# Supporting Information

# Enantioselective Construction of the ABCDE Pentacyclic Core of the *Strychnos* Alkaloids

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# 1. General Experimental

## 1.1 General Information

Reactions were carried out under a nitrogen atmosphere in oven-dried glassware unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents.

## 1.2 Solvents & reagents

Anhydrous tetrahydrofuran, dichloromethane, toluene were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58Å, basic, Sigma-Aldrich) columns. Other solvents were used directly as received from commercial suppliers. Petroleum ether (PE) refers to distilled light petroleum of fraction (30 °C - 40 °C). Bulk solutions were evaporated under reduced pressure using a rotary evaporator. Reagents used were obtained from commercial suppliers and used without purification. $Na_2SO_4$ refers to anhydrous sodium sulphate. Catalyst **8** was synthesized according to a literature procedure.[1]

## 1.3 Chromatography

Column chromatography was carried out using VWR Kieselgel 60 silica gel (60-63 μm). Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica which were visualized under UV light (254 nm) and by staining with ethanolic vanillin or aqueous potassium permanganate solutions.

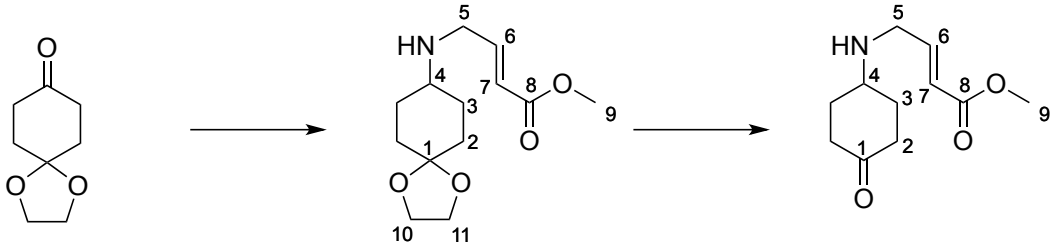
## 1.4 Spectroscopy

All $^{1}H$ and $^{13}C$ NMR spectra were recorded using a Bruker 500 MHz and Bruker 400 MHz spectrometers and are quoted in ppm for measurement against residual solvent peaks as internal standards. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The $^{1}H$ NMR spectra are reported as follows: δ/ppm (multiplicity, coupling constant *J*/Hz (where appropriate), number of protons). Multiplicity is abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, quint = quintet, m = multiplet, td = triplet of doublet, ddd = doublet of doublet of doublet, "d" = apparent doublet, "t" apparent triplet. For rotameric compounds the major rotamer has been fully assigned. Compound names are those generated by ACD LABS 12.0 following IUPAC nomenclature. The $^{13}C$ NMR spectra are reported as follows: δ/ppm (multiplicity, number of carbons). Two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy were used to assist the assignment of signals in the $^{1}H$ and $^{13}C$ NMR spectra. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film deposited onto a sodium chloride plate and only selected maximum absorbances ($\nu_{max}$) are reported ($cm^{-1}$). High resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer (ESI) by the internal service at the Department of Organic Chemistry, University of Oxford. Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

[1] Gammack Yamagata, A. D.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 4899–4903

# 2. Experimental procedures and characterisation data

## 2.1 Synthesis and characterisation of 6
**(*E*)-methyl 4-((4-oxocyclohexyl)amino)but-2-enoate**




To a solution of ketone **5** (1 eq., 25.6 mmol, 4 g) in MeOH (130 mL), was added amine (*E*)-4-aminobut-2-enoate (1.1 eq., 28.1 mmol, 3.24 g) and allowed stir at room temperature for 30 min. The reaction mixture was subsequently cooled to 0 °C and $NaBH_3CN$ (1.1 eq., 28.1 mmol, 1.74 g) was added portion wise. TFA (1.1 eq., 28 mmol, 3.24 g, 2.2 mL) was added dropwise dropwise, subsequently warmed to rt and allowed to stir for 8 h. The reaction mixture was added NaOH until pH 9 was obtained and extracted with EtOAc (3 × 250 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to afford **19** as a dark brown oil.
This residue (1 eq., assumed 25.6 mmol) was redissolved in THF (125 mL) and cooled to 0 °C. HCl (1 M; 5 eq., 128 mmol, 128 mL) was added slowly and subsequently warmed to rt and allowed to stir for 48 h.
The reaction mixture was cooled to 0 °C and basified carefully wit 8 M NaOH until pH 9 was obtained and was quickly extracted with EtOAc (3 × 250 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated *in vacuo* and purified by flash column chromatography (EtOAc:MeOH:$Et_3N$ 95:2.5:2.5) to give **6** as dark yellow viscous oil (60%, 3.24 g).

Characterisation data for **19**

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 3012, 2358, 1724.
**$^1$H-NMR** (400 MHz, $CDCl_3$) 6.95 (dtd, J = 15.6, 5.3, 3.0 Hz, 1H, H-6), 5.94 (d, J = 15.7 Hz, 1H, H-7), 3.93–3.85 (m, 4H, H-10 & H-11), 3.68 (d, J = 2.7 Hz, 3H, H-9), 3.39 (dd, J = 4.7, 2.9 Hz, 2H, H-5), 2.51 (tt, J = 9.9, 4.4 Hz, 1H, H-4), 1.86–1.76 (m, 2H, H-2a), 1.75–1.68 (m, 2H, H-3a), 1.55–1.43 (m, 1H, H-3b), 1.42–1.32 (m, 1H, H-2b), 1.3 (br s, 1H, N–H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$) 166.8 (C-8), 147.6 (C-6), 120.8 (C-7), 108.5 (C-1), 64.22 (C-10 or C-11), 64.18 (C-10 or C-11), 54.4 (C-4), 51.5 (C-9), 47.6 (C-5), 32.8 (C-2), 30.1 (C-3).

**HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{13}H_{22}NO_4)$+ requires *m/z* 256.1543, found *m/z* 256.1540.

Characterisation data for **6**

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 3014, 1718, 1650.

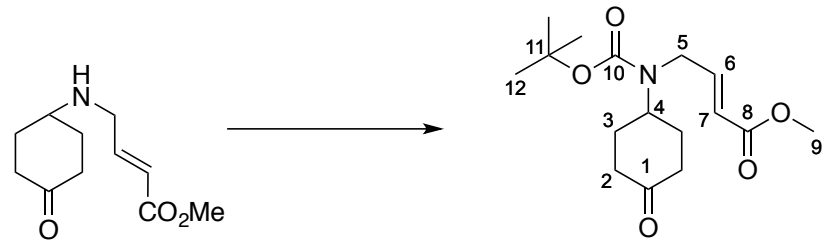
**$^1$H-NMR** (400 MHz, $CD_3OD$) 6.99 (dt, J = 15.7, 5.5 Hz, 1H, H-6), 5.99 (dt, J = 15.7, 1.8 Hz, 1H, H-7), 3.71 (s, 3H, H-9), 3.45 (dd, J = 5.5, 1.8 Hz, 2H, H-5), 2.97 (tt, J = 8.3, 3.5 Hz, 1H, H-4), 2.46 (dt, J = 12.0, 5.7 Hz, 2H, H-2a), 2.27 (ddd, J = 15.0, 10.2, 5.8 Hz, 2H, H-2b), 2.11–1.97 (m, 5H, C-3a, 1.66 (dtd, J = 13.3, 9.1, 4.8 Hz, 2H, C-3b).

**$^{13}$C-NMR** (101 MHz, $CD_3OD$) 207.1 (C-1), 162.8 (C-8), 143.1 (C-6), 117.2 (C-7), 49.0 (C-4), 47.6 (C-9), 43.8 (C-5), 34.4 (C-2), 27.9 (C-3).

**HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{11}H_{18}NO_3)^+$ requires *m/z* 212.1281, found *m/z* 212.1279.

## 2.2 Synthesis and characterisation of 7

**(*E*)-Methyl 4-((tert-butoxycarbonyl)(4-oxocyclohexyl)amino)but-2-enoate**




**6** **7**

To a solution of amine **6** (1 eq., 15.1 mmol, 3.2 g) in MeOH (75 mL) at rt was added $Boc_2O$ (1.15 eq., 17.4 mmol, 3.8 g) and stirred for 10 hours. The resulting solution was concentrated *in vacuo* and purified by flash column chromatography (elutes with EtOAc:PE 40:60) to give **7** as a white solid (92%, 4.7 g).

**mp** 106-108 °C.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 1739, 1722, 1685.

When $CD_3OD$ is used as NMR solvent, the ratio of rotamers reduces to 3:1.

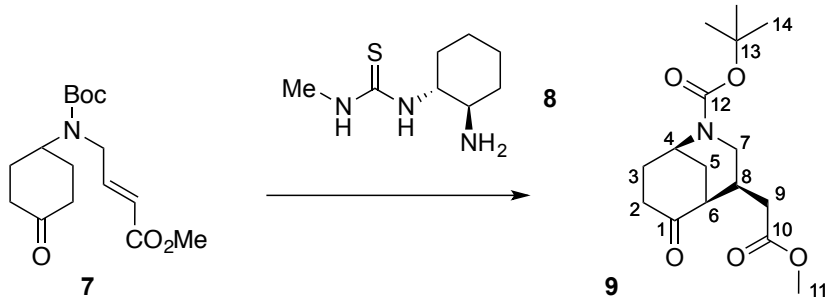
**$^1$H-NMR** (400 MHz, $CD_3OD$) Major rotamer: 6.88 (dt, J = 15.7, 5.0 Hz, 1H, H-6), 5.91 (dt, J = 15.7, 1.7 Hz, 1H, H-7), 4.54–4.21 (br m, 1H, H-4), 3.98 (d, J = 3.3 Hz, 2H, H-5), 3.72 (s, 3H, H-9), 2.56 (td, J = 14.2, 6.6 Hz, 2H, H-2), 2.33 (dt, J = 14.9, 2.3 Hz, 2H, H-2), 2.06–1.86 (m, 4H, H-3), 1.47 (s, 9H, H-12).

**$^{13}$C-NMR** (101 MHz, $CD_3OD$) 210.9 (C-1), 167.2 (C-8), 155.7 (C-10), 146.6 (C-8), 121.13 (C-7), 80.8 (C-11), 53.58 (C-4) 51.2 (C-9), 44.1 (C-5), 39.6 (C-2), 29.7 (2C-3), 27.7 (C-12).

HRMS (ES+) exact mass calculated for [M+Na]+ (C16H25NNaO5)+ requires m/z 334.1625, found m/z 334.1627.

## 2.3 Synthesis and characterisation of 9

**(1*R*,4*S*,5*S*)-tert-Butyl 4-(2-methoxy-2-oxoethyl)-6-oxo-2-azabicyclo[3.3.1]nonane-2-carboxylate**




To a solution of **7** (1 eq., 12.8 mmol, 4 g) in $CH_2Cl_2$ (64 mL) in a pressure vessel was added (+)-**8**[2] (5 mol%, 0.64 mmol, 120 mg), benzoic acid (0.0125 eq., 0.16 mmol, 20 mg) and was sealed. The reaction mixture was heated to 50 °C for 72 hours and subsequently concentrated *in vacuo* and purified by flash column chromatography (eluted with EtOAc:PE 20:80 → 60:40) to give (–)-**9** as a white solid (86%, 3.44 g).

This solid was added MeOH (10 mL) and heated to reflux, at which point it dissolved to give a colourless solution. This solution was allowed to cool slowly to rt overnight for crystallisation to occur, after which the crystals were filtered and washed with cold MeOH to afford (–)-**9** in an augmented ee (99.9%, 90% yield for crystallisation step, 3.1 g).

**$[\alpha]_D$** = –17.1 (c 3, $CDCl_3$). **mp** 125-127 °C. **IR** (film)/$cm^{-1}$ $\nu_{max}$ 1734, 1703, 1685.

Compound **9** is rotameric in $CD_3OD$ (ratio = 1:1). In the proton signal the difference in chemical shift is small enough that the signals from the same protons from the two rotamers overlap and appear as broad multiplets. The exception to this is H-7b which appears as two distict triplets which are labelled as H-7b and H-7b'.

**$^1$H-NMR** (500 MHz, $CD_3OD$) 4.39–4.30 (m, 1H, H-4), 4.04–3.95 (m, 1H. H-7a), 3.57 (s, 3H, H-11), 2.91 and 2.81 (t, J = 13.2 Hz, 1H, H-7b and H-7b'), 2.51–2.38 (m, 2H, H-2 & H-6), 2.35–2.16 (m, 3H, H-2 & H-8 & H-9), 2.11–1.84 (m, 5H, H-3 & H-5 & H-9), 1.38 (s, 9H). **$^{13}$C-NMR** (126 MHz, $CD_3OD$) C-1 (214.0 & 213.8), C-2 (39.8 & 39.7), C-3 (33.0 & 32.8), C-4 (46.1 & 45.0), C-5 (30.5 & 29.8), C-6 (48.5 & 48.4), C-7 (46.0 & 45.3), C-8 (35.9 & 36.6), C-9 (36.8 & 36.6), C-10 (173.50 & 173.45), C-11 (52.20), C-12 (155.3), C-13 (81.4), C-14 (28.7).

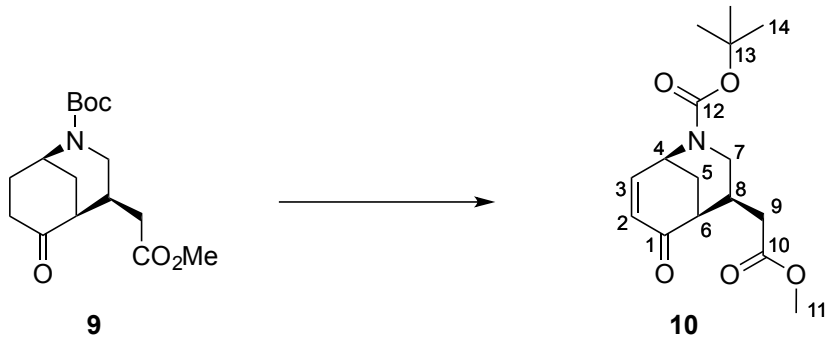
**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(CH_{25}NNaO_5)^+$ requires *m/z* 334.1625, found *m/z* 334.1627.

**HPLC**: ee = >99.9% (Chiralcel AS-H, 90:10 hexane/isopropanol, flow rate 1.0 mL/min, 210 nm, $t_R$ (major) = 20.2 min, $t_R$ (minor) = 12.2 min.

[2] Gammack Yamagata, A. D.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 4899–4903

## 2.4 Synthesis and characterisation of 10

**(1*S*,4*S*,5*S*)-*tert*-Butyl 4-(2-methoxy-2-oxoethyl)-6-oxo-2-azabicyclo[3.3.1]non-7-ene-2-carboxylate**




To a solution of (−)-**9** (1 eq., 10 mmol, 3.1 g) in PhCl (64 mL) was added IBX (2.5 eq., 25 mmol, 7.0 g) and the resulting suspension was heated to 100 °C (105 °C external temperature) for 36 h. The solution was cooled to rt, filtered through Celite® and concentrated *in vacuo*. The resulting cream solid was mostly pure but further purification through a silica plug (eluted with PE:EtOAc 80:20 → 60:40) removed redidual IBX impurities and afforded (−)-**10** as a white solid (92%, 2.8 g).

**$[\alpha]_D$** = -36.2 (c 2.4, $CDCl_3$)

**mp** 115–117 °C.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 2980, 1737, 1692, 1680.

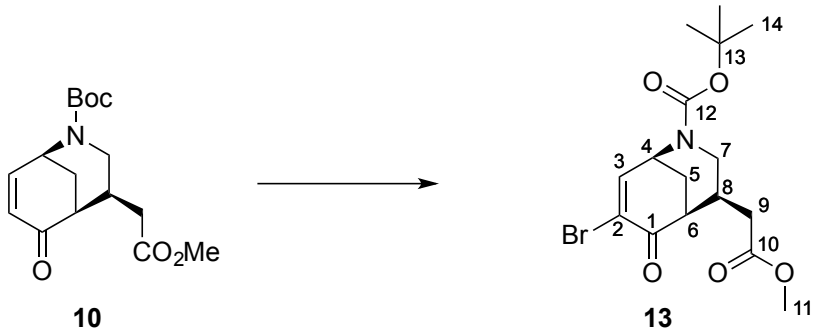
Major rotamer: **$^1$H-NMR** (400 MHz, $CD_3OD$) 6.84 (ddd, J = 10.0, 6.5, 1.5 Hz, 1H, H-3), 6.23 (d, J = 10.0 Hz, 1H, H-2), 4.97–4.89 (m, 1H, H-4), 4.05 (dd, J = 13.5, 5.0 Hz, 1H, H-7), 3.69 (s, 3H, H-11), 2.72–2.46 (m, 2H, H-6 & H-7), 2.43–2.27 (m, 3H, H-5a & H-8 & H-9a), 2.12 (dd, J = 16.5, 7.0 Hz, 1H, H-9b), 1.98 (d, J = 13.0 Hz, 1H, H-5b), 1.49 (s, 9H, H-13).

**$^{13}$C-NMR** (101 MHz, $CD_3OD$) 200.7 (C-1), 172.5 (C-10), 155.2 (C-12), 143.3 (C-3), 132.8 (C-2), 81.0 (C-13), 51.2 (C-11), 45.3 (C-6), 45.2 (C-4), 41.2 (C-7), 35.7 (C-8), 35.3 (C-9), 32.6 (C-5), 27.6 (C-14).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{16}H_{23}NNaO_5)^+$ requires *m/z* 332.1468, found *m/z* 332.1470.

## 2.5 Synthesis and characterisation of 13

***tert*-Butyl (1*S*,4*S*,5*S*)-7-bromo-4-(2-methoxy-2-oxoethyl)-6-oxo-2-azabicyclo[3.3.1]non-7-ene-2-carboxylate**




To a solution of (–)-**10** (1 eq., 8.66 mmol, 2.68 g) in $CH_2Cl_2$ (22.5 ml) at <0 °C (external bath –10 °C) was added a stock solution of $Br_2$ (1.02 eq., 8.84 mmol, 1.42 g, 453mL) in $CH_2Cl_2$ (22.5 mL) dropwise quickly making sure the temperature of the reaction did not exceed 0 °C. 5 minutes after the addition of bromine, $Et_3N$ (1.6 eq., 17.3 mmol, 1.75 g, 2.4 ml) was added in one portion. The reaction mixture was allowed to warm to rt and stirred for a further 1 h after which it was concentrated *in vacuo* and purified by flash column chromatography (elutes EtOAc:PE 20:80) to give (–)-**13** as a white solid (92%, 3.10 g).

**$[\alpha]_D$** = –67.6 (c 2.6, $CDCl_3$).

**mp** 154–156 °C.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 1934, 1737, 1687, 1597.

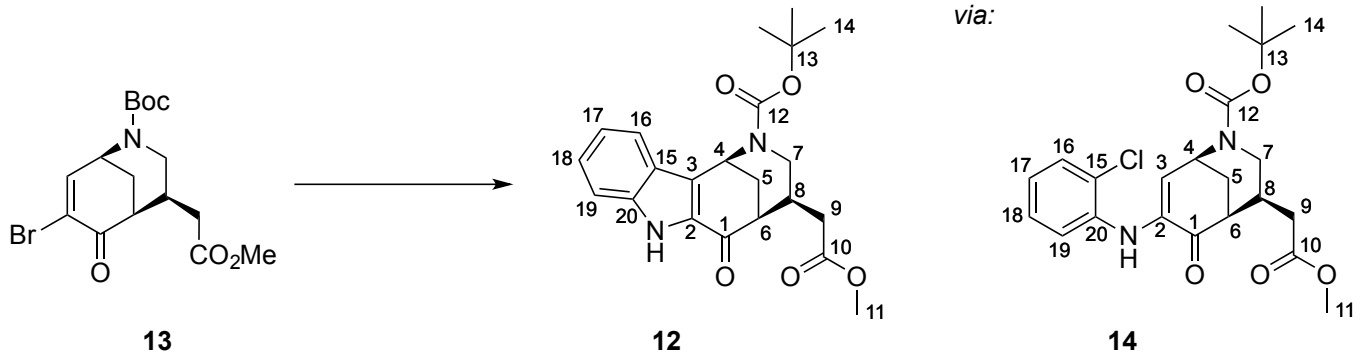
Major rotamer: **$^1$H-NMR** (500 MHz, $CD_3OD$) 7.31 (dd, J = 7.0, 1.5 Hz, 1H, H-3), 5.09–4.93 (br m, 1H, H-4), 4.09 (dd, J = 13.5, 5.0 Hz, 1H, H-7a), 3.71 (s, 3H, H-11), 2.90 (q, J = 3.5 Hz, 1H, H-6), 2.65–2.46 (br m, 1H, H-7b), 2.48–2.36 (m, 2H, H-5a & H-8), 2.31 (dd, J = 17.0, 7.0 Hz, 1H, H-9a), 2.14 (dd, J = 17.0, 7.0 Hz, 1H, H-9b), 2.00 (dt, J = 13.0, 3.0 Hz, 1H, H-5b), 1.51 (s, 9H, H-14).

**$^{13}$C-NMR** (126 MHz, $CD_3OD$) 191.6 (C-1), 172.0 (C-10), 154.6 (C-12), 143.9 (C-3), 127.3 (C-2), 80.9 (C-13), 50.8 (C-11), 36.5 (C-4), 45.3 (C-6), 35.4 (C-8), 34.8 (C-9), 32.0 (C-5), 27.1 (C-14).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{16}H_{22}BrNNaO_5)^+$ requires *m/z* 410.0574, found *m/z* 410.0577.

## 2.6 Synthesis and characterisation of 12 and 14

**_tert_-Butyl (1*S*,4*S*,5*S*)-4-(2-methoxy-2-oxoethyl)-6-oxo-1,3,4,5,6,7-hexahydro-2*H*-1,5-methanoazocino[4,3-*b*]indole-2-carboxylate (12) and _tert_-butyl (1*S*,4*S*,5*S*)-7-((2-chlorophenyl)amino)-4-(2-methoxy-2-oxoethyl)-6-oxo-2-azabicyclo[3.3.1]non-7-ene-2-carboxylate (14)**




$Pd_2dba_3$ (5 mol%, 0.194 mmol, 177 mg), BrettPhos (20 mol%, 0.77 mmol, 414 mg) and $Cs_2CO_3$ (4 eq, 15.5 mmol, 5 g) were added to a flask and subsequently evacuated and purged with $N_2$ (3×). Toluene (18 mL) was added and this mixture was allowed to stir under $N_2$ for 15 minutes. Bromide (–)-**13** (1 eq., 3.87 mmol, 1.5 g) and 2-chloroaniline (1.5 eq., 5.81 mmol, 0.74 g, 0.61 mL) were added under $N_2$. The reaction mixture was subsequently heated to 110 °C for 24 hours. The reaction mixture was then diluted with EtOAc and filtered through Celite®, concentrated *in vacuo*, and purified by flash column chromatography ((–)-**12** elutes with $Et_2O$:PE 30:70 and (–)-**14** elutes with 80:20) to give indole (–)-**12** as a solid (56%, 859 mg) and intermediate (–)-**14** (24%, 410 mg) as an oil.

Characterisation data for indole (–)-**12**.

**[α]$_D$** = –71.3 (c 4, $CDCl_3$)

**mp** 178–180 °C.

**IR** (film)/cm$^{-1}$ $\nu_{max}$ 3273, 2976, 1737, 1689, 1649, 1620, 1537.

**$^1$H-NMR** (500 MHz, $CDCl_3$) 9.41 (s, 1H, N–H), 7.92 (d, J = 8.0 Hz, 1H, H-16), 7.52–7.44 (m, 1H, H-19), 7.43–7.36 (m, 1H, H-18), 7.24–7.14 (m, 1H, H-17), 5.90 (t, J = 3.0 Hz, 1H, H-4), 3.81 (dd, J = 13.5, 5.0 Hz, 1H, H-7a), 3.73 (s, 3H, H-11), 2.96–2.86 (m, 1H, H-6), 2.65–2.53 (m, 2H, H-5a & H-8), 2.54–2.41 (m, 1H, H-9a), 2.43–2.31 (m, 1H, H-7b), 2.29–2.20 (m, 1H, H-5b), 2.13 (dd, J = 16.0, 6.5 Hz, 1H, H-9b), 1.42 (s, 9H, H-14). **$^{13}$C-NMR** (126 MHz, $CDCl_3$) 191.3 (C-1), 172.2 (C-10), 154.6 (C-12), 138.4 (C-20), 132.9 (C-2), 127.5 (C-18), 125.5 (C-3), 124.5 (C-15), 122.8 (C-16), 121.2 (C-17), 112.4 (C-19), 80.2 (C-13), 51.8 (C-11), 45.1 (C-6), 42.6 (C-4), 42.2 (C-7), 36.2 (C-5), 35.8 (C-8), 35.7 (C-9), 28.3 (C-14).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{22}H_{26}N_2NaO_5)^+$ requires *m/z* 421.1734, found *m/z* 421.1732.

Characterisation data for intermediate (–)-**14**.

**$[\alpha]_D$** = –59.7 (c 3, $CDCl_3$).

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 3360, 2976, 1737, 1677, 1627, 1592, 1525.

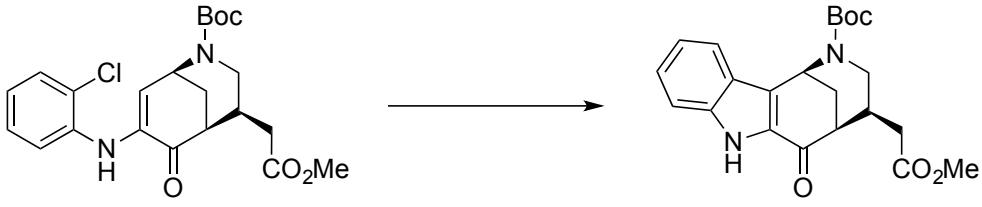
Major rotamer: **$^1$H-NMR** (500 MHz, $CDCl_3$) 7.38 (d, J = 8.0 Hz, 1H, H-16), 7.29 (d, J = 8.0 Hz, 1H, H-19), 7.21 (t, J = 7.5 Hz, 1H, H-18), 6.98 (s, 1H, N–H), 6.90 (t, J = 7.5 Hz, 1H, H-17), 6.22–6.09 (br m, 1H, H-3), 5.22–5.06 (br m, 1H, H-4), 3.99–3.88 (br m, 1H, H-7a), 3.72 (s, 3H, H-11), 2.91–2.82 (br m, 1H, H-6), 2.79–2.62 (br m, 1H, H-7b), 2.52–2.31 (m, 3H, H-8 & H-5a & H-9a), 2.14 (dd, J = 16.5, 6.5 Hz, 1H, H-9b), 2.05–1.97 (m, 1H, H-5b), 1.47 (s, 9H, H-14).

**$^{13}$C-NMR** (126 MHz, $CDCl_3$) 195.6 (C-1), 172.0 (C-10), 154.5 (C-12), 138.6 (C-2), 137.4 (C-20), 130.0 (C-16), 127.4 (C-18), 124.2 (C-15), 122.2 (C-17), 118.7 (C-19), 109.1 (C-3), 80.4 (C-13), 51.9 (C-11), 44.5 (C-4), 44.0 (C-6), 41.9 (C-7), 36.0 (C-8), 35.5 (C-9), 32.9 (C-5), 28.4 (C-14).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{22}H_{27}ClN_2NaO_5)$+ requires *m/z* 457.1501, found *m/z* 457.1498.

## 2.7 Synthesis of 12 from 14

Synthesis of indole (–)-**12** from intermediate (–)-**14**.



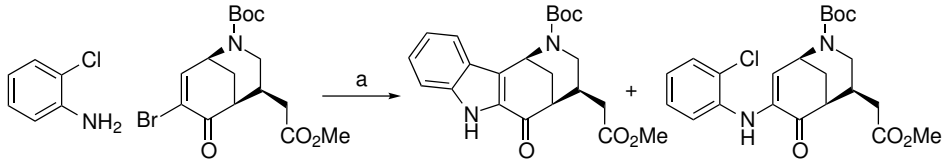

**14** **12**

$Pd_2dba_3$ (5 mol%, 0.94 mmol, 47 mg), BrettPhos (20 mol%, 0.19 mmol, 100 mg) and $Cs_2CO_3$ (4 eq, 3.77 mmol, 1.23 g) were added to a flask and subsequently evacuated and purged with $N_2$ (3×). Toluene (4.4 mL) was added and was allowed to stir under $N_2$ for 15 minutes. Intermediate (–)-**14** (1 eq., 0.944 mmol, 410 mg) was added under $N_2$ and subsequently heated to 110 °C for 24 hours. The reaction mixture was diluted with EtOAc and filtered through Celite®, concentrated *in vacuo*, and purified by flash column chromatography (elutes with $Et_2O$:PE 80:20) to give indole (–)-**12** as a solid (66%, 375 mg).

**Spectroscopic data of 12 consistent with those reported on pg 10.**

## 2.8 Screening of ligands in the Barluenga coupling

**Table 1:** Screening of conditions for the synthesis of indole **12** using the Barluenga protocol.

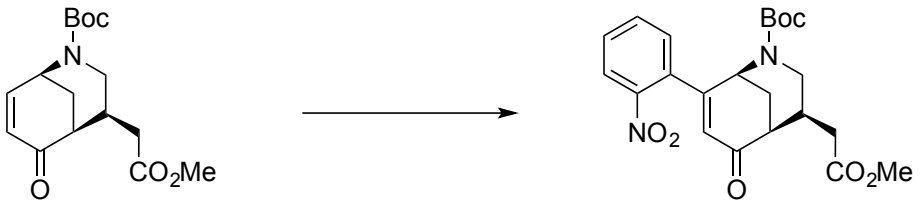



| Entry[a] | Pd source (5 mol%) | Ligand (20 mol%) | Temp °C | Time h | Yield **12**[b] (**14**) % |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | Xphos | 100 | 24 | 0 (67) |
| 2 | $Pd_2(dba)_3$ | Davephos | 100 | 24 | 0 (74) |
| 3 | $Pd_2(dba)_3$ | RuPhos | 100 | 24 | trace (55) |
| 4[c] | $Pd_2(dba)_3$ | RuPhos | 110 | 24 | trace (61) |
| 5[d] | $Pd_2(dba)_3$ | RuPhos | 110 | 12+24 | 6 (27) |
| 6 | $Pd_2(dba)_3$ | BrettPhos | 100 | 24 | 46 (36) |
| 7 | $Pd_2(dba)_3$ | BrettPhos | 100 | 37 | 40 (17) |
| 8[e] | $Pd_2(dba)_3$ | BrettPhos | 110 | 24 | 56 (24) |
| 9[f] | $Pd_2(dba)_3$ | BrettPhos | 110 | 24+12 | 51 (15) |
| 10[g] | Brettphos-Pd-G3 | Brettphos | 110 | 11 | Complex mixture |
| 11 | $Pd_2(dba)_3 \cdot CHCl_3$ | Brettphos | 110 | 24 | 42 |

[a]Reaction conditions: **13** (1 eq.), 2-chloroaniline (1.5 eq.), Pd–source, ligand, $Cs_2CO_3$ (2.5 eq. for entries 1–6, 4 eq. for entries 5–11), toluene, temp, time.
[b]Isolated yield after flash column chromatography.
[c]10 mol% $Pd_2(dba)_3$ and 40 mol% RuPhos was used.
[d]An additional amount of $Pd_2(dba)_3$ (5 mol%) and RuPhos (20 mol%) was added after 12 hours.
[e]Performed on 1.3 g
[f]An additional amount of $Pd_2(dba)_3$ (5 mol%) and BrettPhos (20 mol%) was added after 24 hours.
[g]10 mol% Brettphos-Pd-G3 and 10 mol% BrettPhos was used.

## 2.9 Synthesis and characterisation of 11

***tert*-butyl (1*S*,4*S*,5*S*)-4-(2-methoxy-2-oxoethyl)-8-(2-nitrophenyl)-6-oxo-2-azabicyclo[3.3.1]non-7-ene-2-carboxylate**




Synthesis of **11** was performed on racemic enone **10**.

To a flask was added (±)-**10** (1 eq., 1.62 mmol, 500 mg), 2-nitrobenzoic acid (3 eq., 4.85 mmol, 810 mg), $Pd(TFA)_2$ (0.2 eq., 0.32 mmol, 107 mg), $Ag_2CO_3$ (3 eq., 4.85 mmol, 1.337 g), a solution of DMF/DMSO (8.05 mL, DMSO/DMF 5% v/v). The suspension was evacuated carefully under vacuum and purged with $N_2$ (3x) and heated to 125 °C for 3 hours. 8 such reactions were conducted in parallel amounting to a total of 4g of starting material (±)-**10**. All 8 reactions were combined and the resulting thick black suspension was diluted with EtOAc. $H_2O$ was added and vigorously stirred for 10 min. $Na_2SO_4$ (20 g) was added and vigorously stirred for another 20 minutes. Filtration through Celite® and concentration of the filtrate gave a black sludge. Two purification steps *via* flash column chromatography are required for the purification of **11**. The first flash column elutes nitrobenzene dimer quickly using neat $C_6H_6$ as solvent to give a mixture of (±)-**10** and (±)-**11**. The second uses EtOAc:PE (20:80 ➔ 30:70 ➔ 40:60 ➔ 50:50) to give (±)-**11** as a yellow solid (19%, 1.16 g) and starting material (±)-**10** as a yellow solid (46%, 1.84 g).

**mp** 169–171 °C

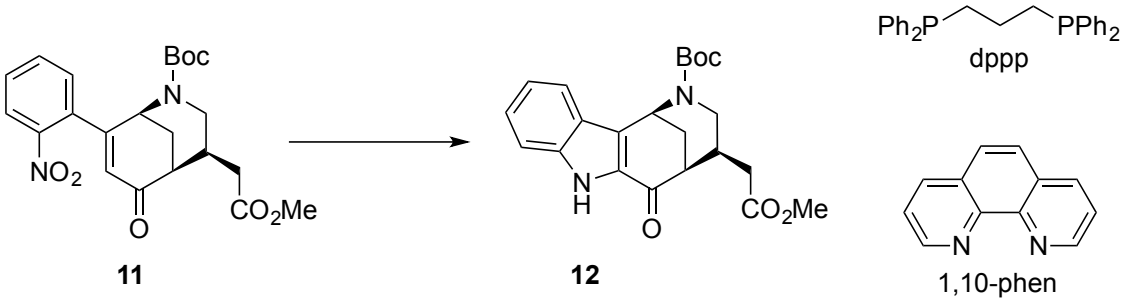
**IR** (film)/$cm^{-1}$ $\nu_{max}$ 2971, 1737, 1692, 1672, 1605, 1571, 1524.

Major rotamer: **$^1$H-NMR** (500 MHz, $CD_3OD$) 8.32 (dd, *J* = 8.0, 1.5 Hz, 1H, H-19), 7.81 (td, *J* = 7.5, 1.5 Hz, 1H, H-17), 7.75 (td, *J* = 8.0, 1.5 Hz, 1H, H-18) 7.35 (dd, *J* = 7.5, 1.5 Hz, 1H, H-16), 6.16 (s, 1H, H-2), 4.91 (t, *J* = 3.0 Hz, 1H, H-4), 4.11 (dd, *J* = 13.5, 5.0 Hz, 1H, H-7a), 3.73 (s, 3H, H-11), 2.76--2.62 (m, 3H, H-7b & H-6 & H-5a), 2.52--2.37 (m, 2H, H-8 & H-9a), 2.29--2.18 (m, 1H, H-9b), 2.16 (ddd, *J* = 13.0, 3.5, 2.0 Hz, 1H, H-5b), 1.04 (s, 9H, H-14).

**$^{13}$C-NMR** (126 MHz, $CD_3OD$) 199.5 (C-1), 172.2 (C-10), 154.3 (C-3), 153.7 (C-12), 146.6 (C-20), 134.6 (C-17), 134.4 (C-15), 131.0 (C-16), 130.4 (C-17), 128.6 (C-2), 125.0 (C-19), 80.4 (C-13), 50.8 (C-11), 49.6 (C-4), 43.6 (C-6), 40.8 (C-7), 35.3 (C-8), 35.1 (C-9), 32.5 (C-5), 26.6 (C-14).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{22}H_{26}N_2NaO_7)+$ requires *m/z* 453.1632, found *m/z* 453.1633.

## 2.10 Synthesis of 12 from 11 *via N*-heteroannulation.

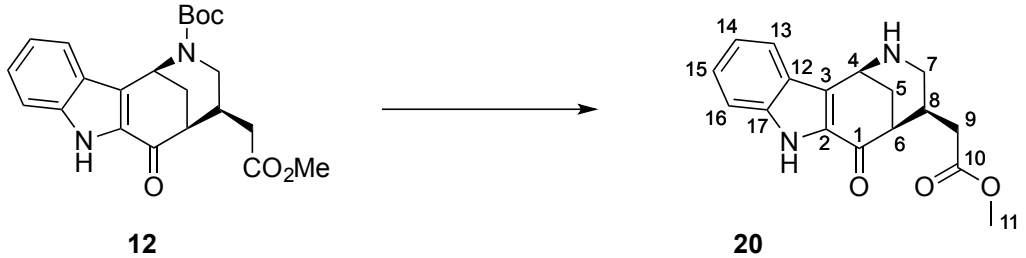



To a flask was added (±)-**11** (1 eq., 2.79 mmol, 1.2 g), $Pd(dba)_2$ (0.1 eq., 0.28 mmol, 160 mg), dppp (0.1 eq., 0.28 mmol, 115 mg), and 1,10-phenanthroline (0.2 eq., 0.558 mmol, 110 mg) and DMF (29 mL). The flask was evacuated under vacuum and purged with CO(g) to saturate the solvent with gas. The reaction mixture was subsequently placed under CO(g) pressure with the aid of a balloon (5 balloons within each other, approx 1.35 atm) and heated to 95 °C for 2.5 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (elutes with $Et_2O$:PE 60:40 to 70:30 to 80:20) to give (±)-**12** as a yellow solid (79%, 879 mg).

**Spectroscopic data of 12 consistent with those reported on pg 10.**

## 2.11 Synthesis and characterisation of 20

**Methyl 2-((1*S*,4*S*,5*S*)-6-oxo-2,3,4,5,6,7-hexahydro-1*H*-1,5-methanoazocino[4,3-*b*]indol-4-yl)acetat**




**12** **20**

To a solution of (–)-**12** (1 eq., 2.39 mmol, 950 mg) in $CH_2Cl_2$ (21 mL) at 0 °C was added TFA (7 mL). The reaction mixture was maintained at this temperature until all starting material had been consumed (approx 2.5 h). The reaction mixture was then diluted with toluene (21 mL) at 0 °C and concentrated *in vacuo*, first at rt to remove the $CH_2Cl_2$ and TFA and subsequently at 30 °C to remove toluene to give TFA salt of **20** as a brown residue. This was subsequently basified with 1 M NaOH, extracted with EtOAc (3 × 20 mL) and concentrated *in vacuo* to give (–)-**20** as a yellow gum (92%, 647 mg). This was sufficiently pure to use in the subsequent step without further purification.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 3266, 2923, 2854, 2359, 2341, 1734, 1647.

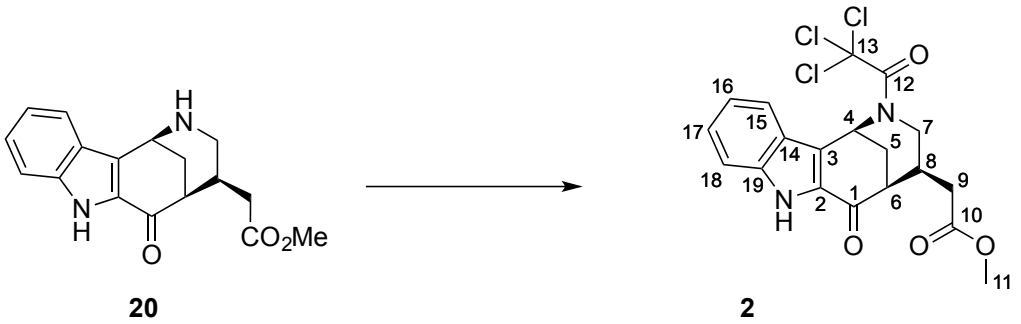
**$^1$H-NMR** (500 MHz, $CDCl_3$) 9.72 (s, 1H, N–$H_{Ind}$), 7.71 (dt, J = 8.0, 1.0 Hz, 1H, H-13), 7.50 (dt, J = 8.5, 1.0 Hz, 1H, H-16), 7.39 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, H-15), 7.19 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, H-14), 4.66 (t, J = 3.0 Hz, 1H, H-4), 3.71 (s, 3H, H-11), 2.86–2.80 (m, 2H, H-6 & H-7a), 2.63–2.51 (m, 2H, H-8 & H-5a), 2.48 (dd, J = 16.5, 7.0 Hz, 1H, H-9a), 2.38 (t, J = 12.5 Hz, 1H, H-7b), 2.33 (dt, J = 12.5, 3.0 Hz, 1H, H-5b), 2.11 (dd, J = 16.5, 7.5 Hz, 1H, H-9b), 1.85 (s, 1H).

**$^{13}$C-NMR** (126 MHz, $CDCl_3$) 191.9 (C-1), 172.5 (C-10), 138.6 (C-17), 133.3 (C-2), 127.2 (C-15), 126.0 (C-3), 124.2 (C-12), 121.1 (C-13), 121.0 (C-14), 112.9 (C-16), 51.7 (C-11), 46.0 (C-6), 44.6 (C-4), 43.3 (C-5), 37.4 (C-5), 36.3 (C-9), 35.9 (C-8).

**HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{19}N_2O_3)$+ requires *m/z* 299.1390, found *m/z* 299.1387.

## 2.12 Synthesis and characterisation of 2

**Methyl 2-((1*S*,4*S*,5*S*)-6-oxo-2-(2,2,2-trichloroacetyl)-2,3,4,5,6,7-hexahydro-1*H*-1,5-methanoazocino[4,3-*b*]indol-4-yl)acetate**




**20** **2**

To a solution of (–)-**20** (1. eq., 2.29 mmol, 681 mg) in $CH_2Cl_2$ (23 mL) at 0 °C was added $Et_3N$ (1.25 eq., 2.86 mmol, 288 mg, 400mL) and trichloroacetyl chloride (1.05 eq., 2.40 mmol, 436 mg, 268mL). The reaction was allowed to warm to rt and stirred for an additional 7 h. Aqueous sat. $NaHCO_3$ was added and subsequently extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried over $Na_2SO_4$, concentrated *in vacuo*, purified by flash column chromatography to give (–)-**2** as a white solid (90%, 909 mg).

**$[\alpha]_D$** = -131.4 (c 3.6, $CDCl_3$).

**mp** 220–222 °C.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 3270, 2926, 1735, 1657, 1620.

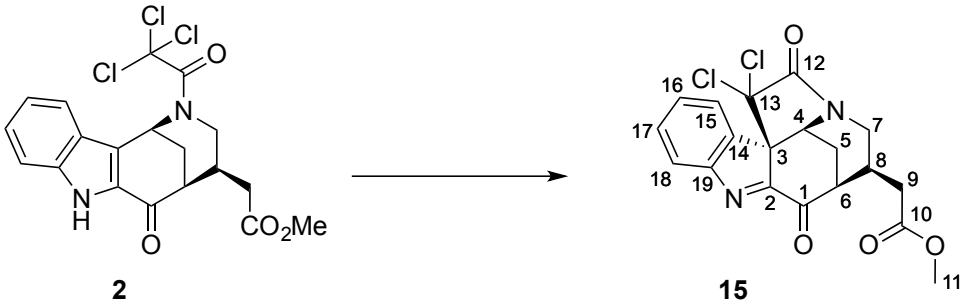
**$^1$H-NMR** (500 MHz, CD2Cl2) 9.25 (s, 1H, N–H), 7.80 (d, J = 8.0 Hz, 1H, H-15), 7.51 (dt, J = 8.5, 1.0 Hz, 1H, H-18), 7.42 (ddd, J = 8.5, 7.0, 1.2 Hz, 1H, H-17), 7.22 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, H-16), 6.26 (t, J = 2.5 Hz, 1H, H-4), 4.43 (dd, J = 14.0, 5.0 Hz, 1H, H-7a), 3.68 (s, 3H, H-11), 2.92 (app q, J = 3.5 Hz, 1H, H-6), 2.85 (t, J = 13.5, 12.5 Hz, 1H, H-7b), 2.75–2.64 (m, 2H, H-5a & H-8), 2.51 (dd, J = 16.5, 6.5 Hz, 1H, H-9a), 2.39–2.32 (m, 1H, H-5b), 2.12 (dd, J = 16.5, 8.0 Hz, 1H, H-9b).

**$^{13}$C-NMR** (126 MHz, CD2Cl2) 190.2 (C-1), 171.5 (C-11), 159.5 (C-12), 138.1 (C-19), 133.6 (C-2), 127.7 (C-17), 124.4 (C-14), 123.5 (C-3), 121.9 (C-15), 121.7 (C-16), 112.6 (C-18), 93.1 (C-13), 51.8 (C-11), 45.8 (C-7), 45.3 (C-6), 44.8 (C-4), 35.6 (C-5), 35.4 (C-9), 35.0 (C-8).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{19}H_{17}Cl_3N_2NaO_4)^+$ requires *m/z* 465.0146, found *m/z* 465.0141.

## 2.13 Synthesis and characterisation of 15

**Methyl 2-((3a*S*,5*S*,11b*S*,12*S*)-1,1-dichloro-2,6-dioxo-1,2,3a,4,5,6-hexahydro-5,3-ethanopyrrolo[2,3-*d*]carbazol-12-yl)acetate**




Trichloroacetamide (–)-**2** (1 eq., 1.13 mmol, 500 mg), $CuCl^3$ (2.2 eq., 2.48 mmol, 246 mg) and TBTA (2.2 eq., 2.48 mmol, 1.358 g) was added to a Schlenk flask and evacuated under vacuum and purged with argon (3×). Thoroughly degassed and anhydrous MeCN (0.023 M, 50 mL) was added *via* syringe and the reaction allowed to stir at rt for 10 min whilst a lime green precipitate forms. The resulting suspension was heated to 55 °C (external temperature) and stirred for 30 min. The reaction mixture was cooled to rt, filtered through a sintered funnel and concentrated *in vacuo*. The resulting green oil was purified by flash column chromatography (PE:EtOAc 50:50) to give (–)-**15** as a light yellow solid (67%, 308 mg).

**$[\alpha]_D$** = -108.4 (c 3, $CDCl_3$).

**mp** decomposition at 243 °C.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 2952, 1730, 1652, 1556.

**$^1$H-NMR** (500 MHz, CD2Cl2) 7.80 (d, J = 7.5 Hz, 1H, H-15), 7.74 (d, J = 8.0 Hz, 1H, H-18), 7.55 (td, J = 7.5, 1.0 Hz, 1H, H-17), 7.42 (td, J = 7.5, 1.0 Hz, 1H, H-16), 4.64 (dd, J = 6.0, 1.0 Hz, 1H, H-4), 3.86 (dd, J = 14.35, 1.5 Hz, 1H, H-7a), 3.65 (s, 3H, H-11), 3.25 (dd, J = 14.5, 8.0 Hz, 1H, H-7b), 2.93–2.79 (m, 3H, H-6 & H-8 & H-9a), 2.54–2.43 (m, 1H, H-9b), 1.99 (ddd, J = 15.0, 6.0, 1.5 Hz, 1H, H-5a), 1.51 (dd, J = 15.0, 4.0 Hz, 1H, H-5b).

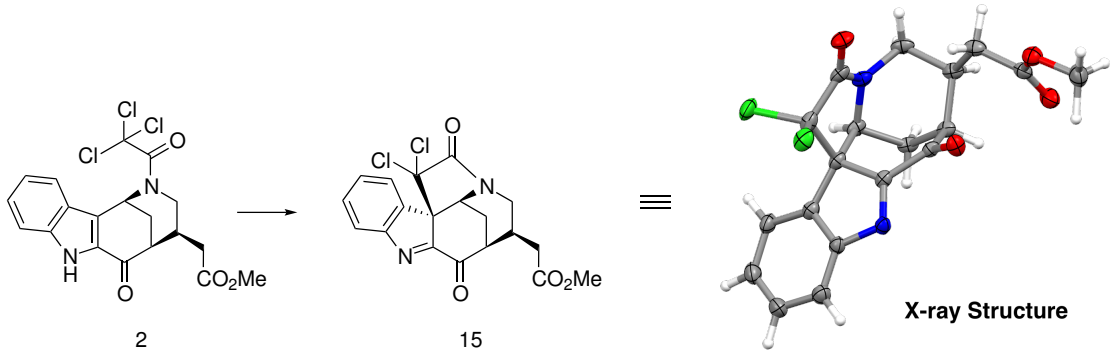
**$^{13}$C-NMR** (126 MHz, CD2Cl2) 198.5 (C-1), 176.5 (C-2), 172.3 (C-10), 165.9 (C-12), 156.2 (C-19), 131.5 (C-17), 130.8 (C-14), 128.1 (C-16), 126.7 (C-15), 123.8 (C-18), 83.9 (C-13), 76.1 (C-3), 56.6 (C-4), 51.8 (C-11), 45.2 (C-6), 41.0 (C-8), 40.3 (C-7), 37.2 (C-9), 24.1 (C-5).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{19}H_{16}Cl_2N_2NaO_4)^+$ requires *m/z* 429.0379, found *m/z* 429.03782.

[3] >99.995% putity based on trace metals basis from Sigma Aldridge.

## 2.14 Screening of conditions in the ATRC

**Table 2:** Atom transfer radical cyclisation of indole **2**.

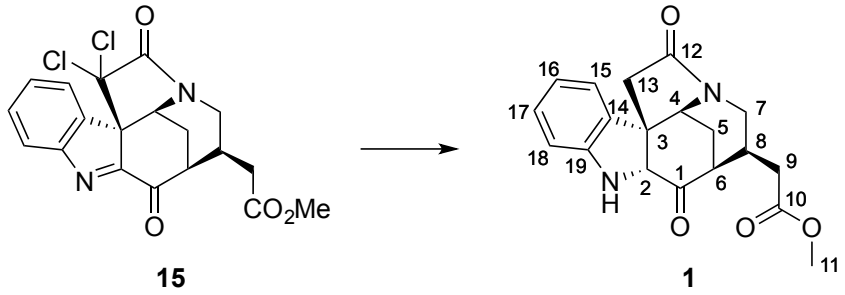



| Entry[a] | TBTA eq. | CuCl eq. | Base | Base eq. | Temp °C | Time | Yield %[b] |
|---|---|---|---|---|---|---|---|
| 1 | 0.1 | 0.1 | – | – | 55 °C | 6 h | trace |
| 2 | 1 | 1 | – | – | 55 °C | 5 h | 39 |
| 3 | 2.2 | 2.2 | – | – | 55 °C | 30 min | 67 |
| 4 | 3 | 3 | – | – | 55 °C | 30 min | 65 |
| 5 | 1 | 1 | $Et_3N$[c] | 2 | 55 °C | 30 min | NR |
| 6 | 1 | 1 | $Et_3N$[d] | 2 | 55 °C | 30 min | NR |
| 7 | 1 | 1 | $K_2CO_3$ | 1.1 | 55 °C | 3 h | 31 |
| 8 | 1 | 1 | $Cs_2CO_3$ | 1.1 | 55 °C | 3 h | 26 |
| 9 | 1 | 1 | TBTA | 1.1 | 55 °C | 5h | 43 |

[a]Reaction conditions: **2** (1 eq.), CuCl, ligand, solvent, additional base, temp, time.
[b]Isolated yield after flash column chromatography.
[c]$Et_3N$, CuCl and TBTA added from the beginning of the reaction
[d]$Et_3N$ after the formation of the CuCl · TBTA complex.

## 2.15 Synthesis and characterisation of 1

**Methyl 2-((3a*S*,5*S*,6a*R*,11b*S*,12*S*)-2,6-dioxo-1,2,3a,4,5,6,6a,7-octahydro-5,3-ethanopyrrolo[2,3-*d*]carbazol-12-yl)acetate**




To a solution of (–)-**15** (1 eq., 0.49 mmol, 200 mg) in MeOH (8 ml) in a presurisable vessel was added activated zinc powder[4] (30 eq., 14.8 mmol, 964 mg) and AcOH (30 eq., 14.8 mmol, 844 mL). The reaction vessel was sealed and heated to 85 °C for 18 h. The reaction was vented every 4–6 h to realease $H_2$ gas generated in the reaction. After the reaction was complete, the reaction mixture was diluted with EtOAc (30 mL) and filtered through a sintered funnel, concentrated *in vacuo* and purified by flash column chromatography (elutes with EtOAc) to give (–)-**1** as a white solid (78%, 130 mg).

**$[\alpha]_D$** = –42.4 (c 2.9, $CDCl_3$)

**mp** 234–236 °C.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 3344, 2951, 1728 (shoulder), 1707, 1687.

**$^1$H-NMR** (500 MHz, $CDCl_3$) 7.21–7.14 (m, 2H, H-15 & H-17), 6.88 (td, J = 7.5, 1.0 Hz, 1H, H-16), 6.72 (dd, J = 8.0, 1.0 Hz, 1H, H-18), 4.21 (d, J = 5.0 Hz, 1H, N–H), 3.91 (d, J = 6.0 Hz, 1H, H-4), 3.88 (d, J = 4.8 Hz, 1H, H-2), 3.76–3.69 (m, 1H, H-7a), 3.71 (s, 3H, H-11), 3.14 (d, J = 16.0 Hz, 1H, H-13a), 3.13–3.06 (m, 1H, H-7b), 2.89–2.73 (m, 3H, H-6 & H-8 & H-9a), 2.50–2.44 (m, 2H, H-5a & H-9b), 2.42 (d, J = 16.0 Hz, 1H, H-13b), 1.94 (dd, J = 14.5, 6.0, Hz, 1H, H-5b).

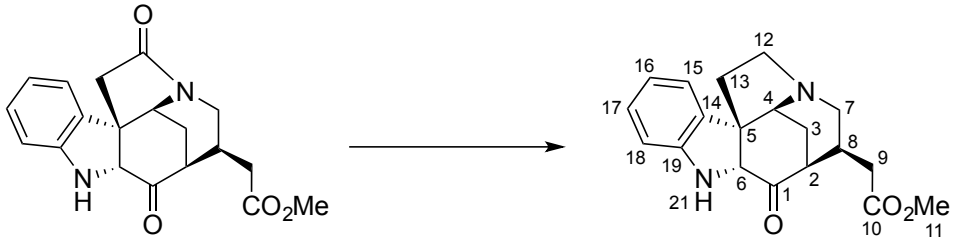
**$^{13}$C-NMR** (500 MHz, $CDCl_3$) 208.3 (C-1), 172.9 (C-10 or C-12), 172.8 (C-10 or C-12), 150.7 (C-19), 129.6 (C-15 or C-17), 126.7 (C-14), 123.3 (C-15 or C-17), 120.2 (C-16), 111.0 (C-18), 73.4 (C-2), 60.2 (C-4), 56.9 (C-3), 51.7 (C-11), 43.9 (C-13), 41.2 (C-8), 38.8 (C-6), 38.5 (C-7), 37.8 (C-9), 22.8 (C-5).

**HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{19}H_{20}N_2NaO_4)^+$ requires *m/z* 363.1315, found *m/z* 363.1314.

[4] Zn powder washed with 2 M HCl, water, acetone and ether and subsequently dried under vacuum.

## 2.16 Synthesis and characterisation of 18

**Methyl [(3a*S*,5*S*,6a*R*,11b*S*,12*S*)-6-oxo-1,2,3a,4,5,6,6a,7-octahydro-3,5-ethanopyrrolo[2,3-*d*]carbazol-12-yl]acetate**




To a solution of (–)-**1** (1 eq., 0.35 mmol, 120 mg) in $CH_2Cl_2$ (3.5 mL) at rt was added Vaska's catalyst (5 mol%, 17.6 μmol, 13.75 mg) and TMDS (2 eq., 0.71 mmol, 95 mg, 124mL) and allowed to stir for 1 h. MeOH (3.5 mL) was added to the reaction mixture and when effervescence stopped, $NaBH_3CN$ (0.5 eq., 0.175 mmol, 11 mg) was added followed by glacial AcOH (1 eq., 0.35 mmol, 22.75 mg, 21mL) and allowed to stir for 12 hours. 1 M NaOH was added to the reaction until pH 10 was obtained and was subsequently extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$, concentrated *in vacuo*, and purified by flash column chromatography (elutes with $CHCl_3$/MeOH 95:5) affording (–)-**18** as a yellow solid (78%, 75 mg).

**$[\alpha]_D$** = -75.1 (c 3.1, $CDCl_3$).

**mp** 181–183 °C.

**IR** (film)/$cm^{-1}$ $\nu_{max}$ 3360, 2952, 2362, 2342, 1734, 1703, 1605.

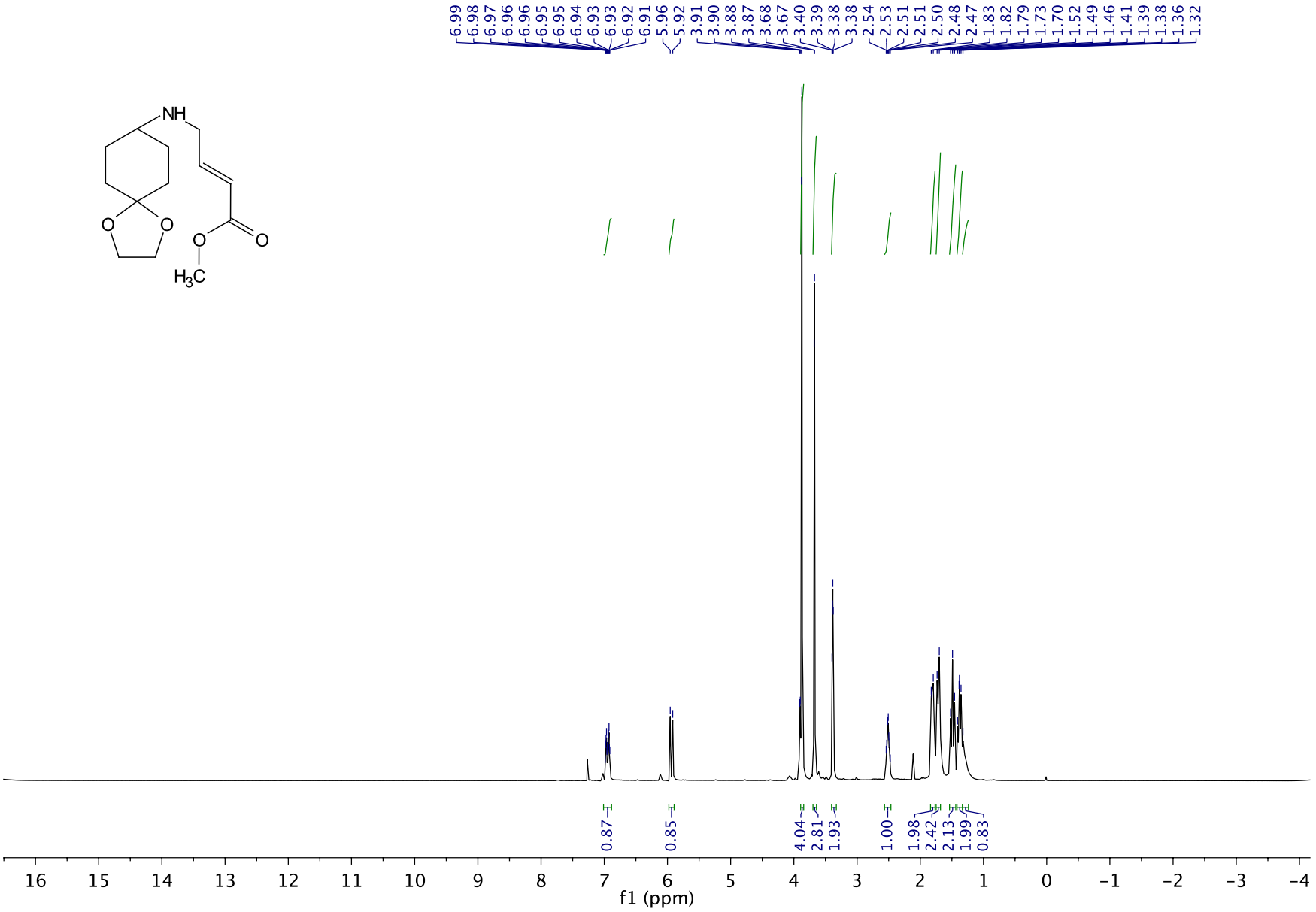
**$^1$H-NMR** (500 MHz, $CDCl_3$) 7.08–7.03 (m, 2H, H-15 & H-17), 6.80 (td, J = 7.5, 1.0 Hz, 1H, H-16), 6.65 (dt, J = 7.5, 1.0 Hz, 1H, H-18), 4.66 (d, J = 2.5 Hz, 1H, N–H), 3.69 (s, 3H, H-11), 3.62 (d, J = 2.5 Hz, 1H, H-6), 3.30 (t, J = 3.0 Hz, 1H, H-4), 3.23 (dt, J = 12.5, 9.5 Hz, 1H, H-12a), 3.07 (ddd, J = 12.0, 5.0, 1.0 Hz, 1H, H-7a), 2.97 (ddd, J = 12.5, 8.5, 2.0 Hz, 1H, H-12b), 2.62–2.59 (m, 1H, H-2), 2.58–2.51 (m, 1H, H-8), 2.50–2.44 (m, 1H, H-13a), 2.44–2.39 (m, 1H, H-9a), 2.29–2.25 (m, 1H, H-13b), 2.24–2.19 (m, 1H, H-3a), 2.13 (dd, J = 16.0, 7.0 Hz, 1H, H-9a), 2.06 (t, J = 12.5 Hz, 1H, H-7b), 1.99 (dt, J = 14.0, 3.0 Hz, 1H, H-3b).

**$^{13}$C-NMR** (126 MHz, $CDCl_3$) 212.31 (C-1), 172.11 (C-10), 149.37 (C-19), 133.54 (C-14), 128.27 (C-17), 122.34 (C-15), 120.02 (C-16), 109.81 (C-18), 76.49 (C-6), 64.83 (C-4), 55.51 (C-5), 54.72 (C-12), 53.11 (C-7), 51.96 (C-11), 44.93 (C-2), 43.65 (C-13), 36.68 (C-9), 36.11 (C-8), 26.43 (C-3).

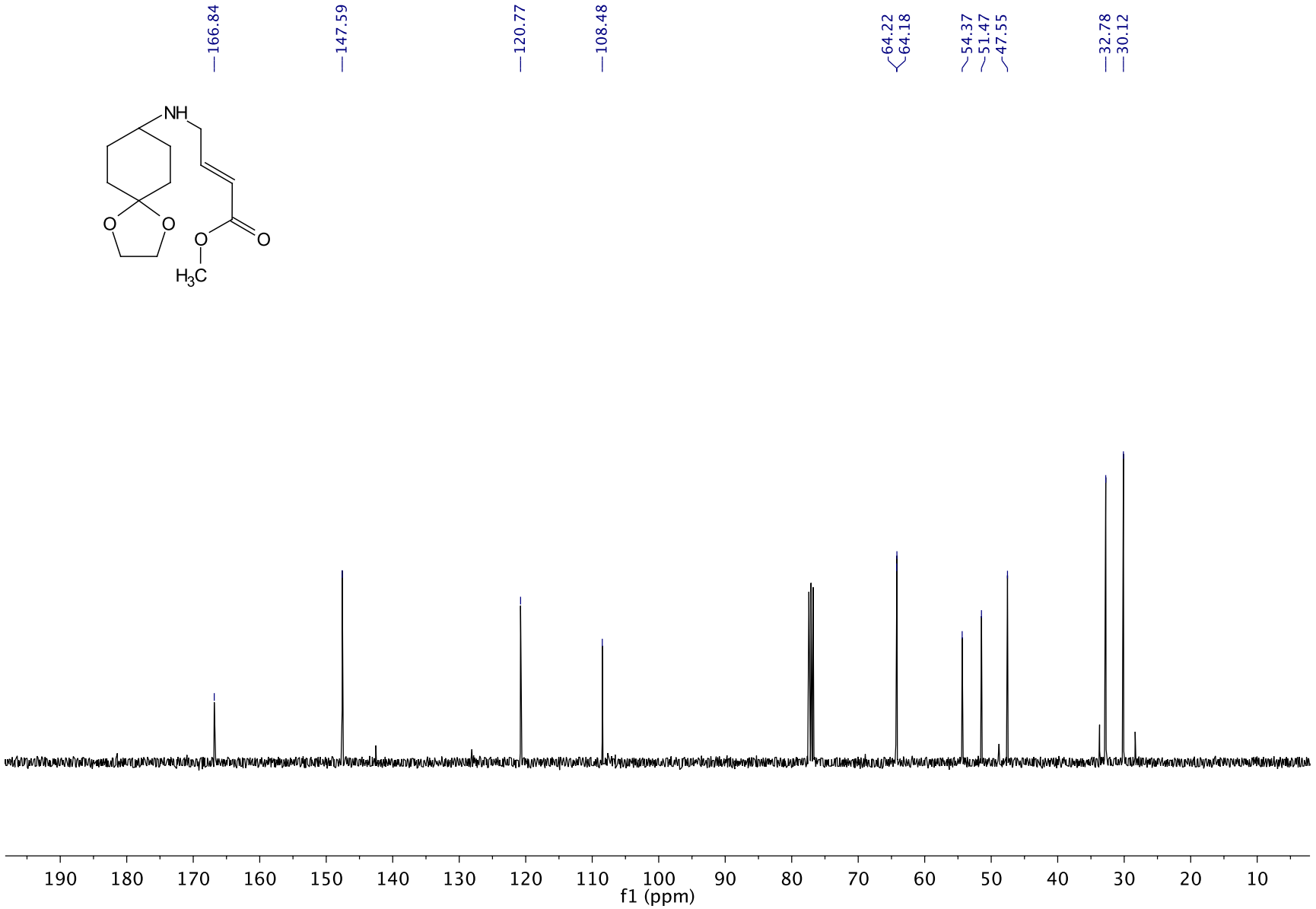
**HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{19}H_{23}N_2O_3)^+$ requires *m/z* 327.1703, found *m/z* 327.1704.

# 3. NMR Spectra and HPLC traces

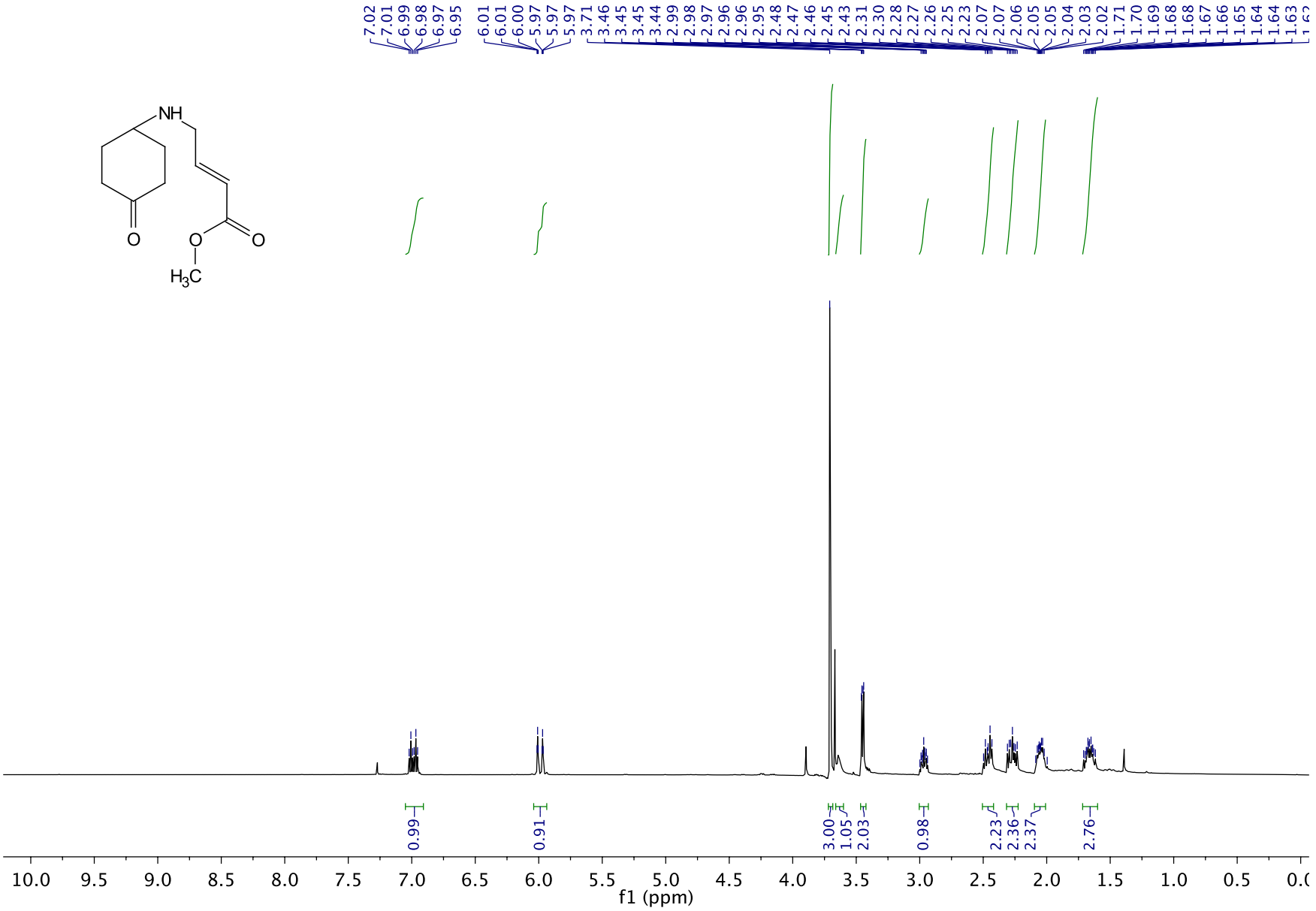
**$^{1}$H NMR of 19**


6.99
6.98
6.97
6.96
6.96
6.95
6.95
6.94
6.93
6.93
6.92
6.91
5.96
5.92
3.91
3.90
3.88
3.87
3.68
3.67
3.40
3.39
3.38
3.38
2.54
2.53
2.51
2.51
2.50
2.48
2.47
1.83
1.82
1.79
1.73
1.70
1.52
1.49
1.46
1.41
1.39
1.38
1.36
1.32
NH
O
O
O
O
H3C
0.87
0.85
4.04
2.81
1.93
1.00
1.98
2.42
2.13
1.99
0.83
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
−4
f1 (ppm)

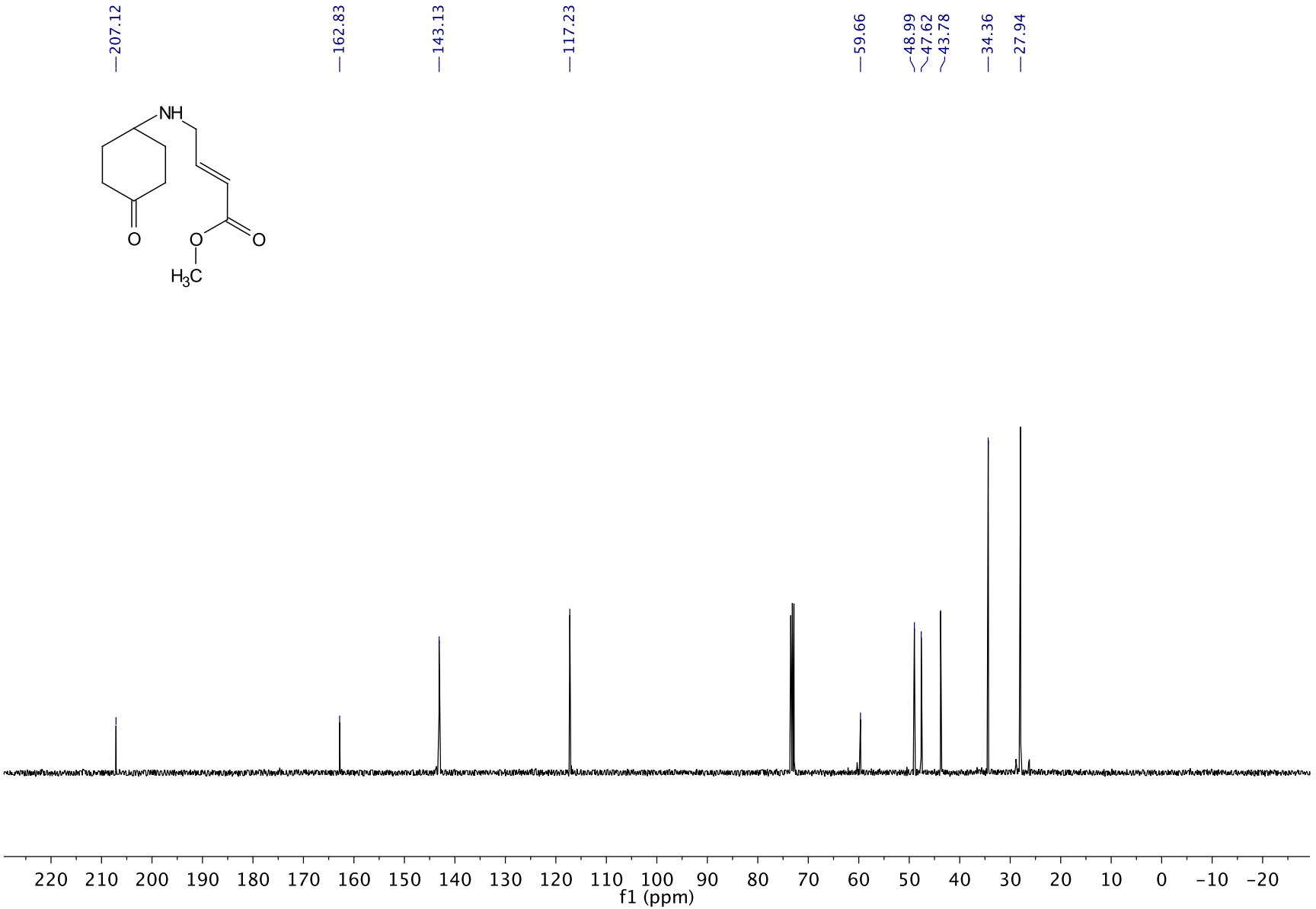
**$^{13}$C NMR of 19**


166.84
147.59
120.77
108.48
64.22
64.18
54.37
51.47
47.55
32.78
30.12
NH
O
O
O
O
H3C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

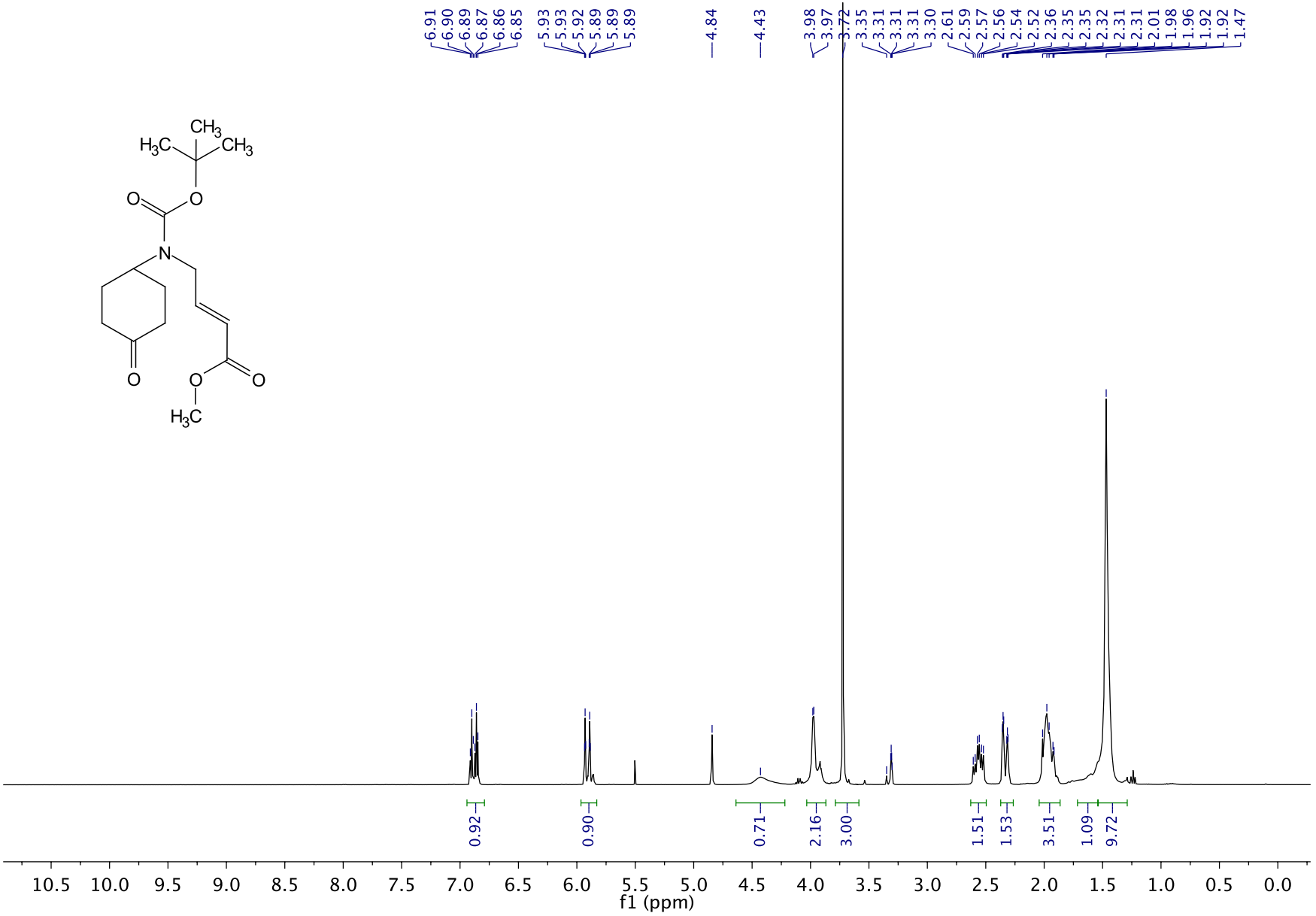
**$^{1}$H NMR of 6**


NH
O
O
O
H3C
7.02 7.01 6.99 6.98 6.97 6.95
6.01 6.01 6.00 5.97 5.97 5.97
3.71 3.46 3.45 3.45 3.44 2.99 2.98 2.97 2.96 2.96 2.95 2.48 2.47 2.46 2.45 2.43 2.31 2.30 2.28 2.27 2.26 2.25 2.23 2.07 2.07 2.06 2.05 2.05 2.04 2.03 2.02 1.71 1.70 1.69 1.68 1.68 1.67 1.66 1.65 1.64 1.64 1.63
0.99
0.91
3.00
1.05
2.03
0.98
2.23
2.36
2.37
2.76
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

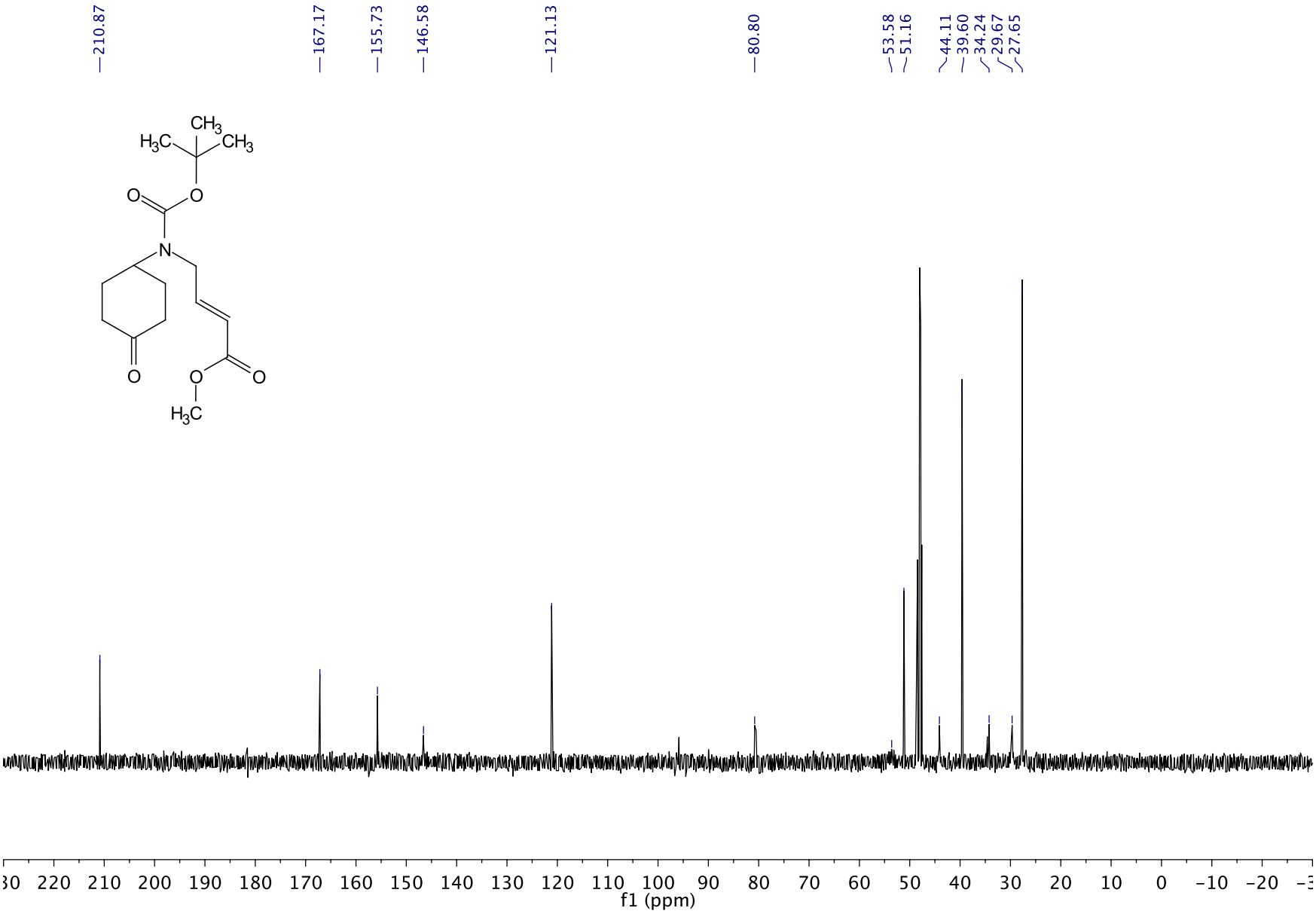
**$^{13}$C NMR of 6**


207.12
162.83
143.13
117.23
59.66
48.99
47.62
43.78
34.36
27.94
NH
O
O
O
H3C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

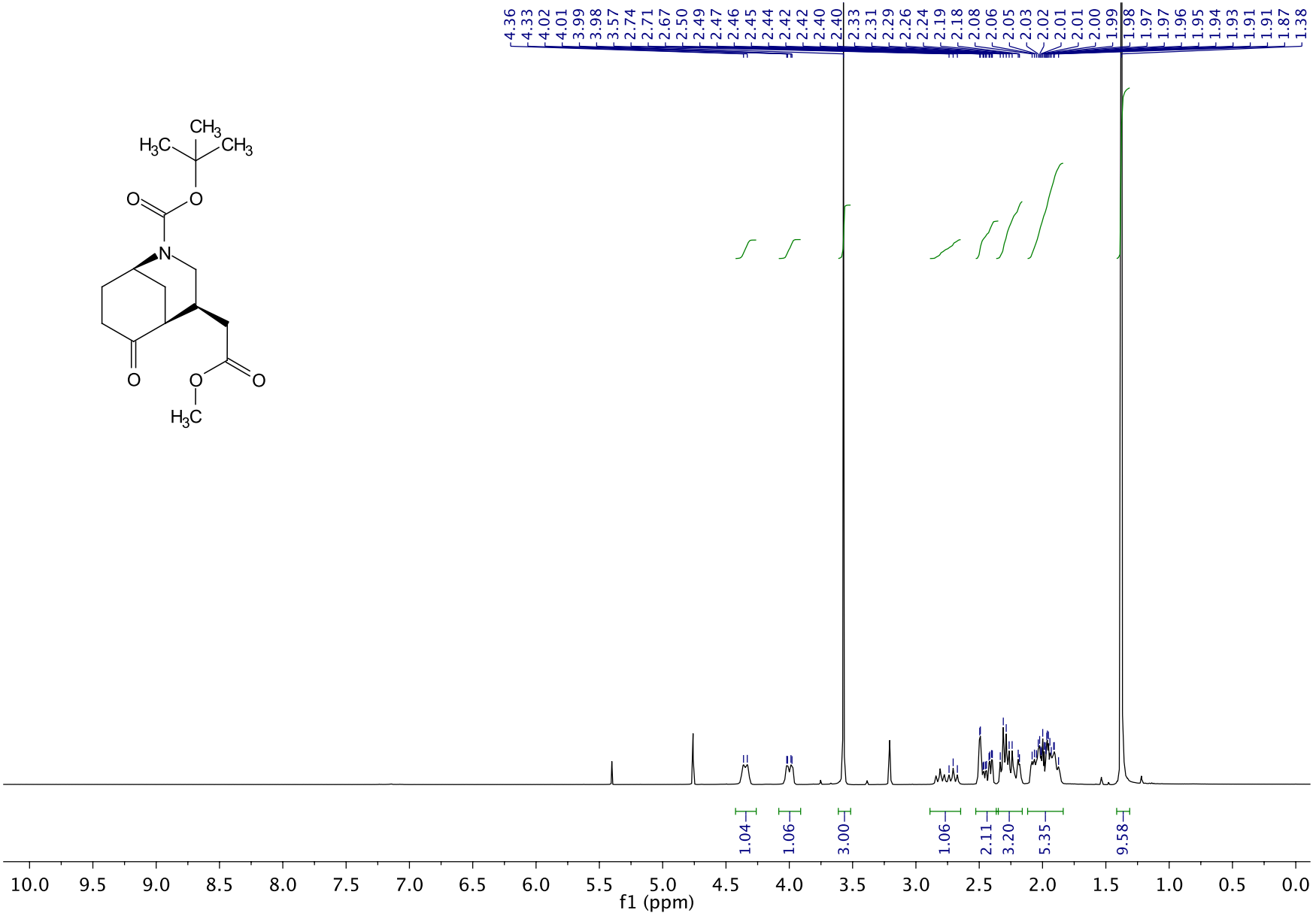
**$^{1}$H NMR of 7**


6.91
6.90
6.89
6.87
6.86
6.85
5.93
5.93
5.92
5.89
5.89
5.89
4.84
4.43
3.98
3.97
3.72
3.35
3.31
3.31
3.31
3.30
2.61
2.59
2.57
2.56
2.54
2.52
2.36
2.35
2.35
2.32
2.31
2.31
2.01
1.98
1.96
1.92
1.92
1.47
0.92
0.90
0.71
2.16
3.00
1.51
1.53
3.51
1.09
9.72
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

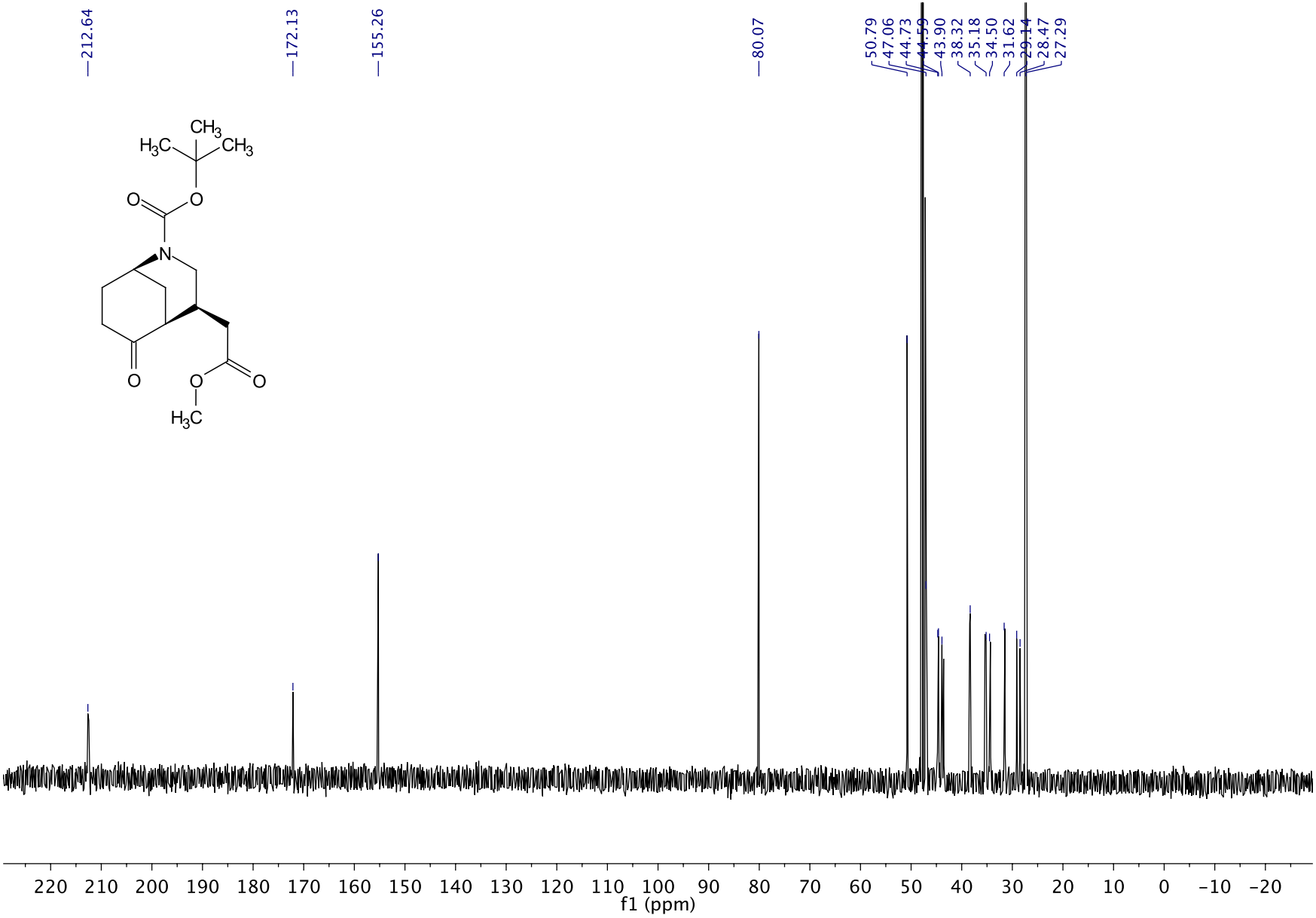
**$^{13}$C NMR of 7**


210.87
167.17
155.73
146.58
121.13
80.80
53.58
51.16
44.11
39.60
34.24
29.67
27.65
CH3
H3C
CH3
O
O
N
O
O
O
O
H3C
f1 (ppm)

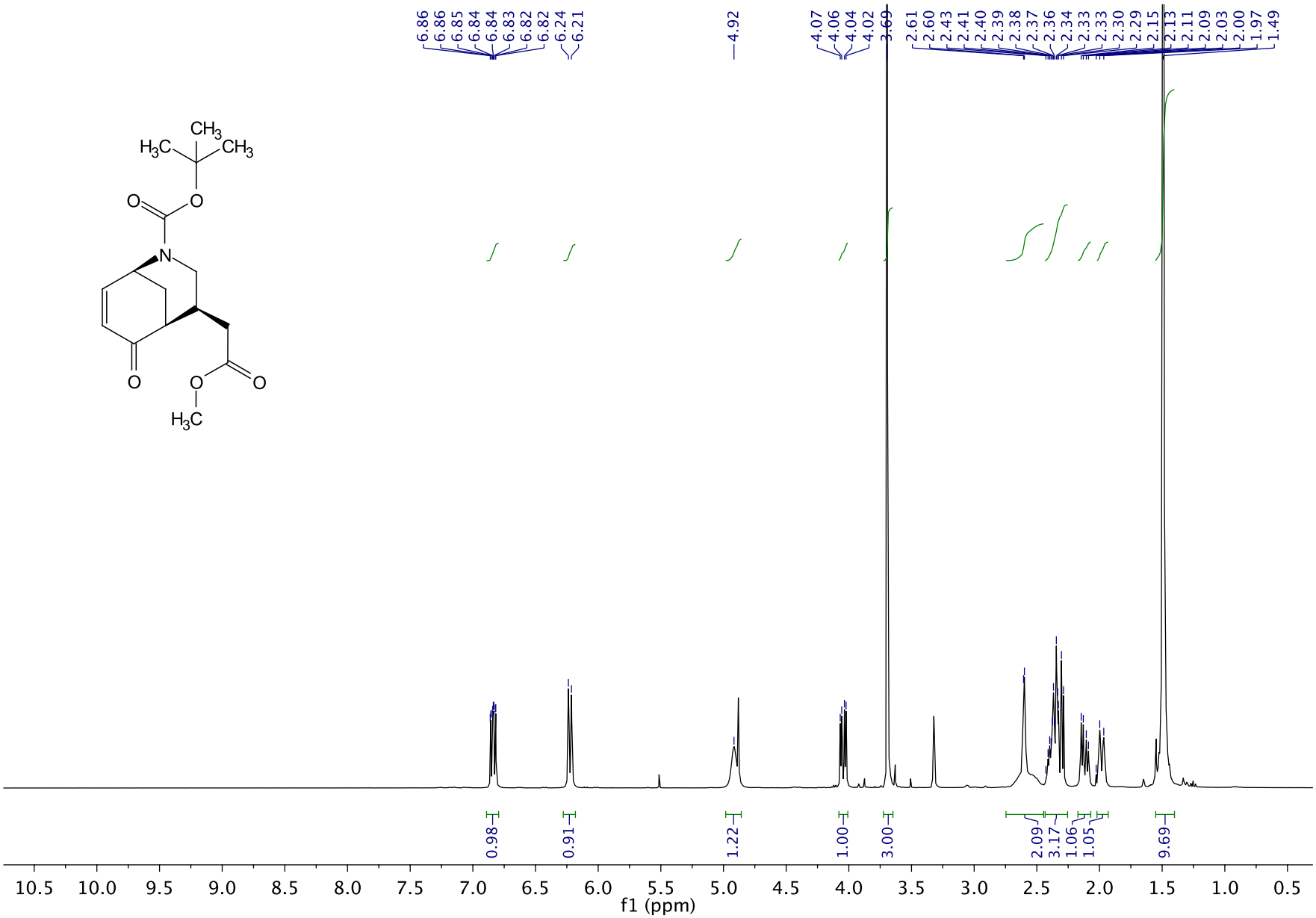
**$^{1}$H NMR of 9**


4.36
4.33
4.02
4.01
3.99
3.98
3.57
2.74
2.71
2.67
2.50
2.49
2.47
2.46
2.45
2.44
2.42
2.42
2.40
2.40
2.33
2.31
2.29
2.26
2.24
2.19
2.18
2.08
2.06
2.05
2.03
2.02
2.01
2.01
2.00
1.99
1.98
1.97
1.97
1.96
1.95
1.94
1.93
1.91
1.91
1.87
1.38
1.04
1.06
3.00
1.06
2.11
3.20
5.35
9.58
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

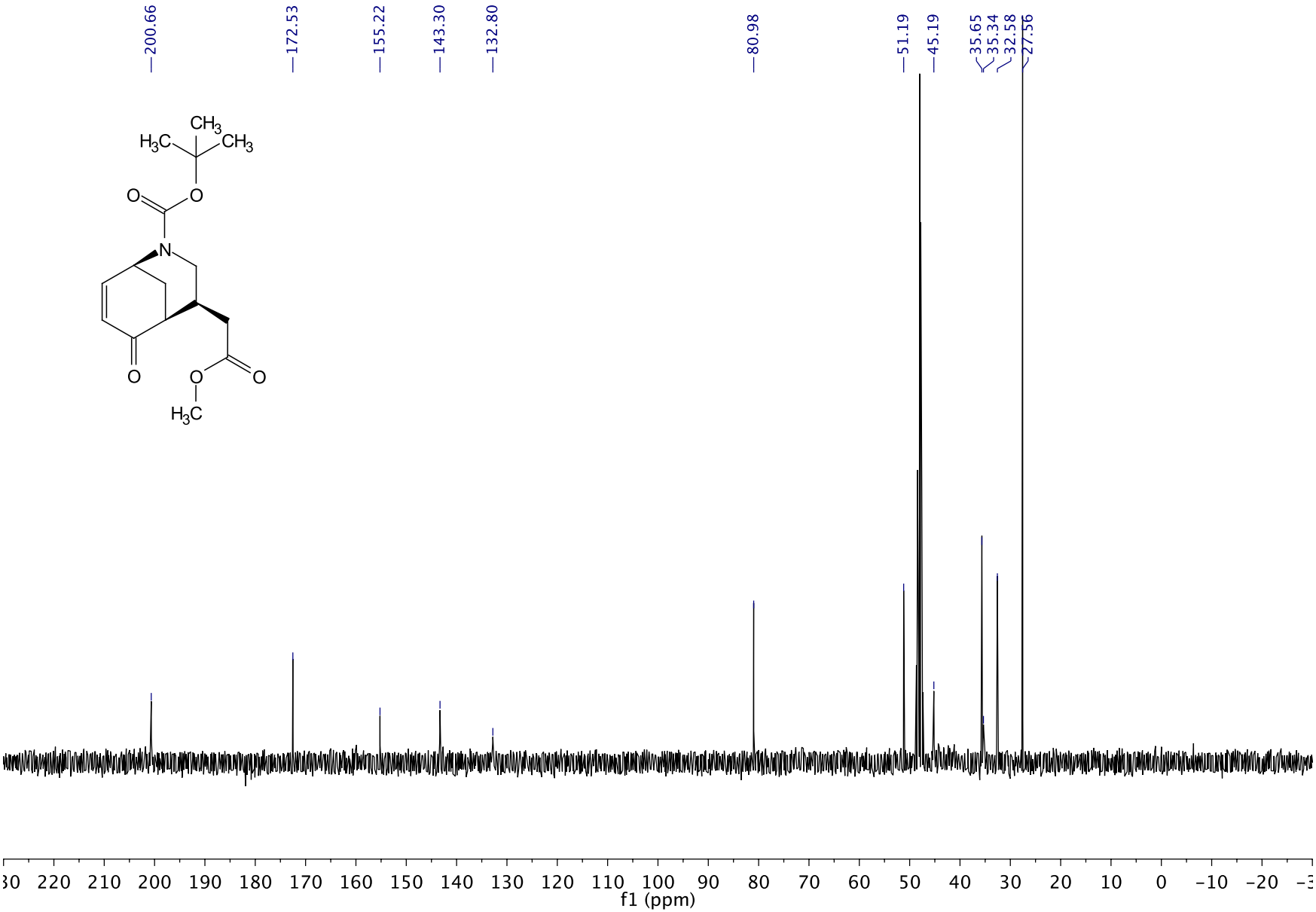
**$^{13}$C NMR of 9**


212.64
172.13
155.26
80.07
50.79
47.06
44.73
44.59
43.90
38.32
35.18
34.50
31.62
29.14
28.47
27.29
CH3
H3C
CH3
O
O
N
O
O
O
O
H3C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

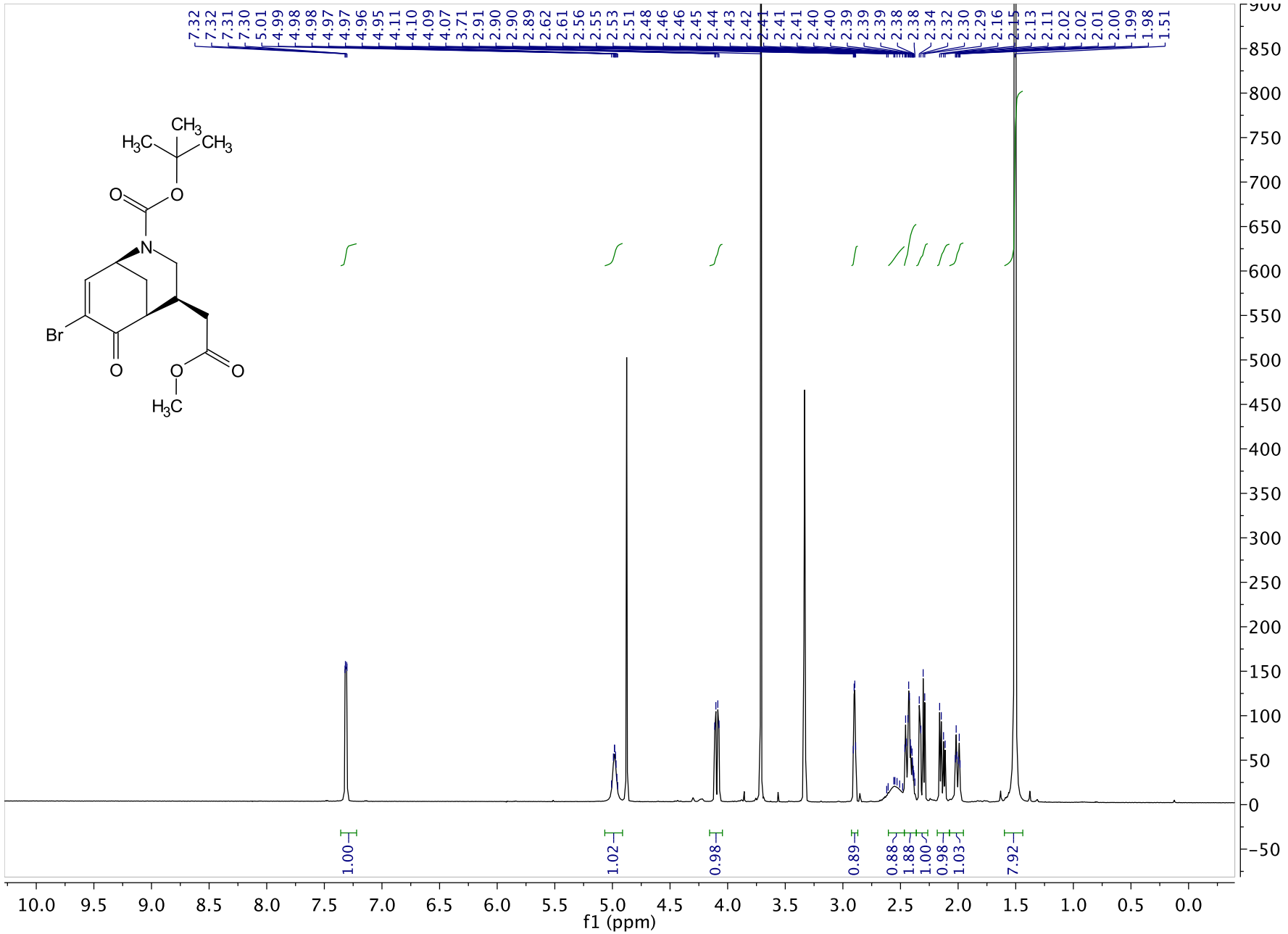
**$^{1}$H NMR of 10**


6.86
6.86
6.85
6.84
6.84
6.83
6.82
6.82
6.24
6.21
4.92
4.07
4.06
4.04
4.02
3.69
2.61
2.60
2.43
2.41
2.40
2.39
2.38
2.37
2.36
2.34
2.33
2.33
2.30
2.29
2.15
2.13
2.11
2.09
2.03
2.00
1.97
1.49
0.98
0.91
1.22
1.00
3.00
2.09
3.17
1.06
1.05
9.69
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

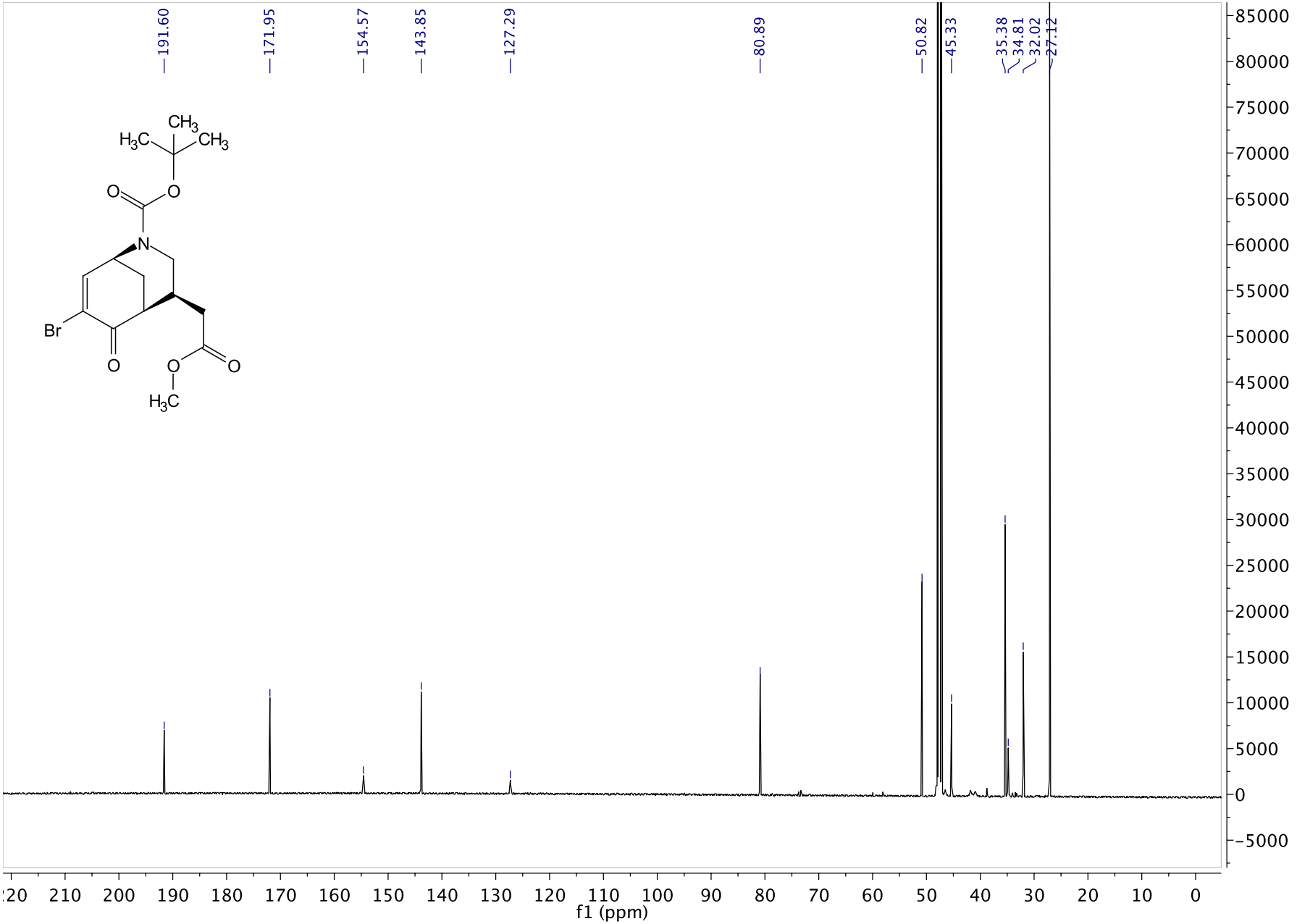
**$^{13}$C NMR of 10**


200.66
172.53
155.22
143.30
132.80
80.98
51.19
45.19
35.65
35.34
32.58
27.56
CH3
H3C
CH3
O
O
N
O
O
O
H3C
f1 (ppm)

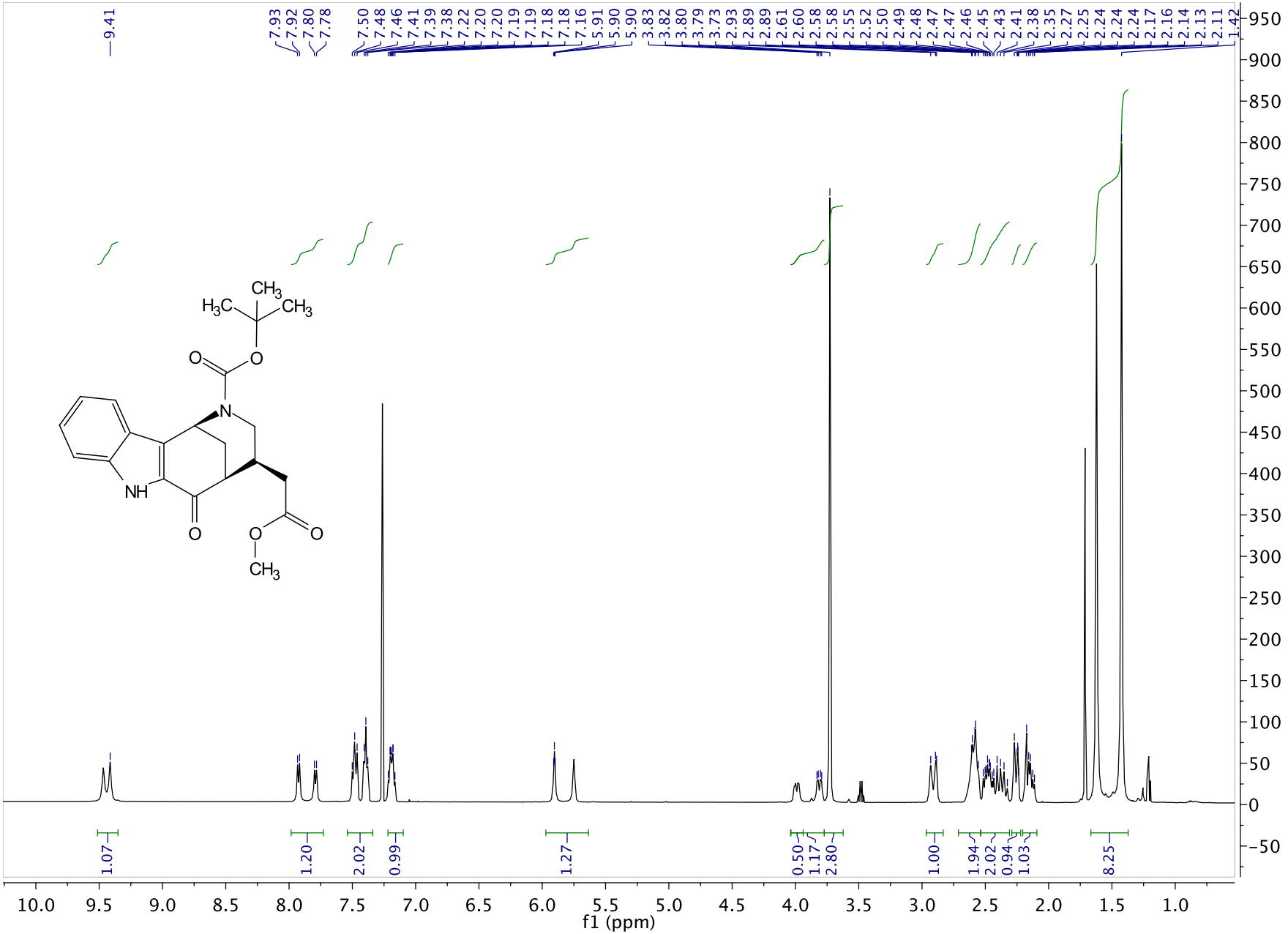
**$^1$H NMR of 13**


7.32 7.32 7.31 7.30 5.01 4.99 4.98 4.98 4.97 4.97 4.96 4.95 4.11 4.10 4.09 4.07 3.71 2.91 2.90 2.90 2.89 2.62 2.61 2.56 2.55 2.53 2.51 2.48 2.46 2.46 2.45 2.44 2.43 2.42 2.41 2.41 2.41 2.40 2.40 2.39 2.39 2.39 2.38 2.38 2.34 2.32 2.30 2.29 2.16 2.15 2.13 2.11 2.02 2.02 2.01 2.00 1.99 1.98 1.51
CH3
H3C
CH3
O
O
N
Br
O
O
O
O
H3C
1.00
1.02
0.98
0.89
0.88
1.88
1.00
0.98
1.03
7.92
f1 (ppm)

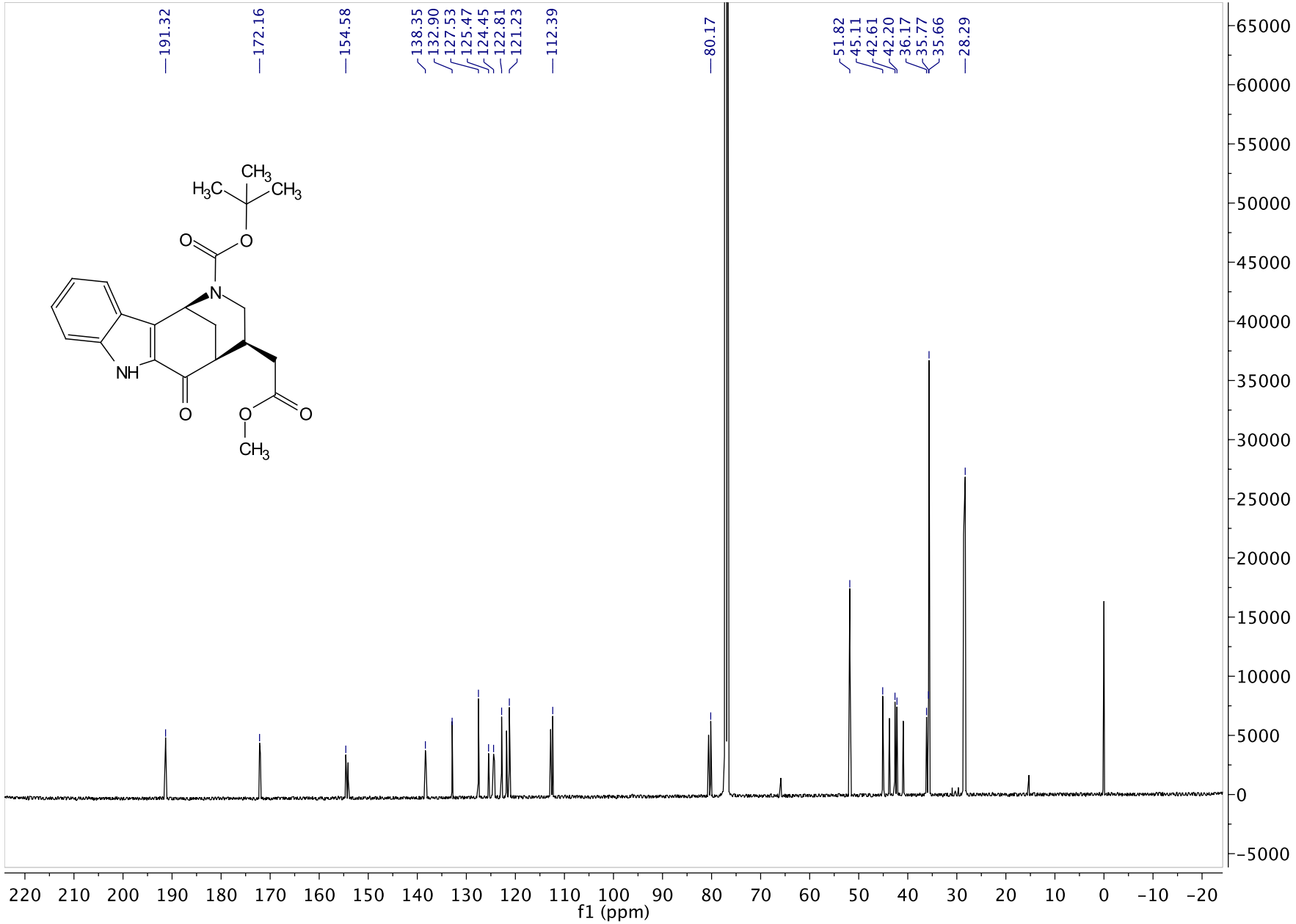
**$^{13}$C NMR of 13**


191.60
171.95
154.57
143.85
127.29
80.89
50.82
45.33
35.38
34.81
32.02
27.12
CH3
H3C
CH3
O
O
N
Br
O
O
O
O
H3C
85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

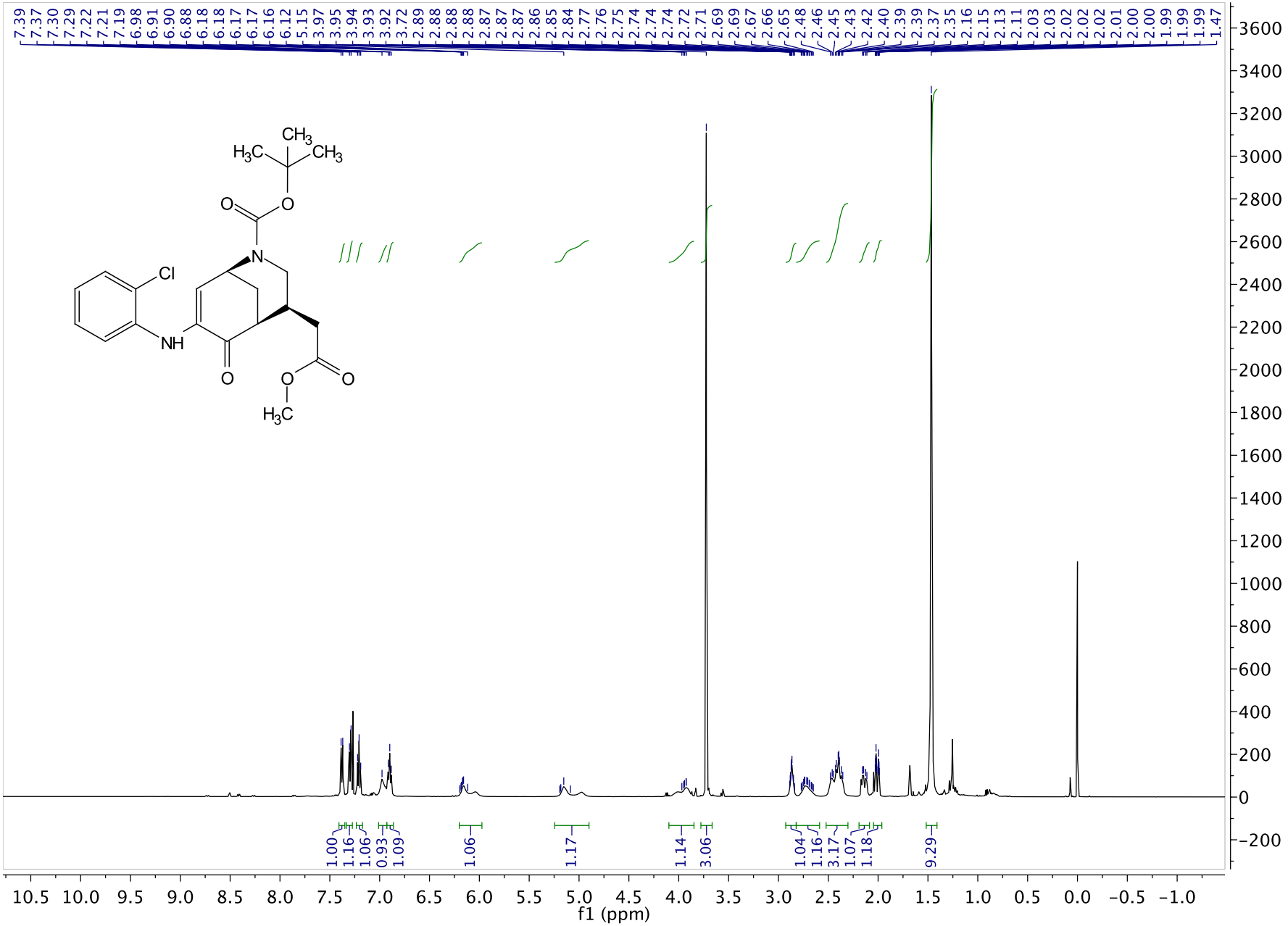
**$^{1}$H NMR of 12**


9.41
7.93
7.92
7.80
7.78
7.50
7.48
7.46
7.41
7.39
7.38
7.22
7.20
7.20
7.19
7.19
7.18
7.18
7.16
5.91
5.90
5.90
3.83
3.82
3.80
3.79
3.73
2.93
2.89
2.89
2.61
2.60
2.58
2.58
2.55
2.52
2.50
2.49
2.48
2.47
2.47
2.46
2.45
2.43
2.41
2.38
2.35
2.27
2.25
2.24
2.24
2.24
2.17
2.16
2.14
2.13
2.11
1.42
1.07
1.20
2.02
0.99
1.27
0.50
1.17
2.80
1.00
1.94
2.02
0.94
1.03
8.25
f1 (ppm)

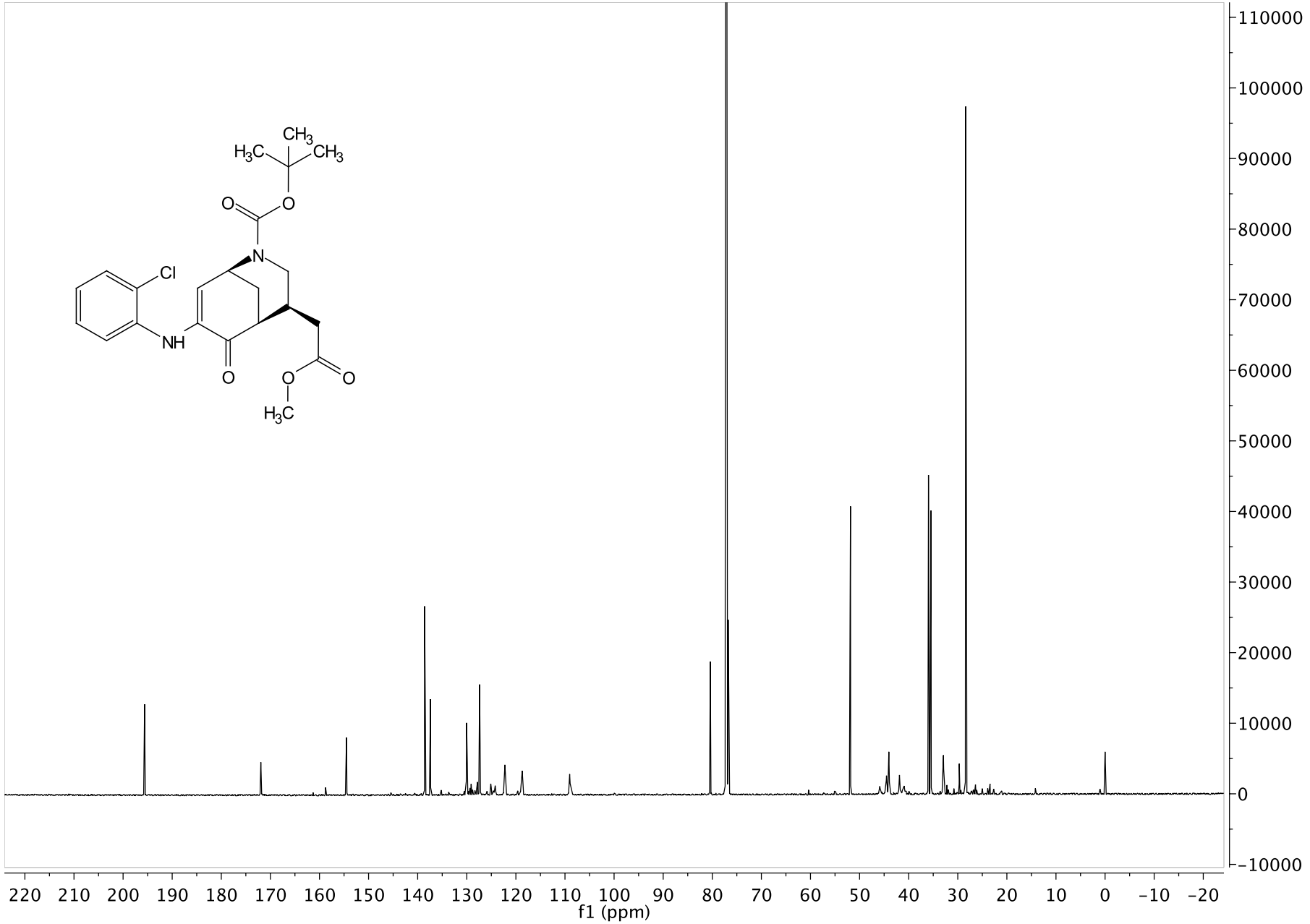
**$^{13}$C NMR of 12**


191.32
172.16
154.58
138.35
132.90
127.53
125.47
124.45
122.81
121.23
112.39
80.17
51.82
45.11
42.61
42.20
36.17
35.77
35.66
28.29
CH3
H3C
CH3
O
O
N
NH
O
O
O
CH3
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

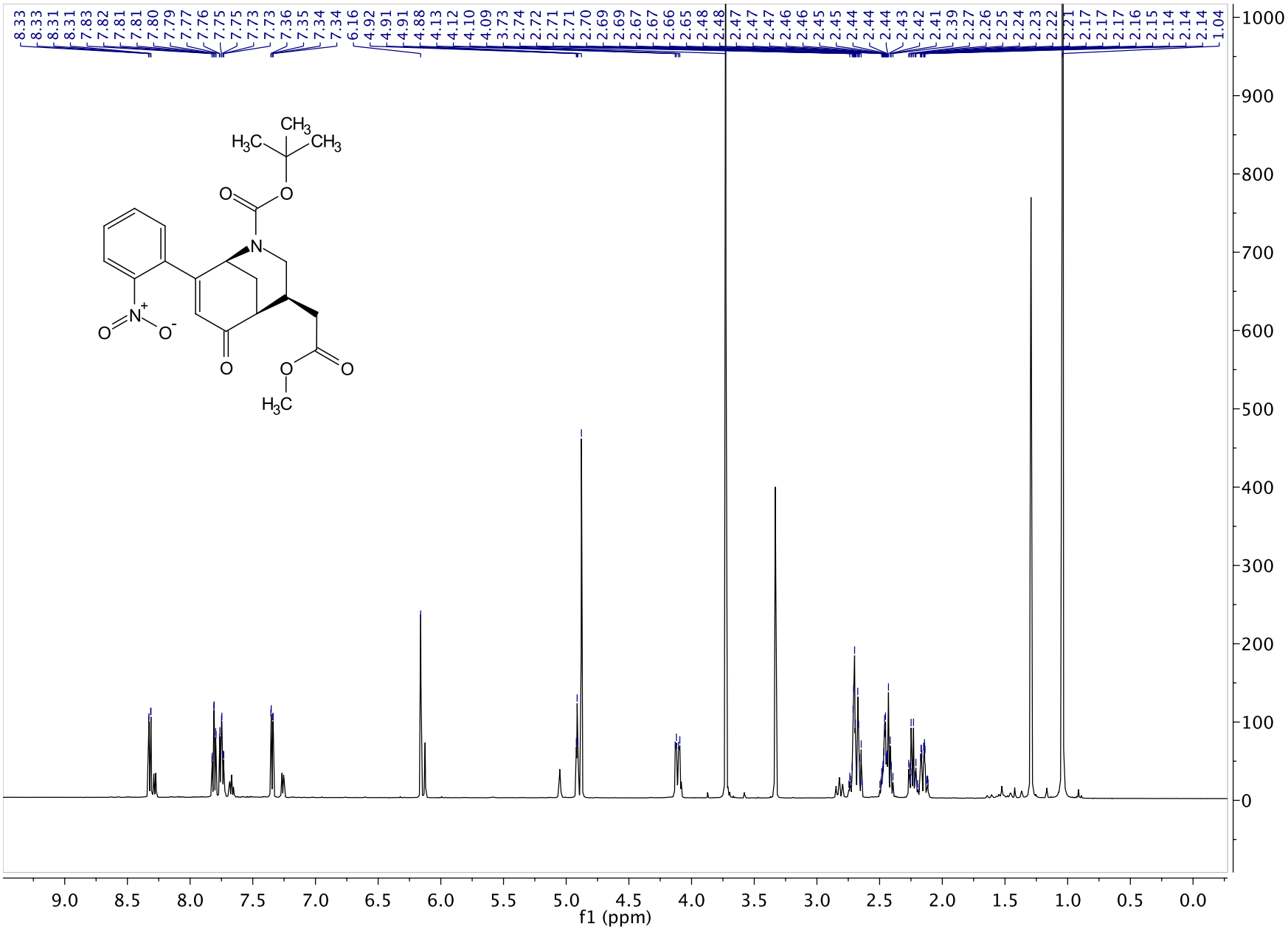
**$^1$H NMR of 14**


7.39 7.37 7.30 7.29 7.22 7.21 7.19 6.98 6.91 6.90 6.88 6.18 6.18 6.17 6.17 6.16 6.12 5.15 3.97 3.95 3.94 3.93 3.92 3.72 2.89 2.88 2.88 2.88 2.87 2.87 2.87 2.86 2.85 2.84 2.77 2.76 2.75 2.74 2.74 2.74 2.72 2.71 2.69 2.69 2.67 2.66 2.65 2.48 2.46 2.45 2.43 2.42 2.40 2.39 2.39 2.37 2.35 2.16 2.15 2.13 2.11 2.03 2.03 2.02 2.02 2.02 2.01 2.00 2.00 1.99 1.99 1.99 1.47
CH3
H3C
CH3
O
O
N
Cl
NH
O
O
O
O
H3C
1.00 1.16 1.06 0.93 1.09 1.06 1.17 1.14 3.06 1.04 1.16 3.17 1.07 1.18 9.29
f1 (ppm)

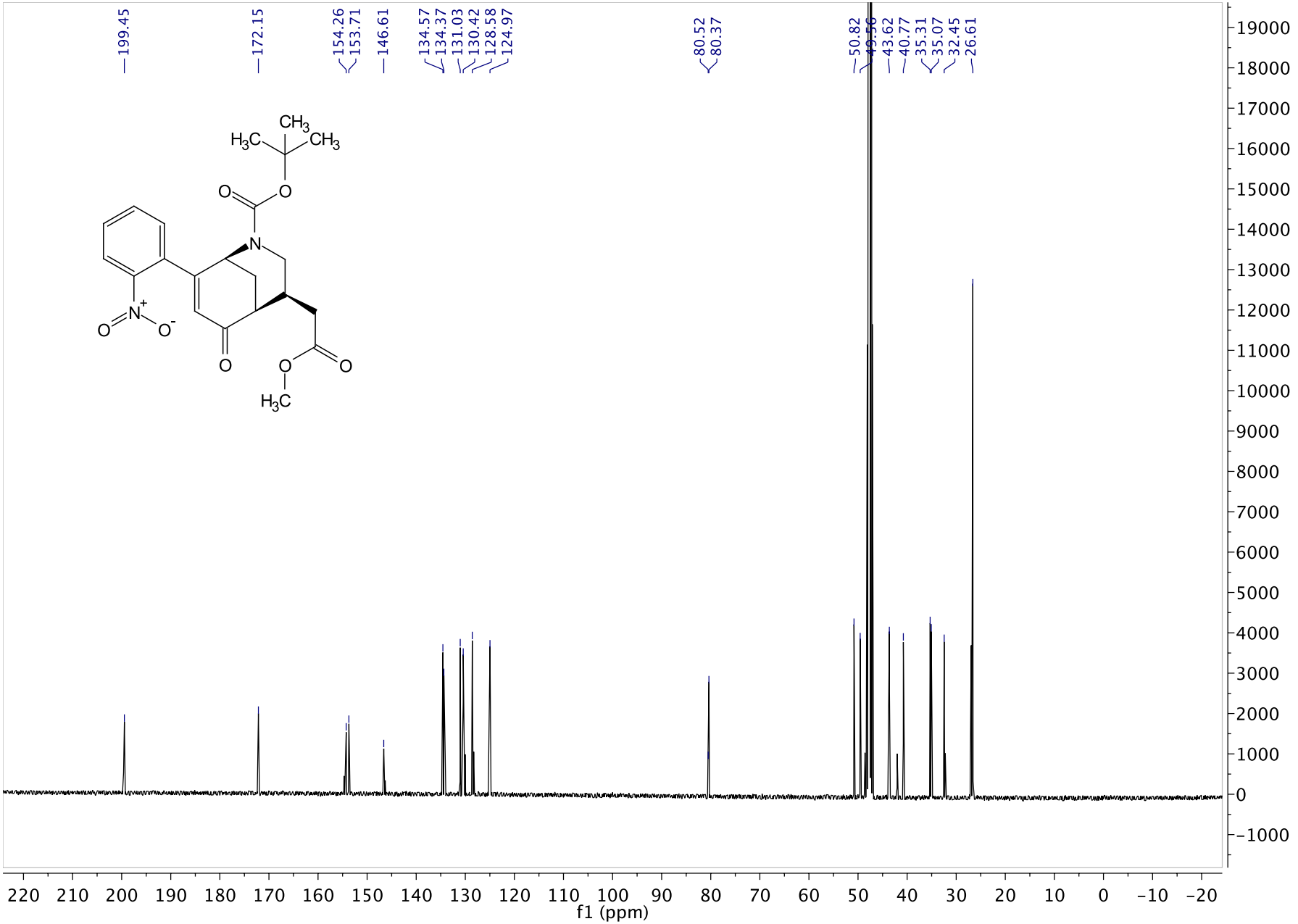
**$^{13}$C NMR of 14**


CH3
H3C
CH3
O
O
N
Cl
NH
O
O
O
H3C
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

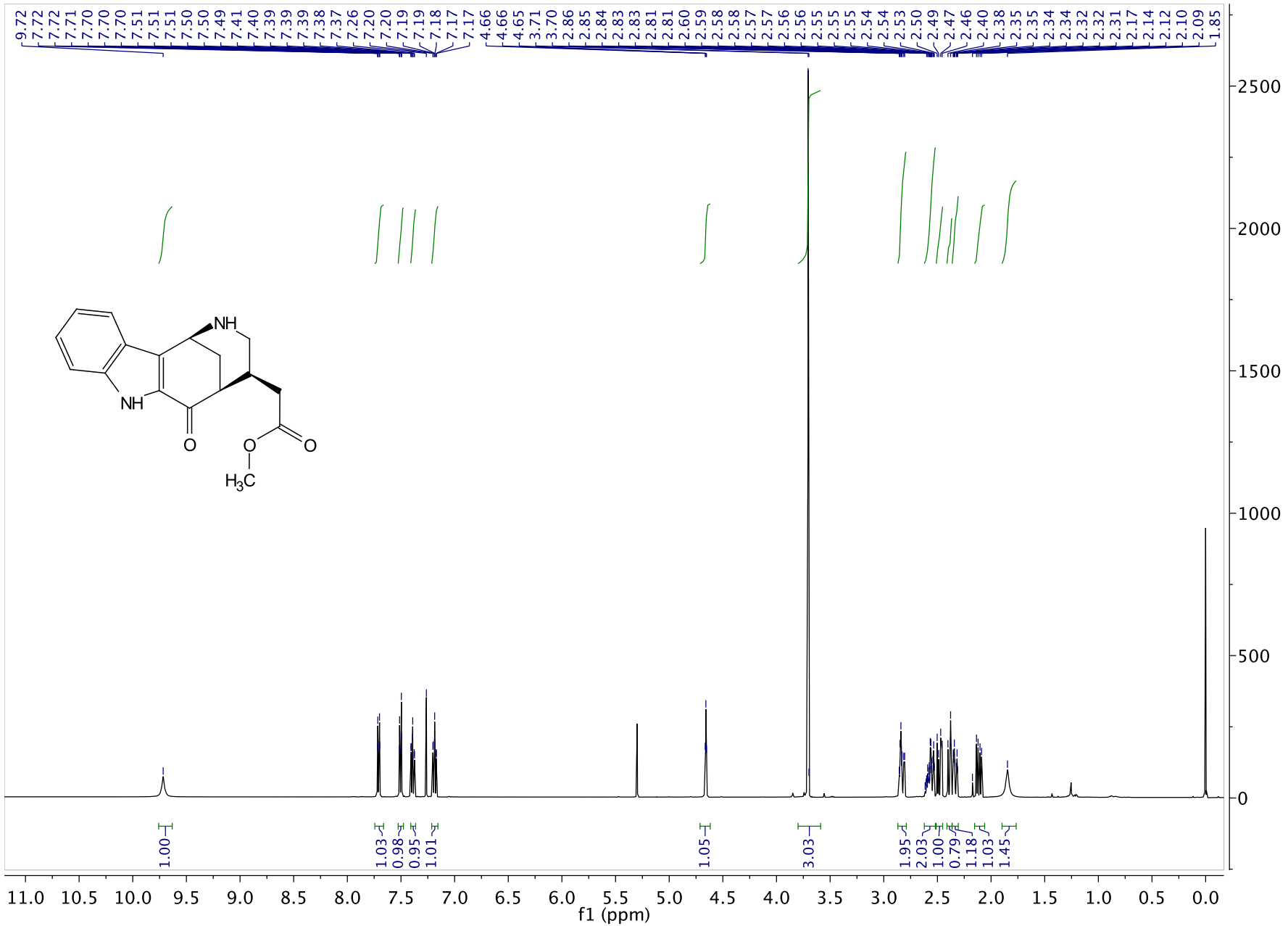
**$^1$H NMR of 11**


8.33 8.33 8.31 8.31 7.83 7.82 7.81 7.81 7.80 7.79 7.77 7.76 7.75 7.75 7.73 7.73 7.36 7.35 7.34 7.34 6.16 4.92 4.91 4.91 4.88 4.13 4.12 4.10 4.09 3.73 2.74 2.72 2.71 2.71 2.70 2.69 2.69 2.67 2.67 2.66 2.65 2.48 2.48 2.47 2.47 2.47 2.46 2.46 2.45 2.45 2.44 2.44 2.44 2.43 2.42 2.41 2.39 2.27 2.26 2.25 2.24 2.23 2.22 2.21 2.17 2.17 2.17 2.16 2.15 2.14 2.14 2.14 1.04
CH3
H3C
CH3
O
O
N
O
N+
O-
O
O
O
H3C
1000
900
800
700
600
500
400
300
200
100
0
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

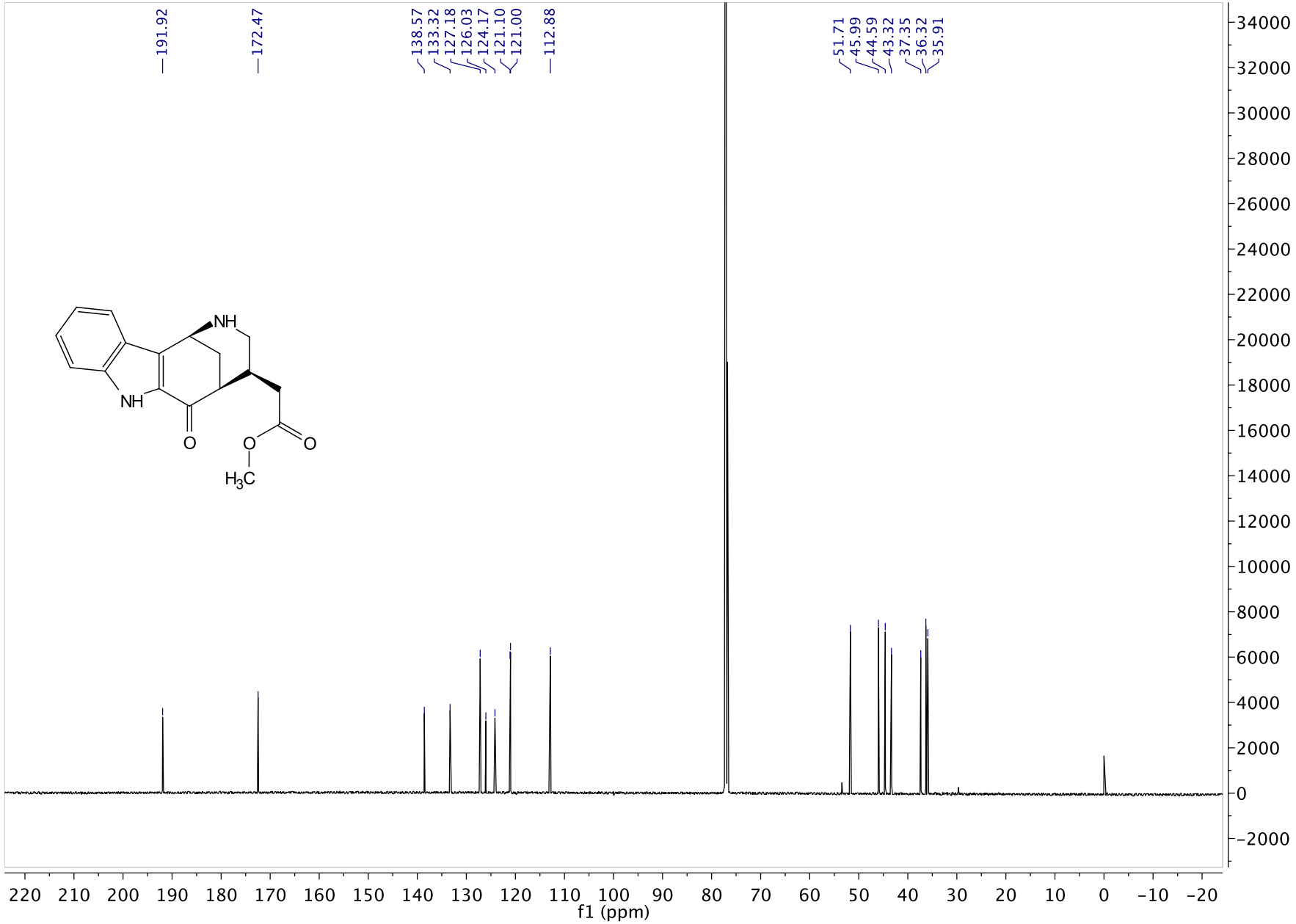
**$^{13}$C NMR of 11**


199.45
172.15
154.26
153.71
146.61
134.57
134.37
131.03
130.42
128.58
124.97
80.52
80.37
50.82
43.62
40.77
35.31
35.07
32.45
26.61
CH3
H3C
CH3
O
O
N
O
N+
O-
O
O
O
H3C
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

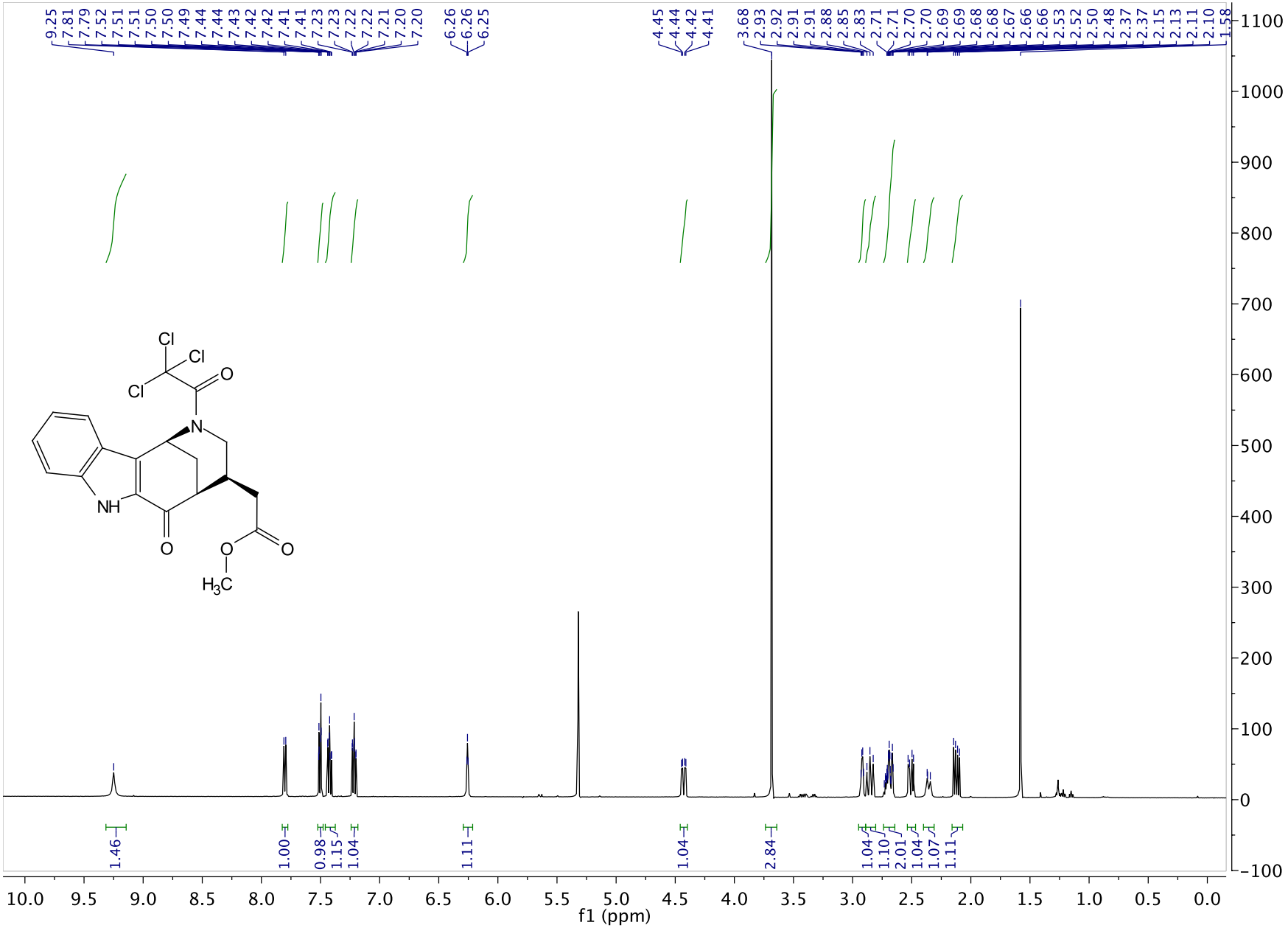
**$^{1}$H NMR of 20**


9.72 7.72 7.72 7.71 7.70 7.70 7.70 7.70 7.51 7.51 7.51 7.50 7.50 7.49 7.41 7.40 7.39 7.39 7.39 7.38 7.37 7.26 7.20 7.20 7.19 7.19 7.18 7.17 7.17
4.66 4.66 4.65 3.71 3.70 2.86 2.85 2.84 2.83 2.83 2.81 2.81 2.60 2.59 2.58 2.58 2.57 2.57 2.56 2.56 2.55 2.55 2.55 2.54 2.54 2.53 2.50 2.49 2.47 2.46 2.40 2.38 2.35 2.35 2.34 2.34 2.32 2.32 2.31 2.17 2.14 2.12 2.10 2.09 1.85
NH
NH
O
O
O
H3C
2500
2000
1500
1000
500
0
1.00
1.03
0.98
0.95
1.01
1.05
3.03
1.95
2.03
1.00
0.79
1.18
1.03
1.45
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

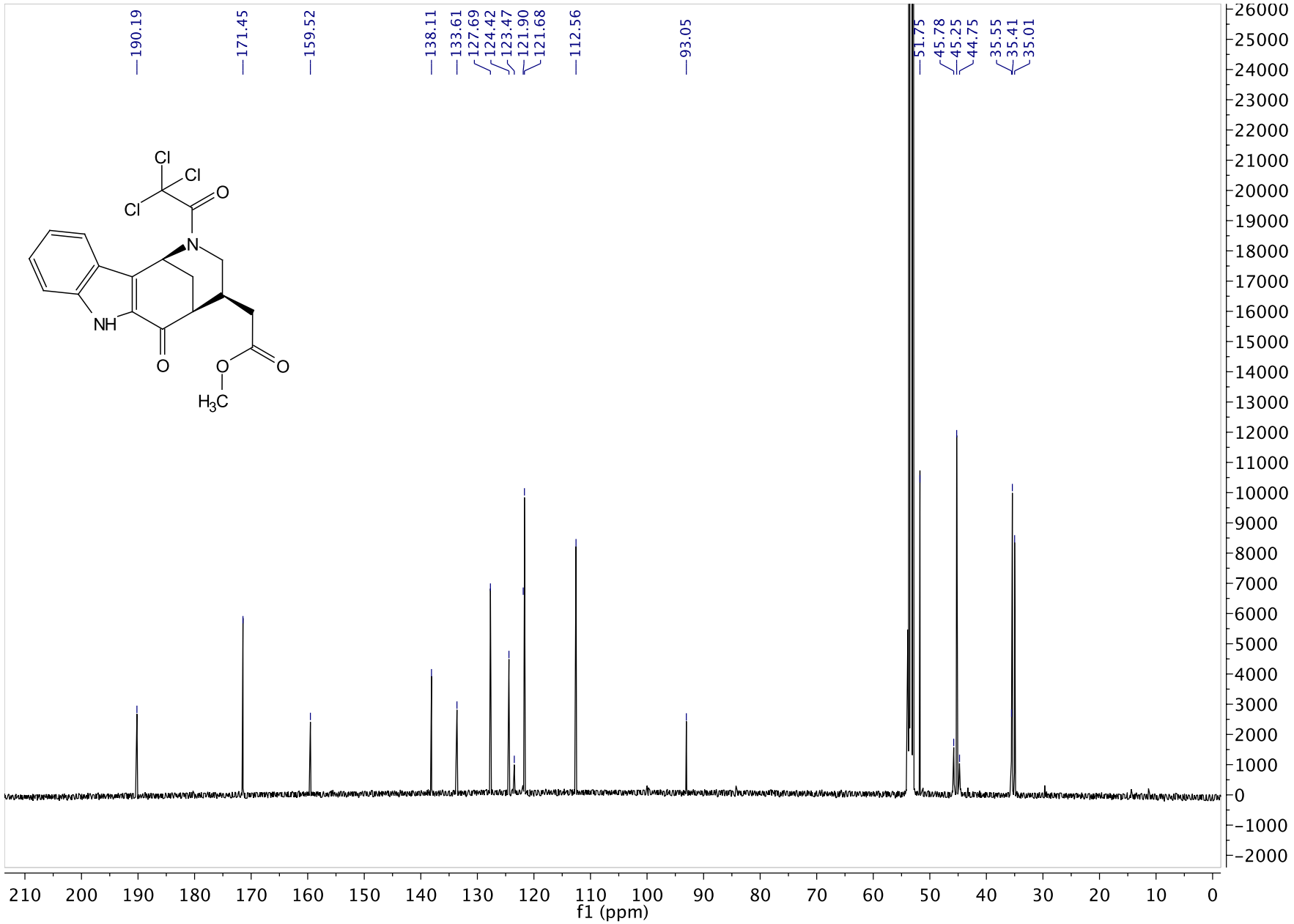
**$^{13}$C NMR of 20**


191.92
172.47
138.57
133.32
127.18
126.03
124.17
121.10
121.00
112.88
51.71
45.99
44.59
43.32
37.35
36.32
35.91
NH
NH
O
O
O
H3C
f1 (ppm)

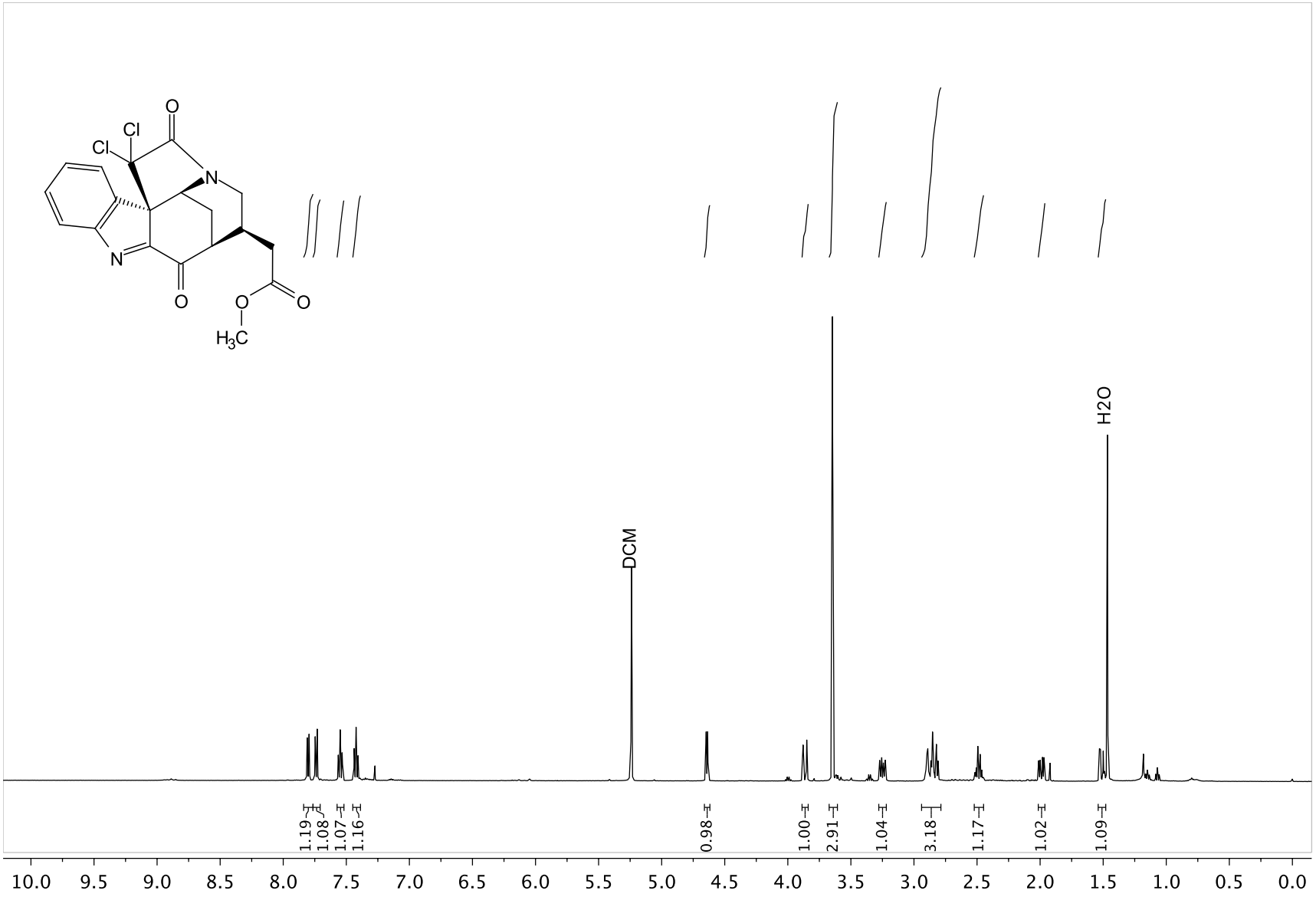
**$^{1}$H NMR of 2**


9.25 7.81 7.79 7.52 7.51 7.51 7.50 7.50 7.49 7.44 7.44 7.43 7.42 7.42 7.41 7.41 7.23 7.23 7.22 7.22 7.21 7.20 7.20
6.26 6.26 6.25
4.45 4.44 4.42 4.41
3.68 2.93 2.92 2.91 2.91 2.88 2.85 2.83 2.71 2.71 2.70 2.70 2.69 2.69 2.68 2.68 2.67 2.66 2.66 2.53 2.52 2.50 2.48 2.37 2.15 2.13 2.11 2.10 1.58
Cl
Cl
Cl
O
N
NH
O
O
O
O
H3C
1.46
1.00
0.98
1.15
1.04
1.11
1.04
2.84
1.04
1.10
2.01
1.04
1.07
1.11
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

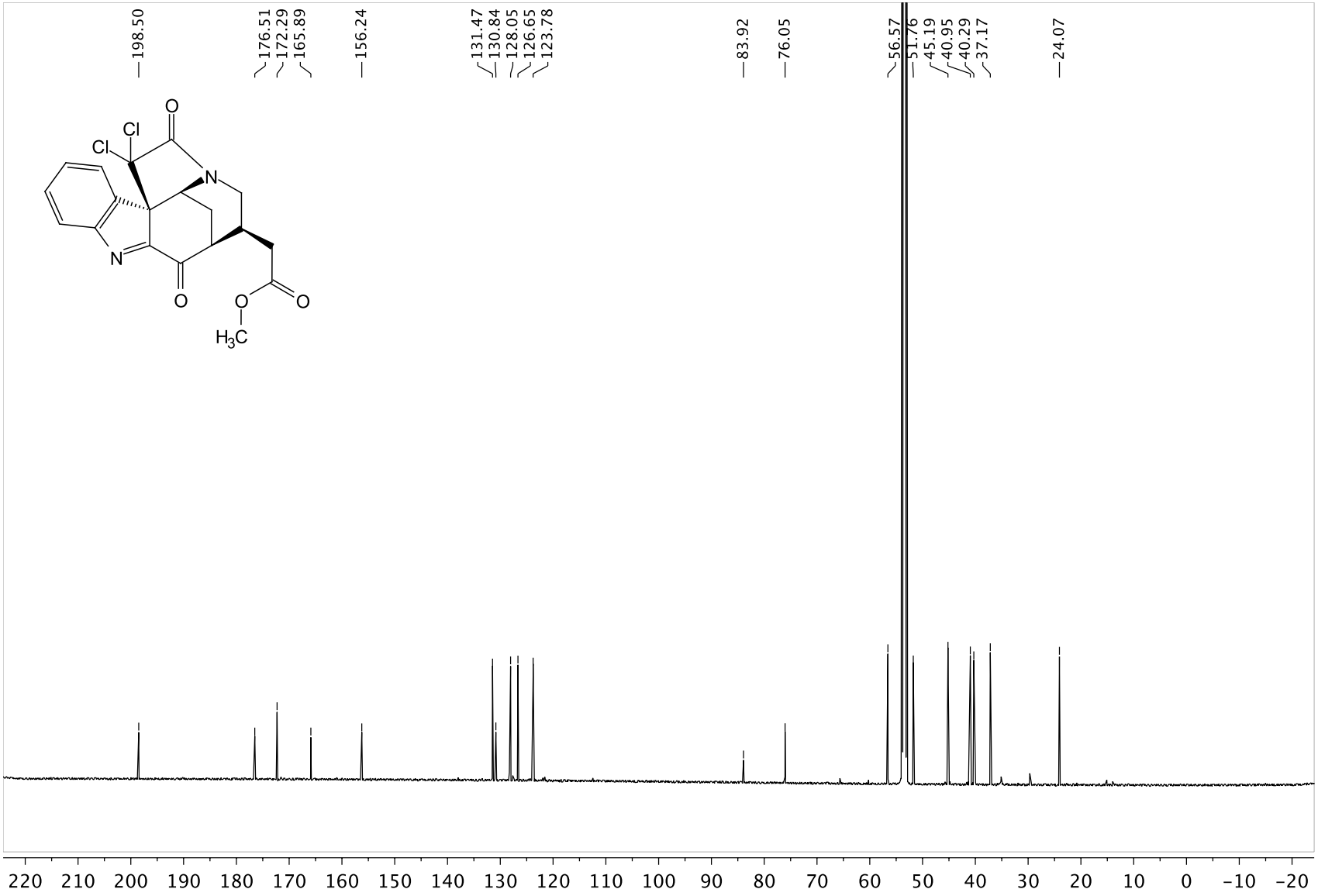
**$^{13}$C NMR of 2**


190.19
171.45
159.52
138.11
133.61
127.69
124.42
123.47
121.90
121.68
112.56
93.05
51.75
45.78
45.25
44.75
35.55
35.41
35.01
Cl
Cl
Cl
O
N
NH
O
O
O
O
H3C
f1 (ppm)

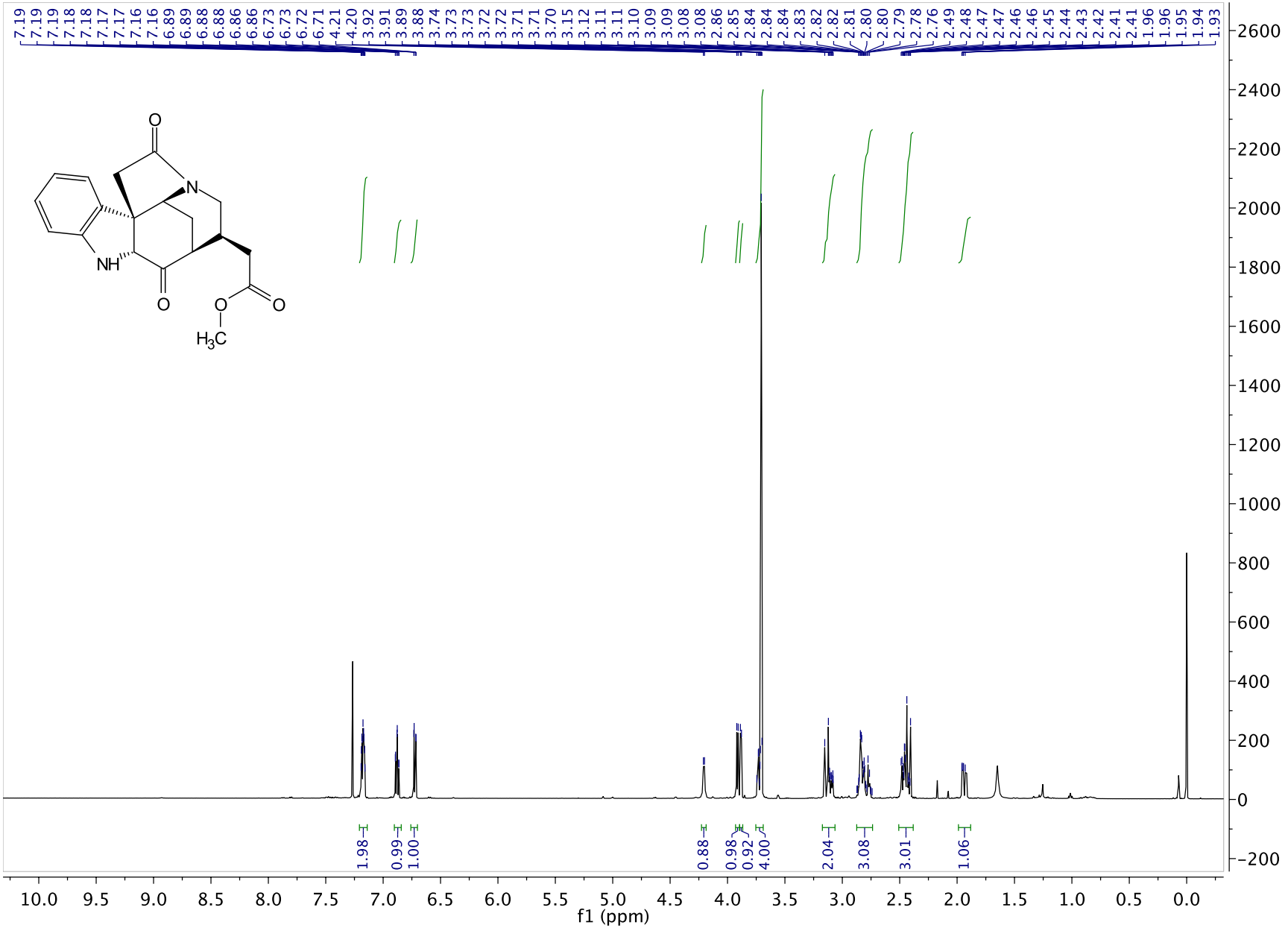
**$^{1}$H NMR of 15**


Cl
Cl
O
N
N
O
O
O
O
H3C
DCM
H2O
1.19
1.08
1.07
1.16
0.98
1.00
2.91
1.04
3.18
1.17
1.02
1.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

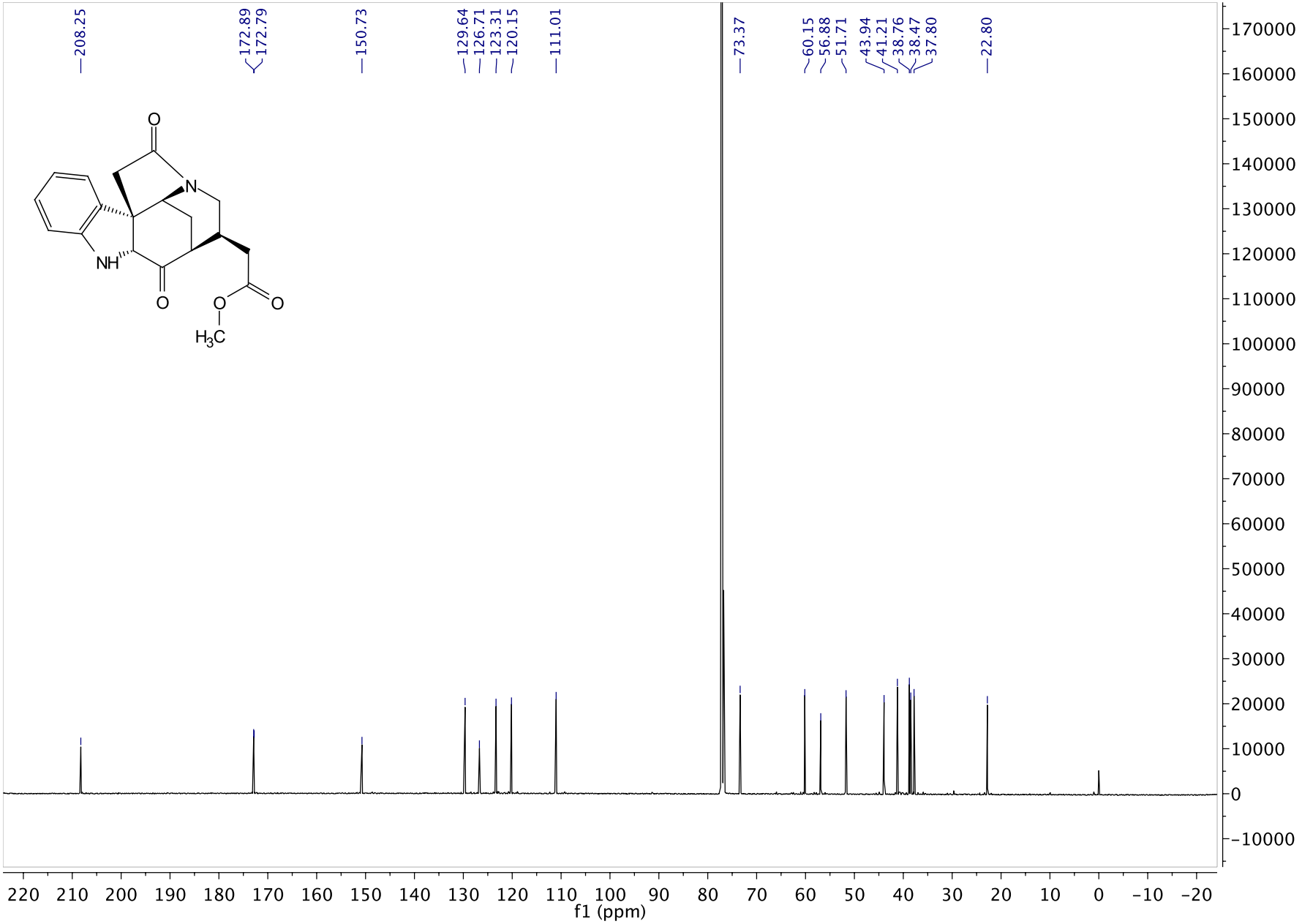
**$^{13}$C NMR of 15**


198.50
176.51
172.29
165.89
156.24
131.47
130.84
128.05
126.65
123.78
83.92
76.05
56.57
51.76
45.19
40.95
40.29
37.17
24.07
Cl
Cl
O
N
N
O
O
O
$H_3C$
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

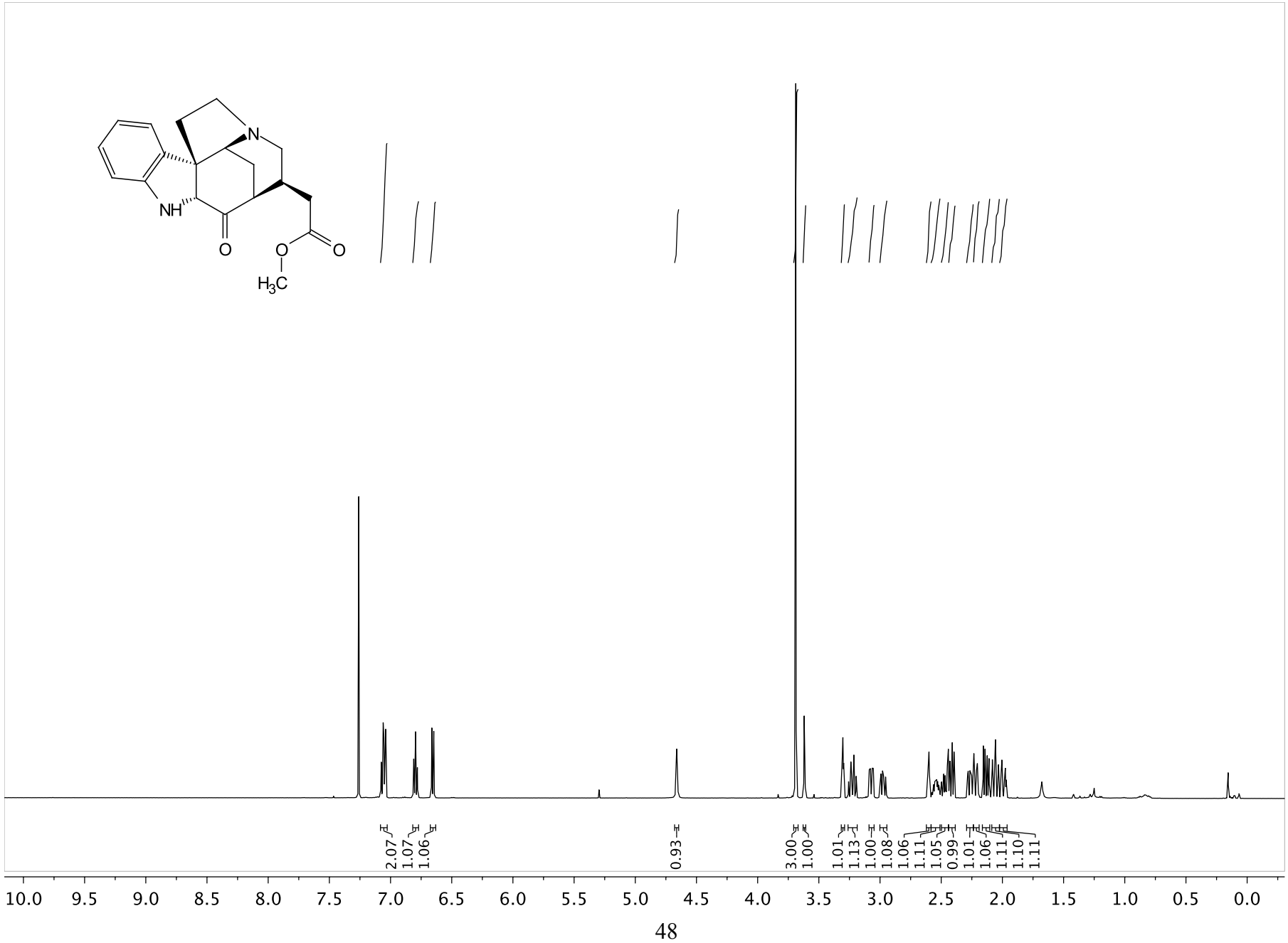
**$^{1}$H NMR of 1**


7.19 7.19 7.19 7.18 7.18 7.17 7.17 7.16 7.16 6.89 6.89 6.88 6.88 6.86 6.86 6.73 6.73 6.72 6.71 4.21 4.20 3.92 3.91 3.89 3.88 3.74 3.73 3.73 3.72 3.72 3.71 3.71 3.70 3.15 3.12 3.11 3.11 3.10 3.09 3.09 3.08 3.08 2.86 2.85 2.84 2.84 2.84 2.83 2.82 2.82 2.81 2.80 2.80 2.79 2.78 2.76 2.49 2.48 2.47 2.47 2.46 2.46 2.45 2.44 2.43 2.42 2.41 2.41 1.96 1.96 1.95 1.94 1.93
O
N
NH
O
O
O
O
H3C
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
1.98
0.99
1.00
0.88
0.98
0.92
4.00
2.04
3.08
3.01
1.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

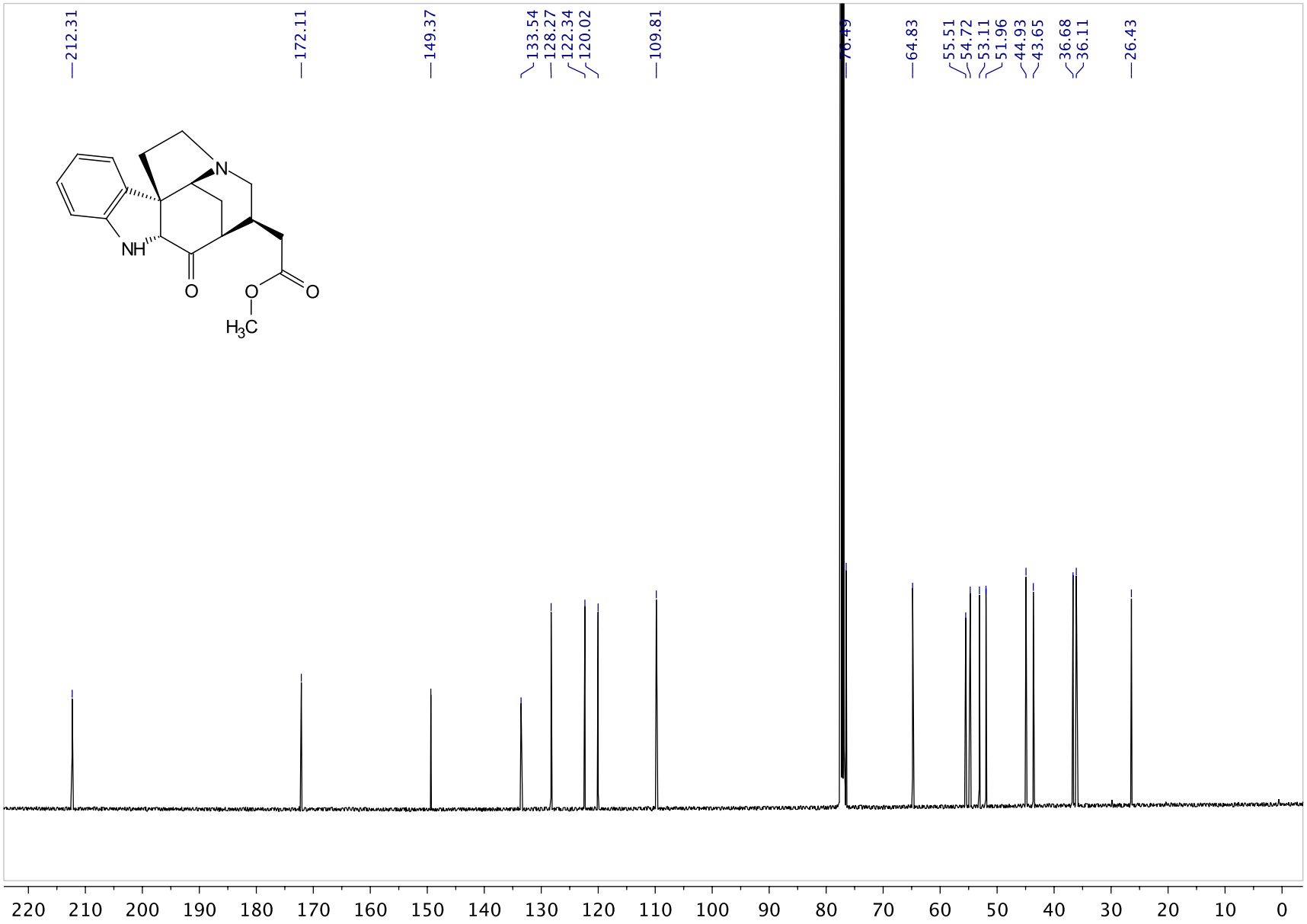
**$^{13}$C NMR of 1**


208.25
172.89
172.79
150.73
129.64
126.71
123.31
120.15
111.01
73.37
60.15
56.88
51.71
43.94
41.21
38.76
38.47
37.80
22.80
O
N
NH
O
O
O
H3C
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

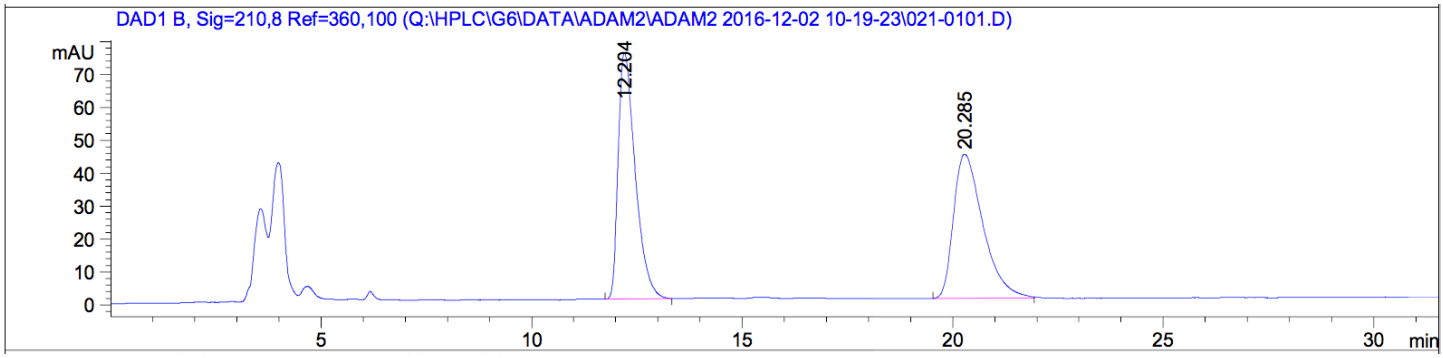
**$^1$H NMR of 18**


N
NH
O
O
O
H3C
2.07
1.07
1.06
0.93
3.00
1.00
1.01
1.13
1.00
1.08
1.06
1.11
1.05
0.99
1.01
1.06
1.11
1.10
1.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

**$^{13}$C NMR of 18**


212.31
172.11
149.37
133.54
128.27
122.34
120.02
109.81
78.49
64.83
55.51
54.72
53.11
51.96
44.93
43.65
36.68
36.11
26.43
N
NH
O
O
O
H3C
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

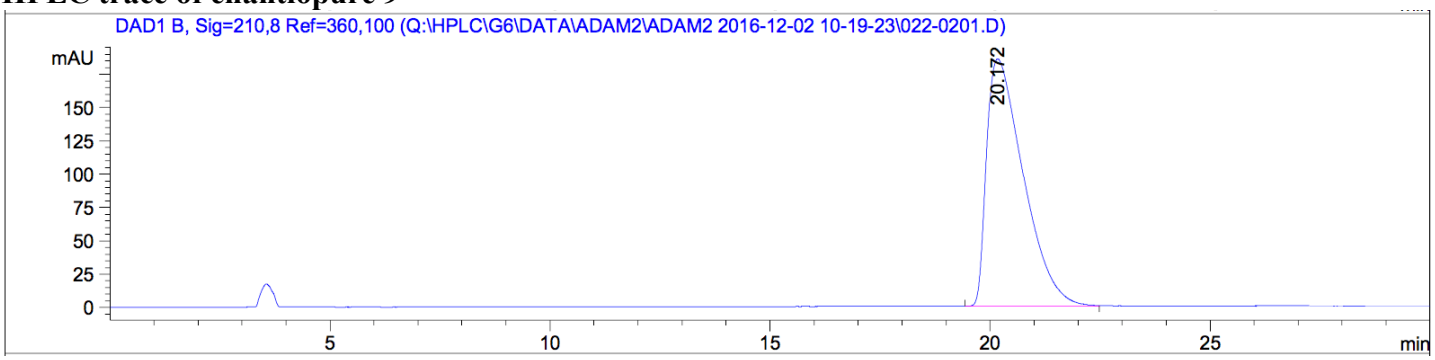
## HPLC trace of racemic 9




Signal 2: DAD1 B, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 12.204 | BB | 0.4325 | 2105.58130 | 74.77023 | 49.6720 |
| 2 | 20.285 | BB | 0.7526 | 2133.38574 | 43.77039 | 50.3280 |
| Totals : | | | | 4238.96704 | 118.54062 | |

## HPLC trace of enantiopure 9




Signal 2: DAD1 B, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 20.172 | BB | 0.8708 | 1.07678e4 | 185.60228 | 100.0000 |
| Totals : | | | | 1.07678e4 | 185.60228 | |