Supporting Information

Exploiting a Novel Size Exclusion Phenomenon for Enantioselective Acid / Base Cascade Catalysis

Michael E. Muratore,[‡] Lei Shi,[‡] Adam W. Pilling,[†] R. Ian Storer,[Ω] and Darren J. Dixon[‡*]

[‡] *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK,* [†] *School of Chemistry, The University of Manchester, Oxford Road, Manchester, Lancashire, M13 9PL, UK,* [Ω] *Pfizer Neusentis, The Portway Building, Granta Park, Cambridge, CB21 6GS, UK*

1. General Information

All reactions were performed in open, round-bottom flasks, unless otherwise stated. Solvents were used as purchased unless otherwise stated. Commercial reagents were used as purchased without any further purification.

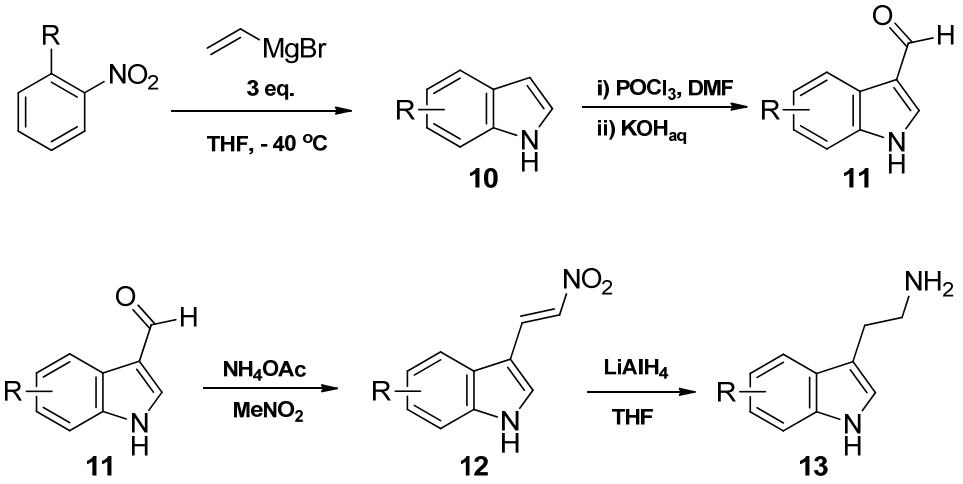
Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was carried out using Merck Kieselgel 60 silica gel (230-400 mesh). Thin-layer chromatography was carried out using Merck Kieselgel 60 F_{254} (230-400 mesh) fluorescent treated silica which were visualized under UV light (254 nm) or by staining with an aqueous potassium permanganate solution or a *para*-anisaldehyde alcoholic solution.

^{1}H NMR spectra were recorded in deuterated solvents on Bruker 500 or 400 spectrometers, at 500 or 400 MHz, with residual protic solvent as the internal standard. ^{13}C NMR spectra were recorded in deuterated solvents on Bruker 500 or 400 spectrometers, at 125 or 100 MHz, with the central peak of the deuterated solvent as the internal standard. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz) rounded to the nearest 0.5 Hz. The ^{1}H NMR spectra are reported as δ/ppm downfield from tetramethylsilane (multiplicity, number of protons, assignment, coupling constant *J*/Hz). The ^{13}C NMR spectra are reported as δ/ppm. Assignments are aided by the use of DEPT-135, COSY, HMQC and HMBC spectra where necessary. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer, from a thin film deposited on a sodium chloride plate and only diagnostic absorbances (λ_{max}) are reported (OOP = bending out of plan). Low resolution mass spectra were recorded on a Waters LCT premier XE mass spectrometer. High resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer (ESI); in the particular cases where electrospray ionisation was not a suitable technique, chemical ionisation was used and high resolution mass spectra were recorded on a Micromass GCT. Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on an Agilent Technology 1200 Series system (column and solvent conditions are given with the compound). Melting points were recorded on a Leica Galen III apparatus, at ambient pressure and are uncorrected. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg.cm^2.g^{-1}; concentrations (*c*) are quoted in g/100 mL; *D* refers to the D-line of sodium (589 nm); Temperatures (*T*) are given in degrees Celsius (°C).

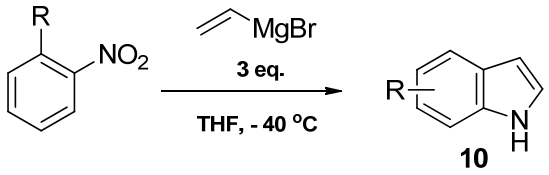
All atom numbering used in this section is arbitrary and does not follow any particular convention.

2. Preparation of starting materials

2.1. Preparation of substituted tryptamines 13



2.1.1. General procedure A for the preparation of substituted indoles 10

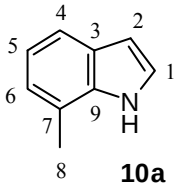


According to a modified literature procedure.[1]

The desired *ortho*-substituted nitro benzene substrate (1 equivalent) was dissolved in anhydrous tetrahydrofuran (4 mL per mmol of substrate) in a dry flask under nitrogen. The solution was cooled to − 40 ºC and a 1M solution of vinylmagnesium bromide in tetrahydrofuran was added quickly to the vigorously stirred solution, at − 40 ºC. The dark brown mixture was left stirring for 1 hour at − 40 ºC and then quenched by the addition of a saturated aqueous solution of ammonium chloride (at − 40 ºC, 3 mL per 1 mmol). The suspension was then allowed to warm to room temperature and stirred vigorously for 5 minutes. Ethyl acetate (2 mL per 1 mmol) was added and the organic layer separated. The aqueous layer was re-extracted with ethyl acetate (4 × 1 mL per 1 mmol). The combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. The brown residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 95:5 to 9:1.

Preparation and characterisation of 7-methyl-1*H*-indole 10a

The title compound was synthesised according to general procedure **A**, on a 90.0 mmol scale (12.4 g of 2-nitrotoluene) and isolated as a pale brown solid (4.0 g, 34%). Analytical data in agreement with the literature.[2]

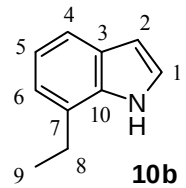


10a

m.p. 69-72 ºC (lit.[1] 80-82 °C); **FT-IR** ν_{max}(NaCl) 3402 cm^{-1} (N-H), 1590 cm^{-1} (ArC=C), 1340 cm^{-1} (CH_3), 782 cm^{-1} (ArC-H OOP), 722 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.28 (s, 3H, H-8), 6.52 (app. dd, 1H, H-2, *J* 3.0 Hz, 2.5 Hz), 6.81 (t, 1H, H-1, *J* 3.0 Hz), 7.00 (d, 1H, Ar-H, *J* 7.0 Hz), 7.09 (t, 1H, H-5, *J* 7.5 Hz), 7.45 (br s, 1H, NH), 7.54 (d, 1H, Ar-H, *J* 7.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.3 (C-8), 102.5 (C-2), 118.2 (Ar-CH), 119.8 (C-5), 120.2 (C-7), 122.2 (Ar-CH), 124.0 (C-1), 127.1 (C-3), 135.1 (C-9); ***m/z*** (ES−) 130 ($[M-H]^-$, 30%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_9H_8N^-$) requires ***m/z*** 130.0662, found ***m/z*** 130.0661.

Preparation and characterisation of 7-ethyl-1*H*-indole 10b

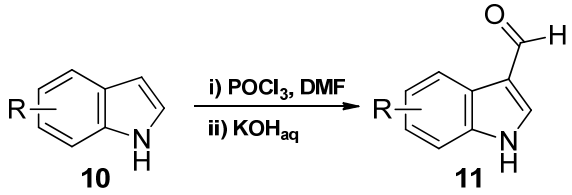
The title compound was synthesised according to general procedure **A**, on a 50.0 mmol scale (7.56 g of 1-ethyl-2-nitrobenzene) and isolated as a pale yellow oil (3.0 g, 41%). Analytical data in agreement with previous report.[3]



10b

FT-IR ν_{max}(NaCl) 3420 cm^{-1} (N-H), 2966 cm^{-1} (C-H), 1608 cm^{-1} (C=C), 1590 cm^{-1} (C=C), 1431 cm^{-1} (CH_2), 1342 cm^{-1} (CH_3), 728 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.49 (t, 3H, H-9, *J* 7.5 Hz), 2.93 (q, 2H, H-8, *J* 7.5 Hz), 6.72 (app. dd, 1H, H-2, *J* 3.0 Hz, 2.0 Hz), 7.17-7.23 (m, 2H, H-1, Ar-H), 7.28 (t, 1H, H-5, *J* 7.5 Hz), 7.70 (d, 1H, Ar-H, *J* 8.0 Hz), 7.98 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.7 (C-9), 23.9 (C-8), 102.8 (C-2), 118.3 (Ar-CH), 120.0 (C-5), 120.3 (Ar-CH), 123.8 (C-1), 126.4 (Ar-Cquat.), 127.5 (Ar-Cquat.), 134.5 (C-10); **HRMS** (CI+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}N^+$) requires ***m/z*** 146.0970, found ***m/z*** 146.0966.

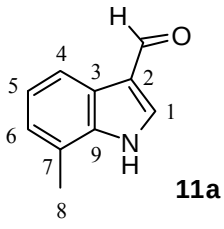
2.1.2. General procedure B for the preparation of substituted indole-3-carbaldehydes 11



Phosphorus oxychloride (1.2 equivalents) was added dropwise to dimethyl formamide (4.4 equivalents) with ice-bath cooling. The mixture was stirred for 1.5 hours, then the chosen indole **10** (1 equivalent) was added as a dimethyl formamide solution (0.5 mL per 1 mmol of indole). The mixture was then allowed to warm to room temperature and stirred for 10 minutes (the mixture became a heavy suspension that required vigorous stirring). 3.8 M aqueous potassium hydroxide (10 equivalents) was added v*ia* a dropping funnel and after addition the mixture was heated to 105 ºC for 1 hour. It was cooled to room temperature before adding saturated aqueous ammonium chloride (5 mL per 1 mmol of indole) and ethyl acetate (10 mL per 1 mmol of indole). The aqueous layer was re-extracted with ethyl acetate (4 × 5 mL per 1 mmol of indole) and the combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to furnish the desired aldehyde that was further purified by column chromatography on short-path silica gel column.

Preparation and characterisation of 7-methyl-1*H*-indole-3-carbaldehyde 11a

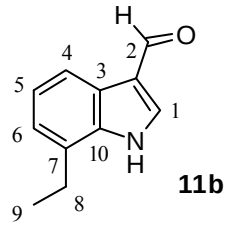
The title compound was prepared according to general procedure **B**, on a 30 mmol scale and isolated after chromatography eluting with dichloromethane/acetone 9:1 to 3:1 as a pale brown solid (82% yield, 3.91 g). Analytical data in agreement with the literature.[4]



11a

m.p. 209-211 ºC; **FT-IR** ν_{max}(NaCl) 3243 cm^{-1} (N-H), 1649 cm^{-1} (C=O); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 2.54 (s, 3H, H-8), 7.09 (d, 1H, Ar-H, *J* 7.5 Hz), 7.16 (t, 1H, H-5, *J* 7.5 Hz), 8.07 (d, 1H, Ar-H, *J* 7.5 Hz), 8.16 (d, 1H, H-1, *J* 3.0 Hz), 10.03 (s, 1H, C(O)H), 11.18 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 16.8 (C-8), 119.8 (Ar-CH), 120.5 (Ar-Cquat.), 122.4 (Ar-Cquat.), 123.3 (C-5), 125.1 (Ar-CH), 125.2 (Ar-Cquat.), 137.6 (C-1), 185.4 (C=O); ***m/z*** (ES−) 158 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{10}NO^+$) requires ***m/z*** 160.0757, found ***m/z*** 160.0758.

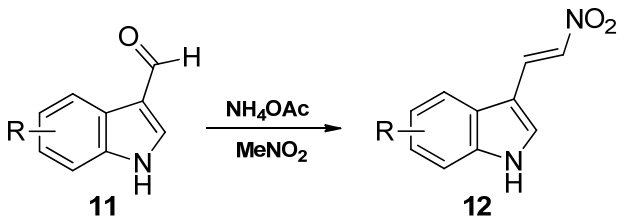
Preparation of 7-ethyl-1*H*-indole-3-carbaldehyde 11b



11b

The title compound was prepared according to general procedure **B**, on a 24.1 mmol scale and used without further purification in the next reaction (3.50 g, 84% yield crude).

2.1.3. General procedure C for the preparation of substituted indole nitro-olefins 12

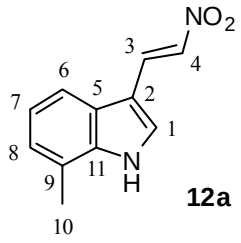


11 **12**

Indole-3-carbaldehyde **11** (1 equivalent) was suspended in nitromethane (2.5 mL per 1 mmol of aldehyde). Dry ammonium acetate (0.7 equivalents) was added to the vigorously stirred suspension. The mixture was heated at reflux for 1-5 hours (disappearance of the starting material monitored by ^{1}H NMR) and the reaction was stopped immediatedly after full consumption. The solvent was removed under reduced pressure and the residue partitioned between water (5 mL per 1 mmol) and ethyl acetate (20 mL per 1 mmol). The aqueous layer was re-extracted with ethyl acetate (4 × 10 mL per 1 mmol) and the combined organics dried over magnesium sulphate, filtered and concentrated *in vacuo*. The residue was purified by short-path silica gel column chromatography.

Preparation and characterisation of 7-methyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole 12a

The title compound was synthesised according to general procedure **C** on a 25 mmol scale and was obtained as an orange solid after purification by short-path silica gel column chromatography eluting with dichloromethane (4.95 g, 98%).



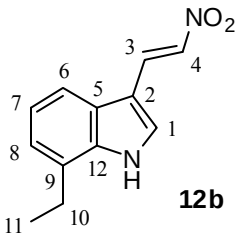
12a

m.p. 226-230 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3263 cm^{-1} (N-H), 1611 cm^{-1} (C=C), 1587 cm^{-1} (C=C), 1522 cm^{-1} (NO_2), 1301 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 2.54 (s, 3H, H-10), 7.11 (d, 1H, Ar-H, *J* 7.0 Hz), 7.20 (t, 1H, H-7, *J* 7.5 Hz), 7.76 (d, 1H, Ar-H, *J* 8.0 Hz), 7.89 (d, 1H, H-4, *J* 13.5 Hz), 8.11 (d, 1H, H-1, *J* 3.0 Hz), 8.36 (d, 1H, H-3, *J* 13.5 Hz), 11.24 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 16.8 (C-10), 110.0 (C-2), 118.9 (Ar-CH),

123.0 (Ar-Cquat.), 123.1 (C-7), 125.1 (Ar-CH), 125.6 (Ar-Cquat.), 132.7 (C-4), 134.8 (C-3), 135.3 (C-1), 138.3 (C-11); ***m/z*** (ES+) 225 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{10}N_2O_2Na^+$) requires ***m/z*** 225.0634, found ***m/z*** 225.0636.

Preparation and characterisation of 7-ethyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole 12b

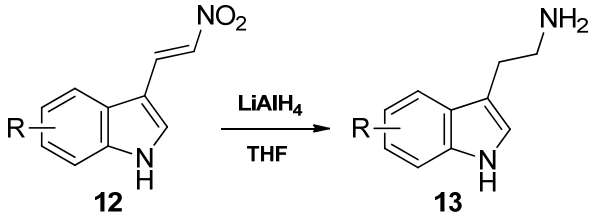
The title compound was synthesised according to general procedure **C** on a 19 mmol scale (theoretical) and was obtained as an orange solid after purification by short-path silica gel column chromatography eluting with dichloromethane (2.50 g, 60% over 2 steps).



12b

m.p. 203-206 ºC; **FT-IR** ν_{max}(NaCl) 3333 cm^{-1} (N-H), 1615 cm^{-1} (C=C), 1553 cm^{-1} (C=C), 1523 cm^{-1} (NO_2), 1302 cm^{-1} (NO_2); **^{1}H NMR** (d_4-MeOD, 500 MHz) δ_H 1.32 (t, 3H, H-11, *J* 7.5 Hz), 2.91 (q, 2H, H-10, *J* 7.5 Hz), 7.11 (d, 1H, H-8, *J* 7.5 Hz), 7.21 (t, 1H, H-7, *J* 7.5 Hz), 7.63 (d, 1H, H-6, *J* 8.0 Hz), 7.86 (d, 1H, H-4, *J* 13.0 Hz), 7.89 (app. s, 1H, H-1), 8.37 (d, 1H, H-3, *J* 13.0 Hz); **^{13}C NMR** (d_4-MeOD, 125 MHz) δ_C 14.9 (C-11), 25.0 (C-10), 110.4 (C-2), 118.9 (C-6), 123.5 (2 signals, C-7, C-8), 126.2 (C-5), 129.8 (C-9), 132.4 (C-4), 135.8 (2C, C-1, C-3), 138.0 (C-12); ***m/z*** (ES+) 239 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}N_2O_2Na^+$) requires ***m/z*** 239.0791, found ***m/z*** 239.0788.

2.1.4. General procedure D for the preparation of substituted tryptamines 13



12 **13**

Under a nitrogen inert atmosphere, a tetrahydrofuran solution (10 mL per 1 mmol of nitro olefin) of nitro olefin **12** (1 equivalent) was added to a stirred slurry of lithium aluminium hydride powder (6 equivalents) in tetrahydrofuran (equal volume) at 0 ºC. The mixture was allowed to warm to room temperature and stirred for 36 hours. The reaction was quenched by dropwise addition of water until effervescence ceased. The mixture was then diluted with diethyl ether before addition of a saturated aqueous solution of Rochelle's salt and the subsequent biphasic mixture was stirred for 24 hours. The layers were separated and the organic layer was extracted with 1 M aqueous hydrochloric acid. The aqueous phase was basified with 3 M aqueous potassium hydroxide, extracted with diethyl ether,

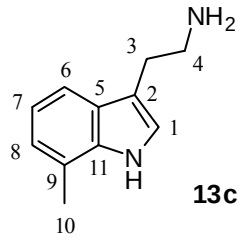
dried over sodium sulphate, filtered and concentrated *in vacuo* to furnish the desired tryptamine which required no further purification.

Remark: the work-up can be simplified by using sodium sulphate decahydrate to quench the excess LAH. $Na_2SO_4.10H_2O$ was added slowly by portion until ≈ 2.5 g of salt was added per 1 g of LAH used. The mixture was then stirred vigorously for 6 hours (colour faded to pale yellow / colourless) and the suspension filtered over celite. The flask and resulting cake were washed thoroughly with diethyl ether (volume identical to tetrahydrofuran used) and then dichloromethane (volume identical to tetrahydrofuran used). The combined organics were concentrated to afford the desired tryptamine that did not require further purification.

*N.B. Tryptamine (**13a**) was purchased from Aldrich and used without further purification. 5-bromo tryptamine (**13b**) was prepared as previously described.*[5]

Preparation and characterisation of 2-(7-methyl-1*H*-indol-3-yl)ethanamine 13c

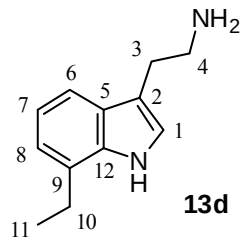
The title compound was synthesised according to general procedure **D** on a 24 mmol scale and was isolated as a brown gum that was used without further purification (4.14 g, 99%).



13c

FT-IR ν_{max}(NaCl) 3338 cm^{-1} (N-H), 3286 cm^{-1} (N-H), 1588 cm^{-1} (C=C), 741 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 2.44 (s, 3H, H-10), 2.88 (br s, 4H, H-3, H-4), 6.84 (br s, 2H, 2 × Ar-H), 7.13 (br s, 1H, H-1), 7.35 (br s, 1H, Ar-H), 10.84 (br s, 1H, NH indole); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 16.8 (C-10), 27.7 (C-3), 41.8 (C-4), 112.3 (C-2), 116.0 (Ar-CH), 118.4 (Ar-CH), 120.5 (C-9), 121.4 (Ar-CH), 122.6 (C-1), 126.9 (C-5), 135.9 (C-11); ***m/z*** (ES−) 173 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{11}H_{13}N_2^-$) requires ***m/z*** 173.1084, found ***m/z*** 173.1077.

Preparation and characterisation of 2-(7-ethyl-1*H*-indol-3-yl)ethanamine 13d



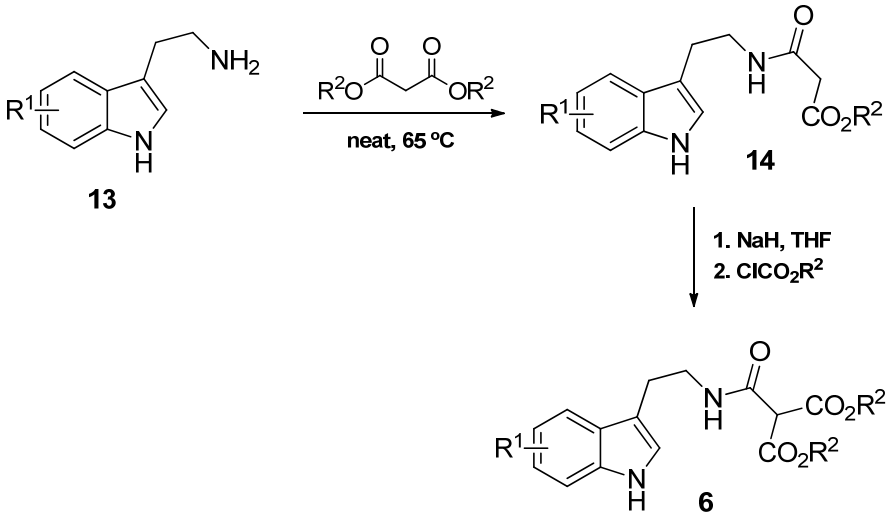
13d

The title compound was synthesised according to general procedure **D** on a 11.6 mmol scale and was isolated as a pale brown solid that was used without further purification (2.20 g, 99%).

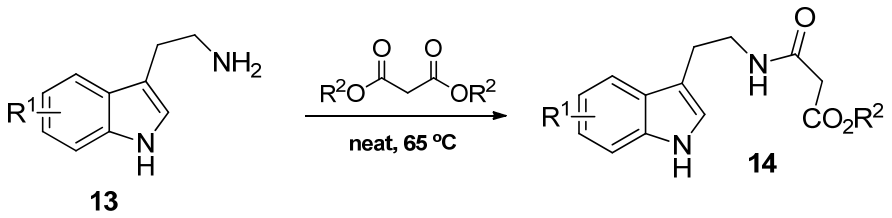
m.p. 203-205 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3398 cm^{-1} (N-H), 3282 cm^{-1} (N-H), 1586 cm^{-1} (C=C), 1473 cm^{-1} (CH_2), 743 cm^{-1} (ArC-H OOP); **^{1}H NMR**

(d_6-DMSO, 400 MHz) δ_H 1.26 (t, 3H, H-11, *J* 7.5 Hz), 2.86 (q, 2H, H-10, *J* 7.5 Hz), 3.07 (app. s, 4H, H-3, H-4), 6.88-6.98 (m, 2H, H-7, Ar-H), 7.24 (d, 1H, H-1, *J* 2.5 Hz), 7.42 (d, 1H, Ar-H, *J* 7.5 Hz), 11.05 (br s, 1H, NH indole); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 14.5 (C-11), 23.3 (C-10), 23.8 (C-3), 39.3 (C-4), 110.1 (C-2), 115.9 (Ar-CH), 118.8 (Ar-CH), 118.9 (Ar-CH), 123.1 (C-1), 126.8 (Ar-Cquat.), 127.1 (Ar-Cquat.), 135.1 (C-12); ***m/z*** (ES−) 223 ([M+Cl]$^-$, 35%), **HRMS** (ES−) exact mass calculated for [M+Cl]$^-$ ($C_{12}H_{16}N_2Cl^-$) requires ***m/z*** 223.1007, found ***m/z*** 223.1001.

2.2. Preparation of pro-nucleophiles 6



2.2.1. General procedure E for the preparation of malonate monoamides 14

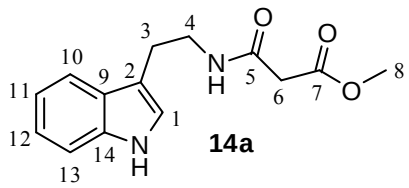


Prepared *via* a slight modification of a literature procedure.[6]

A tryptamine derivative **13** (1 equivalent) was suspended in the corresponding neat malonate (5 equivalents). The suspension was heated at 65 ºC for 48 to 96 hours. The brown viscous solution was loaded on silica gel and the mixture was eluted with petroleum ether/ethyl acetate to afford the desired dicarbonyl **14**.

Preparation and characterisation of methyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14a

Synthesised according to general procedure **E** on 30 mmol scale of **13a** (4.8 g). Purified by column chromatography eluting with petroleum ether/ethyl acetate 2:1 to 2:3 to give the title compound as a pale yellow solid (5.75 g, 74%). Analytical data in agreement with the literature.[7]

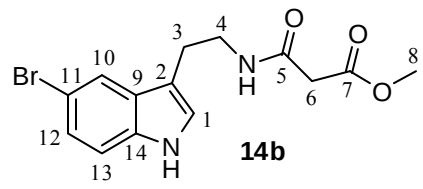


14a

m.p. 105-108 ºC; **FT-IR** ν_{max}(NaCl) 3353 cm^{-1} (br with shoulder, N-H), 1734 cm^{-1} (C=O ester), 1652 cm^{-1} (C=O amide), 742 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.29 (s, 2H, H-6), 3.65 (app. q, 2H, H-4, *J* 7.0 Hz), 3.70 (s, 3H, H-8), 7.04 (br s, 1H, NH amide), 7.08 (d, 1H, H-1, *J* 2.5 Hz), 7.14 (t, 1H, H-11, *J* 7.5 Hz), 7.22 (t, 1H, H-12, *J* 7.5 Hz), 7.39 (d, 1H, H-13, *J* 7.5 Hz), 7.62 (d, 1H, H-10, *J* 7.5 Hz), 8.09 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 25.1 (C-3), 40.0 (C-4), 41.2 (C-6), 52.3 (C-8), 111.3 (C-13), 112.6 (C-2), 118.6 (C-12), 119.3 (C-11), 122.0 (C-10), 122.1 (C-1), 127.3 (C-9), 136.4 (C-14), 164.9 (C-5), 169.7 (C-7); ***m/z*** (ES+) 283 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2O_3Na^+$) requires ***m/z*** 283.1053, found ***m/z*** 283.1063.

Preparation and characterisation of methyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14b

Synthesised according to general procedure **E** on 8.4 mmol scale of **13b** (2.0 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to give the title compound as a pale yellow oil (2.0 g, 70%).



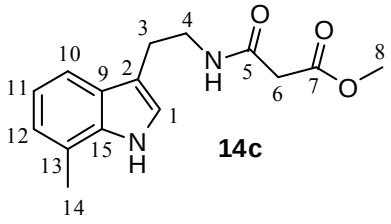
14b

FT-IR ν_{max}(NaCl) 3303 cm^{-1} (br with shoulder, N-H), 1738 cm^{-1} (C=O ester), 1654 cm^{-1} (C=O amide), 754 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.95 (t, 2H, H-3, *J* 7.0 Hz), 3.30 (s, 2H, H-6), 3.60 (app. q, 2H, H-4, *J* 7.0 Hz), 3.70 (s, 3H, H-8), 7.06 (s, 1H, H-1), 7.15 (br s, 1H, NH amide), 7.24 (d, 1H, H-13, *J* 8.5 Hz), 7.27 (dd, 1H, H-12, *J* 8.5 Hz, 1.5 Hz), 7.72 (d, 1H, H-10, *J* 1.5 Hz), 8.33 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.9 (C-3), 39.9 (C-4), 40.9 (C-6), 52.4 (C-8), 112.6 & 112.7 (C-2 & C-11), 112.7 (Ar-CH), 121.3 (C-10), 123.3 (C-1), 124.9 (Ar-CH), 129.1 (C-9), 134.9

(C-14), 164.9 (C-5), 169.8 (C-7); ***m/z*** (ES−) 337, 339 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}N_2O_3BrNa^+$) requires ***m/z*** 361.0158, found ***m/z*** 361.0161.

Preparation and characterisation of methyl 3-{[2-(7-methyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14c

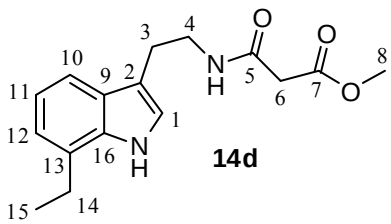
Synthesised according to general procedure **E** on 10.0 mmol scale of **13c** (1.74 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:2 to give the title compound as a pale brown crystalline solid (1.9 g, 69%).



m.p. 106-108 ºC; **FT-IR** ν_{max}(NaCl) 3387 cm^{-1} (N-H), 3301 cm^{-1} (N-H), 1739 cm^{-1} (C=O ester), 1656 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.49 (s, 3H, H-14), 3.01 (t, 2H, H-3, *J* 7.0 Hz), 3.25 (s, 2H, H-6), 3.63 (app. q, 2H, H-4, *J* 7.0 Hz), 3.69 (s, 3H, H-8), 7.00-7.15 (m, 4H, 2 × Ar-H, H-1, NH amide), 7.48 (d, 1H, Ar-H, *J* 7.5 Hz), 8.62 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.6 (C-14), 25.2 (C-3), 40.1 (C-4), 41.7 (C-6), 52.4 (C-8), 113.0 (C-2), 116.3 (Ar-CH), 119.6 (Ar-CH), 120.6 (C-13), 122.0 (Ar-CH), 122.6 (Ar-CH), 126.9 (C-9), 136.0 (C-15), 165.1 (C-5), 169.6 (C-7); ***m/z*** (ES+) 297 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_3Na^+$) requires ***m/z*** 297.1210, found ***m/z*** 297.1207.

Preparation and characterisation of methyl 3-{[2-(7-ethyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14d

Synthesised according to general procedure **E** on a 5.85 mmol scale of **13d** (1.1 g). Purified by column chromatography on silica gel eluting with diethyl ether to diethyl ether/ethyl acetate 3:1 to give the title product as a pale brown oil (1.2 g, 71%).

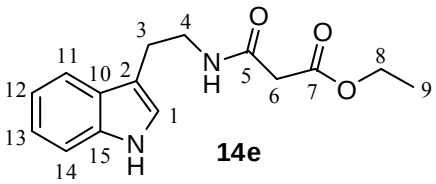


FT-IR ν_{max}(NaCl) 3383 cm^{-1} (N-H), 3310 cm^{-1} (N-H), 1741 cm^{-1} (C=O ester), 1659 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.37 (t, 3H, H-15, *J* 7.5 Hz), 2.87 (q, 2H, H-14, *J* 7.5 Hz), 3.01 (t, 2H, H-3, *J* 7.0 Hz), 3.28 (s, 2H, H-6), 3.64 (app. q, 2H, H-4, *J* 6.5 Hz), 3.70 (s, 3H, H-8), 7.03-7.13 (m, 4H, H-1, 2 × Ar-H, NH amide), 7.47 (dd, 1H, Ar-H, *J* 7.5 Hz, 1.0 Hz), 8.28 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-15), 23.9 (C-14), 25.1 (C-3), 39.9 (C-4), 41.2 (C-6), 52.3 (C-8),

113.1 (C-2), 116.3 (Ar-CH), 119.7 (Ar-CH), 120.6 (Ar-CH), 121.7 (Ar-CH), 126.7 (Ar-Cquat.), 127.0 (Ar-Cquat.), 135.2 (Ar-Cquat.), 164.9 (C-5), 169.6 (C-7); ***m/z*** (ES−) 287 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{16}H_{20}N_2O_3Na^+$) requires ***m/z*** 311.1366, found ***m/z*** 311.1366.

Preparation and characterisation of ethyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14e

Synthesised according to general procedure **E** on a 30 mmol scale of **13a** (4.8 g). Purified by column chromatography eluting with petroleum ether/ethyl acetate 2:1 to 1:2 to give the title product as a pale yellow oil (6.0 g, 73%). Analytical data in agreement with previous report.[7]

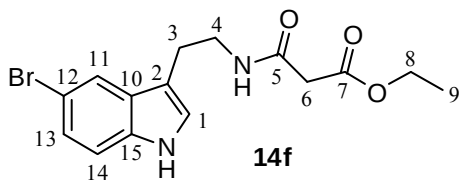


14e

FT-IR ν_{max}(NaCl) 3393 cm^{-1} (N-H), 3309 cm^{-1} (N-H), 1732 cm^{-1} (C=O ester), 1658 cm^{-1} (C=O amide), 746 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.25 (t, 3H, H-9, *J* 7.0 Hz), 3.00 (t, 2H, H-3, *J* 7.0 Hz), 3.25 (s, 2H, H-6), 3.63 (app. q, 2H, H-4, *J* 7.0 Hz), 4.14 (q, 2H, H-8, *J* 7.0 Hz), 7.01 (s, 1H, H-1), 7.09-7.17 (m, 2H, H-12, NH amide), 7.20 (t, 1H, H-13, *J* 7.5 Hz), 7.36 (d, 1H, H-14, *J* 7.5 Hz), 7.61 (d, 1H, H-11, *J* 7.5 Hz), 8.56 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-9), 25.0 (C-3), 39.9 (C-4), 41.3 (C-6), 61.4 (C-8), 111.2 (C-14), 112.4 (C-2), 118.4 (C-11), 119.1 (C-12), 121.8 (C-13), 122.1 (C-1), 127.1 (C-10), 136.3 (C-15), 165.2 (C-5), 169.1 (C-7); ***m/z*** (ES+) 297 ([M+Na]$^+$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{15}H_{18}N_2O_3Na^+$) requires ***m/z*** 297.1210, found ***m/z*** 297.1211.

Preparation and characterisation of ethyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14f

Synthesised according to general procedure **E** on a 10 mmol scale of **13b** (2.4 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 7:2 to 1:1 to give the title product as a pale yellow oil (2.03 g, 58%).



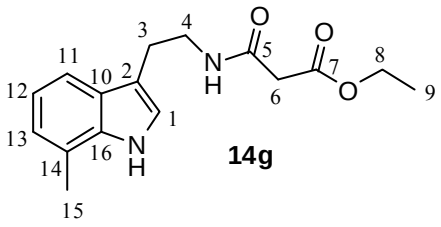
14f

FT-IR ν_{max}(NaCl) 3313 cm^{-1} (br with shoulder, N-H), 1725 cm^{-1} (C=O ester), 1653 cm^{-1} (C=O amide), 750 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.25 (t, 3H, H-9, *J* 7.0 Hz), 2.94 (t, 2H, H-3, *J* 7.0 Hz), 3.28 (s, 2H, H-6), 3.59 (app. q, 2H, H-4, *J* 7.0 Hz), 4.15 (q, 2H, H-8, *J* 7.0 Hz), 7.03

(d, 1H, H-1, *J* 2.0 Hz), 7.18-7.28 (m, 3H, H-13, H-14, NH amide), 7.71 (d, 1H, H-11, *J* 1.5 Hz), 8.49 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 (C-9), 24.9 (C-3), 39.9 (C-4), 41.1 (C-6), 61.5 (C-8), 112.5 & 112.6 (C-2 & C-12), 112.7 (Ar-CH), 121.2 (C-11), 123.3 (C-1), 124.8 (Ar-CH), 129.1 (C-10), 134.9 (C-15), 165.1 (C-5), 169.4 (C-7); ***m/z*** (ES−) 351, 353 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{17}N_2O_3BrNa^+$) requires ***m/z*** 375.0315 & 377.0295, found ***m/z*** 375.0316 & 377.0294.

Preparation and characterisation of ethyl 3-{[2-(7-methyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14g

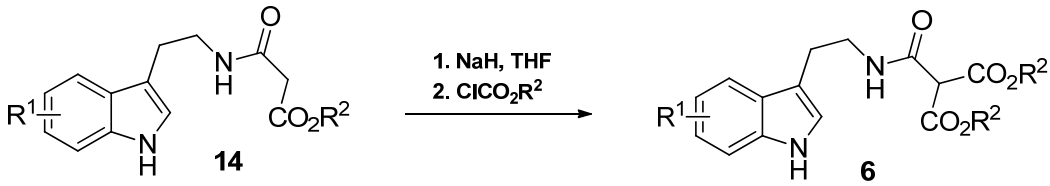
Synthesised according to general procedure **E** on a 11.2 mmol scale of **13c** (1.95 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1 to give the title compound as an off-white solid (2.08 g, 64%).



14g

m.p. 82-84 ºC; **FT-IR** ν_{max}(NaCl) 3383 cm^{-1} (N-H), 3306 cm^{-1} (N-H), 1734 cm^{-1} (C=O ester), 1658 cm^{-1} (C=O amide), 750 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.26 (t, 3H, H-9, *J* 7.0 Hz), 2.49 (s, 3H, H-15), 3.00 (t, 2H, H-3, *J* 7.0 Hz), 3.27 (s, 2H, H-6), 3.64 (app. q, 2H, H-4, *J* 6.5 Hz), 4.15 (q, 2H, H-8, *J* 7.0 Hz), 6.99-7.09 (m, 3H, H-1, H-12, Ar-H), 7.12 (br s, 1H, NH amide), 7.46 (d, 1H, Ar-H, *J* 8.0 Hz), 8.22 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-9), 16.5 (C-15), 25.2 (C-3), 39.9 (C-4), 41.3 (C-6), 62.4 (C-8), 113.2 (C-2), 116.3 (Ar-CH), 119.6 (Ar-CH), 120.4 (C-14), 121.8 (Ar-CH), 122.6 (Ar-CH), 126.8 (C-10), 135.9 (C-16), 165.0 (C-5), 169.3 (C-7); ***m/z*** (ES−) 287 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2O_3Na^+$) requires ***m/z*** 311.1366, found ***m/z*** 311.1367.

2.2.2. General procedure F for the preparation of pro-nucleophiles 6

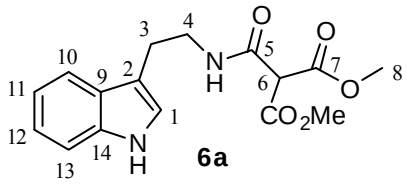


Sodium hydride (1 equivalent) was suspended in tetrahydrofuran (5 mL per 1 mmol of dicarbonyl), and the suspension was cooled to 0 ºC. Dicarbonyl **14** (1 equivalent) was added dropwise as a solution in tetrahydrofuran (2 mL per 1 mmol). The suspension was stirred for 1.5 hours at 0 ºC (it became

clear meanwhile) and the relevant chloroformate (0.5 equivalents) was added in one portion to the vigorously stirred mixture. The resulting solution was stirred for 1 hour at 0 ºC and further 30 minutes at room temperature. It was quenched with a saturated aqueous solution of ammonium chloride (3 mL per 1 mmol of substrate). The aqueous layer was diluted with water (3 mL per 1 mmol), and ethyl acetate was added (3 mL per 1 mmol). The layers were separated and the aqueous was re-extracted with ethyl acetate (2 × 3 mL per 1 mmol). The combined organics were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel eluting with petroleum ether / diethyl ether (see eluent conditions for each compound).

Preparation and characterisation of dimethyl {[2-(1*H*-indol-3-yl)ethyl]carbamoyl}malonate 6a

Synthesised according to general procedure **F** on a 22.1 mmol scale of **14a** (5.75 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether and then diethyl ether/ethyl acetate 9:1 to give the title product as an off-white solid (2.96 g, 84%).

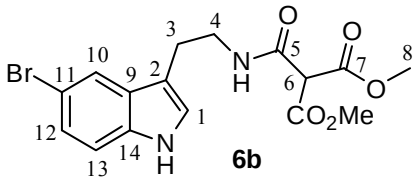


6a

m.p. 82-84 ºC; **FT-IR** ν_{max}(NaCl) 3389 cm^{-1} (N-H), 3321 cm^{-1} (N-H), 1740 cm^{-1} (C=O ester), 1663 cm^{-1} (C=O amide), 747 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.01 (t, 2H, H-3, *J* 7.0 Hz), 3.64 (app. q, 2H, H-4, *J* 7.0 Hz), 3.74 (s, 6H, H-8), 4.36 (s, 1H, H-6), 7.04 (d, 1H, H-1, *J* 2.5 Hz), 7.12 (ddd, 1H, H-11, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.20 (ddd, 1H, H-12, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.33-7.40 (m, 2H, H-13, NH amide), 7.61 (d, 1H, H-10, *J* 8.0 Hz), 8.44 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.8 (C-3), 40.2 (C-4), 53.3 (C-8), 58.6 (C-6), 111.2 (C-13), 112.2 (C-2), 118.5 (C-10), 119.2 (C-11), 121.9 (C-12), 122.3 (C-1), 127.1 (C-9), 136.3 (C-14), 161.9 (C-5), 165.9 (C-7); ***m/z*** (ES+) 341 ($[M+Na]^+$, 80%), 659 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}N_2O_5Na^+$) requires ***m/z*** 341.1108, found ***m/z*** 341.1108.

Preparation and characterisation of dimethyl {[2-(5-bromo-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 6b

Synthesised according to general procedure **F** on a 2.16 mmol scale of **14b** (730 mg). The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether to give the title compound as a pale yellow oil (280 mg, 65%).

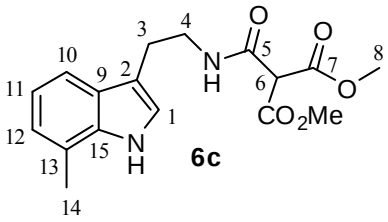


6b

FT-IR ν_{max}(NaCl) 3374 cm^{-1} (N-H), 3308 cm^{-1} (N-H), 1739 cm^{-1} (C=O ester), 1662 cm^{-1} (C=O amide), 756 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.96 (t, 2H, H-3, *J* 7.0 Hz), 3.62 (app. q, 2H, H-4, *J* 7.0 Hz), 3.76 (s, 6H, H-8), 4.35 (s, 1H, H-6), 7.07 (d, 1H, H-1, *J* 1.0 Hz), 7.26 (d, 1H, H-13, *J* 8.5 Hz), 7.27 (dd, 1H, H-12, *J* 8.5 Hz, 1.5 Hz), 7.39 (br s, 1H, NH amide), 7.72 (d, 1H, H-10, *J* 1.5 Hz), 8.30 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.8 (C-3), 40.2 (C-4), 53.4 (C-8), 58.5 (C-6), 112.3 (C-2), 112.7 (2C, C-11, Ar-CH), 121.2 (C-10), 123.5 (C-1), 124.9 (Ar-CH), 129.1 (C-9), 134.9 (C-14), 161.9 (C-5), 166.0 (C-7); ***m/z*** (ES−) 395, 397 ($[M-H]^-$, 90%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{17}N_2O_5BrNa^+$) requires ***m/z*** 419.0213 & 421.0193, found ***m/z*** 419.0211 & 421.0192.

Preparation and characterisation of dimethyl {[2-(7-methyl-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 6c

Synthesised according to general procedure **F** on a 7.3 mmol scale of **14c** (2.00 g). The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 3:1 to 95:5 to give the title compound as a colourless crystalline solid (650 mg, 54% [92% brsm]).

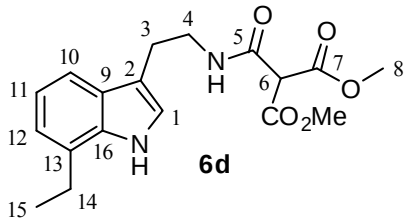


6c

m.p. 86-89 ºC; **FT-IR** ν_{max}(NaCl) 3385 cm^{-1} (N-H), 3313 cm^{-1} (N-H), 1739 cm^{-1} (C=O ester), 1664 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.49 (s, 3H, H-14), 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.65 (app. q, 2H, H-4, *J* 7.0 Hz), 3.76 (s, 6H, H-8), 4.35 (s, 1H, H-6), 7.00-7.10 (m, 3H, 3 × Ar-H), 7.31-7.38 (m, 1H, NH amide), 7.47 (d, 1H, Ar-H, *J* 7.5 Hz), 8.16 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.6 (C-14), 25.1 (C-3), 40.3 (C-4), 53.4 (C-8), 58.7 (C-6), 113.0 (C-2), 116.4 (Ar-CH), 119.7 (Ar-CH), 120.5 (C-13), 122.0 (C-1), 122.6 (C-11), 126.8 (C-9), 136.0 (C-15), 161.8 (C-5), 166.1 (C-7); ***m/z*** (ES−) 331 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2O_5Na^+$) requires ***m/z*** 355.1264, found ***m/z*** 355.1264.

Preparation and characterisation of dimethyl {[2-(7-ethyl-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 6d

Synthesised according to general procedure **F** on a 3.82 mmol scale of **14d** (1.1 g). The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 2:1 to 1:1 to give the title product as a pale yellow oil (0.44 g, 67% [91% brsm]).

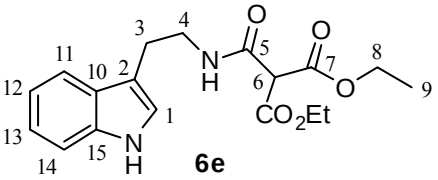


6d

FT-IR ν_{max}(NaCl) 3384 cm^{-1} (N-H), 3324 cm^{-1} (N-H), 1740 cm^{-1} (C=O ester), 1663 cm^{-1} (C=O amide), 752 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.37 (t, 3H, H-15, *J* 7.5 Hz), 2.87 (q, 2H, H-14, *J* 7.5 Hz), 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.65 (app q, 2H, H-4, *J* 7.0 Hz), 3.75 (s, 6H, H-8), 4.36 (s, 1H, H-6), 7.03-7.13 (m, 3H, H-1, H-11, Ar-H), 7.34 (br s, 1H, NH amide), 7.48 (d, 1H, Ar-H, *J* 8.0 Hz), 8.17 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-15), 23.9 (C-14), 25.0 (C-3), 40.2 (C-4), 53.3 (C-8), 58.7 (C-6), 113.0 (C-2), 116.3 (Ar-CH), 119.7 (Ar-CH), 120.6 (Ar-CH), 121.8 (Ar-CH), 126.6 (Ar-Cquat.), 126.9 (Ar-Cquat.), 135.2 (C-16), 161.8 (C-5), 166.0 (C-7); ***m/z*** (ES+) 369 ($[M+Na]^+$, 90%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2O_5Na^+$) requires ***m/z*** 369.1421, found ***m/z*** 369.1422.

Preparation and characterisation of diethyl {[2-(1*H*-indol-3-yl)ethyl]carbamoyl}malonate 6e

Synthesised according to general procedure **F** on a 10 mmol scale of **14e** (2.74 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 5:1 to 3:2 to give the title compound as a pale yellow oil (860 mg, 50%).



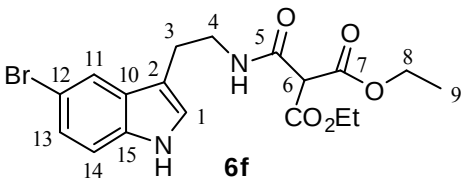
6e

FT-IR ν_{max}(NaCl) 3384 cm^{-1} (N-H), 3314 cm^{-1} (N-H), 1734 cm^{-1} (C=O ester), 1662 cm^{-1} (C=O amide), 746 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.26 (t, 6H, H-9, *J* 7.0 Hz), 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.65 (app. q, 2H, H-4, *J* 7.0 Hz), 4.22 (q, 4H, H-8, *J* 7.0 Hz), 4.32 (s, 1H, H-6), 7.06 (s, 1H, H-1), 7.13 (ddd, 1H, H-12, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.20 (ddd, 1H, H-13, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.35-7.43 (m, 2H, H-14, NH amide), 7.62 (d, 1H, H-11, *J* 8.0 Hz), 8.28 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-9), 24.9 (C-3), 40.2 (C-4), 59.1 (C-6), 62.5 (C-8), 111.2 (C-14), 112.5 (C-2), 118.6 (C-11), 119.3 (C-12), 122.0 (C-13), 122.2 (C-1), 127.2 (C-10), 136.3 (C-15), 162.1

(C-5), 165.6 (C-7); ***m/z*** (ES−) 345 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{18}H_{22}N_2O_5Na^+$) requires ***m/z*** 369.1421, found ***m/z*** 369.1421.

Preparation and characterisation of diethyl {[2-(5-bromo-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 6f

Synthesised according to general procedure **F** on a 5.7 mmol scale of **14f** (2.0 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether to give the title product as a pale yellow oil (510 mg, 42%).

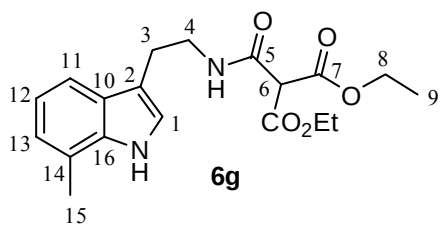


6f

FT-IR ν_{max}(NaCl) 3372 cm^{-1} (N-H), 3311 cm^{-1} (N-H), 1733 cm^{-1} (C=O ester), 1661 cm^{-1} (C=O amide), 755 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.26 (t, 6H, H-9, *J* 7.0 Hz), 2.95 (t, 2H, H-3, *J* 7.0 Hz), 3.61 (app. q, 2H, H-4, *J* 7.0 Hz), 4.21 (q, 4H, H-8, *J* 7.0 Hz), 4.31 (s, 1H, H-6), 7.06 (d, 1H, H-1, *J* 2.0 Hz), 7.23 (d, 1H, H-14, *J* 8.5 Hz), 7.25 (dd, 1H, H-13, *J* 8.5 Hz, 1.5 Hz), 7.44 (br s, 1H, NH amide), 7.71 (d, 1H, H-11, *J* 1.5 Hz), 8.43 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-9), 24.8 (C-3), 40.2 (C-4), 59.0 (C-6), 62.6 (C-8), 112.2 & 112.6 (C-2 & C-12), 112.7 (Ar-CH), 121.2 (C-11), 123.5 (C-1), 124.8 (Ar-CH), 129.0 (C-10), 134.9 (C-15), 162.2 (C-5), 165.6 (C-7); ***m/z*** (ES−) 423, 425 ([M−H]$^-$, 55%), 847, 849, 851 ([2M−H]$^-$, 50%, 100%, 50%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{18}H_{21}N_2O_5BrNa^+$) requires ***m/z*** 447.0526 & 449.0506, found ***m/z*** 447.0524 & 449.0504.

Preparation and characterisation of diethyl {[2-(7-methyl-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 6g

Synthesised according to general procedure **F** on a 7.2 mmol scale of **14g** (2.08 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether and then diethyl ether/ethyl acetate 4:1 to give the title compound as an off-white solid (1.0 g, 77%).

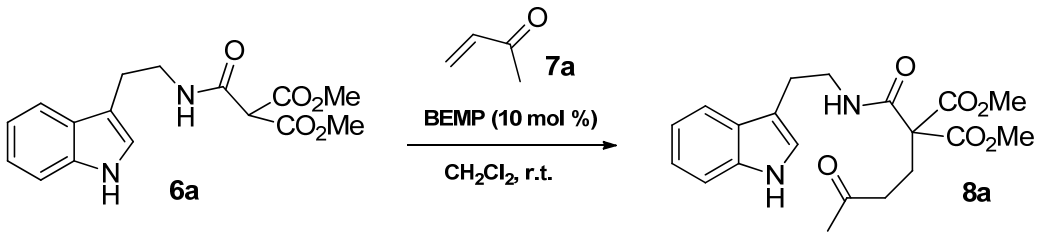


6g

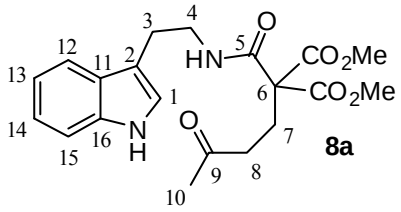
m.p. 83-87 ºC; **FT-IR** ν_{max}(NaCl) 3384 cm^{-1} (N-H), 3319 cm^{-1} (N-H), 1733 cm^{-1} (C=O ester), 1662 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.27 (t, 6H, H-9, *J* 7.0 Hz), 2.49 (s, 3H, H-15), 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.65 (app. q,

2H, H-4, *J* 7.0 Hz), 4.22 (q, 4H, H-8, *J* 7.0 Hz), 4.32 (s, 1H, H-6), 6.99-7.10 (m, 3H, 3 × Ar-H), 7.35-7.42 (m, 1H, NH amide), 7.48 (d, 1H, Ar-H, *J* 8.0 Hz), 8.17 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-9), 16.6 (C-15), 25.2 (C-3), 40.2 (C-4), 59.1 (C-6), 62.6 (C-8), 113.1 (C-2), 116.4 (Ar-CH), 119.6 (Ar-CH), 120.4 (C-14), 122.0 (C-1), 122.6 (C-12), 126.8 (C-10), 136.0 (C-16), 162.1 (C-5), 165.7 (C-7); ***m/z*** (ES−) 359 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{19}H_{24}N_2O_5Na^+$) requires ***m/z*** 383.1577, found ***m/z*** 383.1576.

2.3. Preparation and characterisation of dimethyl {[2-(1H-indol-3-yl)ethyl]carbamoyl}(3-oxobutyl)malonate 8a (substrate for optimisation)

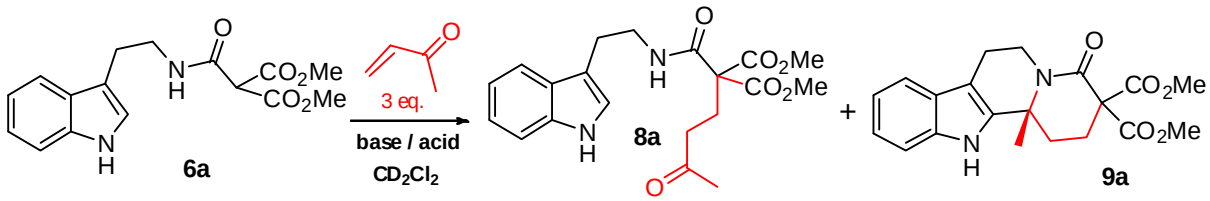


Pro-nucleophile **6a** (420 mg, 1.32 mmol, 1 equivalent) was dissolved in dichloromethane (5 mL) and stirred vigorously at room temperature. Liquid BEMP (45 µL, 0.16 mmol, 0.1 equivalents) was added to the solution immediately followed by the addition of MVK **7a** (0.41 mL, 4.90 mmol, 3 equivalents). The mixture was left stirring at room temperature for 16 hours (completion confirmed by TLC and LC-MS). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 4:1 to 1:2 to afford the title product as a colourless gum (420 mg, 82%).



FT-IR ν_{max}(NaCl) 3386 cm^{-1} (N-H), 3352 cm^{-1} (N-H), 1731 cm^{-1} (C=O ester), 1659 cm^{-1} (C=O amide), 749 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.99 (s, 3H, H-10), 2.39 (t, 2H, H-7, *J* 7.5 Hz), 3.49 (t, 2H, H-8, *J* 7.5 Hz), 3.06 (t, 2H, H-3, *J* 7.0 Hz), 3.68-3.77 (m, 8H, H-4, 2 × CO_2CH_3), 7.09 (s, 1H, H-1), 7.14 (t, 1H, H-13, *J* 7.5 Hz), 7.21 (t, 1H, H-14, *J* 7.5 Hz), 7.39 (d, 1H, H-15, *J* 8.0 Hz), 7.65 (d, 1H, H-12, *J* 8.0 Hz), 8.16 (t, 1H, NH amide), 8.88 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.7 (C-3), 28.1 (C-8), 29.4 (C-10), 38.2 (C-7), 39.8 (C-4), 53.0 (2 × CO_2CH_3), 62.8 (C-6), 111.1 (C-15), 111.8 (C-2), 118.3 (C-12), 118.9 (C-13), 121.6 (C-14), 122.2 (C-1), 127.0 (C-11), 136.2 (C-16), 165.6 (C-5), 168.9 (2 × CO_2CH_3), 206.7 (C-9); ***m/z*** (ES−) 387 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{20}H_{24}N_2O_6Na^+$) requires ***m/z*** 411.1527, found ***m/z*** 411.1527.

3. *Proof of principle for the site-isolated PS-BEMP and bulky BPA catalysed Michael addition/enantioselective N-acyliminium cyclisation cascade*



General procedure

tert-Butylbenzene (9.3 mg, 0.0694 mmol) was dissolved in 2.00 mL of CD_2Cl_2. 0.2 mL of this solution (0.0069 mmol, 0.069 eq.) were added to a solution of **6a** (31.8 mg, 0.1 mmol, 1 eq.) and (*R*)-**3** (5 mol %: 4.3 mg, 0.005 mmol; 10 mol %: 8.6 mg, 0.01 mmol; 20 mol % 17.3 mg, 0.02 mmol) in CD_2Cl_2 (0.5 mL) in an NMR tube at room temperature. PS-BEMP (4.5 mg, 0.01 mmol, 10 mol %) was added, immediately followed by the addition of MVK (27 µL, 0.3 mmol, 3 eq.) in one portion. The resulting mixture was stirred (600 rpm) at room temperature and the conversion of **6a** into **8a**/**9a** was monitored by NMR analysis. After full conversion of **6a**, the crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether.

Table 1. **Proof of principle for the site-isolated base and acid catalysed tandem Michael addition / enantioselective *N*-acyliminium cyclisation**

Entry	Base (10 mol %)	Acid[a]	Time	Yield of 8a (%)	Observation
1	PS-piperidine	–	24 h	N.R.	-
2	PS-BEMP	–	6 h	93	-
3	Liq. BEMP	–	2 h	89	-
4	–	DPP	24 h	N.R.	-
5	–	TPS-BPA	24 h	N.R.	-
6	Liq. BEMP	DPP	24 h	N.R.	-
7	Liq. BEMP	TPS-BPA	24 h	N.R.	-
8	PS-BEMP	DPP	24 h	N.R.	-
9	PS-BEMP	TPS-BPA[b]	13 h	91	< 1% of **9a**
10	PS-BEMP	TPS-BPA	57 h	88	3% of **9a**
11	PS-BEMP	TPS-BPA[c]	57 h	37 (79.5% conv. **6a**)	**8a**/**9a** ~ 2:1

[a] 10 mol % unless otherwise stated; [b] 5 mol %; [c] 20 mol %; N.R. = no reaction.

4. *Titration experiments*

Procedure for the titration of DPP

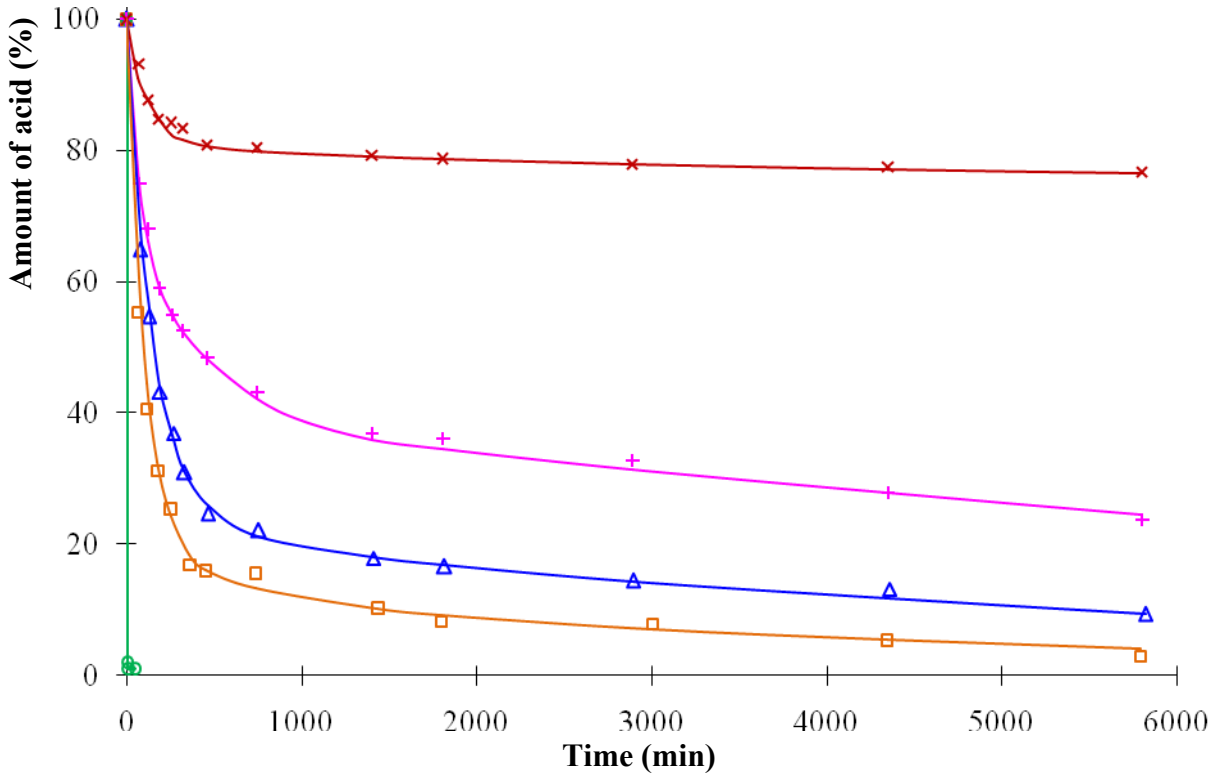
tert-Butylbenzene (3.1 mg, 0.0231 mmol) was dissolved in 5.00 mL of CD_2Cl_2. 0.2 mL of this solution were added to a solution of DPP (12.5 mg, 0.05 mmol in 0.5 mL of CD_2Cl_2) in an NMR tube

at room temperature, immediately followed by the addition of PS-BEMP (22.7 mg, 0.05 mmol) in one portion. The resulting mixture was stirred (600 rpm) at room temperature and the amount of acid in solution was monitored by NMR analysis and measured accurately against the internal standard (*tert*-butylbenzene).

Procedure for the titration of TPS BPA (R)-3

tert-Butylbenzene (2.1 mg) was dissolved in 5.00 mL of CD_2Cl_2. 0.5 mL of this solution were added to a solution of (*R*)-**3** (21.6 mg, 0.025 mmol in 0.2 mL of CD_2Cl_2) in an NMR tube at room temperature, immediately followed by the addition of PS-BEMP (0.5 eq.: 5.7 mg; 1 eq.: 11.4 mg; 2 eq.: 22.7 mg; 3 eq.: 34.1 mg) in one portion. The resulting mixture was stirred (600 rpm) at room temperature and the amount of acid was monitored by NMR analysis and measured against the internal standard (*tert*-butylbenzene).

Plots of the amount of acid in solution



Graph 1: **Titration of TPS BPA (*R*)-3 in the presence of PS-BEMP**

Red crosses × : 0.5 eq. of PS-BEMP; **Magenta crosses + :** 1 eq. of PS-BEMP; **Blue triangles Δ :** 2 eq. of PS-BEMP; **Orange squares □ :** 3 eq. of PS-BEMP.

5. *NMR conversions of 6[a] into 8[a] in the presence of 10 mol % of PS-BEMP and varying amounts of acid 3*

General procedures for the NMR experiments

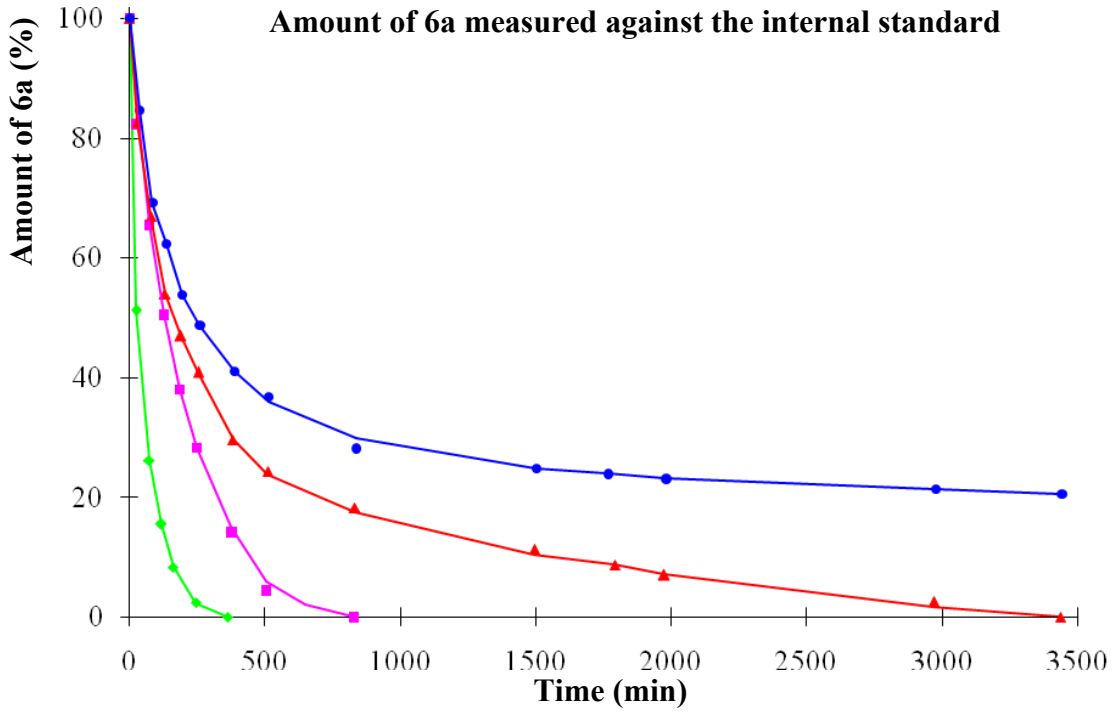
Experiment with 10 mol % of PS-BEMP and no acid

tert-Butylbenzene (5.6 mg) was dissolved in 2.00 mL of CD_2Cl_2. 0.6 mL of the above CD_2Cl_2 solution were added to a solution of **6a** (31.8 mg, 0.1 mmol, in 0.1 mL of CD_2Cl_2) in an NMR tube at room temperature. PS-BEMP (4.5 mg, 0.01 mmol) was added, immediately followed by the addition of MVK (27 µL, 0.3 mmol) in one portion. The resulting mixture was stirred (600 rpm) at room temperature and the conversion of **6a** into **8a** was monitored by NMR analysis and measured against the internal standard (*tert*-butylbenzene).

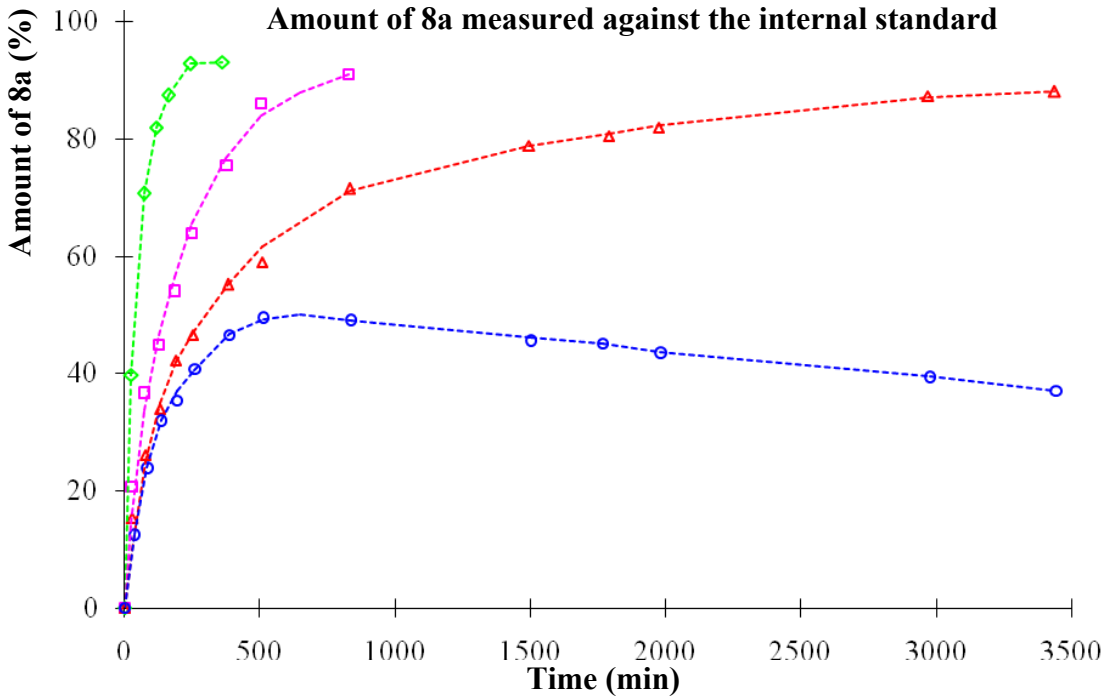
*Experiment with 10 mol % of PS-BEMP and 5 to 20 mol % of acid (R)-**3***

tert-Butylbenzene (9.3 mg, 0.0694 mmol) was dissolved in 2.00 mL of CD_2Cl_2. 0.2 mL of the above CD_2Cl_2 solution were added to a solution of **6a** (31.8 mg, 0.1 mmol in 0.5 mL of CD_2Cl_2) and (*R*)-**3** (5 mol %: 4.3 mg, 0.005 mmol; 10 mol %: 8.6 mg, 0.01 mmol; 20 mol % 17.3 mg, 0.02 mmol) in an NMR tube at room temperature. PS-BEMP (4.5 mg, 0.01 mmol) was added, immediately followed by the addition of MVK (27 µL, 0.3 mmol) in one portion. The resulting mixture was stirred (600 rpm) at room temperature and the conversion of **6a** into **8a** was monitored by NMR analysis and measured against the internal standard (*tert*-butylbenzene).

Plots of the conversion of 6a into 8a in the presence of 10 mol % of PS-BEMP and varying amounts of (R)-3

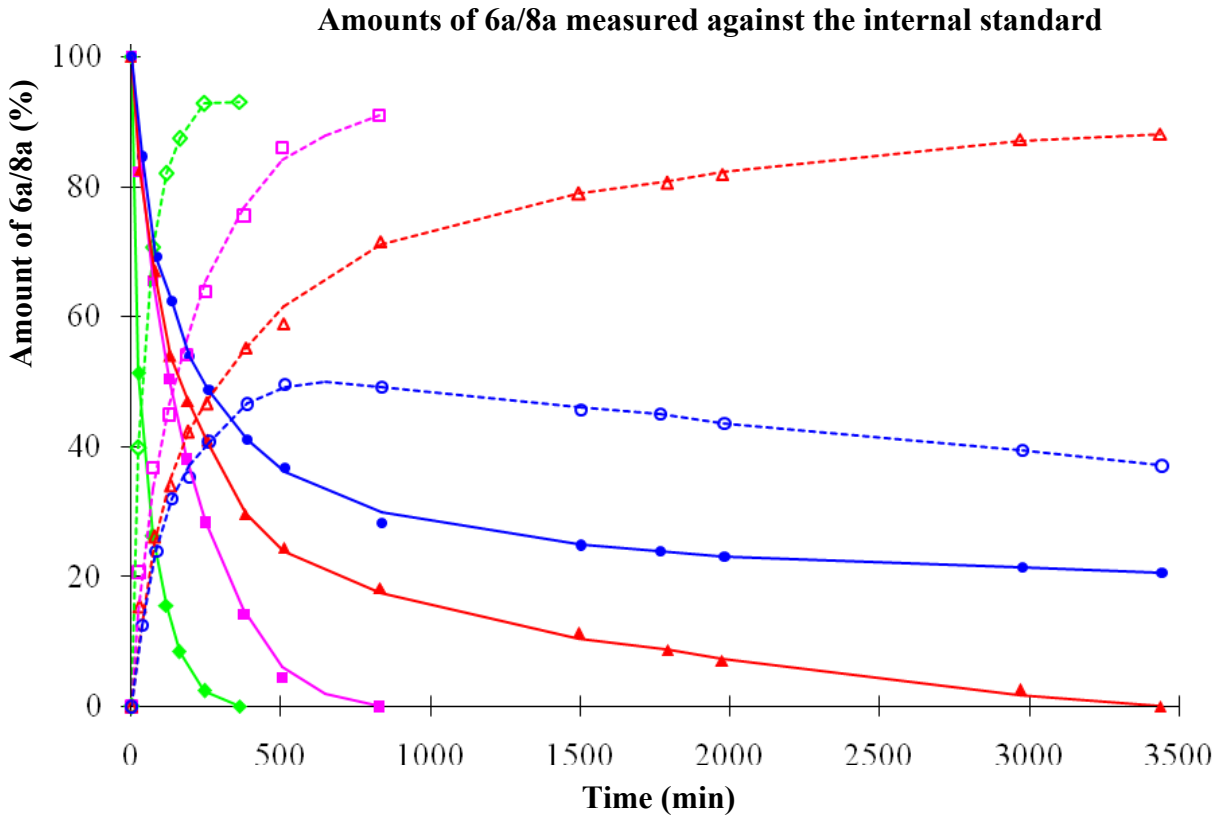


Graph 2: **^{1}H NMR Conversion of 6a -** **Green diamonds ♦** : no acid; **Magenta squares ■** : 5 mol % of (*R*)-**3**; Red triangles ▲: 10 mol % of (*R*)-**3**; **Blue circles ●** : 20 mol % of (*R*)-**3**;



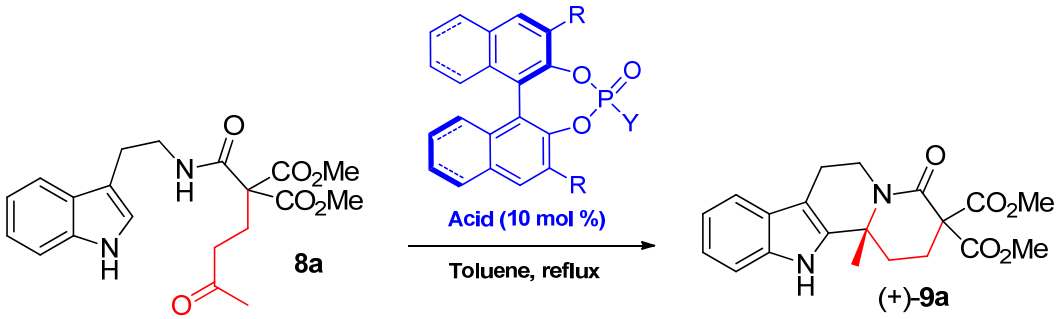
Graph 3: **Formation of 8a measured by ^{1}H NMR - Green diamonds ♦ :** no acid; **Magenta squares ■ :** 5 mol % of (*R*)-**3**; Red triangles ▲: 10 mol % of (*R*)-**3**; **Blue circles ● :** 20 mol % of (*R*)-**3**;

Superimposed disappearance of 6a / Formation of 8a



Graph 4: **Conversion of 6a into 8a measured by ^{1}H NMR - Filled markers** (solid curves): amount of **6a**; **Hollow markers** (dashed curves): amount of **8a**; **Green diamonds ♦ :** no acid; **Magenta squares ■ :** 5 mol % of (*R*)-**3**; **Red triangles ▲:** 10 mol % of (*R*)-**3**; **Blue circles ● :** 20 mol % of (*R*)-**3**;

6. Optimisation of the enantioselective N-acyliminium cyclisation



Procedure for the N-acyliminium cyclisation of 7a

8a (19.4 mg, 0.05 mmol, 1 equivalent) was dissolved in toluene (7 mL). The stirred mixture was heated to reflux and the catalyst (*R*)-**3**, (*R*)-**4** or (*R*)-**15** was added (0.01 mmol, 0.1 equivalents). The mixture was heated at reflux for 16-48 hours (completion monitored by TLC and LC-MS (ES+)). The

solvent was removed, the residue redissolved in the minimum amount of dichloromethane and the product purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1. The enantiomeric excess of the combined collected fractions was measured.

Table 2: **Optimisation of the enantioselective *N*-acyliminium cyclisation**

Entry	$[7a]_i$ (mM)	Acid	R / Y	Time	Yield (%)	e.e. (%)
1	7 mM	(*R*)-**3**	$SiPh_3$ / OH	12 h	99	52
2	7 mM	(*R*)-**4**	[H_8] $SiPh_3$ / OH	24 h	99	60
3	7 mM	(*R*)-**15a**	$SiEt_3$ / OH	65 h	76	35
4	7 mM	(*R*)-**15b**	$Si(^iPr)_3$ / OH	18 h	87	49
5	7 mM	(*R*)-**15c**	$SiPh_2{}^tBu$ / OH	48 h	81	38
6	7 mM	(*R*)-**15d**	$SiMe_2{}^tBu$ / OH	12 h	99	16
7	7 mM	(*R*)-**15e**	Si(*m*-xylyl)$_3$ / OH	48 h	99	27
8	7 mM	(*R*)-**15f**	3,5-$(CF_3)_2$Ph / OH	12 h	95	52
9	7 mM	(*R*)-**15g**	2,4,6-$(^iPr)_3$Ph / OH	16 h	92	58
10	7 mM	(*R*)-**15h**	[H_8] 2,4,6-$(^iPr)_3$Ph / OH	30 h	49	65
11	7 mM	(*R*)-**15i**	9-anthryl / OH	16 h	98	29
12	7 mM	(*R*)-**15j**	9-phenanthryl / OH	16 h	92	26
13	7 mM	(*R*)-**15k**	$SiPh_3$ / NHTf	16 h	99	45
14	5 mM	(*R*)-**4**	[H_8] $SiPh_3$ / OH	20 h	99	55
15	10 mM	(*R*)-**4**	[H_8] $SiPh_3$ / OH	8 h	99	55
16	17 mM	(*R*)-**4**	[H_8] $SiPh_3$ / OH	7 h	99	50

(*R*)-**3** and (*R*)-**15f** (3,5-$(CF_3)_2$Ph BPA) induced similar levels of enantioselectivity (52% e.e., entries 1 and 8). Interestingly, (*R*)-**15g** (TRIP BPA) slightly improved the enantioselectivity to 58% e.e. (entry 9). When H_8-BINOL derivative (*R*)-**4** was evaluated in the cyclisation, it enhanced the selectivity to 60% e.e. (entry 2). The H_8-BINOL-derived analogue (*R*)-**15h** of BPA (*R*)-**15g** was assessed and as expected it improved on the selectivity observed for the binaphthyl derivative (65% e.e. vs. 58% e.e., entries 10 and 9 respectively). The influence of the concentration was also studied and as observed in our previous studies, the optimal concentration was found to be 7 mM (60% e.e. with (*R*)-**4**, entry 2) and the selectivities were diminished at higher or lower dilution (entries 14-16).[5,8]

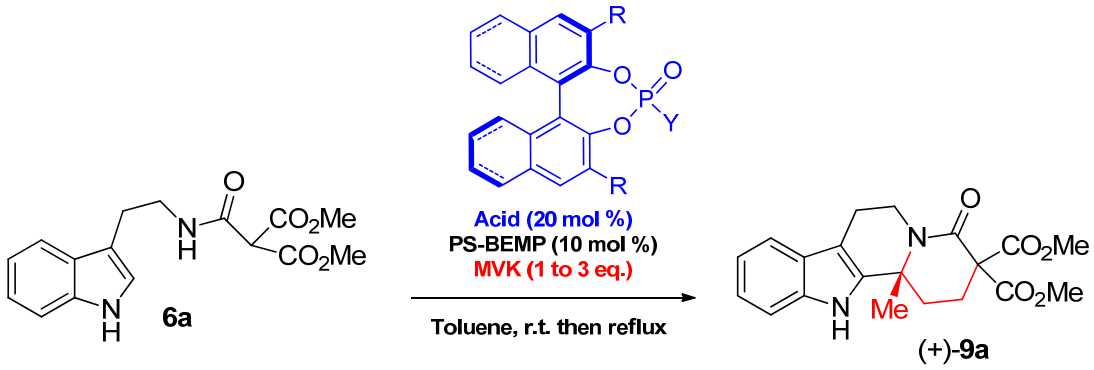
7. Optimisation of the base and acid catalysed tandem Michael addition / enantioselective N-acyliminium cyclisation of 6a into 9a

General procedure

6a (31.8 mg, 0.1 mmol, 1 equivalent), PS-BEMP **1a** (4.5 mg, 0.01 mmol, 0.1 eq.) and catalyst (*R*)-**3**, (*R*)-**4** or (*R*)-**15** (0.2 eq.) were placed in a dry RB-flask and toluene (14 mL) was added. The mixture

was stirred at r.t. and MVK **7a** (0.15-0.3 mmol, 1.5 to 3 eq.) was added. The mixture was stirred at room temperature (time indicated in Table 3). It was then heated at reflux (time indicated in Table 3). The solvent was removed, the residue redissolved in the minimum amount of dichloromethane and the product purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1.

Table 3: **Optimisation of the base and acid catalysed tandem Michael addition / enantioselective *N*-acyliminium cyclisation of 6a ino (+)-9a**

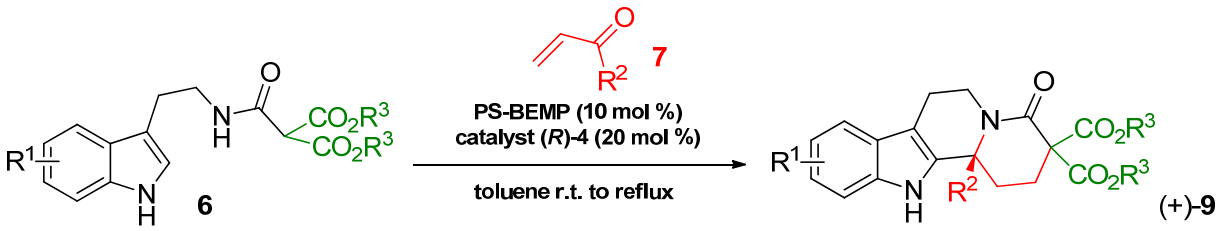


Entry	MVK	Acid	R / Y	Time (r.t.)	Time (reflux)	Yield	e.e.
1	1.5 eq.	(*R*)-**3**	$SiPh_3$ / OH	16 h	36 h	25%	51%
2	2 eq.	(*R*)-**3**	$SiPh_3$ / OH	48 h	12 h	90%	43%
3	3 eq.	(*R*)-**3**	$SiPh_3$ / OH	17 h	20 h	78%	49%
4	3 eq.	(*R*)-**15h**	[H_8] 2,4,6-$(iPr)_3$Ph / OH	20 h	48 h	N. O.	-
5	3 eq.	(*R*)-**4**	[H_8] $SiPh_3$ / OH	24 h	24 h	81%	57%

N.O. = Not observed.

Our initial attempt to perform a one-pot cascade using 1.5 eq. of MVK resulted in the isolation of a moderate yield of desired product with a pleasing 51% ee (25% yield, entry 1). To improve the reactivity (the rate of the Michael addition), larger amounts of MVK were used and with 3 equivalents of the Michael acceptor, the reaction proceeded in high yield and good enantioselectivity (entry 3). When **6a** was treated with the previously identified optimal catalyst and under the optimal conditions found for the cascade, we observed that (*R*)-**15h** failed to provide the desired reactivity, however (*R*)-**4** participated in the dual catalysis to yield (+)-**9a** in a pleasing 81% yield and an improved 57% ee (entry 5). The latter conditions were used to probe the scope of the cascade.

8. *General procedure G for the base-catalysed Michael addition / acid-catalysed enantioselective N-acyliminium cyclisation cascade*



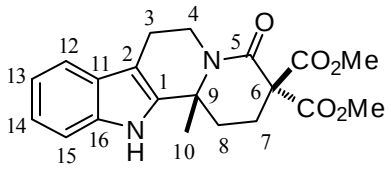
Pro-nucleophile **6** (0.2 mmol, 1 equivalent), PS-BEMP **1a** (0.02 mmol, 0.1 equivalents, 9.0 mg) and catalyst (*R*)-**4** (0.04 mmol, 0.2 equivalents, 34.9 mg) were placed in a dry flask and dry toluene (28 mL) was added immediately followed by the addition of vinyl ketone **7** (0.6 mmol, 3 equivalents) in one portion. The resulting suspension was stirred at room temperature until full conversion to the Michael adduct (**8**) (LC-MS (ES+) monitoring). The mixture was then heated at reflux until full conversion to the tetracycle **9** (monitoring by LC-MS and TLC). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel.

Note: All racemates were prepared in a one pot procedure using BEMP (0.1 equivalents) followed by addition of *para*-toluenesulphonic acid (0.2 equivalents) when the Michael addition was complete.

Preparation and characterisation of dimethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9a

Prepared according to general procedure **G**. Stirred at room temperature for 17 hours then heated at reflux in toluene for 36 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1 to afford the title product as an off-white solid (56 mg, 76%).

56% e.e. (Chiralcel OD, 85:15 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 16.7 min, minor t_R = 13.7 min); $[\alpha]_D^{25}$ = + 53.0 (*c* 1.0, $CHCl_3$).



(+)-**9a**

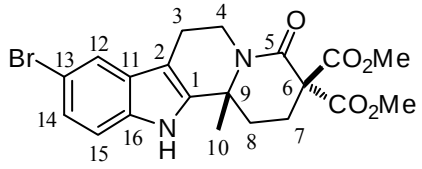
m.p. 232-237 ºC; **FT-IR** ν_{max}(NaCl) 3305 cm^{-1} (N-H), 1748 cm^{-1} (C=O ester), 1735 cm^{-1} (C=O ester), 1628 cm^{-1} (C=O amide), 749 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.73 (s, 3H, H-10), 2.00 (ddd, 1H, H-8a, *J* 14.0 Hz, 12.0 Hz, 3.0 Hz), 2.20 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.55 (ddd, 1H, H-7a, *J* 14.0 Hz, 6.0 Hz, 3.5 Hz), 2.65 (ddd, 1H, H-7b, *J* 13.5 Hz, 12.0 Hz, 3.0 Hz), 2.76 (ddd, 1H, H-3a, *J*

15.5 Hz, 4.5 Hz, 1.5 Hz), 2.87 (ddd, 1H, H-3b, *J* 15.5 Hz, 11.5 Hz, 5.5 Hz), 3.12 (ddd, 1H, H-4a, *J* 12.5 Hz, 11.5 Hz, 4.5 Hz), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 5.09 (ddd, 1H, H-4b, *J* 12.5 Hz, 5.0 Hz, 1.0 Hz), 7.14 (app. td, 1H, H-13, *J* 7.5 Hz, 1.0 Hz), 7.21 (app. td, 1H, H-14, *J* 7.5 Hz, 1.5 Hz), 7.35 (d, 1H, H-15, *J* 8.0 Hz), 7.51 (d, 1H, H-12, *J* 7.5 Hz), 7.79 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$:d_4-MeOD 19:1, 100 MHz) δ_C 21.0 (C-3), 25.0 (C-8), 26.5 (C-10), 31.7 (C-7), 37.6 (C-4), 53.2 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 57.7 (C-9), 63.5 (C-6), 107.4 (C-2), 111.0 (C-15), 118.1 (C-12), 119.2 (C-13), 121.7 (C-14), 126.3 (C-11), 136.3 (C-1), 137.4 (C-16), 163.4 (C-5), 168.4 ($\underline{C}O_2Me$), 168.7 ($\underline{C}O_2Me$); ***m/z*** (ES−) 369 ($[M-H]^-$, 80%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{22}N_2O_5Na^+$) requires ***m/z*** 393.1421, found ***m/z*** 393.1420.

Preparation and characterisation of dimethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9b

Prepared according to general procedure **G**. Stirred at room temperature for 48 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1 to afford the title product as an off-white solid (71 mg, 79%).

77% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 14.1 min, minor t_R = 43.8 min); $[\alpha]_D^{25} = +41.1$ (*c* 1.20, $CHCl_3$).



(+)-**9b**

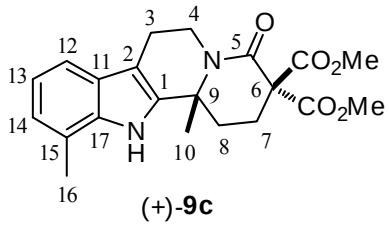
m.p. 241-247 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3291 cm^{-1} (N-H), 1748 cm^{-1} (C=O ester), 1735 cm^{-1} (C=O ester), 1628 cm^{-1} (C=O amide), 756 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.69 (s, 3H, H-10), 1.96 (ddd, 1H, H-8a, *J* 14.5 Hz, 12.5 Hz, 3.0 Hz), 2.25 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.49 (ddd, 1H, H-7a, *J* 14.0 Hz, 6.0 Hz, 3.5 Hz), 2.60 (app. td, 1H, H-7b, *J* 13.0 Hz, 3.0 Hz), 2.68 (dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.79 (ddd, 1H, H-3b, *J* 17.0 Hz, 11.5 Hz, 5.0 Hz), 3.08 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.0 Hz), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 3.80 (s, 3H, $CO_2C\underline{H}_3$), 5.02 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.17 (d, 1H, H-15, *J* 8.5 Hz), 7.21 (dd, 1H, H-14, *J* 8.5 Hz, 1.5 Hz), 7.57 (d, 1H, H-12, *J* 1.5 Hz), 9.28 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.9 (C-3), 25.9 (C-7), 26.7 (C-10), 31.8 (C-8), 37.5 (C-4), 53.3 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 57.5 (C-9), 63.5 (C-6), 107.5 (C-2), 112.5 (C-15), 112.6 (C-13), 120.9 (C-12), 124.6 (C-14), 128.2 (C-11), 134.8 (C-16), 138.6 (C-1), 163.3 (C-5), 168.4 (CO_2Me), 168.6 (CO_2Me); ***m/z*** (ES+) 471, 473 ($[M+Na]^+$, 100%), **HRMS** (ES+)

exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}N_2O_5Br^+$) requires ***m/z*** 449.0707 & 451.0687, found ***m/z*** 449.0703 & 451.0686.

Preparation and characterisation of dimethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9c

Prepared according to general procedure **G**. Stirred at room temperature for 12 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as an off-white solid (69 mg, 90%).

66% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 31.6 min, minor t_R = 25.6 min); $[\alpha]_D^{25}$ = + 56.5 (*c* 1.15, $CHCl_3$).



(+)-**9c**

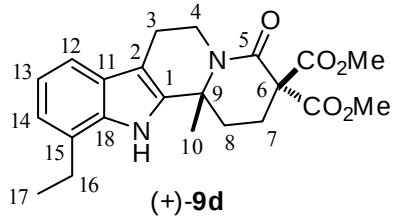
m.p. 216-223 ºC; **FT-IR** ν_{max}(NaCl) 3321 cm^{-1} (N-H), 1736 cm^{-1} (2 signals with a shoulder, 2 × C=O ester), 1629 cm^{-1} (C=O amide), 750 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$:d_4-MeOD 9:1, 500 MHz) δ_H 1.77 (s, 3H, H-10), 2.02-2.11 (m, 1H, H-7a), 2.31-2.40 (m, 1H, H-7b), 2.50 (s, 3H, H-16), 2.56 (ddd, 1H, H-8a, *J* 13.5 Hz, 9.0 Hz, 3.0 Hz), 2.67 (app. td, 1H, H-8b, *J* 13.0 Hz, 2.5 Hz), 2.77 (dd, 1H, H-3a, *J* 16.0 Hz, 4.0 Hz), 2.89 (ddd, 1H, H-3b, *J* 16.0 Hz, 12.5 Hz, 5.5 Hz), 3.16 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.0 Hz), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.83 (s, 3H, $CO_2C\underline{H}_3$), 5.10 (dd, 1H, H-4b, *J* 12.5 Hz, 5.5 Hz), 7.02 (d, 1H, H-14, *J* 7.0 Hz), 7.08 (app. t, 1H, H-13, *J* 7.5 Hz), 7.37 (d, 1H, H-12, *J* 7.5 Hz), 8.39 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$:d_4-MeOD 9:1, 125 MHz) δ_C 16.6 (C-16), 21.2 (C-3), 25.2 (C-8), 26.9 (C-10), 31.9 (C-7), 37.5 (C-4), 53.2 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 57.6 (C-9), 63.5 (C-6), 108.7 (C-2), 115.9 (C-12), 119.9 (C-13), 120.4 (C-15), 122.8 (C-14), 126.1 (C-11), 135.6 (C-17), 137.0 (C-1), 163.2 (C-5), 168.4 ($\underline{C}O_2Me$), 168.6 ($\underline{C}O_2Me$); ***m/z*** (ES+) 407 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2O_5Na^+$) requires ***m/z*** 407.1577, found ***m/z*** 407.1577.

Preparation and characterisation of dimethyl (12b*R*)-11-ethyl-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9d

Prepared according to general procedure **G**. Stirred at room temperature for 24 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica

gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as a pale yellow gum (50 mg, 63%).

68% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 23.1 min, minor t_R = 18.7 min); $[\alpha]_D^{25}$ = + 78.3 (*c* 1.50, $CHCl_3$).

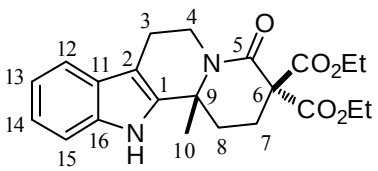


(+)-**9d**

FT-IR ν_{max}(NaCl) 3325 cm^{-1} (N-H), 1749 cm^{-1} (C=O ester), 1736 cm^{-1} (C=O ester), 1630 cm^{-1} (C=O amide), 752 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.37 (t, 3H, H-17, *J* 7.5 Hz), 1.75 (s, 3H, H-10), 2.02 (app. td, 1H, H-8a, *J* 14.0 Hz, 3.0 Hz), 2.30 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.56 (ddd, 1H, H-7a, *J* 14.0 Hz, 6.0 Hz, 3.5 Hz), 2.66 (ddd, 1H, H-7b, *J* 13.5 Hz, 12.5 Hz, 3.0 Hz), 2.76 (dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.82-2.92 (m, 3H, H-3b, H-16), 3.13 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 5.09 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.06 (d, 1H, H-12, *J* 7.5 Hz), 7.11 (t, 1H, H-13, *J* 7.5 Hz), 7.37 (d, 1H, H-14, *J* 7.5 Hz), 8.01 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-17), 21.3 (C-3), 23.9 (C-16), 25.2 (C-7), 27.0 (C-10), 32.2 (C-8), 37.6 (C-4), 53.4 ($CO_2\underline{C}H_3$), 53.5 ($CO_2\underline{C}H_3$), 57.6 (C-9), 63.6 (C-6), 109.1 (C-2), 116.2 (Ar-<u>C</u>H), 120.3 (C-13), 120.9 (Ar-<u>C</u>H), 126.3 (Ar-Cquat.), 126.5 (Ar-Cquat.), 134.9 (Ar-Cquat.), 136.9 (Ar-Cquat.), 163.2 (C-5), 168.5 ($\underline{C}O_2Me$), 168.7 ($\underline{C}O_2Me$); ***m/z*** (ES+) 421 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_5Na^+$) requires ***m/z*** 421.1734, found ***m/z*** 421.1734.

Preparation and characterisation of diethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9e

Prepared according to general procedure **G**. Stirred at room temperature for 17 hours then heated at reflux in toluene for 46 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as an off-white solid (69 mg, 86%).



(+)-**9e**

67% e.e. (Chiralcel IA, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 26.3 min, minor t_R = 46.5 min); $[\alpha]_D^{25}$ = + 62.4 (*c* 1.76, $CHCl_3$).

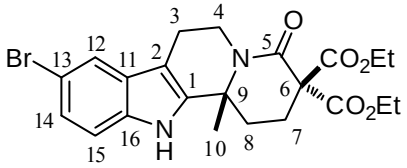
m.p. 93-98 ºC; **FT-IR** ν_{max}(NaCl) 3303 cm^{-1} (N-H), 1745 cm^{-1}

(C=O ester), 1731 cm^{-1} (C=O ester), 1629 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.17 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.5 Hz), 1.32 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.5 Hz), 1.73 (s, 3H, H-10), 2.01 (app. td, 1H, H-8a, *J* 14.0 Hz, 3.0 Hz), 2.25 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.53 (ddd, 1H, H-7a, *J* 13.5 Hz, 5.5 Hz, 3.0 Hz), 2.65 (app. td, 1H, H-7b, *J* 13.0 Hz, 3.0 Hz), 2.76 (ddd, 1H, H-3a, *J* 15.5 Hz, 4.0 Hz, 1.5 Hz), 2.87 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 5.5 Hz), 3.12 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 4.13-4.38 (m, 4H, 2 × $CO_2C\underline{H}_2CH_3$), 5.10 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.13 (app. td, 1H, H-13, *J* 8.0 Hz, 1.0 Hz), 7.20 (app. td, 1H, H-14, *J* 8.0 Hz, 1.0 Hz), 7.34 (d, 1H, H-15, *J* 8.0 Hz), 7.50 (d, 1H, H-12, *J* 8.0 Hz), 8.02 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 ($CO_2CH_2\underline{C}H_3$), 13.9 ($CO_2CH_2\underline{C}H_3$), 21.2 (C-3), 25.1 (C-7), 26.9 (C-10), 32.0 (C-8), 37.6 (C-4), 57.5 (C-9), 62.3 ($CO_2\underline{C}H_2CH_3$), 62.4 ($CO_2\underline{C}H_2CH_3$), 63.6 (C-6), 108.2 (C-2), 111.1 (C-15), 118.4 (C-12), 119.7 (C-13), 122.1 (C-14), 126.6 (C-11), 136.1 (C-16), 137.4 (C-1), 163.5 (C-5), 168.0 ($\underline{C}O_2Et$), 168.2 ($\underline{C}O_2Et$); ***m/z*** (ES−) 397 ($[M-H]^-$, 80%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{27}N_2O_5^+$) requires ***m/z*** 399.1914, found ***m/z*** 399.1913.

Characterisation of diethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9f

Prepared according to general procedure **G**. Stirred at room temperature for 31 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as an off-white solid (86 mg, 90%).

82% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 30.3 min, minor t_R = 19.9 min); $[\alpha]_D^{25} = +43.5$ (*c* 1.08, $CHCl_3$).



(+)-**9f**

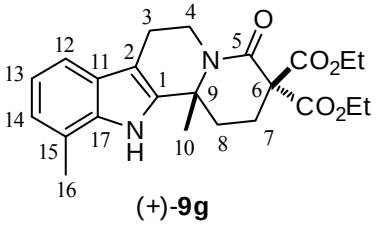
m.p. 186-190 ºC; **FT-IR** ν_{max}(NaCl) 3287 cm^{-1} (N-H), 1731 cm^{-1} (2 signals with shoulder, CO_2Me), 1628 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.16 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.30 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.74 (s, 3H, H-10), 1.94-2.04 (m, 1H, H-7a), 2.24-2.33 (m. 1H, H-7b), 2.52 (ddd, 1H, H-8a, *J* 13.5 Hz, 5.5 Hz, 3.0 Hz), 2.60-2.73 (m, 2H, H-3a, H-8b), 2.81 (ddd, 1H, H-3b, *J* 16.0 Hz, 12.0 Hz, 5.5 Hz), 3.05-3.15 (m, 1H, H-4a), 4.13-4.35 (m, 4H, 2 × $CO_2C\underline{H}_2CH_3$), 5.07 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.18-7.27 (m, 2H, H-14, H-15), 7.60 (s, 1H, H-12), 8.76 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 & 13.9 (2 × $CO_2CH_2\underline{C}H_3$), 21.0 (C-3), 25.0 (C-8), 26.9 (C-10), 32.0 (C-7),

37.5 (C-4), 57.4 (C-9), 62.4 (2 signals, 2 × $CO_2C\underline{H}_2CH_3$), 63.6 (C-6), 108.0 (C-2), 112.6 (C-14), 112.9 (C-13), 121.1 (C-12), 124.9 (C-15), 128.4 (C-11), 134.8 (C-16), 138.7 (C-1), 163.5 (C-5), 167.9 ($\underline{C}O_2Et$), 168.1 ($\underline{C}O_2Et$); ***m/z*** (ES−) 475, 477 ($[M-H]^-$, 20%), 511, 513 ($[M+Cl]^-$, 40%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{25}N_2O_5BrNa^+$) requires ***m/z*** 499.0839 & 501.0820, found ***m/z*** 499.0836 & 501.0814.

Characterisation of diethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9g

Prepared according to general procedure **G**. Stirred at room temperature for 20 hours then heated at reflux in toluene for 60 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:1 to afford the title product as an off-white solid (69 mg, 83%).

62% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 19.6 min, minor t_R = 26.0 min); $[\alpha]_D^{25}$ = + 71.3 (*c* 2.23, $CHCl_3$).



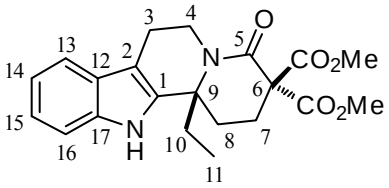
(+)-**9g**

m.p. 101-106 ºC; **FT-IR** ν_{max}(NaCl) 3318 cm^{-1} (N-H), 1744 cm^{-1} (C=O ester), 1732 cm^{-1} (C=O ester), 1630 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.18 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.32 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.75 (s, 3H, H-10), 1.97-2.10 (m, 1H, H-8a), 2.32 (ddd, 1H, H-8b, *J* 14.0 Hz, 5.5 Hz, 2.5 Hz), 2.46-2.59 (m, 4H, H-16, H-7a), 2.66 (app. td, 1H, H-7b, *J* 13.5 Hz, 2.5 Hz), 2.75 (app. dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.86 (ddd, 1H, H-3b, *J* 16.5 Hz, 11.5 Hz, 5.0 Hz), 3.12 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.0 Hz), 4.15-4.38 (m, 4H, 2 × $CO_2C\underline{H}_2CH_3$), 5.09 (dd, 1H, H-4b, *J* 12.5 Hz, 4.5 Hz), 7.00 (d, 1H, H-14, *J* 7.0 Hz), 7.07 (app. t, 1H, H-13, *J* 7.0 Hz), 7.36 (d, 1H, H-12, *J* 7.5 Hz), 8.11 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 ($CO_2CH_2\underline{C}H_3$), 13.9 ($CO_2CH_2\underline{C}H_3$), 16.7 (C-16), 21.2 (C-3), 25.1 (C-7), 27.0 (C-10), 32.1 (C-8), 37.5 (C-4), 57.5 (C-9), 62.2 ($CO_2\underline{C}H_2CH_3$), 62.3 ($CO_2\underline{C}H_2CH_3$), 63.6 (C-6), 108.9 (C-2), 116.1 (C-12), 120.0 (C-13), 120.2 (C-15), 122.8 (C-14), 126.2 (C-11), 135.6 (C-17), 137.1 (C-1), 163.4 (C-5), 167.9 ($\underline{C}O_2Et$), 168.2 ($\underline{C}O_2Et$); ***m/z*** (ES−) 411 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{29}N_2O_5^+$) requires ***m/z*** 413.2071, found ***m/z*** 413.2074.

Characterisation of dimethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9h

Prepared according to general procedure **G**. Remark: xylene was used as solvent instead of toluene.

Stirred at room temperature for 48 hours then heated at reflux in xylene for 7 days. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as a pale yellow oil (64 mg, 83%).



(+)-**9h**

71% e.e. (Chiralcel IA, 85:15 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 12.6 min, minor t_R = 21.6 min); $[\alpha]_D^{25}$ = + 78.9 (*c* 0.96, $CHCl_3$).

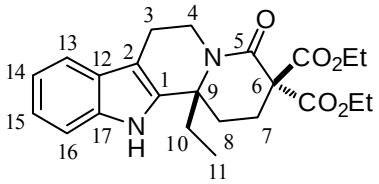
FT-IR ν_{max}(NaCl) 3308 cm^{-1} (N-H), 1749 cm^{-1} (C=O ester), 1737 cm^{-1} (C=O ester), 1628 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.99 (t, 3H, H-11, *J* 7.5 Hz), 1.96-2.14 (m, 3H, H-8a, H-10), 2.22 (ddd, 1H, H-8b, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.32 (ddd, 1H, H-7a, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.51 (ddd, 1H, H-7b, *J* 13.5 Hz, 8.0 Hz, 3.0 Hz), 2.73 (dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.97 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.20 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.72 (s, 3H, CO_2CH_3), 3.86 (s, 3H, CO_2CH_3), 5.01 (dd, 1H, H-4b, *J* 13.0 Hz, 5.0 Hz), 7.13 (app. td, 1H, H-14, *J* 7.5 Hz, 1.0 Hz), 7.20 (app. td, 1H, H-15, *J* 7.5 Hz, 1.0 Hz), 7.35 (d, 1H, H-16, *J* 8.0 Hz), 7.51 (d, 1H, H-13, *J* 8.0 Hz), 8.15 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 8.7 (C-11), 20.8 (C-3), 25.0 (C-7), 27.8 (C-8), 33.4 (C-10), 37.4 (C-4), 53.3 (CO_2CH_3), 53.3 (CO_2CH_3), 61.3 (C-9), 63.8 (C-6), 109.3 (C-2), 111.0 (C-16), 118.4 (C-13), 119.8 (C-14), 122.2 (C-15), 126.9 (C-12), 135.1 (C-17), 136.5 (C-1), 164.4 (C-5), 168.3 (CO_2Me), 168.7 (CO_2Me); ***m/z*** (ES−) 383 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2O_5Na^+$) requires ***m/z*** 407.1577, found ***m/z*** 407.1576.

Characterisation of diethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9i

Prepared according to general procedure **G**. Remark: xylene was used as solvent instead of toluene.

Stirred at room temperature for 48 hours then heated at reflux in xylene for 4 days. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 2:1 to afford the title product as a pale yellow oil (60 mg, 73%).

76% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 8.1 min, minor t_R = 18.8 min); $[\alpha]_D^{25}$ = + 86.6 (*c* 1.12, $CHCl_3$).



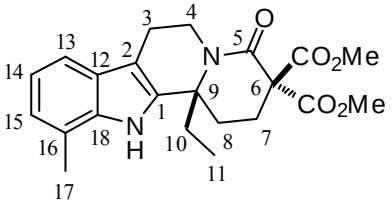
(+)-**9i**

FT-IR ν_{max}(NaCl) 3308 cm^{-1} (N-H), 1746 cm^{-1} (C=O ester), 1733 cm^{-1} (C=O ester), 1629 cm^{-1} (C=O amide), 748 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.00 (t, 3H, H-11, *J* 7.5 Hz), 1.19 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.34 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.94-2.13 (m, 3H, H-8a, H-10), 2.23 (ddd, 1H, H-8b, *J* 13.0 Hz, 10.0 Hz, 3.0 Hz), 2.31 (ddd, 1H, H-7a, *J* 13.0 Hz, 10.0 Hz, 3.0 Hz), 2.51 (ddd, 1H, H-7b, *J* 13.0 Hz, 8.5 Hz, 3.0 Hz), 2.72 (app. dd, 1H, H-3a, *J* 15.5 Hz, 4.0 Hz), 2.95 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.18 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 4.14-4.22 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.30-4.36 (m, 2H, $CO_2C\underline{H}_2CH_3$), 5.02 (dd, 1H, H-4b, *J* 13.0 Hz, 5.0 Hz), 7.13 (app. td, 1H, H-14, *J* 7.5 Hz, 1.0 Hz), 7.20 (app. td, 1H, H-15, *J* 7.5 Hz, 1.0 Hz), 7.34 (d, 1H, H-16, *J* 8.0 Hz), 7.50 (d, 1H, H-13, *J* 8.0 Hz), 7.87 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 8.9 (C-11), 13.8 ($CO_2CH_2\underline{C}H_3$), 14.0 ($CO_2CH_2\underline{C}H_3$), 20.8 (C-3), 24.9 (C-7), 28.0 (C-8), 33.5 (C-10), 37.4 (C-4), 61.1 (C-9), 62.3 ($CO_2\underline{C}H_2CH_3$), 62.4 ($CO_2\underline{C}H_2CH_3$), 63.8 (C-6), 109.5 (C-2), 110.9 (C-16), 118.4 (C-13), 119.8 (C-14), 122.2 (C-15), 126.9 (C-12), 135.8 (C-17), 136.6 (C-1), 164.4 (C-5), 167.8 ($\underline{C}O_2Et$), 168.3 ($\underline{C}O_2Et$); ***m/z*** (ES−) 411 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{23}H_{28}N_2O_5Na^+$) requires ***m/z*** 435.1890, found ***m/z*** 435.1891.

Characterisation of dimethyl (12b*R*)-12b-ethyl-11-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-9j

Prepared according to general procedure **G**. Remark: xylene was used as solvent instead of toluene.

Stirred at room temperature for 48 hours then heated at reflux in xylene for 10 days. The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as a pale yellow oil (48 mg, 60%).



(+)-**9j**

75% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 7.8 min, minor t_R = 12.5 min); $[\alpha]_D^{25}$ = + 112.4 (*c* 1.40, $CHCl_3$).

FT-IR ν_{max}(NaCl) 3327 cm^{-1} (N-H), 1748 cm^{-1} (C=O ester), 1737 cm^{-1} (C=O ester), 1629 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H

OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.00 (t, 3H, H-11, *J* 7.5 Hz), 1.99 (dq, 1H, H-10a, *J* 14.5 Hz, 7.5 Hz), 2.06-3.14 (m, 2H, H-8a, H-10b), 2.23 (ddd, 1H, H-8b, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.32 (ddd, 1H, H-7a, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.47-2.55 (m, 4H, H-7b, H-17), 2.71 (dd, 1H, H-3a, *J* 15.5 Hz, 4.0 Hz), 2.97 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.18 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 3.87 (s, 3H, $CO_2C\underline{H}_3$), 5.01 (dd, 1H, H-4b, *J* 13.0 Hz, 5.5 Hz), 7.02 (d, 1H, H-15, *J* 7.5 Hz), 7.07 (t, 1H, H-14, *J* 7.5 Hz), 7.36 (d, 1H, H-13, *J* 8.0 Hz), 7.65 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 8.7 (C-11), 16.7 (C-17), 20.9 (C-3), 25.0 (C-7), 27.9 (C-8), 33.5 (C-10), 37.4 (C-4), 53.3 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 61.3 (C-9), 63.8 (C-6), 110.1 (C-2), 116.1 (C-13), 120.1 (2C, C-14, C-16), 123.0 (C-15), 126.5 (C-12), 135.3 (C-18), 136.2 (C-1), 164.3 (C-5), 168.3 ($\underline{C}O_2Me$), 168.7 ($\underline{C}O_2Me$); ***m/z*** (ES−) 397 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_5Na^+$) requires ***m/z*** 421.1734, found ***m/z*** 421.1727.

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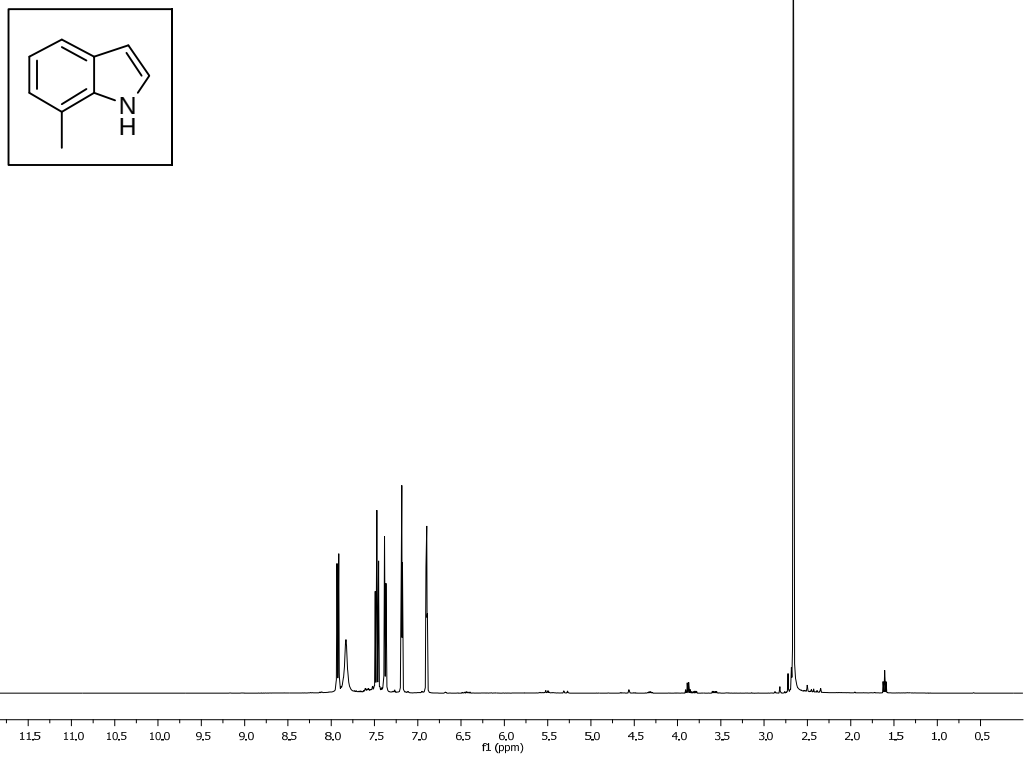
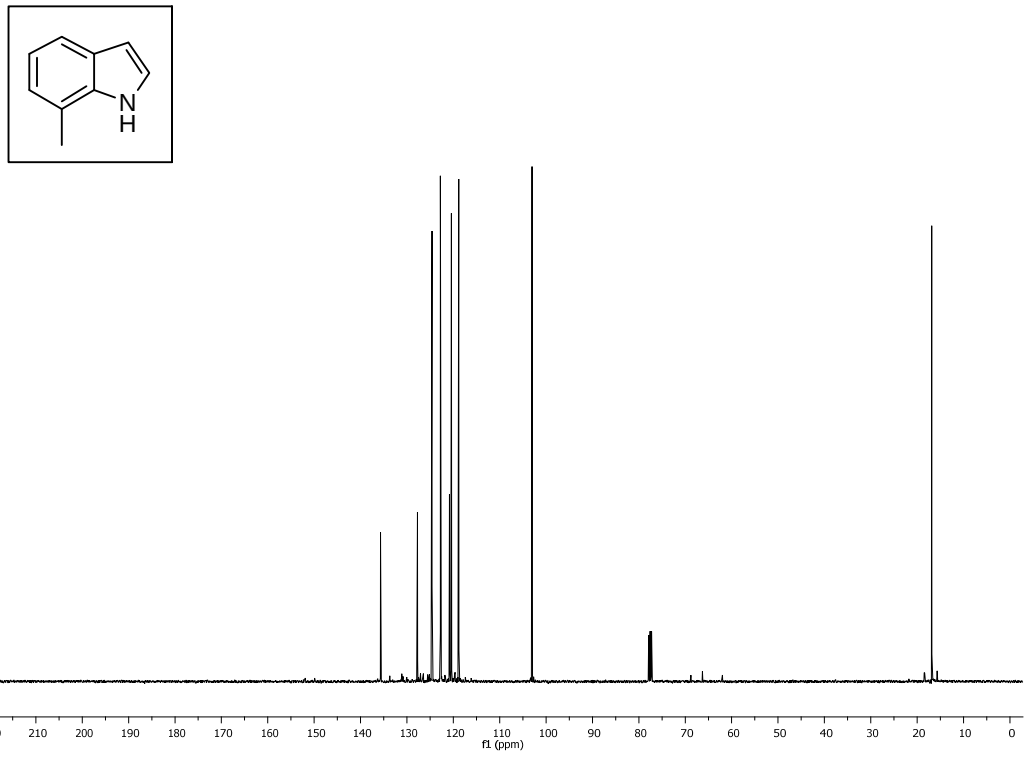
^{1}H NMR spectrum of 7-methyl-1*H*-indole 10a



^{13}C NMR spectrum of 7-methyl-1*H*-indole 10a



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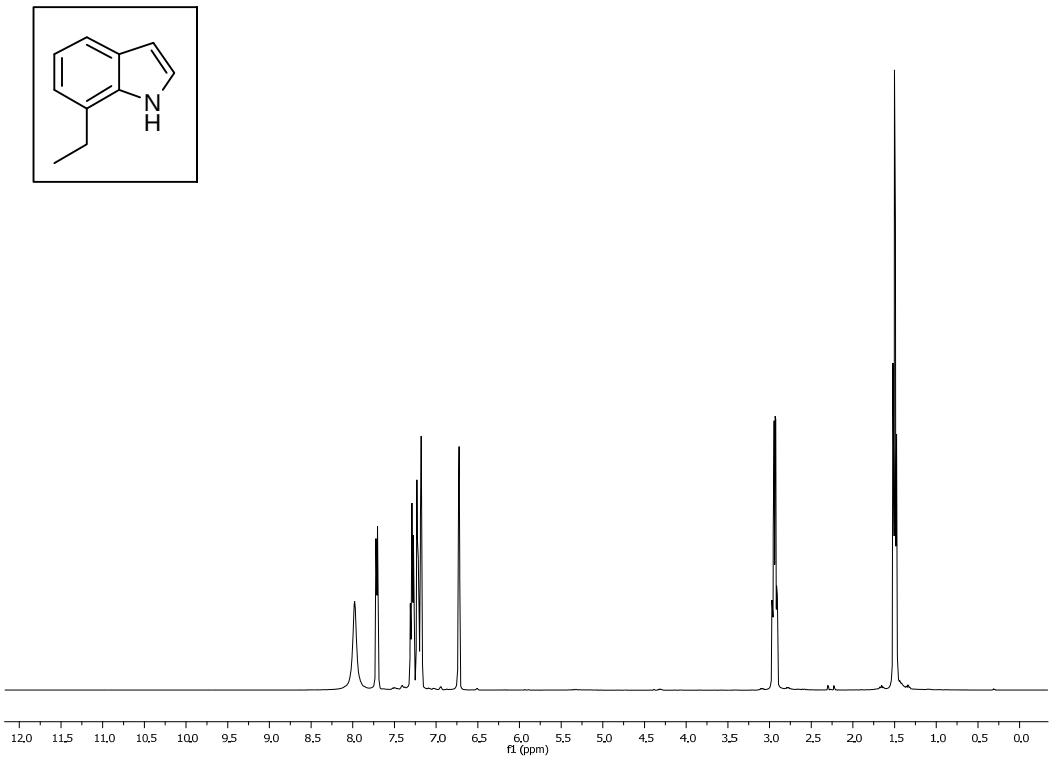
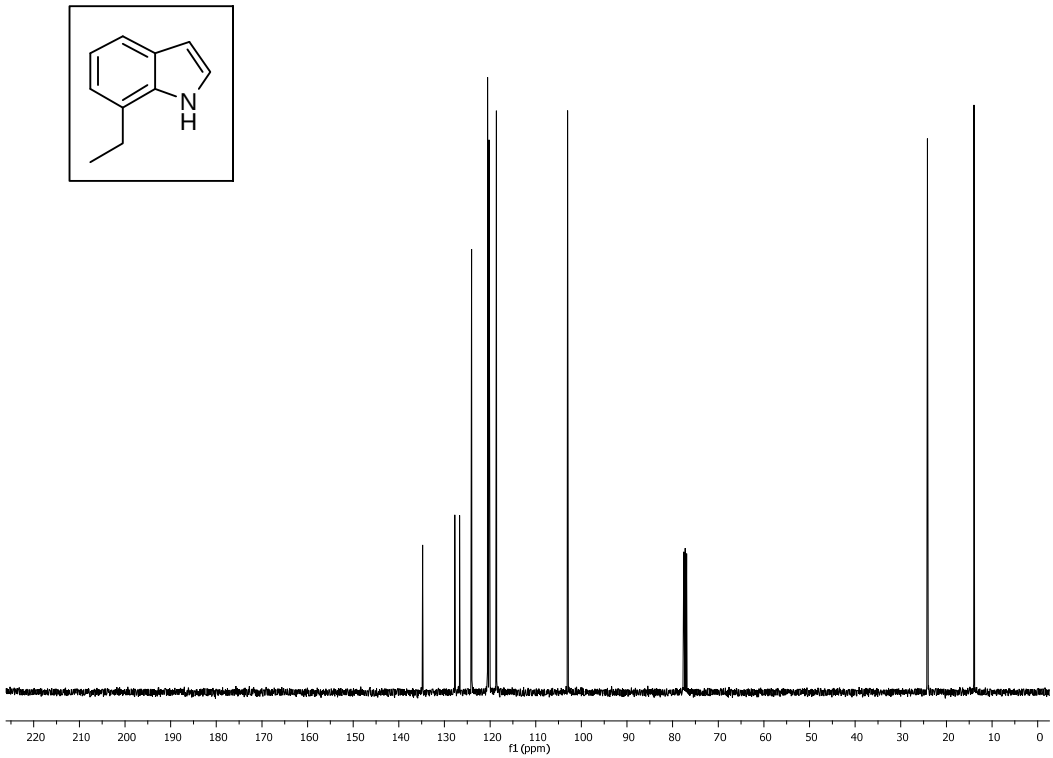
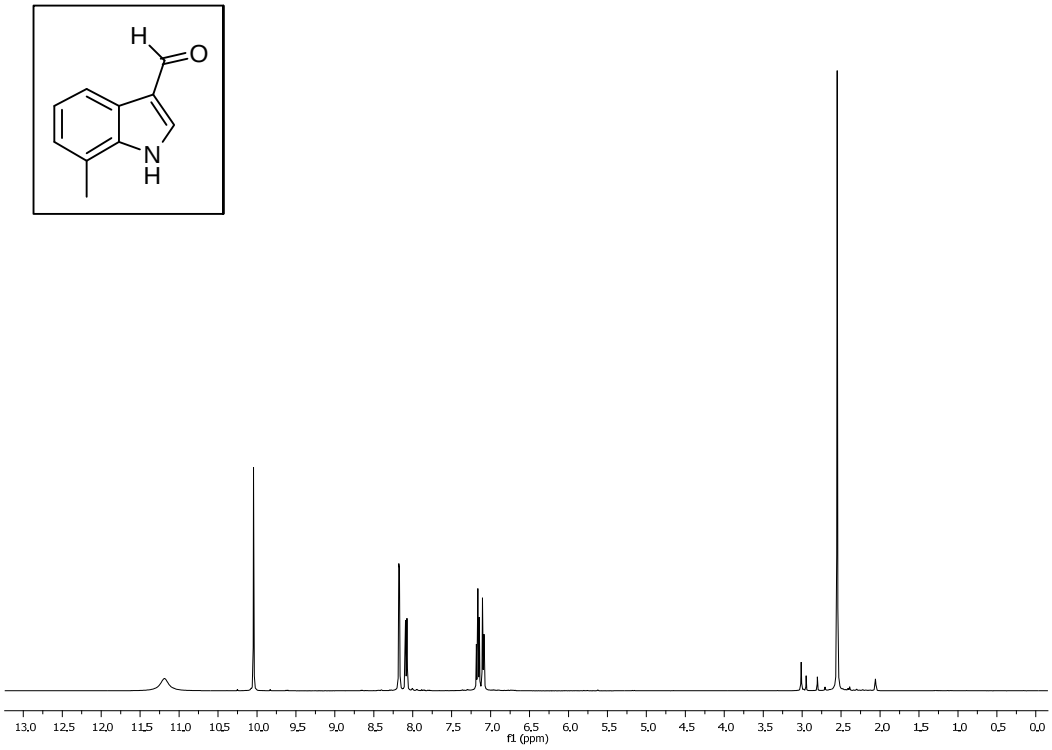


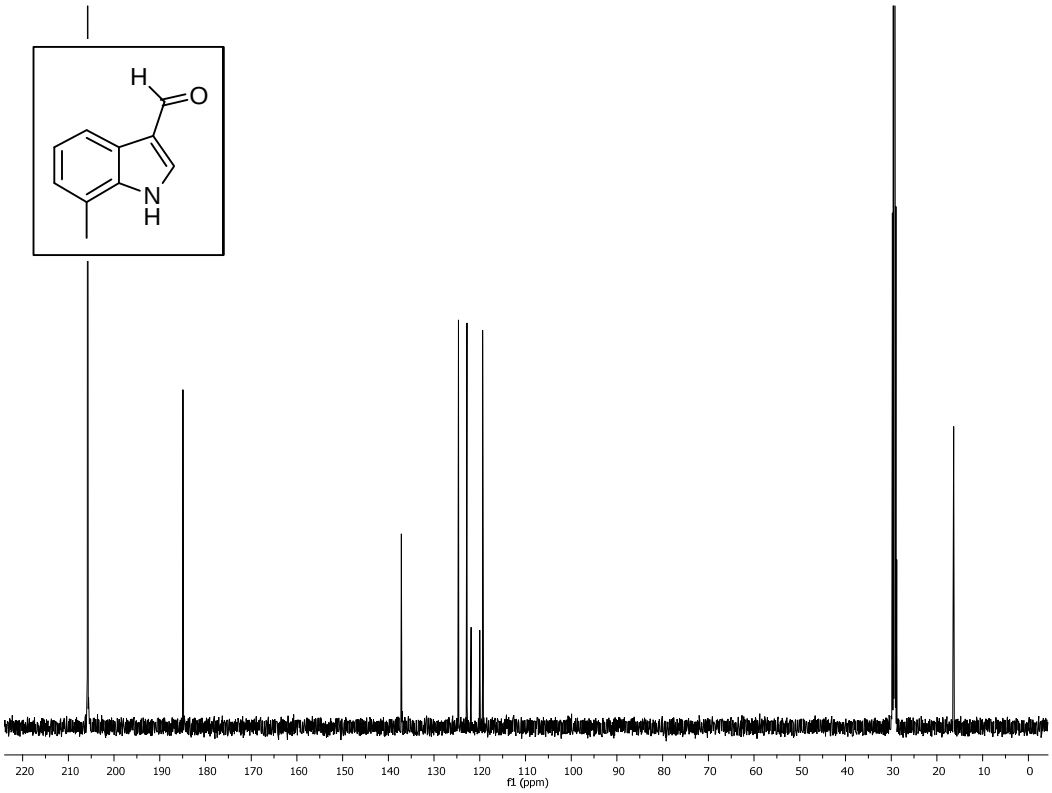
^{13}C NMR spectrum of 7-ethyl-1*H*-indole 10b



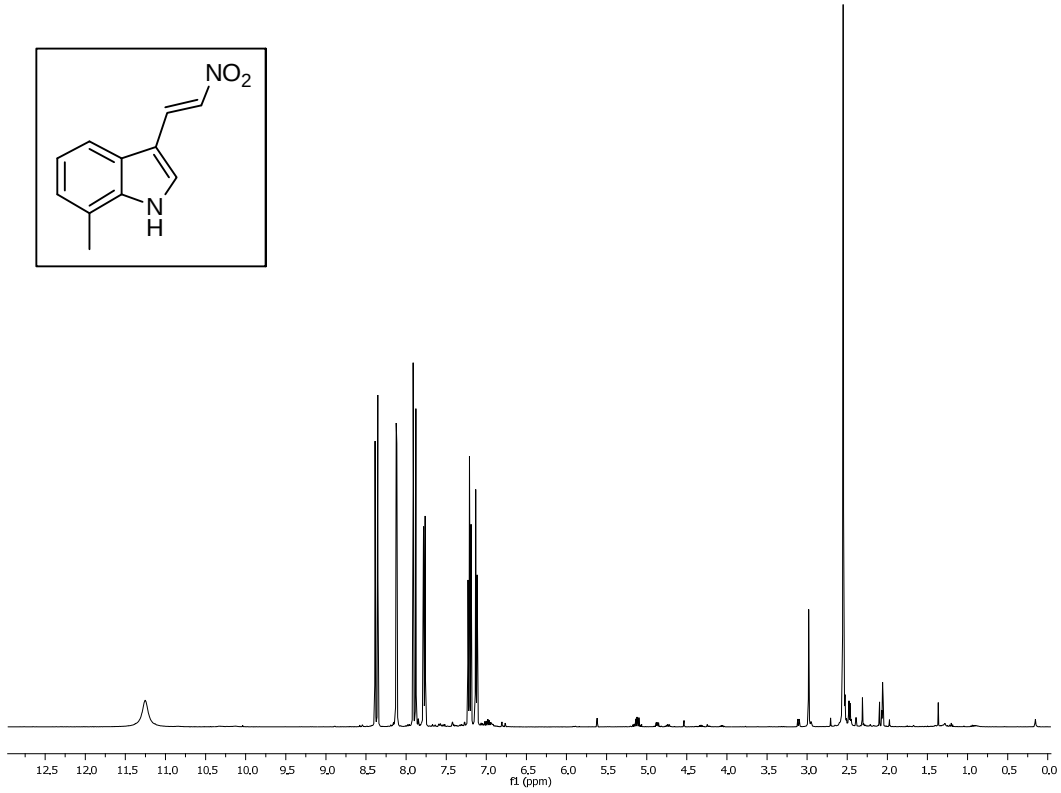
^{1}H NMR spectrum of 7-methyl-1*H*-indole-3-carbaldehyde 11a



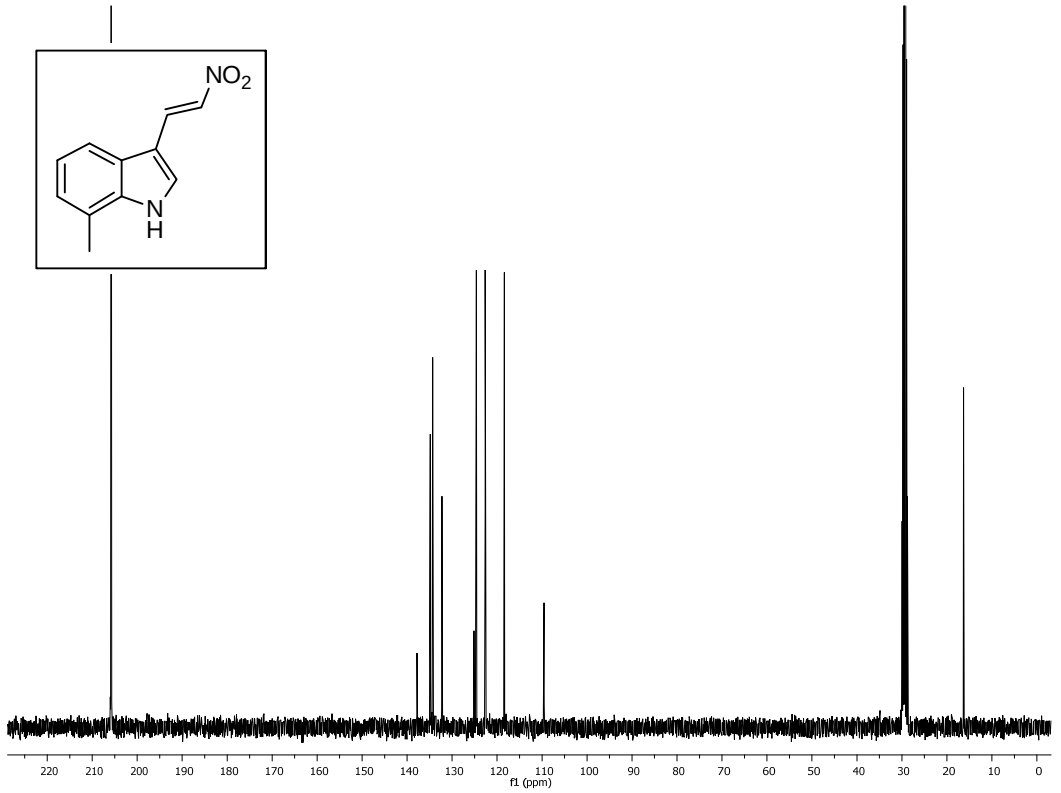
^{13}C NMR spectrum of 7-methyl-1*H*-indole-3-carbaldehyde 11a



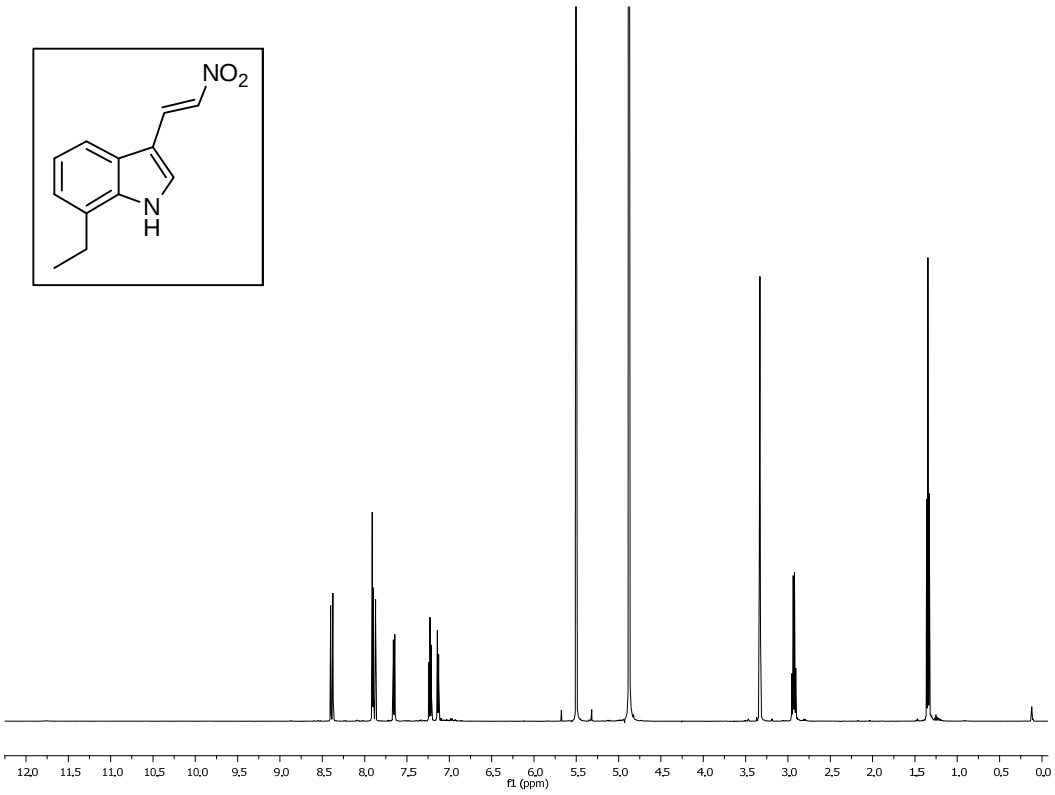
^{1}H NMR spectrum of 7-methyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole 12a



^{13}C NMR spectrum of 7-methyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole 12a



^{1}H NMR spectrum of 7-ethyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole 12b



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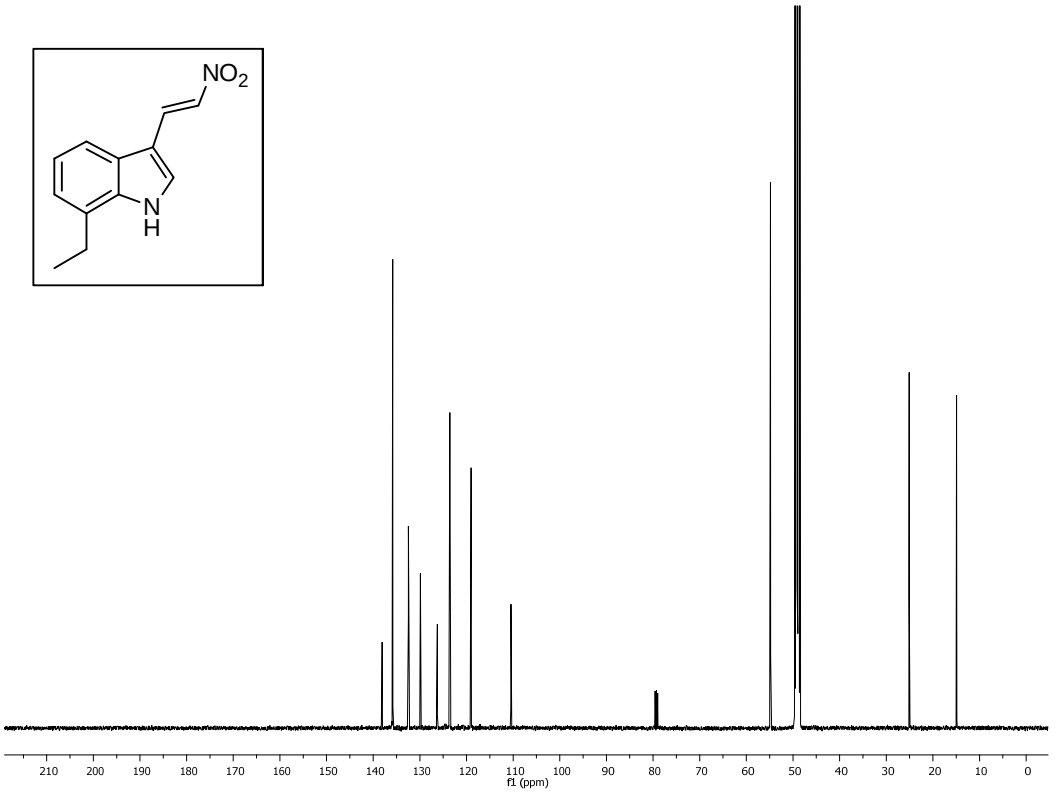
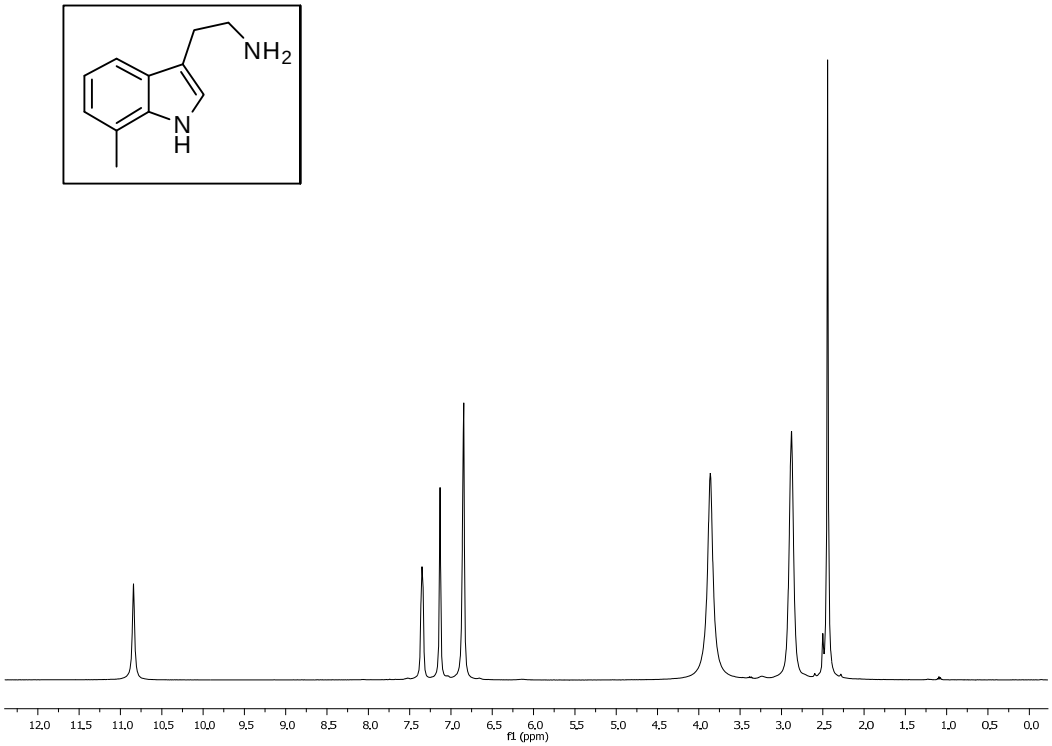


^{1}H NMR spectrum of 2-(7-methyl-1*H*-indol-3-yl)ethanamine 13c



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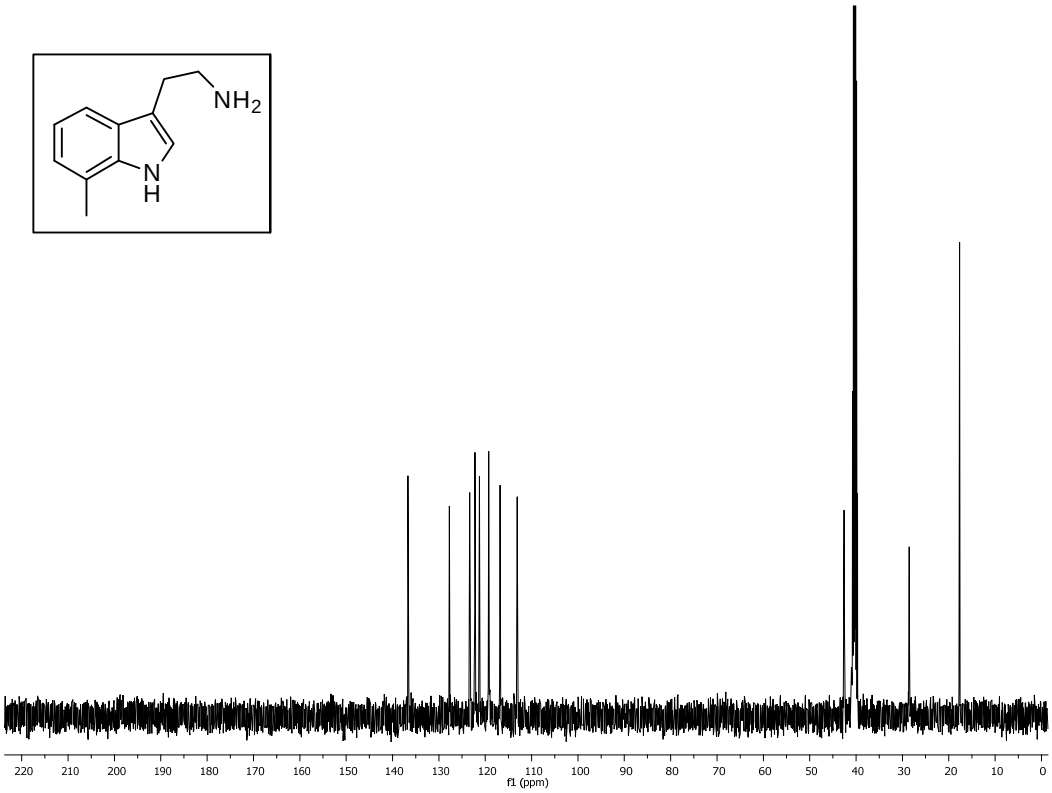
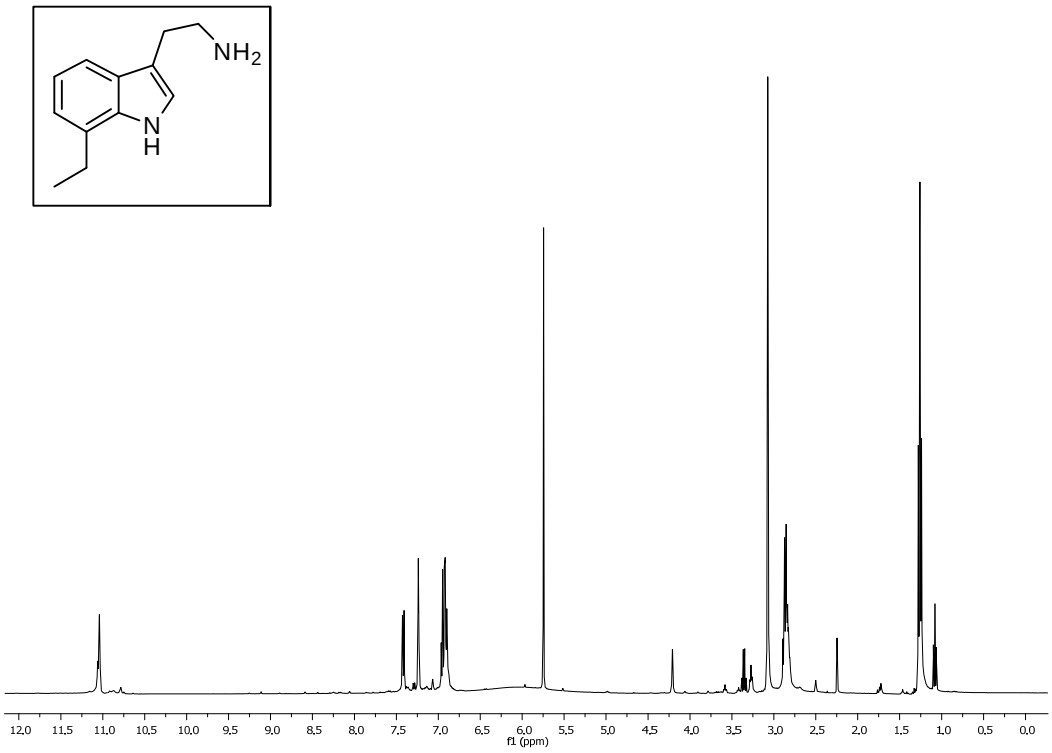
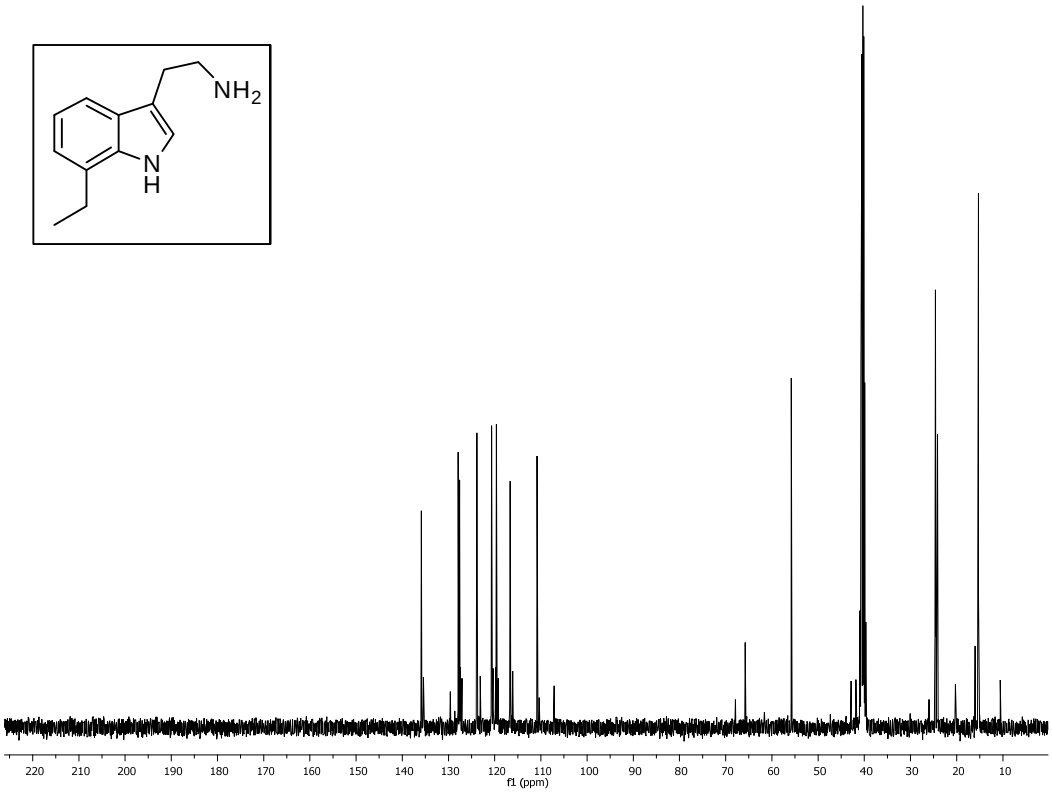


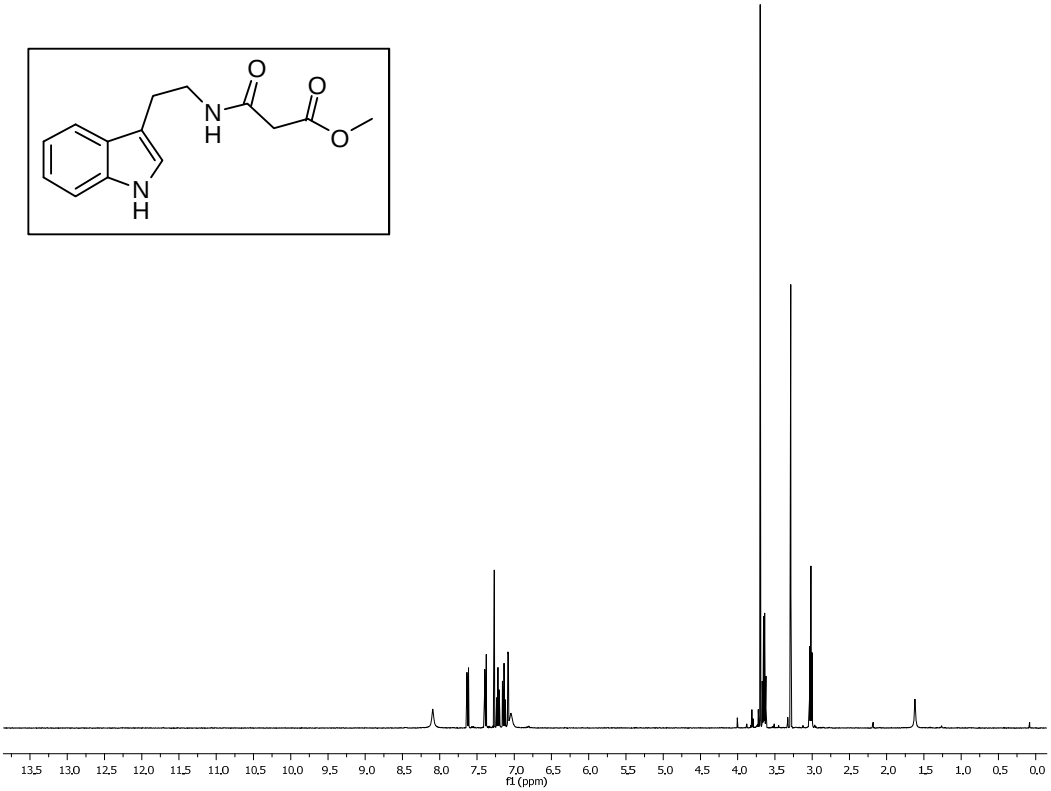
^{1}H NMR spectrum of 2-(7-ethyl-1*H*-indol-3-yl)ethanamine 13d



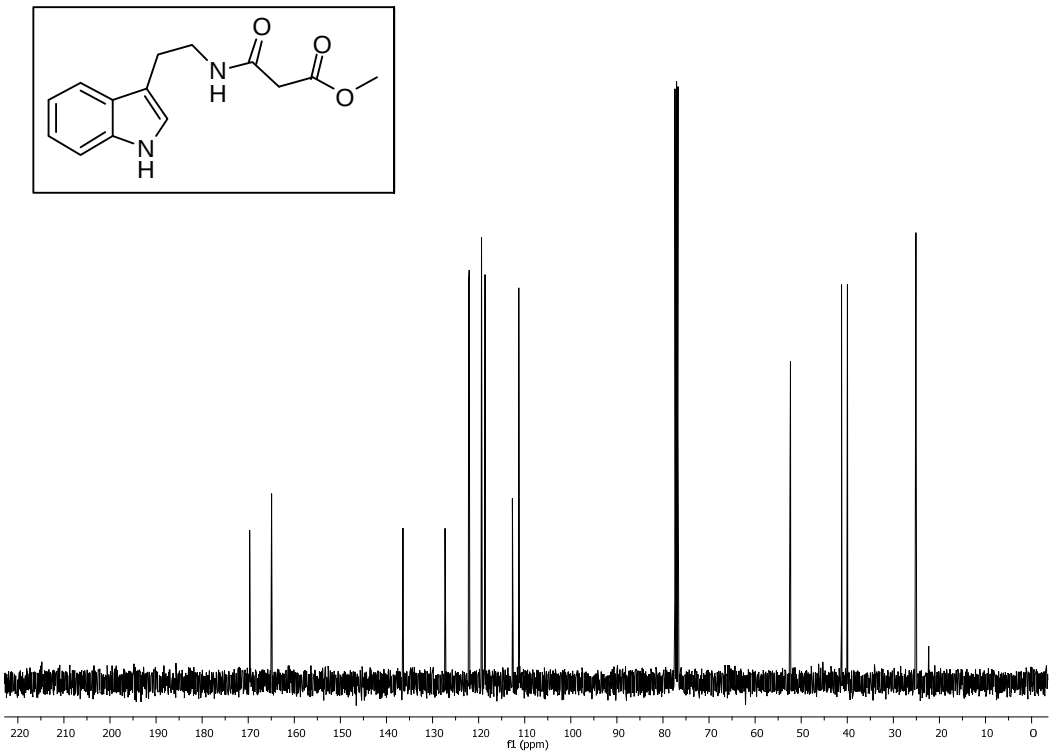
^{13}C NMR spectrum of 2-(7-ethyl-1*H*-indol-3-yl)ethanamine 13d



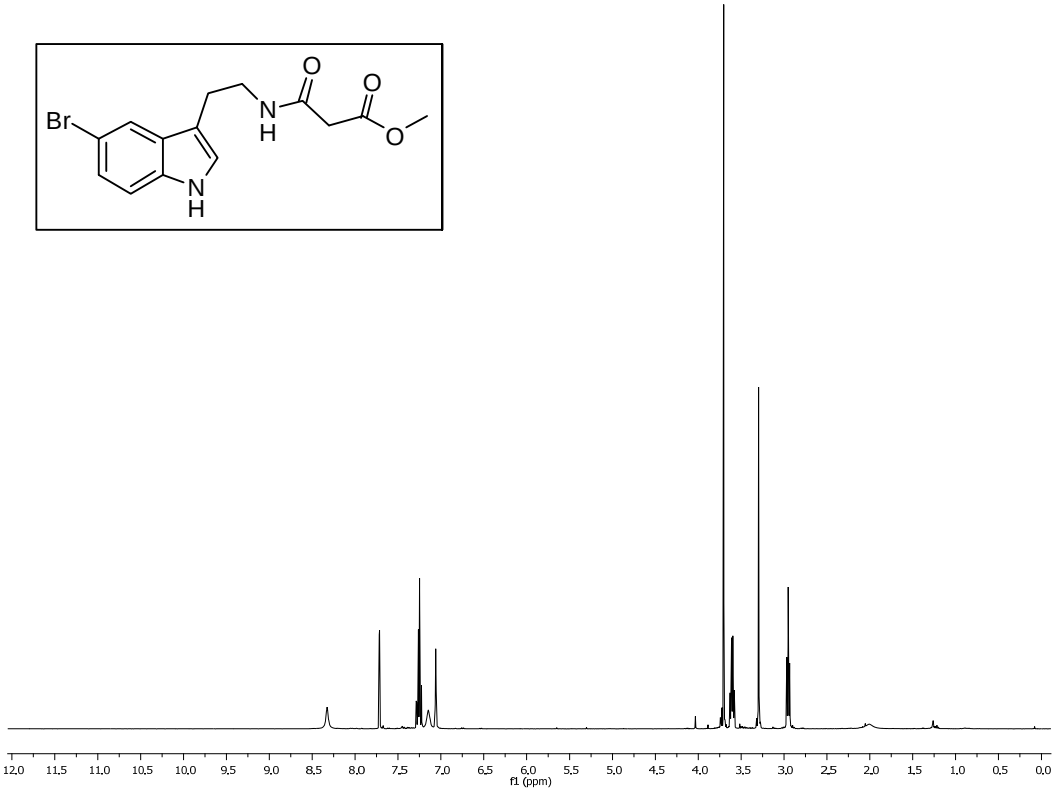
^{1}H NMR spectrum of methyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14a



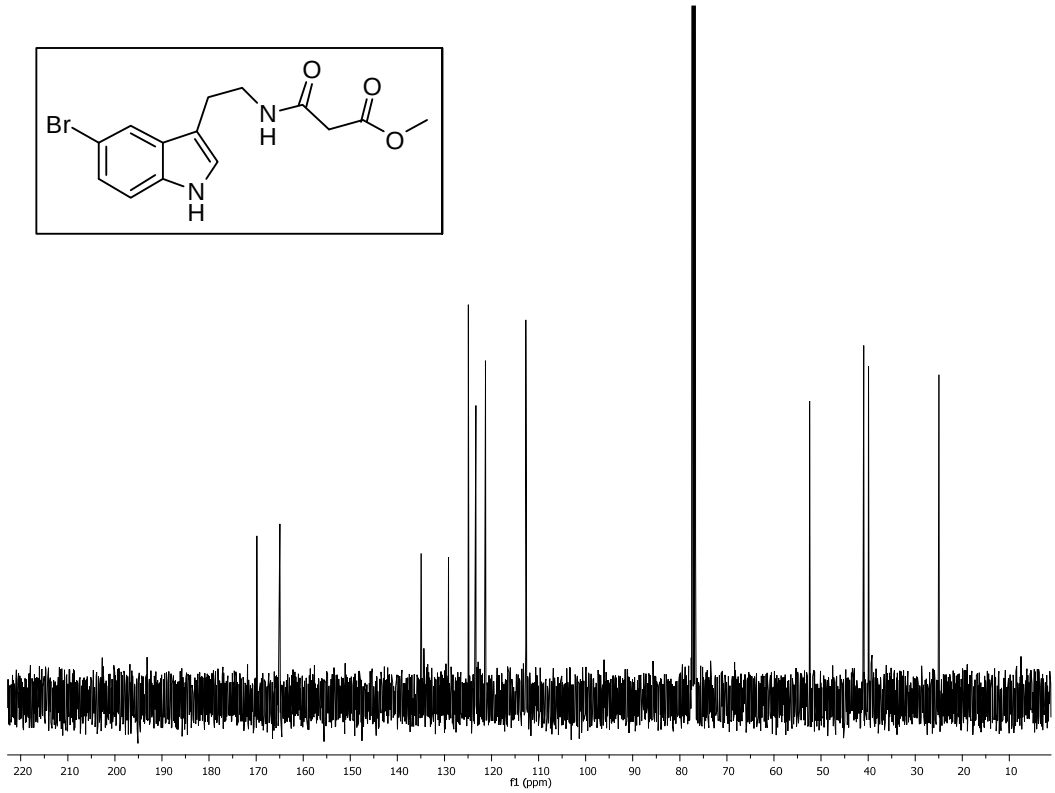
^{13}C NMR spectrum of methyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14a



^{1}H NMR spectrum of methyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14b



^{13}C NMR spectrum of methyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14b



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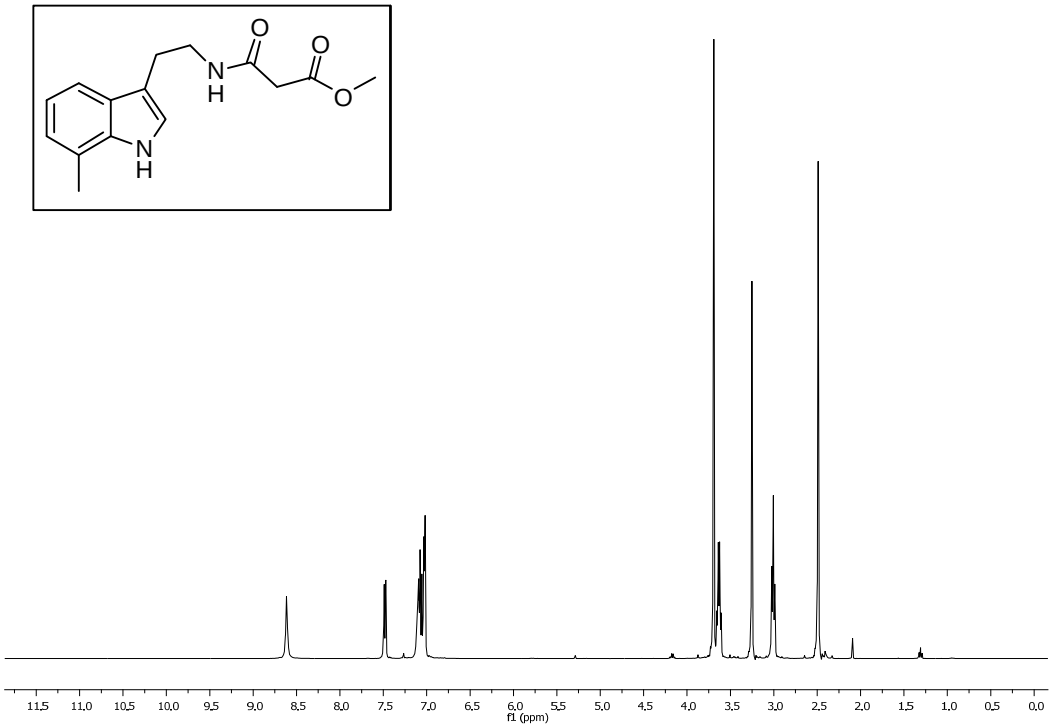

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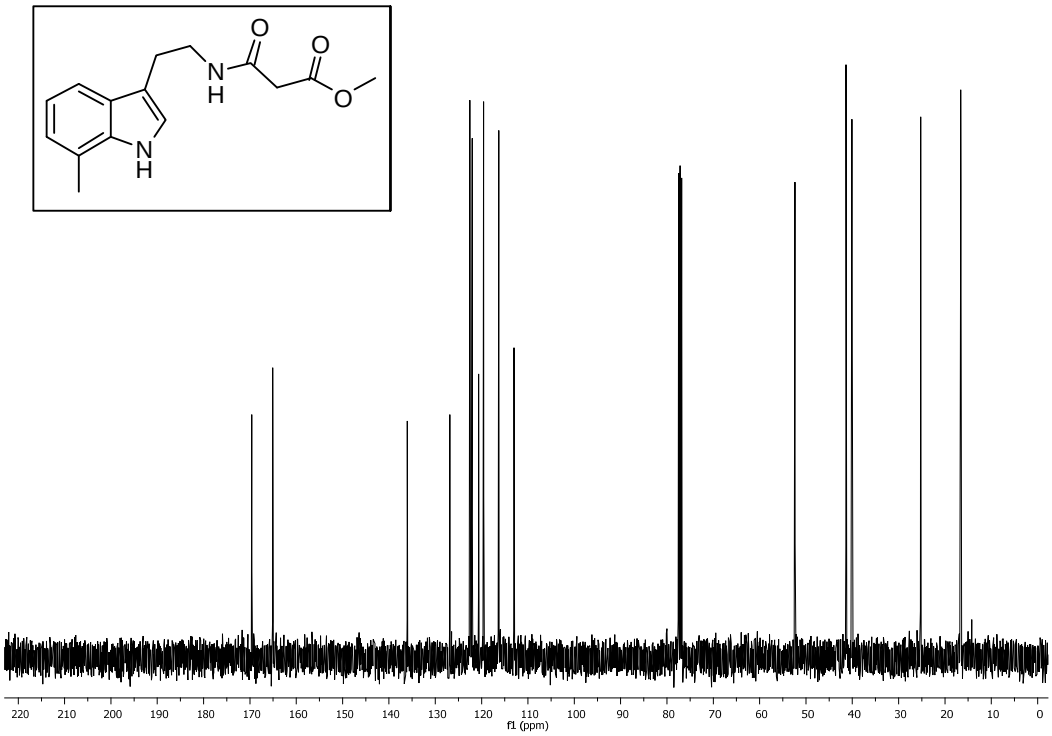
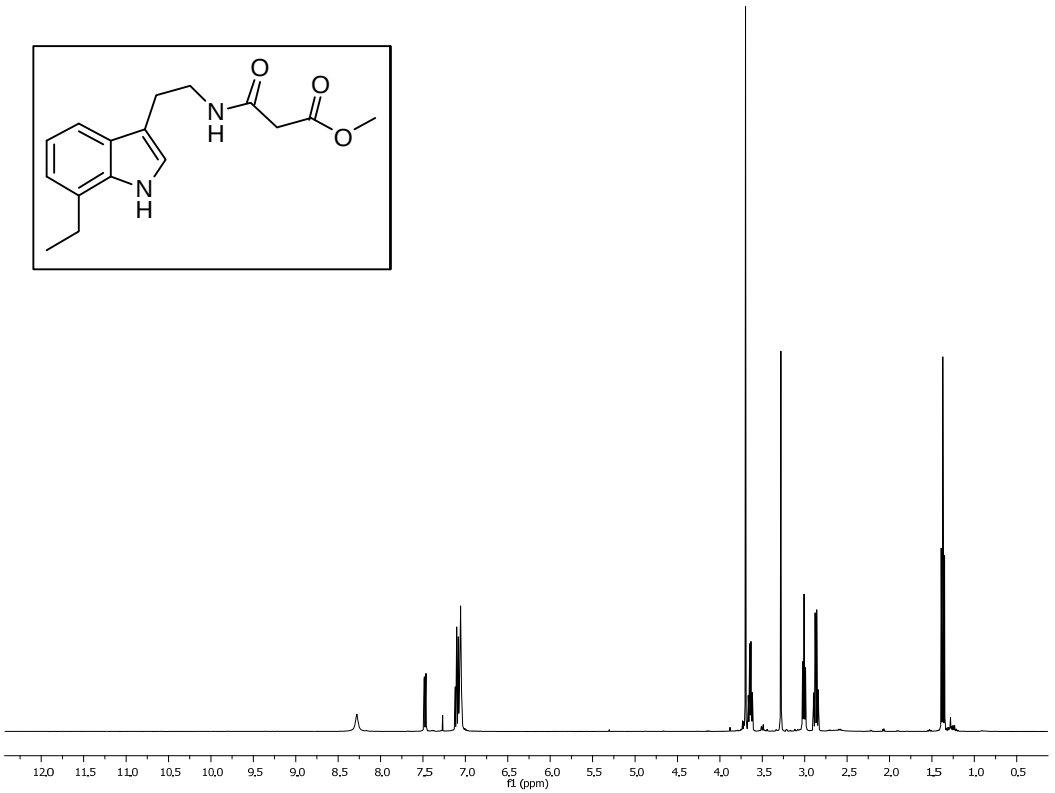


^{1}H NMR spectrum of methyl 3-{[2-(7-ethyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14d



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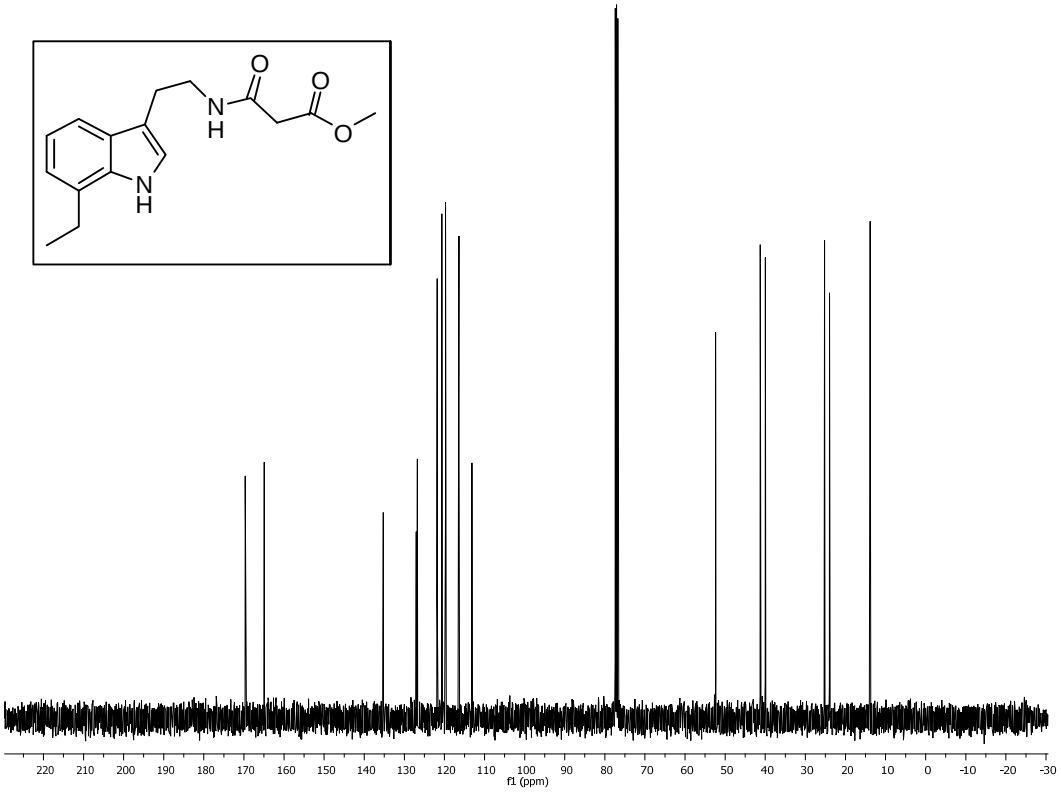
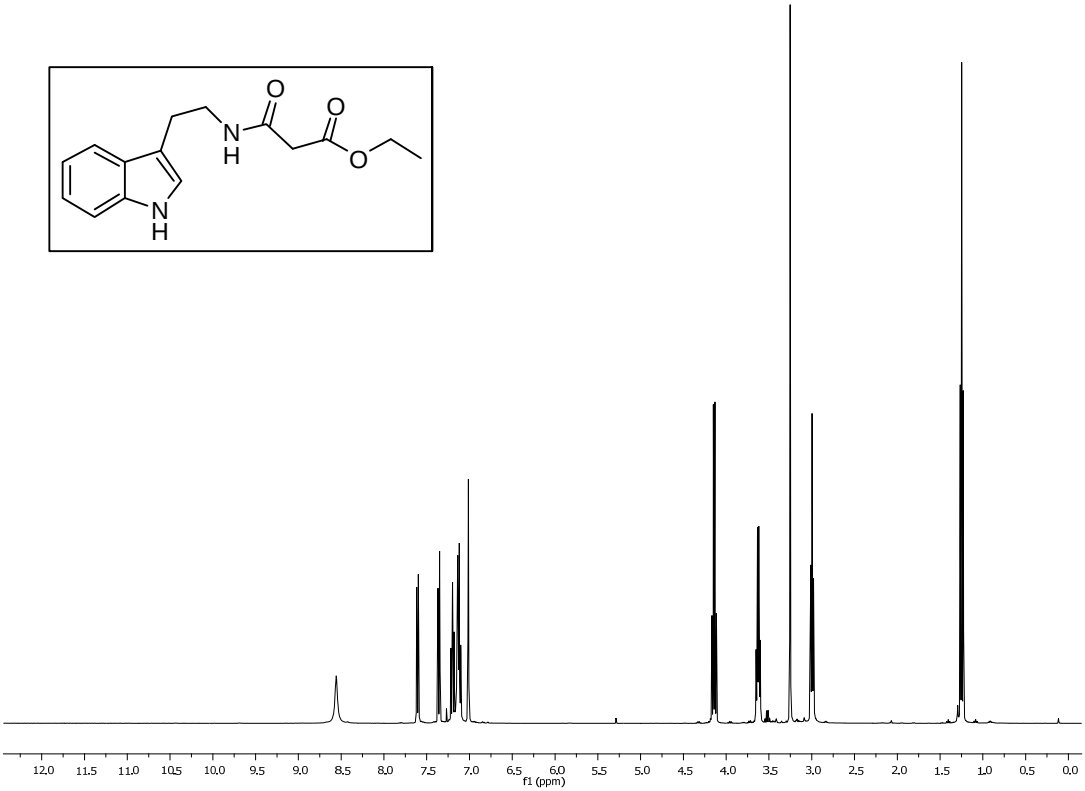
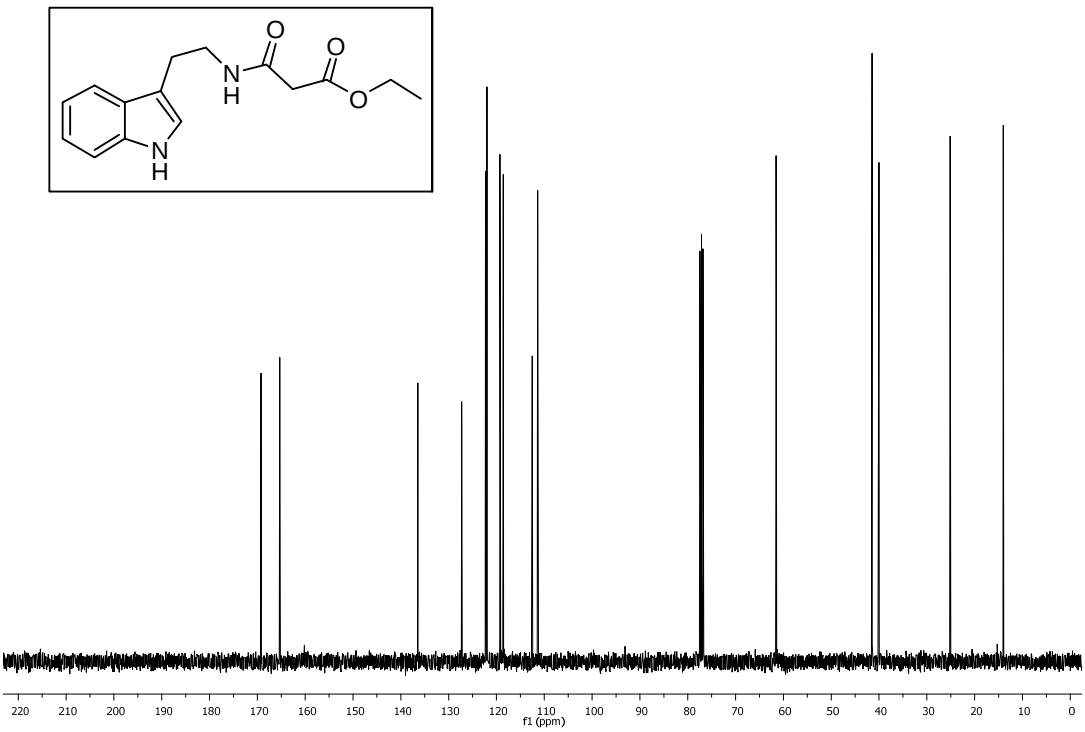


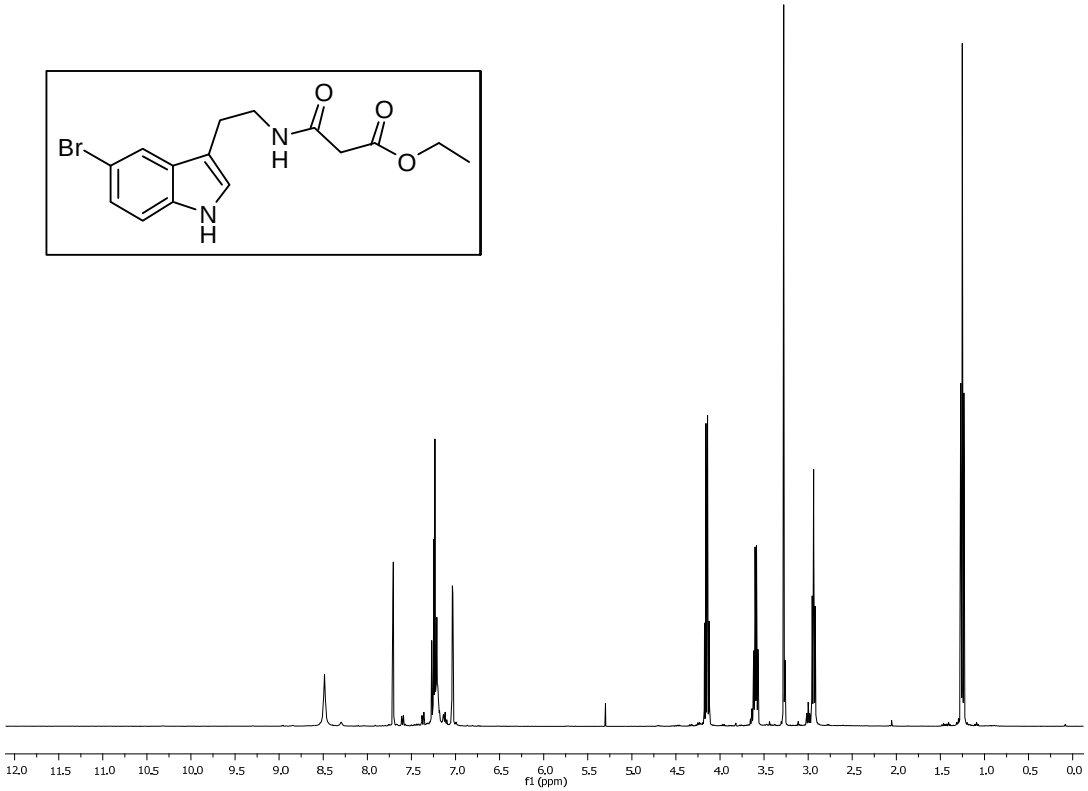
^{1}H NMR spectrum of ethyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14e



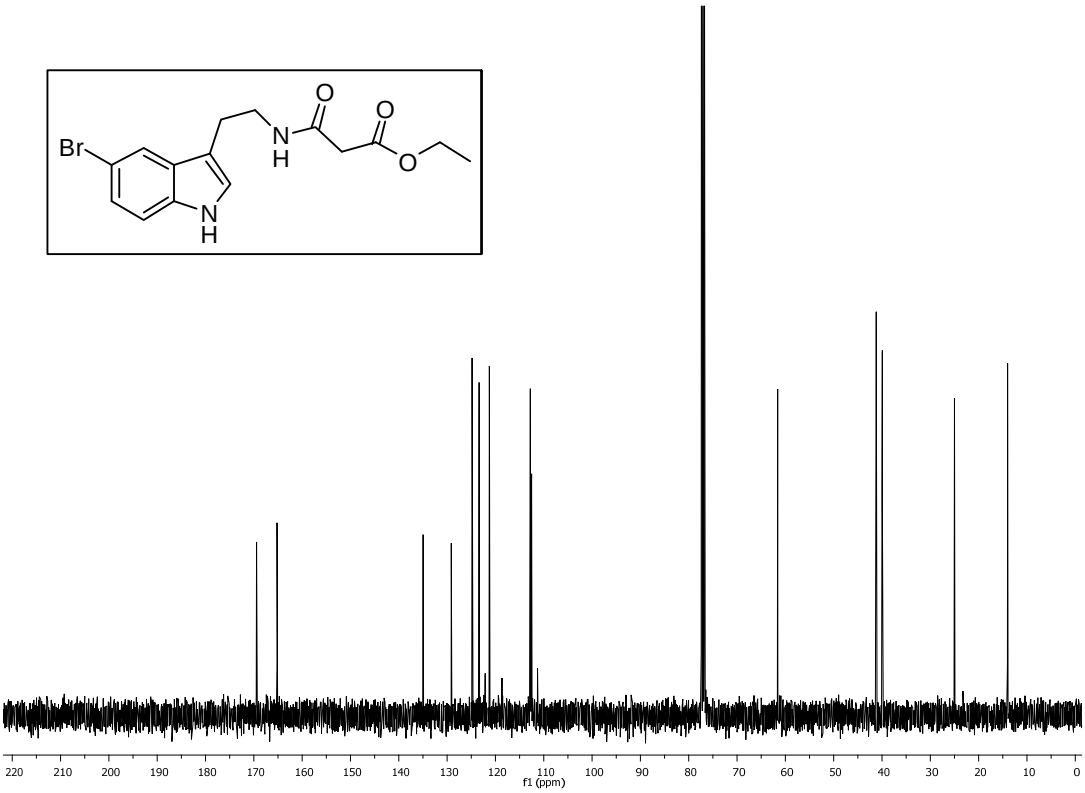
^{13}C NMR spectrum of ethyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14e



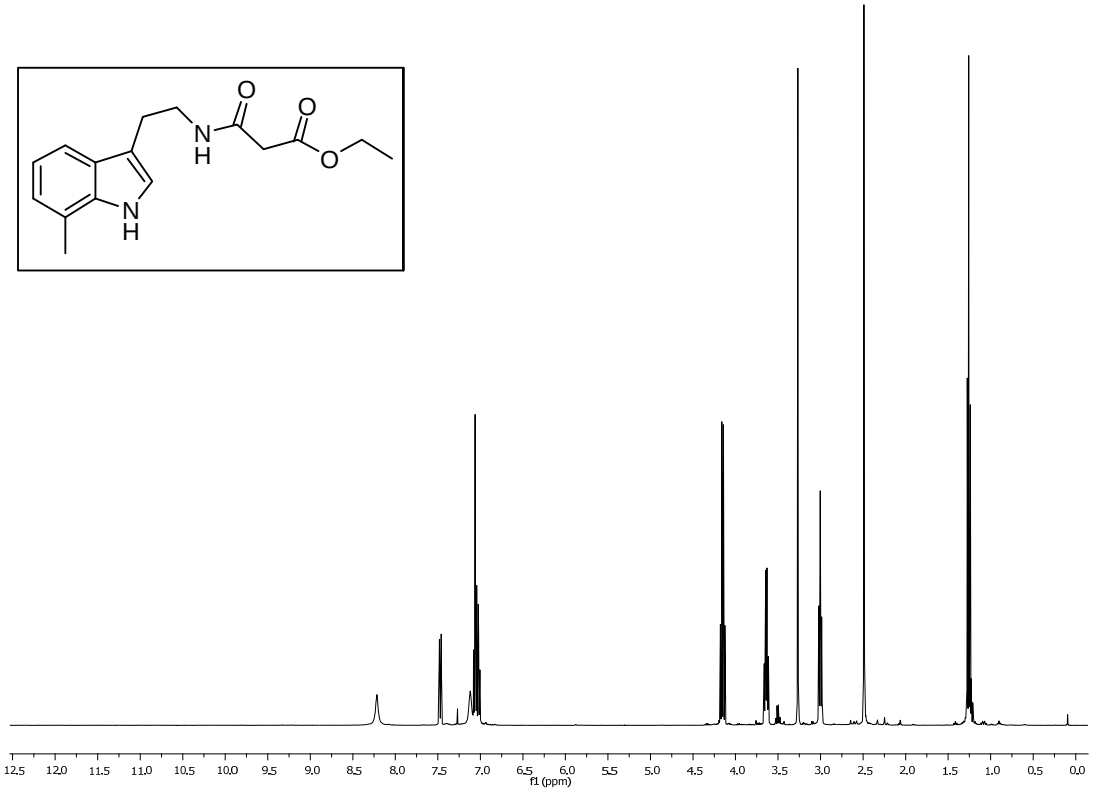
^{1}H NMR spectrum of ethyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14f



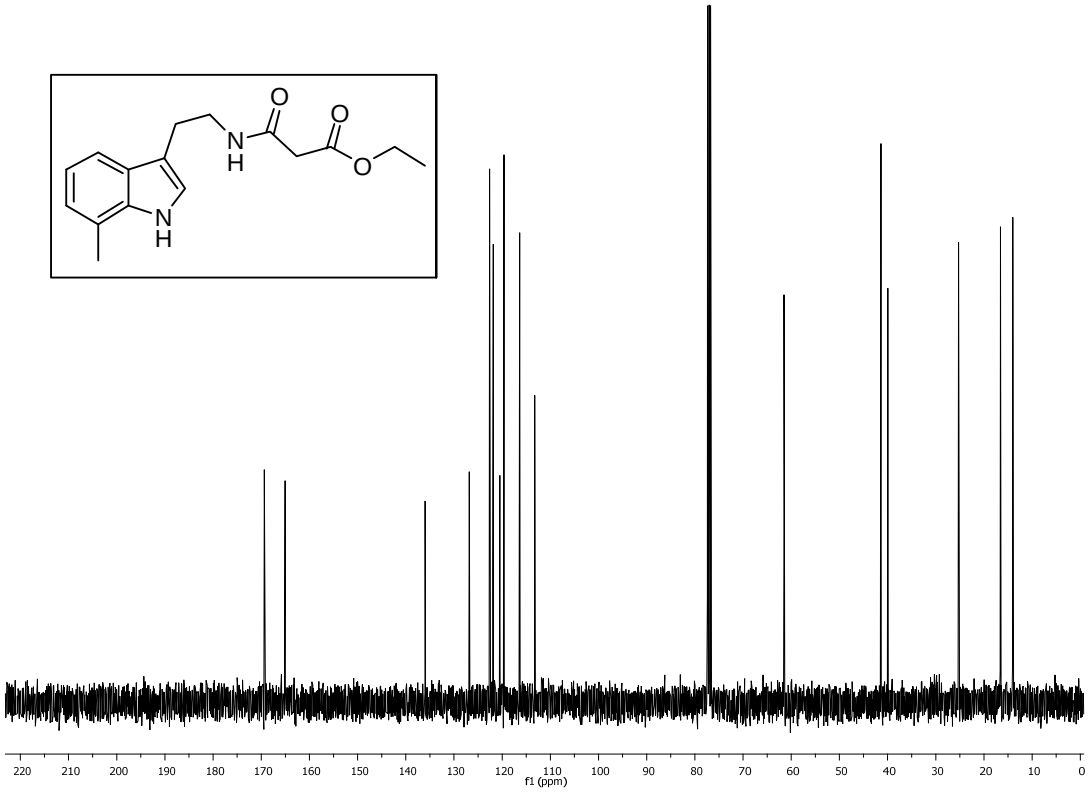
^{13}C NMR spectrum of ethyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14f



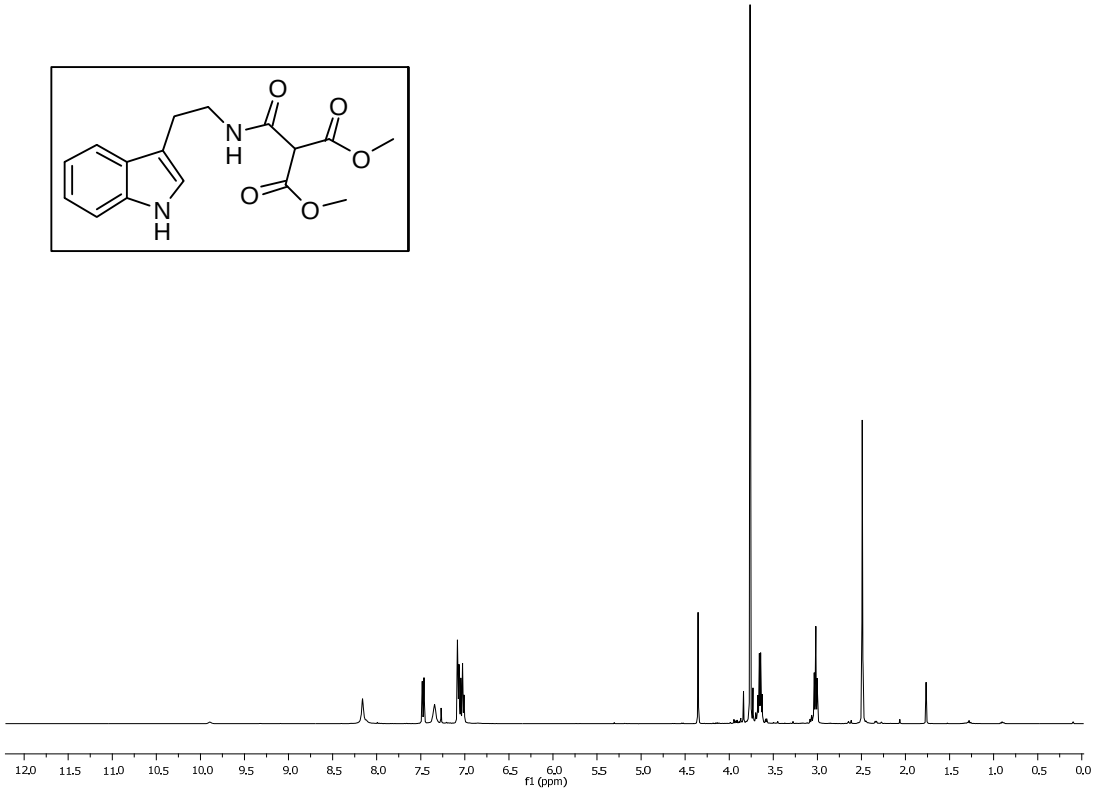
^{1}H NMR spectrum of ethyl 3-{[2-(7-methyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14g



^{13}C NMR spectrum of ethyl 3-{[2-(7-methyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 14g



^{1}H NMR spectrum of dimethyl {[2-(1*H*-indol-3-yl)ethyl]carbamoyl}malonate 6a



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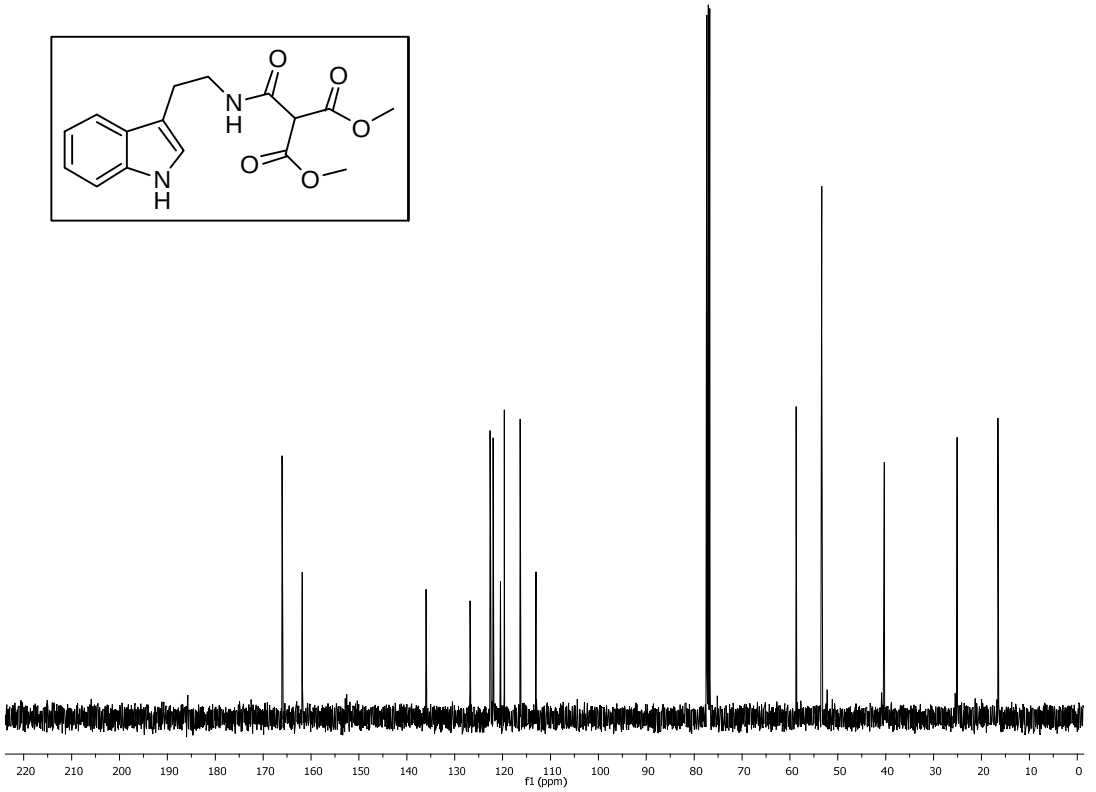
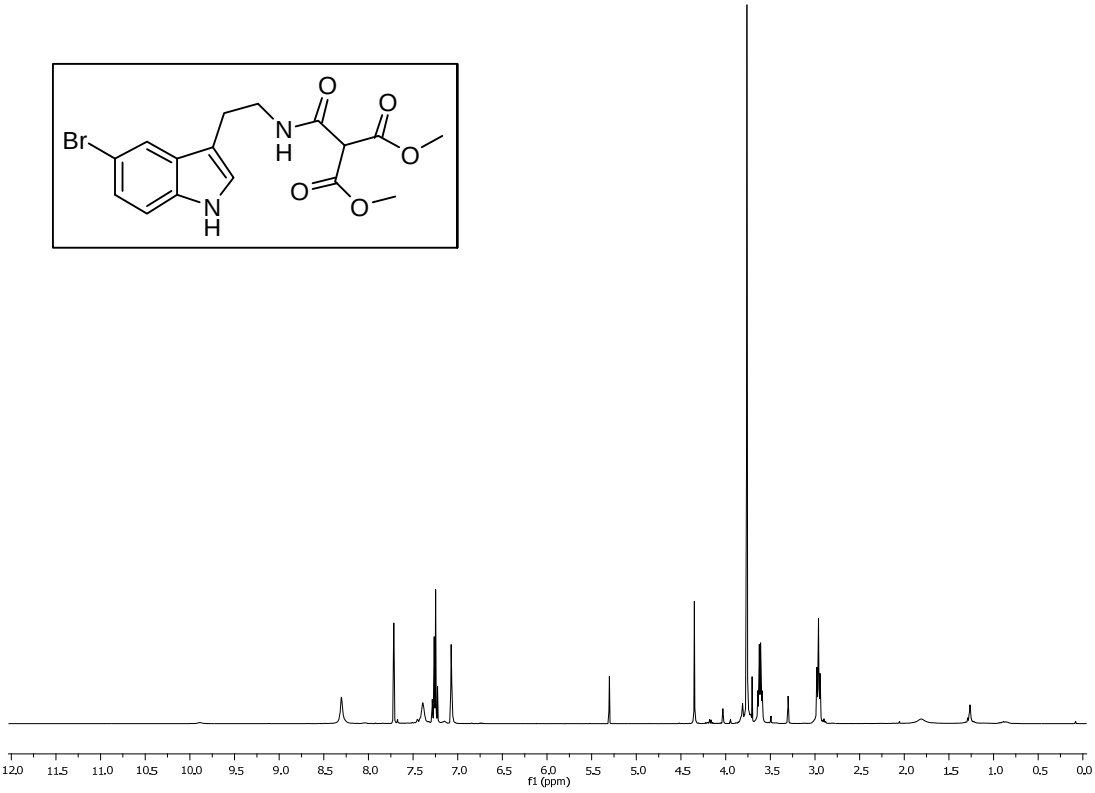


^{1}H NMR spectrum of dimethyl {[2-(5-bromo-1*H*-indol-3-yl)ethyl]carbamoyl}malonate 6b



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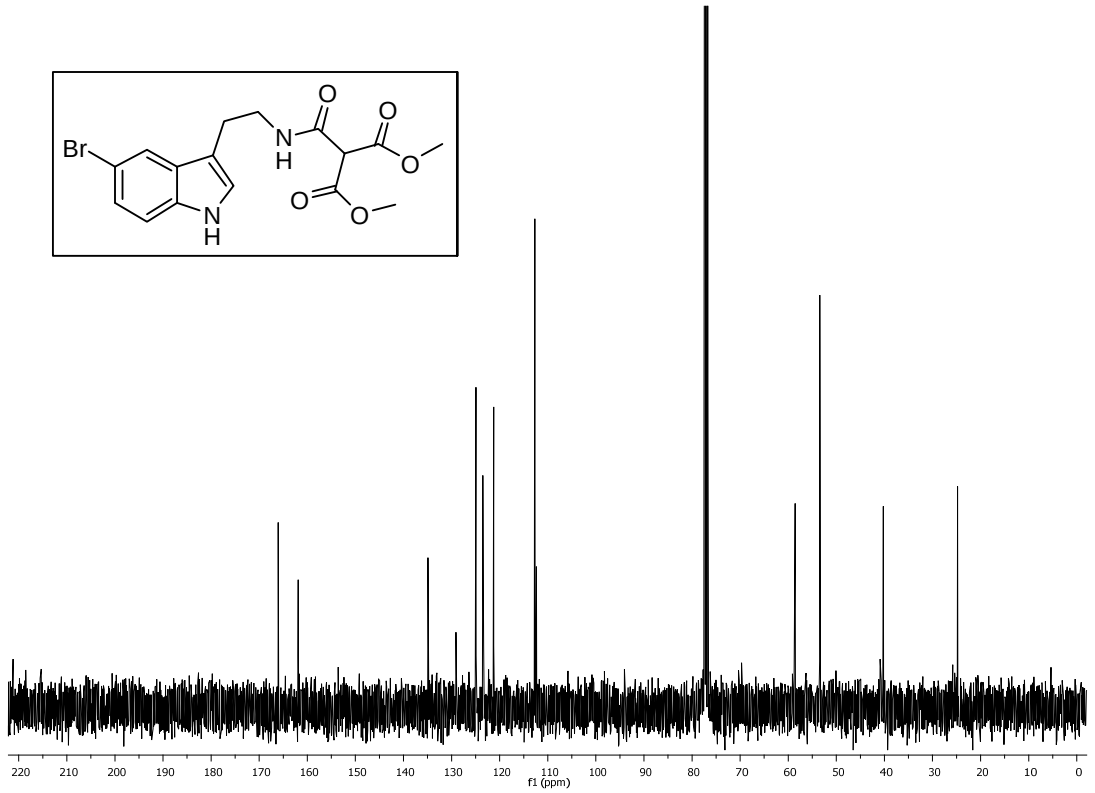

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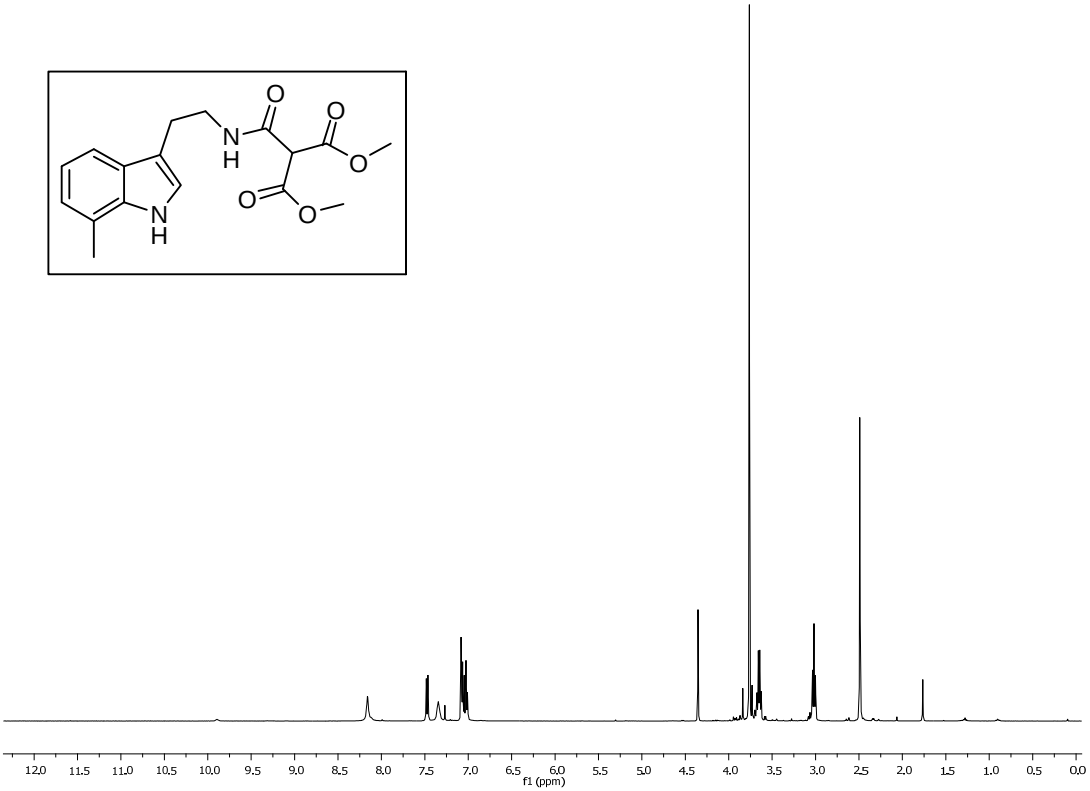

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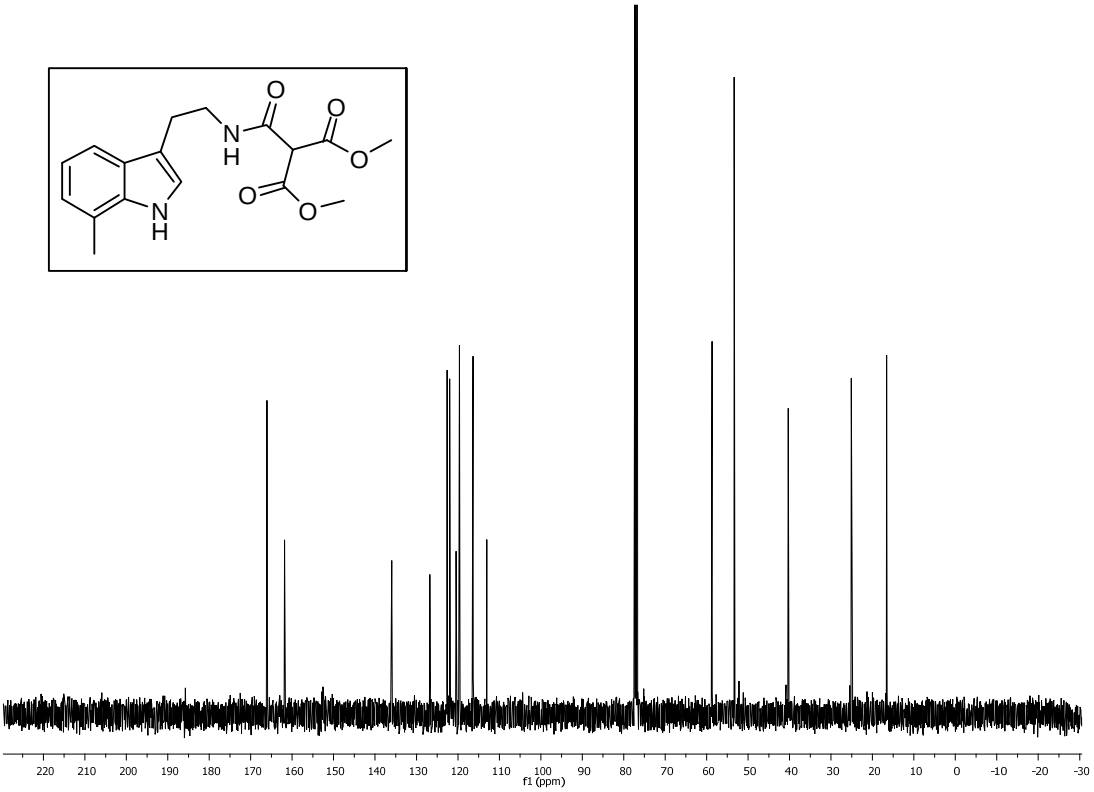
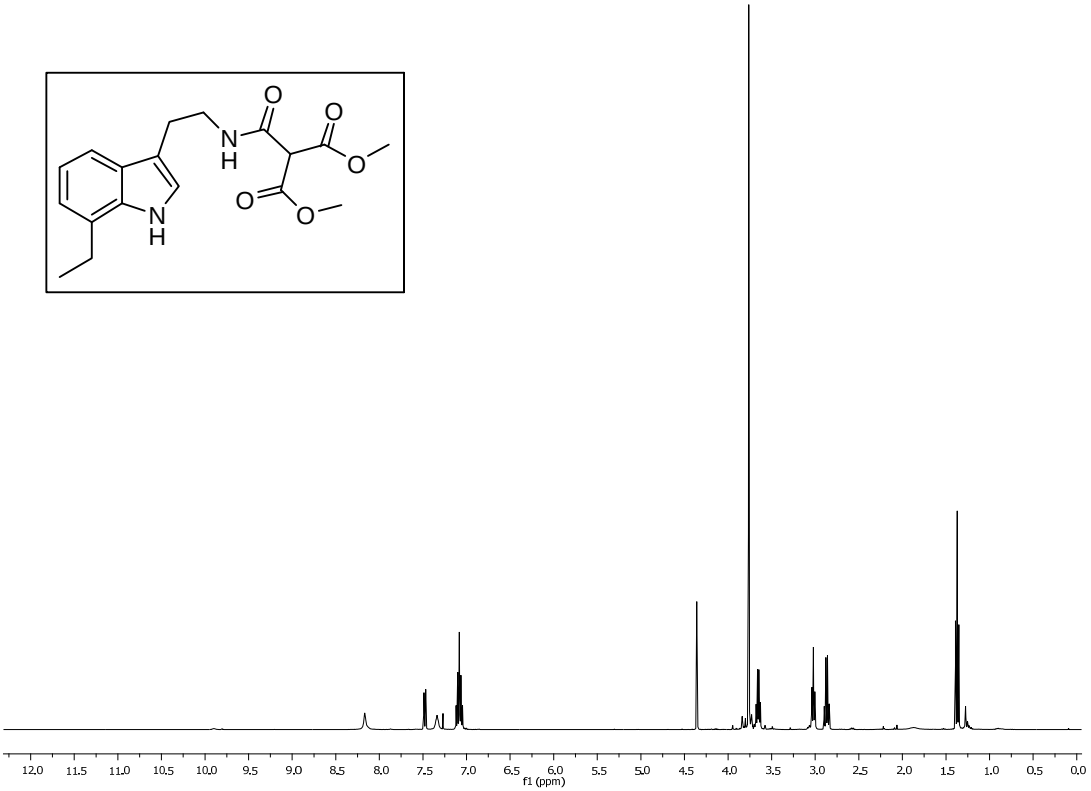


^{1}H NMR spectrum of dimethyl {[2-(7-ethyl-1*H*-indol-3-yl)ethyl]carbamoyl}malonate 6d



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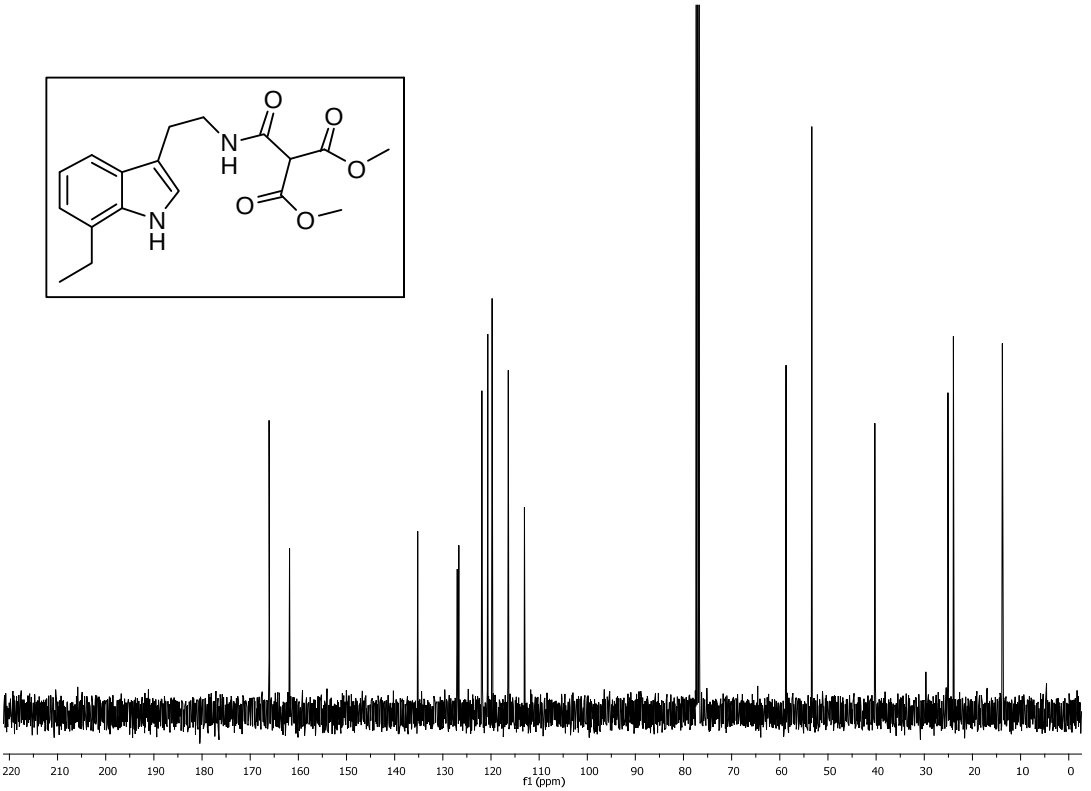

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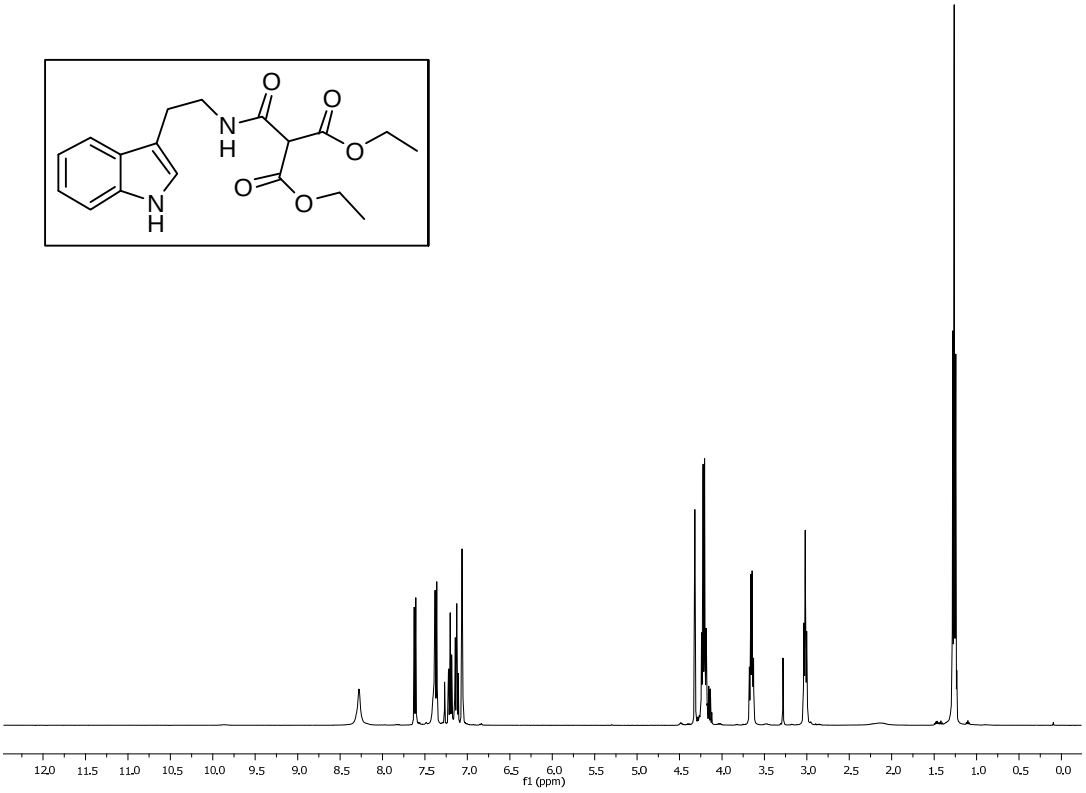

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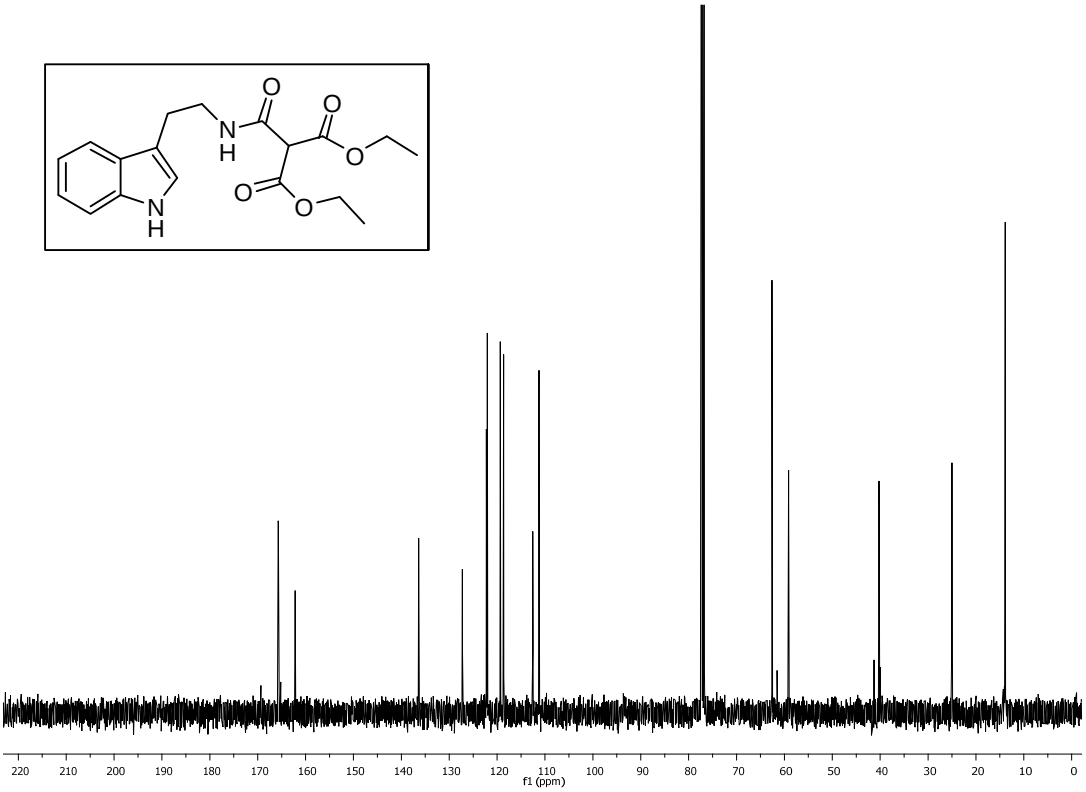

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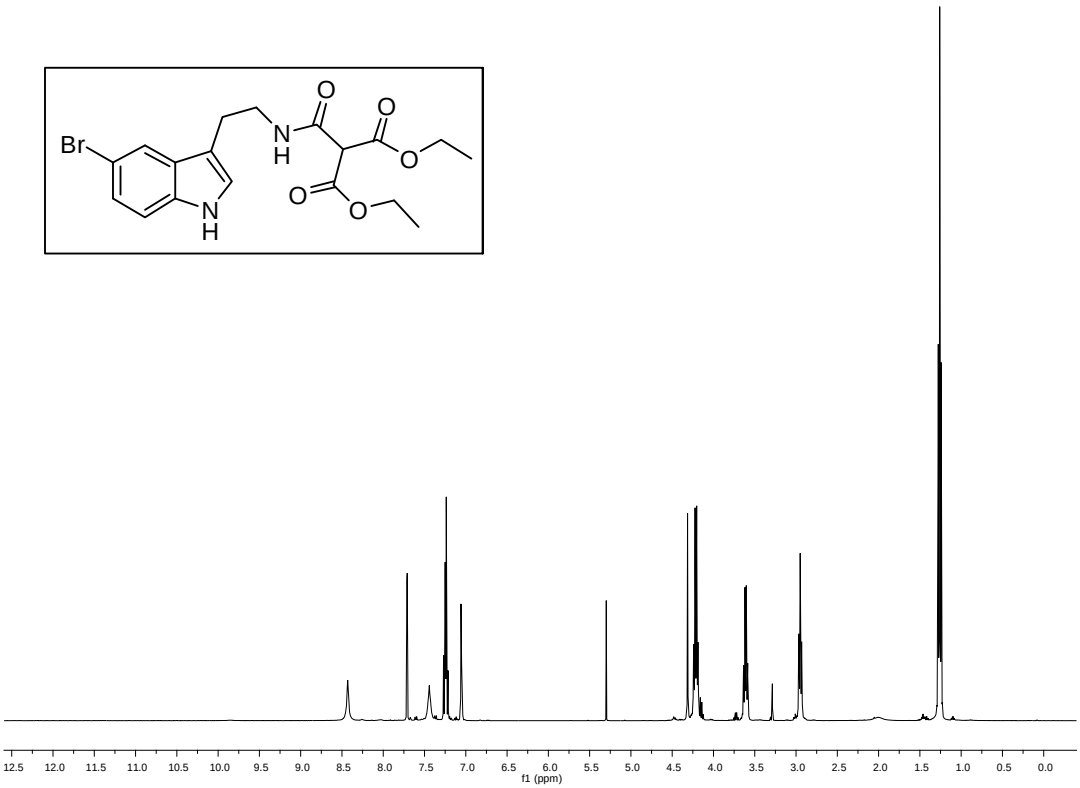

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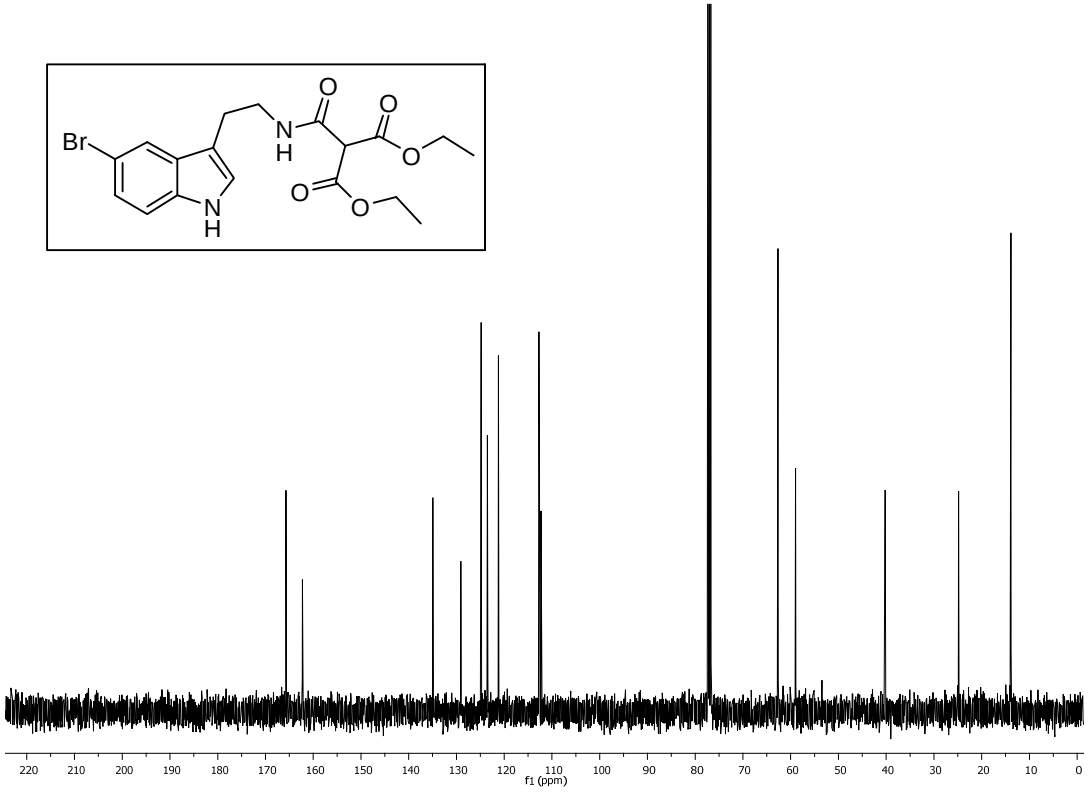

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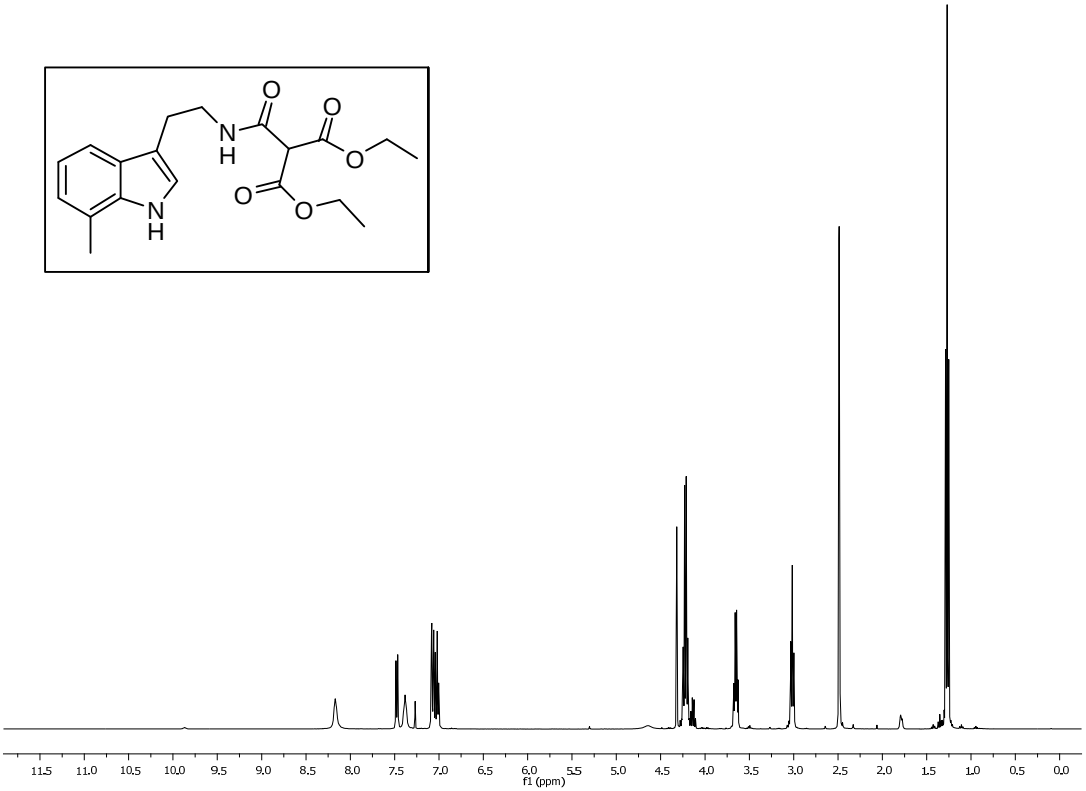

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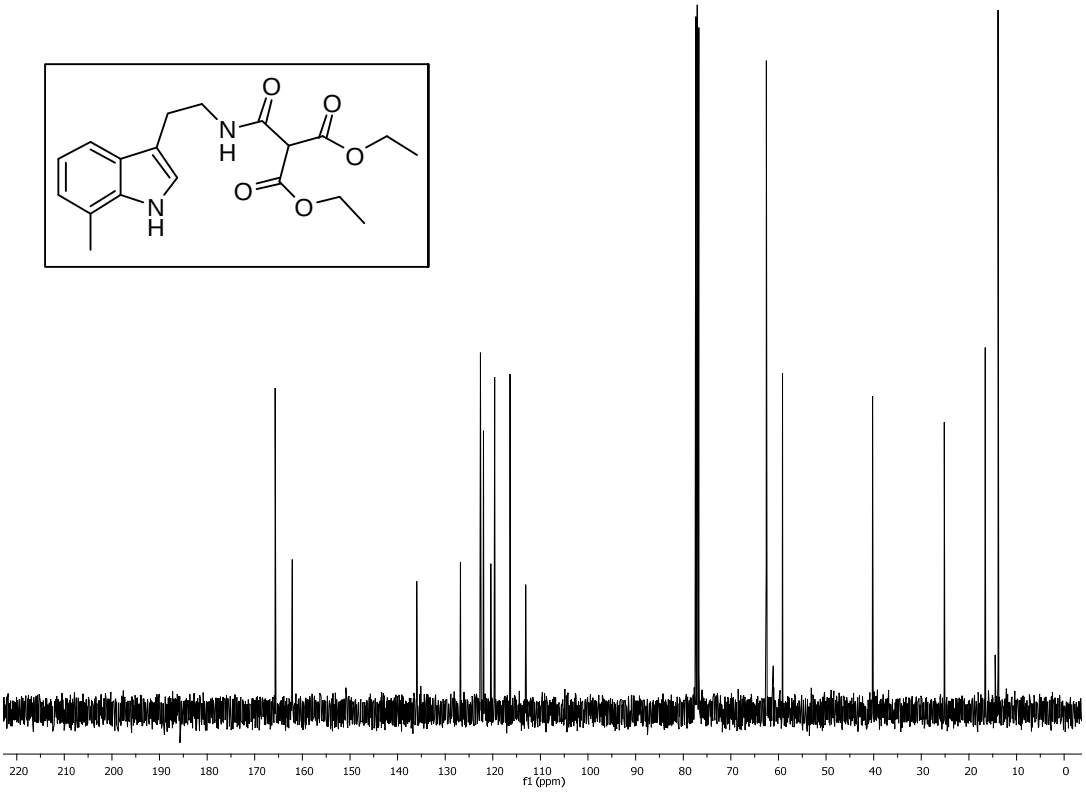
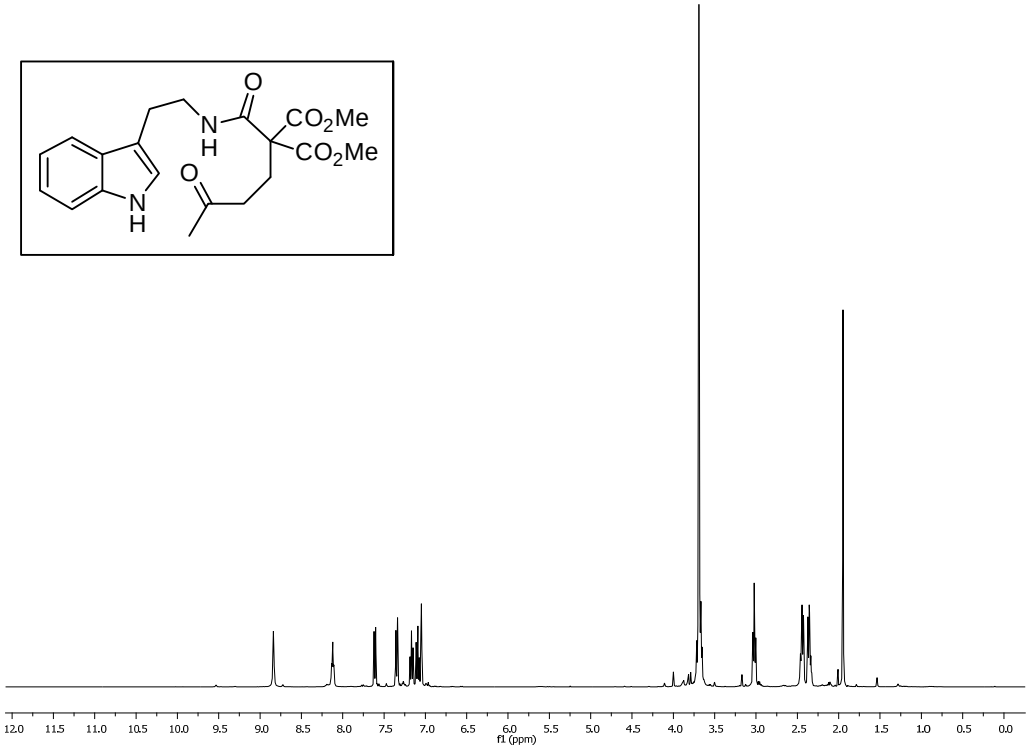


^{1}H NMR spectrum of dimethyl {[2-(1*H*-indol-3-yl)ethyl]carbamoyl}(3-oxobutyl)malonate 8a



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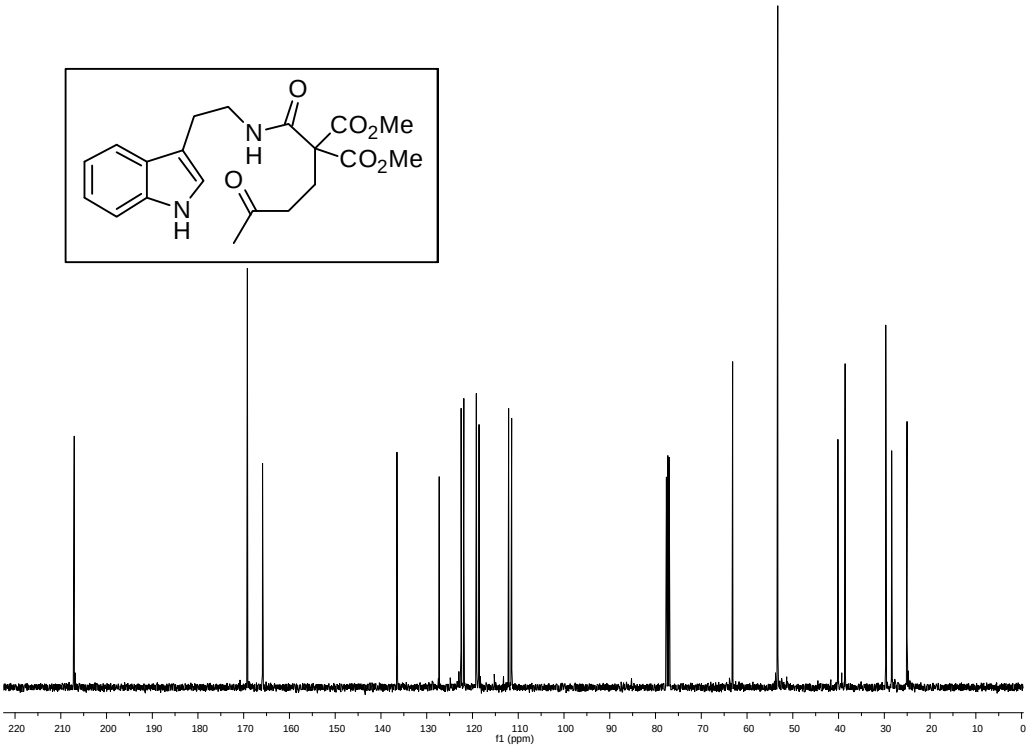
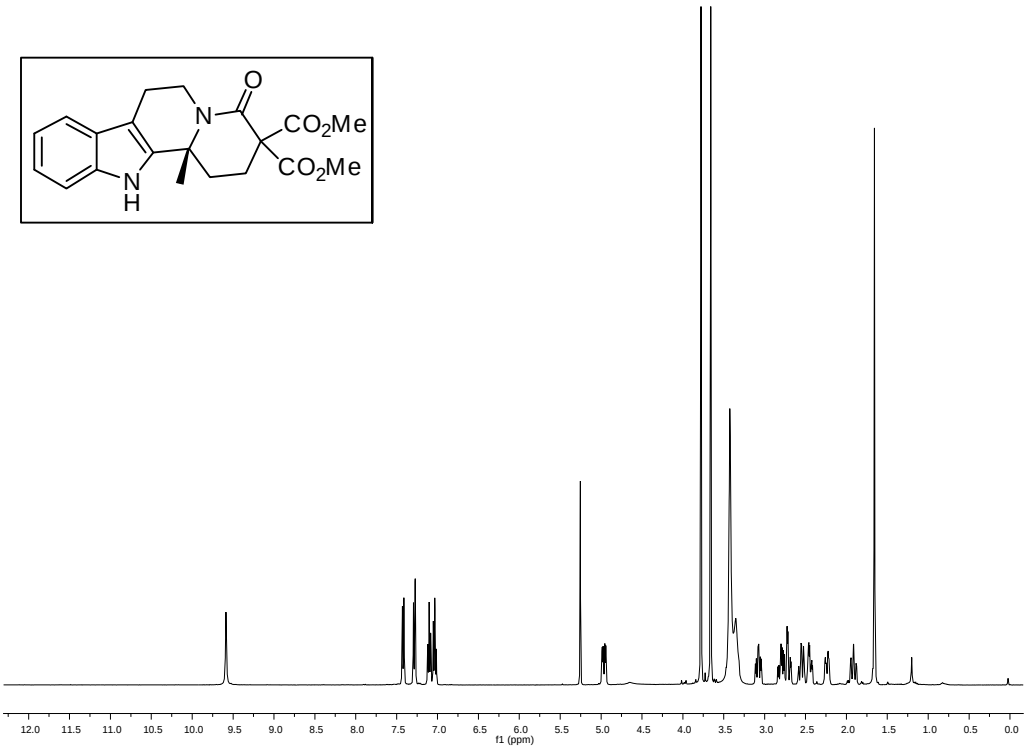
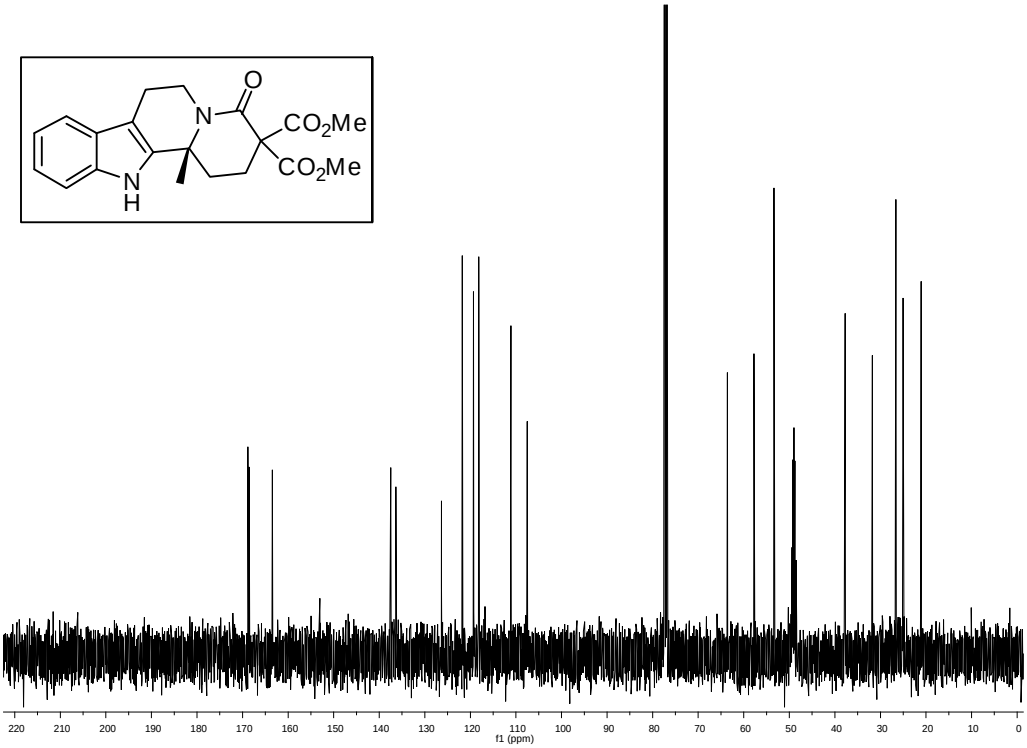


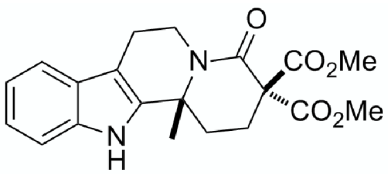
^{1}H NMR spectrum of dimethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9a

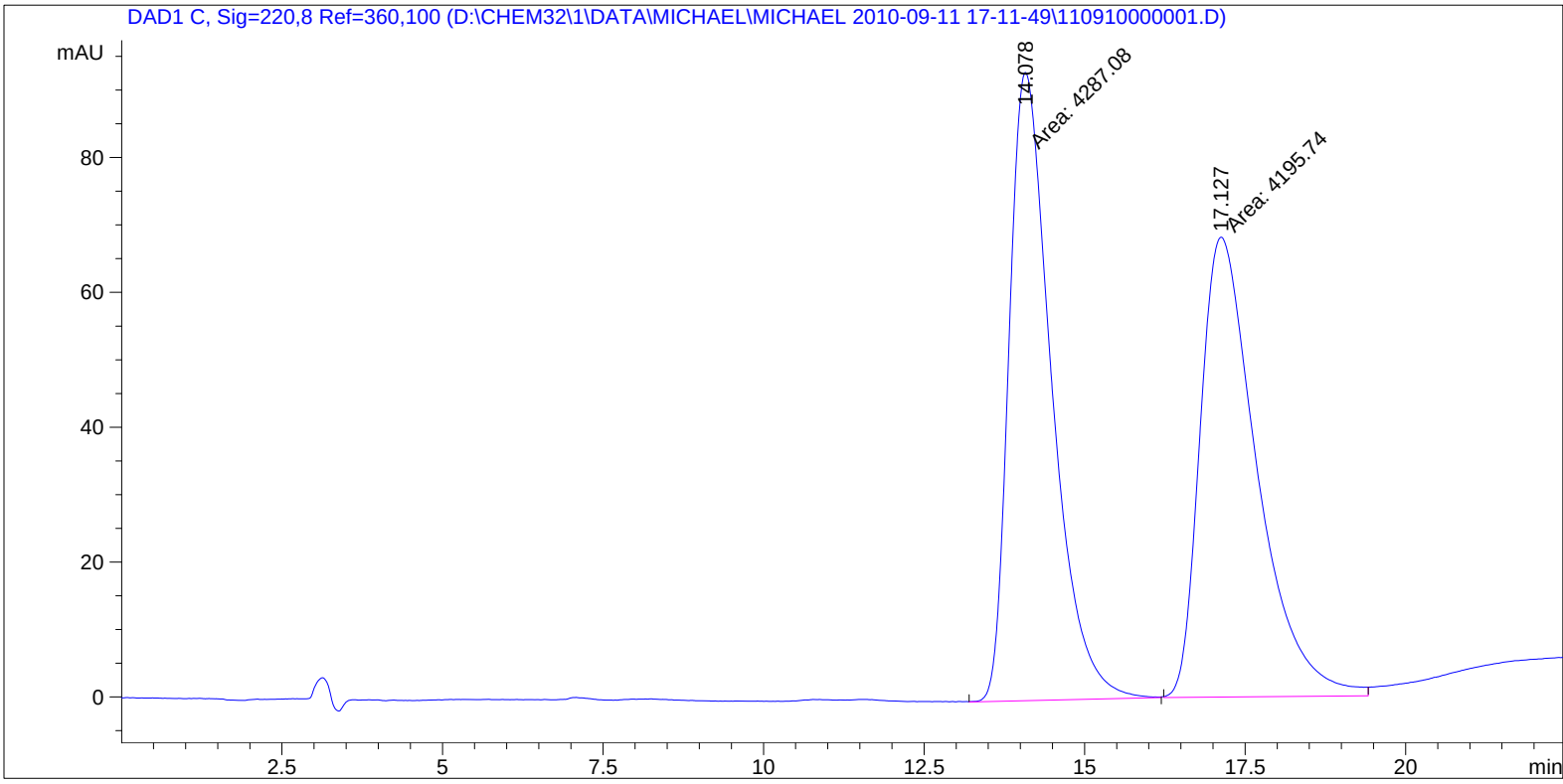


^{13}C NMR spectrum of dimethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9a



HPLC trace of racemic β-carboline (±)-9a



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Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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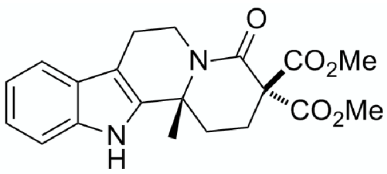
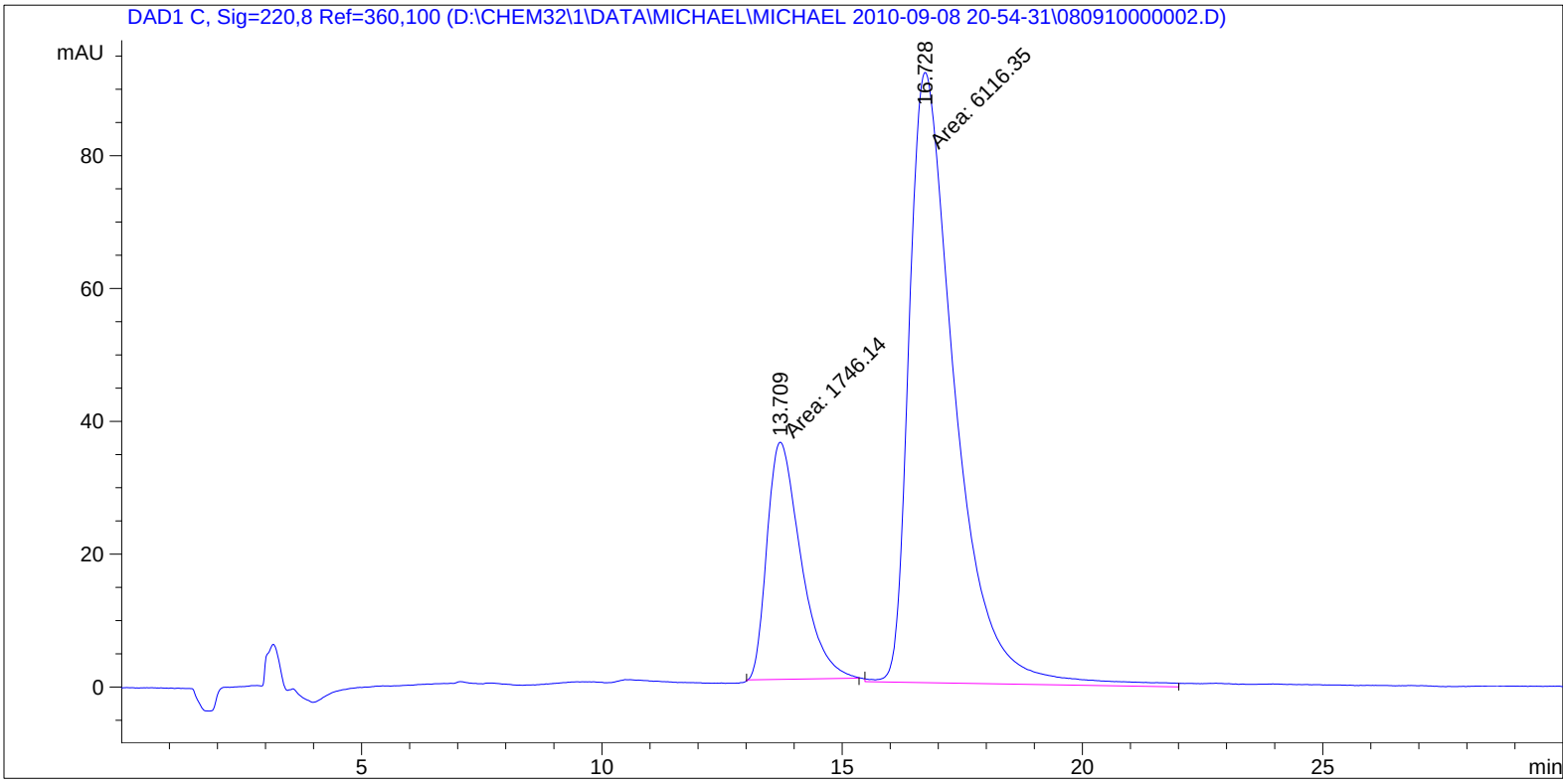
HPLC trace of enantioenriched β-carboline (+)-9a



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Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

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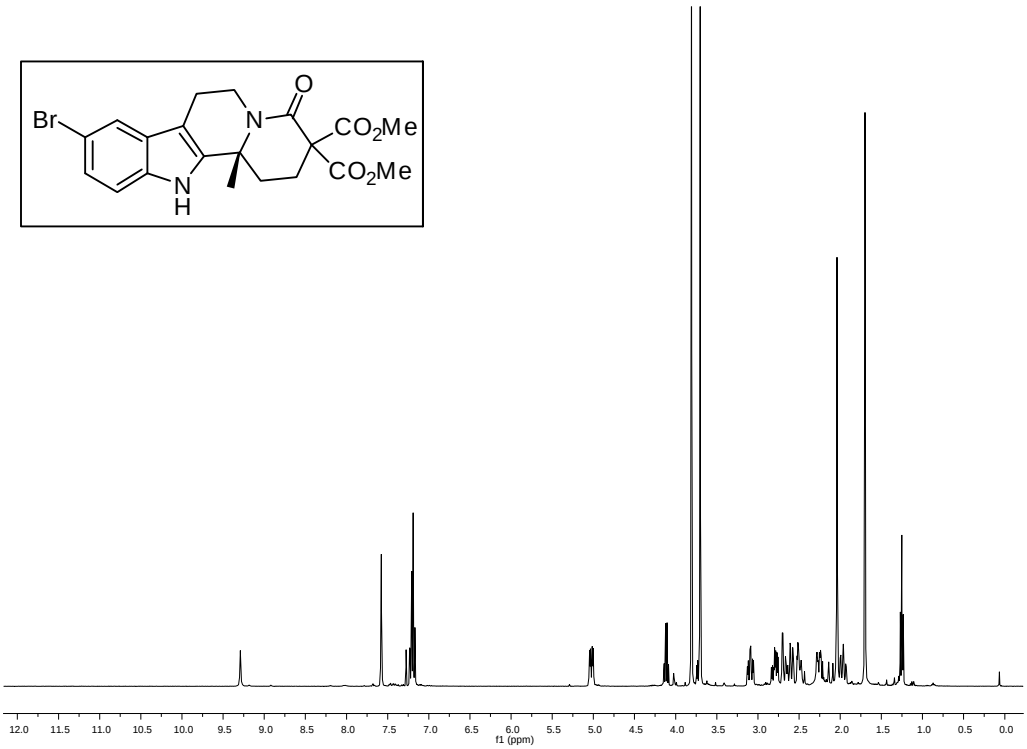
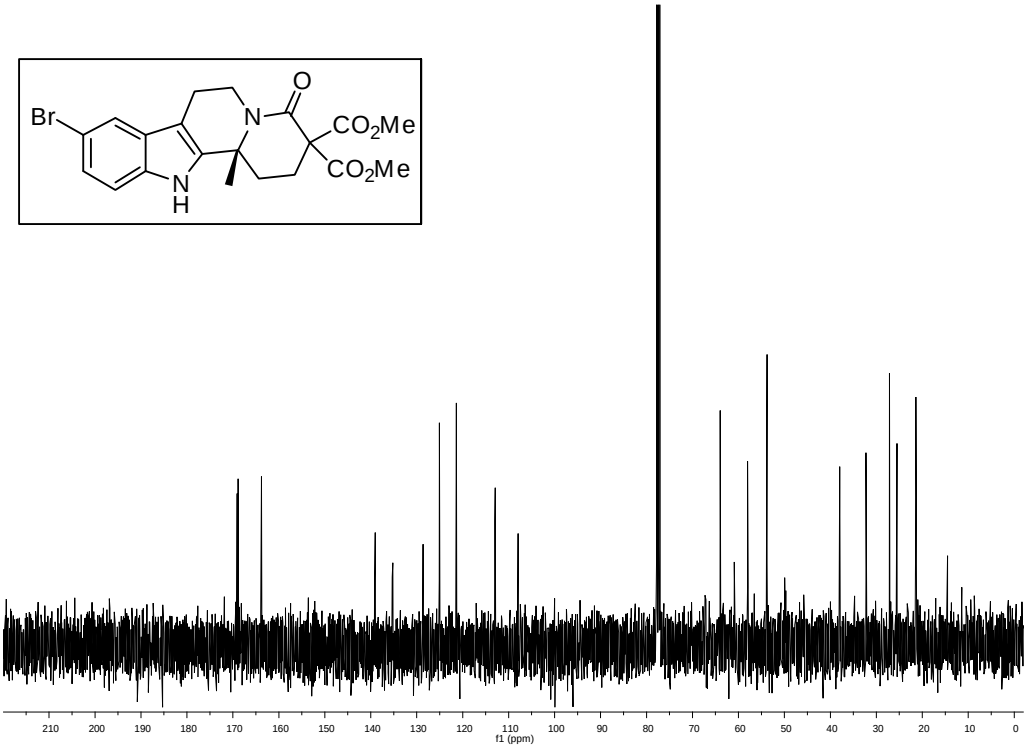
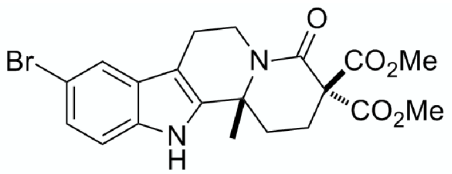
^{1}H NMR spectrum of dimethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9b



^{13}C NMR spectrum of dimethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9b



HPLC trace of racemic β-carboline (±)-9b



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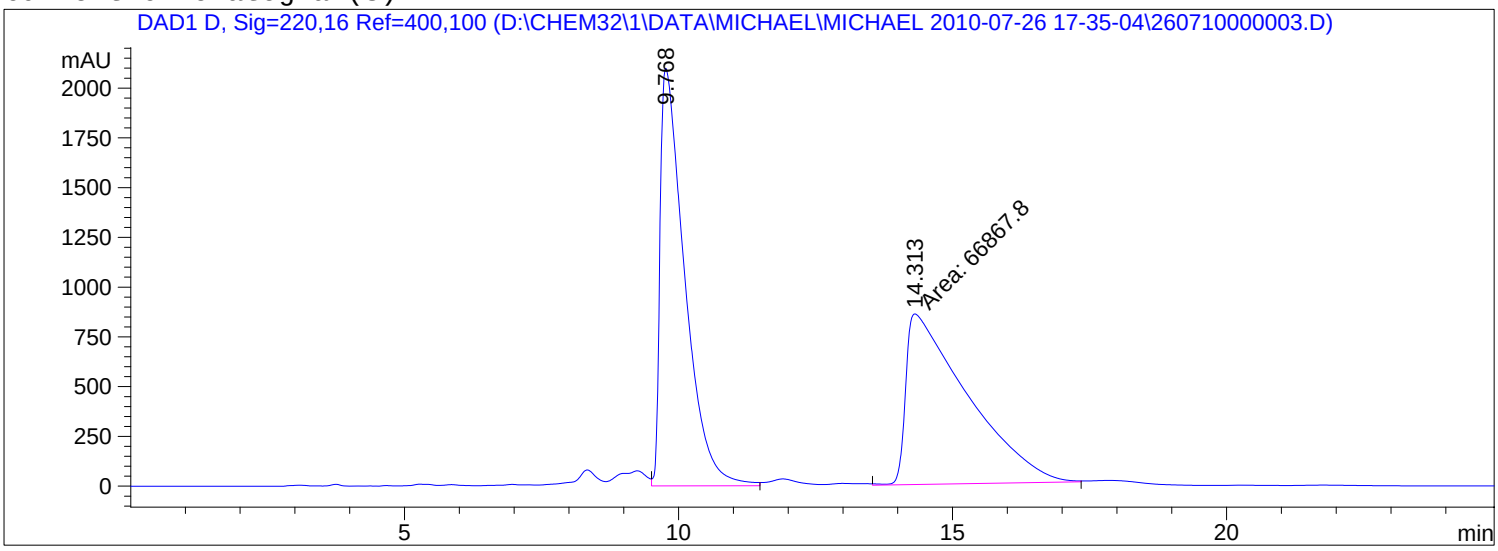

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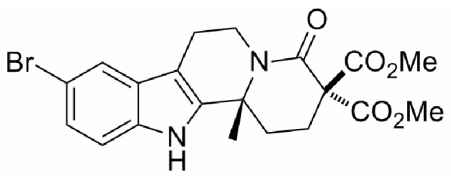
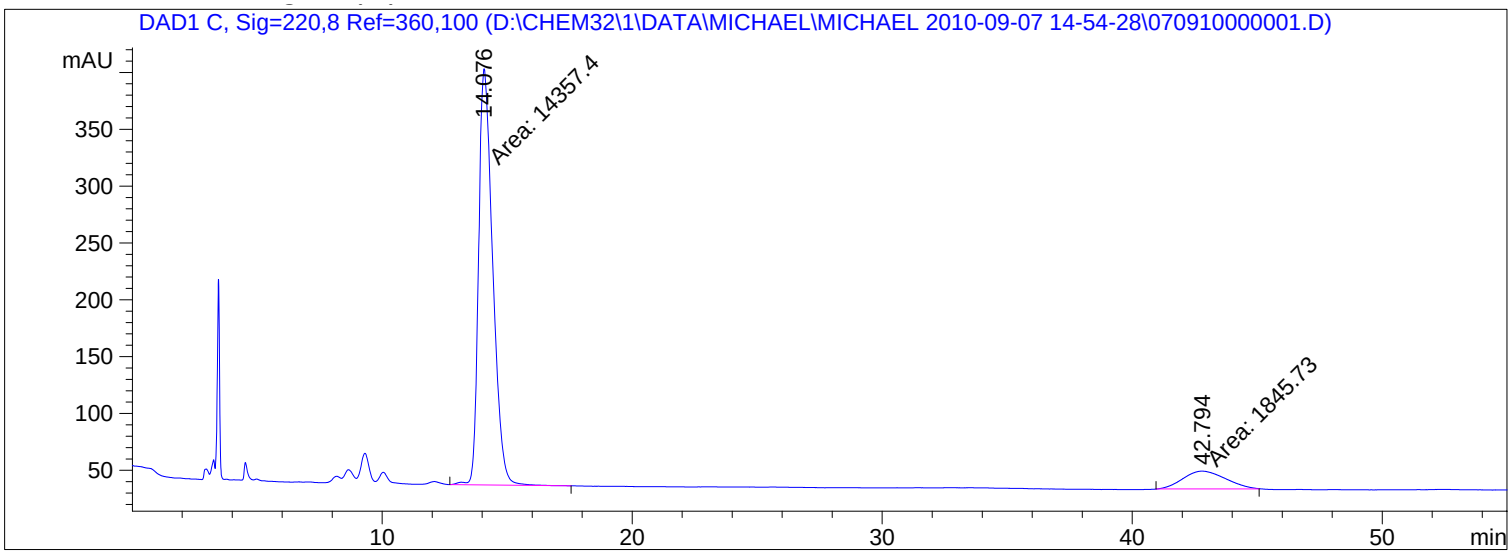
HPLC trace of enantioenriched β-carboline (+)-9b





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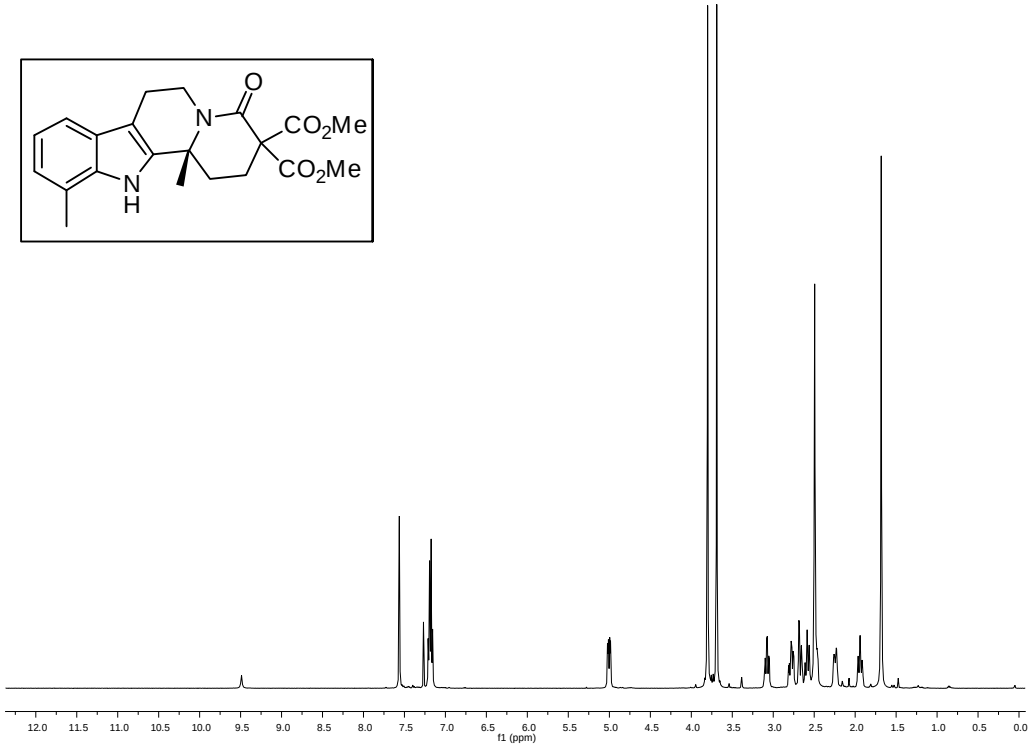
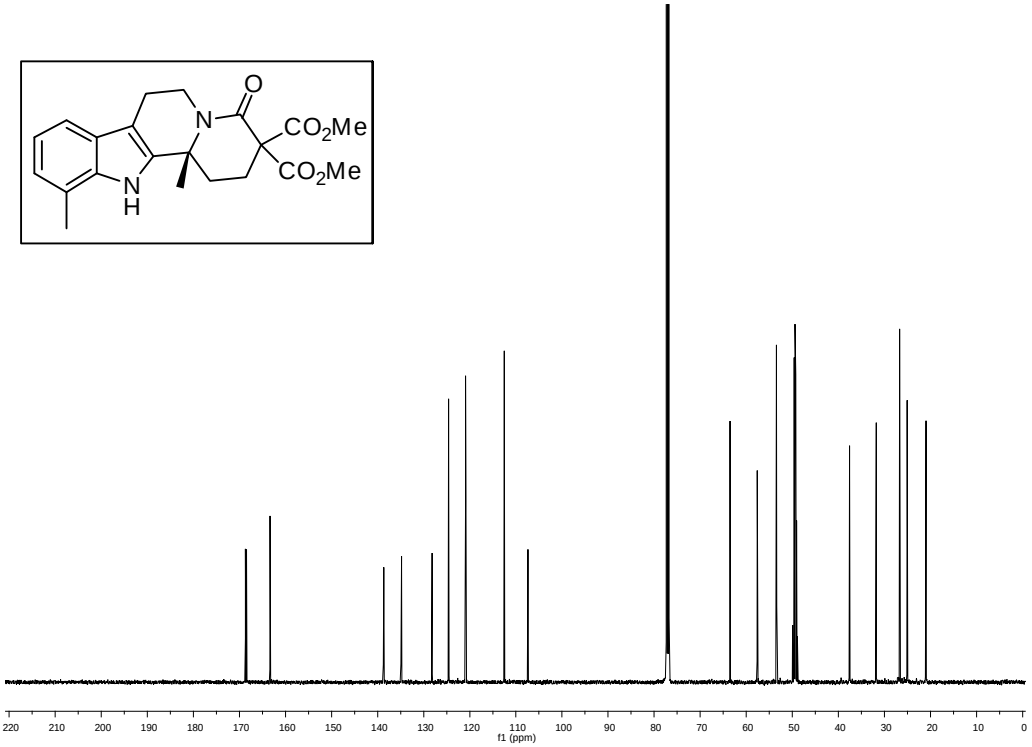
Totals :				1.62031e4	381.74448	

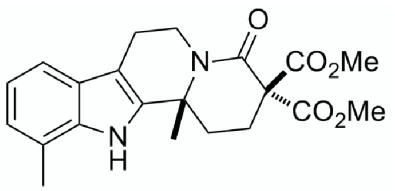
^{1}H NMR spectrum of dimethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9c

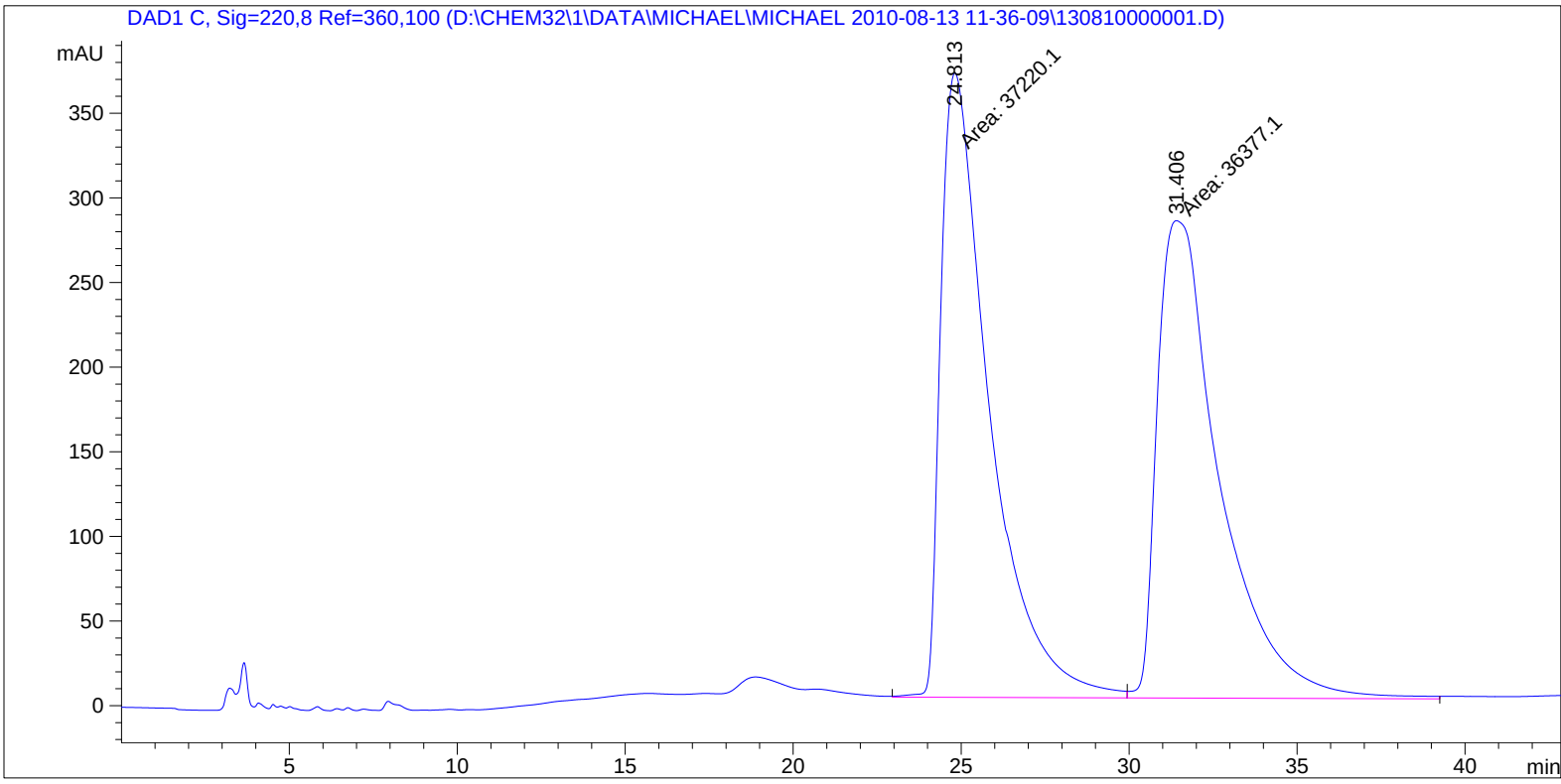


^{13}C NMR spectrum of dimethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9c



HPLC trace of racemic β-carboline (±)-9c



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                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  24.813 MF    1.6818 3.72201e4   368.84409  50.5727
   2  31.406 FM    2.1498 3.63771e4   282.01553  49.4273
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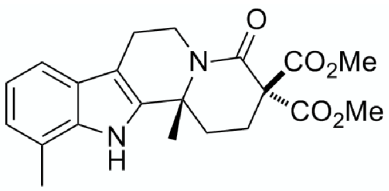
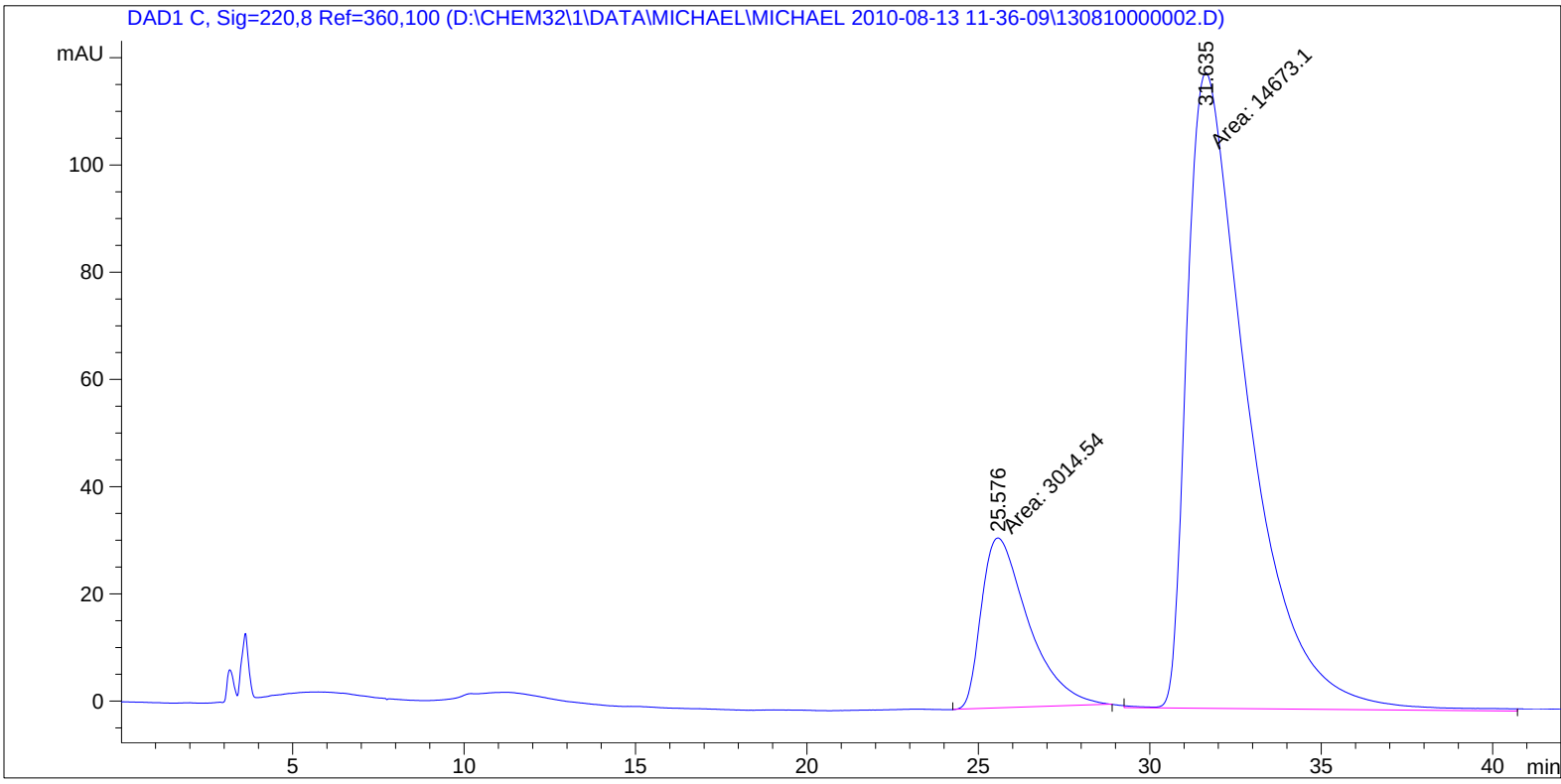
HPLC trace of enantioenriched β-carboline (+)-9c



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                        Area Percent Report
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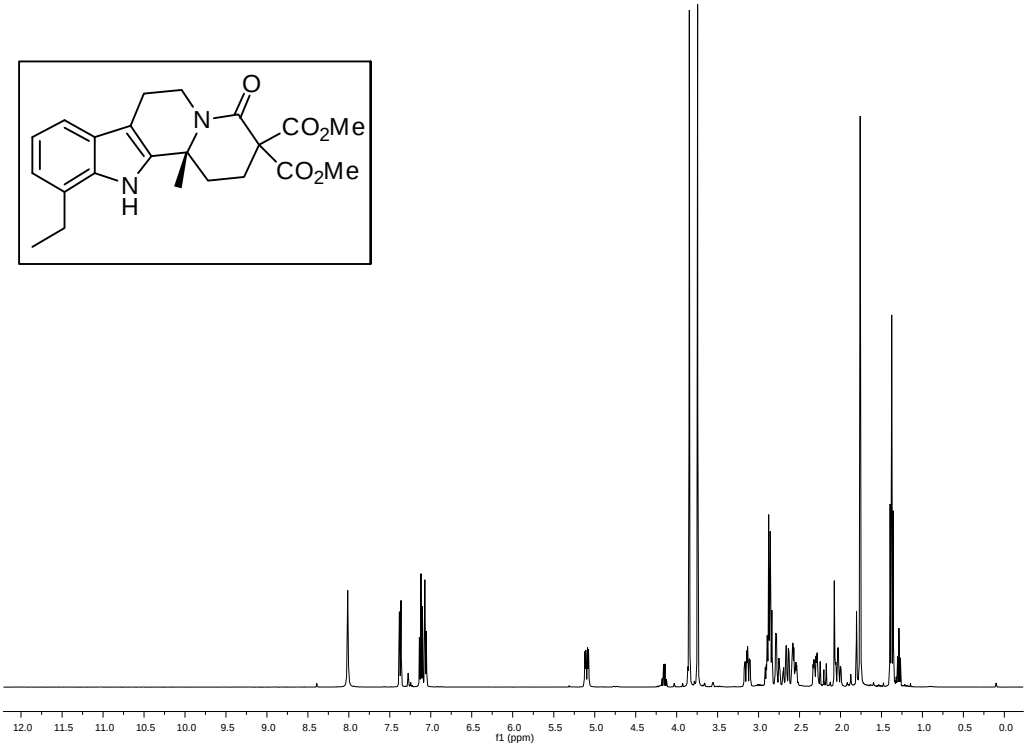
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

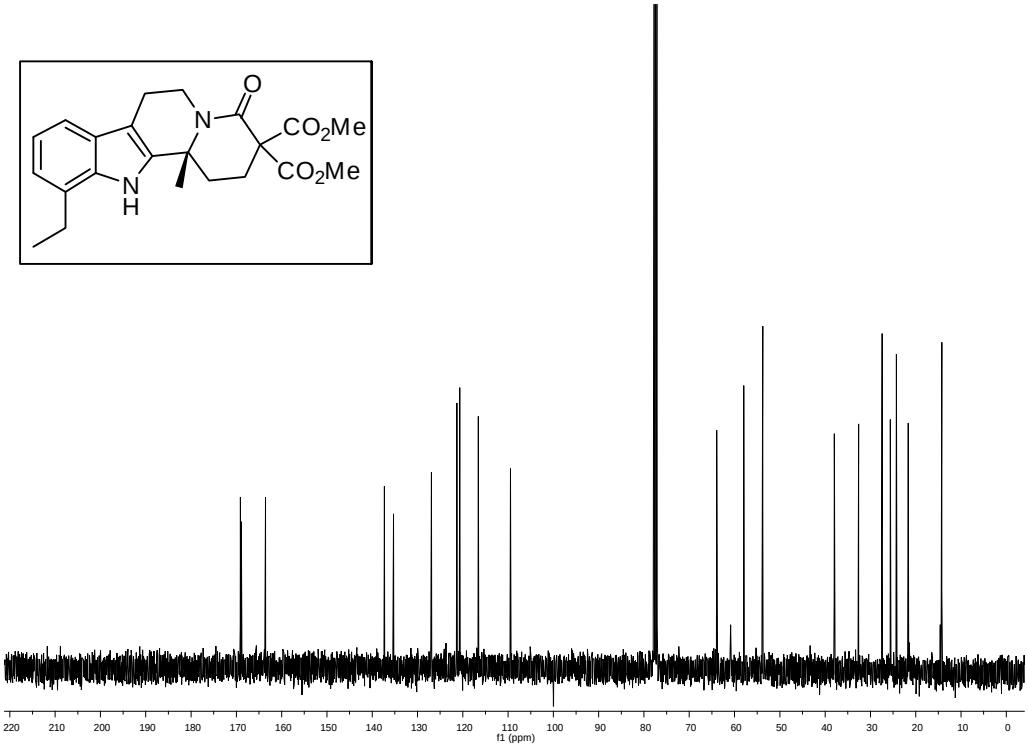

Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  25.576 MM    1.5854 3014.53564   31.69057  17.0432
   2  31.635 MM    2.0636 1.46731e4   118.50961  82.9568
```

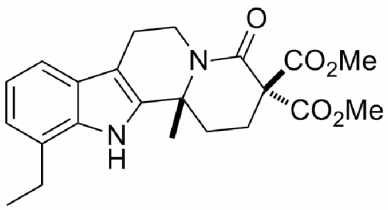
^{1}H NMR spectrum of dimethyl (12b*R*)-11-ethyl-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3*a*]quinolizine-3,3(4*H*)-dicarboxylate 9d

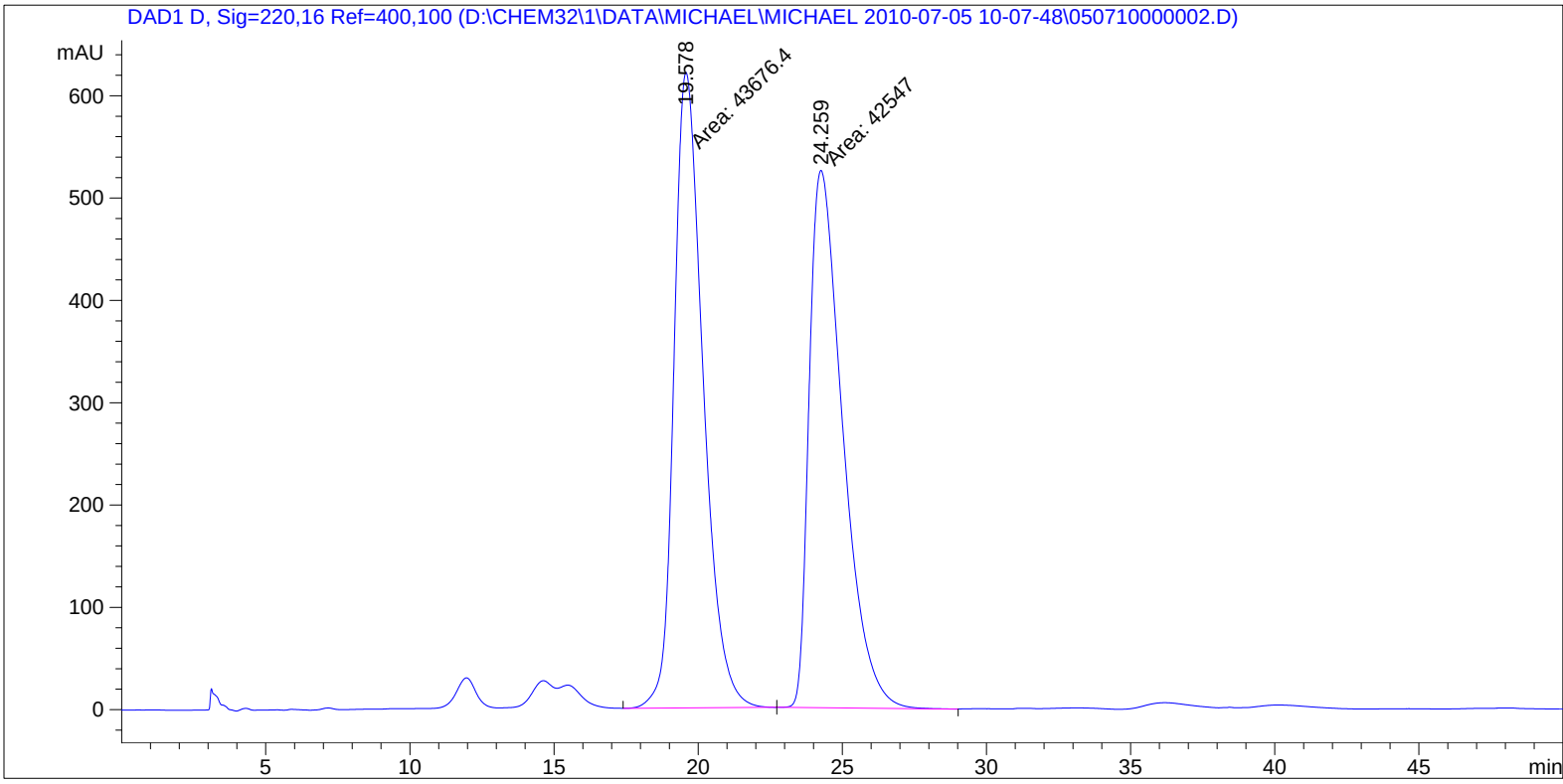


^{13}C NMR spectrum of dimethyl (12b*R*)-11-ethyl-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3*a*]quinolizine-3,3(4*H*)-dicarboxylate 9d



HPLC trace of racemic β-carboline (±)-9d



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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=220,16 Ref=400,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.578 MM    1.1721 4.36764e4   621.06903  50.6549
   2  24.259 MM    1.3499 4.25470e4   525.29303  49.3451
```
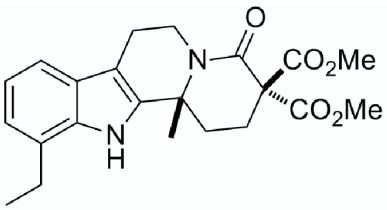
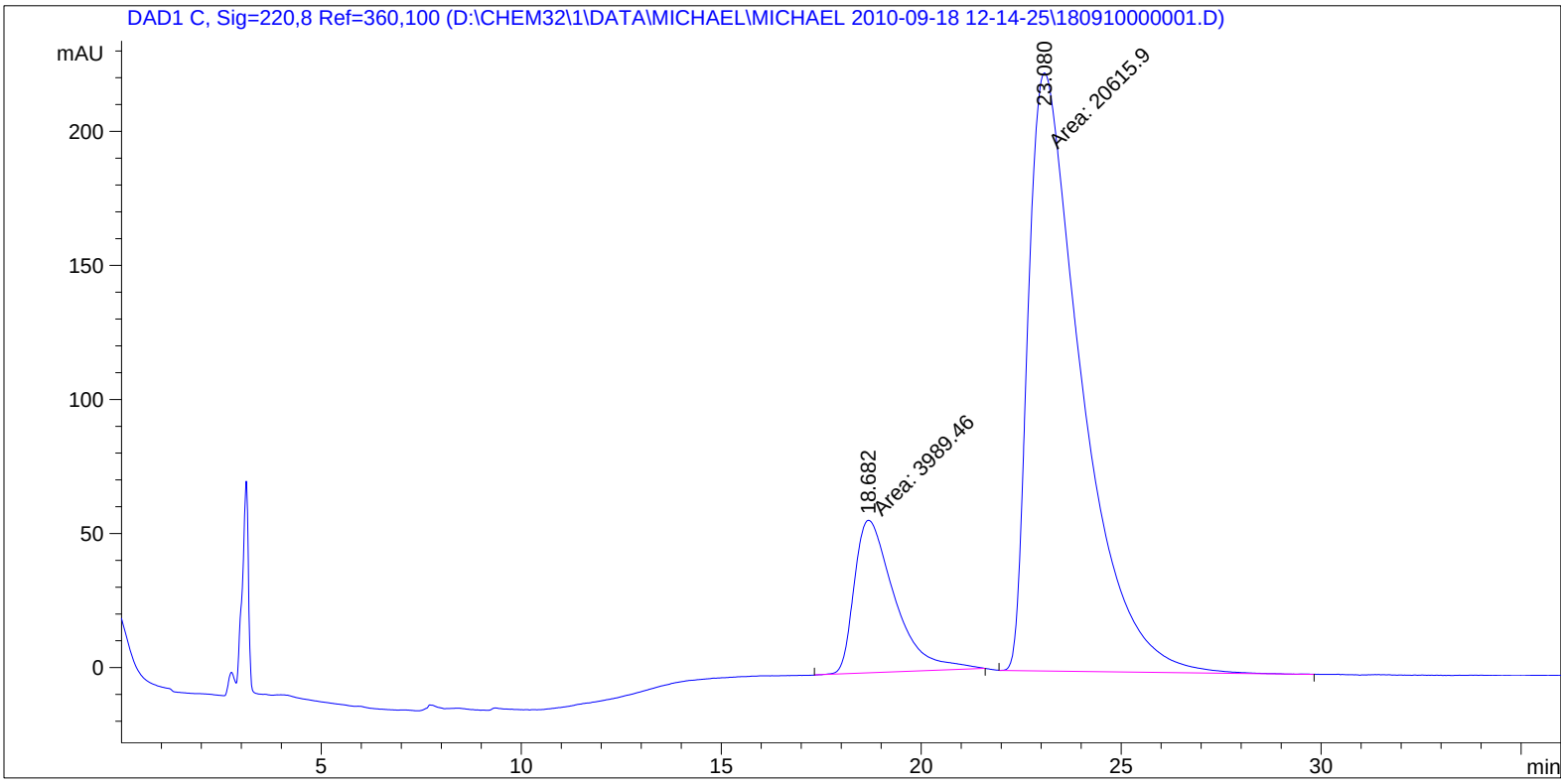

HPLC trace of enantioenriched β-carboline (+)-9d



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                        Area Percent Report
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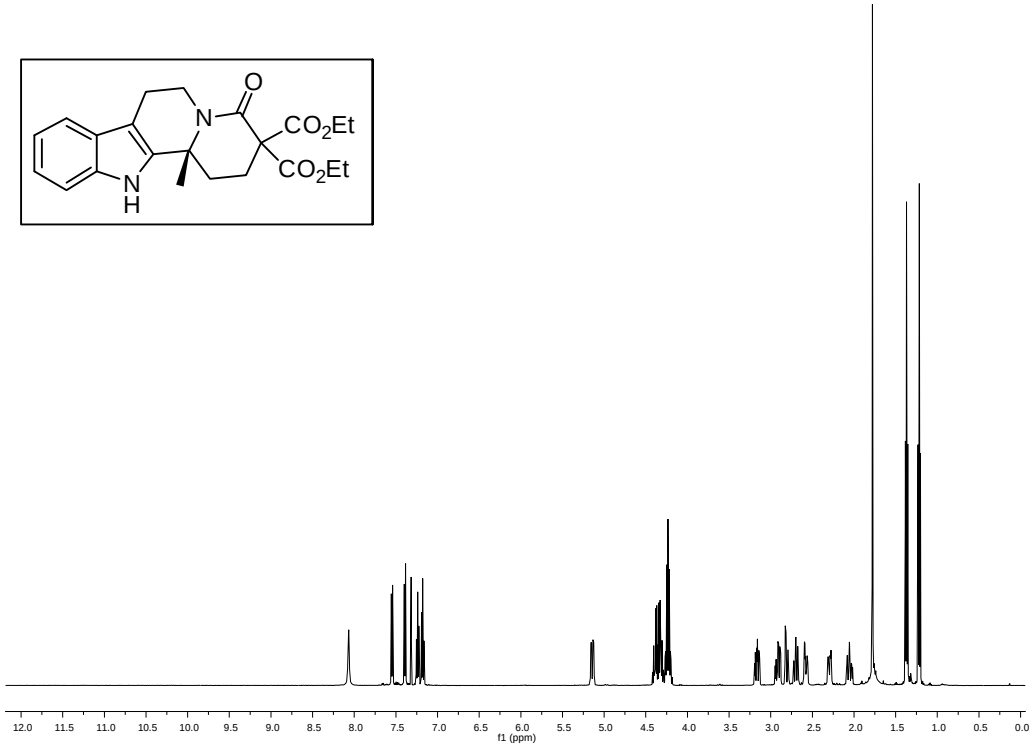
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

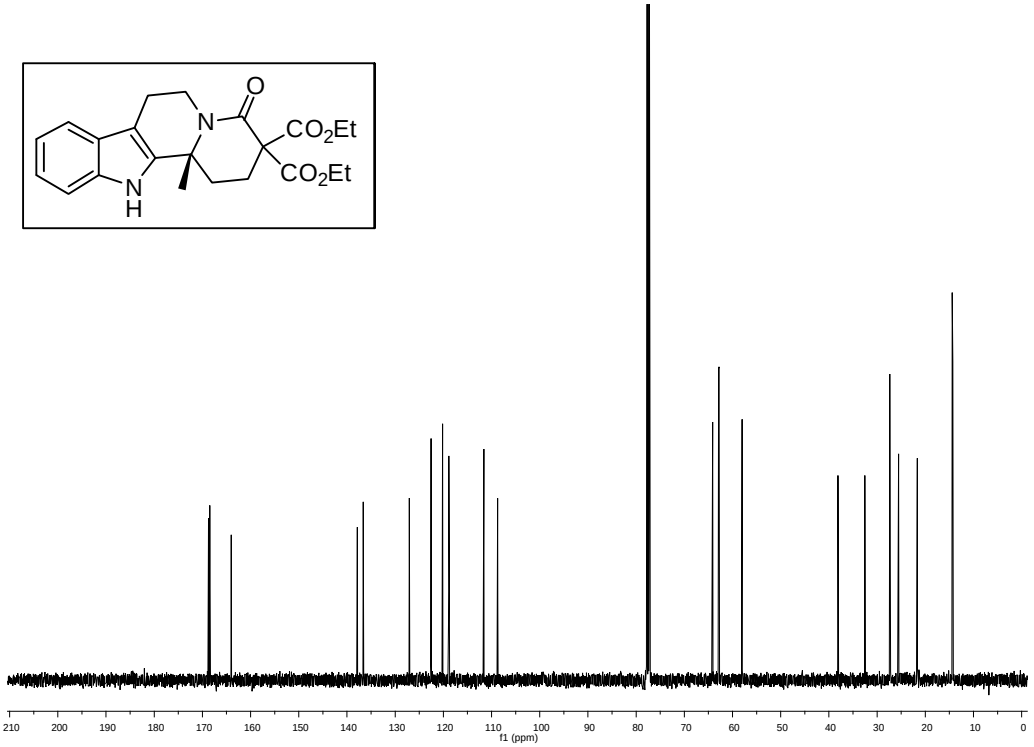

Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.682 MM    1.1689 3989.46143   56.88504  16.2138
   2  23.080 MM    1.5404 2.06159e4   223.05655  83.7862
```

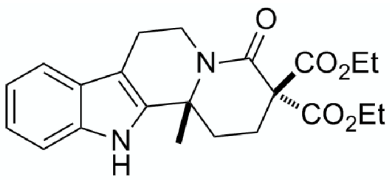
^{1}H NMR spectrum of diethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9e

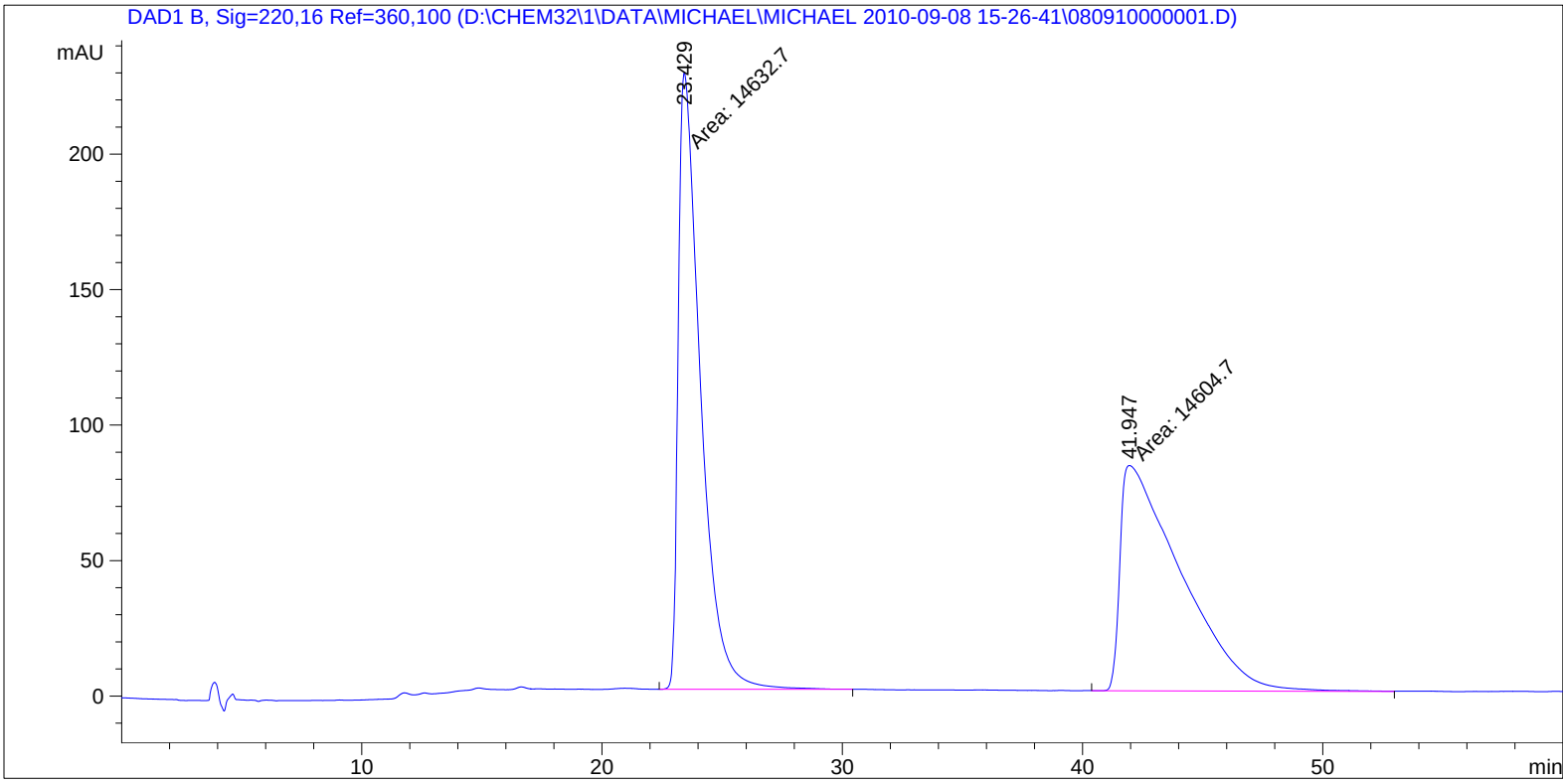


^{13}C NMR spectrum of diethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9e



HPLC trace of racemic β-carboline (±)-9e



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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=220,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.429 MM    1.0712 1.46327e4   227.65962  50.0479
   2  41.947 MM    2.9263 1.46047e4    83.18184  49.9521
```
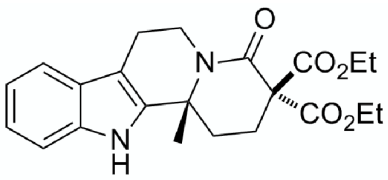
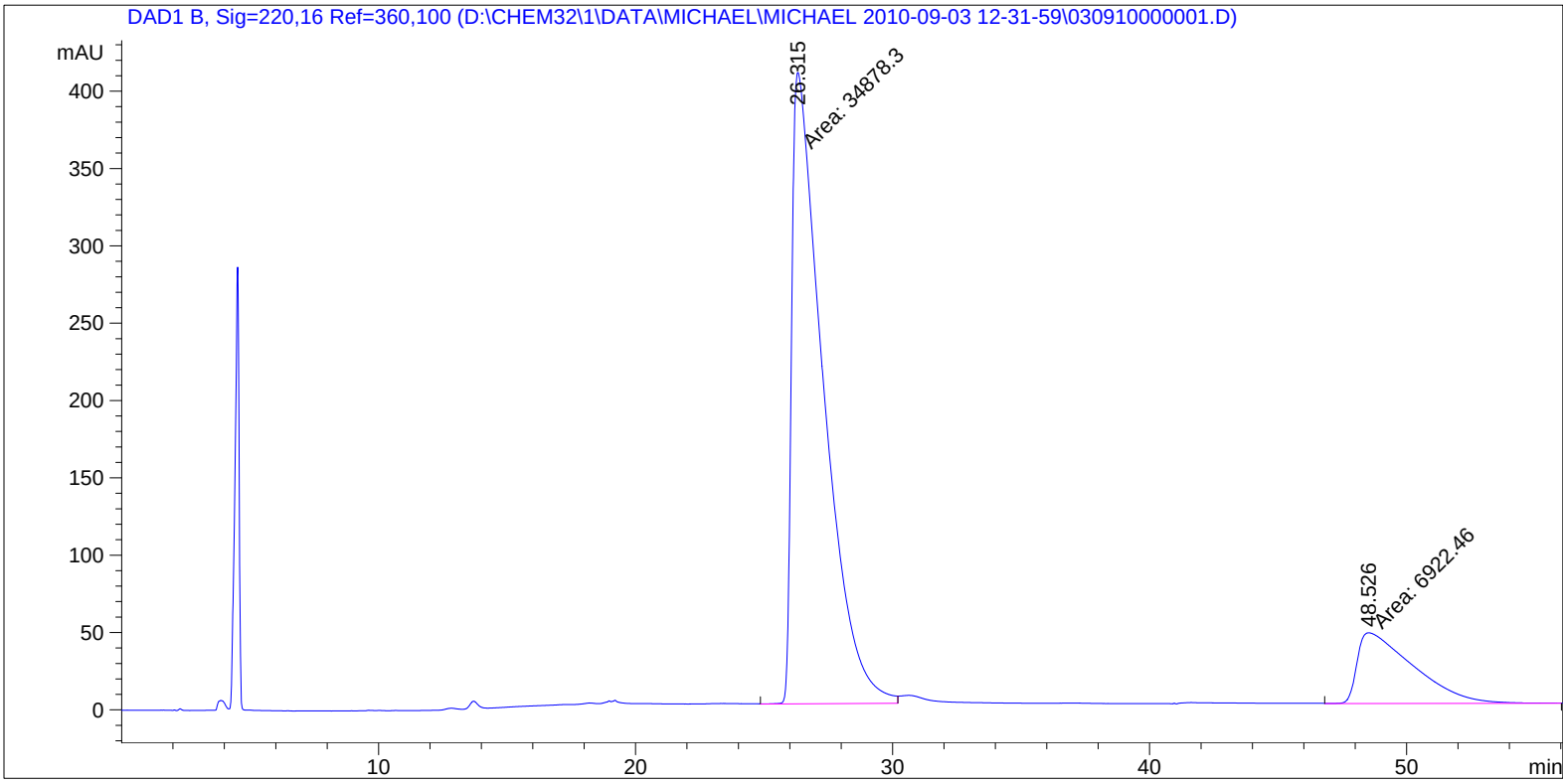

HPLC trace of enantioenriched β-carboline (+)-9e



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                      Area Percent Report
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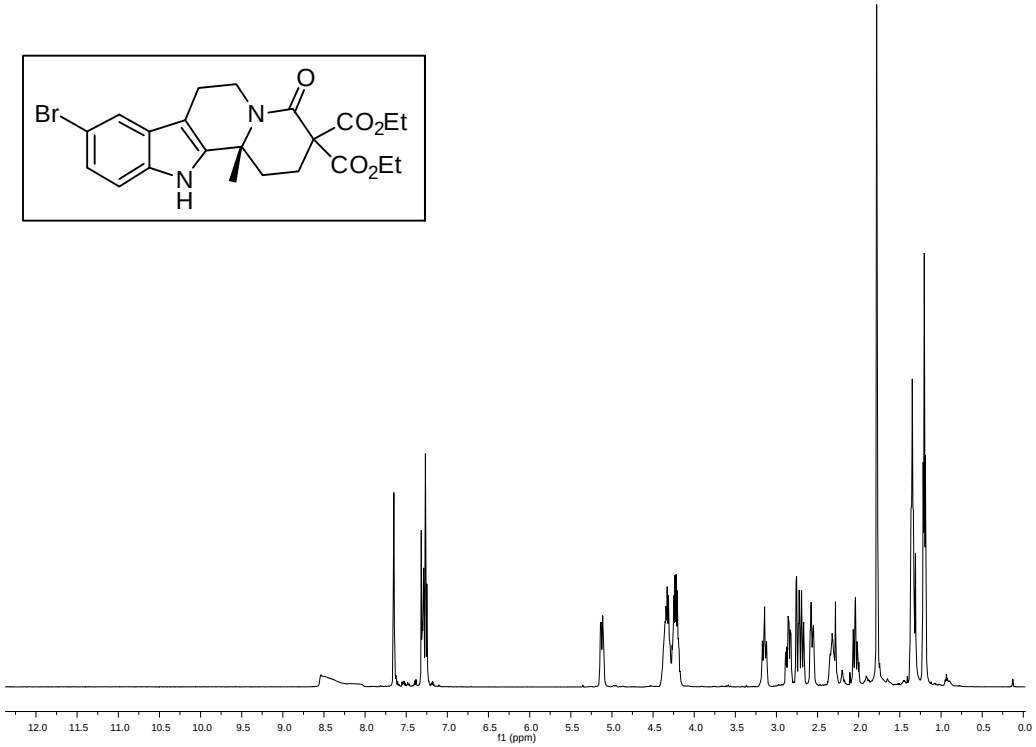
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

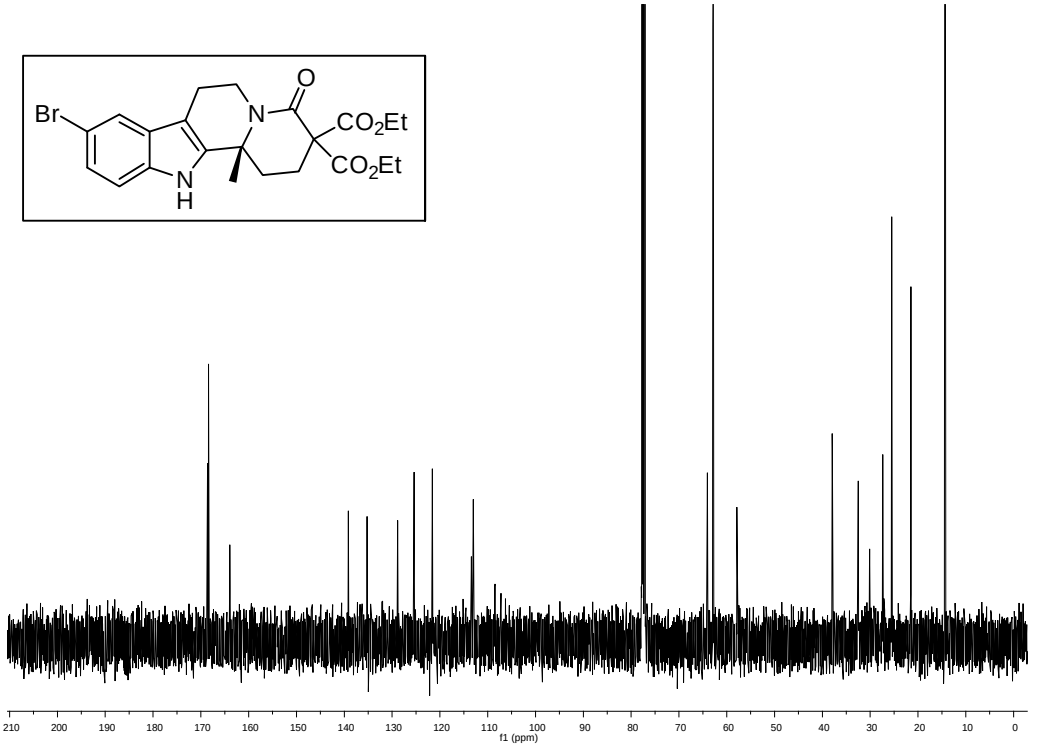

Signal 1: DAD1 B, Sig=220,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  26.315 MM    1.4240 3.48783e4   408.20990  83.4394
   2  48.526 MM    2.5241 6922.46338   45.70938  16.5606
```

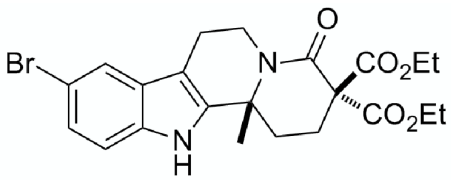
^{1}H NMR spectrum of diethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9f

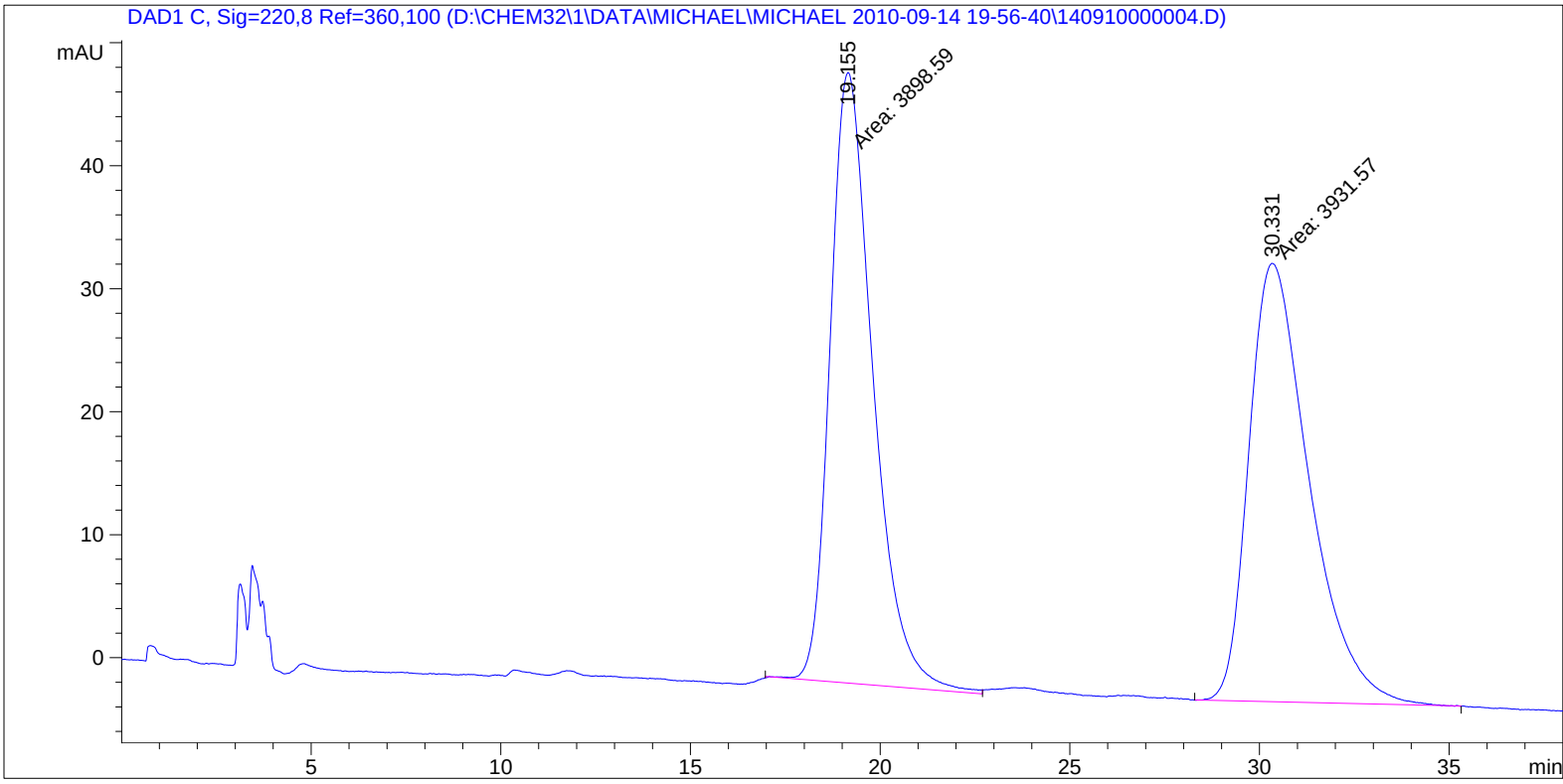


^{13}C NMR spectrum of diethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9f



HPLC trace of racemic β-carboline (±)-9f



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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.155 MM    1.3088 3898.58789   49.64620  49.7894
   2  30.331 MM    1.8383 3931.57251   35.64463  50.2106
```
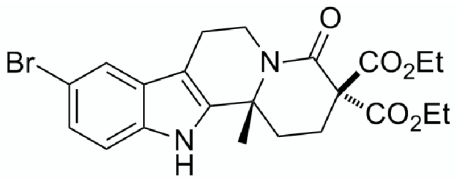
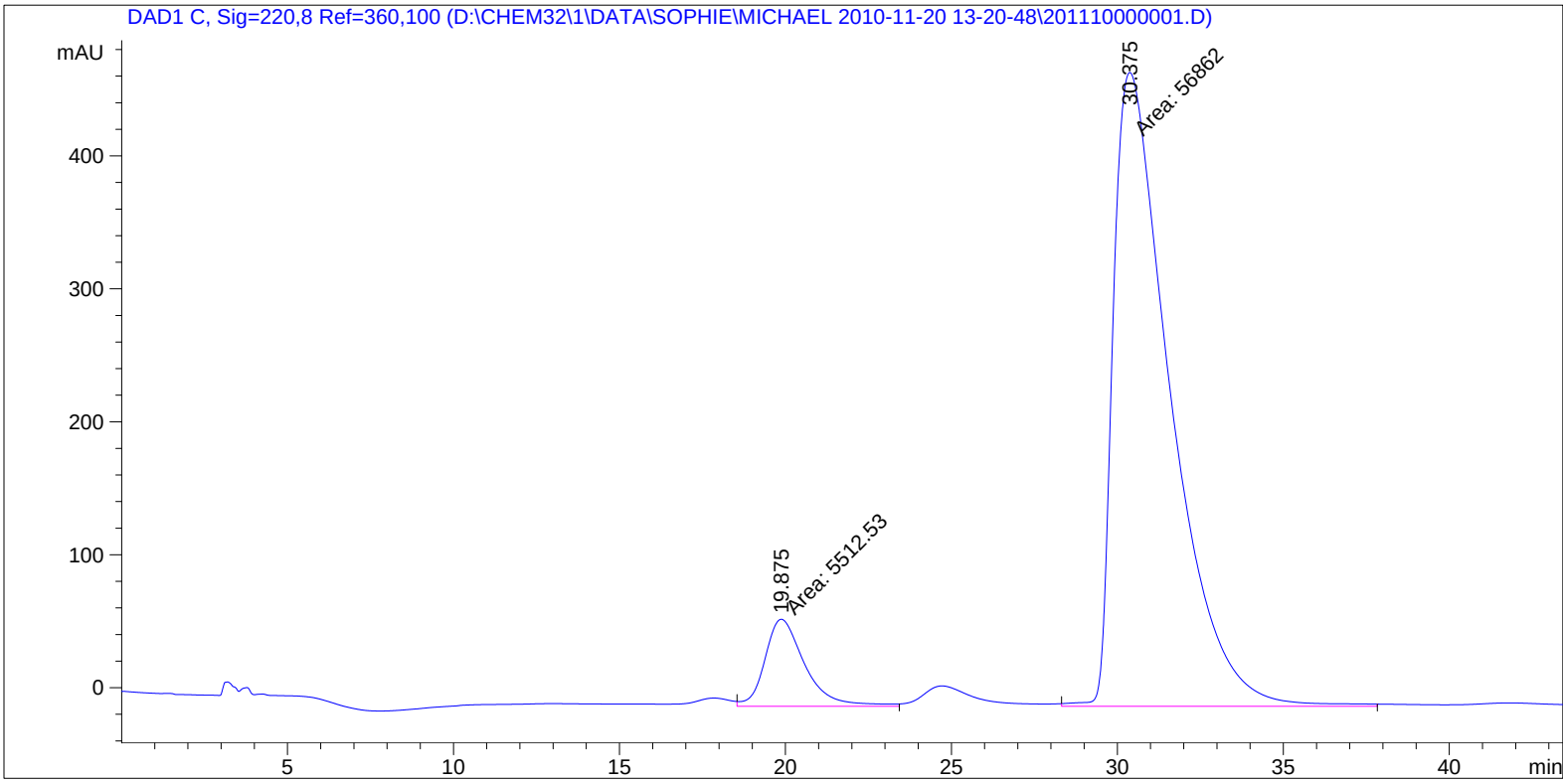

HPLC trace of enantioenriched β-carboline (+)-9f



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                      Area Percent Report
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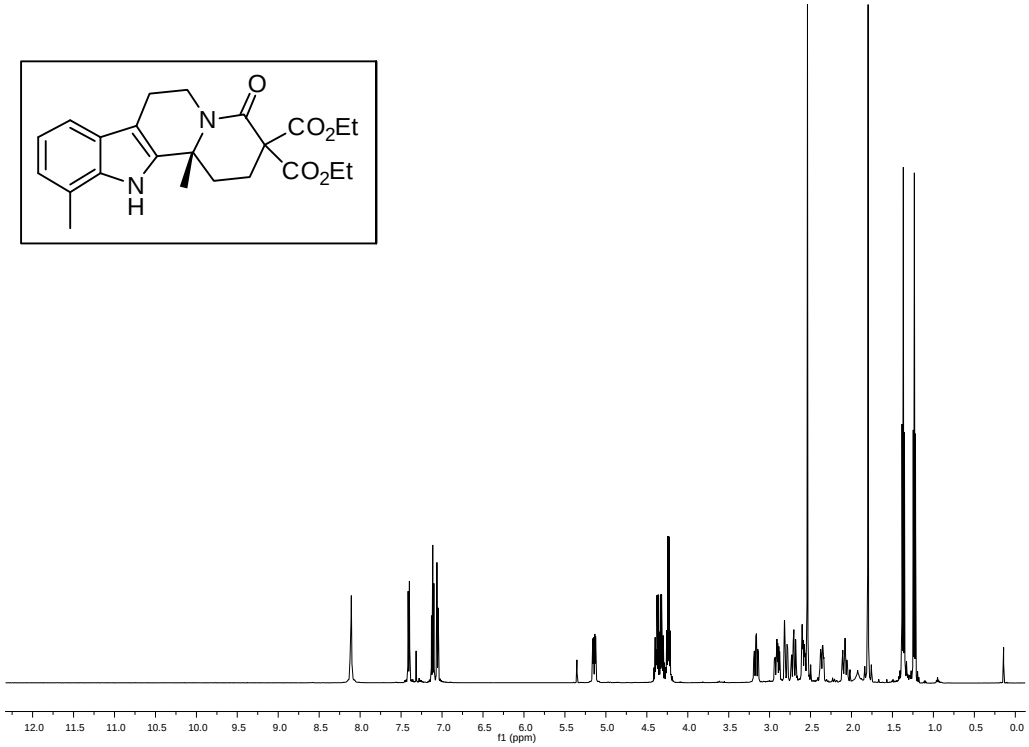
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

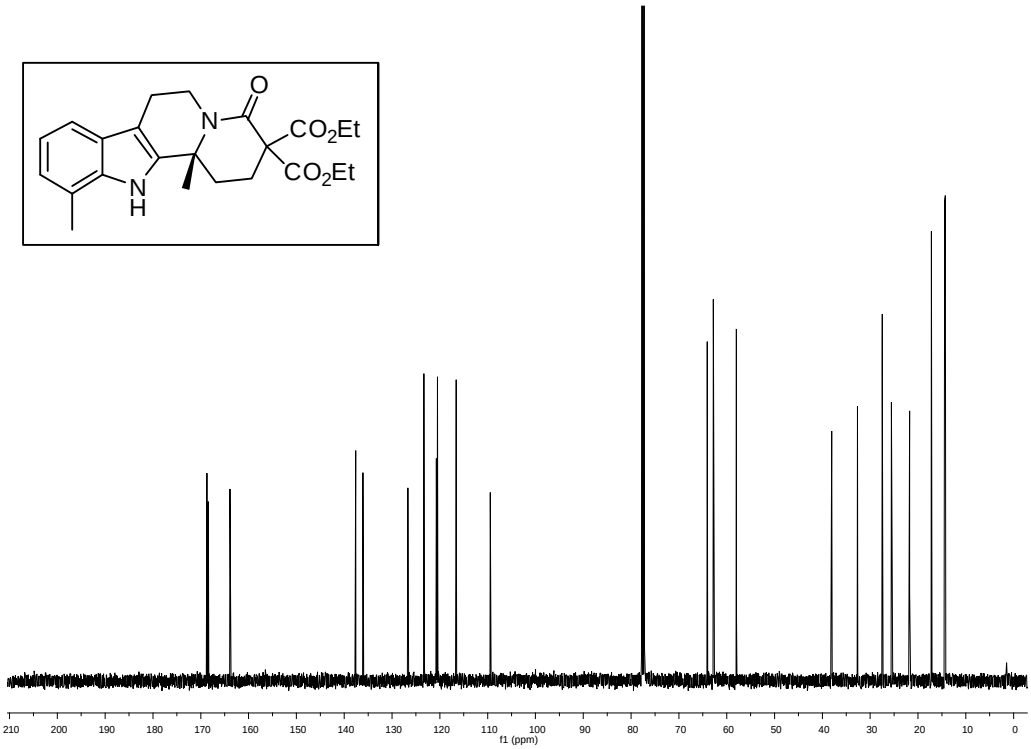

Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.875 MM    1.4031 5512.52783   65.47871   8.8378
   2  30.375 MM    1.9878 5.68620e4   476.76862  91.1622
```

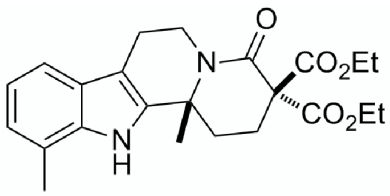
^{1}H NMR spectrum of diethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9g

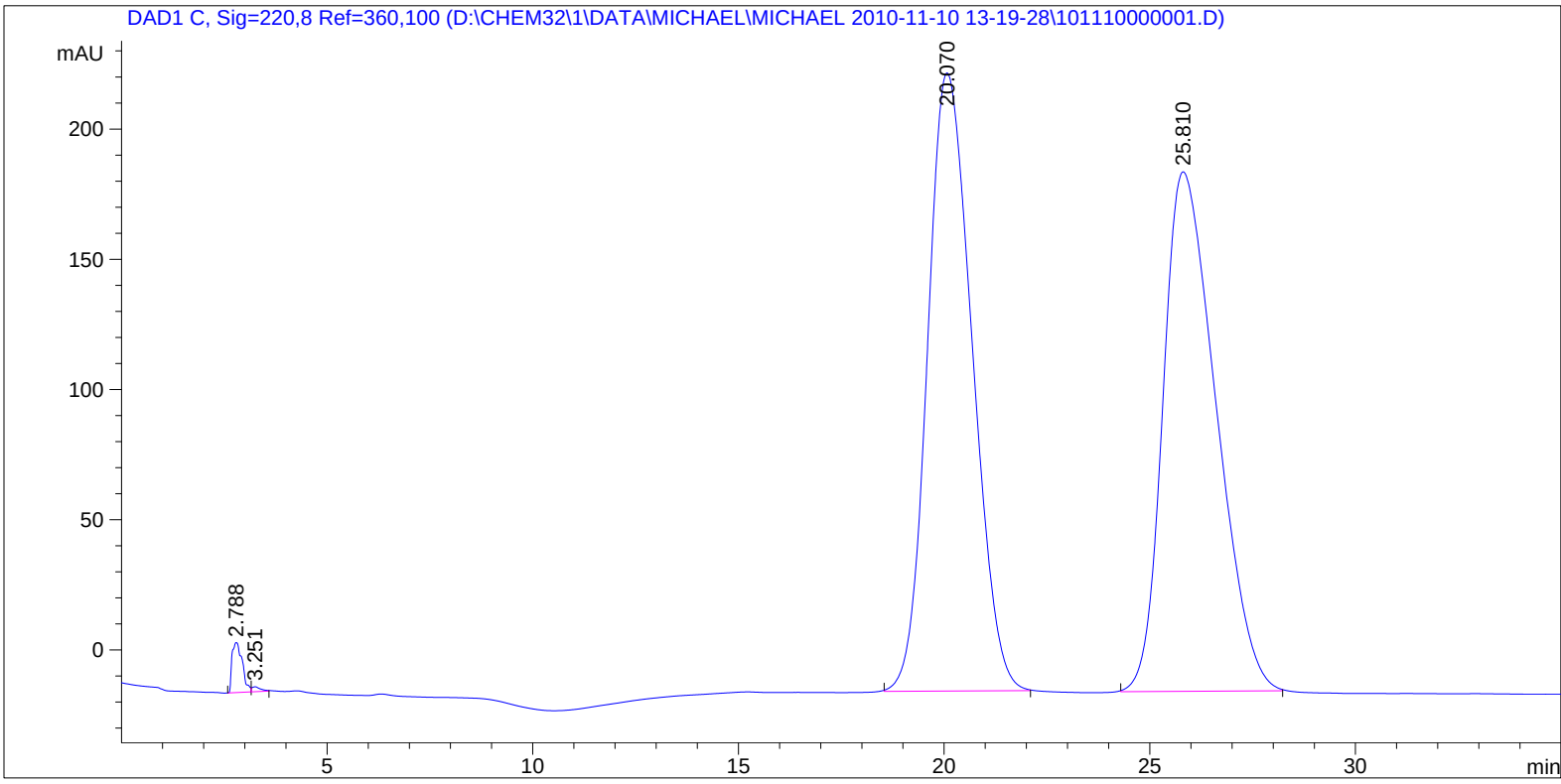


^{13}C NMR spectrum of diethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9g



HPLC trace of racemic β-carboline (±)-9g



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                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   2.788 BV    0.2324  332.81735   19.18505   0.9233
   2   3.251 VB    0.2119   27.81184    1.88751   0.0772
   3  20.070 BB    1.1832 1.78855e4   237.33351  49.6172
   4  25.810 BB    1.3770 1.78008e4   199.49512  49.3824
```
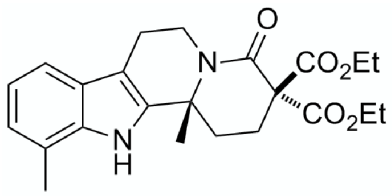
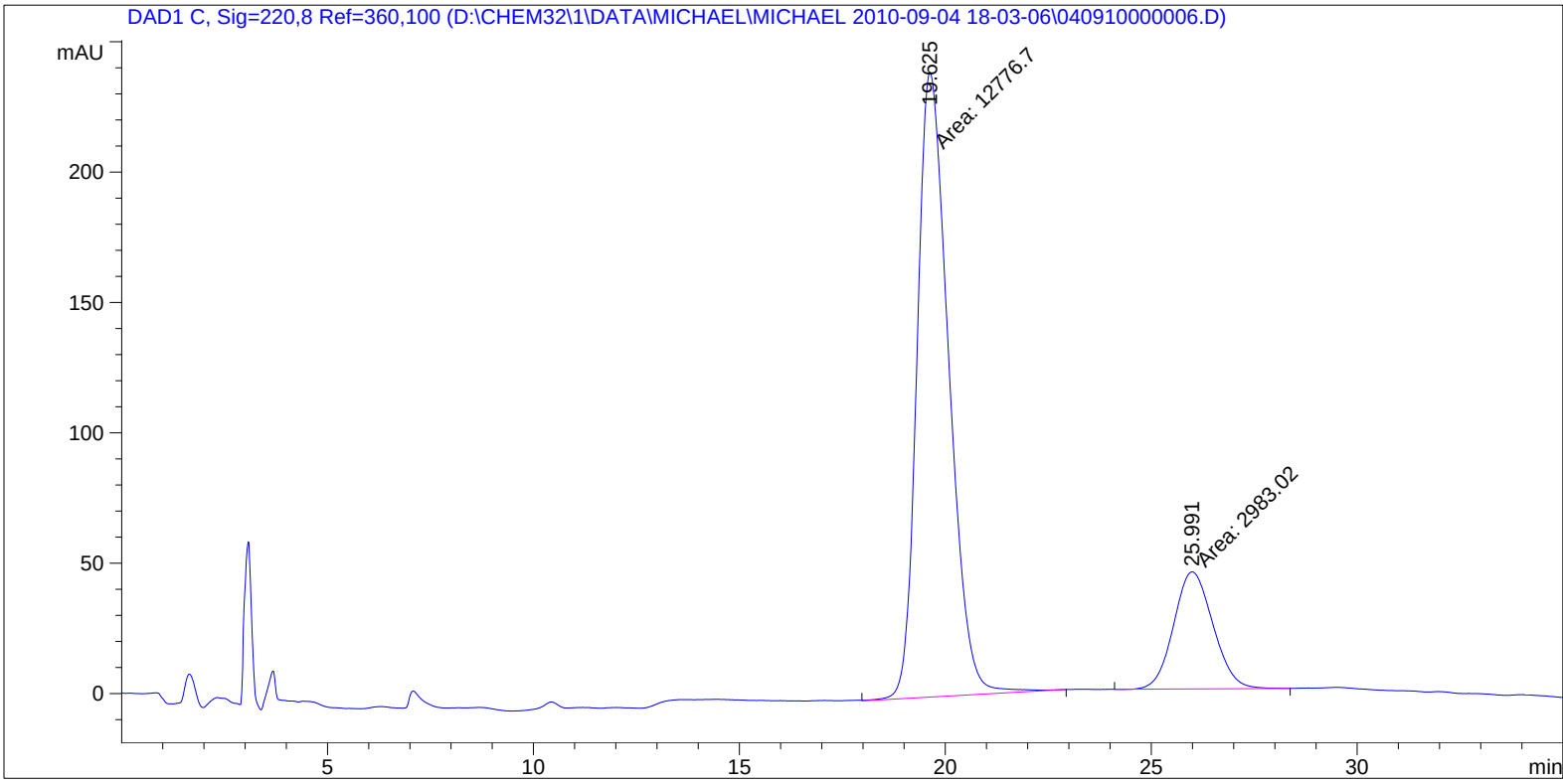

HPLC trace of enantioenriched β-carboline (+)-9g



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                      Area Percent Report
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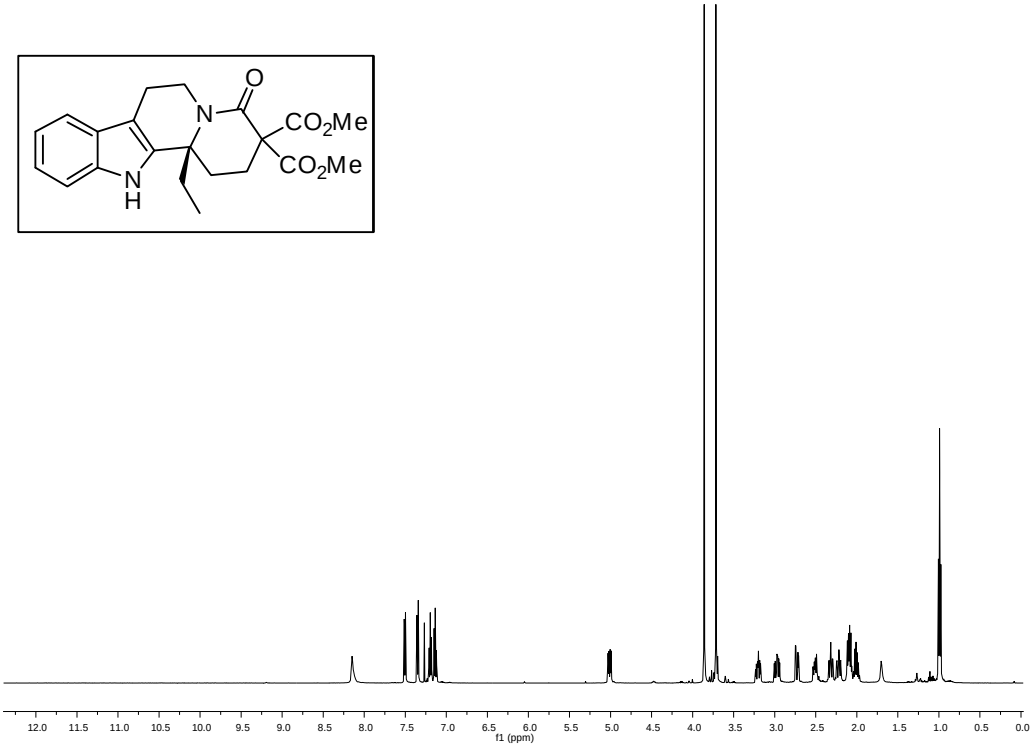
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

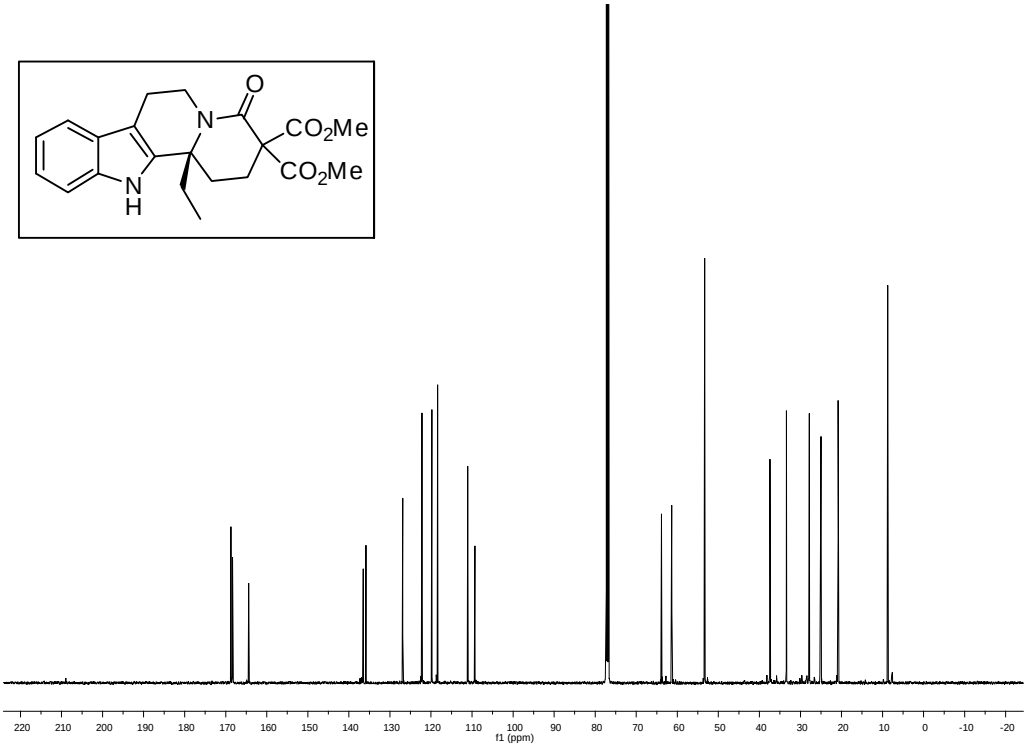

Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.625 MM    0.8889 1.27767e4   239.56836  81.0719
   2  25.991 MM    1.1065 2983.01831   44.93362  18.9281
```

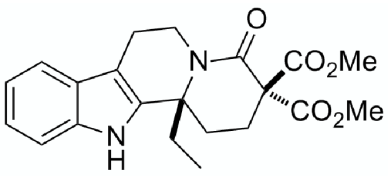
^{1}H NMR spectrum of dimethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9h

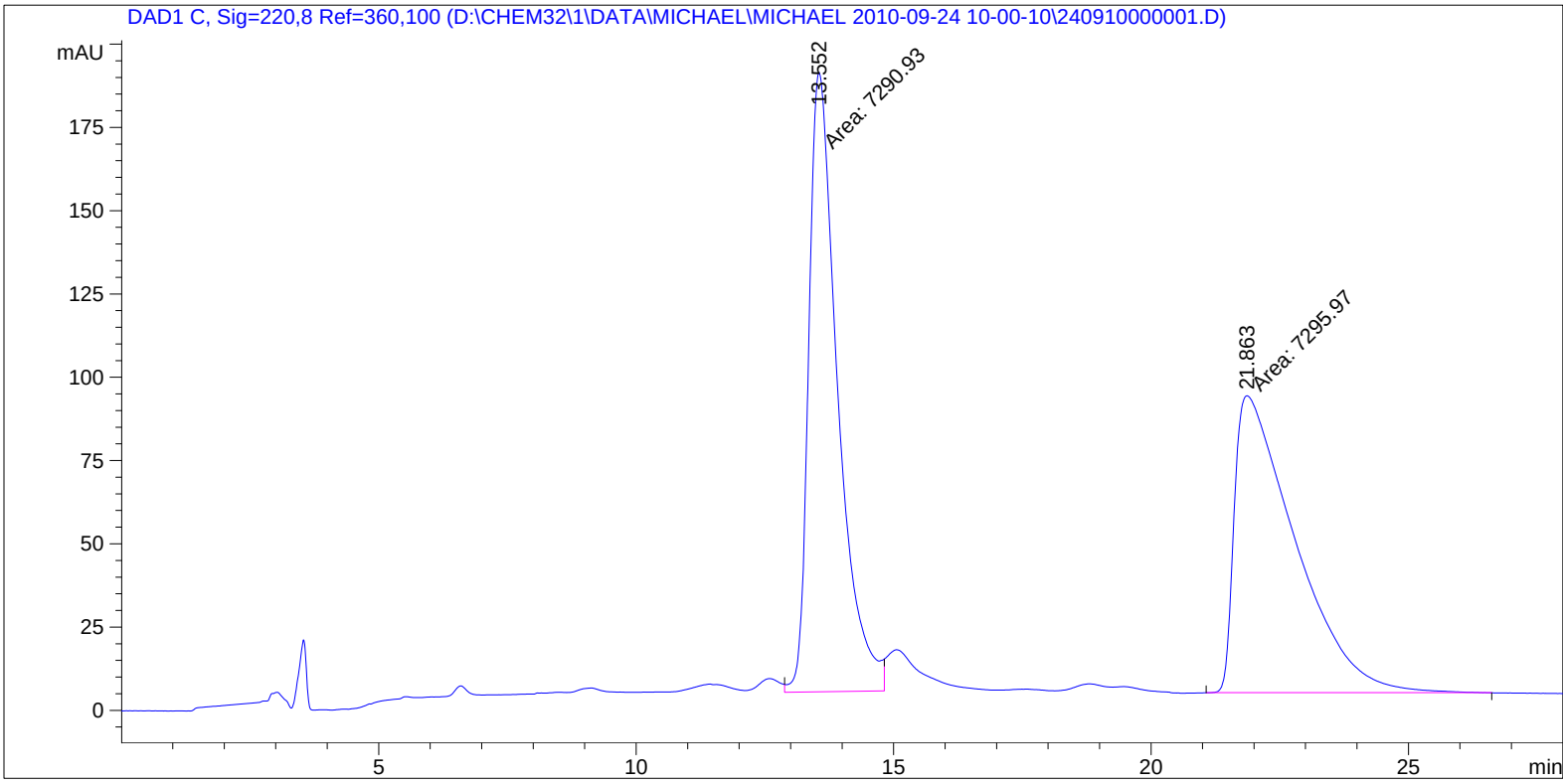


^{13}C NMR spectrum of dimethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9h



HPLC trace of racemic β-carboline (±)-9h



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                      Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.552 MM    0.6535 7290.93115  185.94194  49.9827
   2  21.863 MM    1.3643 7295.96777   89.12964  50.0173
```
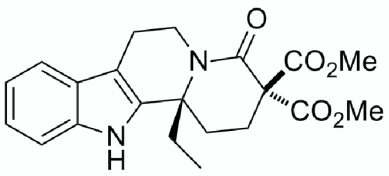
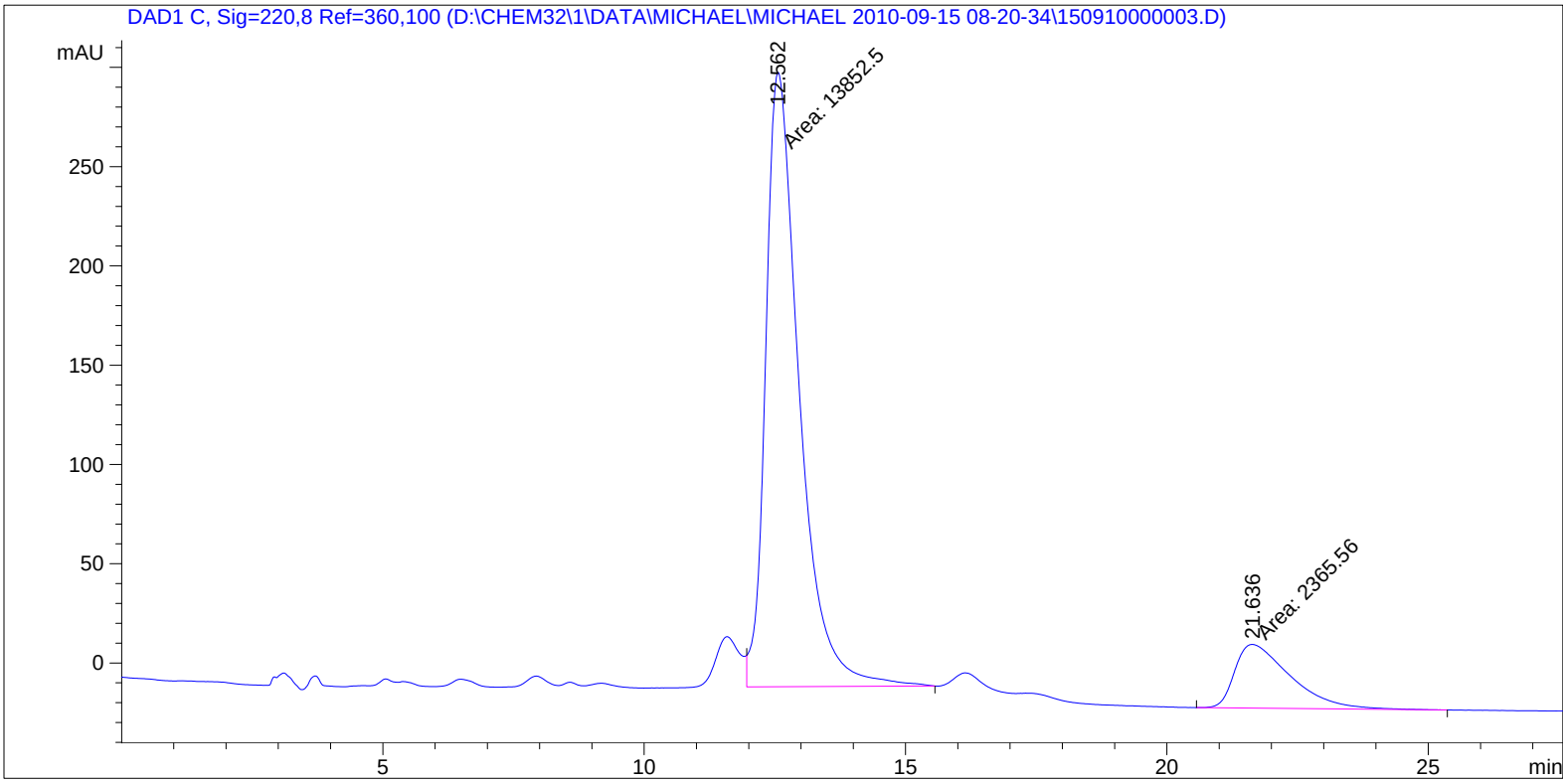

HPLC trace of enantioenriched β-carboline (+)-9h



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                      Area Percent Report
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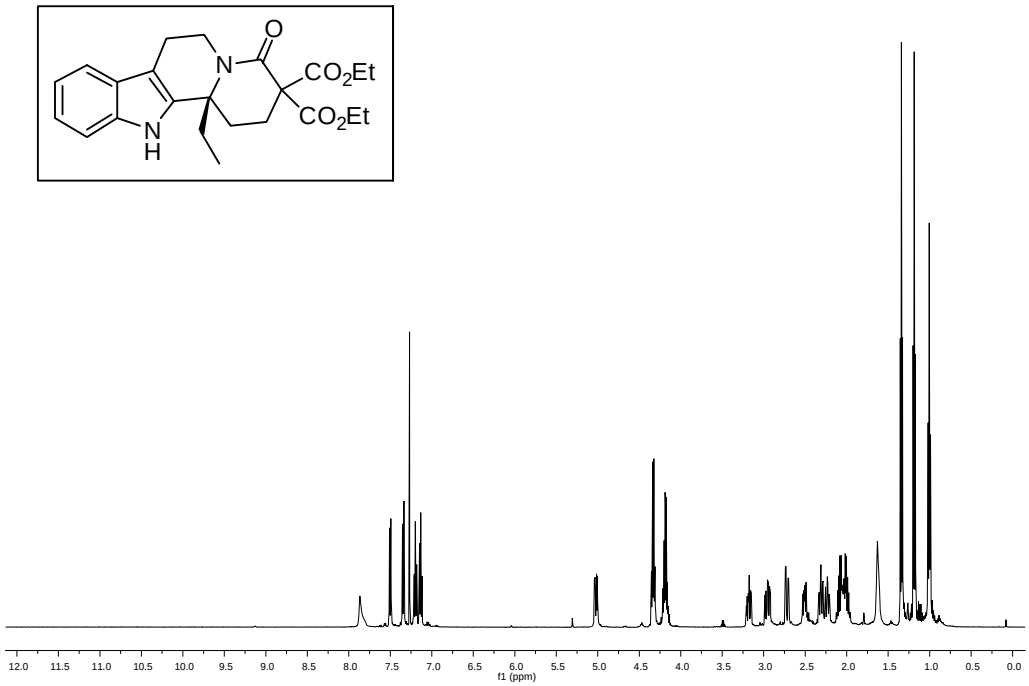
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

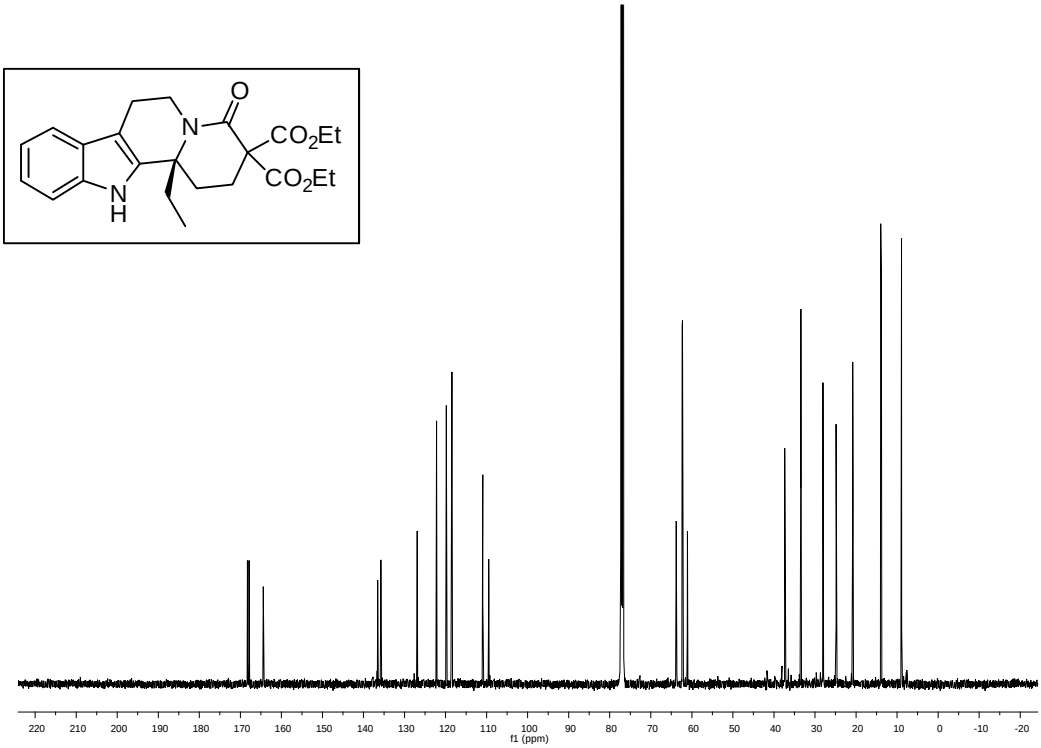

Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.562 FM    0.7461 1.38525e4   309.43198  85.4141
   2  21.636 MM    1.2300 2365.55811   32.05275  14.5859
```

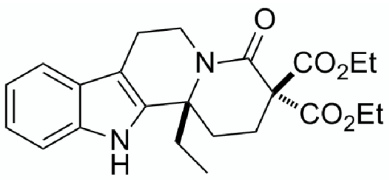
^{1}H NMR spectrum of diethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9i

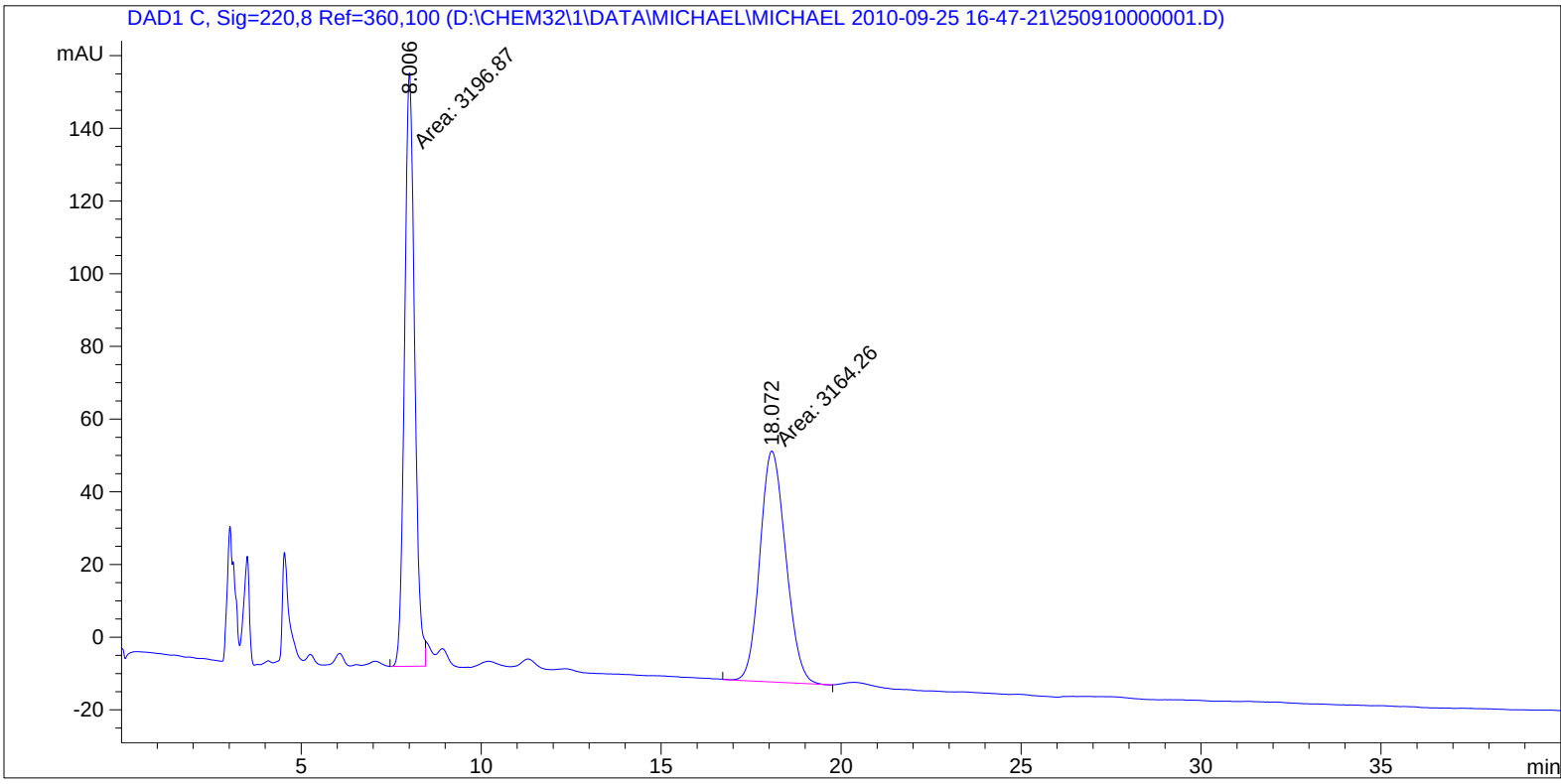


^{13}C NMR spectrum of diethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9i



HPLC trace of racemic β-carboline (±)-9i



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                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.006 MM    0.3264 3196.87256  163.24565  50.2564
   2  18.072 MM    0.8300 3164.25732   63.53744  49.7436
```
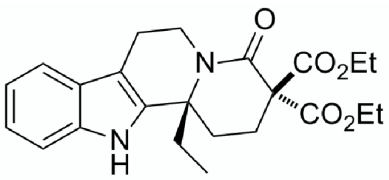
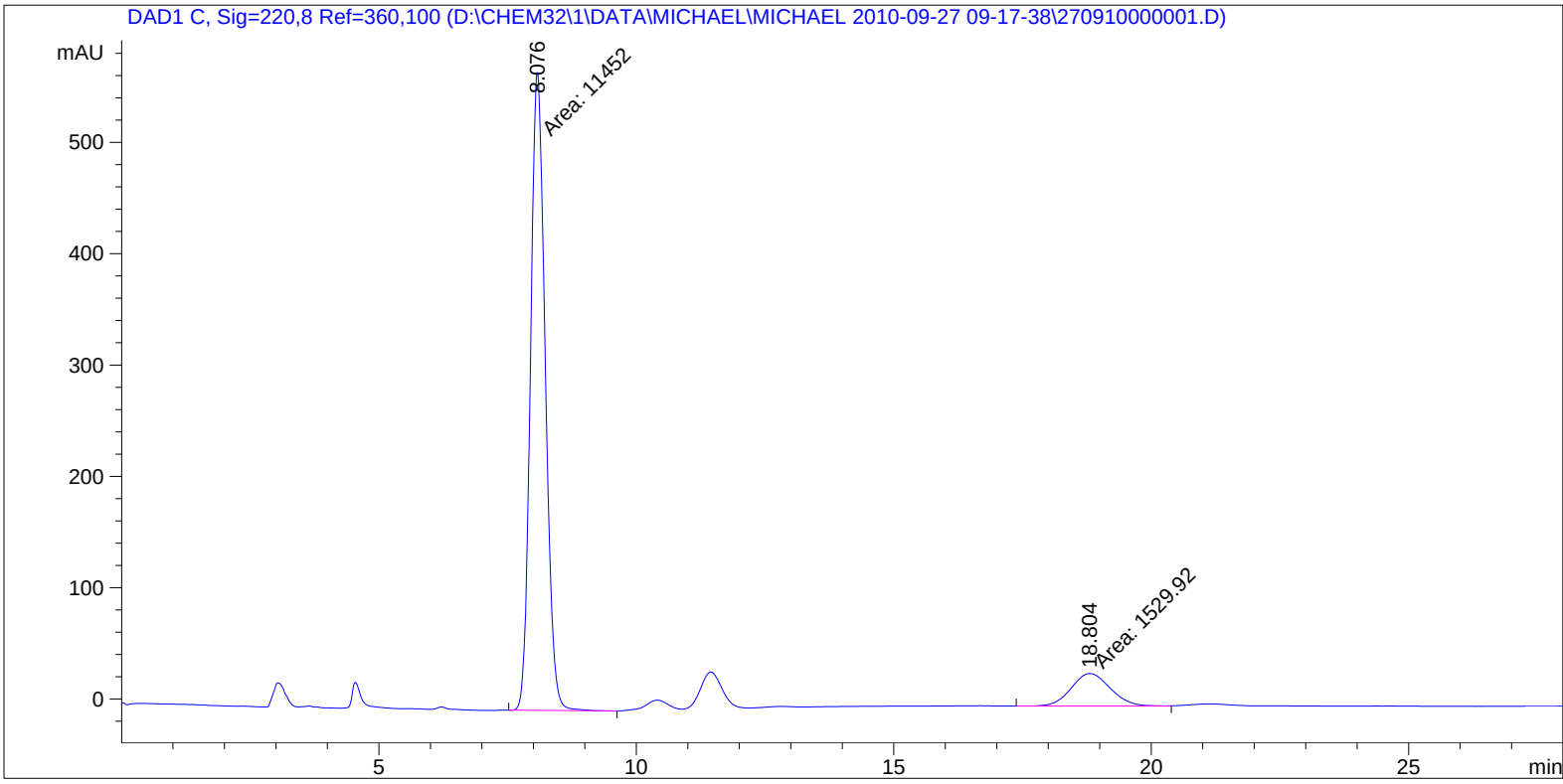

HPLC trace of enantioenriched β-carboline (+)-9i



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                          Area Percent Report
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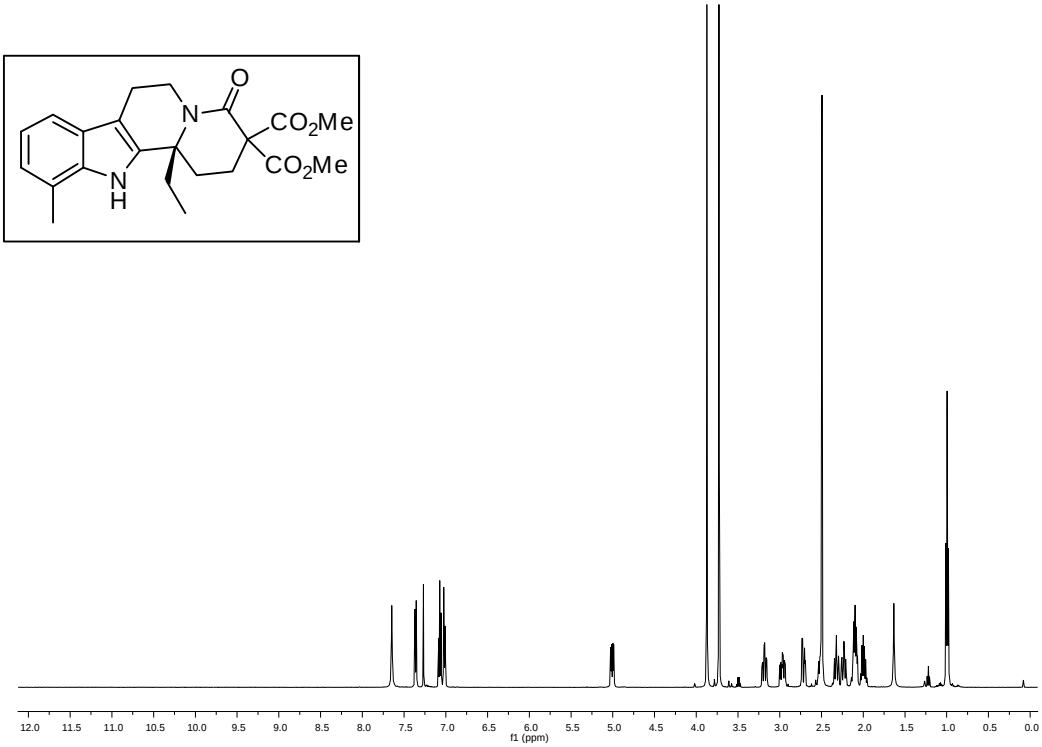
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

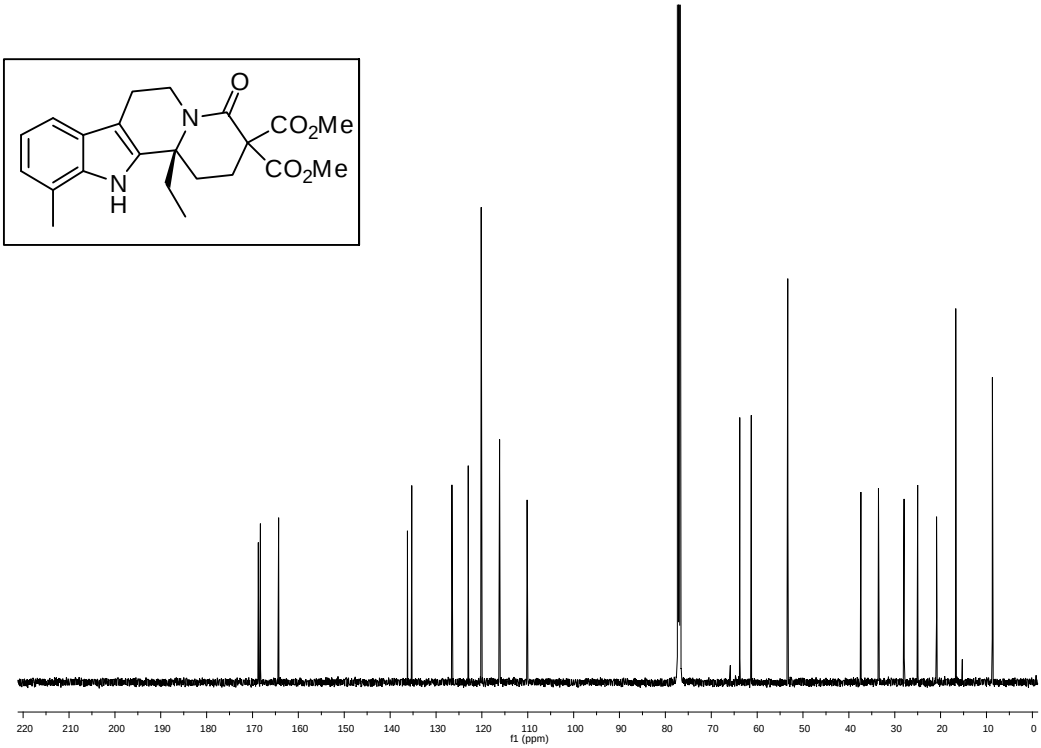

Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.076 MM    0.3330 1.14520e4   573.11499  88.2150
   2  18.804 MM    0.8726 1529.92029   29.22136  11.7850
```

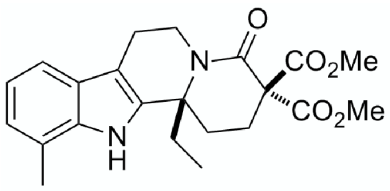
^{1}H NMR spectrum of dimethyl (12b*R*)-12b-ethyl-11-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9j

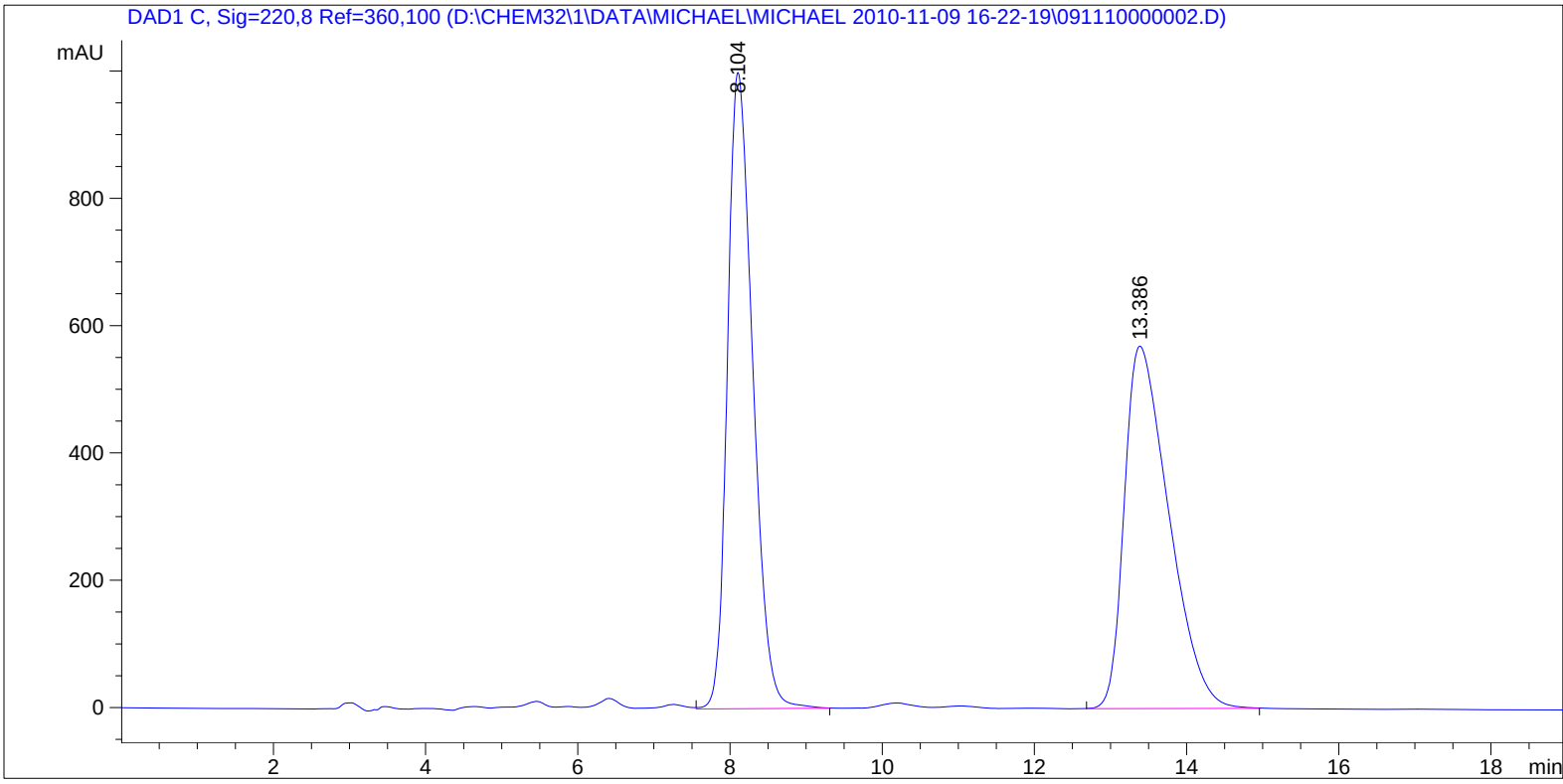


^{13}C NMR spectrum of dimethyl (12b*R*)-12b-ethyl-11-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate 9j



HPLC trace of racemic β-carboline (±)-9j



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                      Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.104 VB    0.3603 2.31584e4   999.51569  50.0747
   2  13.386 BB    0.6211 2.30893e4   569.34216  49.9253
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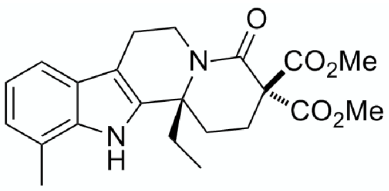
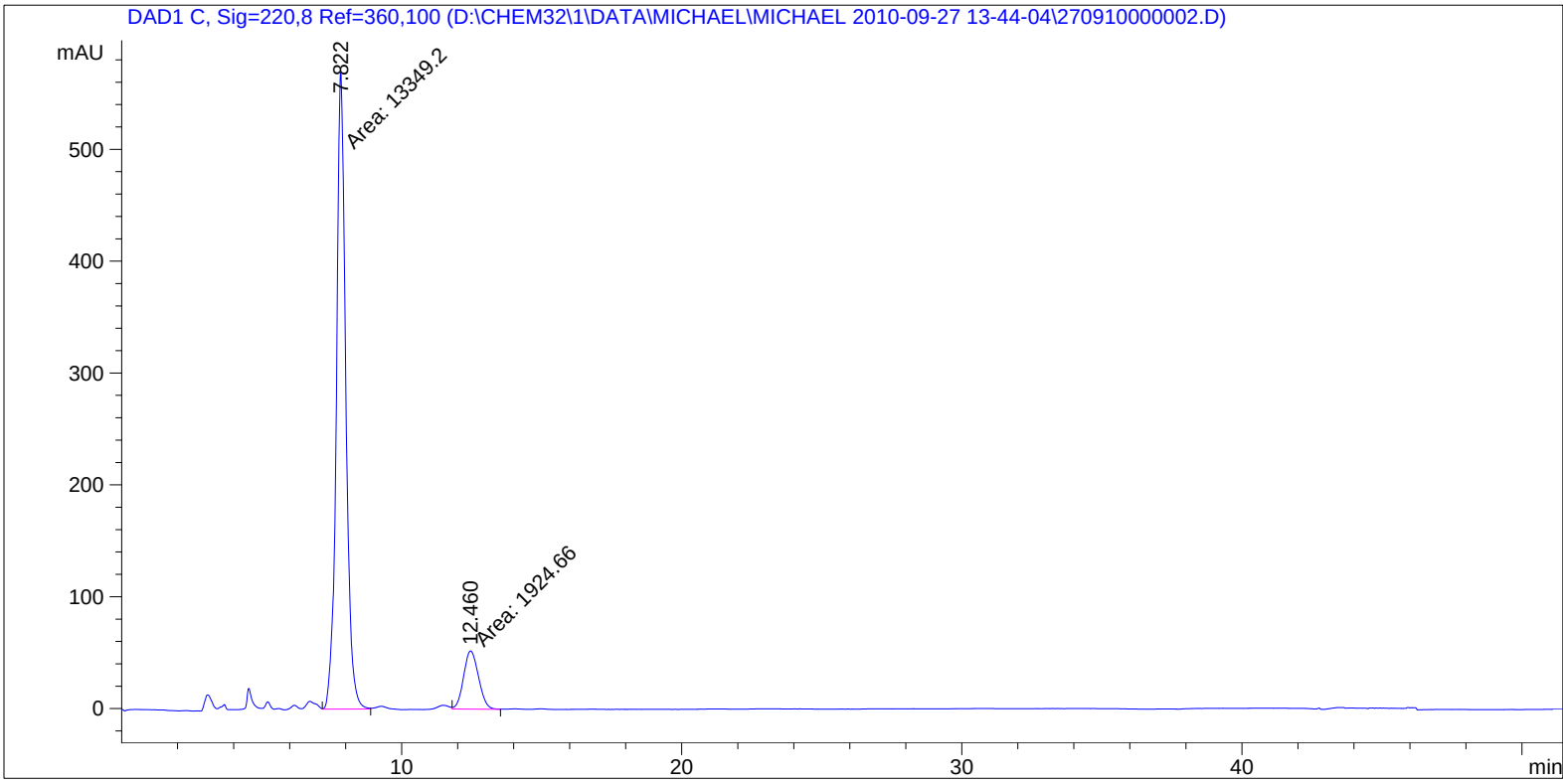
HPLC trace of enantioenriched β-carboline (+)-9j



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                          Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.822 MM    0.3908 1.33492e4   569.25592  87.3990
   2  12.460 MM    0.6170 1924.66101   51.98965  12.6010
```