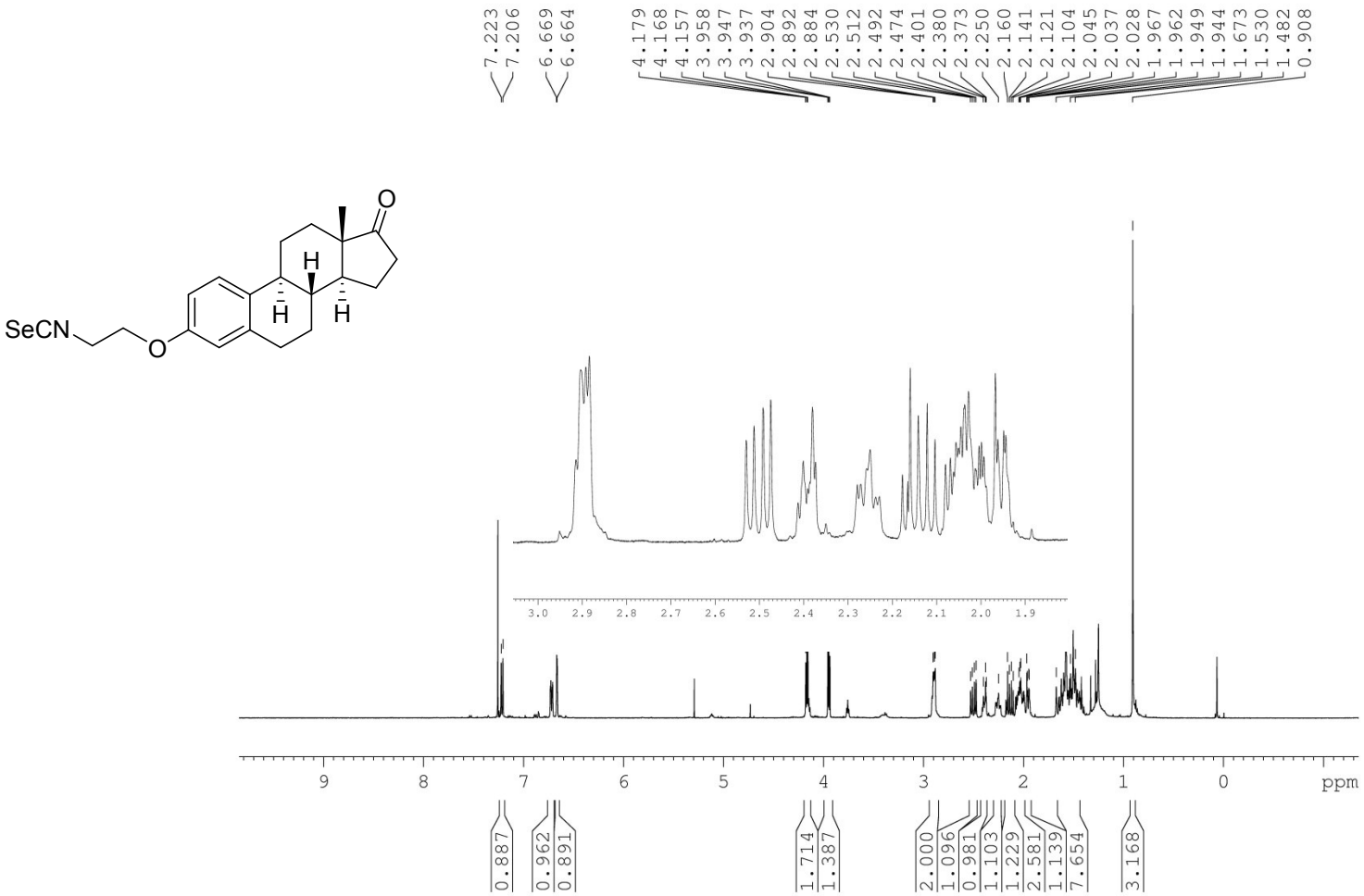
^{13}C-NMR (500 MHz, $CDCl_3$) of **40**



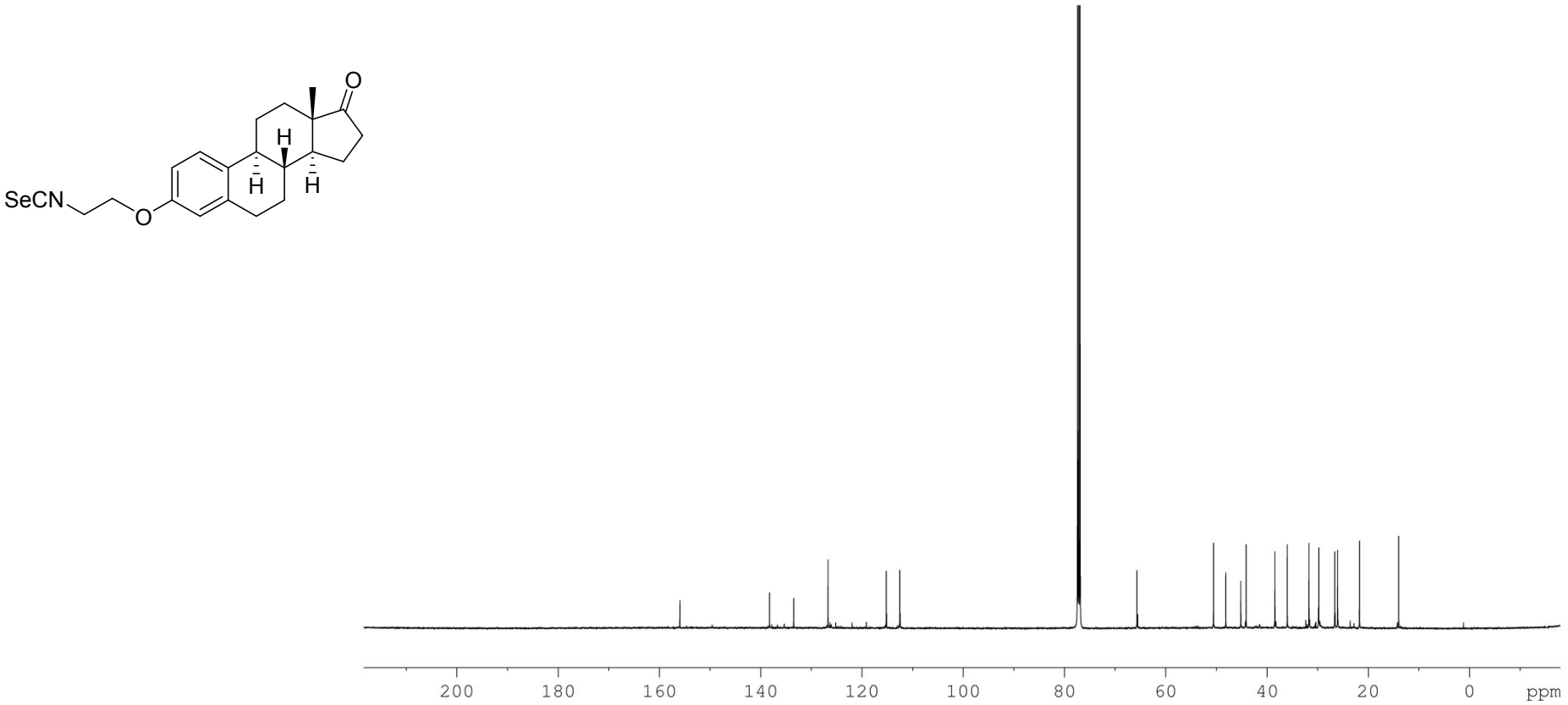
^{1}H-NMR (500 MHz, $CDCl_3$) of **41**



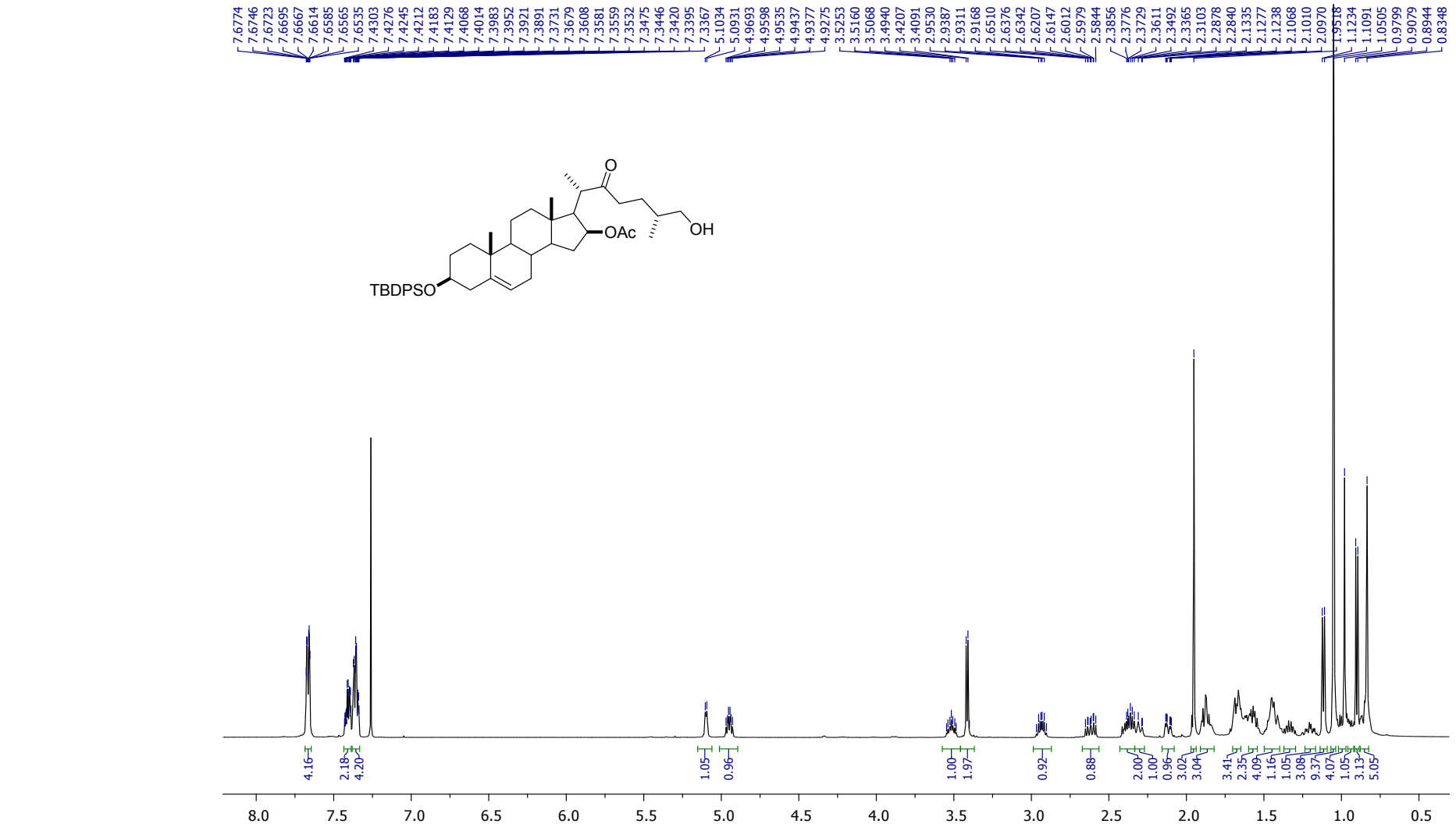
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **41**



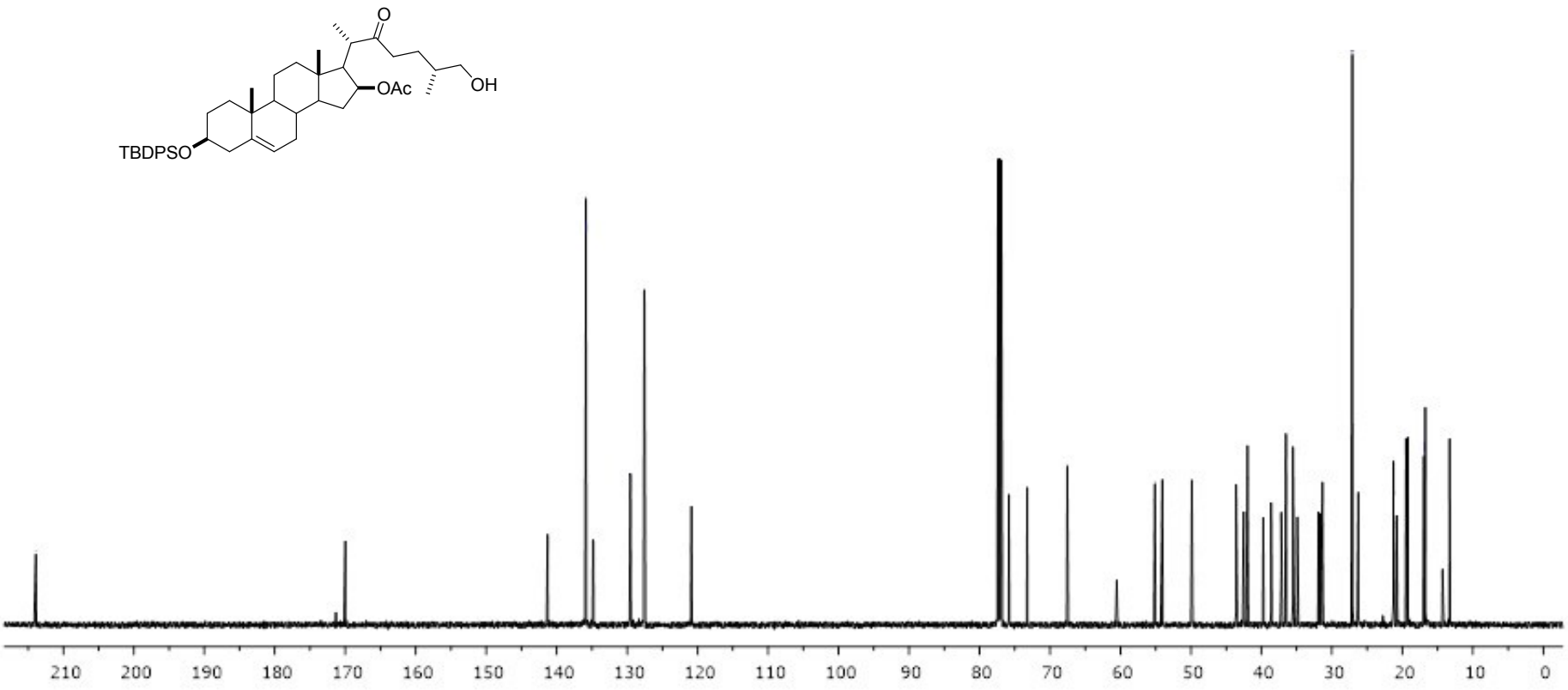
^{1}H-NMR (500 MHz, $CDCl_3$) of **42**



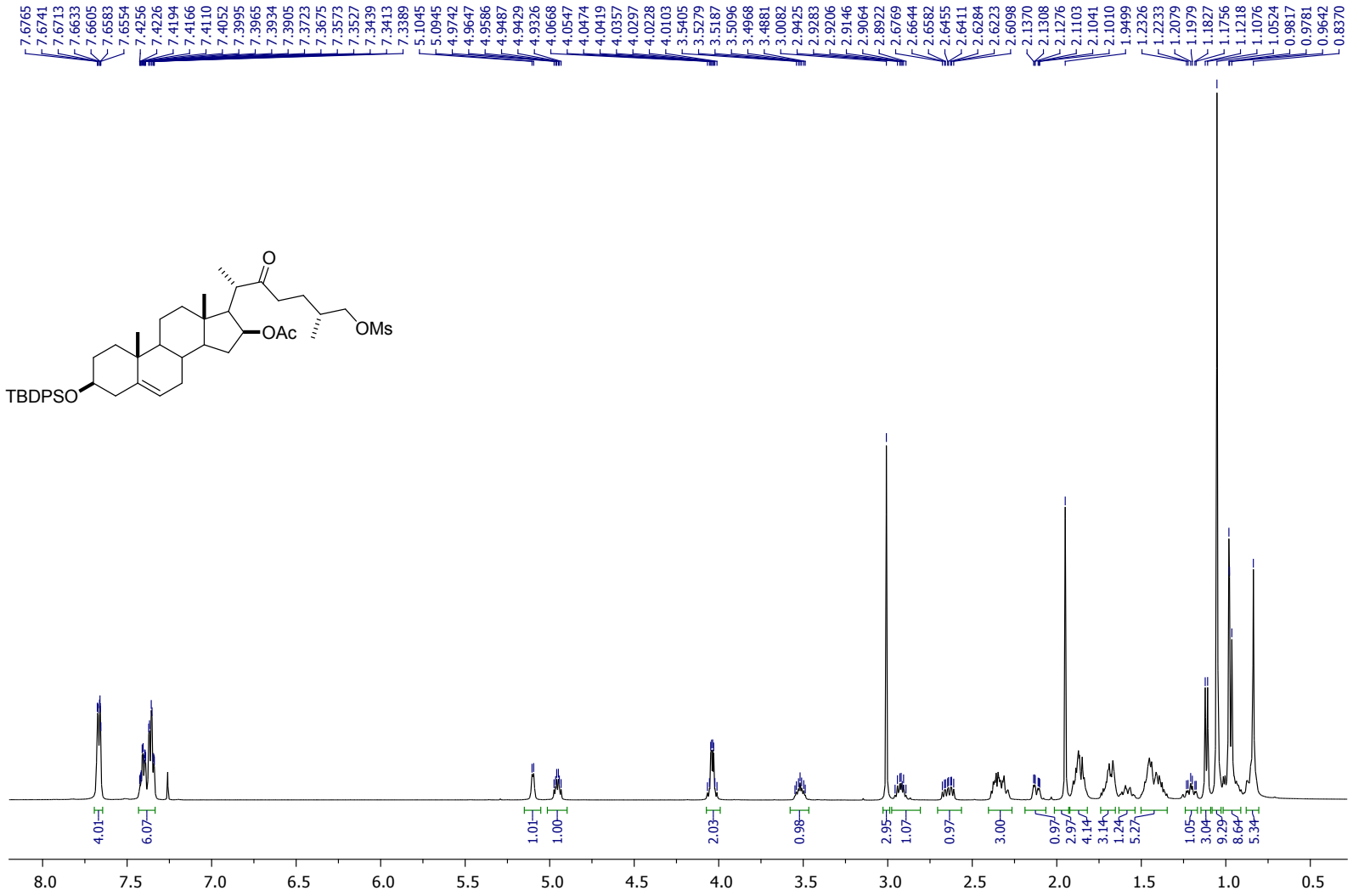
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **42**



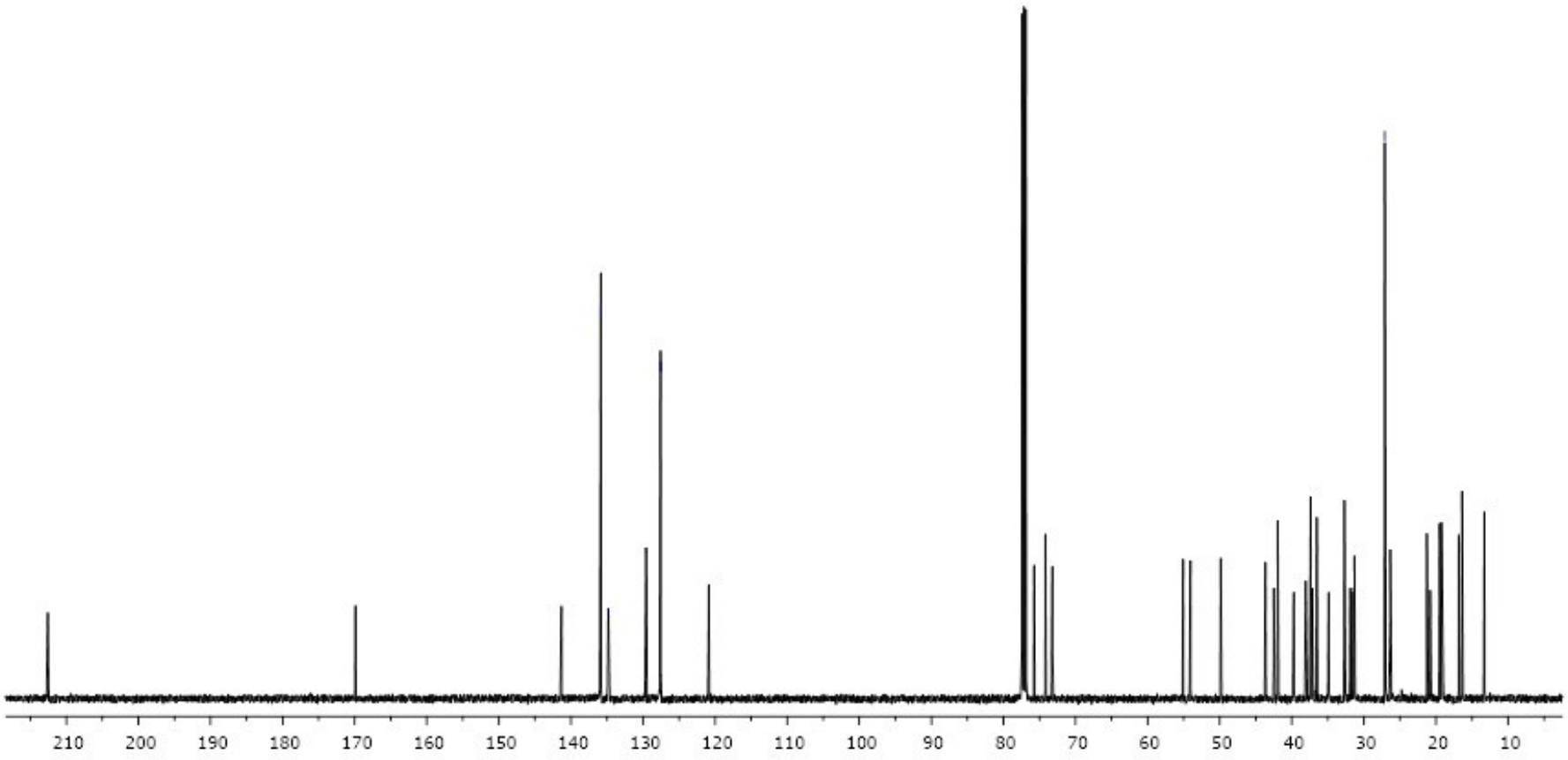
^{1}H-NMR (500 MHz, $CDCl_3$) of **44**



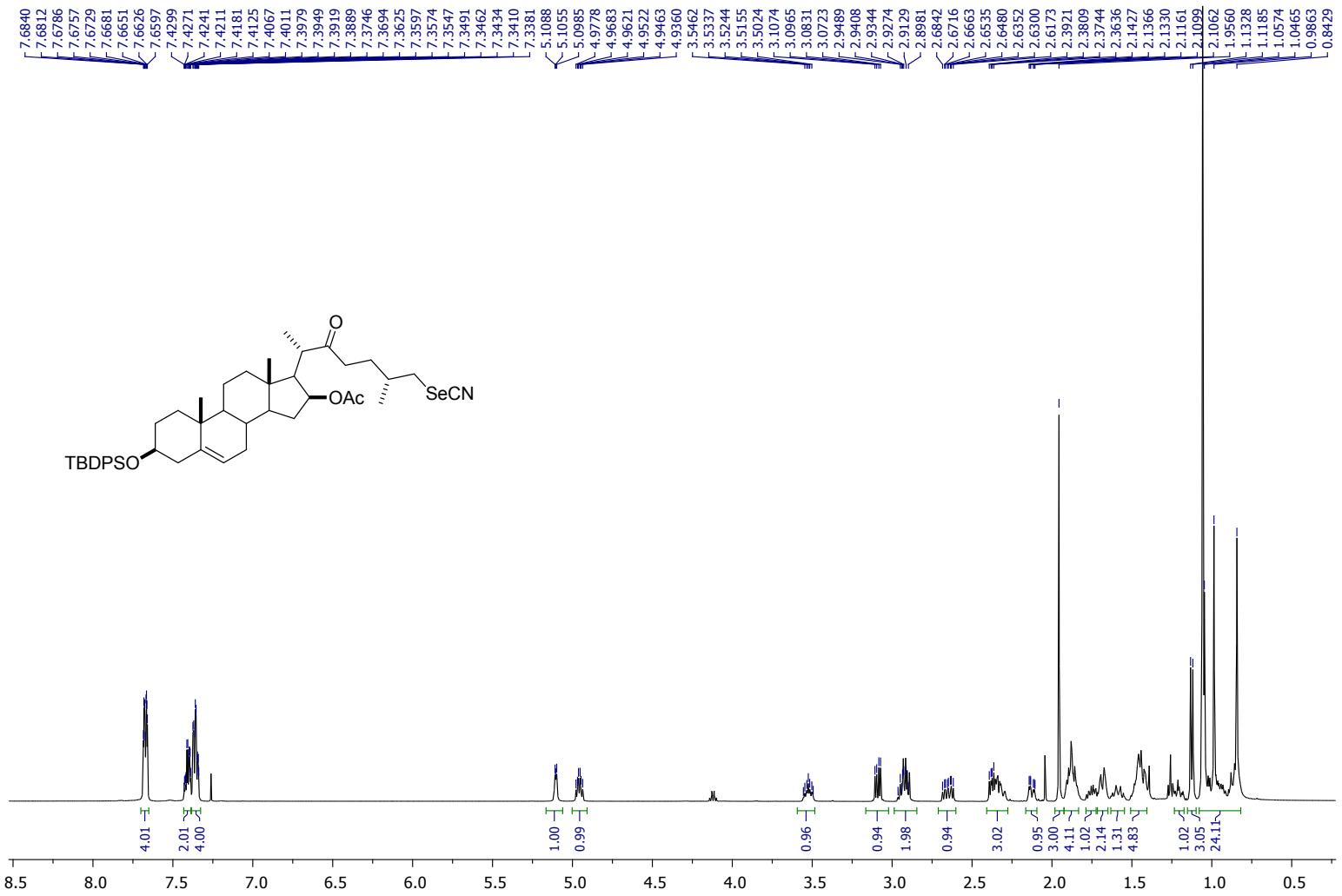
^{13}C-NMR (125.7 MHz, $CDCl_3$) of **44**



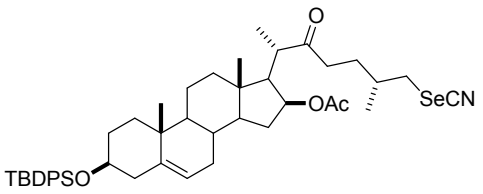
^{1}H-NMR (500 MHz, $CDCl_3$) of **45**

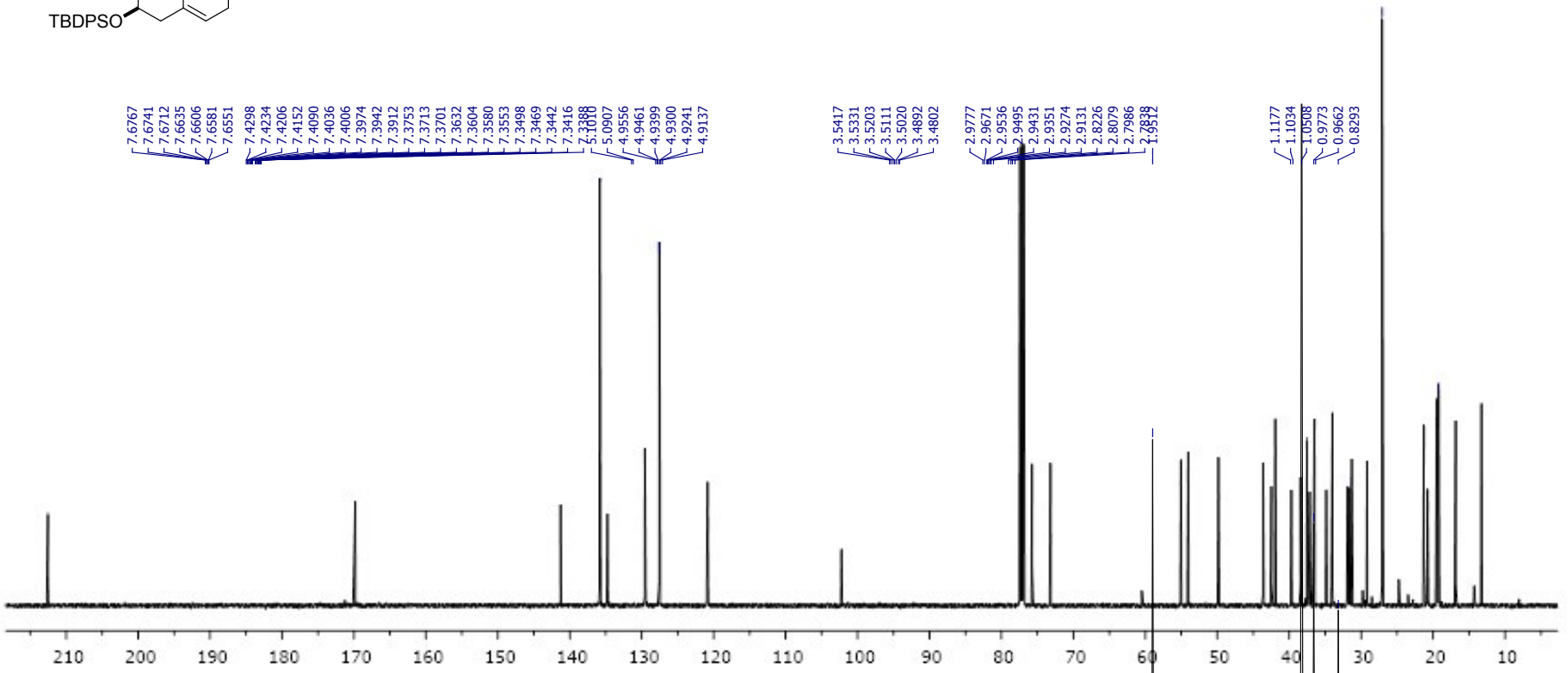


^{13}C-NMR (125.7 MHz, $CDCl_3$) of **45**

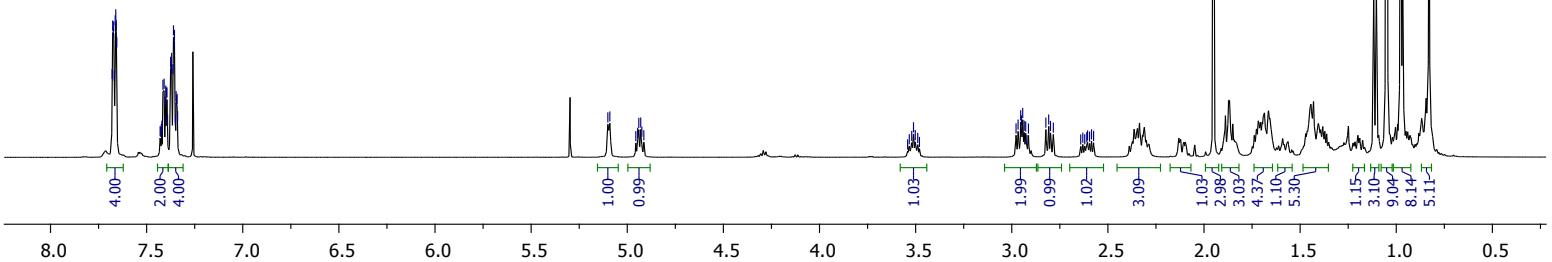


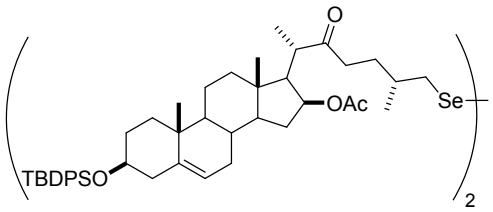
^{1}H-NMR (500 MHz, $CDCl_3$) of **46**



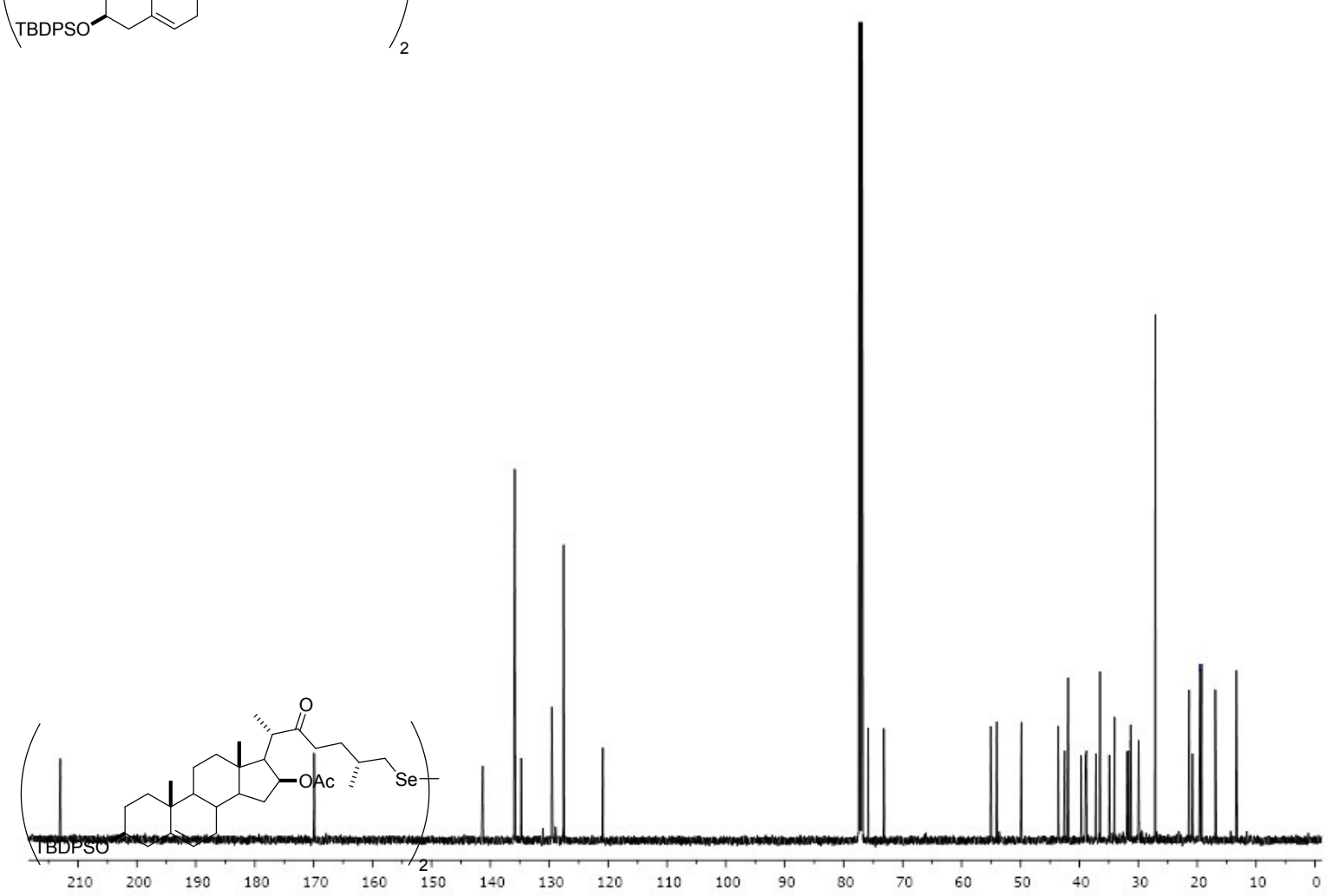


^{13}C-NMR (125.7 MHz, $CDCl_3$) of **46**

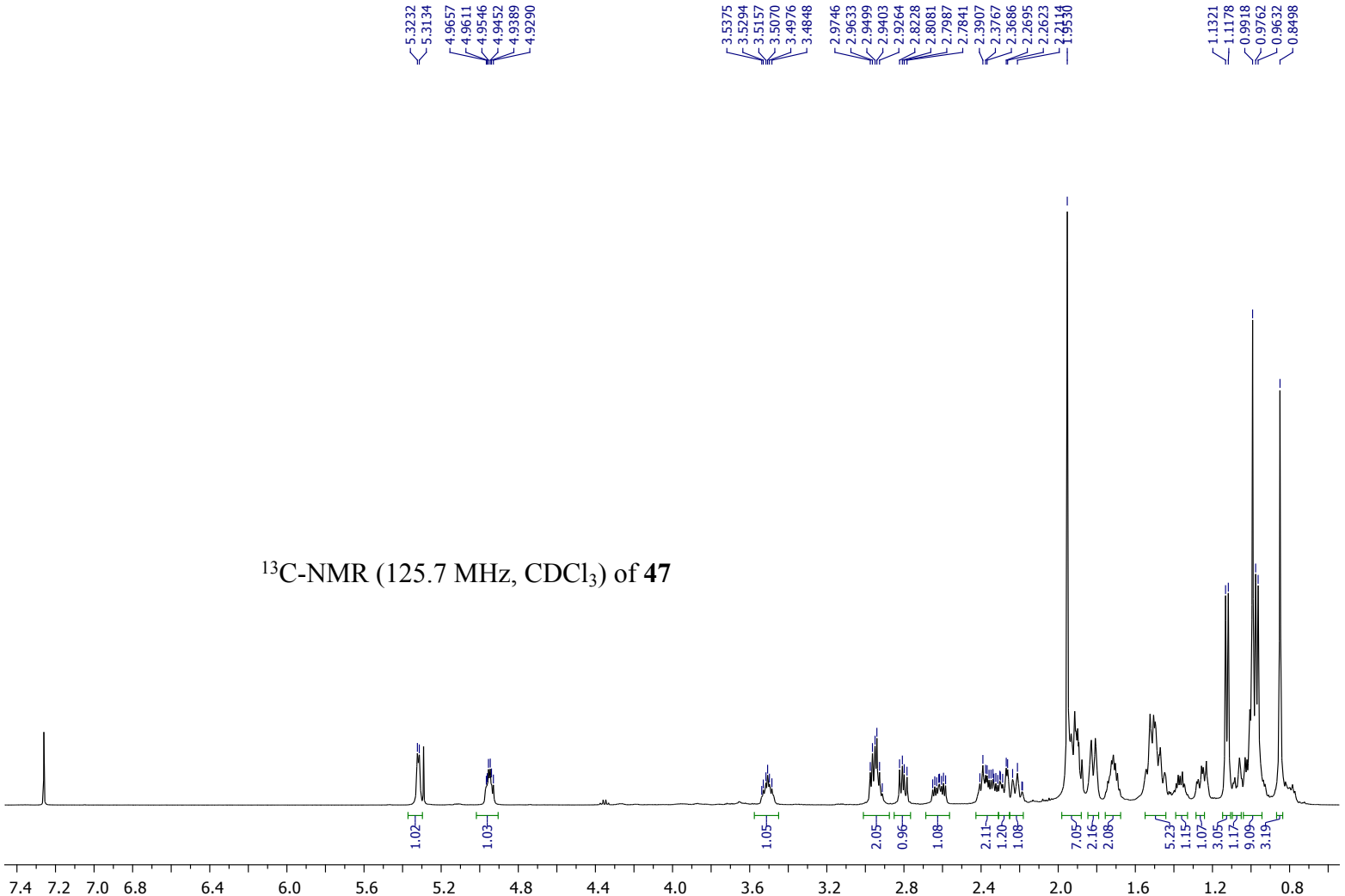


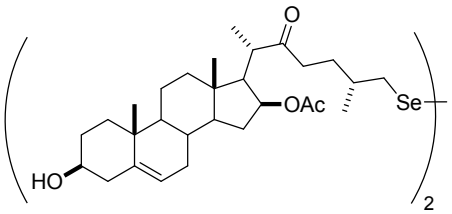


^{1}H-NMR (500 MHz, $CDCl_3$) of **47**

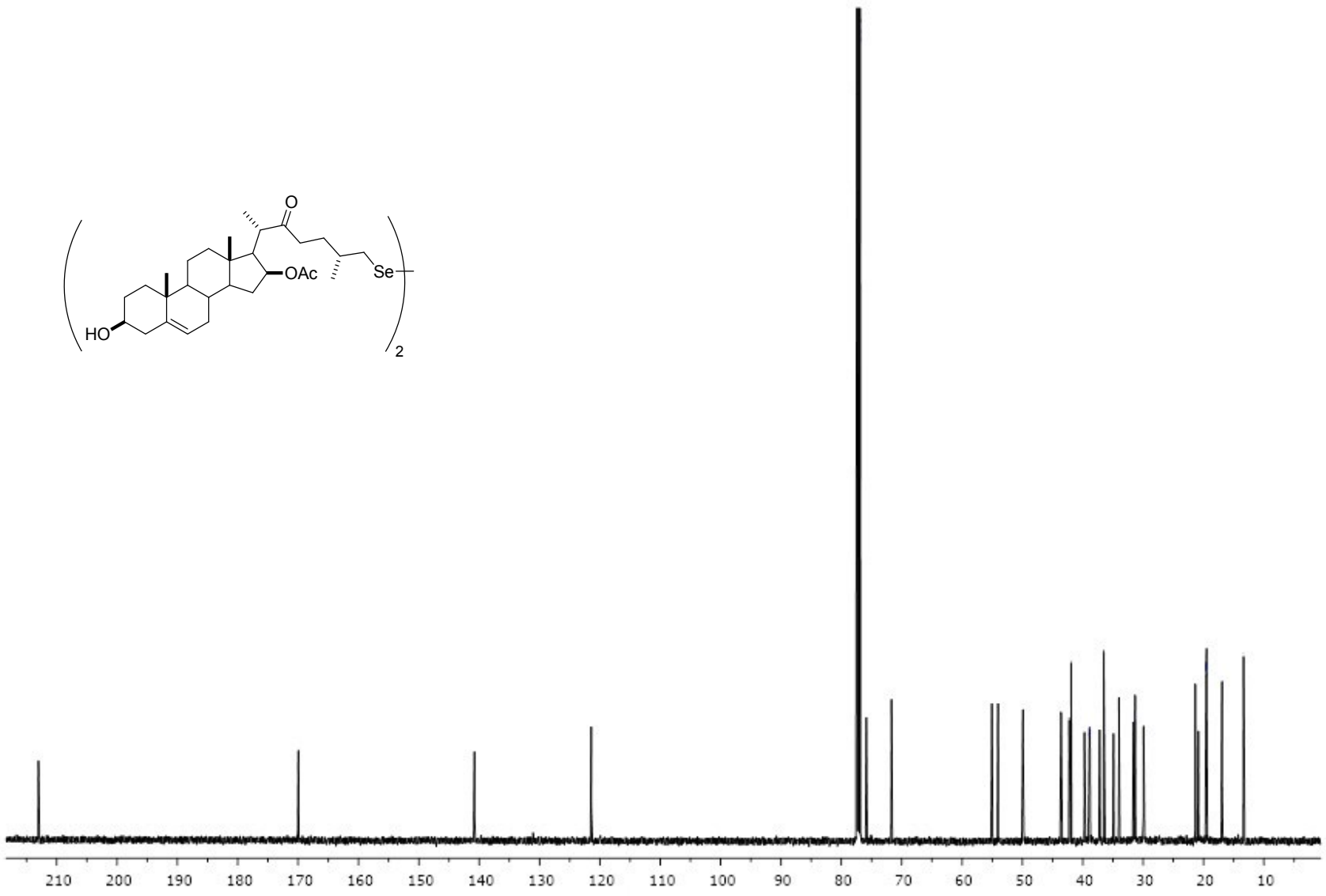


^{13}C-NMR (125.7 MHz, $CDCl_3$) of **47**

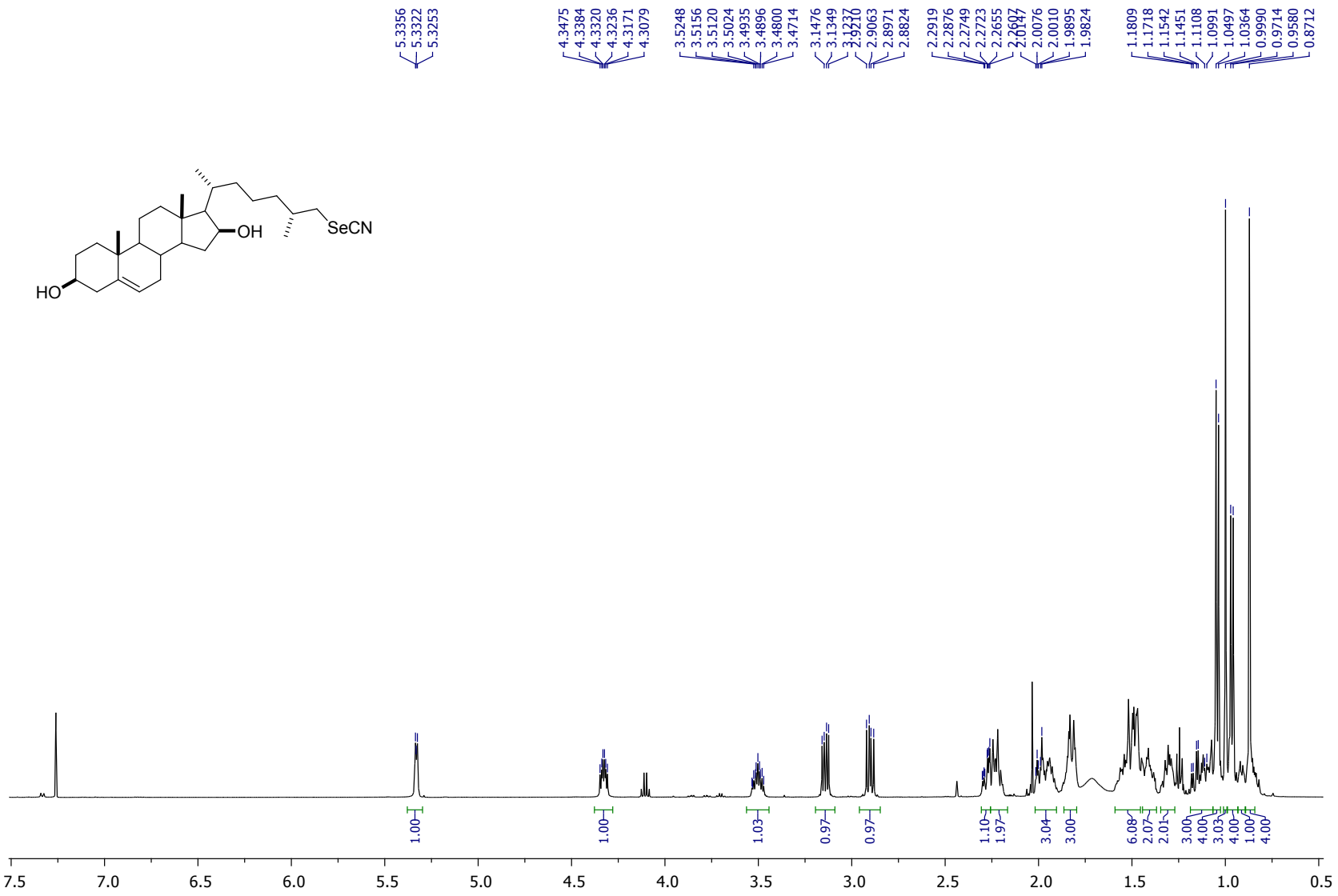




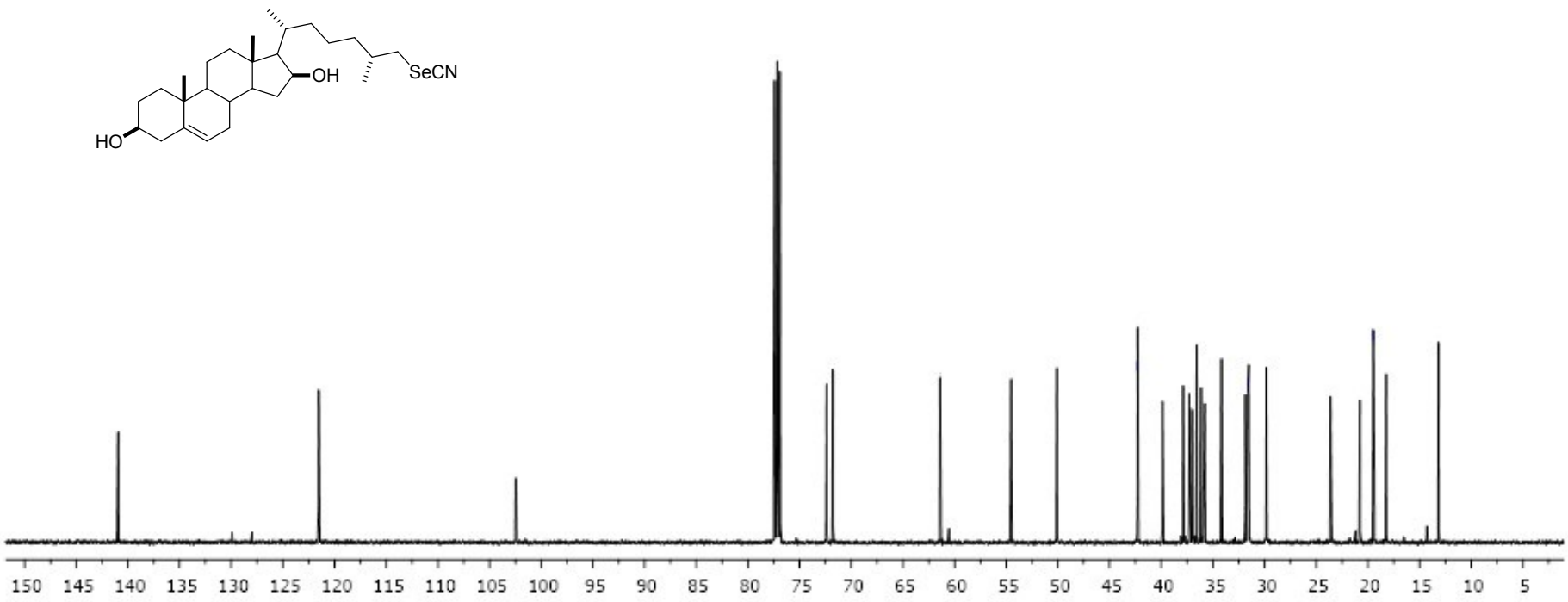
^{1}H-NMR (500 MHz, $CDCl_3$) of **48**



^{13}C-NMR (125.7 MHz, $CDCl_3$) of **48**



^{1}H-NMR (500 MHz, $CDCl_3$) of **51**



^{13}C-NMR (125.7 MHz, $CDCl_3$) of **51**